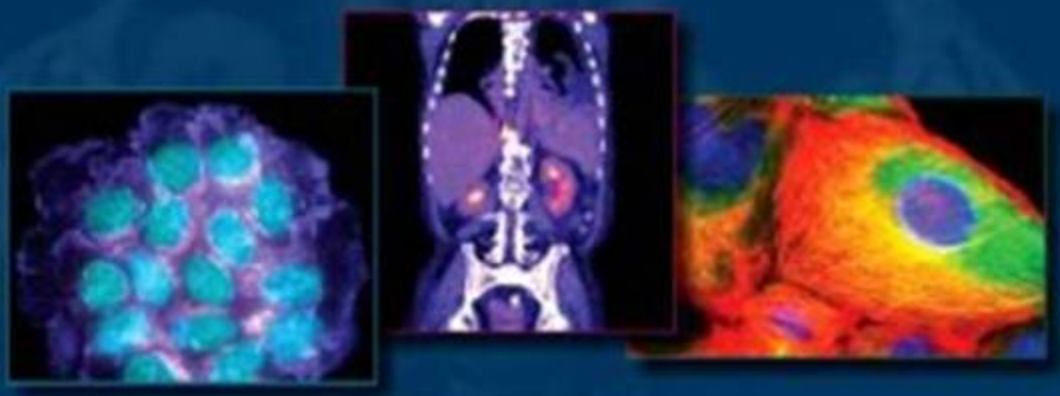
FOURTH EDITION

ABELOFF'S CLINICAL ONCOLOGY

MARTIN D. ABELOFF • JAMES O. ARMITAGE
JOHN E. NIEDERHUBER • MICHAEL B. KASTAN
W. GILLIES MCKENNA

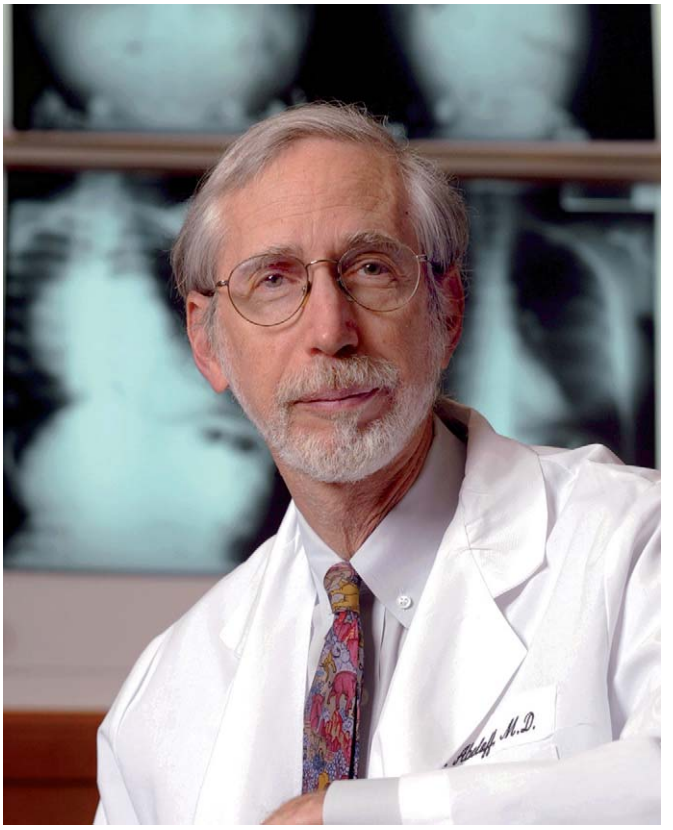


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Memorial



Martin D. Abeloff, MD

Martin D. Abeloff, a founding editor of *Clinical Oncology,* died on September 14, 2007 in Baltimore, Maryland after a courageous battle with cancer, a disease he had dedicated his life to fighting. He was a wonderful and caring clinician, an extremely effective leader, and a beloved mentor to many trainees and young faculty. Marty was the kind of friend you hope to have and the kind of clinician and clinical scientist that you would want to be. He will be sorely missed as a colleague, a physician, a father, a husband, and a friend.

Marty was born on April 4, 1942 in Shenandoah, Pennsylvania. He received his BA from The Johns Hopkins University in 1963, and his MD from The Johns Hopkins University School of Medicine in 1966. He spent the next year as an intern at the University of Chicago Hospitals and Clinics. In 1967, he eclipsed his already numerous accomplishments by marrying Diane Kaufman. The two daughters of this union, Alisa and Jennifer, represent Marty's most enduring and important legacy.

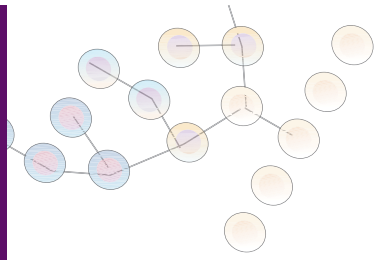
His second legacy, in medicine, was established on his return to Baltimore in 1971, as a fellow in clinical oncology. He would spend the rest of his career at The Johns Hopkins Hospital. He achieved the rank of Professor of Medicine in 1990 and, at various times, served as the training program director, chief of medical oncology, clinical director of the cancer center, oncologist in chief at The Johns Hopkins Hospital, and, since 1992, the director of The Johns Hopkins Oncology Center, later renamed the Sidney Kimmel Comprehensive Cancer Center. During that time, Marty brought to life the idea of a comprehensive, user-friendly textbook of oncology that would be as valuable to the practicing oncologist as to the primary care physician and physicians-in-training. The first edition of *Clinical Oncology* was published in 1995 to a gratifying response. It is now established as a cornerstone reference for those caring for patients with cancer.

In the fourth edition, we mourn the loss of our friend and colleague, but we continue Marty's vision for a better, unique, and

user-friendly text. In his honor, this edition has been renamed *Abeloff's Clinical Oncology* so that future generations of oncologists will remember his inspiration and leadership.

The editors, all of whom were recruited by Marty to work with him on this book, dedicate this text, which is already a tangible aspect of his legacy in medicine, as a living memorial to him. *Abeloff's Clinical Oncology* will serve as a reminder to all its users of this extraordinary person and exemplary physician who went before them. It was a privilege to have worked with him.

James O. Armitage, MD
John E. Niederhuber, MD
Michael B. Kastan, MD, PhD
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Preface

Few specialties in medicine are experiencing the rapid advancement in both laboratory and clinical science that is occurring in clinical oncology. The genetic mechanisms underlying cancer and their downstream effects are quickly becoming understood. This improved understanding of the molecular pathways in specific cancers is being translated into improved therapy. The development of antibodies and small molecules aimed at specific molecular targets that are key in the neoplastic process provide the promise of less toxic and more effective therapeutic options. Cancer prevention as a clinical science is making advances both in eliminating known carcinogens (e.g., tobacco) and in the development of drugs that inhibit carcinogenesis. The accumulative effect of these advances is, for the first time, sustained reduction in the age-adjusted death rate from cancer in the United States.

The fourth edition of *Abeloff's Clinical Oncology* incorporates these exciting changes. Each chapter begins with a summary highlighting the key points that would, for example, allow one to pass a board exam. In addition to a critical analysis of the literature, authors present their own opinions in specially identified boxes and algorithms. The use of color throughout the text makes the material more easily understood.

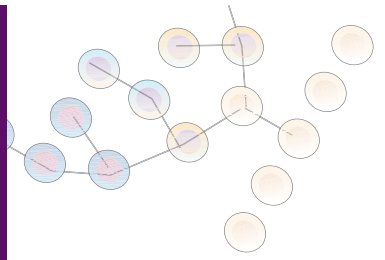
Our goal is to provide a textbook that is the most useful, understandable, attractive, and thorough in presenting the principles of clinical oncology. It is meant to be equally useful to students and trainees, experts in the various disciplines of oncology, and as a reference text for physicians from other disciplines who also see patients with cancer. It is our hope that readers will find this scholarly textbook properly balanced between the disciplines of science, clinical medicine, and humanism and that it will serve them well in their efforts to prevent, diagnose, and effectively treat their patients suffering from cancer.

The multidisciplinary nature of cancer care is, and will continue to be, reflected in our editors. Specialists in pediatric oncology, surgical oncology, radiation oncology, medical oncology, and hematologic malignancies direct the development of the book. Reflecting the interdisciplinary care necessary for optimal care of patients, many chapters are the joint product of several of these disciplines. The editors are deeply indebted to our outstanding authors who, in a most diligent and thoughtful way, have brought their knowledge and skills to the fourth edition of *Abeloff's Clinical Oncology*.

ACKNOWLEDGMENTS

This fourth edition represents a highly collaborative and dynamic effort between the editors and Elsevier. We are greatly indebted to Dolores Meloni for her creative input and guidance and for turning the principles behind this text into a reality. Mary Beth Murphy and Nancy Lombardi are acknowledged for their truly exceptional support of this project. The expert support provided by Michele Pass, Elaine Ryan, Simone John, Margaret Hall, and Kim Bennett is also greatly appreciated. Finally, we want to express our gratitude to our outstanding authors for their superb contributions and for their generosity and friendship.

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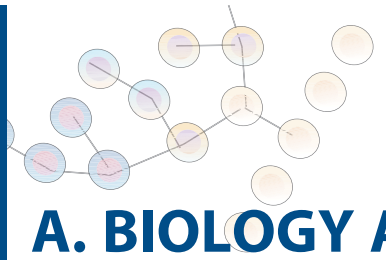
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A. BIOLOGY AND CANCER

1 Molecular Tools in Cancer Research

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SUMMARY OF KEY POINTS

- Our understanding and treatment of cancer have always relied heavily on parallel developments in biological research. Molecular biology provides the basic tools to study genes that are involved in cancer growth patterns and tumor suppression. An advanced understanding of the molecular processes that govern cell growth and differentiation has revolutionized the diagnosis and prognosis of malignant disorders.
- Current cancer research seeks to integrate the complex interaction of the cell's genome with its environment and emphasizes the need for a systematic approach to the analysis of gene function and dysfunction in the context of the intact organism. Discovery of the mechanisms that are responsible for genetic instability may lead to more reliable tests for hereditary susceptibility to cancer and, ultimately, to more effective therapies.
- This introductory chapter relates basic principles of molecular biology to emerging perspectives on the origin and progression of cancer and explains newly developed laboratory techniques, including whole-genome analysis, expression profiling, and refined genetic manipulation in animal models, providing the conceptual and technical background necessary to grasp the central principles and new methods of current cancer research.

INTRODUCTION

Since the previous edition of this book was published, advances in our understanding of the basic mechanisms of cancer have continued to inform and refine clinical approaches to prevention and therapy. New prognostic and predictive markers derived from molecular biology can now pinpoint specific genetic changes in particular tumors or detect occult malignant cells in normal tissues, leading to improved technologies for tumor screening and early detection. Diagnostic approaches have expanded from morphologic criteria and single-gene analysis to whole-genome technologies imported from other biological disciplines. A new systemic vision of cancer is emerging, in which the importance of individual mutation has been superseded by an appreciation for the new parameters set by gene-environment interactions, with profound influences on a tumor cell's transcriptional profile and function. Results from these cross-disciplinary applications underscore the complexity of carcinogenesis and promise to streamline the design of strategies for both cancer prevention and advanced cancer therapy.

This overview will serve as a foundation of conceptual and technical information for understanding the exciting new advances in cancer research that will be described in subsequent chapters. Since the discovery of oncogenes, which provided the first concrete evidence of cancer's genetic basis, applications of advanced molecular techniques and instrumentation have yielded new insights into normal cell biology as well. A basic fluency in molecular biology will soon be a necessary prerequisite for clinical oncologists, since many of the new diagnostic and prognostic tools that are in use today and will be in use tomorrow will rely on these fundamental principles of gene, protein, and cell function.

OUR UNSTABLE HEREDITY

Cancer genetics has classically relied on the candidate gene approach, detecting acquired or inherited changes in specific genetic loci accumulated in a single cell, which then proliferates to produce a tumor composed of its identical clonal progeny. During the early steps of tumor formation, mutations that lead to an intrinsic genetic instability allow additional deleterious genetic alterations to accumulate. These genetic changes confer selective advantages on tumor cell clones by disrupting control of cell proliferation. The identification of specific mutations that characterize a tumor cell has proved invaluable for analyzing the neoplastic progression and remission of the disease.

Methods for mutation detection all rely on the manipulation of DNA, the basic building block of heredity in the cell. DNA consists of two long strands of polynucleotides that twist around each other clockwise in a double helix (Fig. 1-1). Nucleic acid bases attached to the sugar groups of each strand face each other within the helix, perpendicular to its axis. These comprise only four bases: the purines adenine and guanine (A and G) and the pyrimidines cytosine and thymine (C and T). During assembly of the double helix, stable pairings of nucleotides from either strand are made between A and T or between G and C. Each base pair forms one of the billions of rungs in the long, unbroken ladder of DNA that forms a chromosome.

The functional unit of inherited information in DNA—the gene—is most often represented by a discrete section of sequence that is necessary to encode a particular protein structure. Gene expression is initiated by forming a copy of the gene, messenger RNA (mRNA), which is constructed base by base from the DNA template by a polymerase enzyme. Once the sequence is transcribed, an RNA transcript is modified at both ends and then undergoes a highly regulated process called splicing. In higher organisms, most protein-coding gene sequences are interrupted by stretches of noncoding sequences, called introns. The genetic machinery must remove these introns to form a continuous chain of coding sequences, or exons, which subsequently undergo translation into protein. The splicing process requires absolute precision because the deletion or addition of a single nucleotide at the splice junction would throw the three-base coding sequence out of frame.

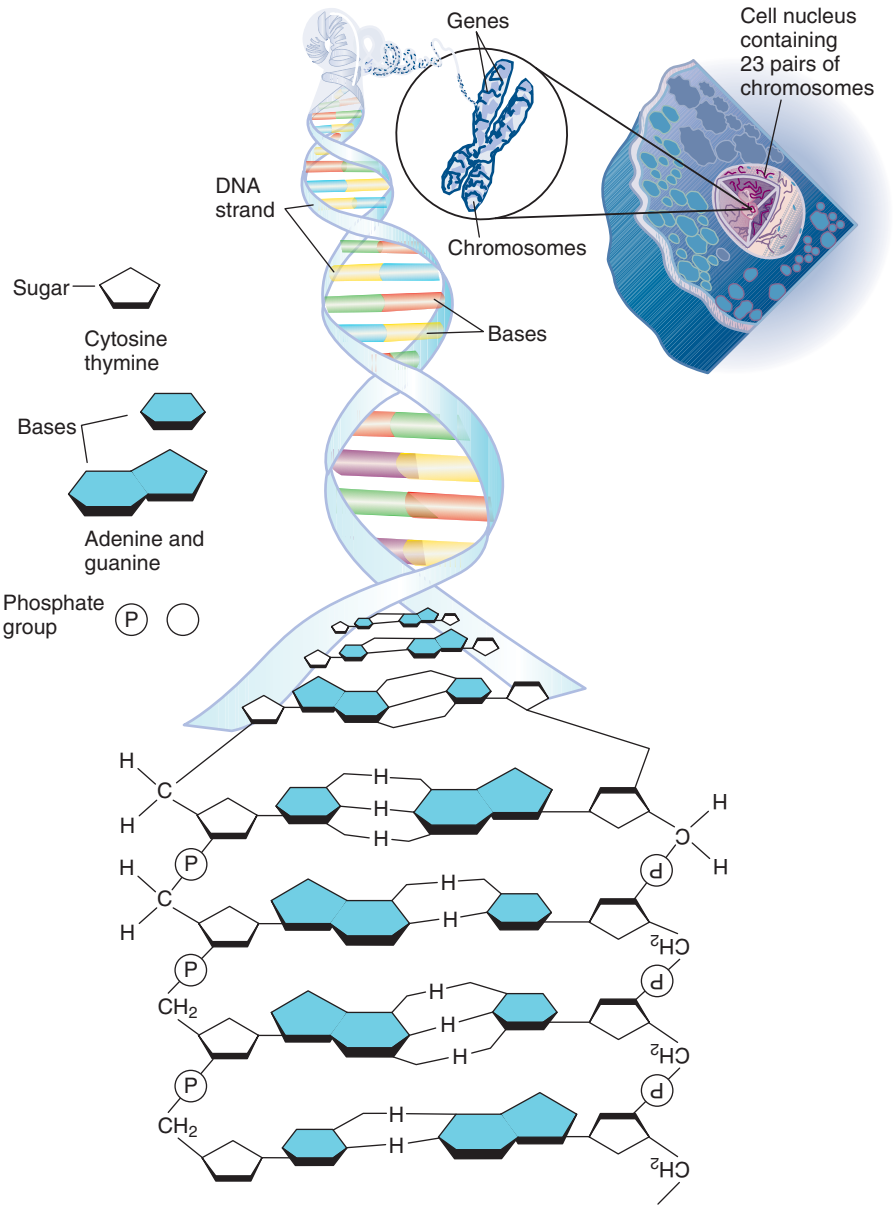


Figure 1-1 • DNA (deoxyribonucleic acid) is the cell's genetic material, contained in single compacted strands comprising chromosomes within the cell nucleus. In the DNA double helix, the two intertwined components of its backbone are composed of sugar (deoxyribose) and phosphate molecules that are connected by pairs of molecules called bases. The sequence of four bases (guanine, adenine, thymine, and cytosine) in the DNA helix determines the specificity of genetic information. The bases face inward from the sugar-phosphate backbone and form pairs with complementary bases on the opposing strand for specific recognition. The arrangement of chemical groups is unique for each base pair, allowing base pairs to be specifically targeted by transcription factors, polymerases, restriction enzymes, and other DNA-binding proteins.

The biologic importance of RNA splicing is not entirely understood, but many medically relevant genes have alternative splice patterns in which different combinations of exons are chosen for the final mRNA transcript, such that one gene can encode many different proteins (Fig. 1-2). The choice of protein isoform to be expressed from a gene with multiple splicing possibilities is a decision that can be perturbed in disease. Since protein synthesis occurs in the cytoplasm, genetic information is transported out of the nucleus by mRNA. In the cytoplasm, proteins are then synthesized, or translated, in macromolecular complexes called ribosomes that read the mRNA sequence and convert the nucleic acid code, based on three-base segments or codons, into a 20-amino-acid code to form the corresponding protein.

The complete set of DNA sequences carried on all the chromosomes is known as the genome. Although the general map of the genome is shared by all members of a species, the recent sequencing of the human genome has given us new tools to reveal the more subtle variations that arise between individuals. These variations are critical, both as a natural engine driving heterogeneity within a species and as a source of predisposition to cancer types. The most common forms of human genetic variations arise as single-nucleotide polymorphisms (SNPs). Because these allelic dissimilarities are abundant, inherited, and dispersed throughout the genome, SNPs can be used to track racial diversity, personal traits, and susceptibility to common forms of cancer (Fig. 1-3).

How do SNPs arise between individuals? One source of variation in DNA sequence derives from deviations in the strict base-pairing rule underlying the structure, storage, retrieval, and transfer of genetic information. The duplicated genetic information in the two strands of DNA not only permits the repair of a damaged coding sequence, but also forms the basis for the replication of DNA. During cell division, polymerase enzymes unwind the DNA strands and copy them, using the base sequences as a template for constructing a new helix so that the dividing cell passes its entire genetic content on to its progeny. Errors in this process are rare, and person-to-person differences make up only about 0.5% of the human genome. SNPs are inherited if they occur in the germline. Most genetic variation is of no obvious functional consequence, occurring in regions that do not

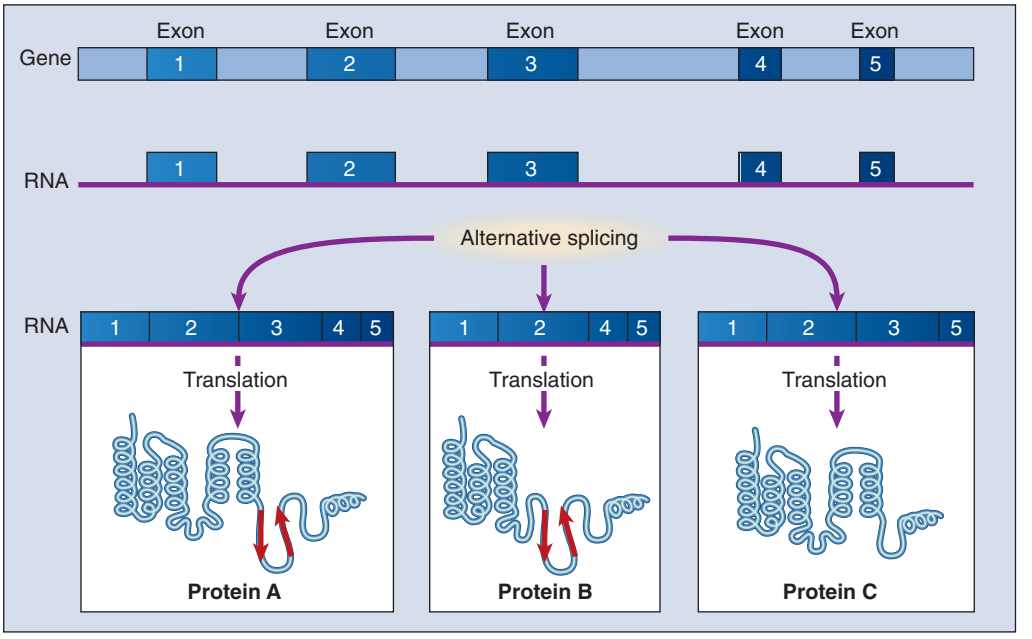


Figure 1-2 • Alternative splicing produces multiple related proteins, or isoforms, from a single gene. (Adapted from Guttmacher AE, Collins F: Genomic medicine: A primer. N Engl J Med 2002;347:1512–1520.)

encode protein or alter the regulation of nearby genes. Given the disruptive effects that even subtle genetic changes can have on cell function, it is important to distinguish SNPs that represent mutations from benign polymorphisms.

Our ability to monitor hundreds of thousands of SNPs simultaneously is one of the most important advances in modern medical genetics. Relatively simple genotyping technologies for SNP detection rely largely on the polymerase chain reaction (PCR). In this procedure, two chemically synthesized single-stranded DNA fragments, or primers, are designed to match chromosomal DNA sequences flanking the segment in which an SNP is positioned. The strands of genomic DNA are separated by heating and, after cooling, the primer

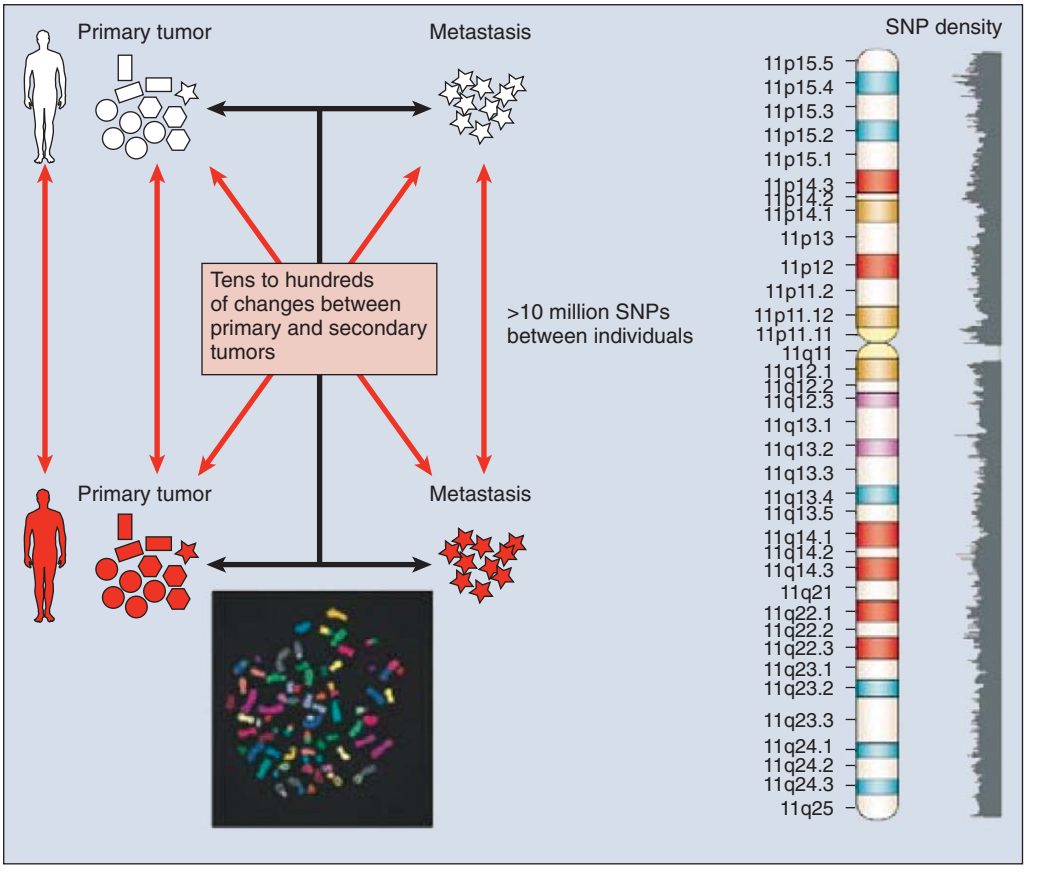


Figure 1-3 • Using SNPs to determine cancer susceptibility. Millions of single-nucleotide polymorphisms (SNPs) exist between individuals, as depicted by the *red arrows* and the SNP density map of human chromosome 11 (*right*). By contrast, point mutations, deletions, insertions, and rearrangements between normal tissues and tumors or between primary and secondary tumors probably number in the tens to hundreds (or potentially thousands), as depicted by the spectral karyotype image at the bottom of the figure. Because the constitutional genetic polymorphisms are present in all of the tissues of the body, it might be possible to distinguish differences in metastatic versus nonmetastatic tumors and in nontumor tissue before they ever happen to develop a solid tumor. (Adapted from Hunter K: Host genetics influence tumour metastasis. Nat Rev Cancer 2006;6:141–146.)

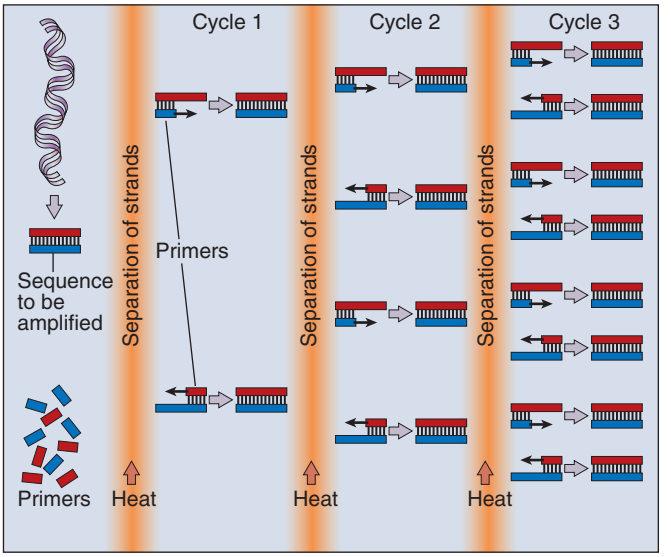


Figure 1-4 • Amplification of DNA by PCR. The DNA sequence to be amplified is selected by primers, which are short, synthetic oligonucleotides that correspond to sequences flanking the DNA to be amplified. After an excess of primers is added to the DNA, together with a heat-stable DNA polymerase, the strands of both the genomic DNA and the primers are separated by heating and allowed to cool. The polymerase elongates the primers on either strand, thus generating two new, identical double-stranded DNA molecules and doubling the number of DNA fragments. Each cycle takes just a few minutes and doubles the number of copies of the original DNA fragment.

binds to its matching sequence in the genomic DNA. With the addition of nucleotide building blocks and a heat-stable DNA polymerase, the primer pairs, or amplicons, initiate synthesis of new DNA strands using the chromosomal material as a template. Each successive copying cycle, initiated by "melting" the resulting double-stranded products with heat, doubles the number of DNA segments in the reaction (Fig. 1-4). The technique is exceptionally sensitive; millions of identical DNA copies can be generated in a matter of hours with PCR using a single DNA molecule as the starting material. Other novel methods for large-scale SNP detection include single nucleotide primer extension, allele-specific hybridization, oligonucleotide ligation assay, and invasive signal amplification, which detect polymorphisms directly from genomic DNA without the requirement of PCR amplification. Regardless of the method that is used to characterize them, the collective SNPs in a selected genomic region characterize a haplotype, or specific combination of alleles at multiple linked genetic loci along a chromosome that are inherited together.

Even when the SNPs within a given haplotype are not directly involved in a disease, they provide markers for clonality and for the loss or rearrangement of specific chromosomal segments in growing tumors. In the human nucleus, each of the 23 tightly compacted chromosomes has a characteristic size and structure and a distinctive base sequence that carries unique protein coding information. Other noncoding DNA sequences are used for directing the transcription of neighboring genes through complex regulatory circuits that involve protein binding and modification of the DNA itself or shifting of its chromosomal packaging. Although genomic instability is generally considered a consequence of tumor formation rather than the initial trigger of cancer, the loss, gain, or rearrangement of chromosomal segments through deletion or translocation is a common form of neoplastic mutation, as protein-coding segments from different genes are combined or regulatory sequences are brought into new proximity to genes that they do not normally control. Gross changes in DNA arrangement can be detected by cytogenetic analysis of chromosomal features on metaphase spreads. Fluorescent in situ hybridization provides greater resolution by localizing specific chromosomal DNA sequences corresponding to fluorescently labeled probes (Fig. 1-5) and can be used to track specific alterations in chromosomal structure where known genes are involved.

Although cytogenetic techniques are useful in detecting consistent, nonrandom structural abnormalities of clonal tumor cells, they

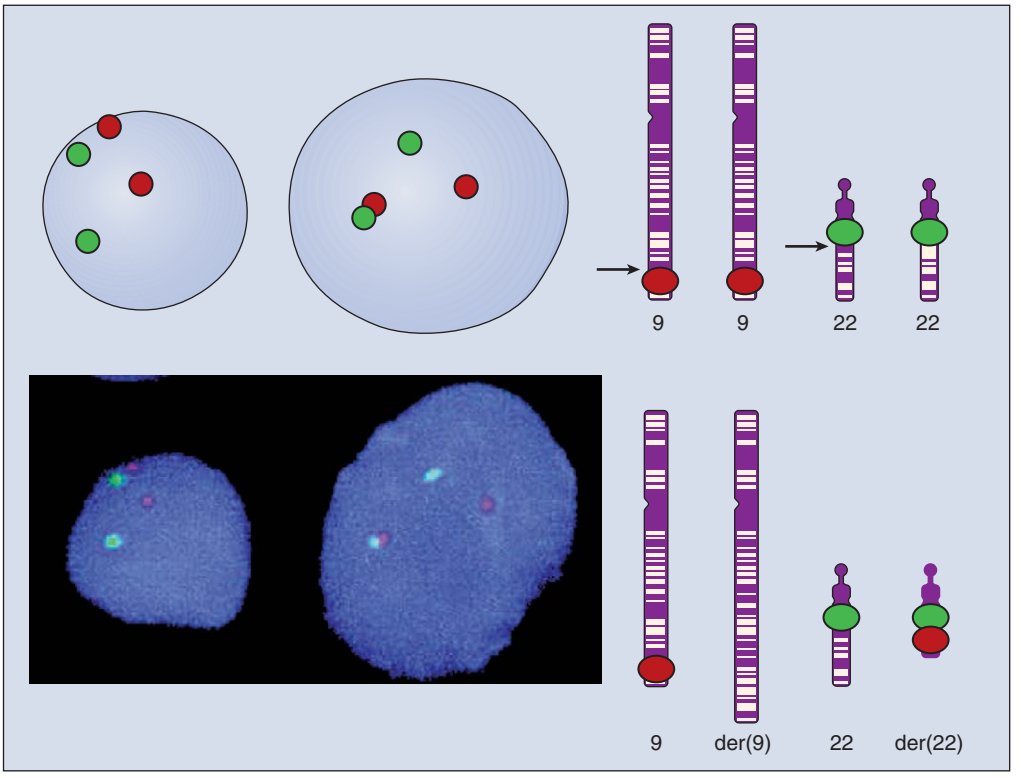


Figure 1-5 • Detection of chromosomal translocations in interphase cells by fluorescent in situ hybridization. This technology uses a labeled DNA segment as a probe to search homologous sequences in interphase chromosomes for the t(9;22)(q34;q11) translocation, associated with chronic myeloid leukemia. On the *left*, patient nuclei were hybridized with probes for chromosome 9 (labeled with SpectrumRed fluorophore) and chromosome 22 (labeled with SpectrumGreen). (Republished with permission of AlphaMed Press, from Oncologist, Varella-Garcia M. Molecular cytogenetics in solid tumors: laboratorial tool for diagnosis, prognosis, and therapy. 2003;45–58; permission conveyed through Copyright Clearance Center, Inc.)

require cell culture, which can limit their usefulness, particularly in analyzing solid tumors. Particularly when chromosomal alterations are too small to be detected by cytogenetic analysis, exploitation of the exquisite sequence specificity of certain bacterial DNA endonucleases, called restriction enzymes, allows the systematic cleavage of very large DNA molecules isolated from tumor samples into predictable, manageable subfragments. These can be identified by hybridization of a short, specific DNA or RNA oligonucleotide probe to its complementary base sequence, or target, in the fractionated genomic material. In most applications, the enzyme-digested sample of DNA is size fractionated by gel electrophoresis and transferred or "blotted" onto a nylon membrane to which labeled probe is then applied. In this procedure, DNA fragments containing sequences that hybridize with radioactively labeled probe can be detected by autoradiography or, alternatively, by nonisotopic colorimetric or chemiluminescent systems (Fig. 1-6). When a SNP occurs in the recognition site of a restriction enzyme, lost or rearranged DNA produces a change in the enzyme cleavage pattern, and these restriction-fragment-length polymorphisms can be detected by blotting analysis. PCR-based analysis using flanking DNA sequences as primers is also used to produce fragments, changes in the size of which, due to addition or loss of DNA bases, can be detected by gel electrophoresis. Subtler single base mutations can be identified by automated DNA-sequencing techniques.

The plethora of data that arise from genome-wide association studies using currently available techniques poses particular challenges to cancer researchers. Discerning the causal genetic variants among genotype-phenotype associations requires extensive replication, control for underlying genetic differences in population cohorts, and consistent classification of clinical outcomes. New technologies must be met with equivalently sophisticated and rigorous analytical methodologies for the true genetic cause of cancer to be teased out from our variable and often unstable heredity.

ENGINEERING GENES

The engineering of genes by recombinant DNA technology evolved from methods that were initially devised to provide sequences in amounts sufficient for biochemical analysis. The original protocol involves clipping the desired segment from the surrounding DNA and inserting it into a bacterial or viral vector, which is then amplified millions of times in a host bacterium. Using recombinant DNA technology, genetic engineering can routinely produce industrial quantities of pure, clinically useful products in a cost-effective way. For diagnostic purposes, it is easier and faster to amplify a known genomic DNA sequence directly from a patient sample with PCR, but the classic approach is still applied to the construction of recombinant DNA libraries.

To be useful, a DNA library must be as complete as possible, with recombinant members, or clones, sufficiently numerous to include all the sequences in an individual genome. For certain kinds of gene linkage analysis that require long, uninterrupted stretches of DNA, special vectors, such as bacterial or yeast artificial chromosomes, can carry foreign DNA fragments of enormous lengths. Chromosomal segments represented in genomic DNA libraries can contain the structure of an entire gene, including the information that regulates its expression and formed the starting material for sequencing the human genome.

For some applications, construction of partial libraries, which contain only the DNA sequences transcribed by a particular tissue or type of cell, is sufficient. The starting material in this case is mRNA. For cloning purposes, the enzyme reverse transcriptase can convert mRNA into complementary DNA (cDNA). Advanced techniques for acquiring full-length copies of RNA transcripts include rapid amplification of cDNA ends. The cDNAs are then incorporated into bacterial vectors. The number of clones in a cDNA library is much smaller than that in a genomic library, since a cDNA library represents only the genes that are expressed by the tissue of interest and contains exclusively the coding portion of genes. Screening DNA libraries for a specific gene classically relied on mass growth of bacterial hosts on agar, transfer of replicates to nylon filter and exposure to a specific DNA probe. The probe's unique sequence of nucleotides ensures that it hybridizes only to a nucleic acid molecule with the complementary sequence, which marks the position of the target clone. Cloning vectors can also be modified to drive the expression of their payload, producing "expression" libraries in bacteria that can be screened for protein production using specific antibodies, a technique that becomes increasingly important in large-scale screening of protein products.

LOSING CONTROL OF THE GENOME

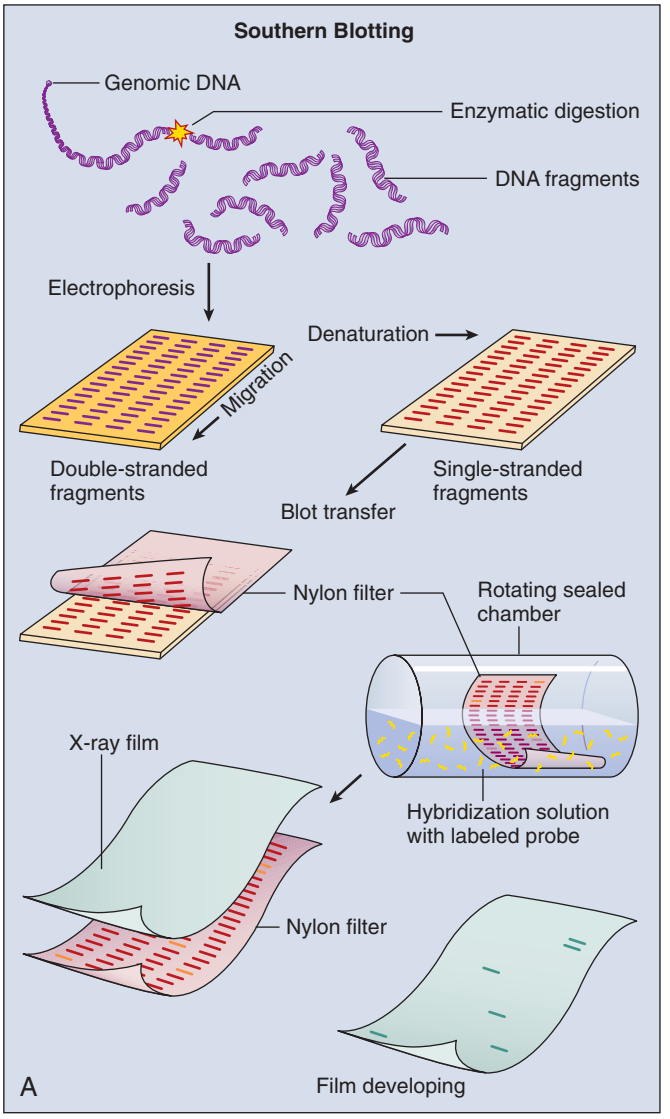
Mutations that lead to oncogenic transformation of a cell invariably affect the expression of its genetic information that specifies functional products, either RNA molecules or proteins used for various cellular functions. The primary level of gene control is the transcription of DNA into RNA. Gene regulation, or the control of RNA synthesis, represents a complex process that is frequently a target of neoplastic mutation.

DNA regulatory sequences do not encode a product. Yet without them, a cell could not coordinate the expression of the hundreds of thousands of genes in its nucleus, select only certain genes for expression, and activate or repress them in response to precise internal or external signals. These control centers of the genome contain binding sites for multiple proteins, called transcription factors, which interact to form regulatory networks that control gene transcription. Their function can be altered by signals that induce modifications such as phosphorylation, or by interactions with other regulators such as steroid hormones. Many of the cell's responses to a wide variety of external stimuli, such as neurotransmitters, antigens, cytokines, and growth factors, are mediated through transcription factors binding to DNA regulatory sequences.

Certain regulatory DNA sequences common to many genes are positioned upstream of the transcription start site (Fig. 1-7). Collectively called the promoter of a gene, these proximal sequences comprise binding sites for the RNA polymerase and its numerous cofactors. Whereas the position of the promoter with regard to the transcription start site is relatively inflexible, other DNA regulatory elements, known as enhancers, occur in unpredictable locations, often at a considerable distance from the genes they control. Some transcription factors bind to particular regions of enhancers and drive their associated genes in many types of cells, whereas others, which are active in only a limited variety of cells, maintain a tissue-specific pattern of gene expression. Enhancers are often responsible for the aberrant expression of genes induced by chromosomal translocation-associated specific forms of cancer; a normally quiescent gene promoting cell growth that is dislocated to a position near a strong enhancer may be activated inappropriately, resulting in loss of growth control.

Enhancers and promoters have been assigned specific roles by means of cell culture assays or in transgenic animals in which putative regulatory DNA sequences are linked to test or "reporter" genes and are examined for their ability to activate expression of the reporter gene in response to the appropriate signals. By assessing the effects of deleting, adding, or changing DNA sequences within the regulatory element, the precise nucleotides that are critical for recognition by transcription factors can be determined.

The interaction between protein and DNA is also used to identify transcription factor-binding sites in a regulatory region. Whereas electrophoretic mobility shift assays, or DNA footprinting, were once standard techniques for determining protein-DNA interactions, emerging genome-wide technologies, such as chip sequencing (see Fig. 1-13 later in the chapter), are revolutionizing the way in which we see the simultaneous interaction of a transcription factor complex


Southern Blotting
Genomic DNA
Enzymatic digestion
DNA fragments
Electrophoresis
Denaturation
Migration
Double-stranded fragments
Single-stranded fragments
Blot transfer
Nylon filter
Rotating sealed chamber
X-ray film
Hybridization solution with labeled probe
Nylon filter
Film developing
A

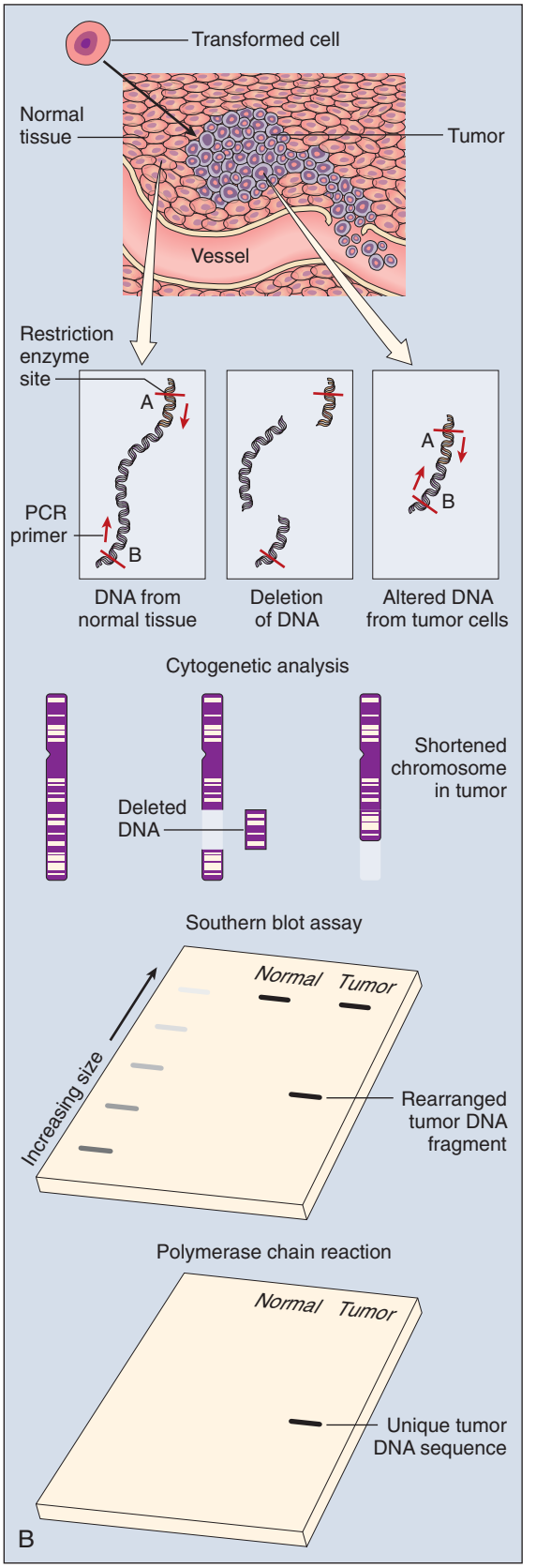

Transformed cell
Normal tissue
Tumor
Vessel
Restriction enzyme site
PCR primer
A
B
DNA from normal tissue
Deletion of DNA
Altered DNA from tumor cells
Cytogenetic analysis
Deleted DNA
Shortened chromosome in tumor
Southern blot assay
Normal
Tumor
Increasing size
Rearranged tumor DNA fragment
Polymerase chain reaction
Normal
Tumor
Unique tumor DNA sequence
B

Figure 1-6 • A, Analysis of DNA by gel electrophoresis and Southern blotting. Genomic DNA is cut with restriction enzymes into fragments before being separated according to size by gel electrophoresis. The four lanes on the gel represent the digestion of the DNA with four different restriction enzymes. In Northern blotting, total cellular RNA, including messenger RNA, can also be separated according to size. After electrophoresis, the nucleic acids in the gel are transferred directly onto a charged nylon filter, to which they are tightly bound. Thus, the filter contains a precise replica of the nucleic acid distribution in the gel. The filter is then hybridized in a rotating sealed chamber with a DNA or RNA probe specific for the target of interest (in this case, sequences in a microbial pathogen). Probes have traditionally been radioactively labeled with nucleotides containing phosphorus 32; however, the use of nonradiolabeled probes is becoming more common. After the probe has hybridized to its target sequence, the nonhybridized probe is washed away, and the filter is exposed to x-ray film. A DNA sequence complementary to the probe is seen as a dark band on the developed film. The position of the hybridized target sequence in each lane is unique to the restriction enzyme that is used to digest the DNA. This procedure is termed Southern blotting when DNA is analyzed and Northern blotting when RNA is analyzed. **B,** Cytogenetic and molecular analyses of tumor cells. Three methods of detecting the specific genetic alterations shared by all the neoplastic cells in a tumor are shown. (1) If the genetic alteration is large enough, as in the deletion of a region of DNA between loci A and B, cytogenetic analysis can detect grossly visible karyotypic changes. (2) Southern blot analysis can detect small changes in gene structure that routine karyotyping studies cannot find. In this example, a probe to locus A normally detects a large DNA restriction fragment, as shown by the band for the normal DNA sample. Because of the deleted DNA segment in the tumor cells, the probe for the region between loci A and B hybridizes to a smaller, rearranged, tumor-specific restriction fragment. The normal, larger band shown on the blot is from DNA contributed by nonneoplastic stromal and reactive cells. (3) In many applications, the polymerase chain reaction (PCR) can detect alterations in DNA structure with the highest degree of sensitivity. Here, the primers that anneal to loci A and B in normal DNA are too far apart to yield an amplified PCR product. The deletion shown in the tumor DNA brings the two annealing sites close to one another, allowing the generation of a novel amplified PCR product. (**A,** Modified from Naber SP: Molecular pathology-diagnosis of infectious disease. N Engl J Med 1994;331:1212–1215. **B,** From Naber SP: Molecular pathology-detection of neoplasia. N Engl J Med 1994;331:1508–1510.)

with virtually all of its potential genomic targets in a particular cell state.

Our appreciation of oncogenic perturbations, either by mutation of regulatory protein-coding genes or in the target sequences these proteins recognize, has recently extended to include epigenetic lesions, although these mechanisms have been more difficult to define. Multiple levels of control are necessary to ensure correct gene expression, which is so central to the normal function of the cell. Epigenetics refers generally to control information that is inherited during cell division along with the DNA sequence itself.

A key component of epigenetic regulation, chromatin, wraps DNA into coils with scaffolding proteins such as histones as a necessary component of chromosomal compaction but also plays a critical role in gene accessibility (Fig. 1-8). Active genetic loci are associated with loosely configured euchromatin, whereas silent loci are condensed in heterochromatin. The formation of chromatin configurations both controls and is controlled by patterns of methylation on specific DNA sequences, relating the underlying genetic information to its higher-order structure that determines whether a particular gene regulatory element is available to transcription factors. These epigenetic modifications of the nuclear environment that determine the accessibility of a gene can persist during cell division, as inherited patterns of methylation provide permanent marks for altered chromatin configuration in daughter cells.

Recent research has linked rearrangement of chromatin and associated DNA methylation with the inactivation of tumor suppressor genes and neoplastic transformation. Defects that could lead to cancer involve perturbations in the "epigenotype" of a particular locus through the silencing of normally active genes or activation of normally silent genes, which are associated with changes in DNA methylation, histone modification, and chromatin proteins (Fig. 1-9). Changes in the number or density of heterochromatin proteins associated with cancer-related genes such as EZH2 or of euchromatic proteins such as trithorax in leukemia can also be associated with abnormal patterns of methylation in gene promoter regions as well as with higher-order chromosomal structures that are only beginning to be understood. Finally, it is increasingly evident that interactions between the "epigenome," the genome, and the environment are a common target for mutation and can have profound effects on the gene expression readout of a cancer cell.

PROFILING TUMORS

Monitoring global gene expression patterns of cells represents one of the latest breakthroughs in developing a molecular taxonomy of cancer. Genome-wide profiling of gene expression in tumors delivers an unprecedented view into the biological processes underlying tumor progression by following the changes in a tumor cell's transcriptional landscape. Relying on two-color fluorescence-based microarray technology (DNA microarray), simultaneous evaluation of thousands of gene transcripts and their relative expression can provide a snapshot of the "transcriptome," the full complement of RNA transcripts that are produced at a specific time during the progression of malignancy.

Transcriptional profiling using microarrays typically involves screens of mRNA expression from two sources (such as tumor and normal cells), using complementary cDNA or oligonucleotide libraries that are arranged in extremely high density on microchips. These are probed with a mixture of fluorescently tagged cDNAs generated from the tumor and normal samples, which results in differential staining of each gene spot. The relative intensity of the two different colors reflects the RNA expression level of each gene in each sample as analyzed with a laser confocal scanner (Fig. 1-10). By using microarrays, single genes that constitute diagnostic, prognostic, or therapeutically relevant markers can be systematically monitored. Alternatively, the entire set of expressed genes can be collectively analyzed by using powerful statistical methods to classify tumors by their transcriptional profile. Microarray analysis has already dramatically improved our ability to explore the genetic changes that are associated with cancer etiology and development and is providing new tools for disease diagnosis and prognostic assessment. For example, DNA microarray analysis of multiple primary breast tumor transcriptomes has revealed a reproducible 70-gene expression signature that was recently cleared by the U.S. Food and Drug Administration for a PCR-based application in which expression analysis of a relatively small gene group can predict the prognosis of early-stage breast cancers. When applied on a larger scale, these assays can predict response to chemotherapy or optimize pharmaceutical intervention by targeting therapeutic approaches to specific patient populations and, ultimately, to individualized therapy.

Serial analysis of gene expression (SAGE) provides a simultaneous, comprehensive evaluation of multiple mRNA species. Unlike microarray analysis, SAGE does not require prior knowledge of the genes of interest and provides quantitative and qualitative data of potentially every transcribed sequence in a particular tissue or cell type. Furthermore, SAGE can quantify low-abundance transcripts and can reliably detect relatively small differences in transcript concentrations between cell populations. The SAGE method generates a short sequence tag that functions as a unique identifier of a transcript, derived from a defined location within that transcript. Many transcript tags are concatenated into a single molecule and then sequenced, revealing the identity of multiple tags simultaneously. The relative presentation of each member of a SAGE tag library is proportional to the corresponding mRNA abundance in the original transcript

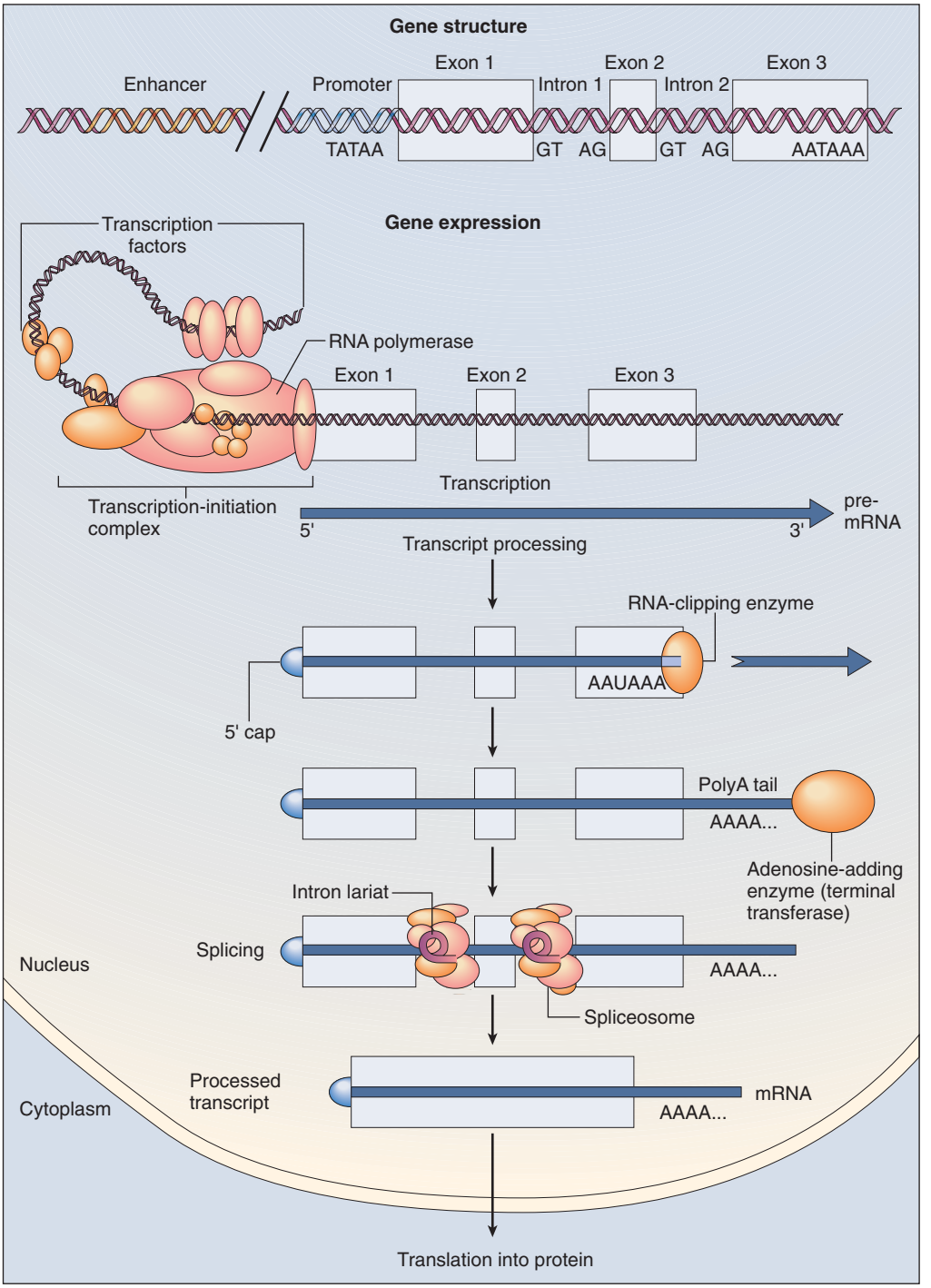


Figure 1-7 • Mammalian gene structure and expression. The DNA sequences that are transcribed as RNA are collectively called the gene and include exons (expressed sequences) and introns (intervening sequences). Introns invariably begin with the nucleotide sequence GT and end with AG. An AT-rich sequence in the last exon forms a signal for processing the end of the RNA transcript. Regulatory sequences that make up the promoter and include the TATA box occur close to the site where transcription starts. Enhancer sequences are located at variable distances from the gene. Gene expression begins with the binding of multiple protein factors to enhancer sequences and promoter sequences. These factors help to form the transcription-initiation complex, which includes the enzyme RNA polymerase and multiple polymerase-associated proteins. The primary transcript (pre-mRNA) includes both exon and intron sequences. Post-transcriptional processing begins with changes at both ends of the RNA transcript. At the 5′ end, enzymes add a special nucleotide cap; at the 3′ end, an enzyme clips the pre-mRNA about 30 base pairs after the AAUAAA sequence in the last exon. Another enzyme adds a polyA tail, which consists of up to 200 adenine nucleotides. Next, spliceosomes remove the introns by cutting the RNA at the boundaries between exons and introns. The process of excision forms lariats of the intron sequences. The spliced mRNA is now mature and can leave the nucleus for protein translation in the cytoplasm. (Adapted from Rosenthal N: Regulation of gene expression. N Engl J Med 1994; 331:931–932.)

population. Comparative expression profiles can then be deduced by comparing the abundance of individual tags within each sample set. This allows changes in global expression profiles of normal or malignant tissues under different therapeutic conditions to be rapidly evaluated.

These technologies can be applied to the analysis of noncoding RNA species as well. Beside the 20,000 protein-coding transcripts that are used to classify a wide variety of human tumors, hundreds if not thousands of small, noncoding interference RNA species have recently been discovered with critical functions in multiple biological processes, many of which are directly or indirectly involved in the control of cell proliferation. Known as microRNAs (miRNAs), these short transcripts arise from primary genome-encoded transcripts of variable sizes that are processed into 70- to 100-nucleotide hairpin-shaped precursors, which are processed into mature miRNAs of 21- to 23-base-pair RNA molecules (Fig. 1-11). miRNAs function by base-pairing with specific mRNAs to inhibit translation or to promote mRNA degradation. In the context of cancer, miRNAs could act in concert with other effectors such as p53 to inhibit inappropriate cell proliferation. A global decrease in miRNA levels is often observed in human cancers, indicating that small RNAs could have an intrinsic function in tumor suppression. The utility of monitoring the expres-

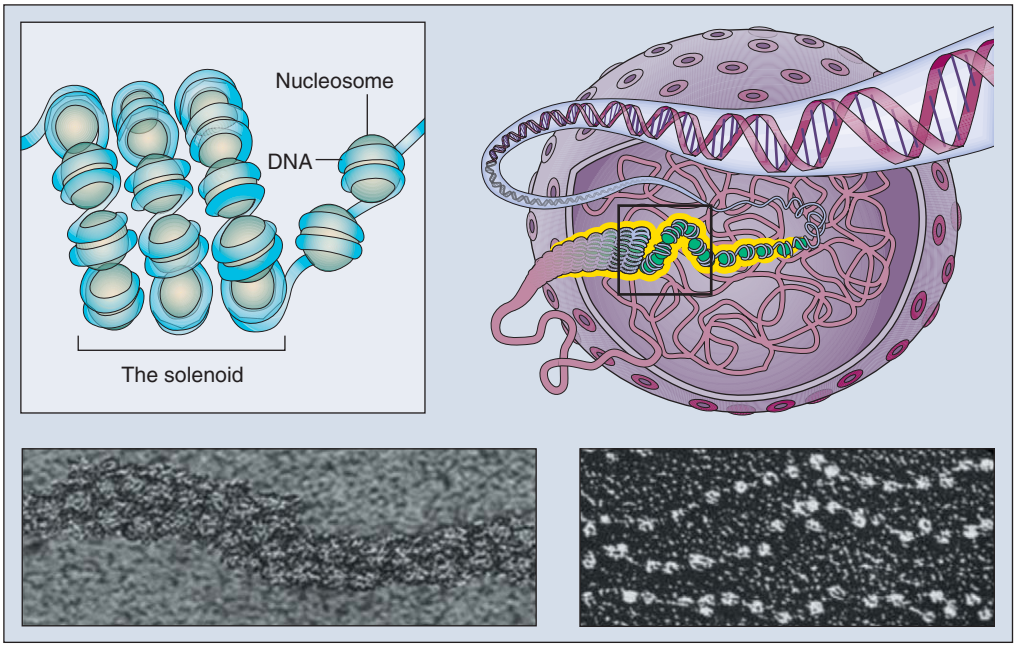


Figure 1-8 • Chromatin packaging of DNA. The 4 meters of DNA in every human cell must be compressed in the nucleus, reaching compaction ratios of 1:400,000. This is achieved by wrapping the DNA (*blue*) around histone protein complexes (*green*), forming nucleosomes that are connected by a thread of free linker DNA. Each nucleosome, together with its linker, packages about 200 base pairs (66 nm) of DNA. The nucleosomes are then coiled into chromatin, a rope of nucleoprotein about 30 nm thick (bottom left electron micrograph). To allow DNA to be accessed by transcription and replication apparatus, chromatin is relaxed (bottom right electron micrograph). (Courtesy of Jakob Waterborg www.umkc.edu/sbs/waterborg/chromat/chromatn.html © 1998 Jakob Waterborg.)

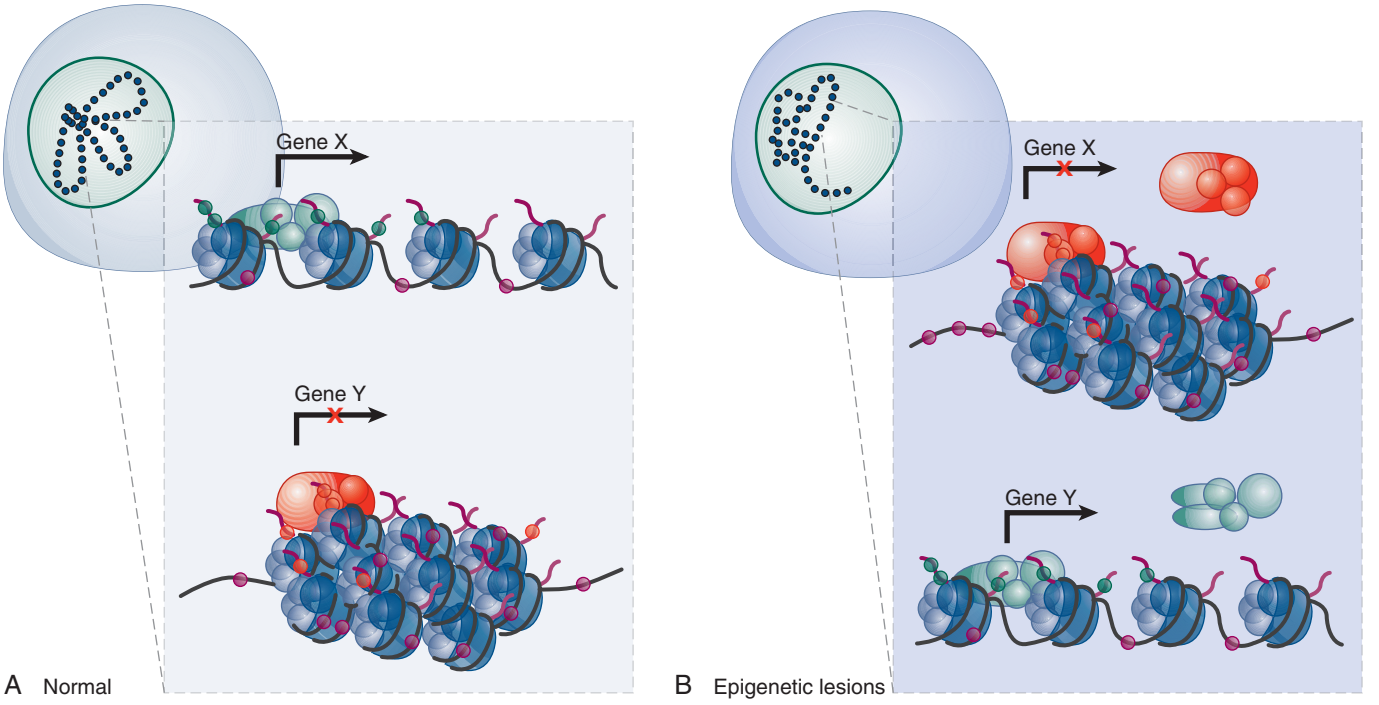


Figure 1-9 • Gene accessibility through epigenetics. The nature of epigenetic lesions. The cartoon depicts known and possible defects in the epigenome that could lead to disease. **A,** X is a transcriptionally active gene with sparse DNA methylation (*brown circles*), an open chromatin structure, interaction with euchromatin proteins (*green protein complex*), and histone modifications such as H3K9 acetylation and H3K4 methylation (*green circles*). Y is a transcriptionally silent gene with dense DNA methylation, a closed chromatin structure, interaction with heterochromatin proteins (*red protein complex*), and histone modifications such as H3K27 methylation (*pink circles*). **B,** The abnormal cell could switch its epigenotype through the silencing of normally active genes or activation of normally silent genes, with the attendant changes in DNA methylation, histone modification, and chromatin proteins. In addition, the epigenetic lesion could include a change in the number or density of heterochromatin proteins in gene X (such as EZH2 in cancer) or euchromatic proteins in gene Y (such as trithorax in leukemia). There may also be an abnormally dense pattern of methylation in gene promoters (shown in gene X) and an overall reduction in DNA methylation (shown in gene Y) in cancer. The insets show that the higher-order loop configuration may be altered, although such structures are currently only beginning to be understood. (Adapted from Feinberg AP: Phenotypic plasticity and the epigenetics of human disease. Nature 2007;447:433–440.)

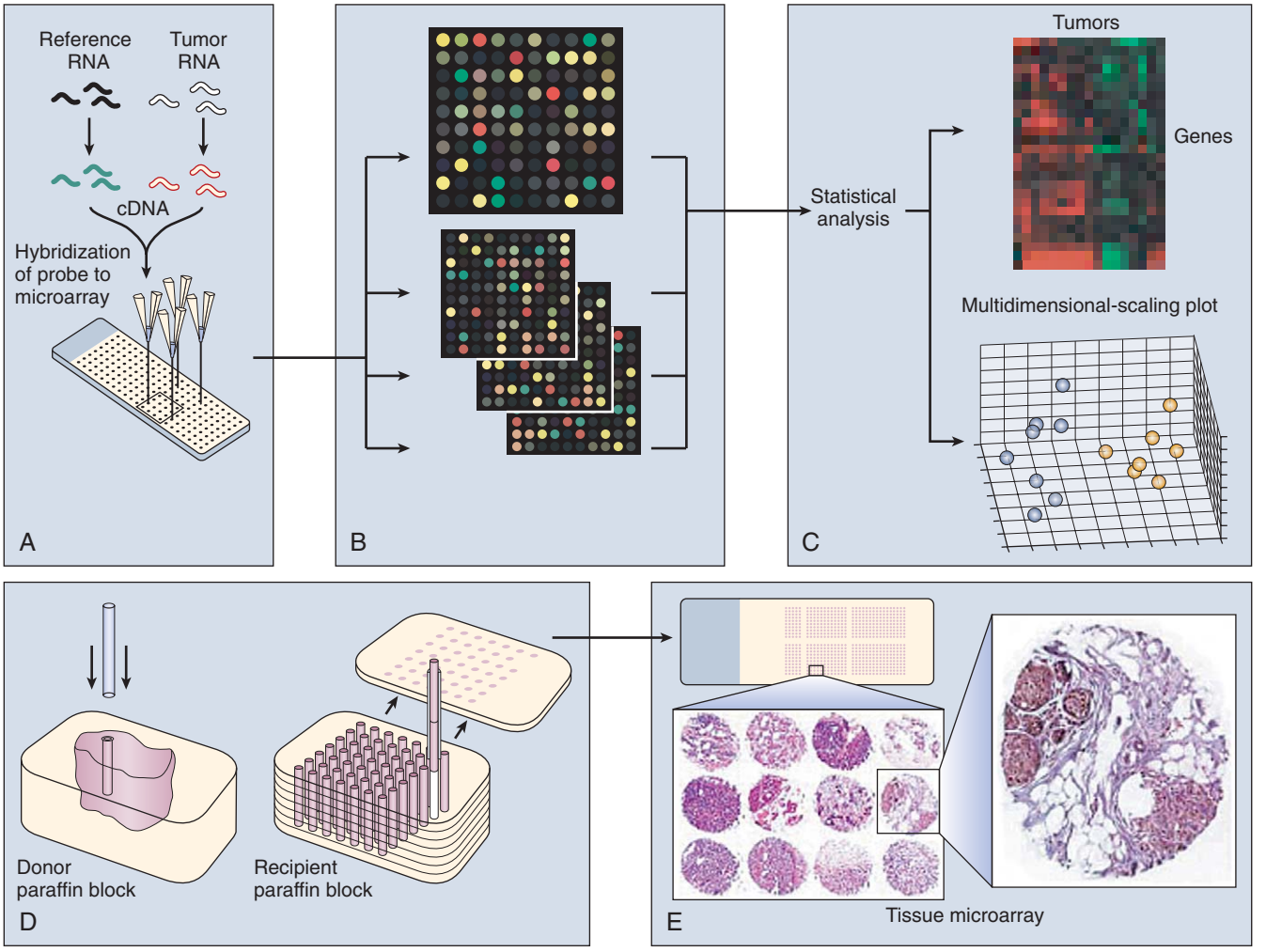


Figure 1-10 • Microarray-based expression profiling of breast tumor tissue. **A,** Reference RNA and tumor RNA are labeled by reverse transcription with different fluorescent dyes (*green* for the reference cells and *red* for the tumor cells) and are hybridized to a cDNA microarray containing robotically printed cDNA clones. **B,** The slides are scanned with a confocal laser scanning microscope, and color images are generated with RNA from the tumor and reference cells for each hybridization. Genes that are upregulated in the tumors appear red; those with decreased expression appear green. Genes with similar levels of expression in the two samples appear yellow. Genes of interest are selected on the basis of the differences in the level of expression by known tumor classes (e.g., BRCA1-mutation-positive and BRCA2-mutation-positive). Statistical analysis determines whether these differences in the gene expression profiles are greater than would be expected by chance. **C,** The differences in the patterns of gene expression between tumor classes can be portrayed in the form of a color-coded plot, and the relationships between tumors can be portrayed in the form of a multidimensional-scaling plot. Tumors with similar gene expression profiles cluster close to one another in the multidimensional-scaling plot. **D,** Particular genes of interest can be further studied through the use of a large number of arrayed, paraffin-embedded tumor specimens, referred to as tissue microarrays. **E,** Immunohistochemical analyses of hundreds or thousands of these arrayed biopsy specimens can be performed to extend the microarray findings. (From Hedenfalk I, Duggan D, Chen Y, et al: Gene expression profiles in hereditary breast cancer. N Engl J Med 2001;344:539–548.)

sion of miRNAs in human cancer is just now being explored, but preliminary findings reveal an extraordinary level of diversity in miRNA expression across cancers and the large amount of diagnostic information that is encoded in a relatively small number of miRNAs. Significant technologic advances facilitating the profiling of the miRNA expression patterns in normal and cancer tissues hint at the unexpected greater reliability of miRNA expression signatures than the respective signatures of protein-coding genes in classifying cancer types. Along with their potential diagnostic value, miRNAs are also being tested for their prognostic use in predicting clinical behaviors of cancer patients.

Although Northern blot analysis is a reliable technique to detect gene expression at the mRNA level, it has some limitations, such as unequal hybridization efficiency of individual probes and difficulty in detecting multiple miRNAs simultaneously. For cancer studies, it is important to be able to compare the expression pattern of all known miRNAs between cancer cells and normal cells. Thus, DNA microarrays are used to detect the full complement of miRNA expression at a single point in time. Since probe specificity in miRNA microarray analysis can be problematic, owing to the small target size, hybridization can first be performed in solution and then quantified by using multicolor flow sorting. Real-time PCR can also be employed to quantify specific miRNA sets or to capture a more detailed picture of their changing expression profiles in tumor progression. Identification of the miRNAs that are involved in tumor pathogenesis and elucidation of their action in a specific cancer will be the next necessary steps for their manipulation in a therapeutic setting.

THE CANCER PROTEOME

The term *proteome* describes the entire complement of proteins that are expressed by the genome of a cell, tissue, or organism. More

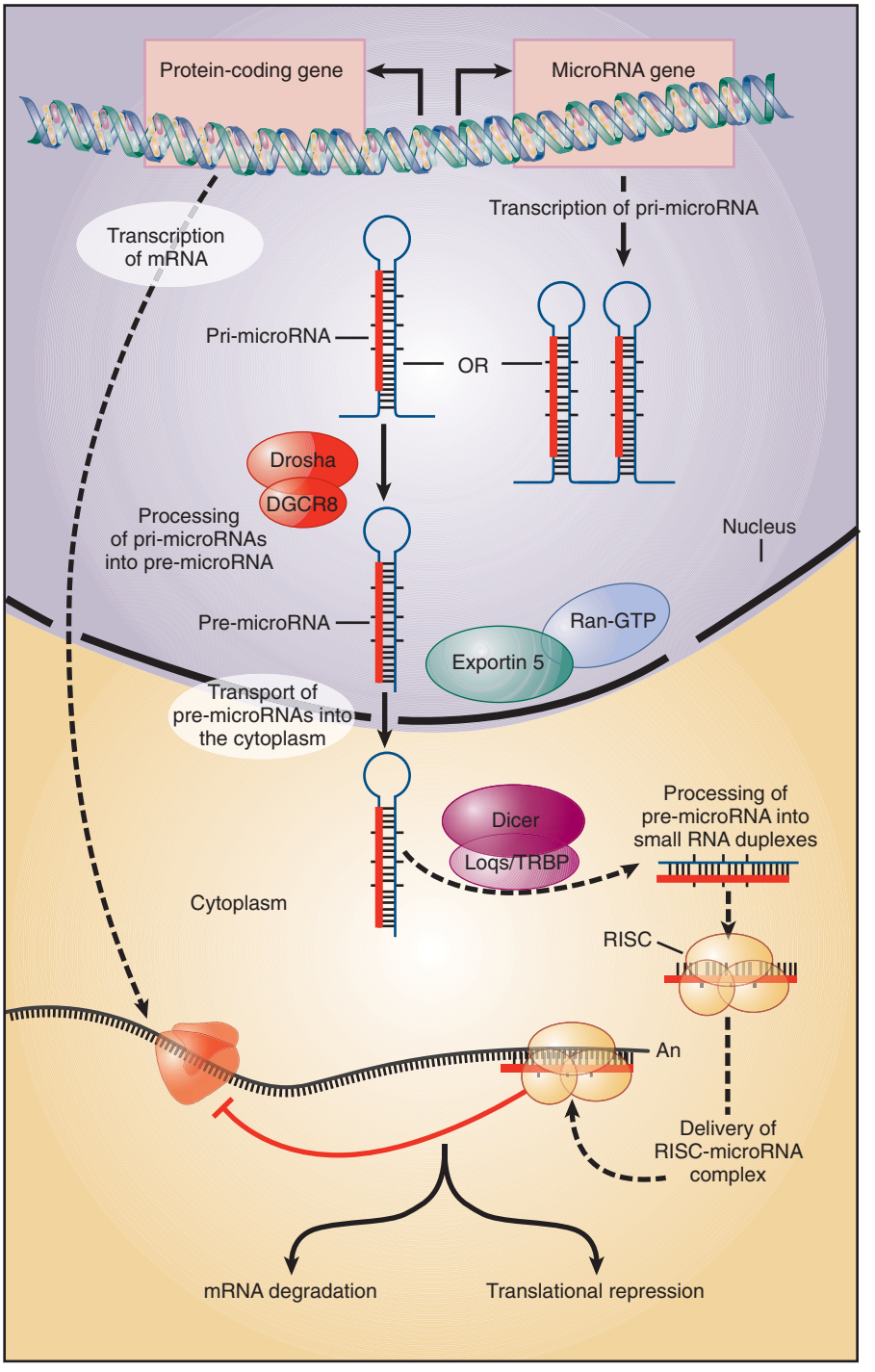


Figure 1-11 • MicroRNA production and gene regulation in animal cells. Mature functional microRNAs of approximately 22 nucleotides are generated from long primary microRNA (pri-microRNA) transcripts. First, the pri-microRNAs, which usually contain a few hundred to a few thousand base pairs, are processed in the nucleus into stem-loop precursors (pre-microRNA) of approximately 70 nucleotides by the RNase III endonuclease Drosha and DiGeorge syndrome critical region gene 8 (DGCR8). The pre-microRNAs are then actively transported into the cytoplasm by exportin 5 and Ran-GTP and further processed into small RNA duplexes of approximately 22 nucleotides by the Dicer RNase III enzyme and its partner Loqacious (Loqs), a homolog of the human immunodeficiency virus transactivating response RNA-binding protein (TRBP). The functional strand of the microRNA duplex is then loaded into the RNA-induced silencing complex (RISC). Finally, the microRNA guides the RISC to the target messenger RNA (mRNA) target for translational repression or degradation of mRNA. (Adapted from Chen C-J: MicroRNAs as oncogenes and tumor suppressors. N Engl J Med 2005;353: 1768–1771.)

specifically, it is used to describe the set of all the expressed proteins at a given time point in a defined setting, such as a tumor. Like RNA transcription, the synthesis of proteins is a highly regulated process that contributes to the specific proteome of a particular cell and can be perturbed in diseases such as cancer.

Advances in protein analytical techniques over the last decade have progressed to the point at which even small numbers of specific proteins expressed in tissues can be used to predict the prognosis of a cancer. The improvement of protein-based assays has made it possible to identify and examine the expression of most proteins and to envision large-scale protein analysis on the level of gene-based screens. Various systematic methodologies contributed to the current explosion of information on the proteome and are being compared for their ability to provide suitable platforms for generating databases on protein structural features, interaction maps, activity profiles, and regulatory modifications.

The yeast two-hybrid system is a popular genetics-based approach for detecting protein-protein interactions inside a cell (Fig. 1-12). One protein that is fused to the DNA binding domain (bait) and a different protein that is fused to the activation domain of a transcriptional activator (prey) are expressed together in yeast cells. If the bait and prey interact, transcription of a reported gene is induced and

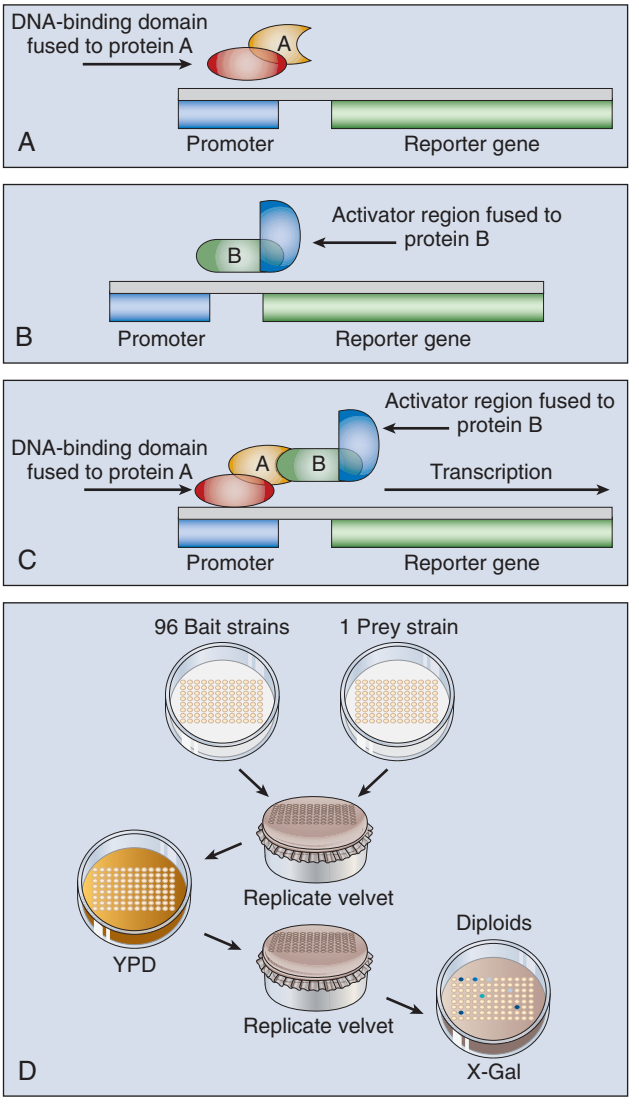


Figure 1-12 • Exploring protein-protein interactions with the yeast two-hybrid system. Two-hybrid technology exploits the fact that transcriptional activators are modular in nature. Two physically distinct functional domains are necessary to get transcription: a DNA-binding domain that binds to the DNA of the promoter and an activation domain that binds to the basal transcription apparatus and activates transcription. **A,** The known gene encoding protein A is cloned into the "bait" vector, fused to the gene encoding a DNA-binding domain from some transcription factor. When placed into a yeast system with a reporter gene, this fusion protein can bind to the reporter gene promoter, but it cannot activate transcription. **B,** Separately, a second gene (or a library of cDNA fragments encoding potential interactors), protein B, is cloned into the "prey" vector, fused to an activation domain of a different transcription factor. When placed into a yeast strain containing the reporter gene, it cannot activate transcription because it has no DNA-binding domain. **C,** When the two vectors are placed into the same yeast, a transcription factor is formed that can activate the reporter gene if protein B, made by the second plasmid, binds to protein A. **D,** Screening a yeast two-hybrid library. The plate on the left holds 96 different yeast strains in patches (or colonies), each of which expresses a different bait protein (*top*). The plate on the right holds 96 patches, each of the same yeast strain (prey strain) that expresses a protein fused to an activation domain (prey). The plate of bait strains and the plate of prey strains are pressed to the same replica velvet, and the impression is lifted with a plate containing YPD medium. After 1 day of growth on the YPD plate, during which time the two strains mate to form diploids, the YPD plate is pressed to a new replica velvet, and the impression is lifted with a plate containing diploid selection medium and an indicator such as X-Gal. Blue patches (*dark spots*) on the X-Gal plate indicate that the lacZ reporter is transcribed, suggesting that the prey interacts with the bait at that location. (**C,** Text after http://www.invitrogen.com/catalog_project/cat_hybrid.html [July, 2000]; figure retrieved from http://www.nature.com/nature/journal/v403/n6770/pdf/403601a0.pdf. **D,** From Bartel PL, Fields S (eds): The Yeast Two-Hybrid System. New York, Oxford University Press, 1997; Finley RL Jr, Brent R: Two-hybrid analysis of genetic regulatory networks. Retrieved from http://www.genetics.wayne.edu/finlab/YTHnetworks.html.)

detected, typically by a color reaction that reflects the transactivation of the reporter gene and, by proxy, the interaction of the two test proteins. The method can also be used for large-scale protein interactions, RNA-protein interactions, and protein-ligand binding.

As a complementary proteomics tool, mass spectrometry is an accurate mass measurement of charged peptides that are isolated by two-dimensional gel electrophoresis, producing a mass-to-charge ratio of charged samples under vacuum that can be used to determine the sequence identity of peptides. Combined with a specific proteolytic cleavage step, mass spectroscopy can be used for peptide mass mapping. Automation of this process has made mass spectroscopy the analytic tool of choice for many proteomics projects.

Monoclonal antibodies (mAbs) have been a cornerstone of protein analysis in cancer research and more recently have risen to prominence as cancer therapeutics based on their exquisite specificity for protein targets and their potent interference with protein function. Laboratory mice have been the animal model of choice for generating a ready source of diverse high-affinity and high-specificity mAbs; however, the use of rodent antibodies as therapeutic agents has been restricted by the inherent immunogenicity of mouse proteins in a human setting. The more recent application of transgenic mouse technology to introduce variable regions encoded by human sequences into the corresponding mouse immunoglobulin genes has enabled the generation of "humanized" therapeutic mAbs with reduced immunogenicity. Numerous of these mAb-based agents are currently in trial or in use as therapeutics for cancer, and the potential for further optimization of mAbs through genetic engineering promises to open new avenues for in vivo therapy.

From an epigenetics perspective, new techniques are enabling the genome-wide characterization of protein-DNA interactions that can uncover novel transcription factor targets, histone modifications, and DNA methylation patterns within a cancer cell. Combining chromatin immunoprecipitation (ChIP) with microarray (ChIP-on-chip) allows genome-wide screening for the binding position of protein factors to their gene targets. In ChIP-on-chip assays, a cross-linking reagent is applied in vivo to proteins associated with DNA in the nucleus, which then can be coimmunoprecipitated with specific antibodies to the protein under analysis. The bound DNA and appropriate controls are then fluorescently labeled and applied to microscopic slides for microarray analysis, rendering a simultaneous profile of all the binding positions of specific proteins in the cancer cell's genome (Fig. 1-13).

After a decade of development, proteomics is still primarily a basic research activity, yet in the near future, this technology is likely to have a profound impact on medicine. By defining the collective protein-protein interactions in a cancer cell (its "interactome"), func-

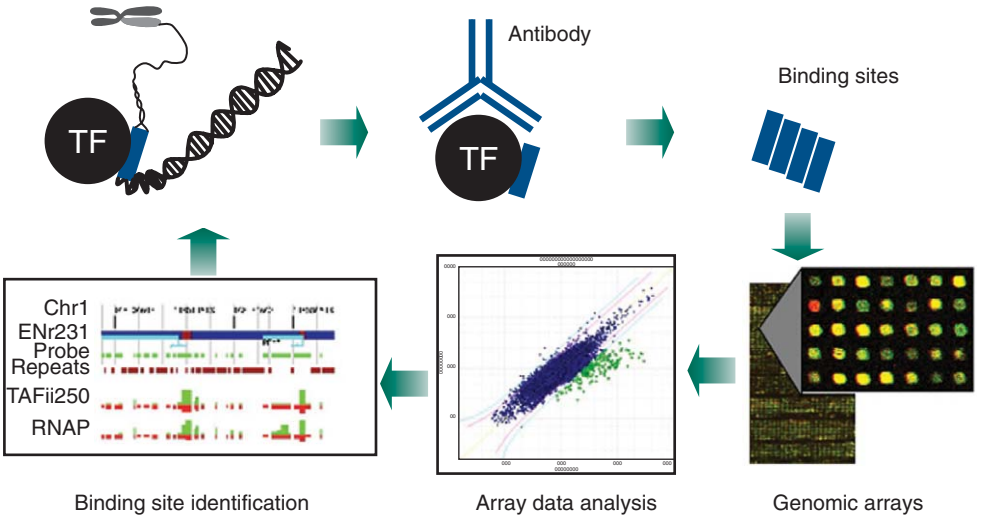


Figure 1-13 • ChIP-on-chip is a technique for location, isolation, and identification of the DNA sequences occupied by specific DNA-binding proteins in cells. These binding sites may indicate functions of various transcriptional regulators and help to identify their target genes during development and disease progression. The types of functional elements that one can identify using ChIP-on-chip include promoters, enhancers, repressor and silencing elements, insulators, boundary elements, and sequences that control DNA replication. (Adapted from Ren lab: www.chiponchip.org/Images/scheme_800x600_crop.jpg.)

tional relationships between disease-promoting genes could be revealed that would provide novel candidates for intervention. Networks of disorder-gene associations are already being built that offer a platform for describing all known phenotype and disease gene associations, often indicating the common genetic origin of many diseases. A precise diagnosis of cancer using proteomics could be envisioned, based on highly discriminating patterns of proteins in easily accessible patient samples. Proteomics information also promises to provide sophisticated mathematical models of the molecular events underlying a process as complex as neoplastic transformation, which will capture the dynamics of the disease with unprecedented power.

MODELING CANCER IN VIVO

Once the mechanistic underpinnings of a particular cancer have been described, creating an animal model to test that mechanism becomes critical to understanding the pathophysiology and to design therapeutic strategies for treatment. Recent advances in manipulating the mouse genome have resulted in more sophisticated models of human cancer. These methodologies can circumvent embryonic death by targeted alteration of gene expression only after a critical period in development and reduce the complexity of gene functional analysis by restricting its pattern of activation. Inducible gene expression or silencing also allows acute, as opposed to chronic, effects to be assessed.

Integrating an oncogene that causes malignancy into the genome of a mouse without altering the mouse's own genes generates a transgenic, cancer-prone mouse that transmits this trait to its offspring with a dominant pattern of inheritance. Although species differences in tumor susceptibility and disease remission exist between mouse and human, the tools for genetic manipulation in mouse are superior to those in other mammals, and useful information about the function of oncogenes can be gained by targeted expression of mutant protein products in mouse tissues.

The technology for producing transgenic mice joins recombinant DNA methodology with standard techniques that are used today by in vitro fertilization clinics, relying on our understanding of mammalian reproduction and the development of protocols to harvest, manipulate, and reimplant eggs and early embryos (Fig. 1-14). The transgene is constructed so that the gene product will be expressed under appropriate spatial and temporal control. In addition to all the standard signals that are necessary for efficient transcription and translation of the gene, transgenes contain a promoter, or regulatory region, that drives transcription in either a ubiquitous or tissue-restricted pattern. This requires an extensive knowledge of genetic regulation in the target cells. A recent advance that circumvents this requirement involves embedding the transgene inside another gene locus that is expressed in the desired pattern. Held in a bacterial artificial chromosome for easier manipulation, this long stretch of DNA surrounding the host gene is likely to carry all the necessary regulatory information to guarantee a predictable expression pattern of the introduced transgene.

The transgene DNA is then injected into the male pronucleus of a fertilized mouse egg, obtained from a female mouse in which hyperovulation has been hormonally induced. The injected eggs are cultured to the two-cell stage and then implanted in the oviduct of another recipient female mouse. Transgenic pups are identified by the presence of the transgene in their genomic DNA (obtained from the tip of the tail and analyzed by PCR). Typically, several copies of the transgene are incorporated in a head-to-tail orientation into a single random site in the mouse genome. About 30% percent of the resulting pups will have integrated the transgene into their germline DNA and constitute the founders of the transgenic lines. RNA analysis of their progeny determines the level of transgene expression and whether the transgene is being expressed in the desired location or at the appropriate time. Given the variability in transgene number and chromosomal location, transgene expression patterns and levels can diverge considerably among different founder lines carrying the same transgene.

In general, transgenesis is optimal for modeling oncogenic mutations that cause a gain of function, producing disease even when they occur in only one of a gene's two alleles. For example, an activating mutation in a growth factor that causes abnormal cell proliferation can be mimicked by introducing a transgenic version of the mutated growth factor gene under the control of an appropriate regulatory sequence for expression in the tissue of interest. The relative susceptibility of such a transgenic mouse to tumorigenesis can help to distinguish between a primary and secondary role of the mutant factor, and established lines of these animals can be used for testing new therapeutic protocols.

The genetic construction of cancer-prone transgenic mice with the capacity to induce oncogene expression in vivo provides a new avenue to modeling the role of oncogenes in tumor generation and maintenance. This technology relies on conditional mutagenesis.

Producing conditional mutations in mice requires a DNA recombinase enzyme that does not recognize any mouse sequence but rather targets short, foreign recognition sequences to catalyze recombination between them. By strategic placement of these recognition sequences in appropriate orientations either beside or within a mouse gene, the

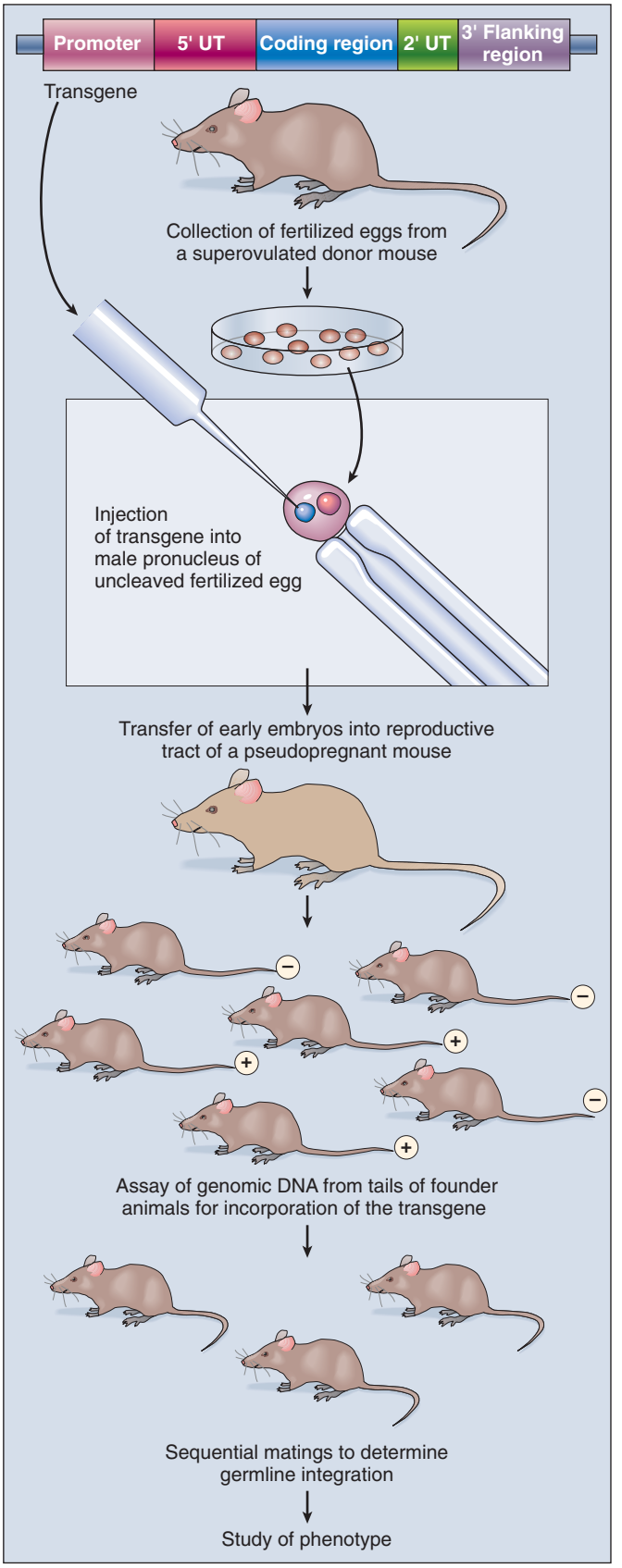


Figure 1-14 • Generation of transgenic mice. The transgene containing the DNA sequences necessary for the expression of a functional protein is injected into the male (larger) pronucleus of uncleaved fertilized eggs through a micropipette. The early embryos are then transferred into the reproductive tract of a female mouse that has been rendered "pseudopregnant" by hormonal therapy. The resulting pups (founders) are tested for incorporation of the transgene by assaying genomic DNA from their tails. Founder animals that have incorporated the transgene (+) are mated with nontransgenic mice, and their offspring are mated with each other to confirm germline integration and to establish a line of homozygous transgenic mice. Several transgenic lines that have incorporated different numbers of transgenes at different integration sites (and thus express various amounts of the protein of interest) are usually studied. UT, untranslated. (Adapted from Shuldiner AR: Transgenic animals. N Engl J Med 1996;334:653–655.)

recombination results in deletion, insertion, inversion, or translocation of associated genomic DNA (Fig. 1-15). Two recombinase systems are currently in use: the Cre-loxP system from bacteriophage P1 and the Flp-FRT system from yeast. The 34–base-pair loxP or FRT recognition sequences do not occur in the mouse genome, and both Cre and Flp recombinases function autonomously, without the need for cofactors. Cre- or Flp-mediated recombination is not distance or cell-type dependent and can occur in proliferating or differentiated tissues.

The general scheme involves two mouse lines, one carrying the recombinase either as a transgene driven by inducible regulatory elements or knocked into one allele of a gene expressed in the desired tissue. The other mouse line harbors a modified gene target, including recognition sequences. Mating the two lines results in progeny carrying both the target gene and the recombinase, which interacts with the target gene only in the desired tissue.

A popular conditional methodology is based on the activation of nuclear hormone receptors to control gene expression. Two current systems involve activation of a mammalian estrogen receptor, an estrogen analog 4-hydroxy-tamoxifen, or an insect hormone receptor with the corresponding ligand ectodysone. Although several variations on these hormone-receptor systems are currently in use, the underlying principle is the same. The Cre recombinase gene or another regulatory protein, such as a transcription factor, is fused with the ligand-binding domain from a nuclear hormone receptor protein. The resulting chimeric transgene is placed under the control of a promoter that directs expression to the tissue of interest, and transgenic animals are generated. In the absence of the hormone or an analog, the fusion protein accumulates in the desired tissue but is rendered inactive through its association with resident heat shock proteins. Administered hormone, either systemically or topically, binds to ligand-binding domain moiety of the fusion protein, dissociates it from the heat shock protein, and allows the transcriptional regulatory component to find its natural DNA targets and promote lox-P mediated recombination or, in the case of an inducible transcription factor, activate expression of the corresponding genes. If the ligand-binding domain is fused to a recombinase, administration of hormone leads to the rearrangement of target sequences. This reaction is not reversible but lends additional temporal control over recombinase-based mutation. If the ligand-binding domain is fused to a transcription factor, removal of hormone leads to inactivation of the fusion protein and gene downregulation.

Another inducible method in use is the tetracycline (tet) regulatory system. In the classic design (tTA or tet-off), a fusion protein combining a bacterial tet repressor and a viral transactivation domain drives expression of the target transgene by binding to upstream tet operator sequences flanking the transgene transcription start site. In the presence of the antibiotic inducer, the fusion protein is dissociated from the operator sequences, inactivating the transgene. In a

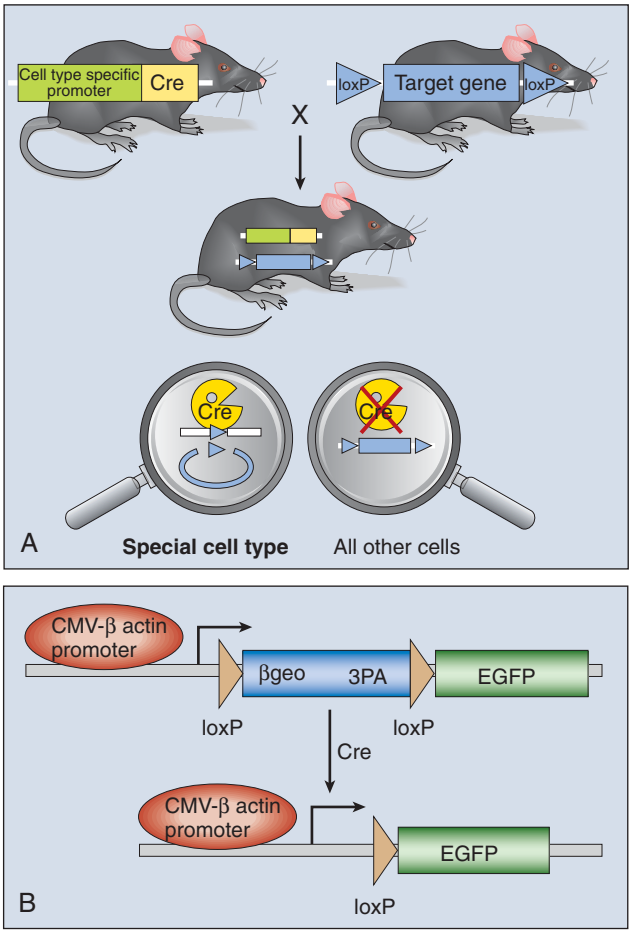


Figure 1-15 • Conditional mutagenesis schemes demonstrated with the Cre-loxP system. **A,** Two mouse lines are required for conditional gene deletion: a conventional transgenic mouse line with Cre targeted to a specific tissue or cell type and a mouse strain that embodies a target gene (endogenous gene or transgene) flanked by two loxP sites in a direct orientation ("floxed gene"). Recombination (excision and consequently inactivation of the target gene) occurs only in cells that express Cre recombinase. Hence, the target gene remains active in all cells and tissues that do not express the Cre recombinase. **B,** The Z/EG double reporter system. These transgenic mice constitutively express lacZ under the control of the cytomegalovirus enhancer/chicken actin promoter. Expression is widespread, notable exceptions being liver and lung tissue. Expression is observed throughout all embryonic and adult stages. When crossed with a Cre recombinase-expressing strain, lacZ expression is replaced with enhanced green fluorescent protein expression in tissues that express Cre. This double reporter system makes it possible to distinguish a lack of reporter expression from a lack of Cre recombinase expression while providing a means to assess Cre excision activity in live animals and cells. (**A,** Courtesy of Kay-Uwe Wagner, National Institutes of Health. **B,** From Novak A, Guo C, Yang W, et al: Z/EG, a double reporter mouse line that expresses enhanced green fluorescent protein upon Cre-mediated excision. Genesis 2000;28:147–155.)

complementary design, called reverse tTA (rtTA or tet-on), structural modification of the tet repressor makes the antibiotic an active requirement for binding of the fusion protein to the operator sequences, such that its administration activates transgene expression at any time during the life span of the mouse, whereas withdrawal results in downregulation of the gene. It is important that the transgene integrate into a genomic locus that permits proper tTA or rtTA regulation so that the system exhibits minimal intrinsic leakiness and good antibiotic responsiveness.

Conditional expression systems have already been developed to generate hematopoietic, leukemogenic, and lymphomagenic mutations in the mouse, as well as solid tumors. These inducible cancer models can be exploited to identify oncogenic signals that influence host-tumor interactions, to establish the role of a given oncogenic lesion in advanced tumors, and to evaluate therapies targeted toward cancer-causing mutations. Potential clinical application of inducible systems include targeting virally delivered transgene expression to malignant tissues by the use of specific inducible regulatory elements, restricting the expression of transgenes exclusively to affected tissues, and increasing the therapeutic index of the vectors, particularly in the context of solid tumors. In all cases, a basic knowledge of the specific mutations that are involved in the molecular genetics of malignancies is required, since it is often unclear that the causal mutation underlying the genesis of neoplasia continues to play a central role in the progression to the fully transformed state. This is particularly important in modeling cancers that are characterized by genetic plasticity, in which drug resistance can arise subsequent to primary tumor formation.

MODELS OF RECESSIVE GENE MUTATIONS IN CANCER

In contrast to dominantly acting oncogenes, recessive genetic disorders, such as loss-of-function mutations in a tumor suppressor gene, require both copies (alleles) of a gene to be inactivated. The methods that are needed to produce animal models of recessive genetic disease differ from those that are used in studying dominant traits. Gene knockout technology has been developed to generate mice in which one allele of an endogenous gene is removed or altered in a heritable pattern (Fig. 1-16). Gene disruption or replacement is first engineered in pluripotent cells, termed *embryonic stem* (ES) *cells*, which are genetically altered by introduction of a replacement gene that is inactive or mutant.

To reduce random integration of the foreign DNA, the replacement gene is embedded into a long stretch of DNA from its native locus in the mouse, which targets the recombination event to the homologous position in the ES cell genome. Inclusion of selectable markers along with the replacement gene allows selection of the cells in which homologous recombination has taken place. Site-specific recombinase systems combined with gene-targeting techniques in ES cells can also be used to inducing recessive single point mutations or site-specific chromosomal rearrangements in a tissue- and time-restricted pattern. In a variation on this theme called knock-in, a foreign gene, such as one encoding a marker, can be placed in the locus of an endogenous gene. The engineered ES cells are then microinjected into the cavity of an intact mouse blastocyst sufficiently early in gestation that these cells can, in principle, populate all the tissues of the developing chimeric embryo. This is rarely the case, so contribution of ES cells to the resulting animal is most often assessed by using ES cells and blastocysts whose genes for coat color differ.

If the ES cells contribute to the germ cells of the founder mouse, their entire haploid genome can be passed on to subsequent generations. By mating subsequent progeny of the founder mouse, both alleles of the mutated gene can be passed to a single animal. Overlapping genetic functions can also be defined by crossbreeding mice with mutations in different genes. In this way, it is possible to study the combinatorial effects of oncogene and tumor suppressor gene mutations.

These experimental systems are of great value in dissecting the pathogenesis of many tumor types. In some knockout studies, the phenotype of the mutated gene is anticipated by prior knowledge of the gene's function. However, unexpected mutant phenotypes may help clarify the mechanism of the underlying neoplasia. Pharmacologic manipulation of transgenic knockout animal models of cancer will prove useful in screening therapeutic agents with

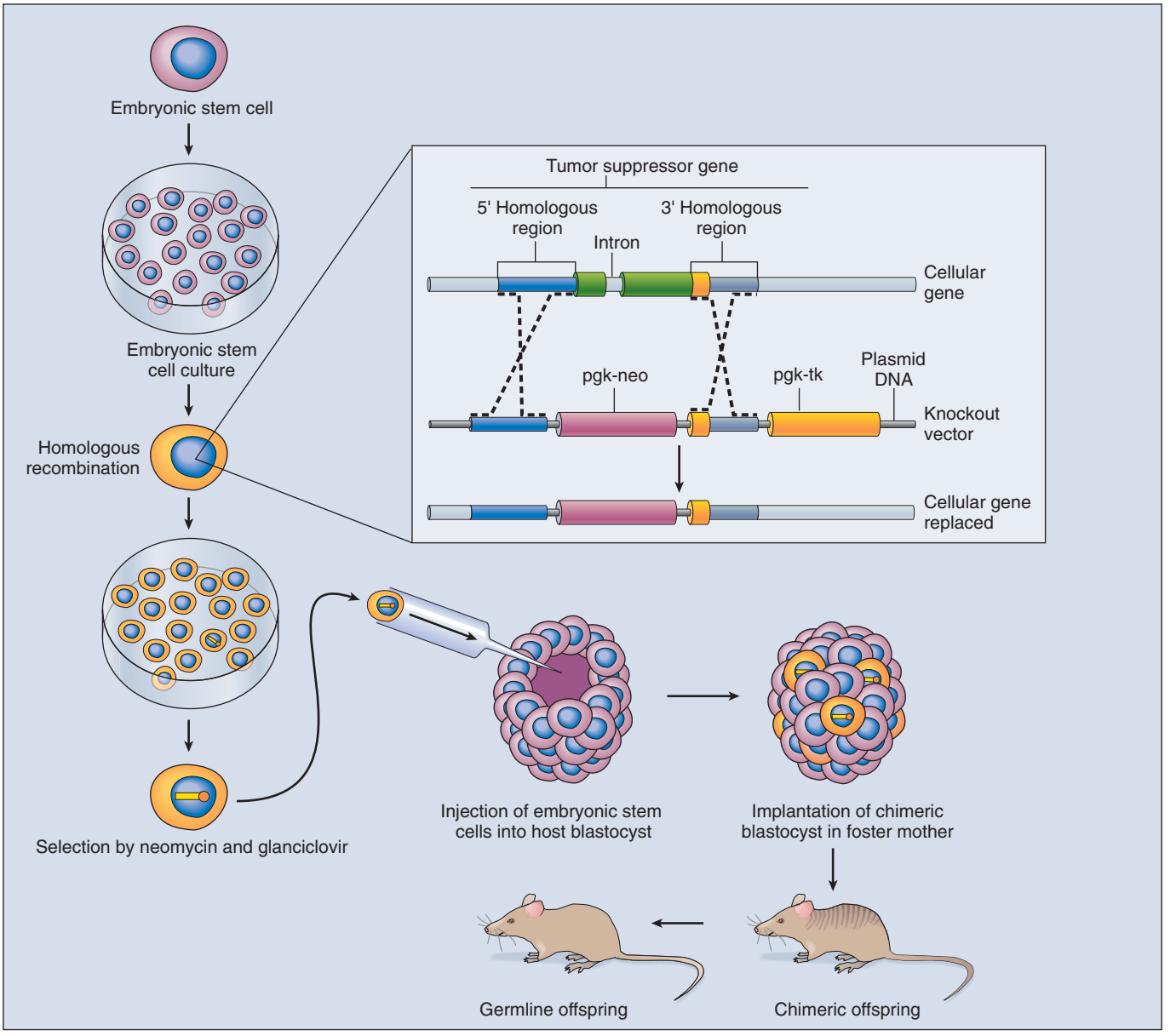


Figure 1-16 • Gene knockout strategy for generating mice that lack a tumor suppressor gene. Embryonic stem cells (*upper left panel*) contain the tumor suppressor cellular gene (*upper right panel*), which consists of exon 1 (*olive green*, a 5′ noncoding region), an intron, and exon 2 (*red*, a protein-coding region, and *yellow*, a 3′ noncoding region). A knockout vector consisting of a collinear assembly of a DNA flanking segment 5′ to the cellular gene (*blue*), the phosphoglycerate kinase-bacterial neomycin gene (pgk-neo, *violet*), a 3′ segment of the cellular gene (*yellow*), a DNA flanking segment 3′ to the cellular gene (*green*), and the phosphoglycerate kinase-viral thymidine kinase gene (pgk-tk, *orange*) is created and introduced into the embryonic stem cell culture. Double recombination occurs between the cellular gene and the knockout vector in the 5′ homologous regions and the 3′ homologous regions (*dashed lines*), resulting in the incorporation of the inactive knockout vector, including pgk-neo but not pgk-tk, into the cellular genomic locus of the embryonic stem cell. The presence of pgk-neo and the absence of pgk-tk in these replaced genes will allow survival of these embryonic stem cells after positive-negative selection with neomycin and ganciclovir. The clone of mutant embryonic stem cells is injected into a host blastocyst, which is implanted into a pseudopregnant foster mother and subsequently develops into a chimeric offspring (*bottom panel*). The contribution of the embryonic stem cells to the germ cells of the chimeric mouse results in germline transmission of the embryonic stem cell genome to offspring that are heterozygous for the mutated tumor suppressor allele. The heterozygotes are mated to produce mutant, cancer-prone mice that are homozygous for tumor suppressor deficiency. (Modified from Mazjoub JA, Muglia LJ: Knockout mice. N Engl J Med 1996;334:904–906.)

potential for study in clinical trials. Therapy involving gene or cell replacement can be also tested in genetically engineered disease models.

Several caveats are important in considering the use of knockout technology. Most knockout mutations are loss-of-function (null) germline mutations. Inactivation of widely expressed genes with multiple functions may have complex phenotypes. Conversely, if the functions of two genes overlap, a mutation in one of the genes might not produce an abnormal phenotype, owing to compensation by the unaltered partner.

Perhaps the greatest drawback of conventional knockout technology derives from the disruption of gene function at the earliest stage of its expression. If the gene has a vital developmental role, the identification of functions later in development can be occluded. There-

fore, although the generation of a null mutation is an excellent starting point for analysis, it is far from being functionally exhaustive. For these reasons, conditional mutagenesis is the method of choice for the elucidation of the gene functions that exert pleiotropic effects in a variety of cell types and tissues throughout the life of the animal, which is particularly relevant for the generation of mouse models of adult-onset diseases such as cancer.

By using recombinase-mediated gene mutation described previously for conditional transgenesis, conditional knockout mutations can be designed to disrupt the function of a target gene in a specific tissue (spatial control) and/or life stage (temporal control). Depending on the design of the experiment, recombinase action can delete an entire gene, remove blocking sequences to induce gene expression, or rearrange chromosomal segments. With the advent of recent internationally coordinated systematic mutagenesis programs that aim to place a conditional inactivating mutation in each of the 20,000 genes in the mouse genome, the possibilities for modeling cancer are limited only by a researcher's choice of the gene loci to test. The constantly evolving techniques for gene manipulation in vivo constitute a major advance in cancer research. They promise to provide integration of underlying molecular biological principles of malignancy with pathophysiologic consequences, generating an invaluable resource for understanding the complex genetics of tumor formation that holds great promise for improved treatment of human cancer.

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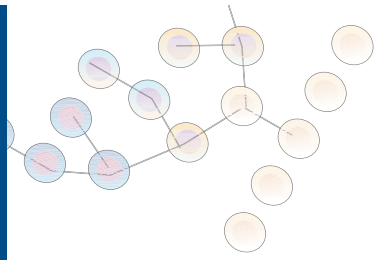
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2 Intracellular Signaling

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SUMMARY OF KEY POINTS

- Cell growth, metabolism, death, differentiation, movement, and invasion are all controlled by intracellular signaling pathways. These pathways are initiated by ligands binding to, and activating, their cognate receptors, which are usually plasma membrane proteins.
- Receptor activation initiates cascades of signaling events, including activation of protein and/or lipid kinases, as well as the recruitment of adaptor proteins, the activation of transcription factors, and changes in the cytoskeleton. Together, these signaling cascades ultimately fashion the response of the cell to the ligand. Intracellular signaling thus translates cues from the extracellular environment, such as peptide growth factors, extracellular matrix proteins, hormones, and cytokines, into appropriate cellular and organismal responses.
- As normal cells make the transition to malignancy, alterations in key receptors and signaling pathways occur. Some of these alterations are a result of activating mutations in receptors and signaling pathway components. Other mutations inactivate negative regulators of these pathways. The net result is both enhanced proliferation and inappropriate survival of the cancer cells, as well as unregulated cell movement and invasive capacity. Together, then, alterations in signaling pathways underlie all aspects of the cancer phenotype.
- In recent years, as the genetic alterations in cancer cells have begun to be characterized, new drugs have been developed that target these unregulated signaling pathways. In several cases, these drugs have been shown to be effective against tumors that harbor the appropriate mutations. Current research and development efforts are aimed at uncovering all aberrant intracellular signaling pathways in cancer cells and designing drugs to control them.

INTRODUCTION

Definition

During embryonic development and in the adult organism, the fate of a cell is decided by the cues it receives from its surroundings. For example, growth factors instruct cells to divide, and extracellular matrix proteins provide survival signals. Other stimuli can cause cells to migrate, to differentiate, to undergo programmed cell death (apoptosis), or to enter a survival state that involves autophagy. Each of these outcomes is initiated by binding of diverse protein and non-protein ligands to receptors, most of which are localized on the cell surface. Receptor activation results in the recruitment of adaptor molecules and enzymes, particularly protein and lipid kinases. These recruited proteins then relay signals to the nucleus, the cytoskeleton, and other subcellular compartments to affect the response. Each type of receptor initiates a discrete set of signaling pathways, such that different ligands binding to the same cell can have different effects. Furthermore, the same ligand can have different effects on different cell types because of innate differences in the signaling components present in the cells. Thus, the combinatorial action of several intracellular signaling pathways dynamically controls the responses of cells and organs to external cues from the environment.

Clinical Relevance

The first clues that components of intracellular signaling pathways are important in causing cancer came from research on tumor viruses in model systems such as chickens and mice.[1] Many RNA tumor viruses (retroviruses) contain cancer-causing genes called oncogenes, which derive from host sequences. For example, the first retroviral oncogene to be discovered, *src*, the transforming gene of Rous sarcoma virus, derives from the cellular *src* gene, which encodes a protein tyrosine kinase. During the transduction event, 3′ sequences of the *src* gene were lost, resulting in the production of a protein that lacks the regulatory carboxy-terminus. Thus, while the cellular Src protein is normally tightly regulated in cells, the viral form of the protein is constitutively active and transforming. Other examples of oncogenes that are transduced by retroviruses include *ras*, *myc*, *sis* (encoding the growth factor PDGF), *akt*, *raf*, *fos*, and many more. Equally important lessons were learned from the study of DNA tumor viruses. The oncogenes of these viruses do not derive from the host genome. Rather, in this case, the oncogenes associate with and modify the functions of key signaling proteins. For example, most DNA tumor viruses encode proteins that are able to inactivate negative regulators of signaling, such as p53 and Rb. Many can also activate signaling by binding to proteins such as Src, the platelet-derived growth factor (PDGF) receptor, and cyclins. These oncogene studies therefore provided the early tools necessary to dissect the signaling pathways that control cell growth. Other important information, particularly on the control of cell survival, has come from the study of genetically tractable organisms such as fruit flies and the nematode *Caenorhabditis elegans.* More recently, whole genome sequencing projects have allowed the direct analysis of human clinical specimens for alterations in key signaling pathways.

With the use of the systems and tools described previously, much progress has been made in the last decades in the characterization of intracellular signaling: Several classes of receptor have been defined,

all protein kinases (the kinome) have been described,[2] and some signaling pathways are now known in their entirety.[3] Furthermore, there has been intense study of the perturbations that occur in intracellular signaling during cancer progression. This effort has resulted in the definition of new molecular targets for cancer drug discovery.[4] Indeed, some new drugs that target cellular signaling have recently been approved, and many more are in clinical testing. While not yet fully realized, the promise is that defining and targeting signaling pathways responsible for all aspects of the cancer phenotype will result in more potent and less toxic chemotherapies.

This chapter reviews the basic principles of intracellular signaling. Then some examples of receptors and their mechanisms of activation are given (antigen and other immune receptors are not discussed). This is followed by an overview of some common signal transduction intermediates and some selected examples of signal transduction pathways elicited by certain receptors. Finally there is a brief discussion of how these signaling pathways are dysregulated in cancer and how this might be exploited for targeted therapeutic intervention. This is not intended to be a comprehensive list of all receptors and signals; rather, examples have been chosen that have relevance to the cancer phenotype. The references that are provided are intended to point the reader to more detailed and thorough reviews of the topics covered; primary references are provided only for new discoveries that have not yet been the subject of reviews. Furthermore, many of the examples and themes that are briefly described in this chapter are explored in more detail in later chapters. For example, in Chapter 5, Craig Thompson and Rebecca Elstrom describe in some detail the control of cell death and in Chapter 4, Jacqueline Lees reviews how signaling pathways feed into the cell cycle. Furthermore, each of the chapters on specific malignancies contains descriptions of the dysregulated signaling pathways that are involved in each disease.

FUNDAMENTAL SCIENCE

General Principles of Intracellular Signaling

Intracellular signaling is the mechanism by which cues that are present in the extracellular environment are relayed and interpreted by the cell. These external cues can be growth factors that signal a cell to divide, extracellular matrix proteins that promote survival, hormones that change the metabolism of the cell, cytokines that instruct the cell to differentiate, or other signals that promote motility and invasive ability. Complex multicellular organisms have evolved to have a large array of receptors for these external cues, as well as an even larger number of intracellular signaling molecules. Both embryonic development and adult homeostasis require specificity as well as temporal and spatial control of these signaling pathways. Many disease states, including cancer, diabetes, and immune disorders, can arise if these signaling pathways are inadequately controlled.

Intracellular signaling can at first glance seem overwhelmingly complicated. A given receptor can engage a number of different signaling pathways, each eliciting a distinct phenotype. One signaling pathway can affect the output of another, a phenomenon known as *cross-talk*. The same ligand can have different effects in different cell types. And the activation of a receptor frequently also elicits negative regulatory pathways that are designed to switch the system off after a defined period of signaling.[5–7] But this complexity can be reduced somewhat. Experimental observation has shown that the members of any given family of receptors signal in approximately the same way. Furthermore, many receptors use similar components to signal; for example, cytokine, growth factor, and G protein-coupled receptors all activate the MAP kinase pathway and the PI 3-kinase pathway.[8,9] Finally, most signaling pathways make use of adaptor or scaffolding proteins. These proteins lack catalytic activity and instead are made up of multiple protein-protein and sometimes also protein-lipid interaction domains.[10,11] In this way, adaptor proteins orchestrate the simultaneous activation of a number of pathways following receptor activation. Signaling specificity can be provided by the recruitment of distinct adaptor proteins by different receptors. A schematic of how signal transduction pathways can involve different components is outlined in Figure 2-1.

Receptor Activation by Ligand

Most of the receptors that receive cues from the extracellular environment are found in the plasma membrane of the cell, where they initiate signaling for those peptide and protein ligands that cannot cross the lipid bilayer. In contrast, receptors for lipid soluble ligands are found in the cytoplasm and the nucleus. A broad overview of the molecular makeup and mechanism of activation of several different classes of receptor will be described later.

G Protein-Coupled Receptors

The largest class of plasma membrane receptor is the so-called G protein-coupled receptor (GPCR) family, which has more than 1000 members.[12] Ligands include agents that stimulate neurotransmission, light and taste perception, and cell division and differentiation as well as the chemokines, which are ligands that are involved in cell attraction.[13] All GPCRs share a common architecture, with seven transmembrane α-helical domains, connected by both extracellular and intracellular loops. Because of this architecture, GPCRs are sometimes also referred to as serpentine or heptahelical receptors. The extracellular domain is responsible for ligand binding, which causes a conformational change such that the G protein binding to the intracellular domain becomes activated. G proteins are heterotrimeric proteins that consist of α, β, and γ subunits. Activation causes the dissociation of the α subunit from the $\beta\gamma$ complex; both separated components then go on to mediate signaling events that are very similar to those initiated by receptor tyrosine kinases.[14]

Receptor Tyrosine Kinases

The next largest class of receptors is the receptor tyrosine kinases (RTKs).[2,15,16] This class consists of approximately 90 members, most of which are involved in the control of cell growth, motility, and differentiation as well as metabolic control. Examples include PDGF receptors, epidermal growth factor (EGF) receptors, the ephrin receptors, hepatocyte growth factor receptors, fibroblast growth factor (FGF) receptors, insulin receptors, and many more. While the ligands for most classes of RTK are now known, some remain "orphans," with their ligands yet to be discovered. At least one RTK, Her2 (also known as ErbB2), has no known ligand but instead signals by heterodimerization with other EGFr family members.[17,18] Also, by sequence analysis of the catalytic domains, several RTKs are predicted to lack catalytic activity. In one of these cases, Her3, the receptor is transphosphorylated when heterodimerized with other EGFr family members (particularly Her2) and acts as an adaptor protein. The majority of the RTKs are single polypeptide chains that contain an extracellular ligand-binding domain, a short hydrophobic transmembrane domain, and a cytoplasmic region containing the kinase domain, as well as other sequences that regulate recycling and/or turnover of the receptor and interaction with signaling molecules. One exception to this rule is the insulin receptor family, which is composed of a disulfide-bonded tetramer, with two identical extracellular ligand binding subunits and two transmembrane subunits with catalytic activity. Another exception is the Met/Hepatocyte growth factor receptor family, in which a single polypeptide chain is cleaved to produce a stable dimer with ligand binding invested in one subunit and catalytic activity in the other. While it is generally thought that the single membrane pass RTKs are monomeric in the absence of ligand,[15,19,20] there is some recent evidence that EGF receptors can exist in a dimeric but inactive state in the absence of ligand.[15]

Some RTK ligands are dimers (e.g., the PDGFs), while others are monomeric (the EGFs). The FGF receptors require both FGF ligands and heparin sulfate proteoglycans for full activation.[21,22] Yet other

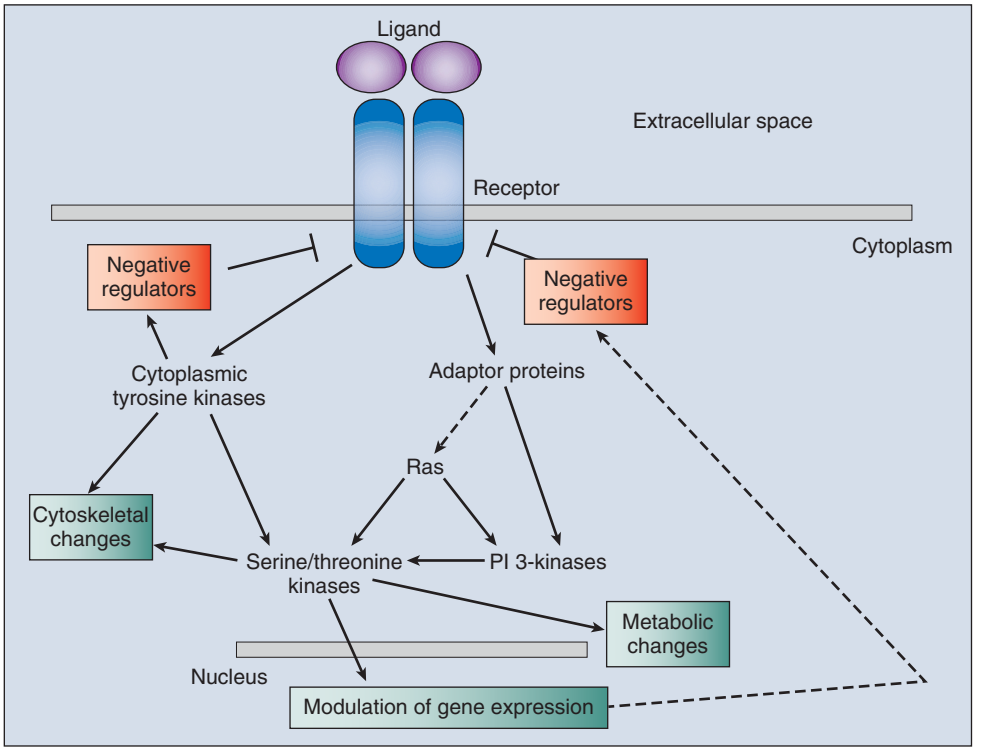


Figure 2-1 • Schematic of intracellular signaling. A prototype receptor is shown. Dimerization of the receptor by ligand elicits multiple signaling pathways, whose outputs result in changes in gene expression, in the cytoskeleton, and in metabolism. These signaling pathways also elicit the production of negative regulators, which ultimately turn the signal off.

RTKs, notably Ret and MuSK, do not bind ligands directly, requiring a coreceptor to present the ligand.[23,24] Despite these differences, RTKs generally share a common mechanism of activation on ligand binding, which involves dimerization and often further oligomerization to form higher-order structures. Recent crystallographic studies have revealed the molecular mechanisms behind ligand-induced activation and how monomer ligands can induce dimerization. In the case of the EGFr, the dimerization occurs at an interface between two receptor monomers, the ligand presumably serving to initiate the domain rearrangements that are necessary to make these contacts.[19,20] In contrast, FGFs, while monomeric, have two receptor-binding sites. Dimerization is thus achieved by interactions between the receptor and the ligand. The heparin sulfate is required to organize and strengthen the interaction of ligand and receptor as well as to provide specificity to the interactions.[21,22] Regardless of how the extracellular domains are brought into close apposition, the result is the juxtapositioning of the two catalytic domains and the subsequent transphosphorylation of tyrosine residues in the activation loop of the kinase domain, as well as elsewhere in the intracellular domain. These phosphorylations serve to initiate further conformational changes that stabilize the active form of the enzyme as well as to provide binding sites for the enzymes and adaptor proteins that are described later.

Serine and Threonine Kinase Receptors

The proteins in this family act as receptors for transforming growth factor (TGF)-β, activins and inhibins, and bone morphogenetic protein.[25] Members of this family of receptors, which together are often known as the TGF-β superfamily, play key roles during development and morphogenesis, as well as in cell cycle progression, motility and wound healing, and immune surveillance.[26] The ligands can be homodimers or heterodimers, and they interact with two single-pass membrane proteins called type I and type II receptors. Both receptor subunits have intrinsic serine/threonine kinase activity in the cytoplasmic domain. Signaling is thought to be initiated by ligand-induced oligomerization of two type I receptors with two type II receptors.[25] The type II receptor, which has constitutive kinase activity, phosphorylates and activates the type I receptor, which then goes on to phosphorylate substrate proteins.

Integrin Receptors

Integrins are heterodimers of an α and a β subunit, each of which is membrane-spanning.[27] Mammals have 18 α subunits and 8 β subunits that can combine to form 24 distinct heterodimers. Integrins derive their name from their ability to bind to ligands outside the cell and cytoskeletal components inside the cell and so integrate the two environments.[28] Their extracellular ligands can be either extracellular matrix proteins or cell surface proteins on neighboring cells. In their low-affinity state, the extracellular domains of the β subunits adopt a "bent" conformation. Ligand binding generates a higher-affinity, straightened structure of the β subunit, corresponding allosteric changes in the extracellular domain of the α subunit, followed by conformational changes in the transmembrane and cytoplasmic domains.[29] Clustering of integrins also occurs because of the multivalent nature of the ligands. The net result is a separation of the cytoplasmic domains of the α and β subunits, which mutational studies have shown is required for this "outside-in" signaling. Integrins do not contain intrinsic kinase activity but instead signal through associated cytoplasmic kinases such as Src and FAK.[30]

Unlike any other class of membrane receptor, integrins can also signal from the cytoplasm to the extracellular space, so-called inside-out signaling.[31] In this form of signaling, cytoplasmic signal transduction pathways, for example, caused by activation of the EGFr or Frizzled receptors, generate a conformational change in the integrin extracellular domain, resulting in increased adhesion to extracellular ligands and subsequent outside-in signaling. Although the exact mechanism by which this conformational change is transmitted was unclear until very recently, it was known that the cytoskeletal protein talin was required. Talin binds to the cytoplasmic tails of most β integrins through its PTB-like domain. Reducing talin expression or preventing its association with the β subunit is sufficient to inhibit inside-out signaling. Talin adopts an autoinhibited structure in

quiescent cells. Intracellular signaling pathways release this inhibition, allowing it to bind to and change the conformation of the integrin, thus promoting high-affinity interactions of the integrins with their ligands.[32]

Cytokine Receptors

The cytokine receptor superfamily consists of the receptors for growth hormone, prolactin, erythropoietin, thrombopoetin, G-CSF, and the interleukins as well as the interferon receptors.[33–35] They are grouped together because of their use of functionally related receptors. Most receptors use a common γ chain, together with variant β chains and sometimes α chains. Structural homologies among these chains include four conserved cysteine residues in the extracellular domain and a WSXWS motif located near the transmembrane domain. The cytoplasmic domains of these subunits lack any catalytic activity but instead have two regions of low homology, called "box 1" and "box 2." Although the exact functions of these boxes are not known, it is clear from mutagenesis studies that they are necessary for receptor function. Activation of cytokine receptors occurs when ligand binding causes dimerization, perhaps by promoting a rotational switch near the WSXWS motif.[36] Kinases of the JAK family, which are constitutively associated with the cytoplasmic domains, then transphosphorylate the receptors to initiate signaling. The most important substrates of the JAKs are the Stat proteins, which have an SH2 domain and a transcriptional activation domain. Signaling by this class of receptors thus involves tyrosine phosphorylation-induced dimerization of the Stats, which renders them transcriptionally competent.[37]

Another class of cytokine receptors is represented by the tumor necrosis factor (TNF) receptor superfamily, also known as death receptors, which control apoptosis in response to exogenous signals.[38] Members of this family include the TNF receptors 1 and 2, Fas, CD40, and TRAIL and are simple single-pass transmembrane proteins, with cysteine-rich ligand-binding domains on the outside and either a death domain (R1 receptor) or a TRAF-binding domain (R2 domain) on the inside.[38] They have no intrinsic catalytic activity. It was originally thought that TNF activated its receptor by inducing trimerization, but it is now known that this class of receptors breaks the ligand-induced oligomerization rule. Instead, the TNF receptors are found as preformed trimers on the cell surface.[39] This is thought to be required for their function. For example, TNF-α signals through TNF-R1 to initiate cell death and through TNF-R2 to activate NFkB. If the ligand were to initiate the formation of trimers, mixed oligomers would form in any cell that expresses both receptors. Since only a trimer of death domain-containing receptors is functional, this would result in the suppression of death signals. Thus, preassembly of receptor complexes might promote the formation of homotypic receptors and confer more specificity in the response. As with other, more conventional receptors, ligand binding is thought to elicit conformational changes that render the cytoplasmic domains competent for signal transduction.

Frizzled Receptors

Frizzled receptors are the binding partners for the Wnt family of ligands.[40] This is a large class of peptides that control a wide array of developmental processes and have also been implicated in cancer. Of particular current interest is the role of Wnts in the control of stem cell fate.[41,42] Frizzled receptors have a cysteine-rich extracellular Wnt-binding domain, followed by seven transmembrane domains and a short cytoplasmic tail. Frizzled alone is unable to transduce Wnt signals. Rather, members of the LRP family, which are single-pass transmembrane proteins, are required as coreceptors. The current model for the way in which Wnts activate their receptors is an interesting and novel one in which it is postulated that Wnts bring LRP and Frizzled into close proximity.[40] In support of this model, coexpression of chimeric fusion proteins that cause the close apposition of Frizzled and LRP is sufficient to induce Wnt-independent signal transduction.

Notch Receptors

There are four mammalian Notch receptors, which play important roles in development and tissue homeostasis, by specifying cell fates and creating boundaries between different cells.[43–47] Each receptor is a single-pass transmembrane protein, with an EGF repeat domain that binds ligand in the extracellular domain, and a cytoplasmic domain that lacks catalytic activity but instead contains several ankyrin repeats and a C-terminal PEST domain. During transport through the Golgi, the receptor is cleaved into ligand-binding and transmembrane domains that remain associated with each other through noncovalent interactions. The ligands for Notch are called DSLs (for delta-serrate-lag2 family), and they are also single-pass transmembrane proteins with EGF-like repeats in their extracellular domains. Signaling between Notch and DSLs therefore takes place when one cell carrying the ligand and one cell expressing the receptor are in close apposition. Unlike the other receptors discussed here, in which ligand binding usually controls oligomerization of the receptor and phosphorylation of the cytoplasmic domains, activation of the Notch receptors is accomplished by regulated and specific proteolysis.[48] The binding of ligand to Notch makes the receptor susceptible to cleavage first by an ADAMs family metalloprotease in the extracellular domain and then by a γ-secretase in the transmembrane domain. This frees the intracellular domain of Notch, which translocates to the nucleus, where, together with a DNA-binding protein called CSL and coactivators, it activates transcription. Uniquely among the plasma membrane receptors, then, the Notch receptor family does not use a series of signal transduction pathways to exert their effects but rather affects gene expression directly.[47]

Nuclear Hormone Receptors

Some receptors, particularly those for estradiol, progesterone, androgen, glucocorticoids, polyunsaturated fatty acids, and the retinoids, predominantly exert their effects by acting as transcriptional activators and/or repressors.[49] These nuclear hormone receptors are regulators of many aspects of homeostasis, as well as sexual development. Many have been implicated in disease, including cancer, lipid disorders, and diabetes.[49,50] In addition, several are the targets of important drugs; for example, PPARγ is the target of the antidiabetes drug rosiglitazone. Most of the nuclear hormone receptors consist of a single polypeptide chain with a DNA-binding domain, a transactivation domain, a ligand-binding domain, and sequences that mediate interaction with coregulators. While some receptors can bind DNA with high affinity as monomers, most require dimerization.[51] This requirement is particularly true of the retinoid receptor family, in which the exact nature of the heterodimers that are formed dictates the transcriptional output. The ligands for the nuclear hormone receptors either diffuse passively into the cell or are produced within the cell during normal metabolism. In some cases, association between receptor and ligand takes place in the nucleus. In other cases, particularly the sex hormone receptors, the receptor is cytoplasmic and bound to chaperone proteins in the absence of ligand. Ligand binding dissociates the chaperones and allows translocation to the nucleus. Once they are nuclear, ligand-dimer complexes interact with DNA and recruit transcriptional regulators to effect their responses. Thus, in this canonical mechanism of action, nuclear hormone receptors as a class do not require intracellular signal transduction pathways. However, there are a growing number of cases, particularly well studied in the case of the estrogen receptor, in which hormone can also bind a plasma membrane receptor.[52,53] Although the identity of the membrane receptor is currently not established (some investigators think that it is the same as the nuclear form, whereas others have suggested it is a GPCR[54]), it is clear that this form of the receptor can elicit canonical signaling involving Src, MAP kinases, and lipid kinases in a similar way to RTKs.[52] The roles of these two forms of receptor signaling, which are often called genomic and nongenomic, particularly in cancer causation, awaits further clarification.

Components of Intracellular Signaling Pathways

With the exception of the nuclear hormone receptors and the Notch receptors, ligand-activated receptors do not have direct mechanisms of action. Rather, their activation results in the initiation of one or more signal transduction cascades that ultimately change the phenotype of the cell. Many general principles and some individual elements of these signal transduction cascades are shared by different classes of receptor. Some of the more commonly used strategies are described in overview here.

Adaptor Proteins

Perhaps one of most common features shared by most receptor signal transduction cascades is the use of adaptor proteins,[10] which are defined as proteins with protein-protein interaction and sometimes also protein-lipid interaction domains. Common protein interaction motifs include SH2 and some PTB domains, which bind to phosphotyrosine-containing peptides[55]; SH3 domains, which bind to proline-rich ligands[56]; WW and WD40 domains, which bind phosphorylated serine and threonine residues, respectively[57,58]; and PDZ domains, which bind carboxy-terminal sequences of proteins.[59,60] In each case, neighboring amino acids provide specificity to the interaction. For example, the SH2 domain of Grb2 preferentially binds a phosphotyrosine followed by the sequence XN, where X is any amino acids and N is asparagine. The SH2 domain of Src, in contrast, prefers the sequence Y(p)EEI. PH, PX, and FYVE domains bind phosphoinositides, particularly those phosphorylated in the 3, 4, and/or 5 positions by phosphatidylinositol (PI) kinases.[61–63]

Since most adaptor proteins have multiple interaction domains, they act as scaffolds that cluster together distinct signaling molecules. Adaptor proteins can serve to give specificity to receptor signaling by clustering distinct sets of signaling proteins in a particular subcellular location. In some instances, the recruited proteins might modify each other's activity, for example, when a kinase phosphorylates a coassociated protein. Some adaptor proteins are selective for certain receptor-signaling systems. For example, death domain-containing adaptors are used exclusively by the superfamily of TNF receptors,[64,65] the insulin receptor substrate family of proteins is dedicated to the insulin receptor and cytokine receptor families,[66,67] and FRS2 is involved in FGF and nerve growth factor signaling.[68] Others, such as Grb2 and Shc and the Gab, Dok, and Vav families, are used by multiple receptor types.

Cytoplasmic Tyrosine Kinases

Some receptors have intrinsic tyrosine kinase activity, while others, such as GPCRs and cytokine receptors, do not. Yet each of these receptor classes uses tyrosine phosphorylation as a signal. They do this by recruiting, or being stably associated with, cytoplasmic tyrosine kinases (CTKs). There are several subfamilies of CTKs,[2] the most important for signal transduction being the Src family, the Abl family, the Tec family, the FAK family, and the JAK family. These kinases become activated by association with the receptor, usually through dimerization and transphosphorylation. In these cases, the CTKs can be considered to be noncovalently associated receptor subunits that provide the required catalytic activity. But it is interesting that even the RTKs recruit CTKs, which is required for their full function.[69,70] An example of this, the recruitment of Src family kinases by the PDGFr, is given later. While these observations led some researchers to speculate that RTKs were able to phosphorylate only associated proteins and therefore required CTKs to phosphorylate all downstream signaling components, it now seems clear that different tyrosine kinase families have broadly different substrate specificities and that some signal transduction pathways are dependent on the substrates phosphorylated by the RTK and some on the CTK substrates. In keeping with this, cytokine receptors and GPCRs also recruit and/or activate more than one class of CTK.

Cytoplasmic Serine and Threonine Kinases

There are 518 protein kinases in the human genome. Of these, 90 are tyrosine kinases, either RTKs or cytoplasmic kinases as described previously. All other members of the kinome phosphorylate serine and threonine residues.[2] While many of these enzymes have housekeeping functions in the control of metabolism, DNA replication, and so on, many more are obligate proximal members of signal transduction cascades from receptors. The best studied of these kinases are the ones that make up what is called the MAP kinase (MAPK) pathway.[8] MAPKs are small single-subunit serine/threonine kinases. They have a number of substrates, but chief among them are transcription factors, whose subcellular localization and activity are regulated by MAPK phosphorylation. MAPKs fall into three classes: the ERKs, the JNKs, and the p38 family. All of these enzymes are normally inactive in quiescent cells, but become activated upon growth and/or stress stimulation of the cells. This activation is accomplished by enzymes that are generally known as MAPK kinases (MKKs). These are dual-specificity enzymes; they phosphorylate MAPKs on both a tyrosine and a threonine in the activation loop phosphorylation, causing a large increase in catalytic activity of the MAPKs. While there is some cross-talk, different MKKs appear to be somewhat selective in activating the different classes of MAPKs (Fig. 2-2). The MKKs in turn need to be phosphorylated to be activated, which is accomplished by a broad range of serine/threonine kinases, generally called MKK kinases (MKKKs), from a number of different families. While the combinatorial complexity of these cascades of kinases could be staggering, recent evidence suggests that scaffold proteins exist that provide specificity and regulation to each cascade.[71]

The best studied of all the MAPK pathways, and one that is central to all mitogenic signaling from receptors, is the one known

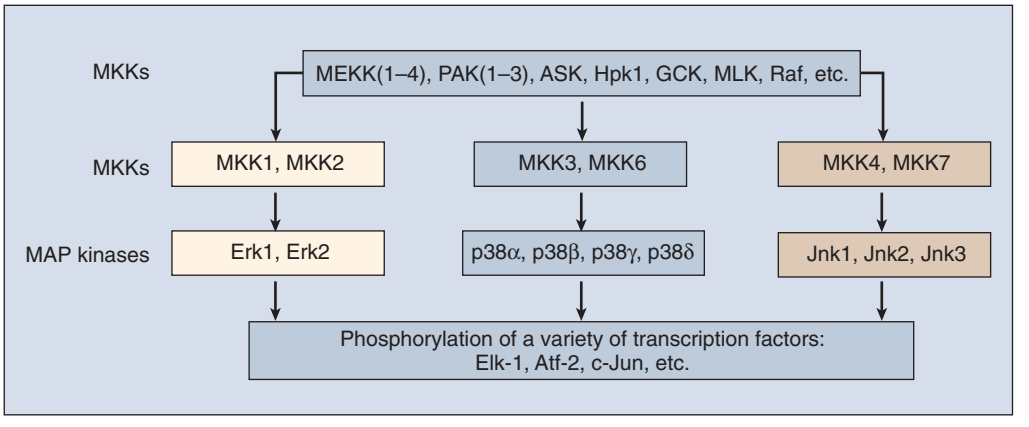


Figure 2-2 • Mitogen-activated protein kinase (MAPK) cascades. Intracellular signaling from various receptors involves activation of members of the mitogen-activated kinases. The MAPKs consist of three families of related kinases (Erks, p38s, and Jnks). Activation of MAPKs is mediated by phosphorylation by a series of related kinases, MKKs (MAPK kinases), which are activated by a broad spectrum of kinases through phosphorylation. Activated MAPKs translocate to the nucleus and phosphorylate a variety of structurally unrelated transcription factors. The transcription factors and gene expression are thus activated.

as the Ras-Raf-MAPK pathway.[72] The Ras family consists of three small GTPases: H-, N-, and K-Ras. Of these, K-Ras has been implicated in many human cancers. For example, more that 90% of pancreatic cancers and approximately 50% of colon cancers have an activating mutation in K-Ras.[73–77] In unstimulated cells, Ras is found in an inactive, GDP-bound form. Many ligands activate Ras, by stimulating the exchange of GDP for GTP, which is accomplished by activating proteins called guanine nucleotide exchange factors and inhibiting proteins called GTPase-activating proteins. In the case of growth factor signaling, the guanine nucleotide exchange factor that is involved is called Sos, which is usually associated in the cytoplasm with an adaptor protein called Grb2. The GTPase-activating protein that is involved is p120Gap. On receptor activation, two different types of adaptor protein, called Shc and Gab, become recruited to receptors in the membrane and phosphorylated on several tyrosine residues. Several of these sites are in YxN motifs, which are canonical binding sites for the Grb2 SH2 domain. Thus, receptor activation results in the following cascade of signaling: Shc (or Gab) > Grb2: Sos > Ras. Once Ras is in the GTP-bound state, it initiates a number of different signaling pathways, including PI 3-kinase activation, and cytoskeletal changes.[78–81] But of particular importance, it recruits the serine/threonine kinase Raf to the plasma membrane, where other signals, including tyrosine phosphorylation, activate its intrinsic kinase activity.[82] Raf then goes on to phosphorylate and activate MEK 1 and 2, which in turn activate ERK1 and 2.

Space does not allow a full description of all serine/threonine kinases that are involved in signal transduction here. But there is one enzyme complex that has attracted much recent attention: mTor (mammalian target of rapamycin).[83–88] mTor is a signal integrator, linking information about nutrients, energy status, and growth factor stimulation to outputs such as protein synthesis, ribosome biogenesis, metabolism, and cell survival and proliferation (Fig. 2-3). There are two structurally distinct mTor complexes, with proteins known as Raptor and Rictor. The mTor/Raptor complex is regulated by a small GTPase known as Rheb, which is normally kept in an inactive state by a GTPase-activating protein consisting of a complex of two tumor suppressors TSC1 and TSC2. A variety of signals, including signals from Akt, ERKs, and other serine/threonine kinases, inactivate the TSC1/2 complex, thus activating Rheb and in turn mTor/Raptor. The signaling outputs from this complex include mRNA translation, ribosome biogenesis, and autophagy through phosphorylation of substrates such as 4E-BP1 and ribosomal S6K. The mTor/Rictor complex is less well understood, but it is activated by RTKs and plays an important role in activating Akt.

Lipid Signaling

As we saw earlier, many adaptor proteins have domains that interact with phosphorylated phosphoinositides, which frequently serves to recruit them to the plasma membrane or subcellular organelles such as endosomes. In other cases, phosphoinositide binding serves to activate the catalytic activity of the enzyme to which it is bound. The most important lipid modifiers in signal transduction pathways are a family of enzymes known as phosphatidylinositol 3-kinases (PI 3-Ks).[9,89] These come in three classes, based on sequence alignment and substrate preference. Class I enzymes have two subunits, one with catalytic activity and one that specifies the association of the enzyme with other signaling molecules. They generally generate PI 3,4,5-P3 (PIP3) from PI 4,5-P2. Class II enzymes have a single subunit, which contains both catalytic activity and regulatory sequences. They predominantly generate PI 3-P and PI 3,4-P2. Class III has just one member, the Vps34 protein, which was originally identified as a gene required for vacuolar sorting in budding yeast and generates PI 3-P. Relatively little is known about the functions of the class II and class III enzymes in mammals, although Vps34 has recently been implicated in mTor regulation and autophagy, suggesting a role in the response of cells to nutrients. Class II enzymes bind clathrin, suggesting a possible role in receptor trafficking and/or endocytosis. But it is the class I family members that have been most intensively studied for their roles in intracellular signaling pathways and cancer.[86,90–93]

Class I enzymes can be further subdivided into Class IA and Class IB. All members have structurally related catalytic subunits. But the regulatory subunits of class IA members all contain 2 SH2 domains, and some also have an SH3 domain, whereas in class IB, the regulatory subunits are structurally distinct. Class IA members are activated by RTKs, whereas class IB members are activated by GPCRs. In all cases, activation occurs when the PI 3-K is recruited to the membrane by regulatory domain sequences, for example, the SH2 domains in the case of class IA. This brings the enzyme into close proximity with its substrate and allows catalysis to take place. PIP3 then acts as a lipid second messenger by binding to PH domains in a variety of proteins, including the serine/threonine kinases PDK1 and Akt (see Fig. 2-3). One important target of Akt is the FOXO family of transcription factors, which are sequestered in the cytoplasm and inactivated by phosphorylation, thus inhibiting gluconeogenesis.[94] Other metabolic targets include the glucose transporter Glut4, glycogen synthase kinase 3, and ATP citrate lyase. Akt also has effects on the cell cycle via its inhibitory effects on FOXO and GSK3 as well as by directly phosphorylating proapoptotic proteins such as BAD. In

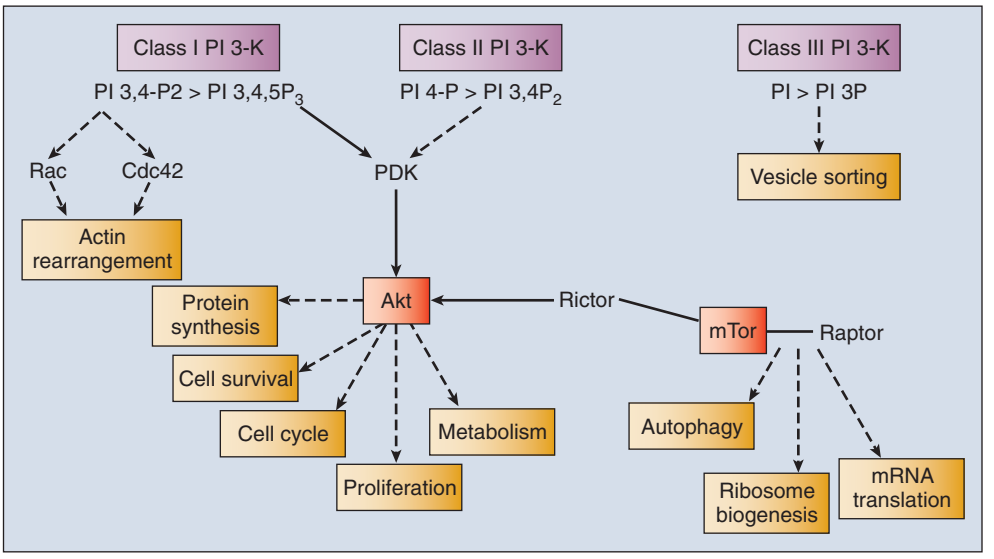


Figure 2-3 • mTor and PI 3-K signaling. The figure illustrates some of the key components of the mTor and PI 3-K signaling pathways and highlights the central role that the serine/threonine kinases Akt and mTor play in the control of several intracellular signaling events. The three classes of PI 3-K are activated by a variety of cell surface receptors and make different lipid products, which bind to lipid-binding domains in a variety of signaling molecules. Lipid binding activates signaling by recruiting the signaling molecules to intracellular or plasma membranes or by causing a conformational change. Once Akt is activated by PDK1 and other serine/threonine kinases, it phosphorylates a number of substrates to cause profound changes in cell homeostasis. mTor responds to changes in nutrients and growth factors and exerts its effects via forming stable complexes with either Rictor or Raptor.

concert with the small GTPases Rac and Cdc42, class I enzymes also control actin dynamics and thus regulate cell polarity and motility.

Negative Regulators of Signaling

Given the power of signal transduction pathways to regulate all aspects of a cell's phenotype, it is vital that these pathways be tightly controlled. Indeed, in the absence of such control, cancer often arises. We have seen that some control is provided in the recruitment and activation of defined signaling modulators. But there are also other layers of control that ensure that the signal is switched off in a timely manner. A number of different mechanisms are used. The first is at the level of the receptor itself. Following ligand binding, most receptors are internalized via mechanisms using clathrin-coated pits and endocytosis.[95–98] In some cases, this results in degradation of both receptor and ligand in lysosomes; in other cases, the unoccupied receptor is recycled back to the plasma membrane. Both RTKs and some cytoplasmic tyrosine kinases are also regulated by ubiquitin-mediated degradation at the proteasome.[99,100] In the case of the EGFr and Src, it is the activation of these proteins that initiates the degradation by recruiting an E3 ubiquitin ligase called Cbl via SH2 domain interactions.[101–104] This ensures that the proteasome selectivity degrades the active forms of the enzymes. Two other inhibitory mechanisms are also elicited by the very signaling pathways that they inactivate. For example, the activation of MAPK-signaling pathways results in the transcriptional activation of a class of enzymes called MAPK phosphatases (MPKs), which, as the name suggests, dephosphorylate and inactivate MAPKs.[5,105] Also, the JAK-Stat signaling pathway results in the production of the SOCS (suppressor of cytokine signaling) proteins, which have an SH2 domain and a region known as a SOCS box. The SOCS proteins are thought to inhibit signaling by binding to specific phosphotyrosine-containing motifs on receptors and the JAK kinases and perhaps initiating ubiquitin-mediated degradation.[6,106] Finally, the action of both phosphoprotein and phospholipid phosphatases can also serve to regulate signaling. Of particular importance is the phosphoinositide phosphatase and tumor suppressor known as PTEN, whose loss has been associated with malignancy in many cancers, particularly glioblastomas and prostate cancer.[93,107]

Selected Examples of Signal Transduction Pathways

Throughout this chapter, we have touched on the concept that many extracellular ligands engage multiple signaling pathways and that there are some common themes to the signaling outputs that emerge. For example, stimulation with most ligands results in profound changes in gene transcription by activating transcriptional regulators such as Fos, Myc, NFkB, Stats, Smads, hormone receptors, and so on. Many factors elicit changes in the cytoskeleton, polarity, and movement of cells. Alterations in metabolism, hormone responses, differentiation, and survival are other common outputs. In this section, a few examples of receptor-initiated signal transduction pathways will be given, illustrating the concepts that have been discussed throughout.

Receptor Tyrosine Kinase PDGFr

There are five PDGF ligands encoded by four different genes (A, B, C and D), and two different receptors encoded by unique genes (α and β).[108] Each ligand is a dimer, with known isoforms including AA, AB, BB, CC, and DD. PDGF AA can bind only to a homodimeric αα receptor, whereas AB, BB, and CC can bind both αα and αβ receptors. PDGF DD binds predominantly to ββ receptors. PDGF acts predominantly on cells on mesenchymal origin and promotes cell growth, migration, and survival. Alterations in PDGFr signaling play a role in sarcomas and gliomas.[109,110] Furthermore, chromosomal translocations that cause the constitutive activation of the kinase domain of PDGFr are found in some leukemias and lymphomas.

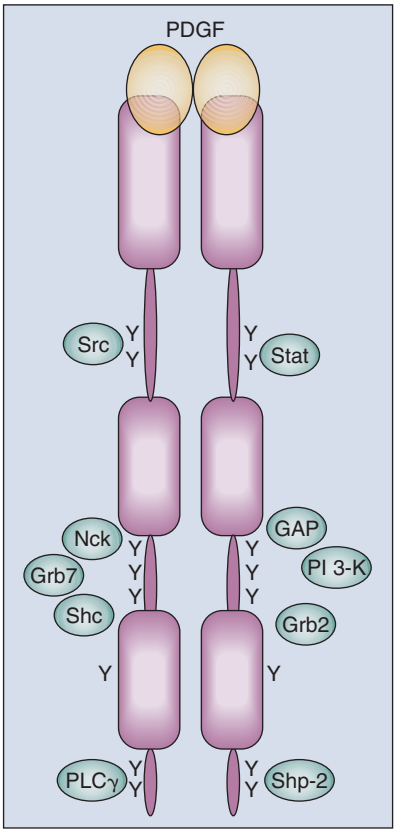


Figure 2-4 • Recruitment of SH2 domain-containing proteins by activated PDGF receptors. The figure illustrates how the ligand PDGF, which is a dimer, causes the dimerization and transphosphorylation of its receptor on a number of tyrosine residues, in the juxtamembrane region, in the kinase insert region, on the activation loop, and on the carboxy-terminal tail sequences. Each one of these phosphorylated tyrosines then binds selectively to SH2 domain-containing proteins, which then initiate a number of different intracellular signaling pathways. The selectivity of SH2 domain binding to each tyrosine is determined by the amino acid sequences immediately proximal to each tyrosine.

Once activated by dimerization and transphosphorylated on several tyrosine residues, the PDGFr recruits at least 10 different SH2 domain-containing signaling molecules to these sites (Fig. 2-4).[69,70,111] One class of binding proteins are members of the Src family of tyrosine kinases (SFKs). These enzymes become activated by this association and then phosphorylate a number of other signaling molecules. While the mechanistic details have yet to be worked out, one important effect of SFK activation is the stabilization of myc mRNA and subsequent transcription.[69] Another important signaling cassette to be recruited is the class IA PI 3-K, which associates directly with the receptor via the SH2 domains on its regulator subunit; the signaling cascades that were discussed earlier are then initiated. Recruitment and phosphorylation of the adaptor protein Shc, together with the subsequent binding of Grb2/Sos, allow the Ras/MAPK pathway to become activated. Other signaling effectors that are more selective for RTKs such as the PDGFr include phospholipase Cγ, the adaptor protein Nck, and the tyrosine phosphatase Shp2, as well as the negative regulators Ras-GAP and Cbl.

It is important to note that the example of signaling that is illustrated here—the recruitment of multiple signaling cascades both to the receptor itself and to adaptor proteins—is a general theme that is seen throughout RTK signaling. Specificity is provided by the nature of the phosphorylation sites on the receptor and the domain makeup of the adaptor proteins that are recruited, as well as the

complement of signaling proteins that are expressed in any given cell type. Furthermore, other receptors, such as integrins and GPCRs, use very similar strategies. In these cases, cytoplasmic tyrosine kinases (FAK and Src in the case of integrins and Src and Tec family members in the case of GPCRs) are responsible for generating the SH2 domain recruitment sites.

TGFβ Receptor

As we saw earlier, the receptors in this family are transmembrane serine/threonine kinases, with ligand stimulating the phosphorylation of the type I receptor by the type II subunit, which activates the intrinsic kinase activity of the type I subunit. The best-characterized intracellular effectors of TGFβ signaling are the Smad proteins.[112–116] There are three types of Smads: R-Smads, a common Smad (in vertebrates this is known as Smad4), and inhibitory Smads. The R-Smads and Smad4 have two conserved domains called MH1 and MH2, joined by linker sequences. In addition, the R-Smads have carboxy-terminal serine phosphorylation sites. On ligand binding, the receptors recruit and phosphorylate one or more R-Smads. The conformational changes that are induced by this phosphorylation release the R-Smads from the receptor and allow the formation of a trimeric complex of two R-Smads with Smad4. This complex translocates to the nucleus, where, along with coactivators such as CBP/p300 and factors such as FOXO and Forkhead, transcription is activated. The specificity of the transcriptional response is provided by the R-Smads that are present in the complex and thus the coactivators and transcription factors that are recruited. In turn, recruitment of individual R-Smads is determined by the exact nature of the heterotetramer receptors that are formed in response to the diverse TGFβ family ligands.[112] In the cases in which the ligand is TGFβ itself or activin, efficient recruitment of R-Smads to the receptor also requires an adaptor protein called SARA, which has a FYVE domain that interacts with PI 3-P, and a Smad binding site.[116,117] The inhibitory Smads interfere with signaling by binding to type I receptors and interfering with R-Smad recruitment.

Although the Smads are the only known mechanism by which TGFβ receptors modulate transcription, other signal transduction pathways also control Smad activation. For example, R-Smads are phosphorylated by MAPKs, which may prevent nuclear localization of the Smads and transcriptional responses. In contrast, phosphorylation by JNK enhances nuclear translocation and activity of Smad3. Other kinases that have been reported to phosphorylate Smads include cell cycle kinases such as Cdk2 and Cdk4, PKC, and CaMKII. In this way, signaling from other receptors can greatly influence the transcriptional responses to TGFβ receptor stimulation.[112]

TNF Receptor

The death receptors are the means by which extracellular signals are linked to the apoptotic machinery of the cell, a process known as *instructional apoptosis*. One of the best characterized of these receptors is called Fas (also known as CD95 or Apo1); it will be used as illustration.[65,118–120] Trimerization of Fas by its ligand clusters the receptor's death domains, leading to the recruitment of the protein FADD by death domain interaction. The death effector domain in FADD then binds to the inactive, zymogen form of caspase-8. The oligomerization of caspase-8 that ensues causes the self-activation of caspase-8 by proteolysis, resulting in the subsequent cleavage and activation of effector caspases such as caspase-9 and commitment to apoptosis.

Wnt Signaling

The last example to be considered is that of Wnt signaling through Frizzled and its coreceptors, the LRPs.[40] One of the most important signaling components in Wnt signaling is the β-catenin protein, which accumulates in the cells in response to the ligand and activates transcription by associating with the DNA-binding protein TCF.[121–123] In unstimulated cells, TCF is in a complex with the negative regulator Groucho and is transcriptionally inactive. In these same cells, β-catenin turns over rapidly, a consequence of its recruitment by a so-called destruction complex. This complex contains Axin, APC, and GSK3, a serine/threonine kinase. Phosphorylation of β-catenin by GSK3 causes β-catenin to become ubiquitinated and targeted for destruction by the proteasome. The binding of Wnt to its ligand causes the phosphorylation of LRP by GSK3 and CK1 and the recruitment of the Axin/APC/GSK3 complex to the receptor (Fig. 2-5). This is presumably sufficient to prevent the phosphorylation of β-catenin, thus allowing its concentration to rise, enter the nucleus to associate with TCF, and activate transcription. Another key intermediate in Wnt signaling is Dsh, which is required upstream of Axin/APC/GSK3. Dsh is also a cytoplasmic protein that becomes recruited to the Frizzle/LRP complex in response to Wnts, but the exact mechanism by which it participates in signaling is unknown at this time.

In an intriguing new twist to the story of Wnt signaling, it was recently found that Wnts can act as ligands for the atypical RTKs, Ryk, Ror1, and Ror2.[124–126] Little is yet known about the signal transduction pathways that are elicited by Wnt2 binding to these RTKs or about the cellular outputs they specify.

CLINICAL RELEVANCE AND APPLICATIONS

From research conducted over the last two decades, it is clear that many human cancers have their origins in dysregulated signaling pathways.[1,127,128] Some of the earliest oncogenic events to be discovered in humans were mutated and activated K-Ras, chromosomal translocations that result in the overexpression of Myc and the production of the Bcr-Abl tyrosine kinase, and chromosomal amplification of the RTK Her2. Since then, many other activating mutations in signaling pathway components have been discovered in cancer cells. Examples include activating mutations in the EGFr in some non-small-cell lung cancers,[129] in B-Raf in most melanomas as well as other tumor types,[82] in Jak2 in myelodysplastic syndromes,[130,131] and in PI 3-K, particularly in breast cancers.[90,91] Furthermore, chromosomal translocations involving the RTKs Kit, Flt3, and PDGFr are detected in gastrointestinal stromal tumors and some lymphomas. Other mechanisms that cancer cells use to promote their growth and survival include the overexpression of the antiapoptotic protein Bcl-2 in lymphoma,[132,133] activating mutations in G proteins in pituitary tumors,[13,134] the acquisition of insensitivity to the inhibitory growth effects of TGFβ while maintaining the positive signals in many carcinomas,[135–137] and the overexpression of estrogen or androgen receptors in breast and prostate cancers, respectively.[52,138–142]

The discovery of each of these activated signaling pathways has been rapidly followed by attempts by both the academic community and the pharmaceutical industry to develop new therapeutics targeting these events.[4,143–145] Some of these attempts have yet to be successful despite enormous effort; for example, the Ras GTPase has so far proved intractable to small molecule inhibition.[72,146] But for other targets, there have been successes, the most notable being the development of imatinib (target: Abl, PDGFr) and later dasatinib (target: Abl, SFKs) for the treatment of chronic myelogenous leukemia[147] (see Chapter 108). Other therapeutics that target signal transduction pathways include antiestrogens and antiandrogens for breast and prostate cancer, respectively[148,149]; trastuzumab for Her2-positive breast cancer[150]; gefitinib and erlotinib (target: EGFr) for lung cancer[151]; sorafenib (targets: VEGFr and Raf) for renal cell carcinoma[152]; and sunitinib (targets: VEGFr, PDGFr, Kit) for renal cell carcinoma and gastrointestinal stromal tumor.[153,154]

It can be anticipated that in the future, most cancers will be classified not just according to anatomic site of origin and histopathology, but also on the basis of the genetic alterations that are present in the tumor, including those in signaling pathways. New therapeutic modalities are likely to include strategies (small molecules, antibodies, microRNA, etc.) to target these activated signaling pathways.

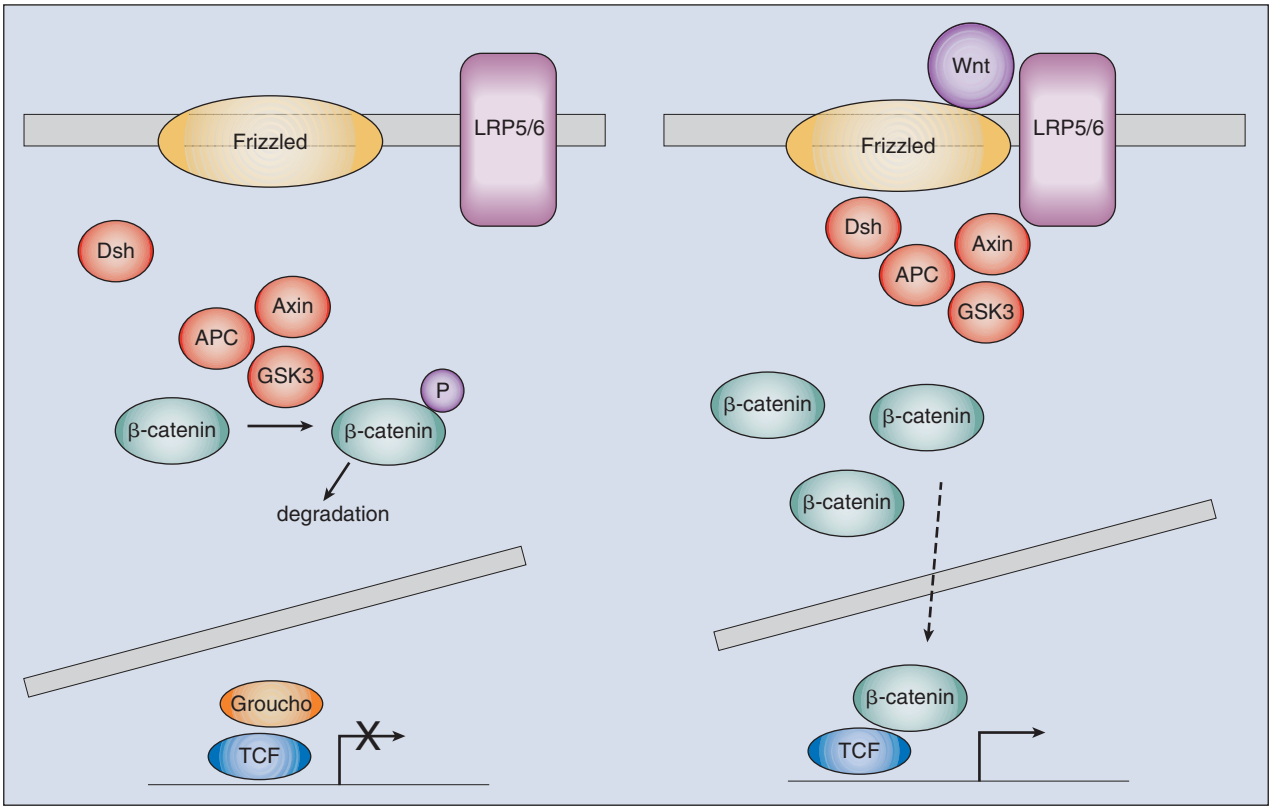


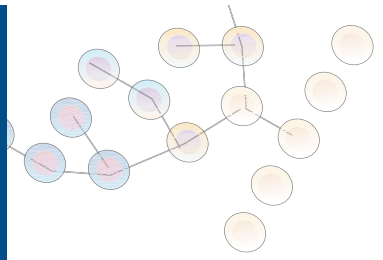
Figure 2-5 • Canonical intracellular signaling from Wnt receptors. In unstimulated cells, a complex of Axin, APC, and GSK (glycogen synthase kinase) phosphorylates β-catenin, which causes its degradation via the proteasome pathway. When Wnt ligand is present, Frizzled and Lrp associate and create binding site for axin, APC, and GSK3 in cooperation with disheveled (Dsh). Phosphorylation of β-catenin is thus prevented, which allows its accumulation and transport into the nucleus. Once in the nucleus, β-catenin displaces the association of Groucho with the transcriptional activator TCF, allowing transcription of several target genes. In some cancer cells, particularly from the colon, mutations in APC prevent the downregulation of β-catenin and thus allow constitutive TCF signaling.

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3 The Cellular Microenvironment and Metastases

Amato J. Giaccia and Janine T. Erler

SUMMARY OF KEY POINTS

- Metastatic disease kills the majority of cancer patients.
- Gene mutations, the tumor microenvironment, and host cells drive the metastatic spread of tumor cells.
- Metastasis can be subdivided into four steps: invasion, intravasation, survival in circulation, and extravasation.
- Colonization of metastatic tumor cells requires the ability to proliferate in a foreign tissue and angiogenesis.
- The formation of a premetastatic niche is essential for the growth of extravasating metastatic tumor cells.
- Organ specificity of tumor metastases is determined both by blood flow and tissue-specific factors.
- Primary tumors possess stem cells that can recapitulate the tumor from a single cell, and a subset of these cancer stem cells may inherently possess altered gene expression changes with increased metastatic potential.
- Antimetastatic therapy will probably require the targeted inhibition of many pathways that control proliferation, invasion, and angiogenesis.

INTRODUCTION

Tumors are described as benign or malignant. Malignant tumors can spread by invasion and metastasis, whereas benign tumors cannot and remain localized. One of the hallmarks of cancer cells is their ability to grow and divide without undergoing senescence, provided they have sufficient oxygen, nutrients, and space. As tumors grow, oxygen and nutrients can quickly become limiting in large part as a result of an inadequate vascular supply. Cancer cells will adapt to these growth-limiting environments and also seek out fresh terrain to take up residence, where neither space nor nutrients are (initially) limiting. The spread of cancer from its primary site to secondary sites in the body is defined as metastasis, which comes from the Greek word meaning "change of state." These secondary sites may be located in a new organ or in a different region of the same organ. In reductionist terms, cancer cells metastasize by dislodging from the primary tumor, penetrating through lymphatic and blood vessels, and establishing new growth at a new site in normal tissue. Cancer cells must acquire the capability for invasion and metastasis to escape the primary tumor mass and colonize new terrain in the body where nutrients and space are not limiting. Acquisition of this capability for invasion and metastasis is another of the hallmarks of cancer[1] and is significantly influenced by changes in gene expression and by microenvironmental factors. It is the ability to spread to other tissues and organs that makes cancer a potentially life-threatening disease, in that metastases are responsible for 90% of cancer patient deaths.[2] Very few treatment options exist for patients with metastatic cancer, and furthering our understanding of the process of metastasis will aid in the development of new approaches to treat metastatic disease.[3]

MULTISTEP PROCESS OF METASTASIS

Metastasis is a multistep process (Fig. 3-1) consisting of a series of discrete biological processes. These steps allow primary tumor cells to invade the surrounding tissue, intravasate through blood vessels to enter the circulatory or lymph system, acquire mutations to survive fluctuating environmental changes, extravasate from the circulatory or lymph system into new tissue, proliferate at secondary sites, and develop a vascular system to support growth of the metastases. In some cases, metastases can also give rise to new metastases. There is a propensity for certain tumors to seed in particular organs in part as a result of blood flow. However, blood flow alone cannot explain the different patterns of metastases found for different primary tumors. The most popular theory to explain the patterns of metastases is the "seed and soil" theory put forth by Stephen Paget over a century ago in 1889.[4] Paget described tumor cells as "seeds" and the host environment as the "soil," and proposed that their interaction determines metastatic outcome.

Although the Paget theory is appealing, we know that metastasis is a very inefficient process, because very few cells that escape the primary tumor take up residence in new tissues. For this reason, the tumor cells that survive the process have been termed by Fidler as the "decathlon champions," because they excel at all the steps in the metastatic process.[5] Metastasis is strongly influenced by the interactions between tumor and host cells, and by both the immediate and extended tumor microenvironments. There is ever more evidence demonstrating that these interactions between tumor and host cells are key determinants for the success of metastatic growth and spread.

The Tumor Microenvironment Acts as a Selection Pressure for Metastatic Tumor Cells

The first step in tumorigenesis is transformation, where cells accumulate mutations in proto-oncogenes that result in dysregulated cell growth and increased life span, and loss of tumor suppressor genes that normally act to limit cell growth and viability. In addition, alterations in DNA damage sensing and repair pathways result in

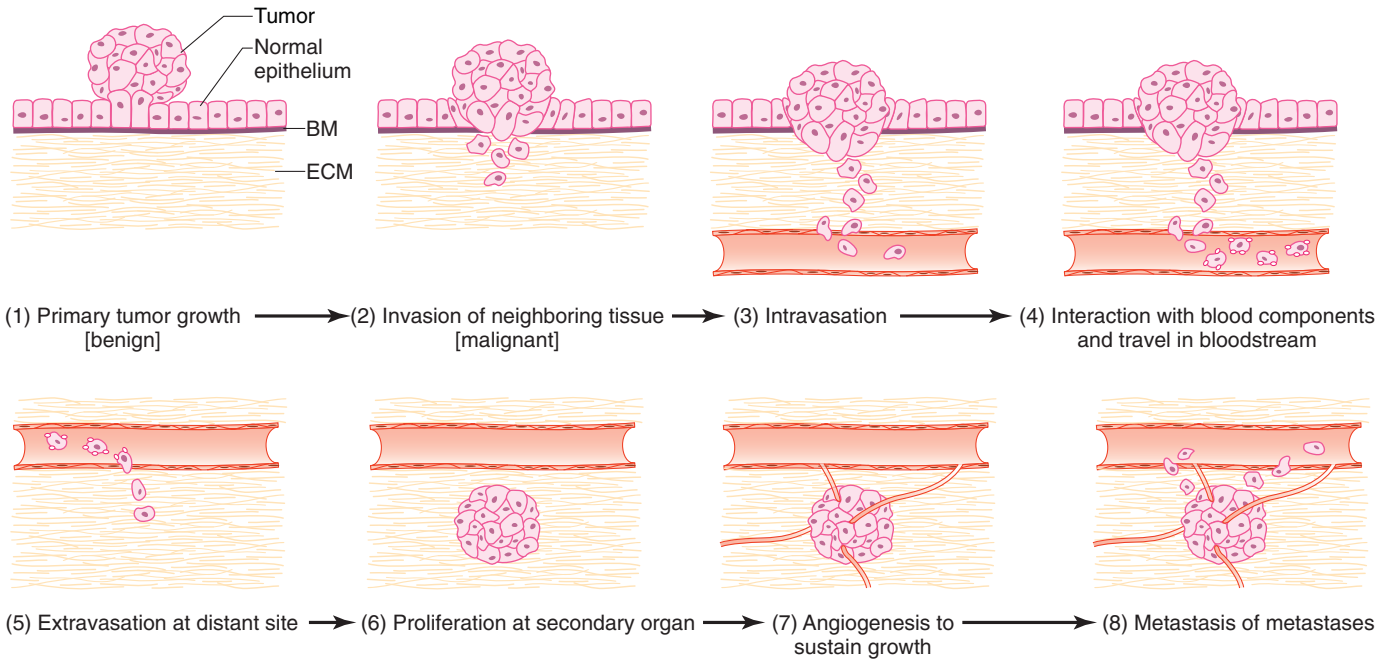


Figure 3-1 • Metastasis is a multistep process consisting of a series of discrete biological events. These allow primary tumor cells to invade the surrounding tissue, intravasate the circulatory system and survive this harsh environment, extravasate into new tissue, proliferate at secondary sites, and develop a vascular system to support growth of the metastases. See text for details. BM, basement membrane; ECM, extracellular matrix. (Adapted from Le QT, Denko NC, Giaccia AJ: Hypoxic gene expression and metastasis. Cancer Metastasis Rev 2004;23:293–310.)

decreased genomic stability and can promote tumor progression. In contrast to cellular transformation, tumor cells must overcome a different set of barriers to metastasize. These are external barriers created by the tumor microenvironment that limit tumor progression (Fig. 3-2). External forces include physical barriers such as extracellular matrix (ECM) components and basement membranes, as well as physiologic barriers such as limited oxygen (hypoxia) and nutrients, changes in pH, and immunologic barriers by the immune system.[2] Cells respond to external microenvironmental influences by altering gene expression such that they are able to adapt and survive. The tumor microenvironment thus exerts a selection pressure for cells capable of overcoming these barriers, driving tumor progression.

Tumor hypoxia is a potent microenvironmental influence and is associated with metastasis and poor survival in cancer patients.[6–9] Hypoxia selects for cells with low apoptotic potential[10–12] and increases genomic instability, allowing rapid mutational adaptations.[13,14] Hypoxia additionally increases the expression of genes involved in glucose transportation, angiogenesis, anaerobic metabolism, cell survival, invasion, and metastasis (a list is given in Table 3-1).[15,16] All of these changes allow cells to adapt to oxygen-deprived conditions and permit cells to escape these conditions by establishing new blood supplies or by physically moving from an oxygen-poor environment to an oxygen-rich environment. A large number of gene expression changes are mediated by hypoxia-inducible factor (HIF)-1, a helix-loop-helix transcription factor that is activated by oxygen-deprived conditions. HIF-1 is often found overexpressed in cancer cells as a result of the hypoxia microenvironment of solid tumors as well as oncogene and tumor suppressor gene mutations, and is associated with metastasis and poor survival.[17] Several HIF-1 targets have been shown to be mediators of metastasis, such as CXCR4, which promotes organ-specific metastasis in renal cancer,[18] and c-met, which increases tumor cell invasion (see section on Invasion).[19,20]

Hypoxia-regulated genes represent potentially specific therapeutic targets that should be highly tumor or metastases specific.[9,21] Recent studies have suggested that lysyl oxidase (*LOX*) is a hypoxia-induced gene that is a very promising target for metastatic disease. Research has demonstrated that inhibition of the secreted protein can prevent both invasion and metastatic growth.[22] In addition, LOX and other HIF-1α targets such as CA-IX have been shown to be independent markers of prognosis.[22–25]

Animal imaging studies have revealed that tumor cells can move rapidly along collagen fibers in the ECM that act as "highways" for metastasis.[26] This process is facilitated by host macrophage cells.[27] Furthermore, increased fiber deposition enhances ECM stiffness,

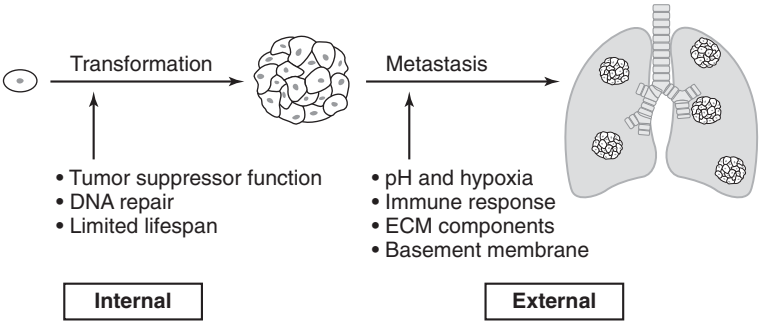


Figure 3-2 • Barriers for tumor progression. The first step in tumorigenesis is cellular transformation where cells must overcome several internal barriers. To metastasize, cells must overcome external barriers put in place by the tumor microenvironment. (Adapted from Gupta GP, Massague J: Cancer metastasis: building a framework. Cell 2006;127:679–695.)

Table 3-1 Hypoxia-Regulated Genes

METABOLISM
Aldolase A, C
Enolase-1
Glucose transporter 1, 3
Glyceraldehyde-3-phosphate dehydrogenase
Hexokinase-1, 2
Lactate dehydrogenase A. B
Phosphoglycerate kinase
6-Phosphofructo-2 kinase
Fructose 2–6 bisphosphatase-3
Pyruvate kinase-M
Transglutaminase-2
Acetoacetyl CoA thiolase
Adenylate kinase-3
Aminopeptidase A
Triose phosphate isomerase
Phosphoribosyl pyrophosphate synthetase
Spermidine N1-acetyltransferase
Tyrosine dehydroxylase
Glycogen branching enzyme
Solute carrier family
Carbonic anhydrase IX, XII
Ceruloplasmin
Erythropoietin
Ferritin light chain
Heme oxygenase
Transferrin & receptor

TRANSCRIPTIONAL FACTORS/GENE EXPRESSION
Early growth response 1
p35srj
ETS-1
Mxi-1
Annexin V
BCL-interacting killer (BIK)
FOS
Jun
Lipocortin
Nuclear factor κB (NF-κB)
NIX
NR3C1 Glucocorticoid receptor-α
Nuclear factor IL-3 (NFIL-3)

GROWTH FACTORS/CYTOKINES
IGF-2
IL-6, 8
Intestinal trefoil factor
Macrophage inhibitory factor (MIF-1)
PDGF-B
Stanniocalcin-2
TGF-α

ANGIOGENESIS
VEGF A, B, C, D
VEGF R1
Placental growth factor
Angiopoietin 2
Adrenomedullin
Endothelin 1, Endothelin 2
Ephrin A1
Nitric oxide synthase
COX1, COX2
Thrombospondin 1, 2
Fibroblast growth factor-3
Hepatocyte growth factor
Transforming growth factor-α, β-1, 3
Tie-2
Nitric oxide synthase

TISSUE REMODELING
Lysyl oxidase
Lysyl hydroxylase-2 (PLOD2)
Galectin-1
CD99
Collagen-5a
Ku 70
LDLR-related protein
Matrix metalloproteinase-7, 13
Vimentin
Integrin 5a
Plasminogen activator inhibitor-1
Urokinase plasminogen activator receptor
Tissue factor
Mucin 1
CXCR-4
Prolyl-4-hydroxylase
Osteopontin
Met tyrosine kinase (HGF receptor)

APOPTOSIS
BNIP3, BNIP3L
IGFBP1, 3, 5
Bid
Pim1, Pim2
Bcl-w like
RTP801
Hepatic fibrinogen/angiopoietin-related protein

STRESS RESPONSE
GRP78, GRP94, ORP150
Gadd153
HAP-1
Thioredoxin
Heat shock factor

PROLIFERATION/DIFFERENTIATION
BTG1
Cyclin G2
DEC1/stra13
Adipophilin
p21 *CDKI*
CDKN1b (p27, kip-1)
N-myc downstream reg-1 (*Cap43*)
Cyclin G2
Mitogen-inducible gene-6 (*MIG-6*)
ID-2 (DNA binding protein inhibitor)

Adapted from Le QT, Denko NC, Giaccia AJ: Hypoxic gene expression and metastasis. Cancer Metastasis Rev 2004;23:293–310.

which has been shown to increase cancer cell malignancy.[28] These events occur through activation of ERK and Rho by integrin clustering (see section on Cell Motility).[29] Production of reactive oxygen and nitrogen species by host immune cells and rapidly proliferating tumor cells not only increases genomic instability but has also been proposed to upregulate the expression of metastasis-promoting genes.[30]

Invasion

Changes in Cell Adhesion

The first step of metastasis is invasion. Cells must undergo changes in their cell-cell and cell-matrix adhesion interactions to dissociate themselves from the tumor.[31] Acquisition of an invasive phenotype requires changes in expression of genes that control cell-cell adhesion as well as proteolytic degradation of the ECM.[32] Cell-cell adhesions are mediated primarily by E-cadherin proteins expressed at junctions between cells.[31] Cadherins bind cells through protein-protein interactions at their extracellular domains, whereas their intracellular domains signal to catenins and the actin cytoskeleton. Changes in E-cadherin expression allow cells to detach from their neighbors and begin their migratory route toward the circulatory or lymphatic system to seek out new terrain. Reduced expression of E-cadherin is often observed in aggressive cancers through epigenetic silencing, proteosomal degradation, proteolytic cleavage, or mutation. In fact, inactivating mutations of E-cadherin have been shown to predispose

patients to gastric cancer, implicating E-cadherin as a tumor suppressor gene.[31]

Loss of E-cadherin is highly associated with epithelial to mesenchymal transition (EMT), a program that is essential for numerous developmental processes.[33] The acquisition of the invasive phenotype has many similarities to EMT, including loss of cell-cell adhesion mediated by E-cadherin repression and an increase in cell mobility. During EMT, there is a switch from E-cadherin (an epithelial cell marker) to N-cadherin expression (a mesenchymal cell marker), which promotes cell-matrix adhesion instead of cell-cell adhesion.[33]

Several signal transduction pathways, such as the Ras-MAPK and Wnt pathways, have been shown to regulate EMT (Fig. 3-3). In particular, the Ras-MAPK pathway activates two related transcription factors known as Snail and Slug.[34,35] Both of these proteins act as transcriptional repressors of E-cadherin, and their expression induces EMT in cancer cells.[36] Studies have indicated that Slug is an independent prognostic parameter for poor survival in colorectal carcinoma patients.[37] Twist, another basic helix-loop-helix transcription factor that is necessary for proper embryonic development, has also been shown to induce EMT through the repression of E-cadherin.[38] Both Twist and Snail expression levels are elevated in breast cancer patients, and are associated with poor prognosis.[38,39] Dysregulation of Wnt signaling is common in many types of human cancers and regulates EMT in part through Snail activation, an important early step in metastasis.[40]

Cell Motility

Cancer cells are able to take advantage of many mechanisms to migrate and invade, including both individual and collective cell-migration strategies (Table 3-2).[32] Most cancer cells of epithelial origin undergo EMT and acquire invasive migration capacity to enter the circulatory or lymphatic system. Invasive migration is a dynamic and complex process involving changes in cell-matrix adhesion and the cytoskeleton (Fig. 3-4). Changes in cell-matrix adhesion are necessary for the leading edge of the cell to grab onto the matrix surrounding it and pull itself forward in a movement similar to an inchworm. This invasive migration can be viewed as cycles of adhesion and detachment, allowing the cell to bind, then detach after pulling forward. Cell-matrix adhesions are in large part regulated by integrin proteins. Integrins are heterodimers of one of 18 alpha and 8 beta transmembrane proteins that bind to specific components of the ECM.[41] They can transmit signals into or out of the cell and are important mediators of malignant transformation.

Integrins are stimulated when they come into contact with specific ECM substrates, or through growth factor-stimulated signaling where they interact with receptor tyrosine kinases.[42–44] For example, hepatocyte growth factor (HGF, also known as scatter factor) influences invasion by signaling through its receptor c-met.[45] Integrin stimulation also promotes formation of focal adhesion contacts, focal adhesion kinase (FAK) activation through phosphorylation, and formation of FAK-Src complexes.[44] It is noteworthy that Src mutations that have been implicated in tumor cell motility are often observed in human cancers such as adenocarcinoma of the colon.[46] Intracellular signaling mediated by FAK activates Rac, RhoC, cdc42, and other guanosine triphosphatases (GTPases) that mediate cellular changes required for invasion.[42] These include actin-myosin contraction that propels the cell forward, and recruitment of matrix metalloproteases (MMPs) to focal adhesion sites where they degrade the ECM,

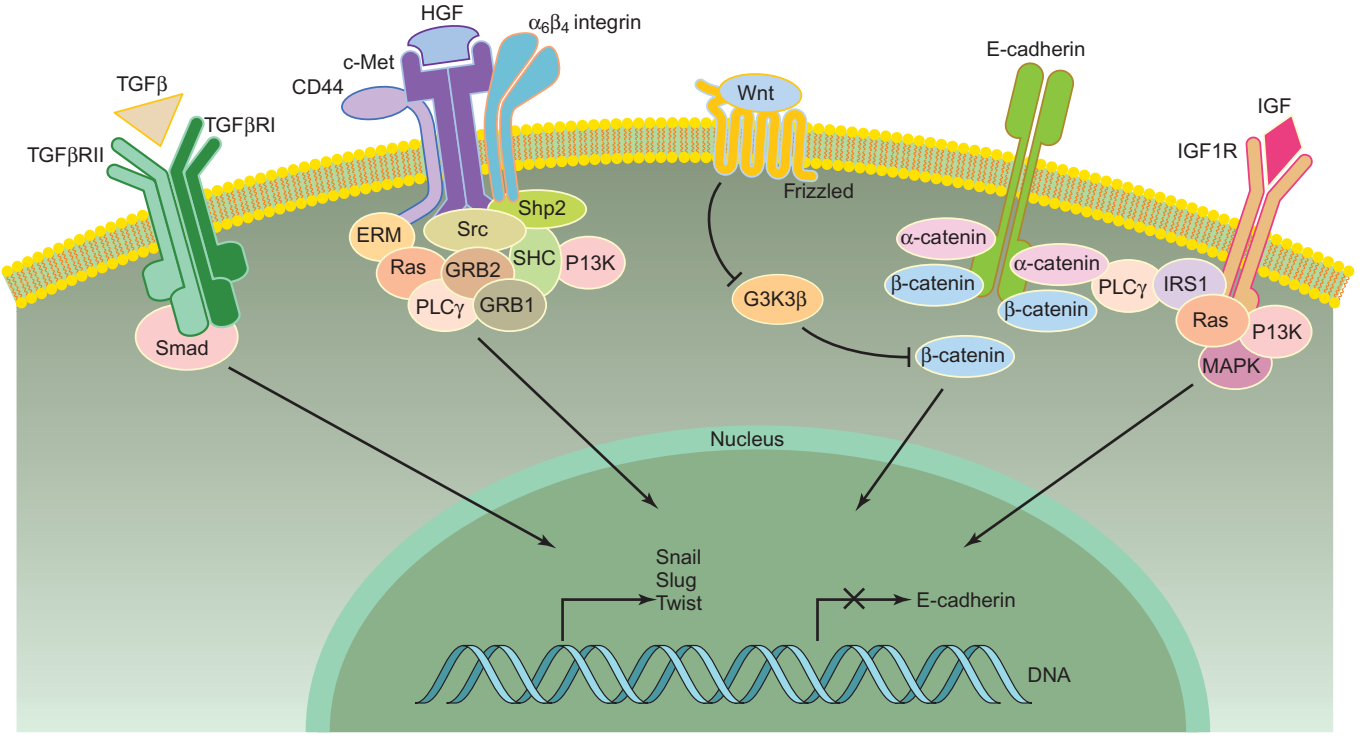
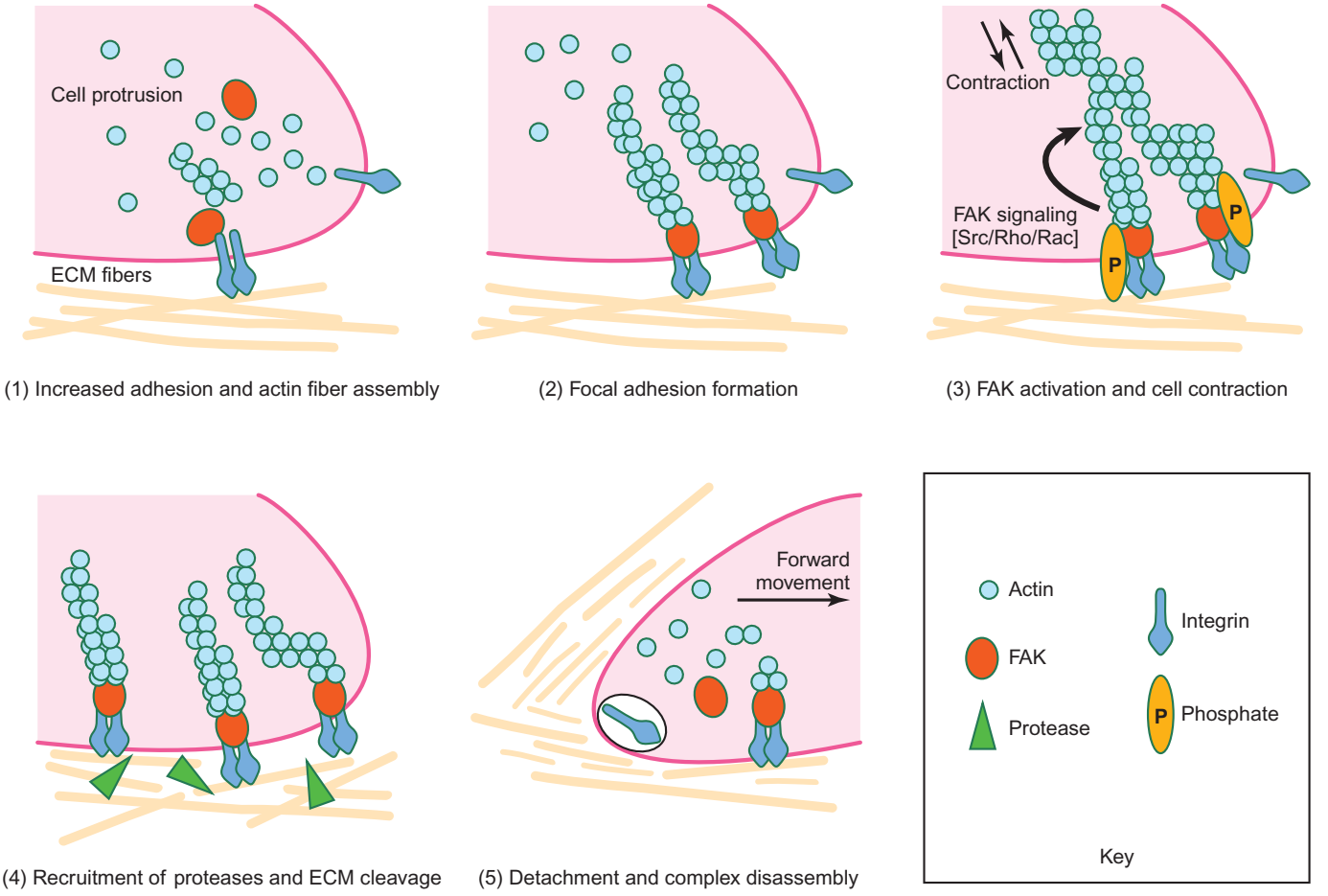


Figure 3-3 • Signaling pathways involved in epithelial to mesenchymal transition (EMT). EMT is a program of development of biological cells essential for numerous developmental processes. Tumor cell invasion has many phenotypic similarities to EMT, including a loss of cell-cell adhesion mediated by E-cadherin repression and an increase in cell mobility. Several signal transduction pathways have been shown to be involved in regulation of EMT. These include Ras-MAPK and Wnt. These pathways are activated by the binding of ligands to transmembrane receptors. These include: TGF-β binding to TGF-βRI and TGF-βRII; HGF binding to c-Met; Wnt binding to Frizzled; and IGF binding to IGF-1R. Activation of these pathways results in transcriptional repression of E-cadherin, and transcriptional activation of Snail, Slug, and Twist. These transcription factors regulate expression of genes involved in EMT. An important repressor of E-cadherin is β-catenin, which is normally targeted for degradation by GSK-3β. Activation of the Wnt pathway inhibits GSK-3β activity, resulting in stabilization of the β-catenin and translocation to the nucleus. (Adapted from Lee JM, Dedhar S, Kalluri R, Thompson EW: The epithelial-mesenchymal transition: new insights in signaling, development, and disease. J Cell Biol 2006;172:973–981.)

Table 3-2 Mechanisms of Cancer Cell Migration

	INDIVIDUAL	COLLECTIVE	
INTEGRINS +PROTEASES ↓	**Ameboid** (e.g., lymphoma, SCLC, leukemia)	**Clusters** (e.g., epithelial cancer, melanoma)	CADHERINS +GAP JUNCTIONS ↓
	Mesenchymal (e.g., fibrosarcoma, glioblastoma, anaplastic tumors)	**Sheets** (e.g., epithelial cancer, vascular tumors)	
			ADHESION INTERACTIONS ↓

Adapted from Friedl P, Wolf K: Tumour-cell invasion and migration: diversity and escape mechanisms. Nat Rev Cancer 2003;3:362–374.



(1) Increased adhesion and actin fiber assembly

(2) Focal adhesion formation

(3) FAK activation and cell contraction

(4) Recruitment of proteases and ECM cleavage

(5) Detachment and complex disassembly

Figure 3-4 • Invasive migration. Invasive migration is a dynamic and complex process involving changes in cell-matrix adhesion and the cytoskeleton. It begins with pseudopod protrusion at the leading edge. This increases cell-matrix interaction, stimulating integrin receptors. Integrin stimulation promotes formation of focal adhesion contacts, focal adhesion kinase (FAK) activation through phosphorylation, and formation of FAK-Src complexes. Intracellular signaling mediated by FAK activates Rac, RhoC, cdc42, and other GTPases that mediate cellular changes required for invasion. These include actomycin contraction that propels the cell forward, and recruitment of proteases to focal adhesion sites where they degrade the ECM, allowing the cell to glide forward when focal adhesion complexes are disassembled after contraction. The remodeled matrix tracks left behind the cell have been shown to facilitate movement of subsequent cells. (Adapted from Friedl P, Wolf K: Tumour-cell invasion and migration: diversity and escape mechanisms. Nat Rev Cancer 2003;3:362–374.)

allowing the cell to glide forward when focal adhesion complexes are disassembled after contraction.[32] In addition, the remodeled matrix tracks left behind the cell have been shown to facilitate movement of subsequent cells, similar to the generation of ski tracks by the first cross-country skier that allow following skiers to move more easily.[26]

Disruption of the Basement Membrane

The basement membrane provides a physical barrier between epithelial cells and the stroma. It is composed of numerous glycoproteins and proteoglycans that provide ligands for integrins permitting control of cell orientation and outside to inside signaling. Epithelial and stromal cells produce a mixture of these components that form a dense meshwork underlying the epithelial cells.

The basement membrane is not normally permeable to cells. Tumor cells overcome this barrier by altering the expression of their cell surface receptors such that they can now adhere to basement membrane components.[32,47,48] For example, tumor cells will increase expression of integrins that can bind laminin and collagen IV.[49] Increased CD44 expression permits cell binding to hyaluronan, a basement membrane proteoglycan, and is observed in several types of human cancer including metastatic colon carcinomas.[50] In addition, cancer cells modify the components of the basement membrane to ease penetration. For example, reduced laminin expression is observed in poorly differentiated human colon carcinomas.[51]

ECM protease activity is tightly regulated by proteins that inhibit their functions.[45,52] Tumor cells proteolytically disrupt the basement membrane by altering the balance between ECM proteases and their inhibitory proteins. For example, elevated MMP expression and activity increases degradation of the basement membrane. MMP-1 (also known as collagenase or gelatinase) degrades collagen IV and is increased in highly metastatic cancer cells.[53] MMP degradation of the ECM not only facilitates cell movement but additionally generates a large number of bioactive cleaved peptides, and releases growth factors and chemokines trapped within the ECM mesh.[52] For example, MMP activity releases active forms of proteoglycans including heparin, hyaluronate, and chondroitin sulfate.[54,55]

Intravasation

The entry of tumor cells into the circulation (intravasation) and the exit of tumor cells from the circulation (extravasation) to host tissue represent critical steps in the metastatic process. One clear difference between intravasation and extravasation has to do with the composition of the blood vessels. Tumor blood vessels are malformed and irregular, often possessing breaks in their thin lining that permit the easy access of tumor cells into the circulation. In contrast, the vasculature of normal tissue where tumor cells extravasate do not have these same features. This very observation suggests that the processes of intravasation and extravasation are distinct and probably require different gene functions. The abnormal vasculature found in tumors is the result of the dysregulated expression of proangiogenic growth factors, inhibition of antiangiogenic genes and pathways, recruitment of vascular progenitor cells from the bone marrow, and, in some cases, vascular memory by tumor cells.

Tumors typically do not possess abundant lymphatics and are under high interstitial pressure. Although tumors secrete lymphangiogenic factors such as vascular endothelial growth factor-C (VEGF-C), the development of lymphatics in tumors is also abnormal. In fact, the intravasation of tumor cells into lymphatics is probably easier than through vasculature in that lymphatic vessels function as a collection point for interstitial fluids.

Our knowledge of the genetic determinants involved in intravasation is limited. Gradients of chemo-attractant proteins such as chemokines have been proposed to guide cells toward the circulatory system.[26] In addition, tumor cells move along collagen fibers produced by invading cells, a process facilitated by host macrophages.[26] Whether or not genes such as *LOX* that are required for cross-linking collagen are involved in this process is still unknown. Interestingly, the transcription factor Twist that is implicated in EMT (as described previously) has also been shown to increase the ability of tumor cells to intravasate.[38] However, the underlying molecular mechanisms involved in promoting intravasation by Twist are as yet unknown.

Survival in the Circulatory System

Tumor cells that have successfully entered the bloodstream through intravasation theoretically have access to most organs in the body. However, before these tumor cells can extravasate into a target tissue they must first survive the environment of the circulatory system. Tumor cells in the circulatory system are subjected to immune attack, circulatory forces, and anoikis (apoptosis induced by loss of adhesion).[2] Circulating tumor cells bind to platelets to protect themselves from these dangers, thus increasing their chance of survival.[56–58] Tumor cells also bind to coagulation factors including thrombin, fibrinogen, tissue factor, and fibrin, creating emboli.[59] These tumor cell emboli are more resilient to both circulatory forces and immune attack, and have been shown to have greater metastatic potential than single tumor cells.[57] In the circulation, aggregates of tumor cells are termed homotypic clumps, because they are homogeneous in their cellular composition, whereas those associated with platelets are termed heterotypic clumps and may possess greater metastatic potential for the reasons described previously.[56,58]

The ability to resist apoptotic cell death is important at a variety of steps in the metastatic process. First, tumor cells must survive the lack of oxygen and nutrients in the primary tumor to be able to migrate and invade. This is particularly noteworthy, because hypoxia increases the metastatic potential of tumor cells. Apoptotic resistance in response to decreased oxygen and nutrients is achieved by loss of the *p53* tumor suppressor gene, increased expression of antiapoptotic members of the Bcl-2 family and decreased expression of proapoptotic members, and increased activity of the HIF transcription factor. Hypoxic tumor cells that are resistant to apoptosis have a greater probability of surviving for sufficient periods of time to intravasate into the circulation.

Apoptosis can also play a role in anoikis, death induced by loss of cell adhesion. Obviously, resistance to anoikis is important both in the early phases of invasion as well as during intravasation and circulation. Although a variety of receptor tyrosine kinases can impart resistance to anoikis,[59] most probably the formation of homotypic and heterotypic cell aggregates promotes resistance to anoikis as well.

Arrest and Extravasation

Much of our knowledge of tumor cell extravasation is patterned after leukocyte transmigration through endothelium. It is well known that leukocytes arrest before transmigration. Similarly, tumor cell arrest can occur passively through mechanical lodging or can be allowed by cell-surface molecules.[60–62] Endothelial cells are constantly shed from the blood vessel walls, creating temporary gaps to which tumor cells can more easily attach because basement membrane components are exposed.[63–65] Vessel wall damage also attracts platelets and tumor cells associated with platelets, which is enhanced by fibrinogen expression on the endothelial cell surface.[66,67] Fibrin blood clots at the sites of tumor cell arrest can further damage vessels, attracting more platelets and circulating tumor cells.[68] Increased blood coagulation is often observed in cancer patients as a result of elevated levels of thromboplastin, procoagulant A, and phosphatidylserine produced by tumor cells.[69,70] The most severe manifestations of this hypercoagulation state were described by Trousseau many years ago. The induction of the enzymes involved in this state can also be enhanced by changes in the tumor microenvironment.[71]

Tumor cell arrest is allowed by endothelial cell P- and E-selectins that bind to the tumor cells[72,73] and by tumor glycosylation patterns

and cell-cell adhesion molecules such as integrins and CD44.[74–78] Increased cell-surface expression of mucin carbohydrate is associated with increased metastatic potential in human colon carcinoma.[79] Tumor clump formation additionally facilitates tumor cell arrest by increasing the number of adhesive interactions. ECM components such as fibronectin and laminin enhance tumor cell arrest, and administration of targeting peptides to fibronectin and laminin can reduce metastatic formation.[80] Tumor cells may reside and grow within the intravascular space until the metastatic lesion physically breaks through the vessel.[81] Tumor cells may also extravasate by inducing endothelial cell retraction permitting cell attachment to the ECM.[81] It is highly noteworthy that VEGF increases vascular permeability and may permit extravasation through Src activation.[82,83] Thus, anti-VEGF therapy could potentially act to inhibit metastases by decreasing vascular permeability. In some cases, tumor cells direct their movement and invasion into new organ terrain by following migrating white blood cells and tissue motility factors.[84]

Proliferation

The final steps of metastasis involve the resumption of cell proliferation at the secondary site and induction of angiogenesis to supply oxygen and nutrients. Studies have shown that the host tissue can influence tumor growth through autocrine, paracrine, and endocrine signals. However, it is the net balance of positive and negative signals that determines metastatic proliferation. This can partially explain organ-specific metastasis, because only certain cells will be able to respond to tissue-specific proliferation-stimulating signals and leave their dormant state.[85] For example, insulin-like growth factor-1 (IGF-1), HGF, and transforming growth factor α (TGFα) are highly expressed in the liver,[86–88] and cancer cells from colon, breast, and bladder overexpress receptors for these ligands such as epidermal growth factor receptor (EGF-R)[89–93] and c-met receptor,[94] resulting in proliferation of metastatic cells in these tissues.

Angiogenesis

The formation of a new blood supply from pre-existing vasculature is stimulated by an angiogenic "switch" that occurs when the ratio of inducers to inhibitors is increased. Inhibitors of angiogenesis include ECM proteins thrombospondin and endostatin.[95–97] Angiogenic inducers include VEGF, platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), TGFβ, and ephrin, and their family members.[3] Of these, VEGF is the best characterized and has successfully been targeted through the use of monoclonal antibodies and soluble receptors.[98] VEGF increases angiogenesis by stimulating endothelial cells, mobilizing endothelial progenitor cells, stimulating outgrowth of pericytes that line the walls of mature blood vessels, and increasing vascular permeability allowing macromolecules to traverse endothelium.[99,100] Furthermore, VEGF is thought to be a key molecule for the homing of VEGFR-positive bone marrow-derived progenitor cells involved in premetastatic niche formation (see later discussion),[101] and for homing of VEGFR-positive tumor cells to metastatic sites.[102] Recruitment of bone marrow-derived circulating endothelial cells additionally increases angiogenesis.[103] Thus, angiogenesis is important both for primary tumor and metastatic tumor growth, making it an attractive target.

Metastasis of Metastases

Tumor cells that have successfully colonized secondary organs are capable of further metastasis and colonization of other organs. Cells within the metastatic tumors are subjected to similar microenvironmental stresses experienced by the primary tumor, and adapt to overcome these external barriers and seed new terrain. These cells from metastases may have an intrinsic colonization capability allowing them to constantly reseed both primary and secondary tumors.[104]

LYMPHATIC METASTASIS

The vascular and lymphatic systems have numerous connections,[105] and metastasizing tumor cells can easily pass from one system to another.[106,107] Invading tumor cells can additionally enter small lymphatic vessels directly and be passively transported to the lymph. Cancer cells may spread to lymph nodes near the primary tumor, known as the regional lymph nodes (RLNs). This is often referred to as nodal involvement, positive nodes, or regional disease. Tumor cells may become trapped in the first lymph node, or form distal nodal metastases referred to as "skip metastases" because they have bypassed the first draining lymph nodes in the area.[4] RLNs may become enlarged and are often removed to prevent cancer spread. Lymph node involvement and presence of micrometastases in the sentinel lymph node (the lymph node draining the tumor site) correlate with decreased survival.[108] Localized spread to RLNs near the primary tumor is not normally considered as metastasis per se, although it is also a sign of worse prognosis.[109,110] Some malignancies, such as sarcomas in contrast to breast carcinomas, do not spread to the RLNs before metastasizing to distant sites. Thus, node status does not always correlate with metastasis.[2]

COLONIZATION BY METASTATIC TUMOR CELLS

The patterns of colonization cannot solely be explained by circulatory routes above. The propensity for certain tumors to seed in particular organs was first discussed as the "seed and soil" theory by Stephen Paget over a century ago in 1889.[4] For example, prostate cancer often metastasizes to the bones, and colon cancer has a tendency to metastasize to the liver. Colonization is an extremely inefficient process that is heavily dependent on the interactions between "seeding" tumor cells and the "soil" microenvironment of the secondary site. Many factors including formation of a premetastatic niche and organ specificity determine these patterns of colonization.

Premetastatic Niche

Recent in vivo data have suggested that the formation of a premetastatic niche is essential for the growth of extravasating metastatic tumor cells.[101] Factors secreted by primary tumor cells stimulate mobilization of bone marrow-derived cells that enter circulation and reside in sites of future metastasis. These bone marrow-derived cells express VEGFR-1, c-kit, CD133, and CD134, and increase angiogenesis at the premetastatic sites. Targeted inhibition of VEGFR-1 prevented niche formation and subsequent metastatic progression. This tissue preconditioning may thus represent a key step that could be targeted therapeutically, although studies with anti-VEGF therapy fail to show significant benefit in preventing metastatic growth for long periods of time. The role of hematopoietic progenitor cells and other bone marrow-derived cells in tumor progression is reviewed by Kaplan and colleagues[111] and shown in Figure 3-5.

An additional function of the premetastatic niche is to guide metastases to specific organs. Kaplan and coworkers demonstrated that injection of secreted factors collected from cancer cells that metastasize to multiple organs could permit cancer cells that only metastasize to the lung when grown as subcutaneous tumors in mice, to display widespread metastasis through governing bone marrow-derived cell accumulation.[101] Elevated fibronectin expression by fibroblasts and fibroblast-like cells resident at premetastatic sites seems to be a critical factor in the development of the premetastatic niche. The key tumor-secreted factors that determine metastatic sites and mediate premetastatic niche formation have yet to be identified, although a role for tumor necrosis factor α (TNFα), TGF-β, and VEGF-α pathways has been demonstrated.[112]

MMPs may also play an important role in this process. For example, VEGF-R1 signaling has been shown to be required for

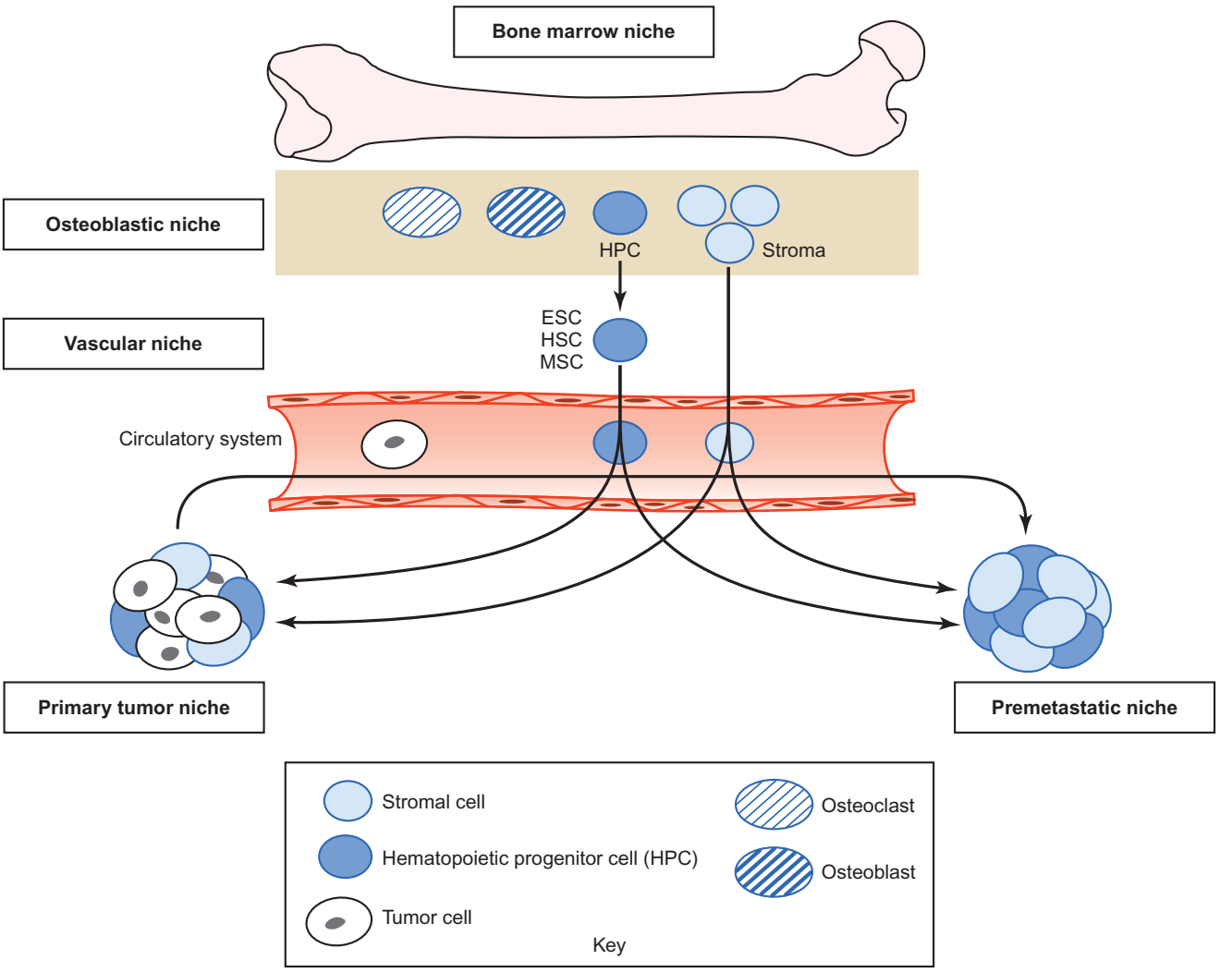


Figure 3-5 • The role of bone marrow-derived cells in tumor progression. Cells derived from the bone marrow niche are involved at many stages during tumor progression. Hematopoietic progenitor cells (HPCs), hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and stromal cells including macrophages and fibroblasts, permit tumor growth and development at primary and metastatic niches. (Adapted from Wong SY, Hynes RO: Lymphatic or hematogenous dissemination: how does a metastatic tumor cell decide? Cell Cycle 2006;5:812–817.)

premetastatic induction of MMP-9 expression in endothelial cells and macrophages of the lungs by distant primary tumors.[113] This is thought to make the lung microenvironment more compliant for invasion of metastasizing cells. This concept is supported by the finding that pericyte recruitment and angiogenesis are not observed in tumor-bearing mice with MMP-9 knockout bone marrow cells.[114] Furthermore, stromal-derived MMP-2 and MMP-9 have also been shown to contribute to establishment and growth of metastases.[115] Thus, whereas there is evidence that MMPs play multiple roles in metastases, clinical trials with MMP inhibitors have failed to show significant efficacy. In large part, this has been due to unexpected normal tissue toxicities and conflicting roles in metastases.

Organ Specificity

The organ distribution of metastases from a primary is not random. Minn and colleagues used bioluminescence imaging to reveal patterns of metastasis formation by human breast cancer cells in mice.[116] They also showed that individual cells from the pleural effusion of a breast cancer patient showed distinct patterns of organ-specific metastasis.[117] Single-cell progenies derived from this population demonstrated different abilities to metastasize to the bone, lung, or adrenal medulla. These studies indicate that there are particular requirements for metastasis to colonize specific organs. Some of the key molecules determining organ-specific metastasis have been identified and are briefly discussed in the following section.

Metastases to the Bone

There are two types of bone metastases: osteoblastic and osteolytic.[118,119] Osteoblastic metastases are observed in patients with advanced prostate cancer. Both the differentiation of osteoblastic precursors as well as the activity of osteoblast cells are stimulated by tumor and microenvironmental signals such as bone morphogenetic protein (BMP), FGFRs, and IGF-1R.[120] Runx-2 is a key transcription factor that regulates the differentiation of osteoblasts and osteoblastic precursor cells,[121] and represents a potential new target for inhibiting osteoblastic metastases by preventing osteoblastic precursor differentiation. In contrast, osteolytic metastases are observed in patients with breast cancer or multiple myeloma,[122,123] and in these patients interactions between tumor cells and the bone microenvironment result in bone resorption and metastatic growth due to the unique interplay between osteoblasts and osteoclasts (Fig. 3-6).[118,122] Parathyroid hormone-related protein (PTHrP) secreted by the tumor cells, stimulates osteoblasts to produce receptor activator of nuclear

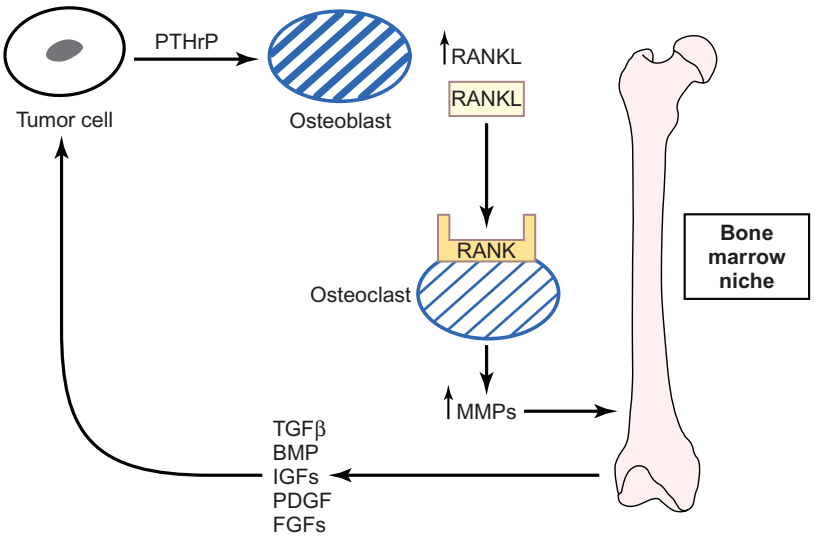


Figure 3-6 • The vicious cycle of osteoclastic bone metastasis. Interactions between the tumor cells and the bone microenvironment create a "vicious cycle" of osteolytic metastatic lesion development. Parathyroid hormone-related protein (PTHrP), secreted by the tumor cells, stimulates osteoblasts to produce RANK ligand (RANKL). Bone-resorbing osteoclast cells are activated by RANKL when it binds to the RANK receptor. The activated osteoclasts upregulate MMPs that degrade the bone matrix-releasing growth factors such as TGFβ, IGFs, PDGF, FGFs, and BMP. These factors stimulate tumor cells to release PTHrP, thus completing the vicious cycle. (Adapted from Steeg PS: Tumor metastasis: mechanistic insights and clinical challenges. Nat Med 2006;12:895–904.)

factor–κB (RANK) ligand (RANKL). Consequently, bone-resorbing osteoclast cells are activated by RANKL when it binds to the RANK receptor. Activated osteoclasts upregulate MMPs, which degrade the bone matrix-releasing growth factors such as TGFβ, IGFs, PDGF, FGFs, and BMP.[118,124,125] These factors stimulate tumor cells to release PTHrP, thus restarting this pathway of bone resorption. Gene profiling has identified other important mediators of osteoclastic bone metastases including CXCR4, MMP-1, CTGF, and osteopontin.[126] Tumor cells additionally induce osteoclast formation by overexpressing interleukins such as IL-8 and IL-11, and by downregulating macrophage colony-stimulating factor.[127,128] All of these latter factors represent new targets for metastases, although the importance of each factor in osteoclastic bone metastases requires further clarification.

Metastases to the Brain

Brain metastases are most commonly observed in patients with breast cancer, lung cancer, and melanoma. Vascular access to the brain is strictly regulated by the blood-brain barrier, an endothelial layer surrounding the brain connected by tight junctions and further lined by a basement membrane, pericytes, and astrocytes.[129] Macromolecules are not usually able to traverse the blood-brain barrier, and it remains unclear how tumor cells are able to penetrate the blood-brain barrier. However, once the tumor cells are within the brain parenchyma, glial cells permit establishment and growth of metastases by secreting chemokines, cytokines, and growth factors.[130] Other neurotransmitter hormones in the brain such as norepinephrine have also been reported to increase tumor cell motility and metastatic spread.[131]

Little is known about the key factors that determine colonization of the brain, mostly because there is a lack of good in vivo models of brain metastasis. Overexpression of Stat3 increases melanoma metastasis to the brain and increases invasion of the melanoma cells and angiogenesis, although the pathways modulated by Stat3 signaling require elucidation.[132] The dependence of brain metastases on VEGF has been demonstrated experimentally in animals through inhibition studies where VEGF neutralization reduces brain metastases.[133,134]

In general, patients with brain metastases have an extremely poor prognosis. It is of concern that there has been an increase in the incidence of brain metastases in patients whose systemic disease is well controlled.[135–137] For example, patients with breast tumors that overexpress Her-2 and who are treated with Her-2 targeting trastuzumab (see later discussion) have an incidence of brain metastases twice that of breast cancer patients who are treated with other agents.[135] This is thought to be because the brain offers a sanctuary when systemic disease is being controlled.[3] The development of drugs that can cross the blood-brain barrier and target brain metastases are of paramount importance in the development of new targeted therapies to tackle this problem. Currently, the best treatment for oligometastases to the brain is radiosurgery.

Metastases to the Lung

Pulmonary metastases are frequently observed in patients with sarcoma, breast, melanoma, gastrointestinal, and kidney cancers. Because cardiac output from the pulmonary artery circulates through the lungs, a high incidence of pulmonary metastases in cancer patients can be expected on the basis of blood flow alone. Metastases therefore often initiate in pulmonary arterioles and later traverse the basement membrane into the lung parenchyma. TGFβ and NF-κB facilitate this process in breast cancer,[138–140] as does osteopontin in hepatocellular cancer,[141] and ezrin in osteosarcoma and breast cancer.[142,143] In vivo studies have identified a gene expression signature for lung metastasis including several membrane-localized and secreted proteins that has been validated in breast cancer patients.[116] Interestingly, this group of genes was able to induce lung metastasis when expressed together but not individually, suggesting essential cooperation between proteins. Increased expression of antiapoptotic proteins such as Bcl-2 and Bcl-xl is also observed in lung metastases, facilitating survival and providing resistance to therapy.[144–148] These studies suggest that multiple targets must be inhibited with combination therapy to effectively inhibit lung metastases.

Metastases to the Liver

Liver metastases are observed in patients with breast, lung, and pancreatic cancers. However, liver metastases are most commonly found in patients with metastatic colorectal cancer, because the liver is the first capillary bed encountered by the metastasizing cells. The circulatory system of the liver, in particular the liver sinusoids, does not have a barrier limiting macromolecule flux, and it is well perfused and highly permeable, permitting metastasizing cancer cells to establish themselves and grow. Thus, tumor cell invasion and survival are probably the key determinants in metastatic colonization of the liver.[149] There are two types of liver metastases: a nonangiogenic "replacement" of liver cells with tumor cells that preserves the stroma,[150] and a "pushing" type of metastasis[3] whereby the liver stroma is not preserved and has higher levels of endothelial cell proliferation.[151,152] In light of the "pushing" type of metastases that stimulate angiogenesis, targeting the VEGF pathway experimentally in vivo has been shown to prevent liver metastases,[153–155] and is effective when combined with cytotoxic agents in patients with metastatic colon cancer.[156,157] Other molecules thought to be important in

colonization to the liver and that could be targeted therapeutically are COX-2,[158,159] integrins,[160] and Src.[161]

HOST-TUMOR CELL INTERACTIONS

Tumor progression requires collaboration between tumor and host cells. Research has revealed much cross-talk between cancer cells and bone marrow-derived host immune and stromal cells.[162] For example, disruption of TGFβ signaling in fibroblasts can induce stomach and prostate cancer in mice.[163] Mutations commonly found in cancer cells, such as *p53* and *PTEN* mutations, can also be found in cancer-associated stroma and have been hypothesized to be important during tumor progression.[164,165] In fact, gene expression profiling of activated fibroblasts in vitro generated a signature that could predict primary tumor metastasis.[166] For example, the chemokine CXCL12 is produced by breast cancer-associated fibroblasts[167] and increases tumor cell migration and recruitment of endothelial progenitor cells expressing CXCR4,[168] a CXCL12 receptor.

Cells that respond to tissue injury (such as leukocytes and lymphocytes) are often associated with tumor cells and enhance their progression, for example by assisting travel in the bloodstream. The tumor-suppressing activities of cells in charge of immune attack (such as natural killer cells and antigen-presenting cells) can be dampened by overexpression of tumor-derived immunosuppressive cytokines such as TGFβ and interleukins,[169–171] and by lack of necessary costimulatory signals from tumor cells.[172] Thus, host cells can directly promote tumor progression by secreting growth factors and cytokines that stimulate tumor metastases and suppress tumor immune surveillance.

Inflammation and Metastases

Ironically, cells involved in chronic inflammation facilitate tumor formation and progression, mostly mediated by NF-κB and COX-2.[173,174] In particular, infiltration of activated macrophages into tumors correlates with poor prognosis.[27,175] The tumor-suppressing and tumor-promoting roles of these tumor-associated macrophages (TAMs) are shown in Table 3-3. TAMs are especially attracted to regions of hypoxia, where they secrete abundant angiogenic inducers and proteases, including VEGF and MMPs,[175,176] that have been reported to enhance angiogenesis.[27] TAMs express high levels of the HIF-2 transcription factor that has been found to be an independent prognostic factor of outcome.[177] Interestingly, work by Cramer and associates[178] has shown that in fact HIF-2 is needed for myeloid cell infiltration and activation. Furthermore, TAMs release growth factors such as PDGF, EGF, and HGF, which enhance proliferation, survival, and invasion.[175] Mutation of the macrophage colony-stimulating factor-1 gene that affects macrophage differentiation has been shown to prevent metastasis in mice bearing aggressive breast cancer tumors.[179] Targeting TAMs may be a viable mechanism for antimetastatic therapies.[180]

Table 3-3 Conflicting Roles of Tumor-Associated Macrophages

Pro-Tumor	Anti-Tumor
Proangiogenic cytokines	Tumor cell lysis
Immunosuppressive cytokines	Immunostimulatory cytokines
Protumorigenic chemokines	Immunostimulatory chemokines
Reactive oxygen species (ROS)	ROS
Elevated MMPs, TF, and uPA	

MMPs, matrix metalloproteinases; TF, tissue factor; uPA, urokinase plasminogen activator.

Adapted from Condeelis J, Pollard JW: Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell 2006;124:263–266.

DORMANT CELLS

The prolonged survival of single cells or micrometastases with no apparent progression is referred to as dormancy.[181] Dormant cells are frequently observed in patients with prostate, melanoma, and breast cancer,[182–184] and are found to reside in the lungs, liver, and bone marrow. These micrometastases represent minimal residual disease that results from the inefficiency of metastasizing tumor cells to colonize organs properly following extravasation.[185] Incompatibilities between tumor cells and their tissue soil, or inability of tumor cells to generate sufficient angiogenesis result in cell-cycle arrest and dormancy.[181] What genes and pathways are important in controlling metastatic dormancy are unknown and are important to identify, because they represent a "metastatic tumor suppressor mechanism."

The presence of dormant tumor cells is associated with poor patient prognosis.[186] Isolation and reimplantation of dormant cells can generate primary tumors, demonstrating that these cells are viable.[185,187,188] In vivo experiments have indicated that growth of dormant metastatic cells can be activated by angiogenesis or removal of the primary tumor,[189] suggesting that limited levels of growth factors or cytokines may induce this dormant state. The angiogenic switch required for dormant cells to grow into tumors may be detectable by markers in the blood, such as VEGF, and could thus be used to monitor undetectable and asymptomatic disease in patients.[190] Interestingly, circulating tumor cells can be detected in breast cancer patients as long as 22 years after mastectomy.[191]

CANCER STEM CELLS AND METASTASIS

Stem cells are primal cells that retain the ability to renew themselves through cell division and can differentiate into a wide range of specialized cell types. They give rise to all tissues during embryogenesis and control tissue homeostasis in the adult. Cells with stem cell properties have been identified in some cancer types.[192–194] These cancer stem cells (CSCs) are able to self-renew and differentiate into multiple cell types and are believed to arise either by mutation of an adult stem cell or fusion of an adult stem cell with a CSC.[195] It is hypothesized that tumors arise from CSCs and that these cells persist in tumors as a distinct population that is responsible for disease relapse and metastasis. Because CSCs are the only cells capable of giving rise to new tumors by themselves, targeting this subpopulation may eradicate cancer.

The recent discovery of CSCs has revolutionized our way of thinking about cancer. Cancer is classically thought of as a disease of progression, facilitated through the accumulation of mutations and driven by microenvironmental signals. Whereas the stem cell microenvironment or niche is thought to be the key determinant for stem cell regulation, the role of CSCs in multistage tumor progression, particularly with respect to metastasis, is poorly understood. There may exist a subset of CSCs with the inherent property to metastasize (Fig. 3-7). Research into these metastatic CSCs is greatly anticipated.

ANTIMETASTATIC THERAPY

The literature is replete with genes that have been implicated in the metastatic process.[196,197] Because of the immense heterogeneity of metastatic cells, metastatic selective therapeutic targets have been difficult to identify and develop for targeted therapy. Clinically, there have been two success stories thus far: bevacizumab and trastuzumab. However, both agents affect both primary and metastatic tumor growth. Bevacizumab targets VEGF and has displayed activity in several metastatic cancer types, especially when administered in combination with cytotoxic compounds.[157] Other small-molecule inhibitors to VEGF-R have also shown some antimetastatic effectiveness. Trastuzumab is a recombinant monoclonal antibody to Her-2 that is very effective against metastatic breast cancer, again, particularly in combination with cytotoxic agents.[198] However, only 30% to 40%

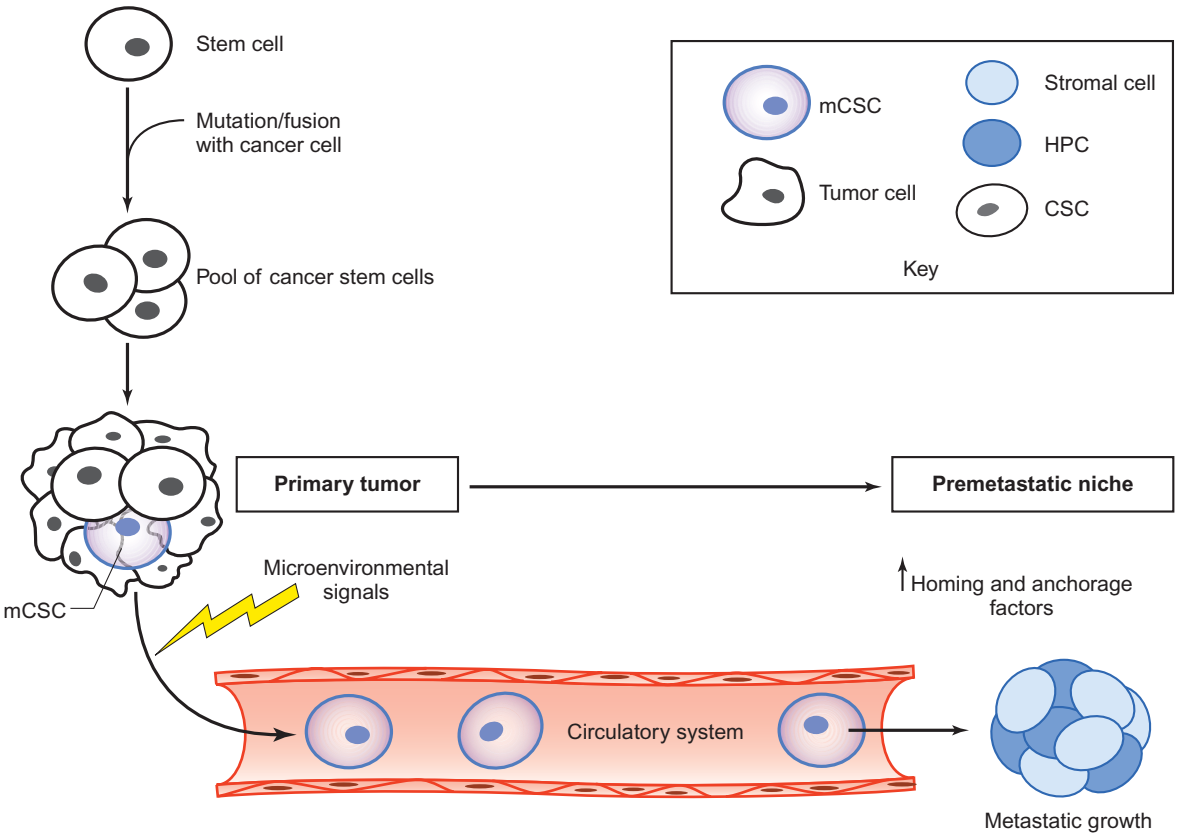


Figure 3-7 • The role of cancer stem cells (CSCs) in metastasis. CSCs are able to self-renew and differentiate into multiple cell types and are believed to arise either by mutation of an adult stem cell or fusion of an adult stem cell with a cancer stem cell. It is hypothesized that a pool of CSCs develops and gives rise to the primary tumor. A subpopulation of CSCs is believed to exist with the inherent property to metastasize. Microenvironmental signals stimulate primary tumor cells to secrete factors involved in premetastatic niche formation, and additionally stimulate invasion and dissemination of the metastatic CSCs (mCSCs). These mCSCs are attracted to homing and anchorage signals produced by bone marrow-derived cells at the premetastatic niche. (Adapted from Al-Hajj M, Clarke MF: Self-renewal and solid tumor stem cells. Oncogene 2004;23:7274–7282.)

of breast cancer patients overexpress Her-2 and are suitable for treatment.[198] In addition, whereas MMP inhibitors demonstrated good antimetastatic effects in vivo, these compounds failed in clinical trials, and additional research has revealed their conflicting roles in metastasis.[199]

A recent study by Gupta and associates[200] analyzed gene expression profiles of metastases from a breast cancer cell line, and identified four genes: epiregulin, which encodes a ligand that binds to the EGFR; cyclooxygenase, which encodes an enzyme that is involved in inflammatory responses and wound healing; and two MMPs that encode proteins involved in tissue remodeling and angiogenesis that affect both primary and metastatic tumor growth. The investigators found that inhibition of each gene individually through genetic knockdown resulted in a modest effect on lung metastases. In contrast, if combinations of these genes were inhibited, there was a significantly greater effect on the metastatic process, suggesting that combination therapy is more effective in controlling metastases. However, many of these reported genes, such as *Her-2/Neu* and *EGFR,* as described previously, affect both primary as well as metastatic tumor growth, somewhat obfuscating their roles as direct modulators of tumor metastases. What the field is desperately in need of is new candidate genes and proteins that specifically affect the metastatic process and have little effect on primary tumor growth.

One very promising target is LOX, a hypoxia-induced secreted protein involved in multiple stages of metastasis (Fig. 3-8).[201] LOX contributes to tumor cell invasion by cross-linking collagens in the ECM, which stimulates integrin-mediated cell-matrix adhesion and activation of FAK, and additionally provides a route ("highway") by which tumor cells may travel. Furthermore, LOX is involved in the formation and maintenance of the metastatic niche, allowing metastatic dissemination and growth. Targeting secreted LOX through antibody or small-molecule inhibition significantly reduced formation and growth of metastases to the lung, liver, bone, and brain, in several models of cancer. These data provide hope for the future, because there is an urgent need for new metastasis-targeting therapies.

CONCLUSION

Metastatic disease, not the primary tumor, kills the majority of cancer patients. For such an important determinant of long-term survival, progress has been slow in understanding the crucial genes and pathways that drive metastatic progression. The reasons for this slow progress have been numerous, including inadequate animal models that reflect the metastatic process in humans, failure to identify genes that specifically affect metastatic tumor growth, the complexity of host and metastatic tumor interactions, and premature clinical trials focusing on "attractive" gene targets. The future for metastasis research looks very promising in large part because we understand the mistakes of the past and are using multiple genomic and proteomic approaches to target what has for so long seemed to be an untractable problem. It is only when we are able to attack the problem of metastases that we will make significant inroads in our war against cancer.

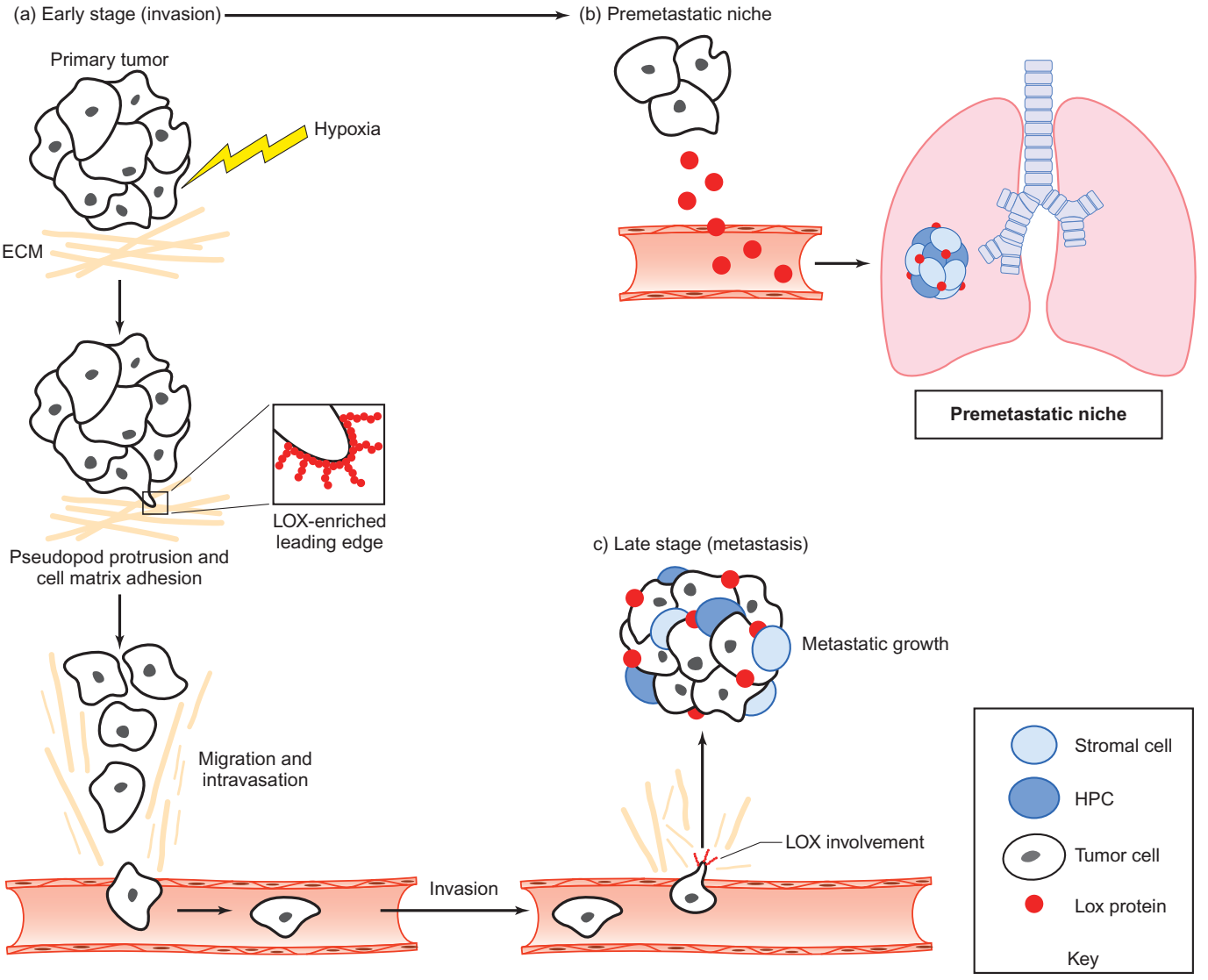


Figure 3-8 • The role of lysyl oxidase in metastasis. Lysyl oxidase (LOX) is a hypoxia-induced secreted protein involved in many stages of metastasis. LOX contributes to early-stage metastasis by increasing tumor cell invasion through the cross-linking of collagens in the ECM, which stimulates integrin-mediated cell-matrix adhesion and activation of focal adhesion kinase. LOX is expressed at the leading edge on invasive cells and extends along hairlike fibers in the ECM. Collagen cross-linking additionally provides a route ("highway") by which tumor cells may travel. LOX secreted by hypoxic cells in the primary tumor is involved in premetastatic niche formation at distant sites. Furthermore, LOX is involved in later stages of metastasis where cell-matrix adhesion interactions are again required for arrest and extravasation, and invasive migration. LOX is further required for the formation of a mature ECM, which is essential for metastatic tumor cell growth.

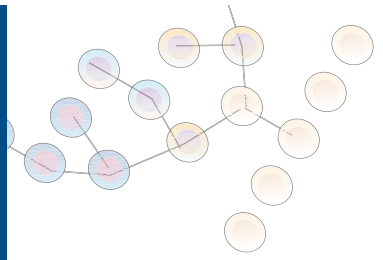
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4 Control of the Cell Cycle

Jacqueline Lees

SUMMARY OF KEY POINTS

- Cells in most postnatal tissues are quiescent. Exceptions include cells of the hematopoietic system, skin, and gastrointestinal mucosa.
- The key challenges for proliferating cells are to make an accurate copy of the 3 billion bases of DNA (S phase) and to segregate the duplicated chromosomes equally into daughter cells (mitosis).
- Progression through the cell cycle is dependent on both extrinsic and intrinsic factors.
- Extrinsic factors include cell-to-cell contact, basement membrane attachments, and growth factor or cytokine exposure.
- The internal cell cycle machinery is controlled largely by oscillating levels of cyclin proteins and by modulation of cyclin-dependent kinase activity.
- One way in which growth factors regulate cell cycle progression is by affecting the levels of the D-type cyclins in the G_1 phase of the cell cycle.
- The restriction point of the cell cycle occurs in late G_1 and is the point beyond which the cell is committed to progress through the rest of the cell cycle. It is governed by a known tumor suppressor, the retinoblastoma protein.
- Cell cycle checkpoints are surveillance mechanisms that link the rate of cell cycle transitions to the timely and accurate completion of prior dependent events.
- Cells can arrest at cell cycle checkpoints temporarily to allow for (1) the repair of cellular damage; (2) the dissipation of an exogenous cellular stress signal; or (3) availability of essential growth factors, hormones, or nutrients.
- The major function of the p53 tumor suppressor protein is to induce cell cycle arrest, senescence, or death in response to cellular stress.
- Activation of the G_1, S, and G_2 phase checkpoints after DNA damage minimizes replication of damaged DNA templates or their segregation to daughter cells.
- Activation of the mitotic spindle checkpoint prevents defects in chromosome segregation and protects against aneuploidy.
- Disruption of cell cycle controls is a hallmark of all malignant cells. Disruption can manifest as alterations of growth factor signaling pathways, dysregulation of the core cell cycle machinery, and/or disruption of cell cycle checkpoint controls.
- Because cell cycle control is disrupted in virtually all tumor types, the cell cycle-related gene products that are mutated in tumors provide therapeutic targets that might preferentially affect tumor cells more than normal tissues.

INTRODUCTION

The majority of the cells in the adult body are arrested in a quiescent state, called the G_0 state. Most of these cells are terminally differentiated and never divide. However, specific populations retain the ability to proliferate throughout the adult life span, and this is essential for viability. For example, cells of the hematopoietic compartment and the gut have a high rate of turnover, and high rates of proliferation are therefore essential for the maintenance of these tissues. On average, about 2 trillion cell divisions occur in an adult human every 24 hours (about 25 million per second). The decision to proliferate or not is very tightly regulated. It is influenced by a variety of exogenous signals, including nutrients, mitogenic (e.g., epidermal growth factor and platelet-derived growth factor) and inhibitory (e.g., transforming growth factor-β) growth factors, and the interaction of the cell with its neighbors and with the underlying extracellular matrix. Each of these factors stimulates intracellular signaling pathways that can either promote or suppress proliferation. The cell integrates all of these signals, and if the balance is favorable, the cell will initiate the proliferation process. Anything that disrupts this balance can lead to either the reduction or expansion of a particular cell population. It is now clear that such changes are a hallmark of tumor cells. They carry mutations that impair signaling pathways that suppress proliferation and/or activate pathways that promote proliferation.

It is essential that proliferating cells copy their genomes and segregate them to the daughter cells with high fidelity. Over the past three decades, extensive effort has been placed on unraveling the basic molecular events that control this process. Studies in a variety of organisms have identified evolutionarily conserved machinery that controls eukaryotic cell cycle transitions through the action of key enzymes called cyclin-dependent kinases (CDKs). Eukaryotic cells have also evolved a series of surveillance pathways, termed *cell cycle checkpoints*, that monitor for potential problems during the cell cycle process. Human cells are continuously exposed to external agents (e.g., reactive chemicals and ultraviolet light) and to internal agents (e.g., by-products of normal intracellular metabolism, such as reactive oxygen intermediates) that can induce DNA damage. The cell cycle checkpoints detect DNA damage and activate cell cycle arrest and DNA repair mechanisms, thereby maintaining genomic integrity. Most, if not all, human tumor cells have mutations within key components of both the cell cycle machinery and checkpoint pathways. This has important clinical implications, as the presence of these defects can modulate cellular sensitivity to chemotherapeutic regimens that induce DNA damage. This chapter focuses on the

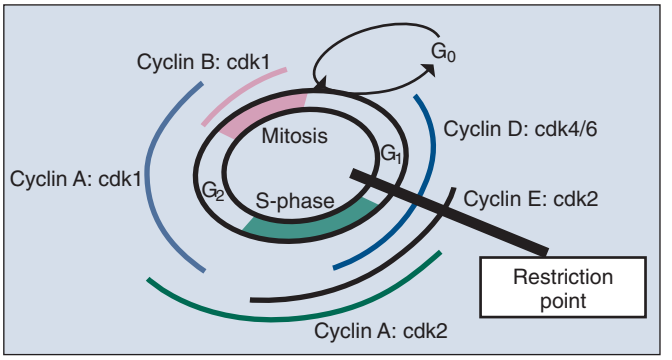


Figure 4-1 • The cell cycle. One round of cell division requires high-fidelity duplication of DNA during the S phase of the cell cycle and proper segregation of duplicated chromosomes during mitosis, or M phase. Before and after the S phase and M phase, the cell transits through "gap" phases, termed G_1 and G_2. The appropriate transition through these stages is controlled by the action of specific cyclin/CDK complexes.

mechanics of the cell cycle and checkpoint-signaling pathways and discusses how this knowledge can lead to the efficient use of current anticancer therapies and to the development of novel agents.

CELL CYCLE MACHINERY

Overview of Cell Cycle Phases

Cell proliferation proceeds through a well-defined series of stages (Fig. 4-1). First, the cell moves from the quiescent G_0 state into the first gap phase, or G_1, in which the cell is essentially readying itself for the cell division process. This involves a dramatic upregulation of both transcriptional and translational programs not only to yield the proteins that are required to regulate cell division but also to essentially double the complement of macromolecules so that one cell can give rise to two cells without a loss of cell size. This protein synthesis phase is frequently referred to as cell growth. Not surprisingly, this takes a significant amount of time (anywhere from 8 to 30 hours) and energy. Studies with cultured cells show that mitogenic growth factors are essential for continued passage through G_1. Specifically, if growth factors are withdrawn at any point during this phase, the cell will not divide. However, as it nears the end of G_1, the cell passes through a key transition point, called the *restriction point*, at which it becomes growth factor independent and is fully committed to undergoing cell division. Within an hour or two, the cell enters the synthesis phase, or S phase, in which each of the chromosomes is replicated once and only once. The cell then enters a second gap phase, called G_2, which lasts 3 to 5 hours, and then initiates mitosis, or M phase, in which the chromosomes are segregated. On completion of mitosis, the daughter cells can enter quiescence or initiate a second round of cell division, depending on the milieu.

Cyclin and Cyclin-Dependent Kinase Complexes

The CDKs constitute a large subfamily of highly conserved ser/thr kinases that are defined by their dependence on a regulatory subunit, called a cyclin.[1,2] Only a subset of these CDKs are specifically involved in cell cycle regulation. Yeast use a single CDK for cell cycle control that is called cdc2 in *Schizosaccharomyces pombe* and cdc28 in *Saccharomyces cerevisiae*. In contrast, mammals employ multiple CDKs.[3] The first identified human CDK, called CDK1 (originally *cdc2*), was cloned by virtue of its ability to complement a mutant *cdc2* yeast strain.[4] Subsequent studies identified additional human CDKs and determined that they regulate distinct cell cycle stages; CDK4 and CDK6 regulate passage through G_1, CDK2 regulates the G_1-to-S transition and S phase, and CDK1 controls G_2 and mitosis. The activity of these kinases is controlled by multiple regulatory mechanisms.[5,6] Most important, the CDKs act in association with a cyclin subunit that binds to the conserved PSTAIRE helix within the kinase.[3,5] Cyclin binding causes a reorientation of residues within the active sites that is essential for kinase activity.[3] The associated cyclin also determines the substrate specificity of the resulting cyclin-CDK complex. The cyclins are quite divergent, especially in their N-terminal sequences, but they all share a highly conserved 100-amino-acid sequence, called the *cyclin box*, that mediates CDK binding and activation. As their name implies, cyclins were originally identified as proteins whose expression was restricted to a particular stage of the cell cycle.[7] This is due to cell cycle-dependent regulation of both cyclin gene transcription and protein degradation. Notably, there is frequently a delay between the formation of a particular cyclin/CDK complex and the appearance of kinase activity (Fig. 4-2). This reflects considerable post-translational regulation of the cyclin/CDK complex.[8–11] First, kinase activation is absolutely dependent on phosphorylation of a threonine residue that is adjacent to the active site (thr 160 in CDK2). This is catalyzed by a kinase, called CDK-activating kinase (CAK).[11–13] In mammalian cells, phosphorylation occurs after cyclin binding. Although there appear to be at least two

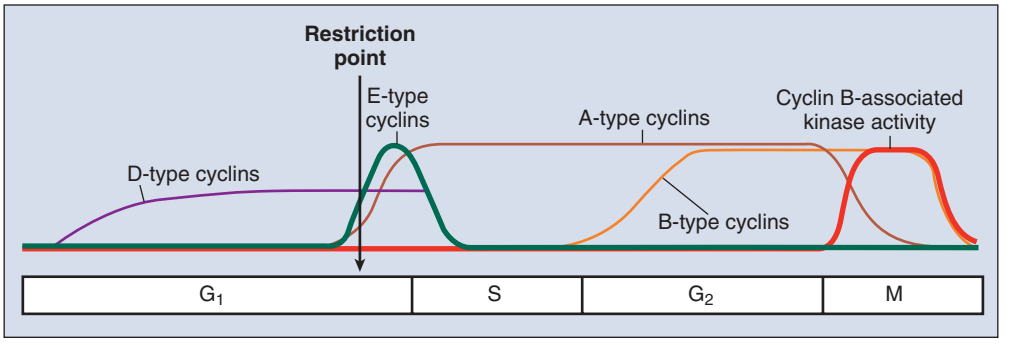


Figure 4-2 • The expression of the cyclin subunits in tightly linked to cell cycle phases. Extracellular stimuli, such as mitogenic growth factors and hormones, induce the expression of the D-type cyclins early in G_1. Cyclin E expression occurs late in G_1, synonymous with the restriction point, and its levels peak at the G_1-to-S transition and then decline during S phase. Cyclin A is induced a little later than cyclin E and is degraded at the metaphase of mitosis. The B-type cyclins are expressed primarily in G_2, and the levels remain high until the anaphase of mitosis. There is typically a delay between the expression of the cyclin protein and the appearance of cyclin-associated kinase activity that results from post-translational regulation. This is most pronounced in the case of cyclin B, for which activation of the cyclin B/CDK1-associated kinase activity does not occur until the G_2-to-M transition.

mammalian CAKs, the major CAK is a trimolecular complex composed of CDK7, cyclin H, and Mat1.[12–14] This kinase is constitutively active, and to date, there is no evidence that it is cell cycle regulated. Indeed, the CDK7-cyclinH-Mat1 complex is also required for the control of basal transcription via regulation of RNA polymerase II function.[12,15] Second, when it is first formed, the cyclin/CDK complex is frequently subject to inhibitory phosphorylation of Thr-14 and Tyr-15 residues within the CDK's active site by the Wee1 (Tyr-15) and Myt1 (Thr-14 and Tyr-15) kinases.[9] Activation of the cyclin/CDK complex is now dependent on the action of a dual-specificity phosphatase called Cdc25.[10] Mammalian cells have three different Cdc25 proteins, called Cdc25A, Cdc25B, and Cdc25C, which show some specificity for different cyclin/CDK complexes.[10]

The mammalian cyclins are divided into four distinct classes—D-type cyclins, E-type cyclins, A-type cyclins, and B-type cyclins—on the basis of both their sequence homology and the stage of the cell cycle at which they act (see Figs. 4-1 and 4-2).[16] Each of these classes has two or three paralogs (cyclin D1, D2, and D3; cyclin E1 and E2; cyclin A1 and A2; and cyclin B1 and B2). The relative roles of these paralogs are still unclear. In some cases, differences exist (e.g., in subcellular localization) that suggest that particular paralogs will have distinct activities or regulation. However, other studies (particularly the analysis of mouse models) show that there is considerable functional redundancy, or at least an ability to substitute for one another, between paralogs of a particular cyclin type.[17,18] For simplicity, we will focus largely on the core properties of the cyclin types.

The D-type cyclins represent an unusual class of cyclins.[16,19] First, they do not participate the cell division process itself. Instead, they play a critical role in determining whether a cell will divide under the direction of external cues. Second, their expression is not really cell cycle regulated; D-type cyclins are present at very low levels in quiescent cells, in large part because they are phosphorylated by an abundant G_0 kinase called GSK3β and then exported to the cytoplasm for degradation, but their expression is induced during G_1, and it persists through all subsequent cell cycle stages.[20] This G_1 induction is a direct consequence of mitogenic signaling. This inhibits expression of GSK3β and activates transcription of the D-type cyclins. Notably, individual mitogenic signaling pathways induce different D-type cyclins. For example, signaling by EGF/ras (via the AP-1 transcription factor) and Wnt/β-catenin (via the Tcf/Lef transcription factor) specifically induces cyclin D1, while c-myc specifically induces cyclin D2.[21–26] This specificity helps to ensure that the presence of multiple proproliferative signals gives rise to more D-type cyclins than a single mitogen does. Importantly, the analysis of mouse models shows that cyclins D1, D2, and D3 are functionally redundant; the key factor appears to be the total level of D-type cyclin that is present in the cell.[27] This promotes cell cycle entry through two distinct mechanisms. First, the D-type cells titrate inhibitory molecules, called CDK inhibitors, away from other CDK-kinase complexes and thereby promote their activation.[5,28,29] Second, cyclins D1, D2, and D3 associate with CDK4 and CDK6, and the resulting complexes phosphorylate the retinoblastoma protein (pRB), a key gatekeeper for cell cycle reentry.[30–34] We will discuss both the CDK inhibitors and pRB in more detail later because of their central importance in controlling cell cycle reentry and their frequent disruption in cancer.

E-type cyclins are expressed during late in G_1 under the control of the E2F transcription factors.[35,36] Cyclin E binds specifically to CDK2, and the resulting complex is required for cells to move through the G_1-to-S transition.[37–39] To date, several cyclin E/CDK2 substrates have been identified. Some cyclin E/CDK2 substrates play a positive role in cell cycle progression. For example, cyclin E/CDK2 phosphorylates NPAT, a transcription factor that mediates transcriptional activation of histone gene clusters.[40–42] The resulting increase in histone pools is essential for the appropriate packaging of newly replicated DNA in S phase cells. Cyclin E/CDK2 also induces the duplication of centrosomes that is required for formation of the mitotic spindle.[43–46] Other cyclin E/CDK2 substrates are key cell cycle inhibitors. First, cyclin E/CDK2 phosphorylates pRB at completely different sites from those that have already been modified by the cyclin D/CDK4/6 kinases, and this is sufficient to inactivate pRB's growth suppressive function.[31,34,47] Second, cyclin E/CDK2 phosphorylates the CDK inhibitor p27 on Thr-187.[48,49] This creates a high-affinity binding site for a ubiquitin ligase, called SCF, which plays a very important role in G_1/S control.[50–53] SCF has three core components: a RING finger protein, called Rbx1, which recruits the E2-ubiquitin conjugate; a cullin (Cul1); and Skp1 (Fig. 4-3).[52–54] Skp1 acts to recruit a family of proteins, called F-box proteins, that determine the target specificity of the SCF complex (see Fig. 4-3). In the case of p27, the F-box

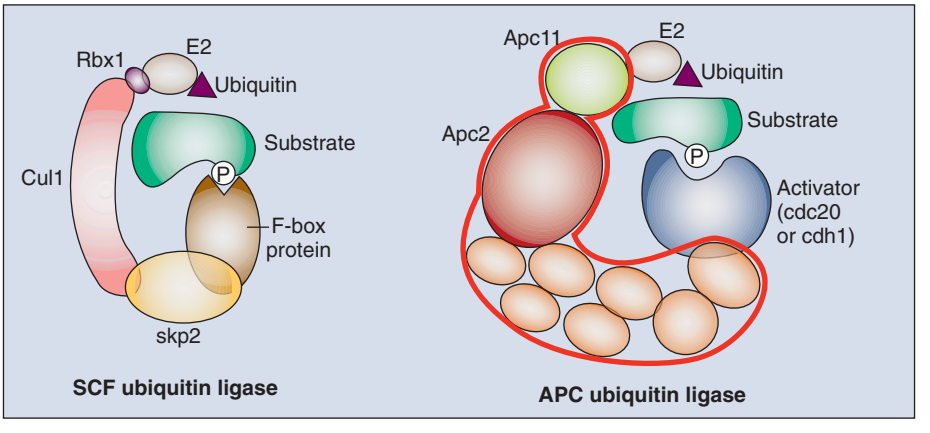


Figure 4-3 • Ubiquitin ligases. The SCF and APC ubiquitin ligases play a key role in enabling forward passage through key cell cycle transitions. These are both large complexes that include three core components: a scaffolding protein called a cullin, a protein that recruits the E2 and its associated ubiquitin molecule, and a specificity factor (called the F-box protein in SCF and the activator in APC) that recruits the substrate. SCF and APC catalyze polyubiquitination of their substrates, and this acts as a signal for substrate degradation by the 26S proteasome. SCF has numerous substrates whose degradation promotes passage through the early stages of the cell cycle, including $p27^{Kip1}$ (the restriction point) and cyclin E, E2F-1, and Cdt1 (S-phase). APC is essential for completion of mitosis (by promoting degradation of securin and the mitotic cyclins) and to allow origin licensing (by promoting degradation of geminin and thereby allowing accumulation of cdt1 during G_1).

protein is Skp2, and the SCF complex is therefore designated as SCF^{Skp2}.[55,56] Once SCF binds its substrate, it transfers a ubiquitin molecule to lysine residues within the target protein and subsequently to lysine residues in the ubiquitin molecule to create a polyubiquitin chain.[54] This polyubiquitin chain targets the substrate to the proteasome for degradation.[54] Notably, SCF is also responsible for the decline in cyclin E/CDK2 levels that is activated during S phase (see Fig. 4-2). First, cyclin E/CDK2 actually phosphorylates itself on multiple sites, creating a recognition site for $SCF^{Fbw7/Cdc4}$ and thereby ensuring its own destruction.[57,58] Second, cyclin A/CDK2 (the S phase kinase) phosphorylates E2F-1, the transcription factor that activates cyclin E transcription, and this is targeted for degradation by SCF^{Skp2}.[59–61] Together, these mechanisms restrict the action of cyclin E/CDK2 to a small window in the cell cycle.

The A-type cyclins are first transcribed during late G_1 under the control of the E2F transcription factors in a similar manner to that of cyclin E. However, in contrast to cyclin E, cyclin A associates with both CDK2 and CDK1 and it acts at two distinct cell cycle stages.[62,63] First, cyclin A/CDK2 is absolutely required for S phase progression. This was established by showing that injection of either cyclin A antisense constructs or antibodies was sufficient to block S phase progression.[62,64] Notably, cyclin A/CDK2 enters the nucleus at the start of S phase, and it is specifically localized at nuclear replication foci and therefore is thought to be actively involved in the firing of replication origins.[65] As was described previously, cyclin A/CDK2 is also required to phosphorylate E2F-1 and mediate its degradation, and this is required to prevent E2F1 from triggering apoptosis.[59–61] Second, cyclin A/CDK1 complexes act during G_2 and at the beginning of mitosis.[62] Here, they are thought to play a key role in initiating the condensation of chromatin and might also participate in the activation of the cyclin B/CDK1 complexes. Cyclin A/CDK2 is destroyed in the prometaphase of mitosis through the action of another ubiquitin ligase, called *anaphase-promoting complex* (APC).[66] APC is a much larger complex that SCF, but it also contains a RING finger protein, called Apc11, to recruit the E2-ubiquitin conjugate, a core cullin subunit (Apc2), and it binds a variety of activators that are required for APC activity and, in a manner comparable to that of the F-box proteins of SCF, establish substrate specificity (see Fig. 4-3).[54,66] In the case of cyclin A/CDK2, the activator is CDC20, and the APC complex is therefore designated as APC^{Cdc20}.

There are two B-type cyclins, B1 and B2, which show significant differences in their subcellular localization. The analysis of mutant mouse models shows that cyclin B2 loss has no detectable effect on development, while cyclin B1 is absolutely required for embryogenesis.[67] This indicates that cyclin B1 is the major B-type cyclin in vivo; therefore, we will restrict our discussion to this isoform. Cyclin B1 protein first appears at the beginning of G_2. It accumulates steadily through G_2 and associates specifically with CDK1.[63] However, the resulting cyclin B1/CDK1 complex is mostly sequestered in the cytoplasm, and it is retained in an inactive form throughout G_2 via the inhibitory phosphorylation of Thr-14 and Tyr-15 in CDK1's active site by the Myt1 and, to a lesser extent, Wee1 kinases.[68–70] Activation of cyclin B1/CDK1 occurs in a highly synchronous manner during the first stage (called prophase) of mitosis (see Fig. 4-2).[71] This activation is mediated by two changes. First, the activities of myt1 and wee1 are dramatically downregulated at the transition between G_2 and M. Second, there is a dramatic increase in the activity of the Cdc25A and C phosphatases that relieves the inhibitory phosphorylation of Thr-14 and Tyr-15.[10] These activity changes are triggered by the phosphorylation of Myt1, Wee1, Cdc25A, and Cdc25C. Three different kinases are thought to contribute to this phosphorylation: polo-like kinase, cyclin A/CDK1, and cyclin B1/CDK1 itself. The involvement of cyclin B1/CDK1 creates a powerful feedforward loop; once a small amount of cyclin B1/CDK1 is activated, it simultaneously inactivates its own inhibitors and activates its activators, enabling a rapid transformation of the entire cyclin B1/CDK1 pool from the inactive state to the active state. Once active, cyclin B1/CDK1 phosphorylates components of the centrosomes and initiates a process called *centrosome separation*, in which the centrosomes move to opposing poles of the nascent spindle, an event that is essential for formation of the mitotic spindle.[72] Cyclin B1/CDK1 then translocates across the nuclear membrane (which is still intact at this point in the mitosis) to orchestrate mitotic events.[73] Notably, cyclin B1/CDK1 is degraded at the end of metaphase (see Fig. 4-2).[74] This is triggered by the ubiquitination of cyclin B1 by the ubiquitin ligase APC and its subsequent recognition and degradation by the proteosome.[66,75,76] This downregulation of mitotic CDKs is required for cytokinesis (the separation of the daughter cells) and reentry into G_0/G_1.[74]

Cyclin-Dependent Kinase Inhibitors

The CDK inhibitors (CDKIs) play a key role in establishing the activity of the cyclin/CDK complexes in response to either external signals or internal stresses.[5] The CDKIs can be divided into two distinct families based on their biological properties. The first CDKI family is named INK4, based on their roles as inhibitors of CDK4. The INK4 family has four members called $p16^{INK4a}$, $p15^{INK4b}$, $p18^{INK4c}$, and $p19^{INK4d}$. These INK4 proteins specifically target CDK4 and CDK6 and not other CDKs. They preferentially target the monomeric CDK and prevent cyclin binding. Consistent with their inhibitory role, the alterations in the *INK4* genes are observed in human tumors.[77] *Ink4a* appears to be most the most frequently affected; it was identified as a tumor suppressor that is associated with familial melanoma, and it is inactivated by point mutation, deletion, and/or promoter methylation in approximately 30% of all human tumors.[78,79] In contrast, point mutations in $p15^{INK4b}$, $p18^{INK4c}$, and $p19^{INK4d}$ are rare, but promoter methylation of *Ink4c* has been detected in Hodgkin lymphomas and medulloblastomas, and reduced $p18^{INK4c}$ protein expression has been seen in a variety of tumor types.[80–84]

The second CDKI family is named CIP/KIP and includes three members: $p21^{Cip1}$ (also called $p21^{Waf1}$), $p27^{Kip1}$, and $p57^{Kip2}$.[5] These CIP/KIP proteins have two major activities. First, they associate with, and inhibit the activity of, the G_1/S and S phase kinases cyclin E/CDK2 and cyclin A/CDK2. Second, $p21^{Cip1}$ and $p27^{Kip1}$ bind to the D-type cyclins outside of the CDK binding site and actually promote assembly of cyclin D/CDK4/6 complexes.[85] These two activities are clearly paradoxical. However, they are critical in establishing how the cell decides whether or not to divide in response to external signals. In general, the expression and/or activity of CDKIs is promoted by growth suppressive signals and inhibited by pro-proliferative signals. For example, the inhibitory growth factor transforming growth factor-β induces transcription of $p15^{INK4b}$, while several mitogenic signaling pathways cause Akt to phosphorylate $p21^{Cip1}$ and $p27^{Kip1}$ and induce their cytoplasmic sequestration.[86–90] Importantly, signaling pathways have the opposite effect on the D-type cyclins: Growth suppressive signals inhibit their expression and activity while mitogens are activating. The opposing regulation of CDKIs and D-type cyclins controls cell cycle entry by creating a tipping point (Fig. 4-4). G_0/G_1 cells have low levels of D-type cyclins and high levels of CDKIs; thus, cell cycle entry is blocked. However, an increase in mitogenic signals boosts the levels of cyclin D, and this eventually exceeds the level of INK4 proteins, which are simultaneously declining. At this point, the D-type cyclins begin to bind to the CIP/KIP proteins. This helps the D-type cyclins to assemble into active cyclin D/CDK4/6 complexes and draws the CIP/KIP proteins away from the cyclin E/CDK2 complexes as they begin to accumulate. The cyclin D/CDK4/6 and cyclin E/CDK2 complexes cooperate in the phosphorylation and inactivation of the pRB protein. This appears to be the tipping point in commitment to cell cycle entry.

pRB Tumor Suppressor

The retinoblastoma protein (pRB) was originally identified by virtue of its association with hereditary retinoblastoma protein.[91] It behaves

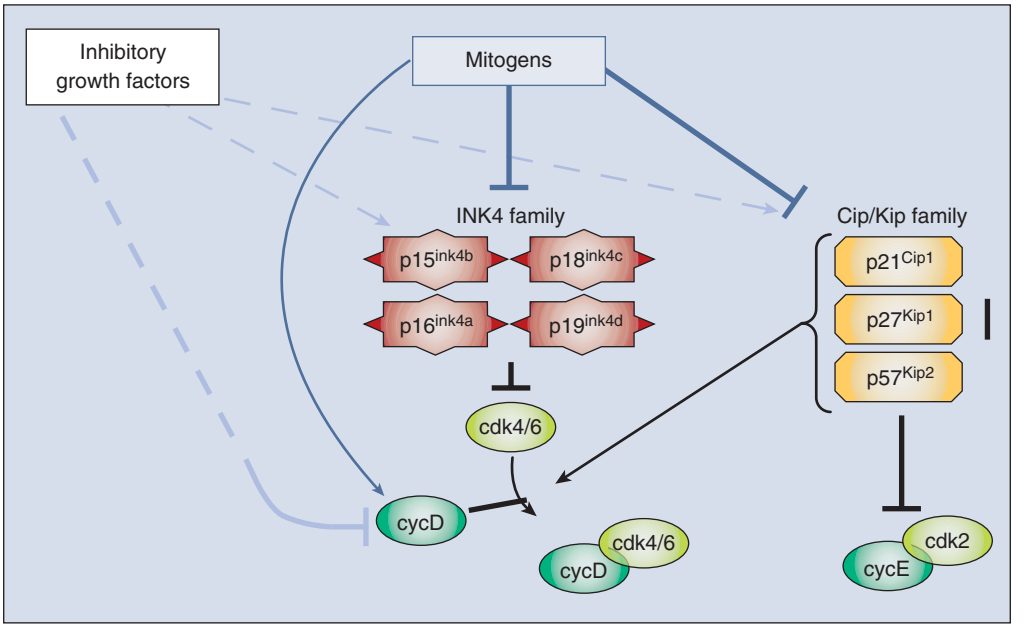


Figure 4-4 • The CDK inhibitors (CDKIs) play a key role in regulating the G_1-to-S transition. The levels of nuclear INK4 and Cip/Kip CDKIs are typically elevated by growth inhibitory stimuli and reduced by mitogenic stimuli. The INK4 family members bind specifically to CDK4 and CDK6 and inhibit their association with cyclin D. The Cip/Kip CDKIs interact with both the cyclin and CDK components and have highest affinity with the intact cyclin–CDK complex. Cip/Kip binds in a different way to cyclin D versus cyclin E complexes, and this has opposing effects on their activity. Cip/Kip binding enables formation of active cyclin D–CDK4/6 complexes. In contrast, Cip/Kip associates with cyclin E–CDK complexes and blocks their activity. Cyclin D complexes have a higher affinity for Cip/Kip than do cyclin E complexes. The mitogen-induced accumulation of D-type cyclins during G_1 titrates Cip/Kip from cyclin E–CDK2 and facilitates activation of both cyclin D–CDK4/6 and cyclin E–CDK2 kinases. Cyclin E–CDK2 can also phosphorylate p27 to promote its ubiquitin-mediated degradation.

as a classic tumor suppressor: Affected individuals inherit a germline mutation within one *Rb-1* allele, and loss of heterozygosity is seen in all of the tumors. Subsequent studies showed that the transforming ability of small DNA tumor viruses, including human papilloma virus, adenovirus, and simian virus, was dependent on the ability of virally encoded oncoproteins (E7, E1A, and SV40, respectively) to bind and inhibit pRB.[92] Moreover, the *RB-1* gene was found to be inactivated in approximately one third of all sporadic human tumors.[91] Thus, pRB is a major human tumor suppressor.

To date, numerous pRB-associated proteins have been identified.[93] However, studies in mouse models indicate that pRB's tumor suppressive activity is largely dependent on its ability to prevent cell cycle entry through inhibition of the E2F transcription factors.[94–96] The E2F proteins regulate the cell cycle-dependent transcription of numerous targets, including core components of the cell cycle control (e.g., cyclin E and cyclin A) and DNA replication (e.g., cdc6, CDT1, and the MCM proteins) machineries.[47,97–99] pRB regulates E2F through two distinct mechanisms. First, its association with E2F is sufficient to block its transcriptional activity.[100] Second, the pRB-E2F complex can recruit histone deacetylases (HDACs) to the promoters of E2F-responsive genes and thereby actively repress their transcription.[101–103] Cell cycle entry requires the sequential phosphorylation of pRB by cyclin D/CDK4/6 and cyclin E/CDK2 complexes and the consequent dissociation of pRB from E2F.[34,47,104] Importantly, tumors that retain wild-type pRB almost always carry activating mutations in *cyclin D1* or *CDK4* or inactivating mutations in the CDK4-inhibitor, *p16*.[104] This suggests that the functional inactivation of pRB, and the resulting deregulation of E2F, is an essential step in tumorigenesis.

Studies to date have identified eight *E2f* genes that encode nine different E2F proteins.[99] pRB and its relatives p107 and p130 (collectively called the pocket proteins) regulate a subset of the E2Fs: E2F1, E2F2, E2F3a, E2F3b, E2F4, and E2F5. These E2F proteins associate with a dimerization partner, called DP, and the resulting complexes function primarily as either activators (E2F1, E2F2, and E2F3a) or repressors (E2F4 and E2F5) of transcription under the direction of the pocket proteins.[47] Most classic E2F target genes are regulated by the coordinated action of these repressor and activator E2Fs (Fig. 4-5). In G_0/G_1 cells, the DP-E2F4 and DP-E2F5 complexes associate with the promoters of E2F-responsive genes and recruit p107 and p130, along with their associated HDACs, to actively repress their transcription.[105,106] At the same time, the activating E2Fs are bound by pRB, inhibiting their potential to activate transcription. Whether complexes containing pRB and activating E2Fs contribute to the repression of E2F target genes is still unclear.[107] In response to mitogenic signaling, CDK activity increases, and the phosphorylation of the pocket proteins causes them to release their associated DP-E2Fs. E2F4 and E2F5 dissociate from the DNA and translocate to the cytoplasm because they have potent nuclear export signals.[108,109] The free E2F complexes—DP-E2F1, DP-E2F2, and DP-E2F3—now occupy the promoters and activate their transcription. Thus, in every cell cycle, there is a coordinated switch from the repressive to the activating E2Fs that enables the simultaneous activation of genes promoting cell cycle progression. Since *cyclin E* is itself an E2F-responsive gene, this regulation creates a strong feedforward loop: The appearance of a small amount of the cyclin E/CDK2 kinase promotes pRB inactivation and further cyclin E expression. This signal is further amplified by cyclin E/CDK2's ability to phosphory-

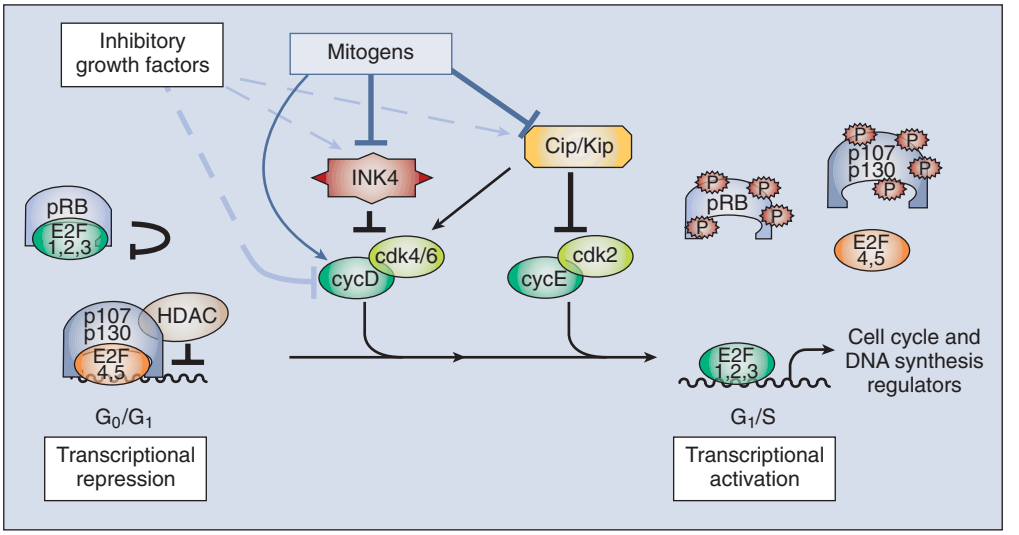


Figure 4-5 • The retinoblastoma protein (pRB) and the restriction point. The pocket proteins—pRB, p107, and p130—regulate a subset of the E2F family of transcription factors. The pocket proteins bind to these E2Fs during G_1 and suppress their activity through two mechanisms. First, pRB binds to E2F1, E2F2, and E2F3a (collectively called the activating E2Fs) and blocks their transcriptional activity. Second, p107 and p130 associate with E2F4 and E2F5 (together called the repressive E2Fs), and the resulting complexes recruit histone deacetylases (HDACs) to the promoters of E2F-responsive genes and actively repress their transcription. E2F-responsive genes encode core components of the cycle control and DNA replication machinery, and cell cycle entry is impossible without these products. Mitogenic signaling leads to the sequential activation of cyclin D–CDK4/6 and cyclin E/CDK2, and these phosphorylate the pocket proteins and release their associated E2Fs. This causes the repressive E2Fs to dissociate from E2F-responsive promoters and allows the activating E2Fs to bind and activate their transcription.

late p27 and signal its destruction. Importantly, pRB-inactivation is largely synonymous with the restriction point, defined as the point at which cells become committed to divide even in the absence of mitogenic stimuli.[110,111] Consistent with this model, the exogenous expression of any individual activating E2F in cell culture is sufficient to stimulate DNA synthesis in the absence of growth signals.[112–116]

DNA Replication

The DNA replication machinery is optimized to ensure that the genome is copied once—and only once—in each cell cycle.[117–120] This is achieved through a two-step process that first establishes a prereplication complex (pre-RC) at each origin of replication, a process that is frequently referred to as *origin licensing*, and subsequently transforms pre-RCs into the preinitiation (pre-IC) complex that activates DNA replication (Fig. 4-6). These two steps occur at distinct stages of the cell cycle to ensure that origins are only licensed once per cell cycle, and rereplication cannot occur. Pre-RC formation takes place during G_1. The first step in this process is the recruitment of the multiprotein complex called the *origin recognition complex* (ORC) to the origin DNA.[121,122] Although ORC binds a subset of genomic sites, there is no evidence that ORC exhibits sequence-specific DNA binding, and it is still unclear how ORC is recruited to specific sequences. Once bound, ORC recruits additional proteins including Cdc6, Cdt1, and finally the MCM complex, a helicase that is required to unwind the DNA strands to form the pre-RC. Once cells enter S phase, the transformation of the pre-RC to the pre-IC requires the activity of two kinases: a CDK (likely, but not yet proven, to be cyclin A/CDK2) and the Ddf4-dependent kinase, which is composed of the Dbf4 regulatory subunit and the Cdc7 kinase.[123,124] In mammals, the precise target(s) of these kinases is still unclear. However, the action of these kinases allows numerous additional proteins to associate with the pre-RC and form the pre-IC.[125] Assembly of the pre-IC is thought to trigger DNA unwinding by the MCM complex, recruitment of the DNA polymerases, and initiation of the replication process, frequently called origin firing.

The transformation of the pre-RC to the pre-IC can occur at different time points in S phase, depending on whether the origin fires early or late.[118–120] The system can tolerate this heterogeneity because the pre-RC is disassembled after firing and cannot reform until the subsequent cell cycle. This occurs through several mechanisms. The MCM complex travels with the replication fork in its role as the DNA helicase. There is also some evidence that phosphorylation of ORC1 reduces its ability to bind to origins. Finally, and most important, Cdt1 is prevented from participating in pre-RC formation outside of G_1 phase in two distinct ways. First, Cdt1 is marked for destruction by ubiquitination.[126] This is mediated by SCF^{Skp2} and particularly by an E4 ubiquitin ligase that includes Rbx1 (to recruit the E2-ubiquitin), a cullin (Cul4), Ddb1, and Dtl/Cdt2 (the substrate specificity factor).[127–129] Importantly, this Cul4-$Ddb1^{Dtl/Cdt2}$ complex functions independently of Cdt1 phosphorylation. Instead, Cdt1 is targeted only when proliferative cell nuclear antigen is present on the DNA, which occurs primarily as a consequence of the initiation of DNA replication.[130] Second, cells possess a protein called geminin that sequesters Cdt1 and prevents it from participating in pre-RC formation. Geminin is present specifically in S, G_2, and early M phase cells. However, the two major mitotic APC complexes, APC^{Cdc20} and APC^{Cdh1}, ubiquitinate geminin and thereby trigger its destruction. This creates a window between anaphase of mitosis and late G_1 (when APC^{Cdh1} is inactivated) in which geminin is absent and therefore Cdt1 is free to participate in pre-RC formation. The importance of both the Cul4-$Ddb1^{Dtl/Cdt2}$ complex and geminin is underscored by the finding that the loss of either one of these regulators is sufficient to trigger inappropriate Cdt1 accumulation and rereplication of the genome.[128,129,131,132]

Mitosis

The mitotic machinery is optimized to ensure that the replicated chromosomes are faithfully segregated to the daughter cells. This is achieved through the use of a specialized microtubule-based structure, the mitotic spindle, on which the original chromosomes and

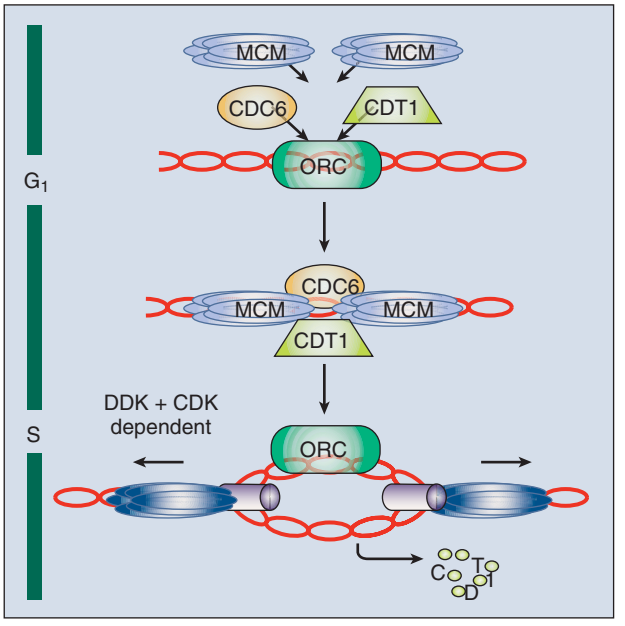


Figure 4-6 • Origin licensing and firing. The origin replication complex (ORC) associates with replication origins. During G_1, Cdc6 and Cdt1 are loaded on chromatin, and they in turn load the MCM complex on chromatin, at which point licensing is considered complete, and the multiprotein complex is called the pre-RC. Once cells pass the G_1-to-S transition, this complex is activated to form the pre-IC, and DNA replication is initiated. Activation requires both CDK and Ddf4-dependent kinase activity. It results in recruitment of numerous proteins and activation of the MCM complex, which unwinds the DNA. Subsequently, core components of the replication machinery, including DNA polymerase α and DNA polymerase ε, are recruited to initiation sites. The transition from pre-RC to pre-IC results in inhibition of cdt1 by ubiquitin-mediated degradation and geminin binding. Origin licensing cannot occur again until activation of APC at the end of mitosis allows accumulation of cdt1.

their newly replicated copies, called sister chromatids, align and are then partitioned to opposite poles of the cell. The appropriate side-by-side alignment of the sister chromatids, termed *biorientation*, is facilitated by the physical tethering of the sister chromatids to one another. This process, called *cohesion*, actually occurs in S phase in a manner that is coordinated with the replication process.[133,134] Cohesin is mediated by four proteins that together make up the cohesin complex. Two of these proteins, Smc1 and Smc3, have a long coiled-coil structure with a dimerization domain at one end that allows them to heterodimerize to form a V-like structure. Importantly, the remaining ends of Smc1 and Smc3 can associate with each another to form a functional ATP domain. This acts in an ATP-dependent manner to recruit two additional proteins, Scc1 and Scc3, that form a closed ring structure.[135] It is still unclear precisely how this ring links the sister chromatids; some investigators hypothesize that the cohesin complex encircles the chromosomes; others argue that the ring (which is known to be approximately 50 nM) is too small to surround complex chromatin structures. Regardless of the mechanism, the cohesin complex links the sister chromatids at the centromeres and at periodic intervals along the arms. The sister chromatids are essentially strung out and become entangled. Consequently, the chromosome structure must be modified before segregation. This occurs toward the end of G_2 and the beginning of mitosis. Largely on the basis of morphologic features, mitosis is divided into five different stages—prophase, prometaphase, metaphase, anaphase, and telophase (Fig. 4-7)—prior to separation of the daughter cells or cytokinesis.

Prophase is essentially a preparative stage. One of the major events is the modification of the DNA. In a process called *resolution*, the sister chromatids are untangled via the action of topoisomerase II.[133,134] Resolution requires removal of the chromosome arm cohesin through phosphorylation of Scc3 by polo-like kinase and histone H3 by the aurora B kinase. Importantly, the cohesin complex at the centromere is somehow protected from this modification by a protein called shugosin (Sgo).[136] This is the glue that keeps the sister chromatids together until the appropriate point in mitosis. In addition to resolution, the sisters undergo condensation, essentially packaging into a more compact chromatin structure. This process involves two multimeric complexes, condensin I and II, which also contribute to sister chromatid resolution, and it requires phosphorylation by mitotic CDKs.[133,134] During prophase, the nuclear envelope is still intact; consequently, differences in subcellular localization of the condensin and CDK complexes allow only condensin II and cyclin A/CDK1 (nuclear), and not condensin I and cyclin B/CDK1 (cytoplasmic), to initiate condensation. The second major event in prophase is the activation of the cytoplasmic cyclin B1/CDK1. This initiates formation of the mitotic spindle by triggering the centrosomes, which are located in the cytoplasm and are already nucleating microtubules, to segregate to the opposite poles of the nascent spindle. The active cyclin B1/CDK1 complex then translocates into the nucleus. Once there, it phosphorylates components of the nuclear envelope and triggers its breakdown.[137,138] This defines the transition from prophase to prometaphase.

During prometaphase, the condensation process is accelerated because condensin I and cyclin B/CDK1 now have access to the DNA. The sister chromatids become attached to spindle microtubules through a structure called the *kinetochore*, which is assembled onto centromeric DNA.[139] Microtubules nucleated from the centrosomes attach to the kinetochore through a process called *search and capture*, in which individual microtubules grow and shrink until they contact and bind the kinteochore.[140] Typically, one sister chromatid of the pair attaches first, and this attachment is further stabilized through the recruitment of additional microtubules from the same pole of the mitotic spindle to create a kinetochore fiber: highly bundled microtubules bound to the kinetochore. The sister chromatids oscillate in the cell until the second sister chromatid is captured by microtubules emanating from the other pole. These oscillations continue until all of the chromosomes are properly aligned on the metaphase plate during metaphase.

Metaphase is defined as the point at which all of the chromosome pairs are fully condensed, attached to the mitotic spindle, and aligned at the center—termed the *metaphase plate*. The pulling of the kinetochore fibers toward the poles creates tension through the cohesin complex at the kinetochores that indicates that the sister chromatids have achieved appropriate biorientation. The cell constantly monitors the attachments of microtubules to the chromosomes, and the tension that is generated by microtubules on the kinetochores ensures that the sister chromatids are properly aligned at the metaphase plate.[141] This is one of several cell cycle checkpoints, called the *mitotic spindle checkpoint*, that we will describe in more detail in the following sections.

Anaphase is characterized by the segregation of the chromosomes. This event is controlled by the mitotic ligase APC^{Cdc20}.[75,76,141–144] APC^{Cdc20} ubiquitinates, and thereby triggers the degradation of, a protein called securin that exists to bind and inhibit a protease called separase. Once released, separase cleaves the Scc1 component of the cohesin complex. This opens the cohesin ring, unlinking the sister chromatids and allowing them to be pulled to opposite poles. The spindle poles then move farther apart to ensure that the chromosomes are fully segregated. APC^{Cdc20} also activates the ubiquitination and degradation of geminin, allowing accumulation of Cdt1 for origin relicensing in the subsequent G_1 phase, and the mitotic cyclins, allowing loss of CDK kinase activity. This latter event is critical to the completion of mitosis and cytokinesis.

During telophase, the mitotic spindle disassembles, leaving a single centrosome and a single set of chromosomes with each nascent

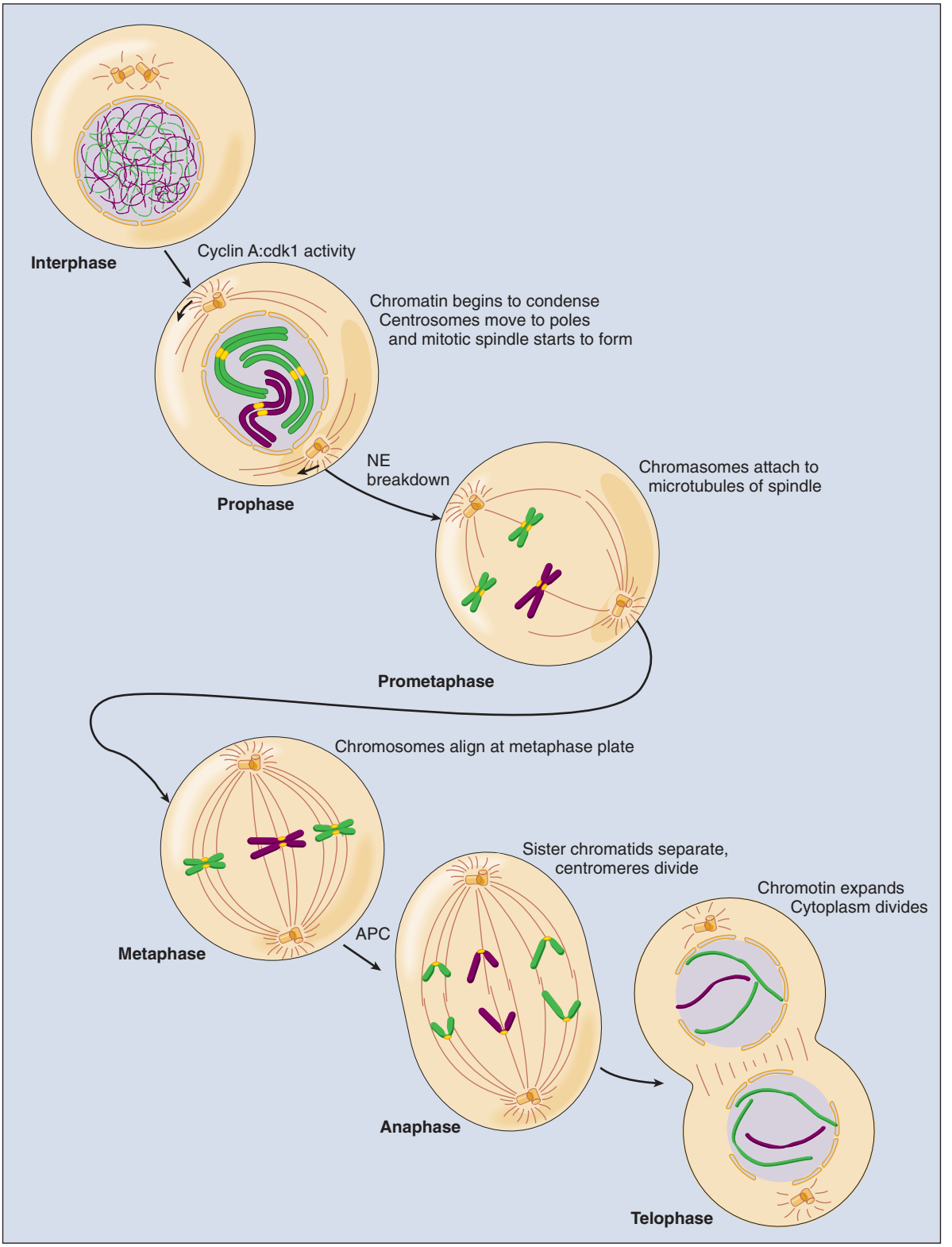


Figure 4-7 • Key stages of mitosis. As the parent cell enters prophase, the chromosomes begin to condense, and proteins associate to form the kinetochores. The centrosomes segregate to the poles to begin formation of the mitotic spindle. Nuclear envelope (NE) breakdown denotes the start of prometaphase. In this phase, the sister chromatids continue to condense, and they attach to spindle microtubules via their kinetochores. During metaphase, the sister chromatids align at the metaphase plate and eventually achieve appropriate biorientation. At the onset of anaphase, the sister chromatids separate and move toward the poles of the spindle. During telophase, the parent cell is divided into two daughter cells by cytokinesis.

daughter cell. As the DNA begins to decondense the nuclear envelope reforms around the segregated chromosomes to create two nuclei. These events are dependent on the loss of CDK kinase activity and the dephosphorylation of CDK substrates.

Finally, the cell undergoes cytokinesis, or cytoplasmic division. This involves formation of an actin- and myosin-containing structure, called the *contractile ring*, on the inner face of the cell membrane. The position of the contractile ring is carefully controlled. For most mammalian cells (ones that are not undergoing asynchronous division), the ring begins to form in anaphase and its position is established by the position of the metaphase plate. As the membrane grows, the contractile ring contracts steadily to form a constriction, termed the *cleavage furrow*, which ultimately separates the two nuclei and forms the two daughter cells. These cells can adopt either a G_0 or a G_1 state, depending on the extrinsic signals that exist.

CELL CYCLE CHECKPOINTS

At key transitions during eukaryotic cell cycle progression, signaling pathways monitor the successful completion of events in one phase of the cell cycle before proceeding to the next phase. These regulatory pathways are commonly referred to as *cell cycle checkpoints*.[145–147] In a broader context, cell cycle checkpoints are signal transduction pathways that link the rate of cell cycle phase transitions to the timely and accurate completion of prior dependent events. Checkpoint surveillance functions are not confined to monitoring normal cell cycle progression; they are also activated by both external and internal stress signals. To minimize the possibility of errors, checkpoints exist at four different points in the cell cycle: G_1/S, intra-S, G_2/M, and at the metaphase to anaphase transition (called the *spindle checkpoint*).

The best-studied of the cell cycle checkpoints are those that monitor the status and structure of chromosomal DNA during cell cycle progression.[147–149] In particular, cells scan the chromatin for partially replicated DNA as well as DNA strand breaks and other DNA lesions that can result from both extrinsic (e.g., chemicals, ionizing or ultraviolet radiation) and intrinsic (e.g., by-products of intracellular metabolism) DNA-damaging agents. The checkpoint pathways include sensor proteins that detect these DNA lesions and simultaneously trigger two processes: They recruit additional complexes to repair the DNA and activate signaling pathways that induce a temporary cell cycle arrest. In certain situations, which are determined by the cell type and the degree of damage, the checkpoint pathways can induce permanent cell cycle arrest (a process called *senescence*) or apoptosis.

The central components of the DNA damage response (DDR) are two members of the phosphoinositide 3-kinase-related kinase family: ATM and ATR.[147,148] ATM was original identified by virtue of its mutation in a hereditary syndrome, ataxia-telangiectasia, which is associated with radiation hypersensitivity and cancer predisposition.[150] ATR is also associated with a hereditary syndrome called Seckel syndrome. Early studies suggested that ATM and ATR played distinct roles in the response to double-stranded DNA breaks (ATM) versus replicative defects and single-stranded breaks (ATR). However, we now know that the regulation is more complex; there is considerable cross-talk between ATM and ATR, and they share many mediators and effectors, but the precise composition and role of the DDR complexes vary depending on both the type of the damage and the stage of the cell cycle.[151] In this chapter, we focus primarily on how the DDR activates cell cycle checkpoints (Fig. 4-8). However, it is important to note that many of the components of the core DDR machinery are affected in hereditary disease syndromes and/or

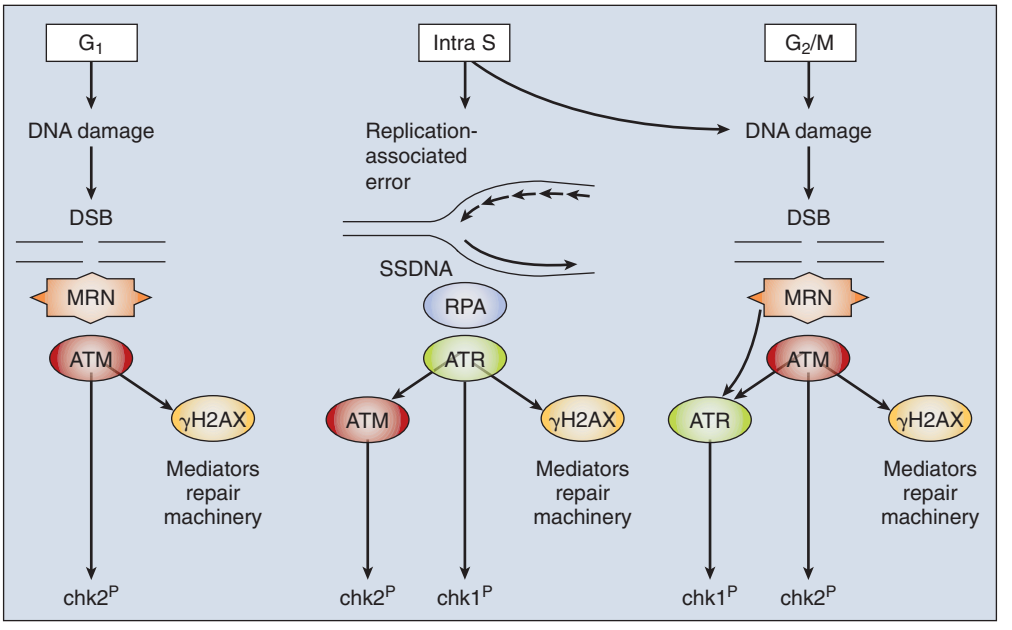


Figure 4-8 • ATM/ATR signaling is activated by DNA damage and replication stress. The cell constantly monitors the chromatin for lesions, using complex signal transduction pathways that center on the ATM and ATR kinases. The precise mechanism of response varies according to the type of DNA damage and the cell cycle stage. Double-stranded breaks (DSBs) are the most deleterious form of DNA damage. DSBs are recognized by the MRN complex that consists of Mre11, Rad50, and Nbs1. This complex recruits ATM to the site of damage. ATM phosphorylates histone H2AX, to form γH2AX, and this creates a binding platform for additional proteins that propagate the DNA damage response and activate repair. For S and G_2 phase cells, but not G_1 cells, ATR is also recruited to the damage site. ATR and/or ATM signal to their effector kinases—CHK1 and CHK2—respectively, to influence cell cycle progression as described in Figure 4-9. Errors in DNA replication can also activate the DNA damage response machinery through the presence of single-stranded DNA (ssDNA) that is a hallmark of the replication fork. The ssDNA is coated with RPA and bound by ATR. Active ATR then recruits the DNA damage and repair machinery, including ATM, leading to the sequential activation of CHK1 and then CHK2.

abrogated in human tumors (e.g., NBS1, BRCA1, BRCA2, and the Franconi's anemia proteins).

G_1/S Checkpoint

In G_1 cells, double-stranded DNA breaks (DSBs) are the most common and most deleterious type of DNA damage. These DSB breaks are recognized by the multifunctional Mre11-Rad50-Nbs1 (MRN) complex.[147] This complex recruits ATM to the site of damage. It is still unclear whether ATM activation occurs before or in response to MRN binding. The active ATM then recruits proteins to modify the chromatin at the region of the break and activate repair and signaling. As a first step in this process, ATM phosphorylates histone H2AX, to form γH2AX. This helps to hold the damaged ends together and acts as a binding platform for additional factors, including Mdc1, 53BP1, and BRCA1, as well as more MRN and ATM. In contrast to the S and G_2 response, there is no recruitment of ATR to DSB in G_1 cells; therefore, ATM is solely responsible for checkpoint activation. The recruitment of additional ATM amplifies the signal, and ATM acts via phosphorylation and activation of the effector kinase CHK2.[152,153]

CHK2 influences G_1 cell cycle arrest via two mechanisms (Fig. 4-9). First, it phosphorylates all three members of the Cdc25 family. Phospho-Cdc25A is ubiquitinated by the $SCF^{Trcp\beta}$ and degraded, while phospho-Cdc25B and phospho-Cdc25C are bound and sequestered by a cytoplasmic protein called 14–3-3.[10,154,155] This is a rapid response that can take effect within minutes after DNA damage, and it has a widespread effect on cell cycle progression by preventing activation of all CDK2 and CDK1 complexes. In the case of the G_1/S checkpoint, cyclin E/CDK2 is the relevant target. Second, CHK2 phosphorylates p53, a critical regulator of cell cycle checkpoints.[156] In normal, nonstressed cells, p53 protein is maintained at low steady-state levels because it has a very short half-life. This half-life is a result of rapid ubiquitination of p53 by HDM2 (the human ortholog of murine MDM2 protein) and its consequent degradation. The importance of MDM2 for maintenance of appropriate p53 levels in vivo is highlighted by the fact that absence of MDM2 in knockout mice results in early embryonic lethality that is rescued by a dual knockout of MDM2 and p53.[157] Phosphorylation of p53 by CHK2 is sufficient to prevent its association with HDM2/MDM2.[158] This leads to an accumulation of p53, which functions as a transcriptional activator. p53 induces expression of many genes. One of the key targets for the G_1/S (and also G_2/M) checkpoint is the CDK inhibitor $p21^{Cip1}$.[159,160] This p53-mediated arrest takes longer to develop than Cdc25 response (because it requires transcription and protein synthesis) but appears to be much more robust. Moreover, in addition to inducing cell cycle arrest, p53 has the capacity to induce apoptosis through the transcriptional activation of proapoptotic regulators (e.g., the BH3-only proteins PUMA and NOXA).[161] How p53 chooses to activate arrest versus apoptosis targets is not fully understood, but it is clearly influenced by both the cell type and the level of damage.[161]

Importantly, p53 is also activated by other stress signals (see Fig. 4-9). In particular, it is now well established that numerous oncogenes trigger a stress response (called *oncogene-induced stress*) that leads to the activation of p53.[162–165] The emerging view is that this occurs through two distinct mechanisms. First, oncogene activation is thought to yield replicative stress that activates p53 via activation of CHK kinases and phosphorylation of HDM2/MDM2 as just described.[166,167] Second, many oncogenes activate transcription of *Arf*.[168] This gene is encoded by the *INK4a/Arf* locus, and it actually shares two coding exons, which are read in alternate reading frames (hence the name ARF), with the $p16^{Ink4A}$ tumor suppressor.[169] The *Arf* protein product, called $p14^{Arf}$ in humans and $p19^{Arf}$ in mouse, binds to HDM2/MDM2 and prevents it from regulating p53.[170–174] As with the DDR, this frees p53 to activate the transcription or proarrest or proapoptotic targets. The central importance of this p53 pathway is underscored by the finding that the majority of human tumors carry mutations in p53, have upregulated HDM2 (typically by gene amplification), or have inactivated $p19^{Arf}$.[169] This is very analogous to the selective pressure to deregulate pRB pathway components (pRB, cyclin D/CDK4, and $p16^{Ink4A}$) that was discussed previously.[104] Together, the pRB and p53 pathways are critical gatekeepers of G_1-to-S progression in normal cell cycle and stress response.

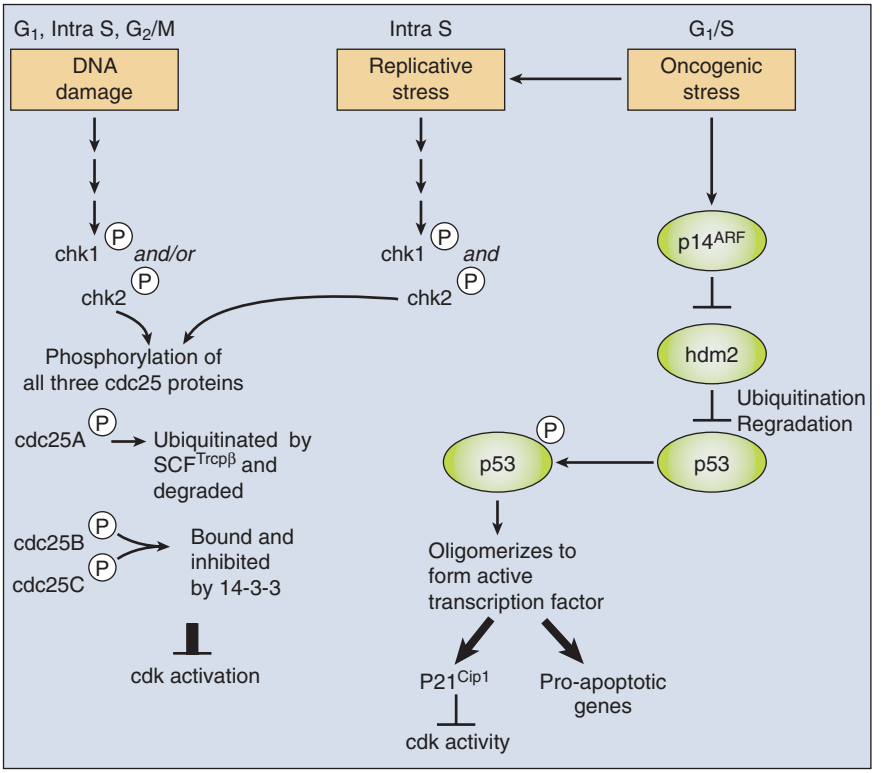


Figure 4-9 • DNA damage, replicative stress, and oncogenic stress induce cell cycle arrest. DNA damage and replication stress lead to the rapid phosphorylation and activation of the CHK1 and/or CHK2 kinases. These enforce cell cycle arrest through two mechanisms. CHK1 and CHK2 both phosphorylate the cdc25 phosphatases, and this triggers their ubiquitination and degradation (cdc25A) or binding and inhibition by 14-3-3 (cdc25B and cdc25C), thereby preventing activation of either cyclin/CDK2 or cyclin/CDK1 kinases. CHK1 and CHK2 also phosphorylate p53 and prevent it from being targeted by HDM2 for ubiquitin-mediated degradation. As a result, p53 accumulates and activates transcription of $p21^{Cip1}$, inhibiting CDK2 and CDK1 kinase complexes, or proapoptotic genes. Oncogenic stress also leads to cell cycle arrest by activating replicative stress and/or inducing transcription or the $p14^{Arf}$ tumor suppressor and suppressing HDM2-mediated inhibition of p53.

As an additional DNA damage response in G_1 cells, genotoxic agents also inhibit origin licensing by way of an ATM/ATR-independent process. This is achieved through regulation of Cdt1.[127–129,175] As was described previously, Cdt1 is required for pre-RC formation. In an undamaged cell, Cdt1 is available during G_1 but is inhibited after origin firing by degradation (mediated by the SCFskp2 and Cul4-Ddb1-Dtl/Cdt2 ubiquitin ligases) and geminin binding. As a key feature of this regulatory system, Cdt1 is completely resistant to Cul4-Ddb1-Dtl/Cdt2 in the G_1 phase. However, DNA damage allows Cul4-Ddb1-Dtl/Cdt2 complex to ubiquitinate Cdt1 and induce its degradation. This process requires binding of Cdt1 to proliferative cell nuclear antigen, but the mechanism by which this induces Cdt1 ubiquitinylation is not understood. Importantly, the degradation of Cdt1 is extremely rapid, occurring within minutes of the DNA damage. As a result, origin licensing is completely blocked until the damage is repaired and Cdt1 is resynthesized.

Intra-S Phase Checkpoint

One of the major goals of cell cycle checkpoints is to prevent the deleterious consequences of replicating damaged DNA. Therefore, S phase cells must respond virtually instantaneously to DNA damage to halt initiation of new replication forks throughout the S phase.[149] The most deleterious damage is DSBs. These can occur through the action of DNA damaging agents (from either extrinsic or intrinsic sources) or as a consequence of the replication process itself, for example, if the replication fork passes through nicked DNA or replication stalls at sites of DNA damage. The cell senses the damage in different ways depending on whether or not the lesion is associated with replication. Ultimately, both ATM and ATR are recruited to the site of damage, but the order of binding is different.[149,151] Replication-linked DSBs are distinguished by the presence of single-stranded DNA, a hallmark of the replication process. The single-stranded DNA is coated by RPA and bound by ATR and its regulator subunit ATRIP, even during the normal replication process. In response to DNA damage, the ATR kinase is activated, and it then recruits a variety of complexes that mediate both repair and checkpoint activation, including ATM. In contrast, nonreplication-associated DSBs initially recruit and activate ATM through the MRN-dependent process described previously for G_1/S checkpoint. However, in S phase cells, DSB resection causes the formation of single-stranded DNA (through the action of the MRN endonuclease), and this is then bound by RPA and ATR/ATRIP.[149,151] Thus, in S phase cells, ATR and ATM jointly orchestrate the DDR. ATR contributes to the checkpoint response in a similar manner to ATM: It activates an effector kinase, called CHK1, which can also phosphorylate the cdc25 proteins and p53.[176–179]

G_2 Checkpoint

The G_2 checkpoint is required to prevent the passage of DNA lesions to two daughter cells during mitosis.[147,180] DSBs are detected exactly as we described previously for the S phase nonreplication-associated DSBs. Similarly, the ATR/CHK1 and ATM/CHK2 pathways enforce arrest through inhibition of G_2 and mitotic CDK complexes via the rapid removal of the cdc25 phosphates and the p53-dependent induction of the $p21^{Cip1}$ CDKI.

Spindle Checkpoint

The preceding sections focused on the steps the cell takes to prevent the propagation of DNA errors to the daughter cells. In contrast, the spindle checkpoint acts to ensure that there is appropriate partitioning of the chromosomes.[181] We have already introduced the concept that chromosome segregation is prevented until all of the condensed sister chromatid pairs are aligned at the metaphase plate with the appropriate biorientation. This is actually controlled by a signaling network that constitutes the spindle checkpoint (Fig. 4-10). The core components of the spindle checkpoint—called MAD1, MAD2, BUBR1, and BUB1 in humans—were originally identified through screens in yeast for "mitotic arrest deficient" (MAD) and "budding uninhibited by benzimidazole" (BUB) mutants.[181] These proteins become active in the prometaphase of mitosis (see Fig. 4-10). They

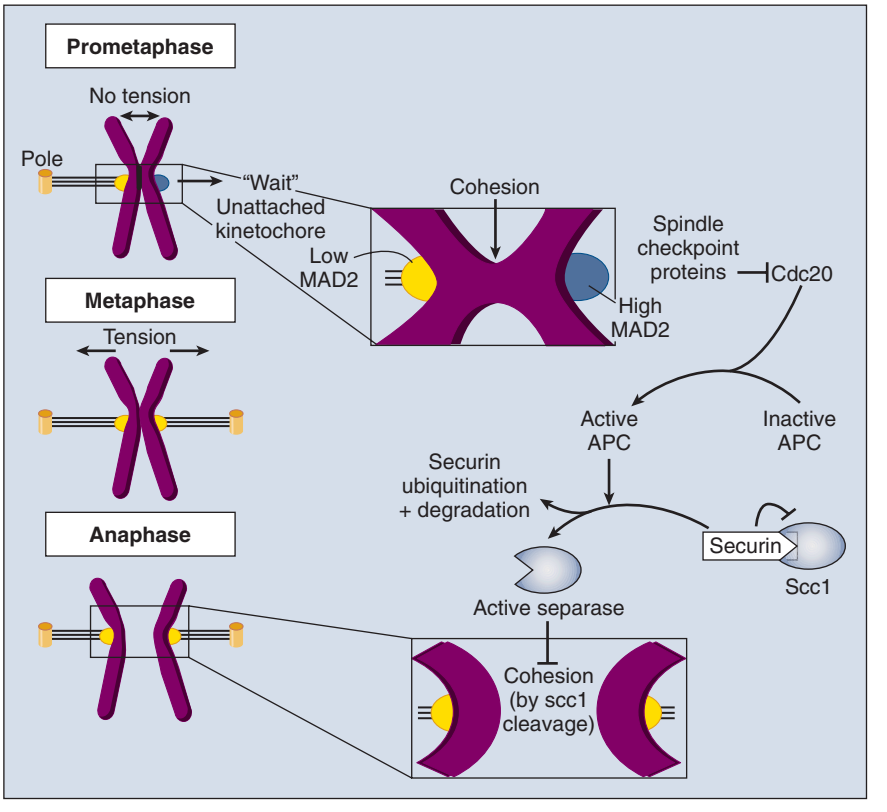


Figure 4-10 • The spindle checkpoint. Improper chromosome alignment on the mitotic spindle, disruption of microtubule dynamics, or unattached kinetochores can activate the spindle checkpoint. Spindle checkpoint signaling is mediated by the Bub1, Bub3, BubR1, and Mad2 proteins, which all localize to kinetochores. These core spindle checkpoint regulators prevent the activator protein Cdc20 from binding to APC and therefore protects securin, a major APC^{cdc20} target, from ubiquitin-mediated degradation. As a result, securin remains bound to separase, and this prevents cleavage of Scc1 and loss of centromeric cohesin. The spindle checkpoint is relieved at the end of the metaphase by the appropriate biorientation of the sister chromatids at the metaphase plate. The sensing mechanism involves detecting tension through the cohesin complex at the kinetochores that is created by the pulling of the spindle fibers toward the poles. Mad2 then dissociates from the attached kinetochore, and this allows cdc20 to activate APC and trigger sister chromatid segregation.

associate with the kinetochore and, in the absence of biorientation, prevent the CDC20 activator from binding to the APC. As a result, separase is sequestered by securin and unable to cleave the centromeric cohesin (see Fig. 4-10). It is still unclear precisely how the spindle checkpoint is inactivated by appropriate biorientation. However, it involves monitoring the tension through the cohesin complex at the kinetochores (created by the pulling of the spindle fibers toward the poles) and the dissociation of MAD2 from the attached kinetochore (see Fig. 4-10). Because aneuploidy is a shared feature of many cancer cells, there has been considerable speculation that disruption of the spindle checkpoint could occur during tumor progression.[182–184] Notably, inactivating mutations in *Bub1* have been identified in human colon carcinoma cell lines, which are known to have a high degree of aneuploidy.[185] Moreover, haploinsufficiency of Mad2 has been shown to cause elevated rates of lung tumor development in $Mad2^{+/-}$ mice compared with age-matched wild-type mice.[186] However, it is still an open question whether spindle checkpoint defects make a significant contribution to tumor development.

CELL CYCLE DEREGULATION IN HUMAN CANCERS

Molecular analysis of human tumors demonstrates that alterations in components of the cell cycle machinery and checkpoint-signaling pathways occur in the majority of human tumors (Table 4-1). This finding underscores how important maintenance of cell cycle control is in the prevention of human cancer. The alterations in the cell cycle machinery that occur most frequently include loss or mutation of the pRB tumor suppressor; overexpression of cyclins, CDKs, and Cdc25 phosphatases; and loss of expression of CDKIs. The most frequently altered cell cycle checkpoint-signaling molecule is the p53 tumor suppressor. Proteins that reside upstream of p53 (including ATM and CHK2) are also targeted for mutation in human tumors, and their discovery and analysis have greatly deepened our insight into DNA damage response-signaling pathways. Mutations that affect the pRB pathway have been identified in the majority of human cancers.[91,187] The *RB-1* gene was originally identified by virtue of its mutation in both familial and sporadic retinoblastoma, but it is defective in many other tumor types, especially osteosarcoma and lung cancer. Indeed, more than 90% of small-cell lung cancers have mutant *RB-1*, suggesting that disruption of the pRB pathway (through the genetic or epigenetic targeting of *RB-1* or upstream signaling components) is a requirement for the genesis of lung cancer.[188] It is important to note that inactivation of the parallel and interconnecting $p14^{Arf}$-p53 axis is also essential in functionally pRB-deficient lung cells to bypass efficient apoptosis.[169] In breast cancer, loss of normal pRB function due to *RB-1* mutation is observed in 20% of tumors.[189] In the 80% of breast carcinomas that lack *RB-1* mutations, alterations in components of the signaling pathways that regulate pRB are frequently found, including cyclin D1 and cyclin E overexpression and *cdk4* and *cdk6* gene amplification.[190–192] Nearly 50% of invasive breast cancers have elevated cyclin D expression compared with surrounding normal breast epithelium, while transgenic mice with overexpression of human cyclin D1 or cyclin E in mammary gland cells develop mammary adenocarcinomas.[193–195] Similarly, *cdk4* and *cdk6* gene amplification occurs in breast cancers, sarcomas, gliomas, and melanomas.[196]

Table 4-1 Mutations of Cell Cycle Checkpoint Regulators in Human Tumors*

Gene/Protein	Tumors Associated with Mutations or Altered Expression	Hereditary Syndromes Associated with Germline Mutations
ATM	Breast carcinomas, lymphomas, leukemias	Ataxia-telangiectasia
Bub1	Colorectal carcinomas	NR
BRCA1	Breast and ovarian carcinoma	Familial breast and ovarian cancer
Cdc25A	Carcinomas of breast, lung, head and neck, and lymphoma	NR
Cdc25B	Carcinomas of breast, lung, head and neck, and lymphoma	NR
Cdk4	Wide array of cancers	NR
Cdk6	Wide array of cancers	NR
Chk1	Colorectal and endometrial carcinomas	NR
Chk2	Carcinomas of breast, lung, colon, urogenital tract, and testis	Li-Fraumeni syndrome
Cyclin D1	Wide array of cancers	NR
Cyclin D2	Lymphoma and carcinomas of the colon, testis and ovary	NR
Cyclin D3	Lymphoma, pancreatic carcinoma	NR
Cyclin E	Wide array of cancers	NR
MDM2	Soft tissue tumors, osteosarcomas, esophageal carcinomas	NR
MRE11	Lymphoma	Ataxia-telangiectasia-like disorder
NBS	Lymphomas, leukemias	Nijmegen breakage syndrome
$p15^{INK4b}$	Wide array of cancers	NR
$p16^{INK4a}$	Wide array of cancers	Familial melanoma
$p27^{KIP1}$	Wide array of cancers	NR
p53	Wide array of cancers	Li-Fraumeni syndrome
$p57^{KIP2}$	Bladder carcinomas	NR
p130	Wide array of cancers	NR
pRB	Wide array of cancers	Familial retinoblastoma

NR, not reported.
*Only alterations that are present in more than 10% of primary tumors are represented.

Modifications of CDKIs that act upstream of pRB activity are also commonly found in human tumors. The CDK inhibitor $p27^{Kip1}$ is often aberrantly expressed in human breast cancer, and reduced $p27^{Kip1}$ protein levels are correlated with more aggressive breast tumors.[197,198] Likewise, decreased expression of the CDK inhibitor $p57^{Kip2}$ is found in human bladder cancers.[199] Germline mutations in $p16^{INK4a}$ predispose individuals to melanoma, while deletion of $p15^{INK4b}$ and $p16^{INK4a}$ is linked to the pathogenesis of lymphomas, mesotheliomas, and pancreatic cancers.[78,79,196,200] In tumor types in which $p15^{INK4b}$ and $p16^{INK4a}$ are not deleted, methylation of the gene locus leads to transcriptional repression and loss of gene expression. In some tumors, hypermethylation prevents expression of both $p16^{INK4a}$ and $p14^{Arf}$, which are encoded by alternative reading frames of the *Ink4a/Arf* locus.[199] Both Cdc25A and Cdc25B phosphatases are overexpressed in more than 30% of primary breast tumors, 40% to 60% of non-small-cell lung cancers, 50% of head and neck tumors, and a significant fraction of non-Hodgkin's lymphomas.[10,201,202] Elevation of these oncogenic phosphatases can result in increased activation of CDK and override of checkpoint arrest.

p53 mutation is the most frequently observed mutation in the majority of human tumors. The importance of p53-dependent signaling in tumor suppression is underscored by the frequency of mutation in sporadic tumors and the finding that germline mutations of *p53* result in Li-Fraumeni syndrome, a highly penetrant familial cancer syndrome that is associated with significantly increased rates of brain tumors, breast cancers, and sarcomas.[203,204] In human tumors that lack p53 gene mutation, p53 function may be disrupted by alterations in cellular proteins that modulate the levels, localization, and biochemical activity of p53. For example, in some tumors with wild-type *p53* alleles, MDM2 gene amplification occurs, resulting in MDM2 protein overexpression and subsequent p53 inactivation.[205] In human papillomavirus-induced cervical carcinoma, *p53* is typically not mutated; however, the human papillomavirus E6 protein binds p53 and targets it for degradation, abrogating p53-dependent signaling.[206]

Mutation in components of the DNA damage response pathway also leads to enhanced tumorigenesis, as was discussed previously. For example, *ATM* mutations occur in ataxia-telangiectasia, a disorder in which patients have increased sensitivity to radiation and an elevated incidence of leukemias, lymphomas, and breast cancer.[150,207] ATM-null mice exhibit growth retardation, neurologic dysfunction, infertility, defective T lymphocyte maturation, and sensitivity to ionizing radiation.[208,209] The majority of ATM-deficient animals develop malignant lymphomas by 4 months of age, while $ATM^{-/-}$ fibroblasts have abnormal radiation checkpoint function after exposure to ionizing radiation.[208,209] The DNA double-strand break repair gene *MRE11* is mutated in individuals with an ataxia-telangiectasia-like disorder.[210] Mutations of *Chk2* and *Chk1* also arise in human cancers. *Chk2* mutations have been reported in several cancers, including lung, while *Chk1* mutations have been observed in human colon and endometrial cancers.[211,212] In addition, heterozygous alteration of *Chk2* occurs in a subset of individuals with Li-Fraumeni syndrome who lack p53 gene mutations.[213] These findings support the theory that in human tumors in which *p53* is intact, the function of this tumor suppressor might be disrupted by alterations in cellular proteins that modulate the levels or activity of p53. In addition, the breast cancer susceptibility tumor suppressors BRCA1 and BRCA2 are known to participate in the DNA damage response and repair.[214] Similarly, the Fanconi's anemia proteins, which were originally identified by virtue of their association with a recessive development disorder called Fanconi's anemia, which is associated with increased cancer predisposition (particularly acute myeloid leukemia), also function in the DNA damage response.[214]

The spindle checkpoint disruption has also been linked to the pathogenesis of several human tumors. *BUB1* mutations have been identified in human colon carcinoma cells, and Bub1 mutation facilitates the transformation of cells that lack the breast cancer susceptibility gene, BRCA2.[185,215] Moreover, Michel and colleagues demonstrate that $Mad2^{+/-}$ mice have significantly higher rates of lung tumor development than do age-matched wild-type mice.[186]

THERAPEUTIC MANIPULATION OF CELL CYCLE CONTROLS

Research over the past two decades has shown that alterations in cell cycle machinery and checkpoint signaling lead to tumorigenesis. These findings have important implications for the optimization of current therapeutic regimens and for the selection of novel cell cycle targets for the future development of anticancer agents. A leading goal of cancer-based research is to identify compounds that will target key cell cycle controls in a tumor-specific manner.

Targeting Cyclin-Dependent Kinase Activity

There has been considerable debate about whether inhibition of CDK activity is a rational strategy for anticancer therapies. CDK activity is frequently elevated in human tumors, but it is also required to maintain specific cells populations in the adult (e.g., the hematopoietic compartment and gut) that are essential for viability. Thus, the key issue is whether there is sufficient difference in the CDK activity in tumor versus normal cells to create a therapeutic window. Over the last few years, the analysis of CDK and cyclin mouse models has yielded considerable insight into this question but has also raised additional questions.[18] On the positive side, studies in mouse models clearly show that tumors can be more dependent on CDK activity, or at least a specific CDK activity, than normal tissues can. For example, loss of D-type cyclins has been shown to have little or no effect on the development and maintenance of many tissues, but loss of cyclin D-associated kinase activity can greatly suppress the development of certain tumor types, depending on the tissue and the identity of the initiating oncogenic lesions.[22,29,216] On the negative side, the mouse models also show that the cell cycle machinery is extremely robust; it adapts easily to the loss of CDKs or cyclins by using other CDKs or cylins to substitute for the missing activity. For example, CDK2 knockout mice are fully viable because CDK4/6 and CDK1 now form novel cyclin/CDK complexes and assume roles that are normally specific to CDK2.[217–219] This raises the possibility that tumor cells will rapidly develop resistance to CDK-inhibitory drugs by simply adapting their cell cycle machinery. In light of these complexities, efforts have been placed on generating pharmacologic inhibitors of CDKs that either are CDK-specific or have pan-CDK activities. Numerous small molecule inhibitors have been developed, and many are in clinical trials.[220,221]

One of the first compounds to be tested, flavopiridol, is a pan-CDK inhibitor that inhibits CDK4/6, CDK2, and CDK1 kinase activity. Consistent with this broad action, flavopiridol arrests cells at G_1/S (in a pRB-dependent manner) and G_2/M. This antiproliferative activity against a variety of human cancer cell lines produced favorable clinical responses in phase I and phase II studies of patients with renal, colorectal, gastric, lung, and esophageal carcinomas.[222–224] Notably, it was also determined that if target cells are first induced to induced to enter S phase, then treatment with flavopiridol had significant cytotoxic effects.[221] This arises through two mechanisms. First, flavopiridol inhibits the action of cyclin A/CDK2 and thereby prevents the phosphorylation of E2F1 and its subsequent degradation.[59,61] The persistence of E2F1 in late stages of the cell cycle is known to trigger apoptosis, and this effect shows strong specificity for tumor cells versus normal cells, presumably because of higher E2F1 levels. Second, flavopiridol suppresses the activity of CDK7 (which functions both as a component of both CAK and as a RNA polymerase II CTD kinase that promotes transcriptional elongation) and CDK9 (which acts in association with cyclin T to form another CTD kinase called P-TEFb).[225,226] Inhibition of CDK7 and CDK9 suppresses mRNA synthesis, and this leads to a rapid loss of

transcripts that have short half-lives, including many cell cycle regulators (e.g., cyclins) and antiapoptosis regulators. As a result of these observations, clinical trails have been conducted using sequential treatment of an S phase chemotherapeutic agent, gemcitabine, and then flavopiridol.[221] On a similar theme, sequential treatment with paclitaxel (which inhibits mitotic spindle function) and then flavopiridol also yields cytotoxic synergy.[221] In this case, flavopiridol is acting by inhibiting cyclin B/CDK1 and thus prevents phosphorylation and stabilization of a protein, called *survivin*, that is required to maintain the spindle checkpoint. Thus, the cells proceed through cytokinesis and enter G_1 without segregating their chromosomes, and this triggers apoptosis. Phase I and phase II trials have been conducted with paclitaxel and flavopiridol, and currents efforts are focused on optimizing the dosage and the time interval of administration.[221] More selective CDK inhibitors are also being analyzed.[220,221] These include small molecules that show a strong selectively for CDK2 and CDK1 or are highly specific for CDK4/6. Cell- and animal-based studies show that these drugs yield the anticipated affects. For example, the CDK4/6 inhibitor PD0332991 yields a G_1/S arrest in an pRB-dependent manner, and it can yield regression of xenografts generated from pRB-positive cell lines.[227] Many of these drugs have yet to be tested in clinical trials.

Targeting DNA Damage Response Proteins

In the last decade, there has been a growing appreciation that many tumors cells carry mutations that disrupt their DNA damage response (DDR). This is a major factor in establishing the resistance of tumors to chemotherapeutic agents, many of which work by causing DNA damage and triggering apoptosis through induction of DNA damage pathways. Therefore, considerable attention has focused on designing cancer treatments that would be effective in cells with an impaired DDR. Since it is hard to restore the function of mutant or missing proteins, the prevailing strategy is to identify drugs that would synergize with the defective DDR to selectively kill the tumor cells and not the normal cells. For example, inhibitors of poly(ADP-ribose) polymerase selectively kill cells that lack either BRCA1 or BRCA2.[228–230] The rationale for this is that these proteins provide two alternative repair mechanisms in response to DNA damage: homologous recombination (BRCA1 and BRCA2) and base excision repair (poly(ADP-ribose) polymerase). Therefore, loss of one but not both of these pathways can be tolerated. As a second example, inhibition of CHK1 sensitizes *p53* mutant cells to DNA damage.[220] Since *p53* is mutated in approximately half of all human tumors and the absence of p53 is a major predictor of poor response to classic chemotherapeutic agents, considerable efforts are being made to develop small molecular inhibitors of CHK1.

SUMMARY

Over the past several decades, investigators have uncovered a wealth of information about the proteins that control cell growth and division in human cells. A key finding is that deregulation of the cell cycle machinery and/or checkpoints is a universal alteration that has been identified in human cancer.[104,231] Although numerous genetic alterations can result in loss of normal checkpoints, the hope is that common strategies will be developed against a wide variety of cancers. Even though several of the currently used anticancer therapies target nonselective and non-mechanism-based targets, their effectiveness, albeit limited in many cases, is likely due to the fact that they ultimately target cell cycle regulatory or DDR-signaling pathways, the status of which is different in normal cells versus tumor cells. Identifying all the components of the cellular machinery that control the cell cycle both positively and negatively is vital to the continued development of anticancer agents that can preferentially eliminate cancer cells and minimize the toxicity to normal tissues. The information that is generated by the genomic and proteomic approaches using eukaryotic model systems will continue to reveal new cell cycle regulatory molecules. As our understanding of cell cycle regulation and checkpoint signaling improves, the goal is to use this knowledge in the design of mechanism-based therapeutics that will bring anticancer therapy to a new level. There can be little doubt of the value of targeting the cell cycle in drug discovery.

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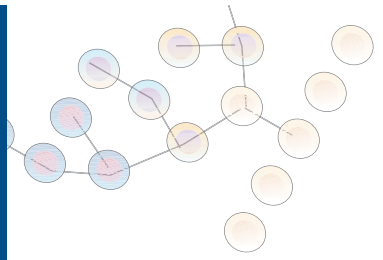
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5 Cell Life and Death

Rebecca L. Elstrom and Craig B. Thompson

SUMMARY OF KEY POINTS

- Apoptosis control mechanisms seem to be impaired in virtually all tumors, suggesting that a required step in carcinogenesis is to disengage the apoptotic machinery.
- Two basic pathways of apoptosis have been described: the extrinsic or death receptor-mediated pathway and the intrinsic or mitochondrial pathway.
- The fate of a cell is determined by the balance of proapoptotic and antiapoptotic factors within the cell.
- Oncogenic transformation promotes proapoptotic pathways. Cancer cells must disable tumor suppressor molecules and/or activate survival signals to evade programmed cell death.
- Therapeutic strategies aimed at restoring tumor suppressors and interfering with survival factors are playing increasingly important roles in antineoplastic treatments.
- There is a growing understanding of the role of alternative forms of cell death, particularly necrosis, in the response of cancer cells to treatment.

INTRODUCTION

The evolution of a normal cell into cancer involves disruption and deregulation of several basic cellular processes. Multicellular organisms, in their evolution from simple, single cells, have developed redundant controls through which the homeostasis between different cell types is maintained. One of the safeguards that prevents excess cell accumulation is the presence of cell-intrinsic programs that can induce programmed cell death, the best studied being apoptosis. The growing understanding that transforming mutations can activate this intrinsic death response has emphasized the importance of this process in preventing cancer cell development. Apoptosis control mechanisms seem to be impaired in virtually all tumors, suggesting that a required step in carcinogenesis is to disengage the apoptotic machinery.

The concept that genes regulating cell death could play a role in tumorigenesis arose in the mid-1980s, when investigators first discovered that a translocation commonly found in follicular lymphoma, between chromosomes 14 and 18, brings a region on chromosome 18 called breakpoint cluster region 2 (*Bcl-2*) into close proximity with the immunoglobulin heavy chain enhancer on chromosome 14, resulting in overexpression of the *Bcl-2* gene.[1] Later work showed that the Bcl-2 gene product promotes oncogenesis by a novel mechanism.[2,3] Instead of inducing cell proliferation or invasion, the Bcl-2 protein inhibits the normal programmed death of B cells, resulting in the failure to eliminate the clonal B cells as they accumulate in excess. These findings demonstrated for the first time that disarming death pathways within a cell could predispose to development of malignancy.

Since the description of *Bcl-2,* extensive progress has been made in understanding both the mechanisms of apoptosis and the ways in which this process contributes to tumorigenesis. The identification of a family of genes related to *Bcl-2* that contribute to the balance between life and death, together with the discovery of the critical role of mitochondria in cellular homeostasis and apoptosis, have broadened our understanding of the dynamic interplay of forces determining the fate of cells.

In addition to progress in elucidating apoptotic mechanisms and deregulation, there has been an increasing understanding of the role of nonapoptotic mechanisms of cell death in both organismal homeostasis and pathogenic states such as cancer. Necrosis, a death process traditionally considered as unregulated and catastrophic, may instead represent a regulated event that contributes to organismal development and homeostasis. Autophagy, in which a cell "eats itself," is also under investigation as a form of nonapoptotic cell death, although the function of this process, whether to induce death or, conversely, to maintain survival, is controversial.

Harnessing these forces will improve our capability not only to understand the mechanisms by which normal cells become malignant but also to prevent and treat cancer in humans.

FUNDAMENTAL SCIENCE

Cell death occurs by two general classes of mechanism: apoptosis, or programmed cell death, and necrosis. Autophagy has been proposed as a third potential mechanism of cell death, although the physiologic functions of this process remain under study.

The process of apoptosis involves a cell-intrinsic suicide program that not only kills the cell but also stimulates the clearance and complete degradation of the corpse without inducing an inflammatory reaction. Apoptosis differs from other forms of cell death, such as necrosis, in that clearance of the cell is controlled through the activity of caspases—cysteine proteases with aspartate specificity that normally exist in an inactive, zymogen form. The initiator caspases 8 and 9 are activated by cellular signals and subsequently cleave downstream effector caspases, such as caspases 3, 6, and 7. These effector caspases set into motion the degradation of cellular components such as structural proteins, cell cycle machinery, and DNA. These processes result in the characteristic morphology of apoptotic cells, membrane blebbing, cell shrinkage, and DNA fragmentation. The end result is the disposal of the cell in a controlled manner, allowing turnover and phagocytosis without the inflammatory reaction to intracellular substances that accompanies death by necrosis.

As noted in the preceding discussion, the caspase cascade is initiated through specific cellular signals. These signals come through one of two major pathways: the extrinsic, receptor-mediated pathway, or the intrinsic, mitochondrial pathway. Although these pathways often are considered separately, extensive cross-talk exists between them.

Cell Death by Murder

In some cases, apoptosis is initiated through ligation of specific cell-surface receptors, the death receptors (Fig. 5-1). These molecules are members of the tumor necrosis factor receptor (TNFR) family. The best studied of these include Fas and TNFR1.[4,5] These receptors exist as trimers at the cell surface that are activated on binding of ligand, Fas ligand, and TNF, respectively. The intracellular domains of these receptors contain death domains which, on activation of the receptor, can recruit a death-inducing signaling complex, which leads to activation of a caspase cascade. The Fas death domain binds the Fas-associated death domain (FADD) adapter protein, which directly recruits caspase 8 and allows its cleavage and activation.

Activation of TNFR1, on the other hand, has multiple potential downstream effects.[6] TNFR1 binds the TNFR-associated death domain (TRADD) adapter protein, which in turn might recruit FADD, resulting in caspase 8 activation and apoptosis, as with Fas. TRADD also, however, can bind TNFR-associated factor-2, which may recruit inhibitor of apoptosis proteins (IAPs), which bind the death-inducing signaling complex and inhibit activation of caspase 8. Alternatively, TNFR-associated factor-2 may recruit components of the mitogen-activated protein kinase (MAPK) cascade, leading to activation of Jun-N-terminal kinase (JNK) and c-jun. Although in some systems JNK seems to promote TNFR1-induced apoptosis, these findings are inconsistent, and the role of JNK in receptor-mediated apoptosis is controversial. Finally, TRADD can bind receptor-interacting protein (RIP), resulting in activation of NF-κB, which antagonizes the apoptotic program. NF-κB is a transcription factor that activates expression of survival molecules such as IAPs and c-FLIP, a direct inhibitor of caspase 8 activation.[7] IAPs were first described in baculoviruses, where they were shown to inhibit apoptosis of host cells following viral infection.[8] Homologs such as XIAP and c-IAP-1 and -2 have since been identified in mammals; they seem to function by inhibiting caspase activation in both the death receptor and mitochondrial pathways.[9–11]

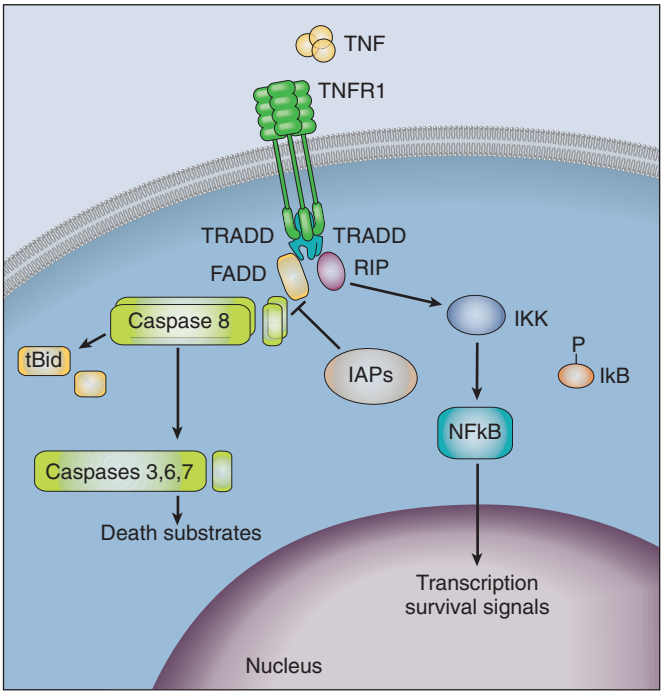


Figure 5-1 • Death receptors can initiate apoptosis or promote cell survival. On ligation of the death receptor, adaptors are recruited. For TNFR1, the outcome of ligand binding depends on the state of the cell. TRADD might bind the FADD molecule, which recruits caspase 8, resulting in its oligomerization and activation. Active caspase 8 in turn cleaves and activates effector caspases and the BH3-only molecule Bid, initiating an apoptotic cascade. This process is inhibited by IAPs. Alternatively, binding of TNFR1 might induce recruitment of RIP and IκB kinase (IKK), resulting in release of the NF-κB transcription factor from its inhibitor, IκB. NF-κB then enters the nucleus, activating transcription of survival genes such as IAPs, therefore antagonizing the proapoptotic factors.

Another ligand-receptor pair that functions in both immune regulation and control of cancer is the TNF-related apoptosis-inducing ligand, TRAIL, and its receptors, TRAIL-R1/DR4 and TRAILR2/DR5.[12,13] TRAIL induces apoptosis in a variety of transformed cells but is much less toxic to normal cells than to abnormal ones. The intracellular signaling pathways induced by TRAIL are similar to those of the TNFR1. TRAIL is expressed as a cell-surface molecule on natural killer cells, and it can inhibit tumor growth.[14] TRAIL also binds to decoy receptors TRAILR3/DcR1 and TRAIL-R4/DcR2, which sequester TRAIL from the signaling receptors, blocking TRAIL-induced apoptosis.[15,16] Expression of these decoy receptors might provide the mechanism by which normal cells escape TRAIL-induced death, in that many tumor cells show lower expression of the decoy receptors.

Cell Death by Suicide

The importance of mitochondria in apoptosis was demonstrated in 1996, when Liu and colleagues[17] demonstrated that cytochrome *c,* a component of the electron transport chain normally contained in the mitochondrial intermembrane space, could initiate programmed cell death when present in the cytosol. This finding led to the demonstration that the intrinsic, or mitochondria-dependent, cell death program resulted from loss of mitochondrial integrity with release of intermembrane space contents (Fig. 5-2). Cytochrome *c,* on release into the cytosol, forms a complex with Apaf-1 and adenosine triphosphatase (ATP). This complex, known as the apoptosome, binds and activates procaspase 9.[18] Other mitochondrial contents also participate in apoptosis. For example, Smac/DIABLO,[19,20] Htra2,[21] apoptosis-inducing factor (AIF), and endonuclease (endo) G also contribute to the cell death program.[22–24] Inhibitory proteins such as XIAP and cIAPs-1 and -2 bind to the apoptosome and inhibit activation of caspases. Smac/DIABLO and Htra2 function by inhibiting the inhibitors, which allows apoptosis to proceed. The progression of the cell death program seems to depend on the relative ratios of apoptosis promoters and inhibitors. Evidence suggests that AIF, on the other hand, might function independently of caspase activity. Upon release from mitochondria, AIF translocates to the nucleus, where, in cooperation with endo G, it can initiate large-scale fragmentation of DNA.

Controversy exists over the mechanism by which mitochondria lose integrity, resulting in release of their contents and initiation of the caspase cascade. General mechanisms proposed include mitochondrial dysfunction leading to matrix swelling and outer membrane rupture. Alternatively, loss of mitochondrial integrity could involve formation of specific pores large enough to release the intermembrane components. Another controversy exists over the importance of caspases in the actual death of cells following mitochondrial compromise as opposed to their role of simply orchestrating cellular disposal. Some investigators have shown that once mitochondria lose integrity, cells will die even in the absence of caspase activation.[25] This finding is consistent with the idea that release of mitochondrial contents proceeds from large-scale catastrophe to the mitochondria, with cellular viability impossible in the absence of mitochondrial function. Others have suggested that, under some circumstances, cells can recover even after cytochrome *c* release if caspases are held in check.[26] The function of IAPs in preventing apoptosome activity suggests that in some cases death can be prevented, but the role of caspases probably varies with different apoptotic stimuli.

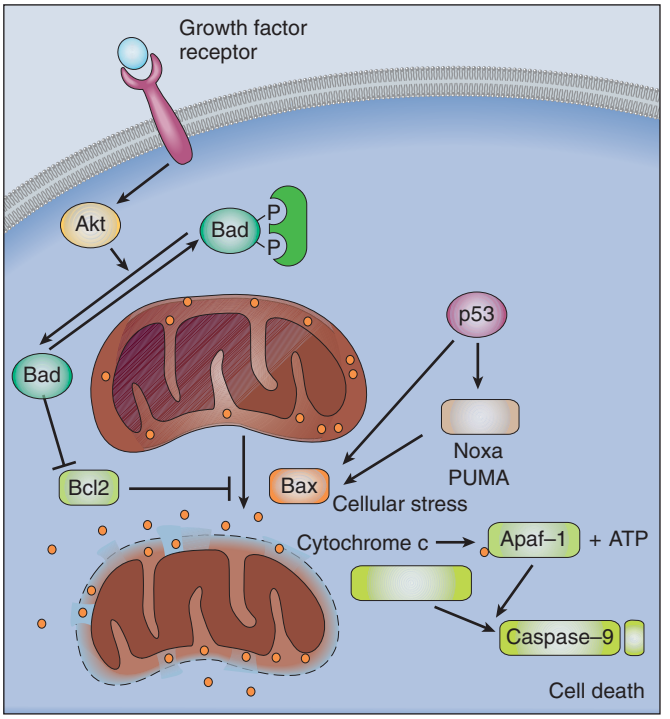


Figure 5-2 • Mitochondria-dependent apoptosis. Under conditions of cellular stress, the proapoptotic molecules Bax and/or Bak oligomerize at the mitochondria and induce release of mitochondrial contents, including cytochrome *c*. Cytochrome *c* then binds Apaf-1, and in combination with ATP forms the apoptosome. The apoptosome induces cleavage and activation of caspase 9, which activates a caspase cascade culminating in cell death. This process might be stimulated by DNA damage, which results in activation of p53, which, among several functions, promotes transcription of the BH3-only molecules Noxa and PUMA. The apoptotic pathway is antagonized by Bcl-2, which can block cytochrome *c* release and mitochondrial dysfunction. Growth factor stimulation might also antagonize apoptosis, in part through activation of such survival factors as Akt, which can phosphorylate and inactivate proapoptotic molecules such as the BH3 protein, Bad.

Bcl-2 Family

Bcl-2 family proteins play a key role in regulation of mitochondrial integrity and programmed cell death. The Bcl-2 family includes proteins with both antiapoptotic and proapoptotic function. Bcl-2, the first identified member of this family, acts to prevent apoptosis, as do Bcl-XL and Mcl-1. Bax and Bak antagonize the function of the antiapoptotic family members and are critical in promoting apoptosis through the mitochondrial pathway. All these family members have multiple domains, termed Bcl-2 homology (BH) domains. A third type of Bcl-2 family member, exemplified by Bad, Bim, and others, consist of a single BH domain and are termed BH3-only molecules. The BH3-only family members also play a key role in promoting apoptosis.

Extensive progress has been made in understanding the mechanisms by which these Bcl-2 family members regulate mitochondrial integrity and apoptosis, although many questions remain. The antiapoptotic molecules Bcl-2 and Bcl-XL localize to the mitochondria and maintain mitochondrial integrity. This could occur through promotion of exchange of metabolic substrates across the mitochondrial membrane, allowing maintenance of respiration.[27] Alternatively, antiapoptotic Bcl-2 family members might bind and inhibit the function of proapoptotic family members.[28] The multidomain proapoptotic molecules, Bax and Bak, are required for mitochondrial apoptosis initiated through most stimuli.[29] Mice with targeted knockouts of either of these molecules show largely normal apoptotic function, but loss of both Bax and Bak results in a severe defect in apoptosis.[30] This finding suggests that although these two molecules might have largely redundant functions, presence of one or the other is critical to allowing apoptosis to proceed. The BH3-only molecules, in contrast, seem to have a signaling function. Various apoptotic stimuli induce expression and/or activation of specific BH3-only family members, which translocate to the mitochondria and initiate Bax/Bak-dependent apoptosis (Fig. 5-3). They could operate either by activating Bax and Bak or by inhibiting the antiapoptotic function of Bcl-2 and Bcl-Xl. It has been suggested that different members of this group could have distinct functions—some directly binding and activating Bax/Bak, and others indirectly activating these proapoptotic molecules by binding and antagonizing Bcl-2/Bcl-XL.[31]

The BH3-only protein Bid provides an example of cross-talk between the receptor-mediated and mitochondrial pathways of apoptosis. Bid is a target of active caspase 8.[32,33] Once cleaved, this truncated form of the protein, tBid, can translocate to mitochondria, inducing cytochrome *c* release and amplification of the apoptotic signal. Although in some cell types death receptor engagement can kill cells independently of mitochondrial participation, in other cell types, this amplification step is critical to effect cell death.

Necrosis

In contrast to apoptosis, necrosis has largely been considered an uncontrolled, default form of cell death. Morphologically, necrosis is characterized by swelling of organelles and loss of plasma membrane integrity, and it can be induced by exposure of cells to overtly pathologic conditions such as extreme temperature or pH, or mechanical force. Increasingly, however, it is being recognized that at least in many cases, necrosis can occur through a highly regulated process, dependent, as in apoptosis, on specific signaling pathways. The critical components of this process include effectors that induce irreversible bioenergetic compromise in the cell, and those that result in release of inflammatory mediators from the cell, inducing a host response.

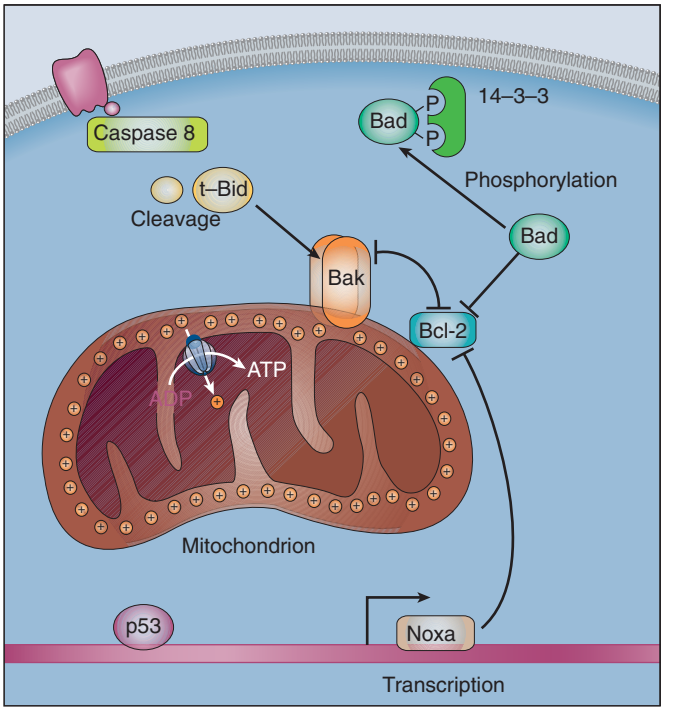


Figure 5-3 • BH3-only proteins initiate apoptosis. Several BH3-only proteins exist and could function in various ways to promote apoptosis. Bid is cleaved by caspase 8 on death receptor stimulation and subsequently translocates to mitochondria, where it can activate oligomerization of Bax and Bak. Other proteins, such as Bad and Noxa, function by inhibiting antiapoptotic Bcl-2 molecules. Noxa is transcriptionally regulated by p53, and Bad is regulated by inhibitory phosphorylation, which is growth factor dependent.

Necrosis can be activated both by death receptor signaling and by cell-intrinsic events. The absence of specific caspase activities, such as caspase 8, or the presence of apoptosis inhibitors, such as may be present in viral infection, may block apoptotic death in response to TNFR or Fas ligand stimulation, but induce a necrotic program. The regulated nature of this necrotic stimulus is illustrated by the fact that blocking the activity of the RIP kinase blocks necrotic cell death.[34]

Programmed necrosis may also be an important way in which organisms dispose of cells that have accumulated DNA damage. Although cells sustaining DNA damage in many cases die an apoptotic death, a functioning apoptotic pathway is not required for DNA damage–induced death. Zong and colleagues have shown that the activation of poly(ADP-ribose) polymerase (PARP) in response to DNA damage plays a critical role in the death of actively growing cells sustaining such damage.[35] PARP binds to DNA strand breaks, catalyzing the synthesis of poly(ADP-ribose) polymers on histones, promoting recognition of strand breaks by DNA repair enzymes. β-nicotinamide adenine dinucleotide (NAD) is a critical substrate of this reaction, and therefore PARP activation leads to depletion of NAD from the cytosol. Because cytosolic NAD is required for glycolytic metabolism, this consumption of NAD in response to DNA damage compromises the production of ATP in cells that are dependent on glycolysis, rather than mitochondrial metabolism, for energy production, such as rapidly proliferating cells and most cancer cells. In contrast, vegetative cells, deriving the bulk of their ATP from oxidative phosphorylation, remain bioenergetically intact. This necrotic death via PARP activation does not depend on apoptotic mediators such as Bak and Bax.

The activation of programmed necrosis might act as a warning system to the organism, resulting in release of proinflammatory mediators and activation of the immune system. This could be of particular benefit in the cases discussed previously, viral infection and cancer, in allowing the organism to mount an effective, global response to the insult.

Autophagy

Autophagy is a cellular process in which cytoplasmic components, including proteins and organelles, are sequestered into acidic vacuoles for degradation. The degradation products then become available as a source to support biosynthesis and energy production. Autophagy is promoted by metabolic stress and forms a response to metabolic emergencies within the cell.

The role of autophagy in cell death is not clear and is under active investigation. Some have hypothesized that autophagy is in and of itself a mechanism of cell death. Other investigators, however, have suggested that autophagy is instead a protective mechanism, allowing the cell to maintain bioenergetic integrity in the face of an inability to access nutrients. In this scenario, death would occur as a result of the depletion of intracellular resources, despite, not because of, autophagy.

Support for both these hypotheses can be found in the experimental literature. Lum and colleagues demonstrated that cells deprived of growth factors, leading to a defect in nutrient uptake, could maintain survival through activation of autophagy.[36] Inhibition of autophagy induction in this system led to rapid cell death. On the other hand, the loss of beclin-1, a gene product necessary for the induction of autophagy in mammals, predisposes to cancer in animal models,[37,38] and loss of beclin-1 is seen in some tumor types. The mechanism by which beclin-1 functions as a tumor suppressor is unclear, however. Beclin-1 associates with Bcl-2 and therefore might have a more direct role in apoptosis. Further investigation will be needed to clarify the role of autophagy in cancer.

APOPTOSIS IN CANCER

The events that can lead to mitochondrial apoptosis are varied. These include loss of normal survival-promoting extrinsic signals, DNA damage, metabolic stress such as hypoxia and nutrient limitation, oncogenic stresses, and toxins. Under normal circumstances, cells require extrinsic signals to promote cellular homeostasis and survival. These signals include growth factors and cell-cell or cell-matrix contact. Survival signals demonstrate to the cell that it is in an appropriate location and that cells like it are present in an appropriate number. Loss of these signals can occur if the cell finds itself in an ectopic position (loss of cell-cell or cell-matrix contact) or when specific cell types are in excess numbers (causing competition for growth factors), resulting in apoptosis.

Oncogenes as Triggers of Apoptosis

Oncogenic stresses, such as activation of Myc or loss of Rb with subsequent uncontrolled activation of the cell cycle machinery, can induce apoptosis. The mechanisms by which this occurs are not clear, but it is well demonstrated that oncogenesis through these pathways requires the additional step of inhibition of programmed cell death. In that Myc promotes activity of biosynthetic pathways, one possibility is that it promotes metabolic stress.[39,40] Other oncogenic stresses, such as loss of the Rb tumor suppressor or DNA damage, promote activity of the tumor suppressor p53.[41]

Research performed in recent years has demonstrated clearly the importance of apoptotic pathways in control of tumorigenesis. Cancer cells, through inappropriate growth and proliferation, outstripping of resources, and translocation to environments to which they are not adapted, subject themselves to death triggers and therefore must disable the apoptotic response to survive. A critical point in understanding the role of apoptosis in cancer is that lack of death alone does not suffice to make a cancer cell. Rather, tumors must activate proliferative, growth, and invasion programs—the targets of traditional oncogenes. It is these programs and their tendency to overwhelm the cell's survival signals that place the cell under apoptotic stress. Disabling of apoptotic pathways makes the cancer cells intrinsically defective in initiation of programmed cell death; such disabling promotes resistance to antineoplastic therapy but also suggests that many cancer cells live constantly "on the edge" of death. It is possible that restoration of apoptotic function could suffice for, or at least contribute to, the elimination of a tumor.

Tumor Suppressors Promote Apoptosis

p53

p53 is one of the best studied tumor suppressors, and its function is lost in at least half of human solid tumors. p53 activity is induced through stabilization of the protein in response to various oncogenic signals (including DNA damage), resulting in inhibition of cell growth through either cell cycle arrest or induction of apoptosis.[42] The specific mechanisms by which one or the other response occurs are not completely clear but could include duration of activity or the prevailing state of the cell. The activity of p53 seems to be mediated largely through its ability to act as a transcription factor, playing the roles of both transcriptional activator and repressor for different targets.

p53 activity and levels are controlled in large part by its upstream regulator, MDM2. MDM2 protein binds p53 and exports it from the nucleus, blocking its ability to act as a transcriptional regulator. MDM2 also targets p53 for proteasome-dependent degradation through its activity as a ubiquitin ligase. MDM2, in turn, is inhibited in its inhibition by p14ARF. In the absence of loss of p53 itself, overexpression of MDM2 can act as an oncogene, functionally suppressing p53 activity. MDM2 is overexpressed in multiple human tumor types, including lung cancer, brain cancers, and breast cancers.[43,44] p14ARF, conversely, has been shown to be lost in various tumors, including colon cancers.[45] Abnormalities of these upstream regulators tend to occur in tumors that retain wild-type p53, dem-

onstrating that dismantling of the p53/MDM2/p14ARF pathway plays a key role in tumorigenesis.

In addition to regulation by MDM2, post-translational modifications of p53 also influence its biologic activity. Phosphorylation and acetylation affect p53 stabilization and DNA-binding activity, and it seems that both these modifications promote p53 function. Mutant p53 proteins found in cancer cells are in some cases highly acetylated and phosphorylated, leading to stabilization and accumulation of the mutant protein.[46] This stabilized mutant protein can then act as a dominant negative, forming inactive complexes with residual wild-type protein.

The antitumor activity of p53 is mediated largely through its transcriptional effects. p53-dependent genes play multiple roles in apoptosis. For example, several proapoptotic Bcl-2 family members are transcriptionally activated by p53, including Bax and the BH3-only proteins Noxa and PUMA.[47,48] Expression of Apaf-1, another important element in the mitochondrial pathway, is induced through p53 activity. p53 promotes death receptor pathways through activation of Fas transcription, and it inhibits survival signaling through induction of PTEN (see later discussion).[42] Although this list of antitumor effects of p53 is far from exhaustive, the foregoing examples provide insight into the importance of this pathway in blocking tumorigenesis. Nontranscriptional roles for p53 in apoptotic regulation have also been proposed, including direct binding and inhibition of the activity of Bcl-X_L and Bcl-2.[49–51]

Proapoptotic Bcl-2 Family Members

In contrast to the oncogenic effects of the antiapoptotic Bcl-2 family members, proapoptotic family members, particularly Bax, have been implicated as tumor suppressors. Bax and its functional homolog, Bak, are critical in mediating apoptosis through the mitochondrial pathway induced by many cellular stresses.[30,46] Experimental models have suggested that Bax and Bak have p53-independent function in suppression of tumorigenesis and act as tumor suppressors.[52] In one study, murine cells expressing adenoviral E1A, a proliferative factor, and dominant negative p53 were unable to form tumors in mice. Additional loss of Bax and Bak, however, resulted in the formation of highly invasive tumors, emphasizing the capability of these molecules to inhibit carcinogenesis. Furthermore, mutations in Bax and Bak have been identified in many colon and gastric cancers.[53,54]

BH3-only proteins could also be important in preventing tumorigenesis. Although evidence implicating them as bona fide tumor suppressors is scant, BH3-only proteins play a role in the response to apoptotic stimuli of various death pathways, including p53 and death receptors.

PTEN

The activity of the survival pathway mediated through PI3K and Akt, discussed subsequently, is antagonized by phosphatase and tensin homolog on chromosome 10 (PTEN), a dual-specificity (protein and lipid) phosphatase that degrades phosphatidylinositol-3,4,5-triphosphate [Ptd(3,4,5)P3] back to the bisphosphate form, terminating the signal of PI3K. PTEN was discovered in the search for a tumor suppressor on chromosome 10 that is frequently lost in glioblastoma and prostate cancer. Since its discovery, researchers have shown that PTEN acts as a negative regulator of Akt.[55] Tumorigenesis in response to loss of PTEN depends in part on deregulation of Akt activity.[56]

The frequency of PTEN loss in human tumors is exceeded only by that of p53. PTEN function is abnormal in the majority of glioblastomas and prostate cancers and has been described in many other human cancers, including breast cancer and endometrial cancer. Furthermore, mice bearing an inactive allele of PTEN develop tumors in multiple organ systems.[57,58] The loss of a single allele of PTEN seems to be sufficient to promote tumorigenesis, as haploinsufficient mice frequently do not lose the second allele upon development of tumors, and loss of the second allele is a late event in many tumors.

Survival Factors Prevent Apoptosis in Cancer Cells

Antiapoptotic Bcl-2 Family Members

The central role of Bcl-2 family members in control of apoptosis suggests that these proteins may be appropriate targets of dysregulation in tumorigenesis, and, as predicted, many tumors show alterations in these proteins. The earliest description of antiapoptotic activity in cancer was that of overexpression of Bcl-2 in follicular lymphoma. This overexpression is brought about by the t(14;18) translocation, which brings the Bcl-2 gene locus into juxtaposition with the immunoglobulin heavy-chain enhancer, an abnormality found in at least 85% of follicular lymphomas. Since this discovery, Bcl-2 overexpression has been found in a multitude of different cancers, including other types of lymphoma and solid tumors such as breast cancer.[59]

The importance of Bcl-2 in the pathogenesis of cancer has also been demonstrated in experimental models. For example, mice expressing transgenic c-Myc in B cells develop lymphoma with a long latency period, suggesting the need for other transforming mutations for tumorigenesis. Coexpression of Bcl-2 markedly shortens the latency period, demonstrating synergy of these two molecules in lymphomagenesis.[2] Myc activation in cell lines induces apoptosis, in part through activation of p53. These experiments imply that a critical step in Myc-induced transformation is inhibition of apoptosis, and that Bcl-2 can provide this function. Bcl-Xl, another antiapoptotic family member with function similar to Bcl-2, also seems to play a role in both experimental and naturally occurring human tumors.[60–62]

Mice expressing transgenic Bcl-2 and Bcl-XL illustrate the important concept that inhibition of apoptosis alone does not induce tumorigenesis. Enforced expression of these molecules in B lymphocytes of mice leads to accumulation of lymphocytes, but lymphoma develops only rarely.[63] Instead, Bcl-2 and Bcl-XL facilitate lymphomagenesis by inhibiting the death that normally accompanies oncogenic activation. Likewise, lymphocytes bearing the t(14;18) can be detected in some healthy people with no evidence of lymphoma.[58] Taken together, these points of evidence emphasize that although suppression of apoptosis is an important step in transformation, it is not sufficient to drive carcinogenesis.

NF-κB

Another pathway through which tumor cells might suppress apoptosis is the nuclear factor-κB (NF-κB) pathway. As discussed previously, activation of NF-kB during death receptor stimulation sets into motion a transcriptional program that inhibits apoptosis and promotes survival. NF-κB, under normal circumstances, is held in check by binding of the inhibitor of NF-κB, IκB. NF-κB is released on phosphorylation of IκB through activity of two IκB kinases, IKK-α and IKK-β.[64] Phosphorylation targets IκB for ubiquitination and degradation by the 26S proteasome, releasing NF-κB to translocate to the nucleus and activate its target genes (Fig. 5-4). Oncogenic stimuli, as well as survival signals, promote NF-κB activation. For example, Ras-mediated transformation stimulates transcriptional activity of NF-κB.[65] Furthermore, the Bcr-Abl fusion protein, a causative mutation in chronic myeloid leukemia, activates NF-κB by promoting nuclear translocation.[66] Virally induced transformation by human leukemia/lymphoma virus type 1 is dependent in part on Tax-mediated activation of IKKs.[67]

The proto-oncogene *Bcl-3* was identified on one arm of a translocation found in some lymphoid malignancies, t(14;19). This translocation brings the *Bcl-3* gene in proximity to the immunoglobulin heavy-chain enhancer, resulting in its overexpression. The *Bcl-3* gene encodes a member of the IκB family, but this gene product seems to function differently from other IκBs.[68] Specifically, Bcl-3 localizes to the nucleus and modifies the function of NF-κB subunits.[69] When overexpressed in normal T cells, Bcl-3 promotes survival following cellular activation, and expression seems to be induced on treatment

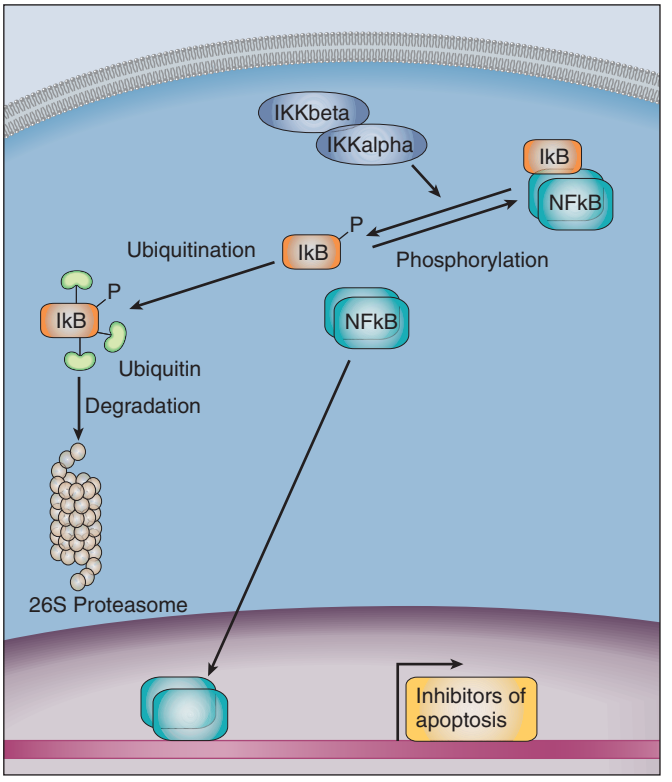


Figure 5-4 • NF-κB is a transcriptional activator of multiple antiapoptotic genes. Under resting conditions, NF-κB is bound by its inhibitor, IκB, which prevents its transcriptional activity by maintaining it in the cytoplasm. Activation signals stimulate activity of IκB kinases (IKK), which phosphorylate IκB. Phosphorylated IκB can then be ubiquitinated and targeted to the proteasome for degradation. This process releases NF-κB to enter the nucleus, where it activates transcription from its target promoters.

with immunologic adjuvants, suggesting a physiologic survival role for it in the immune system.[70] Mice expressing a *Bcl-3* transgene in B lymphocytes do not develop lymphoma, but they do show accumulation of B cells and hyper-responsiveness of the immune system, similar to the findings in *Bcl-2* transgenic mice.

PI3K/Akt

Many tumors lose extracellularly derived survival signals during pathogenesis, either by outstripping limited growth factors or by translocating to inappropriate environments. One signaling pathway that has been implicated in provision of survival signals is the phosphatidylinositol-3-kinase (PI3K) pathway.[71,72] Many growth factors, including interleukin-2, interleukin-3, platelet-derived growth factor, and insulin-like growth factor, signal in part through PI3K. PI3K phosphorylates phosphatidylinositide-4,5-bisphosphate (Ptd(4,5)P2) to Ptd(3,4,5)P3, which acts as a second messenger, activating downstream effectors such as the serine/threonine kinase Akt, also known as protein kinase B (PKB; Fig. 5-5). Akt seems to be a critical survival factor in many cell types, and its activity might promote survival through multiple functions, such as phosphorylation and inactivation of the BH3-only protein Bad, and through the Forkhead family transcription factor FKHRL1.[73] In addition, Akt acts in the insulin signaling pathway to promote glucose uptake, and it seems to play a similar role in non-insulin-responsive cells, promoting glucose uptake and glycolysis upon growth factor stimulation. It has been proposed that this metabolism-promoting effect of Akt might protect mitochondrial integrity through maintenance of substrate availability, thereby preventing apoptosis (Box 5-1).[74,75]

Another important mediator in the PI3K/Akt pathway is the mammalian target of rapamycin (mTOR). Akt indirectly activates mTOR through inhibitory phosphorylation of the TSC1/TSC2 complex,[76] leading to a complex interplay of proteins culminating in mTOR activation. Once active, mTOR promotes protein translation, leading to cell growth and proliferation. The complexity of this pathway, however, including multiple interacting protein partners and feedback mechanisms, makes it clear that the exact effects of mTOR activity on cell fate and cancer development require further elucidation.

Multiple studies have demonstrated the importance of Akt activity in tumorigenesis, either through amplification of one of the three AKT genes, or through loss of PTEN function. Amplification of *Akt* results in a similar phenotype to PTEN loss and has been found in gastric cancers, breast cancers, and other tumor types.[77–79] Furthermore, animal models also have demonstrated the role of Akt in tumorigenesis. Mice expressing constitutively active Akt in T cells develop thymic lymphoma at a high rate.[80] Furthermore, inhibition of mTOR activity diminishes tumor formation in mice heterozygous for PTEN, demonstrating the importance of mTOR in tumorigenesis mediated by this pathway.[81]

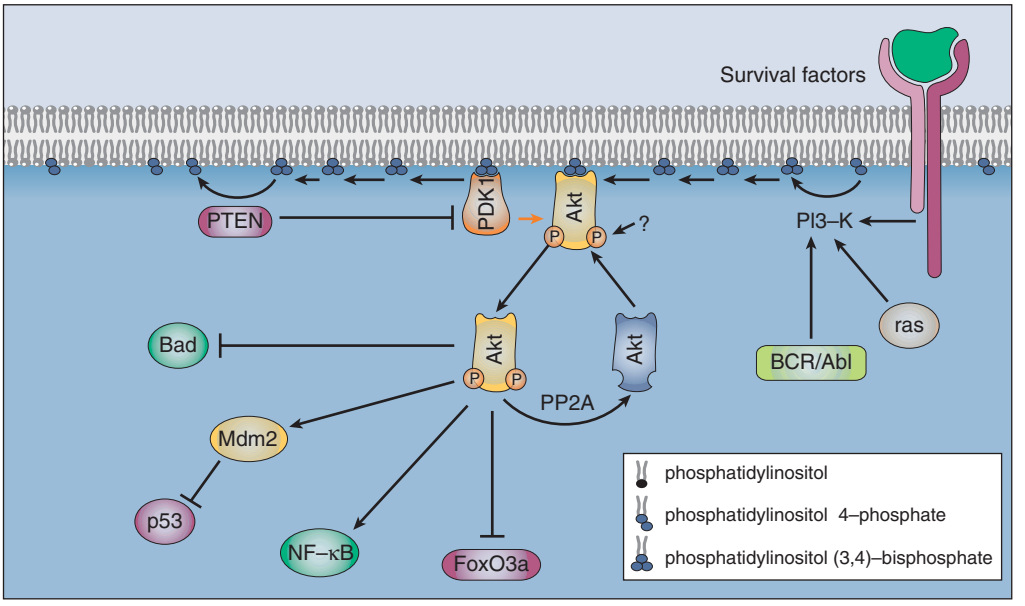


Figure 5-5 • The PI3K-Akt pathway is activated by multiple growth factor receptors and oncogenes and plays a critical role in promoting cell survival. PI3K is activated by growth factor stimulation or intracellular signals such as activated Ras or the oncogene *BCR-Abl*. Active PI3K phosphorylates phosphatidylinositols to phosphatidylinositol-3,4,5-triphosphate (PIP3) at the plasma membrane. PIP3 recruits Akt and its activating kinases, PDK1 and an uncharacterized PDK2, to the membrane, where Akt is phosphorylated and activated. Akt then promotes survival functions such as Bad and Forkhead inactivation, activation of NF-κB and MDM2, and glucose metabolism. PI3K activity is antagonized by the phosphatase PTEN, which degrades PIP3.

Box 5-1. METABOLIC DEREGULATION IN CANCER

Cells that lose survival signals fail to maintain themselves and undergo progressive atrophy. Loss of survival-inducing signal transduction leads to downregulation of cell-surface nutrient transporters (e.g., glucose transporters) and to a decreased rate of glucose metabolism, as indicated by decreased levels of hexokinase and phosphofructokinase, two key regulatory enzymes in the glycolytic pathway.[69,100–102] The loss of glycolytic products reduces delivery of substrate to the mitochondria, resulting in mitochondrial damage.

Nutrient limitation might have similar metabolic effects when cells accumulate in excess of the existing vascular supply.

In the 1920s, Warburg observed that cancer cells metabolize glucose at a higher rate than their normal counterparts. Furthermore, he found that the malignant cells relied on glycolysis for a disproportionate amount of their ATP production, with comparatively little energy produced by oxidative phosphorylation. Warburg hypothesized that this shift to aerobic glycolysis resulted from defects in mitochondrial function in the cancer cells.

Other researchers have subsequently confirmed Warburg's findings of increased aerobic glycolysis in cancer cells. The high rate of glucose uptake in tumors has formed the basis of a novel imaging modality, positron emission tomography (PET), using a fluorine-18-labeled glucose analog. A study evaluating PET scanning in lymphoma showed that more than 90% of lymphomas—including very indolent tumors—metabolize glucose at an abnormally high rate.[103] Although several research groups have found mutations in genes that encode mitochondrial enzymes in cancer cells, the fact that normal lymphocytes are unable to maintain glucose uptake and glycolysis in the face of dropping ATP levels suggests an alternative hypothesis. In this scenario, normal cells lack the ability to take up sufficient glucose to maintain themselves and instead are dependent on extrinsic signal transduction to maintain the expression and function of nutrient transporters. As a corollary, mutations that activate such signaling pathways could permit the cell to take up glucose in excess of that needed for bioenergetic or synthetic activities. Under such conditions, cells would secrete the excess glucose as lactate and have sufficient bioenergetic reserves to support entry into and progression through the cell cycle.

These findings raise the possibility that cancer cells, in the process of transformation, turn on signaling pathways that allow autonomous access to nutrients and metabolic pathways, rendering the cells independent of the extracellular signals normally required to maintain nutrient uptake. This facilitated access to nutrients would provide substrate to mitochondria, allowing maintenance of mitochondrial function and suppression of apoptosis even in the absence of growth factor signaling. If this hypothesis is true, autonomous access to nutrients is probably accomplished in multiple ways by different tumors.

One potential contributor to this goal is Akt. Akt is critical in the insulin signaling pathway to activate glucose uptake in insulin-responsive tissues, and it seems to play a similar role in non-insulin-responsive cells on growth factor stimulation. Although the role of *Akt* as an oncogene might include several functions, it clearly has the potential to promote glucose transporter expression and activity of glycolytic enzymes.

The role of metabolic control in tumorigenesis is poorly understood. Elucidation of this fundamental process in cancer might offer greater appreciation for the mechanisms of carcinogenesis.

Furthermore, the recognition of the importance of metabolic control in cancer could offer new therapeutic targets, improving our chances of defeating cancer in the future.

Epigenetic Gene Silencing

Inhibition of expression of tumor suppressor genes through epigenetic mechanisms is emerging as an important mechanism by which tumor cells might disable proapoptotic pathways. Promoter methylation at CpG islands could repress transcription of genes in the absence of mutation (Fig. 5-6). In addition, histone deacetylation might also turn off gene expression, possibly by inhibiting access of transcription factors (TF). For example, Soengas and associates[82] have shown that many melanoma cells (both primary tumors and cell lines) suppress Apaf-1 expression. This results in inhibition of p53-dependent apoptosis in these cells and renders them resistant to chemotherapy. Apaf-1 suppression is mediated not by mutation of *Apaf-1* but instead through methylation, because treatment with the methylation inhibitor 5-azacytidine restores both Apaf-1 expression and chemosensitivity. Methylation seems to play an important role in suppression of tumor suppressors in other tumors as well. For example, childhood neuroblastomas show loss of expression of caspase 8 through methylation of its promoter at high frequency.[83] Finally, promoter methylation of the *p14ARF* locus might suppress its expression in multiple tumor types.[84]

Acetylation of histones can also repress transcription of genes important in regulation of cell death. Global changes in histone acetylation have been found in cancer cells and are hypothesized to contribute to aberrant gene expression promoting survival and malignancy.[85]

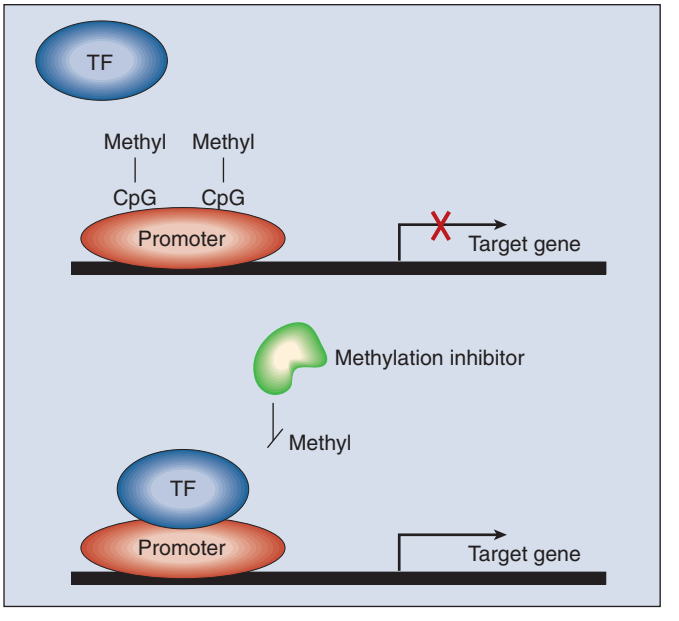


Figure 5-6 • Epigenetic gene silencing is a mechanism by which cancer cells turn off tumor suppressor gene expression. In the process of development or oncogenesis, genes might be silenced through promoter methylation. In tumors, promoters of tumor suppressor genes such as *Apaf-1* and caspase 8 are frequent targets of methylation. Methylation inhibitors such as 5-azacytidine reactivate expression of these tumor suppressor genes, potentially contributing to anticancer therapy.

MANIPULATING CELL DEATH IN CANCER TREATMENT

As discussed previously, cancer cells must dismantle or inhibit apoptotic pathways to maintain their transformed phenotype. Many trans-

formation-inducing mutations also have the effect of promoting programmed cell death, and cells are unable to pass through these initial changes to become cancer unless apoptosis is inhibited. This fact has two correlates. First, most traditional cancer chemotherapies act through induction of apoptosis, and the intrinsic apoptotic defects of these cells could make them inherently resistant to chemotherapy. On the other hand, cancer cells are constantly living "on the edge," pushed beyond the normal limits of cell viability. This fact might make tumor cells profoundly susceptible to apoptosis if either the defect can be corrected or another death pathway can be activated. This reasoning is the basis of the many attempts currently in progress to design therapies that will attain one of these objectives.

Restoration of Apoptotic Capability

Restoration of lost apoptotic pathways can be accomplished by several methods. First, if a proapoptotic gene, such as *p53,* is mutated, gene therapy provides a direct way in which to restore expression of the missing protein. One approach has been to attempt to deliver the gene in question via an adenoviral vector, for example with *p53* in tumors of the head and neck, and in lung tumors[86,87]; some success has been seen with intratumoral injections. Systemic therapy poses an additional challenge, however, in terms of both feasibility and safety. The effect of gene therapy with *p53* would be expected to be seen only in cells in which the transgene is expressed, requiring that every cell be infected by the vector. Furthermore, the safety of adenovirus vectors remains at issue.

Another, similar approach has been to target cancer cells lacking *p53* by taking advantage of the fact that adenovirus must inactivate *p53* to replicate in cells. Usually this is accomplished through the activity of the virus's E1Bp55 protein, which binds and inactivates p53. A virus that lacks E1Bp55 is unable to replicate in normal cells. Cancer cells that lack *p53* present a viable target, however, allowing the virus to accomplish its lytic life cycle and killing the cell. This approach is being used clinically with the drug ONYX-015, which, similar to *p53* gene therapy, has shown success with intratumoral injection in combination with chemotherapy in head and neck cancers.[88] Once again, systemic delivery seems more problematic.

In a strategy that is growing in importance in cancer therapy, small molecules targeting the p53 pathway have been designed to restore p53 function. One approach takes advantage of the fact that, in most cancers, *p53* is inactivated not by deletion but rather through a point mutation that results in accumulation of inactive protein. CP-31398 is a drug found in a screen for therapeutic agents that restore wild-type conformation to mutant p53 in tumor cells.[89] Since its identification, researchers have found conflicting data regarding its ability to restore p53 function in tumor cells, with some studies finding evidence of restoration of p53 function but others reporting nonspecific toxicity.[90,91]

Another approach has been to target the interaction of p53 with the inhibitory molecule MDM-2. Small-molecule inhibitors have been identified and have shown promise in preclinical studies.[92] Early-phase clinical studies using this approach are expected to be underway shortly.

The realization that many cancer cells turn off expression of proapoptotic genes by epigenetic mechanisms has provided another approach to the restoration of tumor suppressor function. Histone deacetylase inhibitors have entered clinical trials and have shown evidence of activity.[93,94] One of these, suberoylanilide hydroxamic acid, has shown activity in several tumor types and has been approved for use in cutaneous T-cell lymphomas. DNA methylation inhibitors are also in development.[95] The lack of specificity of these treatments raises theoretical concerns that genes which have been silenced in differentiation (e.g., *hTERT,* the human telomerase gene that might play a role in tumor promotion) or other tumor-promoting genes could be turned on through demethylation or deacetylation. Silencing of TRAIL decoy receptors through methylation has been demonstrated in cancer cells.[96] The end result of these therapies could depend on the balance of genes silenced through epigenetic mechanisms in each cancer, but early clinical trials are promising.

Inhibition of Survival Factors

Small-molecule inhibitors might show promise in the inhibition of survival factors expressed in cancer cells. The 26S proteasome is important in myriad cellular pathways, but its importance in activation of NF-κB, through degradation of IκB, has raised the possibility that inhibition of proteasomal degradation could have proapoptotic effects in cancer cells. Akt has also been reported to phosphorylate the tumor suppressor genes *TSC1* and *TSC2* and target them for proteasomal degradation.[97] Bortezomib, a proteasomal inhibitor, has shown activity in several hematologic malignancies, notably multiple myeloma,[98] in which it has been approved by the FDA for use, and mantle cell lymphoma. The activity of bortezomib as a sensitizing agent, lowering the threshold for apoptosis in response to other cytotoxic agents, is also under active investigation.

Small-molecule inhibitors targeting several other components of survival pathways are under development. Inhibitors of mTOR and Akt are currently in clinical trials, and a small-molecule inhibitor of Bcl-2 is undergoing preclinical testing at the time of this writing.[99] Inhibitors of IAP molecules are also drawing interest and under preclinical development.

Antisense strategies have been explored to target antiapoptotic molecules. Antisense oligonucleotides act by binding to specific messenger RNAs, forming double-stranded RNA complexes.These complexes might inhibit expression of the target messenger RNAs, either by blocking translation or through targeting them for destruction by the cell through recognition of abnormal double-stranded RNA. The most developed of these antisense oligonucleotides is one targeted against *Bcl-2,*[100–102] oblimersen, also known as Genasense. Trials in hematologic malignancies and in several solid tumors have shown some activity and it might be particularly useful as a sensitizing agent when used in combination with other cytotoxic therapies.

Death Receptor Activation

As discussed in previous sections, death receptor signaling seems to play an important role in some tumors. Initial studies examined the use of Fas and TNF as death-inducing ligands. Yet, although these molecules demonstrated antitumor activity, their utility as therapeutic agents has been compromised by toxicity, with both normal cells and malignant cells targeted for death.

Investigations of TRAIL have raised the possibility that this ligand might be more selective for tumor cells. Most normal cells express decoy receptors that sequester TRAIL, preventing it from sending an intracellular death signal. Tumor cells seem to be uniquely sensitive to the apoptotic stimulus of TRAIL; one reason might be downregulation of decoy receptor expression, possibly by promoter methylation.[87] Studies in mice and nonhuman primates have demonstrated minimal toxicity to normal cells with administration of TRAIL.[103,104] When researchers examined the effects of TRAIL on human hepatocytes in vitro, however, it was found to cause significant cell death, raising the question whether TRAIL, like its counterparts Fas and TNF, might be too toxic for use in humans at therapeutic doses.[105] Early-phase clinical trials of TRAIL are underway.

Induction of Necrosis

The recognition of necrosis as a regulated, physiologic process raises the possibility that induction of necrotic cell death might present advantages in targeting cancer cells. Some currently used therapeutics might act in large part through inducing necrosis, and a strategy priming cells for necrotic cell death could contribute to the effectiveness of these treatments. As discussed previously, the metabolic state of a cancer cell seems to predispose it to necrosis in response to DNA damage through loss of the ability to produce ATP through glycolysis. Cancer cells might be sensitized to the effects of DNA-damaging

agents if also treated with agents that interfere with glycolysis. Whereas all cells depend to some extent on glycolytic metabolism, a modest inhibition of glycolysis in cells that are highly dependent on this pathway could potentially enhance the effects of DNA damage-based treatments. Other strategies to induce necrosis, such as induction of reactive oxygen species and promotion of RIP activity, might also be optimized as our understanding of these pathways increases. A potential advantage of necrosis as a treatment strategy lies in the potential to promote an immune reaction, and therefore possibly recruit the immune system to assist in fighting the tumor.

SUMMARY

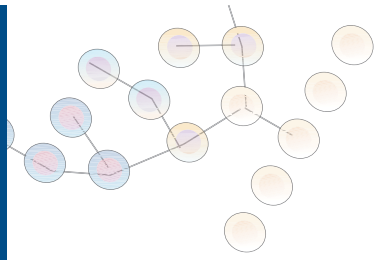
Understanding of mechanisms of cell death and their importance in tumorigenesis is evolving rapidly. Our interpretation of these findings will certainly undergo revision as more information constantly becomes available. The current appreciation for these processes, however, already has provided opportunities for advancement of patient care.

In the future, research further clarifying the basic mechanisms of programmed cell death—including events mediating mitochondrial demise along with a better understanding of the nature of death signals—will continue to improve our arsenal of potential weapons against cancer. As has been found with traditional antineoplastic therapies, success will most likely be found with a combination of therapeutic approaches. These might include the addition of apoptosis-based therapies to traditional agents, combining proapoptotic with antisurvival approaches, along with strategies to manipulate both forms of cell death that await development as knowledge of these complex processes evolves.

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6 Cancer Immunology

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SUMMARY OF KEY POINTS

- Cancer cells develop, grow, invade, and metastasize in the context of an organized microenvironment. This is reflected by the fact that for many cancers the majority of cells within the tumor mass are nontransformed.
- The relationship between the tumor cells and the nontransformed cells composing the tumor microenvironment is dynamic and active.
- The immune system is a major component of the tumor microenvironment, and therefore, the tumor must actively organize the immunologic component of its microenvironment.
- Because the immune response—particularly that mediated by killer T cells and cells of the innate immune system—can be a potent enemy to the tumor, a successful cancer must develop mechanisms to instruct the immune system to "tolerate" its existence, particularly when it is invading through tissue barriers and metastasizing to many organ sites.
- If a tumor fails to develop these tolerance induction and immunologic resistance mechanisms, the immune system will eliminate it.
- Oncogenic pathways in the tumor not only mediate cell growth, metabolic activity, and antiapoptotic activity, they also mediate interactions with the immune system.
- Ultimately, tumors do more than merely inhibit effecter functions of the immune system that can be detrimental to them. Tumors can in fact alter immunologic activity to promote tumor growth and development.
- We are now beginning to understand the molecular and cellular basis for tumor–immune system interactions, providing specific molecular targets for immunologic intervention.

OVERVIEW

Historically, interest in cancer immunology stemmed from the perceived potential activity of the immune system as a weapon against cancer cells. In fact, the term "magic bullet," commonly used to describe many visions of cancer therapy, was coined by Paul Ehrlich in the late 1800s in reference to antibodies targeting both microbes and tumors. Central to the concept of successful cancer immunotherapy are the dual tenets that tumor cells express an antigenic profile distinct from their normal cellular counterparts and that the immune system is capable of recognizing these antigenic differences. Support for this notion originally came from animal models of carcinogen-induced cancer in which it was demonstrated that a significant number of experimentally induced tumors could be rejected upon transplantation into syngeneic immunocompetent animals.[1–4] Extensive studies by Prehn on the phenomenon of tumor rejection suggested that the most potent tumor rejection antigens were unique to the individual tumor.[5]

As cancer genetics and genomics has exploded over the past decade, it is now quite clear that altered genetic and epigenetic features of tumor cells indeed result in a distinct tumor antigen profile. Overexpression of "oncogenic" growth factor receptor tyrosine kinases such as HER2/Neu and epidermal growth factor receptor (EGFR) via epigenetic mechanisms has provided clinically relevant targets for one arm of the immune system—antibodies.[6,7] Indeed, monoclonal antibodies are the largest growing single class of cancer therapeutics based on successful new U.S. Food and Drug Administration approvals. In striking contrast, cellular immunotherapy of cancer has been quite disappointing in establishing therapeutic success in clinical trials thus far. Emerging insights about the nature of the interaction between the cancer and the immune system have led us to understand why cell-based cancer immunotherapy approaches such as therapeutic vaccines have been less potent against established cancer than originally imagined. In general, we have learned that tumors use mechanisms of tolerance induction to turn off T cells specific for tumor-associated antigens. Oncogenic pathways in tumors result in the elaboration of factors that organize the tumor microenvironment in ways that are quite hostile to antitumor immune responses.

Not only is the cancer capable of inducing potent tolerance among tumor-specific T cells, we now know that there are distinct forms of inflammatory and immune responses that are procarcinogenic. Thus, two frontiers in cancer immunology are the elucidation of how the tumor organizes its immune-microenvironment as well as the nature of immune responses that are anticarcinogenic versus procarcinogenic. As the receptors, ligands, and signaling pathways that mediate immune tolerance and immune-induced procarcinogenic events are elucidated, these factors and pathways can be selectively inhibited by both antibodies and drugs in a way to shift the balance to antitumor immune responses. This chapter will outline the major features of tumor–immune system interactions and set the stage for molecularly based approaches to manipulate immune responses for successful cancer therapy.

HOW DO TUMORS DIFFER FROM SELF TISSUES?

Tumors differ fundamentally from their normal cell counterparts in both antigenic composition and biologic behavior. Genetic instability, a basic hallmark of cancer, is a primary generator of tumor-specific antigens. The most common genetic alteration in cancer is mutation,

which arises from defects in DNA damage repair systems of the tumor cell.[8–15] Recent estimates from genome-wide sequencing efforts suggest that every tumor contains a few hundred mutations in coding regions.[16] Additionally, deletions, amplifications, and chromosomal rearrangements can result in new genetic sequences resulting from juxtaposition of coding sequences not normally contiguous in untransformed cells. The vast majority of these mutations occur in intracellular proteins, and thus, the "neoantigens" they encode would not be readily targeted by antibodies. However, the major histocompatibility complex (MHC) presentation system for T-cell recognition makes peptides derived from all cellular proteins available on the cell surface as peptide-MHC complexes capable of being recognized by T cells. Based on analysis of sequence motifs, it is estimated that roughly one-third of the mutations identified from genome sequencing of 22 breast and colon cancers[16] were capable of binding to common human lymphocyte antigen (HLA) alleles based on analysis of sequence motifs (J.P. Allison, personal communication).

In accordance with the original findings of Prehn,[5] the vast majority of tumor-specific antigens derived from mutation as a consequence of genetic instability are unique to individual tumors. The consequence of this is that antigen-specific immunotherapies targeted at most truly tumor-specific antigens would by necessity be patient specific. However, there are a growing number of examples of tumor-specific mutations that are shared. The three best-studied examples are the Kras codon 12 G→A (found in roughly 40% of colon cancers and >75% of pancreas cancers), the BRAF V599E (found in roughly 70% of melanomas) and the p53 codon 249 G→T mutation (found in ~50% of hepatocellular carcinomas).[17–20] As with nonshared mutations, these common tumor-specific mutations all occur in intracellular proteins, and therefore require T-cell recognition of MHC-presented peptides for immune recognition. Indeed, both the Kras codon 12 G→A and the BRAF V599E mutations result in "neopeptides" capable of being recognized by HLA class 1- and class II-restricted T cells.[21–24]

The other major difference between tumor cells and their normal counterparts derives from epigenetics.[25] Global alterations in DNA methylation as well as chromatin structure in tumor cells results in dramatic shifts in gene expression. All tumors overexpress hundreds of genes relative to their normal counterparts, and in many cases, turn on genes that are normally completely silent in their normal cellular counterparts. Overexpressed genes in tumor cells represent the most commonly targeted tumor antigens by both antibodies and cellular immunotherapies. This is because, in contrast to most antigens derived from mutation, overexpressed genes are shared among many tumors of a given tissue origin or sometime multiple tumor types. For example, mesothelin, which is targeted by T cells from vaccinated pancreatic cancer patients,[26] is highly expressed in virtually all pancreatic cancers, mesotheliomas, and most ovarian cancers.[27,28] Whereas mesothelin is expressed at low to moderate levels in the pleural mesothelium, it is not expressed at all in normal pancreatic or ovarian ductal epithelial cells.

The most dramatic examples of tumor-selective expression of epigenetically altered gene are the so-called cancer-testis antigens.[29] These genes seem to be highly restricted in their expression in the adult. Many are expressed selectively in the testis of males and are not expressed at all in females. Expression in the testis seems to be restricted to germ cells, and some of these genes actually seem to encode proteins associated with meiosis.[30–32] Cancer-testis antigens therefore represent examples of widely shared tumor-selective antigens whose expression is highly restricted to tumors. Many cancer-testis antigens have been shown to be recognized by T cells from nonvaccinated and vaccinated cancer patients.[29] From the standpoint of immunotherapeutic targeting, a major drawback of the cancer-testis antigens is that none appear to be necessary for the tumors' growth or survival. Therefore, their expression seems to be purely the consequence of epigenetic instability rather than selection, and antigen-negative variants are easily selected out in the face of immunotherapeutic targeting.

A final category of tumor antigen that has received much attention encompasses tissue-specific antigens shared by tumors of similar histologic origin. Interest in this class of antigen as a tumor-selective antigen arose when melanoma-reactive T cells derived from melanoma patients were found to recognize tyrosinase, a melanocyte-specific protein required for melanin synthesis.[33,34] In fact, the most commonly generated melanoma-reactive T cells from melanoma patients recognize melanocyte antigens.[35] Although one cannot formally call tissue-specific antigens tumor specific, they are nonetheless potentially viable targets for therapeutic T-cell responses when the tissue is dispensable (e.g., prostate cancer or melanoma).

From the standpoint of T-cell targeting, tumor antigens upregulated as a consequence of epigenetic alterations represent "self-antigens" and are therefore likely to induce some level of immune tolerance. However, it is now clear that the stringencies of immune tolerance against different self-antigens differ according to tissue distribution and normal expression level within normal cells. The mesothelin antigen described previously is such an example. In a recent set of clinical pancreatic cancer vaccine studies, mesothelin-specific T-cell responses were induced by vaccination with genetically modified pancreatic tumor cell vaccines and induction of mesothelin-specific T cells correlated with ultimate disease outcome. Given that the immune system is capable of differential responsiveness determined by antigen levels, it is quite possible to imagine generating tumor-selective immune responses against antigens whose expression level in the tumor is significantly greater within normal cells in the tumor-bearing host. Additionally, upregulated antigens that provide physiologically relevant growth or survival advantages to the tumor are preferred targets for any form of therapy, because they are not so readily selected out.

Beyond the antigenic differences between tumor cells and normal cells, there are important immunologic consequences to the distinct biologic behavior of tumor cells relative to their normal counterparts. Whereas uncontrolled growth is certainly a common biologic feature of all tumors, the major pathophysiologic characteristics of malignant cancer responsible for morbidity and mortality are their ability to invade through natural tissue barriers and ultimately to metastasize. Both of these characteristics, never observed in nontransformed cells, are associated with dramatic disruption and remodeling of tissue architecture.

Indeed, the tumor microenvironment is quite distinct from the microenvironment of normal tissue counterparts. One of the important consequences of tissue disruption, even when caused by noninfectious mechanisms, is the elaboration of proinflammatory signals. These signals, generally in the form of cytokines and chemokines, are potentially capable of naturally initiating innate and adaptive immune responses. Indeed, the level of leukocyte infiltration into the microenvironment of tumors tends to be significantly greater than the leukocyte component of their normal tissue counterparts. Cancers are therefore constantly confronted with inflammatory responses as they invade tissues and metastasize. In some circumstances these inflammatory and immune responses can potentially eliminate a tumor—so called immune surveillance. However, as will be discussed, oncogenic pathways in the tumor seem to organize the immunologic component of the microenvironment in a fashion that not only protects itself from antitumor immune responses, they can qualitatively shift immune responses to those that actually support and promote tumor growth. Thus, just as with Annekin Skywalker, the tumors can entice the immune system to the dark side. It is these elements of the cancer–immune system interaction that will be the central targets of future immunotherapeutic strategies.

EVIDENCE PRO AND CON FOR IMMUNE SURVEILLANCE OF CANCER

The fundamental tenet of the immune surveillance hypothesis, first conceived nearly a half-century ago,[36,37] is that a fundamental role of

Box 6-1. HOW IMPORTANT IS IMMUNE SURVEILLANCE OF CANCER?

Few questions in cancer immunology have been more controversial than the immune surveillance hypothesis. First put forward by Lewis Thomas over a half century ago, the original immune surveillance hypothesis proposed that a natural role for the immune system was to survey the body for tumors similarly to the way the immune system surveys the body for invading foreign pathogens. Tumors were proposed to be distinguished from self-tissues by virtue of expression of tumor-specific antigens (TSAs). One aspect of this hypothesis that has held up to experimental testing has been the existence of TSAs. We now know that the genetic instability of tumor cells generates genetic and epigenetic changes that translate to antigens capable of being recognized by the immune system. However, because tumors seem to have developed mechanisms to subvert immunogenicity and tolerize the immune system, it is generally no longer believed that immune surveillance represents a major endogenous defense against tumorigenesis. It is likely that guardians of the genome that sense DNA damage, such as the ATR/ATM/p53 system, are much more fundamental mechanisms to protect against transformation. However, certain specialized components of the immune system, such as interepithelial lymphocytes activated by stress-induced ligands, may indeed play a complementary role in immune surveillance among specific epithelial tissues that are frequently exposed to carcinogenic stress. The best example is the intraepithelial lymphocytes within cutaneous epithelium that is constantly exposed to carcinogenic ultraviolet irradiation. A more moderate view of immune surveillance has been summarized by the hypothesis of Schreiber and colleagues that tumors "edit" themselves to either become resistant to immunologic surveillance or upregulate pathways (such as the STAT3 pathway) that actively induce tolerance among components of the immune system capable of recognizing TSAs.[57–59]

the immune system is to survey the body for tumors as it does for infection with pathogens, recognizing and eliminating them based on their expression of tumor-associated antigens (Box 6-1). In animal models, carcinogen-induced tumors can be divided into those that grow progressively (termed progresser tumors) and those that are rejected after an initial period of growth (termed regresser tumors).[1,2] The phenomenon of regresser tumors was thought to represent an example of the ongoing process of immune surveillance of cancer. A corollary to the original immune surveillance hypothesis is that progresser tumors in animals (presumed to represent clinically progressing cancers in humans) fail to be eliminated because they develop active mechanisms of either immune escape or resistance (Fig. 6-1).

A fundamental prediction of the immune surveillance hypothesis is that immunodeficient individuals would display a dramatic increase in tumor incidence. After an extensive analysis of spontaneous tumor formation in immunodeficient nude mice, which have atrophic thymi and therefore significantly reduced numbers of T cells and T-cell-dependent immune responses, no increased incidence of tumors was observed.[38–42] These studies were taken as a major blow to the immune surveillance hypothesis. However, a caveat to the interpretation of these results is that nude mice still produce diminished numbers of T cells via thymus-independent pathways and therefore can mediate some degree of T-cell-dependent immunity. In addition, nude mice frequently display compensatory increases in innate immunity that, as in the following discussion, may represent a potent form of antitumor immunity and could contribute to immune surveillance of cancer.

Epidemiologic studies of patients with heritable immunodeficiencies revealed a significantly increased risk of certain cancers that are distinct from the epithelial cancers commonly observed in normal immunocompetent adults.[43–45] Many of these cancers are also observed in transplant patients on chronic pharmacologic immune suppression as well as in human immunodeficiency virus/acquired immunodeficiency syndrome patients whose immune system is depressed. The most common cancers in these individuals include lymphoplastic lymphomas as well as Kaposi's sarcoma; however, certain epithelial cancers, such as stomach cancer, were also observed at increased frequency. A unifying theme for the majority of cancers observed in immunodeficient individuals is their microbial origin. The majority of lymphoplastic lymphomas are Epstein-Barr virus-associated lymphomas,[46] and Kaposi's sarcoma is a result of infection with the herpesvirus KSHV (Kaposi's sarcoma herpesvirus).[47] Other virus-associated cancers such as cervical cancer (from human papillomavirus [HPV])[48,49] are also observed at increased frequency. It is now appreciated that stomach cancer is associated with ulcer disease related to infection with the bacterium *Helicobacter pylori*.[50,51] From these studies, the notion emerged that immune surveillance indeed protects individuals against certain pathogen-associated cancers by either preventing infection or altering chronic infection by viruses and other microbes that can eventually induce cancer. These studies were taken to represent evidence that the common non-pathogen-associated cancers most commonly seen in adults in developed countries (e.g., prostate cancer, colon cancer, lung cancer) are not subject to immune surveillance.

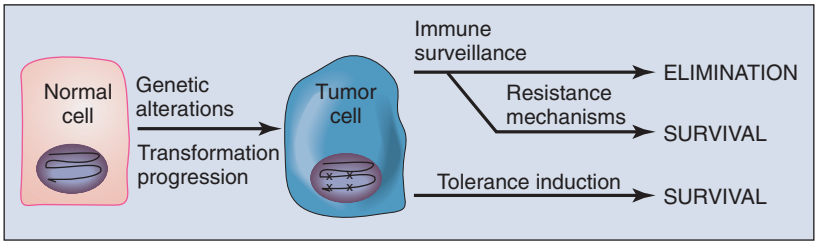


Figure 6-1 • The balance among immune surveillance, resistance, and tolerance. Transformation of normal cells to cancer cells involves the creation of true neoantigens resulting from mutation as well as upregulation of self-antigens resulting from epigenetic forces. Successful immune surveillance of tumors based on recognition of these tumor-specific antigens would lead to tumor elimination at early stages. Clinically relevant tumor survival and progression requires that tumors develop resistance mechanisms that inhibit tumor-specific immune responses to kill tumor cells. Alternatively, if the tumor develops mechanisms to induce immune tolerance to its antigens, antitumor effector responses do not develop. Evidence is accumulating that tumors actively develop immune resistance mechanisms as well as immune tolerance mechanisms to survive despite displaying antigens capable of recognition by the immune system.

Two caveats to this interpretation must be noted, however. First, detailed epidemiologic analyses of immunodeficient individuals were performed at a time when these patients rarely lived beyond their 20s and 30s, when cancer incidence normally increases most significantly. It is therefore possible that a more subtle cumulative increased incidence of common non-pathogen-associated cancers would have been observed had these individuals lived further into adulthood. Indeed, more recent analyses definitively demonstrate an increased incidence of some non-pathogen-associated cancers, in immunodeficient individuals, particularly melanoma.[52]

In addition to epidemiologic data, dramatic anecdotal examples are difficult to ignore. There have been reports that patients receiving kidneys from a cadaver donor that had been in complete remission from a melanoma before organ donation each rapidly developed metastatic melanoma of donor origin after the transplant.[53–55] These results indicate that at least for some non-pathogen-associated tumors, the immune system can play a significant role in maintaining the micrometastatic disease in a dormant state. Whether this principle applies to other non-pathogen-associated human tumors besides melanoma remains to be demonstrated.

Several recent studies reevaluating tumor immune surveillance in genetically manipulated mice have revealed clear-cut evidence that various components of the immune system can at least modify, if not eliminate, both carcinogen-induced and spontaneously arising cancers. In a series of studies by Schreiber and colleagues reexamining cancer incidence in mice rendered immunodeficient via genetic knockout of either the *RAG2* gene (deficient in both B and T cells), the γ-interferon receptor gene, *STAT 1* gene, or the *type 1 interferon receptor* gene.[56–59] When these knockout mice are either treated with carcinogens or crossed onto a cancer-prone *p53* knockout background, the incidence of cancers was modestly but significantly increased relative to nonimmunodeficient counterparts when observed over an extended period (longer than 1 year). Transplantation studies demonstrated that direct γ-interferon insensitivity by the developing tumors played a significant role in the defect in immune surveillance. Interestingly, in contrast to γ-interferon receptor knockout mice, the mechanism for increased tumor incidence in tumors in *type 1 interferon receptor* knockout mice did not involve sensitivity by the tumor to type 1 interferons but rather reflected the role of the type 1 interferons in induction of innate and adaptive immunity. Even animals not crossed onto a cancer-prone genetic background or treated with carcinogens developed an increased incidence of invasive adenocarcinomas when observed over their entire life span.

Furthermore, γ-interferon, *RAG2* double-knockout mice developed a broader spectrum of tumors than *RAG2* knockout mice. All of the tumors that arise in these genetically manipulated immunodeficient animals behave as regresser tumors when transplanted into immunocompetent animals. These findings indeed suggest that tumors that arise in immunodeficient animals would have been eliminated had they arisen in immunocompetent animals.

The relatively subtle effects on tumorigenesis, requiring observation over the life span of the animal, suggest that the original concept of immune surveillance of tumors arising on a daily basis is in fact not correct. Instead, it is clear that the presence of a competent immune system "sculpts" the tumor through a process that has been termed immunoediting. One of the caveats in the interpretation of these studies comes from the work of Enzler and Dranoff, who studied mechanisms of increased tumorigenesis in granulocyte-macrophage colony-stimulating factor (GM-CSF), γ-interferon double-knockout mice.[60] Although they observed an increase in gastrointestinal and pulmonary tumors, they noted that such animals harbored infection with a particular bacterium not normally observed in immunocompetent animals. Maintenance of these double-knockout mice on antibiotics essentially eliminated the increased rate of tumor formation. Thus, it is possible that some of the increased tumor rates in genetically immunodeficient animals could be related to unappreciated chronic infections that develop in these animals, which are not housed under germ-free conditions. Nonetheless, although the classic concepts of immune surveillance of cancer remain unsupported by experimental evidence, studies on tumorigenesis in genetically manipulated immunodeficient mice indeed suggest that developing tumors must actively adapt themselves to their immune microenvironment to exist within the context of a competent immune system.

INNATE IMMUNITY, EPITHELIAL IMMUNITY, AND TUMOR IMMUNE SURVEILLANCE

Although much emphasis has been placed on the role of adaptive immunity, particularly of conventional T cells in immune surveillance of cancer, a confluence of more recent findings points to innate immunity and epithelial immunity in the immunologic sensing of carcinogenic events in the skin, gut, and possibly other sites. Much of the evidence focuses on the NKG2D receptor. NKG2D was originally defined as an activating natural killer (NK) receptor.[61–63] Most NK receptors seem to be inhibitory when engaged; this inhibition is often associated with ITIM (immunoreceptor tyrosine kinase-based inhibitory motif) domains in the cytoplasmic tails. ITIMs provide docking sites for phosphatases that oppose the activity of tyrosine kinases involved in lymphocyte activation. NK activation status is a balance between engagement of activating and inhibitory receptors. NKG2D, the best-studied activating receptor on NK cells, is somewhat unusual in that it does not contain an ITAM (immunoreceptor tyrosine kinase-activating motif) and is associated with an adaptor molecule, DAP 10, which contains neither conventional ITIMs nor ITAMs.[64] Instead, DAP 10 contains a KYXXM motif that seems to bind to phosphatidyl inositol (PI) 3 kinase upon phosphorylation of the tyrosine in this motif. NKG2D is expressed on all NK cells as well as on some αβ and γδ T cells. Beyond NK cells, NKG2D is expressed at high levels on a number of subsets of interepithelial lymphocytes (IELs).

IELs represent a distinct population of lymphocytes residing in epithelial tissues that display features of both adaptive and innate immune responses.[65–69] They are thought to represent a major first line of defense against pathogens attempting to invade across epithelial linings exposed to the environment (i.e., skin, gut, respiratory tract). Fifty percent of the IELs of the gut express the γδ T-cell receptor (TCR), which is normally expressed by less than 3% of circulating T cells, whereas the other 50% express the common αβ TCR. γδ TCR-expressing IELs in different compartments express a very restricted repertoire and are thought to recognize certain types of microbial antigens or potentially self-antigens associated with stress or inflammatory responses to microbial infection. Even the αβ TCR-expressing IELs have an extremely restricted TCR repertoire similar to invariant NK T cells. A significant subset of gut IELs express a particular $V_\alpha V_\beta$ and are thought to recognize a limited subset of microbial or self nonpeptide antigens presented by nonclassical class 1 MHC molecules. Thus, NKG2D expression marks diverse subsets of lymphocytes that, though expressing different families of recognition receptors, act as components of innate immunity in that they recognize a stereotypical set of antigens associated with infection or stress (see later discussion).

The first evidence that the NKG2D receptor might play a role in tumor immune surveillance came from the finding that normal colonic epithelium as well as a significant proportion of tumors could express the two defined human ligands for NKG2D: MICA and MICB. MICA and MICB, which represent nonclassical MHC class I-type molecules whose structure demonstrates no antigen-binding groove characteristic of most MHC molecules, are stress-induced proteins whose genes contain stress response elements in their promoters.[70,71] Raulet and colleagues have demonstrated that upregulation of MICA/B is induced through the ATM/ATR/Chk1 pathway of DNA damage recognition.[72] An analysis in human cancer suggested a correlation between expression of MICA/B and infiltration of certain subsets of γδ T cells that express NKG2D. Initially it was proposed

that MICA and MICB were direct ligands for specific γδ receptors themselves as well as NKG2D,[73,74] but this idea is controversial.

MICA and MICB do not have any murine orthologs, but murine NKG2D does bind to products of the retinoic acid-inducible gene family, RAE-1α-RAE-1ε, as well as the product of the *H60* gene. ULBP3 is an additional NKG2D ligand to be described.[75,76] These NKG2D ligands seem to be involved in immune recognition and possibly tumor surveillance in mice.[77–79] Recognition and killing of murine skin keratinocytes or intestinal epithelial cells by γδ IELs require expression of NKG2D ligands and are blocked by anti-NKG2D antibodies. Trasnfection of murine tumors with genes encoding NKG2D ligands renders them susceptible to NKG2D-dependent killing by NK cells. Emerging data on NKG2D function on IELs together with the potentially stress-induced nature of its ligands suggests that the IEL system of immune surveillance may indeed be relevant to carcinogenesis as well as infectious challenges.[80] The major initiating event of carcinogenesis in the skin—ultravioleet light—is a potent source of DNA damage that, as mentioned previously, has been shown to induce NKG2D ligands via the ATM pathway. Thus, in addition to endogenous killers of genome-damaged cells, such as p53, IELs and NK cells may represent an extrinsic sensor of DNA damage and genotoxic stress via recognition of cells that have upregulated NKG2D ligands (Fig. 6-2).

As with the case of classic immune surveillance mediated by classical T cells, the emergence of a clinically evident cancer implies that the tumor has developed a mechanism to circumvent or evade any innate immune surveillance systems. In the case of the NKG2D system, Spies and colleagues have provided suggestive evidence that tumors can shed MICA/B in a soluble form as a means of evading NKG2D-dependent recognition. They demonstrated that certain tumors are associated with high levels of shed MICA/B and that soluble MICA/B binds to and downmodulates NKG2D on NK cells, thereby acting as an antagonist to NKG2D activation via cell surface-bound MICA/B.[81] Although this mechanism remains to be proven as a true evasion system for NKG2D-dependent tumor recognition, it points out the diversity of mechanisms that tumors utilize to evade immune recognition. It also points out straightforward approaches to block these evasion systems. If indeed soluble MICA/B does represent a mechanism for tumor immune evasion of innate immune recognition, antibodies that would bind to and clear soluble MICA/B but not block the interaction between cell membrane MICA/B and NKG2D on NK cells could potentially restore the capacity of NK cells to recognize MICA/B-expressing tumors.

IMMUNE TOLERANCE AND IMMUNE EVASION—THE HALLMARK OF A SUCCESSFUL TUMOR

Although controversy over the ultimate role of immune surveillance in natural modulation of cancer development and progression will

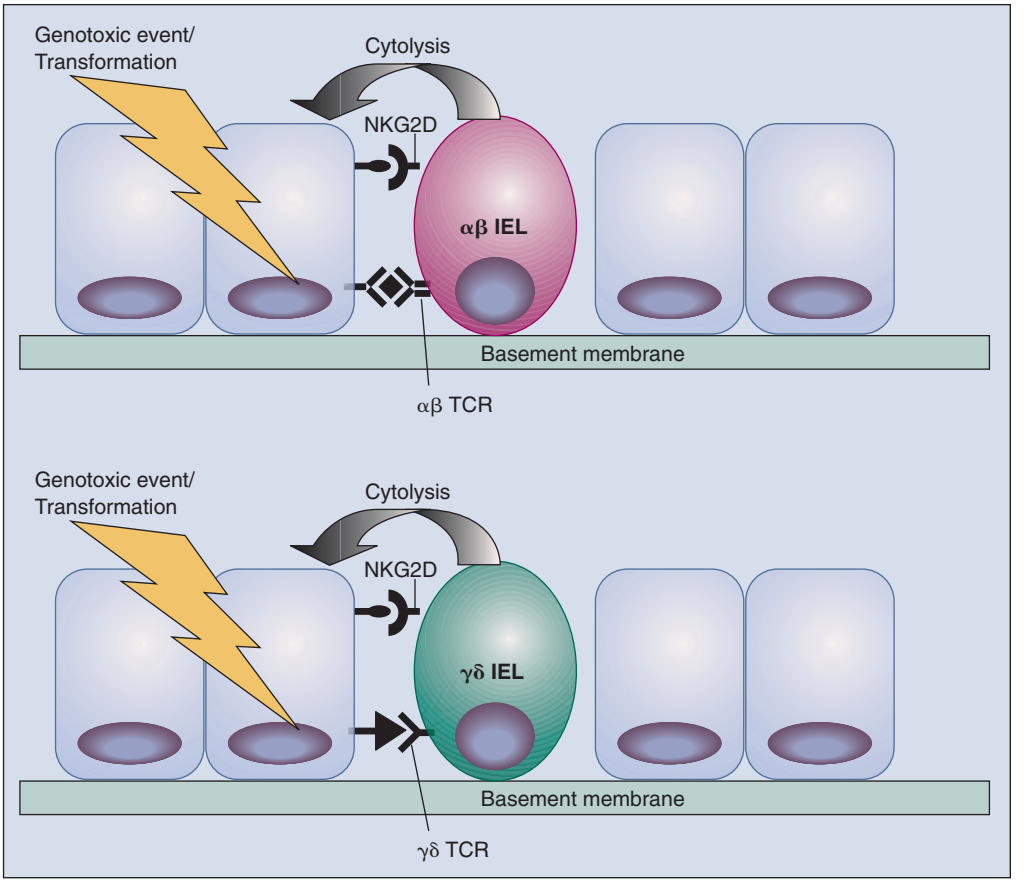


Figure 6-2 • Epithelial linings contain intraepithelial lymphocytes that can recognize epithelial cells undergoing genotoxic stress. Intraepithelial lymphocytes (IELs) fall into two categories: those that express the classical αβ T-cell receptor (TCR) that recognizes peptide-MHC complexes on the cell surface and those that express the γδ TCR, whose ligands are less well characterized. IELs also express the NKG2D receptor, which serves as a costimulatory receptor for activation of IELs. The ligands for NKG2D, MICA, and MICB in humans and RAE1α–RAE1ε, H60, and ULBP-3 in mice, are induced by genotoxic stress via the ATM/ATR pathways. This is a mechanism by which IELs can survey for damaged epithelial cells due to irradiation (skin) or mutagens that can cause transformation.

undoubtedly continue into the future, one can summarize the current state of knowledge as supporting the notion that natural immune surveillance plays a much smaller role than originally envisioned by Thomas and Burnet. However, developing tumors need to adapt to their immunologic milieu in a manner that either turns off potentially harmful (to the tumor) immune responses or creates a local microenvironment inhibitory to the tumoricidal activity of immune cells that could inadvertently become activated in the context of inflammatory responses associated with tissue invasion by the tumor. These processes—tolerance induction and immune evasion—have become a central focus of cancer immunology efforts and will undoubtedly provide the critical information necessary for development of successful immunotherapies that break tolerance to tumor antigens and break down the resistance mechanisms operative within the tumor microenvironment (see Fig. 6-1).

Evidence from both murine tumor systems as well as human tumors strongly demonstrates the capacity of tumors to induce tolerance to their antigens. This capacity to induce immune tolerance may very well be the single most important strategy that tumors use to protect themselves from elimination by the host's immune system. Tolerance to tumors seems to operate predominantly at the level of T cells; B-cell tolerance to tumors is less certain, because there is ample evidence for the induction of antibody responses in animals bearing tumors as well as human patients with tumors. However, with the exception of antibodies against members of the EGFR family, there is little evidence that the natural humoral response to tumors provides significant or relevant antitumor immunity. In contrast, numerous adoptive transfer studies have demonstrated the potent capacity of T cells to kill growing tumors, either directly through cytotoxic T-lymphocyte (CTL) activity, or indirectly through multiple CD4-dependent effector mechanisms. It is thus likely that induction of antigen-specific tolerance among T cells is of paramount importance for tumor survival.

The first direct evidence for induction of T-cell tolerance by tumors was provided by Bogen and colleagues, who examined the response of TCR-transgenic T cells specific for the idiotypic immunoglobulin expressed by a murine myeloma tumor.[82,83] They first demonstrated induction of central tolerance to the myeloma protein followed by peripheral tolerance. Using influenza hemagglutinin as a model tumor antigen, Levitsky and colleagues demonstrated that adoptively transferred hemagglutinin-specific TCR-transgenic T cells were rapidly rendered anergic by hemagglutinin-expressing lymphomas and hemagglutinin-expressing renal carcinomas.[84,85] Tolerance induction has been demonstrated in both the CD4 and CD8 compartment. In general, initial activation of tumor-specific T cells is commonly observed; however, the activated state of T cells is typically not sustained with failure of tumor elimination as a frequent consequence.

Tolerance induction among tumor antigen-specific T cells is an active process involving direct antigen recognition, although in some murine systems, tolerance to tumors seems to be associated with failure of antigen recognition by T cells—that is, the immune system "ignores" the tumor.[86,87] Beyond studies on transplantable tumors, more recent analyses of immune responses to tumor antigens in tumor-transgenic mice developing spontaneous cancer have further emphasized the capacity of spontaneously arising tumors to induce tolerance among antigen-specific T lymphocytes. In a model of prostate tumorigenesis, Drake and associates evaluated CD4 responses to hemagglutinin in double-transgenic animals expressing hemagglutinin and simian virus 40 (SV40) T antigen under control of the prostate-specific probasin promoter.[88] Development and progression of prostate tumors did not result in enhanced activation of adoptively transferred hemagglutinin-specific T cells. Tolerance to hemagglutinin as a normal prostate antigen occurred largely through ignorance, because there was no evidence for antigen recognition by hemagglutinin-specific T cells. However, increased recognition was observed upon either androgen ablation (which causes massive apoptosis within the prostate) or development of prostate cancer. Nonetheless, enhanced antigen recognition was not accompanied by activation of effector functions such as γ-interferon production. Analysis of the consequences of transformation in additional tumor-transgenic mouse systems has also been performed.

Willimsky and Blankenstein evaluated T-cell responses and rejection in a model of sporadic induction of tumors associated with expression of a tumor-specific antigen only at the time of transformation.[89] They found that preimmunization of mice against the tumor-associated antigen prevented the development of tumors. However, nonimmunized mice developed spontaneous tumors without any significant evidence of natural immune surveillance in the absence of preimmunization. They further demonstrated that an initial antigen-dependent activation of tumor-specific T cells could be observed at the time of spontaneous tumor induction but that this recognition ultimately resulted in an anergic form of T-cell tolerance similar to that observed by Drake and colleagues in the prostate system.

The capacity of spontaneously arising tumors to tolerize T cells has not been uniformly observed. A contrasting result by Ohashi and colleagues was observed when lymphocytic choriomeningitis virus (LCMV) GP33-specific TCR-transgenic CD8 T cells were adoptively transferred into double-transgenic mice expressing both SV40 T antigen and LCMV GP33 under control of the rat insulin promoter.[90] These animals develop pancreatic islet cell tumors that express GP33. These investigators found that as tumors progressed in the mice, enhanced T-cell activation occurred. CD8 T-cell activation was demonstrated through bone marrow chimera experiments to occur exclusively via cross-presentation in the draining lymph nodes. Despite the activation of tumor-specific T cells, the tumors grew progressively, indicating that the degree of immune activation induced by tumor growth was insufficient to ultimately eliminate the tumors. These results suggest that developing tumors can induce immune responses but may titrate their level of immune activation to one that ultimately does not "keep up" with tumor progression. Such a circumstance is one that is highly susceptible to the immunoediting concept put forward by Schreiber and colleagues, in which the tumor edits itself genetically to maintain a sufficient level of resistance to induced immune responses.

In the case of the LCMV GP33 T antigen-transgenic mice, because neither anergic nor deletional tolerance was observed, animals treated with the dendritic cell (DC) stimulatory anti-CD40 antibody demonstrated significant slowing of tumor growth. Thus, it may be possible under some circumstances to shift the balance between tumor immune evasion and tumor immune recognition by agents that affect the overall activation state of either antigen-presenting cells (APCs) or T cells (see later discussion).

It has been more difficult to obtain definitive evidence that human cancers tolerize tumor-specific T cells, because humans cannot be manipulated the way mice are. However, the T cells that are grown out from patients with cancer tend to be either of low affinity for their cognate antigen or recognize antigens that bind poorly to their presenting HLA (human MHC) molecule, resulting in inefficient recognition by T cells. Recently, the first crystal structure of the TCR-peptide-MHC trimolecular complex has been solved for an MHC class II-restricted human tumor antigen.[91] Interestingly, the orientation of the TCR, which is of low affinity for the peptide-MHC complex, is distinct from trimolecular complexes for viral (foreign) antigens and is partially similar to trimolecular complexes for a self-antigen. Thus, there may be fundamental structural features of tumor antigen recognition that lie between those of foreign-antigen and self-antigen recognition.

As will be discussed later, one of the features of the tumor microenvironment that is probably central to the capability of tumors to tolerize tumor-specific T cells is the immature or inactive state of tumor-infiltrating DCs. DCs are the major APCs that present peptides to T cells to initiate adaptive immune responses. In the context of infection, microbial ligands or endogenous "danger signals" associated with tissue destruction activate DCs to a state whereby they

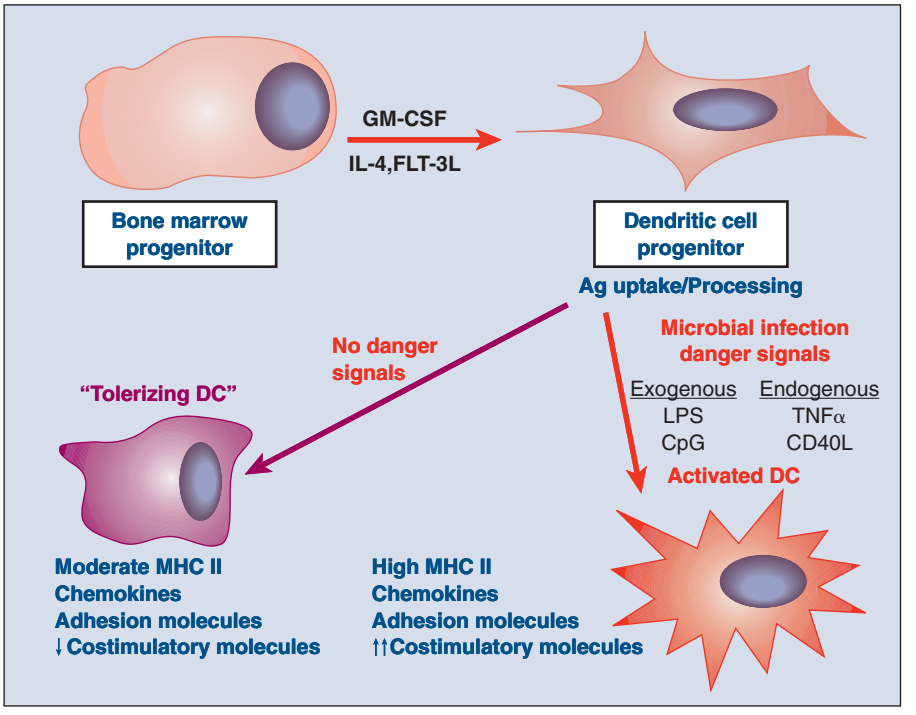


Figure 6-3 • Dendritic cells (DCs) can either activate adaptive immunity or tolerize T cells depending on their state of maturation. DC progenitors develop from hematopoietic (bone marrow-derived) progenitors under the influence of various cytokines, particularly GM-CSF. Under circumstances of microbial infection, specific pathogen-associated molecular patterns (termed PAMPs) engage pattern recognition receptors (PRRs), leading to release of proinflammatory danger signals that induce DC maturation. DC maturation leads to upregulation of costimulatory molecules, MHC, and chemokines that result in activation of T cells to effector cells (*right*). In the absence of these "danger signals," DCs follow a default pathway (*left*) in which they become "tolerizing DCs" that present antigen (Ag) to T cells in the absence of costimulatory signals. This represents a steady-state pathway for continuous presentation of self-antigens. The consequence is that these T cells are turned off (anergy), inducing tolerance.

present antigens to T cells together with costimulatory signals that induce T-cell activation and development of effector function. However, in the absence of microbial products or danger signals, DCs remain in an immature state in which they can still present antigens to T cells but without costimulatory signals. These immature DCs function as "toleragenic" DCs, inducing a state of antigen-specific T-cell unresponsiveness (termed anergy; Fig. 6-3). It is thought that steady-state presentation of self-antigens by immature DCs is an important mechanism of peripheral self-tolerance. Thus, if a tumor is able to produce factors that inhibit local DCs from becoming activated in response to the endogenous danger signals associated with tissue invasion, it could shift tumor-specific T cells from a state of activation (Fig. 6-4A) to one of tumor-specific tolerance (Fig. 6-4B).

REGULATORY T CELLS AND CANCER

Over the past 10 years, regulatory T (T_{reg}) cells have emerged as a central player in maintenance of the tolerant state as well as general downregulation of immune responses to pathogens.[92,93] Not surprisingly, they seem to play a role in tolerance to tumor antigens as well as in the resistance of tumors to immune-mediated elimination.[94,95] In contrast to the ephemeral CD8 suppressor cells of the 1970s that failed to withstand experimental scrutiny, the more recently defined $CD4^+$ regulatory T cells are characterized by expression of a central master regulatory transcription factor—FoxP3—whose role in the gene expression programs of regulatory T cells is being actively studied.[96] Although $CD4^+$ regulatory T cells selectively (but not specifically) express several cell membrane molecules, including

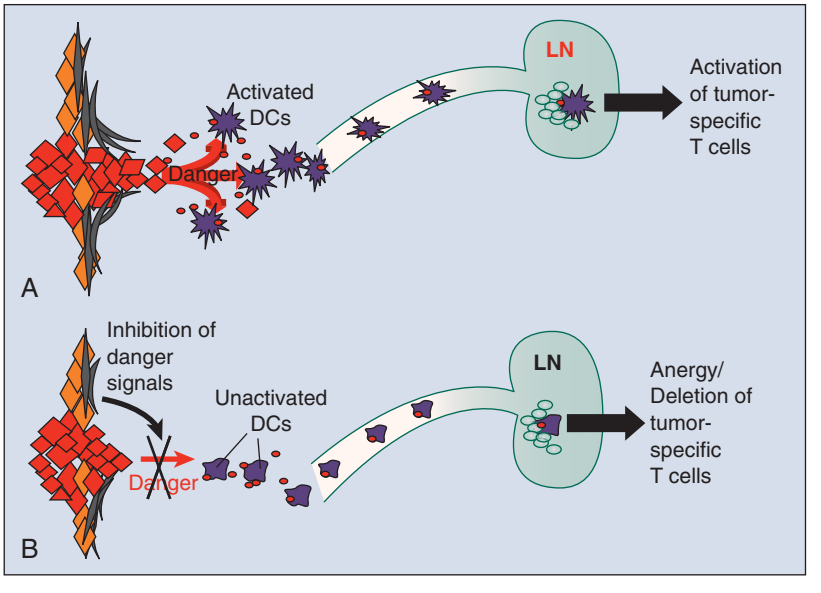


Figure 6-4 • Inhibition of DC activation in the tumor microenvironment can shift tumor-specific immune responses from activation to tolerance. Based on the scenario presented in Figure 6-3, if a tumor is able to produce factors that inhibit local DCs from becoming activated in response to the endogenous danger signals associated with tissue invasion, it could shift tumor-specific T cells from a state of activation (**A**) to one of tumor-specific tolerance (**B**). LN, lymph nodes.

CD25, neuropilin, GITR, and LAG3,[92,97–99] their overall genetic program and inhibitory capacity is absolutely dependent on sustained expression of FoxP3.[100,101]

Mechanisms of immune suppression by regulatory T cells vary and include production of inhibitory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β).[102–104] In keeping with the emerging appreciation that tumors are by nature highly toleragenic, numerous murine studies have demonstrated that T_{reg} cells expand in animals with cancer and significantly limit the potency of antitumor immune responses—either natural or vaccine induced. For example, in a study by Sutmuller and coworkers a combination of GM-CSF–transduced tumor vaccine plus anti-CTLA4 antibodies was much more effective at eliminating established tumors when animals were treated with anti-IL-2 receptor α antibodies to eliminate $CD4^+$ T_{reg} cells.[105]

It is now appreciated that treatment with low-dose cytoxan is a relatively simple and reasonably effective way to temporarily eliminate cycling T_{reg} cells.[106–109] This seems to be a major mechanism by which pretreatment with low-dose cytoxan before vaccination can significantly enhance the capacity of vaccines to break tolerance. As new cell membrane molecules that define T_{reg} cells are identified, the capacity to block regulatory T-cell activity with antibodies to these molecules presents new opportunities for immunotherapeutic strategies to break tolerance to tumor antigens.

ONCOGENIC PATHWAYS ACTIVELY MEDIATE TUMOR–IMMUNE SYSTEM INTERACTIONS

The previous sections outline the complex interplay between tumor and host immune system and describe the experimental evidence that the immune system is in general tolerant to tumors and their antigens under circumstances in which a tumor has established and is expanding within the host. Is this tolerance to tumor antigens a passive default pathway, or does the tumor actively manipulate its immune microenvironment in a way to render the immune system tolerant to its antigens. Indeed, evidence is accumulating that activation of oncogenic pathways in the tumor as well as inactivation of tumor suppressor genes have immunologic consequences far beyond the more commonly studied roles in growth regulation and antiapoptosis. Critical signaling pathways whose role has been studied in this context include STAT3, NF-κB, BRAF, and PTEN. Although each of these pathways (either activation or inactivation) has been well studied for its role in "classic" tumor biology such as dysregulated growth, regulation of apoptosis, and resistance to DNA-damaging agents, additional roles in the organization of the immune microenvironment of the tumor have also been elucidated recently.

The best-studied oncogenic pathway to play a role in tumor immune evasion is the STAT3 pathway. STAT3 is one of two STATs (the other being STAT5A) to be constitutively activated in many diverse tumor types.[110–113] Activation of STAT3 involves tyrosine phosphorylation resulting in homodimerization in the cytosol that leads to nuclear transport where it participates in transcriptional activation (and in some cases repression) of diverse genes. Although synthetic mutations in STAT3 can confer upon it oncogenic activity, constitutive activation of STAT3 in tumors is not a consequence of mutation. Instead, STAT3 is downstream of several important oncogenic tyrosine kinases, both receptor tyrosine kinases and src family tyrosine kinases. Several receptor tyrosine kinases that play important roles in human cancer, including EGFR, HER2/Neu, and cMet, signal in part through STAT3.[114–116] In addition, src and potentially other src family tyrosine kinases can activate STAT3.[117] In fact, the original association of STAT3 with oncogenesis came from the demonstration that src-dependent transformation required STAT3.[118] Activated STAT3 in tumors participates in transcriptional activation of several genes associated with common cell-autonomous and non-cell-autonomous mechanisms of carcinogenesis and cancer promotion. These include cell cycle regulation (e.g., cyclin D1), antiapoptosis (e.g., BCL-Xl and survivin), and angiogenesis (e.g., vascular endothelial growth factor [VEGF]).[119,120]

In addition, STAT3 activation in tumors has been shown to repress the production of proinflammatory cytokines and chemokines that could enhance antitumor immune responses.[121] These include proinflammatory cytokines such as type 1 interferons and tumor necrosis factor as well as proinflammatory chemokines such as RANTES and IP-10. Thus, blockade of STAT3 signaling in tumor cells results in the release of multiple proinflammatory mediators and consequent infiltration with cells of both the innate and adaptive immune system that ultimately inhibit tumor growth.

Beyond simply repressing the production and release of molecules that could promote antitumor immune responses, STAT3 signaling also induces the release of factors that inhibit activation of multiple immune cell types in the tumor microenvironment. These include DCs, NK cells, and granulocytes, which, though present in significant numbers within tumors, are generally found in an unactivated state.

Some of the STAT3-regulated factors that induce this "quiescent microenvironment" include IL-10, VEGF, IL-6, and possibly IL-23. As will be described later, some of these cytokines promote distinct forms of immune responses that promote rather than inhibit tumor growth. The receptors for each of these factors are expressed on cells of the hematopoietic system and signal through STAT3. Thus, infiltrating hematopoietic cells within the tumor microenvironment are found to also express constitutively activated STAT3. Blockade of STAT3 in the hematopoietic system (for example, via hematopoietic-specific STAT3 knockout) results in dramatically enhanced activation of DCs and cells in the innate immune system (such as NK cells and granulocytes) and leads to antitumor immune responses. In fact, even aggressive tumors fail to grow when transplanted into animals with hematopoietic STAT3 knockout.[122] Thus, STAT3 seems to be an important global signaling pathway that restrains antitumor immunity.

Another immunologically relevant pathway that is commonly constituently activated in cancer is the NF-κB pathway.[123,124] Normally, NF-κB is activated in a highly stimulus-dependent fashion, but is constitutively activated in many types of tumors. Multiple NF-κB family members participate in either a canonical or noncanonical NF-κB activation pathway. Common to both pathways is the activation of IκB kinase (IKK), which phosphorylates IκB leading to ubiquitin-dependent degradation and release of NF-κB to traffic from the cytosol to the nucleus and activate gene transcription programs.[125] Alternatively, IKK phosphorylation can result in cleavage of a precursor protein for the activation of the noncanonical NF-κB pathway. The mechanism for constitutive NF-κB activation in tumors is not currently known. Normally, NF-κB plays a central role in the activation of virtually all cells in the immune system—both innate and adaptive. In the case of innate immunity, Toll-like receptors (TLRs) on the surface of cells or intracellular sensors of viral RNA or DNA (the RIGI or MDA5 pathway) result in a signaling cascade that activates NF-κB via TRAF6.[126,127] Paradoxically, constitutive activation of NF-κB in tumors is associated predominantly with activation of antiapoptotic genes, whereas many of the typical NF-κB-responsive proinflammatory/proimmunity genes are not activated in tumors. Recently, it was demonstrated that the selective NF-κB gene activation program in tumors is dependent on its association with STAT3. Indeed, coactivation of STAT3 and NF-κB is commonly observed in tumors. This coactivation seems in part to be due to a newly defined role for STAT3 in enhancing acetylation of NF-κB p50 subunit, resulting in enhanced retention of active NF-κB in the nucleus of tumor cells. This retention seems to be through the p300 acetyl transferase. The result is a shift in equilibrium toward nuclear retention of NF-κB. In addition, STAT3–NF-κB complexes fail to bind promoters of proinflammatory/proimmunity genes that are typically repressed in tumor cells, whereas STAT3–NF-κB dimers

are found associated with promoters driving antiapoptotic genes such as BCL-Xl and survivin. These findings highlight the interactivity between key signaling pathways of tumor cells as well as the interplay between gene expression programs mediating tumor immunity versus tumor survival.

An additional oncogenic pathway that seems to play a role in tumor immune evasion is the BRAF pathway.[128] BRAF is constitutively activated in the majority of human melanomas as a result of a single activating mutation. Kawakami and colleagues[128] have demonstrated that factors produced by melanoma cells that inhibit DC activation are in part driven by Braf. Knockdown of Braf with short interfering RNA abrogates the production by melanoma cells of factors that inhibit DC activation. This inhibition seems to be independent of but complementary to that provided by STAT3 activation in melanoma cells. Thus, it seems that multiple oncogenic pathways active in tumor cells may contribute to the release of factors that inhibit DCs and other components of innate immunity, shifting the balance of immune responses toward tolerance.

In addition to oncogenic pathways, inactivation of tumor suppressor pathways may also play a role in immune evasion by tumors. In one example, Parsa and colleauges demonstrated that expression of a T-cell-inhibitory molecule by tumors, B7-H1 (see later discussion), is linked to inactivation of PTEN. PTEN, an inhibitor of the oncogenic AKT pathway, is emerging as one of the most important tumor suppressor pathways in cancer.[129] More recently, Lowe and colleagues provided evidence that the p53 pathway may play a role in inhibiting innate immune responses to tumors. In a transgenic system in which inactivated p53 is conditionally reexpressed in tumors, they found that the inhibition of tumor growth induced by reactivation of p53 might be in part dependent on induction of innate immune responses mediated by NK cells.[130]

Taken together, these findings strongly suggest that oncogene and tumor suppressor gene pathways in tumors play important roles in orchestrating the interaction between the tumor cell and its immune microenvironment such that immune responses induced by the invasion and metastasis process do not eliminate the tumor cell itself. Whereas most of the focus on the function of oncogenic and tumor suppressor pathways has been on cell-autonomous functions within the tumor such as growth regulation, there is growing appreciation that these pathways additionally affect the tumor microenvironment via nontransformed cells. As an integral part of the tumor microenvironment, the immune system is clearly subject to regulation by these pathways. Understanding of the immunologic consequences of these pathways ultimately provides direct opportunities to develop therapeutic approaches that integrate inhibitors of oncogenic pathways, activators of tumor suppressor pathways, and other immunotherapeutic approaches to cancer.

IMMUNOLOGIC CHARACTERISTICS OF THE TUMOR MICROENVIRONMENT

Ultimate understanding of the relationship between the tumor and the host immune system requires elucidation of local cross-talk at the level of the tumor microenvironment. As mentioned at the outset, the hematopoietic/immune system is a major component of the tumor microenvironment. The systemic tolerance to tumor antigens begins with events that occur in this microenvironment. Beyond mechanisms that skew tumor-specific T cells toward immune tolerance, the tumor microenvironment is replete with mechanisms that dampen antitumor immune responses locally (Fig. 6-5). This represents an important barrier to successful immunotherapy even when activated effector responses can be generated with vaccines. As the specific cells and molecules within the tumor microenvironment that mediate this hostile immune environment are elucidated, inhibitors are being developed and tested to use as adjuncts to vaccination that will allow activated immune cells to function more effectively within the tumor microenvironment.

The previous section described how oncogenic pathways in the tumor cell directly affect the immune microenvironment of the tumor. In addition to its role in inhibiting the activation and effector function of DCs, granulocytes, and NK cells in the tumor microenvironment, STAT3 signaling has also been reported to play a role in guiding immature myeloid cells (iMCs) in the tumor microenvironment to differentiate into myeloid suppressor cells (MSCs) rather than DCs with APC activity. iMCs[131,132] and MSCs[133–136] represent a cadre of myeloid cell types, including tumor-associated

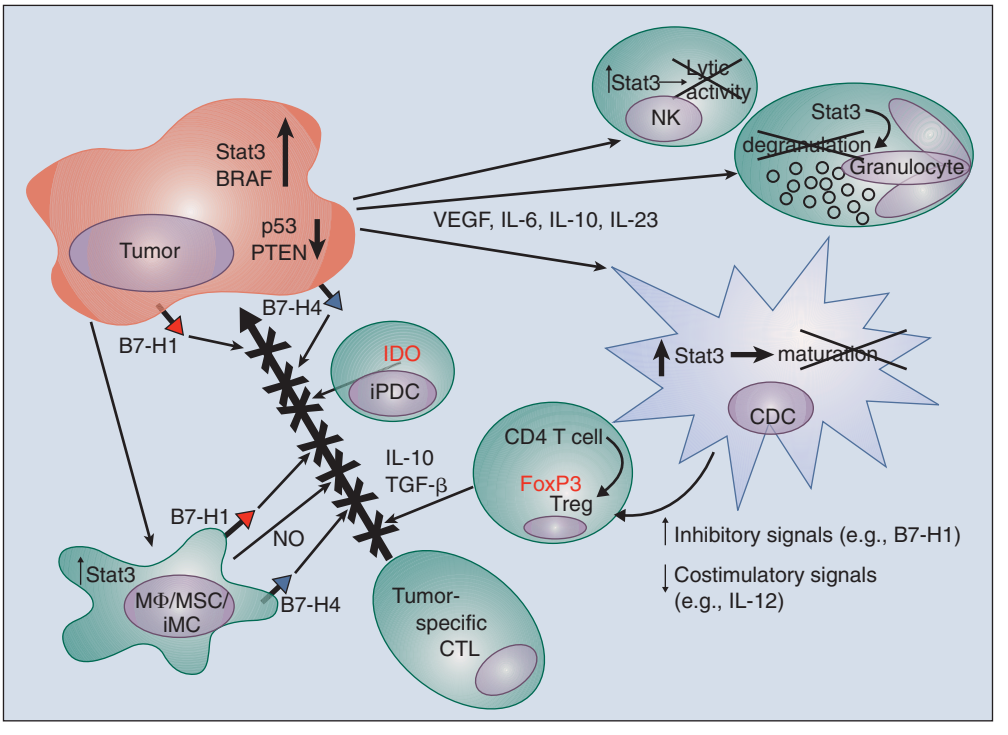


Figure 6-5 • The hostile immune microenvironment of the tumor. Activation of oncogenic pathways and inactivation of tumor suppressor pathways in the tumor lead to a cascade of molecular and cellular processes in the tumor microenviroment that block the killing function of innate immune effectors such as NK cells and granulocytes and block DC maturation (see Figs. 6-3 and 6-4). In addition, multiple cell membrane molecules such as IL-10, TGF-β, B7-H1, and B7-H4 are upregulated. These molecules bind to receptors that inhibit T-cell effector function. Immature myeloid cells (iMC) produce NO, which inhibits T cells, and immature plasmacytoid DCs (iPDC) produce indoleamine dioxygenase (IDO), which depletes tryptophan. Regulatory T cells also accumulate in the tumor microenvironment, further blunting antitumor T-cell responses.

macrophages, that share the common feature of inhibiting both the priming and effector function of tumor-reactive T cells. It is still not clear whether these myeloid cell types represent distinct lineages or different states of the same general immune-inhibitory cell subset.

In mice, iMCs and MSCs are characterized by coexpression of CD11b (considered a macrophage marker) and Gr1 (considered a granulocyte marker) while expressing low or no MHC class II or the CD86 costimulatory molecule. In humans, they are defined as $CD33^+$ but lack markers of mature macrophages, DCs, or granulocytes and are $HLA\text{-}DR^-$. Several molecular species produced by tumors tend to drive iMC/MSC accumulation. These include IL-6, CSF-1, IL-10, and gangliosides. IL-6 and IL-10 are potent inducers of STAT3 signaling. Another cytokine reported to induce iMC/MSC accumulation is GM-CSF.[137] This finding is somewhat paradoxical, in that GM-CSF is a critical inducer of DC differentiation and GM-CSF–transduced tumor vaccines enhance antitumor T-cell immunity via accumulation of DCs at the vaccine site followed by increased DC numbers in vaccine draining lymph nodes. It seems that the paradox is solved based on levels of GM-CSF. High local levels drive DC differentiation at the vaccine site, whereas chronic production of low levels of GM-CSF can promote iMC/MSC accumulation. GM-CSF–transduced vaccines that produce extremely high GM-CSF levels can induce iMC/MSC accumulation at distant sites (i.e., spleen and lymph nodes), because they release enough GM-CSF systemically to drive iMC/MSC accumulation.

Several mechanisms have been proposed to explain how iMC/MSC inhibit T-cell responses within the tumor microenvironment. Most include the production of reactive oxygen species (ROS) and/or reactive nitrogen species. Nitric oxide production by iMC/MSC as a result of arginase activity, which is high in these cells, has been well documented, and inhibition of this pathway with several drugs can mitigate the inhibitory effects of iMC/MSC. ROS, including hydrogen peroxide, have been reported to block T-cell function associated with the downmodulation of the ζ chain of the TCR signaling complex,[138] a phenomenon well recognized in T cells from cancer patients and associated with generalized T-cell unresponsiveness.

Another mediator of T-cell unresponsiveness associated with cancer is the production of indolamine-2,3 dioxygenase (IDO).[139] IDO seems to be produced by DCs either within tumors or in tumor-draining lymph nodes. Interestingly, IDO in DCs has been reported to be induced via backward signaling by B7-1/2 upon ligation with CTLA-4.[140,141] Apparently, the major IDO-producing DC subset is either a plasmacytoid DC (PDC) or a PDC-related cell that is $B220^+$.[142] IDO seems to inhibit T-cell responses through catabolism of tryptophan. Activated T cells are highly dependent on tryptophan and are therefore sensitive to tryptophan depletion. Thus, Munn and Mellor have proposed a bystander mechanism, whereby DCs in the local environment deplete tryptophan via IDO upregulation, thereby inducing metabolic apoptosis in locally activated T cells.[139]

Another inhibitory molecule produced by many cell types that has been implicated in blunting antitumor immune responses is TGF-β, which is produced by a variety of cell types, including tumor cells, and which has pleiotropic physiologic effects. For most normal epithelial cells, TGF-β is a potent inhibitor of cell proliferation, causing cell cycle arrest in the G1 stage.[143] In many cancer cells, however, mutations in the TGF-β pathway confer resistance to cell cycle inhibition, allowing uncontrolled proliferation. Additionally, in cancer cells the production of TGF-β is increased and may contribute to invasion by promoting the activity of matrix metalloproteinases. In vivo, TGF-β directly stimulates angiogenesis; this stimulation can be blocked by anti-TGF-β antibodies.[144] A bimodal role of TGF-β in cancer has been verified in a transgenic animal model using a keratinocyte-targeted overexpression.[145] Initially, these animals are resistant to the development of early-stage or benign skin tumors. However, once tumors form, they progress rapidly to a more aggressive spindle-cell phenotype. Although this clear bimodal pattern of activity is more difficult to identify in a clinical setting, it should be noted that elevated serum TGF-β levels are associated with poor prognosis in several malignancies, including prostate cancer,[146] lung cancer,[147] gastric cancer,[148] and bladder cancer.[149]

From an immunologic perspective, TGF-β possesses broadly immunosuppressive properties and TGF-β knockout mice develop widespread inflammatory pathology and corresponding accelerated mortality.[150] Interestingly, a majority of these effects seem to be T-cell mediated, in that targeted disruption of T-cell TGF-β signaling also results in a similar autoimmune phenotype.[151] Recent experiments by Chen and associates rather convincingly demonstrated a role for TGF-β in T_{reg}-mediated suppression of CD8 T-cell antitumor responses.[152] In these experiments adoptive transfer of $CD4^+$ $CD25^+$ regulatory T cells inhibited an antitumor CD8 T-cell effector response, and this inhibition was ameliorated when the CD8 T cells came from animals with a dominant negative TGF-β1 receptor.

One of the unresolved issues in the study of tumor immune evasion relates to the mechanisms by which tumors induce antigen-specific T-cell tolerance. Whereas the many mechanisms described previously, including STAT3 signaling-dependent mechanisms, IDO, ROS, reactive nitrogen species, TGF-β, and others, clearly inhibit priming of T-cell responses and/or tumor killing by activated effector T cells, it remains to be definitively determined which processes actively induce antigen-specific T-cell tolerance that has been documented in transgenic models. Self-tolerance induction for peripheral tissue antigens is now thought to involve specific presentation of tissue-specific antigens to mature T cells in the absence of appropriate costimulatory signals. Similar mechanisms are probably operative in the case of tumor-induced tolerance. Originally, the relevant costimulatory signals were envisioned to be provided by B7 family costimulatory molecules expressed by DCs.[153] It is now becoming clear that additional proinflammatory cytokines such as interferons, IL-12, tumor necrosis factor, and others are critical in the distinction between effector T-cell induction and tolerance induction.

An emerging concept is that immature or not fully matured DCs are critical in presenting self-antigens to induce T-cell tolerance in the absence of TLR-mediated danger signals associated with infection.[154,155] Unquestionably, DCs found within the tumor microenvironment have a relatively immature, unactivated phenotype characterized by low levels of proinflammatory cytokine production, and CD86 and surface MHC class II expression. As described previously, a major inhibitory signaling pathway induced in tumor-infiltrating DCs is the STAT3 pathway, which, when activated, strongly antagonizes TLR- and CD40-mediated DC activation. As mentioned, tumor-derived factors such as IL-10, IL-6, and VEGF (in part induced by STAT3 signaling in the tumor cell) can induce STAT3 activation in DCs. As described in the previous section, constitutive BRAF signaling in melanoma cells has additionally been shown to induce release of factors that inhibit DC activation.[128] These immature "activation-inhibited" DCs clearly represent a prime candidate for the induction of tumor-specific T-cell tolerance.

It remains an open question whether iMC/MSC represent a distinct intertumoral cell subset capable of presenting antigens to T cells in a toleragenic fashion.[156] A recent report indeed suggested that iMCs loaded with antigen and adoptively transferred into mice can induce antigen-specific T-cell tolerance. Finally, it has been suggested that IDO-expressing DCs can induce antigen-specific T-cell tolerance, because IDO-mediated tryptophan selectively kills or inhibits proliferation of activated T cells.[157] According to this model, IDO-expressing DCs would present antigen to T cells inducing activation followed by activation-associated cell death mediated by depletion of local tryptophan stores by the IDO in the presenting DCs. As described later, regulatory T cells play an additional important role in induction of or maintenance of tumor antigen-specific T-cell tolerance. Whether T_{reg} cells mediate T-cell tolerance independently from immature or toleragenic APCs, or whether the two mechanisms are completely interrelated (i.e., toleragenic DCs inducing a T_{reg}

phenotype among antigen-specific T cells and antigen-specific T_{reg} cells acting upon DCs to enhance their toleragenic capacity), remains to be definitely determined.

One of the most important classes of immune-inhibitory molecules shown to be expressed by both tumors and myeloid cells in the tumor microenvironment are members of the growing class of B7 molecules. Originally, B7.1 (also called CD80), and then B7.2 (CD86), were identified as critical costimulatory molecules expressed by APCs (first found on B cells, then macrophages, then DCs). Costimulation of T cells, defined as amplification of activation signals delivered through engagement of the TCR by antigen, was shown to be mediated by binding of B7.1 and B7.2 to CD28, expressed on all naive T cells. Subsequently, feedback inhibition of T-cell activation was shown to be mediated by inhibitory signals delivered by a second receptor for B7.1 and B7.2, termed CTLA-4. CTLA-4 is not expressed on the surface of naive T cells but is rapidly induced after T-cell activation, and, as is the case for TGF-β, CTLA-4 knockout mice develop lymphoproliferative autoimmunity, indicating a tonic role for CTLA-4–B7-1/B7-2 interactions in the prevention of autoimmunity.[158] According to these data, CTLA-4 blockade would be expected to function mostly during T-cell priming events, facilitating or enhancing an immune response. In several murine systems, CTLA-4 blockade exerts a pronounced antitumor effect,[159] generating enthusiasm for translating these observations to the clinic.[160]

A second coinhibitory molecule on T cells is PD1 (programmed death 1), a T-cell surface molecule originally discovered in a T-cell hybridoma undergoing apoptosis.[161] Further studies of PD1 identified expression on activated, but not naive T and B cells, in addition to potential overexpression in anergized CD4 T cells.[162] Recent data show that PD1 is also expressed on the surface of certain CD8 T cells, where it serves as a marker for T cells that have been "exhausted" by exposure to persistent viral antigen in vivo. As is the case for CTLA-4 and TGF-β, PD1 knockout mice develop strain-dependent autoimmune disease.[163] In murine models of experimental autoimmune encephalomyelitis and diabetes, anti-PD1 antagonist antibodies enhance disease progression.[164–166]

There are currently two known ligands for PD1: B7-H1 (also known as PD-L1) and B7-DC (also known as PD-L2). B7-H1 and B7-DC represent two of the five additional B7 family members identified over the past 10 years. These ligands have very different tissue distribution patterns, with B7-DC expression primarily confined to DCs and macrophages.[167] B7-H1 messenger RNA is widely expressed, but cell surface protein is not detectable in normal tissues other than a subset of macrophages.[168] Interestingly, B7-H1 expression can be detected in several tumor types,[169] and engagement of PD1 by tumor-associated B7-H1 promotes CD8 T-cell apoptosis.

In addition, B7-H1 has been reported to be upregulated on both DCs and macrophages within the tumor microenvironment. Clinically, it has been reported that B7-H1 expression is correlated with poor prognosis in renal cell carcinoma.[170] Interestingly, whereas B7-H1 expression on tumor cells was correlated with poor clinical prognosis, combined expression on tumor cells together with hematopoietic cells within the tumor sections was even more highly correlated with poor clinical outcome. Thus, it seems that PD1/B7-H1 interactions mediate a potent and specific immunoregulatory effect, preventing activated and trafficking CD8 T cells from lysing their targets in vivo. In recent data, this observation has been confirmed in murine tumor models, where blockade of either PD1 or of the PD1 ligand B7-H1 potentiates an antitumor immune response.[171] In contrast, the molecular role of B7-DC ligation in an immune response is complex,[172] and under some circumstances ligation of B7-DC on APCs seems to potentiate a costimulatory interaction with T cells.[173]

Another more recently identified inhibitory B7 family member, B7-H4, also seems to play an important role in the tumor microenvironment.[174] The receptor for B7-H4 has not yet been identified, but this molecule has been definitively shown to play an inhibitory role because treatment of mice with blocking antibodies and gene knockout resulted in increased immune responses. As with B7-H1, B7-H4 is expressed by several tumors and also by macrophages in the tumor microenvironment.[175] B7-H4 is regulated differently than B7-H1 and there seems to be a distinct pattern of tumor-selective expression for the two molecules, with some overlap. Recently, B7-H4 expression in human renal cancer has been shown to correlate with poor clinical prognosis, similarly to B7-H1. Patients whose tumors expressed high levels of both molecules displayed the worst clinical outcome, with almost all developing distant metastases.[176]

PROCARCINOGENIC VERSUS ANTICARCINOGENIC ROLES OF THE IMMUNE RESPONSE

Much to the chagrin of the immunotherapy community, skepticism among the oncology community regarding the capacity to induce therapeutically meaningful antitumor immune responses has been accompanied by increasing focus on the capacity of immune responses to induce cancer and potentially enhance cancer progression. Understanding the paradox between the potential procarcinogenic and anticarcinogenic immunity is arguably the most important frontier in cancer immunology (Fig. 6-6).

The capacity of inflammatory (i.e., innate) immune responses to enhance carcinogenesis has become well appreciated on the basis of clinical observations that chronic infections that induce chronic inflammation can lead to cancer. One of the best examples is hepatitis C virus (HCV) infection.[177] HCV infection leads to a chronic persistent state in the majority of infected individuals associated with chronic hepatitis. This chronic hepatitis is associated with development of hepatocellular carcinoma at the rate of roughly 1% per year. In contrast to other procarcinogenic chronic infections with viruses such as HPV that carry their own oncogenes, the HCV genome contains no oncogenes or genes encoding proteins that inactivate tumor suppressor genes. Thus, the evidence is quite strong that the chronic inflammatory response to HCV is responsible for the genesis of hepatocellular carcinoma. Similarly, the inflammatory responses associated with chronic *H. pylori* infection of the stomach are thought to be central to the genesis of stomach cancer.[178] Further evidence for the procarcinogenic effects of inflammation come from the findings that anti-inflammatory drugs, such as COX-2 inhibitors, can decrease the incidence of colon cancer.[179] Additional evidence includes the propensity of patients with certain forms of chronic colitis (e.g., ulcerative colitis) to develop colon cancer and the association of microinflammatory foci in the prostate with prostate intraepithelial neoplastic lesions.[180]

In animal models, experimental induction of inflammation in both the colon and the liver are associated with increased incidences of cancer. Recently, Karin and colleagues have used conditional knockouts of IKK to demonstrate an important role for NF-κB signaling in experimental models of colonic carcinogenesis.[181] Interestingly, they found that tissue-specific knockout of IKKβ in both colonic epithelial cells as well as in myloid cells resulted in a diminished incidence of dextran sulfate (DSS)-induced colon cancers. Epithelium-specific knockout of IKKβ resulted in a decreased incidence, whereas myeloid-specific knockout of IKKβ resulted in both decreased incidence and decreased progression rate. The effects of myeloid-specific IKK knockout were taken as evidence for an NF-κB-dependent proinflammatory role in carcinogenesis. More recently, carcinogen-induced liver cancer and colon tumor development in mice bearing heterozygous adenomatous polyposis coli gene mutations (Min mice) was shown to be dependent on MyD88, an adapter for TLR signaling that is necessary for TLR-dependent NF-κB activation.[182,183] In one case, IL-6 production was found to be an important downstream cytokine for liver carcinogenesis.

Although the majority of evidence linking immunity to cancer involves the innate immune system, Coussens and colleagues have

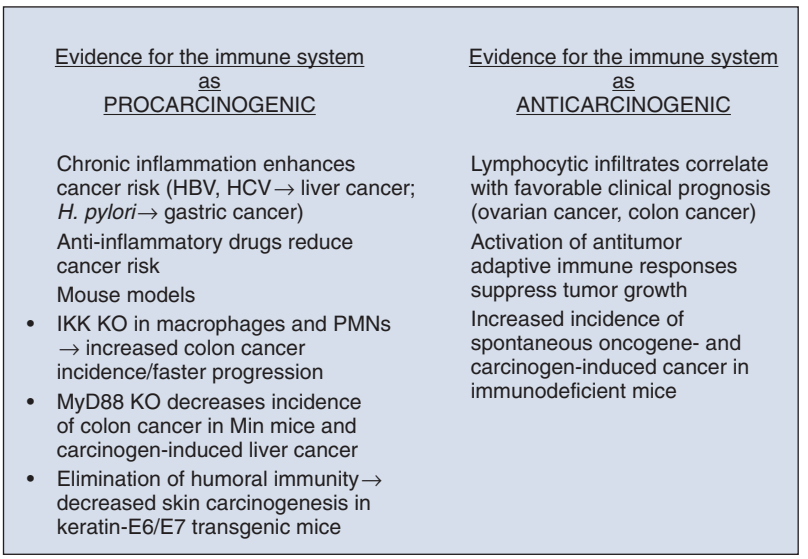


Figure 6-6 • Evidence for procarcinogenic and anticarcinogenic roles of the immune system. Ample evidence exists in both animal models and human disease settings that immune responses can promote or inhibit cancer development.

provided evidence that components of the adaptive immune response could contribute to carcinogenesis in a positive fashion. In a transgenic model of HPV E6/E7-induced skin carcinogenesis, they demonstrated that elimination of B cells resulted in a decreased incidence of tumorigenesis.[184] Surprisingly, T-cell knockout did not alter the incidence of tumorigenesis. The ultimate mechanism by which B cells contribute to carcinogenesis in this system is not fully defined, although antibody production seems to be involved.

Understanding the paradox between procarcinogenic versus anticarcinogenic effects of the immune response will be critical to ultimately defining successful immunotherapies. Recent studies suggest a solution to this paradox and provide insight into the notion that different forms of immune responsiveness can respectively be anticarcinogenic or procarcinogenic. Much evidence has been accumulated that a certain type of T-cell response, termed Th1, can be potently anticarcinogenic. Th1 responses are characterized by production of γ-interferon by CD4 T cells as well as induction of CTL responses by CD8 T cells. γ-interferon not only can enhance the activity of CD8 CTLs, it can also activate components of innate immunity such as macrophages that can kill tumors. Th1 responses are induced by STAT1 signaling and are significantly enhanced by IL-12 that can be produced by macrophages or DCs. Indeed, IL-12 activates not only Th1 responses but also innate immune responses by NK cells that can additionally kill tumor cells.[185,186]

Recently, a distinct IL-12 family cytokine, termed IL-23, has been discovered.[187,188] IL-23 shares the same β chain as IL-12 but has a distinct α chain, termed IL-23 p19. Likewise, the IL-23 receptor shares a common β chain with the IL-12 receptor but also has a distinct IL-23 receptor-specific α chain. Several immunopathologic states related to autoimmune disease that had been attributed to IL-12 and linked Th1 responses have now been shown to be instead attributable to IL-23.[189] Analogous to IL-12 driving both NK-dependent innate as well as Th1-type adaptive immune responses, IL-23 drives distinct innate immune responses from IL-12 that are just now being elucidated (characterized by granulocyte recruitment). In addition, IL-23 promotes the growth of a distinct type of helper T cell, termed Th17.[190–193] Th17 is applied to this helper T-cell pathway, because it is characterized by production of cytokine IL-17a rather than γ-interferon.

Recently Langowski and coworkers evaluated skin carcinogenesis and tumor growth in mice with either an IL-23 p19 gene knockout or an IL-12 specific p35 gene knockout.[194] As predicted from previous studies on the role of IL-12 in promoting both innate and Th1-dependent antitumor immunity, tumor formation in a carcinogen-induced skin cancer model as well as growth of transplanted tumors was increased in IL-12 p35 knockout mice. In striking contrast, carcinogenesis and tumor growth was decreased in the IL-23 p19 knockout mice. Carcinogenesis and tumor growth was also reduced in knockout mice for p40, the common subunit for IL-12 and IL-23. This result suggests that the procarcinogenic effects of IL-23 production dominate over the anticarcinogenic effects of IL-12 production. Although these initial findings will require extensive follow-up, they support the notion that qualitatively distinct types of immune responses, characterized by distinct cytokines that mediate distinct functions, can be procarcinogenic or anticarcinogenic.

Analysis of signaling pathways involved in the IL-12–Th1 axis and the IL-23–Th17 axis further suggest a model of "competition" between these two immune pathways. Th1 responses depend on signaling through STAT1, which is essential for commitment to the Th1 lineage, and STAT4, which is the major signal transducer for the IL-12 receptor. In contrast, both IL-23 transcription as well as IL-23 receptor transcription and signal transduction require STAT3 signaling. IL-17 production also requires STAT3 signaling, which is generated by IL-6, which, together with TGF-β, is a critical cytokine for Th17 development from naive T cells.[195,196] This may explain the role of IL-6 in the MyD88-dependent carcinogenesis described previously.[182] At several levels, STAT3 signaling and STAT1 signaling are mutually antagonistic such that increases in STAT3 signaling inhibit STAT1-induced gene expression programs whereas increases in STAT1 signaling inhibit STAT3-dependent gene expression programs.[197] This finding suggests that therapeutic manipulations of STAT signaling could potentially convert procarcinogenic to anticarcinogenic pathways of immune responsiveness. Ultimately it will be critical to evaluate the qualitative nature of immune responses in chronic infections that lead to carcinogenesis to determine whether this "yin-yang" paradigm of procarcinogenic IL-23–Th17 immunity versus anticarcinogenic IL-12–Th1 immunity represents a general principle translatable to human cancer initiation or promotion (Fig. 6-7).

CLINICAL IMPLICATIONS FOR MANIPULATION OF THE IMMUNE RESPONSE TO TUMOR CELLS

Fundamentally, we now have clear-cut evidence that antibodies and T cells can selectively recognize and kill cancer cells in patients. Cancer genetics, epigenetics, and genomics have provided us with a

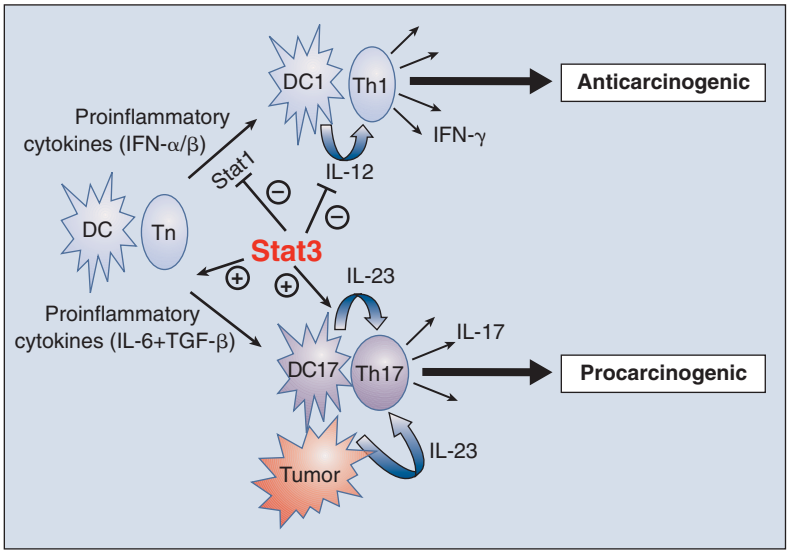


Figure 6-7 • Two mutually inhibitory pathways of immunity may inhibit or promote cancer. The Th1 pathway is promoted by STAT1 and STAT4 signaling, is initiated by type I interferons, and depends on IL-12. Th1 cells are characterized by production of γ-IFN but also produce many other cytokines. The IL-12/Th1 pathway is typically anticarcinogenic. The Th17 pathway is promoted by Stat3 signaling, is initiated by IL-6 and TGF-β, and depends on IL-23. Th1 cells are characterized by production of IL-17a but also produce many other cytokines. Evidence exists that the IL-23-Th17 pathway can promote carcinogenesis. These pathways are mutually inhibitory in a yin-yang fashion.

Box 6-2. CAN THE IMMUNE SYSTEM BE MANIPULATED TO OVERCOME TUMOR-INDUCED TOLERANCE AND IMMUNE EVASION?

One of the most consistent therapeutic failures thus far has come from attempts to treat cancer with tumor vaccines. Evidence has now mounted that a major reason for the lack of efficacy of tumor vaccines and other immunotherapeutic interventions is the barrier of immune tolerance to tumor antigens as well as the upregulation of molecules in the tumor microenvironment that inhibit effector immune responses. The bad news from these insights is that therapeutic efficacy of tumor vaccines used as single agents will probably always be limited, no matter how effective the vaccine is in inducing immunity in a naive host. It is likely that the only viable therapeutic application of cancer vaccines used as single agents will be in the setting of minimal residual disease. However, as the specific molecular pathways of immune tolerance and immune evasion are defined, antibodies as well as small molecule agonists and antagonists are being developed that can either enhance costimulatory pathways that amplify immune responses or specifically block receptors and pathways that inhibit immune effectors such as cytotoxic T cells. Preclinical experiments as well as very early-stage clinical experience suggest that combinations of vaccines that direct immune responses to particular tumor antigens together with agents that either enhance or costimulate immunity, as well as agents that block immune checkpoints, produce strong synergy in enhancing antitumor immune responses. It is likely that these combinatorial approaches will be the most fruitful for developing clinically relevant immune therapies of cancer.

far better understanding of the nature and specificity or selectivity of tumor antigens, providing new opportunities for targeted antigen-specific immunotherapy. We know much more about the details of antigen recognition by T cells allowing for the opportunity to modify antigens at critical residues to provide for enhanced immune-stimulatory capacity. Finally, we are learning much about the ligands, receptors, and signaling pathways that regulate immune responses and how they are expressed within the tumor microenvironment. Elucidation of these regulatory pathways has demonstrated that the outcome of antigen recognition is in large part determined by the balance between costimulatory signals and inhibitory signals.

These relatively recent insights into the molecular basis of immune regulation are demonstrating profound significance for the development of more potent combinatorial immunotherapy approaches to cancer (Box 6-2). Several consensus have emerged from both preclinical immunotherapy models as well as analysis of cancer patients. First and foremost, the natural state of endogenous tumor-reactive T cells is characterized by general hyporesponsiveness or anergy. This is probably due to several mechanisms that tumors utilize to induce tolerance as they develop. Whereas a number of the newer generation vaccines such as recombinant viral vaccines or GM-CSF gene-modified vaccines can effectively transfer antigen to and activate DCs, T-cell tolerance remains a major barrier that is difficult to overcome by vaccination alone. Preclinical models demonstrate that for poorly immunogenic tumors, once tolerance has been established, therapeutic vaccines alone are ineffective at curing animals with a significant established tumor burden. However, strategies combining vaccination with inhibitors of immunologic checkpoints and agonists for costimulatory pathways are proving capable of overcoming tolerance and generating significant antitumor responses even in cases of established metastatic cancer.

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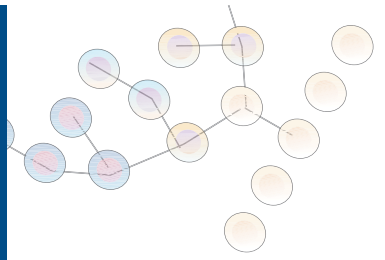
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7 Stem Cells, Cell Differentiation, and Cancer

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SUMMARY OF KEY POINTS

- Most cancers arise in tissues (e.g., the gut, breast, prostate, lungs, and bone marrow) that contain a stem cell population.
- Stem cells have three fundamental properties: the ability to divide and give rise to a new stem cell in a process called self-renewal, the ability to give rise to the differentiated cells of an organ, and genetic constraints on expansion.
- The fact that stem cells are the only long-lived cells in most tissues in which cancers arise suggests that early mutations that lead to cancer accumulate in stem cells.
- In addition to classes of oncogenes that affect cell survival and proliferation, there is a class of oncogenes that permits cells to self-renew. Thus, in some cancers, the target cells for neoplastic transformation may be progenitor cells that have acquired the ability to self-renew as a result of one or more mutations.
- New data suggest that in both leukemia and solid tumors, including tumors of the breast, colon, head and neck, pancreas, and prostate, a small, phenotypically distinct subset of cancer cells has the exclusive ability to form tumors.
- At present, therapeutic targets are selected on the basis of the proposition that all of the cancer cells within a particular tumor are capable of driving tumor formation and metastasis. However, because the bulk of the cancer cells in the tumor are unable to form tumors and most cancer agents are selected to reduce the bulk, these cells are the targets of many therapies.
- To be effective, therapies must target the critical tumorigenic cancer cell population.
- The ability to prospectively identify tumorigenic cancer cells should allow the identification of new diagnostic markers and therapeutic targets.

INTRODUCTION

Common cancers arise in tissues that contain a large subpopulation of proliferating cells that are responsible for replenishing the short-lived mature cells. In such organs, cell maturation is arranged in a hierarchy in which a rare population of stem cells, which perpetuate themselves through a process called *self-renewal,* gives rise to intermediate progenitors and then mature cells, neither of which self-renew.[1–11] Because of their rarity, stem cells must be isolated prospectively to study their biologic, molecular, and biochemical properties. Although it is likely that each tissue regenerates from tissue-specific stem cells, stem cells have been rigorously identified and purified in only a few. The stem cells that give rise to the lymphohematopoietic system, called *hematopoietic stem cells* (HSCs), have been isolated from mice and humans and are the best-characterized stem cells. The utility of tissue containing HSCs has been demonstrated in cancer therapy with its extensive use for bone marrow transplantation to regenerate the hematolymphoid system after myeloablative protocols.[12] The prospective isolation of HSCs from patients can result in a population of cancer-free cells for autologous transplantation.[13–17]

Understanding the cellular biology of the tissues in which cancers arise, and specifically that of the stem cells that reside in those tissues, could provide new insights into cancer biology. Several aspects of stem cell biology are relevant to cancer. First, both normal stem cells and cancer stem cells undergo self-renewal, and emerging evidence suggests that similar molecular mechanisms regulate self-renewal in normal stem cells and their malignant counterparts. Next, it is quite likely that mutations that lead to cancer accumulate in normal stem cells.[18] Finally, as was stated previously, it is likely that tumors contain a minority "cancer stem cell" population with indefinite proliferative potential that drives the growth and metastasis of tumors.[19–28]

PROPERTIES OF NORMAL STEM CELLS

HSCs are the most studied and best understood somatic stem cell population and serve as a model for stem cells from other tissues.[1,9,27,29,30] Hematopoiesis is a tightly regulated process in which a pool of HSCs eventually gives rise via oligo lineage intermediates[1,31–33] to the lymphohematopoietic system consisting of the formed blood elements (e.g., red blood cells, platelets, granulocytes, macrophages, and B and T lymphocytes). These cells are important for oxygenation, prevention of bleeding, immunity, and fighting infections. In the adult, HSCs have three fundamental properties. First, HSCs need to self-renew to maintain the stem cell pool. Self-renewal is not synonymous with proliferation. Self-renewal is a cell division in which one or both of the daughter cells remain undifferentiated and have the ability to give rise to another stem cell as well as to the spectrum of more differentiated progenitors. Second, HSCs must undergo differentiation to maintain a constant pool of mature cells in normal conditions and to produce increased numbers of a particular lineage in response to stresses such as bleeding or infection. Third, the total number of HSCs is under strict genetic regulation.[34]

In the mouse hematopoietic system, multipotent cells constitute 0.05% of bone marrow cells and are heterogeneous with respect to their ability to self-renew. There are three different populations of multipotent cells: long-term self-renewing HSCs, short-term

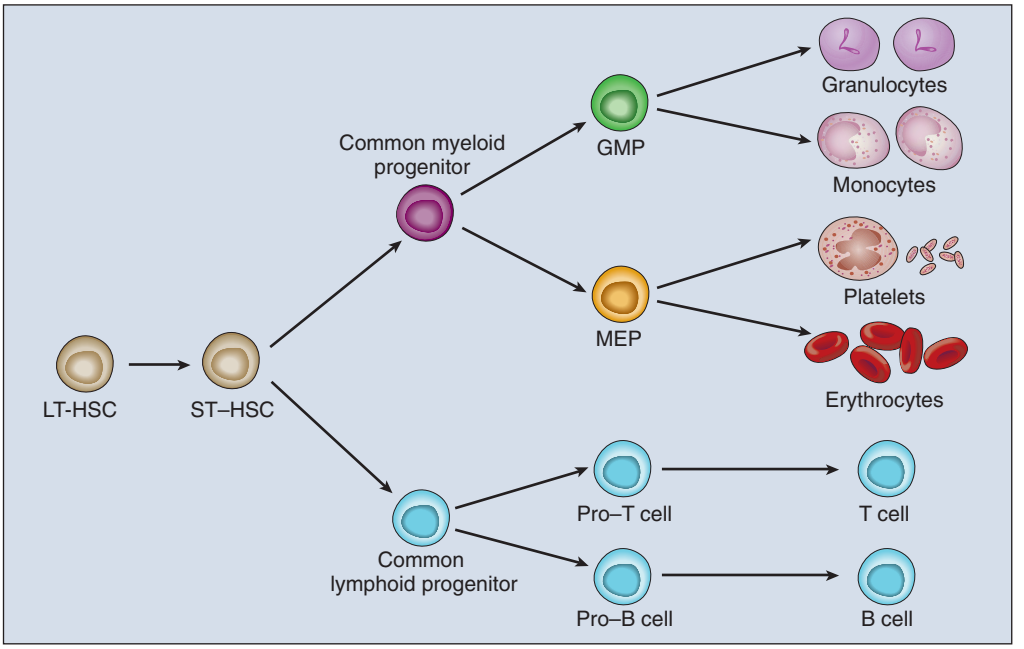


Figure 7-1 • Blood development hierarchy. All of the diverse mature blood cells arise from the hematopoietic stem cells (HSCs). The cells that are capable of multilineage reconstitution of a lethally irradiated mouse are contained within two identifiable and separate populations of cells: the long-term hematopoietic stem cells HSCs (LT-HSCs) and the short-term hematopoietic stem cells HSCs (ST-HSCs). Only the LT-HSCs are capable of self-renewal for the lifetime of the animal. In contrast, other cells, even the ST-HSCs that can give rise to large numbers of mature blood cells, have very limited life spans (measured in hours to 1 or 2 months). GMP, granulocyte-macrophage progenitors; MEP, myeloid-erythroid progenitors.

self-renewing HSCs, and multipotent progenitors without detectable self-renewal potential.[7,35] These populations form a hierarchy in which the long-term HSCs give rise to short-term HSCs, which in turn give rise to multipotent progenitors[7] (Fig. 7-1). As HSCs mature from the long-term self-renewing pool to multipotent progenitors, they become more mitotically active but lose the ability to self-renew. Only long-term HSCs can give rise to mature hematopoietic cells for the lifetime of the animal, whereas short-term HSCs and multipotent progenitors reconstitute in lethally irradiated mice for fewer than 8 weeks.[7]

Despite the fact that the phenotypic and functional properties of mouse and human HSCs have been extensively characterized,[2] understanding of the fundamental stem cell property, self-renewal, is minimal.[27,29,36] In most cases, HSCs differentiate when exposed to combinations of growth factors that can induce extensive proliferation in long-term cultures.[37] Although recent progress has been made in identifying culture conditions that maintain HSC activity in culture for a limited period,[38] it has proven to be exceedingly difficult to identify tissue culture conditions that promote a significant and prolonged expansion of progenitors with transplantable HSC activity.

GENETIC REGULATION OF SELF-RENEWAL IN NORMAL STEM CELLS AND CANCER CELLS

Maintenance of a tissue or a tumor is determined by a balance of cell proliferation and cell death.[39] As would be expected, many of the mutations that drive tumor expansion regulate either cell proliferation or survival. For example, the prevention of apoptosis by enforced expression of the oncogene Bcl-2 promotes the development of lymphoma and also results in increased numbers of HSCs in vivo, suggesting that cell death plays a role in regulating the homeostasis of HSCs; enforced expression of bcl2 does not endow short-term HSCs or multipotent progenitors with self-renewal properties.[40,41] In fact, the progression to experimental acute myelogenous leukemia (AML) in mice requires at least four independent events to block the several intrinsically triggered and extrinsically induced programmed cell death pathways of myeloid cells.[42] Proto-oncogenes such as c-myb and c-myc that drive proliferation of tumor cells are also essential for HSC development[43–46] as well as increased expression of the telomere regenerating enzyme and RNA.[47]

Self-renewal is critical for both normal stem cells and cancer stem cells. In a normal tissue, stem cell numbers are under tight genetic regulation, resulting in the maintenance of a constant number of stem cells in the organ.[34,48,49] In contrast, cancer stem cells have escaped this homeostatic regulation, and the number of cells within a tumor with the ability to self-renew is constantly expanding, resulting in the inevitable growth of the tumor. Because cancer cells and normal stem cells share the ability to self-renew, it is not surprising that a number of genes classically associated with cancer may also regulate normal stem cell development.[27,50] In combination with other growth factors, sonic hedgehog (Shh) signaling has also been implicated in the regulation of self-renewal by the finding that cells that are highly enriched for human HSCs ($CD34^{+}Lin^{-}CD38^{-}$) exhibit increased self-renewal in response to Shh stimulation in vitro.[51] Several other genes related to oncogenesis have been shown to be important for stem cell function. For example, mice that are deficient for *tal-1/SCL,* which is involved in some cases of human acute myeloid leukemia, lack embryonic hematopoiesis,[52] suggesting that *tal-1/SCL* is required for intrinsic or extrinsic events necessary to initiate hematopoiesis, for maintenance of the earliest definitive blood cells, or for the formation of blood cells downstream of embryonic HSCs.[52,53] Members of the Hox family have also been implicated in human leukemia, and enforced expression of *HoxB4* can affect stem cell functions.[54,55] One of the major targets of the p53 tumor suppressor gene is $p21^{cip1}$. Bone marrow from $p21^{cip1}$-deficient mice has a reduced ability to serially reconstitute lethally irradiated recipients. Failure at serial transfer could result from exhaustion of the stem cell pool, loss of telomeres, or loss of transplantability.[18,56,57] Thus, many genes that are involved in decisions about stem cell fate are also involved in malignant transformation.

The notion that the function of certain oncogenes is to regulate self-renewal is perhaps best illustrated by studies of the oncogene *bmi-1.* In mice, *bmi-1* cooperates with c-myc to induce lymphoma.[58,59] The number of HSCs is markedly reduced in postnatal $bmi\text{-}1^{-/-}$ mice, and transplanted $bmi\text{-}1^{-/-}$ fetal liver and bone marrow cells are able to contribute only transiently to hematopoiesis, indicating a cell autonomous defect of HSC self-renewal in $bmi\text{-}1^{-/-}$ mice.[60] The expression of stem cell-associated genes,[3] cell survival genes, transcription factors, and genes that modulate proliferation, including $p16^{Ink4a}$ and $p19^{Arf}$, is altered in bone marrow cells of $bmi\text{-}1^{-/-}$ mice. This suggests that the function of *bmi-1* is to regulate a cascade of genes

that modulate stem cell self-renewal. In a mouse model of leukemia, leukemic cells that lack expression of *bmi-1* eventually undergo proliferation arrest associated with signs of differentiation and apoptosis when they are transplanted in syngenic hosts. Infection of the cells with a *bmi-1* retrovirus completely rescues the proliferative defect of the *bmi-1*$^{-/-}$ leukemic stem cells.[61] Along a similar line, the regulated postnatal deletion of junB, an AP1 transcription factor, results in HSC expansion and then the development of a chronic myeloproliferative disorder that resembles human chronic myelogenous leukemia (CML) in its chronic phase.[62] Transduced overexpression of junB in HSCs inhibits or prevents their self-renewing proliferations. In the junB knockout HSCs, *p16*^{ink4a} and *p19*^{Arf} levels are lowered, and the antiapoptotic proteins bcl2 and bclx are increased, while the reverse is true in HSCs that have junB overexpression.[55] Only HSCs transplant this chronic phase of the disease, but later, in blast crisis, cells at a more differentiated stage emerge that transplant the blast crisis disease.[62,63] These studies conclusively demonstrate that malignant transformation requires not only activation of proliferation pathways, as well as inactivation of cell death and cell cycle arrest pathways, but also activation of self-renewal pathways.

Two other signaling pathways that are implicated in oncogenesis in both mice and humans, the Wnt/β-catenin and Notch pathways, may play central roles in the self-renewal of both normal and cancer stem cells. The Notch family of receptors was first identified in *Drosophila* species and has been implicated in development and differentiation.[64] In *Caenorhabditis elegans,* Notch plays a role in germ cell self-renewal.[65] In neural development, transient Notch activation initiates an irreversible switch from neurogenesis to gliogenesis by embryonic neural crest stem cells.[10] Notch activation of HSCs in culture with either of the Notch ligands Jagged-1 or Delta transiently increases the primitive progenitor activity both in vitro and in vivo, suggesting that Notch activation promotes either the maintenance of progenitor cell multipotentiality or HSC self-renewal.[66,67] Although the Notch pathway plays a central role in development and the mouse oncogene int-3 is a truncated Notch 4,[68] the role of Notch in de novo human cancer is complex and less well understood. Various members of the Notch signaling pathway are expressed in cancers of epithelial origin, and activation of the Notch pathway by chromosomal translocation is involved in some cases of leukemia.[69–73] Microarray analysis has shown that members of the Notch pathway are often overexpressed by tumor cells.[70,71] A truncated Notch 4 messenger RNA is expressed by some breast cancer cell lines.[74] Overexpression of Notch1 leads to growth arrest of a small cell lung cancer cell line, whereas inhibition of Notch1 signals can induce leukemia cell lines to undergo apoptosis.[64,66,75] Elegant work by Weizen and colleagues[76] showed that activation of Notch1 signaling maintains the neoplastic phenotype in Ras-transformed human cells. They also found that in de novo cancers, cells with an activating Ras mutation also demonstrate increased expression of Notch1 and Notch4.

Wnt/β-catenin signaling also plays a pivotal role in the self-renewal of normal stem cells and malignant transformation.[77–79] The Wnt pathway was first implicated in mouse mammary tumor virus-induced breast cancer in which deregulated expression of Wnt-1 caused by proviral insertion resulted in mammary tumors.[80,81] Subsequently, it has been shown that Wnt proteins play a central role in pattern formation. Wnt-1 belongs to a large family of highly hydrophobic secreted proteins that function by binding to their cognate receptors, members of the Frizzled and low-density lipoprotein receptor-related protein families, resulting in activation of β-catenin.[50,70,77,82,83] In the absence of receptor activation, β-catenin is marked for degradation by a complex consisting of the adenomatous polyposis coli, Axin, and glycogen synthase kinase-3β proteins.[78,79,84–87] Wnt proteins are expressed in the bone marrow, and activation of Wnt/β-catenin signaling by Wnt proteins in vitro or by expression of a constitutively active β-catenin expands the pool of early progenitor cells and enriched normal transplantable HSCs in tissue culture and in vivo.[27,79,84] Inhibition of Wnt/β-catenin by ectopic expression of Axin, an inhibitor of β-catenin signaling, leads to inhibition of stem cell proliferation both in vitro and in vivo. Addition of Wnt3a to purified HSC leads to their expansion, presumably self-limited usually by the expression of the β-catenin-induced transcription of axinII; transduction of purified HSC with axin prevents their expansion in vitro or in vivo.[88,89] Other studies suggest that the Wnt/β-catenin pathway mediates stem or progenitor cell self-renewal in other tissues.[85,86,90,91] The level of β-catenin in a particular keratinocyte directly correlates with its proliferative capacity.[85,86,91] As in their normal HSC counterparts, enforced expression of an activated β-catenin in epidermal stem cells increases their ability to self-renew and decreases their ability to differentiate. Mice that fail to express TCF-4, one of the transcription factors that is activated when bound to β-catenin, soon exhaust their undifferentiated crypt epithelial progenitor cells, further suggesting that Wnt signaling is involved in the self-renewal of epithelial stem cells.[50,90]

Activation of β-catenin in colon cancer by inactivation of the protein degradation pathway, most frequently by mutation of adenomatous polyposis coli, is common.[50,70,78,87] Expression of certain Wnt genes is increased in some other epithelial cancers, suggesting that activation of β-catenin might be secondary to ligand activation in such cancers.[77,92–97] There is evidence that constitutive activation of the Wnt/β-catenin pathway might confer a stem/progenitor cell phenotype to cancer cells. Inhibition of β-catenin/TCF-4 in a colon cancer cell line induced the expression of the cell cycle inhibitor p21^{cip-1} and induced the cells to stop proliferating and to acquire a more differentiated phenotype.[97] Enforced expression of the proto-oncogene c-*myc*, which is transcriptionally activated by β-catenin/TCF-4, inhibited the expression of p21^{cip-1} and allowed the colon cancer cells to proliferate when β-catenin/TCF-4 signaling was blocked, linking Wnt signaling to c-*myc* in the regulation of cell proliferation and differentiation.[97]

The implication of roles for genes such as Notch, Wnt, c-*myc*, and Shh in the regulation of self-renewal of HSCs, and perhaps of stem cells, from multiple tissues suggests that there might be at least some common self-renewal pathways in many types of normal somatic stem cells and cancer stem cells. It will be important to identify the molecular mechanisms by which these pathways work and to determine whether the pathways interact to regulate the self-renewal of normal stem cells and cancer stem cells.

TARGET CELLS FOR MALIGNANT TRANSFORMATION

If oncogenic mutations often target signaling pathways that regulate proliferation and self-renewal, then are stem cells, highly proliferative progenitor cells, or both the target of neoplastic transformation? Several lines of evidence suggest that stem cells might be involved in the evolution of a cancer. First, the fact that multiple mutations are necessary for a cell to become cancerous[98,99] suggests that in many cases, mutations accumulate in a stem cell. Progenitor cells have a very limited life span, making it less likely that all of the mutations occur during the life of these relatively short-lived cells.[1,7,8,27,29,31,32,100] Second, the regulation of stem cell expansion and self-renewal is under strict genetic regulation by multiple genes, and unregulated expansion of stem cells could, in essence, result in a cancer.[34,48,49] Third, most cancers arise in tissues that contain stem cells that have the intrinsic ability to self-renew. Because cancer cells must undergo self-renewal, this suggests that stem cells might more easily undergo steps in the progression to malignant transformation than will progenitor cells that lack this fundamental property and must therefore activate these self-renewal pathways to become malignant. In the hematopoietic system, the only cells that have the ability to self-renew are HSCs and mature lymphocytes. The common blood cancers, acute leukemias and lymphomas, may arise from the HSCs or lymphocytes, respectively, via constitutive activation of mitogenic pathways associated with the proliferation of normal cells.[27,39,101,102] Although stem cells

may undergo steps toward malignant transformation, it is possible, if not likely, that in many cases, their progenitor cells that inherit the changes in stem cells, and in addition add the ultimate transforming event, give rise to cancer. For example, the initial mutations that occur in the stem cell could permit a single mutation to transform a progenitor cell, or perhaps events that shut down self-renewal could occur in stem cells, but only progenitors outside of the stem cell regulatory niche expand as cancer stem cells.[18] It is also possible that certain oncogenic mutations such as *bmi-1* or its downstream targets could confer the property of self-renewal on a progenitor cell.

The target cells for transformation are best understood in hematopoietic malignancies because the developmental hierarchy of the blood is well established.[1,7,31,32] One of the most frequent mutations in AML in elderly patients is the t(8;21) translocation, which results in the expression of a chimeric AML-ETO transcript in the leukemic cells.[103–105] Marrow samples from patients with early onset 8;21 leukemia in Hiroshima Hospital had $CD34^{+}Thy1(CD90)^{+}CD38^{-}Lin^{-}$ HSCs, which, when isolated from patients in clinical remission, had up to 90% incidence of the chimeric AML-1-ETO transcript.[105] When these HSCs were analyzed by means of in vitro differentiation assays, the HSCs gave rise to normal myeloerythroid progeny, demonstrating that the mutation was present in the otherwise normal stem cells. In these patients, the CD90 neg subset of $CD34^{+}CD38^{-}Lin^{-}$ cells gave rise to leukemic colonies in vitro; this could represent HSCs that have lost Thy1 expression or downstream multipotent progenitors[106] that have gained self-renewal capacity.[105] Taken together, these observations support the notion that mutations accumulate in stem cells and that subsequent mutations in either the stem cells or their progeny result in overt leukemia.

Although stem cells are frequently the target of mutations that are on the path to malignant transformation, it is likely that their clonal progenitor cells may be transformed by subsequent genetic events that confer immortality, self-renewal potential, or both to these normally non-self-renewing cells (Fig. 7-2).[18] In patients with CML, the BCR-ABL mutation is present in both normal and leukemic stem cells. In otherwise normal hematopoietic cells, the BCR-ABL mRNA is expressed solely by the progenitor cells.[2,107,108] In a mouse model of CML, BCR-ABL expression targeted to myeloid progenitor cells by the hMRP-8 promoter resulted in CML-like disease in a subset of the mice. Furthermore, when $hMRP8p210^{BCR/ABL}$ mice were crossed with hMRP8bcl-2 mice, a proportion of the mutant mice developed a disease resembling AML or myeloid blast crisis.[109] Although the expression of transforming genes was targeted to early progenitor cells, the appearance of the leukemia cells and clinical course resembled human CML and AML in the $hMRP8p210^{BCR/ABL}$ mice and the $hMRP8p210^{BCR/ABL}$/hMRP8bcl-2 mice, respectively. In the chronic phase of human CML, the CML phenotype of the CML stem cell is identical to that of a normal HSC. β-Catenin signaling is active in both the normal HSCs and the CML stem cells but not in the progenitor cells. When CML progresses to "myeloid blast crisis," the patients develop an acute leukemia-like disease. The leukemic stem cell in CML blast crisis phenotypically is at the developmental stage of a granulocyte-macrophage progenitor cell that transplants the disease to immunodeficient mice and that self-renews replating potential in vitro.[110] Furthermore, the CML blast crisis stem cells appear to have activated the β-catenin signaling pathway and are inhibited in their in vitro self-renewal by transduced axin. Thus, disease progression in human CML appears to result from activation of self-renewal pathways in a progenitor cell population or, more likely, failure to shut down this pathway in the HSC to granulocyte-macrophage transition. These studies strongly suggest that the leukemia stem cell in CML blast crisis is derived from a progenitor cell, not from a normal stem cell, although the initial event and likely several progression events are in successive subclones of the initial bcr-abl HSC stage cells.

In a mouse model of high-grade glioblastoma, enforced expression of the epidermal growth factor receptor-enriched populations in either Ink4a/Arf null neuronal stem cells or Ink4a/Arf null astrocytes led to malignant glioblastomas when the cells were injected orthotopically into mice.[111] Notably, in the majority of the cases, the transformed astrocytes appeared to acquire an immature phenotype in the brains of the mice, suggesting to some researchers that there was "dedifferentiation,"[111] although we have never documented a case of dedifferentiation with purified normal hematopoietic progenitor cells. There are two other possible explanations for these results. First, the astrocyte tissue culture cells could have contained a rare population of neuronal stem cells that were transformed, and these stem cells were responsible for generating the tumors. Second, it is possible that the tissue culture conditions could have caused the dedifferentiation of the astrocytes and that unless the astrocytes are grown in tissue culture, they cannot give rise to glioblastomas in an animal. These observations in humans and mice support the notion that oncogenic mutations accumulate in the stem cells, but expression of the mutated gene by progenitors downstream of the stem cells can lead to their neoplastic transformation of progenitor cells. These observations have implications for targeted therapies.

It is possible that only a minority of the mice whose progenitors express BCR-ABL develop leukemia because the progenitors must acquire an additional mutation or epigenetic change that causes deregulated self-renewal. Two lines of evidence support this notion. First, expression of *bmi-1* is necessary for the self-renewal of adult HSCs, and the blast cells of patients with AML express large amounts of this protein.[101] Although expression of *HoxA9* and *Meis1* induces transplantable AML in normal mice, expression of these genes in the absence of *bmi-1* does not.[60,61] This suggests that both normal HSCs and leukemic stem cells require *bmi-1* to self-renew. Second, deregulated β-catenin signaling occurs in many de novo human cancers and causes cancer in transgenic mouse models. Because expression of a constitutively active β-catenin can promote the self-renewal of normal HSCs, as well as stem cells from other tissues, it is quite plausible that activation of this pathway promotes self-renewal of the cancer cells.[2,27,90,91,97,102,107,109,112,113] From these results, it is evident that

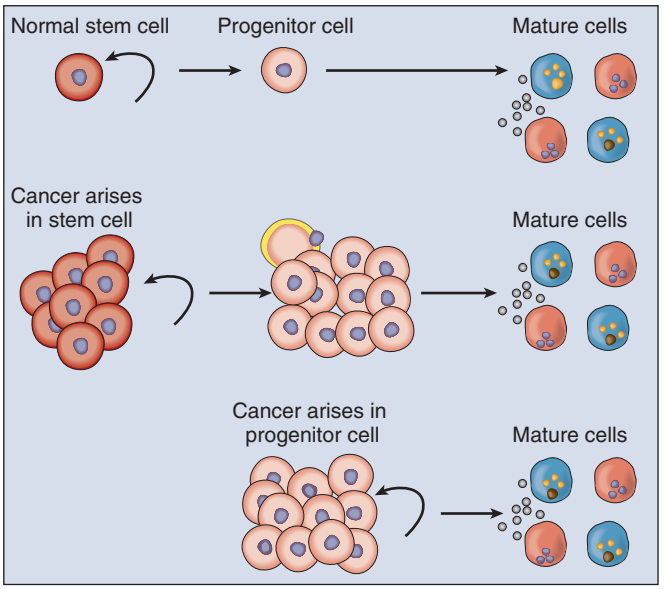


Figure 7-2 • Target cells for neoplastic transformation. In many tissues in which cancers arise, the stem cells are the only long-lived cells and are the only cells capable of self-renewal. Because they are already capable of extensive self-renewal, they are good targets for neoplastic transformation. Dysregulation of the self-renewal process may be simpler in these cells than in progenitor cells that lack this ability. For progenitor cells to undergo malignant transformation, they must acquire the ability to undergo extensive self-renewal as a result of oncogenic mutations.

future studies focusing on the molecular regulation of the self-renewal of normal stem cells and cancer cells will likely lead to more effective therapies for cancer.

EVIDENCE FOR CANCER STEM CELLS

It has long been known that cancers consist of phenotypically heterogeneous populations of cancer cells.[23–26,114–117] These phenotypically distinct cell populations could arise in part from sequential mutations caused by genetic instability, environmental factors, or both (Fig. 7-3A). Alternatively, a tumor can be viewed as an aberrant organ containing a tumorigenic (stem cell) population that drives tumor growth. These tumorigenic cells would have acquired oncogenic mutations and epigenetic changes that result in unregulated self-renewal, extended cell survival, and avoidance of innate and adaptive immune surveillance and would also give rise to phenotypically diverse populations of tumor cells that lack the ability to self-renew (Fig. 7-3B). Several lines of evidence suggest that the latter model accounts for some of the cellular heterogeneity that is seen in tumors, although genetic instability and environmental factors could also contribute to the variability in phenotypes.[118,119] It is well documented that many types of cancer contain heterogeneous populations of cells that variably express differentiation markers that reflect the tissues from which the tumors originate, as well as cancer cells that have an immature appearance.[115,120,121] Examples of this include the variable expression of milk proteins by some breast cancers and the variable expression of myeloid markers, lymphoid markers, or both in CML and AML. Perhaps the most striking example of abnormal differentiation in cancer is the variable expression of diverse tissues in some germ cell tumors. Mature tissues such as teeth, skin, and hair are present in some cases of teratocarcinomas (Fig. 7-4). In contrast, in some tumors, only a minority of the cancer cells express immature cell markers such as α-fetoprotein (see Fig. 7-4). Because the terminally differentiated cells that form the teeth and hair in the tumors are unlikely to be able to proliferate and form new tumors, these data suggest that the minority population of α-fetoprotein-expressing cancer cells has the exclusive ability to form new tumors consisting of more tumorigenic cells, as well as the phenotypically diverse populations of non-self-renewing abnormally differentiated cells. If this is true, these cells can thus be considered cancer stem cells.

If a tumor is viewed as an abnormal organ, then the principles of stem cell biology can be applied to better understand the biology of these diseases.[1,8,9] It was first shown in hematopoietic malignancies and subsequently in solid cancers that only a subset of cancer cells were clonogenic when placed in tissue culture or injected into immunodeficient mice.[21,23–25,115,117,122,123] For example, only 1 in 100 to 1 in 10,000 mouse myeloma cells obtained from ascites fluid formed in in vitro colony-forming assays. Similarly, only 1% to 4% of leukemic cells formed spleen colonies when transplanted into mice. In solid cancers, only 1 in 1000 to 1 in 5000 ovarian cancer or lung cancer cells formed colonies in soft agar. Because only a minority of normal bone marrow cells was also clonogenic, the clonogenic cancer cells were described as *cancer stem cells,* implying that only a distinct population of cancer cells was able to proliferate extensively in these assays. However, an alternative explanation is that all the cancer cells had an intrinsic ability to proliferate extensively but only a minority of cells did so in a particular assay.[117] Variable plating efficiency in a variety of in vitro cells and cell lines could have accounted for the poor performance of such cells, and in none of the assays did the investigators prospectively purify the plating cell to show that it was, or was not, a cancer stem cell.

To prove that a phenotypically distinct population of cancer cells is solely responsible for perpetuating the disease, it is necessary to isolate different populations of cancer cells and demonstrate that one or more groups are enriched for the ability to initiate disease and other populations lack this ability. This was done in the case of AML, when it was shown that in most cases of human AML, a leukemic tumor initiating subpopulations of cells could be identified prospectively and enriched from the bone marrow of multiple patients. In most cases of AML, the minority population of $CD34^{+}CD38^{-}$ cells was the only group of cells that was capable of establishing human AML in the bone marrow of nonobese diabetic/severe combined immunodeficient (NOD/SCID) mice.[124,125] Remarkably, within the $CD34^{+}CD38^{-}$ population are $Thy1^{+}CD34^{+}CD38^{-}$ $Lineage^{-}$ normal HSCs[2,100,105,124–127] as well as $Thy1^{-}CD34^{+}38^{-}Lineage^{-}$ progenitors.[106] Because normal HSCs, but not their leukemic initiating cell counterparts, express Thy1, it is likely that the early mutations occurred in the HSCs and the final transforming mutations occurred either in early downstream progenitors or in HSCs if, as a consequence of neoplastic transformation, Thy1 expression was lost.[105]

Recently, tumorigenic and nontumorigenic subsets of cancer cells have been isolated from human breast cancer tumors. When a similar model for human breast cancer was used in which isolated

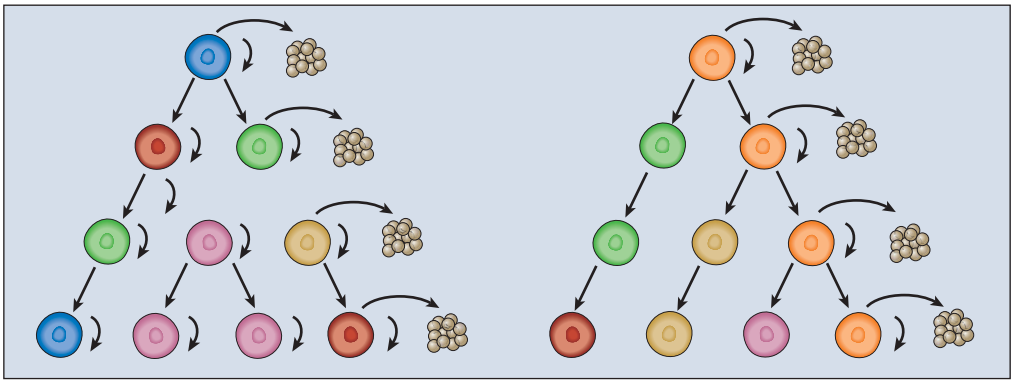


Figure 7-3 • The two most likely models of heterogeneity of the cancer cells, shown as different colored cells within a tumor. **A,** Heterogeneity is due to environmental factors (*gold, red, green,* and *blue* cells) or due to ongoing mutations in the cancer cells (*magenta* cells). In this model, all of the cancer cells have the intrinsic ability to form tumors. **B,** Cancer stem cells (*yellow* cells) have the exclusive ability to self-renew. As in normal tissues, the stem cells would give rise to more stem cells with the capacity to form new tumors, as well as the other heterogeneous populations of cancer cells that lack the ability to form new tumors. To date, therapeutic and diagnostic strategies have been based on model A, but these strategies might be limited because they might not target the rare population of cancer stem cells depicted in model B.

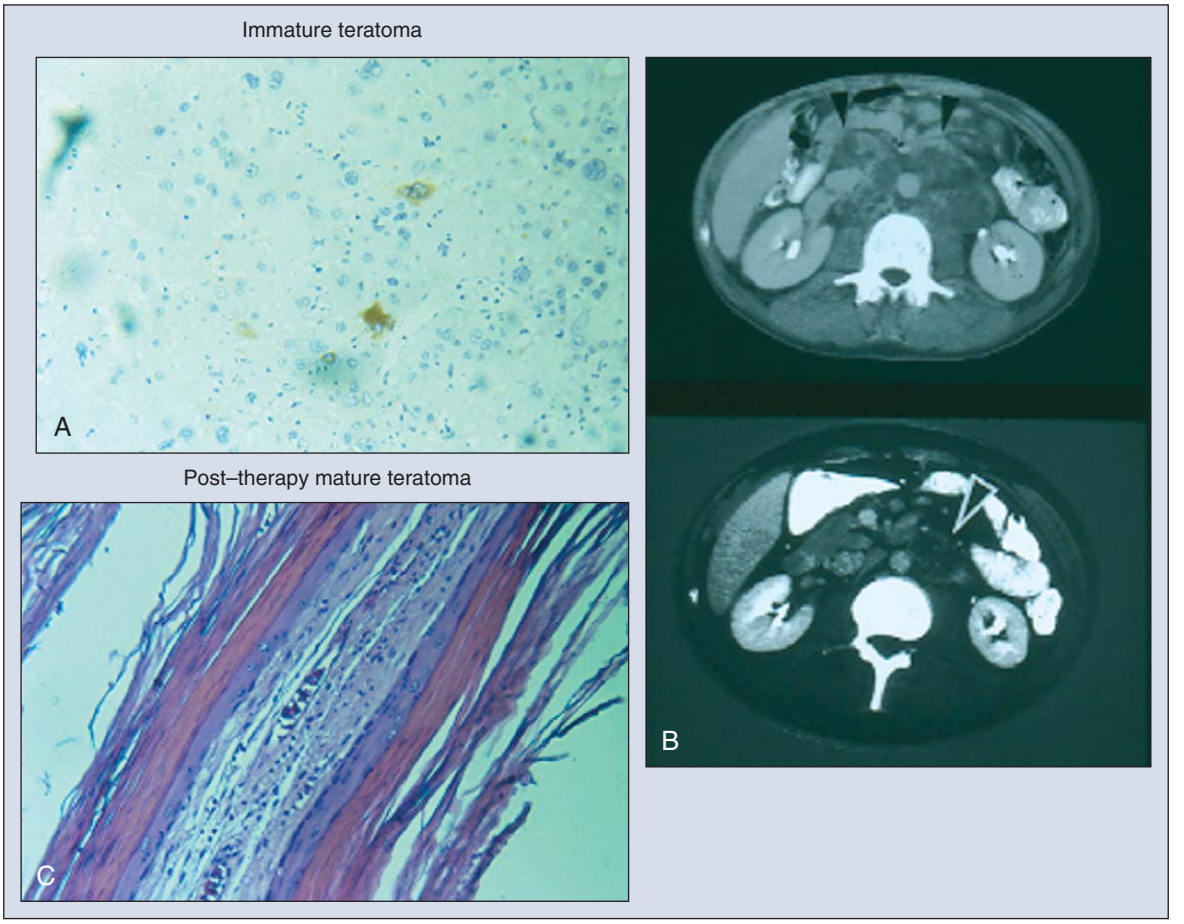


Figure 7-4 • Clinical evidence for the stem cell model. The clinical and radiographic information for a patient with metastatic teratocarcinoma of the testis is shown. **A,** In the original testicular biopsy specimen, expression of α-fetoprotein by only rare cancer cells (*brown* cells) was detected by immunohistochemistry of the original testicular tumor. The original histologic finding in this patient was believed to represent a teratoma. **B,** Computed tomographic scans before treatment (*upper panel*) demonstrated large retroperitoneal masses that were still present after four courses of platinum-based chemotherapy (*lower panel*). **C,** Biopsy specimen of the residual mass revealed only mature teratoma. No cells expressed the immature marker α-fetoprotein. The patient has survived for more than 10 years without recurrence of his germ cell cancer. This suggests that in some patients, therapies that selectively eliminate the rare stem cell population while sparing the "nontumorigenic" cancer cells could be curative.

cells were grown in immunocompromised mice, a minority population of breast cancer cells that had the ability to form new tumors was identified.[19] Tumorigenic cells could be distinguished from nontumorigenic cancer cells on the basis of surface marker expression. In eight of nine patients, tumorigenic cells could be prospectively identified and isolated as $CD44^+CD24^{-/low}Lineage^-$ cells.[19] As few as 100 $CD44^+CD24^{-/low}Lineage^-$ cells were able to form tumors, whereas tens of thousands of cells from other populations of cells within the tumor failed to form tumors in NOD/SCID mice. These tumorigenic cells could be serially passaged in mice, and each time, cells within this population generated new tumors containing additional $CD44^+CD24^{-/low}Lineage^-$ tumorigenic cells, as well as phenotypically mixed populations of other nontumorigenic cancer cells. These data demonstrate the presence of a hierarchy of cells within a breast cancer tumor in which only a fraction of the cells have the ability to proliferate extensively and other cells have only a limited proliferative potential, suggesting that the tumorigenic cells can both self-renew and differentiate. The phenotype of the tumorigenic breast cancer cells may be similar to that of normal breast epithelial stem or progenitor cells, because early multipotent epithelial progenitor cells have been reported to express epithelial cell antigen and CD44.[128–130]

The $CD44^+CD24^{-/low}Lineage^-$ tumorigenic breast cancer cell and the $CD34^+CD38^-CD90^-$ leukemia-initiating cells share with normal stem cells the abilities to proliferate extensively and to give rise to diverse cell types with reduced developmental or proliferative potential.[5,19] The extensive proliferative potential of the tumorigenic breast cancer cell population was demonstrated by the ability of as few as 200 tumorigenic breast cancer cells or several thousand leukemia-initiating cells to give rise to tumors that could be serially transplanted in NOD/SCID mice. This extensive proliferative potential contrasts with the bulk of the breast cancer cells that lack the ability to form detectable tumors. Not only was the $CD44^+CD24^{-/low}Lineage^-$ population of cells able to give rise to additional tumorigenic $CD44^+CD24^{-/low}Lineage^-$ cells, it was also able to give rise to phenotypically diverse nontumorigenic cells that made up the bulk of the tumors. Thus, both tumorigenic breast cancer cells and leukemia-initiating cells from most tumors appear to exhibit properties of cancer stem cells. However, before these cells can definitively be called cancer stem cells, new assays are needed to demonstrate that a single transplanted cell gives rise to all of the diverse populations of cancer cells within a tumor.

Cancer stem cells have since been identified in multiple tumors, including cancers arising in the brain, head and neck, pancreas, colon, and prostate.[131–135] Interestingly, CD44 seems to be useful as a marker for isolation of cancer stem cells from multiple types of tumors of epithelial origin, including head and neck cancer. Importantly, in histology sections, the cancer stem cells in well-differentiated or mod-

erately differentiated tumors showed that the cancer stem cells, but not the nontumorigenic cancer cells, expressed CD44 and *bmi-1,* which had previously been shown to be involved in self-renewal in some types of stem cells.[133] However, the nontumorigenic cells expressed mature cell markers, while the cancer stem cells did not.[133] These studies demonstrate that the differential expression of the stem cell markers was not an artifact of flow cytometry.

IMPLICATIONS OF CANCER STEM CELLS FOR THE DIAGNOSIS AND TREATMENT OF CANCER

Although the immunocompromised mouse model provides compelling evidence in support of the stem cell model of cancer, the ultimate confirmation of the hypothesis requires proof in humans. If the growth of solid cancers is driven by cancer stem cells, this would have profound implications for the diagnosis and treatment of cancer. At present, all of the phenotypically diverse cancer cells are treated as if they possess the ability to form tumors and the ability to metastasize. However, if in most tumors, only a small population of cancer cells has the ability to self-renew and other populations of cancer cells have only limited ability to proliferate, then this would explain several conundrums of cancer biology. For example, for many years, it has been recognized that disseminated cytokeratin-positive breast cancer cells can be detected in the bone marrow of patients who never experience relapse, even without adjuvant therapy.[136–143] One possibility is that the cancer cells lie dormant until some unknown event triggers them to proliferate. Another explanation is that the cancer cells in the bone marrow in this group of patients arose from the spread of nontumorigenic cancer cells, and only when the cancer stem cells metastasize and subsequently self-renew will frank tumors form. Thus, the development of diagnostic reagents that allow cancer stem cells to be identified may have prognostic significance for patients with breast cancer.

The ability to prospectively isolate cancer stem cells and nontumorigenic cancer cells makes it possible to do molecular analyses of each population of cancer cells in a tumor. A 186-gene signature, called the invasiveness gene signature (IGS), was derived by identifying genes that are differentially expressed by breast cancer stem cells and normal breast epithelial cells.[144] The IGS was used to stratify patients with early stage breast cancer on the basis of the similarity of the gene expression of the whole tumor to the cancer stem cell-derived signature. Remarkably, the IGS was associated with both survival and the risk of developing metastasis. The prognostic power of the IGS was greater than gene signatures derived from the nontumorigenic cancer cells, indicating that the IGS contained both cancer-specific and cancer stem cell-specific elements. The prognostic power of the IGS was even greater when combined with a wound repair signature[145] derived from serum-stimulated fibroblasts. This suggests that cancer stem cells interact with normal tumor stromal elements. Such an interaction is further supported by the observation that the cancer stem cells are adjacent to normal stromal elements in well-differentiated and moderately differentiated head and neck tumors.[133]

Another example of the implications of cancer stem cells is the observation that in most solid cancers, such as breast cancers, chemotherapy can frequently shrink tumors, but in most patients, the tumors rapidly recur, and there is only a small impact on patient survival.[13,146,147] Most of the cancer therapeutic agents that are in current use have been developed largely for their ability to shrink a tumor. If only a minority of the cancer cells are tumorigenic and are responsible for driving tumor growth and metastasis, then tumor shrinkage must reflect primarily the elimination of the bulk population of nontumorigenic cells. If a substantial number of tumor stem cells were spared, then the tumors would regenerate from these cells. In support of this model, many patients who are treated with chemotherapy experience an initial shrinkage of their tumors, but tumors recur in sites of prior disease.

The similarities of the AML tumor-initiating cells and normal HSCs suggest that the AML tumor-initiating cells may be more resistant to chemotherapy than the bulk population of leukemic blasts. Compared with their differentiated progeny, normal HSCs express high levels of genes that make them more resistant to cytotoxic agents including antiapoptotic members of the bcl-2 family, as well as members of the ABC transporters that pump many drugs out of the cell.[30,41,148–151] If the same is true for their cancer stem cell counterparts, then these cells may be significantly more resistant to cytotoxic agents than their nontumorigenic progeny. In support of this possibility, although the chemotherapeutic agent cytosine arabinoside very efficiently killed leukemic blast cells isolated from many patients, the leukemia-initiating cells were selectively spared.[152] In glioblastoma, the cancer stem cells are more resistant to radiation than are their nontumorigenic cancer cell counterparts.[153] These observations suggests that the effect of a particular therapeutic agent on the cancer stem cell population must be taken into account when its curative potential is evaluated.[154]

Because therapeutic agents are selected on the basis of their ability to shrink tumors rapidly, agents that selectively target the cancer stem cells could be overlooked in screens to identify potential therapeutic agents. Initially, such agents would be expected to slow the growth of a tumor only modestly. However, the elimination of the cancer stem cells would eventually halt the spread of the tumor. Perhaps the best clinical evidence of this model occurs in patients with teratocarcinoma. Platinum-based chemotherapy is curative in the majority of these patients;[155] however, many patients are left with residual masses (see Fig. 7-4). After surgical resection, the immature cancer cells have been eliminated, leaving only differentiated cancer cells in a mature teratoma (see Fig. 7-4). Patients with mature teratomas only occasionally have metastases, and most are cured, demonstrating that the elimination of the presumed stem cell population by the chemotherapy is sufficient for curing this solid cancer. Box 7-1 discusses alternative models for cancer cell heterogeneity.

Box 7-1. ALTERNATIVE CANCER CELL HETEROGENEITY MODELS

An alternative explanation for the ability of a single, phenotypically unique population of AML cells or breast cancer cells to engraft in NOD/SCID mice is that all cancer cells are tumorigenic in humans but that only the $CD34^+CD38^-Thy1^-Lineage^-$ AML cells or the $CD44^+CD24^{-/low}Lineage^-$ breast cancer cells are able to proliferate in mice. However, there are several reasons that this appears unlikely. First, NOD/SCID mice have previously been validated as in vivo models for the growth of normal human HSCs and human neural stem cells.[2,9,126,156–158] Second, tumors that are passaged in mice contain heterogeneous cancer cells that are phenotypically similar to the cancer cells that were present in the original tumors from patients, including both tumorigenic and nontumorigenic fractions.[19,20,125,126] This demonstrates that the mouse environment is not incompatible with the survival of the nontumorigenic cell fractions. Third, in the case of breast cancers, the tumorigenic and nontumorigenic fractions of cancer cells exhibit a similar cell cycle distribution in mouse tumors, demonstrating that the nontumorigenic cells are able to divide in mice.[19] Thus, on the basis of these data and the data obtained for other types of normal and malignant human stem cells, the NOD/SCID mouse model reliably supports the engraftment of clonogenic human progenitors. However, human data are required to completely exclude the possibility that different populations of cancer cells are clonogenic in mice than are clonogenic in humans. Because ethical issues preclude the injection of cancer cells into humans, unequivocal proof of the stem cell model will require clinical studies that confirm that therapeutic agents that effectively target cancer stem cells in the immunodeficient mice also eliminate cancer stem cells in patients and result in clinical cures.

FUTURE IMPLICATIONS OF CANCER STEM CELLS

The ability to prospectively identify cancer stem cells should have a major impact on the development of new diagnostic and therapeutic agents. At present, all of the cancer cells within a tumor are treated as if they had the ability to drive tumor growth, invasion, and metastasis. The ability to identify these crucial cells will allow efforts to develop new diagnostic markers and therapies to be focused on the cells that are responsible for the maintenance of the malignancy—the cancer stem cells. For example, in efforts to identify the genes and proteins expressed by cancer cells, either whole tumors or all of the phenotypically diverse cancer cells within a tumor are currently used. Because the cancer stem cells represent only a minority of the cancer cells in most tumors, it is nearly impossible to identify diagnostic markers or therapies that target these cells. However, directing expression analyses to enriched populations of cancer stem cells should allow the identification of novel diagnostic markers and novel therapeutic targets that can be exploited to more effectively diagnose and treat cancer. This principle is illustrated by the observation that BCR/ABL oncogene mRNA is not expressed by HSCs that carry the mutation in their DNA;[159,160] such an approach may have implications even when oncogenic mutations are targeted.

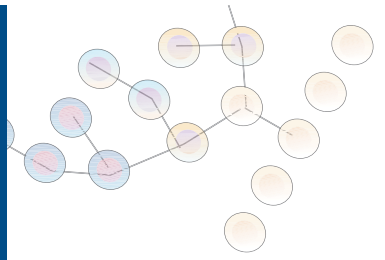
The ability to prospectively identify the cancer stem cells should also improve the ability to evaluate the curative potential of new therapeutic agents. Although cancer cell lines are useful for evaluating particular biologic pathways, they have proven to be somewhat unreliable when used in attempts to predict the clinical efficacy of a particular therapeutic agent in patients.[159,160] Because the tumors that arise in immunodeficient mouse models of human cancer appear to more closely recapitulate the phenotypic diversity of patients' original tumors, including the generation of tumorigenic and nontumorigenic cells, these models might more effectively predict the potential usefulness of a particular drug. New agents could be tested for their ability to eliminate the tumorigenic (cancer stem cell) component of tumors from multiple patients, allowing the agents that have the greatest curative potential to proceed to human clinical trials.

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8 Vascular and Interstitial Biology of Tumors

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SUMMARY OF KEY POINTS

- A solid tumor is an organ composed of neoplastic cells and host stromal cells nourished by the vasculature made of endothelial cells—all embedded in an extracellular matrix. The interactions among these cells and between these cells, their surrounding matrix, and their local microenvironment control the expression of various genes. The products encoded by these genes, in turn, control the pathophysiologic characteristics of the tumor. The tumor pathophysiology governs not only tumor growth, invasion, and metastasis but also the response to various therapies.
- Tumor vasculature is made of host vessels co-opted by tumor cells and by new vessels formed by the processes of vasculogenesis and angiogenesis. A constellation of positive and negative regulators of angiogenesis governs the process of neovascularization.
- Tumor vessels are abnormal in terms of their organization, structure, and function. These abnormalities contribute to heterogeneous vascular permeability, blood flow, and microenvironment.
- Tumor interstitial matrix is formed by proteins secreted by host and tumor cells and by those leaked from the nascent blood vessels.
- Tumor interstitium is heterogeneous, with some regions fairly permeable and others difficult to penetrate. Modification of the collagen matrix can improve penetration of large-molecular-weight therapeutics.
- Interstitial hypertension is a hallmark of solid tumors and results from vessel leakiness, lack of functional lymphatics, and compression of vessels by proliferating cancer cells.
- Judicious application of angiogenic therapy can normalize the tumor vessels and make them more effcient for delivery of oxygen (a known radiosensitizer) and drugs. Antiangiogenic agents can prune tumor vessels, induce cancer cell apoptosis, reduce the number of blood circulating endothelial cells and progenitor cells, and lower interstitial hypertension in tumors.
- Thus far, three antiangiogenic agents have been approved for patients with certain types of cancer. Based on these successes, antiangiogenic therapy is expected to make a difference in many other tumor types. Two main hurdles to further development of antiangiogenic agents are the better understanding of the mechanisms of action of these agents and developing biomarkers to monitor their effects.

INTRODUCTION

A solid tumor is an organ composed of neoplastic cells and host stromal cells nourished by the vasculature made of endothelial cells—all embedded in an extracellular matrix (Fig. 8-1). The interactions among these cells and between these cells, their surrounding matrix, and their local microenvironment, control the expression of various genes. The products encoded by these genes, in turn, control the pathophysiologic characteristics of the tumor. The tumor pathophysiology governs not only the tumor growth, invasion, and metastasis but also the response to various therapies. In this chapter we will discuss various pathophysiologic parameters that characterize the vascular and extravascular compartments of a tumor and the mechanisms governing the formation and function of these compartments.

VASCULAR COMPARTMENT

Neoplastic cells, like normal cells, need oxygen and other nutrients for their survival and growth. Every normal cell in our body is located within 100 to 200 μm from a blood capillary so that it can receive oxygen and other nutrients by the process of diffusion. Likewise, cells undergoing neoplastic transformation depend on nearby capillaries for growth. These preneoplastic (i.e., hyperplastic or dysplastic) cells can grow as a spherical or ellipsoidal cellular aggregate. Once the size of the cellular aggregate reaches the diffusion limit for critical nutrients and oxygen, however, the aggregate as a whole can become dormant. Indeed, human tumors can remain dormant for many years because of a balance between neoplastic cell proliferation and apoptosis. However, once they have access to new blood vessels they may grow and metastasize. What triggers the growth of new vessels? What molecular and cellular mechanisms are involved? How do these vessels compare with normal vessels with respect to structure and function? Can we prevent or delay tumor progression only by interfering with the neovascularization process?

New Vessel Formation

It has been known for nearly a century that the vascular system is associated with tumor growth in animals and humans.[1] Powerful insights into the neovascularization of transplanted tumors using the transparent window techniques were developed in the 1940s.[2–5] The possibility that tumors produce an "angiogenic" substance was suggested in 1968.[6,7] The hypothesis that blocking angiogenesis should

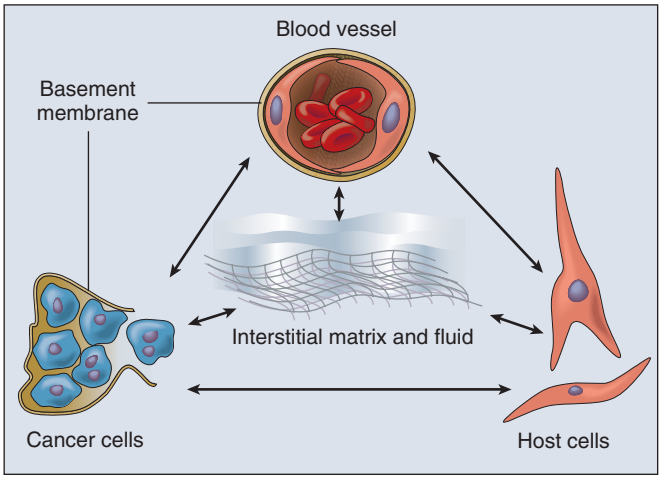


Figure 8-1 • Schematic representation of a solid tumor. The key components include cancer cells, host cells, and vasculature made of endothelial cells—all embedded in a matrix bathed in interstitial fluid. Arrows indicate interactions between the components. (Adapted from Jain RK: Angiogenesis and lymphangiogenesis in tumor: insights from intravital microscopy. Cold Spring Harbor Symp Quant Biol [The Cardiovascular System] 2002;67:239–248.)

block tumor growth and metastasis was proposed shortly thereafter in 1971.[8] The concept that a tissue acquires angiogenic capacity during neoplastic transformation—and, by extension, that antiangiogenesis could be used to prevent cancer—was put forward in 1976.[9] The first antiangiogenic agent approved for cancer patients was bevacizumab, an antibody specific to vascular endothelial growth factor (VEGF), on the basis of the increased survival seen in metastatic colorectal cancer patients with the combination of bevacizumab with standard chemotherapy in a pivotal randomized placebo-controlled phase III trial.[10] At present, various anti- and proangiogenesis strategies are being evaluated clinically to prevent or treat a large number of diseases, including cancer.[11–13] Both normal and pathologic angiogenic processes are governed by the net balance between pro- and antiangiogenic factors.[14,15] This balance is spatially and temporally regulated under physiologic conditions, so that the "angiogenic switch" is "on" when needed (e.g., during embryonic development, wound healing, formation of the corpus luteum) and "off" at other times. During neoplastic transformation and tumor progression, this regulation is deranged, and blood vessels form ectopically to support a growing tumor mass.

Cellular Mechanisms

At least four cellular mechanisms are involved in the vascularization of tumors: co-option, intussusception, sprouting (angiogenesis), and vasculogenesis (Fig. 8-2).[11] Tumor cells can co-opt and grow around existing vessels to form "perivascular" cuffs. However, as stated earlier, these cuffs cannot grow beyond the diffusion limit of critical nutrients and may actually cause the collapse of the vessels due to the growth pressure (referred to as "solid stress"). Alternatively, an existing vessel may enlarge in response to the growth factors released by tumors, and an interstitial tissue column may grow in the enlarged lumen and partition the lumen to form an expanded vascular network. This mode of intussusceptive microvascular growth has been observed during tumor growth, wound healing, and gene therapy.[16–19] "Sprouting" angiogenesis is perhaps the most widely studied mechanism of vessel formation. During sprouting angiogenesis, the existing vessels become leaky in response to growth factors released by normal cells or cancer cells; the basement membrane and the interstitial matrix dissolve; pericytes dissociate from the vessel; endothelial cells (ECs) migrate and proliferate to form an array/sprout; a lumen is formed in the sprout (a process referred to as canalization); branches and loops are formed by confluence and anastomoses of sprouts to permit blood flow; and finally, these immature vessels are invested in basement membrane and pericytes. During physiologic angiogenesis, these vessels differentiate into mature arterioles, capillaries, and venules, whereas in tumors they remain largely immature.[5,11,12,20] During embryonic development, a primitive vascular plexus is formed from endothelial precursor cells (EPCs, also known as angioblasts) by a process referred to as vasculogenesis. In adults, EPCs—mobilized from bone marrow niches into the peripheral blood circulation—can also contribute to neovascularization (process referred to as "postnatal" vasculogenesis) in tumors and other tissues.[21–23] The current challenge is to discern the relative contribution of each of the four

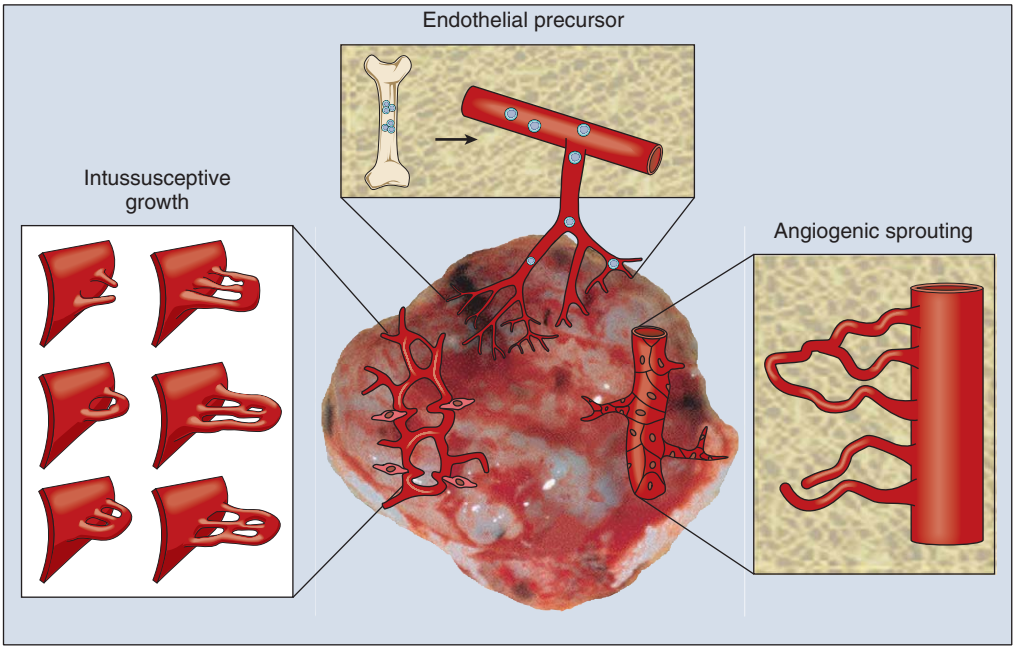


Figure 8-2 • Cellular mechanisms of vascularization in tumors. At least four mechanisms are involved: (1) intussusception, where tumor vessels enlarge and an interstitial tissue column grows in the enlarged lumen, expanding the network; (2) vasculogenesis, where endothelial precursor cells mobilized from the bone marrow or peripheral blood contribute to the endothelial lining of tumor vessels; (3) "sprouting" angiogenesis, where the existing vascular network expands by forming sprouts or bridges; and (4) co-option (not shown), where tumor cells grow around existing vessels to form "perivascular" cuffs. (Adapted from Jain RK, Carmeliet PF: Angiogenesis in cancer and other diseases. Nature 2000;407:249–257.)

mechanisms of neovascularization during the growth and/or during treatment of tumors.[24]

Molecular Mechanisms

Various pro- and antiangiogenic molecules that orchestrate different steps in vessel formation, along with their functions, are listed in Table 8-1. VEGF is currently considered the most critical proangiogenic molecule. Originally discovered in 1983 as the vascular permeability factor and cloned in 1989, VEGF increases vascular permeability, promotes migration and proliferation of ECs, serves as an EC survival factor, can mobilize EPC populations from the bone marrow, and is known to upregulate leukocyte adhesion molecules on ECs.[16,22,25–27] During tumor progression, or with treatment, the number of distinct angiogenic molecules produced by a tumor can increase.[28–30] Thus, after VEGF signaling is blocked, a tumor might rely on other, alternative angiogenic molecules (e.g., basic fibroblast growth factor [bFGF], stromal-derived factor 1α [SDF1α], placental-derived growth factor [PlGF], or interleukin-8 [IL-8]).[31] Other positive regulators of angiogenesis include the angiopoietins that are involved in stabilizing vessels and controlling vascular permeability; various proteases involved in dissolving/remodeling matrix and releasing growth factors; and recently discovered organ-specific angiogenic stimulators (e.g., endocrine gland VEGF).[20,32,33] Angiogenesis inhibitors include endogenous soluble receptors of various proangiogenic ligands (e.g., sVEGFR1) and molecules that downregulate the expression of stimulators (e.g., interferons) or that interfere with the release of the stimulators or binding with their receptors (e.g., platelet factor 4). Thrombospondins are among the first and most well-characterized endogenous inhibitors that interfere with the growth, adhesion, migration, and survival of ECs.[14] Other endogenous inhibitors include fragments of various plasma or matrix proteins (e.g., angiostatin, a fragment of plasminogen; endostatin, a fragment of collagen XVIII; tumstatin, a fragment of collagen IV).[34–36] Neither the mechanisms of action of the matrix-derived inhibitors nor their physiologic role are well understood.[37] The generation of pro- and antiangiogenic molecules can be triggered by metabolic stress

Table 8-1 Angiogenesis Activators and Inhibitors*

Activators	Function	Inhibitors	Function
VEGF family members†‡	Stimulate angio/vasculogenesis, permeability, leukocyte adhesion	VEGFR-1; soluble VEGFR-1; soluble neuropilin-1 (NRP-1)	Sink for VEGF, VEGF-B, PlGF
VEGFR‡, NRP-1, NRP-2	Integrate angiogenic and survival signals	Ang 2†‡	Antagonist of Ang 1
EG-VEGF	Stimulate growth of endothelial cells derived from endocrine glands	TSP-1,2	Inhibit endothelial migration, growth, adhesion, and survival
Ang 1 and Tie 2†‡	Stabilize vessels	Angiostatin and related plasminogen kringles	Inhibit endothelial migration and survival
PDGF-BB and receptors	Recruit smooth muscle cells	Endostatin (collagen XVIII fragment)	Inhibit endothelial survival and migration
TGF-β1§, endoglin, TGF-β receptors	Stimulate extracellular matrix production	Tumstatin (collagen IV fragment)	Inhibit endothelial protein synthesis
FGF, HGF, MCP-1	Stimulate angio/arteriogenesis	Vasostatin; calreticulin	Inhibit endothelial growth
Integrins $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_5\beta_1$	Receptors for matrix macromolecules and proteinases	Platelet factor-4	Inhibit binding of bFGF and VEGF
VE-cadherin; PECAM (CD31)	Endothelial junctional molecules	Tissue-inhibitors of MMP (TIMPs); MMP-inhibitors; PEX	Suppress pathologic angiogenesis
Ephrins‡	Regulate arterial/venous specification	Meth-1; Meth-2	Inhibitors containing MMP-, TSP-, and disintegrin domains
Plasminogen activators, MMPs	Remodel matrix, release growth factor	IFN-α, -β, -γ; IP-10, IL-4, IL-12, IL-18	Inhibit endothelial migration; downregulate bFGF
PAI-1	Stabilize nascent vessels	Prothrombin kringle-2; antithrombin III fragment	Suppress endothelial growth
NOS; COX-2	Stimulate angiogenesis and vasodilation	16 kD-prolactin	Inhibit bFGF/VEGF
AC133	Regulate angioblast differentiation	VEGI	Modulate cell growth
Chemokines§	Pleiotropic role in angiogenesis	Fragment of SPARC	Inhibit endothelial binding and activity of VEGF
Id1/Id3	Inhibit differentiation	Osteopontin fragment	Interfere with integrin signaling
		Maspin	Protease inhibitor
		Canstatin, proliferin-related protein, restin	Mechanisms unknown

See text for explanation of abbreviations.
*Selected list updated from ref. 11; for complete function and references, see supplementary information (http://steele.mgh.harvard.edu).
†Also present in or affecting nonendothelial cells.
‡See ref. 20.
§Opposite effect in some contexts.

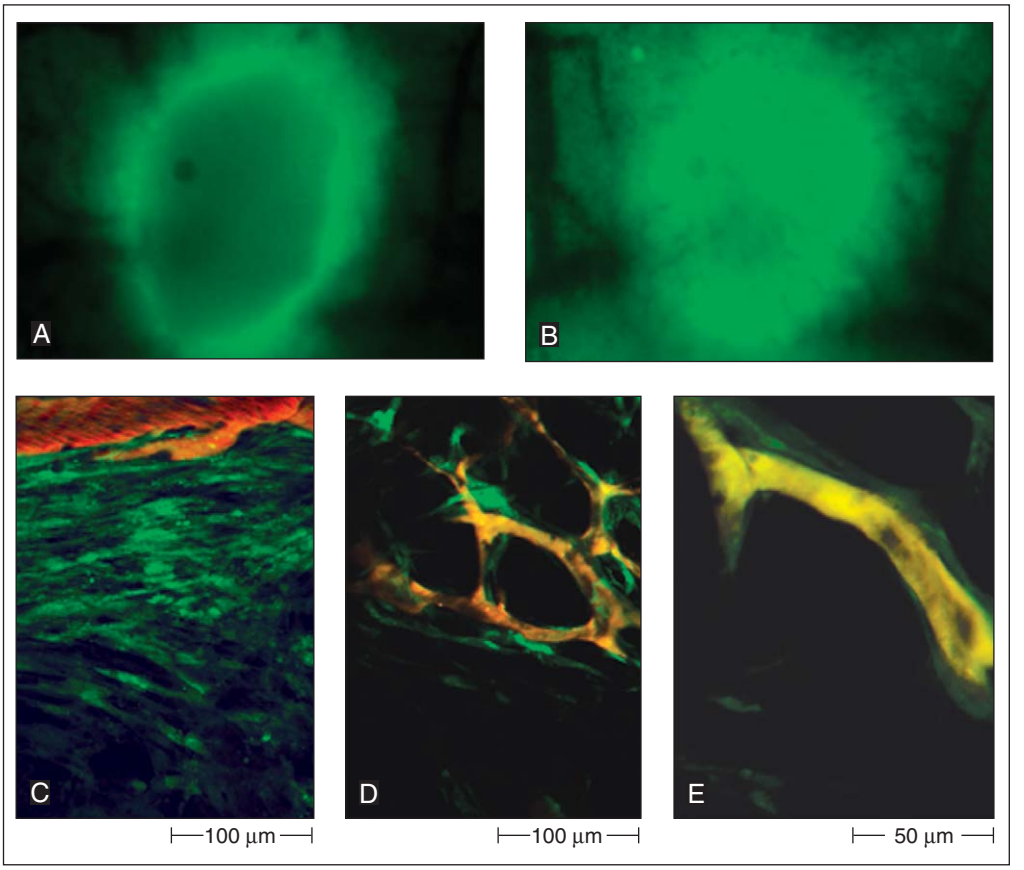


Figure 8-3 • Tumor induction of host promoter activity in stromal cells. The expression of VEGF in host cells can be examined using transgenic mice expressing a green fluorescent protein (GFP) under the control of the VEGF promoter. **A,** A murine mammary carcinoma xenograft shows host cell VEGF expression mainly at the periphery of the tumor after 1 week. **B,** After 2 weeks, the VEGF-expressing host cells have infiltrated the tumor. **C,** A GFP-expressing layer of host cells can be seen at the tumor-host interface. **D** and **E,** The VEGF-expressing host cells colocalize with the angiogenic tumor vessels. (**A** and **B,** From Fukumura D, Xavier R, Sugiura T, et al: Tumor induction of VEGF promoter activity in stromal cells. Cell 1998;94:715–725. **C–E,** From Brown EB, Campbell RB, Tsuzuki Y, et al: In vivo measurement of gene expression, angiogenesis and physiological function in tumors using multiphoton laser scanning microscopy. Nat Med 2001;7:1069.)

(e.g., low pO_2, low pH, or hypoglycemia), mechanical stress (e.g., shear stress, solid stress), immune/inflammatory cells that have infiltrated the tissue, and genetic mutations (e.g., activation of oncogenes or deletion of suppressor genes that control the production of angiogenesis regulators).[14,15,38–41] These molecules can emanate from cancer cells, endothelial cells, stromal cells, blood, and extracellular matrix (Fig. 8-3).[42–45] Because the normal host cells differ among organs, the detailed mechanisms of angiogenesis might depend on the specific host-tumor interactions operating within a given tissue.[46–53] Furthermore, because the tumor microenvironment is likely to change during tumor growth, regression, and relapse, profiles of pro- and antiangiogenic molecules are likely to change with time and space.[54,55] The challenge currently is to develop a unified conceptual framework to describe the temporal and spatial profiles of this increasingly diverse array of angiogenesis regulators with the aim of developing effective therapeutic strategies.[56,57]

Vascular Architecture

In a normal tissue, blood flows from an artery to arterioles to capillaries to venules to a vein. Although the tumor vasculature originates from these host vessels and the mechanisms of angiogenesis are similar, its organization may differ dramatically, depending on the tumor type, its location, and whether it is growing, regressing, or relapsing.[16,58–61] In general, tumor vessels are dilated, saccular, tortuous, and chaotic in their patterns of interconnection.[62] For example, whereas normal vasculature is characterized by dichotomous branching, tumor vasculature has many trifurcations and branches with uneven diameters.[63,64] The fractal dimensions and minimum path lengths of tumor vasculature are different from those of normal host vasculature.[58–60] The molecular mechanisms of this abnormal vascular architecture are not understood, but it seems reasonable to hypothesize that the imbalance of VEGF and angiopoietins is a key contributor.[20,65] In mice, "normalization" of the tumor vasculature observed during therapies that reduce VEGF (e.g., hormone withdrawal from a hormone-dependent tumor), interfere with VEGF signaling (e.g., treatment with anti-VEGF or anti-VEGFR2 antibody; Fig. 8-4), or mimic an antiangiogenic cocktail (e.g., trastuzumab [Herceptin] treatment of a HER2-overexpressing tumor) is in concert with this molecular hypothesis.[12,54–56,66] Mechanical stress generated by proliferating tumor cells also can lead to the partially compressed or totally collapsed vessels often found in tumors.[67,68] The decompression of blood vessels observed after induction of apoptosis in perivascular cells supports this mechanical hypothesis.[69,70] Perhaps the combination of both molecular and mechanical factors renders the tumor vasculature abnormal, and, thus, both types of factors must be taken into account when designing novel strategies for cancer treatment.

Blood Flow and Microcirculation

Blood flow in a vascular network, whether normal or abnormal, is governed by the arterio-venous pressure difference and flow resistance. Flow resistance is a function of the vascular architecture (referred to as geometric resistance) and of the blood viscosity (rheology, referred to as viscous resistance).[62] Abnormalities in both vasculature and viscosity increase the resistance to blood flow in tumors.[64,71–73] As a result, overall perfusion rates (blood flow rate per unit volume) in tumors are lower than in many normal tissues.[74–76] Both macroscopically and microscopically, tumor blood flow is temporally and spatially chaotic. Macroscopically, four spatial regions can be recognized in a tumor (Fig. 8-5):

1. An avascular necrotic region
2. A semi-necrotic region
3. A stabilized microcirculation region
4. An advancing front[77,78]

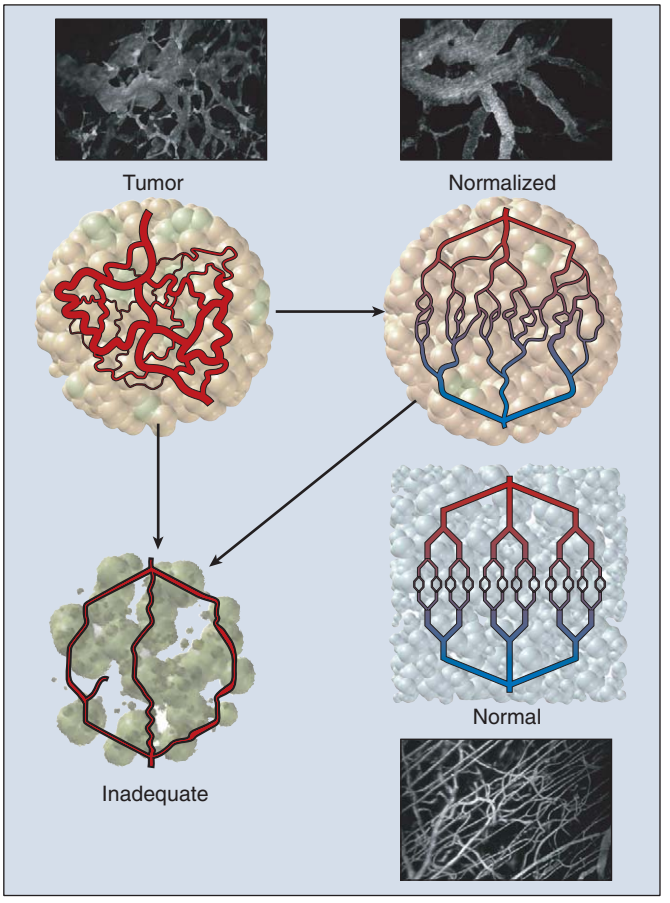


Figure 8-4 • Normalization of tumor vasculature. Normal vessels are well organized with even diameters. In contrast, tumor vessels are tortuous, with increased vessel diameter, length, density, and permeability. Antiangiogenic therapies "normalize" the tumor vascular network and could ultimately reduce the vasculature to the point at which it provides inadequate support for tumor growth. (Adapted from Jain RK: Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. Nat Med 2001;7:987–989; Jain RK: Angiogenesis and lymphangiogenesis in tumor: insights from intravital microscopy. Cold Spring Harbor Symp Quant Biol [The Cardiovascular System] 2002;67:239–248; Jain RK, Carmeliet PF: Vessels of death or life. Sci Am 2001;285:38.)

At the microscopic level, in normal tissues, erythrocyte velocity is dependent on vessel diameter, but there is no such dependence in most tumors.[47,52,79] Furthermore, the average erythrocyte velocity can be an order of magnitude lower in some tumors as compared with that of normal host tissue (Fig. 8-6).[52] In a given vessel within a tumor, blood flow fluctuates with time and can reverse its direction.[77,79,80] In addition to the elevated geometric and viscous (rheologic) resistance, other molecular and mechanical factors contribute to this spatial and temporal heterogeneity. These include imbalance between pro- and antiangiogenic molecules, "solid stress" generated by proliferating cancer cells, vascular remodeling by intussusception, and coupling between luminal and interstitial fluid pressure via hyperpermeability of tumor vessels.[17,57,58,67–69,81–83] As we will learn later, this heterogeneity contributes to both acute and chronic hypoxia in tumors—a major cause of resistance to radiation and other therapies. Considerable effort has gone into increasing tumor blood flow for improving radiation therapy, or decreasing tumor perfusion in the case of hyperthermia. This has been difficult to achieve reproducibly, because tumor vasculature consists of both vessels co-opted from the pre-existing host vasculature and vessels resulting from the angiogenic response of host vessels to cancer cells. The former are invested in normal contractile perivascular cells, whereas the latter lack these perivascular cells or these cells are abnormal.[42,62,84] Presumably as a result, efforts to increase the tumor blood flow by pharmacologic or physical agents have not always been reproducible or successful.[62,75] On the other hand, the strategy of decreasing or shutting down the tumor blood flow—by "stealing" blood away from the "passive component" of the tumor vasculature by vasodilators, by vascular targeting, or by intravascular coagulation—has shown promise in experimental systems.[75,76,85–87] It also appears that judiciously applied antiangiogenic therapy could "normalize" the abnormal tumor microcirculation by pruning the immature vessels (see Fig. 8-4), thus rendering the remaining vasculature more responsive to vasoactive agents.[88]

VASCULAR PERMEABILITY

Once a blood-borne molecule has reached an exchange vessel, its extravasation occurs by diffusion, convection, and, to some extent, presumably by transcytosis.[88] The diffusive permeability, *P*, of a molecule depends on the size, shape, charge, and flexibility of the molecule, and on the size, shape, charge, and dynamics of the transvascular transport pathway. In normal vessels, these pathways include diffusion along the EC membrane (for lipophilic solutes), trans-EC diffusion, interendothelial junctions (<7 nm), open or closed fenestrations (<10 nm), and transendothelial channels (including vesicles or vesicovacuolar channels).[16,89] Some of these anatomical pathways may be lined with glycocalyx on EC, thus effectively reducing the size of the pathway. A basement membrane may further retard the movement of molecules. Ultrastructure studies show widened interendothelial junctions, increased numbers of fenestrations, vesicles, and vesicovacuolar channels in tumor vessels, and a lack of normal basement membrane and pericytes.[16,49,84,89,90] In concert with these ultrastructural findings, both vascular permeability and hydraulic conductivity (a measure of water movement by pressure gradient) of

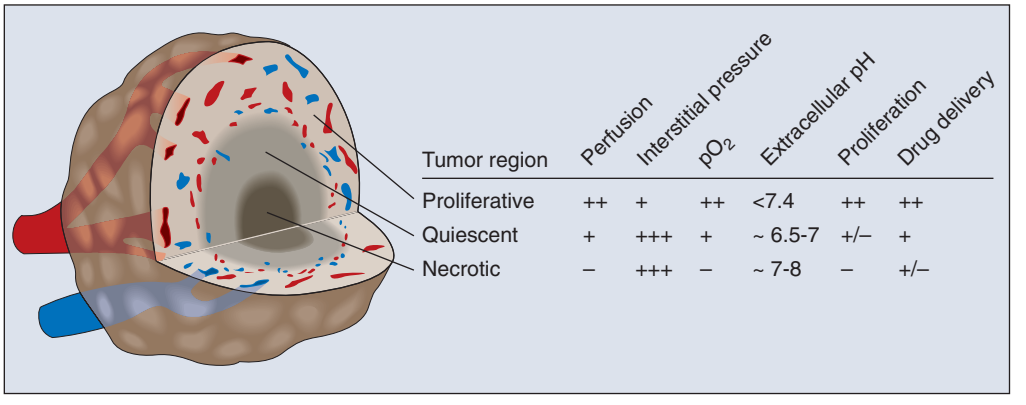


Figure 8-5 • The tumor microenvironment is heterogeneous with proliferative, quiescent, and necrotic regions. These regions can be characterized in terms of various physiologic parameters. Decreasing magnitude of these parameters is indicated as +++, ++, +, +/–. and –. (From Jain RK, Forbes NS: Can engineered bacteria help control cancer? Proc Natl Acad Sci USA 2001;98:14748–14750.)

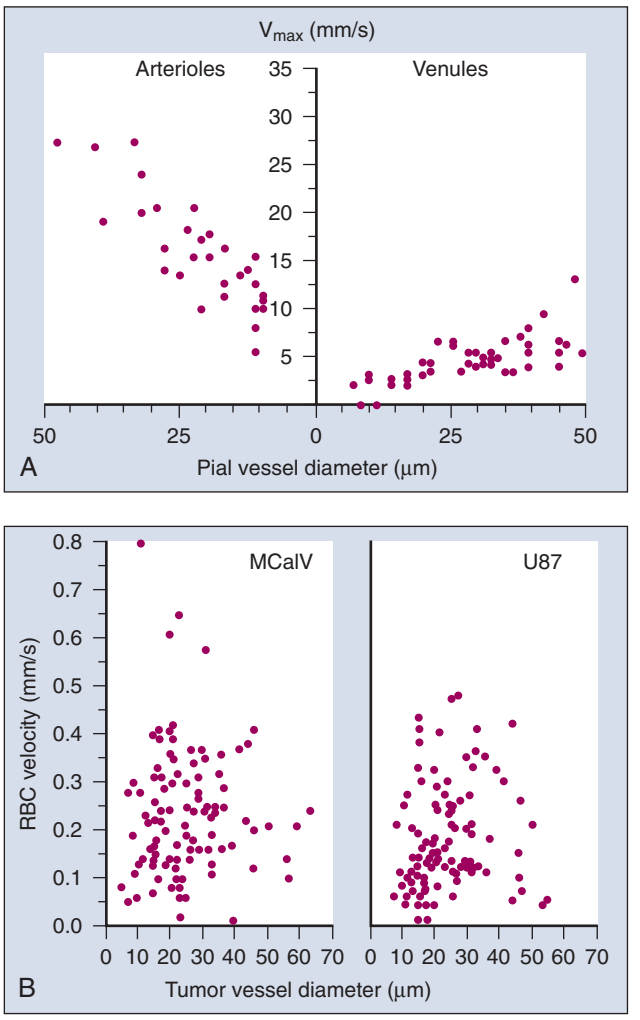


Figure 8-6 • Blood velocity as a function of vessel diameter. **A,** Normal pial vessels. **B,** MCaIV (mammary carcinoma) and U87 (glioma) tumors xenografted on the pial surface. The measured tumor blood velocities are an order of magnitude lower than the velocities in the normal host tissue and are not related to the vessel density. (From Yuan F, Salehi HA, Boucher Y, et al: Vascular permeability and microcirculation of gliomas and mammary carcinomas transplanted in rat and mouse cranial windows. Cancer Res 1994;54:4564–4568.)

tumors, in general, are significantly higher than those for various normal tissues.[52,91–95] Furthermore, unlike normal vessels, tumor vessels lack selectivity in permeability to different molecules.[96] Positively charged molecules have a higher affinity for the negatively charged angiogenic tumor vessels.[97–99] Despite increased overall permeability, not all blood vessels of a tumor are leaky (Fig. 8-7A). Even the leaky vessels have a finite pore size that is tumor dependent (Fig. 8-7B), and ultrastructural studies show that the larger pore size in tumors represents wide interendothelial junctions.[49,90] Not only do the vascular permeability and pore size vary from one tumor to the next (see Fig. 8-7A–C), but within the same tumor they vary spatially and temporally, as they do during tumor growth, regression, and relapse.[49,54,55] The local microenvironment plays an important role in controlling vascular permeability (Fig. 8-7D). For example, a human glioma (HGL21) has fairly leaky vessels when grown subcutaneously in immunodeficient mice, but it exhibits blood-brain barrier properties in the brain.[52,65] Such site-dependent differences for other tumors have been observed in other orthotopic sites.[47,50,51] One possible explanation is that the host-tumor interactions control the production and secretion of cytokines associated with permeability increase (e.g., VEGF) and decrease (e.g., angiopoietin 1).[20,33,65,100,101] A better understanding of the molecular mechanisms of permeability regulation in tumors is likely to yield strategies for improved delivery of molecular medicine to tumors.

Movement of Cells across Vessel Walls

Both cancer cells and immune cells frequently move across the walls of blood vessels—the former in the process of metastasis and the latter during immune response or cell-based immunotherapy. Both transendothelial (through ECs) and periendothelial (between ECs) pathways have been proposed as a route for intravasation and extravasation of cells. Very little is known about intravasation except that tumors might shed more than a million cells per gram per day and most of these are not clonogenic.[102–105] More is known about the molecular and cellular mechanisms of extravasation.[106] When a cell enters a blood vessel, it can continue to move with the flowing blood, collide with the vessel wall, adhere transiently or stably, and finally extravasate. These interactions are governed both by local hydrodynamic forces and adhesive forces. The former are determined by the vessel diameter and fluid velocity and the latter by the expression, strength, and kinetics of bond formation between adhesion molecules and by the surface area of contact.[107–111] Deformability of cells affects both types of forces.[112] In addition, cancer cells may grow intravascularly at the distant site (e.g., in the lungs).[113]

Rolling of endogenous leukocytes is generally low in tumor vessels, whereas stable adhesion (≥30 sec) is comparable between normal vessels and tumor vessels.[114] On the other hand, both rolling and stable adhesion are nearly zero in angiogenic vessels induced in collagen gels by bFGF or VEGF, two of the most potent angiogenic factors.[46] Whether this observation is due to a low flux of leukocytes into angiogenic vessels and/or to downregulation of adhesion molecules in these immature vessels is currently not known. The age of the animal also plays an important role in leukocyte-endothelial interactions.[115] Further insight into the types of cells that adhere to tumor vessels comes from studies on the localization of IL-2–activated natural killer (A-NK) cells in normal and tumor tissues in mice using positron emission tomography.[116,117] After systemic injection, these cells localized primarily in the lungs immediately after injection and could not be detected in the tumor.[116] Increased rigidity caused by IL-2 activation might contribute to the mechanical entrapment of these cells in the lung microcirculation.[118,119] Constitutive expression of certain adhesion molecules in the lung vasculature might also facilitate their retention in the lungs.[106] One approach to reducing lung entrapment is to reduce the rigidity of these cells.[112,117] Alternatively, the lung can be circumvented by injecting A-NK cells directly into the blood supply of tumors. In this case, A-NK cells, both xenogenic and syngeneic, adhered to some blood vessels in three different tumor models via CD18 and very large antigen-4 (VLA-4) on the A-NK cells and intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin on the activated endothelium of angiogenic vessels.[27,117,120–123] These molecules can be upregulated by tumor necrosis factor-α (TNF-α) and a protein of 90 kd molecular weight (p90) that is secreted by some neoplastic cells and downregulated by transforming growth factor-β (TGF-β)—also, presumably, secreted by cancer cells.[48,107,124–128] Surprisingly, the proangiogenic VEGF also can upregulate these molecules, presumably via VEGFR1, whereas another proangiogenic molecule, bFGF, can downregulate these molecules.[27,45,55,66,129] On the other hand, inflammatory cells such as monocyte/macrophages or neutrophils are also recruited by VEGF and may play important roles in promoting matrix remodeling and angiogenesis.[130] The challenge currently is to decrease nonspecific entrapment of immune cells in normal vessels and to increase their delivery to tumor vessels to improve various cell-based therapies, including gene therapy.

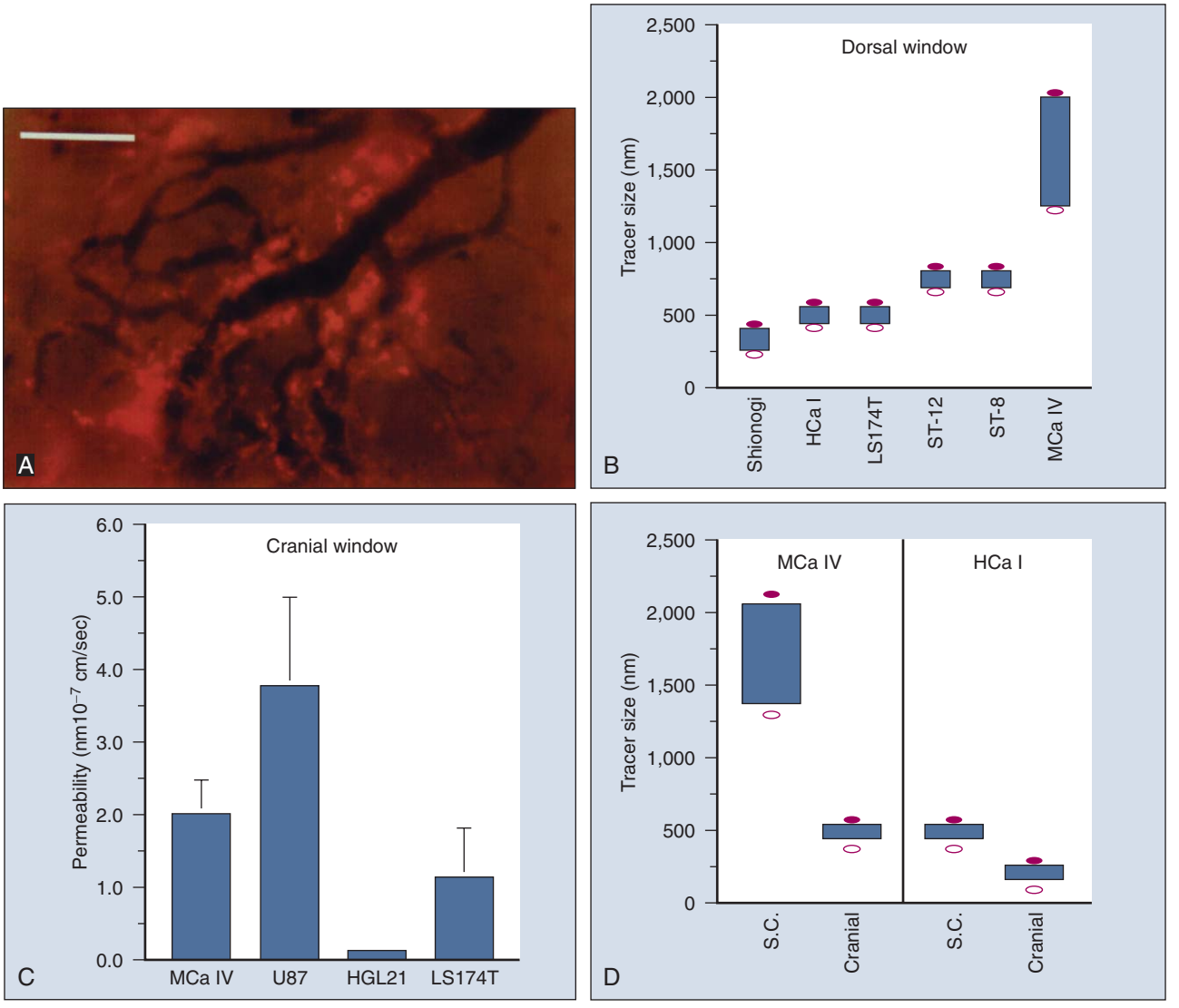


Figure 8-7 • Heterogeneous permeability of tumor vessels. Vessel permeability varies spatially within a given tumor, between tumors of identical type implanted in different host organ environments, and between different tumor types in the same organ environment. **A,** Vessels within a given tumor are leaky in some areas and relatively impermeable in others. **B** and **C,** Tumors of different types grown in the same environment show variations in both vessel pore size and permeability. Pore sizes are measured by the largest tracer particle able to permeate the vessel wall. **D,** MCaIV and HCaI tumors implanted in two different sites (subcutaneous and cranial) have vessels with different pore sizes. For both tumor types, larger pore sizes are observed in the subcutaneous (S.C.) tumors compared with the cranial tumors. (**A** and **C,** From Yuan F, Leunig M, Huang SK, et al: Microvascular permeability and interstitial penetration of sterically stabilized [stealth] liposomes in a human tumor xenograft. Cancer Res 1994;54:3352–3356. **B** and **D,** From Hobbs SK, Monsky WL, Yuan F, et al: Regulation of transport pathways in tumor vessels: role of tumor type and microenvironment. Proc Natl Acad Sci USA 1998;95:4607–4612.)

EXTRAVASCULAR COMPARTMENT

Composition and Origin

The extravascular compartment of a solid tumor consists of neoplastic cells (parenchyma) and host cells (e.g., inflammatory cells, fibroblasts) residing in an interstitial matrix bathed by the interstitial fluid (see Fig. 8-1). Depending on the tumor type and its stage of differentiation, neoplastic cells might be dispersed in the matrix as individual cells (e.g., lymphomas, melanomas) or as clumps, sheets, or nests (e.g., carcinomas). More than 80% of tumors are carcinomas arising from epithelial cells. The remaining include sarcomas arising from mesenchymal cells (e.g., bone or muscle cells), lymphomas arising from lymphoid tissue, leukemias arising from hematopoietic cells, and hemangiomas arising from ECs. In a poorly differentiated carcinoma, the cancer cells might be packed loosely in clumps, whereas in a well-differentiated carcinoma, the cells might be connected with intercellular junctions and tightly packed in a nest enveloped by a basement membrane. With tumor progression, cancer cells can invade the basement membrane and spread to other regions.[16] These various types of normal host cells must migrate into the tumor from normal tissue. Inflammatory cells might enter the tumor via blood vessels or might infiltrate from the adjacent tissue or lymphatics.[106] Other host cells, such as fibroblasts, might proliferate and migrate from the adjacent connective tissue.[20,42,43] The interstitial subcompartment of a tumor is bounded by the walls of the blood vessels on one side and by the membranes of cancer and stromal cells on the other. In normal tissues, the blood vessels are surrounded by a basement membrane, which, as discussed before, is defective in tumors.[20] In addition, functional lymphatics might be confined to

the tumor margin.[131,132] The interstitial space of tumors, like that of normal tissues, is composed of a collagen and elastin fiber network that provides structural support to the tissue. Interdispersed in this cross-linked structure are the interstitial fluid and macromolecular constituents (polysaccharides, hyaluronan, and proteoglycans), which form a hydrophilic gel. Compared with our understanding of blood vessel formation, our understanding of stroma generation is minimal. Dvorak and coworkers have proposed that the extravasated plasma protein fibrinogen, a key component of the tumor interstitial fluid, clots to form fibrin, which serves as a major component of the provisional stroma. This provisional stroma eventually is replaced by more mature connective tissue stroma. The tumor interstitial fluid also contains several other Arg-Gly-Asp (RGD)-containing proteins, including fibronectin, vitronectin, osteopontin, thrombospondin, decorin, and tenacin.[16] These proteins are present in both free and bound forms. Their Arg-Gly-Asp sequence provides a binding site for adhesion that assists in the migration of various cells, including stromal cells. In addition to extravasating from the leaky tumor vessels, these proteins, along with collagen and various proteoglycans, are also synthesized by the stromal cells, albeit in a form that differs from that in the plasma or normal tissues.[16] Tumor interstitial fluid also can contain various growth factors that facilitate stroma formation. For example, in vitro studies suggest that platelet-derived growth factor-ββ (PDGF-ββ) is involved in the recruitment of fibroblasts to tumors, and TGF-β induces the production of collagen and other matrix molecules in tumors.[20,133] With the increasing interest in using the fragments of matrix constituents for controlling angiogenesis, our understanding of the molecular and cellular mechanisms of stroma generation in tumors will increase.[37]

Interstitial Transport

Once a molecule has extravasated, its movement through the interstitial space occurs by diffusion and convection.[134] Diffusion is proportional to the concentration gradient in the interstitium, and convection is proportional to the interstitial fluid velocity, which, in turn, is proportional to the pressure gradient in the interstitium. Just as the interstitial diffusion coefficient D (cm^2/s) relates the diffusive flux to the concentration gradient, the interstitial hydraulic conductivity K ($cm^2/mmHg/sec$) relates the interstitial velocity to the pressure gradient.[134] Values of these transport coefficients are governed by the structure and composition of the interstitial compartment and by the physicochemical properties of the solute molecule.[135–144] The value of K for a human colon carcinoma xenograft (LS174T), measured using two different methods, was found to be higher than that of a hepatoma, which, in turn, was higher than that of the normal liver.[140,145,146] Using fluorescence recovery after photobleaching, D of various molecules in tumors was found to be about one-third that in water and higher than the values in the host tissue (Fig. 8-8A).[136,147] Collagen content and structure have a significant effect on D in tumors.[142,143,145,148–150] This is surprising because hyaluronan and proteoglycans, not collagen, account for most of the resistance to transport in normal tissues. Because collagen is produced by host cells (e.g., fibroblasts), the penetrability into a tumor depends on the host-tumor interaction (see Fig. 8-8A). Thus, agents that interfere with collagen synthesis and/or organization (e.g., relaxin, bacterial collagenase) might increase interstitial transport in tumors[144,150] (Fig. 8-8B). The time constant for a molecule with diffusion coefficient D to diffuse across a distance L is approximately $L^2/4D$. For diffusion of immunoglobulin G (IgG) in tumors, this time constant is on the order of 1 hour for a 100-μm distance, days for a 1-mm distance, and months for a 1-cm distance. So for a 1-mm distance in tumor, diffusional transport would take days, and for a 1-cm distance in tumor, it would take months. If the central vessels have collapsed completely due to cellular proliferation and interstitial matrix rearrangement, the reduced delivery of macromolecules by blood flow would make diffusion the primary mechanism of delivery to this necrotic center.[67,69] Binding of a low- or high-molecular-weight drug to plasma proteins and various tissue components could further retard their transport in tumors.[147,151–157] The role of binding is clearly illustrated in Figure 8-8C, which compares the rate of fluorescence recovery of a photobleached spot in tumor tissue injected with a nonspecific vs. a specific IgG. In addition to the heterogeneity of D in tumors, the most unexpected result of these photobleaching studies was the large extent (30% to 40%) of nonspecific binding.[147] These results collectively suggest that the interstitial compartment of a tumor can be a formidable barrier to the uniform delivery of therapeutic macromolecules (e.g., antibodies, genes) in tumors, and strategies are needed to modify this barrier.

Lymphangiogenesis and Lymphatic Transport

In most normal tissues, extravasated plasma and macromolecules are taken up by the lymphatics and returned to the blood circulation. It is widely accepted that lymphatic vessels are present in the tumor margin and the peritumoral tissue (Fig. 8-9A). Indeed, invasion of peritumoral lymphatics is considered to be a poor prognostic factor for several tumors (e.g., breast, colorectal, and endometrial cancers), and lymphatic metastasis is a major cause of morbidity and mortality for others (e.g., melanoma, head and neck cancer, lung cancer, and cervical cancer). The hotly debated issue for nearly a century has been whether anatomically defined lymphatic vessels are present within solid tumors and, if so, whether they function (see Fig. 8-9A).[74,158] Currently available immunohistochemical markers stain for structures in some tumors that resemble lymphatic vessels. Because many of these markers lack specificity, however, it is not clear whether they stain functional lymphatic vessels, ECs from remnant lymphatic vessels, or some other structures (e.g., preferential fluid channels).[132,145,159,160] It is likely that the "mechanical" stress induced by proliferating cancer cells compress and impair lymphatic vessels that are co-opted or formed within a tumor.[67,70] The impaired lymphatic vessels, in turn, contribute to the interstitial hypertension characteristic of animal and human tumors (to be discussed shortly). Embryonic lymphatic vessels originate primarily from blood vessels according to the following process (Fig. 8-9B).[161–163]

1. In the early embryo, endothelial cells of the cardinal vein express lymphatic vascular endothelial receptor-1 (LYVE-1) and VEGFR3, molecules observed primarily (but not exclusively) on lymphatic vessels in normal adult tissues.
2. A yet unknown signal triggers the expression of the homeobox gene *Prox-1* so that the protein is displayed in a polarized fashion in the endothelial cells of the cardinal vein. This marks the first stage of commitment to the lymphatic lineage.
3. These $LYVE\text{-}1^+VEGFR3^+Prox\text{-}1^+$ cells then start to bud, again in a polarized fashion.
4. At this stage, these early lymphatic endothelial cells start expressing secondary lymphoid chemokine and increased levels of VEGFR3, markers of mature lymphatic ECs.
5. They then begin to form the lymphatic system.

Members of the angiopoietin family (Ang-2) and its receptor (Tie-2), as well as podoplanin are presumably involved in the maturation and patterning of these nascent lymphatic vessels.[164] The hematopoietic signaling pathway, Syk/SLP-76, contributes to the separation of lymphatics from blood vessels. The molecules involved in angiogenesis are also involved in lymphangiogenesis. For example, VEGF-C and -D can induce both angiogenesis and lymphangiogenesis and are associated with lymphogenic metastasis in a variety of tumors.[131] Their receptor VEGFR3 is present in both lymphatic and selected vascular endothelium. As is the case with vascular angiogenesis, other positive and negative regulators (e.g., angiopoietins) and other receptors (e.g., chemokine receptors and neuropilins) could be involved in lymphangiogenesis, and as discussed already, mechanisms analogous to co-option, intussusception, sprouting, and vasculogen-

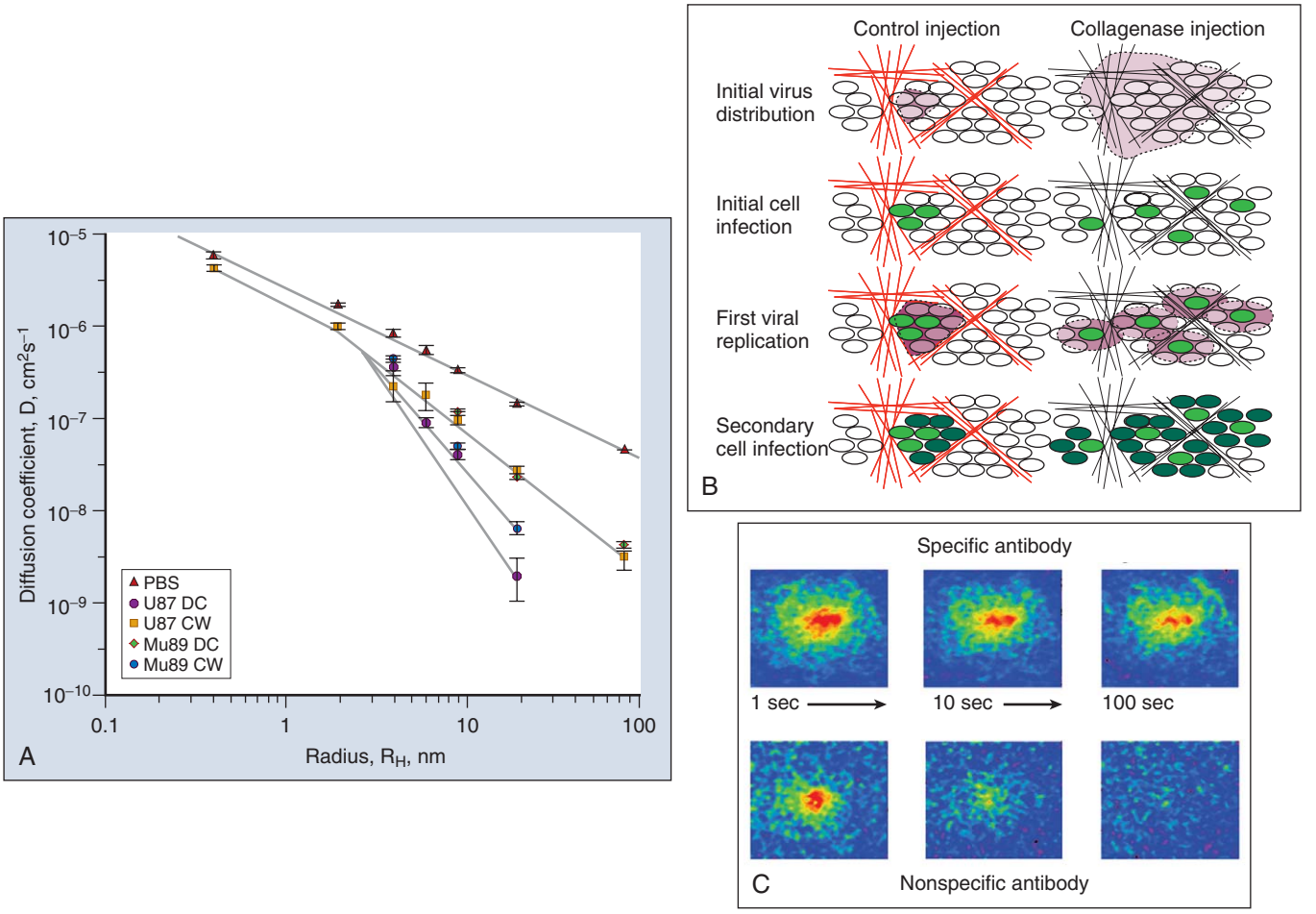


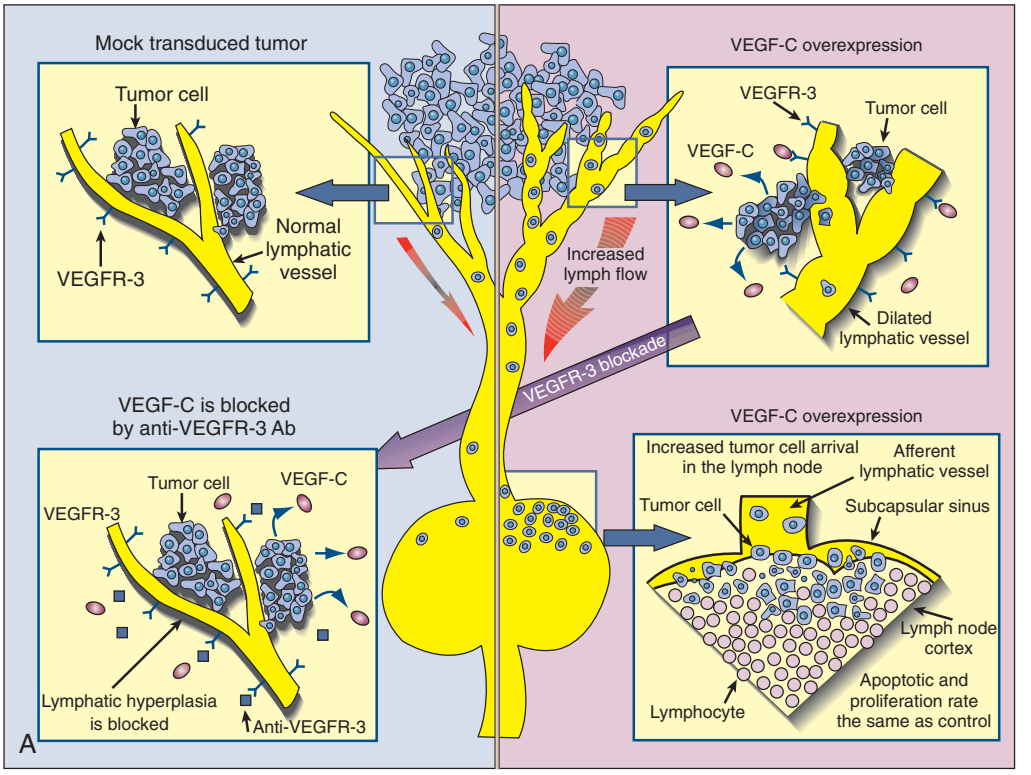
Figure 8-8 • Interstitial transport in tumors. Transport of molecules through a tumor is affected by several factors. **A,** Diffusivity of a molecule in a tumor decreases with increasing molecular weight and is dependent on the host-tumor interaction. The diffusivity of macromolecules is lower in subcutaneous (sc) tumors in dorsal chamber (DC, octagons-U87 glioblastoma and diamonds-Mu89 melanoma) than in the same tumors grown in cranial windows (CW, squares-U87 and triangles-Mu89), and both are less than in phosphate-buffered saline (PBS). **B,** A representative model of improvement in oncolytic viral distribution and tumor cell infection by collagenase treatment. Following direct intratumor injection, viral spread (red area) is limited by fibrillar collagen (red lines) and results in a cluster of infected cells (*light green*). The collagen network also restricts the distribution of subsequent viral progeny, and tumor cell infection beyond the initial injection site is not achieved. In contrast, injection of virus together with collagenase results in a more diffuse distribution of viral particles and a greater number of initially infected cells (*light green*). Viral particles released by these cells have greater access to neighboring uninfected cells. This process results in more widespread secondary infection (*dark green*) and ultimately greater therapeutic efficacy. **C,** Interstitial transport is also reduced by binding. The fluorescence of a photobleached spot recovers much more slowly with a specific antibody than with a nonspecific antibody. The binding of the specific antibody hinders the transport of the molecule into the photobleached spot, slowing the fluorescence recovery. (**A,** From Pluen A, Boucher Y, Ramanujan S, et al: Role of tumor-host interactions in interstitial diffusion of macromolecules: cranial vs. subcutaneous tumors. Proc Natl Acad Sci USA 2001;98:4628–4633. **B,** McKee TD, Grandi P, Mok W, et al: Degradation of fibrillar collagen in a human melanoma xenograft improves the efficacy of an oncolytic herpes simplex virus vector. Cancer Res 2006;66:2509–2513. **C,** Adapted from Berk DA, Yuan F, Leunig M, Jain RK: Direct in vivo measurement of targeted binding in a human tumor xenograft. Proc Natl Acad Sci USA 1997;94:1785–1790.)

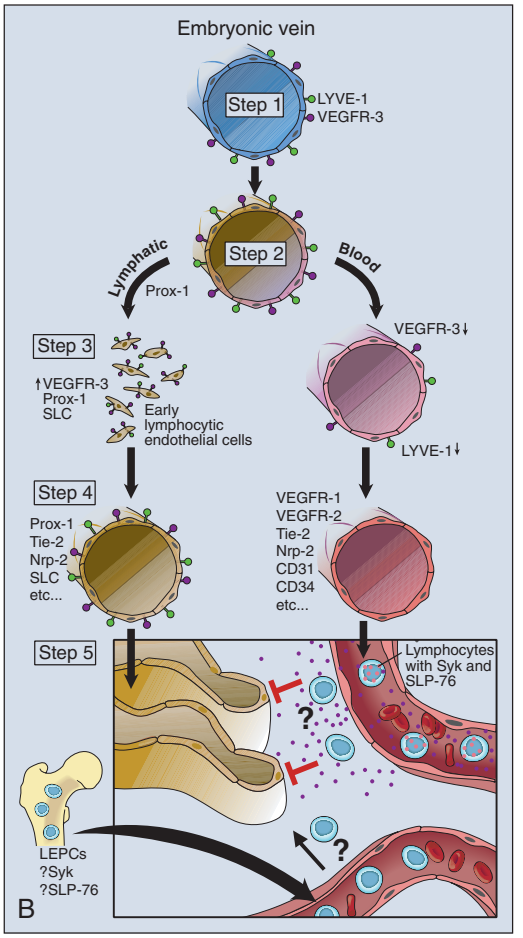
esis might operate in lymphatic growth.[11,164] Similar to the recently discovered organ-specific angiogenic molecule (EG-VEGF) and endothelial precursor cells, there could be organ-specific lymphangiogenic molecules and lymphatic EPCs that contribute to tumor-associated lymphangiogenesis.[22,32,163] Moreover, the proteolytic processing of lymphangiogenic molecules and the phenotype and function of the resulting lymphatics might depend not only on the tumor type but also on the host organ in which the tumor is growing.[66,159,161,163]

The mechanical and/or molecular signals that could trigger the lymphangiogenic switch are unknown. Because lymphatic vessels help maintain the balance of fluid in tissues, hydrostatic pressure is a probable trigger. Whether the hyperplasia and the increased density of lymphatic vessels seen in the tumor margins are a response to elevated hydrostatic pressure in tumors and whether the newly formed lymphatics are able to remain open and carry cancer cells are open questions. Techniques such as microlymphangiography, reagents that block signaling of VEGF-C and -D, and lymphangiogenic factors yet to be discovered will allow us to answer these important questions.[4,159,163,165–170]

Interstitial Hypertension

Unlike normal tissues, in which the interstitial fluid pressure (IFP) is around 0 mmHg, both animal and human tumors exhibit interstitial hypertension (Table 8-2).[132,134,146,171–182] The tumor IFP begins to increase as soon as the host vessels become leaky in response to permeability factors such as VEGF, and, thus, IFP can be lowered by antibodies against VEGF or VEGFR2.[183–185] The IFP increases with tumor size in some tumors and remains independent of tumor size


Mock transduced tumor
Tumor cell
VEGFR-3
Normal lymphatic vessel
VEGF-C overexpression
VEGFR-3
Tumor cell
VEGF-C
Dilated lymphatic vessel
Increased lymph flow
VEGFR-3 blockade
VEGF-C is blocked by anti-VEGFR-3 Ab
Tumor cell
VEGF-C
VEGFR-3
Lymphatic hyperplasia is blocked
Anti-VEGFR-3
VEGF-C overexpression
Increased tumor cell arrival in the lymph node
Afferent lymphatic vessel
Tumor cell
Subcapsular sinus
Lymph node cortex
Lymphocyte
Apoptotic and proliferation rate the same as control
A


Embryonic vein
Step 1
LYVE-1
VEGFR-3
Step 2
Lymphatic
Prox-1
Blood
VEGFR-3↓
Step 3
↑VEGFR-3
Prox-1
SLC
Early lymphocytic endothelial cells
LYVE-1↓
Step 4
Prox-1
Tie-2
Nrp-2
SLC
etc...
VEGFR-1
VEGFR-2
Tie-2
Nrp-2
CD31
CD34
etc...
Step 5
Lymphocytes with Syk and SLP-76
?
?
LEPCs
?Syk
?SLP-76
B

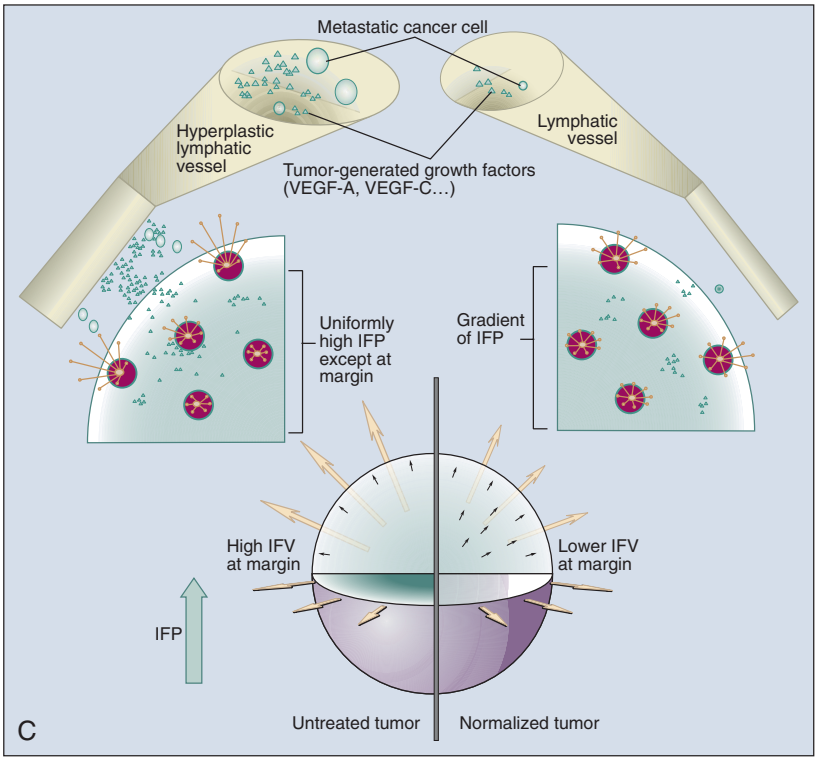

Metastatic cancer cell
Hyperplastic lymphatic vessel
Lymphatic vessel
Tumor-generated growth factors (VEGF-A, VEGF-C…)
Uniformly high IFP except at margin
Gradient of IFP
High IFV at margin
Lower IFV at margin
IFP
Untreated tumor
Normalized tumor
C

Figure 8-9 • **A,** Schematic of lymphatics in tumors. It is widely accepted that peritumoral lymphatics exist and that metastasis can occur via these lymphatic vessels. Recent evidence shows that structures within tumors that stain for lymphatic markers are not functional. The lower-left insert shows the molecular players in lymphangiogenesis. **B,** Mechanisms of lymphatic vessel formation and separation from blood vessels. **C,** The tumor is modeled as a sphere of radius *R,* embedded in a body fluid (e.g, peritoneal cavity, pleural cavity) or host tissue. The interstitial fluid oozing from the tumor periphery carries therapeutics (e.g, monoclonal antibodies), growth factors (e.g, VEGF-A, -B, -C, and -D), and cells (e.g., metastatic cells) into the surrounding fluid/tissue. The result may be higher fluxes of cancer cells and growth factors from the tumor into the surrounding tissue or body fluid. The growth factors (including VEGF-A, B, C, and D) can induce angiogenesis and lymphangiogenesis, and the cancer cells can contribute to metastatic dissemination via the lymphatic or blood vessels. Fluid seeping from the tumor surface can also cause edema (e.g., around brain tumors) and ascites formation (e.g., ovarian cancer). Antiangiogenic therapy can "normalize" the tumor vasculature, leading to lower interstitial fluid pressure (IFP) at the center, less steep IFP gradients and lower fluid flow rates at the tumor margin, thus potentially reducing peritumor edema, ascites formation, and lymphatic metastasis. Furthermore, the normalized vessels may be more resistant to cancer cell intravasation, a prerequisite for hematogenous metastasis. (**A,** From Jain RK, Fenton BT: Intratumoral lymphatic vessels: a case of mistaken identity or malfunction? J Natl Cancer Inst 2002;94:417–421. **B,** From Jain RK, Padera TP: Lymphatics make the break. Science 2003;299:209–210. Illustration: Katherine Sutliff. Reprinted with permission from AAAS. **C,** From Jain RK, Tong RT, Munn LL: Effect of vascular normalization by anti-angiogenic therapy on interstitial hypertension, peritumor edema and lymphatic metastasis: insights from a mathematical model. Cancer Res 2007;67:2729–2735).

in others.[171,172,175,176] Three mechanisms contribute to interstitial hypertension in tumors. In normal tissues, the lymphatics maintain the fluid homeostasis; thus, the lack of functional lymphatics in tumors is a key contributor. Indeed, DiResta and colleagues have been able to lower the IFP by placing "artificial lymphatics" in tumors.[186] The second contributor is the high permeability of tumor vessels. As a result, the hydrostatic and oncotic (colloid osmotic) pressures become almost equal between the intravascular and extravascular spaces.[174,187] At least two pieces of evidence support this hypothesis. First, reducing permeability by blocking VEGF signaling lowers IFP.[184,185,188,189] Second, IFP increases and decreases with the microvascular pressure within seconds.[190–192] The two mechanisms described thus far can only explain interstitial hypertension up to 20–30 mmHg, the microvascular pressure of most exchange vessels (the hydrostatic pressure within the lumina of capillaries) in our bodies, but IFPs as high as 94 mmHg have been measured in human tumors.[173] Because microvascular pressure (MVP) is the driving force for IFP in tumors, these tumors must have a high MVP. Indeed, this is the case.[174] There are two possible explanations for elevated MVP in tumors: the tumor vessels have reduced arterial resistance so that the MVP becomes closer to arterial pressure, and/or the tumor vessels have increased venous resistance due to compression and tortuousity so that the whole intratumor vascular network is under hypertension. Indirect evidence for the latter comes from the decrease in IFP after decompression of tumor vessels by taxol-induced apoptosis of perivascular cells.[69]

The elevated pressure can compromise the tumor microcirculation and delivery of therapeutics in three ways:

1. Reduced transmural pressure gradients due to equilibrium between MVP and IFP reduce convection across tumor vessel walls and thus compromise the transport of macromolecules.[174,192]
2. Because IFP is nearly uniform throughout a tumor and drops precipitously in the tumor margin, the interstitial fluid oozes out of the tumor into the surrounding normal tissue, carrying macromolecules with it (Fig. 8-10).[171,193]
3. Finally, transmural coupling between IFP and MVP due to high permeability of tumor vessels can lead to blood flow stasis in tumors without physically occluding the vessels.[81–83]

The enhanced permeability can also facilitate lymphatic metastasis (Fig. 8-9C). Thus, decreasing vascular permeability might restore the transmural pressure gradients and potentially resume/reestablish blood flow in the nonperfused regions of tumors. Some direct and indirect antiangiogenic therapies might "normalize" the tumor vasculature through this mechanism (see Fig. 8-4).[88] This normalization can also reduce the number of cells shed into peritumor lymphatics and alleviate peritumor edema (see Fig. 8-9C).[194]

Table 8-2 Interstitial Fluid Pressure (mmHg) in Normal and Neoplastic Tissues in Patients

Tissue Type	*N*	Mean	Range	References
Normal skin	5	0.4	–1.0–3.0	(166)
Normal breast	8	0.0	–0.5–3.0	(166)
Head and neck carcinomas	27	19.0	1.5–79.0	(165)
Cervical carcinomas	12	15.7	10.0–26.0	(163)
Cervical carcinomas	102	19.0†	–3.0–48.0	(172)
Lung carcinomas	26	10.0	1.0–27.0	(123)
Metastatic melanomas	14	21.0	0.0–60.0	(167)
Metastatic melanomas	12	14.5	2.0–41.0	(162)
Breast carcinomas	13	29.0	5.0–53.0	(169)
Breast carcinomas	8	15.0	4.0–33.0	(166)
Brain tumors*	17	7.0	2.0–15.0	(168)
Brain tumors*	11	1.0	–0.5–8.0	(171)
Colorectal liver metastasis	8	21.0	6.0–45.0	(166)
Lymphomas	7	4.5	1.0–12.5	(167)
Renal cell carcinoma	1	38.0	—	(166)

*Patients were treated with anti-edema therapy.
†IFP given is a median value.

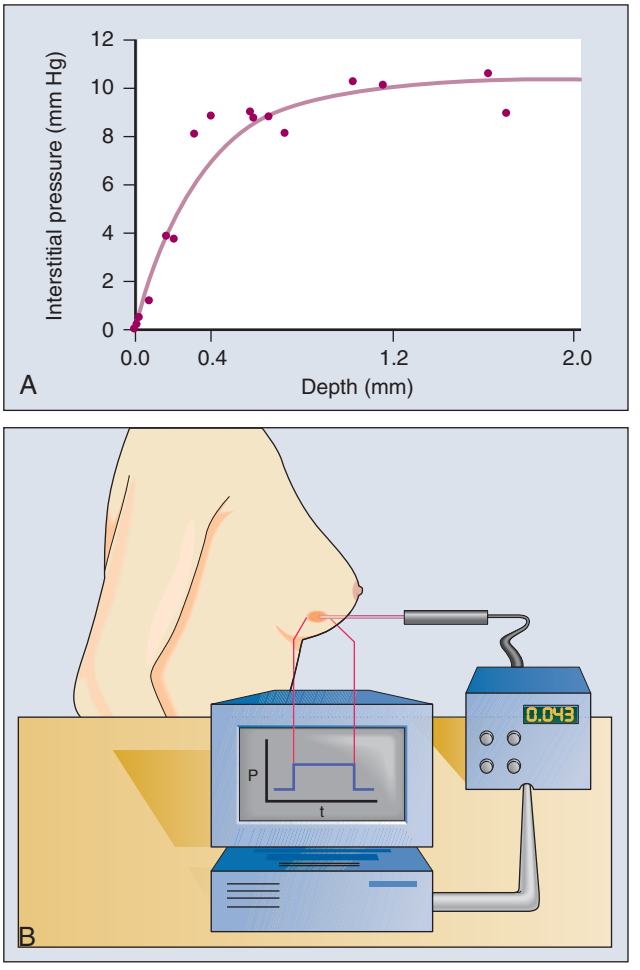


Figure 8-10 • Interstitial fluid pressure (IFP) profile in a tumor and its potential application. **A,** IFP is elevated and nearly uniform in the bulk of the tumor and drops precipitously in the tumor margin. **B,** This elevated pressure can be exploited to determine the location of a tumor precisely. (**A,** Adapted from Boucher Y, Baxter LT, Jain RK: Interstitial pressure gradients in tissue-isolated and subcutaneous tumors: implications for therapy. Cancer Res 1990;50:4478–4484. **B,** From Jain RK, Boucher Y, Stacey-Clear A, et al: Method for locating tumors prior to needle biopsy. United States patent US 19955396897. 1995.)

METABOLIC ENVIRONMENT

Hypoxia

A key function of the vasculature is to provide adequate levels of nutrients and oxygen to the parenchymal cells and to remove waste products. Based on the anatomy of the capillary bed and a mathematical model of oxygen diffusion and consumption, the Nobel laureate August Krogh introduced the concept of a diffusion limit for oxygen of 100–200 μm nearly a century ago.[195] This unit of tissue—a single capillary surrounded by a 100- to 200-μm-radius cylinder—is referred to as a "Krogh cylinder" in physiology. Nearly 50 years later, Thomlinson and Gray identified similar "cords" in human lung cancer and found necrotic cells beyond 180 mm away from blood vessels, presumably as a result of lack of oxygen.[196] This is referred to as "chronic hypoxia" or "diffusion-limited" hypoxia. Although various hypoxia markers and microelectrodes have suggested these gradients, the first direct measurements of these perivascular gradients, along with pO_2 and blood flow rate of the same vessels, became possible only recently with the development of phosphorescence quenching microscopy (Fig. 8-11A).[197,198] As discussed previously, blood flow in tumor vessels is intermittent, and, thus, some regions of a tumor are starved for oxygen periodically. The resulting hypoxia is referred to as "acute hypoxia" or "perfusion-limited hypoxia."[199,200] A necessary consequence of intermittent blood flow is the resumption of blood flow after shutdown, and the resulting production of free radicals can lead to "reperfusion injury" or "reoxygenation injury," applying additional selection pressure on cancer cells.

Low pH

Another consequence of the abnormal microcirculation of the tumor is low extracellular pH. There are at least two sources of H^+ ions in tumors—lactic acid and carbonic acid.[201] The former results from glycolysis and the latter from conversion of CO_2 and H_2O via carbonic anhydrase. The intracellular pH of cancer cells remains neutral or alkaline (pH 7.4), however, despite the acidic extracellular pH. Because carbonic anhydrase-9, various glucose transporters (GLUT1, GLUT3), and enzymes in the glycolytic pathway are upregulated by hypoxia, one would expect low extracellular pH and hypoxia to track each other and to colocalize with regions of low blood flow.[202] Surprisingly, there is a lack of spatial correlation among these parameters (Fig. 8-11B), a discovery made possible by recent developments in optical techniques that permit the simultaneous high-resolution mapping of multiple physiologic parameters.[198] A potential explanation for this lack of concordance is that some perfused tumor vessels carry hypoxic blood.[198] Thus, although they might not be able to deliver adequate oxygen to the surrounding cells, they may be able to carry away the waste products (e.g., lactic acid).

Molecular, Cellular, and Therapeutic Consequences

The presence of oxygen during irradiation makes the damage to DNA produced by radiation-induced free radicals permanent, whereas such damage can be repaired under hypoxic conditions.[203] Therefore, hypoxia in solid tumors significantly reduces their radiation sensitivity. Tumor hypoxia is also associated with resistance to some chemotherapeutics.[203] Similarly, low extracellular pH can affect the cellular uptake and cytotoxicity of some therapeutics adversely or favorably.[204–206] As a result, for nearly half a century, considerable preclinical and clinical efforts have been focused on alleviating hypoxia by improving tumor perfusion with various therapies, including the following:

- Mild hyperthermia or drugs
- Increasing oxygen content of the blood (via hyperbaric oxygenation, for example)
- Increasing hemoglobin/hematocrit (via erythropoietin, for example)
- Developing radiation sensitizers

Unfortunately, the clinical outcome has not met expectations for multiple reasons. These include the inability to increase pO_2 in all regions of tumors to optimal levels and/or to deliver radiation sensitizers or chemotherapeutic drugs to all regions of a tumor at therapeutically effective levels. As a result, three broad strategies are emerging:

1. Use hypoxia and/or low pH to activate drugs or to attract anaerobic bacteria.
2. Dissect hypoxia-induced pathways to identify novel targets for drug development.
3. Normalize tumor vasculature.[207]

The first strategy has led to the development of drugs such as tirapazamine and to the rejuvenation of interest in bacteriolytic therapy; both approaches are in clinical trials.[78,203] The second strategy has revealed several molecular determinants of the physiologic

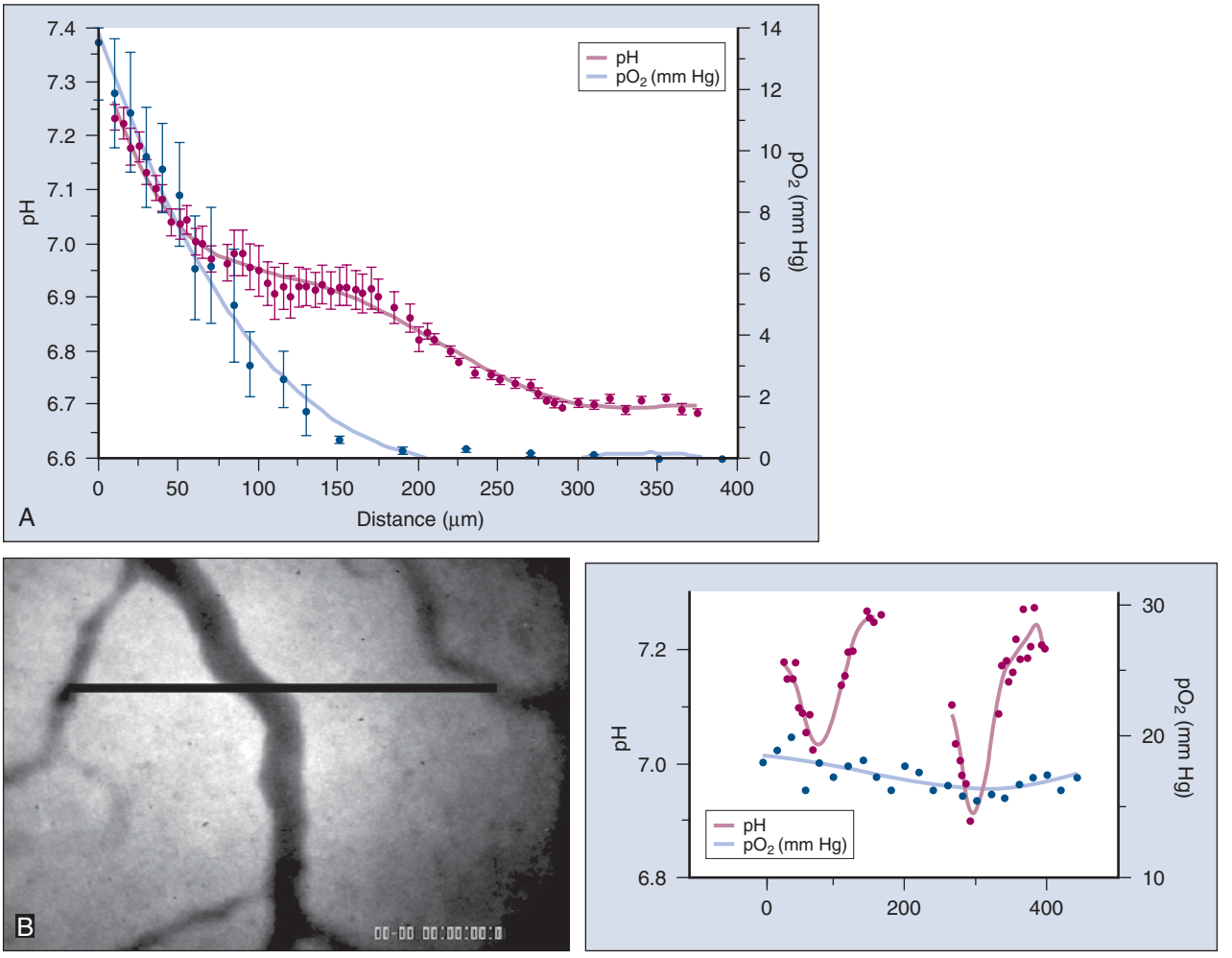


Figure 8-11 • **A,** pH and pO_2 as a function of distance from a blood vessel in a tumor. The tumor environment becomes progressively more hypoxic and acidic farther away from a blood vessel. **B,** Lack of correlation between pH and pO_2 in tumors. (From Helmlinger G, Yuan F, Dellian M, et al: Interstitial pH and pO_2 gradients in solid tumors in vivo: high-resolution measurements reveal a lack of correlation. Nat Med 1997;3:177.)

and pathophysiologic responses to hypoxia.[202] The balance between hypoxia-induced apoptosis/necrosis on one hand, and the increased resistance to cell death mediated by various hypoxia-induced pathways on the other, determines whether a tumor can survive and even grow under hypoxic conditions. Ultimately, hypoxia might select for tumor cells that are more malignant, more invasive and genetically unstable, and less susceptible to apoptosis, thus rendering them resistant to various therapies. Therefore, several molecules in the hypoxia-induced pathways are now being targeted in the development of diagnostic and therapeutic agents. Finally, normalization of tumor vessels by antiangiogenic agents may reduce hypoxia within tumor environment and synergize with radiation therapy.[207]

Hypoxia-induced pathways include genes involved in the following processes:

- Oxygen delivery (e.g., heme oxygenase 1, erythropoietin)
- Glycolysis and glucose uptake (e.g., GLUT1 and GLUT3, hexokinase-1 and -2)
- pH control (e.g., carbonic anhydrase-9 and -12)
- Stress-response pathways (e.g., growth arrest- and DNA damage-induced gene *GADD153*)
- Growth factor signaling (e.g., IL-6, IL-8, insulin-like growth factor-2 [IGF-2])
- PDGF-β
- Angiogenesis (e.g., VEGF-A, VEGFR1, Ang-2, Tie-2, FGF-3, TGF-β, nitric oxide synthase [NOS], cyclooxygenase-2 [COX-2], hepatocyte growth factor [HGF])
- Transcription (e.g., HIF1α and HIF2α, JUN, FOS, nuclear factor κB [NF-κB])
- Apoptosis (e.g., BCL-interacting killer [BIK], annexin V, 19-kd interacting protein-3 [NIP3], NIP3-like protein X [NIX])
- Growth inhibition signaling factors (e.g., p21, p27, GADD153)
- Invasion and metastasis (e.g., metalloproteinases [MMPs], MMP-13, plasminogen activator inhibitor-1 [PAI-1])[202]

Of the various molecules involved in sensing and responding to hypoxia, HIF1α has received the most attention. This transcription factor is upregulated in several human tumors.[202] Regulated by a proline hydroxylase, HIF1α can activate the genes for angiogenesis, vasodilation, glycolysis, and erythrocyte production by binding to the hypoxia-response element. Surprisingly, teratomas arising from $HIF1\alpha^{-/-}$ embryonic stem cells grow more rapidly despite lower levels of VEGF and angiogenesis.[45,208] This counterintuitive finding could be a result of the ability of $HIF1\alpha^{-/-}$ cells to survive under hypoxic conditions instead of undergoing apoptosis.[42] Interestingly, other $HIF1\alpha^{-/-}$ cancer cells lead to slowly growing tumors. As a result, molecular therapies that target HIF1α or hypoxia-response element are under intensive investigation for cancer detection and treatment.[202]

ANTIANGIOGENIC AGENTS IN THE CLINIC

Two major problems currently plague the nonsurgical treatment of malignant solid tumors. First, physiologic barriers within tumors impede the delivery of therapeutics and oxygen (a key sensitizer to ionizing radiation) at effective concentrations to all cancer cells.[209,210] Second, inherent or acquired resistance resulting from genetic and epigenetic mechanisms reduces the effectiveness of both conventional and novel therapies.[211] Can we take advantage of the unique pathophysiology of tumors to overcome these problems for better management of cancer?

Mechanisms of Action

As discussed next, recent clinical data offer great hope, with three VEGF-blocking antiangiogenic agents (bevacizumab, sorafenib, and sunitinib) already in clinical use.[212] Our studies in rectal cancer and glioblastoma patients have largely confirmed the hypotheses that anti-VEGF therapy has antivascular effects and can induce vascular normalization in cancer patients.[31,188,189,212] In brief, bevacizumab alone reduced the tumor tissue vascular density by approximately half at day 12 after first infusion, reduced significantly the tumor blood flow evaluated on computed tomography scans and the number of viable circulating endothelial cells and progenitor cells. Clinically, both the low-dose-bevacizumab and the high-dose-bevacizumab infusion showed a less hyperemic/hemorrhagic appearance, but no significant tumor regression after bevacizumab treatment at flexible sigmoidoscopy.[188,189] Although the significant pruning of tumor vasculature led to a significant increase in cancer cell apoptosis, it also led to a more mature (pericyte-covered) tumor vasculature, and a stable or increased cancer cell proliferation (Fig. 8-12A–D).[188,189] Whether the increase in tumor cell apoptosis was due to a direct or indirect effect of bevacizumab is currently unclear. Similarly, the role of VEGF blockade on immune or stromal cells in patients is not yet understood. After bevacizumab therapy alone, the tumor IFP was consistently decreased, particularly in the patients with high baseline values.[188,189] This suggested that in human tumors, similar to mouse models, the tumor microenvironment was normalized by the reduction of the excessive vascularization and potentially sensitized the tumor to the subsequent cytotoxic therapy within the "normalization window."[185,207] Imaging studies landed more supportive data for the normalization hypothesis: despite the significant reduction in vessel density and blood flow, the fluorodeoxyglucose uptake measured on positron emission tomography scans (a measure of tumor metabolic activity) and the $P \cdot S$ product (proportional to the penetration of tracer in tumor) evaluated on computed tomography scans did not significantly change at day 12.[188,189] A recent study of antiangiogenic therapy in recurrent glioblastoma demonstrated the existence of a window of vascular normalization in cancer patients (Fig. 8-12E and F).[31]

Biomarkers

Biomarker identification and validation for this novel type of therapy are also facing important hurdles. Unlike preclinical models, the phase III bevacizumab experience in metastatic colorectal cancer patients did not identify p53, k-ras, or b-raf status, VEGF or thrombospondin-2 (TSP2) expression, or microvascular density at baseline as predictive markers of response.[213,214]

Our results in rectal cancer patients demonstrated that bevacizumab decreased tumor microvascular density and the number of viable circulating ECs, consistent with an antivascular effect.[188,189,215] Whether these changes have predictive value is currently being investigated in an ongoing phase II trial. Plasma angiogenic proteins have also been investigated in multiple phase I–II and in some phase III trials. We reported that the plasma levels of VEGF and PlGF are significantly increased in cancer patients receiving bevacizumab.[189] Other groups have reported similar observations with a variety of anti-VEGF agents, and have also found a decrease in soluble VEGFR2 levels in plasma.[216,217] These data strongly suggest a potential "pharmacodynamic biomarker" value for these three plasma markers. Of great interest for the field would be to identify biomarkers that predict disease progression through anti-VEGF therapy. Although in the rectal cancer patients we were unable to identify significant changes in bFGF, our data from a recently completed phase II trial of AZD2171 in recurrent glioblastoma patients showed a highly significant correlation between bFGF and SDF1α and tumor progression.[31] These differences may be due to the excellent clinical response in rectal cancer patients, or to disease or agent specificity. In addition, we discovered that viable circulating ECs correlate with progression of glioblastoma during antiangiogenic therapy, whereas circulating progenitor cells predicted relapse after drug interruptions.[31] With the development and improved flow cytometry and protein array analysis techniques and subsequent standardization, circulating cell and plasma protein measurements hold great promise for biomarker validation for antiangiogenic therapy.

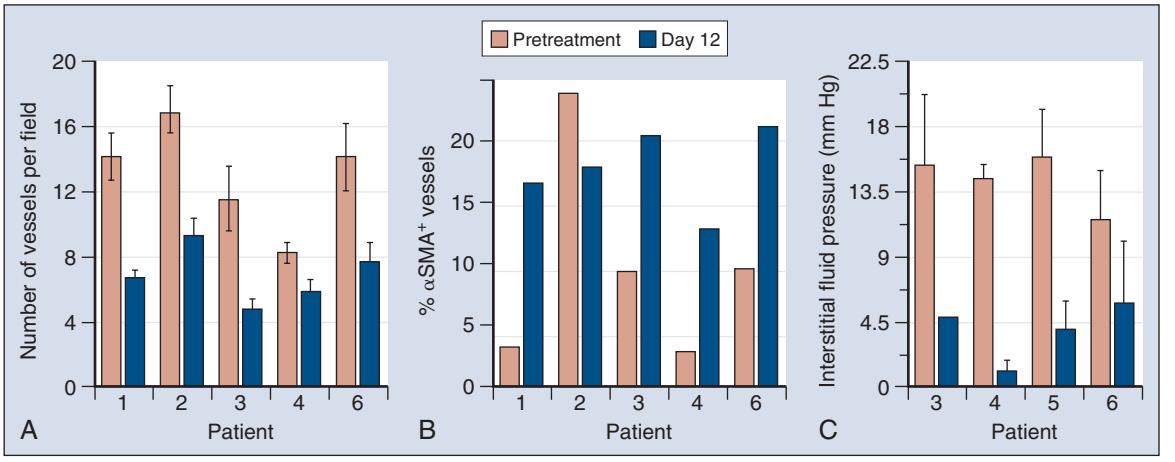
Toxicity

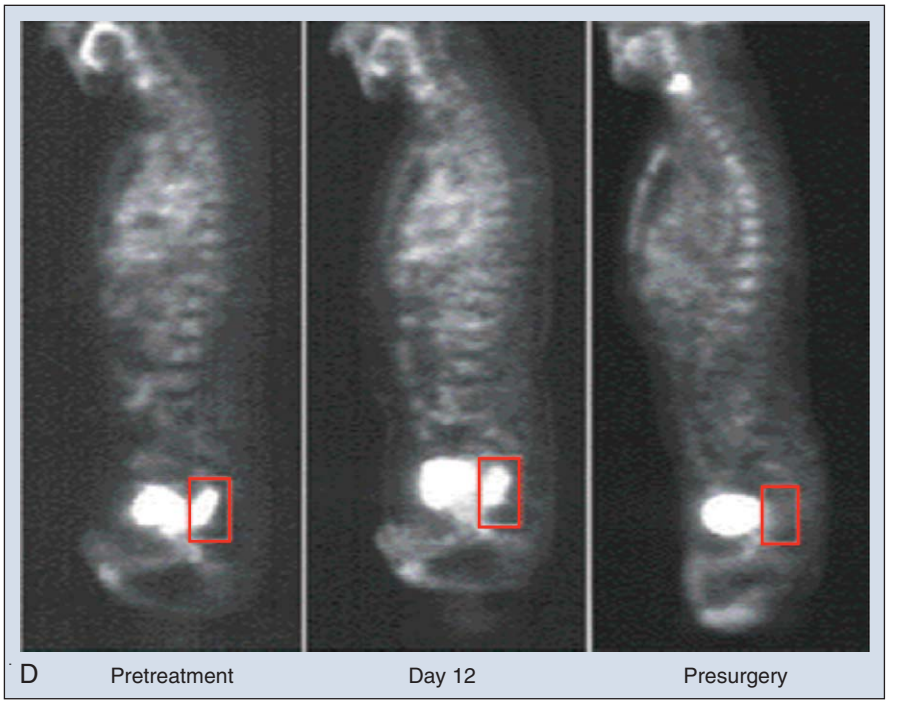
Experimental studies have shown that, in 11 of the 17 healthy organs studied, VEGF blockade can significantly decrease the number of normal capillaries.[218] In cancer patients, most anti-VEGF agents often induce proteinuria, hypertension, thyroid-stimulating hormone elevation, and gastrointestinal toxicity, but agent-specific toxicities have also been reported.[13] In addition, the long-term effects of antiangiogenic therapies in patients with less advanced lesions remain to be established.

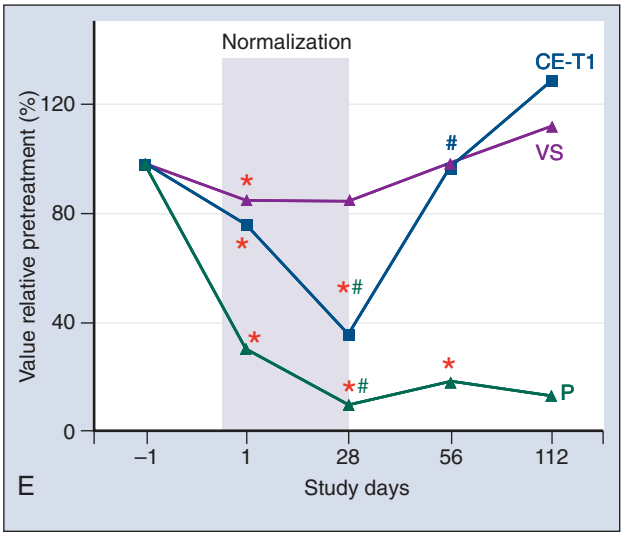
Perspective

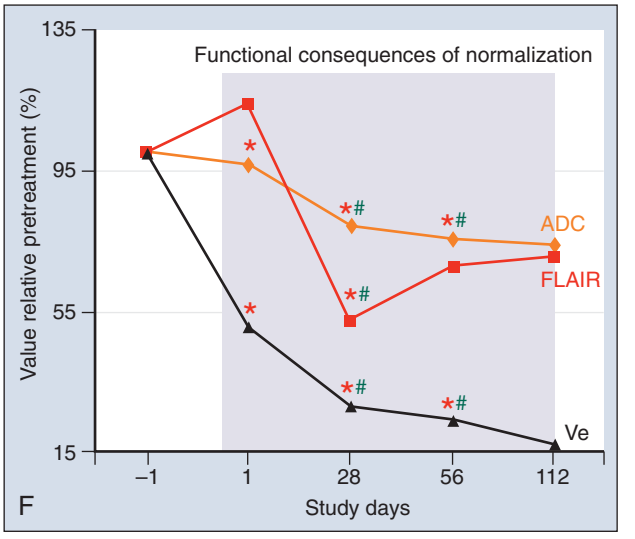
The major directions for the immediate future are further understanding of the mechanisms of action and identification of the first biomarkers for anti-VEGF therapy.[212] Achieving these goals would allow optimization of treatment protocols and reduction of the adverse effects.

Figure 8-12 • Vascular "normalization" in cancer patients. In rectal cancer patients, tumor vessel "normalization" following a single injection of bevacizumab is suggested by the **(A)** reduced tumor microvessel density, **(B)** increased fraction of tumor vessels with pericyte coverage, and **(C)** reduced interstitial fluid pressure. **(D)** Positron emission tomography reveals no change in 18-fluorodeoxyglucose (FDG) uptake after a single dose of bevacizumab and complete resolution of FDG uptake following neoadjuvant chemoradiation (bevacizumab, 5-fluorouracil, pelvic external beam radiation therapy). The stability of FDG uptake following bevacizumab monotherapy, despite marked reductions in microvessel density, suggests the efficiency of persistent tumor blood vessels after bevacizumab treatment is improved. **E** and **F,** Changes in magnetic resonance imaging parameters in glioblastoma patients receiving AZD2171 over time. **E,** Median values for contrast-enhancement T1-weighted tumor volume (CE-T1), vessel size (VS), and permeability (P) of the tumor over time as measured by an independent expert. Day –1 was set as 100% in all lesions, and changes during AZD2171 treatment were plotted for all 16 patients. Note the rebound of volume and vessel size after day 28, which indicates a partial closure of the normalization window. **F,** Median values of T2-weighted abnormality volume measured in fluid-attenuated inversion recovery images (FLAIR), apparent diffusion coefficient (ADC), and extracellular-extravascular volume fraction (Ve) before and during treatment showing a sustained decrease of edema while taking AZD2171. (*$P < 0.05$ for values compared with day –1, whereas # represents $P < 0.05$ for values compared with day +1.) (**A–D,** From Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. Nat Med 2004;145–147. **E** and **F,** From Batchelor TT, Sorensen AG, di Tomaso E, et al: AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell 2007;11:83–95.)


Pretreatment
Day 12
Number of vessels per field
% αSMA+ vessels
Interstitial fluid pressure (mm Hg)
Patient
A
B
C


D
Pretreatment
Day 12
Presurgery


Normalization
CE-T1
VS
P
Value relative pretreatment (%)
Study days
E


Functional consequences of normalization
ADC
FLAIR
Ve
Value relative pretreatment (%)
Study days
F

First, identifying the vascular "normalization window" in patients would allow synergistic combinations with chemotherapeutics or radiotherapy. Second, understanding the mechanisms of vessel pruning and cancer cell apoptosis induced by anti-VEGF therapy, and tumor escape from it, may allow further sensitization of tumor cells to cytotoxic therapies. Third, characterization of the effect of anti-VEGF therapy on bone marrow-derived cells' contribution to tumor growth and relapse would allow judicious and more effective approaches to therapy involving these cells. Finally, clarification of other mechanisms involving the immune system or the stromal and interstitial matrix compartments would contribute to establishing more efficacious combinatorial strategies.

In this respect, new biomarkers and improved imaging techniques will play a major role in monitoring the effects and stratifying the patients with the ultimate goal of individualized therapy.

CONCLUSION

The recent successes of the anti-VEGF agents have raised great hope and have taught us important lessons about the significance of the target, timing, and dosage of each agent[212]:

- According to the results of the phase III trials completed to date, bevacizumab can increase median survival when combined with standard chemotherapy, but not when used as monotherapy.
- Anti-VEGF therapy with bevacizumab can increase overall survival and/or progression-free survival in colorectal, breast, and lung cancer patients when combined with cytotoxic agents.
- Improved survival has been observed with broad-spectrum multitargeted tyrosine kinase inhibitors (e.g. sorafenib, sunitinib) when used in monotherapy.
- In colorectal cancer patients, vatalanib, a VEGF receptor–selective tyrosine kinase inhibitor, does not confer the same survival advantage as bevacizumab when combined with chemotherapy.
- Anti-VEGF therapy can prune and "normalize" tumor vasculature, and decrease the number of circulating endothelial cells and progenitor cells.
- There is an urgent need to identify biomarkers to guide anti-VEGF therapy and combination therapies using anti-VEGF agents.

Antiangiogenic agents are now expected to make a difference in cancer patients with a wide variety of tumor types. With the advent of specific and potent new agents—approved or in the process of being approved—oncologists have a variety of direct and indirect antiangiogenic agents to choose from when designing therapy protocols. Determining whether the regimens used in the successful trials are optimal, however, and whether antiangiogenic agents will work in patients outside the rigorous inclusion criteria used for those trials, will be critical for deciding the standard of care for different malignancies. Establishing the most advantageous combinations will require a better understanding of the mechanisms of action of each anti-VEGF agent and the sensitivity of each tumor type, as well as development of robust biomarkers and imaging techniques to guide patient selection and protocol design. A deeper understanding of the mechanisms of antitumor activity of specific and multitargeted antiangiogenic agents in patients, how they can best be combined with other treatment approaches such as chemotherapy and radiation therapy, and how optimization of these effects can be monitored clinically, should contribute to significantly improved cancer treatment and extend survival of cancer patients in the near future, as well as enhance the prospects of developing curative treatment for different cancers in the more-distant future.

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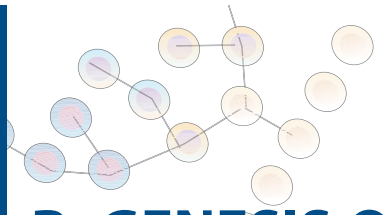
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B. GENESIS OF CANCER

9 Environmental Factors

Paul T. Strickland and Thomas W. Kensler

SUMMARY OF KEY POINTS

History of Identification of Human Carcinogens

- The carcinogenic effects of many environmental and occupational agents were first described in humans.
- Beginning in the 20th century with the advent of animal bioassay programs, evidence of carcinogenicity in experimental animals has preceded evidence from epidemiologic or case studies in humans.
- The majority of human cancers probably result from the interaction of several or more carcinogenic influences (often unidentified) along with intrinsic factors (inherited genes, hormones, immune status).

Role of Environmental Agents in the Etiology of Human Cancer

- Although the causes of most human cancers remain unidentified, cumulative data support the opinion that environmental agents are the principal causes of human cancers.
- Cigarette smoking could be responsible for 25% of all cancers in the United States.
- Chemical carcinogens include aromatic amines, benzene, aflatoxins, tobacco chemicals, and chemotherapeutic agents.
- Radiation carcinogens include ultraviolet radiation, ionizing radiation, and radon.
- A number of metal carcinogens have been identified, including arsenic, nickel, cadmium, and chromates. These have been associated largely with occupational exposures.
- Fibers (asbestos, silica) and dusts are well established as etiologic agents in lung cancers.
- Many components in the diet can influence the development of cancer through carcinogenic or anticarcinogenic mechanisms.

Exposure Biomarkers and Susceptibility Factors and Chemoprevention

- The identification of molecular biologic markers of exposure, effect, and susceptibility (reflecting events before clinical disease) will help to further our understanding of human carcinogenesis.
- The characterization of the human genome has permitted study of the roles of common polymorphisms in carcinogen metabolism or of DNA repair genes in susceptibility to cancer.
- Primary and secondary approaches to the prevention of cancer will be greatly facilitated by the development of noninvasive biomarkers that identify high-risk individuals.
- Tertiary prevention might also be enhanced by characterizing cancers with respect to etiology, genetic profile, or metabolic capacity.

INTRODUCTION

The carcinogenic effects of a sizable number of environmental or industrial chemicals have first been described in humans. The influences of occupation and lifestyle in cancer occurrence were observed at least as early as the 16th century. Ramazzini in 1700 noted that nuns showed a higher frequency of breast cancer than was observed among other women. Also in that century, Paracelsus and Agricola described Bergkrankheiten in miners in the Schneeberg and Joachimstal regions of Europe. Bergkrankheiten was later recognized as lung cancer, probably caused by uranium and its decay product radon.[1] Subsequently, in 1761 Hill associated the use of tobacco snuff with cancer in the nasal passage, and in 1775 Pott noted the occurrence of soot-related scrotal cancer among chimney sweeps. In 1895 Rehn published evidence that occupational exposure to aromatic amines was associated with bladder cancer, whereas Unna in 1894 associated sunlight exposure with skin cancer. It was not until the early 20th century that animal models for chemical carcinogenesis were developed. For example, Yamagiwa and Ichikawa reported in 1915 on the production of skin tumors following topical application of crude coal tar to the ears of rabbits, and Sasaki and Yoshida reported in 1935 that feeding of azo dyes to rats led to the development of liver tumors. In the intervening decades, there has been substantial growth in our understanding of the roles of chemicals (both manufactured and naturally occurring), radiation, and viruses in the cancer process. Of particular importance has been the recognition that these extrinsic factors interact with intrinsic factors (e.g., inherited genes, hormones, immune status) to determine overall susceptibility and risk. A central role of diet in these interactions is featured by observations that diet can both enhance and inhibit tumor formation.

Contrary to experiences in earlier centuries, with the advent of animal bioassay programs, evidence of carcinogenicity in experimental animals has preceded evidence obtained from epidemiologic studies or case reports in many instances. Although the term carcinogen means "giving rise to carcinomas" (e.g., epithelial malignancies) in general, broader operational definitions are used for carcinogens in animal bioassays. A carcinogen may be defined as an agent whose administration to previously untreated animals leads to a statistically significant increased incidence of malignant neoplasms, compared with the incidence in appropriate untreated control animals, whether the control animals have a low or high spontaneous incidence of the neoplasms in question. Chemicals, radiation, and

Table 9-1 Agents and Processes Considered Carcinogenic in Humans by the International Agency for Cancer Research

Agent or Process	Common Organ or Tissue Sites of Cancer
AMBIENT AND DIETARY EXPOSURE	
Aflatoxins	Liver
Arsenic and arsenic compounds	Lung, skin
Erionite	Pleura, peritoneum
CULTURAL HABITS	
Alcoholic beverages	Oral cavity, pharynx, larynx, esophagus, liver
Betel quid with tobacco	Oral cavity
Tobacco products, smokeless	Oral cavity
Tobacco smoke	Respiratory tract, urinary bladder, renal pelvis, pancreas
Salted fish, Chinese style	Nasopharynx
Solar radiation	Skin
OCCUPATIONAL	
Aluminum production	Lung, urinary bladder
4-Aminobiphenyl	Urinary bladder
Asbestos	Lung, pleura, peritoneum, larynx, gastrointestinal tract
Auramine O, manufacture of	Urinary bladder
Benzene	Leukemia
Benzidine	Urinary bladder
Beryllium	Lung
Bis(chloromethyl)ether and chloromethyl methyl ether	Lung
Boot and shoe manufacture and repair	Nasal sinus
Cadmium	Lung
Chromium (VI) compounds	Lung
Coal gasification	Lung, urinary bladder, scrotum
Coal-tar pitches	Skin, scrotum, lung
Coal tars	Skin, lung
Coke production	Skin, scrotum, lung, urinary bladder
Dioxin	All cancers combined
Ethylene oxide	Lymphatic, hematopoietic
Formaldehyde	Liver
Furniture and cabinet making	Nasal sinus
Iron and steel founding	Lung
Isopropyl alcohol manufacture (strong acid process)	Nasal sinus
Magenta, manufacture of	Urinary bladder
Mineral oils (untreated and mildly treated)	Skin, scrotum
Mustard gas	Lung, larynx/pharynx
2-Naphthylamine	Urinary bladder
Nickel and nickel compounds	Lung, nasal sinus
Painting	Lung
Benzo[*a*]pyrene	Lung
Rubber industry	Urinary bladder, leukemia
Shale oils	Skin, scrotum
Silica, crystalline	Lung
Soots	Skin, scrotum, lung
Strong inorganic acid mists containing sulfuric acid	Larynx
Talc containing asbestiform fibers	Lung
Underground mining with exposure to radon	Lung
Vinyl chloride	Liver, lung, gastrointestinal tract, brain
Wood dust	Nasal cavities, paranasal sinuses
THERAPEUTIC USE	
Analgesics mixtures containing phenacetin	Renal, urinary bladder
Azathioprine	Leukemia
N,*N*-Bis(2-chloroethyl)-2-naphthylamine	Urinary bladder
1,4-Butanediol dimethanesulfonate	Leukemia
Chlorambucil	Leukemia
Cyclosporin	Lymphoma
Cyclophosphamide	Urinary bladder, leukemia
Estrogen replacement therapy	Endometrium, breast
Estrogen, nonsteroidal	Cervix/vagina, breast, endometrium, testes
Estrogens, steroidal	Endometrium, breast
Melphalan	Leukemia
8-Methoxypsoralen plus UV radiation	Skin
Methyl-CCNU	Leukemia
MOPP	Leukemia
Oral contraceptives (combined)	Liver
Oral contraceptives (sequential)	Endometrium
Tamoxifen	Endometrium
Thiotepa	Leukemia
Treosulfan	Leukemia
INFECTIOUS AGENTS	
Epstein-Barr virus	Lymphoma
Helicobacter pylori	Stomach
Hepatitis B virus	Liver
Hepatitis C virus	Liver
Human immunodeficiency virus type 1	Kaposi's sarcoma
Human papilloma viruses types 16, 18, others	Cervix
Human T-cell lymphotropic virus type I	Adult T-cell leukemia/lymphoma
Opisthorchis viverrini	Cholangiocarcinoma
Schistosoma haematobium	Urinary bladder

methyl-CCNU, semustine; MOPP, mechlorethamine, vincristine, procarbazine, and prednisone (combination therapy).

Data from International Agency for Research on Cancer: IARC monographs on the evaluation of carcinogenic risk to humans, Vol. 1–88, Lyon, IARC, 1970–2006. An updated listing of the overall evaluation of carcinogenicity to humans can be accessed on the Internet at http://monographs.iarc.fr under the heading "classifications". (Note: for examples of carcinogenic ionizing radiations, see Table 9-3).

viruses are the primary agents identified. Synthetic and naturally occurring chemicals compose the largest group of known human carcinogens. More than 100 chemicals, chemical mixtures, biologic agents, physical agents, or industrial processes have been classified as human carcinogens (Table 9-1) and more than 300 chemicals have been identified as animal carcinogens so far. These figures evolve from an environmental milieu of perhaps 10^7 chemicals, although the vast majority of these agents have not been evaluated for carcinogenicity.

Chemical carcinogens comprise a diverse array of chemical structures, including both organic and inorganic compounds. Relatively few carcinogens are direct acting, because the innate reactivity of such compounds also tends to make them unstable. Instead, most carcinogens require metabolic activation to reactive species, often in the target cells. Once formed, the reactive intermediates can interact with DNA to produce genetic lesions that can result in mutation of critical cellular genes, including oncogenes and tumor suppressor genes. Metabolic pathways can be influenced strongly by a variety of extrinsic and intrinsic factors and are important determinants of both interindividual and target organ susceptibilities to carcinogens. Carcinogenesis is a dynamic, multistage process through which a normal cell is converted into a malignant one. Although our understanding of the neoplastic process is incomplete, current knowledge provides considerable insight into the critical actions of carcinogens. The goal of this chapter is to highlight the roles of discrete chemical and physical agents in the etiology of human cancers. In turn, fuller understanding of the mechanistic basis for the actions of these carcinogenic agents will allow for more effective means to identify other carcinogens in our environment and to develop preventive strategies to interrupt, block, or reverse the neoplastic process.

ROLE OF ENVIRONMENTAL AGENTS IN THE ETIOLOGY OF HUMAN CANCERS

The causes of most human cancers remain unidentified; however, considerable evidence suggests that "extraconstitutional" or environmental and lifestyle issues are important contributors. For example, cigarette smoking could be responsible for 25% of all cancers in the United States. The opinion that environmental agents are the principal causes of human cancers is derived largely from the following series of epidemiologic observations:

- Although the overall incidence of all cancers is reasonably constant among countries, incidences of specific cancer types can vary up to several hundred fold.
- There are large differences in tumor incidence within populations of a single country.
- Migrant populations assume the cancer incidence of their new environment within one to two generations.
- Cancer rates within a population can change rapidly.

Although the extent to which environmental agents contribute to human carcinogenesis remains to be defined precisely, a considerable number of epidemiologic studies indicate important roles for the various naturally occurring and manufactured chemicals, radiations, metals, and fibers found in our individual environments.

Chemicals

Polycyclic Aromatic Hydrocarbons

The English surgeon Percival Pott[2] was among the first to document the association of an environmental agent with cancer. During the late 18th century, he determined that the unusually high incidence of scrotal cancer among chimney sweeps was due to their occupational exposure to soot and tar. As a consequence, recommendations for bathing and use of protective clothing were promulgated by chimney sweepers' guilds in parts of Europe, but not in England. Subsequent decreases in the incidence of scrotal cancer were observed in continental Europe, demonstrating the efficacy of simple prevention efforts. It was not until the present century that the active carcinogens in soot and coal tar were shown to be polycyclic aromatic hydrocarbons (PAHs).[3] This result was accomplished through the application of coal tar and fractions thereof to the skins of test animals that subsequently developed malignant skin tumors. Although many PAHs were identified in coal tar, most of the carcinogenic activity was attributed to the PAH benzo[*a*]pyrene.

Humans are exposed to PAHs from a variety of sources that include occupation, smoking, diet, and air.[4] PAHs are readily absorbed into the body through the skin, lungs, and gastrointestinal tract. Occupational and medicinal exposures constitute the highest levels of human PAH exposure (albeit in small groups within the population), whereas diet and smoking are the major sources of exposure to PAHs in the general population. Air concentrations of greater than 10 μg benzo[*a*]pyrene/m^3 are characteristic of topside gas and coke work environments. Broiled, barbecued, or smoked meats and fish contain relatively high concentrations of benzo[*a*]pyrene (1–20 μg/kg).

Cutaneous occupational exposure to PAHs has been associated with increased risk of skin and scrotal cancers in chimney sweeps and in individuals exposed to unrefined lubricating oils in the textile and machining industries.[1] Scrotal cancer among mule spinners in the Manchester (UK) cotton industry was attributed to the saturation of the workers' trousers with lubricating oil. A review of all admissions for scrotal cancer to the Royal Manchester Infirmary from 1902 to 1922 indicated that 49% had worked as mule spinners, while 16% had worked with tar or paraffin. As the textile industry declined in the middle 20th century, an increasing proportion of scrotal cancer was associated with cutting oils used in metal machining.

An excess of lung cancer has been demonstrated among individuals with substantial inhalation exposure to PAHs, including roofers and pavers, coke oven workers, certain steel and iron manufacturing workers, and aluminum production workers.[5] In addition, several studies suggest that workers highly exposed through inhalation might also be at increased risk of cancer at sites other than skin and lung. The strongest evidence for such an association is for bladder cancer, where a dose-response relationship has been demonstrated between PAH exposure and bladder cancer risk in aluminum workers after adjustment for smoking. Other sites with suggestive increases in risk include the pancreas and upper gastrointestinal tract.

Several biochemical pathways are involved in the metabolism of PAHs and of benzo[*a*]pyrene in particular (Fig. 9-1).[3] The initial step in benzo[*a*]pyrene metabolism involves the epoxidation of an aromatic double bond by one of the cytochrome P-450 monooxygenases (CYP1A1). The epoxide-benzo[*a*]pyrene intermediates might form phenols or glutathione conjugates or be further oxidized by epoxide hydrolase to form dihydrodiol-benzo[*a*]pyrene. This latter metabolite can undergo a second oxidation step, resulting in the highly reactive 7,8-dihydrodiol-9,10-epoxide benzo[*a*]pyrene. Experimental studies demonstrate that cultured human lung or colon tissue metabolizes benzo[*a*]pyrene to the proximate carcinogen 7,8-dihydro-7,8-dihydroxybenzo[*a*]pyrene and that benzo[*a*]pyrene metabolites bind to DNA in cultured tissue. Oral administration of benzo[*a*]pyrene to rodents produces benzo[*a*]pyrene-DNA adducts in liver, stomach, colon, and intestine, and cancers of the esophagus, forestomach, intestine, lungs, and mammary gland.

Aromatic Amines

The occurrence of bladder cancer among dye industry workers was reported in 1895 by the German physician Ludwig Rehn, who suggested a causal relationship. With the rapid expansion of the chemical industry during and after World War I, increased risk of bladder cancer was observed among workers employed in chemical manufacturing and textile dyeing.[6] An industry-wide study of workers exposed to dyes in England and Wales demonstrated increased risks of bladder cancer among men exposed to 1-naphthylamine (observed

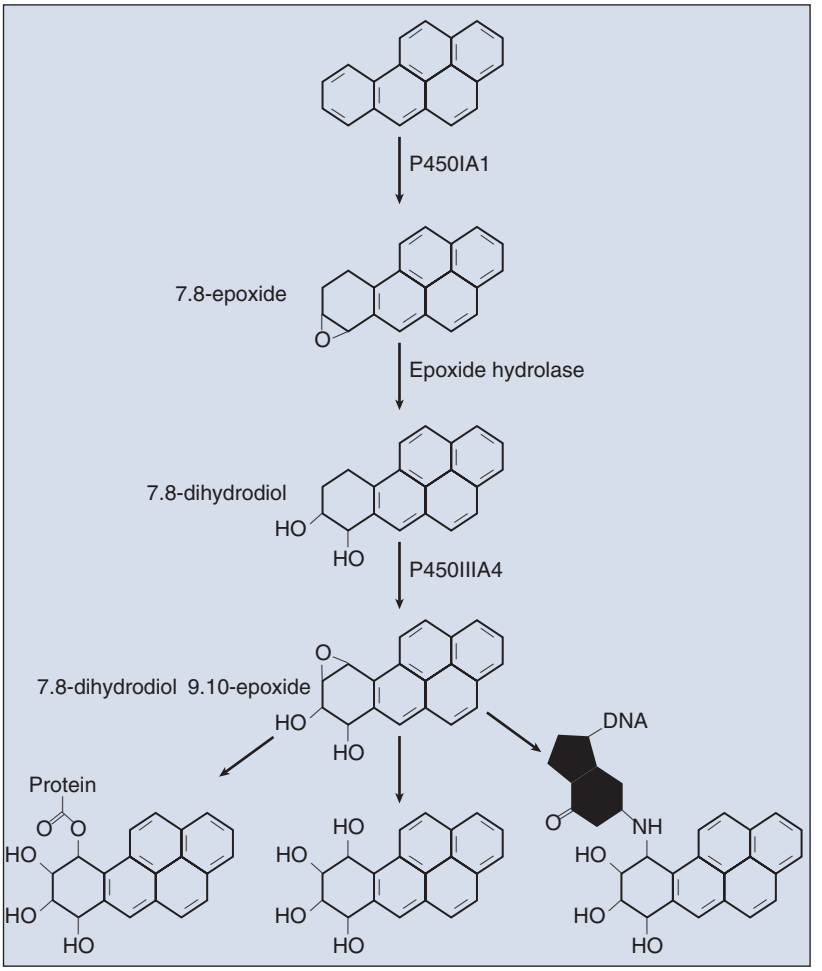


Figure 9-1 • Metabolic activation of benzo[*a*]pyrene and formation of DNA and protein adducts.

[O]/expected *[E]* = 8.6), benzidine (*O*/*E* = 13.9), 2-naphthylamine (*O*/*E* = 86.7), or mixed dyes (*O*/*E* = 54.7). The International Agency for Research on Cancer subsequently considered that the cancer hazard associated with exposure to 1-naphthylamine was due to the probable contamination of commercial-grade 1-naphthylamine with 4% to 10% 2-naphthylamine.[7] Additional studies in the dye industry identified auramine O and magenta as human bladder carcinogens. Increased risk of bladder cancer among rubber workers and in the electric cable industry has been attributed to the naphthylamine added to rubber as an antioxidant.

Excess risk of bladder cancer has been observed in the silk-dyeing industry, in which benzidine-based dyes are used extensively. Elevated incidence of bladder cancer associated with benzidine manufacturing and production in the United States and Japan is complicated by probable coexposure to 2-naphthylamine and *o*-toluidine. The production of these aromatic amines has declined in recent years; the result has been a considerable reduction in bladder cancer among workers in these industries.

Aromatic amines are metabolized and excreted through a process involving acetylation by *N*-acetyltransferase.[8] Genetic variation in one of the genes, *NAT2,* encoding this enzyme produces either rapid or slow metabolic phenotypes in humans. Analysis of the NAT2 phenotypes of patients with bladder cancer from the dye industry indicates that individuals showing the slow phenotype could be more susceptible to bladder cancer caused by aromatic amines. This is consistent with a recent meta-analysis indicating that NAT2 slow acetylation status is associated with an increased risk of bladder cancer in the general population.[9]

Benzene

Exposure to benzene was suspected to be the cause of leukemia in a number of individual cases and case series reported worldwide between 1928 and 1976.[1] Case-control studies indicated increased risks of nonlymphocytic leukemia among workers in Sweden exposed to benzene-containing petroleum products and for lymphomas among workers in New York State exposed to benzene. Prospective studies conducted in the rubber industry provide the most convincing evidence for an association between benzene exposure and leukemia. Most of the excess leukemia in this industry is found among rubber workers exposed to solvents, including benzene. Excess mortality from leukemia has been observed among former employees of a rubber film production plant (*O*/*E* = 4.7) and a rubber coating plant (*O*/*E* = 3.7).

Aflatoxins

The hepatotoxic effect of aflatoxins was first recognized when aflatoxin-contaminated feed was inadvertently fed to poultry. Subsequent animal studies demonstrated the carcinogenic potential of the aflatoxins, particularly aflatoxin B_1. The aflatoxins are produced by the fungal strains *Aspergillus flavus* and *A. parasiticus.* Grains and foodstuffs for human consumption such as corn, peanuts, and rice can become contaminated with aflatoxin during growth or storage. The considerable variation in levels of human exposure to aflatoxin worldwide is determined by climate and by the preventive measures used to protect susceptible foods from mold contamination and growth.[10]

Dietary aflatoxin is correlated with high liver cancer rates in sub-Saharan Africa and Asia. Case-control studies in the Philippines and Mozambique show an increased risk of liver cancer with estimated levels of aflatoxin consumption. The co-carcinogenic role of hepatitis B virus (HBV) infection and dietary aflatoxin in liver cancer has been the focus of several studies. The incidence of liver cancer in different regions of Swaziland correlated more closely with aflatoxin intake than with HBV infection. A prospective study conducted in Guangxi Province, China, compared the incidence of liver cancer in regions of high and low aflatoxin contamination and determined HBV infection status.[10] A strong interaction between aflatoxin exposure and HBV-positive status was observed for relative risk of liver cancer. Among HBV-positive individuals, the incidence of liver cancer was 649 per 100,000 in the high-aflatoxin region and 66 per 100,000 in the low-aflatoxin region, whereas among HBV-negative individuals, the incidence of liver cancer was 99 per 100,000 and <1 per 100,000 in high- or low-aflatoxin regions, respectively.

The new techniques of molecular dosimetry for human carcinogen exposure have been applied in populations exposed to aflatoxin. With individual exposures often in excess of 10 to 100 µg/day, the presence of aflatoxin metabolites and DNA adducts can be quantified in the urine after exposure. The association of urinary aflatoxin-DNA adducts with risk of liver cancer has also been demonstrated in a prospective epidemiologic study.[11]

Tobacco Chemicals

Tobacco use causes more cancer deaths worldwide than any other human activity. Cigarette smoking is associated with cancers of the lung, oral cavity, pharynx, larynx, esophagus, bladder, renal pelvis, and pancreas. The use of smokeless tobacco (chewing tobacco or snuff) leads to cancer of the oral cavity. Thus, although combustion enhances the carcinogenic properties of tobacco, it is not required for cancer induction.

Although the carcinogenic properties of tobacco tar were first demonstrated experimentally during the 1920s, evidence of a human cancer risk from the use of tobacco did not appear until 1939, when Muller and colleagues[12] reported an association between tobacco use and lung carcinoma in Germany. Subsequent epidemiologic studies conducted in the United States and the United Kingdom during the next decade confirmed this causal relationship. These findings met with considerable resistance in both the scientific community and the general public, however. Unlike occupational exposure to carcinogens, which was subject to regulation in many countries, tobacco exposure was a personal habit considered by many users to be more pleasurable than dangerous. Unfortunately, the addictive characteristics of nicotine, a major constituent of tobacco, made it more difficult for tobacco users to reduce their consumption. Societal acceptance of a causal association with lung cancer was advanced by the first reports from the Royal College of Physicians in the United Kingdom (1962) and from the Surgeon General in the United States (1964) regarding the risks of tobacco use. By contrast, the tobacco industry has steadfastly resisted attempts to educate the public to the health hazards of tobacco use and has continued to market cigarettes aggressively, particularly in developing countries. Explosive increases in the incidence of lung cancer, probably even outranking those already occurring in the United States, can be anticipated in these countries over the next few decades. Based on tobacco usage trends, it is estimated that more than one million new cases per year of lung cancer will occur in China in the 21st century.[12]

More than 3000 chemicals have been identified in cigarette smoke, of which at least 30 are known to be carcinogenic in animals (Table 9-2). The gas phase of tobacco smoke contains several carcinogenic or tumor-promoting compounds, including dimethylnitrosamine, dialkylnitrosamines, vinyl chloride, acrolein, and benzene. The particulate phase contains carcinogenic and co-carcinogenic PAHs, methylated PAHs, heterocyclic hydrocarbons, chlorinated hydrocarbons, phenols, catechols, and metals. Organ-specific

Table 9-2 Tumorigenic Agents in Tobacco Smoke

Compounds	Mainstream Smoke Compounds (per Cigarette)
PAHS	
Benzo[*a*]anthracene	20–70 ng
Benzo[*b*]fluoranthene	4–22 ng
Benzo[*f*]fluoranthene	6–21 ng
Benzo[*k*]fluoranthene	6–12 ng
Benzo[*a*]pyrene	20–40 ng
Chrysene	40–60 ng
Dibenz[*a,h*]anthracene	4 ng
Dibenzo[*a,i*]pyrene	1.7–3.2 ng
Dibenzo[*a*-1]pyrene	Detectable
Indenol[1,2,3-*c,d*]pyrene	4–20 ng
5-Methylchrysene	0.6 ng
AZA-ARENES	
Quinoline	1–2 µg
Dibenz[*a,h*]acridine	0.1 ng
Dibenz[*a,j*]acridine	3–10 ng
7H-Dibenzo[*c,g*]carbazole	0.7 ng
N-NITROSAMINES	
N-Nitrosodimethylamine	0.1–180 ng
N-Nitrosethylmethylamine	3–13 ng
N-Nitrosodiethylamine	0–25 ng
N-Nitrosopyrrolidine	1.5–110 ng
N-Nitrosodiethanolamine	0–36 ng
N-Nitrosonornicotine	0.12–2.7 µg
4-(Methylnitrosamine)-1-(3-pyridyl)-1-butanone	0.08–0.77 µg
N-Nitrosoanabasine	0.14–4.6 µg
AROMATIC AMINES	
2-Toluidine	30–200 ng
2-Naphthylamine	1–22 ng
4-Aminobiphenyl	2–5 ng
ALDEHYDES	
Formaldehyde	70–100 µg
Acetaldehyde	18–1400 ng
Crotonaldehyde	10–20 µg
MISCELLANEOUS ORGANIC COMPOUNDS	
Benzene	12–48 µg
Acrylonitrile	3.2–15 µg
2-Nitropropane	0.73–1.21 µg
Ethylcarbamate	20–38 ng
Vinyl chloride	1–16 ng
INORGANIC COMPOUNDS	
Hydrazine	24–43 ng
Arsenic	40–120 ng
Nickel	0–600 ng
Chromium	4–70 ng
Cadmium	41–62 ng
Polonium-210	0.03–1.0 pCi

From Reducing the Health Consequences of Smoking: 25 Years of Progress. Washington, DC, U.S. Department of Health and Human Services, 1989.

carcinogens in the particulate phase include N-nitrosamines (and precursors), which have been associated with esophageal and pancreatic cancers, and aromatic amines, which are associated with kidney and bladder cancers. An important finding from experimental studies is the strong interactive effect observed when certain mixtures of these compounds are assayed for carcinogenic potential.

Chemotherapeutic Agents

The systemic toxicity of sulfur mustard gas among soldiers exposed during World War I led to investigations of the mechanism of action of nitrogen mustard compounds. The cytotoxic effect observed in lymphatic tissues was subsequently replicated and studied in experimental animal models. This property of nitrogen mustards and other alkylating compounds prompted their use as antineoplastic drugs during the 1940s. Several other types of drugs were developed at that time for use in the treatment of cancer, including the antibiotic actinomycin A and the antimetabolite methotrexate. Later decades saw the introduction of a variety of alkylating agents (e.g., chlorambucil, cyclophosphamide, bis-chloroethylnitrosourea, busulfan, cisplatin), antimetabolites (5-fluorouracil, 6-mercaptopurine), antibiotics (adriamycin, bleomycin, daunomycin), and mitotic inhibitors (vincristine, vinblastine) as antineoplastics.

As early as 1948, the carcinogenic properties of the anticancer drug 4-aminostilbene and its metabolites were reported. This and subsequent findings led to the institution of carcinogenesis bioassays for new anticancer drugs under development by the National Cancer Institute. Preneoplastic dysplasias were frequently observed in the epithelial tissues of patients with cancer undergoing chemotherapy. The appearance of frank second malignancies among patients treated by chemotherapy was reported during the 1970s. In addition, renal transplant patients receiving anticancer drugs for immunosuppression showed excess risks of mesenchymal and epithelial cancers.

The successful treatment of Hodgkin's disease with multiagent chemotherapy is associated with the long-term complication of acute myeloid leukemia (AML) and non-Hodgkin's lymphoma. Increased risk of acute myeloid leukemia among patients treated for non-Hodgkin's lymphoma, ovarian cancer, multiple myeloma, or small-cell carcinoma of the lung has also been attributed to antineoplastic therapy. The risk of acute myeloid leukemia is most strongly associated with the alkylating antineoplastics—particularly cyclophosphamide, melphalan, busulfan, treosulfan, and semustine (methyl-CCNU)—or with combination chemotherapies that include alkylating agents.

A large case-control study conducted in collaboration with 11 population-based cancer registries and two large oncology hospitals in Europe and Canada identified 114 cases of leukemia among 99,113 ovarian cancer survivors.[13] Patients receiving chemotherapy alone had a relative risk for leukemia of 12 as compared with patients treated by surgery alone. By contrast, patients receiving radiation therapy alone (as compared with surgery alone) had no significant increase in the risk of leukemia. In order of decreasing leukemogenic potency, the drugs melphalan, thiotepa, chlorambucil, cyclophosphamide, and treosulfan were independently associated with significantly increased risk of leukemia. Combination treatment with adriamycin and cisplatinum also increased the risk of leukemia, indicating that one or both of these drugs is leukemogenic in humans.

Radiation

Ultraviolet

Solar ultraviolet (UV) radiation is the major physical carcinogen in our environment and the primary cause of skin cancer in humans. More than 800,000 individuals will develop new basal cell carcinoma or squamous cell carcinoma of the skin each year in the United States, making nonmelanoma skin cancer the most common cancer.[7] The incidence of both nonmelanoma and melanoma skin cancer among light-skinned individuals is increasing at a rate of 3% to 5% per year in the United States. This increase has been attributed to changing lifestyle and leisure habits over the past five decades, resulting in an increase in the number of people receiving greater exposure to sunlight. Although basal cell carcinoma occurs more frequently than squamous cell carcinoma (the ratio of basal cell to squamous cell carcinoma is approximately 3:1), the incidence of squamous cell carcinoma seems to be increasing more rapidly than that of basal cell carcinoma. In addition, squamous cell carcinoma metastasizes more frequently and is responsible for more deaths than are caused by basal cell carcinoma.

The relationship between solar UV exposure and skin cancer in humans has been demonstrated from incidence data in human populations residing at different latitudes. The incidence of nonmelanoma skin cancer shows a generally increasing trend with decreasing latitude among individuals with similar skin types.[7] Nonmelanoma skin cancers and the premalignant skin neoplasm, actinic keratosis, are also associated with cumulative lifetime UV exposure estimated from outdoor activities. This is particularly apparent among those with outdoor occupations such as farmers and sailors. The anatomic distribution of these skin neoplasms, primarily on sun-exposed areas, including the face, ears, neck, and hands, is consistent with a solar etiology. The phenotypic characteristics of light skin complexion, ease of sunburning (skin type), and light hair color are known to enhance the risk of nonmelanoma skin cancer. Pigmentation of the skin, either constitutive or induced (as in tanning), clearly plays an important role in protecting skin from the carcinogenic effects of UV radiation. Individuals with moderately to heavily pigmented skin (Latin, Hispanic, Negroid) show much lower rates of skin cancer than do those with poorly or nonpigmented skin (Celtic, albino). The importance of pigmentation is also demonstrated by the finding that susceptibility to sunburn is a strong indicator of risk of both basal and squamous cell carcinoma.

Molecular evidence also supports an etiologic role of solar UV in human skin cancer. Increased levels of DNA photodamage are detected in the normal epidermis of individuals following exposure to solar UV radiation. In addition, analysis of mutational spectra in human nonmelanoma skin cancer DNA shows that mutations specific for UV radiation (dipyrimidine mutations) are frequently present.

Animal studies confirm the carcinogenic effects of UV radiation and indicate that the UV-B portion (280–320 nm) of the solar spectrum is primarily responsible for the carcinogenic properties of sunlight. This wave band encompasses the long-wavelength end of the absorbance spectrum of DNA and has been shown to cause mutations in mammalian cells. Stratospheric ozone efficiently absorbs UV-B wavelengths below 300 nm, thereby determining the short-wavelength end of the solar spectrum reaching the earth's surface. Concern over the destruction of stratospheric ozone due to environmental pollution with chlorofluorocarbons, resulting in increased intensity of UV-B radiation at the earth's surface, has encouraged the refinement of risk estimates for human skin cancer under conditions of reduced atmospheric ozone.

Ionizing

The discovery and manipulation of ionizing radiation in the early 20th century led to detrimental health effects among many researchers. Toxicity, radiation burns, and cancer were observed among handlers of radioactive materials. The deaths of Marie Curie and Thomas Edison's assistant from cancer have been attributed to severe radiation exposure. The use of radium in luminous paint during the 1930s led to a high incidence of osteosarcoma among dial painters who inadvertently ingested radium when shaping their brush tips with the tongue.[1] By the 1940s, an elevated incidence of leukemia was observed among radiologists. After World War II, excess leukemia was observed among atomic bomb survivors and among patients treated with x-rays.

Epidemiologic studies of populations exposed to high doses of radiation indicate increased risks for a variety of cancers, depending on the type of radiation and route of exposure (Table 9-3). Among atomic bomb blast survivors, excess leukemias appeared within several years of exposure, whereas excess cancers of the breast, lung, esophagus, thyroid, colon, bladder, and ovary, as well as multiple myeloma appeared only 20 to 25 years later. In contrast, populations exposed to nuclear weapons fallout show only excess risk of thyroid cancer due to radioactive iodine. Heavy exposure to x-rays for diagnostic or therapeutic procedures has been associated with increased risk of the following types of cancers: leukemia after in utero exposure; breast cancer after repeated chest exposure; leukemia, lung, stomach, and esophagus after spinal exposure; and thyroid, skin, and neck after scalp or thymus exposure.[5]

The use of cobalt-60 x-ray treatment for cervical cancer is associated with leukemia and cancers of the stomach, rectum, bladder, vagina, buccal cavity, nasopharynx, and lung. Because most radiation exposure in ambient or occupational environments occurs as protracted low-dose exposure, an important public health concern is the cancer risk from low-level exposure. However, most risk estimates are extrapolated from high to low doses and from acute to chronic exposures and are therefore subject to several assumptions that profoundly influence the resulting low-level risk estimates. Populations with potential (or known) low-level radiation exposures include employees in the nuclear industry, individuals living near nuclear production or storage facilities, military personnel participating in atmospheric nuclear weapons tests or living near test sites, patients receiving diagnostic radiation, and residents of buildings with radon contamination. In addition, nuclear accidents such as the Chernobyl incident in the former Soviet Union produce both acute and chronic exposure to local and distant populations.

Radon

Radon gas is encountered in hard rock mining for iron, tin, fluorspar, and uranium.[7] The radioactive decay of radon and its products produces alpha particles. The earliest reports defining an association between lung cancer and mining described the high rate of lung cancers among uranium miners in the Schneeberg region of Czechoslovakia in the late 19th century. Many potential causes were proposed, including radon inhalation. Studies of lung cancer mortality among Colorado uranium miners demonstrated dose-related increases in lung cancer risk in miners with protracted exposure to radon.[1] In addition, small-cell undifferentiated carcinomas predominated in highly exposed miners, in contrast to the typical distribution of pulmonary cancer pathology in the general U.S. population. Elevated risk of lung cancer has also been reported for iron ore miners in England, France, and Sweden; however, the proportion of risk attributable to radon in these populations is more difficult to assess.

Analysis of lung cancer mortality and smoking in Colorado uranium miners suggests a greater than additive mortality rate for cumulative radon exposure and cumulative cigarette smoking.[7] In other words, the increased risk of lung cancer among miners as compared with nonminers is larger when comparing smokers than when comparing nonsmokers. Interestingly, among atomic bomb survivors, cigarette smoking and radiation exposure have only an additive effect for lung cancer risk. This anomaly has been attributed to the different exposure patterns experienced by atomic bomb survivors (acute) and uranium miners (protracted).

Table 9-3 Examples of Radiation-Induced Cancers

Sources of Exposure	Exposure Circumstances	Cancer Types
EXPLOSIONS OF NUCLEAR WEAPONS		
Blast	Atomic bombing survivors in Hiroshima and Nagasaki	Leukemia, breast, lung, thyroid, stomach, colon, multiple myeloma, esophagus, ovary
Fallout	Populations exposed through atmospheric testing, including Marshall Islanders, veterans in the Pacific, general population in Nevada, Utah	Thyroid
DIAGNOSTIC PROCEDURES		
X-rays	Children exposed in utero	Leukemia
Thorotrast	Cerebral and limb angiography; of biliary passages	Liver
Fluoroscopic x-ray	Monitoring of lung infections in patients with tuberculosis	Breast
THERAPEUTIC PROCEDURES		
X-ray	Postpartum mastitis	Breast
X-ray	Ankylosing spondylitis	Leukemia, lung, stomach, esophagus
Cobalt-60	Treatment for cancer of the cervix	Leukemia, stomach, rectum, bladder, vagina, female genital, lung, buccal cavity, nasopharynx, esophagus
X-ray	Treatment of benign head and neck conditions	Thyroid, skin, central nervous system
Radium-224	Ankylosing spondylitis, bone tuberculosis	Bone sarcoma
PROFESSIONAL EXPOSURES		
X-ray	Early radiologists	Skin, leukemia
Radon	Uranium, hard-rock miners	Lung cancer
X-ray, γ-rays, neutrons	Nuclear industry	Multiple myeloma
Radium isotopes	Radium dial painters	Bone, head sarcoma

Adapted from Higginson J, Muir CS, Munoz N: Human Cancer: Epidemiology and Environmental Causes. Cambridge monographs on cancer reseach. Cambridge, Cambridge University Press, 1992.

Metals

Arsenic

Medicinal use of inorganic arsenic was associated with skin cancers in the early 20th century. More recently, excess skin cancer has been observed in populations exposed to arsenic-contaminated drinking water, whereas excess lung cancer has been found in populations with occupational exposure to inorganic arsenic compounds.[1] An increased risk of lung cancer of 6- to 14-fold was reported for gold miners in Rhodesia, where the ore contains arsenic. Chronic arsenism was also prevalent among these miners. Several studies in Japan, Sweden, and the United States have documented excess lung cancers among workers involved in copper smelting. Inorganic arsenic is a byproduct of the smelting process and is also used as a hardener. Two large retrospective studies of copper smelters have shown that lung cancer mortality is related to estimated arsenic exposure.

Another source of occupational exposure is the manufacture and use of arsenical pesticides.[1] An early study of mortality among workers at a factory manufacturing arsenical sheep dip in Wales found an excess of skin and lung cancers, particularly among those directly involved in the chemical processes. Case-control studies in two U.S. plants manufacturing arsenical pesticides found arsenic dose-related increases in risk of lung cancer. Reports of skin and lung cancers among vineyard workers with exposure to arsenic fungicides and pesticides appeared during the late 1950s. An autopsy series of 82 vineyard workers exposed in Germany found 61 deaths from cancer, including 44 respiratory tract cancers; many skin cancers and Bowen's disease were also reported.

Nickel

The nickel refining industry was established in South Wales around 1900. During the subsequent 40 years, evidence accumulated for increased rates of nasal cancer, and later, lung cancer among workers in nickel refineries.[7] Several prospective studies in England and Wales found elevated risks of nasal cancer (O/E = 12) and lung cancer (O/E = 16), particularly among process workers in the refinery. The highest cancer risk was associated with the calcination of impure nickel copper sulfate. Further studies indicated that the cancer risk began to decline when environmental controls were introduced in the industry during the 1930s. Evidence of excess cancer risk associated with nickel exposure as late as the 1950s was reported in a refinery in Norway, however. Excess nasal, laryngeal, and lung cancers were observed; smoking and nickel exposure seemed to contribute to lung cancer risk in an additive manner.

Cadmium

Elevated risk of prostate and lung cancer among workers exposed to cadmium has been reported. Cadmium exposure has a stronger association with lung cancer than with prostate cancer.[7] Several small historical prospective studies of cadmium smelters and battery workers show increased risks of prostate cancer (O/E = 1.2 to 3.5) and lung cancer (O/E = 1.35); however, a larger study of 7000 workers exposed to cadmium for at least 1 year showed no increased risk of prostate cancer. A major nonoccupational source of cadmium exposure is from cigarette smoke, which contains 1 to 2 μg cadmium per pack of cigarettes.

Chromates

Several reports of lung cancer in chromate industry workers appeared in Germany during the 1930s. Subsequent epidemiologic investigations examined this association in workers involved in chromate production, chromate pigment manufacture, and chrome plating.[7] Excess lung cancer was found among workers in three chromate production plants in England (threefold excess) and in a production plant in Baltimore (twofold excess). Exposure to lead and zinc chromate pigments, but not to lead pigment alone, was related to excess lung cancer in a British study. Confirmatory results have been reported for workers exposed to lead and zinc chromates in the Netherlands, West Germany, and Norway. Experimental investigations indicate that the hexavalent salts of chromium are highly carcinogenic, whereas trivalent chromium is not carcinogenic.

Fibers and Dusts

Asbestos

The appearance of lung cancer in asbestosis patients was first reported in the 1930s. Over the next 50 years, many different study complications were recognized and overcome in the process of determining the lung cancer risk associated with the naturally occurring silicate fiber, asbestos.[5] A major problem was exposure assessment, in that many workers were mobile, having variable levels of exposure in a variety of industries or worksites. Furthermore, measurement techniques for asbestos fibers were also variable, making the use of historical measurements suspect. Some studies did not report asbestos type; that is, chrysotile, amosite, anthophyllite, or crocidolite. The long latency period between first exposure and lung cancer also complicates risk estimates. Misdiagnosis of the cancer pathologies specific to asbestos (mesothelioma) is a potential problem, especially in studies that depend on death certificates.

More than 30 epidemiologic studies have been mounted to examine lung cancer risk in workers with potential exposure to asbestos during mining, milling, manufacturing, insulating, and shipbuilding.[1] In general, these studies demonstrate enhanced risk of lung cancer, and possibly enhanced risk of laryngeal cancer. The association between asbestos exposure and mesothelioma of the lung, a relatively rare cancer, was reported in the early 1960s. This finding was confirmed among insulation workers, asbestos manufacturing workers, and other occupationally exposed populations.

Cases of pleural malignancies in Denmark and Germany in the 1930s were reported to be concentrated in seaport towns rather than in other urban areas. Later studies of the geographic distribution of mesothelioma deaths in England and Wales demonstrated a correlation between mesothelioma and areas of high asbestos use related to shipbuilding, gas mask manufacture, or asbestos manufacturing. Further studies led to the conclusion that risk of mesothelioma was not limited to the workers but extended to members of their household and to residents living in the vicinity of asbestos-related industries.

Evidence of a synergistic effect of asbestos and smoking for lung cancer risk was found among insulation workers in New York.[7] The age-standardized mortality ratio for lung cancer was 5.2 for nonsmoking asbestos-exposed workers (compared with nonexposed nonsmokers), 10.8 for nonexposed smokers, and 53.2 for asbestos-exposed smokers. Thus, the risk of lung cancer from both smoking and exposure to asbestos is much greater than the sum of the risks associated with either exposure. A similar result was reported for female workers at a British asbestos factory, but the results for male workers at the same factory could not distinguish between additive or multiplicative effects.

Silica

Exposure to silica dusts occurs in several occupational groups, including foundry workers, pottery workers, miners, and quarry workers. Examination of occupational mortality statistics in high-exposure segments of these industries consistently show an increased risk for lung cancer among silica-exposed workers.[1] Two studies using silicosis registries have shown an association between silicosis and lung cancer. Excess mortality from lung cancer (O/E = 2.8) was found among 3600 men recorded in the Swedish silicosis registry from 1931 to 1969. An excess of lung cancer deaths (O/E = 2.0) was also found among 1910 miners registered with silicosis in Ontario, Canada, from 1940 to 1975. Pottery workers in the United States showed a significant excess of lung cancer among men whose work entailed making ceramic plumbing fixtures.

Wood Dust

The cancer risk associated with wood dust has been investigated in furniture workers, carpenters, woodworkers, lumberjacks, sawmill workers, and paper or pulp mill workers.[7] Excess nasal adenocarcinoma is found consistently among furniture workers in several countries, primarily with exposure in the 1920s and 1930s. The highest risk is seen among those with exposure to hardwood dusts, and after a latent period of 30 years. Small increases in risk of larynx cancer, lung cancer, and Hodgkin's disease have also been reported among persons with these occupations.

DIETARY MODIFIERS OF CARCINOGENESIS: NATURALLY OCCURRING CARCINOGENS AND ANTICARCINOGENS

Most of the known human carcinogens discussed in the foregoing sections have been identified from occupational and iatrogenic exposures; however, with the exception of tobacco, such agents are rather minor contributors to the current overall cancer burden. Exposures to many of these agents have been typically at high doses in small, well-defined cohorts. Most human cancers probably result from interactions of several or more carcinogenic influences, none of which singly is readily detectable. The carcinogenic process is subject to influence by many modifying variables, which in the aggregate probably represent the largest determinant of human cancer. These variables can be constitutive, including age, gender, immunologic status, and genetic composition. Extraconstitutional variables are also very important, particularly diet and lifestyle habits such as smoking and alcohol consumption. Many epidemiologic studies indicate that general increases in consumption of fiber-rich cereals, fruits, and vegetables and decreased consumption of fat-rich foods and excessive alcohol will serve as prudent approaches to reducing overall cancer risk.

Many components in the diet can contribute to carcinogenesis. Two major influences are fat and calorie consumption. Fat consumption is most strongly associated with the hormone-dependent cancers (breast, ovary, and endometrium in females and prostate in males) and the gastrointestinal cancers (gallbladder, colon, and rectum in both sexes). It is not known whether these relationships are causal and, if so, whether they relate to the type of fat (saturated, unsaturated, polyunsaturated) or to the overall caloric content of the diet. Dietary fat intervention studies such as the Women's Health Trial might provide direct information on the effects of reducing dietary fat consumption on the incidences of cancer and other diseases. Decreased fat consumption could exert protective effects through both direct and indirect means. Fats can promote tumor development directly and are also a major source of calories (Box 9-1). Animals fed high-fat diets consistently demonstrated enhanced tumorigenic outcomes. Conversely, it has been recognized for decades that caloric restriction has a very powerful, general inhibitory effect on carcinogenesis in many induced and spontaneous laboratory animal tumor models. The behavioral changes required to effect comparable population-wide reductions in fat and/or calorie consumption, however, pose formidable challenges.

Many minor dietary components act as carcinogens or anticarcinogens.[14] Dozens of natural mutagens and carcinogens derived from plant, fungal, and bacterial sources have been described, which present a significant carcinogenic challenge to humans. These natural carcinogens, however, are opposed by an equally expansive array of food-derived anticarcinogens. These anticarcinogens consist of both nutrient (e.g., vitamins, minerals) and non-nutrient components,

Box 9-1. DO CARCINOGENS IN FRIED AND BROILED MEATS CONTRIBUTE TO RISK OF COLON CANCER?

The risk of colon cancer is strongly associated with consumption of red meat and animal fat. This association has been observed in several international correlative studies and case-control studies. Prospective studies of colon cancer risk demonstrate an association with consumption of red meat and animal fat (but not with vegetable fat), independent of total energy intake.[26] The increased risk associated with animal fat is due primarily to meat intake as opposed to dairy product intake. Other studies have addressed cooking practices, finding that consumption of fried foods and barbecued, broiled, or smoked meats is associated with increased risk of colorectal cancer.

Despite these observations, and despite rapid advances in the molecular genetics of susceptibility and predisposition, the specific chemical etiologies of colon and other diet-associated cancers remain unclear. Several hypotheses have been proposed to explain the strong association of colon cancer risk with red meat and animal fat. Diets high in fat increase the incidence of chemically induced colon cancers in rats and also increase the excretion of primary bile acids, which are converted to secondary bile acids by bacterial metabolism. Some secondary bile acids (e.g., deoxycholic and lithocholic acid) are colon tumor promoters in animal models. Thus, it has been hypothesized that increased animal fat in the human diet leads to promotion of colon tumors by secondary bile acids. An alternative (or complementary) hypothesis is that carcinogens in cooked meats contribute to colon carcinogenesis. The cooking of meat produces at least two major classes of carcinogens—polycyclic aromatic hydrocarbons (PAHs) and heterocyclic aromatic amines—which induce genotoxic damage or cancer in the gastrointestinal tracts of animals receiving these compounds orally.[27] Because cooked meats are a major source of animal fat in Western diets; it has been suggested that cooking-induced carcinogens in meat, rather than animal fat, play a causative role in colon cancer. Estimates of average daily ingestion of PAHs and heterocyclic amines from diet are comparable (0.1–10 μg/day).

Recent studies have explored the role of cooking-induced carcinogens as risk factors for colorectal carcinogenesis by administering food frequency questionnaires with detailed sections on cooking methods and doneness levels. This information is then linked to PAH and heterocyclic amine databases of food items cooked or prepared under a variety of conditions. One such study reported increasing risk for colorectal adenoma with quintile of daily intake of benzo[*a*]pyrene.[28]

In addition to PAHs, highly mutagenic heterocyclic amine compounds are formed during the broiling or frying of meat and fish as a result of pyrolysis of amino acids and proteins. More than a dozen heterocyclic amines have been identified; the most common forms are quinolines, quinoxalines, pyridines, and carbolines.[27] These compounds are highly mutagenic in bacteria and carcinogenic in animals, causing colon cancer, mammary cancer, liver cancer, prostate cancer, and lymphoma. PhIP (2-amino-1-methyl-6-phenylimidazo(4,5-β)pyridine) is one of the most common heterocyclic amines formed in broiled and fried meats, occurring at levels comparable to or greater than those of benzo[*a*]pyrene. Male rats fed PhIP develop colon adenocarcinomas, whereas female rats develop mammary adenocarcinomas. A recent study assessing heterocyclic amine intake in colon cancer cases and controls found an increased risk for colon cancer among those who had the highest quintile of heterocyclic amine intake.[29] The precise role of heterocyclic amine compounds and PAHs in the etiology of human colon cancer, however, requires further confirmation.

many of which function as antioxidants. In addition to scavenging oxidants, many of the non-nutrient anticarcinogens in plants alter the balance between the metabolic activation and inactivation of chemical carcinogens. Inverse epidemiologic associations between risk of cancer at several sites and ingestion of fruits and vegetables have been observed.[15] These associations might be linked to β-carotene, other carotenoids, folate, fiber, vitamin C, and other antioxidants, and to other components of the fruits and vegetables. Although a protective role of specific nutrients has been difficult to establish in many instances, inverse relationships between intake of foods rich in vitamin C and oral, esophageal, and gastric cancer incidence and between β-carotene intake and lung cancer incidence have been described. A fuller understanding of the role of dietary factors in human carcinogenesis is destined to have a significant impact on disease incidence.

EXPOSURE BIOMARKERS AND SUSCEPTIBILITY FACTORS

Assessing Human Exposure: Role for Intermediate Biomarkers

Increased understanding of the mechanistic basis of carcinogenesis provides opportunities for the identification of molecular biologic markers reflecting events occurring between exposure and clinical disease. These molecular biologic markers can be classified into three major categories:

1. Markers of exposure reflecting either an internal or a biologically effective dose of carcinogen
2. Markers of effect indicating a biologic response to an exposure
3. Markers of susceptibility that characterize the inherent susceptibility of an individual to a carcinogenic agent[16]

It is anticipated that the use of biologic markers will help define the roles of environmental agents (particularly in complex mixtures) in the etiology of human cancer.

The interaction of a carcinogen with macromolecules was demonstrated by Miller and Miller in 1947, when they showed that azo dye bound to the liver protein of treated rats. Later studies indicated the importance of carcinogen modification of DNA (either directly or after metabolic activation) in the cancer process. The measurement of carcinogen metabolites, carcinogen-DNA adducts, or carcinogen-protein adducts in human tissues or fluids provide the basis for molecular dosimetry research and the rapidly expanding field of "molecular" cancer epidemiology. The potential advantage of this approach is that more accurate assessments of individual or group dose may be achieved than through estimates of carcinogen exposure in the environment or workplace.

Carcinogen-DNA and carcinogen-protein adducts have been detected in tissues from a variety of human populations with known or suspected carcinogen exposure.[16,17] PAH-DNA adducts are elevated in white blood cells from individuals occupationally exposed to airborne PAHs, including coke oven workers, foundry workers, and aluminum plant workers. Increased levels of PAH-DNA adducts have also been reported in lung tissue from heavy smokers. DNA isolated from exfoliated bladder epithelial cells of cigarette smokers has been shown to contain 4-aminobiphenyl adducts. Alkylation damage has been detected in DNA from esophageal tissue of persons living in regions with documented dietary exposure to nitrosamines. Aflatoxin adducts are found in hepatic DNA following dietary exposure to this mycotoxin. Cisplatin-DNA intrastrand adducts have been measured in white blood cells of patients undergoing cancer chemotherapy.

Carcinogen-DNA adducts excreted in urine provide a noninvasive means for quantifying DNA damage. Urinary concentration of aflatoxin-guanine adducts is strongly correlated with dietary aflatoxin intake. In addition to their use as indicators of previous carcinogen exposure, DNA adducts have the potential for use as direct indicators of future cancer risk. The first prospective test of this application appeared in 1992, when detectable levels of aflatoxin-guanine adducts, as well as several other aflatoxin metabolites, in urine were shown to be predictive of liver cancer development.[11] Furthermore, an interactive effect for liver cancer risk was seen between urinary aflatoxin biomarkers and HBV infection history.

Carcinogen-protein adducts have also proved useful as biomarkers of human exposure. Alkylation damage in hemoglobin has been used as an exposure index in risk assessment analyses of individuals occupationally exposed to ethylene oxide. 4-aminobiphenyl adducts in hemoglobin are highly specific (and sensitive) markers of exposure to cigarette smoke.[16] The level of 4-aminobiphenyl hemoglobin adducts is related to the number of cigarettes smoked, the type of tobacco, and the metabolic phenotype of the smoker. The levels of these adducts drop markedly after smoking cessation.

Unreacted carcinogen metabolites excreted in urine are also used to monitor human exposure to and uptake of carcinogens and related compounds. Concentrations of hydroxylated PAHs (e.g., 1-hydroxypyrene) in urine are elevated in smokers, in patients after topical treatment with coal tar, in road pavers, in coke oven workers, in aluminum plant workers, and in individuals ingesting PAHs from food.[18] In occupational settings, the concentration of urinary 1-hydroxypyrene is highly correlated with estimated or measured concentrations of airborne PAHs. This noninvasive approach to exposure assessment has potential application as a routine biomonitoring tool. In all these studies, significant differences in adduct or metabolite levels are often observed between individuals with similar carcinogen exposure. These differences have been attributed to several factors, including individual biologic variability, exposure misclassification, and confounding variables such as diet, physical activity, smoking, or personal environment. An understanding of the true basis for these differences will be useful in elucidating the determinants of individual susceptibility to cancer. By identifying specific modulators that enhance or inhibit carcinogen metabolism and the formation of adducts, it will be possible to examine their effects on human cancer risk.

Metabolic Polymorphisms and Human Susceptibility

Another major area of research in molecular cancer epidemiology is the study of individual metabolic phenotypes and their roles in determining biomarker levels and human susceptibility to carcinogens.[19] Certain cytochrome P-450 metabolic enzymes are known to be involved in the activation of specific human carcinogens, and some have been linked to increased cancer risk. For example, inducible CYP1A1 activity is higher in cultured lymphocytes from lung cancer cases than in controls. Genetic polymorphisms in the *CYP1A1* structural gene have also been associated with lung cancer risk in Asian populations.

Hepatic arylamine *N*-acetyltransferase correlates with individual differences in susceptibility to human bladder cancer.[19] A series of genetic polymorphisms of this enzyme exist in humans, resulting in slow- and rapid-acetylator phenotypes. The rapid-acetylator phenotype seems to protect aromatic amine-exposed individuals from bladder cancer These results are attributed to the competition of N-acetylation of arylamines against the formation of reactive arylamine metabolites that reach the bladder.

A recent meta-analysis of 22 case-control studies in the general population examined the effect of slow acetylation on risk of bladder cancer.[9] Overall, the slow-acetylation phenotype/genotype was found to increase risk of bladder cancer by about 40% as compared with rapid acetylators (odds ratio of 1.4, with 95% confidence interval of 1.2–1.6). This is the clearest example of a common metabolically modified cancer risk in the general population. The carcinogenic exposure in this case is, presumably, due to aryl amine compounds from various sources, including cigarette smoke.

DNA Repair and Human Susceptibility

An important mechanism that protects the genome from mutagenic effects of carcinogens is the repair of cellular DNA. The importance of this protection is perhaps best illustrated by the unusually severe effects of sunlight on individuals who are deficient in DNA repair.[20] The rare inherited disorder xeroderma pigmentosum (XP) is characterized by various levels of DNA-repair deficiencies. Individuals with XP show an unusually high incidence of multiple skin cancers and rarely live beyond early adulthood in the absence of protective measures against sunlight. The median age of onset for nonmelanoma skin cancers among XP patients is approximately 8 years of age, as compared with about 60 years of age in the general population. In addition, the prevalence of melanoma of the skin is unusually high among XP patients.

Several other inherited diseases show altered cellular response to DNA damage.[21] Ataxia telangiectasia, Bloom syndrome, and Fanconi's anemia are autosomal recessive genetic disorders characterized by chromosomal instability, with patients developing malignancies more frequently and at younger age than occurs in the general population. Approximately 10% of individuals with ataxia telangiectasia develop malignancies, primarily of the lymphoreticular system, before the age of 20. Heterozygous relatives of individuals with ataxia telangiectasia and those with Fanconi's anemia are also at moderately increased risk of cancer as compared with unrelated persons.

Although these diseases clearly represent unusual cases, some forms of these diseases (e.g., complementation group XP-E) show only moderate deficiencies in DNA repair—approximately 60% to 90% of normal—yet remain unusually susceptible to cancer. This finding suggests that small reductions in DNA repair efficiency can lead to considerable increases in cancer susceptibility. Interestingly, significant variability in DNA repair proficiency has been demonstrated among disease-free "normal" individuals. This variability in the general population could contribute to differences in susceptibility not only to skin cancer but also to cancers of other organs.

PUBLIC HEALTH APPROACHES TO CANCER PREVENTION

An aging population and a decline in mortality from cardiovascular disease could soon herald the emergence of cancer as the major cause of death in the United States. Moreover, the curative treatment of many established (and especially disseminated) malignancies remains an enigmatic problem for which progress is measured in small steps. Clearly, the optimal way for dealing with virtually all diseases, including cancer, is prevention. As a consequence, the challenge to public health professionals is to devise and implement preventive measures against cancer.

As presented in Figure 9-2, the prevention of cancer can take several forms. Primary prevention targets healthy individuals and can be achieved by avoiding exposure to risk factors. Another approach is to stimulate the defense mechanisms of the host to interfere with the carcinogenic process. Secondary prevention measures use early detection and intervention before pathologic conditions are clinically apparent. The success of these strategies will be greatly facilitated by the development of noninvasive biomarkers that identify high-risk individuals. Finally, tertiary prevention is aimed at minimizing the effect of existing disease and consequent disability by avoiding development of new cancers and complications or relapses after therapy for initial malignancies.

Identifying Human Carcinogens

The major current strategy for cancer prevention is the avoidance of exposure to environmental, industrial, and social hazards (Box 9-2). Identification of human carcinogens takes two forms. In several instances (e.g., soot and coal tars, aromatic amines, vinyl chloride, and benzene), carcinogenic compounds were discovered after they were suspected of being involved in the development of cancers in humans. However, currently most carcinogenic substances are identified in the course of long-term toxicologic studies in animals. The value of this approach is buttressed by the fact that for those chemicals identified as being causally associated with human cancer, and for which there has been adequate experimental evaluation, all have been shown to cause cancer in laboratory animals.[22] However, animal bioassays for carcinogenicity are very costly (several million dollars per compound) and time consuming (5 years). Therefore, much attention is being directed toward the development and validation of short-term tests for carcinogens. Many assays for genotoxicity using mutagenesis, chromosome damage, or DNA repair as endpoints are used to screen chemicals for carcinogenic potential. Short-term assays for modifying factors such as co-carcinogens, tumor promoters, and anticarcinogens are being developed as well. A major difficulty in the use of animal bioassays is estimation of risk to humans. The assumptions contained in interspecies comparisons and high- to low-dose extrapolations render a straightforward assessment difficult. Bioassays are typically conducted with high doses of carcinogens to provide adequate tumor yields and statistical strength; however, there are strong concerns on mechanistic grounds as to the relevance of these types of exposures to chronic low-dose exposures in human populations. Protective host defense systems could be overwhelmed in these aberrant exposure settings. Another controversial issue in dose-response relationships is whether no-effect or threshold levels exist for chemical carcinogens. Based on considerations of metabolism, the barriers to electrophiles reaching critical targets in DNA, multiple alleles for transforming and/or suppressor genes, DNA repair, and other factors, it seems likely that for every carcinogen there must be a threshold. It could be very low for powerful carcinogens and correspondingly higher for weak carcinogens. Faced with the inability in practice to define human thresholds, however, prudent policy dictates avoidance of carcinogens wherever possible. The current regulatory posture in the United States assumes that all animal carcinogens are potential human carcinogens.

Cancer Chemoprevention

The use of chemical or dietary interventions to alter the susceptibility of humans to the actions of carcinogens and to retard, block, or reverse carcinogenesis can be applied to all levels of prevention and has been termed chemoprevention.[23] There are many indications that these strategies are extremely effective in laboratory animals. Moreover, chemoprevention against cancer also works in humans.[24] Recent investigations have established significant site- and agent-specific effects in the prevention of invasive skin, upper aerodigestive tract, and breast cancers in high-risk groups.

It was first observed in the early part of the 20th century that carcinogenesis could be modified by discrete chemical agents. These initial experiments demonstrated that the formation of skin tumors in rodents could be blocked by local application of chemopreventive agents. The protective agents used in these early studies, however, were typically carcinogens or toxins themselves. Consequently, their application to humans did not appear to be practical. Thus, the field of cancer chemoprevention did not receive significant attention until the early 1970s, when Wattenberg demonstrated that dietary antioxidants could protect against tumor formation.[25] The experimental observations that seemingly innocuous preservatives found in the Western diet could dramatically protect against diverse carcinogens at distal sites sparked the development of chemoprevention as a viable strategy for the reduction of human cancers. Thus far, more than 20 classes of discrete chemicals have been shown to be effective inhibitors of experimental carcinogenesis.[25]

The expectation that effective chemoprotection against cancer can be achieved is supported by the view that cancer is unlikely to be the exception to the history of other major (infectious and noninfectious)

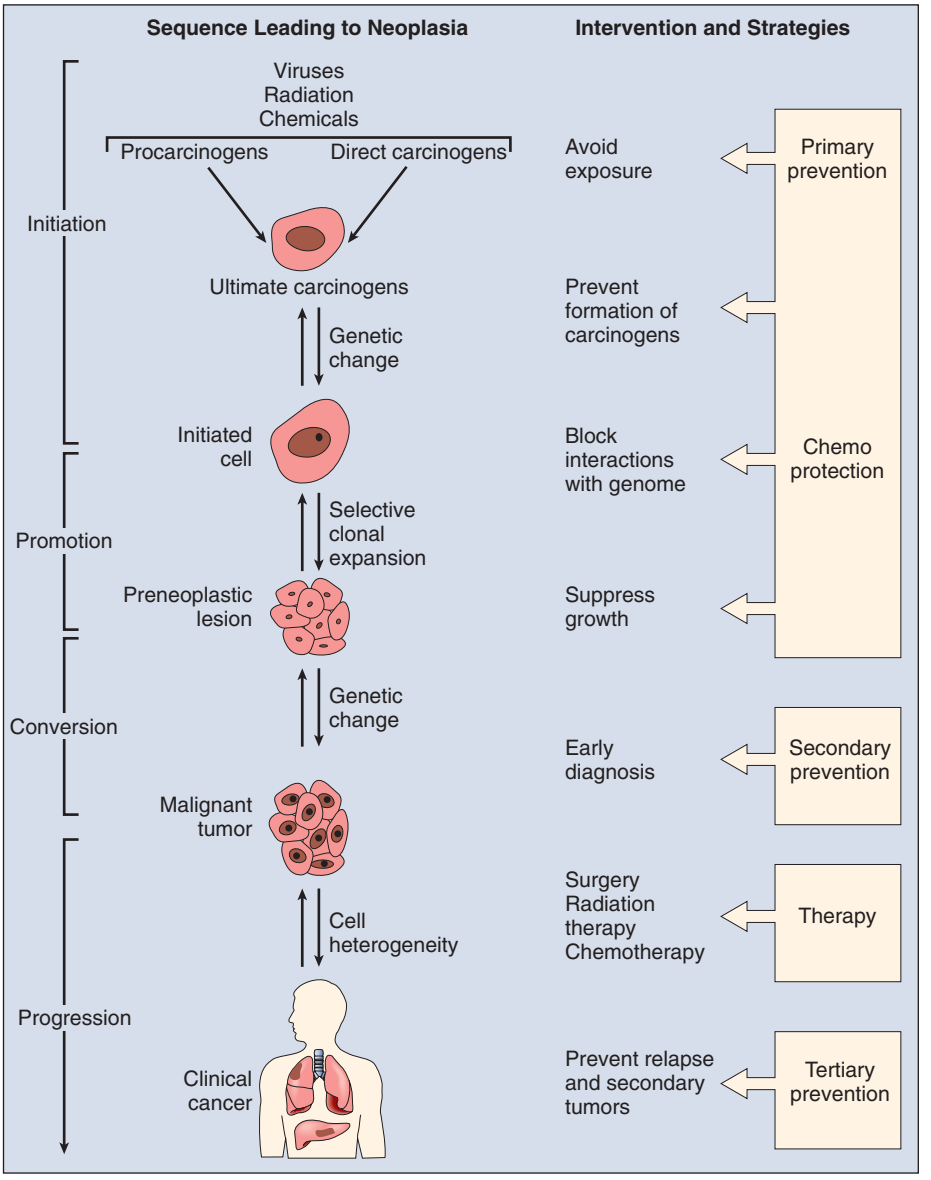


Figure 9-2 • Strategies for prevention of multistage carcinogenesis.

diseases of humans, in which the mortality began to decline as a result of protective and preventive measures far in advance of specific treatments. Cancer chemoprevention could be especially valuable in populations at high risk of certain neoplasms, particularly as improved molecular techniques allow for the identification of these high-risk individuals. Preventive strategies can involve both prescriptive interventions with specific nutrients, non-nutrients, and drugs in selected populations at high risk of cancer, and lifestyle changes that include altered nutrition and social habits. These latter approaches might ultimately play an even greater role in the overall reduction of cancer in the general population.

SUMMARY

The carcinogenic effects of many environmental and occupational agents were first described in humans. These observations were replicated in animal models beginning in the early 20th century. Whereas carcinogenic agents come in many forms, including naturally occurring and manufactured chemicals, radiations, metals, fibers, and viruses, tobacco use is probably the single most important cause of cancer. Nonetheless, the majority of human cancers probably result from interactions of several or more carcinogenic influences, none of which singly is readily detectable. Elucidation of the carcinogenic process has led to the recognition that both extrinsic and intrinsic factors interact to determine overall susceptibility and risk.

The identification of molecular biologic markers of exposure, effect, and susceptibility, reflecting events occurring before clinical disease, will help to further our understanding of human carcinogenesis. It is anticipated that the use of biologic markers will help define the roles of environmental agents (particularly in complex mixtures) in the etiology of human cancers. With the recent characterization of the human genome, much attention has focused on the role of common polymorphisms in carcinogen metabolism or of DNA repair genes and susceptibility to cancer. By identifying specific factors that enhance or inhibit carcinogen metabolism and biomarker formation, it will be possible to examine their effects on human cancer risk.

Primary and secondary approaches to the prevention of cancer will be greatly facilitated by the development of noninvasive biomarkers that identify high-risk individuals. Tertiary prevention might also be enhanced by characterizing cancers with respect to etiology, genetic profile, or metabolic capacity. The use of chemical or dietary

Box 9-2. HEALTH EFFECTS AND CONTROL OF SMOKING

A series of reports from the U.S. Surgeon General since 1964 have argued that cigarette smoking is the most significant source of preventable morbidity and premature mortality in developed countries. An estimated annual excess mortality of 350,000 is attributed to cigarette smoking in the United States. These deaths are the result of coronary heart disease, cancer, and various respiratory diseases.[30] Cancers associated with smoking or smokeless tobacco use include those of the lung, oral cavity, esophagus, pharynx, larynx, and bladder. Weaker associations have been reported for cancers of the pancreas, kidney, stomach, nasopharynx, and cervix.[12] The overall increase in risk of disease among smokers compared with nonsmokers is about tenfold for lung cancer, sixfold for chronic obstructive pulmonary disease, and twofold for myocardial infarction. The combined effect of smoking-related diseases on the average life expectancy of smokers is a reduction of 5 to 8 years.

On a worldwide basis the data are equally disturbing. An estimated 4 to 5 million deaths per year are attributed to tobacco use—the majority of these in developed countries. If current usage trends continue unabated, estimates as high as 10 million deaths due to tobacco use annually could be expected by the year 2030.[30] Most of these deaths (approximately 7 million) are expected to occur in developing countries, where tobacco use is increasing rapidly. Whereas percentage of world tobacco consumption in developing countries was 49% in 1974 through 1976, this figure increased to 61% in 1984 through 1986 and to 70% in the year 2000. Per capita consumption of cigarettes is increasing most rapidly in developing Asian countries. Although the majority of tobacco is produced in developing countries, the declining market in developed countries has refocused the efforts of producers in these countries toward developing countries for continued growth.

The addictive properties of tobacco smoking, due primarily to nicotine, cause both physiologic and psychologic dependence. Withdrawal symptoms can be severe and include irritability, aggressiveness, hostility, depression, difficulty concentrating, and a craving for tobacco. These pharmacologic factors are reinforced by social factors such as peer pressure, emulation of family role models, and cultural influences. Because most smokers begin smoking, and often form lifelong smoking habits, in their teenage years, preventive educational measures should be focused on this age group.

Smoking control measures use various strategies: cessation programs, clinical or community interventions, governmental or private-sector regulations, taxation of tobacco products, and smoking prevention programs. Although the majority of ex-smokers have achieved abstinence without extensive personal assistance from organized cessation programs, other control measures (national health education programs, physician counseling, indoor smoking regulations) and family pressure are important influences contributing to smoking cessation. Smoking prevention programs, particularly in schools, and government taxation have been somewhat effective in reducing the initiation of smoking among children and adolescents in developed countries. These approaches will need to be applied in developing countries to stem the expansion of smoking worldwide.

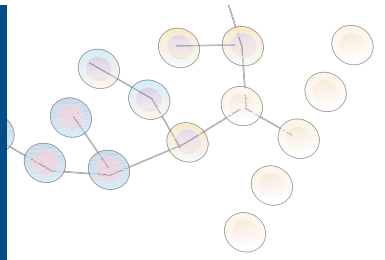
interventions to alter the susceptibility of humans to the actions of carcinogens and to retard, block, or reverse carcinogenesis can be applied to all levels of prevention and has been termed chemoprevention. Preventive strategies can involve both prescriptive interventions with specific nutrients, non-nutrients and drugs in selected populations at high risk of cancer, and lifestyle changes that include altered nutrition and social habits.

The major current strategy for cancer prevention is the avoidance of exposure to environmental, industrial, and social hazards that increase the risk of cancer. Currently, most carcinogenic substances are identified in the course of long-term toxicologic studies in animals. Much attention is also directed toward the development and validation of short-term tests for carcinogens, such as mutagenicity, chromosome damage, or DNA repair.

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10 DNA Damage Response Pathways and Cancer

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SUMMARY OF KEY POINTS

- DNA repair and the cellular response to DNA damage are critical for maintaining genomic stability.
- Defects in DNA repair or the response to DNA damage encountered from endogenous or external sources results in an increased rate of genetic mutations, often leading to the development of cancer.
- Inherited mutations in DNA damage response pathway genes often result in cancer susceptibility.
- The major active pathways for DNA repair in humans are nucleotide excision repair, base excision repair, mismatch DNA repair, translesional DNA synthesis, and homologous recombination or nonhomologous end joining processes for double-strand break repair.
- Defects in nucleotide excision repair lead to the skin cancer-prone syndrome xeroderma pigmentosum, as well as Cockayne syndrome and trichothiodystrophy.
- Defects in base excision repair can result in enhanced colon adenomas and cancers.
- Defects in mismatch repair result in hereditary nonpolyposis colorectal cancer syndrome.
- Defects in DNA double-strand break repair and response pathways underlie a number of cancer-prone disorders, including ataxia-telangiectasia, Nijmegen breakage syndrome, Bloom syndrome, Werner syndrome, Rothmund-Thompson syndrome, and Fanconi anemia.
- The highly cancer-prone Li-Fraumeni syndrome, due to inherited p53 mutations, and breast-ovarian cancer syndrome, due to inherited mutations of the BRCA1 and BRCA2 genes, exhibit defects in multiple DNA repair and DNA damage response pathways.

INTRODUCTION

Cancer is a genetic disease that is caused by the accumulation over time of changes to the normal DNA sequence resulting in alterations, loss, or amplification of genes that are important for normal cellular functions and growth properties, including many proto-oncogenes and tumor suppressor genes. Nearly all cancers are clonal in origin; that is, they originate from a single progenitor cell rather than a group of cells. The development of cancer in a particular cell type or tissue is caused by a series of specific mutations, each of which could be caused by DNA replication errors or unrepaired endogenous or exogenous DNA damage or be the result of inherited mutations. For the most common cancers, multiple genetic events occur in many different genes during the process of carcinogenesis, suggesting that an early and perhaps necessary event in the cancer process is an underlying defect in mechanisms to maintain genomic stability.[1] In fact, alterations in the specific genes that are required for recognizing, processing, and responding to DNA damage may result in an enhanced rate of accumulation of additional mutations, recombinational events, chromosomal abnormalities, and gene amplification.[2]

In addition, cancer cells must be able to tolerate increased amounts of unrepaired DNA damage associated with genomic instability and therefore frequently inactivate DNA damage-inducible signaling and checkpoint pathways. Therefore, DNA repair and the DNA damage response are essential not only for the basic processes of transcription and replication required for cellular survival, but also for maintaining genomic stability and avoiding the development of malignancies. Numerous links have been identified between oncogenesis and acquired or inherited defects in genomic stability that cause a "mutator" phenotype, highlighting the key role of DNA protection systems in tumor prevention. This chapter reviews the major DNA repair mechanisms that are active in mammalian cells and our emerging understanding of DNA damage-signaling pathways that integrate with other cellular processes that regulate transcription, replication, cell division, and apoptosis in response to DNA damage. The relevance of these mechanisms to cancer is explored by focusing on several human cancer predisposition syndromes that are caused by underlying defects in DNA damage processing.

Advances in cancer genetics have defined three general groups of genes that are involved in the development of human cancers: oncogenes, tumor suppressor genes, and DNA damage repair and response genes. The latter set of genes is particularly important to hereditary cancer susceptibility, owing to their direct involvement in maintaining genomic stability. Much of what we know about cancer genes in sporadic tumors comes from the study of relatively rare inherited cancer syndromes caused by mutations passed along in the germline DNA of families and predisposing to the development of cancers, often at a very young age and at a high incidence, in affected carriers. Individuals who inherit a germline mutation in genes that are involved in or required for DNA repair usually are at increased risk for the development of cancer, owing to the enhanced frequency of mutations and increased genomic instability. Susceptibility to cancer may also be affected by environmental factors and multiple low-penetrance modifier genes.

Many converging lines of experimental evidence reveal the complexity of the cellular responses to DNA damage and their role in malignant transformation.[3] A number of interrelated biochemical pathways exist that influence the following actions: (1) the

Table 10-1 Human DNA Repair Pathways

DNA Repair Pathway	Type of DNA Damage	Approximate No. of Genes
Nucleotide excision repair	Bulky or helix-distorting DNA adducts, e.g., ultraviolet photoproducts, carcinogen adducts	37
Base excision repair	Oxidative DNA damage	40
	Spontaneous depurination	
Mismatch repair	Mispaired nucleotides	26
	1–15 nucleotide insertion-deletion loops	
Homologous recombination	Double-strand DNA breaks, DNA cross-links	20
Nonhomologous end joining	Double-strand DNA breaks	10

metabolism of potentially mutagenic or carcinogenic agents, (2) the efficiency and manner by which damaged DNA is recognized and repaired, (3) cell cycle progression and the coordination of DNA replication and cell division relative to the repair of lesions, and (4) the decision point determining survival or the active induction of programmed death of cells that carry different types and amounts of DNA damage. Many cellular pathways have evolved that require hundreds of gene products for the direct repair of DNA damage and involve excision of damaged DNA bases and joining of broken DNA strands (Table 10-1). The central role of DNA damage responses in neoplastic transformation has been highlighted by the discovery that mutations in several classes of genes that are required for DNA repair and the maintenance of genomic integrity result in a predisposition to the development of certain malignancies.[4] In fact, a number of rare inherited disorders have been described that appear to be caused by defects in the repair of DNA lesions (Table 10-2), and many of these are associated with an increased risk of developing certain cancers.[5]

TYPES OF DNA DAMAGE

DNA undergoes several types of spontaneous modifications, and it also can react with many physical and chemical agents, some of which are endogenous products of normal cellular metabolism (e.g., reactive oxygen species) whereas others, including ionizing radiation and ultraviolet light, are threats from the external environment (Fig. 10-1). One pronounced example is exposure to genotoxic compounds in cigarette smoke, which contributes to the development of some of the most common cancers seen in Western countries. Most active chemotherapeutic agents function by damaging DNA through alkylation, cross-linking, and other means, and mechanisms to repair these lesions determine the sensitivity of a tumor to such treatments. Damage to DNA can cause genetic mutations, and these mutations can lead to the development of cancer. DNA damage also may result in cell death, which can have serious consequences for the organism of which the cell is a part, for example, loss of irreplaceable neurons in the brain. Accumulation of damaged DNA is thought to contribute to some of the features of aging. Therefore, it is not surprising that a complex set of cellular surveillance and repair mechanisms has evolved to reverse or limit potentially deleterious DNA damage. Some of these DNA repair systems are so important that life cannot be sustained without them. An increasing number of human hereditary diseases that are characterized by severe developmental problems or a predisposition to cancer have been found to be linked to deficiencies in DNA repair (see Table 10-2).

CONSEQUENCES OF DNA DAMAGE

The results of DNA damage are diverse and frequently adverse. Acute effects arise from disturbed DNA metabolism, triggering cell cycle arrest or cell death. Long-term effects result from irreversible mutations contributing to oncogenesis and inherited genetic disorders. Many lesions block transcription, and this has elicited the development of a dedicated repair system, transcription-coupled repair (TCR), which displaces or removes the stalled RNA polymerase and assures preferential repair of lesions within the transcribed strand of expressed genes.[6–8] Transcriptional stress due to DNA lesions that block RNA polymerase and DNA strand breaks caused by DNA damage or stalled replication forks constitute two major signals for DNA damage-inducible responses, including apoptosis,[9–11] through both p53-dependent and independent mechanisms.[12]

Lesions also may interfere with DNA replication. Recently, a class of at least 10 specialized DNA polymerases was discovered that appear devoted to overcoming damage-induced replication stress.[13–15] These special polymerases take over temporarily from the stalled replicative DNA polymerases. Though translesion polymerases protect the genome, this solution to replication blocks comes at the expense of a higher replicative error rate, and mutations in some of these polymerases cause cancer susceptibility.[5] Therefore, detection of DNA lesions may occur by blocked transcription, replication, or specialized sensors. Although the precise molecular mechanisms by which the cell senses altered DNA remains obscure, such signals result in a complex cellular response that includes cell cycle checkpoints, DNA repair, and apoptosis.

DNA DAMAGE RESPONSE PATHWAYS

DNA damage checkpoints initially were defined as regulatory pathways that control the ability of cells to arrest the cell cycle in response to DNA damage, allowing time for repair.[16] However, in addition to controlling cell cycle arrest, proteins that are involved in these pathways have been shown to control the activation of DNA repair pathways,[3,17–21] the movement of DNA repair proteins to sites of DNA damage,[22–27] and activation of transcriptional responses.[28–30] When damage is too significant or it benefits the tissue or organism as a whole, a cell may opt for the ultimate mode of rescue by initiating its own death via apoptosis.[31–33] As the DNA damage response pathway has been better defined at a molecular level, it has been seen as a network of interacting pathways that together execute the response.[34] Initial recognition of DNA damage occurs by a variety of damage-specific DNA binding proteins that either by themselves or together with complexes of associated proteins that are not directly involved in DNA repair may signal the DNA damage response.[35] Transduction and amplification of the DNA damage signal often is carried out by an overlapping set of conserved protein kinases, including the phosphoinositide-3-kinase-related proteins, which include ataxia-telangiectasia mutated (ATM) and ATM-Rad3-related (ATR) proteins, the checkpoint kinases Chk1 and Chk2, and others.[3,36–41] Many of these protein kinases are themselves targets for phosphorylation and activation; they then further target downstream genes that

Table 10-2 Human Genetic Diseases Involving Defects in DNA Damage Response Pathways

Syndrome	Gene(s)	Biologic Functions	Clinical Features	Hypersensitivities
Xeroderma pigmentosum	XPA–XPG XPV	Nucleotide excision repair Translesional DNA synthesis	Sunlight hypersensitivity Neurologic defects Skin cancers	UV, chemical carcinogens
Cockayne syndrome	CSA, CSB XPB, XPD, XPG	Transcription-coupled repair	Growth retardation Mental retardation Premature aging Sunlight hypersensitivity	UV, chemical carcinogens Reactive oxygen species
Trichothiodystrophy	XPB, XPD, TTDA	Nucleotide excision repair Transcription	Sulfur-deficient brittle hair Dry, scaly skin Mental and physical retardation Sunlight sensitivity	UV
Hereditary nonpolyposis Colorectal cancer (Lynch syndrome)	MLH1, MSH2, MSH6, PMS1, PMS2	Mismatch repair	Colorectal, endometrial, gastric, bile duct cancers	6-Thioguanine and cisplatin resistance
Ataxia telangiectasia	ATM	DNA damage-responsive kinase	Cerebellar ataxia Telangiectasia Immunodeficiency Lymphomas	Ionizing radiation
Ataxia telangiectasia–like disease	MRE11	Double-strand break repair	Similar to AT	
Nijmegen breakage syndrome	NBS1	Double-strand break repair	Microcephaly Immunodeficiency Lymphomas, neuroblastoma Rhabdomyosarcoma	Ionizing radiation
Bloom syndrome	BLM	DNA helicase Homologous recombination at stalled replication forks?	Sunlight hypersensitivity Growth retardation Leukemias, lymphomas Breast and intestinal cancers	UV, hydroxyurea
Werner syndrome	WRN	DNA helicase Homologous recombination? Translesional synthesis?	Premature aging Atherosclerosis Soft tissue sarcomas Melanoma, thyroid cancer	4-NQO, camptothetin Hydroxyurea
Rothmund-Thompson syndrome	RECQL4	DNA helicase	Growth deficiency Sunlight sensitivity Osteogenic sarcomas Squamous cell carcinomas	UV
Fanconi anemia	FANCA—G BRCA2	Interstrand crosslink repair Homologous recombination	Growth retardation Anatomic defects Bone marrow failure Myeloid leukemia Squamous cell cancers	Bifunctional alkylating agents Ionizing radiation
Li-Fraumeni syndrome	p53	Apoptosis Cell cycle checkpoints Nucleotide excision repair	Breast cancer Brain cancers Adrenocortical carcinoma Leukemia Bone and soft tissue sarcomas	?
Li-Fraumeni–like syndrome	Chk2	DNA damage responsive kinase	Similar to Li-Fraumeni syndrome	
Breast-ovarian cancer syndrome	BRCA1 BRCA2	Double-strand break repair Nucleotide excision repair	Breast cancer Ovarian cancer	Ionizing radiation? UV, cisplatin

UV, ultraviolet.

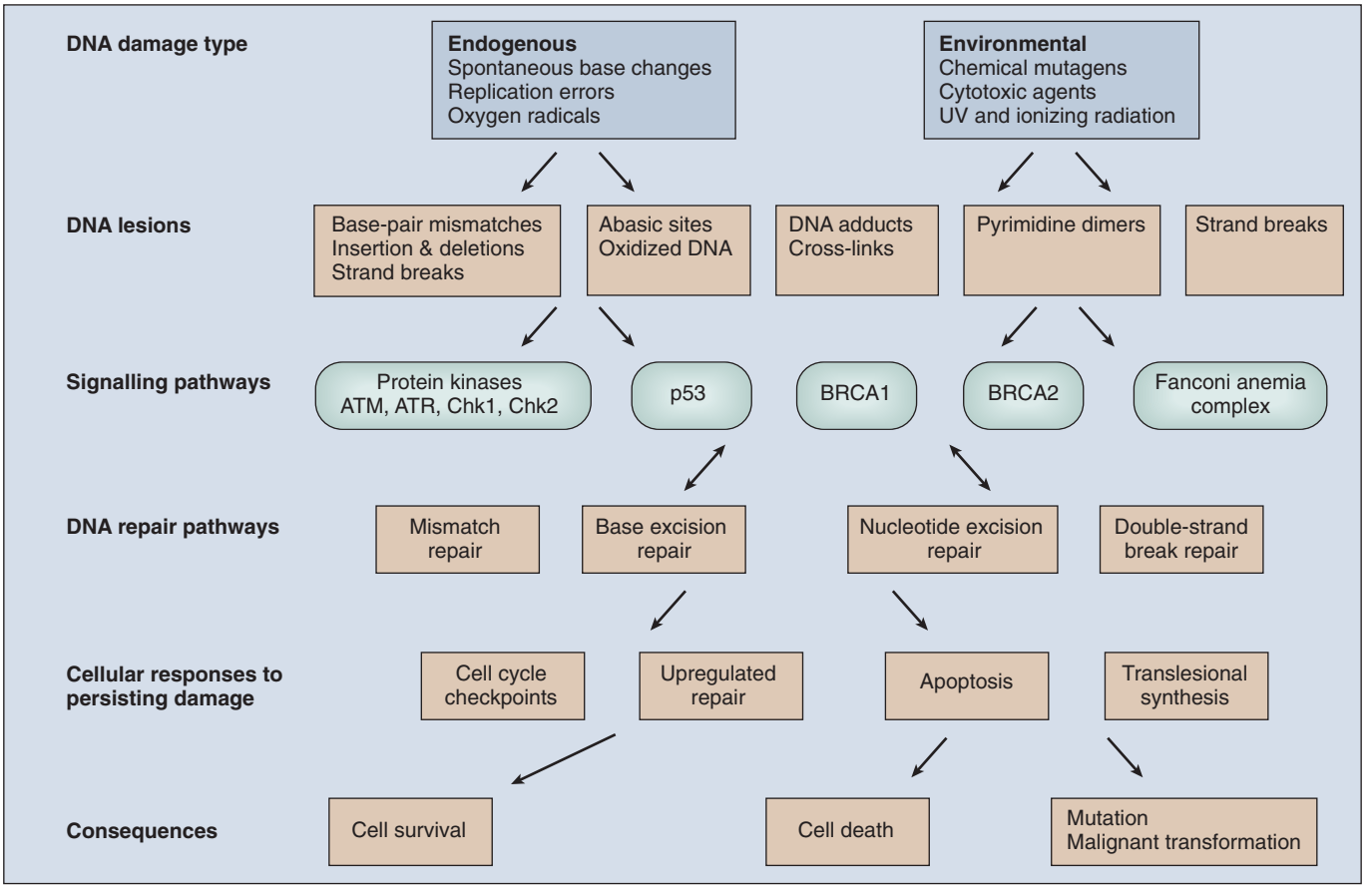


Figure 10-1 • Cellular responses to DNA damage. Different types of DNA damage cause a variety of different types of lesions, and these, in turn, are dealt with by a variety of DNA repair mechanisms and signal various cellular response pathways. The outcome of DNA damage may be cell survival of a normal cell, cell death, or mutagenesis, possibly leading toward malignant transformation.

are critical to oncogenesis such as p53 and BRCA1.[34,36,42–44] The ultimate targets of this highly regulated DNA damage response include mechanisms for DNA repair, and although much of DNA repair is constitutive, a number of regulatory connections between the DNA damage response pathway and DNA repair have emerged.[3] In mammals, a large number of genes that are involved in DNA repair are transcriptionally induced in response to DNA damage, suggesting that many facets of repair are inducible, similar to the RecA-dependent SOS response in bacteria that enhances DNA repair and mutagenesis following DNA damage.[3,21,45] In fact, the p53 tumor suppressor gene is a central mediator of the DNA damage-inducible transcriptional response in humans, and p53 mutant mammalian cells are deficient in several aspects of DNA repair.[17–21,46] Therefore, the mammalian DNA damage-inducible response pathway is highly regulated and fine-tuned to determine whether a particular cell type proceeds to a cell cycle checkpoint and DNA repair or to cell death following a significant damage insult. Defects at any level of these pathways can alter repair and result in carcinogenesis (see Fig. 10-1).

TYPES OF DNA REPAIR AND THEIR CONTRIBUTION TO CANCER

DNA repair may be defined as the cellular responses that are associated with the restoration of the normal nucleotide sequence following events that damage or alter the genome.[47] Given the wide variety of DNA damage that a cell encounters, it is not surprising that a large number of repair systems are available to handle these insults. Indeed, many of the repair systems are broadly overlapping and interacting, several sharing certain strategies and even specific gene products. Much of what is known about the basic mechanisms of many types of DNA repair comes from the study of lower organisms, such as bacteria and yeast, since many aspects of these pathways have been conserved through evolution. Inherited defects in any of the major DNA repair pathways in humans, in general, predisposes to malignancy, and several of these syndromes will be discussed in detail. In humans, a great deal has been learned about DNA repair from the often rare, autosomal recessive hereditary syndromes associated with defects in DNA repair genes.[5]

Nucleotide Excision Repair

The most versatile and ubiquitous mechanisms for DNA repair are those in which the damaged or incorrect part of a DNA strand is excised and then the resulting gap is filled by repair replication using the complementary strand as template. The redundancy of genetic information provided by the duplex DNA structure is essential to the maintenance of the genome by this "cut and patch" mode known as *excision repair*. Each DNA strand can serve as a template for replication-based repair of the other strand. Excision repair was discovered in the early 1960s through basic studies on the effects of ultraviolet (UV) irradiation on DNA synthesis and repair replication in bacteria.[48–50] Nucleotide excision repair (NER) functions to remove many types of lesions, including bulky base adducts of chemical carcinogens, intrastrand cross-links, and UV-induced cyclobutane primidine dimers (CPDs) and 6-4 photoproducts. Such lesions may serve as structural blocks to transcription and replication owing to distortion of the helical conformation of DNA, and they also may result in

mutations if translesional replication occurs or if they are not repaired correctly. The sequential steps for NER are (1) recognition of the damaged site, (2) incision of the damaged DNA strand near the site of the defect, (3) removal of a stretch of the affected strand containing the lesion, (4) repair replication to replace the excised region with a corresponding stretch of normal nucleotides using the complementary strand as a template, and (5) ligation to join the repair patch at its 3′ end to the contiguous parental DNA strand (Fig. 10-2).[51,52] This excision repair pathway can remove DNA damage from sites throughout the genome and is termed *global genomic repair* (GGR). The majority of human NER genes have been identified and cloned, and many have been shown to be mutated in hereditary NER-deficient, cancer-prone diseases.[21,46,53]

A unique problem arises if a bulky lesion is encountered by a translocating RNA polymerase making messenger RNA, before repair enzymes have removed the damage and restored intact DNA. The polymerase may be arrested at the site of the lesion and prevent access to the damage by repair enzymes. Furthermore, the arrest of transcription in human cells is a strong signal for p53 activation and can trigger apoptosis.[12] In this situation, a dedicated excision repair pathway known as *transcription-coupled repair* (TCR) comes to the rescue to displace the RNA polymerase and then efficiently repairs the blocking lesion so that transcription may resume—and so that the cell may survive.[45] The existence of a mechanism to facilitate the preferential repair of the transcribed strand of active genes in both eukaryotes and prokaryotes raises a number of questions as to its evolutionary role. Certainly, strand-specific repair of active genes should be important for maintaining genomic stability in multicellular organisms by helping to avoid transforming mutations in expressed proto-oncogenes and tumor suppressor genes. However, the lack of an increased incidence of malignancy in individuals with Cockayne syndrome (CS), a disease in which TCR has been selectively lost but GGR has been retained, argues against the idea that this NER pathway is critical in the process of transformation. The existence of TCR in unicellular and prokaryotic organisms suggests that its function might be more important to the basic processes of transcription and replication required for cellular survival than for avoidance of transforming mutations. Recent evidence suggests that cells from patients with CS, trichothiodystrophy (TTD), and xeroderma pigmentosum/CS share a defect in repair of oxidative DNA damage that might explain the overlapping progeroid features of these syndromes.[54]

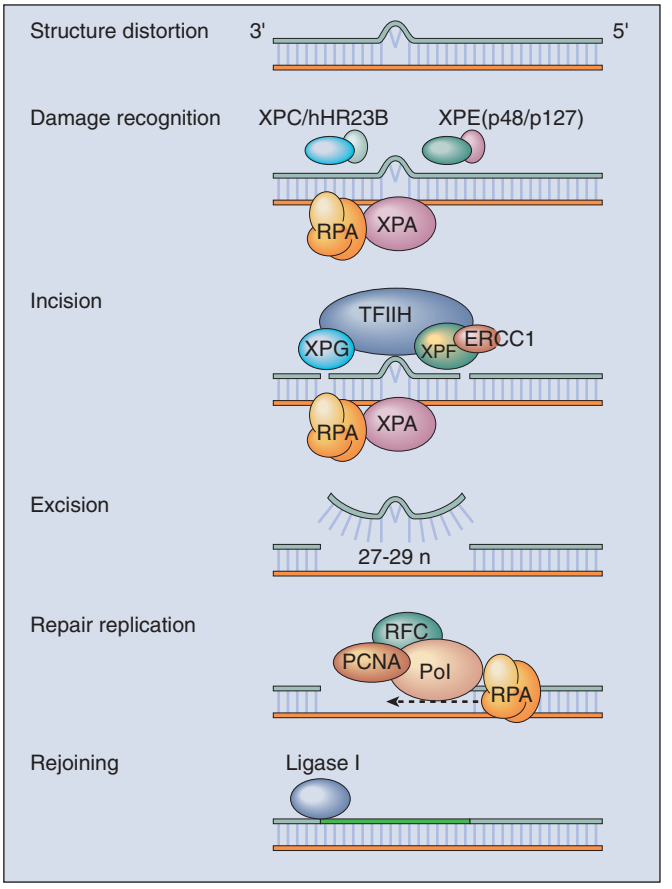


Figure 10-2 • Mechanism for human nucleotide excision repair. Ultraviolet irradiation-induced adducts in genomic DNA are recognized by the XPE and XPC/hHR23B protein heteroduplexes that recruit the XPA/RPA complex and the larger TFIIH protein complex. Dimers that occur in the transcribed strand of an expressed gene result in a blocked RNA polymerase II molecule, which together with the CSA and CSB gene products serves to recruit the downstream repair machinery. The TFIIH complex contains helicases, including XPB and XPD, that unwind the DNA and allow the other repair proteins access for incision and excision of the damaged DNA oligonucleotide. After excision, repair replication based on the normal DNA template and ligation of the newly synthesized DNA sequence occurs. In total, more than 25 proteins participate in NER.

Recently, it has become apparent that the GGR subpathway of NER is damage inducible and highly regulated by both transcriptional and post-translational mechanisms following DNA damage, in concert with damage inducible cell cycle checkpoints and apoptosis.[3,46] In fact, the p53 gene, which is central to maintaining genomic stability in human cells, is required for efficient GGR of UV-light- and carcinogen-induced DNA damage and functions as a DNA damage-activated transcription factor that directly regulates the expression of several NER damage recognition genes.[19–21] Similarly, several other important cancer-related genes have been shown to transcriptionally regulate the DNA damage recognition NER genes XPC and DDB2, including BRCA1 and E2F1.[55,56] Therefore, the GGR pathway of NER appears relevant to suppressing DNA damage-induced malignancy and highly regulated by genes involved in tumor suppression.

Further evidence for the importance of exquisite regulation of DNA damage recognition and repair activity to carcinogenesis come from a new appreciation for the role of the ubiquitin-proteasome system in maintenance of genomic stability.[57] Many complex intracellular signaling processes, including DNA repair, are controlled not only by the regulated expression of proteins, but also by their assembly and targeted degradation through post-translational ubiquitination. With regard to NER, the same DNA damage recognition proteins that are found to be transcriptionally induced following DNA damage (XPC and DDB2) are also rapidly ubiquitinated following DNA damage by an E3 ubiquitin ligase activity that contains the DDB2 binding partner DDB1, resulting in a higher order of regulation.[46] The ubiquitin-proteasome system has been found to regulate other repair pathways as well, including translesional synthesis, and the Fanconi anemia–associated homologous recombination.[57] Therefore, mammalian cells have evolved a proteolytic pathway to limit their repair capability through restricting certain types of DNA repair activities. Considering that most DNA damage recognition complexes identify a variety of DNA damages or metabolic conditions rather than binding to specific DNA sequences, it is plausible that a "checkpoint" mechanism is required to limit DNA damage binding from interfering with other cellular processes involving unconventional DNA structures and that following inducible expression of DNA repair genes, levels are actively reduced to avoid gratuitous DNA repair and associated mutagenesis mediated by error-prone polymerases.

Recently, a class of specialized error-prone DNA polymerases, termed ζ (zeta) to σ (sigma), were discovered that seem to be devoted specifically to overcoming damage-induced replicational stress.[13–15,58] These special polymerases take over temporarily from the stalled

replicative DNA polymerases (δ [delta] and ε [epsilon]). They have more flexible base-pairing properties permitting translesion DNA synthesis, with each polymerase probably designed for a specific category of injury. Though translesion polymerases protect the genome, this solution to replication blocks comes at the expense of a higher error rate. For instance, inherited defects in pol η (eta), encoded for by the XPV/POLH/RAD30 gene, which specializes in relatively error-free bypassing of UV-induced cyclobutane pyrimidine dimers, causes a variant form of the skin cancer–prone disorder xeroderma pigmentosum.[59,60]

Human Nucleotide Excision Repair–Deficient Syndromes and Cancer

A direct correlation between unrepaired DNA damage and carcinogenesis in humans was first established when James Cleaver found that the cancer-prone hereditary disease xeroderma pigmentosum (XP) involved a defect in the repair of DNA lesions produced by UV light.[61] Since then, at least three syndromes have been attributed to inborn errors in NER: XP, CS, and TTD, all characterized by exquisite sun sensitivity.

XP is a rare, autosomal recessive disease in which homozygous individuals display several characteristics: (1) extreme sensitivity of the skin to sun exposure that is evident by 1 year of age, (2) pigmentation abnormalities and premalignant lesions in sun-exposed skin, (3) increases up to 4000-fold in the incidence of skin cancers (predominantly squamous and basal cell carcinomas but also melanomas) and ocular neoplasms, occurring three to five decades earlier than in the general population, and (4) a 10- to 20-fold increased incidence of internal cancers in non-sun-exposed sites.[5,62,63] Overall, the life span is reduced by approximately 30 years among patients with XP, and many die due to malignancies.[64] Approximately 20% of patients with XP also display progressive neurologic degeneration, characterized by peripheral neuropathy, sensorineural deafness, progressive mental retardation, and cerebellar and pyramidal tract involvement.[65] XP occurs worldwide, in all ethnic groups and with a frequency varying from one to ten patients per million.

The biochemical defect in cells from most XP individuals is in NER,[61] though in a small number of cases (termed XP-variants), excision repair appears normal, and a defect exists in bypass replication at unrepaired lesions due to a mutation in the pol η (eta) translesional synthesis gene (XPV).[66] Complementation analysis via fusion of cells from different patients has demonstrated genetic heterogeneity within XP and has provided evidence for the existence of at least seven excision-deficient complementation groups, termed XP-A to XP-G, in addition to XP-variant.[5]

CS is another autosomal recessive disease that is associated with defective TCR of UV-damaged and oxidative-damaged DNA.[67–69] It is characterized by cutaneous photosensitivity, cachectic dwarfism, skeletal abnormalities, retinal degeneration, cataracts, severe mental retardation, and neurologic degeneration characterized by primary demyelination.[65,70] In contrast to patients with XP, those with CS are not at increased risk for developing skin cancers. The average life span of individuals with CS is only 12 years, most patients succumbing to infectious or renal complications rather than cancer.[71] CS is characterized by the existence of at least three complementation groups. Several patients have been described in XP groups B, D, and G who share the DNA repair defects and clinical features of CS together with the cutaneous manifestations of XP.[72,73]

TTD is an autosomal recessive condition that shares many of the signs and symptoms of CS, with the additional hallmark of brittle hair and nails, due to reduced sulfur content in the component proteins. As with CS, XPB and XPD are among the responsible genes that are implicated, but there is a third complementation group, TTD-A, for which no gene has been identified. The favored model for TTD is that of a transcription deficiency with respect to the genes relevant to the phenotype, including sulfur-containing proteins.[74] It is also conceivable that TTD and CS could be diseases of "premature cell death" in which the transcription deficiency and deficiency in TCR could cause the apoptosis of certain classes of metabolically active cells that sustain significant endogenous oxidative damage (e.g., neurons).

Analysis of the specific abnormalities in NER displayed by the various genetic complementation groups of XP, CS, and TTD allow correlations to be drawn with their heterogeneous clinical features. Specifically, only those subgroups of patients who display a defect in GGR are at significantly increased risk for developing UV-induced malignancies. In contrast, the neurologic symptoms and developmental abnormalities that are associated with other complementation groups of XP and CS are found only in the groups that are defective in TCR. The fact that the TFIIH complex, containing the XPB and XPD proteins, is common to both core NER and transcriptional initiation, supports the suggestion that the clinical phenotype of patients with defects in TCR might actually be due to abnormalities in transcription rather than in repair itself.[74]

Although these observations might explain the molecular basis for many of the clinical characteristics of XP and CS, they present an apparent paradox with regard to these patients' cancer risk. Many currently recognized oncogenes and tumor suppressor genes are known to possess important cellular functions and to be actively expressed in normal cells. Because CS cells are defective in the repair of actively expressed genes, it would be reasonable to expect that these patients would acquire mutations in genes leading to transformation more readily than normal patients. However, this is not supported by the clinical picture. It has been demonstrated that defects in TCR specifically activate DNA damage induced apoptosis,[9,10] which may eliminate potentially mutagenic, premalignant cells.

Another puzzling aspect of the clinical phenotype of XP is why these patients do not appear to be at a greater risk for developing neoplasms other than skin cancers. Although a disproportionate number of relatively rare tumors such as brain sarcomas and extraglossal carcinomas of the oral cavity have been described in XP patients under 40 years of age,[62] individuals with XP do not appear to be at significantly increased risk for more common solid or hematologic malignancies. It might be that the early mortality that XP patients experience or a decreased exposure to non-UV environmental carcinogens during early life may partially explain these observations. However, modest alterations in NER activity caused by functional polymorphisms in XP genes may contribute to the risk of solid tumors.[75,76]

Base Excision Repair

A major source of DNA damage to cellular genomes arises from normal metabolism in the cytoplasmic environment through hydrolysis and exposure to reactive metabolites that cause oxidation and alkylation of DNA. The repair system that is primarily involved in identifying and removing such lesions, as well as for dealing with the spontaneous loss of purines from DNA, is the base excision repair (BER) pathway.[77,78] The essential nature of BER for viability is highlighted by the fact that although a number of BER proteins have been discovered, only recently has a single human hereditary disease been identified that appears to result from a mutation in a gene that is unique to this pathway.[79–82] The enormous task that is required for BER is exemplified by the fact that a human being spontaneously loses on the order of a trillion guanines from the DNA in his or her body every hour and each of these must be replaced. Similarly, a large number of cytosines become deaminated spontaneously, and the resulting product, uracil, must be removed and replaced with cytosine to restore the correct nucleotide sequence. In most cases, BER is initiated by one of a set of lesion-specific glycosylases that recognize the altered or inappropriate base and cleaves it from its sugar moiety in the DNA (Fig. 10-3). Different DNA glycosylases remove different kinds of damage, conferring specificity to the process. Once the

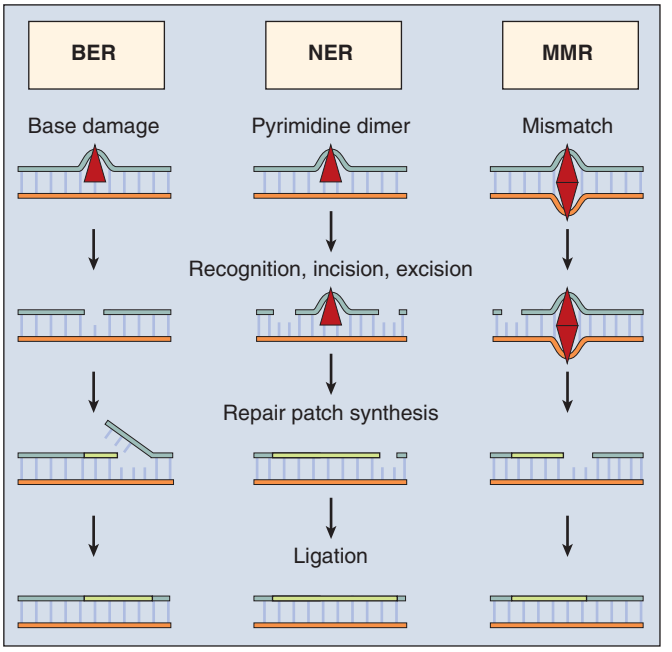


Figure 10-3 • Excision repair pathways for DNA damage. The three main excision repair pathways in human cells—base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR)—proceed through similar steps to restore the normal DNA sequence. Following recognition of altered DNA bases, employing lesion-specific glycosylases for BER, XP proteins for NER, and MutS homologs for MMR, incision of DNA is achieved by endonucleases and displacement or degradation of single-stranded sections of DNA that contain the damage by enzymes with helicase and exonuclease activity. Repair replication of the resulting DNA gap and strand ligation results in the repaired double-stranded DNA molecule. The many repair enzymes that are involved in each specific step are tightly coupled and may be regulated or inducible by DNA damage response pathways.

base is removed, the apurinic/apyrimidinic (AP)-site is removed by an AP-endonuclease or an AP-lyase, which cleave the DNA strand 5′ or 3′ to the AP-site, respectively. The remaining deoxyribose phosphate residue is excised by a phosphodiesterase with the resulting gap filled by a DNA polymerase and the strand sealed by DNA ligase. The major oxidized purine lesion is 8-oxo-7,8-dihydroguanine (8-oxoG), which is abundant and has strong mutagenic properties. Oxidized pyrimidines include thymine glycol, 5-hydroxycytosine, and formamidopyrimidines. Oxidized bases, including both 8-oxoG and thymine glycol, share the property of blocking DNA replication and transcription and must be repaired efficiently to maintain genomic stability.[83,84]

In mammalian cells, the gene functions that are responsible for the strand incision steps of BER include the glycosylases hNTH1, which removes oxidized pyrimidines; hOGG1, which targets oxidized purines; and MYH, which removes adenines mispaired with an 8-oxoG, together with AP endonuclease 1 (APE1).[85] Attempts to engineer mice that are deficient in the core enzymes that are required for BER have typically resulted in early embryonic death, whereas knockout of individual glycosylases produce mice with no overt phenotype at all.[86] This attests to the importance of the repair of DNA lesions from endogenous causes during embryonic development as well as the likely redundancy between individual glycosylases. It is also consistent with the near absence of known human hereditary diseases characterized by defects in BER genes.

However, given the mutagenic and cytotoxic potential of the classes of DNA damage that are BER substrates, it seems likely that altered activity in these pathways would result in enhanced cancer risk. The most direct evidence for a role for BER in cancer comes from the discovery that germline mutations in the MYH gene, involved in processing 8-oxoG lesions, is associated with recessive inheritance of a predisposition to develop multiple colorectal adenomas (polyposis) and colon cancers.[79–81] Tumors from affected individuals exhibit excess transversions of a guanine-cytosine pair to a thymine-adenine pair in the APC gene, itself associated with colon carcinogenesis and causative of familial adenomatous polyposis. Therefore, biallelic inherited mutations in MYH result in a polyposis-like syndrome termed MYH-associated polyposis (MAP). Patients with MAP tend to develop tens to hundreds of polyps by the age of 40, and nearly 50% present with colon cancer.[82] Box 10-1 discusses the affect of genetic variations in other DNA repair genes.

Mismatch Repair

Mismatch repair (MMR) is another example of an excision repair mechanism that utilizes a similar strategy for genomic maintenance (see Fig. 10-3). MMR is a process that corrects mismatched nucleotides in the otherwise complementary paired DNA strands, arising from DNA replication errors and recombination, as well as from some types of base modifications.[94–96] This repair mode also can deal with small loops of single-stranded DNA at sites of insertions or deletions in the duplex DNA structure. The importance of this repair mechanism in maintaining genetic stability is illustrated by the observation that its absence results in a large increase in the frequency of spontaneously occurring mutations, particularly in microsatellite sequences of highly repetitive DNA.[97] Some of these spontaneous mutations arise from mistakes that are introduced during DNA replication, in spite of the operation of a "proofreading" system that also helps to ensure the high fidelity of replication. In humans, genetic defects in several mismatch repair genes have been linked to hereditary nonpolyposis colon cancer (HNPCC) as well as to sporadic cancers that exhibit instability in regions of DNA containing short repetitive sequences of nucleotides, a feature that is known as microsatellite instability (MSI).

As with other modes of excision repair, four principal steps are required for MMR: (1) mismatch recognition, (2) recruitment of additional MMR factors, (3) identification of the newly synthesized DNA strand containing the mismatched nucleotides, followed by their excision, and (4) resynthesis of the excised tract and ligation. The biochemical workings of this pathway are best understood in bacteria, but a similar set of events occurs in human cells. On the basis of functional homologies to their bacterial counterparts and sequence homology to corresponding yeast genes, a number of human genes have been cloned that participate in MMR, including those that are homologous to the bacterial MutS mismatch recognition protein (hMSH2, hMSH3, and hMSH6) and to the bacterial MutL gene (hMLH1 and hPMS2).[98–100] In humans, heterodimers of the MSH2/6 proteins recognize single-base-pair mismatches and short insertion-deletion loops, whereas MSH2/3 dimers recognize longer loops. Heterodimeric complexes of MLH1/PMS2 and MLH1/PMS1 interact with the MSH complexes and replication factors for strand discrimination and DNA excision. Similar to NER and BER, additional proteins are then recruited for repair replication on the basis of the original DNA template.

The MMR system also might interact with DNA damage due to certain alkylators and intercalating agents that assume structural alterations in DNA similar to those of mismatches and might actually result in erroneous or futile MMR cycles, resulting ultimately in apoptosis. Thus, intact MMR might confer chemosensitivity to these chemotherapeutic agents, and MMR-defective tumors may exhibit resistance to certain drugs.[101]

Human Mismatch Repair Deficiency and Cancer

HNPCC, also known as Lynch syndrome, is the most common hereditary colorectal cancer predisposition syndrome.[102,103] HNPCC is an autosomal dominant inherited condition with an incidence of

Box 10-1. GENETIC VARIATION IN DNA REPAIR GENES: IMPLICATIONS FOR CANCER RISK AND PREVENTION

Despite many decades of investigation, the exact cause of most cancers remains unknown, with a few important exceptions (e.g., certain cancers of the lung, skin, and cervix). Rather, cancer is associated with a broad and heterogeneous group of genetic and environmental influences, making the development of schemes for risk assessment and targeted prevention difficult. However, 30 years ago, prior to much of our current understanding of the specific molecular and genetic changes associated with cancer, Dr. Larry Loeb proposed that a common early event in the development of many cancers is the expression of a "mutator phenotype" resulting from functional mutations in genes that normally function to maintain genetic stability.[87] On the basis of calculations of the estimated fidelity of DNA replication and repair in normal human cells and the rarity of spontaneous mutations that occur in normal cells, Loeb noted the statistical unlikelihood that the large number of chromosomal aberrations and genetic mutations that are observed in human malignancies would occur by chance in a single cell. However, he speculated that if a cell exhibited unusual levels of genetic instability due to inherited or acquired mutations in the genes that regulate the processes of DNA replication and repair, the rate of additional mutations occurring in other genes important for carcinogenesis will be dramatically elevated. As is obvious from the many specific examples that are discussed in this chapter, Loeb's prediction has been borne out by many subsequent studies of multistep carcinogenesis and the identification of cancer susceptibility syndromes caused by inherited mutations in DNA repair genes.[88] However, these highly penetrant hereditary cancer syndromes (e.g., HNPCC) caused by inactivating mutations in tumor suppressor or DNA repair genes account for only a fraction of most common types of cancers (usually fewer than 10%). Therefore, an emerging hypothesis is that more common polymorphic genetic variation in DNA repair genes may result in variability in DNA repair capacity between individuals and result in altered cancer susceptibility.[76] Rapid advances in DNA sequencing technologies have allowed for large-scale genetic epidemiology studies to be performed to address this possibility. To date, the results have been rather inconsistent. A meta-analysis of associations between single-nucleotide polymorphisms (SNPs) in base excision repair genes and cancer risk found SNPs in the 8-oxoguanine DNA glycosylase (OGG1), apurinic/apyrimidinic endonuclease (APE1/APEX1) and XRCC genes affected lung cancer risk.[89,90] Several other studies show similar results, though many do not find significant increased relative risk of cancer associated with DNA repair SNPs. This may be due to methodologic limitations, such as study size, false positives, and population heterogeneity, but an important possibility is that a single common sequence variant might not be detectable in population association studies. Rather, a combination of multiple variants in the same gene or genes in common pathways might be more important in carcinogenesis. Sir Walter Bodmer proposed just this by suggesting that multiple rare low-penetrance SNPs might together account for a substantial proportion of inherited cancer susceptibility, and recent results from his work in colon polyps and colon cancer support these ideas.[91,92]

The mutator phenotype theory and individual genetic variation in DNA repair capacity also have major implications for the prevention of cancers. Whole-genome approaches to mapping genetic variation in DNA repair genes, potentially in combination with functional assays for individual DNA repair capacity,[93] might allow for targeted approaches for cancer prevention. Reducing the amount of DNA damage to which normal or premalignant cells are particularly vulnerable could slow the accumulation of additional mutations. Certainly, reducing exposure to known environmental carcinogens is important in this goal, but the majority of DNA damage likely occurs as the result of endogenous reactants of normal cellular metabolism, such as oxygen-reactive species, activated lipids, and metal cations. In fact, it has been estimated that oxidative radicals generate up to 10,000 DNA damage events per cell per day. Therefore, means to reduce the amount of oxidative DNA damage or enhance its repair, might slow the carcinogenic process sufficiently to prevent the clinical occurrence of some cancers. Indeed, evidence from several fields suggests that antioxidants might have chemopreventative properties. For example, epidemiologic evidence suggests that diets that are rich in the common trace element selenium might be associated with reduced cancer risk. However, clinical trials of antioxidant approaches to cancer prevention have not generally been successful. Given the complex genetic pathways that are involved, it is hoped that individualized risk assessment by using genetic approaches will allow for the identification of specific pharmacologic agents for cancer prevention. Certainly, our rapidly increasing understanding of processes for the prevention and repair of DNA damage provides many new targets for rational drug development.

one in 1000 in the general population. It accounts for approximately 5% of all colorectal cancers patients with HNPCC, who are also at elevated risk for cancers of the endometrium, ovary, stomach, small bowel, and other sites. Patients with HNPCC have an 80% lifetime risk for colorectal cancer and a 50% lifetime risk for endometrial cancer. The discovery of MSI, that is, the frequent alteration in the tract lengths of certain short repetitive nucleotide sequences, in some hereditary colorectal cancers provided the first indication that the etiology of these cancers might involve a problem in the MMR system.[104] The finding of germline MMR gene defects in patients with HNPCC established that these defects are the cause of the enhanced incidence of cancer.[98–100] Germline mutations in MLH1 and MSH2 together account for more than half of all cases of HNPCC. Defects in MSH6 cause a late-onset HNPCC phenotype. No strong genotype-phenotype correlations have been observed to date, but mutations in the MSH2 gene do appear to be associated with more extracolonic manifestations than are seen with mutations in the MLH1 gene.

MSI has been identified as a source of the genomic instability driving tumorigenesis in a number of sporadic tumor types in addition to those that arise in the context of inherited germline mutations of MMR genes.[104,105] For example, up to 20% of sporadic colon cancers exhibit MSI, particularly when presenting in the ascending colon and in individuals younger than 50 years old, the majority due to epigenetic silencing of MLH1 gene expression by promoter hypermethylation.[106,107] Whether through genetic or epigenetic inactivation, loss of MMR results in an elevated rate of mutations, particularly at microsatellite sequences, several of which occur in the coding sequences of other genes that are often found mutated in cancers, including TGF beta type II receptor, BAX, and the mismatch repair genes MSH3 and MSH6, themselves. Therefore, clear genetic evidence demonstrates that the phenotype of genetic instability associated with defects in MMR results in the genotype of tumors that arise owing to these defects.[108] Intriguingly, the survival of patients with MSI-associated colorectal cancer is better than those with more typical tumors exhibiting chromosomal instability.[109–111] These tumors also demonstrate different sources of genomic instability, resulting in distinct biologic and pathological characteristics.[112] Whether their more favorable outcome reflects differences in clinical behavior, responsiveness to therapy, or both remains to be fully determined.

Double-Strand Break Repair

Double-strand breaks (DSBs) in DNA that are induced by ionizing radiation, endogenously produced reactive oxygen radicals, chemicals, replication across single-strand breaks, and during repair of interstrand DNA cross-links are dealt with through either the recombination machinery or the relatively error-prone nonhomologous end-joining pathway (Fig. 10-4). An unrepaired DSB is a highly lethal event, and even a single occurrence in the entire genome is thought to be sufficient to signal cell cycle checkpoints that prevent attempted DNA synthesis or cell division until repair has been completed or apoptosis if improperly repaired. DSBs also pose problems during mitosis, because intact chromosomes are a prerequisite for proper chromosome segregation during cell division. Thus, these lesions often induce various sorts of chromosomal aberrations, including aneuploidy, deletions (loss of heterozygosity), and chromosomal translocations, all of which are associated with carcinogenesis. Genetic recombination is the principal mechanism in cycling cells for dealing with DSBs that involve homologous stretches of nucleotides at the ends to be joined. If no such homology is present or if the cell is not cycling, then there is a system for nonhomologous end joining, which is more error-prone.

Recent studies have identified a cascade of protein kinases that are involved in signaling cellular processes in response to DSBs. Many of these have been found to be defective in cancer-prone disorders that exhibit genomic instability, such as the ATM protein,[41] and the Chk2 protein kinase associated with a Li-Fraumeni–like cancer susceptibility syndrome.[113–115] A major target for these kinase activities is the p53 tumor suppressor gene. When activated, this protein is involved in inducing G1 arrest or apoptosis following ionizing radiation and other cellular stresses.[36,37,116–120] Germline mutation of p53 results in the Li-Fraumeni cancer susceptibility syndrome. Many other enzymes that are involved in processes required for effective DSB repair have been found in cancer-prone disorders, including MRE11 (AT-like disorder), NBS1 (Nijmegen breakage syndrome), BRCA1 and BRCA2 (breast-ovarian cancer syndrome), and the RecQ-like helicases (Werner, Bloom and Rothmund Thomson syndromes).[121]

Ataxia Telangiectasia

Ataxia telangiectasia (AT) was first identified as a disorder characterized by progressive neurodegeneration, immune deficiency, and cancer predisposition. A link to DNA damage responses arose when AT patients with lymphomas exhibited severe reactions to radiation therapy that was used to treat their tumors. A single gene, ATM, is responsible for the multiple and surprisingly diverse symptoms of this disease, including the predisposition to lymphoma and leukemia. It has been estimated that over 10% of AT patients develop cancer at an early age. AT is an autosomal recessive disease with an incidence of nearly one in 100,000 live births. Persons who are heterozygous for AT mutations, about 1% of the general population, may have an increased predisposition to cancer, in particular breast cancers, especially in individuals who express an ATM with missense mutations resulting in a dominant-negative effect on their wild-type ATM gene.[122–124] The ATM gene product is a central signaling protein in the DNA damage response, and cells lacking ATM fail to execute many critical cellular responses to DNA damage. For example, one hallmark of AT is what has been termed X-ray resistant DNA synthesis. It is now know that the ATM gene product is a key element in delaying the initiation of DNA replication following DNA damage resulting in strand breaks.

ATM is a protein kinase that is activated by introduction of DSBs into the genome and phosphorylates numerous substrates involved

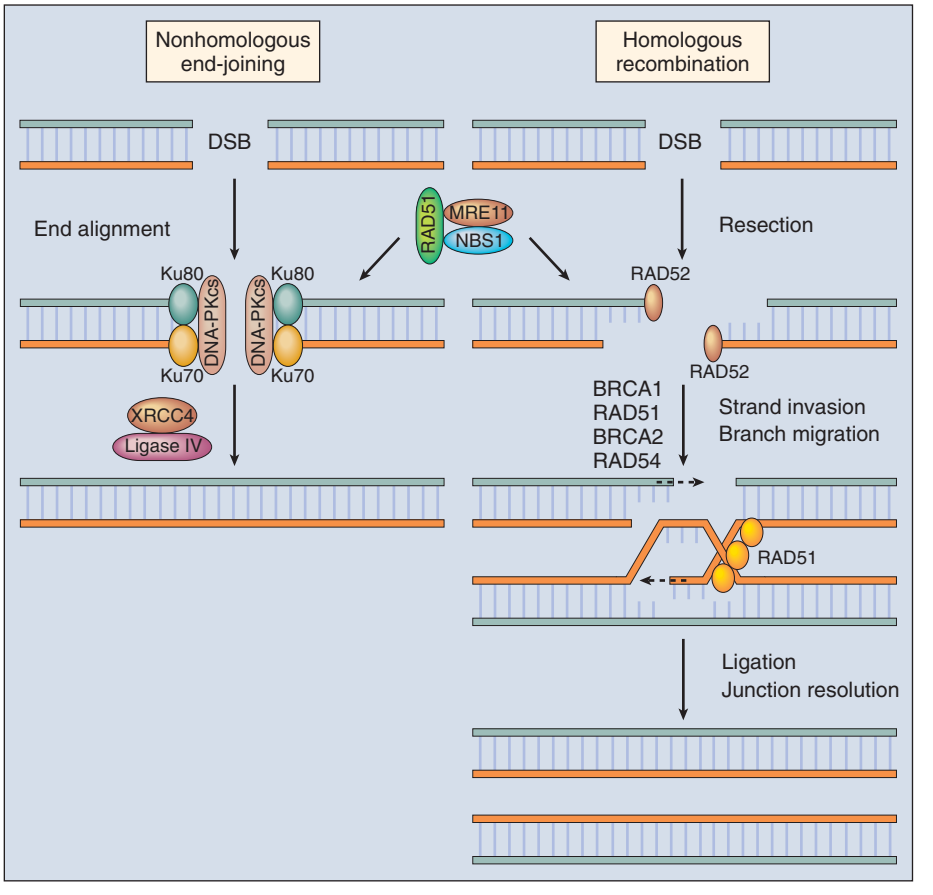


Figure 10-4 • Mechanisms for DNA double-strand break repair. The repair of DNA DSBs is carried out by two mechanisms. *Left,* The rapid, but error-prone, nonhomologous end-joining that directly seals breaks but may result in the gain or loss of several nucleotides due to short areas of microhomologies used for annealing prior to ligation. Exposed DNA ends are recognized by the Ku70/80 heterodimer that recruits the DNA-dependent protein kinase catalytic subunit and other proteins assisting in strand alignment. The XRCC4-ligase IV heteroduplex joins the breaks. *Right,* The high-fidelity, homologous recombination of sister chromatids at sites of DSBs is the less prominent mode in mammalian cells. This DNA repair pathway is mediated by RAD51-associated proteins, including RAD52 that recognizes single-strand DNA ends and together with other proteins results in short nuclease-mediated resection. RAD51 then forms a nucleoprotein filament on the exposed strand and, probably with BRCA2 and other proteins, promotes strand invasion and displacement at homologous sequences. Thus, the undamaged sister molecule acts as a template for the resynthesis of the missing nucleotides.

in controlling cellular responses to DNA damage, including p53, BRCA1, and CHK2.[34] In addition, ATM directly phosphorylates the NBS1 protein, which exists in a complex with the MRE11 and RAD50 proteins, a complex that is required both for nonhomologous end-joining and homologous recombination of DSBs.[125] Inherited germline mutations of the NBS1 and MRE11 genes, themselves, result in clinical variants of AT, termed *Nijmegen breakage syndrome* and *AT-like disorder,* respectively.[126,127] In fact, it has recently been shown that cells from patients with NBS have defective ATR-dependent signaling and appear phenotypically similar to ATR-defective Seckel syndrome.[127] Therefore, ATM is central to a DNA damage response pathway that is critical for regulating cellular responses to stress, including recombination and repair following DSBs. Defects in many of the component proteins in the pathway result in genomic instability and a predisposition to cancer.

OTHER CANCER-PRONE DISORDERS ASSOCIATED WITH GENOMIC INSTABILITY

Diseases Involving Homologs of *recQ*

There are at least three cancer-prone diseases in humans in which the defect is in a homolog of the *recQ* gene that was originally discovered in bacteria.[128] The product of *recQ* is a helicase, which in *E. coli* is involved in processing the nascent DNA at arrested replication forks. Helicases are enzymes that separate the complementary strands of nuclei-acid duplexes using energy that is derived from ATP hydrolysis. In humans, recQ helicases are thought to function at the interface between DNA replication and recombination in dealing with damaged replication forks and interact with many other nuclear proteins that are required for DNA metabolism.[129] The biologic and clinical effects of the homozygous deficiency of these genes can be quite dramatic and profound. Bloom syndrome, a disorder that is caused by homozygous loss of the BLM helicase, is characterized by an extremely high frequency of genetic exchanges (so-called sister chromatid exchanges) that cause genomic instability and lymphoma, leukemias, and solid tumors of the GI tract and breast.[130,131] Of interest, recent studies have identified an increased risk that individuals who are heterozygous for a BLM mutation will develop colorectal cancer, potentially due to haploinsufficiency.[132,133] Werner syndrome results from a deficiency in another *recQ* homolog, WRN, and has features of profound premature aging as well as predisposition to sarcomas, melanoma, and cancer of the thyroid.[134–136] Yet another *recQ* homolog defect, Rothmund-Thompson syndrome, is characterized by growth deficiency and cancer predisposition, in particular to osteogenic sarcomas.[137,138]

p53 Gene and Li-Fraumeni Syndrome

The discovery of the p53 tumor suppressor gene over 25 years ago inspired widespread investigations with the aim of understanding the basic biology behind its role in maintaining genomic stability and the cellular response to DNA damage. p53 is one of the most commonly mutated genes in human cancers[139] and its product is a multifunctional protein that regulates many physiologic processes, including cell cycle checkpoints, apoptosis, and DNA repair.[21,116,117,140,141] The primary role of p53 in tumor suppression has been attributed to its function as a transcription factor, regulating expression of several hundred different cellular genes,[142] although it appears to exhibit transcription-independent activities as well. Indeed, p53 appears to act as a central "node" that lies at the intersection of upstream signaling cascades induced by DNA damage and cellular stress responses and downstream DNA repair and DNA damage response pathways. In response to a variety of genotoxic stimuli, p53 protein is induced and stabilized.[34,143] This activated p53 protein binds to DNA in a sequence-specific manner and regulates the transcription of downstream target genes that contain a consensus p53 response element in their promoter or intronic segments. These p53 target genes include those that are important for cell cycle checkpoints, such as p21;[144] apoptosis, such as BAX and PERP;[145] and DNA repair, such as the DDB2 and XPC genes that are required for NER.[19–21,46] In addition, some evidence suggests that p53 protein might act in a transcription-independent manner to modulate BER through interactions with DNA polymerase beta and OGG1, and homologous recombination in conjunction with *recQ* proteins.[141]

Patients with the rare autosomal dominant Li-Fraumeni syndrome (LFS) are at increased risk for developing a number of common tumors at an early age due to an inherited germline defect in one allele of the p53 gene, including soft-tissue and osteosarcomas, breast cancer, brain tumors, lymphomas, leukemia, and adrenocortical carcinomas. Mutations in the p53 tumor suppressor gene account for 70% to 85% of classic LFS cases.[146–148] Although the heterozygote carriers of a defective p53 allele do not appear to have clinical problems or DNA repair defects, when the second allele has been mutated or lost, the absence of functional p53 results in severe problems for the cell. First of all, the p53-controlled pathway of apoptosis is disengaged, so severely damaged cells will survive and be at risk for carcinogenic transformation because of their genomic instability. That genomic instability derives from the fact that p53 is also an important regulator of cell cycle checkpoints. Thus, as with the situation in AT, the cells continue to progress through their growth cycle rather than pausing to allow time for DNA lesions to be repaired. Loss of p53 also leads to increased aneuploidy of cells, further contributing to genetic instability and the progression to malignancy or metastasis. Finally, p53 serves an important regulatory function in NER and perhaps in BER and recombination, and in its absence, some important mutagenic lesions are simply not repaired. That, of course, is a major contributor to the genomic instability and the consequent development of tumors. See Box 10-2 for a discussion of DNA repair and cancer treatment.

BRCA1, BRCA2, and Breast-Ovarian Cancer Susceptibility

Hereditary breast cancer includes a broad group of hereditary predisposition conditions in which breast cancer is a component tumor; these account for approximately 5% to 10% of all breast cancer cases. Hereditary syndromes of breast and ovarian cancer susceptibility have been particularly associated with germline mutations of two genes, BRCA1 and BRCA2, as well as rare cases due to mutations in the p53 gene in LFS, the PTEN gene in Cowden disease, and perhaps the ATR gene, Chk2 gene, and others. Recent experimental data suggest that both the BRCA genes might be involved in multiple DNA repair activities.[21,55,149,150,157–159]

The BRCA1 and BRCA2 genes are large and complex. Many hundreds of different germline mutations have been detected in each, but only rare sporadic breast or ovarian cancers have been found to harbor BRCA1 mutations. The exact biochemical functions of these proteins remain unknown, but increasing evidence suggests that they might be involved in various aspects of DNA repair and DNA damage response pathways. For example, BRCA1 is phosphorylated after exposure to DNA-damaging agents by ATM, ATR, and Chk2 and associates with a number of DNA repair proteins including MSH2, MSH6, ATM, RAD51; and the RAD50-MRE11-NBS1 protein complex following DNA damage and localizes to nuclear foci with these proteins after treatment with ionizing radiation and UV radiation.[24,160,161] The association of BRCA1 with RAD51, an enzyme that is involved in the coordination of recombination, suggests its involvement in DSB repair, and strong data exist that implicate BRCA1 in homologous recombination.[149,162] Other studies suggest that BRCA1 might regulate cellular processes through transcriptional coactivation. BRCA1 has been shown to transcriptionally regulate the NER genes XPC and DDB2 and affect GGR of UV and cisplatin-induced DNA damage.[55,150,163] Chromosomal instability also is

Box 10-2. DNA REPAIR AND CANCER TREATMENT

As was discussed in this chapter, many genes that are implicated in the development of cancer play roles in DNA repair. The mechanism of action for most cancer chemotherapeutic drugs, as well as radiation therapy, is thought to be through DNA damage. Therefore, it seems logical that cancers that acquired defects in DNA repair during the tumorigenic process would also be particularly susceptible to the cytotoxic effects of DNA-damaging therapeutic agents. However, for most common cancers, the clinical experience suggests otherwise. It is likely that the frequently concurrent inactivation of cell cycle checkpoints and apoptotic processes during tumorigenesis obscures the effect of DNA repair defects; therefore, the response of clinical tumors to various treatments remains very difficult to predict, even with genetic information. Nevertheless, several examples have emerged in which a detailed understanding of the DNA repair defects that are present in a particular tumor type might allow for the rational selection of certain treatment approaches that are likely to be more effective.

One example relates to the function of the BRCA1 gene, which is involved in several types of DNA repair, including double-strand break repair, nucleotide excision repair, and DNA cross-link repair.[46,149,150] Germline mutations in the BRCA1 gene predispose individuals to a very high risk for developing breast and ovarian cancers, and somatic inactivation of BRCA1 activity has also been observed in sporadic breast and ovarian cancers due to promoter methylation. Clinical and experimental data suggest that breast and ovarian tumors that are deficient in BRCA1 function are particularly sensitive to the chemotherapeutic drug cisplatin, which causes DNA damage to be repaired through the nucleotide excision and cross-link repair pathways, and ionizing radiation, which causes double-strand DNA breaks.[150] Another very exciting recent finding relates to the selective activity of PARP-1 inhibitors in tumors that are deficient for BRCA1/2.[151,152] PARP-1 is the first described member of a large family of enzymes that can detect and bind to DNA nicks and strand breaks and is thought to play a key role in base excision repair.[153] Chemical inhibitors of PARP activity are thought to enhance killing of cells defective in double-strand break repair through synthetic lethality. The success of this approach in preclinical models has led to the rapid development of clinical trials of PARP inhibitors in breast cancers in women with known BRCA1/2 mutations, as well as in "triple-negative" breast cancers (ER/PR/Her-2 negative) that share phenotypic activity with BRCA1/2 mutant tumors.[154,155]

A quite different example relates to the 15% to 20% of colorectal cancers that have inactivated the mismatch repair pathway and exhibit microsatellite instability (MSI). It has been appreciated for some time that individuals with colorectal cancer who express high levels of MSI have longer survival than do stage-matched patients with colorectal cancer without MSI.[109] However, whether these prognostic differences related to differences in tumor biology or sensitivity to chemotherapy was unclear. Recently, though, clinical studies suggest that patients with surgically resected stage II or III MSI-positive colorectal cancer do not benefit from 5-fluorouracil based adjuvant chemotherapy, as do patients with mismatch repair–intact colorectal cancers but nevertheless have better outcomes even without additional therapy. Experiments with mismatch repair–defective colon cancer cell lines suggest that they are also resistant to the cytotoxic effects of oxaliplatin (in fact, an intact mismatch repair pathway may be necessary to confer the apoptotic effects of platinum-induced DNA damage) but susceptible to the topoisomerase I inhibitor, CPT-11.[156] Since both these drugs are now being used for the treatment of colorectal cancer, concurrent diagnostic testing of tumors for MSI and mismatch repair activity may help guide their selection and use in individual patients. These examples and others suggest that our rapidly improving knowledge of the role of specific cancer genes in DNA repair pathways may significantly impact the treatment of human cancers. Efforts to obtain genotypic and phenotypic information from individual tumors will hopefully allow for tailored, rational selection of therapies for cancer treatment, an approach that is central to the emerging field of pharmacogenomics.

characteristic of breast tumors that harbor BRCA2 mutations, probably owing to defective recombination-mediated DSB repair. BRCA2 has been shown to bind to the RAD51 protein, an enzyme that is involved in the coordination of recombination, and together they colocalize to nuclear sites that contain DNA strand breaks caused by ionizing radiation. Structural studies of BRCA2 DNA-binding domains suggest that it might facilitate interactions of RAD51 with single-stranded DNA during recombination.[164,165] The genomic instability that is associated with mutations of BRCA1 and 2 therefore might be due in part to the intact but error-prone nonhomologous end-joining repair pathway.[158]

MDC1 is another important regulator of ATM-dependent phosphorylation of BRCA1 and is required to activate Chk2 as part of the response of mammalian cells to DNA damage.[149] Therefore, a hypothesis is that BRCA1 lies at a critical intersection of the DSB response pathways. Post-translational regulation of BRCA1 by phosphorylation has established a link between BRCA1 and Chk2, BRCA2, ATR, and ATM and suggests mechanisms that promote genomic instability and increased susceptibility to cancer when mutant.

Fanconi Anemia, Cancer, and Interstrand Cross-Link Repair

The centrality and interwoven nature of DNA repair pathways for genomic stability have been highlighted by findings regarding Fanconi anemia, a rare, autosomal recessive disease that confers an increased risk of acute myeloid leukemia, squamous cell carcinomas of the head and neck and esophagus, gynecologic carcinomas, and liver tumors at a young age.[166,167] At least 13 subtypes of Fanconi anemia have been determined by complementation analyses, and germline mutations in genes have been identified for most of them.[168,169] The proteins that are encoded by these Fanconi anemia genes all cooperate in a common DNA repair pathway that is involved in interstrand cross-link repair. Germline homozygous inactivating mutations of the BRCA2 gene result in the D1 group.[170] Eight of these proteins are subunits of a nuclear E3 ligase, required for the monoubiquitination of the downstream D2 protein, which itself links Fanconi anemia proteins to BRCA1 in the response to DNA damage by colocalizing to nuclear sites occupied by RAD51 and BRCA2.[171] This process also is regulated by the ATM protein kinase, which phosphorylates FANCD2 in response to DNA damage.[172] It has long been appreciated that cells from Fanconi anemia patients are hypersensitive to DNA cross-linking agents, such as mitomycin C and cisplatin, in addition to being modestly sensitive to ionizing radiation. Although DNA cross-link repair in mammalian cells is poorly understood, it has been proposed that it utilizes components of both the excision repair and DSB repair systems to sequentially incise DNA near the site of a cross-link followed by homologous recombination or nonhomologous end-joining.[167] Therefore, the Fanconi anemia proteins appear to function at an interface between several DNA repair and DNA damage response pathways.

CONCLUSIONS AND FUTURE DIRECTIONS

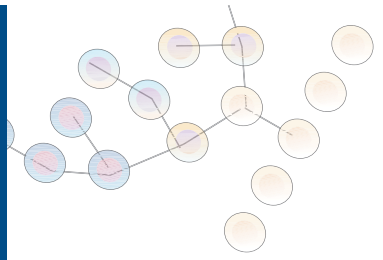
Recent molecular biology and genetic research has provided ample evidence to support the long-standing prediction that genomic instability is a major factor driving the onset and progression of carcinogenesis.[88] Overlapping and interacting mechanisms for DNA repair and the cellular response to DNA damage are critical components for the maintenance of genomic stability. Alterations in these pathways often are early events in the multistep acquisition of genetic mutations that lead to cancer development. Continued exploration of the DNA damage response will prove important for our improved understanding of cancer etiology, prevention, genetic susceptibility, diagnosis, and treatment.

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11 Viruses and Human Cancer

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SUMMARY OF KEY POINTS

- The last 35 years have revealed the existence of human tumor viruses.
- Human tumor viruses contribute to at least 15% of all human cancers.
- The study of tumor viruses led to the discovery of cellular oncogenes and tumor suppressor genes, which are key contributors to cancers regardless of the etiology.
- Virally induced tumors can be eradicated by the development of prophylactic viral vaccines, or other public health measures for preventing transmission.

INTRODUCTION

Viruses cause cancers in people. Today, approximately 15% of all human cancers are thought to have a viral etiology,[1] and this fraction is likely to grow as we investigate additional cancers for a potential viral cause and identify new human viruses. Identifying a human cancer as having a viral etiology has substantive consequences both for its treatment and for its prevention. The known virally caused human cancers often express virally encoded products in the tumor cells. These viral products are potential targets for antiviral, tumor-specific therapies. Viral infections can be prevented by vaccines; therefore, it might be possible to eliminate those human cancers that require viral contributions for their development.

HUMAN TUMOR VIRUSES

The search for human tumor viruses has been propelled by a long appreciation that viruses can cause cancers in birds and rodents. Viruses were isolated as filterable extracts from avian tumors in the first decade of the twentieth century and were shown to induce tumors in susceptible animals.[2,3] Parallel findings were made in mice in the 1940s.[4] These animal tumor viruses were in the retrovirus family and led researchers to look for retroviruses as human tumor viruses in the 1960s and 1970s. However, most of the human tumor viruses that were subsequently identified are in different virus families and do not conform to some of the expectations that have been derived from the study of highly oncogenic animal retroviruses. For example, highly oncogenic tumor viruses induce tumors in animals rapidly. The inoculation of Rous sarcoma virus into the wing web of newborn chicks can induce fatal sarcomas within 2 weeks in 100% of susceptible animals.[5] In addition, highly oncogenic tumor viruses are oncogenic because they have acquired and express potent derivatives of cellular proto-oncogenes. In fact, many of the known human proto-oncogenes were first identified as homologs of the oncogenes that are transduced by the highly oncogenic animal retroviruses.[6] Known human tumor viruses, however, usually do not induce cancers rapidly; often, 15 to 50 years will elapse between the primary infection and tumor development. Nor do human tumor viruses express cellularly derived oncogenes; rather, some of them have evolved to inhibit cellular tumor suppressor genes. These differences between highly oncogenic animal viruses and human tumor viruses probably have contributed to the reticence in our recognizing that viruses do cause cancers in people.

A second obstacle in our recognizing that viruses can be tumorigenic in their human host is that we lack convincing animal models in which to test these viruses directly. For all practical purposes, all known human tumor viruses infect only people. In addition, we now know that human viruses that are found not to be tumorigenic in people are tumorigenic when experimentally introduced into test animals. For example, human adenovirus 12, which causes only respiratory infections in people, is highly oncogenic when inoculated into newborn hamsters.[7] The lack of an experimentally tractable animal host for human tumor viruses has required multiple lines of evidence to affirm that a given virus can contribute to a given human cancer. In particular, epidemiologic findings have been combined with genetic and molecular analyses in cell culture to identify human tumor viruses. Experiments with mice that are transgenic for viral genes have also supported these identifications.

Here, we shall introduce the six known human tumor viruses, the tumors with which they are associated, data that support these associations, and models to explain the viral contributions to these tumors. These viruses will be presented in the order of their discovery; early findings have often provided insights for analyses of subsequently identified viruses. Finally, we shall outline the kinds of virus-specific therapies that it might be possible to develop and the likelihood of developing vaccines to human tumor viruses in order to limit or eliminate specific human cancers.

Epstein-Barr Virus

Epstein-Barr Virus (EBV) was identified through the insight and advocacy of Dennis Burkitt, who, as a young surgeon, having identified Burkitt's lymphoma as a new disease entity, analyzed the geographic and climatic distribution of this childhood lymphoma, determined that it overlapped with that of malaria, and posited it to have an infectious etiology.[8] At his urging and with his proffered biopsy samples, Tony Epstein and his colleagues identified EBV in Burkitt's lymphoma–derived cells.[9] To do so, they developed the expertise to propagate these cells in culture.[10] Cell lines derived from EBV-positive Burkitt's lymphomas proved to be powerful tools to

associate EBV with different human diseases. Different EBV-positive cell lines express different viral antigens and thereby have served as test samples for patients' expressing antibodies to EBV-encoded antigens.

The analyses of these antibodies by serology led the Henles in Philadelphia to propose EBV as the cause of infectious mononucleosis.[11,12] A colleague in their laboratory who had lacked antibodies to EBV-encoded antigens developed those antibodies on presenting with infectious mononucleosis. The etiologic role for EBV in this "self-limiting lymphoproliferation" was subsequently established by careful, prospective epidemiologic studies in which serology was used to demonstrate that only immunologically naive people were at risk of developing infectious mononucleosis; on doing so, they would express antibodies first to EBV-encoded antigens of the IgM class and only later to those of the IgG class.[13] Thus, about 85% of infectious mononucleosis cases were shown to arise from a primary infection with EBV. Serologic studies also allowed the Henles to propose that nasopharyngeal carcinoma (NPC) might be caused by EBV because NPC patients were characterized by having atypically high titers to EBV-associated antigens.[14] However, the data that linked EBV causally to Burkitt's' lymphoma and NPC by the early 1970s was only "guilt by association." While EBV caused most infectious mononucleosis on primary infection, serology had also demonstrated that children in the parts of Africa in which Burkitt's lymphoma is endemic and adults in the parts of China in which NPC is prevalent had all been infected with EBV, that is, were "EBV-seropositive," long before they developed these cancers.

The serologic analyses of EBV in the 1960s and 1970s illustrate a conundrum for viruses and human cancers: "How can many people be infected with a given virus, and yet how can that virus contribute to tumor development in only a few infected subjects after long periods of time?" This apparent paradox applies, in fact, to most cancers associated with human tumor viruses and explains a major reluctance to consider viruses as etiologic agents for human cancers. The World Health Organization, without resolving this conundrum, sponsored a prospective epidemiologic survey in Uganda to assay 42,000 youngsters serologically for evidence for or against EBV's contributing causally to Burkitt's lymphoma. The region that was studied had a high incidence of this cancer. Children were bled, their serum was stored, and those who were later identified as developing Burkitt's lymphoma were bled again, and their titers to EBV-antigens were determined. This prospective survey found 14 youngsters who developed Burkitt's lymphoma over the 5 years they were followed, and those who did develop the lymphoma had, prior to tumor development, on average a 3.4-fold higher titer of antibodies to one class of EBV-antigens than did the children who did not develop the lymphoma.[15] That is, for children in the portions of the world in which EBV-associated Burkitt's lymphoma is endemic, a high titer of antibodies to a given set of EBV-encoded antigens represents a 30-fold risk factor for developing Burkitt's lymphoma.[15]

Do these findings prove that EBV causes Burkitt's lymphoma? No, they do not; proof in such cases for which direct experiments are not feasible ultimately comes from the accretion of supporting findings in the absence of confounding data. The World Health Organization study did, however, make it unlikely that EBV is a passenger virus that merely replicates well in tumor cells, because the antibody titers were elevated 7 to 54 months before tumor detection.[15] Similar prospective surveys were carried out in China and identified antibodies of the IgA class to the same set of EBV antigens as a risk factor for developing NPC.[16]

The association of EBV with Burkitt's lymphoma and NPC and the demonstration that EBV causes the bulk of infectious mononucleosis have led researchers to consider other diseases with which EBV might be associated. During the last 20 years, EBV has also been linked to post-transplant lymphoproliferation disease (PTLD),[17] oral hairy leukoplakia,[18] approximately one third to one half of Hodgkin's disease,[19,20] and one tenth of gastric carcinomas.[21] These linkages have been made not only through serology, but also by molecular genetic analyses that render the linkages more robust. The latter analyses have been made possible by the elucidation of the molecular virology of EBV in cell culture.[22]

EBV is a herpesvirus; it has a double-stranded DNA of 165,000 to 170,000 base pairs[23] and encodes approximately 80 genes[24] (Fig. 11-1). Like other herpesviruses, EBV has two distinct phases to its life cycle. It can infect cells, express a small subset of its genes (see Fig. 11-1), and cohabit with the cell without killing it. This is its "latent" phase. EBV can also emerge from its latency, express all or most of its genes, amplify its DNA, assemble progeny virions, and kill its host cell by lysis. This is its "lytic" phase. Unlike neurotropic herpesviruses such as herpes simplex virus type 1 and varicella zoster virus, EBV in its latent phase need not be maintained in a nonproliferating host cell. Rather, it has the capacity to both initiate and maintain proliferation in at least the B-lymphocytes that it infects in cell culture and at early stages of primary infection in vivo.[25,26] It is EBV's ability to affect proliferation and survival of its infected host cell that likely renders it oncogenic.

EBV induces and maintains infected B-lymphocytes to proliferate by maintaining its DNA extrachromosomally and expressing at least five viral genes that regulate expression of both viral and cellular genes and control viral DNA replication.[27] EBV-infected cells that contain intact viral DNA and express two or more viral genes are hallmarks of all EBV-associated diseases. The identification of viral DNA and of viral gene products, our gradual appreciation of the functions of these viral gene products, and the immune responses to them now constitute much of the persuasive evidence linking EBV causally to its associated cancers.

EBV clearly can induce and maintain proliferation of infected B cells. Genetic experiments in which two viral genes, *EBNA2* and *LMP1* (see Fig. 11-1), within the context of the virus are expressed conditionally demonstrate that each gene product when assayed alone needs to function for infected B cells to continue to proliferate.[28,29] These observations are particularly telling because they help to explain the multistep evolution of Burkitt's lymphoma. Many other genetic analyses have shown that three additional viral genes—*EBNA1, EBNA3a,* and *EBNA3c* (see Fig. 11-1)—contribute to some facet of cell proliferation.[27] *EBNA1* has recently been found to be required for survival of infected cells and, at least indirectly, to be required to maintain cell proliferation as well.[30] *EBNA3a* acts at the stage of initiation of proliferation.[31] All of these viral "transforming" genes except for *EBNA1* are recognized by the host's cytotoxic T-cell response.[32] *EBNA1* encodes a stretch of gly-gly-ala residues that inhibits its proteolytic degradation and subsequent presentation by class I HLA molecules.[33] The host's cytotoxic response is sufficiently robust that patients recovering from infectious mononucleosis lack B cells that express RNAs encoding these transforming genes. The surviving EBV-infected B cells are in distinct, differentiated states in which they no longer proliferate and detectably express only another viral protein, *LMP2* (see Fig. 11-1), a viral gene product that is not required for cellular proliferation.[34,35]

The failure of this robust immune response to EBV's transforming proteins contributes to PTLD. The infected proliferating B cells in these immunosuppressed patients express all five of EBV's transforming proteins.[6] Two kinds of successful treatments for PTLD demonstrate the critical role of the patient's immune response in failing to limit this "iatrogenic" tumor. First, if immunosuppression can be reduced for the patient such that the transplant is still tolerated, PTLD may regress. Second, several groups have amplified the donor's T cells that are cytotoxic for EBV's transforming proteins prior to bone marrow transplantation. Treatment of PTLD patients with these syngenic, specific T-killer cells has cured the disease.[36] These encouraging findings underscore the important role of the immune response in limiting the survival of EBV-infected cells.

Two startling features of tumor cells that have been freshly isolated from Burkitt's lymphoma biopsies help to explain the evolution

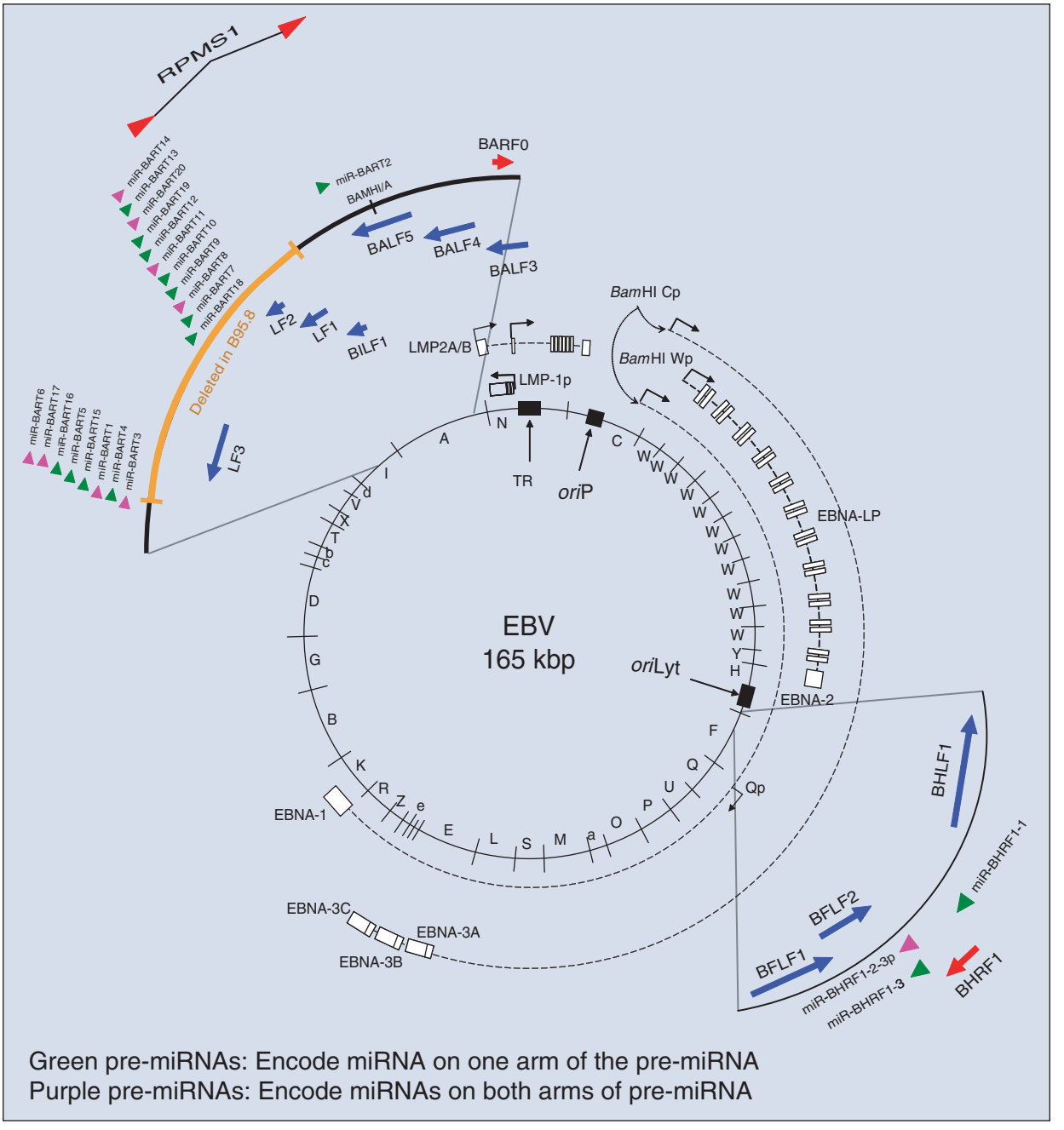


Figure 11-1 • Map of the EBV genome. The genome of the B95-8 strain of EBV in its circular double-stranded DNA form of 165 kbp is depicted as it is found in latently infected B cells. The genome is a linear DNA within the viral particle and is circularized on infection at its terminal repeat (TR) elements found at the ends of the linear molecule. The segments of the circle denoted with *letters* represent the fragments of the DNA generated by cleavage with the BamHI enzyme and used to map EBV's open reading frames. The EBV genome encodes approximately 100 genes. Shown as *boxes* are the exons for coding segments of those viral genes that are expressed in B cells infected in vitro, including *EBNA1, EBNA2, EBNA3A/B/C, EBNA-LP, LMP1,* and *LMP2A/B.* The boxes denoted EBERS are the two small RNAs that are encoded by EBV. *Dashed lines* represent primary transcripts originating from viral promoters denoted with a lowercase p. Also shown are the positions of the origins of replication, OriP and OriLyt, that support the latent and lytic replication of the viral genome, respectively. The *expanded arcs* represent the two regions of EBV DNA found recently to encode miRNAs (miRNAs derived from the BHRF1 and the BART transcripts). Many of these miRNA genes are deleted in the B95-8 strain.

of this tumor when considered in the context of EBV's transforming genes and the immune response to them. These tumor cells express only *EBNA1* among the required viral transforming proteins, yet they proliferate.[37] They also display a chromosomal translocation between one of three human immunoglobulin loci and the c-myc proto-oncogene.[38,39] The juxtaposition of an immunoglobulin locus to c-myc drives expression of the proto-oncogene in these B cells, as it does in murine plasmacytomas that display similar translocations.[40] These observations can be arranged to provide a satisfying, though necessarily speculative, model for the genesis of Burkitt's lymphoma. First, EBV infects young children living in regions of central Africa in which malaria is endemic.[41] The malaria is a T-cell

immunosuppressive that decreases the children's ability to limit proliferation of infected cells.[42] Youngsters with severe infections do have increased antibody titers to viral antigens but have more proliferating B cells and are at increased risk for the chromosomal translocations, fostered by the recombination mechanism, that occur in B cells and use signals at immunoglobulin loci.[43] A rare immunoglobulin/c-myc translocation provides the cell constitutive proliferative signals that can substitute for those provided by EBV's *LMP1, EBNA2, EBNA3a,* and *EBNA3c.* A developmental switch occurs in a cell such that these four viral transforming genes are not transcribed, *EBNA1* is transcribed from a different promoter, and the cell continues to proliferate but can no longer be recognized by the host's residual cytotoxic T-cell response. The cell proliferates, acquires additional mutations (often mutations inactivating *p53*), and evolves rapidly into a Burkitt's lymphoma.[44] This model fits well with what we know today. However, each of the cancers with which EBV is causally associated is sufficiently idiosyncratic to make it impractical to extend this model beyond Burkitt's lymphoma.

All of EBV-associated cancers do contain EBV DNA and express *EBNA1* and EBERs (see Fig. 11-1), which are small viral RNAs, and some also express *LMP1.*[45] We know less about the genesis of these other tumors, but recent findings with NPC provide evidence for an unexpected contribution of EBV to its etiology. Huang and colleagues have shown that EBV infects cells that already can be distinguished as being "preneoplastic" in the evolution of NPC.[46] This finding might lead one to think that EBV is merely a passenger in this tumor. However, 100% of NPC tumors are infected with EBV, making it likely that the virus contributes some selective advantage to infected, preneoplastic cells such that they are the ones that evolve into tumors. It is not known what this selective advantage is, but it is reasonable to hypothesize that EBV could provide these cells proliferative or survival signals, as it does to Burkitt's lymphoma cells during their evolution.

Two additional cancers associated with EBV differ dramatically from Burkitt's lymphoma, NPC, and PTLD in their viral association. Whereas effectively all cases of Burkitt's lymphoma in Africa, all of NPC, and all of PTLD are EBV-positive, only approximately 30% to 50% of cases of Hodgkin's disease and 10% of cases of gastric carcinoma are EBV-positive.[20,47] This lack of a general association makes it difficult to demonstrate a causal role for EBV in the fraction of tumors that are virus-positive. However, in the cases that are EBV-positive, it has been claimed that all of the tumor cells have been infected. This finding depends on single-cell assays to detect viral gene products such as the EBERs and the *LMP1* protein in the tumor cells. Such assays are not 100% efficient, nor is the identification of tumor cells perfect, so it is accurate to conclude only that the bulk of the tumor cells are infected. Were we to know that all of the tumor cells in a given patient are EBV-positive, then we could conclude that viral infection was an early event in the evolution of that tumor. The retention of this extrachromosomal genome would favor the virus's contributing a selective advantage to the evolving tumor cell such that the rare infected cell outgrew any uninfected, precancerous siblings. Any contributions of EBV to virus-positive Hodgkin's disease and gastric carcinoma are therefore uncertain. The strongest evidence for there being some viral contribution is the recognition that EBV does contribute to the other cancers for which most or all cases are EBV-positive.

The many clinical and basic scientific studies of EBV and its associated cancers can be extracted to yield some lessons for tumor viruses in general. First, the viral genomic nucleic acid remains in tumor cells and expresses one or more viral genes. Second, the virus contributes information to infected cells, which provides them a selective advantage in evolving towards tumor cells. However, this information is not sufficient for tumor formation. Additional, multiple rare events must occur in the infected cells for them to evolve into tumors. These additional essential events explain both why only a fraction of the people who become infected with a given tumor virus develop the associated tumors and why they usually do so only after long delays.

Hepatitis B Virus

Hepatitis B virus (HBV) was identified by virtue of its being recognized as an antigen in sera of donors by antibodies in sera of other infected donors.[48] Thoughtful analyses by Blumberg and his colleagues correlated the presence of the antigen with hepatitis, a correlation that was strengthened by the seroconversion of a lab member who contracted hepatitis.[48] By the late 1960s, blood that was donated to blood banks was screened for the antigen, positive samples were removed, and only negative samples were used for transfusions. This early insightful intervention led to a significant reduction in transfusion-associated hepatitis.[49] Blumberg and his colleagues also demonstrated a striking association between HBV, antibodies to its antigens, and hepatocellular carcinoma (HCC).[48] These early findings have been built on to demonstrate that HBV does cause HCC, which is either the fifth or sixth most common cancer in people today. HBV is estimated to cause between 50% and 70% of the approximately 500,000 new cases of HCC in the world each year.[50,51] Most of the rest of these cases are attributable to hepatitis C virus (HCV), a member of the flavivirus family.

Two kinds of data have established HBV's causal role in HCC. A prospective survey of 22,707 male civil servants in Taiwan was initiated at the end of 1975.[52] Of these subjects, 3454 were found to be positive for HBV's surface antigen (HBsAg), indicating that they were chronically infected with HBV. The whole group of 22,707 members was observed on average for 8.9 years. By the end of 1986, 152 of the 3454 HBsAg-positive men had developed HCC, while only 9 of the 19,253 HBsAg-negative men had developed it. The relative risk of the HBsAg-positive cohort for developing HCC was therefore 100 times greater than that for the negative group.[53] This prospective epidemiologic study provides robust data that the presence of HBV is strongly associated with the development of HCC.

The second kind of data demonstrating that HBV can cause HCC has been derived by removing HBV from a population and determining whether the incidence of HCC declines in the population. Taiwan began vaccinating children in 1984, first with a plasma-derived antigen and eventually with a recombinant antigen. Between 1984 and 1994, the incidence of infection as monitored by the presence of HBsAg dropped from 9.8% to 1.3% among children 12 years or younger.[54]

Similar findings have been made in the Gambia, where children who are vaccinated during their first year develop into only 10% as many chronically infected 9-year-olds as do unvaccinated children.[55] HCC is a cancer that peaks in people between 50 and 60 years of age but does occur rarely in children from 6 to 14 years of age. The incidence of HCC in this latter population in Taiwan dropped from 0.64 per 100,000 per year when averaged from 1981 to 1990 to 0.36 per 100,000 per year when averaged between 1990 and 1994 and is statistically significant ($P < 0.01$).[56] This decline presumably reflects the eightfold reduction of chronic HBV infection in children who are at risk for developing HCC. The finding that removing a virus from a population decreases an associated cancer in that population is compelling evidence that the virus contributes causally to the cancer. We can expect that a decline of HCC in the vaccinated adult population will be more striking in decades to come.

Although it is clear that HBV causes HCC in people, it is not clear how it does so. Researchers now invoke two distinct contributions, direct or indirect, to explain HBV's oncogenesis. HBV encodes one gene, pX (Fig. 11-2), that can affect viral and cellular transcription and has been proposed to contribute directly to oncogenesis. HCC in general evolves in patients who have marked liver cirrhosis. HBV can contribute to that cirrhosis by providing targets for T-cell killing and thereby could contribute indirectly to oncogenesis. The

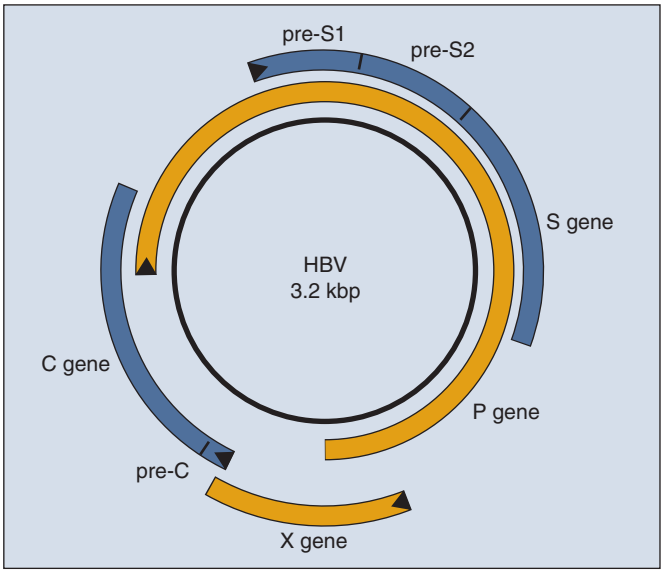


Figure 11-2 • Map of the HBV genome. The 3200-bp genome of HBV is a circular double-stranded DNA in infected cells *(black)*. The genome in the viral particle is partially double-stranded DNA because of an incomplete extension of the plus-strand by the viral DNA polymerase, P. Shown as *colored boxes* are the coding segments for the structural *(blue)* and nonstructural *(yellow)* viral genes. The arrowheads represent the sites at which translation of the viral proteins initiates. These viral proteins are translated from multiple mRNAs: one for Pre-S1, Pre-S2, and S; one for Pre-S2 and S; one for core and P; and one for x. See Ganem and Schneider[280] for details of HBV's genome and life cycle.

molecular virology of HBV has illuminated the viral life cycle but has yet to identify its mode of oncogenesis.[57] HBV is a small, enveloped virus with a double-stranded DNA genome, one strand of which is incomplete. The complete viral duplex DNA is 3.2 kbp in length (see Fig. 11-2), serves as a template for transcription by RNA polymerase II, and is replicated via reverse transcription of a greater than full-length RNA transcript of approximately 3.4 kbp. All members of the hepadnavirus family preferentially infect hepatocytes. This tropism is apparently mediated by a cellular receptor that is expressed in hepatocytes and by viral transcription being controlled in part by cellular transcription factors principally expressed in hepatocytes. Unlike most DNA viruses, HBV undergoes its complete life cycle to yield progeny virions, which exit from hepatocytes via secretory pathways, without killing the host cell. This anomalous behavior of hepadnaviruses means that in the absence of an exogenous function of the host, an infected hepatocyte could survive, carry out its normal functions, and release large amounts of infectious HBV for long periods of time. Accordingly, some chronically infected people do have large amounts of HBV in their sera.

Mammalian hepadnaviruses encode pX, which is not found in the avian species; only the mammalian members are known to cause HCC in their hosts. This correlation has focused interest on pX as being likely to contribute to the oncogenesis of mammalian hepadnaviruses. It is difficult to gauge pX's potential role in HBV's oncogenesis; however, much information about it is in the literature, yet no ready synthesis of this information explains such a role. Most HCC tumor biopsies retain viral sequences encoding pX,[58] but few express the protein detectably.[59] It has been proposed that pX associates with *p53* and inhibits its activation of apoptosis[60]; however, pX is not detected in HCC biopsies,[59] and between 30% and 90% of such biopsies have mutations in *p53*.[58,59] The viral protein pX in studies in cell culture can bind one subunit of RNA polymerase II as well as TFIIB.[61,62] It also associates with Smad4, an integral member of the TGF-β signaling pathway, to foster this pathway's signaling.[63] How these different transcriptional activities of pX might contribute to the evolution of HCC is unclear.

HBV is often integrated in HCC tumors,[64] and it has been proposed that integration of the viral DNA could affect transcription of nearby cellular genes. This suggestion has been strengthened by the recognition that the woodchuck member of the hepadnavirus family does contribute to HCC via insertional mutagenesis.[65] However, HBV has not been found to integrate at sites that can be interpreted to affect its oncogenesis. In addition, HBV DNAs cloned from HCC biopsies have been tested and found not to score as enhancer sequences in hepatoma cells in culture.[66]

The hypothesis that HBV contributes to the development of HCC indirectly by inducing rounds of cirrhosis and subsequent liver regeneration is appealing. HBV infection can be acute or chronic; it appears that acute infection correlates with a robust cytotoxic T-cell response to all viral antigens, while chronic infection correlates with a weak T-cell response.[67] These cytotoxic responses do lead to death of hepatocytes; however, experiments in mice that are transgenic for HBV genes and in infected chimpanzees indicate that there is also a potent noncytotoxic mechanism for limiting viral expression in infected hepatocytes.[68,69] In these experiments, immune cells release γ-interferon, which by some means inhibits viral gene expression and promotes loss of viral DNA from infected cells.[68,69] The administration of IL-18 limits viral replication efficiently in a transgenic mouse model by inducing production of both type 1 and type 2 interferons.[70] Chronic, not acute, infection correlates with the eventual development of HCC. How these two modes of eliminating infected cells would be balanced to yield long-term or chronic infection, the resulting cirrhosis, and the concomitant hepatocellular regeneration required for the accumulation of mutations predisposing to HCC is not known.

A role for cytotoxic T cells in the evolution of HCC has been modeled in mice that are transgenic for HBV surface proteins (see Fig. 11-2). These mice are tolerant to these viral antigens, but when the mice are reconstituted with syngeneic, nontransgenic bone marrow and subsequently challenged with syngeneic, immune, nontransgenic splenocytes, they develop cirrhosis and maintain cytotoxic T cells that are specific for HBsAg.[71] These animals have long-term liver damage and develop HCC by 18 to 20 months of age.

There are two consequences of the model in which HBV contributes to HCC indirectly. The first is that HBV's oncogenesis should be limited to the liver because it depends on the liver's capacity to regenerate to provide the proliferation required to accumulate mutations that predispose to cancer. HBV does cause only HCC. Second, no function of HBV would be required to maintain proliferation of tumor cells. This latter consequence would mean that therapies targeting functions such as pX's enhancement of transcription would be ineffective.

Human Papillomaviruses

Cervical cancer is caused by human papillomaviruses (HPVs). Over 100 genotypes of HPVs have been identified to date. Most HPV genotypes infect squamous epithelia lining the skin; a subset are mucosotropic and infect stratified, squamous epithelia lining the anogenital tract and oral cavity. A subset of these mucosotropic HPVs, the so-called high-risk HPVs, are associated with more than 99% of human cervical cancers, other anogenital cancers, and a subset of squamous carcinomas of the head and neck, particularly those of the oropharynx. HPV16 and HPV18, the high-risk HPVs that are most common in cancers, are present in over 85% of human cervical carcinomas. The mucosotropic HPVs are thought to be transmitted sexually. The association of specific mucosotropic HPVs with human cancers was first recognized in the 1980s when Harald zur Hausen and associates at the German Cancer Research Institute in Heidelberg detected the presence of then novel HPV genotypes in human cervical cancers and in cell lines derived from such cancers.[72,73]

In these cell lines, which include HeLa cells, the HPV DNA is often integrated into the host genome, and only a subset of viral genes, *E6* and *E7,* is expressed.[74,75] This discovery led to the hypothesis that HPV *E6* and *E7* genes contribute to cervical cancer, a premise that is now well supported by experimental research.

An association of papillomaviruses with cancer was first demonstrated in the early 1930s with the recognition that a subcellular, transmittable (i.e., infectious) agent causes squamous carcinomas in cottontail rabbits.[76] The agent was later identified to be a virus, cottontail rabbit papillomavirus, that induces warts in the rabbits. A subset of these infected rabbits develops cancers at the original site of cottontail rabbit papillomavirus infection. Other animal papillomaviruses induce frank cancer. Bovine papillomaviruses (BPV), which represent a class of papillomaviruses that induce fibropapillomas, characterized by hyperplasia of both the dermal fibroblasts and epidermal epithelial cells, can induce epithelial tumors of the alimentary canal in cows.[77] Such tumors are thought to arise when animals ingest bracken fern, which contains quercetin, a potent chemical carcinogen.[78–80] Thus, papillomaviruses and chemical carcinogens act together to induce tumors in cattle.

The study of papillomaviruses in the laboratory began in earnest in the late 1970s when Doug Lowy, Peter Howley, and their colleagues at the National Institutes of Health in Bethesda discovered that BPV-1 infects and transforms a mouse fibroblast cell line, C127, in cell culture.[81–83] The parental C127 cells, while immortalized, are contact inhibited. Infection by BPV-1 or transfection of C127 cells with a bacterial recombinant plasmid containing the entire BPV-1 genome yields foci of cells that are no longer contact inhibited. Transformed C127 cells harbor the viral genome as a nuclear plasmid and express viral early genes. The viral gene products *E5* (E referring to "early," 5 referring to the fifth largest translational open reading frame), *E6,* and *E7*[84–89] contribute to this transformation (Fig. 11-3). Thus, by the time HPVs were recognized as potential etiologic agents in human cervical cancers in the mid-1980s, a wealth of information pointing to the transforming potential of animal papillomaviruses in tissue culture had been established.

The seminal studies of zur Hausen and colleagues in the early to mid-1980s, identifying HPV DNA in cell lines derived from cervical cancers, checkmated a long-argued role for herpes simplex virus type II (HSV-II) in human cervical cancer. The posited role for HSV-II in cervical cancer arose from findings that cervical cancer patients often had antibodies to HSV-II, a sexually transmitted agent. However, their tumor cells lack HSV-II DNA, and today it is accepted that HSV-II does not contribute causally to cervical cancer. This early error provides an important lesson to researchers and epidemiologists who are trying to identify biologic agents that contribute to cancer. Proof by today's standards requires a smoking gun (in this case, the gun includes the viral genome and expression of viral genes in cancer cells).

In 1985, both the zur Hausen and Howley laboratories reported that HPV DNAs (see Fig. 11-3) were integrated in chromosomal DNAs in cell lines derived from cervical cancers.[74,75] This finding initially led to speculation that HPVs contribute to cervical cancer by integrating in or nearby to cellular genes that protect against cancer (i.e., inactivating tumor suppressor genes) or activate those cellular genes that can promote cancers (i.e., promoter/enhancer insertion at proto-oncogenes), akin to the mechanism of oncogenesis by certain oncogenic avian and rodent retroviruses. However, a role for HPV as an insertional mutagen in cancer is not consistent with its different sites of integration in different cancers, which have not been found to be near known or suspected tumor suppressor genes or proto-oncogenes. Rather, it is likely that the integration of the HPV genome leads to the selective upregulation of expression of two viral genes, *E6* and *E7* (see Fig. 11-3), which encode gene products that directly contribute to cancer. The mechanism for this upregulation remains poorly understood but might reflect (1) derepression of *E6* and *E7* expression from the viral promoter resulting from the disruption of a viral transcription factor, *E2,* that can repress their transcription[90]; (2) an increase in the stability of the *E6* and *E7* mRNAs resulting from the disruption on integration of an mRNA instability element present in the 3′ end of the *E6* and *E7* mRNAs[91]; or (3) increased transcriptional initiation from the viral promoter directing expression of *E6* and *E7* following integration of the viral DNA. The recognition of the increased expression of *E6* and *E7* in cervical carcinomas, coupled with the knowledge that *E6* and *E7* contribute to the transforming potential of BPV-1 in mouse fibroblasts, has provided the impetus to examine the tumorigenic activities of these two viral genes.

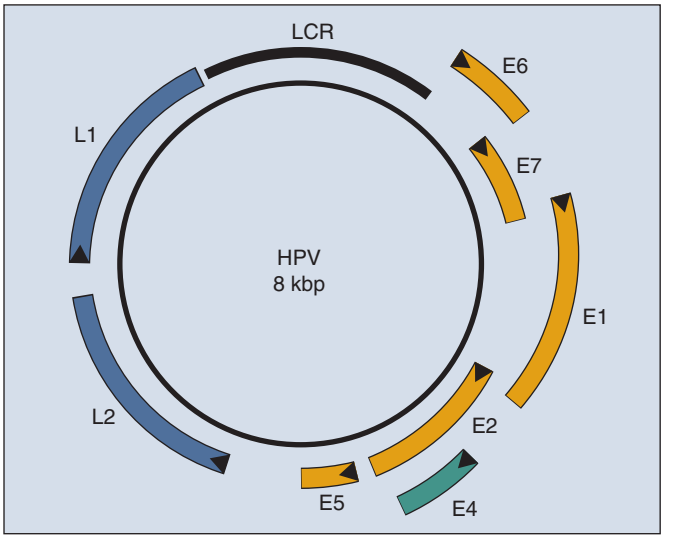


Figure 11-3 • Map of the HPV genome. Indicated by the circle is the approximately 7900-bp circular double-stranded DNA genome of HPV16 as found in viral particles and infected cells. Shown by the *boxes outside the circle* are the various translational open reading frames (ORFs) that encode the viral proteins. These include the early (E) and late (L) ORFs. Most early ORFs (those highlighted in *yellow*) are found expressed throughout the viral life cycle within stratified squamous epithelia, whereas the late ORFs, which encode the capsid proteins (highlighted in *blue*), and *E4* (highlighted in *green*), are selectively expressed in the productively infected, terminally differentiated epithelial cells. Note, among the early ORFs are *E6* and *E7,* the two ORFs encoding like-named oncoproteins that are commonly found expressed in HPV-associated anogenital and oral cancers. RNA synthesis of papillomaviruses is complex, yielding many potential mRNAs, all of which terminate at polyadenylation sites located at the end of the *E5* and *L1* open reading frames. The LCR or long control region encodes multiple *cis*-acting elements that regulate viral transcription and synthesis of viral DNA. See Howley and Lowy[281] for details of the HPV genome and life cycle.

Evidence for a critical role of increased expression of HPV *E6* and *E7* in the genesis of cervical cancers comes from multiple studies: (1) Cervical epithelial cells harboring integrated HPV16 DNA have a selective growth advantage over cells harboring normal extrachromosomal viral genomes, and this growth advantage correlates with the increased expression of *E6* and *E7.*[92] (2) *E6* and *E7* bind and inactivate the tumor suppressor gene products, *p53* and *pRB,* respectively.[93,94] (3) *p53* and *pRB* are wild-type in cell lines derived from HPV-positive cervical cancers, whereas they are mutated in HPV-negative, cervical cancer-derived cell lines.[95] (4) The expression of the *E6* and *E7* viral genes is required for survival of cervical cancer-derived cell lines.[96–101] Together, these observations strongly support the hypothesis that *E6* and *E7* contribute causally to human cervical cancers at least by blocking the functions of cellular tumor suppressors.

The *E6* and *E7* genes from the high-risk HPVs are transforming in tissue culture. They act independently or synergistically to immortalize multiple cell types, including human foreskin keratinocytes,

cervical epithelial, or mammary epithelial cells.[102–107] In addition, *E7* cooperates with an activated *ras* to transform baby rat kidney or human cervical epithelial cells.[108–110] The oncogenic properties of high-risk HPV *E6* and *E7* in vivo have been validated through the characterization of HPV transgenic mice.[111–118]

E6 and *E7* are best known for their ability to associate with the cellular tumor suppressors, *p53* and *pRB*, respectively.[93,94] The discovery of these interactions represents a major advance in our understanding of the mechanisms of oncogenesis: The inhibition of tumor suppressors predisposes cells to evolve into tumors. *E6* induces degradation of *p53*, at least in part via recruitment of a ubiquitin ligase, E6-AP.[119–121] *E6* inhibits *p53* protein's transcriptional regulatory activities in tissue culture cells.[122,123] Association of *E7* with *pRB* also promotes the degradation of *pRB*[124,125] and disrupts *pRB*'s capacity to bind and functionally inactivate the cellular E2F transcription factors.[110,126] While these abilities of *E6* and *E7* to inactivate *p53* and *pRB,* respectively, likely play an important role in their oncogenic potentials, it is important to recognize that *E6* and *E7* both can bind additional cellular factors, and certain of these interactions likely contribute to HPV-associated carcinogenesis.[127,128] Which of these many interactions contribute to oncogenic potential largely remains to be determined. In the case of *E6*, one group of cellular interacting partners implicated in *E6*-mediated carcinogenesis are the PDZ domain proteins such as Dlg and Scribble, proteins that were originally identified in *Drosophila* to be tumor suppressors.[128,129]

E6 proteins from multiple papillomaviruses bind to cellular proteins other than *p53* and *E6AP.* These other interacting partners include p300,[130,131] paxillin,[132,133] E6 target protein-1 *(E6TP1),*[134] interferon regulatory factor-3 (IRF3),[135] *E6* binding protein-1 (*E6BP1*),[136] Bak,[137] protein kinase PKN,[138] myc,[139] the mammalian homolog of *Drosophila* disk-large tumor suppressor gene product (DLG),[140,141] Scribble,[142] MAGI-1,[143] and MUPP1[144] In addition, *E6* can induce expression of telomerase activity by a yet-to-be-defined activity,[145–148] a property that correlates with *E6*'s immortalizing potential.

In addition to binding *pRB, E7* can bind to other cellular proteins, including p107 and p130, which are related to *pRB* protein,[149] and can interact with different members of the E2F family of transcription factors.[150,151] *E7* also is argued to complex with cyclins[149,152–154] and to inactivate cyclin-associated kinase inhibitors, p21 and p27.[125,155] Thus, *E7* can associate with and/or alter the activities of multiple cellular factors that themselves interact normally and thereby contribute to the normal regulation of the cell cycle. Still other interactions have been identified between *E7* and cellular factors, including S4 subunit of the 26 S proteasome;[156] Mi2-beta, a component of the NURD histone deacetylase complex;[157] the fork-head domain transcription factor MPP2;[158] the transcription factor AP-1;[159] insulin-like growth factor-binding protein 3;[160] TATA box-binding protein (TBP);[161,162] TBP-associated factor-110;[163] and a novel human DnaJ protein, hTid-1.[164] It remains unclear whether any of these additional interactions contribute to *E7*'s oncogenic potential.

There is a growing appreciation of HPV's role not only in anogenital cancers such as cervical cancer, but also in head and neck cancers of the oral cavity and in skin cancers.[165–168] The multiple interactions of *E6* and *E7* with cellular proteins that have regulatory functions is consistent with *E6* and *E7* contributing to cancers through multiple mechanisms. Studies in tissue culture strongly support the hypothesis that continued expression of *E6* and *E7* is required for the continued growth of cervical cancer cells[96–100] and, perhaps, with other cancers to which HPVs contribute causally.

Cervical cancers take decades to arise in most patients after initial infection with high-risk HPVs. During this time, the HPV must persist in the patient. Strategies that can interfere with viral persistence could prove effective in preventing the development of cancer. *E6* and *E7* are important to the replicative phase of the HPV life cycle and therefore for viral persistence, indicating that they are also appropriate targets for antiviral and antitumor drug development. Recent studies have used organotypic tissue culturing to recapitulate the life cycle of HPVs in fully differentiating, stratified squamous epithelial cells. These studies have implicated *E7* in reprogramming cells within the terminally differentiating compartment of the epithelia to support the amplification of the viral DNA genome, likely through its inactivation of *pRB.*[169] *E6*'s inactivation of *p53* might be necessary for viral replication by inhibiting cellular stress responses elicited by *E7*'s inactivation of *pRB.*[170] At least two more HPV proteins, *E1* and *E2* (see Fig. 11-3), contribute to the replication of the viral genome.[171] *E1* and *E2* bind to an origin-of-DNA replication on the viral genome.[172] *E1* is a DNA helicase that unwinds the viral double-stranded DNA genome at its origin and, together with *E2,* recruits cellular DNA replication proteins that then synthesize the viral DNA.[172–174] Thus, *E1* and *E2* both represent potentially useful targets for intervening in the viral life cycle.

One desirable, long-term public health strategy for dealing with this and other human tumor viruses is generation of an effective, prophylactic vaccine for prevention of initial infection. Such a vaccine has recently received FDA approval in the case of the mucosotropic HPVs that are implicated in cervical cancer, although several issues complicate the potential success of this strategy. This vaccine is discussed later. Another approach that is being pursued is the generation of microbicides that could be used to prevent infection by sexually transmitted HPVs.

Human T-Cell Leukemia Virus I

Adult T-cell leukemia/lymphoma (ATLL), a tumor of $CD4^+$ T cells, is caused by human T-cell leukemia virus type I (HTLV-I), the only retrovirus that is now accepted as being oncogenic in people. HTLV-I is found worldwide, with approximately 10 million to 20 million people estimated to be infected today. This number is likely an overestimate because of a failure to distinguish serologically between HTLV-I and HTLV-II.[175,176] HTLV-I is particularly prevalent in restricted sites, including southern Japan, the Caribbean, and West Central Africa. ATLL is prevalent in those areas in which HTLV-I is common, and it is estimated that as many as 5% of HTLV-I-positive carriers will develop ATLL in their lifetime.[177] HTLV-I also causes a progressive, paralytic myelopathy termed *HTLV-I-associated myelopathy* or *tropical, spastic paraparesis.* This neurologic disorder appears to arise preferentially in patients whose HLA haplotypes fail to limit viral load.[178]

The data that link HTLV-I causally to ATLL are varied. ATLL can occur in familial clusters. It is characterized by an average age at onset of 56 years and proves rapidly fatal, 50% of patients dying within 6 months of diagnosis.[177] Patients generally have antibodies to HTLV-I-encoded proteins,[179] and in 88 of 88 primary biopsies of ATLL examined, all had single copies of integrated HTLV-I proviruses.[180] The presence of the provirus of HTLV-I in all of the tumors makes it likely that infection with the virus is an early, contributing event in the evolution of the tumor. The presence of ATLL in familial clusters is consistent with the routes of transmission of HTLV-I. HTLV-I is passed from male to female via semen and from mother to child by breast milk. The latter route has been demonstrated prospectively. Encouraging carrier mothers to refrain from breast-feeding has decreased transmission of HTLV-I to their children by 80%.[181] It appears highly likely that this form of public health intervention will lead to a corresponding decrease in ATLL in Japan in the future. Such a decrease would constitute formal proof of the oncogenic role of HTLV-I in ATLL.

HTLV-I clearly differs from the highly oncogenic animal retroviruses that encode oncogenes derived from cellular proto-oncogenes. HTLV-I is a complex retrovirus that encodes multiple open reading frames in addition to the *gag, pol,* and *env* genes that are common to simple retroviruses (Fig. 11-4). However, none of these additional viral genes is obviously related to known proto-oncogenes, and all are thought to affect the viral life cycle either directly or indirectly by

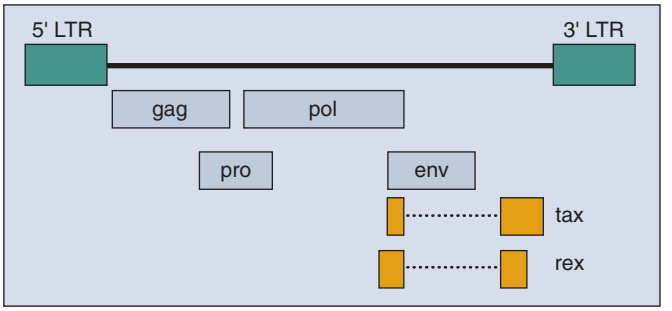


Figure 11-4 • Map of the HTLV-I genome. Indicated by the line drawing is the approximately 9000-bp DNA proviral form of the HTLV-I genome as it is found integrated into the host genome. The genome as present in the viral particle consists of two copies of a single-stranded positive-strand, RNA. Shown are the long terminal repeats (LTRs, *green*) flanking the unique region that contains the translational open reading frames (*boxes*) for structural *(blue)* and nonstructural *(yellow)* viral proteins. The LTRs contain *cis*-acting elements that are required for transcription and replication of the viral genome. The structural genes are transcribed late in the viral life cycle from the 5′ LTR while the nonstructural proteins are transcribed early from the 5′ LTR from different, spliced transcripts. See Green and Chen[282] for details of the genome and life cycle of HTLV-I.

affecting the host cell.[182,183] It is accepted that one viral protein Tax (see Fig. 11-4), which regulates both viral and cellular gene expression, is a major contribution of HTLV-I to leukemogenesis. It is also evident that viral infection precedes onset of ATLL by 50 years or more, that many cells are infected, and that only a minority of infected people develop this clonal tumor. These combined observations indicate that multiple rare events in an HTLV-I-infected $CD4^+$ T cell must occur for that cell to evolve into ATLL.

Multiple approaches demonstrate that Tax can transform cells in culture and be oncogenic in animal models. The introduction of a vector that expresses Tax into established, adherent rodent cells can transform them to grow in an anchorage-independent fashion.[184] Strains of rodent cells can be transformed with Tax in combination with the *ras* oncogene to yield cells that are tumorigenic in nude mice.[185] Tax has also been recombined into *Herpesvirus samiri* and has been introduced into resting human T cells. These infected cells can proliferate and yield infected, immortalized progeny, whereas the Tax-negative parental virus cannot do so.[186] In accord with these data, variants of HTLV-I from which the Tax gene has been deleted no longer can immortalize human T cells in culture.[187] These results in culture are paralleled and bolstered by others in transgenic animal models. Expression of Tax from the HTLV-I long terminal repeat, LTR (the viral promoter), in transgenic mice leads to mesenchymal tumors.[188] When its expression is directed to lymphoid cells, the transgenic animals develop leukemias.[189] However, the exact means by which Tax transforms cells in culture or is oncogenic in animal models is not obvious.

Tax can be considered a paradigm for viral proteins that affect host cells in that it has multiple, distinct functions that are not found in any one cellular protein. Apparently, HTLV-I during its evolution has assimilated multiple cellular activities in this one gene product. Tax can be viewed as having at least three kinds of activities: It activates transcription via NF-κB and CBP, the CREB (cyclic AMP response element-binding protein)-binding protein; it inhibits transcription, perhaps through binding histone deacetylase-1, HDAC-1; and it inhibits several tumor suppressor gene products.[182,190–194] Tax potently activates transcription from HTLV-I's own LTR[195] and activates the promoters for IL-2, IL-2 receptor α chain, and c-fos.[196–198] This transcriptional activation could obviously contribute to proliferation of an infected T cell. It also can activate the promoter for Bcl-x and thereby help to inhibit apoptosis.[199] Tax can positively regulate transcription by binding CREB and CBP as well as some members of the NF-κB family.[200–202] Tax not only binds members of the NF-κB family directly, but also can activate NF-κB's homing to the nucleus by binding to IκBα and promoting its degradation.[203,204] Some of Tax's protein : protein associations have been functionally validated through chromatin immunoprecipitations that have documented the binding of Tax, CREB, and CBP to HTLV-I's LTR in intact, HTLV-I-transformed T cells.[205]

Tax can also inhibit transcription. It has been shown to inhibit both expression of the β-DNA polymerase gene[190] and some promoters that are regulated by CBP/p300.[206] It has been proposed that the latter inhibition occurs by Tax's binding to CBP and effectively sequestering CBP such that it is unavailable to bind other DNA-binding transcriptional factors. It has also been shown that Tax binds HDAC-1 as measured by coimmunoprecipitations.[191] Were Tax to tether HDAC-1 to a promoter, the resulting localized histone deacetylation would presumably lead to its decreased support of transcription.[207]

A third activity of Tax is its inhibition of some cellular tumor suppressors. Tax has been shown to bind to and inhibit the function of p16INK4A.[192] p16INK4A binds cyclin-dependent kinase 4 (CDK4), a kinase that, when activated, can phosphorylate pRb, yielding release of E2F transcription factors and promotion of the G1 to S transition of the cell cycle. On binding p16INK4A, Tax can increase the kinase activity of CDK4 kinase.[192] p16INK4A is often found to be mutationally inactivated in tumors. Consistent with Tax's functionally inactivating p16INK4A, p16INK4A was shown to be wild-type in sequence in two HTLV-I-infected T-cell lines in which Tax is expressed but deleted in four uninfected T-cell lines.[192] Tax also appears to bind cyclin D3 and might thereby foster, by a second means, the activity of CDK4 and CDK6.[193] Tax's binding to p16INK4A and cyclin D3 would inhibit control of the cell cycle and promote cell proliferation. Tax can also inhibit the transcriptional activity of *p53* by an NF-κB-dependent mechanism that culminates in the phosphorylation of *p53* as certain residues.[194,208] Such an inhibition of *p53* is likely to limit its induction of apoptosis and increase the rate of survival of HTLV-I-infected, proliferating T cells.

The multiple activities of Tax likely contribute to HTLV-I's associated leukemogenesis but must be insufficient for the development of ATLL. Multiple T cells are initially infected by HTLV-I, but over the course of the 50 to 60 years of its development, only one infected cell and its progeny give rise to the tumor. The additional genetic and epigenetic events that are necessary for this evolution are not known. It is also clear that the expression of viral genes in infected cells is surprisingly low; measurements of RNAs encoding Tax indicate that between 0.1% and 10% of freshly harvested, infected T cells express any Tax message in vivo.[209] These findings indicate that the regulation of HTLV-I expression, be it at the level of T-cell development or immune response to viral antigens, is likely also to be critical to the development of ATLL.

Human Hepatitis C Virus

Human HCV is accepted as an etiologic agent for hepatocellular carcinoma (HCC) along with HBV. Approximately half of the cases in the U.S. are ascribed to HCV.[210] Infection with HCV constitutes a 20-fold risk for men in Taiwan to develop HCC.[211] HCV represents the most common chronic viral infection among blood-borne pathogens in the United States, where the rate of infection during the period from 1988 to 1994 was estimated to be 1.8%.[212] The World Health Organization estimates the worldwide infection rate to be 3%, yielding over 170 million infected individuals.[213] The rates of infection vary widely, with rates as low as 0.01% to 0.1% in Scandinavia and the United Kingdom and as high as 17% to 26% in Egypt.[212] Infection is thought to arise from contaminated blood, use of shared needles among intravenous drug users, organ transplantation, hemodialysis, sexual transmission, and vertical transmission. The establishment of sensitive tests for identifying contaminated

blood and blood products fortunately has now greatly reduced the rate of infection in the general population. As with people who are chronically infected with HBV, HCC in HCV-positive individuals correlates with chronic hepatitis and cirrhosis. Di Bisceglie has estimated that 20% of people who are chronically infected with HCV develop cirrhosis per decade, and by two decades, 2% to 7% of chronically infected people develop HCC.[214] It is argued that the hyperproliferative state that is induced by chronic hepatitis and cirrhosis leads to an accumulation of genetic changes and contributes to the onset of liver cancer. What specifically HCV contributes to this scheme is not known.

HCV is a flavivirus, indicating that it is unique among the human tumor viruses for having RNA as its only genetic material (Fig. 11-5). It was identified in 1989 during a search for the causal agent of non-A, non-B hepatitis.[215] This flavivirus contains a 9.6-kbp, positive-stranded RNA as its genome, which encodes a single translation product of approximately 3000 amino acids (see Fig. 11-5). This polyprotein is cleaved by both cellularly and virally encoded proteases to yield at least 10 proteins.[216] The study of HCV has been daunting for at least two reasons. Its sequence varies in infected people such that there are six recognized genotypes with multiple subtypes among patients and a spectrum of quasispecies within any one infected individual.[217] Members of these quasispecies within one patient vary by 1% to 2% in their sequence.[218] In addition, there is no available cell culture for HCV. Researchers have made heroic efforts to overcome this latter hurdle and have met with partial success.

In 1999, Lohmann and colleagues described the replication of a subgenomic derivative of HCV in a cell line derived from a human hepatocellular carcinoma.[219] These subgenomic replicons were difficult to establish, but once established, they exhibited bona fide characteristics of flaviviral nucleic acid replication. One thousand to five thousand molecules of plus-strand RNA were present in each cell; minus-strand RNA was present at 10% to 20% of the level of the plus-strand; and this viral RNA replication was insensitive to treatment of cells with actinomycin D.[219] This mode of nucleic acid replication in cells will allow the elucidation of the *cis* and *trans* elements it requires but with an unexpected twist. The efficient replication of the subgenomic derivatives of HCV requires mutations in at least two viral genes that enhance replication in cells but abrogate infectivity of intact HCV RNA.[220] Chimpanzees are the only nonhuman host for HCV. The parental strain of HCV that is used to derive the subgenomic replicons is infectious in this primate host, while a derivative of it, containing the mutations required for the efficient replication of the subgenomic replicons, is not.[220] This finding must limit the conclusions to be drawn from the analyses of replication of these mutated subgenomic replicons in cells. They also indicate that the generation of the many sequence variants that constitute the quasispecies within any one infected patient might contribute to the successful replication of HCV.

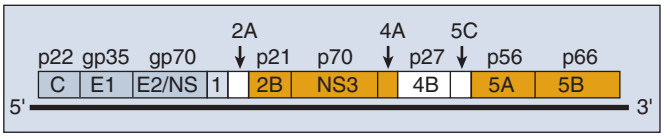


Figure 11-5 • Map of the HCV genome. The 9500-nucleotide-long positive-strand RNA of HCV is shown in *black.* It encodes a single 3000-amino-acid polyprotein that is proteolytically cleaved into mature proteins (indicated on the map by *labeled boxes* with alternative names indicated above the boxes) by virally encoded proteases (NS3/4A and possibly 2B). At the 5′ and 3′ ends are short noncoding regions that contain signals for replication of the viral genome. The 5′ NCR also contains an internal ribosome entry site. Structural proteins are shown in *blue.* Nonstructural proteins, including proteases, helicases and RNA polymerase, are shown in *yellow.* See Majo and colleagues[283] for details of HCV's genome and life cycle.

The lack of a cell culture host for infection with HCV and/or a practicable animal host has led researchers to seek chimeric animal models of infection. Researchers formerly developed a chimeric animal model for HBV, which has been adapted to the study of HCV. Mice that are transgenic for the plasminogen activator urokinase, expressed in the liver (uPA), have hepatocytes with a selective disadvantage such that transplanted, nontransgenic hepatocytes repopulate the liver.[221] When these animals are crossed with nu/nu mice, they not only can tolerate rat hepatocytes, but also support rat hepatocytes reconstituting their livers.[222] These findings paved the way for Petersen and colleagues to cross mice that are transgenic for uPA with mice that are null for Rag-2, which eliminates their B- and T-cell responses, and to repopulate their livers with woodchuck hepatocytes.[223] These chimeric animals now supported infection with woodchuck HBV and became chronically infected with 106 to 1011 virions per milliliter of serum.[223] Human hepatocytes can also repopulate the livers of uPA-transgenic animals as long as they cannot reject the xenograft. SKID mice that are homozygously transgenic for uPA accept human hepatocytes such that 50% or more of their hepatocytes are of human origin.[224] These animals can be infected with HCV such that 75% of them become persistently infected with 104 to 106 viral RNA molecules per milliliter of serum, and the infections can be passaged serially in them.[224] These reconstituted animals are obviously difficult to generate but should provide some insights into the life cycle of HCV and could serve as models in which to test inhibitors of HCV infection.

Evidence for a direct role of HCV in HCC has come from studies of the HCV Core protein. The HCV Core protein can cooperate with an activated form of the *ras* oncogene to transform primary rodent cells in tissue culture.[225] Mice that are transgenic for the HCV Core protein develop HCC.[226] Several potential mechanisms have been invoked to explain the transforming potential of HCV Core protein. It has been found to enhance cell proliferation through the stimulation of the mitogen-activated protein kinase[227,228] In addition, HCV Core protein can inactivate a transcription factor, lZIP, and this inactivation correlates with transformation in rodent cells.[229]

More recently, the Core protein has been found to activate STAT3, and this activation may contribute to its transforming potential.[230] Whether the HCV Core protein contributes directly to human HCC is uncertain. Neither replication of subgenomic replicons in cell culture nor infection of chimeric mice populated with human hepatocytes will allow ready testing of the possible role of the Core protein in HCV's oncogenesis.

Current treatments for HCV are unsatisfactory. The combination of interferon α plus ribovirin, a general antiviral nucleotide analog, has supported a clearance of detectable HCV in 40% of a treated group over 1 year. Those who responded had higher titers of the virus.[231] These observations may indicate that treatments with multiple, independently acting drugs are the most likely route to successful treatments for HCV.[232] In the United States, approximately 10,000 deaths are attributed to HCV each year, and today infection with HCV is the leading indication for liver transplantation.[212] Clearly, this mode of treatment is not practical for most infected people. The lack of satisfactory treatments for chronic HCV infection and its associated HCC make it important to continue to develop tractable means for studying HCV's life cycle and to elucidate its mode of oncogenesis.

Kaposi's Sarcoma Herpes Virus

The identification of Kaposi's sarcoma herpesvirus (KSHV) represents the culmination of much scientific detective work. Kaposi's sarcomas (KS) were known before the AIDS epidemic[233,234] but increased markedly among HIV-positive people. Researchers therefore looked for molecular evidence of an infectious agent present in KS lesions. In 1994, Chang and Moore and their colleagues used a newly developed enrichment procedure based on PCR to identify

DNA sequences that are present in KS but absent in normal cells. They identified a new herpesvirus, KSHV (also termed *human herpesvirus 8,* or HHV-8), which is related to EBV and *Herpesvirus saimiri.*[235] Retrospective studies indicate that KSHV was prevalent in different parts of the world prior to the spread of HIV and that in Africa, for example, the prevalence of KSHV has not changed. What has changed there is the incidence of KS; in regions where it was formerly infrequent, the incidence of KS rose threefold between 1988 and 1996.[236] Similarly, the frequency of infection with KSHV of certain cohorts in the United States has not altered with the advent of HIV,[237] but the incidence of KS has.[238] KSHV has also been detected in one class of lymphomas termed *body-cavity-based lymphomas* or *primary effusion lymphomas* (PEL)[239] and in an atypical lymphoproliferative disorder termed *multicentric Castleman's disease.*[240]

KSHV is now accepted as contributing causally to KS and PEL. Each of these malignancies displays intriguing features that are likely to reflect their viral etiology. Single-cell assays of early KS lesions have detected KSHV in a minority of cells that surround their vascular spaces, while in the more advanced, nodular lesions, more than 90% of the spindle cells characteristic of these lesions are KSHV-antigen-positive.[241] The viral antigen-positive cells also stain with antibodies against the VEGF receptor-3, indicating that they are lymphatic or proliferating endothelial cells.[241] That only a subset of the cells that are characteristic of early KS lesions appear to be infected with KSHV likely indicates that infected cells affect the development of their neighbors. This possibility is supported by the multiple cellular homologs of cytokines and receptors encoded by KSHV that may allow infected cells to interact with adjacent, uninfected cells.[242,243]

PEL cells are B cells in origin and, in six of seven cases examined, have nongermline immunoglobulin mRNAs, indicating that they are likely derived from B cells that have encountered antigen.[244] They often, however, fail to express B-cell activation antigens.[245] PEL cells usually, but not always, are coinfected with EBV.[239,245] The role of EBV in the etiology of this lymphoma has not yet been clearly determined. However, because EBV is often retained in these cells as they are propagated in vitro and is maintained in them in vivo, EBV is likely to provide the tumor cells some selective advantage.

KSHV encodes many genes with clear homologies to cellular genes, some of which are candidates for contributing to viral oncogenesis (Fig. 11-6). Three categories of these cellular homologs are particularly likely to be important for tumor development: cyclins, inhibitors of apoptosis, and cytokines and receptors. KSHV encodes

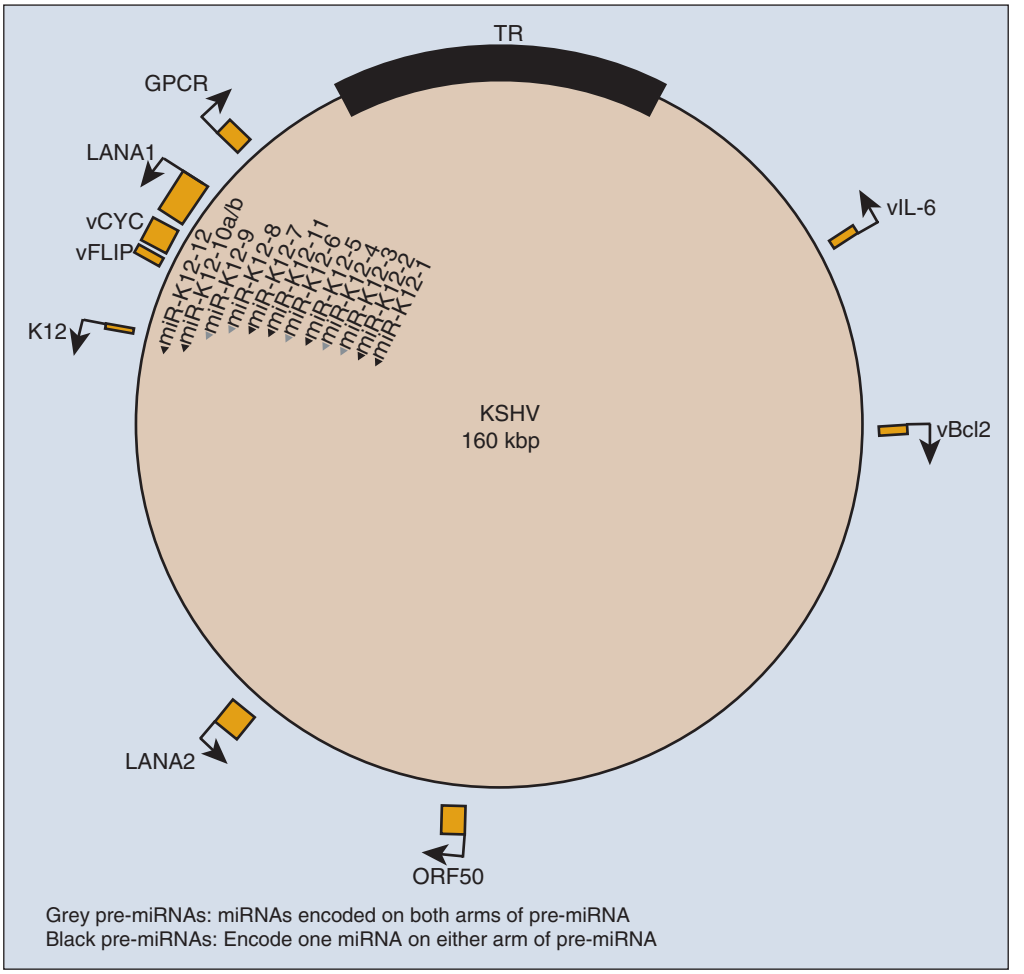


Figure 11-6 • Map of the KSHV genome. The genome of KSHV consists of approximately 160 kbp of linear double-stranded DNA in the viral particle. The viral genome becomes circularized on infection via the 20 to 40 copies of terminal repeats found at the ends of the linear genome. The terminal repeats also contain the origin of plasmid replication used during the latent phase of the viral life cycle. Shown by the *boxes* are positions of those viral genes that are expressed during latency and/or are thought to contribute to oncogenesis by KSHV. The *arrows* represent the positions from which the RNAs encoding the labeled proteins are expressed. Several of these primary transcripts are polycistronic. Shown on the inside of the circle are the positions of the recently identified miRNAs that are encoded by KSHV. These also are derived from a polycistronic message.

its own cyclin. Cellular cyclins bind specific, dependent kinases (CDK) whose activities promote progression through the cell cycle and are controlled by cellular inhibitors, including p16INK4A, p21CIP1, and p27Kip1. The KSHV-encoded cyclin can promote cellular proliferation in part by overcoming these cellular inhibitors. It does so apparently by extending the substrates that are phosphorylated by CDK6 to include p27Kip1.[246,247] Phosphorylation of p27Kip1 at position 187 leads to its downregulation and promotes passage through the G1 phase of the cell cycle. One measure of the activity of the KSHV cyclin CDK6 complex is that it can foster progression of nuclei isolated from cells in G1 to undergo DNA synthesis.[248] The KSHV cyclin can also induce cells to undergo apoptosis.[249] It is striking that in cells lacking *p53,* the expression of the KSHV cyclin promotes cells both to become aneuploid and to survive so that they continue to proliferate. In fact, mice that are transgenic for KSHV cyclin and are *p53*-null develop T- and B-cell lymphomas with a mean latency of 3 months, which is shorter than the latency for the *p53*-null mice alone.[250]

KSHV also encodes its own inhibitors of apoptosis: viral Bcl-2 and viral FLIP (an inhibitor of cellular FLICE, a protein that mediates Fas ligand–induced cell death) (see Fig. 11-6). The viral Bcl-2 shares its limited sequence homology with cellular Bcl-2 in those regions that are critical for inhibiting apoptosis and fails to dimerize with cellular Bcl-2 and Bcl-XL, thus avoiding regulation by potential cell-binding partners.[251] It can inhibit the apoptosis that is induced by efficient expression of KSHV's cyclin.[252] Viral FLIP can inhibit apoptosis mediated by the Fas pathway and induced by cytotoxic T-lymphocytes.[253] Finally, KSHV encodes homologs of cytokines and cytokine receptors (see Fig. 11-6). Its viral IL-6 may promote proliferation of PEL cells, although they appear to be dependent on cellular IL-6 and not viral IL-6 for their continued growth.[254] KSHV also encodes a G protein-coupled receptor, viral GPCR, which is likely to be pivotal for the development of KS. The expression of viral GPCR in endothelial cells in mice leads to KS-like tumors, while the individual expression of KSHV cyclin, KSHV Bcl-2, or KSHV FLIP does not.[255] What is particularly exciting is that cells that are inoculated into mice that express viral GPCR promote tumor formation by coinoculated cells that individually express viral cyclin, viral FLIP, or both.[255] These findings support a model in which viral GPCR contributes to the development of KS by affecting neighboring cells not infected by KSHV. The model is also supported by the findings that viral GPCR induces expression of the cellular VEGF receptor-2 in endothelial cells that proliferate in the presence of VEGF and that viral GPCR induces expression of VEGF.[256,257] Clearly, these observations define an autostimulatory loop in which KSHV GPCR alone can maintain proliferation of endothelial cells. These collected observations help to explain the viral contributions to KS and perhaps PEL. These explanations are not yet complete, however, because several of these putative viral oncogenes, including viral IL-6, viral Bcl-2, and viral GPCR, are expressed during the lytic phase of KSHV's life cycle. The lytic phase of a herpesvirus is traditionally thought to lead to death of the host cell. How these putative viral oncogenes could affect oncogenesis and be expressed only in cells that are destined to die soon is an enigma that has yet to be resolved.

Recent studies of cell lines derived from PEL and human endothelial cells are providing the foundation for understanding infections by KSHV in vivo. PEL cells maintain KSHV DNA extrachromosomally and consistently express the viral protein LANA-1 (see Fig. 11-6), which is required for viral plasmid replication.[258,259] In general, these cells support the latent phase of KSHV's life cycle and also express FLIP, the viral cyclin and the viral inhibitor of cellular FLICE, but few other viral proteins. Some PEL cell lines support an inefficient spontaneous conversion to the lytic phase of the viral cycle, which can be further induced by treatment of cells with tetradecanoyl phorbol acetate or introduction of a plasmid that includes ORF50 (see Fig. 11-6), a viral inducer of the lytic cycle.[260] The released virus is infectious on human dermal microvascular endothelial cells.[261,262] These dermal microvascular endothelial cell cultures can be passaged to yield populations in which all cells are infected, express LANA-1, assume a spindle-cell morphology, and can proliferate indefinitely.[262] The spindle shape is characteristic of cells in KS lesions in vivo. Staining of these infected dermal microvascular endothelial cell-derived spindle cells indicates that 5% to 10% of them spontaneously support early stages of KSHV's lytic cycle and 1% to 2% express genes diagnostic of the late stages of the viral life cycle.[262] If endothelial cells that are infected in vivo by KSHV display a similar distribution of cells supporting the latent, early, and late lytic phases of the viral life cycle, then the enigma of the oncogenic contribution of viral genes that are expressed only during the lytic cycle may be resolved. A sustained, spontaneous conversion of 5% to 10% of KSHV-infected cells to support the viral lytic cycle might allow enough infected cells to express enough KSHV GPCR to promote the bystander-dependent tumor evolution proposed by Bais and colleagues.[257]

TREATMENT AND PREVENTION OF VIRAL TUMORS

Tumors that are associated causally with viruses are treated variously: Surgical resections, when appropriate, are used in combination with chemotherapy and/or radiation therapy. These treatments are disappointing in that overall survival rates are often low and so far have not been able to capitalize on any specific antiviral therapies. Current survival rates after different therapies obviously vary with the malignancy, its stage, and the setting in which it is treated. For example, youngsters with Burkitt's lymphoma have a 4-year overall survival rate of 65%.[263] Approximately 45% of NPC patients remain disease-free after treatment for 10 years, but this value is highly dependent on the stage at which the NPC was diagnosed.[141] In the United States, 26% of HBV-positive, surgically resected HCC patients have a 5-year, local disease-free survival compared with 38% for the analogous HCV-positive group.[264] A retrospective study of German patients with a mix of HBV- and HCV-associated HCC found a median survival of 7 years.[265] The 5-year median survival for cervical carcinoma patients ranges from 65%[266] to 75% to 90%[267] in different studies. The median survival for patients once they have been diagnosed with ATLL is only 10 months.[268] The overall survival rates of KS patients who are HIV-positive have changed with the introduction of highly active antiretroviral therapies. Prior to this therapy, median overall survival was 13 months; with highly active antiretroviral therapies, it surpasses 28 months.[269] The median survival for PEL patients has been described as "dismal," but there are case reports of some combination therapies being helpful.[270] These actuarial findings indicate that developing antiviral therapies directed at those viral gene products that maintain tumor phenotypes is a highly desirable goal.

Early detection of premalignant disease has been an effective means for reducing the incidence of cervical cancer. The introduction of routine cytological (Pap smear) screening of women in the United States and other countries with well-developed health care systems has led to an approximate threefold decline in cervical cancers over the last 40 years. Pap smears represent a first-level screening tool for the clinician. Women with positive Pap smears are routinely subjected to further examination with histopathologic examination and, if necessary, removal of lesions. More recently, HPV DNA testing has emerged as an alternative means for identifying women who are at risk of developing cervical cancers, although the utility of this testing appears to be restricted to women 40 years of age or older. This restriction reflects the fact that many younger women who are sexually active will have nascent infections that will be detected by using the HPV DNA test but are not necessarily going to lead to cancer because many HPV infections will spontaneously resolve. The detection of high-risk HPVs in older women, on the other hand, is more likely to indicate the presence of persistent HPV infections, which are highly correlative with progressive cervical disease leading

to cancer. Another use of HPV DNA testing is as an adjunct screen for women with positive Pap smears, that is, to determine whether they are infected with high-risk HPVs associated with cervical cancer.

The ultimate goal, the development of effective vaccines that can prevent initial infection or induce the elimination of viral persistence, is being pursued for all human tumor viruses. Success or the glimmer of success has been achieved for two of them: HBV and HPV.

Hepatitis B Virus Vaccine

Although there are four serotypes of HBV, highly effective vaccines for HBV have been developed that consist only of its surface antigen, HBsAg. Today, this subunit vaccine is usually synthesized with a recombinant DNA that is expressed in yeast. Vaccines for HBV began to be used in the early 1980s, and since 2001, 129 countries throughout the world routinely vaccinate infants and/or adolescents against HBV.[271] These vaccinations are effective. The fraction of children who are infected with HBV has been reported to have declined between 7.5- and 10-fold in Taiwan and the Gambia, respectively.[54,55] This decline has been paralleled by a detectable drop in the frequency of HCC in children in Taiwan, an age group for which this viral tumor is rare.[56]

The current HBV vaccines apparently are free of unwanted side effects but can select for variants of HBV that are resistant to the neutralizing antibodies they elicit.[271] One domain of the HBsAg in particular elicits neutralizing antibodies efficiently, and mutations in it can allow for viral escape. The frequency of these escape mutants in populations of vaccinated children has risen significantly.[272] One means to overcome the selection for such escape mutants would be to generate vaccines for HBV that include more than the HBsAg as an immunogen. Such vaccines are now being developed.

Human Papillomavirus Vaccine

The second family of human tumor viruses for which an effective prophylactic vaccine has been developed are those human papillomaviruses that are associated with cervical cancer, other anogenital cancers, and certain head and neck cancers, in particular, HPV16 and HPV18. These two viruses account for approximately 85% of cervical cancers worldwide and, in a recent study, 16% of new infections.[273] Several HPV prophylactic vaccines, designed to prevent or eliminate acute infections by HPV16 and HPV18, have recently gone through clinical trials.[274] These vaccines are based on the production of virus-like particles (VLPs) composed of the major capsid protein of HPV16 and HPV18, L1, which self-assembles into icosahedrons (see Fig. 11-3). These L1-based VLPs induce neutralizing antibodies in vaccinated individuals. Preclinical studies with cottontail rabbit papillomavirus and canine oral papillomavirus demonstrated the effectiveness of VLP-based vaccines in protecting animals from cottontail rabbit papillomavirus and canine oral papillomavirus infection.[275,276] Clinical trials likewise demonstrated the effectiveness of HPV16 VLP-based vaccines in inducing neutralizing antibodies that are specific for HVP16 and preventing HPV16 infections and in reducing the incidence of premalignant disease.[277,278] One of these HPV vaccines, Gardosil, which is a product of Merck, received FDA approval in 2006 for administration to young women in the United States. It has also been approved for use in many other countries. A second vaccine, which is being developed by GSK, is expected to gain FDA approval in 2008. One issue that is of relevance to the effectiveness of these vaccines is the specificity of immune responses invoked by VLP-based vaccines for specific HPV genotypes. Approximately two dozen HPV genotypes are associated with anogenital cancers. VLP-based vaccines induce protective immunity that is highly specific for the genotype from which the VLP is generated. This specificity has led to the development of polyvalent vaccines composed of a mixture of VLPs generated with L1 proteins from multiple mucosotropic HPV genotypes. For example, Gardosil is a polyvalent vaccine that is composed of HPV16, HPV18, HPV6, and HPV11 VLPs. HPV6 and HPV11 are low-risk mucosotropic HPVs that induce genital warts but do not contribute to cervical cancer. It remains to be seen whether, once a population is protected from HPV-16- and HPV-18-induced cancers, other HPV genotypes arise to induce a greater incidence of cervical cancers than they currently cause. Studies now in progress are designed to increase the cross-genotype neutralizing capacity of the VLP-based vaccines. Incorporation of the minor capsid protein, L2, might contribute to this property, because neutralizing antibodies induced against L2 tend to be more generally effective at neutralizing multiple genotypes.[279] There is a concern whether the HPVs, particularly HPV16 and HPV18, will evolve to become resistant to VLP-based vaccines. Assuming a high effectiveness of the vaccines that are currently in development and their worldwide distribution and given the long latency of cervical cancer, it is estimated that prophylactic HPV vaccines will lead to a reduction of deaths due to cervical cancer no earlier than 2040.

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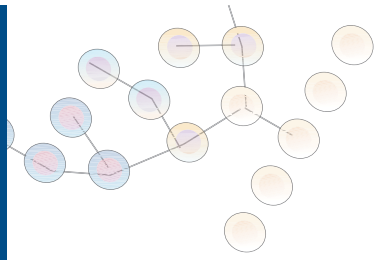
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12 Genetic Factors: Hereditary Cancer Predisposition Syndromes

Kenneth Offit, Peter Thom, and Donna Bernstein

SUMMARY OF KEY POINTS

- The discovery of inherited mutations of oncogenes and tumor suppressor genes associated with increased risk for cancer provides important clinical opportunities for early detection and prevention of common and rare forms of human malignancies.
- Syndromes of cancer predisposition often involve multiple organ systems, affect paired organs with bilateral or multifocal tumors, and have onset at an earlier age compared to nonfamilial tumors. The diagnosis of particular cancer predisposition syndromes can usually be confirmed with molecular genetic testing of patients who have hereditary malignancies. Genetic testing can then be extended to relatives as a predictive test to guide their preventive management.
- Medical, surgical, and radiation oncologists, genetic counselors, and allied professionals are playing a leading role in the integration of genetic testing into the practice of preventive oncology. This chapter reviews both common and more recently described familial cancer syndromes, with an emphasis on the clinical application of cancer genetic testing in the management of patients who have or are at risk for cancer.

Over the past decade, the availability of clinical testing for inherited mutations of cancer predisposition genes has had a major impact on the practice of clinical oncology.[1] As these genes were identified and characterized, guidelines for the responsible clinical translation of this information were developed by medical and surgical subspecialty societies (e.g., the statements of the American Society of Clinical Oncology in 1996[2] and 2003[3] and related educational materials[4–6]). These guidelines emphasized that in the process of offering a predictive genetic test to a patient or family that is affected by cancer, the provider and the individual who is being tested must be prepared to deal with all the medical, psychological, and social consequences of a positive, negative, or ambiguous result. These guidelines define the form and content of genetic counseling as a component of cancer risk assessment and management.

A selected set of syndromes of cancer predisposition, listed in Table 12-1, is reviewed in this chapter. More detailed discussions of breast and colon cancer susceptibility are found in the chapters that discuss these tumors. A more comprehensive list of syndromes is provided in Table 12-2. Whether offered by a physician, genetic counselor, or other health care professional, genetic testing for inherited cancer risk requires careful informed consent. The elements of informed consent for genetic testing are summarized in Box 12-1.

Genes whose alterations result in hereditary predisposition to cancers have been classified as oncogenes or tumor suppressor genes. The molecular mechanisms of these two classes of genes are presented in previous chapters. A minority of human cancer predisposition syndromes result from inherited mutations of oncogenes (e.g., *RET, MET, KIT*). The majority of cancer predisposition syndromes are due to inherited defects in tumor suppressor genes. The tumor suppressor genes have been subdivided into "gatekeepers" such as *APC, p53, Rb,* and *VHL,* which directly prevent runaway cell growth, and "caretakers" such as *ATM, MSH2,* and *MLH1,* defects which indirectly cause neoplasia by leading to increased mutations of other critical genes.[7] Yet a third class of genes, including *PTEN* and *SMAD4,* act as "landscapers," since defects in these genes cause alterations in the "terrain" for epithelial cell growth, leading to eventual neoplastic changes. Complicating this descriptive approach is the observation that the same gene may act as a "landscaper" for one tumor system and a "gatekeeper" for another, violating the principle of Occam's razor; furthermore, some recently characterized pathways do not fit any of these models. In practice, this etiologic nosology of genetic mechanisms is of less clinical relevance than are the phenotypes of these cancer susceptibility syndromes (see Table 12-2). For this reason, the discussion that follows is grouped by the major component tumors of the organ system that is primarily affected. The syndromes that are included in this chapter are the ones that are most commonly encountered in oncologic practice, as well as several recently defined entities associated with mutations of novel cancer susceptibility genes. The most common of these syndromes, predisposing to cancers of the breast, ovary, colon, and prostate, affect tens of thousands of Americans who are diagnosed with these cancers each year in the United States and result in increased risk for a second neoplasm for the millions of cancer survivors.

MAJOR SYNDROMES OF CANCER PREDISPOSITION

The major syndromes of cancer predisposition that affect adults include common syndromes associated with breast, ovarian, colon, and prostate cancer as well as a number of other less common but equally important cancer predispositions. Some of these syndromes, including multiple endocrine neoplasia type I, retinoblastoma, melanoma, and von Hippel Lindau syndrome, are described elsewhere in this text. For comprehensive reviews of these cancer predispositions, see the following sources: for multiple endocrine neoplasia type I, Lakhani and colleagues[8] and Marx[9]; for retinoblastoma, Balmer and colleagues[10]; for melanoma, Hayward[11] and Felsani and colleagues[12]; and for von Hippel Lindau syndrome, Kaelin[13], Woodward and

Table 12-1 Selected Cancer Predisposition Syndromes

Syndrome	Gene
Major cancer predisposition syndromes	
Hereditary breast and ovarian cancer syndromes	*BRCA1, BRCA2*
Familial adenomatous polyposis	*APC, MYH*
Hereditary nonpolyposis colon cancer syndrome	*hMSH2, hMLH1, hMSH6*
Hereditary prostate cancer	Multiple loci
Multiple endocrine neoplasias (I, II)	*MEN1, RET*
Hereditary melanoma syndromes	*CDKN2A^{p16}, CDK4*
Familial retinoblastoma	*RB1*
Neurofibromatosis I, II	*NF1, NF2*
von Hippel Lindau syndrome	*VHL*
Recently described cancer predisposition syndromes	
Gorlin syndrome	*PTCH*
Carney complex	*PRKAR1A*
Cowden syndrome	*PTEN*
Birt-Hogg-Dubé syndrome	*BHD*
Rhabdoid predisposition syndrome	*hSNF5/INI1*
Hereditary gastric cancer	*CDH1*
Hereditary leiomyomatosis and renal cell cancer syndrome	*FH*
Paraganglioma/chemodectoma syndromes	*SDH-A, -B, -C, -D*

Box 12-1. ELEMENTS OF INFORMED CONSENT FOR GENETIC CANCER TESTING

1. *What the test is intended to do,* that is, determine whether a mutation can be detected in a specific cancer susceptibility gene.
2. *What can be learned from both a positive and negative test,* including information on the magnitude of health risks associated with a positive test as well as the risks that may remain even after a negative test.
3. *The possibility that no additional risk information will be obtained* after testing or that the test will result in a finding of unknown significance (e.g., a polymorphism) that might require further studies.
4. *The options for approximation of risk without genetic testing,* for example, using empiric risk tables for breast cancer given differing family histories.
5. *The risk of passing a mutation on to children,* including options for assisted reproduction (e.g., preimplantation genetics, if discussion appropriate).
6. *The importance of notification of family members that they might share a hereditary risk for cancer* with every effort made to assist in contacting of family members and providing them access to counseling and testing.
7. *The medical options and limited proof of efficacy for surveillance and cancer prevention for individuals with a positive test* as well as the accepted recommendations for cancer screening even if genetic testing is negative.
8. *The technical accuracy of the test,* that is, the sensitivity and specificity of the analytic methodology.
9. *The risks of psychological distress and family disruption* whether a mutation is found or not found.
10. *The risk of employment and/or insurance discrimination* following disclosure of genetic test results and the *level of confidentiality of results* compared to other medical tests and procedures.
11. *The risks that nonrelatedness of family members will be discovered* and how this information will be disclosed (or not disclosed).
12. *The fees and costs of testing,* including the laboratory test and the associated consultation by the health professional who is providing pretest education, results disclosure, and follow-up, and the costs of preventive procedures, which might not be covered by third-party payers.

Modified from Offit K: Clinical Cancer Genetics: Risk Counseling and Management. New York, Wiley-Liss, 1998, with permission.

Maher,[14] and Sudarshan and Linehan.[15] For reviews of neurofibromatosis, which are not covered elsewhere in this text, see Ferner,[16] Lee and Stephenson,[17] and Hottinger and Khakoo.[18]

Breast and Ovarian Cancer Syndromes

Clinical Features

Although only about 18,000 cases of breast cancer each year are associated with an obvious hereditary predisposition, over 200,000 breast cancer survivors in the United States developed primary cancers as a result of a hereditary predisposition and remain at risk for secondary cancers.[19,20] Genetic testing has emerged as one of the most important indicators of risk factors pointing to a need for intensified screening for breast cancer.[21] When detected at an early stage, more than 90% of breast cancers are curable. These statistics underscore the rationale for the use of genetics in clinical oncology. The details of the management of women and men who are at hereditary risk for breast cancer have recently been reviewed in detail[22] and will be summarized here.

From 1 in 150 to 1 in 800 individuals in the population carry a genetic susceptibility to breast cancer,[23–25] and the prevalence is much higher in certain ethnic groups. Syndromes of breast cancer susceptibility are linked to mutations of *BRCA1* and *BRCA2,* as well as a smaller number of cases with germline mutations of *p53, PTEN, CHEK2,* and rarer syndromes (Table 12-3).

Cowden syndrome was initially described as a dominant inheritance of multiple hamartomatous lesions, including papillomas of the lips and mucous membranes and acral keratoses of the skin.[26] As described following, this syndrome was ultimately linked to germline mutations of *PTEN*. In Li-Fraumeni syndrome, early-onset breast cancer occurs with soft-tissue sarcomas, osteosarcoma, leukemia, brain tumors, adrenal cortical tumors, and other cancers. Rarely, a typical breast-ovarian kindred may be found to have a germline *p53* mutation.[27] In Northern European families, specific mutations of *CHEK2* are associated with familial breast cancer.[28] However, the common European *CHEK2* mutation is rare in North America.[29] Both benign and malignant breast tumors occur in Muir-Torre syndrome, a variant of hereditary nonpolyposis colon cancer that is associated with germline mutations of *MSH2* and *MLH1*. Women with Peutz-Jeghers syndrome carry germline mutations in the *STK11* gene and are at increased risk for breast cancer. Although this situation is still under study, initial studies of selected kindreds demonstrated that carriers of some *ATM* mutations have an elevated breast cancer risk.[30]

All told, linkage studies suggest that in about 50% of breast cancer kindreds, the cancer was linked to *BRCA1,* in 30% to *BRCA2,* and in the remainder to *BRCA3* and other as yet unidentified genes.[31] In up to two thirds of families with both male and female breast cancer, the cancers were due to *BRCA2,* while over 80% of families with both breast and ovarian cancer harbored *BRCA1* mutations.[32] Multiple, common, lower-penetrance genes are likely to account for a significant component of currently unexplained familial breast cancer

Table 12-2 Syndromes of Inherited Cancer Predisposition in Clinical Oncology

Syndrome (OMIM* Entry)	Component Malignancies	Mode of Inheritance	Genes
HEREDITARY BREAST CANCER SYNDROMES			
Hereditary breast and ovarian cancer syndrome	Breast cancer	Dominant	*BRCA1*
	Ovarian cancer		*BRCA2*
113705	Colon cancer		
600185	Prostate cancer		
	Pancreatic cancer (medulloblastoma/ Fanconi anemia)	Recessive	*BRCA2*
Li-Fraumeni syndrome	Soft-tissue sarcoma	Dominant	*p53*
151623	Breast cancer		*CHK2*
	Osteosarcoma		
	Leukemia		
	Brain tumors		
	Adrenocortical carcinoma		
Cowden syndrome	Breast cancer	Dominant	*PTEN*
158350	Thyroid cancer		
	Lhermitte-Duclos disease		
	Other cancers		
Bannayan-Riley-Ruvalcaba syndrome	Breast cancer	Dominant	*PTEN*
153480	Meningioma		
	Thyroid follicular cell tumors		
Ataxia telangiectasia	Leukemia	Recessive	*ATM*
208900	Lymphoma		
	Ovarian cancer		
	Gastric cancer		
	Brain tumors		
	Thyroid, parotid cancer		
	Colon cancer		
	Other cancers		
HEREDITARY GASTROINTESTINAL MALIGNANCIES			
Hereditary nonpolyposis colon cancer (HNPCC), including "Lynch II" syndrome	Colon cancer	Dominant	*MSH2*
	Endometrial cancer		*MLH1*
120435	Ovarian cancer		*MSH6*
120436	Pancreatic cancer		
114500	Stomach and small bowel cancers		
114400			
Familial adenomatous polyposis (including attenuated phenotype and Ashkenazi low-penetrance phenotype)	Colon cancer	Dominant, recessive	*APC, MYH*
	Gastric cancer		
175100	Thyroid cancer		
	Hepatoblastoma		
	Medulloblastoma		
	Astrocytoma		
Hereditary gastric cancer	Stomach cancers	Dominant	*CDH1*
137215	Lobular breast carcinomas		
	Colon cancer		
Juvenile polyposis	Gastrointestinal cancers	Dominant	*SMAD4/DPC4*
174900			*BMPR1A PTEN*

Continued

Table 12-2 Syndromes of Inherited Cancer Predisposition in Clinical Oncology—cont'd

Syndrome (OMIM* Entry)	Component Malignancies	Mode of Inheritance	Genes
Hereditary pancreatic cancer susceptibility 606856	Pancreatic cancer	Dominant	Palladin
Peutz-Jeghers syndrome 175200	Colon cancer Small bowel cancer Breast cancer Ovarian cancer Pancreatic cancer	Dominant	*STK11*
Hereditary melanoma pancreatic cancer syndrome 606719	Pancreatic cancer Melanoma	Dominant	*CDKN2A/p16*
Hereditary pancreatitis 167800	Pancreatic cancer	Dominant	*PRSS, SPINK1, CFTR*
Turcot syndrome 276300	Colon cancer Basal cell carcinoma Ependymoma Medulloblastoma Glioblastoma Papillary thyroid carcinoma Leukemia	Dominant	*MLH1* *APC* *PMS2*
Familial gastrointestinal stromal tumor 606764	Gastrointestinal stromal tumors	Dominant	*c-KIT*
GENODERMATOSES WITH CANCER PREDISPOSITION			
Melanoma syndromes 155600 155601	Malignant melanoma	Dominant	*CDKN2 (p16)* *CDK4* *CMM*
Basal cell cancers (Gorlin syndrome) 109400	Basal cell cancers Brain tumors	Dominant	*PTCH*
Cowden syndrome	See above	Dominant	*PTEN*
Neurofibromatosis 1 162200	Neurofibrosarcomas Pheochromocytomas Optic gliomas	Dominant	*NF1*
Neurofibromatosis 2 101000	Vestibular schwannomas	Dominant	*NF2*
Tuberous sclerosis 191100	Myocardial rhabdomyoma Multiple bilateral renal angiomyolipoma Ependymoma Renal cancer Giant cell astrocytoma	Dominant	*TSC1* *TSC2*
Carney complex 160980	Myxoid subcutaneous tumors Primary adrenocortical nodular hyperplasia Testicular Sertoli cell tumor Pituitary adenoma Mammary ductal fibroadenoma Schwannoma Pheochromocytoma	Dominant	*PRKAR1A*

Table 12-2 Syndromes of Inherited Cancer Predisposition in Clinical Oncology—cont'd

Syndrome (OMIM* Entry)	Component Malignancies	Mode of Inheritance	Genes
Muir Torre syndrome	Sebaceous carcinoma	Dominant	*MLH1*
158320	Sebaceous epitheliomas		*MSH2*
	Sebaceous adenomas		
	Basal cell carcinoma		
	Colon cancer		
	Duodenal carcinoma		
	Laryngeal carcinoma		
	Malignant gastrointestinal tract tumors		
	Malignant genitourinary tract tumors		
	Breast cancer		
Xeroderma pigmentosum	Skin cancer	Recessive	*XPA*
278730	Melanoma		*XPC*
278700	Leukemia		*XPD (ERCC2)*
278720			*XPF*
278760			
Rothmund-Thomson syndrome	Basal cell carcinoma	Recessive	*RECQL4*
268400	Squamous cell carcinoma		*RECQL5*
	Osteogenic sarcoma		
LEUKEMIA/LYMPHOMA PREDISPOSITION SYNDROMES			
Bloom syndrome	Leukemia	Recessive	*BLM*
210900	Carcinoma of the tongue		
	Esophageal carcinoma		
	Wilms' tumor		
	Colon cancer		
Fanconi anemia 607139, 300515, 227645, 605724, 227646, 600901, 602956, 605882, 608111, 603467, 609644, 610832	Leukemia Esophogus cancer Skin carcinoma	Recessive	*FANCA, FANCB, FANCD1, FANCC, FANCE, FANCD2, FANCF, FANCG, FANCL, FANCJ, FANCM, FANCN*
Shwachman-Diamond syndrome	Hepatoma	Recessive	*SBDS*
260400	Myelodysplasia		
	Acute myelogenous leukemia		
Nijmegen breakage syndrome	Lymphoma	Recessive	*NBS1*
251260	Glioma		
	Medulloblastoma		
	Rhabdomyosarcoma		
Cannale Smith syndrome	Lymphoma	Dominant	*FAS*
601859			*FASL*
Immunodeficiency syndromes			
Wiskott Aldrich	Hematopoietic malignancies	X-linked recessive	*WASP*
301000	Lymphomas		
Common variable immune deficiency		Recessive	*TNFRSF13B*
240500		Dominant	Unknown

Continued

Table 12-2 Syndromes of Inherited Cancer Predisposition in Clinical Oncology—cont'd

Syndrome (OMIM* Entry)	Component Malignancies	Mode of Inheritance	Genes
Severe combined immune deficiency	B-cell lymphoma	X-linked recessive	*IL2RG*
102700		Recessive	*ADA*
300400			*JAK3*
202500			*RAG1*
			RAG2
			IL7R
			CD45
			Unknown
X-linked Lymphoproliferative syndrome	Lymphoma	X-linked recessive	*SH2D1A*
308240			
GENITOURINARY CANCER PREDISPOSITION SYNDROMES			
Hereditary prostate cancer	Prostate cancer	Dominant	*HPC1*
176807			*HPCX*
601518			*PCAP*
			PCBC
			PRCA
Simpson-Golabi-Behmel syndrome	Embryonal tumors	X-linked recessive	*GPC3*
312870	Wilms' tumor		
Von Hippel Lindau syndrome	Hemangioblastomas of retina and central nervous system	Dominant	*VHL*
193300	Renal cell cancer		
	Pheochromocytomas		
Beckwith-Wiedemann syndrome	Wilms' tumor	Dominant	*CDKN1C*
130650	Hepatoblastoma		
	Adrenal carcinoma		
	Gonadoblastoma		
Wilms' tumor syndrome	Nephroblastoma	Dominant	*WT1*
194070			
WAGR (Wilms tumor, aniridia, growth retardation)	Wilms' tumor	Dominant	*WT1*
194072			
Birt-Hogg-Dubé syndrome	Renal tumors	Dominant	*FLCL*
135150			
Papillary renal cancer syndrome	Renal cancer	Dominant	*MET*
605074			
164860			
Constitutional t(3;8) translocation	Renal cell cancer	Dominant	*TRC8*
603046			
Hereditary bladder cancer	Bladder cancer	Sporadic	Unknown
		Unknown	
109800			
Hereditary testicular cancer	Testicular cancer	Possibly X-linked	Unknown
273300		Possibly recessive	Unknown
Rhabdoid predisposition syndrome	Rhabdoid tumors	Dominant	*HSNF5/INI1*
601607			

Table 12-2 Syndromes of Inherited Cancer Predisposition in Clinical Oncology—cont'd

Syndrome (OMIM* Entry)	Component Malignancies	Mode of Inheritance	Genes
CENTRAL NERVOUS SYSTEM/VASCULAR CANCER PREDISPOSITION SYNDROMES			
Hereditary paraganglioma	Paraganglioma	Dominant	*SDHD*
185470	Pheochromocytoma		*SDHC*
115310			*SDHB*
Retinoblastoma	Retinoblastoma	Dominant	*RB1*
180200	Osteosarcoma		
Rhabdoid predisposition syndrome	Rhabdoid tumors	Dominant	*HSNF5/INI1*
601607	Medulloblastoma		
	Choroid plexus tumors		
	Primitive neuroectodermal tumors		
SARCOMA/BONE CANCER PREDISPOSITION SYNDROMES			
Multiple exostoses	Chondrosarcoma	Dominant	*EXT1*
133700			*EXT2*
133701			
Leiomyoma/renal cancer syndrome	Papillary renal cell carcinoma	Dominant	*FH*
605839	Uterine leiomyosarcomas		
Carney complex	See above	Dominant	*PRKAR1A*
Werner syndrome	Sarcoma/osteosarcoma	Recessive	*WRN*
277700	Meningioma		*RECQL2*
			RECQL3
Li-Fraumeni syndrome	Soft tissue sarcoma	Dominant	*TP53, CHEK2*
151623	Osteosarcoma		*LFS3*
609266	Breast cancer		
	Brain tumors		
	Pancreatic cancer		
	Lung cancer		
	Leukemia		
	Adrenocortical cancer		
	Prostate cancer		
	Colon cancer		
	Wilms' tumor		
ENDOCRINE CANCER PREDISPOSITION SYNDROMES			
MEN1	Pancreatic islet cell tumors	Dominant	*MEN1*
131100	Pituitary adenomas		
	Parathyroid adenomas		
MEN2	Medullary thyroid cancers	Dominant	*RET*
171400	Pheochromocytoma		
	Parathyroid hyperplasia		
Hereditary papillary thyroid cancer	Papillary thyroid cancer	Dominant	*RET*
188500			

*OMIM, On-Line Mendelian Inheritance in Man: http://www3.ncbi.nlm.nih.gov/Omim/.

Table 12-3 Known Genes Associated with Hereditary Breast Cancer Predisposition

Gene	Syndrome	Relative Risk of BC	BC Risk by Age 70	Associated Cancers
HIGH PENETRANCE				
BRCA1[a–f]	HBOC	17 (20–29) 32 (40–49) 14 (60–69)	39–87%	Ovarian, other
BRCA2[a,c–f]	HBOC	19 (20–29) 10 (40–49) 11 (60–69)	26–91%	Ovarian, pancreatic, prostate, other
p53[g–i]	Li-Fraumeni syndrome	1.46 overall 5.96 (15–29)	56% to 45 years >90% to 70 years	Soft-tissue sarcoma, osteosarcoma, brain tumors, adrenocortical carcinoma, leukemia, other
PTEN[j–l]	Cowden disease Bannayan-Riley-Ruvalcaba syndrome Proteus Proteus-like syndrome	~2–4	25–50%	Thyroid (follicular and rarely papillary) endometrial, genitourinary, other
STK11/LKB1[m,n]	Peutz-Jeghers syndrome	~15	54%	Small intestine, colorectal, uterine, testicular and ovarian sex chord tumors, other
CDH1[o–q]	Hereditary diffuse gastric carcinoma	~3.25	39%	Lobular breast, diffuse gastric, other
LOW PENETRANCE				
ATM (heterozygote)[r–t]	Ataxia-telangiectasia in homozygotes	~3–4	—	Undefined in heterozygotes
CHK2 (CHEK2)[u–x]	Li-Fraumeni variant	2 (women) 10 (men)	—	Undefined
BRIP1[y]	Fanconi anemia in heterozygotes/ compounds	2	—	Undefined in heterozygotes
PALB2[z]	None known	2.3	—	Undefined in heterozygotes

BC, breast cancer; HBOC, hereditary breast and ovarian cancer syndrome.

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risk.[33] Two such low-penetrance breast cancer alleles that were revealed in large population studies are *BRIP1* and *PALB2*.[34–36] Recently, a host of putative lower-penetrant gene mutations have been identified through whole-genome association studies,[37,38] although the clinical relevance of these associations remains unclear.

Compared to the 10% breast cancer risk for women in the general population, estimates of the breast cancer risk that is conferred by a common susceptibility gene ranged from 67% to 69% by age 70 based on epidemiologic analyses.[23,24] Genetic linkage studies of families that were selected because of early-onset breast or ovarian cancer gave risk estimates as high as 70% to 90% in families in which mutations of either of these two genes were segregated.[39–41] Ovarian cancer risks in these families varied from 10% to 80%, and risk for a second breast cancer was as high as 64% by age 70. More recent estimates based on population studies led to slightly lower risk estimates, with a lifetime breast cancer risk of 56% by age 70 (confidence interval: 40% to 73%), and ovarian cancer risk estimated at 16%.[42] Penetrance estimates that were determined through clinic-based ascertainment of families revealed a 64% risk for breast or ovarian cancer by age 70.[43] The role of ascertainment and other possible biases in deriving these estimates as well as risks for cancer of the prostate, colon, pancreas, and other sites in *BRCA* mutation carriers has been reviewed.[44] In addition to Fanconi anemia, individuals with compound *BRCA2* mutations may develop childhood medulloblastomas.[45]

Genetics

BRCA1 is a large gene, spanning over 100,000 bases of genomic DNA with 22 coding and 2 noncoding exons. *BRCA2* is also large, consisting of 27 exons across 70 kb of genomic DNA. Both genes, by coincidence, have a large exon 11. An update of reported mutations is accessible through the Internet at http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic.

The majority of *BRCA1* mutations cause premature truncation of the peptide by frameshift or nonsense sequence changes. However, many of the 5% to 10% of *BRCA* mutations that are missense are problematic because they are of unknown clinical significance. The proportion of these variants that are of unknown significance was as high as 10% to 23% in some series, posing counseling challenges.[46,47] The role of *BRCA1* and *BRCA2* in DNA damage response and homologous recombination is reviewed elsewhere.[48]

Founder *BRCA* mutations have been documented in genetically isolated populations. In North American families, the most common founder mutations occur in individuals of Ashkenazi Jewish origin. These include a two-base-pair deletion in codon 23 of *BRCA1,* termed 185delAG, another *BRCA1* mutation, 5382insC, and the 6174delT mutation in *BRCA2*.[49–51] About 1 in 40 Ashkenazi Jews harbor one of the common *BRCA1* or *BRCA2* mutations,[42,43,50] a relatively high carrier frequency for an inherited cancer predisposition syndrome. Other mutations in *BRCA1* and *BRCA2* occur in the Ashkenazim; 16 out of 737 Ashkenazi Jews who were tested in a clinic-based ascertainment had a nonfounder mutation (2%).[52] In another study of Ashkenazi individuals with a personal history of breast or ovarian cancer who had previously been shown not to have a founder mutation, 3 of 70 (4.3%) had a deleterious nonfounder mutation.[53] Founder mutations in populations other than the Ashkenazim have also been observed.[54–56]

BRCA1-linked tumors are associated with a medullary subtype and higher mitotic indices.[57] They were of higher grade, were more frequently estrogen and progesterone receptor negative,[58,59] and demonstrated a basal-like phenotype.[60] They displayed a more "aggressive" phenotype, including a higher proportion of cells in S phase, and other indices.[57,59,61–63] The prognostic significance of *BRCA* mutations is still being defined.

Clinical Management

Three elements of breast surveillance that are recommended to *BRCA* heterozygotes are self-examination, clinician examination, and mammography. The evidence base underlying these recommendations has been reviewed,[22,64] and updated guidelines are available on the Web.[65]

Increasingly, breast cancer screening including mammography and magnetic resonance imaging (MRI) together have been shown to have greatest sensitivity.[66] For women who are at the highest hereditary risk for breast cancer, those whose breasts are difficult to examine, or those who have had biopsies showing atypia, it might be appropriate to discuss the option of removing the healthy breasts as a preventive measure (prophylactic mastectomy). Retrospective studies support the risk-reducing role of surgery in high-risk patients[67,68] (also reviewed in the work of Kinzler[7]). Prospective and combined consortium studies have also shown the efficacy of this approach.[69,70]

Because of their antiestrogen properties, tamoxifen, raloxifene, and a newer class of synthetic estrogen receptor modulators emerged as hormonal chemopreventive agents that have been shown to decrease breast cancer rates in individuals who are at increased risk.[71] The safety of these drugs in premenopausal women remains to be established. Two studies on the impact of tamoxifen on subsequent breast cancer risk in *BRCA1* and *BRCA2* mutation carriers have shown conflicting conclusions,[72,73] though only one of these studies was sufficiently powered to reach significant results. Tamoxifen was confirmed to decrease contralateral breast cancer risk in a follow-up of one of these studies of *BRCA* mutation carriers.[74]

Small trials have demonstrated the ability of ultrasound with Doppler and CA-125 to find early-stage ovarian cancers in *BRCA* mutation carriers.[75,76] However, the efficacy of this approach has not been proven in large, prospective studies. Therefore, prophylactic removal of the ovaries is presented as an option to women with strong family histories of ovarian cancer, in families linked to *BRCA1* or *BRCA2,* or to women who are considering hysterectomy in the setting of a germline mutation associated with nonpolyposis colon cancer syndrome. Studies have confirmed that such surgeries may not only decrease the incidence of subsequent breast and ovarian cancer, but also find occult early stage ovarian neoplasms,[77,78] decreasing mortality.[79] These studies have also confirmed that serous surface carcinoma, also called *papillary serous carcinoma,* can still occur following prophylactic oophorectomy,[80,81] leading most authors to use the term *risk-reducing* salpingo-oophorectomy.

Combination oral contraceptives that contain estrogen and high-dose progestin result in a time-dependent, protective effect against ovarian cancer in some but not all studies of *BRCA* mutation carriers.[82–84] There remains the concern of a small increased risk of breast cancer due to oral contraceptives in this group, particularly in those with *BRCA1* mutations.[85]

Common Colon Cancer Predisposition Syndromes

Highly penetrant, dominant, susceptibility syndromes account for about 5% of colon cancer. The most common syndrome is hereditary nonpolyposis colon cancer, with familial adenomatous polyposis constituting a rarer familial syndrome. For adults, genetic epidemiologic analyses suggested a common susceptibility allele for both colon cancer and adenomatous polyps that accounted for at least 15% and possibly half of cases.[86,87]

Polyposis Syndromes

FAMILIAL ADENOMATOUS POLYPOSIS

CLINICAL FEATURES. Familial adenomatous polyposis (FAP; adenomatous polyposis coli) presents with hundreds to thousands of adenomatous polyps at a young age. Virtually all affected individuals exhibit polyposis by age 35 years, and all will develop colon cancer. Colon cancer is therefore inevitable if the colon is not removed; the cancer occurs at an average age of 39 years. Flexible sigmoidoscopy at an early age establishes the diagnosis, and prophylactic colectomy is performed in the teen years. Patients remain at risk for primary

adenomas and carcinomas of the duodenum and rectum as well as desmoid tumors, osteomas, thyroid carcinoma, hepatoblastoma, and other hepatopancreatic tumors.[88]

Genetics. FAP arises from germline mutations in the *APC* gene.[89] Genotype phenotype correlations have been described, particularly for congenital hypertrophy of the retinal epithelium and the number of polyps observed. An attenuated form of FAP is associated with mutations at the extreme 5′ and 3′ ends of the gene.[90,91] Up to 30% of patients with multiple adenomas (15 to 100 adenomas) who test negative for *APC* mutations carry biallelic mutations in *MYH,*[92] discussed in detail later.

Clinical Management. In classic FAP, *APC* gene testing should be performed by 10 to 12 years of age, about the time that sigmoidoscopy begins. Unaffected individuals with wild-type *APC* who have an affected family member with a known mutation are screened in the same way as the general population.[93] In the case of attenuated FAP, in which adenomas might not occur until the twenties or thirties, the age at which genetic testing and clinical surveillance begin is not clearly defined. Once an *APC* gene mutation has been identified and when adenomas are found, prophylactic colectomy is performed, usually in the teen years.[94] Sulindac, a nonsteroidal anti-inflammatory drug, may reduce adenoma development in individuals with FAP, and similar effects were noted with celecoxib, a COX-2 inhibitor.[95,96] However, the possibility of delaying colectomy while patients are treated pharmacologically has not yet been established. Patients require lifelong surveillance for extracolonic tumors, including tumors of the upper GI tract as well as the ileal pouch (if proctocolectomy is performed).[97]

***MYH*-ASSOCIATED POLYPOSIS.** Some FAP probands carry biallelic mutations in the base excision repair gene, *MYH.*[92,98] *MYH*-associated polyposis (MAP) is considered a recessive syndrome; parents of affected homozygote or compound heterozygote mutation carriers have been reported to be unaffected.[99] However, both monoallelic and biallelic germline mutations in *MYH* have been associated with multiple adenomas.[99,100] Biallelic carriers have a higher frequency of CRC than do monoallelic patients.[101] Patients with multiple adenomas (more than 15) without *APC* mutations are more likely to have biallelic *MYH* mutations than are controls[100,102] Combining *APC* and *MYH* sequencing increases the yield of diagnosis from 34.4% to 41.3%.[103] The mutations Y165C and G382D are recurring in Caucasian Europeans, making up 86% of biallelic mutations in three series.[99–101] In 358 early-onset polyposis cases that were unselected for *APC* mutation status, two cases carried biallelic *MYH* mutations, and eight *MYH* mutation heterozygotes were identified. No *MYH* mutations were detected in 354 controls, leading the authors to conclude that biallelic *MYH* mutations might account for up to 3% of early onset colorectal cancer. Patients in this series did not exhibit profuse polyposis, consistent with previous reports, and distally located tumors were prevalent.[104,105]

Management. As with FAP, prophylactic colectomy is generally recommended for *MYH*-associated polyposis. Because over one third of biallelic *MYH* mutation carriers might not develop multiple polyps but remain at elevated colorectal cancer risk, colonoscopy with polypectomies is thought to be not sufficiently preventive for this population.[106] Surgical options for *MYH* mutation carriers include ileorectal anastomosis for younger patients with few rectal adenomas and a milder family history or with attenuated FAP or total proctocolectomy with the creation of an ileal pouch and anal anastomosis for more diffuse polyposis.

Hereditary Nonpolyposis Colon Cancer

CLINICAL FEATURES. A constellation of colon and endometrial cancers became known as Lynch syndrome or hereditary nonpolyposis colon cancer (HNPCC).[107] Five additional tumor sites demonstrated increased observed/expected (O/E) ratios in HNPCC kindreds: cancers of the stomach (O/E = 4.1), ovary (O/E = 3.5), small intestine (O/E = 25), ureter (O/E = 22), and kidney (O/E = 3.2).[108] There is a 70% to 75% risk of colon cancer by age 65 in HNPCC families.[109,110] The penetrance was 92% by age 60 in one series,[111] with a median age at colon cancer diagnosis of 44 to 46 years. A 40% to 60% endometrial cancer risk by age 70 was reported,[112–115] with a median age of onset from the late forties to early fifties.[116] The risk for endometrial cancer in the general population is 3%.

At a 1991 meeting in Amsterdam, the International Collaborative Group on HNPCC defined the syndrome as (1) histologically verified colorectal cancer in three or more relatives, including a first-degree relative of the other two; (2) colorectal cancer involving at least two generations; and (3) one or more colorectal cancers diagnosed before 50 years of age. The subsequent "Amsterdam II criteria" for HNPCC were redefined to include extracolonic HNPCC-associated cancers.[117] In 1996, guidelines known as the Bethesda criteria delineated individuals at risk for HNPCC for whom molecular genetic analysis may be considered.[118] A revised set of Bethesda Guidelines was developed to identify subjects who are at high risk of having a germline mismatch repair gene mutation[119] Multivariate logistic regression risk models using personal and family medical histories estimate the probability of carrying an HNPCC mutation.[120–122]

While there do not appear to be defining histologic features of HNPCC tumors, mucinous types are more common. Adenomas, like the cancers in HNPCC, appear more frequently on the right side. Multiple lesions occur in about 20% of at-risk individuals. Generally, fewer than 100 polyps present in these cases.[123]

GENETICS. About 45% to 70% of HNPCC families harbor mutations in one of the three genes: *MSH2, MLH1,* and *MSH6.*[124–127] Mutations in two other genes, *PMS1* and *PMS2,* have been associated with HNPCC syndrome,[128] and rare, atypical Lynch syndrome pedigrees with identifiable *MLH3* mutations have also been described.[129] Of these, mutations of *MSH2* and *MLH1* were far more frequent than the others, accounting for about 30% each of families meeting Amsterdam criteria for HNPCC. Over 75% of mutations in *MSH2* and *MLH1* were inactivating insertions, deletions, alterations in premessenger RNA splicing signals, and nonsense mutations. However, 23% of 120 mutations surveyed were missense mutations.[130] Mutations of *MSH6* less frequently result in the "replication error repair" phenotype but account for a significant number of familial colon cancer families.[131] The replication error repair phenotype is commonly detected as microsatellite instability (MSI) utilizing polymerase chain reaction screening of tumors with microsatellite markers. The MSI phenotype is present in about 80% of HNPCC-associated colon cancers[132] and in about 15% of sporadic colon tumors,[133] as well as in other tumors associated with HNPCC (e.g., uterine, gastric cancers). MSI results in a genome-wide increased mutation rate, causing mutations in oncogenes, tumor suppressors, and in microsatellite regions.[134]

In young patients (less than 35 years old), the detection of the MSI phenotype is quite common (seen in 58%) and may be associated with detectable HNPCC gene mutations in only half of the cases.[135] Testing for MIS and/or immunohistochemistry (IHC) for HNPCC-associated protein expression is recommended in all patients with colorectal cancer who are younger than 50 years of age, have a family history of colon or endometrial cancer, or have a personal history of metachronous colon or endometrial cancers.[136]

Lack of MLH1 or MSH2 protein expression in tumors is correlated with MSI, allowing the use of immunohistochemistry along with MSI analysis.[137] Lack of expression of the *MLH1* protein indicates that germline testing should begin with the *MLH1* gene. Similarly, if there is no expression of MSH2, the germline testing should begin with *MSH2* gene. Immunohistochemical analysis can also be

utilized to evaluate MSH6 and PMS2 protein expression. In older patients with colorectal cancer, hypermethylation of the *MLH1* promoter may account for the lack of MLH1 protein expression.[138] This epigenetic (nonhereditary) mechanism of *MLH1* promoter hypermethylation is responsible for the majority of the remaining patients whose tumors are characterized by defective DNA mismatch repair.[139]

CLINICAL MANAGEMENT. It has been shown that screening for cancer in HNPCC improves patient survival.[140] Individuals with HNPCC are advised to undergo colonoscopic surveillance every 1 to 2 years, preferably annually, starting at age 20 to 25 years and perhaps at age 30 for *MSH6* mutation carriers.[141,142] Endometrial cancer screening generally includes transvaginal ultrasound and endometrial biopsy at age 30 to 35 years. Annual urinalysis with cytology is also recommended, although minimal data support the efficacy in detecting urothelial tumors. A baseline upper endoscopy should be performed, but the optimal subsequent screening interval has yet to be established. Prophylactic subtotal colectomy is generally performed after the first malignancy diagnosis, sparing the rectum.[143] A retrospective study of prophylactic bilateral oophorectomy and hysterectomy showed protection from uterine and endometrial cancer,[144] though the estimates were influenced by a retrospective study design.[145] Nonetheless, a combination of risk-reducing bilateral oophorectomy and hysterectomy is a reasonable option after childbearing or at the time of subtotal colectomy for a colon cancer occurring in women with HNPCC.

Prostate Cancer

Clinical Features

Of the quarter of a million men who will be diagnosed with prostate cancer in 2008, about 5% to 10% will have a strong family history of the disease. The estimated prostate cancer susceptibility allele frequency is 0.003 to 0.006, meaning that about 1 in 170 to 1 in 85 individuals has inherited a genetic mutation, which in males confers susceptibility to prostate cancer. The penetrance for this dominant prostate cancer susceptibility syndrome was estimated to be 88% by age 85. The syndrome may account for 43% of prostate cancers that are diagnosed before age 56 and 9% that are diagnosed by age 85.[146,147] While only an estimated 2% of prostate cancer in the general population is diagnosed before age 56, this proportion is increasing with the introduction of newer screening modalities. The clinical features, stage, histology, and PSA at diagnosis of hereditary prostate cancer were comparable to those of nonhereditary cases.[147]

As Table 12-4 shows, hereditary prostate cancer has enormous genetic heterogeneity.[148] The first putative gene that was identified, *HPC1,* emerged after a genome-wide scan of 66 high-risk prostate cancer families revealing linkage to 1q24-25. Subsequently, germline *RNASEL* mutations on chromosome 1q25 were identified in high-risk prostate cancer families.[149] Analysis of 600 individuals from 91 prostate cancer kindreds revealed linkage to a locus on chromosome 1q24-q25, as did a meta-analysis of 772 prostate cancer kindreds by the International Consortium for Prostate Cancer Genetics. However, it was suggested that this region might be responsible for only a subset of hereditary prostate cancer.[150] *RNASEL* polymorphisms have been inconsistently associated with prostate cancer susceptibility; a meta-analysis supported only a modest effect.[151]

Table 12-4 Genetic Heterogeneity of Hereditary Prostate Cancer

Locus Name	Location	Putative Gene
HPC1	1q24-q25	*RNASeL*
HPC2	17p11	*ELAC2*
PCAP	1q42-q43	?
CAPB	1p36	*EPHB2*
HPCX	Xq27-q28	?
HPC20	20q13	?
—	8q24	?
—	7q11-21	?
—	3p26	?

In 2001, Tavtigian and colleagues performed a study of high-risk prostate cancer families from the Utah Population Database, providing evidence for linkage to *HPC2* on chromosome 17p.[152] Common variants of *ELAC2* segregated with prostate cancer in two of the pedigrees. Among 266 prostate cancer cases that were unselected for family history and 359 controls, two variants, Ser217Leu and Ala541Thr, were identified in 31.6% and 2.9%, respectively. Interestingly, the Ala541Thr genotype was found only in individuals with the Ser217Leu variant, conferring an elevated prostate cancer risk with an odds ratio of 2.37.[153] These findings were not supported by a subsequent series of 159 hereditary prostate cancer probands, 249 incident prostate cancer cases, and 222 controls[154] or by other series. A review of pooled data from various *ELAC2* studies that were analyzed by the investigators who originally identified *ELAC2* as a prostate cancer susceptibility gene confirmed that this gene does confer increased prostate cancer risk for approximately 2% of prostate cancer cases in the general population.[152,155]

Linkage analyses of 360 prostate cancer kindreds from North America, Sweden, and Finland demonstrated significant linkage to *HPCX* on Xq27-28, estimated to account for up to 16% of hereditary prostate cancer,[156] a finding that was confirmed by two other studies with no male-to-male transmission.[157,158] Another Finnish genome-wide linkage analysis identified 3p26 as a major prostate cancer susceptibility locus.[159] Genome-wide linkage studies identified 7q11-21 as a putative region for prostate cancer susceptibility among 36 Ashkenazi Jewish prostate cancer kindreds.[160] Recently, whole-genome admixture scans in 1597 African Americans identified a 3.8 Mb interval on chromosome 8q24 as significantly associated with susceptibility to prostate cancer,[161] and subsequent studies have confirmed 8q24 as a locus for up to three prostate cancer susceptibility alleles.[162] Linkage to *HPC20* at 20q13 was implicated in one study of 162 North American kindreds[163] but not in another study of 172 unrelated prostate caner kindreds.[164] A French series of 159 affected individuals identified *PCAP* at 1q42.2-43 as a prostate cancer susceptibility locus among Southern and Western Europeans with prostate cancer diagnosed at age 65 or younger, with no evidence for linkage to the other regions that were analyzed, including *HPC1* at 1q24-25, *HPCX* at Xq27-28, and *CAPB* at 1p36.[165]

Prostate cancer with a family history of brain cancer has shown linkage to 1p36.[166] However, an international collaborative analysis did not confirm linkage to 1p36 with prostate and brain cancer susceptibility exclusively, assessing five brain-prostate cancer kindreds that did show linkage to this region as a chance association.[167] *EPHB2* at 1p36 was biallelically disrupted in prostate cancer lines of brain metastasis origin.[168]

Other putative prostate cancer susceptibility loci that have been identified by linkage studies include 17q22, 15q11 in late-onset kindreds, and 4q35 with four or more affected family members[169]; a 79 C→T polymorphism in the cell cycle gatekeeper/tumor suppressor gene *CDKN1B* at 12p13[170]; the polymorphism H6D in *MIC-1*, a regulator of macrophage activity in inflammatory response[171]; a tetranucleotide TTTA repeat number polymorphism in the *CYP19* estrogen synthesis aromatase gene[172]; and mutations in the *p53* regulator *CHEK2.*[173–175]

Genetic heterogeneity remains the central issue in prostate cancer genetics. A large study of 1233 prostate cancer kindreds found significant positive LOD scores, suggesting linkage to at least nine

different regions.[176] At least two population-based series suggested a recessive mechanism because risk of disease was greater in siblings than in children of those who were affected.[177,178]

Candidate susceptibility alleles for hereditary prostate cancers have also included genes that encode receptors for two steroid hormones that influence cell division within the gland. A case-control study of 57 prostate cancer cases and 169 controls revealed that individuals carrying polymorphisms in the genes encoding the androgen receptor and vitamin D receptors were at increased risk for prostate cancer.[179] Despite an extensive literature, associations of the CAG repeat number polymorphism in exon 1 of the androgen receptor gene have generally not been confirmed in large cohorts,[180,181] emphasizing the importance of ethnic variance and other factors.[182] In some families, prostate cancer may be associated with already known cancer predisposition syndromes, such as *BRCA2* and *p53*.[183–185]

Clinical Management

The normal concentration of prostate-specific antigen (PSA) in the serum is 0 to 4 ng/mL. Values greater than 10 ng/mL are more likely to be associated with cancer. Transrectal ultrasound is performed in the setting of an increased PSA, with transrectal needle biopsy of any suspicious area guided by ultrasound or digital rectal examination. Current recommendations of the American Cancer Society and other professional societies include digital rectal examination and PSA screening for men between the ages of 50 and 70.[186] Initial evidence for the efficacy of this approach in decreasing mortality was demonstrated in a trial of 45,000 men.[187]

A study of individuals at increased risk for prostate cancer by virtue of a family history demonstrated the efficacy of intensive screening (PSA, digital rectal examination, transrectal ultrasound, and systematic as well as directed core biopsies).[188] Additional studies of annual PSA and biopsy for PSA greater than 3.0 targeted to those who are at hereditary risk are in progress.[189] A future option for hereditary prostate cancer risk reduction may include hormonal chemoprevention.[190] A large-scale chemoprevention trial of finasteride showed a modest delay in the appearance of prostate cancer but also sexual side effects and an increased risk of high-grade prostatic neoplasms.[191]

Multiple Endocrine Neoplasia Type 2

Clinical Features

Multiple endocrine neoplasia type 2a (MEN2a) is characterized by multiple endocrine tumors, particularly medullary thyroid carcinoma and pheochromocytoma. There is also hyperplasia of the parathyroid in one quarter of cases. Hypertension is the common presenting symptom, with diagnosis classically made by measurement of urinary VMA and metanephrine. Routine MEN2a screening has been directed to thyroid medullary lesions, with pentagastrin challenge to measure calcitonin response.[192] Measurement of serum ionized calcium has also been performed in the diagnostic evaluation.

MEN2b has an earlier age of onset than MEN2a; enlarged, nodular lips; a Marfanoid habitus; ganglioneuromatosis of the intestine; and other abnormalities.[193] This phenotype also includes medullary thyroid carcinoma, which may be more aggressive, and pheochromocytoma. Parathyroid disease is less common than in MEN2a.

Medullary thyroid carcinoma runs in families about 25% of the time, as a syndrome of site-specific familial medullary carcinoma of the thyroid (FMCT) or as MEN2.[194] Cases usually present in the third and fourth decades and are often bilateral and multifocal. Familial papillary thyroid cancer is distinct from FMCT and is associated with an increased incidence of colorectal cancer.[195]

Genetics

In 1993, it was observed that *RET* gene mutations were associated with MEN2a, MEN2b, and FMCT.[196,197] Specific *RET* gene mutations have been associated with MEN2a, MEN2b, and FMCT.[196,198–200] *RET* testing of sporadic cases of medullary carcinoma of the thyroid will yield a relatively low (5%) rate of diagnosis of MEN2a in the absence of a family history of the disease, C cell hyperplasia, or multifocality.[201,202] Nonetheless, *RET* testing is more sensitive than traditional biochemical screening is. Asymptomatic children with *RET* mutations and normal plasma calcitonin levels had small foci of medullary carcinoma of the thyroid at time of "prophylactic" surgery.[203] These findings were confirmed in a large study in the United States.[204]

A study of 477 MEN2a families showed an association between codon 634 mutations and pheochromocytoma and between mutations at codons 768 and 804 and FMCT, while codon 918 mutation is MEN2b-specific. Rare families with both MEN2 and Hirschsprung disease have MEN2-specific codon mutations.[205] A 611 codon mutation is associated with a mild form of FMCT with slow progression. The classic M918T mutation in exon 16 is found in MEN2b, and a less common mutation in *RET* codon 883 has also been reported.[206,207]

Clinical Management

RET testing has been established as the gold standard for MEN2a screening, and prophylactic thyroidectomy has been established as the primary preventive intervention. The age at which surgery is recommended is 3 to 5 years at most centers. Genetic testing should therefore be performed by this age and perhaps even earlier in families with MEN2b, since the thyroid cancers can occur at an earlier age.[208] Heterozygotes for *RET* mutations in the setting of MEN2a are screened with abdominal ultrasound and computed tomography (CT), as well as 24-hour urine studies through the adult years, at least to age 35. Plasma screening for the pheochromocytomas has been suggested (see the section on von Hippel Lindau syndrome). The treatment of choice for patients with MEN2a or MEN2b with a unilateral pheochromocytoma is unilateral resection, since substantial morbidity and mortality are associated with the Addisonian state after bilateral adrenalectomy.[209]

RECENTLY CHARACTERIZED CANCER PREDISPOSITION SYNDROMES

Gorlin Syndrome and Nevoid Basal Cell Carcinoma Syndrome

Basal cell carcinomas (BCCs) are the most common malignancy in humans, with three quarters of a million cases each year. In a small subset of families, BCCs occur at early age and in great numbers. The nevoid basal cell carcinoma syndrome (NBCCS) consists of multiple BCCs, usually presenting after puberty, accompanied by odontogenic jaw cysts, congenital skeletal abnormalities, ectopic calcification of the falx cerebri, and characteristic pits in the skin of the palms and soles.[210,211]

A hallmark of the syndrome is the increased susceptibility of the skin to the damaging and tumor-inducing effects of ionizing radiation.[212] Multiple BCCs have developed within 6 to 36 months following radiation therapy. Unlike Bloom syndrome or ataxia telangiectasia, there is no in vitro evidence of chromosome fragility.

One estimate of the prevalence of the syndrome, 1 in 57,000, comes from a study of a population of 4 million people in northwest England.[213] As described by Gorlin in 1987, penetrance for the syndrome is virtually 100% over a lifetime.[211] NBCCS is diagnosed in individuals with two major and one minor criterion or one major and three minor criteria.[214] Major criteria include bilamellar calcification of the falx cerebri at less than 20 years of age; odontogenic (jaw) keratocyst; palmar/plantar pits (three or more); multiple (more than 2) BCCs or a BCC before the age of 20 years; bifid, fused, or markedly splayed ribs; or a first-degree relative with NBCCS.[215,216] Minor criteria include childhood medulloblastoma (also called primitive

neuroectodermal tumor); lymphomesenteric or pleural cysts; macrocephaly; cleft lip/palate; vertebral anomalies on X-ray; bifid vertebrae; preaxial or postaxial polydactyly; ovarian/cardiac fibroma; and ocular anomalies (cataract, developmental defects, and pigmentary changes of the retinal epithelium). One study showed that approximately 5% of Gorlin syndrome patients develop medulloblastoma in the first few years of life and that 10% of patients with medulloblastoma diagnosed at age 2 years or under have Gorlin syndrome.[217] For diagnostic purposes, it might be salient that one study found that the only histopathologic subtype of medulloblastoma in NBCCS patients is the desmoplastic subtype, which occurs in only 20% of sporadic medulloblastoma cases. The authors suggest that the occurrence of the desmoplastic subtype in a patient younger than 2 years of age is pathognomic.[218]

Genetics

In 1996, Johnson and coworkers found mutations in exon 15 of the human homolog of the Drosophila *patched* gene (called *PTH* or *PTCH*)[219] in two of 60 typical NBCCS kindreds. An analysis of 71 unrelated individuals with NBCCS revealed 26 with mutations scattered throughout the 23 exons of the gene. In 86%, the mutations caused a truncated protein.[220] NBCCS is caused by germline mutations of the gene *PTCH* mapped to chromosomal locus 9q22.3. The *PTCH* gene consists of 23 exons and encodes an integral membrane protein with 12 transmembrane regions and two extracellular loops and a putative sterol-sensing domain. Mutations of *PTCH* are the only known genetic alterations associated with NBCCS.[221] However, several studies have found no genotype/phenotype correlations,[220,222,223] which suggests that other factors might add to the development of patients' clinical features. For kindreds with diagnostic clinical findings of NBCCS that test negative for a mutation by sequence analysis, Southern blot analysis may be performed to detect large deletions. About 70% to 80% of probands have inherited the condition from a parent, and about 20% to 30% of probands have a de novo mutation.

Risk Management Recommendations

Life expectancy in NBCCS is not significantly different from average. The major clinical issues revolve around the cosmetic effects of treating multiple skin tumors and jaw keratocysts, which can recur. The jaw cysts may also undergo malignant transformation.[224] Interaction with oral and plastic surgeons and dermatologists is important. Because of early-onset disease risk, for example, for medulloblastomas, genetic testing of children is appropriate for this condition. Evaluation of members of NBCCS kindreds includes skin examination; measurement of head circumference; and radiographic examination of the skull, spine, ribs, and jaws.[225] Ophthalmologic and dental examination and radiographic monitoring of the jaw cysts (oropantomography) may be performed on affected individuals. MRI scans of at-risk children can diagnose medulloblastomas, though it is unclear whether this improves outcome. If no physical or radiographic stigmata are noted by 5 years of age in the child of an affected patient, the chances that the child is a heterozygote are small.[214] As has been mentioned, radiotherapy for large basal cell cancers should be avoided, because this can lead to the development of thousands of BCCs in the radiation field.[211,212] Prenatal testing for NBCCS is possible if the disease-causing mutation has been identified in an affected family member.

Carney Complex

Clinical Features

Carney complex (CNC) is a multiple neoplasia syndrome that is referred to by acronyms such as NAME[226] and LAMB syndrome in the medical genetics literature.[227,228] As described by Carney in 1985,[229] the complex is characterized by myxomas, skin pigment abnormalities, endocrine tumors, and schwannomas. The median age at diagnosis is 20 years, spotty skin pigmentation and heart myxomas being the most common initial clinical manifestations.[230] The skin abnormalities involve the lips, the conjunctiva and inner or outer canthi, and the mucosa of the vagina or penis. Atrial myxomas are by far of greatest clinical concern, since they usually result in a decreased life span and account for the major causes of mortality in affected individuals; cardiac myxoma can cause stroke and death.[230] Ductal breast adenoma has been described as part of the Carney complex, as well as myxoid fibroadenomas and other findings on breast imaging.[231] In one study of 338 individuals diagnosed with CNC, 34 of 194 (17.5%) females had breast myxomas, often bilateral.[232] Large-cell calcifying Sertoli cell tumor, a frequent component of CNC in males, detected as early as 2 years of age, has been associated with infertility due to hormonal imbalance.[233]

Primary pigmented nodular adrenocortical disease occurs most frequently in association with CNC. A study by Stratakis in 1999 showed that for 95% of the patients, primary pigmented nodular adrenocortical disease occurred as a component of CNC, and 14% had Cushing syndrome.[234] Thus, the diagnosis of primary pigmented nodular adrenocortical disease should prompt screening for CNC. Other organs that are involved in CNC are the thyroid gland and ovaries. Thyroid gland lesions include follicular hyperplasia, follicular adenoma, and follicular and papillary carcinoma. Ultrasonography is useful for screening and diagnosis of these lesions.[235] Ovarian serous cystadenomas have been described in the literature, suggesting that pelvic ultrasound may be indicated as a part of evaluating women with CNC.[236]

Diagnostic criteria for CNC[232] require two or more of the manifestations or one major manifestation and one of the minor criteria. Major criteria are skin pigmentary abnormalities (multiple lentigines of the face, blue nevus, or epithelioid blue nevus); myxoma (cutaneous or mucosal myxomatosis); cardiac myxoma; endocrine tumors/overactivity (primary pigmented nodular adrenocortical disease, a micronodular form of adrenal hyperplasia, growth hormone-producing pituitary adenoma, large-cell calcifying Sertoli cell tumor, or thyroid adenoma or carcinoma); psammomatous melanotic schwannoma; thyroid carcinoma or multiple thyroid nodules on ultrasound in a young patient; multiple breast ductal adenomas; and osteochondromyxoma. To make the diagnosis, an individual must have two of the components listed or one of the manifestations in addition to an affected first-degree relative or have an inactivating mutation of the *PRKAR1A* gene. A malignant neoplasm is a relatively uncommon finding in affected patients.

Genetics

Mutations in *PRKAR1A* (17q23-q24) are identified in about 40% of individuals with CNC.[237] *PRKAR1A* codes for the RI-α subunit of *PKA,* a critical cellular component of a number of cyclic nucleotide-dependent signaling pathways.[238] *PRKAR1*-α frameshift mutations cause haploinsufficiency of R1-α and manifest as CNC. As predicted by the Knudson "two-hit" hypothesis, loss-of-heterozygosity of the normal allele supports the model that R1-α may have tumor suppression function in the target tissues in this syndrome. The most common mutation in CNC patients, a two-base-pair deletion (TGdel) in exon 5 of *PRKAR1,* has also been found de novo in several kindreds, suggestive of a mutational hot spot in the gene.[239] About 17% of diagnosed individuals harbor de novo mutations.

Clinical Management

Recommendations include annual echocardiography, annual measurement of urinary free cortisol, testicular sonogram in males at their initial visit, thyroid ultrasound at initial visit and as needed thereafter, pelvic ultrasound in female patients at their initial visit, breast imaging, spine MRI, pituitary MRI, and adrenal CT scan.[239] Children should have echocardiography during the first 6 months of life and annually thereafter to detect potentially lethal myxomas. Children with large-cell calcifying Sertoli cell tumor may require

monitoring of growth rate and pubertal status. Bone age determination and further laboratory evaluation might be necessary if gynecomastia is present.[212]

Cowden Syndrome

Clinical Features

Cowden syndrome (CS) is an autosomal dominant disorder characterized by multiple hamartomas with a high risk of benign and malignant tumors of the thyroid, breast, and endometrium. Consensus diagnostic criteria for CS establish three diagnostic categories.[240]

Pathognomonic criteria include mucocutaneous lesions, facial trichilemmomas, acral keratoses, papillomatous lesions, and mucosal lesions. Major criteria include breast cancer, thyroid cancer (especially follicular histology), macrocephaly, Lhermitte-Duclos disease (defined as presence of a cerebellar dysplastic gangliocytoma),[241] and endometrial carcinoma. Minor criteria include other thyroid lesions (e.g., goiter), mental retardation, hamartomatous intestinal polyps, fibrocystic breast disease, lipomas, fibromas, and GU tumors (e.g., uterine fibroids, renal cell carcinoma) or GU malformation. The diagnosis of CS is made if an individual meets any one of the following criteria: pathognomonic mucocutaneous lesions alone if there are: six or more facial papules, of which three or more must be trichilemmoma, or cutaneous facial papules and oral mucosal papillomatosis; or oral mucosal papillomatosis and acral keratoses; or six or more palmoplantar keratoses. Alternatively, the individual may fulfill two major criteria, but one must have either macrocephaly or Lhermitte-Duclos disease. Alternatively, the individual may have one major and three minor criteria or four minor criteria.

The palmar and plantar hyperkeratotic pits usually become evident later in childhood. Subcutaneous lipomas and cutaneous hemangiomas are seen in CS with low frequency.[242] An increased risk of early-onset male breast cancer has been noted in mutation carriers.[243]

Genetics

The gene for CS, *PTEN,* was mapped to 10q22-23.[244] *PTEN* acts as a tumor suppressor by mediating cell cycle arrest, apoptosis, or both.[245] Full sequencing and molecular testing by Southern blot are available clinically and on a research basis. Heterozygous germline mutations in *PTEN* cause most cases of CS. Nonsense, missense, and frameshift mutations that are predicted to disrupt normal *PTEN* function have been identified in certain families,[246] including mutations that disrupt the protein tyrosine/dual-specificity phosphatase domain. A *PTEN* mutation can be detected in about 80% of patients with CS.[247]

Risk Management Recommendations

Individuals with known germline *PTEN* mutations should undergo appropriate cancer screening.[228,248] Female patients with CS should be screened for breast cancer, starting clinical breast examination at age 25 and annual mammography at age 30 or 5 years younger than the earliest age of breast cancer diagnosis in the family. Men should perform monthly breast self-examination. Female patients should receive endometrial cancer screening beginning around age 35 years or 5 years before the youngest endometrial cancer diagnosis in the family, as well as a comprehensive annual physical examination starting at age 18 years with screening for skin and thyroid lesions, including a baseline thyroid ultrasound. Individuals with CS should undergo a colonoscopy at age 50 years and annual urinalysis to detect renal carcinoma. Finally, prenatal testing for CS can be done if a mutation is described in a parent.

Birt-Hogg-Dubé Syndrome

Clinical Features

Birt-Hogg-Dubé (BHD) cancer predisposition syndrome was recently molecularly characterized, though it was first described in 1977.[249] This rare genodermatosis comprises an interesting triad of findings: fibrofolliculomas that appear as white or skin-colored papules on the face and upper torso, spontaneous pneumothorax, and kidney tumors.[250] Approximately 15% to 30% of patients with cutaneous BHD syndrome develop renal tumors. A recent review of 130 solid renal tumors resected from 30 patients with BHD in 19 different families revealed that renal tumors were multiple and bilateral and were noted at an early age (mean: 50.7 years). The vast majority were hybrid oncocytic neoplasms with areas reminiscent of chromophobe renal cell carcinoma and oncocytoma, while a significant number were chromophobe renal cell carcinomas, and a minority were conventional clear cell renal carcinomas.[251,252] The cutaneous lesions usually appear in the region of the head, neck, and upper part of the trunk in the third or fourth decade of life, and about 15% to 30% of patients with skin lesions of BHD syndrome develop renal tumors. Khoo and colleagues described an association with colorectal neoplasia in some families with BHD.[253] However, other reports did not confirm this.[254] Individuals with BHD syndrome are at markedly increased risk of spontaneous pneumothoraces. In a recent study, 64 of 198 (32%) BHD-affected individuals had a history of spontaneous pneumothorax.[255] The syndrome is also associated with a progressive flecked chorioretinopathy with constricted visual fields.[256]

Genetics

BHD is inherited in an autosomal dominant manner. The recently identified *BHD* gene has been mapped to chromosome 17p11.2[257] expressing a novel protein folliculin.[258] The exact function of this protein is not known. Affected individuals exhibit loss of protein function, usually due to a frameshift mutation in the coding sequence. In a recent study, 27 of 52 BHD-affected families had an insertion/deletion in exon 11 of the gene (c.1733insC or c.1733delC). Phenotype manifestations among those with either the insertion or the deletion were similar for fibrofolliculomas and pneumothoraces. However, the incidence of renal tumors was significantly higher among those with the C-insertion compared to the C-deletion (33% versus 6%).[255]

Risk Management

Patients with BHD syndrome and their relatives should undergo abdominal CT and renal ultrasound screening for renal tumors. Lung cysts are best seen on CT scans. Dermatologic consultation is advised. Ophthalmologic examination should be performed in patients with BHD syndrome owing to the high incidence of chorioretinopathy.

Rhabdoid Predisposition Syndrome

Clinical Features

Rhabdoid predisposition syndrome (RPS) was initially described in 1999 by Sévenet and colleagues.[259] RPS results in pediatric cancer predisposition, including renal and extrarenal malignant rhabdoid tumors; choroid plexus carcinomas; central, primitive, neuroectodermal tumors; and medulloblastomas.[260,261] In the families that have been described with RPS, the penetrance appears to be quite high at a very young age. In the initial study, all of the first cancers occurred before the age of 3 years in mutation carriers, and no mutation carriers were unaffected.[259] Pediatric brain tumors are emerging as an important component of this syndrome.[262] The spectrum of cancers that have been observed in RPS overlaps somewhat with Li-Fraumeni syndrome. Pediatric medulloblastomas may also occur in Gorlin syndrome and in compound *BRCA2* heterozygotes, as was noted previously.

Genetics

RPS is caused by mutations in *hSNF5/INI1* at 22q11.2 (also known as *SMARCB1*). Most mutations in the *hSNF5/INI1* gene are truncating.[263] The *hSNF5/INI1* gene encodes a subunit of the *SWI/SNF* family of chromatin-remodeling complexes. The spectrum of tumors

with somatic mutations of *hSNF5/INI1* is similar to the tumors that are seen in the hereditary syndrome.[263] A recent paper[264] describes a family with two children, one affected with rhabdoid tumor of the kidney and the other with atypical teratoid/rhabdoid tumor. Though both children satisfied the morphologic and clinical features for a diagnosis of RPS, neither of their tumors showed *hSNF5/INI1* inactivation, both had normal expression of the gene in nuclei of tumor cells, and haplotype analysis showed that each received a different set of maternal/paternal alleles. This suggests genetic heterogeneity and warrants further molecular studies to determine the etiology of this syndrome.

Risk Management

Since this syndrome has only recently been described, clinical management is still evolving. As with Li-Fraumeni syndrome, screening for component tumors is unproven. The average survival of infants following diagnosis of malignant rhabdoid tumors with abnormalities of chromosome 22q11 is less then 6 weeks.[265] Fewer than 25% of infants and young children with rhabdoid tumor of the kidney survive.[262,266,267]

Familial Gastric Cancer

Clinical Features

The International Gastric Linkage Consortium specifies criteria for a clinical diagnosis of familial diffuse gastric cancer. These criteria consist of either two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one diagnosed before age 50, or three or more cases of diffuse gastric cancer in first- or second-degree relatives, independent of age of onset.[268]

Genetics

Approximately 30% of familial diffuse gastric cancer kindreds have mutations in the E-cadherin (*CDH1*) gene.[269] The lifetime penetrance of *CDH1* mutations is estimated to be 70% to 80%.[269] However, diffuse gastric cancer has been diagnosed in affected individuals as young as 14 years of age, and the majority of mutation carriers die younger than age 40.[270,271] Clinical consensus is that individuals with diffuse gastric cancer who are younger than 35 years of age should be considered for *CDH1* testing.[271] Because of the early age of onset, similar to that of FAP, and the estimated 10% 5-year survival rate after diffuse gastric cancer diagnosis, individuals who are as young as 13 years and able to give informed consent or assent should be considered for genetic counseling.

Clinical Management

The management options are surveillance upper GI endoscopy or prophylactic gastrectomy. Gastrectomy has a significant effect on quality of life and should be undertaken only after extensive genetic counseling. The long-term morbidity that can result from gastrectomy includes weight loss, lactose intolerance, fat malabsorption and steatorrhea, dumping syndrome, bacterial overgrowth, postprandial fullness, and vitamin deficiencies. On the basis of the experience of Japan, which has population-based upper endoscopy screening programs to detect gastric cancer, early detection of gastric cancer can lead to 5-year survival rates greater than 90%.[271] Therefore, upper endoscopy surveillance may be a viable approach to management. Clinical consensus is for a 30-minute endoscopy exam every 6 months by experienced practitioners.[270] Because of the diffuse distribution of the lesions, chromoendoscopy may be more sensitive for early detection, and ultrasound is less likely to be effective. It is currently not well established whether any other sites develop cancer with increased frequency with *CDH1* mutations, except for the elevated risk of lobular breast cancer. There are no clear guidelines for additional surveillance, though breast cancer screening 5 to 10 years younger than the earliest breast cancer in the family may be advisable.[272,273]

Asian, African, and Caribbean families with Lynch syndrome generally have greater incidence of stomach cancer compared to kindreds from North America, South America, and Europe, where colorectal cancer predominates.[274–276] An important clue in this clinical presentation is the existence of both endometrial and stomach cancer in the same family. It has been speculated that the shift in the GI cancer susceptibility to a rostral-caudal axis has reflected changes in food preparation and content. In particular, the decreased use of smoked and cured meats resulting from refrigeration and the high fat content of the modern European-American diet have been proposed as important factors.[276] The smoking process of meats can introduce heterocyclic amine byproducts, and the curing process involves nitrate salts that cause nitroso-compounds, which may act as potential mutagens. Epidemiologic and animal model studies provide evidence for this model.[277,278] The first HNPCC family to be identified was described by a pathologist, Aldred Warthin, in 1913 in Europe and is referred to as Family G.[276,279] In the early twentieth century, the GI tumors in Family G and other similar kindreds were distinguished largely by an excess of stomach adenocarcinoma.[280] In the middle and late twentieth and early twenty-first centuries, the GI cancer susceptibility has shifted to include mostly colorectal cancers.

Hereditary Leiomyomatosis Renal Cell Cancer Syndrome

Clinical Features

The autosomal dominant, hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC) predisposes to benign cutaneous and uterine leiomyomas (fibroids), uterine leiomyosarcomas, and papillary type II renal cell cancer or renal collecting duct carcinoma.[281–284]

Kidney tumors in HLRCC are aggressive, often single, small lesions of high malignant potential. The age of onset of four cases of kidney cancer in one HLRCC kindred with 11 affected family members ranged from age 33 to 48 years, and all were diagnosed in females.[281,285] A Finnish series of 98 HLRCC cases found a standardized incidence ratio of 6.5 for renal cell cancer and 71 for uterine leiomyosarcoma. In a separate series, renal cancer occurred in 62% of 21 patients with HLRCC, and 76% had cutaneous leiomyomas. Uterine leiomyomas occur in 90% to 100% of women with HLRCC.[286] One series also reports adrenal gland adenoma and kidney cysts as well as breast and bladder carcinoma.[287] However, a study of 85 breast cancer patients with a family history of HLRCC found no increased breast cancer risk, though a considerably larger sample size could be more informative.[288] Cutaneous leiomyomas were present in 14 of 16 cases from five kindreds. They arise from the arrector pili, can be red or skin colored, can be evident as only a few to about 100 lesions, and are sensitive to touch and to cold temperature. Cutaneous lesions may be diffuse and symmetric or present in segmental bands along the lines of Blaschko. Of 11 females, 9 had uterine leiomyoma and 9 presented with cutaneous leiomyomas.[289,290] Leiomyomas of the uterus resulted in hysterectomy by age 30 in over 44% of women with HLRCC.[283]

Genetics

The gene that is responsible for hereditary leiomyomatosis and renal cell cancer on 1q42.3-q43 encodes fumarate hydratase (*FH*), a tricarboxylic acid/Krebs cycle, mitochondrial enzyme. Dominant mutations in fumarate hydratase cause HLRCC in a manner that is consistent with Knudsen's two-hit tumor suppressor model. Germline biallelic mutations in *FH* cause the mitochondrial encephalomyopathy, fumarate hydratase deficiency, and obligate carriers have presented with HLRCC.[291–294] Mutations in the fumarate hydratase gene are detected in about 75% to 100% of patients with multiple cutaneous and uterine leiomyomatosis.[282,284,286] One mutation, R190H, was detected in 11 of 31 unrelated, North American HLRCC kindreds, and the mutation R58X has also been identified in multiple unrelated kindreds.[286] Additionally, a mutation, 905-1G>A, was

found in four Iranian HLRCC kindreds, possibly representing a founder mutation in this population.[295] Reduced *FH* activity in lymphoblastoid and fibroblast cells of HLRCC patients may facilitate confirmation of clinical diagnosis via enzymatic testing.[296]

Although the molecular mechanisms underlying HLRCC have yet to be fully characterized, glycolysis dependence appears to be a contributing factor.[297] The genes *HIF-1a* and *HIF-2a* target GLUT1, all of which are elevated in HLRCC tumors. This pathway is being explored for chemotherapeutic intervention, including the agent bevacizumab, as are Hsp90 inhibitors. NAD(P)H dehydrogenase quinone 1-mediated 17-AAG antitumor activity is also under exploration in treating HLRCC related cancers.[283]

Clinical Management

Screening at regular intervals for renal lesions utilizing CT with contrast is indicated in patients with fumarate hydratase mutations. MRI is recommended for uterine leiomyoma screening, and ultrasound can also be utilized.[298]

Chemodectoma and Paraganglionoma Syndromes

Clinical Features

Chemodectomas are also known as glomus tumors or paragangliomas of the head and neck. These tumors are formed from neuroectodermal and mesodermal origins and most frequently are observed in the carotid, aortic, jugular, or vagal bodies. Of 30 cases reviewed in one series, about half were bilateral, with a family history of chemodectoma in about one third of these cases.[299,300] Most of the familial cases presented with multiple tumors. The remarkable feature about hereditary chemodectomas is the evidence of imprinting; children of affected fathers develop chemodectomas, but the children of affected mothers do not.[301]

Genetics

In paraganglioma syndromes, mitochondrial succinate dehydrogenase gene complex (*SDH-A, -B, -C,* and *-D*) has been implicated, given the oxygen sensor function of the carotid body, a common site for chemodectomas.[302] Mutations in *SDH-D* exhibit autosomal dominant inheritance, with an imprinting mechanism,[302] whereas *SDH-B* and *SDH-C* mutations do not appear to be imprinting genes. Although maternally derived *SDH-D* cases have been reported, further analysis revealed that a paternal mutation on an 11p15.5 allele was also necessary to result in paraganglioma.[303] *SDH-D* mutations give rise to more frequent head and neck tumors, whereas *SDH-B* mutations exhibit a greater propensity for malignancy and also are associated with renal cell cancers.[304]

Of 271 paraganglioma and/or pheochromocytoma patients with no family history, germline mutations were identified in 66 patients (24%), with *SDH-D* and *SDH-B* mutations accounting for 23 cases. Of the remaining 43 germline mutation cases, 30 were attributed to von Hippel Lindau syndrome mutations, and 13 were caused by mutations in the *RET* gene.[305] Given the high frequency of germline mutations in paraganglioma cases, diagnosis should prompt consideration of genetic testing to be offered to these patients.[306]

Clinical Management

Treatment for paraganglioma is surgical. Minimal morbidity occurs with small tumors, but once the size is greater than 5 cm, cranial nerve loss and baroreceptor failure may be postoperative sequelae. Screening for pheochromocytoma is by serum and/or urinary metanephrines. Screening for renal cancers is unproven, but abdominal/pelvic imaging seems reasonable.

OTHER FAMILIAL NEOPLASMS

Familial aggregations of individuals affected by Wilms' tumors, leukemias, lymphomas, gastric cancer, testicular cancer, and lung cancer as well as other malignancies have been described. A group of autosomal recessive disorders, including Bloom syndrome, Fanconi anemia, ataxia telangiectasia, and xeroderma pigmentosum, are associated with an increased susceptibility to a variety of neoplasms. A number of additional hereditary syndromes are characterized by both nonmalignant (congenital) features as well as a predisposition to cancer.[1] With the identification of genes associated with many of these syndromes, presymptomatic testing and counseling will be available.

The highly penetrant susceptibility alleles associated with the syndromes reviewed in this chapter account for a minority of human cancers. Nonetheless, the number of molecularly characterized highly penetrant cancer syndromes continues to grow. A larger proportion of human cancers may be associated with genetic polymorphisms that confer a lesser cancer risk. It was predicted on the basis of the Utah genealogies[307] that inherited susceptibility to environmental carcinogens would emerge as a major focus for the next era of research in oncogenetics. Recent completion of whole-genome association studies for breast cancer,[37,38] prostate cancer,[161,162] and other common malignancies have begun to lay the foundation for genomic approaches to low-penetrance cancer predisposition. Integrating these new markers of significant but lesser cancer risk into clinical practice looms as the next challenge in preventive oncology.

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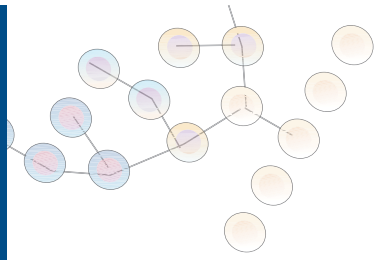
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13 Genetic Factors: Finding Cancer Susceptibility Genes

Elaine A. Ostrander and Danielle M. Karyadi

SUMMARY OF KEY POINTS

- The identification of cancer susceptibility genes by either linkage studies within families or association studies in populations is a useful way to understand defining events in tumor development and to identify cellular pathways that are likely to be important in cancer.
- Cancer susceptibility genes can be either strongly penetrant, in which case individuals born with a mutant allele have a high probability of developing cancer, or weakly penetrant, for which the probability of developing cancer is lower.
- Ideal families for linkage studies are large, include many affected individuals who can be readily examined and interviewed, and include individuals with similar clinical features of disease from multiple generations. This allows large data sets associated with genetic heterogeneous forms of cancer to be stratified into homogenous subsets, thus increasing the power to detect genes.
- Linkage between polymorphic markers and a disease state is assessed by using a number of statistical tools, including the parametric LOD score and nonparametric NPL score.
- Association studies that include populations of affected cases and controls are useful for identifying and testing hypotheses about candidate genes and alleles that might be associated with disease. A precisely defined set of cases and matched controls is important.
- Association studies and linkage-based studies both require collection of accurate clinical and family history data by clinicians, and both offer hope for future genetic testing.

INTRODUCTION

Cancer susceptibility genes are those that, when mutated, increase an individual's risk of having cancer. If an individual is born with one mutant copy of a cancer susceptibility gene, subsequent mutations in the wild-type allele within the relevant tissues can result in a lack of functional gene product, leading to tumor formation.[1] Genetic mapping of cancer susceptibility genes allows identification of both genes and pathways that play a role in cancer susceptibility. Although the direct public health impact associated with cloning any specific cancer gene may be minimal, the contributions to understanding of tumor development and metastasis that such advances make are potentially enormous.

Population-based studies reveal excess familial cancer aggregation for most organ sites.[2] However, cancer susceptibility genes have been mapped for only a few cancer sites to date, and the underlying mutations have been identified for even fewer. Several studies suggest that the overall percentage of cancers in the general population that are caused by highly penetrant inherited mutations is low, likely less than a few percent, even when all organ sites are considered.[3] For breast cancer and prostate cancer, the numbers are probably among the best supported; 5% to 10% of cases of each are thought to be due to mutations in inherited susceptibility loci.[4–7] The remaining cancer cases, making up the majority, are considered sporadic in nature. They are probably caused by a mixture of specific environmental and weakly penetrant genetic factors, with genetic background remaining poorly understood.

Cancer susceptibility alleles associated with a given gene may be either strongly penetrant, leading to a high probability that individuals born with a mutant allele will have the disease in question, or weakly penetrant, with carriers having a proportionately lower probability of having the disease. Allele penetrance associated with susceptibility alleles is often age-dependent, with the probability of having the disease increasing with each decade of life. Genetic mapping of cancer susceptibility genes is extremely difficult, in part because genetic background and environmental exposures are likely to affect penetrance. In addition, both highly and weakly penetrant alleles can be associated with the same gene. Further, the same allele can be associated with widely varying age-dependent penetrance within a single family as different family members have independent genetic backgrounds as well as unique life experiences and environmental exposures. Finally, stochastic effects likely play a role as well.

Highly penetrant disease alleles are best identified by family-based linkage analysis studies. The segregation of a defined chromosomal segment with affected individuals in multiple families suggests the presence of a cancer susceptibility gene within the genomic region tested. Statistical analysis that is performed after genotyping of appropriate numbers of families with markers spanning the whole genome allows researchers to calculate the probability that any given chromosomal region carries a susceptibility gene. Weakly penetrant alleles are more easily identified by association tests after analysis of DNA from two distinct populations, for example, patients with cancer together with an appropriately matched set of control subjects. Weak alleles are hypothesized to be more common in the general human population and are therefore likely to account for a higher percentage of cancer in the population overall. In this chapter, we investigate the ways in which both highly and weakly penetrant disease alleles are identified and studied.

FUNDAMENTAL SCIENCE

Hereditary Cancer Families

Strong and Amos[8] have defined a general paradigm for population studies that can be applied to identifying genes that are important in predisposition to cancer. The hypothesis that a particular cancer has an identifiable genetic component usually occurs through family history analysis of sequential cancer cases, general clinical observations, and, finally, epidemiologic studies. Epidemiologic studies assess whether there is significant evidence for an increased cancer risk at a particular organ site that can be associated with a family history of the disease. If so, a segregation analysis may be undertaken to identify features of the putative susceptibility loci. Typical analyses address mode of inheritance (dominant, recessive, or X-linked) and estimate frequency and penetrance of the disease allele(s) in the general population, age-dependent penetrance, and potential number of loci contributing to the disease. In the event that genetic linkage studies are eventually undertaken, data from the segregation analysis are key in developing statistical models for analyzing subsequent linkage data.

Familial aggregation is a general term that describes the occurrence of multiple cases of cancer within a family (Fig.13-1). Such clustering may be due to shared environment, shared alleles of particular genes, or simply chance if the tumor is very common in the population. The successful mapping of cancer susceptibility genes for breast, colon, and prostate cancer has led to the development of a strictly defined term, *hereditary cancer,* which describes families with three or more first-degree relatives with a given cancer, three successive generations with cancer, or at least two siblings with the same cancer detected at a relatively young age.[4] First-degree relatives are defined as parents, offspring, or siblings.

Many epidemiologic studies indicate that a family history of a specific cancer within first-degree relatives is associated with a doubling or more of risk among relatives.[9] In the case of prostate cancer, for instance, studies of selected hospital-based patient populations,[10,11] population-based case-control studies,[12–14] and cohort studies[2,15] all demonstrate that a family history of disease increases an individual's risk. If the affected family members are first-degree relatives (e.g., brothers or fathers and sons), the risk increases from 1.7-fold to 3.7-fold. Younger ages at diagnosis and multiple affected relatives with the disease tend to be associated with even higher relative risk (RR). For example, men with three or more first-degree relatives with prostate cancer have almost an 11-fold increased risk of the disease compared with men who have no family history of the disease.[10] For this reason, families that are ascertained for linkage analysis studies tend to be large, have multiple affected individuals, and feature people who were diagnosed with the disease at a comparatively young age.

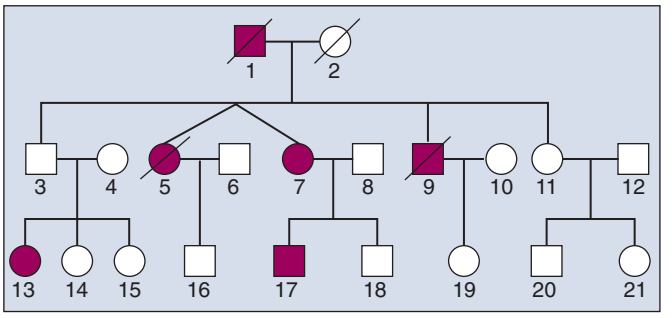


Figure 13-1 • Theoretical pedigree of a family segregating an autosomal dominant disorder. Individuals are numbered 1 to 21. Males are indicated by squares, and females are indicated by circles. Symbols for affected individuals are filled (numbers 1, 5, 7, etc.). A diagonal line through the symbol indicates that individual is deceased (1, 2, 5, and 9). A horizontal line between symbols indicates a mating (1+2, 3+4, etc.). Perpendicular lines drawn from mating lines indicate children (e.g., 13, 14, and 15 are all daughters of 3 and 4). Siblings are designated as shown for individuals 3, 5, 7, and 9; and individuals 5 and 7 are twins.

Linkage Mapping and Finding Cancer Susceptibility Genes

Several requirements must be met to successfully identify cancer susceptibility genes. First, a large number of so-called high-risk or hereditary families must be ascertained by using appropriate guidelines for working with human subjects. Clinical features and family history data must be recorded, and DNA samples must be obtained. Once purified, DNA samples from appropriate family members need to be screened by using a set of highly polymorphic markers that span the genome at a high density. Historically, genome scans have used microsatellite-based markers distributed approximately every 10 million base pairs. Recent studies suggest that a denser scan with highly polymorphic markers every 5 million base pairs or even biallelic markers, such as single nucleotide polymorphisms (SNPs) placed every 2 to 3 million base pairs may be preferable. Finally, the data must be interpreted or analyzed in the context of the disease in question. Creating stratified data sets, which allow analysis of families with a common disease or family history features, is important and may increase the chance of finding a susceptibility-associated locus. These issues are discussed in the following sections.

Family Collection

Most cancers are heterogeneous diseases that likely involve multiple susceptibility genes. In a statistically ideal situation, a given set of affected individuals within a family would all have cancer for the same reason; that is, each member would have inherited a mutated copy of the same gene. But in truth, for common cancers such as those of the breast, prostate, and colon, any given family may have individuals whose disease is due to mutations in multiple different genes, some highly penetrant and some weakly penetrant, as well as family members whose disease is sporadic.[16] Often, disease presentation is similar in genetic and sporadic cases, and examination of clinical or pathologic features is uninformative for determining whether a specific patient represents a genetic or sporadic case.

Figure 13-2 demonstrates two types of seemingly useful families for linkage-mapping studies. Both include a significant number of affected members. The first family, in particular, has a large number of affected individuals (see Fig.13-2A). However, some individuals were affected very early in life, whereas others were diagnosed at later ages. It is likely that some individuals have the disease because they inherited mutated copies of a particular gene, whereas others have the disease for sporadic reasons unrelated to the disease allele segregating in the family. Ideally, age at onset provides some guidance as to which individuals are more likely to have hereditary versus sporadic forms of the disease; but this is not absolute, and in the case of a disease with age-dependent penetrance, some people will be affected late in life even though they carry a mutant allele, and others will be affected early in life for sporadic reasons. The family shown in Figure 13-2B also appears to be informative for and conducive to linkage mapping studies. There are several affected individuals in the family, and all were affected at a relatively early age. However, the presence of disease segregating on both sides of the family should be noted. The affected individuals in the youngest generation could have cancer because they inherited mutant alleles from one or both sides of their family, and one or multiple genes could be involved. Therefore, the family is of limited utility for mapping studies.

Obtaining good clinical information for all individuals in a family mapping study gives geneticists the power to stratify the data into more homogenous subsets. This increases statistical power for finding the genes associated with any one particular aspect of a phenotype. If a subset of individuals in the family in Figure 13-2B all had tumors of similar stage and grade, the data from this homogenous subset of

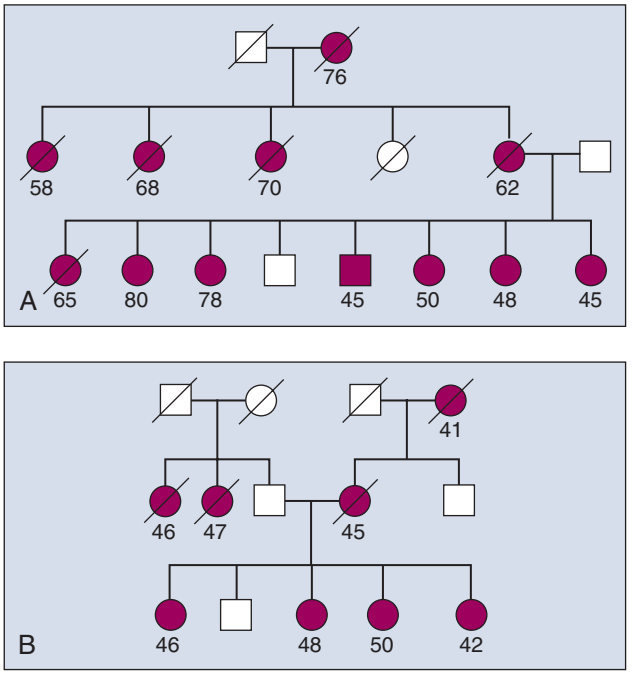


Figure 13-2 • Two theoretical breast cancer families. Age at diagnosis is indicated below the symbol; males are indicated by squares, and females by circles. **A,** The family has many members affected with breast cancer, but some were given diagnoses relatively early in life (<50 years), whereas others were much older at diagnosis (>70 years). The utility of this family for genetic-mapping studies is thus limiting, because it likely contains individuals with both sporadic and hereditary breast cancer. **B,** All individuals were affected at an early age, but breast cancer, caused by mutations in either the same or different genes, is present on both sides of the family. Because there is no way to distinguish the number of mutant genes a priori, the utility of this family for a genome-wide scan is also somewhat limited.

individuals could be considered in isolation from the rest of the affected cases, reducing heterogeneity and increasing power. In addition to clinical features of disease, family history, age at onset, and presence or absence of other cancers are all ways to stratify data into homogenous subsets and improve the likelihood of finding causative genes. In the case of prostate cancer, several recent studies have focused on families with an excess of men presenting with a high Gleason tumor grade at diagnosis. Recall that the Gleason score reflects the pathologic architecture of the tumor at diagnosis. Several regions are scored and assigned a grade of 1 to 5, representing a well to poorly differentiated pattern, respectively. The two predominant grades are added to give a summary score of between 2 to 10, most tumors being in the range of Gleason 5 to 7. Recent studies of prostate families reveal a set of specific loci for families in which two or more men from whom DNA could be genotyped presented with high Gleason scores or other measures of aggressive disease.[17] Indeed, some studies suggest a difference in men who present with a Gleason 3 + 4 versus 4 + 3, the latter representing a higher-risk class of study subjects with regard to higher frequency of biochemical failure, systemic recurrence, and cancer-specific death.[18,19]

Identification of cancer families and collection of critical medical information, including family history, medical record data, and DNA samples, are generally regulated by institutional review boards. Families must be identified in a way that is neither intrusive nor coercive. For these reasons, genetic epidemiologists are increasingly turning to advertisement in periodicals such as supplements to popular newspapers or widely read periodicals[20] to recruit eligible families. A particularly innovative approach used by investigators trying to find hereditary prostate cancer families was to establish a toll-free telephone number, which was then advertised on a popular syndicated television talk show.[21] Listeners whose family history matched that described were encouraged to call for a preliminary phone screening and to obtain more information about the study.

For linkage-based approaches to correctly identify associated loci, rigorous quantitative data regarding strength of phenotype must be available for multiple generations of the family. Medical record data must be carefully and systematically extracted into well-protected databases. Family history data must also be obtained redundantly from multiple members of the family, and care must be taken to resolve discrepancies. Consent to contact other family members regarding the study is needed, as is permission to obtain medical records. Individual privacy must also be protected and personal identifiers such as names and addresses must remain confidential.

Locus Heterogeneity

If a particular trait is controlled by a large number of genes, each of which contributes only minimally to the final complex phenotype, it will be difficult to dissect the contributions of any one gene by studying a small number of families. If the phenotype is controlled largely by a small number of genes, however, the underlying genetics will be much easier to resolve. The breast cancer susceptibility genes BRCA1 and BRCA2 were likely among the first to be mapped for several reasons related to this point.[22,23] First, only two genes appear to control the majority of the hereditary breast cancer in the general population.[24] Had the number of highly penetrant genes in the population been larger, the task would have been proportionately greater. Second, in both cases, large and well-characterized families had been meticulously ascertained. This ensured that there was sufficient statistical power to undertake the genome scan. Third, the power of any given data set can be increased dramatically by identifying families in which several members share minor disease features, thus making it likely that their disease is due to mutations in the same gene. The presence of ovarian cancer in some families and not others and the presence of breast cancer in some male carriers allowed for the creation of data sets that were enriched for the BRCA1 and BRCA2 genes, respectively.[22,23] Finally, it is always useful to remove from a data set families whose disease is known to be caused by any given gene. The identification of the BRCA1 gene and subsequent removal of BRCA1-linked families from remaining data sets provided further useful enrichment for BRCA2-linked families.[23,25]

Initially, in the case of breast cancer, investigators did not know the number of genes likely to be involved in genetic susceptibility. Detailed segregation analysis had suggested that the gene or genes responsible for breast cancer were likely to be highly penetrant and autosomal and to produce patterns of age-dependent penetrance. A segregation analysis typically involves interviewing a large number of sequential case patients who share common features of the disease. Once a segregation analysis is complete, the resulting data can be factored into the resulting genome-wide scan. This allows data from some individuals to be weighed more significantly. Segregation analyses have now been done for nearly all types of cancer,[4,7,26–29] providing investigators with an array of clues with which to begin their search for genes of interest.

After families are designated for a genome-wide scan, a power analysis is performed to determine whether there is sufficient statistical power in the specific group of families collected to find linkage to the trait in question, given a certain set of assumptions. The assumptions include how many markers are being tested, how informative each marker is likely to be, and the composition of the families in question. The scenario in which a given set of families offers sufficient power to find a gene only if one of the markers is extremely close to the locus occurs frequently and is particularly associated with diseases such as cancer, for which locus heterogeneity is common. The power to find genes decreases dramatically as the number of genes that contribute to a phenotype increases.[30]

Another way to reduce locus heterogeneity is by studying families from isolated or inbred populations. Fewer disease alleles are predicted to segregate with a particular phenotype in a population derived from a limited number of founders. Studies of colon cancer in Finland and studies of breast cancer in Iceland and in Ashkenazi Jewish populations illustrate these points very well. In Finland, two variants in the DNA mismatch repair gene, MLH1, termed mutations 1 and 2, account for 51% of all Finnish families with verified or putative cases of hereditary nonpolyposis colorectal cancer.[31] Nineteen mutation 1 and six mutation 2 families were further investigated by haplotype analysis using 15 microsatellite markers surrounding the MLH1 locus. The presence of two distinct large conserved disease haplotypes, one in mutation 1 and the other in mutation 2 families, indicated that these families are likely to descend from two common ancestors born in the sixteenth century and eighteenth century, respectively.[31]

For the breast cancer susceptibility genes, BRCA1 and BRCA2, several founder mutations have been identified in different populations.[32] For instance, a single BRCA2 mutation, 999del5, was found in 16 of 21 Icelandic breast cancer families.[33] All 16 of these families share a haplotype or pattern of alleles within the BRCA2 gene, suggesting a common ancestral origin. Studies of breast cancer in Jewish families have also demonstrated this point, contributing enormously to our knowledge of founding mutations for both BRCA1 and BRCA2.[34,35] The three common founder mutations in this population, BRCA1-185delAG, 5382insC, and BRCA2-6174delT, have a combined prevalence of 2% to 2.5%.[32,34,36,37] With these observations in mind, investigators have frequently sought families for genetic-mapping studies from regions of the world where marriage between related individuals is not taboo and where geographic barriers have restricted gene flow. This is especially important for genetically heterogeneous diseases, such as prostate cancer. Indeed, support for the existence of a locus on the X chromosome, HPCX, was found in a subset of Finnish families, suggesting that the HPCX locus might contain a founder mutation in Finland.[38]

Principles of Genetic Linkage Analysis

The principles of meiotic recombination are key to understanding linkage analysis. In meiosis, the cell division leading to gamete formation, homologous chromosomes are paired. Each chromosome consists of two identical strands (chromatids), each chromosome pairing being composed of four strands. Homologous chromosomes separate from each other during the process of meiosis except at one or two zones of contact in a process that leads to genetic recombination (Fig.13-3). Mendel's second law, of independent assortment, states that alleles of genes at unlinked loci segregate or assort independently of one another. Deviations from independent assortment occur when genes are located close to one another, in which case alleles assort together more than 50% of the time. In this scenario, the associated loci are said to be linked. However, if two loci are located on different chromosomes or far apart on the same chromosome, their alleles will assort randomly, a given set of alleles being transmitted to the same gamete 50% of the time. Such loci are said to be unlinked.

For any given chromosomal segment, the probability of a genetic recombination event occurring between a pair of markers or a marker and a gene is proportional to the distance between them. This probability is expressed as a recombination frequency (q), where

$$\theta = \text{Number of recombinant offspring/Number of total offspring}$$

Recombination frequency ranges from 0 for genes that are so closely linked that crossover events essentially never occur to 0.5 for genes that assort randomly. Within small intervals, when the probability of multiple crossovers is negligible, the relationship between the recombination fraction (θ) and the distance between two genes (x) is simply $x = \theta$.[39] After a minor mathematical adjustment for the possibility of double recombinants is made, recombination fractions

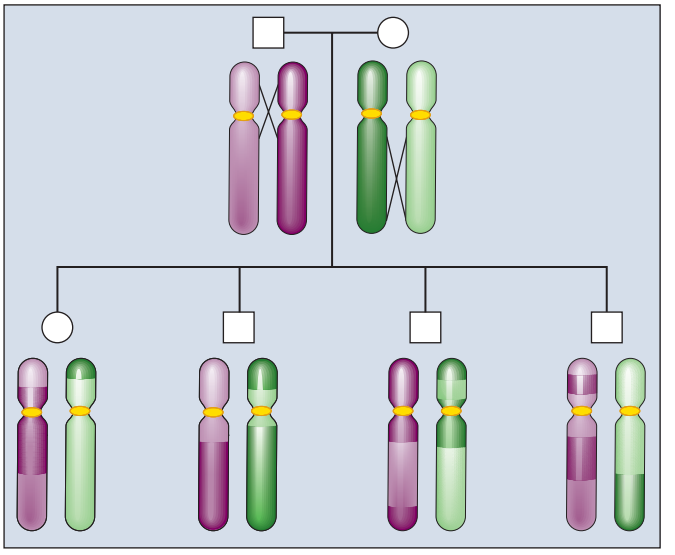


Figure 13-3 • Genetic recombination is the process of exchanging genetic information between two chromatids during meiosis. The recombination events for a single chromosome within a family are illustrated. The father's homologous chromosomes are light and dark purple, and the mother's are light and dark green. Recombination events occurring during meiosis create unique parental chromosomes.

are expressed in units called *centimorgans* (cM), named after the geneticist Thomas Hunt Morgan.[40] One percent recombination ($\theta = 0.01$) is equal to 1 cM, which in the human genome corresponds to about one million base pairs. The entire human genome is estimated to be about 3300 cM.

Genetic linkage mapping queries whether any given portion of the genome is consistently inherited with the disease status. The ordered set of alleles associated with a particular part of the genome received by an offspring from one parent is called a haplotype (Fig. 13-4). Recombinant haplotypes are generated when a crossover occurs between two linked markers (see Fig.13-3). In Figure 13-4, the father is a heterozygote for two loci (AB for locus 1 and XY for locus 2). The mother is homozygous at both of the same loci but with different alleles (CC and ZZ), and as a result, all offspring will inherit the C, Z haplotype. If these two markers are unlinked, as they would be if they were on different chromosomes or far apart on the same chromosome, four types of gametes would be expected from the father (A,X; B,Y; A,Y; and B,X) in approximately equal proportions (see Fig.13-4A). However, if the markers are linked (see Fig.13-4B), the father would be expected to produce an excess of the two "parental" haplotypes (A,X and B,Y) over a smaller number of the "nonparental" or "recombinant" haplotypes (A,Y and B,X).

GENOME-WIDE SCANS

Marker Informativeness

Key to the success of any genome scan is the development of a well-defined set of markers that completely span the genome at defined intervals. The number of markers used determines the resolution of the resulting scan. A 10-cM genome scan, for instance, will allow localization of a disease locus only to within 5 million base pairs, whereas a 1-cM density scan, composed of approximately 3000 informative markers, will localize a gene to within half a million base pairs.

A genetic marker, by definition, has two or more alleles. If the frequency of the most common allele is less than 95%, the marker is said to be polymorphic. One measure of polymorphism is called *polymorphism information content* (PIC).[41] PIC defines the probability

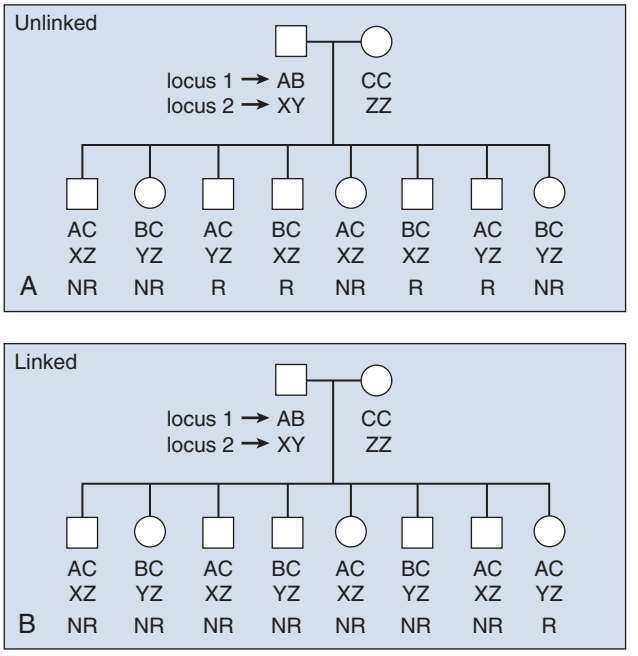


Figure 13-4 • Linked and unlinked markers segregating in two families. Below the symbols, the genotypes for both markers are listed. Offspring have either recombinant (R) or nonrecombinant (NR) haplotypes. The father is heterozygous for marker 1, AB, and marker 2, XY; and the mother is homozygous for both markers, CC and ZZ. **A,** If the markers were unlinked, there would be equal numbers of R and NR haplotypes from the father (AX, BY, AY, and BX). **B,** There is an excess of NR haplotypes (AX and BY), and only one R haplotype appears. Therefore, these loci are linked.

that the genotype of a specific offspring will be sufficiently informative to determine which of two parental alleles has been inherited. Markers are assigned PIC values between 0 (minimally informative) and 1.0 (perfectly informative). A second measure of polymorphism is called heterozygosity. Heterozygosity (H) is calculated as $H = 1 - \sum(\text{Pi})^2$. Pi is a measure of the allele frequencies for a given marker in the population under consideration.[42] There are currently several thousand well-characterized genetic markers with assigned PIC and/or heterozygosity values whose chromosomal locations in the human genome are well known.

Several different types of genetic markers are currently in use for genetic linkage mapping, each with different strengths. Microsatellites are small stretches of repetitive DNA composed of repeated motifs of mono-, di-, tri-, or tetranucleotides, such as (CA)n or (GAG)n, located randomly in the genome.[43–45] They occur frequently in mammalian populations, with a dinucleotide (CA)n repeat found, on average, every 30 to 60 kilobases.[45,46] Microsatellites occurring in human DNA are extremely polymorphic, a given marker occasionally having in excess of 20 alleles. Microsatellite alleles are sufficiently stable in the population and therefore can be reliably used to track inheritance of chromosomal segments through several generations in a family. Yet with an estimated mutation rate of 5×10^{-4} to 10^{-5} per allele per meiosis, new alleles appear frequently in the population, contributing to their overall utility as genetic markers.[47]

Individual microsatellite markers are distinguished from one another after amplification of the locus by polymerase chain reaction and separation of the resulting alleles by electrophoresis[48,49] (Fig. 13-5). Among the most popular platforms is the Applied Biosystems (ABI) Capillary system using the GeneScan software.

One disadvantage of (CA)n repeat–based microsatellite markers is that the resulting variant alleles are so similar in size that they can sometimes be hard to separate on a gel. For this reason, most genome scans today are done by using commercially prepared sets of markers based largely on trinucleotide and tetranucleotide repeats.[50] Although less frequent than (CA)n repeats in the genome, they are easier to automate, and the resulting data are assessed with generally lower error rates. Sets of markers that are known to be very polymorphic and to have 5-cM or 10-cM spacing, and are thus optimized for genome-wide scans, are commercially available for the human, mouse, rat, and dog genomes. Commercially prepared marker sets are optimally designed so that the markers can be multiplexed, making it possible to analyze several markers simultaneously in a single gel lane.

SNPs (pronounced "snips") occur when a single base in the genome is altered. It is estimated that polymorphic SNPs with a minor allele frequency greater than 5% occur once every 450 base pairs in the human genome and thus offer an unending resource for tracking variation.[51] However, since SNPs are biallelic, the overall informativeness of a single marker is less then the average microsatellite. As a result, thousands of SNPs are required to perform a complete genome-wide linkage scan.

The recent development of high-throughput SNP genotyping platforms for linkage studies by Affymetrix (10K GeneChip microarray, Fig. 13-6) and Illumina (Linkage IV panel, Fig. 13-7) have not only made SNP-based linkage scans realistic, but significantly reduced the time required to interrogate a complete genome. Dense SNP genotyping also increases the information content in families in which the parental genotypes are not available, as is typically the case for late-onset diseases like most cancers. For example, researchers at the Mayo Clinic analyzed a linkage study of prostate cancer families with both a 10-cM spaced microsatellite and the Affymetrix 10K SNP genome-wide scans.[52] They concluded that for families that lack parental genotypes, the SNP scan had significantly higher information content than did the microsatellite scan (61% versus 41%). This concept is an important consideration in experimental design. Measures of linkage can be limited by both lack of critical family members and marker informativeness. The increase in information content associated with a dense SNP genome-wide scan will improve measures of linkage at loci, which are truly linked.

However, genome-wide SNP linkage scans do have some limitations. Each individual SNP is not very informative; therefore, tracking the inheritance of chromosomal segments through a family or the detection of Mendelian errors requires the assembly of data into haplotypes (Fig. 13-8). A haplotype represents a set of alleles associated with an ordered set of markers inherited together on a

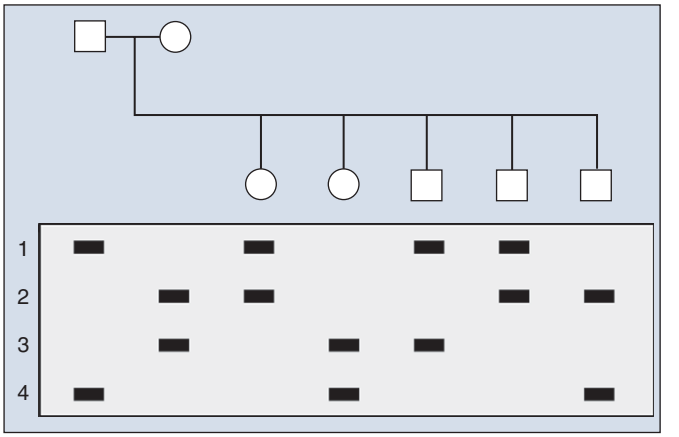


Figure 13-5 • Schematic agarose gel electrophoresis of a microsatellite marker analyzed on a single family. Males are indicated by squares, and females by circles. Four alleles are segregating; the father has alleles 1 and 4, and the mother carries alleles 2 and 3. Each child has inherited one allele from each parent, together with the surrounding genomic information.

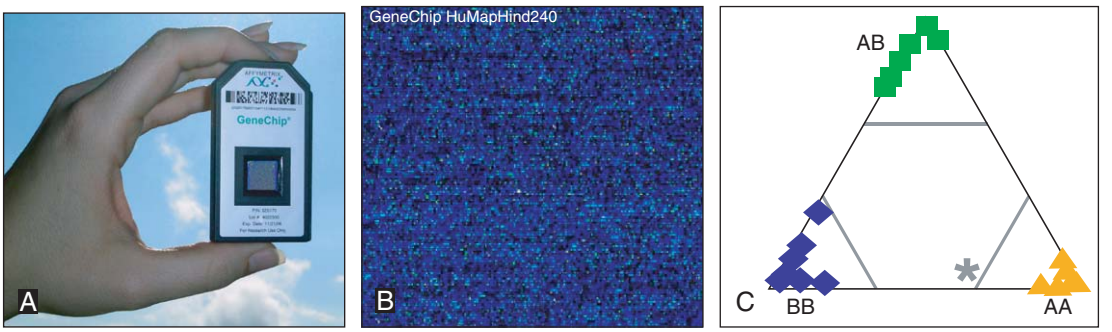


Figure 13-6 • Affymetrix's high-throughput SNP genotyping platform. **A,** Affymetrix GeneChip can assay over 250,000 SNPs per sample on a single GeneChip. Oligonucleotide probes are spotted to a glass microchip, where each SNP is interrogated with approximately 40 different probes. **B,** A pseudocolored scan of a single Human Mapping 100K Hind GeneChip. **C,** The GTYPE software displays the genotype calls of several samples for a single SNP (C versus T). The orange triangles are homozygous CC, the green squares are heterozygous CT, and the blue diamonds are homozygous TT.

chromosome that form either the maternal or paternal ancestry. Computer programs such GENEHUNTER and MERLIN are available to assist in assembling haplotypes.[53,54] The process is most efficiently expedited, however, by the collection and genotyping of critical family members, such as grandparents, whether they carry the disease in question or not. It is also important to note that linkage disequilibrium between SNPs can artificially inflate measures of linkage. This is more problematic with SNPs then with microsatellites, as the SNP markers are most closely spaced and are thus more likely to be coinherited as a block. So for any data set, the linkage disequilibrium between SNPs needs to be carefully assessed and SNPs that are in high linkage disequilibrium with other SNPs need to be removed from the data set.

Measures of Linkage

Calculating LOD Scores

On completion of a genome-wide scan, extensive checking is done by using programs such as PEDCHECK, PREST, RELPAIR, and MERLIN to detect potential genotyping errors by checking, for instance, Mendelian inheritance.[54–57] Data are then analyzed to determine which, if any, markers are closely linked to a putative disease locus. The likelihood for linkage ($\theta < 0.5$) versus the likelihood for recombination ($\theta = 0.5$) is calculated on the basis of the number of observed recombinant and nonrecombinant offspring produced by a given mating. Conventionally, the logarithm of the likelihood ratio, or LOD score, is

$$Z(\theta) = \log_{10}[L(\theta)/L(0.5)]$$

and is used as the measure of support for linkage versus nonlinkage. For example, if n observations consist of k recombinants and $n - k$ nonrecombinants, the corresponding LOD score is given by

$$Z(\theta) = n \log(2) + k \log(\theta) + (n - k)\log(1 - \theta), \text{ if } \theta > 0$$

$$Z(\theta) = n \log(2), \text{ if } \theta = 0$$

It is often stated that linkage is "found"; that is, a marker under consideration is said to be linked to a putative disease locus when a recombination fraction of $\theta < 0.5$ is supported by a LOD score of at least 3.0.[58] However, in searching for genes, it is important to distinguish between pointwise significance levels and genome-wide significance levels.[59] The pointwise or nominal significance level is the probability that one would encounter such an extreme deviation at a specific locus by chance. The genome-wide significance level is the probability that one would encounter such a deviation somewhere in the whole genome scan (Box 13-1). The former is an evaluation of a single test of the null hypothesis of no linkage (testing for linkage of a favorite candidate gene to a disease locus); the latter involves screening over a large number of tests (i.e., running a large number of markers spanning the genome) to find the most significant result.

In assessing the significance of a putative linkage result, Lander and Kruglyak[59] have assigned the following descriptors. Suggestive linkage is that which would be expected to occur one time at random in a genome scan. Significant linkage would be expected to occur 0.05 times in a genome-wide scan. Highly significant linkage that is considered statistically significant is expected to occur 0.001 times in a genome scan. It is generally the norm to report all regions with a nominal P value of $P = 0.05$ in a complete genome scan. These may indicate places in the genome where additional families, markers, or both are needed. A LOD threshold of 3.3, corresponding to $P = 5 \times 10^5$, is the value that is now accepted as indicating a genome-wide significance level of 5%. Thus, in the context of a genome-wide scan, a marker is said to be linked to a disease locus if a LOD score of 3.3 is achieved[59] (Box 13-2).

Limitations and Sources of Error

Linkage analysis is an inherently error-prone approach. It is fairly easy to arrive at an incorrect conclusion because of the large number of

Box 13-1. LOD SCORES VERSUS PROBABILITY MEASURES

It is noteworthy that there is frequent confusion in the literature about LOD scores versus probability measures. Again, according to the example provided by Lander and Kruglyak, a LOD score of 3.0 means that the observed data are 1000 times more likely to arise under a specific hypothesis of linkage than under the null hypothesis of independent assortment. A P value of 10^{-3} means that the probability of encountering as large a LOD score as is observed is 10^{-3} under the null hypothesis.

Box 13-2. CONFIRMATION LINKAGE STUDIES

Clinicians often choose to participate in studies that are aimed at confirmation of previously published linkage reports. For confirmation of published findings of linkage in an independent data set, a nominal P value of 0.01 is required. Because linkage from any previously published reports may hinge on precise features of the clinical diagnosis or stratification of the data set based on features of family history, it is vital that participating physicians record their clinical observations as accurately as possible.

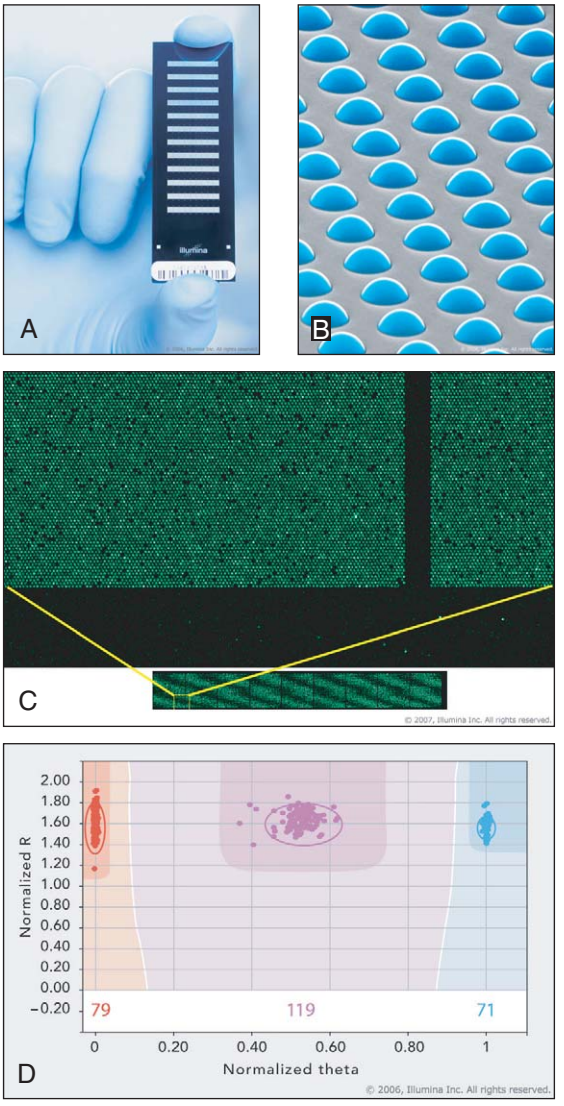


Figure 13-7 • Illumina's high-throughput SNP genotyping platform. **A,** Illumina's Infinium BeadChip can assay over 650,000 SNPs per sample on a single BeadChip. **B,** Illumina's BeadArray Technology is based on 3-micron silica beads. Each bead is covered with over 100,000 copies of a specific oligonucleotide that act as the capture sequence in the Illumina assay. **C,** BeadScan Software scans the results of a single-color BeadChip. Each green dot represents one 3-micron bead and the specific oligonucleotide attached to it. **D,** BeadStudio Genotyping Software displays the cluster plot for the results of a single SNP (A versus G). The genotypes of the 79 red samples are homozygous AA, the 119 purple samples are heterozygous AG, and the 71 blue samples are homozygous GG.

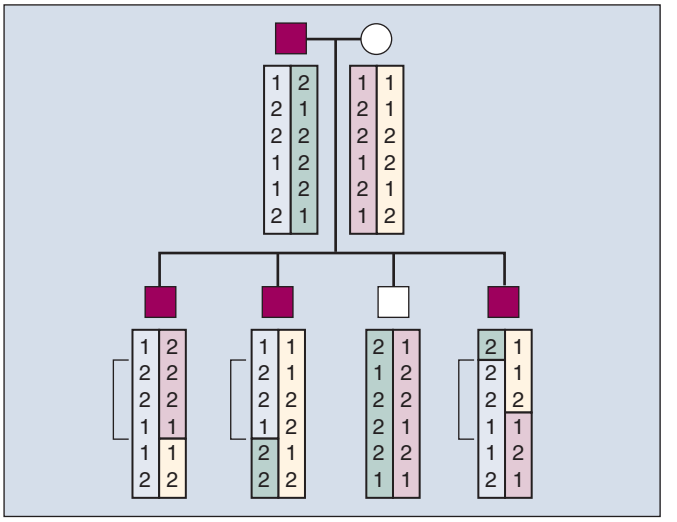


Figure 13-8 • SNP haplotypes in a prostate cancer family. Males are indicated by squares, and females are indicated by circles. Each individual's haplotype for a chromosomal region of interest is drawn below the symbols. The father's two haplotypes are blue or green, and the mother's are red or yellow. The three affected brothers and father all share the haplotype shaded blue, whereas the unaffected brother has inherited the haplotype shaded green. There are recombination events in brothers 2 and 4, restricting the region of interest to that defined by SNPs 2, 3, and 4 (indicated by the brackets).

assumptions that must be made in the calculation. For instance, calculation of LOD scores is dependent on accuracy of the linkage model.[60] The model is typically based on assumption regarding mode of inheritance or frequency of mutant alleles in the population which may be derived from segregation analysis conducted in one geographic region at one hospital, thus introducing potential bias. In addition, studies have shown that LOD score analysis of a small number of families is very sensitive to changes in a few key data points. Small errors in genotyping or misclassification of affected status have the potential to artificially inflate or deflate a particular LOD score. Consider, for example, age at onset. The linkage calculation will weigh the value of information provided by any given family member compared with that of every other person in the study. So if early-onset disease is a defining part of the phenotype, the genotyping data from an individual woman who was diagnosed with the disease at the age of 30 years will be weighted more in the linkage statistic than will data from a person who was diagnosed at 80 years. Therefore, it is vitally important that the clinician participating in the study obtain the most current and accurate information available from any patient who is likely to be a study participant, including the age at which various family members had cancer.

One additional problem with linkage calculations is the loss of power associated with missing data. In principle, an individual who is a heterozygote at two loci A and B (AaBa) could have received his or her A allele in coupling with either the B or the b allele from one parent. To distinguish recombinants from nonrecombinants, the parental and nonparental haplotypes must be known. If the A and B alleles were inherited together on the same chromosome, they are said to be in phase. Unfortunately, when mapping diseases such as cancer, in which late age of onset is common, two-generation families are typically all that are available for sampling, thus limiting the ability to determine phase. However, collection and analysis of data from spouses or offspring of deceased affected individuals may allow researchers to reassemble the genotype of the deceased individual. Similarly, collection of DNA samples from unaffected siblings can be very useful for establishing parental phase.

Nonparametric Analysis

Because calculation of LOD scores is dependent on models of linkage that are notoriously difficult to derive,[61] researchers are turning increasingly to nonparametric linkage (NPL), or nonmodel-based approaches for mapping genes.[53] Such approaches use only the data from affected individuals; therefore, no assumptions are made as to whether an unaffected person is more or less likely to have cancer and, if so, at what age. In an NPL analysis, haplotypes are built across the relevant regions of the genome by using computer programs such as GENEHUNTER or MERLIN.[53,54] The data are compared, and *P* values are calculated to assess the degree of significance observed between inheritance of a disease state and a specific haplotype.

Nonparametric approaches have the disadvantage of being less powerful than LOD score–based approaches because data from unaffected individuals, which could have contributed to the LOD score, do not contribute to the NPL score. For diseases that are genetically heterogeneous, such as common cancers, this is more than made up for by the lack of reliance on incomplete or inaccurate linkage models.

One final consideration is that of age at diagnosis versus age at onset, which, depending on the disease and available diagnostics, can differ by several years. Diagnosis of prostate cancer by prostate-specific antigen (PSA) testing provides an interesting example. The widespread use of screening for prostate cancer by serum PSA measurements has dramatically changed the patterns of disease diagnosis in the United States.[62] Reported rates increased rapidly between 1986 and 1993, in part because of the detection of latent prostate tumors in the general population as a result of PSA screening.[63] It is generally believed that PSA can detect tumors from 2 to 5 years earlier than methods such as digital rectal examination.[64–66] Therefore, data from a man who was given a diagnosis of prostate cancer at age 65 in 1995 should contribute differently to a genome scan than data from a man given the diagnosis at the same age in 1975. The man who was given the diagnosis in 1975, assuming that he participated in screening, would probably have been given the diagnosis in his early sixties if he were alive today. Developing statistical methods to account for these differences can be extremely difficult.

It is also important to note the difference between untested and unaffected individuals. Patients are more likely to know that they are truly unaffected with a disease such as prostate cancer (as defined by PSA status) than they are likely to know they are truly unaffected with other cancers, such as pancreatic or ovarian cancer, for which vigilant screening is not the norm. For this reason, in some genome-wide scans for cancer susceptibly genes, clinical status of putatively unaffected individuals may be coded as "unknown" rather then "unaffected." It is important that the interviewing physician make the distinction when recording any patient's family and medical history.

Positional Cloning Resources

Meiotic linkage studies may define a region of interest as small as a few thousand bases or as big as several million bases. The latter may span more than a hundred genes[67,68] and must be further reduced before mutation scanning can realistically begin. Several strategies exist for narrowing the search. Among the most common is the search for genomic rearrangements in tumors, which may indicate chromosomal regions where cancer susceptibility genes are likely to be located. Expression arrays identify genes that are differentially expressed in tumors compared to matched normal tissue. Additionally, intriguing candidate genes within the region of interest may be selected for priority sequencing based on known biologic function or a previous association with cancer.

Comparative Genome Hybridization

Comparative genome hybridization (CGH) can be used to acquire information about gains and losses of chromosomal regions in tumors.[69,70] CGH allows investigators to perform genome-wide analysis of DNA sequence copy number in a single tissue. Traditionally, differentially labeled genomic DNA from a "test" and a "reference" cell population are cohybridized to normal metaphase chromosome spreads. Regions of gain or loss of chromosomal segments, such as deletions, duplications, or amplifications, are seen as changes in the ratio of the intensities of the two fluorochromes. The procedure works because the ratio of fluorescence intensities along the length of the chromosome is proportional to the ratio of the copy numbers of the corresponding DNA sequences in the test and reference genomes at each point in the chromosome. More recent innovations with this technique allow investigators to circumvent the low resolution associated with metaphase spreads and very precisely determine DNA copy number by combining traditional CGH with arrays of bacterial artificial chromosomes (BACs) or oligonucleotides.[71,72] Array CGH studies have contributed to the identification of the genetic alterations involved in cancer progression and metastasis and highlight the importance of studying tumors at various stages of progression.

Expression Arrays

Another method for refining linkage data before proceeding with candidate genome analysis is the use of expression arrays. Expression arrays analyze differences in gene expression on a large scale by assaying thousands of genes in one experiment. For one type, DNA microarrays, DNA sequences from the coding regions of known or putative genes are assayed with probes made from messenger RNA, which determines an expression profile of genes for a certain cell type or under specific experimental conditions. In terms of cancer genomics, normal cells may express different portions of the genome or different genes at different levels when compared with their neoplastic counterparts, which may indicate biologic networks or pathways involved in disease pathogenesis.[73] Microarray experiments have led to molecular classification of many cancer types according to differences in gene expression, including breast cancer,[74] lymphomas,[75] and soft-tissue tumors.[76] Integration of DNA microarray data with genetic mapping results will help to prioritize candidate genes in regions of known linkage. As single gene traits are defined and researchers' interest turns increasingly to multigene traits, a combination of traditional and twenty-first century approaches will most likely define the genes of interest.[77]

Tissue Banks

One problem that is not infrequently encountered with CGH and expression array studies is lack of reproducibility across studies. This is due to both the limited number of tumors typically available for studies and the heterogeneity in the tumors themselves. One way to circumvent both problems is to develop tumor banks in which investigators can deposit well-characterized tissues for a variety of research purposes.[78] One potential complication is the rigor with which such banks must be maintained. It is important that complete pathologic records accompany each tissue and that the tissue deposited be as free as possible of adjacent noncancerous tissue. Toward this end, researchers have turned increasingly to the use of laser capture microdissection as a way to isolate virtually pure populations of tumor for CGH and expression array studies.[79]

ASSOCIATION STUDIES

Association studies are distinct from linkage analysis in that specific alterations in the DNA are assessed in both affected and unaffected individuals to determine whether the variant is found more often in individuals with the disease and whether this difference in the frequency of the variant allele is statistically significant. Association studies are widely used to assess the significance of variants in candidate genes and just recently are being used to identify susceptibility genes in genome-wide association studies.

Assessment of Candidate Genes

Once a candidate gene is proposed, association studies are important to determine whether sequence level changes in the gene are associated with the disease of interest. Candidate genes are identified in a variety of ways. For instance, the biologic function of a known gene might suggest a role in cancer susceptibility. Alternatively, the sequence of the gene might suggest that it is a member of a protein family that is known to play a role in cancer biology. Genes that are important in DNA repair, apoptosis, and cell cycle regulation are all

likely candidates. Finally, the gene in question might be located at a locus identified by linkage analysis of high-risk families. Thus, it may be one of a large number of genes under consideration.

Genome-wide Association Studies

Since association studies have greater power to identify common genetic variability compared to linkage studies, the ability to conduct these experiments has been highly anticipated. Genome-wide SNP association studies have become more practical in the past few years owing to the information gained from the HapMap project (www.hapmap.org) and the development of technologies to genotype hundreds of thousands of SNPs in a single experiment. The International HapMap project aimed to identify genetic similarities and differences in human populations. The initial data were generated from four different populations with African, Asian, and European ancestry. These data allow for the identification of minimal sets of informative SNPs to tag variation throughout the genome for a given population. Also important for the advancement of genome-wide association studies was the development of high-throughput genotyping assays, which are cost-effective, accurate, and reproducible. Currently, the two leading high-throughput genotyping platforms are from Affymetrix and Illumina. The Affymetrix GeneChip microarrays (see Fig. 13-6) are available to genotype 10K, 100K, or 500K genome-wide SNPs in a single experiment. From Illumina, the Infinium HumanHap300 and HumanHap550 (see Fig. 13-7) are specifically designed for whole-genome genotyping of tag SNPs derived from the HapMap project. The study design and caveats for genome-wide association studies are similar to the candidate gene approach and will be discussed briefly in the following sections. However, adjusting for multiple testing is a particular concern for genome-wide association studies as the number of SNPs tested in a given experiment is large.

Study Design

Two primary types of study design are typically used: cohort and case-control studies. In a cohort study, subjects are selected, individuals with the disease of interest (i.e., prevalent cases) are excluded, one or more exposures of interest are measured, and then the cohort is monitored over time to determine who develops cancer or the outcome(s) of interest and the degree to which the exposure is associated with disease incidence. In genetic epidemiology, the primary "exposure" is the genetic variant under consideration. This type of cohort study is prospective in nature, the health outcomes (presence or absence of cancer over time) occurring after the enrollment of study subjects. Exposure is measured at baseline, when the cohort is initially established, and may be updated over the period of follow-up for those exposures that may change over time (obviously, the germline variant or variants a given individual carries do not change over time). The advantages of cohort studies include minimized information and selection biases and the ability to directly calculate disease incidence in exposed and unexposed groups and thus the relative risk (RR) and absolute risk (attributable risk, AR). RR is the risk of developing a disease given a particular exposure and is calculated as the incidence of cancer among a set of individuals with a particular genotype, divided by the incidence of cancer among a set of individuals who do not carry that genotype. Disadvantages include the fact that prospective cohort studies are expensive and time-consuming and large numbers of study subjects are typically required to obtain sufficient numbers of outcomes (e.g., cancer cases) to have adequate power to determine associations. Loss of subjects to long-term follow-up over time is also an issue because it may affect the ability to draw conclusions.

Cohort studies may also be retrospective in nature, when the exposure and subsequent development of the disease occur before the study begins. For the purpose of finding associations between disease status and genotype, retrospective cohorts depend on existing medical records to identify all cancer diagnoses in the population of interest during a specified time period. As such, if any of the medical information documenting either the exposure(s) or the disease is not completely accurate, then bias or error would be introduced into the study.

Case-control studies differ from cohort studies in that the selection of subjects is based on their disease status. Case-control studies have the potential to examine multiple risk factors simultaneously. Two very popular case-control designs are population-based and hospital-based. For each, it is important to select case patients and control subjects who are similar with respect to recognized confounding factors such as age, sex, race, and ethnic background.[80–85] Another critical factor for study design is that the controls must be selected from the same underlying population from which the cases were ascertained. The purpose of the control group is to provide valid data on exposure prevalence (e.g., distribution of genotype) in the same population from which cases were accrued.

Population-based case-control studies draw on a well-defined source population such as a particular geographic region defined by state, county, or city for ascertainment of both case patients and unaffected control subjects. Popular mechanisms include use of cancer registries, such as Surveillance Epidemiology and End Results, or health care provider databases. Control subjects should be selected from the same source population or geographic region by a method designed to randomly sample individuals, such as random-digit telephone dialing.[86] Selection bias, in which selection of case patients, control subjects, or both is influenced by prior exposures, is a particular concern in case-control studies.[83–85,87,88] Proper design of the selection process can help to reduce this problem. Multiple studies have shown, for instance, that nonparticipants in such studies are more likely to smoke than are individuals who agree to participate.[88] Thus, there is concern that participants might be more health conscious than nonparticipants.

In comparison, hospital-based case-control studies enlist a sequential series of patients who are admitted to the hospital or clinic during a specific period. Case patients are enrolled because they have the cancer of interest, whereas control subjects are determined to be cancer-free, although they may be patients at the same clinic or hospital for unrelated reasons. Significantly more potential for bias exists in hospital-based case-control studies. Depending on the clinic or hospital from which patients are drawn, disease presentation, severity, and treatment outcome may be nonrandom among study subjects. Often, cases are drawn from so-called high-risk clinics. In such situations, both case patients and control subjects might be more likely to carry a specific genotype. They might have been referred to a high-risk clinic because of their family history status. A particular concern is that hospital- or clinic-based controls might not accurately reflect the frequency of the exposure in the underlying population from which cases were ascertained. Thus, it might be difficult to generalize results from a hospital-based case-control study to the general population.

Confounders and Sources of Bias

Confounders are factors that are associated with both the exposure and the disease and are outside of the causal pathway of the exposure. Age is a frequent confounder, as it is often associated with the frequency and level of exposures and many diseases increase in incidence with advancing age. In the study of genetic risk factors and disease, an important confounder is ethnic background. For example, in a study of the association between human leukocyte antigen (HLA) genotypes and cervical cancer, ethnic background must be addressed as a potential confounder because HLA genotypes can vary by ethnic background and lifestyle factors that contribute to disease can be associated with ethnic differences.[89] When the association between HLA genotype and cancer was calculated, ethnic background was adjusted to minimize the potential for bias caused by this confounder.[89] In addition to statistical adjustment for ethnic background,

exposure-disease associations can also be examined and reported separately according to ethnic background.

Another source of bias that is specific to case-control studies and retrospective cohorts is recall bias.[90] Study subjects might find it difficult to correctly remember information related to subjective factors that are potentially important in disease susceptibility such as those related to environmental or lifestyle factors, such as diet, smoking, exercise, and stress levels.[91] Recall bias can lead to incorrect or incomplete measurement of exposures and potential confounders. This introduces error into the calculation of the association between the exposure and the disease because of the inability to fully adjust for the effects of confounders.

SNP Genotyping and Association Studies

In an ideal situation, collection of blood samples from all eligible study subjects, both cases and controls, is undertaken as part of any genetic epidemiology study. The resulting DNA samples can then be used to test for association of candidate genes and features of disease. Several types of low- to mid-throughput assays are frequently used to genotype SNPs, including direct sequencing, Sequenom, Taqman and SNPlex (both by Applied Biosystems), as well as custom Illumina's GoldenGate bundles and many others. Most assays available start with small quantities of DNA, and polymerase chain reactions amplify specific regions of DNA before querying the different SNP alleles and calling the genotypes.

SNPs that introduce nonsense changes, causing premature termination of the protein, and SNPs that alter a key amino acid sequence in the encoded protein are the focus of much of the current literature with regards to nearly all cancers.[92] Other SNPs of interest change single amino acids in key protein motifs or occur in splice domains. Much less well understood are SNPs that are found to be in association with the disease state but located in noncoding regions of the gene.[93–95] Association studies are observational in nature and define genotypes or exposures that are simply "associated" with a particular disease, but they might not actually cause the disease of interest. In such situations, the SNP is thought to be in linkage disequilibrium with an as yet unidentified disease-causing mutation.

SNPs within the vitamin D receptor gene provide a set of interesting examples. Single base changes in intron 8 and within exon 9 affect recognition sites for the restriction enzymes BsmI and TaqI. Neither variant apparently affects the resulting protein sequence, but both have been associated with prostate cancer risk.[93,95] Additionally, variation in the 3′ untranslated region of the poly A tail is similarly associated with prostate cancer risk,[94] but the alteration appears to have no obvious effect on mRNA stability.[96] All three polymorphisms have been reported to be in at least partial association with one another in a subset of studies and, in all likelihood, serve as markers for an as yet undiscovered disease-causing variant.[96,97] In addition to these variants, some investigators report a variant in exon 2, which creates a FokI restriction enzyme site and results in a new start codon for the protein, generating a transcript with three additional amino acids.[98] It is unknown whether this change itself is disease-associated or whether it, too, is simply a marker for an unknown variant. Functional studies are needed to test the role of all of these variants on protein function.

Relative Risks

Results of an association study are evaluated by calculation of a RR or an odds ratio (OR), which is an estimate of the RR derived from a case-control study. Values greater than 1.0 indicate that the exposure (in this case, a particular genotype) is associated with an increased risk of the cancer under consideration. In comparison, values less than 1.0 indicate a decreased risk for the disease associated with that genotype. In cohort studies, RR can be calculated directly as the likelihood of developing cancer among a set of individuals with a particular genotype, divided by the likelihood of developing cancer among a set of individuals who do not carry that genotype. Thus, the RR is the risk or probability of developing cancer in the defined source population, given a particular genotype.

A different statistical method is used for assessing risk in case-control studies, because subjects are selected according to disease status and not exposure, as they would be in a cohort study. The OR is an estimation of the RR and is calculated as the odds of exposure for cases divided by the odds of exposure for controls. For both point estimates of the RR and OR, 95% confidence intervals are calculated to determine statistical significance of the risk estimate. For example, at the $\alpha = 0.05$ level, statistically significant risk estimates are those in which the 95% confidence interval excludes 1.0, that is, the null hypothesis of no association. For a more stringent test, 99% confidence intervals may be calculated.

Logistic regression is often used to calculate ORs when multiple potential confounding factors are expected to affect the risk of the disease. Such calculations are made to account for the contribution of other disease-associated factors that are also correlated with the exposure of interest. If high-quality information about other characteristics of subjects is collected, data sets can be stratified by age, family history, or clinical features of the disease before calculation of the association between genotype and disease, as a way of identifying important modifiers of risk in relation to genotype.

GENETIC COUNSELING AND TESTING

Patients will frequently approach clinicians with questions about genetic-testing opportunities for specific cancers. If appropriate tests are available, identifying a person with increased risk for a particular cancer is useful for at least three reasons. First, it can suggest a particular clinical course that will reduce the chance of having cancer, such as treatment with tamoxifen or prophylactic surgery for women who are at risk for hereditary breast cancer.[99–101] Second, it can induce patients at risk to undergo more vigilant screening, such as frequent colonoscopy examinations for patients who are at risk for colon cancer. Finally, an individual's quality of life can sometimes be improved by having specific knowledge about the more precise risk for disease or recurrence. In addition, such information is frequently sought by unaffected individuals who perceive themselves to be at increased risk.

The National Society of Genetic Counselors defines genetic counseling as a "the process of helping people understand and adapt to the medical, psychological, and familial implications of the genetic contributions to disease."[102] Therefore it should be offered only in consultation with certified genetic counselors who serve to (1) help patients comprehend the medical facts and risks associated with their disease, (2) help patients understand their alternatives for dealing with both risk of disease and recurrence, (3) help patients choose a clinical course that best meets their needs, and (4) provide support and guidance for patients experiencing difficulty in dealing with unexpected results. Patients often approach genetic testing with strong preconceived notions about the likelihood that they either do or do not have an inherited mutation. Thus, "unexpected" is likely to apply to both carriers and noncarriers.

In advising patients whether it is appropriate to consider genetic testing, it is important to remember that many currently available tests have limitations. *Clinical validity* is the term that is used to describe the predictive value of a test for clinical outcomes.[103] It is affected by both the sensitivity and the specificity of the test, as well as a host of factors that are beyond laboratory control, such as penetrance of the mutant allele. The latter may itself be a function of genetic background, environmental exposures, or both. Most mutations associated with cancer susceptibility genes are not fully penetrant. There will therefore be a small group of individuals who, even if they live into their eighties, will not get cancer even if they carry protein-truncating mutations in a gene associated with a particular cancer. Helping patients to understand these concepts can be difficult.

One additional concern is what to tell patients who do not have obvious protein-truncating mutations but who do carry missense changes in the coding region of a cancer susceptibility gene. Again, particularly interesting examples are provided by the BRCA1 gene. More than 300 independent missense changes have been reported for BRCA1 to date.[104] Disease association status is known for only a fraction of these, such as those occurring in the RING finger domain[105] and the C-terminal region of the protein.[106,107] In the case of RING finger mutations, these conclusions are supported by the existence of dozens of families in which RING finger mutations are shown to closely segregate with disease state.[108,109] Other single amino acid changes are known to be inconsequential polymorphisms that clearly do not affect protein function. For instance, some 40% of the population is heterozygous for the substitution of leucine for proline at position 871, as reported in the canonical sequence. Both residues are hydrophobic, and the location is not one that is well conserved evolutionarily; and this is likely to be an inconsequential polymorphism in the gene. Of particular concern, rather, are the large number of missense changes that are reported in patients with breast cancer whose disease association status is unknown. Phylogenetic analysis provides some insight as to which are likely to be important,[110] and functional assays are useful for testing mutations in some regions of the gene.[107,111] However, at this time, little guidance is available for most patients carrying such changes.

IMPLICATIONS FOR THE FUTURE

The sequence of the human genome has been referred to as an "instruction book for human biology."[112] Locked within the sequence of each individual's DNA is the genetic code necessary to develop a complete and healthy individual, but encoded as well is the sequence-level variation that will determine each person's susceptibility to a host of diseases. Variation is important in defining the field of genomic medicine. A more complete understanding of the molecular pathways involved in cancer susceptibility will suggest avenues for the development of both methods of diagnosis and treatment. Identification of specific genes offers the promise of genetic testing to individuals who are at risk, as well as the hope for targeted therapeutics. Finally, understanding the specific variation offers the promise of twenty-first century "personalized medicine" in which lifestyle, diet, and preventative therapies come together to offer patients a full spectrum of choices for maintaining their personal health.

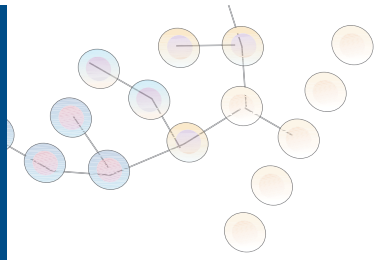
It is clear that the Human Genome Project has had and will continue to have an effect on human health and biology.[112] What remains to be seen is the rate at which the successes of the Human Genome Project will move from bench to bedside. In a sense, that rate will be determined by practicing physicians. Knowledge of the underlying principles of genetic analysis is fundamental for today's practicing clinician. The ability to accurately record family history and medical record data affects the integrity of all subsequent studies for which those data are used. An understanding by physicians of the findings generated through both association studies and family-based linkage studies is key to both moving research forward and prioritizing new hypotheses for researchers to consider. Finally, as twentieth century–born patients struggle to make personal health care choices in the twenty-first century, communicating what genomic medicine has to offer is a complicated task at which every physician must now excel.

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14 Progressing from Gene Mutations to Cancer

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SUMMARY OF KEY POINTS

- A root cause of cancer is the accumulation of defects in genes that play critical roles in regulating cell proliferation, cellular differentiation, and cell death. The mutations in cancer cells are of two types: gain-of-function mutations in oncogenes and loss-of-function mutations in tumor suppressor genes.
- Epigenetic mechanisms can substantially alter expression of proto-oncogenes and tumor suppressor genes, leading to essentially the same consequences as if the structure and/or sequence of the genes were affected by mutation.
- Clinical and pathologic studies indicate that most cancers arise from pre-existing benign lesions, and it is estimated that six to seven mutations are needed for development of a clinically recognizable cancer. On the basis of molecular analyses of cancers, multiple gene defects may often accumulate in a cancer cell during its development, and benign lesions generally have fewer defects than do their malignant counterparts.
- A process termed *clonal selection* has a key role in determining the particular constellation of genetic and epigenetic defects that are present in a cancer cell. Clonal selection is essentially a punctuated evolutionary process that promotes outgrowth of precancerous and cancerous cells carrying those mutations and gene expression changes that confer the most potent proliferative and survival properties upon the cancer cells, in a given context.
- Although a diverse array of mutations and gene expression changes have been implicated in cancer pathogenesis, the defects appear to affect a more limited number of conserved signaling pathways or networks. The proto-oncogenes and tumor suppressor genes that are most frequently mutated in cancer cells most likely represent particularly critical hubs in the cell's regulatory circuitry.
- Although cancer represents a very heterogeneous collection of diseases, the development of all cancers, regardless of type, appears to be critically dependent on the acquisition of certain traits that allow the cancer cells to grow in an unchecked fashion in their tissue of origin and to grow as metastatic lesions in distant sites in the body. Signature traits that are likely to be inherent in the majority, if not all, of cancer cells include the following: (1) an increased tendency to manifest a stem cell or progenitor-like phenotype, (2) an enhanced response to growth-promoting signals, (3) a relative resistance to growth inhibitory cues, (4) an increased mutation rate to allow for the rapid generation of new variant daughter cells, (5) the ability to attract and support a new blood supply (angiogenesis), (6) the capacity to minimize an immune response and/or evade destruction by immune effector cells, (7) the capacity for essentially limitless cell division, (8) a failure to respect tissue boundaries, allowing for invasion into adjacent tissues and organs as well as blood vessels and lymphatics, and (9) the ability to grow in organ sites with microenvironments that are markedly different from the one where the cancer cells arose.
- Certain gene defects in cancer cells may contribute to a few or perhaps even only one of the signature traits of cancer cells. However, many of the gene defects and expression changes might have been selected for in large part because they exert pleiotropic effects on the cancer cell phenotype.
- Despite the fact that some gene defects may arise early in the development of certain cancer types, advanced cancer cells might still be critically dependent on the "early gene defects" for continued growth and survival. Such findings imply that agents that specifically target key signaling pathways and proteins could have utility in advanced cancers even if the signaling pathway defect arose very early in cancer development.
- Future studies will further clarify the role of gene defects in cancer phenotype, allowing more definitive and more specific strategies for inhibiting cancer cells.

INTRODUCTION

A genetic basis for human cancer has been recognized for perhaps more than a century and has been supported by data from familial and epidemiologic studies and animal studies. However, only in the past 25 years has convincing molecular evidence been obtained to support the view that cancer is a genetic disease. Studies from many different fields, including tumor virology, chemical carcinogenesis, molecular biology, somatic cell genetics, and genetic epidemiology, have provided fundamental insights into mechanisms underlying cancer development. While environmental and dietary factors as well as other genes undoubtedly have substantial roles in cancer development, it is now well established that the accumulation of multiple mutations in a single cell plays a fundamental role in the pathogenesis of cancer. The mutations occur in two distinct classes of cellular genes: oncogenes and tumor suppressor genes. As was noted in earlier

chapters, some mutations may be present in individuals' germline and may predispose to particular cancers. Such mutations can also be passed on to future generations. The nature and role of germline mutations in cancer development are of great interest to cancer biologists because the mutations provide powerful clues about the identity of genes and pathways that play particularly critical roles in the malignant conversion of cells. Nevertheless, germline mutations in oncogenes or tumor suppressor genes likely have a major contributing role in only a small fraction of cancers, and the vast majority of mutations in cancer are somatic (i.e., present only in the tumor cells).

A subset of the cellular genes that are affected by inherited and somatic mutations in human cancer will be discussed in more detail later. Brief mention will be made here of some general properties of the genes. Oncogenes, when mutated, act in a positive fashion to promote tumorigenesis. Their normally functioning cellular counterparts, termed *proto-oncogenes*, have been found to be important regulators of many aspects of cell growth. The proteins that are encoded by various proto-oncogenes can be found in virtually all subcellular compartments. The term *proto-oncogene* does not imply that genes of this class lie dormant in the cell with the purpose of promoting tumorigenesis. Rather, the terminology reflects the fact that mutations in cancer cells alter the normal structure and/or expression pattern of the proto-oncogene, generating oncogenic variant forms with altered function. In genetic terms, oncogenic alleles have gain-of-function mutations that confer enhanced or novel functions.

In contrast to the activating mutations in oncogenes, loss-of-function defects in tumor suppressor genes are found in cancer cells. The term *antioncogene* has sometimes been used with respect to the tumor suppressor class of genes. The term suggests that the primary function of the genes might be to act in direct opposition to activated oncogenes. While some of the proteins that are encoded by tumor suppressor genes do in fact bind to and regulate the function of proto-oncogenes or function in pathways that directly regulate proto-oncogene activity, it is not by necessity a general principle.[1] Hence, genes that contribute to cancer by virtue of inactivating or loss-of-function mutations in human cancers will be referred to here as *tumor suppressor genes*. Similarly to the proto-oncogenes, the normal functions of tumor suppressor genes are diverse, and the proteins that are encoded by these genes are found in essentially all compartments of the cell. Compared to the vast array of oncogenic alleles that are seen in human cancer, a somewhat more limited number of tumor suppressor genes have been identified at the molecular level thus far. This finding might not be an accurate representation of the prevalence of oncogene versus tumor suppressor gene mutations in cancer. Rather, it might reflect the practical difficulties that are associated with experimental strategies to identify genes that negatively regulate the growth of cells.

Much evidence indicates that mutations in genes that regulate the recognition and repair of DNA damage play critical roles in tumorigenesis. The DNA damage recognition and repair genes could be considered to constitute a distinct class of cancer genes. However, because DNA repair genes appear nearly invariably to be affected by loss-of-function mutations in cancer, they will be classified here as tumor suppressor genes. Nevertheless, on the basis of certain features, DNA damage recognition and repair genes might constitute a potentially unique subset of tumor suppressor genes. Specifically, in comparison to the presumed direct role of many tumor suppressor genes in regulation of cell growth and programmed cell death, at least some of the DNA repair proteins might have a more passive role in growth, differentiation, and cell survival. Their inactivation in tumor cells might lead predominantly to the acquisition of a "mutator phenotype," with a resultant increased rate of mutations in other cellular genes with rate-determining roles in the cancer process, that is, oncogenes and tumor suppressor genes.

In addition to the well-established role of oncogene and tumor suppressor gene mutations in cancer, there is a large and growing body of data indicating that epigenetic mechanisms might play critical roles in altering the patterns and levels of expression of certain proto-oncogenes and tumor suppressor genes in cancer. For instance, in some cancers, defects in transcriptional regulatory mechanisms can lead to markedly increased levels of proto-oncogene expression, akin to the level that is seen in cancer cells with mutational defects that alter the structure or copy number of the proto-oncogene. Conversely, gene-silencing mechanisms can exert dramatic effects on the expression of certain tumor suppressor genes in cancer cells, essentially rendering the genes functionally inactive in the absence of any mutations.

Given the enormous advances over the past two decades in defining oncogene and tumor suppressor gene mutations and gene expression defects in cancer, it will not be possible in this chapter to review in a comprehensive fashion the vast collection of gene defects that have been identified in human cancers. Nor will it be possible to discuss in great detail the possible contributions of the many different gene defects to alterations in cell signaling and cell physiology. Rather, the primary aim of this chapter will be to offer a framework for understanding the relationship between gene defects in cancer cells and the impact of the accumulated defects on the cancer cell phenotype. Although some details on the identity and nature of gene defects in cancer will be offered here, the emphasis will be on concepts that are likely to have biologic and clinical significance.

CANCERS ARISE FROM THE ACCUMULATION OF MULTIPLE GENE DEFECTS

On the basis of a simple consideration of the likely large number of mutations that arise in normal cells during the many years of life, it would seem quite unlikely that cancers arise as the result of any single gene defect. Even in individuals who are strongly predisposed to cancer as a result of a germline mutation in a specific oncogene or tumor suppressor gene, the vast majority of cells in the individual never develop into cancer or even display definitive morphologic changes akin to those that are seen in benign tumors. In fact, depending on the inherited cancer syndrome, a significant fraction of those that carry specific germline mutations in oncogenes or tumor suppressor genes never develop cancer. Therefore, any model for cancer must incorporate these data, suggesting that cancers likely arise as the result of the accumulation of multiple gene defects in an affected cell. Another issue to consider before formulating genetic models for cancer development is that clinical and histopathologic data indicate that the development of nearly all cancers, regardless of the organ site, is often, if not invariably, preceded by precancerous phases or stages in which the neoplastic cells manifest increasing disordered patterns of differentiation and morphology.

Given this background, it would appear that there is compelling evidence that cancers arise from accumulated defects in several genes and precancerous (benign) precursor lesions contain by necessity fewer of the key gene defects. One question, therefore, is how many rate-limiting defects or "hits" are required for cancer development? While a definitive answer to this question cannot be given at this point, some estimates can be offered. Most common cancers show dramatically increased incidence with increasing age. On the basis of analysis of the age-specific incidence of a number of common cancers and some straightforward assumptions about the rate of mutations and the size of the target cell population, it was argued as early as the mid-1950s that most common epithelial cancers arise as the result of four to seven rate-limiting events.[2,3] It was inferred that these rate-limiting events represented mutational events. Moreover, benign lesions were inferred to arise as the result of fewer gene defects, consistent with the fact that recognizable benign lesions that are often found show an age-incidence distribution that was shifted roughly one to two decades earlier in life than cancers arising in the corresponding organ or tissue sites. Nevertheless, confounding the use of age-incidence data to model the number of rate-limiting mutations

were questions about certain key biologic assumptions underlying the multihit models. Given the attendant uncertainties with estimates of rate-limiting mutation numbers derived largely or solely from age-incidence data and the practical difficulties in defining the nature and significance of all inherited and somatic gene defects in cancer, a definitive answer to the number of rate-determining mutations for a particular cancer type has not yet been obtained. However, at the very least, it is encouraging to note that molecular analyses of a number of common cancers, such as those of the colon,[4,5] breast,[5] lung,[6] and pancreas,[7] indicate that five or more gene defects are not infrequently seen in cancers, and fewer of the gene defects are seen in certain of the precancerous precursor lesions that are associated with these common cancers.

CLONAL SELECTION AND EVOLUTION IN CANCER

As was noted previously, most, if not all, cancers are thought to arise from pre-existing precancerous populations of cells, and multiple rate-limiting mutations (events) are likely needed for conversion of a normal cell to a cancerous cell. Molecular studies of cancers of various types and their corresponding associated precancerous lesions have yielded some fundamental insights into the processes likely to be critical in emergence of the cancer. First, while normal tissues and tissues from noncancerous disease states display polyclonal (balanced) cell populations, the neoplastic component that is present in benign lesions and cancers invariably displays a clonally related cell population, consistent with the notion that neoplastic transformation of one or at most a few cells within a tissue gave rise to all daughter cells that are present in the tumor. Second, in tumors where it has been possible to analyze both cancer cells and associated precancerous cell populations, a subset of the somatic gene defects that are present in the cancer are clonally represented in the precancerous cell population. Other somatic gene defects appear to be acquired during progression from the precancer subclones to the dominant subclone in the cancer.

These molecular findings in benign and malignant tumors are essentially consistent with a model that was initially proposed by Foulds[8] and subsequently advanced by Nowell[9] (Fig. 14-1). In brief, the clonal evolution model predicts that cancers arise as the result of successive expansions of clonally related cell populations. The successive expansions are driven by the punctuated acquisition of mutations and gene expression changes that endow a particular cell and its progeny with a selective growth and survival advantage over cells that do not harbor the gene defects. In essence, clonal selection is an evolutionary process that allows the outgrowth of precancerous and cancerous cells that carry mutations and gene expression changes that confer the most potent proliferative and survival properties on the cancer cells. It is important to note the specific constellation of genetic and epigenetic changes that are present in precancerous and cancerous cells is context-dependent and likely varies considerably from one cancer type to another and perhaps even to a significant degree among cancers that display quite similar clinical and histopathologic features. The basis for the context-dependent relationship of the changes that confer a selective growth advantage in a particular cancer may reflect physiologic differences in organ site and the tissue microenvironment within the organ site, the identities of the preceding somatic gene defects in the precancerous or cancerous clone, and even the constitutional sequence variations and particular gene expression patterns that are present in nonneoplastic tissues of a given patient. This issue of context-dependent effects of gene defects that promote clonal selection in neoplastic cells will be addressed further in the following sections.

The clonal evolution model has some important biologic and clinical ramifications, just a few of which will be mentioned here. First, the clonal gene defects that are present in a cancer can be traced in precancerous lesions from the same organ site with a goal of attempting to clarify the preferred order in which gene defects arise in the natural history of a particular cancer type. The particular order in which defects accumulate during the initiation and subsequent progression of one cancer type often differs from that in another

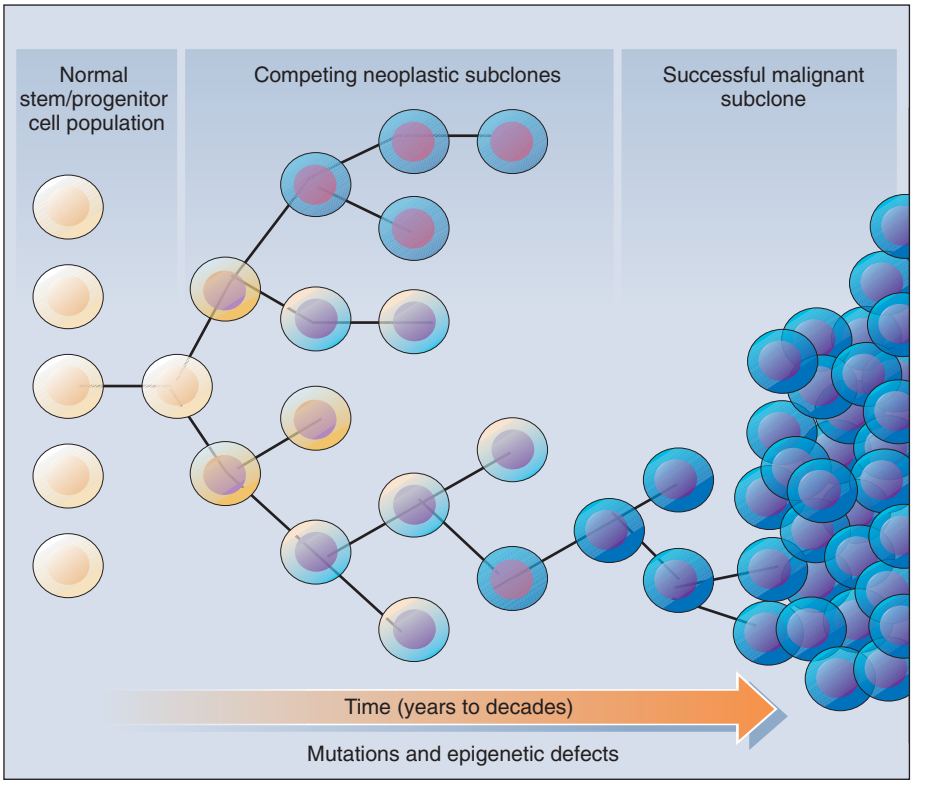


Figure 14-1 • Role of clonal selection in cancer development and progression. Clonal selection is essentially a punctuated evolutionary process that promotes outgrowth of precancerous and cancerous cells that carry the mutations and gene expression changes that confer the most potent proliferative and survival properties on the cancer cells in a given context. The schematic diagram indicates that the stepwise emergence of benign and malignant cells over time is critically influenced by mutations and epigenetic defects. Neoplasms most likely arise from a stem cell or progenitor cell population that is capable of additional cell divisions and acquisition of certain differentiated characteristics. Following the accumulation of a particular constellation of mutations and epigenetic defects in oncogenes and tumor suppressor genes, a successful malignant subclone will outgrow the various competing neoplastic subclones. Further genetic heterogeneity within the malignant subclone (not depicted) is possible, and the genetic heterogeneity in the malignant subclone might give rise to new subclones that display increased invasive and metastatic potential. (Modified from Kern SE: Progressive genetic abnormalities in human neoplasia. In Mendelsohn J, Howley PM, Israel MA, Liotta LA [eds]: The Molecular Basis of Cancer, 2nd ed. Philadelphia, WB Saunders, 2001, pp 41–69.)

cancer type. As a result, a genetic or epigenetic change that is critical in tumor initiation in one cancer type might contribute to tumor progression in another tumor type and vice versa. Second, defects that arise at "early" stages of tumorigenesis might play a vital role not only in tumor initiation but also in the aggressive behavior of advanced stage cancers. Third, the model predicts that the acquisition of further genetic heterogeneity will be a common and important factor in primary cancer lesions and metastases. Genetic heterogeneity likely plays a significant role in resistance to chemotherapy and the emergence of aggressive cell populations in patients with advanced cancer.[10]

It is important to note that clonal somatic mutations are often presumed to have a causal role in promoting further tumor outgrowth or progression because somatic mutations can become clonal (i.e., present in all neoplastic cells) by only a limited number of mechanisms. For instance, the genetic alteration itself could have been selected for because it provided the neoplastic cell with a growth advantage, allowing it to become the predominant cell type in the tumor (clonal expansion). Genes with critical roles in promoting clonal outgrowth in a given cancer have been termed *drivers*.[11] Alternatively, a somatic mutation, when detected, might have arisen essentially coincident with another, perhaps undetected, alteration that was the crucial change underlying clonal outgrowth. Somatic mutations of this latter type have been termed *passengers*.[11] Genes that are mutant in a significant fraction of cancers and for which other lines of evidence link them to the cancer process can more readily be classified as drivers. However, on the basis of early data from some large-scale sequencing analyses that reveal large numbers of distinct genes that are each mutated in only a minority of cancers of a given type,[5,12,13] sorting out drivers and passengers might not be entirely straightforward, based solely on sequencing data, but will likely require a significant body of functional studies and data.[11]

Given this discussion about the potential uncertainties associated with linking specific somatic mutations to cancer development, it is perhaps apparent why it is even more problematic to assign causal significance to gene expression changes in precancerous and cancerous cells. In particular, the ambiguities in assigning a causal role to gene expression and epigenetic changes in the absence of mutations are in large part due to difficulties in determining whether these changes merely reflect or are causally involved in the cancer process. Nonetheless, if a specific gene alteration can be shown to promote tumorigenesis or neoplastic transformation in in vitro models or animal model experiments or if the same gene or chromosomal region is recurrently altered in tumors, then it might be reasonable to infer that the particular defect might indeed have a causal (driver) role in tumorigenesis.

ONCOGENE AND TUMOR SUPPRESSOR GENE DEFECTS IN CANCER TARGET CONSERVED SIGNALING PATHWAYS

Recurrent Mutational Targets in Cancer

As was noted previously, in genetic terms, oncogenic alleles have gain-of-function mutations. Oncogenic variant alleles that are present in cancer are generated from the normal counterpart proto-oncogenes by various mutational mechanisms, including point or localized mutations, gross chromosomal rearrangements, or gene amplification. Some representative oncogene mutations in human cancer are summarized in Table 14-1. From a brief review of the data in Table 14-1, several generalizations are apparent. First, the mutations affect proteins functioning in various compartments of the cell, including growth factor receptors, cytoplasmic signal tranducers, and nuclear proteins, such as transcription factors. Second, although some oncogene mutations may be unique to cancers of a particular type, such as the specific chromosomal translocations and resultant fusion proteins that are seen in cancers of hematopoietic origin (e.g., the BCR-ABL translocation that is seen in chronic myelogenous leukemia and a subset of acute lymphoid leukemias and the PML-RARα translocation that is seen in acute promyelocytic leukemia), other mutations, such as those affecting the K-RAS, β-catenin, and c-MYC genes, are found in a broad spectrum of different cancer types. Third, oncogene mutations in cancer are nearly always somatic, as only a very limited number of germline mutations in proto-oncogenes have been linked to cancer predisposition thus far.[14] Fourth, some proto-oncogenes, such as K-RAS or BCL2, are somatically altered in cancer by a single mutational mechanism, namely, point mutations in the K-RAS gene and chromosomal translocations affecting the BCL2 gene. In contrast, other proto-oncogenes, such as c-MYC, may be activated by more than one mechanism in cancer, including chromosomal translocation and gene amplification. Both mutational mechanisms lead to increased levels of c-MYC transcripts and protein. In fact, specific missense mutations at threonine58 of the c-MYC gene in some lymphomas may further enhance c-MYC protein levels by abrogating a phosphorylation-ubquitination mechanism targeting c-MYC for proteasomal degradation.[15,16]

In contrast to the activating mutations that generate oncogenic alleles from proto-oncogenes, inactivation of the normal function of tumor suppressor genes is critical in tumorigenesis. Akin to the proto-oncogenes, the functions of tumor suppressor genes are diverse, and proteins that are encoded by these genes reside in practically all subcellular compartments (Table 14-2). Many tumor suppressor genes were identified by virtue of the fact that they are mutated in the germline of individuals who are affected by a known Mendelian cancer syndrome or who at the very least display a markedly elevated risk of cancer. The link between a germline-inactivating mutation in a purported tumor suppressor gene and increased cancer predisposition provides very persuasive evidence of the functional significance of the gene in the cancer process. Nevertheless, for the vast majority of tumor suppressor genes, in terms of their magnitude, somatic inactivating mutations play a far more significant role in cancer development than do germline mutations.

Another important point to consider is that much of the attention for tumor suppressor genes has been focused on demonstrating that cancer cells carry biallelic inactivating mutations. Clearly, a diverse array of mechanisms can inactivate gene function, including nonsense, frameshift, and nonconservative missense mutations, as well as gross deletions of the gene or even the chromosome region that contains the gene. In a number of cases, studies of the chromosomal mechanisms associated with tumor suppressor gene inactivation in cancer tissues, such as loss of the parental heterozygosity (i.e., LOH) that is present in normal tissues, have even been used to infer the existence of tumor suppressor genes in particular chromosomal regions prior to the actual identification of the tumor suppressor gene of interest. The emphasis on defining biallelic inactivating mutations in tumor suppressor genes has been stimulated in large part by the Knudson hypothesis,[2,17] which predicted that recessive genetic determinants played a critical role in retinoblastoma and many other cancers and that inactivation of both alleles of a tumor suppressor gene was needed to abrogate tumor suppressor gene activity. Nevertheless, as will be discussed in a bit more detail in the following sections, a variety of observations indicate that epigenetic (nonmutational) mechanisms might play a prominent role in inactivating tumor suppressor gene function in sporadic tumors. Furthermore, for certain tumor suppressor genes, inactivation of only one of the two alleles of a tumor suppressor gene might significantly impair cell growth regulation or programmed cell death. For example, p53 proteins that carry missense mutations in the central (DNA-binding region) of the protein likely potently interfere via dominant negative mechanisms with the wild-type p53 protein in the cell because p53 functions as a homotetrameric protein and all subunits must be wild type for intact p53 function in transcriptional regulation.[18,19] In addition to the likely dominant negative role of mutant p53 in inhibiting the function of wild-type p53, several lines of evidence suggest that

Table 14-1 Representative Oncogene Mutations in Cancer

Gene	Activation Mechanism	Protein Properties	Tumor Types
K-RAS	Point mutation	Signal transducer	Pancreatic, colorectal, lung (adeno), endometrial, other carcinomas
N-RAS	Point mutation	Signal transducer	Myeloid leukemia, colorectal cancer
H-RAS	Point mutation	Signal transducer	Bladder carcinoma
EGFR (ERBB)	Amplification, mutation	Growth factor (EGF) receptor	Gliomas, lung (non-small cell) carcinoma
NEU (HER2/ERBB2)	Amplification	Growth factor receptor	Breast, ovarian, gastric, other carcinomas
c-MYC	Chromosome translocation	Transcription factor	Burkitt's lymphomas
	Amplification		Small cell lung carcinoma (SCLC); other carcinomas; glioblastoma
N-MYC	Amplification	Transcription factor	Neuroblastoma, SCLC; glioblastoma
L-MYC	Amplification	Transcription factor	SCLC, ovarian carcinoma
BCL-2	Chromosome translocation	Antiapoptosis protein	B-cell lymphoma (follicular type)
CYCD1	Amplification	Cyclin D, cell cycle control	Breast and other carcinomas
	Chromosome translocation		B-cell lymphoma, parathyroid adenoma
BCR-ABL	Chromosome translocation	Chimeric nonreceptor tyrosine kinase	CML, ALL (T cell)
RET	Chromosome translocation	GDNF receptor tyrosine kinase	Thyroid cancer (papillary type)
	Point mutation		Thyroid cancer (medullary type: germline mutations)
CDK4	Amplification	Cyclin-dependent kinase	Sarcoma, glioblastoma
	Point mutation		
MET	Point mutation	Hepatocyte growth factor (HGF) receptor	Renal carcinoma (papillary type: germline mutations)
SMO	Point mutations	Transmembrane signaling molecule in sonic hedgehog pathway	Basal cell skin cancer
β-CAT (CTNNB1)	Point mutation, in-frame deletion	Transcriptional coactivator, links E-cadherin to cytoskeleton	Melanoma; colorectal, endometrial, ovarian, hepatocellular, and other carcinomas, hepatoblastoma, Wilms' tumor
HST	Amplification	Growth factor (FGF-like)	Gastric carcinoma
PML-RARα	Chromosome translocation	Chimeric transcription factor	APL
E2A-PBX1	Chromosome translocation	Chimeric transcription factor	Pre-B ALL
MDM-2	Amplification	p53 binding protein	Sarcoma
GLI	Amplification	Transcription factor	Sarcoma, glioma
TTG	Chromosome translocation	Transcription factor	T-cell ALL
AKT2	Amplification	Signal transducer (serine/threonine kinase; downstream effector of PI3K)	Pancreatic and ovarian carcinoma
PIK3CA	Amplification	Catalytic subunit of PI3K	Ovarian carcinoma
STK15	Amplification	Centrosome-associated kinase	Breast, colon, ovarian, and prostate carcinomas gliomas
TMPRSS2-ERG	Chromosome translocation	Transcription factor (ETS family)	Prostate cancer
TMPRSS2-ETV1			
TMPRSS2-ETV4			

ALL, acute lymphocytic leukemia; APL, acute promyelocytic leukemia; CML, chronic myelogenous leukemia; EGF, epidermal growth factor; FGF, fibroblast growth factor; GDNF, glial-derived neurotrophic factor; GTPase, guanine trinucleotide phosphatase; HGF, hepatocyte growth factor; PI3K, phosphatidylinositol 3-kinase; SCLC, small cell carcinoma of the lung.

mutant p53 protein might have some gain-of-function properties that contribute to the tumor phenotype.[18,19] For other tumor suppressor proteins, such as the cyclin-dependent kinase inhibitory protein p27, reduction of protein levels to 50% of the levels present in normal cells might result in significant detrimental effects on the ability of the cell to appropriately regulate growth.[20,21]

Epigenetic Mechanisms of Proto-oncogene Activation and Tumor Suppressor Inactivation

The preceding discussion largely emphasized the role and significance of somatic and germline mutations in proto-oncogenes and tumor suppressor genes in cancer. The rationale for focusing on the role of

Table 14-2 Representative Tumor Suppressor Gene Mutations in Cancer

Gene	Associated Inherited Cancer Syndrome	Cancers with Somatic Mutations	Presumed Function of Protein
RB1	Familial retinoblastoma	Retinoblastoma, osteosarcoma, SCLC, breast, prostate, bladder, pancreas, esophageal, others	Transcriptional regulator; E2F binding
TP53	Li-Fraumeni syndrome	Approximately 50% of all cancers (rare in some types, such as prostate carcinoma and neuroblastoma)	Transcription factor; regulates cell cycle and apoptosis
$p16^{INK4A}$	Familial melanoma, familial pancreatic carcinoma	Approximately 25% to 30% of many different cancer types (e.g., breast, lung, pancreatic, bladder)	Cyclin-dependent kinase inhibitor (i.e., CDK4 and CDK6)
$p14^{Arf}$ ($p19^{Arf}$)	Familial melanoma(?)	Approximately 15% of many different cancer types	Regulates Mdm-2 protein stability and hence p53 stability; alternative reading frame of $p16^{INK4A}$ gene
APC	Familial adenomatous polyposis coli (FAP), Gardner syndrome, Turcot's syndrome	Colorectal carcinomas, desmoid tumors hepatocellular carcinoma, breast (rare)	Regulates levels of β-catenin protein in the cytosol; binding to EB1 and microtubules
WT-1	WAGR, Denys-Drash syndrome	Wilms' tumor	Transcription factor
NF-1	Neurofibromatosis type 1	Melanoma, neuroblastoma	p21ras-GTPase
NF-2	Neurofibromatosis type 2	Schwannoma, meningioma, ependymoma	Juxtamembrane link to cytoskeleton at adherens junction
VHL	Von Hippel Lindau syndrome	Renal (clear cell type), hemangioblastoma	Regulator of protein stability
BRCA1	Inherited breast and ovarian cancer	Ovarian (~10%), rare in breast cancer	DNA repair; complexes with Rad 51 and BRCA2; transcriptional regulation
BRCA2	Inherited breast (both female and male), pancreatic cancer	Rare mutations in pancreatic, others (?)	DNA repair; complexes with Rad 51 and BRCA1
MEN-1	Multiple endocrine neoplasia type 1	Parathyroid adenoma, pituitary adenoma Endocrine tumors of the pancreas	Nuclear protein; unknown function
PTCH	Gorlin syndrome, hereditary basal cell carcinoma syndrome	Basal cell skin carcinoma, medulloblastoma	Transmembrane receptor for sonic hedgehog factor; negative regulator of smoothened protein
PTEN/MMAC1	Cowden's syndrome; sporadic cases of juvenile polyposis syndrome	Glioma, breast, prostate, follicular thyroid carcinoma, head and neck squamous carcinoma	Phosphoinositide 3-phosphatase; protein tyrosine phosphatase
SMAD4	Familial juvenile polyposis syndrome	Pancreatic (~50%), approximately 10% to 15% of colorectal cancers, rare in others	Transcriptional factor in TGF-β-signaling pathway
BMPR1A	Familial juvenile polyposis syndrome	Not known	Receptor for bone morphogenetic protein
MSH2, MLH1 PMS1, PMS2, MSH6	Hereditary nonpolyposis colorectal cancer	Colorectal, gastric, endometrial, ovarian	DNA mismatch repair
CDH1	Familial diffuse-type gastric cancer	Gastric (diffuse type), lobular breast carcinoma, rare in other types (e.g., ovarian)	E-cadherin cell-cell adhesion molecule
LKB1/STK11	Peutz-Jeghers syndrome	Lung adenocarcinoma (~30%); rare pancreas cancers; absent in most other cancers	Serine/threonine protein kinase
EXT1	Hereditary multiple exostoses	Not known	Glycosyltransferase; heparan sulfate chain elongation
EXT2	Hereditary multiple exostoses	Not known	Glycosyltransferase; heparan sulfate chain elongation
TSC1	Tuberous sclerosis	Not known	Hamartin; binds tuberin (TSC2); regulates cell size by inhibiting target of rapamycin (TOR) function and protein synthesis
TSC2	Tuberous sclerosis	Not known	Tuberin (see above regarding TSC1)

DNA sequence alterations in cancer initiation and progression is based chiefly on the view that it is arguably more straightforward to ascribe a causal role in cancer to specific mutations in the tumor cell genome than it is to attribute a causal role in cancer to apparent changes in the levels and/or patterns of gene expression in cancer cells. Potential difficulties in assigning a causal role in cancer to changes in the expression of various proto-oncogenes or tumor suppressor genes include uncertainties about whether the apparent differences in gene expression reflect authentic changes in gene expression or simply the possibility that the cancer might have arisen from neoplastic transformation of a cell type that had differences in gene expression than the majority of normal cells in the tissue from which the cancer originated.

In spite of the fact that changes solely in the expression, but not the structure or sequence, of proto-oncogenes and tumor suppressor genes have been more difficult to implicate definitively in the cancer process, genuine progress in the cancer epigenetics area has been made. Arguably the most compelling data for assigning a critical and likely causal role to changes in gene expression in the cancer process are for those genes that have already been well established in prior studies to function as tumor suppressor genes. Hence, the emphasis here will be placed on illustrating how epigenetic mechanisms have been assigned a causal role in silencing tumor suppressor genes in cancer. This emphasis is largely due to space limitations and not simply because of the absence of data implicating epigenetic mechanisms in proto-oncogene activation in cancer. Indeed, a priori, there is no reason why epigenetic mechanisms cannot lead to substantial increases in the expression of proto-oncogenes, with expression changes in some cancers perhaps on the order of those that are seen in cancers with high copy amplification of the respective proto-oncogene. In some cases, epigenetic mechanisms likely do lead to overexpression of certain proto-oncogenes in a variety of cancer types, such as for c-MYC,[22] the epidermal growth factor receptor,[23] and the aurora-2 kinase and closely related kinases.[24]

As is summarized in Table 14-2, somatic inactivation of tumor suppressor genes resulting from well-established genetic mechanisms has been seen in many cancers. However, there is also a robust and growing body of data to support the view that epigenetic mechanisms somatically inactivate selected tumor suppressor genes in certain cancer types[25] (Fig. 14-2). While data are only now emerging on the specific transcriptional and chromatin remodeling mechanisms that are responsible for epigenetic silencing of tumor suppressor genes, many studies have demonstrated that increases in the methylation of CpG-rich sequences (CpG islands) in the regulatory regions (i.e., promoter/enhancer) of tumor suppressor genes are often linked to loss of tumor suppressor gene expression. For instance, while the *VHL* gene is inactivated by mutational mechanisms in roughly 80% of renal carcinomas of clear cell type, in the majority of the clear cell renal carcinomas in which specific *VHL* mutations cannot be detected, loss of *VHL* gene expression appears to be tightly linked to hypermethylation of the *VHL* promoter.[25] For some other tumor suppressor genes, including the $p16^{INK4a}$, *BRCA1*, and *MLH1* genes, promoter hypermethylation has also been implicated as key mechanism of inactivation.[26] In fact, on the basis of studies of genes that display extensive CpG island methylation and decreased or absent gene expression in cancer cells of one type or another, it has been suggested that aberrant CpG methylation might play a very broad and important role in the cancer process.[25,26]

Nevertheless, at this point, it might be reasonable to offer a few cautionary comments regarding the linkages between CpG island methylation, gene silencing, and tumor suppressor genes. One issue to reflect on is the uncertainty about what fraction of the genes whose promoters show increased methylation in cancers actually function in vivo as tumor suppressor genes. Promoter hypermethylation and loss of gene expression might be best considered as potentially useful but insufficient criteria for establishing tumor suppressor gene function in the absence of other supporting data. For instance, additional supportive evidence of tumor suppressor gene function might include data indicating that the methylation status of a promoter is tightly linked to its expression in a large panel of primary cancer specimens and data showing that gene expression can be readily and fully restored by treatment of cancer cells with demethylating agents and/or other agents that affect chromatin functional state, such as histone deacetylase inhibitors. In addition, data showing that biallelic inactivation of the methylated gene occurs by mutational mechanisms (e.g., localized mutation and LOH) or a combination of mutational and epigenetic mechanisms in at least some cancers might also represent a potentially critical set of observations. Yet another caveat to be aware of is that because several transcription factors that specifically act to repress tumor suppressor gene expression have been identified, such as the Snail and Slug proteins and their ability to repress E-cadherin in breast cancer[27] and the bmi-1 oncoprotein and its

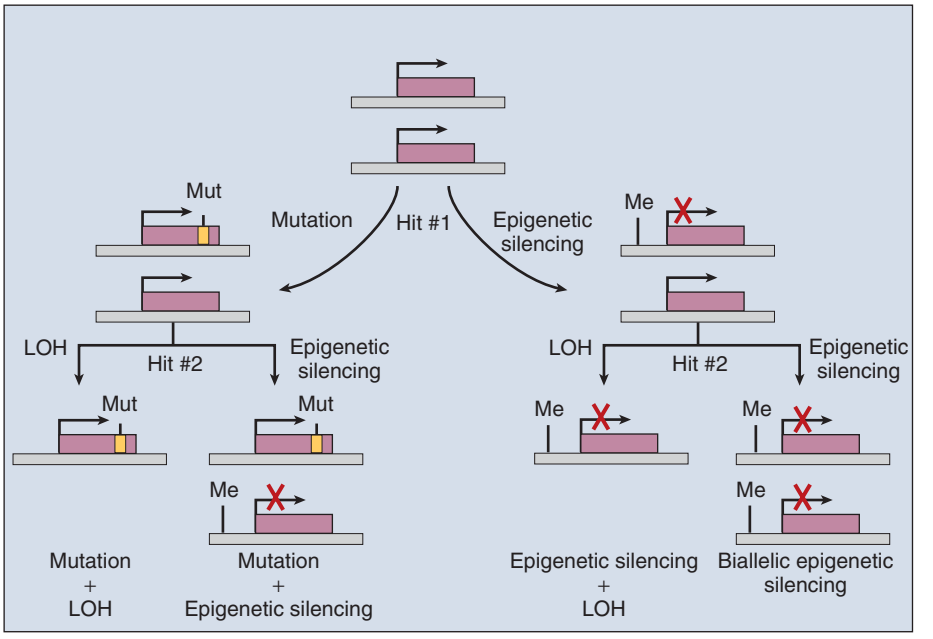


Figure 14-2 • Knudson's two-hit hypothesis revised. In brief, Knudson's hypothesis predicted that both alleles of a tumor suppressor gene would need to be inactivated by germline and/or somatic mutations to elicit critical phenotypic alterations associated with cancer development. The revised version of Knudson's two-hit hypothesis considers the possibility that tumor suppressor gene inactivation can result from either genetic (mutation) or epigenetic silencing events. The two functional alleles of a given tumor suppressor gene are indicated by the two purple boxes (*top*). The first inactivating event affecting one of the two tumor suppressor gene alleles could be either a mutation, such as the localized defect indicated by the yellow box (*left*), or transcriptional silencing associated with or caused by hypermethylation of CpG-rich sequences in the promoter/regulatory region (*right*). The inactivating event for the second tumor suppressor gene allele (i.e., "Hit #2") could be a nondisjunction event resulting in loss of the chromosome containing the wild-type tumor suppressor gene allele (loss of heterozygosity, LOH) or epigenetic silencing. (Modified from Jones PA, Laird PW: Cancer epigenetics comes of age. Nat Genet 1999;21:163–167.)

repression of *p16*^{INK4a} and *p19*^{ARF},[28] in some cases promoter hypermethylation may be principally a reflection rather than a proximate cause of tumor suppressor gene inactivation in cancer. It should be noted, however, that certain subtypes of colorectal cancers have been identified that preferentially inactivate genes by promoter hypermethylation, suggesting that in at least some of the cases, a so far unidentified alteration in the methylation/demethylation machinery might support the development of cancers.[29]

Alterations in Cancer Target Conserved Signaling Pathways and Networks

As was noted previously and summarized in Tables 14-1 and 14-2, the protein products of proto-oncogenes and tumor suppressor genes have been implicated in diverse cellular processes. In light of the potentially vast complexity that is suggested by the diverse array of gene defects in cancer, it is somewhat reassuring to note that some general concepts have emerged with respect to the means by which genetic and epigenetic alterations contribute to cancer initiation and progression. Perhaps the principal overarching theme is that the protein products of oncogenes and tumor suppressor genes function in highly conserved signaling pathways and regulatory networks.

The network in which the pRb tumor suppressor protein functions is one of the more intensively studied oncogene-tumor suppressor gene networks.[30,31] The pRb protein regulates cell cycle progression, in large part via its ability to bind to E2F transcription factor proteins.[30,31] In addition to its role as a cell cycle regulator, the pRb protein has been implicated in regulation of cellular differentiation, survival, and even angiogenesis in certain settings.[32,33] The binding of pRb to E2F proteins allows pRb to silence expression of E2F-regulated or "target" genes, such as those needed for the DNA synthetic (S) phase of the cell cycle. The ability of the pRb protein to bind to E2F proteins and to function in transcriptional repression appears to be tightly linked to its phosphorylation status, with the hyperphosphorylated forms of pRb incapable of binding to and regulating E2F proteins. Strong evidence indicates that the cyclin D1 protein and its associated protein kinase, cyclin-dependent kinase 4 (CDK4), negatively regulate pRb by phosphorylating it. The *p16*^{INK4a} tumor suppressor protein is a critical inhibitor of the CDK4/cyclin D1 complex (Fig. 14-3) and can therefore prevent the inactivation of pRb. As is noted in Table 14-2, a subset of sporadic cancers of various types has inactivating mutations in the *RB1* gene.[34] In other cancers, pRb function appears to be critically compromised as a result of mutations in other components of the network or pathway.[34] For example, in many cancers that lack *RB1* mutations, inactivating mutations in the *p16*^{INK4a} gene have been noted. In others, including some breast cancers, gene amplification and overexpression of cyclin D1 is found. In yet others, such as some glioblastomas and sarcomas, amplification and overexpression of the *CDK4* gene has been seen. The net effect of mutations in the pRb pathway, whether in *RB1* itself or in other genes, such as *p16*^{INK4a}, *cyclin D1*, or *CDK4*, is to inactivate pRb function and its ability to regulate expression of critical E2F target genes (see Fig. 14-3).

Studies of other proto-oncogenes and tumor suppressor genes have also supported the existence of conserved regulatory networks in which multiple different tumor suppressor gene and proto-oncogene protein products function. Although the APC (adenomatous polyposis coli) tumor suppressor protein may have roles in regulating various processes in the cell,[35–37] a key function of APC is to participate in a multiprotein complex that regulates the levels of the β-catenin protein in the cytoplasm and nucleus (see Fig. 14-3). Components of the multiprotein complex that regulates β-catenin include the APC protein, another tumor suppressor protein known as AXIN1, and a kinase known as glycogen synthase kinase 3β (GSK3β). Inactivation of APC or AXIN1 function in cancer cells appears to lead to an inability to phosphorylate β-catenin and hence target it for recognition and subsequent ubiquitination by the βTrCP ubiquitin ligase and ultimately its destruction by the proteasome. As a result, cancer cells with APC or AXIN1 inactivation display increased levels of β-catenin in the cytoplasm and nucleus and essentially constitutive complexing of β-catenin with transcription factors of the T cell factor (TCF) family, such as TCF-4. When bound to TCF-4, β-catenin can function as a transcriptional coactivator, and in cancers with APC inactivation, such as colorectal carcinomas, or cancers with AXIN1 inactivation, such as hepatocellular carcinomas, TCF transcriptional activity is clearly deregulated. In a subset of the colorectal carcinomas that lack APC inactivation and in a variety of other cancer types (see Table 14-1), activating (oncogenic) mutations in the β-catenin protein have been found.[38] These missense and in-frame deletion mutations affect key phosphorylation sites in the

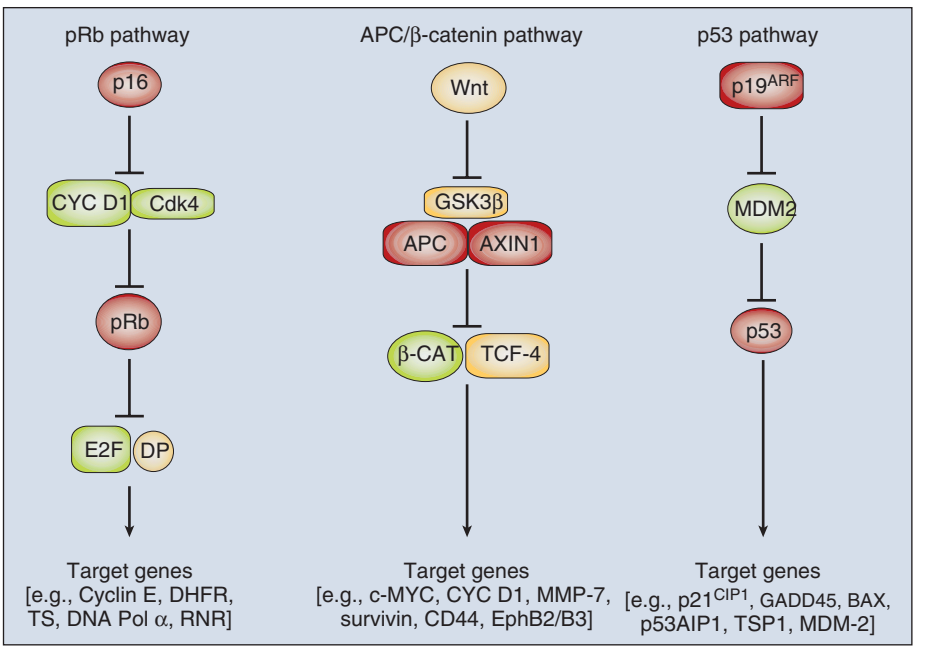


Figure 14-3 • Recurrent gene defects in conserved signaling pathways in cancer. Three signaling pathways that are commonly affected by mutations in various cancers are shown. Selected interactions between components of the pRb (*left*), APC/β-catenin (*middle*), and p53 pathways (*right*) are shown. Tumor suppressor proteins are indicated with *red* symbols, oncogene products are indicated by *green*, and those proteins that are not known to be affected by mutational or epigenetic defects in human cancer are indicated in *yellow*. Inhibitory interactions between proteins are indicated by *perpendicular lines*, and activating effects are indicated by *arrows*. Presumptive downstream genes whose expression is affected by the pathways are noted. APC, adenomatous polyposis coli; β-CAT, β-catenin; Cdk4, cyclin-dependent kinase 4; CYC D1, cyclin D1; DHFR, dihydrofolate reductase; DNA Polα, DNA polymerase α; GADD45, growth arrest and DNA damage inducible gene 45; GSK3β, glycogen synthase 3β; MMP-7, matrix metalloproteinase 7, p21^{CIP1}, p21 CDK-interacting protein 1; p53AIP1, p53-regulated apoptosis-inducing protein 1; RNR, ribonucleotide reductase; TCF-4, T-cell factor-4; TS, thymidylatesynthase; TSP1, thrombospondin 1.

N-terminus of β-catenin, essentially rendering β-catenin resistant to regulation by the APC/AXIN/GSK3β complex. Hence, the mutant β-catenin protein accumulates in the cell and deregulates TCF transcription. Of some interest, and a point that will be discussed more later, transcription of several proto-oncogenes appears to be activated directly by the β-catenin/TCF complex, including the *c-MYC* and *cyclin D1* genes.[38]

Other tumor suppressor gene regulatory networks have been defined, including the p53/MDM2/$p19^{Arf}$ pathway (see Fig. 14-3), the PTCH/SMO/GLI pathway, and the MSH2/MLH1/PMS2 DNA mismatch recognition and repair pathway. Similar to the situation for the pRb, APC/β-catenin, and p53 pathways, mutations in cancer cells not infrequently target the PTCH/SMO/GLI and MSH2/MLH1/PMS2 pathways, either activating an oncogene within the pathway (e.g., SMO or GLI for the PTCH/SMO/GLI pathway) or inactivating one of the key tumor suppressors (e.g., either MLH1 or MSH2 in the mismatch repair pathway).

Although a large collection of genetic and biochemical data support the proposed protein functions and interactions depicted in Figure 14-3, it seems likely that the situation in vivo is far more complex. For example, on the basis of the regulatory scheme outlined for the pRb pathway in Figure 14-3, it might appear that the phenotypic consequences of pRb or $p16^{INK4a}$ inactivation are functionally equivalent. However, patients with germline mutations that inactivate pRb are predisposed to retinoblastomas and osteosarcomas, while those with germline defects in $p16^{INK4a}$ are predisposed predominantly to melanoma and pancreatic cancer.[39,40] Furthermore, while those with germline mutations that affect pRb or $p16^{Ink4a}$ are predisposed to a rather limited spectrum of cancers, somatic defects in the pRb pathway (e.g., including mutations in pRb, $p16^{Ink4a}$, cyclin D1, and CDK4) are seen in the majority of a broad array of cancer types.[39,40] Unfortunately, at present, although there is no compelling mechanistic explanation for these observations, perhaps a general explanation can be offered. Specifically, the genetic pathways in which certain oncogenes and tumor suppressor genes function are not simply linear pathways as indicated schematically in Figure 14-3 but more likely represent much more complex networks. The branches of the network may even vary considerably, depending on cell type and developmental context, though it seems reasonable to predict that the genes and the protein products recurrently affected by mutation in human cancer represent particularly critical hubs in the pathways and networks.

CONTRIBUTION OF GENE DEFECTS TO THE SIGNATURE TRAITS OF CANCER CELLS

Defining Signature Traits of Cancer Cells

Cancer represents a highly heterogeneous collection of diseases. Each cancer type has distinct biologic and clinical features and a variable prognosis. Even cancers that arise in a single organ site, such as the ovary, kidney, or lung, represent a hodgepodge of different diseases. Morphologic features often allow the particular cancer types to be distinguished to some degree from one another. Yet even for patients whose cancers have essentially identical gross and microscopic appearances and very similar clinical manifestations, there may be vast differences in outcome. In spite of this complexity, the development of all cancers, regardless of type, is likely to be critically dependent on the acquisition of certain phenotypic features that allow the cancer cells not only to grow in an unchecked fashion in their tissue of origin, but also to gain the ability to disseminate into surrounding tissues and organs, lymphatics, and the bloodstream and ultimately to grow as metastatic lesions in distant sites in the body.[41] As is indicated in Figure 14-4, among the signature traits that are likely to be inherent in the majority, if not all, of cancer cells are the following: (1) an increased tendency to manifest a stem cell or progenitor-like phenotype, (2) an enhanced response to growth-promoting signals, (3) a relative resistance to growth-inhibiting cues, (4) an increased mutation rate to allow for the rapid generation of new variant daughter cells, (5) the ability to attract and support a new blood supply (angiogenesis), (6) the capacity to minimize an immune response and/or evade destruction by immune effector cells, (7) the capacity for essentially limitless cell division, (8) a failure to respect tissue boundaries, allowing for invasion into adjacent tissues and organs as well as blood vessels and lymphatics, and (9) the ability to grow in organ sites with microenvironments markedly different from the one where the cancer cells arose. The development of some traits is likely to be associated with certain stages of tumorigenesis (see Fig. 14-4), but acquisition of signature traits in cancers is far more likely to show a preferred order than an invariant order.[41] Furthermore, many of the signature traits of cancer cells that were elaborated previously represent complex biologic capabilities (e.g., angiogenic activity, immune evasion/resistance, metastatic competence). Therefore, it is likely that substantial changes in many signaling pathways are needed for the cancer cell to manifest the traits.

An exhaustive cataloging of the observations that link specific gene defects to the altered phenotype of cancer cells will not be offered here, in part because of space limitations and in part because of uncertainties about the significance of some of the linkages between single gene defects and cancer phenotype. Nonetheless, some general concepts regarding the relationships among gene defects and cancer cell phenotype have emerged, and two of these concepts are offered here. First, while some specific mutations and major gene expression defects that are seen in cancer cells may contribute predominantly to a few or perhaps even only one of the signature traits of cancer cells listed in the preceding list, it seems likely that many of the gene defects and expression changes have been selected for in large part because they exert pleiotropic effects on the cancer cell phenotype. Second, for some tumor types, it has been possible to gain insights into the apparent order in which genetic and epigenetic changes might arise and contribute to cancer pathogenesis. The data suggest that defects in certain genes and signaling pathways might be strongly selected for at certain point in cancer development and progression, perhaps in large part because the alterations allow the precancerous or cancerous cells to acquire certain critical phenotypic features. Of some interest, gene defects that might be nearly uniformly present in early-stage lesions of one tumor type might preferentially arise in later-stage tumors in another organ site. These data suggest that cellular and tissue context have critical, albeit poorly understood, modifying effects on the specific genetic defects that give rise to neoplastic transformation and clonal outgrowth. The two concepts—the often pleiotropic effects of the gene defects that are present in cancer cells and the context-dependent effects of the defects—will be expanded on later, with presentation of some concrete examples.

Contribution of APC Inactivation and β-Catenin Deregulation to Cancer Phenotype

As was noted previously, mutational defects that lead to deregulation of the signaling activity of the β-catenin protein are present in a relatively broad array of cancer types, including colorectal tumors, in which upward of 80% to 90% of colorectal adenomas and carcinomas harbor inactivating mutations in APC or AXIN1 or AXIN2 or gain-of-function mutations in β-catenin itself.[36] On the basis of the observation that germline-inactivating mutations in APC markedly increase the rate at which adenomatous lesions arise in the colon and rectum and extensive descriptive molecular studies showing that somatic mutations in APC or β-catenin are present in even microscopic adenomatous lesions in the colon,[42,43] it appears that dysregulation of β-catenin likely plays a central role in the earliest stages of colon cancer development. In other cancer types in which β-catenin

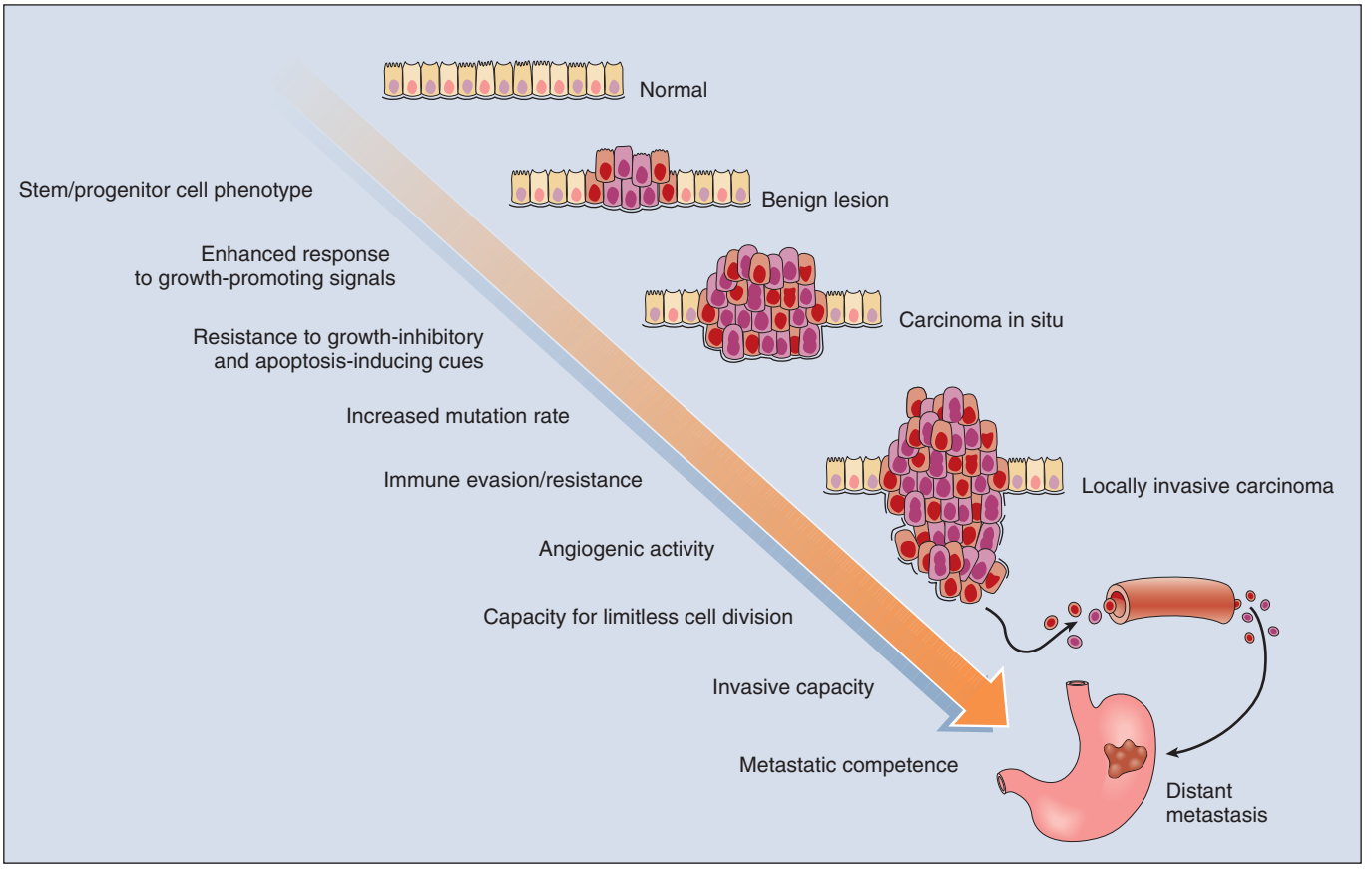


Figure 14-4 • Acquisition of signature traits in neoplastic cells during cancer progression. Depicted in the figure are representative stages in the development of a cancer, perhaps a typical epithelial cancer, such as those that typically arise in the lung, colon, breast, or prostate. The schema suggests that most advanced cancers arise via clonal selection from subclones present in earlier stage benign and localized lesions (e.g., carcinoma in situ and locally invasive carcinoma). Some of the properties of advanced cancer cells are depicted by the ability of the cells to enter the bloodstream and to seed and grow in distant organ sites, such as the liver (*bottom*). Nine signature traits of cancer cells are listed. The relative time at which neoplastic cells acquire some of the traits is uncertain, though it seems likely that some traits, such as the expression of a stem/progenitor cell phenotype or enhanced response to growth-promoting signals, may be acquired earlier in cancer development. Other traits, such as invasive capacity and/or metastatic competence, may be acquired later. Many signature traits of cancer cells are in fact complicated biologic capabilities (e.g., angiogenic activity, immune evasion/resistance, metastatic competence) and likely depend on defects in a number of different factors and signaling pathways.

is often deregulated by mutational mechanisms,[36] such as hepatocellular and endometrial cancers, the timing of β-catenin mutations in the natural history of disease is less certain.

Given this background, what might be the contribution of β-catenin defects to the development and biologic behavior of colon and perhaps other cancers? As was highlighted previously, β-catenin, upon its association with TCF transcription factors, has been implicated in activating expression of genes that likely play critical roles in stimulating progression through the G_1-to-S transition, including cyclin D1 and c-MYC. Effects of cyclin D1 activation on the pRb pathway and progression through the G_1/S phase of the cell cycle were mentioned in the preceding discussion. As is indicated in Figure 14-5, one of the apparent consequences of c-MYC activation of colon cancer cells is repression of the expression of the $p21^{CIP1}$ cyclin-dependent kinase inhibitor,[44,45] and inhibition of $p21^{CIP1}$ might contribute to defective cell cycle control.[44–46] In addition to effects on cyclin D1 and c-MYC, deregulation of β-catenin/TCF transcription has been implicated in activation of a number of genes that might play a role in maintaining or inducing a progenitor cell or stem cell-like phenotype in colon cells that should otherwise be destined for differentiation or apoptosis[38,45] (see Fig. 14-5). Genes that might play a role in conferring a progenitor cell phenotype include the cell surface protein CD44 and the EphB2 and EphB3 receptors and their ligand ephrin-B1.[45,47] Either individually or collectively along with other molecules, the cell surface proteins might exert potent effects on colonic epithelial cell fate, perhaps in part by inhibiting appropriate migration of cells in the crypt and hence favoring response to proliferation-inducing signals over differentiation-inducing cues.[45,47]

Another presumptive β-catenin/TCF target gene with a potential role in acquisition of several critical cancer phenotypic traits is the matrix metalloproteinase-7 (MMP-7, also known as matrilysin)[48] (see Fig. 14-5). MMP-7 itself has a number of potential roles in cancer progression,[49,50] including the ability to cleave and downregulate the activity of the E-cadherin tumor suppressor protein[51] and the ability to cleave osteopontin and apparently activate osteopontin's cell migration-stimulating activity.[52] Besides the role of dysregulated β-catenin in activating transcription of TCF target genes, there is evidence that elevated levels of nuclear β-catenin in cancer cells can interfere with NF-κB function and NF-κB's ability to activate key downstream effectors of apoptosis, such as Fas and TRAF1[53] (see Fig. 14-5). Finally, the carboxyl-terminus region of the APC tumor suppressor protein confers binding to the EB1 protein, a microtubule-binding protein, as well as to microtubules.[35] Given the apparent role of EB1 in regulating microtubule dynamics, cell polarity, and chromosome stability and the evidence that APC inactivation in certain cellular contexts could confer a chromosome instability phenotype, it is possible that APC inactivation also contributes to a chromosomal instability phenotype in colorectal cancer cells.[35,54,55]

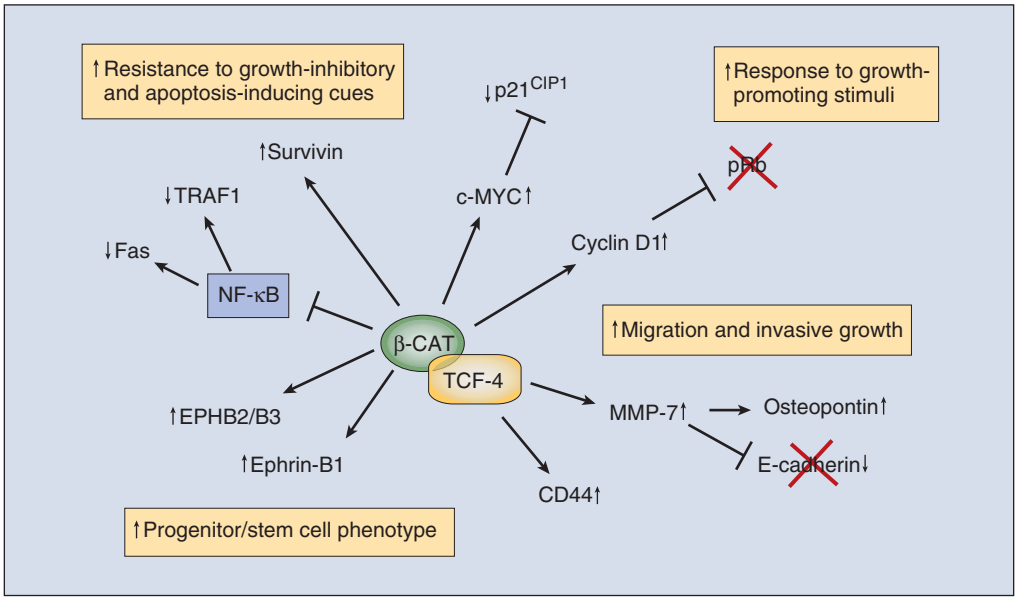


Figure 14-5 • Potential contributions of β-catenin deregulation to cancer cell signature traits. Inactivation of the APC tumor suppressor protein or activating (oncogenic) mutations in β-catenin can lead to marked increases in the levels of free β-catenin protein in the cytoplasm and nucleus, enhanced binding of β-catenin to the TCF-4 (T cell factor-4) transcription factor, and activation of β-catenin/TCF-4 regulated genes. Some of the genes that might be directly regulated by the β-catenin-TCF-4 transcription process include the genes for c-MYC, cyclin D1, MMP-7, survivin, CD44, the EPHB2 and EPHB3 receptors, and their ligand Ephrin-B1. Some of the potential effects resulting from activation of these target genes are indicated. In addition to β-catenin's role in activating expression of TCF-4-related genes, β-catenin appears to inhibit the activity of NF-κB and NF-κB's ability to activate genes with potential roles in apoptosis, such as Fas and TRAF1. The potential contributions of β-catenin to cancer cell traits are discussed in more detail in the text.

Contribution of RAS-Signaling Pathway Defects to Cancer Phenotype

RAS gene mutations were the first somatic gene defects to be characterized at the molecular level in cancer cells, and we now know that mutations in the three RAS genes—H-RAS, K-RAS, and N-RAS—are among the most common oncogene defects in cancer, with an estimated 20% of all cancers carrying a point-mutated, activated RAS allele.[56–58] RAS proteins appear to play key roles in several important signaling pathways (Fig. 14-6), and proteins that function upstream or downstream of the RAS proteins are affected by mutations in certain cancers. For instance, mutational activation and/or overexpression of growth factors upstream of RAS, such as epidermal growth factor receptor and/or ERBB2 (also known as HER2/Neu), can be commonly seen in a number of epithelial cancers, including breast and ovarian carcinomas (see Table 14-1). Mutations in effectors downstream of RAS can also be seen in cancers, including defects in the mitogen-activated protein kinase (MAPK) pathway as a result of BRAF gene mutations[56,59] or defects in phosphatidylinositol 3-kinase (PI3K) signaling, as result of amplification and overexpression of AKT2, activating mutations of AKT1, or inactivating mutations in the PTEN (phosphatase and tensin homolog) tumor suppressor gene.[58–61] Sometimes mutations in Ras and the downstream effectors are mutually exclusive (e.g., Ras and B-Raf), while in other cases (e.g., Ras and PI3K catalytic subunit), the mutations coexist.[5,58]

The consequences of RAS mutations specifically and RAS-signaling pathway defects more generally are varied and undoubtedly depend on cell context, because constitutive activation of RAS signaling in certain contexts can promote apoptosis rather than cell proliferation or neoplastic transformation.[62,63] In brief, activated mutant RAS alleles have been implicated in enhanced response to proliferative cures, perhaps to a certain extent owing to the ability of RAS-MAPK activation to enhance expression of cyclin D1, and cyclin D1's ability to inactivate pRb function via phosphorylation[59,63] (see Fig. 14-6). RAS pathway activation can also interfere with apoptosis induction, perhaps in part via activation of the PI3K pathway and its ability to antagonize the proapoptotic factor BAD and perhaps other molecules that are important in promoting programmed cell death[59,61] (see Fig. 14-6). In addition to the potential ability of RAS pathway activation to enhance cell proliferation and inhibit programmed cell death in cancer cells, RAS activation has been implicated in transcriptional activation of vascular endothelial growth factor (VEGF),[64] a potent stimulator of angiogenesis. Furthermore, RAS activation has been linked to increased invasive potential.[59] The role of RAS in promoting invasiveness might be mediated through RAC-dependent effects on the cytoskeleton as well as MAPK pathway-dependent activation of matrix metalloproteinases,[59] such as MMP-9, which can function in degradation of the basement membrane component type IV collagen[50] (see Fig. 14-6). Interestingly, MMP-9 has also been implicated in promoting angiogenesis in some settings via its ability to stimulate release of VEGF from poorly defined extracellular reservoirs.[65]

MicroRNAs as Post-transcriptional Regulators of Gene Function

It has been recognized in the last few years that the translation of mRNA transcripts into proteins is highly regulated by a novel class of short noncoding RNAs, the so-called microRNAs (miRNAs). The mature forms of miRNAs are 18 to 24 nucleotides in length and are generated by successive cleavages by the Drosha and Dicer nucleases from longer precursor transcripts that contain characteristic hairpin formations.[66] Recognition of target transcripts occurs by binding of the miRNA to the 3′ untranslated regions (3′UTR). Depending on the degree of homology to their target sequence, miRNAs induce translational repression or cleavage of mRNAs. More than 500

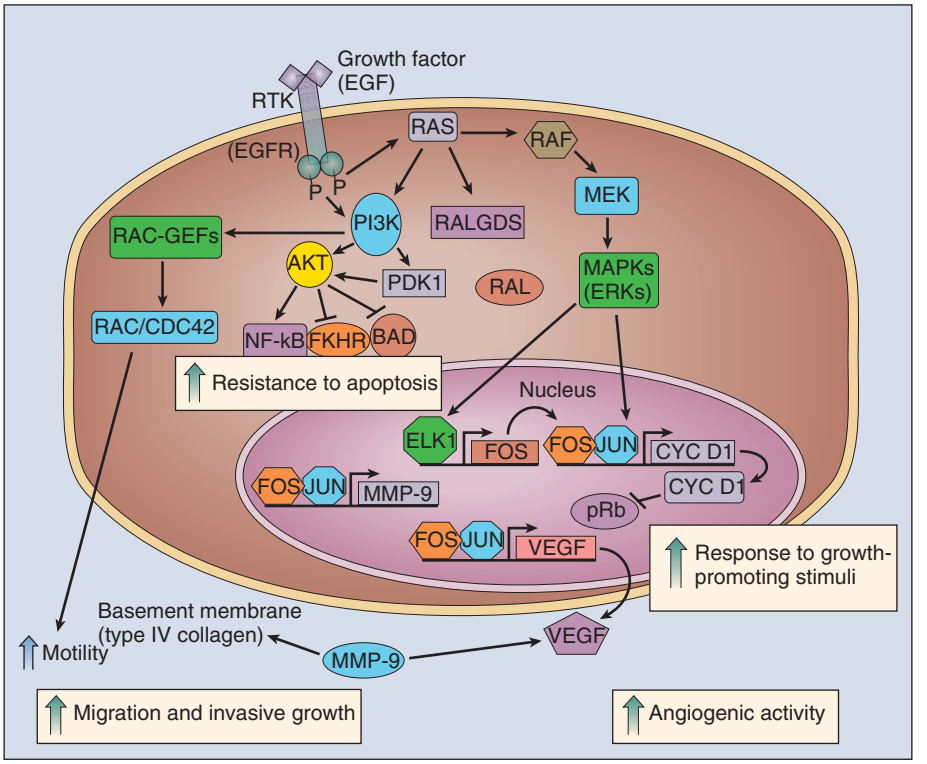


Figure 14-6 • Potential contribution of RAS pathway defects to the cancer cell phenotype. The RAS protein is indicated near the top of the figure, and selected upstream and downstream factors are also indicated relative to their likely location in the cell. RAS pathway-signaling interactions are complex, and only selected functional interactions upstream and downstream of RAS are indicated. As is indicated in the figure and discussed in more detail in the text, RAS pathway activation can likely enhance the response to growth-promoting stimuli via effects on cyclin D1 (CYC D1) expression and pRb phosphorylation and activity. These effects on cyclin D1 expression are likely to be mediated by the RAF/MAPK (mitogen activated protein kinase) signaling cascade and its effects on downstream conscription factors, including JUN and the ETS-related protein ELK1, which activates expression of JUN's dimeric partner, FOS. RAS pathway activation also likely acts to increase resistance to apoptosis in some settings through effects on AKT and its ability to inhibit factors with proapoptotic roles (e.g., Forkhead in human rhabdomyosarcoma [FKHR] or BAD) or AKT's ability to activate NF-κB's survival function. Besides these effects, RAS pathway activation might act to stimulate vascular endothelial growth factor (VEGF) production and angiogenesis. RAS can enhance cell migration and invasion via RAC/CDC42-mediated effects on the cytoskeleton and possibly FOS/JUN-mediated increases in the expression of some matrix metalloproteases, such as MMP-9. Finally, MMP-9 can also promote release of VEGF from extracellular reservoirs, perhaps further enhancing VEGF effects on angiogenesis.

human miRNAs have been described, and each single miRNA can target hundreds to a thousand or more mRNAs.[66] This ability allows for substantial combinatorial complexity and functional redundancy, making the identification of specific functions of miRNAs as well as their involvement in oncogenic or tumor suppressive networks difficult. The fact that miRNAs act via base-pairing of the miRNA with the 3′UTR also implies that alterations of both miRNA sequence and miRNA target sequence might have functional consequences. So far, large-scale sequencing efforts have been focused mainly on the coding sequence of genes, which means that a significant number of functionally relevant alterations might have been missed.

Several lines of evidence make it likely that miRNAs do play a role in the development of cancers. For instance, global inhibition of miRNA production seems to facilitate the acquisition of a neoplastic phenotype in primary mouse cells, suggesting that the net effect of all miRNAs might be a tumor suppressive effect.[67]

The genomic location of many miRNAs maps close to common chromosomal breakpoints in cancer. In most cases, however, it is still unclear whether the miRNAs are actually involved in conferring the selective advantage that is gained by these translocations or whether miRNAs for other reasons are localized in regions of high genomic fragility.[68]

Comprehensive analyses of miRNA expression patterns in human cancers have revealed that different cancer types have distinct miRNA expression patterns. In fact, in many instances, miRNA expression patterns might be more precise in determining the tissue of origin than mRNA expression profiles.[69] Similar to the situation with protein-coding genes, in most cases, it is unclear which expression changes are causative and which are secondary to the development of the tumors.[70]

Several miRNAs seem to play a role as part of classical tumor suppressive or oncogenic signal transduction pathways (Table 14-3). The miRNA17–92 locus has been described as a direct transcriptional target of the c-MYC and E2F oncogenes.[71] This polycistron locus encodes for seven miRNAs and has been shown to be genomically amplified and overexpressed in some human B-cell lymphomas and lung cancers. When overexpressed, it can cooperate with c-MYC to accelerate lymphoma development in a murine model system. In

Table 14-3 Putative Tumor Suppressor or Oncogenic miRNAs

miRNA	Chromosomal Location	Expression	Target Genes/Effect
PUTATIVE TUMOR SUPPRESSOR miRNAs			
miRNA15/16	13q14	CLL and pituitary adenoma	BCL2
miRNA34a	1p36	p53 target gene; loss in neuroblastoma	BCL2, MET, Cyclin E2
miRNA34b/c	11q21	p53 target gene; loss in NSCLC	BCL2, MET
let-7a-2	11q24	Loss in lung cancer	K-RAS, HMGA2
PUTATIVE ONCOGENIC miRNAs			
miRNA17–92	13q14	c-MYC target gene Up in B-cell lymphoma, lung cancer	Cooperates with c-MYC and regulates E2F1
miRNA372/373	19q13	Up in germ cell tumors	LATS2 tumor suppressor → p53 inactivation
miRNA10a	19q13	Up in metastatic breast cancer	Metastatic phenotype
miRNA155	21q21	Up in breast cancer, lymphoma	?
miRNA21	17q23	Up in pancreatic, breast and CNS cancer	PTEN tumor suppressor
TRANSLOCATIONS INVOLVING miRNAs OR miRNA TARGET SITES			
miRNA142	t(8;17)(q24;q22)	B-cell lymphoma	miRNA promoter drives c-MYC expression
HMGA2	12q15 translocations	Benign salivary gland tumors	Translocation removes let-7 recognition sites from the HMGA2 transcript

CLL, chronic lymphocytic leukemia; NSCLC, non-small-cell lung cancer.

Modified from Calin GA, Croce CM: Chromosomal rearrangements and microRNAs: a new cancer link with clinical implications. J Clin Invest 2007;117:2059–2066; and Garzon R, Fabbri M, Cimmino A, et al: 206 MicroRNA expression and function in cancer. Trends Mol Med 2006;12:580–587.

addition, miRNA372 and miRNA373 have been implicated as oncogenes in the development of germ cell tumors at least in part by inactivating the p53 tumor suppressor pathway.[72] Recently miRNA10a has been suggested to be a major driving force behind the metastatic progression of breast cancer cell lines.[73]

Members of the let-7 family of miRNAs have been proposed as tumor suppressor genes in lung cancer, supposedly in part by their ability to inhibit the translation of the K-Ras and HMGA2 oncogenes.[74] The members of the miRNA34 family have recently been shown to be direct transcriptional targets of the p53 tumor suppressor gene and seem to play a significant role in p53 activity.[75,76]

Role of Tissue and Context Differences in the Contributions of Gene Defects to Cancer Cell Phenotype

The published literature on the potential contributions of gene defects to the altered phenotype of cancer cells has offered some suggestions about how to consider the role of the gene defects in cancer pathogenesis. For instance, terms such as *gatekeeper* and *caretaker* have been used to classify the contributions of genes to cancer development.[77] "Gatekeeper" genes have been suggested to be those genes that play particularly critical roles in regulating cell proliferation and inhibiting cancer development in certain tissues, such as the APC gene in colorectal cancer, and the tumor suppressive function of the genes must be overcome for cancers to arise in a given tissue or organ site.[77] "Caretakers" have been generally defined as those genes that do not play direct roles in growth control but rather likely play important roles in a number of tissues in maintaining the fidelity of the genome via their role in DNA damage recognition and repair processes. The MLH1 and MSH2 mismatch repair genes have been proposed to be representative caretaker genes,[77] and some researchers have suggested that perhaps the BRCA1 and BRCA2 genes also represent caretaker genes.[78] The use of terms such as *gatekeeper* and *caretaker* might have some merit. However, as will be illustrated in the following discussion, given the apparently important role of "gatekeeper" gene defects in cancers that arise in various organ sites but the quite variable timing of "gatekeeper" gene defects in the natural history of one cancer type versus another, the term *gatekeeper* might be more confusing than illuminating. In the case of some presumed "caretaker" genes, the genes might not be playing the passive role in the cancer process that has been assigned to them. This view is based on three lines of argument: (1) the apparent tissue specificity of the tumors that arise in individuals who harbor germline mutations in the "caretaker" genes, such as in individuals who are affected by hereditary nonpolyposis colorectal cancer and germline MLH1 or MSH2 mutations[79]; (2) the likely variable time in cancer development at which "caretaker" mutations may arise from one tumor to the next, with sporadic colon tumors not usually manifesting mismatch repair gene inactivation and microsatellite instability until the carcinoma stage, despite the fact that adenomas in individuals with hereditary nonpolyposis colorectal cancer often show high-frequency microsatellite instability[80,81]; and (3) the evidence that "caretaker" genes might actually play key roles in regulating cell proliferation and promoting apoptosis in certain contexts.[82]

In general, individuals who harbor a germline mutation in a specific tumor suppressor gene or proto-oncogene are predisposed to a very limited spectrum of cancer types. This observation is puzzling for a couple of reasons. The majority of genes that are affected by germline mutations in specific inherited cancer syndromes are essentially ubiquitously expressed in adult tissues. Furthermore, for a number of the tumor suppressor genes, mutations are often found to inactivate the gene in a much broader collection of sporadic cancer types than the types that commonly arise in germline mutation carriers. Children who carry a germline mutation in the *RB1* gene have a very elevated risk of developing retinoblastoma and a more modest risk of developing osteosarcoma but no dramatic increase in the risk of most common adult cancers. Yet somatic defects in pRb have been found and are believed to be critical in the development

of many different cancers, such as small cell lung carcinomas, in which the vast majority have pRb defects.[40,82]

There are potential explanations for these puzzling observations. For instance, while pRb might have an essential role in regulating retinoblast cell proliferation and/or differentiation, in other tissues, such as lung or breast epithelial cells, pRb might have a redundant role in growth control, perhaps because of the contribution of pRb-related proteins, such as p107 and p130.[30,31] Under this scenario, pRb inactivation in most cell types might not promote neoplastic growth unless other defects, such as those in pRb-related proteins, are also present. An alternative and perhaps more likely possibility is that somatic inactivation of pRb might trigger apoptosis in many cell types unless other somatic gene defects have arisen previously and these other defects interfere with the cell's ability to undergo apoptosis following disruption of *RB1* function (Fig. 14-7). Evidence that pRb inactivation can act in a context-dependent fashion to promote apoptosis versus neoplastic transformation has been offered.[83,84] The tissue specificity of cancers that are seen in individuals who carry germline mutations in inherited cancer genes is not restricted to the case of pRb. Germline *p53* mutations predispose primarily to osteosarcoma, soft tissue sarcoma, leukemia, brain tumors, and breast cancer in women; and $p16^{INK4a}$ germline mutations predispose primarily to melanoma and pancreatic cancer. In spite of the relatively limited spectrum of cancer types that are seen in people who carry germline p53 or $p16^{INK4a}$ mutations, the *p53* and $p16^{INK4a}$ genes are very commonly altered in human cancer, each of the genes being inactivated in upward of 35% to 50% of many different sporadic cancer types.

Finally, some genes with prominent roles in the development of a variety of different cancer types are sometimes presumed to have essentially singular functions in the cancer process in spite of data that suggest otherwise. As an example, the E-cadherin protein plays an important role in cell-cell adhesion via the ability of its extracellular domain to form adhesive interactions with E-cadherin molecules on opposing cell surfaces and the ability of the E-cadherin cytoplasmic domain to link to the actin cortical cytoskeleton via interactions with catenin proteins at the plasma membrane.[85] Early functional studies have suggested that restoration of E-cadherin in cancer cells that had endogenous E-cadherin defects interfered with the invasive properties of cancer cells in selected in vitro assays.[86] Perhaps in large part because of these observations, the loss of E-cadherin expression in cancer has nearly invariably been assigned a role in promoting invasive behavior in advanced cancer cells. While loss of E-cadherin function might indeed contribute to invasive behavior in cancers arising in vivo, it is worth bearing in mind that defects in E-cadherin could in fact play a distinct role in altering cell

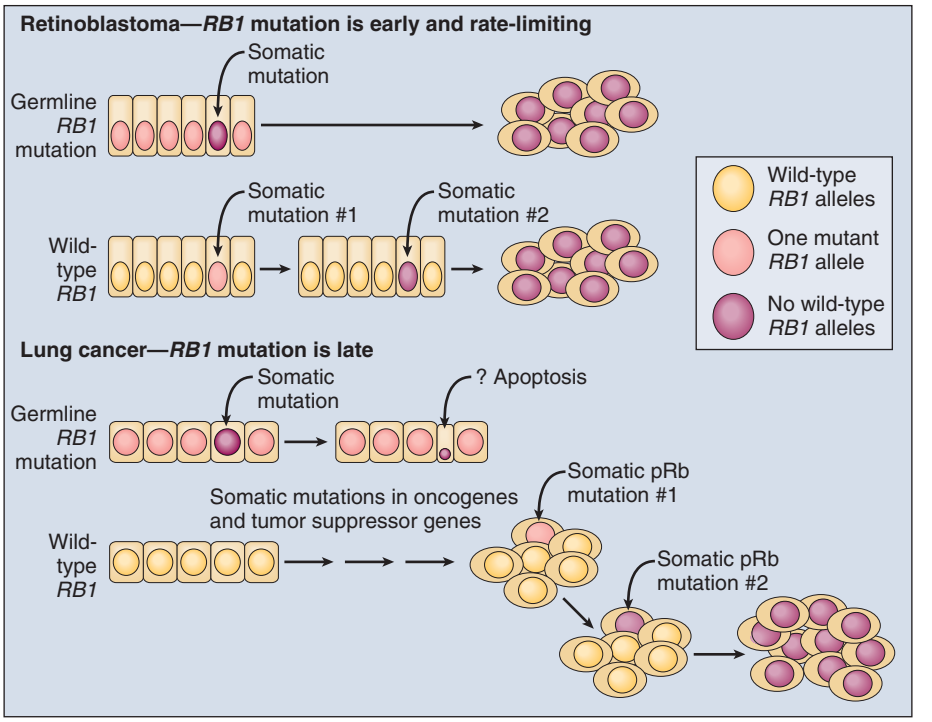


Figure 14-7 • Mutations in the retinoblastoma tumor suppressor gene (*RB1*) contribute to inherited and sporadic cancers. The figure indicates that cell context affects the contribution of *RB1* mutations to cancer development. In individuals who carry a germline mutation in one *RB1* allele, somatic inactivation of the remaining *RB1* allele is an early and rate-limiting event in retinoblastoma formation. Sporadic forms of retinoblastoma are dependent on inactivation of both *RB1* alleles. Because somatic inactivation of both *RB1* alleles must occur in a single developing retinoblast before tumor formation can ensue, retinoblastoma is a rare disease in people who do not carry a germline *RB1* mutation (i.e., the general population). Those who carry a germline *RB1* mutation do not manifest a markedly increased risk to many common cancers, such as lung cancer, despite the fact that *RB1* mutations are frequently observed in sporadic forms of lung cancer (e.g., small cell lung carcinoma). These observations imply that *RB1* mutations might contribute to tumor progression rather than tumor initiation in most cancer types other than retinoblastoma and perhaps osteosarcoma. Possible explanations for this phenomenon include the possibility that inactivation of both *RB1* alleles prior to the acquisition of defects in other oncogenes or tumor suppressor genes is not associated with any growth advantage and *RB1* activation in some contexts might even induce apoptosis. (Modified from Haber DA, Fearon ER: The promise of cancer genetics. Lancet 1998;351[suppl 2]:1–8.)

growth very early in the neoplastic transformation process in some tumor types, such as the gastric carcinomas that arise in patients who carry germline E-cadherin mutations.[87]

CLINICAL IMPLICATIONS

On the basis of review of the data on the apparent contributions of gene defects to cancer phenotype, some clinical implications are apparent. The genes and the protein products that are recurrently altered by mutations and/or epigenetic defects in human cancer more than likely represent particularly critical hubs in the pathways and networks that regulate cell growth, differentiation, and programmed cell death. Hence, efforts to target the proteins and pathways with apparently central roles in the pathogenesis of a number of different cancer types would appear to offer potentially the broadest impact. Additionally, because the gene defects that promote clonal selection during cancer development might have particularly pleiotropic effects on the cancer cell phenotype, targeting of the central pathways in cancer might also be expected to have some of the most dramatic effects on cancer cells. For example, in light of the important role of RAS pathway defects in a broad array of cancer types and the view that RAS pathway deregulation exerts pleiotropic effects on the cancer cell phenotype, drugs that inhibit the activity of Raf, MEK, or MAPK might have potent anticancer activity in a subset of the many cancers with RAS pathway defects.[88] Moreover, even though RAS pathway defects may arise at early to intermediate stages of tumor development in some cancer types, such as colorectal cancer, it is encouraging to learn that quite dramatic effects can be seen on the growth of advanced cancer cells when the activity of the mutant RAS protein is antagonized.[89,90]

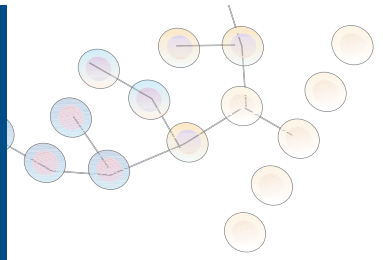
In spite of the generally optimistic view that is offered as a result of our rapidly expanding understanding of the nature and contribution of gene defects in cancer pathogenesis, some significant challenges remain if novel and specific new anticancer therapies are to be achieved in the near term. In particular, for a fair number of the specific signaling pathways that are commonly disrupted in cancer, it might prove difficult to define readily tractable targets for therapeutic intervention. For instance, in the case of the p53 pathway, it is unclear how effectively p53 function can be restored in the proteins that carry missense substitutions or when the p53 protein is intact and simply antagonized by upstream defects (e.g., $p19^{ARF}$ or MDM2 defects). In the case of cancers with mutations leading to β-catenin deregulation, a potential goal might be to define agents that specifically interfere with the nuclear function of β-catenin in transcriptional activation of β-catenin/TCF-regulated target genes. While this is not an unreasonable notion, given the rather limited successes to date in defining small molecules that specifically affect transcription factor complexes, it could be very challenging to target β-catenin via conventional pharmacologic approaches. Similar concerns could be perhaps raised regarding the merits of attempting to specifically target other nuclear proteins and transcription factors that are deregulated in cancer cells.

Given these concerns regarding the likelihood for success in defining small molecules that effectively target some of the pathways that are most commonly deregulated in cancer, emphasis for therapeutic targeting in the near term might be placed on potentially more promising molecular targets in cancer, such as CDK4 (e.g., for cancers with an intact pRb protein but defects in $p16^{INK4a}$, cyclin D1, or CDK4) or various effector molecules in the PI3K-AKT pathway, such as the AKT or mTOR proteins (e.g., for cancers with PTEN defects).[61] While the success of approaches to target cancer cells more selectively remains to be broadly established, it is obvious that the efforts to understand the relationship between gene defects, altered cell signaling and physiology, and cancer phenotype have already shaped and will continue to shape our views of how best to proceed with novel therapeutic interventions.

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15 Immunodeficiency and Cancer

Alexandra H. Filipovich and Thomas G. Gross

SUMMARY OF KEY POINTS

- Neoplasms are the second most common cause of mortality (after infections) among patients with primary and acquired immunodeficiencies.
- Infections, whether de novo, reactivated, or chronic, play a pivotal role in promoting development of both lymphomas and carcinomas. Examples include the following:
  - Epstein-Barr virus (EBV) associated with lymphoproliferative disorders
  - *Helicobacter pylori* associated with gastric carcinomas and mucosa-associated lymphoid tissue (MALT) lymphomas
  - Human papillomavirus associated with skin and cervical carcinomas
- Categories of genetic immunodeficiencies with increased risk of developing tumors include the following:
  - Combined defects with T-cell dysfunction (e.g., Wiskott-Aldrich syndrome)
  - Defects that inhibit lymphoid apoptosis (e.g., autoimmune lymphoproliferative syndrome [ALPS])
  - Defects of genomic instability (e.g., ataxia telangiectasia)
- Categories of acquired immunodeficiencies with increased risk of developing tumors include the following:
  - Recipients of solid-organ allografts
  - Recipients of T-cell-depleted mismatched allogeneic hematopoietic stem cells
  - HIV/AIDS patients
- The risk of lymphoproliferative disorders in immunodeficient hosts can be reduced by the following:
  - Correction of primary immunodeficiencies with bone marrow transplant
  - Reduction of immune suppression in allograft recipients
  - Aggressive treatment for HIV

INTRODUCTION

Retrospective surveys of patients with primary and acquired immune deficiencies have revealed several patterns of increased risk for specific cancer types. In the majority of immunodeficiency conditions—whether de novo, reactivated, or chronic—infections play a pivotal role in promoting the development of both lymphomas and carcinomas. Specifically, patients with primary (genetically determined) or acquired immune deficiencies that affect primarily T-cell function are at increased risk of developing cancer. This risk group includes patients who are immune suppressed following solid-organ allografting, hematopoietic stem cell transplantation (HSCT), or secondary to human immunodeficiency virus (HIV) infection. Chronic immune suppression also increases the risk for carcinomas that are linked to infection with viruses, such as human herpesvirus 8 or Kaposi's sarcoma–associated herpesvirus associated with Kaposi's sarcoma or human papillomavirus associated with squamous cell carcinoma of the skin and cervix. People with congenital humoral immune defects (especially IgA deficiency) who are persistently colonized with *Helicobacter pylori* experience a higher rate of gastric carcinomas and gastric mucosa–associated lymphoid tissue (MALT) lymphoma. A minor, but biologically instructive, category of individuals at increased risk of tumors of both hematopoietic and epithelial origin are those with inherited defects of genomic instability, which may lead to both immunodeficiency and propensity to tumor development. Examples of such disorders include ataxia telangiectasia and Bloom's syndrome.

Although tumors in immune-deficient persons remain a major cause of morbid and fatal complications, progress has been made in reducing the risk of malignant transformation in many patients through better understanding of the etiopathogenesis. The risk of life-threatening "lymphomas" can be reduced substantially by correcting the underlying primary immune defect via HSCT, by minimizing immune suppression in transplant recipients, and by aggressive anti-HIV therapy in HIV/AIDS patients. More recently, the availability of sensitive methods for monitoring reactivation of EBV in immune-compromised populations using quantitative polymerase chain reaction (PCR) techniques, combined with the pre-emptive or therapeutic use of anti-CD20 antibodies to thwart EBV-associated lymphoproliferation, have led to successful control of post-transplant "lymphomas." Highly active antiretroviral therapies (HAART) and other approaches that maintain and strengthen cell-mediated immunity in HIV-infected individuals have reduced their risk of "opportunistic" cancers. Rapid and reliable diagnosis of *H. pylori* infection and appropriate antibiotic treatment for susceptible hosts diminishes the risks of both carcinomas and lymphomas of the stomach.

HISTORY

In 1959, Lewis Thomas[1] proposed the concept that immune surveillance was an active process controlling the emergence of malignant clones from somatic cells that undergo precancerous mutations during the lifetime of a normal, immune-competent individual. This hypothesis predicted that immune-deficient subjects should

experience much higher rates of all types of cancers as compared with the general population. Indeed, surveys of patients with primary and acquired immune deficiencies have demonstrated increased incidence of cancer but not substantiated an increased risk of all cancer types.[2] Retrospective clinical investigations have revealed several patterns of association between certain malignancies and underlying disease types. In many cases, de novo, reactivated, or chronic infections play a substantial role in tumor development. Specifically, patients with primary (genetically determined) or acquired immune deficiencies that affect primarily T-cell function are at increased risk of developing lymphomas, often associated with EBV.[3,4] Chronic immune suppression also increases a patient's risk of developing carcinomas that are linked to infection with viruses. For example, HIV-infected subjects and solid-organ allograft recipients run an increased risk of Kaposi's sarcoma, which is associated with human herpesvirus-8 or also known as Kaposi's sarcoma–associated herpesvirus. Solid-organ allograft recipients are also at greater risk of developing squamous cell carcinoma of the skin and cervix associated with HPV. Persons with congenital humoral immune defects (especially IgA deficiency) who are persistently colonized with *H. pylori* experience higher rates of gastric carcinomas and gastric MALT lymphomas. The third category of patients at increased risk of tumors of hematopoietic and epithelial origin is individuals with inherited defects of genomic instability, which lead to both immune deficiency and propensity to tumor development.[5]

Even among classic primary immunodeficiencies, the array of tumors observed varies among the specific immunodeficiency diagnoses. The recent delineation of precise genetic causes for many of the primary immune deficiencies has made possible initial molecular dissection of affected pathways of cellular proliferation and programmed cell death in distinct disorders and has helped to reconcile the differences in tumors seen among patients with those disorders.

Although tumors in immune-deficient persons remain a major cause of morbid and fatal complications, progress has been made in reducing the risk of malignant transformation in many patients through better understanding of the etiopathogenesis. The risk of life-threatening "lymphomas" can be reduced substantially or even eliminated in some patients by correcting the underlying primary immune defect via HSCT, by minimizing immune suppression in recipients of transplantation, or by aggressive anti-HIV therapies in HIV/AIDS patients.[6–8] More recently, the availability of sensitive methods for monitoring reactivation of EBV in immune-compromised populations using quantitative PCR techniques, combined with the pre-emptive or therapeutic use of anti-CD20 antibodies to thwart EBV infection, have led to successful control of post-transplant "lymphomas."[9–11] Newer antiretroviral therapies and other approaches that maintain and strengthen cell-mediated immunity in HIV-infected individuals have reduced their risk of "opportunistic" lymphomas. Rapid and reliable diagnosis of *H. pylori* infection and appropriate antibiotic treatment for susceptible hosts diminishes the risks of both carcinomas and lymphomas of the stomach.[12–14]

At the same time, new medical advances could create new populations of patients at risk for lymphoid tumors in particular. Use of ever more intensive therapies to eradicate cancer in adults, such as nonmyeloablative but highly immunosuppressive HSCTs, and use of immune-ablative chemotherapy in the setting of autologous transplants for underlying autoimmune diseases place subjects at risk for reactivation of EBV for many months or years after these procedures.[15–17] In all of these settings there is a significant probability of prolonged erasure of the immune repertoire "memory," with a limited capacity to restore thymopoiesis. Finally, genetic manipulation of the immune system that bypasses normal regulatory mechanisms has the potential to create rather than reduce lymphoproliferative consequences, as is seen in murine and human trials of gene therapy for primary immunodeficiencies.

LYMPHOMAS AND IMMUNODEFICIENCY

Contributors to Increased Risk of Lymphoproliferative Disorders in Primary and Secondary Immunodeficiencies

Three general biologic circumstances, often occurring in concert, predispose individuals with primary or acquired immunodeficiencies to the development of lymphoproliferative disorders:

1. The endemic incidence of EBV infection
2. The predominance of type 2 cytokine production in susceptible hosts and in the case of primary immune defects
3. Disruption of normal pathways that regulate lymphocyte cell cycling and survival by genetic mutations

EBV is a major cofactor in many lymphomas (lymphoproliferative tumors) in the setting of immune compromise, as a result of the unique properties of EBV as a transforming agent of B cells and its expression of genes that inhibit human cell-mediated immunity. Because of the ubiquitous presence of EBV, most people become infected during their lifetime, leading to a state of lifelong viral latency. The latent state of EBV is maintained by host-specific, cell-mediated immune responses (conferred by T and natural killer [NK] cells). In cases in which cell-mediated control of EBV latency is inadequate (because of genetic immunodeficiency) or fails (after immune suppression or destruction), EBV-immortalized B cells are able to proliferate unchecked, which can result in sequential loss of heterozygosity mutations and/or frank cytogenetic rearrangements. The emergence and persistence of EBV-transformed B cells and resultant lymphoproliferative disorders is further favored by a type 2–skewed cytokine milieu, inhibiting the type 1 cellular immunity that is essential for the control of EBV-bearing B cells.[18] Type 2 cytokine skewing has been observed in patients with several different primary immune defects characterized by compromised quantity, maturity, diversity, and/or responsiveness of T cells. Disorders such as Omenn's syndrome (a form of severe combined immunodeficiency [SCID]) and Wiskott-Aldrich syndrome (WAS) are examples of such primary immunodeficiencies. Patients recovering from HSCT and solid-organ allograft recipients immunosuppressed with calcineurin inhibitors (FK506 or cyclosporine A) also develop type 2 skewing, as do HIV-infected patients, who demonstrate progressive loss of CD4 cells. Identification of many of the specific molecular defects responsible for primary immunodeficiencies reveal additional mechanisms that could contribute to lymphomagenesis in some of the diseases.

Clinical Characteristics of Lymphomas in Primary Immune Deficiencies

Advances in prevention and treatment of opportunistic infections now allow patients with primary immunodeficiencies to enjoy longer lives than ever before; however, neoplastic disorders—particularly lymphoproliferative complications—remain the second most common cause of premature mortality (still preceded by infections).[19] The incidence of tumors in patients with certain immunodeficiency diseases, such as WAS, ataxia telangiectasia, and common variable immunodeficiency, is estimated at between 15% and 25%, with a substantially increased risk of developing lymphoma that increases with advancing age.[20,21]

An important early contribution to the relationship between primary immunodeficiency and cancer was provided by the international Immunodeficiency Cancer Registry (ICR), which evolved in the 1970s as an outgrowth of the observations of Good and Gatti[22] regarding cancers diagnosed in immunodeficient children. This voluntary registry was pivotal in the description of the distribution of tumor types in patients with primary immunodeficiencies, pointing to the remarkable predominance of lymphomas across

Table 15-1 Immunodeficiency Cancer Registry Cases: Distribution of Tumors and Immunodeficiencies

Immunodeficiency	Adenocarcinoma	Lymphoma	Hodgkin's Disease	Leukemia	Other Tumors	Total
Severe combined immunodeficiency	1 (2.4%)	3 (73.8%)	4 (9.5%)	5 (11.9%)	1 (2.4%)	42 (8.4%)
X-linked agammaglobulinemia	3 (14.3%)	7 (33.3%)	3 (14.3%)	7 (33.3%)	1 (4.8%)	21 (4.2%)
Common variable immunodeficiency	20 (16.7%)	55 (45.8%)	8 (6.7%)	8 (6.7%)	29 (24.2%)	120 (24.0%)
IgA deficiency	8 (21.1%)	6 (15.8%)	3 (7.9%)	0 (0%)	21 (55.3%)	38 (7.6%)
Hyper-IgM syndrome	0 (0%)	9 (56.3%)	4 (25.0%)	0 (0%)	3 (18.8%)	16 (3.2%)
Wiskott-Aldrich syndrome	0	59 (75.6%)	3 (3.8%)	7 (9.0%)	9 (11.5%)	78 (15.6%)
Ataxia telangiectasia	13	69 (46.0%)	16 (10.7%)	32 (21.3%)	20 (13.3%)	150 (30.0%)
Other immunodeficiencies	1 (4.0%)	12 (48.0%)	1 (4.0%)	4 (16.0%)	7 (28.0%)	25 (5.0%)
Total immunodeficiency categories	46 (9.2%)	252 (50.4%)	43 (8.6%)	63 (12.6%)	96 (19.2%)	500 (100%)

virtually all diagnoses. Table 15-1 is a reproduction of earlier publications of the ICR data listing tumor types reported for various immunodeficiency diseases. In recent times, with the advantage of retrospective review of clinical and pathologic materials from the early cases, we recognize imperfections in the original cataloging. For example, it is likely that a significant proportion of the boys listed as having hypogammaglobulinemia, because they had normal numbers of lymphocytes, who developed lymphomas were actually affected with X-linked severe combined immunodeficiency (XSCID). Similarly, review of slides from cases of "leukemia" in patients with SCID, hypogammaglobulinemia, and WAS suggest that these were actually disseminated lymphoproliferative disorders of mature B cells. Nonetheless, the general outline of tumor types and their proportional distribution among patients with various immunodeficiencies that was provided by the ICR has withstood the test of time.

The descriptive information provided by the ICR has made possible a comparison of clinical characteristics and response to chemotherapy for non-Hodgkin's lymphomas (NHL) and Hodgkin's disease between patients with primary immunodeficiencies and the general population, guiding clinicians with these unique cases. Table 15-2, also a reproduction of previously published ICR data, summarizes clinical characteristics of reported cases of NHL. The data highlight several features, including the following:

- Male predominance, even in patients with autosomal recessive disorders such as ataxia telangiectasia
- Young median age at diagnosis
- High frequency of extranodal presentation involving predominantly gastrointestinal, central nervous system (CNS), or disseminated sites

EBV has been identified as a common cofactor in the predominant B-cell phenotypes but also in cases of T-cell NHL and Hodgkin's disease. In contrast to tumors in patients with other types of immunodeficiency, lymphomas in patients with ataxia telangiectasia are usually EBV^-. This finding is consistent with the hypothesis that genetic predisposition to tumorigenesis in patients with ataxia telangiectasia occurs as a result of mutations arising from the chromosomal repair defect.

Lymphoproliferative disorders or "lymphomas" in both primary and secondary immunodeficient states span the spectrum from reactive hyperplasias through frank malignancy. Not all lymphomas in immunodeficient hosts, despite clonal origin or malignant histologic appearance, require intensive chemotherapy to achieve remission.

Table 15-2 Characteristics of Non-Hodgkin's Lymphomas in the Immunodeficiency Cancer Registry*

Immunodeficiency	*N*	Gender† (M:F)	Median Age at Diagnosis (Yr)	Primary Tumor Sites (%)‡			
				CNS	GI Tract	Lymph Node	Multiple
Severe combined immunodeficiency	31	23:7	1.6	6.5	3.2	9.7	48.4
X-linked agammaglobulinemia	7	7:0	1.2	0	14.3	14.3	14.3
Common variable immunodeficiency	55	30:23	23.0	1.8	12.7	12.7	25.5
IgA deficiency	6	4:1	9.4	16.7	0	0	0
Hyper-IgM syndrome	9	7:2	7.8	11.1	22.2	22.2	0
Wiskott-Aldrich syndrome	59	59:0	6.2	23.7	6.8	8.5	20.3
Ataxia telangiectasia	69	40:24	8.5	0	8.7	10.1	14.5
Other immunodeficiencies	4	4:0	4.0	0	0	0	0
Total immunodeficiency categories	240	174:57	7.1	7.9	8.8	10.4	21.7

GI, gastrointestinal tract.
*This table excludes cases of non-Hodgkin's lymphoma in immunodeficiency categories with fewer than two cases reported.
†Sex reported where known.
‡For 51.3% of ICR cases, primary tumor site is other or unknown.

Resolution has occurred with antibiotic therapy in MALT lymphomas and with steroids, interferon-α, low-dose chemotherapy, or rituximab in EBV$^+$ tumors.

Historically, treatment of NHL with conventional doses of chemotherapy and radiation met with inferior results in immunodeficient patients.[23,24] Tumor responses were reported as inferior to those observed in the general population for reasons that remain quite obscure, although the major reported causes of early mortality in the 1950s to 1980s were opportunistic infections. In the current era, improved antiviral and antifungal therapies allow most patients with immunodeficiencies who have cancer to be treated more aggressively. Ideally, achievement of remission should be followed by reconstituting HSCT if a suitable donor is available.

Based on ICR reporting, Hodgkin's disease accounts for approximately 10% of tumors arising in patients with immunodeficiencies and occurs at an early median age—less than 10 years of age.[25] A case-control study performed by the ICR in the late 1980s compared the immunodeficiency cases with other pediatric cases from a multiinstitutional international cooperative study group. Immunodeficient patients with Hodgkin's disease presented earlier in life (mean age, 7.8 years vs. 11.5 years in the general population) and were significantly less likely to achieve initial remission. Hodgkin's disease in immunodeficient patients far more commonly presented with histologies of mixed cellularity and lymphocyte depletion (now recognized as representing feeble immune response to the true malignant population) when compared with presumed nonimmunodefcient subjects.[25] For immunodeficient patients who achieved remission of Hodgkin's disease, the probability of survival is also inferior as compared with patients in the general population. Patients with primary immunodeficiency who achieve remission of Hodgkin's disease should be considered for allogeneic bone marrow transplantation.

Primary Immunodeficiencies Associated with Lymphomas

Table 15-3 lists some of the primary immunodeficiencies associated with lymphomas and epithelial cancers, identifying the underlying molecular defects and other biologic characteristics associated with predisposition to lymphoma development.

Severe Combined Immunodeficiencies

SCID is a collection of more than a dozen genetically distinct disorders with severe impairment of both cellular and humoral immune function, leading to early mortality from opportunistic infections during infancy in the absence of aggressive medical intervention.[26] SCID patients who have developed lymphomas share the characteristics of presence of B cells (targets for EBV transformation) and severe quantitative or qualitative defects in T cells. Examples of such conditions include the following:

- XSCID, in which loss of function mutations in the X-linked common γ-chain gene of multiple interleukin receptors block T-cell development, but B-cell numbers are generally plentiful
- Purine nucleoside phosphorylase deficiency, in which T-cell expansion and function are impaired by accumulation of toxic intracellular metabolites, with lesser effects on B cells
- Omenn's syndrome, caused by mutations in *RAG1* genes predominantly, resulting in severe restrictions on both B- and T-cell repertoire development leading to marked skewing toward a type 2 cytokine production

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome (WAS), an X-linked disorder of broad-ranging and variable immunodeficiency and microthrombocytopenia, results from mutations in the *WASP* gene.[27] The *WASP* gene encodes a large intracellular protein with several functional domains involved with cytoskeletal integrity and signal transduction. Several molecules reported to be associated with *WASP* are involved in normal progression through the cell cycle. WASP is expressed in cells of hematopoietic origin and in the thymus. Experimental evidence suggests that WAS B cells are relatively resistant to apoptosis, and rare reports of EBV$^-$ B-cell lymphomas have surfaced, especially among adult males with clinically milder forms of WAS that are sometimes termed X-linked thrombocytopenia.

Table 15-3 Primary Immunodeficiencies: Predominant Reported Tumors

Disorders	Inheritance	Gene Defect	Susceptibility to EBV	Type 2 Cytokine Skewing	Disruption of Normal Apoptosis	Tumors
Severe combined immunodeficiency						
X-SCID	X	Common γ- chain†	+			Lymphoma
Omenn's	AR	*RAG 1/2*‡	+	+		Lymphoma
PNP deficiency	AR	*PNP*§	+	+		Lymphoma
Wiskott-Aldrich syndrome	X	*WASP*	+	+	+	Lymphoma*
CD40-L deficiency	X	*CD40 L*	+		+	HD, biliary tract tumors
X-linked lymphoproliferative syndrome	X	*SH2D1*	+			Lymphoma*
Chédiak-Higashi syndrome	AR	*LYST*[16]	+			Lymphoma*
ALPS	AD, AR	*FAS*[21]			+	Lymphoma
Hyper-IgE syndrome	AD	?		+		Lymphoma
IgA deficiency/CVID	AD, S	?				Lymphoma*, GI carcinoma

AD, autosomal dominant; ALPS, autoimmune lymphoproliferative syndrome; AR, autosomal recessive; CVID, common variable immunodeficiency; EBV, Epstein-Barr virus; GI, gastrointestinal; HD, Hodgkin's disease; PNP, purine nucleoside phosphorylase; S, sporadic; SCID, severe combined immunodeficiency; X, X-linked.

*Frequently associated with EBV.

†From Noguchi M, Yi H, Rosenblatt HM, et al: Interleukin-2 receptor gamma chain mutation results in X-linked severe combined immunodeficiency in humans. Cell 1993;73:147–157.

‡From Villa A, Sobacchi C, Notarangelo LD, et al: V(D)J recombination defects in lymphocytes due to RAG mutations: severe immunodeficiency with a spectrum of clinical presentations. Blood 2001;97:81–88.

§From Markert ML: Purine nucleoside phosphorylase deficiency. Immunodefic Rev 1991;3:45–81.

X-Linked Lymphoproliferative Syndrome

X-linked lymphoproliferative syndrome (XLP), long recognized as a condition associated with severe or fatal complications of EBV infection and a high risk of lymphoma, results from mutations in the *SH2D1A* or *SAP* (slam-associated protein) gene on the X chromosome.[28,29] Clinical features of XLP include an excessively intense immune reaction to EBV associated with hemophagocytosis and liver failure, lymphomas, aplastic anemia, and/or acquired hypogammaglobulinemia. SAP, an adaptor protein linked to at least four known regulatory molecules, can alter T and NK cell functions in both activating and downregulating directions and is thought to be involved in T-cell/B-cell interactions through cytokine regulation.[28] Analyses from the XLP (Purtilo) registry indicate that many of the lymphomas occurring in patients with XLP are EBV^-, contrary to early predictions.[30] More recently, cases of boys who have developed separate, clonally distinct tumors years apart have been found to be due to XLP.[31]

Chédiak-Higashi Syndrome

Chédiak-Higashi syndrome (CHS) is an autosomal recessive disorder characterized by recurrent bacterial infections, oculocutaneous albinism, abnormal platelets, varied neurologic dysfunction, and a 90% probability of developing a lethal hemophagocytic complication associated with EBV infection (referred to as the accelerated phase) before age 20.[32] As part of the "accelerated phase," some patients develop disseminated lymphoproliferative disorder. CHS is caused by mutations in the *LYST* gene (lysosomal trafficking regulator), and giant lysosomes are characteristic findings in leukocytes on blood smear. Because lysosomes are the key storage compartments for cytolytic proteins (including perforin and granzyme B), the cytotoxic effector function of NK and T cells is typically impaired in CHS, presenting a vulnerability to control of EBV infection.[33] A transport defect inhibiting peptide loading and antigen presentation by human lymphocyte antigen class II molecules on EBV-transformed CHS B lymphocytes has also been proposed as an additional mechanism contributing to escape of transformed B cells from immunologic control.

X-Linked Hyper-IgM Syndrome (X-Linked CD40 Ligand Deficiency)

X-linked hyper-IgM (XHIM) results in failure of immunoglobulin switching by B cells (which requires signaling through CD40) and in decreased development and maintenance of type 1 cell–mediated responses (including NK cell function) due to impaired responsiveness of CD40-expressing monocyte-derived antigen-presenting cells.[34] Patients with XHIM seem to have an increased risk of lymphomas, but especially of Hodgkin's disease associated with EBV infection. Presumably, depressed cell-mediated function required for control of EBV is responsible for this occurrence. Patients with XHIM are also at increased risk for biliary carcinomas, because there is a high rate of sclerosing cholangitis in patients with a history of chronic cryptosporidiosis.[35] In parts of the world where cryptosporidial infection is less prevalent, this complication of XHIM is rarely observed.

Autoimmune Lymphoproliferative Syndrome

Autoimmune lymphoproliferative syndrome (ALPS) represents a constellation of genetic apoptosis defects associated with mutations in FAS, Fas ligand, and caspase 8 genes.[36] Most of the cases described have had heterozygous, dominant-negative mutations involving FAS. Characteristic clinical features of the syndrome present in early childhood or even at birth. These include chronic multifocal lymphadenopathy, splenomegaly, autoimmune hemolytic anemia (and often other immune cytopenias), with increased proportions of circulating senescent T cells ($CD3^+$, αβ T-cell receptor $[TCR]^-$, $CD4^-CD8^-$), so-called double-negative T cells. The majority of patients experience symptomatic improvement with steroid therapy, and generally, autoimmune complications lessen in severity with advancing age. The estimated risk of lymphoma, B-cell, T-cell or Hodgkin's disease, in such patients ranges around 30%, however, and some patients have developed more than one lymphoid tumor over time.[37] Patients who have the most severe forms of ALPS should be considered for correction with HSCT. Recently, use of rituximab and rapamycin, agents that induce apoptosis in the senescent lymphocytes bypassing the FAS/FAS ligand signal, have been shown to reduce lymphadenopathy and autoimmune symptoms in patients with ALPS.[38] Whether such strategies will ultimately reduce the risk of lymphomas remains to be determined.

Clinical Characteristics of Lymphoproliferative Disorders in Acquired Immunodeficiencies

Patients recovering from HSCT or solid-organ allografting and patients with HIV infection all demonstrate rates of lymphoproliferative complications substantially exceeding those seen in the general population.

Epstein-Barr Virus Post-transplant Lymphoma after Hematopoietic Stem Cell Transplantation

After HSCT, the incidence of post-transplant lymphoma (PTLD) ranges from approximately 1% or less after unmanipulated matched-sibling donor transplants or autologous transplants to greater than 30% after T-depleted haploidentical (mismatched) transplants in patients with certain underlying immunodeficiencies (e.g., WAS).[39] Virtually all cases of PTLD are associated with EBV and generally present during the first 6 months after transplantation—the period when T-cell immune reconstitution is still very poor. The majority of cases of PTLD occur in donor-derived EBV-transformed B cells, although occasionally EBV reactivation in host cells is demonstrated. Several risk factors for development of PTLD—both host- and transplant-related—have been identified. These include the following:

- T-cell depletion of the stem cell product (a procedure aimed at decreasing the risk of graft-vs.-host disease after allogeneic transplantation); T-cell specific depletion increases risk more than pan–lymphocyte depletion methods
- HLA mismatching
- Older age of the transplant recipient
- Use of anti-T-cell antibody therapy, which is commonly used in newer, reduced-intensity protocols

PTLD after HSCT has several symptomatic presentations. Failure to diagnose and treat patients early and effectively can lead to dissemination with B-cell infiltration of the marrow, lungs, reticuloendothelial system, and CNS, which once developed is usually fatal. It is likely that many cases of PTLD still go unrecognized premortem, and given the low rate of autopsy in post-transplant deaths, the actual incidence has probably been underestimated. Sustained remission of PTLD has been shown to coincide with the development of donor-type EBV-specific cytotoxic T lymphocytes. A common strategy is to monitor the EBV level in peripheral blood by PCR in high-risk patients and initiate anti-CD20 (rituximab) as pre-emptive therapy to "buy time" for EBV cytotoxic T lymphocyte reconstitution.[11,40] Adoptive T-cell therapy with EBV-specific cytotoxic T lymphocytes has been demonstrated to be effective at preventing and treating PTLD following HSCT, but this therapy is limited to few centers.[41]

Post-transplant Lymphoma after Solid-Organ Grafting

The use of immunosuppression after allografting heightens the risk of PTLD in previously immunocompetent subjects. Use of more intensive and prolonged immunosuppression—especially use of

anti-T-cell monoclonal antibody for treatment of graft rejection—has been associated with an increased PTLD risk in patients with all types of organ transplants.[42] Rates of PTLD range from 1% to 5% after kidney transplantation (increased 30- to 50-fold over age- and sex-matched general population) to as high as 25% after visceral organ transplants (liver and small bowel), especially in EBV^- pediatric recipients of EBV^+ organs, who have a higher rate of PTLD than adult transplant recipients.[43] As opposed to HSCT, PTLD after solid-organ transplantation is associated with EBV in only 70% to 80% of cases, with late-occurring PTLD (more than 1 year post-transplant) more likely not to be EBV-associated.[44] Presentation of PTLD varies considerably, ranging from a systemic mononucleosis-like disease, to solid lymphoid lesions (often in extranodal sites that include the CNS), or even with disseminated lymphoma. Histologies range from B-cell hyperplasia to frank lymphoma and may be polyclonal, oligoclonal, or monoclonal.[43] Although the incidence of PTLD as a complication of immune suppression after organ transplantation has declined, the mortality rate from this cause remains at approximately 50% in affected patients and has changed little over time.[24,42,45] The critical role of intact cell-mediated immunity in control of EBV-associated PTLD is demonstrated in cases in which regression occurs after reduction in immune suppression, at the risk of organ rejection. Surgical excision and/or radiation of limited disease are associated with a high rate of durable remissions.[43] In more aggressive or persistent tumors, rituximab and other anti-B-cell therapies have been used successfully.[46,47] Chemotherapy is usually reserved for the most resistant disease because of high treatment-related mortality.[24,46] A low-dose chemotherapy approach has been shown to be effective in PTLD observed in children.[48] It is still unclear whether use of rituximab alone or in combination with chemotherapy is optimal.

Lymphomas Associated with HIV Infection

The incidence of lymphomas among HIV-infected adults during the early years of the worldwide epidemic was reported to exceed 20%.[49] Incidence of cancer has decreased since the introduction of HAART.[8] However, the incidence of Hodgkin's disease seems to be increasing in the HIV population,[50] and causes of death in a U.S.-based population that had received HAART shows increasing proportions of death from non-AIDS-defining malignancies and chronic disorders of adulthood.[51] Although the reported association of lymphomas with EBV in HIV-infected persons ranges between 30% and 60%, extranodal and CNS sites are more frequently seen in HIV-infected patients than in age- and gender-matched controls in the general population.[52] In the current era of supportive care, it is recommended that HIV patients with cancer be treated with standard therapies used for nonimmunocompromised patients; however, infectious complications are increased and outcomes usually inferior to the general population.

CARCINOMAS ASSOCIATED WITH IMMUNE DEFICIENCIES

Gastric Carcinomas and Mucosa-Associated Lymphoid Tissue Lymphoma

A relationship between gastric atrophy, long-standing dyspepsia and gastric ulcer disease, and the development of gastric carcinomas in adults with common variable immunodeficiency was observed decades before the discovery of a causal link to chronic *H. pylori* infestation.[53] A retrospective study of banked sera from a group of presumed nonimmunodeficient adult patients diagnosed with gastric carcinoma revealed an increased incidence of IgA deficiency in cancer-bearing subjects (1 in 20) as compared with the general blood donor pool (1 in 400), further implicating defective humoral immunity as contributory to this unusual type of tumor.[54]

It is now recognized that *H. pylori* infection is the most common cofactor for gastric carcinoma and is associated with MALT lymphomas in nonimmunodeficient whites.[54] Chronic inflammation from *H. pylori* incites local cytokine production, which alters adhesive properties of local epithelial surfaces and promotes ectopic lymphoid proliferation. Mucosa-associated lymphoid tissue is not present in healthy gastric mucosa, but it can develop in sites of long-persisting inflammation.[55] MALT lymphomas are generally monoclonal and can take on the appearance of aggressive, large B-cell lymphomas. These tumors are reported not only in adults with primary immunodeficiency but also in immunosuppressed organ transplant recipients, to the extent that diagnostic endoscopy is now recommended as part of the post-transplant follow-up for symptomatic individuals.[14] Fortunately, effective eradication of *H. pylori* with antibiotics, antacid therapy, and (occasionally) surgical excision is highly curative for many of these gastric carcinomas and MALT lymphomas.[14] Presumably, surveillance for *H. pylori* infection and antibiotic suppression can prevent these tumors in immune-deficient populations in the future.

Carcinomas after Allografting

The risk of post-transplant carcinomas after bone marrow transplantation is influenced by several factors, the strongest of which is probably the patient's inherent susceptibility to carcinogenesis. For example, patients who have an underlying systemic defect in DNA repair (e.g., Fanconi anemia) might be "cured" of their marrow failure or acute leukemia by replacement of genetically normal hematopoietic stem cells but remain at high risk for epithelial cancers, especially in areas of transplant-related radiation such as the head and neck.[56] Even among patients without obvious susceptibility to DNA damage, differences in response to the radiation commonly used in transplant treatment of patients with hematologic malignancies could account for future risk of skin, bone, and CNS tumors (Box 15-1).

The incidence of cancer in solid-organ transplant recipients increases greater than 1% per year after transplant such that about 20% of patients will experience a cancer within 10 years following transplantation.[42,57] Many of these cancers involve the skin and are enhanced by increased sun exposure (i.e., time to development of skin cancer decreases with increasing latitude). Compared with the

Box 15-1. FOSTERING AWARENESS ABOUT CARCINOMAS IN ORGAN TRANSPLANT RECIPIENTS

The cumulative risk of cancer in solid organ transplant recipients exceeds 50% 20 years after grafting. Compared with the general adult population, the risk of developing cancer after organ transplantation increases three- to fivefold. Patient education about specific cancer risks and preventive lifestyle, coupled with regular medical examinations screening for early malignancy, might reduce cancer mortality in organ recipients. The skin and lips are the most common sites of cancer in allograft recipients; development of squamous cell carcinomas is markedly accelerated by sun exposure in this population. In addition to squamous cell carcinoma, unusual skin cancers such as Merkel cell cancer and Kaposi's sarcoma occur with markedly increased incidence after organ transplantation. Cervical cancer accounts for 10% of cases of post-transplant cancers in women; although the rate of breast cancer does not seem to increase, mortality from more advanced-stage disease is increased. De novo lung cancer in immune-suppressed individuals carries a particularly poor prognosis regardless of histologic type. Thus, recommendations regarding avoidance to sun exposure, regular dermatologic and gynecologic screening, and intervention to achieve sustained smoking cessation should be included as part of routine long-term transplant follow-up.

Table 15-4 Incidence of Carcinomas following Solid-Organ Transplantation

Incidence	Incidence vs. General Population	Factor Increasing Risk
Skin cancer		
Squamous cell carcinoma	40- to 50-fold	Sun exposure, latitude
Basal cell carcinoma	10-fold	
Melanoma	5-fold	
Cervical cancer*	14-fold	Human papillomavirus infection
Endometrial cancer	2-fold	
Bladder cancer	4-fold	
Kidney cancer	8-fold	Usually developing in native kidney
Ureteral cancer	1000-fold	
Kaposi's sarcoma	1000-fold	Kidney transplant, Mediterranean descent

*Majority in situ.
Data provided by the Israel Penn Transplant Tumor Registry, Cincinnati, Ohio.

general population, the risk of developing cancer after organ transplantation is increased three- to fivefold. Table 15-4 tallies the relative increased risks of certain carcinomas in organ transplant recipients as collected through the Israel Penn Tumor Transplant Registry in Cincinnati, Ohio.[42]

Skin and lip cancers account for nearly 40% of all post-transplant cancers, showing a male predominance of 2:1. With close surveillance, deaths are infrequent. An unusual "skin" cancer diagnosed in transplant recipients is Merkel cell cancer, a highly aggressive neuroendocrine tumor arising principally in the head and neck region. No clear association with an inciting pathogen is known for this unusual tumor, which is usually seen in elderly whites; organ transplant recipients account for nearly 8% of the fewer than 1000 cases of Merkel cell cancer reported worldwide.[42]

Kaposi's sarcoma has long been identified as one of the "opportunistic tumors" in organ transplant recipients, with a nearly 1000-fold increase over the general population, although it is not reported after HSCT or in primary immunodeficiencies. Kaposi's sarcoma is more commonly reported after renal transplantation and in individuals of "Mediterranean" descent, such as Greeks, Italians, Turks, and Arabs. In this setting it is usually not associated with HIV infection. Other de novo sarcomas also account for some of the post-transplant risk of malignancy and seem to have a particularly aggressive biologic activity.[42]

Cervical cancer accounts for about 10% of post-transplant cancers in women. Fortunately, 75% of the lesions are in situ. It is hoped that future vaccine interventions against human papillomavrus can lower the rate of this complication for women in general. The number of breast cancer cases after allografting is comparable to that expected among women of like age; however, a higher mortality has been observed among stage III and IV patients when compared with non-immunosuppressed women.[58] Thus, more frequent screening, if it identifies earlier, lower grade malignancies, could be indicated for female organ transplant recipients.

Immunodeficiency and Cancer in Genetic Disorders of DNA Repair

Table 15-5 lists several rare genetic disorders of DNA repair in which resultant immune deficiency and intrinsic susceptibility to carcinomas have been identified. DNA is constantly exposed to potentially damaging insults, both external (e.g., environmental radiation) and intrinsic (e.g., byproducts of cellular metabolism). Several molecular strategies have evolved to maintain genomic stability. Mechanisms used in eukaryotes include those involved in the following processes:

- Recognition and direct repair of DNA damage
- Cell-cycle checkpoints that pause cell-cycle progression in the presence of damage, allowing the time needed for repair
- Mechanisms for removal of irreversibly damaged cells, such as the triggering of apoptosis (discussed previously in the section on ALPS)

DNA double-strand breaks represent the most potentially serious damage to the genome. Two major pathways exist to repair such damage: homologous recombination repair and nonhomologous end joining. Defects in either of these pathways can result in chromosomal rearrangements, loss of heterozygosity, and gene mutations leading to cancers.

On the other hand, generation of immunologic diversity among both B and T cells requires a well-orchestrated "creation" of DNA breaks followed by rearrangement of immunoglobulin and T-cell

Table 15-5 Genetic Disorders Associated with Chromosomal Instability That Result in Immunodeficiency and Predisposition to Cancer

Disorder	Gene Defect	Immune Defects	Cancers Reported
Ataxia telangiectasia	*ATM*[60]	IgA deficiency, ↓T cells	Lymphoma, leukemia, hepatocarcinoma, genitourinary carcinoma, skin cancer
Nijmegen breakage syndrome	*NBS1*[64]	Hypogammaglobulinemia, lymphopenia	Myeloid leukemia, lymphoma
Bloom's syndrome	*BLM*[65]	Hypogammaglobulinemia, natural killer cell deficiency	Lymphoma, epithelial cancer
Werner's syndrome	*WRN*[66]	Antibody deficiency?	Lymphoma

receptor gene sequences and repair to stabilize the final genetic product. In this process of gene rearrangement, sequence changes such as mutations and additions, which contribute to the desired diversity of new coding regions, occur frequently. Mechanisms creating this immunologic diversity probably include helicases, polymerases, and DNA ligases. Several of the known genetic defects associated with immunodeficiency and predisposition to cancers are described in the following sections. Many other rare cases with immunodeficiency and cancers have been identified, but the specific molecular defects are still unknown.

Ataxia Telangiectasia

Ataxia telangiectasia is an autosomal recessive disorder with cancer predisposition that has variable and profound immunologic and other systemic manifestations, principally cerebellar degeneration.[59] For some time, it has been recognized that ataxia telangioectasia cells fail to activate cell-cycle checkpoints normally after exposure to γ-irradiation or radiomimetic agents. The mutant gene in ataxia telangiectasia (*ATM*) is a member of the phosphotidylinositol kinase family of molecules involved in signal transduction and has also been implicated in meiotic recombination.[60] *ATM* seems to act as a sensor of double-stranded DNA breakage (e.g., in response to oxidative stress), activating numerous damage repair pathways, including cell-cycle checkpoint control, *p53* activation, and DNA repair. Mutations in *ATM* lead to accelerated telomere loss and premature aging.[61] In the context of normal lymphopoiesis, *ATM* is clearly involved in control of productive gene rearrangements of the B- and T-cell immune receptor molecules, in that lymphocytes from persons with ataxia telangiectasia demonstrate a 25-fold increase in nonrandom rearrangements of immunoglobulin and TCR genes as compared with lymphocytes from normal individuals.[62] Thymic output in ataxia telangiectasia is very reduced. The consequent restricted T-cell repertoire emerges from oligoclonal post-thymic expansion.[63] Some of the nonrandom rearrangements involve translocation of immunoglobulin chains with c-Myc, reflecting, in magnified proportion, commonly seen cytogenetic rearrangements in general lymphomagenesis. In addition to the predominant lymphoid tumors (both lymphomas and leukemias), individuals with ataxia telangiectasia experience high rates of epithelial cancers involving the skin, gastrointestinal tract, genitourinary tract, and CNS. Multiple tumors can be present simultaneously or can develop sequentially. Early reports from the ICR discussed concordance of histologies in tumors affecting ataxia telangiectasia siblings from the same family—an intriguing but still mysterious observation. The extent of response of tumors in ataxia telangiectasia patients to conventional chemotherapy remains controversial; however, the frequent development of chronic lung disease in ataxia telangiectasia and the tendency by treating physicians to reduce chemotherapy intensity could contribute to poorer outcomes.

Nijmegen Breakage Syndrome

Nijmegen breakage syndrome (NBS) is another rare autosomal recessive syndrome, which, like ataxia telangiectasia, is associated with both humoral and T-cell defects, clinical radiosensitivity, chromosomal instability, and predisposition to lymphoid and epithelial cancers.[64] Other characteristics of patients with NBS are growth retardation, microcephaly, and "birdlike" facies. The protein defective in NBS (NBS1, nibrin, or p95) seems to function together with ATM to "sense" DNA double-strand breaks and activate a diversity of corrective actions. As in ataxia telangiectasia, lymphocytes of patients with NBS display frequent chromosomal aberrations at the sites of TCR and IgH rearrangement.

Bloom's Syndrome

Bloom's syndrome has autosomal recessive inheritance involving mutations in the *BLM* gene.[65] In addition to immunodeficiency—especially humoral defects and predisposition to cancer—patients with Bloom's syndrome experience growth retardation, progeria, impaired fertility, sun-sensitive erythema of the face, and chronic lung disease (similar to patients with ataxia telangiectasia). The protein defective in Bloom's syndrome is a member of the RecQ helicase family and seems to function during DNA replication or in the postreplication process to resolve aberrancies incurred during replication. The BLM protein colocalizes with a gene, *hMLH1,* which is linked to mismatch repair. A propensity to colonic adenomas, epidermal carcinomas, and acute myeloid leukemia has been reported in patients with Bloom's syndrome.

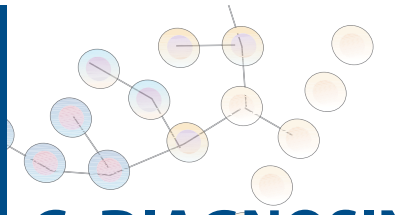
Werner's Syndrome

Werner's syndrome, an autosomal recessive disorder with features of progeria and multiple endocrine neoplasias, results from loss-of-function mutations in the *WRN* gene, which encodes a helicase/exonuclease.[66] Reports of immunodeficiency are not well substantiated, but predilection to sinopulmonary infections is noted. Genomic instability in Werner's syndrome is typified by elevated illegitimate recombination events and accelerated loss of telomerase sequences.

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C. DIAGNOSING CANCER: PATHOLOGY AND LABORATORY MEDICINE

SECTION NOTES

The number and types of diagnostic modalities available to characterize cancer has increased dramatically over the past few decades. Although histopathologic diagnosis using techniques that date back over a century remains the gold standard, radiologic techniques are becoming increasingly precise diagnostic instruments, and more and more supplemental laboratory techniques are becoming critical to accurate diagnosis. These latter methods, including cytogenetics and flow cytometry, first introduced in the 1970s and 1980s, and molecular pathology, a more recent addition, greatly expand the armamentarium of tests now available. The past few years has seen an even more rapid evolution in these newer tests. Fluorescence in situ hybridization is a very powerful technique that is changing the way many cytogenetics labs operate. Molecular diagnostics, which originally had a limited test menu largely applicable to hematology, now has a much larger range of tests with applicability to both inherited and sporadic cancers of all types.

Diagnostic radiology is also at a crossroads. The oncologist evaluating a patient can choose among everything from a simple roentgenogram to a complex alphabet of imaging studies—CT, CTA, MRI, MRS, PET, PET/CT and SPECT and SPECT/CT. In the right hands, newer imaging studies have incredible power to improve sensitivity and specificity of diagnosis. In the last several years, PET/CT using the radiotracer 18F-FDG has had a great impact on the management of many common cancers providing staging, treatment planning, and treatment response assessment information more quickly and robustly than by standard anatomic metrics. These technological advances present both opportunity and challenge. The opportunity is to provide better and more accurate methods for detecting and defining the presence of cancer. The challenge is to use the right techniques for the right indications. The overuse of highly sensitive tests results in increased false-positive diagnoses, whereas using highly specific tests inappropriately increases the risk of a false-negative diagnosis. Many newer diagnostic tests are expensive, so that cost is a critically important factor for the clinician to consider, but the cost implications of inappropriate intervention due to inappropriate testing go far beyond the simple expense of the test. Thus, the right algorithm of test use is critical to getting the right diagnosis in the most cost effective and timely manner to optimize patient outcome.

The expertise of the diagnostic pathologist or clinical laboratory scientist is critical in both the selection and interpretation of modern tests for cancer diagnosis. For more subjective tests such as routine histology, flow cytometry, or cytogenetics, experience and skill are well recognized as key determinants for accurate interpretation. More analytically precise tests such as serum tumor marker assays or molecular diagnostics also require a high degree of sophistication by the lab director to ensure the data obtained are accurate and not the result of artifact or sampling error. Experience and skill in both test use and interpretation are critically important in dealing with analytic as well as biologic predictive value. Similarly, for imaging, as in pathology, experience and skill in test use in different modalities such as nuclear medicine, MRI, cross-sectional imaging and ultrasound are critical to optimal use of the technologies to assure that results are robust and technical artifacts are avoided. Given the complexities involved, such expertise may not lie in the hands of a single physician.

The goal of this section is to provide the clinical oncologist with an understanding of the use and interpretation of the current diagnostic modalities available for the evaluation of cancer patients. The goal is not to provide an exhaustive review of tests and details that would be more appropriate for pathologists or radiologists. We have somewhat arbitrarily grouped the many laboratory cancer diagnostics that are now available into five chapters: surgical pathology, flow cytometry, cytogenetics, molecular diagnostics, and clinical chemistry; each chapter outlines the methods, applications, and interpretation of the tests in that area. Following these, there is separate chapter on radiologic diagnosis. This section will provide insight on the best use of tests in different settings and pitfalls in interpretation, so as to be of value to clinical oncologists in interacting both with their patients and with their colleagues in pathology, laboratory medicine, and radiology.

16 Principles of Oncologic Surgical Pathology

Peter B. Illei and William Westra

SUMMARY OF KEY POINTS

Key Method

- Routine histopathologic examination is the cornerstone of cancer diagnosis.
- Immunohistochemistry is an important adjunct that allows more precision in diagnosis, classification, and prognosis.
- Fine-needle aspiration, when used properly, is very valuable to guide treatment decisions.

Specific Roles of Pathologic Examination of Tissues

- Histologic diagnosis and classification of cancer
- Assignment of pathologic grade and stage
- Intraoperative consultation to direct a surgical procedure and ensure that appropriate diagnostic tissue is obtained
- Triage of tissue for specialized testing, and banking for research purposes

INTRODUCTION

Pathology as a medical discipline can be traced back to Renaissance Italy, when the autopsy was valued for correlating clinical history with pathologic findings.[1] During the nineteenth century, pathologists were primarily academicians who studied and taught the causes, mechanisms, and consequences of disease. Direct diagnostic application was, at best, a peripheral concern of a small group of full-time autopsy pathologists whose primary role was to confirm a diagnosis in the dead rather than to formulate a diagnosis in the living.[2] At the turn of the twentieth century, pathology became a more clinically relevant discipline for several reasons. Technical innovations in microscopy permitted detailed microscopic descriptions of tissue patterns and cell structures that, in turn, dramatically improved diagnostic capabilities. The introduction of anesthesia and aseptic techniques allowed surgeons to perform longer and more complicated procedures that required improved diagnostic skills, which, together with the invention of the freezing microtome,[3] made intraoperative consultation possible. Finally, an enlightened medical community and the public at large came to recognize that small and subtle tumors were easier to eradicate than were large and conspicuous ones.[4]

Given this new emphasis on early cancer detection and treatment, oncologic surgeons no longer could rely on their own clinical skills and gross observations to evaluate the presence and full extent of tumor growth. Instead, a new breed of physician/pathologist evolved with specialized training in the histologic characteristics of tumors. Beginning in 1926, the American College of Surgeons insisted on properly staffed hospital laboratories under the direction of physicians trained in clinical pathology and called for the mandatory systematic examination of all surgical specimens to culminate in a report detailing the pathologic findings.

The role of the modern surgical pathologist is that of a consultant clinician who is closely affiliated with many branches of medicine, including all surgical specialties, internal medicine, medical oncology, dermatology, neurology, and diagnostic and therapeutic radiology.

ONCOLOGIC SURGICAL PATHOLOGY REPORT

The surgical pathology evaluation of a presumptive tumor specimen strives to specify clearly and comprehensively the presence, nature, and extent of a tumor in a way that guides further therapy, measures results, and predicts future outcome. The report integrates the macroscopic and microscopic findings and the results of ancillary techniques such as immunohistochemistry and molecular genetic analysis. The scope and complexity of the surgical pathology report have increased dramatically over recent years, and groups such as the Association of Directors of Anatomic and Surgical Pathologists and the Cancer Committee of the College of American Pathologists recently have issued a number of standardized protocols that are organ and/or tumor specific.[5–9]

For any style and format, the contents of the surgical pathology report always include information regarding the presence or absence of tumor, size and location of the tumor, histologic classification, pathologic staging, adequacy of tumor removal (i.e., status of the surgical margins), and tumor grade.[10] These anatomic measurements are supplemented by relevant immunohistochemical, cytogenetic, and molecular biologic information to refine tumor classification and to guide the selection of therapeutic options.

Tumor Classification

As strategies for the treatment of oncology patients become increasingly sophisticated and individualized, current classification schemes aim to categorize tumors in ways that are precise, reproducible, and clinically relevant. The classification of tumors is hierarchical, progressing from fundamental distinctions in biologic potential (e.g., benign vs. premalignant vs. malignant) to broad separation in cellular differentiation (e.g., epithelial vs. mesenchymal vs. lymphoid vs. melanocytic) to much finer dissection of phenotypic expression (e.g., squamous vs. glandular, chondroid vs. osteoid, B cell vs. T cell).

Standardized international nomenclature for tumor classification has been promoted successfully by a variety of professional organizations. Most notably, the Armed Forces Institute of Pathology (AFIP) continues to update its series on tumor pathology, the *Atlas of Tumor Pathology,* in an effort to "promote a consistent, unified, and biologically sound nomenclature; guide the surgical pathologist in the diagnosis of the various tumors and tumor-like lesions; and provide relevant histogenetic, pathogenetic, and clinicopathologic information on these entities."[11] The World Health Organization also has implemented a program with similar aims. Its recent collection of books on the classification of tumors has taken a more deliberate approach to incorporate relevant genetic data as a component in naming and characterizing tumors.[12]

Pathologic Staging

Stage and grade traditionally have been used as parameters to characterize the clinical severity of a tumor. Stage outweighs grade in importance as an indicator of patient outcome for most cancers, with the notable exception of many soft tissue sarcomas. Stage is a measure of tumor growth. It takes into account the size of a tumor and the anatomic extent to which it has spread. Tumor staging permits valid comparison between groups of patients, facilitates exchange of information among treatment centers, guides selection of therapy, and allows empirical estimation of patient outcome.[13] The widely used TNM system uses three components to express the anatomic extent of disease: *T* is a measure of the local extent of tumor spread (size of tumor); *N* indicates the presence or absence of metastatic spread to regional lymph nodes; and *M* specifies the presence or absence of metastatic spread to distant sites. T, N, and M classifications are combined to provide a stage grouping. Additional histologic features also can be important in certain tumor types and may provide prognostic information (e.g., presence and amount of necrosis in osteosarcoma after neoadjuvant therapy). The TNM system is not used for lymphomas, though staging still is an important parameter to predict outcome.

Clinical staging (cTNM) defines the anatomic extent of a tumor based on clinical evidence before the initiation of treatment. It incorporates findings obtained from the physical examination, imaging studies, surgical exploration, and tissue biopsy. Clinical stage is used as a guide for the selection of primary therapy. In contrast, pathologic staging (pTNM) is based on examination of the surgically resected specimen. Assessment of pathologic stage is contingent on the recognition and removal of tumor to allow meaningful anatomic assessment of tumor origin and local extension. Thus, the pathologist's ability to render an accurate pathologic stage sometimes is compromised by the surgical approach, especially when a tumor is fragmented or removed laparoscopically. Pathologic staging is used mainly to direct adjuvant therapy, estimate prognosis, and report results, but does not invalidate the clinical stage (and vice versa).

Tumor Grading

Tumor grade is a semiquantitative measurement of histologic differentiation compared to the normal tissue from which the tumor arises. Well-differentiated tumors (grade 1) closely resemble their non-neoplastic counterparts; poorly differentiated tumors (grade 3 or 4) do not. As a rule of thumb, the more poorly differentiated a tumor, the more aggressive its behavior; however, the impact of tumor grade on tumor behavior is highly tumor-specific. For example, the expected behavior and treatment of soft tissue sarcomas is profoundly influenced by tumor grade. In contrast, most lung carcinomas are uniformly aggressive, regardless of histologic grade. For other tumor types, the utility of histologic grading falls somewhere between these two extremes.

No single uniform scheme has been established for the histologic grading of malignant neoplasms; grading schemes are tumor-specific. For some tumors, histologic classification defines tumor grade. Small cell carcinoma of the lung, anaplastic carcinoma of the thyroid, and Ewing sarcoma are, by definition, high-grade (i.e., poorly differentiated) tumors, whereas carcinoid tumor of the lung, polymorphous low-grade carcinoma of the salivary glands, and small lymphocytic lymphoma are, by definition, low-grade (i.e., well-differentiated) tumors. Some tumor types are graded based on the severity of cytologic atypia (e.g., leiomyosarcoma, renal cell carcinoma); others are graded on the basis of architectural growth patterns (e.g., adenocarcinoma of the prostate); and still others are graded by the combination of cellular atypia and architectural disarray (e.g., ductal carcinoma of the breast). Effective grading strategies strive to minimize inconsistency in application and maximize the prognostic significance of tumor stratification.

INTRAOPERATIVE CONSULTATION

The aim of intraoperative consultation is to provide rapid assessment of the tissue and to answer specific questions raised by the surgeon. The term "intraoperative consultation" is preferred over "frozen section," because in a significant number of cases no frozen section is performed. It is the surgical pathologist's responsibility to decide which method should be used and whether the diagnosis can be made on careful gross examination alone or on touch imprint preparations without the need for freezing the tissue, thus preserving the morphology for permanent sections. Touch preparations are made by gently touching or scraping the surface of the tissue without causing permanent damage to the rest of the tissue, whereas for frozen sections the tissue must be thinly sectioned, then frozen, and, finally, sectioned using a special microtome. To benefit fully from the diagnostic value of intraoperative consultation, the surgeon and the pathologist must communicate clearly and must have a balanced appreciation for its strengths and limitations.[14]

Requests for intraoperative consultation are appropriate in four common situations (Box 16-1):[15]

1. To establish a diagnosis or determine pathologic stage to guide the type or extent of the operation. For example, the use of a frozen-section or touch preparation to detect metastatic melanoma in sentinel lymph nodes now makes possible the identification of patients who would benefit from one-step lymph node dissections.
2. To determine the adequacy of tumor removal. Frozen-section analysis of surgical margins provides assurance of complete tumor removal at the time of surgery and thus minimizes the need for additional operations for revisions of positive margins.
3. To confirm the nature of the lesion. This is important to guide fresh tissue distribution for appropriate laboratory studies, e.g., to the microbiology laboratory for culture studies, to the flow-cytometry laboratory for immunophenotypic analysis, and to the genetics laboratory for cytogenetic or molecular analysis. Confirmation can be achieved with either touch preparations or frozen sections, depending on the specimen and suspected process.
4. To assess the presence and quality of lesional tissue before the operation is completed. In this instance, the frozen section serves not to establish an intraoperative diagnosis but to ensure that adequate, lesional tissue has been secured such that a definite diagnosis can be rendered on permanent histologic examination.

Accurate frozen-section diagnosis is compromised by inherent limitations of the technique,[16,17] especially suboptimal preservation of cytologic and histologic detail. Tissue fragmentation due to the presence of fat, bone, or foreign material and tissue distortion secondary to ice crystal formation may obscure the true identity of the pathologic process. Some specimens, particularly delicate tissue fragments in which important diagnostic distinctions are made on the basis of subtle architectural and cytologic alterations, are particularly susceptible to frozen section-induced morphologic alterations. In these cases, frozen-section analysis may be counterproductive and may compromise an accurate tissue diagnosis. For example, frozen-section evaluation of nonpalpable breast lesions, once a routine practice, is no longer encouraged because of a high error rate and a propensity to obscure irrevocably the subtle morphologic distinction between benign hyperplasia and intraductal carcinoma.

Accuracy of the frozen section also is limited by time constraints, so that a cursory microscopic evaluation of large specimens is highly vulnerable to sampling error. Thus, invasion within a large villous adenoma of the colorectum, transcapsular extension of an encapsulated follicular neoplasm of the thyroid, or malignant transformation within a benign mixed tumor of the parotid may elude detection when microscopic examination is limited to one or two frozen sections.

When the frozen section is used properly, its diagnostic accuracy now routinely exceeds 97% in both academic centers and general practice settings.[18,19] Diagnostic accuracy is especially high when the frozen section is used to make broad and fundamental distinction between pathologic processes (e.g., presence of tumor vs. absence of tumor, inflammatory process vs. neoplastic process, benign tumor vs. malignant tumor). Conversely, accuracy diminishes with increasing demands for precise tumor subclassification. Regardless of the situation, accuracy is improved when the pathologist is provided with appropriate clinical information and the indication for the consult.

Box 16-1. APPROPRIATE USE OF FROZEN SECTIONS IN SURGICAL PATHOLOGY

Frozen section, used appropriately, is an important tool in the management of a cancer patient. Several important indications can lead to a specific action on the part of the surgeon, but inappropriate uses run the risk of compromising care.

Frozen sections should be used to establish the following:

- A diagnosis or pathologic stage, and thereby determine the type and extent of the operation needed
- The status of the surgical margin to determine whether a wider local excision is necessary
- The presence and nature of appropriate lesional tissue to distribute fresh tissue for additional laboratory studies, such as microbiology culture, flow cytometry, or molecular assays
- The adequacy of a biopsy, thereby ensuring that a definitive diagnosis will be rendered on permanent histology.

Frozen sections should not be used in the following situations:

- For curiosity with no clear-cut plan to use results, as this is unnecessarily costly, may tie up pathology resources, and may result in artifacts that limit interpretation of the permanent sections.
- To establish a diagnosis when there is a threat of irreparable damage to tissue architecture that would preclude a definite diagnosis on permanent histology
- To document a focal microscopic finding in a large specimen, because sampling error may lead to an erroneous conclusion and, consequently, an inappropriate surgical approach.

IMMUNOHISTOCHEMISTRY

Immunohistochemistry (IHC) localizes specific constituents in tissues based on antibody recognition of tissue antigens. It was developed initially by Coons in 1940 as an investigative immunofluorescence technique to detect antigens in frozen tissue sections.[20] However, technical advances over the past three decades have thrust the technique into the forefront of diagnostic pathology.[21] The development of nonfluorescent chromogens has allowed visualization of antigen-antibody binding by using the conventional light microscope. The introduction of various amplification steps (e.g., peroxidase-antiper-

oxidase method, avidin-biotin conjugate method, polymer-based labeling system) has significantly improved sensitivity and specificity. The development of novel protocols that use two or more primary antibodies that are detected by two different detection systems has enabled us to make more accurate diagnoses, even in small biopsies with limited amount of tissue. The discovery of means to "unmask" antigens (e.g., enzyme digestion, heat-induced epitope retrieval) in formalin-fixed archival tissue has permitted consistency in staining despite variations in tissue fixation and processing. Finally, the development of techniques to manufacture highly specific monoclonal antibodies has greatly expanded the arsenal of probes that can target virtually any immunogenic marker.[22] With the adaptation of the technique to formalin-fixed and paraffin-embedded tissues, IHC now is compatible with standard tissue-processing procedures and can even be performed retrospectively on tissue blocks that have been archived for many years. IHC now is used routinely to address a range of key diagnostic questions.[23]

Is It a Tumor?

In some specific instances, markers identified by IHC can help make the fundamental distinction between a malignant tumor and some benign process. For example, the demonstration of kappa or lambda light-chain restriction by IHC is a good indicator of monoclonality in B-cell processes, and can help distinguish malignant lymphoma from an inflammatory process. In the prostate, loss of a basal cell layer, as indicated by the absence of high-molecular-weight cytokeratin and p63 immunostaining, helps to distinguish adenocarcinoma of the prostate from benign adenosis and other conditions that may mimic malignancy.[24,25] As our understanding of the molecular genetic basis of human tumors expands, antibodies to products of oncogenes and tumor-suppressor genes hold much promise in recognizing neoplastic processes.

What Type of Tumor Is It?

The most basic application of IHC is tumor classification. For tumors that show no specific differentiation at the light-microscopic level, IHC can make critical distinctions among epithelial, mesenchymal, lymphoid, melanocyctic, and germ cell neoplasms (Fig.16-1). Even for differentiated tumors, IHC provides a detailed phenotypic description that goes well beyond the resolution capabilities of the standard light microscope. In studies emphasizing the importance of second-opinion surgical pathology, the use of IHC has been identi-

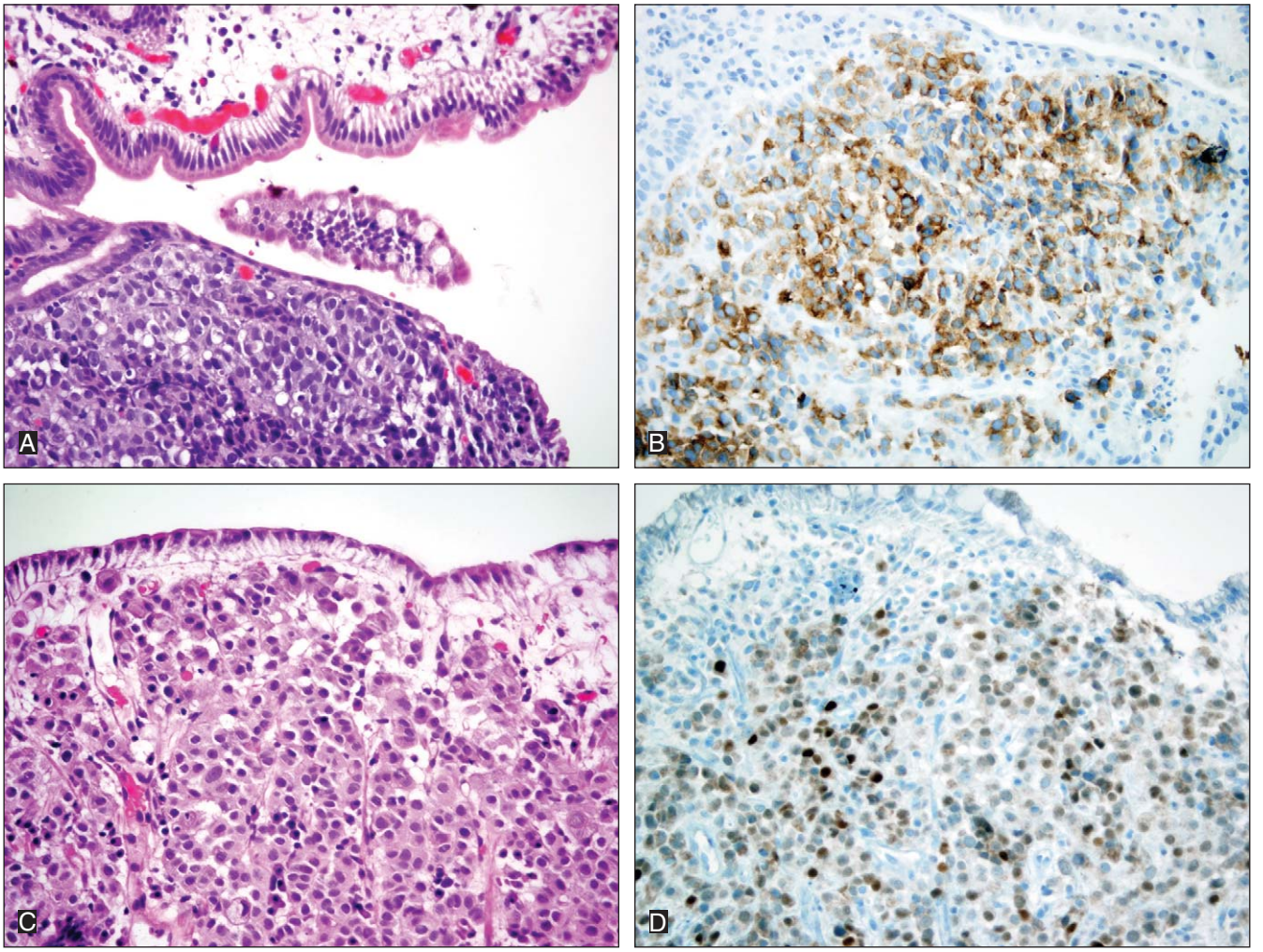


Figure 16-1 • Impact of immunohistochemistry on tumor classification. **A,** The small bowel biopsy shows sheets of histologically uniform epithelioid tumor cells in the lamina propria (H&E stain). **B,** Immunohistochemistry demonstrates that the tumor cells are diffusely positive for Melan-A, consistent with metastatic malignant melanoma. **C,** The gastric biopsy of another patient shows sheets of histologically similar-appearing tumor cells in the lamina propria (H&E stain). **D,** Immunohistochemistry demonstrates that the tumor cells are positive for estrogen receptors. The tumor cells are also positive for progesterone receptors, growth cystic fluid protein, and Her2/Neu, consistent with metastatic adenocarcinoma of the breast. In both examples, the differential diagnosis on H&E sections includes a primary or metastatic carcinoma and metastatic melanoma. The accurate diagnosis can be made easily if immunohistochemistry is used as an adjunct test.

fied as a key factor resulting in major therapeutic and prognostic modifications for patients sent to large referral hospitals for oncologic surgery.[26,27] Hematopathology is one example of a field that has become increasingly reliant on IHC, where the availability of antibodies to lineage-restricted antigens has made possible high-resolution and clinically relevant classification of hematolymphoid neoplasms.[28] IHC is having a similar impact on soft tissue sarcomas, primitive round blue cell tumors, and other areas of diagnostic pathology in which precise tumor classification is beyond the reach of conventional hematoxylin and eosin (H&E) histology.[29,30]

What Is the Tissue of Origin for the Tumor?

Expression of some markers is so highly tissue specific that a single IHC stain can establish the most likely primary site for a neoplasm of unknown origin. Most tumors, however, display a distinctive pattern of IHC staining against a selected array of antibody probes, a pattern sometimes referred to as an "immunohistochemical profile." For example, metastatic adenocarcinoma of the prostate may present as a tumor of unknown origin, and because most adenocarcinomas of the prostate are positive for prostate-specific membrane antigen (PSA) or prostein (p501s), prostatic origin can be readily identified by one or both of these markers in almost all cases.[31] In another application, the difficult distinction between malignant mesothelioma and peripheral lung adenocarcinoma is aided by unique IHC fingerprints when using a panel of antibody probes.[32] With the regular introduction of new antibodies into the diagnostic armamentarium, these profiles are becoming increasingly elaborate. Internet-accessible databases have become very useful in disseminating updated information regarding IHC profiles of various tumor types based on published data.[33]

Is There Evidence of Metastasis?

IHC can optimize detection of micrometastases when traditional microscopic examination is too crude to detect scattered individual tumor cells. Staining of sentinel lymph nodes with cytokeratin to detect metastatic breast carcinoma and melanocytic markers (e.g., Hmb-45, Melan-A) to detect metastatic melanoma is now used routinely for the accurate pathologic staging of regional lymph nodes.[34,35]

What Is the Prognosis?

IHC also can help to measure determinants of disease outcome. For various tumor types, a high proliferation rate portends aggressive tumor behavior and poor outcome. The traditional practice of counting mitotic figures as a crude measure of tumor proliferation is being replaced by more quantitative assessment of proliferation activity as measured by IHC detection of certain nuclear antigens that are expressed during stages of active cell division (e.g., Ki-67).[36] Perhaps more important, IHC can help predict tumor response to certain therapies. Detection of estrogen receptors, progesterone receptors, and HER-2/neu has direct and immediate therapeutic implications for breast cancer treatment, as do prognostic indicators that now are routinely incorporated into surgical pathology reports of all invasive breast carcinomas.[37,38] A wave of new antibody probes against oncogene products, tumor-suppressor gene products, and various cell cycle signaling proteins (e.g., activated kinases) may help individualize treatment regimens based on specific expression profiles.[39] However, the application of these markers to prognosis will require standardized technical protocols, defined cutoff values for positive results, and clinical validation studies with uniform treatment arms and adequate follow-up.[40]

FINE-NEEDLE ASPIRATION

In contrast to tissue histopathology with its strong reliance on architectural patterns of tumor growth, cytopathology extracts diagnostic information from the appearance of individual cells and cell clusters. Although its use has surged over the last two decades, cytopathology is hardly a new technique. Indeed, attempts to define distinctions between benign and malignant cells scraped from the surfaces of tumors constitute the origin, not the pinnacle, of contemporary diagnostic pathology.[3] George Papanicolaou (1883–1962) usually is credited with the rediscovery of cytopathologic examination. He not only demonstrated its value regarding diagnostic accuracy, but he launched its routine use as a highly effective means of reducing cancer-related morbidity and mortality.

Fine-needle aspiration (FNA) uses a fine-gauge needle to remove cells from a suggestive mass for microscopic examination. Its primary role is to guide treatment decisions, and in this role, FNA offers several significant advantages over the frozen section:

- It provides a preoperative rather than intraoperative diagnosis. Some researchers estimate that up to 80% of all thyroid surgery can be avoided by routinely aspirating thyroid nodules.[41]
- It is cost-effective. FNA is a simple technique that is inherently economical and often circumvents the need for a much more costly surgical intervention.
- It is safe. FNA eliminates the need for general anesthesia and minimizes the risk of complications associated with more invasive procedures for tumor acquisition.

With notable exceptions (e.g., testicular masses, ovarian masses, primary malignant melanomas), FNA is no longer believed to facilitate tumor spread or induce severe hemorrhage, an occasional complication of larger-bore needles.[42]

Although reported accuracy rates for FNA range from 90% to 99%, divergent opinions persist about its reliability and its role in clinical management. Most authorities, however, would accept the following generalities:[43]

- Accuracy is related to the site and nature of the neoplasm. FNA is not very useful in those situations in which tumor classification depends less on cytologic features and more on architectural patterns, such as locally invasive tumor growth. When dealing with encapsulated neoplasms of the thyroid, for example, FNA is notoriously inaccurate in separating follicular adenomas from follicular carcinomas, because a diagnosis of malignancy is contingent on the histologic demonstration of tumor invasion.
- Accuracy is related to the scope of the clinical question. FNA is highly reliable when grappling with broad distinctions (e.g., presence of tumor vs. absence of tumor, inflammatory process vs. neoplastic process, benign tumor vs. malignant tumor), but accuracy diminishes for precise tumor subclassification. Moreover, largely due to the impact of limited tumor sampling by FNA, a malignant tumor is more likely to be misdiagnosed as benign (i.e., false-negative result) than a benign tumor is to be misdiagnosed as malignant (i.e., false-positive result).
- Accuracy is related to the experience of the cytopathologist and the quality of the slide preparations, which, in turn, depends on the experience of the aspirator. Under ideal conditions the aspiration is performed by a cytopathologist trained to do fine-needle aspirations or, alternatively, in the presence of a cytopathologist, thus allowing an immediate assessment of the quality and quantity of the aspirate. Because of the combined impact of these factors, FNA is best used as an adjunctive diagnostic tool. It should complement, not supplant, the clinical, radiographic, and laboratory findings.

FUTURE DIRECTIONS

Breakneck developments in molecular biology, biotechnology, and bioinformatics are driving a molecular revolution in pathology. Contemporary research resulting in the identification of thousands of new genes and providing insight into the function and complex interaction of these genes will present the pathologist with new opportunities for solving old diagnostic problems. The technologic

armamentarium of the surgical pathologist, once reliant solely on the light microscope to detect phenotypic alterations, now includes sophisticated tools to isolate and compare single cell populations in a tumor and to detect submicroscopic alterations in gene integrity, gene expression, and gene translation.[44,45]

The direct application of molecular techniques to diagnostic oncologic pathology has just begun, but as discussed in subsequent sections, a growing number of examples bolster the bold claims that molecular analysis will profoundly aid the diagnosis, prognosis, and treatment of tumors. For hematologic neoplasms, delineation of various chromosomal translocations has allowed more clinically relevant classification of leukemias and lymphomas.[46,47] Genetic analysis is having a similar impact on soft tissue tumors, as detection of tumor-specific translocations can be essential to classify these neoplasms.[48] Increased access to detailed genetic information also will provide a clearer picture of patient outcome and help individualize treatment plans. For hematopoietic neoplasms, detection of specific translocations already provides prognostic information independent of morphologic and immunophenotypic characterization. Moreover, the products of these transforming genes provide attractive targets for promising new therapeutic agents.

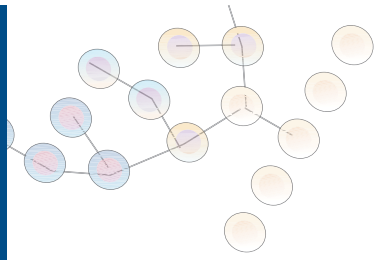
For sporadic epithelial neoplasms, the molecular genetic makeup of a tumor is not currently integrated into the inventory of more classic prognostic and predictive determinants. Efforts to do so have been stalled by the number and complexity of genetic alterations, the absence of standardized methods to measure and interpret test results, the high cost and limited availability of the technology, and the absence of well-designed clinical studies to assess clinical utility.[49] The application of such techniques is well appreciated in breast cancer, for which quantitative measures of hormone-receptor expression and HER-2/neu gene amplification now are routinely incorporated to assess outcome and guide therapy. These applications in breast cancer forecast a coming era when pharmacologic and radiation sensitivity profiles based on molecular genetic alterations will permit customized treatment of individual patients.

The molecular revolution will enhance the role of the surgical pathologist in the multidisciplinary approach to the patient with cancer, but it will not replace it. Advances in basic tumor research depend on the involvement of well-trained pathologists, not only to characterize tumors accurately with respect to site of origin and pathologic grade but also to distinguish normal and neoplastic tissue, and identify subtle degrees of morphologic changes in an individual section. With all the developments of new technology and approaches, classic light microscopy remains the cornerstone of tumor diagnostics and the starting point for the application of any new prognostic or therapeutic marker.

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17 Flow Cytometry in Oncologic Diagnosis

Michael J. Borowitz

SUMMARY OF KEY POINTS

Key Methods
- Fluorescently conjugated antibodies, bound to cell-surface or intracellular proteins, allow enumeration and detailed characterization of subsets of cells in heterogeneous mixtures.
- Fluorescent DNA-binding dyes allow determination of tumor ploidy and can assess cell-cycle characteristics of tumors.

Applications

Acute Leukemia
- Used for lineage assignment and classification of leukemia
- Certain phenotypes correlate with molecular abnormalities.
- Minimal residual disease detection is prognostic in both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML).

Lymphoma and Chronic Lymphoproliferative Disorders
- Suitable for use on cell suspensions of tissue, fine-needle aspirates, fluids, and blood and marrow.
- Clonality of B-cell processes readily detected by light-chain restriction assay.
- Many lymphoid disorders are defined by phenotypic profiles.

Solid Tumors
- DNA ploidy and S-phase fraction can be detected.
- Prognostic significance is controversial, but measurement has value in certain tumors.
- Methodologic difficulties have contributed to lack of acceptance.

INTRODUCTION

Flow cytometry is used to study attributes of individual cells in a suspension. Over the past two decades, flow cytometry has become increasingly sophisticated; high-speed sorters and analyzers capable of detecting more than a dozen colors simultaneously have kept flow cytometry in the forefront as a tool for the fundamental investigation into cancer. At the same time, flow cytometry has matured from a research technology to one that is part of the routine clinical laboratory. This chapter focuses on diagnostic aspects of flow cytometry.

METHODS

A flow cytometer analyzes large numbers of cells one at a time, making it an ideal tool for examination of the properties of populations of cells. It is complementary to imaging: although it does not provide as much detail about individual cells, it provides much better statistical measurements, and is able to characterize different groups of cells in heterogeneous mixtures. It also can physically sort specifc subpopulations of cells. Although a detailed discussion of the workings of a flow cytometer is outside the scope of this chapter, the chapter begins with a discussion of a few general principles.

Functional Components

A flow cytometer has three separate components: a fluidics system; an optical platform; and signal-processing electronics. The fluidic system aspirates the sample, mixes it with a sheath fluid to produce laminar flow, and conducts the cell suspension past the sensing zone where individual cells are examined. The optical platform consists of the laser light source(s), lenses to focus the light on the passing cell stream, band-pass filters to capture light of restricted wavelengths, and photomultiplier tubes (PMTs) that capture the emitted signals. The electronics convert photons to electrical signals in proportion to the total light contacting the PMTs, and amplify and scale the signals so that data can be readily analyzed. The value of each collected parameter is "quantitized" and assigned to a particular channel. Higher channels reflect brighter signals. Current software packages reprocess collected data electronically in a variety of formats; this flexibility of data analysis is a critical part of what makes this technology useful.

Electronically reprocessed data are displayed by software programs in the form of dot plots or histograms. The most useful displays usually correlate one parameter with another, with each dot representing a single event (i.e., cell) with the x- and y-channel values for the two chosen parameters. In addition to fluorescence, forward scatter and right-angle or side scatter can be displayed. Forward scatter is roughly proportional to the size of the cells, whereas side scatter is a measure of internal cellular complexity, which for hematopoietic cells usually means granularity. Typically, dot plots of either forward versus side scatter, or scatter versus fluorescence, are used to identify populations of interest in a process called *gating*, and additional displays show additional fluorescence or scatter characteristics of these populations. Because scatter measurements are made parallel to, and independent of, the fluorescence measurements, four-color flow cytometry, for example, is equivalent to six-parameter cytometry. The term *multiparameter flow cytometry* typically is used to define simultaneous analysis of five or more parameters on individual cells.

Fluorochromes and Fluorescence

Fluorochromes have spectral characteristics that allow them to absorb light of certain wavelengths and then to emit light at longer

wavelengths. Emission, a specific characteristic of the compound, is not limited to a fixed wavelength, but, rather, constitutes a spectrum, with variable numbers of photons emitted at different wavelengths. Different fluorochromes, including fluorescein isothiocyanate (FITC) and phycoerythrin (PE) as well as others, all have the capacity of absorbing light at 488 nm but emit it at different wavelengths, thereby making it possible to perform multicolor flow cytometry with a single laser emitting at 488 nm. Tandem conjugates, which covalently couple two fluorochrome molecules, allow emitted light to be transferred from one molecule to the other and can greatly increase the number of colors that can be detected with a single laser. Additional dyes such as allophycocyanin, which emit longer wavelengths, cannot be excited by a 488-nm laser but require a second light source, most frequently one emitting light at 635 nm. The combination of new dyes, more tandem conjugates, and new instruments with even more lasers has made it possible to perform flow cytometry to detect more than a dozen colors, and 6- or even 8- to 10-color flow cytometry is now being performed routinely in clinical laboratories.

APPLICATIONS OF FLOW CYTOMETRY TO CLINICAL ONCOLOGY

Flow cytometry plays a significant role in the diagnosis, classification, and management of patients with acute leukemia, chronic lymphoproliferative disorders, and non-Hodgkin's lymphoma. The early promise of this technology in the management of patients with solid tumors has not been completely realized, but it still plays a role in certain areas.

Acute Leukemia

Flow-cytometric immunophenotyping has become standard in the evaluation of new patients with acute leukemia. The most obvious role of flow cytometry is in distinguishing lymphoid from myeloid leukemia, but flow cytometry can help in the diagnosis and management of these patients in many ways (Box 17-1).

Lineage Assignment in Acute Leukemia

Phenotypic analysis of a bone marrow that is completely replaced by blasts is an almost elementary problem. Multiparameter flow cytometry, however, can dissect and categorize all populations in bone marrow, and, most important, can distinguish leukemic cells from normal, even when the leukemic cells are not the majority population. The antibody panel used to study patients with acute leukemia typically contains representative markers of all lineages, with some redundancy to allow recognition and classifcation because many antigens may be aberrantly lost or acquired in leukemic cells.[1,2] No standard combinations of antibodies are used by all laboratories, but certain combinations have proved particularly useful not only for the most economical classification of leukemia, but also for their ability to demonstrate characteristic aberrant patterns that may be extremely useful for the detection of residual disease in follow-up samples, as discussed later in this chapter.

Diffculties encountered in the interpretation of flow cytometry data derive largely from two problems. First, in cases in which leukemic cells are not an obviously dominant population, it is important to ensure that the cells of interest are analyzed. The most useful general approach for this takes advantage of the fact that the common leukocyte antigen CD45 is differentially expressed on different types of hematopoietic cells, and, when combined with side scatter, produces a display in which blasts occupy a unique position not occupied by normal cells (Fig. 17-1).[3] Thus,combining CD45 in one color with multiple combinations of antibodies in additional colors allows detailed characterization of blast populations in marrow even when they are present only in low numbers.

Failure to select the leukemic cell population for analysis, or including a mixture of leukemic and normal cells in a gate, may cause confusion in the reporting of flow cytometry results. It is best to identify the leukemic population visually and to provide a detailed description of the antigens expressed on the leukemic population, especially in myeloid leukemias, in which the dynamic patterns of maturation associated with morphologic variation in AML are

Box 17-1. APPLICATIONS OF FLOW CYTOMETRY IN HEMATOLOGIC NEOPLASIA

Acute Leukemia

Distinction of myeloid and lymphoid leukemia
Distinction of T-ALL from precursor B-ALL
Subclassification of lymphoid and myeloid leukemia
Identification of phenotypes associated with characteristic molecular and cytogenetic abnormalities
Identification, enumeration, and characterization of blasts in heterogeneous samples
Identification of abnormal phenotypes for purposes of monitoring patients after therapy (minimal residual disease)
Identification of hyperdiploidy in pediatric ALL
Identification of abnormal patterns of myeloid maturation in myelodysplastic syndromes

Lymphoma and Lymphoproliferative Disorders

Identification of clonal B-cell proliferations
Subclassification of B-cell lymphomas and leukemias
  Diagnosis of chronic lymphocytic leukemia
  Diagnosis of hairy cell leukemia
  Identification of characteristic phenotypes in other lymphomas
Prognosis of CLL (CD38 and ZAP 70 expression)
Identification of phenotypically abnormal T cells
Subclassification of T-cell lymphoproliferative disorders
Diagnosis of plasma cell dyscrasias
Identification of abnormal phenotypes for purposes of monitoring patients after therapy (minimal residual disease)

ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia.

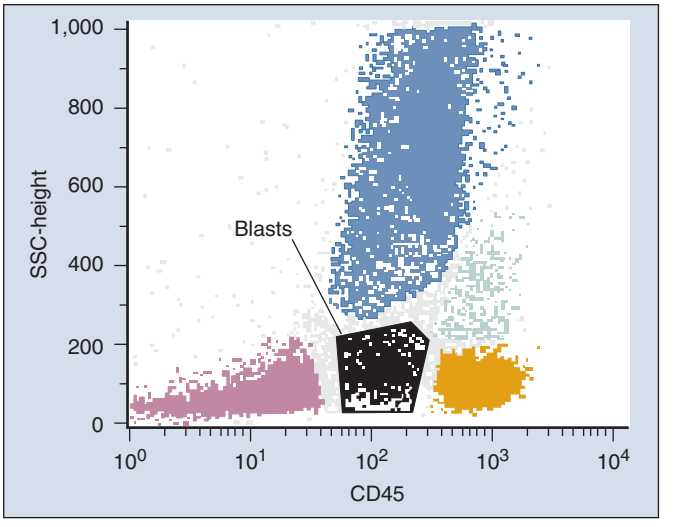


Figure 17-1 • CD45 gating in acute leukemia. Dual-parameter display of CD45 and side scatter of bone marrow containing increased blasts. These two parameters can readily separate lymphocytes (*yellow*), granulocytes (*blue*), monocytes (*light blue*), and nucleated red cells (*pink*). In normal marrow, a "hole" is found with few events in the low side scatter (SSC)/intermediate CD45 region, but in this case a distinct population can be identified. This distinction allows gating and analysis of antigen expression on just the blast population.

reflected in changes in both light scatter and antigen expression as the leukemic cells mature. Tabular arrays of "percentage positive" are not recommended as part of a flow cytometry report, because they cannot reflect this complexity and may cause confusion.[4]

The second problem in interpreting flow cytometry results in leukemia derives from the fact that most of the reagents used in classifying leukemia are only relatively rather than absolutely specific. Thus, correct classification requires not only a panel with some redundancy, but also an understanding of patterns of reactivity of the antibodies. Markers such as CD13 and CD33, which are considered *myeloid antigens* because they originally were produced against myeloid leukemia cells, are found in up to 50% of cases of lymphoid leukemia,[5] and interpretation of leukemias positive for these markers continues to be a cause of confusion. Generally speaking, the most specific markers of a given lineage are not highly sensitive, and the most sensitive ones are not specific. This is true more of myeloid markers than of lymphoid markers, so that lymphoid leukemias usually can be recognized precisely, whereas poorly differentiated myeloid leukemias usually are defined by the presence of myeloid markers in the absence of specific lymphoid antigens.

Acute Leukemias of Indeterminate or Ambiguous Lineage

Although almost all cases of acute leukemia can be categorized easily regarding lineage, the lack of absolute specificity of most markers, and the promiscuity of their expression, implies that some cases cannot be resolved easily. Unfortunately, considerable controversy exists about the use of the terms *mixed lineage* and *biphenotypic leukemia*. Leukemias that express myeloid- and lymphoid-associated markers in combination represent a heterogeneous group of diseases. A scoring system has been proposed[6] that assigns various point values to different antigens, with a diagnosis of "biphenotypic leukemia" rendered if the score is high for more than one lineage. Although this is an objective method of defining lineage, it mixes different kinds of cases with different molecular abnormalities. The scoring system as originally conceived also does not distinguish between cases in which blasts coexpress antigens of different lineages and those in which there are distinct leukemic blast populations. The latter situation is much less common, but can be thought of properly as true mixed-lineage leukemia. Certain of these, such as the combination of B-precursor ALL and AML in patients with the Philadelphia chromosome, represent distinct entities.

Association of Immunophenotype and Molecular Abnormalities

Many phenotypes in both ALL and AML are highly associated with characteristic cytogenetic abnormalities.[7] In ALL, these include cases associated with MLL rearrangements, TEL-AML1 or E2A-PBX1. In AML, the most important link is in promyelocytic leukemia with the t(15;17). Whereas lack of HLA-DR is the best-known abnormality, only about half of cases of DR-negative AMLs turn out to be acute promyleocytic leukemia (APL), and other combinations of marker expression are much more sensitive and specific for APL.[8] AML associated with the t(8;21) also shows a characteristic phenotype.[9]

Minimal Residual Disease Detection in Acute Leukemia

Several recent studies have demonstrated that the presence of residual leukemic cells in the marrow of patients in clinical and morphologic remission is a very strong adverse prognostic factor.[10–16] Although the most extensive data exist in childhood ALL,[10–12] the principle has also been shown to apply to adult ALL[13] and to AML.[14–16]

Both molecular and flow-based methods have been used to detect minimal residual disease (MRD). Flow-based assays of MRD are based on the principle that nearly all leukemias show a pattern of expression of antigens that is aberrant compared with the pattern seen in normal differentiation.[10–15] This aberrancy can take several forms. Some leukemic cells can abnormally express antigens of a different lineage or show loss of expression of a normal lineage marker. A more common finding is expression of normal differentiation antigens, but at an intensity that is different from that expected for a particular stage of differentiation. This latter attribute makes flow MRD analysis applicable to most cases of leukemia. Nonetheless, recognizing these deviations requires a clear understanding of patterns of maturation in normal differentiation, including marrow regeneration, as viewed in multiparameter space.

The pattern of antigen acquisition and loss during B-cell maturation in the bone marrow has been very well characterized, and certain markers are particularly useful for distinguishing normal and leukemic maturation. Consideration of markers including intensity of CD45, CD34, CD10, CD58 and CD38 or aberrant coexpression of myeloid or other unexpected antigens can allow detection of as few as 1 in 10^4 leukemic cells, even when normal B-cell precursors are present in significant numbers (Fig. 17-2). Marrow T-ALL can also be distinguished from normal T cells, most readily by coexpression of cytoplasmic CD3 and TdT, which is never seen on any normal cell.[10] Detection of myeloid MRD usually is a more elaborate process because of the greater phenotypic heterogeneity in AML. Certain aberrant combinations, including coexpression of CD34 and CD56, CD117 and CD15, or CD7 and myeloid antigens occur with sufficient frequency to be useful in a large number of cases.[14–16] To achieve 10^{-4} sensitivity in essentially all cases may require design of custom panels unique to a particular leukemia. Because abnormal populations at diagnosis may not persist at recurrence, monitoring patients with acute leukemia requires following more than one aberrant phenotype.

Myelodysplasia and Chronic Myeloproliferative Disorders

Recently it has become apparent that flow cytometry can detect abnormalities in marrow disorders other than acute leukemia. Patients with chronic myeloproliferative disorders invariably show abnormalities in either blast phenotype or maturation pattern,[17] although routine clinical phenotyping of MPDs is not performed in most cases. Interest in using flow cytometry as a primary diagnostic modality in myelodysplastic syndromes is increasing. In addition to finding phenotypically abnormal blasts, many studies have demonstrated characteristic phenotypic abnormalities in either myeloid or erythroid maturation in myelodysplastic syndrome (MDS), as well as describing abnormalities in granulocyte light scatter that correspond to the morphologic finding of hypogranularity.[18–20] Although a scoring system has been proposed to use flow cytometric characteristics to diagnose MDS,[20] the sensitivity and specificity of these findings have not been rigidly established, and it is not clear whether flow cytometry significantly improves the accurate diagnosis of early MDS. Nevertheless, it is clear that the technique can add useful adjunctive information to the diagnosis and possibly the prognosis of MDS.

Chronic Lymphoproliferative Disorders and Lymphoma

Lymphoid Tissue Analysis

Flow-cytometric immunophenotyping plays a major role in the evaluation of a patient with lymphoma (see Box 17-1).[21–23] Lymphoid tissue first must be disaggregated to produce a cell suspension suitable for flow-cytometric analysis. Although this is readily accomplished in most low-grade lymphomas, high-grade lymphomas may give a nonrepresentative sample because of the greater fragility of the neoplastic cells compared with residual normal cells. Fibrosis also may make disaggregation difficult or result in disruption of neoplastic cells. Consequently, flow-cytometric analysis of lymphoma requires careful gating to ensure that the cells of interest are analyzed.

In contrast to the situation with acute leukemias, no single antibody serves as a useful surrogate for the neoplastic population. However, in B-cell malignancies, neoplastic B cells usually greatly outnumber normal cells (although there may be normal T cells), so

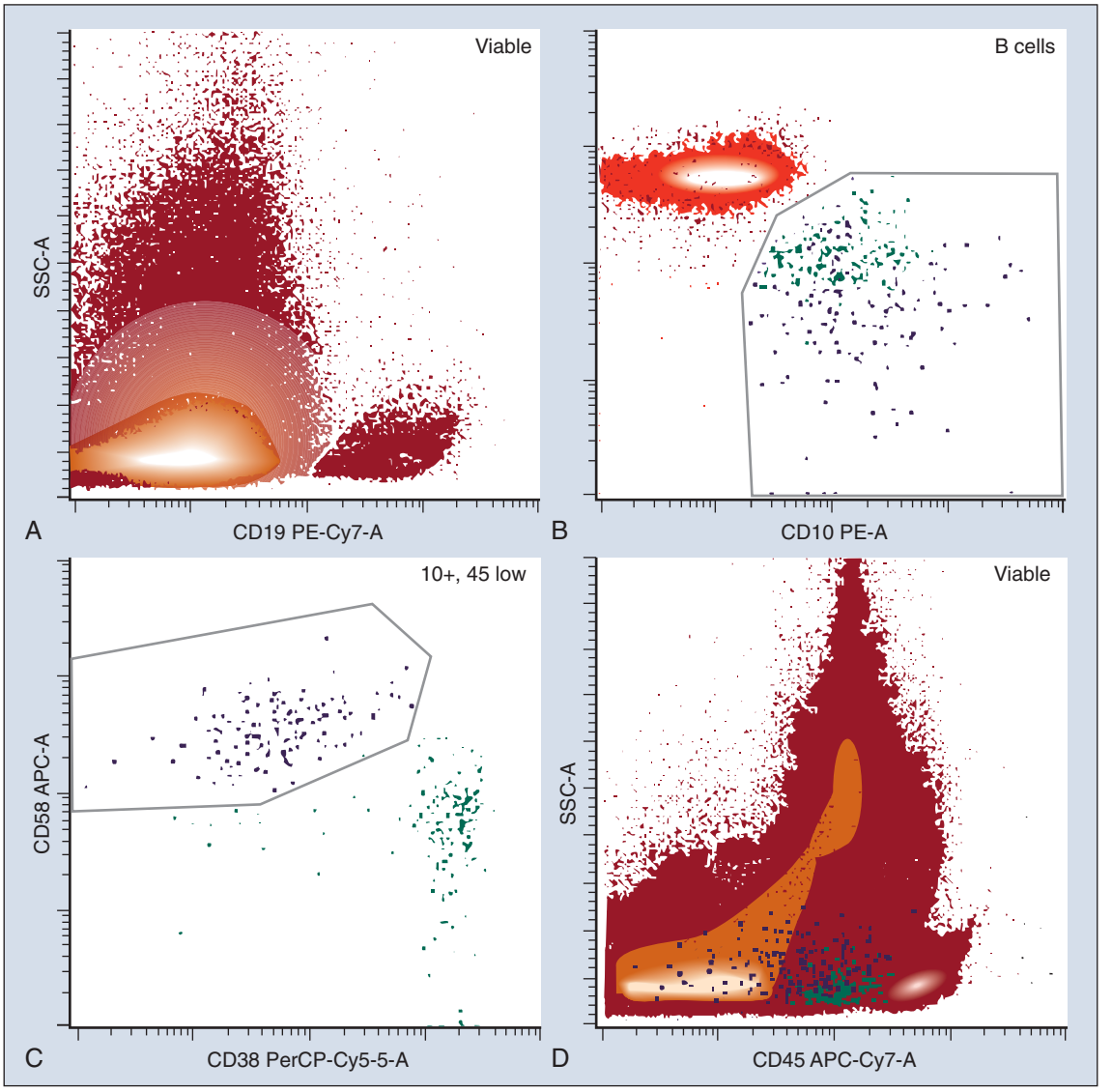


Figure 17-2 • Minimal residual disease detection in acute lymphoblastic leukemia. Normal B cells have a fixed pattern of expression of different antigens as they mature. Leukemic cells depart from this normal pattern. In this case, an end induction marrow was stained by 6-color flow cytometry with the combination CD20-FITC/CD10-PE/CD38-PerCPCy5.5/CD58-APC/CD19-PE-Cy7/CD45-APCCy7, and the abnormal population revealed by sequential gating. Only selected correlated antigens are displayed. **A,** CD19+ B cells are gated, so that the great majority of the 750,000 events collected are not displayed (**B,** which only shows B cells). CD45-low, CD10+ cells are gated and displayed in the next panel. **C,** Normal B cell precursors (*green*) are recognized because they have relatively bright CD38 and relatively dim CD58, while the leukemic cells (*blue*) are bright 58 and dim 38. **D,** The few leukemic cells are superimposed on a CD45 vs SSC display of the entire sample. MRD accounted for 0.02% of the total cells.

that use of a pan-B-cell antibody such as CD19 or CD20 can help to isolate the neoplastic cells for analysis. In addition, forward scatter, as a marker of cell size, may be a very useful parameter to help distinguish frequently larger neoplastic cells from smaller normal counterparts.

Although some laboratories prefer tissue immunohistochemistry to flow cytometry for phenotyping lymphomas, the two techniques are complementary. The principle advantages of flow cytometry relate to its speed and its ability to identify and phenotype precisely the neoplastic elements in a heterogeneous sample. A complete phenotypic characterization, and, in many cases, a diagnosis can be achieved within a few hours from the time of biopsy, rather than the several days needed for histopathologic examination and immunostaining. Flow cytometry also is far better than immunohistochemistry for demonstrating light-chain restriction, and therefore clonality, in B-cell neoplasms.

The disadvantages of flow cytometry come from the architectural disruption created by making a cell suspension and the aforementioned possible loss of cells of interest. Hodgkin's lymphoma, in particular, is not diagnosed by routine flow cytometry, although recent studies have demonstrated that careful attention to the procedures used for phenotyping can overcome this drawback.[24] Even in non-Hodgkin's lymphoma, grading may be difficult from flow-cytometric immunophenotyping alone, and precise classification can be accomplished only rarely; lymphoma classification still relies heavily on morphology, and this must be correlated with flow-cytometric information.

Classification of lymphoma and grading, in particular, can be improved by assessment of DNA content by flow cytometry (as discussed later in this chapter), because S-phase fraction is closely correlated with grade. Burkitt's lymphoma, which has the highest S

fraction of any neoplasm, usually can be reliably identifed by flow cytometry. However, in lesions such as follicular lymphoma, grading systems still are based on morphologic criteria, and although there may be reason to expect that flow-based methods might be more objective, these have not been validated in large series to the point at which they are generally accepted.

One of the most fruitful applications of flow cytometry in the diagnosis of lymphoma is in the analysis of specimens from fine-needle aspiration (FNA).[25,26] Cells obtained by FNA already are in suspension, and flow-cytometric analysis contributes significantly to the cytopathologic diagnosis of lymphoma, which is notoriously difficult. Although FNA has been used for years in the evaluation of recurrent adenopathy in patients with known lymphoma, it can serve as a primary diagnostic modality in lymphoma when combined with flow cytometry. Most non-Hodgkin's lymphomas can be recognized and graded, and, importantly, lymphomas also can usually be excluded. Optimal application of this technology, however, requires close collaboration between the cytopathologist and flow cytometrist, a clear understanding of the strengths and limitations of the two techniques, and a willingness to revert to open biopsy in ambiguous cases.

Blood and Marrow Analysis

Limitations attendant on generating cell suspensions do not apply to patients with blood or marrow involvement by chronic lymphoproliferative disorders. Subclassification of these lesions relies heavily on flow cytometry.[21,23,27–29] Chronic lymphocytic leukemia (CLL) is essentially defined by its immunophenotypic characteristics. Other B-cell lymphoproliferative disorders have characteristic, if not always absolutely specific, phenotypes.[21,23,27,28,30] Mantle cell lymphoma often can be recognized in its leukemic phase, although the most specific marker, cyclin D1, is very difficult to detect by flow with current techniques. Hairy cell leukemia, conversely, has not only a characteristic but also a highly specific phenotype[23,31]; occasionally patients with unexplained pancytopenia can be determined to have hairy cell leukemia when only a tiny number of blood cells with the classic phenotype are identified[31] (Fig. 17-3).

Recently, considerable attention has been paid to the use of flow cytometry to detect prognostic factors in CLL. Recognizing that CLL can be subdivided into a poor-prognosis type associated with nonmutated immunoglobulin V region genes and a better-prognosis mutated phenotype, several studies have attempted to identify flow surrogates. The first marker found to be prognostic was CD38, although the correlation with either mutational status or prognosis is imperfect.[32–34] Zeta-chain-associated protein kinase 70 (ZAP 70) appears to be a much better surrogate marker for either prognostication or V-region status.[35–37] However, even though this assay is widely available, particularly in commercial reference laboratories, there can be significant variability in how the assay is performed,[38,39] so that it is not always certain that a commercially available assay is the same as that in the published literature. For this reason, many researchers recommend caution in interpreting these results. Other attempts have been made to define prognostically significant subsets of patients with CLL using other combinations of markers,[40] but these have not been adopted in routine practice.

The primary value of flow cytometry in chronic leukemias is its ability to demonstrate clonality in B-cell populations, based on restricted expression of one type of immunoglobulin light chain.[21–23] This feature is particularly valuable in the evaluation of patients with unexplained lymphocytosis[41,42] and also is useful for staging patients with B-cell non-Hodgkin's lymphoma,[43,44] because the presence of as little as 0.5% to 1% of a clonal B-cell population, or even less, can be demonstrated in the marrow or blood of some patients. The high sensitivity of flow cytometry for detecting clonal populations has, however, demonstrated small clonal B-cell populations in some patients without obvious lymphoma or leukemia.[45] Thus, the finding of a small marrow clone, in the absence of other evidence of lymphoma, should be interpreted with caution, analogous to finding a monoclonal gammopathy in a patient without evidence of myeloma.

Some controversy exists about the applicability of flow cytometry to patients with myeloma. Whereas plasma cells have a characteristic phenotype, including very bright expression of CD38 and expression of CD138,[46,47] plasma cells are underrepresented on marrow aspirates studied by flow compared with the prevalence of cells on films or in biopsies. Nevertheless, the unique phenotype of plasma cells makes them easy to recognize, and with the use of membrane-permeabilization techniques, it is easy to demonstrate cytoplasmic immunoglob-

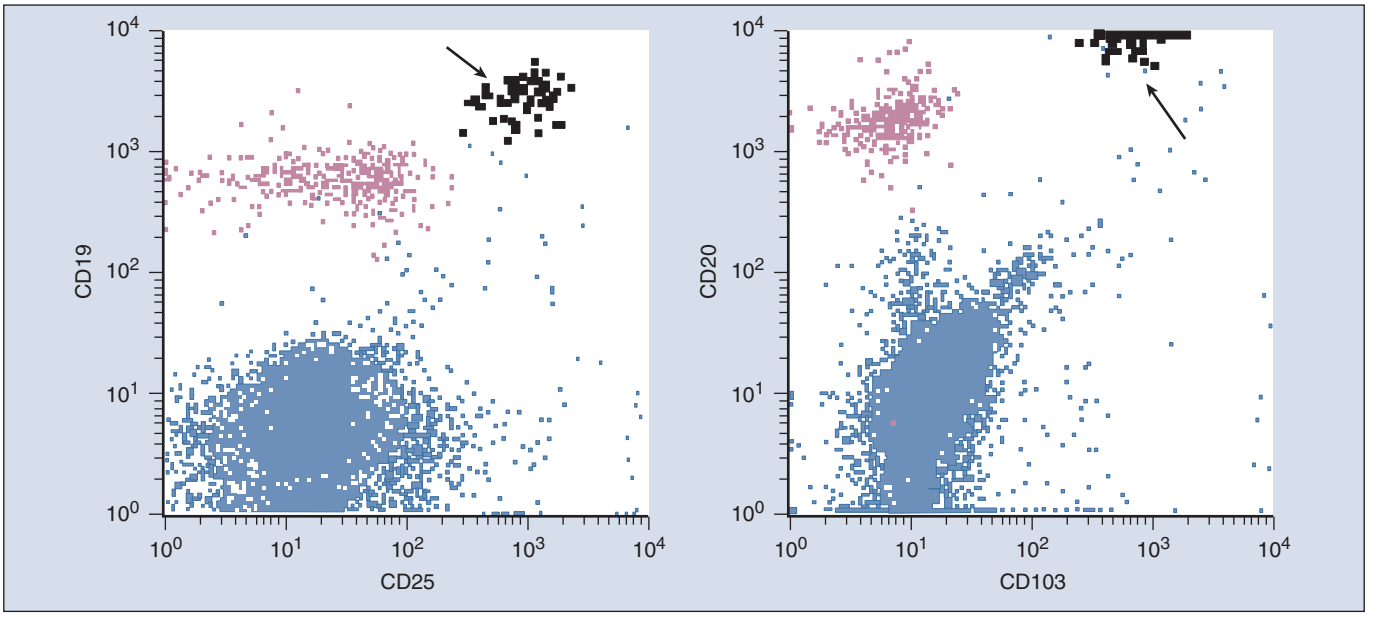


Figure 17-3 • Flow-cytometric detection of hairy cell leukemia. A small population (*arrows*) accounts for less than 1% of this peripheral blood sample and can readily be recognized. Expression of CD19 and CD20 is brighter than the background normal B cells (*blue*), and the abnormal cells also express CD103 and CD25.

ulin (Ig) light-chain restriction.[47] It is of more significance that neoplastic plasma cells usually have abnormal phenotypes. Although no single specific phenotypic abnormality permits distinction between benign monoclonal gammopathy and myeloma, the relative proportion of abnormal versus normal plasma cells has been suggested to be a predictor of behavior.[48] Moreover, flow cytometric detection of circulating plasma cells or persistence of an abnormal phenotype after therapy is predictive of outcome in patients with myeloma.[49–52]

Clonality of T cell populations also can be demonstrated by flow cytometry, although the method is more complex and is not as widely available as that used for B cells. This technique is based on demonstration of restriction of V-beta gene use in T-cell leukemias.[53,54] T-cell malignancies also often show abnormal T-cell phenotypes, most often characterized by loss of a normal pan-T antigen, or expression of a T-cell antigen at abnormal intensity.[55,56] Because certain small, unusual, and even clonal T-cell populations may be seen in small numbers in non-neoplastic conditions, this technique has more limited sensitivity than demonstration of a clonal B-cell population. However, when abnormal T cells account for more than a very small percentage of cells, multiparameter flow cytometry easily demonstrates them and plays a significant role in categorizing these uncommon tumors.

Residual Disease Detection in Chronic Lymphoproliferative Disorders

As with acute leukemia, MRD can be detected by flow cytometry in chronic lymphoproliferative disorders. The most work has been done with CLL. Although detection of light-chain-restricted clones is difficult when the level is much below 0.1%, aberrant phenotypes that allow detection with a sensitivity of at least 1 in 10^{-4} can be detected in most cases of CLL.[57,58] Just as in acute leukemia, the presence of MRD in patients considered to be in remission by standard criteria is associated with an adverse prognosis,[58] whereas clearance of MRD after therapy is associated with a good outcome.[59]

Solid Tumors: Analysis for DNA Content

Numerous fluorescent dyes bind stoichiometrically to cellular DNA and thus can provide an accurate assessment of DNA content of cells. In a single-parameter fluorescence histogram, tumors with abnormal numbers of chromosomes show a distinct peak separate from the normal G_0/G_1 peak of diploid cells. Such tumors are referred to as *aneuploid*. Moreover, cells progressing through the cell cycle show incrementally increased levels of DNA while they are in S phase, and those in G_2 or in mitosis show exactly twice the amount of DNA as that represented by the G_0/G_1 population. Thus, integration of the area under the curve between the G_0/G_1 and G_2/M peaks gives the proportion of cells in S phase, commonly referred to as *S-phase fraction*. A variety of software packages are available to calculate S-phase fraction from these histograms.

DNA content analysis in tumors was one of the earliest applications of flow cytometry in tumors. Many studies have attempted to define the prognostic significance of either ploidy or S-phase fraction in a large number of different solid tumors. This proliferation of studies was made possible by the finding that fixed, paraffin-embedded tissue sections could be used for DNA analysis by flow, which resulted in many retrospective studies on archival material for which outcome was already known.[60] However, the literature is confusing and contradictory, and the early promise of this measurement as an important diagnostic and prognostic marker in cancer has not been realized. Although some studies have demonstrated prognostic significance to measurements of ploidy, and especially S-phase fraction in a number of tumors—most specifically bladder, prostate, and breast cancer—many studies conflict, with the result that this technology has not been widely embraced in clinical oncology. In some practices, it is used occasionally to help manage certain subgroups of patients with some cancers. For example, some practices use S-phase fraction to help manage patients with early-stage, node-negative breast cancer, whereas others use ploidy of superficial bladder cancers to help identify patients whose tumors might progress. One reason for the lack of acceptance of this measurement is the difficulties that have been encountered in standardization. S-phase fraction, in particular, has shown very poor interlaboratory reproducibility.[61] The ultimate effect of these technical problems is that it is very difficult for an individual laboratory to offer clinicians a test result that helps them decide how to manage a particular patient. The inability of this technology to make significant inroads in the clinic is unfortunate, because some more recent studies, by using highly sophisticated analytic methods, suggest that in breast cancer, at least, both ploidy and S-phase fraction are powerful independent prognostic markers.[62] A detailed summary of all the controversies is outside the scope of this chapter, but several reviews have been published.[63,64]

FUTURE OF FLOW CYTOMETRY IN CLINICAL ONCOLOGY

Flow cytometry in the clinical laboratory is at something of a crossroads. On the one hand, improvements in standardization and the technology itself have made it possible to develop easy-to-operate instruments that fit well with the model of the clinical laboratory. On the other hand, with the notable exception of MRD assessment, no significant growth has occurred in the applicability of this technology to cancer. Empirical classification of leukemia and lymphoma with new markers has not, in general, been fruitful. At the same time, technologic advances in cancer diagnosis currently seem to be focusing on methods of assessing genetic lesions in cancer. However, although genetic abnormalities clearly produce cancer, they do so through production of abnormal proteins, and detection of a number of different proteins in specific cell populations is what flow cytometry does best.

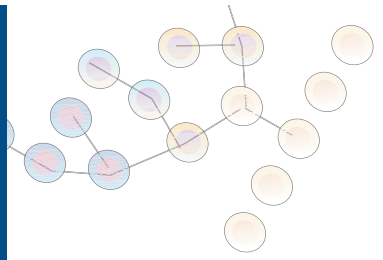
Thus it would appear that flow cytometry is well suited to validate, and to translate into clinical practice, many of the exciting findings that derive from genomics. One of the areas that has seen significant attention is the flow cytometric detection of phosphorylated signaling molecules. These studies have greatly added to our understanding of the operation of signaling pathways,[65] can be used to demonstrate alterations in signaling in leukemia, and are ideally suited to use as surrogate markers to validate the action of new drugs.[66,67] While these measurements have not yet been incorporated into routine clinical practice, they are already being used in clinical trials,[68] and it is likely that the most robust and informative of them will soon find their way into the routine laboratory.

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18 Conventional and Molecular Cytogenetics of Neoplasia

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SUMMARY OF KEY POINTS

Key Methods

- Conventional cytogenetic analysis uses chromosome banding to analyze structural and numeric chromosomal aberrations; dividing cells are required.
- Molecular cytogenetic or fluorescence in situ hybridization (FISH) analysis complements and extends analysis for specific genetic aberrations; viable tumor is not required.
- Additional methods include multiplex (M-FISH), spectral karyotyping (SKY), comparative genomic hybridization (CGH), and microarray-based CGH (aCGH).

Applications

Acute Leukemias

- Document clonal aberrations at diagnosis.
- Subclassify genetic types of leukemias; provide diagnostic, prognostic, and patient management information.
- Monitor response to therapy; assess disease progression.
- Monitor post-transplantation engraftment; detect minimal residual disease.

Lymphoma and Chronic Lymphoproliferative Disorders

- Subclassify lymphomas with specific translocations.
- Provide prognostic genetic information for lymphoproliferative disorders.
- Detect diagnostic translocations in many tissue types.

Solid Tumors

- Differentiate and subtype small round cell tumors; differentiate spindle cell tumors.
- Detect prognostic or therapy-specific genetic information in many solid tumors.
- Detect and assess gene amplification.

INTRODUCTION

Cytogenetic analysis uses tissue culture and specialized techniques to provide genetic information about cells and tissues. Cancer cytogenetic analysis focuses on defining the genetic aberrations of neoplastic tissues. As early as 1890, David von Hansemann speculated that the abnormal mitotic figures in cancer biopsies were important to the origin and development of malignancy, and in 1914, Theodor Boveri[1] published a systematic somatic mutation theory of cancer positing that chromosome abnormalities were responsible for cellular changes that caused normal cells to become malignant. However, it was not until the 1960s that the first nonrandom chromosome abnormality was associated with a particular neoplastic disorder.

In 1960, Nowell and Hungerford[2] noted a very small "deleted" chromosome in cases of chronic myelocytic leukemia. Methods for banding and identifying individual chromosomes, developed in the early 1970s, made it possible to identify this chromosome as a deleted chromosome 22. This deletion chromosome 22 was named the "Philadelphia chromosome." Rowley[3] showed in 1973 that the del(22) was part of a reciprocal translocation with chromosome 9 [i.e., t(9;22)]. Since that discovery, rapid scientific and technological advances have profoundly changed the understanding of tumorigenesis and the genetics of cancer.

Conventional cytogenetic analysis, although one of the oldest methods, remains a powerful tool for genetic diagnosis and classification of hematologic malignancies and solid tumors. Cytogenetic detection of acquired clonal chromosome aberrations confirms that a process is neoplastic and rules out a reactive or non-neoplastic disorder. Chromosomal abnormalities occur nonrandomly and continually bring newly identified recurring breakpoints to attention as the sites of "disease" genes.[4] Molecular cytogenetic or fluorescence in situ hybridization (FISH) analysis targets these sites, permitting detection of specific diagnostic rearrangements. Disease or disease-subtype-specific chromosomal anomalies provide diagnostic information when histopathologic parameters are indeterminate. In addition, many abnormalities contribute prognostic information and guide therapeutic decisions.

Investigators have elucidated the physiologic function of many "disease" genes and shed light on the mechanisms of their mutations. This information provides the basis for the recent and rapid increase in tumor-specific or gene-mutation-specific therapeutic agents.[5] One example of this is the advent of tyrosine kinase inhibitors (TKIs), small molecules designed to affect molecular targets identified by recurrent cytogenetic aberrations. The efficacy of TKIs for several hematologic malignancies is now well established,[6,7] and there is increasing evidence that TKIs will play a major role in treatment of solid tumors.[8] The future holds promise for ever more effective therapies for preventing and treating malignancies. Conventional cytogenetic analysis, FISH, and newer array-based technologies have an increasingly important role in contributing information needed for optimal individualized patient management.

This chapter provides a brief overview of cytogenetics, clinical indications for conventional and molecular cytogenetic testing, and a synopsis of what the clinician should expect from a cytogenetic laboratory. A summary of diagnostic, prognostic, and clinically relevant chromosome aberrations is provided in tabular form.

METHODS AND APPLICATIONS

Specimens

Successful conventional cytogenetic studies of neoplastic tissues and cells require an adequate specimen of viable tumor cells, pertinent

patient information, and prompt delivery to the processing laboratory. Tumor cell viability is crucial, because metaphase chromosomes for cytogenetic analysis can be obtained only from dividing cells. Although tumor cells may be long-lived in the human body, they quickly lose viability once removed, making prompt delivery to the laboratory essential. Appropriate specimen processing depends on the information that accompanies the sample. Critical information includes patient demographics, differential diagnosis, symptoms, and other laboratory findings. The cytogenetics laboratory uses the information to choose the best methods for the suspected disease process. In the absence of adequate information, the specimen may not be processed optimally to yield the malignant clone.

For hematologic tumors, 2 to 3 mL of bone marrow aspirate collected in sodium heparin is the specimen of choice. When a bone marrow aspirate cannot be obtained because of marrow fibrosis, a packed marrow, or other reasons, a bone marrow trephine biopsy or a peripheral blood specimen may be successful. For a blood specimen to yield information about clonal chromosome aberrations, however, the peripheral blood white cell differential must be abnormal (i.e., abnormal or immature cells must be present). The laboratory needs the white blood cell count and differential to inoculate the cell cultures correctly with appropriate numbers of cells. For routine studies of neoplastic hematologic disorders, no cell mitogens are used in culture. The malignant cell population will divide spontaneously to yield metaphase cells. Only when the disease process is known to be a T-cell or B-cell disorder will T- or B-cell mitogens, respectively, be used in one of several initiated cultures.

Depending on the disease process, other specimen types may be appropriate for cytogenetic analysis. Virtually all body fluids and tissues are candidates for tissue culture and capture of metaphase cells. Useful sources include ascitic and pleural fluids, effusions, and, occasionally, cerebrospinal fluid. Tissues with solid aggregates of tumor cells (e.g., spleen or lymph node involved by lymphoma, or masses of myeloid sarcoma or neuroblastoma) also may be used. Such specimens should be acquired in a sterile fashion and placed in medium supplied by the cytogenetic laboratory for transport. The tissue sample should be selected to contain viable tumor, avoiding normal and necrotic tissues. Adequate sample size is variable, but if available, a sample volume of 500 mg or a sample measuring in aggregate $0.5 \times 0.5 \times 0.5$ cm is recommended.

Many specimen types may be used for FISH analysis. Cytogenetically prepared metaphase and/or interphase cells are most commonly used. However, formalin-fixed paraffin-embedded tumor, air-dried or alcohol fixed touch preparations, cytospin preparations, and blood or bone marrow smears may be used when fresh tumor material is unavailable or conventional cytogenetic analysis is unsuccessful. Tissues that have been processed with B-5 fixative or decalcified are not recommended, because probe hybridization may be suboptimal.

Assays

Conventional cytogenetic analysis allows visualization and screening of the entire genome for anomalies and remains one of the most basic and essential methods for genetic evaluation of hematolymphoid and solid tumors. Conventional analysis uses chromosome-banding methods to bring out the A-T and G-C rich band pattern intrinsic to each chromosome. This unique band pattern permits identification and description of each chromosome, normal or abnormal (Fig. 18-1). The chromosome bands are numbered so recurring chromosome breakpoints can be recognized, recorded, and communicated with a descriptive human cytogenetic nomenclature[9] (Table 18-1).

Molecular cytogenetic or FISH analysis[10] uses known fluorochrome-labeled DNA sequences or probes to hybridize to the DNA or chromosomes of the cells under investigation. The basis for the test is the natural tendency for a DNA strand to hybridize with its complementary DNA sequence. The specificity of the hybridization provides explicit information about the region probed.

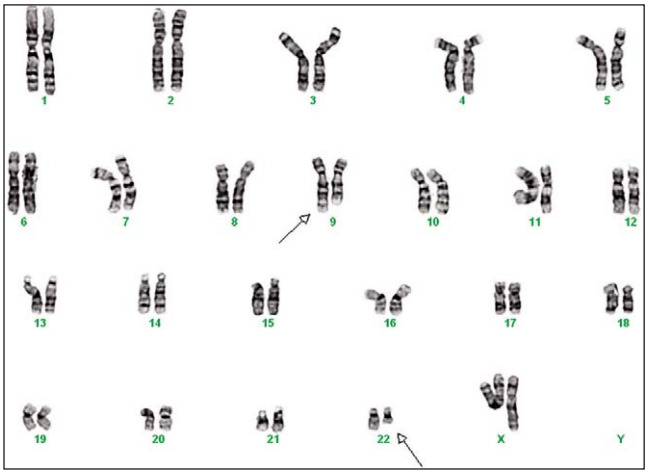


Figure 18-1 • Karyotype illustrates standard arrangement and Giemsa-trypsin banding of chromosomes in a female patient with chronic myeloid leukemia. The karyotype nomenclature is written as 46,XX,t(9;22)(q34;q11.2) (*arrows* to derivative chromosomes 9 and 22).

At the time of diagnosis, conventional cytogenetic analysis, with or without FISH analysis, should be done to characterize all malignancies as completely as possible to aid diagnosis, therapy selection,

Table 18-1 Cytogenetic Nomenclature

NOMENCLATURE ABBREVIATIONS
t(9;22)(q34;q11.2) example
t, translocation
(9;22), chromosomes involved
(q34;q11.2), breakpoints of chromosomes involved
q34, breakpoint of chromosome 9
q11.2, breakpoint of chromosome 22
q, long arm
p, short arm
del, deletion
dup, duplication
inv, inversion
add, added unidentified material
mar, marker; unidentified chromosome
+ or –, gain or loss of chromosome noted
XX, female
XY, male
TUMOR CELL DNA CONTENT: "PLOIDY"
Diploid, 2n or 46 chromosomes
Haploid, 1n or 23 chromosomes
DNA Index (DI), DNA content of cell
46 chromosomes, DNA Index of 1.0
Pseudodiploid, 46 chromosomes with aberrations
Tetraploid, 4n or 92 chromosomes
Aneuploid, chr number not exact multiple of haploid set
DI × 46 = approx chr number in clone: 1.16 × 46 = ~53 chr

Chr, Chromosome.

Table 18-2 Cytogenetic Analysis

INDICATIONS
Provide diagnostic and prognostic information
Provide information for therapy selection
Determine genetic subtype of myeloid disorders
Subclassify lymphoproliferative disorders
Distinguish prognostic groups in childhood ALL
Differentiate small round cell tumors
Differentiate sarcomas
Subtype solid tumors
Obtain information for follow-up testing
Detect clone after therapy or after transplantation
Determine donor cell engraftment status
Reassess clone at relapse for new anomalies
BENEFITS
Visualize entire genome with karyotype
Determine genetic aberrations at diagnosis
Detect disease progression
DISADVANTAGES
Turn-around time is days to weeks (solid tumors)

ALL, acute lymphoblastic leukemia.

and patient management. If assessment is inadequate at diagnosis, the interpretation and clinical utility of future studies will be compromised significantly. For example, without diagnostic genetic data, it would not be possible to determine whether clonal evolution had occurred; it might not be possible to distinguish between recurrent disease and a new disease process; and follow-up FISH studies might be misinterpreted.[11] Chronic myelogenous leukemia (CML) exemplifies the need for both cytogenetic and FISH evaluation at diagnosis, because certain FISH patterns that are associated with *BCR/ABL1* gene rearrangement may mimic a remission pattern. Monitoring these patients by FISH for minimal residual disease (MRD) requires knowledge of that particular patient's diagnostic pattern. Results from subsequent specimens in patients with this type of pattern must be interpreted using explicitly defined validation and control parameters to prevent an incorrect diagnosis of remission while *BCR/ABL1*-bearing cells with this unique pattern are actually still present.

Although conventional chromosomal analysis plays a defining role in characterizing tumors, FISH analysis now is an integral component of the diagnostic evaluation in a large percentage of cases (Table 18-2). FISH analysis has unique utility in the detection of gene rearrangements or gene amplification, chromosomal deletions, duplications, and aneuploidies, low-frequency chromosome aberrations, and elucidation of unbalanced or complex chromosome rearrangements[12] (Table 18-3). FISH analysis is the best method in diagnostic scenarios where a rapid result is needed,[13] such as in newly diagnosed acute promyelocytic leukemia, and an important adjunct when the yield of clonal aberrations by conventional cytogenetics is low,[14] as in chronic lymphocytic leukemia. FISH analysis is the preferred method when breakpoint heterogeneity compromises the usefulness of PCR-based assays or when detection of numerical aberrations is indicated. Although histopathologic evaluation is the currently accepted method to assess response to therapy in leukemias, FISH analysis offers a more reliable and sensitive method for detection of residual disease. FISH analysis is particularly useful in post-transplantation patients who have an identified clonal abnormality and an opposite-sex donor. A combination of sex chromosome- and clone-detecting probes can screen thousands of cells quickly for host cells and then determine whether the host cells carry the original clonal aberration.[15] This method provides crucial information for patient management that may not be obtained with other technologies.

Most cytogenetic laboratories provide a broad FISH test menu using commercially available FISH DNA probes. Other laboratories augment their capabilities by making "home brew" probes. In addition to identifying reciprocal translocations, deletions, and chromosome copy number aberrations, FISH may also provide additional patient-specific information beyond that obtained with conventional cytogenetic analysis. These data can be used to create FISH strategies for patients with unique aberrations that are not detectable with rt-PCR-based assays or specific translocation probe sets. This information, gathered at the time of diagnosis, is invaluable for follow-up assessment for therapy response and detection of residual disease.

FISH probes are designed to detect gene rearrangement in different ways with (1) "break-apart probes" that separate when a translocation has occurred, or (2) "single fusion, dual fusion, or extra signal translocation probes" that come together when a translocation has occurred. Chromosome enumeration probes and locus-specific probes detect copy number of either the centromere of a specific chromosome or a specific chromosome locus, respectively. Whole or partial chromosome paint probes cover the entire area of the chromosome for which they are designed with fluorescence.[12] Combinations of chromosome probes are available for specific disease entities, for example, Chronic Lymphocytic Leukemia panel (Vysis, Inc.) for use in assessing prognostic genetic anomalies in CLL, and Chromoprobe Multiprobe—System Octochrome (Cytocell Technologies) whole chromosome paint probes for use in determining unknown chromosomal material. New probes are coming on the market ever more rapidly, permitting detection of a much wider range of chromosome aberrations than was possible just a few years ago. This trend is likely to continue as individuals and companies use the genome database to design probes to keep up with the emerging gene-specific therapies.

Table 18-3 Fluorescence in situ Hybridization Analysis

INDICATIONS
Identify specific diagnostic and/or prognostic aberrations
Detect reciprocal translocations, gene rearrangements
Detect deletions, duplications
Detect chromosome or gene copy number
Detect gene amplification
Identify unrecognized chromosome material
Identify clonal aberrations for follow-up testing
Assess donor cell engraftment (opposite-sex donor)
Assess remission status
Detect recurrent disease
Detect minimal residual disease
BENEFITS
Analyze dividing and nondividing cells
Analyze fixed tissues
Easy to examine large numbers of cells
Rapid turnaround
DISADVANTAGES
Provides information only for locus of probe tested
Requires knowledge of chromosome anomaly or diagnosis

Other molecular cytogenetic methods[16] include comparative genomic hybridization (CGH), multiplex FISH (M-FISH), spectral karyotyping (SKY), and chromosomal microarray-based CGH[17] (aCGH). These specialized methods have been primarily the purview of research laboratories, but as technological advances occur, they are being brought on board in diagnostic laboratories. Conventional CGH uses a cocktail of tumor DNA and normal reference DNA, each labeled with a different fluorochrome. This cocktail is hybridized to normal metaphase chromosomes to detect regional genomic DNA gains and losses. This computer-based method screens the genome and allows analysis of tumor DNA when chromosomes cannot be obtained. Both SKY and M-FISH methods use multiple fluorochrome labels and computer software to "paint" each chromosome a different color. When the fluorochromes are hybridized to the abnormal tumor metaphase-cell chromosomes, computer analysis of the painted chromosomes can detect rearrangements and provide information about unidentified marker chromosomes and chromosome rearrangements that are not recognized by conventional banded cytogenetic analysis. Microarray CGH, still in its infancy, is a high-throughput and high-resolution method for the detection of microscopic and submicroscopic chromosomal imbalances. Microarrays are small, solid supports, usually glass slides, onto which thousands of different gene sequences are fixed. DNA from tumor cells and normal control cells is tagged with fluorescent molecules and hybridized to the microarray. A "reader" detects the fluorescent tags, and a computer program calculates the red-to-green fluorescence ratio to detect changes in the copy number of DNA sequences.

Cytogenetic Aberrations

Chromosomal aberrations in neoplasia can be grouped according to type. In the first type, no loss of genetic material occurs. Rearrangements of this type include reciprocal translocations and inversions that are known to relocate genes with resultant expression of altered gene products. The second type results in loss or gain of genetic material, and the pathogenic effect depends on which genes are gained or lost. Included in this type are nonreciprocal translocations, deletions, and duplications, as well as loss or gain of whole chromosomes. A third type of aberration results in amplification of genetic material from a specific gene or gene region. This is seen at the chromosome level as double minute chromosomes (small, paired, dot-like acentric chromosomes) or as homogeneously stained regions within a chromosome. Gene amplification, an uncommon aberration, is associated with specific neoplasias and most often correlated with aggressive disease, as, for example, in neuroblastoma.

The karyotype of a tumor may show single or multiple aberrations.[18] Some tumors demonstrate a single anomaly, such as a reciprocal translocation or a gain of an extra chromosome. Other tumors show many aberrations that may include reciprocal or nonreciprocal translocations, deletions, loss, or gain of chromosomes, and so forth. For some types of tumors, a complex karyotype indicates advanced or aggressive disease. The prognostic significance of a karyotype, however, depends on the specific aberrations present. Whereas some tumors have characteristic single anomalies, other tumors have patterns of multiple chromosome aberrations. An example of the former would be the reciprocal t(9;22) in poor-prognosis childhood acute lymphoblastic leukemia (ALL), and the latter example could be the favorable-prognosis hyperdiploid karyotype of childhood ALL that typically shows 53 or more chromosomes and extra copies of specific chromosomes, most commonly X, 4, 6, 10, 14, 17, 18, and 21.[19]

The utility of a cytogenetic analysis of tumor tissue depends on finding the abnormal population of cells that represents the neoplastic process. Cytogenetically, a clone is defined as present when two or more cells with the same chromosomal anomaly are found. A subclone is a second population of cells that contains the original chromosome anomaly and one or more additional anomalies in two or more cells. A subclone indicates clonal evolution and may portend a change to a more aggressive disease state. For instance, chronic-phase CML with the t(9;22) often shows clonal evolution when the disease transforms to the accelerated phase by the gain of an extra der(22) or "Ph" chromosome, trisomy 8, or an isochromosome 17q (Fig. 18-2).

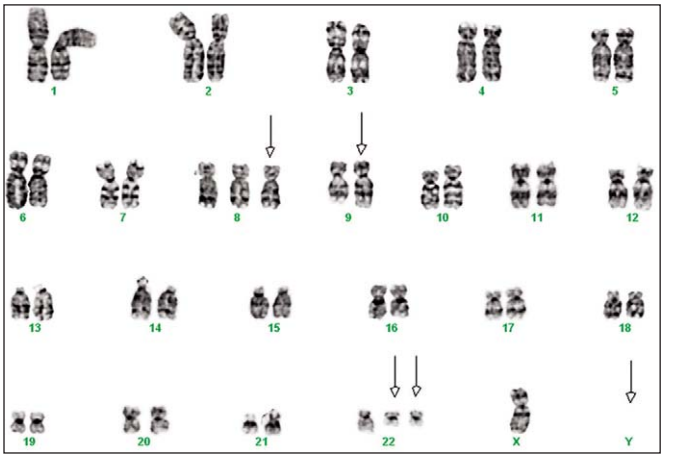


Figure 18-2 • Karyotype of clonal evolution in a male patient with chronic myeloid leukemia in blast crisis. The karyotype is 47,X,–Y,+8, t(9;22)(q34;q11.2),+der(22)t(9;22) (*arrows* to derivative chromosomes 9 and 22, extra chromosome 8, and missing sex chromosome).

Cytogenetic analysis is a valuable tool in the workup of a patient with a neoplastic process. In addition to defining the clonal chromosome abnormality of a tumor at diagnosis, conventional and molecular cytogenetic studies are indispensable for assessing disease status after therapy or transplantation and at disease relapse.

Chromosomal aberrations that provide diagnostic, prognostic, and patient management information are summarized in Tables 18-4, 18-5, and 18-6, and the genes known to be affected by the chromosomal aberrations are listed. Today the majority of these chromosomal aberrations and gene rearrangements can be detected by FISH methods. In some disorders, for example, CML, the genetic abnormality defines the disease process. In others, for example, AML with recurrent cytogenetic abnormalities, the aberrations define distinct entities within a heterogeneous disease. Cytogenetic aberrations within a disease category, for example, glial brain tumors, may provide critical information for therapy selection. No attempt is made in the tables to include all known chromosomal aberrations or their associations; only those with proven diagnostic or clinical significance are shown. Many of these aberrations are discussed in more detail in the discussion of specific tumors elsewhere in this book.

SUMMARY AND FUTURE DIRECTIONS

Cytogenetic analysis of tumor material provides an opportunity to visualize all genetic material in a cell as chromosomes. Almost all neoplasms have shown cytogenetic aberrations, and many of these are disease- and subtype-specific. In addition to providing diagnostic information, clonal chromosomal aberrations provide information vital to therapeutic management.

Cytogenetic information about tumor tissues has been accumulating since the 1960s. Today, cytogenetic studies are used to provide information about a patient's particular disease process, the best way to manage it, and the outcomes that can be expected. Not all tumors yield specific diagnostic or prognostic information, but sufficient valuable information is obtained to warrant cytogenetic study with or without FISH at the time of diagnosis for all childhood hematopoietic disorders and solid tumors, all adult hematopoietic disorders, sarcomas, central nervous system tumors, and select epithelial tumors.

Text continued on p. 262.

Table 18-4 Myeloid Disorders: Cytogenetic Aberrations with Diagnostic or Clinical Significance

Disease Entity	Chromosomal Aberration	FISH Genes Involved	Clinical Significance	References
Acute myelocytic leukemia	t(8;21)(q22;q22)	*RUNX1T1/RUNX1*	Favorable prognosis	Marcucci et al[a]; Schlenk et al[b]
	inv(16)/t(16;16)	*CBFB/MYH11*	Favorable prognosis; increased risk of CNS disease/relapse	Delaunay et al[c]
	t(15;17)(q22;q21)	*PML/RARA* and variants	Favorable prognosis; responsive to ATRA	Arber et al[d]
		ZBTB16/RARA and variants	Variant translocation—poor response to ATRA	Jaffe et al[e]
	t(11q23;v)	*MLL*	Short overall survival	Arber et al[d]; Ravindranath et al[f]
AML-M7	t(1;22)(p13;q13)	*RBM15/MKL1*	Defines infant AML-M7 subgroup	Dastague et al[g]
CEL, HES	del(4q12)	*FIP1L1/PDGFRA*	TKI responsive; *CHIC2* surrogate gene for testing purposes; unresponsive to TKI w/ non-activating *KIT* mutation (D816V)	Pardanani et al[h]; Cortes et al[i]
	Normal karyotype	*CEBPA* mutation	Increased survival; decreased relapse rate	Marcucci et al[j]; Jabbour et al[k]
		NPM1 mutation	Increased survival; must be present without *FLT3*-ITD/mutation	Mrozek et al[l]
		BAALC overexpression	Decreased survival; expression studies from peripheral blood	Jabbour et al[k]; Bloomfield et al[m]
		ERG overexpression	Shorter overall survival; expression studies from blood	Bloomfield et al[m]; Mrozek et al[l]
		FLT3 ITD/mutation	Decreased survival; increased relapse rate; worst prognosis with no or low *FLT3* wild type expression	Kottaridis et al[n]; Mrozek et al[l]
		MLL PTD	Increased relapse rate	Bloomfield et al[m]; Jabbour et al[k]
			Potential TKI responsive	Jabbour et al[k]; Kindler et al[o]
Systemic mastocytosis		*KIT* activating mutation	Less responsive with nonactivating KIT mutation D816V	Pardanani et al[h]; Droogendijk et al[p]
Myelodysplastic syndromes and AML	5q- sole abnormality		Longer survival; 5q- syndrome elderly w/ macrocytic anemia	Germing et al[q]; Giagounidis et al[r]
	–7		Poor outcome; short survival	Greenberg et al[s]; Frohling et al[t]; van der Holt et al[u]
	–5/5q-; –7/7q– together		Poor outcome; often in complex karyotype	Greenberg et al[s]; Frohling et al[t]; Giagounidis et al[r]
	+8 in noncomplex k-type		Intermediate <60 yrs; poor >60 yrs	Frohling et al[t]; Wolman et al[v]
	+11 in noncomplex k-type		Intermediate <60 yrs; poor >60 yrs	Frohling et al[t]
	t/del(11q)	*MLL*	Intermediate to poor prognosis	Greenberg et al[s]; Frohling et al[t]
	inv(3)(q21q26.2), t(3;21)	*RPN1* and *EVI1*	Poor outcome; short survival	Greenberg et al[s]; van der Holt et al[u]
	complex k-type (≥3 abn)		Poor outcome; short survival	Greenberg et al[s]; Chen et al[w]
	20q–, –Y		Good outcome; generally indolent course	Greenberg et al[s]; van der Holt et al[u]
CMML	t(5;12)(q31-q32;p13)	*PDGFRB/ETV6*	TKI responsive	Pardanani et al[h]; Apperley et al[x]
	t(5;17)(q31-q32;p13.2)	*PDGFRB/RABEP1*	TKI responsive	Pardanani et al[h]; Apperley et al[x]
Aplastic anemia	+6		Poor response to immunosuppressive therapy	Ohga et al[y]; Gupta et al[z]
Therapy-related AML/MDS	t(8;21), inv(16), t(15;17)	Same genes as de novo	t(8;21) longer survival than other 21q22 abnormalities	Shali et al[aa]; Schoch et al[bb]
	21q22 abnormalities	*RUNX1*	More common with topoisomerase II inhibitors	Shali et al[aa]
	11q23	*MLL*	More common with topoisomerase II inhibitors	Shali et al[aa]; Schoch et al[bb]; Mauritzon et al[cc]
	3q26.2 abnormalities	*EVI1*	Short overall survival	Shali et al[aa]; Schoch et al[bb]
	Chr 5 and 7 abnormalities		More common with alkylating or radiation therapy	Schoch et al[bb]; Mauritzon et al[cc]
	17p abnormalities	*TP53*	Short overall survival	Schoch et al[bb]

Continued

Table 18-4 Myeloid Disorders: Cytogenetic Aberrations with Diagnostic or Clinical Significance—cont'd

Disease Entity	Chromosomal Aberration	FISH Genes Involved	Clinical Significance	References
Chronic myelocytic leukemia	t(9;22)(q34;q11.2)	*BCR/ABL1*	TKI responsive; TKI resistance due to *ABL1* amplification or *ABL1* kinase domain mutations, specific testing is available	Baccarani et al[dd]; Hughes et al[ee] Lahaye et al[ff]; Arora et al[gg]
	t(9;22), + del(9q)	*ASS1* deletion	Reduced survival with *ABL1/BCR/ASS1* deletions	Huntly et al[hh]; Cohen et al[ii]
	t(9;22), +Ph, +8, +19, i(17q)		Indicates transition to blast phase	Johansson et al[jj]; O'Dwyer et al[kk]
Other MPD	13q-, 20q-, +9, +8, +1q	*BCR/ABL1* negative	Distinguish from CML; *JAK2* mutation analysis permits diagnosis and predicts response to treatment	Campbell et al[ll]
MM/Myelofibrosis	20q-, 13q-	*BCR/ABL1* negative	Favorable in myelofibrosis	Tefferi et al[mm]
CMPD, atypical	t(5;10)(q31q32;q21)	*PDGFRB/CCDC6*	TKI responsive	Pardanani et al[h]
	t(1;5)(q21;q33)	*PDE4DIP/PDGFRB*	TKI responsive	Pardanani et al[h]
	t(4;22)(q12;q11.2)	*PDGFRA/BCR*	TKI responsive	Pardanani et al[h]

abn, abnormalities; ATRA, all-trans retinoic acid; CEL, chronic eosinophilic leukemia; CMML, chronic myelomonocytic leukemia; CMPD, chronic MPD; CNS, central nervous system; FISH, fluorescence in situ hybridization; HES, hypereosinophilic syndrome; ITD, internal tandem duplication; k-type, karyotype; MM myeloid metaplasia; MPD, myeloproliferative disorders; Ph, Philadelphia chromosome; PTD, partial tandem duplication; TKI, tyrosine kinase inhibitor.

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Table 18-5 Lymphoproliferative Disorders: Chromosome Aberrations with Diagnostic or Clinical Significance

Disease Entity	Chromosomal Aberration	FISH Genes Involved	Clinical Significance	References
Acute leukemia				
ALL				
B-precursor	t(9;22)(q34;q11.2)	*BCR/ABL1*	Very high risk disease; response to TKIs	Pui et al[a]; Jones et al[b]; Heerema et al[c]
	t(9;22)(q34;q11.2), –7, 7p–, 9p–	*BCR/ABL1, CDKN2A*	Worst outcome risk with high WBC	Heerema et al[c]
	t(4;11)(q21;q23)	*AF4/MLL*	High risk disease; often found in infants	Hilden et al[d]
	t(11q23) variants	*MLL*	>80% of infants with ALL	Hilden et al[d]
	t(12;21)(p13;q22)	*ETV6/RUNX1*	Low risk disease	Pui et al[e]; Al-Sweedan et al[f]; Stams et al[g]
	t(1;19)(q23;)(p13.3)	*TCF3/PBX1*	Favorable with intensified therapy	Pui et al[h]
	54–65 chr with +4, +10, +17	Chromosome enumeration	Low risk	Sutcliffe et al[i]
	<44 chr	Chromosome enumeration	High risk	Harrison et al[j]; Heerema et al[k]
	Near-haploid 23–29 chr	Chromosome enumeration	Very high risk	Harrison et al[j]; Heerema et al[k]
	Low hypodiploid 33–39 chr	Chromosome enumeration	Very high risk	Harrison et al[j]; Heerema et al[k]; Charrin et al[l]
	Near-tetraploidy	*ETV6/RUNXI*	Favorable; often associated with *ETV6/RUNX1*	Raimondi et al[m]
	der(21):*RUNX1* amplification	*RUNX1*	Unfavorable; older youth	Harewood et al[n]
B-cell	t(8;14)(q24.1;q32.3) or variants	*MYC/IGH@*	Improved outcome with lymphoma therapy	See below
T-cell	t(1p32) or del(1p32)	*TAL1*	Favorable prognosis	Van Grotel et al[o]; Graux et al[p]
	t(5;14)(q35;q32)	*TLX3*	?Favorable	Van Grotel et al[o]; Graux et al[p]; Cave et al[q]
	t(10;14)(q24;q11)	*TLX1*	Favorable	Van Grotel et al[o]; Graux et al[p]
	t(10;11)(p13;q14)	*PICALM/MLLT10*	Unfavorable	Van Grotel et al[o]; Graux et al[p]
	t(11;19)(q23;p13.3)	*MLL/MLLT1*	Favorable prognosis	Rubnitz et al[r]
	del(9p21)	*CDKN2A, CDKN2B*	?Favorable prognosis	Graux et al[s]
	t(9;9)(q34;34), *ABL1* amplification	*NUP214/ABL1*	Response to TKIs	Graux et al[p]
Chronic leukemia				
CLL, B-cell	+12		Intermediate prognosis	Dohner et al[t]; Byrd et al[u]; Dewald et al[v]
	del(13q14) or –13	D13S319 or *RB1* as surrogate FISH markers	Favorable as sole anomaly	Athanasiadou et al[w]
	del(11q21)	*ATM*	Shortened survival	Dohner et al[t]; Byrd et al[u]; Dewald et al[v]
	del(17p13)	*TP53*	Unfavorable	Dohner et al[t]; Byrd et al[u]; Dewald et al[v]
	t(14;19)(q32;q13)	*BCL3*	Often young adults	Michaux et al[x]

Continued

Table 18-5 Lymphoproliferative Disorders: Chromosome Aberrations with Diagnostic or Clinical Significance—cont'd

Disease Entity	Chromosomal Aberration	FISH Genes Involved	Clinical Significance	References
Plasma cell				
Multiple myeloma/ plasma cell leukemia	Hyperdiploid +3, 5, 7, 9, 11, 15, 19		Longer OS and EFS	Smadja et al[y]; Chng et al[z]
	Nonhyperdiploid		Unfavorable; <46, 46, and >81 chromosomes	Smadja et al[y]; Fonseca et al[aa]
	−13 or del(13q14)	*DBM/RB1*	Unfavorable	Chiecchio et al[bb]; Zhan et al[cc]
	del(17p13)	*TP53*	Unfavorable; common in PCL; CNS disease	Schilling et al[dd]
	t(11;14)(q13;q32)	*CCND1/IGH@*	Improved survival with intensive therapy	Fonseca et al[ee]; Soverini et al[ff]
	t(4;14)(p16;q32)	*FGFR3/IGH@*	Unfavorable; most common in PCL	Keats et al[gg]; Fonseca et al[hh]
	t(8;14) & variants	*MYC/IGH@*	Present in ~15% of MM	Avet-Loiseau et al[ii]
	t(14;16)(q32;q24)	*IGH@/MAF*	Unfavorable; most common in PCL	Fonseca et al[hh]
	t(14;20)(q32;q11.2)	*IGH@/MAFB*	Unfavorable	Boersma et al[jj]
Lymphoma				
Mature B-cell				
Follicular	t(14;18)(q32;q21)	*IGH@/BCL2*	Poor prognosis with *MYC* rearrangement	Kanungo et al[kk]
MZBCL MALT	t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21)	*API2/MALT1*, *BCL10/IGH@* *IGH@/MALT1*	Resistant to *Helicobacter pylori* therapy	Farinha et al[ll]
t(11;18) negative MALT	+3, +18, +18q21	3, 18, *MALT1*	Poor outcome, risk to transform to DLBCL	Streubel et al[mm]; Remstein et al[nn]
Mantle cell	t(11;14)(q13;q32)	*CCND1/IGH@*	Distinguish MCL from CLL; FISH best for dx	Bertoni et al[oo]; Belaud-Rotureau[pp]
Burkitt	t(8;14)(q24.1;q32.3)	*MYC/IGH@*	Favorable with aggressive therapy	Bociek et al[qq]; Lones et al[rr]; Dave et al[ss]
	t(8;22)(q24.1;q11.2)	*MYC/IGL@*	Favorable with aggressive therapy	Bociek et al[qq]; Lones et al[rr]
	t(2;8)(p11.2;q24.1)	*MYC/IGK@*	Favorable with aggressive therapy	Bociek et al[qq]; Lones et al[rr]
T-cell	t(14q11), t(7q35)	TCR sites	Most common rearrangements	Jaffe et al[tt]
Anaplastic large cell	t(2;5)(p23;q35) and variants	*ALK/NPM*	*ALK*+ tumors better survival	Jaffe et al[uu]

ALL, acute lymphoblastic leukemia; CLL, chronic lymphocytic leukemia; CNS, central nervous system; EFS, event free survival; FISH, fluorescence in situ hybridization; MALT, mucosa-associated lymphoid tissue; MZBCL, marginal zone B-cell lymphoma; OS, overall survival; TCR, T-cell receptor; TKIs, tyrosine kinase inhibitors; WBC, white blood count.

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Table 18-5 Lymphoproliferative Disorders: Chromosome Aberrations with Diagnostic or Clinical Significance—cont'd

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Table 18-6 Solid Tumors: Chromosome Aberrations with Diagnostic or Clinical Significance

Disease Entity	Chromosomal Aberration	FISH Genes Involved	Clinical Significance	References
Genitourinary				
Renal				
Clear cell RCC	–3 or del(3p)	3p, *VHL*, other unknown gene	Characterize nonpapillary RCC	Kardas et al[a]
	del(3p) with gain 5q	3p, 5q	Favorable prognosis	Kardas et al[a]
	del(3p) with loss 5q	3p, 5q	Metastasis, unfavorable	Kardas et al[a]
	–14 /del(14q)	14, *IGH@*	Unfavorable, shorter survival	Kardas et al[a]
Papillary RCC	+7, +17, –Y, 9p–	7, 17, Y, *CDKN2A*	Characterize adult papillary RCC	Hansel[b]

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Table 18-6 Solid Tumors: Chromosome Aberrations with Diagnostic or Clinical Significance—cont'd

Disease Entity	Chromosomal Aberration	FISH Genes Involved	Clinical Significance	References
t(Xp11.2) RCC	t(X;1)(p11.2;q21.2)	*PRCC/TFE3*	Characterize pediatric papillary RCC	Ramphal et al[c]
	t(X;17)(p11.2;q25)	*ASPLCR1/TFE3*	Balanced translocation in RCC	Ramphal et al[c]
	t(X;17)(p11.2;q23)	*CLTC/TFE3*	Characterize pediatric papillary RCC	Ramphal et al[c]
	t(X;1)(p11.2;p34)	*PSF/TFE3*	Characterize pediatric papillary RCC	Ramphal et al[c]
t(6;11) RCC	t(6;11)(p21;q12)	*ALPHA/TFEB*	Subset of RCC, children, young adult	Argani et al[d]
Chromophobe RCC	Loss 1, 2, 6, 10, 13, 17, 21	Chromosome enumeration	Distinguish from oncocytoma	Hes et al[e]
Oncocytoma	1p–, t(11q13)	1p, *CCND1*	Distinguish from chromophobe	Jhang et al[f]
Rhabdoid	–22/22q–	*SMARCB1; BCR* as surrogate	Diagnostic	Biegel et al[g]
CMN	t(12;15)(p12;q25), +11, +17, +20	*ETV6/NTRK3*	Diagnostic	Sandberg et al[h]
Bladder, papillary	del(9)(p21)	*CDKN2A*	Homozygous deletion higher grade, stage	Wolff et al[i]
	8p–	8p, unknown gene	Higher recurrence rate, progression	Wolff et al[i]
	+7, +17	*FGFR3, TP53, MYC*	Genetic instability	Wolff et al[i]
Wilms' tumor	16q–, +1q, 1p–, –22, 17p–	1p, 1q, 16q, 17p, 22, *WT1*	Unfavorable histology; augmented chemotherapy if 1p–, 16q–	Perlman[j]
Prostate	+7q31, 8p22–, +8q24, 17p13–	7, *LPL, MYC, TP53*	High frequency in carcinoma	Qian et al[k]; Bastacky et al[l]
	17p13–, +8q24	*TP53, MYC*	Progression, higher Gleason score	Qian et al[k]
	10q–	*PTEN*	High grade PIN or carcinoma	Yoshimoto et al[m]
Gastrointestinal				
GIST	–14/14q–, –22/22q–	14, 22, *KIT* mutations	Distinguish from smooth muscle tumors	Sandberg et al[n]; Miettinsen et al[o]
			Response to TKIs	
Liver				
Hepatoblastoma	+20, +2, +8, t(1q12-q21)	Chr 2, 8, 20, 1q	Distinguish from HCC, HMH	Tomlinson et al[p]
HMH	t(11;19)(q13;q13.4), t(19q13.4)	19q	Distinguish from hemangioma or malignant tumor	Rakheja et al[q]
Salivary gland				
Pleomorphic adenoma	t(3;8)(p21;q12)	*PLAG1*	Diagnostic benign	Martins et al[r]
Mucoepidermoid cancer	t(11;19)(q21;p13)	*MECT1/MAML2*	Diagnostic malignant	Enlund et al[s]
Warthin's tumor	t(11;19)(q21;p13)	*MECT1/MAML2*	Benign tumor	Enlund et al[s]
Breast				
Invasive intraductal	dmin, hsr	*ERBB2* amp	Worst prognosis, response to TKIs, Mab	Tanner et al[t]; Geyer et al[u]
		ERRB2, TOP2A co-amp	Co-amplification, better response to FEC	Tanner et al[t]
Secretory breast	t(12;15)(p13;q25)	*ETV6/NTRK3*	Favorable; distinguish from IDC	Makretsov et al[v]
CNS				
Astrocytic tumors	+7, –10/10q–	*EGFR, PTEN*	Short survival, aggressive course	Fuller et al[w]
	9p21–	*CDKN2A*	Sensitive to antimetabolite therapy	Fuller et al[w]
	19q–	19q	Long-term survival	Fuller et al[w]

Table 18-6 Solid Tumors: Chromosome Aberrations with Diagnostic or Clinical Significance—cont'd

Disease Entity	Chromosomal Aberration	FISH Genes Involved	Clinical Significance	References
Glioblastoma	+7, 10q–, 9p–	*PTEN*, *EGFR*, *CDKN2A*	Short survival assoc w/ 10q-/*PTEN* loss	Ohgaki et al[x]
Oligodendroglial tumors				
Anaplastic	1p–, 19q–, der(1;19)(q10;p10)	1p36, 19q13.3	Longer survival, sensitive to therapy	Eoli et al[y]; Brandes et al[z]; Griffin et al[aa]
Mixed oligoastrocytoma	+7, –10/10q–, 15q–	*EGFR, PTEN*	High grade, progression	Koschny et al[bb]
Oligoastrocytoma	19q–	19q13.3	Favorable outcome	Fuller et al[w]
	1p–	1p36	Favorable outcome	Eoli et al[y]
Ependymoma				
Spinal	+7, –22q, 14q–	7, 14, 22q, *NF2*	Distinguish subtype	Mendrzyk et al[cc]
Intracranial	+1q, 6q–, +7, 9p–	1q25, p16, *EGFR*, *CDKN2A*	Pediatric, high risk	
Medulloblastoma	i(17q), 17p–, –10/10q–, +7	*MYCN, MYC*	Large cell/anaplastic morphology	Pan et al[dd]; Lamont et al[ee]; Gajjar et al[ff]
		ERBB2	High risk	
Supratentorial PNET	+1q, 16q–, 19p–	1q, 19p	Lacks i(17q), poor prognosis	Inda et al[gg]
AT/RT	–22 or del(22q11.23)	*SMARCB1; BCR* as surrogate	Distinguish from MB, PNET, CPC	Judkins et al[hh]; Biegel[ii]
Meningioma	–22 or del(22q11.2)	22q, *NF2*	Primary abnormality	Fuller et al[w]
	1p–, –14/14q–	1p, *IGH@*	Increased risk of recurrence, anaplastic	Espinosa et al[jj]
Choroid plexus tumors				
Carcinoma	Loss 2, 3, 4, 5, 6, 8, 10, 11, 13, 14, 15, 16, 17, 18, 19, 22	Chromosome enumeration	Distinguish from papilloma	Rickert et al[kk]; Bhattacharjee et al[ll]
Papilloma	Gain 7, 8, 9, 12, 14, 15, 17, 18, 19, 20	Chromosome enumeration	Distinguish from carcinoma	Rickert et al[kk]; Bhattacharjee et al[ll]
Small round cell tumors				
Alveolar RMS	t(2;13)(q37;q14)	*PAX3/FOXO1A*	Older youth, poorer outcome	Sorenson et al[mm]
	t(1;13)(p36;q14)	*PAX7/FOXO1A*	Younger, extremity location	Sorenson et al[mm]
	t(X;2)(q13;q35), t(2;2)(q35;p23)	*PAX3/AFX, PAX3/NCOA1*	Variant translocations	Nishio et al[nn]
		IGF1R amp	Disease progression	Bridge et al[oo]
Embryonal RMS	Gain 2, 7, 8, 11, 12, 13, 20	Chromosome enumeration	Distinguish from alveolar subtype	Bridge et al[oo]
	Loss 1p, 3p, 9q, 10q, 16q, 17p, 22	*IGF1R* amp	Gene amplification with anaplasia	Bridge et al[oo]
Neuroblastoma	del(1p), del(11q) w/o *MYCN* amp	1p, 11q, *MYCN*	Unfavorable in Stage I, II, IVS	Attiyeh et al[pp]; Spitz et al[qq]; Maris et al[rr]
	del(1p), +17q, *MYCN* amp	1p, 17q, *MYCN*	Unfavorable all stages	Janoueix-Lerosey et al[ss]; Spitz et al[qq]
	triploidy w/o above abn	Chromosome enumeration	Favorable	Maris et al[rr]
EWS/pPNET	t(11;22)(q24;q12) & variants	*FLI1/EWSR1*	Diagnostic, distinguish from other SRCTs	Bernstein et al[tt]
	t(21;22)(q22;q12)	*ERG/EWSR1*		Bernstein et al[tt]
	del(9p), 17p–, der(1;16)(q10;p10)	*CDKN2A, TP53*	Unfavorable prognostic factor	Bernstein et al[tt]

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Table 18-6 Solid Tumors: Chromosome Aberrations with Diagnostic or Clinical Significance—cont'd

Disease Entity	Chromosomal Aberration	FISH Genes Involved	Clinical Significance	References
DSRCT	t(11;22)(p13;q12)	*WT1/EWSR1*	Distinguish from other SRCTs	Chang et al[uu]; Sandberg et al[vv]
Clear cell sarcoma	t(12;22)(q13;q12)	*ATF1/EWSR1*	Absent in cutaneous MM	Patel et al[ww]; Sandberg et al[xx]
Retinoblastoma	del(13q14), gain 1q, 6p	*RB1, DEK, E2F3*	Hallmark of retinoblastoma	Grasemann et al[yy]
Lymphomas	specific translocations		Distinguish from other SRCTs	See Table 18-5
Bone, soft tissue				
CFS/CMN	t(12;15)(p12;q25), +11, +17, +20	*ETV6/NTRK3*	Distinguish CFS from fibrosarcoma	Sandberg et al[h]
Synovial sarcoma	t(X;18)(p11.2;q11.2)	*SSX1/SS18*	Biphasic—most SYT/SSX1, unfavorable	Terry et al[zz]; Surace et al[aaa]
		SSX2/SS18	Monophasic-SYT/SSX1 or SYT/SSX2	Sandberg et al[bbb]; Ladanyi et al[ccc]
Lipoma	t(3;12)(q27–28;q14–15), variants	*HMGA2/LPP*	Distinguish from LPS	Sandberg[ddd]
Liposarcoma				
Myxoid, round cell	t(12;16)(q13;p11)	*FUS/DDIT3*	Diagnostic for myxoid LPS	Sandberg[eee]
Myxoid	t(12;22)(q13;q12) variant	*DDIT3/EWSR1*	Variant of t(12;16)	Sandberg[eee]
Well-differentiated	rings, markers, dmin	*MDM2, CDK4* amplification	Distinguish from lipoma	Sandberg[eee]
Leiomyoma	t(12;14)(q15;q24)	*HMGA2*	Distinguish from leiomyosarcoma	Sandberg[fff]; Sandberg[ggg]
ASPS	der(17)t(X;17)(p11.2;q25)	*ASPLCR1/TFE3*	Unbalanced translocation specific for ASPS	Sandberg et al[hhh]; Huang et al[iii]
EMC	t(9;22)(q22;q12)	*NR4A3/EWSR1*	Diagnostic, tumor specific	Sandberg et al[jjj]; Sandberg[kkk]
	t(9;17)(q22;q11.2)	*NR4A3/TAF15*	Variant translocation	Sandberg et al[jjj]; Sandberg[kkk]
	t(9;15)(q22;q21)	*NR4A3/TCF12*	Variant translocation	Sandberg et al[jjj]; Sandberg[kkk]
Dermal tumors				
DFSP	der(22)t(17;22)(q22;q13.1) or r(22)t(17;22)	*COL1A1/PDGFB*	Distinguish from atypical DF, MFH Response to TKIs	McArthur et al[lll]; Kaur et al[mmm] Sirvent et al[nnn]
GCF	t(17;22)(q22;q13.1)	*COL1A1/PDGFB*	Similar to DFSP	Sirvent et al[nnn]
Bednar tumor	der(22)t(17;22)(q22;q13.1) or r(22)t(17;22)	*COL1A1/PDGFB*	Similar to DFSP	Sirvent et al[nnn]
Hidradenoma	t(11;19)(q21;p13)	*MECT1/MAML2*	Same as Warthin's tumor	Behboudi et al[ooo]
Lung tumors				
NSCLC	3p-, +7, *EGFR* high copy number or amplification	*EGFR*	Response to TKIs	Cappuzzo et al[ppp]
Germ cell tumor				
Dysgerminoma, ovary	i(12p), 12p overrepresentation	12p	Distinguish from non-GCTs	Cossu-Rocca et al[qqq]
TGCTs, seminoma, NS	i(12p), 12p amplification	12p	Most common aberration, invasive disease	Zafarana et al[rrr]

ASPS, alveolar soft part sarcoma; AT/RT, atypical teratoid/rhabdoid tumor; CFS, congenital fibrosarcoma; CMN, congenital mesoblastic nephroma; CPC, choroid plexus carcinoma; DF, dermatofibroma; DFSP, dermatofibrosarcoma protuberans; DSRCT, desmoplastic small round cell tumor; EMC, extraskeletal myxoid chondrosarcoma; EWS, Ewing's sarcoma; FEC, fluorouracil, epirubicin, cyclophosphamide; GCF, giant cell fibroblastoma; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HMH, hepatic mesenchymal hamartoma; IDC, intraductal carcinoma; Mab, monoclonal antibody; MFH, malignant fibrohistiocytoma; MM, malignant melanoma; NS, nonseminoma; NSCLC, non-small-cell lung cancer; PIN, prostate intraepithelial neoplasia; PNET, primitive neuroectodermal tumor; pPNET, peripheral primitive neuroectodermal tumor; RCC, renal cell carcinoma; RMS, rhabdomyosarcoma; TGCTs, testicular germ cell tumors; TKIs, tyrosine kinase inhibitors.

Table 18-6 Solid Tumors: Chromosome Aberrations with Diagnostic or Clinical Significance—cont'd

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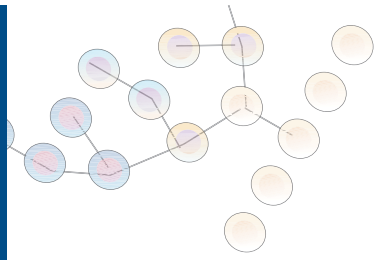
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As technology and knowledge advance, cytogenetic laboratories will continue to provide the basic genetic picture of disease states using conventional cytogenetic analysis. FISH will play an expanding role in the diagnosis and management of neoplasias—for example by detection of molecular targets for therapeutic agents. FISH methods are evolving to accommodate tumor materials prepared, preserved, or stored in multiple ways. FISH commonly is used now to anchor a diagnosis or provide prognostic information, and is used as a post-therapy evaluation tool for residual disease for some tumors. Because FISH offers a more sensitive and specific method for residual disease detection than do histopathologic parameters,[20] it is likely to see increasing use for this purpose in the future. Combining FISH with other methods such as flow cytometry can provide an even better assessment of therapeutic response[21] As genomic information continues to be generated, new FISH probes and strategies will be developed to meet diagnostic needs. CGH, SKY, and M-FISH will continue to play a role in elucidation of genetic aberrations, and microarray-based CGH in particular appears to hold exciting potential for moving the field of molecular cytogenetics forward.

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19 Molecular Diagnostics

Jeffrey A. Kant

SUMMARY OF KEY POINTS

Key Methods

- Polymerase chain reaction (PCR) amplification is a component of most molecular diagnostic applications.
- Automated and quantitative methods now exist that improve reproducibility and clinical application.
- Direct sequencing methods for acquired and germline mutations have a focused role.
- Interrogation and integration of data from multiple molecular targets is becoming more common.

Applications

Hematologic Malignancies

- Clonality is demonstrated using immunoglobulin and T-cell–receptor gene rearrangement assays.
- Tumor burden is quantitatively assessed targeting translocations that define many leukemias or lymphomas.
- *JAK2* V617F is used as a molecular marker for chronic myeloproliferative diseases.
- Identify markers are used in transplantation to match human leukocyte antigens and to assess engraftment and chimerism

Solid Tumors

- Identification of specific mutations facilitates diagnosis and management of de novo and hereditary cancers.
- Many soft tissue tumors can be diagnosed and classified based on specific translocations (see Chapter 97).
- Assays that indicate genetic instability have selected utility.

Assays in Development

- Profiles of gene or micro-RNA expression will play an increasing role in diagnosis and patient management.
- DNA methylation assays show promise for early diagnosis and classification of cancers.
- Pharmacogenetic assays will be coupled to existing and new drugs to optimize dosing.

INTRODUCTION

Characteristic markers involved in the molecular pathogenesis of cancer have been described with increasing regularity over the last three decades. "Molecular diagnostics" in the context of cancer generally refers to the analysis of nucleic acid (DNA or RNA) in patient samples to detect markers for purposes of diagnosis or prognosis. Most of these markers are acquired during cancer development and restricted to neoplastic cells. A subgroup of germline mutations found in all body cells that predispose to cancer at different ages is significant for the management and counseling of individuals and family members.

Sensitive detection technologies facilitate the use of molecular markers to track residual cancer, thus assisting with monitoring and adjusting therapy. Molecular tools can detect agents of etiologic interest (e.g., human T-cell leukemia virus, human herpesvirus) and also assist with the selection of therapeutic cell products (e.g., high-resolution histocompatibility typing for bone marrow transplantation). After transplantation, molecular methods are used to assess engraftment. The evolving potential of molecular diagnostic assays to yield information allowing individually tailored drug selection and dosage is commonly referred to as "personalized medicine." Because the functional manifestations of most nucleic acid changes are mediated through proteins produced (or not produced) from affected genes, the term *molecular diagnostics* also is used occasionally in the context of applications that involve the analysis of proteins (i.e., proteomics; see Chapter 20).

This chapter focuses on nucleic acid-based applications for which clinical validity and utility has been established. Molecular cytogenetic applications, including fluorescent in situ hybridization (FISH) and array comparative genome hybridization (CGH), are discussed in Chapter 19. Selective background is offered for a number of promising future molecular diagnostic applications currently under study. Clinicians in the United States should keep in mind that assays that yield information on which patient management is based must be performed in Clinical Laboratory Improvement Act (CLIA)-licensed laboratories.

METHODS

Specimens

Assays begin with extraction of target nucleic acid from a sample. Nucleic acid typically is obtained from the nucleus or cytoplasm of disrupted cells but may be derived from cell-free portions of the sample and even serum or plasma. Because nucleated cells are the primary source of DNA, paucicellular samples of bone marrow and blood or tumors following therapy may not reflect the state of a diagnostic sample. After taking tissue for histopathologic examination or other studies, it is crucial, if possible, to set aside a portion of the "diagnostic" specimen for nucleic acid preparation or storage, on which assays can be performed subsequently if desired. Blood, bone marrow, and body fluid samples must be anticoagulated adequately, because appreciable numbers of nucleated cells are lost in

Table 19-1 Sample Handling Tips for Molecular Diagnostic Testing

DO

- Submit samples for testing or nucleic acid preparation/storage at initial diagnosis, not only following therapy
- Send samples quickly to the clinical laboratory for processing
- Use EDTA or citrate-based anticoagulants for blood or bone marrow specimens; avoid heparin if possible
- Request re-analysis and comparison of material from prior diagnostic specimens against follow-up samples if you wish to evaluate possible clonal evolution.

DON'T

- Place an entire tissue sample or bone marrow sample in fixative unless necessary for pathologic examination; process the remaining portion appropriately.
- Freeze peripheral blood or bone marrow specimens for storage; refrigerate or place in satisfactory preservative.

clots. Ethylenediaminetetraacetic acid (EDTA) or citrate is preferable to heparin as an anticoagulant because heparin may bind nucleic acids or other reagents and potentially interfere with molecular assays. (Washing heparinized samples can help.) Heparin is the anticoagulant of choice for cytogenetic analysis, so it often is desirable to obtain two samples or split a sample when both assays are performed (Table 19-1). Tissue (at least 100–200 mg) can be frozen at −80°C or in liquid nitrogen and processed subsequently for nucleic acid or protein. DNA (and RNA) can be obtained from archival paraffin-embedded specimens, but typically there is appreciable fragmentation and/or degradation, and the preferred sample for molecular diagnostic analysis is a fresh sample. Assessment of molecular markers in cell-free samples (plasma or serum) has been demonstrated and may offer advantages; tumor-associated DNA and RNA presumably reside in cell-free domains protected from degradation.[1–4] Enrichment of tumor tissue from paraffin sections via manual or laser capture microdissection is increasingly useful in evaluating solid tumors.[5,6]

Samples should be submitted to the laboratory in a timely fashion, particularly if RNA is to be assayed. Collection tubes are available to immediately stabilize collected samples, although weekend blood or bone marrow samples from which nucleic acid is extracted often perform satisfactorily after several days at refrigerator (not freezer) temperatures. Usually, 4 to 6 μg of DNA is obtained per 1 million nucleated cells, so nucleic acid yield is problematic only in hypocellular samples, such as those derived from cerebrospinal fluid or bone marrow after treatment. In such cases, DNA may be insufficient to perform certain assays (e.g., Southern blotting).

Polymerase Chain Reaction

Polymerase chain reaction (PCR)[7] underlies the vast majority of molecular diagnostic assays. Isolated double-stranded DNA first is denatured to single strands, to which short single-stranded DNA oligonucleotide primers are bound, flanking the region of interest. Enzymatic extension from the primer copies the targeted region on each strand, effectively producing twice the amount of original nucleic acid target. Repeated cycles of denaturation, annealing, and extension amplify the targeted region many million-fold and facilitate the analysis of samples with low levels of target nucleic acid. One to as many as 10 to 15 assays generally can be performed for each microgram of DNA obtained.

For sensitive qualitative detection of unique DNA or RNA constructs such as chromosomal translocations, *nested PCR* can be per-

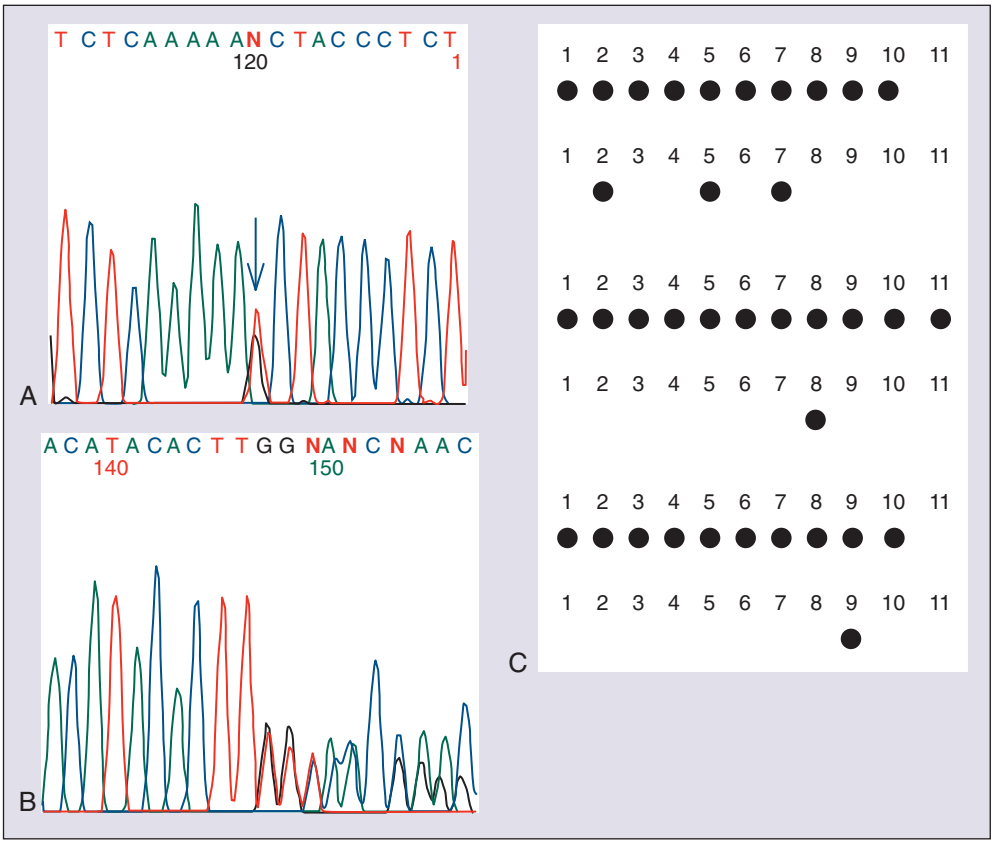


Figure 19-1 • Direct mutation detection. Forward-strand DNA sequences are shown for missense (p.Ile127Ser) **(A)** and frameshift (c.153_154insT) **(B)** mutations in the *SDHB* gene. **C,** Allele-specific hybridization for, *top* to *bottom, BRCA1* (185delAG, 5282insC) and *BRCA2* (6174delT) mutations. Specific probes for normal (WT) and mutant sequence are used on samples amplified together for BRCA1 exons 2 (*top*) and 20 (*middle*) and BRCA2 exon 11 (*bottom*). Patient samples tested in duplicate are 1,4, 2,5, 3,6. Heterozygous controls are samples 7, 8, 9. Sample 10 is a normal control. Sample 11 is a minus-DNA control (except 5382, where it is another normal control).

formed, in which an aliquot of the initial PCR reaction undergoes a second PCR series using a new primer set targeting sequences on both sides of the target but internal to the initial flanking primers. Nested PCR offers sensitivity with increased risks of contamination; increasingly, PCR is done on "real-time" platforms, which offer broad linear ranges and provide quantitative or qualitative results.[8,9] PCR assays can amplify DNA regions up to several kilobases. "Long distance" PCR,[10,11] which amplifies larger regions of DNA, is appealing for some applications but is not in widespread clinical use.

For PCR assays in which RNA is the starting material (RT-PCR), RNA first is incubated with the enzyme reverse transcriptase (RT) in the presence of either general or sequence-specific oligonucleotide primers. RT makes a DNA copy strand (cDNA) from the RNA template. The cDNA products then are subjected to standard PCR amplification.

DNA Sequencing

DNA sequencing typically is performed from primary PCR products.[12,13] Oligonucleotide primers bound to the "ends" of forward and reverse strands of PCR fragments are copied into single strands of varying lengths, allowing the DNA sequence to be read directly from capillary or gel-based laser systems (Fig. 19-1). This is accomplished by using a mixture of normal and fluorescently labeled dideoxynucleotides with termination of the copying reaction each time a dideoxynucleotide is inserted. Pyrosequencing, by contrast, determines DNA sequence over short stretches of nucleotides by measuring the amount of pyrophosphate generated after sequential addition of differing nucleotides.[14–16] Pyrosequencing in nanoliter chambers followed by software assembly of overlapping short sequences is the technical basis for high throughput sequencers capable of determining millions of nucleotides.[17]

Southern Blotting

Southern blotting is a venerable but increasingly less-used technique for assessing clonality or chromosomal translocations in hematologic or solid tumors (Fig. 19-2).[18] Restriction endonuclease-digested fragments of total sample DNA are separated in gels by size, then replica-transferred in denatured single-stranded form to a reinforced membrane where those fragments binding a labeled complementary probe can be visualized. Physical restructuring of a chromosomal region by translocation or physiologic elimination of DNA segments from immunoglobulin and T-cell receptor genes during lymphocyte development creates restriction fragments of new lengths characteristic of clonal cells that have expanded to form the cancer.

Southern blot assays have a number of disadvantages. They require moderate amounts of nucleic acid, typically several micrograms per lane evaluated. Southern blots also are labor-intensive, technically demanding, and typically take 5 to 7 days to deliver an answer.

Other DNA Assays

Numerous di-, tri-, and tetranucleotide sequences, known as *simple tandem repeats* (*STRs*) or *microsatellites* throughout the genome, demonstrate polymorphisms of varying lengths on maternally and paternally inherited alleles. Such markers are useful in segregation (or linkage) analysis to follow at-risk chromosomes passed within families, in the assessment of bone marrow engraftment, and in the comparison of the relative abundance of STRs in tumor and normal tissues to determine allelic loss (loss of heterozygosity [LOH]). The human genome also features large numbers of single-nucleotide polymorphisms (SNPs) that can be used to assess allelic loss as well as gain or loss of chromosomal regions.

Microarray "chips" composed of high-density assemblies of oligonucleotides or cDNA probes on glass or silica surfaces can be used to assess the array of transcripts or SNPs in normal or tumor DNA.[19,20] A particularly powerful application of chips is *expression profiling* of tumors to provide a relative assessment of RNA transcript levels from many genes in a tumor population. Powerful software analysis programs assemble such data into patterns that indicate the origin or behavioral profile of a tumor.[21,22]

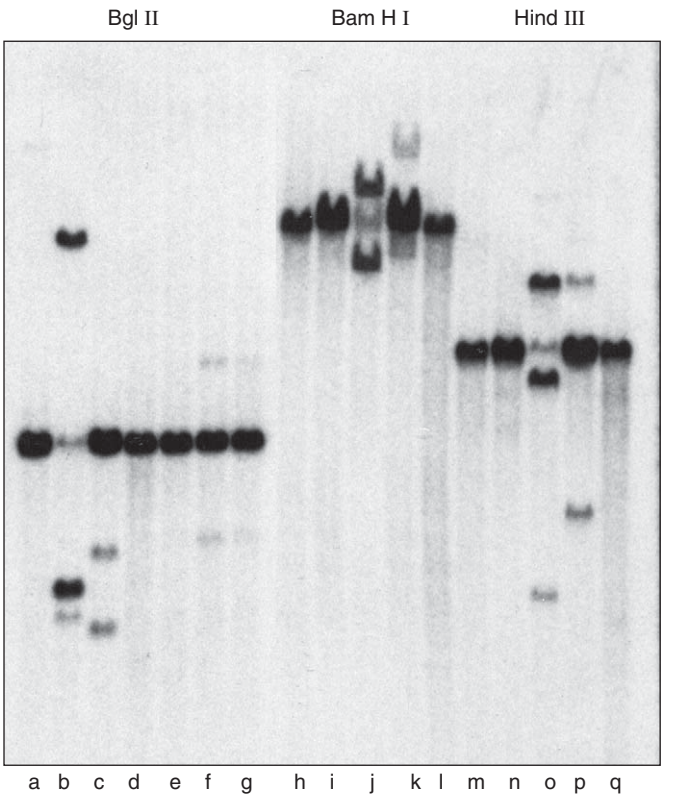


Figure 19-2 • Immunoglobulin heavy-chain gene assessment by Southern blot. Typical three-restriction enzyme analysis (using enzymes Bgl II, Bam HI, and Hind III) of five patient specimens (patient 1: lanes a, h, m; patient 2: lanes b, j, o; patient 3: lanes c, k, p; patient 4: lanes d, i, n; patient 5: lanes e, l, q). Note the different order of patients for Bgl II versus the other enzymes. A single germline band is seen in all enzyme digests for the normal control (patient 1). Lanes f and g are mixtures of 10% and 4% B-cell lymphoma DNA in normal DNA (note faint rearranged alleles above and below the germline band on the Bgl II digest); these serve as positive and sensitivity controls. Two rearranged alleles for both immunoglobulin heavy-chain genes are seen in patient samples 2 and 3. Patient 2 demonstrates an additional faint band, with enzymes Bgl II and Hind III supporting clonal evolution. Note also the reduced intensity of the germline allele for patient 2, indicating that this sample contains a high fraction of neoplastic cells. Patients 4 and 5 are normal for all enzyme digests.

APPLICATIONS

Clinical applications exist for (1) hematolymphoid neoplasms for which a large variety of molecular tests have evolved over two decades and (2) selected solid tumors. While molecular diagnostic assays that drive management of patients with solid tumors are still limited, with improved understanding of pathogenesis and related development of new therapies, they will be a major area of future growth.

Most molecular oncology assays are methods developed in individual laboratories. External proficiency surveys are available for some hematolymphoid and solid tumor assays, but standardization is limited. This lack of standardization results from a combination of factors, including low test volumes and limited incentive for commercial development, the tendency of academic laboratories to be early developers of new testing, and the fact that it is cheaper to perform laboratory-developed assays even when commercial assays are available.

Hematolymphoid Neoplasms

Molecular assays for hematolymphoid neoplasms are useful if the information provided by histology or immunophenotypic assessment is insufficient for diagnosis.[23] If the plan is to use a molecular marker to monitor disease following treatment, it is useful to confirm that that marker is present in diagnostic material, or store sample nucleic acid for future analysis. Molecular assay results typically are best evaluated in the broader context of clinical, histologic, immunophenotypic, and other information to arrive at the best picture of a patient's disease. Typically, this is done by a hematopathologist. Properly chosen assays can help in both the diagnosis and classification of neoplasms. *Clonality assays,* which are first-line tests for suspected hematolymphoid neoplasms, are directed at populations that demonstrate immunoglobulin heavy chain (IgH) or T-cell receptor (TcR) gene rearrangement or a specific chromosomal translocation.[24]

Gene Rearrangement Assays

Gene rearrangement assays look for a significant clonal B- or T-lymphoid population. Each tumor cell contains the same rearranged IgH or TcR gene, and Southern or PCR-based assays can detect down to 1% to 5% tumor cells. IgH gene rearrangement typically is assessed first for B cells, because this gene undergoes initial rearrangement during B lymphoid development. Light chain genes, particularly the kappa gene, also may be assessed. T-cell receptor beta or gamma chain genes commonly are examined for T-lymphoid cells. Southern blot testing is more common for beta genes, although PCR assays exist for both. Clinical assays for rearrangement of lambda light chain, T-cell receptor alpha, or T-cell receptor delta chain genes are uncommon.

Although Southern blot analysis is performed by a steadily diminishing number of laboratories, it is still the gold standard for B and T cell clonal assessment. In this technique, a labeled probe that recognizes the IgH or TcR gene is hybridized to restriction-endonuclease digested sample DNA. New hybridizing bands of different size indicate clones with rearranged IgH or TcR alleles (see Fig. 19-2). Rearrangement seen with two (or more) restriction enzymes for the sample is scored as positive.[25] Clonal evolution within a neoplasm sometimes may be observed as new hybridizing bands in the presence of previously demonstrated ones (see Fig. 19-2).

Increasingly, PCR assays alone (Fig. 19-3) are performed to look for clonal rearrangements of immunoglobulin and TcR genes. Rela-

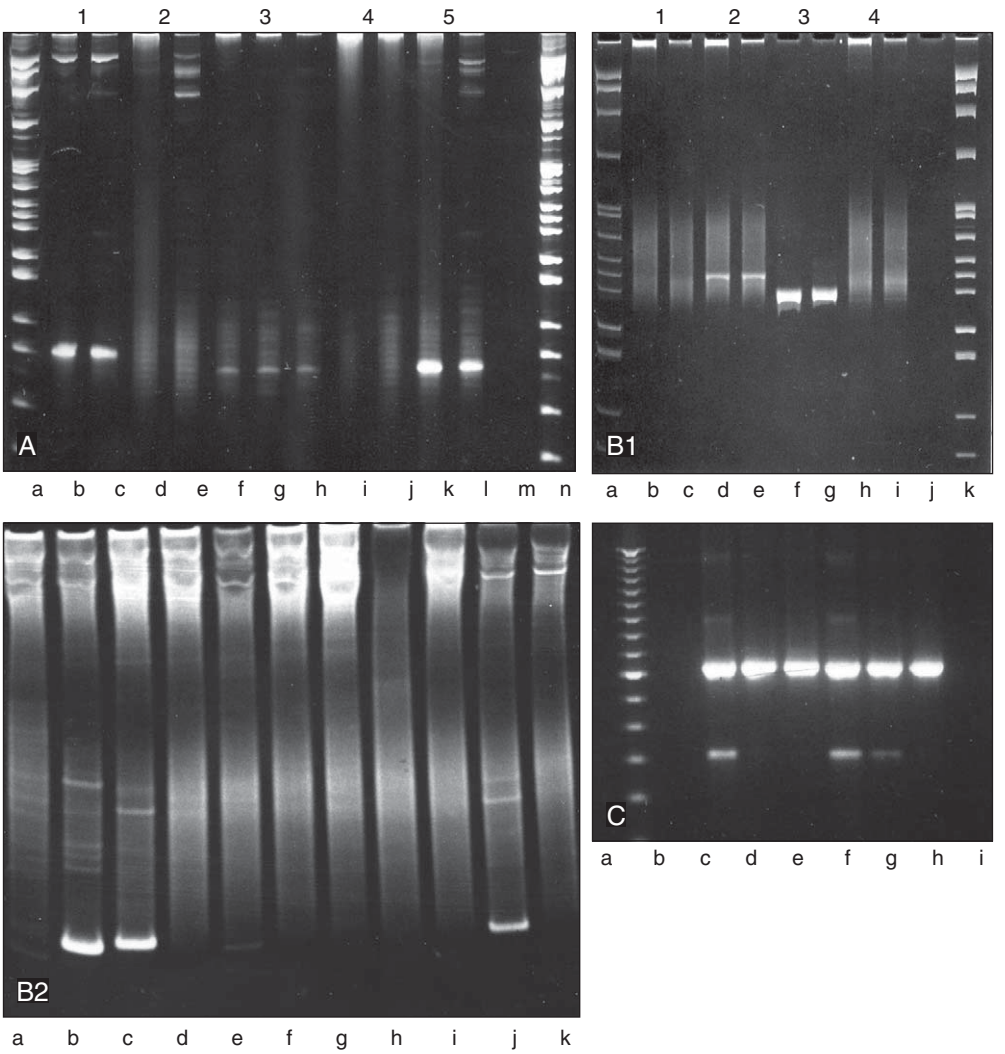


Figure 19-3 • Polymerase chain reaction (PCR) and reverse transcriptase (RT-PCR) analysis in hematolymphoid neoplasia. **A,** Immunoglobulin heavy chain gene PCR analysis. Testing is done at two or more different DNA concentrations for each of five patients. Lanes a and n are molecular size standards; lane m is a minus-DNA control to rule out potential PCR contamination. Patients 4 and 5 are known reactive (polyclonal) and lymphoma (monoclonal) samples, respectively. Patient 1 has a monoclonal process involving most cells in the specimen; patient 2 has a polyclonal process, and patient 3 has a subtle monoclonal process in a polyclonal background. **B1,** T-cell receptor gamma chain gene PCR analysis, straight electrophoresis. Patients 3 and 4 are known lymphoma and reactive samples. Patient 1 is polyclonal; patient 2 has a monoclonal process in a polyclonal background. **B2,** T-cell receptor gamma chain gene PCR analysis, homoduplex analysis. Samples are denatured following PCR amplification, allowed to renature and run on a polyacrylamide gel. Homoduplex bands at the "leading edge" of migration represent clearcut clonal specimens (lanes b,c); samples with polyclonal T-cell populations do not show distinct bands (lanes a,d,f,g,h,i). Lanes j (10% clonal + 90% polyclonal DNA) and k (100% polyclonal) are controls. A low-predominance clonal population in sample E is of uncertain clinical significance. **C,** Allele-specific amplification for *JAK2* V617F mutation. A common 3′ primer and two 5′ primers are used in a multiplex reaction; one primer amplifies all species in this area of the *JAK2* gene *(upper band),* whereas the other amplifies only species with the V617F nucleotide variant. Lane a is a molecular size ladder; lane b is empty; lanes c and f are positive patient samples; lanes d and e are negative patient samples; lane g is positive and sensitivity control with 2% JAK2 V617F in normal DNA; lane h is a normal patient; and lane i is a minus DNA control. *Note:* Size separations are shown on gels; capillary electrophoresis is an alternate analysis method.

tively conserved "framework" areas of variable (V) region gene segments serve as targets for upstream PCR primers; similarly conserved regions in joining (J) or adjacent sequences are targeted by downstream primers. Advances in PCR assay detection sensitivity and standardization have accompanied the European BIOMED-2 study, which developed and tested multiplexed groups of PCR primers that together detect the large majority of immunoglobulin and TcR gene rearrangements.[26] At this time, BIOMED-2 reagents are available in the United States only labeled as "research use only, not for use in diagnostic procedures."

The sensitivity of PCR assays typically is no more than 85% to 95% of those achieved with Southern blot.[26,27] Hematolymphoid neoplasms negative by PCR arise, presumably because PCR primers do not bind equally well to all V or J region gene segments that may participate in clonal rearrangement. The analytic sensitivity of PCR assays usually is modestly better and, in some specialized applications, markedly better than Southern assays. Samples can be analyzed rapidly if desired, and the low levels of DNA required for testing expand the range of evaluable samples, including, importantly, paraffin-embedded specimens. Immunoglobulin and T-cell receptor genes typically are tested for suspected B and T lymphoid proliferations, respectively. Immunoglobulin heavy chain gene-negative cases may show rearrangement of light chain genes or kappa-deleting elements.[26,27]

Low-level "clones" detected by PCR and Southern blot assays must be interpreted cautiously. These may represent low levels of neoplastic disease, but they also may be expansions of normal B or T cells responding to discrete antigens or other stimuli. The polyclonal ladder pattern seen in IgH PCR assays (see Fig. 19-3) is an example of this phenomenon. It is important to interpret low-predominance clonal populations in the broader context of a case. Conditions that enhance immune reactivity such as autoimmune disease may provide particular challenges. Important interpretive elements of clonality assays, and especially PCR assays, are given in Table 19-2.

Chromosomal Translocations

Molecular detection of a translocation confirms diagnosis and provides a sensitive marker for monitoring tumor burden. Molecular cytogenetic assays, such as FISH, usually are appropriate substitutes for DNA- or RNA-based assays to identify translocations in diagnostic samples. However, the ability of PCR methods to detect very low levels of tumor or minimal residual disease (MRD), makes molecular assays the standard of practice for monitoring disease (Table 19-3; Fig. 19-4). Either blood or bone marrow usually can be followed; bone marrow may have slight advantages.[28] Nested PCR/RT-PCR methods offer high detection sensitivity, but as endpoint assays cannot accurately determine levels of tumor. Most MRD assays employ real-time quantitative PCR or RT-PCR to follow the level of translocation relative to a reference transcript or gene found uni-

Table 19-2 Interpretive Cautions for Clinicians Ordering Hematolymphoid Clonality Assays

- Negative PCR results for IgH and TcR gene rearrangement or chromosomal translocation assays do not fully exclude the possibility of neoplasia, because the assay may not detect all rearrangements or translocations.
- If results are negative and a case is suggestive of neoplasia, make sure that laboratory reports indicate controls have been performed to exclude inhibitors of PCR amplification.
- Results described as "oligoclonal" or "indeterminate" for IgH or TcR gene rearrangement PCR assays should be interpreted conservatively. These may reflect self-limited reactive expansions of lymphocytes.
- Ultrasensitive qualitative "nested" PCR or RT-PCR assays for certain chromosomal translocations (e.g., BCL2/IgH, BCR/ABL) may be positive in normal individuals. It is uncommon to see such false-positive results using quantitative assays.

IgH, immunoglobulin heavy chain; PCR, polymerase chain reaction; RT, reverse transcriptase; TcR, T-cell receptor.

Table 19-3 Comparison of Methods for Minimal Residual Disease Assessment

Method	Sensitivity
Cytogenetics, conventional	1%–10%
Cytogenetics, FISH	0.2%–10%
Southern blot	1%–10%
Flow cytometry	$1/10^3$–$1/10^4$
PCR/RT-PCR, quantitative	$1/10^3$–10^5
PCR/RT-PCR, nested	$1/10^5$–10^6

FISH, fluorescence in site hybridization; PCR, polymerase chain reaction; RT, reverse transcriptase.

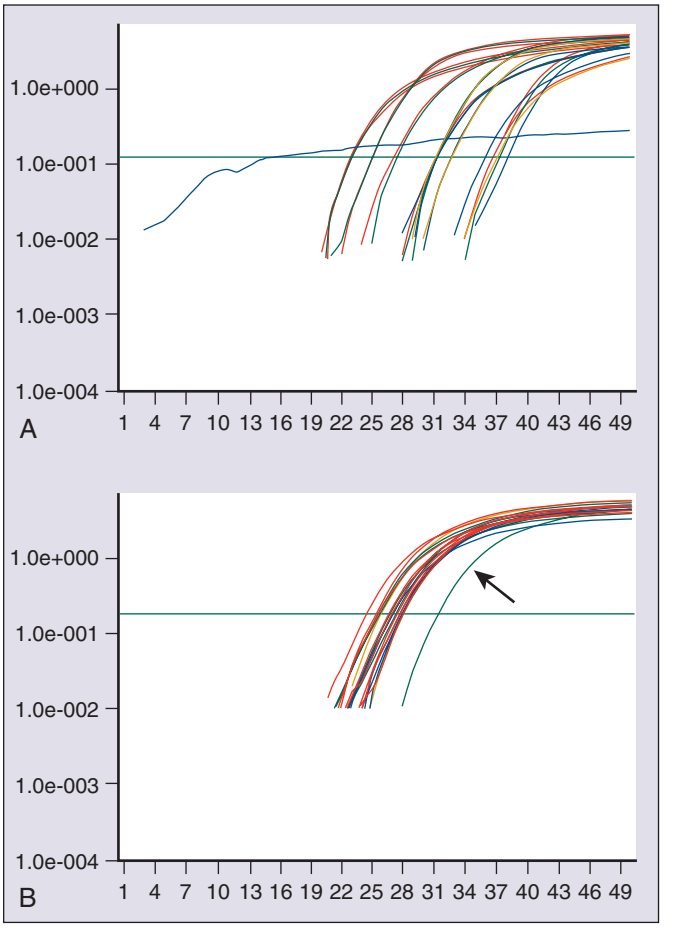


Figure 19-4 • **A,** *BCR/ABL1* transcript assessment by quantitative real-time RT-PCR. Numbers on the X axis indicate PCR amplification cycles. This panel shows amplification (the PCR cycle number at the rising curve crosses a threshold) for samples with high, 22–27 intermediate, 30–31 and lower 35–38 levels of *BCR/ABL1* major breakpoint transcript. **B,** Internal housekeeping transcript (*GUS,* beta glucuronidase) level in samples. Note that most are similar over a three-cycle range. One sample *(arrow)* is partially degraded. The ratio of *BCR/ABL1* to *GUS* transcript levels versus known standards is used as a relative quantitative measure of how much *BCR/ABL1* is present, and the logarithm reported of the fold reduction versus a baseline for patients with untreated CML.

formly in tumor and normal cells as a quality indicator.[29] Results often are provided as a $\log_{10}$ reduction or increase relative to a laboratory baseline for patients with full-blown disease.[30,31] Any value that increases or decreases by 1 log (less in some laboratories) over a prior sample is significant. Calibrators are being developed to standardize such assays among laboratories.

High-sensitivity PCR testing is not suitable to screen for disease. Low level false-positive results for *BCL2/IgH* and *BCR/ABL* translocations have been described in normal individuals and raise cautions for interpreting minimal residual disease.[32,33] Such results presumably indicate small populations of cells with a translocation that have not progressed through additional steps necessary to manifest neoplasia.

Assays in Bone Marrow Transplantation

The human leukocyte antigen (HLA) histocompatibility locus on human chromosome 6 is an exceptionally diverse region with well over 1000 alleles identified.[34,35] HLA matching of donors and recipients for bone marrow transplantation at class I and class II loci is a complex and important molecular diagnostic application in clinical oncology. Millions of potential donors have been pretyped through programs such as the National Marrow Donor Program in the United States.[36] Molecularly discrete alleles that share the same serologic (or antigenic) activity have been identified, and it is clear that high-resolution molecular typing to match donors and recipients offers benefits over low-resolution serologic typing for graft survival and graft-versus-host disease.[37] The best results with high-resolution typing are seen in those patients with the fewest class I or class II mismatches.[38] High-resolution DNA-based HLA typing is performed first with sequence-specific PCR primers or oligonucleotide probes, often followed by DNA sequencing when allele families are identified.

STR markers are used to assess engraftment and potential mixed chimerism following bone marrow transplantation.[39,40] These identity markers permit unambiguous determination of donor and recipient alleles and low levels of mixed chimerism down to a few percentage points. This information is useful in making decisions for pancytopenic patients regarding levels of immunosuppressive therapy as well as treatment for infection or recurrent disease.

Gene Mutations

Applications that target specific acquired mutations of selected genes are increasing in number. The *JAK2* V617F variant,[41] found in half or more of patients with chronic myeloproliferative disorders (CMPD), and rarely in other neoplastic myeloid disorders, has dramatically altered diagnostic approaches to patients suspected of CMPD.[42] It can be detected readily in blood; bone marrow specimens may offer increased sensitivity. Heterozygous versus homozygous status has not yet been convincingly shown to be clinically significant, but patients with polycythemia vera appear to have homozygous mutations more frequently. Should V617F become a therapeutic target,[43] quantitative assays for MRD assessment will likely follow.

Studies have revealed a range of interesting markers in patients with a normal karyotype who have AML.[44] More than one of these markers may occur in the same clone, and prognostic studies should be assessed with that knowledge. Duplications—and, to a lesser extent, point mutations[45] within the *FLT3* gene are associated with a poorer prognosis[46,47]; point mutations in selected regions of the *NPM1* gene are associated with either a normal or improved prognosis.[48–50] Expression levels of several other genes (*CEBPA, MLL, BAALC, ERG*) also have been reported to affect prognosis.[46,51–54] IgH gene variable region mutational status, perhaps combined with clinical stage, is among the most useful prognostic markers in chronic lymphocytic leukemia.[55,56] Patients with unmutated (<2% variation from consensus germline sequences) IgH genes in the chronic lymphocytic leukemia (CLL) clone do more poorly than those with mutated (>2% variation) genes.

Sequence analysis of the *ABL* kinase domain often is pursued to guide alternate therapies in patients who develop resistance to Gleevec.[57,58] RNA or protein-based assays that assess expression of drug resistance proteins such as multidrug resistance-associated P glycoprotein (*PGP*) or breast cancer resistance protein (*BCRP*) remain under investigation.[59,60]

Other Applications in Hematolymphoid Neoplasia

PCR is performed to look for viral agents associated with bone marrow failure or neoplasia—for example, parvovirus B19, human herpes virus types 6 and 8, human T-cell leukemia virus (HTLV), and Epstein-Barr virus (EBV). Quantitative levels of viruses are increasingly requested to distinguish between infection and rejection in immunocompromised patients following bone marrow transplantation. Some reports suggest that quantitative PCR assessment of EBV viral DNA levels may be a useful indicator to follow for possible emergence of post-transplant lymphoproliferative disease following solid organ transplantation.[61] Southern blot assessment of clonal or polyclonal integration of EBV viral DNA also may be useful in assessing potential cases of cases post-transplant lymphoproliferative disease for neoplastic risk. Microarray-based expression profiling applications are discussed in a following section.

SOLID TUMORS

Although useful applications of nucleic acid-based markers for diagnosis and management of patients with solid tumors have lagged behind their use for hematolymphoid neoplasia, there is recent significant growth. A range of molecular abnormalities can be detected, including chromosomal translocations, point mutations, allelic loss, gene amplification, microsatellite instability, epigenetic abnormalities such as methylation, and altered expression of single or multiple genes. Translocation, deletion, and amplification often can be detected by FISH as well as PCR or Southern blot methods for tumors with molecular abnormalities detectable by cytogenetic or molecular methods (see Table 1-6 in Chapter 18, Conventional and Molecular Cytogenetics of Neoplasia). A rich array of molecular diagnostic applications relating to sarcomas is discussed separately (see Chapter 97).

Hereditary Cancer Syndromes

Molecular genetic testing is important for a range of autosomal dominant familial cancer syndromes in patients with appropriate family history and/or clinical phenotypes. Testing usually is done on adults, but it may include children.[62] For common cancers, the nature of family history is crucial to decide whether testing a single gene makes sense.[63] Patients undergoing gene testing should receive pre- and post-test counseling and give written informed consent; they also should consider consulting a genetic counselor or geneticist.

Hereditary cancers with mendelian inheritance are a small subset (<5%) of solid tumors, but the detection of a disease-causing mutation is enormously beneficial to these patients and family members. Major syndromes include hereditary breast and ovarian cancer (*BRCA1, BRCA2, TP53,* and *CHEK2* genes), hereditary colorectal cancer with polyposis (*APC* gene), and hereditary non-polyposis colorectal carcinoma (*MSH2, MLH1* and other genes). Familial cases testing negative for mutations likely arise from undetected mutations (discussed in the following paragraphs) or complex inheritance due to abnormalities in several genes impacted by hormonal or environmental factors.

Hereditary cancers present a testing challenge because typically many mutations are spread over large areas of causative genes. This necessitates sequencing many or all exons to include exon–intron junctions or performing "mutation scanning" assays followed by sequencing regions with abnormalities. Scanning techniques such as single-strand conformation polymorphism (SSCP) analysis and denaturing high pressure liquid chromatography (DHPLC) reveal subtle physical differences caused by nucleotide changes and typically detect more than 95% of simple mutations. Guidelines exist for the functional interpretation of sequence variants,[64] which is crucial for counseling patients and family members. Previously described mutations

and neutral polymorphisms (i.e., nucleotide changes *not* associated with disease) often are available in disease-specific databases. Previously undescribed sequence variants that produce prematurely truncated proteins via nonsense, frameshift, and splice site mutations are likely to cause disease. New missense mutations that change single amino acids have uncertain functional consequences and often are reported as "variant of uncertain significance (VUS)." Segregation studies of a variant among family members may be helpful, and conversion analysis, a technology that separates and allows study in isolation of mutant patient alleles, facilitates functional resolution for many alleles that fall into the VUS category.[65] Major structural changes such as partial loss or duplication within a gene can be the basis for mutation in 15% to 20% of cases in hereditary cancers such as breast cancer due to *BRCA1*.[66] Sequencing and screening methods rarely detect major structural changes, because no unique DNA nucleotide changes result. Newer methods such as MLPA[67] permit comprehensive screening for duplications and deletions focused on changes in copy number of exons.[68–71]

Many other hereditary cancer syndromes can be sought clinically or on a research basis. A selected group with genes that can be analyzed focusing on fewer than 10 exons includes MEN-2; type 2 multiple endocrine neoplasia (*RET*)[72,73]; hereditary paraganglioma/pheochromocytoma (*SDHD, SDHB, SDHC*)[74,75]; Li-Fraumeni syndrome (*TP53*)[76]; von Hippel-Lindau syndrome (*VHL*)[77,78]; type 1 multiple endocrine neoplasia (*MEN1*)[79–81]; and Cowden syndrome (*PTEN*).[82,83]

Allele Imbalance and/or Copy Number Variation

The development of solid tumors commonly is accompanied by genetic instability leading to loss and, less commonly, amplification of small or larger regions of DNA from various chromosomes.[84,85] Such loss of heterozygosity (LOH) can be measured in two ways: (1) via PCR assays directed at microsatellite length polymorphisms that occur throughout genome, or (2) using single-nucleotide polymorphism (SNP) microarrays.[20,86] In the first, the ratio of different-sized alleles in the sample of interest can be compared to the ratio obtained from a normal (often adjacent) sample of the same individual. These ratios normally should be ~1.0. Because of connective tissue and vascular and inflammatory cells within a tumor, a marker may not be lost entirely, and conservative ratios (e.g., <0.66 or >1.50) typically are used to determine whether there is LOH for a marker. In a SNP array, hybridization levels of labeled sample DNA are compared to normal patterns at thousands of known normal and variant genomic sequences represented on the array.

Useful clinical applications of LOH analysis include evaluation of oligodendrogliomas, where LOH for markers on the short arm of chromosome 1 and the long arm of chromosome 19 are both diagnostic and prognostic[87,88]; to detect recurrence in bladder cancer[89]; and to discriminate, by comparing LOH patterns, de novo second primary tumors from metastatic spread of a single primary tumor.[90] Potential utility also has been demonstrated with cytologic bile duct brushing samples for pancreatic neoplasia, which can be combined with direct analysis for *KRAS* mutations.[91,92] Because STR analysis is a form of genetic identity testing, these sorts of sample screens also are useful to resolve the vexing question of whether a tissue "floater" from one specimen has somehow become included in the paraffin block of another.[93] High-resolution SNP arrays produce complex data that must be correlated clinically but show promise for revealing patterns in neoplastic or preneoplastic lesions.[94,95]

Gene Mutations

In addition to full gene or targeted sequencing in hereditary cancer syndromes, specific somatic sequence alterations have been described in various tumor specimens. Given the variability among studies, well-designed clinical trials are essential to establish the utility of individual biomarkers or panels in diagnosis, prognosis, selection of therapy, and population screening.

One useful application not directed at a specific gene or mutation is microsatellite instability (MSI) analysis.[96,97] In some tumors, additional, often minor, bands of different size are noted in addition to the bands corresponding to germline alleles seen in normal cells. MSI bands reflect genetic instability leading to insertions or deletions of nucleotides within an STR or single nucleotide repeat sequence; the additional alleles are believed to result from defects in mismatch repair (MMR) systems under control of genes such as *MSH2* and *MLH1*. MSI is useful as a screening assay for colon (Fig. 19-5) or other tumor tissue from patients suspected of the HNPCC syndrome. A positive MSI result typically triggers immunohistochemical testing of MMR gene expression and, based on those results, direct sequencing to identify potential germline mutations.[98] Whether MSI contributes to improved survival in colon cancer is controversial; disease-free but not overall survival may be improved.[99] A small percentage (~15%) of sporadic colorectal cancers also demonstrate MSI, and screening for the common *BRAF* mutation may allow their identification, thus saving workup for HNPCC.[100]

Mutations in the tyrosine kinase domain of the epidermal growth factor receptor (*EGFR*) gene identified in 10% to 20% of North American, and a higher percentage of Asian, non-small-cell lung cancers initially were thought to correlate with higher response rates to the EGFR-targeted agents gefitinib and erlotinib,[101] although a clear survival benefit has been difficult to demonstrate and results have varied among studies. *EGFR* mutations are more common in patients with adenocarcinomas, women, and individuals who have never smoked. Targeted sequencing of *BRAF*, *RET/PTC* and *RAS* genes for specific mutations may offer potentially useful information for prognosis and management in patients with papillary thyroid carcinoma,[102] although the frequency of their detection appears to be method-dependent.[103] Oncogenic mutations of *KIT* or platelet-derived growth factor receptor alpha (*PDGFRα*) are common and serve as useful therapeutic targets for tyrosine kinase inhibitors in gastrointestinal stromal tumors (GIST); as in CML, development of secondary mutations leads to resistance.[104] Mutations in the p53 (*TP53*) gene, a prominent feature of the hereditary Li-Fraumeni syndrome, occur in somatic form in half of all human cancers, with lower levels in leukemia and higher levels in colorectal and ovarian cancer. A number of studies suggest a role for this central mediator of cell death in tumor behavior and response to treatment, but its

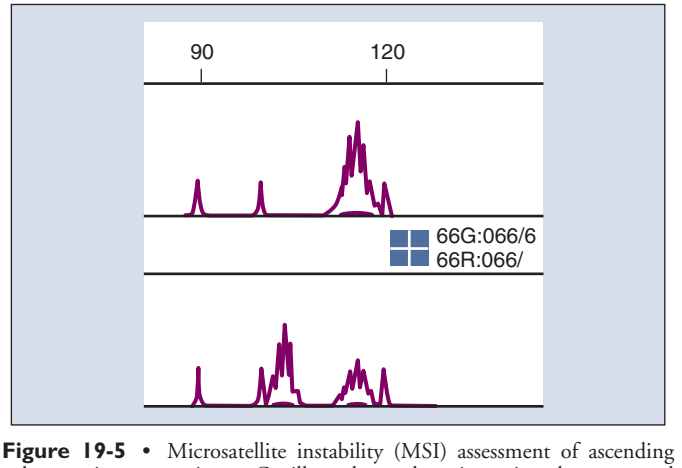


Figure 19-5 • Microsatellite instability (MSI) assessment of ascending colon carcinoma specimen. Capillary electrophoresis tracing shows normal *(upper)* and tumor *(lower)* analysis by STR (BAT26) analysis. The jagged peak in the upper tracing represents apparent homozygosity for a single allele. The jagged appearance arises from "stutter" during PCR amplification. Note the novel, smaller (left-shifted) allele in the tumor. This sample showed additional MSI using other markers; immunohistochemistry demonstrated MSH2 protein expression in normal colonic eithelium but not in tumor cells. (Courtesy of Antonia Sepulveda, MD.)

interactions are complex, and diagnostic, prognostic, or therapeutic utility requires much study.[105,106]

The potential to look for mutations from desquamated adenoma or carcinoma cells in stool as a screening approach for colonic cancer has been entertained for some time.[107] DNA seems to be stable for reasonable amounts of time as it traverses the colon and in collected stool. Studies targeting stool in large numbers of patients using multitarget assays that detect 15 to 21 mutations have performed better than fecal occult blood detection in detecting invasive cancers or adenomas with high-grade dysplasia; however, these assays still are not as good as colonoscopy.[108,109]

Extremely-high-throughput picoliter DNA sequencing platforms offer the potential to assess the full spectrum of simple nucleotide sequence mutations in cancers at very low levels and to follow changes over time.[110,111] Early studies indicate enormous breadth and complexity for investigators to probe and validate for clinical significance.

NEWER DIAGNOSTIC TECHNIQUES AND POTENTIAL APPLICATIONS

Epigenetic Markers

Another approach to detection of cancer-related alterations in a wide range of tumors[112] is the study of cytosine methylation status in upstream CpG islands; these show promise as early screening markers for cancer in relatively noninvasively obtained specimens such as saliva, sputum, pleural fluid, pancreatic juice, or even peripheral blood.[113–117] Silencing/inactivation has been associated with hypermethylation of tumor suppressor genes, DNA repair genes, or proto-oncogenes believed to be causal or linked to mutational changes in the development of cancer. Evidence also has been presented that as neoplasia develops, hypermethylation affects different gene groups progressively. Methylation markers may be useful for tumor diagnosis or subclassification.[118] The most extensively studied genes and tumors include *MSH2, MLH1,* and *CDKN2A*-p14 (colorectal, including patients with ulcerative colitis), *GSTP1* and *RASSF1A* (prostate), and *CDKN2A*-p16 (lung, esophagus, and pancreas). A number of other hypermethylated genes also have been described in lung and other cancers. For some genes (*KRAS, HRAS, MYC, FOS, BCL2*) hypomethylated status has been associated with neoplasia. Methylation status in some tumors correlates with their response to therapy,[119] and prognostic differences in leukemia or myeloma suggest possible therapeutic use of hypomethylating agents.

Pharmacogenetic Assays

The pharmacogenetic paradigm for personalized medicine in cancer is thiopurine-S-methyl transferase,[120] the homozygous absence of which in 1 of 300 individuals can lead to marrow aplasia following standard doses of 6-mercaptopurine or azathioprine in patients with acute leukemia or inflammatory bowel disease or post transplantation. An understanding of increasing numbers of common and rare gene polymorphisms associated with metabolism of anticancer drugs such as glucuronidation of irinotecan by *UGT1A1*[121,122] holds promise of developing a better dose schedule for effective treatment and fewer adverse reactions. Many pharmacogenetic relationships are complex, and clinicians understandably hesitate to use assays in the absence of validated algorithms. Genotyping by molecular methods offers distinct advantages, but may produce some false negative results.[123,124]

Microarrays

Microarray expression profiling for diagnosis, classification, and therapeutic selection in an assortment of leukemias and lymphomas has demonstrated impressive power in investigational studies.[125–132] Expression profiling also has been a powerful tool for biomarker discovery in the diagnosis and management of patients with solid tumors, and profiling studies of solid tumors have provided exciting results despite the seemingly greater challenge of analyzing samples with varying numbers of nonneoplastic vascular, stromal, and inflammatory cells. Initially dogged by reproducibility issues among laboratories, recent consortium studies indicate that commercially manufactured arrays are promising for clinical use.[133–135] The first cancer-directed microarray assay was approved by U.S. regulatory agencies in February 2007 for breast cancer assessment,[136] and other applications are in the pipeline, including those for assessment of metastatic tumor of unknown origin, leukemia, lymphoma, and colorectal cancer. Although clinical trials data are lacking, arrays theoretically offer platforms to predict response and aid selection of individualized therapies.[137] Because a modest number of targets (<100, or possibly even <10) may contain the bulk of useful information, targeted assays using quantitative RT-PCR or low-density-array platforms may be viable clinical platforms.[138–143] Prior studies and recent data suggest there may be overlapping or even distinct sets of genes that give comparable predictions.[144] Some assays may be done on paraffin-embedded tumor samples, but if array-based assays become more prevalent, pathologists and surgeons accustomed to placing biopsy specimens in fixative for morphologic and immunohistochemical analysis may need to adapt, because RNA from fresh tissues is likely to provide the highest-quality results. The use of microdissection (manual and laser-capture aided) to enrich with relevant regions for analysis is likely to increase.

Cancer-Specific Detection at Low Levels in Blood, Bone Marrow, and Tissue

For some time, investigators have probed the utility of tumor-specific molecular markers to identify metastatic carcinoma cells in sentinel or other lymph nodes or circulating in the blood with the hope of using such assays to determine patient prognosis and, in some cases, management.[145] Work has continued to detect cells by both molecular and nonmolecular methods.[146,147] Some groups have developed rapid PCR methods that would allow such markers to be used intraoperatively,[148] but these applications have remained resistant to clinical application in the absence of prospective trials. Difficulties have included false-positive results due to a lack of specific expression or expression from pseudogenes. False-positive results also have been noted in normal control samples. Advances in assays performed on cell-free circulating nucleic acids[149] offer alternate possibilities.

MicroRNAs

It has become increasingly clear that microRNAs (miRNAs), which are small RNA molecules of 19 to 24 nucleotides, play important roles in the regulation of normal gene expression. Accumulating evidence indicates that miRNAs, individually or in groups, act as tumor suppressors or oncogenes in hematolymphoid and solid tumors.[150–152] Assays that target or profile miRNAs are very likely to become available in the near future.

BUSINESS, REGULATORY, AND ETHICAL ISSUES IN MOLECULAR DIAGNOSTICS

Business and regulatory trends continue to affect molecular diagnostic testing in oncology. Oncologists probably will see package inserts recommending pharmacogenetic testing for increasing numbers of pharmaceuticals. As noted earlier in this chapter, interpretation of genotypes in the context of other medications and patient status probably will be complex.

Intellectual property positions on tumor markers, nucleic acid variations, techniques, and clinical applications are significant.[153,154] The *BRCA1* and *BRCA2* genes for hereditary breast and ovarian cancers are a well-known example. Patents to both genes are held by a single entity, and full gene analysis in the United States is restricted to a single laboratory. Exclusive licensing of patents also leads to single-provider situations. Conflicts have not yet emerged, but clini-

cians and laboratories remain concerned that panels of molecular markers in microarrays or other platforms may be delayed or difficult to offer because of multiple and conflicting patents.

There is continued government and public interest in oversight of molecular testing, particularly laboratory-developed tests. The Food and Drug Administration (FDA) has circulated revised guidelines for analyte-specific reagents, the basis for laboratory-developed tests. It appears that the FDA will require review and clearance of "special controls" for a new class of assays—in vitro diagnostic multi-analyte index assays—which process multiple laboratory results and, sometimes, clinical information to provide treatment recommendations via proprietary interpretive algorithms. Both developments may affect the types of complex assays available. Standards and calibrators should produce improved comparability of results among laboratories and methods. Beyond hereditary cancer syndromes, it is unclear whether establishing a genetic specialty area for laboratory accreditation, proposed by some, might affect molecular testing in oncology.

Payment for increasingly complex molecular assays continues to be a challenge. Reimbursement for molecular testing is governed largely by Current Procedural Terminology (CPT) codes, whose levels were undervalued initially and have gone largely unrevised for 15 years. Reimbursement levels typically are not sufficiently attractive to justify investment in oncology assay development at biotechnology companies, a situation that has prompted developers of complex assays to approach third-party payers directly to request payment under "miscellaneous" billing codes. Proposals have been advanced regarding improved payment for new technologies, but with political pressures for budget neutrality, the possibility of better reimbursement remains uncertain.

SUMMARY

Over the next two decades, molecular diagnostic assays will become increasingly important tools for the determination of tumor diagnosis, prognosis, and residual presence, as well as initial and follow-up therapy. Targeted individual molecular markers probably will remain useful, and may even be predominant for the near future. However, validated panels of markers or expression profiling of tumors using microarrays or proteomic methods show potential to dramatically supplement or replace single markers in determining diagnosis, prognosis, and whether available therapies will be beneficial. New understandings of molecular pathogenesis in cancer will develop from continuing research with microarrays and proteomic methods, leading, we hope, to targeted therapies and opportunities to monitor treatments with molecular assays. Intellectual property and regulatory actions may limit the rate at which clinical applications are developed because of licensing and cost considerations. There will be increasing demands on physicians to ensure that patients understand the impact molecular tests have on decisions for their management, and, with a plethora of possibilities, to choose wisely for cost-effectiveness.

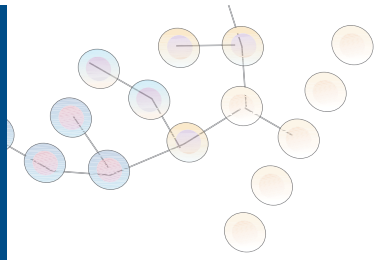
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20 Biomarkers for Cancer Diagnostics

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SUMMARY OF KEY POINTS

Serum Tumor Markers

Key Methods

- Radioimmunoassay and, more recently, enzyme and other immunoassays are cornerstones of cancer diagnostic methods.
- Monoclonal antibodies have been produced against a wide variety of secreted antigens.

Applications

Screening and Early Detection

- In most tumor systems, biomarkers do not have sufficient sensitivity and specificity for routine population screening, although combining them with other approaches can improve utility.
- In some high-prevalence situations tumor marker screening is appropriate (e.g., prostate-specific antigen [PSA] for prostate cancer).

Diagnosis

- Levels of particular markers are useful adjuncts to diagnosis in many tumor systems, including ovarian cancer, germ cell tumors, or neuroendocrine tumors.
- In some tumor systems, serum markers contribute to staging information and help direct therapy.

Monitoring

- Most serum tumor markers are useful to monitor treatment or progression of cancer.
- A decrease in tumor marker levels can be used as a means to assess the success of surgery or chemotherapy.
- An increase in a tumor marker can be a harbinger of relapse or disease progression.

INTRODUCTION

Tumor markers, also called *cancer markers, biomarkers*, and, in some instances, *cancer-associated antigens*, are substances present in or produced by a tumor itself or produced by the host in response to a tumor that can be measured in the blood or secretions and used to differentiate a tumor from normal tissue or to determine the presence of a tumor. Such substances can be found in cells, tissues, or body fluids. They can be measured qualitatively or quantitatively by chemical, immunologic, or molecular biologic methods to identify the presence of a cancer. A wide spectrum of molecules may be classified as tumor markers, including enzymes, hormones, oncofetal antigens, carbohydrate markers, blood group antigens, proteins, receptors, and genes or gene products.[1] Although, strictly speaking, tumor markers can be recovered from any tissue or fluid, this chapter is devoted largely to those that are secreted or shed and detectable in serum.

The first recognized tumor marker was the Bence-Jones protein, discovered in 1847 by precipitation of a protein in acidified boiled urine. This protein, the monoclonal light chain of immunoglobulins secreted by tumor plasma cells, still is used in the diagnosis of multiple myeloma. The first half of the twentieth century included the discovery of hormones, for example, human chorionic gonadotropin (hCG); enzymes, for example, acid phosphatase (for prostate cancer); and isoenzymes and proteins whose concentrations are altered in biologic fluids in malignancy. The discoveries of α-fetoprotein (AFP) and carcinoembryonic antigen (CEA) in the 1960s led to the use of tumor markers for monitoring and to the use of the term *oncodevelopmental markers*, coined because these markers were produced both in fetal development and in tumors.

An ideal tumor marker should be specific for a given type of cancer and undetectable in healthy people or in those with benign disease, as well as sensitive enough to detect small tumors for early diagnosis or during screening. Unfortunately, most known tumor markers are neither specific nor sensitive enough for these purposes. Other desirable characteristics include concentrations proportional to tumor volume; short half-lives to allow early assessment of response to therapy; predictable increases and decreases in concentration responding to cancer progression and regression; and ability to be measured in a standardized and reproducible fashion in easily accessible specimens. In practice, tumor markers are most useful in evaluating the progression of disease status after the initial therapy and in monitoring the effectiveness of subsequent treatment.[1–3]

Despite the numerous tumor markers that have been identified, relatively few are in routine clinical use. Practice guidelines and recommendations for the use of tumor markers in a range of cancers have been developed by groups of scientists and clinicians from the National Academy of Clinical Biochemistry[4,5] and the European Group on Tumor Markers,[6] although scientist and clinician viewpoints on the use of tumor markers do not always agree. The use of tumor markers is also included in *Practice Guidelines in Oncology* from the National Comprehensive Cancer Network,[7] and the American Society for Clinical Oncology has published recommendations for selected cancers.[8,9] Practice guidelines from these and other national and international organizations are summarized by Fleisher and colleagues[4] and Sturgeon.[10]

Tumor marker use in the United States is limited compared with that in other countries as a result of required approval by regulatory agencies such as the U.S. Food and Drug Administration (FDA), which influences reimbursement. In addition, the FDA typically

Table 20-1 FDA-Approved Tumor Markers

Analyte	Associated Cancer	Designated Indication
Serum, Plasma		
CA15-3, CA27.29	Breast	Monitoring; recurrence
HER-2	Breast	Monitoring
Circulating tumor cells (CellSearch; whole blood)	Breast	Prognosis in metastatic disease
CA125	Ovarian	Monitoring; second-look evaluation
CA19-9	Pancreatic	Monitoring
Total PSA, complexed PSA (cPSA)	Prostate	Detection in men aged ≥50 y in conjunction with DRE; monitoring; prognosis
Free PSA	Prostate	Aid in distinguishing prostate cancer from benign prostate conditions in men ≥50 y with a total PSA of 4–10 ng/mL and nonsuggestive DRE in conjunction with total PSA (% free PSA)
Prostatic acid phosphatase	Prostate	Monitoring
Carcinoembryonic antigen	Colorectal, breast, lung	Monitoring; prognosis
AFP	Nonseminomatous testicular	Monitoring
AFP-L3	Hepatocellular	Risk assessment
Des-γ-carboxy prothrombin	Hepatocellular	Risk assessment
Thyroglobulin	Thyroid	Monitoring (in patients without thyroglobulin autoantibodies)
Soluble mesothelin-related peptides	Mesothelioma	Monitoring
β-human chorionic gonadotropin	None	Detection of pregnancy (not approved as a tumor marker)
Urine		
BTA stat, BTA TRAK	Bladder	Management in conjunction with cystoscopy
NMP-22	Bladder	Diagnosis in symptomatic patients or those with risk factors; recurrence
Tumor cell markers (ImmunoCyt)	Bladder	Management in conjunction with urine cytology and cystoscopy
Tissue		
Estrogen and progesterone receptors	Breast	Assessing the likelihood of response to therapy; prognosis and management
HER-2	Breast	Identify patients eligible for trastuzumab (Herceptin) treatment
EGFR	Colorectal	Identify patients eligible for cetuximab treatment

AFP, α-fetoprotein; BTA, bladder tumor antigen; DRE, digital rectal examination; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; NMP, nuclear matrix protein; PSA, prostate-specific antigen.

approves assays for specific clinical applications that may limit their use in other clinical settings. Currently approved markers and associated cancers and applications are listed in Table 20-1.

METHODS

A new era in the tumor marker field began with the introduction of radioimmunoassay in the 1960s. In the 1970s, the development of enzyme-linked immunosorbent assays (ELISAs) and the discovery of monoclonal antibodies led to improvements in marker measurement and discovery of new markers. Cell-surface antigens identified with the use of monoclonal antibodies, such as the carbohydrate antigens CA125 and CA15-3, demonstrate improved clinical sensitivity and specificity compared with the oncofetal antigens. Recently, studies of oncogenes and tumor-suppressor genes, as well as development of molecular techniques such as recombinant DNA technology, polymerase chain reaction (PCR), and automated sequencing, have resulted in the understanding and use of tumor markers at the molecular level.[1,2] New genomic and proteomic methods, such microarrays and matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry[11,12] will affect not only the discovery of new tumor markers, but also the way they are measured.

CLINICAL APPLICATIONS OF TUMOR MARKERS

Screening and Early Detection

Several factors must be taken into account when screening for a disease. The disease must be important, common, and the cause of substantial morbidity and mortality. An understanding of the natural history of the disease must ensure that early detection can affect the clinical course, and effective treatment must be available. The testing method also should be economical and noninvasive. When deciding to apply screening techniques, particularly if biochemical or immunochemical markers are used, an understanding of the analytic sensitivity (i.e., lowest detectable limit) and analytic specificity (i.e., extraneous interference) is essential. The precision of the assay (i.e., its ability to reproduce the results) also must be known and acceptable for use in large population studies. Clinical sensitivity and specificity, combined with the prevalence of the disease in the population, will affect the positive predictive value.[13]

Screening programs are most successful in regions or populations where specific cancers are highly prevalent. AFP concentrations have been used as a screening test for hepatocellular carcinoma in high-

incidence areas including China, Japan, Taiwan, Africa, and Alaska. With a cutoff in the range of 10 to 20 μg/L, AFP has been shown to have a sensitivity of between 60% and 90% and a corresponding specificity of 70% to 80%, although hepatitis and cirrhosis also may cause elevated values.[1,3] The American Cancer Society (ACS) has published specific recommendations for the early detection of breast, colorectal, prostate, and cervical cancers,[14] although among these cancers, the only serum tumor marker that is part of any screening algorithm is PSA.

Although controversy still exists on the value of early detection programs for prostate cancer, the ACS and the American Urological Association recommend PSA and digital rectal examination (DRE) annually beginning at age 50 for men with a life expectancy of at least 10 years.[14] It is recommended that prior to testing, men be offered information about the benefits and limitations of PSA testing so that they can make an informed decision with the assistance of their clinician. Other professional organizations, including the U.S. Preventive Services Task Force (USPSTF), American Academy of Family Physicians, and the American Medical Association advocate individualized testing decisions between patients and their clinicians, but do not recommend routine prostate cancer screening with either DRE or PSA. The USPSTF acknowledges that PSA testing is effective in identifying early prostate cancer, but did not find sufficient evidence that early detection improved health outcomes.[15]

Although PSA is for all intents and purposes organ specific, it is not cancer specific. PSA may be elevated (>4 ng/mL) in men with benign prostatic disease such as benign prostatic hyperplasia (BPH). PSA elevations also may occur with aging and with conditions such as prostatitis. Thus a number of methods have been proposed to increase the clinical utility of PSA for the early detection and diagnosis of prostate cancer, particularly in the diagnostic gray zone of 4 to 10 ng/mL, where there is significant overlap in PSA concentrations between prostate cancer and BPH. These approaches include age-specific reference ranges, PSA density, PSA velocity, and PSA molecular forms.[16,17] The premise behind age-specific references (0–2.5, 3.5, 4.5, and 6.5 ng/mL for age ranges 40–49, 50–59, 60–69, and 70–79 years, respectively) is that lowering the upper end of the reference range in younger men would potentially increase sensitivity and aid in detecting organ-confined tumors earlier when surgery may be curative, whereas extending the range in older men would increase specificity, taking into account small increases in prostate volume, and PSA production and secretion with aging. However, because extending the range in older men may miss significant cancers, the use of age-adjusted ranges is controversial.

Assessment of PSA density, the ratio of PSA to prostate volume determined by transrectal ultrasound, is another method to increase PSA specificity; this assessment attempts to adjust for the increased volume often found in BPH. Limitations to PSA density include inaccuracies in measurement of prostate size and reduced sensitivity of prostate cancer detection. PSA velocity, similar to an approach used with CA125 for ovarian cancer, is defined as the change in PSA concentrations over time. A velocity of 0.75 ng/mL per year or more is suggestive of cancer. At least three PSA measurements 12 to 18 months apart are needed to calculate velocity. The effectiveness of this approach may be diminished by interassay and interlaboratory variation.

The most successful approach to increase the clinical utility of PSA in the 4- to10-ng/mL range is assessment of the free and complexed forms of the PSA molecule. In the early 1990s, it was discovered that the majority of PSA measured in serum is complexed to protease inhibitors (~80% to 90%), with only a small portion in the free or unbound form. It also was discovered that men with prostate cancer, benign prostate disease, and no disease may differ in the proportions of free PSA and PSA bound to α_1-antichymotrypsin. Although the mechanism currently is unknown, patients with prostate cancer have a lower percentage of free PSA (free PSA/total PSA) compared with men with benign disease. By using a cutoff of 25% in men with a negative DRE, 95% of cancers can be detected while sparing 20% of unnecessary biopsies.[16]

In other tumor systems, in most cases individual tumor markers lack sufficient sensitivity and specificity for screening. For this reason, an approach to improve their utility is to combine analysis of the marker with other procedures. In ovarian cancer, for example, strategies have included combining CA125 with ultrasound or using a two-stage strategy in which ultrasonography is performed only if CA125 concentrations are elevated. In a study of 4000 women, the specificity of CA125 plus ultrasound was 99.9% compared with 98.3% for CA125 alone. Other strategies that have been proposed to improve the specificity of CA125 include the use of multiple markers, including OVX1 and M-CSF. However, requiring elevation of all markers, while increasing specificity, sacrifices sensitivity; similarly, when markers are complementary, if elevation of only one marker is used as an indicator of disease, then specificity is lost.[18,19]

Tumor Markers in Diagnosis

Lack of sensitivity and specificity limits the use of tumor markers for cancer diagnosis, although in contrast to screening of the general population, the prevalence of disease is likely to be higher in diagnostic situations. In most cases, histologic confirmation in tissue remains the gold standard for primary diagnosis, although tumor markers can still play a useful role, especially when combined with other methods, and may aid in differentiating benign and malignant disease or in identifying histologic tumor type.

For example, CA125, although still controversial as a screening marker, is more accepted as an adjunct in distinguishing benign from malignant disease in women, particularly in postmenopausal women with ovarian masses,[20] where elevated concentrations of CA125 greater than 95 U/mL in postmenopausal women can discriminate malignant from benign pelvic masses with a positive predictive value of 95%.[16] In premenopausal women, benign conditions resulting in elevated CA125 levels may be a confounding factor. The multiple markers approach has been applied to the preoperative discrimination of malignant and benign pelvic masses by using a number of analytic techniques.[21,22]

AFP and hCG can play a useful role in the classification of germ cell tumors. AFP is the major serum protein of the early fetus synthesized by the fetal gut, liver cells, and yolk sac. hCG is a glycoprotein consisting of two distinct subunits and is synthesized and secreted by the placental syncytiotrophoblast. In seminomas, AFP is not elevated, but hCG is present in 10% to 30% of cases. Either hCG or AFP or both are produced by 60% to 90% of nonseminomatous germ cell testicular tumors at the time of diagnosis. Both markers are elevated in embryonal carcinoma (hCG > 65%; AFP > 70%), but these markers are not useful in teratomas. AFP is elevated in yolk sac tumors, whereas hCG is elevated in choriocarcinomas, and therefore useful in gestational trophoblastic disease as well. Typical reference values for AFP are 10 to 15 μg/L, whereas 5 IU/L is often used as a cutoff for hCG in testicular cancer. Clinically, assays for total β-hCG, measuring both intact hCG and the free β-subunit, may be preferable because of the production of free β-subunits in cancer.[1]

Other tumor markers play a role in testicular cancers. Placental alkaline phosphatase, another oncodevelopmental marker, can be elevated in seminomas and in a number of other cancers. Sensitivity is increased when it is combined with the nonspecific enzyme marker lactate dehydrogenase (LDH). LDH concentrations further correlate with tumor burden and, therefore, with prognosis.[1,23]

Tumor markers also may play a role in the diagnosis of neuroendocrine tumors.[1,3,24] For example, the diagnosis of pheochromocytoma usually is established with an increase in the urinary excretion of catecholamines or catecholamine metabolites. Similarly, catecholamine metabolites vanillylmandelic acid (VMA) and homovanillic

acid (HVA) are useful markers for neuroblastoma. Calcitonin is used in medullary thyroid cancer, with increased diagnostic sensitivity resulting from stimulation of calcitonin release with pentagastrin, whereas urinary 5-hydroxyindoleacetic acid (5-HIAA) is the primary test for overproduction of serotonin in carcinoid tumors. Specific circulating serum tumor markers may aid in the diagnosis of pancreatic endocrine tumors (e.g., insulin in insulinomas, gastrin in gastrinomas, glucagon in glucagonomas, and somatostatin in somatostatinomas). It also has been suggested that neuron-specific enolase (NSE), an isoenzyme of the glycolytic enzyme enolase found predominantly in neurons and neuroendocrine cells and elevated in neuroendocrine tumors, may be helpful in the diagnosis of small cell lung cancer in the small percentage of cases in which it is not possible to establish a diagnosis by biopsy.

Prognosis and Prediction of Therapeutic Response

The clinical staging of cancer can be aided by tumor markers, because the serum level of the marker typically reflects tumor burden. The marker value at the time of diagnosis may be used as a prognostic indicator for disease progression and patient survival. Tumor markers may be included as staging criteria for some cancers, as, for example, with CEA and colorectal cancer,[25] LDH in lymphoma,[26] or LDH, hCG, and AFP in testicular germ cell tumors.[27] They also may be combined with other clinical parameters in staging nomograms, such as PSA with preoperative clinical stage and biopsy Gleason score to predict pathologic stage in men with prostate cancer.[28]

In contrast to serum tumor markers, a number of tissue markers play a significant role in predicting response to therapy, particularly in breast cancer, where estrogen and progesterone receptors are used as predictive indicators for response to hormonal treatment and measurement of *c-erb*B-2 (HER-2) overexpression is used to identify patients for whom treatment with trastuzumab (Herceptin) may be beneficial.

Monitoring Disease

Most serum tumor markers are used to monitor treatment and progression of cancer. Markers may be used to determine the success of the initial treatment (e.g., surgery or radiation), detect recurrences of cancer, and monitor the effectiveness of treatment.[1] If surgery is successful, a marker level that was elevated before surgery should decrease afterward. The expected rate of decrease is projected from the half-life of the marker. If the half-life after treatment is longer than the marker's known half-life, it can be assumed that the treatment has not been successful in removing the tumor. The magnitude of marker reduction may, however, reflect the degree of success of the treatment or the extent of disease involvement. PSA is particularly useful for determining the success of initial surgical or radiation treatment of prostate cancer. If the tumor was organ confined and all prostatic tissue was removed, after radical prostatectomy PSA concentrations should decrease to undetectable levels. After allowing for sufficient clearance of pretreatment PSA (total PSA half-life of 2 to 3 days), finding detectable post-treatment PSA suggests remaining prostate tissue or the presence of metastases.[18]

In recurrent cancer after a successful initial treatment, marker values may not appear within the normal half-life. They may decrease to a steady level that is higher than normal, or remain within the reference interval for healthy individuals. A subsequent increase in the marker values suggests recurrence of the cancer.[1] Serum tumor markers may detect "biochemical recurrence of disease" before clinical evidence. Ultrasensitive PSA assays allow earlier detection of prostate cancer after radical prostatectomy. In patients with breast cancer receiving adjuvant chemotherapy, elevation of the breast cancer marker CA27.29 has been shown to indicate recurrent disease before any clinical evidence appears. Early detection of cancer recurrence may be helpful if it makes it possible to initiate early treatment or change therapy, but it is useful only if effective treatment is available.[13]

Levels of most tumor markers correlate with the effectiveness of treatment and response to therapy. In breast cancer, the concentration of markers such as CA27.29 changes with the treatment and the clinical outcome of the patient, as does CEA in colorectal cancer, CA 19-9 in pancreatic cancer, and CA125 in ovarian cancer. Marker values usually increase with progressive disease, decrease with remission, and do not change significantly with stable disease. Tumor-marker kinetics are, in general, more important than individual values, although interpretation of kinetic changes may be complicated. For example, marker levels in response to treatment may show an initial delay before demonstrating the expected pattern of change.[29]

The Working Group on Tumor Marker Criteria of the International Society for Oncodevelopmental Biology and Medicine[30] has published the following criteria for the interpretation of changes in tumor marker values:

- "If no therapy is given, at least a linear increase in three consecutive samples (i.e., two time intervals) on a log scale should be registered to establish a recurrence. Usual intervals could be 3 months but are clinically determined. After a first increase, next samples should be taken after 2 to 4 weeks, irrespective of the absolute level." If therapy is given, the changes in marker values should reflect the clinical progression of the disease.
- "Progressive disease is defined by an increase in the marker level of at least 25%. Sampling should be repeated within 2 to 4 weeks for additional evidence. The sampling interval during therapy may depend on the type of tumor and should be related to clinical follow-up." A decrease in marker value of at least 50% is indicative of partial remission "with the concept that tumor load is related to the changes in serum tumor marker levels."
- The Working Group also provided a general statement that "a complete remission cannot be determined by tumor marker levels, but if tumor marker levels are elevated, the clinical decision of complete remission based on conventional methods should be considered incorrect unless an explanation for the presence of an elevated level is given."

ANALYTIC CONSIDERATIONS

A number of clinical and analytic limitations should be considered in the interpretation and use of tumor markers.[29,31,32] Physiological influences to be considered include biologic variability, effects of aging and menopause, and half-life and route of elimination. Tumor markers can be elevated as result of renal failure, liver failure, and cholestasis, depending on whether the marker is eliminated through glomerular filtration or metabolized by the liver. For example, serum CEA concentrations may be elevated in patients with liver disease. A false-positive PSA, for example, may be seen with prostatitis, while inflammation of serous membranes or biliary ducts may falsely elevate CA125 or CA19-9, respectively.[31] Smokers have higher concentrations of CEA in comparison to nonsmokers, and reference ranges for CEA in lung cancer typically are stratified by smoking status. This underscores the importance of selection of cutoff values with respect to selection of reference groups. Knowledge of whether the reference group is based on healthy individuals or patients with benign diseases will influence interpretation.[29]

Knowledge of the tumor marker level before surgery is important for subsequent use in monitoring, because markers are not 100% sensitive, even in advanced disease. Tumors can be nonsecreting, or host genetic factors can affect the ability to detect an antigen. For example, CA 19-9, a sialylated derivative of the Lewis(a) blood group antigen, is not expressed in the estimated 3% to 5% of the population with the Lewis(a-b-) genotype.[1] Treatment also may influence marker concentrations, with increased release with chemo-

therapy or surgery, such as the spike observed in CA125 concentrations after abdominal surgery.[3] Tumor manipulation also can influence concentrations, as evidenced by the increased PSA concentrations observed after prostate biopsy, transurethral resection, prostate massage, or other procedures. Although the influence of DRE is thought to be minimal, it is recommended that blood for PSA measurements be drawn before the procedure or a minimum of 1 week after the DRE.[33]

One of the most critical analytic considerations in tumor-marker result interpretation is the fact that different assays, specifically immunoassays, may give different values for the same marker. Differing results among assays can be attributed to calibration differences resulting from different materials, value assignments, antibody types and specificities, assay designs and kinetics, variations in reference ranges or cutoffs, and assay robustness.[31,34,35] Therefore, values cannot be used interchangeably, and it is recommended that patients be followed up using the same laboratory method. Clinicians also should be informed when laboratories change tumor marker assay methods and should be offered a crossover period and an explanation of the association between the old and new assays.

Factors affecting assay robustness include the measuring range of the assay, encompassing the detection limit and upper limit where sample dilution is not required; accuracy and precision of dilutional linearity; high-dose hook or prozone effect leading to falsely low results; and interferences from endogenous antibodies. Endogenous antibodies include either anti-analyte antibodies such as thyroglobulin autoantibodies or anti-reagent antibodies such as heterophile and human anti-mouse antibodies (HAMA). HAMA, which may be produced as a result of treatment with monoclonal antibodies or immunoscintigraphy with antibodies similar to assay antibodies, can bind to reagent antibodies with resulting falsely high or low values, depending on assay design. HAMA can be minimized by using chimeric antibodies in vivo and at the assay level by choice of assay antibodies and inclusion of nonimmune animal serum as a blocking technique.[1,35]

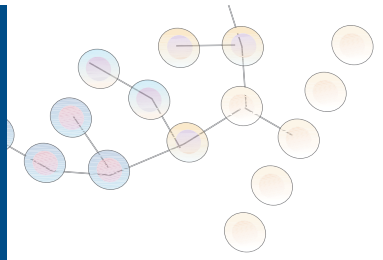
FUTURE DIRECTIONS

With current advances in proteomic and genomic technology, the diagnosis of disease in the future will be based on a combination of methods, with classification based on molecular as opposed to morphologic features. Unique gene or protein profiles of multiple biomarkers, accounting for cancer heterogeneity, will be measured in tissue, cells, and body fluids. The analysis of panels of protein biomarkers may be performed by traditional immunoassay, antibody-based protein chips, or microarrays. Furthermore, many more diagnostic tests will be generated as the result of genomic and proteomic discoveries. For example, serum biomarkers for a number of cancers recently have been identified using mass spectrometry.[36,37] Integrated diagnostic tools that combine these methods with molecular imaging techniques will be used, and bioinformatics will play a key role. The rapid translation of tests from the laboratory to the bedside will elevate the importance of laboratory testing in cancer diagnosis and care of the cancer patient.

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21 Imaging

Richard L. Wahl

SUMMARY OF KEY POINTS

- Noninvasive medical imaging often is essential to cancer management at multiple times in the course of the illness.
- Imaging currently is used for screening to detect cancer, characterizing lesions, performing locoregional and systemic staging, providing prognostic information, assessing response during and after therapy, restaging after treatment, performing follow-up of patients for recurrence, and precisely guiding therapies such as external beam radiation, brachytherapy, or thermal ablation.
- More invasive interventional radiologic procedures also can guide and monitor vascular or intraluminal delivery of treatments such as radioactive microspheres, embolic materials, radiofrequency or cryoablation, and therapeutic drugs.
- Imaging methods range from the traditional anatomic methods—x-ray, computed tomography (CT), and ultrasound—to the more functional methods of magnetic resonance imaging (MRI) and nuclear medicine methods, including positron emission tomography (PET) and single-photon-emission computed tomography (SPECT), and planar nuclear imaging. Optical imaging is promising, but limited by penetration of tissues to superficial structures in most cases.
- Plain films and mammography remain useful techniques, with mammography the only imaging method clearly proven effective when applied in the screening setting.
- CT remains the cornerstone technology for most oncologic imaging, and CT technology allowing for rapid-sequence angiography is finding new applications, as is three-dimensional reconstruction of CT data sets. Screening data with CT-colonography continues to improve, and in some studies it has been found to be comparable to traditional colonoscopy for colon cancer screening. CT scanning for lung cancer screening remains under evaluation and shows promise in high-risk populations.
- MRI is the imaging tool of choice for central nervous system, spinal, and musculoskeletal neoplasms, as well as in assessing vascular and some hepatobiliary and pelvic lesions. MRI also can be used to detect breast cancers, especially in women with dense breasts. Recent concerns regarding gadolinium-associated nephrogenic systemic fibrosis (NSF) have led to cautions in the use of MRI contrast medium in patients with impaired renal function.
- Bone scans using single-photon methods (^{99m}Tc methylene diphosphonate) remain the dominant procedure for detecting suspected bone metastases; however, this technology probably is less sensitive than MRI and PET techniques for detecting bone metastases of many tumors.
- PET and PET/CT technology using ^{18}fluorodeoxyglucose (FDG) continues to grow in a wide variety of applications and its use is becoming increasingly routine in the management of patients with cancer at varying states of the disease process. PET is used with increasing frequency in the staging and follow-up of lung, colorectal, and head and neck cancers, as well as lymphomas and other types of tumors, and is now a routine tool in lymphoma management at several points in the disease. PET with non-FDG tracers is a promising research area with growing clinical applications.
- The fusion of anatomic and functional images to create hybrid "anatomolecular images" with software or dedicated instruments such as PET/CT or SPECT/CT devices also is seeing rapid growth in applications in cancer imaging. Fully diagnostic CT scans coupled with PET imaging in the form of PET/CT often provide valuable composite imaging for cancer management.
- Imaging management for staging lung cancer and characterizing solitary pulmonary nodules often includes PET in addition to CT when the technology is available because PET has high accuracy in lung cancer assessments compared with CT.
- Imaging management of suspected recurrences of colorectal cancer, head and neck cancer, lymphoma, and several other cancers often now includes the use of PET in addition to CT. Use of PET at earlier stages in the workup is becoming increasingly common, as is the use of PET in early assessments of the efficacy of cancer therapies.
- In prostate cancer, available imaging methods remain suboptimal for detection of primary tumor and early determination of local or systemic tumor spread. MRI nodal contrast agents are promising but not yet routinely available, and MR spectroscopy has had only limited success in the prostate.
- Visceral angiography for diagnostic purposes is being supplanted by CT and MRI methods; however, it remains important as a tool for intravascular delivery of therapies such as chemotherapy, coils, or radioactive microspheres.
- CT, ultrasound, fluoroscopy, and innovative MRI systems can guide interventional procedures such as thermal and cryotherapeutic lesion ablations.

- Highly specific probe-reporter systems are being developed to allow for optical and radionuclide imaging of transfected gene biodistribution and function.
- Combined anatomic and functional information is being applied to allow for more precise planning of external beam radiation therapy, including IMRT and conformal therapy, methods that potentially allow for increasing dose escalation and minimization of toxicity to normal tissues.
- Emerging imaging methods are proving increasingly useful in providing information on the physiology and molecular characteristics of lesions, which means that a multiparametric biologic imaging phenotype for tumors can be obtained. This phenotype can more precisely guide individualized tumor treatment to yield a higher probability of success without excessive toxicity for treatment of the selected neoplastic process.

INTRODUCTION

Noninvasive imaging is of fundamental and increasing importance in the daily management of the patient with cancer. Although physical examination and laboratory diagnosis remain key for planning treatment, for solid tumor management, imaging tests represent a major objective metric of disease activity and may be used at different times during the course of the disease to monitor the efficacy (or lack of efficacy) of treatment. Imaging tumor size is an objective endpoint in disease management used to compare different types of cancer treatment and treatment across institutions. The use of imaging also is increasing in the drug development process and in developing new cancer therapies.

Specific clinical questions addressed by imaging include screening for the presence of cancer, characterizing anatomic lesions as malignant or benign, and staging a neoplasm—that is, determining the size and local extent of a primary lesion and determining whether it is localized or locoregionally or systemically metastatic. Such studies are essential for determining whether the patient is a candidate for surgical resection, identifying the extent of the field for radiation therapy, and determining whether systemic chemotherapy is appropriate. Initial staging of tumor size and extent also can provide important prognostic data. During the course of treatment, imaging is used to determine response of the cancer. Imaging also is used to follow patients for recurrence or development of second malignancies. Imaging is being used more often as a method to assist delivery of minimally invasive therapeutic procedures to ablate cancers and to guide the dosing of therapeutic drugs, including radiopharmaceuticals, more precisely.[1]

Imaging often is the best means of noninvasively identifying and assessing tumors. With information gleaned from imaging studies, the prognosis can be established and treatment decisions made with greater certainty. Before discussing the varying imaging methods available for cancer, this chapter considers some general principles that are applicable to all imaging tests.

Tasks for Imaging

The major roles of imaging in the current and evolving practice of cancer management are shown in Table 21-1.

GENERAL CONSIDERATIONS

Performance of Imaging Tests

Noninvasive imaging is used to perform a wide variety of important tasks. Although the best way to determine the medical utility of a diagnostic test can be argued, a few key concepts are required to understand and compare diagnostic tests. These can be applied to one of the most basic tasks (i.e., determining whether tumor is present) and also to the ability of imaging to predict resectability or response to treatment.

Sensitivity

Sensitivity describes how often the imaging test would give a "positive result" in a patient with cancer (i.e., true-positive [TP] finding). Ideally, the test precisely detects and locates one or multiple cancers in a given patient. Thus,

$$\% \text{ sensitivity} = 100 \times (\text{test positive/disease present}).$$

Sensitivity can be calculated on a per-patient basis or a per-malignant lesion basis. The per-patient basis most commonly is used in screening studies for early diagnosis, whereas the per-lesion basis may be used in patients expected to have multiple sites of tumor. Per-lesion detection analyses can be misleading because they can be heavily biased by a single patient's results if that patient has multiple tumor foci.

It can be difficult to judge how good a test is by reading the literature. Sensitivity is supposed to be substantially independent of

Table 21-1 Imaging in Cancer: Key Current Clinical Uses in Cancer Management

SCREENING
Lesion characterization: malignant or benign, size, local invasion
Tumor staging: locoregional, systemic, at initial presentation or on retreatment
Size and extent of tumor: to plan radiation or other local therapy
Prognostic information
Defining sites for biopsy and subsequent analysis by pathology
Guidance of interventional therapy
Assessment of response to treatment
Restaging tumor after treatment
Assessment of normal organ function or status before, during, and after treatment
Assessment for toxicity or complications of treatment
90% SENSITIVE AND SPECIFIC TEST
50% Prevalence of cancer in the population imaged
1000 Independent scans
50 False-positive findings in healthy patients (10% of 500)
450 True-positive findings in patients with disease (90% of 500)
Positive predictive value (disease positive/test positive): 450/500 (90%)
Possible conclusion: An excellent test!
90% SENSITIVE AND SPECIFIC TEST
10% Prevalence of cancer in the population imaged
1000 Independent scans
90 False-positive findings in healthy patients (10% of 900)
90 True-positive findings in patients with disease (10% of 900)
Positive predictive value (disease positive/test positive): 50/100 (50%)
Possible conclusion: A rather lousy test!
But these are the same test!

study composition, but as discussed in the next section, certain imaging tests may be insensitive for some very early-stage disease, but very, very sensitive for more advanced disease. Thus, the patient population and, very often, the tumor burden and average tumor size can make a difference in the sensitivity of a test. Virtually all noninvasive imaging tests are less sensitive for small-volume disease than for large-volume disease. For example, if an imaging test is used in a patient population in which patients have advanced disease before seeking medical attention (e.g., they are symptomatic at presentation), the imaging test may have far greater sensitivity than if it were used in patients with earlier-stage, smaller tumors. For example, positron emission tomography (PET) with ^{18}fluorodeoxyglucose (FDG) has been reported to be more than 90% sensitive for detecting metastatic melanoma, but it is less than 20% sensitive in detecting early (low tumor volume) nodal metastases of melanoma at initial surgical resection. A test with high sensitivity has a low number of false-negative results.[2] The false-negative fraction usually is expressed as 1 − sensitivity.[3]

Specificity

Specificity is the frequency with which a test result is negative if no disease is present, or the true-negative (TN) ratio. As a percentage, specificity is

$$100 \times (\text{test negative/disease negative}).$$

Again, specificity can be calculated on a per-patient basis or a per-lesion or per-region basis. The per-patient calculations commonly are performed in the screening setting. They also can be done per region of the body (e.g., Is the liver free of tumor? Are the draining lymph nodes free of tumor?). Specificity can be affected substantially if there is a population characteristic that can result in false-positive results for the imaging test. For example, inflammatory and infectious lung disease, such as active tuberculosis or sarcoidosis, if present in a patient population, can result in false-positive findings on PET or CT scans or other imaging methods. In this situation, the specificity of FDG-PET, and likely of CT, for staging the mediastinum for cancer would vary. Thus, the specificity of PET for assessing mediastinal lymph nodes may be much lower in areas of the world with endogenous TB than in developed areas without it. Therefore, an imaging test that is very useful in one part of the world may be far less useful in another part of the world. A highly specific test has a low frequency of false-positive results (i.e., a low frequency of a positive test results in the patient population that does not have the disease). The ideal imaging test has both high sensitivity and high specificity, although none of our current imaging tests have perfect sensitivity and specificity.[2]

Accuracy of Imaging

For detection of disease, a binary, yes-or-no answer as to whether disease is present or absent is desirable. When such binary answers can be provided, it is simple to mathematically provide an accuracy value for a diagnostic imaging test. Thus, accuracy is

$$100 * (TP + TN)/(TP + FP + TN + FN).$$

A highly accurate test is one with a low prevalence of false-positive and false-negative results.

Positive and Negative Predictive Values

Sensitivity and specificity define a test reasonably well, but its performance in a specific patient is affected by the characteristics of the population from which the patient is drawn. A physician normally wants to know whether an individual patient has cancer and whether the tumor is localized or metastatic. The correct answer is binary in most cases, but imaging does not always reveal the true status of the individual patient. Thus, the statistical likelihood of the accuracy of the result might be conveyed in the clinical imaging test report. This statistical likelihood will be related to the accuracy of the test as well as to the patient population characteristics. Thus, the positive predictive value often is of considerable clinical relevance. For example, the positive predictive value of a test with 90% sensitivity and 90% specificity will vary markedly, depending on the frequency of disease in the population. With these test performance characteristics, the clinician could reach two different conclusions regarding the same imaging test.

Thus, a test that is effective in a patient population with a high prevalence of a disease may be far less valuable in a patient population with a lower prevalence of the same disease, because there would be far too many false-positive results. The most effective use of imaging technology is in groups of patients in whom the imaging characteristics are expected to be robust enough to allow for predictions in individual patients. These challenges are particularly apparent when a test that was developed in a patient population with disease is used to evaluate individuals with a low prevalence of tumor (i.e., screening). In this situation, the number of false-positive findings may rise dramatically, sometimes nearly completely negating the value of the test.[4]

Receiver Operator Characteristic Curves

Cancer imaging tests are interpreted by imaging specialists, often radiologists. As with all of medicine, there is considerable science involved in image interpretation, but the human element, or "art," as it is referred to in some settings, also is involved. In developed countries, medical specialty boards have been established to ensure that practitioners have a basal level of training and knowledge, thereby providing some level of uniformity to image interpretations. However, even with board certification and extensive training, not all imaging specialists interpret a given imaging study in the same manner. Thus, although the goal of an imaging test often is a simple binary "yes, there is tumor" or "no, there is not tumor" answer, there are varying degrees of certainty in the interpretation of an image in most instances. Some readers read with high sensitivity, whereas others read with high specificity. Unless a test is very robust, it is hard to achieve both high sensitivity and high specificity.[5]

An example of a receiver operator characteristic (ROC) curve is shown in Figure 21-1. This set of curves reflects the performance of PET imaging in detecting axillary metastases in patients with newly diagnosed breast cancer. The axes of the curves are the true-positive fraction (sensitivity/100), which forms the y-axis, and the false-

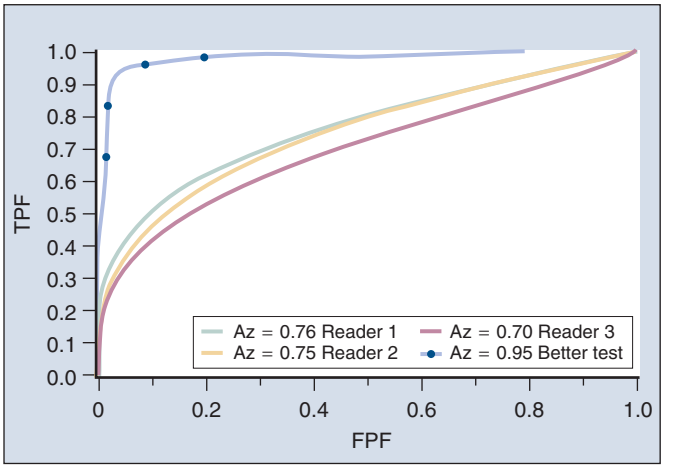


Figure 21-1 • Receiver operator characteristic (ROC) curves plotting the true-positive fraction (TPF) [sensitivity] vs. the false-positive fraction (FPF) [1 − specificity] for the three independent readers of the entire analysis data set. A hypothetical curve for the test if it had 95% accuracy also is shown. Az, estimated area under the ROC curve.

positive fraction (1 − specificity/100), which forms the x-axis, on a scale of 0 to 1. A perfect diagnostic test would yield no false-positive or false-negative results. The greater the area under an ROC curve, the greater the accuracy of the test. The results shown in the figure are from three readers who graded PET scans using a five-point certainty scale (i.e., not a simple yes/no, but a continuum from definitely abnormal to definitely normal). The three readers had similar ROC curves, indicating that they were of generally comparable accuracy. For the same test, however, two readers may be reading at different points on the ROC curve, meaning that one is more sensitive and one is more specific, but both are of equal accuracy. An excellent reader may have a greater area under the ROC curve than a less skilled reader, meaning that the more experienced (and more capable) reader is both more sensitive and more specific than a less experienced (and less capable) reader. Nonetheless, virtually none of our imaging tests is perfect, and varying "cut points" between disease and normalcy often are made, affecting the overall performance of the test. In this study, the area under the curve (AUC) of 0.7 to 0.76 was not viewed as sufficiently good for the task of nodal detection of metastatic cancer spread to the axilla. Despite this, a very high sensitivity or a very high specificity can be achieved depending on which part of the curve one operates in. A higher, hypothetical curve, with an AUC of 0.9, is shown for a more robust test, such as a higher-resolution PET system devoted to imaging the axilla. In practice, sentinel node sampling, often guided by imaging or a radionuclide-sensitive probe system, is assuming a very important role in this area of tumor staging.[6]

Other Approaches to Assessing the Value of Imaging

Although sensitivity, specificity, and accuracy commonly are used to characterize the tumor detection process, other metrics may be of greater importance. For example, some studies have focused on how often imaging substantially changes management. This kind of study is of great practical interest, but the optimal methods to assess such changes in treatment decisions are evolving. Ideally, one would like to show that the use of imaging, especially a new imaging technology, when applied randomly to half of the study population, provided a reduction in the number of adverse events in the imaged population or improved survival. As an example, a reduction in the number of "futile thoracotomies" has been used as a metric of success for PET vs. CT in planning the treatment of newly diagnosed lung cancer.[7] Ideally, randomization of patients to imaged versus not imaged groups can be shown to improve survival. However, performance of randomized trials in which half of the patients undergo imaging and the other patients do not (or they obtain different kinds of imaging), with an endpoint of survival, will be of great interest. Unfortunately, such studies are complex because management of patients after imaging may be altered markedly based on the imaging results. Thus, it can be difficult to separate the imaging study effect from the treatment effect. Ultimately, however, for some imaging studies to be adopted, such evaluations of survival will be needed. This point is particularly relevant to screening, as discussed later.

Screening Concepts and Challenges

Screening programs for cancer often have taken the form of laboratory tests such as the Papanicolaou (Pap) smear, or, more recently, blood tests for tumor markers. The success of the Pap smear in reducing societal mortality rates from cervical cancer is incontrovertible. The use of imaging in screening for cancer is an example of success and considerable interest, but also a source of considerable controversy. As discussed in detail in the chapter on breast cancer (see Chapter 95), screening mammography programs have been shown to be capable of saving lives in women older than 50 years of age. These programs also may save lives in women 40 to 50 years of age, but the data are less compelling.[8]

Studies have been initiated in which CT scanning is used in an attempt to detect early lung cancer.[9] Screening high risk populations with CT imaging has not yet been proven to affect mortality. However, the Early Lung Cancer Action Project (ELCAP), a large study screening patients at increased risk of lung cancer with low-dose CT, reported promising results in 1999.[10] Preliminary results from that trial showed that lung cancers are detected at a smaller size and that patients whose cancers are detected by screening live longer following diagnosis than patients whose tumors are not detected by screening. Whether this turns into longer-term survival for the screened population remains unclear. The ELCAP study further evaluated 31,567 asymptomatic persons at risk for lung cancer using low-dose CT from 1993 through 2005, and from 1994 through 2005; 27,456 repeated screenings were performed.[11] A diagnosis of lung cancer was made in 484 participants based on screening. Of particular note, 412 patients (85%) had clinical stage I lung cancer. Ten-year survival approached 90% in this group.[10,11] This study clearly demonstrated that annual spiral CT screening can detect lung cancer that is curable. Another large randomized trial of lung cancer screening currently is underway in which both CT scanning and chest x-ray screening are used. This trial has raised some controversies, because many small pulmonary nodules are identified that are not malignant, the costs of the trial as well as of the medical care for incidentally detected lesions are substantial, and a substantial radiation burden, which, in principle, could be carcinogenic, is delivered to patients receiving the screening. However, there is considerable hope that screening programs can achieve a reduction in lung cancer mortality. For example, as discussed later in this chapter, CT colonography holds excellent promise as a screening method for colon cancer, as an alternative to optical colonoscopy.

Other areas in which screening by noninvasive imaging has been performed include colorectal cancer, where virtual colonoscopy can be used to look for early colon cancers, and in the pelvis in women who are at risk for ovarian cancer. More recently, screening CT centers offering a virtual evaluation of the entire body have become available, and even more recently, MRI and PET screening have been offered in some locales. The growth of these centers has been driven emotionally and economically; these tests are not yet well-founded scientifically in the screening setting.

Screening carries challenges, risks, and costs that are beyond the scope of this overview chapter. However, several key points apply to all screening approaches, including those using noninvasive imaging. These points include (1) whether a screening program is reasonable to consider; (2) lead time bias; (3) length bias; and (4) the overall cost implications of screening, especially the costs of investigating false-positive results.

The requirements that a screening program must meet to be considered "reasonable" may differ substantially based on the specific society's values and a specific individual's perception of risk. However, in general, the following characteristics are important for cancer screening:

- The cancer must have a considerable public health effect.
- The disease must have an asymptomatic period in which detection by imaging is possible.
- A therapeutic intervention that can lead to better survival or quality of life must be available.
- The prevalence of the disease must be sufficient in the population being screened to justify screening (especially the cost).
- Medical, surgical or other treatment must be available for the early-stage cancer identified by screening.
- There must be a high likelihood that the patients in whom early cancer is identified by image-based screening will go on to have a suitable therapeutic intervention.

Further, the imaging test itself must be acceptable to patients (in terms of level of discomfort and cost), and it must be sufficiently sensitive to identify cancer often and sufficiently specific to minimize false-positive results. Finally, the costs of the screening process must be compatible with the society's or the individual's economic system,

and the screening procedure must pose little or no risk to the patient.[4]

Another important consideration in screening programs is lead time bias. This concept, simply stated, indicates that if the natural history of a disease is unchanged, but the diagnosis is made earlier in the course of the illness, the apparent survival will be improved. For example, let us assume that tumor X has a 6-year natural history from its beginning until the death of the patient, and that treatment was ineffective. The disease might become clinically detectable after 4 years and lead to death in 6 years, a 2-year survival after diagnosis. With screening, if the tumor is detected 3 years after the onset of disease and no improvement in treatment occurs, then the survival in the screened population would appear to increase from 2 to 3 years after diagnosis. This illusion of improved survival in the screened population is a considerable concern and can lead to inappropriate enthusiasm for screening programs.[4]

Another important consideration in screening is the possibility of length bias. This is a more complex concept, but it may be related to the types of cancer that can be detected by screening programs. A possibility is that very rapidly growing and presumably highly lethal cancers are less likely to be detected by annual screening programs, whereas more slowly growing cancers, which have an intrinsically better prognosis, may be detected more frequently by screening. In fact, some of the early cancer discovered may not be biologically relevant at all. If so, the patients with cancers identified in the screened population could appear to have a better survival than the patients with cancers identified in the unscreened population.

A third factor is the selection bias that is difficult to control for in observational studies. Selection bias occurs when there are unintended differences between the groups observed that, while they are associated with the variable used to sort the groups—for example, exposure in case-control studies and outcome in cohort studies—affect measurement of the study variable.[12] For instance, in a case control design on the effects on disease specific mortality of a particular screening program, investigators would look at patients who have died from the disease in question, versus those who have not, then determine the rates of the screening intervention in these two populations. However, it is possible that those likeliest to have sought screening were the ones at highest risk for the disease. Results for the screening's effect on mortality could be underestimated in such a scenario. Selection bias also can work in the opposite direction, where the high risk/poor prognosis individuals are less likely to seek screening. With the relative absence of large randomized prospective trials, as is the case when evaluating imaging as a screening tool, we may be tempted to base our conclusions on cohort or case control studies. However, the most accurate conclusions would be drawn from a randomized study design.

Collectively, lead time bias and length bias and, at times, selection bias, can make screening programs appear to improve the survival of patients with cancer. Because of these major biases intrinsic in screening, very large, randomized, studies are required to show that overall cancer-specific mortality (and ideally mortality from all causes) declines as a result of screening programs.

The advent of imaging and other screening tools that uncover a tumor long before it is symptomatic also brings up the need for biomarker discovery to help physicians to determine whether to treat what has been discovered through screening. The experience with prostate specific antigen (PSA) screening in prostate cancer serves to illustrate the point that not all cancers identified by screening eventually lead to death. Discovering and validating biomarkers that can help to distinguish reliably between lethal and nonlethal tumor types will be of great help in reducing unnecessary treatment in patients with less active disease.

Screening Costs

The determination of whether a screening program is valuable is based on its cost and benefit. The concept of quality-adjusted life-years (QALYs) often is applied. This concept is defined as the economic cost to society required to result in 1 additional year of quality life for a member of the society. In many western countries, a figure of $50,000 has been considered a useful guide, with QALYs lower than this amount considered cost-effective. Such a guideline, however, does not necessarily apply when individuals make their own determinations as to whether to pay for a screening test. For example, it is reasonable to expect that those with greater disposable income would be willing to pay more per QALY than those with less disposable income. Thus, it can be difficult to generalize about the cost efficacy of screening procedures.[13]

Even when people choose to undergo a screening test at their own expense, considerable costs can be transferred to society as a result of the screening program. For example, if a screening test has a high rate of false-positive results, a substantial number of follow-up biopsies or procedures will occur and can cost a great deal of money. Such costs can dramatically raise the total cost per QALY. Particularly invasive procedures also can increase the likelihood of morbidity or death as a result of additional investigations. To determine the true cost per QALY associated with screening, these additional costs and risks must be considered. Thus, screening remains an area of great promise, but also of considerable controversy. Screening beyond breast imaging must overcome major hurdles before it is likely to be accepted. It is quite possible, however, that in high-risk patient groups, such as those with a family history of cancer or major carcinogen exposure, with a high penetrance or of early onset, that screening may prove of greater value than in the general population.

Size of Detectable Lesions

Noninvasive imaging methods in humans cannot detect and localize a single malignant cell, although flow cytometric methods are very sensitive for finding a very few cancer cells in a patient's blood. Imaging methods are improving, however, and detection of a much smaller number of cells is possible in small animal models. However, it has been estimated that by the time a tumor reaches 3 to 5 mm in diameter, which is the lower limit in size for detection by the best current noninvasive methods in humans, the tumor has undergone more than 25 doublings and contains 0.1 to 1 billion cells, depending on their size.[1] In contrast, a cytologist, on a very good day, may be able to identify a single cell as malignant using a microscope.

Realistically, even for histologic assessment of malignancy, typically a group of tumor cells must be present before cancer is diagnosed. However, light microscopy and more sensitive techniques such as immunohistochemistry and polymerase chain reactions mean that pathologic techniques potentially will be more sensitive than imaging methods. One very important proviso is that for pathologic methods to be effective, actual examination of the malignant cells is required; the sample containing the tumor must be cut appropriately and viewed under a microscope. This task may be impossible, because the 8-μm sections that are used for pathologic examination typically are taken only from a small portion of a tumor or lymph node, whereas most of the tumor or node will be unexamined (e.g., to assess a 1-cm node using 8-μm-thick sections, approximately 125 sections would be required). This large number of sections is not typically obtained. Despite the markedly superior sensitivity of histologic methods over noninvasive imaging, there is a major sampling error issue, and, paradoxically, imaging in some diseases potentially may be more sensitive than histologic examination for cancer. This situation can arise in mammography, where small tumor foci can be seen on the mammogram but can be missed on cytological sampling, possibly due to sampling error. When tumors are imaged by noninvasive methods, the entire tumor is visualized, not just a small portion. So, paradoxically, imaging, despite limited resolution, can be more sensitive than cytology or pathology. However, if exhaustive and thorough sampling is performed, with microscopic examination of

tissue, there usually is greater sensitivity for tumor than there is with current noninvasive imaging techniques.

Stage Migration

One of the major goals of noninvasive imaging is to stage the tumor precisely to allow the clinician to best choose treatment and determine the prognosis. The evolving concepts of tumor staging are discussed elsewhere in this text, but improvements in detection technology can change the understanding of the natural history of a given stage of disease. Patients with small or microscopic metastases to the mediastinum are likely to do better than patients with bulky metastases, but both may have the same stage of disease. As the sensitivity for detecting small lesions improves, it becomes possible to identify more patients with small primary tumors and small metastases to the lymph nodes or systemic disease. Thus, when primary tumors are detected at ever earlier and less advanced stages as imaging methods improve, patients are assigned to a higher stage than was used historically. Their presence in the advanced-stage group appears to improve survival and outcome in that group. Moreover, the outcome of the lower-staged group also may improve because a subset of patients with now-detectable tumors has been removed from that group. The outcome of the overall group will not have changed. Thus, one has to be very cautious in extrapolating historical survival data based on an insensitive staging method with that seen with a more sensitive method.[4]

MAJOR IMAGING MODALITIES

Broadly stated, cancer imaging can be performed using anatomic or functional imaging methods.[1] The traditional imaging of the patient with cancer, and the most established methods, are based on anatomic imaging. However, interest is increasing in more functional methods in cancer imaging. Further, several anatomic imaging methods offer functional components that complement the anatomic method. Hybrid images, derived from and displaying both functional and anatomic data, also are becoming more widely available, often coming from the same hybrid imaging machine.[14,15] Imaging data are increasingly digital or digitized and suitable for postprocessing and image exchange. The major imaging modalities are discussed in the following section.

Plain Film X-Rays

The traditional x-ray remains an important part of cancer imaging. It commonly is used to detect bone tumors and can be used to detect lung cancers in the thorax. The method displays mainly water and calcium density and is affected by overlapping tissue in front of or behind the lesion. X-rays have become increasingly digitized in the last few years, with the introduction of film digitization and phosphor screen capture devices. X-rays offer exceptional resolution, but provide relatively little image contrast if there is not much calcium present. The radiation dose from a plain film x-ray depends on which portion of the body is being examined. In most centers, plain film radiographs for cancer management are being used less often, with CT scanning increasingly replacing radiographs in the abdomen and MRI in the brain and extremities.[16]

Mammography

Mammography is a specialized form of plain x-ray. Very high-resolution images of the breast are obtained using specialized devices optimized for breast cancer detection. Digital mammography is now available, and offers greater flexibility of image display because of the digital image format. A limitation of the digital format, however, is the field of view of the imaging phosphor, which may be too small to fully include some breast tissue. In the last several years, there has been a major shift toward digital mammography. The recent Digital Mammographic Imaging Screening Trial (DMIST), which included nearly 50,000 women, showed comparable overall accuracy between film screen and digital mammography in the overall study. A higher accuracy for cancer detection in women under 50, women with radiodense breasts, and pre- and perimenopausal women was seen with digital mammography as compared with film-screen mammography.[17] Despite this higher accuracy, the reported sensitivity for both techniques for cancers was only 41% with a positive predictive value of 12%, albeit with 98% specificity. This is far from ideal performance for a screening test. The move to digital mammography is in part to increase diagnostic accuracy but also to allow digital images to be viewed on picture archiving and communication system (PACS), as is the case with virtually all other diagnostic imaging methods in more and more imaging centers.[17,18] A newer technique, tomosynthesis, is under evaluation in which a number of "slices" of the breast are generated during a mammographic image acquisition. This approach offers considerable promise going forward, but is early in its evolution technically.

Computed Tomography

CT is now established as the dominant imaging technique for cancer detection and follow-up. Currently, tumor response and staging criteria very commonly are based on tumor size as measured on CT. CT scanners acquire images using an x-ray source and digital detector elements. The x-ray source rotates rapidly around the patient, commonly with a single scan level taken in 0.5 seconds or less. Faster and faster rotation speeds of the scanners, along with multiple simultaneous detectors capable of imaging multiple slice thicknesses in a rapid spiral motion, are being used. Scanners with 16 and 64 simultaneous slices are commonly in use, with scanners with 256 slices now in use in some devices. Large-field-of-view detectors may allow even more of the body to be evaluated nearly instantaneously. Current fast scanners can potentially evaluate the entire body in a fraction of a minute. Although such evaluations provide key information about lesion size, some lesions may elude detection unless contrast medium is given intravenously, orally, or both. With such devices, it also is possible to capture contrast in arteries or veins to provide superior visualization of these structures, which can then be displayed three-dimensionally or in a volume-rendered fashion. While more slices in a CT scanner make for faster CT scans, it is not clear that having more slices always results in a superior diagnostic quality scan. More slices and faster scans do mean that whole-body scans in a single breath hold can be obtained, which is advantageous, because it can reduce the frequency of breathing artifacts. A clear disadvantage of CT is its cost, both technically and in terms of the radiation dose. In the past several years, increased concern has developed regarding the total radiation dose being delivered by CT, particularly in children, due to the potential risks of carcinogenesis. Although CT is an exceptional technique, it remains a predominantly anatomic imaging method. While there is information in the timing of IV CT contrast enhancement, it is not easily extracted without a substantial radiation dose from repeated images. Thus, only a limited number of post-IV contrast images are obtained with CT, to limit radiation dose. All CT images are digital. A major challenge with CT is the large amount of image data generated for analysis, data that can take the radiologist a long time to interpret fully.[19]

Angiography

Historically, angiography has been performed after intravascular insertion of catheters into arteries, followed by rapid injection of iodinated contrast media, along with rapid-sequence filming of the images. The improving ability of rapid-sequence CT scanning to show the vascular anatomy (CT angiography) has caused it to rapidly replace angiography for diagnostic purposes. Angiography still can be used to produce the most precise maps of vascular anatomy before organ transplantation or radical cancer surgery. Most angiography

now is performed using digital image-capture devices, known as digital angiography.

Angiographic delivery of therapy is, however, an important area. This form of imaging can allow for therapeutic delivery of embolization materials such as coils, delivery of chemotherapeutic agents regionally, or delivery of radioactive microspheres, for example.

Angiography has high resolution, but typically delivers a high dose of radiation energy to the patient. The use of angiography remains essential for studies to evaluate GI bleeding, but with CT angiography continuing to improve in quality, the use of diagnostic angiography has become less frequent in routine clinical practice.[20]

Ultrasound

Ultrasound uses reflected beams of high-frequency sound rather than ionizing radiation to generate images. Ultrasound provides high resolution and some functional information, specifically about the presence and direction of blood flow in tissues. It also provides some information regarding tissue characterization properties, and is very effective in determining whether a tissue is cystic or solid. The method also is excellent for detecting vascular structures and determining extent of flow. Ultrasound provides real-time imaging capability to guide biopsies and procedures effectively. Ultrasound is less effective in the evaluation of deeper structures, and requires access to a sonographic window. Thus, it has only a modest role in evaluating deep abdominal structures. Ultrasound is used commonly in evaluations of the pelvis, neck (including the thyroid), and gallbladder and liver areas. Agents that can enhance the visualization of vessels or can be specifically retained in clots are under evaluation, suggesting that ultrasound can offer some functional information beyond the purely anatomic.[21]

Ultrasound contrast agents are being applied to a limited extent. Currently, these agents are mainly for intravascular use. High-energy focused ultrasound remains under development as a tool to ablate, or at least deliver thermal energy to, tumors with therapeutic intent. Ultrasound coupled with needle aspiration biopsy has been used in some settings as a minimally invasive procedure to characterize nodal metastases. Ultrasound combined with mammography also is being evaluated as a screening method for breast cancers, but results in high-risk patients have shown disappointingly low detection rates relative to MRI.[22]

Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy

In many clinical settings, MRI, as applied in imaging for most cancers, is used predominantly as an anatomic imaging method that does not use ionizing radiation. MRI offers superb contrast resolution between tissues and excellent spatial resolution. MRI also offers a variety of forms of functional information. However, it does not offer the level of temporal resolution, in general, seen with ultrasound, fluoroscopy, or recent-generation, multiple-slice CT scanners. However, MRI technology has moved forward inexorably, and rapid-pulse sequences allowing gating of images now are available for several types of scanners. MR images can be of a variety of pulse sequences, allowing visualization of several parameters. However, visualization of hydrogen nuclei is the major approach with conventional 1.5T and 3T (Tesla) machines. Visualization of blood, especially with contrast materials such as gadolinium chelates, and of altered vascular permeability is routinely applied.[23]

MRI is the preferred procedure in evaluating neoplasms of the brain and spinal cord regions as well as musculoskeletal tumors. MRI also is being used with increasing frequency in the evaluation of tumors of the extremities, such as sarcomas. With gadolinium contrast enhancement, MRI also can be useful in locating tumors of the breast, which appear as areas of contrast enhancement. Such studies have shown the higher sensitivity of MRI versus mammography. However, there remain concerns that MRI may achieve this sensitivity with an accompanying relatively high false-positive rate, depending on the methods used for interpretation. Still, MRI probably is our most accurate technique for detecting and characterizing breast masses. MRI also can provide valuable information about tumors in close proximity to vascular structures as well as in the liver and upper abdomen. Tumors in the upper abdomen and liver can be degraded in their appearance on MRI because of respiratory motion artifacts. Therefore, this approach is applied less commonly than in other situations, such as in the lower pelvis, where there often is less respiratory motion artifact. Research currently is working on developing agents that can facilitate specific MRI contrast enhancement. More rapid whole-body MRI acquisition methods also are under evaluation, which may broaden the use of MRI.

In magnetic resonance spectroscopy (MRS), tissue characterization can be achieved by sampling its magnetic spectrum at 1.5T. Some devices now provide a 3T or higher field strength signal for evaluation, offering the possibility of more refined tissue characterization. Opportunities to detect increased content of choline (often increased in tumor foci) versus other substituents can be helpful in separating tumor from nonmalignant tissues in the brain and elsewhere. Spectroscopy also can provide information on lactate concentration and pH, among other parameters. A limitation of spectroscopy is resolution, which typically is not nearly as fine as that of MRI itself. Thus, spectroscopy has only limited application in most oncologic practice.[24]

Recently, diffusion MRI has shown promise in tumor response assessment. This depends on the freer movement of nuclei in areas of necrosis as compared with the motion of nuclei in fully viable tumors. This technique is demonstrating considerable potential for response assessment in brain tumors and recently has shown promise in tumors in the bones.[25]

Nephrogenic systemic fibrosis (NSF) recently has been linked to Gd-containing MRI contrast agents.[26] This condition has been described in patients with substantially impaired renal function who receive MRI contrast intravenously. "Black box" warning labels now appear on the product inserts for MRI, and we are seeing increased use of alternative imaging methods to MRI in patients with low creatinine clearance rates followed by sequential imaging studies. Gadolinium may be responsible in part for this process as it has been found in the skin of some of such affected patients.[27,28] In 2007, black box warning labels were added to the package inserts related to Gd-containing MRI contrast (Box 21-1).

Box 21-1. FDA BLACK-BOX WARNING REGARDING GADOLINIUM MRI CONTRAST MEDIUM

Warning: Nephrogenic Systemic Fibrosis

Gadolinium-based contrast agents increase the risk for nephrogenic systemic fibrosis (NSF) in patients with

- Acute or chronic severe renal insufficiency (glomerular filtration rate <30 mL/min/1.73 m^2)

OR

- Acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

With these patients, avoid the use of gadolinium-based contrast agents unless the diagnostic information is essential and not available with noncontrast enhanced magnetic resonance imaging (MRI). NSF may result in fatal or debilitating systemic fibrosis affecting the skin, muscle, and internal organs. Screen all patients for renal dysfunction by obtaining a history and/or laboratory tests. When administering a gadolinium-based contrast agent, do not exceed the recommended dose and allow a sufficient period of time for elimination of the agent from the body prior to any readministration (See WARNINGS).

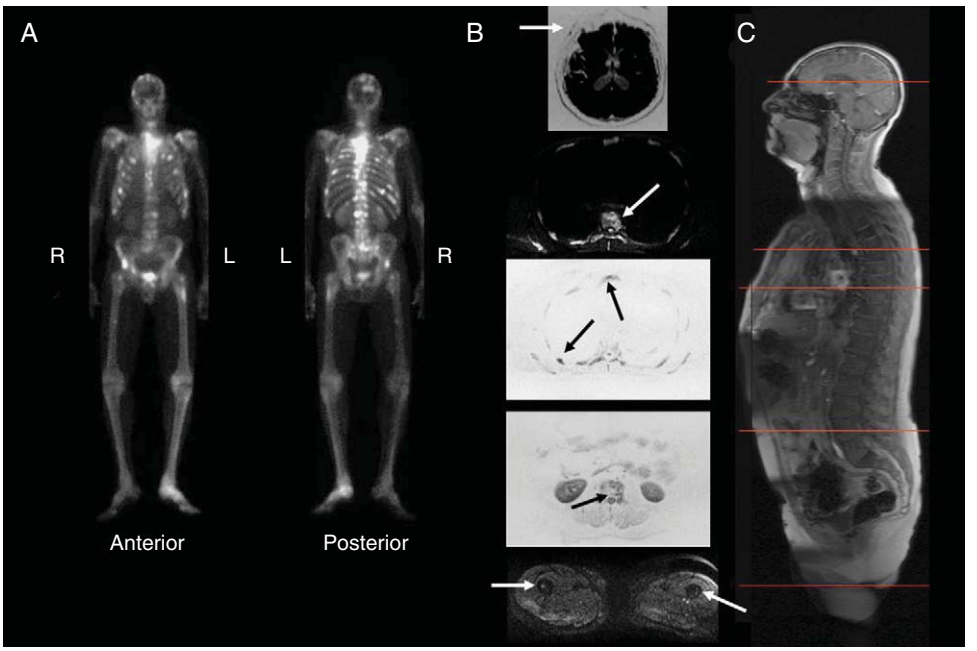


Figure 21-2 • Representative 64-year-old patient with metastatic disease. **A,** Tc99m MDP bone scan obtained after injection of the istotope 21 μCi. The bone scan demonstrates multiple areas of increased uptake in the calvarium, sternum, ribs, vertebra, pelvis, and femur. Degenerative and inflammation changes are noted in the left knee and left ankle (postfracture due to fall). **B,** Axial diffusion-weighted images (b = 300–600 s/mm^2) of corresponding areas of metastatic sites. Note that the sternum metastases are clearly seen, as are those in the rib and femur (*arrows*). **C,** Sagittal image showing whole-body coverage.

An exciting area of application of MRI technology is in the field of whole-body MRI. Such a test may begin to offer whole-body cancer surveys with no ionizing radiation delivered to the patient. Such applications to date have been less sensitive than whole-body PET imaging, but this area is emerging very rapidly[29] (Figs. 21-2 and 21-3).

Nuclear Medicine and Positron Emission Tomography

Radionuclide methods can provide a great deal of functional information, but the anatomic resolution often is limited. Broadly, there are single-photon and positron-emitting isotopes. Single-photon emitters typically have longer half-lives than positron emitters, and decay in a different fashion, emitting gamma rays. Depending on the ligand attached to the radioactive isotope, a wide variety of processes can be imaged. For single-photon imaging, the most common isotope is ^{99m}Tc, which can be used to image bone (bone scan with ^{99m}Tc methylene diphosphonate) or thyroid (technetium pertechnetate), for example. With positron emitters, the most commonly used tracer is F18, which is used as the radiolabel for FDG, an agent that images glycolysis in vivo. Because tumors have increased glycolytic metabolism in general, use of this agent in tumor imaging is increasing very rapidly, especially in lung and colorectal tumors and lymphomas.[30]

Both PET and SPECT have very high sensitivity for a small number of radioactive molecules in vivo as well as the ability to quantitate the radioactivity concentration precisely. Thus, these methods are important as both clinical and research tools. The intrin-

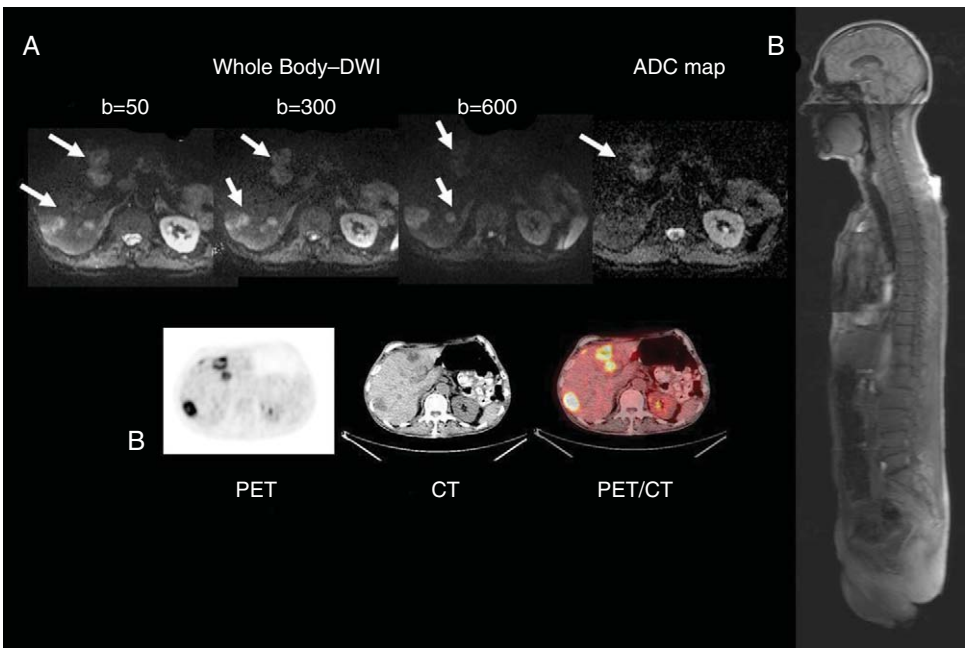


Figure 21-3 • This 72-year-old man had colorectal cancer and metastatic disease in the liver. **A,** Diffusion-weighted images of different b values in the liver. **B,** Corresponding PET, CT, and PET/CT images.

sic lack of anatomic resolution for PET and SPECT can be partly addressed by fusing the PET or SPECT images to CT using computer software. More recently, dedicated hybrid imaging devices, including both PET and CT or SPECT and CT in a single device, have been applied to the imaging practice of cancer.

Higher doses of radioactive isotopes also can be therapeutic. For example, ^{131}I is used for the treatment of thyroid cancer, as sodium iodide. The same isotope, conjugated to an anti-CD20 monoclonal antibody, has been approved by the U.S. Food and Drug Administration to treat low-grade and transformed B-cell non-Hodgkin's lymphoma that is considered refractory to standard treatments. The tracer doses are used to guide the treatment doses in such instances or at least to determine if the radioantibody has any unexpected targeting behavior.[31]

Optical Imaging Methods

Optical imaging methods are applied in a variety of ways. The external physical examination of a patient involves visual interrogation of reflected light. Infrared and transmitted light also are used to a limited extent in evaluating small parts of the body. Optical imaging has been limited in clinical deployment by the limited penetration depth of a variety of forms of light in the body. Thus, this type of approach may prove of greatest utility in evaluating small animals as part of experimental studies, or for superficial organs, such as the breast. Similarly, the technique may have greater utility in evaluating intraoperative procedures. The possibility of constructing light-emitting contrast media is a real one, and optical imaging has the potential to provide remarkable sensitivity and resolution in superficial structures. However, it is not routinely applied in cancer imaging, with the exception of visualization of the interior of the eye, visualization of the cervix, and endoscopy from above and below.[32] The strengths and weaknesses of the major imaging methods are contrasted in Table 21-2.

ANATOMIC VERSUS FUNCTIONAL IMAGING

Limitations of Anatomic Imaging of Cancer

Anatomic imaging has been the fundamental approach to cancer imaging for more than 100 years. These methods are quite robust, as is supported by their daily use in managing individual patients with cancer. Anatomic imaging normally detects a phenotypic alteration that is sometimes, but not invariably, associated with cancer—a mass. However, with anatomic imaging, we often do not know whether masses are the result of malignant or benign etiologies, as in solitary pulmonary nodules or borderline-size lymph nodes. Similarly, small cancers are undetectable with traditional anatomic methods, because they have not yet formed a mass. After surgery, it is even more difficult to assess for the presence of recurrent tumor with anatomic methods. Post-treatment scans are complicated by the need for comparisons with normal anatomy to detect altered morphologic findings as a result of cancer. Anatomic methods do not predict the response to treatment and do not quickly document tumors responding to therapy.[33] Despite these challenges, anatomic images remain routine in cancer management. PET, a functional imaging method, helps to address many of the limitations of anatomic imaging, and when combined with anatomic images in fusion images, is emerging as a particularly valuable tool, providing both anatomic precision and functional information in a single image set.[4]

Molecular and Functional Alterations in Cancer

The molecular bases of neoplasia are increasingly well defined. Mutations in genomic DNA precede the development of overt neoplasia.[34] With sufficient alterations in genotype, phenotypic changes occur. These genotypic and phenotypic changes in cancer antedate the development of a discrete mass lesion, and represent potential targets for innovative imaging agents. The concepts of altered "genome," "proteome," and "methylome" resulting in alterations in metabolism, consistent with an altered "metabolosome," are increasingly recognized as present in cancers. PET, because of its superb sensitivity to low signal levels, can detect signals from tracers, targeting such alterations that are preferentially present in cancer.

PET has led the growing field of molecular imaging to the clinic, in part because of the quantitative capabilities of PET and the sensitivity of electronic collimation, but also because of the choice of a proper radiotracer for cancer imaging. Although a wide variety of molecular, proteomic, and metabolic alterations occur in cancers, and many of these can or ultimately may be imaged with PET, the most useful target in the clinical practice of PET is the increased glucose metabolism present in most cancers. Other PET tracers, such as those targeting hypoxia, proliferation, amino acid transport, blood-brain barrier permeability, and protein synthesis, are discussed in the following sections. The challenge with all imaging modalities is how best to integrate them into clinical practice. The next section addresses these issues.

DISEASE-SPECIFIC IMAGING RECOMMENDATIONS

Brief discussions of the role and possible role of imaging in managing several common cancers follow. There is great variation in the imaging workup of specific types of tumors, depending on the type of therapy planned.

Table 21-2 Imaging Methods

Modality	Resolution	Sensitivity	Specificity	Functional Imaging Ability
Magnetic resonance imaging	1–2 mm	Moderate	Moderate	Moderate with spectroscopy
Computed tomography	1–2 mm	Moderate	Moderate	Low, except angiography
Radiographs	1–2 mm	Low	Moderate	Very little
Single-photon-emission computed tomography	1 cm	High	Moderate	Excellent
Positron emission tomography	5 mm	High	Relatively high	Excellent
Ultrasound	2 mm	Low	Low	Some, especially with contrast
Mammography	1–2 mm	Moderate	Relatively low	None
Angiography	1–2 mm	Moderate	Moderate	Low

Bragg DG, Rubin P, Hricak H: Imaging strategies for oncologic diagnosis and multidisciplinary treatment. In Bragg D, Rubin P, Hricak H (eds): Oncologic Imaging, 2nd ed. Philadelphia, WB Saunders, 2002, pp 3–20.

In general, the more aggressive and radical the planned treatment, the more critical the need is for accurate determination of the location of all foci of tumor through imaging. Similarly, the intensity and frequency of follow-up imaging examinations must be guided by the potential importance of the information gained. For example, if no effective salvage therapy is available, intensive surveillance for recurrent tumor makes little sense, except to provide reassurance to patients when test results are negative. This may seem self-evident, but it is surprising how practice patterns vary. The National Comprehensive Cancer Network recently has published recommendations on imaging approaches in specific cancers. In addition, the American College of Radiology has provided "appropriateness guidelines" for a variety of cancer therapies. These guidelines inherently lag behind developments in technology, but are based on careful analyses of the literature and expert opinion, and thus are worth consulting as they continue to be updated.

Lung Cancer

The initial diagnosis of lung cancer often is based on incidental detection of an abnormality on an imaging study, although more advanced lung cancer can cause hemoptysis, cough, weight loss, hoarseness, infection, or shortness of breath. There has been a great deal of interest in testing screening programs for lung cancer in high-risk groups such as heavy smokers. Both chest x-ray screening and CT screening have been evaluated. Chest x-ray screening has not been proven to be effective at reducing mortality from lung cancer. CT-based screening programs are of greater interest, and it is clear that these programs can detect lung cancers at an earlier stage, when they are smaller than lung cancers diagnosed by other methods. Patients with such cancers tend to live longer than patients with cancers diagnosed at a more advanced stage. However, detecting additional cancers is dependent upon detection of small lung nodules and many small lung nodules, and most of these are not of malignant etiology. The costs, both economic and in terms of risks from invasive diagnostic procedures, are considerable. In addition, concerns exist that the cancers detected by such an approach may be the more slowly growing cancers. Results from the National Lung Cancer Screening Trial are expected to be forthcoming to help assess this issue in the coming years.

The Fleischner Society has offered guidelines for dealing with small, incidentally detected pulmonary nodules, which involve imaging follow-up for lesions greater than 5 mm in size. Growing lesions require additional investigation.

Certainly, if a solitary pulmonary nodule 8 mm or larger in diameter is identified on a chest x-ray or on screening CT, the workup to determine whether it represents lung cancer can take a variety of forms. Comparison with old anatomic images is essential, but if none are available, a decision must be made whether to perform a biopsy or remove the tumor or follow the abnormality. A variety of factors can be considered, including patient age, smoking history, lesion size, and history of exposure to potential infectious agents.

The morphology of the nodule is investigated to determine whether it has characteristics that suggest malignancy or benignity. The margin and internal density of the lesion are examined. Smooth, well-defined margins suggest a benign nodule, but these also are seen in 21% of malignant nodules.[35] A lobulated margin suggests cells of different lines with uneven growth, but can be seen in 25% of benign nodules. A spiculated margin is highly suggestive of malignancy. Both benign and malignant nodules can be homogeneous and can cavitate. A cavity with a wall thickness of 4 mm or less is likely benign in 95% of cases, a wall thickness of 5 to 15 mm is indeterminate, and a wall thickness of more than 15 mm is likely malignant in 95% of cases.[35] If the lesion contains fat, it is specific for a hamartoma, and 50% of hamartomas have fat on CT.

Benign calcifications are central in the lesion, diffuse and solid, laminated, or popcorn-like. Calcification is seen in 6% of lung cancers on CT, and tends to be eccentric or amorphous.[35] Thus, calcification alone does not indicate benignity in a lung nodule. If contrast is administered and the lesion is monitored over 5 minutes, enhancement of less than 15 Hounsfield units (HU) suggests a benign lesion and enhancement of greater than 20 HU suggests a malignant lesion, with reported sensitivity of as high as 98%, specificity of 73%, and accuracy of 85%.[36] However, these CT criteria rely on very small changes in CT attenuation levels. These subtle changes may be insufficient to allow for reliable stratification of nodules as malignant or benign, because timing of the CT bolus also is an important consideration. The growth rate of the lesion also can be evaluated, but this is difficult for subcentimeter lesions. Computer programs for nodule detection are being developed that also provide lesion volume, and this may prove useful in follow-up.

However, for a significant number of patients, the risk of cancer remains intermediate. For such patients, FDG-PET imaging may be useful. PET has been reported to have sensitivity of approximately 96% for detecting cancer in solitary pulmonary nodules (predominantly ≥1 cm in diameter) in a retrospective meta-analysis,[37] with specificity of approximately 80%. However, some histologies are less well detected, such as those of bronchioloalveolar carcinomas. Nonetheless, the PET scan can help to determine which patients require immediate biopsy or excision of a nodule (i.e., a nodule with intense FDG uptake) versus those who can be observed (some of those with low or no tracer uptake). The use of PET varies widely, but it can be a valuable tool for helping to determine which patients need invasive procedures for pulmonary nodules. Because false-negative findings occur, however, patients who do not have surgery should be followed up regularly for up to 2 years to ensure that there has been no lesion growth. Figure 21-4A shows "hot" and "cold" nodules in the same patient.

Once lung cancer is diagnosed, an appropriate staging workup should be undertaken. The workup for non-small-cell lung cancer often is done to determine whether the patient is a candidate for surgery. Because FDG-PET imaging is at least 20% more accurate than CT imaging, PET is commonly recommended as a staging procedure for the mediastinum and for systemic evaluation for metastases.[38] In a prospective randomized trial, PET reduced the number of futile thoracotomies by half, from 41% to 21%, vs. algorithms in which PET was not performed.[39] This occurred, in part, because remote foci of metastatic disease that were not identified by standard staging methods were identified by PET. Consensus is developing on how PET should be used in staging non-small-cell lung cancer, but many centers routinely perform PET/CT before surgery, with the incremental benefit being most apparent (in terms of detecting additional remote disease from the primary lesion) in patients with larger primary lung cancers. It usually is considered prudent to perform a biopsy on FDG-avid tissues to prove that they represent cancer. Many would argue that mediastinoscopy is no longer essential for patients who have negative mediastinal PET and CT scans, although in some patients, cancer in nodes is detected only surgically. An example of a positive PET scan with ipsilateral and contralateral mediastinal tumor involvement is shown in Figure 21-4B. The role of PET/CT in lung cancer is to provide a thorough whole-body screening assessment.

For mediastinal nodes, a short-axis diameter of greater than 1 cm is considered abnormal on CT. Larger nodes can be reactive, and nodes smaller than 1 cm can contain tumor, leading to sensitivity of 40% to 67% and specificity of 79% to 86% for metastatic disease.[40]

The hybrid PET/CT technology is significantly superior to PET alone for the staging of lung cancer.[41] The best algorithm for staging the mediastinum is evolving, but PET and PET/CT are the most accurate noninvasive methods. Some argue that mediastinoscopy is necessary in each case, however, because PET may produce false-negative results in patients with a low tumor burden, although the negative predictive value of a negative PET scan and a negative CT scan is approximately 95%. Others, however, would argue that

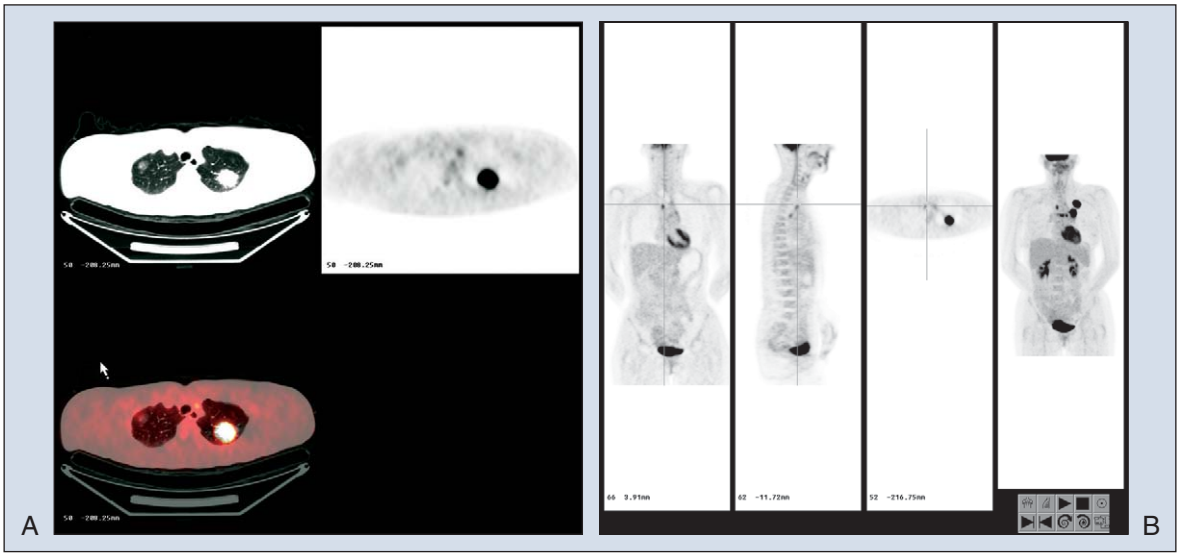


Figure 21-4 • **A,** Images obtained using positron emission tomography (PET) and CT. The upper left image is CT, the upper right image is PET, and the lower left image is a fusion of PET and CT data. The CT scan shows a smaller right apical nodule and a large left upper lung nodule. PET shows increased uptake of ^{18}fluorodeoxyglucose (FDG) in the left apical nodule, consistent with cancer, whereas only minimal uptake is seen in the right apical lesion, consistent with benign disease. Fused PET and CT images confirm the location of increased apical FDG uptake, as in the left lung nodule. **B,** Whole-body images from PET scans of the patient shown in part A. The images include coronal, sagittal, transverse, and "projection" whole-body views, from left to right. They show cancer in the left upper lung, mediastinal involvement, and a right paratracheal tumor focus. Normal uptake is seen in the heart, brain, and excretory system (bladder).

patients with a low tumor burden, below the level of detectability with PET and CT, may be suitable candidates for surgery without mediastinoscopy. Positive PET scans for metastases usually require tissue confirmation of the most advanced site of tumor to avoid false-positive imaging findings that indicate a tumor is not resectable. Figure 21-5 illustrates detection of lung cancer on CT and the use of reformatted virtual images.

MRI with contrast is recommended for imaging the brain. It usually is performed if patients have larger primary tumors or any symptoms that suggest central nervous system involvement, although in some centers, MRI with contrast is performed in every patient with lung cancer in whom resection for cure is planned. Evaluation for bone metastases currently is performed by bone scan. Any patient with bone pain or an elevated alkaline phosphatase level should undergo this study. In practice, where PET is available, bone scans are increasingly being replaced by PET scans. This area is evolving, and the bone scan remains the routine procedure in most centers when bone metastases are suspected, but FDG-PET can

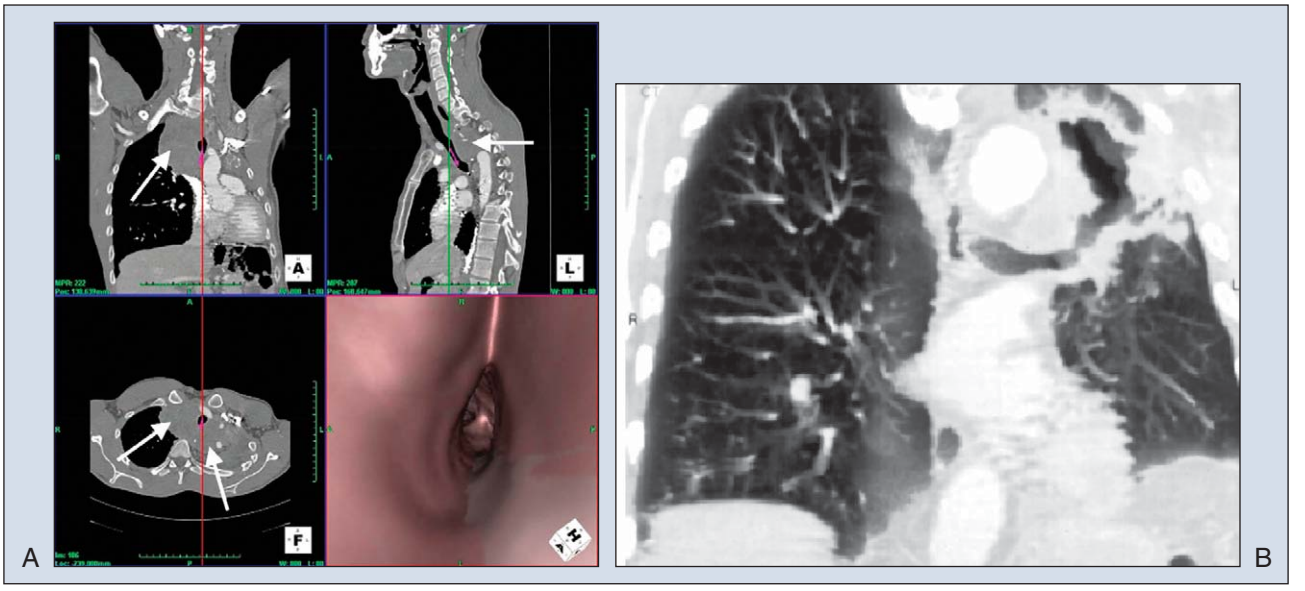


Figure 21-5 • Lung cancer. **A,** Axial CT image *(lower left)* shows a mediastinal mass *(arrows)* narrowing the airway. Coronal *(top left)* and sagittal *(top right)* reconstructed images show narrowing of the airway by a mass *(arrows).* The virtual bronchoscopy image *(lower right)* shows an endoluminal view of the narrowed airway. **B,** Coronal reconstruction of CT data in a different patient shows a cavitating mass in the left upper lobe. (Courtesy of Dr. Leo Lawler, Johns Hopkins University.)

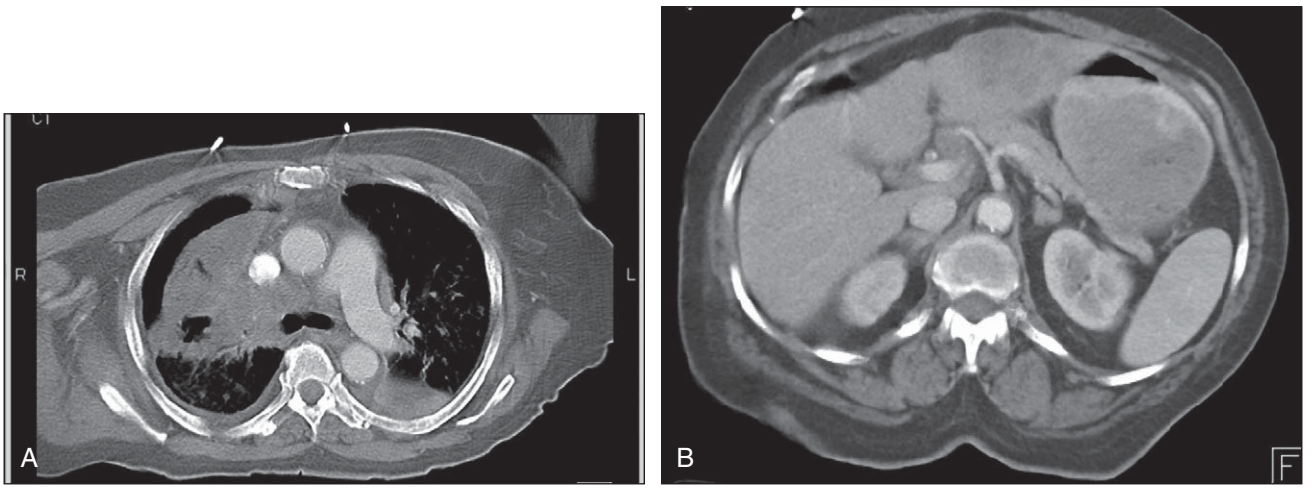


Figure 21-6 • Lung cancer. **A,** Axial CT scan of the chest with IV contrast shows a mass obstructing the right upper lobe bronchus. **B,** CT scan of the abdomen shows a metastatic hypodense lesion in the left lobe of the liver.

detect lung cancer metastases to bone that are not detected on CT alone.

In institutions where PET is not available, bone scan, MRI of the brain and CT of the chest and abdomen, to include the adrenals, are recommended. The abdominal CT should be performed with contrast to best evaluate the liver. Figure 21-6 shows extensive mediastinal disease and liver metastases on CT. In some centers, PET and diagnostic quality CT used together provide sufficient diagnostic information that no additional studies are required.

For small cell lung cancer, it must be determined whether the disease is extensive or localized before the form of therapy can be decided upon. CT is essential for the chest and upper abdomen. MRI of the brain typically is performed, and a bone scan is done to search for bone metastases. PET scans have been shown to upstage about 10% of patients with limited stage small cell lung cancer to extensive disease and to find lesions not identified by CT. FDG-PET identifies essentially all lesions detectable with CT.[42] Thus, many centers are using FDG-PET more routinely for this type of staging. PET also is useful in the evaluation of small cell lung cancers and mesotheliomas, although the data are evolving, and CT is the established method for this type of evaluation. For follow-up of lung cancer, the guidelines are more challenging because the available therapeutic options often are more limited. PET has a growing role because it can better separate residual scarring from viable tumor than can CT.

Evaluation of the Adrenal

Adrenal masses occur in approximately 9% of the population. These masses can be benign adenomas, metastatic disease from primary tumors such as lung cancer, or primary adrenal cortical carcinoma. CT and MRI are used to distinguish adenomas from malignant lesions in the adrenals. Adrenal adenomas have low attenuation on noncontrast CT as a result of elevated lipid content. If a threshold value of 0 HU is used, sensitivity is 47% and specificity is 100% for the diagnosis of adenoma.[43] If a threshold value of 10 HU is used, sensitivity is 71% and specificity is 98% for the diagnosis of adenoma.

Adenomas take up contrast material, but the washout of contrast material from an adenoma is faster than from a metastatic lesion. On 10-minute delayed images obtained after contrast injection, a decrease in the density of the lesion greater than 50% is specific for an adenoma.[43] If the lesion is atypical on CT, chemical shift imaging on MRI is used to determine whether it is an adenoma. An adenoma has both lipid and water content, and decreases in signal are seen on out-of-phase T1-weighted images. PET has a growing role in evaluating the adrenals, with accuracy of 90% and greater reported in some series. High FDG uptake typically is seen in metastases to the adrenal. Caution is in order, however, in that some adrenal adenomas can have moderately high FDG uptake. Figure 21-7 illustrates detection of adrenal and systemic metastases on CT and PET.

Breast Cancer

Mammography is the major imaging tool in breast cancer, allowing for early detection of tumors. When properly used, mammographic screening programs have been shown to save lives when compared with unscreened populations, and these programs are routinely implemented in many countries.[44]

Although mammography is a reasonably sensitive and specific procedure, the relatively low prevalence of cancer means that many

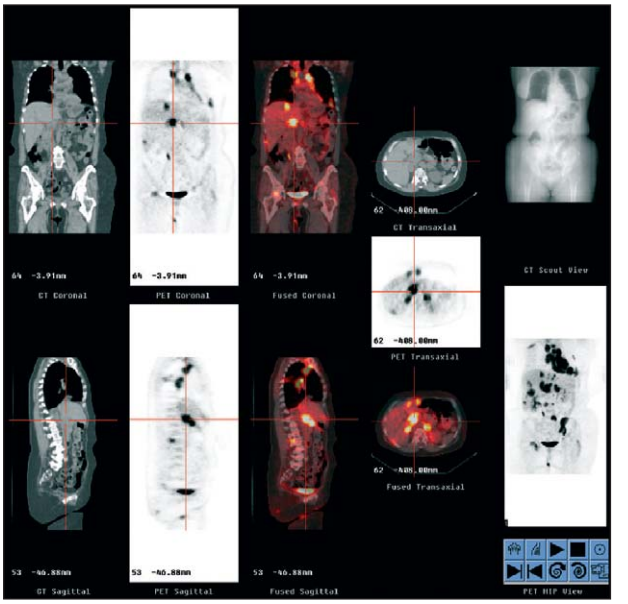


Figure 21-7 • PET and CT image panel shows a variety of PET, CT, and fused images that show diffusely metastatic lung carcinoma. Notable are adrenal metastases that are best seen on the transverse images, although many metastases are visible in a variety of locations. This figure also shows the multiple types of images available from a PET and CT system.

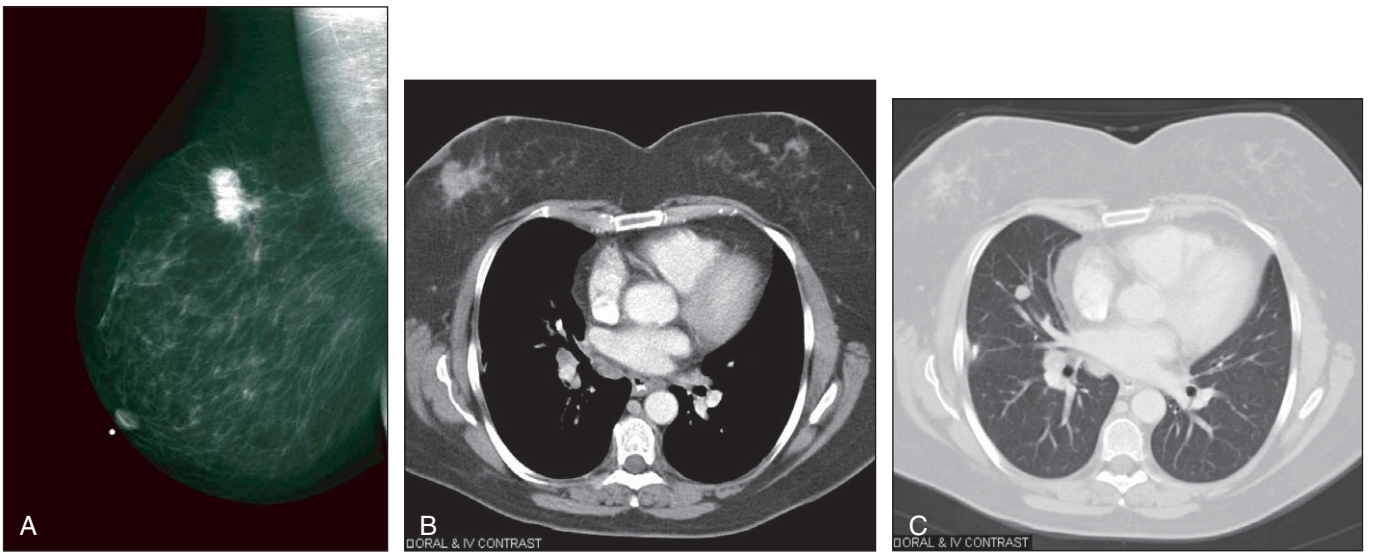


Figure 21-8 • Breast cancer. **A,** Mammogram of the right breast shows cancer. **B,** Axial CT image shows an irregular soft tissue primary mass in the right breast in a different patient. **C,** Axial CT image with a lung window shows a metastatic nodule in the right lung. (**A**, Courtesy of Dr. Nagi Khouri, Johns Hopkins University.)

image-directed biopsies show no tumor; thus, the results of the mammogram were falsely positive. Stereotactic biopsy devices have greatly facilitated nonsurgical breast biopsies. Although the sensitivity of mammography is generally considered "good," an overall sensitivity of less than 50% was seen for x-ray mammography in the Digital Mammography Imaging Screening Trial (DMIST). Even though this can be improved upon through the use of digital rather than film screen mammography, these results indicate clearly that mammography is far from perfect as a screening tool. Early efforts with tomosynthesis of the breasts, a mammographic method that provides a number of "slices" of the breast for analysis, are promising.[45] This approach can help remove overlying structures from the breast image, potentially improving lesion detection. It also is possible that use of IV contrast may enhance mammographic results.[46] Although other techniques can detect breast cancer, only ultrasound is used fairly commonly in most imaging centers to help to separate cystic from solid lesions or to help to locate and evaluate palpable but mammographically negative lesions. MRI with gadolinium contrast is used because it is a very sensitive technique and can help to determine whether disease is unifocal or multicentric. An example of a positive mammogram is shown in Figure 21-8A.

MRI has been evaluated as a tool for characterizing substantially abnormal mammograms or ultrasounds. The prospective multicenter NIH-sponsored trial of 821 patients referred for breast biopsy for American College of Radiology category 4 or 5 mammographic assessment or suspicious clinical or ultrasound findings were studied by MRI and showed an AUC of 0.88 in a population with 404 cancers present, with dichotomized data demonstrating sensitivity of 88% and a specificity of 68%. The positive predictive value was about 72%. The high sensitivity was still insufficient to obviate the need for biopsy in these patients, however.[47] Recently, MRI has been found to detect breast cancer in the contralateral breast of women with newly diagnosed primary breast cancers in approximately 3% to 4% of cases.[48] These additional cancers are found at a rate of about 25% in the lesions identified in this manner (i.e., 75% of the biopsies are negative). In addition, MRI has been used to screen high-risk women (e.g., those with the BRCA1 or 2 mutations) for breast cancer to some advantage. This higher sensitivity comes at the cost of more false-positive results and challenges in biopsy, which have limited deployment of the method. However, increased uniformity of reporting and greater similarities in technique are leading to more use of this methodology, which recently has been comprehensively reviewed.[49] PET methods occasionally are applied in the breast, but they are used for diagnosis infrequently due to the low sensitivity of whole-body PET scanners to small tumors. PET is used more commonly in disseminated disease.

Breast cancer often metastasizes first to locoregional lymph nodes. Current noninvasive imaging methods do not evaluate the axillary nodes effectively. However, imaging can help to define which lymph nodes should be resected for histologic sampling. Sentinel node imaging or detection using a radiation-sensitive probe system is becoming increasingly more important in axillary assessment of patients with breast cancer.[50] This procedure is discussed in more detail elsewhere in the text, but imaging is used, especially in European centers, to better localize the axillary nodes for intraoperative assessment and determine atypical routes of lymphatic drainage. Studies have shown sentinel node sampling procedures to be at least 90% sensitive—which is considered useful sensitivity—relative to axillary dissection, and they are virtually 100% specific.[51] FDG-PET is not sufficiently sensitive to detect small metastases and has an accuracy of only about 75% in axillary nodal staging.[52]

The extent of systemic imaging required in the initial workup of a patient with breast cancer depends on the size of the primary tumor and the status of the axillary nodes at biopsy. It can be argued that the likelihood of systemic metastatic disease is higher for patients with positive nodes; thus, more intensive evaluation may be more appropriate. Some would suggest a baseline bone scan and CT of the chest and abdomen at this time. The frequency of follow-up is debated, given the improbability of curing recurrent systemic disease, and some have advocated only limited biochemical follow-up. However, this area is controversial. Examples of primary and metastatic breast cancers imaged on CT are shown in Figure 21-8B and C. PET is a highly effective tool for evaluating soft tissue involvement and quickly assessing treatment response.[53] FDG-PET imaging can detect disseminated cancers; however, the optimal role of PET in imaging is evolving. PET is now approved for monitoring treatment response of breast cancer.

Prostate Cancer

The role of imaging in newly diagnosed prostate cancer is evolving. Although there is great interest in this area, currently available

imaging techniques are far from ideal and continue to evolve. The serum PSA test is controversial, but it has allowed the detection of smaller prostate cancers than generally are detectable clinically, along with opportunities for earlier interventions. In addition, mortality from prostate cancer has declined in the past 15 years. Many believe these two observations are not random associations, though this is discussed in more detail elsewhere in this book. However, this is an area of great controversy, though there is some evidence that early surgical resections are more closely associated with diminished mortality from prostate cancer than is watchful waiting. Thus, imaging in prostate cancer could play several roles: detecting cancer in the prostate; detecting the extent of tumor; and determining whether the tumor has spread beyond the prostate locally or systemically.

Evaluation of the Prostate

Unfortunately, intraprostate carcinoma is not detected particularly well by imaging with ultrasound or other methods. Although transrectal ultrasound has been used to guide biopsies, up to 40% of prostate cancers are isoechoic (and thus undetectable) by this method. Similarly, the positive predictive value of hypoechoic lesions of the prostate typically is well below 50%. Ultrasound can be used to detect abnormalities and guide biopsy of the entire prostate because it does an excellent job of defining the overall shape, size, and location of the prostate for purposes of systematic biopsy. A sextant approach often is used to sample the base, middle, and apex of the prostate bilaterally, in addition to taking biopsy samples of any suspicious areas. Although this technique is less than perfectly accurate for detecting prostate cancers, on ultrasound, tumors in the peripheral zone are more readily visible than tumors in the inner gland. The peripheral zone is echogenic, and tumors that are hypoechoic to it (approximately 60%) can be detected.[54] However, hypoechoic lesions also can be caused by inflammatory processes, and the positive predictive value of ultrasound is approximately 18% to 52%.[54] Contrast enhancement of the prostate on ultrasound has been used to some advantage to enhance detection rates and positive yields on biopsies of the prostate.[55] Similarly, on MRI, cancers that are hypointense on T2-weighted images are seen, but the findings are not specific for tumor. Extension of cancer beyond the prostate capsule is suggested on ultrasound when the capsule margin is irregular or the seminal vesicles are abnormal in morphology; however, sensitivity of as low as 20% has been reported. The sensitivity of MRI for extracapsular invasion is approximately 50%, and specificity is 95%.[54] Patients at intermediate risk for invasion, with a PSA level of 10 to 20 ng/mL and a Gleason score of 5 to 7, may benefit from MRI staging of local extension.[54] MRI methods are improving, especially with the use of spectroscopy.[54,56] However, spectroscopy is still applied mainly at a few centers with specialized expertise, so it is not yet a routine part of management of prostate cancer. Increased field strength for MRI is now being more systematically assessed and appears promising as a tool to separate benign from malignant prostate tissue by detecting tissue with increased ratios of choline/citrate.[57]

CT has no established role in evaluating the prostate itself or local invasion (25% sensitivity for capsular invasion), although tumors sometimes can be seen on CT (Fig. 21-9A). CT is used to detect bladder and rectal invasion, adenopathy, and distant metastases, and MRI is used to assess local extent. Similarly, the sensitivity for detecting nodal metastases has been reported to be as low as 30% with CT. Higher sensitivity can be achieved, but with lower specificity. Pathologic proof is desirable before it is concluded that a patient has metastatic disease to the lymph nodes, and if metastatic disease is demonstrated, radical prostatectomy is considered inappropriate. Large nodal metastases are easily detected on CT imaging, however (Fig. 21-9B).

It is not clear that MRI is better than CT; however, recent data on MRI using a node-specific paramagnetic contrast agent have shown very high sensitivity and accuracy in the detection of nodal metastases.[56] There is considerable hope for this method, but it has not yet been approved by the FDA.[58] Given the traditionally low sensitivity of CT and MRI to nodal metastases, it has been recommended that the serum PSA level be at least 20 ng/mL before CT is performed. If the CT findings are positive, then biopsy can be performed of the enlarged node or nodal sampling can be performed before radical prostatectomy. CT also is the test of choice for visceral metastases.

A bone scan is a sensitive technique relative to x-rays for bone metastases. The results of a bone scan can be positive when radiographs of bone are essentially normal. The current recommendation is that a radionuclide bone scan be performed only if the serum PSA level at presentation is greater than 10 ng/mL. Only very rarely is a bone scan positive for tumor at lower levels at the time of diagnosis. Some argue that for large primary tumors or very high Gleason scores a bone scan still may be appropriate at staging.

Thus, imaging is used selectively in patients with newly diagnosed prostate cancer. A bone scan commonly is used for recurrent prostate cancer whenever the PSA level begins to rise. New PET methods are promising in prostate cancer, but are not in widespread use in the United States. FDG-PET often is falsely negative in prostate cancer, especially for disease in the earliest stages.[46] Similarly, MRS has shown promise in evaluating the prostate gland and determining whether the tumor has spread beyond the prostate.

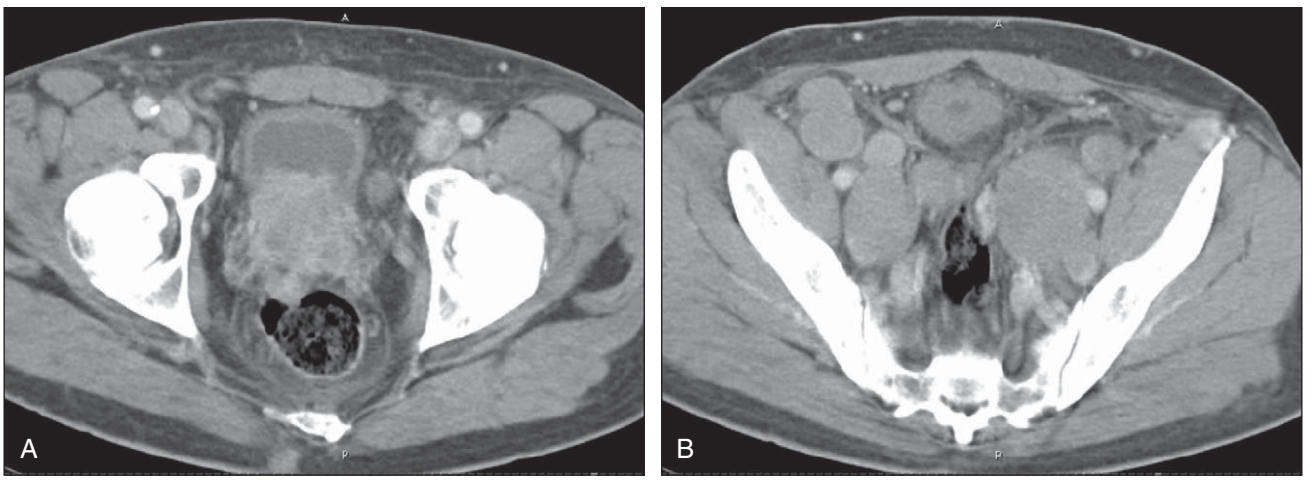


Figure 21-9 • Prostate cancer. **A,** Axial CT image shows an enlarged prostate with an enhancing mass and irregular margins. **B,** More superior image shows enlarged bilateral pelvic nodes from metastatic disease.

Much monitoring of prostate cancer now involves sequential blood tests to measure the PSA level. When the PSA level rises persistently, the tumor has recurred, but determining the site of recurrence often is problematic. Bone scans and CT often are used, with radioantibody imaging for anti-prostate membrane specific antigen antibodies used only infrequently because of limited diagnostic accuracy, although some promising results have been obtained by experienced groups.

Colon Cancer

The role of noninvasive imaging in the diagnosis of the primary lesion in colon cancer has changed over the last several decades. At one time, barium enema studies were used extensively to search for colorectal cancer. They have been replaced, in large measure, by fiberoptic colonoscopy. However, there is a growing level of interest in virtual colonoscopy, which is performed using CT scanning and per-rectum insufflation after thorough bowel preparation. This procedure is used to a limited extent for screening. The technique faces challenges because it requires bowel preparation and interpretation is quite time-consuming. Screening for colon cancer is an area of considerable opportunity for noninvasive imaging. Infrequently, these cancers can be detected by other methods such as ultrasound. The performance of virtual colonoscopy has been directly compared to that of optical colonoscopy in a study of over 6000 patients. Patients were randomized to either an optical or CT colonographic (CTC) group and were compared for the detection of advanced neoplasia and the total number of harvested polyps. Advanced neoplasia was confirmed in 100 of the 3120 patients in the CTC group (3.2%) and in 107 of the 3163 patients in the OC group (3.4%). There were seven colonic perforations in the OC group and none in the CTC group. Primary CTC and OC screening strategies resulted in similar detection rates for advanced neoplasia, although the numbers of polypectomies and complications were considerably smaller in the CTC group. CT colonography also was much less expensive than optical colonoscopy.[59]

Interestingly, the detection rate for polyps requiring biopsy was statistically identical between the two groups of patients. A large multicenter study is being performed in the United States to compare the two methods. A concern with the virtual colonoscopy method (CT colonography) is that it is highly interpreter-dependent. Before it can be recommended routinely, certainty of its performance across various medical centers will be highly desirable, though in expert hands it currently appears to be a viable alternative to colonoscopy and is considerably less expensive. It is probable that CT colonography methodology will assume a growing role in cancer screening in the coming years.

Regardless of means of detection, the extent of preoperative imaging performed before resection of primary colon cancer is variable, based on the institution. In general, the larger the primary tumor is, the more aggressive is the staging procedure required. In most instances, the primary tumor must be surgically resected for palliation (or cure), even if metastatic tumor is present. For staging, the most common studies include CT scan with contrast of the abdomen and pelvis, CT scan of the thorax (or chest radiograph), and bowel imaging to exclude the presence of a second primary colon cancer. In institutions in which PET imaging is available, PET is used somewhat more frequently at presentation; however, it is much more commonly applied in the setting of suspected recurrence.

For colorectal cancer, many advocate regular imaging studies after surgery for "cure," because isolated metastases or oligometastases of colorectal cancer can be resected from the liver or lungs; in some instances, the patient is disease-free for a long period. Thus, before such removal of a limited number of metastases is contemplated, a thorough imaging procedure is undertaken. This usually includes CT of the abdomen and pelvis with contrast and CT of the thorax without contrast. CT of the thorax may be replaced by a chest x-ray, but chest x-rays are less sensitive for pulmonary metastases.

PET is applied very often in this setting and in the setting of a rising carcinoembryonic antigen level after surgery. The precise timing of follow-up studies can be variable, but they often are done every 6 to 12 months in the early years after surgery. Considerable evidence supports the idea that PET can detect more metastatic foci than CT in the setting of a rising carcinoembryonic antigen level.[60] An example of a patient initially believed to have only a limited number of liver metastases is shown in Figure 21-10; however, more extensive disease was identified (Fig. 21-10B). PET/CT has been shown to offer higher accuracy than PET alone in recurrent colorectal cancer.[61]

Although immunoscintigraphy has been used, it has been rendered essentially obsolete due to the availability of FDG-PET. FDG-PET often does not detect small (<5 mm) tumors, however, and is

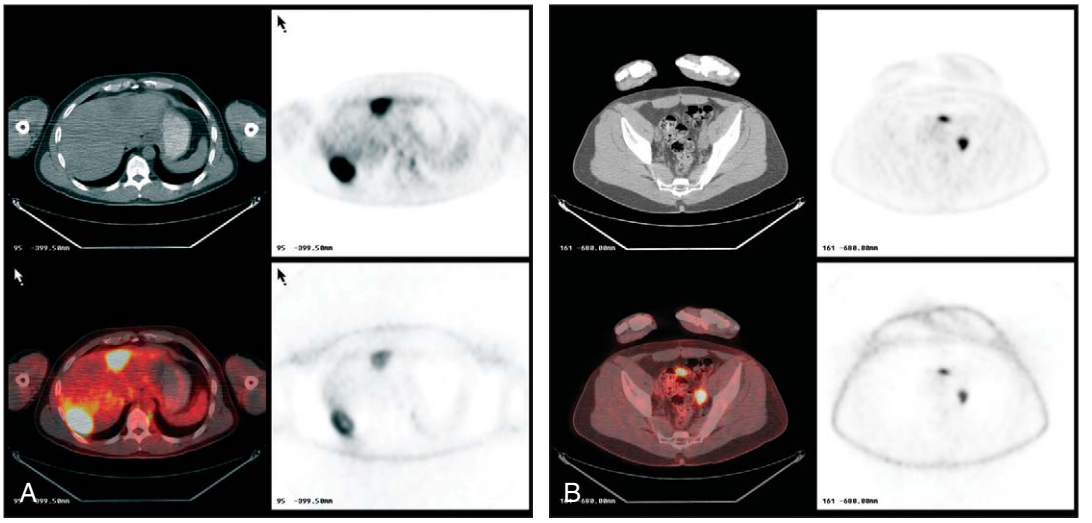


Figure 21-10 • Colon cancer. **A,** PET and CT image display of a patient with two ^{18}FDG-avid lesions in the liver. These are seen on the CT scan *(upper left)*, the attenuation-corrected PET scan *(upper right)*, the non–attenuation-corrected PET scan *(lower right),* and fused images *(lower left).* **B,** PET and CT images of the pelvis, oriented as in part A, show increased FDG uptake in a left external iliac lymph node metastasis.

known to be less sensitive for tumors of mucinous histology, so opportunities for improvement remain.

Ultrasound can detect many liver lesions, and is a very useful technique for guiding biopsies of the liver.[24] For liver metastases, CT is still the most commonly used procedure, but in a meta-analysis, PET was a more robust test to identify the presence and location of hepatic metastases of colorectal cancer compared with CT, MRI, or ultrasound methods.[62]

Gynecologic Neoplasms

Screening for gynecologic neoplasms usually is not performed by imaging, except for very limited programs that have evaluated the use of either transabdominal or, more commonly, transvaginal ultrasound of the pelvis to detect masses that may represent ovarian cancer. These programs have been combined with serum biomarkers. Such programs have not been proven cost-effective and are not widely applied, but they warrant further study, because this is a very important health problem. In women with high genetic risk of ovarian cancer, such as those with the BRCA mutation, screening may have greater value.

In cervical carcinoma, screening using the Pap smear has a large effect in terms of lowering mortality rates by detecting premalignant changes and early-stage disease. Although much of the staging of cervical carcinoma is performed by physical examination, for larger primary tumors, imaging has an important role. Both CT and MRI are used in the pelvis; however, the use of PET for tumor staging is increasing. As in other tumors, PET appears to be more sensitive than anatomic imaging methods. Emerging data show that PET provides better prognostic value than anatomic imaging in cervical cancer.[63–65]

In ovarian cancer, no technique is able to detect microscopic metastatic disease. Ultrasound is the main method by which ovarian tumors are identified at their earliest stages; however, the unfortunate fact is that these tumors are usually diagnosed at an advanced stage. Imaging can be used in an attempt to determine the extent of the surgical procedure that will be required. Both CT and MRI are used to assess the extent of ovarian cancer, with CT the preferred method (Fig. 21-11). PET is not sensitive to tumor foci smaller than 8 mm to 1 cm, but it is reasonably reliable in detecting larger tumor foci. For this reason, some advocate the use of PET to determine whether tumor debulking should be performed. PET has a role in the setting of a rising CA125 level in patients with normal CT findings.[66]

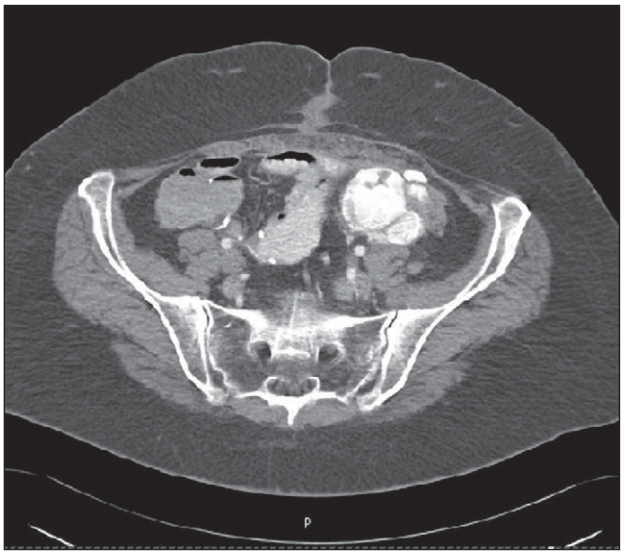


Figure 21-11 • Axial CT image shows a dense, calcified mass in the left pelvis, compatible with a metastatic implant from ovarian cancer.

The use of serum markers and imaging is recommended for surveillance after surgery for ovarian carcinoma. The aggressiveness of imaging follow-up depends on the treatments available. PET has an emerging role in this setting, although practice patterns vary widely. PET also has been shown to provide information related to treatment response in preliminary studies.[67,68]

Lymphoma

For both Hodgkin's and non-Hodgkin's lymphomas, accurate staging is important. For both types of lymphoma, accurate definition of the tumor burden is needed for effective treatment planning, especially treatment with external beam radiation. CT is the historically accepted method for noninvasive staging of lymphoma, with PET being used increasingly because many studies have shown it to be capable of locating more tumor foci than CT.[69] An example of CT imaging of abdominopelvic lymphoma is shown in Figure 21-12. In most lymphoma histologies, FDG-PET is more sensitive than CT, often detecting 20% more lesions than are seen on CT alone.[70] PET can detect disease in the bone marrow and spleen in some instances. In fact, marrow involvement seen on FDG-PET often is associated with a negative CT scan.[71]

CT is traditionally used for follow-up of lymphoma, and there are clear response criteria in place to follow lymphoma therapy. One of the challenges in lymphoma is that large masses often do not normalize in size after treatment, leading to questions in interpretation of a residual mass lesion. Determining whether these lesions contain a viable tumor is important, because it defines whether more treatment is needed. Data indicate that gallium (Ga)-67 scintigraphy can be effective for assessing the viability of residual Hodgkin's lymphoma and intermediate- and high-grade non-Hodgkin's lymphoma. However, multiple studies now have been published on FDG-PET in this setting, and this imaging modality has essentially replaced Ga-67 scintigraphy in assessing the viability of residual masses of lymphoma. If a residual mass of lymphoma shows increased FDG uptake, that usually is indicative of residual viable tumor; however, scans also can be falsely negative, because some tumor foci may be smaller than the resolution of PET imaging.[72] False-positive results have been described in patients with Hodgkin's lymphoma, however.[73]

Positive midtreatment Ga-67 and PET scans predict a poor outcome from therapy, and positive PET scans at the conclusion of a therapeutic regimen also indicate a poor prognosis. It is increasingly appreciated that PET findings soon after treatment is initiated can be highly predictive of ultimate outcome of the therapy.[74,75]

Challenges associated with PET include reactive lymph nodes and nodes involved with inflammatory processes such as sarcoidosis, which can be very FDG-avid. Similarly, uptake of FDG in brown fat in the neck and thymus can be confusing.[76]

Although anatomic imaging has been the key for lymphoma assessment, there is a growing trend to greater use of PET. PET imaging and PET/CT imaging, providing additional functional information, are of growing utility. A limitation of PET-only methods had been the lack of a standardized set of response criteria. Tracer activity in PET images generally decreases more rapidly than tumor shrinkage occurs (i.e., anatomic changes of treatment lag behind metabolic changes detectable by PET). For these reasons, PET scans may appear normal before CT scans do. A concern is that there is not strong evidence showing that a negative PET scan should be used to truncate the duration of lymphoma therapy. For example, if a PET scan became negative after two cycles of treatment, this would not justify, based on current data, discontinuing treatment. However, if a treatment involved a standard of four possible courses of treatment and PET became negative after these courses were completed, available data suggest that this portends a very good prognosis vs. a positive PET scan. Recently, new criteria for response including PET were developed for lymphoma. For FDG-avid lymphomas, a negative PET scan is required to determine a complete response.[77–79]

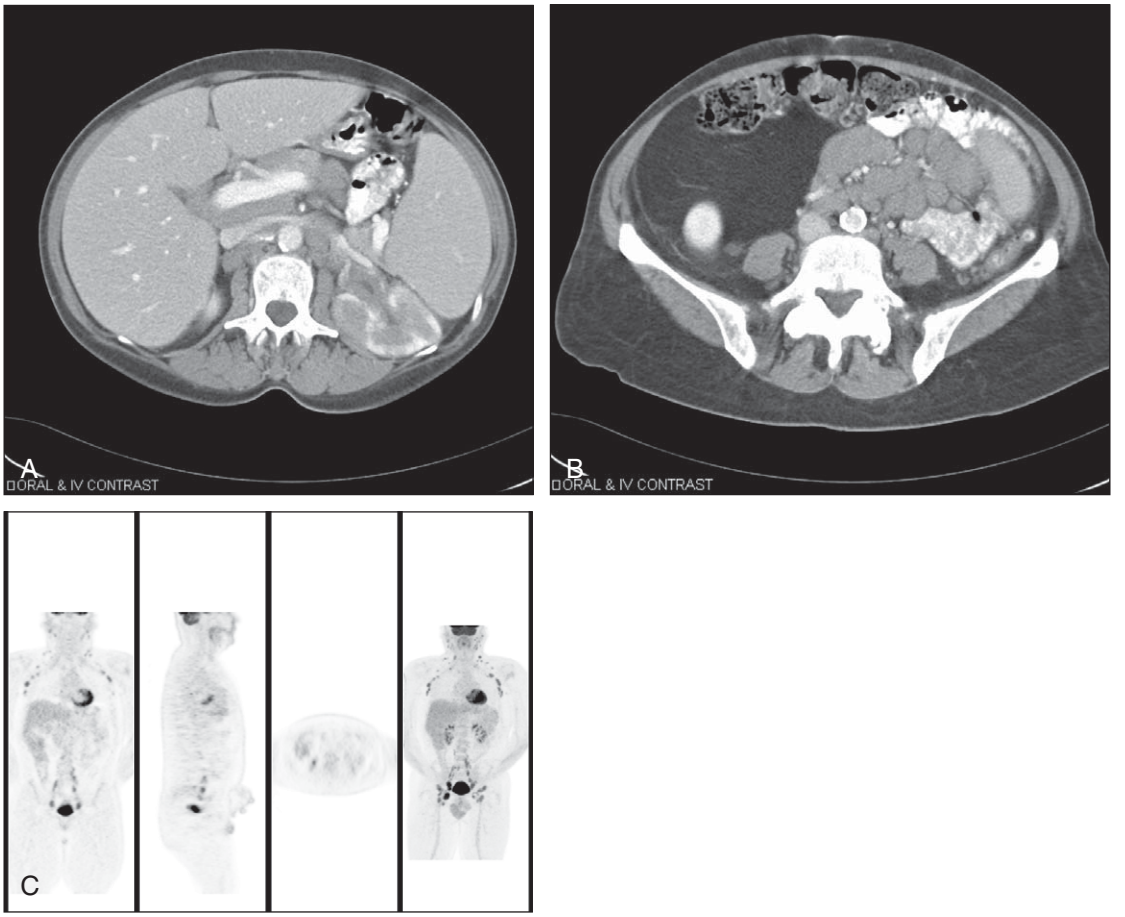


Figure 21-12 • **A,** Axial CT image with oral and IV contrast shows para-aortic adenopathy and infiltration of the left kidney by lymphoma. **B,** Image of the lower abdomen in the same patient shows enlarged mesenteric nodes. **C,** PET-only images (left to right: coronal, sagittal, transverse, and anterior projections) show focal areas of increased ^{18}FDG uptake in multiple lymph node groups, including the axillary, inguinal, and iliac regions, consistent with disseminated lymphoma.

It can be argued that PET is not essential in all patients with lymphoma. However, the use of PET and PET/CT is becoming increasingly the norm in centers where this technology is available. Because PET can find some lymphomatous tumors that cannot be detected by CT, this method is increasingly finding routine application in the care of patients with lymphoma (Fig. 21-12C).

An exciting new opportunity for the use of PET in non-Hodgkin's lymphoma is in the setting of a "response adaptive" approach. In such treatment approaches, patients who are poorly responding can be identified by PET performed soon after treatment is initiated. This approach can allow segregation of responding from non-responding patients. In the responding patients, standard treatment is given, whereas in the poorly responding patients, alternative approaches such as stem cell transplants are used. This approach currently is investigational, but it is an area of great promise because it allows the potential for tailoring the therapy to the individual patient's responsiveness to the treatment algorithm.[80] Recently, use of such an approach has been shown feasible in a clinical comparative trial on Hodgkin's lymphoma.[81]

Melanoma

The imaging management of melanoma varies based on the stage of disease. Radiologic imaging has no significant role in the diagnosis of primary melanomas. Lymphoscintigraphy—the injection of radiolabeled colloidal material, typically technetium ^{99m}Tc sulfur colloid, into the subcutaneous tissues or intradermally to locate lymphatic drainage routes, and thus lymph nodes with the potential for metastatic involvement—commonly is performed for primary melanomas of intermediate thickness. Although practice patterns vary, this method typically is used for melanomas that are more than 1 mm thick without other evidence of metastases. If the sentinel node identified by surgery (often using radionuclide guidance) is involved with tumor, additional staging procedures often are done.[82] These procedures most commonly include CT of the chest and abdomen, and of the pelvis as well if the melanoma affected the lower extremities. If there are systemic metastases, brain imaging is performed, using MRI with and without gadolinium contrast enhancement.

PET and PET/CT with FDG also are potent methods for detecting metastatic melanoma, often detecting more tumor foci than CT. PET can detect nodal metastases, but is not as sensitive as sentinel node imaging and is not a replacement for sentinel node imaging and removal. PET is particularly good for soft tissue metastases, but cannot detect microscopic disease. Thus, sentinel lymph node biopsy is used in preference to PET for detecting early metastases. There is some evidence that ultrasound can detect small nodal metastases of melanoma, but it is not widely applied and is also less sensitive than sentinel node imaging.[1] However, PET can detect most tumor foci larger than 6 mm and sometimes can detect smaller tumor foci. CT is a more robust technique for small pulmonary nodules than is PET.[83]

Melanoma metastases, especially if they are localized, can be resected surgically. However, identifying whether only one or two vs. many metastases are present is a major challenge. Aggressive surgical procedures are not appropriate if there are disseminated metastases. For these reasons, staging imaging procedures are performed aggressively before major surgery is undertaken to resect melanoma metastases. PET commonly is part of such a staging evaluation. For systemically metastatic melanoma, PET has been reported to have sensitivity well over 90%. Thus, although anatomic imaging dominates, PET has a growing role in melanoma assessment.[84] For bone metastases, radionuclide bone scanning also is an important diagnostic procedure. Recently, it has been shown that the performance of FDG-PET in melanoma is significantly enhanced if the CT scan portion of PET/CT is analyzed very carefully. This appears to increase both sensitivity and specificity of the method.[85]

Bladder Carcinoma

Bladder carcinoma often presents at an early stage, and no imaging evaluation is performed to determine whether there are locoregional or systemic metastases. However, ultrasound has been used to determine the depth of penetration of primary bladder carcinomas. An important consideration in bladder carcinomas is that uroepithelial tumors are often multicentric. Thus, intravenous pyelogram examinations to evaluate the entire genitourinary system commonly are performed early in the diagnostic algorithm. Although ultrasound can detect many bladder cancers 5 mm and larger, transurethral sonography is more sensitive; obviously, however, it is invasive. MRI is used more commonly than CT for assessing primary bladder lesions because of its superior soft tissue contrast characterization abilities.[86]

For larger primary tumors that are invasive, imaging evaluation is important to help to determine whether surgery is appropriate. Metastatic disease to locoregional nodes or systemic metastases indicates disease with a poorer prognosis, and tumor invading local structures or metastatic either to nodes or systemically often is considered unresectable. CT is used most commonly for local nodal staging, but MRI also can be used. Small nodal metastases usually are not detected using CT, because they have not enlarged the lymph nodes sufficiently to allow the tumor-involved nodes to be detectable. CT has a reported sensitivity of 60% to 70%. Biopsy commonly is used to determine whether an enlarged node seen on CT truly contains tumor. MRI probably is more sensitive than CT in detecting nodal metastases, and new contrast agents that accumulate in normal nodes are potentially important for enhancing the diagnostic accuracy of MRI in detecting nodal metastases.[87] Initial data with MRI contrast agents support the accuracy of this approach, but also point out that the interpreter's experience is important.[88] Such agents are not yet routinely available or FDA-approved.

FDG-PET has been used and is promising in bladder carcinoma; however, images of the pelvis can be degraded by intense F18 activity in the bladder. The use of PET in bladder cancer is enhanced by PET/CT and iterative reconstruction methods that make for better assessments of the pelvis with less degradation due to the bladder radiotracer activity. For bone metastases, radionuclide bone scan remains the procedure of choice, and MRI also can be sensitive. PET/CT is quite sensitive for metastatic disease beyond the pelvis and is being applied to a greater extent due to the availability of the CMS registry in the United States.[89]

Follow-up of bladder carcinoma usually involves the use of CT scans. Follow-up for new or recurrent bladder carcinoma within the bladder usually requires direct visualization of the bladder by cystoscopy.

Head and Neck Cancer

Head and neck cancers often are associated with cigarette smoking and alcohol use or abuse. Human papillomavirus also has been linked to head and neck cancers as well, especially in younger women. Most malignancies in the head and neck (except for lymphomas, as discussed earlier) are of squamous cell etiology. A key issue in these lesions is determining whether the disease is localized to the head and neck or whether metastatic disease or a second primary lesion is present. Thus, imaging of the lungs usually is done to exclude a primary or metastatic lung tumor. The physical examination is very important in assessing a primary lesion in the head and neck, but both CT and MRI are very potent methods. MRI typically is performed before and after gadolinium contrast is administered; CT scanning usually is performed after contrast enhancement (Fig. 21-13A). Because MRI is subject to respiratory and motion artifacts, CT is used somewhat more commonly in the initial staging of these tumors.[90]

CT and MRI can characterize the extent of primary tumors; however, CT is more effective than MRI in assessing the extent of involvement of cartilage or bone. For nodal metastases, current diagnostic schemes are based mainly on nodal size. Nodal size is an imperfect indicator of tumor involvement, however.

Increasingly, FDG-PET is being applied to the assessment of head and neck cancers. Although several studies have suggested that PET, MRI, and CT have similar sensitivity, more recent studies have suggested that PET is more accurate in staging (Fig. 21-13B and C). However, PET can detect increased glucose uptake in nonmalignantly involved inflamed nodes (false-positive findings). These can occur in patients with head and neck or gingival infection or the common cold. Defining the precise extent of tumor is important to determine whether surgery or radiation therapy should be performed, because more extensive tumors are less amenable to surgical resection.

Occasionally, head and neck cancers present as isolated nodal metastases without the location of the primary tumor being evident. Imaging has a role in such cases. Often MRI is performed as well as extensive inspection and biopsies; however, FDG-PET also has been applied. This method can detect as many as 15% to 30% of primary tumors.

For recurrent tumors, PET appears to be a more robust test than MRI or CT, especially when timed properly, probably because contrast enhancement can be seen in both postoperative changes (and postradiation tissue) and tumors. In general, FDG uptake is a more reliable predictor of tumor than the anatomic methods. PET is useful in surveillance for the recurrence of these tumors, but it is not yet considered the standard of care.

Thus, for head and neck cancers, MRI offers excellent contrast resolution for soft tissues, but can be degraded substantially by motion. For this reason, CT with contrast is much more commonly performed. FDG-PET is assuming a growing role in cancer management, especially for recurrence and for assessment of response to treatment. PET with CT is being used more often to stage and monitor these tumors during and after treatment, and may become the standard of care.[91] A recent comparison of PET/CT to MRI and PET alone showed superior accuracy of PET/CT versus the other methods.[92]

Pancreatic Carcinoma

The standard of care for the imaging diagnosis of pancreatic cancers is CT scanning. Although MRI can be useful, CT, including CT angiography, is the main method used for staging and assessing tumor invasion of vessels (Fig. 21-14). Some studies have shown FDG-PET to be somewhat more sensitive for detecting tumors and to have moderately high accuracy—approximately 85%—in characterizing pancreatic lesions as malignant or benign.[93–95] Ultrasound is used to assess cystic lesions. After treatment, salvage therapy is ineffective, and these patients often are less aggressively monitored than those with other, more treatable cancers. Neuroendocrine tumors of the pancreas often can be detected using 111n-pentetreotide (Octreoscan),

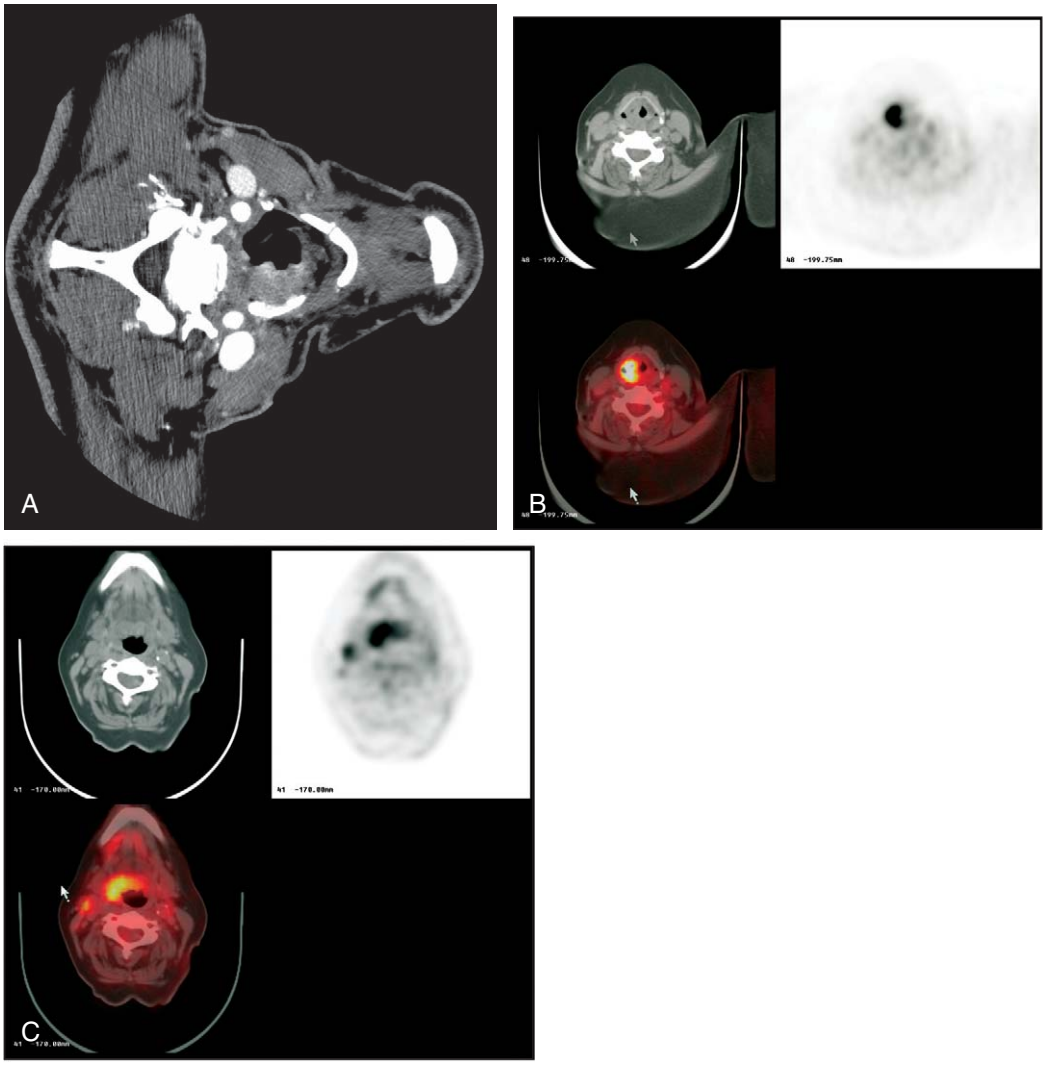


Figure 21-13 • Head and neck tumors. **A,** Axial CT image of the neck with IV contrast shows a mass in the left piriform sinus. **B,** PET and PET/CT images show right vocal cord cancer with intense tracer uptake. **C,** PET and PET/CT images from the lower level of the neck show nodal tracer uptake consistent with metastases. (Courtesy of Dr. David Yousem, Johns Hopkins University.)

a SPECT procedure. Recently, positron emitter-labeled analogs of somatostatin have been developed and show encouraging biological characteristics compared with single photon agents.[96]

Liver Cancer

Hepatic malignancies, especially hepatomas, are common worldwide. Both CT and MRI can be very effective in detecting these lesions. They sometimes are challenging to assess, because the appearance of cirrhosis with regenerating nodules and tumors can overlap. Multiphase CT imaging, CT angiography, and MRI with and without gadolinium contrast are commonly used in hepatomas. PET is less reliable, because approximately half—and sometimes more—of hepatomas are not FDG-avid. There has been some use of alternative PET tracers such as C-11 acetate to image some pancreatic cancers, because some FDG-negative tumors are C-11 acetate avid.[97] Ultrasound also can be used to assess the liver and guide biopsies.

Metastatic lesions to the liver also are common, especially in the United States. For most tumors, CT is the initial method used for assessing whether tumor is present. However, FDG-PET is more sensitive than CT in detecting liver metastases in common cancers such as colorectal cancer.[60,62] Thus, PET is seeing greater application in assessing suspected liver metastases, although ultrasound, CT, and MRI also are important methods and still are more commonly applied in many centers (Fig. 21-15).

Kidney Cancer

In the past, renal cancers were detected by intravenous pyelograms; currently, however, the most common method for detection is CT. Renal cell cancer commonly is detected incidentally because of the widespread use of cross-sectional imaging. Between 25% and 50% of surgically treated renal cell cancers are discovered incidentally.[98] Renal lesions are classified as cysts or solid masses, depending on their characteristics as shown by imaging. Renal cysts are fluid-filled and appear anechoic with increased through-transmission on ultrasound. They show water density without enhancement on CT, and appear hyperintense on T2-weighted images, also without enhancement, on MRI. Renal masses typically are evaluated by CT because of its short examination times and ease of evaluation, even in patients with a large body habitus, which can make ultrasound difficult. MRI typically is used for problem-solving. Multiphasic scanning is performed

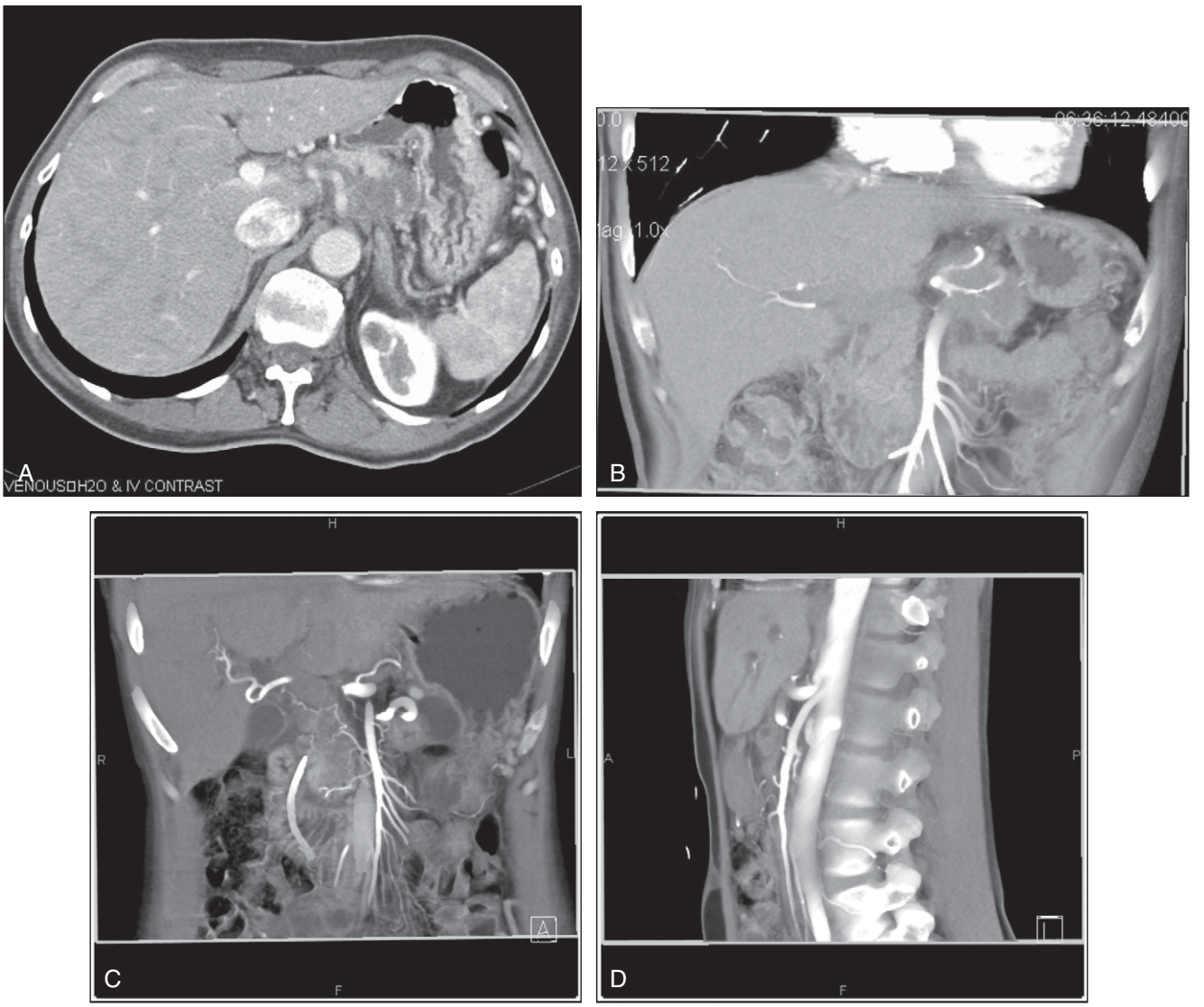


Figure 21-14 • Pancreatic cancer. **A,** Axial CT image shows a mass in the pancreatic body, encasing the splenic artery. **B,** Coronal volume-rendered three-dimensional CT image shows tumor encasing the splenic and left gastric arteries. **C,** Coronal volume-rendered maximum-intensity projection. **D,** Sagittal volume-rendered three-dimensional CT images show a mass in the pancreatic head without invasion of the superior mesenteric artery or vein. A common bile duct stent also is seen.

on CT to evaluate the density of lesions before contrast and as contrast filters from the cortex into the medulla and collecting system. An increase in density by greater than 20 HU corresponds to lesion enhancement and confirms the presence of a solid mass. CT is used to stage the tumor by determining the presence of renal vein invasion, adenopathy, local extension, and distant metastases. CT's accuracy for staging is 91%.[98] For resectable lesions, CT can provide information on whether the lesion is amenable to nephron-sparing surgery or partial nephrectomy. Lesions that are smaller than 4 cm, polar, and cortical, and do not involve the renal hilum or collecting system may be candidates for partial nephrectomy. Although CT, MRI, and ultrasound can all be used to assess renal lesions, CT with contrast is the dominant method (Fig. 21-16). PET is useful only when the tumor is FDG-avid. However, the normal excretion of FDG by the kidneys makes evaluation of the kidneys more challenging than other tissues, and some renal masses are not very FDG-avid. Thus, FDG-PET is not currently recommended for renal cancers, at least not for reliably characterizing renal masses as malignant or benign. Metastatic renal cancer is more accurately imaged on FDG-PET than is primary renal cancer.[99,100]

Endocrine Tumors

Imaging is used to study several types of endocrine tumors in a variety of locations. For adrenal tumors, CT is the procedure of choice, with metaiodobenzyl-guanidine ^{123}I (MIBG) scanning and MRI scanning also proving useful for lesion characterization.[100] MIBG accumulates selectively in pheochromocytomas. Adrenal masses with low HU values (<10 HU) typically are adenomas, which are lipid-rich. For the thyroid gland, radioiodine imaging commonly is used. For non–radioiodine-avid thyroid cancers, FDG-PET is very useful for lesion detection and is recommended in the setting of a rising serum thyroglobulin level with a normal ^{131}I or ^{23}I scan, particularly when recombinant TSH stimulation is used (Fig. 21-17).[101] For neuroendocrine tumors such as carcinoid tumors, CT and radiolabeled octreotide analogs are very useful. Several newer PET imaging agents

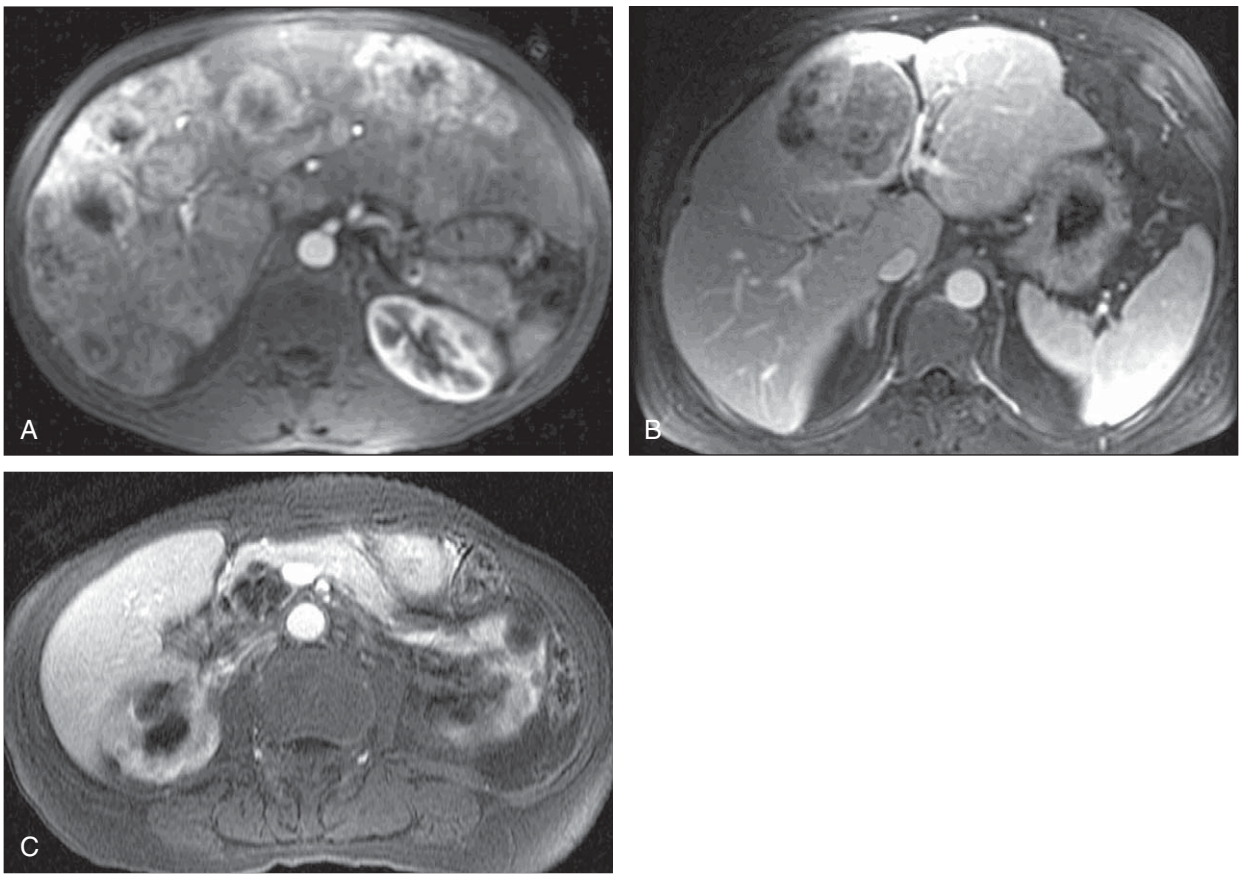


Figure 21-15 • **A,** Carcinoid metastases to the liver. Axial MR image with gadolinium shows multiple enhancing masses in both lobes of the liver. **B,** Hepatoma. Axial MR image with gadolinium shows a solid mass in the left lobe of the liver. **C,** Intraductal papillary mucinous tumor of the pancreas. Axial T1-weighted MR image of the abdomen shows a low-signal-intensity cystic mass in the head of the pancreas. (Courtesy of Dr. Ihab Kamel, Johns Hopkins University.)

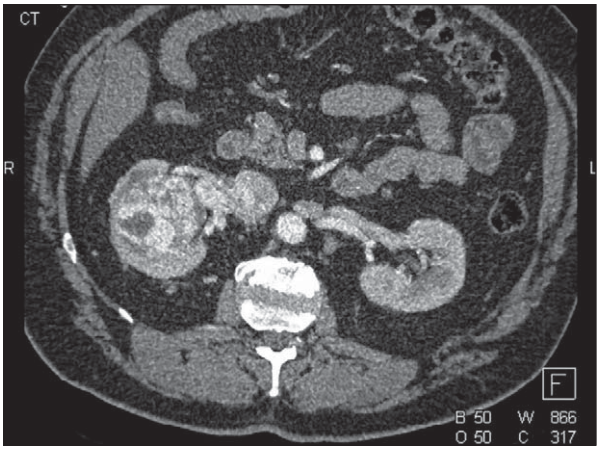


Figure 21-16 • Axial CT images of the abdomen with IV contrast show enhancing renal cell carcinoma in the right kidney. Enhancing tumor invades the right renal vein.

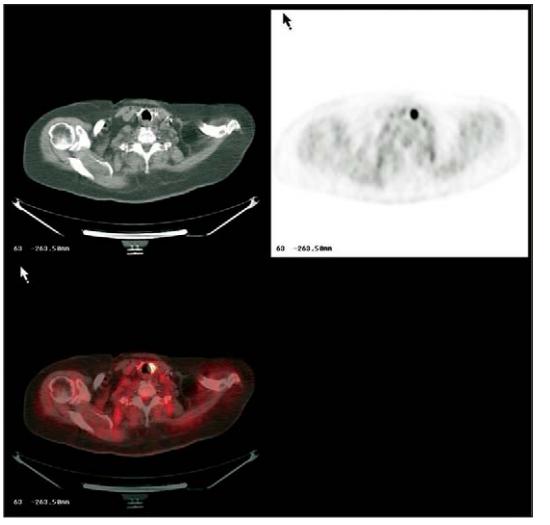


Figure 21-17 • PET and CT image panel showing an intense ^{18}FDG uptake focus near clips in the left thyroid bed, consistent with recurrent thyroid cancer.

are under study for endocrine imaging, but are not yet widely available or widely applied.[96,102]

Brain Tumors

The dominant method for the assessment of brain tumors is the MRI scan, which is the preferred method for initial detection, assessment of extent of disease, and assessment of efficacy of therapy. The superior soft tissue contrast provided by MRI places it ahead of CT for lesion characterization (Fig. 21-18).

Unfortunately, even sophisticated MRI techniques, often relying on tumor enhancement using gadolinium, cannot detect microscopic disease. MRI findings, although fairly specific for tumor, are not completely specific. Thus, infarcts, infections, and foci of demyelination occasionally can mimic tumor foci on MRI. FDG-PET has a very limited role but can be useful in assessing residual tumor after radiation therapy and determining whether residual masses are caused by tumor or tumor necrosis. It is most accurate in highly aggressive tumors where brain tumor uptake of FDG is greater than that of normal brain tissue. Recently, other tracers, such as FDOPA and FLT, have shown results more promising than those for FDG.[103,104]

MRS also can be useful in evaluating this issue because tumors typically have high levels of choline and low levels of N-acetyl-aspartate. Angiography, although a historically useful method, is performed less frequently for diagnostic purposes in brain tumors. MRI, CT, and PET can guide biopsies. Further, MRI can be used intraoperatively to guide therapy.[105]

Pediatric Tumors

CT usually is the method of choice for evaluation of pediatric tumors. For tumors of the central nervous system and for sarcomas, MRI is preferred. FDG has a growing role, especially for lymphomas and sarcomas. MIBG scanning often is used in neuroblastomas. CT scanning should be performed with a reduced tube current and energy to minimize the radiation dose while preserving the quality of the diagnostic image. Multiphase CT should be avoided in children unless it is clearly indicated to minimize the radiation dose to the child.[106] PET/CT has shown broad utility in pediatric cancers, although the available literature is quite modest at present.

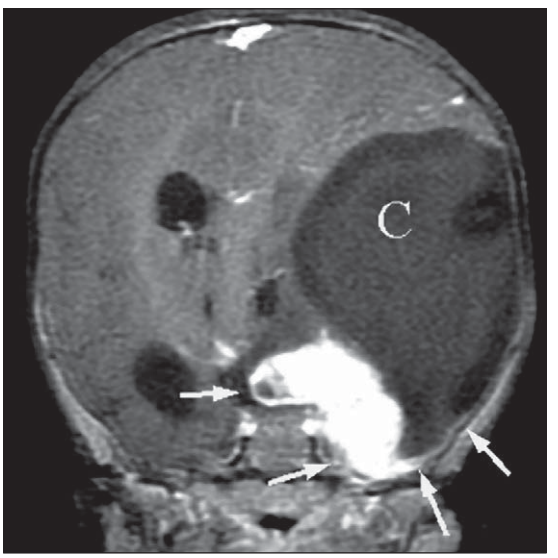


Figure 21-18 • Coronal MR image with gadolinium of the brain shows a mass with peripheral enhancement *(arrows)*, compatible with tumor, and a more hypointense necrotic area.

Esophageal and Gastric Cancer

CT scanning is the method of choice for initial staging of esophageal and gastric cancer. Endoscopic ultrasound is the most sensitive and accurate method for determining whether tumor has invaded the wall of the esophagus or involved the periesophageal nodes. PET scanning is very sensitive in determining whether stage IV disease is present, and typically is performed as part of the initial staging evaluation, at least for esophageal cancer, to identify patients who are clearly not candidates for surgery.[107] FDG-PET also is being used with increasing frequency to assess treatment response in patients with esophageal cancer, as early changes in glycolysis after treatment appear related to treatment efficacy.[108]

Sarcomas

MRI is the method of choice for detection and assessment of soft tissue sarcomas. Gadolinium contrast enhancement is commonly used as well. FDG-PET imaging has been useful in assessing primary sarcomas for aggressiveness and defining possible sites for biopsy as well as for defining prognosis and grade.[109,110] It also has been used to assess and predict the response of sarcomas to therapy.[111]

Gastrointestinal Stromal Tumors

GI stromal tumors are relatively infrequent, but have been studied extensively with both CT and PET imaging in the past few years. These tumors often are responsive to imatinib and other tyrosine kinase inhibitors, in part due to their constituitive overactivity of a mutated KIT oncogene. These tumors have been shown to be typically FDG-avid. FDG accumulation declines very rapidly with effective treatments, earlier than changes in tumor size. Of interest is that recently revised CT criteria may allow CT to assess response more quickly to treatment in such tumors, with changes in tumor HU one of the characteristic findings of response. Both PET and CT thus have a role in this somewhat uncommon tumor, especially for the early assessment of treatment response.[112]

DEFINING NORMAL ORGAN FUNCTION FOR CANCER THERAPY

Several tests are used to determine whether a patient is a suitable candidate for aggressive therapy. These tests include myocardial perfusion imaging at stress to determine whether ischemia is present, because if present it could increase the risk for a major surgical procedure. Echocardiography also is used for this purpose. Myocardial function often is evaluated before chemotherapy is given. This may be done using a myocardial blood pool study or, less commonly, an echocardiogram to determine chamber size and ejection fraction.

Pulmonary function usually is determined by pulmonary ventilatory function tests; however, split lung function and regional function may be determined by pulmonary perfusion imaging with ^{99m}Tc MAA (macro-aggregated albumin; i.e., a quantitative lung scan). Regional ventilation also can be assessed quantitatively. Such determinations help to predict the level of pulmonary function expected after surgery. Split assessment of renal function sometimes is performed before removal of a renal cancer to ensure that the remaining kidney will be functional.

Functional imaging can identify the location of eloquent brain activity and evaluate motor cortex function. It also can help to guide brain tumor surgery by avoiding key areas of the brain.

GUIDANCE OF RADIATION THERAPY

Radiation therapy can be palliative, or it may be performed with curative intent. In general, the goal is to deliver maximum radiation to the tumor while minimizing radiation delivery to normal tissues. This delicate balance is achieved through increasingly sophisticated

dose delivery systems. The anatomic location of a tumor most commonly is defined by treatment-planning CT. The CT data are used to define tumor and normal tissues with a therapy-planning system. The planning potentially can be enhanced by better definition of the gross tumor volume (or biologic tumor volume) versus anatomic tumor volume, which are not always the same. FDG-PET is beginning to be used to better define the biologic tumor volume, often with data from PET/CT. Although this procedure is hardly the norm, it is clear that imaging is key to the optimal planning of radiation therapy ports. Substantial potential exists to target areas of tumor that are not identified on CT (expand port size) or reduce ports to areas that are not involved with tumor, because the goal is to irradiate tumor while not irradiating normal tissues.[113] A substantial number of centers now include PET imaging as part of their radiation therapy planning in a broad range of diseases.[114] Treatment plans for radiation therapy are discussed in a separate chapter in this book.

INTERVENTIONAL PROCEDURES

Increasingly, imaging is being combined with a therapeutic procedure to provide minimally invasive therapeutics. Examples include the use of CT to guide thermal ablation of the liver or lung and the use of MRI to guide ablation of brain and prostate tumors (through heat and cold). The ability to locate tumors and follow, in near real time, the response to treatment is of tremendous potential.

Catheter-based delivery systems also are important. For example, angiographic catheters can be used to deliver regional chemotherapy, emboli, or radioactive or chemical microspheres to treat tumors. Radioactive microspheres also are assuming a growing role in interventional oncologic radiology.[115]

EMERGING OPPORTUNITIES IN IMAGING

Functional imaging methods such as PET and varying innovative MRI techniques are being used increasingly to assess treatment response early after treatment is begun.[25] Beyond this, a variety of imaging methods are being developed to image key aspects of tumor biology (Table 21-3). An exciting area for both MRI and PET is in detection of hypoxia, which is common in a broad range of malignancies and which represents a possible target for cancer treatments.[116]

Table 21-3 Emerging Uses of Imaging

INDIVIDUAL PATIENT MANAGEMENT DECISIONS
Screening
Phenotyping of the tumor and host
TUMOR
Viability, proliferation, extent of necrosis or apoptosis, hypoxia, prognosis, type of treatment most likely to be effective based on receptors or presence of imageable pathways
HOST
Individualized assessment of pharmacokinetics of the drug and of organ function and pharmacodynamics
DRUG DEVELOPMENT
Does the tumor have a relevant target?
Does the drug reach the target?
Is the target pathway affected by treatment?
Is the proper dose of drug being given?
Does alteration of the target pathway alter the tumor biology?

In addition to hypoxia, tumor perfusion can be imaged with a variety of approaches.

Even though the process is difficult, interest remains in gene therapeutic approaches, which has led to attempts to determine, through imaging, whether genes, when delivered, actually reach tumors and, more importantly, whether they express in vivo the desired levels of gene product expected to be required to achieve a therapeutic effect. For example, dopamine receptors have been transfected into cells and imaged with radioligands capable of binding to the D2 dopamine receptor. Similarly, genes have been transfected that express varying thymidine kinase activities. This agent is suitable for gene therapy and can be imaged with radiolabeled substrates such as FMAU.[117,118]

Similarly, a great deal of interest has been expressed in stem cell biology and the potential for stem cells to allow for regeneration of tissues. Tracking these stem cells in vivo and determining their biodistribution and ultimate proliferation are exceptional opportunities for imaging. These goals have been achieved with both nuclear medicine and MRI methods.

Small animal imaging devices of a variety of types are now being used to help in drug development. Small animal PET, SPECT, MRI, and CT scanners have been used to assess treatment response and aspects of tumor biology. Such methods are of critical importance for assessing the response of cancers to treatment with newer agents and understanding therapeutic effects. Even combined human PET/CT devices have been used for imaging and can provide useful information for drug development in cancer.

Some methods are of tremendous importance in preclinical studies, but will be more difficult to extend to human studies. One example is optical imaging. Such methods are capable of tremendous sensitivity and excellent resolution in vivo in small animals. A variety of approaches can be used, with emitted light, transmitted light, and reflected light. With bioluminescence approaches, a very small number of cancer cells can be identified in vivo in small animals. Such approaches, although very potent in vivo in small animals and capable of being combined with radionuclide and other methods, are not likely to be easily translated into humans, at least for broad applications, because of the limited penetration in tissue of light photons. However, in a broad range of detection issues the light can reach detectors, both intraoperatively and endoscopically for superficial structures, so this area is likely to be increasingly translated to practice. Thus, small animal imaging is a key element of progress allowing for proof of concept and refinement of tumor biological processes before translation to human use.

SUMMARY

Anatomic imaging of cancer using x-rays has been and remains extremely useful, and in the more modern form of CT is the dominant approach to imaging the patient with visceral cancer. Anatomic methods, although very potent, have clear limitations, but continue to improve, as evidenced by digital mammography and other techniques. Screening programs with mammography, CT of the thorax, and CT colonography are showing promise as methods to detect disease at earlier stages and potentially change outcomes. Anatomic methods can detect disease early, and such methods reliably show whether a mass is present. However, they provide limited information regarding the composition of the mass. In addition, they can be insensitive to small tumor foci, may be slow to change in response to therapy, are not predictive of response, and may be more challenging to apply in evaluating the postoperative patient. The functional information provided by MRI, including diffusion characteristics and, to a lesser extent, MR spectroscopy, adds to the anatomic signature of the lesions and continues to grow in application. Imaging additional phenotypic alterations of cancers with functional imaging methods such as PET adds information that often is clinically valuable for patient management in many common cancers.

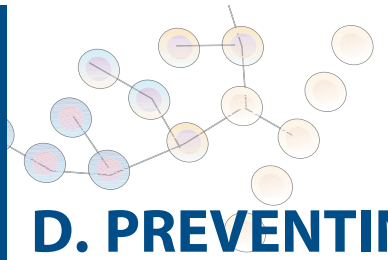
Although many molecular alterations are present in cancer, the one that is by far most exploited in clinical practice and clinical research is the accelerated glucose metabolism present in most cancers. This process is well imaged with the radiotracer FDG. The ability to localize the molecular alterations of cancer spatially, through qualitative cognitive methods performed by the imaging specialist, computer fusion of image sets, or fused "anatomolecular" image sets using dedicated PET/CT, is key to optimal use of the imaging methods. Increasingly, the ability of PET imaging to quickly assess treatment response is allowing adaptation of treatments depending on the response of a specific patient's tumor to treatment. This response adaptive approach is expected to grow in the coming years. Functional imaging also is revising the approach to radiation therapy treatment planning. Functional "molecular" imaging methods such as PET, SPECT, and varying methods of MRI, in addition to optical and ultrasound imaging and technical improvements in CT and interventional techniques, are expected to enhance the care of the patient with cancer in the coming years and will likely continue to change the way oncology is practiced.

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D. PREVENTING AND TREATING CANCER

22 Biostatistics and Bioinformatics in Clinical Trials

Steven Piantadosi and Jeanne Kowalski

SUMMARY OF KEY POINTS

Source of Uncertainty in Clinical Trials

- Uncertainty in trials can be classified as systematic error (bias) or random error.
- These types of errors can be controlled principally through the design of the medical study but not reliably through analysis alone.
- The strength of the evidence produced by a clinical trial depends on its design, primarily the amount and nature of the bias and random error that it controls.

Developmental Clinical Trials

- Clinical trials are designed primarily to meet specific developmental questions.
- An early developmental question is the relationship between dose and safety (phase I).
- These studies also address mechanistic questions such as pharmacokinetics and pharmacodynamics.
- The second major developmental step is providing evidence of safety and activity, usually in a disease specific cohort (phase II).
- These middle developmental trials provide evidence to support or discourage definitive, long-term, and expensive comparative trials.

Comparative Studies

- Comparative trials (phase III) often use randomization to remove treatment selection bias.
- Clinically definitive endpoints, such as disease progression and survival, are employed.
- Other systematic effects can be minimized by using masking.
- Random errors are minimized by employing sufficiently large sample sizes. These studies also require sophisticated infrastructures for data management, study monitoring, and multisite coordination.

Analysis

- The most appropriate methods to apply for analysis of a clinical trial depend strongly on the purpose and the design used for the study.
- All analyses begin with quality control data and sophisticated descriptive views of the data.
- Comparative studies require estimates of clinically relevant quantities such as risks or relative risks of the defined outcomes.
- Design flaws cannot be reliably corrected by sophisticated analyses.
- As a general principle, analyses unconditionally include all patients who meet the eligibility criteria and are based on treatment assignment.

Representation of Evidence

- The most clinically relevant summary of evidence from a trial is the estimate of the magnitude of treatment effect.
- In addition to magnitude, the precision with which an effect is estimated is often useful (e.g., 95% confidence interval).
- *P* values are deficient as measures of strength of evidence and should not be the primary currency of clinical trial results.

INTRODUCTION

The purpose of this chapter is to review biostatistical concepts that are helpful to clinicians in planning, conducting, and assessing clinical trials in oncology, and to provide some insight into the direction that future trials might take in light of the genomics era. For review, we describe areas where a statistical perspective can lead to improved design, execution, analysis, and interpretation of clinical studies. Several good texts and expository articles provide additional details regarding these concepts. These include history and policy,[1,2] general discussions,[3–12] cancer trials,[13–16] ethics,[17–19] prognostic factor analyses,[20,21] and reporting.[22–33]

Much of this chapter pertains to study design, because a well-designed and well-executed trial addressing an important therapeutic or management question will usually provide cogent evidence without an elaborate analysis. In fact, statistical analysis can do little to make the results of a poorly designed or executed trial compelling. This is not to trivialize analysis; an improper one can distort the findings of a well-designed and well-executed trial. To this end, our first topic is outlining some of the sources of uncertainty in inferences from clinical trials including dose-finding (phase I) studies, safety and activity (phase II) studies, and comparative (phase III) studies. Following this are discussed five areas of statistical activity that are important to the success of a program of studies in the management of oncologic disease: (1) formulation and refinement of an important therapeutic question through the use of developmental trials, (2) designing comparative trials, (3) implementing a trial and assuring quality control, (4) data analysis, and (5) describing results and preparing publications.

Later in this chapter, we discuss the future direction of cancer trials considering the combined roles of biostatistics and bioinformatics in cancer research, using vaccine trials as an example. Gene expression microarrays and gene expression databases provide new opportunities for the discovery of drug targets and for determining a drug's mode of action. Bioinformatics provides the computational tools by which to extract this information. Biostatistics provides the analytic tools to incorporate this information into clinical trial design and analysis. We later revisit concepts introduced at the begining of

this chapter within the context of cancer vaccine trials, because such trials represent a premier application of both fields with the development of immuno-based therapies designed to target discovered genes' function.

Many medical advances have been, and continue to be, made without conducting formal clinical trials. For example, when treatment effects are large, they usually become evident despite the variability and bias present in less formal methods of evaluation. However, many important treatment effects are characterized by natural variability of about the same magnitude as the treatment effect itself. In these circumstances, only careful design and conduct of clinical trials will separate treatment effect from bias and error reliably. Well-designed studies will estimate the magnitude of important clinical effects, quantify errors resulting from chance, reduce or eliminate bias, provide a high degree of credibility and reproducibility in results, and influence future clinical practice.

To meet these goals, investigators often conduct a variety of types of clinical studies. It is helpful to distinguish clinical trials from other types of medical investigations on the basis of who controls three essential components of design: treatment or exposure of the subjects, endpoint ascertainment (i.e., collection of outcome data), and analysis. True experiments place all three components under the control of the investigator. For example, a case report is relatively weak evidence, because it is a demonstration only that some event of clinical interest is possible. A case series is a demonstration of possibly related clinical events but is subject to large selection biases. In a database analysis, treatment is not determined by design but by patient or physician preference, permitting large biases. In an observational study the investigator takes advantage of natural exposures or treatment selection and chooses an appropriate comparison group by design. However, confounders may not be controlled adequately. In a clinical trial, treatment assignment is by design and endpoint ascertainment is actively performed on all subjects.

Using this type of hierarchy, one can see that the strength of evidence in medical studies is directly related to the amount of prospective design in the investigation. The more control exerted by the investigators over the essential components, the stronger will be the design and the more credible will be the results. See Byar[34] for a general discussion of this topic.

SOURCES OF UNCERTAINTY IN CLINICAL TRIALS

The most convincing clinical trials make use of methods to control and minimize relevant sources of uncertainty. Two types of uncertainty or errors can result when making inferences about treatment effects in medical studies: bias (systematic error) and random error. Both types of error can be controlled by using proper design. However, neither type of error can be reliably controlled by analysis alone.

Bias

There are numerous sources and types of bias in clinical trials; for example, see Sackett[35] or Chalmers.[36] All biases produce systematically high or low mis-estimates of the true treatment effect. Most of the time we do not know the direction of a particular bias, which means that it can either mimic a treatment effect or obscure it. Because, in human studies, we are often interested in treatment effects that are about the same magnitude as potential biases (and natural variation), control of systematic errors is critical. Consequently, we routinely attempt to eliminate bias through the appropriate use of design features such as eligibility criteria, randomization, objective endpoints, active ascertainment of outcomes, and treatment masking.

Patients who agree to participate in a clinical trial are usually not perfectly representative of the population with the disease (selection bias). Although this is often said to affect the external validity of the study, it is unlikely to affect the estimates of treatment differences. When the comparison group is subject to the same selection effect, as in randomized studies, relative treatment effects are estimated essentially without bias and are likely to generalize to individuals who do not meet the eligibility criteria. More clinically consequential biases arise from exclusion of patients after study entry, loss of data for reasons associated with outcome or prognosis, differential assessment of outcomes in treatment groups, and retrospective definitions or analyses. For example, it often seems clinically appropriate to exclude patients because of nonevaluability or nonadherence with the study protocol. However, such definitions are applied after registration or randomization and are therefore outcomes as well as potential predictors. One cannot reliably make exclusions based on such outcomes without the potential for bias.

Some data can be missing for reasons associated with outcome. For example, a recurrence (or death) event may not be observed because the patient has not returned to clinic for follow-up visits. Commonly used life table methods assume that such study subjects are censored at the time of last follow-up. Yet informative censoring results in an under-reporting of events and can only be corrected by actively ascertaining the status of all patients.

Random Errors

In later sections of this chapter we emphasize estimation of effects and confidence intervals as being the most clinically useful summary of data. However, because statistical hypothesis tests have had a prominent role in the design and analysis of trials and still provide a useful perspective on errors of inference, we discuss errors attributable to chance in these traditional terms. The two types of random error that can result from a formal hypothesis test are shown in Table 22-1. The type I error is a false-positive result and occurs if there is no treatment effect or difference but the investigators wrongly conclude that there is. The chance of making a type I error is frequently under the control of the investigator, even into the analysis stage of a clinical trial. This is true because the type I error can usually be controlled through the level of significance chosen for statistical tests.

The type I error must be carefully considered during the design of a clinical trial when multiple statistical tests are to be performed, a process that inflates the overall type I error. This happens, for example, when investigators intend to examine accumulating data and repeatedly perform statistical tests, as is done in sequential or group sequential interim monitoring of clinical trials. Failing to account properly for the effect of such repeated hypothesis tests can greatly increase the type I error rate. This point will be expanded later in a discussion of sequential methods.

The type II error is a false-negative result and occurs when we fail to detect a treatment effect or difference that is actually present. The power of a clinical trial is the chance of declaring a treatment effect of a specified size to be statistically significant (i.e., not making a type II error). The type II error can only be controlled by proper design, specifically a sufficiently large sample size, and not by procedures used in the analysis of the study.

A small study can yield a high power to detect a large treatment difference. However, as indicated previously, clinicians are usually

Table 22-1 Random Errors from Hypothesis Tests

	True State of Nature	
Result of Hypothesis Test	**H_0 True**	**H_0 False**
Reject H_0	Type I error	No error
Do not reject H_0	No error	Type II error

genuinely interested in modest-sized or small treatment effects. A small study will have low power to detect small differences. There is little sense in undertaking a complex expensive trial when the chance of missing a clinically important effect is larger than the chance of finding it.

A power calculation is hypothetical based on a specified, but as yet unobserved, treatment effect. Some observers of trials consider the power of a completed study against the observed difference, so-called post hoc power. When the observed treatment difference is smaller than anticipated, the post hoc power of the trial against that difference will be low, which seems to provide a cogent criticism. But after the study the treatment effect is no longer hypothetical, making a power calculation uninteresting unless someone intends to perform a new study in exactly the same circumstance. When a trial is finished, all of the information about the treatment effect is contained in the estimated value and its confidence interval; a post hoc power calculation adds nothing.

TYPES OF CLINICAL TRIALS

The use of clinical trials in oncology is similar to that in medical disciplines studying prevention, drugs, and devices. During the early developmental stages of new therapies, physicians evaluate evidence regarding related treatments and perform noncomparative clinical trials on the therapy under investigation. Statistical thinking is of great benefit in areas such as critical review of relevant literature, overviews of previous trial results, translational research studies, designing dose finding and toxicity studies, and designing studies to estimate treatment effects and feasibility.

Translational Trials

Only a small fraction of therapeutic ideas progress to developmental clinical trials. The transition from laboratory to clinic is guided by small targeted studies rather than large clinical trials. These small experiments, translational trials, may be the most common types of clinical trials performed. The methodology of translational clinical trials has not been fully formulated in the literature. This discussion is based on earlier work.[37] Nearly every new therapy depends on a transition from laboratory to clinic. Translational studies can sometimes be part of later developmental trials, provided that the subjects and the questions are compatible with it. The traditional dividing line between laboratory and clinical development is often said to be the phase I study (discussed later). In fact the interface between laboratory research and clinical development is formed by translational clinical trials.

The outcome in a translational trial is a biologic marker (target) that may require validation as part of the study. This is not a surrogate outcome, because it is not used to assess clinical benefit, although it might anticipate later questions of clinical benefit. The action of the treatment on the target defines the next experimental steps to be taken. In particular, the absence of a positive change is evidence of inactivity of the treatment.

A biologic outcome provides definitive evidence—an irrefutable signal—within the accepted paradigm of disease and treatment. The signal must be positive to support further clinical development. Good biologic signals might be based on a change in levels of a protein or gene expression, or the activity of some enzyme. As an example we consider a new drug for secondary prevention. The goal might require reducing the presence of biomarkers in the tissue. The absence of these effects would necessitate discarding or modifying the drug (or choosing a different target). Positive biomarker changes might suggest the need for preclinical improvements. Neither result would establish clinical efficacy. The basic characteristics of a translational trial are described in Table 22-2.

"A clinical trial where the primary outcome: (1) is a biological measurement (target) derived from a well established paradigm of disease, and (2) represents an irrefutable signal regarding the intended therapeutic effect. The design and purposes of the trial are to guide further experiments in the laboratory or clinic, inform treatment modifications, and validate the target, but not necessarily to provide reliable evidence regarding clinical outcomes."[37]

Table 22-2 Translational Trial: Basic Characteristics

The trial is predicated on promising preclinical evidence.
The treatment algorithm can be changed.
The treatment and target evaluation are fully specified in a protocol.
The evaluation relies on one or more biologic targets that provide definitive evidence of mechanistic effect.
The outcome is measurable with small uncertainty. Target validation may also be an objective, in which case imprecision in the outcome measurement could also represent a failure.
Large effects on the target are sought.
The protocol clearly defines "lack of effect" or failure to affect the target.
The protocol specifies the next experimental steps to be taken for any possible outcome of the trial.
The study is sized to guide additional experiments but not necessarily to yield strong statistical evidence.

Translational trials have continued experimentation as the primary context. The trial may provide evidence about the utility of more than one outcome. Many therapeutic ideas will prove useless during the laboratory-clinic iteration.

There are noteworthy deficiencies in these designs. One is the lack of proven clinical validity for the outcome. A second is the poor statistical properties of estimates. Not so obvious is that the translational trial paradigm confounds three effects: (1) the correctness of the disease paradigm, (2) the relevance of the biologic outcome, and (3) the action of the therapy. Errors in any of these can masquerade for either a positive or negative treatment effect. However, the correctness of the disease paradigm and the selection of a relevant outcome are usually based on strong evidence from earlier studies.

Dose Finding

Clinical trials that focus primarily on the relationship between dose and safety of new drugs or biologics are often termed phase I trials, particularly in oncology. Their purpose is to study drug distribution, metabolism, excretion, and toxicity and, in the case of cytotoxic drugs, to determine the dose associated with tolerable and reversible side effects. Until the last decade or so, statistical thinking contributed relatively little to the design of these studies. However, the relatively informal methods for dose finding have been steadily improved in recent years by statistical approaches. In oncology, dose-finding studies are often done in patients who have been previously treated with standard therapies. The features of classic phase I designs include (1) prior selection of a small set of drug doses to be tried, (2) treatment of a small number (e.g., three) patients at each dose with toxicity monitoring, (3) decision rules for stopping the trial based on clinical outcomes, (4) decision rules for escalating or de-escalating the dose in a subsequent cohort. Often a few additional patients are studied at the final dose, with the total number of patients treated being usually less than 25 to 30. This type of design alleviates certain practical and ethical problems in administering agents with unknown properties to humans. For example, it tends to minimize the number of patients treated at high (toxic) doses of the drug. It also tends to treat relatively larger numbers of patients at lower (ineffective) doses.

Such designs are inefficient. These properties tend to select conservative doses for later developmental testing.

Improved dose-finding designs have been suggested that correct such problems.[38,39] In some of these designs, doses are not prespecified but are determined from the current results and a mathematical model of the dose-toxicity curve. The final sample size of the trial is not fixed in advance but depends on the toxicities observed. The continual reassessment method is a prototypical design with these features. Some appropriate variant of the continual reassessment method has to be considered the design of choice for dose-finding trial of cytotoxic agents.

Safety and Activity

After determining the pharmacologic properties of a new drug and a clinically useful dose, trials focus on obtaining evidence of treatment safety and activity. These are conventionally termed phase II trials or safety and activity trials. The principal question to be addressed in this stage of development is whether or not the new treatment has enough promise to warrant testing against standard therapy in a large comparative trial—that is, a rigorous study with an internal control group. In this middle developmental step, the study design usually chosen to answer this question is a single cohort trial with an external control group. The control group comparison is usually based on the literature, prior investigator experience, or consensus opinion as to what constitutes a worthwhile level of activity in a given disease.

Such studies usually make use of surrogate clinical outcomes instead of definitive outcomes such as survival. Surrogate outcomes are chosen because ideally they are known soon after treatment, are easily and accurately measured, and are thought to be informative with respect to later definitive outcomes. Tumor shrinkage (response rate) is a classic surrogate outcome for activity in this setting, based on the cytotoxic model where it would imply tumor cell killing.

Unfortunately, tumor shrinkage is a poor surrogate for survival. Furthermore, some therapies would not be expected to produce tumor shrinkage in the usual cytotoxic model. An example might be cytostatic agents. Some caution has to be exercised when making developmental decisions on the basis of surrogate outcomes. For certain agents, safety and activity trials should make use of definitive outcomes such as survival (overall failure rate), making them somewhat larger and lengthier than conventional designs. For other agents, such as those based on vaccines, there has been much attention given to the potential use of molecular biomarkers based on gene discovery associations with cancer prognosis as surrogate outcomes; this is discussed further in the latter part of this chapter.

Two types of designs are commonly used in middle development: fixed sample size and staged. In fixed sample size trials, the number of study subjects is chosen in advance, for example to yield a specified precision in the estimated response rate. Staged designs use a treatment evaluation after groups of subjects have been entered, permitting early termination of accrual if high or low response rates are observed. Excellent working designs can be obtained from only two stages.[40] Numerous other statistical issues arise in the design and evaluation of phase II trials. Questions include patient selection, how to quantitatively evaluate response, patient exclusions, and the role of randomization. Space does not permit discussing these issues here. Reviews can be found in Buyse and colleagues.[13]

Sample Size for Middle Developmental Trials

There is a large literature concerning the quantitative design of middle developmental (phase II) trials. Here we consider some simple concepts to illustrate the connection between biologic outcomes and study size. Consider a phase II trial in which patients with esophageal cancer are treated with chemotherapy before surgical resection. A complete response is defined as the absence of macroscopic and microscopic tumor at the time of surgery. We suspect that this might occur 35% of the time and would like the 95% confdence interval of our estimate to be ±15%. Approximate 95% confidence intervals for a proportion, P, are

$$P - p \pm 1.96' \sqrt{[P(1-P)/n]}$$

where n is the number of patients tested and 1.96 is the quantile from the normal distribution corresponding to a two-sided probability of 5%. Substituting into this formula yields

$$0.15 = 1.96' \sqrt{[0.35(1-0.35)/n]}$$

or $n = 39$ patients required to meet the requirements for precision. Because 35% is just an estimate of the proportion and some patients may not complete the study, the actual sample size might be increased slightly. Expected accrual rates may be used to estimate the required duration of this study in a straightforward fashion.

A useful, but rough, rule of thumb for estimating sample sizes needed for proportions may be derived in the same way. Because $P(1 - P)$ is maximal for $P = 0.5$, an approximate and conservative relation between n, the sample size, and w, the width of the 95% confidence interval is $n = 1/w^2$. Thus, to achieve a precision of ±10% (.10) requires 100 patients, and a precision of ±20% (.20) requires 25 patients. This inverse-square relation demands large sample sizes for high precision. This rule of thumb is not valid for proportions that deviate greatly from .5. For example, for proportions less than about .2 or greater than about .8, exact binomial methods should be used to estimate precision and sample size.

Similarly, consider a middle developmental trial in which a definitive outcome such as reduction in the overall failure rate is required. On a log scale, the confidence interval for the hazard ratio is logD ± Z_a/D, where D is the hazard ratio, d is the total number of failures, and $Z_a = 1.96$ for a two-sided 95% interval. Like that for a response rate, this confidence interval can be made as small (precise) as necessary by observing more events.

Compared with a reference failure rate on standard therapy, a reduction of 33% on a new treatment (hazard = 0.2; ratio = 0.67) might be considered a useful improvement. If the reference failure rate is 0.3 per person-year (corresponding to median failure time of 2.3 years) and accrual proceeds at 75 subjects per year for 2 years with 1 additional year of follow-up, then we would expect to observe about 48 failures. This number of events would yield a precision of about ±0.06 (95% confidence interval) in the observed failure rate. Thus, such a study has to be larger and longer than a conventional safety and activity trial with a surrogate outcome.

COMPARATIVE STUDIES

Helping to design a comparative trial is a major responsibility for the biostatistician. The process involves detailed discussions with other investigators to resolve issues such as (1) what population should be studied, (2) are the treatment methods unambiguously defined, (3) how will patients be assigned to treatment groups, (4) how will outcomes be measured, and what can be done to assure that measurements will be obtained uniformly on all patients regardless of treatment assignment, and (5) what can be done to minimize loss to follow-up and to promote compliance to the treatment protocol.

In what follows, we outline some points of good design (Table 22-3) that are not intended to be taken chronologically. In fact, many of them must proceed simultaneously. However, attention to each of these items will probably result in a stronger trial.

Dual Roles of the Physician

Physicians who develop new treatments have two roles that are sometimes dissonant with each other. The first is as an advocate for the care and interests of the individual patient. The second is as a scientist representing the needs of others. The conduct of clinical trials is

Table 22-3 Ten Concepts in Comparative Trial Design

1. Review ethical issues and consent.
2. Quantify objectives.
3. Define the study population using eligibility and exclusion criteria.
4. Assess accrual resources.
5. Specify treatments.
6. Define endpoints and methods of assessment.
7. Calculate quantitative properties of the design.
8. Establish procedures for managing data.
9. Establish procedures for monitoring.
10. Control treatment allocation and bias.

one of many areas where these roles can, but do not necessarily, conflict. From a clinical trials perspective, physician advocacy for the individual patient is an ideal and not an exclusive standard of conduct. This ideal is not met in circumstances of triage, allocation of scarce and expensive technologies such as organ transplantation, training of new physicians, and vaccination. All of these circumstances knowingly place some patients at risk for the benefit of others.

Even if we accept the individual advocacy ideal, some patients will always receive an inferior treatment as a result of physician error. Failure to learn from such mistakes can hardly be considered ethical. It is incumbent upon the physician to learn quickly and convincingly from the inevitable use of less effective treatments so that their scope of application is minimized.

Controlled experiments in the proper clinical setting are the most reliable way to accomplish this. Conversely, we must learn about efficacious new therapies as quickly as possible so that they can be used broadly.

Although clinical trials are conducted worldwide, there are concerns voiced occasionally about the ethics of randomization. Although any medical technology can be used inappropriately in specific instances, there is nothing inherently unethical in the use of randomization when it is used because physicians lack knowledge about the superiority of treatments and to eliminate bias so that the best possible evidence can be gathered. There will always be circumstances of collective uncertainty in which randomized treatment comparisons are the most ethical course of action.

In some circumstances, evidence becomes available during the conduct of the trial that one treatment is superior. This can happen, for example, if one treatment is unexpectedly better or worse or has unacceptable side effects. Investigators are ethically bound to learn of such circumstances as early as possible by monitoring the accumulating data and closing the inferior treatment arm if necessary. The administrative and statistical plans to meet this contingency require planning during the design phase of the trial.

Quantification of Objectives

An important task in designing a clinical trial and drafting the study protocol is to convert clinical objectives into quantitative measurements of outcome variables. For example, we might be interested to know if a certain therapy "results in lower morbidity." However, the measurement of morbidity is not automatically well defined, particularly if the study involves more than one investigator. At least three aspects of morbidity must be defined. The first is a window of time during which adverse events can plausibly be attributed to the therapy. The second is a list of specific diagnoses or complications to be included. The third is a list of procedures required to establish each diagnosis definitively.

Definition of the Study Population Using Eligibility and Exclusion Criteria

Differences in eligibility criteria probably explain many of the discrepant results in the clinical literature from seemingly identical clinical trials. Even when several institutions use the same protocol, differences in interpretation of eligibility criteria and type of patients referred contribute to differences in outcomes. As a consequence, trials from different institutions and or periods of time may not be comparable even if the eligibility criteria are the same. This is one argument in favor of randomized concurrent controls.

To some extent, study results can be shaped by the eligibility and exclusion criteria. Consider how drug toxicity or operative morbidity can be reduced by the careful selection of patients. Age restrictions can reduce the number and severity of many chemotherapy toxicities, although such restrictions are seldom made explicit. Eligibility criteria can be used to define a more homogeneous study population, reducing the interpatient variability in outcomes. However, this will not necessarily reduce the size of a trial. For example, patients with poor prognosis may respond to treatment in the same way as those with good prognosis. If so, a trial excluding poor-prognosis patients would be needlessly prolonged.

In many instances endpoints may be evaluated more easily if certain complicating factors are prevented by patient exclusion. For example, if patients with recent nonpulmonary malignancies are excluded from a lung cancer trial, evaluation of tumor recurrences and second primaries might be made simpler.

Ethical considerations also suggest that patients who are unlikely to benefit from the treatment (e.g., because of organ system dysfunction) not be allowed to participate in the trial. Whenever possible, quantitative parameters such as laboratory values should be used to make these definitions rather than qualitative clinical assessments. Some studies in patients with advanced cancer call for a "life expectancy of at least 6 months." A more useful and reproducible criterion might be Karnofsky performance status greater than, say, 8.

Assessment of Accrual Resources

One unfortunate and preventable mistake made in clinical trials is to plan and initiate a study, only to have it terminate early because of low accrual. This situation can be avoided with some advance planning. First, investigators should be aware of the accrual rate required to complete a study in a certain fixed period of time. This is a best-case projection. Most researchers would like to see comparative treatment trials completed within 5 years and pilot or feasibility studies finished within a year or two. Disease prevention trials may take longer. In any case, the accrual rate required to complete a study within the time targeted can be estimated easily from the total sample size required.

Second, investigators must obtain realistic estimates of accrual rates. The raw number of patients with a specific diagnosis can often be determined easily from hospital or clinic records but is a large overestimate of potential study accrual. It must be reduced by the proportion of subjects likely to meet the eligibility criteria, and again by the proportion of those willing to participate in the trial (e.g., consenting to randomization). This latter proportion is usually less than half. Study duration can then be projected based on this potential accrual rate, which might be one fourth to half of the patient population.

Third, investigators can project trial duration based on a worst-case accrual. The study may still be feasible under such plans. If not, plans for terminating the trial because of low accrual are needed so as not to waste resources. In particular, accrual estimates from participating institutions other than the investigators' own are suspect. How long will the study take as a single-institution trial?

To estimate accrual more accurately, participants can be formally surveyed before accrual starts. As patients are seen over a period of time, a record can be kept to see if they match the eligibility criteria.

To estimate the proportion willing to give consent, one could briefly explain the proposed study and ask if they would hypothetically be willing to participate.

Treatment Specification

Control of treatments and their allocation is a defining characteristic of true experimental designs. In practical situations, explicit plans are needed for modifications in the treatment of individual patients. To satisfy scientific objectives, essential components of the therapy should be guided by the protocol, but modifications that are unlikely to affect the outcome should be left to the treating physician.

Physicians participating in trials are always obligated to replace protocol treatments with others when they feel that it is in the best interests of the patient. However, sufficient flexibility in the treatment specification, especially concerning complications, toxicity, or side effects, may permit most patients to continue following the protocol. This could contribute more information to the trial results and enhance the credibility of the study report.

Definition of Endpoints and Methods of Assessment

Selection of endpoints and the use of prospective methods of assessment greatly affect the strength of a trial. Important characteristics of the endpoint are that it correspond to the scientific objectives of the trial, as well as to be biologically meaningful within the context of the therapy or intervention under investigation; see further discussion on this point in the Design section. The method of assessing endpoints should be accurate and free of bias. This is helpful for both subjective endpoints and objective ones such as survival and recurrence time. Even when using well-defined event times, incomplete follow-up can create bias.

From a biostatistical perspective, there are three types of endpoints that are likely to be used widely in oncology trials: (1) continuously varying measurements, (2) dichotomous outcomes, and (3) event times. We will briefly discuss each of these.

Continuously Varying Measurements

Measurements that can theoretically vary continuously over some range are common and useful types of assessments. Examples include many laboratory values, blood or tissue levels, functional disability measures, or physical dimensions. In a study population these measurements have a distribution, often characterized by a mean or other location parameter, and variance or other dispersion parameter. Consequently, these outcomes will be most useful when the primary effect of a treatment is to raise or lower the average measure in a population. Typical statistical tests that can detect differences such as these include the *t*-test or a nonparametric analog and analyses of variance (for more than two groups). To control the effect of confounders or prognostic factors on these outcomes, linear regression models might be used.

Dichotomous Measures

Some assessments have only two possible values, for example, present or absent. Examples include some imprecise measurements such as tumor size, which might only be described as responding or not, and outcomes like infection, which is either present or not. Inaccuracy in measurement can make a continuous value ordinal or dichotomous. In the study population these outcomes will be frequently summarized as a proportion. Comparing proportions might lead to tests such as the chi-square or exact conditional tests. Another useful population summary is the odds or log-odds. The effect of prognostic factors or confounders on this outcome can often be modeled using logistic regression.

Event Times

Event times are common and useful outcome measurements in clinical trials. Survival time and disease-free or recurrence time are well-known examples. However, many other intervals might be of clinical importance, such as time to hospital discharge or time spent on a ventilator. The distinguishing feature of event time outcomes is the possibility of censoring. This means that some subjects under observation may not experience the event by the end of the study. Using the information in the censored observation time requires some special statistical procedures. In the study population, event time or "survival" distributions (e.g., life tables) might be used to summarize the data. Clinicians are also accustomed to seeing medians or fixed time proportions used to summarize these outcomes. Perhaps the most useful summary is the hazard, which can be thought of as a proportion adjusted for follow-up time. The effect of prognostic factors or confounders on hazard rates can often be modeled using survival regression models.

Other Endpoints

There are several other types of endpoints that are important for some medical studies but are not used frequently in oncology. These include counts, multiple-category outcomes, ordered categories, disease intensity measures, and repeated measurements. For example, units of blood used might be described as a count and chemotherapy toxicities are often described in ordered categories. As another example, cytogenetic responses are often recorded as categorical outcomes, and have received much attention for their use in assessing minimal residual disease (MRD) and in vaccine trials of chronic myeloid leukemia (CML). There has also been much discussion among clinical trial designers recently concerning the use of intermediate endpoints that become known early after treatment but are very reliably associated with definitive outcomes. Examples include premalignant lesions in cancer prevention studies and CD4 lymphocyte counts in acquired immunodeficiency syndrome (AIDS). Intermediate endpoints are probably not as relevant to oncologic studies as to these others areas of study. One notable exception is the use of prostate-specific antigen to monitor prostate cancer recurrence.

Control Treatment Allocation and Bias

Randomization

Randomization is one of the most effective means for reducing bias, because it guarantees that treatment assignment will not be based on patients' prognostic factors. The benefits derived from randomized treatment assignment are well known.[36,41] Following randomization, treatment differences can be attributed to the true treatment effect plus random variability.

One argument against randomization is that it is unnecessary because confounders can be controlled in the analysis by using statistical adjustment procedures. The extent to which this can be done relies upon two additional assumptions: (1) the investigators have measured the confounders in the experimental subjects, and (2) the assumptions of the statistical models or other adjustment procedures are known to be correct. Randomization is a more reliable method than adjustment, because it controls bias without these assumptions. Moreover, it controls the effects of confounders whether they are known to the investigator or not. Critics of randomization often overlook this last point, which provides randomized studies with their high degree of credibility.

Blinding or Masking

Masking (blinding) is another bias-reducing technique in which the patient (single-blind), physician (double-blind), and perhaps the monitors (triple-blind) in a clinical trial are unaware of the individual patient treatment assignments. As a result of blinding, treatment assessments can be made without prejudice, increasing the utility of both objective and subjective outcomes. Masking of drugs is often simple to implement, particularly with the assistance of a hospital pharmacy or pharmaceutical company. In oncology, treatment masking is frequently possible though sometimes logistically impractical.

Calculation of Quantitative Properties of the Design (Precision, Power, Duration)

Questions regarding the quantitative properties of clinical trial designs are among those most frequently asked by clinicians. It is not possible to specify a universally valid approach to answering such questions. Instead, we provide some basic ideas and examples. For a more statistically oriented review, see Donner.[42] Although computer software is available to perform many power and sample size calculations (e.g., Hintze[43]), most programs are written for a statistical user.

Two basic considerations in estimating precision and power are the purpose of the trial and its primary endpoint. For noncomparative designs, the goals of the study are often to estimate some useful clinical quantity with a specified precision. Examples of endpoints with clinical interest are average blood or tissue levels of a drug, the proportion of patients responding or meeting other predefined criteria, or population failure rates. A useful measure of precision is the confidence interval of the estimate. For example, narrow 95% confidence intervals indicate a higher degree of certainty about the location of a true effect than wide 95% confidence intervals do. Because confidence intervals depend on the number of subjects studied, targets for precision can often be translated into requirements for sample size.

Comparative clinical trials require more complicated methods to estimate sample size and power. Often, comparative studies are designed to yield statistical hypothesis tests with desirable properties, such as a high power to detect important clinical differences reliably. In trials with survival time as the primary endpoint, the power of the study depends on the number of events (e.g., recurrences or deaths). Confusion can arise over the number of patients placed on study versus the number of events required for the trial to have the intended statistical properties. As a test of equality between treatment groups, it is common to compare the ratio of hazard (or failure) rates (see following definition) versus 1.0. Under fairly flexible assumptions, the size of such a study should satisfy

$$d = [(Z_a + Z_b)^2(D + 1)^2]/(D - 1)^2$$

where d is the total number of events needed on the study, D is the ratio of hazards in the two treatment groups, and Z_a and Z_b are the normal quantiles for the type I and II error rates.[43]

For example, with this formula, to detect a hazard rate of 1.75 as being statistically significantly different from 1.0 by using a two-sided 0.05 α-level test with 90% power requires

$$[(1.96 + 1.282)^2(1.75 + 1)^2]/(1.75 - 1)2 = 141 \text{ events}$$

This is not the final sample size, as suggested by the safety and activity trial example discussed earlier. A sufficient number of patients must be placed in the study to yield 141 events in an interval of time appropriate for the trial. For example, if 50% of patients remain event-free (censored) at the end of the trial, 282 subjects are required. In general, the sample size, n, is $n = d/(1 - p)$, where p is the proportion censored.

TRIAL IMPLEMENTATION

Establishment of Procedures for Managing Data

All trials require certain minimal standards for collecting, quality controlling, and reporting data. Although many investigators use their own staff to perform such duties, sufficient skill is required to suggest that these activities be housed in groups dedicated to the purpose. Resources for this might exist on a departmental or institutional level. In other circumstances, an external or privately run coordinating center might be used. In no cases should this reduce access to the data or substitute for skilled translation of data elements from clinical and laboratory sources to study database.

There are at least five conceptual components to processing information from patients on a clinical trial: (1) eligibility check and registration/randomization, (2) data acquisition from the clinical record, (3) editing, error checking, building a database, and quality control, (4) interim reporting, and (5) analysis. Each of these, when properly performed, will reduce the frequency and severity of certain types of errors. Although one could write extensively about this subject, we summarize only a few important points about each component.

The eligibility check and registration is a simple but important quality control point. Even the knowledge that eligibility will be impartially checked causes many investigators to take entry criteria more seriously. Usually, a phone call requiring only a few moments is all that is needed. Using this opportunity, an identifying number can be assigned, a database record can be started, the pharmacy can be notified (if necessary), and other study bookkeeping can be initiated.

Data acquisition from the clinical record must be performed by an individual with sufficient clinical, protocol, and medical record knowledge. In some cases this requires the investigator's expertise, whereas in other circumstances a research nurse or data specialist can succeed. Unless studies are subject to external auditing, it is uncommon to catch errors made at this stage. Thus the principal investigator can have a major beneficial impact on the quality of data by being active here.

A simple and straightforward system for building and managing a database might begin with paper records or data forms that contain the information of clinical importance to the study. It is not necessary to record all the information needed for the care of the patient but rather only those items that correspond to the outcomes and objectives of the study. Ideally, one would not collect any items that do not need analysis. Information from these forms can be transcribed onto an appropriate computer database. Numerous quality control checks and edits are necessary to be certain that the database produced from paper records accurately represents the clinical record. For example, audits may compare the database with the chart. Within a single patient's record, computerized checks of bounds and internal consistency can be performed. When reviewed by a knowledgeable person, lists and summaries of the data can trap many errors.

Computer software has made some of these tasks more simple and reliable. Many investigators use spreadsheets to assist with these tasks in small studies, although database software is more powerful. When existing databases and human resources are available, investigators should attempt to use them rather than building a system for each study independently. In any case, the investigator should understand the flow of data from the clinical record through the final analysis. This flow of data, however, may involve metadata through the use of genomic information into clinical trials, in which case new technologies for storing, retrieving, and analyzing such information creates a challenge for medical informatics. Until recently, medical informatics has been an established field that pioneered the development and introduction of informatics methods in clinical medicine. With the increasing desire to transfer genomic results into medicine, bioinformatics has posed a challenge to the field of medical informatics for the development of novel clinically oriented methods to ensure success in such a transfer.[45,46] Indeed, the new era of genomics-based approaches to medicine, such as in defining and evaluating genome-related risk factors for various diseases, developing diagnostic tests, creating updated cancer cell classifications, or integrating genetic and medical data in clinical practice, will require support from both bioinformatics and medical informatics to address the collecting, quality controlling, and reporting data as part of clinical trials design, and prompts the need for new standards in such areas.[47]

Interim reporting serves several purposes. It provides an opportunity for the investigators to review accumulating data related to administrative aspects of the study such as accrual rates and delinquent observations. Complication and toxicity rates can be reviewed

to be certain that the type, frequency, and severity of such events is reasonable. Also, efficacy endpoints can be reviewed, following appropriate statistical guidelines, to satisfy ethical concerns. Much has been written about these subjects, and we discuss more details in the following sections.

Establishment of Procedures for Monitoring

Plans for monitoring and early stopping of accrual are another element of good trial design that can greatly alleviate problems in conducting studies. Researchers have an ethical obligation to learn about treatment differences as quickly as possible and to minimize the number of patients who are placed on a convincingly inferior treatment. By planning for early termination of accrual when unexpectedly large differences are observed, investigators can make a clinical trial more acceptable to other researchers and patients. A full discussion of sequential and group sequential methods for use in this context is beyond the scope of this chapter. These methods are now commonly implemented using well-described techniques.[48,49] Investigators can insure that monitoring methods are effectively implemented by having the accumulating data reviewed formally at intervals by a monitoring committee.

Repeatedly performing statistical significance tests on accumulating data increases the overall type I error. If 10 interim analyses were conducted with the conventional significance level of 0.05, the resulting overall type I error might be as high as 15%. This inflation of the type I error can be even higher if many interim looks at the data are performed. To compensate for this and control the type I error, investigators must prospectively plan the analysis points and the significance level for each analysis.

To control the overall type I error at 5%, each interim look should use a significance level smaller than 0.05. For example, in a clinical trial comparing response rates and two-sided testing for significance five times, a frequently used group sequential method[50] indicates that the analyses should be conducted with significance levels of approximately 0.0000075, 0.0013, 0.0085, 0.023, and 0.041, to control the overall type I error at the conventional 5%. Using this method, note that the final analysis is conducted using a significance level near, but less than, the usual 5%. Early in the trial, achieving statistical significance is more difficult.

Unplanned interim analyses may have undesirable properties and can pose serious problems in interpretation for researchers and regulators. Attempts have been made to alleviate this problem by retrospectively applying group sequential methods, although this has difficulties of its own. Another alternative for monitoring is the use of Bayesian statistical methods, which have much appeal to clinicians but have not gained as widespread use as other methods.[51] For a general discussion of monitoring alternatives, see Gail,[52] and for a practical discussion see DeMets[53] or O'Fallon.[54] In any case, the time to plan properly for trial monitoring is during the design phase of the study.

A second reason for terminating a trial early is when interim analyses demonstrate the near equivalence of the treatments and continuing the trial would be unlikely to demonstrate clinically significant differences. In this circumstance, early stopping has been based on conditional power calculations.[55] Using this technique reduces the size and length of trials that show no effect or treatment difference but still yields clinically useful information.

ANALYSIS

The exact procedures necessary for analyzing a clinical trial depend on the design and purposes of the study. For example, pharmacologic studies might require modeling and estimation of physiologic parameters in each patient to meet their objectives, whereas comparative trials usually require summaries of relative treatment effects and confidence intervals. Analyses for these differing types of studies seem to have very little in common. However, when we consider that all trials should inform us about the population being studied, the need for unbiased statistical estimation of clinical effects, and the need to summarize data in the most clinically useful form, much common ground is evident.

The approach we recommend to analysis and reporting emphasizes estimation rather than hypothesis testing.[29–31] Measuring and reporting clinical effects and associated estimates of variability (or confidence intervals) is more informative and useful than focusing attention on formal tests of statistical hypotheses and *P* values. A simple example should make the difference clear. Suppose a clinical trial is performed comparing two treatments, A and B, and the major outcome is survival. Investigators might perform a statistical hypothesis test comparing treatments A and B and report "survival on treatment A is significantly longer than on B ($P < 0.05$)." Alternatively, when emphasizing estimation, investigators might report the estimated hazard ratio (A vs. B) for death was 2.0 (95% confidence limits 1.5–2.3). In the first case, the reader is left only with a *P* value to summarize the data, whereas in the second case the treatment difference is described more completely. Some journals have adopted guidelines for reporting.[56] Our recommendations are similar in spirit to those. Although we have suggested some specific statistical methods and summaries for certain kinds of data, there are additional or alternative analytic procedures that should be adopted in special cases and we do not seek to limit analyses or reports. However, the basic concepts and approaches outlined here should prove to be helpful both clinically and statistically for correctness, lack of bias, completeness, and consistency. In this spirit we offer the following basic steps in the analysis of clinical trials (Table 22-4). We emphasize that these

Table 22-4 Basic Steps in the Analysis of Clinical Trials

1. Approach the trial as a test of treatment policy, not a test of treatment received. This is the "intent to treat'" principle.
2. Include all patients who meet the eligibility criteria.
3. Examine the data and correct errors.
4. Describe the population in the study.
5. Verify the comparability of treatment groups.
6. Estimate the effect of treatment and other prognostic factors on the major outcome (univariate analyses). Estimate confidence intervals.
7. Use standard statistical methods or models (e.g., linear, logistic, or proportional hazards regression), to re-estimate the treatment effect while adjusting for the following:
   - Statistically significantly imbalanced prognostic factors
   - Strong or influential prognostic factors, whether imbalanced or not
   - Any prognostic factor for which it is important to demonstrate convincing control
8. Consult the biostatistician concerning special methods to address secondary clinical questions. Any analyses not protected by the randomization should correspond to clinical hypotheses stated as study objectives. Control prognostic factors.
9. Consider repeating steps 1–6 after excluding ineligible patients—that is, patients who are ineligible based on entry criteria.
10. Cautiously conduct exploratory or hypothesis-generating analyses:
    - Any analysis suggested by the data and not by hypothesis
    - Any analysis that excludes patients based on postentry criteria
    - Subset analyses

These final steps should never be the "primary" analysis.

steps are conceptual and do not necessarily occur in the order listed. Also, some steps are relevant only to randomized or comparative trials.

Intention to Treat

It is unfortunate that investigators conducting clinical trials cannot guarantee that the patients who participate will definitely complete (or even receive) the treatment assigned. Thus, a clinical trial can be viewed as a test of treatment policy, not a test of treatment received. Many factors contribute to patients failing to complete the intended therapy including severe side effects, disease progression, strong preference for a different treatment, and a change of mind. Many such factors are strongly correlated with outcome, which can render a strong bias if such patients are removed from the analysis.

From a clinical perspective, postentry exclusion of eligible patients is essentially an attempt to use information from the future. When selecting a therapy for a new patient, the physician is primarily interested in the unconditional probability that the treatment will benefit the patient. Because the physician has no knowledge of whether or not the patient will complete the treatment intended, inferences that depend on events in the patient's future (i.e., adherence to therapy) are not helpful to that goal. In other words, adherence is both an outcome of the trial as well as a potential predictor. These two roles of adherence cannot be disentangled by removing patients from consideration. Consequently, the physician will be most interested in clinical trial results that include all patients who were assigned to the therapy.

To be certain that the trial results closely reflect the effect of the treatment, the eligibility criteria should exclude patients with characteristics that might prevent them from completing the therapy. For example, if the therapy is lengthy, perhaps only patients with good performance status should be eligible. If the treatment is highly toxic, only patients with normal function in major organ systems will be likely to complete the therapy.

Following on these considerations, the most important analysis includes all patients registered or randomized on the trial regardless of postentry events. This analysis is the intention-to-treat analysis. It is possible to exclude patients who were retrospectively found not to meet the eligibility criteria—that is, those who were mistakenly placed on study—without creating bias. Ideally, such patients would not have gone on study because they would have been found to be ineligible. However, only eligibility or pre-entry criteria should be used to make such exclusions. If patients are excluded on the basis of "evaluability" or other postentry criteria, the possibility of bias increases. Evaluability criteria are outcomes, no matter how well defined clinically. If we exclude subjects based on outcomes, the potential for bias is great.

Examination of the Data

The first practical step in any analysis is to look at the data. This includes examining lists and other simple tabulations that might highlight incorrect data values. Many problems in analyzing clinical trials can be prevented by correcting errors that become apparent in this way. This is also a step that knowledgeable investigators can perform quickly but very efficiently. With the widespread use of computers and automated analysis procedures to manage clinical information, it is possible to produce results from clinical studies without carefully examining the data. This is unfortunate, because even a cursory examination of raw data by a technically knowledgeable person can detect many errors of importance to the analysis.

Some of the errors that are amenable to detection by inspection include (1) incorrectly missing data (patient had level measured but not recorded in the database), (2) incorrect decimal points (80 recorded instead of 8.0), (3) failure to convert numerical codes for special values, (calcium becomes 99 instead of "missing"), (4) out-of-range or impermissible values (0.0 recorded instead of 8.0), (5) mislabeled variables (age is mistaken for calcium and vice versa), and (6) coding and recoding errors (0 should mean normal and 1 should mean abnormal, but values are reversed).

Inspection of the data is particularly important for small or single-investigator studies in which the data management techniques are not subject to regular quality control procedures as might be the case in multi-institutional cooperative group studies. Errors in small studies can be particularly influential. Many times, small studies are recorded entirely on paper with transcription to a computer at a later time, creating another opportunity for errors. Other times, data are stored on computers using convenient but unsophisticated software such as spreadsheets rather than database management programs that permit validation and checking. Fortunately, the quantity of data from such small studies is often very amenable to checking by inspection. It is embarrassing, frustrating, and bad for morale to have to ask that analyses be repeated because data errors were discovered late.

Description of the Study Population

Clinical trials are studies of particularly well-defined and often relatively small cohorts. Although the eligibility criteria define a target population of particular interest, the patients actually accrued on a trial may differ because of chance or subtle institutional characteristics. Investigators will want to describe the observed cohort, particularly with regard to important prognostic factors. Simple population measures and summary statistics usually suffice for this purpose. This process is also both a byproduct of and valuable in error checking.

Verification of the Comparability of Treatment Groups

In reports of many randomized studies, the first table presented is often intended to show the comparability of treatment groups. Actually, a lack of statistically significant differences between the treatment groups does not guarantee the absence of influential imbalances but only demonstrates the effectiveness of randomization. Even so, this is important, because readers will have increased confidence in the validity of the findings if imbalances are either absent or detected and controlled in the analyses. Although we will take note of any statistically significant differences between groups, nonsignificant imbalances in strong prognostic factors can influence treatment comparisons. This is discussed more completely in the later section on deciding when to adjust. Second, and conversely, statistically significant imbalances are not necessarily influential; the imbalance may occur in an inconsequential factor. For the clinician comparing groups, the magnitude of the difference is more important than the *P* value.

Estimation of Treatment and Prognostic Effects

As mentioned previously, some outcomes that are likely to be useful in oncology trials are group averages (or differences between group averages), probability of response (or odds ratios), and hazards (or hazard ratios). We omit discussion of methods for group averages, because they are well known and focus on dichotomous outcomes and event times. These outcomes have similarities with respect to their summary statistics and presentation. Odds ratios are useful summaries of data to describe the effects of dichotomous variables. For example, differences in the probability of response might be described by an odds ratio. Similarly, hazard ratios are useful for describing differences in risk of failure over time. For example, differences in recurrence or survival curves might be described by a hazard ratio.

To illustrate these and other aspects of the estimation of clinical effects, we consider simulated data from a hypothetical randomized trial comparing two treatments (A and B) for solid tumors. Simple randomization was used in this study, with 101 patients on treatment A and 99 patients on treatment B. Data on response to

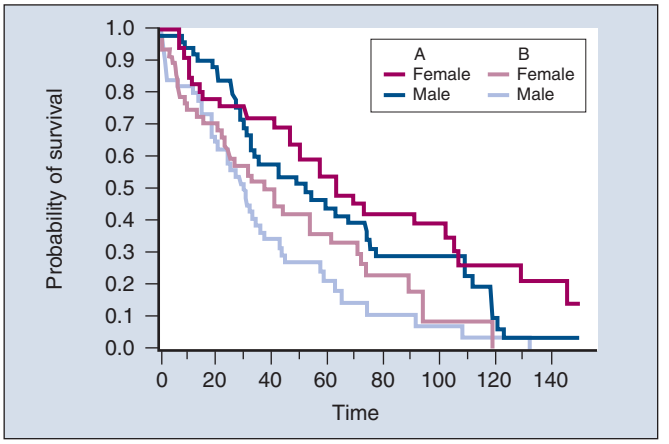


Figure 22-1 • Survival by treatment group and sex on a hypothetical clinical trial.

treatment were collected as an example of a dichotomous outcome, and patients were followed for survival as an example of an event time endpoint. Differences in response and survival attributable to sex are also thought to be important. Nonparametric estimates of survival for subgroups defined by treatment-sex combinations are shown in Figure 22-1.

The advantage to using simulated data, aside from convenience, is that the "true" treatment and covariate effects are known. In this case, the true treatment effects were a 4-fold odds of response and a 2-fold risk of death in favor of treatment A. For sex, the odds of response was 2-fold and the risk of death was 1.5-fold, both in favor of females. Response and survival were independent of one another. In what follows, the estimated effects will differ from these values because of random variation.

Odds and Hazard Ratios

The simulated-response data for the two treatment groups are shown in Table 22-5. The estimated response rate (probability) on treatment A was 0.376 compared with 0.182 on treatment B. The odds of response for treatment A is

$$\text{odds}_A = P/(1 - P) = 0.376/0.624 = 0.063$$

A more useful quantity for judging the relative effect of treatment on response is the odds ratio. The estimate of the overall odds ratio for group A versus group B, ORd_{AB} is

$$\text{ORd}_{AB} = (38 \times 81)/(18 \times 63) = 2.71$$

Because the odds of response on treatment A are almost threefold higher than on treatment B, this might be a clinically important difference. The decision to use the odds ratio of A versus B (or vice versa) is purely a matter of convenience. The data relating sex and response are shown in Table 22-6.

In treatment group A, the odds ratio for males versus females is 0.395/0.920 = 0.429. In group B the corresponding ratio is 0.707.

Table 22-5 Responses on Treatments for Solid Tumors

Treatment	Response	No Response
Group A	38	63
Group B	18	81

Table 22-6 Example of Odds Summary Data

Group	Sex	No. of Patients	No. of Responses	Response Odds
A	Males	53	15	.395
	Females	48	23	.920
	Overall	101	38	.603
B	Males	51	8	.186
	Females	48	10	.263
	Overall	99	18	.222

Thus, it seems that male subjects are less likely to respond than female subjects, and this is explored further later in the analysis.

For event time endpoints, the quantities of interest are the number of events in the groups and the total follow-up or exposure time (in years; Table 22-7).

The total exposure time is obtained by summing all follow-up times without regard to censoring. This represents the aggregate time at risk for the group. Thus, the estimated overall hazard of death in group A, l_A, is

$$l_A = 70/5614 = 0.012 \text{ per person-year},$$

and for group B, is

$$l_B = 77/3434 = 0.022 \text{ per person-year}$$

From these data we would conclude that the risk of death following treatment B is higher and that this difference might be of clinical importance. Here also, sex seems to influence the risk of death. The estimated hazard ratios for males versus females are 1.27 and 1.37 on treatments A and B. The effect of sex will be explored later in more detail.

This example has shown the utility of odds and hazard ratios in summarizing clinical effects. The next section will illustrate additional utility for confidence intervals.

Confidence Intervals

Informally, a confidence interval is a region in which we are confident that a true parameter or effect lies. Although this notion is not too misleading, confidence intervals are really probability statements about an estimate and not about the true parameter value. A 95% confidence interval indicates the region that would contain the true parameter value 95% of the time if we repeated the experiment. In other words, given the estimates resulting from a series of experi-

Table 22-7 Example of Hazard Summary Data

Group	Sex	No. of Patients	Exposure Time	No. of Deaths	Hazard
A	Males	53	2768	40	.014
	Females	48	2846	30	.011
	Overall	101	5614	70	.012
B	Males	51	1632	42	.026
	Females	48	1802	35	.019
	Overall	99	3434	77	.022

ments, the true value will fall within the 95% confidence regions 95% of the time.

The value of confidence intervals is that they convey both the magnitude of the estimated clinical effect and a sense of its precision. In many cases, simple hypothesis tests are analogous to the confidence interval. Also, when summarizing results from several studies, estimates and confidence intervals are more useful than *P* values.

Continuing with the preceding example of the randomized clinical trial, we first consider confidence intervals for the probability of response. Using the methods already discussed, an approximate 95% confidence interval for the probability of response on treatment A is

$$0.36 \pm 1.96 \times \sqrt{[0.376(1-0.376)/101]}$$
$$= 0.376 \pm 0.094 = [0.282 - 0.470]$$

Similarly, an approximate 95% confidence interval for response on treatment B is 0.182 ± 0.076 = [0.106 − 0.258]. Because of the large sample size and the intermediate size of the probabilities, these intervals are close to those that would be obtained by using exact binomial methods, which are [0.282 − 0.478] and [0. − 0.272] for groups A and B, respectively.

For odds and hazard ratios, calculating confidence intervals on a log scale is relatively simple. An approximate confidence interval for the log odds ratio for A versus B is

$$\log\{2.71\} \pm Z_a \times \sqrt{1/63 + 1/38 + 1/81 + 1/18}$$

where Z_a is the point on normal distribution exceeded with probability $a/2$ (e.g., for $a = 0.05$, $Z_a = 1.96$). This yields a confidence interval of [0.35–1.65] for the log odds ratio or [1.41–5.21] for the odds ratio. Because the 95% confidence interval for $\hat{o}R_{AB}$ excludes 1.0, the difference is "statistically significant." The statistical test of the null H_0:$\hat{o}R_{AB} = 1.0$ is rejected with significance level $P = 0.003$.

A similar method can be used for the hazard ratio. An approximate confidence interval for the log hazard ratio is

$$\log\{1.83\} \pm Z_a \times \sqrt{1/77 + 1/70}$$

This yields a confidence interval of [0.264–0.911] for the log hazard ratio or [1.30–2.49] for the hazard ratio. Again, the confidence interval excludes 1.0, indicating a statistically significant difference in the death rates between the groups ($P < 0.001$).

Problems with *P* Values

There are many circumstances in which *P* values are useful, particularly in well-designed hypothesis tests. However, *P* values have properties that make them poor summaries of clinical effects. In particular, *P* values do not convey the magnitude of a clinical effect. The size of the *P* value is a consequence of two things: the magnitude of the estimated treatment difference and its estimated variability (which is itself a consequence of sample size). Thus, the *P* value partially reflects the size of the experiment, which has no biologic importance. The *P* value also hides the size of the treatment difference, which does have major biologic importance.

Some investigators conclude things like "the effect might be statistically significant in a larger sample." This, of course, misses the point, because any effect other than zero will be statistically significant in a large enough sample. What the investigators should really be talking about is the size and clinical significance of an estimated treatment effect rather than its *P* value. In summary, *P* values only quantify the type I error and incompletely characterize the biologically important effects in the data.

To illustrate the advantage of estimation and confidence intervals over *P* values, consider a discussion over the prognostic effect of perioperative blood transfusion in lung cancer.[57–63] Several studies (not clinical trials) of this phenomenon have been performed because of firm evidence in other malignancies and diseases that blood transfusion has a clinically important immunosuppressive effect. Disagreement over the study results has stemmed, in part, from too strong an emphasis on hypothesis tests instead of accepting the estimated risk ratios and confidence limits. Some study results are shown in Table 22-8. Although the authors of the various reports came to different conclusions about the risk of blood transfusion because of differing *P* values, the estimated risk ratios adjusted for extent of disease seem to be consistent across studies. Based on these results, one might be justified in concluding that perioperative blood transfusion has a modest adverse effect on lung cancer patients.

Table 22-8 Summary of Studies Examining the Perioperative Effect of Blood Transfusion in Lung Cancer

Study	Endpoint	Hazard Ratio*	95% Confidence Limits
Tartter et al.[58]	Survival	1.99	1.09–3.64
Hyman et al.[59]	Survival	1.25	1.04–1.49
Pena et al.[60]	Survival	1.30	0.80–2.20
Keller et al.[61]	Recurrence		
	Stage I	1.24	0.67–1.81
	Stage II	1.92	0.28–3.57
Moores et al.[62]	Survival	1.57	1.14–2.16
	Recurrence	1.40	1.01–1.94

*All hazard ratios are transfused versus untransfused patients and are adjusted for extent of disease.

Adjustments

Not all clinical trial statisticians agree on the need for adjusted analyses in clinical trials. However, many investigators believe that the difference in estimated treatment effects before and after adjustment often conveys useful knowledge. Furthermore, nonrandomized studies, such as cohort studies, are invariably analyzed with adjustment for confounders or prognostic factors. The same kinds of systematic errors that can arise in observational studies can arise in clinical trials by chance. This seems to provide a firm rationale for examining the results of adjusted analyses.

One of the principal advantages of using statistical models to help analyze trial results is the straightforward generalization to multiple regressions suitable for adjusted analyses. Using these methods, investigators can estimate the treatment effect while adjusting for prognostic factors. One should consider adjusting for variables that meet any of three criteria: (1) prognostic factors that are statistically significantly imbalanced between the treatment groups, (2) strong or influential prognostic factors, whether imbalanced or not, (3) to prove that a particular prognostic factor does not artificially create the treatment effect.

The philosophy underlying adjusting in these circumstances is to be certain that the observed treatment effect is not due to confounding. The effects of clinical interest with adjustment are changes in relative risk parameters rather than changes in *P* values.

Regression Methods

Regression is an unfortunate historically anomalous name for a very important statistical method. A more descriptive name might be statistical modeling of multiple effects. In any case, the essential idea is to relate an outcome of interest to one or more predictor variables using a statistical model. The theoretical components of the model are its deterministic form (structural equation), probabilistic form (how it models errors), and parameters (biologic constants), whereas the empirical components are the observed data. If the model is approximately correct, it should predict the observed data well

Table 22-9 Logistic Regression Models Illustrating Adjusted Treatment Effects

Model	Variable	Odds Ratio	95% Confidence Limits	*P* Value
1	B vs. A	0.368	0.19–0.71	0.003
2	Male vs. female	0.542	0.29–1.01	0.055
3	B vs. A	0.358	0.19–0.69	0.002
	Male vs. female	0.520	0.27–0.99	0.046

provided we choose appropriate parameter values. Conversely, we can choose those parameter values that make the predictions and observations (data) close in some well-defined way. This latter sense is the way in which most statistical models are used. Trustworthy fitting methods exist, such as maximum likelihood, to estimate the best parameter values.

If the model has been constructed so that the parameters also correspond to clinically interesting effects, it yields a way of estimating the influence of several factors simultaneously on the outcome. In practice, models also provide a means for obtaining confidence intervals, testing hypotheses, and even revising the model itself.

Statistical models such as logistic regression for dichotomous outcomes and survival regression for event times are likely to be useful both for estimating odds and hazard ratios and performing multiple regression adjustments. Provided the assumptions of these models are met, they can provide estimates of the appropriate relative risk parameter(s), confidence limits, and *P* values.

We return to the hypothetical randomized clinical trial outlined previously, in which sex seemed to influence response rate and survival. For response, an appropriate statistical model is the logistic regression model, the results of which are shown in Table 22-9.

Models 1 and 2 show the overall odds ratios, confidence limits, and *P* values for treatment and sex considered individually. Model 3 shows the joint effects of sex and treatment group on response. When the effect of treatment is taken into account, females are seen to have a higher response odds. Because the estimated odds ratios don't change very much after adjustment, this suggests that sex and treatment have nearly independent effects on response. For the survival endpoint, the results of proportional hazards regression models are shown in Table 22-10.

The estimated hazard ratios are quantitatively similar to those determined previously and show a higher risk for males. Differences are due to different methods of calculation. The effect of treatment controlling for sex is significant. The adjusted hazard ratios (model 3) also suggest independent effects for sex and treatment on survival time.

Table 22-10 Proportional Hazards Regression Models Illustrating Adjusted Treatment Effects

Model	Variable	Hazard Ratio	95% Confidence Limits	*P* Value
1	B vs. A	1.91	1.36–2.66	<0.001
2	Male vs. female	1.32	0.95–1.82	0.100
3	B vs. A	1.92	1.37–2.68	<0.001
	Male vs. female	1.34	0.96–1.85	0.083

Special Methods

Frequently, special analyses are needed to address specific clinical questions or secondary goals of the trial. In some prognostic factor studies, special regression models may be needed, such as time-dependent covariate models, to account correctly for the effects of predictors that change over time. Other examples of situations that may require sophisticated analytic methods are repeated longitudinal measurements, Bayesian methods, nonindependent observations, and accounting for restricted randomization schemes. Aside from the lack of software for many needs, extra care is required to be certain that the assumptions of the analytic methods are met.

Repeat Analyses

Although we have tried to be firm about the value of the intention-to-treat analysis, there are circumstances in which one would like to know if the exclusion of some patients on the basis of clinical criteria affects the results. One such situation is the exclusion of ineligible patients in a randomized trial. Actually, exclusions based on eligibility criteria do not violate the intention-to-treat principle. However, investigators may sometimes feel the need to exclude eligible patients. One can consider repeating steps 1–6 after doing so. Provided the fraction of patients excluded is small, say 5%, and affect both treatment groups (if the trial is comparative), it is likely that the results will agree with the intention-to-treat analysis. This is as much an argument not to exclude patients as it is to allow exclusions.

Data Exploration

Clinicians generally need very little encouragement to conduct exploratory analyses of their data. By exploratory analyses, we mean those that do not follow directly from the design of the experiment. Such analyses are neither automatically inappropriate nor wrong. However, the conclusions derived from these analyses can be unreliable. Therefore, they should serve only to generate hypotheses to be tested more rigorously in the future. Reasons why exploratory analyses may be unreliable include the following:

- A comparison suggested by the data and not by prior hypothesis is likely to have a type I error larger than the nominal *P* value. This occurs because investigators have a tendency to only test those differences that are large, most of which are probably due to chance.
- An analysis that excludes patients based on postentry criteria (responses) will probably produce biased results.
- Subset analyses are likely to be influenced by uncontrolled prognostic factors.
- Investigating large numbers of subsets can lead to "significant" differences purely by chance (i.e., inflated type I error).

By relying on estimation of clinical effects rather than unplanned tests of statistical hypotheses, the utility of these exploratory analyses might be increased. Investigators might be less likely to misinterpret the results or to exaggerate their clinical utility. In any case, these types of exploratory analyses should never be the primary analysis of a clinical trial.

PUBLICATION AND INTERPRETATION

As with analysis, the most informative summaries and amount of detail to report from a clinical trial will depend largely on the nature of the clinical hypotheses being studied. This section will outline basic reporting guidelines (Table 22-11) that follow an estimation and confidence interval approach and that should be helpful for reporting many types of clinical trials. These guidelines should also be useful for reviewing and interpreting published reports of trials and prognostic factor analyses. Reports of clinical trial results may be subject to constraints that analyses are not. For example, reports often

Table 22-11 Ten Concepts in Reporting

1. Report all clinically relevant descriptions of the trial population including patients who met the eligibility criteria but chose not to participate.
2. Describe those patients who were retrospectively found to have failed the eligibility criteria and those patients who failed to complete the assigned treatment.
3. Report all statistical methods and assumptions made.
4. For univariate analyses, report estimated treatment effects (log odds ratios or hazard ratios), confidence intervals, and significance levels of tests of no treatment effect (*P* values).
5. Report adjusted estimates of treatment effects, confidence intervals, and *P* values.
6. When no treatment effect is found, do not report the power of the study. Instead use point estimates and confidence limits.
7. Report any differences between "intention-to-treat" analyses and "eligible patient" analyses.
8. Results with strong biologic or clinical justification and *P* values near 0.05 could be called "statistically significant."
9. Results without biologic or clinical backup or those that seem contradictory should be reported but interpreted with caution.
10. Represent exploratory or hypothesis-generating analyses accurately.

require a consensus among investigators and must undergo an imperfect editorial process before publication. We can offer little help here in navigating these difficulties except to suggest a certain minimal content and structure.

Description of the Study Population

Clinically relevant descriptions of both the study and target population should be reported. It may also be important to describe patients who met the eligibility criteria but chose not to participate in the trial, when this information is available. The need for this might arise when patients from a large group are asked to participate, but many refuse. As pointed out previously, it may be difficult to generalize from these situations. For nonrandomized designs, even detailed descriptions of the study group may not provide a convincing basis on which to make comparisons with other studies. Thus, comparison is not the motivation, but thoroughness is.

Treatment and Eligibility Failures

As mentioned previously, it is acceptable to perform statistical analyses on only the subset of eligible patients, even when eligibility is corrected in retrospect. This does not create bias in the estimate of relative effects within the trial. Investigators should report those patients who were retrospectively found to have failed the eligibility criteria as well as those patients who failed to complete the assigned treatment.

There are situations in which a large fraction of patients complete the assigned therapy but may receive additional therapy not specified by the protocol or design of the trial. For example, patients with esophageal cancer may undergo resection and chemotherapy, and have a variety of second-line treatments if signs of disease progression or recurrence are observed. If some of these latter treatments are active, the results of an initial treatment comparison based on recurrence or survival may be skewed. In fact, in general, it is difficult or impossible to use the statistical information in studies that permit "crossovers" either to new treatments or to the other treatment arm. One cannot exclude these patients but can use only the information up to the time of stopping the assigned treatment.

Statistical Methods and Assumptions

Readers should be made aware of any assumptions made in both the design and analysis of a clinical trial. For a discussion of some practical issues, see DerSimonian and associates.[27] The assumptions and limitations of many common statistical procedures are well understood by clinicians. However, the readers of clinical trial reports should be convinced that the data analyst has verified all important assumptions and reported the methods in detail for less well-known statistical procedures. Examples of assumptions that are often made in analysis, often violated by the data, and also likely to be consequential are distributional assumptions underlying the *t*-test or other statistical hypothesis tests, error distributions in linear regression analyses, and proportionality of hazards in life table regressions. For example, the *t*-test assumes that the distributions being compared are normal with equal variances. It can yield incorrect results when either of these assumptions is false, particularly if distributions are not symmetric. Proportional hazards regression models most often assume that the effects of predictors is to multiply a baseline risk and that the multiplicative factor is constant over time. Although the model is robust to departures from this assumption—that is, it will often yield the correct estimates of relative risk and significance levels anyway—it is helpful to validate the assumptions.

Univariate Analyses

It is likely that the data analyst will test the effect of all potentially important prognostic variables on the major outcomes. For these univariate analyses investigators should report estimated treatment effects (odds ratios or hazard ratios), confidence intervals, and significance levels of tests of no treatment effect (*P* values). This does not preclude presenting other displays of univariate analyses (e.g., survival curves or 2×2 tables) if these analyses are especially relevant. However, the investigators should keep in mind that univariate analyses, particularly in uncontrolled studies, are subject to confounding. Consequently, these analyses should probably not be emphasized or presented in excessive detail.

Adjusted Analyses

In a randomized trial, the univariate comparison of treatment groups is a simple and valid summary. However, many investigators attempt to show that the treatment effect is not due to any measured confounders by using adjusted analyses. The best style of reporting multivariate analyses is the same or similar to that for univariate effects. However, the adjusted analyses reported are usually selected from a larger set of less informative or preliminary results. As an example, consider a life table regression model attempting to predict time to cancer recurrence. The "best" (most predictive but parsimonious) model might be built using a step-down procedure from a large set of potential prognostic factors. Each step in the analysis need not be reported, but the final model is a major objective of the analysis.

For multiple regression analyses, investigators usually report adjusted estimates of treatment effects, confidence intervals, and *P* values. Not all prognostic factors retained in multiple regression models must be "statistically significant." It is often useful to keep nonsignificant effects in a multiple regression model to demonstrate convincingly that the treatment effect persists in their presence.

Negative Findings

When no statistically significant treatment effect or difference is found, the power of the study is sometimes called into question. However, the absence of a significant difference is not the same as evidence of no effect. Because clinical effects are measured by risk

ratios rather than *P* values, the preceding guidelines emphasizing estimated treatment differences rather than hypothesis tests are important. Helpful advice regarding negative clinical trials is provided by Detsky and Sackett.[64,65] Power calculations performed after the study is completed are rarely, if ever, helpful.

Effect of Patient Exclusions

Although we have emphasized the value of the intent-to-treat principle and related analyses, in practice, many exploratory analyses will be done. Investigators should report any differences between intention-to-treat analyses and eligible patient analyses. If subset analyses are performed, discrepancies between these and the major analyses of the clinical trial should be reported.

What Is Significant?

The *P* value should not be the only criterion for "significance." Results with strong biologic or clinical justification and *P* values near 0.05 are "statistically significant." When biologic justification is strong, effect estimates are large, and confidence intervals or *P* values indicate significance near conventional levels, it seems appropriate to label these results as "statistically significant." Conversely, results with no biologic or clinical justification or those which seem paradoxical should be reported and interpreted with caution, even when *P* values are smaller than 0.05. There is no way to separate type I errors from truly significant results, except to rely on additional evidence and biologic rationale. It is wise to report cautiously results that seem not to make sense.

Exploratory Analyses

Exploratory or hypothesis-generating analyses should be only informally reported. They should not be emphasized as the primary findings of a clinical trial unless supported by the design and a priori hypothesis.

BIOINFORMATICS AND CLINICAL TRIALS

Bioinformatics, a yet developing field, focuses on the interaction between computer science and biology. Medical informatics, an established field, focuses on the interaction between computer science and clinical medicine. Although these are separate fields, the emerging need to correlate genotypic with phenotypic information has created a need to bring both disciplines together to support genomic medicine. The large amounts of genetic, genomic, and proteomic data offer opportunities for new research targets, with novel therapies for established diseases being developed. These innovative approaches, however, cannot be sustained without effectively dealing with the vast amounts of data generated in the laboratory. Equally important is the integration of clinical data generated by medical records with genomic information. Biomedical informatics is an emerging discipline that aims to create a common conceptual information space in which to further the discovery of novel diagnostic and therapeutic methods in support of genomic medicine.

Genomic technologies will revolutionize drug discovery and development; that much is universally agreed upon. The high dimension of data from such technologies has challenged available data-analytic methods; that much is apparent. Researchers have been hard at work marrying the latest technologies with drug design to more closely examine whether a drug is having any biologic impact (clinical trial), what the effect is (measure of endpoint), when it stops working (onset of resistance), and what can be done about it (alternate therapies). Gene therapy, cancer-killing viruses, and new drugs highlight a few of the novel approaches to cancer treatment. The emergence of promising new molecular targeted agents and new technologies for screening and early detection through the application of bioinformatics has prompted new opportunities in biostatistics for clinical trial designs and analysis that integrate therapy and prevention endpoints.

Cancer has long been understood to be a genetic disorder, and the growing sophistication of genetic resources and tools are contributing greatly to the fight against it. Well before the Human Genome Project, classic cytogenetics revealed gross deletions, amplifications, and rearrangements in cancer cells, which changes can now be analyzed at base-pair resolution with technologies including single-nucleotide polymorphisms and comparative genomic hybridization-based genomic arrays. Expression studies that were done one gene at a time are now conducted across the entire transcriptome with 1.5 million feature expression arrays, and can be used to evaluate the changes wrought by epigenetic therapeutics such as histone deacetylases. Genes that are involved in cancer and carcinogenesis include tumor suppressor genes and oncogenes, often found in regions that are respectively deleted or amplified. All are important to our understanding of cancers, and many may be targets for prevention or cure. A therapy target is a gene whose expression can be changed by treatment. Tumor suppressor genes make good targets as some that have been turned off by epigenetic silencing can be turned on with treatment.

All of these advances provide a wealth of data and potential therapeutic targets that will require evaluation through clinical trials; this, in turn, has prompted a re-evaluation of set standards and procedures, such as those discussed in this chapter. What is needed is not so much ways to analyze expression per se but rather effective ways to channel the new technologies' flows of copy-number (deletion and amplification regions) and expression (treated/untreated fold-change) data into a manageable stream of candidate treatments and genes, and at the same time, new methods to appropriately evaluate the treatments' outcomes for the targets they are intended. In this section we highlight two previously discussed basic concepts, endpoint definition and monitoring, within the context of the impact of the genomics era on them and in particular, cancer vaccines as they represent a premier example of the translation of genomic information from bench to bedside.

DESIGN

Conventional oncology drug development paradigm is to investigate four phases, discussed previously in this chapter: phase I to determine safety and dose, phase II to evaluate effectiveness and look for side effects, phase III to verify effectiveness, and phase IV for postmarketing surveillance. With cancer vaccines, for several reasons, there is no clear delineation of such phases, calling for the development of a different paradigm. First, there are typically little to no serious toxicity risks and no proof for a linear dose-response relationship and thus no need for conventional dose escalation to establish the maximum tolerable dose. Dose and schedule are not determined through escalation based on toxicity. Cancer vaccines are not metabolized, and thus, there is no need for conventional pharmacokinetics. Many cancer vaccines are designed to address one tumor type, and thus, there is no need for mixed tumor trials for target selection. Conventional short-term response criteria (e.g., response criteria in solid tumors, RECIST) are not efficiently applicable to cancer vaccines (discussed in detail later), and historical control comparisons on response rate are not useful, because proof-of-principle endpoints should reflect biologic activity, including immunogenicity. There have been discussion and working groups formed to instead propose the development of a proof-of-principle trial followed by an efficacy trial, with proposed endpoints based on evidence of "signal of activity" of the vaccine.

Clinical Endpoint

In general, an endpoint is a measure to determine whether a therapy is working or not. In cancer vaccines the general goal is to develop a therapy that targets cancer cells, and thus, an examination of tumor response (as opposed to patient response) to therapy seems quite

reasonable. Unlike other vaccines and passive therapeutic modalities (e.g., chemotherapeutic agents and radiation therapy), targeted therapies, including cancer vaccines and other immuno-based treatments, initiate a dynamic process of activating the host's (patient's) own immune system; as such, there is potential for patient response to the therapy under consideration, as well as postvaccination therapies.

Ongoing therapeutic cancer vaccine trials have yet to show evidence of vaccines initiating a patient's immune system to shrink tumors, yet patients who receive these vaccines tend to live longer and respond better to subsequent treatment, prompting a question of whether we are looking at cancer vaccine trials the wrong way. Are we appropriately measuring "response to therapy"? To address this question, it is important to understand the process underlying therapeutic cancer vaccines.

Unlike preventative vaccines, such as those designed to protect against the flu, cancer vaccines are administered to treat an existing condition or disease. Such vaccines fall under one of two general types: (1) cell-based, created using cells from the patient's own immune system that have been activated to the presence of cancer antigens and delivered back to the patient along with additional proteins that facilitate immune activation, or (2) vector-based, wherein an engineered virus (vector) is used to introduce cancer proteins and other molecules to stimulate the immune system. In either case both approaches are designed to mount and prepare the patient's immune system into attacking existing tumor cells.

In their review, Schlom and coworkers[66] examine two cell-based vaccines, Sipuleucel-T (Provenge) and GVAX, in addition to three trials using an engineered pox-virus vector. Although their review article focuses on prostate cancer vaccines, the researchers consider these trials as examples of ongoing progress in similar vaccine therapies for lymphoma, melanoma, pancreatic, lung, and other types of cancer. According to their review of five prostate cancer vaccine trials, Schlom and colleagues[66] offer evidence that patients who receive vaccines may respond better to subsequent chemotherapy or hormone treatment, leading to improved patient survival. However, the endpoints of these trials were not long-term survival but a reduction in tumor size. With this endpoint, such vaccines may be deemed ineffective and abandoned, because the primary endpoint (tumor size reduction) was not achieved, despite their real therapeutic value in prolonging patient survival. The data prompt the rethinking of clinical vaccine trial design and in particular, the current approach to measuring cancer vaccine effectiveness. In this case, it may seem more reasonable to think of the effectiveness of a therapeutic vaccine in terms of the response of the patient, rather than the response of the tumor. Although RECIST standards work well to evaluate therapies that are toxic to tumors, such as radiation therapy or chemotherapy, they are less capable of measuring more subtle systemic effects of immune response. With this in mind, patient response to therapy may be long-term, in which case other markers as surrogates for patient response to a vaccine's "signal of activity" may be considered. In particular, the pursuit of molecular biomarkers and their appropriate use as surrogate endpoints in clinical trials is emerging with advances in cell biology, genetics, microbiology, and other fields.

Surrogate Endpoint

The demand for new and improved biomarkers is a reflection of the emerging drug development due in part to genomic advances that led to a better understanding of the disease processes. One example of such progress in measuring biomarkers to guide therapeutic development is the potential use of human immunodeficiency virus plasma RNA load (viral load) in AIDS. There are many new ways to discover drugs in light of gene target discoveries. The use of molecular targets to design new chemical compounds has provided many new candidates for testing, resulting in a pressing need for more efficient ways to design trials. The identification of highly precise and accurate biomarkers could allow the testing of more candidate drugs, reduce the number of patients required to conduct trials, expand on our capacity to predict adverse events, and potentially improve regulatory decision making. In oncology in particular, we are entering an era of sophistication in making more precise diagnoses and more informed choices about therapy. Biomarkers of immune system function and viral replication, such as CD4 cell counts and human immunodeficiency virus viral load, have helped in the initial evaluation of new AIDS therapies, which have subsequently been demonstrated to extend life and improve its quality.

To understand the link between a biomarker, clinical endpoint, and surrogate endpoint, we must first clarify their definitions. A biomarker (or biologic marker) is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. A clinical endpoint is a characteristic that reflects patients' responses (e.g., how they feel, function, or survive). These endpoints are distinct measures of disease characteristics that reflect the effect of a therapeutic intervention. A surrogate endpoint, in brief, is a biomarker intended to substitute for a clinical endpoint. Although all surrogate endpoints are biomarkers, not all biomarkers are surrogate endpoints, and in fact, only a very few biomarkers may be considered for use as surrogate endpoints. For a biomarker to be considered as a surrogate endpoint, it is required to predict clinical benefit based on epidemiologic, therapeutic, pathophysiologic or other scientific evidence. Additionally, the utility of a biomarker as a surrogate endpoint requires demonstration of its accuracy (the correlation of the measure with the clinical endpoint) and precision (the reproducibility of the measure).

One approach to establish the link between a biomarker and clinical endpoint is to estimate the proportion of treatment effect that is accounted for by the surrogate endpoint for which there are several ways to make this determination.[67] Strictly speaking, if a surrogate endpoint is to be valid as a clinical endpoint, the biomarker must be able to account for all of the effects of the intervention on the clinical outcome (endpoint). In practice, however, it may be too much to ask of a single biomarker to fully capture all of a treatment's effect. To this end, the use of multiple biomarkers representing various components of complex disease pathways may yield surrogate endpoints that are more comprehensive in the ability to assess effects of therapeutic interventions.

A timely example of such a need for multiple biomarkers lies in cancer vaccine trials, where "signal of activity" of a vaccine may be defined in terms of three characteristics: clinical response, biologic activity, or immune response. For biologic activity, potential measures may include regulatory T-cell activity or immune response against target cells, or molecular response (MRD). An immune profile may be assessed by sequential samples collected over time points (e.g., baseline, follow-up visits) to assess reproducibility of assay results. As for clinical activity, there is no current mandate to demonstrate clinical activity with conventional oncology endpoints in proof-of-principle trials, and thus, typically no end-stage patients, so a homogeneous population is selected. As for surrogate endpoints in trials with cancer vaccines, molecular response is being considered. Cancer vaccines are expected to work best in MRD populations. Molecular markers that allow uniform assessment of MRD and the impact of a vaccine on the target disease may function as a measure of biologic and/or clinical activity. Some examples include CML, with a well-defined chromosomal abnormality (BCR-ABL) that is detectable by reverse transcriptase–polymerase chain reaction (RT-PCR), and acute myeloid leukemia, wherein multiple heterogeneous chromosomal abnormalities are not present in all patients, requiring an array of markers to determine biologic activity.

Monitoring

To control patients' responses to therapies and maintain proper doses, monitoring is necessary. The advent of the genomics era has

prompted the potential use of molecular endpoints for monitoring patients' responses to therapy. To gain a better perspective on this issue, in this section, we revisit concepts introduced earlier in this chapter for monitoring within the context of CML.

Historically, studies of CML therapies have used cytogenetic responses, the different phases of CML, remission, and even death to monitor treatment response and ascertain treatment efficacy. These endpoints carry the greatest weight in clinical practice, because observed differences in them signify tangible differences in treatment benefit. The effectiveness of molecular targeted therapy, such as tyrosine kinase inhibitors (TKIs) at helping patients with CML to achieve a MRD but not eradicating the disease, has prompted consideration of combination therapies in treating CML. Thus, as therapy for CML improved, the low rate of disease progression has made it impractical to use clinical events as primary endpoints in trials of short duration. On the other hand, the ability to measure the amount (number of transcripts) of the hallmark gene in CML patients, *bcr-abl*, has made it possible to compare expression with received treatment, which is a more sensitive marker for therapies than cytogenetic response, and is able to detect MRD. Almost all CML therapy trials now incorporate this molecular assay as part of monitoring treatment response, yet *bcr-abl* as a marker for some clinical event is not accepted by the US Food and Drug Administration (FDA) for product registration for agents other than TKIs, with no formal guidelines on its use.

Although quantitative PCR testing of *bcr-abl* in patients with CML has become the predominant molecular monitoring technique for CML therapy, with correlations established with the probability of relapse, it is regarded as a risky endpoint from a regulatory perspective, with no absolute guidelines for monitoring. The difficulty with using changes in *bcr-abl* transcripts as a marker to evaluate treatment response is that the assay itself has issues of lower detection limits and large variability. These issues are particularly seen in CML patients with MRD, an ever-increasing patient pool, due to the effectiveness of TKIs. Devising a monitoring strategy for CML patients is thus a challenge ideally suited for a comprehensive statistical approach, requiring the development of models fully informed by current biomedical knowledge, efficient inference that extracts maximal information, and a design that combines the population with individual data.

A marker endpoint is considered a good surrogate for a clinical endpoint if treatment effects on the marker reliably predict treatment effects on the clinical endpoint. For this condition to hold, the marker (1) must be correlated with the clinical outcome and (2) must fully capture the effect of the treatment on the clinical endpoint.

Whereas most candidate markers typically adhere to the first condition, the second is more stringent, resulting in many markers as partial mediators of treatment response. Data now exist to support the importance of achieving molecular milestones when treating patients with TKIs. Newly diagnosed CML patients treated with the particular TKI, Gleevec, who achieved a 3 log reduction in *bcr-abl* transcripts at 12 months following its initiation, have been shown to improve in their progression-free survival as compared with patients who did not reach a 3 log decrease. This and related observations have led many investigators to use endpoints based on *bcr-abl* testing, although their surrogacy for a clinical endpoint has not been fully examined and validated. Within the context of understanding the significance of improving on Gleevec's clinical success with new combinations, there are two critical issues that must be broached. The first is the determination of whether additional reductions in PCR levels are of clinical importance (e.g., is a 3 log reduction as informative as a 4 log reduction or undetectable values?) and to translate such reductions into additional progression-free survival. The second requires ongoing modifications and enhancements of the molecular assay measuring *bcr-abl*. Disease burden measures at or near the assay's limit of detection seem to have large sample-to-sample variability. A criterion of "undetectable" as an endpoint can be confounded by sample handling, because undetectable values can be due to low-quality RNA or poor RNA yield and further, the limit of detection is sample- and run-specific.

The ability of a trial to answer the posed clinical question depends on whether the marker endpoint is indeed a surrogate for the clinical outcome of interest. There is a clear need for guidelines on the use of *bcr-abl* transcript changes as a molecular endpoint to monitor and assess treatment response. Molecular techniques will play a large role in monitoring the progress of CML and in reassessing therapeutic strategies. Many groups are at work to create standards that can be used to cross-validate results from individual laboratories, with their focus on creating a standardized assay that is universally accepted and used. Alternative strategies have been to create a series of statistical models whose results will be used to devise a monitoring strategy for implementation to achieve standardization of results. The potential use of molecular endpoints for monitoring of patients' response to therapy will have tremendous impact, especially with the advent of new efficient drugs and combination therapies, because results from clinical trials will be obtained faster than with a clinical endpoint, and in turn, clinicians will be able to adapt the new treatment faster.

Future Directions

The advances made in cancer biology have provided us with a better fundamental understanding of cancer but with yet slow progress in translating such knowledge into medical practice. As a result, the American Association for Cancer Research (AACR) together with the FDA and National Cancer Institute (NCI) have formed the AACR-FDA-NCI cancer biomarkers collaborative to facilitate the use of valid biomarkers in clinical trials and ultimately in evidence-based oncology and cancer medicine. Research is under way to find new ways of exploring the use of biomarkers in cancer detection and treatment that will, in turn, require a new generation of clinical trials that modernize the processes and methods used to evaluate safety and efficacy for evaluation of novel, gene-based therapies without sacrificing high standards.

SUMMARY AND CONCLUSIONS

In developing new cancer treatments, investigators are often interested in treatment effects and differences that are about the same size as the variability or the bias that is a part of all clinical studies. The only solution for making valid inferences in the face of these potential errors is to properly design, conduct, and analyze clinical trials. There are a small number of important design considerations to help control bias and random errors including the use of randomization, blinding, stratification, minimizing postentry exclusions, adequate sample size, and planned interim monitoring.

Clinical trials have limitations, partly because of the rigor required to implement them. Investigators contemplating the use of these important scientific tools should focus most efforts on the design aspects of the study and concern themselves little with analysis. This is because most of the serious errors that can be made when performing clinical trials can be prevented or minimized by correct design. In this regard, consultation with an experienced clinical trial methodologist early in the design stage of an investigation will be of enormous benefit.

When analyzing and reporting the results of clinical trials, investigators should follow a simple approach. The purpose of a trial is to estimate an effect or treatment difference, which if present would have clinical utility when treating new patients. Procedures or methods that do not facilitate estimating and reporting the treatment effect with precision and without bias are likely to mislead investiga-

tors. Often in clinical trials, investigators are interested in estimates of odds or hazard ratios between treatment groups.

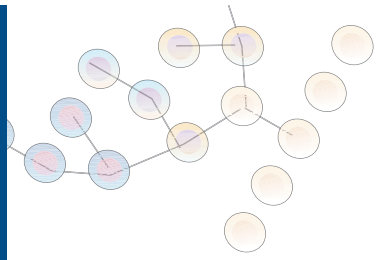
These ideas suggest that the most useful results from clinical trials will be estimated risk ratios and their confidence limits. Especially in oncology studies, where disease progression, recurrence, and death are of interest, estimates of risk difference are very relevant. Hypothesis tests and associated *P* values, though often (or exclusively) reported, are of lesser utility because they do not fully summarize the data. These recommendations are similar to those in many journals.

Despite some technical disagreement among statisticians regarding the need for adjusted analyses for imbalanced prognostic factors, we believe that it is wise to see if treatment effects change after accounting for imbalances. When this occurs, it seems likely that it will be of clinical interest. Although we discourage analyses that exclude any patients who meet the eligibility criteria, some circumstances will require that this be done (e.g., when a patient refuses to participate after randomization). Investigators should report, and emphasize as primary, those analyses that include all eligible patients.

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23 Structures Supporting Cancer Clinical Trials

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SUMMARY OF KEY POINTS

- Cancer clinical trials provide the evidence on which sound oncology practice is based.
- Fewer than 5% of adult cancer patients participate in cancer clinical trials.
- Providing greater access to clinical trials has been a major goal of the National Cancer Institute, cancer centers, and patient advocacy groups.
- There are now many opportunities for physicians in private practice to participate in clinical trials sponsored by the National Cancer Institute and/or the biopharmaceutical industry.
- Successful participation in clinical trials includes the following clinical components:
  - The attitude and commitment of the physician
  - Sufficient preparation and infrastructure
  - Trained staff, including at least some of the following:
    Clinical research nurse
    Clinical research associate
    Pharmacist
  - Affiliation with an institution or network that provides the protocol and scientific and administrative support, such as the following:
    Cooperative group
    Cancer Trials Support Unit
    Cancer center network
    Biopharmaceutical industry network
    Research institution
  - Access to an authorized Institutional Review Board
  - Access to adequate laboratory facilities to process protocol-required specimens
  - Adherence to good clinical practices
  - Accurate and timely data reporting
  - Proper maintenance of primary source documentation
  - Adequate preparation for on-site audits
  - Adequate extramural financial support
- Many organizations now provide access to clinical trials and/or provide the necessary training and certification; relevant Web sites are included in this chapter.

INTRODUCTION

Modern oncology practice is founded on results from thousands of clinical trials conducted over the last four decades; thousands more clinical trials are ongoing at any given time and provide the evidence base for the rapidly changing therapeutic practices of this specialty. Motivations for the decision by an oncologist to participate actively in this extensive system of medical and scientific inquiry range from the ability to offer patients state-of-the-art treatments available through well-designed clinical trials, to the personal satisfaction and benefits that can be achieved from participation in this process. The commitment of time and resources necessary to participate effectively in such clinical research, and sometimes the unfamiliarity with clinical research requirements and procedures, prevent many oncologists from taking part. It has been estimated that only 3% to 5% of adult cancer patients in the United States are treated while taking part in clinical trials, with even lower rates of participation in many other countries. The lack of patient participation has been due, in part, to inadequate understanding of the clinical trials process. Fortunately, owing to intense publicity and educational programs by both patient advocacy groups and clinical trials organizations and widespread access to clinical trials information on the Internet, a growing number of patients now expect that available clinical trials will be included in the discussion of options for the treatment of their cancers. The purpose of this chapter is to describe some of the requirements, resources, and structures that are available to enable practicing oncologists to participate in clinical trials and to discuss the responsibilities that come with such participation. Numerous opportunities now exist for practicing physicians and their patients to participate in cancer clinical trials, including treatment, prevention, and cancer control trials, whether conducted by the National Cancer Institute (NCI), cancer treatment institutions, or the biopharmaceutical industry. Widespread access to the Internet has revolutionized communication and made it possible to provide regulatory information, educational and training materials, data forms, and documents online. A wide array of resources is now available to assist physicians and their staffs in placing their patients on clinical trials.

NATIONAL CANCER INSTITUTE–SPONSORED CLINICAL TRIALS ACTIVITIES

The NCI supports the development of over 100 agents (many in collaboration with pharmaceutical and biotechnology companies) and has an extensive clinical trials system that encompasses treatment, prevention, and cancer control studies. More than 800 trials are active at any given time, and several hundred new trials open each year. In the treatment area, the NCI has programs for early therapeutics development (primarily phase I and II trials), including many sites with grants and contracts to complete these early trials. The NCI also supports a large program of Clinical Trials Cooperative Groups that conduct later-phase trials, predominantly pilot studies and phase III trials. Phase III trials are conducted nationally, and participation in them is now possible even for oncology physicians who are not Cooperative Group members. Clinical Trials Cooperative Groups funded by the NCI (Box 23-1) provide a standing mechanism for performing large-scale multicenter treatment and prevention trials.

Box 23-1. NATIONAL CANCER INSTITUTE–FUNDED COOPERATIVE GROUPS

American College of Radiology Imaging Network (ACRIN): http://www.acrin.org
American College of Surgeons Oncology Group (ACOSOG): http://www.acosog.org
Cancer and Leukemia Group B (CALGB): http://www.calgb.org
Children's Oncology Group (COG): http://www.childrensoncologygroup.org
Eastern Cooperative Oncology Group (ECOG): http://www.ecog.org
European Organization for Research and Treatment of Cancer (EORTC): http://www.eortc.be/default.htm
Gynecologic Oncology Group (GOG): http://www.gog.org
National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG): http://www.ctg.queensu.ca
North Central Cancer Treatment Group (NCCTG): http://ncctg.mayo.edu
National Surgical Adjuvant Breast and Bowel Project (NSABP): http://www.nsabp.pitt.edu
Radiation Therapy Oncology Group (RTOG): http://www.rtog.org
Southwest Oncology Group (SWOG): http://www.swog.org

Over the years, this system has supported an experienced cadre of clinical researchers, biostatisticians, and research support staff who can respond to new clinical discoveries by organizing definitive phase III clinical trials. Because of their size and complexity, these trials require extensive infrastructure support to manage the necessary regulatory and data-reporting tasks. Although these Cooperative Group trials have provided a significant proportion of the evidence on which oncology practice is based, public advocacy for more rapid progress, increasing fiscal pressures on medical practice, and the accelerated pace of drug discovery caused the NCI to review and restructure aspects of its clinical trials program in 1998 and again in 2005. The major goals of these restructuring efforts were to increase access to NCI trials for patients and their physicians; to eliminate barriers to participation in clinical trials; to improve the coordination and cooperation among the functionally diverse elements of the NCI's clinical trials program, including relationships with industry and the U.S. Food and Drug Administration; to improve the prioritization process for developing clinical trials leading to increased scientific quality; to enhance the standardization of tools for clinical trial design and data capture; and to increase operational efficiency so that trials could be executed in a more timely manner.

From the mid-1980s to the mid-1990s, accrual to Cooperative Group treatment trials reached a plateau at about 20,000 patients annually. Whereas the pediatric groups consistently enrolled about 70% of all cancer patients, the adult groups were able to accrue only fewer than 2% of all cases. Phase III trials in the adult groups took an average of 4.5 years to enroll patients and an additional 3 to 4 years of follow-up before a result was known. This approximately 8-year cycle before potential treatment advances could be confirmed was clearly too long. It therefore became imperative to enable more rapid accrual to clinical trials.

Surveys among physicians and the public found that the obstacles to accrual in adult oncology were multifactorial (Table 23-1).[1–5] With these barriers in mind, the NCI undertook the extensive review of the clinical trials system noted previously, involving a wide range of stakeholders that included Cooperative Group and Cancer Center leaders, patient advocates, representatives from the FDA and the pharmaceutical industry, and government staff. The detailed reports of these reviews are available online from the 1998 review (http://ctep.cancer.gov/forms/ArmitageReport.pdf) and from the 2005 review (http://integratedtrials.nci.gov/ict/ctwg_report_June2005.pdf from 2005). Several pilot projects were developed from the 1998 restructuring effort that were aimed at modernizing the clinical trials regulatory and data collection systems, opening access to trials to more patients and investigators, and simplifying the role of local institutional review boards in multi-institutional clinical trials. New opportunities were created for community physicians to participate in a broad array of clinical trials, and new tools were created to enable this. Two major initiatives, the Cancer Trials Support Unit and the Central Institutional Review Board, are now integral parts of NCI's clinical trials system and are described next.[6]

Table 23-1 Barriers to Clinical Trial Participation

Physician Related	Patient Related
• Inadequate funding for data management personnel	• Doctor never discussed or offered
• Burdensome regulatory requirements	• Unaware of trials as option
Institutional Review Board	• Concerns about insurance coverage
Informed consent	• Fear of receiving placebo
Conflict of interest	
• Inadequate reimbursement	
• Lack of time	
• Resistance by third-party payers	

Cancer Trials Support Unit

The Cancer Trials Support Unit (CTSU) is designed to facilitate one-stop online access to a broad menu of predominantly phase III trials by a national network of NCI investigators. The network investigators include not only members of Cooperative Groups, but also physicians in practice with no group affiliation. They can access the CTSU menu of treatment trials from the public Web site (www.ctsu.org). The menu consists primarily of Cooperative Group phase III trials, although selected internationally led phase III trials, Cooperative Group phase II trials, and some trials led by U.S. cancer centers are also available. The scientific leadership for each study remains within the organization that developed the trial, but patient enrollment can come from any network physician across the country. By providing more physicians and their patients the opportunity to choose from a broader menu of trials, the CTSU promotes faster accrual to individual trials, allows increased access and broader treatment options to more patients nationwide, and renders trials involving uncommon cancers more feasible. Although the clinical trials menu is the most visible aspect of the CTSU, another major function of the CTSU is its centralized regulatory database. For all Cooperative Group members and nonmember physicians in the network, the CTSU maintains important demographic information about their sites or practices, including Cooperative Group(s) and academic/practice affiliation(s), Office for Human Research Protection assurance numbers for their sites, Institutional Review Board (IRB) approvals for specific protocols, and conflict of interest forms for investigators. This enables physicians, nurses, and clinical research associates to register once annually instead of having to register for each group or trial in which they participate. Initiated in 2002, the Regulatory Support System requires that investigators complete a 1572 investigational drug form once yearly, along with a supplemental information form and a conflict of interest form.[7] Nurses and clinical research associates who participate in group trials also register once annually online (registration is available at https://iapps-ctep.nci.nih. gov/ctepar/main.htmlfiReset). Information from this registration database is accessible to all Cooperative Groups, as the CTSU Web-based system is shared and maintained in a coordinated manner with all the Cooperative Group operations offices. Centralizing regulatory data has reduced the workload for investigators in the field,

consolidated duplicative work, and allowed Cooperative Group staff to partially offload this activity to the CTSU and focus instead on protocol development and analysis.

Cancer Trial Support Unit Trial Services

The CTSU maintains a public Web site that provides patients with information about all the clinical trials on the menu.

The widespread availability of Internet access in physicians' offices has made it possible for the CTSU to make the necessary documents, forms, and tools readily available. For physicians and their staffs, a password-protected members site contains the information that is needed to enroll a patient in one of the trials on the menu. Online access is provided to the protocol, case report forms, adverse event reporting forms, NCI pharmacy forms, site registration documents, patient enrollment documents, and education and training materials. Informed consent documents with Spanish translations are also available. In addition, detailed IRB application packets can be downloaded so that the process of obtaining local IRB approval is much less time consuming.

Regardless of which organization is leading a protocol on the CTSU menu, the CTSU manages site registration, protocol eligibility checks, and treatment randomization, obviating the need to interact with multiple different Cooperative Groups to treat patients on a variety of different protocols. Local site registrars can verify online that their site has successfully completed all the registration requirements for a specific protocol. In addition to the documents that are needed to conduct the study, the CTSU provides abstracted Time and Events Calendars and Protocol Schemas to assist medical staff with protocol adherence, a PowerPoint slide presentation to help physicians promote the trial, and patient education materials that provide information about both clinical trials in general and the specific trial under consideration. Physicians can also obtain quarterly accrual reports by study and by site and can order copies of investigator brochures when trials involve experimental drugs.

Data collection has been standardized on CTSU trials across all different Cooperative Groups and across diseases, to the extent possible, to facilitate ease of reporting, data sharing, and exchange. This has been possible because of the development of Common Data Elements (CDEs) through a project that NCI began several years ago in collaboration with the Cooperative Groups. For each disease, there now exists a set of commonly defined terms and values that are used to report information in a uniform manner. CDEs have now been developed for all the diseases that are treated in phase III studies by the adult groups and are currently being developed for pediatric and phase I and II trials. Currently, data collection is done by using paper case report forms. However, following an extensive evaluation, an electronic remote data capture system that will help to standardize the entire NCI Cooperative Group clinical trials system is on the verge of adoption. This effort, performed in conjunction with the larger NCI-wide bioinformatics initiative (caBIG, the cancer bioinformatics grid), will help to standardize clinical trials reporting not only for the Cooperative Groups but for all clinical trials supported by the NCI. The common CDE vocabulary system has also made rapid development of electronic case report forms more feasible. With the increasing availability of electronic data reporting for group trials, speed and data accuracy should improve owing to real-time data queries, thereby reducing time-consuming follow-up queries that currently arise weeks to months later when patient information is less readily retrievable.

The CTSU also manages two additional tasks: auditing and research reimbursement. Trials performed via the CTSU are audited in a fashion similar to other Cooperative Group trials (see the section entitled "Quality Assurance and Audits") to verify data accuracy and quality by comparing the primary record with the research forms that the site submits. Given that sites may now participate in trials led by multiple groups, the CTSU patient charts are simply added to a scheduled audit when a group is visiting a member site, to avoid burdening sites with multiple Cooperative Group audits. Depending on the number of CTSU accruals at a site, the audit team is sometimes supplemented with members from other groups or CTSU staff to ensure sufficient expertise. Similarly, the CTSU has used existing contractual relationships between groups and their members to forward payments to group members who have participated in trials via the CTSU. Physicians who are not group members are supported via direct contracts and are paid by the CTSU directly.

Cancer Trial Support Unit and Cooperative Group Interactions

The introduction of the CTSU was the first major structural change to NCI's multicenter trials system since its inception more than 50 years ago. The CTSU has assumed a major role as a support structure that complements the work of the Cooperative Groups. The CTSU is not a scientific structure and does not develop or analyze the studies that it supports. Rather, all the data that it receives are passed on to the group that is leading the trial for analysis. By reducing the duplicative administrative work that was traditionally done at each Group Operations Office and by offering more clinical trials to each group member, the CTSU allows the groups to focus on their prime missions: developing important clinical trial questions and analyzing these trials rigorously.

CENTRAL INSTITUTIONAL REVIEW BOARD

Background

In NCI-sponsored multicenter trials, the identical protocol is carried out at many sites, averaging about 100; each site requires its own local institutional review board (LIRB) to conduct an initial full-board review and subsequent annual reviews, adverse event reviews, and amendment reviews. These multiple IRB reviews create a largely redundant, time-consuming workload at these sites, compounding the ever-mounting pressures on the nation's IRB system, which have been well documented.[8] To provide an idea of the scope of the duplicative effort that occurs, consider that NCI has more than 8000 registered investigators at more than 1500 sites. On average, there are 160 ongoing phase III trials and 30 new trials entering the NCI system annually, resulting in approximately 16,000 IRB reviews (3000 initial reviews) conducted each year.[9] In addition, investigators often mention that the amount of time, paperwork, and (more recently) funding required of them to obtain IRB approval is a serious barrier to opening trials. These factors provided the impetus for the NCI to develop a new, centralized approach to human subjects protection for its large, phase III trials program.

Customarily, central institutional review boards (CIRB) models were instituted when LIRBs were lacking. In these cases, for-profit central IRBs contract their services to institutions without IRBs and maintain close contact with the sites by sending staff for frequent visits, thereby fulfilling the Office for Human Research Protection requirement that the IRB of record have knowledge of the local context. By contrast, LIRBs exist throughout the NCI system, and this fact led NCI to use a model in which responsibility is shared between the CIRB and LIRB. The CIRB provides the initial full-board review and then transmits its decision and detailed minutes of the meeting to the LIRB participants via a confidential Web site. These sites have the option to perform a facilitated review, whereby a LIRB chair (or a designated subcommittee) can review the CIRB documents rapidly, determine whether or not there are local issues that should be addressed, and then expeditiously approve the protocol, without the need for a full-board review at the local level. If facilitated review is accepted by the local site, then the CIRB becomes the IRB of record for that protocol. This means that the CIRB will perform the continuing annual reviews, adverse event reviews from

all sites participating in the trial, and the amendment reviews. This process relieves the LIRB of the burden of review for these multicenter trials, but the LIRB still has the responsibility to review adverse events that occur at the local site (but can now view them in the context of the overall adverse event review provided by the CIRB). The LIRB also retains responsibility for the medical and ethical conduct of the investigators and their staffs at their institution. To formalize this division of responsibility, a written agreement is signed by the LIRB when it joins the CIRB Initiative (available at http://www.ncicirb.org).

NCI's CIRB is composed of a distinguished panel of oncology physicians, nurses, and patient representatives and includes a pharmacist, an ethicist, and a lawyer. Recently, a pediatric CIRB was initiated. The two NCI CIRBs review all phase III studies from the Adult Cooperative Groups as well as any phase III trials that have been opened in the CTSU and trials from the Children's Oncology Group. Unlike most LIRBs, the CIRB is focused exclusively on cancer trials and has sufficient time and expertise to review each protocol in detail. In addition, compared with LIRBs, the CIRB by design has more leverage to request changes in the protocol and informed consent, as NCI requires that studies obtain CIRB approval before they can open.

This new model for human subjects protection in multicenter trials is now utilized by over one third of all major NCI-designated Cancer Centers and many other university medical centers. A major goal will be a significant reduction in review workload for LIRBs while preserving their role as the primary overseers of the actual conduct of the research at the local site. Patients and investigators should benefit from the ability to open trials rapidly using this mechanism and from the greater availability of trials that should result.

Clinical Trials Working Group Initiatives

The Clinical Trials Working Group proposed 22 initiatives to improve the NCI's clinical trials system in 2005. Although it is early in the implementation of these recommendations, several activities have already entered into their pilot phase of development. To facilitate coordination of the entire NCI clinical trials enterprise, a new Federal Advisory Committee-approved advisory group reporting to the NCI director, the Clinical Trials Advisory Committee, has been initiated with a specific charge to monitor the implementation of the Clinical Trials Working Group recommendations and to provide oversight for NCI's clinical trials program. This committee has already taken up a review of the funding guidelines for the NCI-supported Cooperative Groups, Cancer Centers, and Specialized Program of Research Excellence program with the goal of providing clear incentives for these major NCI research programs to work harmoniously in the clinical trials arena. To enhance the scientific quality of the clinical trials that are supported by the NCI, the initial disease-specific scientific steering committees called for in this report have been formed. Their function is to coalesce investigators in both translational and clinical science supported by the NCI with community-based clinical trialists and patient advocates to develop a broad consensus around scientifically outstanding clinical trials that are likely to reach their accrual goals in a timely fashion.

To assist in the process of standardizing the clinical trials infrastructure for NCI-supported investigations, the caBIG workspace for clinical trials has been expanded, and the caBIG has begun work on the creation of a comprehensive database of the clinical trials that are funded by all NCI funding mechanisms. A public-private partnership group has also been formed to develop commonly accepted clauses for clinical trial contracts to reduce the lead time that is needed to open studies. Finally, initial studies have been conducted to investigate the major process roadblocks to timely clinical trial initiation.[10] These investigations will undoubtedly lead to additional recommendations to streamline the clinical trials process further.

OTHER NATIONAL CANCER INSTITUTE–SPONSORED STRUCTURES SUPPORTING CLINICAL TRIALS

Although the CTSU, the CIRB, and the national scientific steering committees represent new mechanisms to reduce barriers and facilitate broader clinical trials participation by practicing oncologists, advocates, and translational scientists, a number of other important mechanisms provide additional options for support and participation (Fig. 23-1).

Clinical Trials Cooperative Groups

Physicians who wish to be more actively involved in the intellectual and scientific aspects of clinical trials and who can commit to accruing at least 5 to 10 patients per year to group studies, should seriously consider joining a Cooperative Group. Most groups have an affiliate program that allows community sites to partner or affiliate with a main member who assumes a number of the management and monitoring responsibilities for the affiliate. Procedures for joining can be found on the groups' Web sites (see Box 23-1). Affiliate members attend the semiannual meetings of the groups and are actively involved in the scientific agenda, protocol development, and publications of the group. In addition to intellectual satisfaction, career development, and networking opportunities, members have access to

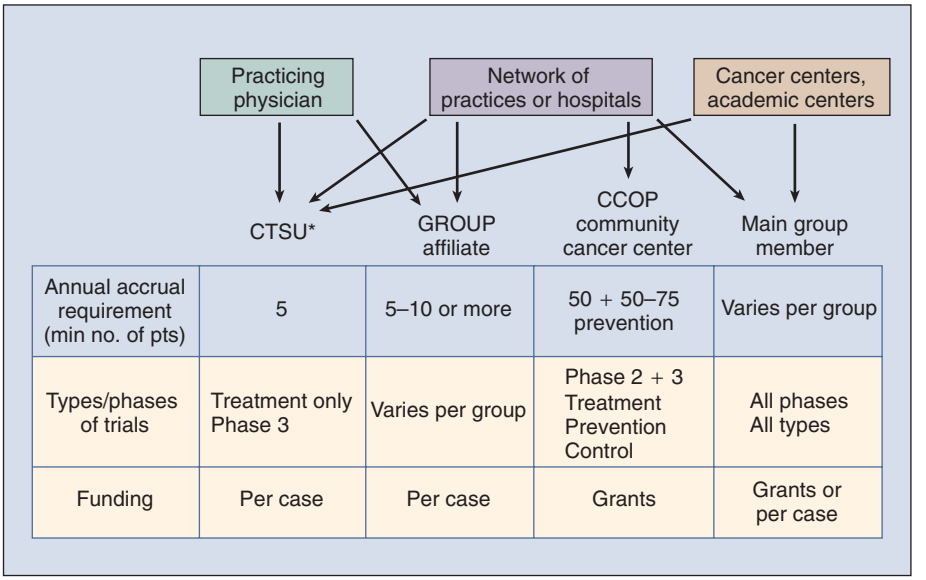


Figure 23-1 • Mechanisms for participating in NCI-sponsored clinical trials. *All members (affiliate, CCOP, main) have access to the CTSU menu of trials regardless of whether or not they are members of the group leading the trial.

a broader array of clinical trials for their patients, including phase I, phase II, and pilot trials that are not available on the CTSU menu and therefore are not accessible to nonmembers. Cooperative Groups also provide training and networking opportunities for research staff, including research nurses and clinical research associates, at group meetings and in other venues.

Community Clinical Oncology Program

For practices or groups or networks of practices that already have research experience and that can commit to enrolling significant numbers of patients in clinical trials, NCI grant funding through the Community Clinical Oncology Program (CCOP) mechanism offers many opportunities. CCOPs must document the ability to enroll 50 patients in cancer treatment studies plus 50 to 75 patients in prevention studies and/or trials focused on symptom management and cancer control. The grants provide important up-front funding to enable sites to hire critical staff from the start to support the substantial patient accrual that is required. In addition, special minority-based CCOPs are funded and provide additional support for groups or networks that serve predominantly minority populations. Minority-based CCOPs strive to increase cancer prevention and control activities in minority and underserved communities in addition to increasing access to clinical trials for minority patients. The CCOP program, funded by the NCI's Division of Cancer Prevention, has been in existence since 1983 and now funds over 50 research sites in 34 states. Details on these programs can be found on the Division of Cancer Prevention's Web site (http://www3.cancer.gov/prevention/ccop/).

Children's Oncology Group

Tremendous strides have been made over the past 50 years in the treatment of childhood cancers, transforming a once-fatal disease of children into a highly curable one. This success has been due in large part to the participation of large numbers of children with cancer in clinical trials. It is estimated that some 70% of children who are diagnosed are entered into clinical trials, and this has been a key factor in the rapid progress that has been made. In March 2000, four NCI-sponsored pediatric groups—the Children's Cancer Group, the Pediatric Oncology Group, the Intergroup Rhabdomyosarcoma Study Group, and the National Wilms' Study Group B—agreed to consolidate their efforts and formed the Children's Oncology Group. The Children's Oncology Group has more than 230 member institutions, which include all major U.S. universities and teaching hospitals, as well as sites in Europe and Australia. Individual practices seeking affiliate membership can receive information at http://www.childrensoncologygroup.org.

National Cancer Institute Cancer Centers Program

NCI-designated Cancer Centers exist in nearly every state and are funded by NCI to support a broad research infrastructure, including the personnel and physical resources to conduct a variety of clinical trials. While serving as tertiary referral centers, the Cancer Centers increasingly have recognized the desirability of forging links with community practitioners. The resultant research networks enable Cancer Centers to complete trials more quickly while providing practitioners and their patients with access to new drugs and techniques at an early stage of their development. These partnerships are flourishing in some areas of the country, and the model is likely to be replicated widely. For more information about Cancer Centers in your area, consult http://www3.cancer.gov/cancercenters.

Phase I and II Early Therapeutics Development Networks

The NCI supports a network of individual academic institutions and academic consortia to support the conduct of phase I and early phase II clinical trials, often performed with pharmacokinetic and correlative pharmacodynamic studies. These institutions enroll approximately 2000 patients per year in clinical trials, often first-in-human studies, that often set the standard for the further investigation of individual new agents or combinations of investigational agents by the Cooperative Groups or by industry. A major feature of this network is the expertise of the investigators and their institutions in blood and tumor sample acquisition, pharmacokinetic assay development and monitoring, and the development of pharmacodynamic assays.

National Community Cancer Centers Program

The NCI has very recently launched a new pilot program, the National Community Cancer Centers Program, to encourage collaboration between private practice medical, surgical, and radiation oncologists and large community hospital systems to explore ways to share information related to cancer care and expand and standardize the collection of blood and tissue specimens for cancer research. The program will also extend other NCI initiatives in the area of clinical trials and reduction of health care disparities. The major goal of this program is to provide access to research-based cancer care to a broader range of hospitals and clinics where most patients are treated.

BIOPHARMACEUTICAL INDUSTRY–SPONSORED CANCER CLINICAL TRIALS

During the first decades of the development of the field of medical oncology, there was relatively little industry participation in cancer therapeutics development. In part, this was a reflection of the complexity of therapeutics development in the field during a period when the lack of a sufficiently detailed understanding of cancer biology prevented a fully rational basis for new drug development. This relative lack of industry involvement, coupled with the significant public health problem presented by cancer, was responsible for the development of the large NCI-sponsored clinical trials apparatus described in detail in this chapter. The past decade, however, has seen a significant increase in biopharmaceutical investment in cancer discovery research and a parallel increase in both the extent and sophistication of industry sponsorship of clinical trials for the development of new cancer therapeutics. Hundreds of new agents are currently in different stages of clinical evaluation by the industry, either alone or in cooperation with the National Cancer Institute or similar organizations in other parts of the world.

Purpose and Nature of Industry-Sponsored Clinical Trials

The primary goal of therapeutic agent investigation by the biopharmaceutical industry is the evaluation of promising agents for eventual registration and commercialization. Because registration of a new cancer drug requires the demonstration of safety and efficacy for the new agent in the context of currently available therapy for the cancer being treated, the spectrum of clinical trials sponsored by industry often overlaps with the range of trials conducted by the Cooperative Groups. Furthermore, there is a long tradition of industry providing investigational agents for the conduct of clinical investigations through NCI-sponsored mechanisms, and there are many examples of new agents or indications that have received FDA approval on the basis of NCI-sponsored clinical trials. Ethical considerations regarding human investigation and expectations regarding adherence to standards for the conduct of clinical trials do not differ between NCI-sponsored and industry-sponsored clinical trials; therefore, the fundamental processes of conducting clinical trials are similar in both cases. Despite these similarities, however, there are some differences between industry trials and those sponsored by NCI.

Particular Characteristics of Industry-Sponsored Trials

Biopharmaceutical development proceeds in a heavily regulated environment, with detailed regulations from various government agencies covering the spectrum of activities ranging from those related to preparing an agent for first entry into humans, through the years of clinical investigation in patients, to postapproval restrictions on public discussion regarding possible uses of the agent for indications other than those for which the drug was approved. As a result of the requirements of working in such an environment, corporate clinical investigations tend to be focused on the "clinical development plan," the specific plan of clinical trials that will produce an appropriate evidentiary base to allow for regulatory review of the safety and efficacy profile of the agent. During the investigational phase of an agent's life cycle, therefore, companies might restrict the general availability of the agent to individual investigators for clinical study. This perceived need for containment and control can lead to tension between the investigative community and the industrial sponsor. Other potential sources of tension in the interaction between companies and investigators relate to the investigators' perceptions of the need for independence and objectivity in the conduct of multicenter trials. Historically, for example, many companies have generated phase III protocols internally, although usually with considerable input from both external advisors and regulatory bodies. The trial would be conducted by company personnel, and authorship would be conferred on the principal investigator of the largest accruing site. Increasingly, a new model is emerging in which a recognized expert is appointed as the principal investigator; this individual has a much greater role in the design, monitoring, and eventual analysis and publication of the trial than might have been the case historically. Similarly, recent years have seen the almost universal adoption of independent Data and Safety Monitoring Committees for late-stage clinical trials to oversee safety-related information as it emerges from the ongoing trial and to make recommendations to company staff about appropriate actions.

Impact of Globalization on Pharmaceutical Development

Pharmaceutical products increasingly are marketed globally, and large multinational pharmaceutical companies, therefore, need to conduct clinical development from a global perspective. Clinical trials with investigational agents with which the FDA is involved are being conducted in over 75 countries. This tendency toward global development has been greatly accelerated by the International Committee on Harmonization process, which facilitated standardization of many of the activities that are involved in preparing agents for clinical investigation, conducting those investigations, and then preparing the information for registration. Now a single set of standards exists for the conduct of industry-sponsored trials worldwide. Attempts are therefore made to harmonize the development process to produce a globally accepted drug registration package to the greatest extent possible.

Models for the Conduct of Industry Clinical Trials

Biopharmaceutical industry sponsors usually produce the investigational agent in their own facilities, as they anticipate eventually being responsible for the commercial production and distribution of the agent. They also can conduct the series of required clinical trials directly using their own clinical trials personnel, which may include internal company physicians, statisticians, monitors, data managers, quality assurance auditors, and the rest of the required infrastructure, such as company standard operating procedures, company information system support, and drug distribution apparatus. Alternatively, drug sponsors may utilize a contract research organization to perform the actual clinical trials. In fact, for large development programs, it is not unusual for large companies to coordinate clinical trials programs using a mixture of both internal and externally acquired resources. Contract research organizations are companies in the business of conducting clinical trials. Over the last decade, following the explosion in growth of biopharmaceutical clinical investigation, a large number of such companies have been created, some capable of conducting global trials. The actual arrangement—direct or indirect—that a drug sponsor uses for a particular clinical trial is important to the investigator and staff at the clinical trial site, because it determines the predominant source of interactions and contact during the actual conduct of the trial.

Different models exist, as well, for investigator participation in clinical trials with industry. Traditionally, pharmaceutical sponsors have dealt either with individual investigators or with individual institutions, as in the case of academic centers. Clinical trial contract budgets have included direct trial-related costs such as performing additional laboratory studies that are not being done as part of usual medical care plus direct site-related costs associated with the time spent on the trial by the various participating staff and indirect costs for institutional overhead. Recent years have seen the emergence of consortia of investigators (sometimes under the rubric of a Site Management Organization) or consortia of institutions presenting themselves to companies as clinical trial entities, often linked by a single central IRB and often offering the advantage of working under a single negotiated contract. In addition, individual academic centers sometimes have formed networks of oncologists within their referral area for the purpose of presenting themselves as more efficient entities for interaction. New models continue to evolve. These new models make it easier for companies to engage the several hundred sites that are required to conduct major phase III registration-directed trials in a much more efficient manner.

Good Clinical Practice and Other Issues

One area of drug development that has been the focus of International Committee on Harmonization activities is the development of good clinical practice guidelines for the conduct of clinical trials. Good clinical practice describes international ethical and scientific quality standards for designing, conducting, recording, and reporting trials that involve the participation of human subjects. The very useful and informative document "ICH E6 Consolidated Guidance for Good Clinical Practice for Industry" (available at http://www.fda.gov/cder/guidance/index.htm) represents a summary of good clinical practice guidance for the generation of clinical trial data that are intended for submission to regulatory authorities. This document comprehensively summarizes the responsibilities of IRBs, investigators, and sponsors, as well as issues regarding the clinical protocol, investigator's brochure, and the documents that are essential in the conduct of a trial. Although investigators participating in an industry-sponsored clinical trial can expect help in the preparation of the required documents, it is important that they understand their responsibilities both to their patients and to the industry sponsor within the context of a global registration program.

Recent concerns regarding investigator conflict of interest in new drug development have led many institutions to develop policies regarding the extent of financial involvement by investigators in companies sponsoring trials in which the investigators are participating. Industry sponsors have also developed conflict-of-interest policies. In addition, as part of drug approval submissions in the United States, companies must now provide financial disclosure statements from individual investigators who are participating in the registration-directed trials.

Changing Nature of Oncology Trials: Impact on Infrastructure

The same explosion in understanding cancer biology that has led to the increase in the number of new agents under development brings with it a realization that the most appropriate tests of those biologi-

cally targeted agents are clinical trials in which the patients who participate have tumors that are biologically appropriate for the agent. For example, imatinib administered to all newly diagnosed patients with any form of leukemia would have a response rate much lower than that in the biologically appropriate group of newly diagnosed patients with chronic myelogenous leukemia; selection of patients with chronic myelogenous leukemia allows for a focused development program leading to rapid initial registration. The same considerations can logically be extended to matching any biologically directed agent with any cancer patient population and argues strongly for more complete biologic characterization and continued monitoring of patients entering cancer clinical trials. Regardless of whether such characterization is prospective or retrospective in clinical trial design and analysis, it can be expected that the increased need for collection of peripheral blood for germline DNA studies; plasma for proteomics studies; fresh tumor tissue for DNA, RNA, and/or protein studies; and tumor tissue blocks for DNA or immunohistochemical studies or for specialized imaging studies will all place new demands on the infrastructure that is required to conduct trials. These requirements will also introduce new challenges for quality control on sample collection and storage and will increase the resource requirements for trials. It is also likely, however, that such clinical trials will become much more informative. The potential exists in the future for smaller, more definitive trials in more biologically homogeneous groups of patients than is possible with the classic histopathology that is currently used to characterize patients; this potential should lead to more effective and well-tailored treatments.

Challenges to the Conduct of Industry Oncology Clinical Trials

Numerous challenges exist both to the oncologist who wants to participate in the clinical trials process and to the corporate sponsor that wishes to conduct such registration-directed trials. From the individual oncologist's perspective, the bureaucratic hurdles that are associated with the clinical trials administration process can appear daunting, particularly when added to the responsibilities of using investigational agents in patients. Acquiring sufficient trained personnel to conduct such trials is a challenge. Unless participation in a particular trial is part of a broader commitment to the clinical trials process with supportive infrastructure in place and experience in the conduct of several simultaneous ongoing trials, successful participation is unlikely. For these reasons, oncologists who are already participating in Cooperative Group trials through one or another mechanism already have in place some of the required infrastructure for the local conduct of industry-sponsored clinical trials. The corporate sponsors of oncology drugs that are undergoing development face their own challenges and uncertainties. Cancer drug development traditionally has been a high-risk field. Many agents fail in late-stage development, a time when significant time and resources have already been expended. Although it is hoped that the kind of increased linkage of biologic study with therapeutics development will eventually make this whole process more predictable, the development of new cancer drugs remains an expensive and high-risk activity. Development is carried out through a clinical trials process that remains highly inefficient and lacking in standardized information collection, systems, and processes and without many biological markers to aid in decision making early enough in the clinical trials process to decrease risks in development. Continued improvements in efficiency and productivity of the clinical trials system remain a high priority in order to accelerate the delivery of effective new agents to patients.

EXPECTATIONS OF CLINICAL RESEARCH SITES

Staffing is foremost among the critical components for an effective research practice listed in Box 23-2. The number and precise composition of the necessary staff depend on the number of patients who are enrolled in clinical trials and the nature of the practice. In some settings, in which the number of patients in studies is small, one good research nurse can perform many of the required functions. At more active sites, research nurses, clinical research associates, and research pharmacists perform separate functions. For budgeting purposes, for example, it is often estimated that one full-time clinical research associate can handle 25 new patients and up to 50 patients in follow-up in a year. Some of the structures that support clinical trials participation, such as the CCOP program, provide substantial up-front funding to support salaries for the necessary staff in return for a commitment to substantial accrual. Many others, including the CTSU and the Cooperative Groups, provide a small amount of funding when each patient is accrued. The latter approach allows sites to introduce clinical research into their practices at a more gradual pace.

Box 23-2. COMPONENTS OF AN EFFECTIVE RESEARCH PRACTICE

- The presence of committed physicians who are willing to devote the time and energy necessary to conduct clinical research and to accept conscientiously the significant responsibility inherent in the conduct of human research.
- The availability of suitably trained staff (preferably an experienced research nurse) with enough time to assist in screening patients for protocol eligibility and for following patients on protocol treatment.
- The availability of suitable staff to administer the required treatments in the protocol-prescribed manner; increasingly, this might include administration of a wide range of potential therapeutics including, but not limited to, more conventional intravenous chemotherapy and, in some cases, radiation.
- Adequate and committed pharmacy capabilities to handle and account for investigational agents if these are part of the protocol treatment.
- Adequate data management staff to handle the data-reporting requirements for patients who are being treated on protocols.
- Access to an Institutional Review Board (IRB) with Office for Human Research Protections assurances to approve the protocol and monitor the progress of the research.
- Access to suitable laboratory facilities to complete the studies that the protocol requires.
- Willingness to comply with certain federal regulatory requirements, including adequate privacy procedures and training in human subjects protection (available as an online course through NIH at http://cme.cancer.gov/c01/).

Quality Assurance and Audits

Because the accuracy of the data that are collected on clinical trials is critical to the validity of the conclusions from the trials, all clinical trials organizations include quality assurance and audit programs. Although these are structured somewhat differently depending on the mechanism of participation (industry conducting the most frequent and extensive audits), all such programs have certain features in common. All send queries to the site when discrepancies or suspected errors are noted in submitted information, and all compare data that are submitted from the sites to the primary medical or research record for verification at on-site audits. NCI audits are typically conducted every 3 years and review a sample of patients enrolled on a variety of protocols. In addition to verifying data accuracy and protocol adherence, informed consents are reviewed, as are adverse event reporting compliance, pharmacy practices, and timeliness of required

IRB submissions and approvals. Preparation for audits is time consuming for the sites, as all relevant records, including laboratory studies and films (computed tomography, magnetic resonance imaging, etc.) required to document tumor measurements and response verification, must be gathered for the audit team. Some participants consider this work onerous; however, audits fulfill an important educational role in addition to ensuring the quality of the data and clinical trial procedures at participating sites. Data quality initially became a concern when clinical trial participation moved beyond academic sites to community practices. A number of evaluations in the 1980s, however, documented the ability of community sites to perform at a level comparable to that of academic institutions in terms of data quality, protocol adherence, and patient outcome.[11,12] Indeed, over 30% of the accrual to adult Cooperative Group trials now comes from community practices in the CCOP, and additional accrual comes from Cooperative Group affiliates, predominantly community sites.

As was noted previously, although regulatory standards regarding the conduct of clinical trials impose similar overall expectations, for its own reasons industry monitoring is both more extensive and frequent than the usual cooperative group monitoring. The basic tenet of monitoring for both industry-sponsored and NCI-sponsored clinical trials is similar: the need to verify data accuracy by comparing case report forms, whether submitted by paper or electronically, with source data in the patient's medical record. The sponsor-assigned clinical trial monitor will visit the site regularly, educate the involved staff about the goals and particular details of the protocol, and then track the progress of protocol-related activities throughout the conduct of the trial. Monitoring responsibilities include confirmation of appropriate local IRB review, investigator registration via completion of the FDA 1572 form, the existence of timely informed consent documents for each patient, inspection of drug accountability records, confirmation of timely and complete submission of serious adverse events reports, and ensuring appropriate and timely handling of amendments. These activities all fall within the responsibility of the clinical trial monitor, whether the monitor is provided directly from the company sponsor or through a contract research organization. Furthermore, regardless of whether the clinical trial is conducted directly by its own organization or by a contract research organization, biopharmaceutical companies often conduct their own quality assurance audits and monitoring associated with the trial, to further ensure the integrity of the submitted data. The intensity of clinical trial monitoring tends to increase as clinical trials mature and the data management group prepares to officially "lock" the database before the conduct of prespecified analysis and reporting activities. The intensity of quality assurance auditing also increases for a particular clinical trial when it has been identified as part of a New Drug Application or Biologic Licensing Application for drug registration with the FDA. Monitoring and data management activities are evolving with the widespread introduction of electronic data collection and submission systems that are replacing traditional paper-based case report form approaches.

Educational and Training Tools

As has been described previously, participation in clinical trials adds many complexities to care of cancer patients and can require that physicians, nurses, and other office staff acquire new and different skills. Fortunately, because of the widespread interest in clinical trials in the cancer community, there are many resources for gaining information about clinical trials and for acquiring the necessary skills. Professional societies are a good source for educational programs and materials, and some, such as the Oncology Nursing Society (http://www.oncc.org/), the Society of Clinical Research Associates (http://www.socra.org/), and the American Society of Health-System Pharmacists (http://www.ashp.org/), actually offer certification programs that can serve as important career development incentives to office staff. The American Society of Clinical Oncology (http://www.asco.org) also has a very useful Web site with links to a variety of sites that provide information about available clinical trials and detailed information about chemotherapy agents for physicians and nurses. NCI-sponsored Cooperative Groups provide regular educational activities for physicians, statisticians, nurses, and data managers who participate in their trials. Furthermore, the biopharmaceutical industry sponsors a wide range of educational activities that are conducted by both academic institutions and professional societies (e.g., the American Society of Clinical Oncology and the American Association of Cancer Research) about the clinical trials process in general and about the responsibilities of the individual clinical investigator.

The NCI's home page (http://www.cancer.gov/) provides a gateway to the many Web sites at the NCI and provides links to many other useful sites. It contains extensive information about cancer in general and cancer statistics, as well as detailed information about clinical trials with direct links to the Physician Data Query (PDQ). PDQ (http://cancer.gov/cancerinfo/pdq/) is a database maintained by the NCI that provides a comprehensive listing of NCI-sponsored clinical trials, along with extensive and detailed listings of trials (including international trials) that are submitted voluntarily by cancer centers, private hospitals, and the pharmaceutical and biotechnology industries. The PDQ search engine allows searches by geographic location and site or investigators, as well as by tumor type, stage, and other relevant categories, and it provides contact information to facilitate patient referral when appropriate. In addition, PDQ provides detailed information about the treatment of many cancers, as well as information on screening, prevention, genetics, and supportive care. Useful information on insurance coverage for patients on clinical trials, including the coverage offered by specific insurance carriers, can also be obtained from www.cancer.gov.

The NCI site also provides a link to the Cancer Therapy Evaluation Program, which coordinates NCI-funded clinical trials in treatment across the country. The Cancer Therapy Evaluation Program Web site contains detailed information related to the conduct of clinical trials, including the following:

- Human research protections and the required online course for all research teams conducting NIH-funded research
- The Investigators' Handbook and other tools for protocol development
- Information on data-reporting requirements and on the monitoring and auditing of clinical trials

The Web site of the Division of Cancer Prevention (http://www3.cancer.gov/prevention/) provides similar information on the conduct of cancer prevention and control studies. Other NCI resources include the Cancer Information Service (1-800-4-CANCER), a telephone service that provides information in both English and Spanish, answers many patient questions, and refers callers to other resources when appropriate.

CONCLUSION

Although the involvement of oncologists in clinical trials introduces additional complexities to their practice of oncology, it also provides substantial benefits to all participants and ultimately contributes to the goals of improving cancer treatment and prevention. A growing number of clinical practices have been able to integrate active clinical research into their activities successfully. To help facilitate this participation, the NCI began a small pilot in 2002 to allow sites without Cooperative Group affiliation to join Group-led trials directly via the CTSU.[13] A number of sites became involved successfully, and the NCI developed a number of tools that are now available through the CTSU. These tools include IRB submission packets, protocol calendars, and summaries, among others (Box 23-3). It is envisioned that the availability of a central IRB nationally and an electronic data reporting system will eliminate critical barriers and will make it easier

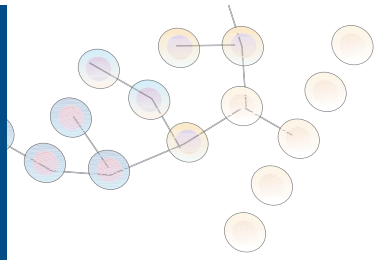
Box 23-3. USEFUL WEB SITES FOR CLINICAL TRIALS RESOURCES AND INFORMATION

National Cancer Institute: http://www.cancer.gov
Cancer Trials Support Unit (including links to cooperative groups): http://www.ctsu.org
Cancer Therapy Evaluation Program (CTEP): http://ctep.info.nih.gov
Community Clinical Oncology Program (CCOP): http://www3.cancer.gov/prevention/ccop
Cancer Centers Program: http://www3.cancer.gov/cancercenters
Central IRB: http://www.ncicirb.org
Physician's Data Query (PDQ): http://cancer.gov/cancerinfo/pdq

for community physicians to participate. Similarly, the biopharmaceutical industry continually seeks interested, conscientious physicians to participate in its trials. The shortage of such physicians creates a potentially serious limitation on the rate of development of new treatments for cancer. Surveys that have been done under the auspices of the Coalition of National Cooperative Groups suggest that the attitude of the treating physician is perhaps the most critical factor in patient enrollment in clinical trials.[2,5] With the right attitude, an increasing number of resources and tools are now available to make access to clinical trials a reality for many more patients, with the potential to benefit both themselves and future patients with cancer.

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24 Economic Analysis of Cancer Treatment

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SUMMARY OF KEY POINTS

- Cancer care accounts for the largest number of dollars spent on any medical condition in the United States.
- Cancer accounts for 10% of all Medicare expenditures.
- Fewer than half of the states have passed legislation mandating coverage of clinical trials.
- Cost-benefit, cost-effectiveness, cost-utility, and cost-identification analyses are the main methods for evaluating the economics of clinical interventions.
- Empirical studies have found that results of cost-effectiveness studies are associated with pharmaceutical versus not-for-profit funding, although quality is not.
- Few economic studies have been incorporated into clinical trials sponsored by the National Cancer Institute (NCI).
- To date, only seven NCI-sponsored clinical trials have included economic assessments.

CANCER CARE IS EXPENSIVE

The costs of treating patients with cancer contribute substantially to the United States' $1.6 trillion annual health care spending. In fact, the economic burden of cancer is the largest imposed by any medical illness. The high expense associated with cancer is related to a number of factors, including an increase in the prevalence of cancer as people live longer, the high rate of comorbid medical illness in cancer patients, and high costs associated with diagnosis, treatment, and end-of-life and palliative care as new, more expensive treatments become available. The direct costs of cancer care (spent for prevention, screening, diagnosis, treatment, and palliation) accounted for $61 billion in 2002.[1,2] Pharmaceutical costs, which have been growing rapidly, account for a large amount of cancer-related expenditure.[3]

Cost is a major determinant of the type and intensity of cancer care, particularly related to reimbursement of high-tech and high-cost procedures and pharmaceutical products for cancer patients.[4] The physician has a large role in determining the medical costs incurred by individual patients. Medical costs are categorized as (1) direct medical costs; (2) direct nonmedical costs, that is, amounts spent for caregivers and travel; (3) indirect costs, that is, the economic value of lost productivity due to illness, disability, and death (mortality); and (4) intangible costs, that is, costs associated with pain, suffering, and grief. Although several studies have evaluated the direct costs of various types of cancers, few include estimates of direct nonmedical, indirect, and intangible costs. Pilot studies indicate that these costs may be as high as 75% of the total cost of cancer care.[5,6]

In 2006, the most costly cancers for men were prostate cancer followed by lung and colorectal cancer; for women, the most costly cancers were breast cancer followed by colorectal and lung cancer.[7] In addition to considering total costs, it is important to consider the benefit (or value) provided by the intervention in exchange for the amount expended. The number of articles addressing cost-effectiveness of cancer treatments has increased dramatically in the past few years, a large number of these studies addressing supportive care agents.[8–10] Oncologists, insurers, and policymakers increasingly are addressing questions of costs, cost-effectiveness, and quality of life. Many changes have been made in this area since the late 1990s, particularly in relation to the costs of clinical studies. Previously, the national mandate to evaluate the effectiveness of health care, including cancer care, was designed to incorporate cost-effectiveness assessments. The U.S. Healthcare Research and Quality Act of 1999 gave a mandate to the Agency for Healthcare Research and Quality to focus on evidence-based technology assessments, which could then be incorporated by relevant people in the medical community into guidelines produced by physicians or medical societies. Unfortunately, cost considerations are not addressed explicitly in the current mandate. A few of the assessments will, however, provide information that may be applicable to cost-effectiveness analyses that can be conducted by others.

Clinical Trials and Their Reimbursement

The costs of cancer clinical trials have become an important issue related to cancer treatment over the past decade. Findings from pilot studies of about 1300 patients in phase II/III clinical trials estimate that costs ranged from 10% lower to 23% higher for clinical trials in comparison to control groups that received standard medical care.[8–14] On the basis of these findings, nearly half of U.S. states, Medicare, and several private insurers now cover the costs of patient care in "qualifying" clinical trials. Because of economic and other considerations, federal policies were not supportive of clinical trial reimbursement during the 1990s; Medicare excluded coverage of routine costs of care associated with clinical trial participation on the basis that such treatment was experimental or investigational.[10] However, a 1993 review found that Medicare was being billed millions of dollars for patients who received care in clinical trials.[12] The U.S. General Accounting Office estimated that Medicare had paid 50% to 90% of routine patient care costs in clinical trials because fewer than 4% of claims for clinical trial costs incurred by Medicare beneficiaries

were denied and oncologists often submitted bills for components of complex treatments without specifying the procedure itself.[14]

In the late 1990s, there were several unsuccessful proposals, such as the Medicare Cancer Clinical Trial Coverage Act and the Medicare Cancer Clinical Trial Demonstration Act, that would have allocated considerable funds to cover cancer clinical trials sponsored by the National Institutes of Health, the Department of Defense, and the Department of Veterans Affairs. Following years of lobbying by individuals, patient groups, health care workers, and organizations who were concerned about reimbursement denials of clinical trial costs and the low rates of accrual to clinical trials, a 2000 executive order authorized Medicare to cover the costs of any cancer clinical trial that satisfied qualifying criteria. Medicare has paid routine care costs (e.g., office visits and lab tests) for patients enrolled in federally funded clinical trials since 2000. The Centers for Medicare and Medicaid Services revised its National Coverage Determination for off-label use in cancer clinical trials in early 2005. Medicare now pays for both routine and nonroutine costs associated with the patient's care as well as the off-label use of some anticancer drugs.[15–17]

At the state level, the question put before some state legislatures has been whether insurance barriers to clinical research are best removed through voluntary action of health insurers or formal legislation. As of December 2006, 22 states had passed laws mandating coverage of patient care costs associated with treatment provided in specified categories of cancer clinical trials.[18] In the mid-1990s, Rhode Island became the first state to legislate insurance coverage for phase II clinical trials. Since then, Georgia mandated insurance for selected pediatric cancer trials in 1998, and Maryland and Virginia mandated insurance for cancer trials conducted in in-state academic institutions in 1999. Maine requires managed care organizations and private insurers to cover trials approved and funded by the NIH, a NIH-sponsored cooperative group or center, or the U.S. Department of Health and Human Services. Louisiana requires coverage of Phase II, III, and IV clinical trials that are approved by entities such as the Food and Drug Administration (FDA), the Department of Defense, the Veterans Administration, and the Coalition of National Cancer Cooperative Groups. The New Jersey Association of Health Plans agreement is unique in that all private insurers in a single state have voluntarily agreed to provide cancer clinical trial coverage. These coverage mandates are important because without third-party coverage, most patients are unable to bear the cost of participating in a clinical trial.

Today, public payers and several large private health insurers reimburse for medical care costs associated with clinical trials. Concern over variable scientific quality has led many state legislatures to limit reimbursement to trials funded by federal agencies. Moreover, many states have mandated clinical trial coverage by private and public payers for cancer trials but not for other medical conditions. This is in part due to the national infrastructure surrounding cancer trials, which is the most established and comprehensive of any disease clinical trials.

Economic Assessments in Cancer Care

Economic issues in cancer care are paramount in planning for optimal use of scarce resources and in responding to the increased economic pressures faced by the health care system. Physicians and health policymakers need to make judgments on the effectiveness and cost-effectiveness of cancer care based on explicit assessments of the costs and benefits of alternative management strategies. In other words, payers want assurance that expensive treatments are cost-effective. To understand the financial impact of alternative cancer management strategies more clearly, it is essential to understand the basic terminology of economic studies in health care: costs, benefits, cost-effectiveness, cost utility, and cost minimization. It also is important to explain the methods that policymakers and oncology researchers use when they evaluate the costs of cancer care.

When Are Economic Assessments Likely to Be Helpful (or Unhelpful)?

Assessments of the costs of cancer care can be considered when significant resources are being used, when resource considerations have a direct impact on patient care, and when resource allocation decisions are likely to be made.[19] Economic analyses also help to identify the most efficient option when two or more clinically efficacious interventions are available. Examples of situations in which a large amount of resources are used include use of supportive care agents such as antiemetics, erythropoietin, granulocyte colony-stimulating factor (GCSF), and genetic predictors. Resource considerations played a prominent role in the decision to support high-dose chemotherapy with stem cell transplantation for breast cancer before reports of unfavorable results were received from several randomized clinical trials. Economic analyses are unlikely to be helpful in cases in which a treatment works well but only a small number of individuals are affected, thereby limiting the overall cost impact. For example, advanced testicular cancer routinely is treated with chemotherapy. The cure rate is high, but the number of cases is fewer than 10,000 per year. Similarly, data have been collected on the economic implications of high-dose chemotherapy with stem cell transplantation for breast cancer, but they will not be useful to policymakers because this procedure has not been found to be clinically effective.

Types of Economic Analyses

Economic evaluations provide information on the value of an intervention or therapy in relation to its costs when compared to a competing alternative when, ideally, the alternative is the current standard of care. Economic evaluations of cancer interventions can range from decision analytic models to retrospective database comparisons to analyses conducted alongside clinical trials. However, all of the economic analyses of clinical interventions can be grouped into four categories based on the measure of effectiveness used in the analysis: cost-benefit (costs and benefits are measured in the same terms, usually monetary), cost effectiveness (costs measured in monetary terms, effectiveness in clinical terms), cost utility (costs measured in monetary terms, utility measured in terms of utility), and cost identification (costs measured in monetary terms, no effectiveness measurement).[20]

Cost-benefit analysis compares the incremental cost of a medical intervention with its incremental benefit, with both terms measured in monetary units. Therefore, interventions with positive net benefits, in which the value of the incremental benefits is greater than the incremental costs, are cost-beneficial compared to the alternative. In theory, cost-benefit analysis allows for the comparison of health interventions with other programs or interventions from non–health care sectors that may be competing for the same dollars. That is, with a cost-benefit analysis, a government could compare whether to spend monies on a new after-school program for children or use the same monies to fund a breast cancer screening program. However, difficulties in valuing all the relevant factors (e.g., years of life lost and quality of life) in monetary terms limit the use of cost-benefit analysis.

More commonly, economic evaluations in cancer care involve cost-effectiveness analysis. Cost-effectiveness analysis provides information about the value of an intervention or therapy in relation to its costs compared to a competing alternative when effectiveness is measured in clinical terms. The analysis compares two or more interventions and provides information about the differences in costs and effects between comparators. The results are summarized into a ratio that provides the results in terms of the costs per unit of effect. This ratio is referred to as the incremental cost-effectiveness ratio, because it is assessing incremental differences between alternative treatments. Because it is a cost-effectiveness analysis, the denominator of the ratio is valued in natural units, such as years of life, and is calculated by finding the difference in the effectiveness measure between the

alternatives. For example, many cost-effectiveness analyses in cancer treatments report the incremental cost per year of life saved.

Cost-utility analysis is a subset of cost-effectiveness analysis in which the measure of effectiveness is a utility or value. Utilities provide a measure of overall quality of life and are applicable across different types of cancer. The measure is intended to incorporate both positive and negative aspects of treatment. The utility is combined with information on survival to estimate quality-adjusted life years, which are used as the measure of effectiveness in cost-utility analyses. Thus, cost-utility analyses provide an estimate of the cost per quality-adjusted life year gained. In principle, this method can be used to compare the value of screening programs to new chemotherapeutic agents to gauge the relative value of an alternative.

The final type of clinical economic analysis used in cancer studies is cost identification. This technique reports the total types and amounts of resources used in providing medical care, without formal assessments of the clinical benefits of the treatment. This technique is an integral part of the other economic evaluations in that it provides the cost estimate used in the numerator. However, with this method, the benefits are not compared formally among alternatives.

It is important to emphasize that in all types of economic analyses, the way monetary units are assigned to treatments can make important differences. Specifically, costs differ markedly from charges.[21] Costs represent the true opportunity cost of a resource, whereas charges represent the amount that is billed for that resource. There might be little connection between costs and charges, charges typically being much greater than the actual costs. Therefore, it is important to be aware of whether costs or charges are being used to derive the economic estimates.

CANCER COSTS: ESTIMATES FROM MEDICARE POPULATIONS

Total medical care expenditures for oncology account for 10% of all Medicare expenditures.[22] Medicare Part A covers inpatient cancer care. Cancer-screening services are covered for cervical, breast, colorectal, and prostate cancer, and many types of chemotherapy and related treatments are covered under Part B. As of 2006, Medicare Part D provides a drug benefit that covers cancer drugs but requires significant financial contribution from patients who have prescription expenses more than $2,250.[23] In the future, prescription drug data will also be captured via Medicare Part D.

Recent studies have incorporated economic analyses for various cancers experienced by the Medicare population.[1,2,24] Costs have been evaluated for the initial phase, the primary course of therapy, and any adjuvant therapy, continuing care, including surveillance activities for detecting recurrences and new cancers, and the terminal care phase. Data for these analyses derive from the linked Surveillance Epidemiology and End Results (SEER) and Medicare database that includes detailed financial and clinical data elements for cancer patients who received care in 11 geographic regions of the country (see http://seer.cancer.gov). The database provides detailed information for inpatient services (Part A) and payments for outpatient services (Part B). The Medicare-SEER cost files were generated by reviewing monthly cost files for each cancer patient identified in the SEER database. Prices are adjusted using the Medicare per capita index and Medicare-based price indices that account for differences in health care purchasing power over time and location. These data are used to provide estimates of national expenditures according to type of cancer and gender.

Quality Assessment of Economic Analyses

Controversy exists over the quality of economic analyses of medical treatments and has led to the development of grading systems for economic evaluations.[25,26] The quality of the data and the models that are used in these analyses are the major determinants of the results. Additional items that are considered in the quality of economic evaluations include the objective and perspective of the analysis, data sources, type of comparison, handling of uncertainty, the time horizon of the analysis, and the discount rate. Other important considerations are the outcome measure that are used in the analysis, measurement of costs, measurement of effectiveness, and the overall transparency of the analysis (i.e., were the assumptions explicitly stated?).

Study sponsorship is gaining attention as concern has been raised over the potential for conflict of interest to bias the research, affect the design, and skew the interpretation of economic analyses of medical therapies.[27–29] The newness of pharmacoeconomics research and its potential effects on pharmaceutical company revenue make it particularly vulnerable to financial conflicts of interest. Researchers have examined the effects of conflict of interest on pharmacoeconomic research in breakthrough areas in oncology, such as hematopoietic colony-stimulating factors, antiemetics, and taxanes oncology. Published articles were classified according to qualitative conclusion, quantitative result, timing of study initiation, and funding source.

The first study found correlations between funding source and qualitative cost assessment, timing of study initiation, and discrepancies between qualitative conclusions and quantitative results. Favorable conclusions were reached by 81% of the pharmaceutical company-sponsored studies and 48% of the nonprofit-sponsored studies ($P < 0.009$). All of the studies that reached unfavorable conclusions had been sponsored by nonprofit organizations. Although nearly one fourth of the studies gave qualitative conclusions that overstated their quantitative results, this was not significantly greater for pharmaceutical company-sponsored studies than for nonprofit-sponsored studies.[27] More than 80% of economic studies funded by all sources were conducted after favorable clinical trial results were known. The findings of the study demonstrated a strong association between pharmaceutical company sponsorship and favorable economic assessments. Although there is no evidence of bias in individual articles, the results raised concerns about potential bias in pharmacoeconomic studies. Unfavorable cost profiles probably are underreported, and qualitative overstatements about the cost-effectiveness of new agents are not uncommon.

The second study addressed variations in study quality when the 44 pharmaceutical and not-for-profit-funded cost-effectiveness studies of the six breakthrough drugs in oncology were compared.[28] Investigators rated specific aspects of study reporting based on criteria from the U.S. Public Health Service Panel on Cost-effectiveness in Health and Medicine. Dissemination strategies were evaluated by using impact factor scores from the Science Citation Index. Operational aspects of pharmaceutical manufacturer–sponsored study reporting were better overall than were those associated with nonprofit-sponsored studies with respect to the following criteria: The results were more likely to be reported based on data obtained from randomized clinical trials or detailed cost models (90% versus 70%); to include descriptions of the source of cost differences (90% versus 79%); to state whether the study was carried out from a societal, governmental, or insurer perspective (70% versus 42%); and to indicate clearly the time period over which costs were evaluated (65% versus 50%). Nonprofit-sponsored studies were more likely than pharmaceutical-sponsored studies to report the generalizability of the findings to other clinical settings (58% versus 35%), to include statements on the statistical significance of the findings (38% versus 20%), and to clearly outline the cost per unit and data sources for the cost analyses (67% versus 45%). Most studies were published in low-impact-factor, peer-reviewed journals, and journal impact factor scores were similar between pharmaceutical- and nonprofit-sponsored studies. Overall, the study found differences in study reporting but not in types of journals where studies were published. These results, particularly with respect to differences in generalizability, may account in part for the finding that pharmaceutical manufacturer-sponsored studies were less likely to report unfavorable conclusions.

Strategies for Conducting Economic Analyses in Oncology

Because economic assessments are potentially useful as secondary endpoints in clinical trials of new cancer therapies or technologies,[19] cost analyses have been proposed alongside pivotal trials or new technologies. These are appropriate when investigational therapies are resource-intensive or when new technologies or treatments are likely to be used by large numbers of cancer patients. In most cases, these analyses are associated with phase III clinical trials, although inclusion in phase II trials can facilitate the collection of pilot data that can assist in study design for phase III trials. Phase IV studies also are possible sources of data for clinical and economic analyses. Estimates of the potential difference in costs between treatment arms can be helpful to coverage determinations.

The perspective of the economic analysis varies in many of the reported cost-effectiveness analyses. Most commonly, the perspective is that of the third-party payer; however, the societal perspective should also be considered.[21] Many clinical trials report economic data that are based on a "modified" societal perspective; that is, direct medical costs are quantified as societal costs, while direct nonmedical and productivity costs are not evaluated. Data collection can be prospective or retrospective. Prospective studies allow for timely assessment of clinical and economic outcomes at the end of the study. Detailed information on direct medical, direct nonmedical, productivity, and intangible costs can be obtained if careful planning is done before the study begins. Retrospective economic assessments are far less costly to conduct, but they include information on only a limited perspective (generally the third-party payer perspective).

The time interval from randomization to follow-up can influence the findings of the economic analysis, if follow-up is short. Ideally, the time horizon should be the same for the clinical and the economic analysis and should allow for realistic outcome measurement. Some economic analyses consider intermediate outcomes (e.g., response rate); other cost analyses are based on a review of final outcomes (e.g., survival in months or years). In either case, the outcomes should be identified prospectively. Despite increasing discussion about methodologies and practical approaches to including economic analyses in randomized clinical trials, remarkably few of these assessments have been reported in the literature. The National Cancer Institute (NCI)–sponsored Cooperative Trials Groups reported only one prospective and six retrospective economic analyses.[30–35]

One can argue that cost data should be considered as important as clinical data and should be subjected to quality control assessments. Most of the literature related to cost analyses in cancer has been based on retrospective assessments of clinical trials, and these retrospective reviews generally have been funded by the pharmaceutical industry. Combining economic studies and clinical trials requires targeted funding, staff, and cooperation between clinical and economic researchers and analysts. Few independent nonprofit groups have the funds to supported economic analyses. Hence, concerns exist about researcher independence. One privately funded economic assessment of autologous stem cell transplant studies for breast cancer, for example, did not reveal the economic findings until after the clinical trial results were reported as negative. The savvy reader of economic analyses needs to think about the sponsor of a study and that group's motivation for undertaking a study and reporting its findings.

Economic Analyses Conducted by Cancer Clinical Trials Groups

During the 1990s, the NCI supported efforts to integrate economic analyses into cancer clinical trials.[19,20] In 1994, the NCI sponsored a conference with representatives of cancer centers and cooperative groups that addressed the importance, appropriateness, and

Table 24-1 Completed Economic Analyses Conducted by National Cancer Institute-Sponsored Clinical Trials Groups

Study	Treatment Arms	Effectiveness Time Frame	Economic Time Frame	Method	Outcome
Radiation Therapy Oncology Group 90-03 and 91-04[37]	Brain metastases; head and neck cancer	Not measured	Months	Cost estimation	90-03 costs estimated well; 91-04 costs not estimated very well
Eastern Cooperative Oncology Group 1490[35]	GM-CSF vs placebo for older	Weeks	Weeks	Cost minimization	GM-CSF was cost saving, and adults with AML decreased infections
Southwest Oncology Group 9031[33]	GCSF vs placebo for adults with AML	Weeks	Weeks	Cost minimization	GCSF did not add additional costs and decreased hospital stay
Southwest Oncology Group 9509[30]	Vinorelbine + cisplatin vs paclitaxel + carboplatin for non–small cell lung cancer	Months	24 months	Cost minimization	Cisplatin + vinorelbine is less costly
Children's Cancer Study Group[32]	GCSF vs placebo for children with leukemia	Weeks	Weeks	Cost minimization	GCSF did not add additional costs and was associated with shortened duration of neutropenia
Pediatrics Oncology Group[36]	GCSF vs control for children with leukemia	Weeks	Weeks	Cost minimization	GCSF did not add additional costs and was associated with shortened duration of neutropenia
Children's Cancer Study Group 1881, 1882, 1891, 1901, 1922, 1941[31]	Acute leukemia—various treatments	Years	Months	Cost effectiveness	Delayed intensification, augmented therapy, and dexamethasone therapy cost-effective vs treatment of first relapse

AML, acute myelogenous leukemia; GCSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte macrophage colony-stimulating factor.

complexity of these evaluations. The next year, the American Society of Clinical Oncology (ASCO) established a Health Outcomes Working Group, which was charged with developing specific guidelines for implementing economic evaluations in cancer clinical trials.[20] In 1996, the NCI and ASCO convened a second meeting, attended by experts from the NCI-sponsored cooperative groups, NCI staff, and experts in the field of health economics, to consider the practical implementation of economic evaluation in cancer clinical trials. In 1998, a workbook that served as a developing guide designed to be used as practical reference for subsequent economic analyses of cancer clinical trials was published.[17] The first articles describing economic analyses alongside clinical trials conducted by the NCI-sponsored cooperative groups were published in 1997.

Table 24-1 provides information on seven NCI-sponsored studies that have been published to date. The following summary considers some of these real-life examples of the methods and operational considerations researchers face when conducting cancer clinical trials. The first cost-effectiveness study of an NCI-sponsored cooperative group trial was reported in 1997 by investigators who were affiliated with the Children's Cancer Study Group.[32] The clinical trial evaluated the clinical and cost-effectiveness of GCSF as an adjunctive therapy for children with acute lymphoblastic leukemia. The study randomized 164 children and found a reduction in the duration of neutropenia (5.3 versus 12.7 days) and duration of hospitalization (6 versus 10 days). Cost-minimization analyses indicated that GCSF did not add additional costs. Clinical and economic data were obtained directly from the clinical trial participants.

The second economic analysis of an NCI-sponsored cooperative group trial was reported in 1999 by investigators who were affiliated with the Eastern Cooperative Oncology Group.[35] The randomized clinical trial evaluated the clinical effectiveness of the hematopoietic cytokine, granulocyte macrophage colony-stimulating factor (GM-CSF), as an adjunctive therapy for people 55 years of age or older who were receiving induction chemotherapy for acute myeloid leukemia. Patients receiving GM-CSF experienced a 72% reduction in severe infections, four fewer days with an absolute neutrophil count lower than 500 cells/mL, but no significant difference in the duration of hospitalization compared to the group taking the placebo. Decision analytic modeling was used to analyze the costs of GM-CSF use during induction therapy. Clinical probabilities of acquiring an infection were obtained from the clinical trial data; hospital costs per day for infected and uninfected patients were obtained from billing data from seven sites participating in the clinical trial. The significant improvements in rates of severe infections were associated with an estimated $2310 in cost savings per patient. The reduction in costs was particularly evident among individuals who received two cycles of induction chemotherapy. The study was conducted over a six-month period, with funding for the study provided by the pharmaceutical manufacturer.

A retrospective economic analysis of a randomized clinical trial conducted by the former Pediatrics Oncology Group[36] compared the costs of inpatient supportive care for pediatric patients (age 1 to 22 years) with T-cell leukemia and advanced lymphoblastic lymphoma. Patients received either GCSF ($n = 45$) or no GCSF ($n = 43$) following induction and two cycles of maintenance therapy. During maintenance therapy, the patients receiving GCSF had significantly fewer days to an absolute neutrophil count above 500 cells/μL and a trend toward fewer days of hospitalization. The study found that the total median costs of supportive care were similar for all patients in the study. Data on resource utilization were tabulated from case report forms, and costs were derived from national data on hospitalization costs, average wholesale prices of pharmaceuticals, and patient billing information from a single institution. The four-month study was conducted with support from the Cooperative Clinical Trial Group and the pharmaceutical supplier of the study drug.

In 2001, the Radiation Therapy Oncology Group (RTOG)[37] initial pilot study addressed four aims: (1) measurement of radiation therapy treatment costs for patients treated in different arms of two randomized controlled clinical trials, (2) comparison of measured costs to those predicted by an economic model, (3) examination of the distribution of costs among patients treated on the same arm, and (4) assessment of the feasibility of retrospective data collection effort. The RTOG selected two phase III clinical trials to evaluate in this pilot effort. The first study, RTOG 91-04, compared standard treatment to a total dose of 30 Gy with a second arm of accelerated hyperfractionation to a total dose of 54.4 Gy for cancer patients with brain metastases. The second study, RTOG 90-03, was a phase III study of patients with squamous cell carcinomas of the head and neck who received either standard fractionation to a dose of 70 Gy, hyperfractionation to a dose of 81.6 Gy, accelerated fractionation with a split to a total dose of 67.2 Gy, or accelerated fractionation with a concomitant boost to a total dose of 72 Gy. Expected quantities of procedure codes and relative value units associated with Medicare billing efforts were modeled. The median and mean relative value units were within the range predicted by an economic model for all arms of the head and neck cancer study but were above the predicted range for the brain cancer study. Some of the researchers encountered considerable difficulties in collecting the retrospective economic data, suggesting that prospective data collection might be the better strategy for economic analysis of RTOG studies. Clinical trials with complex treatment protocols, such as the head and neck cancer study, appeared particularly difficult to include in retrospective economic analytic efforts.

Nonfinancial metrics can be reported. One study, for example, reported on the feasibility of using duration of hospitalization as a surrogate for cost and event-free survival as a measure of effectiveness to estimate cost-effectiveness ratios of various treatment regimens evaluated in clinical trials of children with acute lymphoblastic leukemia.[26] Metrics included marginal cost-effectiveness estimates of the number of days per patient for delayed intensification and for augmented therapy and relapse-adjusted "savings" associated with augmented therapy (16 days) and with dexamethasone-based therapy (82 days). The study was supported by grants to the office of the cooperative group's chairman and indicated that retrospective economic analyses were feasible, provided that the economic analyses focused on duration of hospitalization.

Researchers affiliated with the Southwest Oncology Group conducted the first prospective economic analysis of a randomized clinical trial conducted by an NCI-sponsored cooperative clinical trial group.[30] The clinical trial included patients who were randomized to receive cisplatin plus vinorelbine versus carboplatin plus paclitaxel. The findings from this study indicated that prospective economic analyses could be conducted alongside randomized clinical trials, although these efforts did require external funding and committed resources from the statistical operations center of the cooperative clinical trial group.

This review of the design, outcome metrics used, and sponsorship of these studies is instructive in identifying potential opportunities and obstacles for future research. Most studies were based on retrospective economic analyses. Funding sources were diverse, most of the analytic efforts being supported by pharmaceutical suppliers.

CONCLUSIONS

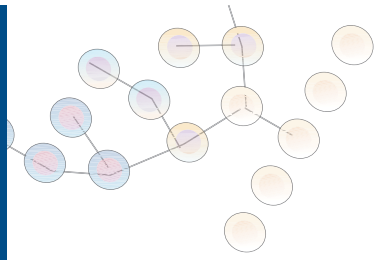
U.S. health care expenditure on cancer care is greater than expenditure for any other illness. It is important to consider both the clinical benefit and the economic value provided by cancer treatment interventions, particularly during their development. Economic tools (cost-benefit, cost-effectiveness, cost-utility, and cost-identification analyses) can provide such information. Despite increases in coverage for patients in "qualifying" clinical trials by Medicare, several private insurers, and many U.S. states, few robust economic analyses have been conducted in trials sponsored by the NCI. Clinical trials that incorporate cost analyses can contribute to an understanding of

the value of an intervention and can do so from a variety of perspectives.

Costs of cancer care can be evaluated in a variety of clinical settings. Economic considerations have important practical implications for oncologists and should be addressed for most new cancer treatments and procedures. Continuing economic pressures facing the health care system in the United States serve as an important reminder of the importance of unbiased cost analyses, particularly for cancer treatments. Despite nearly universal support for economic information, the paucity of cost-effectiveness analyses, especially studies that are not funded by the pharmaceutical industry, is particularly worrisome. Policymakers and physicians strive to make informed decisions about rational allocations of cancer resources. Economic data, if properly obtained, can assist in these decisions.

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25 Use of Epidemiology in Oncology

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SUMMARY OF KEY POINTS

Epidemiology is a design and analytical method used to investigate disease occurrence in human populations. Epidemiology encompasses several different design approaches, including randomized trial and observational approaches; this chapter focuses on observational approaches.

- Epidemiologic methods can be used to address a wide range of hypotheses in biomedical research, including translational and clinical hypotheses generated in oncology.
- To determine the optimal epidemiologic approach for addressing questions in oncology, research questions should be restated as testable hypotheses.
- Elements in the design of studies using observational epidemiologic methods should include the following:
  - Defining the target, source, and study populations
  - Defining the endpoint of interest (e.g., development of disease or recurrence of disease)
  - Defining the factor of interest (e.g., exposures, markers of susceptibility, markers of biological pathways influenced by both genetic and nongenetic factors, characteristics of premalignant lesions, cancer cells/tumors, and surrounding tissues)
  - Choosing the most appropriate study design, the prospective cohort or derivative designs, or the case-control study
- Testing a hypothesis usually involves comparing the occurrence of the endpoint in two or more groups that differ on a factor of interest.
  - Measures of occurrence of an endpoint in a study using the cohort design include the cumulative incidence (risk), which conveys the probability of the endpoint, or the incidence rate, which conveys how fast the endpoint is occurring in a population at risk.
  - Comparing the endpoint occurrence between two groups may involve comparing survival curves or quantifying the magnitude of the difference in the endpoint occurrence using ratio measures such as the *cumulative incidence ratio*, *rate ratio*, or *hazard ratio*, collectively known as the *relative risk* of the endpoint in cohort studies, or the odds ratio in case-control studies.
- The design, statistical analysis, and inference of an observational epidemiologic study should be motivated by temporality and comparability considerations.
  - *Temporality* means that the factor of interest must necessarily precede the occurrence of the endpoint. Lack of temporality can lead to the false conclusion that a factor caused an endpoint or that the factor has predictive capability for a future endpoint.
  - *Comparability* means that the only difference between two or more groups being contrasted is the factor of interest. Lack of comparability can lead to selection bias, observation bias, and confounding, all of which can lead to false conclusions.
- After considering alternative explanations for an epidemiologic finding (selection bias, observation bias, confounding, and chance variability), investigators still cannot conclude that the observed association reflects causation. In epidemiology, any given research question must be evaluated many times using different designs and study populations, and usually by independent investigators.
  - Each epidemiologic study design has a different potential for each type of bias.
  - In general, prospective cohort studies and derivative designs provide stronger evidence for a causal association than case-control studies because they maintain temporality and are less susceptible to selection and observation biases. Although both prospective studies and randomized trials are likely to have the correct temporal sequence, evidence from trials usually trumps evidence from prospective studies because randomization reduces the likelihood of selection bias and confounding.
  - Different study populations may have different characteristics that influence the likelihood or extent of unmeasured or residual confounding.
  - Chance variability is possible in any study.
- When considering whether an observed association between a factor and endpoint is causal, some investigators find it useful to think about the nine "aspects" of an association that Sir Austin Bradford Hill described: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy.
  - Temporality is highlighted in this chapter because it is the only aspect of an association necessary for causality; the other aspects do not rule in or rule out the potential for an association to be causal.
- Obtaining correct inferences from observational epidemiologic studies in oncology hinges on the appropriate study population, design, and analysis, all of which require epidemiologic thinking. For this reason, a multidisciplinary research team that includes collaborators from clinical science, basic science, biostatistics as well as epidemiology is optimal for addressing the complex translational and clinical questions posed in modern oncology.

EPIDEMIOLOGY

Epidemiology is a design and analytical method used to investigate disease occurrence in human populations. Although traditionally used to test hypotheses about disease causation, epidemiologic methods also can be used to address a wider range of hypotheses in biomedical research, including translational and clinical hypotheses generated in oncology. Epidemiology encompasses several different design approaches, including experimental (randomized trial) and observational approaches, but this chapter focuses on observational approaches. To motivate the use of epidemiology in oncology, two hypothetical translational and clinical research questions are posed and used to illustrate concepts and approaches throughout this chapter:

1. *Prognosis:* Basic scientists recently have identified a protein expressed to a greater extent in high- than low-grade prostate tumors and not expressed in normal adjacent epithelium. This protein can be measured in tissue using a newly developed sensitive technique. To help identify which men with prostate cancer should receive adjuvant therapy following prostatectomy, investigators would like to know whether high expression of this protein predicts prostate cancer recurrence after prostatectomy independent of known prognostic characteristics.
2. *Therapeutic effectiveness:* Researchers have determined that a gene encoding a particular P450 metabolic enzyme enhances the action of a chemotherapeutic agent currently being evaluated in combination with standard therapy for treatment of non-Hodgkin's lymphoma. To help determine which patients with non-Hodgkin's lymphoma may benefit most from this new chemotherapeutic agent, investigators would like to know whether a particular haplotype in the gene that encodes the P450 metabolic enzyme predicts overall survival after treatment with the chemotherapeutic agent in combination with standard therapy.

STATING RESEARCH QUESTIONS AS HYPOTHESES TESTABLE USING EPIDEMIOLOGIC METHODS

To determine the optimal epidemiologic approach for addressing translational and clinical research questions in oncology, the research questions should be restated as testable hypotheses. Stating a research question as a testable hypothesis involves determining which groups should be compared. For instance, the *prognosis* and *therapeutic effectiveness* research questions can be restated as testable hypotheses as follows:

Prognosis: To test whether patients with high expression of the tissue marker are more likely to recur after prostatectomy than patients with low expression of the tissue marker.

Therapeutic effectiveness: To test whether patients with non-Hodgkin's lymphoma with a particular haplotype are more likely to survive than patients without the haplotype after treatment with the new chemotherapeutic agent in combination with standard therapy.

ELEMENTS IN THE DESIGN OF STUDIES USING EPIDEMIOLOGIC METHODS

Defining the Target, Source, and Study Populations

Once the research question is defined and stated as a testable hypothesis, the population (*source population*) from which study participants (*study population*) will be drawn can be identified. In selecting the source population, investigators should be cognizant of all patients who may benefit from the results of the study (*target population*), beyond those included in the study (Fig. 25-1).

In the cancer center setting, several source populations from which the study population can be drawn typically are readily available (*convenience sample*): patients seeking screening and risk reduction options because of elevated risks of specific cancers; patients referred because of signs or symptoms suggestive of cancer; patients presenting with newly diagnosed cancer for treatment or a second opinion; patients under surveillance during and after completing treatment; and patients seeking salvage or palliative care for recurrence. For the two hypothetical research questions, possible source populations might be the following:

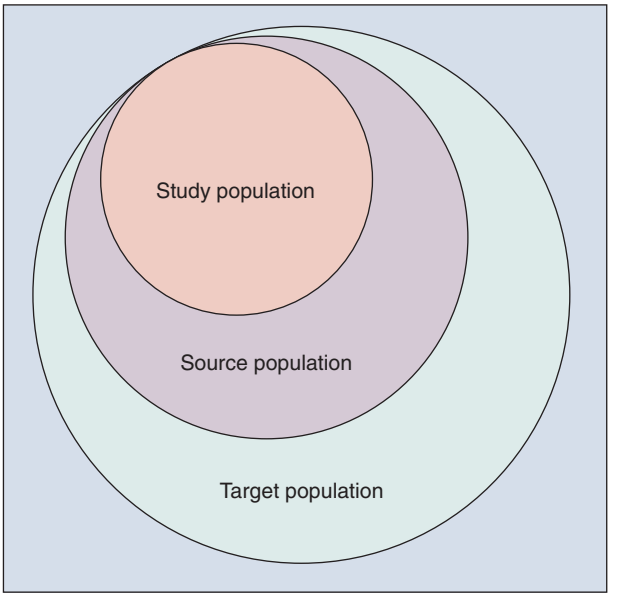


Figure 25-1 • Relationships among study, source, and target populations.

Prognosis: Patients newly diagnosed with prostate cancer eligible for prostatectomy.

Therapeutic effectiveness: Patients with non-Hodgkin's lymphoma eligible to receive the new chemotherapeutic agent.

Although they provide a good start, these definitions of the source population still are too broad. The source population should be narrowly defined with respect to person, place, and time. Doing so reduces the heterogeneity among individuals under study to help investigators draw sound inferences. For the two hypothetical translational and clinical research questions, the source populations can be more narrowly defined as follows:

Prognosis: Men newly diagnosed with clinical stage T1c or T2 prostate adenocarcinoma who underwent radical retropubic prostatectomy between 1993 and 2002 at one academic hospital and for whom resected prostate tissue was collected and stored.

Therapeutic effectiveness: Adult men and women newly diagnosed with diffuse large B-cell lymphoma randomized to the new chemotherapeutic agent arm of a multicenter clinical trial evaluating the efficacy of this agent in combination with standard therapy. All trial participants were required to have a histologically confirmed diagnosis of diffuse large B-cell lymphoma according to the World Health Organization Lymphoma Classification, to be less than 60 years of age, to be CD20-positive, and to have at least two risk factors according to the Age-Adjusted International Prognostic Index. Participants were enrolled in 2000 and followed for 5 years.

The study population typically is a subset of the source population. Reasons for not including all individuals from the source population in the study include feasibility issues, such as assay cost and throughput; patient willingness to participate; and availability or

completeness of medical records and biologic specimens. For instance, in the *prognosis* example, the investigators may have intended to enroll all men with early-stage prostate cancer treated by radical prostatectomy from 1993–2002. However, some men may have chosen not to participate and, therefore, were not included in the study population, although they were included in the source population. Alternatively, the investigators may assemble the study population in 2007 by searching the medical records for men who underwent prostatectomy for early-stage prostate cancer between 1993 and 2002. Some of these men may no longer have archived prostatectomy specimens and, thus, cannot be included in the study population, despite being in the source population.

In the *therapeutic effectiveness* example, the source population is the group of participants consented and randomized to the new chemotherapeutic agent arm of the trial. At the outset, participants may have been asked to provide consent for both randomization to treatment and collection of blood specimens for genetic testing, including testing for the new clinical research question. In this case, the source and study population are one and the same. Alternatively, the new clinical research question may have been posed subsequent to the start of the trial. In this case, the investigators would have had to approach participants at a later trial visit to collect blood specimens for genetic testing. The study population might then differ from the source population because some participants might not have consented to this new correlative study or some might no longer have been participating in the trial because of death or other reasons for withdrawal. Investigators should always consider reasons for differences between the source and study population, as these may affect the results of the study (see section on Comparability).

As stated earlier, when selecting the source population, investigators always should be aware of the target population. For the two hypothetical translational and clinical research questions, possible target populations might be the following:

Prognosis: Men newly diagnosed with clinically organ-confined prostate cancer.

Therapeutic effectiveness: Adult men and women less than 60 years of age newly diagnosed with CD20-positive diffuse large B-cell lymphoma with at least two risk factors according to the Age-Adjusted International Prognostic Index.

Although study populations should be representative of the target population when estimating the occurrence of disease or factor in the target population (e.g., Americans living with cancer in 2007), the source and study populations do not necessarily have to be representative of all patients in the target population when addressing translational or clinical research questions that involve comparing the experiences of two or more groups.

For instance, in the *therapeutic effectiveness* example, members of the study population may be more likely to be white, younger, and healthier, on average, than members of the target population. This difference might arise because members of different groups may choose to participate to differing extents even when effort is made to recruit adequate proportions of each group. Given this difference, an important question to consider is whether findings from the study population will apply to the broader target population. For example, if the new chemotherapeutic agent trial is conducted primarily among white, younger, and healthier patients and it is known that white individuals have a higher frequency than non-white individuals of the haplotype that produces a version of the P450 enzyme that enhances the action of the new agent, would the finding that white patients with the haplotype are more likely to survive after treatment than white patients without the haplotype also apply to non-white patients? All else being equal, it might be expected that the findings would apply; what might differ is the percentage of patients in a particular racial or ethnic group who have the beneficial haplotype and who would thus benefit from treatment with the new agent. Of course, if all else is *not* equal, then the findings might not apply perfectly. For example, if non-white patients tend to have more comorbidities for which they are simultaneously prescribed other medications that compete for activation by the enzyme, then the new agent might be less effective in non-white patients with the haplotype than in white patients with the haplotype. Thus, the gain in survival with the haplotype would appear to be lower in non-whites than in whites. Note that in this example the new agent might still be equally as effective in white and non-white participants with the haplotype who do not have comorbidities, and less effective, but equally so, in white and non-white participants with the haplotype who have comorbidities and are taking the same array of drugs activated by the enzyme.

Therefore, the message is: Before embarking on a study, contemplate the likely generalizability of the findings to other groups of patients beyond those who are most likely to participate in a translational or clinical research study. Then, at the minimum, collect adequate information to characterize the study population so that differences between the participants and the target population are known, and, optimally, design the study and enroll members of the target population so that differences in findings among key segments of the target population may be determined directly.

Defining the Endpoint of Interest

Once the study population is defined, a detailed definition of the endpoint of interest (*case definition*) should be developed. Depending on the translational or clinical research question, a wide range of endpoint definitions is possible in oncologic research. These include cancer-specific endpoints, such as cancer diagnosis, which can be further divided by stage (e.g., localized versus advanced stage), histology, or expression of specific receptors; cancer recurrence or progression; or cancer-specific death. Other possible endpoints include diagnosis of second cancers, death from all causes, or short- and long-term complications of treatment among cancer survivors (e.g., cognition, peripheral neuropathy, or neutropenic sepsis). Optimally, the case definition should be narrow and specific to limit the endpoint spectrum to only those relevant or believed to be relevant to the factor of interest. For the *prognosis* and *therapeutic effectiveness* examples, the endpoint definitions might be as follows:

Prognosis: Prostate cancer recurrence as defined by a rise in serum prostate-specific antigen (PSA) concentration >0.2 ng/mL on two consecutive tests, metastasis, or death from prostate cancer as the underlying cause.

Therapeutic effectiveness: Death from diffuse large B-cell lymphoma as the underlying cause.

Although the endpoint definition ideally should be narrowly defined, investigators tend to use broader endpoint definitions to increase the number of cases. In doing so, however, they may include more cases not related to the factor of interest. In the *prognosis* example, if the tissue marker is expressed only in those cases that have the potential to metastasize and cause death, then the case definition—serum PSA concentration >0.2 ng/mL on two consecutive tests, metastasis, or death from prostate cancer as the underlying cause—is a *sensitive* case definition; the investigators are unlikely to miss cases that ultimately will metastasize and result in death. On the other hand, this case definition is not very *specific*; many of the men who only have PSA recurrence might never develop metastases or die from their prostate cancer.

The undesired effect of a heterogeneous population of cases, which increases the opportunity for including cases that are not related to the factor of interest, is that the association between the factor and the endpoint will be diluted. One way to investigate the possibility of a heterogeneous case mix is to perform separate analyses by characteristics of the endpoint, for example, by PSA recurrence only or by metastasis and death from prostate cancer, or, more generally, by tumor histology, tumor-node-metastasis stage, differentia-

tion status, location in the organ, size, and known molecular markers (e.g., estrogen/progesterone receptor positivity in breast cancer, *BCL/ABL* translocation in chronic myelogenous leukemia).

Defining the Factor of Interest

As for the endpoint of interest, the factor of interest in oncologic research also can be wide-ranging, and does not need to be limited to a simple dichotomy of exposed and unexposed. Depending on the translational or clinical research question, the factor of interest can be the following:

- Exposures, whether measured in a participant's environment (e.g., air pollution, cigarette advertisements); as the participant's behaviors and their extent (e.g., pack-years of cigarette smoking, frequency of intake and dose of selenium from the diet and supplements, cancer screening uptake and frequency, frequency and dose of prescription medications, or reproductive history); or in the participant's blood or target organs (e.g., biomarkers of internal dose of selenium or DNA damage caused by ingestion of heterocyclic amines formed in charred meat)
- Markers of susceptibility, whether measured as germline genetic variation, inherited epigenetic variation (e.g., imprinting), or, possibly, family history of cancer as a surrogate for susceptibility
- Markers of biological pathways influenced by both genetic and nongenetic factors (e.g., age at menarche and menopause, circulating sex steroid hormones, or tissue cytokines)
- Characteristics of premalignant lesions, cancer cells/tumors and surrounding tissues (e.g., altered protein/receptor expression, gain or loss of CpG methylation, chromosomal aberrations, or telomere shortening) among other attributes of the individuals, their tissues, their cancers, and their environments.

In the two hypothetical translational and clinical questions, definitions of the factors of interest might be as follows:

Prognosis: Expression of the tissue marker in foci of prostate adenocarcinoma as detected by image analysis. A composite measure of immunohistochemical staining intensity and the proportion of cells staining positive is used. For possible future use in the clinic, the distribution of the composite measure is dichotomized as high versus low expression.

Therapeutic effectiveness: Carrying no copies versus at least one copy of the specified haplotype that is known to encode a catalytically more active version of the P450 enzyme. Germline DNA extracted from peripheral blood lymphocytes is used to determine haplotypes.

Note that for these particular examples, the factors of interest have been dichotomized for greater ease of description in later analytic sections, although more complicated expressions of the factors could be used (e.g., tissue marker—continuous expression or none, low, medium, high expression; haplotype—0, 1, or 2 copies).

In defining the factor of interest, investigators must consider the most relevant and feasible measure of the factor (*factor definitions*) in relation to the endpoint. For the *prognosis* and *therapeutic effectiveness* examples, the definitions of the factors of interest are relatively straightforward because the investigators can measure the most relevant factors directly at the most relevant times relative to the endpoint. In the *prognosis* example, the investigators are interested in testing whether patients with high expression of the tissue marker in the tumor are more likely than patients with low expression to have recurrences after prostatectomy. The most relevant factor of interest in this case is expression of the tissue marker in the cancer at the time of prostatectomy. In the *therapeutic effectiveness* example, the investigators are interested in testing whether patients with diffuse large B-cell non-Hodgkin's lymphoma with a particular haplotype are more likely to survive than patients without the haplotype after treatment with the new chemotherapeutic agent in combination with standard therapy. In this case, the most relevant factor of interest is a particular haplotype in the gene encoding one of the P450 enzymes. The time at which haplotypes are determined is less important because germline haplotypes remain the same throughout life.

Although the factor definitions for the hypothetical examples were relatively straightforward, there may be other situations in which the factor of interest is much more difficult to define. As an example, in a prognostic study of prostate cancer, the investigators may be interested in testing whether obesity is related to prostate cancer recurrence. However, deciding which is the most relevant measure of obesity (e.g., self-reported or measured/calculated weight, body mass index, waist-to-hip ratio, or percent body fat) and the most relevant and feasible time to measure obesity (e.g., at the time of prostatectomy, in the 10 years before prostatectomy, or in adolescence) may be difficult.

For instance, the most feasible factor for the investigators to measure might be body mass index calculated from self-reported weight and height at the time of prostatectomy, but the most relevant factor for prostate cancer prognosis might be the amount of adipose tissue at the time of prostatectomy. If the investigators choose to use the most feasible factor, then they may observe a weaker association between self-reported body mass index and prostate cancer recurrence than if they had used percent body fat depending on how well self-reported body mass index correlates with the amount of adipose tissue at the time of prostatectomy.

As a more extreme example, if the most relevant factor is the amount of adipose tissue during adolescence (at the time of prostate maturation), but the investigators choose to use the most feasible factor, then they may not observe an association between self-reported body mass index at the time of prostatectomy and prostate cancer recurrence if self-reported body mass index is not correlated (or not sufficiently correlated) with the amount of adipose tissue during adolescence. The investigators might then conclude that obesity is not associated with prostate cancer recurrence, even though obesity during adolescence might be important for prostate cancer prognosis. Therefore, the investigators must carefully consider the factor definition in relation to the proposed hypothesis. Defining and assessing the factor is an art, and may involve trade-offs in feasibility, accuracy, and relevance.

Design Considerations for Causal Inference: The Cohort Study

The typical goal of studies using epidemiologic methods, including translational and clinical studies, is to evaluate whether a factor is causally related to an endpoint of interest. Important considerations in drawing causal inferences include assessment of temporality and comparability.

Temporality

For a factor to be causally related to an endpoint of interest it must necessarily precede the occurrence of the endpoint; that is, *temporality* must be established. This is accomplished in experimental designs, whether in the laboratory or in a clinical trial, by randomly assigning a factor to laboratory animals or human participants, respectively, who do not currently have the endpoint of interest, and then observing these animals or participants over time for endpoint development. Therefore, in these designs it is clear that the factor preceded the endpoint. By contrast, in observational studies, investigators do not assign the factor to study participants. Rather, the investigators measure the existing factor status. Optimally, to establish temporality, the investigators measure the factor in individuals who have not yet experienced the endpoint of interest, but who are at risk for the endpoint, and then they follow those individuals over time for endpoint development. This design is called the *prospective cohort study* (Fig. 25-2). *Prospective* indicates that the factor status and its assessment predate the development of the endpoint. *Cohort study*

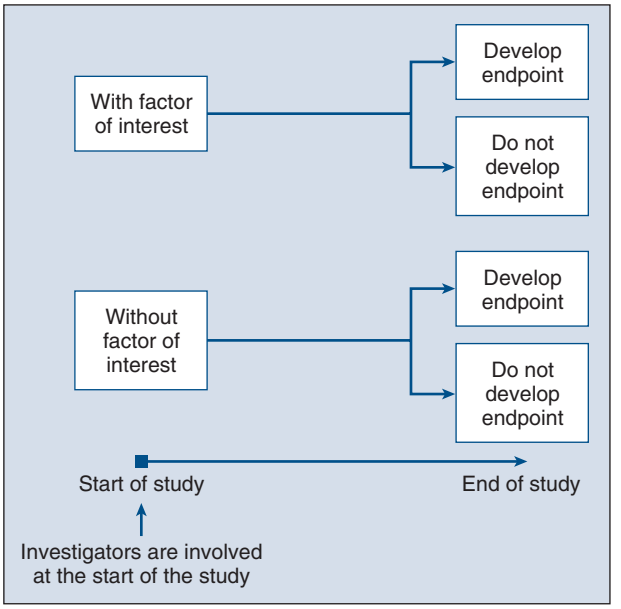


Figure 25-2 • Schematic of the prospective cohort study.

denotes follow-up of a specified group of initially endpoint-free individuals over time for endpoint development. In a simple analysis of the data from a prospective cohort study, the investigators compare the extent of occurrence of the endpoint in those with and without the factor. The prospective cohort study is the gold standard observational design. Returning to the two hypothetical translational and clinical questions, the prospective cohort design is illustrated as follows:

Prognosis: Cohort members are enrolled at the time of prostatectomy. Expression of the marker is assessed in foci of prostate adenocarcinoma from tissue resected at prostatectomy. Cohort members are followed through 2006 (maximum follow-up of 14 years) for recurrence. The frequency of recurrence is compared between those with high and low expression of the tissue marker (Fig. 25-3A).

Therapeutic effectiveness: Cohort members are trial participants randomized to the new chemotherapeutic agent arm. Presence or absence of the haplotype is determined from peripheral blood lymphocytes collected at the start of the trial. Patients are followed through to the end of the trial for death from diffuse large B-cell lymphoma. Survival is compared between those with and without the haplotype. Note that, although the parent study is a randomized clinical trial (of the efficacy of a new chemotherapeutic agent in combination with standard therapy versus standard therapy alone), this example question is not itself investigated using the randomized trial design because participants are not randomized to the factor of interest—haplotype for the gene encoding the enzyme (Fig. 25-3B).

As an alternative to the prospective cohort study design, the investigators may instead identify a cohort of individuals and reconstruct their past factor status using pre-existing records or specimens. This design is called the *retrospective cohort study* (Fig. 25-4). In this case, *retrospective* denotes that the factor status predates endpoint development, but the assessment of the factor postdates endpoint development. Otherwise the approach is the same as in a prospective

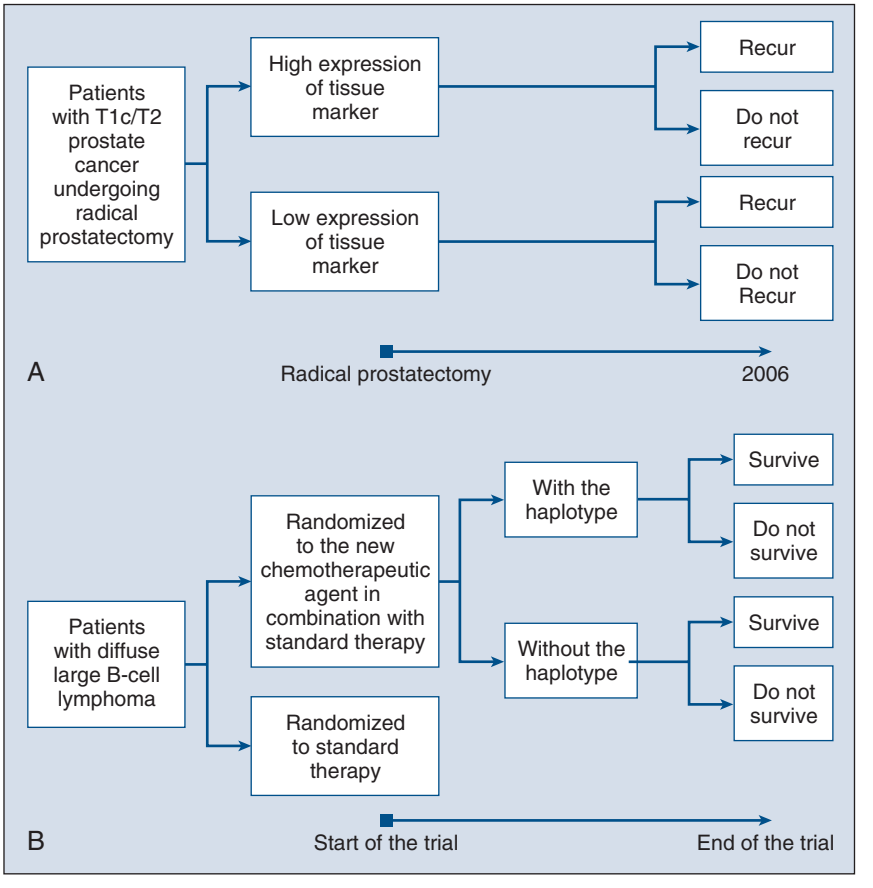


Figure 25-3 • **A,** Schematic of the hypothetical *prognostic* research question as a prospective cohort study. **B,** Schematic of the hypothetical *therapeutic effectiveness* research question as a prospective cohort study.

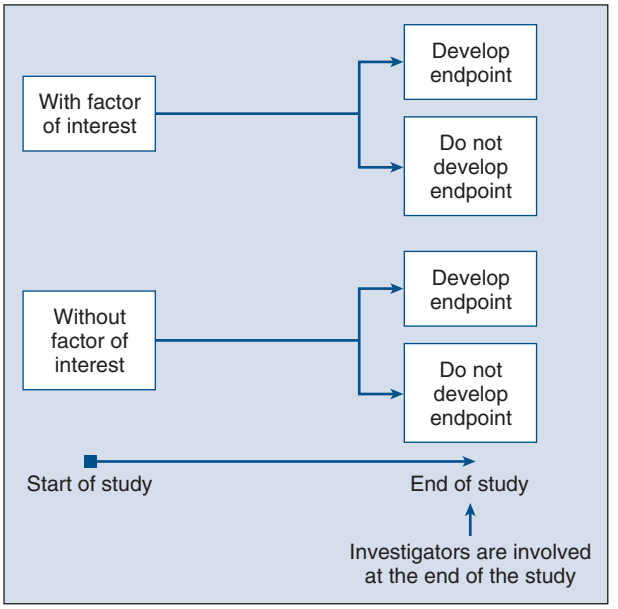


Figure 25-4 • Schematic of the retrospective cohort study.

cohort study. Returning to the hypothetical translational and clinical questions, the retrospective cohort design is illustrated as follows:

Prognosis: The investigators assemble the study population in 2007 by searching the medical records for men who underwent prostatectomy for clinically organ-confined prostate cancer between 1993 and 2002.

Therapeutic effectiveness: After the trial has finished, the investigators identify all participants in the new chemotherapeutic agent arm of the trial, and search each site of the multicenter clinical trial for blood specimens archived at the first visit of the trial.

Although the distinction may seem subtle, the major difference between the prospective and retrospective designs is the position of the investigators relative to factor assessment and follow-up for the endpoint of interest—whether the investigators (1) assemble the cohort and collect information on the factor or samples in which the factor status will be assessed at the start of follow-up, or (2) assemble the cohort sometime after the start of the follow-up and attempt to reconstruct the factor status at the time of the start of follow-up using existing records or samples. The retrospective cohort design may not be optimal because of uncertainties in factor assessment, including incomplete or missing medical or other records, and missing or degraded samples in which the factor status would have been assessed. For example, in the *prognosis* study, prostate tissue from some cohort members might no longer be available because it has already been used for other tissue studies.

A further problem with factor assessment in retrospective cohort studies is that the extent of uncertainty in the factor assessment may differ according to whether or not a participant experienced the endpoint. Say, for instance, in the *therapeutic effectiveness* example that blood specimens were not saved from the first visit of the new chemotherapeutic agent trial. In this case, investigators would have to collect blood samples from participants at a later date in the trial to determine the haplotype status of each participant. Although not consistent with the typical retrospective cohort study design, this approach still maintains temporality because germline haplotypes are present from the time of conception and are invariant throughout life and, therefore, must have preceded the endpoint of interest. However, by collecting blood at a later date in the trial, the investigators may still have introduced a distortion (*bias*) into the results of the study.

For example, suppose that absence of the haplotype is associated with shorter duration of survival after recurrence compared with presence of the haplotype. At the time of blood draw partway through the trial, proportionally more participants without the haplotype (a fact not yet known to the investigators) who had recurrences would not be able to provide a blood specimen because they had already died as opposed to those with the haplotype who had recurred, whereas there would be no difference in the ability to obtain a blood specimen from those who had not yet recurred among those with and without the haplotype. Thus, this differential inclusion of participants by both haplotype and death could then make it appear as though the haplotype were not as protective for death from lymphoma after treatment, not associated with death from lymphoma at all, or even associated with an increased risk of death from lymphoma, depending on the extent to which participants without the haplotype who died were excluded from the study because haplotype status could not be determined. For this and other reasons, investigators should think very carefully about the implications of reconstructing a cohort and its factor status to avoid biased results. Differential inclusion of participants by both the factor of interest and the endpoint of interest, as illustrated in this example, is called *selection bias*, a topic that will be discussed in the next section of the chapter.

Comparability

Another major consideration when drawing inferences from translational and clinical studies that use epidemiologic methods is *comparability* of the two (or more) groups being contrasted. To help think about comparability, consider laboratory animal experiments: the researcher has complete control over the groups being contrasted and, therefore, can make the groups as similar as possible on all aspects except for the factor of interest. The laboratory researcher typically selects genetically identical animals, assigns the factor (or treatment) to half of the animals but otherwise feeds and handles the animals in exactly the same manner, and then euthanizes the animals after a certain length of time to assess the endpoint of interest. The only difference between the two groups being contrasted is the factor of interest; that is, the two groups are comparable save the factor. When coupled with temporality (i.e., the factor/treatment was given before the endpoint occurred), comparability allows the laboratory researcher to conclude that the factor was the cause of the endpoint.

Trialists attempt to accomplish a similar objective in randomized clinical trials by assigning participants to the treatment (or other intervention) group or placebo (or standard of care) group through a random process. This process helps to ensure that participants in the treatment and placebo groups have similar distributions of known and unknown inherent and modifiable characteristics, including those related to disease incidence or prognosis. Although randomization cannot ensure comparability, the larger the number of participants randomized, the more likely it is that the two groups will have similar distributions of known and unknown characteristics. This level of comparability allows the investigators to conclude that the treatment was the likely cause of any observed differences in the occurrence of the endpoint between the two groups.

Had the investigators not used a randomized design, they would not have been able to reach such a strong conclusion about the relation between the treatment and the endpoint. If the investigators had not randomized participants, but instead had allowed patients or their oncologists to choose whether or not to take the new treatment, sicker patients (i.e., those already more likely to die of their cancers) might have been more likely to select the new therapy over the standard of care in the hope that cure might be more likely. In this case, patients receiving the new therapy would not have been comparable to patients receiving the standard of care with respect to disease prognosis. If these two groups had been compared with respect to the occurrence of the endpoint (e.g., death from cancer), as might be the case in a prospective cohort study, then the new treatment would have appeared to be less efficacious than it should. This bias is called

selection bias or *confounding by indication*. Selection bias occurs when enrollment or inclusion of individuals with and without the factor (e.g., those who selected the new treatment and those who selected the standard of care) is differentially dependent on their likelihood of developing the endpoint of interest (e.g., on their likelihood of dying from cancer).

Just as randomization helps to equalize the two groups being contrasted on disease incidence or prognosis, it also helps to equalize the two groups on all other known and unknown characteristics that also could alter the relation between a factor and an endpoint. For instance, in the preceding example, if the investigators had not randomized participants to the new treatment or standard of care, but instead had allowed them to select their treatment, patients or their oncologists might have selected treatment based on cost, rather than (or in addition to) disease prognosis. If oncologists only prescribed the new treatment to patients with higher socioeconomic status whose health insurance would be more likely to cover the cost of the expensive new treatment, and if patients with higher socioeconomic status were less likely to die from their cancer because of better diet, less adverse health behaviors, and greater access to adjuvant therapies, then the new treatment would have appeared to be more efficacious than it should simply because of differences in socioeconomic status between the two groups. In this case, socioeconomic status is called a *confounder*. Simply defined, confounders are factors that are (1) correlated with the factor of interest; (2) associated with the endpoint; and (3) not steps in the pathway in how the factor of interest influences the endpoint. In the preceding example, socioeconomic status is a confounder because it is (1) correlated with treatment; (2) associated with death from cancer; and (3) not a step in the pathway between treatment and death from cancer because it is unlikely that treatment influenced socioeconomic status, which then influenced death from cancer.

For reasons of both *selection bias* and *confounding*, randomized trials are the gold standard design for testing interventions, whether medications, devices, screening and diagnostic tests, other medical procedures and surgeries, or behavioral interventions. However, there are, of course, many circumstances in which a randomized trial would not be ethical, such as when a screening test is already in routine clinical practice, but was never formally tested for efficacy, or when the factor of interest is believed to be harmful. In addition, not all factors of interest in oncology are amenable to randomization because they are inherent characteristics of individuals or are otherwise nonmodifiable, such as family history of breast cancer, or age at menarche. In these cases, the cohort study may be an ethical alternative, and with proper design and analytic consideration, should provide sound inferences. Selection bias can be reduced in cohort studies by restricting the extent of disease among participants (e.g., by limiting the source population to a single stage at diagnosis) or by collecting detailed information on extent of disease at the start of the study, so that it may be taken into account in the statistical analysis (e.g., *adjusting* on stage at diagnosis, see the section on Comparing Two Groups: Measures of Association). Selection bias also is much less likely in cohort studies in which the baseline study population is free of a diagnosis of the endpoint of interest (e.g., a cohort of men and women who do not currently have a cancer diagnosis) as is typically the case in *etiologic studies* (i.e., studies seeking to identify the causes of an endpoint of interest). Selection bias also is less likely in prospective cohort studies than in retrospective cohort studies (see the illustration of selection bias in the retrospective cohort example of therapeutic effectiveness under the section on Design Considerations for Causal Inference: The Cohort Study).

Confounding can be minimized in cohort studies by collecting or measuring information on potential confounders, such as socioeconomic status, at the start of the study. These confounders can then be taken into account in either the design phase (e.g., by restricting to one level of the confounder—high socioeconomic status) and/or the statistical analysis of the study (by adjustment; see the section on Comparing Two Groups: Measures of Association). However, even with forethought, investigators may not always be able to anticipate all confounders or may not measure them perfectly. In such cases, residual confounding may be present and may still explain any observed associations.

Returning to the two hypothetical translational and clinical questions, randomized trials addressing the prognostic ability of the tissue biomarker or the difference in therapeutic effectiveness of the new agent by the enzyme haplotype are not feasible. Both the tissue biomarker and the haplotype are nonmodifiable characteristics of the patients' tumors or the patients themselves. Therefore, these questions are optimally addressed in cohort studies. Comparability in these example cohort studies is discussed here:

Prognosis: Patients whose prostate tumors have high and low expression of the tissue marker are made comparable with respect to a known prognostic factor, clinical stage at diagnosis, in the design phase of the study by restricting patients to only those with clinical stage T1c or T2 disease. In the conduct of the study, information is collected on pathologic stage and grade and other key prognostic factors so that they may be taken into consideration in the analysis to make those patients with high and low expression of the marker even more comparable on likelihood of recurrence. At the time of prostatectomy, demographic, anthropometric, and behavioral characteristics also are collected. These potential confounders can be taken into consideration in the statistical analysis. This level of comparability will allow investigators to determine the independent prognostic value of the tissue marker.

Therapeutic effectiveness: Although this study is embedded in a randomized trial of a new chemotherapeutic agent, the research question about the metabolic enzyme haplotype does not take advantage of the randomization. Only one arm of the trial is used: patients randomized to the new agent in combination with standard therapy. Therefore, comparability of those with and without at least one copy of the haplotype must be carefully considered. Patients with and without the haplotype are comparable with respect to histologic type of non-Hodgkin's lymphoma by design because only patients with diffuse large B-cell lymphoma were included in the trial. Participants also were required to be less than 60 years of age and to have at least two risk factors according to the Prognostic Index, making them more comparable on age and prognosis. Age, specific prognostic factors, and potentially confounding factors collected as part of the parent trial can be taken into consideration in the analysis to make those with and without at least one copy of the haplotype even more comparable on likelihood of survival with non-Hodgkin's lymphoma. This level of comparability will allow the investigators to determine the independent predictive capability of the haplotype for survival after treatment with the new agent.

Another possible source of lack of comparability common to both experimental and observational designs is *observation bias* or *information bias*. This bias occurs when the accuracy of observing the endpoint differs between those with and without the factor. One possible source of observation bias in both experimental (including randomized trials) and observational designs is differential loss-to-follow-up (i.e., loss-to-follow-up that is differential with respect to the likelihood of the endpoint of interest) between those with and those without the factor.

For example, a new complementary cancer treatment is being tested against placebo for improvement in quality of life after cancer treatment. Quality of life is assessed at the start and then again at the end of the trial. Suppose that the new treatment improves quality of life in some patients, but in many other patients quality of life dramatically declines because of an adverse response to the treatment. Those in the complementary treatment arm who experience the adverse response are much less likely to continue participating in the trial than those whose quality of life improves. In the placebo arm in which many fewer patients have dramatic declines in quality of life,

the likelihood of continued participation to the end of the trial is only slightly lower among those whose quality of life does not improve compared with those whose quality of life does improve. This bias would make the complementary treatment appear more efficacious than it is simply because patients receiving the treatment who experienced a decline in quality of life are under-represented in the analysis.

Another possible source of observation bias is detection bias or medical surveillance bias. This bias occurs when those with and without the factor of interest are surveyed for the endpoint to different degrees. For example, in a prospective study of obesity and prostate cancer recurrence, if urologists suspect that obesity may indeed increase the risk of recurrence, they might monitor obese men for a postprostatectomy rise in PSA more often than they monitor nonobese men. Thus, it may appear as though obesity is associated with earlier prostate cancer recurrence simply because obese men are monitored more frequently for recurrence.

In summary, comparability between those with and without the factor of interest is a major consideration in drawing causal inferences in studies using epidemiologic methods. To enhance comparability, investigators should think carefully about selection bias, confounding, and observation bias in the design, conduct, and analysis of their study.

Other Cohort Design Considerations

So far, the cohort design has been described as a single study population divided into those with and without the factor and then followed for the endpoint of interest. This approach of a cohort formed from a single study population is desirable because it helps to ensure that the two groups being contrasted are from a relatively homogeneous population with similar methods of factor, confounder, and endpoint assessment to enhance comparability between the two groups.

However, sometimes investigators cannot identify groups of participants with and without the factor of interest from the same population, and must resort to comparing groups from different populations. The classic example comes from cancer etiology studies in the occupational setting, in which all members of the study population have the factor of interest, such as employment at a large factory that manufactures a particular chemical. To get a sense of the risk experience the employees would have had if they had not been exposed to the chemical, an external unexposed comparison group is needed. One possible comparison group is employees at a factory that does not manufacture the particular chemical, but is otherwise similar to the factory that does manufacture the chemical. Another comparison group could be the entire population of the country in which the factory is located, if the risk of the endpoint (e.g., cancer) is known for that particular country. In using a national comparison group, investigators assume that the general population in that country is not exposed to the factor of interest and is otherwise comparable to the exposed group. This latter assumption should be carefully considered, for reasons such as the fact that workers tend to be healthier on average than the general population because they are able to work (*healthy worker effect*).

In the context of oncology, one setting in which investigators might need to use an external comparison group is in the introduction of a new cancer treatment before it is ready to be tested in a clinical trial. In this case, investigators might use a *historical comparison* group—a group of patients who were treated using the standard of care earlier in calendar time—to contrast with the current group of patients treated with the new surgical or pharmacologic cancer therapy. However, again care should be taken when comparing these two groups because of differences in the case mix and other patient characteristics over time (*secular trends*).

Statistical Analysis of Cohort Studies

Measures of the Occurrence of an Endpoint

The fundamental measure of occurrence of an endpoint (e.g., development of disease or recurrence of disease) in a study using the cohort design is the probability of the endpoint, called the *cumulative incidence* or *risk*. Most simply defined, the cumulative incidence is the number of new endpoints that occur during a particular time interval divided by the number of individuals at risk at the start of follow-up in a cohort study (or clinical trial). The numerator typically only includes new or *incident* endpoints, not existing or *prevalent* cases. In oncology, investigators usually are most interested in the first occurrence of an endpoint (e.g., cancer diagnosis or cancer recurrence). The denominator only includes those able to experience the endpoint (e.g., women who have had a hysterectomy are not at risk for endometrial cancer and would not be included in the denominator when estimating the cumulative incidence of endometrial cancer), and all of the endpoints must have arisen from among individuals at risk in the denominator. As an example of a cumulative incidence calculation, if 100 men and women were enrolled in a cohort study and 25 died by the end of 5 years of follow-up, then the cumulative incidence of death would be 25/100 or 0.25 over 5 years. The range of values for the cumulative incidence is 0 if none of the at-risk individuals experience the endpoint and 1 if all of the at-risk individuals experience the endpoint. The time interval over which the cumulative incidence is estimated must be specified: a 0.25 (or 25%) risk over 1 month is substantially larger than a 0.25 risk over the lifetime.

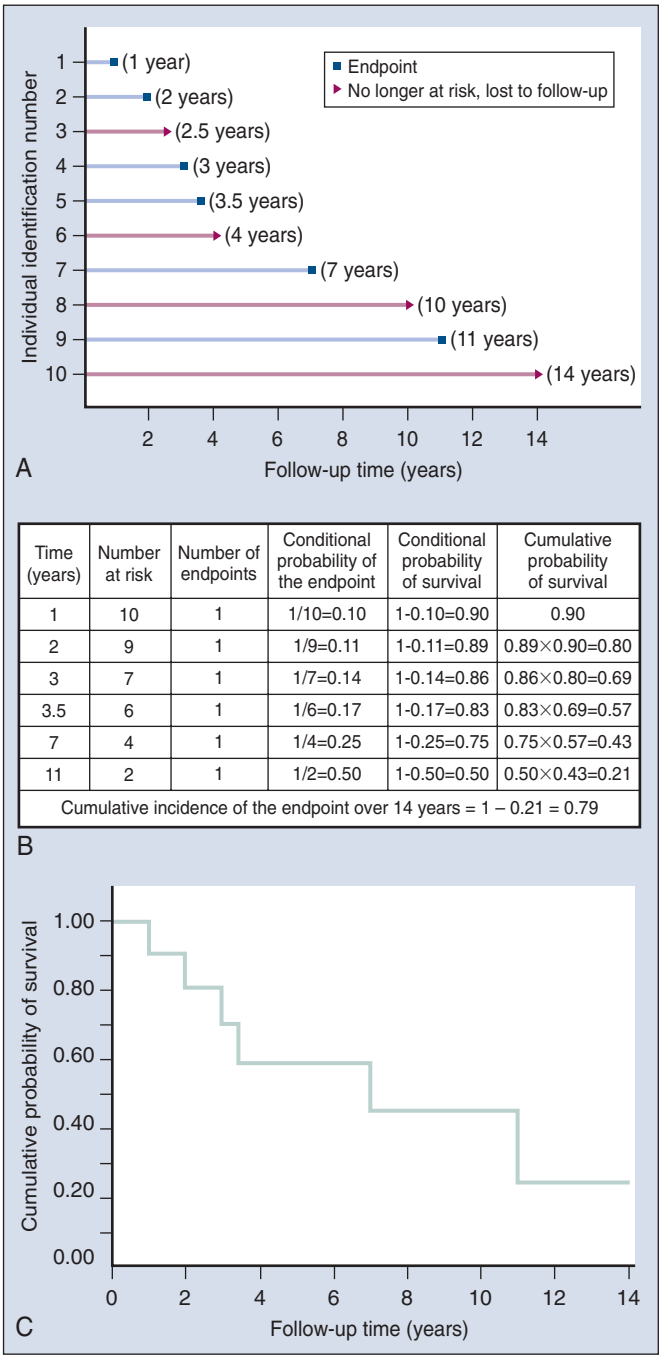
This simple cumulative incidence calculation assumes that all participants enter follow-up at the same time; follow-up time can be expressed as calendar time, age, or time on study (e.g., time since mastectomy irrespective of calendar year or age). It also assumes that follow-up only ends because of occurrence of the endpoint or end of the study (*administrative censoring*). In other words, participants who do not experience the endpoint of interest are assumed to remain at risk for the endpoint of interest (e.g., not die from another disease) and to remain under follow-up (e.g., not stop participating in the study) until the end of the study.

Rarely do all participants remain under follow-up until the end of the study. Some individuals may die of something other than the endpoint of interest. Others may choose not to continue participating or are withdrawn by the investigators. All of these individuals are considered lost to follow-up. In this case, the simple cumulative incidence calculation is not appropriate; the estimate will be too small because the at-risk denominator presumes that all participants were followed for the full study period.

One appropriate method to estimate cumulative incidence when there is loss-to-follow-up is the Kaplan-Meier method. This method allows all of the time during which an individual is at risk and under follow-up to be used, even for participants not observed for the full study period. The first step of the Kaplan-Meier method is to align all participants with respect to follow-up time (e.g., time since mastectomy). Then, at each time that an endpoint occurs, the probability of the endpoint is calculated among only those individuals who survived until the time of that particular endpoint (*conditional probability of the endpoint*). Lack of survival until the time that a particular endpoint occurs may be due to having already experienced the endpoint, no longer being at risk for other reasons (e.g., death from another cause). The group of individuals still at risk at the time each endpoint occurs is called the *risk set*. The next step in the Kaplan-Meier method is to calculate the probability of surviving to the time that each endpoint occurs for each of the risk sets (1 – conditional probability of the endpoint; *conditional probability of survival*). Then, the cumulative probability of survival up to the time of each endpoint is calculated as the product of the conditional probability of survival at the time of each endpoint and the cumulative probability of survival to the time of the prior endpoint.

The cumulative probability of survival over the entire follow-up period is the cumulative probability at the time of the last endpoint. The cumulative incidence over the entire follow-up period can then be calculated as the complement of the cumulative probability of survival over the entire follow-up period (1 – cumulative probability of survival; Figs. 25-5A and B). The cumulative probabilities of

survival at each time an endpoint occurs can be plotted against follow-up time to obtain the Kaplan-Meier survival curve (Fig. 25-5C). Note that survival curves may be generated for endpoints other than death; survival merely means not having had the endpoint of interest and still being at risk and under observation. Survival is assumed to be constant (flat line on the graph) until an endpoint occurs, at which time the cumulative survival drops to the value for the next interval. Direct examination of the Kaplan-Meier curve can show whether survival is constant or changes over follow-up time. In Figure 25-5C, the change in cumulative survival over the first 5 years is greater than the change in cumulative survival in subsequent years as shown by the difference in the steepness of the curve in the first 5 years compared with later years. The Kaplan-Meier curve also can be used to estimate such measures as median survival time by determining the time at which half of the population has experienced the endpoint of interest.



Time (years)	Number at risk	Number of endpoints	Conditional probability of the endpoint	Conditional probability of survival	Cumulative probability of survival
1	10	1	1/10=0.10	1-0.10=0.90	0.90
2	9	1	1/9=0.11	1-0.11=0.89	0.89×0.90=0.80
3	7	1	1/7=0.14	1-0.14=0.86	0.86×0.80=0.69
3.5	6	1	1/6=0.17	1-0.17=0.83	0.83×0.69=0.57
7	4	1	1/4=0.25	1-0.25=0.75	0.75×0.57=0.43
11	2	1	1/2=0.50	1-0.50=0.50	0.50×0.43=0.21
Cumulative incidence of the endpoint over 14 years = 1 – 0.21 = 0.79					

B

Figure 25-5 • Use of the Kaplan-Meier method to calculate the cumulative incidence of the endpoint and to plot the survival curve. **A,** Time at risk for 10 hypothetical individuals. **B,** Calculation of the cumulative probabilities of survival and incidence for the 10 hypothetical individuals. **C,** Kaplan-Meier survival curve for the 10 hypothetical individuals.

Two assumptions are made when using the Kaplan-Meier approach. The first is that individuals who do not experience the endpoint and do not survive until the next endpoint time have a similar risk of the endpoint as individuals who remain under follow-up. If this assumption is violated, then the estimated cumulative incidence will be incorrect. The second assumption is that no change in the background risk occurs over the accrual period (e.g., secular changes in the risk of cancer death might occur if there is a stage shift due to implementation of a new screening test and if this early detection followed by appropriate treatment produces longer survival than if not detected early). If this problem is present, then separate Kaplan-Meier estimates and curves should be presented for different intervals of accrual time.

Other methods of estimating cumulative incidence are available. For example, if the time that the endpoint occurs cannot be pinpointed, as may happen when cancer recurrence is detected on a blood test performed every 6 months, then the actuarial or life-table method may be used. The actuarial method is similar to the Kaplan-Meier method, except that the times of detection of the endpoints are binned into time intervals. For instance, in this cancer recurrence example, the endpoints would be binned into 6-month intervals (see Gordis[1] for further details).

Another measure of endpoint occurrence more typically used by epidemiologists is the incidence rate. When death is the endpoint, the incidence rate of death is usually called the *mortality rate*. The incidence rate conveys how fast the endpoint is occurring in a population at risk. It is used when follow-up for some participants begins later than for others or when some participants are not followed for the full study period. The incidence rate is calculated as the number of new endpoints divided by the person-time at risk. Like the cumulative incidence, the numerator is the number of incident endpoints. The denominator is the sum of the amount of time that each individual is at risk for the endpoint and is under follow-up. In Figure 25-6, individual 1 contributes 1 person-year at risk before he develops the endpoint of interest, individual 3 contributes 2.5 person-years at risk before she stops participating in the study, and individual 10 contributes 14 person-years at risk by the end of the study. Together, these 10 individuals contribute 58 person-years at risk to the denominator of the incidence rate. Whereas the cumulative incidence requires a separate specification of the relevant time period over which it applies, time is inherent in the calculation of the incidence rate. Person-time at risk may be expressed in any unit of time—years, months, weeks, seconds—although person-years are most often used for cancer incidence, recurrence, and death. The incidence rate may range from 0 per person-time if no endpoints occur during follow-up to infinity per person-time if one or more endpoints occur during the briefest instant of follow-up.

As for the calculation of cumulative incidence, several assumptions are made in calculating the incidence rate. The first two assumptions are the same as for the cumulative incidence: (1) individuals who do not experience the endpoint and do not survive until the next endpoint time have a similar risk of the endpoint as individuals who remain under follow-up; and (2) no change in the background risk occurs over the accrual period. A third assumption in calculating the incidence rate is the equivalence of person-time at risk over time and across individuals; that is, 1 person-year contributed by individual 10 during the first year of follow-up is the same as 1 person-year contributed by individual 10 during the last year of follow-up. Likewise,

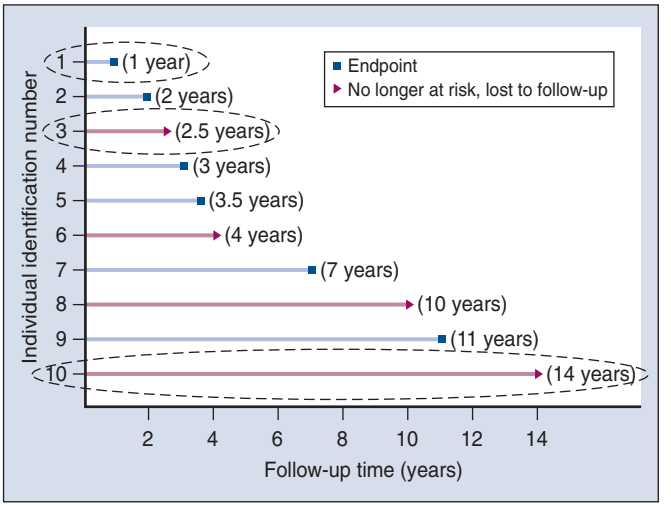


Figure 25-6 • Time at risk for 10 hypothetical individuals. Individual 1 contributes 1 person-year at risk before he develops the endpoint of interest; individual 3 contributes 2.5 person-years at risk before she stops participating in the study; and individual 10 contributes 14 person-years at risk by the end of the study.

any year contributed by individual 5 is the same as any year contributed by individual 7. When this equivalence does not hold, for example when the incidence rate differs by age or calendar time and/or by characteristics of the participants, then separate incidence rates should be calculated by categories of age, time, or participant characteristics.

A third measure of endpoint occurrence is the *hazard*, which is defined as the instantaneous occurrence of the endpoint among those still at risk. Although commonly calculated as part of a ratio (*hazard ratio*), the hazard itself is calculated very rarely because of complexities involved with the calculation.

When should the cumulative incidence versus the incidence rate be presented as the measure of endpoint occurrence? It depends on the goal of the research. If investigators would like to generate information useful for communicating to patients (e.g., What is the likelihood that my cancer will recur after I am treated?), then the cumulative incidence might be the most useful measure. When communicating this measure to patients, oncologists also should make it clear that the cumulative incidence is not specific to any one particular patient, but instead refers to the average cumulative incidence in a group of patients with similar characteristics. The incidence rate typically is calculated in the context of etiologic studies. The risk and the rate are mathematically related, and with certain assumptions, the cumulative incidence can be estimated from the observed incidence rates (see Rothman[2] for further details).

Comparing Two Groups: Measures of Association

Testing a hypothesis usually involves comparing the occurrence of the endpoint in two or more groups that differ on a factor of interest. One approach is to compare the survival curves generated from the Kaplan-Meier method between individuals with and without the factor of interest. The statistical test used to determine whether the survival curves are likely different from each other is called the *log-rank test*.

Sometimes investigators would like to know more than merely whether or not the survival experiences between the two groups differ. Instead, they may want to quantify the magnitude of this difference. If the endpoint experiences of the two groups are expressed as cumulative incidences (calculated from the Kaplan-Meier or other methods) or rates, then either the ratio or the difference of these measures may be calculated. Ratio measures include the *cumulative incidence ratio*, *rate ratio*, or *hazard ratio*, collectively known as the *relative risk* (RR) of the endpoint. The RR is calculated as follows:

Cumulative incidence ratio =
(cumulative incidence in group 1)/(cumulative incidence in group 2)

Rate ratio = (incidence rate in group 1)/(incidence rate in group 2)

The hazard ratio rarely is calculated directly because, as stated in the previous section, individual hazards are difficult to calculate.

The order of the two groups being compared in the calculation of the RR has direct bearing on its interpretation. Typically, in studies using epidemiologic methods, investigators are particularly interested in the endpoint experience in one group, the group with the factor of interest, as compared with a second group, the group without the factor of interest. In this case, the investigators would calculate the RR as follows:

RR = (occurrence of the endpoint in the group with the factor)/
(occurrence of the endpoint in the group without the factor)

Alternatively, investigators might be interested in comparing those without the factor of interest to those with the factor. The choice of which group belongs in the numerator of the ratio and which belongs in the denominator depends on the statement of the research question. For instance, in the *prognosis* example, the investigators asked whether high expression of the tissue marker is associated with greater prostate cancer recurrence; thus, they would calculate the RR as the cumulative incidence of prostate cancer recurrence in patients with high expression of the tissue marker divided by the cumulative incidence of prostate cancer recurrence in patients with low expression of the tissue marker. If the cumulative incidence were higher among patients with high expression than among patients with low expression, then the RR would be greater than 1 and the magnitude of the RR would indicate how many times higher the cumulative incidence of recurrence was in those with high expression than in those with low expression of the tissue marker (i.e., it would indicate the *strength of the association*). If contrary to the hypothesis, the cumulative incidence were lower among patients with high expression than among patients with low expression, then the RR would be less than 1 and the magnitude of the RR would indicate how many times lower the cumulative incidence of recurrence was in those with high compared with low expression. The RR is unitless and can range from 0 to infinity.

Measures of the difference in the occurrence of the endpoint include the *cumulative incidence difference* and *rate difference*, collectively known as the *risk difference*. The risk difference is calculated as follows:

Cumulative incidence difference = (cumulative incidence in group 1) − (cumulative incidence in group 2)

Rate difference = (incidence rate in group 1) − (incidence rate in group 2)

As for the RR, the order of the two groups also is important in the interpretation of the risk difference. Typically, investigators calculate the risk difference as the occurrence of the endpoint in the group with the factor of interest minus the occurrence of the endpoint in the group without the factor of interest. The cumulative incidence difference and rate difference have the same units as the cumulative incidence and rate, respectively. The cumulative incidence difference can range from −1 to 1, while the rate difference can range from minus infinity to positive infinity.

Whereas the RR often is calculated in studies using epidemiologic methods, the risk difference is calculated less often. It usually is calculated only when the factor has been identified as a likely cause of the endpoint and when the absolute size or burden of the endpoint attributable to this factor is of interest. For this reason, the risk difference also is known as the *attributable risk*. Another way to interpret

the attributable risk is the extent of occurrence of the endpoint that would have been avoided in individuals with the factor if they had never experienced the factor. Note that a high RR does not necessarily imply a high attributable risk. If, for instance, the cumulative incidence in those with the factor is 1 in 10,000,000 people over the lifetime and the cumulative incidence in those without the factor is 1 in 100,000,000 people over the lifetime, then the RR is 10 (large), but the attributable risk is only 9 in 100,000,000 over the lifetime (small). Sometimes the *population attributable risk percent* is reported as a measure of a population's excess burden due to some members of the population having the factor of interest. Another way to view this measure is the proportion of the occurrence of the endpoint that would have been avoided in a population if individuals with the factor had never experienced the factor. The population attributable risk percent is calculated as the cumulative incidence (rate) in the total population minus the cumulative incidence (rate) in those without the factor all divided by the cumulative incidence (rate) in the total population.

As alluded to in the discussion of comparability, it may be necessary to take potentially confounding factors into account in the estimation of the RR or the risk difference. Two main statistical approaches may be used: stratification or adjustment. *Stratification* involves estimating the RR or risk difference in categories of the potential confounder known as *strata*. Within each stratum of the confounder, all individuals have the same confounder status, and thus the stratum-specific association between the factor of interest and the endpoint is independent of the confounder. If an unconfounded summary estimate of the RR or risk difference is desired, then the summary estimate can be calculated as the weighted average (often using Mantel-Haenszel weights) of these independent stratum-specific estimates. Note that age-standardization, which is used routinely to adjust cancer incidence and mortality rates for confounding by age (because different populations may have different age structures), is merely a form of stratification with weights derived from a specified standard population, such as the 2000 U.S. Census Population as used by the National Cancer Institute's Surveillance, Epidemiology, and End Results Program (*http://seer.cancer.gov/*) or the World Standard Population as used by the World Health Organization (Globocan: *http://www-dep.iarc.fr/*).

Another statistical method that takes confounding into account is adjustment using regression techniques. Detailed descriptions of regression models can be found in biostatistics textbooks. Briefly, choice of the appropriate regression model is determined by the nature of the endpoint of interest. For instance, is the endpoint binary? This often is the type of endpoint studied in oncology (e.g., cancer diagnosis or cancer recurrence). Currently, there are no straightforward methods for modeling the cumulative incidence ratio when some participants are lost to follow-up, and thus it is difficult to calculate an adjusted estimate of association. If, instead, the rate ratio or the hazard ratio is the desired measure of association, then either Poisson regression or Cox proportional hazards regression, respectively, can be used to calculate adjusted estimates. The Cox model circumvents difficulties in directly estimating individual hazards by allowing the unmeasured hazard in those without the factor to vary from moment to moment, and then assuming that the ratio of the hazards in those with and without the factor is constant, allowing it to only estimate the hazard ratio.

Design Considerations for Causal Inference: Alternative Prospective Designs

Nested Case-Control Study

So far, this chapter has discussed only the cohort approach to addressing research questions. However, sometimes it is not feasible to evaluate the factor status of each participant in the cohort study, for example, when the factor is assessed using an expensive or labor-intensive method.

In this case, alternative prospective epidemiologic designs can be used that maintain the correct temporal sequence between the factor and the endpoint, but use a smaller sample size—the nested case-control study and the case-cohort study. In these designs, all individuals in the cohort must still be followed for the endpoint of interest, and material—either biological (e.g., blood specimen) or physical (e.g., paper medical records)—from which to ascertain the factor must be collected before the endpoint occurs. In the nested case-control study (Fig. 25-7), all individuals who develop the endpoint of interest (or a random sample of these individuals) are selected as *cases*. Then, at each time that a case occurs, one or more individuals are randomly selected from the *risk set*, which consists of those who have not yet developed the endpoint and who are still at risk and under follow-up. These individuals are called *controls*. Only these cases and controls are then tested for the factor of interest.

Looking at Figure 25-7, at the time that individual 1 recurs, individuals 2 through 10 are still at risk of recurrence and under follow-up. Individual 9 is randomly selected to be the control. At the time that individual 4 recurs, individuals 5 through 10 are still at risk of recurrence and under follow-up. Individual 6 is randomly selected to be control. This method of control sampling is called *incidence density sampling*. Note that an individual who later becomes a case may be sampled earlier as a control for another case (individual 9). Additionally, the same individual may be sampled as a control for more than one case. Individual 9 could have been sampled as a control for both case 1 and case 4.

To help illustrate why this sampling approach is correct, consider how in the Kaplan-Meier method the conditional probability of the endpoint is estimated at each endpoint time as the number of cases divided by the number of individuals still at risk and under follow-up; that is, each individual contributes to the estimate of the conditional probability at each time that an endpoint occurs, including individuals who later become cases. In the nested case-control study, each control is sampled from the risk set to reflect the risk of the members of the risk set. As in the Kaplan-Meier method, each individual still at risk and under follow-up has the opportunity to be sampled each time an endpoint occurs.

To enhance the statistical ability to adjust for confounding, control subjects often are sampled such that they have characteristics similar to the cases, a process called *matching*. In a nested case-control study with incidence density sampling of controls, cases and controls are necessarily matched on follow-up time by design. Note that statistical analysis of matched cases and controls should take into account

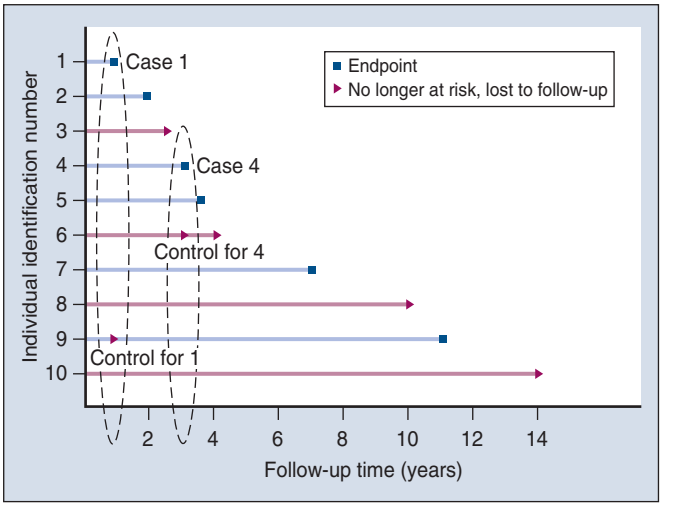


Figure 25-7 • Schematic of a nested case-control study within a prospective cohort of 10 hypothetical individuals. All cases are sampled. A subset of all possible controls is sampled using incidence density sampling.

the matched design (see section on Statistical Analysis of Case-Control Studies). Despite the incorrect common belief that matching itself enhances comparability and reduces confounding, not considering the matching in the analysis may produce a biased estimate of the association.

Rather than selecting controls from the risk set, it might be tempting to select controls from among individuals who never experience the endpoint of interest by the end of cohort follow-up (i.e., not matched on follow-up time). For two reasons, this approach is not optimal. First, because of the requirement that individuals sampled as controls remain free of the endpoint until the end of follow-up, they are less likely to include individuals who later become cases than incidence density sampled controls, who are required to be free of the endpoint only until the time of case diagnosis. Thus, if the factor of interest is associated with the endpoint, then the prevalence of the factor will be even lower (if the factor increases the risk or even higher if the factor decreases the risk) in controls selected from the end of follow-up than in controls selected at the time of case diagnosis. This lower prevalence of the factor results in an overestimation of the true rate/hazard ratio (see section on Statistical Analysis of Case-Control Studies).

The second reason that selecting controls at the end of study follow-up is not optimal is that, because controls are required to remain free of the endpoint until the end of follow-up, they also typically are required to remain alive for a longer period of time than cases who may die after their diagnosis. Therefore, if the factor of interest is associated with longevity, then investigators may observe an association between the factor of interest and the endpoint simply because controls are required to remain alive for a longer period of time than cases. This bias is called *survival bias*.

Case-Cohort Study

Another alternative to the prospective cohort design is the case-cohort design. It is used in the same settings as the nested case-control study, albeit less frequently, because in the past software to analyze data from this design was not readily available. In the case-cohort study (Fig. 25-8), the entire cohort is followed for the endpoint of interest, and material from which to ascertain the factor is collected before the endpoint occurs for all individuals. Then, individuals who develop the endpoint of interest (or a random sample of these individuals) are selected as cases. Next, a random sample (or random samples within categories of characteristics) of the entire cohort at the start of the study is selected and called the *subcohort*. All of the cases and all of the members of the subcohort are tested for the factor of interest. Looking at Figure 25-8, at the time that individual 6 recurs, individuals 7 through 15 in the subcohort are still at risk and under follow-up. Thus, individual 6 is compared to individuals 7 through 15, but not to individuals 1 through 5, who are not members of the subcohort. At the time that individual 1 recurs, individuals 7 through 15 in the subcohort are still at risk and under follow-up. In this case, individual 1 is compared with individuals 7 through 15. Thus, similar to controls in nested case-control studies, members of the subcohort in any given risk set are used to reflect the risk of all members in the entire cohort who would have been in that risk set. However, in contrast to the nested case-control setting, a greater number of individuals typically are used to reflect the risk set in the case-cohort setting than in the nested case-control setting.

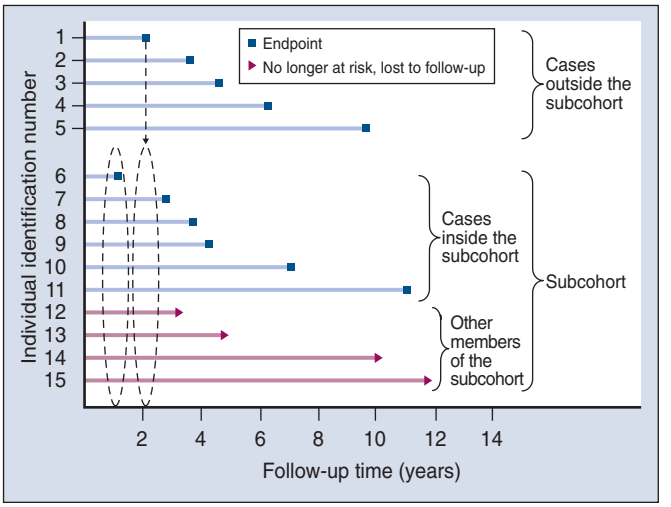


Figure 25-8 • Schematic of a case-cohort study within a prospective cohort of 10 hypothetical individuals. All cases are sampled. A subset of the entire cohort at baseline is sampled.

When should a case-cohort design be used instead of a nested case-control design? If investigators have several endpoints of interest, it might be more cost-effective to use a case-cohort design in which the subcohort can be used to reflect the risk experience of the entire cohort for multiple case groups rather than selecting a separate control group for each case group as would be done in a nested case-control study.

Statistical Analysis of Alternative Prospective Designs

Data from both the nested case-control and case-cohort approaches require special analytic techniques, conditional logistic regression, and Cox proportional hazards regression with a variance correction, respectively. The measures of association estimated from these data approximate the hazard ratio. Adjustment for potentially confounding factors in these models is done as usual.

Design Considerations for Causal Inference: The Case-Control Study

Thus far, all of the epidemiologic study approaches described have been variations on the cohort design. However, the cohort design often is not practical or feasible in oncologic research, for example when the source population is not enumerable, when the endpoint of interest is very rare, or when investigators do not have time to wait until enough endpoints have accrued in a cohort. For these reasons, investigators may choose to use the case-control design (Fig. 25-9). In this design, cases are individuals with the endpoint of interest, and controls are individuals who do not have the endpoint, but are at risk for its occurrence. Once cases and controls have been identified, the factor of interest is assessed at the time that the case or control is ascertained for the study. Thus, in contrast to prospective designs in which assessment of current or prior factor status is made before the case is diagnosed, in case-control designs, assessment of current or prior factor status is made *after* case diagnosis. Controls are used to obtain an estimate of the prevalence of the factor in the source population at risk for the endpoint.

In case-control studies, cases may be identified from several different sources: hospitals and clinics, community outreach screenings, and cancer and other state and national registries. Controls may be identified from those same sources, as well as from other types of registries, such as drivers, voters, population (e.g., in Scandinavia), and the Centers for Medicare and Medicaid Services (United States), or from a general population using mechanisms such as random-digit dialing. Two classic types of case-control studies have been defined: hospital (clinic)-based and population-based. In a hospital-based case-control study, cases and controls are sampled from the same practice, clinic, hospital, or medical care system. Typically, controls are individuals diagnosed with conditions other than the endpoint of interest that are thought not to be related to the factor of interest (i.e., the prevalence of the factor in the controls is expected to be the same as in the source population). This assumption can be difficult to prove, and, if incorrect, can lead to a biased estimate of the association between the factor and the endpoint. In a population-based case-control study, cases and controls are sampled from the same catchment area or the general population. For instance, cases may be

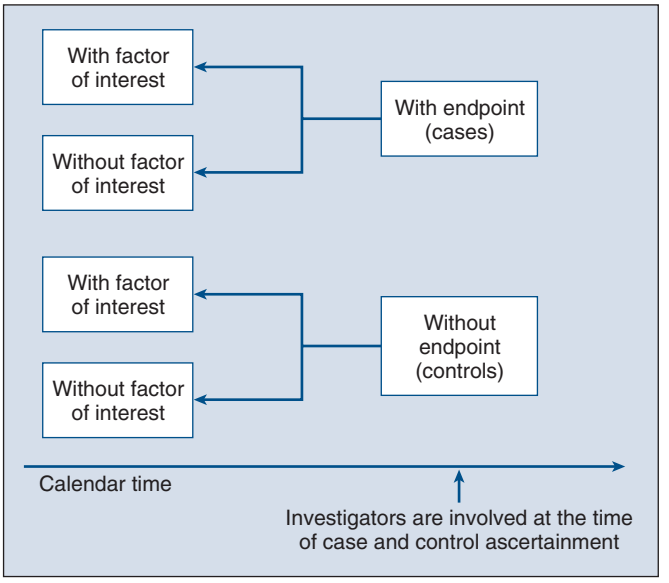


Figure 25-9 • Schematic of a case-control study.

sampled from a community hospital, and controls may be randomly sampled from the residents of the hospital's catchment area. Alternatively, cases may be sampled from a state cancer registry and controls may be sampled from residents of the state by random-digit dialing.

The factor of interest and its extent may be assessed using several possible methods. These include review of medical records, interview or administration of a questionnaire, or measurement of biological specimens, again at the time of ascertainment of the cases and controls.

As a simple illustration of the case-control design, consider a new hypothetical research question addressing second cancer risk:

To appropriately counsel women diagnosed with premenopausal breast cancer, oncologists would like to know whether these women have a higher risk of developing ovarian cancer than women not diagnosed with premenopausal breast cancer. If oncologists do not have access to a large cohort of women with information on breast and ovarian cancer diagnoses, then they may consider conducting a case-control study to address their research question in a faster and less expensive way than might be done if they developed a new prospective cohort study. In this case, the investigators would identify cases of ovarian cancer and controls without ovarian cancer and then ascertain the women's prior history of premenopausal breast cancer. Incident cases of ovarian cancer could be identified from the state cancer registry during a specified number of years, and controls free of a diagnosis of ovarian cancer could be identified from random-digit dialing of state residents who must have been residing in the state during the same time interval as the cases. Both cases and controls could then be sent a questionnaire asking them about their prior history of premenopausal breast cancer, and medical record information could be requested to confirm any reported diagnoses.

At first glance, the case-control design might appear simple and thus, straightforward to conduct. Oncologists have access to cases and "just need to find some controls." In fact, studies of this design require substantial forethought in sampling cases and controls and in assessing the factor of interest to avoid inaccurate results. Thinking back to the cohort design, two considerations for causal inference were described—temporality and comparability.

Temporality

In the case-control design, temporality cannot be ensured because the factor is determined at or after the occurrence of the endpoint of interest, rather than before the occurrence of the endpoint. For example, if investigators collect information about cases' and controls' recent history of the factor, they may not capture the relevant factor status because cases may have changed their factor status as a result of having experienced the endpoint (e.g., cases may change their diet near the time of recurrence due to prodromal symptoms). Likewise, high-grade tumors (cases) may have higher expression of a biomarker (factor of interest) in tissue removed at surgery than low-grade tumors (controls) because the tumor influenced the production of the factor, rather than the factor influencing the development of high-grade disease.

Comparability

In contrast to cohort studies, where *comparability* refers to similarity of those with and without the factor of interest, in case-control studies it refers to similarity of those with and without the endpoint of interest. Comparability encompasses similarity in (1) recruitment from the source population; (2) assessment of the factor of interest; and (3) assessment and handling of confounders. Pertinent to recruitment from the same source population, a classic problem in case-control studies is selection bias, which occurs when inclusion of individuals with and without the endpoint is differentially dependent on whether or not they have the factor of interest. Recall that selection bias in a cohort study occurs when inclusion of individuals with and without the factor is differentially dependent on their likelihood of developing the endpoint of interest. In a case-control study, selection bias can result from differences in the mechanisms and timing of selection of cases and controls. Selection bias can be induced unwittingly by the investigators or by mechanisms beyond the control of the investigators.

Ideally, controls should be sampled at the same time (or during the same interval of time) as cases (Fig. 25-10) to avoid differences in the factor experience of the source population over time. Time refers to the most relevant time axis, for instance, calendar time, age or time since cancer treatment. Looking at Figure 25-10, the source population can be visualized as an at-risk cohort, although the cohort is not enumerated and the cohort members are not observable during their entire time at risk. At the time that individual 5 develops the endpoint, individuals 2 and 8 are eligible to serve as controls because they have not yet developed the endpoint. Individual 8 might be selected as a control. Note how similar this diagram is to earlier diagrams of the Kaplan-Meier method and the nested case-control study design. To illustrate this sampling scheme, consider the second cancer example:

Cases are women recently diagnosed with ovarian cancer identified from a state cancer registry. At the time (i.e., calendar time) that each case is diagnosed, investigators select a woman who is the same age as the case (±2 years) and who has not been diagnosed with ovarian cancer to serve as the control from the female population of the state obtained through random-digit dialing. In this way, cases and controls are matched on both age and calendar time and, thus, should have a similar opportunity to develop premenopausal breast cancer and ovarian cancer.

Sometimes in oncologic case-control studies, controls are selected after ascertaining cases for practical reasons (Fig. 25-11). For instance, in the second cancer example, it may take investigators 10 years to identify a sufficient number of cases because ovarian cancer is a relatively rare cancer. Investigators may decide that it is too time-consuming and expensive to ascertain controls at the same time as cases. Instead, they may decide to sample controls after all of the cases have been ascertained. However, by sampling controls later in calendar time than cases, controls may not necessarily be sampled from the same source population as cases because time has elapsed. This sampling scheme may lead to at least two possible biases. The first is selection bias due to secular trends in factors or confounders not recognized, and therefore not measured, by investigators. For instance, in the second cancer example, if the investigators were not aware that

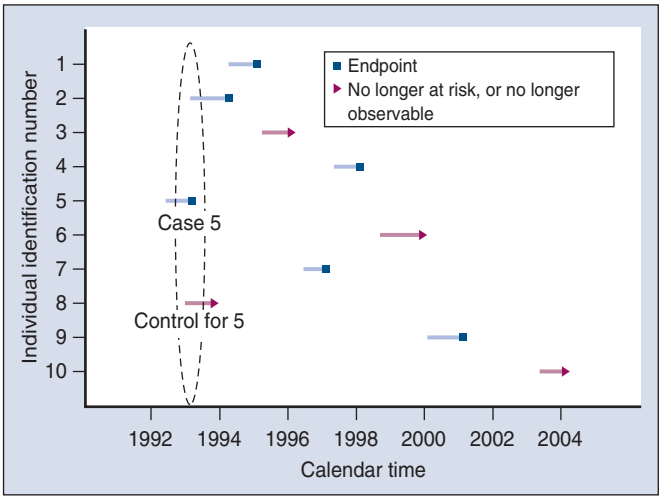


Figure 25-10 • Schematic of a case-control study in which controls are sampled at the same time as the cases.

a mammography campaign had been introduced into the state in the last 3 years of the study, they might observe a higher prevalence of prior premenopausal breast cancer among controls than among cases simply because controls would have been more likely than cases to be screened during the mammography campaign and to have occult breast cancer diagnosed before enrollment in the study.

A second example of selection bias related to sampling controls at a later date than cases is *survival bias*. This bias is the same as the one described earlier (see discussion of Nested Case-Control Study under Design Considerations for Causal Inference: Alternative Prospective Designs) and occurs when the factor of interest is associated with longevity, but not necessarily with the endpoint of interest. In this case, investigators may observe an association between the factor and endpoint merely because controls are required to remain alive for a longer period of time (i.e., to an older age) than cases.

Even if cases and controls are sampled at the same time, selection bias still may be introduced if cases and controls are recruited from different source populations. Consider the second cancer example redesigned as a hospital-based case-control study. Instead of selecting ovarian cancer cases from a state cancer registry and controls from the general population, investigators might decide to select cases and

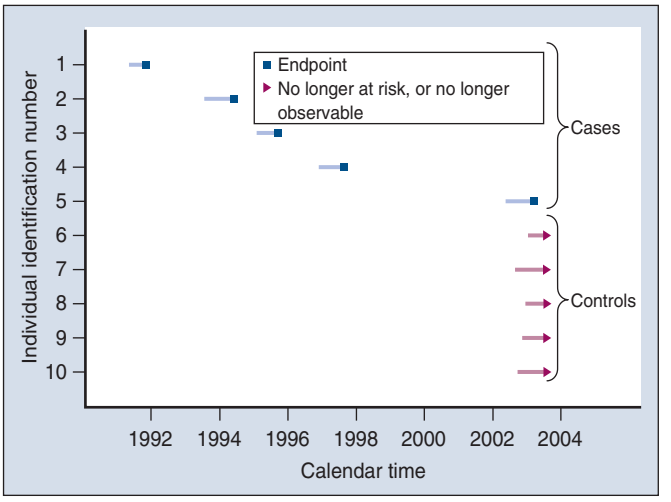


Figure 25-11 • Schematic of a case-control study in which controls are sampled after the cases.

controls from an academic medical center with a large high-risk ovarian and breast cancer clinic. Cases might be defined as women recently diagnosed with ovarian cancer at the high-risk ovarian and breast cancer clinic because it is a convenient source of ovarian cancer cases. Controls might be defined as similarly aged women attending the medical center for minor foot surgery. Cases and controls appear to be sampled from the same source population, namely, the same academic medical center. However, they actually are sampled from two different source populations: cases are sampled from a source population enriched with women with a prior history of premenopausal breast cancer because they are visiting the high-risk clinic, whereas controls are not enriched with women with a prior history of premenopausal breast cancer because they are not visiting the high-risk clinic. Therefore, even if premenopausal breast cancer truly is associated with subsequent development of ovarian cancer, the association will be incorrectly too large because cases and controls were sampled from two different source populations. A better choice of controls for these cases would be other similarly aged women attending the same high-risk ovarian and breast cancer clinic who have not been diagnosed with ovarian cancer.

Another example of selection bias is *detection bias* or *medical surveillance bias*. This bias occurs when those subjects with the factor of interest are more or less likely to be screened or investigated or otherwise more or less likely to have the endpoint detected than those without the factor of interest. In the second cancer example, physicians may screen women with premenopausal breast cancer more often for other types of cancer, such as ovarian cancer, than women without a diagnosis of breast cancer. If investigators do not take differences in ovarian cancer screening into account, then they may observe a higher prevalence of prior premenopausal breast cancer among cases than among controls simply because women with a diagnosis of premenopausal breast cancer are more heavily screened for ovarian cancer than women without a diagnosis of breast cancer.

A further example of selection bias is another form of *survival bias*. This bias occurs when those with the factor of interest have a different likelihood of being ascertained for the study than those without the factor, usually when the factor affects the likelihood of surviving long enough to be enrolled in the study (e.g., to complete a questionnaire or to collect biological samples). In the second cancer example, some women may be too sick or may have died from their ovarian cancer before investigators have the chance to mail them a questionnaire. In this case, only women who live a sufficiently long time after their diagnosis will be able to complete the questionnaire. Therefore, investigators may falsely attribute factors associated with shorter or longer survival following the endpoint to the development of the endpoint itself. Optimally, cases should be ascertained soon after they experience the endpoint of interest; enrolling incident rather than prevalent cases avoids this bias.

In addition to bias introduced in the process of case and control recruitment, bias also can be introduced at the time of factor assessment. This bias is called *observation bias*, and it occurs when the accuracy of assessing the factor of interest differs by case and control status. Sources of observation bias in case-control studies are plentiful. Two examples are given here. Cases may report their factor history more accurately than controls because they are seeking to explain their disease or are more willing to admit their factor history; this form of observation bias is called *recall bias*. One way to reduce the potential for recall bias is to blind cases and controls to the study hypotheses or to ascertain the factor status very soon after diagnosis to reduce the amount of time that the subject can contemplate his or her diagnosis. Recall bias is not the inability to accurately remember one's past factor history; this is merely poor recall. The key to recall bias is that the accuracy (or inaccuracy) of the recollection differs between those with and without the endpoint. Another example of observation bias is when an interviewer prompts cases more than controls, resulting in a more complete factor

history for cases. This form of observation bias is called *interviewer bias*, and can be minimized by blinding the interviewer to case-control status.

As in cohort studies, confounders also may contribute to lack of comparability, although, in this case, it is comparability between cases and controls. In case-control studies, confounders are handled in the same way as in cohort studies. To address confounders in a case-control study, investigators should collect information on potential confounders from cases and controls at the time of enrollment and then take these variables into consideration in the analyses (see the section on Statistical Analysis of Case-Control Studies). However, sometimes the distribution of these potentially confounding variables is very different between cases and controls, making it difficult to take these variables into account using statistical methods. One way to make the distributions of these potentially confounding variables more similar between cases and controls is to match controls to cases on these confounders and then analyze the data, taking into consideration the matching. Matching can be done at the individual level (*individual matching*), where each control is matched to one particular case on potential confounders (including time axes such as age), or at the group level (*frequency matching*), where controls are selected to have the same distribution of potential confounders as the entire group of cases. Matching enhances the ability to take these variables into account in the analysis, but, as noted previously, matching does not eliminate confounding. If cases and controls were matched on a true confounder and the data were not analyzed taking into consideration the matching, the results would be attenuated. The reason for this attenuation is that matching cases and controls on a third factor that is also correlated with the factor of interest (i.e., the confounder) makes cases and controls more similar on the factor of interest. Therefore, an analytic approach that focuses on the remaining differences between cases and controls is necessary.

Other Design Considerations In Case-Control Studies

Stated colloquially, the general principle guiding the design of case-control studies is: whatever investigators do to cases they must also do to controls. Stated more formally, selection of cases and observation of their factor and confounder status should be the same as selection of controls and observation of their factor and confounder status to reduce the possibility for selection bias, observation bias, and confounding.

There are very occasional exceptions to this statement. One is sampling of cases and controls from different source populations in studies of genetic variation and cancer. For example, in a study of polymorphisms (on chromosomes other than X and Y) in relation to testicular cancer, women could potentially be sampled as controls if they were sampled from individuals with the same racial and ethnic heritage as testicular cancer cases (to minimize confounding by race/ethnicity, i.e., *population stratification*), and if they were matched to cases on age (to minimize survival bias). Even though women are not at risk for testicular cancer, and thus are not in the same source population as cases, they could potentially still provide a valid estimate of allele frequencies in the source population that gave rise to the cases. However, investigators should still think very carefully about other potential differences between testicular cancer cases and female controls that might distort the relationship between polymorphisms and testicular cancer.

In contrast to the preceding example, blood bank donors, a convenient source of controls, may not provide a valid estimate of allele frequencies in the population that gave rise to the cases. Blood donors must meet very restrictive eligibility criteria, which may be related to their factor experience, such as susceptibility to infection, risk-taking behaviors, altruism, and so on. Therefore, in general, extreme caution must be taken in using controls that, from the outset, are clearly not from the source population that gave rise to the cases.

Statistical Analysis of Case-Control Studies

Due to differences in the design of case-control and prospective studies, data from case-control studies must be analyzed differently than data from prospective studies. In a case-control study, investigators decide how many cases and controls to sample. Typically, investigators do not select all possible cases and controls from the source population. More often, they select a sample of possible cases and controls, often with a greater sampling fraction for cases than controls. Therefore, even if lack of temporality were not of concern, cumulative incidences (or rates) could not be calculated from case-control data, because investigators set the number of cases relative to controls in the study. For example, in a source population that consists of 1000 people followed for 1 year, of whom 100 develop the endpoint and 900 do not (assuming no losses to follow-up), investigators might sample all of the cases (n = 100, 100% sampling fraction) and an equal number of controls (n = 100, 11% sampling fraction) for their case-control study. If investigators were to calculate a cumulative incidence based on these case-control data, the incorrectly calculated measure would be 100/(100 + 100) = 0.5 over 1 year, whereas the true cumulative incidence of the endpoint is actually 100/1000 = 0.1 over 1 year.

Instead of the cumulative incidence (or rate), the odds of the factor should be calculated in case-control studies in which cases and controls are not matched. The *odds* is the ratio of the probability of having the factor of interest divided by the probability of not having the factor:

$$\text{Odds} = P_F/(1 - P_F),$$

where P_F means the probability of having the factor and $1 - P_F$ means the probability of not having the factor.

The odds can range from 0 when the probability of the factor is 0 to infinity when the probability of the factor is 1. One odds is calculated for cases and another one for controls. Then, to determine the association between the factor of interest and the endpoint, the ratio of the two odds—or the *odds ratio* (OR)—is calculated as follows:

$$\text{OR} = [P_{F|case}/(1 - P_{F|case})]/[P_{F|control}/(1 - P_{F|control})]$$

To illustrate using the second cancer example, the probability of a prior history of premenopausal breast cancer is 15% or 0.15 in ovarian cancer cases and 0.08 in controls without ovarian cancer. The odds of prior premenopausal breast cancer in cases is thus 0.15/0.85 = 0.1765, and the odds of prior premenopausal breast cancer in controls is 0.08/0.92 = 0.08700. The OR then equals 0.1765/0.08700 = 2.03, suggesting a positive association between premenopausal breast cancer and ovarian cancer. A simpler way of calculating the OR is to multiply the number of exposed cases by the number of unexposed controls and then to divide by the product of the number of unexposed cases and exposed controls (Fig. 25-12). The OR is unitless and can range from 0 to infinity.

If cases and controls are individually matched, then the OR is calculated differently. Only pairs in which the case and its control differ on their factor status contribute information. These discordant pairs are used to calculate the matched OR, defined as the number of pairs in which the case has the factor and the control does not, divided by the number of pairs in which the case does not have the factor and the control does have the factor (Fig. 25-13).

Recall that controls should be sampled during the same calendar time as cases (see Fig. 25-10) but sometimes are sampled after the cases have been ascertained (see Fig. 25-11). If the former is done, then the OR is a direct estimate of the true rate/hazard ratio for the same reason as in the nested case-control study, assuming no selection bias, observation bias, or confounding. Note, though, that from an inferential perspective, the case-control study nested within a cohort is preferable to the case-control study in which the source population is not enumerated at baseline, because the factor is assessed

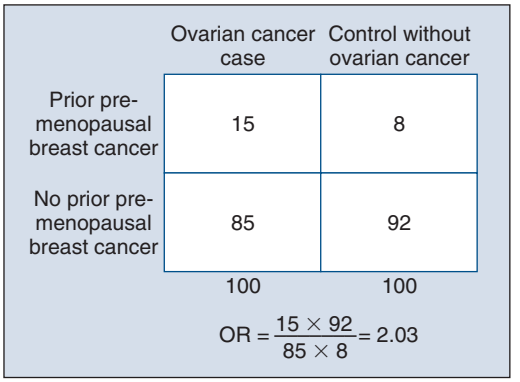


Figure 25-12 • Calculation of the odds ratio as the measure of association in the hypothetical *Second Cancer* case-control study.

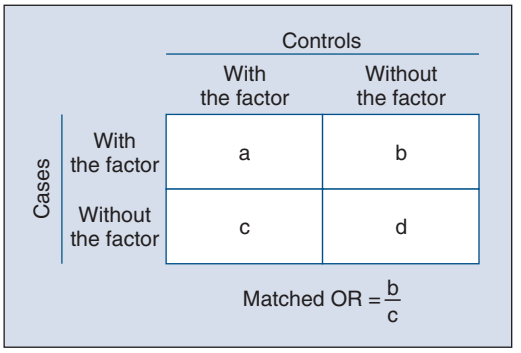


Figure 25-13 • Calculation of the matched odds ratio as the measure of association in a matched case-control study.

before the endpoint occurs, and the likelihood of selection bias is reduced.

When controls are sampled after cases in calendar time, the OR estimates the cumulative incidence ratio (assuming no selection bias, observation bias, or confounding), but only when the endpoint is uncommon in the source population (e.g., ovarian cancer in the second cancer example). Here is the logic:

The OR just described (i.e., the factor OR) is mathematically equivalent to the endpoint OR, which is defined as the odds of the endpoint among those with the factor divided by the odds of the endpoint in those without the factor:

$$\text{Endpoint OR} = [P_{D|F+}/(1 - P_{D|F+})]/[P_{D|F-}/(1 - P_{D|F-})]$$

where $P_{D|F+}$ means the probability of the endpoint among those with the factor and $P_{D|F-}$ means the probability of the endpoint among those without the factor.

The endpoint OR can be written as a function of the cumulative incidence ratio:

$$\text{Endpoint OR} = [P_{D|F+}/P_{D|F-}] \times [(1 - P_{D|F-})/(1 - P_{D|F+})]$$

or

$$\text{Endpoint OR} = \text{cumulative incidence ratio} \times [(1 - P_{D|F-})/(1 - P_{D|F+})]$$

When the endpoint is uncommon—for example, less than 10%—among those with and without the factor in the source population, then

$$1 - P_{D|F-} \cong 1 \text{ and } 1 - P_{D|F+} \cong 1$$

Thus,

$$\text{Endpoint OR} = \text{cumulative incidence ratio} \times [1 - P_{D|F-)}]/[1 - P_{D|F+}]$$

$$\approx \text{cumulative incidence ratio} \times 1$$

$$\approx \text{cumulative incidence ratio}$$

Except when the OR equals 1, the value of the OR is always further away from 1 than the value of the cumulative incidence ratio. For example, when the cumulative incidence ratio is greater than 1

$$P_{D|F+} > P_{D|F-} \text{ and } 1 - P_{D|F+} < 1 - P_{D|F-}$$

$$\text{So, } [1 - P_{D|F-}]/[1 - P_{D|F+}] > 1, \text{ and}$$

$$\text{Endpoint OR} = \text{cumulative incidence ratio} \cdot [1 - P_{D|F-)}]/[1 - P_{D|F+}]$$

Therefore, Endpoint OR is greater than the cumulative incidence ratio.

In this case, the OR suggests a stronger strength of association than the cumulative incidence ratio. If the cumulative incidence ratio had been less than 1, the OR would have been less than the cumulative incidence ratio, suggesting a stronger protective association. The more common the endpoint is in the source population (e.g., death from diffuse large B-cell lymphoma in the *therapeutic effectiveness* example), the greater is the overestimation of the cumulative incidence ratio by the OR.

If investigators wish to take potentially confounding factors into account, then the OR can be estimated by logistic regression for studies in which cases and controls are not matched, and by conditional logistic regression for studies in which cases and controls are matched. Detailed descriptions of these regression models can be found in biostatistics textbooks.

DRAWING INFERENCES FROM STUDIES USING EPIDEMIOLOGIC METHODS

Once the results are in hand, investigators must consider the ability to draw causal inferences—in other words, they must consider all possible explanations for their finding beyond cause. These alternative explanations may include selection bias, observation bias, and confounding, as well as chance variability.

Even if temporality and comparability were considered in the design phase of the study, error still may arise during the conduct of observational studies. For example, even if a rigorous definition of the source population and a rigorous approach to sampling from the source population were used, selection bias still is possible because participation is voluntary. The investigators always must be cognizant of these issues and should try to investigate how likely they were to have occurred and the extent to which they could have affected the results.

Chance variability pertains to the notion that only one sample of all possible members of the underlying population is studied. Assuming no selection bias, this sample should differ from the underlying population only in a random way. Thus, estimates of the measure of endpoint occurrence or association from this sample should differ from the true value in the full underlying population only in a random or nonsystematic way. Chance variability is reduced by studying a larger sample. Therefore, in the design phase of the study, investigators should consider the most appropriate sample size to optimize the statistical ability to detect an association if one truly exists. Sample size determination is based, in part, on the expected cumulative incidence or rate of the endpoint in those without the factor (cohort study), the expected prevalence of the factor among controls (case-control study), and/or the expected size of the association. In the analysis phase of the study, the extent of variability in the estimate of the measure of endpoint occurrence or association

should be quantified, usually with a confidence interval or *P* value. Investigators should then consider this variability when drawing inferences from the study. For instance, if the RR is > > 1, but the *P* is greater than 0.05 (the typical cut-point for statistical significance), is there an association or not? It depends: if the hypothesis were motivated by existing scientific evidence, then the conclusion from the study might be that the findings suggest an association, rather than that no association exists. Interpretation of association magnitudes and significance is an art; it is not dictated by simple rules.

After considering alternative explanations for an epidemiologic finding, investigators still cannot conclude that the observed association reflects causation. In epidemiology, any given research question must be evaluated many times using different designs and study populations, and usually by independent investigators.

Each epidemiologic study design has different potentials for each type of bias. If findings from studies that used different designs are similar, then this may provide evidence in favor of a causal association. If findings differ, then more weight should be given to studies that used designs that maintained temporality and were the least susceptible to bias.

In general, prospective cohort studies and their derivative designs provide stronger evidence for a causal association than retrospective cohort studies and case-control studies, because they maintain the correct temporal sequence between the factor and the endpoint and because they are less susceptible to selection and observation biases. Although both prospective cohort studies and randomized trials are likely to have the correct temporal sequence, evidence from randomized trials usually trumps evidence from cohort studies because randomization reduces the likelihood of selection bias and confounding.

Different study populations (defined, for example, by country, race/ethnicity, or socioeconomic status) may have different characteristics that influence the likelihood or extent of confounding. If findings are the same across study populations, then this may provide evidence in favor of a causal association. If findings differ, reasons may include differences in unmeasured confounders or differences between study populations in the presence and prevalence of factors that might modify the association. At this point, investigators should think about possible reasons for differences across study populations and investigate these reasons in subsequent studies.

Chance variability is possible in any study. When the results from independent epidemiologic studies are not too heterogeneous, meta-analyses can be performed to generate a more stable (i.e., less variable) summary estimate of the association.

When considering whether an observed association between a factor and endpoint is causal, some investigators find it useful to think about the nine "aspects" of an association that Sir Austin Bradford Hill described in 1965[3]:

1. Strength: How big is the measure of association?
2. Consistency: Are findings from studies conducted using different designs in different populations similar?
3. Specificity: Is the factor only associated with the endpoint of interest, and is this the only factor that has been found to be associated with the endpoint of interest?
4. Temporality: Was the factor experienced before the endpoint occurred?
5. Biological gradient: Does the magnitude of the measure of association increase (or decrease) with increasing extent of the factor?
6. Plausibility and 7. Coherence: Is the association supported or refuted by the contemporary biologic literature?
8. Experiment: Does the magnitude of the measure of association decrease (or increase) after changing the factor status?
9. Analogy: Have associations between similar factors and similar endpoints been observed?

Temporality has been highlighted in this chapter because it is the only aspect of an association necessary for causality. The other aspects neither rule in nor rule out the potential for an association to be causal.

In light of all these considerations, the original *therapeutic effectiveness* example is now reexamined. The investigators observed that patients with 2 copies of the haplotype had 0.5 times the risk of death, and patients with 1 copy had 0.7 times the risk of death compared with patients with no copies of the haplotype. These results were statistically significant ($P < 0.05$).

What should investigators infer? They conducted a prospective cohort study in which haplotyping was performed using samples collected at the start of the study; hence, the correct temporal sequence was obtained. All individuals from one arm of the trial were included in the study; therefore, selection bias is unlikely to have been introduced into the study. All trial participants were followed actively and in the same manner for survival. Therefore, it is unlikely that the ability to observe the endpoint differed by haplotype (i.e., no observation bias). The investigators observed that the prevalence of the haplotype did not vary by any of the participant characteristics measured at the start of the study, including race or ethnicity; therefore, confounding also is unlikely. The strength of the association between the haplotype and survival is relatively strong, suggesting that confounding alone is unlikely to explain the association. Although the findings were statistically significant, chance cannot be ruled out as an explanation for the findings. This is the first study of this hypothesis, so there are no other studies to which to compare the findings. The RR of death decreased with increasing number of copies of the haplotype, demonstrating a biological gradient. The hypothesis was well motivated by scientific evidence that the P450 enzyme enhances the action of the chemotherapeutic agent, and that the haplotype of interest encodes a more active form of the enzyme. Findings from this study are analogous to those from a study that investigated genetic variation in a different metabolic enzyme with cancer survival after treatment with a different chemotherapeutic agent.

After contemplating all of these aspects of the study and its findings, the investigators might conclude that the findings are promising, but because the study is observational and the first to investigate this hypothesis, additional studies should be conducted before the findings can be translated into clinical practice. As already mentioned, a randomized trial of this research question is not possible because haplotype is an inherent characteristic of an individual. However, if, in the future, findings from this study are upheld in other studies, the next step might be to conduct a trial in which patients without the beneficial haplotype are randomized to either a drug that induces the P450 enzyme or placebo, concurrent with administration of the new chemotherapeutic agent.

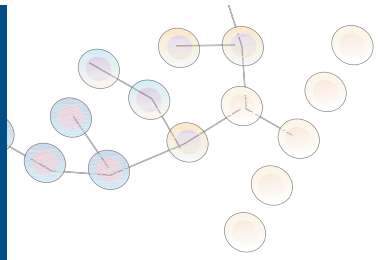
FINAL THOUGHTS ON THE USE OF EPIDEMIOLOGIC METHODS IN ONCOLOGIC RESEARCH

This chapter has described epidemiologic methods for formally testing hypotheses pertinent to oncology and discussed their rationale. Epidemiology is a flexible method that can be applied to many different types of translational and clinical studies that do not necessarily have an etiologic or population-level focus. For instance, in the hypothetical *prognosis* example, the focus of the study appears to be on the measurement of a newly discovered tissue marker using an innovative technique. However, use of this innovative technique does not ensure correct inferences about whether or not the tissue marker predicts prognosis in the study population, nor its applicability to other populations, even if the technique is highly accurate. Obtaining a valid answer also hinges on choosing the

appropriate study population, design, and analysis, all of which require epidemiologic thinking. For this reason, a multidisciplinary research team that includes collaborators from clinical science, basic science, biostatistics, and epidemiology is optimal for addressing the complex translational and clinical questions posed in modern oncology.

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26 Cancer Prevention, Screening, and Early Detection

Jason A. Zell and Frank L. Meyskens

SUMMARY OF KEY POINTS

Etiology and Pathogenesis

- Prevention of cancer is based on an understanding of the etiology and pathogenesis of the individual organ malignancies. The identification of at-risk individuals is based on familial/genetic and environmental influences.
- Smoking tobacco remains the number one cause of malignancy and accounts for about 30% of the mortality from cancer. The role of diet in cancer risk is substantial.
- Infections are an important component of cancer risk, and major etiologic agents for different organs include viruses (hepatitis B and C [hepatocellular], human papillomavirus [cervix and some oral cancers], Epstein-Barr virus [nasopharyngeal carcinoma]), bacteria (*Helicobacter pylori* [stomach]), and parasites (*Schistosoma haematobium* [bladder], *Clonorchis sinensis* [cholangiocarcinoma]).

Screening and Early Detection

- Effective screening and early detection techniques for cancer include visual examination (skin, cervical, and oral cancers), cytology (cervical cancer), mammography (breast cancer), and fecal occult blood, sigmoidoscopy, and colonoscopy (colorectal cancers).
- Screening for prostate cancer by serum prostate-specific antigen (PSA) measurement has been widely adopted, although its impact on overall survival remains uncertain. No successful method has been established for lung cancer screening.

Chemoprevention

- "Proof of principle" for the prevention of primary cancers has been established convincingly for breast cancer (tamoxifen and raloxifene), hepatocellular carcinoma (vaccination against hepatitis virus B), and cervical cancer (vaccination against human papillomavirus).
- Prevention or regression of various intraepithelial neoplasias has been demonstrated: actinic keratoses (diclofenac), oral leukoplakia (retinoids), cervical intraepithelial neoplasms (topical retinoic acid), adenomatous polyps (calcium, aspirin, celecoxib), and gastric dysplasia (anti-*H. pylori* therapy, antioxidants).
- Secondary aerodigestive cancers can be prevented with high-dose 13-*cis*-retinoic acid but at the price of unacceptable toxicity.
- An increased incidence of secondary lung cancers in smokers supplemented with β-carotene or 13-*cis*-retinoic acid demands particular caution in the development of chemoprevention agents.
- Unexpected cardiovascular toxicity demonstrated by selective cyclooxygenase-2 inhibitors demonstrated in colon polyp trials has led to a major concern about risk-risk in the evaluation of risk-benefit.
- Attempts to develop less toxic or low-dose combination interventions for all of the major cancers are being investigated.
- Useful resources for those interested in research in cancer prevention, screening, and early detection are provided.

INTRODUCTION

The guiding principles of this chapter and oncology should be that the best treatment of malignant disease is its prevention, and that the disease to be prevented is carcinogenesis, not cancer (Fig. 26-1).[1]

By the time a cancer is diagnosed, even with the advanced techniques now available, more than 90% of the biologic life of the tumor is over, and the best chance to control the malignant process has been missed. The extensive advances in our understanding of carcinogenesis at the molecular level in the past decade, the rediscovery of intraepithelial neoplasia as an early, recognizable precursor of many solid tumors that can be managed simply, and the well-defined successes of screening and early detection in reducing the morbidity and mortality from several major cancers, need to be brought to bear on the problem of malignancy in a concerted and widespread fashion, with clinical oncologists working closely with primary care physicians and subspecialists. Because fewer than 50% of cancers are cured, once established, and because gains in treatment effectiveness have been increasingly incremental and expensive, early detection and prevention of cancer should be pursued aggressively as a means to reduce morbidity and mortality.

Many major diseases of humankind have been controlled by the systematic application of prevention strategies, including morbidity and mortality from nutritional and infectious diseases and vehicular trauma.[1] Among chronic diseases, the incidence of cardiovascular disease has decreased markedly as smoking has declined, cholesterol and blood pressure lowered, and exercise encouraged. It is likely that these simple approaches have led to a greater overall benefit to health for the population than the effect of all intensive care units, but such direct comparisons are difficult to make. In general, appreciation of the role of prevention strategies in the overall management of cancer has been neglected by clinical oncologists, although health care planners and society as a whole are intensely interested in this topic.[2] Cancer prevention strategies can be considered at three different

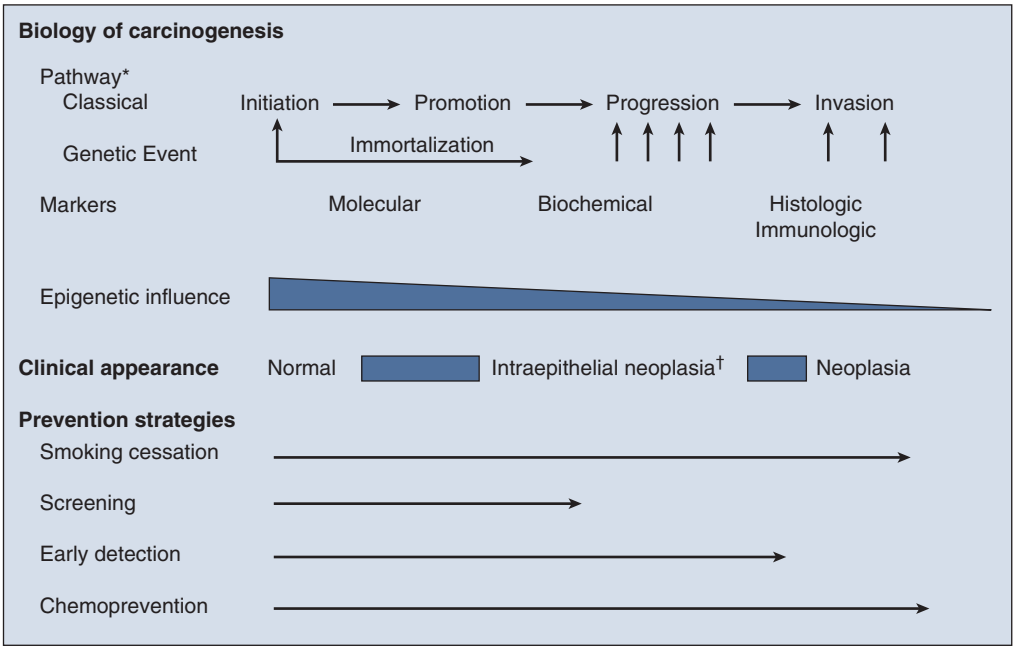


Figure 26-1 • Integration of the biology of carcinogenesis and prevention. *Hereditary alteration(s) or baseline polygenic representation provides the constitutive "set point" on which postzygote changes occur. †Precancer, premalignant lesion in general clinical parlance.

major levels: primary, secondary, and tertiary. This chapter will deal primarily with primary and secondary prevention and with tertiary prevention as represented by chemoprevention of second malignancies.

Normal, asymptomatic individuals are the population at which primary prevention is addressed. Major strategies for risk reduction include changes in diet, increased physical activity, tobacco awareness, decreased exposure to the sun, and reduced intake of alcohol. With the increasing identification of constitutive genetic alterations that predispose individuals to cancer, this group has been targeted for primary interventions such as prophylactic surgery.[3] Annual screening mammography in women older than 50 years of age and smoking cessation or chemoprevention in a group of asymptomatic smoking individuals are also examples of targeted primary prevention.

Secondary prevention is directed toward individuals with evidence of preneoplastic, clinically identifiable progression, but without frank malignancy. The phenomenon of intraepithelial neoplasia, also called preneoplasia or precancer, has become of widespread interest, and management of these lesions has the potential to abrogate the disease process early. Many organ sites have preneoplastic counterparts that should be amenable to early intervention (Table 26-1). Representative examples of this type of secondary prevention include suppression or reversal of oral leukoplakia, cervical intraepithelial neoplasia (CIN) or Barrett's esophagus and inhibition of polyp formation or progression (Fig. 26-2).

Tertiary prevention involves decreasing the morbidity of established disease. Chemoprevention of second malignancies is a good example of tertiary prevention. The distinction between primary, secondary, and tertiary prevention can sometimes become blurred. Further, tertiary prevention and adjuvant therapies can share many of the same goals. From the viewpoint of the clinical oncologist, probably the best way to look at prevention is as one more therapeutic modality for the management of cancer, directed at its control in the earliest stages. The observation that the addition of a retinoid after bone marrow transplantation markedly enhances the survival of children with refractory neuroblastoma represents an informative synthesis of a quaternary treatment approach and a tertiary prevention modality.[4]

Table 26-1 Common Clinical Precursors (Intraepithelial Neoplasia) of Cancer

Organ Site	Precursor	Method of Detection*
Oropharynx	Leukoplakia	Visual†
Skin	Actinic keratoses/moles	Visual†
Esophagus	Barrett's esophagus	Endoscopy
Colon	Adenoma (polyp)	Sigmoidoscopy, colonoscopy
Breast	LCIS, DCIS‡	Mammography, ultrasound, MRI
Cervix	Intraepithelial neoplasia	Colposcopy

*Cytology and/or biopsy is required in almost all cases before definitive therapy can be initiated.

†Elegant in situ optical spectroscopic methods are being developed to detect early preneoplastic changes, including enhancing the signals with fluorescent molecules.

‡Lobular and ductal carcinoma in situ.

Avoidable Causes

An extensive analysis of the topic of avoidable causes of cancer was performed over 2 decades ago by Doll and Peto[5]; these investigators concluded that 50% to 70% of all human cancers were preventable. No new data have emerged that would alter that overall estimate, although some of the specifics have changed.[6] The major avoidable risk factors can be broadly separated into four areas: tobacco, infectious, chemical (including hormonal), and diet.

Tobacco smoke is far and away the most important carcinogen to which humans are exposed on a routine basis. The morbidity and mortality from tobacco smoke is huge and represents the major preventable cause of all diseases, not just cancer, in modern and many undeveloped societies. It is estimated that more than 500 million smokers now living will die of tobacco-related illnesses.[7,8] What is generally not appreciated is the wide carcinogenic range of molecular

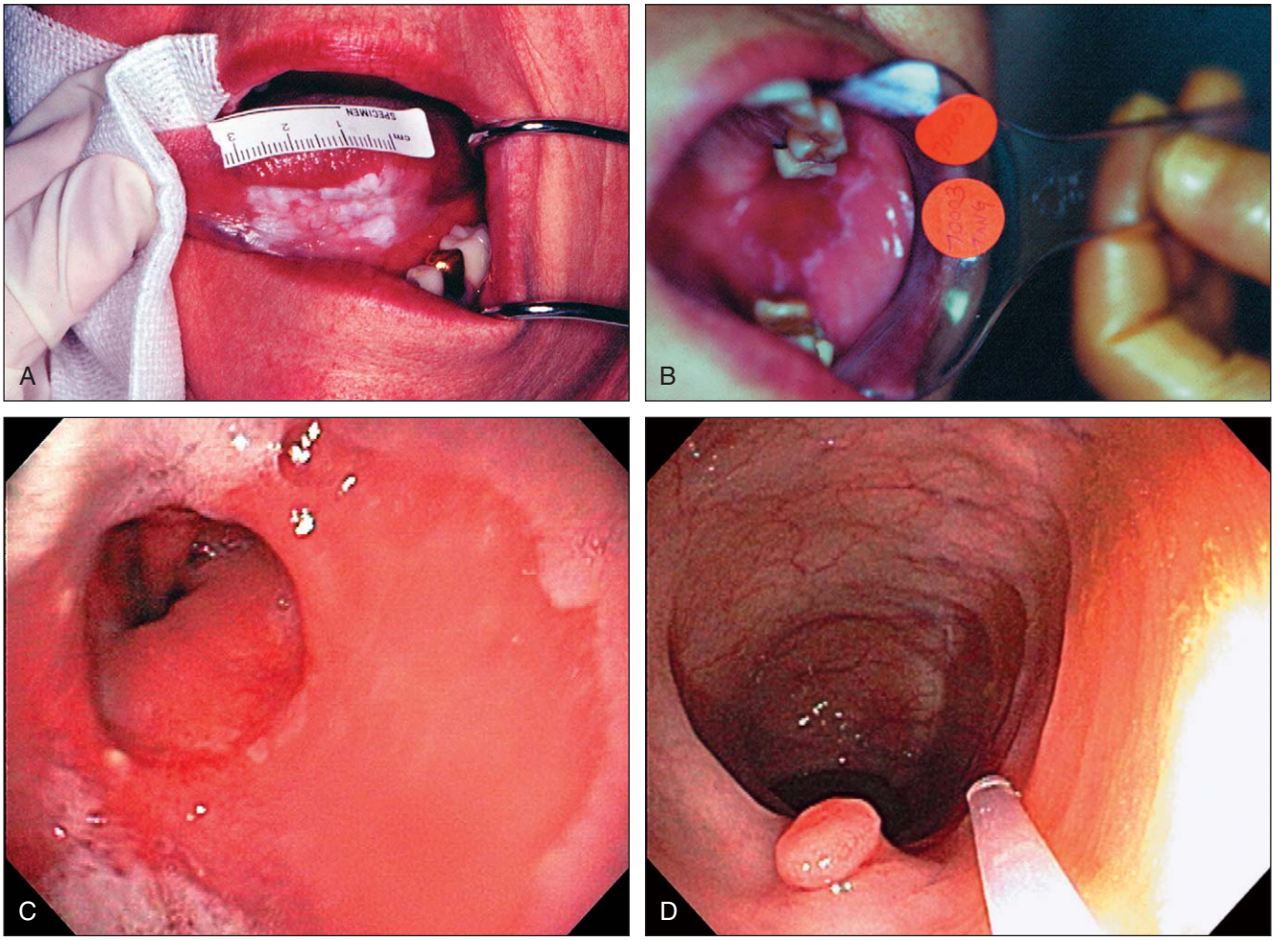


Figure 26-2 • Examples of premalignant lesions. **A,** Leukoplakia. Whitish lesion on side of tongue. **B,** Erythroplakia. Reddish (dark area) lesion in otherwise normal-looking buccal cavity. **C,** Barrett's esophagus (pale area) with high-grade lesion (dark portion). **D,** Adenomatous polyp in proximal sigmoid colon. (Courtesy of Bill Armstrong and Ken Chang.)

damage and the numerous organ sites affected by cigarette smoke.[9,10] In addition to the lungs, cigarette smoking contributes significant attributable risk to the development of cancers of the oropharynx (75%), bladder (50%), esophagus (50%), pancreas (25%), cervix (20%), kidney (15%), and bone marrow (10%). Cigarette smoke facilitates chromosomal instability and enhances transformation at all levels of cancer formation (initiation, promotion, progression), including adversely affecting the natural history of successfully resected early-stage lung cancer.[11] Although the incidence of cigarette smoking has fallen among males, in 1994 lung cancer surpassed breast cancer as the most common cause of death from cancer in females. Lung cancer incidence among females has increased from 1975 through 2003, although the rate of increase has declined since 1991.[12] Well-tested modules have been developed to assist health care workers, including physicians, in applying smoking prevention and cessation strategies.[7] Various forms of nicotine (gum, patch, inhalers, nasal sprays) and behavioral modulators (bupropion) have been effective in increasing the quit rate significantly at very low cost.[8]

The evidence for infectious involvement in human cancer has increased dramatically in the last 15 years (Table 26-2). Hepatitis and human papillomavirus (HPV) clearly play major roles in the development and evolution of hepatocellular and cervical carcinoma, respectively. Vaccines using various viral components as the target have recently been tested; results from these trials strongly suggest that liver cancer and cervical cancer are preventable.[13,14] In addition to the classical and long-recognized associations of the parasites *C. sinensis* to cholangiocarcinoma and *S. haematobium* to squamous cell carcinoma of the bladder, the bacterium *H. pylori* has now been accepted

Table 26-2 Cancers with an Infectious Etiology

Cancer	Agent	Major Mode of Transmission	Intervention
Hepatocellular carcinoma	Hepatitis virus	Maternal, oral	Vaccine
Gastric	*Helicobacter pylori*	Oral	Antibiotics
Cervix	Papillomavirus	Sexual	Vaccine

Several major cancers are of infectious etiology and can be eradicated by preventive intervention.

as an etiologic agent associated with gastric dysplasia, stomach cancer, and a rare type of lymphoma.[15] Early on, these diseases can be treated with antibiotics and the process reversed. Finally, it seems that viruses have a role in the evolution of some lymphomas (human T-lymphotropic virus-1, Epstein-Barr virus [EBV]). These findings all offer new approaches for primary and secondary prevention using standard and new microbiologic and immunologic approaches.

A number of chemicals are known to play a role in cancer causation, perhaps the most widespread being aniline dyes (bladder cancer), asbestos (lung, mesothelioma), and hormones (breast, prostate). The role of endogenous and exogenous hormones in cancer causation is complex and is considered in detail in the sections on breast, prostate, and gynecologic organ sites.[16] Some of the most intensely debated issues in medicine relate to this area. For example, is the overall health benefit of hormone replacement therapy (HRT) worthwhile? Results from the Women's Health Initiative (WHI) trial suggest not,[17] and long-term use of HRT is not recommended.

The question of the specific role of dietary components in cancer prevention remains largely unanswered. Many comprehensive reviews on the topic are available, and the overall recommendation to eat an abundant amount of fruits and vegetables has not changed in 20 years.[18] Ambitious campaigns such as the well-known "5-a-day for better health" campaign to encourage large-scale dietary changes continue.[19] The specific components responsible for the protective effects against cardiovascular disease and cancer remain unclear. The roles of macronutrients, fat, and fiber in prevention have been topics of much discussion. The general recommendation to reduce total calories and fat consumption and to increase fiber is a good one with regard to cardiovascular disease prophylaxis, but whether such a strategy affects cancer outcome remains unproven. Increasing epidemiologic data suggests that physical activity and basal metabolic index play critical roles, and several trials are underway to address these issues.[20]

There is growing evidence that changes in the insulin-like growth factor pathways play an important role in many aspects of lifestyle changes represented by a high basal metabolic index and its control.[20] With increasingly positive protective effects of physical exercise on cardiovascular disease being shown, there has been a renewed interest in the influence of physical exercise on malignant transformation and progression.[21] There has been a great deal of interest in micronutrients as preventive agents, but the results emanating from supplementation in well-done randomized clinical trials thus far have been disappointing.[22] Notable exceptions have included the report that supplementation with a modest dose of vitamin A (25,000 IU per day) can decrease the appearance of cutaneous squamous cell cancer of the skin in individuals with prior actinic keratoses and several trials showing that supplementation with a modest dose of calcium can decrease the subsequent prevalence of cancer polyps by 20%.[23–25]

Probably the most exciting diet-related development has been the identification of a wide range of potentially new and active chemoprevention compounds in food, such as protease inhibitors (soybeans), monoterpenes (citrus fruit oils), polyphenols (nuts), dithiolethiones (cruciferous vegetables), alliums (onion/garlic family), and many others.[26] The opportunity to genetically engineer foods to reduce the risk of heart disease and cancer is a topic of much scientific interest and commercial activity.[27] Nature created these molecules to deal with a hostile toxic environment, and figuring out how to use them for the prevention of cancer should be both scientifically interesting and clinically rewarding.

Screening and Early Detection

Strictly speaking, screening is limited to normal individuals. The science of screening identifies many pitfalls in the design, analysis, and interpretation of such trials, including length and lead-time biases and many others.[28,29] Beyond the technical issues involved in study design, three other requirements addressing implementation, analysis, and interpretation, must be met to demonstrate that a screening test is useful:

1. A test must be available that will detect cancer earlier than routine methods (e.g., clinical or self-examination).
2. There must be evidence that treatment at an earlier stage of disease will result in an improved outcome (decreased cause-specific morbidity or mortality).
3. There must be evidence of a total health benefit. For example, the benefits of early detection via screening that meets the aforementioned criteria must also outweigh the adverse risks of subsequent diagnostic and therapeutic interventions. In current screening trials, disease-specific vs. all-cause mortality, and risk-benefit have become increasingly important issues—particularly among older individuals.[30,31]

Fulfilling these requirements is difficult, and the issues specifically related to screening of different organ sites for precancers or cancers are discussed in those sections. Some generic comments are worthwhile. Enough evidence exists for a specific test for some organ sites that has been proven effective to recommend the routine adoption of screening (Table 26-3). Although the availability of cancer screening is generally increasing, usage is relatively low for some organ sites (e.g., colon) and among groups that lack health insurance or a usual source of care.[32] Many screening tests, however, are ineffective (e.g., routine chest roentgenograms in smokers being the most notable).

Also, a positive screening test may lead to aggressive intervention that could allow "cure" of the organ site disease but result in an overall increased morbidity or mortality that is not efficacious for a person's general health (e.g., radical prostatectomy for older individuals with a minimally increased PSA). Finally, screening for currently incurable malignancies (e.g., pancreatic cancer) offers new ethical dilemmas. If we have little to offer therapeutically, do we want to know the risk? Maybe, maybe not. Perhaps earlier prophylactic surgery might be able to affect the outcome in a few patients—for example, in families with early-onset pancreatic cancer.

Over the past few years, there have been rapid developments applying new imaging modalities for the purpose of cancer screenings. The United States Preventive Services Task Force now recommends screening with imaging techniques for breast cancer (mammography for women aged 40 to 70 years) and colorectal cancer (barium enema, fecal occult blood, endoscopy).[33] Cancer screening trials are ongoing for breast cancer (ultrasound, magnetic resonance imaging [MRI]), colorectal cancer (computed tomography [CT] colonography), liver cancer (ultrasound, CT), and pancreas (endoscopic ultrasound, CT, endoscopic retrograde cholangiopancreatography).[34] Major trials have completed accrual, including the Prostate, Lung, Colorectal and Ovarian (PLCO) trial and the National Lung Screening Trial. Mortality results from the PLCO are expected in 2015 and will assess the role of chest radiography (i.e., x-ray) in lung cancer screening, and transvaginal ultrasound for ovarian cancer screening. Mortality data from the National Lung Screening Trial are expected in 2009, to evaluate low-dose CT for lung cancer screening among high-risk adults.

The age of molecular diagnosis in screening is upon us and holds both promise and peril.[35] Novel functional and molecular imaging techniques for cancer diagnosis currently include measurements of tumor angiogenesis via dynamic contrast-enhanced (DCE)-MRI, DCE-CT with ultrasound, positron emission tomography (PET), and combinations of these techniques.[36] Diffuse optical imaging is another functional imaging technique that has emerged as an adjunct for cancer diagnosis. This noninvasive imaging method uses near-infrared light intensity to address tissue-specific changes between normal and tumor tissue (i.e., tissue hemoglobin concentration, tissue oxygen saturation) in vivo.[37] DCE-MRI, DCE-CT with ultrasound, and PET imaging have varying capabilities to profile microvessel density—a hallmark of angiogenesis—which is essential for tumor growth and invasion. However, even in the setting of cancer diagnosis, these methods are not

Table 26-3 Effectiveness of Major Screening Approaches for Cancer*

Organ Site	Test	Positive Level of Evidence†	Recommended
Breast			
Over age 50	Mammography	Strong	Yes
Age 40–50	Mammography	Fairly strong	Yes
Cervix	Papanicolaou‡	Strong	Yes
Colorectal			
Over age 50	Occult fecal blood	Strong	Yes
	Sigmoidoscopy	Strong	Yes
	Colonoscopy§	Fairly strong	Yes
Lung	Chest roentgenogram	None‖	No
Melanoma	Skin examination	Moderate	Yes
Prostate	Prostate-specific antigen	Moderate	Yes¶

*Listed here are organ sites for which sufficient data exist to make a judgment. Although no specific trial evidence exists, routine physical examination of the skin, oral cavity, testicles, and ovary/uterus is worthwhile, because treatment success is closely related to stage at diagnosis and effective treatment is available in most cases.

†The concept of level of evidence is a valuable approach—a quantitative approach that is presented in detail in the PDQ section of the NCI Web site (http://cancernet.nci.nih.gov/clinpolq/screening). A randomized trial with survival as an endpoint is at the top of the hierarchy, whereas anecdotal evidence by experts is at the lowest.

‡Screening should begin with the onset of sexual activity.

§Evidence also exists that colonoscopy with excisional biopsy is an effective therapeutic maneuver, but the cost of the procedure has precluded its general usage.

‖Several randomized trials of screening chest roentgenograms showed no effect on outcome. Spiral CT is currently being tested in a large national trial.

¶With careful follow-up and appropriate testing.

yet standardized.[36] Appropriate methods for incorporating these functional and molecular imaging techniques into screening trials must be considered, particularly in light of their associated high costs. Thus, the potential impact of such molecular and functional imaging techniques on cancer screening is great, though not yet realized.

Although early detection is, formally speaking, the evaluation of a symptomatic individual for cancer and is therefore different from screening, many of the caveats regarding evaluation of this approach are the same. The increasing ability to identify high-risk populations, either by phenotypic criteria or by genetic analysis, also tends to lead to a blurring of the classic division between screening and early detection. With the rapid advances in molecular diagnostics, routine genetic typing of individuals at risk for major tumor types should not be too distant in the future, and quantitation of that risk (a concept we proposed quite some time ago)[38] and its evaluation at the time of detection leads to real-world angst. Identification and referral of families at high risk for cancer susceptibility should be an increasing emphasis of clinical oncologists, but thus far, participation by oncologists has been low.[2,39] At the very least, the ability to downshift the stage of a disease at the time of detection should eventually lead to improved survival, because new treatment approaches emanate from causative understanding of a particular cancer. Proving this point, though, has been difficult for cancers of many organ sites.

The effectiveness of screening for the major types of cancer is summarized in Table 26-3 and is discussed in detail in the individual sections of this chapter. There are effective screening modalities for breast cancer, colorectal cancers, melanoma, and cervical cancers, whereas no compelling evidence exists for the value of screening for lung cancer. The effectiveness of PSA in screening for prostate cancer has been a subject of intense debate; we feel that the tide of evidence has turned and that the evidence supports the routine use of PSA screening over age 50 with thoughtful management and appropriate follow-up of abnormal values.

Carcinogenesis and Chemoprevention

Carcinogenesis

Advances in our understanding of the biology of carcinogenesis (cancer formation) have sharpened our thoughts about screening and early detection and provided a guide to thinking about risk assessment and chemoprevention.[40] Figure 26-1 serves as a useful general roadmap to reflect on these issues for all tumor types (see Shureiqi and colleagues).[41] The classical model of carcinogenesis divides cancer evolution into three major epochs: initiation, promotion, and progression. This classification has served as a useful heuristic model for which considerable experimental evidence has been developed. In the past 15 years, the genetic paradigm for the development of cancer has been elegantly articulated and experimentally confirmed for some organ sites. A series of steps in response to separate molecular events at the genetic level is a useful platform from which to understand carcinogenesis in human epithelial tumors. Almost all human cancers examined in any detail have shown evidence of several acquired molecular abnormalities. Although the "pathway" is different for each cancer, the tumor suppressor genes p53 and p16 seem to play a central role in many malignancies.[42,43] The expression of these abnormalities has allowed the development of markers that could serve as indicators of cancer risk or disease progression or possibly as surrogate endpoints for chemoprevention agent testing.[44]

Use of markers of carcinogenesis to assess the status of the disease relative to diagnosis and treatment and for assessment of chemoprevention effect is an important and complex issue.[45] The continued development and validation of markers will be critical to the intelligent management of early-stage cancer.[46] What also has become clear is that environmental phenomena (e.g., hormones, diet, carcinogens) can influence the expression of genetic changes. At one extreme of the paradigm is retinoblastoma, in which loss of a single gene inevitably results in an ocular tumor at a young age; however, most common solid tumors in adults seem to have underlying polygenic contributions, which can be affected by a large range of exogenous factors, even when a deleterious mutation such as *BRCA1* or *BRCA2* is present.

Chemoprevention

The idea of the chemoprevention of human cancer has been with us for nearly 3 decades, but only in the recent years have positive clinical trials validated the results of preclinical data and their potential for use in human beings.[47–50] Retinoids are a major group of compounds that have provided convincing "proof of principle" of

chemoprevention in humans, but in general they have been too toxic for widespread use and have not been adopted widely.[51] The overall results of some of the key randomized chemoprevention trials are summarized in Table 26-4 and are discussed in more detail in the individual organ site sections. Major problems in developing chemoprevention as a modality for cancer management have been the length and size of the trials required to show changes in a definitive endpoint.[52,53] Consequently, only the National Cancer Institute and a few large research groups have been able to marshal the resources to develop broad-based chemoprevention efforts. Another significant issue in the design of early trials was that many large studies evolved primarily from epidemiologic observations, with little experimental data available. Because the implementation of large phase III or IV chemoprevention trials is a 10- to 100-million-dollar exercise, political influences on the funding process have also been substantial.

An attempt to develop chemoprevention agents logically has been outlined, and systematic preclinical testing and evolution of sequential clinical trials are likely to avoid some of the mistakes of the past.[53,54] Several key elements are featured in this decision analysis process:

- Preclinical in vitro and in vivo testing against a battery of molecular targets and cellular and animal models
- Accurate identification of side effects and assessment of their importance
- Evidence of modulation of anticipated biochemical or molecular markers in the relevant tissue in short-term human trials
- A randomized 6- to 12-month study of multiple low doses of the candidate agent in a relevant patient/participant population, with careful identification of side effects and assessment of their importance, and evaluation of their biochemical, molecular, and/or histologic effects

In this regard we have performed a particularly informative series of studies in assessing topical all-*trans*-retinoic acid in cervical cancer prevention and difluoromethylornithine (DFMO) in colon cancer prevention,[55–57] whereas the M.D. Anderson group[58] has performed a series of important trials in aerodigestive cancers and the Arizona group has done the same for skin cancers.[59] Following this logical pathway of chemoprevention agent development assures that the probability of conducting a definitive phase III or IV study will be high and maximizes the chance for a successful outcome. Although the term "chemoprevention" has been widely used to describe chemical or dietary intervention to prevent or reverse cancer, it is a misnomer that is out of sync with the nosology used in other areas of medicine. Therapeutic prevention might be a better term—for example, cholesterol-lowering agents and antihypertensives to prevent cardiovascular diseases, prophylactic antibiotics to prevent infections, and many more. Risk-benefit of a drug in a prevention setting has always been a key issue, particularly of individuals at low risk. The unexpected increase of lung cancers and adverse cardiovascular events in two large trials in which β-carotene was administered called this issue into sharp focus in the mid-1990s.[60,61] Recently, a different level of risk has been appreciated, designated risk-risk. In several large trials, selective/specific COX-2 inhibitors markedly reduced the incidence of colonic polyps but at the price of increased serious cardiovascular events.[62,63] A careful analysis indicated that overall morbidity would be increased by using selective COX-2 inhibitors to reduce adenomatous colon polyps in individuals at low risk.[64] These important observations do not necessarily preclude using other nonsteroidal anti-inflammatory drugs (NSAIDs) that have more complex effects on the prostaglandin pathways (e.g., aspirin, sulindac); the results of other trials will help in this decision making, but the unexpected outcomes in the COX-2 inhibitor trials has clouded the field of chemoprevention for reduction of cancer incidence, particularly in

Table 26-4 Current Overall Status of Chemoprevention in Preventing Human Cancers*

Organ Site	Pretrial Level of Evidence	Agent	Status of Chemoprevention	Comment
Breast	Strong	Tamoxifen	Effective	One large trial, very positive; two smaller trials showed no effect. Overall long-term health benefits must be determined.
Cervix†	Strong	Multiple	Ineffective to marginal	Numerous phase III trials of several compounds have not substantiated phase II trials except for topical all-*trans*-retinoic acid.
Colon	Strong	Multiple	Mixed	Slight decrease (25%) in colon polyp recurrence by calcium or aspirin
Head and neck (secondary)	Moderately strong	13-*cis* retinoic acid	Effective but toxic	Follow-up trial at lower dose ineffective
Leukoplakia	Moderately strong	β-carotene	Promising	Single randomized trial needs confirmation.
Tertiary	Strong	13-*cis*- retinoic acid	Effective but toxic	Follow-up studies at lower doses in progress
Lung				
Primary	Strong	β-carotene	Ineffective	More lung cancers and increased higher overall mortality
Secondary (metaplasia)	Strong	Retinoids	Ineffective	Impressively negative
Prostate	Moderately strong	Finasteride	Accrual complete	Results indicate positive effects but are preliminary.
		SELECT‡	Ongoing	Results in 2010
Skin	Strong	Retinoids	Effective in some cases	Seems to depend on stage of cancer development and strength of agent
		Diclofenac	Effective	Causes regression of actinic keratoses

*Details are discussed in individual sections.
†Cervix, effects on regression of cervical intraepithelial neoplasia.
‡Selenium and vitamin E. Epidemiologic data from secondary analysis; experimental data moderate.

individuals at low risk. It is important to recall that the development of cardiovascular risk reduction trials met similar problems in the early days until effective and nontoxic agents were developed, and 20 to 30 years ago the regulatory burdens and the ethical bars were considerably lower.[65]

Although thus far most agents have been developed based on epidemiologic observations or carcinogen models in animals, increasing knowledge about the molecular basis of cancer progression in human tumors should result in the discovery and synthesis of highly specific drugs based on altered biochemical and signaling pathways.[66,67] The number of specific tumors for which prevention strategies could be reviewed is large. In this chapter we review the major organ sites (aerodigestive, colon, breast, prostate) and those sites (skin, ovary, cervix) in which sufficient evidence exists to suggest that preventive strategies currently have a role in clinical oncology. We also offer a few comments on less studied cancers (stomach, liver) that are extremely common outside the United States and Europe. With the rapidly increasing scientific understanding of the biologic basis for many tumor types and the recognition that screening, early detection, and chemoprevention should play a large role in the management of the carcinogenic process, we can anticipate that the list of therapeutic prevention strategies for intraepithelial neoplasia and possibly earlier manifestations of cancer will grow rapidly over the next few years.

AERODIGESTIVE MALIGNANCIES

Risk Reduction

Aerodigestive malignancies encompass a subset of cancers including those that arise from the oral cavity, pharynx, esophagus, and lung.[58] These organ sites have been grouped together, because they share a mucosal epithelial field that is directly subject to malignant transformation by the common toxin (tobacco), the major underlying etiologic agent for these malignancies. In addition to cigarette smoke, smokeless tobacco has also played an increasing contributory role in oral carcinogenesis, and oral cancer in the young adult has become increasingly common.[68] Alcohol also clearly plays a synergistic role with tobacco carcinogens in the development of oral and esophageal cancers, including second cancers.[69,70] Polymorphisms in the alcohol dehydrogenase gene involved with tobacco carcinogen metabolism may also play an important role in determining risk for head and neck and tobacco-related malignancies.[71] The identification of HPV in more than 50% of oropharyngeal and nearly 100% of laryngeal tumors has led to acceptance of the role of HPV in head and neck squamous cell carcinomas (HNSCCs) pathogenesis.[72,73] Compared with HPV-negative HNSCC tumors, which harbor tobacco-induced p53 mutations, HPV-positive HNSCC tumors have wild-type p53, which is inactivated by the viral oncoprotein.[73,74] Interestingly, HPV-positive HNSCC patients have a different clinical profile compared with HPV-negative patients: they are younger, less likely to ingest alcohol or use tobacco, and show equal gender distribution; the tumors show poorly differentiated and basaloid histology, but such patients have improved survival characteristics.[73,75] Progress in understanding the biology of tobacco-associated carcinogenesis in the past few years has been rapid, and molecular models of head and neck and lung cancers have been characterized to a substantial degree.[76] What is clear from cytogenetic genomic hybridization and other studies is that, although aerodigestive cancers share many similar changes early on (e.g., loss and gain of 3p and cyclin alterations), discrete subsets exist.[77] Because different genes are involved, this information should have a practical effect on the development of chemoprevention and other interventions.

In 2006 more than 230,000 cancers are expected to develop in aerodigestive sites, and 188,000 related deaths are anticipated in the United States.[78] Because it is estimated that the etiology of more than 80% of aerodigestive cancers is tobacco related, the cost to society of this legal carcinogen is extraordinarily high. The application of prevention strategies should have a favorable impact on decreasing morbidity and mortality from aerodigestive cancers; particularly important for the medical profession should be the adoption of proven, physician-facilitated smoking cessation methods.[7,8]

Screening and Early Detection

Oropharyngeal cancer occurs in a region of the body that is easily accessible to examination by a health care worker. The morbidity and mortality from oropharyngeal cancer is directly related to the stage at diagnosis, so effective screening and early detection should be worthwhile.[79] However, no definitive trial has demonstrated that an early detection program can downshift stage at diagnosis of oropharyngeal cancer or reduce mortality in a screened population. Nevertheless, an inspection of the oral cavity should be part of every examination in high-risk patients (smokers) and can be made efficacious by careful inspection of the soft palate, tongue, and floor of the mouth, where 90% of all squamous cell cancers occur.[80] The preneoplastic lesions, leukoplakia and particularly erythroplakia, should be identified and biopsy specimens obtained if necessary, because they represent early observable signs of squamous cell carcinomas with different prognoses (see Fig. 26-2A and B). In appropriately screened populations of high-risk smokers and drinkers over age 40, a detection rate of oral cancers as high as 1 cancer in every 200 individuals examined has been achieved.[81] A successful screening program can be mounted using health caseworkers; for example, in Sri Lanka, where oral cancer is a common malignancy, a sensitivity of 58% was obtained for 660 patients with suspected cancers.[82]

Recent advances in optical biology also suggest that screening using autofluorescent techniques may allow detection of premalignant changes before the clinical appearance of disease.[83] The strong association of HPV with oral cancers in young, nonsmoking individuals[72] and the success of screening techniques in detecting cervical intraepithelial neoplasia (see the discussion that follows) suggest that oral screening for HPV should be adopted for those who are sexually active. Established risk factors for HNSCC related to sexual behavior (i.e., history of genital warts, young age at onset of sexual activity, and a high number of sexual partners) indicate that this group is the same population at risk for genital HPV.

Routine screening of esophageal cancer in the United States has not been attempted to a significant degree, because it is relatively uncommon and therapeutic options are poor. In China and other Asian countries, however, the disease is much more common and found at high frequency in certain geographic locales. In these areas, screening and early detection using esophageal cytology are widely used, although the efficacy of these approaches has yet to be firmly established.[84]

Although lung cancer incidence among men has declined since the 1980s, the incidence for females has increased from 1975 through 2003 in the United States.[12] This trend may be changing, in that recent data indicate that the rate of increase among women has declined since 1991.[12] The issue of screening for lung cancer has been a long and complicated one, without a strong supporting evidence base. In the Mayo Lung Project (a large controlled trial designed to assess lung cancer screening with chest roentgenograms and sputum cytology among high-risk adults conducted in the 1970s and 1980s), chest x-ray imaging was noted to detect early-stage lung cancers, without leading to any difference in lung cancer mortality.[85,86] Furthermore, excess cases were noted in the intervention arm, leading to "overdiagnosis."[87] Four large randomized trials of screening chest x-rays in smokers have demonstrated no difference in survival between the randomized groups.[88] In subsequent chest CT screening trials at The Mayo Clinic, CT was shown to detect early-stage tumors, but with a high rate of false-positives (i.e., benign nodule detection). Recent support for lung cancer CT screening among high-risk individuals comes from the singular outcome analysis of a large trial in

which 85% of the screen-detected lung tumors were stage I at diagnosis, and 10-year overall survival was 88% for these stage I patients.[89] Although these observational findings are impressive, we must await the results of confirmatory randomized controlled prospective screening trials before making broad screening recommendations for lung cancer. Thus, the National Lung Screening Trial (CT imaging) and PLCO (chest x-ray) trials for lung cancer screening will serve as important validation studies to evaluate the efficacy of lung cancer screening among high-risk individuals.

Chemoprevention

Epithelial cancers of the upper aerodigestive tract and lungs are the most extensively studied system for chemoprevention in humans, and the results are the most negative. The natural history of the disease process has been studied extensively and provides a rich platform from which to conduct chemoprevention trials. Field carcinogenesis by tobacco carcinogens with its associated epidemiologic risk and characterized molecular changes is a straightforward concept that has guided the development of chemoprevention studies in this area.[46] The recent identification of molecular (e.g., DNA repair, telomerase), metabolic (e.g., cytochrome P450, alcohol dehydrogenase), and mutagen sensitivity profiles that predispose to aerodigestive cancers, acquired chromosomal abnormalities in the field and in the cancers, and alterations of several molecular parameters that predict responsiveness and unresponsiveness, have recently provided useful detail from which to consider the next generation of rational chemoprevention trials.[90] The identification of a variety of molecular changes during head and neck cancer progression, in addition to readily identifiable histologic precursors, has provided a biologic base for understanding the interaction of carcinogenesis and chemoprevention of this disease. Recent studies of the molecular changes that accompany the progression of lung cancer also provide a useful paradigm and platform from which to develop well-considered chemoprevention approaches.

Thus far, however, the results of primary, secondary, and tertiary chemoprevention trials of the lung have been disappointing (see Goodman[91]). Two large placebo-controlled, multiagent randomized trials in heavy smokers (more than 47,000 participants) have been negative and showed no beneficial effect of retinol (vitamin A) or α-tocopherol (vitamin E).[60,61] More disturbingly, these two large, randomized trials indicate that current smokers supplemented with oral β-carotene developed lung cancers at a rate 25% greater than the placebo group and also showed an increased overall mortality. Although these findings remain unexplained, possibilities that might help explain the adverse effect of β-carotene in these studies include the following:

- The formation of cyclic epoxides in the setting of tobacco carcinogens, inflammation, and high β-carotene concentrations
- The suppression of RAR-β, a major transcription factor important for differentiation in epithelial tissues
- Lowering of the concentration of other micronutrients that might be protective
- Stimulation of preneoplastic clones by enhancement of growth factor production
- Complex genetic polymorphisms that lead to alteration of tobacco carcinogen metabolism

Definitive secondary (metaplasia, atypia) and tertiary (second malignancy) chemoprevention trials that use a number of different retinoids and other compounds (folic acid, *N*-acetylcysteine) have also yielded negative results.[91,92] Treatment with anethole dithiolethione (an organo-sulfur compound) was shown in a randomized trial to reduce development of new bronchial dysplasia lesions and to slow progression of pre-existing disease in current or former smokers.[93] However, a randomized trial of inhaled budesonide in smokers with bronchial dysplasia indicated no effect of the active agent in the regression of bronchial dysplastic lesions or prevention of new lesions.[94] A modest decrease in p53 and BCL-2 protein expression in bronchial biopsy specimens was seen, as was a slightly higher rate of resolution of CT-detected lung nodules. Whether budesonide or anethole dithiolthione will be useful in managing preneoplastic lesions of the lung will require assessment in larger and longer trials.

Studies of secondary and tertiary chemoprevention of head and neck cancers have led to somewhat more encouraging results. Randomized trials have shown that isotretinoin causes regression of oral leukoplakia, though accompanied by substantial side effects.[95] Two randomized trials confirmed activity of β-carotene, although results from the later study were less convincing.[96,97] Several other, less toxic agents (retinol, 4-[hydroxyphenyl]-retinamide, and α-tocopherol) and selenium have also produced responses of premalignant lesions in phase II trials.[98] A randomized trial of the cyclooxygenase inhibitor ketorolac as an oral rinse was negative in patients with oropharyngeal leukoplakia.[99] A recently reported phase II trial of the complex retinoid fenretinide suggested activity for this compound in patients with retinoic acid–resistant oral leukoplakia.[100] We have demonstrated substantial potential activity of Bowman-Birk inhibitor (a soybean-derived compound) against oral leukoplakia.[101] The results of randomized studies for these latter two compounds have not yet been reported.

In a randomized phase III adjuvant trial of patients treated for head and neck cancer by local therapy, the synthetic retinoid 13-*cis*-retinoic acid (isotretinoin, Accutane) at a high daily oral dose (50 to 100 mg/m^2) led to a reduction in the incidence of second primary tumors, a difference that was maintained for more than 5 years.[102] The rate of second primary tumors was affected greatly by tobacco smoking status, with the efficacy of chemoprevention decreasing sequentially in current and former smokers as compared with nonsmokers.[103] The side effects in the 13-*cis*-retinoic acid trial were substantial at this dosage level, however. These results with 13-*cis*-retinoic acid were particularly significant in that a similarly designed randomized trial using another retinoid (etretinate) at a high dose showed no reduction of second primary tumors.[104] Therefore, the efficacy of low-dose isotretinoin (30 mg/day) to prevent second primary tumors after treatment of early-stage (I and II) head and neck cancer was tested in a randomized trial, with the hope that side effects could be decreased without losing efficacy. This strategy was unsuccessful, and no difference in the appearance of second malignancies in the placebo and treatment groups could be demonstrated; it is noteworthy that patients who continued to smoke had an increased rate of second primary tumors and death.[105]

The incidence of adenocarcinoma of the esophagus has been increasing over the past 2 decades. Gastroesophageal reflux has been identified as a risk factor leading to the development of a columnar-lined esophagus, called Barrett's esophagus, which progresses to adenocarcinoma via a metaplasia-dysplasia sequence (Fig. 26-2C). Both endoscopic resection and thermal or photodynamic ablation have been used to treat this condition,[106] but long-term benefit is unknown. Epidemiologic and clinical observations also suggest that NSAIDs and aspirin, by inhibiting COX enzymes, and proton pump inhibitors by decreasing gastric reflux[107] should be effective as chemopreventive agents, but randomized controlled trials proving this supposition have not yet been reported. Attempts to reverse or suppress these lesions with 13-*cis*-retinoic acid have been unsuccessful.[108]

Overall, these trials suggest that oral leukoplakia, but not bronchial metaplasia, can be reversed or suppressed by currently available chemopreventive agents. Thus far, "proof of principle" of chemoprevention in head and neck cancers has been achieved. However, large-scale phase III trials will have to show efficacy with a favorable risk-benefit profile before the strategy of chemoprevention can be adopted into standard medical practice for the management of aerodigestive cancers.

COLORECTAL CANCER

Screening for and early detection of colorectal cancers results in 5-year survival rates of 90% for colon cancer and 80% for rectal cancer, providing that diagnosis and treatment occur before the lesions have spread beyond the bowel to regional lymph nodes or distant metastatic sites. Unfortunately, more than 60% of patients still present with higher staged disease, leading to a lower overall 5-year survival rate of 65%.[78] In the United States, colorectal cancer affects 148,000 individuals annually and is responsible for more than 55,000 deaths per year, which is surpassed only by cancer deaths secondary to lung cancer.[78] These statistics highlight the critical importance of identifying individuals at risk for the development of colorectal cancer and of screening and early detection in its management. This section will discuss various risk factors, both modifiable (i.e., extrinsic risk factors) and not modifiable (i.e., intrinsic risk factors), that increase susceptibility for the development of colorectal cancer and will review current screening guidelines. This information can be used to design more effective preventive strategies, which could make use of genetic testing for individuals at risk and apply behavioral modification and chemoprevention.

Pathogenesis

Numerous epidemiologic, international, and experimental studies have evaluated various hereditary and environmental factors that lead directly or indirectly to the development of colorectal cancers. It is believed that colon cancer is the result of a complex series of genetic and epigenetic events that occur when environmental factors interact with an individual's inherited or acquired susceptibility.[42,109] This interaction produces somatic mutations that accumulate over time and lead to neoplastic transformation of normal colonic epithelium into premalignant adenomatous polyps (see Fig. 26-2D) and ultimately into invasive disease. The natural history preceding the development of cancer can progress through several decades. Adenomatous polyps, especially the villous subtype, are the premalignant lesions in more than 90% of colorectal cancers. The risk of malignant degeneration depends on the size of the polyp (increasing greatly in those greater than 1 to 2 cm in size), duration of its presence, number present at the time of the initial examination, and the histologic type.[110] Only adenomatous polyps seem to carry a premalignant risk; however, hyperplastic polyps are diagnosed more commonly in individuals with a smoking or drinking history, two predisposing factors for adenomatous polyp development.[111] The presence of hyperplastic polyps may warrant increased screening and prevention counseling, although further study of this issue is needed before definitive conclusions can be made.

Etiology

Heredity

Our understanding of the genetic and molecular alterations that precede the development of colorectal cancers has broadened and deepened over the past 10 to 15 years (Fig. 26-3).[112] This information has facilitated the identification of individuals who might benefit from early interventions with more vigilant screening, chemoprevention, or treatment. Based on studies of family histories, it is estimated that 20% to 30% of colorectal cancers have a significant hereditary component.[112] Thus far, however, genes associated with only two major syndromes—familial adenomatous polyposis (FAP) and hereditary nonpolyposis colon cancer (HNPCC)—have been identified clearly. Allelic deletions have been identified in patients diagnosed with these two autosomal dominant syndromes, FAP and HNPCC.[113–115] FAP accounts for only 1% of colon cancer cases per year and is associated with a deletion of the *APC* gene on chromosome 5 (band q21). These patients develop thousands of adenomatous polyps that tend to be evenly distributed throughout the colon and rectum by the second or third decades of life. If surgical treatment by complete colectomy is not done, affected individuals are at high risk to develop colon cancer by the age of 40. A highly specific mutation (T to A at nucleotide 3920) has been found in 6% of Ashkenazi Jews, and about 28% of Ashkenazim have a family history of colorectal cancer.[116] This mutation created a small hypermutable region of the gene, thereby indirectly causing predisposition.

The incidence of HNPCC was determined to be less than 1% of annual colon cancer cases in a large population-based study, although estimates of 5% are typically reported from nonpopulation-based studies.[117] Diagnosis requires that three or more relatives be diagnosed with colorectal cancer, representing at least two successive generations, and at least one relative must have been diagnosed before the age of 50.[115] One relative must be a first-degree relative of the proband patient. Patients tend to have cancers that arise in the proximal colon, and they also develop ovarian and endometrial cancers at a higher rate than the population at large. This syndrome is associated with defective DNA repair mechanisms, which lead to aberrant cell growth and tumor formation. These mutations occur on chromosomes 3 (hMLH1, 3p21) and 2 (hMSH2, 2p).[118,119] Based

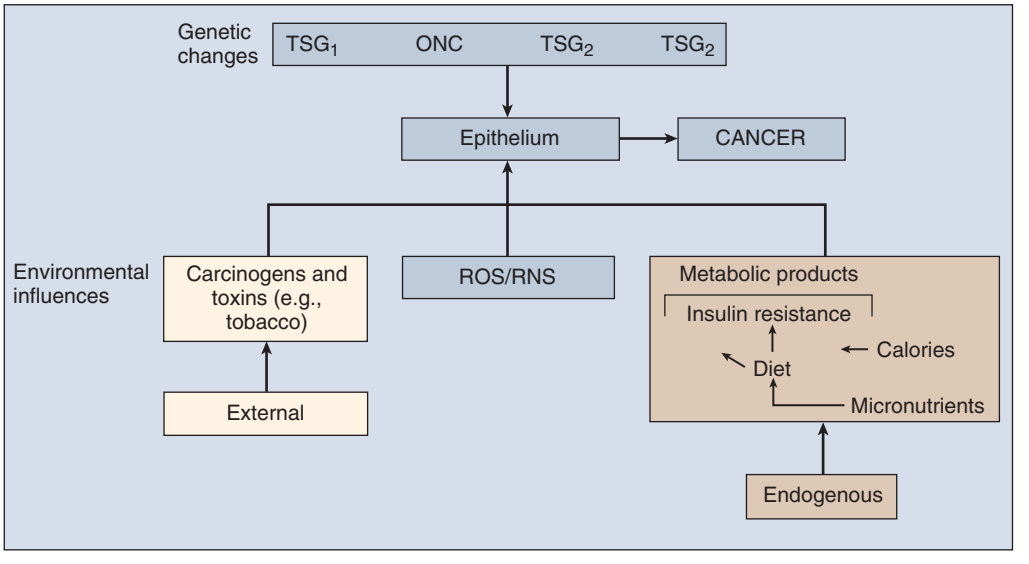


Figure 26-3 • Colorectal cancer results from inherited genetic predisposition and acquired molecular alterations interacting with environmental and endogenous toxins that are themselves modified by gene products. TSG, tumor suppressor gene; ONC, oncogene; ROS/RNS, reactive oxygen and reactive nitrogen species form from normal metabolic processes (endogenous) and from exposure to carcinogens and toxins (external).

on extensive experimental and clinical data, Vogelstein and colleagues[42,113] proposed that it is the progressive accumulation of mutations that ultimately lead to invasive disease. This proposal has been substantiated extensively, and mutations associated with colorectal cancers have been identified involving proto-oncogenes, tumor suppressor genes, and certain key regulatory enzymes, such as cytochrome P450 and acetyltransferase.[120–122] It has been suggested that colorectal cancers in adults develop through one of three different pathways (chromosomal instability, microsatellite instability, and CpG island methylator phenotype) and have different biologic behaviors.[109] The role of polymorphisms in metabolizing key molecules (including those present in the diet) is being examined closely and should provide a platform from which to understand gene-environment interactions. For example, polymorphisms in hepatic cytochrome P450 and acetyltransferase enzymes lead to rapid oxidation and acetylation of genotoxic compounds such as heterocyclic amines, which are present in processed foods.[122] Accelerated metabolism of these compounds increases an individual's risk of developing colorectal cancers threefold.

Diet

Although diet seems to play a significant role in colon carcinogenesis, the degree to which individual macronutrients and micronutrients contribute to the development of colorectal cancer has been elusive. In part, this difficulty stems from differences in design and methodology in studies that have been performed to evaluate this subject, including the type of dietary questionnaire administered, differences in cohorts such as age and ethnicity, confounding effects of other dietary components, selection and recall biases, sample size, and length of follow-up.

The majority of past evidence has demonstrated an increase in incidence and mortality rates from colorectal cancers in groups of people who consume a more "westernized" diet that is high in animal fat, total calories, and red meat but low in fiber and fruit and vegetable intake.[123] International and migrant studies have supported this observation. Recent studies, however, have indicated that the older evidence should be reconsidered. Large prospective cohort studies and several large randomized trials indicate that fiber does not seem to be protective nor fat contributory to colon cancer development.[124–126] In contrast, mechanistic considerations, metabolic studies, and epidemiologic studies suggest a strong protective effect of folate and an important role of insulin and insulin-like growth factors in colon cancer pathogenesis. Potter[109] and other researchers have done a particularly nice job in attempting to relate genetic changes, risk factors (including diet), and downstream molecules and pathogenesis.

Other Factors (Alcohol, Smoking, Exercise, Body Mass Index)

Primary prevention of colorectal cancer also requires that we understand factors other than diet that increase risk for colorectal carcinoma by initiating or promoting carcinogenesis. These include use of alcohol and tobacco, sedentary lifestyle, and the metabolic changes that proceed from these.[18,127]

Many studies have demonstrated a relationship between alcohol use and colorectal cancer and adenoma formation.[128,129] It is still uncertain whether alcohol directly initiates DNA damage or acts as a promoter on cells that already have undergone preneoplastic changes. A low-methionine or low-folate diet might contribute to a situation leading to adenomas and colorectal cancer, in that both methionine and folate are cofactors for DNA synthesis; lowered concentrations of these compounds leads to hypomethylation of DNA, which is a precursor to aneuploidy and loss of heterozygosity.[130] Various forms of a key enzyme, 5,10-methylenetetrahydrofolate reductase, which catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, have also been identified.[131] Some mutations of this enzyme increase its activity, whereas others decrease it. Low activity leads to decreased methionine synthesis and antagonizes methyl group metabolism in DNA synthesis.[131] This theory gained some support in the U.S. Male Health Professionals Study.[111] An association was found between high alcohol intake and methionine-deficient diets, after controlling for intakes of fat, red meat, fiber, level of physical activity, body mass index (BMI), and multivitamin and aspirin supplementation. Alcohol might be particularly important for progression of large adenomas to tumors.[128] Avoiding excess alcohol, while increasing dietary folate and methionine, seems like a reasonable approach to decreasing risk for colon cancer. Several large studies are underway to test whether supplementation with folate can reduce adenomata development.

Cigarette smoking has been consistently associated with adenoma formation but less so with colon tumors, an observation that could be explained by the molecular nature of a subset of colon tumors in which microsatellite instability and/or p53-negative status is a prominent feature.[132] The Health Professionals Follow-up Cohort Study and the Nurse's Health Study observed more adenomas in individuals with a history of smoking than in those who did not smoke.[133] Analysis of the very large American Cancer Society Cancer Prevention II study indicates that 20% of colorectal cancers and 12% of deaths are associated with long-term cigarette smoking[134] (Fig. 26-4).

Physical inactivity and high BMI also increase one's risk for colorectal cancers. A prospective study found a significant inverse association between leisure-time physical activity and incidence of colon cancer in participants of the Nurse's Health Study.[135] An inverse association was also observed between physical activity and the development of large (>1 cm) adenomas in the distal colon. In this same study, more adenomas were observed in individuals with a high BMI. Obesity, and in particular abdominal adiposity, has also been associated with an elevated risk for adenomatous polyps and colon cancer.[136] Recently, two separate cohort studies have demonstrated that physical activity is associated with improved outcomes among resected colon cancer patients.[137,138] Increasing physical activity and maintaining lean body weight for the prevention of colorectal cancer probably has considerable merit for decreasing the incidence of polyps and colon cancer, as well as of other chronic diseases.

The mechanisms underlying these proposed effects are not clear, but a unifying hypothesis has been proposed recently and involves the sequential steps of consumption of excess dietary energy, development of insulin resistance, and increased circulating levels of insulin, triglycerides, and nonesterified fatty acids, which results in secondary colonic epithelial damage.[139] Thus, the beneficial effects of physical activity on colon cancer risk and outcomes represents the sum total of numerous cellular and molecular events. A goal of prevention research is to determine which molecular pathways are being affected by physical activity and to evaluate potential biomarkers in this process. However, validated mechanisms have been lacking. Epidemiologic evidence associating insulin, insulin-like growth factor-1, and insulin-like growth factor–binding protein levels with colorectal cancer incidence provides considerable support for the proposal that changes in diet and physical activity may affect key molecular events.[140]

Screening and Early Detection

Population-Based Data

A definitive amount of data has accumulated indicating that colorectal cancer screening for persons at average risk is effective and reduces colorectal morbidity; agreement on the best screening modality remains unsettled, however.[141] Cost-saving analysis even supports the use of universal colonoscopy over the long term, notwithstanding the considerable practical challenges and total cost in achieving this goal. Probably everyone over 50 years of age should be screened. Yet surprisingly, fewer than 50% of individuals who should be screened are evaluated by fecal occult blood tests (FOBT), digital rectal exams (DRE), and/or sigmoidoscopy.[32]

Conflicting recommendations from government and private agencies contribute to the confusion. In general, all groups advocate

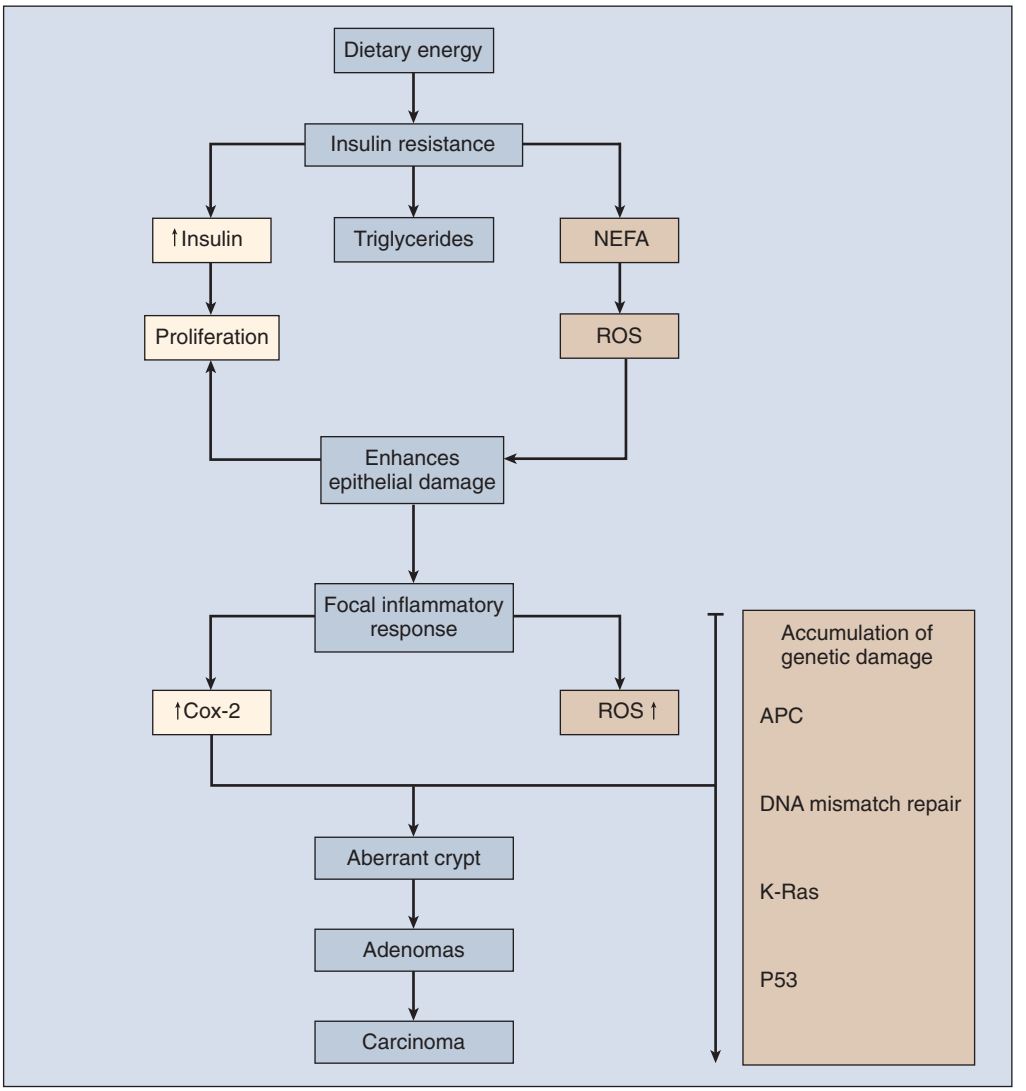


Figure 26-4 • The potential effect of diet on risk of colon cancer. NEFA, nonesterified fatty acids; ROS, reactive oxygen species.

screening in men and women beginning at the age of 50, because the incidence of colon cancer rises sharply between the ages of 50 and 55 and continues to double with each succeeding decade, reaching a peak by the age of 75. The American Cancer Society and the American College of Obstetricians and Gynecologists support yearly DREs beginning at age 40 and FOBTs performed yearly, once a person reaches 50 years of age. Sigmoidoscopy should occur every 3 to 5 years beginning at 50 years of age. Flexible sigmoidoscopy is superior to rigid sigmoidoscopy, because it allows the examiner to visualize up to 60 cm of bowel mucosa and is easier on the patient.

There are numerous studies validating the use of DRE, FOBT, and sigmoidoscopy as effective screening tools, providing regular screening is performed (to detect lesions in this disease with a long preinvasive phase).[142–144] This is particularly important with the FOBT, because reported sensitivities are low and range between 22% and 92%. Sensitivity is higher when at least three tests are performed on different days and the samples are rehydrated with hydrogen peroxide. To decrease false-negative results, which also increases the sensitivity of the test, patients should be instructed to avoid vitamin C and to eat a high-residue diet for several days before the test. The incidence of false positives is lowered when gastrointestinal irritants (e.g., aspirin, oral iron, and meat products) are not consumed a few days before the FOBT. In general, screened, asymptomatic patients have a positive test 4% to 6% of the time. Only 5% to 10% of these individuals have colorectal cancers, and an additional 30% have benign polyps.[145,146] The positive predictive value is only about 20%, so a positive test can be costly, because follow-up requires evaluation by sigmoidoscopy or colonoscopy. Randomized clinical trials have demonstrated a decrease in mortality by 15% to 33% with the regular use of serial FOBT, however.[143] Patients who received FOBT in conjunction with sigmoidoscopy in a Memorial Sloan-Kettering colon cancer trial had a significantly higher survival probability when compared with those who received sigmoidoscopy alone (70% vs. 48%, respectively).[143] This is an impressive result.

Regular screening with sigmoidoscopy among patients over 50 years of age both reduces mortality from colorectal cancer and prolongs survival.[147,148] Studies must be performed to clarify the optimal interval between screening and to develop recommendations for individuals at higher risk for adenomas or colorectal cancers. The early results of a "once-only" sigmoidoscopy at age 60, in which a high yield of adenomas was obtained, suggests that a less intense approach to screening could be a cost-effective strategy to prevent colon cancers.[149] Follow-up colonoscopy suggested that a significant number of proximal adenomas were present. The efficacy of screening

colonoscopy for adenoma detection was directly related to prolonged endoscope withdrawal time in a recent study, a finding that may influence patient management in the near future.[150] There is little doubt that screening colonoscopy is effective at identifying silent, large adenomas and colon cancers, but its cost effectiveness must be demonstrated; so must the optimal usage of fecal occult blood, sigmoidoscopy, and colonoscopy with regard to efficacy and cost. A particularly exciting approach is the identification of colon cancer-specific mutations in fecal DNA.[151] A study of the adenomatous polyposis coli (*APC*) gene, the initiating abnormality in most sporadic colon cancers, in the fecal DNA of normal individuals and patients with polyps shows considerable promise.[152] Although the specificity of this test was high (100%), the sensitivity was only 57%. However, integration of the test into the screening paradigm (perhaps with FOBT) as a low-cost, general screen is an important goal. The DRE should be included in all examinations, because it permits evaluation of the distal rectum and prostate. Its sensitivity has decreased, however, with the temporal shift to more proximal lesions in the colon.[149] Other tests, including double-contrast barium enema, have not been evaluated completely as screening tests and are more expensive than DRE, FOBT, and sigmoidoscopy. We feel that these modalities should be reserved for those patients with positive screening tests.

High-Risk Individuals

More frequent screening is recommended for certain postpolypectomy individuals and other individuals at increased risk for the development of adenomatous polyps or colorectal cancers.[153] One particularly important group includes those who have had previous treatment for a primary colorectal cancer. Recent analysis indicates that evaluation of this high-risk group has been inadequate. Proctosigmoidoscopy or colonoscopy should begin at age 10 for first-degree relatives of individuals with FAP and at age 25 for individuals with a strong family history suggestive of HNPCC.[154,155] Genetic testing for the mutated *APC* gene in peripheral mononuclear cells of patients with early onset of adenomatous polyps or in first-degree relatives of FAP-affected individuals will help to determine who needs closer surveillance.[156] Counseling about diet, chemoprevention, and lifestyle issues can be provided for individuals who test positive for the mutated *APC* gene. In addition, a colectomy should be considered if polyps are found.

Genetic testing for mutations in DNA repair genes should be performed on anyone whose family history is suggestive of HNPCC; counseling can then be provided for individuals who test positive.[157] A positive family history of colorectal cancer that does not meet criteria for FAP or HNPCC probably also warrants earlier screening, but definitive guidelines have not been established. A prospective study of approximately 120,000 men and women who underwent colonoscopy or sigmoidoscopy surveillance concluded that the age-adjusted relative risk for cancer was 1.72 with one first-degree relative with the disease, 2.75 with two first-degree relatives, and 5.37 with one first-degree relative who was under age 45 at the time of diagnosis.[158] It is estimated that as many as 25% of individuals with colon cancer have positive family histories. Baseline colonoscopy before age 50 seems to be a reasonable consideration among this group of patients with a positive family history.

Other high-risk conditions requiring close surveillance include individuals with a long-standing history of inflammatory bowel disease, a prior history of polypectomy or ureterosigmoidostomy, a personal history of ovarian, endometrial, or colon cancer, and finally anyone who has been treated for *Streptococcus bovis* bacteremia.[154,159–161]

Other Health Factors

In considering health care resources, other issues that affect the development of colon cancer should be considered. The role of estrogen replacement in the development of colon cancer and in other health parameters in postmenopausal women is of great importance. The results of the Nurse's Health Study suggested that current estrogen replacement in postmenopausal women can reduce the risk of colon cancer (relative risk = 0.65); this effect disappeared 5 years after discontinuation of estrogen replacement.[162] However, a detailed analysis of the group of postmenopausal women in the WHI trial who received estrogen plus progestin indicated that the colorectal cancers were diagnosed in a more advanced stage even though the number of colorectal cancers was reduced by 45%.[163] When reproductive factors were examined among women who were diagnosed with colon cancer in this study, oral contraceptive pill use and later age of menarche were also associated with a decreased risk. In another study, women who delivered more than five children, especially if they had a positive family history of adenomas, were at increased risk for the development of adenomas.[164] In this study, however, no association was found with age at menarche, menopause, first birth, or oral contraceptive pill use. Although estrogen plus progestin lowered the risk for colorectal cancer in the WHI trial,[163] these favorable results will have to be balanced against the increased risk for breast cancer and cardiovascular disease (see later discussion).

Chemoprevention

Despite the enormous amount of epidemiologic observations and experimental data that support a protective role of many dietary constituents against the development of adenomatous polyps and colorectal polyps, the results from definitive randomized trials have been modest, at best. Many micronutrients and dietary constituents have been studied. Trials using vitamins C, D, and E, and β-carotene as well as supplementation with fiber or lowering of dietary fat have been uniformly negative. Trials in which calcium has been supplemented have been modestly positive with a 25% to 35% reduction of adenomatous polyps demonstrated.[24,25] However, daily supplementation of calcium with vitamin D for 7 years had no effect on the incidence of colorectal cancer among postmenopausal women in the WHI.[165] These results suggest that calcium inhibits colon carcinogenesis at early but not late stages.

Additionally, in a double-blind, randomized, placebo-controlled trial of selenium supplementation for skin cancer prevention, a secondary analysis showed that the numbers of colon, prostate, and lung cancers were found to be reduced by 50% in the treatment arm.[166] The results of additional randomized trials are pending and should become available in the next 3 to 5 years.

Study of the effects of micronutrient supplementation on the formation of polyps and colorectal cancers is difficult, given the inherent complexity of carcinogenesis. Understanding how various dietary components inhibit carcinogenesis will be instrumental to the development of novel dietary-derived chemopreventive agents in the future. Factors such as type of micronutrient, dose, and duration of treatment, as well as cohort demographics (age and geographic location), and endpoints (polyp formation, or changes in the incidence and mortality of invasive cancer) are all important variables that will affect trial results. However, despite these difficulties in study design, analysis, and interpretation, we should not dismiss the large amount of epidemiologic evidence and supportive experimental data demonstrating that the consumption of diets rich in fruits and vegetables, but low in fat, have a lower incidence of bowel cancer and cancer in general.[167] Observational and animal studies suggest that reduction of caloric intake and moderate physical exercise should also decrease the risk of colorectal cancer.[168] Meat consumption—particularly red meat that has been processed, has been associated with increased risk of colorectal cancer in numerous epidemiologic studies. Substances in meat that have been implicated in colon carcinogenesis include the known carcinogens: heterocyclic amines (formed in meat during cooking), polycyclic aromatic hydrocarbons and N-nitroso compounds (both found in processed meats), and the amino acid arginine (i.e., a key substrate of the polyamine synthetic pathway).[169–172] Research from clinical trials should provide us with invaluable data

on which to base dietary and lifestyle recommendations for the prevention of colorectal cancer.

There are also abundant scientific opportunities to explore the role of nondietary chemoprevention compounds in controlling colorectal cancer based on substantial studies of colon carcinogenesis (see review[173]). Some of the more active nondietary compounds being studied include NSAIDs and DFMO. Mechanistic studies indicate that epithelial regeneration and focal inflammation may be important early changes in the pathogenic process,[139,173] so that the use of nontoxic antiproliferative and anti-inflammatory agents as chemoprevention agents has a strong rationale. These biologic features of colon carcinogenesis are also used to support a role for probiotics and prebiotics for the prevention of colorectal cancer.[174]

A considerable amount of experimental and epidemiologic evidence exists to support the use of NSAIDs to decrease the risk of colon cancer.[173] These compounds exert their antiproliferative effects on colonic cells through inhibiting prostaglandin synthesis by reversibly binding to cyclooxgenase as well as through several other newly discovered mechanisms. Laboratory studies have consistently demonstrated that NSAIDs can inhibit chemically induced and transplanted tumors in rodents. The interpretation of epidemiologic trials involving NSAIDs is challenging because of differences in design and methodology, including the particular agent chosen, the dose, frequency, and duration of use, and variable follow-up periods. Nevertheless, most case-control and cohort studies have demonstrated an association of a reduced risk of colon cancer with increased consumption of NSAIDs.

Analyses of subgroups of patients who routinely take these drugs—such as patients with rheumatoid arthritis (aspirin), inflammatory bowel disease (sulfasalazine), and FAP (sulindac)—have reported a decrease in either adenomatous polyp formation or the development of colorectal cancer. A particularly important study was the Nurse's Health Study, which used three consecutive questionnaires to determine the rate of colorectal cancer among women who consumed aspirin and compared these rates to women who reported no aspirin use.[175] After at least a decade of regular aspirin use, at doses similar to those recommended for the prevention of cardiovascular disease, aspirin consumption was found to reduce the risk of colorectal cancer substantially. Both celecoxib and sulindac have been shown to cause regression of polyps in patients with FAP.[176,177] Sulindac was not effective in preventing the development of new polyps in these patients, however.[178]

The results of several large randomized trials using NSAIDs have been reported.[168,179,180] Aspirin has uniformly reduced the recurrence of adenomatous polyps by 25% to 35% in patients at moderate risk with acceptable toxicity. Studies with COX-2 selective inhibitors have produced an unusual conundrum. Several randomized trials have demonstrated substantial benefit with a 40% to 50% reduction in recurrence of adenomas; however, cardiovascular events were markedly increased in the treatment arm.[62,63] These results have put a significant damper on the development of chemoprevention agents for cancer. Whether similar adverse results will be seen with less selective NSAIDs (e.g., sulindac) is unknown and awaits the results of ongoing trials.

DFMO has been found to be a potent inhibitor of carcinogenesis in experimental animal models by reducing the number and size of adenomas and carcinomas. This drug exerts its effects by irreversibly inhibiting ornithine decarboxylase, the first enzyme in the polyamine synthesis pathway. Suppressing intracellular pools of polyamines decreases cell growth and interferes with the process of carcinogenesis in essentially all animal models. We have reported the results of a long-term clinical trial, which serially measured the effects of different doses of DMFO on rectal mucosal polyamines over a 12-month time period and demonstrated consistent suppression without side effects.[57] Demonstration of a dose of a chemopreventive agent that has a substantial biochemical effect without producing clinical side effects is an important goal. Currently, we are studying the prevention of adenomas in patients that have undergone polypectomies for adenomatous polyps. DMFO will be given in conjunction with sulindac over a 3-year period, and its effect in reducing polyp recurrence is being studied in a randomized, placebo-controlled trial.

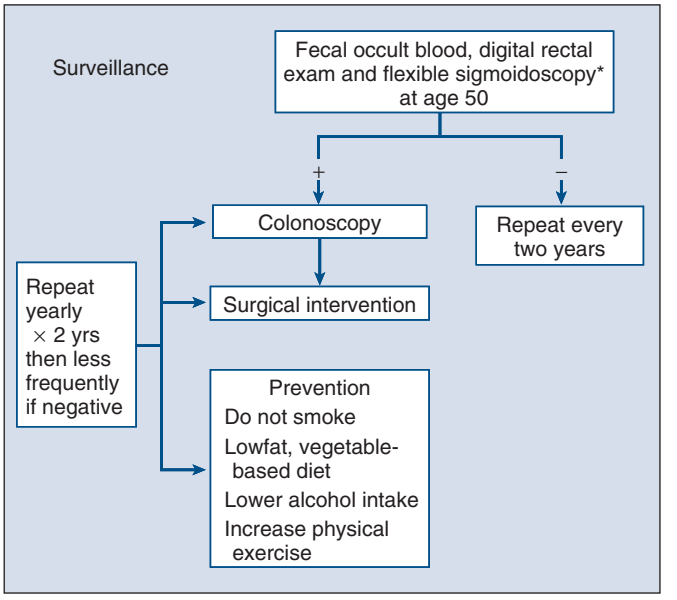


Figure 26-5 • Routine screening and early detection for colorectal cancer and its prevention. *There is a growing consensus that a colonoscopy should be performed at age 50 and all polyps removed. If negative, repeat about every 5 years. If positive, repeat in 3 years. If there is a familial tendency, start 5 years before age of youngest family member with disease.

The role of tertiary prevention in colorectal cancer has been little explored. As effective chemoprevention agents are developed, the group of patients who have been "cured" by standard therapy should become a focus of investigation, because the incidence of second primary colon cancers is high (about 25%).[181]

Integration of Prevention Activities

Several approaches exist to prevent the development of colorectal cancers. Successful primary prevention depends on public education and counseling about behavioral and dietary modifications that can be made to decrease an individual's risk, including increased physical activity and reduction of total calorie intake. In patients with adenomatous polyps, polypectomy is a useful preventive measure. Patients with FAP or HNPCC might require colectomies at a younger age to prevent development of cancer. New advances in genetic testing will help to select people who not only need closer surveillance but also might benefit from surgical treatment before cancer or premalignant polyps develop.

More vigilant screening in individuals at increased risk for the development of colorectal cancer is reasonable, but the appropriate screening tests, and the optimal interval between tests, require further clarification. More important, given that the majority of cancers occur in patients without a family history, everyone probably should be screened beginning at 50 years of age. Clinical applications of chemoprevention with DFMO, NSAIDs, and various micronutrients are still under development but may offer important alternatives for the future or as part of an overall approach to prevention (Fig. 26-5).

BREAST CANCER

The morbidity and mortality from breast cancer remains high despite significant advances in our understanding and management over the

last several decades. Therefore, prevention and early detection have become important challenges for the medical community. In addition to an enormous health benefit, several billion dollars would be saved annually if breast cancer were prevented and/or the disease were detected at an earlier stage. The widespread use of screening mammography, the increasing recognition that breast density is a major risk factor, the identification of high-risk individuals based on family history, the detection of deleterious mutations, and the "proof of principle" that tamoxifen and raloxifene can reduce the risk for breast cancer all anticipate more effective early management of this disease.

Etiology

Heredity

Primary prevention depends on our ability to identify individuals who are at increased risk for the development of breast cancer.[182] Although many risk factors cannot be changed, knowledge of their presence can be used to identify high-risk individuals. Age, socioeconomic class, geographic location, race, and ages of menopause, menarche, and first birth are examples of risk factors that are difficult to change but important to recognize. The incidence of breast cancer, like that of most cancers, increases with age. The majority of cases are diagnosed in women older than 40 years of age, with only 10% to 15% occurring in women younger than 40 years old and fewer than 5% occurring among women younger than 35 years of age. Affluent women and individuals born in colder climates or in the Western hemisphere also tend to have a higher incidence of breast cancer. White women have more breast cancers than black, Asian, Hispanic, or Native American women. It is of considerable interest that Hispanic and Native American women have many of the same demographic variables (obesity, high fat, and low vegetable diet) that are associated with a high incidence of breast cancer in whites, yet their incidence of breast cancer is less than half that of whites.[183] Determining whether this difference is genetically based or if it reflects some other protective dietary or environmental factor is an important issue to address. By identifying who is at higher risk for breast cancer, health professionals can then counsel this subgroup of women and their families about the risks for breast disease and various ways to modify these risks, and they can encourage enrollment into clinical trials aimed at studying novel approaches for breast cancer risk reduction.

The most important step in trying to discern who is at risk is to take a detailed personal and family history extending back at least three generations.[184] Nearly 25% of women diagnosed with breast cancer have a family history of the disease.[184] Recent advances in our understanding of the molecular biology of breast cancer have led to the identification of specific mutations that might help identify women with a hereditary predisposition to developing breast cancer and might help predict who will respond to adjuvant therapy. Medical records, including pathology reports, should be obtained whenever possible to help complete an accurate pedigree. Recall bias is a significant problem when constructing pedigrees and can profoundly influence how we counsel patients; therefore, it is important to collect documentation whenever possible. Family histories must be gathered from the maternal and paternal sides of the family. This latter step is often neglected and makes it impossible to counsel anyone in a meaningful way.

Although most cases of breast cancer are sporadic and a product of many genetic insults, approximately 5% are due to specific inherited germline mutations in the *BRCA1* and *BRCA2* tumor suppressor genes.[185] The estimated lifetime risk for breast cancer in *BRCA1* and *BRCA2* mutation carriers ranges from 55% to 85%, in comparison with the 13% lifetime risk for the general population.[185–187] Women with these mutations are also at increased risk for the development of a second breast cancer; *BRCA1* mutation carriers carry up to a 65% lifetime risk, and *BRCA2* carriers might share a similar risk.[187] Therefore, carriers of mutations in the *BRCA* genes and women with a personal or family history might benefit from prevention strategies and genetic counseling.

Genetic testing should be offered to individuals with a strong family history (breast or ovarian cancer in two or more generations), a history of multiple primaries (ovarian or breast, colon, endometrial), early age of onset of breast cancer (<35 years), or individuals of Ashkenazi Jewish descent, who carry a frequency of mutations in the *BRCA* genes estimated to be 2.2%.[185,186] Approximately one out of every 300 to 800 American women carries a *BRCA1* mutation; however, not every one of these women will develop breast cancer. This variable penetrance seen in *BRCA* mutation carriers highlights one of the dilemmas of genetic testing for *BRCA* gene abnormalities. Furthermore, a negative test might offer false reassurance, because it could represent a false negative. In addition, although a number of mutations in the *BRCA* genes have been sequenced, there are probably many more that we have not identified and for which we therefore cannot test. Practitioners should be aware of the uncertainty inherent in genetic testing for *BRCA* mutations and be prepared to counsel their patients accordingly.

Family history without a clearly defined genetic syndrome is also important in counseling women about their risks for developing breast cancer.[188,189] A woman with a first-degree relative with premenopausal breast cancer carries anywhere between a 1.8- and an 8.8-fold increased risk of developing a breast cancer in the future and is at high risk for harboring a deleterious mutation. This risk decreases to 1.2- to 4.0-fold in a woman who has a first-degree relative who developed breast cancer after menopause. Having a second-degree relative with breast cancer increases a woman's risk by approximately 1.5-fold.

Hormonal Factors

Women with a long lifetime exposure to estrogen are also more likely to develop breast cancer. The risk for breast cancer increases by 20% if menarche occurs before the age of 12.[190] Furthermore, women who experience a late menopause, are nulliparous, or deliver their first child after 30 are also at increased risk. An induced abortion does not result in an increased risk of breast cancer (Box 26-1).[191]

The subject of HRT and its role in the etiology and progression of breast cancer has been among the most intensely studied in medicine. Studies evaluating the role of hormone replacement in postmenopausal women have reported contradictory results—not surprising given that many of the studies evaluated different doses, preparations, follow-up times, and different age cohorts.[192–194] Results from the WHI study (i.e., the largest prospective randomized clinical trial to address the issue of HRT on breast cancer development), however, conclusively demonstrated an increased risk of invasive breast cancer (relative risk = 1.26) among those women taking estrogen plus progestin compared with placebo control subjects.[17] Additionally, the supplementation of postmenopausal women with estrogen plus progestin in the WHI trial led to increased mammographic density and breast cancer,[195,196] These findings have sparked an intense debate, with proponents of HRT advocating no change

Box 26-1. INDICATIONS FOR GENETIC TESTING IN BREAST CANCER*

- A first-degree relative with breast cancer before age 40
- Two or more relatives with breast or ovarian cancer at any age
- Three or more relatives with breast, ovarian, or colon cancer at any age

*The indications for genetic testing in breast cancer and in other cancers are in rapid evolution as the true risks become better defined and as prevention (e.g., tamoxifen) and early detection (e.g., mammography, MRI) strategies mature.

in prescribing habits and opponents vociferously advocating the opposite.

Compelling data in support of the aforementioned WHI results have emerged from recent epidemiologic reports indicating a sharp decrease in breast cancer incidence in 2003, particularly in estrogen receptor (ER)–positive tumors.[197,198] This time period represents the first year after results of the WHI trial were released, with a resultant immediate 50% decrease in HRT use. The rapidity of this observed decreased breast cancer incidence supports an effect of hormone therapy on progression of subclinical lesions. These reports from the California Cancer Registry and in the national U.S. Surveillance, Epidemiology, and End Results (SEER) registry have sparked a renewed debate about the role of HRT in early breast cancer development, because it represents the first significant decrease in breast cancer incidence in the United States in more than half a century.

In contrast, the preponderance of evidence suggests that the risk for breast cancer from oral contraceptive use is very low or nonexistent. An overview of 54 epidemiologic studies evaluating the role of oral contraceptives and breast cancer found the RR of current users to be 1.24 vs. no risk for women who had not taken them for 10 or more years.[199] Thomas[200] summarized the results of five cohort studies and found that the overall risk for ever-users to be 1.06. On the other hand, in a large, matched case-control study of *BRCA* mutation carriers use of oral contraceptives was associated with increased risk of breast cancer in *BRCA1* (overall risk = 1.20) but not in *BRCA2*.[201]

Oral contraceptives are used by more than 150 million women worldwide and offer a number of health benefits, including reduction in dysmenorrhea, fibrocystic breast changes, iron deficiency anemia, pelvic pain secondary to endometriosis, ectopic pregnancy, pelvic inflammatory disease, functional ovarian cyst formation, and the incidence of endometrial and ovarian cancers.[189] Women should be counseled that there could be a slightly increased risk of developing breast cancer, although some believe that the apparent increase is due to surveillance bias, because physicians examine women taking oral contraceptive pills more frequently. Supporting this viewpoint is the observation that women with breast cancer who have taken oral contraceptives in the past do not experience lower survival rates when compared with women who have not taken them. Based on these data, current prescribing practices for oral contraceptives should not be changed, although the special case of *BCRA* mutation carriers must be assessed carefully on an individual basis.[201]

Other risk factors associated with breast cancer, such as proliferative fibrocystic changes in the breast, sedentary lifestyle, and diet, may be used to design preventive strategies for the high-risk woman. Overall, typical or atypical proliferative fibrocystic changes of the breast are associated with a two- to fourfold increased risk for the development of breast cancer.[202] Because the clinical significance varies depending upon the degree of hyperplasia and atypia present, the Cancer Committee of the College of American Pathologists has replaced the term *fibrocystic disease* with *fibrocystic changes.* Possible treatment options for relieving symptoms related to fibrocystic changes include decreasing the consumption of foods rich in methylxanthines (e.g., chocolate, coffee, tea, and cola) or taking a supplement such as vitamin E, or medications such as danocrine, bromocriptine, or tamoxifen. Although consumption of these drugs has been shown to decrease fibrocystic changes in the breast, studies have not been done to evaluate whether these changes actually decrease the increased risk of breast cancer.

Diet

Numerous observational studies have reported on the role of diet in breast cancer development with disparate findings, whereas experimental studies are more definitive.[203–205] Many public health agencies advocate a low-fat, high-fiber diet to prevent breast cancer. Data linking diet to breast cancer come largely from international and migration studies. First-generation Japanese-American women and women who have recently migrated from Japan have risks for the development of breast cancer that approach those of Native American women.[206] Differences are seen among women from various countries as well; for example, women in Great Britain have age-standardized mortality rates of approximately 28 per 100,000 versus those of Japanese women of 6 per 100,000.[207]

The WHI study is the only randomized prospective study performed to address the role of diet in the development of breast cancer, in which women were randomized to low-fat diets or no dietary intervention.[208] In this randomized trial of a low-fat dietary intervention among postmenopausal women aged 50 through 79 years, the low-fat diet resulted in a nonsignificant 8% reduction in breast cancer incidence over an 8-year study period. However, secondary analysis revealed a benefit from the dietary intervention among women with baseline high-fat diets, and women who were strictly adherent to the intervention. Therefore, we consider these results to be promising, if not definitive data related to dietary modification of breast cancer risk. Initial data from the WHI study related to calcium–vitamin D supplementation compared to placebo among postmenopausal women revealed no reduction in breast cancer risk, although the incident breast cancers in the intervention group were smaller in size.[209]

Women of tall stature or who have high body fat and mass have higher rates of breast cancer than other women.[203–205] An increase in estrone and estradiol as BMI increases has also been documented.[210] The recognition that a hormone (leptin) produced by fat cells vigorously stimulates the growth of normal and malignant breast cells may provide an important biologic link to the phenomenologic observation.[211] Some animal studies, however, have shown that caloric restriction in general, rather than a low-fat diet per se, decreases risk of breast cancer. This effect of caloric restriction could underlie the observation that women who exercise have a lower risk of breast cancer. Another consideration is that women who exercise ovulate less frequently and therefore are not exposed to the higher levels of estrogen that normally occur in women who ovulate regularly.

Numerous epidemiologic studies suggest that alcohol has an effect on the development of invasive breast cancer. An extensive and detailed meta-analysis of the six largest prospective cohort studies addressing this issue showed that alcohol consumption was associated with a linear increase in breast cancer incidence for intakes less than 60 g/day (about two to five drinks).[212] The association was not modified by other factors, and higher alcoholic intakes (>60 g/day) were not associated with additional increased risk. Low dietary levels of selenium and antioxidants such as vitamins C and E, and β-carotene have been associated with breast cancer development and differences in survival.[213] β-carotene is the major provitamin A carotenoid and has differentiating and antiproliferative effects on a variety of cells, including mammary carcinomas. Levels of β-carotene have been analyzed in numerous studies and are lower in women with higher staged breast cancer and breast cancer in general. A case-control study from Europe, however, observed no differences in vitamin A or β-carotene levels between cases and control subjects.[214] Studies of soy intake in Singapore Chinese women are of great interest.[210,215] Soy intake was significantly associated with lowered plasma estrone and with more favorable mammographic patterns. Recently, there has been a great interest in gene-environment interactions and studies of micronutrients in relationship to metabolic pathways, and genetic polymorphisms are likely to be informative. Among women at high risk for breast cancer for other reasons (e.g., heredity), reducing alcohol consumption should be a straightforward way to reduce breast cancer risk.

Screening and Early Detection

Secondary prevention is aimed at detecting preinvasive lesions such as ductal carcinoma in situ, lobular carcinoma in situ, or early-staged breast cancers that have the potential to be cured with limited treatment. Screening tests include the breast self-examination, the clinical breast examination administered by health care professionals, and mammography. Successful implementation of wide-scale screening

programs that incorporate these techniques, followed by treatment of detected lesions, is probably responsible for most of the decline in the overall death rate from breast cancer that occurred among American women from 1989 through 1993.[216] This decline continues and probably represents both the increased use of mammography and the effectiveness of systemic adjuvant therapy. Currently, 5-year survival rates for localized breast cancers have increased to more than 98%.[78]

Although we encourage women to perform monthly breast examinations, a randomized trial indicated that this practice does not decrease overall mortality rates.[217] The most effective combination for decreasing the incidence of invasive disease is the clinical breast examination and mammography. The Breast Cancer Detection Demonstration Project showed that the sensitivity of the clinical breast examination and mammogram together was 70% to 80%, with sensitivity increased for older patients.[218] Although it is standard practice for a clinical breast examination to be performed annually, there has been a great deal of controversy surrounding the appropriate time to begin routine screening with mammograms. Randomized controlled trials of a large number of women on trials from several countries have unequivocally demonstrated a 40% decrease in mortality from breast cancer in women who have annual mammograms beginning at the age of 50.[219] Throughout the years, controversies have erupted regarding the magnitude of benefit from screening mammography. We continue to recommend the practice to women beginning at the age of 50 but encourage discussion of the risks and benefits associated with this procedure.

The opinion on routine screening in women between the ages of 40 and 49, however, is mixed.[220] Eight randomized controlled trials performed between 1963 and 1982 do not demonstrate a statistically significant difference in breast cancer mortality within 7 years after screening was initiated in women randomized to receive or not receive screening mammograms. A majority in a recent consensus panel used this information to state that there currently was not sufficient evidence to advocate routine screening mammography in women ages 40 to 49. Five of these trials, however, demonstrated a 16% decrease in mortality if follow-up continued for 10 years, prompting release of a minority report advocating routine screening in the 40 to 49 age group.[220] As the minority report highlighted, the goal of mammography is to detect preinvasive lesions, and 15% to 20% of breast cancers are now diagnosed as ductal carcinoma in situ or lobular carcinoma in situ in younger women. The minority report correctly pointed out that the risk from radiation during mammography screening was overemphasized. The U.S. Preventive Task Force has considered the issues carefully and recommends a screening mammography every 1 or 2 years for women aged 40 and older,[221] a position we favor. An important recent observation is that mammographic density is strongly associated with risk and is heritable.[222] This information should further target the premenopausal woman at higher risk for breast cancer; determination of the underlying genetic basis for breast density has now become of great interest, particularly in that the use of a postmenopausal hormone therapy was strongly associated with an increase in mammographic density in the Postmenopausal Estrogen/Progestin Interventions and WHI trials.[195,196]

New areas that are currently being evaluated for the enhancement of primary and secondary prevention strategies include digital mammography, DCE-MRI, DCE-CT with ultrasound, PET, optical scanning, ductal lavage for cytologies and molecular testing, nipple aspirates, and blood and urine assays for growth factors and autoantibodies to oncoproteins and to tumor DNA. Validated biologic markers of breast cancer risk and/or more sophisticated screening modalities might well increase our ability to detect lesions earlier in high-risk populations.

Chemoprevention

Successful therapeutic prevention for breast cancer has progressed faster than for any other malignancy.[223] Two compounds, tamoxifen and raloxifene, which are estrogen receptor antagonists, have been shown to reduce the incidence of primary breast cancer in women at high risk.[224,225] In a head-to-head randomized trial of tamoxifen and raloxifene, efficacy was comparable with a 50% reduction of breast cancers; the toxicity of raloxifene was considerably less than that of tamoxifen.[226] Based on the positive activity of anastrozole (an inhibitor of estrogen synthesis) in the adjuvant setting and its minimal toxicity,[227] a randomized trial of this compound versus raloxifene in women at high risk for breast cancer is now underway. Preclinical studies at our institution using a transgenic mouse model suggest that antiprogestational agents may be of particular benefit in *BCRA1*-positive breast cancers.[228] The pros and cons of chemoprevention for breast cancer were recently reviewed, and the overall conclusion was that it cannot yet be recommended for general usage but should be useful for reduction of risk among high-risk individuals.[229]

There are several other options for a woman who is at very high risk for breast cancer, including bilateral mastectomy or oophorectomy and lifestyle modification. Prophylactic bilateral mastectomies have been performed on some mutation carriers, but cases of breast cancer developing in the remaining breast tissue after subcutaneous and total mastectomies have been reported. In addition, such surgeries are dramatic procedures for a woman who has only a "probability" of developing breast cancer, and a decision analysis paradigm for these interventions is available.[230] No long-term data exist on the effect of these surgeries in increasing the life expectancy of mutation carriers, yet one meta-analysis reveals considerable global variation in the utility of prophylactic surgery among unaffected *BRCA1* and *BRCA2* mutation carriers.[231] Bilateral oophorectomy has been proposed as another option for premenopausal women who have completed their childbearing. Although castration has been shown to decrease the risk of breast cancer in young, nulliparous women, especially when it is performed before the age of 35, this remains a very controversial area in the management of breast disease. Secondary prevention can be accomplished by instructing these high-risk women about the importance of clinical breast examinations by a physician and screening mammograms, which should begin at a younger age, preferably at least 5 years earlier than the age at which the relative developed breast cancer. Observational studies and initial clinical trials suggest that moderate physical exercise and control of obesity may decrease the risk for breast cancer,[232–234] as has been suggested for colorectal cancer. Recently, several randomized interventional trials have been initiated to definitively address these issues.

PROSTATE CANCER

Etiology

The age-adjusted incidence of prostate cancer rose slowly from 1965 to 1985 for unclear reasons. Parallel with aging of the baby-boomer population, the prevalence has also markedly increased since the general recommendation in the late 1980s by the American Cancer Society and the American Urological Association of yearly screening for PSA after age 50. This recommendation led to widespread screening and a rapid increase in the incidence of prostate cancer that peaked in the early 1990s.[235] In the most recent national estimates using SEER data from 1999 through 2003, the age-adjusted incidence of prostate cancer was 165 cases per 100,000 individuals—the highest rate of any cancer type among men.[12] Major differences in the incidence of prostate cancer are observed across the major U.S. ethnic groups, with blacks having the highest incidence rates (243 per 100,000) and Asian-Pacific Islanders having the lowest incidence rates (104 per 100,000). Overall, 234,460 cases of prostate cancer are expected in the United States in 2006, along with 27,350 deaths—making prostate cancer the third deadliest cancer in men after cancer of the lung and colorectal cancer.[78]

Several factors—age, familial/genetic, environmental, and hormonal—seem to contribute to the development of prostate cancer.[236]

Prostate cancer shows a familial tendency that is currently not well defined, but at least one study suggests that 10% to 15% of cases could have a strong genetic component.[237] The loss of heterozygosity in certain chromosomes in prostate cancer suggests that a gene related to some prostate cancers will be found.[238] The existence of a locus in chromosome 1 (band q 24) that predisposes men to develop early-onset prostate cancer has been verified, but a gene has not yet been isolated.[239]

The androgen dependence of prostate cancer led to the interesting hypothesis that variations in transcriptional activity by the androgen receptor regulated by CAG repeats could determine risk. Subsequent findings, however, argue against such an association, although there may be specific underlying situations in which other genotype influences lead to such an effect.[240] Because these studies concentrate on identifying prostate cancer risk and most prostate cancers are not clinically significant, others have argued for identifying genotypes that are associated with clinically aggressive cancers that predict outcome (mortality). In this regard, a report documenting extensive mitochondrial mutations in primary prostate cancers might provide new insights into progression.[241]

Both epidemiologic and experimental data suggest that hormones, particularly testosterone, play a definitive role in the development of prostate cancer. In the rat model, testosterone induces prostate cancer, and in humans prostate cancer rarely occurs in castrated men.[242,243] Also, black men have a higher incidence of prostate cancer at all ages than white men, and Japanese men have the lowest incidence.[244,245] Whether this racial-ethnic variation in prostate cancer risk has a hormonal basis is still unclear, but a substantive amount of data supports this viewpoint.[245]

A high-fat diet and obesity may be associated with an increased risk of prostate cancer, but the studies to date have yielded inconsistent results.[246] One investigation suggests that the preadult hormonal milieu, as reflected in attained height and childhood obesity, could have a strong influence on prostate carcinogenesis.[247] Epidemiologic, animal model, and in vitro studies indicate that n-3 polyunsaturated fatty acids, lycopene, and selenium might also be important in the pathogenesis of prostate cancer.[248] Additionally, *GSTP1* has been proposed as a caretaker gene that serves to detoxify carcinogens associated with various lifestyle habits.[249]

Screening and Early Detection

The relative benefits and costs of screening for prostate cancer are currently among the most contentious issues in the medical community.[250–252] There are several major reasons why this controversy continues:

- All available first-line techniques (DRE and serum PSA) have high rates of false-positive results. This leads to a relatively low positive predictive value and the unnecessary workup of many normal individuals.
- The natural history of prostatic intraepithelial neoplasia (PIN), the probable precursor of prostate cancer, is highly variable, and the natural history of the disease cannot currently be predicted reliably in any one particular case or by any specific biologic or pathologic marker.
- The workup of abnormal screening tests is invasive, requiring several biopsies of the prostate.
- The treatment of prostate cancer produces significant morbidity and measurable mortality.
- The rate of false-negative results is also high, which can produce a false level of assurance about the reliability of the screening tests (Fig. 26-6).

These same five concerns regarding the use of PSA and DRE for screening also exist for their use for early detection purposes, but the consequences are mitigated somewhat, because individuals are by definition symptomatic on presentation.

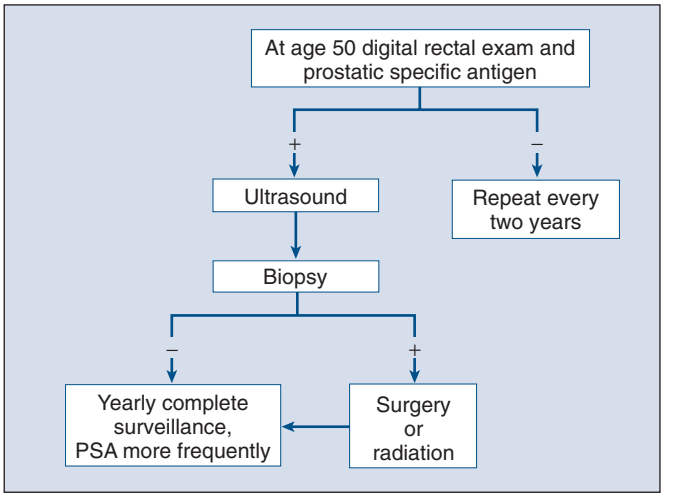


Figure 26-6 • Screening and early detection for prostate cancer.

The two most commonly used screening tests for prostate cancer are PSA and DRE, with transrectal ultrasound (TRUSP) reserved for patients with a positive PSA and/or DRE. Before the 1990s, yearly DRE after age 50 was the standard test used both for detection of prostate cancer and for screening. Although many primary care physicians use the DRE as part of a routine physical examination, assessment of its routine use indicates that DRE is performed in less than 50% of primary care encounters in which one would expect it to be done.[253]

A summary of the data indicates that the positive predictive value of DRE is relatively low (11% to 26%), whereas the negative predictive value (85% to 96%) is relatively high.[254] The most complete assessment thus far evaluated 811 unselected serial patients from 50 to 80 years of age who underwent DREs; 43 patients had a palpable nodule, and the positive predictive value of the 38 patients who underwent biopsy was 25%.[254] It is of great interest that 68% of the detected tumors were clinically localized, but only 30% were pathologically localized after radical prostatectomy. These data and other studies suggest that only about 20% to 25% of cases are localized at the time of a positive DRE; on the other hand, more than 25% of cases of prostate cancer are metastatic by the time a detectable palpable lump is detected on DRE.[254,255] Although the effectiveness of DRE is probably also significantly influenced by the skill of the examiner, the proper technique can easily be taught to health workers, is inexpensive, and is relatively noninvasive. Its usage as a primary screening tool, however, has not been widely adopted, probably because of its inconvenience. Whether routine screening by DRE alone can reduce mortality from prostate cancer is unknown. With the emergence of serum PSA as the screening test of choice, it is unlikely that the specific value of DRE in reducing prostate cancer morbidity and mortality per se will ever be demonstrated conclusively.

Annual measurement of serum PSA as a screening test for prostate cancer has been adopted widely following the initial 1993 recommendation of the American Cancer Society. At the current time, the professional community remains split over the question whether serum PSA should be recommended for routine screening in men older than age 50. The issues have been presented and analyzed extensively, and the same arguments that are used to discourage routine screening are used by others to recommend its widespread use. Estimates of overdiagnosis of clinically insignificant lesions have ranged from 15% to 84% in well-done investigations.[251,252]

Several studies have demonstrated that PSA screening results in a stage downshift and increases the detection rate of early-stage cancers.[256,257] The false-positive rate (25% to 50%) is high, however, resulting in a positive predictive value of PSA in screening studies of

about 30%. Because most of the studies have been done on symptomatic men, the positive predictive values in a true screening effort are likely to be lower (i.e., due to an expected lower prevalence of disease). In practical terms, this observation means that less than one-third of men with an elevated PSA will have biopsy-proven prostate cancer, and two-thirds will have a biopsy result that is negative for prostate cancer. Even if biologically aggressive tumors (and this is unlikely in most cases) were being identified (see the discussion later in this chapter), a large number of men would undergo unnecessary prostate biopsies with the attendant fiscal cost and morbidity.

Because the value of a "normal" level of PSA (<4 ng/mL) is influenced by several physiologic parameters, there has been a great interest in enhancing the specificity of the test. Techniques to improve the positive predictive value of PSA have included using age-adjusted reference ranges, PSA density (PSA level/size of prostate as measured by ultrasound), PSA velocity (change in PSA per unit of time), and ratio of bound to free PSA.[258,259] Although the validity of these strategies is currently unconfirmed, modeling has been important in determining the most effective use of tumor markers in other diseases, and it is likely that with enough time and information, the rate of false-positive results with PSA screening can be reduced. One way to reduce the false-positive rate is to combine PSA screening with DRE, and when appropriate, with TRUSP. A positive DRE increases the likelihood that a positive (i.e., abnormal) determination PSA is a true positive and therefore enhances the positive predictive value of the test. Additional evaluations with TRUSP should further increase the positive predictive value. The prostate component of the large, multicenter, randomized, controlled PLCO Cancer Screening Trial is expected to contribute significantly to our understanding of the value of PSA and DRE screening on mortality among men aged 55 to 74 years. In this study, the intervention arm receives screening examinations at scheduled intervals, but clinical management of these results are left to the individual study clinicians. However, such mortality data are not expected until the year 2015.

Initial reports addressing the rate of diagnostic procedures performed from the PLCO have emerged. At baseline through the year 2000, 4801 men with positive PSA (i.e., >4 ng/mL) or DRE were identified.[260] Among the 2717 men with elevated PSA, 64% received biopsy within 3 years, and among men with positive DRE and negative PSA only 27% underwent biopsy within 3 years. As might be expected, higher biopsy rates were noted for those with PSA above 7 ng/mL as compared with those whose PSA level was 4 to 7 ng/mL. Follow-up data regarding mortality, and also the positive predictive value for PSA, DRE, or both among different demographic strata are not yet available but are expected to assist greatly in our understanding of the utility of these commonly used screening tests.

The second major obstacle to the successful use of any screening modality for prostate cancer is that the biologic aggressiveness of PIN and early prostate cancer is not identified with high reliability by serum PSA. Progressive prostate cancer is a serious disease with high morbidity and mortality; however, not all prostate cancers are serious, and indolent behavior is more common than not. For example, about 30% of men over age 50 have histologic evidence of prostate cancer at routine autopsy, suggesting a prevalence of prostate cancer of about 9 million.[261] About 1.2 to 1.5 million of these 9 million men, or about 15%, will eventually die of their disease. Thus, most prostate cancers in the population are latent and do not progress to clinical adversity; therefore, an aggressive workup of an elevated PSA should not be a reflex action.

A third major consideration in evaluating PSA as a useful screening test is that the subsequent workup and treatment have a significant complication rate. Follow-up testing of an elevated PSA requires a repeat PSA, DRE, TRUSP, and biopsy. These are relatively safe procedures, but about 0.1% to 0.4% of the 20% of screened men who undergo biopsy experience infection or bleeding, and almost all experience considerable anxiety while waiting for the results.[262,263] The potential complications of treatment can be quite serious and include impotence, incontinence, and death from radical prostatectomy. Adverse outcomes of radical prostatectomy have been compared with watchful waiting in a randomized clinical trial. In this study, erectile dysfunction (80% vs. 45%) and urinary leakage (49% vs. 21%) were more common among patients who underwent radical prostatectomy; however, symptoms of urinary obstruction were improved (28% vs. 44%).[264] Radiation therapy is no less benign, but it carries a lower incidence of incontinence, a higher incidence of acute gastrointestinal complications, and a similar incidence of impotence.

A fourth major issue in PSA screening is the high rate of false-negative results. Numerous studies have demonstrated that many individuals (25%) with a normal PSA level have disease beyond the prostate.[265] Such results can lead to false reassurances and decreased follow-up when other factors suggest that a more aggressive workup might be reasonable. Several studies suggest that a rising PSA, even in the normal range, is a cause for concern and reason enough to biopsy.[266,267]

Although serum measurement of PSA has been widely adopted in men over age 50 as a primary screening tool for prostate cancer, its value in improving the overall health of men has not been shown to date. The equally important issue of whether screening does more harm than good also remains unanswered, because the natural history of prostate cancer is so variable.[265] Decision analysis has been used to determine the benefits and risks of age- and quality-adjusted survival, but the results remain inconclusive.[268,269] Other studies suggest that screening might have the potential to decrease survival, particularly in the older individual.[269] There is, of course, no lack of critics of this viewpoint.[270] What information is needed to resolve this difficult and important issue? Perhaps only a series of randomized trials can lay this question to rest, and to this aim, the prostate component of the PLCO Cancer Screening Trial may provide answers to these important questions. The results of a randomized trial involving more than 40,000 men in the city of Quebec have been reported, and those subjects with a regular PSA screening had a 60% decrease in mortality from prostate cancer after 7 years.[271] The conduct and interpretation of this type of trial is complex, and the results of several other large screening studies will have to be available before definitive recommendations about the value of routine screening PSA can be made.[272] These targeted trials, however, will provide only a general guide regarding population-based screening using serum PSA in men over age 50 as an approach to identify potential prostate cancers. The current consensus by the U.S. Preventive Services Task Force is that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA.[272]

An equally important issue is this: How do we identify and distinguish a biologically aggressive tumor in any one individual from those that will remain latent for the life of the individual? This is a very difficult problem to study. Although the earliest features of prostate cancer pathogenesis remain obscure, recent studies of the biologic features of intraepithelial hyperplasia of the prostate and of the "normal" prostate in individuals with a strong family history could shed some light on this issue.[272–274] Recent studies of the cytogenetic and molecular alterations in high-grade PIN have indicated that loss of heterozygosity is prominent and that certain oncogenes are expressed.[274] Defining the biologic features of the preclinical phase of prostate cancer is critical to answer for innumerable reasons, not the least of which is to increase the effectiveness of PSA screening. In this regard, a large, randomized trial of men with T1b, T1c, or T2 prostate cancer demonstrated that radical prostatectomy was superior to "watchful waiting" in terms of disease-free survival but not in terms of overall survival.[275]

Chemoprevention

Although the development of rat prostate tumors has been studied for some time, this model system has been regarded as a poor one

for carcinogenesis of the human prostate. The development of transgenic models that simulate the human disease represents an improvement in this regard.[276] Epithelial changes, including PIN, were identified in the human prostate long ago, although only recently have the biologic (and clinical) implications of these changes been recognized. The importance of these alterations, the recognition of the analogous evolution of the process to other epithelial cancers (e.g., cervical, oral), and its association with a wide spectrum of biologic abnormalities has moved PIN into the forefront as the probable, but clinically uncommon, preneoplastic precursor of prostate cancer.[276] An impressive array of studies measuring various biologic and molecular parameters in PIN have been done, and various biologic changes associated with the progression of prostate cancer have been identified.[277] What should be done now is to relate these biologic findings to the clinical aggressiveness of PIN and/or the eventual outcome of clinically relevant (nonindolent) prostate cancer. To be able to do so will help guide the difficult decisions after detection of an elevated serum PSA in biopsy samples during the screening and/or identification of PIN and during the early detection process. Three major categories of chemoprevention agents are being currently considered: inhibitors of proliferation, hormonal modulators, and stimulators of differentiation.

Thus far, two definitive randomized trials have been launched. The results of a phase III study using the 5α-reductase inhibitor finasteride (thereby lowering levels of dihydrotestosterone, the active metabolite of testosterone) in a high-risk population has been reported. The incidence of prostate cancer was decreased about 25%, and the side effects were minimal.[278] However, conclusions about the overall benefit were compromised by the finding that the risk for higher grade tumors was increased in the treatment arm. Although a large number of explanations have been offered for these contradictory findings, the future of finasteride as a therapeutic agent for prostate prevention is uncertain.

A second trial uses selenium, vitamin E, or both. The rationale for the study was based on secondary analyses of several large intervention trials in which prostate cancer was not the target, although recently some supportive experimental data also have become available.[279,280] Accrual to this 2×2 factorial randomized trial (vitamin E, selenium) is ongoing, and results are anticipated in 2013. A large number of compounds are being investigated at the preclinical level, and a few have advanced to the phase I/II clinical level. Studies of fenretinide failed to show an effect on relevant surrogate markers, whereas DFMO was more successful.[273,281]

Two other relatively unexplored areas of chemoprevention research in prostate cancer should also be mentioned: PIN and familial risk. Just as understanding the biology of PIN will affect our screening and early detection decisions, PIN should also serve as a useful marker in chemoprevention studies. Although the heterogeneity of lesions will make interpretation of effect of an intervention a challenge, PIN represents an important parameter for advancing our knowledge of early prostate cancer carcinogenesis and its modulation by candidate chemoprevention agents. Several studies are in progress to use PIN as a screening tool for new chemoprevention agents including studies of biologic markers to determine risk.[282] The roles of family studies and genetics in identifying individuals at high risk for prostate cancer are in their infancy, but epidemiologic studies support the notion that genetic risk plays a role, and clinical studies support the observation that early prostate cancer in some individuals is highly aggressive, whereas in others it is indolent. Linking these two parameters should identify a population of individuals in whom screening, early detection, and chemoprevention agents should be intensively directed.

Advances in the systemic therapy of advanced prostate cancer have been slow in coming. In a real sense, advances in the management of prostate cancer have been minimal since the introduction of hormonal therapy more than 50 years ago. It is likely that the widespread use of screening and early detection with an appropriate follow-up will reduce the morbidity and mortality from prostate cancer in a substantial way and that effective chemoprevention will be developed, because the major biologic enhancer (androgens) of prostate cancer carcinogenesis is known.

SKIN CANCERS

Each year, more than $2 billion is spent to treat patients diagnosed with skin cancers, the majority of which are malignant melanoma and basal and squamous cell carcinomas. These figures underestimate the true cost, because many of these cancers are treated in physicians' offices, and nonmelanoma skin cancers are not routinely reported to tumor registries. An aging population, depletion of the stratospheric ozone layer, and increased recreational exposure to ultraviolet radiation (UVR) represent some of the factors that contribute to the development of over 1 million cases of nonmelanoma (basal and squamous cell carcinomas), 49,000 cases of melanoma in situ, and 62,000 cases of invasive melanoma diagnosed annually in the United States.[78] Understanding how these and other risk factors lead to alterations in key cellular processes like DNA synthesis and repair, oncogene activation, cell-cycle control, and apoptosis is the focus of intense research efforts aimed at designing novel preventive, diagnostic, and treatment strategies.[59] This section details the various primary, secondary, and tertiary preventive approaches for melanoma and nonmelanoma skin cancers. Incorporating these strategies into medical practice should decrease the incidence and mortality from skin cancer and should also decrease health care costs.

Etiology and Primary Prevention

Environmental

Successful primary prevention depends on the ability to identify individuals at risk for skin cancer and to use this information to educate both high-risk groups and the general population about various ways to reduce risk (Table 26-5). Many factors have been identified that increase an individual's risk for the development of melanoma and nonmelanoma skin cancers. Exposure to UVR is a major risk factor.[283] Not only is cumulative UVR exposure important in the development of skin cancers, but it is apparent that acute, intermittent exposure to UVR is carcinogenic.

The electromagnetic spectrum is composed of infrared, visible, and UV light; the latter is responsible for causing the cellular and architectural changes in the epidermis and dermis that lead to photoaging and skin cancer.[283] Although the UVR spectrum is broad, UVR-B (290–320 nm) and UVR-A (320–400 nm) are the only wavelengths that routinely reach the earth's surface, in that shorter wavelengths (UVR-C) are absorbed by the ozone layer. UVR-B is more potent than UVR-A in inducing neoplastic transformation in epidermal keratinocytes and melanocytes, which give rise to basal and squamous cell cancers, and melanoma, respectively. UVR-A, however, has been found to penetrate the skin more deeply and is the predominant wavelength emitted from artificial lamps found in tanning salons.[283] More than a million adolescent and young women frequent these facilities daily and expose themselves to up to five times the amount of UVR that is emitted from the sun at any given time. The role of UVR-A radiation in the development of skin cancer will increase as this industry continues to grow.

The mechanism of action of UVR on the skin has been studied extensively. Once photons penetrate through the stratum corneum, they are absorbed by cellular DNA and produce base substitutions in pyrimidines.[284] The substitution of thymidine for cytosine is pathognomonic for UVB-induced skin damage and is found in the tumor suppressor gene *p53* in more than 90% of squamous cell skin cancers.[285,286] Basal cell cancers also contain *p53* mutations.[287] Although UVR is regarded as contributing to the pathogenesis of melanoma, these types of mutations are uncommon, therefore raising the likelihood that the role of UVR is associative or complementary to the process. Normally, p53 acts to protect damaged cells by either

Table 26-5 Predisposition and Risk Factors for Skin Cancer

NONMELANOMA
Ultraviolet light (sun) exposure (cumulative)
Genetic
Xeroderma pigmentosum
Nevoid basal cell syndrome
Phenotypic
Skin complexion
Sunburn/tanning response
Degree of freckling
Premalignant dermatoses
Actinic (solar) keratoses
Leukoplakia
Chemical, thermal, and scar keratoses
Chronic inflammation
Immunosuppression
Prior history of skin cancer
MELANOMA
Ultraviolet light exposure (intermittent)
Genetic
Melanocortin receptor variants
Atypical or dysplastic nevi
Dysplastic nevus syndrome
Phenotypic
Less cutaneous pigmentation

inducing cell-cycle arrest (so that mutated DNA can be repaired or excised) or by inducing apoptosis.[288] UVR-induced *p53* mutations disturb the cell cycle by inhibiting cyclin-dependent kinases, leading to uncontrolled cell proliferation. Cells with one mutated *p53* allele can undergo clonal expansion, and, if the other *p53* allele is mutated, neoplastic transformation occurs. Therefore, UVR could both initiate and promote carcinogenesis.[288] UV light might also have immunosuppressive effects by interfering with the ability of Langerhans cells to process antigens.[289]

Other risk factors that increase susceptibility for the development of skin cancers include skin complexion and response to sunlight, degree of freckling, ethnicity, gender, age, geographic location, presence of premalignant skin lesions, medical history of exposure to ionizing radiation or psoralen and UV therapy, chronic skin irritation (ulcers, inflammation, or trauma), or a personal history of a germatodermatoses (xeroderma pigmentosum, nevoid basal cell carcinoma syndrome, and familial dysplastic nevus syndrome), lymphoreticular malignancy, granulomatous diseases, or other immunosuppressed states such as organ transplantation in which development of multiple cutaneous squamous cell carcinomas is a major problem.

Health care providers should be aware of several premalignant dermatoses for the purpose of identifying individuals who are at increased risk for the development of skin cancers. The most common lesion, actinic keratoses (solar keratoses), has been reported to undergo malignant transformation to squamous cell cancer in 12% of patients.[290] Histologic evaluation of white patches occurring on mucous membranes, known as leukoplakia, is also important, because up to 20% could be dysplastic, with 3% to 6% becoming invasive cancers. Atypical and dysplastic nevi, large congenital nevi (>9 cm), and an increased number of moles are common precursor lesions of melanoma.[291] Chronic skin irritation from radiation (radiation dermatitis), chemicals (tar and arsenical keratoses), infrared light (thermal keratoses), and scars (scar keratoses) might also lead to malignant transformation. Any patient who is immunosuppressed (human immunodeficiency virus [HIV] diagnosis or transplant recipient) or who has a history of epidermodysplasia veruciformis or Bowen's disease (an intradermal carcinoma that often occurs on sun-exposed areas) should be considered for prevention protocols. Anyone who has a prior history of skin cancer is also at risk for a second primary cutaneous malignancy.[292,293] Patients diagnosed with thin melanomas (<75 mm in thickness; Breslow staging) were found to have a 4% chance of developing a second primary melanoma.[294] First-degree relatives of skin cancer patients also carry an increased risk.[292]

Recently, a risk model for melanoma risk has been proposed using data from a case-control study, based on similar methodologies developed by Gail for the breast cancer risk model developed nearly 2 decades ago.[295,296] This melanoma risk model incorporates subject responses to simple questions about complexion, history of blistering sunburn, and ability to tan, with findings on examination of the back describing the number of small and large nevi. This risk model captures attributable risk for melanoma development of 86% for men and 89% for women. Though promising, further risk models are still needed for individuals with a history of melanoma or nonmelanoma skin cancer, or persons with a first-degree relative with melanoma. Such models could identify high-risk individuals who could be referred for chemoprevention trials.[297]

Heredity

Several molecular abnormalities have been identified that could be responsible for the genetic instability preceding the development of invasive nonmelanoma skin cancers (Table 26-6). Defects in DNA repair genes, oncogenes, and tumor suppressor genes, as well as allelic losses in a number of chromosomes, have been described.[287] Mutations in the *Ras* oncogene have been shown to initiate epidermal skin cancers.[298] Mutations in DNA repair genes (xeroderma pigmentosum, for example) bring about an inability to repair UVR damage to DNA efficiently, leading to the development of melanoma and epidermal skin cancers.[299] DNA repair capacity might be particularly important for individuals with other strong risk factors, such as low tanning ability and the presence of dysplastic nevi.[300] There are numerous examples of specific chromosomal abnormalities in nonmelanoma skin cancers. Allelic losses have been found in 9p, 13q, 17p, 17q, and 3p in squamous cell cancers and in 9q in basal cell cancers.[298] Studies of keratinocyte transformation have also focused

Table 26-6 Molecular Determinants of Carcinogenesis in Skin Cancer

NONMELANOMA
Mutated *ras* oncogenes (initiation)
Mutation in DNA repair genes (initiation)
Allelic loss in chromosomes 3p, 9p, 13y, 17p (promotion)
MELANOMA
Allelic changes in chromosomes 9p, 15, 16
Progressive mutations
BRAF (immortalization)
DNA repair genes (initiation)
Cyclin-dependent kinases (progression)
Ras oncogene (progression)

on the UVR-mediated phosphatidylinositol 3-kinase and p38 mitogen-activated protein kinase pathways.[301]

The genes and genetics of melanoma have been summarized.[302] One autosomal dominant syndrome that markedly increases an individual's lifetime risk for melanoma is familial dysplastic nevus syndrome. Melanoma in one or more first-degree relatives and the presence of a large number of moles (between 10 and 100) are required to diagnose this syndrome.[303] Rearrangements or deletions of genes have been found to occur in chromosomes 9 and 10 in patients with familial melanoma, atypical nevi, or early melanoma lesions. Two cyclin-dependent, kinase, tumor suppressor genes have been isolated on chromosome 9 (p15, p16). Mutations in this region lead to uncontrolled cell proliferation, because the transition from G1 to S of the cell cycle is no longer inhibited.[304] The finding that the penetrance of one of these genes to frank melanoma is dependent on geographic variation emphasizes the role of environment in genetic expression[305] and the potential interaction of UVR and sunburn genotype.[306] Certain polymorphisms in the melanocortin-1 receptor gene have been shown to correlate with a reduced response to melanotrophin, the major natural hormone that regulates cutaneous pigmentation.[307] Other studies suggest that loss-of-function mutations in the *MCIR* gene sensitize human melanocytes to the DNA-damaging effects of UVR, which could increase melanoma cancer risk.[308]

The identification of frequent *RafB* mutations in both melanomas and benign moles is also of great interest and suggests that this alteration may be the initial molecular change leading to immortalization.[309] Once the significance of the genetic abnormalities in causing nonmelanoma and melanoma skin cancers is understood, we might be able to incorporate this information into new risk models to identify high-risk individuals who would benefit from prevention protocols and increased surveillance.

Preventive Measures

Numerous examples of primary preventive strategies exist. Protective clothing (hats, long sleeves, special fabrics approved by the U.S. Food and Drug Administration), behavioral modification (avoidance of peak sun from 10:00 AM to 3:00 PM, avoidance of sun tanning salons, and use of appropriate shading), and liberal application of sunscreens are three such examples.[310] There are two types of sunscreens: blockers and reflectors. Blockers such as paraminobenzoic acid absorb UVR-B only. Nonparaminobenzoic acid blocker sunscreens absorb both UVR-A and UVR-B. Reflectors such as zinc oxide completely reflect UVR light. The SPF, or sun protective factor, is a measure of the comparison of the minimal erythema dose with and without sunscreen and should be at least 15. Finally, sunscreens should not wash off easily when bathing or sweating.

The current role of sunscreens in preventing skin cancer is the subject of considerable controversy.[311] Randomized trials have demonstrated that sunscreen use encourages prolonged sun exposure.[312] Another randomized study, however, has shown a protective effect of sunscreen use against the development of squamous cell cancer and nevi.[313] Based on these findings, we probably can conclude that regular sunscreen application should be combined with protective clothing to reduce the long-term risk for the development of melanoma and nonmelanoma skin cancers.[283]

In Australia, which has the highest incidence of skin cancers, other approaches have been adopted, including the passage of laws for employers to provide sun protection for employees, distribution of free sunscreens, tree planting campaigns, and public shade structures. In the United States, the Federal Trade Commission requires that protective eyewear be worn in tanning salons. In addition, signed informed consents and signs about health risks of UVR exposure in tanning salons are required. Furthermore, in Texas an adult must accompany children attending tanning salons, and parental permission is mandatory for all minors. Attitude and behavioral modification of children (and their parents) informed by education and knowledge about sun exposure and skin damage/cancer is a reasonable goal and is most effective when started at a young age (Box 26-2).[314,315]

Box 26-2. USEFUL THINGS TO TELL YOUR PATIENTS ABOUT THE PREVENTION OF SKIN CANCER

- Avoid sunburns (know your skin type—do you burn easily?).
- Avoid tanning booths.
- Use sunscreens with high SPF.
- Stay covered.*
- Avoid outdoor recreation between 10 AM and 3 PM.
- Minimize sunlight exposure.
- Know your moles (and other skin lesions) and see a dermatologist promptly if they change or are new.

*A wet T-shirt has an SPF of 0; several companies now make clothes that are specifically treated to give a high SPF.

Screening and Early Detection

The following are essential for effective screening:

- An understanding of the four characteristics of skin lesions that are suggestive of premalignant or malignant changes (i.e., the ABCDs): asymmetry, border irregularity, color variegation, and diameter (6 mm or greater)
- Knowledge of important prognostic factors that should be recorded: anatomic location, ulceration, number of atypical lesions, presence of lymph nodes
- Familiarity with the types and indications for the particular type of biopsy: shave biopsy, incisional biopsy, excisional biopsy, punch biopsy
- Access to skilled pathologists who can comment on key histologic criteria such as thickness (Breslow staging), margins, ulceration, regression, satellitosis, angiolymphatic invasion, mitotic activity, precursor lesions, host response, and growth phase (radial vs. horizontal)

Screening for skin cancer, and in particular for melanoma, is supported by several criteria. Skin cancer is the most common cancer worldwide and is an important public health problem. Melanoma is second only to leukemia in terms of years of potential life lost, because it often affects younger people during the most productive periods of their lives.[315] Although basal and squamous cell cancers have a much better prognosis than melanoma, they cause considerable local disfigurement if not diagnosed and treated early. In addition, screening skin examinations are acceptable to both patients and health care providers. Premalignant cutaneous lesions tend to have a long latent phase, making early diagnosis and treatment possible with evidence that supports subsequent decreases in both incidence and mortality rates.[290]

Although no randomized, prospective studies evaluating the efficacy of screening for skin cancer have been conducted, nonrandomized studies support its practice. Thinner melanoma lesions (stages I and II) are diagnosed more frequently with routine screening and intensive education programs. The Sydney, Australia Melanoma Project demonstrated that widespread screening and education led to a decrease in the thickness of lesions from 2.5 mm to 0.8 mm, a decrease in the number of ulcerated lesions, an increase in the number of melanomas diagnosed in the radial rather than the vertical growth phase, and an increase in the 5-year survival rate to 94%.[316] A decrease in lesion thickness and an increase in the number of melanomas diagnosed were also confirmed in studies in Scotland and the United States.[316,317] Interestingly, a large skin cancer education and screening

demonstration project found that 80% of study participants did not have a regular dermatologist, 50% saw their physician only because of the free skin examination, and 80% were receiving their first skin examination. Another interesting population-based, case-control study investigated whether skin self-examination would reduce the incidence of melanoma.[318] Although only 15% of participants in the study cohort practiced skin self-examination, they found that skin self-examination was associated with a reduced risk of melanoma in general and a reduced incidence of more advanced disease in melanoma patients. The authors concluded that mortality from melanoma might be reduced by as much as 63% if regular skin self-examinations were performed.

New imaging technologies may play increasingly important roles in screening and early detection for skin cancers in the future. To this aim, diffuse optical spectroscopy represents an exciting new technology that is emerging. Recently, diffuse optical spectroscopy technology has been used via a hand-held probe with direct skin contact to define the optical properties of skin in vivo, including quantification of melanin, hemoglobin, and water concentrations.[319] Thus, the potential for noninvasive identification of malignant versus benign skin lesions is an anticipated application for this technology. However, the utility in accurately identifying malignant cutaneous lesions has not been described analytically, and the appropriate validation studies on melanoma and nonmelanoma skin cancers must be performed before widespread usage of this novel screening device can be recommended.

Challenges to effective screening examinations include the following:

- Lack of standardization of the examination and training that health care providers receive
- Lack of accurate reporting to tumor registries (for melanoma; nonmelanoma skin cancers are not reported at all)
- Inability to motivate certain high-risk groups (e.g., white males) to come in for examination
- An inability to screen adequately for the 1% to 2% of amelanotic cases of melanoma

One step toward overcoming these challenges has been to designate the months of May and June as free skin cancer screening months in the United States in an attempt to attract more people for evaluation.

Chemoprevention

Nonmelanoma Skin Cancers

Clinical trials investigating the use of β-carotene, 13-*cis*-retinoic acid, selenium, and NSAIDs have been performed on individuals with a history of nonmelanoma skin cancers. Results using vitamin A derivatives have been mixed, which most likely reflects the complex biochemical and molecular mechanisms underlying the prodifferentiation or promaturation changes that these compounds produce. Three randomized clinical trials did not find a decrease in the recurrence rates of basal or squamous cell cancers in individuals at high risk for new skin cancers. Levine and coworkers[320] found no beneficial effect when using isotretinoin or retinol in high-risk subjects with at least four prior basal cell or squamous cell cancers. The Isotretinoin–Basal Cell Carcinoma Study Group also demonstrated that isotretinoin did not prevent the recurrence of basal cell cancer in patients previously treated for basal cell cancer.[321] Finally β-carotene was not shown to prevent nonmelanoma cancers.[322] In contrast, in 2297 moderate-risk subjects with a history of actinic keratoses and at most two squamous or basal cell carcinomas, supplementation with a moderate dose of retinol (25,000 IU daily) reduced the incidence of squamous cell (but not basal cell) cancers by 25%.[23] In addition, patients with xeroderma pigmentosum develop fewer new skin cancers after receiving high-dose isotretinoin.[323] However, interest in the retinoids as preventive agents has waned, and it is unlikely that their usage will be adopted unless a new generation of nontoxic compounds can be developed.

Negative results have been produced in a large multicenter study involving selenium supplementation.[166] In this double-blind, randomized, placebo-controlled study, 200 μg of selenium daily did nor seem to prevent the development of future nonmelanoma skin cancers in patients with a history of basal or squamous cell skin cancer. A secondary analysis of the effect of NSAIDs in this trial on nonmelanoma skin cancer also suggested no effect for this class of agents.[324] Finally, NSAIDs have been found to prevent the erythema that occurs 6 to 12 hours after acute sun exposure. In a large, randomized trial, topical application of the COX-1 inhibitor diclofenac was superior to placebo in clearing actinic keratosis lesions, and this formulation has now been approved for clinical use, although recent concern about the cardiovascular toxicity of selective COX inhibitors leave its usage uncertain.[325] A small placebo-controlled study of 2-DFMO suggests that this compound might have comparable activity.[326] A comprehensive strategy for the development of chemoprevention drugs for nonmelanoma skin cancers has recently been described.[59]

Melanoma and Dysplastic Nevi

Topical β-all-*trans*-retinoic acid has been demonstrated to cause regression of dysplastic nevi[327,328]; however, the inconvenience of topical application has limited its usage.

The development of chemoprevention agents for melanoma has progressed slowly, although the development of a risk model for melanoma is an important first step, as is the development of an in vitro model for assessing the potential value of chemoprevention agents.[297,324] A great deal of new preclinical work has advanced our understanding of melanoma pathogenesis as well,[329] including a unique redox-based paradigm.[330] The recent development of a transgenic model that simulates the human disease is also an important advance and should lead to a more systematic development of chemoprevention drugs.[331]

Tertiary Prevention

Lifetime surveillance of patients who have been diagnosed and treated for skin cancer is an important component of prevention. Many studies have shown that laboratory and radiologic surveillance do not detect second primaries or recurrences beyond what is found on skin examination in patients with a history of melanoma. Patients with a history of melanoma should be evaluated every 6 months with skin and regional lymph node examinations. Particular attention should be paid to the scar of the previous excision site during these examinations. After 2 years of normal examinations, the interval between visits can be extended to 1 year. If an individual has any atypical moles, a positive family history for melanoma, or other poor prognostic factors, an evaluation (including cutaneous photography) every 3 to 6 months for the first 2 years (lengthening the interval between examinations only if the atypical moles are stable) is recommended. No recent findings have affected these general recommendations. Newer biomarkers are being explored to detect melanoma earlier, but thus far no validated successes have been reported.

Prevention of skin cancer depends on increasing the awareness of health care professionals and the public about the importance of early diagnosis and skin self-examinations. More research needs to be devoted to ways of motivating high-risk individuals to receive screening examinations. Public policy measures should be expanded and consideration given to other approaches, such as mandatory use of sunscreen and adequate clothing in daycare centers and public schools. The true measure of the various prevention strategies will come from studies of their ability to decrease both the incidence of and the mortality from skin cancers. Recent evaluations of the value of screening and early detection for cutaneous melanoma suggest that survival has been increased from 50% 30 years ago to over 85% today.

OVARIAN CANCER

Ovarian cancer will affect an estimated 20,180 women in the United States during 2006 and is the fifth leading cause of cancer mortality among women, after cancer of the lung, breast, colorectum, and pancreas.[78] Approximately 10% of ovarian cancers are associated with a *BRCA* mutation, whereas the remainder are sporadic.[332] The lifetime risk of developing ovarian cancer for the general population is approximately 1.5%.[333] Advanced-stage disease (spread beyond the pelvis or FIGO stage III/IV) is present in 70% of these women; this has led to a 40% overall 5-year survival rate with low 5-year survival rates for advanced-stage disease (stage III 5-year survival, 25.1%; stage IV 5-year survival, 11.1%).[334] Hence, most women who present with advanced disease die from their disease. Therefore, prevention of ovarian cancer is an important goal. Given that 90% of all ovarian cancers arise from the epithelial lining of the ovary rather than from the germ cells or sex-cord derivatives, preventive strategies outlined in the following paragraphs pertain to the prevention of epithelial cancers.

Primary Prevention and Risk Reduction

Epigenetic Factors

Several reproductive, environmental, and genetic factors could influence an individual's risk of developing ovarian cancer (Table 26-7). Advancing age is an important risk factor, in that data from SEER and the National Center for Health Statistics reveal that more than 48% of all cases of ovarian cancer occurred among women older than 65 years of age.[335]

Important protective reproductive factors include increased number of pregnancies, oral contraceptive use, and breastfeeding. Reanalysis of six large case-control studies involving 2768 incident cases demonstrated an overall risk of 0.66 in oral contraceptive users that continued to fall with duration of use; the effect was projected to persist for a lifetime after stopping.[336] Only a limited number of studies have examined the effect of HRT on ovarian cancer development. In the largest investigation reported thus far, a cohort study of 44,241 participants in the Breast Cancer Detection and Demonstration Project (329 cases of ovarian cancer), estrogen-only use (but not combined estrogen-progesterone) was associated with a modest increased relative risk of ovarian cancer.[337] No relationship between ovarian cancer risk and age of menarche, age of menopause, or duration of HRT has been observed in one large meta-analysis.[338] Conversely, increased risk was observed in nulliparous women who had a history of infertility. Critical analysis suggests that women with a history of infertility alone are at increased risk, and fertility drugs might not alter this risk further.[339] Tubal ligation, and to a lesser degree hysterectomy, are associated with decreased risk of ovarian cancer.[340]

A large prospective cohort study of 300,537 women (1511 deaths from ovarian cancer) showed that mortality rates from ovarian cancer were significantly increased in overweight and obese women who had never used HRT.[341] Other dietary factors, such as consumption of milk and selenium, might also modify an individual's risk for ovarian cancer, but the data are not convincing.

Finally, talc has been suggested as a possible factor leading to the development of ovarian cancer, in that epithelial ovarian malignancy shares similarities with mesotheliomas, and talc is structurally similar to asbestos, a proven cause of mesotheliomas. Cramer and associates[342] first reported this association in 1982 when they assessed genital exposure to talc in 215 white females with epithelial ovarian cancer and 215 matched controls. They reported that 92 of the patients (48%) regularly used talc, either as a dusting powder on the perineum or on sanitary napkins, compared with 61 controls (28.4%). A relative risk of 1.92 was associated with these practices in the women with ovarian cancer. In a follow-up study, researchers determined that the risk for ovarian cancer was highest in women who applied talc directly to the perineum or undergarments on a daily basis for more than 10 years.[343]

Table 26-7 Risk Factors for the Development of Ovarian Cancer

GENETIC
Syndromes
Ovarian cancer syndrome
Hereditary breast and ovarian cancer syndrome
Hereditary nonpolyposis colon cancer syndrome (Lynch II)
Age
EPIGENETIC
Reproductive factors
Gravity, parity
History of infertility
Age of menopause and menarche
Oral contraceptive use
Diet
Fat
Fiber
Milk
Selenium
Talc

Genetic Factors

Approximately 10% of all epithelial ovarian cancers are related to genetic mutations (hereditary, familial, other rare syndromes). Women considered to have a hereditary ovarian cancer syndrome must have at least two first-degree relatives with histologically confirmed ovarian cancer. These individuals carry an overall lifetime probability of developing ovarian cancer of approximately 50%. There are three "hereditary" autosomal dominant syndromes, which include the site-specific ovarian cancer syndrome, hereditary breast and ovarian cancer syndrome, and HNPCC, Lynch II.[344] Together, these cancer syndromes account for 1% to 5% of the ovarian cancers that are diagnosed and generally occur 1 to 2 decades earlier than nonhereditary ovarian cancer.[345] The genetic linkage for the majority of the hereditary breast and ovarian cancer and the site-specific ovarian cancer syndromes has been found on the *BRCA1* and *BRCA2* loci on chromosome 17 (band q21). Specifically, the lifetime risk of developing ovarian cancers among *BRCA1* and *BRCA2* carriers is 15% to 60% and 15% to 28%, respectively.[346]

Women who report a family history of either a single first-degree relative and/or one or more non-first-degree relatives with ovarian cancer meet the definition of familial ovarian cancer syndrome. About 5% of diagnosed ovarian cancers fall into this category. Ovarian cancers can also occur as part of other rare, inherited, genetic syndromes such as Cowden's disease or Li-Fraumeni syndrome. Once individuals are identified with a familial or hereditary ovarian cancer syndrome, or a germline *BRCA* mutation carrier, primary preventive strategies can be implemented, including oral contraceptive pill use, risk-reducing salpingo-oophorectomy, and possibly dietary modification.

Prophylactic oophorectomy is a subject of substantial controversy. It has been estimated that 700 prophylactic oophorectomies might need to be performed to prevent one case of ovarian cancer.[347] A person's age, medical history, reproductive plans, and proximity to menopause must be considered when trying to make an informed

decision. In general, postmenopausal women or women older than 50 years are encouraged to undergo this procedure, because the risk of ovarian cancer increases with age. Women who are younger than 50 but older than 40 years of age should be counseled on the risks and benefits associated with surgical menopause and subsequent HRT, and on the risks of developing ovarian cancer based on their pedigree. There are two exceptions to these rules. One is the performance of prophylactic oophorectomies on women who are being operated on for a bowel cancer, because metastases are found in 25% of cases when the ovaries are carefully examined.[347] In addition, women with one of the three hereditary ovarian cancer syndromes, and also *BRCA1* or *BRCA2* carriers should strongly consider risk-reducing salpingo-oophorectomy at age 35 or at the completion of childbearing.[348,349] These women, however, should be counseled that they are still at increased risk for the development of intra-abdominal carcinomatosis, which is histologically similar to epithelial ovarian cancer but arises from the peritoneal lining. As mentioned, carriers of germline mutations in *BRCA1* and *BRCA2* genes should be counseled about the option of prophylactic risk-reducing salpingo-oophorectomy.[350] The recommendation is problematic, however, because there is heterogeneity in the type and number of mutations at the *BRCA* loci, which thus far has made it difficult to quantify an individual's risk of developing ovarian cancer. An interesting decision analysis study has been performed[351] to determine the effect of prophylactic oophorectomy on life expectancy in women with *BRCA1* and *BRCA2* mutations. On average, a 30-year-old woman would increase her life expectancy from 0.3 to 1.7 years after undergoing bilateral oophorectomies. The analysis suggested that a woman could delay oophorectomy until she was 40 years of age with minimal loss of life expectancy.

Screening and Early Diagnosis

Early detection of ovarian cancer has not contributed to an overall improvement in survival of gynecologic malignancies.[352] Effective screening for a disease requires that the disease of interest has a premalignant phase, a long preclinical phase, stage-dependent outcome, curative treatments that are acceptable and readily available, and a cost-effective screening test that demonstrates good sensitivity, specificity, and positive predictive values. Unfortunately, the premalignant condition that progresses to invasive ovarian cancer has not been well defined. In addition, once invasive ovarian cancers develop, the preclinical phase is asymptomatic, with the result that most women present with advanced disease. Survival is not only stage dependent but also grade dependent. Primary treatment is surgical and in general is curative only if disease is confined to the ovaries. The available screening tests (pelvic ultrasound, serum cancer antigen [CA-125] levels, and pelvic examinations) are acceptable to patients and physicians but suffer from decreased specificity secondary to unacceptably high false-positive rates. Furthermore, the likelihood that an individual has ovarian cancer after a positive test (positive predictive value) is too low for available tests to be used for mass screening. In addition, screening might actually increase morbidity and mortality, because surgical exploration is the only way to diagnose ovarian cancer definitively. A decrease in mortality from ovarian cancer will occur only if we can detect early-stage disease reliably, which is not possible given available screening tests. Currently, there is insufficient evidence to support routine screening with transvaginal ultrasound and serial CA-125 serum measurements.

Specific screening tests have been evaluated both individually and together in a variety of populations. Although the pelvic examination should be included in every annual physical examination, studies have shown that it is not extremely effective in diagnosing adnexal masses.[353] CA-125 is an antigenic determinant on a high-molecular-weight glycoprotein that is recognized by a monoclonal antibody (OC125).[354] It is expressed by 82% of ovarian carcinomas and in a percentage of other normal or pathologic conditions including pelvic infections, endometriosis, pregnancy, menstruation, pancreatitis, renal failure, hepatitis, peritonitis, and congestive heart failure. Even in early-stage disease, however, CA-125 can detect only 50% of stage I disease and 60% of stage II disease.[354] Therefore, a normal CA-125 in the setting of an abnormal examination should not keep the physician from performing other diagnostic studies or surgical exploration. The real value of this tumor marker is in a premenopausal or postmenopausal woman who has a pelvic mass, particularly in the postoperative period, to measure response to treatment and progression of disease (Box 26-3).

Box 26-3. PHILOSOPHY OF SCREENING AND EARLY DETECTION FOR OVARIAN CANCER

- No good test for screening is currently available.
- Concentrate on those patients with familial or heritable risk.
- Transvaginal ultrasonography and serum CA-125 are worth doing for selected patients.

Ultrasonography by itself is easy to perform, but like CA-125 measurements, it is not an acceptable enough screening test to warrant its general use. Currently, color flow imaging and measurements of pulsatility indexes are being coupled to transvaginal ultrasound to try to decrease the rate of false-positive results. Improvements in the ability to visualize both ovaries during a given examination might improve the accuracy of transvaginal ultrasound as a screening test. So might more accurate measurements of the morphologic variations that exist between ovaries, among patients, and during different periods of the reproductive life cycle of a woman.[354] Numerous studies have combined pelvic examinations, CA-125 serum measurements, and transvaginal ultrasound. Results from an ongoing National Cancer Institute–supported multicenter trial evaluating the utility of transvaginal ultrasound and serial CA-125 measurements in 74,000 women who have been randomized to either annual pelvic examinations with CA-125 measurements and pelvic ultrasonography or annual pelvic examinations without CA-125 or ultrasound evaluation will help direct future screening practices. Until improvements in test characteristics of the various screening techniques can be accomplished, multimodality screening for ovarian cancer is recommended only for women with a hereditary ovarian cancer syndrome or *BRCA1* or *BRCA2* mutation, although no specific studies are available to support this practice. Individuals with a strong family history that does not demonstrate an autosomal dominant inheritance pattern should be evaluated on a case-by-case basis.

Chemoprevention

Chemoprevention studies for epithelial ovarian cancer have not been performed, although the data for oral contraceptive pills suggest strongly that these agents would be effective. In addition, DePalo and colleagues[355] completed a preliminary analysis of women with T1-T2 breast cancer who were randomized to oral 4-hydroxy-fenretinamide or placebo. Six cases of ovarian cancer were diagnosed in the placebo group vs. none in the treated group ($P = 0.02$).[355] Long-term follow-up after the intervention phase has shown that no significant difference between the two groups was maintained once the intervention was stopped. Fenretinide and its derivatives continue to have considerable appeal, however, and further studies should clarify the role that this vitamin A derivative might play in the chemoprevention of ovarian cancer.[356] Studies in primates suggest a strong synergistic effect of oral contraceptives plus fenretinide on markers that should be associated with a reduction in ovarian cancer[357]; however, proving via a classical randomized trial whether ovarian cancer can be prevented will be difficult.

In conclusion, a great deal of work remains to be done both in establishing the etiology of ovarian cancer and in developing strategies to prevent its occurrence and reoccurrence, but the opportunities seem great.

CERVICAL CANCER

Prevention of cervical cancer is one of medicine's greatest accomplishments. The recent demonstration of an effective vaccine against HPV, the major etiologic agent of cervical cancer, suggests that this disease eventually could become a concern of the past.[358] The U.S. annual mortality rate for cervical cancer has decreased from 26,000 deaths in 1941 to an estimated 3700 deaths in 2006, which is impressive given the twofold increase in population in the United States during the second half of the 20th century.[78] Widespread usage of Papanicolaou smear screening is largely responsible for reduction of cervical cancer from the leading cause of cancer death in American women to an uncommon one. In fact, the incidence of cervical cancer has decreased by 70% since widespread screening began in the early 1940s.

Unfortunately, these favorable statistics cannot be generalized to other countries or to certain subgroups within the United States. Cervical cancer is still the number one killer of women in underdeveloped nations, with 500,000 cases still being diagnosed worldwide every year. Despite the tremendous resources dedicated to improved screening methodologies and identification of high-risk individuals, simple visual inspection of the cervix after acetic acid application is the most effective approach in underdeveloped countries, in terms of both cost and lives saved.[359]

Primary Prevention and Risk Reduction

Numerous risk factors for preinvasive and invasive cervical disease have been identified, some of which are modifiable and others not (Table 26-8). Age and race are nonmodifiable risk factors, whereas socioeconomic status and degree of immunosuppression (HIV-positive individuals, transplant recipients) are risk factors that are difficult to change. Other factors, such as sexual and behavioral risk factors—including a high number of sexual partners for a woman or her partner; early age at first coitus, pregnancy, or marriage; history of sexually transmitted diseases; HPV infection; contraceptive choice; nutritional status; tobacco smoking; and frequency of Papanicolaou smear screening—are modifiable risk factors, and areas for strategic prevention efforts.

Cervical cancer is a sexually transmitted disease. Many of the epidemiologic and behavioral risk factors are direct and indirect surrogate markers for infection with HPV. Recently the National Institutes of Health has released a consensus statement that cervical cancer is largely preventable if young people modify their sexual behavior and decrease their exposure to HPV, which is the most important risk factor for the development of preinvasive and invasive cervical disease.[360] More than 100 types of this double-stranded DNA virus exist, with approximately 50 types found in the epithelial cells of the genital tract. HPV is further subclassified into high-, intermediate, and low-risk types. For example, HPV 16 and 18 are high-risk types and have been found in many high-grade, preneoplastic, and invasive cervical lesions. In contrast, HPV 6 and 11 are low-risk types and are generally found in condylomata accuminata (genital warts) or low-grade cervical lesions. Almost 90% of invasive cervical cancer specimens and more than 75% of high-grade cervical lesions have measurable titers of HPV detected by available molecular biologic techniques (hybridization or the polymerase chain reaction).[361]

Table 26-8 Risk Factors for the Development of Cervical Cancer

Infection with the human papillomavirus (HPV)
Age, race, and socioeconomic status
Degree of immunosuppression (e.g., HIV positivity, transplant patients)
Sexual activity*
Tobacco smoking

*Sexual behavior is probably largely a surrogate for the risk of exposure to HPV.

The mechanism of action of HPV oncogenesis is related to viral production of the E6 and E7 proteins that bind and inactivate tumor suppressor genes such as *p53* and *Rb* (E7) in cervical cells.[362,363] This, in turn, could lead to neoplastic transformation. HPV DNA has been found to integrate into host chromosomal DNA in many high-grade dysplastic and invasive cancer cervical specimens but not in the majority of low-grade cervical cancer precursor lesions. In the latter, the HPV DNA tends to exist in an unintegrated, circular form known as an episome. Molecular epidemiologic studies suggesting that different HPV 16 variants have different oncogenic potential could partly explain the wide geographic variation of CIN and cervical cancer in similarly infected populations.[364]

In general, women with cytologic or histologic evidence of HPV DNA should be counseled that they are at increased risk for the development of cervical disease, even though it is difficult to provide definitive risk assessments. In addition, Koutsky and associates[13] performed two large prospective studies of women who had a normal Pap smear and found that those who tested HPV-positive had a 10- to 15-fold chance of developing a cytologic lesion compared with those who were HPV-negative.[13]

Clearly, not everyone with cytologic evidence of HPV will progress to developing a preneoplastic cervical lesion, and even fewer will progress to invasive disease. Investigators have detected HPV DNA in 6% of women of reproductive age with healthy cervixes.[365] The presence of HPV DNA in women with normal Pap smears might be as high as 40%, however, and it is estimated that approximately 10 to 20 million women in the United States have detectable HPV DNA.[366,367] Although numerous experimental, clinical, and epidemiologic studies have established a definitive role for HPV in the development of cervical cancer, other factors such as age, contraceptive method, smoking history, degree of immunosuppression, and nutritional status probably play a role in the progression and neoplastic transformation of HPV-infected cervical cells.

The grade of the cervical lesion also influences the risk of a cervical lesion progressing to invasive cancer. Many prospective studies have documented the percentage of the different grades of squamous intraepithelial lesions that will progress to higher grade lesions.[368] Estimates indicate that it could take approximately 10 years, on average, for a preinvasive lesion to progress to an invasive cancer. Sixty percent of low-grade lesions spontaneously regress on their own without treatment, in comparison with 30% of high-grade cervical lesions. It is estimated that anywhere from 35% (CIN 2) to 56% (CIN 3) of high-grade lesions will persist.[368] Therefore, the higher the grade of the lesion, the more likely it will either persist or progress. These wide ranges suggest that other factors play a significant role in determining the eventual outcome of premalignant cervical lesions.

Differences in incidence and mortality rates of carcinoma in situ and cervical cancer have been reported across different ethnic groups. Although socioeconomic factors might be substantially responsible for the discrepancies, African Americans and Mexican Americans, especially if they do not speak English, are more commonly diagnosed with cervical cancer and ultimately will die more frequently than white women.[369] The age-adjusted incidence rates for blacks are 14 per 100,000, compared with 7.8 per 100,000 for white Americans.[370] Subsequent data from the National Institutes of Health, however, revealed that the difference in incidence of cervical

cancer between blacks and whites is disappearing, which suggests that efforts to target this high-risk group are succeeding.[360] This is not the case for Hispanics, because approximately 1.6 million Hispanic women remained unscreened in the United States.

Different methods of contraception might have different effects on the development of cervical disease. Barrier methods of contraception have been found to significantly decrease an individual's risk of developing cervical cancer (relative risk ≈ 0.4).[371] Conversely, a weakly positive association has been observed between oral contraceptive use and the development of cervical disease.[372] It is difficult to conclude definitively that oral contraceptive use increases a person's risk for cervical disease because of important confounders such as sexual behavior and HPV infection.[373]

Evidence strongly implicates smoking as an independent risk factor in the development of cervical disease.[374] It has been estimated that smokers have a 4.5-fold increased risk of carcinoma in situ as compared with matched controls.[375] In a 10-year prospective study of cervical dysplasia, tobacco smoking was associated with a two- to fourfold increased risk of CIN 3 and invasive cervical cancer in those women also infected with oncogenic HPV.[376] In addition, a significant dose-response relationship has been observed in women who smoked more or for longer periods of time.[374] Elevated levels of nicotine and cotinine have been found in the cervical mucus of smokers, which could alter local defense mechanisms (such as Langerhans cells) and/or be mutagenic themselves, leading to transformation of HPV-infected cervical cells.[377]

The relationship between immunosuppression and neoplasia is strong and has been documented in several ways. Studies of renal allograft patients have demonstrated a 4- to 16-fold increase in cervical dysplasia, a 2- to 9-fold increase in HPV infection, and a marked increase in synchronous cervical, vulvar, vaginal, and anal lesions.[378] The HIV epidemic has created a large population of immunosuppressed patients at risk for the development of cancer in general. In 1993, cervical cancer was added to Kaposi's sarcoma and non-Hodgkin's lymphoma as an acquired immunodeficiency syndrome–defining malignancy based on published reports describing the development of more aggressive cervical cancers in HIV-infected women.[379] It was observed that HIV-infected women, though still asymptomatic from their disease, presented with more advanced cancers, of higher grade, and at a younger age than what was expected in the immunocompetent population.

Screening and Early Detection

The Pap smear is considered to be medicine's most successful screening test. Although it has never been subject to a randomized controlled clinical trial, this diagnostic test has been in widespread use since Drs. Traut and Papanicolaou published their findings in 1941.[380] International and regional surveys have documented decreases in both the incidence and mortality rates from cervical cancer among clinics that have widely adopted Pap smear screening. Scandinavian countries have reported reductions in mortality rates from cervical cancer by 30% to 80%, depending on the country, the duration of the screening program, and frequency of screening (Iceland, 80% reduction; Finland, 50%; Sweden, 34%).[381] Canada and the United States also have experienced similar reductions in both incidence and mortality rates. The Pap smear is an effective screening test because it can detect disease early—at a stage when it can subsequently be managed by available and effective treatments (Fig. 26-7). In addition, the Pap smear is cost effective and acceptable to both physicians and patients. Currently, 50 million Pap smears are performed annually in the United States.

Despite the profound impact that the Pap test has had on decreasing the incidence of cervical cancer by facilitating early detection of preinvasive lesions, its validity has been questioned periodically. General misperceptions by the media, public regulatory agencies, plaintiffs, physicians, and the community at large exist regarding the role of this screening test.[382]

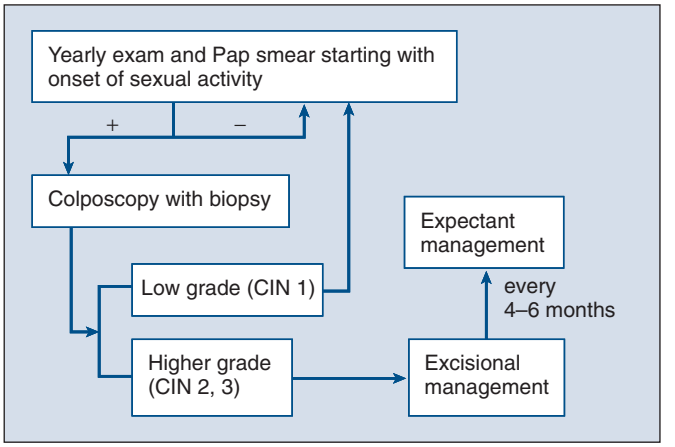


Figure 26-7 • Routine screening and early detection for cervical cancer and its prevention.

Several problems have arisen regarding the Pap smear as a screening tool. A great deal of media attention has focused on screening errors that have occurred in "Pap mills," where technicians were paid according to the number of slides they could screen. Studies have reported that the false-negative rate ranges between 5% and 20% in good laboratories, suggesting that the overall sensitivity is approximately 80%. Many of the false-negative results are actually due to sampling errors rather than to screening or interpretation errors. In sampling errors, abnormal cells are either absent or unidentifiable because of inappropriate technique, unsatisfactory equipment, or difficult patient examination, making it hard to obtain a satisfactory sample. Interpretation errors occur when the health care provider fails to fill out the patient history on the cytology requisition or cytotechnologists are supervised inadequately.

New technologies to improve the accuracy of the Pap smear are emerging, but there are some concerns that these tests might be too costly for high-risk patients who need them the most (low-income, minority, or elderly women). If this new technology improves the sensitivity of testing sufficiently, however, there ultimately might be a positive cost-benefit effect through the prevention of cervical cancer. A detailed analysis of the costs and benefits of different strategies to screen for cervical cancer in less-developed countries has been presented.[383] Compared with no well-organized screening, all strategies saved lives, at costs ranging from $121 to $6720 per life year saved, and they reduced mortality by as much as 58%. The simple approach of visual inspection of the cervix after applying acetic acid with appropriate follow-up was highly cost effective ($524 per life year saved and 83% reduction in mortality) and could be a more reasonable approach in less well-developed countries or certain hard-to-reach populations in the United States.

Current screening guidelines of the American College of Gynecologists and the American Cancer Society include annual Pap smear and pelvic examinations for any woman who is sexually active and/or 18 or more years of age. After three consecutive normal Pap smears and examinations, a "low-risk" patient may increase the interval between screenings from 1 year to 3 years. A high-risk individual is anyone who has had two or more sexual partners in her lifetime, intercourse before 20 years of age, a relationship with a male with multiple sexual partners, history of an abnormal Pap smear or gynecologic cancer, or anyone who is immunosuppressed. Most American women should probably be considered to be at high risk and therefore should undergo yearly Pap smear screening until sexually inactive.

Conventional Pap smear screening has proven to be extremely effective. The success of this test and future screening modalities depends on realistic expectations about screening tests, continued quality assurance, improved sampling of cervical tissue, and the incor-

poration of newer technologies with a view to improving the accuracy of screening and interpretation of Pap smears. Successful implementation, however, must be cost effective and lead to further declines in the incidence of and mortality from cervical cancer. Follow-up rates for abnormal Pap smears, particularly among underserved populations, remain another barrier for successful implementation of this important test. An attempt to improve the follow-up rates for severely abnormal Pap test results in underserved populations has been performed in the setting of a randomized controlled trial.[384] Patients in the single-visit intervention arm were required to wait in the clinic until the Pap smear results were available, and then large-loop electrosurgical excision procedure was performed immediately for severely abnormal results. This single-visit intervention resulted in a higher proportion of patients with abnormal Pap results receiving a full course of therapy within 6 months as compared with those in the usual-care study arm (88% vs. 53%), with a higher rate of follow-up at 1 year (63% vs. 21%). These results demonstrate that a single-visit cervical screening program was feasible among patients in an underserved population. Adoption of such a program could help narrow the gap in cervical cancer rates for underserved and minority populations. The challenge of the next decade will be for cervical cancer screening to optimize the medical outcomes and economic costs in general and in special high-risk populations.[385]

Chemoprevention

The goal of chemoprevention of cervical disease is to prevent or delay the development of cervical cancer and its precursor lesions by interrupting or preventing the process of carcinogenesis at the cellular level. The cervix is ideally suited for clinical studies that evaluate the process of carcinogenesis, because it is easily accessible for evaluation by Pap smear and colposcopy, and in general, abnormal cervical cells progress from low-grade lesions (HPV-positive cells and CIN 1) to high-grade lesions (CIN 2, CIN 3, carcinoma in situ) over an extended period of time.

Numerous experimental and epidemiologic trials have implicated HPV in the etiology of cervical cancer, and several large randomized trials have demonstrated spectacular efficacy (100% effectiveness) of an HPV vaccine in individuals who are sexually naive and/or HPV unaffected,[13] an effect that has been sustained over the long term.[14] Based on these results, a vaccine effective against a range of common subtypes has been approved for administration to young girls.[386,387] Epidemiologic studies of diet have suggested that low intake of several nutrients is associated with cervical cancer; however, the results of supplementation trials thus far have been almost uniformly negative, notwithstanding the experiences with topical retinoic acid and positive results from a recent randomized trial of celecoxib in which a favorable effect on high-grade dysplasia was demonstrated.[388–390] The eventual role of supplementation in late stages of the disease remains unconfirmed; clearly, continuation of smoking has an adverse effect,[391] an observation that remains important for overall cancer control.

INTERNATIONALLY IMPORTANT CANCERS

Hepatocellular carcinoma (HCC) and stomach cancer are the number one and two causes of death from cancer worldwide.[392] With the increasing influx of Asian immigrants, these diseases have become more common in the United States as well. Over the past several years, important advances related to their control have become evident, and therefore a brief review of these findings is presented. An excellent review recently has become available.[393] The major risk factor for HCC is exposure to hepatitis B or C virus, which is typically transmitted vertically (i.e., mother to child) in Asian countries and horizontally (i.e., intravenous injection, sexual contact, blood transfusion) in the United States.[393,394] Contributory risk factors include hepatotoxins such as aflatoxin, excess alcohol exposure, and smoking, as well as male gender.[393,395] Numerous studies have demonstrated that vaccination can prevent the development of HCC caused by hepatitis B.[395,396] Likewise, interferon treatment seems effective in interrupting or slowing the processes that lead to HCC initiated by hepatitis C.[397] A large phase III randomized controlled trial addressing HCC screening is currently underway to evaluate the optimal screening interval (3 months versus 6 months) for liver ultrasonography or CT among cirrhotic patients.[398]

Chemoprevention agents also seem to be effective in populations at risk for HCC due to hepatitis C infection. A randomized trial of a cyclic retinoid has shown that this compound reduced development of a second primary HCC by one-third, but this study has not been repeated or confirmed.[399] A phase III randomized trial of an anti-hepatitis C vaccine is underway, and a unique trial of supplementation with *S*-adenosylmethionine to prevent progression has recently been initiated at the University of California, Irvine. Overall, advances in microbial oncology have led to a great deal of progress in understanding the etiologic basis of HCC and in developing strategies for its eradication and prevention.

Our basic understanding of the etiologic origin of stomach cancer has been affected greatly by a paradigm shift, and the recognition that *H. pylori* infection is central to gastric carcinogenesis in humans has been critical to the development of new prevention strategies.[400] Although individual susceptibility, lifestyle issues, and diet all play a role in the pathogenesis of gastric carcinoma, attributable risks for *H. pylori* range as high as 73%.[401] There now exists a full-fledged attempt to prevent gastric cancer by appropriate screening in high-risk populations followed by *H. pylori* eradication.[401,402] Epidemiologic data are supportive of a protective role for fruit and vegetable consumption. Two large randomized trials suggest that *H. pylori* treatment interferes with the progression of gastric preneoplasia and gastric cancer[403,404] although a definitive trial is needed to prove the latter issue. Supplementation with antioxidants in both trials failed to add benefits to eradication of the bacterium.

Rational approaches to the early detection and prevention of the microbial origin of HCC and stomach cancer are now established. Concerted public health efforts should lead to screening and their eradication.

Nasopharyngeal carcinoma (NPC) is uncommon in the United States but has a high incidence in China and Southeast Asia, due to increased susceptibility to EBV.[405] In the endemic regions NPC is typically undifferentiated carcinoma (World Health Organization [WHO] type 3), whereas in the United States the majority of patients have the keratinizing squamous cell carcinoma (WHO type 1) NPC subtype. The WHO type 1 NPC subtype histologically resembles typical HNSCC and is more commonly associated with tobacco exposure and alcohol consumption. Nearly all type III NPC tumors involve latent EBV infection, whereas EBV infection is absent from type I NPC tumors in nonendemic regions; furthermore, survival is improved for type III NPC as compared with type I NPC.[406] Although the majority of type I NPC patients in the United States are Caucasian, Asian ethnicity within type I NPC has been shown to be an independent prognostic factor for improved survival.[407] This may be related to a higher proportion of EBV-positive type I tumors among U.S. Asians, or genotypic differences such as overexpression of epidermal growth factor receptor 1, which has been associated with poor survival in NPC and HNSCCs.[408–410] Recent advances in molecular targeted therapeutics of HNSCC involving epidermal growth factor receptor small molecule inhibitors and monoclonal antibodies have emerged.[411] Based on the findings and toxicity profile of agents in such therapeutic trials, opportunities may present for a targeted approach to prevention strategies for NPC and HNSCC among selected patients.

USEFUL RESOURCES

For those interested in cancer prevention, particularly useful resources include the *Journal of the National Cancer Institute* and the *Cancer*

Epidemiology Biomarkers and Prevention journal, and publications from the International Agency for Research on Cancer (http://www.iarc.fr/). This latter entity publishes a continuing series on early detection and prevention that represents an invaluable and critical analysis of current controversies. A particularly important Task Force Report from the American Association for Cancer Research on chemoprevention drug development recently has been published.[412] Useful Internet sites include

The Division of Cancer Prevention, National Cancer Institute, National Institutes of Health (http://www.prevention.cancer.gov).
Chemoprevention—The Answer to Cancer? (http://ohioline.ag.ohio-state.edu/hyg-fact/5000/5051.html).
Harvard Center for Cancer Prevention, Harvard School of Public Health (http://www.hsph.harvard.edu/cancer/).
American Institute of Cancer Research (http://www.aicr.org/index).
International Society of Cancer Chemoprevention (http://www.iscac.org).
Cancer Research Foundation of America (http://www.preventcancer.org).
National Foundation for Cancer Research (http://www.nfcr.org).
ClinicalTrials.gov, search words "Cancer Prevention," "Screening," and "Chemoprevention" (http://www.clinicaltrials.gov).
United States Department of Health and Human Services, Agency for Healthcare Research and Quality, United States Preventive Services Task Force (USPSTF) (http://www.ahrq.gov/clinic/prevenix.htm).

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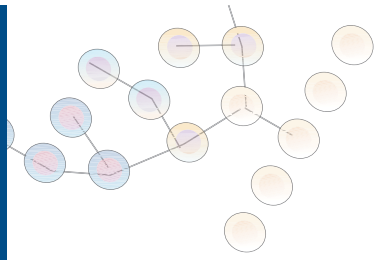
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27 Nicotine Dependence: Current Treatments and Future Directions

Caryn Lerman, Robert A. Schnoll, and Freda Patterson

SUMMARY OF KEY POINTS

Prevalence and Impact
- Approximately one in five American adults are current smokers.
- Smoking accounts for one third of all cancer deaths.

Current Treatments
- Nonpharmacologic treatments include behavioral counseling (e.g., identifying triggers, managing withdrawal), quit lines, and self-help material (e.g., booklets and video).
- These approaches are popular but yield relatively low quit rates.
- The FDA-approved pharmacologic treatments, including nicotine replacement therapies (NRTs; i.e., transdermal patch, gum, nasal spray, inhaler, and lozenge) and bupropion, have been shown to double smoking cessation rates as compared to placebo.
- Varenicline, a new FDA-approved medication, has efficacy superior to that of NRTs and bupropion.

Smoking among Cancer Patients
- Approximately one half of cancer patients continue to smoke after diagnosis, even though tobacco use can heighten risk for a second primary tumor and diminished quality of life.
- Few studies have examined predictors of continued smoking among cancer patients, and even fewer trials of smoking cessation treatments have been conducted among cancer patients.

Barriers to Cessation Treatment in Clinical Oncology
- Physicians have limited time to address smoking among cancer patients, and patients may possess unique psychological characteristics that undermine their ability to quit smoking.
- Systems-level changes and tailored treatment approaches might be needed to lower the rate of persistent tobacco use among cancer patients.

Future Directions
- Research is needed to identify new medications for nicotine dependence and to evaluate these approaches with cancer patients.
- Pharmacogenetics research might help to guide the tailoring of treatments for subgroups of smokers to enhance efficacy and reduce toxicity.

INTRODUCTION

Despite several decades of research to identify new approaches to treat nicotine dependence, about 21% of adults in the United States are regular smokers, suggesting that the Healthy People 2010 objective of reducing U.S. adult smoking to 12% will not be attained.[1] Each year, cigarette smoking causes more than 400,000 premature deaths in the United States and 4.2 million premature deaths around the world from cancer, cardiovascular and respiratory diseases, and perinatal conditions.[1] Tobacco use accounts for at least 30% of all cancer deaths in the United States, and smoking has been causally linked to lung, head and neck, esophageal, pancreatic, bladder, kidney, cervical, endometrial, and gastric cancer and acute myeloid leukemia.[2] Furthermore, persistent tobacco use among cancer patients increases risk for disease recurrence, second-primary tumors, adverse reactions to therapy, diminished quality of life, and reduced survival.[3] Despite these data, 46% to 75% of cancer patients report smoking at the time of their diagnosis, and close to one half of these patients continue to smoke during and following medical treatment.[4]

This chapter provides an overview of the state of the art in smoking cessation treatment. First, we provide an overview of nonpharmacologic and pharmacologic treatments for nicotine dependence and highlights factors that affect treatment response. Second, we review the epidemiology of tobacco use among cancer patients, studies of predictors of tobacco use in this population, and studies of smoking cessation interventions with cancer patients. Third, physician and health care system and patient barriers to smoking cessation are discussed, and methods for overcoming these barriers are suggested. Fourth, we briefly review public policy initiatives that are used to reduce cigarette consumption, such as advertising bans, taxes on cigarettes, and smoke-free policies. We conclude with a brief discussion of potential new pharmacologic treatments for nicotine dependence as well as novel treatment approaches, including pharmacogenetics research. Some material in this chapter was adapted from an earlier publication.[5]

CURRENT TREATMENTS FOR NICOTINE DEPENDENCE

There are two general classes of treatments for nicotine dependence: nonpharmacologic and pharmacologic (Fig. 27-1). In the following sections, we describe these treatment approaches, with an emphasis on efficacy data and moderators of treatment response.

Nonpharmacologic Treatments

Nonpharmacologic smoking cessation treatments such as self-help interventions and behavioral counseling are the preferred mode of

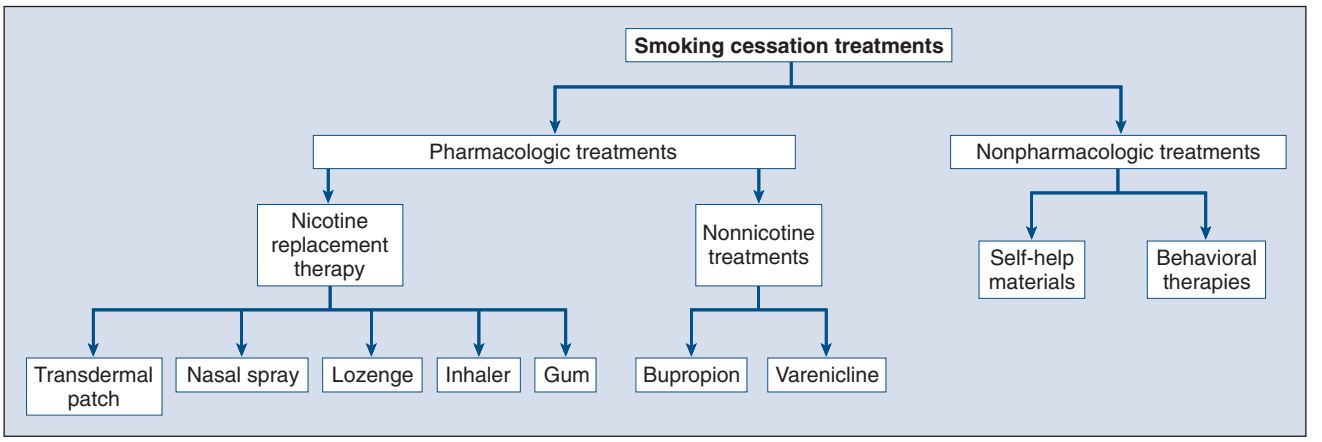


Figure 27-1 • Overview of FDA-approved available smoking cessation treatments.

treatment for most smokers.[6] These include informational booklets, audiotapes and videotapes or DVDs, and Internet-based programs that are designed to help smokers quit on their own.[7] Behavioral therapies include elements of nicotine fading, quit date contracting, management of smoking triggers, and relaxation techniques delivered either in a group or individual context.[7] The efficacy of these approaches is reviewed in the following discussion.

Self-Help Materials

Self-help smoking cessation interventions are reported to produce quit rates in the range of 4% to 11%[8] and are significantly more effective than no intervention at all.[9] Multimodal, more intense interventions are more effective than are single-modal, less intense interventions, while tailoring materials to individual characteristics has also been demonstrated to be a potentially effective strategy to enhance self-help quit rates. For example, in a sample of 300 treatment-seeking smokers, those who received computer-generated, tailored mailed feedback had significantly higher quit rates 1 year following the target quit date than did those who received standard advice (25% versus 10%, respectively).[10] The Internet has emerged as another vehicle through which self-help smoking cessation interventions can be delivered, with over 10 million Internet users in the United States searching for quit smoking information in 2004 and an estimated 75% self-reporting as current smokers.[11] Although only a small number of studies have evaluated the efficacy of Internet-based cessation approaches, one study did report that, at 3 months after the target quit date, a tailored, Internet-based cessation intervention produced a quit rate of 24% versus 5% in the control condition ($P < 0.05$).[12] These data are consistent with other preliminary work showing the efficacy of Internet-based cessation interventions;[13] however, more controlled trials in this area are needed before this approach can be considered a primary mode for the delivery of nicotine dependence treatment programs.

Behavioral Therapies

Behavioral therapies for smoking cessation include elements of nicotine fading, quit date contracting, management of smoking triggers, and relaxation techniques and have been reported to produce quit rates of 7% to 20%.[14,15] In one 3-month cognitive-behavioral smoking cessation program that provided participants with instruction and guidance on nicotine fading, quit date contracting, relaxation strategies, trigger management, and relapse prevention, end-of-treatment quit rates of 17.2% were reported as compared to 5.6% in the educational control condition.[16] No significant differences in individual versus group-based programs have been found.[17]

Telephone-based cessation counseling has become increasingly available in the United States, with 36 states providing quit lines for treatment-seeking smokers.[18] The efficacy of proactive telephone counseling (i.e., the cessation counselor initiates the call) has been well demonstrated,[19] producing 12-month quit rates in the range of 7% to 10%, the higher quit rates being achieved by recipients of more frequent calls.[20,21] Reactive telephone counseling (i.e., the patient initiates contact) such as that provided by state quit lines and hot lines has also been shown to be efficacious.[19,22] However, there is limited literature on the efficacy of statewide smoking cessation hot lines at this time.

Pharmacologic Treatments

FDA-Approved Nicotine Replacement Therapies

Five nicotine-replacement therapies (NRTs) have been approved by the U.S. Food and Drug Administration (FDA) for treating nicotine dependence: transdermal patch, gum, nasal spray, inhaler, and lozenge (Table 27-1); a sixth NRT, the sublingual tablet, is used only in Europe.[23] NRTs treat nicotine dependence by (1) ameliorating withdrawal symptoms that characterize initial physical and psychological reactions to cessation, such as irritability, restlessness, depressed mood, and poor concentration; (2) reducing the experience of nicotine craving on cessation and limiting possible weight gain (for gum and the patch); and (3) providing a safer way to experience the neurobiological and psychophysiologic effects of nicotine. NRTs are tolerable and safe and almost double quit rates compared to placebo (pooled OR = 1.77, 95% CI: 1.66 to 1.88).[24] Indirect[24] and head-to-head[25] comparisons indicate comparable efficacy between NRTs. However, NRTs do not provide nicotine as effectively as cigarettes do or adequately mimic the behavioral ritual of smoking. Furthermore, at best, only one quarter to one third of smokers who use NRTs to quit smoking will remain successfully abstinent 6 months following treatment completion.[24,25]

Identifying factors related to NRT responsiveness, including characteristics of the NRT as well as characteristics of the smoker, may lead to methods for enhancing NRT efficacy. One study found no difference in quit rates when NRT was used for a longer duration;[26] however, large-scale placebo-controlled trials testing the effects of extended NRT use are needed. Other studies have examined the efficacy of higher-dose NRT; however, findings thus far have not been supportive.[27] Meta-analytic reviews of studies that evaluated combination NRT therapy versus a single NRT show that combination therapy is somewhat more effective (OR = 1.42, 95% CI: 1.14 to 1.76[24] versus OR = 1.9, 95% CI: 1.3 to 2.6).[28] However, studies

Table 27-1 FDA-Approved Medications for Tobacco Dependence

Medication	Recommended Duration and Dose*	Estimated Quit Rate† (95% CI) Number of Studies	Advantages	Disadvantages	Cost
Nicotine gum	Up to 12 weeks; 2 mg (for those who smoke <25 cigarettes/day; 4 mg (for those who smoke ≥25 cigarettes/day	17.4% (17% to 18%) 52 trials[24]	Treat oral behavioral ritual and cue-elicited craving; prevent weight gain	Adverse side effects and poor compliance	$4.00 to $5.00/day
Nicotine patch	Up to 10 weeks; dose duration varies by cigarettes/day	13.7% (13% to 15%) 37 trials[24]	Better compliance and nicotine replacement; few side effects	Does not treat cue-elicited craving	$2.50/day
Nicotine spray	Up to 6 months; 8 to 40 sprays/day	24% (20% to 28%) 4 trials[24]	Nicotine is rapidly absorbed; treat cue-elicited craving	Unpleasant side effects and poor compliance	$5.00 to $15.00/day
Nicotine inhaler	Up to 6 months; 6 to 16 cartridges/day	17% (14% to 21%) 4 trials[24]	Treat oral behavioral ritual and cue-elicited craving	Unpleasant side effects and poor compliance	$7.00 to $18.50/day
Nicotine lozenge	Up to 12 weeks; 2 mg (for those who smoke their first cigarette more than 30 minutes after waking) and 4 mg (for those who smoke their first cigarette within 30 minutes of waking)	17% (15% to 20%) 4 trials[24]	Good nicotine replacement; treats oral behavioral ritual and treats cue-elicited craving; few side effects	Compliance is unknown	$3.00 to $4.00/day
Bupropion	Up to 12 weeks; 300 mg/day; 150 mg per day for 3 days, then 300 mg/day from day 4 to end of treatment	19% (Range: 4% to 43%) 2 trials[28] 31 trials[40]	Good side effect profile; low abuse liability; prevent weight gain	Relatively more costly	$4.00 to $5.00 (300 mg)
Varenicline	Up to 12 weeks; 2 mg/day; 0.5 mg for days 1 to 3, 0.5 mg twice daily for 4 days, and 1 mg twice daily from day 8 to end of treatment	30% 2 trials[54,55]	Well-tolerated; reduces withdrawal and reinforcing effects of nicotine	Limited data	Unknown

*Recommendations are taken from the manufacturer of the agent and/or from Fiore[28].
†6-month or greater point-prevalence quit rates, biochemically verified.

in this area have not been entirely consistent.[29] More recently, one study found that using the patch for 2 weeks prior to quitting doubled the likelihood of 4-week continuous abstinence, compared to standard patch use.[30] Finally, since NRT efficacy may be related to how rapidly nicotine is delivered into the central nervous system,[31] studies have begun to investigate rapid-release NRT. Niaura and colleagues[32] found that rapid-release nicotine gum significantly reduced postcessation cravings compared to standard nicotine gum, suggesting the need for clinical trials of rapid-release formulations of NRT.

Likewise, a range of smoker characteristics can affect response to NRTs, suggesting that the tailored use of NRT for subgroups of smokers could improve NRT efficacy.[33] The level of nicotine dependence affects response to NRT, more dependent smokers showing higher quit rates when they receive higher doses of NRTs.[34,35] Lerman and colleagues[25] also found that smokers with low to moderate levels of dependence have higher quit rates with the patch, while those with high levels of dependence have higher quit rates with the nasal spray. Caucasian smokers and nonobese smokers also showed higher quit rates on the patch, whereas smokers from racial and ethnic minority groups and obese smokers showed higher quit rates with the nasal spray.[25] Last, gender may affect response to NRT. While early placebo-controlled trials of NRT reported lower efficacy for women than men, two meta-analyses[36,37] indicate that NRTs have equal efficacy for women and men. However, meta-analytic studies included trials that provided only partial outcome data, omitted some relevant trials, and might have had limited statistical power to examine gender differences in light of low absolute quit rates.[38] Furthermore, another meta-analytic study found that NRT was less effective for maintaining long-term cessation for women versus men.[39]

FDA-Approved Nonnicotine Pharmacologic Treatments

Bupropion SR (Zyban) is an antidepressant that reduces the uptake of dopamine and norepinephrine (see Table 27-1). A meta-analysis[40] of 31 placebo-controlled trials concluded that bupropion more than doubled the likelihood of cessation compared to placebo, up to 12 months from a quit date (OR = 1.94, 95% CI: 1.72 to 2.19). The exact mechanism through which bupropion treats nicotine dependence is not fully known; however, the efficacy of this medication is mediated, in part, by reduction of dopamine and norepinephrine uptake[41] and/or nicotinic receptor antagonist effects.[42] A second mechanism may involve the drug's ability to prevent or diminish postcessation negative affect and weight gain, which are frequently cited as causes of relapse among smokers[43,44] Nevertheless, upward of three quarters of smokers who use bupropion to quit smoking do not achieve long-term abstinence. Therefore, researchers have begun to examine factors related to bupropion response. Research in this area has assessed clinical depression and depressive symptoms as a

moderator of treatment response. To date, no clinical trial has formally examined the role of depression as a moderator of bupropion efficacy by using depression a priori as a stratification variable. However, trials that conducted post hoc analysis to address this issue have not supported the hypothesis that bupropion is more effective for depressed smokers.[45–47] Researchers have also examined gender as a moderator of bupropion response. With few exceptions, placebo-controlled trials indicate comparable efficacy of bupropion for women and men.[48,49] However, there is some indication that the use of bupropion to prevent relapse is less effective for women than for men.[50]

Varenicline (Chantix) is an α4β2 neuronal nicotinic acetylcholine receptor (nAChR) partial agonist (see Table 27-1). By activating α4β2 nAChRs receptors, which are expressed widely on dopamine and GABA neurons in the ventral tegmental area, varenicline attenuates nicotine's effect on dopamine release, while maintaining dopaminergic tone.[51] Varenicline's agonist function may minimize craving and withdrawal, while its antagonist properties may attenuate the reinforcing effects of nicotine, thereby reducing satisfaction from a "slip" cigarette and the likelihood of relapse.[52,53] The recent FDA approval for varenicline was based on the results from three clinical trials. The first two trials randomized 2,052 smokers to placebo, 300 mg bupropion, or 2 mg varenicline for 12 weeks and assessed quit rates up to 1 year following the start of treatment.[54,55] Assessment of continuous quit rates for the last 4 weeks of treatment (weeks 9 to 12) across the two trials at the end of treatment showed an advantage for varenicline (44%) compared to bupropion (30%) and placebo (18%). The continuous quit rate for varenicline at the 1-year follow-up diminished (22%), but it remained significantly better than those for bupropion (16%) or placebo (10%). In a third study,[56] smokers received open-label varenicline (1 mg b.i.d.) for 12 weeks; subjects who remained abstinent at the end of 12 weeks were randomized to 12 additional weeks of 1 mg b.i.d. varenicline or placebo. An assessment conducted 28 weeks from the end of the second 12-week treatment phase showed that extended varenicline use prevented relapse. Across all trials, adverse events and rates of discontinuation were similar for placebo and varenicline, indicating that varenicline is well tolerated.

Since varenicline is a relatively new treatment for nicotine dependence, little is known about moderators of treatment response. Gonzales and colleagues reported gender differences in therapeutic response.[54] Biochemically confirmed continuous abstinence rates for weeks 9 to 12 were equivalent for men and women (43% versus 46%, respectively). Furthermore, there were no gender differences in 12-month quit rates in varenicline-treated participants in a pooled analysis of data from the three trials.[57]

TOBACCO USE IN THE ONCOLOGIC SETTING

While numerous studies have documented the rate of smoking among cancer patients, few studies have examined predictors of smoking by cancer patients and cessation interventions for this population. Accumulating data show that persistent tobacco use following a diagnosis can increase the risk for a second primary tumor, shorten survival duration, exacerbate treatment-related side effects, and diminish quality of life.[3] These findings have sparked greater interest in addressing tobacco use in this population. In the following sections, we provide an overview of the research that has been conducted to date concerning tobacco use among cancer patients.

Smoking Rates among Cancer Patients

Given the etiologic role of smoking in cancer, it is not surprising that rates of tobacco use among certain subgroups of cancer patients exceed rates in the general population. The vast majority of studies in this area have concentrated on lung cancer patients and head and neck cancer patients.[4] However, studies have also evaluated smoking among cervical[58] and bladder[59] cancer patients and among survivors of childhood cancers.[60] Among head and neck cancer patients, prevalence rates of continued smoking range from 25% to 90%.[61–66] Among lung cancer patients, prevalence rates of continued smoking range from 29% to 63%.[67,68] Variability in rates is likely due to methodologic differences across studies, such as inconsistent follow-up intervals, divergent methods for assessing smoking, reductions in baseline smoking rates in the population over time, and differences between the samples in demographic or medical variables. Recent prospective studies that defined smoking as taking a single puff of a cigarette in the past 30 days have reported rates of continued smoking to be 25% to 48% for head and neck cancer patients[66,69–71] and 35% to 40% for lung cancer patients.[68,70] Last, persistent tobacco use has been documented among 69% of bladder cancer patients,[59] 40% of cervical cancer patients,[58] 20% of adult cancer survivors,[72] and 17% to 20% of survivors of childhood cancers.[73–76]

Factors Related to Smoking Cessation among Cancer Patients

Identifying factors that influence smoking behavior among cancer patients is essential for developing and implementing smoking cessation interventions for this population. In the next few sections, we review the available literature concerning demographic, medical, and psychological correlates of smoking cessation among cancer patients.

Demographic Variables

Studies that have assessed demographic correlates of smoking behavioral among cancer patients have yielded few consistent findings. For example, while older cancer patients and survivors were more likely to remain abstinent in several studies,[72,77] this relationship has not been replicated in other studies,[59,70,78] or the opposite result has been reported[74,79] Likewise, while higher educational achievement has been linked with greater abstinence by some,[74,77] this relationship has not been replicated by others,[59,70,71,78] and one study found the opposite relationship.[65] Furthermore, aside from one study that reported that female cancer survivors were more likely to quit smoking, gender has not been found to be a predictor of smoking cessation among cancer patients.[61,65,66,70,77,78]

Smoking history variables (e.g., amount, duration, and level of nicotine dependence) have also been evaluated as correlates of smoking behavior among cancer patients. Amount and duration of tobacco use have been associated with the likelihood of cessation among cancer patients by some studies[74] but not by others.[59,65] In contrast, several studies have shown that patients with a lower level of nicotine addiction show a greater ability to quit smoking.[66,70,78,79] Last, alcohol use has been examined as a correlate of smoking behavior, particularly among head and neck cancer patients, since many head and neck cancer patients abuse (or at least heavily use) alcohol.[80] Vander Ark and colleagues[71] found that heavy alcohol use was a significant predictor of continued smoking by head and neck cancer patients. Chan and colleagues[62] also reported that concurrent alcohol use predicted future smoking. However, this relationship was not found in other studies of head and neck cancer patients.[61,77,79]

Medical Variables

The relationship between disease-related variables and smoking among cancer patients has also been evaluated; however, few consistent findings have emerged. For example, higher rates of abstinence from tobacco use have been noted among head and neck cancer patients with a more advanced disease stage.[65] Similar results were reported in a study with bladder cancer patients.[59] However, several other studies with head and neck cancer patients and lung cancer patients have not replicated this result. Some studies have reported that multimodal medical therapy (e.g., surgery plus radiation) increases quit rates,[65,71] while other studies indicate that it is the pres-

ence of surgery that underlies higher cessation rates (compared to radiation alone[79]). Although this had not been as adequately studied, three studies indicate that as time elapses from the point of diagnosis, the risk of relapsing to smoking increases.[70,78,81]

Psychological Variables

Several studies have also examined psychological correlates of smoking among cancer patients. Head and neck and lung cancer patients who exhibit higher motivation to quit (typically assessed by using the stage-based measure derived from the transtheoretical model) show higher rates of smoking cessation.[66,79,82] Beliefs about smoking behavior have also been correlated with tobacco use among cancer patients. Christensen and colleagues[61] examined whether perceived control (i.e., believing that future health outcomes are affected by one's behavior) and self-blame (i.e., attributing the cause of the diagnosis to one's behaviors) influenced smoking behavior among head and neck cancer patients. A significant interaction effect was detected: A greater proportion of patients with high levels of self-blame *and* low levels of perceived control continued to smoke compared to patients with high levels of self-blame *but* high levels of perceived control (64% versus 25%, respectively).[61] Schnoll and colleagues[78] reported that head and neck cancer patients who report higher quitting self-efficacy (i.e., confidence in their ability to quit) are more likely to abstain from smoking, a finding that was also reported in a prospective study with head and neck cancer patients.[66] Risk perceptions concerning the adverse health effects of tobacco use may be particularly important to address among head and neck cancer patients. In a cross-sectional study, lower perceived risk (e.g., for disease recurrence) was related to a greater likelihood of continued smoking among head and neck cancer patients,[78] a result that was replicated in a prospective study.[70] Lower levels of quitting pros (i.e., advantages of quitting) and higher levels of quitting cons (i.e., disadvantages of quitting) and fatalistic beliefs (i.e., believing that there is no use in quitting) have also been associated with a greater likelihood of continued smoking;[78] higher levels of quitting cons, moreover, predicted persistent smoking and relapse prospectively.[70]

Several studies have shown that negative affect, typically measured by symptoms of depression and anxiety, predict smoking among cancer patients. Cross-sectional studies associated negative mood measured by self-report instruments (e.g., the Hospital Anxiety and Depression Scale) with smoking among head and neck cancer patients.[78,80,83] One prospective study reported that patients who lapsed to smoking were significantly more likely to report anxiety in the week prior to a lapse compared to patients who maintained abstinence.[66] A more recent prospective study, which followed a sample of head and neck cancer patients for 15 months, found that patients who continued to smoke had greater negative mood as compared to nonsmokers.[69]

Smoking Cessation Interventions for Cancer Patients

Despite the high rate of persistent tobacco use among cancer patients and the growing recognition of the adverse effects on clinical outcomes for patients who continue to smoke, relatively few randomized clinical trials have evaluated the efficacy of smoking cessation interventions for cancer patients (Table 27-2).

The first study, with 186 head and neck cancer patients, randomized patients to either "usual care" physician quit advice (e.g., risks of continued smoking and benefits of cessation) or an "enhanced" physician quit advice intervention that included expression of confidence in the patient's ability to quit, a written quit date contract, tailored self-help booklets, and booster advice to remain abstinent.[79] The results showed extremely high continuous quit rates (biochemically confirmed) for both conditions at a 12-month follow-up (usual care = 77%, intervention = 64%), in part owing to strong physician quit advice provided in both study conditions and the inclusion of patients who had not smoked for up to 1 year prior to study recruitment. In a second study, Stanislaw and Wewers[84] randomized cancer patients with various tumor sites to either a usual care or an intervention that consisted of three in-person behavioral counseling sessions and five follow-up phone contacts. At 5 weeks, the quit rate (biochemically confirmed) for the experimental group was 75% (9/12), compared to 43% (6/14) for the control group, although the small sample led to a nonsignificant comparison. In the third study, Griebel and colleagues[85] randomized cancer patients with various types of malignancies to either usual care or to a one-time smoking cessation consultation with an oncology nurse (plus five telephone booster calls).[85] After 6 weeks, 21% (3/14) of experimental patients exhibited cotinine-validated abstinence, compared to 14% (2/14) of the patients in the usual care condition. Again, the small sample size could have led to a nonsignificant comparison of quit rates.

More recently, Schnoll and colleagues conducted two randomized smoking cessation clinical trials with cancer patients. The first trial examined a cognitive-behavioral therapy (CBT), which addressed theoretically derived cognitive and emotional variables linked to tobacco use in this population (e.g., self-efficacy, risk perception[86]). Head and neck and lung cancer patients ($n = 109$) were randomized to either the theoretically based CBT intervention or a general health education (GHE) condition, and all patients received nicotine replacement therapy. Although high quit rates were detected in this trial, no significant difference in 30-day point-prevalence abstinence between the CBT and GHE conditions was detected at either 1-month (45% versus 47%, respectively) or 3-month (43% versus 39%, respectively) follow-up evaluation. The second trial examined the efficacy of a physician-based smoking cessation intervention for cancer patients.[87] Cancer patients ($n = 432$) were randomized to either usual care or a National Institutes of Health physician-based smoking intervention (i.e., the 5As). At 6-month follow-up, there was no significant difference in quit rates between the usual care (12%) and the intervention (14%) group, and there was no significant difference between the usual care (14%) and the intervention (13.3%) group at the 12-month follow-up.

Wakefield and colleagues examined the use of motivational interviewing for promoting smoking cessation among cancer patients.[88] In this study, 137 cancer patients were randomized to either a control group, consisting of quit advice, self-help brochures, and a referral to a quit line, or an intervention arm that included motivational interviewing, smoking cessation self-help booklets, and NRT. After 6 months, the quit rate for the intervention arm was 6%, compared to 5% for the control arm. In a trial of 796 childhood cancer survivors, patients were randomized to either a self-help arm (quit advice letter and self-help booklet) or an intervention arm that consisted of six phone-based counseling sessions from a childhood cancer survivor plus self-help material, and NRT. Quit rates were higher for the peer-counseling condition than for the self-help condition at 8 months (16.8% versus 8.5%) and at 12 months (15% versus 9%).[89]

Barriers to Smoking Cessation Treatment in Clinical Oncology

Quitting smoking following a cancer diagnosis can improve clinical outcomes for patients, and cancer patients exhibit uniquely high levels of quit motivation,[90] suggesting that this can be a teachable moment for smoking cessation. Unfortunately, a cancer diagnosis has been underutilized as a teachable moment for assisting patients to quit smoking.[3] To facilitate greater attention to promoting smoking cessation among cancer patients, barriers to cessation should be identified, including physician and health care system barriers and patient barriers.

Physician and Health Care System Barriers to Smoking Cessation

Because patients visit physicians or members of the health care team repeatedly and view health care professionals as valuable, credible,

Table 27-2 Overview of Smoking Cessation Interventions for Cancer Patients

Study Authors (Year)	Study Population	Study Design and Treatment Groups	Main Results
Gritz et al. (1993)[79]	*N* = 186 Newly diagnosed head and neck cancer patients	Randomized trial in which participants received either one session of "usual care" physician quit advice or an "enhanced" physician quit advice intervention + 6 booster sessions.	12-month follow-up (biochemically confirmed; *n* = 114) continuous abstinence rates: usual care = 77%; intervention = 64%. No significant difference in quit rates between groups.
Stanislaw and Wewers (1994)[84]	*N* = 26 Patients with various cancers undergoing surgery	Randomized trial in which participants were assigned to usual care or an intervention that consisted of three in-person sessions and five weekly phone calls.	5-week (biochemically confirmed) quit rates: experimental group was 75% (9/12) versus 43% (6/14) for the control group. Difference in quit rates was statistically significant ($P < 0.1$).
Griebel et al. (1998)[85]	*N* = 28 Patients with various cancers undergoing surgery	Randomized trial in which participants were assigned either to receive usual care or a one-time 20-minute, postoperative smoking cessation session with an oncology nurse + 5 weekly 10-minute booster phone calls.	6-week (biochemically confirmed) abstinence rate: 21% (3/14) for experimental group and 14% (2/14) for usual care recipients. Quit rate differences between groups not statistically significant.
Schnoll et al. 2005[86]	*N* = 109 Head and neck or lung cancer patients	Randomized trial that compared the efficacy of a cognitive-behavioral therapy (CBT) intervention with a general health education (GHE) intervention for smoking cessation among cancer patients. CBT participants received one in-person session and three telephone counseling sessions that were tailored to their barriers to cessation. GHE participants received general quitting advice. All participants received transdermal nicotine.	No significant differences in cessation rates between the CBT and GHE groups were observed at 1-month (45% versus 47%, respectively) or 3-month (43% versus 39%, respectively) follow-up.
Schnoll et al., 2003[87]	*N* = 432 Patients with various cancers	Randomized trial that compared the effectiveness of a physician-based intervention in which the AHRQ 5 A's was delivered versus usual care (brief quit advice).	No significant differences in cessation rates between the physician-based intervention and the usual care condition were observed at the 6-month (14% versus 12%, respectively) and 12-month (13% versus 14%, respectively) follow-up assessments.
Wakefield et al. (2004)[88]	*N* = 137 Patients with various cancers	Randomized trial in which participants were assigned to receive either brief quit advice control condition (brochure + referral to a quit-line; *n* = 63) or a motivational interviewing experimental condition (*n* = 74) in which they received specific cessation advice and booklets targeted to cessation for cancer patients via telephone and in-person counseling. NRT was provided to those who smoked >15 cigarettes per day.	At 3-month follow-up, 7% of the motivational interviewing and 6% of the control group recipients had biochemically confirmed abstinence. Differences in group quit rates were not statistically significant. Intervention group was significantly more likely than control group to report making a quit attempt (86% versus 62%, respectively).
Emmons et al. (2005)[89]	*N* = 796 Childhood cancer survivors who smoked	Randomized trial in which participants were assigned to either a self-help smoking cessation intervention (physician letter + cessation brochure) or a peer-delivered telephone counseling intervention (up to 6 phone calls tailored to individual's stage of change delivered over 7 months). NRT was also offered to counseling intervention group.	At 3-months follow-up, counseling group had significantly higher quit rates as compared to self-help group (11% versus 5%). At 12-month follow-up, counseling group still had higher quit rates (11% versus 7%, respectively), but differences were not statistically significant.

and reliable sources of health information, they generally adhere to physician advice.[91] Thus, the health care team is a critical resource for addressing patients' tobacco use. Recent national surveys, however, indicate that primary care physicians and nurses are not capitalizing on their opportunity to intervene with patients. A national survey of physicians indicated that while most physicians (75%) advise their patients to quit smoking, fewer than one third of physicians recommend pharmacotherapy "often or always," and fewer than one quarter provide referrals for cessation treatment programs "often or always."[92] Surveys with oncology nurses yield convergent data; about two thirds of nurses document patient smoking status, one third provide cessation advice, and one quarter recommend NRT.[93]

A number of barriers are likely responsible for a failure to fully capitalize on this opportunity. First, pragmatic limitations can make

it challenging for health care professionals to intervene with cancer patients who smoke. Physicians and nurses are extremely busy and have little extra time to provide comprehensive nicotine addiction treatment. Second, a lack of third-party reimbursement for treating nicotine dependence and the expense of ascertaining treatment outside of insurance coverage can undermine commitment from health care professionals to intervene with patients who smoke. Third, certain attitudes that health care professionals have about smoking can undermine the provision of adequate treatment, such as believing that patients are not interested in receiving nicotine dependence treatment, that treatment will be ineffective, that they lack the skills and confidence to intervene, and that it is not part of their professional role.[93,94] These beliefs, in part, stem from an additional barrier to effective treatment of nicotine dependence by physicians and nurses working with cancer patients, namely, the lack of adequate training for health care providers in methods for treating nicotine dependence.[95] Thus, lack of time, financial coverage, and adequate training and specific beliefs undermine the provision of adequate nicotine addiction treatment for cancer patients. Last, health care providers may view nicotine addiction as an acute condition, rather than a chronic illness, and therefore might not provide the sort of ongoing treatment that is required to help patients to quit smoking.

Patient Barriers to Smoking Cessation

Unique aspects of a cancer diagnosis and its treatment undermine effective smoking cessation. First, a cancer diagnosis can produce significant negative affect (i.e., symptoms of anxiety and depression),[96] which, in turn, can undermine the patient's ability to quit smoking. Likewise, ongoing medical treatment, financial pressures, and family strain or conflict can produce stress that undermines quit motivation or triggers relapse following successful cessation. Last, many patients exhibit a fatalistic attitude about quitting smoking (i.e., what is the use of quitting now since the patient has been diagnosed) and low quitting self-efficacy,[96] which diminishes patient commitment to quitting smoking. Second, since cancer patients might be unwilling to admit to smoking, it can be very difficult to ensure that adequate treatment is provided. Third, most cancer patients show very high levels of nicotine dependence and have been smoking for many decades,[96] making treatment more challenging. Last, many cancer patients experience treatment-related side effects that can make it difficult to utilize nicotine addiction treatments, including the nicotine lozenge or gum or bupropion or varenicline (e.g., difficulty with or an inability to swallow), or they might have medical conditions that prevent the use of pharmacotherapy.

Overcoming Barriers

Reducing the prevalence of tobacco use among cancer patients depends on successfully overcoming both physician and patient barriers to cessation. While physicians and health care professionals should not be expected to devote much time to treating nicotine dependence, they should be expected to assess smoking status, deliver cessation advice, and provide a prescription for pharmacotherapy and/or a referral to a local smoking cessation program as needed. Some professional organizations have revised clinical treatment guidelines for smoking cessation from the 5As to Ask, Advise, Refer (see www.askadviserefer.org/about.asp) in order to overcome practical constraints for health care providers. Additionally, systems changes, such as including smoking status as a vital sign within patient records, can facilitate easy and continual assessment of patient smoking status, along with chart reminders and incentives for identifying and referring patients for appropriate cessation treatment.

While many comprehensive cancer centers offer smoking cessation treatment services or access to treatment through clinical trials, economic barriers to access remain. However, many major insurance companies and many state Medicare and Medicaid programs now cover smoking cessation treatment, and upward of 30 states have free quit lines, in addition to national hot lines operated by the National Institutes of Health and the American Cancer Society. As such, assessing smoking status and providing quit advice, self-help material, and a treatment referral should be affordable for all facilities; therefore, all patients should receive at least this minimal level of smoking cessation intervention.

Training oncologists in clinical practice guidelines for smoking cessation (i.e., the 5As) enhances physician adherence to practice guidelines[87] and reduces patient smoking.[97] Additional research is needed to identify effective and affordable methods for training health care professionals in treating nicotine dependence. This training should prepare health care professionals to intervene with patients and address beliefs that might discourage compliance with treatment guidelines, such as low patient interest in receiving treatment and the adoption of a chronic disease model for nicotine dependence.

Last, as new smoking cessation treatment programs are designed for cancer patients, the efficacy of these programs could depend on the degree to which they are tailored to address the specific needs of cancer patients. Many cancer patients will require intervention components that address affective barriers to cessation (e.g., bupropion). In addition, supportive therapies and coping skills training programs might be needed for many patients to assist them in avoiding relapse when stressful events are encountered. Behavioral counseling might also need to address fatalistic beliefs or a critical lack of confidence in quitting smoking. Patients must also be made to feel safe and comfortable to share their smoking status, so interventions must be nonjudgmental and nonconfrontational (i.e., motivational interviewing). Finally, treatments might need to be relatively intense (e.g., combination pharmacotherapy) to address level of nicotine dependence and be continuously provided for an extended period of time. However, practitioners must consider potential treatment side effects and medical contraindications when selecting a particular treatment approach for patients.

PUBLIC POLICY EFFORTS TO REDUCE CIGARETTE CONSUMPTION

A variety of public policy initiatives, such as bans on tobacco advertising, increased taxation on cigarettes, and clean air laws that ban smoking in public places, have come to the fore as being important legislative tools to reduce cigarette consumption. A brief review of these approaches is provided here.

Tobacco Advertising

Exposure to tobacco advertising has been shown to promote experimentation and the development of a regular smoking habit among adolescents,[98,99] as well as continued smoking among adults.[100] Consistent with these data is evidence that national bans on tobacco advertising in countries such as Norway, Finland, New Zealand, and France resulted in a 14% to 37% drop in cigarette consumption.[101] Likewise, bans on tobacco advertising in the United States have correlated with a decline in cigarette consumption . However, there are concerns that partial tobacco advertising bans (e.g., banning only outdoor advertising) might serve to exponentially increase tobacco advertising through other venues such as print media, point-of-purchase advertising, and sponsorships, thus compromising the efficacy of this public health approach to reducing cigarette consumption.[102]

Tobacco Taxes

Excise taxes on cigarettes have been shown to reduce cigarette consumption,[103] federal level tax increases being more effective than increases at the state level.[103] Data also suggest that a 10% increase

in the price of cigarettes would equate to an 8% decline in smoking prevalence among low-income adults and a 4% decline among higher-income adults.[104] In a random-digit-dial telephone survey of 10,000 New York residents, almost half of respondents who smoked reported that they reduced the number of cigarettes they had smoked in response in an increase in cigarette prices;[105] this response was more pronounced among non-Caucasians, people with low incomes, and those without a high school education.[105] Collectively, these data support the use of increased cigarette taxes as a strategy for reducing cigarette consumption.

Smoking Bans

Given evidence that secondhand smoke increases cancer risk, bans on smoking in public places and workplaces are considered appropriate strategies to minimize the negative health effects from secondhand smoke.[106] Smoking bans in countries such as Ireland, Italy, Sweden, and New Zealand and 13 U.S. states have provided the opportunity to assess the health effects of smoke-free environments, and the results have been encouraging. Specifically, Farrelly and colleagues reported on saliva cotinine (an indicator of nicotine exposure) levels in a sample of New York hospitality workers before and after the smoking ban. Results showed a significant decline in nicotine exposure following the ban.[107] These data are consistent with those of a similar study conducted in Ireland.[108] With regard to any positive health effects from living in an area with a smoke-free policy, one study conducted in the town of Helena, Montana, showed a significant decline in hospital admissions for myocardial infarction for a 6-month period while the smoke-free policy was in place compared to the same 6-month period in the previous years when the smoke-free policy was not in place.[109] Notably, hospital admissions for myocardial infarction in the areas outside Helena where the smoke-free policy was not in place showed a nonsignificant increase.[109]

FUTURE DIRECTIONS AND CONCLUSIONS

The potential increases in tobacco use worldwide, in combination with the suboptimal response to currently approved medications for nicotine dependence treatment, highlight the need to both develop more efficacious smoking cessation treatments and to improve the use of currently approved treatments. Toward this end, the identification of novel medications that mimic and/or attenuate nicotine's rewarding effects or reduce nicotine withdrawal is underway and most clearly demonstrated by the recent FDA approval of varenicline. There is also evidence for the efficacy of selegiline, fluoxetine, naltrexone, and mecamylamine in certain subgroups of smokers, although current data are limited or conflicting. In terms of improving the efficacy of currently approved treatments for nicotine dependence, research concerning smoker characteristics related to responsiveness to NRTs and the potential development of fast-acting NRTs could help clinicians to prescribe NRT (type, dose, and duration) based on the smoker's characteristics, thereby enhancing NRT effectiveness. Similarly, reduced NRT costs in conjunction with innovative marketing approaches to increase the appeal of, and access to, NRTs could significantly increase utilization of NRT products, in turn, broadening the impact of over-the-counter therapies on the population smoking rate. Finally, although the results from pharmacogenetic studies of treatments for nicotine addiction offer limited potential for individualizing patient care at this point, future research in this pioneering area might eventually lead to substantial breakthroughs for individualized treatments for nicotine addiction and additional significant reductions in the worldwide prevalence of smoking. Nevertheless, given the projections for substantial increases in the rate of tobacco use in developing countries and given the lack of resources in these countries to sustain the needed infrastructure for effective treatment for nicotine dependence, efforts must be directed toward the development of low-cost treatments that can be broadly disseminated. Low-cost treatments for nicotine dependence, coupled with innovative marketing of these treatments, should also be seen as a priority in developed countries to further the important advances that have been made thus far in reducing the rate of tobacco use over the past several decades. Partnerships between pharmaceutical companies and government agencies to develop, test, and market new treatments for nicotine dependence, as has been done with treatments for other medical illnesses and diseases, could be critical if additional significant reductions in the worldwide prevalence of smoking are to be realized.

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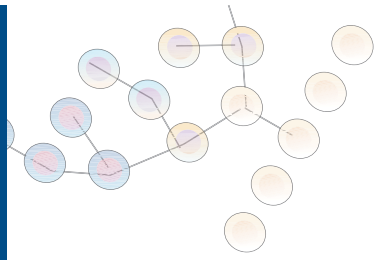
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28 Surgical Interventions in Cancer

John E. Niederhuber

SUMMARY OF KEY POINTS

- Surgeon is part of a multidisciplinary team.
- Surgeon is frequently the "entry point" for patients who are newly diagnosed with cancer.
- Surgeon must have knowledge of the biology and natural history of the cancer to be treated.
- Surgeon must be technically experienced in diagnostic procedures and operative interventions.
- Surgeon must have appropriate knowledge base in medical and radiation oncology.
- Patients treated in a multimodality setting have improved outcomes.
- Training of surgical oncologist must encompass the following:
  - Etiology and genetic predispositions of cancer
  - Prognostic factors and natural history of specific tumors
  - Understanding of how to provide cost-effective treatment
  - Skills to develop, conduct, and manage clinical trials
  - Guidance in management of advanced disease
  - Guidance in offering compassionate support
  - Guidance in determining and evaluating outcomes
- Surgical oncologist should be a participant in clinical trials, providing guidance in design and monitoring of quality control aspects of surgical intervention component as well as overall leadership design and implementation.
- Surgical oncologist should be an educational resource in the community.
- Surgical oncologist plays an important role in prevention and screening.

INTRODUCTION

Historically, surgery was the sole method used for treating cancer. However, with the introduction of ionizing radiation and the development of anticancer drugs, cancer therapy has rapidly progressed to involve the careful integration of an extensive array of therapeutic options in the treatment of both primary and recurrent tumors. As a result, the cancer surgeon no longer works alone but is part of a multidisciplinary team involved in the treatment of most solid tumors and in the design and implementation of clinical trials.

The surgeon must have a clear understanding of the biology of cancer and its natural history and must also be experienced in the technical procedures needed to accurately diagnose and appropriately resect primary cancers and, when indicated, locally recurrent and metastatic tumors. The cancer surgeon must also be prepared, in many cases, to function as the primary cancer care provider, or cancer-oriented "family physician," for the patient. The surgeon must provide for the patient a focus of treatment integration among the various cancer specialists. Cancer surgeons find that it is common for patients to call or visit them for advice about all aspects of their treatment, which often leads to a lifelong relationship of continued care and follow-up.

HISTORICAL PERSPECTIVE

In medicine, professional and public acceptance of a subspecialty has historically depended largely on accomplishment. The development of the surgical oncology subspecialty is no exception and has been intimately tied to the history of surgery. In fact, surgical treatment of cancer has been significantly responsible for the role of surgery in modern medicine. The earliest discussion of surgical treatment of tumors appears in the E.S. Papyrus (ca. 1600 BC), but it is believed to be based on earlier writings dating back to 3000 BC.[1]

Despite this early mention, surgery was primarily reserved for the treatment of abscesses and for managing trauma before the introduction of anesthesia. The few operations performed for tumors were amputations. Not only did patients suffer excruciating pain in the absence of anesthesia, but also, before the advent of antisepsis, the death rate from infection was extraordinarily high. As a result, few patients were willing to undergo such intense pain electively, with so little chance of survival. The development of anesthesia and the introduction of antisepsis made elective surgical techniques for the treatment of cancer much more acceptable, and rapid developments in cancer surgery began to occur during the second half of the nineteenth century as tumor-specific elective surgeries were undertaken and refined.[2,3]

Anesthesia

Some of the first "clinical trials" of ether anesthesia took place in the parlor of Crawford Long, a dentist practicing in Georgia during the early 1840s. Long is said to have invited his friends over for "ether parties" to enjoy a temporary "loss of Southern inhibitions." Long witnessed that his friends lost not only their inhibitions, but also pain sensation. He is said to have used ether anesthesia in his dental practice as early as 1842. Unfortunately, Long's use of ether was not brought to the attention of the medical public.

John Collins Warren is responsible for two significant benchmarks in oncologic surgical history. He published the first American work on tumors in 1838, entitled "Surgical Observations on Tumors

with Cases and Operations,"[4] and he was the surgeon in the first published account of the use of ether anesthesia for removal of a tongue cancer from Gilbert Abbott in 1846.[2] The anesthesia was administered by a dentist, William T. Morton, who had developed the technique. The operation involved excision of the submaxillary gland and part of the tongue.[5]

Antisepsis

Despite the advances made in anesthesia in the 1840s, sepsis remained a major barrier to successful surgery until Joseph Lister (subsequently Baron Lister), an accomplished surgeon, introduced the concept of bactericidal therapy with carbolic acid in 1867.[3] This was an outgrowth of Pasteur's theory that bacteria caused infection. Using carbolic acid as an antiseptic agent in conjunction with heat sterilization of instruments, Lister dramatically decreased the rate of postoperative fatalities. He also developed absorbable ligatures and the drainage tube; both represent significant advances for surgical management of wounds and incisions.

Lister was indirectly responsible for the introduction of the first ready-to-use surgical dressings in 1886. Robert Wood Johnson heard an address in 1876 by James Lister; as a result, he developed sterile dressings wrapped in individual packages suitable for immediate use without the risk of contamination.

Although the value of Lister's contributions was not recognized by his senior colleagues, they were quickly adopted by William Stewart Halsted,[6] the first professor of surgery at The Johns Hopkins Hospital. Halsted introduced the meticulous techniques of tissue handling during surgery and the antiseptic methods proposed by Lister to the United States. Halsted, who had a major interest in cancer, was strongly supported in his work by his close friend and colleague at Hopkins, Sir William Osler. Osler was a student of abdominal malignancies, and the collaboration of these two great American physicians represents one of the earliest occurrences of the multidisciplinary approach to cancer treatment.

SURGICAL ONCOLOGIST

Surgical oncology has emerged to play an increasingly important role in the treatment of cancer (Table 28-1). There are many reasons for this evolution of subspecialization within general surgery, but the most significant are: (1) the increasing complexity of multidisciplinary cancer care; (2) the opportunities for clinical and laboratory investigation of cancer biology; (3) the rapid increase in the number of medical and radiation oncologists, which threatens to diminish significantly the traditional role of the surgeon in coordinating the management of cancer patients (even those with early disease); and (4) the expectation of patients that surgeons have the latest information and newest treatment options.[7]

Table 28-1 Role of the Surgical Oncologist

CONSULTANT
Special training or skills
Tumor board
ORGANIZER AND LEADER
Cancer programs
Cancer committee
Tumor registry
Oncology section
EDUCATOR
Cancer conferences
Teaching programs
RESEARCHER
Clinical protocols

Box 28-1. CANCER SURGEON

Care Provider
Brings surgical skill and compassionate care to patients
Leads screening, prevention, and risk assessment programs
Facilitates molecular characterization of tumor and surrogate tissues
Coordinates multidisciplinary clinical care teams

Researcher
Facilitates laboratory research
Coordinates epidemiologic studies
Conducts clinical trials research
Develops novel approaches to education

Teacher
Ensures excellence in surgical care
Leads a multidisciplinary team to implement integrated oncology training

Today, the surgical oncologist is really a "cancer physician" who interacts with all other members of the cancer therapy team in a knowledgeable and confident manner (Box 28-1). This role requires a sound knowledge of cancer biology (including cancer prevention and the biology of metastasis), imaging technologies, chemical and biologic therapy, and radiation therapy.

In a 1996 address before the American College of Surgeons, Murray Brennan of Memorial Sloan-Kettering Cancer Center in New York stated, "In defining what might be considered the role of the surgeon in cancer care, there are at least seven important areas that I believe need to have renewed emphasis."[8] Brennan used his experience with soft-tissue sarcoma to illustrate the importance of the following performance objectives for the cancer surgeon: (1) understands etiology and genetic predisposition; (2) understands prognostic factors and natural history; (3) performs cost-effective treatment; (4) develops clinical trials; (5) guides advanced disease management; (6) guides compassionate support; and (7) evaluates outcome. Brennan's analysis of the cancer surgeon's role as a member of today's therapy team is an excellent real-life description of the responsibilities involved and the opportunities to provide real leadership in cancer care.

The surgical oncologist thus provides the leadership for cancer care, cancer research, and cancer teaching within the academic or hospital-based surgical community. This is an extremely important role, and it has become increasingly clear that programs that emphasize strong cancer leadership from surgical oncologists have developed solid research and clinical programs for patients seeking cancer treatment.

As part of the greater medical community, the surgical oncologist has the responsibility of introducing to the surgical community new information, new approaches to cancer diagnosis, and new approaches to therapy. The surgical oncologist is most often the one involved in the early stages of cancer diagnosis, an ideal position to provide significant institutional leadership in developing community interest in cancer prevention, including screening and early diagnosis.

In addition to local responsibilities, much ongoing work in national clinical trials depends heavily on surgical oncology leadership directed at establishing quality control of the surgical aspects of multidisciplinary protocols. Cancer surgeons have historically provided significant leadership in the conduct of clinical trials. Most noteworthy have been the National Surgical Adjuvant Breast and

Bowel Project (NSABP), initially under the direction of Bernard Fisher, and more recently, the American College of Surgeons Oncology Group (ACOSOG), originally led by Samuel Wells. Surgeons have also been active participants in several other cooperative groups. The success of these surgeon-sponsored clinical trials placed surgeons as significant contributors to the clinical trials agenda of these groups, and showed the importance of surgical involvement in designing clinical trials and maintaining control of the quality of surgery when it was part of the study. Standardizing and maintaining the quality of surgical intervention has proved especially important in evaluating studies of adjuvant therapy.

The surgical oncologist is an important member of the design team and is critical to providing education to participating surgeons about standards of care, technical guidelines for the operative procedure, and collection of data. The surgeon member of the team is also essential for reviewing the staging data submitted by participating surgeons as well as information provided by quality control reports. When surgery is part of the therapy being evaluated in a clinical trial, it must be performed in a uniform manner by surgeons specifically trained and competent to deliver the procedure in a quality manner.

Surgeons and Surgical Research

Surgeons have been somewhat notorious for the introduction of new surgical procedures and devices without evidence of a random assignment prospective evaluation. Perhaps it is the nature of what we do. We learn from the experience of repeated procedures, and from that experience comes new ideas we believe will improve patient outcomes. Though not wishing in any way to hinder this category of innovation, the surgical oncologist does find it necessary to hasten the introduction of evidence-based results in dealing with such new technologies to eradicate tumors, with lesser operative procedures (e.g., sentinel lymph nodes) and now with the various approaches to minimally invasive surgery.

Training in Surgical Oncology

Historically, training in surgical oncology occurred at the small number of large standalone cancer hospitals in the United States, primarily with the goal of preparing a select group of general surgeons to work as cancer specialists in university hospitals or at large medical centers.

During the 1970s there was more interest in developing the subspecialty of surgical oncology within academic surgery training programs and in obtaining board certification, as had been done for other oncologic subspecialties. This effort by several prominent cancer surgeons encountered considerable difficulties in the ensuing years, and surgical oncology has yet to achieve recognition as a board-certified subspecialty.

There are many reasons for this. First and foremost is that surgical cancer care in the community almost always falls to the general surgeon. Even in the university hospital setting, cancer surgery has not been the exclusive right of the surgical oncologist. The surgical oncologist, as a result, has always been viewed as somewhat redundant by general surgical colleagues. Furthermore, each of the boarded surgical subspecialties also deals with cancer treatment.

To address some of these issues, a conference was held at the National Cancer Institute (NCI) in 1979. It was the consensus of this conference that training in surgical oncology should involve a 2-year period after completion of a general surgery residency.[9] The committee charged a national organization, the Society of Surgical Oncology (SSO), with developing training guidelines and a review and approval process for identifying qualified training programs. Clearly, the hope of those involved was that expertise in surgical oncology could be increased in significant numbers and disseminated more broadly in the community practice arena, not just in academic centers. Further, it was hoped that the development of a number of university training programs would eventually lead to board certification. Guidelines established by the SSO in 2001 call for 12 months of training in the surgical management of cancer cases, with a minimum number of procedures established for specific anatomic categories. In addition to surgical cases, trainees must also gain experience in the other aspects of the multidisciplinary management of cancer. Nonsurgical experience is required in radiation oncology, surgical pathology, medical oncology, and supportive and rehabilitative care. Clinical research on human subjects is required, and participation in laboratory research is encouraged.[10] There are currently 14 approved surgical oncology fellowship programs.

The effort to enhance training in surgical oncology, broaden available training opportunities, and provide a measure of qualification or certification of competence has been supported and nurtured by the SSO, which was founded in 1940 as the James Ewing Society.[11] This society has become the leading academic oncologic society for surgeons around the world. In assuming this leadership role, the SSO has developed and disseminated optimal guidelines for the multidisciplinary care of patients with cancer, provided an important resource for continuing education through its annual meeting, initiated and supported a monthly journal (*The Annals of Surgical Oncology*), and actively stimulated cancer research.[12] The Society has willingly taken on the responsibility of evaluating and approving fellowship programs. It embraced the recommended guidelines proposed by the 1979 NCI Committee and, in 1982, approved the first three training sites.[13] In 1992, the World Federation of Surgical Oncology Societies was inaugurated and immediately worked to develop "standards of education, training, and practice" in surgical oncology.[14,15] These guidelines were published and are summarized in Table 28-2. It is through efforts of the SSO and the World Federation of Surgical Oncology Societies that excellent training opportunities now exist for a significant number of general surgery graduates. Standardization of the process of review and accreditation ensures that more well-qualified cancer surgeons will be available to serve as experts in cancer care within multidisciplinary teams. The SSO deserves much praise and credit for its untiring and expert leadership in the training of future surgical oncologists.

Although the SSO and other such organizations have taken on a leadership role in surgical oncology education, all surgical oncologists have an educational reponsibility and a role in teaching that should extend to their hospital staff, students, residents, fellows, colleagues, and the community. The surgical oncologist should have the capacity to develop effective training programs, laboratory research pro-

Table 28-2 Guidelines for Training of Surgical Oncologists in Europe

- Receive training to a high level of technical competence and attain the clinical skills needed to manage common and complex cancers.
- Receive training in the evolving understanding of tumor biology, mechanisms of spread of disease, and other oncologic principles.
- Understand the principles, scope, and limitations of different modalities of radiation therapy.
- Be conversant with the theoretical and practical applications of cytotoxic chemotherapy.
- Be prepared to study and evaluate evidence from clinical trials and thereby be in a position to propose new avenues of research and study, both in the clinical setting and in the laboratory.
- Be trained to be discriminating in the application of modern technology in the investigation and treatment of malignant disease.
- Be involved, as a member of a team, in each step of the decision-making process in planning the strategy for the patient's care.

Adapted from O'Higgins N: Towards a high standard of surgical oncology throughout Europe. Eur J Cancer 1995;31A(Suppl 6):S22. © 1995 Elsevier Science, with permission.

Table 28-3 Common Predisposing Conditions and Associated Malignancies

Condition	Genes Tested	Associated Malignancy
Cryptorchid testis		Testicular
Chronic ulcerative colitis		Colon
Familial adenomatous polyposis	*APC*	Colon and rectum
Hereditary nonpolyposis colon cancer	*MSH2*	Colon and rectum
	MSH6	
	MLH1	
	PMS1	
	PMS2	
Family history of colon cancer		Colon and rectum
Multiple endocrine neoplasia Type 1	*MEN1*	Pancreatic islet cell, anterior pituitary
Multiple endocrine neoplasia Type 2	*RET* gene	Medullary cancer of the (types II and III) thyroid
Leukoplakia		Squamous
Family history of breast cancer	*BRCA1* and *BRCA2*	Breast and ovary
Family history of ovarian cancer	*BRCA1* and *BRCA2*	Ovary and breast

grams, treatment guidelines, clinical trials, and protocols. In addition, surgical oncologists must teach other surgeons and surgical residents how to incorporate oncology principles into their practice.

SURGEON'S ROLE IN CANCER MANAGEMENT

Prevention and Screening

The most effective weapons against cancer are prevention and early detection. Much of the debate about prevention has focused on the cost of delivering cancer prevention and screening services and the availability of enough adequately trained individuals to perform the appropriate screening test. Furthermore, the application of a screening test is a complex process (Table 28-3), and multiple layers of evaluation are needed to prove test efficacy. Clearly, a screening test must be applied at the right time and to the appropriate population to be effective. Moreover, the screening test itself is merely designed to identify a possible condition that needs further in-depth evaluation. For the surgeon, the effectiveness and cost of screening are directly related to the strategies used to address positive test results.

The level and quality of prevention and screening services may be increased through a greater consensus about goals for cancer prevention, better organization to provide these services more efficiently to large populations, and improvement of health education. Social problems like unemployment, poverty, and limited medical coverage for a large number of people have significantly influenced access to services, and in the poor regions of the world, screening is not even something to be considered. The agenda for the future in cancer prevention should include fundamental research, intervention research, program delivery, patient access through free choice, and surveillance and monitoring.[16,17]

Certain conditions, often congenital or inherited genetic traits, are associated with the subsequent manifestation of cancer. Genetic testing has made it possible to accurately identify the carriers of mutations that increase the risk of the occurrence of certain cancers. Genetic tests available include that for the *RET* proto-oncogene present in multiple endocrine neoplasia type 2 (MEN-2), for the *CDH1* mutation in hereditary diffuse gastric cancer, the *APC* gene in colorectal cancer, and the *BRCA1* and *BRCA2* mutations in breast and ovarian cancers. In patients in whom these syndromes are known to be present by occurrence or genetic testing, and in whom cancers are likely to occur in nonvital organs, it may become necessary to remove the organ to prevent possible malignancy. In these instances, the surgeon has a responsibility to inform and educate the patient about the condition and to alert the family to the hereditary nature of the disorder and its possible occurrence in other family members. The surgeon should also discuss the availability of genetic testing for family members at risk. Table 28-4 outlines some common predis-

Table 28-4 Ten Criteria for Cancer Screening Programs

1. Is the disease an important health problem?
   Probably yes
2. Is there effective therapy for patients with localized disease?
   Probably yes
3. Are treatment facilities for further diagnosis and treatment readily available?
   Probably yes
4. Is there an identifiable latent period or early symptomatic stage of the disease?
   Probably yes
5. Is there an effective screening technique?
   Probably yes
6. Are the tests acceptable to the screened population, particularly groups at increased risk for disease?
   Probably yes
7. Is the natural history of the disease, from its development to clinical manifestation, sufficiently known?
   Probably yes
8. Is there a generally acceptable strategy to identify patients who should receive treatment versus careful observation alone?
   Probably yes
9. Are the costs of screening acceptable?
   Probably yes
10. Does the treatment of early-stage disease have a favorable effect on prognosis?
    Probably yes

Adapted from Littrup PJ: Prostate cancer screening: Appropriate choices? Cancer 1994;74(Suppl):2016. © 1994 American Cancer Society, with permission.

posing conditions, genes associated with these conditions, and their corresponding malignancies.

As an example, 2% of adult women have a family history pattern that is associated with the *BRCA1* or *BRCA2* genes. For these women, the U.S. Preventive Services Task Force recommends referrals for genetic counseling and evaluation for *BRCA* testing.[18] The lifetime risk of developing breast cancer is 35% to 85 % for women with *BRCA* mutations as compared with a lifetime risk of 13.2% in the general population. The numbers for ovarian cancer are 10% to 50% vs. 1.7%. Prophylactic oophorectomy has been shown to reduce the ovarian cancer and breast cancer risk among such women by 83% and 70%, respectively.[19] Prophylactic mastectomy alone has been shown to reduce the breast cancer risk by 90% and in combination with oopherectomy, by 95%.[20] These are a number of options available for the patient, each with its own benefits and drawbacks. The surgeon plays a large role in informing the decisions of women at risk. The lethality of the disease, the risk of cancer, the efficacy of the screening tool, and the availability of effective surveillance options such as mammography in breast cancer, should all be considered in reaching a decision about prophylactic surgery. Even in the absence of an available genetic test, the same analysis can be applied to other high-risk patients.

Cryptorchidism is associated with a higher incidence of testicular cancer, which is often prevented by early prophylactic surgery. Patients with ulcerative colitis (with total and partial colonic involvement) are likely to have cancer of the colon if resection is not performed. The patient and surgeon must carefully balance the benefits and hazards of surgery with an understanding of the factors involved in determining increased risk (see Chapter 26).

Diagnosis

Evaluation for surgical cure should be based on a histologically confirmed diagnosis of a treatable cancer confined to local or regional tissues. The diagnosis of cancer cannot be proven without a biopsy, and biopsy should be repeated if the diagnosis is questionable. There have been remarkable advances in imaging technologies to improve the execution and outcome of selected biopsy procedures. Computed tomography (CT), ultrasonography, and magnetic resonance imaging are now frequently used to enhance needle guidance and placement. These techniques improve the accuracy and safety of needle placement along the target path, while avoiding injury to other structures. The use of three-dimensional stereotactic CT-guided biopsy is becoming increasingly widespread as a diagnostic tool. Stereotactic biopsy is appropriate for any lesion located in the brain stem, pons, or medulla.[21] This technology is also widely used to evaluate nonpalpable mammographically detected breast abnormalities. The use of these guidance techniques requires the surgeon to be familiar with the device and the approach.

Four techniques are currently in use for obtaining tissue for diagnosis:

1. Needle aspiration biopsy. This approach involves aspirating tissue fragments through a needle guided into an area in which disease is suspected. It can usually be performed using local anesthesia or, possibly, no anesthesia. Sampling can be guided by various imaging modalities, including CT and ultrasound. A study of the usefulness of CT-guided fine-needle aspiration in the diagnosis of malignancy in small pulmonary lesions showed 82% sensitivity, 100% specificity, and 88% accuracy.[22] The disadvantage of aspiration biopsy is that it seldom yields a sufficient specimen for histologic diagnosis. As a result, there is always a margin of error in individual cell analysis, even with an exceptionally skilled cytopathologist. Cytology has the disadvantage of being unable to distinguish between invasive and noninvasive cancers, so a more detailed histologic diagnosis is usually necessary.
2. Needle (core) biopsy. This technique entails the retrieval of a small core of tissue, using a specially designed "core-cutting" needle. This specimen is usually sufficient for histologic diagnosis of most tumor types. Like aspiration biopsy, this technique is relatively cost-effective and can usually be performed using a local anesthetic.
3. Incisional biopsy. This technique involves surgical retrieval of a small segment of a larger tumor for diagnosis. The advantage of the procedure is that it yields enough histologic material to provide analysis of tumor markers. It is also often possible to perform this procedure in an outpatient setting using local anesthesia. Incisional biopsies are particularly useful in the diagnosis of sarcomas, large tumors, and unresectable tumors, and when the preferred treatment is nonsurgical. The disadvantages of incisional biopsy include possible sampling errors, the risk of trauma to the tumor, the possible risk of tumor spread, and the need for excisional biopsy if no cancer is diagnosed. Precise technique is essential.
4. Excisional biopsy. This technique is total removal of all suspicious tumor tissue, with little or no margin. The circumstances of the procedure dictate the use of local or general anesthesia. This procedure is the most definitive diagnostic tool of the four described. It provides adequate treatment for nonmalignant tumors and involves minimal trauma to the cancer. It is necessary to perform excisional biopsy if the results of incisional biopsy or core needle biopsy are inconclusive. One of the disadvantages is that it is generally limited to small tumors (e.g., lymph nodes, parotid tumors). It also involves a deeper area of dissection, which necessitates wider margins.

The proper placement of a biopsy incision is vital. Misplacement can compromise subsequent surgical procedures, because the definitive operation will include excision of the surgical tract of the prior incisional or excisional biopsy. The evidence concerning tumor spread from incisional and excisional biopsy is inconclusive. However, the surgeon should take extreme care to avoid using contaminated instruments on new tissue planes and to secure proper hemostasis of biopsy sites to avoid the spread of tumor along tissue planes.

The biopsy technique selected should be appropriate for the suspected lesion and should yield an adequate tissue sample for proper histologic diagnosis. Orientation of the specimen, if applicable, should be marked clearly and carefully by the surgeon to facilitate proper histologic interpretation. Proper handling of excised tissue is the surgeon's responsibility and the surgeon must be knowledgeable regarding procedures required to provide optimal specimens for tissue banking. Although such banking procedures thus far have been ad hoc, the NCI has in place a set of First-Generation Guidelines for the biorepositories that it supports.[23] It is NCI's plan that to qualify for grant support, investigations must use tissue samples from NCI-accredited facilities.[24] Therefore, the surgeon is well advised to be familiar with these guidelines.

In addition to knowledge of such guidelines, it is also important for the surgeon to maintain a close relationship with the pathologist. They are able to provide guidance before staging procedures with regard to tissue requirements. Furthermore, if the patient has a pathologic diagnosis from an outside source, it is always necessary to have the diagnosis confirmed. It may even be necessary to obtain tissue blocks to prepare more slides, to perform more extensive cytologic marker studies, and occasionally, to perform additional biopsies to obtain a definitive diagnosis.

Staging

Staging is the classification of the anatomic extent of cancer in an individual. Specific stage groups categorize cancers of particular anatomic sites. Staging is essential in the treatment process and requires an understanding of the biology of cancer as well as the extent of disease. The tumor-node-metastasis (TNM) classification, detailed in Table 28-5, is the global standard in cancer staging.

Table 28-5 TNM Classification System

TNM SYSTEM

Describes the anatomic extent of disease based on assessment of three components

T	Primary tumor size and extent
N	Regional lymph node involvement
M	Distant metastasis absent or present

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1, T2	Increasing size or local extension
T3, T4	Increasing extent of primary tumor

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1, N2, N3	Increasing involvement of regional lymph nodes

Distant metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis (may be further specified according to site of occurrence)

HISTOPATHOLOGY

Qualitative assessment of category of tissue or cell type based on appearance

Histopathology grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately well differentiated
G3	Poorly differentiated
G4	Undifferentiated

ADDITIONAL DESCRIPTIONS

cTNM (or TNM)	Clinical, increasing size or local extension
pTNM	Pathologic
rTNM	Recurrence of tumor after disease-free interval
aTNM	First determined at autopsy

STAGE GROUPING

0	Tis, N0, M0
I	T1, N0, M0
IIA	T0, N0, M0
	T1, N1, M0
	T2, N0, M0
IIB	T2, N1, M0
	T3, N0

From Rodary C, Flamont F, Donaldson SS: An attempt to use a common staging system in rhabdomyosarcoma: a report of an international workshop initiated by the International Society of Pediatric Oncology (SIOP). Med Pediatr Oncol 1989;17:210.

Over the past decade, there has been a move to using minimally invasive techniques for the staging of a tumor. For instance, although staging for pancreatic cancer has been traditionally done by CT, peritoneal spread of the disease is difficult to interpret by this method. A minimally invasive laparoscopy allows for such a determination and can help detect inoperable candidates.[25] One center's negative exploration rate was reduced from 65% to 24% after the introduction of staging laparoscopy in the treatment protocol.[25] In breast cancer, routine axillary dissection has been replaced by sentinel lymph node biopsy as the standard of care.[26] In validation studies for the procedure, accuracy rates ranged from 95% to 100%, yet carried significantly less morbidity than axillary dissection. Only patients with positive sentinel lymph nodes currently undergo the more extensive procedure. Sentinel lymph node biopsy is also now routinely used in the staging of melanoma and shows promise as a procedure in colorectal cancer.[27,28]

Recently, the role of molecular characterization of sampled lymph node tissue has been shown to demonstrate evidence of tumor when standard cytology and histology cannot. The importance of such findings remains to be demonstrated and certainly will vary depending on the tumor. Increasingly however, molecular characterization will determine therapy.[29]

Multidisciplinary Management

Although the management of cancer formerly involved surgery alone, most solid tumors, even very early cancers, are treated by more than one modality. This multidisciplinary approach to treatment requires the input and coordination of multiple specialists. To complicate matters even further, often more than one therapeutic option exists. This requires the specialists involved to agree on the treatment regimen to be followed.

Although the advances in multimodal therapy have changed the role of the surgeon in the diagnosis and treatment of cancer, the surgeon continues to be the primary care provider for most patients with cancer and frequently coordinates care with other oncology specialists including radiation and medical oncologists. Like the surgeon, the radiation oncologist provides an important modality of local and regional cancer therapy. Often, radiation therapy is used after surgery to improve local disease control rates, or even before surgery, to reduce tumor bulk or downstage the tumor. It is also increasingly common for radiation to be combined with simultaneous administration of chemotherapy or radiation sensitizer agents. The medical oncologist's responsibilities include administering and monitoring the patient's chemotherapy, hormone therapy, and in some instances, biologic therapy. Medical oncologists manage the toxicities of intravenous and oral anticancer therapy, and as a result, provide considerable supportive care, especially as new agents have been developed to better control nausea and fatigue.

It is important and beneficial to the patient that these various caregivers work in a coordinated and collaborative effort toward the optimum outcome. There is evidence that the multidisciplinary approach to cancer management leads to increased survival. A study in the United Kingdom examining standards of care in head and neck cancer[30] showed increases in 2-year survival for patients assessed in a multidisciplinary clinic. An earlier study also confirmed the benefits of multimodal management.[31] Patients with skeletal and soft-tissue sarcomas of the extremity were treated with preoperative intra-arterial doxorubicin and radiation therapy, radical surgical resection, and postoperative chemotherapy or chemoimmunotherapy, resulting in the preservation of a functional extremity in 13 of 14 patients. Seven of eight patients with stage IIIA and IIIB soft-tissue sarcomas that were managed with preoperative intra-arterial doxorubicin and radiation therapy followed by en bloc soft-tissue resection and six patients with bone sarcomas that were managed with preoperative treatment followed by bone resection and replacement with cadaver bone allografts remained free of disease for 4 to 34 months. The results of the combined-modality approach were significantly better than those obtained in patients managed with surgical resection alone or with a combination of surgery and another single modality, in terms of both short-term recurrence-free survival and salvage of a functional extremity.[31]

The surgical oncologist not only is involved with medical oncologists and radiation oncologists in developing the treatment plan but is also responsible for recognizing the need for input from other surgical cancer specialists in other surgical specialties (thoracic, urologic, plastic, head and neck, gynecologic, and orthopedic surgery) or the appropriateness of referring a patient to a clinical trial. Participation in clinical trials has been shown to be of enormous benefit

Table 28-6 American Society of Anesthesiologists Physical Status Classification

Class	Description
I	Healthy patient
II	Mild systemic disease, no functional limitation
III	Severe systemic disease, definite functional limitation
IV	Severe systemic disease that is a constant threat to life
V	Moribund patient unlikely to survive 24 hours with or without operation

From Miller RD: Principles and Practice of Anesthesia, 2nd ed. New York, Churchill Livingstone, 1986, with permission.

to patients. One study in patients with sarcoma noted that longer survival was associated with clinical trial participation in all age groups studied.[32] Although the clinical trials may lack a surgical component, the surgical oncologist can help to provide this benefit by keeping abreast of trials and enrolling eligible participants.

Advancing the development of multidisciplinary cancer care is a growing trend toward freestanding cancer care centers. The critical components of these centers are multidisciplinary cancer care, direct care and support services, a commitment to clinical trials, and a comprehensive program for quality assurance.[33] Comprehensive cancer centers affiliated with academic medical centers have an array of clinically focused investigations, including programs designed to test new therapies and research programs investigating the biology of cancer. These academic comprehensive cancer centers, some 61 supported in part by grants from the NCI, attract the elite of cancer clinician-scientists and basic scientists. As a result, patients receive better cancer care and greater support from experienced ancillary services. This translates into better quality of life as well as a longer life and greater hope for cure.

SURGICAL TREATMENT OF CANCER

Surgical Risk

Assessment of surgical risk is based on several factors. The physical status of the oncologic patient and the debilities that often accompany the disease process present specific challenges to the surgical team. Patients should undergo a complete evaluation before surgery, and any history of cardiac, pulmonary, hepatic, or renal disease should be documented. Emphasis should be placed on physiologic function rather than chronologic age. A study conducted at the Mayo Clinic in 1989 showed that patients 90 years of age and older tolerated the stress of a surgical procedure fairly well.[34] The physical status of the patients in the study was assessed using the American Society of Anesthesiologists Physical Status Classification (Table 28-6).

The performance scales most widely used by oncologic specialists are the Eastern Cooperative Oncology Group Performance Scale (ECOG-PS) and the Karnofsky Performance Status (KPS) rating. These performance scales are also useful to surgeons and anesthesiologists in determining operative risk. A comparison of the ECOG-PS and KPS ratings showed both methods to be valid prognostic indicators of functional status, but the ECOG-PS seemed slightly superior. If necessary, each can be converted to the other with sufficient accuracy.[35] These two classifications are outlined in Table 28-7.

Mortality caused by anesthetic complications is most often related to the physical status of the patient. Highly sophisticated techniques of anesthesia have increased the safety of major oncologic procedures, and many of these advances have their basis in modern cardiac surgery and in transplantation, especially liver transplantation. The choice of anesthetic technique and agent should be appropriate for both the procedure and the patient. For example, surgery in the lower abdominal area, lower extremities, or pelvis may be performed with general or spinal anesthesia, depending on the patient's health status. The risk to the patient who has evidence of congestive heart failure would probably be increased by the use of general anesthesia as opposed to spinal anesthesia. However, patients with a history of ischemic heart disease may become agitated during a surgical procedure in which they are awake, thereby causing myocardial stress. The surgeon should work closely with the anesthesiologist to ensure proper selection of anesthetic application. Epidural-assisted general anesthesia is frequently used for abdominal surgery and provides an opportunity for improved pain management during postsurgical recovery.[36]

The oncologic patient is a particularly challenging surgical candidate. Operative mortality is usually defined as mortality that occurs within 30 days of a major operative procedure. The operative mortality statistics for oncologic patients can be deceptive. For example, patients who undergo a palliative procedure have a very high operative mortality rate, even if the surgery is successful. The cancer surgeon is ultimately responsible for ensuring that surgical intervention is safely undertaken, with an awareness of the possible risks and complications.

Surgery for Primary Cancer

At times, the cancer surgeon alone will be responsible for patient outcome, whereas at other times a combination of therapeutic modalities may enhance the prospect of cure or quality of life. Surgery should always be extended or restricted with these considerations in mind. The cancer surgeon must think first as an oncologist and attempt to envision the entire course of a particular disease and its treatment. The ultimate approach for the patient is multispecialty consultation that develops a consensus-based optimized course of therapy in the context of available clinical trials (the tumor board concept).[37] If surgery is indeed the best treatment option, then the surgeon may act on that conclusion.[38]

Table 28-7 Eastern Cooperative Oncology Group Performance Scale and Corresponding Karnofsky Rating

ECOG-PS Grade	Description	Karnofsky Rating
0	Fully active, able to carry on all predisease activities without restriction	100
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)	80–90
2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours	60–70
3	Capable of only limited self-care; confined to bed or chair 50% or more of waking hours	40–50
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair	≤30

ECOG-PS, Eastern Cooperative Oncology Group performance scale.

Table 28-8 Adequate Margins of Resection

A complete margin of normal tissue around the primary lesion
Frozen sections used to evaluate tissue margins in instances of doubt
Complete removal of involved regional lymph nodes
Resection of involved adjacent organ
En bloc resection of biopsy tracts and tumor sinuses

Appropriate treatment of primary cancer varies with the individual cancer type and the area involved. The cardinal principle of surgical cure is total removal of neoplastic tissue. This involves avoiding implantation of loose tumor cells; minimizing iatrogenic, lymphatic, and vascular dissemination of cancer cells; and obtaining a complete margin of normal tissue around the primary tumor (Table 28-8).

As is the case for staging, minimally invasive procedures have been adopted for the treatment of several malignancies. The main benefits of laparoscopic procedures are a reduction in perioperative trauma, shorter hospital stays, and more rapid recovery. Laparoscopic procedures have been shown to be as effective as open surgery in cancers of the pancreas (lesions left of the portal vein), esophagus, liver, gynecologic malignancies, and colorectal cancer, among others.[39–42] The last has been the subject of debate, due to reports of port site metastases when the procedure was initially introduced.[42] However, later studies reported no increase in recurrence rates for laparoscopic procedures as opposed to open procedures.[43]

Laparoscopic procedures have been enhanced by the use of surgical robots that allow for three-dimensional viewing and greater control over the manipulation of surgical instruments. Robotic surgery has been utilized to enhance laparoscopic procedures in a variety of cancers.[42,44] The advantages afforded by robotic assistance in laparoscopic surgery have not generally been achieved in open procedures. However, there has been success in utilizing robotic assistance in prostatectomy.[42]

Surgical treatment is often combined with other modalities to improve outcome. To coordinate the appropriate care of the patient, the surgeon must fully understand the indications, risks, and benefits of using systemic and radiologic therapy, especially when the benefits of such modalities have been adequately studied in prospective clinical trials.

Surgery for Metastases

In many cases, patients in whom a single site of metastatic disease has been detected can undergo resection with a reasonable rate of success. Many patients with a limited number of metastases to sites such as the liver, brain, or lung can be cured by surgical resection. For example, published experience indicates that resection of colorectal metastases to the liver should be performed when: (1) the number of liver tumors is fewer than four, (2) extrahepatic tumor is not demonstrable, and (3) a tumor-free margin of at least 10 mm can be obtained. The 5-year survival rate is 30% to 40% when all of these criteria are met.[45] The current management of metastatic colorectal cancer is a good example of a more aggressive approach to recurrent disease where ablative procedures added to metastectomy have greatly extended the options (see Chapter 81). Resection of pulmonary metastases in patients with soft-tissue and bony sarcomas can cure as many as 30% of patients. The surgeon must consider several elements before undertaking surgery for metastatic disease. These include tumor histology; disease-free interval; tumor-doubling time; and the location, size, and extent of disease.

Surgery for Debulking

The results of experimental studies suggest that cytoreduction, or debulking of recurrent cancer, has important potential benefits. In the laboratory setting, reduction of the tumor increases the sensitivity of the remaining tumor to chemotherapy and radiation therapy by increasing the proportion of proliferating tumor cells, decreasing the number of therapeutic cycles necessary to eradicate the tumor, increasing cellular distribution of oxygen and nutrient within the tumor, and reducing the likelihood that resistant clones will develop.[46]

Evidence of human clinical benefit seems to be more limited. The benefits of cytoreduction are most dramatic when accompanied by effective chemotherapy or radiation; therefore, the value of cytoreduction has been acknowledged in pediatric solid tumors, lymphoma, and carcinoma of the ovary. Widespread application of cytoreduction, either alone or combined with other treatment modalities, lacks firm clinical support for common carcinomas.

Radiofrequency ablation (RFA) has also been used to some effect for debulking in patients with liver metastases, meeting selection criteria, of primary colorectal, breast and neuroendocrine tumors. Patients treated with RFA had longer median survival times than patients undergoing chemotherapy for the metastases.[47] Among primary tumors the use of RFA appears promising in hepatocellular carcinoma, renal cell carcinoma, and pulmonary neoplasia.[47]

Palliative Surgery

Palliative surgery is undertaken to relieve symptoms in the absence of cure. It is specifically designed to improve quality of life and must be undertaken with this in mind. Examples of palliative surgery include relief of intestinal obstruction, removal of tumors to control pain or hemorrhage, and introduction of a feeding jejunostomy to permit adequate nutrition.

Reconstructive and Rehabilitative Surgery

Quality of life is an important consideration in the care of the patient with cancer. The cancer surgeon has the unique responsibility to attend to the patient's cosmetic as well as curative surgical needs. Breast reconstruction after mastectomy, transfer of tissue after head and neck surgery, and lysis of contractures or muscle transposition to restore muscular function after radiation therapy are examples of techniques that offer the patient with cancer a higher degree of comfort and improved quality of life. Today, it is essential that the reconstructive surgeon be involved with the multispeciality team in planning the course of treatment so as to optimize reconstructive outcomes.

Vascular Access

Placement of short-term and long-term indwelling central venous catheters has become a common surgical procedure performed on cancer patients. These catheters provide venous access for chemotherapeutic infusion and withdrawal of blood. Several important developments in implantation technique and catheter design have decreased operative time and rendered this an almost exclusively outpatient procedure (see Chapter 52).

Surgery for Oncologic Emergencies

The patient with cancer presents a unique surgical risk. These patients are often neutropenic and thrombocytopenic, and have a high risk of hemorrhage and sepsis. The most common emergencies involve hemorrhage, perforation, intestinal obstruction, infection, or vital organ failure (see Chapter 53). When presented with an oncologic surgical emergency, the cancer surgeon must carefully assess the situation.

FUTURE DIRECTIONS

As evidenced throughout the preceding discussion, the role of the surgeon in the management of cancer, and therefore that of the

surgical oncologist, has continued to evolve and grow. Advances in cancer management demand an increasing supply of surgical oncology specialists who can fulfill a wide variety of functions in the rapidly changing environment of cancer care. The scope of these advances requires knowledge across several disciplines and an increased understanding of basic science, especially as it relates to the molecular and cellular processes of cancer development and metastases, and genetics. The completion of the Human Genome Project marked the start of a new era of molecular medicine. Already there are cancers that have been characterized by specific genetic defects, and patients characterized in terms of response to treatment by specific genetic variations. Such knowledge is being used to design highly specific and individual therapy. Greater understanding of the tumor microenvironment as well as the role that tumor stem cells might play in the initiation, metastasis, and recurrence of cancer has the potential to transform the treatment landscape even further.

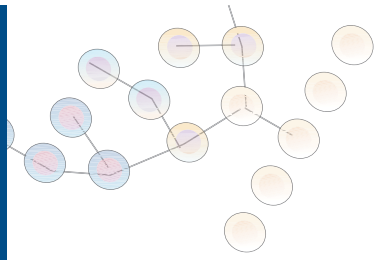
For the cancer surgeon there will be a greater requirement to work in a multidisciplinary fashion in patient care. The cancer surgeon will need to play an increasing role in risk assessment, management of genetic screening, and cancer prevention. As a result, cancer surgeons must be well trained in the fundamentals of cancer biology, pharmacogenetics, and genetics. The cancer surgeon must possess experience and skills in the design and management of clinical trials, monitoring of adverse events, and statistical evaluation of endpoints. The types of cancer operations and the scope of surgical resection may also change as molecular techniques enhance oncologic treatment.[48]

The French philosopher Albert Camus said, "Real generosity toward the future lies in giving all to the present." Care of the patient with cancer is a complex process that requires devotion to the principle that each patient must be provided with the best treatment possible. Surgical oncology is a specialized core body of knowledge that is used to evaluate the best treatment and management options for each patient. The surgical oncologist attends to the future by providing leadership in education and research and forming meaningful partnerships with other oncologic disciplines to continue to provide the best possible patient care.

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29 Basics of Radiation Therapy

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SUMMARY OF KEY POINTS

Historical Perspective
- X-rays were discovered by Wilhelm Conrad Roentgen in 1895.
- Radioactivity was discovered and named by Henri Becquerel, Marie Curie, and Pierre Curie.
- Over the past 3 decades, major advances have been made in conformal external beam radiation therapy, brachytherapy, stereotactic irradiation, proton therapy, systemic targeted radionuclide therapy, and chemoradiation treatments.

Radiation Oncology Physics
- Several different types of ionizing radiation are used to treat patients; most cause low linear energy transfer (LET).
- Therapeutic x-rays (photons) and γ-rays are produced by linear accelerators or by radioactive decay.
- Radiation interacts with matter via several processes, of which the most important in clinical radiation therapy is Compton scatter.
- Megavoltage photons from linear accelerators have a skin-sparing effect, with the maximum dose deposited at depth.

Biological Effects of Radiation
- Direct and indirect damage to DNA in cells, particularly double-strand breaks, is believed to be the dominant form of radiation-induced cell kill.
- Irradiation causes diverse cellular responses that induce molecular mechanisms for DNA damage repair, cell cycle arrest, and cell death.
- The most commonly applied model of cell survival probability is the linear quadratic model, which uses α/β ratios to describe the surviving fractions.
- Cells may repair sublethal and potentially lethal damage after exposure to radiation.
- The radiosensitivity of cells changes as they progress through different stages of the cell cycle; cells are most radiosensitive in G2 and M phases.
- The response of cells to radiation is highly oxygen dependent, an effect expressed by the oxygen enhancement ratio (OER).
- Radiosensitizers, particularly systemic cytotoxic chemotherapy, aim to improve the therapeutic ratio by enhancement of tumor cell killing relative to normal tissues.

Clinical Application of Radiobiologic Principles
- Fractionation of radiation and altered fractionation schedules, such as accelerated hyperfractionated radiation therapy, make use of differences in the responses of normal and malignant tissues to irradiation in order to achieve higher therapeutic ratios.
- Radiation has varied effects on normal tissues, ranging from early effects such as skin erythema to late effects such as carcinogenesis.

Process in Radiation Treatment
- Process in treatment planning and quality control is essential to the safe and effective delivery of clinical radiation therapy.
- Three-dimensional conformal treatment planning and delivery has permitted escalation of dose and improved sparing of normal tissues.
- Radiation therapy is used in more than half of all patients with cancer, either as an adjuvant or neoadjuvant treatment in combination with surgery, as a definitive treatment alone or in combination with chemotherapy, as an organ-sparing therapy, or to palliate symptoms.

New Modalities in Radiation
- Brachytherapy delivers extremely high-dose radiation to tumor tissue with a much lower dose to surrounding normal tissues.
- Systemic targeted radionuclide therapy has been a significant advance in the treatment of hematologic malignancies and is being investigated for the treatment of solid cancers.
- Intensity-modulated radiation therapy (IMRT) uses multiple radiation beam intensities to try to improve the therapeutic ratio.
- Proton therapy has radiobiologic advantages over photon therapy, and it may be used to deliver high doses of radiation to tumors in close proximity to normal structures.

HISTORICAL PERSPECTIVE

In the closing years of the nineteenth century, many physicists were investigating the nature of electricity. It was known that if an electrical potential was placed across two separated platinum electrodes, a spark would leap between them. The British physicist William Crookes demonstrated that if the two electrodes were placed within a glass vessel that was then evacuated, as the vacuum increased the spark would at first be replaced by a glow that filled the whole vessel. As the vacuum was increased still further, a dark space would appear at the cathode electrode and would expand as the vacuum dropped until it filled the whole tube. The walls of the vessel would then begin to fluoresce. On November 8, 1895, while passing electricity through a high-vacuum Crookes tube, Wilhelm Conrad Roentgen noted the fluorescence of a nearby piece of paper painted with barium platinocyanide. Because he had wrapped the Crookes tube in heavy opaque

paper before beginning the experiment, he realized that this fluorescence of the paper could have been caused by a new, invisible type of ray that the tube was now emitting that was affecting both the shielded walls of the tube and the nearby piece of paper. Hence, the "x-ray" was discovered.[1]

Roentgen proceeded to study the intensity and the attenuation of x-rays. He proposed the inverse square law to describe the loss of intensity of the x-rays with the inverse square of the distance between the tube and the plate.[2] He also noted that he could see the shadow of the bones in his hand when it was placed between the Crookes tube and the fluorescent paper. This led to the first human x-ray film on December 22, 1895, when Roentgen placed his wife's hand between the x-ray tube and a photographic plate (Fig. 29-1).[2] Because the x-ray tube was a simple apparatus to replicate, many experiments using x-rays took place worldwide within a short time. This widespread experimentation resulted in rapid advances in the new field, particularly for diagnostic purposes in hospitals.

"Radioactivity" was discovered within a few years of the production of the first x-rays. As the Crookes tubes produced x-rays, the walls of the tube would fluoresce. Other substances were also known to fluoresce spontaneously, and it was thought that these substances might also produce x-rays. This possibility was investigated by Henri Becquerel,[3] who observed the darkening of photographic plates by uranium salts. From this phenomenon, he concluded that x-rays were emitted spontaneously and continuously from the salts. He reported the results of his experiments with uranium to Pierre and Marie Curie, who coined the term *radioactivity* to describe it. They set out to isolate in purer form the radioactive substances within uranium salts, and they reported the discovery of radium in 1898.[4]

The biologic effects of ionizing radiation were recognized very early. Unfortunately, scientists and other workers performing early radiation experiments experienced significant toxic effects. Initially, these side effects were primarily erythema of the skin from exposure to x-rays; the carcinogenic properties of x-rays became evident in later years. For example, Pierre Curie performed an experiment on himself in which he noted skin radiation changes and epilation after exposure to radium for only a few hours.[5] Reading of this, Alexander Graham Bell wrote to a colleague suggesting that if radium "sealed up in fine glass tube" were inserted "into the very heart" of a cancer, it might cause the tumor to regress.[6] Around this time, physicians at St. Louis Hospital in Paris began using radiation to treat patients with cancer. The first reported cure with radiation involved a patient with basal cell epithelioma in 1899.[7]



Figure 29-1 • First radiograph of his wife's hand, exposed by W.C. Roentgen on December 22, 1895.

Hope that further cures for cancer lay in radiation therapy was soon replaced by skepticism when recurrences and toxicities were noted. The early treatments often involved very large single exposures aimed at the complete eradication of tumors. These large exposures, together with the fact that the first x-ray machines were capable of producing only low-energy x-rays with poor tissue penetration, resulted in extensive skin toxicities and other complications. Therefore, only superficial sites were treated by the direct application of radium, with impressive results.[8] Eventually, physicians started to insert radium directly into deep-seated tumors, in the first forms of brachytherapy. Cervical cancer was treated using this method, with dramatic responses.[9] In fact, external beam radiation therapy might have been abandoned had it not been for the work of Claude Regaud and Henri Coutard, who used smaller doses of radiation in several treatments delivered over several weeks to overcome the acute toxicity induced by a large single fraction of radiation therapy.[10] Based on these pioneering studies, radiation oncology became a recognized medical field in 1922, when Coutard and Hautant reported that advanced laryngeal cancer could be cured without severe toxicities using fractionated treatments.[11] By 1934, Coutard had developed a fractionation scheme that remains the basis of radiation fractionation today.

In parallel with advances in the delivery of treatment, advances in measurements were achieved when the *skin erythema dose* (the dose of x-rays required to cause a light skin reaction) was replaced by a unit called the *roentgen* in 1928.[12] The roentgen, which was roughly the exposure received by placing 1 gram of radium at a distance of 1 yard for 1 hour, expressed the radiation exposure and allowed reproducible measurement and standardization of treatment dosages in different departments. It was calibrated by measurement of the ionization of air using ionization chambers. When higher-energy beams were developed, the size of the ionization chamber necessary to measure their effect became impossibly large, and the roentgen was replaced by a new unit, the *rad* (an abbreviation for *r*adiation *a*bsorbed *d*ose). The rad was a measure of the energy deposited per unit mass by all types of ionizing radiation. Biologic effects in tissue exposed to ionizing radiation depend on the energy deposited in the tissue rather than the amount of ionization that the radiation produces in air. One rad was defined as the deposition of 100 ergs per gram of absorbing material. As a general rule, the absorbed dose in soft tissue from 1 roentgen of intermediate-energy x-rays or gamma rays was roughly equivalent to 1 rad. With metric conversion to standard SI (Système International), the rad was replaced by the gray (Gy), a unit named after the British radiobiologist L.H. Gray. One gray is equal to 1 joule of energy absorbed per kilogram of mass. Energy absorbed is dependent on the material used; the material used for radiation therapy definitions is water. For materials with significantly higher atomic numbers than water (e.g., bone), the ratio of mass energy absorption coefficient depends on the energy of the radiation (see later section on Interactions of X-Rays with Matter). Clinical doses often are communicated as centiGray (cGy), equivalent to the older term 1 rad (i.e., 1 G = 100 rad = 1 joule/kg).

RADIATION ONCOLOGY PHYSICS

To understand the role of radiation therapy in curing and palliating disease, a full understanding of the particles and processes involved in the production and delivery of radiation is required. This section provides an introduction to the physical properties of radiation that are fundamental to the clinical applications of radiation.

Types of Radiation

Electromagnetic radiation is energy that is transmitted at the speed of light through oscillating electric or magnetic fields. A photon has wavelength λ, frequency ν, and energy $E = h\nu$, where h is Planck's constant (6.626×10^{-34} Joule seconds). The electromagnetic spec-

trum ranges from wavelengths of 10^5 m for AM radio waves to 10^{-12} m for x-rays and cosmic rays. Although electromagnetic radiation conventionally is described as waves, it also is valid to describe radiation in terms of photons ("packets of energy"). Because energy varies inversely with wavelength, x-rays have a much greater energy than do radio waves. This higher energy gives x-rays the property of being deeply penetrating, which makes it possible to use them therapeutically to treat internal tumors.

Clinical types of radiation therapy include teletherapy (e.g., treatment from a cobalt-60 source), external beam x-rays (from a linear accelerator), and brachytherapy (using a source of radiation inserted or implanted into the patient). X-rays and gamma rays differ only in terms of their production: gamma rays are produced within the nucleus from natural radioactive decay and x-rays are produced outside of the nucleus. In practice, x-rays are produced by machines such as linear accelerators (see the section on Radiation Production from Linear Accelerators) and gamma rays used in radiation therapy are produced by the decay of radioactive substances. There is no difference in their treatment effects. Radiation sources used in brachytherapy and systemic radionuclide therapy (see the section on Systemic Targeted Radionuclide Therapy) include radioactive nuclei that decay and emit positively charged alpha (α) particles, positively charged beta (β^+) particles, or negatively charged beta (β^-) particles (electrons), which may occur with emission of a gamma ray. Clinically, α and β particles do not penetrate deeply, so gamma rays and x-rays are used in external beam radiation therapy to deposit doses at depth.

X-rays, gamma rays, and electrons are termed *low linear energy transfer (LET) radiation* and must be distinguished from high LET radiation such as alpha particles or fast neutrons. LET is defined as energy transferred per unit track length of radiation, equivalent to how often a type of radiation causes ionizations in the tissue it is traveling through. The x-rays, gamma rays, and electrons commonly used in therapy are low-LET radiation, and are, therefore, sparsely ionizing, producing relatively few ionizations in the paths they travel through in the tissue. This is in contrast to high LET radiation such as neutrons (Fig. 29-2), discussed in more detail in the final section of this chapter.

Radiation Production

Radiation Production by Radioactive Decay

The nucleus contains protons and neutrons that usually have stable configurations. When these configurations are not stable, they undergo spontaneous disintegration to attempt to reach a more stable state. The disintegration of radioactive species is called *radioactive decay*. With these disintegrations, energy is released as a photon (gamma ray), which can be used for radiation therapy. The type of radioactive decay and type of particle emitted depend on the nuclear composition of the radioactive species.

The first radioactive species isolated by the Curies was polonium, with radium discovered shortly thereafter.[5] Since that time, many other radioactive species have been discovered and produced artificially. Today, the main use of radioactive species is in brachytherapy and systemic radionuclide therapy, although cobalt-60 units still are used for teletherapy. Radium was the most important implantation source used for more than 5 decades in the twentieth century. However, many properties of radium make it undesirable as a radioactive source for therapy. During its decay, radium produces radon gas, which is colorless and odorless but highly radioactive. Moreover, radium has a very long *half-life* (the time it takes for a radioactive substance to decay to half of its original strength). These qualities make it a significant hazard in the case of contamination. Hence, more suitable isotopes have replaced radium in clinical applications (Table 29-1). Cesium-137 is widely used for gynecologic brachytherapy implants. It has a lower-energy gamma ray than radium (i.e., it is less penetrating and easier to shield), and it has no gaseous daughter nuclei. Palladium-103, iridium-192, and iodine-125 are used for implantation in the body for brachytherapy treatments (see the section on New Modalities later in this chapter). Many of the isotopes used in brachytherapy emit low-energy gamma rays , resulting in a steep fall-off of dose for the surrounding normal tissues and posing no significant risk of radiation exposure for people in the patient's environment. Other isotopes such as strontium-90 or yttrium-90 emit β^- particles (electrons). The advantage of this type of radiation is that it deposits a dose very superficially, for example sparing the outer layers of the walls of arteries during intravascular brachytherapy.

Historically, cobalt-60 is a very important radioisotope because of its use in teletherapy. Cobalt machines were the first practical megavoltage machines, pioneered by the Canadian physicist H.E. Johns.[13] The radioactive decay of cobalt-60 releases gamma rays with energy of approximately 1.2 megavolts (MeV). Because the depth of penetration in tissue increases with increasing x-ray energy, this development allowed the delivery of higher doses of radiation therapy without having to limit the dose due to skin toxicity. This advance drove attempts to generate high-energy x-rays. For example, in the 1930s, St. Bartholomew's Hospital in London had a machine that produced

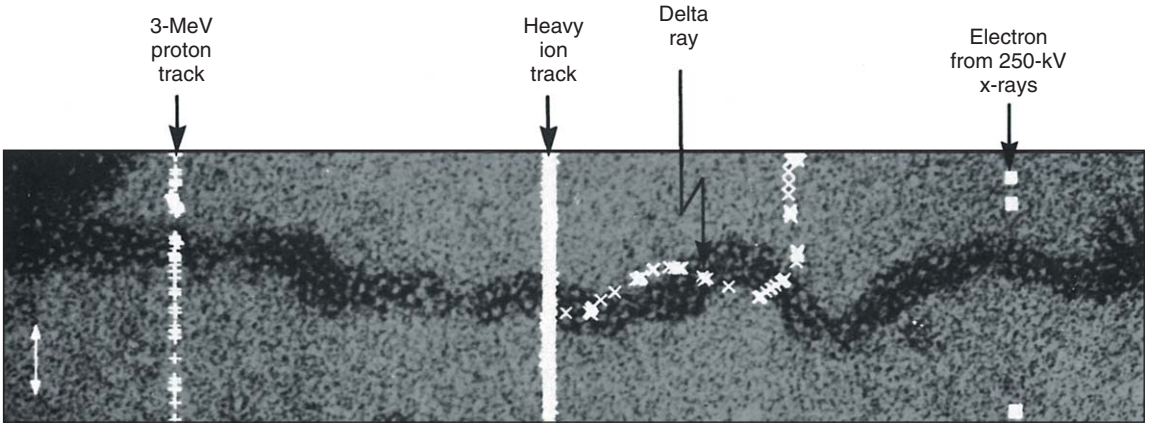


Figure 29-2 • Computer simulations of sections of charged-particle tracks produced by different types of radiation passing through a strand of chromatin. Each cross represents a single ionization of either the chromatin or the surrounding medium. *Right track*, low-linear-energy transfer (LET) 100 keV electron, typical of those produced by 250-kV x-rays. *Center track*, high-LET, high-energy iron ion that produces a dense column of ionization. Note the high-energy secondary delta ray coming out of the track. *Left track*, medium LET 3 MeV proton. The scale bar represents 50 nm. (From Cox JD, Ang KK [eds]: Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 44.)

Table 29-1 Therapeutic Isotopes

Isotope	Half-life Average	Energy (keV)
Photon		
^{226}Ra	1620 y	830
^{137}Cs	30 y	662
^{198}Au	2.7 d	412
^{192}Ir	73.8 d	370
^{125}I	60 d	28
^{103}Pd	16.97 d	21
Isotope	**Half-life**	**Maximum Energy (keV)**
Beta		
^{32}P	14.3 d	1710
^{90}Sr/^{90}Y	28.5 y/2.7 d	550/2280
^{188}W/^{188}Re	69.4 d/17 h	350/2120
^{186}Re	3.8 d	1070
^{62}Zn/^{62}Cu	9.3 h/9.7 min	660/2930
^{133}Xe	5.2 d	360
^{131}I	8.0 d	600
^{89}Sr	50.5 d	1495
^{166}Ho	26.8 h	1850

keV, kiloelectron volt.

From Cox JD, Ang KK (eds): Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 6.

1-MeV rays using an x-ray tube 30 feet long. These machines, however, had low output and small field sizes and were mechanically unreliable. Cobalt 60 machines were simple in design and highly reliable, so they revolutionized the practice of radiation therapy and were used for decades. Their skin-sparing effect made it possible, for the first time, to administer safely the doses of radiation required for treatment without the desquamating skin toxicity that had been the hallmark of kilovoltage radiation therapy. Over the past 3 decades, cobalt machines in the United States have been replaced largely by modern linear accelerators, which have the advantages of producing more sharply defined beams of a variety of different energies and the ability to deliver electrons or x-rays for therapeutic purposes. Linear accelerators also can be used with devices such as computer-controlled multileaf collimators, allowing dose delivery with much greater precision (see the section on Radiation Production from Linear Accelerators). Today, cobalt 60 is used primarily for palliative teletherapy or for stereotactic teletherapy to small malignant lesions in the brain and benign lesions such as acoustic neuromas or arteriovenous malformations. For *sterotactic radiation therapy* or *radiosurgery*, more than 200 narrow beams of gamma rays from a source such as cobalt 60 may be focused on one point, allowing tightly conformed doses of radiation therapy to be delivered as a single fraction or as multiple fractions. Alternatively, a linear accelerator may be used for x-ray production. The treatment requires extremely accurate immobilization of the patient, usually with a head frame or special mask. Lesions must meet stringent criteria to be considered amenable for stereotactic radiation therapy.[14]

Radiation Production from Linear Accelerators

Two processes can produce x-rays when electrons are directed at target atoms. The electrons can ionize the atoms by depositing sufficient energy so that an inner shell electron is ejected. The vacancy in the inner shell is filled by an electron from an outer shell, with the release of a photon called a *characteristic x-ray*. An alternative way of producing x-rays involves the interaction of an electron with the electromagnetic field of a nucleus. This interaction decelerates the electron, with the conservation of energy leading to the production of "bremsstrahlung" (braking energy) x-rays.

Although some centers continue to deliver external beam radiation therapy to skin cancers using a vacuum tube producing x-rays with a maximum energy of about 300 keV, most centers use linear accelerators for general radiation therapy. Modern linear accelerators (Figs. 29-3 and 29-4) use microwaves (with a frequency of ~3000 MHz) to accelerate electrons to very high energies. These electrons strike a target (usually tungsten) to produce a beam of x-rays, mainly by bremsstrahlung effects. The x-ray beam is "flattened" with a filter, so that the beam is uniform, and shaped with the collimators so that the field size is appropriate.

Another type of radiation therapy produced by linear accelerators is the electron beam. To produce an electron beam with a linear accelerator, the electrons strike a thin scattering foil that spreads out the electron beam to an area large enough to be used for treatment. Electrons are used to treat areas of superficial depth, for example, as definitive treatment of skin cancer or as a boost to the tumor bed of breast cancer.

Interaction of X-rays with Matter

X-rays can interact with matter via several different processes. The probability of each interaction type depends on the composition of the matter and the energy of the x-rays. These interactions cause some photons (x-rays) to be removed from the forward-moving x-ray beam, causing an effect called *attenuation*, which, in basic terms, is the loss of intensity and subsequent decrease in the deposition of dose as the beam reaches greater depths. Five possible interactions of x-rays with matter include (1) coherent scattering; (2) the photoelectric effect; (3) Compton scatter; (4) pair production; and (5) photodisintegration. The interactions most relevant to radiation therapy are illustrated in Figure 29-5.

Coherent Scattering

Also called classic scattering, coherent scattering occurs to low-energy x-rays. In coherent scattering, a photon is scattered from an electron, with a resultant change in direction but no change in energy. Only a negligible amount of coherent scattering occurs in therapeutic and diagnostic irradiation. Coherent scattering is important in processes such as x-ray crystallography.

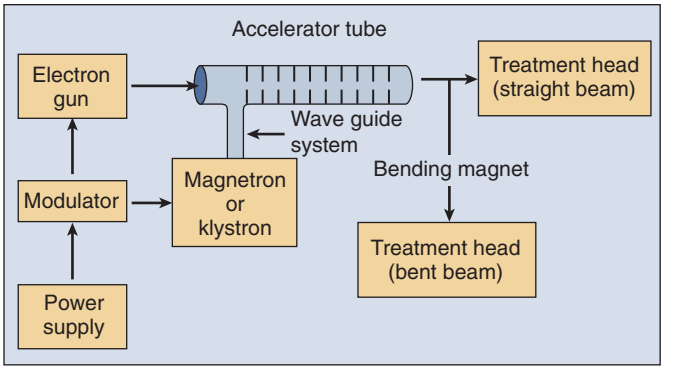


Figure 29-3 • Block diagram representing the mechanism of a typical medical linear accelerator. (From Leibel SA, Phillips TL [eds]: Textbook of Radiation Oncology. Philadelphia, WB Saunders, 1998, p 110.)

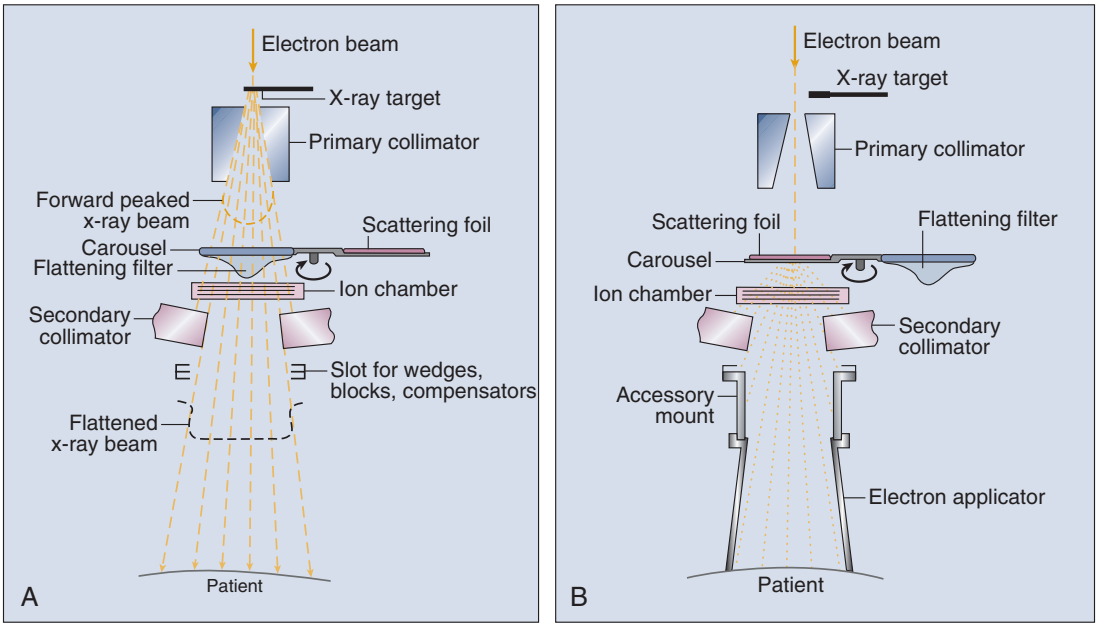


Figure 29-4 • Schematic diagram showing the basic components of the treatment head of a modern linear accelerator. **A,** Components in place for x-ray therapy. **B,** Components in place for electron therapy. (From Leibel SA, Phillips TL [eds]: Textbook of Radiation Oncology. Philadelphia, WB Saunders, 1998, p 100.)

Photoelectric Effect

The photoelectric effect first was described by Albert Einstein, and it was this contribution to physics that led to his Nobel Prize in 1921. In the photoelectric effect, a photon interacts with a tightly bound inner shell electron in the target tissue. Complete absorption of the photon's energy occurs, with the ejection of the electron from the orbit. The probability of a photoelectric interaction is highly dependent on the atomic number (Z) of the material through which the photon is passing. The photoelectric effect is very important in diagnostic radiology; it is the process that is the basis for the radiographic contrast between tissues (e.g., between bone and fat) in plain x-ray films and computed tomography (CT) scanning. With the exception of skin cancer treatment with superficial x-rays, the photoelectric effect is undesirable in radiation therapy. With higher energy x-rays delivered by linear accelerators, the contribution of the photoelectric effect is small to negligible.

Compton Scatter

Compton scatter is the most important interaction for energies within the range generally used for radiation therapy. In Compton scatter, a photon transfers energy to an electron of the target tissue, causing the ejection of this electron. In contrast to the photoelectric effect, however, the energy of the photon is not completely absorbed. Instead, it is scattered at an angle relative to the forward direction of the original photon. This secondary photon interacts with tissue again and again, ionizing and depositing dose with each interaction. These interactions and subsequent ionizations are responsible for the biologic effects on tissues during radiation therapy.

In contrast to the photoelectric effect, Compton interactions are less dependent on the atomic number (Z) of the tissue because these interactions tend to be with the loosely bound outer electrons in atoms, where the energy binding the electron to the atom is much less dependent on Z. This results in a fairly even probability of interaction (and, hence, a fairly even deposition of dose) throughout the different biologic tissues with which the x-rays interact in a patient.

Pair Production

Pair production occurs at high energies. It is the interaction of a photon with a nucleus, with the spontaneous disappearance of the photon and the production of an electron and a positron (a positively charged electron). Pair production becomes the predominant effect in biologic tissues at about 25 MeV. Because 25 MeV is above the range that is typically used in therapy, pair production plays only a small role in most cases.

Photodisintegration

At very high energies, x-rays can deposit so much dose into the nucleus of the target tissue that partial disintegration of the nucleus occurs, with emission of neutrons from the nucleus. Although this has little importance in the clinical interactions used in most radiation therapy, the production of neutrons is important when planning shielding around high-energy linear accelerators to protect patients and personnel from unnecessary exposure to radiation.

Deposition of Dose

As an x-ray beam passes through tissue, the region of rapidly increasing dose is known as the *build-up region*. This rapid increase occurs because of forward-moving photons interacting with electrons of the target tissue via the processes described previously. Because these electrons also are propelled forward but have a shorter course than the photons, there is an area at depth at which the number of electrons entering the plane of interaction from superficial interactions is exactly equal to the amount leaving the plane from interactions in that plane. This plane is termed the D_{max}, as it represents the depth of the maximum number of ionization events (Fig. 29-6). Beyond this point, as more interactions between the photon beam and tissue occur, fewer photons are available to travel forward and deposit dose at greater depths. This process is called *attenuation*. How a photon beam is attenuated (i.e., how much dose it deposits at depth) depends on qualities both within the beam and within the target tissue. The most substantial effect on

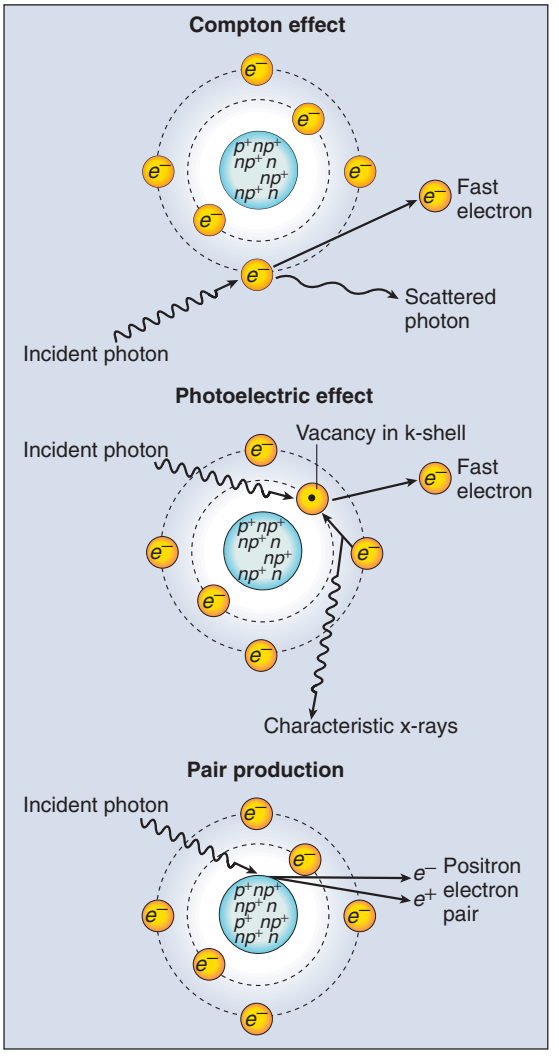


Figure 29-5 • The first step in the absorption of a photon of x-rays or gamma rays is the conversion of the energy of the photon into the kinetic energy of an electron or electron-positron pair. At higher energies, when the energy of the incident photon greatly exceeds the binding energy of the bound electrons in the atoms of the absorber, Compton scatter dominates. Part of the photon energy is given to the electron as kinetic energy, whereas the photon is deflected and has reduced energy.

At lower energies, when the binding energy of the bound electrons of the atoms of the absorber is not small compared to the photon energy, the photoelectric effect is most important. The photon disappears completely as it interacts with a bound electron. The electron is ejected with kinetic energy equal to the photon energy, less the energy required to overcome the electron bond. The vacancy caused by the removal of the electron must be filled by an electron dropping from an outer orbit, giving rise to a photon of characteristic radiation.

At sufficiently high photon energies, the photon might interact with the powerful nuclear forces to produce an electron-positron pair. The first 1.02 MeV of photon energy is used to create the rest mass of the pair, and the remainder is distributed equally between them as kinetic energy. (From Cox JD, Ang KK [eds]: Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 5.)

depth dose from the photon beam itself is the beam's energy (Fig. 29-7).

Linear accelerators typically produce beam energies ranging from 4 to 18 MeV, and the dose deposited at depth increases with beam energy. Therefore, an 18-MeV beam would show more skin sparing and it would have a higher D_{max} than a 4-MeV beam. The depth dose is also affected by the size of the field of radiation used to treat the patient. With a larger field size, there is greater scattering of photons within the field during the interactions with electrons. This scatter effect leads to more interactions, which translates into a higher deposition of dose at depth. In other words, a dose given at a 10-cm depth from a photon beam that has a field size of 20 cm × 20 cm would be higher than the same photon beam with a field size of 5 cm × 5 cm. Many other factors go into the calculation of dose delivered at varying depths in a patient, including scatter from the collimators in the machine, blocks to shield normal tissue, and wedges and compensators (which are used to shape the photon beam). Another main modifier in the target tissue that affects dose at depth is the density of the tissue being treated. Lung, for example, because it is less dense than soft tissue, allows more photon transmission. Additionally, the inverse square law must be taken into account, particularly with

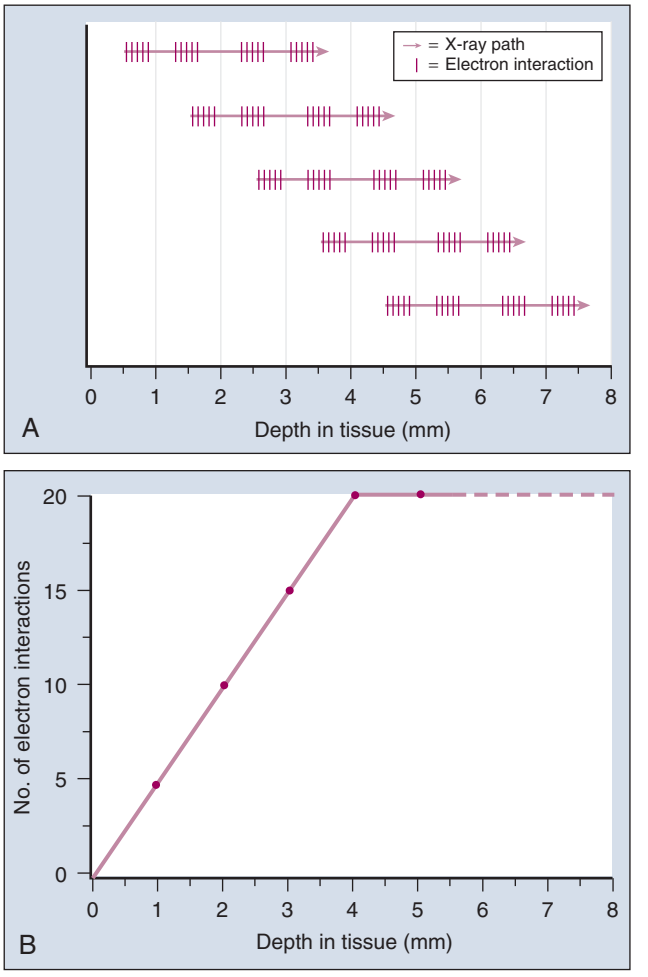


Figure 29-6 • **A,** Simplified explanation of the phenomenon behind skin sparing. Assume that x-rays interact with tissue and liberate electrons that can have subsequent ionizations along their tracks. In this example, the electrons have a range of 4 mm and an average of five interactions (*red lines*) for each millimeter of tissue traversed. **B,** We can then count the number of electron interactions and plot them on a graph. Note that the number of interactions increases with each millimeter of tissue until 4 mm of depth, where the number of interactions (20 in this case) reaches a maximum. If there were no attenuation of beam by tissue, this maximum number of interactions would continue to be observed at all depths. In reality, the intensity of the beam is attenuated by the tissue and, after the point of maximum dose, the number of interactions at greater depths will begin to decrease. (From Lichter AS: Radiation therapy. In Abeloff M [ed]: Clinical Oncology, 2nd ed. London, Churchill Livingstone, 2000, pp 423–470.)

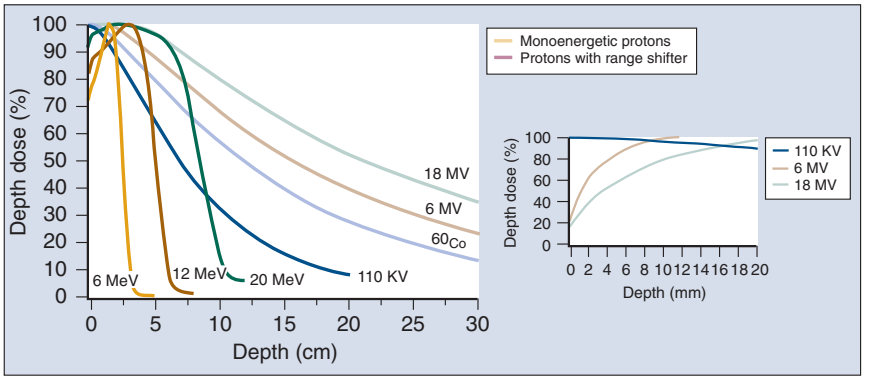


Figure 29-7 • Percentage depth-dose curves for a variety of radiation types used in clinical radiation therapy. These include x-rays and γ-rays (110 kV to 18 MV) and various energies of electrons (6 MeV to 20 MeV). The inset shows the pattern of absorption at shallow depths and provides an illustration of the skin-sparing effect of photons.

regard to the distance from the source to the skin. All of these factors must be taken into consideration when determining the dose being delivered to structures within the patient.

Electrons differ from photons in that electrons travel only a relatively short distance within tissue. They are very light particles compared with the nuclei of the target tissue with which they interact. Hence, they lose a large fraction of their energy as they travel through tissue, leading to much less skin sparing and the deposition of the majority of the dose superficially. Consequently, they are very useful for treatments in which the target of the radiation lies close to the surface of the patient, such as skin cancer, or close to the source of the electrons, such as brachytherapy implants.

BIOLOGIC EFFECTS OF RADIATION

Basic understanding of the physical properties of a radiation beam must be coupled with an understanding of how radiation interacts with biologic tissues to cause damage. Through the interaction processes described earlier, radiation deposits energy as it travels through a patient. These interactions set secondary electrons in motion that go on to produce further ionizations. This ultimately results in the breaking of chemical bonds and damage to molecules and structures within cells. If these broken bonds and subsequent damage occur to cells' critical structures, the most significant effect of the accumulation of radiation damage will be cell killing.

This section describes the complexities of this process. It should be noted that the deposition of radiation dose and the damage it induces are random, and its complexity depends on the type of radiation and the tissue being irradiated.

Interactions with Biologic Materials

Cellular kill occurs when critical targets within the cell are damaged by radiation and the cell is unable to repair that damage. Therefore, a radiation dose deposited near critical structures is statistically more likely to incur a biologic effect. A number of biologic molecules or structures are potential targets for radiation damage, and lively debate continues within the field as to whether there are multiple targets within the cell. Many circumstantial data indicate that DNA is a critical target for the biologic effects of radiation. Measurement of DNA damage after radiation closely correlates with cell lethality.[15,16] Cells that are inhibited from repairing DNA damage or that are naturally deficient in DNA repair enzymes show a distinct radiosensitivity.[17,18] Also, experiments in which the nucleus was irradiated selectively show that radiation caused cell death at a higher rate than did radiation of the cytoplasm.[19]

DNA damage can be termed direct or indirect (Fig. 29-8). If radiation is absorbed by the DNA itself, the atoms of the DNA can become ionized and damaged. This is termed the *direct effect* of radiation. Because the width of DNA is 1 to 4 nm, and there is relatively little DNA in the cell, direct damage must be a relatively rare event.[20] More commonly, water molecules surrounding the DNA are ionized by the radiation. The ionization of water creates hydroxyl radicals, hydrogen peroxide, hydrated electrons, and other oxygen free radicals,[21] all of which are highly reactive, capable of interacting with DNA and causing damage. This is termed *indirect damage*. Eighty percent of a cell is composed of water, suggesting that indirect damage to DNA is common.

Direct and indirect damage can break bonds in DNA. These broken bonds can result in the loss of a base or of the entire nucleotide, or in complete breakage of one or both of the strands of DNA. Single-strand breaks are repaired relatively easily using the opposite strand as a template. Therefore, single-strand breaks are not strongly related to cell killing, though they might result in mutation if the repair fidelity is not high. Chromosomal aberrations such as nondisjunctions and micronuclei are detectable in surviving irradiated cells, which may contribute to the clonal evolution of cancer. Double-strand breaks, on the other hand, are thought to be the most important lesion in determining cell kill.[22] In double-strand breaks, the chromatin is snapped into two pieces. It has been taught traditionally

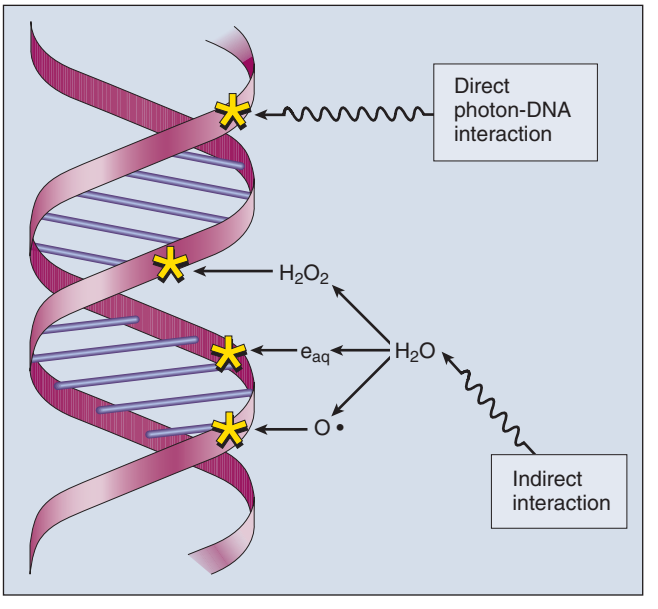


Figure 29-8 • Two types of interactions are possible between x-rays and DNA. In the direct interaction, an x-ray interacts with the DNA molecule itself. This interaction is relatively rare. In the indirect interaction, x-rays ionize water, and the reactive species that are created interact secondarily with DNA, causing damage and DNA strand breakage. (From Lichter AS: Radiation therapy. In Abeloff M [ed]: Clinical Oncology, 2nd ed. London, Churchill Livingstone, 2000, pp 423–470.)

that in an average cell, 1 Gy of low LET radiation causes damage to over 1000 bases in DNA, approximately 1000 single-strand breaks in DNA, and approximately 40 double-strand breaks. Because x-rays are sparsely ionizing, there can be random stochastic processes in regions within the cell where ionization events are much more densely clustered than in other areas. The free radicals produced also are thought to be clustered in discrete areas. Therefore, the multiple broken bonds and resultant DNA damage that occurs could be highly localized. The term *locally multiply damaged site*, or the *cluster hypothesis*, refers to this phenomenon, since they both suggest that it is these clustered regions of DNA damage that lead to clinically significant effects.[23,24]

Most investigators believe that the dominant form of lethal radiation-induced DNA damage is the double-strand break, which ultimately results in cell death if the cell is unable to repair the damage. Cells respond to double-strand DNA damage by invoking mechanisms that sense the damage and mechanisms that actually bring about repair. The earliest detectable event after exposure to ionizing radiation appears to be the phosphorylation of histone H2AX (i.e., the formation of "gamma-H2AX"), a reaction dependent on the ataxia telangiectasia mutated (ATM) protein.[25,26] Major factors that subsequently determine cellular fate include checkpoint proteins (such as ATM, ATR, CHK1, CHK2 and DNA-PK), cofactors and modulating factors that influence *p53* activation, and the success of DNA damage repair (Fig. 29-9).[27]

Two main modes by which cells accomplish repair of double-strand DNA breaks are generally recognized: homologous repair (HR) and repair by non-homologous end joining (NHEJ). In HR, either the undamaged homologous chromosome or the sister chromatid of a replicated chromosome is used as the template to fill in missing DNA sequences in the damaged chromosome. Consequently, HR is most efficient in late S or G2 phase, when the sister chromatids have replicated but not yet separated. The requirement for a template to which the damaged chromosome is matched ensures that HR has great fidelity of repair. Human tumor cells commonly arrest in G2 after double-strand DNA damage, a time when repair activities are detectable. It is, therefore, plausible that irradiation-induced G2 checkpoint delay allows more time for cells to accomplish HR and thereby survive radiation.[28] In contrast to HR, repair by NHEJ is less cell-cycle dependent. In NHEJ, the blunt ends of chromosomes severed by radiation or other agents are directly rejoined. Although repair by NHEJ might, in some ways, be more efficient than by HR, NHEJ lacks fidelity (i.e., it is considered mutagenic) because the template-free rejoining of blunt ends lacks the specificity of HR. In NHEJ, it is possible for the ends of different chromosomes to be rejoined, giving rise to chromosomal aberrations or potentially to the expression of dangerous fusion proteins. It is likely, therefore, that mutagenesis associated with radiation may be due in part to NHEJ.[29]

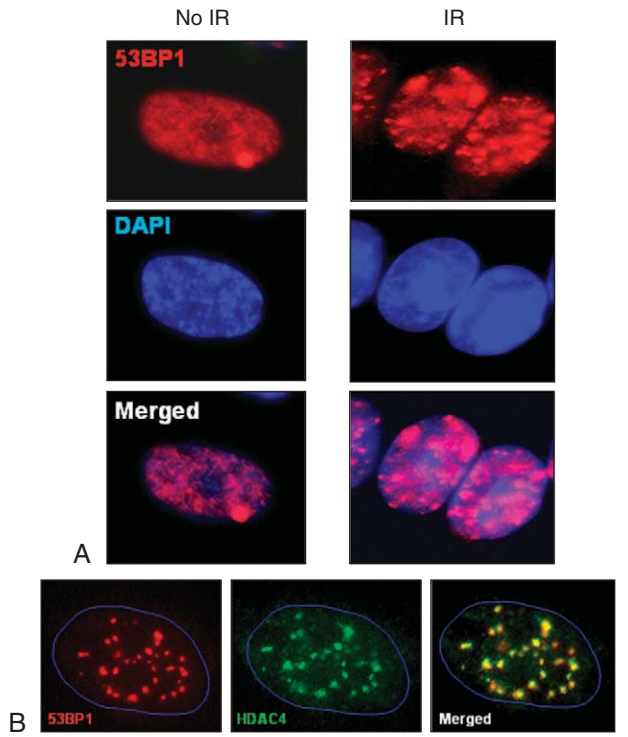


Figure 29-9 • Ionizing radiation induces nuclear 53BP1 foci. B53P1 is a protein that appears to act as a central mediator of several cellular pathways. **A,** 53BP1 protein localizes to nuclear foci at sites of double-strand DNA damage caused by ionizing radiation (IR). **B,** Recruitment of repair and chromatin remodeling factors at IR-induced 53BP1 foci. Bioactive proteins co-localize with 53BP1 at foci, including HDAC4 (shown), BRCA1, and Rad50/NBS. (Used with permission from Gary Kao, MD, PhD, University of Pennsylvania.)

If cells successfully repair DNA damage induced by ionizing radiation, they may resume proliferation. Alternatively, radiation may kill cancer cells by three pathways:

1. Inducing apoptosis by the intrinsic (p53-dependent) or the extrinsic pathway
2. Causing permanent cell cycle arrest or terminal differentiation
3. Inducing "mitotic cell death" from aberrant mitosis, resulting in mitotic catastrophe.

Apoptosis also is known as "programmed cell death." Dependent on the cell type, radiation damage triggers signaling cascades that may involve proteins such as ceramide, p53, MDM2, BAX, PUMA, NOXA, and FAS. The result is self-destruction of the cell. Cells undergoing apoptosis show very characteristic features as they die, including blebbing and fragmentation of the nucleus.[30] Radiation in the doses typically used clinically induce p53-dependent apoptosis in radiation-sensitive organs such as thymocytes and radiosensitive malignancies such as lymphomas, but apoptosis rarely is induced in tumors of epithelial origin.[31] Epithelial tissues and cancers of epithelial origin are more likely to undergo reversible or permanent cell cycle arrest, in which p53 may act as a survival factor for cells, or p53-independent mitotic cell death.[27]

Permanent cell cycle arrest and terminal differentiation also are effective endpoints by which radiation can effect cell kill. Cell cycle perturbations are seen characteristically after radiation exposure and were among the earliest observed biological effects of radiation.[32] Cells can show checkpoints or arrest in any phase of the cell cycle, although the best-described checkpoints with respect to radiation damage are the G1 and G2 checkpoints. Normal cells and cancer cells that retain normal p53 function arrest in the G1 phase of the cell cycle. This is a p53-mediated event.[27] One of the earliest effects seen after radiation damage in cells with normal p53 function is a rise in the intracellular level of p53 due to protein stabilization and decreased protein turnover. This, in turn, leads to an induction of p21, a potent cyclin-dependent kinase inhibitor, leading to blockage of the cells in the G1 phase of the cell cycle.[33] This is only one of the many known functions of p53. It also is involved in the regulation of gene expression, apoptosis, and angiogenesis, among other important cellular processes.[34] The cell cycle arrest induced by p53 often is transient but in some cases can lead the cell to exit the cell cycle permanently and undergo a process that resembles terminal differentiation. The pathways invoked are consequently reminiscent of *cellular senescence*, in which cells have lost the ability to cycle and proliferate.[35]

Many cancer cells, typically those with loss or mutation in the p53 protein pathway, have lost the ability to block in G1. These cells retain the ability to block in the G2 phase of the cell cycle. The G2 block is less well described at the molecular level than the G1 block,

but it also involves effects that regulate the activity of cyclin-dependent kinases that are specific to the G2 phase of the cycle.[34] G2 arrest is clearly related to cellular repair of radiation-induced DNA damage, in that cells that have lost the ability to arrest in G2 are exquisitely sensitive to DNA damage. Even in cells that re-enter the cycle after a G2 block, cell death can be seen subsequently. Such cell death can take several forms. Some cells fail in cytokinesis and form multinucleate giant cells. Some undergo mitotic catastrophe as they attempt to undergo mitosis. Others undergo delayed cell lysis, which, in some cases, may be a delayed form of apoptosis.

Both tumor cells and normal tissues differ in their sensitivity to radiation. In some cases, this is due to differential sensitivity to induction of apoptosis, but in others it is due to molecular mechanisms that are as yet poorly understood. A number of factors have been correlated with radioresistance, such as the presence of hypoxia, which could contribute to the poor prognosis of some tumors. It has been hypothesized that oxygen helps "fix" damage induced by radiation in such a way that the radiation is more lethal to the cancer cells.[36] The specific molecular pathways involved in this phenomenon have not been fully elucidated (see later section on Oxygen Effect).

Most radiobiologists currently think that radiation primarily causes cell death by double-strand DNA damage and that the inability of cancer cells to repair such damage with fidelity results in their death. Although it is clear that cells that lack the ability to repair some forms of DNA damage are extremely sensitive to radiation damage, it is less clear that altered DNA repair capacity contributes to increased resistance to radiation in common cancers.[17] Nevertheless, identifying proteins required to recognize and repair such DNA damage could provide potential targets for sensitizing cells to increase tumor cell kill by radiation.

Other factors that have been implicated in altered cellular sensitivity to radiation include a number of signal transduction pathways, including some that are known to be altered in cancer. For example, EGFR, Ras, and Raf have been implicated in altered cellular sensitivity to radiation, although the molecular mechanisms underlying their effects still are incompletely described.[37–39] Considerable interest also exists as to whether components of the tumor microenvironment might contribute to tumor sensitivity. In particular, persistent production of the cytokine transforming growth factor (TGF)-β1 is an early and consistent finding in tissues exposed to low and high doses of ionizing radiation.[40]

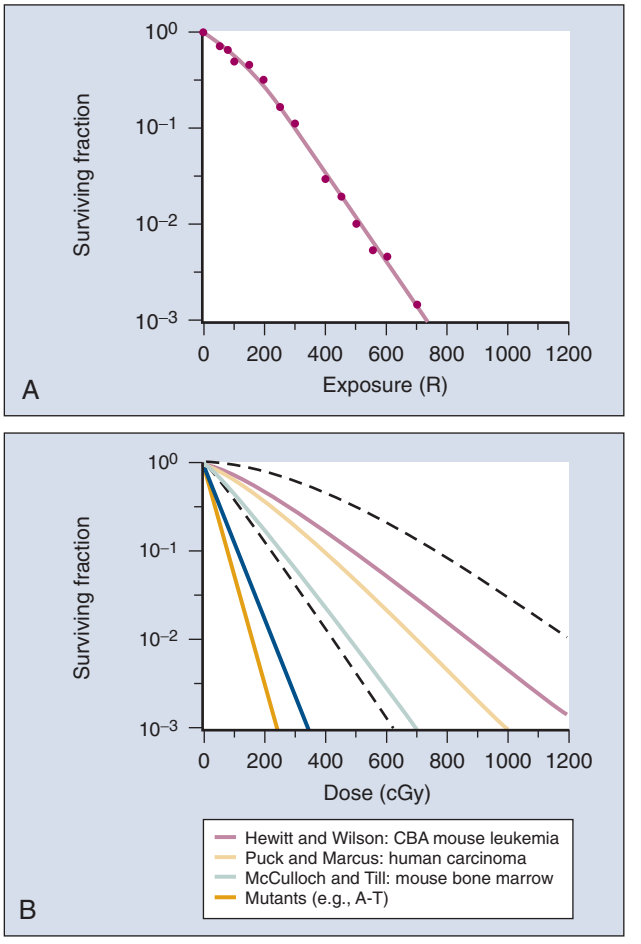


Figure 29-10 • X-ray or gamma ray dose-survival curves for mammalian cells. **A,** The first such curve, reported in 1956 by Puck and Marcus. Note that the dose is expressed in roentgens (R), which, for cells irradiated on the glass, must be multiplied by approximately 1.4 to give the dose in cGy. **B,** A range of survival curves for other mammalian cells. The dashed lines encompass the range for "wild-type" cells of various origins. The steepest curves show a range typical of hypersensitive mutants, such as cells from patients with ataxia-telangiectasia (AT). (From Leibel SA, Phillips TL [eds]: Textbook of Radiation Oncology. Philadelphia, WB Saunders, 1998, p 4.)

Cell Survival Curves

One of the central ideas of radiation biology is that the loss of reproductive integrity in long-term survival assays is important to our understanding of the response of a tumor or a normal tissue to radiation. When cells are exposed to lethal doses of radiation, they might not die immediately or within a few hours of treatment, or even sometimes within a single division of radiation. When cells have been observed by time-lapse cinematophotography after irradiation, it can be seen that some cells survive and go on to form colonies, and some die quickly. Others go through up to several rounds of abortive cell division before finally ceasing to divide and undergoing a variety of possible outcomes that might include terminal differentiation, formation of multinucleate giant cells, mitotic catastrophe, or delayed apoptosis.[41–43] Radiation biologists believe that it is the proportion of cells capable of forming a colony by sustained cell division that most accurately predicts the effects of a dose of radiation. Cell survival curves have been very important in radiation biology to estimate survival of tumor cells within a population with increasing doses of radiation.

The first cell survival curves were demonstrated in the 1950s, when Puck and colleagues[44] plotted the survival of irradiated HeLa tumor cells (Fig. 29-10). HeLa cells were the first continuously cultured human carcinoma strain, named after the patient who donated cervical cancer tissue. Cell survival curves usually are plotted with dose on a semilogarithmic scale. The most striking feature of these curves for low LET radiation is that the effectiveness of killing per unit dose increases with increasing radiation dose. At low doses, the survival curve starts out as a shallow line, with the surviving fraction being an exponential function of dose. At higher doses, the angle of the curve increases, representing more cell kill per increase in unit dose of radiation. Eventually, at higher doses, the curve tends to straighten again. In contrast, high LET radiation cell survival curves on a semilogarithmic plot are straight throughout, albeit with a steeper slope—i.e., survival is an exponential function of dose throughout. Survival curves contrasting low LET and high LET radiation are shown in Figure 29-11.

A number of mathematical models have been devised to attempt to describe the shape of the cell survival curves that are observed experimentally, with an initial shallower slope and eventual bending (the "shoulder") and a final, steeper slope. These include target models, lethal and potentially lethal damage models, and repair saturation models. Some of these have been based on simple mathematical modeling without any real attempt to model known molecular events involved in cell killing, whereas others have been based on

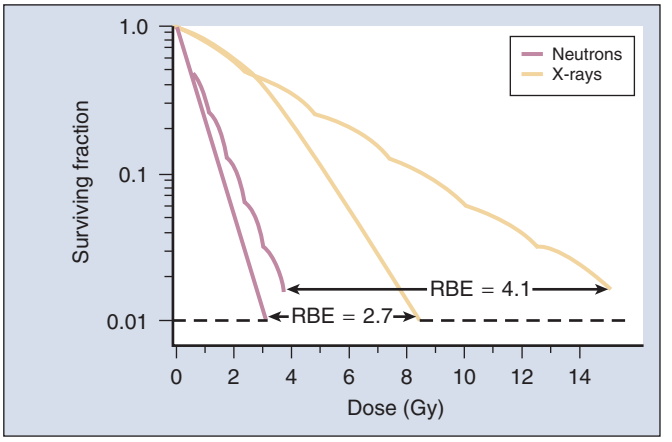


Figure 29-11 • The survival curve for x-rays (low LET radiation) is characterized by a broad initial shoulder, whereas for neutrons (high LET radiation), the survival curve has little or no shoulder. Consequently, the relative biological effectiveness (RBE) gets larger as the dose gets smaller. When a dose is fractionated, the RBE is larger for a given level of cell killing than if the dose is given in a single exposure because the large shoulder of the x-ray dose-response curve is repeated each time. (From Cox JD, Ang KK [eds]: Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 45.)

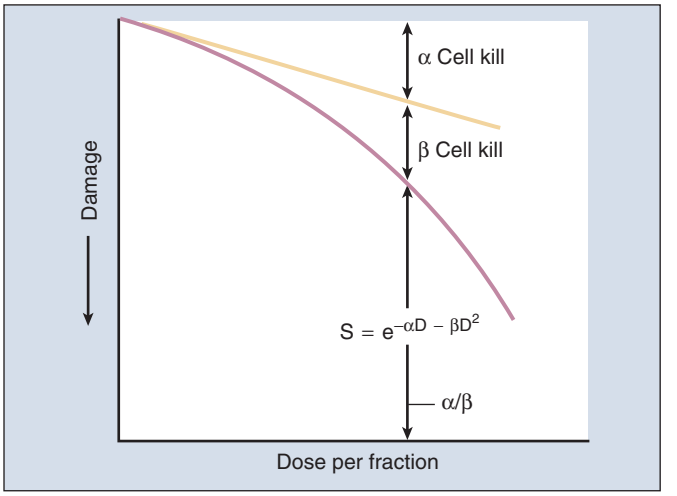


Figure 29-12 • Dose response curves for mammalian cells are adequately fitted by the linear-quadratic relationship, at least over the range of doses of concern in radiation therapy. The form of the equation is

$$S = e^{-\alpha D \beta D^2}$$

where S is the fraction of cells surviving a dose (D), and α and β are constants. Cell killing by the linear and quadratic term are equal when

$$\alpha D = \beta D^2.$$

This occurs when $D = \alpha/\beta$. (From Cox JD, Ang KK [eds]: Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 14.)

attempts to model some of the known molecular events (e.g., chromosome breaks or DNA repair) that are involved in cell killing. All of the models can describe the shape of the survival curve to a first approximation. None do so perfectly, and none take into account all the events and all of the possible mechanisms involved in cell death. For a more detailed discussion of the limitations of each model, the interested reader is referred to one of the textbooks of radiobiology.[45]

One model that has been most influential on clinical practice is the *linear quadratic model*, because it is the model that best fits the behavior of cells after exposure to radiation doses within the range used in the clinic.[46] In their original thesis, Kellerer and Rossi proposed that radiation-induced cell killing resulted from two potential events, one with a linear relation to dose ($\exp[-\alpha D]$) and the other having a quadratic relation to dose ($\exp[-\beta D^2]$). This was expressed mathematically by the "alpha-beta" equation,

$$S = e^{-(\alpha D + \beta D^2)},$$

which was shown to fit most experimentally observed survival curves. S represents survival of a cell population after a dose, D (Fig. 29-12). For many cell types, the linear-quadratic model is useful in describing dose responses for a population of cells.

Derived from this model is the α/β ratio, obtained by manipulating the equation just described. A point on the survival curve can be defined at which the components of cell killing can be seen to be equal to each other—that is, $\alpha D = \beta D^2$, or $D = \alpha/\beta$. In other words, for a cell population there exists a dose of radiation where the linear (α) and quadratic (β) contributions to cell killing are equal. This dose is the dose equal to the ratio of α and β—the α/β ratio. The α/β ratio is specific to a cellular population and reflects the sensitivity of the cell to the two supposed types of damage. By this formulation, tissues that have an early response to radiation (skin, gut epithelium, and tumor cells) have a high α/β ratio. In other words, their survival curves stay straight for a longer period before the bend, with a higher contribution of single-event or α killing. Late-responding tissues such as spinal cord, kidney, and muscle have survival curves that bend earlier, with resultant lower α/β ratios (Table 29-2). These late-responding tissues have "shoulders" on their survival curves within the range of doses commonly used in radiation therapy.

This formulation led to the concept that altered fractionation schedules could be used to exploit this difference and treat tumor populations more effectively (with regard to damage to late-responding tissues, discussed in more detail later). This concept has resulted in several clinical trials of altered fractionation schemes, such as the concomitant boost technique for head and neck cancer and the CHART (continuous hyperfractionated accelerated radiation therapy) regime for lung cancer.[47,48] Altered fractionation schemes are described later in this chapter.

Table 29-2 Ratio of Linear to Quadratic Terms from Multifraction Experiments

Reaction Sites	α : β (Gy)
EARLY REACTIONS	
Skin	9–12
Jejunum	6–10
Colon	10-11
Testis	12–13
Callus	9–10
LATE REACTIONS	
Spinal cord	1.7–4.9
Kidney	1.0–2.4
Lung	2.0–6.3
Bladder	3.1–7.0

From Cox JD, Ang KK (eds): Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 27.

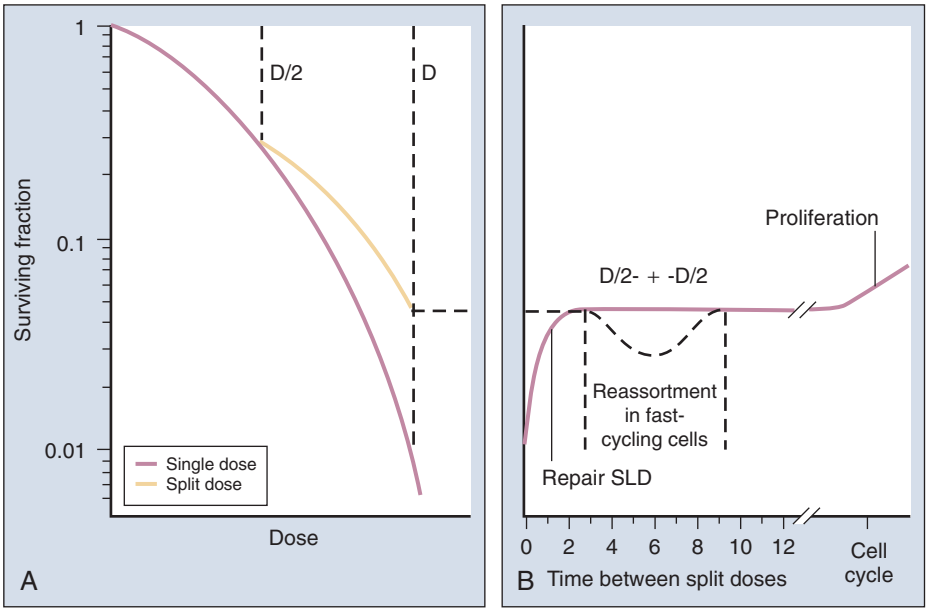


Figure 29-13 • **A,** Increase in cell survival observed when a dose of radiation is delivered in two fractions separated by a time interval adequate for repair of sublethal damage. When the dose is split into two fractions, the shoulder must be expressed each time. **B,** The fraction of cells surviving a split dose increases as the time interval between the two dose fractions increases. As the time interval increases from zero to two hours, the increase in survival results from the repair of sublethal damage. In cells with a long cell cycle, or cells that are out of cycle, cell survival cannot be further increased by separating the dose by more than two or three hours. (From Cox JD, Ang KK [eds]: Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 24.)

Cellular Repair

Cells have complex mechanisms that are responsible for repairing radiation-induced damage. As described earlier, the shoulder on the cell survival curve is thought to relate to the cell's ability to repair DNA damage. One of the clearest demonstrations of the cell's ability to repair radiation damage is a phenomenon called *sublethal damage repair*. It has been observed that two doses of radiation given separated in time are less effective than the sum of the two doses given at the same time. The implication is that in the time interval between the first dose and the second dose, some of the damage from the first dose is repaired. Consistent with this conclusion is that the more closely the two doses are given in time, the more they resemble the effects of a large single dose, implying that repair has measurable kinetics.

Repair of sublethal damage was first reported in 1959 by Elkind and Sutton,[49] who noted that damage caused by radiation did not always produce cell killing and that this sublethal damage became lethal only when the total amount of damage had accumulated to a sufficient level. Since then, sublethal damage has been demonstrated in virtually every biologic system tested, predominantly by split-dose experimentation (Fig. 29-13).[50–52] It is important to remember that a correlation exists between cell kill and the production of asymmetric chromosomal aberrations (e.g., dicentrics and rings) from the interactions of double-strand breaks in the DNA. Therefore, sublethal damage repair can be interpreted as the repair of DNA damage that would have formed double-strand breaks by two separate hits (β killing). Because high LET radiation interacts almost without exception by α killing, sublethal repair is not considered relevant to the radiobiology of particle therapy.

Cellular repair of DNA lesions classified as "sublethal" is evidenced by the existence of the shoulder on the cell survival curve. Cells show increased survival with split-dose radiation because the shoulder of the survival curve must be repeated with every fraction. In other words, the shoulder of the survival curve represents the accumulation and repair of sublethal damage. Cells that have a broad shoulder that starts at low doses, with a resultant shallow initial slope, have a propensity for sublethal repair. These tissues, described as *late-responding tissues with low α/β ratios*, exhibit extensive sublethal repair and are spared preferentially by fractionation (Fig. 29-14).

A second type of cellular recovery after radiation, described in 1966 by Phillips and Tolmach,[53] is *potentially lethal damage repair*. This type represents radiation damage that may or may not lead to the killing of a cell, dependent on the cell's condition and environment in the period following irradiation. The researchers noted that cells that are not proliferating, either because they are out of the cell cycle due to contact inhibition or are being held in poor conditions that do not favor growth, show less killing after irradiation than the same cells did when dividing rapidly under optimal conditions. They postulated that resting cells had more time to repair DNA damage before re-entering the cell cycle than those cells that were dividing actively, thus potentially contributing to resistance to radiation therapy.

The extent of recovery from both sublethal damage and potentially lethal damage has been correlated with the repair of DNA and with the rejoining of chromosomal breaks.[54,55] Both processes increase the survival of a cell population with fractionated radiation schedules.

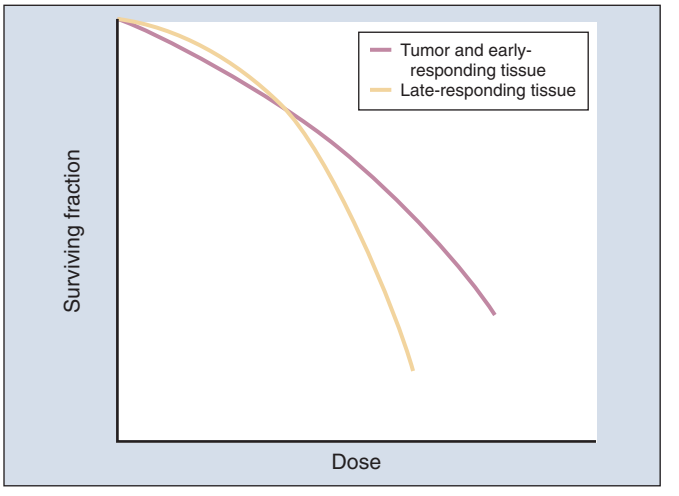


Figure 29-14 • The dose-response relationship for late-responding tissue is "curvier" than for early-responding tissue. The dose at which cell killing is equal by the linear and quadratic components is $\alpha : \beta$. This is about 2 Gy for late-responding tissues and 8 to 10 Gy for early-responding tissues. (From Cox JD, Ang KK [eds]: Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 27.)

This can be manifested clinically either by an increase in normal tissue tolerance or by a decrease in tumor control. The time required for most sublethal/potentially lethal damage repair seems to be approximately 6 hours. If radiation therapy fractions are too closely spaced, unrepaired injury will accumulate between dose fractions, with the result that successive doses become more and more damaging to normal tissues. This factor should be borne in mind when designing fractionated courses of radiation to optimize tumor cell kill.

Dose Rate Effects

There is preferential sparing of late-responding tissues by fractionated radiation therapy due to sublethal damage repair. It should be kept in mind, however, that this sparing is relative to early-responding tissues. In other words, as a radiation dose is split and delivered over more than one treatment, the killing of cells within the tumor also decreases, although not by as much as late-responding tissues. When determining cell survival and toxicity (both early and late) of radiation therapy, other factors are involved. One of the most prominent of these factors is *cell repopulation*. As the total treatment time to deliver a dose of radiation lengthens, cells within a tissue have the ability to replenish, called *repopulation*. During a course of fractionated radiation therapy, the effects of sublethal repair and repopulation lead to diminished cell death with protraction of treatment times.

Dose rate effects can occur due to interfraction repopulation. In studies by Fowler and colleagues[56] using pig skin, it was shown that as overall treatment time was lengthened, additional radiation was required to elicit the same effect. Because both fraction size and fraction number were kept constant, this finding was believed to reflect the contribution of repopulation to the effect of the radiation.

Dose rate effects also have been demonstrated during each fraction of radiation. Bedford and Hall[57] demonstrated that the survival of cells increased as dose rate decreased from 7.3 Gy per minute to 0.1 Gy per hour. There also exists a dose rate below which reproduction of cells can continue despite continued radiation delivery. This threshold varies with tissue type, based on factors such as the sensitivity of the stem cells required to repopulate the cell population, the duration of the cell cycle, and the amount of adaptation that cells can undergo in response to radiation.[58]

The response to radiation injury and the survival of cells exposed to radiation are complex. Obviously, cell kill increases as radiation dose increases. Many other factors also contribute to survival, many of which are still not known. Early-responding tissues such as skin, mucosa, bone marrow, and tumor cells are likely to experience acute toxicities, which occur during the radiation course or within a few weeks thereafter. These tissues have stem cells for repopulation, which mature into functional cells. They exhibit rapid cell turnover from these stem cells. The intensity of the toxicity in these tissues reflects the balance between cell killing and the regeneration of cells from surviving stem cells. This balance depends primarily on accumulation of radiation dose. Larger fraction sizes are a factor in determining the severity of acute toxicities, with larger fraction sizes resulting in higher toxicity than smaller fraction sizes. The dependence on fraction size for acute toxicities is much more pronounced than for late effects. Moreover, dose rate has been shown to correlate with tumor cell kill and hence with the development of acute toxicity. One more very important parameter that corresponds with tumor cell kill and acute toxicity is the overall treatment time. As treatment time is extended, the development of acute toxicities decreases. It also has been demonstrated that long treatment times also reduce the likelihood of cure by virtue of reduced tumor cell kill because of the concept of *accelerated repopulation*, particularly beyond 4 to 6 weeks of treatment.[7]

In contrast to acute toxicities in early-responding tissues, late effects occur in late-responding tissues such as spinal cord, central and peripheral nerve tissue, heart myocytes, and kidney nephrons. Late effects often are of more concern to radiation oncologists than early effects, because they result in irreversible end-organ damage from radiation and, therefore, limit dose. Provided that sufficient time (generally agreed to be more than 6 hours) is allowed between fractions to allow for the complete repair of sublethal damage, classical late effects have no dependence on overall treatment time. An exception occurs if the treatment course is intense enough to cause such severe acute toxicities as to reduce the stem cells of early-responding tissues below a threshold; acute toxicity then can progress to chronic tissue injury, termed *consequential late effects*. Late-responding tissues usually are characterized by slow cellular turnover, with little repopulation during radiation treatments. Therefore, dose rate and overall treatment time play a minor role in the development of late toxicity. As stated previously, these tissues have a low α/β ratio, with the potential for significant sublethal damage repair between fractions. Hence, late-responding tissues are extremely sensitive to changes in dose per fraction.

Cell Cycle Effects

An important aspect of the effect of radiation on cells depends on their progression through different stages of the cell cycle.[59,60] With tumor cells, which have a high growth fraction, modulation of this factor is potentially of great importance. The radiosensitivity of cells changes as the cell progresses through the cell cycle, with cells in late G2 and mitosis being the most sensitive. Cells in mid- to late S phase and early G2 phase are the most resistant to radiation. Moderate sensitivity exists for those cells in late G1 and early S phase, and cells in mid G1 are moderately resistant.

These differences in sensitivity allow for preferential killing of cells in those stages that are sensitive to radiation, with a subsequent relative accumulation of cells in the resistant S phase of the cell cycle. This accumulation translates into relative radioresistance of the remaining cells to additional doses of radiation, if reassortment into other phases of the cell cycle through natural progression of cell division does not occur (Fig. 29-15).

Radiation also disrupts progression through the cell cycle. Doses of radiation cause blocks in the G2- to M-phase transition and in the G1- to S-phase transition. These delays are governed by cell cycle "checkpoint" genes, which are responsive to DNA damage and transmit feedback addressing the readiness of the cell to progress to the next phase of the cell cycle. The radiation-induced G1 block is p53 dependent.[27] Because most tumors in adults are mutant or otherwise deficient in p53, the G2 block might be the more important block in tumor response to radiation. The G2 block is dose dependent, averaging 1 to 2 hours per Gy with increasing doses.[60] The G2 delay also varies in time, depending on where the cell was in its cycle when it was irradiated. The delay is longest for cells irradiated in S and early G2 phase and shortest for cells irradiated in G1 phase.[60]

These variations in sensitivity with cell cycle changes could be related to the propensity of the DNA to be damaged or repaired in the various phases of the cell cycle. In late S and early G2 phases, repair of double-strand breaks by homologous repair is most efficient, compared with the G1 and early S phases (when a homologous chromosome is not available) and late G2 phase (when the chromatin is highly condensed and less accessible to repair).[61] Similarly, DNA is uncoiled at the beginning of the S phase, perhaps leading to increased susceptibility to radiation damage in this phase. The preferential susceptibility with respect to the cell cycle reiterates the importance of splitting the total radiation doses into fractions.

Fractionation

The biologic basis of fractionation in radiation therapy makes use of the "four Rs of radiobiology"—*r*epair of sublethal damage, *r*eassortment (redistribution) of cells within the cell cycle, *r*epopulation, and *r*eoxygenation.[45] Dividing the total dose into a number of smaller

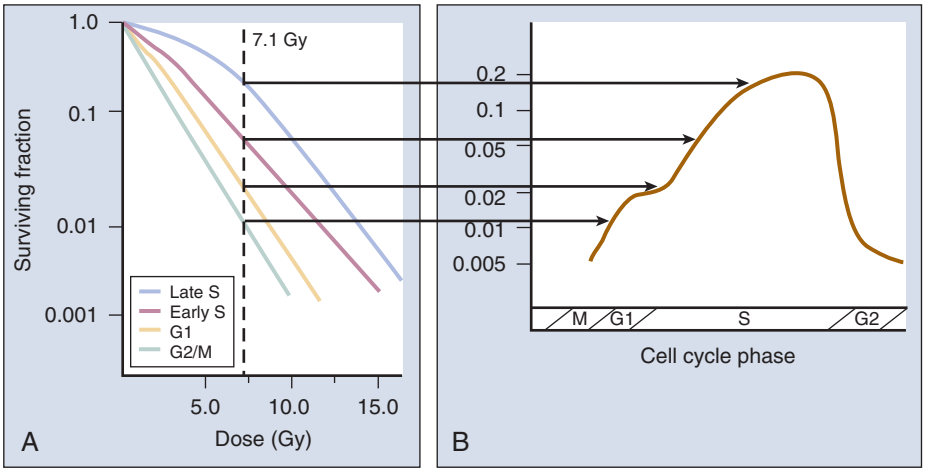


Figure 29-15 • **A,** Cell survival curves for populations of Chinese hamster cells irradiated in different phases of the cell cycle. **B,** Graphic illustration of how these radiosensitivity differences translate into age response patterns.

fractions allows for normal tissue sparing because of the repair of sublethal damage between fractions. Fractionating the therapy also allows for reassortment of tumor cells into radiosensitive phases of the cell cycle, with reoxygenation of the tumor cells causing them to be more radiosensitive. If too much time is allowed between fractions, repopulation or proliferation of the tumor cells can occur. Although this theory forms the basis for fractionated therapy, the reality is much more complex. Tumor populations and normal tissue represent a heterogeneous group of cells, all responding to the radiation and the fractionation scheme differently. Some general characteristics are presented in the following paragraphs.

Early-responding tissues include those tissues that are rapidly dividing and repopulating; these tissues are responsible for the acute toxicity seen with radiation therapy. The severity of acute toxicity reflects the rate of cell killing of early-responding tissues counteracted by regeneration by those tissues' surviving stem cells. This balance is based mainly on total treatment time. Prolonging overall treatment time spares the patient from the severity of acute toxicity, with short, intense treatment courses leading to severe acute toxicity. Severe acute toxicity can progress to consequential late effects.[62]

Late-responding tissues are responsible for the late toxicity from radiation therapy. These tissues are composed primarily of terminally differentiated cells with no stem cell population. Usually, therefore, there is no turnover of cells within a radiation treatment course and no opportunity for regeneration during treatment. In contrast to early-responding tissues, the overall treatment time has little importance in determining late toxicity. Instead, late toxicity depends mainly on total dose and dose per fraction.

These differences are seen by observing the dose-response relationships of the two types of tissue. Late-responding tissues have dose-response relationships that are more curved (i.e., with a larger shoulder) than those of early-responding tissues. In terms of the linear quadratic model, this translates into a higher α/β ratio for early effects (generally thought to be at ~10 Gy), compared with the ratio for late effects (thought to be at ~2 Gy). This has different consequences for each type of tissue. For early effects, the α/β ratio is large, meaning that the survival curve has an initial slope and no bend until higher doses. For late effects, the α/β ratio is small, with a short initial slope and a bend at low doses.[63] This creates a discrepancy between the two curves so that at certain doses, early-responding tissues (including many tumors) will be killed preferentially compared with late-responding tissues (see Fig. 29-14). As fraction upon fraction of radiation is given at these doses, the killing of tumor cells is much greater than that of cells of many normal organs, which are late responding. However, as fraction size increases, cells in late-responding tissues are killed in greater numbers. This explains the observation that late-responding tissues exhibit a much more marked change in survival with changes in dose per fraction. In other words, late-responding tissues are preferentially spared by dose fractionation.

The reason for the difference in these curves is not completely understood, although some possible explanations have been presented. The first deals with cell cycle-specific sensitivity. Cells are sensitive to radiation during mitosis and G2 phase and resistant to radiation during S and early G1 or G0 phases. Although this resistance eventually is overcome with high doses, late-responding tissues have many quiescent cells, hence incurring radioresistance as these cells rest in G0. On the other hand, tumor cells and early-responding cells reassort themselves into sensitive phases of the cell cycle, leading to radiosensitivity at smaller doses.

Another explanation of the differences in the dose-response curves relates to repair of DNA damage. Late-responding tissues have a greater capacity for sublethal repair than do early responding tissues, hence the lower α/β ratio and the shallower survival curve at low doses. Although late-responding tissues have a higher repair capacity than early-responding tissues, the repair kinetics themselves do not differ systematically between the two types of tissues.[64] Therefore, there is a minimum limit of time that is needed between fractions so that repair in late tissues can be completed. If this is not allowed, severe toxicity can result. This has been noted in studies that used fractionation schedules in which the interval between doses was less than 4.5 hours.[65] Although the explanation that these toxicities were due solely to incomplete repair has been questioned, most protocols now stipulate a minimum of 6 hours between fractions to allow for sufficient repair to take place.

Provided that sufficient recovery occurs between each fraction and the next, late radiation effects classically show no dependence on treatment course duration. In contrast, overall treatment time has a large effect on both acute toxicity in early-responding tissues and the cure of tumors. This implies that the tumors that show a decrease in curability with longer treatment times have rapid regeneration in response to the cell killing that occurs with radiation.

Altered Fractionation Schemes

All of the factors described so far must be taken into consideration when a fractionation scheme is being designed. The "standard" fractionation schedule differs in many parts of the world. In the United States, 1.8 to 2.0 Gy per day is the conventional fractionation. The standard of five fractions per week delivering a total dose of 9 to 10 Gy per week has evolved not as a biologically designed, optimal method for administration of radiation but rather from considerations such as the convenience of patients and staff, the availability of equipment, and financial constraints. Outside the United States, the same nonmedical constraints have dictated the development of

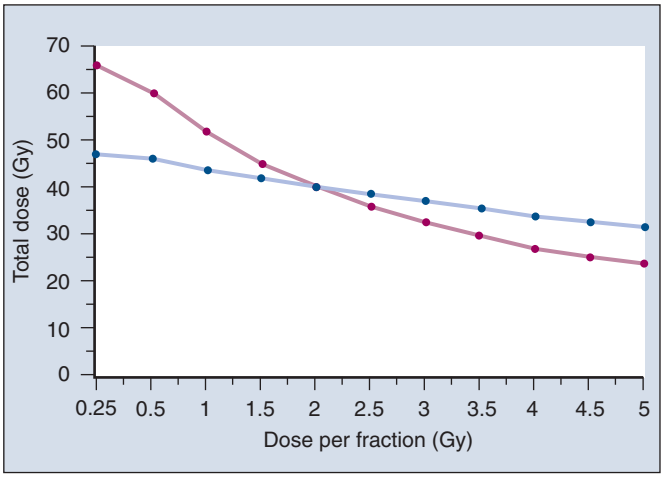


Figure 29-16 • Influence of fraction size on complications in early- vs. late-reacting tissues. The α/β ratio for the early tissue (*blue curve*) was set at 10 in this example; the α/β ratio for the late tissue (*red curve*) was 2.5. The tissues were presumed to have equal reactions to 40 Gy delivered at 2 Gy per fraction. Note that for equal reactions, the early-reacting tissue is far less dependent on fraction size. For large daily fractions, the late-reacting tissue will require substantial dose reduction to maintain equal clinical effects. Conversely, if fraction size is reduced, the late-reacting tissue will tolerate substantially higher doses of radiation. (From Lichter AS: Radiation therapy. In Abeloff M [ed]: Clinical Oncology, 2nd ed. London, Churchill Livingstone, 2000, pp 423–470.)

other fractionation regimens that may employ fewer fractions over a shorter time.

In the 1990s, more attention was paid to attempts to alter the customary fractionation protocols to provide schemes that could improve the therapeutic outcome, through either increased tumor sterilization or decreased normal tissue toxicity. These attempts were undertaken based on the knowledge that the effects of radiation on acutely reacting tissues (e.g., skin and mucosa) are different from those on late-reacting tissues (e.g., nerve and connective tissue).

The reactions in early-reacting tissues, which determine the patient's tolerance to treatment during the course of radiation, are time dependent. Because these tissues proliferate rapidly, prolonging the total time of therapy allows proliferation to take place and thus lessens the severity of the overall reaction. This is especially important in terms of breaks (days off) from treatment, particularly weekends, during which time a mucosal or skin reaction can heal substantially. Late-reacting tissues are not sensitive to overall treatment time, but they are very sensitive to fraction size. It is clear from a number of clinical studies that, given the same total dose, late reactions are worse when large fractions are used than with smaller ones.[66] This is understandable based on the shape of the cell survival curves for early- and late-reacting tissue. Late-reacting tissues have low α/β ratios, and their survival curves bend at higher doses, causing a substantial difference in cell kill with large rather than small fractions. With little proliferation to make up the difference, early-reacting tissues are extremely fraction-size dependent. If large fractions are used, the total dose must be lowered to achieve the same effect on long-term toxicity. Clinical examples of this effect are found most often in palliative regimens, in which 20 Gy in five fractions or 30 Gy in 10 fractions are given to bone metastases for the rapid relief of pain (Fig. 29-16). Although a few large fractions preferentially damage late-reacting tissues, a larger number of smaller fractions preferentially spares them.

The other side of this coin is tumor proliferation. If many small fractions are used and the time it takes to deliver a course of radiation is protracted, tumor proliferation could negate potential gains. When the aims are to take advantage of the sparing of late tissue damage and avoid having treatment last for too many days or weeks, treatment has been given with multiple fractions per day. Several alternative fractionation schemes are presented in Table 29-3. These schemes can be categorized according to two basic strategies: hyperfractionation and accelerated fractionation. In *hyperfractionation*, the fraction number is increased without altering the total treatment time. Although the dose per fraction is reduced, the total dose administered is larger, which allows for the safe escalation of dose with respect to late normal tissue toxicity, because the individual fraction sizes are quite small. An example of hyperfractionation is the treatment of head and neck cancer with 1.15 Gy twice daily (11.5 Gy per week). Following this schedule, instead of a typical 7-week course of treatment delivering 63 Gy at standard fractionation, 80.5 Gy is delivered in the same time period.[67] Several single-arm retrospective studies have reported results with hyperfractionated treatment of head and neck cancer that suggest benefit in terms of local control.[68,69] A large randomized trial in T2 and T3 oropharyngeal carcinoma showed a statistically significant (approximately 35%) increase in local control in the hyperfractionated group.[67] Although not all studies have shown an advantage for hyperfractionated regimes compared to conventional fractionation, overall the literature suggests that an advantage may exist for hyperfractionation in terms of local control of head and neck cancer (in the absence of concomitant chemotherapy).

In *accelerated fractionation*, the overall time of therapy (i.e., total number of days/weeks) is reduced. The number of fractions, fraction size, and total dose may or may not be reduced. The theoretical advantage is that a reduction in overall treatment time could counteract accelerated repopulation in the tumor. Based on the principles discussed previously, late effects should be similar to conventional fractionation, because the fraction size is standard (or reduced) and

Table 29-3 Schematic Representation of Altered Fractionation Protocols

	Week	1	2	3	4				Fx. No.	Fx. Size	Total
ACCELERATED	AM	|||||	|||||	|||||	|||||	|*			42	1.6 Gy	67.2 Gy
FRACTIONATION*	PM	|||||	|||||	|||||	|||||	|					
	Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Fx. No.**	**Fx. Size**	**Total**
HYPERFRACTIONATION	AM	|||||	|||||	|||||	|||||	|||||	|||||	|||||	70	1.15 Gy	80.5 Gy
	PM	|||||	|||||	|||||	|||||	|||||	|||||	|||||			
	Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Fx. No.**	**Fx. Size**	**Total**
ACCELERATED	AM	|||||	|||||	|||||	|||||	|||||	|||||		40	1.8 Gy	69 Gy
BOOST	PM					|||||	|||||			1.5 Gy	

*May include a break after two weeks to reduce acute toxicity.

the total dose is not increased. An example of accelerated fractionation is the British experience of continuous hyperfractionated accelerated radiation therapy (CHART) to treat non-small-cell lung cancer using 1.5 Gy three times daily for 12 consecutive days, delivering 54 Gy in 36 treatments in 1.5 weeks.[48] Another example of accelerated fractionation is the widely recognized scheme called the "concomitant boost" schedule for head and neck cancer, in which the first 36 Gy is given in four weeks at 1.8 Gy per fraction, and while that larger field continues to a total of 54 Gy, a smaller boost field is added as a second daily treatment for the last 2 to 3 weeks, bringing the total dose to 72 Gy in 6 rather than 8 weeks.[70] The results of a large randomized trial in patients with head and neck cancer showed a local control advantage for this technique.[47] To date, no overall survival benefit has been demonstrated for any altered fractionation schedule other than CHART.

One practical difficulty with hyperfractionated or accelerated schemes is the increased toxicity that can be seen in patients receiving concomitant chemotherapy (see the section on Radiosensitizers, Radioprotectors, and Concomitant Systemic Therapies). Combining chemo- and radiation therapy is becoming increasingly routine in the treatment of many cancers, for example, head and neck cancer and cervical cancer. Furthermore, these schemes, especially those that involve separation of doses in time, require the patient to come to the clinic more than once daily, which tends to be inconvenient for most patients. Therefore, many clinicians feel that these strategies must show an unequivocal benefit on overall survival to be worthwhile. Nevertheless, because of its simplicity and convenience, the concomitant boost technique has become an established and accepted technique worldwide for patients with many cancers, particularly head and neck cancer.

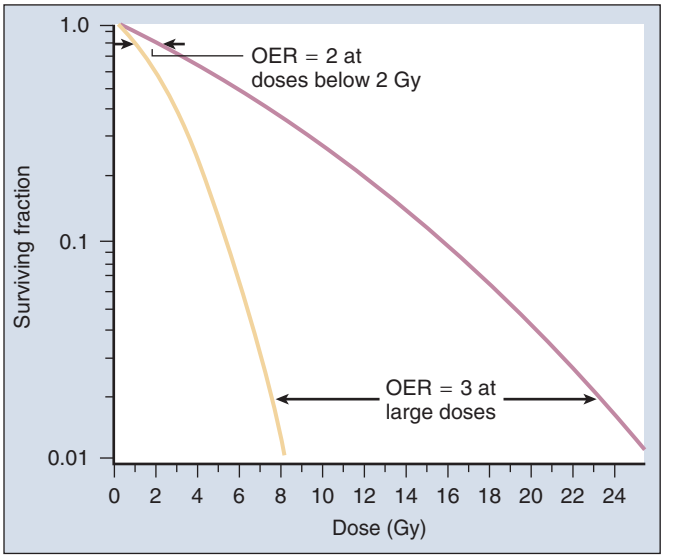


Figure 29-17 • Cells irradiated in the presence of molecular oxygen are more sensitive to killing by x-rays than cells that are hypoxic (deficient in oxygen). The ratio of doses that produce the same level of biological damage in the absence of oxygen and in the presence of oxygen is known as the oxygen enhancement ratio (OER). At high doses, the OER has a value of about 3; its value seems to be smaller (close to 2) at doses below 2 Gy. (From Cox JD, Ang KK [eds]: Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 34.)

Oxygen Effect

Many agents have been observed to modify the responses of cells and tissues to radiation. One of the most extensively studied chemical modifiers is oxygen. The response of cells to ionizing radiation is strongly oxygen dependent, with well-oxygenated cells showing as much as threefold greater sensitivity to the killing effects of ionizing radiation than the same cells under hypoxic conditions.[45]

The effect of oxygen has been known for nearly a century. In 1912, Swartz noted a reduction of radiation effect if blood flow to an exposed area was reduced.[71] Although many suspected the modifying properties of oxygen, the oxygen effect was not demonstrated quantitatively until 1955.[72] This important discovery by Gray and Tomlinson had significant implications, because it became clear that tumors have a much higher proportion of hypoxic cells than do normal tissues. Many attempts have been made to circumvent this "built-in" radioresistance of tumor cells, but tumor hypoxia continues to be a problem in therapeutic radiation oncology.

The oxygen enhancement ratio (OER) is the ratio of hypoxic to aerated doses needed to achieve the same biologic effect. For x-rays, the oxygen enhancement ratio usually is between 2 and 3, becoming more pronounced at higher doses (Fig. 29-17). In other words, the presence of oxygen in cells increases cell killing by radiation. The mechanism behind oxygen's radiosensitizing effect is thought to lie in the process of indirect damage, which is DNA damage resulting from the production of free radicals from water molecules. These free radicals break chemical bonds and produce chemical changes, initiating the chain of events that result in the expression of biological damage. After DNA damage from free radicals occurs, the damaged targets usually are quickly repaired by a reduction reaction involving reducing species such as thiols and intracellular glutathione, which restores the target to its original condition. Oxygen inhibits this repair of free radical-induced damage by forming irreversible peroxides in the injured biomolecules, thus "fixing" the radiation damage.

Consistent with this explanation of oxygen's effect is the fact that oxygen need not be present at the time of radiation for sensitization to occur, but it must be present shortly thereafter. Oxygen could be added after the radiation to sensitize cells, provided the delay is no longer than 5 msec.[73] Also consistent with this theory is the fact that high-linear-energy transfer radiation has a lower oxygen enhancement ratio than does low linear energy transfer radiation.

The concentration of oxygen required for radiosensitization is remarkably small. Air has an oxygen concentration of approximately 155 mm Hg. Hypoxic resistance occurs at concentrations between 0 mm Hg and 20 mm Hg. By the time a 20-mm Hg concentration of oxygen is reached, the cell survival curve is similar to the curve obtained under fully oxygenated conditions. This is less than half of the partial pressure of oxygen normally found in tissues (~40 mm Hg). A concentration as small as 5 mm Hg results in a radiosensitivity halfway between hypoxic and fully oxygenated conditions. In practice, this means that hypoxia is not a major consideration for normal tissues; the minimum oxygen concentration to which most tissues will be exposed is at the level of venous blood (around 40–50 mm Hg), well above the borderline for the oxygen sensitizing effect. Some normal tissues (e.g., cartilage or skin) might contain borderline hypoxic cells.[74]

Although the oxygen tension of normal tissues is similar to that of venous blood (40 mm Hg), the oxygen tension within the cells themselves is heterogeneous. Some normal tissues contain a small percentage of cells that are borderline radiobiologically hypoxic. This percentage is amplified greatly in tumor tissues due to both chronic hypoxia and acute hypoxia. Chronic hypoxia (also termed *diffusion-limited hypoxia*) results from the propensity of tumors to outgrow their blood supplies. Tomlinson and Gray calculated the distance to which oxygen could diffuse in respiring tissues to be 100 to 180 μm.[72] Cells beyond this distance would be expected to be dead or dying, producing the observed areas of necrosis seen in tumors, but those on the fringe of this distance would make up a large hypoxic region of cells. Acute hypoxia, also known as perfusion-limited hypoxia, results from the transient closing of blood vessels within the tumors themselves. Other possible causes include changes in overall blood flow or decreases in red blood cell delivery. Like chronic hypoxia,

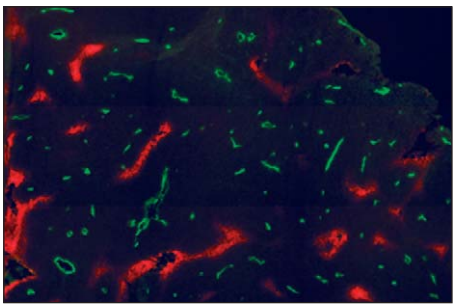


Figure 29-18 • Microscopic photo of a leiomyosarcoma of the extremity stained with EF-5, displaying the heterogenicity of hypoxia within the tumor. Green color corresponds to capillaries within the tumor. Red areas correspond to areas of hypoxia, which are at a notable distance from the blood supply. (Used with permission from Sydney Evans, VMD, University of Pennsylvania.)

acute hypoxia can create a substantial hypoxic population of cells within a tumor.[74]

These populations of hypoxic cells within tumors can significantly limit the efficacy of radiation therapy. Although cells within these hypoxic parameters retain properties of clonogenicity, they are protected from the killing effects of radiation because of the absence of oxygen to fix the radiation damage. Therefore, the presence of even a small population of hypoxic cells could limit the overall success of radiation therapy in clinical situations. It has been estimated that hypoxic fractions account for up to 50% of tumors, with 15% of all tumor cells, on average, being hypoxic (Fig. 29-18).[75]

Given that tumors contain hypoxic cells that greatly limit the success of radiation, how are clinical successes with radiation obtained? The answer might lie in the reoxygenation of tumor cells after radiation that has been observed in rodent tumors.[76,77] Reoxygenation occurs with both the chronic and acute mechanisms of hypoxia. In terms of chronic hypoxia, reoxygenation involves shrinking the tumors during a course of radiation therapy. As cells die from exposure to radiation, surviving cells that previously were beyond the range of oxygen diffusion are brought closer to a blood supply and then reoxygenate. This process is fairly slow, taking place over a period of days, depending on the rate of tumor regression. Reoxygenation also occurs in terms of the mechanism responsible for acute hypoxia. Assuming that blood flow resumes in areas of acute hypoxia, reoxygenation could take place within minutes or hours.

The process of reoxygenation is thought to be important in the practice of radiation oncology and again suggests the importance of using a protracted, fractionated course of radiation therapy. If human tumors reoxgenate as efficiently as animal tumors do, using multiple fractions could be sufficient to deal with the problem of hypoxic cell populations. Attempts at increasing the partial pressures of oxygen in tumors and using oxygen-mimetic chemicals to increase the sensitivity of tumor cells to radiation have yielded mixed results. A number of pharmacologic agents (e.g., 5-fluoro-etanidazole and pimonidazole) are being studied to allow more accurate assessment of the role of hypoxia in human tumors and cancer management.[78]

Radiosensitizers, Radioprotectors, and Concomitant Systemic Therapies

Although oxygen may be the most effective radiosensitizer, there are limitations to achieving levels of oxygen sufficient for sensitizing all tumor cells. Chemicals have been developed, therefore, to try to sensitize hypoxic tumor cells to kill by radiation. All have a similar electron affinity for the electrons produced by the ionization of biomolecules. The nitroimidazoles, including metronidazole, misonidazole, and etanidazole, represent molecules with such characteristics. Although these compounds are efficient radiosensitizers in animal model studies, clinical trials have shown them to have limited efficacy in humans,[74] for several possible reasons. As laboratory studies have continued to show encouraging results, diffusion into tissues seems to be the limiting quality in these compounds, just as it is for oxygen itself. In addition, severe side effects—most notably peripheral neuropathy—have been noted with some of these compounds at the drug concentrations required to produce radiosensitizing effects on tumors.[78] An additional problem is that in animal models (particularly rodent models), tumors grow rapidly and consequently might have more hypoxia. Also, tumors in animal models are more uniform than human cancers. The design adopted for the clinical trials of these compounds, particularly patient selection, also has been debated.

In response to the lack of efficacy seen with hypoxic cell radiosensitizers, other approaches have emerged to attack the hypoxia problem encountered in tumors. Tirapazamine is a prodrug that is activated to a cytotoxic molecule preferentially under hypoxic conditions.[79] Data suggest a synergistic effect when this compound is given with radiation. Clinical progress with tirapazamine has been slow, perhaps because of the severe nausea or muscle cramping experienced by some patients.[80] Clinical trials are underway with this drug and other prodrugs, such as AQ4N, which is selectively and irreversibly converted to AQ4 in hypoxic tumor cells where it acts as an inhibitor of topoisomerase II.[81]

Compounds that interact with DNA also may act synergistically with radiation. In 1960, it was found that pyrimidines could be halogenated and incorporated into DNA because the van der Waal's radius of chlorine, bromine, or iodine was similar to the size of a methyl group side chain on uridine and because a halogenated uridine would be recognized by DNA polymerase. Therefore, halogenated pyrimidines (e.g., uridine with a bromine atom replacing the methyl group [BUDR] or an iodine replacing the methyl group [IUDR]) could be substituted in DNA for a normal thymine.[82] DNA containing substituted halogenated pyrimidines is more susceptible to DNA double-strand breaks when exposed to ultraviolet light or ionizing radiation.[83] Although this finding relates to cell kill in preclinical models, in clinical trials to date, these compounds have not been shown to be efficacious.[84] It has been postulated that insufficient halogenated pyrimidines are incorporated into the DNA of tumor cells, resulting in inadequate radiosensitization.

Although the therapeutic ratio can be improved with radiosensitization, a therapeutic benefit in terms of the relative sparing of normal tissues could also be attained using *radioprotectors*. The most abundant radioprotectors are sulfhydryl-containing compounds. Cysteine was the first of these to be shown to protect against the effects of radiation, by Pratt and colleagues in 1948.[85] Since then, many other compounds have been found to be effective radioprotectors, the most efficient of which has a free SH group separated from the rest of the molecule. The mechanisms of the radioprotection afforded by sulfhydryl-containing molecules include free radical scavenging and hydrogen donation to facilitate DNA repair (Fig. 29-19). The radioprotector most commonly used clinically today is WR-2721 (amifostine), developed at the Walter Reed Institute of Research. It is converted to the active metabolite WR-1065 inside the cell and acts as a free radical scavenger. Given intravenously or subcutaneously, it has been demonstrated to be efficacious in reducing toxicity in head and neck cancers and lung cancer and its application is being tested in the treatment of other malignancies.[86]

Currently, the most widely used radiosensitizers are *chemotherapeutic agents*. Originally, the rationale for the combination of chemo- and radiation therapy was to attack two different problems, termed *spatial cooperation*. Whereas radiation would address local control issues, chemotherapy was thought to treat micrometastases located beyond the tumor bed. However, evidence of increased local control in patients receiving combined treatment is now considered evidence of chemotherapy's radiosensitizing effects, which have been demonstrated in many tumors. Examples include the use of platinum agents

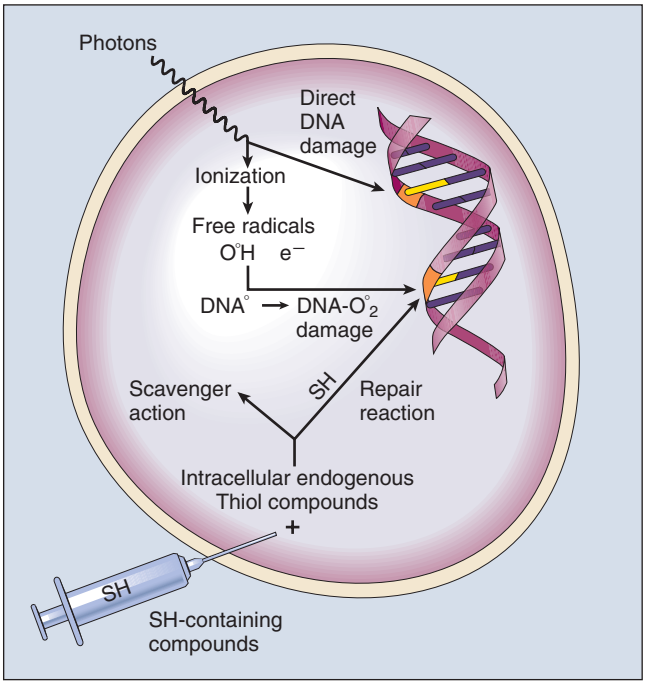


Figure 29-19 • Chemical protectors: competition model. There is a dual action to chemical radioprotection: (1) thiols and sulfhydryl compounds act as repair compounds; (2) they compete with free radicals (scavenging effect). (From Leibel SA, Phillips TL [eds]: Textbook of Radiation Oncology. Philadelphia, WB Saunders, 1998, p 50.)

in lung cancer, head and neck cancer, cervical cancer, rectal cancer, and bladder cancer; mitomycin-C in anal cancer; and 5-FU in esophageal, gastric, and pancreatic cancers (Table 29-4).[87–91] Although some of the improved outcomes in these studies are due to the elimination of micrometastases, improved local control from radiosensitization has been shown to be an important component. Recently a multicenter European–Canadian trial of patients with glioblastoma multiforme has reported improved local control and a significant improvement in overall survival with a combined modality approach using concomitant and adjuvant temozolamide chemotherapy with high-dose radiation therapy.[92]

Over the past decade, the emphasis of drug development in oncology has shifted toward new classes of molecularly targeted agents, particularly antibodies and small molecule inhibitors. It is increasingly apparent that many of these agents can act as radiation-specific sensitizers or protectors. Potential targets for radiosensitization include the following:

- Signal transduction pathways, for which targeting agents are in clinical trials (see later discussion)
- Pathways clearly involved in sensitivity to drugs and radiation, for which agents currently are in preclinical trials
- Investigation of the molecular mechanisms involved in the most highly conserved cellular responses to cytotoxic stress

The first large-scale-example of the clinical benefit that can be obtained by combining a molecularly targeted agent with radical radiation therapy is provided by cetuximab, an IgG1 monoclonal antibody directed against the ligand binding domain of the epidermal growth factor receptor (EGFR; see Chapters 34 and 72). Cetuximab enhances the cytotoxic effects of radiation in preclinical models of squamous cell carcinoma.[93,94] An international multicenter randomized controlled trial has demonstrated in the treatment of locoregionally advanced head and neck cancer that, compared to high-dose radiation therapy alone, concomitant high-dose radiation therapy plus cetuximab improves locoregional control and reduces mortality without increasing the common toxic effects associated with radiation therapy.[95]

CLINICAL APPLICATION OF RADIOBIOLOGIC PRINCIPLES

The goal of all investigations into the physical aspects and biologic principles behind radiation therapy is to attempt to increase the *therapeutic index*, which is defined as the tumor response for a fixed level of normal tissue damage.[96] Or, to restate it another way, the goal is to increase tumor cell kill and hence tumor control while maintaining normal tissue toxicity within a tolerable range. When discussing normal tissue toxicity, late effects that translate into end-organ damage usually are considered the dose-limiting toxicity.

All organs have a threshold for normal tissue toxicity. These thresholds, though, often lack rigidity and are poorly defined, because they depend on the interaction of many factors. The most important factors in terms of normal tissue tolerance and toxicity are total dose delivered and the volume of the organ exposed to this dose. It is not as simple to calculate this relationship for normal tissue as it is for tumors. When speaking in terms of tumor cure, the fraction of cells surviving determines the success of treatment, because a single surviving cell might suffice for regrowth of the tumor. For normal tissues, the tolerance depends heavily on the ability of stem cells to maintain a sufficient number of mature cells for proper organ function. This statement is an oversimplification, because the tolerance of an organ also depends on its structural organization, which some radiobiologists have termed *functional subunits*.[45,74,97] For example, consider the kidney and the spinal cord. If radiation permanently damages a number of nephrons, the end-organ function might not be affected as long as enough nephrons remain to maintain function. The functional subunits of the kidney, then, are said to be arranged in parallel. On the other hand, if one section of the spinal cord is damaged, the entire cord distal to the lesion will be disrupted. Organs such as the spinal cord, in which damage to one portion of the organ affects

Table 29-4 Example of Chemotherapy Agents That Sensitize Tissues to the Effects of Radition

Drug	Proposed Mechanism Enhancement	Clinical Use
5-Fluorouracil	Inhibits thymidylate synthase	Head and neck, gastrointestinal, bladder, anus
Platinum agents	DNA cross-linking and adduct formation	Head and neck, gynecologic, bladder, lung, anus
Mitomycin C	DNA cross-linking and adduct formation	Anus, bladder
Gemcitabine	Inhibits ribonucleotide reductase	Pancreas, head and neck, lung, bladder
Paclitaxel	Inhibits microtubule polymerization	Lung, gynecologic malignancies, head and neck
Temozolamide	Alkylation and methylation of DNA	Glioblastoma multiforme

the function of the entire organ, have what is called *serial functional subunits*.

Functional subunits have yet to be described for many organs, and the use of functional subunits to describe radiation tolerance of many organs remains theoretical. It is clear, however, that as the irradiated volume of an organ increases, the complications also increase. Although the volume of the organ that is exposed to radiation is important, this exposure might not be observed as toxicity if the total dose delivered remains below the dose that would damage the normal tissue in question. The concept of a threshold for total dose exposure becomes important as we attempt to escalate dose to increase tumor control. Clinical and preclinical data are consistent with the view that increased dose kills more cells, though few clinical trials have demonstrated this directly. Retrospective data have confirmed a dose response in the treatment of many clinical sites, including head and neck, Hodgkin's disease, high-grade glioma, non-small-cell lung cancer, prostate cancer, breast cancer, and cervical cancer.[98–103]

Therefore, the total dose to the tumor and the volume of normal tissue treated must be considered when designing a radiation treatment course. Success might be possible in any tumor, regardless of size and histology, if sufficiently high doses are used. Clinically, however, this consideration must be balanced against the toxicity that would result to normal tissue. To increase the therapeutic ratio, many of the radiobiologic and physical principles of radiation have been used, including tumor localization, choosing the optimal energy and radiation modality, manipulating the dose rate, fractionation schemes, and the use of radiosensitizers and radioprotectors or targeted therapies. All depend on accurate localization of the tumor and the precise delivery of radiation.

Effects of Radiation on Normal Tissue

The effects of radiation on normal tissue limit the doses of therapeutic radiation that can be administered safely. For some clinical presentations—for example, a responsive tumor (e.g., lymphoma) located in radiation-tolerant tissues such as the low neck—cure is possible without a major risk of serious complications. In other situations—such as the setting of advanced prostate cancer, where rectal complications can occur—cure is possible, but the risk of long-term complications cannot be dismissed. In still other situations—such as damage to normal brain tissue while treating high-grade gliomas—cure might not be possible without the risk of severe disability. Finally, an increase in the control rate in many clinical situations might be possible only at the expense of more complications unless ways can be found to increase the tumor dose without substantially increasing the dose to surrounding normal tissues. The latter concept underlies the increased use of interstitial implantation techniques and three-dimensional conformal dose delivery, discussed in detail later in this chapter.

It should be remembered that complication risk and chances of cure trade off against one another. Complications are an inherent risk of any medical treatment, and one must weigh the risks of failure to control the tumor against the advantage of local control associated with a complication. Consideration also should be given to whether a complication can be managed with other types of treatment, for example surgical transposition of the ovaries to reduce the chances of radiation menopause in a young female patient undergoing radiation treatment to the pelvis. Understanding the effects of radiation on normal tissues is critical to the proper use of this treatment modality in the context of a patient's treatment as a whole.

Acute Effects on Normal Tissues

The acute effects of radiation result from direct damage to parenchymal cells of organs that are sensitive to radiation. Traditionally, an *acute effect* has been defined as an effect seen during treatment and up to 3 months from the conclusion of therapy. A detailed discussion of this subject is beyond the scope of this chapter; it has been reviewed in other textbooks.[7,104] Table 29-5 summarizes the acute effects of radiation and their management.

Late Effects on Normal Tissues

Late effects are those that occur more than 3 months from the end of therapy. Virtually any organ or tissue that is treated can express a syndrome of late radiation damage. The mechanism of late tissue damage is likely to be multifactorial. Some radiobiologists believe that it is due to slow dropout of small vasculature, leading to organ cell loss, fibrosis, and eventual late organ failure.[105] Evidence for this viewpoint is supplied by morphologic studies of irradiated tissues, where decreased vascularity can be observed in virtually every tissue type.[105] Others believe that late damage is due in large part to direct damage to parenchymal cells. This theory is plausible, as organs have widely differing sensitivities to radiation, but there is little evidence

Table 29-5 Acute Effects of Radiation

Organ	Symptom/Sign	Management
Systemic	Lethargy, fatigue	Symptomatic
Skin	Erythema, dry desquamation, pruritus, moist desquamation	Observation; low-dose topical corticosteroids for pruritus; avoidance of occlusive dressings or clothing; aqueous creams
Oral mucous membranes/teeth	Mucositis, ulceration	Dental consultation pretreatment; rinse with sodium bicarbonate; fluoride treatment; viscous xylocaine and oral analgesics for pain; watch for and treat candidiasis
Esophagus	Esophagitis	Systemic analgesics; consider diagnosis of opportunistic inflection
Lung	Pneumonitis, cough	Observation in mild cases; prednisone in severe cases
Liver	Radiation hepatitis	Symptomatic management; prednisone in severe cases
Bowel	Cramping, diarrhea, nausea, vomiting	Antidiarrheal agents; sulcralfate; antiemetics; low-residue diet
Bladder	Frequency, urgency, dysuria, hematuria	Analgesia; antimuscarinics for bladder instability; alpha$_1$-blockers for obstructive symptoms in men
Rectum	Proctitis, bleeding, tenesmus	Symptomatic; corticosteroid suppositories
Hematopoietic	Lymphopenia, thrombocytopenia, anemia, cytopenia	Supportive; transfusions; aggressive treatment of infections

Form Lichter AS: Radiation therapy. In Abeloff M (ed): Clinical Oncology, 2nd ed. London, Churchill Livingstone, 2000, pp 423–470.

Table 29-6 Approximate Organ Tolerance Doses in Radiation Therapy Estimated from Preclinical and Clinical Data

Organ	Toxicity	Tolerance Dose (cGy)*
Brain	Necrosis	6000
Eye	Cataract	600
	Keratitis	5000
	Retinal damage	4500
Pituitary	Hypopituitarism	4500
Spinal cord	Paralysis	5000 (5-cm segment)
Skin	Necrosis	6000 (10 × 10 cm)
Salivary gland	Xerostomia	4000
Thyroid	Hypothyroidism	4500
Lung	Pneumonitis	2000
Heart	Peri-/paracarditis	4500
Esophagus	Stricture	6000
Liver	Hepatitis	3000
Stomach	Ulcer/hemorrhage	5000
Kidney	Nephritis	2000
Rectum	Ulcer/hemorrhage	6000
Ovary	Sterility/menopause	600
Testis	Sterility	200
Bladder	Contracture	6500

*Dose to whole organ at 200 cGy per fractron, 5% complication level.
From Lichter AS: Radiation therapy. In Abeloff M (ed): Clinical Oncology, 2nd ed. London, Churchill Livingstone, 2000, pp 423–470.

to suggest that blood vessels in one part of the body are more or less radiosensitive than in any other part. Thus, if vascular damage were a final common pathway, then most organs should share similar radiation tolerance doses, and they do not.[106] In all likelihood, late damage represents a combination of vascular damage and direct organ cell depletion.[107,108] Table 29-6 provides a summary of organ tolerances to radiation.

Carcinogenesis

Because radiation causes damage to DNA and some of the damage is misrepaired, it is not difficult to conceive that a radiation-damaged piece of DNA could be misrepaired with a small but nonlethal mistake. Alternatively, a base in the DNA strand could be damaged in a manner that is nonlethal, but alters the base sequence. Such a change in the sequence of DNA bases is called a *mutation*, and some mutations can lead to malignant transformation of the cell. Thus, radiation would be expected to be a carcinogen, and decades of research have confirmed this fact. In fact, radiation probably is the most thoroughly studied carcinogen. Its ability to induce malignancy was first seen in the pioneers of clinical radiation research, many of whom lost limbs or their lives to multiple aggressive skin cancers caused by repeated exposure to x-rays. Over the years, a number of radiation-exposed populations have been studied, including radium watch dial painters and patients exposed to radiation for benign diseases. Five well-known examples of the latter are tuberculosis victims examined with multiple fluoroscopies over the course of many years, patients with postpartum mastitis whose breasts were irradiated, patients with ankylosing spondylitis who received spinal irradiation, children who received scalp irradiation for tinea capitis, and children treated with radiation to reduce thymic enlargement.[109–113] Two of the largest and most carefully studied populations exposed to ionizing radiation have been the survivors of the atomic bomb explosions from Japan during World War II and the survivors of the Chernobyl nuclear accident in the former Soviet Union in 1986.[114–116]

Several basic principles of radiation-induced carcinogenesis have been elucidated by studying these populations:

- Radiation-induced cancer appears several years after exposure, often 4 to 10 years later for radiation-induced leukemias and 10 to 30 years later for solid malignancies.[117]
- Leukemia is the most common primary tumor associated with previous radiation exposure, with relative risks of 30 or greater over that of the general population. The incidence of leukemia peaks 6 to 8 years after radiation exposure, after which time the incidence tails off.[118]
- Not all cancers can be associated with previous radiation exposure. Whereas thyroid and breast cancer are commonly associated, pancreatic and rectal carcinomas appear to have little association with previous radiation induction. No discernible pattern of organ sensitivity has been deduced.[119]
- Radiation induction of cancer is age sensitive. For example, radiation of breast tissue during the teens and 20s is more commonly associated with subsequent breast cancer than irradiation after age 50 years.[120]
- The age distribution of radiation-induced cancers is similar to the naturally occurring incidence pattern. This finding suggests that radiation facilitates the appearance of malignancy rather than being entirely causative of the problem.[121]
- There is a relationship between radiation dose and cancer induction. Cancers are induced with increased frequency as dose increases up to a point, after which increasing dose decreases the appearance of malignancy in both experimental and clinical situations (Fig. 29-20).[74] This is likely due to the amount of DNA damage being caused; at lower doses, cells can survive while sustaining nonlethal mutations, whereas at high doses, lethal mutations dominate. This finding implies that a high-dose therapeutic course of radiation should not induce large numbers of cancers in survivors. This

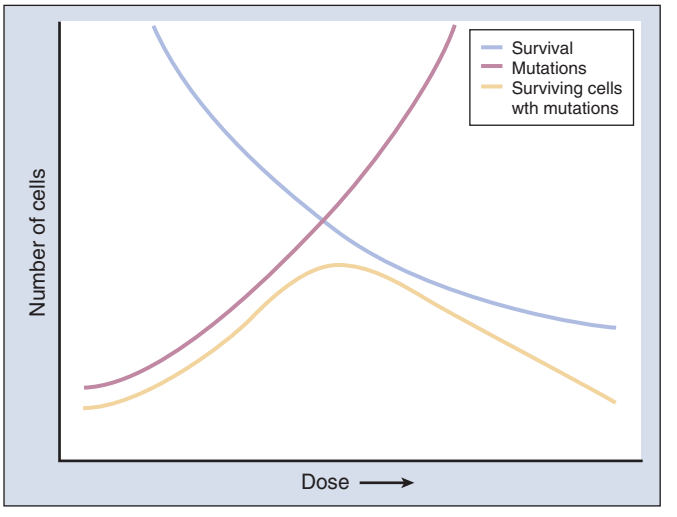


Figure 29-20 • Relationship between dose and viable mutations. As the dose increases, the number of mutations increases. As dose increases, however, survival of cells decreases. The composite, labeled "surviving cells with mutations," has a characteristic shape. Mutations increase up to a relatively low dose level and then begin to decrease. High-dose therapeutic radiation produces a very small number of secondary induced cancers. (From Lichter AS: Radiation therapy. In Abeloff M [ed]: Clinical Oncology, 2nd ed. London, Churchill Livingstone, 2000, pp 423–470.)

appears to be the case, although it should be emphasized that cancer induction from high dose radiation treatment has been clearly documented.[122]

Although low doses of radiation can cause cancer, it is not known whether any dose is so low as not to be dangerous—i.e., whether a threshold for adverse effects exists below which small doses of radiation have no biologic effects. Our information on radiation carcinogenesis comes from dosage data in the tens and hundreds of centigrays (cGy). We have little or no data from doses in the 1- or 2-cGy range, and even fewer data in the tenths of cGy range, which are the doses associated with many diagnostic x-ray exposures and with some population exposures relating to emissions from nuclear facilities, working with tracer doses of radionuclides, or visiting a patient with a radioactive implant in the hospital.[123] If a safe threshold were determined, it would make the public health aspects of radiation protection much less problematic. Currently, a conservative approach to radiation exposure is followed in most developed countries, although rules vary locally. In general, it is assumed that any radiation exposure is associated with risk in a linear fashion. Furthermore, population protection levels are calculated with an even more conservative concept of person-cGy, which implies that the same cancer risk will occur if one person is exposed to 1000 cGy that will occur if 1000 persons are each exposed to 1 cGy. From a biologic point of view, this type of calculation seems illogical, but it forms the basis of estimates for the amount of radiation to which the general population can be exposed with safety.[124] Overall, it is prudent to eliminate as much unnecessary radiation exposure as possible. On the other hand, medically necessary radiation in the form of diagnostic or therapeutic radiation can be more life saving compared to the risk of exposure and usually can be justified under even the most stringent estimates of carcinogenic risk of radiation.

PROCESS IN RADIATION TREATMENT

Radiation therapy is an important component of many patients' treatment regimens. It often is combined with surgery or chemotherapy for optimal treatment of cancer. After the patient has been evaluated and the decision to use radiation has been made, perhaps the most important step in a radiation treatment course is the design of the radiation treatment itself.

Treatment Planning

Successful treatment planning is imperative to the success of a radiation treatment course. Formulation of the management plan for an individual patient involves discussion among radiation oncologists, radiologists, pathologists, surgeons, physicians, nurses, and radiographers. The basis for the prescription of radiation therapy takes into account diagnostic studies, the limitations of radiologic studies, evaluation of tumor extent (staging), knowledge of pathologic characteristics of the disease, a clear definition of the goal of therapy, and consideration of appropriate and alternative treatment modalities. The optimal dose of irradiation depends on the volume to be treated, the anatomic location, the histologic type of the tumor, the stage, and the potential regional spread. The dose-limiting factor usually is one or more normal structures in the region. The patient's general condition must be evaluated initially, with periodic assessment of treatment tolerance during irradiation. The goal is to identify the full extent of the tumor and areas of possible spread. Several considerations must be taken into account when determining the volume to be treated. These considerations include the tumor histology; the extent of gross disease; regions of microscopic spread but no gross disease; whether the treatment is being given postoperatively or in an undisturbed tumor bed; and the tolerances of adjacent structures. A plan must then be devised to treat this entire region to the dose desired for each region while keeping the volume of normal tissue below its tolerance dose.

The process of designing a radiation field starts with *simulation*, which is used to map out the extent of disease and its relationship to other organs when the patient is in the treatment position. Once simulation has been performed, the treatment position cannot be altered without the risk of inaccurate treatment delivery. Initially conventional simulators were fluoroscopy units designed to mimic the geometry of the treatment machines. Fluoroscopy was used to outline the boundaries of the field, with plain film x-rays being taken to include the general outline of the area to be treated. Although fluoroscopic simulators still are in use, many three-dimensional (3-D) treatment planning systems now are available to permit more accurate or more conformal delivery of radiation treatment. 3-D treatment planning systems use CT data (in some cases, augmented by fusion with other radiologic modalities) to simulate radiation delivery. This can be accomplished in a variety of ways:

- The field can be set up by transferring CT data onto conventional simulation films.
- CT images can be transferred to a computer-based treatment planning system. The fields are designed using the CT-based planning system, with verification (i.e., checking the treatment position) performed by taking x-ray films on a conventional simulator.
- The third and most efficient method is to use a CT simulator to set up the radiation fields. The CT simulator combines the processes of obtaining CT images and field design. CT images of the patient are transferred directly to a computer system that allows the physician to outline the tumor volume and critical structures on individual CT slices. This, in effect, produces an accurate 3-D recreation of both the tumor that is to be treated and normal tissues that are to be avoided during the delivery of radiation.
- Additional data from magnetic resonance imaging (MRI) scanning or positron emission tomographic imaging can be fused with images obtained in the CT simulator in order to improve the accuracy of planning.

After the image data sets are obtained in any type of simulation, careful review of the clinical data must be done to delineate the tissue to be treated. The volume to be treated is defined as the *target volume* and is created by adding three components together.[125] First, the gross tumor volume (GTV) is delineated. The *gross tumor volume* consists of all known detectable disease, including any abnormal regional lymph nodes. This volume refers to the total volume of tumor detectable by diagnostic procedures such as CT or MRI scanning and endoscopic procedures. The *clinical tumor volume* (CTV) encompasses the gross tumor volume plus regions considered to harbor potential microscopic disease and other areas at risk for spread, such as draining lymphatic regions. The *planning target volume* (PTV) includes a margin around the clinical target volume to allow for internal target motion, other anatomic motion during treatment (e.g., respiration), and variations in treatment set-up. Finally, a margin must be added to account for the physical characteristics of radiation such as the penumbra (the edge of the beam where dose falls off rapidly). After a complete surgical resection with no residual detectable tumor and clear surgical margins, a GTV cannot be defined and the radiation oncologist will proceed directly to outline a CTV. Examples of 3-D treatment planning are shown in Figure 29-21.

The planning process also involves choosing the number of radiation beams required, the energy of these beams, the angles, and the weighting (i.e., proportion of total energy deposition) of these beams needed to deliver the required radiation dose to the tumor with optimal sparing of normal tissues. Beams also may be modified to improve the delivery of dose. After the plan has been designed by radiation physicists, *digitally reconstructed radiographs* are produced from CT data to represent the treatment fields. *Beam's eye views* also are valuable to the radiographers delivering the treatment, since they offer a radiographic representation of the orientation of each beam. The availability of 3-D treatment planning has allowed for much more complex plans in the attempt to increase the therapeutic ratio

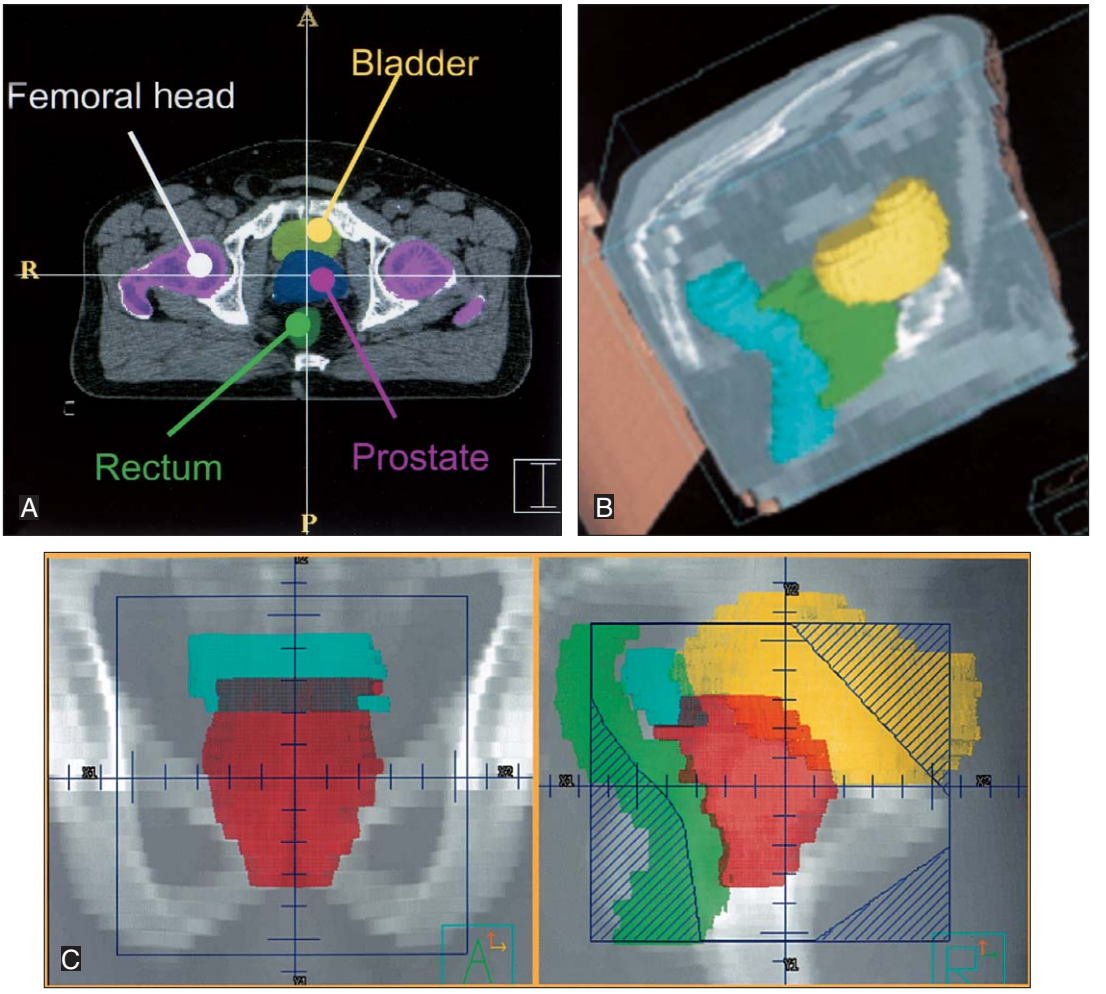


Figure 29-21 • **A,** Transverse CT scan of a male pelvis with simulated organs shown. **B,** Three-dimensional surfaces of the prostate (*green*), rectum (*blue*), and bladder (*yellow*) reconstructed from outlines drawn on CT images. **C,** Digitally reconstructed radiographs (DRRs) of conventional anteroposterior and lateral fields. Prostate is shown in red, seminal vesicles in blue, rectum in green, and bladder in yellow. (From Cox JD, Ang KK [eds]: Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003.)

via the design of radiation fields, as the doses to the tumor and normal organs can be evaluated accurately and three dimensionally. This evaluation process allows assessment of the possible toxicity that could result from the radiation treatment via the evaluation of a *dose volume histogram*, which shows the dose delivered throughout the volume of the tumor and each normal organ in the radiation field. Although usually it is unacceptable to treat an entire organ beyond its tolerance, there are circumstances when portions of an organ may be treated to close to or even beyond tolerance. A consideration is whether the organ in question is considered to have a serial or parallel structure (see previous discussion). In an organ with a serial structure, failure of any component of the organ will cause failure of the entire organ. An example of this might be the spinal cord, where taking any segment of the cord beyond cord tolerance will cause failure of everything downstream. In a parallel organ, however, such as the lung or kidney, the patient might be able to tolerate loss of part of the organ's function, provided certain volume considerations are not exceeded (Fig. 29-22).

Normal tissues can be shielded within radiation beams in various ways. The first shields or blocks were manually placed pieces of lead or depleted uranium that were inserted in the radiation field to shield the structures below them. Following the discovery of a low-melting-point alloy of lead with similar beam attenuating properties, it became possible to create complex blocks that followed the divergent properties of the beam to shield organs defined on the simulation films more accurately.[126] Blocks were custom made for each patient, taking into account the divergence of the beam from its source. A newer method of shielding available in modern linear accelerators involves the use of a *multileaf collimator* (MLC). The MLC system uses 1- or 0.5-cm "leaves" that actually are partitioned jaws of the collimator in the head of the treatment machine. These leaves can be moved in from the edges of the field to block the radiation field and effectively shape the beam as desired (Fig. 29-23).

Once treatment planning is completed, including verification of the treatment position if required, the patient begins the course of radiation therapy. Each day, the patient is positioned by treatment radiographers in the exact position in which the simulation and verification were done. To aid in positioning, immobilization devices are often used, such as foam knee supports, vacuumed bags for limbs, body casts, or perspex/thermoplastic head masks ("shells"). These are made prior to simulation and are kept for use throughout the entire radiation course. For young children (generally less than 4 years of age) or for any patient unable to keep still when left alone in the treatment room, general anesthesia may be required for simulation and for each fraction of radiation therapy. Most modern radiation treatments are *isocentric*, meaning that there is one point around

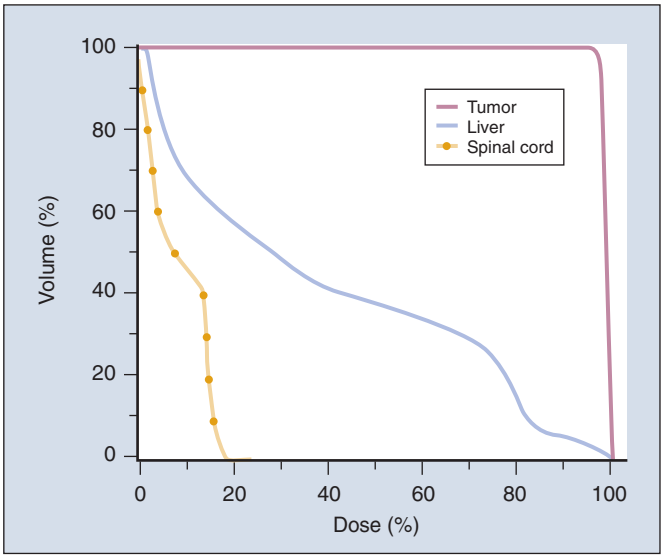


Figure 29-22 • Dose-volume histogram. The percentage of the volume of a structure receiving a percentage dose level or more is illustrated in this cumulative histogram. For the tumor, 100% of the volume receives 100% of the dose, which is the desirable situation. For normal structures, lesser doses are given. In this example, 40% of the liver received 40% or more of the dose, and 20% of the spinal cord received approximately 17% or more of the dose. A small portion of the liver received more than 90% of the prescribed dose, while no portion of the spinal cord received more than 20% of the prescribed dose. This plot is quite useful in presenting a large amount of complex three-dimensional dose-volume information in a fashion that can be assimilated quickly. (From Lichter AS: Radiation therapy. In Abeloff M [ed]: Clinical Oncology, 2nd ed. London, Churchill Livingstone, 2000, pp 423–470.)

which the treatment machine ("gantry"), the couch, and the collimator in the head of the treatment machine rotate. Laser lights in the simulator and the treatment room are used to assist in the positioning of the patient relative to the isocenter. The reproducibility of the patient's treatment position is monitored on a daily or weekly basis by the use of portal images taken from the treatment machine while the patient is in the treatment position. Because treatment machines produce megavoltage radiation, the quality of these images is inferior to those produced by diagnostic machines, which produce radiation in the kilovoltage range (see the section on Photoelectric Effect).

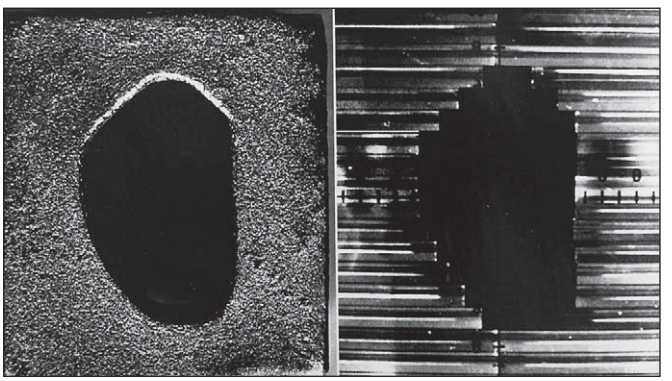


Figure 29-23 • Traditionally, radiation fields have been shaped by molding blocks made from a low-melting-point lead alloy (*left*). The same shape can be created within seconds using a multileaf collimator (*right*). Multiple pairs of thin leaves are each driven by their own motor. The desired shape of the field is entered into a computer that drives the leaf motors and creates the desired shape. (From Lichter AS: Radiation therapy. In Abeloff M [ed]: Clinical Oncology, 2nd ed. London, Churchill Livingstone, 2000, pp 423–470.)

Clinical Use of Radiation Therapy

Radiation is employed to treat cancer in most parts of the body. It can be used as definitive treatment (with or without chemotherapy) where radiation is the sole curative modality (Table 29-7). This type of definitive radiation therapy is used in place of a surgical procedure, and it is often referred to as "organ sparing" or "organ preserving." Examples include the treatment of laryngeal cancer, cervical cancer, and localized bladder cancer.[87,127,128] Brachytherapy also is used in this context (see later discussion). If the cancer is not eradicated completely by radiation therapy, or if it recurs, subsequent surgical resection is described as *salvage*.

Radiation also can be used prior to surgical excision ("neoadjuvant radiation therapy") or after a definitive surgical procedure ("adjuvant radiation therapy"), either to reduce the morbidity of surgery or to increase the likelihood of local and regional control.[129,130] The aim of combining treatments usually is to improve the chances of cure and to preserve organ function. Clinical examples of these strategies include the treatment of breast cancer and soft tissue sarcoma.

As described earlier in this chapter, chemosensitization of tissues to radiation can have a synergistic effect on tumor cell kill, thus increasing the therapeutic index. Such effects have been demonstrated in the treatment of head and neck cancer, small cell lung cancer, non-small-cell lung cancer, cervical cancer, bladder cancer, anal cancer, pancreatic cancer, glioblastoma multiforme, and esophageal cancer.[87–92,131] The most prominent examples of the importance of combining concomitant chemotherapy with definitive radiation therapy are improvements in survival that have been demonstrated by the addition of cisplatin to radical radiation therapy for locally advanced cervical cancer and locally advanced head and neck cancer.[87–89] According to two large multicenter phase III trials studying postoperative radiation treatment of locally advanced head and neck cancer, concomitant cisplatin chemotherapy improves local control and progression-free survival, but it is associated with increased morbidity.[90,132] The reader interested in the use of cisplatin or cetuximab in combination with high-dose radiation therapy for head and neck cancer is referred to Chapter 72. The risk of severe or fatal toxicity to normal tissues should be considered carefully when planning clinical trials of chemosensitization combined with novel approaches to radiation therapy, because fatalities have been reported.[133,134]

Worldwide, radiation therapy is the most widespread method employed to palliate symptoms related to tumor spread or growth.[7,135] The most common example of this clinical use is the treatment of bone metastases with hypofractionated (i.e., a small number of large fractions) courses of radiation therapy to provide rapid relief of pain. Although the feasibility depends on the dose previously delivered and normal tissues within the field, retreatment with radiation should always be discussed with the patient's radiotherapist to provide rapid palliation. Radiation remains the main treatment modality for the relief of symptoms in patients with progressive and incurable cancers. It often is employed to stop bleeding, to relieve obstruction (e.g., of airway, gut lumen), and to relieve pain. Some of the most gratifying experiences in radiation oncology come from the ability to relieve symptoms in patients with progressive cancer and to diminish their reliance on major opioids for analgesia. Further examples of improving a patient's quality of life with radiation therapy are early intervention for spinal cord compression caused by multiple myeloma or treatment of painful bone metastasis from prostate cancer. Radiation oncology in this manner epitomizes Osler's dictum, "To cure sometimes, to relieve often, to comfort always—this is our work."

Table 29-7 Postulated Inter-relationship of Biological Dose, Tumor Size, and Control by Irradiation

Total Dose (Gy)*	Histology	Size	Control (%)
50	Squamous	Subclinical (<10^6 cells)	95+
	Adenocarcinoma		
60	Squamous	<2 cm	85
		>4 cm	50
65	Squamous	2–4 cm	70
70	Squamous	2–4 cm	90
	Adenocarcinoma	>4 cm	60
75+	Squamous	>4 cm	90

*Approximation based on a minimum tumor dose of 2 Gy per fraction and five fractions per week.
From Cox JD, Ang KK (eds): Radiation Oncology Rationale, Technique, Results, 8th ed. St. Louis, Mo, Mosby, 2003, p 33.

NEW MODALITIES IN RADIATION

In addition to research directed at increasing the therapeutic ratio in radiation therapy, many of the largest advances in radiation oncology have resulted from improvements in the technology used to deliver radiation. Although it is not feasible to cover all the recent major advances in radiation therapy in this section, the basic principles are described for four modalities that have been adopted as important radiation treatments by large cancer centers.

Brachytherapy

Derived from ancient Greek word for "short distance" (*brachy*), the term *brachytherapy* refers to the placement of radioactive seeds or sources inside or next to a tumor. It is also known as *sealed source radiation therapy* or *endocurietherapy*. The seeds/sources deliver radiation directly to the tumor, potentially sparing surrounding healthy tissue better than external beam therapy or teletherapy.[135] If brachytherapy is used as an alternative to surgery, for example, in prostate or cervical cancer, it is described as "organ sparing." The radioactive sources are referred to as *sealed sources*, as opposed to systemic targeted radionuclide therapy (see the section on Systemic Targeted Radionuclide Therapy), in which the radioactivity is unsealed. Thin needles or hollow applicators often are used to insert sealed sources into the tumor. Interstitial, intracavitary, and intravascular brachytherapy currently are practiced.

Interstitial Brachytherapy

In interstitial brachytherapy, sealed sources are inserted into tissue, for example, the oral cavity, skin, or anus. The most common sealed source is iridium 192 wire. Iridium wire can be arranged using either the Manchester or the Paris systems; the latter was designed specifically to take advantage of the new nuclide.[136–138] The aim is to treat all parts of the target volume within 10% of the prescription dose. This form of brachytherapy can be further subdivided into two types: permanent, in which sealed sources remain inside the body; and temporary, in which the seeds are removed from the body after the treatment. Cancers treated with temporary implants include soft tissue sarcoma and squamous cell carcinoma of the oral cavity. In the treatment of prostate cancer, radioactive seeds (e.g., iodine 125) about the size of a grain of rice stay within the treatment area permanently. Some migration of the seeds may occur with time.

Intracavitary Brachytherapy

Intracavitary brachytherapy places the sources inside a pre-existing body cavity. The most common applications of this method are gynecologic, particularly for cervical cancer, although it also can be used in other cavitary structures such as the nasopharynx or rectum. The move to reduce the medical staff's radiation exposure led to the introduction of *remote afterloading* brachytherapy devices, in which hollow tubes are connected to a safe containing a small radioactive source welded to a wire that is driven out by a stepping motor to predetermined positions to deliver radiation treatment. The motor is engaged only when all staff have left the shielded room that holds the patient for the duration of the treatment. Over 50 different types of intracavitary applicators exist for remote afterloading.[136] Although *high-dose-rate* (HDR) brachytherapy, often using iridium 192, may be performed as an outpatient procedure, low-dose-rate (LDR) brachytherapy with cesium 137 requires hospital admission because of the length of continuous treatment.

Intravascular Brachytherapy

Intravascular brachytherapy places a catheter with the sealed sources inside a blood vessel, usually an artery. The most well-established application of this method uses strontium 90 as a treatment for coronary artery stenosis in ischemic heart disease. More recently, glass or resin microspheres containing yttrium 90 have been developed to treat hepatocellular carcinoma or liver metastases.[139]

Systemic Targeted Radionuclide Therapy

Systemic targeted radionuclide therapy involves the delivery of radioisotopes specifically to cancer cells. This can be achieved through the design of radiolabeled pharmaceuticals targeted against cell surface molecules that are differentially expressed in cancer compared to normal cells. The radiobiologic effects of these agents depend on the physical characteristics of the radionuclide, such as half-life and the nature of the particulate radiations that are emitted, and on the abundance and distribution of the target molecule within the tumor.[140] An important example of systemic radiation therapy is the use of ^{131}I-NaI to treat thyroid cancer and nonmalignant hyperthyroidism.[141] The success of this treatment is due to the selective uptake and concentration of iodine by the thyroid. This treatment has been used for over half a century, and hundreds of thousands of patients have received this therapy worldwide. Radioiodine therapy is remarkably safe; the only common side effect is hypothyroidism. An overview of long-term safety data suggests that the risk of developing thyroid cancer or other primary malignancies is not increased by radioiodine therapy.[7]

Delivering radioisotopes to cancers of other organs with similar precision has proved more challenging. The discovery of monoclonal antibodies (mAb) in the mid-1970s (see Chapter 34) gave rise to much optimism that, if directed against tumor-associated antigens, they could be used to deliver radioisotopes specifically to tumors.

After years of development and research, this treatment modality, called radioimmunotherapy (RIT), has come to fruition. The CD20 differentiation antigen, expressed by more than 95% of B cell lymphomas, is targeted by mAbs conjugated to iodine 131(^{131}I-tositumomab; Bexxar [GlaxoSmithKline]) and ytrrium 90-^{90}Y-ibritumomab tiuxetan; Zevalin [Biogen Idec Inc]). Both agents are approved for use in the treatment of relapsed low-grade or follicular B cell lymphoma, with an overall response rate of about 80%.[142] These drugs often are effective even in tumors that are resistant to treatment with a naked anti-CD20 antibody, rituximab. Other indications for RIT in the treatment of non-Hodgkin's lymphoma, such as in the adjuvant setting after chemotherapy and as preparation for stem cell transplantation, are being explored in clinical trials.[143]

In contrast to the successful treatment of hematologic malignancies, RIT of the common solid malignancies has been severely limited by toxicity to the bone marrow, poor tumor penetration, the significantly lower radiosensitivity of these malignancies compared to NHL, and the development of an immune response to the mAbs, which has restricted the ability to administer repeated treatments. Numerous phase I and II trials of radiolabeled antibodies directed against a variety of tumor-associated antigens have been conducted.[144] A few patients have achieved complete response, but more often partial or minor responses are reported. Some encouraging results have been reported in the setting of minimal residual disease, because small tumor deposits and micrometastases accumulate disproportionately high amounts of radioimmunoconjugates compared to larger tumors. Several research strategies are being pursued in an effort to improve the RIT of solid tumors.[145,146]

An important development in the field of systemic targeted radiation therapy has been the recognition that small peptides that are natural ligands of surface receptors might be used as vehicles for radioisotope delivery. This form of treatment has been called *peptide receptor radiation therapy*.[147] The low molecular weight of peptides results in efficient tumor penetration. Peptides are rapidly eliminated from the blood by renal excretion, which results in lower bone marrow toxicity and permits dose escalation. Peptide-directed radiation therapy using radiolabeled octreotide (a synthetic analogue of somatostatin) has been tested extensively in tumors that express somatostatin receptors.[148]

In general, β-emitters have been use for systemic radiation therapy. Since β particles have a track length of a few millimeters, not every cell within a tumor need be directly targeted. Adjacent cells will be irradiated through the so-called "crossfire" effect. Unfortunately, the crossfire effect also may result in the irradiation of normal cells and contributes to toxicity. For this reason there has been recent interest in isotopes that emit α-particles or Auger electrons.[149,150] These have much shorter track lengths and, therefore, if they can be accurately delivered to malignant tissue, are less likely to cause serious normal tissue damage.

Radioimmunotherapy now plays a central role in the treatment of non-Hodgkin's lymphoma. With further advances in the field, molecularly targeted radiotherapeutic agents are likely to be increasingly important in the treatment of cancer.

Intensity-Modulated Radiation Therapy

Radiation therapy is the earliest example of a targeted therapy for cancer: it aims to deliver a dose to tumor and to diminish the dose to adjacent normal structures. The concept of conformal radiation is not new. The first report of field shaping to conform to the shape of the tumor was published in 1959.[151] Remarkably, automated computer-driven treatment planning also was reported in the 1950s.[152] A great advance was made in the 1970s in making the computer and the conformal planning more three-dimensional by virtue of the development of the beam's-eye view display.[153] The beam's-eye view display is reconstructed from x-ray or CT data and provides a view from the source of the radiation beam. This technological advance, coupled with the development of the diagnostic CT scanner, led to the prospect of anatomy definition that had not been possible in radiation treatment planning and resulted in significant improvement in defining tumor volumes and critical structures.[154] In the late 1980s, 3-D radiation treatment planning systems began to be used more widely.[155] Significant additional technological advancements in 3-D treatment planning systems continue to be made to improve radiation therapy, particularly with regard to the integration of CT and MRI into the planning, verification and monitoring processes.

The goal of 3-D conformal radiation therapy is to shape the area of high dose to the tumor volume while minimizing the dose to the surrounding tissues. The high dose is delivered to the tumor volume using a set of fixed radiation beams, with normal tissue surrounding the tumor volume shielded from receiving the full dose of radiation. This shielding classically has been done with blocks made from Cerrobend, a lead alloy, which stop the transmission of photons to those areas desired to be shielded. The development of the linear accelerator offered the ability to deliver shaped uniform beams from multiple angles as it rotated around the patient. The introduction of the multileaf collimator, whereby the machine shaped the beams rather than requiring additional beam-shaping devices such as Cerrobend blocks, made conformal radiation therapy significantly easier and more widely available.

Because the leaves in a multileaf collimator are computer driven, it also is possible to move the leaves continuously during treatment. Treatment has thus become *four-dimensional* (i.e., in time and space), and allows the use of beams that are deliberately nonuniform to deliver varying doses to varying parts of the treatment field. The CT simulator allows the treatment to be simulated in virtual time rather than in real time, allowing the physicist and physician, assisted by sophisticated computer software, to evaluate dozens or hundreds of treatment plans to optimize the dose to the tumor. This technology forms the basis for intensity-modulated radiation therapy (IMRT).[156] IMRT involves variation in the intensity of the x-ray output from a linear accelerator and the use of multiple shaped treatment fields. Although the treatment can be delivered by standard modern linear accelerators, the planning process is significantly more labor intensive than conventional radiation therapy and requires the use of more sophisticated modeling software for optimization.[157]

Several IMRT delivery techniques are available, such as combining photon and electron beams, including serial tomotherapy, or using a conventional multileaf collimator (Fig. 29-24).[156,157] In tomotherapy, radiation is delivered in narrow slit beams, analogous to the techniques used for CT imaging systems.[157] Treatment is delivered to a narrow slice of the patient in an arc-type rotation. As the machine rotates around the patient, delivering radiation in an arcing manner, "beamlets" of varying intensity of radiation delivered are created by dynamic movement of the machine's multileaf collimator. In areas to which more dose is to be delivered, the leaves of the multileaf collimator are out of the field longer compared with those areas that require less deposition of dose. The end result of these interactions in serial adjoining axial slices is the conformal treatment that is desired. IMRT also can be done using static field techniques, where the beam moves to various fixed positions around the patient, but the multileaf collimator is used to vary the intensity of different parts of the beam during treatment of each field.

In these highly evolved treatments, optimization of these plans would not be possible without specialized computer software.[158] An important concept used for most IMRT is that of *inverse planning*, in contrast to the forward planning that is used for most conventional treatment planning. In forward treatment planning, the beam orientation, shape, size, modifiers, and so on are defined first, followed by the calculation of dose that results from this design. Changes to achieve better dose distribution are made by modifying the beam weighting, adding or subtracting beams, and so forth, until the desired dose distribution is achieved. In inverse treatment planning, the desired dose distribution is stated first, followed by computer

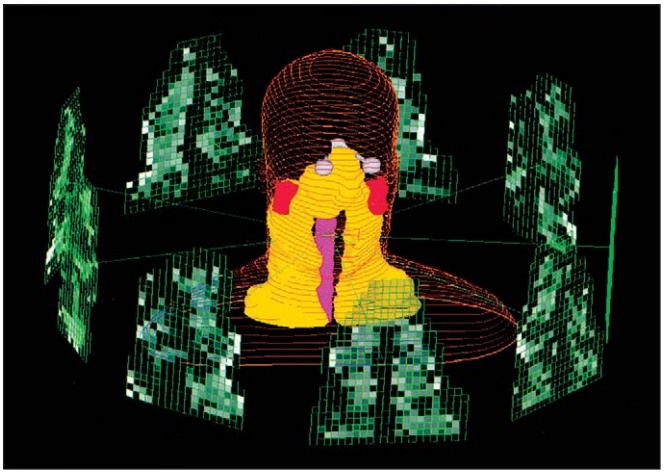


Figure 29-24 • Advanced form of 3-D IMRT, which is based on the use of optimized nonuniform radiation beam intensities incident on the patient. Shown are a 3-D view of the patient, the PTV, spinal cord, parotid glands, and the nine intensity-modulated beams (with gray levels reflecting the intensity value) used to generate the IMRT dose distribution.

optimization to adjust beam intensities to attempt to achieve that dose distribution. *Optimization* includes stating the dose that the tumor bed or areas at risk should receive, as well as limits of dose that normal tissues will be permitted to receive. These parameters are based on maximizing the probability of tumor control and minimizing the toxicity profiles of the various normal tissues and organs. Because normal tissues have different tolerances, different organs will have different thresholds. After the computer optimizes the dose distribution, the physician may choose what is deemed to be an optimal plan (Fig. 29-25).

Many clinical studies have verified that IMRT provides superior dose distribution over conventional 3D conformal radiation, although most of these studies have reported on small numbers of patients.[159–163] Since the goal of IMRT is to increase the therapeutic ratio, delivering a higher tumor dose relative to normal tissues, IMRT can be used to escalate the tumor volume to a higher dose while maintaining normal tissue toxicity at a tolerable level. Among the cancer sites investigated using IMRT to escalate total dose are non-small-cell lung cancer, head and neck cancer, intracranial tumors, and prostate cancer.[159–163] Alternatively, IMRT can be used to deliver conventional doses to the tumor bed, resulting in lower dose to normal tissues, with hopes of reducing toxicity. It is anticipated that favorable dose distributions should result in decreased toxicity,

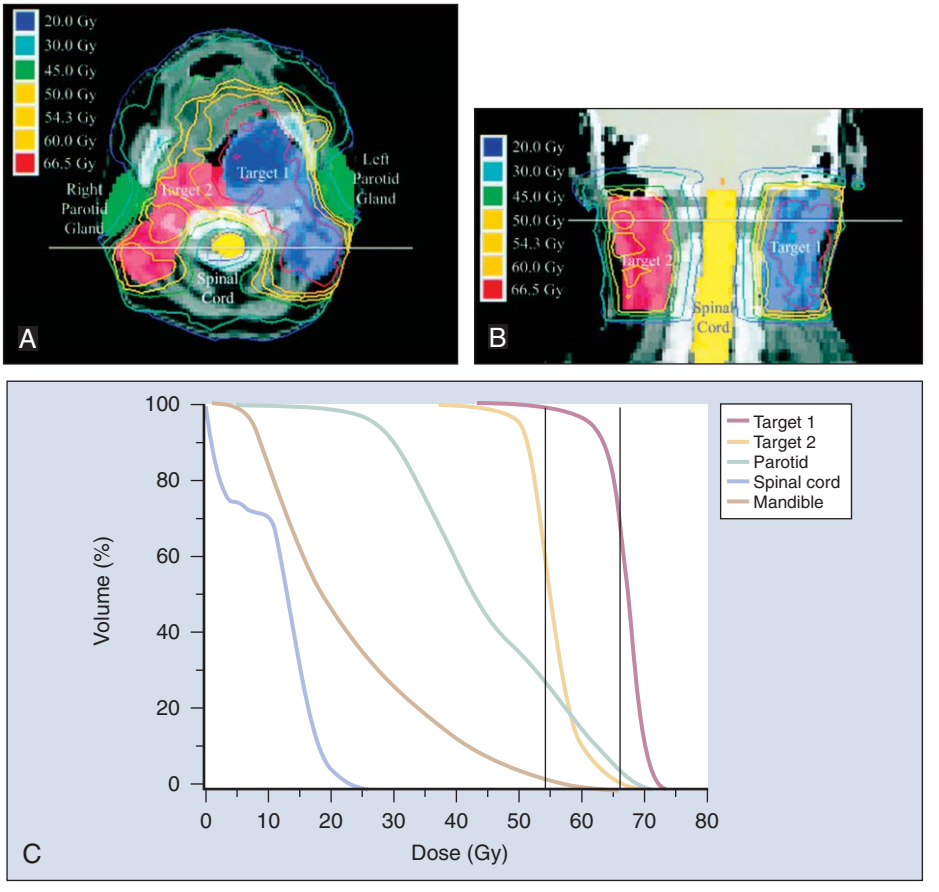


Figure 29-25 • Typical head-and-neck IMRT treatment plan showing conformal avoidance of the spinal cord and parotid glands, while simultaneously delivering multiple dose prescriptions (66.5 Gy and 54.3 Gy) to the two target volumes. **A,** Transverse cross-section. White line corresponds to the position of the coronal cross-section. **B,** Coronal cross-section. White line corresponds to the position of the transverse cross-section. **C,** DVHs of the target volumes and selected critical structures. Vertical bars indicate the prescription doses and highlight the increased dose heterogeneity often encountered as a consequence of conformal avoidance.

although no definitive study has yet demonstrated the clinical impact of IMRT in reducing toxicity to normal tissues. Because the dose distributions made possible by IMRT's planning and treatment delivery are superior to conventional conformal 3D plans, improvements in clinical outcomes are expected, although the long-term safety of IMRT remains to be demonstrated.

As with all technological advances, a number of potentially difficult problems with IMRT exist and need to be addressed.[164,165] With IMRT, it is much more difficult than with 3-D conformal therapy to verify that treatment has been delivered correctly to the patient and to keep a long-term record of that treatment. If there is organ motion—which is inevitable for every organ below the calvarium—then there is a possibility that the dose delivered may differ significantly from the dose planned and recorded, as planning was performed on static images. Finally, as more beams are added to the treatment and the daily treatment time increases, then, although less normal tissue will be treated to tolerance doses, the volume of normal tissue that receives some dose of radiation (e.g., scattered radiation), in fact, increases, as does the total-body dose of radiation. It remains to be seen how significant these problems will be over the longer term.

Particle Radiation Therapy

Particle beam therapy utilizes subatomic particles instead of x-rays or gamma rays to deliver the dose of radiation. The development and application of particle radiation therapy has been motivated by two main factors. One is the physical property that allows for precise dose localization and superior depth dose distribution with heavy charged particles such as protons. The other is the potential radiobiologic advantage of high-linear-energy-transfer (LET) particles. High-LET radiation deposits more dose along its path than conventional x-rays, which are low LET. This offers advantages for several potential reasons. Firstly, high-LET radiation is more damaging to hypoxic cells. Secondly, there is less repair of damage induced by high linear energy transfer radiation. Thirdly, damage from high-LET radiation is less cell cycle dependent.[74]

Neutron Therapy

Neutron radiation therapy first was applied in the late 1930s to attempt to increase killing of hypoxic cells.[166] Because there was little understanding of the high-LET and resultant high relative biologic effectiveness of neutrons, there were severe radiation sequelae with treatment.[167] It was not until the 1960s that clinical trials in neutron therapy were resumed, with adjustments in dose compensating for the high-LET and relative biologic effectiveness of neutrons.[168] Early trials failed to confirm the efficacy of neutron therapy, but because of the potential advantages of high-LET radiation, neutron therapy has been used widely in the attempt to control various tumors (Fig. 29-26). Approximately 30,000 patients have received neutron therapy worldwide, with mixed results.

The most quoted site said to show an advantage for neutrons over conventional photons was unresectable salivary gland carcinomas. Early single-institution studies indicated a therapeutic advantage of neutron therapy over photon therapy, prompting a phase III RTOG/MRC trial that showed a significant local control advantage of neutrons over photons (56% vs. 17%), but with no overall survival advantage due to distant metastases.[169] This advantage also has been shown more recently in both major and minor salivary gland tumors.[170]

Neutron therapy also has been investigated in soft tissue, osteogenic, and chondrogenic sarcomas. These tumors are thought to be radioresistant to conventional x-rays and responsive to neutron therapy.[171] Phase II data and single-institutional data show the pos-

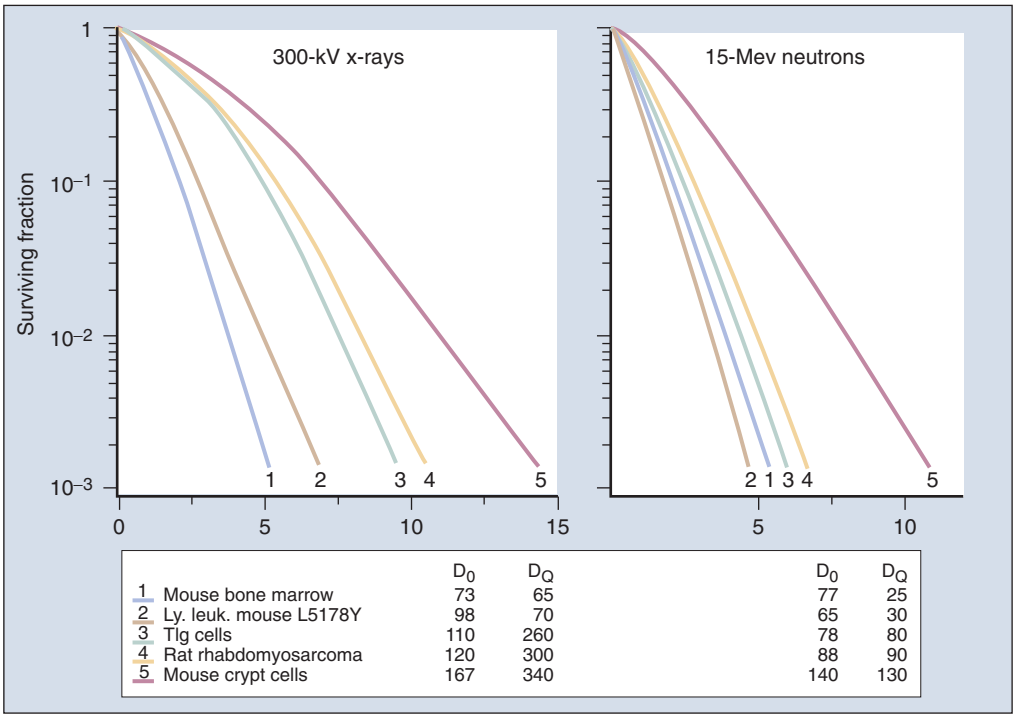


Figure 29-26 • Survival curves for various types of clonogenic mammalian cells irradiated with 300-kV x-rays or 15 MeV $d^+ \rightarrow T$ neutrons. *Curve 1*, Mouse hematopoietic stem cells. *Curve 2*, Mouse lymphocytic leukemia (Ly. leuk.) L5178Y cells. *Curve 3*, Tlg cultured cells of human kidney origin. *Curve 4*, Rat rhabdomyosarcoma cells. *Curve 5*, Mouse intestinal crypt stem cells. The variation in radiosensitivity between different cell lines is markedly less for neutrons than for x-rays. (From Cox JD, Ang KK [eds]: Radiation Oncology: Rationale, Technique, Results, 8th ed. St. Louis, Mosby, 2003, p 46.)

sibility of an advantage in unresectable sarcomas, though this has never been tested in a large-scale randomized clinical trial.[172,173]

Results of neutron therapy in head and neck cancer and in non-small-cell lung cancer have not been as encouraging. Phase III data from head and neck neutron therapy trials indicate higher toxicity with no definite advantage in terms of local control, regional control, or survival with neutrons.[174–176] Similarly, the results of studies done with neutrons in patients with non-small-cell lung cancer are inconclusive, showing no definite advantage with neutrons over conventional photons.[171]

Two randomized clinical trials have compared neutron therapy with photon therapy in patients with prostate cancer.[177,178] These studies show an advantage of neutrons in terms of locoregional control, with one study showing an overall survival advantage. Neither study showed an advantage in terms of disease-specific survival.

There are no active clinical studies involving neutron therapy. It is used selectively in certain specialist centers for inoperable tumors (e.g., salivary gland tumors, selected sarcomas) in which there is some evidence for its effectiveness and in which the dose distribution is superior to conventional radiation therapy. Given its potential for causing late toxicity[179] and because neutron therapy often produces dose distributions that are less desirable than charged particle therapy, interest in neutron therapy has waned.

Proton Therapy

Although protons have a slightly higher linear energy transfer than x-rays, they are not generally considered high-linear-energy transfer particles. Most of their their advantage over x-rays is achieved in their physical dose distribution. When a heavy, charged particle, such as a proton, passes through tissue, the dose it deposits increases slowly with depth, then reaches a sharp increase at its maximum depth of penetration. This is called the Bragg peak (Fig. 29-27). The maximum depth of penetration can be adjusted by varying the energy of the proton beam or by adding or removing compensating material placed in the path of the beam. In clinical use, the Bragg peak often is spread out in depth using specialized filters to achieve the dose deposition pattern desired, but still with the desirable sharp dose fall-off at the deep edge of the beam. Using multiple beams or varying compensators, it is possible to design a 3-D dose deposition that is precisely confined to the tumor volume with minimal dose to the surrounding normal tissue.

Most patients treated with proton therapy have had tumors in close proximity to critical structures.[180] The precise dose deposition patterns of protons made it possible to treat these tumors without crossing the threshold of critical toxicity of the surrounding normal structures (Fig. 29-28).

Uveal melanoma is a malignancy that had been difficult to treat with photons on account of toxicity to normal structures of the eye. Surgical enucleation traditionally has been the treatment of choice. Proton therapy has become an alternative treatment for uveal melanomas. Massachusetts General Hospital has reported a 10- and 15-year actuarial local control rate of 95%, using 70 Gy-equivalent doses. Enucleation was avoided in the great majority of patients, with only 2% to 10% (depending on size of the primary tumor) requiring subsequent enucleation.[180,181] This high rate of control also has been reported by the group at the Paul Sherrer Institute in Switzerland, with a 10-year local control rate of 95%.[182] Again, subsequent enucleation rate was low (8%), with a 15-year overall eye retention rate of 84%.[183] With these outcome data, all patients could be considered for what is basically organ-sparing treatment in the form of proton beam therapy.

Tumors of the paranasal sinuses also have been treated using proton beam therapy, with the precision of proton beams allowing dose escalation up to 76 Gy-equivalent. Using a combination of photons and protons after partial resection or biopsy, local control rates for T3-T4 tumors have been reported up to 85%, again with low toxicity.[180,184]

More commonly occurring tumors have also been treated with proton beam radiation therapy, with the high precision allowing for dose escalation in diseases that are difficult to control with conventional doses. A phase II study in 23 patients with glioblastoma multiforme was undertaken at the Massachusetts General Hospital with dose escalation up to 90 Gy-equivalent using proton beams. Such doses cannot be achieved with photons due to toxicity to critical brain structures. Median survival was 20 months, with a 3-year actuarial survival of 18%. Recurrence was seen in only one patient treated at the 90 Gy-equivalent dose level, but radiation necrosis was observed in 7 of the 23 patients treated.[185]

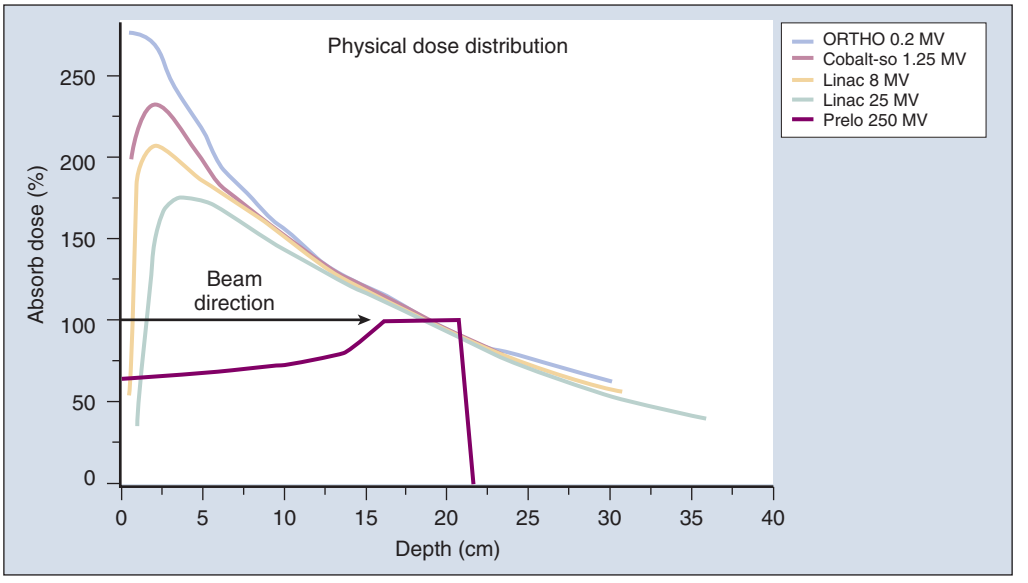


Figure 29-27 • Depth-dose distributions for a proton beam compared with other photon beams. The dose for the proton beam is limited for the entrance tissues, reaches a Bragg peak at the desired depth, then displays an extremely sharp fall-off.

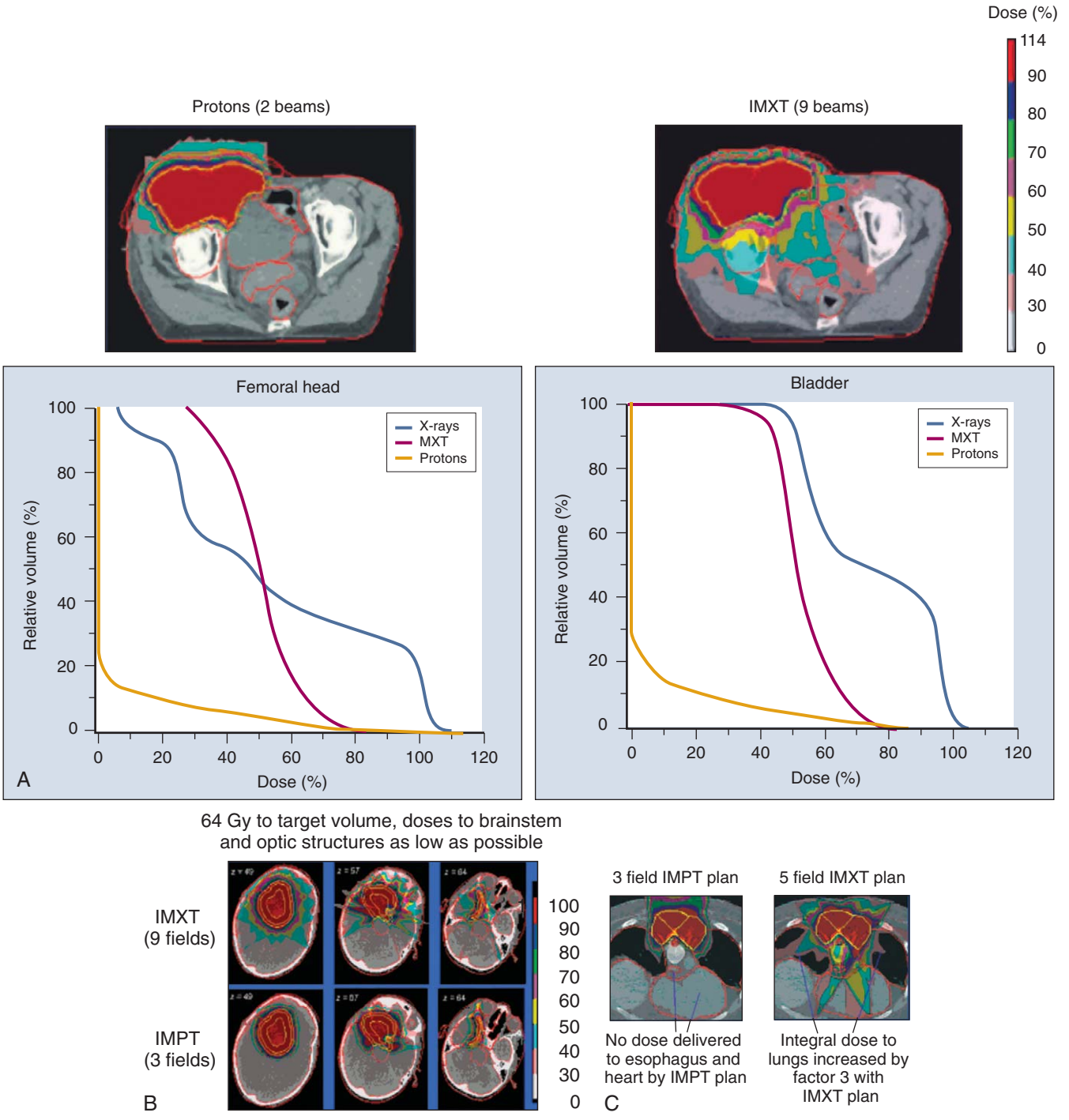


Figure 29-28 • **A,** Proton beam arrangement compared with a complex IMRT plan of nine beams for the treatment of malignant melanoma. Note the full coverage of the target volume with sparing of normal tissues. **B,** Proton beam arrangement compared with an IMRT plan for treatment of a pediatric meningioma. **C,** Treatment of a thoracic paraspinal chordoma requiring contouring of the dose distribution around the spinal cord, while continuing to provide full coverage to the target volume, more easily attained with proton beams than with a complex IMRT plan. (Used with permission from Anthony Lomax, PhD, Paul Scherrer Institute, Switzerland.)

Meningiomas are another type of CNS tumor that has been treated with protons. In a study of 46 patients with partially resected, biopsied, or recurrent meningiomas, a combination of photons and protons was used to deliver a median dose of 59 Gy-equivalent to the macroscopic tumor volume. The recurrence-free rates at 5 and 10 years were 100% and 88%, respectively. Eight patients, however, developed severe ophthalmologic, neurologic, or otologic long-term toxicity from radiation therapy.[186]

Prostate cancer is the only tumor in which dose escalation with protons has been tested against conventional radiation in a randomized trial.[187] Patients with T3 or T4 prostate cancer who received 50.4 Gy via photons to a pelvic field were randomized to receive either an additional 16.8 Gy with photons or 25.2 Gy equivalent with protons. There was no difference in overall survival, disease-specific survival, or local control between the two groups. Additionally, there was an increase in toxicity in the proton arm, owing to the

higher dose delivered to the rectum.[188] This study was done in the 1970s, prior to the recognition of the importance of volume considerations in determining rectal toxicity. More recent studies have demonstrated that sparing of the rectum during prostate irradiation can be achieved with proton therapy.[189]

The role of proton therapy is currently being studied in patients with prostate cancer, hepatocellular carcinoma, and non-small-cell lung cancer, and in combination with stereotactic radiosurgery (see previous discussion).[180,190–192] Proton therapy provides a further example of the application of technological advances in the field of radiation oncology (Box 29-1). Because it represents the optimal therapeutic ratio available in terms of dose delivery for many cancers, its availability as a standard treatment modality is anticipated to become more widespread.

CONCLUSIONS

Radiation therapy has progressed rapidly since the discovery of x-rays over 100 years ago. Understanding of the physical and biologic properties of radiation has led to great advances in the field of radiation therapy, making it possible to cure hundreds of thousands of patients worldwide and spare thousands more from the mutilating consequences of surgery. With the advent of computers and conformal 3-D treatment planning, the field of radiation oncology has advanced further in recent decades. The therapeutic index has been increased by dose escalation and more accurate shielding of normal tissues. Recent innovations such as systemic targeted radionuclide therapy, novel approaches to brachytherapy, and dose escalation with IMRT offer hope for further improvements in radiation treatments for patients with cancer. Clinical studies investigating these modalities and the strategic development of combination treatments, particularly with cytotoxic chemotherapy and molecular biology-based targeted therapies, will ensure continued advancement of the field of radiation oncology in years to come.

Box 29-1. TREATMENT STRATEGIES FOR CHORDOMA OF THE BASE OF SKULL

Tumors of the skull base are difficult to treat because of their location. The base of the skull involves and is surrounded by critical structures such as the brain stem, the optic chiasm, the optic nerves, the cranial nerve roots, the arterial circle of Willis, and the cervical spinal cord. Two primary malignant tumors that arise in the skull base are chordomas and chondrosarcomas, both of which can cause debilitating morbidity or even death due to the position in which they arise. Both types of tumor are difficult to treat, either with surgery or conventional radiation therapy, without the risk of leaving the patient with significant disability. These tumors require high doses of radiation if local control is to be achieved, and retreatment with radiation usually is not feasible without significant risk of morbidity.

Using a combination of 3-D conformal x-ray therapy and charged particle therapy (protons), a more desirable dose distribution can be achieved than that obtained using conformal megavoltage photon radiation alone. The Bragg peak (see Fig. 29-27) can be used to allow a steep fall-off of dose within a few millimeters of critical organs. In two reported series of patients with chordomas arising in this anatomic region, the application of this novel combination of radiation modalities has resulted in local control rates of 65% to 70%.* In these small series, median tumor dose was 70 Gy-equivalent (physical dose ×1.1—the relative biologic effectiveness for protons). A low incidence of long-term toxicities was reported.

*Austin-Seymour M, Munzenrider J, Goitein M, et al: Fractionated proton radiation therapy of chordoma low-grade chondrosarcoma of the base of the skull. J Neurosurg 1989;70:13–17; and Fagundes MA, Hug EB, Liebsch NJ, et al: Radiation therapy for chordomas of the base of skull cervical spine: patterns of failure outcome after relapse. Int J Radiat Oncol Biol Phys 1995;33:579–584.

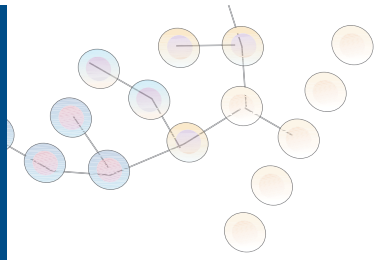
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30 Systemic Therapy

Carl E. Freter and Michael C. Perry

SUMMARY OF KEY POINTS

History of Drug Discovery

- The history of cancer chemotherapy and of the disciplines of medical oncology has been that of drug discovery.

Development of Combination Chemotherapy

- Virtually all of the curative chemotherapy regimens that have been developed for hematologic malignancies and for advanced solid tumors use combinations of active agents.
- Mathematical models describing tumor cell kinetics and tumor cell drug resistance have had a strong influence on the development of clinical regimens.
- A series of principles for the development of effective combination regimens was developed in the 1970s and continues to be used today.
- The concepts of alternating, non-cross-resistant chemotherapy, hybrid chemotherapy, dose-intense chemotherapy, and dose-dense chemotherapy have generated hypothesis-driven clinical research that has led in some cases to superior chemotherapy regimens.

Targeted Agents and New Directions in Drug Development

- New categories of agents include tyrosine kinase and multikinase inhibitors, differentiating agents, antiangiogenesis agents, monoclonal antibodies, gene therapy, and vaccines.
- An increasing number of these targeted agents are becoming established in standard therapy, often as part of combination chemotherapy regimens.
- Computer modeling and combinatorial chemistry are powerful new tools for drug development.
- The roles of pharmacogenetics, pharmacogenomics, pharmacoproteomics, pharmacokinetics, and pharmacodynamics are likely to become increasingly important in oncology.

Clinical Uses of Chemotherapy

- Adjuvant chemotherapy is the logical extension of the use of chemotherapy in patients who remain at high risk of recurrence after all clinically detectable disease has been eradicated (Box 30-1).
- In specific cancers, the application of chemotherapy prior to any other anticancer therapy (neoadjuvant therapy) can provide improved survival and/or organ sparing and preservation of function.
- The most common use of cancer chemotherapy is in the management of advanced and metastatic disease. Although curative for several advanced cancers, chemotherapy is largely palliative for metastatic disease.

Chemotherapeutic Process

- The choice of chemotherapy for a specific patient must take into account physiologic age, performance status, nutritional status, prior therapy, pharmacogenetics, and comorbid conditions.
- The principles of drug selection include the pharmacologic characteristics of the individual agents, the route of administration, and the toxicity profile.
- Information regarding individual chemotherapeutic agents is presented according to drug class, mechanism of action, dosage forms, drug interactions, pharmacokinetics and metabolism, indications, and toxicity.

INTRODUCTION

Systemic therapy is defined as chemotherapy, hormonal therapy, or targeted therapy. Although chemotherapy is a relatively recent addition to the therapeutic armamentarium for the treatment of patients with cancer, its role is expanding, and cytotoxic agents are used at some point during treatment for most patients with cancer. Historically, chemotherapy was used principally as therapy for metastatic cancer after failed local therapies, and it remains the treatment of choice for such patients. However, the evolution of cancer therapy over the past several decades has resulted in increased recognition of the important role that chemotherapy can play in the management of apparently localized and surgically resectable disease. This recognition has led to the development of other applications for systemic therapy designed to decrease postsurgical recurrences, when given as adjuvant therapy, or to allow more limited organ- and function-sparing surgical procedures when chemotherapy is given preoperatively or concurrently with radiation therapy. The recent addition of molecularly targeted therapies raises new possible therapeutic options.

Box 30-1. MANAGEMENT APPROACH: CANCERS THAT ARE TREATED EFFECTIVELY BY ADJUVANT CHEMOTHERAPY

Wilms' tumor
Osteosarcoma
Breast cancer
Colorectal cancer

Perhaps more than any other disease, cancer requires close interaction among medical specialties. As our knowledge of how to combine available therapies evolves and as the efficacy and specificity of available chemotherapeutic agents improve, chemotherapy will play an even greater role in improving both the survival and quality of life for patients with cancer.

HISTORY OF DRUG DISCOVERY

Paul Ehrlich coined the term *chemotherapy* in reference to the systemic treatment of both infectious diseases and neoplasia. Although the concept of treating cancers with drugs can be traced back several centuries, there were no examples of truly successful systemic cancer chemotherapy until the 1940s. Gilman and Philips[1] conducted the first clinical trial of nitrogen mustard in patients with malignant lymphomas at Yale University in 1942. The use of nitrogen mustard as a chemotherapeutic agent was suggested by the serendipitous findings of marrow and lymphoid hypoplasia in seamen who had been exposed to mustard gas after the explosion of a ship that contained material manufactured for use in chemical warfare in World War II.[2] This discovery supported previous evidence of a systemic lympholytic effect from alkylating agents of this type. The dramatic regressions of the lymphomas that were noted in this original study generated tremendous excitement for this new field of medicine, although enthusiasm was dampened by the fact that regrowth of tumor seemed inevitable. The results, initially published in 1946, could be said to mark the beginning of modern chemotherapy.

Other "experiments of nature" and the observations of well-trained scientists have yielded a number of other important leads, including the recognition by Farber and colleagues[3] of the importance of folates in cell growth in acute leukemia in children and the subsequent development of the first antifolate antimetabolites. This class of compounds produced perhaps the first examples of drug-induced cures of a metastatic cancer in gestational choriocarcinoma, and they remain in wide clinical use today.[4] For their recognition of the importance of nucleic acid synthesis to inhibition of cell growth and for the development of effective antipurine analogs for cancer and other diseases, Elion[5] and Hitchings were awarded the Nobel Prize for Medicine in 1988. Serendipity also played a role in the recognition of the potential of vinca alkaloids, epipodophyllotoxins, and platinum coordination complexes as chemotherapy agents.[6,7] This scenario has been repeated with sufficient frequency that drug discovery programs such as that of the National Cancer Institute have made extensive use of the approach of mass screening of both natural products and synthetic compounds to identify lead compounds with potent antitumor activity and unique mechanisms of action.

Screening is key to the process of drug development because it narrows the enormous number of candidate drugs to a more manageable number for further study and possible clinical evaluation. Traditionally, this screening system has used transplantable murine tumors to search for evidence of biologic activity.[8] Although this system identified a series of compounds for clinical trial, there was continued uncertainty regarding the relevance of these murine cell lines to human cancers. The current screening system employs a panel of human cancer cell lines grown in culture that represent the major histologic subtypes and sites of origins of human cancer. It is also possible, and probably important, to include cell lines that express various drug resistance phenotypes, such as multidrug resistance, to evaluate new agents against tumor cells that manifest these potentially clinically important cellular characteristics. It also has been possible to automate the testing of candidate drugs in this system so that high-volume screening can be maintained.[9] Because this screening system uses human cancer cell lines, it is hoped that it will identify agents that have unique promise against advanced solid tumors that would not be identified by using other methods.

This organized approach to random screening of large numbers of compounds must be complemented in the drug development effort, however, by attempts to exploit new therapeutic targets that are identified in ongoing basic cancer research. When a putative target is identified on the basis of its biologic significance in the cancer cell, this strategy suggests that the ability of potential therapeutic agents to interact with this target and to inhibit or modify its function should be evaluated as a primary screening procedure. This mechanism-based screening is often performed in simple cell-free systems in which the target and effector are isolated. Drugs that have been identified as promising candidates by this mechanism-based approach to drug development also require test systems that have been developed to validate their biologic activity in whole cells and experimental animal tumor models. Active new agents are needed for the treatment of all common human cancers. The ongoing work in drug development is crucial if our use of chemotherapy is to continue to improve and if its role in potentially curative therapy is to expand. A number of promising and novel strategies are undergoing clinical trials, including antiangiogenesis factors, drugs that affect intracellular signaling pathways, differentiating agents, agents that affect a cell's ability to undergo apoptosis, and gene-specific therapies such as antisense oligonucleotides and ribozymes. These approaches and others that will undoubtedly follow offer great promise for the future of cancer treatment.

DEVELOPMENT OF COMBINATION CHEMOTHERAPY

Chemotherapy initially involved the use of single agents that were associated with responses but almost universal disease progression and dose-limiting toxicity. The development of new agents quickly led to the birth of the concept of combination chemotherapy. However, single-agent therapy retains an important place especially in palliative therapy after initial combination chemotherapy fails. The principles of combination chemotherapy were developed both empirically and with a theoretical basis provided by the fields of tumor cell growth kinetics and drug resistance.

Tumor Cell Growth Kinetics

More than 30 years ago, Skipper and Schabel used a murine leukemia model to define the concept of logarithmic cancer cell growth with the corollary concept that a specific dose of a chemotherapeutic agent would produce an associated specific log cell kill that was independent of the number of cells in the tumor.[10] These studies established the important concepts of growth rate, tumor bulk (or cell number), and chemotherapy dose as determinants of therapeutic outcome. While appealing in its mathematical simplicity, pure logarithmic tumor cell growth is, in fact, the exception rather than the rule. This is particularly true in solid tumors, whose growth involves complex functions of heterogeneous growth kinetics, cell death, and development of cancer-promoting growth properties, including the capacity for invasion, metastases, angiogenesis, elaboration of growth factors, and development of mechanisms of chemotherapy resistance (see later discussion). Hence, most of the available data suggest that cancers generally do not grow with a constant doubling time.[11–15] In these cases, the data support a Gompertzian model of tumor growth and regression. In Gompertzian growth, the doubling time increases and the growth fraction of tumor decreases as the tumor becomes larger. Experimental models suggest that this observation is the result of decreased cell production rather than of increased cell loss in larger tumors.[16,17] A tumor theoretically responds to therapy depending on where it lies on the Gompertzian growth curve. In a patient with an advanced cancer and large tumor bulk, this model predicts a lower growth fraction and a lower fraction of cells killed by a given dose of therapy than would be the case with a smaller tumor. The Norton-Simon[18–20] model for the response of tumors to chemotherapy has used the concept of Gompertzian growth to explain clinically observed phenomena and to suggest treatment strategies. The Norton-Simon

model predicts that the log cell kill will be greater for very small cancers than for large cancers and favors, particularly for small tumors, multiple sequential agents at high doses and alternating regimens over more than one cycle to achieve optimum cell kill. The Norton-Simon model has also afforded useful insights into clinical cancer biology. For example, Gompertzian growth kinetics have clarified the rate of tumor regrowth from residual cells that remain after chemotherapy that fails to achieve a cure.[19,20] The increased rate of tumor cell growth that is seen when tumors are small will minimize the differences in survival among patients with advanced disease who achieved complete versus partial responses to systemic chemotherapy, because the residual tumor in the complete responders grows back faster.

Drug Resistance

The earliest experience with chemotherapy made it clear that cancers that are initially sensitive to chemotherapy unfortunately eventually become resistant. The process of bacterial mutation rates of resistance to bacteriophage killing, which was studied and mathematically modeled by Luria and Delbruck,[21] formed the conceptual basis for the Goldie-Coldman model, a mathematical model of genetic resistance of cancer cells to chemotherapy drugs. The Goldie-Coldman hypothesis mathematically describes the likelihood that drug-resistant cancer cells are present in a patient at diagnosis.[22] A fundamental tenet of the Goldie-Coldman model is that chemotherapy mutations that confer chemotherapy resistance occur in 10^3 to 10^6 cells, substantially lower than the limit of clinical detection, which is about 10^9 cells or a 1 cm^3 mass. Goldie and Coldman proposed that tumor cells could acquire drug resistance before drug exposure on the basis of the spontaneous mutation rate that is intrinsic to the genetic instability of a particular tumor. The likelihood that resistant cells are present can be modeled as a function of tumor size or the number of tumor cells and the spontaneous mutation rate of the cells. The predicted frequency of spontaneous mutation of $1 : 10^{-5}$ to $1 : 10^{-6}$ divisions in proliferative tumor cells is consistent with in vitro studies of this phenomenon.[23] Although this discussion has focused on this phenomenon as a means by which cells might acquire drug resistance, it is equally plausible that the same type of genetic events could lead to an increase in vascular invasion and local spread or to an increased tendency to develop systemic metastases.[24] Preclinical studies have demonstrated clearly that the development of the metastatic potential can be the result of genetic instability.[25]

The Goldie-Coldman model predicts that to overcome cancer cell drug resistance most effectively, (1) multiple active agents should be given over the shortest period of time as early in the growth of a cancer as possible, and (2) multiple agents that are given simultaneously will be more effective than sequential agents given at individually higher doses.

Principles of Combination Chemotherapy

Combination chemotherapy has developed both empirically and through the application of principles and predictions of cancer cell kinetics (Norton-Simon hypothesis), and drug resistance (Goldie-Coldman model), into the following principles for combination chemotherapy regimens (Box 30-2):

- All drugs must be active as single agents. The practice of adding an ineffective drug to promote biochemical synergy has rarely produced effective regimens.
- Drugs should be chosen for nonoverlapping toxicity. This spreads toxicity over multiple organ systems, allowing recovery for chemotherapy on schedule, and avoids damaging toxicity to any single organ.
- Drugs should be chosen for different or synergistic mechanisms of action. This achieves the attacking of multiple different cellular targets and the overcoming of resistance at any single target or biochemical pathway.

Box 30-2. MANAGEMENT APPROACH: PRINCIPLES OF COMBINATION CHEMOTHERAPY

1. Only agents that have been proven effective should be used.
2. Each agent used should have a different mechanism of action.
3. Each drug should have a different spectrum of toxicity and (ideally) of resistance.
4. Each drug should be used at maximum dose.
5. Agents with similar dose-limiting toxicities can be combined safely only by reducing doses, resulting in decreased effects.
6. Drug combinations should be administered in the shortest interval between therapy cycles to allow for the recovery of normal tissue.

- Drugs should be chosen that have different mechanisms or patterns of resistance. Cancer cells with resistance to one drug can be attacked by other drugs to which resistance has not developed.
- Drugs should be given according to the optimum dose and schedule. This allows maximum cell kill with a given drug dose and avoids unnecessary toxicity, drug resistance, and "kinetic" chemotherapy failure.
- Drug doses should be individually titrated to end-organ toxicity in individual patients. Reproducible standard toxicity criteria are used for individual organ systems (bone marrow, gastrointestinal, neurologic, dermatologic, etc.). This allows adequate recovery from toxicity to allow cyclic chemotherapy on schedule at the maximum tolerated dose.

Clinical application of the preceding principles has led to a number of concepts with testable hypotheses for the design of chemotherapy regimens. These have included *alternating non-cross-resistant chemotherapy, hybrid chemotherapy, dose-intense chemotherapy* (increased total dose of chemotherapy during a fixed cycle period), and *dose-dense chemotherapy* (increasing dose per unit time, generally by shortening cycle interval). Alternating non-cross-resistant chemotherapy involves the use of multiple active chemotherapy agents with different mechanisms of action organized into two different combination chemotherapy regimens administered on an alternating basis. The Goldie-Coldman hypothesis would suggest frequent alternation of these regimens (e.g., every second cycle), and this has been the general approach taken in prospective clinical trials that have examined this question. A more recent variation on this theme has been the development of hybrid regimens, in which elements of each regimen are administered during each cycle (e.g., on day 1 and day 8) rather than during every second cycle.

In small cell lung cancer, several chemotherapy regimens are available that have roughly equal antitumor efficacies, and alternating chemotherapy regimens have been studied frequently in this disease. Early trials of this strategy in extensive small cell lung cancer demonstrated minimal survival benefit from the use of alternating chemotherapy regimens and a short prolongation of the duration of initial remission in some studies.[26–29] Other studies have suggested that the benefits of using more than one chemotherapy regimen in small cell lung cancer might be more apparent in limited-stage disease, in which a survival advantage has been shown in several small studies.[30,31] In Hodgkin's disease, randomized trials of MOPP versus ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) versus MOPP alternated with ABVD have shown superiority of the alternating regimen and ABVD to MOPP alone in terms of both survival and complete remission.[32] A hybrid regimen of MOPP-ABVD has been shown to be superior to MOPP followed by ABVD.[33] In both cases, however, the testing of the hypothesis is clouded by the fact that in these cooperative group studies, the MOPP regimen consistently required significant dosage reductions. In metastatic breast cancer, studies with a similar design have failed to demonstrate an

advantage of alternating cycles of CMFVP (cyclophosphamide, methotrexate, 5-fluorouracil [5-FU], vincristine, prednisone) and VATH (vinblastine, doxorubicin, thiotepa, halotensin) to either CAF (cyclophosphamide, doxorubicin, 5-FU) or VATH alone.[34] Collectively, these data suggest that the use of alternating non-cross-resistant chemotherapy regimens is an acceptable, but still not mandatory, alternative therapeutic strategy for these diseases.

The Norton-Simon approach advocates a crossover strategy by which each active regimen is used for a longer period of time (i.e., several cycles) before switching to the alternative regimen. Theoretically, this approach accomplishes two important goals. First, it maintains the most dose-intense administration of each regimen by giving it during every cycle rather than during alternate cycles. Second, it addresses the heterogeneous populations of cells, killing the most sensitive, rapidly growing cells first and then treating the slower-growing, more resistant cells as efficiently as possible.

The concept of dose-dense chemotherapy received additional support with the recent publication of a Cancer and Leukemia Group B study in the adjuvant therapy of node-positive breast cancer.[35] A 2×2 factorial design was used, with patients randomized to receive concurrent adriamycin/cyclophosphamide followed by paclitaxel, each for four cycles, or sequential single-agent adriamycin, cyclophosphamide, and paclitaxel, each for four cycles. Patients were also randomized to receive their therapy at 3-week (standard) or 2-week (dose-dense) intervals. Growth factor support was added to the 2-week schedule. Dose-dense treatment improved disease-free survival and overall survival compared with the 3-week cycles. There were no differences in terms of outcome between concurrent or sequential schedules.

The lack of difference between sequential and concurrent therapies raises fundamental questions about the conventional wisdom of combination therapies always being superior to sequential single agents. Although the results might be drug- and disease-specific, the data are consistent with the Norton-Simon predictions that dose density would improve therapeutic results and that giving drugs in sequence while maintaining dose density would maintain efficacy and reduce toxicity.[35]

These concepts have not been definitively tested clinically, and the available results do not totally support either approach. A direct comparison of alternating and sequential chemotherapy in the adjuvant chemotherapy of breast cancer was conducted by using doxorubicin and the CMF (cyclophosphamide, methotrexate, and 5-FU) regimen.[35] In one arm of this study, patients received four courses of doxorubicin followed by eight courses of CMF; in the second arm, patients received two cycles of CMF alternating with one course of doxorubicin. This sequence was repeated four times, for a total of 12 cycles of chemotherapy. The total dose of all drugs was equal, but the patients in the first arm experienced significantly better disease-free and overall survival. In this case, the sequential approach was superior to the alternating schedule.

An intergroup trial involving patients with Hodgkin's disease came to a different conclusion.[33] In this study, a hybrid MOPP-ABV chemotherapy regimen was superior in terms of complete remission, failure-free survival, and overall survival, compared with the sequential use of MOPP followed by ABVD. Whether this study is a valid test of the concept or whether the results reflect the significant dose modifications in the MOPP arm remains unclear.

The Goldie-Coldman and Norton-Simon hypotheses have provided an important paradigm for hypothesis-driven clinical trials in cancer research. Taken together, the results of these trials have been limited by the lack of "ideal" drugs and combination regimens with which to test these hypotheses and perhaps the simplicity of these models in the face of the biological complexity of cancer. The study of drug resistance and tumor cell kinetics has provided important insights into the mechanisms of "chemotherapy failure." However, developing insights into cancer biology suggest that chemotherapy resistance and "kinetic failure" might not be the only mechanisms by which chemotherapy can fail. The existence of tumor stem cells that have different properties and chemosensitivity than their progeny,[36] for example, continues the challenge to develop effective chemotherapy based on hypothesis-driven clinical research.

TARGETED AGENTS AND NEW DIRECTIONS IN DRUG DEVELOPMENT

The term *targeted agents* has come to refer to a growing class of drugs that specifically target cancer cell-specific pathways on a molecular level, including gene expression, growth regulation, cell cycle control, apoptosis, and angiogenesis. The targeting of specific molecular pathways on which cancer cells are differentially dependent offers the attractive advantage of cancer-specific therapy with reduced toxicity to normal tissues. This disparate and growing group of drugs and treatment approaches includes small molecule tyrosine kinase and multikinase inhibitors, differentiating agents, angiogenesis inhibitors, monoclonal antibodies, proteosome inhibitors, histone deacetylase inhibitors, gene therapy strategies, and vaccines. The developing experience with kinase inhibitors, angiogenesis inhibitors, and monoclonal antibodies is that while they produce responses, they are generally not curative and are associated with the development of resistance. This has led to efforts to understand how best to combine these agents with more conventional chemotherapy agents to capitalize on the strengths of each.

Tyrosine Kinase and Multikinase Inhibitors

Basic oncology research has given us many important clues as to the molecules that drive the malignant phenotype. Although the basic defect is in the genome, the expression of that defect is manifested in how the cell interacts with its surrounding milieu, which can include other malignant cells, nearby normal cells, the extracellular matrix, and humoral factors. This interaction affects the cell via surface membrane receptors and second messengers within the cell. These second messengers affect gene expression and cell phenotype via kinase cascades (signal transduction pathways) that are specific to the receptor/second messenger system that is activated. Within these receptor/second messenger systems, many oncogenes are mutated proteins that confer abnormal cellular responses to malignant cells.

An important paradigm for drug discovery in oncology has been identifying recurrent specific chromosomal markers as guideposts to discovery of the biology of their associated genetic alterations in a specific cancer. This might then allow the development of molecularly designed therapy to correct or circumvent biologic changes sustaining the cancer phenotype. A striking example of this approach has been the development of the tyrosine kinase inhibitor imatinib to inactivate the constitutively expressed fusion protein BCR-abl, the biologic abnormality that drives CML, defined decades earlier by the Philadelphia chromosome.[37] Imatinib has subsequently been used to target c-Kit in gastrointestinal stromal tumors,[38] and the success of this approach has driven the development of a growing number of tyrosine kinase inhibitors, including dasatinib, a multikinase inhibitor that targets BCR-Abl, SRC-family kinases, c-kit, EPHA2, and PDGFR-beta, indicated for treatment of CML with resistance to prior therapy including imatinib and resistant Ph+ ALL.[39] Erlotinib, an oral tyrosine kinase inhibitor targeting the epidermal growth factor receptor, has been approved for treatment of non-small-cell lung and pancreatic cancers.[40,41] Sorafenib is an oral multikinase inhibitor that targets Raf, tumor signaling, and tumor vasculature and is approved in advanced renal carcinoma.[42] Sunitinib is another multikinase and angiogenesis inhibitor that is approved in renal cell and gastrointestinal stromal tumors.[43] Lapatinib, a tyrosine kinase inhibitor of HER2/neu and EGFR, has activity in HER2/neu-positive breast cancer progressing after trastuzumab-based therapy (see later discussion).[44] Other members of this family of small molecule kinase and multikinase inhibitors are in active clinical development.

Differentiating Agents

Several classes of compounds have potent in vitro and in vivo differentiating effects on the malignant cell phenotype. These include retinoids, vitamin D analogs, cyclooxygenase inhibitors, and hypomethylating agents. These agents do not eliminate the malignant clone or affect its genotype, but their continued application can cause regression of malignancy, and they might have a role in chemoprevention. All-*trans* retinoic acid represents an example of a targeted therapy that causes striking granulocytic differentiation of the leukemic cells in acute promyelocytic leukemia, in which the chromosomal translocation 15 : 17 results in the expression of an aberrant fusion gene involving the retinoic acid receptor PML-RAR-α.[45] 5-Azacytidine and decitabine are DNA hypomethylating agents that act to restore cellular differentiation in myelodysplastic syndrome and certain leukemias.[46] The COX-2 inhibitor celecoxib has activity in reducing polyps in familial adenomatous polyposis[47] and is being tested in other chemoprevention settings.

Angiogenesis Inhibitors

Solid tumors must stimulate the growth of new blood vessels, a process called *neovascularization,* to obtain oxygen, nutrients, and growth factors to be able to grow and successfully metastasize. Study of the molecular basis of tumor angiogenesis has led to important insights into tumor biology as well as targeted molecular strategies to inhibit tumor angiogenesis. An established agent is bevicizumab, a humanized monoclonal antibody that targets the angiogenic growth factor VEGF. Bevicizumab has modest single-agent activity but has been associated with survival prolongation when combined with conventional chemotherapy for lung, colon, and breast cancer.[48,49] Thalidomide and lenalidomide, established agents in multiple myeloma, have complex mechanisms of action, including inhibition of tumor necrosis factor-α, interleukin-6, basic fibroblast growth factor, and antiangiogenic activity through inhibition of vascular endothelial growth factor (VEGF).[50]

Monoclonal Antibodies

Malignant cells are vulnerable to treatments that are directed at unique antigens expressed on their surface. Monoclonal antibodies that are directed against growth factor receptors or other specific cancer cellular targets have increasingly established roles in therapy. Antibody binding to the surface of the malignant cell can lead to complement-mediated lysis, antibody-dependent cellular cytotoxicity, or signal transduction-mediated apoptosis. The monoclonal antibody can either be of murine origin or, through recombinant DNA techniques, be made partly human (chimeric) or nearly completely human (humanized). Rituxan, directed against the lymphoid cell surface marker CD20, is widely used in chemotherapy of lymphoid malignancies,[51,52] as well as in other settings for its immunosuppressive properties. Alemtuzumab, defined by the lymphoid marker CD52w against which it is directed, is approved for treatment of CLL. [53] Trastuzumab, a humanized monoclonal antibody against the HER2 protein, is established in treatment of HER2/neu-positive breast cancer.[54] Cetuximab, a recombinant human/mouse chimeric monoclonal antibody is directed against the extracellular domain of the human epidermal growth factor receptor (EGFR), and has activity in colorectal and head and neck cancers.[55,56] Panitumumab is another EGFR-directed monoclonal antibody that is indicated for treatment of patients with EGFR-expressing metastatic colorectal cancer that is resistant to conventional chemotherapy.[57] Monoclonal antibodies have also been used to "target" cancer cell antigens with attached cytotoxic moieties, including radionuclides, as in the case of anti-CD20 conjugates, I-131-conjugated tositumomab,[58] or yttrium-90-conjugated ibritumomab tiuxetan[59] for B-cell lymphomas. Immunoconjugates have also been constructed with biological toxins or antitumor antibiotics as in the case of the anti-CD-33-calicheamicin conjugate gemtuzumab ozogamicin for acute myelogenous leukemia.[60] Denileukin diftitox is an example of a recombinant fusion product with cellular binding and toxic moieties combining interleukin-2 and diphtheria toxin to inhibit cellular protein synthesis and induce apoptosis in the treatment of cutaneous T-cell lymphomas.[61]

Proteosome Inhibitors

The ubiquitin-proteosome pathway involves targeted proteolysis of "ubiquitin-tagged" intracellular proteins. Inhibition of the normal essential function of this pathway leads to disruption of multiple intracellular signaling pathways and programmed cell death. Bortezomib, the first approved drug in the proteosome inhibitor class, is a reversible inhibitor of the 26S proteosome, and an established agent in multiple myeloma and some non-Hodgkin's lymphomas.[50]

Histone Deacetylase Inhibitors

The family of histone deacetylases catalyzes the deacetylation of lysine residues on protein substrates including histones and transcription factors. Histone deacetylation is believed to control expression of oncologically relevant genes, including tumor suppressors, and genes involved in differentiation, proliferation, and cell cycle control. Inhibition of overexpressed histone deacetylases in cancer cells is thought to lead to cell cycle arrest and apoptosis. Vorinostat is an oral histone deacetylase inhibitor with activity against a spectrum of histone deacetylases with an indication for treatment of refractory cutaneous T-cell lymphoma.[62]

Gene Therapy

Treatment strategies incorporating specific ribonucleotide sequences come in many different varieties, such as antisense therapy (RNA). An example is the antisense oligonucleotide against bcl-2 RNA, oblimersen, being studied in CLL, melanoma, and other malignancies as a strategy to increase sensitivity to apoptosis with conventional chemotherapy drugs.[63] Other approaches that are under study include systemic viral vector transfection (RNA or DNA), DNA injection into tumors, and ex vivo transfected and selected tumor cells, immune cells, or bone marrow progenitors (DNA). Most of these techniques have demonstrated some effectiveness in animal models, and clinical trials are ongoing. No proof of efficacy has been shown, however, and the technical hurdles are still daunting.

Vaccines

Vaccine strategies to treat cancers have been used for more than 100 years. The principles of immune surveillance and tumor rejection have been well demonstrated in animal models and form the justification for human vaccine strategies. In the last 10 years, many human tumor antigens (and the humoral and cellular immune responses to them) have been characterized. To date, no convincing clinical evidence exists for sufficient efficacy of cancer vaccines, and the ability to correlate immune response to a vaccine and clinical effectiveness has been elusive. Recent advances in molecular immunology might hold the key to solving the puzzles of reinstating and measuring clinically relevant tumor immunogenicity. Several possibly effective cancer vaccines are currently in large phase III trials, which could lead to FDA approval. The recent approval of a vaccine against human papillomavirus to prevent HPV-associated cervical cancer represents the first application of a cancer prevention vaccine.

PHARMACOLOGIC APPROACHES

Drug Development

Although approximately 100 drugs are now in use to treat human cancers, the vast majority of cancers are not cured by chemotherapy. Since it no longer seems possible to identify one specific abnormality

between cancerous and normal cells, additional agents with different modes of action must be sought. Although some chemotherapeutic agents (e.g., 5-FU) have been designed rationally, others (e.g., cisplatin) have been found by chance. The National Cancer Institute is developing a chemical screening system that permits the identification of a compound of interest—a lead compound—that can then be modified or enhanced, and the interaction of the compound with its target (enzyme, growth factor, or oncogene product) can be characterized. Appropriate bioassays are required for each lead agent as it is developed.

A significant fraction of our currently available chemotherapeutic agents are either natural products or derived from natural products, which often have complex structures that complicate synthesis efforts. Problems commonly arise in supply of starting material, the development of drug synthesis methods, and successful formulation of the drug so that it is absorbed and distributed appropriately. The problems of chemistry compound the difficulty in bringing drugs to clinical trials.

Computer Modeling and Combinatorial Chemistry

The pioneering discoveries of the early days of chemotherapy have permitted the development of a paradigm for drug discovery that persists, with modifications, to the present day. This organized approach to random screening of large numbers of compounds, however, must be complemented in the drug development effort by attempts to exploit new therapeutic targets that are identified in ongoing basic cancer research.

The molecular basis for antineoplastic therapy has been rapidly being unveiled since the 1990s. For many chemotherapy agents, the molecules that are responsible for drug transport, binding, effector mechanism, detoxification, and efflux out of cells are known. Therefore, new and better agents that result in tumor cell death and clinical response can be designed to exploit these known targets. This effort requires powerful computer programs, advanced chemistry techniques, three-dimensional modeling capabilities, and nucleotide sequences of all the relevant target protein genes. With these tools in place, one can create new small or large molecules or modify existing molecules by the addition or subtraction of functional groups to direct the binding, specificity, inhibition, duration of action, and toxicity of these molecules on the basis of chemical interactions with the target molecules. This process is called *mechanistic drug development,* and it uses computer modeling to predict the chemical composition of the new drugs, whether they be small molecule inhibitors, peptides, proteins, or nucleotide sequences.

A related endeavor that is occurring in the pharmaceutical industry and elsewhere is called *combinatorial chemistry.*[64–69] This process tests for binding interactions between new compounds or molecules and known targets that result in the desired cellular and clinical effect. The target is usually placed on a solid phase, and the candidate molecule is tested for binding to this solid phase. Once specific binding is documented, this compound is then tested for in vitro and in vivo biologic modulation (inhibition or stimulation) of the target molecule function. From there, standard testing of preclinical and clinical activity can be carried out with existing or new methods.

This ongoing work in drug development is crucial if our use of chemotherapy is to continue to improve and if its role in potentially curative therapy is to expand. Standard approaches and mechanistically based drug development will continue in parallel, and many new agents will undoubtedly follow, offering great promise for the future of cancer treatment.

Pharmacogenetics

It is now clear that much of the variability in response to drugs is inherited. The genetically determined variability of drug response characterizes a research area known as pharmacogenetics. Phase III clinical trials frequently report grade 4 toxicities in various solid tumors and hematologic malignancies that have been traditionally regarded as an acceptable alternative to underdosing with ineffective therapy. Identifying genes and allelic variants of genes that affect response to cancer chemotherapy drugs holds great promise for more individualized therapy to avoid untoward toxicity as well as underdosing. One of the first clinically important applications of pharmacogenetics was the identification of single-nucleotide polymorphisms in the gene for the enzyme thiopurine methyltransferase, which is responsible for metabolism of the antitumor agents, 6-thioguanine and 6-mercaptopurine. Children with inherited thiopurine methyltransferase deficiency develop severe hematologic toxicity when exposed to such drugs, while those with high levels of the enzyme require higher doses to achieve the desired effect.[70] Identification of children with thiopurine methyltransferase polymorphisms has the potential to ameliorate toxicity and improve therapeutic outcome.[71] To be clinically useful, such a polymorphism needs to be identified as associated with a correctable untoward clinical outcome and be rapidly detectable with a sensitive, specific test of reasonable cost. Early in the clinical experience with irinotecan in colorectal cancer, an unacceptable early death rate attributable to diarrhea and neutropenia was observed.[72] This was identified as being due to a polymorphism in the gene that encodes uridine diphosphate glucuronosyltransferase 1A1, patients who were homozygous for UGT1A1*28 allele being at increased risk. A genetic test performed on genomic DNA from peripheral blood is available and recommended to screen such patients.[73]

While this patient-tailored approach to chemotherapy drugs is developing, the related fields of pharmacogenomics and pharmacoproteomics hold promise for large-scale genomic and proteomic screening for heritable variation in drug metabolism and other areas of cancer biology. Either technique allows the formulation of a pattern of phenotypic or genotypic expression of the cancer cell, from which patterns of gene expression and therapeutic targets can be discerned. For example, reverse-phase protein microarrays can be used to analyze patient biopsy specimens to measure hundreds of phosphorylated proteins in multiple signaling pathways relevant to the malignant phenotype.[74]

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics is the relationship between plasma concentration of a drug and time and is concerned with the drug's absorption, distribution, metabolism, and excretion. It is what the body does to the drug. The interpretation of pharmacokinetic data is usually based on assessment of total plasma clearance, by measurement of either the area under the plasma concentration–time curve or the steady-state plasma concentration during a constant infusion. A critical issue is intersubject variability in clearance; here, several factors come into play, including saturation of the major metabolic or excretory sites, protein binding, and body size. The evidence for the use of body surface area in dosing oncology drugs is scarce, and other methods could be preferable.

Conversely, pharmacodynamics—the relationship between plasma concentration of the drug and its effects—is what the drug does to the body. Pharmacodynamics analyses have increasingly been incorporated into cancer drug development and complement pharmacokinetic studies, as pharmacodynamics, in conjunction with pharmacokinetics, permits a better prediction and understanding of effect, rather than evaluating plasma concentrations of unclear significance. To date, the influence of pharmacodynamics in oncology has been relatively limited, owing to the tendency to use combination chemotherapy for most malignancies and to the considerable heterogeneity of the cancer population. Many oncology patients are older and have comorbidities that could affect pharmacokinetic-pharmacodynamic variability; hepatic metastases could alter drug metabolism; and there is often a significant lag time between the last measured plasma concentration and the first major therapeutic or

toxic effect. The net result is that such studies are often not practical at the present time. This is a field of active investigation, however, and advances in this area might yield great benefits in tailoring treatment to the individual patient.

CLINICAL USES OF SYSTEMIC THERAPY

Adjuvant Therapy

Systemic therapy can be used in a number of ways in the treatment of cancer. The vast majority of cancer chemotherapy treatments or hormonal therapies are administered to patients with clinically obvious disease. The notable exception is adjuvant therapy, which uses chemotherapy or hormonal therapy for patients who remain at high risk of recurrence after the primary tumor and all evidence of cancer have been surgically removed or treated definitively with radiation. Despite an apparently successful resection of primary breast, colon, or other primary cancers along with the regional lymph nodes, patients can be prospectively identified who are at high risk of recurrence of their disease. These criteria might differ for each tumor, but in general, the degree of local extension of the primary tumor, the presence of positive lymph nodes, and certain morphologic or biologic characteristics of the individual cancer cells are important determinants of that risk. The need for effective adjuvant therapy is strongly emphasized by the fact that systemic therapy usually fails to cure these cancers once recurrence has taken place. The theoretical advantage of treating patients with small total body tumor burden is very compelling, but, in fact, some patients who will receive adjuvant therapy have already been rendered disease free by the local therapy and would be cured without it (Box 30-3).

The use of chemotherapy when the tumor burden is minimal avoids the problems of increasing tumor cell number, decreasing growth fraction, decreased vascular supply, hypoxia, tumor cell heterogeneity, and the likelihood of emergence of drug resistance, all of which occur with increasing frequency as tumors enlarge. Considerable experimental evidence suggests that cancers are most sensitive to chemotherapy during the early stages of growth. This increased sensitivity is believed to be the result of the high growth fraction and shorter cell cycle times, so a given dose of drug might exert a greater therapeutic effect than it would in a larger, quiescent tumor.[75]

The selection of the specific chemotherapy or hormonal therapy regimen to be used as part of adjuvant therapy for a particular cancer is based on objective response rates observed for patients with advanced cancers of the same type. These regimens should be selected carefully, as it is unrealistic to expect a chemotherapy regimen to be effective in preventing recurrences in the adjuvant setting if the regimen does not have a substantial response rate in advanced disease. The selection of patients for adjuvant therapy is based on the expected rate of recurrence for their initial clinical stage of cancer after local treatment alone. Initial demonstration of the efficacy of an adjuvant therapy regimen requires comparison with a control group that receives no therapy beyond local management in a prospective clinical trial. Historical controls are notoriously unreliable in this regard and are not adequate to prove efficacy.

The typical endpoints of systemic therapy—shrinkage of measurable tumor on physical examination or serial radiographic studies—are not available in this situation; in clinical trials of adjuvant therapy, relapse-free survival and overall survival are the principal measures of treatment effect. For an individual patient, there are no means to determine whether the adjuvant therapy and its resultant toxicity and expense have been beneficial or necessary.

This strategy of adjuvant therapy has been attempted in a wide variety of pediatric and adult tumors with some success, and the principles of adjuvant therapy strategy are well established. In the cases of breast cancer and colon cancer, the number of lives saved by the adjuvant therapy approach is significant because of the large number of affected patients, despite the modest differences that are seen between treated and control patients with current treatment programs.

Neoadjuvant Chemotherapy

A second strategy that acknowledges the presence of micrometastatic disease at sites remote from the primary tumor at diagnosis is that of neoadjuvant chemotherapy (Box 30-4).[76] As with adjuvant chemotherapy, treatment is directed at the possibility of systemic disease in patients with apparently localized disease, although in this instance, chemotherapy is administered before surgery is performed. This approach has several potential advantages over conventional postoperative adjuvant chemotherapy. First, neoadjuvant or preoperative chemotherapy provides earlier exposure of potential micrometastases to chemotherapy than is achieved with the standard adjuvant approach. If the advantages of early chemotherapy treatment that are observed in the laboratory are exportable to the clinic, this should be an optimal approach to the treatment of micrometastases. Second, an objective response to chemotherapy in the primary lesion provides important in vivo evidence that the therapy that is being used has antitumor activity and suggests that the tumor at remote subclinical sites will be sensitive as well. By contrast, if the primary lesion does not respond, the likelihood of success of the initial chemotherapy regimen in eradicating micrometastases would seem to be greatly diminished. Monitoring the response thus provides an early opportunity to consider alternative chemotherapy approaches. This approach has perhaps best been described for osteosarcoma.[77] Third, significant regression of the primary tumor might allow local management to be tailored to the individual patient. For example, surgery might be technically easier because of the reduced tumor bulk, a more conservative surgical procedure could be considered, or radiation therapy might be administered in lieu of surgery. The recent use of the aromatase inhibitors in locally advanced breast cancers is another example of the utility of this approach.

The latter two approaches could permit organ sparing and function preservation for some patients. In some situations, preoperative chemotherapy is administered concurrently with radiation therapy to

Box 30-3. MANAGEMENT APPROACH: PRINCIPLES OF ADJUVANT CHEMOTHERAPY

1. Effective chemotherapy must be available.
2. Known tumor should be removed by surgery.
3. Chemotherapy should be started as soon as possible postoperatively.
4. Chemotherapy should be given in maximally tolerated doses.
5. Chemotherapy should continue for a limited time period.
6. Chemotherapy should be intermittent, when possible, to minimize immunosuppression.

Box 30-4. MANAGEMENT APPROACH: CANCERS THAT ARE TREATED EFFECTIVELY BY NEOADJUVANT CHEMOTHERAPY

Soft-tissue sarcoma
Osteosarcoma
Anal cancer
Bladder cancer
Larynx cancer
Esophageal cancer
Locally advanced breast cancer

improve local disease control and to treat systemic micrometastases. For cancer of the anal canal and bladder cancer, this approach has allowed organ-sparing procedures for a high percentage of patients. It has also served as highly effective preoperative therapy for esophageal cancer and squamous cell cancer of the head and neck.

The potential disadvantages of the neoadjuvant approach are also very real. First, chemotherapy is being used as initial therapy for a group of patients with cancers that are potentially curable by surgery alone in a small percentage of patients. If chemotherapy proves ineffective and the cancer becomes unresectable during treatment, great harm could be done. Second, the use of preoperative chemotherapy could obscure the true pathologic stage of the cancer by altering tumor size and margins and converting histologically positive nodes to negative. The inaccuracy of clinical staging for many cancers makes it difficult to be confident that a homogeneous group of patients has been treated, and this fact might confound interpretation of results of clinical trials. Third, if a dramatic clinical response results in the performance of an inappropriately conservative procedure or poor patient acceptance of the recommended procedure and if the cancer then recurs, a significant disservice has been done to the patient.

Approximately seven types of cancers have been managed effectively by using neoadjuvant chemotherapy. In all cases, this "effectiveness" might not imply improved survival. In some cases, organ sparing or function preservation is routinely possible and is ample justification for the use of this approach.

Management of Advanced and Metastatic Disease

The most common use of systemic therapy is for the management of advanced or metastatic disease after failed local therapies or in treating disease for which no alternative therapy has been found. This is perhaps the sternest test for chemotherapy, as tumor volume is significant and patients are often physically compromised by the effects of their disease. It is this clinical situation, however, in which the activity of new anticancer agents and combination chemotherapy regimens are initially evaluated. In treating patients with advanced cancer, it is possible both to determine the antitumor activity of the therapy on an individual patient basis and to define the response rate for the therapy accurately by entering an appropriate number of patients with the same diagnosis and similar pretreatment characteristics in a clinical trial. The benefit of systemic therapy to patients can be inferred by the degree to which measurable or evaluable tumor responds to therapy.

Clearly, the most important measure of the efficacy of systemic therapy is the achievement of a complete response, defined as the disappearance of all radiographic and clinical evidence of measurable or evaluable tumor (Box 30-5). It is the necessary first step to achieving a clinical cure. The achievement of a complete response results in a significant decrease in or disappearance of disease-related symptoms and generally translates into a meaningful prolongation of survival, even for patients who ultimately relapse. Therapy can be said to be curative only when the complete response is maintained after treatment is discontinued. The clinical importance of a complete response is therefore measured by the disease-free or relapse-free survival time. Partial responses are defined as a 50% decrease in cross-sectional area of measurable tumor masses and also can result in symptomatic benefit for patients, although survival is rarely significantly prolonged. Continued administration of the chemotherapy regimen is usually required to maintain the partial response. Unless the regimen is extremely well tolerated, the cumulative effects of therapy might ultimately limit the benefit to the patient. The median duration of response among the complete and partial responders is often used as an endpoint in clinical trials of therapies.

Perhaps the greatest value to clinical investigators of documenting partial responses is in the evaluation of investigational new drugs, in which preliminary evidence for antitumor activity of new drugs is often first observed. New agents that produce partial responses in patients with advanced cancer in phase I or II trials might warrant further evaluation at earlier stages of disease or in combination with other active agents. Patients who have stable disease while receiving therapy—that is, responses that do not meet the criteria for either an objective response or progressive disease—are reported in some clinical trials, although the scientific value of this measure in evaluating therapy can be legitimately questioned. For individual patients who experience extended periods of stable disease and symptomatic palliation on treatment after a period of rapid progression, the clinician (and patient) might consider the therapy of value and continue it on that basis. The importance of this endpoint has increased as novel agents that are not truly cytotoxic, such as antimetastatic agents, differentiating agents, or agents that affect intracellular signaling, enter clinical trials. In these cases, it is possible that evidence of biologic effect will take a different form from that to which we have become accustomed with conventional cytotoxic agents.

Although objective responses, duration of survival, and cure rates have been our traditional systemic therapy endpoints, it has become increasingly clear that clinical researchers and clinicians caring for patients must consider other outcomes or endpoints also. These generally fall under the rubric of palliation of symptoms and improved quality of life.[78,79] Although these endpoints might be more subjective than the traditional ones, it is important that criteria for their evaluation be agreed on and that they be used routinely in clinical trials in which an improved cure rate is not a likely outcome. The palliative benefit to patients who do not have a curable disease is not well defined by our current criteria, and the addition of a semiquantitative means of assessing palliative benefit is critical.

Despite the obvious limitations of our current cytotoxic agents, chemotherapy is curative for several advanced human cancers. These diseases include gestational trophoblastic disease and several hematologic malignancies, but only one advanced solid tumor—germ cell cancer of the testis—can be said to be routinely curable with chemotherapy alone. Another group of cancers, such as small cell lung cancer and ovarian cancer, is occasionally cured with chemotherapy. The most common solid tumors, however—for example, cancers of the breast, lung, prostate, or gastrointestinal tract—when metastatic are not curable with current therapies. These diseases will provide the greatest challenge to the process of drug development and the practice of chemotherapy in the future and will continue to be the focus of active investigative efforts.

The reader is directed to the discussions of the management of individual cancers in Part III of this textbook, "Specific Malignancies." General principles regarding selection of systemic therapy and characteristics of specific drugs are discussed later in this chapter.

Box 30-5. MANAGEMENT APPROACH: CANCERS THAT ARE CURABLE OR OCCASIONALLY CURABLE WITH CHEMOTHERAPY ALONE

Cancers That Are Curable with Chemotherapy Alone
Gestational choriocarcinoma
Hodgkin's disease
Germ cell cancer of the testis
Acute lymphoid leukemia
Non-Hodgkin's lymphoma (some subtypes)
Hairy cell leukemia (probable)

Cancers That Are Occasionally Cured with Chemotherapy
Acute myeloid leukemia
Ovarian cancer
Small cell lung cancer (with radiation)

Box 30-6. MANAGEMENT APPROACH: REQUIREMENTS FOR CHEMOTHERAPY

1. Biopsy-proven residual or metastatic disease*
2. Indicator lesion*
3. Satisfactory performance score and nutrition
4. Patient capable of informed consent
5. Minimal bone marrow, renal, and hepatic function (occasionally pulmonary or cardiac function important)
6. Available monitoring and support functions

*Exception: adjuvant chemotherapy.

CHEMOTHERAPEUTIC PROCESS

The choice of chemotherapy as the treatment modality for a given patient has significant implications and requires a detailed knowledge of the patient and his or her medical problems and social and emotional background, a general knowledge of chemotherapy, a specific knowledge of the program to be used, and the availability of laboratory and support services (Box 30-6). The occasional therapist cannot expect to become an expert, any more than one can expect to become an accomplished chef simply by using a cookbook. Indicator lesions may be physical findings (e.g., lymphadenopathy, hepatomegaly, splenomegaly, subcutaneous nodules), radiologic abnormalities, or tumor markers in body fluids.

Patient Selection

Physiologic Age

Advanced age alone is seldom a valid criterion for excluding patients from chemotherapy. Nevertheless, age-related alterations (in addition to disease-related changes) in organ function suggest that aggressive (or even nonaggressive) programs could result in unacceptable toxicity. Examples of such changes include decreased bone marrow reserve with the possibility of enhanced myelosuppression, reduced renal function with the possibility of enhanced methotrexate or cisplatin toxicity, variable gastrointestinal absorption of oral chemotherapeutic agents, and altered drug metabolism by the liver, resulting in possible decreased effectiveness of chemotherapy.[80] Treatment decisions must also take into account the likelihood of benefit. The decision to treat acute granulocytic leukemia in an elderly patient, for whom toxicity is certain and the likelihood of benefit is small, is an example of a difficult situation.

Performance Score

Whether the Karnofsky or Zubrod scale is used, performance status or score (Table 30-1) correlates closely with survival in certain settings. This is most clearly expressed in non-small-cell lung cancer, in which each decrement of 10% in the Karnofsky score results in a measurable decrease in survival. The implication is that patients with Zubrod performance scores of 3 or 4 or Karnofsky scores of less than 30% are usually not candidates for chemotherapy unless the tumor is untreated and especially likely to respond.

Table 30-1 Patient Performance Score Using Zubrod and Karnofsky Scales

Zubrod	Karnofsky (%)	Definition
0	100	Asymptomatic
1	80–90	Symptomatic, fully ambulatory
2	60–70	Symptomatic, in bed <50% of day
3	40–50	Symptomatic, in bed >50% of day, but not bedridden
4	20–30	Bedridden

Nutrition

Although maintenance of usual body weight might be impossible in the setting of advanced malignancy, the ingestion of 1500 to 2000 calories daily is necessary to permit a satisfactory chance of tumor response. This is best accomplished through oral intake, if possible, using supplemental sources as necessary. If the patient cannot ingest enough calories, enteral or parenteral feeding should be considered.

Obesity

Chemotherapy in the massively obese patient carries a potential risk of overdosage if the patient's actual weight is used, whether dosing is on a milligram-per-kilogram basis or according to body surface area. There are no guidelines for this situation, and the pharmacokinetics of antineoplastic drugs in obese patients are poorly understood. It has been suggested that when patients are to be treated with curative intent, they should receive full-dose intensity, using body surface area calculated on actual body weight or on ideal body weight, with dose escalations if tolerated.[81] Patients who are to receive palliative therapy can more safely be given doses based on ideal body weight.[82]

Prior Therapy

In breast cancer, in spite of positive estrogen/progesterone receptors, failure to respond to a hormonal manipulation decreases the likelihood of a response to subsequent hormonal treatment. Similarly, in virtually all malignancies, failure to respond to a first chemotherapy program lessens the probability of a response to second-line therapy, often because of the development of multidrug resistance.

Organ Function

Altered end-organ function (bone marrow, renal, hepatic, cardiac, pulmonary) could eliminate the use of some chemotherapeutic agents entirely or require dose modification.[83] To avoid undue toxicity, it is essential to know the process of drug disposition and metabolism in this setting. Most oncologists find it useful to determine baseline bone marrow function by peripheral blood counts, hepatic and renal function by chemistry profiles, and (occasionally) cardiac function by echocardiography and gated pool cardiac scans or pulmonary function by chest radiography and spirometry.

Coexisting Illnesses

Other nonneoplastic illnesses might modify the choice of chemotherapeutic agents, even if they do not eliminate the rationale of the use of chemotherapy. For instance, congestive heart failure rules out the possibility of the cardiotoxic drug doxorubicin, and severe chronic obstructive pulmonary disease should eliminate the use of the pulmonary toxin bleomycin. Similarly, diabetes might be aggravated by the use of corticosteroids.

Pharmacogenetics

The evolving field of pharmacogenetics has revealed that unexpectedly severe toxicity from 5-FU could be due to a deficiency of dihydropyrimidine dehydrogenase.[84] The prevalence of this enzyme deficiency in the general population is unknown, as is the impact of the heterozygous state on susceptibility to 5-FU toxicity. Similarly, determination of acetylator phenotype as defined by caffeine metabolism can accurately predict the extent of acetylation of amonafide, a DNA-intercalating agent.[85] Determination of acetylation phenotype can thus be used to modify drug dosing to prevent excess toxicity.

Principles of Drug Selection

Single-agent therapy has largely been replaced by combination chemotherapy when cure is the goal of treatment. There are, however, circumstances in which single agents can be used with curative intent. These include methotrexate or dactinomycin in choriocarcinoma and interferon, pentostatin, or cladribine (chlorodeoxyadenosine) in hairy cell leukemia.

Combination therapy is now the standard for the treatment of many disseminated or metastatic diseases and is curative in some.[86] Unfortunately, most of these diseases are relatively uncommon hematologic or pediatric malignancies, and the more common neoplasms of adults, such as cancers of the colon and rectum, lung, or breast, once metastatic, are seldom cured.

Chemohormonal therapy is the use of chemotherapeutic agents and hormonal agents, such as prednisone in the MOPP combination program, or prednisone with vincristine and daunorubicin in the treatment of acute lymphocytic leukemia (ALL). The inclusion of tamoxifen after cytoxan and doxorubicin in the chemotherapeutic program for breast cancer is another example. Biologic response modifiers, such as interferon or interleukin-2, are used singly or in combination with chemotherapeutic agents.

Differentiating agents, the newest class of anticancer therapies, are currently represented by just one compound, all-*trans*-retinoic acid, which is effective in acute progranulocytic leukemia.

Route of administration has been usually a straightforward decision. Most chemotherapeutic agents are given intravenously, eliminating problems of compliance and absorption. Many of the hormonal agents and some chemotherapeutic agents, such as alkeran, chlorambucil, myleran, 6-mercaptopurine, and 6-thioguanine, are given by the oral route. More recently, oral etoposide and capcitibine, an oral form of 5-FU, have been added to the armamentarium of oral cytotoxic drugs. Absorption could be enhanced if these drugs are taken on an empty stomach. Methotrexate can be given orally, intravenously, intramuscularly, or intrathecally. Interferon and interleukin-2 are usually given subcutaneously. Some chemotherapeutic agents can be instilled in body cavities to treat effusions, as in the example of bleomycin to treat pleural effusions. Continuous infusion therapy offers a potential advantage for cell cycle-specific drugs, such as antimetabolites, in which prolonged exposure might increase cell kill. Cytosine arabinoside is most effective in the treatment of acute granulocytic leukemia, for example, when used as a continuous infusion over 7 days.

Venous access must also be considered, and intravenous therapy might not be feasible if this cannot be established. Fortunately, the development of subcutaneously implanted venous access devices (central or peripheral), multilumen external catheters, and peripherally inserted catheters (PIC lines) has permitted the use of chemotherapy in many circumstances in which this was not possible previously.[87]

Drug programs, including dose, should be extracted from published articles and modified according to the patient's end-organ function (Table 30-2).

Table 30-2 Dose Modifications for Chemotherapy (% of Dose to Be Given)

HEMATOLOGIC TOXICITY

	Granulocytes/Total WBC			
Platelet Count (/mm³)	*>2000/3500*	*1500–1999/3000–3499*	*1000–1499/2500–2999*	*<1000/2499*
>100,000	100	75	50	0
50,000–90,000	50	50	50	0
<50,000	0	0	0	0

NEPHROTOIXCITY

	Creatinine Clearance			
Drug	*>60 mL/min*	*30–60 mL/min*	*10–30 mL/min*	*<10 mL/min*
Bleomycin	NC	75	75	50
Cisplatin	NC	50	Omit	Omit
Cyclophosphamide	NC	NC	NC	50
Methotrexate	NC	50	Omit	Omit
Mithramycin	NC	75	75	50
Mitomycin	NC	75	75	50
Nitrosoureas	NC	Omit	Omit	Omit

HEPATOTOXICITY

		Drug				
Bilirubin (mg/dL)	*SGOT (IU)*	*Adriamycin*	*Daunorubicin*	*Vinblastine + Vincristine + VP-16*	*Cyclophosphamide + Methotrexate*	*5-FU*
<1.5	<60	100	100	100	100	100
1.5–3.0	60–180	75	75	50	100	100
3.1–5.0	>180	50	50	Omit	175	100
5.0		Omit	Omit	Omit	Omit	Omit

5-FU, 5-fluorouracil; NC, no change; SGOT, serum glutamic-oxaloacetic transaminase.

Dose Modification Guidelines

Drug doses are routinely modified for decreases in blood counts and for changes in renal or hepatic function. Individual protocols should be consulted for possible modifications. Table 30-2 outlines commonly used guidelines for dose reductions. The occurrence of certain toxicities, such as neurotoxicity from the vinca alkaloids or mucositis from methotrexate, is also used as an indication for reduction in dose or cessation of the drug.

Response Criteria

Complete response implies disappearance of all measurable or evaluable disease, signs, symptoms, and biochemical changes related to the tumor for at least 4 weeks, during which time no new lesions may appear. Partial response implies a reduction of greater than 50% in the sum of the products of the perpendicular diameters of all measurable lesions (compared with pretreatment measurements) lasting at least 4 weeks, during which no new lesions may appear and no existing lesion may enlarge. For hepatic lesions, a reduction of greater than 30% in the sum of the measured distances from the costal margin at the midclavicular line and at the xiphoid process to the edge of the liver is required. Stable disease is a less than 50% reduction or a less than 25% increase in the sum of the products of the two perpendicular diameters of all measured lesions and the appearance of no new lesions for 8 weeks. Progression or relapse is defined as an increase in the product of two perpendicular diameters of any measurable lesion by more than 25% over the size that is present at entry into the study, or, for patients who respond, over the size at time of maximum regression, or the appearance of new areas of malignant disease (usually excluding central nervous system metastases). A two-step deterioration in performance status, greater than 10% loss of pretreatment weight, or increasing symptoms in and of themselves, do not constitute progression. Their appearance, however, should initiate a new evaluation for disease extent.

Follow-up

Adjuvant therapy is usually given for a set number of cycles, such as six cycles (or months) of chemotherapy after a modified radical mastectomy or lumpectomy for stage I or II breast cancer. For other situations, such as metastatic disease, it is common to reevaluate the patient after two to three cycles (months) of therapy to determine its effectiveness. If therapy has clearly produced a response (using the criteria discussed previously) and is tolerable for the patient, it is usually continued for a set number of cycles or for two courses past a complete response (to eliminate any remaining microscopic tumor). If the disease has progressed during this interval, therapy is discontinued, and a reevaluation is undertaken. Stable disease after therapy represents the most difficult clinical situation that is encountered. If the patient can tolerate the therapy in terms of side effects, then a mutual decision to continue is reasonable, with the realization that eventually, progressive disease will be seen.

CHEMOTHERAPEUTIC AGENTS

The information about the agents in the following list is taken from multiple sources, but the latest information from the manufacturer should be sought before initiating therapy.[82,88–93] Unless otherwise specified, all chemotherapeutic agents are capable of producing some degree of nausea and/or vomiting with administration and myelosuppression, alopecia, and mucositis and/or diarrhea after treatment. Because most agents are also harmful to the gonads and fetus, these toxicities will not be spelled out. Administration of chemotherapy during pregnancy is warranted only in special circumstances and requires a particularly high level of expertise.[94] The increasing incidence of second malignancies as a late complication following successful chemotherapy should also be noted.

Alemtuzumab (Campath)
- Drug Class: Recombinant humanized monoclonal antibody that targets the CD 52 antigen present on most normal and malignant B- and T-cell lymphocytes. This results in antibody-dependent cellular toxicity and complement binding, then apoptosis and activation of T-cell-induced cytotoxicity.
- Dosage Form: 30-mg vial.
- Drug Interactions: None.
- Pharmacokinetics/Metabolism: Metabolic fate unknown.
- Toxicity: Anaphylactoid reactions. Immunosuppression with decreased CD4 and CD8 counts with resulting increase in opportunistic infections. Myelosuppression. GI toxicity: nausea, vomiting, diarrhea. Constitutional symptoms.
- Indications: Food and Drug Administration (FDA) approved for treatment of relapsed or refractory B-cell chronic lymphocytic leukemia and refractory T-cell prolymphocytic leukemia.
- Dosing: 30 mg/day IV infusion three times weekly for up to 12 weeks.

Altretamine (Hexalen)—Hexamethylmelamine, HMM
- Drug Class: Alkylating agent.
- Dosage Form: 50-mg capsules.
- Drug Interactions: Metabolism may be slowed by cimetidine or enhanced by Phenobarbital.
- Pharmacokinetics/Metabolism: Well absorbed by mouth, metabolized in the liver. Elimination half-life 4 to 13 hours. Metabolites largely excreted in the urine.
- Toxicity: Myelosuppression is dose limiting. Leukopenia, thrombocytopenia, nausea, and vomiting are common. Neurologic toxicity, including confusion, lethargy, weakness, and sensory changes, is common.
- Indications: FDA approved for refractory ovarian carcinoma.
- Dosing: 4 to 12 mg/kg/day in divided doses for 3 to 6 weeks or 150 mg/m^2/day for 14 days each cycle; higher doses have been used.

Amifostine (Ethyol)—WR-2721, ethiofos
- Drug Class: Cytoprotectant; free-radical scavenger.
- Dosage Form: 500 mg of powder in vial.
- Drug Interactions: Not known to decrease the effectiveness of any cytotoxic drug but not yet adequately studied.
- Pharmacokinetics/Metabolism: Poorly absorbed in the GI tract. After IV infusion, the drug is metabolized to inactive forms in the plasma. Metabolites are cleared in the urine.
- Toxicity: Transient hypotension is dose limiting. Nausea, vomiting, and somnolence are common. Sneezing, hypocalcemia, and flushing can be seen.
- Indications: FDA approved for pretreatment with cisplatin. Useful as a bone marrow, kidney, and nerve cytoprotectant. Useful with other alkylators as well. Also FDA approved as a radiation protectant to reduce xerostomia.
- Dosing: 740 mg/m^2 IV infusion over 15 minutes given 15 to 30 minutes before the cytotoxic agent or radiation. Lower doses and subcutaneous administration have also been used.

Anagrelide (Agrylin)
- Drug Class: Inhibitor of platelet aggregation with an exploitable side effect of thrombocytopenia, for which the mechanism is unclear.
- Dosage Form: 0.5-mg capsules.
- Drug Interactions: Sucralfate may decrease absorption.
- Pharmacokinetics/Metabolism: Good oral bioavailability; maximum plasma concentration occurs after 1 hour. The plasma half-life is 1.3 hours. The drug is metabolized extensively in the liver. Metabolites are excreted in the urine.
- Toxicity: Other than thrombocytopenia, common toxicities include hypotension, headache, and palpitations. Rare toxicities include anemia, arrhythmias, angina pectoris, and congestive heart failure.

Indications: FDA approved for treatment of essential thrombocytosis as an orphan drug.
Dosing: 0.5 mg four times daily or 1 mg twice daily.

Anastrazole (Arimidex)
Drug Class: Nonsteroidal aromatase inhibitor; blocks estrogen production selectively.
Dosage Form: 1-mg tablets.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Well absorbed from the GI tract, with maximum plasma levels achieved within 2 hours. Terminal elimination half-life is 50 hours. The drug is extensively metabolized in the liver and is eliminated in the urine as metabolites and 10% unchanged drug. Despite hepatic and renal clearance being important, no adjustments are needed for abnormal function of these organs due to the wide therapeutic index of this drug. Eliminated in the urine as metabolites and 10% unchanged drug.
Toxicity: The drug is very well tolerated. Asthenia, headache, and hot flashes occur in fewer than 15% of women. Diarrhea, abdominal pain, anorexia, nausea, and vomiting occur in 10% or fewer. Thrombophlebitis has been reported.
Indications: As adjuvant therapy of breast cancer and for treatment of postmenopausal women with breast carcinoma who have progressed on tamoxifen therapy.
Dosing: 1 mg PO every day. Higher doses are no more effective.

Arsenic Trioxide (Trisenox)
Drug Class: Novel arsenical differentiating agent.
Dosage Form: Ampules containing 10 mg of drug in 10 mL solution.
Drug Interactions: None known.
Pharmacokinetics/Metabolism: Half-life of this compound is unknown. It is methylated in the liver and eliminated in the urine.
Toxicity: The "differentiation syndrome" is dose limiting and includes leukocytosis, fever, dyspnea, chest pain, tachycardia, hypoxia, and sometimes death. Corticosteroids seem to benefit this syndrome. QT prolongation is common. Common side effects include rash, pruritus, headache, arthralgias, anxiety, bleeding, nausea, and vomiting. Liver and renal toxicity are uncommon.
Indications: FDA approved for relapsed acute promyelocytic leukemia.
Dosing: 0.15 mg/kg/day in 100 to 250 mL of D5W until remission, not to exceed 60 doses, then up to 25 doses over five weeks for consolidation starting 3 to 6 weeks after achievement of remission.

L-Asparaginase (Elspar)—colaspase
Drug Class: Naturally occurring enzyme derived from *Escherichia coli* or *Erwinia carotovora* that cleaves the amino acid asparagine, which is an essential amino acid required by rapidly proliferating cells.
Dosage Form: 10,000-IU vial of lyophilized cake.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Not orally bioavailable. After IV or IM injection, the drug is metabolized intravascularly by proteolysis. Elimination half-life of 8 to 30 hours. No excretion is required.
Toxicity: Hypersensitivity can be life threatening, requiring anaphylaxis precautions and a 2-unit test dose. Coagulopathy is common and requires monitoring. Nausea, vomiting, abdominal cramps, anorexia, elevated liver function tests, and transient renal insufficiency are common. Lethargy, somnolence, fatigue, depression, and confusion are seen, as are pancreatitis and fever.
Indications: FDA approved for acute lymphoblastic lymphoma (ALL); also used in AML, late-stage chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL), and non-Hodgkin's lymphomas.
Dosing: After a 2-unit intradermal test dose, an IM dose of 6000 to 10,000 IU/m^2 every 3 days for nine doses, or 1000 IU/kg/day IV over 30 minutes for 10 days, has been used.

PEG-Asparaginase (Oncaspar)—pegaspargase
Drug Class: Naturally occurring enzyme, covalently linked to polyethylene glycol to reduce immunogenicity, slow metabolism, and prolong half-life. The enzyme cleaves the amino acid asparagine, which is an essential amino acid required by rapidly proliferating cells.
Dosage Form: 750 IU/mL in a 5-mL vial No reconstitution or dilution necessary.
Drug Interactions: None noted. Can reduce effectiveness of methotrexate if given beforehand, due to inhibition of cell division.
Pharmacokinetics/Metabolism: The drug is not absorbed by the GI tract. When given by IM injection, it has an elimination half-life of approximately 5 days and is not detected in urine or bile. Metabolized completely, clearance not dependent on renal or hepatic function.
Toxicity: Although less immunogenic that the non-PEGylated form, hypersensitivity and anaphylaxis can still occur. Toxicities similar to those of the non-PEGylated forms are seen, including elevated liver enzymes, coagulopathy, hypercholesterolemia, pancreatitis, hyperglycemia, fever, chills, anorexia, lethargy, confusion, headache, seizures, and azotemia.
Indications: FDA approved for treatment of ALL, and, like asparaginase, is also used for other leukemias and non-Hodgkin's lymphomas.
Dosing: 2,500 IU/m^2 IM every 14 days with other chemotherapy agents for induction or maintenance.

Azacitadine—NSC-102816 (investigational)
Drug Class: Antimetabolite, cytidine analog; incorporated into nucleic acids, causing interruption of or errors in transcription and replication of DNA.
Dosage Form: 100-mg vial of lyophilized powder: 100-mg vial diluted to 20 mL in sterile water, and then rapidly diluted to a final concentration of 0.2 to 2 mg/mL in normal saline or 5% dextrose in water.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Not orally bioavailable. When administered by IV infusion, the drug is activated inside cells to the triphosphate form. It is deaminated in the liver. The elimination half-life is 3 to 6 hours. Parent drug and metabolites are excreted in the urine.
Toxicity: Myelosuppression is dose limiting. Leukopenia can be prolonged. Nausea and vomiting are common and can be severe. Diarrhea is common; stomatitis is rare. Hepatic enzyme elevation and liver function compromise are common. Transient azotemia is seen. Lethargy, confusion, and coma have been reported.
Indications: Investigational agent for AML.
Dosing: 150 to 300 mg/m^2/day for 5 days every 3 weeks, or 150 to 200 mg/m^2 twice weekly for several weeks.

Azacytidine (Vidaza)
Drug Class: Antimetabolite. 5-AZA induces hypomethylation of DNA, which may either induce apoptosis or restore normal function. At higher doses, it acts as a cytidine analog.
Dosage Form: 100-mg vial of lyophilized powder: 100-mg vial diluted to 20 mL in sterile water, and then rapidly diluted to a final concentration of 0.2 to 2 mg/mL in normal saline or 5% dextrose in water.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Not orally bioavailable. Metabolized by the liver and excreted in urine. Elimination half-life of 4 hours.

Toxicity: Myelosuppression is dose limiting. Leukopenia, thrombocytopenia, and transient elevation of liver function tests are common; nausea and vomiting and abdominal pain are common.
Indications: Myelodysplastic syndromes.
Dosing: 75 to 100 mg/m^2 for 7 days; repeated every 4 weeks for 4 to 6 cycles.

Azathioprine (Imuran)
Drug Class: Purine analog antimetabolite, which is converted to 6-mercaptopurine in vivo.
Dosage Form: 50-mg tablets and 100-mg vials of lyophilized powder.
Drug Interactions: Azathioprine may inhibit the anticoagulant effects of warfarin. Allopurinol blocks the xanthine oxidase-mediated metabolism of azathioprine, requiring reduction of dose for patients taking allopurinol. Angiotensin-converting enzyme inhibitors may exaggerate the myelosuppressive effects of azathioprine.
Pharmacokinetics/Metabolism: Azathioprine has good oral bioavailability and is rapidly converted to mercaptopurine in the blood compartment. The parent drug and thiol metabolites have a half-life of about 5 hours, but the metabolism of active forms is very rapid, with virtually no azathioprine detectable in urine after a dose. Metabolism occurs in blood and liver. Inactive metabolites are excreted in the urine.
Toxicity: Myelosuppression is expected and dose limiting. Due to chronic dosing of this drug, the effects on leukocytes, platelets, and to a lesser extent red cells are slow in onset and usually rapidly reversible. A rare metabolic disorder called thiopurine methyltransferase deficiency results in extreme sensitivity to this drug in affected persons. Nausea and vomiting are common but usually mild and transient during chronic therapy. Opportunistic infections are uncommon. Diarrhea, fever, myalgias, skin rashes, and interstitial pneumonitis are rare. Secondary malignancies have been reported. This drug should not be used during pregnancy or nursing.
Indications: FDA approved for renal transplant recipients and for rheumatoid arthritis. Also used in some hematologic malignancies.
Dosing: Chronic dosing for the preceding indications is in the range of 1 to 3 mg/kg/day. Higher doses, using the intravenous formulation, are used in the immediate post-transplant period.

Bacillus Calmette-Guérin (TICE BCG, TheraCys)—BCG
Drug Class: Immunostimulant/vaccine; induces a cellular immune response at the site of instillation.
Dosage Form: Freeze-dried powder in vials, 27 mg/vial, supplied with diluent.
Drug Interactions: Immunosuppressive drugs may block the reaction to BCG and also make the patient more prone to clinical infection from viable BCG organisms.
Pharmacokinetics/Metabolism: BCG is a live, attenuated bacteria culture, and as such, it does not enter the body in viable form in any quantity. Therefore, it has no detectable pharmacokinetic fate. In rare cases, however, a clinical infection can result from treatment, indicating invasion of the body at the site of administration into the systemic circulation.
Toxicity: Urinary symptoms predominate, including dysuria, hematuria, hesitancy, urgency, frequency, and secondary infection. Other toxicities include fever, chills, malaise, myalgias/arthralgias, anorexia, nausea, vomiting, and anemia. Clinical mycobacterial infection is rare and generally seen only in immunocompromised patients.
Indications: Intravesical instillation is FDA approved for noninvasive bladder cancer after removal of papillary tumors. Also used for some experimental vaccine programs as an adjuvant to the vaccine.
Dosing: 81 mg per treatment, in 53 mL total volume, instructions as previously given. Given once weekly for 6 doses and then at 3, 6, 12, 18, and 24 months after the induction.

Bevacizumab (Avastin)
Drug Class: Recombinant humanized monoclonal antibody that binds to all human forms of vascular endothelial growth factor (VEGF), preventing binding to it receptors.
Dosage Form: 100-mg and 400-mg vials of lyophilized powder: 100-mg vial diluted to 20 mL in sterile water and then rapidly diluted to a final concentration of 0.2 to 2 mg/mL in normal saline or 5% dextrose in water.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Administered by IV infusion. Half-life is 20 days. The fate of parent drug and metabolites is unknown.
Toxicity: Most common: asthenia, pain, nausea/vomiting, diarrhea, anorexia, stomatitis, dermatitis, hypertension, proteinuria. Infusion-related reactions are rare. Hemoptysis, hemorrhage, delayed wound healing, gastrointestinal perforations; increased risk of thromboembolic events can be severe or fatal.
Indications: FDA approved for metastatic colorectal cancer, breast cancer and non-small-cell lung cancer.
Dosing: 5 to 15 mg/m^2/day IV every 3 weeks.

Bexarotene (Targretin)
Drug Class: Synthetic retinoid, differentiating agent.
Dosage Form: 75 mg capsules.
Drug Interactions: No formal studies done. Drugs which inhibit cytochrome P450 3A4 such as ketoconazole, erythromycin, and gemfibrozil expected to increase plasma levels and half-life of bexarotene. Known to decrease plasma levels of tamoxifen with concomitant administration.
Pharmacokinetics/Metabolism: Good oral bioavailability increased by a high-fat meal. Metabolized in the liver to oxidative metabolites by cytochrome P450 3A4, glucuronidated, eliminated in the bile.
Toxicity: Hyperlipidemia is dose-limiting and should be monitored while on therapy and treated as appropriate. Pruritus, leukopenia, diarrhea, fatigue, headache, and liver function test elevation can also be dose limiting. Rash, edema, fever, chills, and nausea are uncommon. Excessive bleeding and back or abdominal pain are rare.
Indications: FDA approved for treatment of cutaneous T-cell lymphoma (mycosis fungoides) refractory to at least one prior therapy.
Dosing: 300 mg/m^2/day orally, dose adjusted for toxicity.

Bicalutamide (Casodex)
Drug Class: Nonsteroidal antiandrogen.
Dosage Forms: 50-mg tablet.
Drug Interactions: Bicalutamide may enhance the anticoagulant effects of warfarin.
Pharmacokinetics/Metabolism: Bicalutamide is well absorbed after oral administration. It is highly protein-bound. It undergoes conversion to inactive metabolites in the liver via oxidation and glucuronidation. It has a terminal half-life of several days. Parent drug and metabolites are excreted in the urine and feces.
Toxicity: Constitutional symptoms predominate, including hot flashes, decreased libido, depression, weight gain, edema, gynecomastia, early disease-site pain (flare reaction), and constipation. Nausea, vomiting, anorexia, diarrhea, and dizziness are uncommon. Dyspnea, anemia, fever, and rashes are rare.
Indications: FDA approved for stage D2 prostate cancer, in combination with a luteinizing hormone–releasing hormone (LHRH) agonist agent.
Dosing: 50 mg by mouth daily, in combination with an LHRH agonist agent.

Bleomycin (Blenoxane)—Bleo
- Drug Class: Antitumor antibiotic; causes DNA strand breaks directly in normal and neoplastic cells.
- Dosage Forms: Available as 15-unit (15-mg) vials of lyophilized powder.
- Drug Interactions: None noted.
- Phamakokinetics/Metabolism: Bleomycin is not orally bioavailable. After an IV infusion, it has an elimination half-life of 3 to 5 hours. Bleomycin is incompletely metabolized by intracellular aminopeptidases. It is excreted in the kidney as unchanged drug and metabolites.
- Toxicity: Pulmonary toxicity, including reversible and irreversible fibrosis, is dose limiting. Other common toxicities include fever, chills, rash, exfoliation, and anorexia. Nausea, vomiting, myelosuppression, anaphylaxis, and mucositis are rare.
- Indications: FDA approved for germ cell tumors, Hodgkin's disease, and squamous cell cancers; used off-label for melanoma, ovarian cancer, and Kaposi's sarcoma. Also used as a sclerosing agent for malignant pleural or pericardial effusions
- Dosing: After 1 to 6 hours of observation following a 2-unit IV test dose given over 15 minutes, the full dose can be given. The usual dose is 10 to 20 units/m^2 IV, IM, or SC one to two times per week, or 15 to 20 units/m^2/day as a continuous infusion over 3 to 7 days. As a sclerosing agent 60 units is generally used.

Buserelin (Suprefact)—HOE 766
- Drug Class: LHRH agonist; shuts off luteinizing hormone and follicle-stimulating hormone secretion, thereby resulting in chemical castration.
- Dosage Form: Available as vials for injection at 1 mg/mL and as an intranasal spray in a 10-mL canister.
- Drug Interactions: May cause pain flares in bone metastases if not given with a direct hormonal antagonist.
- Pharmacokinetics/Metabolism: Intravascular and extravascular proteolysis.
- Toxicity: Flare reactions as noted previously, which can be prevented. Castration symptoms such as hot flashes and decreased libido common. Other nonspecific symptoms include headache, nausea, vomiting, diarrhea, constipation, and weakness.
- Indications: FDA approved for prostatic cancer.
- Dosing: 500 μg SC tid for the first week, then 200 μg/day, or intranasally 800 μg tid followed by 400 μg tid.

Busulfan (Myleran)—BSF
- Drug Class: Alkylating agent.
- Dosage Form: 2-mg scored tablets (an IV form is not yet widely available).
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Excellent oral bioavailability, with peak levels in serum occurring at about 1 hour. Elimination half-life of 2.5 hours. Metabolized partially in liver. Parent drug and metabolites excreted in the urine.
- Toxicity: Myelosuppression, partly chronic and cumulative, is dose limiting. Other common toxicities include nausea, vomiting, anorexia, mucositis, hyperpigmentation, and elevated liver function tests (or veno-occlusive disease of the liver at transplant doses). Neurologic toxicity, including blurred vision, dizziness, and confusion, and interstitial lung disease are less common.
- Indications: Regular-dose therapy in CML (FDA approved) and polycythemia vera. High-dose therapy in bone marrow transplant.
- Dosing: Regular dose: 4 to 8 mg/day. High dose: 8 to 16 mg/kg total dose.

Capecitibine (Xeloda)
- Drug Class: Oral antimetabolite prodrug.
- Dosage Form: 150-mg and 500-mg tablets.
- Drug Interactions: Capecitibine increases the half-life, area under the curve (AUC), and prothrombin time effect of warfarin. Maalox, when given immediately after capecitibine, increases the oral bioavailability of capecitibine.
- Pharmacokinetics/Metabolism: Readily absorbed by the GI tract, metabolized in vivo to fluorouracil in the liver by carboxylesterase and cytidine deaminase, and then in turn in the peripheral tissues and tumor tissue by thymidine phosphorylase. Capecitibine appears to produce higher levels of fluorouracil in tumor tissue than in normal tissues, probably because thymidine phosphorylase is expressed at higher levels in most tumor tissues.
- Toxicity: Myelosuppression and palmar-plantar erythrodysesthesia are dose limiting. Diarrhea, fatigue, stomatitis, and hyperbilirubinemia are uncommon. Nausea, vomiting, and rash are rare.
- Indications: FDA approved for metastatic breast cancer and metastatic colorectal cancer. Used also in head and neck squamous cell cancer.
- Dosing: The approved dose and schedule is 1250 mg/m^2 every 12 hours for 14 days every 21 days. Dose reductions are often required. Treatment delays are sometimes required. Other doses and schedules have been used.

Carboplatin (Paraplatin)—Carbo, CBDCA
- Drug Class: Atypical alkyator; produces intrastrand and interstrand cross-links in DNA via association bonds with the platinum molecule, leading to DNA strand breakage during replication.
- Dosage Form: Available as powder in glass vials: 50, 150, and 450 mg/vial.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Carboplatin is not orally bioavailable. It is rapidly cleared from the bloodstream after IV infusion, with a terminal half-life of 2.5 hours. It is cleared largely as unchanged drug by the kidneys.
- Toxicity: Myelosuppression, especially thrombocytopenia, is dose limiting. Nausea and vomiting are mild. Renal and neuronal toxicity are rare.
- Indications: FDA approved for ovarian cancer and used extensively in testicular cancer, squamous cell cancers of the head and neck and cervix, and lung cancer.
- Dosing: Dosing can be done on a per-meter-squared basis or through several formulas that take into account renal function and desired level of thrombocytopenia (such as Calvert's formula). Typical doses with normal renal function are in the 300- to 500-mg/m^2 range as an IV infusion.

Carmustine (BiCNU)—BCNU, bis-chloronitrosourea
- Drug Class: Alkylator agent in the nitrosourea class. Cell cycle-independent mechanism.
- Dosage Form: 100-mg vial of carmustine powder and 3-mL vial of ethanol.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Poorly available by the oral route. After an IV infusion, the drug is rapidly taken up by tissues, including the CNS. Extensively metabolized in the liver. The serum half-life is only 15 to 20 minutes. The parent drug and metabolites are cleared by the kidney.
- Toxicity: Myelosuppression, which is slow in onset and cumulative, is dose limiting. Nausea and vomiting are common and can be severe. Hyperpigmentation and renal toxicity can be seen. Interstitial lung disease, including fibrosis, is rare but can occur with any dose. Transplant doses can cause severe liver toxicity and more frequent lung toxicity.
- Indications: FDA approved for brain tumors, multiple myeloma, Hodgkin's disease, lymphoma. Also used for breast cancer, melanoma, stomach cancer, colon cancer, and liver cancer.

Dosing: Single-agent dose is 150 to 200 mg/m^2 every 6 weeks. For transplant, the dose is as high as 600 mg/m^2, along with other drugs.

Carmustine impregnated wafer (Gliadel)—polifeprosan 20 with carmustine implant.
- Drug Class: Novel delivery mechanism for classical nitrosourea alkylating agent.
- Dosage Form: Each individually packaged, sterile wafer contains 7.7 mg of carmustine.
- Drug Interactions: None known.
- Pharmacokinetics/Metabolism: More than 70% of the copolymer degrades by 3 weeks. Gliadel wafers produce minimal systemic exposure to carmustine. The copolymer itself is biodegradable, but metabolites of the polymer have no known or expected pharmacologic implications.
- Toxicity: None.
- Indications: FDA approved for adjuvant treatment of recurrent glioblastoma multiforme. Being tested in the setting of initial resection.
- Dosing: Up to eight wafers are placed in the resection cavity at the time of craniotomy and operative resection.

Cetuximab (Erbitux)
- Drug Class: Monoclonal antibody.
- Dosage Form: IV.
- Drug Interactions: None known.
- Pharmacokinetics/Metabolism: A recombinant humanized monoclonal antibody targeted against the epidermal growth factor receptor. It competitively inhibits growth factor binding and inhibiting autophosphorylation and cell signaling. Metabolism is poorly understood. Half-life is 5 to 7 days with minimal clearance by kidneys or liver.
- Toxicity: Infusion reaction, characterized by rapid onset dyspnea, fever, chills, urticaria, flushing, angioedema, and hypotension is seen in 40% to 50% of patients. Acneiform rash is common. Constitutional symptoms. Hypomagnesemia. Interstitial lung disease is rare.
- Indications: Metastatic colorectal cancer, head and neck cancer in combination with radiation.
- Dosing: 400 mg/m^2 IV, followed by 250 mg/m^2 weekly.

Chlorambucil (Leukeran)
- Drug Class: Alkylating agent. Cell cycle independent.
- Dosage Form: 2-mg tablets.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Excellent oral bioavailability; maximum plasma level at 1 hour. Elimination half-life of 1 to 2 hours. Extensively metabolized in the liver to active and inactive metabolites, which are excreted via the kidneys.
- Toxicity: Myelosuppression is dose limiting and universal, and it can be cumulative. Nausea, vomiting, and diarrhea are mild and uncommon. Sterility and alopecia occur in a minority of patients. Pulmonary fibrosis and neurologic side effects are quite rare.
- Indications: FDA approved for CLL and low-grade lymphomas. Also used for Waldenstrom's macroglobulinemia, multiple myeloma, hairy cell leukemia, and rarely in some solid tumors.
- Dosing: 16 mg/m^2/day for 5 days every 4 weeks, or 0.4 mg/kg every 2 to 4 weeks, or 0.1 to 0.2 mg/kg/day for 3 to 6 weeks.

Cisplatin (Platinol)—cDDP, DDP, cisplatinum, *cis*-diamminedichloroplatinum (II)
- Drug Class: Atypical alkyator; produces intrastrand and interstrand cross-links in DNA via association bonds with the platinum molecule, leading to DNA strand breakage during replication.
- Dosage Form: Lyophilized powder in sealed vials of 10 and 50 mg, and as a 1-mg/mL solution in bottles of 50 and 100 mg/bottle.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Poor oral bioavailability. After IV infusion, rapid distribution to tissues takes place, and the drug is over 90% protein bound. While the distribution half-life is less than 1 hour, the terminal half-life is 60 to 90 hours due to tissue retention. Not extensively metabolized. Elimination is via the kidneys.
- Toxicity: Nephrotoxicity is dose limiting for an individual dose, while neurotoxicity, especially painful peripheral neuropathy, is dose limiting for cumulative doses. Myelosuppression is mild. Nausea and vomiting are common but manageable, and anorexia and diarrhea are common. Cumulative ototoxicity is also common. Chronic renal magnesium and potassium wasting is common and sometimes not reversible. Elevated liver transaminases can be seen, while alopecia and cardiac conduction abnormalities are rare.
- Indications: Used for almost every class of solid tumor and lymphoma. FDA approved for testicular and ovarian cancer and transitional cell carcinoma.
- Dosing: Cisplatin can be given all in one IV infusion or given daily as an IV infusion for several days for each cycle. Daily divided doses are somewhat better tolerated. The total dose per cycle ranges from 80 to 160 mg/m^2. Continuous infusion can also be used. Dose should be reduced for a creatinine clearance below 60 mL/min. Adequate renal perfusion and urine output are critical for minimizing renal toxicity; therefore, prehydration and adequate post-treatment hydration are used, usually with normal saline with or without mannitol, potassium, and magnesium, along with the cisplatin. Cisplatin 100 to 200 mg/m^2 is also used intraperitoneally for ovarian cancer.

Cladribine (Leustatin)—chlorodeoxyadenosine, 2-CdA
- Drug Class: Antimetabolite, purine analog; cytotoxic to dividing and nondividing cells via disruption of DNA function.
- Dosage Form: 1-mg/mL solution in 20-mL vials.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Not orally bioavailable. After IV administration, it has a distribution half-life of 36 minutes and an elimination half-life of 7 hours. Resistant to adenosine deaminase. Chemical conversion to the active form takes place intracellularly in all cells that have deoxycytidine kinase activity. Further information on metabolism and excretion is not available.
- Toxicity: Renal toxicity is dose limiting, but at the typical doses used, myelosuppression is most prominent, including universal lymphopenia and common neutropenia and thrombocytopenia. Fever is common, while nausea and vomiting are rare and mild, and neurologic reactions are rare.
- Indications: FDA approved for hairy cell leukemia. Also used in chronic and acute leukemias, lymphoma, and mycosis fungoides.
- Dosing: For hairy cell leukemia, the dose is 0.1 mg/kg/day for 7 days as a continuous IV infusion, as a single treatment or repeated once. Other doses have ranged from 0.1 to 0.3 mg/kg/day for 5 to 7 days. Can also be given subcutaneously.

Clofarabine (Clolar)
- Drug Class: Antimetabolite.
- Dosage Form: IV 20-mL vials.
- Drug Interactions: None known.

Pharmacokinetics/Metabolism: Purine nucleoside antimetabolite. Metabolized intracellularly to the 5′ monophosphate metabolite and then phosphorylated to active triphosphate form. Inhibits DNA synthesis by decreasing deoxynucleoside triphosphate pools by inhibiting ribonucleotide reductase. Incorporates into DN, inhibiting DNA repair. Negligible hepatic metabolism. Most of drug is excreted unchanged in the urine.

Toxicity: Myelosuppression. Nausea and vomiting. Hepatobiliary toxicity. Cardiac toxicity (decrease in ejection fraction and tachycardia). Capillary leak syndrome.
Indications: Relapsed or refractory acute lymphoblastic leukemia in children.
Dosing: 52 mg/m^2 IV over 2 hours daily for 5 days, repeated every 2 to 6 weeks.

Cyclophosphamide (Cytoxan, Neosar)—CTX, CPM, Cy
Drug Class: Prototypical alkylator drug. Cell cycle independent.
Dosage Form: 25-mg and 50-mg tablets for oral use, and vials of powder in 100-, 200-, 500-, 1000-, and 2000-mg sizes for IV administration.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: 75% oral bioavailability; peak serum levels occur approximately 1 hour after administration. Activated by hepatic enzymes and metabolized to inactive forms in the liver as well. Elimination half-life is 3 to 10 hours. Parent drug and metabolites are excreted in the urine.
Toxicity: Myelosuppression is dose limiting, leukopenia being most significant. Nausea and vomiting are common and can be chronic with oral administration. Hemorrhagic cystitis is uncommon with standard doses but is common with doses over 2 g/m^2. Other toxicities of high-dose therapy include syndrome of inappropriate secretion of antidiuretic hormone, pulmonary fibrosis, and hemorrhagic myocarditis. Secondary malignancies are rare but well documented.
Indications: FDA approved for many malignancies and used for even more. Most commonly used for breast carcinoma, non-Hodgkin's lymphoma, ovarian carcinoma, and testicular cancer.
Dosing: Doses range from 50 mg/m^2 for 14 days every 28 days, to standard IV doses of 600 to 2000 mg/m^2 once every 21 to 28 days, to transplant doses of 60 mg/kg IV for 2 days.

Cytarabine (Cytosar-U)—AraC, cytosine arabinoside
Drug Class: Antimetabolite; incorporated into DNA during replication, leading to strand termination. This drug is S-phase specific.
Dosage Form: Comes in 100-mg through 2000-mg vials of powdered drug.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Parenteral bioavailability only. After an IV dose, it is rapidly distributed into tissues, where it is converted to AraC triphosphate and rapidly deaminated in the blood. It has an elimination half-life of 2 to 3 hours. Eliminated through the kidneys.
Toxicity: Myelosuppression, often severe and prolonged, is dose limiting. It affects all lineages. Nausea, vomiting, anorexia, mucositis, and diarrhea are common. Skin erythema with exfoliation is common. Keratitis and conjunctivitis are common. Hepatic inflammation and elevation of liver function tests are common. Flu-like syndrome with fever is common. Neurologic toxicity, mostly central with ataxia being predominant, is common and usually mild, but it is dose dependent and may leave permanent dysfunction. It is more common with intrathecal administration. Pulmonary infiltrates after administration are uncommon but can be fatal. Cardiac complications are rare.
Indications: AML, ALL, and non-Hodgkin's lymphoma. Intrathecal use in acute leukemia.
Dosing: Doses range from 100 mg/m^2/day for 7 days as bolus or continuous infusion to 3 g/m^2 every 12 hours for 3 days. Doses less than 500 mg/m^2 are considered standard, while doses of 1 g/m^2 or more are considered high. The intrathecal dose is generally from 12 mg total dose up to 30 mg/m^2, given intermittently during systemic treatment.

Cytarabine, liposomal (DepoCyt)
Drug Class: Novel liposomal preparation of an antimetabolite for extended exposure to cancer cells in the cerebrospinal fluid.
Dosage Form: Vials containing 50 mg of drug in aqueous liposomal solution.
Drug Interactions: Minimal systemic exposure after intrathecal administration. Drug interactions are not considered clinically important.
Pharmacokinetics/Metabolism: After intrathecal administration of liposomes, peak levels of cytarabine occur in the CSF at 5 hours, and the half-life of cytarabine in the CSF is 100 to 200 hours. Cytarabine and metabolites eventually enter the plasma compartment, where they are eliminated in the urine.
Toxicity: Chemical arachnoiditis is common and dose limiting. Headache and back pain are the major clinical manifestations. Myelosuppression is common but usually mild. Fever, nausea, and vomiting are uncommon. Neurologic side effects are also uncommon.
Indications: FDA approved for treatment of lymphomatous meningitis. Appears to active in leukemic meningitis and carcinomatous meningitis, but published experience is limited.
Dosing: 50 mg intrathecally via spinal needle or Ommaya reservoir over 1 to 5 minutes every 14 days for up to 9 doses and then every 28 days for up to 4 doses.

Dacarbazine (DTIC-Dome)—DTIC, DIC, imidazole carboxamide
Drug Class: Atypical alkylator; methylates guanine bases preferentially. Non-cell cycle dependent.
Dosage Form: Vials of lyophylized drug containing 100, 200, or 1000 mg.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Not orally bioavailable. After IV administration, the drug is activated by demethylation by microsomal enzymes in the liver and further metabolized to inactive forms. The elimination half-life is 3 to 5 hours. Active and inactive metabolites are largely excreted in the urine.
Toxicity: Myelosuppression is dose limiting. Nausea and vomiting are severe without aggressive antiemetic therapy. Fever is common, and flu-like syndrome is uncommon, as are diarrhea, stomatitis, alopecia, rash, or significant liver or renal toxicity.
Indications: FDA approved for the treatment of malignant melanoma and Hodgkin's disease; also used for adult sarcomas and neuroblastoma.
Dosing: Given by intravenous piggyback in doses of 375 to 1450 mg/m^2 every 2 to 3 weeks or 50 to 250 mg/m^2/day for 5 to 10 days every 3 to 4 weeks.

Dactinomycin (Cosmegen)—actinomycin D, ACT-D
Drug Class: Antitumor antibiotic, inhibits transcription by complexing with DNA.
Dosage Form: Available in vials of 0.5 mg of lyophilized drug.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Poor oral bioavailability. After an IV dose, the drug is widely distributed except to the cerebrospinal fluid. It is metabolized in the liver. It has an elimination half-life of 30 to 40 hours. Dactinomycin and its metabolites are excreted in both bile and urine.
Toxicity: This drug is a moderate vesicant. Myelosuppression is dose limiting. Nausea, vomiting, skin erythema, acneiform lesions, and hyperpigmentation are common, while mucositis, diarrhea, and anorexia are uncommon. Hepatitis, ascites, fever, and hypocalcemia are rare.
Indications: FDA approved for Wilms' tumor, Ewing's sarcoma, rhabdomysarcoma, uterine carcinoma, germ cell tumors, and sarcoma botryoides; also used for other sarcomas, melanoma, acute myeloid leukemia, ovarian cancer, and trophoblastic neoplasms.
Dosing: 1 to 2 mg/m^2 every 3 weeks or continuous infusions of 0.25 to 0.6 mg/m^2/day for 5 days every 3 to 4 weeks.

Darbopoetin alfa (Arenesp)
Drug Class: Erythropoietic growth factor, modified recombinant DNA peptide product.

Dosage Form: Vials containing 25, 40, 60, 100, 150, 200, 300, and 500 μg of drug in 1 mL of either albumin or polysorbate aqueous solution.
Drug Interactions: No formal drug studies have been done. Exogenous testosterone and erythropoietin products used together could cause polycythemia.
Pharmacokinetics/Metabolism: After subcutaneous administration, absorption into the bloodstream is slow and dose limiting. Peak concentration occurs at approximately 30 hours and half-life in the bloodstream is 30 to 90 hours. Metabolic fates and routes of elimination have not been formally studied.
Toxicity: Polycythemia can occur and thus hemoglobin must be monitored during therapy. No other form of dose limiting toxicity is known. Either hypertension or hypotension are common. Headache is uncommon. Cardiovascular events including myocardial infarction, arrhythmia, or stroke are uncommon but can be serious. Fever, edema, or pain are rare.
Indications: FDA approved for anemia caused by cancer chemotherapy for nonmyeloid malignancies and anemia associated with chronic renal insufficiency.
Dosing: For anemia and renal insufficiency, the indicated dose is 0.45 μg/kg SC or IV once weekly, titrated upward to achieve the target hemoglobin level of 12 g/dL. For anemic cancer patients receiving chemotherapy, the recommended dose is 2.25 μg/kg SC once weekly, again with slow upward titration as needed to achieve a specific hemoglobin goal. Every other week and every 3 week doses are currently under evaluation.

Dasatinib (Sprycel)
Drug Class: Anthracycline antitumor antibiotic, intercalating agent.
Dosage Form: 20-mg vials of powdered drug for reconstitution.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Not orally bioavailable. After IV bolus, the drug is widely distributed and is metabolized in the liver to active and inactive metabolites. The elimination of the parent drug is 18 hours, and that of the active metabolite daunorubicinol is about 25 hours. Elimination of parent drug and metabolites is via the biliary and renal routes.
Toxicity: Daunorubicin is a vesicant. Precautions are necessary. Myelosuppression is dose limiting. Alopecia, nausea, vomiting, and stomatitis are common. Diarrhea, rash, elevated liver function tests, and transient arrhythmias are uncommon. Dose-related cardiomyopathy is uncommon below cumulative doses of 400 to 500 mg/m^2.
Indications: FDA approved for AML and ALL.
Dosing: Given as a single IV injection daily for 1 to 5 days. Total dose per course up to 150 mg/m^2. A typical dose would be 45 mg/m^2/day for 3 days.

Daunorubicin, liposomal (Daunosome)
Drug Class: Novel liposomal preparation of the anthracycline DNA intercalating agent daunorubicin which modifies the pharmacokinetics and toxicities of the drug.
Dosage Form: Single-use vials containing 50 mg of daunorubicin in an aqueous liposomal solution at a concentration of 2 mg/mL.
Drug Interactions: Significant interactions of liposomal daunorubicin and other drugs have not been observed.
Pharmacokinetics/Metabolism: Daunorubicin liposomes have a small volume of distribution after IV administration but are rapidly cleared from the plasma compartment into peripheral tissues with a half-life of about 4 hours. Low levels of metabolites are detected in the plasma, likely due to slow distribution of parent drug from the peripheral tissues to the liver for metabolism. Metabolic fates are the same as for the conventional drug.
Toxicity: In general, this agent has a milder side effect and toxicity profile that conventional daunorubicin. Myelosuppression is mild but still dose limiting. An acute syndrome of back pain, chest tightness, and flushing can occur uncommonly during administration, which can usually be treated symptomatically. Other cardiac side effects are rare. Skin rashes are rare. Nausea, vomiting, and alopecia are rare.
Indications: FDA approved for treatment of AIDS-associated Kaposi's sarcoma. Some experience in other solid tumors.
Dosing: 0 mg/m^2 IV infusion over 60 minutes every 2 weeks, with reduction and delay for significant myelosuppression.

Decitabine (Dacogen)
Drug Class: Antimetabolite.
Dosage Form: Oral.
Drug Interactions: None known.
Pharmacokinetics/Metabolism: Inhibits DNA methyltransferase, causing hypomethylation of DNA. This may induce apoptosis or restore normal function to genes that control cellular differentiation and proliferation. Deaminated by cytidine deaminase, found in liver, granulocytes, gut, and blood. Elimination half-life is 30 minutes.
Toxicity: Myelosuppression. Nausea, vomiting, abdominal pain. Constitutional symptoms. Elevated liver functions, blood sugar, low serum magnesium, low serum potassium. Respiratory toxicity.
Indications: Myelodysplastic syndromes.
Dosing: 15 mg/m^2 by continuous infusion over 3 hours, every 8 hours for 3 days, repeated every 6 weeks for a minimum of 4 cycles.

Denileukin diftitox (Ontak)
Drug Class: Recombinant DNA peptide fusion product combining interleukin-2 and a diphtheria toxin, allowing relative specificity of diphtheria toxin toward interleukin-2 receptor-expressing cells.
Dosage Form: Vials of 300 μg in 2 mL frozen aqueous solution.
Drug Interactions: None known.
Pharmacokinetics/Metabolism: After IV administration, the plasma half-life of denileukin diftitox is about 80 minutes. Radiolabeling studies show that the drug accumulates in the vasculature, liver, and kidneys, but its specific metabolic fates are unknown. Antibodies against the drug have been shown to slow its clearance.
Toxicity: Denileukin diftitox has a broad range of toxicities similar to other peptide biologic response modifiers, with hypotension and other manifestations of vascular leak syndrome being dose limiting. Fever, chills, edema, rash, fatigue, headache, nausea, vomiting, anorexia, and diarrhea are common. Dyspnea, cough, arthralgias, myalgias, and pharyngitis are uncommon. Infections associated with drug administration are common. Arrhythmias and significant neurologic, hepatic, or renal complications are rare.
Indications: FDA approved for recurrent cutaneous T-cell lymphoma (mycosis fungoides).
Dosing: 9 or 18 μg/kg/day for 5 days as an IV infusion over at least 15 minutes, repeated every 21 days.

Dexamethasone (Decadron)—Dex, DXM
Drug Class: Corticosteroid that has pleiotrophic properties in various body tissues. Directly toxic to benign and malignant lymphocytes. Potent anti-inflammatory action.
Dosage Form: Tablets ranging from 0.25 to 6 mg are available, as well as an oral solution at 0.1 mg/mL and a solution for injection at 4 to 24 mg/mL.
Drug Interactions: Drugs that induce hepatic microsomal enzymes can enhance the metabolism of dexamethasone and decrease its effectiveness. This includes phenytoin, tegretol, and dilantin.
Pharmacokinetics/Metabolism: Well absorbed by the GI tract. Metabolized in the liver. Elimination half-life is 3 to 4 hours.

Elimination of metabolites is primarily renal, with some biliary component.
Toxicity: Toxicities are shared with other corticosteroids and include leukocytosis, hyperglycemia, mood changes, euphoria, insomnia, increased appetite, weight gain, dyspepsia, exacerbation of peptic ulcer disease, cataracts, adrenal suppression, edema, and osteoporosis.
Indications: Used for many purposes in oncology and hematology patients, including treatment of multiple myeloma, CLL and ALL, non-Hodgkin's lymphoma, immune thrombocytopenic purpura, and hemolytic anemia. Also used to alleviate symptoms from brain or spinal cord metastases and other metastatic sites where edema and inflammation exist. Used as an adjunctive antiemetic medication as well.
Dosing: Oral and parenteral dosing are equivalent. Dosage for acute indications or active treatment involves total daily doses of 16 to 40 mg, sometimes with an initial "bolus" dose of up to 100 mg. Tapering treatments will decrease down to 1 to 2 mg/day. As an antiemetic, 10 to 20 mg is the standard dose.

Dexrazoxane (Zinecard)—ADR-529, ICRF-187
Drug Class: Iron-chelating agent that serves as a free-radical scavenger/cytoprotectant.
Dosage Form: Lyophilized powder, 500 mg/vial, with diluent.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: The drug is not bioavailable by the oral route. After an IV dose, distribution in the body is widespread and rapid. Metabolism is predominantly hepatic. The terminal half-life is 3 to 4 hours. Parent drug and metabolites are excreted by the kidneys.
Toxicity: Dexrazoxane appears to worsen slightly the leukopenia induced by doxorubicin. Mild nausea and vomiting are common, fever, stomatitis, fatigue, anorexia, and hypotension are uncommon. Seizure, respiratory arrest, deep venous thrombosis, and significant liver toxicity are rare.
Indications: FDA approved as an "orphan drug" to prevent doxorubicin-induced cardiomyopathy.
Dosing: Administered just prior to a dose of doxorubicin as a 15- to 30-minute infusion at a dose of 500 to 1000 mg/m^2.

Docetaxel (Taxotere)—RP-56976
Drug Class: Docetaxel is a semisynthetic taxane, a class of compounds that inhibit the mitotic spindle apparatus by stabilizing tubulin polymers, leading to death of mitotic cells.
Dosage Form: 20- and 80-mg vials at a concentration of 40 mg/mL in polysorbate 80 solvent.
Drug Interactions: Docetaxel given concurrently with cisplatin has been reported to increase the incidence and severity of peripheral neuropathy.
Pharmacokinetics/Metabolism: The drug has poor oral bioavailability. After a 1-hour infusion, docetaxel is widely distributed and has a triphasic elimination course, with a distribution half-life of 4 minutes, an elimination half-life of 1 hour, and a terminal half-life of 18 hours. The extent and by-products of metabolism are not well known. The main excretion route is biliary.
Toxicity: Myelosuppression is universal and dose limiting. Alopecia is also universal. Edema and fluid accumulation, including pleural effusions and ascites, are common and can be dose limiting. Fluid accumulation is partially preventable with corticosteroid treatment before and after each cycle of docetaxel. Mild sensory or sensorimotor neuropathy is common. Mucositis and diarrhea are common and usually mild. Hypersensitivity reactions are uncommon and can largely be prevented through premedication with corticosteroids and antihistamines. Rash and elevated liver function tests are uncommon.
Indications: FDA approved for metastatic breast cancer and first and second line non-small-cell lung cancer. Clinical experience is increasing in ovarian cancer and other epithelial neoplasms.
Dosing: The standard dose is 100 mg/m^2 IV over 1 hour every 3 weeks. Higher doses and other schedules have been used.

Doxorubicin (Adriamycin, Rubex)—Adria, hydroxydaunorubicin
Drug Class: Anthracycline antitumor antibiotic, intercalating agent.
Dosage Form: Available in vials of lyophilized powder containing 10 to 150 mg of drug and as vials of 2-mg/mL solution in 10- to 200-mg vials.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: The drug has poor oral bioavailability. After an IV dose, it is widely distributed in tissues and is 70% protein bound. It is metabolized in the liver to active and inactive forms. It has an elimination half-life of 18 hours or more. Most of the drug and metabolites are excreted through the biliary route.
Toxicity: Doxorubicin is a potent vesicant, and extravasation precautions are a must. Myelosuppression is universal and usually dose limiting with each individual cycle. Cardiotoxicity is common and can be dose limiting, though usually subclinical. Chronic, cumulative cardiomyopathy is expected when total dose exceeds 400 to 500 mg/m^2. This toxicity can be lessened by the addition of dexrazoxone or by longer infusions. Acute cardiac effects, including arrhythmias, are less often seen and are unpredictable. Nausea and vomiting are common but manageable. Diarrhea and stomatitis are common but usually mild. Alopecia, rash, and hyperpigmentation are common.
Indications: FDA approved for a variety of cancers and used for many more. Most commonly used for breast carcinoma, adult sarcomas, pediatric solid tumors, Hodgkin's disease, non-Hodgkin's lymphomas, and ovarian cancer.
Dosing: Standard doses range from 60 to 90 mg/m^2 IV as a bolus or continuous infusion over 48 to 72 hours every 3 to 4 weeks. Weekly and biweekly schedules are also used, with lower doses. Doses are usually reduced for elevated bilirubin levels.

Doxorubicin, liposomal (Doxil)
Drug Class: Novel liposomal preparation of the anthracycline DNA intercalating agent doxorubicin.
Dosage Form: Vials of 20 mg in 10 mL and 50 mg in 25 mL of doxorubicin in aqueous liposomal dispersion.
Drug Interactions: No formal drug interaction studies have been conducted. No important drug interactions have been reported.
Pharmacokinetics/Metabolism: The parent drug, doxorubicin, is metabolized in the liver and excreted primarily in the bile. Significant levels of the principal metabolite doxorubicinol, have not been observed with the liposomal preparation, likely due to the slow distribution of free doxorubicin to the liver. Half-life of the liposomes in the plasma compartment is approximately 55 hours.
Toxicity: Myelosuppression is mild but dose limiting. Palmar plantar erythrodysesthesia is common and can occasionally be severe and dose limiting. Stomatitis and nausea are common but usually mild. Alopecia is uncommon. Acute infusion reactions including chest pain, back pain, dyspnea, and wheezing can occur uncommonly.
Indications: FDA approved for recurrent metastatic ovarian cancer and AIDS-related Kaposi's sarcoma. Also used commonly in metastatic breast cancer and multiple myeloma.
Dosing: 50 mg/m^2 IV infusion over 1 hour for ovarian cancer, 20 mg/m^2 IV infusion over 30 minutes for Kaposi's sarcoma.

Epirubicin (Ellence)
Drug Class: Anthracycline DNA intercalating agent.
Dosage Form: Vials of 50 mg in 25 mL or 200 mg in 100 mL of aqueous solution.

Drug Interactions: Additive toxicities with other cytotoxic drugs should be expected. Cardiac toxicity of epirubicin can be enhanced when used with other drugs that can temporarily or permanently impair cardiac function. Cimetidine increases the AUC of epirubicin and should be stopped before starting epirubicin.

Pharmacokinetics/Metabolism: Epirubicin is metabolized primarily by the liver. The parent drug and metabolites are glucuronidated and are excreted in the bile much more than via renal clearance. Doses should be reduced for patients with mild to moderate hepatic dysfunction. Severe hepatic dysfunction is a contraindication for using epirubicin. Half-life of plasma levels is about 30 to 35 hours after IV administration.

Toxicity: Myelosuppression is universal and dose limiting. Alopecia is expected. This drug is a vesicant, and precaution must be taken to avoid extravasation into soft tissue around veins. Nausea and vomiting are common but usually manageable. Stomatitis is common. Fatigue is common. Detectable cardiac dysfunction is uncommon to rare. Secondary leukemia is rare.

Indications: FDA approved for adjuvant therapy after optimal surgical treatment of localized breast cancer with involved axillary lymph nodes.

Dosing: 100 to 120 mg/m^2 by intravenous infusion every 3 to 4 weeks. Usually combined with cyclophosphamide and 5-fluorouracil.

Erlotinib (Tarceva)

Drug Class: Targeted agent.

Dosage Form: 25-mg, 100-mg, 150-mg tablets.

Drug Interactions: Drugs that stimulate or inhibit liver CYP3A4 enzymes. Warfarin.

Pharmacokinetics/Metabolism: Inhibits the tyrosine kinase domain of the epidermal growth factor receptor, leading to inhibition of EGFR autophosphorylation and signaling.

Toxicity: Acneiform rash. Diarrhea. Interstitial lung disease.

Indications: Second- or third-line therapy of non-small-cell lung cancer. Pancreatic cancer, in combination with gemcitabine.

Dosing: Lung cancer: 150 mg/day. Pancreatic cancer: 100 mg/day.

Erythropoietin (Epogen, Procrit)—EPO, epoitin alpha

Drug Class: Hematopoietic growth factor. Stimulates erythrocytic precursors.

Dosage Form: Vials of 2000, 4000, and 10,000 units in solution.

Drug Interactions: Erythropoietin may temporarily decrease the effectiveness of heparin when the two drugs are given simultaneously. Oral aluminum-containing antacids may decrease the effectiveness of erythropoietin.

Pharmacokinetics/Metabolism: This peptide must be given parenterally. After IV or subcutaneous dosing, it is detectable in plasma for 24 hours. It is distributed to a volume approximating the total blood volume. It is degraded by proteolysis within the blood compartment. Half-life ranges from 4 to 27 hours. Onset of therapeutic effect takes at least 7 days. Excretion of intact peptide is negligible.

Toxicity: Hypertension is common but usually mild and not dose limiting. Injection site pain is common but mild. Flu-like syndrome and diaphoresis are uncommon. Nausea and vomiting are rare. Seizures have been reported in dialysis patients receiving the drug. Iron deficiency anemia can occur after prolonged therapy, and concomitant iron administration may increase the effectiveness of erythropoietin. Hematocrit values should be monitored closely while on therapy to prevent polycythemia and hyperviscosity.

Indications: The oncology indication is chemotherapy-induced anemia that is symptomatic. Also used for anemia of chronic renal failure and human immunodeficiency virus (HIV)-associated anemia.

Dosing: Starting doses of 150 units/kg SC three times per week were recommended, with increases up to 300 units/kg if there is suboptimal effect after 6 to 8 weeks, although 40,000 units weekly with increases to 60,000 units is the most commonly used program.

Estramustine (Emcyt)

Drug Class: A conjugate of estrogen and an alkylating moiety, estramustine appears to work through estrogen-binding proteins to kill malignant cells through a nonalkylator mechanism, perhaps by inhibition of microtubules.

Dosage Form: 140-mg capsules.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Well absorbed by mouth, subject to hepatic metabolism, with a terminal half-life of about 20 hours. Excretion route is not clearly delineated.

Toxicity: Nausea and vomiting are common and dose limiting but diminish over time. Headache, edema, decreased libido, and impotence are common. Gynecomastia and breast tenderness can be seen. Rash, alopecia, myelosuppression, hepatic toxicity, and thromboembolic events are rare.

Indications: FDA approved for the treatment of prostate cancer. Not used commonly for any other types of cancer.

Dosing: The usual dose for prostate cancer is 15 mg/kg/day, which is typically given as 420 mg PO tid for most men.

Etoposide (Vespid)—VP-16, epipodophyllotoxin; also available as etoposide phosphate (Etopophos)

Drug Class: Plant alkaloid; topoisomerase II inhibitor. Partially cell cycle dependent.

Dosage Form: Etoposide comes in oral form as 50-mg capsules and in parenteral form as 100-mg multidose vials in solution at 20 mg/mL. Etoposide phosphate is available in 100-mg single-dose vials as lyophilized powder.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Etoposide phosphate is rapidly converted to etoposide after IV infusion. Etoposide itself is extensively protein bound, is metabolized in the liver, and has an elimination half-life of about 10 hours. About 50% of oral etoposide is absorbed via the GI tract, requiring oral doses to be twice as high as parenteral doses. Excreted both unchanged in the urine and as metabolites in the bile.

Toxicity: Myelosuppression, primarily leukopenia, is universal and dose limiting. Nausea and vomiting are common with PO administration but rare when the drug is given IV. Stomatitis and diarrhea are rare with normal doses but common with high doses. Alopecia is mild or absent. Hepatic toxicity and neurologic effects (peripheral neuropathy and CNS changes) are rare. Hypotension can occur with rapid administration of etoposide but does not occur commonly when etoposide phosphate is infused over 5 minutes. Secondary AML has been reported after etoposide.

Indications: FDA approved for germ cell tumors and SCLC. Also used for lymphomas, AML, brain tumors, non-SCLC, and as high-dose therapy in the transplant setting for breast cancer, ovarian cancer, and lymphomas.

Dosing: Etoposide can be given either over several days or at lower doses over many days. Typical doses are 50 to 120 mg/m^2/day for 3 to 5 days given IV. Oral doses are generally twice the IV doses. A typical protracted oral course would be 50 mg/m^2/day for 21 days given every 28 days. Transplant doses up to 1200 mg/m^2 over 1 to 3 days have been used.

Exemestane (Aromasin)

Drug Class: Hormonal agent, steroidal aromatase inhibitor.

Dosage Form: 25-mg tablets.

Drug Interactions: In spite of the fact that exemestane is metabolized by cytochrome P450 3A4, ketoconazole does not affect its half-life or AUC, and no other drug-drug interactions have been identified.

Pharmacokinetics/Metabolism: After oral administration, approximately 40% of exemestane is absorbed from the gastrointestinal tract. Absorption is increased by a fatty meal. It is highly protein bound in the plasma. Exemestane is metabolized in the liver by cytochrome P450 3A4 and aldoketoreductase. Metabolites are eliminated equally in urine and feces.

Toxicity: Though generally well tolerated, exemestane is expected to cause or exacerbate hot flashes or intermittent flushing in some women. Fatigue and mild nausea are common. Vomiting, headache, and dyspnea are uncommon. It is teratogenic and should not be used in premenopausal women.

Indications: FDA approved for treatment of estrogen-responsive metastatic breast cancer in postmenopausal women who have progressed on prior hormonal therapy.

Dosing: 25 mg orally once daily after a meal.

Filgrastim (Neupogen)—G-CSF

Drug Class: Hematopoietic growth factor, relatively specific for the granulocyte lineage.

Dosage Form: Available in single-use vials of 300 and 480 μg, in solution.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: After a bolus SC injection, peak plasma levels of filgrastim occur in 2 to 6 hours, while the elimination half-life is generally 7 hours or less. Metabolism is via proteolysis in the blood compartment. The intact molecule is largely absent from bile or urine.

Toxicity: Mild bone pain is common. Low-grade fever, myalgias, arthralgias, and transient hypotension are uncommon, as are hyperuricemia and elevations of lactate dehydrogenase and alkaline phosphatase. Leukocytosis leading to hypoxia or capillary leak syndrome has been reported. Anaphylaxis or allergic reaction are rare.

Indications: FDA approved for minimization of granulocytopenia after myelosuppressive chemotherapy. Also used to speed recovery of granulocytes in the setting of neutropenic fever after chemotherapy, for myelodysplastic syndromes, for congenital agranulocytosis, for cyclic neutropenia, and for mobilization of peripheral blood stem cells from patients or donors for transplant.

Dosing: Starting dose is 5 μg/kg/day until neutrophil recovery (discontinue the drug after an absolute neutrophil count of 10,000 or greater has been achieved), although generally either the whole 300 μg or 480 μg vial is used. For post-transplant or high-dose chemotherapy applications, 10 μg/kg/day is the typical dose. There is no known maximum dose.

Floxuridine (FUDR)—FdUR, fluorodeoxyuridine

Drug Class: Pyrimidine nucleotide analog, antimetabolite. Cell cycle dependent.

Dosage Form: Available in 500-mg vials of lyophilized powder.

Drug Interactions: Leucovorin will enhance the toxicity of floxuridine.

Pharmacokinetics/Metabolism: After infusion into the hepatic artery, the drug is phosphorylated to the active monophosphate form and incorporated into cells. Further hepatic metabolism to inactive forms is rapid. The elimination half-life is 30 minutes. Metabolites are cleared by the kidneys.

Toxicity: When given as a bolus, myelosuppression is dose limiting, while diarrhea and stomatitis are the dose-limiting toxicities of the more common protracted infusions. Other GI toxicities, all rare, include nausea, vomiting, anorexia, gastritis, cramping, enteritis, and duodenal ulcers. Liver toxicity, usually a cholestatic picture, is dose limiting with intrahepatic arterial infusions. Serious neurologic side effects, including ataxia and visual changes, are rare, as is fever.

Indications: FDA approved for regional (intra-arterial) treatment of GI adenocarcinomas metastatic to the liver. Sometimes used intravenously for the same tumors.

Dosing: Protracted intra-arterial infusions are generally given at 0.1 to 0.6 mg/kg/day until grade III toxicity, sometimes according to a circadian schedule. IV doses range up to 60 mg/kg/week by various infusion schedules.

Fludarabine (Fludara)—FAMP

Drug Class: Purine nucleotide analog antimetabolite. Only partially cell cycle dependent.

Dosage Form: Vials containing 50 mg each of lyophilized drug. Add 2 mL of sterile water to the vial to make a 25-mg/mL solution, and then dilute the desired dose further to a concentration of 0.04 to 1 mg/mL (depending on the infusion schedule).

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Fludarabine is available only by the parenteral route. After IV administration, the drug is metabolized to 2-fluoro-araA and widely distributed in tissues. It has an elimination half-life of 9 to 10 hours. The drug and metabolite are excreted primarily by the kidneys.

Toxicity: Neurotoxicity, including cortical blindness, confusion, somnolence, coma, and demyelinating lesions, is dose limiting, but the lower doses that are conventionally used rarely produce these side effects. At these doses, mild myelosuppression is the most common toxicity, cumulative lymphopenia being the most clinically important. Nausea, vomiting, and other GI toxicities are rare. Alopecia and rash are also rare.

Indications: FDA approved for the treatment of CLL. Also used for low-grade lymphomas and for AML.

Dosing: The standard regimen is 25 mg/m^2/day for 5 days by short IV infusion. Prolonged infusions have also been used.

5-Fluorouracil (Adrucil, Efudex)—5-FU

Drug Class: Pyrimidine antimetabolite; inhibitor of thymidylate synthase. Partially cell cycle dependent.

Dosage Form: Available in solution in 0.5- to 5-g ampules or vials at a concentration of 50 mg/mL.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Parental bioavailability only. After an intravenous dose, 80% of the drug is metabolized to the inactive dihydro-5-FU by dihydropyrimidine dehydrogenase in the liver. The rest of the drug is activated to fluorodeoxyuridine monophosphate in the target cells. The elimination half-life is about 20 minutes. Excretion is via the kidneys.

Toxicity: GI toxicities, primarily mucositis for bolus injections and diarrhea for prolonged infusions, are dose limiting. Rare patients with dihydropyrimidine dehydrogenase deficiency have excessive GI toxicity. Myelosuppression is generally less with continuous infusion schedules. Nausea and vomiting are uncommon and mild. Dermatitis and other cutaneous toxicities, including hand-foot syndrome, are common. Cerebellar ataxia and myocardial ischemia are rare.

Indications: FDA approved for colon, rectum, gastric, pancreas, and breast carcinomas and used for a wide range of other neoplasms in combination regimens. Used for intrahepatic arterial infusion for liver metastases from GI tumors; also used topically for various cutaneous neoplasms and disorders.

Dosing: IV dosing schemes include weekly bolus, 5 days of bolus every 28 days, 4 to 5 day continuous infusions. Doses range from 300 to 3000 mg/m^2/day depending on the dosing scheme and schedule.

Fluoxymesterone (Halotestin, Oro-Testryl)

Drug Class: Synthetic steroidal androgen. Antagonizes estrogenic effects in estrogen-dependent target cells.

Dosage Form: 2-, 5-, and 10-mg tablets.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: The drug is available by the oral route, is metabolized in the liver, and has an elimination half-life of about 10 hours. Route of excretion is unknown.

Toxicity: Androgenic effects predominate. Hirsutism, amenorrhea, hoarseness, acne, and increased libido occur in women; men may have gynecomastia. Mild edema is common. Liver abnormalities, including transaminitis, fatty change, cholestatic jaundice, and rarely carcinoma, are not uncommon. Polycythemia may occur.

Indications: FDA approved for the treatment of hormone-sensitive breast cancer and for hypogonadism in males.

Dosing: The total daily dose for breast cancer is usually between 10 and 40 mg, divided into two or three doses per day.

Flutamide (Eulexin)

Drug Class: Nonsteroidal antiandrogen.

Dosage Form: 125-mg capsules.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Good oral bioavailability, with peak plasma levels after an oral dose at 1 to 2 hours. The drug is metabolized to active and inactive forms in the liver. The elimination half-life is 8 to 10 hours. Parent drug and metabolites are excreted in the urine.

Toxicity: Generally well tolerated. Gynecomastia, galactorrhea, and impotence are common. Nausea, vomiting, diarrhea, mild myelosuppression, myalgias, and elevated liver function tests are rare.

Indications: FDA approved for prostate carcinoma.

Dosing: The standard dose is 250 mg PO three times daily. Often given in conjunction with an LHRH agonist such as leuprolide to create complete androgen blockade.

Fulvestrant (Faslodex)

Drug Class: Estrogen receptor antagonist.

Dosage Form: 250mg/5 mL and 125 mg/2.5 mL prefilled syringes.

Drug Interactions: None known.

Pharmacokinetics/Metabolism: Binds to the estrogen receptor (ER), leading to degradation and loss of ER from the cell. Peak plasma levels reached in 7 days, half-life is 40 days. Metabolized by the liver microsomal P4503A4 system and excreted primarily in the feces.

Toxicity: Constitutional symptoms, including hot flashes. Peripheral edema. Nausea, vomiting.

Indications: Estrogen receptor positive metastatic breast cancer in postmenopausal women.

Dosing: 250 mg IM monthly.

Gallium Nitrate (Ganite)

Drug Class: Heavy metal that antagonizes iron metabolism in tumor cells preferentially. Causes hypocalcemia by a similar mechanism.

Dosage Form: 500-mg vials (20-mL vials of a 25-mg/mL solution).

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: This drug is not metabolized and has an elimination half-life of about 5 hours. Cleared unchanged in the urine.

Toxicity: Renal toxicity, including glomerular and tubular defects, is dose limiting but partly preventable with adequate hydration during therapy. Hypocalcemia is expected and common and can be dose limiting. Nausea, vomiting, diarrhea, and anorexia are not uncommon. Mild myelosuppression, rashes, hearing loss or tinnitus, visual disturbances, and transient neurologic symptoms are rare.

Indications: FDA approved for the treatment of malignancy-related hypercalcemia. Also used for advanced bladder carcinoma.

Dosing: The standard dose and schedule is 300 mg/m^2/day for 7 days by continuous IV infusion in a volume of 1000 mL of normal saline.

Gemcitibine (Gemzar)

Drug Class: Antimetabolite. Gemcitibine is a nucleoside analog that exhibits cell cycle-dependent and S-phase-specific cytotoxicity, likely due to inhibition of DNA synthesis.

Dosage Form: Supplied as lyophilized powder in vials containing 200 and 1000 mg of drug.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Gemcitibine has poor oral bioavailability. After IV infusion, the drug is rapidly distributed and has a half-life of less than 2 hours. It is metabolized throughout the body to inactive forms. Parent drug and metabolite are excreted principally by the kidneys.

Toxicity: Myelosuppression, including anemia, is mild but dose limiting. Nausea and vomiting are mild but common. Diarrhea and edema are sometimes seen. Elevated transaminases are common, as is fever during drug administration. Hematuria and proteinuria are uncommon. Acute dyspnea and rash are uncommon. Paresthesias and CNS depression are rare.

Indications: FDA approved for advanced pancreatic adenocarcinoma, NSCLC, and metastatic breast cancer; extensively used in bladder cancer also.

Dosing: The usual dose in pancreatic cancer is 1000 mg/m^2 as an IV bolus weekly for up to 7 weeks, followed by a week of rest before another cycle is begun. Similar doses in combination with or without platinating agents are used for the other indications.

Gemtuzumab ozogamicin (Mylotarg)

Drug Class: Novel toxin-conjugated monoclonal antibody directed at myeloid lineage cells.

Dosage Form: Amber single use vials containing 5 mg of drug as a lyophilized powder.

Drug Interactions: No formal studies done, and no important drug interactions yet noted. Other medications that cause myelosuppression would be expected to worsen myelosuppression caused by gemtuzumab.

Pharmacokinetics/Metabolism: Gemtuzumab is given as a 2-hour IV infusion, after which the total calicheamycin (ozogamicin released from the antibody by hydrolysis) has a half-life of 45 hours for the first dose and 60 hours after the second dose. Metabolism of the toxin is hepatic. The elimination routes of the toxin and the antibody are unknown.

Toxicity: This peptide antibody linked to a toxin, given in a group of patients with poor prognosis who are often medically fragile, can have marked acute toxicities. These include somewhat common typical antibody infusion side effects, including fever, chills, hypotension, dyspnea, and wheezing, and other uncommon toxicities including tachycardia, renal insufficiency, hepatic compromise (including hepatic veno-occlusive disease), dizziness, headache, and rash. Leukopenia is expected and can be prolonged, causing a high risk of bacterial, fungal, and sometimes viral infections. Thrombocytopenia and anemia are common also. Nausea and vomiting and diarrhea are common. Serious coagulopathy or hemorrhage are rare.

Indications: FDA approved for relapsed AML.

Dosing: 9 mg/m^2 as a 2-hour IV infusion given once up front and then again in 14 days.

Goserelin Acetate (Zoladex)

Drug Class: LHRH that inhibits pituitary-gonadal axis function. This drug causes steroid hormone withdrawal from dependent tissues, including prostate cancer and breast cancer cells.

Dosage Form: 3.6-mg prefilled syringes.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: After the contents of the syringe are injected SC into adipose tissue, the depot of drug is slowly released over 28 days, peaking at 12 to 15 days. The elimination half-life is 4 hours, and the drug is not appreciably metabolized. Excretion in almost entirely by the urinary route.

Toxicity: Toxicity is mild. Endocrine side effects are most prominent and include hot flashes, diminished libido, impotence, gynecomastia, amenorrhea, and breakthrough vaginal bleeding. Other toxicities include flares of pain early during treat-

ment in sites of disease, local tenderness at injection sites, headache, nausea, depression, and elevated cholesterol levels.
- Indications: FDA approved for advanced prostate cancer; used also in metastatic breast cancer.
- Dosing: 3.6 mg SC usually in the abdomen, every 28 days.

Hydroxyurea (Hydrea)—hydrocarbamide
- Drug Class: Antimetabolite; inhibitor of ribonucleotide reductase, which converts nucleotides to the deoxyribose forms for DNA synthesis. Cell cycle dependent.
- Dosage Form: 500-mg capsules.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: After oral administration, the drug is well absorbed, and drug levels peak in the blood 2 hours after a dose. The elimination half-life is 2 to 5 hours. Metabolism to inactive forms occurs in the liver. Renal excretion is the route of elimination.
- Toxicity: Myelosuppression is common and dose limiting. Other toxicities include rash, headache, fever, and hyperuricemia. Nausea and vomiting are uncommon. Liver toxicity and serious neurologic toxicity are rare.
- Indications: FDA approved for CML; commonly used for other myeloproliferative disorders; also used occasionally for metastatic melanoma, refractory ovarian carcinoma, and squamous cell carcinoma of the cervix and the head and neck.
- Dosing: For CML, the dose is 1000 to 3000 mg/day; in solid tumors, the dose is either 80 mg/kg every third day or 1.25 g/m^2 every 8 hours for five doses once a week.

Ibritumomab tiuxetan—Yttrium-90 (Zevalin)
- Drug Class: Monoclonal antibody directed to the B-cell surface antigen CD20 linked to beta-emitting radionuclide yttrium-90.
- Dosage Form: Kits for preparation of either the In-111 (used for predicting drug distribution) or Y-90 (used for therapy) form of the drug include a vial containing 3.2 mg of the antibody in saline solution along with three other vials for mixing. Y-90 is sent with the Y-90 kit. Rituxan and In-111 must be ordered separately.
- Drug Interactions: None known. Formal studies have not been conducted.
- Pharmacokinetics/Metabolism: Optimal irbitumomab/Y-90 binding and clinical effect require pretreatment with unconjugated ibritumomab. The physical half-life of Y-90 is 64 hours, but the biological half-life of the agent in the body in terms of radioactivity detected is 30 hours. Metabolic and excretory fates of the radionuclide and antibody are not known.
- Toxicity: Ibritumomab/Y-90 should not be administered if the biodistribution of ibritumomab/In-111 is altered significantly. Antibody toxicities can include fever, chills, dyspnea, wheezing, urticaria, and rash. Radionuclide or total agent side effects include lymphopenia, and myelosuppression of other cell lines, which can be prolonged. Infection risk is increased accordingly. Nausea, vomiting, and diarrhea are uncommon, as are arthralgias, myalgias, or neurologic side effects.
- Indications: FDA approved for treatment of relapsed and/or transformed follicular B-cell lymphomas.
- Dosing: The first step of therapy is administration of a 250 mg/m^2 dose of rituximab, followed by a 1.6 mg/5 mCi dose of ibritumomab/In-111 as a 10-minute infusion; 9 days later, if biodistribution of the In-111-labeled product is normal, the same dose of rituximab is followed by a 1.6 mg/0.4 mCi/kg dose of ibritumomab/Y-90 as a 10-minute infusion.

Idarubicin (Idamycin)—4-demethoxydaunorubicin
- Drug Class: Anthracycline intercalating agent. Non-cell cycle dependent.
- Dosage Form: Lyophilized powder in vials of 5 and 10 mg.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Idarubicin has poor oral bioavailability. After an IV dose, the drug is metabolized in the liver to active and inactive forms. The elimination half-life of the parent compound is 13 to 26 hours. Metabolites and some of the unchanged drug are almost exclusively excreted in bile.
- Toxicity: Myelosuppression is common and generally dose limiting for each dose. The cumulative dose-limiting toxicity is cardiomyopathy, but idarubicin is less cardiotoxic than daunorubicin or doxorubicin. Nausea and vomiting are common but usually mild. Diarrhea and stomatitis are sometimes seen. Idarubicin is a weak vesicant or irritant.
- Indications: FDA approved for the treatment of AML.
- Dosing: The standard dose as part of a "7 plus 3" regimen (with cytarabine) is 12 mg/m^2/day for 3 days for induction or reinduction/intensification. Other doses have been used.

Ifosfamide (Ifex)
- Drug Class: Classic alkylating agent. Non-cell cycle dependent.
- Dosage Form: Available in 1- and 3-g vials of powdered drug.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: After an intravenous dose, ifosfamide is activated by hepatic microsomal enzymes. It is then converted to inactive metabolites in the liver. The active form of the drug is the same as that for cyclophosphamide. The elimination half-life of the drug is 7 to 15 hours. The metabolites and some unchanged drug are excreted in the urine.
- Toxicity: Myelosuppression, hemorrhagic cystitis, and CNS toxicity are all fairly common and can be dose limiting. Hemorrhagic cystitis can largely be prevented by coadministration of the uroprotective agent mesna, and nausea and vomiting are minimized with modern antiemetic regimens. The CNS toxicity, including lethargy, stupor, coma, myoclonus, and seizures, is usually mild and completely reversible. It is worse with impaired renal function. Renal dysfunction, usually reversible, is also seen with ifosfamide. Hepatic toxicity, diarrhea, and rash are rare.
- Indications: FDA approved for the treatment of recurrent germ cell tumors. Used for many other tumor types, including adult sarcomas, lymphoma, Hodgkin's disease, breast cancer, and ovarian cancer.
- Dosing: fosfamide is generally given IV over 3 to 5 days with a total dose of 8 to 12 g/m^2/cycle, repeated every 3 to 4 weeks. It can be given as a short infusion each day or as a continuous infusion. Mesna is given IV concurrently, also by short infusion or continuous infusion. Hydration of greater than 3 L/day total, with saline or alkali solutions, is also recommended.

Imatinib mesylate (Gleevec)
- Drug Class: Specific receptor tyrosine kinase inhibitor, which selectively inhibits the tyrosine kinases of bcr-abl, c-kit, and PDGF receptors.
- Dosage Form: 100-mg capsules.
- Drug Interactions: Imatinib plasma levels are enhanced by ketoconazole, and imatinib increases the plasma levels of other drugs that are metabolized by cytochrome P450 3A4. Inducers of this enzyme such as phenytoin would be expected to lower the plasma levels of imatinib.
- Pharmacokinetics/Metabolism: Imatinib has good oral bioavailability, reaches peak serum levels in about 3 hours, and has an elimination half-life of 18 hours. It is metabolized in the liver by cytochrome P450 3A4 among other isoforms, with the demethylated metabolite showing activity similar to that of the parent drug. The parent drug and major metabolite are excreted primarily in the feces.
- Toxicity: Imatinib has no definite dose-limiting toxicity. Myelosuppression is significant in chronic myelogenous leukemia

(CML) but mild in gastrointestinal stromal tumors. Hepatotoxicity is common but usually mild. Liver function tests should be monitored closely during therapy. Fluid retention is common but usually mild, as are nausea, vomiting, and diarrhea. Rash and fever are uncommon.

Indications: FDA approved for treatment of CML in the frontline setting, in accelerated phase, and in blast crisis. It is also approved for the treatment of recurrent inoperable or metastatic gastrointestinal stromal tumors.

Dosing: Total daily doses of 400 mg to 800 mg, once daily, or divided.

Interferon-α (IntronA, Roferon)—α-interferon, IFN-α

Drug Class: Biologic response modifier, antiviral, immunostimulant.

Dosage Form: Available in vials of lyophilized powder or aqueous solution in quantities from 3 million to 50 million IU/vial.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: After parenteral administration, peak levels of IFN-α in the blood occur in 30 minutes to 8 hours depending on the route. The elimination half-life is 2 to 9 hours. IFN-α is catabolized throughout the body through proteolysis but primarily in the renal tubules. Excretion of intact drug is minimal and not significantly affected by organ function.

Toxicity: Constitutional symptoms are predominant side effects and are dose limiting in both the short and long term in lower dose schedules. Acute side effects include fever, chills, nasal congestion, diarrhea, and malaise. Chronic side effects include fatigue, anorexia, weight loss, and depression. Neutropenia and thrombocytopenia, both of which are transient, are dose limiting at higher doses. Anemia may also occur, albeit with more chronic administration. Cardiac toxicity, including congestive heart failure and arrhythmias, is rare and almost always reversible. Serious CNS toxicity, including delirium and psychosis, or peripheral neuropathies are also rare and reversible. Hypocalcemia and hyperglycemia can also occur.

Indications: FDA approved for nonmalignant conditions and malignancies including melanoma, CML, hairy cell leukemia, Kaposi's sarcoma, and cutaneous T-cell lymphoma. Also used in multiple myeloma and low-grade lymphomas.

Dosing: Dose depends on both the diagnosis and the brand or type of IFN-α. The doses for malignant conditions range from 2 million up to 30 million units/m^2 by the SC, IM, or IV route from three times per week to every day. Adjustments are made on the basis of patient tolerance and laboratory parameters.

Interleukin-2 (Proleukin)—aldesleukin, IL-2

Drug Class: IL-2 is a glycoprotein cytokine, previously known as T-cell growth factor, that stimulates antigen-specific and nonspecific T-cell and other lymphocyte subsets and also triggers an inflammatory cytokine cascade. Its antineoplastic effects are dependent on an intact immune system.

Dosage Form: Vials of lyophilized drug containing 18 million IU.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: IL-2 is available by the parenteral route only. It has an elimination half-life of 30 to 60 minutes. It is catabolized by proteolysis throughout the body. Negligible amounts of intact drug are found in urine or bile.

Toxicity: IL-2 has a wide range of moderate to severe toxicities that are both dose and schedule dependent. Toxicities tend to follow immediately after a bolus dose but gradually accumulate during a continuous infusion. Toxicities are higher for a given dose with continuous infusion as compared to bolus dosing. Capillary leak syndrome, which is dose limiting for most IL-2 administration schedules, results in hypotension, edema, pulmonary congestion, renal insufficiency, arrhythmias, diarrhea, and possibly some of the CNS and hepatic toxicity seen with IL-2. Transient myelosuppression or more prolonged anemia occurs commonly, as does transient hyperbilirubinemia, elevation of transaminases, and electrolyte imbalances. Other constitutional symptoms that occur with IL-2 include fever, chills, malaise, arthralgia/myalgias, erythroderma, nasal congestion/rhinorrhea, and nausea/vomiting. Other serious and less common toxicities include lethargy or delirium, angina pectoris, congestive heart failure, frank respiratory failure, and infections, particularly gram-positive bacteremia.

Indications: FDA approved for high-dose bolus treatment of metastatic renal cell cancer and metastatic melanoma. Also used at lower doses for metastatic melanoma and for maintenance treatment of acute myeloid leukemia.

Dosing: The FDA-approved dose for renal cell carcinoma and melanoma is a 600,000 to 720,000 IU/kg IV bolus every 8 hours for a maximum of 14 doses on days 1 to 5 and 11 to 15 every 6 weeks. Lower doses are more commonly used, especially continuous infusions of 3 million to 18 million IU/m^2/day for 96 hours. SC administration at similar daily doses has also been attempted with reasonable patient tolerance.

Irinotecan (Camptosar)—CPT-11

Drug Class: A semisynthetic camptothecin, which functions as a topoisomerase I inhibitor. Partly cell cycle dependent.

Dosage Form: Available in 100-mg vials as a 20-mg/mL aqueous solution.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Irinotecan is available only by the parenteral route. After IV administration, the drug is converted partially from the active lactone form to the inactive carboxylate form through hydrolysis. The parent drug is metabolized in the intestine, liver, and plasma. The active metabolite of irinotecan, SN-38, also exists in the lactone and inactive carboxylate form in equilibrium in plasma. SN-38 is inactivated by glucuronidation in the liver. SN-38 is responsible for the majority of antitumor activity attributed to the parent drug. The elimination half-life of irinotecan is 8 hours, while the elimination half-life of SN-38 is about 12 hours. Excretion of parent drug and metabolites is largely via the bile.

Toxicity: Myelosuppression, primarily neutropenia, is common and dose limiting. Diarrhea is also common and can be dose limiting. Diarrhea can occur as part of a cholinergic syndrome, along with cramping, nausea, and vomiting, during or immediately after drug administration or for several days after drug administration. Anticholinergics and antidiarrheals will curtail the immediate diarrhea and other GI symptoms partially but are less effective in treating the delayed diarrhea. Flushing, rash, and alopecia are common. Significant hepatic, renal, neurologic, or pulmonary toxicities are rare.

Indications: Irinotecan is FDA approved for refractory or recurrent metastatic colon cancer, and it has now been used in other malignancies, including lung cancer, ovarian cancer, and lymphoma.

Dosing: The recommended dosage for recurrent colon cancer is 125 mg/m^2 as a 90-minute IV infusion every week for 4 weeks, with this cycle repeated every 6 weeks. Other doses and schedules have been used.

Isotretinoin (Accutane)—13-cis-retinoic acid, 13-CRA

Drug Class: Isotretinoin is a retinoid derivative of vitamin A that binds to specific nuclear receptors and leads to changes in gene expression. This results in apoptosis or differentiation of many malignant or premalignant cell lines.

Dosage Form: 10-, 20-, and 40-mg capsules.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Oral bioavailability is about 25%, and the drug is highly protein bound in plasma. It is metabolized in the liver and has an elimination half-life of 10 to 20

hours. Parent compound and metabolite are excreted in both the urine and feces.

Toxicity: Isotretinoin is teratogenic and should not be given to women of childbearing age without adequate contraception. Mucocutaneous side effects are common and dose limiting and include xerostomia, stomatitis, conjunctivitis, dry skin, pruritus, cheilitis, rash, patchy alopecia, fragility of nails and skin, photosensitivity, and epistaxis. Other less common side effects include elevations in transaminases and bilirubin or frank hepatitis, hyperlipidemia, nausea, vomiting, anorexia, diarrhea, headache, fatigue, depression, and myalgias/arthralgias. Anemia and pseudotumor cerebri are rare.

Indications: FDA approved for acne vulgaris. Has shown some effectiveness in chemoprevention of aerodigestive malignancies. Ongoing studies are testing its chemopreventive potential in other malignancies.

Dosing: Daily oral doses of 0.5 to 4 mg/kg/day have been used in the chemoprevention trials for durations of 2 to 6 months.

Ketoconazole (Nizoral)

Drug Class: Oral antifungal agent that also acts as an androgen antagonist at high doses.

Dosage Form: 200-mg tablets.

Drug Interactions: Ketoconazole is a potent inhibitor of cytochrome P450 3A4 . As such, it increases the potency of other drugs that are metabolized by that enzyme isoform, including terfenadine, astemizole, cisapride, midazolam, triazolam, and loratadine and possibly cyclosporin, tacrolimus, methylprednisolone, and warfarin. Rifampin and isoniazid decrease the potency of ketoconazole. Ketoconazole has been reported to cause a disulfiram-type reaction when used with alcohol.

Pharmacokinetics/Metabolism: Ketoconazole has good oral bioavailability. Its level peaks in the plasma in about 2 hours. It has a terminal half-life of about 8 hours. It is metabolized in the liver to several inactive metabolites. The metabolites are excreted in the bile.

Toxicity: This drug is not strictly an antineoplastic drug and is generally very well-tolerated. Nausea, vomiting, headache, dizziness, fever, chills, impotence, gynecomastia, leukopenia, hemolytic anemia, urticaria, and anaphylaxis are all rare. Hepatic toxicity is also rare. It has been fatal in unusual cases. Administration with terfenadine and astemizole has resulted in prolonged QT interval, arrhythmias, and deaths in rare cases. Other potential drug interactions are possible, as listed previously.

Indications: FDA approved for fungal infections, primarily yeast infections. Used in doses of up to 1200 mg/day for androgen-dependent or -independent prostate cancer.

Dosing: As per preceding instructions, used alone or in combination with chemotherapy, including doxorubicin.

Lenalidomide (Revlimid)

Drug Class: Antiangiogenesis agent, immunomodulator.

Dosage Form: 5-mg, 10-mg capsules.

Drug Interactions: None known.

Pharmacokinetics/Metabolism: Mechanism of action not fully characterized. An immunomodulatory agent that inhibits angiogenesis in some cells. Inhibits bone marrow secretion of IL-6, VEGF, and TNF-α.

Toxicity: Myelosuppression. Diarrhea, rash, fatigue. Increased risk of DVT and PE.

Indications: Transfusion dependent anemia due to low or intermediate risk myelodysplasia with 5q deletion. Multiple myeloma.

Dosing: For MDS: 10 mg daily. For myeloma: 25 mg daily for 21 of 28 days.

Letrozole (Femara)

Drug Class: Nonsteroidal aromatase inhibitor.

Dosage Form: 2.5-mg tablets.

Drug Interactions: Studies have revealed no interactions between letrozole and warfarin or cimetidine. No other formal drug interaction studies have been done.

Pharmacokinetics/Metabolism: Letrozole has nearly 100% bioavailability, is metabolized in the liver, is glucuronidated, and is excreted by the kidneys. It has a terminal half-life of about 2 days. With daily administration, steady-state plasma levels are reached in 2 to 6 weeks.

Toxicity: This drug is generally well tolerated. Muscle aches and nausea are uncommon; hot flashes and fatigue are uncommon; weight change, urticaria, and dyspepsia are rare.

Indications: FDA approved for treatment of metastatic estrogen-responsive breast cancer in postmenopausal patients.

Dosing: 2.5 mg orally once daily.

Leucovorin Calcium (Wellcovorin)—citrovorum factor, folinic acid, FA, LV

Drug Class: Tetrahydrofolate derivative and enzyme cofactor for thymidylate synthase and other purine and pyrimidine synthesis steps. Leucovorin bypasses the dihydrofolate reductase step, which is inhibited by methotrexate and therefore can be used to "rescue" normal cells from the toxicity of methotrexate after high doses are administered. In addition, leucovorin potentiates the toxicity of fluoropyrimidines such as fluorouracil by strengthening the association of the drug with its target enzyme, thymidylate synthase.

Dosage Form: Tablets in 5- to 25-mg sizes, powder for oral solution, and as vials of powdered drug in 3- to 350-mg sizes.

Drug Interactions: Reduces the effectiveness and toxicity of dihydrofolate reductase inhibitors such as methotrexate.

Pharmacokinetics/Metabolism: Leucovorin has excellent bioavailability by the oral or parenteral route. It is oxidized in cofactor reactions throughout the body, and is also partly metabolized. It has an elimination half-life of 2 to 4 hours. Excreted in the urine.

Toxicity: Leucovorin is generally very well tolerated. It occasionally causes stomach upset or nausea, rash, diarrhea, and headache. Allergic reactions have been reported.

Indications: Used for rescue of high-dose methotrexate therapy for a variety of neoplasms and as a potentiator of fluoropyrimidine therapy in gastrointestinal malignancies, particularly colorectal cancer.

Dosing: For rescue from methotrexate, the usual dose is 10 to 25 mg/m^2 orally or IV every 6 hours starting up to 24 hours after the methotrexate, until methotrexate levels are less than 1×10^{-8} molar. When used to potentiate 5-FU, doses ranging from 20 to 500 mg/m^2, usually given IV, have been used, depending on the 5-FU dose.

Leuprolide Acetate (Leupron)—leuprorelin acetate

Drug Class: Gonadotropin-releasing hormone agonist, which serves to paradoxically shut down the pituitary release of gonadotropins with chronic exposure. This results in a dramatic decrease in gonadal estrogens and androgens and growth inhibition of hormone-dependent neoplasms.

Dosage Form: Available in vials for monthly administration (depot) containing 3.75 and 7.5 mg of powder, along with diluent and syringe. A multidose vial containing 2.8 mL of a 5-mg/mL solution along with syringes is also available for daily administration.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Leuprolide is bioavailable only by the parenteral route. After a SC injection, about 90% of the drug is eventually absorbed. The depot form of the drug is absorbed slowly over days, while the injectable solution is absorbed over several hours. The elimination half-life of the drug once in the serum is 3 hours. Metabolism and excretion are not well delineated but are clinically unimportant.

Toxicity: Usually well tolerated, but side effects can affect many systems, including endocrine (hot flashes, impotence, gynecomastia, breast tenderness, diminished libido, amenorrhea, atrophic vaginitis, increased cholesterol); GI (nausea, constipation, anorexia, diarrhea); hepatic (elevation of transaminases); dermatologic (rash, changes in body hair composition, pruritus); and neuropsychiatric (insomnia, depression, emotional lability, lethargy, memory loss). Significant cardiac toxicity is rare.

Indications: FDA approved for the treatment of hormone-dependent advanced prostate cancer. Also used for breast cancer and endometriosis.

Dosing: The usual dose for prostate cancer is 7.5 mg of the depot form by SC injection once every month or 1 mg of the injectable solution SC daily.

Lomustine (CeeNU)—CCNU

Drug Class: Nitrosourea alkylating agent. Cell cycle independent.

Dosage Form: Available as 10-, 20-, and 100-mg capsules.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Well absorbed after oral administration. Widely distributed in the body, including the cerebrospinal fluid. Metabolized extensively in the liver to active metabolites. Elimination half-life is 72 hours. Metabolites are excreted in the urine.

Toxicity: Myelosuppression is dose limiting and tends to be cumulative. Nausea and vomiting are common but usually mild to moderate. Anorexia is also common but short lived. Pulmonary fibrosis can occur with long-term administration. Other toxicities, including CNS effects, hepatic or renal dysfunction, and secondary leukemia, are rare.

Indications: FDA approved for primary brain tumors and Hodgkin's disease. Also used in melanoma, multiple myeloma, other lymphomas, and breast cancer.

Dosing: The recommended dose for brain tumors is 100 to 130 mg/m^2 orally every 6 weeks. Other doses and schedules have been used.

Mechlorethamine (Mustargen)—nitrogen mustard, HN2

Drug Class: Classic alkylating agent. Cell cycle independent.

Dosage Form: Vials of lyophilized powder containing 10 mg of drug.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Mechlorethamine is not orally bioavailable. After an IV dose, the drug is rapidly deactivated in the blood by reaction with biomolecules. It has an elimination half-life of 15 minutes and has no significant organ metabolism. Virtually no excretion of the drug is detected in urine or stool.

Toxicity: This drug is a powerful vesicant, so optimal extravasation precautions are a must, as well as rapid infusion. Tissue necrosis will occur if the drug extravasates, although sodium thiosulfate is a somewhat effective antidote. Vein discoloration and scarring are common. Nausea and vomiting are common, potentially severe, and often dose limiting. Myelosuppression is expected and also often dose limiting. Alopecia and infertility are often seen. Less common toxicities include anorexia, diarrhea, jaundice, tinnitus, and skin rash (common with topical treatment). Secondary leukemia and permanent hearing loss are rare.

Indications: FDA approved for a variety of hematologic malignancies and solid tumors but generally used less in the last decade. Still used for Hodgkin's disease and topically for cutaneous T-cell lymphoma.

Dosing: The standard dose for Hodgkin's disease as part of the MOPP regimen is 6 mg/m^2 IV over 1 to 5 minutes on day 1 and day 8 of a 28-day cycle. The topical form is usually a 10-mg/60-mL solution or 10-mg/dL ointment.

Medroxyprogesterone acetate (Provera, Depo-Provera)

Drug Class: Steroidal progestational agent.

Dosage Form: Available as tablets in sizes of 2.5, 5, and 10 mg, and as a suspension for depot injection as 100 or 400 mg/m.

Drug Interactions: The metabolism of medroxyprogesterone acetate may be enhanced by aminoglutethamide, leading to decreased effect for a given dose.

Pharmacokinetics/Metabolism: This drug has good oral bioavailability. It is metabolized in the liver to inactive metabolites and has an elimination half-life of up to 60 hours. Parent drug and metabolites are excreted in the urine and bile.

Toxicity: Toxicities are mostly constitutional and not dose limiting. They include menstrual changes, amenorrhea, gynecomastia, hot flashes, edema, weight gain, fatigue, acne, hirsutism, anxiety, depression, sleep disturbance, and headache. Nausea, significant skin reactions or allergy, jaundice, and thrombophlebitis are uncommon.

Indications: FDA approved for treatment of advanced endometrial or renal cell carcinoma. Also used occasionally for breast or prostate cancer.

Dosing: Loading doses of up to 1000 mg IM weekly and 400 mg IM every month have been used, while oral doses range from 100 to 300 mg/day. Much lower doses are used for gynecologic indications.

Megestrol Acetate (Megace)—megestrol

Drug Class: Steroidal progestational agent.

Dosage Form: 20- and 40-mg tablets and 40-mg/mL oral solution.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: The drug is well absorbed by mouth, is metabolized in the liver to inactive compounds, and has an elimination half-life of 15 to 20 hours. Parent drug and metabolites are excreted in the urine.

Toxicity: Toxicities are similar to those of other progestins as noted previously. They include menstrual changes, hot flashes, edema, weight gain, fatigue, acne, hirsutism, anxiety, depression, sleep disturbance, and headache. Urinary frequency can also occur. Nausea, vomiting, diarrhea, skin rash or allergy, jaundice, and thrombophlebitis are uncommon.

Indications: FDA approved for treatment of breast and endometrial carcinoma. Also used for renal cell carcinoma and for appetite stimulation in HIV disease and cancer patients.

Dosing: The standard dose for cancer treatment is 160 mg/day in divided doses or a single dose. The dose for appetite stimulation may be as high as 800 mg/day, which is where the concentrated oral solution is useful.

Melphalan (Alkeran)—l-PAM, l-phenylalanine mustard, l-sarcolysin

Drug Class: Classical alkylating agent. Cell cycle independent.

Dosage Form: 2-mg tablets and vials for injection at 50 mg/vial.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Melphalan has unpredictable GI absorption, is highly protein bound, and is rapidly autometabolized by hydrolysis in the plasma. It has an elimination half-life of about 2 hours. Ten percent to 15% is excreted as unchanged drug in the urine.

Toxicity: Myelosuppression is expected and is dose limiting. Recovery may be prolonged, and effects can be cumulative. Large doses may cause significant nausea and vomiting. Diarrhea and stomatitis are uncommon. Vein reactions including scarring may occur, but this agent is not known as a vesicant. Other skin reactions are uncommon, as are pulmonary fibrosis, vasculitis, infertility, alopecia, and secondary leukemia.

Indications: Used primarily for multiple myeloma, but also FDA approved for ovarian carcinoma. May also be useful in high-dose chemotherapy/transplant settings and in regional perfusion of extremities for melanoma and sarcoma.

Dosing: Doses for myeloma are typically in the range of 0.1 mg/kg/day for 2 to 3 weeks or up to 6 mg/m^2/day for 5 days every

6 weeks. Transplant doses (IV or PO) range up to 140 mg/m^2 total. Doses for perfusion are either 0.45 to 0.9 mg/kg or dosed for a certain concentration in the perfusate.

Mercaptopurine (Purinethol)—6-MP, 6-mercaptopurine
- Drug Class: Purine analog antimetabolite; predominantly S-phase specific.
- Dosage Form: 50-mg tablets. An IV formulation is investigational.
- Drug Interactions: Allopurinol inhibits first-pass metabolism of mercaptopurine in the liver by xanthine oxidase, and therefore dose reduction is required if allopurinol is also being given.
- Pharmacokinetics/Metabolism: 6-MP has good oral bioavailability, undergoes extensive first-pass metabolism in the liver, and has an elimination half-life of about 7 hours. Intact drug and metabolites are excreted by the kidneys.
- Toxicity: Myelosuppression is common and dose limiting. Nausea and vomiting occur occasionally but are usually mild. Diarrhea, anorexia, and stomatitis are less common. Headache and rash are uncommon. Fulminant hepatic toxicity is very rare, but lesser degrees of cholestasis and hepatitis are sometimes seen.
- Indications: Mercaptopurine is FDA approved for treatment of acute lymphoblastic leukemia. It is occasionally used for other hematologic malignancies. There is an investigational IV formulation that does not yet have clinical indications.
- Dosing: The usual dose is 70 to 100 mg/m^2/day for a defined period of days during induction or maintenance.

Mesna (Mesnex)—mercaptoethanesulfonate sodium, uromitexan
- Drug Class: Thiol uroprotectant; binds to and inactivates acrolein, the highly reactive metabolite of cyclophosphamide and ifosfamide, helping to prevent hemorrhagic cystitis.
- Dosage Form: Available as aqueous solution at a concentration of 100 mg/mL.
- Drug Interactions: Mesna does not decrease the effectiveness of cytotoxic drugs or radiation.
- Pharmacokinetics/Metabolism: Mesna has an oral bioavailability of about 50% and is usually given IV. After an IV dose, mesna is converted in the plasma to dimesna, is filtered by the kidneys, and is converted back into mesna in the urine. It has an elimination half-life of 1 hour.
- Toxicity: Mesna is usually very well tolerated. It has been described to occasionally cause nausea, vomiting, diarrhea, rash, fatigue, headache, hypotension, or arthralgias.
- Indications: FDA approved for use as a uroprotectant when administering ifosfamide. Also effective for high-dose cyclophosphamide.
- Dosing: The usual daily dose of mesna is 60% of the daily milligram amount of the ifosfamide, given by IV bolus before, 4 hours after, and 8 hours after the chemotherapy or as a continuous infusion with a loading dose before the chemotherapy. Mesna may be continued for up to 24 hours after the chemotherapy has been completed.

Methotrexate (Mexate, Folex, others)—MTX, amethopterin
- Drug Class: Antifolate antimetabolite; interferes with nucleotide synthesis by inhibiting dihydrofolate reductase. Cell cycle dependent.
- Dosage Form: 2.5-mg tablets, vials of powder for injection of 20 to 1000 mg/vial, and as a 2.5- and 25-mg/mL aqueous solution for injection.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Methotrexate has good oral bioavailability at low doses. After oral or IV dosing, it is distriuted throughout the body water compartment. It will accumulate in "third-space" fluid compartments and exhibit prolonged toxicity and therefore should be used with caution, if at all, in patients with significant pleural or peritoneal fluid. The drug is minimally metabolized in the liver and has an elimination half-life of about 3 hours, and even low concentrations of drug after most of the drug is eliminated can contribute to significant toxicity. Therefore, dosing based on renal function is critical. Excretion of this drug is entirely renal.
- Toxicity: Myelosuppression is expected and is usually dose limiting. Stomatitis and diarrhea are common. Nausea and vomiting are uncommon. Renal toxicity is uncommon and usually reversible but can be severe. Many types of skin reactions can occur but are uncommon. Pulmonary fibrosis and hepatic fibrosis are rare. Encephalopathy is rare with moderate to low-dose therapy but is more common with high doses, intrathecal administration, or concomitant CNS radiation. It can be severe and permanent.
- Indications: FDA approved for a wide spectrum of malignant and nonmalignant diseases. Most often used for acute leukemias, lymphomas, breast cancer, bladder cancer, squamous cell cancers, and sarcomas.
- Dosing: For malignant conditions, doses up to 100 mg/m^2 are considered low dose, 100 to 1000 mg/m^2 moderate dose, and over 1000 mg/m^2 high dose. Moderate and high doses require leucovorin rescue. Doses can be given weekly or at longer intervals. IV infusions can be 30 minutes or longer, including 24-hour continuous infusions. Methotrexate is also commonly given intrathecally, usually as a 12-mg dose in 10 mL of preservative-free saline.

Mitomycin C (Mutamycin)
- Drug Class: Antitumor antibiotic; inhibits DNA and RNA synthesis.
- Dosage Form: Vials of powder in 5-, 20-, and 40-mg sizes.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Poor oral bioavailability. After an IV dose, mitomycin C is rapidly metabolized to inactive forms in the liver, spleen, and kidneys, with an elimination half-life of about 1 hour. Parent drug and inactive metabolites are excreted in the urine.
- Toxicity: Mitomycin C is a vesicant; extravasation precautions are a must. Myelosuppression is expected and is dose limiting, with a white blood cell nadir at 4 weeks and full recovery at 6 to 7 weeks. Mild nausea, vomiting, anorexia, and fatigue are common. Uncommon toxicities include diarrhea, stomatitis, rash, fever, and renal insufficiency. Rare toxicities include veno-occlusive disease of the liver, hemolytic-uremic syndrome, and interstitial pneumonitis.
- Indications: FDA approved for adenocarcinomas of the stomach and pancreas. Also used commonly in breast cancer and lung cancer.
- Dosing: The usual dose is 10 to 20 mg/m^2 IV over 2 to 5 minutes every 6 to 8 weeks.

Mitotane (Lysodren)—o,p′-DDD
- Drug Class: Adrenal cortical cytotoxin.
- Dosage Form: 500-mg tablets.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: This drug has moderate oral bioavailability, with a peak plasma level about 4 hours after an oral dose. Significant therapeutic effect is not seen until up to 4 weeks of continuous usage. Mitotane is metabolized in the liver and has a variable elimination half-life (due to storage of the drug in adipose tissue) of up to 160 hours. Mitotane is eliminated in the urine and bile.
- Toxicity: Adrenal insufficiency is expected and must be abrogated with concomitant oral glucocorticoid usage (and sometimes mineralocorticoids as well). Anorexia, nausea, vomiting, sedation, and lethargy are common. Hypercholesterolemia and elevation of liver function tests are also common. Rash is seen frequently but is usually mild. Myelosuppression, diarrhea, fever, wheezing, changes in blood pressure, and flushing are

uncommon. Permanent CNS changes, retinopathy, nephrotoxicity, and hemorrhagic cystitis are rare.
Indications: FDA approved for adrenal cortical carcinoma.
Dosing: The initial dose is usually 1 g/day in four divided doses; this is increased up to 10 g/day as tolerated.

Mitoxantrone (Novantrone)—DHAD, dihydroxyanthracenedione
Drug Class: Anthracycline antitumor antibiotic.
Dosage Form: Vials of 2-mg/mL solution.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Mitoxantrone has poor oral bioavailability. After an IV dose, it exhibits a large volume of distribution, undergoes metabolism in the liver, and has an elimination half-life of 24 to 37 hours. Mitoxantrone is eliminated through the bile.
Toxicity: Mitoxantrone is not a tissue vesicant. Myelosuppression, mostly limited to leukopenia, is expected and dose limiting. Nausea and vomiting are common but mild, stomatitis is common, and diarrhea and anorexia are less common. Elevated liver function tests are common, but significant hepatic toxicity is rare. Cardiotoxicity is uncommon and dose dependent. Pulmonary or neurologic toxicity is rare.
Indications: FDA approved for AML and prostate carcinoma. Also used for breast cancer, lymphoma, and hepatocellular carcinoma.
Dosing: For AML, the typical dose is 10 to 12 mg/m^2/day for 3 days by 30-minute infusion, along with AraC. For solid tumors, 12 mg/m^2 is given over 30 minutes every 3 to 4 weeks.

Nelarabine (Arranon)
Drug Class: Antimetabolite.
Dosage Form: IV.
Drug Interactions: None known.
Pharmacokinetics/Metabolism: A prodrug of deoxyguanosine analog 9-β-D-arabinofuranosylguanine (ara-G). After demethylation by adenosine deaminase to ara-G, it is converted to its active triphosphate form ara-GTP. Incorporation of ara-GTP into DNA inhibits DNA synthesis and function.
Toxicity: CNS toxicity is dose limiting, with somnolence, headache, dizziness, peripheral neuropathy, seizures, and coma, which may be severe and permanent. Myelosuppression. GI toxicities. Respiratory toxicity. Fatigue, fever, asthenia, blurred, vision, and edema.
Indications: Refractory or resistant T-cell acute lymphoblastic leukemia/lymphoma as third-line therapy.
Dosing: 1500 mg/m^2 IV over 2 hours days 1, 3, and 5 every 21 days.

Nilutamide (Nilandron)
Drug Class: Orally administered nonsteroidal antiandrogen.
Dosage Form: 50-mg and 150-mg tablets.
Drug Interactions: Inhibits activity of several cytochrome P450 isoenzymes and thus may increase the potency of several potentially toxic drugs such as warfarin, theophylline, and phenytoin. Caution and careful monitoring are advised during concomitant use of nilutamide with such medications.
Pharmacokinetics/Metabolism: Rapid and complete GI absorption has been demonstrated. Elimination half-life is about 45 hours. The drug is metabolized in the liver and eliminated in the urine.
Toxicity: Hot flashes, body hair loss, fatigue, loss of libido, and weight gain are common but usually mild. Loss of visual adaptation to the darkness is common but transient, and nausea and fever and dyspepsia are uncommon. Interstitial pneumonitis is rare.
Indications: FDA approved for treatment of metastatic prostate cancer.
Dosing: The usual dose is 300 mg once daily for 30 days followed by 150 mg daily.

Octreotide, Octreotide long-acting (Sandostatin, Sandostatin LA)—L-cysteinamide
Drug Class: Synthetic peptide analog of somatostatin; inhibits other GI peptide actions, such as serotonin, insulin, glucagon, and gastrin.
Dosage Form: Ampules containing 0.05, 0.1, and 0.5 mg in 1 mL of aqueous solution.
Drug Interactions: May interfere with insulin action, requiring increase in insulin dosage.
Pharmacokinetics/Metabolism: Not orally bioavailable but rapidly absorbed after SC administration. Metabolized by hydrolysis throughout the body. No active metabolites. Half-life of elimination is about 1.5 hours. Intact drug is cleared via the kidneys.
Toxicity: GI side effects are dose limiting and include abdominal pain, vomiting, loose stool, occasional fat malabsorption, bloating, and cholelithiasis. Elevations of liver function tests can also occur, but frank hepatitis is rare. Skin reactions, such as pain at the injection site or flushing, rash, or skin thinning, are sometimes seen. Constitutional symptoms, including rhinorrhea, xerostomia, sweating, throat discomfort, and vertigo, can be bothersome. Either hyperglycemia or hypoglycemia can occur. Cardiac side effects, including angina, congestive heart failure, and hypotension or hypertension, are uncommon. Anxiety, depression, fatigue, and anorexia are uncommon, and seizures are rare.
Indications: FDA approved for carcinoid tumors causing carcinoid syndrome and for vasoactive peptide-secreting tumors. Also used for refractory diarrhea, either cancer related or treatment related, in cancer patients.
Dosing: Doses from 50 μg twice a day to 1000 μg four times a day injected SC have been used. Continuous IV infusions or administration of drug in total parenteral nutrition solutions has also been used.

Oprelvekin (Neumega)—interleukin-11, IL-11
Drug Class: Recombinant polypeptide cytokine molecule; multiple cellular actions, including stimulation of megakaryocyte proliferation and platelet production from megakaryocytes.
Dosage Form: Vials containing 5 mg of lyophilized powder.
Drug Interactions: None noted.
Pharmacokinetics/Metabolism: Oprelvekin is available only by parenteral routes. With SC administration, it is absorbed into the circulation with a peak plasma concentration of 3 hours and has an elimination half-life of about 7 hours. This polypeptide agent is metabolized throughout the body by proteolysis. Excretion of drug is not substantial, owing to degradation.
Toxicity: Headache, fever, malaise, dyspnea, rash, conjunctival irritation, fluid retention, and edema are common during administration but are not usually severe. Oral thrush, dizziness, diarrhea, pleural effusions, and transient anemia are uncommon. Paresthesias, ocular hemorrhage, atrial arrhythmias, and exfoliative dermatitis are rare.
Indications: FDA approved for prevention of severe chemotherapy-related thrombocytopenia.
Dosing: 50 μg/kg/day SC injection until the postnadir platelet count is greater than 50,000/mm^3, starting 1 day after the completion of chemotherapy.

Oxaliplatin (Eloxatin)
Drug Class: New generation platinating agent. Disrupts DNA via intrastrand and interstrand cross-links with two strong platinum association bonds in the molecule, which induces apoptosis beyond a certain level of DNA damage in malignant cells.
Dosage Form: Clear glass single-use vials containing 50 mg or 100 mg of drug as a lyophilized powder.
Drug Interactions: No drug-drug interaction studies have been done, and no interactions have yet been identified. Expected

additive toxicities with other antineoplastic agents and neurotoxic drugs. Nephrotoxic drugs may slow clearance of oxaliplatin.

Pharmacokinetics/Metabolism: Oxaliplatin has poor oral bioavailibility. After IV administration, rapid distribution into tissues occurs, as well as rapid spontaneous conversion via hydrolysis into active drug and metabolites. The terminal half-life is long (>300 hours) but represents minimal plasma levels of the hydrolyzed drug. Elimination of platinum metabolites is via the kidneys.

Toxicity: Neurotoxicity, in the form of a transient neuropathy with each dose and a persistent, cumulative typical sensory polyneuropathy, is very common and dose limiting. Myelosuppression is expected but mild and only sometimes dose limiting. Fatigue and nausea are common but mild. Diarrhea, stomatitis, edema, cough, hypersensitivity reactions, and extravasation injury are rare.

Indications: FDA approved for metastatic colorectal cancer in combination with 5-fluorouracil/leucovorin. Has been used as a single agent in this disease and is being studied in other malignancies.

Dosing: With 5-fluorouracil and leucovorin, the dose and schedule is 85 mg/m^2 IV every 2 weeks as a 2-hour infusion in 250 to 500 mL of D5W. As a single agent, the most studied doses are the same 2-week dose or 130 mg/m^2 IV every 3 weeks.

Paclitaxel (Taxol, Onxol)

Drug Class: Naturally occurring taxane molecule; inhibits depolymerization of tubulin in the spindle apparatus, thereby inducing apoptosis in dividing cells.

Dosage Form: Vials containing 30 and 100 mg of drug in nonaqueous solution.

Drug Interactions: Cisplatin administered before paclitaxel may enhance the myelosuppressive effect of paclitaxel. Coadministration of paclitaxel and doxorubicin may enhance the cardiotoxicity of doxorubicin.

Pharmacokinetics/Metabolism: Paclitaxel has poor oral bioavailability. After IV administration, the drug exhibits a large volume of distribution and undergoes metabolism in the liver. The elimination half-life is 15 to 50 hours. Excretion of drug and metabolites is predominantly via the bile.

Toxicity: Paclitaxel is an irritant or mild vesicant when extravasated into subcutaneous tissue. Myelosuppression, predominantly neutropenia, is expected and is dose limiting. Shorter infusions of the same dose produce less neutropenia. Mucositis is also very common, particularly with longer infusions. Peripheral neuropathy is common, usually mild, and increases with cumulative dose. Acute neuromyopathy is also common and occurs for several days after each dose. This syndrome may require opiate analgesics to control pain. Cardiovascular side effects, including hypertension, hypotension, premature contractions, and bradyarrhythmias, are common but rarely require intervention. Hypersensitivity reactions to paclitaxel, including urticaria, wheezing, chest pain, dyspnea, and hypotension, are common but are reduced in frequency and severity by premedication with corticosteroids and histamine$_1$ and histamine$_2$ antihistamines (the recommended regimen is dexamethasone 20 mg PO 12 and 6 hours prior to paclitaxel and diphenhydramine 50 mg and cimetidine 300 mg IV 30 minutes prior to paclitaxel). Alopecia, usually complete, is expected. Other toxicities are uncommon and include nausea, vomiting, diarrhea, liver toxicity, and interstitial pneumonitis.

Indications: FDA approved for salvage therapy in ovarian cancer and for breast cancer in both the metastatic and adjuvant settings. Used also in lung cancer, head and neck cancer, and bladder cancer.

Dosing: 135 to 250 mg/m^2 IV over 3 hours or 24 hours every 3 weeks. Weekly schedules and longer infusions have also been used.

Paclitaxel, Protein bound (Abraxane)

Drug Class: Taxane; an albumin-bound form of paclitaxel with a mean particle size of approximately 130 nanometers.

Dosage Form: 100-mg vial.

Drug Interactions: Potential interactions with substrates or inhibitors of CYP2C8 and CYP3A4.

Pharmacokinetics/Metabolism: Not studied in patients with hepatic or renal dysfunction.

Toxicity: Neutropenia, thrombocytopenia, anemia, hypersensitivity reactions, hypotension, cardiovascular events, dyspnea, cough, sensory neuropathy, arthralgias/myalgias, nausea/vomiting, asthenia.

Indications: Treatment of metastatic breast cancer after failure of combination chemotherapy or relapse with 6 months of adjuvant chemotherapy.

Dosing: 260 mg/m^2 IV over 30 minutes every 3 weeks.

Pamidronate (Aredia)—APD, aminohydroxypropylidene diphosphonate

Drug Class: Organic bisphosphonate; inhibitor of bone resorption by osteoclasts.

Dosage Form: Vials of lyophilized powder containing 30 mg of drug.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Pamidronate is available only by the parenteral route. After IV administration, the drug concentrates in the bone, spleen, and liver. Its metabolism is not well characterized. It has a terminal half-life of about 27 hours. Fifty percent of the parent drug is eliminated in the urine.

Toxicity: Pamidronate is usually quite well tolerated. Hypotension, syncope, tachycardia, and even atrial fibrillation have been reported uncommonly during the infusion. Hypocalcemia, hypophosphatemia, hypokalemia, and hypomagnesemia occur commonly but only rarely require intervention. Nausea, vomiting, and somnolence are rare.

Indications: FDA approved for malignancy-induced hypercalcemia. May lead to pain relief and even tumor shrinkage of bone metastases in multiple myeloma, breast cancer, and prostate cancer.

Dosing: 60 to 90 mg/m^2 IV over 24 hours, although the clinical experience with infusions of 1 to 3 hours is extensive. Treatment may be repeated every 1 to 3 weeks. Peak effect occurs 3 to 7 days after a dose.

Panitumumab (Vectibix)

Drug Class: Monoclonal antibody.

Dosage Form: IV.

Drug Interactions: None known.

Pharmacokinetics/Metabolism: A recombinant, fully humanized IgG2 kappa monoclonal antibody that binds to the epidermal growth factor receptor. Binds specifically to EGFR, competitively inhibiting ligand binding to the receptor. Steady-state levels are reached by the third infusion. Elimination half-life is about 7.5 days.

Toxicity: Rash, which may be severe. Diarrhea. Infusion reactions. Hypomagnesemia. Pulmonary fibrosis.

Indications: Previously treated EGFR expressing metastatic colorectal cancer.

Dosing: 6 mg/m^2 IV every 2 weeks.

Pegfilgrastim (Neulasta)

Drug Class: Long-acting (PEGylated) recombinant DNA granulocytic growth factor polypeptide.

Dosage Form: Syringes containing 6 mg of drug in 0.6 mL aqueous solution with a 27-gauge needle.

Drug Interactions: No formal drug interaction studies have been done.

Pharmacokinetics/Metabolism: PEGylation of filgrastim increases its half-life by decreasing renal clearance. After subcutaneous administration, half-life is between 15 and 80 hours, with biologic activity lasting much longer.

Toxicity: Toxicity and side effect profile is essentially no different than those of filgrastim. Bone pain is common and usually mild and treatable but can be dose limiting. Nausea, fatigue, weakness, and diarrhea are rare. Very rare instances of adult respiratory distress syndrome, sickle cell crisis, splenic rupture, and severe allergic reaction have been seen with the parent drug filgrastim.

Indications: FDA approved for prevention of severe granulocytopenia from cytotoxic chemotherapy for nonmyeloid malignancies.

Dosing: 6 mg SC after each chemotherapy cycle (generally used for a 3- or 4-week cycle duration).

Pemetrexed (Alimta)

Drug Class: Antimetabolite.

Dosage Form: 500-mg vials.

Drug Interactions: Salicylates and NSAIDS may decrease the renal excretion, increasing toxicity. Nephrotoxic drugs may also lead to decreased renal clearance. Thymidine rescues the toxic effects of pemetrexed.

Pharmacokinetics/Metabolism: Inhibits folate-dependent enzymes thymidylate synthetase, dihyrofolate reductase and glycinamide ribonucleotide formyltransferase which are involved in the de novo synthesis of thymidine and purine nucleotides, leading to inhibition of DNA and RNA synthesis and function. Metabolized intracellularly to its highly active polyglutamated form. Excreted in urine with 90% of drug unchanged.

Toxicity: Myelosuppression. Nausea, vomiting, diarrhea. Rash. Dyspnea and fatigue.

Indications: Mesothelioma and non-small-cell lung cancer.

Dosing: 500 mg/m^2 IV every 3 weeks. Note: All patients must be given folic acid and vitamin B12 supplementation to decrease toxicity, starting 1 week prior to therapy.

Pentostatin (Nipent)

Drug Class: Antimetabolite, purine antagonist.

Dosage Form: 10-mg vial.

Drug Interactions: Toxicity is increased with vidarabine, and fatal pulmonary toxicity has resulted from the concomitant use of fludarabine.

Pharmacokinetics/Metabolism: Enzyme adenosine deaminase, found in high concentration in lymphocytes, leading to accumulation of deoxyadenosine and deoxyadenosine triphosphate (dATP), which are cytotoxic to lymphocytes. Elevated dATP levels inhibit ribonucleotide reductase, which inhibits DNA synthesis and function. Undergoes little metabolism, and more than 90% of the drug is excreted in the urine with an elimination half-life of about 5 hours.

Toxicity: Myelosuppression. Increased risk of opportunistic infections. Hypersensitivity reactions. CNS toxicity. Ophthalmologic and otologic complications.

Indications: Hairy cell leukemia, chronic lymphocytic leukemia, cutaneous T-cell leukemia.

Dosing: 4 mg/m^2 IV every 2 weeks.

Plicamycin (Mithracin)—mithramycin

Drug Class: Antitumor antibiotic. Partly cell cycle dependent.

Dosage Form: Supplied as lyophilized powder in vials containing 2.5 mg of drug.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Available only by the intravenous route. After an IV dose, the drug is metabolized by the liver and has an elimination half-life of about 2 hours. Parent drug and metabolites are eliminated via the kidneys.

Toxicity: Plicamycin is a vesicant if extravasated into soft tissues. Hemorrhage, due to both thrombocytopenia and coagulopathy, is dose limiting. Other hematologic toxicities are uncommon. Nausea and vomiting are common but not severe. Stomatitis, diarrhea, and anorexia are less common. Rash is common, but severe cutaneous reactions, such as toxic epidermal necrolysis, are rare. Depletion of calcium, potassium, phosphate, and magnesium are expected but rarely require intervention. Renal toxicities, including proteinuria and azotemia, are uncommon. Elevated liver function tests and neurologic toxicity (including lethargy, weakness, anxiety, somnolence, and headache) are uncommon.

Indications: FDA approved for treatment of malignancy-induced hypercalcemia, and also for treatment of germ cell tumors. Also has been used for CML in blast crisis.

Dosing: The typical dose for germ cell tumors is 25 to 30 μg/kg/day IV infusion over 60 minutes for 8 to 10 days. For hypercalcemia, the same dose is given one to three times per week.

Prednisone (Deltasone, others)

Drug Class: Corticosteroid.

Dosage Form: Tablets in sizes from 1 to 50 mg and oral solution.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Prednisone has good oral bioavailability and is extensively metabolized in the liver, primarily to the active form of the drug, prednisolone. It has an elimination half-life of approximately 4 hours. Liver disease may decrease conversion to the active form, requiring use of prednisolone instead of prednisone. Routes of excretion are not well delineated.

Toxicity: Toxicity is mostly in the form of constitutional symptoms, including mood changes (depressive, anxious, or euphoric), insomnia, indigestion, enhanced appetite, weight gain, acne, and cushingoid features. Other side effects may be more serious but are less common. Hyperglycemia and increased stomach acid predisposing to ulceration occur acutely, while osteopenia, cataracts, skin atrophy, and adrenal insufficiency occur with prolonged use.

Indications: FDA approved for a wide variety of malignant and nonmalignant conditions. Used in oncology for lymphoid malignancies, for palliative care, and for management of side effects/toxicities.

Dosing: Lympholytic doses are generally in the range of 50 to 100 mg/m^2/day for 5 to 14 days. Higher or lower doses are also used, depending upon the indication.

Procarbazine (Matulane)—N-methylhydrazine

Drug Class: Alkylating agent. Cell cycle independent.

Dosage Form: 50-mg capsules.

Drug Interactions: This drug has monoamine oxidase inhibitory activity and therefore should not be taken with certain types of food, including beer, wines, fermented cheese, chocolate, and fava beans, or with certain medications, including ethanol, decongestants, tricyclic antidepressants, antihypertensives, antihistamines, narcotics, barbiturates, phenothiazines, or other monoamine oxidase inhibitors.

Pharmacokinetics/Metabolism: Well absorbed by the oral route, reaching peak plasma levels in 1 hour, with good distribution to the cerebrospinal fluid. Procarbazine is metabolized by the liver and has an elimination half-life of about 1 hour. Largely excreted in the urine.

Toxicity: Myelosuppression is expected and dose limiting, but anemia is uncommon. Nausea and vomiting are common and can be dose limiting as well. Rash, hives, and photosensitivity sometimes occur. Other side effects are uncommon and include anorexia, diarrhea, stomatitis, hypotension, tachycardia, syncope, flu-like syndrome, interstitial pneumonitis, CNS excitation including seizures, and secondary malignancies.

Indications: FDA approved for Hodgkin's disease, and may also be useful in non-Hodgkin's lymphoma, multiple myeloma, brain tumors, melanoma, and lung cancer.

Dosing: In Hodgkin's disease regimens such as MOPP, the dose is 100 mg/m^2/day for 14 days during each cycle.

Rituximab (Rituxan)
- Drug Class: Monclonal antibody directed against the B-cell surface antigen CD20.
- Dosage Form: Sterile vials containing 100 and 500 mg of antibody in aqueous solution (10 mg/mL).
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Not available by the oral route, but when given IV, it is taken up by B lymphocytes and then degraded throughout the body by proteolysis, with a wide ranging serum half-life of 11 to 105 hours (mean 60 hours) with the first dose. There is no appreciable excretion of this polypeptide.
- Toxicity: Fever, chills, and malaise are common during administration, even with premedication with acetaminophen and diphenhydramine. Other infusion-related symptoms include nausea, vomiting, flushing, urticaria, angioedema, hypotension, dyspnea, bronchospasm, fatigue, headache, rhinitis, and pain at disease sites. These symptoms are generally self-limited, improve with slowing of the infusion, and resolve after infusion. Short-lived myelosuppression, abdominal pain, and myalgia are uncommon. Arrhythmias and angina pectoris are rare.
- Indications: FDA approved for relapsed or refractory low-grade or follicular, CD20-positive, B-cell lymphomas.
- Dosing: The recommended dose is 375 mg/m^2 by IV infusion (starting at 50 mg/hr and increasing to 400 mg/hr maximum) weekly for 4 weeks. Higher doses, more doses, and longer courses are being used in other lymphoid malignancies.

Sargramostim (Leukine, Leukomax)—granulocyte-macrophage colony-stimulating factor (GM-CSF)
- Drug Class: Cytokine; exhibits pleiotropic stimulatory effects on bone marrow progenitor cells.
- Dosage Form: Vials containing 250, 400, and 500 μg of lyophilized GM-CSF.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Not available by the oral route but has similar bioavailability when given IV or SC. Degraded throughout the body, predominantly in the liver and kidneys, with an elimination half-life of 2 hours. No appreciable excretion of this peptide occurs.
- Toxicity: Constitutional symptoms, which tend to decrease over time, predominate at standard doses. Higher doses may cause capillary leak syndrome. Side effects include flushing, hypotension (or hypertension), dyspnea, fever, nausea, vomiting, fatigue, myalgias, bone pain, headache, and skin rash. Thrombocytopenia may also occur. Fluid retention and edema rarely occur at standard doses. Progression of myelodysplastic syndrome has been documented in patients on GM-CSF.
- Indications: FDA approved for the treatment of myelosuppression after ABMT. May be useful to minimize myelosuppression after standard-dose chemotherapy or to shorten the course of neutropenic fever. Immunostimulatory properties of GM-CSF are still being investigated.
- Dosing: 250 μg/m^2/day for 21 days or 5 μg/ kg/day for 10 to 14 days.

Sorafenib (Nexavar)
- Drug Class: Targeted agent: Multikinase inhibitor.
- Dosage Form: 200-mg tablets.
- Drug Interactions: The AUC of doxorubicin is increased by 21% with concomitant use of sorafenib.
- Pharmacokinetics/Metabolism: An oral multikinase inhibitor that interacts with multiple intracellular (CRAD, BRAF) and cell surface kinases (KIT, FLT-3, VEGFR-2, VEGFR-2, and PDGFR-β. May inhibit angiogenesis. Metabolized in the liver. Drug and metabolites are excreted primarily in the feces.
- Toxicity: Skin toxicity with rash and hand-foot syndrome. Nausea, vomiting, anorexia, diarrhea. Asthenia, pain, arthralgias. Hypertension. Bleeding events, especially in anticoagulated patients. Cardiac ischemia. Myelosuppression.
- Indications: Advanced renal cell carcinoma.
- Dosing: 400 mg twice daily.

Streptozocin (Zanosar)
- Drug Class: Alkylating agent. Cell cycle independent.
- Dosage Form: Vials containing 1 g of lyophilized streptozocin.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Streptozocin is bioavailable only by the IV route. It is metabolized primarily in the liver and has an elimination half-life of less than 1 hour. Parent drug and metabolites are excreted in the urine.
- Toxicity: GI side effects (nausea, vomiting, and cramping) or nephrotoxicity (glomerular and tubular damage) are common and potentially dose limiting. Myelosuppression is less often dose limiting. Elevated liver function tests can occur occasionally but are rarely clinically significant. Fever, delirium, and depression occur rarely. Streptozocin is an irritant if extravasated into perivenous soft tissue.
- Indications: FDA approved for metastatic islet cell carcinoma and may also be useful for advanced carcinoid tumor, pancreatic carcinoma, and Hodgkin's disease.
- Dosing: The usual dose is 500 to 1000 mg/m^2/day by IV bolus for 5 days every 4 weeks.

Sunitinib maleate (Sutent)
- Drug Class: Receptor tyrosine kinase inhibitor.
- Dosage Form: 50-mg tablets.
- Drug Interactions: Medications that inhibit or induce CYP3A4; St John's wort.
- Pharmacokinetics/Metabolism: Inhibits multiple receptor tyrosine kinases. Inhibits PDGFRα and PDGFRβ, VEGFR1–3, stem cell factor receptor, FLT-3, CSF-1R, and the neurotrophic factor receptor. This inhibition inhibits tumor growth and metastases. Metabolized in the liver with elimination primarily in the feces. Half-life is 40 to 60 hours for the drug and 80 to 110 hours for its primary metabolite.
- Toxicity: Cardiotoxicity-usually reversible. Bleeding event, epistaxis most common. Hypertension. Myelosuppression. Nausea, vomiting. Rash. Liver function test alterations.
- Indications: Advanced renal cell carcinoma. Second-line therapy for gastrointestinal stromal (GIST) cell tumors.
- Dosing: 50 mg daily for 4 weeks, with a 2-week rest.

Tamoxifen (Nolvedex)
- Drug Class: Nonsteroidal antiestrogen; cytostatic effects on estrogen-dependent and nondependent malignant cells.
- Dosage Form: 10-mg tablets.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Tamoxifen has good oral bioavailability, is metabolized in the liver, and has an elimination half-life of about 7 days. Neither tamoxifen nor its major metabolite is found in the bile or urine.
- Toxicity: Tamoxifen is usually very well tolerated. Constitutional symptoms are most prevalent and usually dose limiting. Hot flashes, sweating, mood changes, weight gain or loss, and stomach upset are most common. Nausea, vomiting, diarrhea, and constipation are less common. Menstrual changes, including significant vaginal bleeding, are uncommon. Venous thromboembolism, myelosuppression, and retinopathy are rare.
- Indications: FDA approved for the treatment of breast cancer, generally in postmenopausal patients or those with estrogen receptor-positive tumors. The same dose has been approved for chemoprevention of breast cancer in high-risk individuals. Higher doses are used for melanoma and pancreatic cancer.
- Dosing: The standard dose for breast cancer is 10 mg PO bid (or 20 mg once a day).

Temozolomide (Temodar)
- Drug Class: Atypical alkylator (semiselective DNA methylator) drug sharing the same active metabolite as dacarbazine, MTIC but, unlike dacarbazine, is spontaneously converted to MTIC and also penetrates the blood-brain barrier effectively.
- Dosage Form: Capsules containing 5 mg, 20 mg, 100 mg, and 250 mg of temozolomide.
- Drug Interactions: Coadministration with valproic acid results in decreased oral bioavailability of temozolomide by a minor amount. No other drug interactions have been identified.
- Pharmacokinetics/Metabolism: Temozolomide had good bioavailability, enhanced by an empty stomach. After absorption into the bloodstream, it is spontaneously converted to the active moiety MTIC. Peak plasma concentrations occur in about 1 hour. The elimination half-life is about 1.8 hours. Parent drug, MTIC, and other metabolites are eliminated in the urine.
- Toxicity: Myelosuppression is expected and dose-limiting. It may be cumulative. Nausea is common but generally mild and treatable. Headache and fatigue are common. Rash or other cutaneous reactions are uncommon. Infections are common in this population, and some are probably caused by immunosuppression that is known to occur with temozolomide.
- Indications: FDA approved for treatment of recurrent high-grade astrocytomas. Used commonly for other gliomas and also for metastatic melanoma.
- Dosing: 200 mg/m^2 PO on an empty stomach daily for 5 days on a 28-day cycle. Other doses and schedules have been used with similar clinical results.

Teniposide (Vumon)—VM-26, PTG
- Drug Class: Inhibitor of topoisomerase II; similar in action to etoposide.
- Dosage Form: Vials of 10-mg/mL solution containing 50 mg of drug.
- Drug Interactions: Metabolism of teniposide is increased by inducers of liver microsomal enzymes such as phenobarbital and carbamazepine.
- Pharmacokinetics/Metabolism: Teniposide is only available by the IV route. It is extensively protein bound in the plasma and undergoes near-complete metabolism in the liver. It has an elimination half-life of 5 hours. Metabolites are excreted in the bile and urine.
- Toxicity: Myelosuppression, predominantly leukopenia, is universal and dose limiting. Otherwise usually well tolerated. Nausea, vomiting, diarrhea, stomatitis, and anorexia are uncommon. Alopecia is generally mild. Elevated liver function tests can occur but are not usually clinically significant. Allergic reactions, hypotension, fatigue, seizures, somnolence, fever, renal insufficiency, and secondary leukemia are all rare.
- Indications: FDA approved for childhood ALL. Not used commonly for other malignancies, but does have activity against SCLC.
- Dosing: 100 mg/m^2 once or twice weekly or 20 to 60 mg/m^2/day for 5 days as a slow IV infusion (at least 30 minutes).

Thalidomide (Thalomid)
- Drug Class: Novel antiangiogenic and immunomodulating agent.
- Dosage Form: 50-mg tablets.
- Drug Interactions: Increases the sedative properties of barbiturates, chlorpromazine, and ethanol.
- Pharmacokinetics/Metabolism: While it has acceptable bioavailibility, thalidomide is slowly and incompletely absorbed from the GI tract. Metabolism appears to be via spontaneous hydrolysis, with an elimination half-life of about 6 hours. Exact quantification of elimination routes are unknown.
- Toxicity: Historical teratogenicity has led to required strict evaluation and monitoring for those taking thalidomide, called the S.T.E.P.S. Program. Strict procedures to prevent conception include barrier contraception for men, since the drug is present in semen of men who are taking it. Fatigue and peripheral neuropathy are the main toxicities and are dose limiting. Myelosuppression is uncommon and usually mild. Rash and headache uncommon.
- Indications: FDA approved for cutaneous leprosy. Used in oncology for multiple myeloma, renal cell carcinoma, metastatic melanoma, and malignant gliomas. Also used as a treatment for cachexia owing to its mild anabolic and appetite-stimulating properties.
- Dosing: Oncology doses range for 50 mg/day up to 1200 mg/day.

Thioguanine (Tabloid)—6-TG, aminopurine-6-thiol hemihydrate
- Drug Class: Purine analog antimetabolite. Cell cycle dependent.
- Dosage Form: 40-mg tablets.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: Thioguanine has modest but slow oral route absorption. It is almost completely metabolized in the liver and has an elimination half-life of up to 11 hours. Metabolites are excreted in the urine.
- Toxicity: Thioguanine is usually well tolerated. Leukopenia and thrombocytopenia are common and dose limiting. Nausea and vomiting, stomatitis, diarrhea, rash, elevated liver function tests, hyperuricemia, and renal insufficiency are uncommon.
- Indications: FDA approved for AML in all phases of treatment. May be useful in other leukemias. An injectable formulation does not yet have FDA approval.
- Dosing: The usual dose for leukemias is 2 to 3 mg/kg/day as part of an ongoing multidrug regimen.

Thiotepa (TESPA)—triethylenethiophosphoramide, TSPA
- Drug Class: Classical alkylating agent. Cell cycle independent.
- Dosage Form: Available as lyophilized powder in vials containing 15 mg of drug.
- Drug Interactions: None noted.
- Pharmacokinetics/Metabolism: With poor oral bioavailability, thiotepa is available only by the parenteral route. Extensive metabolism occurs in the liver, and the drug has an elimination half-life of 2 to 3 hours. Metabolites are excreted in the urine.
- Toxicity: Myelosuppression, predominantly leukopenia, is expected and dose limiting and may be cumulative. Nausea, vomiting, anorexia, stomatitis, and diarrhea are uncommon. Infertility, fever, and angioedema or urticaria are uncommon. Second malignancies such as acute leukemia are rare. With high-dose therapy and bone marrow rescue, stomatitis and cognitive impairment can be severe. Intravesical administration leads to predominant urinary symptoms, including pain, hematuria, hemorrhagic cystitis, and rare ureteral obstruction.
- Indications: FDA approved for the treatment of breast and ovarian carcinoma, as well as Hodgkin's disease and non-Hodgkin's lymphoma. Used for intravesical therapy of superficial bladder cancer and may also be used for intracavitary and intrathecal administration. Used in the transplant setting for ovarian and breast carcinoma.
- Dosing: The usual dose is 12 to 16 mg/m^2 IV over 10 minutes every 1 to 4 weeks. In the transplant setting, doses up to 900 mg/m^2 have been used. The bladder instillation dose is 30 to 60 mg once weekly for 4 weeks. The intrathecal dose is 1 to 10 mg/m^2 one to two times per week.

Topotecan (Hycamtin)—hycamptamine
- Drug Class: Semisynthetic camptothecin molecule; an inhibitor of topoisomerase I, which is required by cells for both transcription and replication.
- Dosage Form: 5-mg vials of lyophilized powder.
- Drug Interactions: None noted.

Pharmacokinetics/Metabolism: No oral form of this drug is available. After IV administration, the drug is not extensively metabolized, and it has an elimination half-life of about 3 hours. A significant portion of the drug is excreted unchanged in the urine.

Toxicity: Myelosuppression, especially leukopenia, is expected and dose limiting. Thrombocytopenia and anemia are common but mild. Nausea, vomiting, and diarrhea are common but usually not severe. Headache, fever, fatigue, anorexia, malaise, and elevated liver function tests are also common. Hypertension, tachycardia, urticaria, renal insufficiency, hematuria, neuropathy, and mucositis are uncommon.

Indications: FDA approved for the treatment of refractory, relapsed ovarian carcinoma and for relapsed small cell lung cancer. Also used in myeloid leukemias.

Dosing: The standard dose for ovarian cancer is 1.5 mg/m^2/day for 5 days as a 30-minute infusion.

Toremifene (Fareston)

Drug Class: Nonsteroidal antiestrogen; cytostatic effects on estrogen-dependent and nondependent malignant cells.

Dosage Form: 60-mg tablets.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Toremifene has good oral bioavailability and is extensively bound to plasma proteins. It is metabolized in the liver to active metabolites and has an elimination half-life of about 5 days. Parent drug and metabolites are excreted in the bile.

Toxicity: Toremifene is usually very well tolerated. Hot flashes, nausea, sweating, dizziness, and fatigue are the most common side effects. Vomiting, diarrhea, anorexia, vaginal discharge, vaginal bleeding, and headache are less common. Venous thrombosis and pulmonary embolism are rare.

Indications: FDA approved for the treatment of postmenopausal or estrogen receptor-positive metastatic breast cancer.

Dosing: 60 mg PO every day.

Trastuzumab (Herceptin)

Drug Class: A genetically engineered humanized mouse monoclonal antibody directed against the her2/neu growth factor receptor that is overexpressed in many invasive breast carcinomas. Mechanism of action for clinical activity in breast cancer is unknown but may be complement mediated cell lysis, antibody-dependent cellular cytotoxicity, or induction of apoptosis.

Dosage Form: Vials of 440 mg.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Binding studies show strong binding to cells overexpressing her2/neu molecules. Very little else is known regarding the distribution and metabolic fates of this molecule. Half-life should be very short with minimal distribution outside the vascular compartment and minimal clearance by kidneys or liver (similar to other monoclonal antibodies and polypeptide agents).

Toxicity: Common toxicities include acute fever, chills, nausea, vomiting, and headache. Trastuzumab seems to worsen leukopenia, anemia, and diarrhea when given with chemotherapy compared to chemotherapy alone. Also, trastuzumab may have uncommon acute cardiotoxicity, which may add to the more common anthracycline-induced cardiotoxicity; therefore, the use of trastuzumab with doxorubicin is not indicated by the FDA.

Indications: FDA approved for her2/neu overexpressing metastatic or locally advanced breast cancer; has shown clinical benefit as a single agent and in conjunction with paclitaxel-based chemotherapy.

Dosing: Loading dose of 250 mg or 4 mg/kg by intravenous infusion followed by weekly intravenous infusions of 100 mg or 2 mg/kg for up to 10 weeks (or longer).

Tretinoin (Vesanoid)—ATRA, all-trans-retinoic acid.

Drug Class: A naturally occurring retinoid; induces differentiation and apoptosis of malignant promyelocytes in acute promyelocytic leukemia.

Dosage Form: 10-mg capsules.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: This drug has good oral bioavailability and a very short elimination half-life of about 40 minutes. It induces its own metabolism in the liver, leading to decreased levels and clinical effect with continued administration. No appreciable excretion of the parent compound is evident.

Toxicity: Tretinoin is teratogenic, so women of childbearing age who take this drug must be on optimal contraceptive measures. Leukostasis and hemorrhage due to leukocytosis are dose limiting but uncommonly life threatening if the drug is stopped. "Retinoic acid syndrome," although not common, can be dose limiting and consists of fever, chest pain, dyspnea, hypoxia, pulmonary infiltrates, and pleural/pericardial effusions. It can be lethal but improves with cessation of the drug and is treatable with corticosteroids. Dry skin, exfoliation, xerostomia, and cheilitis are common. Elevations in liver function tests and hyperlipidemias are also common. Headache is often seen, but pseudotumor cerebri or other neurologic occurrences are uncommon.

Indications: FDA approved induction therapy for acute promyelocytic leukemia. Also of benefit in the maintenance phase of this disorder and may have clinical activity in other hematologic malignancies.

Dosing: For induction, the dose is 45 mg/m^2/day PO for 30 to 90 days, depending on the clinical response.

Vinblastine (Velban, Velsar, others)—VLB, vincaleukoblastine

Drug Class: Vinca alkaloid; inhibitor of tubulin polymerization and thereby mitosis. G_2-phase specific.

Dosage Form: Vials of drug in solution (1 mg/mL), or lyophilized powder containing 10 mg of drug.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: Poor oral bioavailability. After an IV dose, the drug undergoes deacetylation in the liver to an active metabolite, followed by further metabolism. The elimination half-life is about 20 hours. Excretion is predominantly via the bile.

Toxicity: Vinblastine is a soft tissue vesicant, requiring extravasation precautions during administration. Myelosuppression, especially leukopenia, is expected and dose limiting. Anemia and thrombocytopenia are less common. Peripheral and autonomic neuropathy are less common than that observed with vincristine. Nausea and vomiting are uncommon, but constipation is more often seen. Acute reactions during administration, including dyspnea, wheezing, chest pain, tumor pain, and fever, are uncommon. Syndrome of inappropriate antidiuretic hormone secretion occurs rarely, as does angina pectoris.

Indications: FDA approved for multiple hematologic and solid neoplasms. Most often used for Hodgkin's disease, non-Hodgkin's lymphoma, germ cell tumors, and breast cancer.

Dosing: Typical doses are between 6 and 10 mg/m^2 by IV push every 2 to 4 weeks, combined with other drugs. Can also be given as a continuous infusion over 96 hours at a dose of 1.7 to 2.0 mg/m^2/day.

Vincristine (Oncovin, Vincasar)—leurocristine, VCR

Drug Class: Vinca alkaloid; inhibitor of tubulin polymerization and thereby mitosis. G_2-phase specific.

Dosage Form: Available as solution (1 mg/mL) in vials containing 1 to 5 mg of drug and in syringes containing 1 or 2 mg.

Drug Interactions: L-Asparaginase may decrease hepatic metabolism of vincristine.

Pharmacokinetics/Metabolism: Vincristine is bioavailable only by the IV route. It is metabolized by the liver. The elimination half-life is variable but usually greater than 10 hours. Parent drug and metabolites are primarily excreted in the bile.

Toxicity: Vincristine is a vesicant and should be administered with extravasation precautions. Neurotoxicity is dose limiting in the form of peripheral neuropathy, which is related to total cumulative dose. Autonomic neuropathy is less common, and CNS toxicity is rare. Myelosuppression is mild. Nausea and vomiting are rare, but constipation is fairly common. Acute cardiopulmonary or pain symptoms occurring during administration are uncommon. Transient elevation of liver function tests is sometimes seen.

Indications: FDA approved for Hodgkin's disease and other lymphomas, acute leukemias, rhabdomyosarcoma, neuroblastoma, and Wilms' tumor. Used for many other neoplasms as well.

Dosing: The usual dose is 0.5 to 1.4 mg/m^2 IV push every 1 to 4 weeks. A continuous infusion of 0.5 mg/m^2/day over 96 hours has also been used.

Vinorelbine (Navelbine)—5′-noranhydrovinblastine, NVB

Drug Class: Semisynthetic vinca alkaloid; inhibitor of tubulin polymerization and thereby mitosis. G_2-phase specific.

Dosage Form: Available as vials of 10-mg/mL solution.

Drug Interactions: None noted.

Pharmacokinetics/Metabolism: This drug has fair oral bioavailability but is currently available only as an IV preparation. It is metabolized by the liver and has an elimination half-life of about 24 hours. Excretion is predominantly in the bile.

Toxicity: Vinorelbine is a mild vesicant, requiring extravasation precautions. Myelosuppression, mostly leukopenia, is expected and dose limiting. Significant nausea and vomiting are uncommon. Neurotoxicity in the form of neuropathy is less common and milder than that seen with vincristine. Tumor pain during administration has been reported. Acute reaction such as dyspnea, chest pain, and wheezing have occurred during administration and may be prevented by premedication with corticosteroids.

Indications: FDA approved for the treatment of relapsed metastatic breast cancer and for NSCLC as a single agent or combined with a platinating agent.

Dosing: The recommended dose is 30 mg/m^2 IV over 20 minutes every week, with dose adjustments based on leukocyte counts.

Zolendronic Acid (Zometa)

Drug Class: Bisphosphonate inhibitor of bone metastases.

Dosage Form: Vials containing 4 mg of zolendronic acid in powder form.

Drug Interactions: No studies have identified interactions. Theoretical concerns include exacerbation of hypocalcemia if zolendronic acid is coadministered with aminoglycosides or thiazide diuretics. Also, zolendronic acid could exacerbate the renal effects of other nephrotoxic drugs.

Pharmacokinetics/Metabolism: Zolendronic acid is poorly absorbed by the GI tract and is therefore given as an intravenous infusion. It is not metabolized and is excreted by the kidneys. It has a plasma terminal elimination half-life of about 150 hours.

Toxicity: Zolendronic acid is generally well tolerated. The most common infusional side effect is fever, which is usually mild and treatable. Nausea and constipation are also common. Dyspnea, fatigue, diffuse pain, rash, and headache are uncommon. Renal insufficiency is uncommon and generally reversible after discontinuation of the drug, but it is more likely with higher doses than with the approved and recommended 4-mg dose.

Indications: FDA approved for treatment of hypercalcemia of malignancy and for prevention of pathologic fractures in multiple myeloma and solid tumors with known bone metastases.

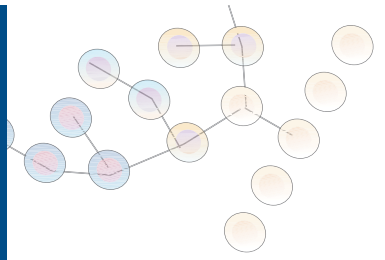
Dosing: 4 mg IV injection over 15 minutes once monthly.

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31 Principles of Molecularly Targeted Therapy: Present and Future

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SUMMARY OF KEY POINTS

- Molecularly targeted anticancer agents (MTAs) are those that selectively target specific molecular features of cancer cells such as aberrations in genes, proteins, or pathways that regulate tumor growth, progression, and survival.
- Molecular targets include the following: products of activating mutations and translocations, growth factors and receptors, aberrant signal transduction and apoptotic pathways, factors that control tumor angiogenesis and microenvironment, dysregulated proteins, DNA repair machinery, and aberrant epigenetic mechanisms.
- The development of MTAs requires innovative strategies that differ from those traditionally applied to nontargeted conventional chemotherapy.
- Successful development of an MTA depends largely on the importance of the target in controlling tumor cell proliferation and survival, a qualified assay to measure target modulation, and careful attention to patient selection.
- Primary objectives of clinical trials of MTAs differ from those used in trials of conventional chemotherapy. An important objective in phase I trials of MTAs is determination of a phase II dose based on optimal target modulation (i.e., a biologically effective dose) rather than on maximum tolerated dose. In addition, objective tumor response may not be an adequate endpoint for the efficacy evaluation of MTAs, because they may have antitumor effects that are more cytostatic than cytotoxic in nature. Progression-free survival may be a more appropriate endpoint.
- MTAs may be more effective when used in combination.
- Functional and molecular imaging plays an increasingly important role in the development of MTAs.

INTRODUCTION

Recent advances in cancer biology and synthetic chemistry have generated extraordinary opportunities for the development of molecularly targeted cancer therapeutics. Molecularly targeted anticancer agents (MTAs) are defined here as those that selectively target specific molecular features of cancer cells such as aberrations in genes, proteins, or pathways that regulate tumor growth, progression, and survival. In contrast, nontargeted therapeutics such as standard chemotherapeutic agents tend to be nonselective and thus produce considerable toxicity against normal cells. By identifying ways that cancer cells differ from normal healthy cells at the molecular level, scientists are now in a better position to exploit these differences to develop drugs that more effectively attack cancer cells while sparing normal cells. Consequently, an increasing number of MTAs are being developed with the goal of producing more effective and minimally toxic anticancer therapeutics. Furthermore, progress in the development of MTAs can shape cancer therapeutics into a more personalized form of cancer medicine. This chapter will review the principles of molecularly targeted therapy including strategies for preclinical and clinical development.

MOLECULAR TARGETS

There is an increasing number and assortment of molecular targets, broadly categorized according to genetic or functional properties including the following: products of activating gene mutations and translocations; growth factors and receptors; aberrant signal transduction and apoptotic pathways; factors that control tumor angiogenesis and the tumor microenvironment; dysregulated proteins; DNA repair machinery and aberrant epigenetic mechanisms (Table 31-1). Understandably, any such categorization of targets contains considerable overlap. For example, activation of the growth factor receptors epidermal growth factor receptor (EGFR) and HER2 can occur by a variety of mechanisms including altered transcriptional control, gene amplification, and activating mutations.[1,2] Similarly, platelet-derived growth factor receptor (PDGFR)-α and PDGFR-β are receptors for growth factors in many types of tumors but are also expressed in stromal tissue and play a role in angiogenesis.[3] In addition, abnormal expression of PDGFR-α and PDGFR-β can result from genetic abnormalities; activating mutations of PDGFR-α in some cases of gastrointestinal stromal tumor (GIST)[4] and chromosomal translocations resulting in the TEL/PDGFR-β fusion protein in chronic myelomonocytic leukemia.[5]

The most promising molecular targets are those solely responsible for sustaining tumor growth and survival. Agents that potently and selectively inhibit these critical targets are likely to have a major clinical impact. Probably the best example of a critical target is BCR-ABL in chronic myelogenous leukemia (CML). BCR-ABL is a fusion protein formed by the reciprocal translocation of chromosomes 9 and 22. Knowledge that this dysregulated tyrosine kinase played a causal role in the pathogenesis of essentially all cases of CML spurred preclinical studies that led to the development of a potent and selective ABL tyrosine kinase inhibitor, imatinib mesylate.[6] Subsequent clinical trials established imatinib mesylate as the first highly effective molecularly targeted therapy for CML and a prototype for the

Table 31-1 Tumor Targets

Validated*

Target	Disease Indication	FDA-Approved Agents(s)	Agent Type
CHROMOSOMAL TRANSLOCATIONS			
BCR-ABL	Ph+ CML, ALL	Imatinib mesylate, dasatinib	TKI
PML-RAR	Acute promyelocytic leukemia	All-*trans* retinoic acid	Retinoid
PDGFR-β	CMML, DFSP	Imatinib mesylate	TKI
SOMATIC MUTATIONS			
KIT	GIST	Imatinib mesylate, sunitinib malate	TKI
PDGFR-α	GIST	Imatinib mesylate, sunitinib malate	TKI
GROWTH FACTORS/RECEPTORS			
EGFR	Non-small cell lung cancer	Erlotinib	TKI
	Colorectal cancer	Cetuximab, panitumumab	Mo-Ab
	Head and neck cancer	Cetuximab	Mo-Ab
ErbB-2	HER-2 overexpressing breast cancer	Trastuzumab	Mo-Ab
		Lapatinib	TKI
ANGIOGENESIS			
VEGF	Colorectal cancer, non-small cell lung cancer	Bevacizumab	Mo-Ab
VEGFR	Renal cell carcinoma	Sunitinib malate, sorafenib	TKI
mTOR	Renal cell carcinoma	Temsirolimus	Rapamycin analogue
EPIGENETIC SILENCING			
DNA methyltransferase	Myelodysplastic syndrome	Azacitidine, decitabine	Pyrimidine analogue
Histone deacetylase	Cutaneous T-cell lymphoma	Vorinostat	Hydroxamic acid
DYSREGULATED PROTEINS			
Proteosome	Multiple myeloma	Bortezomib	26S proteasome inhibitor

Agents under Clinical Development

Target	Role of Target	Disease Indication	Examples of Agents in Clinical Development	Ref.
SOMATIC MUTATIONS				
FLT-3 (FMS-like tyrosine kinase-3)	Regulates cell cycle progression, proliferation, and survival	Acute myeloid leukemia	Sunitinib	90
			CEP-701	91
			MLN518	92
bRAF mutation	Effects cell proliferation and angiogenesis via amplification of signal transduction in RAS/MAPK pathway	Papillary thyroid carcinoma Melanoma	PLX4032	93
DNA REPAIR MACHINERY				
PARP	Single-strand DNA break repair	Various solid tumors	AG014699	94
		BRCA-positive breast and ovarian cancer	ABT-888	35
			KU59436	95
			BSI-201	77
			INO-1001	96
O^6-Alkylguanine DNA alkyltransferase	Prevents intrastrand DNA crosslinks		O^6-benzylguanine	97
GROWTH FACTORS/RECEPTORS				
IGF-1R	Regulates cell proliferation, differentiation and survival	Various adult and pediatric tumors	IMC-A12 (monoclonal antibody)	98
			CP-751,871 (monoclonal antibody)	99
			NVP-AEW541 (IGF-1R kinase inhibitor)	100
			IGF-1R/AS ODN (antisense oligodeoxynucleotide)	101

Table 31-1 Tumor Targets—cont'd

	Agents under Clinical Development			
Target	**Role of Target**	**Disease Indication**	**Examples of Agents in Clinical Development**	**Ref.**
IGFBP3	Regulates cell proliferation, differentiation and survival	Various adult and pediatric tumors	INSM-120-101 (recombinant IGFBP3)	102
ANGIOGENESIS				
Hypoxia-inducible factor-1α	Regulates tumor cell response to oxygen deprivation	HIF-1α expressing solid tumors	Topotecan	25
$\alpha_v\beta_3$-integrin receptor	Involved in cell adhesion	Glioma and various solid tumors	Cilengitide (cyclic Arg-Gly-Asp peptide; EMD 121974)	103
ABERRANT SIGNAL TRANSDUCTION AND APOPTOTIC PATHWAYS				
Syk	Inhibits differentiation and induces growth factor–independent proliferation of pre–B cells	B-cell lymphomas	R788	104
MET	Regulate cell growth, antiapoptosis, altered cytoskeletal function	Solid tumors	PF-2341006	105
			PHA665752	106
			XL880	
MEK1/2	Regulates tumor cell proliferation and survival		PD0325901	107
			AZD6244 (ARRY-142886)	108
RAS	Promote cell proliferation and survival	AML	Tipifarnib	109
				110
RAF	Regulates tumor cell proliferation and survival	Melanoma and other solid tumors	Sorafenib	111
RET	Regulates tumor cell proliferation and survival	Medullary thyroid cancer	Sorafenib	111
			Sunitinib	90
			Vandetanib	112
Akt kinase	Regulator of cell cycle and apoptotic pathway	Variety of solid and hematologic cancer	Perifosine	113
Clusterin	Promotes cell survival	Variety of solid tumors	OXG-011	114
DYSREGULATED PROTEINS				
HSP-90	Chaperone for several oncogenic proteins and growth factors	Myeloid leukemia and solid tumors	17-AAG	115
			Alvespimycin (17-DMAG)	116
			IPI-504	117
APOPTOSIS				
Bcl-2	Antiapoptotic	Lymphomas, solid tumors	ABT-737	118
			AT-101	119
			Obatoclax mesylate (GX15-070MS)	
TRAIL	Apoptotic mechanism	Various types of cancer	Mapatumumab	120
			Apo2L/TRAIL	121

ALL, acute lymphoblastic leukemia; CMML, chronic monomyelocytic leukemia; DFSP, dermatofibrosarcoma protuberans; HIF-1α, hypoxia-inducible factor-1α; IGF-1R, insulin-like growth factor-1 receptor; IGFBP3, insulin-like growth factor binding protein-3; Mo-Ab, monoclonal antibody; mTOR, mammalian target of rapamycin; PARP, poly (ADP-ribose) polymerase; Ph + CML, Philadelphia chromosome positive myelogenous leukemia; TKI, tyrosine kinase inhibitor. TRAIL, tumor necrosis factor-related apoptosis-inducing ligand.

*Valid to the degree that agents directed against them have proven effective in the treatment of one or more disease indications bearing the target.

development of others in the class.[6–8] Imatinib mesylate is also a potent inhibitor of other tyrosine kinases including PDGFR and KIT, and it is highly effective in the treatment of GIST bearing activating c-*KIT* mutations, and in some GIST bearing activating *PDGFR* mutations.[4]

Unfortunately, the majority of human tumors, including the most common types, are genetically complex and do not have a single critical target. In addition, what may be a critical target in one type of tumor may be expressed but not be as relevant in another. Most tumor types have various genetic and molecular abnormalities driving their growth and survival. The existence of multiple abnormalities is one mechanism to explain resistance to molecularly targeted therapy and provides a rationale for treatment strategies combining two or more targeted agents.[9] However, recent information suggests cancer cells

may become "addicted" or physiologically dependent on the sustained activity of specific oncogenes for maintenance of a malignant phenotype and for survival**.** This dependence mechanism, termed oncogene addiction[10,11] (Fig. 31-1), is associated with differential attenuation rates of prosurvival and proapoptotic signals stemming from the oncoprotein, with predominant apoptotic signals resulting in cell killing. The latter process, termed "oncogenic shock,"[12] could explain the remarkably rapid clinical responses to tyrosine kinase inhibitors in some patients with solid tumors,[13] including those typically having complex molecular abnormalities. Other possible factors controlling sensitivity or resistance to molecularly targeted therapy include increased expression of the target due to gene amplification or transcription, emergence of resistant target gene mutations, and overexpression of multidrug transporter membrane proteins.[8,14]

There has been increased attention to the development of molecular therapy directed at factors controlling angiogenesis since approval by the United States Food and Drug Administration (FDA) of several agents that target vascular endothelial growth factor (VEGF) and its receptor (VEGFR). The VEGF pathway, involving the VEGF family of proteins and their receptors, is an important regulator of both physiologic and pathologic angiogenesis. Through its signaling pathways, VEGF/VEGFR activation contributes to increased vascular permeability, mobilization of bone marrow-derived endothelial cell precursors, degradation of the extracellular matrix, and endothelial cell division, differentiation, migration, and survival.[15,16] VEGF overexpression occurs in most types of cancers, including colorectal, gastric, pancreatic, liver, lung, breast, thyroid, genitourinary, and in glioma and other intracranial tumors, as well as hematologic malignancies.[17,18] In addition, VEGF overexpression is associated with tumor growth and clinical outcome in several of these tumor types.[17]

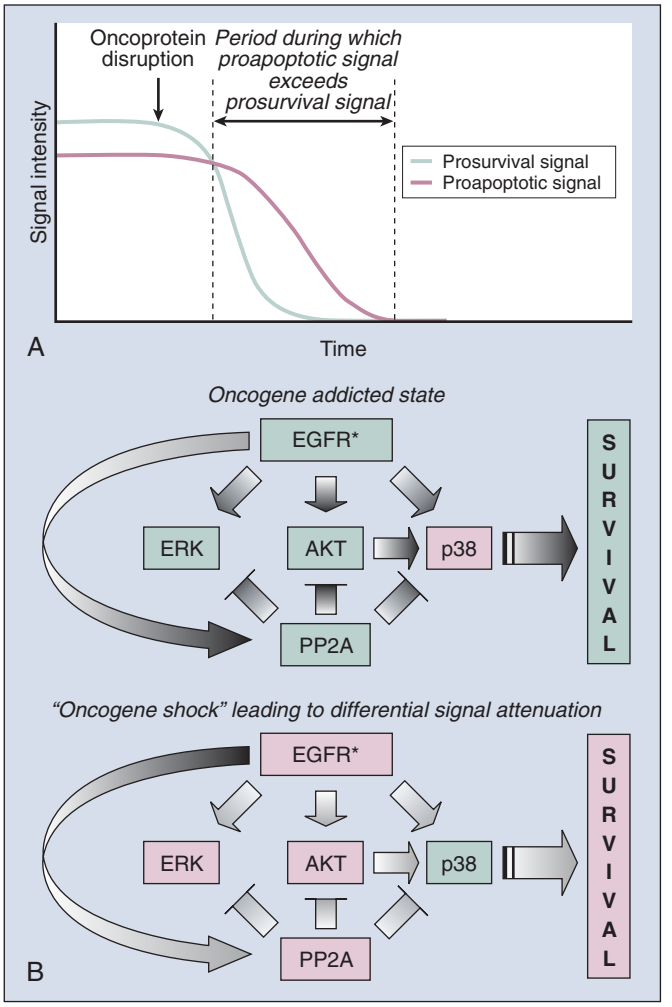


Figure 31-1 • Proposed model of oncogene addiction. **A,** Proposed role of differential signal attenuation in creating a temporal window during which apoptotic signals persist in the absence of prosurvival signals following acute oncogene inactivation to promote cell death. **B,** Proposed role of differential signal attenuation in the cell death response to acute inactivation of oncogenic EGFR (EGFR*) upon which a tumor cell has become dependent. The upper panel illustrates the oncogene "addicted" state in which cells survive, and the lower panel illustrates the shift in the balance of prosurvival and proapoptotic signaling shortly after EGFR inactivation. Red, "off"; green, "on." (From Sharma SV, Gajowniczek P, Way IP, et al: A common signaling cascade may underlie "addiction" to the Src, BCR-ABL, and EGF receptor oncogenes. Cancer Cell 2006;10:425–435.)

Potential therapeutic strategies to inhibit signaling through VEGF and VEGFR pathway activation include monoclonal antibodies directed against VEGF or VEGFR, tyrosine kinase inhibitors, and antisense strategies (antisense oligodeoxynucleotides, antisense RNA, small interfering RNAs). In 2004, the FDA approved bevacizumab, a humanized murine monoclonal antibody directed against VEGF, for treatment of metastatic colorectal cancer when used in combination with fluorouracil-based chemotherapy.[19] Subsequently, two small molecule tyrosine kinase inhibitors with activity against VEGFR, sunitinib and sorafenib, became FDA approved for the treatment of advanced renal cancer.[20,21] In addition, sorafenib is effective in the treatment of hepatocellular carcinoma,[22] a tumor against which standard cytotoxic chemotherapy has little or no activity. The experience with these agents established the VEGF/VEGFR pathway as a valid target for cancer therapeutics.

Mammalian target of rapamycin (mTOR) has also emerged as a validated target with the demonstration that the small molecule mTOR inhibitor, temsirolimus, is effective in the treatment of renal cell carcinoma.[23] This activity of temsirolimus is attributed to the downregulation of factors that control cell growth and angiogenesis such as hypoxia inducible factor-1 (HIF-1).[24] Several other strategies to inhibit HIF-1 are under development including the use of the chemotherapeutic agent topotecan, which at low doses administered for relatively long periods has been shown in in vitro and animal models to reduce HIF-1 protein production thus inhibiting angiogenesis.[25]

PRECLINICAL DEVELOPMENT OF MOLECULARLY TARGETED ANTICANCER AGENTS

The discovery and development of MTAs requires closely aligned laboratory and clinical research, integrating drug discovery, development, and clinical investigation. In such a cooperative setting, researchers can effectively take rational and iterative steps from target identification to clinical evaluation (Fig. 31-2; Table 31-2). A crucial early step in developing an MTA is target validation, defined as experimental evaluation of the role of a given gene or protein in cancer.[26,27] The process of target validation involves a variety of preclinical approaches, including genetic, cell-based, and animal models.[26,28,29] Validation and prioritization of molecular targets for therapeutic development depends on a variety of criteria taking into consideration chemical, biologic, clinical and practical factors (Table 31-3).[27] The fundamental goal is to provide evidence that the target is valid (affecting the target inhibits tumor growth, progression, or survival) and that making drugs that hit the target is feasible. The next major step in the development of MTAs is finding compounds directed against the target.

Empirical approaches traditionally used to screen for cytotoxic agents are not optimal for MTAs. Rather, screening for MTAs should be target based. The increasing number of potential targets and the

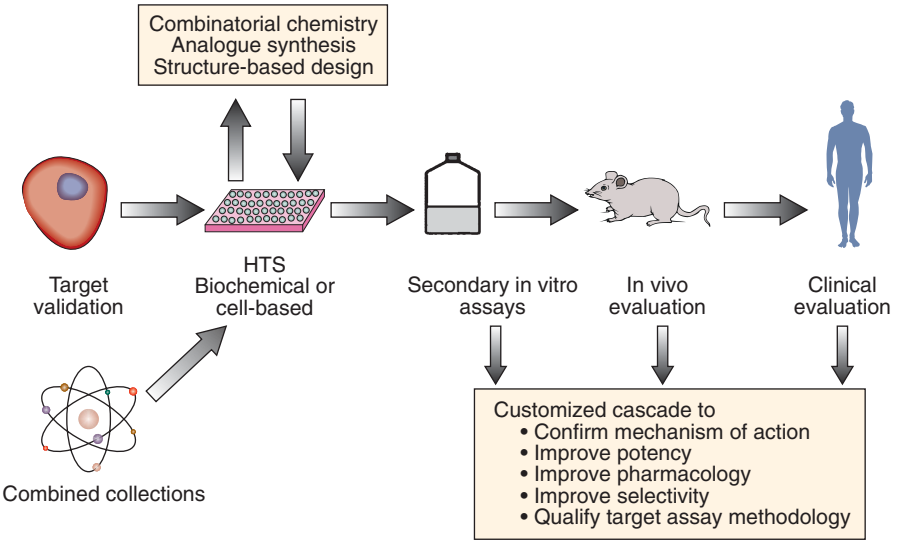


Figure 31-2 • Central role of high-throughput screening (HTS) in the mechanism-based drug discovery process. (With permission from Aherne GW, McDonald E, Workman P: Finding the needle in the haystack: why high-throughput screening is good for your health. Breast Cancer Res 2002;4:148–154.)

availability of sophisticated high-throughput screening technology provide tremendous opportunities to screen an enormous set of diverse small molecular compounds for promising therapeutics.[27] Furthermore, the availability of genetically engineered mouse models provides the opportunity to better screen compounds in vivo.[28,29] A more in-depth discussion of these important drug discovery tools and their implications to the molecularly targeted drug development process is beyond the scope of this chapter.

Optimal development of an MTA requires careful assessment of pharmacokinetic (PK) and pharmacodynamic (PD) effects in relevant nonclinical models before initiating clinical trials. Preclinical in vivo pharmacologic and toxicologic testing is required to establish starting dose and schedule for clinical trials, evaluate effects on normal host tissue, and help make predictions about serum and tissue levels required for target modulation as well as effects on tumor growth. At present most in vivo efficacy studies involve human tumor cell murine xenograft models.[30,31] However, xenograft models have limitations including the requirement for an immunocompromised host, and they are not an ideal method to simulate the complex relationship between tumor and microenvironment such as the angiogenesis process.[28] Moreover, xenograft models have not been very predictive of drug efficacy in cancer patients; activity in a particular histology in a xenograft tumor model does not closely correlate with activity in the same human cancer histology.[32] However, agents that have activity against a broad range of tumor types in xenografts have a better chance of clinical activity than those that do not. Major variables to consider in designing xenograft studies include the origin of the tumor, mutation status, site of implantation, size of the tumor at commencement of drug treatment, and dose and schedule of administration. Clearly, the future development of MTAs would benefit from more predictive in vivo models. Those based on target

Table 31-2 Steps in Discovery and Preclinical Development of Molecularly Targeted Therapy

Identify the molecular target against which an agent will be developed.
Validate the molecular target; confirm that affecting the target inhibits tumor growth/survival.
Screen for compounds that "hit" target (i.e., high-throughput screening).
Optimize compounds: select or modify structure to increase activity and selectivity while maintaining favorable pharmacologic drug properties.
Qualify assay methodology for drug-target effect, in in vitro and in animal models.
Evaluate lead drug(s) in vivo for efficacy and safety.
Prioritize and select drug candidate(s) for clinical testing.
Conduct necessary preclinical animal toxicology and pharmacokinetic studies to support investigational new drug status for first-in-human trial.

Table 31-3 Validation Criteria and Prioritization of New Targets for Drug Screening

High frequency of genetic or epigenetic deregulation of the molecular target or pathway in human cancer—indicates that the target or pathway is probably important in driving the disease.
Linkage of the deregulation to clinical outcome—strengthens case for causal involvement.
Evidence in a model system that the target pathway causes or contributes to the malignant phenotype—demonstrates a direct causal role in malignancy.
Demonstration of reversal of the malignant phenotype—provides greater confidence that modulation of the target by a drug will produce an anticancer effect.
Demonstration of "drugability" of the target (e.g., enzymes are generally much more druggable than are large-domain protein-protein interactions).
Availability of a robust, efficient biological test cascade to support the drug discovery program—to allow evaluation of lead compounds and to select a development candidate for preclinical toxicology testing and clinical trials.
Feasibility of establishing, validating, and running an affordable and robust high-throughput screen.
Potential for a drug design approach based on structural biology; such an approach, based on an x-ray crystallographic or nuclear magnetic resonance structure, can be highly complementary to a screening strategy.

Adapted from Aherne GW, McDonald E, Workman P: Finding the needle in the haystack: why high-throughput screening is good for your health. Breast Cancer Res 2002;4:148–154.

expression rather than histology promise better success, but this will require substantial additional testing.

CLINICAL DEVELOPMENT OF MOLECULARLY TARGETED AGENTS

Successful development of MTAs may require different strategies than those traditionally used for the development of conventional cytotoxic chemotherapeutic agents (Table 31-4).[33] Consequently, the discovery of an increasing number of molecularly targeted compounds has created major challenges in drug development, both for dose determination and efficacy evaluation. In animal models, many of these newer agents may show marked growth-inhibitory and antimetastatic effects without impressive tumor regression, properties commonly referred to as cytostatic. Although the specific effects of each class are dependent on the target or targets inhibited, in patients many are more likely to result in tumor growth inhibition rather than tumor regression. Pivotal clinical trials of sorafenib in renal cell and hepatocellular carcinoma, for example, substantiate the cytostatic properties of this small molecule VEGFR inhibitor, with results showing marked improvement in progression-free survival with minimal objective tumor response by RECIST criteria.[21,22]

Dose Determination

The primary objective of phase I trials of conventional cytotoxic agents is ordinarily to define maximum tolerated dose (MTD), under the assumption that the higher the dose the greater the antitumor activity (Fig. 31-3A). Thus, the dose recommended for phase II efficacy trials is typically the MTD. However, MTAs are generally less toxic and, because of their selectivity, may be effective at doses much lower than the MTD (Fig. 31-3B). MTAs act on highly specific targets differentially expressed or activated in cancer cells. Thus, they tend to spare normal tissue except at higher doses, resulting in a wide therapeutic index. Therefore, increasing the dose in a traditional phase I trial to the point of normal tissue tolerance (MTD) may be an irrelevant or nonachievable endpoint with an MTA. Rather, target inhibition may be a better endpoint, with the primary objective of determining the "optimal biologic dose," that is, the lowest dose that maximally inhibits the relevant target or pathway.[33–35]

Phase I trials intended primarily to determine a dose that optimally inhibits a target in tumor tissue usually involve pre- and post-treatment biopsies. However, the requirement for tissue biopsies is costly and hampers enrollment, because only patients with tumors

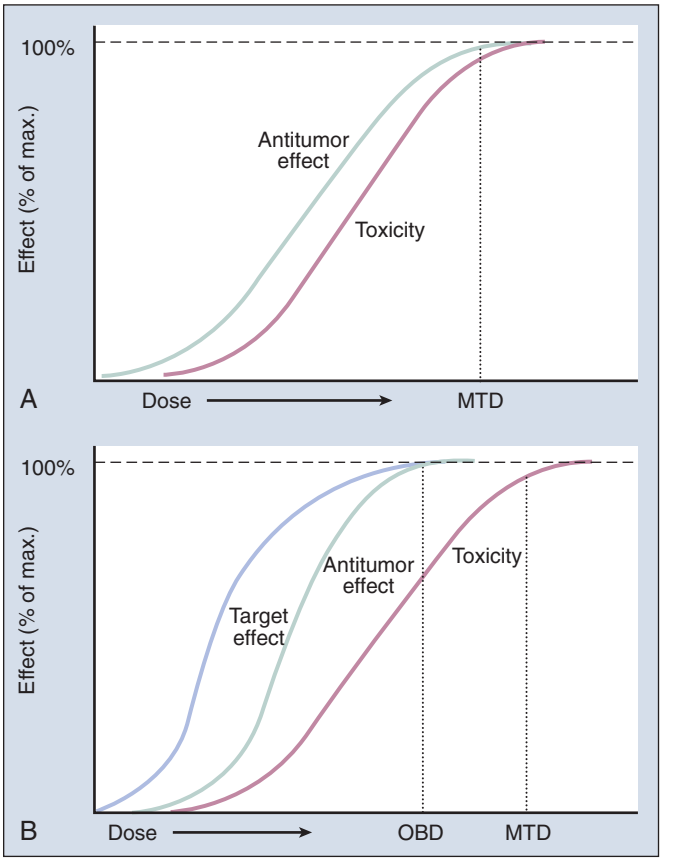


Figure 31-3 • **A,** Hypothetical dose-effect curves for the antitumor and toxic effects of a conventional nontargeted cytotoxic agent. The therapeutic index is narrow, with the maximum antitumor effect close to the maximal tolerable dose (MTD). **B,** Hypothetical dose-effect curves for the antitumor and toxic effects of an MTA. The therapeutic index is relatively wide, with the optimal biologic dose (OBD) antitumor dose occurring at a dose considerably lower than the MTD.

Table 31-4 Properties and Development of Nontargeted versus Molecularly Targeted Anticancer Agents

	Nontargeted Chemotherapy	Molecularly Targeted
Drug discovery	Empirical approaches; screening for compounds that inhibit tumor growth/survival	Target-based approaches; screening for compounds that hit tumor target
Antitumor effects	Cytotoxic; tumor shrinkage	May be cytostatic; growth inhibition
Host toxicity	Nonselective, toxic to many normal organ systems	Selective; depends on target(s) specificity; "off-target" effects
Therapeutic window	Usually narrow	Usually wider
Phase I primary endpoints	DLT and MTD; PK	Target inhibition and OBD; PK
Dosing	Intermittent	Intermittent or continuous
Phase II efficacy trial endpoints	Objective tumor response (tumor shrinkage)	Tumor response or progression-free survival
Phase II dose	Based on MTD	OBD
Patient selection	Histology	Target expression, if possible
Interval to clinical response	Relatively short (e.g., 4–8 weeks)	Variable

DLT, dose-limiting toxicity; MTD, maximum tolerated dose; OBD, optimal biologic dose; PK, pharmacokinetics.

accessible to biopsy are eligible, and not all otherwise eligible patients consent to the procedure. Therefore, in lieu of tumor biopsies, one strategy to evaluate target modulation and determine a biologically active dose is to use less invasive procedures involving target or biomarker assessment in surrogate tissue expressing the target, such as skin or peripheral blood mononuclear cells (PBMCs).[35–38] For example, demonstrating a "biologically effective dose" in PBMCs may serve as a guide in dose-finding trials. This approach was invaluable in the initial studies of the proteasome inhibitor bortezomib.[36] Because a sufficiently sensitive PK assay was not yet available, the study used PBMC proteasome levels as a bioassay surrogate. This turned out to be a successful method for dose determination pending a sensitive PK assay. Phase I trials could also use target modulation in surrogate tissue such as PBMCs to determine a dose level to start obtaining more invasive tumor biopsies, based on the premise that measurable effects in tumor tissue are not likely to occur at lower doses.[35]

However, this approach may not be adequate for dose determination with all types of molecularly targeted therapy. For example, a phase I trial of the alkylguanine DNA alkyltransferase depleting agent O^6-benzylguanine determined that substantially higher doses of the drug were required to inhibit the enzyme in tumor tissue as compared with PBMCs.[37] Thus, before relying on PBMCs or other potential surrogates for target effect in tumor tissue, authenticating studies should be done to directly compare the effects in the potential surrogate versus tumor tissue, preferably first performed in animal models and then confirmed in pre–phase I or phase 0 clinical trials.[39]

Another strategy to help define the optimal biologically effective dose is to incorporate into dose-finding trials noninvasive molecular and functional imaging, such as innovative magnetic resonance imaging (MRI) and positron emission tomography (PET).[40,41] Dynamic contrast enhanced MRI (DCE-MRI), which can measure tumor permeability and vascularity, may be a useful biomarker for dose determination in studies of angiogenesis inhibitors. For example, assessment of changes in tumor vascularity and permeability by DCE-MRI has been successfully used in phase I studies as a biomarker for defining pharmacologically active doses for small molecule tyrosine kinase angiogenesis inhibitors.[42,43] DCE-MRI is also applicable to the evaluation of early evidence of tumor responsiveness, a topic addressed later in this chapter.

Given the growing number of targeted agents in development and the complexities of determining a dose that yields optimal biologic activity based on target or biomarker inhibition rather than on toxicity, there is an increasing need for novel adaptive phase I trial statistical designs. One such design recommended for phase I trials of MTAs is based on the assumption that the target response in individual patients is a binary value (positive or negative) determined in each individual patient.[44] The goal of the design is to study a minimum number of patients to find a biologically adequate (rather than optimal) dose, with the intent to obtain sufficient data to move as quickly as possible from dose-finding to evaluating efficacy. Based on limited simulations, this type of design seems to perform adequately with only three or four patients treated at each dose level. The efficacy of this approach for dose determination for targeted agents warrants prospective evaluation in future clinical trials.[33,39,44]

However, to define a biologically effective dose it is essential to have a validated target (as defined previously) and a reliable and reproducible assay to evaluate for target inhibition. This is best accomplished by having a clear understanding of the dynamics and consequences of target inhibition, the degree of target effect required for tumor growth inhibition, whether the target must be inhibited continuously or intermittently, and the function of the target in normal cells. Thus, optimal clinical development of MTAs requires extensive preclinical studies, including better animal models that are predictive of eventual clinical effect and are applicable to thorough assay interrogation.[45] Following this, the drug and its effect on tumor (as evaluated by the assay) should preferably then be evaluated in first-in-human prephase I or "phase 0" studies before definitive phase I trials.[33,39]

In addition to the potential to start substantially earlier than traditional phase I trials, phase 0 trials provide a better opportunity to establish feasibility and qualify target assay methodology in limited numbers of human samples before embarking on studies that involve larger numbers of patients receiving higher and potentially toxic doses of the study agent (Table 31-5). Phase 0 trials characteristically involve rigorous preclinical development of assays for target modulation and PK analysis in advance of clinical investigation, and real-time analysis of patient samples incorporated into the clinical trial.

Table 31-5 Phase I versus Phase "0" Clinical Trials

	Phase I Trials	Phase "0" Trials
Primary endpoint	Establish maximum tolerated dose.	Target modulation or ability to image target of interest.
Dose escalation	Determine safety and toxicity.	Achieve desired systemic exposure or target modulation, allowing dose selection for future studies.
Preclinical biomarker studies	Not consistently performed before initiating the trial	Required to have plasma drug (pharmacokinetic) and preclinical biomarker (pharmacodynamic) assay development and assay qualification before the initiation of the clinical trial
Biomarker assays	Not performed consistently, most phase I trials do not emphasize pharmacodynamic markers	Biomarker assays and/or imaging studies are integrated to establish mechanism of action in actual patient samples.
Number of patients	Usually >20	10–15
Dosing	Multiple	Limited
Therapeutic benefit	None expected; however, tumor response is evaluated to permit continued dosing in case evidence of clinical benefit is found.	None
Tumor biopsies	Optional	Serial tumor biopsies required to evaluate drug effect on target(s)
Pharmacokinetic/ pharmacodynamic analysis	Samples are usually batched and analyzed at a later time point.	Real-time

Adapted from Kummar S, Kinders R, Rubinstein L, et al: Compressing drug development timelines in oncology using phase "0" trials. Nat Rev Cancer 2007;7:131–139.

Because these pilot prephase I studies involve a limited number of subjects and very limited drug exposure with no therapeutic intent, fewer preclinical toxicity data may be required for them to be initiated in accordance with the FDA guidance for Exploratory Investigational New Drug (IND) studies.[46] There are several types of studies that can potentially be conducted under the purview of an Exploratory IND. These include studies that provide important PK information (e.g., oral bioavailability), are designed to select the most promising lead agent from several candidates, determine whether a mechanism of action (e.g., target inhibition) observed in animal models can be observed in humans, and evaluate in vivo binding properties of novel imaging agents using extremely small doses of the test agent ("microdosing").

Another approach to determine an optimal dose of an MTA is to conduct a randomized phase II trial with a clinical response endpoint comparing two or more different doses. This approach may be necessary if dose-selection cannot rely on a biologic marker. However, if this design is to be effective, the agent must have some degree of clinical activity, yielding objective responses or affecting progression-free survival. Under these circumstances, the randomized phase II design is useful in selecting a maximally efficacious dose with the least amount of toxicity that is applicable to subsequent phase III trials.[47–49]

Efficacy Evaluation

Because of the expanding number of anticancer agents under development with novel mechanisms of action, there is an increased need to develop novel paradigms for demonstrating efficacy. A primary endpoint of objective response rate, considered standard for most phase II trials of traditional cytotoxic agents, is not adequate for targeted agents that produce growth inhibition without tumor regression.

Standard cytotoxic agents result in cell kill and eventual tumor shrinkage, whereas cytostatic agents inhibit tumor growth without direct cytotoxicity. MTAs tend to be more cytostatic than cytotoxic. As a result of their specificity and growth-inhibitory properties, the efficacy evaluation of these agents should apply different approaches than those commonly used for nontargeted cytotoxic chemotherapy (see Table 31-4).[34,50,51]

Phase II trials of nontargeted cytotoxics commonly use objective response rate as a measure of activity warranting further clinical evaluation. Furthermore, evidence of a therapeutic response to cytotoxic drugs is expected to occur relatively early in the course of treatment (e.g., after one to two cycles). MTAs have a wider therapeutic window, may require dosing for longer periods at low doses to be efficacious, may have maximum clinical effects in combination rather than as single agents, and may be cytostatic instead of cytotoxic. Because cytostatic drugs may not necessarily cause tumor shrinkage, the traditional criteria of objective tumor response may not be optimal in assessing efficacy.[50] This is exemplified by the clinical development of sorafenib. The single-agent rate of objective response, using RECIST criteria, with this multitargeted tyrosine kinase inhibitor is minimal (2% to 3%) in patients with advanced renal cell carcinoma. Yet a phase III trial of the agent in renal cell carcinoma resulted in a marked improvement in progression-free survival, forming the basis for FDA approval.[21] Similarly, sorafenib has minimal objective response activity (response rate < 3%) in hepatocellular carcinoma, but a phase III trial resulted in marked improvement in time to tumor progression and a 44% increase in overall survival.[22] If the main decision factor for further development had been objective tumor response, the true effectiveness of sorafenib may not have been established. For this reason, exploratory efficacy trials of molecularly targeted cytostatic agents increasingly include progression-free survival as a primary endpoint.

However, molecular heterogeneity and differences in patient and tumor characteristics make evaluation of progression-free survival difficult to interpret, particularly in relatively small exploratory studies without concomitant comparator controls. One trial design proposed to overcome some of these concerns is the randomized discontinuation design, which is considered a type of enrichment trial.[51,52] With one such design, all eligible patients receive a study agent for a defined period followed by restaging; patients with a predefined degree of tumor shrinkage remain on drug and those with progressive disease are taken off study; only those patients who show evidence of stable disease undergo randomization to receive either the study drug or placebo. Thus, the randomized population is enriched with sensitive patients, because only those patients without early drug failure continue on therapy. That all patients have the opportunity to receive the investigational drug is considered a major attraction of this study design.[52]

The application of the randomized discontinuation design or other types of novel screening designs in exploratory phase II trials may be particularly useful in the early development of a molecularly targeted cytostatic agent for which a dependable assay to select patients based on target expression is not available.[49,53] Furthermore, randomized phase II designs, in general, are applicable to exploratory trials evaluating two or more doses or schedules.[47,48,54,55]

Sometimes the approach taken to evaluate the efficacy (e.g., progression-free survival) of an MTA is to conduct a trial comparing the results of treatment with the targeted agent in combination with a standard agent or regimen to that with the standard regimen alone. The intent of such studies is to show superior efficacy with the combination. The "add-on" approach is useful for the evaluation of agents expected to have little efficacy when used alone, and is particularly attractive because all patients receive an active agent or regimen. For example, these designs were critical to the successful development of trastuzumab in breast cancer and bevacizumab in colorectal cancer.

The approach, however, is not without significant risk of failure, as was the case with the randomized trials of gefitinib and erlotinib combined with chemotherapy in non-small-cell lung cancer.[56,57] Reasons for failure include suboptimal dose of the MTA, antagonism between the MTA and the chemotherapy, lack of synergistic or additive antitumor effects, or dilution of the study population with patients having insensitive tumors.[58] Such designs should only be considered if there is a reasonable estimate of the single-agent activity of the MTA in the specific patient population to be studied, the agent is administered at an optimally efficacious dose, and the combination is supported by a strong scientific rationale. Furthermore, for those agents with targets expressed in only a small proportion of patients, the study should be enriched with patients who have tumors that express the target or have another marker predictive of activity.

Use of Pharmacodynamic Markers

Trial designs for exploratory studies of MTAs may need to rely more on PD endpoints as markers or surrogates for antitumor effect than on toxicity or objective tumor response. This requires the development of PD assays that reliably measure drug-target effect. To do so, the assay must be accurate, precise, reproducible, sensitive, and robust, as well as having a dynamic range tight enough to detect differences between baseline and post-treatment values (Table 31-6).[39] Furthermore, the assay methodology assessing drug effect on the target should be developed and authenticated first in in vivo animal models and then in prephase I or phase 0 clinical trials.

The development of mechanism-based biomarker assays would significantly expedite drug development, because such assays aid in determining early on if a drug modulates the target. This approach could also help select the lead agent from a group of compounds, help determine dose, guide patient selection and assessment of response, and provide the basis for combination trials.[33,59–61] However, this requires having a validated target, understanding the biology of

Table 31-6 Pharmacodynamic Assay Glossary

Accuracy: The ratio of the observed assay readout to the actual quantity of bona fide analyte present at any point within the dynamic range of the assay. Traditional methods of establishing accuracy include recovered fraction of a known mass of the analyte added to a clinical specimen (spike recovery), and measurement of interferences from materials likely to be found in a typical specimen.

Dynamic range: The range of concentrations in which the assay is capable of accurately measuring analyte; ideally concentrations present in both treated and untreated specimens without additional specimen dilutions or processing steps.

Precision: A measure of variability of results for a specimen around the determined value, performed in the range in which measured values approximate the true value; usually accomplished by repeated assays of a set of specimens by multiple technicians on multiple days.

Reproducibility: The closeness of agreement between independent results obtained with the same method on identical test material but under different conditions (different operators, different apparatus, different laboratories, and/or after different intervals of time). It is measured as the total imprecision of the assay from all sources, measured at several points within the dynamic range of the assay. This imprecision must be much less than the clinical endpoint selected: that is, if an undeveloped assay had a total imprecision of about 40%, this would make measurement of a 50% effect impossible.

Robustness: The assay must be transferable to other laboratories. The results obtained from the assay must be stable over time.

Sensitivity: Analytically, this is the slope of the standard curve. The assay should be sensitive enough to allow repeat determinations of the same specimen.

Adapted from Kummar S, Kinders R, Rubinstein L, et al: Compressing drug development timelines in oncology using phase "0" trials. Nat Rev Cancer 2007;7: 131–139.

target inhibition, and defining optimal target inhibition. The evaluation of target expression is demanding, because it requires the development of a reliable assay to measure the target, as exemplified by the comparative value of the measurement of Her2/neu by immunohistochemistry versus fluorescence in situ hybridization before selection for trastuzumab therapy.[62,63]

Adequate clinical evaluation of PD endpoints as markers of drug-target effect in tumor tissue in exploratory trials of MTAs requires pre- and post-treatment biopsies. To do this effectively, such trials require careful attention to the use of standardized and validated procedures for tissue acquisition, handling, processing, and assay methodology. This is critical, because these factors could significantly influence biologic processes and significantly increase inter- and intrapatient variability, making the interpretation of the results problematic. In addition, different tissue handling procedures may change the expression or level of activity of targets, such as enzymes or protein substrates. If care is not taken to stabilize the analyte immediately, it may degrade completely and produce a false positive effect. The standard operating procedures from tissue acquisition to target assay methodology should be developed and qualified before initiating clinical trials.

As discussed previously, to minimize the need for invasive tumor biopsies in subsequent trials, early exploratory studies should evaluate effects in other tissues such as skin or PBMCs as potential surrogates. Exploratory efficacy trials should also utilize newer techniques like molecular profiling of the tumor and normal tissue, and there should be a better understanding of the effects of inhibiting the target both in tumor and host tissue. As such, these approaches depend heavily on the availability of clinical and laboratory based investigators and their willingness to collaborate.

RATIONAL USE OF FUNCTIONAL AND MOLECULAR IMAGING

There is an increasing interest in utilizing novel imaging technologies in the development of MTAs.[64,65] Molecular imaging has the potential to monitor both normal and abnormal biochemical and physiologic parameters in individual patients. Unlike anatomic imaging, molecular imaging displays biochemical and physiologic abnormalities underlying disease, rather than the structural consequences of these abnormalities. Functional and molecular imaging can be helpful in phase I studies for dose determination, as discussed previously, and may be applicable as noninvasive tools to detect drug-target effect, as well as to provide early evidence of efficacy. It may also prove useful in patient selection.

Detecting and monitoring responsiveness to a cytostatic agent is more difficult than doing so with a cytotoxic. Clinical efficacy of cytotoxic agents is usually associated with relatively early evidence of tumor shrinkage that is easily discernable by anatomic imaging with computed tomography (CT) or MRI. Conversely, a molecularly targeted agent could halt tumor growth without demonstrable changes visible by CT or MRI; but evidence of response may be detectable with the use of functional imaging, such as [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET). Uptake of the glucose analogue FDG by tumor cells is a marker of glucose metabolism, number of viable cells, and the level of cell proliferation in a tumor mass. Thus, treatment that causes metabolic changes associated with inhibition of tumor cell proliferation or that causes cell death should have a relatively rapid affect on the degree of FDG uptake. Decrease in the maximum standardized uptake value (SUV_{max}) on FDG-PET was found to be an early predictor of response of advanced GIST to imatinib therapy.[66,67] These changes can occur as early as 24 to 48 hours after initiating imatinib and predict for objective response or stabilization of disease as determined subsequently by CT scanning. Conversely, failure to achieve a decrease in FDG-PET uptake following treatment with imatinib is predictive of a poor clinical response for patients with GIST.

DCE-MRI is another noninvasive modality for evaluating pharmacologic response to MTAs; it is particularly useful in the development of angiogenesis inhibitors. Measurement of DCE-MRI parameters pre- and post-treatment has proven helpful in evaluating changes in tumor blood flow and vascular permeability in early-phase trials of a variety of antiangiogenesis inhibitors including the anti-VEGF antibody bevacizumab[68] and small molecule VEGFR inhibitors.[42,69] DCE-MRI provides the potential to evaluate not only treatment-related changes in tumor vasculature and determination of PK-PD relationships but may also be a relevant marker for predicting clinical outcome.[42,70]

Another promising area of mounting interest is the use of PET and novel imaging probes to visualize cancer targets and processes in vivo.[60] These include a wide variety from small molecules, peptides, and antibodies (Table 31-7). The processes that can be imaged include cell proliferation, angiogenesis, apoptosis, hypoxia, PK, and multidrug resistance. In addition, probes exist or are in development to image tumor cell receptors such as EGFR, HER2, and bombesin, to name a few. Future progress in the clinical application of molecular imaging depends on developing probes that have better sensitivity and specificity as well as probes that increase the signal-to-noise or spatial resolution of molecular imaging devices.

3′-[^{18}F]Fluoro-3′-deoxythymidine PET is particularly useful as an in vivo marker of tumor cell proliferation and for monitoring response to antiproliferative therapy.[71] Finally, there is increasing interest in the use of optical imaging by spectral fluorescence enhancement because of its sensitivity and ability to detect very small clusters of cancer cells.[72] However, optical imaging has the disadvantage of being limited to settings where direct imaging is possible (e.g., intraoperative or endoscopic), because whole-body imaging is not yet feasible. Unquestionably, noninvasive imaging will have increasing

Table 31-7 Imaging Probes Used to Visualize Molecular Targets and Processes in Cancer

Molecular Target/Process	Imaging Probes
SMALL MOLECULE PROBES	
Proliferation	2-[^{11}C]Thymidine, FLT, 1-(2′-deoxy-2′-fluoro-β-D-arabinofuranosyl) thymine, 2′-deoxy-2′-fluoro-5-fluoro-1-β-D-arabinofuranosyluracil, [^{124}I]iododeoxyuridine
Apoptosis	[^{99m}Tc]Annexin V, [^{18}F]Annexin V
Hypoxia	[^{18}F]misonidazole, 2-(2-nitro-1H-imidazol-1-yl)-*N*-(2,2,3,3,3-pentafluoropropyl) acetamide, fluoroerythronitroimidazole, fluoroetanidazole, diacetyl-bis(*N*^{4}-methylthiosemicarbazone) copper (II), [^{124}I]iodo-azomycin-galactoside, fluoroazomycinarabinofuranoside
Pharmacokinetics	5-Fluorouracil, *N*-[2-(dimethylamino)ethyl]acridine-4-carboxamide,1,3-bis(chloroethyl)-1-nitrosourea, [^{11}C]temozolomide, [^{13}N]cisplatin
Multidrug resistance	[^{99m}Tc]sestamibi, [^{11}C]verapamil, [^{11}C]daunorubicin, [^{11}C]colchicine, [^{99m}Tc]methoxyisobutylisonitrile
Breast cancer (ER)	FES
Prostate cancer (androgen receptor)	FDHT
PEPTIDE PROBES	
Somatostatin/somatostatin receptor	[^{90}Y]1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-Tyr^3-octreotide, [^{111}In]diethylenetriamine pentaacetic acid-D-Phe(1)-octreotide, [^{90}Y]1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-lanreotide/vapreotide
Vasoactive intestinal peptide/vasoactive intestinal peptide receptor-1	^{123}I-labeled vasoactive intestinal peptide, [^{99m}Tc]TP3654
Bombesin, gastrin-releasing peptide/ gastrin-releasing peptide receptor	^{99m}Tc-labeled bombesin
Cholecystokinin, gastrin/cholecystokinin receptor	^{111}In-labeled diethylenetriamine pentaacetic acid-minigastrin
Angiogenesis	^{18}F-labeled Arg-Gly-Asp peptide targeted to $\alpha_v\beta_3$ integrin
Cathepsin proteases	Prosense (VM102)
ANTIBODY PROBES	
Angiogenesis	Paramagnetic nanoparticles using antibodies to integrin $\alpha_v\beta_3$, the integrin $\alpha_v\beta_3$ ligand, vascular cell adhesion molecule 1, E-selectin
CEA	Arcitumomab (CEAscan), satumomab
Prostate-specific membrane antigen	Capromab pendetide (ProstaScint)
CD20	^{131}I-labeled tositumomab (Bexxar), ^{90}Y-labeled ibritumomab tiuxetan (Zevalin) (FDA approved)
CD22	Bectumomab

CEA, carcinoembryonic antigen; FDHT, 16-fluoro-5-dihydrotestosterone; FES, 16α-fluoroestnadiol-17β; FLT, 3′-[18F]fluoro-3′-deoxythymidine.

Adapted from Kelloff GJ, Krohn KA, Larson SM, et al: The progress and promise of molecular imaging probes in oncologic drug development. Clin Cancer Res 2005;11:7967–7985.

importance in the development and application of molecularly targeted therapy.

PATIENT SELECTION

An important consideration in the enrollment of patients on exploratory efficacy trials of MTAs is the use of patient selection that optimizes the chance for a positive effect. This is not feasible unless patients enrolled have tumors that express or have a high probability of expressing the target. Until recently, essentially all phase II trials have evaluated a drug in tumors based on organ of origin with further categorization by histologic type (e.g., breast cancer, non-small-cell lung cancer). The presumption is that a given histologic type within an organ site represents a relatively uniform disease entity. However, there is increasing evidence that tumors are very heterogeneous at the molecular level within any given histologic type in a particular organ and that genetic variations in the tumor may significantly affect drug sensitivity. Clearly, patient selection beyond organ site and histologic type is becoming increasingly important in drug development.

Good examples of patient selection based on molecular phenotype include the use of the estrogen and progesterone receptor expression and HER2/neu expression to select breast cancer patients for treatment with selective estrogen receptor modulators (such as tamoxifen) and trastuzumab, respectively. Another example is the use of EGFR expression to identify patients with colorectal cancer amenable to treatment with cetuximab, an anti-EGFR monoclonal antibody FDA approved in this indication.

Further support for selection based on molecular phenotype is the exceptional responsiveness of non-small-cell lung cancer patients who have exon 19–21 *EGFR* gene mutations to the small molecule EGFR tyrosine kinase inhibitor gefitinib.[73] Because these mutations occur in only about 8% of non-small-cell lung cancer patients, the potential benefit of gefitinib in this small proportion of patients can be missed in a group of unselected patients, unless an extraordinary number of patients are studied (Table 31-8).[58] Similarly, exon 11 mutations of c-kit in GIST[4] and T315I bcr/abl mutations in CML,[74] confer sensitivity and resistance to imatinib, respectively.

Thus, it is increasingly important when designing phase II clinical trials of MTAs to consider the effect of molecular heterogeneity on drug efficacy.[75] For example, to maximize the chance of success in non-small-cell lung cancer trials of EGFR tyrosine kinase inhibitors, enrollment should be restricted to patients with a reasonable proba-

Table 31-8 Number of Patients Required for Randomization in Trial of a Target-Directed Agent*

Percent of Patients with Target in Study	Hazard Ratio for Benefit in Patients with Target		
	1:3	1:5	2:0
10	32,000	11,000	3,900
30	3,600	1,800	600
50	1,700	780	280
70	900	400	150

*The model makes several assumptions: all patients are eligible regardless of target expression, only patients with the target benefit from treatment, target expression does not affect prognosis, lack of target does not result in a negative effect with treatment, median survival is about 10 months, about 100 patients are entered per month over 1–6 years and are followed up for 1.5–2 years, and the study has a power of 0.8 (a one-sided α of 0.05).

Data from Dancey JE, Freidlin B: Targeting epidermal growth factor receptor—are we missing the mark? Lancet 2003;362:62–64.

bility of responding, for example those with tumors that are EGFR positive by immunohistochemistry, have increased numbers of copies of the *EGFR* gene, or where the presence of EGFR activating mutations can be demonstrated.[76] Another example is evaluating poly(ADP-ribose) polymerase inhibitors in breast and ovarian cancer patients with *BRCA1–BRCA2* mutations, who may be a uniquely sensitive patient population.[77]

RATIONAL APPROACHES TO COMBINATION THERAPY

An increasing number of MTAs in development have some clinical activity against selected types of cancer. However, with few exceptions, such as imatinib in the treatment of CML and GIST, MTAs have limited effectiveness as single agents and any clinical benefit is restricted to a relatively small proportion of patients. Consequently, there is a clear need to improve the effectiveness and utility of MTAs in the treatment of the vast majority of malignancies. One approach to improve the therapeutic potential of MTAs is to use them in combination with other agents or modalities (Table 31-9).

As noted previously, the use of MTAs in combination with standard chemotherapy has met with mixed success. Among the successes are trials demonstrating improved survival with the addition of trastuzumab in breast cancer[63] and bevacizumab in colorectal[19,78] and non-small-cell lung cancer.[79] Among the failures are randomized trials of gefitinib and erlotinib combined with chemotherapy in non-small-cell lung cancer.[56,57] The reasons why these latter trials failed to show superiority of the combination over chemotherapy alone are not clear, but they include the possibility of suboptimal dosing (as may have been the case for gefitinib), antagonism with the chemotherapy agents, or dilution of the study population with patients having insensitive tumors.[58] Consequently, there is a need to better elucidate these variables in the future using reliable predictive preclinical models and appropriately designed early-phase clinical trials in advance of large phase II–III clinical trials.

There is increasing interest in developing MTAs in combination with radiotherapy based on the premise that some may function as effective radiation sensitizers or modulators without increasing normal tissue toxicity. Radiation can activate multiple cellular processes and signaling pathways, which in turn can regulate radiation-induced cell death.[80] For example, radiation-induced signaling through growth factor receptors such as EGFR may activate multiple downstream compensatory signals that provide radioprotection.[81] In addition, radiation increases the expression of EGFR in cancer cells, overexpression of EGFR correlates with radiation resistance, and blocking EGFR signaling sensitizes cells to radiation effects.[82,83] Furthermore, clinical data support the radiation-sensitizing effects of EGFR inhibition. For example, the administration of radiotherapy in combination with the anti-EGFR monoclonal antibody cetuximab in patients with head and neck cancer results in a significant improvement in local tumor control and reduced mortality without increased toxicity as compared with radiation alone.[84]

Table 31-9 Strategies Combining Molecularly Targeted Anticancer Agents with Other Modalities

Combination Strategies	Potential Mechanism
MTAs plus cytotoxic therapy	Modulate targets involved in tumor sensitivity/resistance or repair mechanisms.
Combination with chemotherapy	
Combination with radiotherapy	
Two or more MTAs	
Antibody directed at ligand or receptor plus a small molecule TKI directed at the same receptor (e.g., anti-VEGF antibody plus VEGFR TKI)	Maximizes target inhibition.
Agents that inhibit two or more signal transduction molecules in the same pathway (e.g., EGFR TKI plus RAF inhibitor)	Maximizes pathway inhibition.
Agents that inhibit parallel pathways (EGFR inhibitor plus HER2 inhibitor)	Maximize tumor inhibition by affecting multiple cellular mechanisms.
Agents that inhibit a target and a compensatory feedback loop (e.g., mTOR inhibitor plus an Akt inhibitor)	Maximize tumor response by inhibiting compensatory resistance mechanisms.
Agents that target the tumor microenvironment/vasculature plus an agent directed against tumor cell proliferation	Maximize clinical benefit by inhibiting tumor cell proliferation, invasion and metastasis.
Epigenetic remodeling agents (e.g., DNA methylation inhibitors; histone deacetylase inhibitors) used in combination or in concert with agents directed against a re-expressed target	Enhance restoration of expression of tumor suppressor genes, apoptotic mechanisms, or tumor antigens.
MTA plus surgery	
Administer MTA following complete anatomic resection	Maximize benefit by targeting minimal residual disease.

MTA, Molecularly targeted anticancer agents; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor.

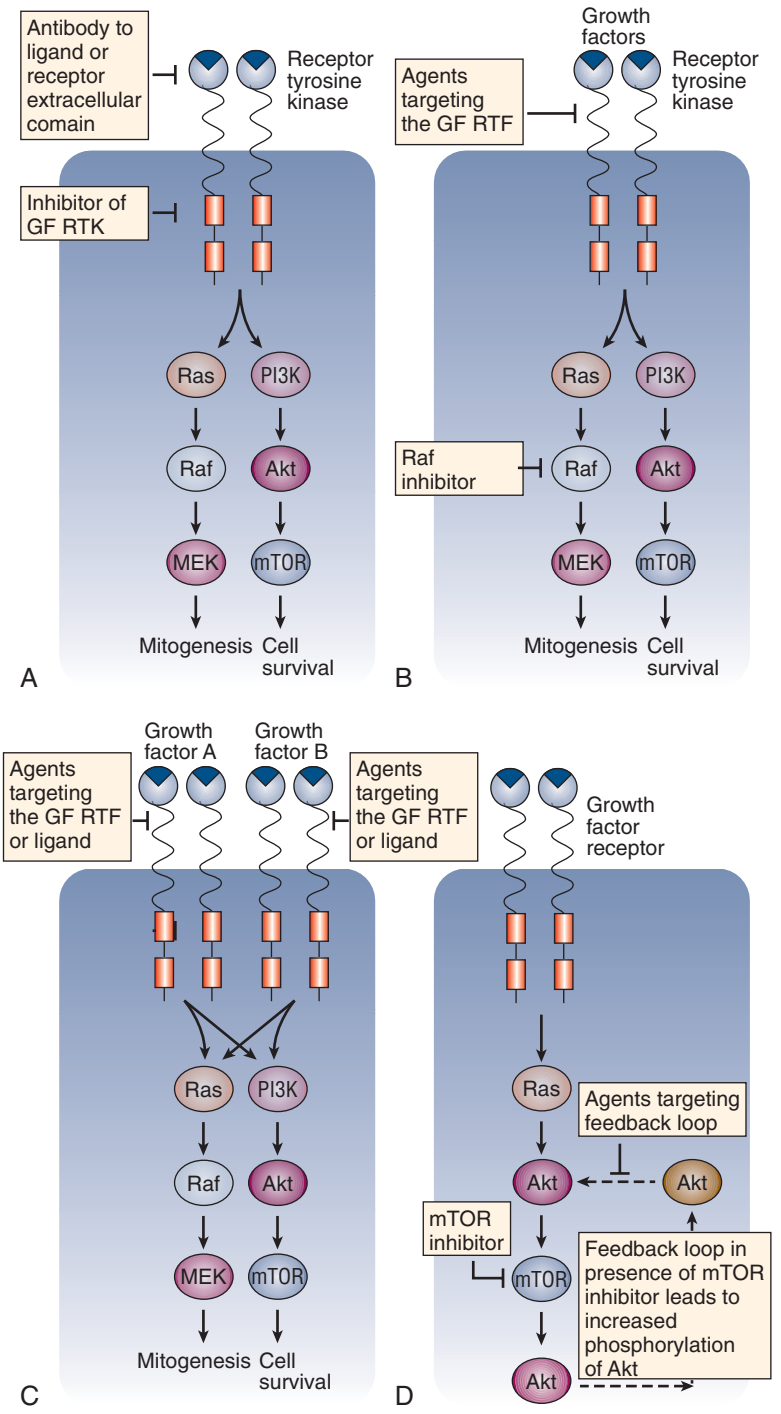


Figure 31-4 • **A,** Maximize inhibition of a target such as a growth factor (GF) receptor by inhibiting both receptor-ligand binding and tyrosine kinase activity. **B,** Maximize inhibition of a pathway by inhibiting a series of signaling components within the pathway. **C,** Inhibit parallel pathways by inhibiting two growth factor receptors or inhibiting downstream components in parallel pathways. **D,** Inhibit a target and the feedback loop that results in resistance. MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; RTK, receptor tyrosine kinase. (From Dancey JE, Chen HX: Strategies for optimizing combinations of molecularly targeted anticancer agents. Nat Rev Drug Discov 2006;5:649–659.)

Although the results with cetuximab plus radiation in head and neck cancer are very encouraging, the use of an MTA directed at a single target may not be sufficient for optimal radiation sensitizer/modulator effects, because many pathways and processes can regulate radiation-induced cell death. A potentially more effective approach is to target many radiation response–regulatory molecules. One recent line of research focuses on the role of the molecular chaperone heat shock protein 90 (Hsp90), because Hsp90 has several client proteins, many of which are involved in signal transduction and critical to the regulation of radiosensitization. Hsp90 inhibition destabilizes client proteins, leading to their ubiquitination and proteasomal degradation. Preclinical in vitro and in vivo experiments demonstrate that the Hsp90 inhibitor 17-(dimethylaminoethylamino)-17-demethoxygeldanamycin (17-DMAG) sensitizes tumor cells to the effects of radiation therapy, possibly by abrogating radiation-induced G_2 - and S-phase arrest.[85] The potential effectiveness of 17-DMAG and other agents that modulate multiple signal transduction pathways and processes is under clinical investigation.

Because molecular abnormalities in cancer are usually complex and involve multiple processes and pathways responsible for tumor cell proliferation and survival, the likelihood that hitting any one specific target will have a major antitumor impact is relatively low. Consequently, there is considerable interest in developing combinations of MTAs that strategically hit two or more critical targets with

the expectation that such regimens will have more pronounced antitumor effects.[9] However, given the large number of targets and MTAs in development, the number of potential combinations is almost limitless. Thus, the design of clinical trials evaluating MTAs in combination should not be empiric but based on a sound scientific rationale. Examples of rational combinations are those that maximize inhibition of a single target or pathway, those that inhibit two or more parallel cellular processes or pathways, those that inhibit tumor cellular processes and the microenvironment in concert, and those that use epigenetic remodeling agents to increase the expression of a target (Fig. 31-4 and see Table 31-9). In regard to the last example, inhibitors of DNA methyltransferase and histone deacetylase are being studied alone and in combination to restore the expression of tumor suppressor genes and other genes silenced by DNA methylation, including for example hormone receptors and tumor antigens, with the intent to make tumor cells more sensitive to targeted hormonal and vaccine therapy, respectively.[86]

An increasing number of clinical trials are evaluating combinations of two or more MTAs; these trials have recently demonstrated greater than expected level of responsiveness than treatment with either agent alone. Such is the case with the combination of the anti-VEGF antibody bevacizumab plus the VEGFR/RAF kinase inhibitor sorafenib in patients with advanced ovarian cancer.[87] Another promising combination is bevacizumab plus erlotinib in non-small-cell lung cancer.[88] Because this is a very promising area of research, many additional studies exploring rational combinations of MTAs are underway.

The potential advantages of using two or more MTAs in combination are clear. However, another approach to disrupting multiple molecular targets is to design a single agent with specificity against multiple targets of interest. One successful example is the small molecule HER2/EGFR inhibitor lapatinib, an agent that recently received FDA approval for the treatment of advanced breast cancer.[89] Incentives for pharmaceutical companies to take this latter approach are to avoid complex trial designs that may be necessary to isolate the effects of each agent, as well as complicated intellectual property negotiations with another company. Regardless of whether developing single agents with multiple targets or combinations of agents that focus on a limited number of targets, it is important to minimize the risk of toxicity if possible by avoiding overlapping or off-target toxicity.

CONCLUSIONS AND FUTURE DIRECTIONS

Recent advances in cancer genetics, biology, and drug discovery, as well as an enhanced capacity to characterize tumors at the molecular level have created many opportunities for improved treatment of malignancy and accelerated development of new molecularly targeted therapeutics. The expansion of MTAs with more selectivity and less toxicity than conventional chemotherapy over the past decade has been remarkable. However, this paradigm shift has presented new challenges.

The development of MTAs requires different strategies than those traditionally applied to nontargeted conventional chemotherapy. Empirical methods used in the past for the development of standard agents are mostly inadequate for the development of MTAs. Rather, optimal development of MTAs from drug discovery to clinical testing requires the integration of innovative methods that are mainly target based. Furthermore, novel clinical trial designs have evolved with the introduction of MTAs. Most phase I trials of MTAs should have as a primary objective the determination of a recommended phase II dose based on optimal target modulation, because escalation to MTD may not be needed or feasible; however, accomplishing this successfully requires the development of reliable procedures for tissue acquisition and handling and reproducible authenticated assay methodologies to measure target modulation. These target assay procedures are best performed in preclinical in vitro and in vivo models and, if feasible, in phase 0 clinical studies in a limited number of patients in advance of large, more definitive trials.

Another challenge is designing clinical trials that sufficiently evaluate the efficacy of MTAs administered alone or in combination. Because many MTAs are more cytostatic than cytotoxic, objective tumor response defined by RECIST criteria may not be adequate. In addition, it is increasingly apparent that it may be better to base patient selection on target expression rather than on histology and organ site. There is also an increasing appreciation of the value of integrating innovative molecular and functional imaging technologies into early-phase clinical trials as noninvasive means for assessing target modulation, dose determination, patient selection, and early evidence of clinical response.

The development of MTAs has taken cancer therapeutics further on the road of personalized medicine. The major challenge in further advancing and refining these agents lies in understanding them within the context of networks in the cancer cell as well as in association with similar intracellular networks within the tumor microenvironment at both the primary and metastatic sites. The evaluation of the efficacy of MTAs must be based on this complex analysis of the target within the patient. Progressive advancements in molecularly targeted therapy required to meet this challenge are expected in the near future with the development of preclinical models more predictive of human outcome, applications of rationally designed MTA combination therapy, and the more effective integration of molecular imaging and profiling into clinical trials.

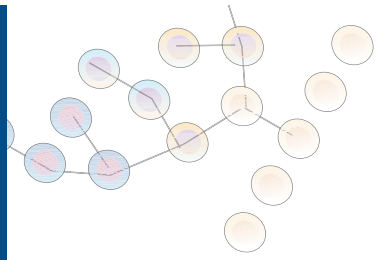
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32 Hematopoietic Stem Cell Transplantation

Michael R. Bishop and Steven Z. Pavletic

SUMMARY OF KEY POINTS

- Allogeneic or autologous hematopoietic stem cell transplantation (HSCT) is established and curative therapy for many patients with high-risk hematologic malignancies and a critical part of their treatment algorithms.
- Hematopoiesis and immune function can be restored after marrow ablative therapy with hematopoietic stem cells obtained from the bone marrow, peripheral blood, or fetal cord blood.
- The major complication and contribution to mortality and morbidity of allogeneic transplants is acute and chronic graft-versus-host disease (GVHD), which occurs in about 50% of patients; however, most patients ultimately are able to discontinue systemic immunosuppression. GVHD also contributes to the immune-mediated graft-versus-tumor effects. Adequately assessing risk and benefits is a critical part of therapeutic decision-making when deciding whether to recommend transplantation.
- The use of allogeneic transplantation to treat malignancy is limited by lack of a donor—only one fourth to one third of Americans have a human leukocyte antigen (HLA)-matched sibling. However, the unrelated marrow donor volunteer registry continues to grow, and chances of finding a matched unrelated donor today are about 50%; with improving techniques, results of matched unrelated donor transplants today are similar to outcomes when using sibling donors.
- Reduced-intensity (i.e., mini- or nonmyeloablative allogeneic) transplants use less-intensive preparative regimens aimed at the host T cells in an attempt to allow engraftment (and the subsequent immune attack on the cancer) while reducing the early toxicity and mortality. Such procedures permit allogeneic transplantation in older patients (up to age 70 years), in whom cancer is more common, who would not have been eligible for conventional high-dose transplant treatments.
- Autologous transplantation has become standard therapy for recurrent Hodgkin's disease and chemotherapy-sensitive aggressive non-Hodgkin's lymphoma, consolidation of initial response in multiple myeloma, some pediatric malignancies, and refractory testicular cancer. Although autologous transplant is much safer than allogeneic HSCT, the limiting problem is tumor recurrence.
- Adequate supportive care, and prevention and treatment of infections by a well-coordinated multidisciplinary team of subspecialists are critical for a successful transplant procedure. Due to increasing number of long-term survivors after transplantation, oncologists should be aware of late effects of transplantation therapy such as chronic GVHD, second cancers, endocrine, bone metabolism, or other organ system effects.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is the process and intravenous infusion of hematopoietic stem and progenitor cells to restore normal hematopoiesis and/or treat malignancy.[1,2] The term *HSCT* has replaced the archaic term *bone marrow transplantation* (*BMT*), because hematopoietic stem cells can be derived from a variety of sources other than the bone marrow, including the peripheral blood and umbilical cord blood.[3,4] Stem cells used for HSCT are of hematopoietic origin; the distinction is made due to the growing interest in using more primitive stem cells for regenerative therapy due to their plasticity and unique biologic characteristics.[5] Hematopoietic stem cells are further characterized according to their source, that is, from whom they are obtained (Table 32-1). Hematopoietic stem cells obtained from the patient him- or herself are referred to as *autologous*.[1,3] Hematopoietic stem cells obtained from an identical twin are referred to as *syngeneic HSCT*, and hematopoietic stem cells obtained from someone other than the patient or an identical twin are referred to as *allogeneic*. HSCT is most commonly used to restore normal hematopoiesis following the treatment of cancer with chemotherapy and/or radiation at doses that result in severe, often irreversible, damage to bone marrow. The healthy new cells transplanted from a syngeneic or allogeneic source also may allow the restoration of an intact immune system, provide an antitumor effect or, in the case of HSCT for congenital diseases, provide cells that are no longer deficient in certain vital components.

The clinical application of HSCT originated in the identification of the severe myelosuppressive effects of radiation that were observed among nuclear bomb survivors at Hiroshima and Nagasaki.[6] Intensive research efforts were made at that time to develop methods to reverse the myelosuppressive effects of radiation, including the infusion of bone marrow.[7–11] In 1949, Jacobson and colleagues[7] at the University of Chicago reported on the effects of shielding the spleen of mice from lethal does of irradiation. Shielding of the spleen protected nearly all mice at a total body irradiation dose of 700 cGy, whereas unshielded mice all died from marrow aplasia. As the dose of radiation was raised to 1050 cGy, approximately one third of the shielded mice survived, and a dose of 1200 cGy was lethal to all mice. At autopsy, these latter radiation groups were found to have died from fibrosis of the lungs, liver, and kidneys. The authors

Table 32-1 Comparison of Allogeneic and Autologous Hematopoietic Stem Cell Transplantation

	Allogeneic	Autologous
Oldest age to which applicable		
Myeloablative	40–60 y	60–70 y
Nonmyeloablative	65–75 y	N/A
Major problem in finding a donor	Finding a closely HLA-matched sibling or unrelated donor	Ability to collect sufficient numbers of hematopoietic progenitor cells uncontaminated by tumor cells
Most important complication	Graft-versus-host disease	Relapse of original disease
Anti-cancer effect of infused cells	Proved or suspected in a number of malignancies	Probably no
Most commonly treated cancers	Acute leuekemias	Multiple myeloma
		Non-Hodgkin's lymphoma
		Hodgkin's disease

Modified from Armitage JO: Bone marrow transplantation. N Engl J Med 1994;330:827.

unfortunately concluded that shielding the spleen was protecting a humoral factor that affected hematopoiesis; however, it subsequently was determined that early hematopoietic progenitors actually were protected from the effects of radiation. From these early studies, theories evolved into the concept that radiation and chemotherapy could be administered at controlled yet highly myelosuppressive doses, which were capable of eliminating malignant hematopoietic clones, and normal hematopoiesis could be re-established by the infusion of normal bone marrow. Early animal studies of HSCT were thwarted by incompatibility between bone marrow recipients and donors, which led to a high degree of graft rejection.[11] Among animals that did not reject their marrow grafts, a syndrome of weight loss, alopecia, diarrhea, and eventually death was commonly observed. This syndrome, originally referred to as "runting" disease, now is referred to clinically as *graft-versus-host disease* (GVHD) and is discussed in more detail later in this chapter.[12] Understanding of the major histocompatibility complex (MHC) and human leukocyte antigens (HLA) as the major determinants of graft rejection, which was developed subsequently, significantly advanced laboratory studies and clinical application of allogeneic HSCT.[13]

The first successful clinical bone marrow transplantation trials among patients with severe combined immunodeficiency disorders and advanced acute leukemias were reported in the late 1960s and early 1970s (Fig. 32-1), after clinical methods to determine HLA were developed, permitting the "matching" of bone marrow donors and recipients.[1,11] Subsequently, in the late 1970s, reports were published on the successful use of high-dose chemotherapy and autologous BMT to treat patients with advanced lymphomas.[14] Today allogeneic HSCT is a standard treatment for many immunodeficiency states, metabolic disorders (e.g., Hurler's syndrome), and defective hematopoietic states (e.g., severe aplastic anemia, thalassemia). Autologous HSCT currently is being investigated in nonmalignant diseases, including autoimmune diseases (e.g., multiple sclerosis), and the emerging field of regenerative medicine, which takes advantage of the plasticity of stem cells to repair defective or damaged tissues (e.g., cardiac muscle after a myocardial infarction).[15,16] Both autologous and allogeneic HSCT are standard treatment options for a variety of hematologic malignancies and selected solid tumors. This chapter focuses primarily on the rationale for the application of HSCT in the treatment of malignancy.

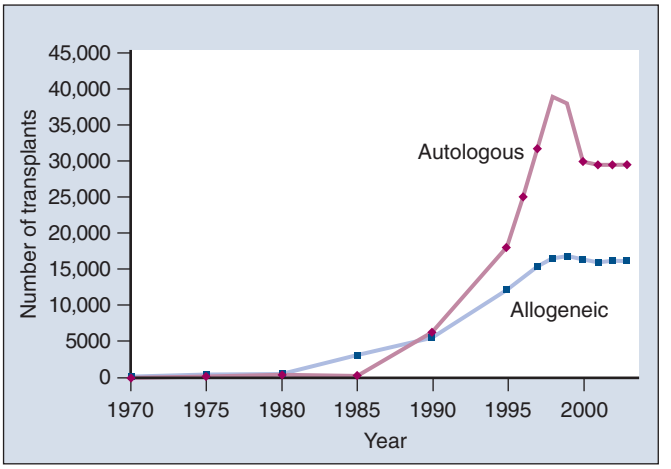


Figure 32-1 • Annual numbers of blood and marrow transplants worldwide, 1970–2003. (Data from the Center for International Blood and Marrow Transplant Research, Milwaukee, WI.)

TYPES OF HEMATOPOIETIC STEM CELL TRANSPLANTATION

The type of HSCT that a patient receives—allogeneic versus syngeneic versus autologous—usually is predetermined, because very few patients have an identical twin (i.e., syngeneic), and the availability of an allogeneic donor is limited even with potential use of unrelated donors and stored cord blood units. Autologous hematopoietic stem cells are available to most patients provided that the autologous hematopoietic stem cells product, bone marrow or peripheral blood, is relatively free of contamination by malignant cells and that prior therapy has not limited the number of cells that can be collected.

Allogeneic Hematopoietic Stem Cell Transplantation

In allogeneic HSCT, stem cells are obtained from a donor other than the recipient. Donor and recipient usually are identical or "matched" for HLA, which is derived from the MHC located on chromosome 6.[17] A single set of MHC alleles, described as a *haplotype*, is inherited from each parent, resulting in HLA pairs. The most important HLAs include HLA-A, HLA-B, HLA-C, DR, and DQ loci. Among siblings, the genes which encode for HLA-B and HLA-C are located so close to each other in the MHC that one is rarely inherited without the other. As a result, an HLA match among siblings is referred to a "6 of 6," as they are matched for HLA-A, B, and DR; however, in actuality they are matched for all of the HLA antigens.[3] The other antigens, such as HLA-C, become more important in alternative sources of hematopoietic stem cells, such as unrelated donors and cord blood, which are described in more detail later in this chapter.[18,19]

The distinctive characteristics of allogeneic HSCT are that the stem cell graft (1) is free of contamination by malignant cells and (2) contains T cells that are capable of mediating an immunologic reaction against foreign antigens. This latter characteristic can be a major advantage if the immunologic response is directed against malignant cells—the *graft-versus-leukemia* or *graft-versus-tumor effect*—thus potentially eradicating disease and reducing the chance of disease relapse. However, if the immunologic response is directed against antigens present on normal tissues, it can lead to the destruction of normal organs, described clinically as GVHD. The risk of both graft rejection (host-versus-graft reaction) and GVHD rises with HLA disparity.

The graft-versus-leukemia effect first was recognized in animal models and subsequently was noted among patients undergoing allogeneic HSCT for acute and chronic leukemias.[20–23] The clinical importance of the interactions between immunocompetent donor T cells and tumor cells in mediating a graft-versus-leukemia effect is supported by an increased rate of relapse in allogeneic stem cell grafts from which T cells have been removed (T-cell depletion), an inverse correlation between relapse and severity of GVHD, and increased rate of relapse after syngeneic or autologous HSCT using the same myeloablative conditioning regimen.[23,24] These data suggested that T cells within the allograft were involved directly in eradicating leukemia. Finally, the most compelling evidence for a T-cell-mediated graft-versus-leukemia effect originates from the observation that infusion of allogeneic lymphocytes, a donor lymphocyte infusion, at a time remote from the transplant conditioning regimen, can treat leukemia relapse successfully after allogeneic HSCT.[25–28] In an early report, donor lymphocyte infusion therapy was given to three patients with chronic myelogenous leukemia whose disease had recurred after an allogeneic HSCT.[25] The donor lymphocyte infusion, without any additional cytotoxic therapy, resulted in sustained cytogenetic and molecular remissions. Over time it became increasingly apparent that a significant part of the curative potential of allogeneic HSCT could be directly attributed to the graft-versus-leukemia effect. However, there is tremendous variability relative to the clinical effectiveness of the graft-versus-leukemia effect against different malignancies after allogeneic HSCT.

The choice of donor for an allogeneic HSCT takes into account several factors, including the patient's disease, disease state, and urgency in obtaining a donor. When allogeneic HSCT is being considered for a patient, a fully HLA-matched sibling is the preferred donor source, because the risk of graft rejection and GVHD is lowest with this source of allogeneic stem cells. As described earlier, a haplotype is inherited from each parent, and by simple Mendelian genetics it would be expected that the probability that two siblings would share the same haplotypes would be 1 : 4. The probability of having an HLA-matched sibling increases with the number of siblings within a specific family. The probability can be estimated using the following formula: The chance of having an HLA-matched sibling = $1 - (.75)^n$, where n is the number of potential sibling donors.[3] There is an approximately 1% chance of crossing over (i.e., genetic material switched between chromosomes during meiosis), primarily between the HLA-A and the HLA-B loci. The clinical outcomes for allogeneic HSCT using a sibling with a single HLA mismatch are similar to those with a fully HLA-matched sibling.[29]

For patients who lack a fully HLA-matched sibling donor, the preferred alternative sources for allogeneic stem cells include an unrelated fully HLA-matched donor, a partially HLA-matched cord blood unit, or a partially HLA-matched family member.[30–32] A closely HLA-matched volunteer hematopoietic stem cell donor may be identified through a bone marrow donor registry, such as the National Marrow Donor Program in the United States, which includes about 6 million potential donors. Many HLA phenotypes are possible, which sometimes makes the identification of a matched unrelated donor difficult and time consuming.[33,34] Depending on the ethnic descent of both patient and donor, the probability of identifying an HLA-matched unrelated donor is between 50% and 80%.[8,9] Due to advances in HLA-typing through the use of molecular typing techniques and improved supportive care over the last decade, current results of matched unrelated donor transplants for malignancy are not significantly different when compared to HSCT from matched sibling donor transplant.[19,35]

One major disadvantage of using an unrelated donor is that the average time required to identify and procure an HLA-matched unrelated donor is approximately 2 to 3 months, which may be too long for patients with rapidly progressive malignancies.[36] The alternative stem cell source to an unrelated bone marrow donor for allogeneic HSCT is stored umbilical cord blood.[31,36,37] The major advantages of umbilical cord stem cells are that they can be obtained in less than 4 weeks and that even cord blood units mismatched in up to 2 of 6 HLA may be used for allogeneic HSCT. This degree of HLA mismatching is acceptable, because the overwhelming percentage of T cells within the cord blood unit are naïve, and the incidence of acute GVHD is comparable to or less than that associated with an HLA-matched unrelated bone marrow donor. The major disadvantage of umbilical cord blood units is they are associated with a relatively high degree of graft rejection, especially in adults.[31,37] Engraftment and treatment-related mortality appear to be directly related to umbilical cord cell dose. It may be that the limitation of cell dose can be overcome by the use of more than one cord blood unit; this approach currently is under clinical investigation.[38] The other significant disadvantage is that once the cord blood unit is used, there is no way to go back and get additional cells for a donor lymphocyte infusion or in the event of graft failure.

The other alternative source of allogeneic hematopoietic stem cells is to identify among the patient's first-degree relatives individuals who share at least one haplotype (haplo-identical) with the potential recipient.[32] The major advantage with the use of a partially HLA-matched family member is that the donor is readily available for almost all patients. The major disadvantages are an increased risk of graft rejection, GVHD, and severe immune dysregulation, which rises with higher degrees of HLA-mismatching. Haplo-identical allogeneic HSCT has been limited primarily to use in children.[32,39]

Once an allogeneic stem cell source has been identified, patients are put on regimens with the intent of "conditioning" or "preparing" them for the infusion of hematopoietic stem cells. Most conditioning or preparative regimens use a combination of radiation and chemotherapy.[1,3] They also may contain radioimmunoconjugates and/or monoclonal antibodies that target T cells (e.g., alemtuzumab).[40] The choice of a specific conditioning regimen depends on the disease that is being treated. The earliest conditioning regimens were designed to permit the administration of maximum doses of chemotherapy and/or radiation (i.e. "high-dose" regimens) for the eradication of disease and to be adequately immunosuppressive to prevent graft rejection. The most commonly used chemotherapy agents in these regimens are alkylating agents (e.g., cyclophosphamide and/or etoposide) with or without total lymphoid or total body irradiation at doses varying between 800 to 1440 cGy. The doses of chemotherapy and radiation used in these regimens are referred to as *myeloablative*, because they result in a degree of myelosuppression and immunosuppression that is nearly universally fatal without the infusion of hematopoietic stem cells as a rescue product.[41]

Allogeneic HSCT with myeloablative conditioning regimens has been performed successfully in patients older than 60 years of age; however, survival after these transplants declines with increasing age, limiting the application of allogeneic transplantation to a minority of patients who potentially could benefit from this procedure. However, the demonstration that an immune-mediated graft-versus-leukemia effect plays a central role in the therapeutic efficacy of allogeneic HSCT led to the hypothesis that myeloablative conditioning regimens were not essential for tumor eradication.[42] This idea subsequently led investigators to develop less intense conditioning regimens, which were adequately immunosuppressive to permit the

engraftment of donor hematopoietic stem cells, decrease toxicities associated with myeloablative conditioning regimens, and serve as a platform for the administration of donor T cells as adoptive cellular therapy. A variety of nonmyeloablative and reduced-intensity conditioning regimens has been reported.[43–46] These regimens are associated with decreased early post-transplant morbidity and mortality; however, the important clinical question is whether this reduction in toxicity comes at the cost of a loss of antitumor activity within the conditioning regimen.

Syngeneic Hematopoietic Stem Cell Transplantation

Syngeneic HSCT utilizes stem cells from an identical twin.[47,48] Because the hematopoietic stem cells are genetically identical with the recipient, the major advantage of a syngeneic HSCT is that it is not associated with GVHD or graft rejection, resulting in a relatively low risk of treatment-related morbidity and mortality. Another significant advantage of syngeneic HSCT, which is shared with allogeneic HSCT, is there is no risk of contamination by malignant cells. The major disadvantage is that syngeneic HSCT does not provide the graft-versus-leukemia effect that is associated with allogeneic HSCT. The greatest disadvantage is that far fewer than 1% of patients have an identical twin, and consequently, this is not an option for most patients. However, when an identical twin is available, syngeneic HSCT is considered the preferred type of HSCT in almost all clinical situations.

Autologous Hematopoietic Stem Cell Transplantation

Autologous HSCT employs stem cells from the patient him- or herself. The principle behind autologous HSCT, as well syngeneic HSCT, is that certain malignancies, such as leukemias, have a steep dose-response curve to chemotherapy and, to a relative degree, radiation.[49–51] The major limitation to the administration of higher doses of chemotherapy or radiation is the myelosuppressive effects of these therapies. Autologous, allogeneic, and syngeneic hematopoietic stem cells permit the administration of high-dose chemotherapy and/or radiation by restoring hematopoiesis. The major advantages of autologous HSCT compared with allogeneic HSCT are that (1) the patient can serve as his or her own donor and (2) it may be performed in older patients with significantly decreased mortality, due to the absence of GVHD as a major complication. However, autologous HSCT can be associated with more morbidity than conventional doses of radiation and chemotherapy. A potential disadvantage of autologous HSCT is the possible reinfusion of viable tumor cells.[52] Numerous methods, including in vitro treatment with chemotherapeutic agents or monoclonal antibodies plus complement, have been developed to remove contaminating tumor cells from the graft, a process often referred to as *purging*, or to concentrate hematopoietic stem cells, a process referred to as *positive selection*.[53–56] Retrospective analyses have suggested that purging leads to a reduced relapse rate in patients with acute myelogenous leukemia and B-cell non-Hodgkin's lymphomas.[57,58]

Hematopoietic Stem Cell Acquisition and Processing

Hematopoietic stem cells may be obtained from the bone marrow, the peripheral blood, and umbilical cord blood. Hematopoietic stem cells from bone marrow are used in both autologous and allogeneic HSCT, although less frequently than in the past. Peripheral blood hematopoietic stem cells are used in approximately 90% of autologous HSCT and in approximately 70% of allogeneic HSCT.[59] The greater use of peripheral blood hematopoietic stem cells is related to their relative ease of attainment and moderate improvement in the rate of hematopoietic recovery after infusion as compared to hematopoietic stem cells derived from bone marrow. In steady-state, the concentration of hematopoietic stem cells and myeloid progenitor cells is quite low, and prior to collection of peripheral blood hematopoietic stem cells by apheresis, attempts are made to increase or "mobilize" the number of circulating hematopoietic stem cells by various techniques.[60] Hematopoietic stem cells may be mobilized into the peripheral blood following administration of myeloid hematopoietic growth factors (e.g., granulocyte colony-stimulating factor), during the recovery phase from exposure to chemotherapy, or by using both chemotherapy and growth factors.[61–64] Collection of peripheral blood hematopoietic stem cells from a normal donor for allogeneic HSCT is performed following mobilization with myeloid hematopoietic growth factors only. In general, at least 1×10^6 CD34+ cells/kg of recipient weight are collected from the peripheral blood by apheresis. The cells are then processed with dimethylsulfoxide (DMSO) with or without hydroxyethylstarch and then stored in liquid nitrogen until needed for transplantation.[65]

Methods for collecting or "harvesting" hematopoietic stem cells from bone marrow are modifications of the technique initially reported by Thomas and Storb.[66] The bone marrow harvest usually is performed under general anesthesia and generally is well tolerated.[67,68] Bone marrow hematopoietic stem cells usually are harvested by repeated aspirations from the posterior iliac crest until an adequate number of cells have been removed. If sufficient cells cannot be obtained from the posterior iliac crest, marrow also can be harvested from the anterior iliac crest and sternum. The minimal number of nucleated marrow cells required for long-term repopulation in humans is not precisely known. In practice, the number of nucleated marrow cells harvested is usually $1 - 3 \times 10^8$/kg of recipient weight, depending on the diagnosis (i.e., higher for aplastic anemia), the type and intensity of pretransplant conditioning, and whether the marrow graft will be modified in vitro. Marrow sometimes is treated in vitro to remove unwanted cells before it is returned to the patient. In allogeneic HSCT with major ABO incompatibility between donor and recipient, it is necessary to remove the mature erythrocytes from the graft to avoid a hemolytic transfusion reaction.[69] After collection and processing, hematopoietic stem cells from bone marrow may be directly infused or cryopreserved in an identical manner as hematopoietic stem cells from the peripheral blood.

Hematopoietic stem cells from cord blood are collected immediately after delivery. A minimally acceptable cord blood unit dose is 1.7×10^5 CD34+ cells per the patient's weight in kilograms to ensure engraftment in the allogeneic HSCT setting.[70] This criterion is a significant problem for adult patients, where the application of cord blood transplantation has been associated with delayed hematopoietic recovery, especially platelets, graft failure, and a relatively high treatment-related mortality in comparison to other sources of allogeneic hematopoietic stem cells.

MALIGNANT DISEASES TREATED WITH HEMATOPOIETIC STEM CELL TRANSPLANTATION

Clinical evidence exists that syngeneic, autologous, and allogeneic HSCT all provide benefit—defined as response, freedom of progression, or overall survival—for most hematologic malignancies and for a minority of solid malignancies (Fig. 32-2).[3] However, the beneficial effects of these various forms of HSCT vary greatly with each type of malignancy. Data indicate that due to their relative responsiveness to cytotoxic therapy, myeloablative conditioning regimens with syngeneic, autologous, or allogeneic HSCT result in higher response rates than cytotoxic or conventional agents for almost all hematologic malignancies. However, the durability of these responses and their effect on survival varies from disease to disease. Similarly, there is evidence of a clinical graft-versus-leukemia effect in almost every hematologic disease; however, the potency and clinical relevance are highly variable. Interpretation of the results of trials of HSCT always is complicated by issues of patient selection. This can lead to either

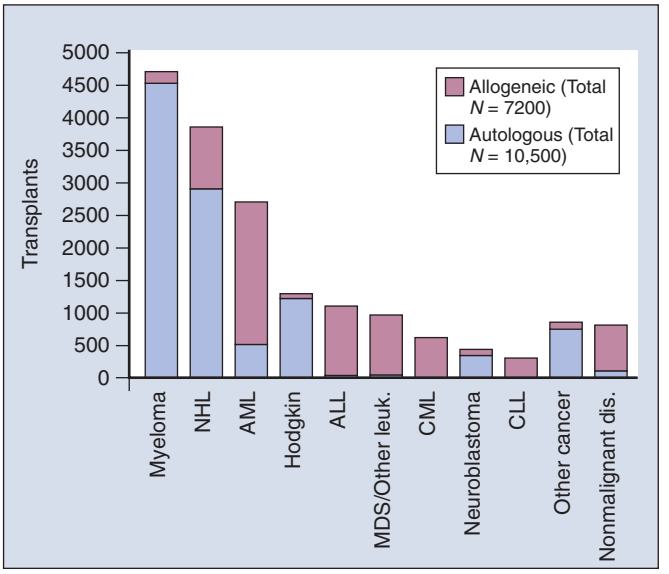


Figure 32-2 • Indications for blood and marrow transplantation in North America in 2003. ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; NHL, non-Hodgkin's lymphoma; MDS, myelodysplastic syndrome. (Data from the Center for International Blood and Marrow Transplant Research, Milwaukee, WI.)

underestimating the efficacy of HSCT if it is used after exhausting all other available therapies or overestimating its efficacy if only the patients with favorable prognostic characteristics are selected. The specific indications for HSCT are covered in the chapters for each respective disease. This section briefly addresses the outcomes for malignancies with different forms of HSCT.

Acute Myelogenous Leukemia

Acute myelogenous leukemia (AML) and acute lymphocytic leukemia (ALL) were the first malignancies in which all forms of HSCT were demonstrated to be effective.[22,24,71] Initial studies of myeloablative allogeneic HSCT demonstrated that this treatment was capable of resulting in long-term survival for a minority of patients with refractory and relapsed AML.[71] Unfortunately, the cure rate in these latter cases is only about 10%. Long-term survival and an apparent cure rate of 20% to 40% have been achieved in patients treated in second or subsequent complete remission, and cure rates of 40% to 70% have been reported in patients given transplants in their first complete remission.[72–75] Randomized controlled trials comparing autologous and allogeneic HSCT to conventional chemotherapy in patients with AML in first complete remission have demonstrated improved leukemia-free survival with both forms of HSCT; however, there has been no significant improvement in overall survival.[76–79] The one exception has been in pediatric AML, where allogeneic HSCT has been demonstrated to improve both leukemia-free and overall survival for patients transplanted in first complete remission.[80] The lack of improvement in overall survival in adults is attributed to high rates of treatment-related mortality with allogeneic HSCT, high relapse rates with autologous HSCT, and the fact that patients could successfully undergo HSCT at first sign of relapse.[81] Because a significant proportion of patients can be cured with standard chemotherapy regimens without HSCT and because cure rates of 20% to 30% have been reported for HSCT in early first relapse, withholding HSCT until the first sign of treatment failure is an alternative treatment strategy.[82] Reduced-intensity and nonmyeloablative conditioning regimens may increase the applicability of allogeneic HSCT for older patients. The Acute Leukemia Working Party and European Group of Blood and Marrow Transplant compared the results of reduced-intensity conditioning with myeloablative regimens in patients with AML over 50 years of age undergoing allogeneic HSCT from HLA-matched siblings.[83] Transplant-related mortality was significantly decreased, but the relapse incidence was significantly higher after reduced-intensity conditioning. Leukemia-free survival was not statistically different between the two groups.

Myelodysplastic Syndrome

The only known curative treatment for myelodysplastic syndrome (MDS) is allogeneic HSCT. In this setting, long-term disease-free survival of greater than 40% has been obtained.[84] The best results have been obtained in relatively younger patients, who are earlier in their disease course and have not received any prior therapy. To identify factors influencing transplantation outcome for MDS, the International Bone Marrow Transplantation Registry (IBMTR) studied 452 recipients of HLA-identical sibling transplants for MDS.[85] Sixty percent of patients had refractory anemia with excess blasts ($N = 136$) or with excess blasts in transformation ($N = 136$). Three-year transplantation-related mortality, relapse, disease-free survival, and overall survival rates were 37%, 23%, 40%, and 42%, respectively. Multivariate analyses showed that young age and platelet counts higher than 100 at transplantation were associated with lower transplant-related mortality and higher disease-free and overall survival rates. Because the optimal timing for bone marrow transplantation for MDS is unknown, the IBMTR constructed a Markov model to examine three transplantation strategies for newly diagnosed MDS: transplantation at diagnosis; transplantation at leukemic progression; and transplantation at an interval from diagnosis but prior to leukemic progression.[86] Analyses using individual patient risk-assessment data from transplantation and nontransplantation registries were performed for all four IPSS risk groups with adjustments for quality of life. For low and intermediate-1 IPSS groups, delayed transplantation maximized overall survival. Transplantation prior to leukemic transformation was associated with a greater number of life years than transplantation at the time of leukemic progression. In a cohort of patients under the age of 40 years, an even more marked survival advantage for delayed transplantation was noted. For intermediate-2 and high IPSS groups, transplantation at diagnosis maximized overall survival. There is evidence that reduced-intensity allogeneic HSCT may benefit older patients with MDS.[87,88] The use of autologous HSCT for MDS remains investigational.[89]

Acute Lymphocytic Leukemia

The results of standard therapy in childhood acute lymphocytic leukemia (ALL) are sufficiently good with intensive chemotherapy regimens that HSCT probably should be performed as part of primary therapy only in special situations, such as in patients with childhood ALL who are Philadelphia (Ph) chromosome-positive, in whom the cure rate with standard therapy is very low.[90] However, the overall prognosis for both pediatric and adult patients with relapsed ALL is relatively poor, and the general treatment strategy is to obtain a second complete remission and then proceed to an allogeneic HSCT.[91,92]

In light of this significantly higher relapse rate with conventional therapy, there has been strong interest in the use of both allogeneic and autologous stem cell transplantation as consolidation of adult patients with ALL who are in first complete remission.[93–95] The French protocol LALA 87 was designed to compare chemotherapy alone versus autologous or allogeneic HSCT as postinduction (i.e., consolidation) strategies in adult ALL.[93] This trial demonstrated a significant superiority of allogeneic bone marrow transplantation in high-risk patients with ALL. A trend also was detected in favor of autologous BMT over chemotherapy in those same patients. The BGMT Group performed a prospective, randomized trial in adults to compare disease-free survival after allogeneic or autologous bone

marrow transplantation in a total of 135 previously untreated adult patients with ALL.[94] The 3-year post–complete remission probability of disease-free survival was significantly higher in the allogeneic stem cell group. The authors concluded that early allogeneic transplantation was an effective consolidation treatment for adult patients with ALL in first complete remission. The French LALA-94 trial determined the benefits of a risk-adapted postremission strategy hematopoietic stem-cell transplantation in 922 adult patients with ALL.[95] The study demonstrated that allogeneic HSCT improved disease-free survival in high-risk ALL in the first complete remission, whereas autologous HSCT did not confer a significant benefit over chemotherapy for high-risk ALL.

Multiple Myeloma

Both allogeneic and autologous HSCT have been performed for multiple myeloma, because standard chemotherapy regimens rarely, if ever, cure the disease. The efficacy of high-dose chemotherapy in multiple myeloma has led to inclusion of autologous HSCT as part of its initial therapy.[96,97] Its unique biologic characteristics have led to clinical data demonstrating that the inclusion of more than one cycle of high-dose chemotherapy with autologous HSCT may improve upon the results of a single transplant.[98] Although clear evidence exists of a graft-versus-leukemia effect against multiple myeloma, a tumor-specific antigen has not been identified. The use of myeloablative allogeneic HSCT is controversial, because it has been associated with a high mortality rate.[99] Results of allogeneic HSCT in multiple myeloma have improved with the use of nonmyeloablative conditioning regimens, and there is evidence to suggest that this approach can result in an improvement in progression-free and overall survival.[100]

Chronic Myelogenous Leukemia and Other Myeloproliferative Disorders

Chronic myelogenous leukemia (CML) is highly susceptible to the graft-versus-leukemia effect, as evidenced by the long-term, leukemia-free survival rates exceeding 70% for patients who were transplanted in early chronic phase and the response of CML to donor lymphocyte infusion.[101–104] Allogeneic HSCT from an HLA-matched sibling or unrelated donor previously was the treatment of choice for patients of an appropriate age with chronic-phase CML.[101–103] However, due to the tremendous clinical success of imatinib (STI-571, Gleevec), the emerging predominant strategy is to use allogeneic HSCT in patients with more advanced CML, and it is reserved for patients who have failed or progressed on imatinib.[105] Autologous HSCT has limited efficacy in CML due to the relative lack of sensitivity of CML to cytotoxic therapy and the difficulty of obtaining a relatively tumor-free autograft.[106]

Myeloproliferative disorders usually are chronic in nature but can progress to a "spent" phase and develop myeloid metaplasia, which is characterized by bone marrow fibrosis and a generally poor prognosis with transformation into acute leukemia and a median survival of less than 3 years.[107,108] Conventional treatment options at this state of the disease are limited, and the accepted standard of care for myeloid metaplasia/myelofibrosis is allogeneic stem cell transplantation with a myeloablative conditioning regimen.[109,110] There have been anecdotal reports of the use of nonmyeloablative allogeneic HSCT for myelofibrosis and other myeloproliferative disorders.[111]

Chronic Lymphocytic Leukemia

Both allogeneic and autologous HSCT have been used for the treatment of chronic lymphocytic leukemia (CLL).[112–114] However, the application of allogeneic and autologous HSCT for CLL has been limited by treatment-related mortality and relapse for each type of HSCT. Considerable interest and research has been devoted to the use of nonmyeloablative and reduced-intensity conditioning regimens prior to allogeneic HSCT for CLL in hopes of reducing the treatment-related mortality.[115–117] The Chronic Leukemia Working Party of the European Blood and Marrow Transplant Group reported on 77 patients with CLL who underwent a nonmyeloablative allogeneic HSCT.[115] Treatment-related mortality after 12 months was 18%. At a median follow-up of 18 months, the 2-year probability of relapse was 31%. Event-free and overall survival rates at 24 months were 56% and 72%, respectively. The Cooperative German Transplant Study Group reported on 30 patients with advanced B-cell CLL who underwent reduced-intensity allogeneic stem cell transplantation from either related (N = 15) or unrelated (N = 15) donors.[116] The probabilities of overall survival, progression-free survival, and treatment-related mortality at 2 years were 72%, 67%, and 15%, respectively. These data indicate that allogeneic HSCT after reduced-intensity conditioning can result in relatively high, durable, complete response rates (>50%) with acceptable treatment-related mortality rates.

Non-Hodgkin's Lymphoma

Allogeneic, syngeneic, and autologous HSCT have been reported to yield long-term disease-free survival and an apparent cure for patients with intermediate and high-grade non-Hodgkin's lymphomas (NHL).[118–120] Due to its relative sensitivity to chemotherapy, there is substantial evidence that autologous HSCT is efficacious for patients with primary refractory or chemotherapy-sensitive recurrent NHL of specific histologies including "intermediate-grade" (e.g., disease-diffuse, large B-cell) NHL.[121] It is now apparent that patients who fail to achieve an initial complete remission, but who do not have other adverse prognostic factors such as poor performance status or bulky disease, also can achieve long-term disease-free survival.[122] Because of the superior results achieved in patients treated earlier in the course of the disease, a number of investigators have incorporated high-dose therapy and autologous HSCT into the primary treatment of patients with intermediate and high-grade non-Hodgkin's lymphoma.[123,124]

Autologous HSCT also has been used to treat patients with indolent ("low-grade") NHL (e.g., follicular center cell) with either purged bone marrow or peripheral blood stem cells, resulting in disease-free survival rates as high as 60%.[125,126] However, the late relapses seen in this illness and long overall survival observed with conventional therapy make very long follow-up necessary to document the efficacy of this approach.

The demonstration of a potent graft-versus-leukemia effect against NHL is less clear, and the efficacy of donor lymphocyte infusion in lymphoma is anecdotal at best.[126–128] Consequently, the specific role of allogeneic HSCT has not been defined. However, there are data that myeloablative allogeneic HSCT can result in long-term survival for patients with recurrent or refractory NHL,[120,129] and evidence exists that nonmyeloablative allogeneic HSCT may provide benefit for patients with recurrent follicular non-Hodgkin's lymphoma. Some evidence, however, indicates that this approach requires that the disease remains chemotherapy-sesitive.[130]

Hodgkin's Disease

High-dose therapy with autologous or allogeneic HSCT has been widely used in patients with recurrent Hodgkin's disease (HD; also known as Hodgkin's lymphoma).[131–133] As in NHL, patients with HD whose disease fails to respond to front-line therapy can derive benefit from high-dose therapy and autologous HSCT.[134] Allogeneic HSCT has had a limited role in the treatment of HD due to the efficacy of autologous HSCT, the treatment-related toxicities associated with myeloablative allogeneic HSCT, and lack of evidence of a graft-versus-leukemia effect against HD. However, recent data indicate that reduced-intensity allogeneic HSCT may benefit patients with recurrent HD, and a graft-versus-leukemia effect against HD may exist.[135]

Soft Tissue Sarcomas and Neuroblastoma

High-dose therapy and autologous HSCT have been used as either consolidation of primary therapy or treatment of metastatic or recurrent soft tissue sarcomas, such as Ewing's sarcoma, rhabdomyosarcoma, and osteosarcoma in children.[136,137] Burdach and colleagues reported a 45% relapse-free survival for patients with poor-risk and recurrent Ewing's sarcoma who received high-dose therapy and autologous HSCT, as compared with 2% for a historical control group.[136] The European BMT Solid Tumor Registry reported the results from 21 European transplant centers on 50 patients with Ewing's sarcoma in first or second complete remission consolidated with high-dose chemotherapy and autologous HSCT.[137] Thirty-two patients with high-risk or metastatic disease in first complete remission achieved an actuarial event-free survival of 21% at 5 years. Results of prospective studies of high-dose therapy and autologous HSCT in soft tissue sarcomas, primarily in children, suggest a possible improvement in remission duration and possibly on overall survival.[138,139] Autologous HSCT remains investigational in adults with sarcomas.

Autologous HSCT has been found to be beneficial for both newly diagnosed and recurrent neuroblastoma.[140–143] The Children's Cancer Group assessed whether high-dose therapy and autologous bone marrow transplantation improved event-free survival as compared with chemotherapy alone.[140] All patients were treated with the same initial regimen of chemotherapy, and those without disease progression were then randomly assigned to receive continued treatment with high-dose therapy and purged autologous bone marrow transplantation or to receive three cycles of intensive chemotherapy alone. The mean event-free survival rate was significantly better among the patients who were assigned to undergo transplantation.

Germ Cell Tumors

In patients with germ cell tumors for whom platinum-based chemotherapy regimens fail to effect a cure, the use of high-dose chemotherapy and autologous BMT has resulted in prolonged disease-free survival, including patients with refractory disease.[144,145] Evidence exists suggesting that tandem transplant may result in improved results; however, no direct comparison of single versus tandem transplants has been performed.[146]

Other Solid Tumors

Several nonrandomized trials and retrospective analyses had suggested that high-dose chemotherapy and autologous stem cell transplantation were beneficial in regard to prolongation of survival in stage II/III breast cancer.[147,148] Subsequently, several randomized trials addressed the role of high-dose therapy and autologous stem cell transplantation in patients with stage II/III breast cancer.[149–153] Most of these trials found no evidence of a survival advantage for patients randomized to receive high-dose therapy, although some of the trials suggested an improvement in event-free survival in the high-dose arm. Evidence also is lacking that high-dose chemotherapy and autologous HSCT improve survival in metastatic breast cancer.[154]

There has been considerable interest in investigating the presence of a "graft-versus-tumor" effect in a variety of solid tumors, including renal cell carcinoma and breast cancer.[155–157] Childs and colleagues[155] reported on a series of 19 patients with metastatic renal cell carcinoma who underwent nonmyeloablative allogeneic stem cell transplantation. Nine patients had responsive disease (47%), of which three were complete responses.

COMPLICATIONS AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION

In addition to the acute toxicities associated with prolonged cytopenia, other organ toxicities can be associated with transplantation. A simple index, based on pretransplant comorbidities, has been developed that reliably predicts nonrelapse mortality and survival.[158] This comorbidity index is useful for patient counseling prior to HSCT. The late toxicities always must be kept in mind when choosing therapies for patients.[159]

Graft Rejection

Graft rejection occurs when immunologically competent cells of host origin destroy the transplanted cells of donor origin.[160] This complication occurs more commonly in patients who receive transplants from alternative or HLA-mismatched donors, in T cell-depleted transplants, and in patients with aplastic anemia who receive a non–total body irradiation (TBI)-containing regimen. Graft rejection is less likely to occur in nontransfused patients with aplastic anemia.

Cardiac Toxicity

Most transplant centers screen potential patients for underlying cardiac abnormalities that would place them at potential increased risk during the procedure.[161] Despite this screening, however, a small number of patients experience cardiotoxicity, either acutely during the transplant or at a later time, manifested as a cardiac arrhythmia, congestive heart failure, or cardiac ischemia due to the large volumes of fluids administered during the procedure or from the added physiologic stress.[162] Complications associated with a pericardial effusion can be seen in some patients during or after transplant and are more common in patients with disease near that area and those receiving radiation therapy in that field. An idiosyncratic cardiomyopathy associated with the administration of high doses of cyclophosphamide can be demonstrated in a small number of patients. Viral cardiomyopathies also can be seen as a late transplant complication.

Engraftment Syndrome

Engraftment syndrome occurs during neutrophil recovery following both autologous and allogeneic HSCT.[163] It consists of a constellation of symptoms and signs that may include fever, erythrodermatous skin rash, and noncardiogenic pulmonary edema, and, in its most extreme forms, acute renal failure and diffuse alveolar hemorrhage. These clinical findings reflect the manifestations of increased capillary permeability. Making a distinction from hyper-acute GVHD in the allogeneic setting has been difficult, however. Corticosteroid therapy often is dramatically effective for engraftment syndrome, particularly for the treatment of the pulmonary manifestations.

Pulmonary Toxicities

Pulmonary toxicities are common during and after transplantation. Patients who receive certain chemotherapeutic agents, such as 1,3-bis (2- chloroethyl)-1-nitrosourea (BCNU; carmustine) have an increased incidence of chemotherapy-induced lung tissue damage after transplant, which usually can be treated successfully with the prompt initiation of corticosteroid therapy.[164] In addition to these complications, patients who are undergoing allogeneic transplant are at increased risk for pneumonitis caused by cytomegalovirus, fungal infections due to the patient's increased immunosuppression, and adult respiratory distress syndrome or interstitial pneumonia of unknown etiology. Chronic GVHD also can manifest as bronchiolitis obliterans in the lung.[165]

Liver Toxicity

The most common liver complication associated with transplantation is veno-occlusive disease (VOD [sinusoidal obstruction syndrome of the liver]).[166,167] Symptoms associated with VOD include jaundice, tender hepatomegaly, ascites, and weight gain. Progressive hepatic failure and multiorgan system failure can develop in the most severe cases. Predisposing factors appear to be previous hepatic injury, use of estrogens, and high-dose intensity conditioning.[167]

Table 32-2 Graft-versus-Host Disease Categories

Category	Time of Manifestation after HSCT or DLI	Presence of GVHD Features	
		Acute	Chronic
ACUTE GVHD			
Classic acute GVHD	≤100 d	Yes	No
Persistent, recurrent, or late-onset acute GVHD	>100 d	Yes	No
CHRONIC GVHD			
Classic chronic	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

DLI, donor lymphocyte infusion; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation.

Renal Toxicity

Acute renal failure requiring dialysis during the transplant occurs infrequently.[168] However, patients with underlying renal dysfunction are at risk for this complication. The judicious use of nephrotoxic agents can decrease its incidence. The need for dialysis typically is a short-term complication, because the patient's underlying problem (e.g., a septic event) either improves with time or becomes life-threatening, sometimes leading to death. An idiopathic or cyclosporine-induced hemolytic-uremic syndrome can be a serious complication after allogeneic stem cell transplantation, posing a high mortality risk or resulting in end-stage renal disease. Recently, nephrotic syndrome and membranous nephropathy have been described in long-term survivors; these complications seem to be associated more commonly with chronic GVHD and nonmyeloablative conditioning.[169]

Graft-versus-Host Disease

In the setting of allogeneic HSCT, complications associated with acute and chronic GVHD also are of concern. Previously, acute and chronic GVHD were distinguished chronologically by whether GVHD occurred before or after the fist 100 days after transplant, respectively. However, acute or chronic GVHD is a clinical diagnosis, based on the characteristic clinical manifestations and context, and neither is specifically defined by the "day 100" dichotomy any longer (Table 32-2). In the evaluation of both acute and chronic GVHD, which usually includes a tissue biopsy, it is important to exclude other potential diagnoses such as infection, drug reaction, or second malignancies, which can mimic GVHD. Acute GVHD is manifested by symptoms in several organ systems, including the skin, gastrointestinal tract, and liver (Table 32-3).[170] This complication typically occurs within the first 100 days after transplantation. The skin manifestations range from a maculopapular rash up to generalized erythroderma or desquamation. The severity of liver GVHD is scored on the basis of the bilirubin and the gastrointestinal severity on the quantity of diarrhea per day.

Patients who receive transplants from unrelated donors are at much higher risk for GVHD, the incidence and severity of which rise with the age of the patient. Other risk factors for the development of GVHD include a female donor (particularly a multiparous donor), more advanced age, and cytomegalovirus seropositivity of the donor or patient. Patients receive prophylaxis for GVHD prevention most commonly with cyclosporine, with or without methotrexate and corticosteroids.[171] Treatment for acute GVHD includes high-dose corticosteroids, antithymocyte globulin, or various monoclonal antibodies.[172–174]

Chronic GVHD occurs most commonly between 100 days and 2 years from the transplant and has polymorphic features similar to a number of autoimmune diseases. It is most likely to develop in older patients who also had acute GVHD or received peripheral blood rather than bone marrow grafts.[175] Symptoms associated with chronic GVHD include sicca syndrome, rashes or skin thickening, diarrhea, wasting syndrome, bronchiolitis obliterans, or liver function abnormalities.[176–178] Patients also are at greatly increased risk for infectious complications, due to either the GVHD itself or the treatment administered. Adverse prognostic factors include thrombocytopenia, a progressive clinical presentation, extensive skin involvement, and an elevated bilirubin. Treatment for the chronic form of the disease includes corticosteroids, cyclosporine, thalidomide, ultraviolet light treatments, or other immunosuppressive agents.[179,180]

Infertility

Many of the preparative regimens used for transplant are associated with a high incidence of permanent sterility. The use of TBI almost

Table 32-3 Classification of Patients with Acute Graft-versus-Host Disease

CLINICAL STAGING

Stage	Skin	Liver	Gut
+	Rash <25% BSA	Total bilirubin 2–3 mg/dL	Diarrhea 500–1000 mL/day
++	Rash 25%–50% BSA	Total bilirubin 3–6 mg/dL	Diarrhea 1000–1500 mL/day
+++	Generalized erythroderma	Total bilirubin 6–15 mg/dL	Diarrhea >1500 mL/day
++++	Desquamation and bullae	Total bilirubin >15 mg/dL	Pain, with or without ileus

CLINICAL GRADING

	Stage			
Grade	Skin	Liver	Gut	PS
0 (none)	0	0	0	0
I	+ to ++	0	0	0
II	+ to +++	+	+	+
III	++ to +++	++ to +++	++ to +++	++
IV	++ to ++++	++ to ++++	++ to ++++	+++

BSA, body surface area.

always is associated with sterility. However, successful pregnancies have occurred after the use of non–TBI-containing regimens.[181] This is most likely to be the case in patients who were less heavily retreated before the transplant and were under the age of 25 years at the time of transplant.

Secondary Malignancies

With the increasing number of long-term survivors following HSCT, complications that develop years later are beginning to be recognized. One complication of the chemo- plus radiotherapy that is used to treat a malignancy is the development of a secondary malignancy.[182,183] Several reports have now been published of the development of secondary AML or MDS after autologous transplantation. Some studies have suggested that the use of TBI may increase the risk of these complications.[183] It is unclear to what degree the transplant itself contributed to the development of the AML/MDS, because all patients received chemotherapy or radiotherapy, or both, before the transplant and, in some cases, after the transplant.

CONCLUSION

There has been tremendous success since the 1980s in the increased safety of hematopoietic stem cell transplantation and in the expanding application of this treatment to more patient populations. Areas currently under development that may further improve the use and efficacy of transplantation include continuous improvements in supportive care for transplant patients, broadened use of alternative donors, more refined graft manipulations, and further improvements in the nonmyeloablative transplantation techniques and GVHD prevention. Future progress depends on our ability to identify safer and better-targeted antitumor therapies that can be incorporated in the transplantation regimens without attenuating the graft-versus-tumor responses. This remains a challenge for future clinical research.

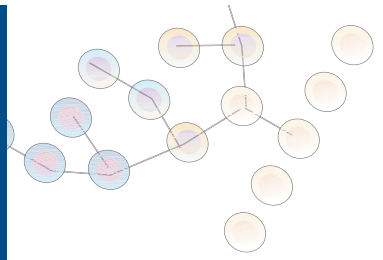
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33 Gene Therapy in Oncology

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SUMMARY OF KEY POINTS

Recent Major Improvements in Gene Therapy

- Vector development
- Vector targeting
- Regulated transgene expression
- Clinical development strategies

Ideal Vector Attributes

- Can be targeted either physically or via promoter expression, and is nontoxic, noninflammatory, and nonimmunogenic
- Should have the potential to incorporate a large transgene and result in high levels of both transduction and transgene expression
- Duration of transgene expression and/or genomic integration ought to be regulatable

Current Concerns Regarding Gene Therapy

- Gene therapy has been implicated in the death of at least one patient, resulting in the temporary suspension of clinical trials (2000) with adenovirus (Adv) vectors in the United States. The first gene therapeutic to be approved (China, 2003) was an Adv vector with a p53 transgene used in combination with chemotherapy for the treatment of head and neck squamous cell carcinoma (HNSCC). A second, conditionally replicative Adv vector, H101 (ONYX-015), was approved in China in December of 2005.
- Leukemic transformation by insertional mutagenesis occurred in several patients treated with retroviral vectors. However, because retroviral vectors have been successful in the treatment of patients with severe combined immune deficiency (SCID-X1) for whom no other therapy is available, their use continues to be approved on a case by case basis.

Future Directions of Gene Therapy

- The choice of disease, clinical implementation, and vector are critically important to the future development of successful gene therapy.
- Because of deficiencies in gene delivery and targeting, as well as expression levels, it is critical to pair protocols with specific vector attributes.

INTRODUCTION

The development of nucleic acid technologies has provided insight into the molecular basis of neoplasia. The resultant detection of phenotypic and genotypic alterations in neoplastic diseases has increased optimism that molecular intervention might lead to improved clinical care for patients with cancer. One such approach is gene therapy, which is the introduction of a nucleic acid sequence into a target cell. The objectives are the delivery of a transgene to an adequate number of cells and at an effective level of expression sufficient to result in therapeutic outcomes. Both criteria require the use of a vector and potentially, a formulation such that these objectives can be met. Although this approach is both simple and attractive, thus far gene therapy has promised much and delivered little because of the technical hurdles. Several preclinical studies and clinical trials have been undertaken to improve gene transfer systems. In 2003 the first gene therapeutic was approved in China. This was an adenovirus (Adv) serotype 5 vector engineered to express TP53 (Gendicine) for treatment of patients with head and neck squamous cell carcinoma (HNSCC).[1] A second gene therapy product, H101 (ONYX-015), an Adv vector modified to replicate in and kill cancer cells with TP53 mutations, was approved in December 2005.[2] Regardless of these approvals, the primary challenges in gene therapy remain improvements in the targeting of our existing vectors and increasing gene transduction efficiency. Overcoming these obstacles will facilitate the development of targetable vectors and, given the systemic nature of most malignancies, help in the development of vectors that can be administered intravenously (IV). This chapter focuses on strategies to improve efficacy, as well as ongoing gene therapeutic strategies. We also will examine and discuss recent advances and indicate areas that require further development for clinical gene therapy to become a widely used treatment modality.

VECTORS

Viral Gene Transfer Vectors

Viral gene delivery has developed from a virus' innate ability to infect cells, which offers many intrinsic advantages:[3,4]

- Specific cell-binding and cell-entry properties
- Efficient targeting of the transgene to the nucleus of the cell
- Ability to avoid intracellular degradation

Most viral vectors are based on the principle that an intact wild-type (wt) virus can be modified for safe and effective gene transfer. In general, the more severely attenuated the viral vector is from the wt, the safer the virus is for use in gene therapy protocols, yet the poorer the yield obtained after propagation. Typically, two (or preferably, three) noncontiguous partial or complete gene sequences are deleted to reduce the potential for homologous recombination. Specific genes critical to viral replication are then modified or deleted, resulting in a recombinant viral vector that is "replication defective."

The transgene to be delivered by the virus is then inserted into the viral genome at the site created by the removal of the viral replication genes. The transgene must be a smaller size to fit within the available space, which is a critical characteristic because the transgene cannot be packaged into an infectious particle if the new viral genome is too large. Many of the viruses that are used as vectors lack genes for replication in normal cells; therefore, the recombinant virus and its transgene must be grown in a packaging cell line that provides the complementary genes required for viral replication. The recombinant viral particles are purified as live infectious viruses and are replication incompetent in the absence of the packaging cell line. Alternatively, the packaging cell line can be used to infect (transduce) cells or tissues in vitro.

Retroviridae—Retrovirus

The Retroviridae is a large family of ribonucleic acid (RNA) viruses including Moloney-murine-lentivirus-related viruses (e.g., Moloney murine leukemia virus [MMLV]) and lentiviruses (e.g., human immunodeficiency viruses 1 and 2 [HIV-1 and HIV-2]).[5] Their genomes consist of two identical positive-sense, single-stranded RNA molecules (~3.5 kb), and are encased in a capsid along with integrase and reverse transcriptase enzymes. Initially, retroviral vectors were the most widely used viral vectors, a distinction that has been replaced by Adv vectors in recent years. Retroviruses can transduce only those cells that are actively undergoing mitosis, limiting their utility with certain cell populations, especially hematopoietic stem cells. Retroviral vectors provide good gene expression and are technically easy to produce, although the titers obtained are suboptimal. In addition, the production of retroviral vectors requires careful monitoring because of the potential for helper virus contamination.

RECOMBINANT MOLONEY MURINE LEUKEMIA VIRUS. Most of the retroviral vectors that are used for gene therapy are based on MMLV. Vector replication is prevented by the deletion of the *gag, pol,* and *env* gene regions. The *gag* region encodes the capsid proteins, the *pol* region encodes reverse transcriptase and integrase, and the *env* region encodes proteins required for receptor recognition and envelope anchoring (Fig. 33-1). The genome includes long terminal repeats at either end that play a vital role in initiating deoxynucleic acid (DNA) synthesis and regulating transcription of the viral genes. The *gag, pol,* and *env* gene products are supplied by a complementary packaging cell line. When a retroviral vector plasmid is introduced into a packaging cell line, viral RNA is produced, packaged into virions, and secreted into the medium. Each resultant viral particle is able to integrate itself into the genome of the host cell, but is unable to produce additional viral particles because it lacks the *gag, pol,* and *env* genes. The transduced DNA sequences are stably integrated into the chromosomal DNA of the target cells and in this way are transferred to cellular progeny of transduced cells. Highlights of results obtained to date with retroviral vectors include the therapeutic studies in children with severe combined immune deficiency (SCID-X1), which will be discussed later in this review, as well as the gene-marking studies of Malcolm Brenner and others.[6,7] In the latter studies, it was shown that tumor cells within autologous stem cell transplant products could be responsible for tumor relapse, at least in leukemia patients.

RECOMBINANT LENTIVIRUS. The most recently discovered members of the retrovirus family are the human and simian immunodeficiency viruses (HIVs and SIVs, respectively), which belong to a subclass of retroviruses known as lentiviruses.[8,9] The development of HIV gene therapy vectors has several potential advantages based on the following characteristics:

- Transduce actively dividing and nondividing cells.
- Long-term, stable transgene expression occurs due to genetic integration.
- Inherent tropism for CD4 T cells, macrophages, and hematopoietic stem cells.

Genetic modifications, such as the introduction of vesicular stomatitis virus G protein into the lentiviral envelope, can widen the tropism of this vector. Until it has been demonstrated that HIV-based vectors are safe, however, the use of these vectors for therapies targeting diseases other than HIV could be difficult to initiate clinically.[10] The in vitro efficiency of lentiviral vectors is at an acceptable level; however, in vivo expression has not been demonstrated at an acceptable level for clinical utility. In addition, there is a need to find protocols and/or procedures that can elevate the expression levels of the HIV virus in nondividing cells.[11]

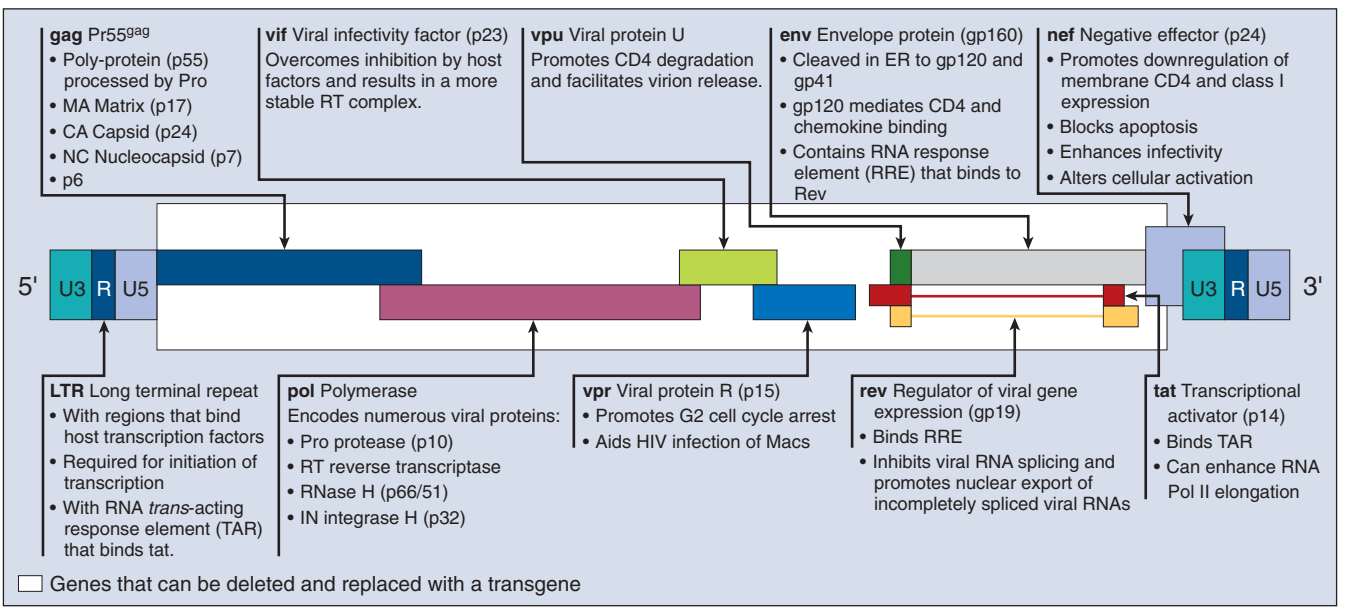


Figure 33-1 • Retrovirus proviral genome and gene product functions. Overview of the 9-kb genome of the HIV provirus and a brief summary of the functions for the 9 genes encoding 15 proteins.

The first clinical study using a lentivirus vector was undertaken in HIV-infected patients.[12] This study investigated the safety of infusing autologous T cells modified with an HIV type 1 (HIV-1)–based lentiviral vector expressing an antisense gene against the HIV envelope. Five patients with HIV infections that were resistant to antiviral therapy and had viral loads of more than 5000 copies/mL and $CD4^+$ T cells counts between 200 and 500 cells/mm^3 were treated. The primary endpoints included adverse events, viral load, $CD4^+$ counts, and the emergence of replication-competent lentivirus derived from the vector. In this phase I study, one subject was reported to have a sustained decrease in viral load. The CD4 counts remained steady or increased in the other four subjects, and sustained gene expression was observed. These preliminary studies support the safety of lentivirus vectors.

Recombinant Adenovirus

Recombinant Adv is a nonenveloped, icosahedral, double-stranded DNA virus with a capsid containing 252 capsomeres (240 hexons and 12 pentons).[13] The large genome of Adv (36 kilobases, kb) allows large genes to be inserted into an Adv-based vector. Transgenes in Adv vectors are not incorporated into the genome of transduced cells but instead remain as an extrachromosomal entity in the nucleus. First isolated from U.S. army recruits who had acute respiratory symptoms, Adv vectors have been found to be common human pathogens. To date, 49 serotypes have been characterized and associated with a variety of symptoms, ranging from a mild cold to acute febrile pharyngitis.[14] Replication-defective recombinant Adv vectors are currently the most commonly used viral vectors in clinical trials. Ad2 and Ad5 are used primarily for gene therapy applications. Recently, however, the Ad11 and Ad35 serotypes were shown to exhibit a unique tropism that includes hematopoietic stem cells, a finding that potentially widens their utility.[15–17]

The Adv vector's genome (Fig. 33-2) can be divided into two main regions: early (E) and late (L) according to the time at which their genes are expressed during virus replication. There are four regions of early genes that are termed *E1, E2, E3,* and *E4,* and one region of late genes comprising the five coding units termed *L1, L2, L3, L4,* and *L5.* The *E1* region is essential for viral replication; therefore, recombinant Advs without the *E1* region are considered replication defective. In a replication-defective Adv vector, the *E1* region can be replaced with a transgene for expression. Moreover, removal of genetic material from the vector, such as the *E3* and/or the *E4* region(s), allows for larger genes to be inserted and reduces the viral immunogenicity.[18] Viruses without the *E3* and *E4* regions are referred to as "gutless" and have decreased antigenicity.[19]

The *E1* region of Adv vectors is subdivided into *E1A* and *E1B.* The *E1A* gene product is a viral transcription unit that activates the expression of other Adv transcription units by binding to viral promoters. The *E1B* region codes for a 55-kd protein that interacts with the cellular p53 tumor suppressor protein and regulates the host cells' cycle progression supporting viral replication. *E1B* also binds to viral *E4* proteins and to p53, which together act to depress host protein synthesis. The *E2* region codes for viral DNA polymerase and the Adv single-stranded DNA-binding protein. The *E3* region is not required for in vitro replication; however, it does offer the virus some protection against host defense mechanisms. The *E4* region codes for proteins involved in

- Regulation of viral and cellular protein expression
- Replication of viral DNA
- Switching off of host protein synthesis

The late genes (*L1–L5*) are expressed at the onset of viral DNA replication and encode structural polypeptides that are needed for virion assembly. This understanding of viral replication has allowed the development of extremely elaborate, conditionally replicative Adv vectors capable of replication only in cancer cells.[20]

The transduction efficiency of Adv vectors is high as compared with that of most other viral vectors. Because of the structural stability of the capsid polypeptides of Adv, viral particles can be purified and concentrated to a very high titer of ~1×10^{12} plaque-forming units (pfu)/mL. This is in contrast to retroviral titers that achieve much lower titers (~1×10^7 pfu/mL) because of their envelopes' instability. Another distinguishing characteristic of Adv vectors is their lack of integration into the human genome. The Adv genome remains in the nucleus of the target cells as a nonreplicating extrachromosomal entity, thereby avoiding any potential for mutagenic effects caused by random integration into the host.

However, Adv vectors have potential shortcomings, including

- Transient expression because the viral DNA does not integrate into the host
- Viral protein expression by the Adv vector after administration into a host
- A common pathogen and in vivo delivery could be hampered by the prior induction of host immunity.[3]

The period of Adv transgene expression is relatively short; therefore, this is a suboptimal vector if expression is desired for longer than 10 to 14 days. This short expression time is due primarily to the induction of a cytotoxic T lymphocyte (CTL) response to viral polypeptides, as well as potentially to the transgene itself, especially if it is not expressed normally. Because the Adv genome does not integrate into the target cell, only one of the daughter cells (if the target cells are dividing) will contain the transgene. Manipulation of the immune response can result in longer expression; however, Adv gene delivery is ideally suited to those situations that require only a single period of transgene expression in which transient expression is desired, for

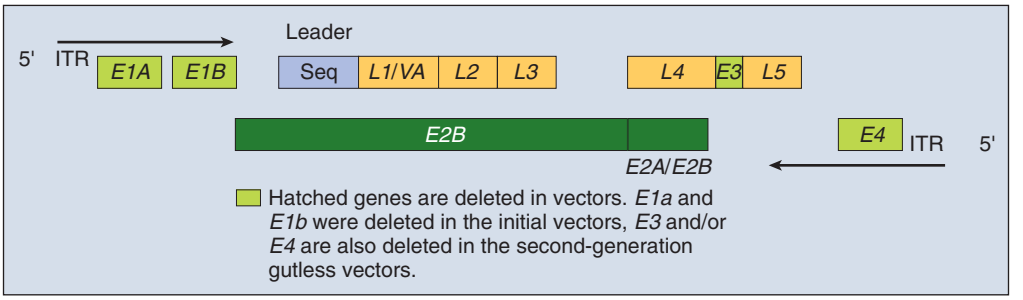


Figure 33-2 • Adenovirus genome. The Adv genome is composed of early and late genes. The *E1A* gene encodes the initial viral transcription unit and must be deleted to prevent the recombinant virus from replicating. In most of the original Adv vectors, *E1A* and *E1B* are deleted. The second-generation vectors (known as gutless vectors) typically also have the *E3* and/or *E4* genes deleted. This deletion allows larger transgenes to be inserted into the Adv vector, and the deletion of *E4* significantly reduces vector immunogenicity with the potential for a more prolonged transgene expression.

Box 33-1. ADENOVIRAL VECTORS

Adenoviral (Adv) vectors have a number of positive and negative attributes. The positive attributes include the transduction of a wide profile of cellular phenotypes such as epithelial, carcinoma, and hematopoietic cells. Further, the use of Adv vectors results in a high frequency of transduction and high levels of transgene expression. A negative attribute of Adv vectors is transient expression, although for appropriate targets such transitory infection is a positive attribute. The transient expression is due, in part, to the high level of innate vector immunogenicity, which can limit multiple cycles of transduction and chronic transgene expression. The resulting Adv profile of activity is ideal for the transduction of dendritic cells (DCs) as vaccines, the purging of tumor cells from stem cell products, and intralesional injection of carcinomas. Further, the ability to develop Adv vectors that are conditionally replicative has great potential for the treatment of neoplastic disease. It is noted that two Adv vectors have received regulatory approval in China. These controversial studies have resulted in the treatment of several thousand patients, supporting the safety of these vectors.

example, growth factor therapy. A second major disadvantage of Adv vectors used in vivo is the immune response (CTL and antibody [Ab]), both endogenous and induced, which can preclude infection and cause the destruction of transduced cells, resulting in local tissue damage and inflammation. This shortcoming was demonstrated in the initial studies with intrabronchial delivery of Adv for the treatment of cystic fibrosis.[21] Host cells presenting peptides from Adv-encoded transgene products target the host cell for CTL-mediated destruction. A third major disadvantage of Adv vectors is that most humans are primed against at least one serotype, because Adv is a naturally occurring virus. Using the same serotype in a gene therapy context will probably result in a rapid and vigorous immune response such that high levels of Adv-specific Abs occur in the sera within days of Adv vector administration. Another similar problem is the potential secondary immune response induced by the readministration of a vector. It must be stressed that transgene expression can occur during a boost, although a shortened duration is observed. The augmentation of a CTL response by an Adv vector suggests the utility of Adv vectors as vaccine adjuvants (Box 33-1).

Recombinant Adeno-associated Virus

Adeno-associated virus (AAV) vectors offer many of the same advantages as Adv vectors, including a wide host-cell range and a relatively high transduction efficiency.[22,23] AAV vectors stably integrate at specific sites in the host genome, resulting in a longer lasting transgene expression. In addition, these stable vectors can infect a variety of dividing and nondividing cells without inducing an immune response. AAV vectors cause little damage to target cells—unlike Adv vectors that can cause a high degree of cytopathogenicity. There is evidence, however, to suggest that AAV vectors are significantly less efficient than retroviral vectors at transducing primary cells, because most of their DNA remains extrachromosomal and does not integrate into the host genome. Furthermore, they cannot incorporate genes larger than 5 kb and must be screened closely for Adv contamination.

Recombinant Herpes Simplex Virus

Herpes simplex virus (HSV) vectors are developed primarily for protocols that target neuronal tissue.[24] Similar to Adv vectors, HSV vectors are maintained as an extrachromosomal DNA element in the nucleus of host cells, but can establish long-lived asymptomatic infections in the sensory neurons of the peripheral and central nervous tissue.[25] HSV vectors also have a wide host range and are similar to Adv vectors in that they allow large gene inserts of up to 20 kb. These vectors are infective even with multiple deletions of immediate-early (*IE*) genes that are essential for replication, resulting in less cytotoxic vectors, thereby reducing safety concerns.[26] HSV vectors can be produced at high titers and express transgenes for a long period of time in the central nervous system.[27] The major concern associated with HSV is the potential for wt virus to replicate lytically in the human brain, resulting in encephalitis. Other significant disadvantages with HSV vectors include

- Requirement for additional engineering to increase efficiency[26]
- Transient expression associated with lytic infection and viral protein expression
- Relatively low transduction efficiency

Recombinant Pox Vectors

The origin of vaccinia virus (VV), the virus used for vaccination against smallpox, is not known, but it was probably derived from cowpox virus, variola virus, or a hybrid of the two.[28,29] Percutaneous VV vaccine administration results in protective cellular and humoral immune responses in greater than 95% of primary vaccinees. Recombinant VV vectors are highly attenuated, host-restricted, and non- or poorly replicating poxvirus strains (including the modified vaccinia Ankra [MVA] and canarypox or avipox vector [Alvac]) and thus do not create productive infections.[30,31] MVA is avirulent in normal and immunosuppressed animals, and safe in humans.[32] Recent studies using transgenic mice provided a comparison of VV immunogenicity, including MVA and Western Reserve (WR). These studies demonstrated that MVA vaccines elicited $CD8^+$ T-cell responses that are comparable to those induced by the replication-competent WR strain. Furthermore, MVA vaccination was shown to be protective against a lethal respiratory challenge with the virulent WR strain.[33] The most frequent adverse complication of VV vaccination is inadvertent inoculation (usually autoinoculation) at other sites. Serious complications, which are more common among primary vaccinees and infants than among revaccinees and adults, include the following:

- Generalized vaccinia in otherwise healthy individuals, which is generally self-limiting
- Eczema vaccinatum, which consists of disseminated cutaneous lesions in highly susceptible patients with eczema or other chronic skin diseases, which can be severe or even fatal
- Progressive vaccinia (vaccinia necrosum), which is a severe, potentially fatal illness seen in patients with immunodeficiency, whether congenital, acquired (e.g., via leukemia or lymphoma), iatrogenic (e.g., via chemotherapy or glucocorticoid treatment), or HIV induced
- Postinfectious encephalitis, which is rare (three cases per million primary vaccinees), but can be fatal in 15% to 25% of cases and can leave 25% of patients with permanent neurologic sequelae

Similar to Adv vectors, VV vectors are used for immune manipulation and as a vector for vaccines.[34] VV vectors have been used worldwide to eradicate smallpox and as discussed earlier, provide a relatively safe live vaccine. Vaccinia vectors do not integrate into the genome of the host cell; however, they can accommodate large transgenes and are extremely immunogenic. VV vectors are used to immunize patients against tumor antigens (Ags) by cloning Ags and/or genes encoding proteins with adjuvant activity (e.g., cytokine or costimulating factor genes) into the viral genome. Most transgenes are expressed at high levels in vivo, eliciting an Ag-specific response. Vector-induced immunity, however, can limit the ability of the vaccinia transgenes to boost an immune response, which is an observation similar to that seen with Adv vectors. The current emphasis is on VV infection of dendritic cells (DCs) using a vector with an antigenic transgene.[34,35]

In association with the immunogenicity of VV vectors and their ability to deliver an antigenic transgene, they have been used clinically

as a melanoma vaccine. In clinical studies by Wallack and colleagues,[36] a phase III trial of a vaccinia melanoma oncolysate, delivered as an active specific immunotherapy, was found to increase the disease-free or overall survival of patients with stage III melanoma in a surgical adjuvant setting. Other studies have used VV mutants that are conditionally replicative and can lyse cancer cells after viral replication. These vectors have been used in a strategy whereby insertional inactivation of the VV thymidine kinase (tk) gene was used to limit viral replication in cells with large intracellular nucleotide pools, such as tumor cells. In a similar approach, Mastrangelo and coworkers[37] inserted the gene for granulocyte-macrophage colony-stimulating factor into the VV tk gene locus as a strategy to generate an oncolytic virus that induced antitumor immunity after infection of malignant melanoma. This vector is currently in a clinical trial of intralesional administration to patients with refractory recurrent melanoma. In the first seven patients studied, two patients had a complete response and three other patients had partial responses. Other oncolytic VV vectors have been engineered with complementary DNAs for cytokines such as interleukin 2 or with prodrug-activating enzymes such as cytosine deaminase to augment antineoplastic efficacy.[38,39]

The role of VV vectors as vaccines has focused predominantly on carcinoembryonic Ag (CEA) as the vaccine Ag. CEA is a glycoprotein self-Ag found on breast, lung, gastric, colon, and ovarian tumors. One such vector is a recombinant VV containing the CEA gene (rV-CEA).[40,41] In a phase I clinical trial, the safety of rV-CEA was demonstrated; however, no significant antineoplastic effects were observed.[42] Possible reasons for the lack of clinical efficacy in these trials include

- Prior exposure to the VV, leading to the development of anti-vaccinia immune responses after repeated vaccinations
- Advanced state of the patients' tumors
- Potentially compromised immune status of the patients

Another phase I rV-CEA vaccine study demonstrated that CEA-specific T-cell responses could be generated in humans after vaccination.[42] A second recombinant anti-CEA vaccine, Alvac-CEA, has been developed.[43,44] Similar to rV-CEA, Alvac-CEA contains the CEA gene; however, unlike rV-CEA, it cannot replicate in mammalian cells. The safety of Alvac-CEA has been documented in phase I trials in patients with advanced carcinomas.[45] A moderate but statistically significant increase in the number of CEA-specific CTL precursors was observed in seven of nine HLA-A2$^+$ patients treated with Alvac-CEA, although objective anticancer effects were not observed. Preclinical studies have suggested that the combination of rV-CEA and Alvac-CEA in a prime and boost protocol can induce a more vigorous T-cell response than either vaccine alone.[44] In a clinical prime-and-boost study, 18 patients with advanced tumors expressing CEA were randomized to receive either rV-CEA followed by three Alvac-CEA vaccinations, or Alvac-CEA (three times) followed by one rV-CEA vaccination. In this study, vaccination with rV-CEA followed by Alvac-CEA resulted in an increased frequency of Ag-specific interferon γ cells by enzyme-linked immunospot assay (ELISPOT) relative to the reverse order of vaccination.[46]

Another method to enhance the responses to a vaccine is to incorporate a costimulatory signal. In the absence of a costimulatory signal, presentation of an Ag to T cells can result in anergy.[47] B7.1, which binds to CD28 on T cells, is one such costimulatory signal that results in the production of interleukin 2 and interferon γ by T cells. In a vaccine study using VV vectors, 39 patients were treated with Alvac-CEA B7.1.[48] In one study using the Alvac-CEA-B7.1 vaccine, patients with metastatic CEA-expressing adenocarcinomas received vaccine intradermally every 2 weeks for a total of four injections. In this phase I trial, 27% of the patients had disease stabilization after four vaccinations. Six of 31 patients with elevated serum CEA levels had a temporary decline in CEA. In addition, HLA-A2$^+$ patients demonstrated increased CEA-specific T-cell frequencies after three vaccinations. Based on these studies and additional phase II data, a phase III trial was initiated in 255 patients with advanced pancreatic cancer at approximately 60 medical centers.[49] The protocol was powered to detect a 2-month improvement over control chemotherapy based on a median overall survival of 6 months. Unfortunately, this study did not meet its primary endpoint of improving overall survival compared with palliative chemotherapy or best supportive care. However, this outcome is not unexpected, because patients with advanced pancreatic cancer have a rapid disease progression and are poorly responsive to intervention in general (Box 33-2).

Box 33-2. VACCINIA VIRAL VECTORS

Vaccinia viral (VV) vectors have a profile of activity analogous to that of adenoviral (Adv) vectors. That is, they can easily transduce a wide range of cells, resulting in transient expression, and have as a negative attribute a brief transgene expression due to the innate antigenicity of the vector. In contrast to Adv vectors, VV vectors almost inevitably lyse the transduced cell, rendering it potentially less attractive as a vector (especially for dendritic cell [DC] transduction) due to the shorter half-life of the transduced cell. Significant experience with the administration of both VV and Adv vectors as vaccines has provided a strong safety profile for both. In theory, the concomitant use of VV and Adv vectors makes possible cycles of vaccine delivery via transduced DCs, allowing a prime and boost immunization with DCs, which have a high frequency of transduction and levels of transgene expression, while reducing the concerns associated with the innate antigenicity of the viral vectors.

Recombinant Alphavirus Vectors (Sindbis)

High-titer alphavirus vectors can provide efficient gene delivery both in vitro and in vivo. In addition, efficient central nervous system infections via intranasal and vascular injections with virulent and avirulent replication-competent Semliki Forest virus (SFV) strains have been shown in animal models.[50–52] Replication-deficient alphavirus particles have a high local and transient transgene expression in rodent brains. Furthermore, repeated SFV injections are possible in the absence of an immunogenic response against SFV, which is in contrast to Adv and VV vectors. Modifications to the envelope structure of Sindbis virus are possible with resultant changes in host range and targeting. The favorable characteristics of alphavirus vectors include

- Rapid production of high-titer virus
- Broad host range
- High RNA replication rate in the cytoplasm
- High transgene expression levels

Negative attributes include

- Short-term expression
- Strong cytotoxic effects on host cells

Nonetheless, both these properties are advantageous for certain indicators, particularly vaccine production.

Nonviral Gene Transfer Vectors

Nonessential genes can be removed from viral vectors to allow room for transgene(s) to reduce inflammatory responses and to increase safety.[53,54] This process involves simplifying the virus, sometimes to an extreme. After undergoing such a process, a virus vector can be an artificial "vector shell" allowing the gene of interest to be expressed at high levels, in a highly regulated manner, and for a controlled period of time. Another approach to achieve the same result is to produce a vector that can introduce genetic material to the nucleus of cells.[53,55,56] This strategy has resulted in the development of several

nonviral vector systems; however, the efficiency of "naked DNA" as a therapeutic is suboptimal without some form of carrier or formulation.

Direct DNA Injection and Transduction

One form of nonviral gene delivery is the use of purified DNA plasmids.[55] The transgene expression is low following intramuscular or intratumoral injection; however, high levels are observed if hydrodynamic injection is used.[57,58] The approach of naked DNA injection is typically done as an intramuscular or intratumoral injection. Despite the simplicity of this approach, transfection efficiency is low and results in limited expression. Various formulations, including lipid or pluronic formulations, and incorporation into nanoparticles or liposomes, have been used to improve transduction efficacy and gene expression (Box 33-3).[59–61]

Nonviral liposomal delivery systems can be IV injected with limited vector-associated toxicity, but with transgene expression, especially in the lungs.[62] Tumor targeting using tumor-specific promoters, ligandation of receptors to the liposome surface, and pegylation of liposomes have all been studied.[63–69] Although some degree of tumor targeting has been observed using these delivery systems, the level of transgene expression is generally low. Studies have revealed that liposome-DNA complexes can also elicit an inflammatory response when injected systemically, resulting in suppression of transgene expression.[70–72] Furthermore, failure to achieve increased or sustained gene expression after repeated injections has been a major obstacle in the development of liposomes.[70,73] Recently, it was shown that cationic liposome (DOTAP : cholesterol or DOTAP : Chol)–DNA complexes can achieve effective levels of transgene expression in tumor-bearing lungs and when injected IV can achieve levels sufficient to cure immunocompetent mice with disseminated experimental metastases.[74] Furthermore, repeated daily injections can result in a dose-dependent increase in transgene expression in tumor-bearing lungs.[75]

Hydrodynamic Gene Delivery

Hydrodynamic tail-vein plasmid delivery results in high levels of transgene expression in the livers of rodents.[76] Lower levels of transgene expression (100- to 1000-fold) are found in the spleen, heart, kidneys, and lungs. This simple nonviral gene transfer procedure entails the rapid delivery of naked plasmid DNA in a relatively large volume of physiologic saline.[57] In a typical mouse, weighing 20 g, the plasmid is delivered in a total volume of 2.0 mL over a period of 5 to 7 sec. Although there are toxicity issues, clinical studies are under discussion for the delivery of dystrophin into the arms of Duchenne muscular dystrophy patients.[77]

Liposomes and Virosomes

In their most basic form, liposomes consist of two lipid species: a cationic amphiphile and a neutral phospholipid.[75,78] Liposomes spontaneously bind to and condense DNA to form complexes that have a high affinity for the plasma membranes of cells, resulting in the uptake of liposomes to the cytoplasm by endocytosis. Many variations of this approach are used, resulting in varying levels of gene expression. Unfortunately, liposome-facilitated gene delivery is relatively ineffectual in vivo. More recently, some of the advantages of viral delivery vectors have been combined with the safety and "simplicity" of the liposome to produce fusigenic virosomes.[78] Virosomes are engineered by forming complexes of the membrane fusion proteins with liposomes that have already-encapsulated plasmid DNA. The inherent ability of the viral proteins in virosomes to fuse with cell membranes results in the efficient introduction of DNA to the target cell, providing improved gene expression. Viral vectors have limitations based on the size of transgene that can be incorporated; in contrast, no such limit exists for virosome or liposome technology (at least in theory).

Ballistic Delivery (Gene Gun)

This physical method of gene delivery involves microcarriers (usually gold particles) coated with DNA and "fired" at high velocity using an explosive or gas-powered ballistic device called a "gene gun."[79–81] Once the particles are inside the target cell, the DNA is slowly released from the microcarriers, resulting in gene transcription and translation. This application has been used extensively in vivo, but its clinical use is restricted to exposable surfaces or ex vivo transduction because the fired particles do not penetrate tissues deeply.[82]

Nanoparticles

Novel polymeric delivery systems (e.g., nanospheres) that can be administered in novel ways are being developed.[83–85] These particles are potentially useful because the smaller the condensed DNA particles are, the better will be their in vivo diffusion toward target cells and the trafficking within the cell. Individual plasmid molecules can be collapsed into a nanoparticle using detergents. For example, nanoparticle-based gene delivery was targeted to the neovasculature of mice using an integrin-targeting ligand, resulting in tumor regression.[86] Nonetheless, the size of the transgene that can be delivered by nanoparticles is limiting, and the primary focus has been on small interfering RNA (siRNA) delivery, which will be discussed in the following section.

Box 33-3. PLASMID AND RETROVIRAL VECTORS

The transduction efficiency of plasmid vectors is low, even with the use of formulations to improve transfection efficiency and increase transgene expression. Further, this approach appears to work better in vitro than in vivo. In contrast to viral vectors, plasmid vectors offer little innate antigenicity, although there have been reports of immune responses to bacterial genes. Positive attributes of plasmid vectors include the low level of innate immunogenicity and the potential for genomic integration. The use of hydrodynamic delivery in rodents has provided a powerful preclinical tool. However, clinical translation is problematic with the potential for utilization in an isolated limb. In contrast, retroviral and lentiviral vectors provide the same characteristics with higher levels of transgene expression and improved transduction efficiency relative to plasmids. However, the improved transgene expression and transduction levels of retroviral and lentiviral vectors remain significantly lower than those of adenoviral and vaccinia vectors.

Nucleic Acid-Based Therapeutics

DNA Transduction

High-molecular-weight, double-stranded DNA constructs containing transgenes, which encode specific proteins, are classically used in gene therapy to introduce transgenes into cells that inherently lack the ability to produce a protein of interest. In addition to being used to treat congenital diseases, DNA vectors can be used as vaccines for genetic immunization.[87] Suicide gene therapy is another rapidly emerging strategy for the induction of transgenes.[88,89] In this approach, chemosensitization genes are delivered to tumor cells, which upon gene expression convert a separately administered, nontoxic prodrug into a chemotoxic drug. Because only the transfected tumor cells can convert the prodrug, the susceptibility to the chemotoxic entity is limited to the tumor cells—hence the term suicide gene therapy.

RNA Transduction

Thus far the primary transgene source for DC transduction is DNA, although other Ag sources are also used with DCs, including peptides, recombinant or purified proteins, cellular extracts from tumor

cells, apoptotic bodies, and RNA or DNA plasmid vectors. Nevertheless, the carrier of choice for loading DCs with tumor Ags is DNA or RNA.[90] Nucleic acid transfection leads to the display of multiple antigenic epitopes by both class I and II major histocompatibility complex via the Ag-processing machinery of the patients' DCs, resulting in the display of the "most appropriate" peptides. This is in contrast to vaccine strategies based on synthetic peptides, which require the knowledge of the patient's unique peptide epitopes. Thus, nucleic acid transfection of DCs offers several advantages for both immunologic and practical considerations.

The bias for the use of DNA vectors includes an increased stability as compared with RNA, the ability to produce plasmids in large quantities, and the ease with which the sequence can be modified to regulate expression.[91] In several respects, however, RNA vectors are also advantageous when compared with DNA transfection. RNA vector advantages include the ability to use total messenger RNA (mRNA) isolated from tumors to transfect DCs with no intervening cloning steps and the ability to express several or potentially all tumor-derived genes within DCs. Transfected RNA need only reach the cytoplasm of DCs, whereas DNA requires entry into the nucleus and subsequent transcription. Furthermore, it has been suggested that the low level of antigenic epitope expression that occurs with RNA-transfected DCs could be advantageous, provided that expression levels are sufficient to generate a T-cell response.[90,91] When low levels of antigenic peptides are presented by DCs, only those T cells with high-affinity recognition are activated, thus skewing the response toward T cells that can better recognize the tumor cells. Conversely, when DCs present high levels of antigenic peptides, T cells of low affinity may be activated, thus masking or even preventing the activation of high-affinity T cells. This could result in T cells that kill cells with high Ag expression but cannot kill tumor cells, which typically express low Ag levels. Thus, RNA-transfected DCs might have greater efficacy for the activation of high-affinity T cells.[91]

Oligonucleotides

Oligonucleotides are short single-stranded segments of DNA or RNA that upon cellular internalization can selectively inhibit the expression of a single protein.[92] Multiple forms of oligonucleotides are used in gene therapy including antisense, siRNA, and ribozymes. Most of these constructs form a duplex with the mRNA or the pre-mRNA and inhibit their translation or processing, consequently inhibiting protein biosynthesis. This occurs by multiple mechanisms, as discussed in the following section.

Small Interfering RNA

RNA interference is a recently discovered mechanism for silencing the transcription of mRNA. siRNA is generated by dicer, an endonuclease that cleaves long double-stranded RNA molecules into fragments of 21 to 23 base pairs (bp) and is highly specific for the nucleotide sequence of its target mRNA siRNAs.[93–96] These siRNAs associate with helicase and nuclease molecules and form a large complex, which is termed RNA-induced silencing complex that unwinds siRNA and directs precise, sequence-specific degradation of mRNA. Although RNA interference was discovered only recently, the field has exploded.[97] It is now apparent that RNA interference is a highly conserved molecular mechanism that is used by eukaryotic organisms to control gene expression during development and to defend their genomes against invaders, such as transposons and RNA viruses. Recently, it was shown that siRNA is active in vivo with resultant therapeutic activity.[98] In one study, siRNA knockdown of the mutant K-*ras* oncogene had pronounced antitumor activity.[99] In this study, siRNA was delivered as a nonreplicative retroviral transgene and was shown to inhibit the relevant mutant K-*ras* and prevent anchor-independent growth and tumorigenicity.

Antitumor activities can also be induced in vivo through siRNA knockdown of other critical components of tumor growth, metastasis, angiogenesis, and chemoresistance.[100] Stable transfection and expression of siRNA is obtained with nonreplicating viruses[101,102]; however, oncolytic virus vectors provide a potential method to extend bioactivity. The tumor-selective infectivity has the potential to restrict transgene expression to the cancer microenvironment, potentially reducing toxicity and extending transgene expression via viral replication and multiple cycles of the infection of permissive cancer cells.[103,104] Furthermore, viral oncolysis has the potential to augment antitumor outcomes by siRNA-mediated therapeutic activity. In a recent study,[105] the replication-competent, oncolytic adenovirus, ONYX-411, was used to deliver a mutant K-*ras* siRNA transgene. In this study, additive tumor growth-inhibitory responses via siRNA-mediated K-*ras* knockdown and ONYX-411–mediated oncolysis were observed. Therapy with ONYX alone or ONXY-411 with green fluorescent protein siRNA as controls had significantly lower therapeutic activity.

Antisense

The principles of antisense technology are conceptually simple. Oligonucleotides are designed to hybridize to a defined target mRNA and to inhibit its translation into protein.[106,107] This approach was first employed in 1978 by Stephenson and Zamecnik[108] to inhibit the Rous sarcoma virus expression in chicken fibroblasts. Several antisense oligonucleotides are in clinical trials, and one has received Food and Drug Administration (FDA) approval for the treatment of cytomegalovirus retinitis. Currently, an antisense to Bcl2 has been submitted for licensing by the Food and Drug Administration for the treatment of leukemia.[109] Although it is relatively easy to synthesize phosphodiester oligonucleotides, they cannot be used as drugs because of their sensitivity to nuclease degradation. To improve their resistance to nuclease digestion, different chemical modifications are used, including phosphorothioates, methylphosphonates, and phosphoramidates.[110] These modifications increase the stability of oligonucleotides, but they also alter the capacity to hybridize with RNA and reduce cellular internalization.

Ribozymes

Ribozymes are RNA molecules capable of sequence-specific cleaving of mRNA molecules.[111] They selectively bind to target mRNAs and form a duplex that is easily hydrolyzed, suppressing specific genes.[54] Two types of ribozymes, the hammerhead and hairpin, have been extensively studied.[112] However, the RNA backbone in ribozymes is an easy target for RNases, so they are biologically unstable in vivo.[54] Ribozymes have been used primarily for gene suppression, the induction of apoptosis, and antiproliferative effects. Phase I clinical trials using ribozyme gene therapy to treat AIDS patients are ongoing.[113]

GENE TARGETING

Targeted gene therapy of cancer can be achieved through

- Targeted gene expression
- Vector targeting[13,114,115]

Although it is less important during ex vivo or intratumoral gene delivery, targeted gene therapy becomes crucial with systemic gene transfer. Impediments to gene therapy include the poor selectivity of existing vectors and the low efficiency of gene transfer. Overcoming these hurdles is critical to achieving vectors that can be targeted and injected IV—an important goal given the systemic nature of cancer.

Conditional Gene Targeting

Vector targeting is a goal for both viral and nonviral vectors[13,114]; however, the current emphasis is on tissue- or target-specific promoters. Transcriptional regulatory sequences are used because they are responsible for protein production in carcinoma cells such as oncogene products. One example is the use of tissue-specific promoters to

facilitate tumor-specific killing via expression of a suicide gene (such as the HSV-tk) followed by exposure to ganciclovir, or the expression of the cytosine deaminase gene and exposure to 5-fluorocytosine. In addition, transcriptional targeting is used to achieve conditionally targeted transgene expression.

Tissue-Specific Promoters

The production of proteins within a cell requires that the appropriate gene be transcribed into mRNA and then translated to protein.[116] This process is under multiple levels of control, with the regulation of transcription mediated by interactions between the enhancer/promoter region of the appropriate piece of DNA and the specific proteins or transcription factors that bind to this region. Activation or repression of promoters is achieved through interactions with specific transcription factors. Thus, some tissues might express specific proteins because the promoter for that gene is activated in that tissue alone. The success of transcriptional targeting is dependent on achieving a differential gene expression in cancer cells as compared with normal cells. Transcriptional control of gene therapy is an important goal for two reasons:

1. Current gene transfer vectors can be inefficient in gaining entry into the types of cells needing treatment.
2. Many therapeutic genes can be toxic if delivered to an unintended cellular target.

Criteria for selecting a promoter for use in a gene therapy protocol include consideration of the promoter's strength, tissue specificity, and size. Promoter candidates include regulatory elements that are already expressed by the malignant cell, tissue-specific promoters, or externally inducible sequences. Unfortunately, any of these candidate promoters can lack sufficient activity, specificity, or both. To address promoter potency, promoters and enhancers that retain cell-specific function are often linked to transactivators. Additional strategies to enhance promoter activity in malignant tissues include the use of cell-cycle elements, normal or abnormal tissue differentiation factors, hormones, cytokines, chemicals, or physical stimuli.

A convenient classification of candidate promoters for cancer gene therapy (Table 33-1) includes tumor-associated, tissue-specific, and inducible promoters. These are further discussed in the ensuing sections, as is the role of transcriptional regulation of replication-competent viruses. Specific examples are provided that are the most mature developmentally but should be viewed as representative. The most focused reviews and articles are referenced.

Tumor-Associated Promoters

Selective delivery of a transgene to a tumor is not currently an achievable clinical goal. Consequently, tissue and tumor promoters are used to regulate transgene expression in a given tumor tissue with the goal of reducing nonspecific transgene expression. However, this approach retains challenges, including the infection of only a small fraction of tumor cells within the target tissue. As such, tumor-specific and associated promoters are also extensively utilized to target transgene expression, especially ones associated with the tumor vasculature.[117–119]

TELOMERASE. Telomerase, an RNA-dependent DNA polymerase that synthesizes new telomeric repeats at the end of chromosomes, is expressed in high levels in malignant tumors, stem cells, and germ cells, but not in normal tissues. It is thought to be essential for the maintenance of the proliferative capacity of tumor cells and, for this reason it represents an attractive target for gene therapy. The human telomerase reverse transcriptase is regulated primarily at the transcriptional level, and its promoter has the potential for targeted cancer gene therapy.[120,121]

TUMOR VASCULATURE. Another target for gene therapy is provided by the tumor's vasculature. The tumor vasculature has excellent accessibility to systemic delivery across all solid tumor types.[122] Indeed, high levels of vascular endothelial growth factor (VEGF), a growth stimulus for endothelial cells, have been correlated with a poor prognosis for specific tumor histotypes. VEGF activity is mediated by two high-affinity receptors: the tyrosine kinases VEGFR-1/fms-like tyrosine kinase (Flt-) 1 and VEGFR-2/flk-1. These ligand-stimulated tyrosine kinases are induced in a tumor stage-dependent manner during cancer progression and are expressed exclusively in tumor vascular endothelial cells.[123] This suggests that VEGF receptors are promising targets for tumor endothelial cell-specific therapy.[122,124] Thus, the 939-bp Flk-1 promoter fragment and an enhancer element located in a 2.3-kb fragment upstream have been used to induce tumor endothelium-specific reporter gene expression in transgenic mice.[125] Targeting of the VEGF receptor/ligand system has been shown to be a useful approach with which to inhibit tumor growth and prolong survival in colon cancer.[124] The human preproendothelin-1 promoter has also been shown to have specificity for breast microvascular endothelial cells using a recombinant retroviral vector.[126]

Tumor-Specific Promoters

PROSTATE-SPECIFIC ANTIGEN. Prostate-specific Ag (PSA) is expressed at a high level in the luminal epithelial cells of the prostate and is absent or expressed at low levels in other tissues. The PSA promoter is usually regulated by androgens, but it might retain its activity in an androgen-free environment. The minimal PSA promoter, however, is weak in both PSA^+ and PSA^- cells and does not respond to androgenic stimuli. Nonetheless, the PSA promoter has been used to target the delivery of therapeutic genes to prostate tumors.[127,128]

TYROSINASE. Specificity for malignant melanoma may be conferred by the human tyrosinase promoter.[129,130] Driven by this promoter, in vitro and in vivo melanoma transduction by constructs results in selective transgene with the potential to induce tumor regression. Similarly, a construct consisting of the human tyrosinase promoter linked to two enhancer elements causes high-level, melanoma-specific expression of a reporter gene in transient transfection assays. The murine tyrosinase promoter-enhancer expression cassette expressed by an Adv vector maintains transcriptional specificity for pigment cell lineages, especially human melanoma cell lines.

Conditional Replication and Inducible Promoters

During evolution, various stress response genes developed, and their promoters are now considered as gene therapy transcriptional regulators. Heat, hypoxia, glucose deprivation, irradiation, and chemotherapeutic agents upregulate stress response genes. Because of the relative weakness of tissue- and tumor-specific promoters, these inducible promoters are attractive as mediators of transient transgene activation. Promoters of these genes are also attractive for cancer gene therapy because they depend to a large extent on the biology of the tumor or are already induced by various therapeutic modalities.[131,132]

STRESS-ASSOCIATED GENES. Genes that are upregulated during stress include *ABCB1*, human heat-shock protein (*HSP*), *VEGF,* irradiation-inducible *EGR1* (early growth response gene), and the tissue plasminogen activator (tpa) promoters. Irradiation-responsive promoter sequences have been identified for the tpa and *EGR1* genes.[133] The first irradiation-inducible promoter system used in combination with gene therapy involved the *EGR1* promoter driving either the radiosensitizing cytokine tumor necrosis factor α (TNF-α) or tk. The HSP family is induced by a variety of environmental conditions, including heat, irradiation, photobeam irradiation, hypoxia, acidosis, hypoglycemia, and osmotic changes. These conditions can exist in poorly vascularized tumors and can trigger anticancer gene expression linked to the *HSP70* promoter.[134] It is significant that HSP70 expression is upregulated in p53-deficient tumor cells, thereby providing transcriptional targeting.

Table 33-1 Transcriptional Regulation for Cancer Gene Therapy

Transcriptional Mechanism	Promoter	Target Tumor
TISSUE SPECIFICITY	PSA, Kallikrein	Prostate
	Tyrosinase	Melanoma
	CEA	Hepatocellular carcinomas (HCC): breast, lung, and pancreas cancers
	α-fetal protein (AFP)	HCC
	c-erb B2	Pancreas
	Amylase	Pancreas
	SP-B	Lung cancer
	Grp	Small cell lung carcinoma
	AVP	Small cell lung cancer
	Immunogloblin heavy chain	B lymphomas
	AP-2	Breast cancer
	α-lactalbumin	Breast cancer
	Osteocalcin	Osteosarcoma
	Prolactin	Prolactinoma
	Insulin	β-islet cells
	Whey acidic protein	Breast cancer
	Cirulatory leukoprotease inhibitor (CLPI)	Lung, colon, breast, bladder, oropharyngeal, ovarian, and endometrial carcinomas
	Glial fibrillary acidic protein	Brain astrocytes, glioma cells
	Albumin	Liver
	T-cell receptor	T lymphocytes
	Her 2/*neu*	Breast, pancreatic, and gastric carcinomas
	Myc-Max responsive element	Lung cancer
	MUC-1	Adenocarcinomas
ABERRANT TUMOR BIOLOGY	Telomerase	Urinary bladder and HCC
	FLK-1	Melanoma, fibrosarcoma and breast tumor vessels
	E-selectin	Tumor vasculature
	VEGF	Lung cancer
	Hexokinase II	Lung cancer
	c-erb B2	Breast and pancreas tumors
	c-Myc	Small cell lung cancer
	L-plastin	Ovarian carcinoma
	SLPI	Lung and ovary tumors
INDUCIBLE PROMOTER	EGR-1	Glioma
	Hsp70	Prostate, breast, and melanomas
	Grp78	Fibrosarcoma
	ABCB1	Breast

MULTIDRUG RESISTANCE GENES. ABCB1 encodes a membrane effluxing glycoprotein, whose expression is induced by vincristine, actinomycin D, and doxorubicin. Its promoter is indirectly transactivated by these compounds and induces transcription and expression of therapeutic genes, such as TNF-α in tumors exposed to chemotherapy.[135] Chemotherapy can also induce another mechanism of drug resistance, namely, activation of the glutathione detoxification system and apoptosis-controlling gene alterations (especially p53 and bcl-2). Because the ABCB1 promoter contains heat-responsive elements, it is also activated by HSP. In addition to its promoter activity, ABCB1 can be transduced into hematopoietic stem cells to reduce the myelosuppressive effects of chemotherapy and radiotherapy.[136]

DEXAMETHASONE. Several drug-related gene expression systems are available to control target gene transcription through the use of small-molecule-inducing compounds.[137,138] Although the utility of such systems has been demonstrated in vitro and in transgenic mice, they are also targeting use in a therapeutic context.[139,140] Dexamethasone, a synthetic glucocorticoid, can selectively activate the p21 promoter in rat hepatoma cells via a glucocorticoid-responsive region between nucleotides 21481 and 21184.[141] This region

does not contain a canonical glucocorticoid response element, but it confers specific dexamethasone responsiveness to heterologous prostate promoters.

TETRACYCLINE RESPONSE ELEMENTS. The Tet-controlled transcription system is made up of Tet-off and Tet-on transcriptional regulation, derived from the *Escherichia coli* Tet-resistance operon.[142] The Tet-R system can be used to suppress or induce cytotoxic and reporter gene expression.[143,144] The latter selects gene expression to p53-deficient tumor cells. Similar to Tet-R, mifepristone is an orally bioavailable antiprogestin that can switch on gene expression in allosteric systems, whereby a chimeric transactivator activates a target gene.[145] This system can circumvent constitutive expression of transgenes in normal tissues by drug-specific and temporal regulation of the target gene. In addition, the replacement of the activation domain of the chimeric transactivator with a transcriptional repressor domain results in inducible repression of the transgene.[146]

Conditionally Replicative Viruses

Toxic or tumor suppressor gene expression from nonreplicative vectors, as a single therapeutic, is inadequate to control solid-tumor growth in humans.[147,148] Thus, replication-competent viruses have been developed and tested as therapeutic agents in cancer. Adv vectors are the most commonly used agents in this context, although retrovirus, reovirus, HSV, and vesicular stomatitis virus are all used for the treatment of malignancies.

The criteria governing the utility of replication-competent viruses include infection efficacy, replication selectivity, viral dispersion from the injection site, and evasion of the host immune response. Augmented gene transfer efficiency has been reported for Adv vectors based on the coxsackievirus Adv receptor (CAR)-independent cellular entry pathways.[149] Propagation of these vectors within tumor tissue remains a challenge, however. Recent improvements in our understanding of cancer biology have made possible the development of viral vectors with improved tumor-selective replication and the restriction of lytic effects to cancer cells. Dysregulation of the normal control over cell cycle and circumvention of physiologic apoptotic signals might allow tumor-selective replication of an engineered virus and, subsequently, direct oncolysis by viral cell killing.[150]

Conditionally Replicative Adenoviruses

Conditionally replicative Ads (CRAds) are designed by the deletion of Adv natural genes encoding cell-cycle regulatory proteins and/or by placing a tissue-specific promoter to control a viral gene essential for viral replication. An example of a vector with a deleted Adv gene is the deletion of CRAd *E1A* (Table 33-2). This results in a loss of its conserved region 2, which precludes binding to the retinoblastoma gene (*Rb*) and eliminates the inhibitory effect of *Rb* on *E2F*. Consequently, the engineered Adv replicates selectively within cells in which the G1-S phase checkpoint is impaired (i.e., tumor cells).[151,152] Deletion of the Adv *E1B* 55-kd protein was initially suggested to be selective for replication in p53-mutant cells, but this hypothesis has since been questioned.[153,154] Despite the mechanistic uncertainty, the *E1B*-deleted ONYX-015 virus selectively infects head and neck tumor cells and could show a clinical benefit in patients with recurrent carcinomas.[155] Although ONYX-015 does not have a therapeutic transgene and relies on its lytic effect, this is the first clinical utility of a CRAd for cancer therapy. It should be remarked that development of ONYX-015 by the American biotechnology company, ONYX Pharmaceuticals, was halted primarily because of financial concerns. Shanghai Sunway Biotech Co. licensed world rights to ONYX-015 and obtained regulatory approval in China in December 2005.[2] This gene therapy product, H101 (ONYX-015), is a recombinant Adv modified to selectively replicate in and kill tumor cells with TP53 mutations. This involves a loss-of-function mutation at the *E1B* locus. The *E1B* locus product is a 55-kd protein that binds to and inactivates the p53 tumor suppressor protein. Thus, the vector is crippled in its ability to grow in cells with wt TP53, and replicates and causes the death of cells with mutant TP53.[156] Phase I, II, and III clinical trials undertaken in China have been reported to show the safety of H101 with efficacy demonstrated in patients with HNSCC. Approval was based on a study that combined H101 and chemotherapy, which was reported to be effective in 78.8% of patients with this disease.[157]

Recently, mutants of human Adv 5 (Ad5) with enhanced oncolytic activity have been isolated using a procedure termed bioselection. In this process, Ad5 is mutagenized and repeatedly passaged in a human colorectal cancer cell line. From such a cell line, mutants can be found that replicate more rapidly than wt Ad5 and that lyse cells up to a thousand-fold more efficiently.[158] Another strategy for designing CRAds uses tissue-specific promoters to drive expression of *E1A,* thereby restricting viral replication to specific tissues or tumors.[159] The application of heterologous promoters in Adv vectors is difficult because their activity and specificity are often affected by viral enhancers and promoters. The *E1A* gene expressed from the alpha fetoprotein (*AFP*) gene promoter induces relatively selective replication in hepatocellular carcinoma cells.[159] Control of Adv *E1A* expression under the minimal PSA enhancer/promoter has also been shown to confer prostate-specific oncolytic viral replication.[160] Recently, a reengineered Adv vector with enhanced oncolytic efficacy was developed. This vector contained a novel regulatory circuit in which p53-dependent expression of an antagonist of the *E2F* transcription factor inhibits viral replication in normal cells. In tumor cells, however, the combination of the p53 pathway defects and deregulated *E2F* allows replication at near-wt levels. This Adv vector also has significantly enhanced efficacy for the treatment of human xenograft tumor models compared with the extensively studied *E1B*-deleted Adv vectors.[20]

CRAds for breast tumors have been created using the DF3/MUC1 promoter (which is abnormally activated in breast tumors) and are

Table 33-2 Transcriptional Regulation of Adv Replication

Genetic Modification	Biologic Result
Deletion of E1A (AA 121–127)	Transformation deficiency
Deletion of E1B 55 K protein	Susceptibility to apoptosis
E1A control by the αFP promoter	E1A transcription limited to αFP^+ cells
E1A control of the PSA promoter	E1A transcription limited to PSA^+ cells
E1A control by the DF3/MUC1 promoter	E1A transcription limited to $DF3/MUC1^+$ cells
E1A control by the pS2 promoter	E1A transcription limited to estrogen $receptor^+$ cells
E1A control by the Sp-B promoter	E1A transcription limited to surfactant producing cells
E1 deletion	Selective DNA replication of Adv vectors in trans-complementing tumor cells

used to drive the expression of *E1A.* This CRAd selectively replicates in MUC1$^+$ cells and can inhibit the growth of human breast cancer xenografts.[161] Another approach is to target CRAd replication within estrogen receptor (ER)-positive tumors based on replacing the *E1A* and *E4* promoters with a portion of the pS2 promoter containing two estrogen-responsive elements.[162] This promoter induces transcriptional activation of the *E1A* and *E4* in response to estrogen in cells that express an ER. This CRAd is able to lyse ER$^+$ human breast cancer cell lines as efficiently as Adv, with decreased capacity to affect ER$^-$ cells.

Another strategy that has been reported recently makes use of the generation of a functional promoter/gene constellation only on Adv DNA replication, thereby providing selective transcriptional activation.[163] These strategies to discriminate between tumor and normal tissue are based on selective DNA replication of Adv vectors with the entire *E1* gene in tumor cells deleted. An *E1* deletion is considered to abolish Adv replication; however, human tumor cell lines apparently can support DNA replication of Ad with an *E1* deletion. Inverted repeats insert into the *E1* region of AdE1 vectors can mediate genomic rearrangements, and bring a transgene into control of a promoter. Thus, formation of a functional expression cassette depends on viral DNA replication, which is expected to occur specifically in tumor cells.

Vector Targeting

Targeted in vivo gene transfer is becoming a reality as a result of an improved understanding of influences that govern gene delivery.[13,14,114] Viral-based vectors are designed to avoid gene transfer through their native receptors and are redirected to tissue- and tumor-specific receptors. In most therapeutic applications, the vector is introduced into a mixed population of cells with the goal of delivering the therapeutic transgene to specific cells. Transduced stem cells can also be targeted to treat certain genetic diseases, improve tolerance to chemotherapy, or assist in tissue repair and remodeling. DCs can also be targeted for the development of improved vaccines. Finally, a systemically administered, targeted vector can potentially reach systemic disease. Nevertheless, these vectors require additional development, including clinical testing, reduced liabilities (including innate and acquired immune augmentation), and an improved understanding of the mechanisms that govern biodistribution and pharmacokinetics.

Ligand-directed targeting of gene vectors allows control of the site at which genes are expressed by imparting the capacity to distinguish between target and nontarget tissue(s). These ligand-directed targeting vectors achieve this capability through the addition of ligands to the vector that recognize receptors specific for a tissue or disease. This approach has met two goals:

1. Improved efficiency for the current gene transfer vectors in transducing the targeted cells that need treatment
2. Reduction in the toxicity due to delivery of therapeutic genes to unintended target cells

Thus, ligand-directed targeting can potentially improve both the safety and the efficacy of gene transfer and make possible therapies that could not be envisioned with standard gene transfer vehicles.

Although targeting gene transfer to specific cells and tissues holds promise, it is a challenge for vector design. Regardless of the vector, three variables are critical to ligand-directed targeting. These include cellular specificity, physical barriers, and the host innate or acquired response, which could eliminate the vector from the circulation. Cellular specificity can be achieved by the use of ligands that recognize cell-specific receptors. For viral-based vectors, specificity requires a targeting element plus modification of the vector so that it no longer binds to its native cellular receptors. In the case of nonviral vectors, targeting requires modification of the vector to avoid nonspecific uptake. Apart from cellular specificity, physical barriers (e.g., the cellular matrix) can limit access of the vector to the target cell. Finally, avoiding elimination and neutralization of vectors by innate and acquired immunity is critical to gene transfer. This is critical, because Abs and serum proteins can directly inactivate the vector or direct it to the liver for rapid clearance, if the vector is given systemically.

Adenoviral Vectors

Our improved understanding of the attachment and entry processes of Adv vectors has facilitated the development of Adv-targeting vectors.[13,34,114] The nonenveloped subgroup C Adv vectors use at least two coat proteins to gain entry into cells. The knob portion of the fiber coat protein binds to the cellular receptor, CAR, and mediates virus attachment.[164,165] At the base of the fiber protein, the penton base coat protein contains an Arg-Gly-Asp (RGD) motif that binds to integrins and facilitates vector uptake into the cell.[166] Compared with a vector with native receptor binding interactions intact, gene expression in the liver and other organs is substantially reduced after systemic administration of a vector containing mutations that ablate CAR and integrin binding.[167] This observation suggests that these receptor interactions are important for in vivo gene transfer. The loss of CAR and integrin binding also reduces gene transfer after direct injection. Furthermore, it allows Adv vectors to be retargeted genetically.[17,168] Ablation of CAR binding alone does not significantly reduce liver gene transfer, which suggests that the standard two-step model of attachment via the CAR and entry by means of integrins does not apply to in vivo gene transfer to the liver, which instead probably involves Kupffer cells.

Adv vectors have been retargeted by both genetic and nongenetic means. Peptides (including the fiber, penton base, and hexon) have been functionally incorporated into coat proteins, although few functional peptide ligands have been identified thus far.[166,169–173] In addition to genetic modifications for retargeting viral vectors, ligation approaches have also been used with Adv vectors. Such approaches involve a bifunctional adaptor or bridging molecule that binds to the vector and to a target receptor. Such systems have demonstrated the feasibility of targeting conventional Adv vectors to more than 20 different receptors, including α_v integrins, endoglin, E-selectin, EpCAM, and folate receptors.[114] Specific targeting to the lung vasculature has also been demonstrated through a combination of receptor-based targeting via lung endothelial-specific receptor, angiotensin-converting enzyme, and promoter-based targeting through the endothelial-specific promoter, Flt-1.

Structural Modification of the Fiber Protein

One approach to Adv retargeting involves engineering of the knob domain of the fiber protein. In this domain, the introduction of heterologous cell targeting peptides requires consideration of the structural limitations of the fiber three-dimensional configuration. The fiber is synthesized as a monomer, which undergoes trimerization before its attachment to the penton base. Thus, any modification of the knob domain of the fiber must not impair trimer formation. In addition, the final quaternary configuration of the new fiber must make the incorporated ligand accessible to target cell receptor recognition and binding.

Recombinant Adv vectors have been constructed with a heparin/heparan sulfate-binding domain, consisting of polylysine residues added to the C terminus of the fiber. Gene transfer to different mammalian cells has been obtained with a level of efficiency 10- to 300-fold higher as compared with unmodified vector.[174] The main drawback with this approach is the lack of specificity, because most mammalian cells express heparin-containing cellular receptors. Genetic modification of the Adv fiber C terminus is limited, because the addition of more than 25 to 30 amino acid residues renders the fiber trimer unstable and limits function.[175] The modification of Adv vectors by placing an RGD peptide in the HI loop rather than in the C terminus of the fiber knob domain was reported recently.[176] This

modification resulted in an increase in gene transfer to ovarian cancer cell lines (30- to 600-fold) and ovarian cancer cells (twofold to threefold).

Modification of the Penton Base

Retargeting of Adv vectors has also focused on the modification of the penton base, which mediates the second step of Adv infection (i.e., internalization). Recombinant Adv vectors have been generated in which the RGD motif in the penton base has been replaced by the FLAG peptide. A complex of this vector with a bispecific Ab—consisting of a monoclonal Ab to the FLAG epitope and a monoclonal Ab to integrins—was shown to target cells lacking the Adv fiber receptor, such as endothelial cells or human intestinal smooth muscle cells. Thus, the first two steps of Adv infection binding and internalization are both mediated by α integrins.[177] In addition, recombinant Adv vectors can be constructed of chimeric penton base proteins that recognize tissue-specific integrin receptors.[178]

Retroviral Vectors

Retroviral vectors were the first viral vectors to be targeted and the first to demonstrate the promise of vector targeting.[34,114] Since that time, the challenge has been to incorporate targeting ligands without compromising vector entry into target cells. There are now several approaches used to address this problem. One approach exploits pseudotyping, classically with the G-glycoprotein from the vesicular stomatitis virus, in which entry events are mediated through common membrane phospholipids.[179] Pseudotyped lentiviral and retroviral vectors have also been generated with glycoproteins from a variety of enveloped viruses, including Ebola virus, Marburg virus, rabies virus, lymphocytic choriomeningitis virus (LCMV), Mokola virus, human foamy virus, gibbon ape leukemia virus, murine leukemia virus, influenza virus, avian leukosis-sarcoma virus, and respiratory syncytial virus.[180–184] Although these pseudotyped vectors vary in terms of degree of envelope shedding, efficiency of packaging, titer, and stability, they can be concentrated to high titers for in vivo comparisons of cellular tropisms.

Another vector modification involves the ligation of polypeptides at the N terminal of env to extend the host range of ecotropic murine leukemia virus (MLV). Examples include erythropoietin, heregulin, and CD4.[185–187] It should be stressed that coexpression of the wt env protein is necessary for infection to occur, possibly because incorporation of the engineered env protein in the virons can be facilitated by the oligomerization of both wt and chimeric env proteins. Another approach for engineering of the ecotropic MLV env protein involves the display of different polypeptide binding domains to the N terminus of the ecotropic MMLV surface protein. Examples include the N-terminal moiety of the amphotropic MLV env, single-chain Abs recognizing different cell surface receptors, heregulin, and epidermal growth factor.[188–191] In some of these studies, infection specificity was redefined, though with lower efficiencies than those obtained with viruses expressing wt amphotropic envelopes.[192,193]

Bifunctional bridging agents that recognize both the retrovirus and the targeted cell surface molecule provide evidence that retroviruses can enter cells via cell surface molecules that are not viral receptors. Such bridging agents have been used to infect human cells that are naturally resistant to ecotropic MLV-based vectors. The agents used usually consisted of an Ab to the MLV envelope protein connected to either another Ab or a growth factor that would bind to the appropriate receptor such as the epidermal growth factor receptor, the insulin receptor, or major histocompatibility complex class I and class II molecules. Unfortunately, infection efficiencies for these agents are extremely low, emphasizing that binding of a retrovirus to a target other than the natural receptor cannot guarantee success.[194,195]

Nonviral Vectors

Nonviral vectors have no native receptor binding, yet do have a high incidence of nonspecific gene transfer from the high positive charge on many nonviral vectors.[54–56] Many nonviral vectors transduce lung vasculature, potentially as a result of vector-mediated red blood cell aggregation and arrest in the lung subsequent to IV administration. The solution to the problem of nonspecific delivery is to shield the vectors, either with hydrophilic polymers such as polyethylene glycol (PEG) or with a ligand to reduce the surface charge. This type of shielding is applied successfully to lipid-based systems and to cationic polymer-based systems (polyplex).

Ligand-directed liposomes have shown some success in targeting tumors. Coupling of a synthetic $\alpha_v\beta_3$-integrin ligand to cationic liposomes permits the selective delivery of a mutant *Raf* gene that causes apoptosis in angiogenic blood vessels within tumors. Systemic injection of the $\alpha_v\beta_3$-targeted liposome results in apoptosis of tumor-associated endothelium and the regression of primary and metastatic tumor(s). This accomplishment highlights the extension of this approach from in vitro to in vivo efficacy.[86]

Another promising advance is to coat polyethylenimine (PEI)-DNA polyplexes with a ligand, such as transferrin or transferrin plus PEG. Shielding by PEG or transferrin prevents nonspecific interactions with plasma proteins and erythrocytes but does not interfere with target cell interactions. When systemically administered in a subcutaneous tumor mouse model, the shielded complexes were shown to selectively transduce a well-vascularized, rapidly growing tumor. Although the specificity of this approach is high, the overall level of transduction is low.[196]

In all the studies to date that use nonviral approaches, the need for relatively high dosing levels (~100 mg/mouse) suggest that innate clearance mechanisms might have to be saturated before substantial gene transduction can occur. Other potential issues that remain include determining whether the high doses used in the animal studies can be manufactured and delivered successfully for human studies. Attaining further improvements in the efficiency of gene transfer and better defining the toxicity profiles associated with these vectors are also critical steps.

CLINICAL TRIAL STRATEGIES

The development of gene therapy over the last decade has been on a roller-coaster ride that has yet to fulfill the promise of this exciting new research and therapeutic tool. Retroviral gene therapy has inarguably been shown to reverse congenic diseases. This was the first success for gene therapy, whereby a retroviral-based treatment was undertaken for infants suffering from X chromosome-linked SCID-X1. These studies provided the first demonstration of the potential for long-term treatment of hereditary diseases.[197] The success of this approach is due not only to gene therapy but also to improvements in our understanding of hematology and the availability of clinical-grade cytokines to support the transduction of adequate numbers of stem cells. These studies have resulted, however, in the concept of retroviral insertional carcinogenesis moving from a theoretic to a real concern in recent months. Two of the initial 11 children who received retroviral gene therapy for the treatment of SCID developed a leukemia-like condition.[198] Both of these cases, as well as a third in which leukemia has not yet developed, seem to be due to the insertion of the corrective gene near another gene called *Lmo2,* which helps to control cell growth and can contribute to cancer if turned on at the wrong time.[198] Nonetheless, the unique nature of this therapeutic strategy for patients who have no other viable therapeutic modality, and the responsiveness of the resultant leukemias to chemotherapy, suggest that it remains a justifiable therapeutic strategy for those patients who have no matching allotransplant donor.

Therapeutic activity has also been demonstrated[199] for retroviral vector transduced stem cells in infants with a defective gene for adenosine deaminase (ADA-SCID). In contrast to children with SCID-X1, enzyme replacement therapy has been available for children with ADA-SCID using pegylated ADA (PEG-ADA). Initially,

ethical concerns required that gene therapy studies in ADA-SCID patients be undertaken concomitant with PEG-ADA therapy. A generalized schema for these gene therapy protocols is shown in Figure 33-3. However, the SCID-X1 studies by Cavazzana-Calvo revealed that a strong selective pressure was needed to expand the transduced cells following infusion.[197] This revelation provided the impetus for studies in ADA-SCID whereby PEG-ADA was discontinued, allowing the selection of transfected stem cells and more importantly differentiated T cells. In addition, nonmyeloablative conditioning with busulfan was used to provide space in the marrow for the infused stem cells. Although insertional mutagenesis remains a concern, no clonal expansion has been reported to date. A recent follow-up at a median of 3 years was presented at the 2006 American Society of Hematology (ASH) annual conference and reported that seven of eight children responded to gene therapy, with approximately 95% of T cells expressing ADA. The one patient who did not show improvement was treated at an older age, suggesting a higher level of disease damage.

The second vector type that has shown significant clinical potential is Adv vectors. In contrast to retroviral vectors, Adv vectors induce a transient gene expression and demonstrate both high transduction efficiency and high transgene expression; in addition, these vectors can be grown to high titer for virus stocks. Furthermore, the activity profile of these vectors (particularly transient gene expression) provides an attractive characteristic for many current clinical development strategies. Most notably, these protocols involve the induction of tumor apoptosis via systemic or intralesional injection of vectors with transgenes that induce apoptosis or result in the activation of cytotoxic drug precursors, such as TK or cytosine deaminase. In addition, Adv vectors are being used to deliver Ags to Ag-presenting cells (e.g., DCs), resulting in the induction of an Ag-specific immune response and (theoretically at least) therapeutic activity.

In a recent phase I/II trial of extensive stage, small cell lung cancer,[200] 29 patients received standard first-line chemotherapy and three vaccinations with Adv-transfected DCs as a vaccine. Patients with stable disease to first-line chemotherapy had DCs prepared from enriched monocytes, which were then transfected with Adv-p53 and the resultant p53-DC injected three times. Following disease progression, patients received second-line chemotherapy. The objective response rate to vaccine alone was low, although it was reported that following p53-DC vaccination one patient had lymph node metastasis regress with the remainder of patients rapidly progressing. In contrast, 60% of patients with progressive disease following vaccination had objective clinical responses to second-line chemotherapy, resulting in an overall survival of greater than 11 months after immunotherapy. Indeed, the major response rate to second-line chemotherapy (complete and partial responses) was 90% in those patients who developed an immune response to p53 as compared with 40% for those patients who did not develop an immune response. In this disease, aggressive combination chemotherapy regimens can extend the median survival time to 9 to 10 months from diagnosis, as compared with 2 to 3 months if untreated.

Similar to retroviral vectors, Adv vectors have experienced "growing pains." Although the majority of the vectors used in current

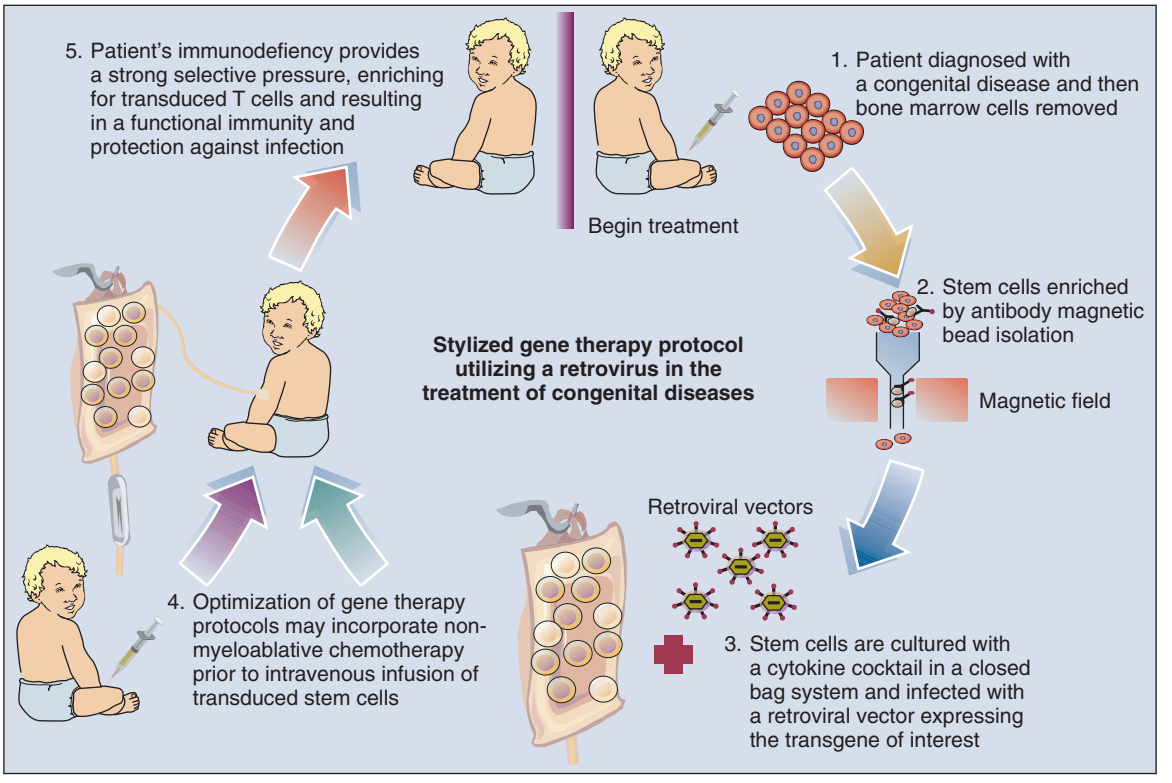


Figure 33-3 • Characteristic protocol for retroviral treatment of congenital diseases. An improved understanding of stem cell culture has facilitated therapeutic efficacy for the treatment of children with common γ-chain, severe combined deficiency; SCID-X1; and ADA-SCID. Protocols for other congenital diseases are similar. In general, children have a bone marrow harvest either in utero or more commonly in the first few years of life. The harvested cells are briefly cultured, typically with a mixture of cytokines active on primitive hematopoietic stem cells; transfected with a retroviral vector; and then cultured again to allow transgene insertion into the chromosome. The patient may also undergo nonmyeloablative conditioning, typically with busulfan, before receiving the transfected cells. Several studies have shown that supportive therapy must be withdrawn to allow selection of the transfected cells. Typically within a few weeks post-transplant, a high percentage of the circulating T cells are transduced with retroviral vector, resulting in normalization of T-cell numbers and a significant decrease in infections.

practice have been replication incompetent, the routes of administration and therapeutic targets have been variable and—in part because of this—various toxicity issues have developed. Studies using Adv-p53 vectors have shown clearly that these can be injected at doses up to approximately 7.5×10^{13} for intraperitoneal administration, and 2.5×10^{13} viral particles has been identified as the maximum total dosage.[201] This same particle number, administered via the hepatic artery for the treatment of hepatic metastasis, has also been identified as the maximum total dosage.[202] Initially, Adv vectors were delivered based on plaque-forming units, a strategy found to be less rigorous quantitatively when compared with a particle number strategy.[203] Yet, despite the known biodistribution and toxicity profile of Adv vectors—including Adv vectors delivered by vascular injection—one child with a non-life-threatening disease, ornithine transcarbamylase deficiency, was dosed with a high number of viral particles, resulting in his untimely demise.[204] The incident resulted in a regulatory hold on Adv for a period of time, which limited the use of Adv vectors. This toxicity problem has largely been overcome with increased clinical conservatism. Similarly, the immunologic reaction to the Adv vectors can be reduced as shown with some second- or third-generation vectors (gutless), providing a significant impact on safety, transgene expression, and duration of expression.[205] Indeed, Adv vectors have been used to deliver receptors for retroviral vectors to improve their transduction frequency.[206] Thus, in addition to "naked DNA" vectors, retroviral and Adv vectors have been used predominantly in the clinic thus far. Clearly, other agents are used, including AAV, α viruses, and herpes vectors, but to a lesser extent.

Several factors directly related to vectors have hampered the clinical progression of gene therapy. These include

- Inefficient gene delivery, which is associated predominantly with nonviral and retroviral vectors that have reasonable gene delivery efficacy in vitro but disappointing efficacy in vivo
- Poor ability to target transgene expression to either cells or tissues of interest to avoid expression of toxic gene products in healthy or unintended target tissue
- Short duration of expression due to poor replication and/or stability of episomal vectors and to inefficient or inappropriate integration of vectors into the host genome
- Poor production of vectors at high titer, which is developmentally limiting in the cases of retroviral and gutless Adv vectors
- Safety, which is a prerequisite for clinical gene therapy trials. Safety includes not only issues of direct toxicity but also the potential for homologous recombination, which has to be maintained at theoretically acceptable levels. Furthermore, targeted genomic integration has also recently been shown to be potentially critical.

Because of the challenges associated with targeting and transfection efficiency, the therapeutic strategies currently in use take advantage of the positive aspects of the vectors and limit their deficiencies. There are four overall approaches that reduce the challenges associated with the targeting and delivery of the transgene:

1. Hepatic arterial delivery of Adv-p53 for the treatment of hepatic metastasis[202,207,208]
2. Intratumoral administration of Adv vectors for head and neck tumors[155,209,210]
3. Intralesional injection for the treatment of bladder cancer with Adv vectors[211]
4. Intralesional injection for the treatment of lung cancer

The use of Adv vectors to purge hematopoietic stem cell products is also an exciting strategy that initially targeted breast cancer.[212–216] It has become a historical approach, however, with the reduction in transplantation for the treatment of metastatic breast cancer. These are the types of approaches that are needed for the successful development of gene therapeutics. The future of gutless vectors or vectors with improved targeting is bright, but at present such vectors introduce additional deficiencies such as low manufacturing titers.

In 2004, Adv-p53 vectors were approved in China for the treatment of patients with HNSCC.[1] This approval was based on a single clinical study using an Adv serotype 5 vector engineered to express p53 (Gendicine). In this multicenter, randomized clinical trial, 135 patients were randomized and entered to receive Gendicine in combination with radiotherapy (GTRT) or radiotherapy alone (RT). It was reported that the response rate in the GTRT group was 93%, with 64% showing complete regressions and 29% partial regressions. This contrasts with a phase I study in the United States by Introgen that entered 106 patients, which were reported to have only a 10% tumor response rate, defined as a 30% reduction in tumor size, in patients who received gene therapy alone.[217] This response increased to 26.5% for the clinical biomarker defined population, resulting in a progression-free interval of greater than 12 months from initial treatment of patients who had prior chemotherapy. In the overall treatment population, tumor response was associated with a significant increase in survival. The median survival of responders was 16.9 months, a significant increase as compared with 5.4 months for nonresponders. Thus, there is some controversy regarding the Chinese studies; however, the resulting population of patients that have received Gendicine (≥3,000) has provided valuable information. One such observation is that Gendicine has a better response if injected directly into the tumor. This potentially minimizes any immune reaction against the Adv vector and improves the efficiency of p53 delivery.

The majority of gene therapy trials are focused on cancer, and to date, approximately 66% of the over 1000 gene therapy trials in the United States have been initiated for this indication. This represents approximately 63% of all clinical trials. The predominance of clinical vectors used is retroviral vectors, although Adv vectors are also being used extensively. The majority of therapeutic strategies are focused on immunotherapy, with the predominance of transgenes used being either cytokine or Ag. When one considers the timeline for most drug development, gene therapy is on target. Although there was considerable initial optimism, the reality is that a period of time and appropriate attention to toxicities, adverse events, and pharmacologic issues (including biodistribution and cell targeting) are required before success can be achieved. Great strides have been made as vector biology begins to catch up with improvements in vectors. It is our expectation that future successes (such as those found with SCID and retroviral vectors) can be expected, although future frustrations are also to be expected and appropriate conservatism must be maintained. One area that has a high potential for success is the utility of vectors such as VV and Adv to deliver Ags to DCs as a vaccine for the treatment of infectious diseases or tumors. Clearly, Adv and VV vectors have innate vector antigenicity, which is limiting these approaches and providing opportunities for "naked DNA" and formulated "naked DNA" for either vaccine priming or boosts. A successful clinical protocol will be achieved only if these liabilities are considered carefully, with appropriate attention to well-designed protocols that take advantage of the positive attributes of vectors and minimize their negative attributes. Within this review, we have attempted to stress the great strides have been made recently with targeting and to illustrate that the future is clearly bright.

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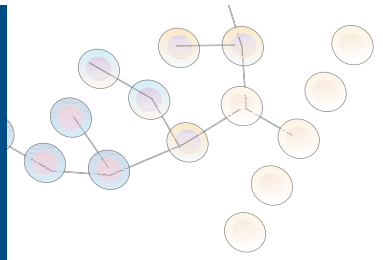
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34 Therapeutic Antibodies and Immunologic Conjugates

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SUMMARY OF KEY POINTS

- Because of their tumor selectivity, monoclonal antibodies offer exceptional opportunities for targeted therapy.
- As naked antibodies, they kill tumors by receptor blockade and by actively inducing apoptosis.
- Tumor cytotoxicity is mediated in the presence of white cells by activating antibody-dependent cell-mediated cytotoxicity; and in the presence of serum, it is mediated by complement.
- The effector functions of antibodies can be greatly enhanced as immunoconjugates, which include radioimmunoconjugates, immunocytokines, immunotoxins, immunoenzymes, immunoliposomes, and cellular immunoconjugates.
- Naked antibodies can, on occasion, have overlapping toxicity profiles with chemotherapy and radiation therapies.
- Dose-limiting toxicities of immunoconjugates depend on the cytotoxic moiety (e.g., myelosuppression in radioimmunoconjugates) being used.
- Antibodies are likely to be most beneficial at the time of minimal residual disease, especially when used in conjunction with standard therapy.
- The following antibodies have been licensed by the FDA for specific cancers:
  - Alemtuzumab (Campath): B-chronic lymphocytic leukemia (CD52)
  - Bevacizumab (Avastin): colorectal cancer (VEGF)
  - Cetuximab (Erbitux): colorectal cancer, head and neck cancer (EGFR)
  - Gemtuzumab ozogamicin (Mylotarg): acute myelogenous leukemia (calicheamicin, CD33)
  - Ibritumomab (Zevalin): non-Hodgkin's lymphoma (^{90}Y, CD20)
  - Rituximab (Rituxan): non-Hodgkin's lymphoma (CD20)
  - Tositumomab (Bexxar): non-Hodgkin's lymphoma (^{131}I, CD20)
  - Trastuzumab (Herceptin): breast cancer (HER2)
- In the coming decade, other monoclonal antibodies that are currently in various phases of clinical trial as well as those approved for nononcologic indications could be added to the list. The prospects for further innovation in this maturing modality are highly favorable.

INTRODUCTION

The clinical development of antibody therapy was accelerated by the introduction of the hybridoma technique in 1975 and the emergence of recombinant technology.[1] Through these innovations, individual plasma cells can be immortalized, and cloning of heavy and light chain repertoires from animals and humans is now possible. In the last three decades, monoclonal antibodies (MAb) have evolved from research tools to inclusion in a rapidly increasing list of licensed pharmaceuticals. They have generated excitement on many fronts and will likely play a pivotal role in the history of cancer medicine (Box 34-1). The clinical utility of MAb for in vitro diagnosis and ex vivo manipulation of blood or stem cells is well recognized. Their role in the treatment and prophylaxis of graft versus host disease is detailed in Chapter 32. The use of B-cell idiotype and anti-idiotypic antibodies as tumor vaccines is described in Chapter 6. This chapter summarizes the application of therapeutic antitumor MAb and immunologic conjugates in cancer therapy.

EFFECTOR MECHANISMS OF MONOCLONAL ANTIBODIES

Antitumor MAb can mediate highly effective tumoricidal functions both in vitro and in vivo (Fig. 34-1). These include signaling through receptor binding, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC).

Signaling by Receptor Cross-Linking and Receptor Blockade

When the antigen is a cell surface receptor, its clustering by multivalent MAb can induce apoptosis.[2] Apoptosis increases with hyper-cross-linking (e.g., CD20 target on lymphoma cells).[3–5] Both caspase dependent and independent programmed cell death pathways appear to be involved.[6] In AIDS-related lymphoma, anti-CD20 MAb diminishes p38MAPK signaling and Bcl-2 expression, while in non-AIDS-related lymphoma, signaling through CD20 inhibits AP-1 in addition to NF-κB, leading to downregulation of Bcl-$_{XL}$, sensitizing lymphoma cells to chemotherapy.[7] Direct receptor blockade by MAb has also been reported for EGF-R1[8] and HER-2 (EFG-R2),[9] leading to upregulation of the BH3-only protein Bnip3L, thereby sensitizing tumor cells to chemotherapy.[10] MAb inhibition of VEGF-R1[11] or VEGF-R2[12] can also enhance the efficacy of chemotherapy.

Cytophilic MAb and ADCC

The Fc region of IgG MAb interacts with both activating and inhibitory Fc receptors (FcγR).[13] In humans, there are four activating FcγRs: FcγRI (CD64) is a high-affinity FcγR, whereas FcγRIIA

Box 34-1. ANTIBODY THERAPY OF CANCER: HISTORICAL PERSPECTIVE

1901: Nobel prize awarded to Emil von Behring for work on serum therapy in collaboration with Shibasaburo Kitasato
1908: Nobel prize awarded to Paul Ehrlich for his work on passive immunization
1927: Serotherapy of chronic myelogenous leukemia
1975: Hybridoma technique of Hans Kohler and Caesar Milstein (winners of 1986 Nobel prize)
1980: MAb therapy of lymphoma
1986: FDA approval of MAb as standard pharmaceuticals
1992: Murine ^{111}In-anti-B72.3 for imaging colon and ovarian cancer
1997: Chimeric anti-CD20 (rituximab) for B-cell lymphoma
1998: Humanized anti-HER2 (trastuzumab) for breast cancer
1999: Humanized anti-CD33 immunotoxin for acute myelogenous leukemia
2001: Humanized anti-CD52 (alemtuzumab) for B-chronic lymphocytic leukemia
2002: ^{90}Y-anti-CD20 (Ibritumomab) for B-cell lymphoma
2003: Murine ^{131}I-anti-CD20 (tositumomab) for B-cell lymphoma
2004: Chimeric anti-EGFR (cetuximab) for colorectal cancer and head and neck cancer
2004: Humanized anti-VEGF (Bevacizumab) for colorectal cancer

(CD32A), FcγRIIIA (CD16A), and FcγRIIIB (CD16B) are low-affinity FcγRs. FcγRIIB (CD32B) is the only known inhibitory FcγR (Table 34-1). All FcγRs (except FcγRIIIB) are transmembrane glycoproteins that are anchored on neutrophils by glycosylphosphatidylinositol. Activating FcγRs (with the exception of FcγRIIA) require the accessory γ chain, which carries a cytoplasmic immunoreceptor tyrosine-based activation motif for activation. Immunoreceptor tyrosine-based activation motif becomes tyrosine phosphorylated by members of the Src-kinase family with subsequent recruitment of SH2-containing kinases. These events lead to the activation of phosphatidylinositol 3-kinase and phospholipase-Cγ, followed by protein kinase C activation and sustained calcium elevation.[13] These biochemical cascades trigger phagocytosis, degranulation, cytokine release, and antibody-dependent cell-mediated cytotoxicity. In sharp contrast to activating FcγRs, FcγRIIB is a single-chain receptor that carries the immunoreceptor tyrosine-based inhibitory motif in its cytoplasmic domain. Engagement of this inhibitory receptor downregulates both biochemical and cellular functions. The ratio of activating to inhibitory FcγRs on immune cells, such as dendritic cells, macrophages, and neutrophils, can greatly influence the antitumor properties of MAb.

Inflammatory mediators (interferon-γ or C5a) increase activating FcγRs and downregulate inhibitory FcγRIIB, while IL-4, IL-10, and TGF-β upregulate FcγRIIB, thereby raising the thresholds for cell activation. Removing the inhibitory signals by FcγRIIB-blocking antibodies have shown efficacy in preclinical models.[13] This is particularly relevant for cross-presentation of antigens that are acquired

Table 34-1 Properties of IgG Fc Receptors[13]

Fc Receptor	Function	Affinity for hIgG	Distribution on WBC
CD64			
FcγR1	A	High	PMN, MONO, MΦ, DC
CD32			
FcγRIIA	A	Low*	PMN, MONO, MΦ, DC, NK
FcγRIIB	I	Low*	PMN, MONO, MΦ, B-cell
FcγRIIC	A	Low*	PMN, MONO, MΦ
CD16			
FcγRIIIA	A	Intermediate	MONO, MΦ, NK, DC
FcγRIIIB†	A	Low*	PMN

A, activating; DC, dendritic cells; hIgG, human IgG; I, inhibiting; MONO, monocytes; MΦ, macrophages; PMN, neutrophils; WBC, white blood cells.
*Prefers antibody-antigen complex.
†Glycosylphosphatidylinositol-anchored.

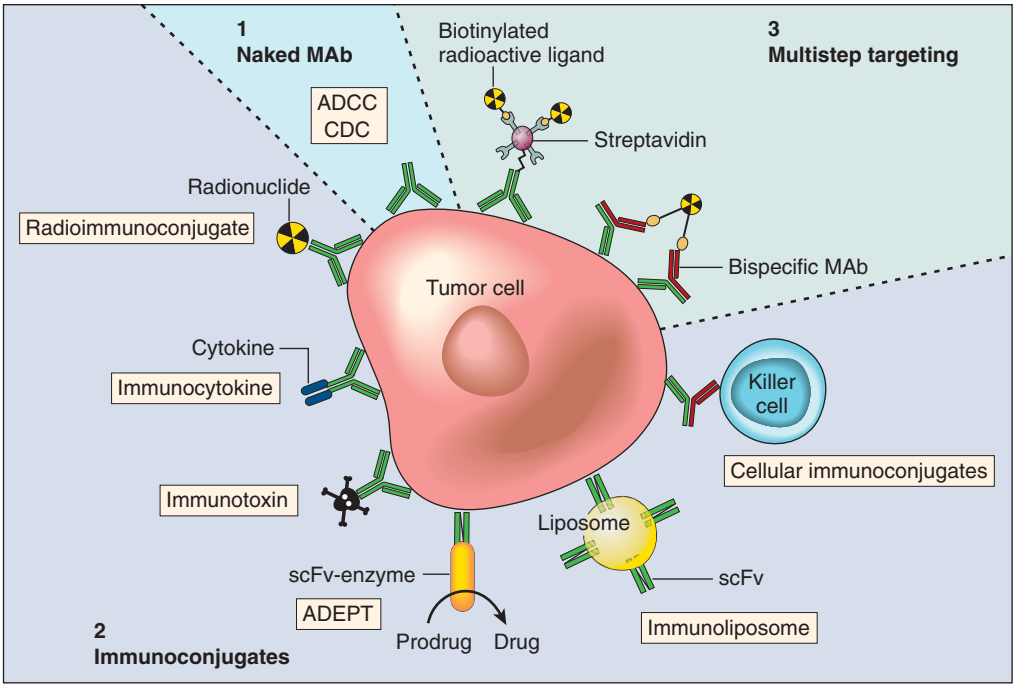


Figure 34-1 • Effector mechanisms of monoclonal antibodies. ADEPT, antibody-directed enzyme prodrug therapy; ADCC, antibody dependent cell-mediated cytotoxicity; CDC, complement-dependent cytotoxicity; MAb, monoclonal antibody; scFv, single-chain variable fragment. (Modified from Carter P, Improving the efficacy of antibody-based cancer therapies. Nat Rev Cancer 2001;1:118–129.)

endocytically through Fc receptors on dendritic cells during the induction of tumor-specific T-cell responses.[14] In addition to these FcγRs, a unique class of Fc receptor called FcRB (Brambell)/FcRn (neonatal) is found on endothelial cells and regulates antibody catabolism.[15] Although most therapeutic antibodies have been primarily IgGs, both IgA1 and IgA2 can also mediate efficient ADCC by binding to FcαRI (CD89) on human neutrophils and monocytes/macrophages.[16]

Certain cancer cells, such as colon carcinoma, lymphoma, leukemia, neuroblastoma, and melanoma, are effectively killed by natural killer (NK) lymphocytes, granulocytes, and activated monocytes in vitro in the presence of specific MAb. Depending on the affinity of the MAb for the individual FcγR, both NK cells (carrying FcγRII and FcγRIII) and neutrophils (bearing all three FcγRs) can mediate efficient ADCC. Because of the high affinity, FcγRI is generally occupied by monomeric IgG in human plasma. Human IgG subclasses (IgG1, IgG2, IgG3, and IgG4) have differential affinity for FcγRII and FcγRIII. Chimeric or humanized IgG1 antibodies (e.g., Lym-1 specific for HLA-DR and ch14.18 for GD2) exploit FcγRIII for lymphocyte ADCC while using FcγRII for myeloid ADCC.[17,18] Among the four IgG subclasses, IgG2 has the lowest affinity for the inhibitory receptor FcγRIIB.[13] Mouse IgG3 (e.g., 3F8 specific for GD2) can engage both FcγRII and FcγRIII in ADCC,[19] despite its low affinity for human FcγRs. The correlation of patient FCGR2A[20,21] and FCGR3A polymorphism[21,22] with clinical responses to MAb suggests that affinity for Fc receptor can influence antitumor responses in patients. In addition to FcγRs, adhesion molecules are critical for MAb-mediated ADCC. These molecules include CR3 (CD11b/Cd18),[17–19] plus CD66b[17] for neutrophil ADCC and LFA-1 (CD11a/CD18) for lymphocyte ADCC.[23] Because cytokines can increase the expression of adhesion molecules, GM-CSF or interferon-γ has been used to activate granulocyte ADCC,[18,24–26] and IL-2 has been used similarly for lymphocyte ADCC.[27,28] Furthermore, because both GM-CSF and IL-2 expand the effector cell pools, they can have additional benefits in tumor therapy. Optimal combinations of MAb and cytokines in the appropriate clinical setting are being explored.[29–31]

Complement Activation

IgG initiates the classical complement cascade by binding C1q to its CH2 domain. C1q is more avid for human IgG1 and IgG3 than for IgG2 and has no affinity for IgG4.[32] CDC potency of individual MAbs is also correlated with its slow off-rate.[33] Although some tumor cell lines (e.g., lymphoma and neuroblastoma) are sensitive to CDC, many are resistant to complement because of anticomplement surface proteins such as decay-accelerating factor (DAF, CD55),[34–36] homologous restriction factor (CD59),[34,37,38] and membrane cofactor protein (CD46).[35–37,39] The effect of complement activation extends beyond direct tumor lysis. Following complement activation, tumor-bound C3b is cleaved rapidly by plasma protease factor I to iC3b. Through CR3 (Mac-1 or $\alpha_M\beta_2$-integrin) and CR4 (CD11c/CD18, $\alpha_X\beta_2$-integrin) receptors on leukocytes, tumor cells are opsonized.[40] C3a and C5a, by-products of complement activation, are also potent mediators of inflammation[41] and are chemotactic for phagocytic leukocytes, drawing them to the tumor sites. C5a can also downregulate the inhibitory receptor FcγRIIB[13] or induce secondary cytokines to increase vascular permeability for both MAb and effector cells.

CLINICAL APPLICATION OF NAKED MAb DIRECTED AT CANCER CELLS

Lymphoma and Leukemia

In 1997, the anti-CD20 chimeric antibody rituximab became the first MAb to be approved by the U.S. Food and Drug Administration (FDA) for the treatment of cancer (Table 34-2). In a single-arm multicenter study of 166 patients with relapsed or refractory, low-grade, or follicular non-Hodgkin's lymphoma (NHL), rituximab at a dose of 375 mg/m^2 four times weekly produced an overall response (OR) rate of 48%, a complete response (CR) rate of 6%, and a partial response (PR) rate of 42%. Median time to progression in responders was 13.1 months.[42] In this study, rituximab demonstrated activity in chemoresistant disease (29%) and in patients relapsing after anthracycline therapy (51%). FDA approval was later expanded to include patients with bulky disease, retreatment of responders, and an extended treatment schedule of eight infusions. For most patients, rituximab was well tolerated.[43] Severe adverse events that were thought to be secondary to complement activation often occurred with the first infusion,[44] especially if there were high numbers of circulating tumor cells. These infusion-related reactions usually appeared 30 to 120 minutes after MAb injection and typically were associated with severe cardiopulmonary events, with deaths (<0.1%) occurring within 24 hours. B-cell depletion occurred in most patients, although serum IgG level remained normal for 12 months or longer without increased incidence of infection.[42] Severe mucocutaneous reactions occurred rarely (0.07%), resulting in some fatalities.

Because of its chemosensitization, rituximab was tested in diffuse large B-cell NHL. Chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]) plus rituximab was superior (76% CR, 69% progression-free survival [PFS], 83% overall survival [OS]) to CHOP alone (60%, 49%, and 68%, respectively).[45] In a randomized trial of 399 elderly subjects with previously untreated

Table 34-2 Naked MAb for Cancer Therapy

Antibody	Antigen	Antibody Form	Cancer	Effector Function/Molecule	Drug Status
Alemtuzumab[191]	CD52	huIgG1	CLL, PLL	ADCC, CDC	Campath: Licensed
Bevacizumab[222]	VEGF	huIgG1	CRC	Neutralizing VEGF	Avastin: Licensed
Centuximab[74]	EGFR	chIgG1	H&N CRC	ADCC, CDC; interrupts signaling pathways	Erbitux: Licensed
Rituximab[108]	CD20	chIgG1	CLL	ADCC, CDC; interrupts signaling pathways	Rituxan: Licensed
Trastuzumab[58]	HER2	huIgG1	Breast cancer	ADCC, CDC, receptor blockade	Herceptin: Licensed
3F8[29]	GD2	mIgG3	NB	ADCC, CDC	Phase II
ch14.18[62]	GD2	chIgG1	NB	ADCC, CDC	Phase II/III
Epratuzumab[46]	CD22	huIgG1	NHL	ADCC, CDC; interrupts signaling pathways	Phase III

ADCC, antibody-dependent cell-mediated cytotoxicity; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; APL, acute promyelocytic leukemia; CDC, complement-dependent cytotoxicity; CRC, colorectal cancer; ch, chimeric; CLL, chronic lymphocytic leukemia; EGFR, epidermal growth factor receptor; H & N, head and neck cancer; hu, humanized; Ig, immunoglobulin; Licensed, licensed by the FDA; MAb, monoclonal antibody; MDS, myelodysplastic syndrome; NB, neuroblastoma; NHL, non-Hodgkin's lymphoma; PLL, prolymphocytic leukemia; VEGF, vascular endothelial growth factor.

diffuse large B-cell lymphoma, CHOP plus rituximab compared to CHOP produced an OR of 76% compared to 63% and a 2-year OS of 70% compared to 57%, respectively.[46] Other antibodies in active clinical trials included epratuzumab (huIgG1 anti-CD22) for NHL, as single agents[47,48] or in combination with rituximab,[49] and SGN-30 (chIgG1 anti-CD30) for Hodgkin's disease.[50]

Campath-1H (Alemtuzumab), a humanized rat IgG1 anti-CD52 MAb, has activity against recurrent chronic lymphocytic leukemia and T-cell prolymphocytic leukemia.[51,52] In an international phase II study involving 21 centers ($n = 93$ patients), Campath-1H was administered at 30 mg three times weekly for a maximum of 12 weeks to patients with relapsed or refractory B-cell chronic lymphocytic leukemia who had previously failed fludarabine therapy. OR was 33% (CR: 2%, PR: 31%). The median times to response and progression were 1.5 and 4.7 months, respectively, and median survival was 16 months. Grade 3 or 4 infections were reported in 26.9% of patients.[53] On the basis of this study, the FDA approved Campath-1H. Other clinical trials have also reported opportunistic infections, including bacterial sepsis and viral infections, as well as marrow aplasia following Campath-1H treatment.[52,54]

In myeloid leukemia, the addition of lintuzumab (huM195, IgG1, anti-CD33) to salvage induction chemotherapy was safe but did not result in a statistically significant improvement in response rate or survival in patients with refractory/relapsed AML.[55]

Solid Tumors

Trastuzumab (Herceptin) is a humanized MAb against the receptor tyrosine kinase ERBB2 (also known as HER-2/NEU) on breast cancer cells. It can mediate a diverse spectrum of antitumor effector mechanisms. Besides CDC and ADCC, it can induce HER-2 protein downregulation, prevent HER-2-containing heterodimer formation, initiate G1 arrest, induce p27, prevent HER-2 cleavage, and inhibit angiogenesis.[56] The application of trastuzumab in metastatic breast cancer achieved OR of 15% (3.6% CR, 11.7% PR, $n = 222$) with median response duration of 9.2 months and OS at 13 months.[57] Its efficacy in patients with recurrent or refractory ovarian cancer was limited by the low expression of HER-2 among these patients.[58] On the basis of its synergy with chemotherapy in vitro,[59,60] trastuzumab was tested in a large phase III trial of 469 patients with breast cancer, in which its combination with chemotherapy produced a longer median response duration (9.1 versus 6.1 months), higher OR (50% versus 32%), and lower death rate at 1 year (22% versus 33%)[61] than chemotherapy alone. However, there was a significant increase in cardiotoxicity. On the basis of this trial, the FDA approved the use of trastuzumab and paclitaxel as a first-line treatment of HER-2-overexpressing metastatic breast cancer. Subsequent studies showed that one year of treatment with trastuzumab after adjuvant chemotherapy significantly improved disease-free survival among women with HER-2-positive breast cancer (either node-negative or node-positive) after locoregional therapy and at least four cycles of neoadjuvant or adjuvant chemotherapy.[62] When combined with paclitaxel after doxorubicin and cyclophosphamide, trastuzumab also improved outcomes among women with surgically removed HER-2-positive breast cancer.[63]

Cetuximab (chIgG1 anti-EGFR) is another FDA-approved antibody designed to induce receptor blockade. It showed activity when given alone or when combined with irinotecan in patients with colorectal cancer (CRC).[64] In 346 patients with metastatic CRC that was refractory to irinotecan, oxaliplatin, and fluoropyrimidines, the overall response was approximately 12%.[65] An acneiform rash occurred in 82.9% of patients; a grade 3 rash was observed in 4.9%. Response and survival correlated strongly with the severity of the rash. In contrast, clinical benefit did not relate to EGFR immunostaining. Neither EGFR kinase domain mutations nor EGFR gene amplification appeared to be essential for response to cetuximab in this setting. When combined with radiotherapy for squamous cell carcinoma of head and neck (H&N), cetuximab improved the duration of locoregional control from 14.9 to 24.4 months, increased OS from 29.3 to 49 months, and improved PFS.[66] Except for the known acneiform rash and infusion reactions due to cetuximab, the incidence of grade 3 or greater toxic effects, including mucositis, did not differ significantly between the two groups. In phase I/II combinations with chemotherapy, cetuximab had activity for both H&N[67] and CRC.[65] In a phase III randomized study, cetuximab plus cisplatin significantly improved response but not PFS or OS among patients with metastatic/recurrent H&N cancer.[68] The addition of cetuximab to chemotherapy for non-small-cell lung cancer showed only slight benefit.[69] Panitumumab, a fully human antibody that is specific for EGFR generated by using human IgG-transgenic mouse technology, also showed promise in phase II/III clinical trials.[70]

Despite initial enthusiasm,[71] adjuvant therapy with edrecolomab (17–1A, Panorex), a mouse IgG_{2a} antibody specific for EpCAM on malignant and normal epithelial cells, did not improve DFS or OS in subsequent phase III studies in CRC.[72,73] Even with the lack of clinical efficacy, anti-idiotype network and T-cell responses against antibody-modified tumors were found.[74,75] Oregovomab (MAb B43.13, anti-CA125), a murine IgG_1 antibody for ovarian cancer, did not improve time to relapse in a phase III randomized trial of 145 patients.[76] A correlation of improved survival and human anti-mouse antibody (HAMA)/idiotype network response was of biologic interest.[77]

Among the ganglioside antigens on neuroectodermal tumors, GD3 (MAb R24 for melanoma)[78] and GD2 (MAb 3F8 and ch14.18 for neuroblastoma)[79,80] have been tested clinically. GD2 is present on a variety of solid tumors in addition to neuroblastoma, including osteosarcoma, retinoblastoma, some soft-tissue sarcomas, and brain tumors. Although the clinical effectiveness of anti-GD2 MAb for soft-tissue disease was modest, response of microscopic marrow disease was consistent.[31,81] Clinical development of anti-GD2 MAb was limited by its pain side effects, precluding dose escalation. At current doses, optimal application of anti-GD2 antibody is at the time of minimal residual disease.[82,83] An association of HAMA response and favorable patient outcome plus the induction of Ab2 and Ab3 through the idiotype network has also implicated a potential role of the host immune response in maintaining clinical remission.[84,85]

Complications and Contraindications

Toxicities of MAb are in general manageable and self-limited. Common acute reactions include fever, chills, headache, nausea, fatigue, angioedema, urticaria, pruritus, blood pressure fluctuations, and bronchospasm. Lethal or irreversible side effects include cytokine release (antilymphocyte MAb) and complement activation (anti-CD20) syndromes,[44] immune suppression (anti-CD52),[52,54] and cardiotoxicity (anti-HER-2).[61] A severe self-limited side effect is the pain syndrome from cross-reactivity of anti-GD2 MAb with peripheral pain fibers.[79,80] Murine MAb induces HAMA responses that can alter the pharmacokinetic and pharmacodynamic properties of repeat MAb injections. HAMA is directed primarily to the murine Fc portion of the antibody, although anti-idiotypic responses have also been reported.[86] With chimeric, humanized, primatized, and human antibodies, immunogenicity is drastically reduced.[87,88]

IMMUNOCONJUGATES

The clinical utility of naked MAb can be limited by both host (number and activity of effector cells, FcR polymorphism, and interference by inhibitory FcR) and tumor factors (antigen heterogeneity and complement regulatory proteins). Although the CDC and ADCC functions of naked MAb (see Fig. 35-1) can be improved by altering the Fc protein structure[87] or by modifying Fc-glycosylation,[89–91] substantial gains in clinical potentials of MAb can derive from immunoconjugates. These include (1) radioimmunoconjugates to deliver β- and α-emitters,[92] (2) immunocytokines to deliver cyto-

kines to tumor sites while minimizing systemic toxicities,[93] (3) immunotoxins,[94] (4) antibody-directed enzyme prodrug therapy (ADEPT) to pretarget enzymes to tumor sites for prodrug activation so that high local concentrations of active drugs are released without triggering systemic toxicities,[95] (5) immunoliposomes to deliver drugs or toxins,[96] and (6) bispecific MAb (pretargeted to tumor or by ex vivo arming) to direct cells or ligands selectively to tumor.[97] More recently, a multistep targeting strategy has been developed to enhance tumor to normal tissue ratios (see Fig. 35-1).[98,99] The tumor is pretargeted using an antibody construct which has affinity for the tumor on one arm and for a radiolabeled hapten on the other arm (e.g., bispecific antibody or single-chain Fv-streptavidin systems). The radiolabeled hapten is administered after the antibody construct is cleared from circulation. Substantial improvements in the therapeutic index can be achieved.[92,100,101]

Radioimmunoconjugates[92]

MAb have the potential to target and ablate tumors in radioimmunotherapy (RIT). Radioimaging can map the biodistribution of MAb and quantify the relative amounts of MAb deposited in various tissues and organs, thus allowing more precise radiation dose estimates in therapeutic studies. With the advent of single photon emission computed tomography and positron emission tomography, accurate dosimetry is readily achievable. In preclinical models, ablation of established xenografts is possible, although radiation damage to the marrow remains dose-limiting. For patients with lymphoma and leukemia, antitumor activity of RIT is highly reproducible, but major responses in solid tumors are rare. Unlike naked antibodies, the bystander effect of RIT from cross-firing of the radioisotopes accounts for most of the toxicities of radioimmunoconjugates, hence limiting their efficacy.

Choice of Radioiosotopes for Radioimmunoconjugates

Most clinical applications of RIT utilize β-emitting radioimmunoconjugates (Table 34-3). β-Particles have a relatively long range (0.8 to 5 mm) and low linear energy transfer (approximately 0.2 keV/μm). This long range results in the delivery of radiation not only to the antigen-positive tumor cells, but also to antigen-negative tumor cells, as well as to the surrounding normal tissues. Thus, β-emitters can treat bulky diseases effectively but are not optimal for killing single cells or micrometastasis. Most early human studies of RIT have used iodine-131 (^{131}I), a long-lived β-particle emitter. Because of its γ-particles emission, it is also suitable for dosimetry studies. However, this γ-particle emission poses a radio hazard at high treatment doses, necessitating patient isolation. In vivo dehalogenation can compromise tumor dose with subsequent thyroid damage from the released iodide. Yttrium-90 (^{90}Y) is a pure β-emitter; its lack of γ-radiation allows outpatient treatment. However, ^{90}Y has its limitations, including deposition in bone when dissociated from the MAb complex. Unlike ^{131}I, which binds directly to tyrosine residues on the MAb, ^{90}Y requires the coupling of a chemical chelator to the MAb. Furthermore, the lack of γ-emissions means that biodistribution and dosimetry studies of ^{90}Y necessitate trace-labeling with indium-111 (^{111}In), the biodistribution of which is not identical to that of ^{90}Y. Besides ^{90}Y, other β-emitters that have recently been explored include rhenium-186 (^{186}Re), rhenium-188 (^{188}Re), copper-67 (^{67}Cu), and lutetium-177 (^{177}Lu), but all have limitations.

Alpha-particles are helium nuclei; when compared with β-particles, they have a shorter range (50 to 80 μm) and a higher linear energy transfer (approximately 100 keV/μm).[102] As few as one or two α-particles can destroy a target cell. Radioimmunotherapy using α-emitters should result in less nonspecific toxicity to normal bystanders as well as more efficient single-cell killing. This is ideal for controlling minimal residual disease. α-Particle-emitting isotopes such as astatine-211 and bismuth-213 have been tested in clinical trials. ^{213}Bi-HuM195 (anti-CD33) administered intravenously for AML[103] and ^{211}At-8C16 administered intraventricularly or intrathecally for gliomas[104] have been well tolerated and produced clinical responses. The relative lack of extramedullary toxicities should encourage further development of this targeting technique for micrometastases or neoplasms on the surface of body compartments, such as ovarian cancer and leptomeningeal metastasis.[105–107]

Radiolabeled MAb for Lymphoma

In patient studies of RIT, sequestration of MAb in liver or spleen can compromise tumor delivery. To overcome uptake by the reticuloendothelial system, a large dose of naked anti-CD20 antibody is needed to reduce liver uptake before RIT (Table 34-4).[108] In a three-component regimen (Zevalin), rituximab at 250 mg/m^2 at the rate of 100 mg/h was first administered to clear peripheral blood B cells, followed within 4 hours by ^{111}In-ibritumomab tiuxetan and ^{90}Y-ibritumomab tiuxetan infusion. At 0.2 to 0.4 mCi/kg (7.4 to 15 MBq/kg) of ^{90}Y-ibritumomab, dosimetry data derived from four large trials showed median radiation absorbed doses of 7.4 Gy to spleen, 4.5 Gy to liver, 2.1 Gy to lung, 0.23 Gy to kidney, 0.62 Gy (blood-derived method) and 0.97 Gy (sacral image–derived method) to red marrow, and 0.57 Gy to total body, with a median effective blood half-life of 27 h.[109] Grade 4 neutropenia, thrombocytopenia, and anemia occurred in 30% to 35%, 10% to 14%, and 3% to 8% of patients, respectively. Myelodysplasia and acute myelogenous leukemia (AML) were reported in 1% of patients 8 to 34 months after treatment.[110] Serious grade 3 and 4 toxicities occurred in 3% of patients, and life-threatening events occurred in 1% to 5%. Four weeks after therapy, no circulating B cells could be detected, and recovery began about 12 weeks after therapy, usually to normal limits by 9 months. Serum IgG and IgA remained unchanged throughout, while IgM dropped below normal and recovered by 6 months; 3.8% of patients developed HAMA or human

Table 34-3 Choice of Radioisotopes for Radioimmunotherapy

Isotope	Particle(s) Emitted	Half-Life Hours	Maximum Energy (keV)	Mean Range of α- or β-Particle Emission (mm)
Iodine-131 (^{131}I)	β, γ	193	610	0.8
Yttrium-90 (^{90}Y)	β	64	2280	2.7
Copper-67 (^{67}Cu)	β	62	577	1.8
Lutetium-177 (^{177}Lu)	β	161	496	1.5
Rhenium-188 (^{188}Re)	β, γ	17	2120	2.4
Actinium-225 (^{225}Ac)	α	240	5935	0.05–0.08
Astatine-211 (^{211}At)	α	7.2	7450	0.05–0.08
Bismuth-213 (^{213}Bi)	α	0.77	5982	0.05–0.08

Table 34-4 Radiolabeled MAb for Radioimmunotherapy

Antibody Status	Antigen	Antibody Form	Cancer	Isotope	Drug	Status
Tositumomab[114–118]	CD20	muIgG2a	NHL	^{131}I	Bexxar	Licensed
Ibritumomab[109–111]	CD20	muIgG1	NHL	^{90}Y	Zevalin	Licensed
hMN14[92] (Labetuzumab)	CEA	huIgG	CRC	^{90}Y	CEA-Cide	Phase I/II
Epratuzumab[92]	CD22	huIgG	NHL	^{90}Y	LymphoCide	Phase III
Pemtumomab[92]	MUC-1	muIgG1	Ovarian	^{90}Y	Theragyn	Phase III

CRC, colorectal cancer; hu, humanized; Ig, immunoglobulin; Licensed, licensed by the FDA; mu, murine; NHL, non-Hodgkin's lymphoma.

antichimeric antibody. Among patients with relapsed or refractory NHL,[111] OR rate was 83% (37% CR and 40% PR). Median time to progression was 9.4 months. In a phase III randomized study, a single dose of 0.4 mCi/kg ^{90}Y-ibritumomab ($n = 73$) was more effective than rituximab, 375 mg/m^2/week for 4 weeks in patients ($n = 70$) with relapsed or refractory low-grade, follicular, or transformed NHL.[112,113] This difference was statistically significant for OR (80% versus 56%), CR (30% versus 16%), and the probability of ≥6-month durable responses (64% versus 47%), respectively. In other studies, increasing the dose or dose intensity of rituximab has not produced a meaningful improvement in outcome.

^{131}I-tositumomab (Bexxar, anti-CD20) achieved 71% OR (34% CR) in a phase II trial ($n = 59$) of chemotherapy-refractory/relapsed patients with NHL. In 17% of patients, HAMA was induced.[114] Using myeloablative doses of 280 to 785 mCi (calculated to deliver 25 to 72 Gy to critical organs), 30 of 36 patients (83%) achieved durable CR, with OS of 68% and PFS of 42% (median follow-up, 42 months).[115,116] Hypothyroidism developed in 60% of patients 6 to 12 months after therapy, and secondary myelodysplastic syndrome/AML was reported in 2% to 5%.[116,117] Similarly, myeloablative doses (10 to 31 Gy) of ^{131}I-anti-CD37 MAb produced 84% CR and 11% PR in patients with NHL, with eight patients in continual remission 46 to 95 months after therapy. Extramedullary toxicities were mild at doses of less than 23 Gy, beyond which cardiopulmonary toxicity became dose-limiting.[118]

Because the B-cell antigen CD22 is internalized, anti-CD22 antibody may be more effective when used in RIT than in its naked form. ^{131}I-epratuzumab (LL2, humanized anti-CD22),[119] ^{90}Y-epratuzumab,[120] and ^{186}Re-epratuzumab[121] have all shown antitumor activity against B-cell lymphoma. In addition, unlike anti-CD20, good biodistribution was achieved with a humanized antibody (hLL2) without the need for preinjection of unlabeled antibody. Other promising antigen systems for RIT include internalizing antigens such as CD19[122] and HLA-DR,[123] CR2,[124] CD37,[125], CD30,[126] and B-cell idiotypes.[127] In one study, HAMA response to the MAb Lym-1 appeared to correlate with improved survival.[128]

As part of autologous hematopoietic cell transplant conditioning for patients with NHL, cyclophosphamide and etoposide were combined with ^{131}I-tositumomab[129] or ^{90}Y-ibritumomab tiuxetan in one study.[130] In another study, carmustine, etoposide, cytarabine, and melphalan were combined with ^{131}I-tositumomab.[131] There were no significant added toxicities from RIT, and the EFS and OS were highly favorable when compared to historical controls. In stem cell transplant for relapsed mantle cell lymphoma, ^{131}I-tositumomab when added to high-dose etoposide plus cyclophosphamide also produced encouraging results.[132] The addition of RIT therapy to conventional conditioning regimens deserves to be explored further, especially among patients with high-risk aggressive lymphomas, mantle cell lymphoma, and relapsed follicular NHL.[133] Rituximab is an accepted treatment strategy for most patients with NHL.[134] However, most if not all patients eventually relapse and require further therapy. Although it can achieve a second response in follicular or low-grade NHL, resistance usually develops requiring switching to radioimmunotherapy with ^{131}I-tositumomab or ^{90}Y-ibritumomab.[135] The outcome for patients who are treated first with a radiolabeled antibody and then with an unconjugated antibody has not been evaluated. However, because of myelosuppression, patients might not tolerate other therapy after failing RIT. A general approach in NHL is to use rituximab after chemotherapy failure, followed by RIT if rituximab fails.

Radiolabeled MAb for Leukemia

Radiolabeled MAb targeted to lineage specific antigens have been safely administered to patients with leukemia.[136] ^{90}Y-anti-CD25 was active in acute T-cell leukemia (2 CR, 7 PR among 16 evaluable patients),[137] and myelosuppression was the primary toxicity. ^{131}I-anti-CD33 (AML, myelodysplastic syndrome [MDS], myeloblastic CML),[138,139] ^{90}Y-anti-CD33,[136] ^{131}I-anti-CD45 (AML, acute lymphoblastic leukemia, MDS),[140] and ^{188}Re-anti-CD66c (AML, ALL, CML)[141] all delivered significant radiation doses to the bone marrow and are particularly effective as part of a conditioning regimen for hematopoietic stem cell transplantation. Radioconjugates that emit α-particles (^{213}Bi-anti-CD33 and ^{225}Ac-anti-CD33) might be better suited for the treatment of small-volume disease.[142,143]

Radioimmunotherapy of Solid Tumors

The antitumor activity of RIT in solid tumors is less impressive (see Table 34-4).[144] A number of radiolabeled MAb have been tested in phase I/II setting in CRC with modest clinical benefit: ^{131}I-17-1A (specific for Ep-CAM), ^{131}I-B72.3 (pancarcinoma), ^{131}I-anti-CEA (carcinoembryonic antigen), ^{90}Y-CC49 (a second-generation murine antibody of B72.3), and ^{131}I-CC49 or ^{131}I-A33, some at myeloablative doses (50 to 300 mCi/m^2).[144] ^{131}I-hMN-14 (humanized anti-CEA IgG at 60 mCi/m^2) has been administered to patients in remission or with small-volume colorectal metastasis; the potential for long-term benefit will have to await formal randomized trials.[92] For breast cancer and ovarian cancer, RIT targets have included MUC1, B72.3, L6, CEA, and gp38, whereas in renal cell cancer, G250 has been the main antigen of interest.[144]

Intravenous anti-GD2 ^{131}I-3F8 was tested in children with metastatic neuroblastoma at high doses (6 to 28 mCi/kg).[145] Responses were seen in both soft-tissue masses and bone marrow. The use of myeloablative ^{131}I-3F8 (20 mCi/kg) to consolidate remission was tested in 35 patients (>1 year of age) with newly diagnosed stage 4 neuroblastoma.[31] Extramedullary toxicities were limited to hypothyroidism, which occurred despite aggressive thyroid protection using potassium iodide, liothyronine (T3), and potassium perchlorate. Intrathecal and intraventricular administration for leptomeningeal carcinomatosis and intratumoral therapy of malignant brain tumors using ^{131}I-81C6 (anti-tenascin MAb) have produced objective responses and prolonged patient survival.[146,147] ^{211}At-81C6 is an example of α-particle therapy for minimal residual disease in malignant glioma.[148] Intraventricular ^{131}I-3F8[149] and ^{131}I-8H9[150] are also being tested in RIT for leptomeningeal cancers in both children and

adults, with highly favorable CSF to blood radiation dose ratios; among children with recurrent neuroblastoma metastasized to the CNS, long-term remissions have been achieved.[151]

Multistep Targeting or Pretargeting

To improve tumor uptake and reduce systemic toxicity, a multistep procedure that pretargets the antibody before the binding of the cytotoxic ligand to the tumor has been employed successfully.[152] Generally, a tumor-specific antibody is conjugated to a ligand binder, such as streptavidin or avidin (with high affinity for biotin), or a ligand-specific antibody (binding to metal chelators such as diethylenetriamine pentaacetic acid [DTPA] or 1,4,7,10-tetraacetic acid [DOTA]).[98,153] In the first step, these antibody-streptavidin or F(ab′)2-streptavidin conjugates (172 to 200 kd) are allowed to localize to tumors in vivo, and any excess is cleared from the blood. A small radiolabeled ligand (or its biotinylated form) is then injected intravenously. The ligand penetrates tissues rapidly and, by virtue of the high affinity interaction, binds tightly to the antibody-conjugate at the tumor site. Unbound ligand is quickly excreted through the kidneys. Because of the short transit time of the toxic ligand (radionuclides or toxins), a substantial improvement in the therapeutic ratio is achievable without sacrificing the percent injected dose per gram in tumor.

Antibody pretargeting has improved tumor imaging for colorectal, lung, and medullary thyroid cancers, especially when positron emission tomography radioisotopes are used. Multistep targeting of 110 mCi/m^2 of ^{90}Y-DOTA was well tolerated except for dose-limiting gastrointestinal toxicity that was thought to be related to MAb NT-LU-10 cross-reactivity with the gut.[154] Delayed renal toxicity was also observed. A similar approach that was applied to MAb CC49 in GI cancer[155] and anti-CD20 MAb in NHL[156,157] achieved tumor doses of 0.289 Gy/mCi and 0.26 Gy/mCi, respectively, although the tumor-to-kidney dose ratio was less than 2.5. A three-step approach, which used biotinylated MAb, followed by avidin/streptavidin and then by biotinylated radiometal-chelate, was also applied to glioma with encouraging results.[100,158] The bispecific antibody pretargeting system takes advantage of a bivalent hapten that binds to the two arms of a tumor-localizing bispecific antibody.[92] When anti-CEA bispecific antibody was tested in patients with SCLC[159] and in patients with medullary thyroid carcinoma,[160,161] an average tumor dose of 0.192 Gy/mCi was achieved, accompanied by tumor stabilization in 45% of patients. Building on these early results, clinical studies combining with chemotherapy are under way.[162] Furthermore, pretargeting concepts may be potentially useful in targeting small ligands in addition to radioisotopes.

Immunocytokines

Cell-mediated cytotoxicity has been highly effective against tumors in vitro and in animal models. Immunocytokines[93,163] have shown remarkable success in activating and redirecting effectors to human tumors. Most of these studies have focused on NK, natural killer T, or T cells[93] and granulocytes.[18] Antibody-IL-2 immunocytokine can eradicate metastatic murine neuroblastoma while inducing long-term antitumor immunity.[93,163] Following initial successes with IL-2 immunocytokine, constructs containing other cytokines also have been tested with encouraging results.[93] These include IL-12, tumor necrosis factor, and lymphotoxin. This emerging technology has been successfully applied to a number of antigens and tumor models, including GD2, human epithelial cell adhesion molecule (hEpCAM), CEA, EGF-R, HER2, folate receptor, and B-cell idiotype. More recently, the combination of a plasmid DNA vaccine and IL-2 immunocytokine in the mouse model was shown to be more effective than when either one was administered alone.[164] KS-IL-2 (anticolorectal CA) and 14.18-IL-2 (anti-GD2) are both in clinical trials; their toxicity profiles are generally acceptable, but clinical efficacy has yet to be established.

Immunotoxins

Ribosome-inactivating toxins can be potent cancer drugs. One major limitation is the lack of tumor selectivity.[165] Two-chain toxins (e.g., ricin and diphtheria toxin [DT]) utilize their B chain for cell-binding and their A chain for inhibition of protein synthesis; other toxins (e.g., Pseudomonas exotoxin [PE], Pokeweed antiviral protein, and gelonin) have a built-in receptor for cell attachment. When conjugated to MAb, they become immunotoxins. These toxins can be genetically modified for MAb conjugation and for improved safety profile.[94] In recombinant toxins (e.g., PE40, PE38, or diphtheria toxin DAB_{486}), the cell-binding domains are replaced by single-chain variable fragments (scFv).[94,165]

Various monoclonal MAb have been conjugated to different toxins for clinical trials:[165] ricin toxin A chain (RTA conjugated to anti-CD7, anti-CD22, and anti-CD25), DT (anti-IL-2R), and PE (anti-CD25, anti-CD22,[166] anti-Lewis Y,[167] and anti-HER-2). A common toxicity is the vascular leak syndrome, characterized by marked fluid overload, dyspnea, and sensorimotor neuropathies.[168] Deglycosylated RTA devoid of mannose and fucose has reduced hepatic sequestration, allowing longer serum half-life. An OR of 31% (2.6% CR, 29% PR) was achieved in patients with NHL following anti-CD22-deglycosylated RTA treatment.[169] Among 16 patients with cladribine-resistant hairy cell leukemia, anti-CD22-dsFv-PE (RFB4[dsFv]-PE38, BL22) induced 11 CR and 2 PR.[170] In addition to transient hypoalbuminemia and elevated aminotransferase levels, 2 patients had serious but reversible hemolytic-uremic syndrome. Other highly toxic natural compounds have also been explored recently, such as calicheamicins[171] and maytansinoids.[172] Gemtuzumab ozogamicin (Mylotarg) is an anti-CD33 antibody that is conjugated to calicheamicin. Acting like a prodrug, calicheamicin is released from the antibody following internalization, forming a diradical that induces double-strand DNA breaks. Gemtuzumab was active in childhood refractory AML[173] and achieved a 30% response rate among refractory AML patients 60 years of age or older.[174] In contrast, antimucin MAb-calicheamicin conjugate has not been successful to date in solid tumors.[175] With most immunotoxins, immunogenicity has been a major constraint, although pegylation may reduce immunogenicity.[176]

Immunoenzymes for ADEPT and Drug-Antibody Conjugates

To enhance the effector functions of MAbs, drugs have been conjugated to MAb for selective tumor delivery. Doxorubicin, melphalan, methotrexate, and vinca alkaloids conjugated to MAb have limited clinical success. BR96-doxorubicin directed at Lewis Y antigen has shown no clinical benefit in phase II trials in breast cancer[177] or gastric cancer.[178] Another novel approach (ADEPT) uses MAb to deliver a covalently conjugated enzyme to the tumor, which can then activate a nontoxic prodrug.[95,179] Despite preclinical successes, ADEPT has been difficult to translate into clinical benefit. Significant impediments to broaden their clinical implementation include immunogenicity of antibody-enzyme conjugate, as well as the presence of endogenous enzymes or endogenous substrates and endogenous inhibitors of these enzymes within the tumors.

Immunoliposomes

With advances in liposome technology, several liposomal agents have been licensed for use in cancer patients.[180,181] When coated with polyethylene-glycol, uptake by the reticuloendothelial system is inhibited, thereby prolonging residence time in the blood. Concurrent developments in drug-loading technology have improved the efficiency and stability of drug entrapment in liposomes. Although there is passive accumulation of liposomes in tumors through enhanced permeability and retention, their uptake can be greatly enhanced when engrafted with surface antibodies or their derivatives.

For example, scFv or Fab can target liposomes for uptake into tumors bearing CD19,[182] HER-2,[183] EGFR,[184] and GD2.[185] When liposomes fuse with the tumor targets, their contents can be efficiently delivered intracellularly. While their potential is high, the clinical benefit of MAb-targeted liposomes remains to be proven.

Cellular Immunoconjugates with Bisepecific Antibodies

Tumor-selective MAb can be rendered cytophilic by conjugation with MAb that are specific for trigger molecules on T-lymphocytes, NK cells, and granulocytes.[186–188] These molecules include CD3, CD28, Fc receptors (CD64, CD16), and FcαRI (CD89).[97] One binding site of the bispecific antibody engages CD3 on T-cells; the other binding site determines tumor specificity, for example, B-NHL (CD19),[189] breast cancer (HER-2),[190] and Hodgkin's lymphoma (CD30).[191] Similar successes have been reported for the trigger molecule CD28 for acute lymphoblastic leukemia (CD19 and CD20)[192,193] and Hodgkin's disease.[194] A phase I trial of the bispecific (HER-2, CD3) and trifunctional (metastatic breast cancer, T cells and FcγRI/III) antibody at low doses (100 μg per injection) was tolerable, tumor responses being noted in 5 of 15 patients.[195] Bispecific MAb targeted at FcγRI can redirect ADCC to specific tumors, including epithelial cancer (EGF-R)[196] and breast cancer (HER-2),[197] while those directed at FcγRIII have been successful against Hodgkin's disease (CD30)[198] and breast cancer (HER-2).[197] Because serum IgG competes for FcγR, bispecific MAb that is made to recognize the FcγR outside its Fc-binding domain is also being tested. Although bispecific MAb can induce generalized cytokine release from leukocytes and trafficking of effector cells into tumors is limited,[186] this treatment modality is being actively explored in clinic trials.

IMPROVING THE EFFICACY OF ANTIBODY-BASED CANCER THERAPIES

Measures have been taken to improve the efficacy of antibody-based cancer therapies.[199] To reduce immunogenicity, MAb have been chimerized and humanized, cloned from phage display libraries,[200] or produced in human IgG-transgenic or human transchromosomal mice (Fig. 34-2). Chimeric MAb are made by joining the antigen-combining variable domains of a mouse MAb to human constant domains: mouse VL to human CL and mouse VH to human CH1-CH2-CH3.[87] In humanized MAb, the antigen-binding loops, known as complementarity-determining regions from a mouse MAb are grafted into a human IgG.[201] Human antibodies can also be derived from scFv or Fab phage display libraries,[202] which are particularly useful for self-antigens.[203] Alternatively, human MAb can be made from hIgG-transgenic mice.[204]

Because Fc is necessary for antitumor effect, chimerizing mouse MAb with the human IgG1 or IgG3 Fc regions can improve ADCC and CDC functions. Similarly, removing FcγRIIB inhibitory receptor recognition also can enhance antitumor activity.[205] Point mutations in the Fc region have increased its affinity for activation receptors or decrease its affinity for the inhibitory receptor.[206] Glycosylation of IgG at Asn297 stabilizes the tertiary structure of the C_H2 domain, which is critical for effector function.[207] Glycosylation depends on the producer line, and increasing the bisected complex oligosaccharides in the Fc region[89] or defucosylation has greatly improved ADCC properties of MAbs.[90] Complement-dependent cytotoxicity can also be improved by Fc region mutations to increase C1q binding.[208]

The antigen-binding affinity, molecular architecture, and oligomerization states of MAb can be reengineered to enhance tumor delivery and therapy.[209] For example, affinity can be increased by using phage display libraries,[210] ribosome display,[211] DNA shuffling,[212] or yeast display combined with DNA shuffling.[213] However, because the binding-site barrier can impede tumor penetration if the MAb has high affinity,[214] the optimal MAb may indeed be a low-affinity IgG binding to a surface antigen that is expressed at high density. In addition, the size of the MAb is critical. ScFv are small (25 kd) and rapidly cleared by the kidney. On the other hand, oligomers with molecular weights in the range of 100 to 200 kd should be ideal for tumor targeting. Besides increasing avidity, oligomerization can increase antitumor activity through a multitude of mechanisms, including CDC/ADCC, induction of apoptosis, growth arrest, and synergy with chemotherapy or immunotoxins.[4] While scFv are a powerful building block for polymeric forms or novel fusion proteins,[215,216] single-domain antibodies may further expand the possibilities of antibody-based cancer therapies.[217]

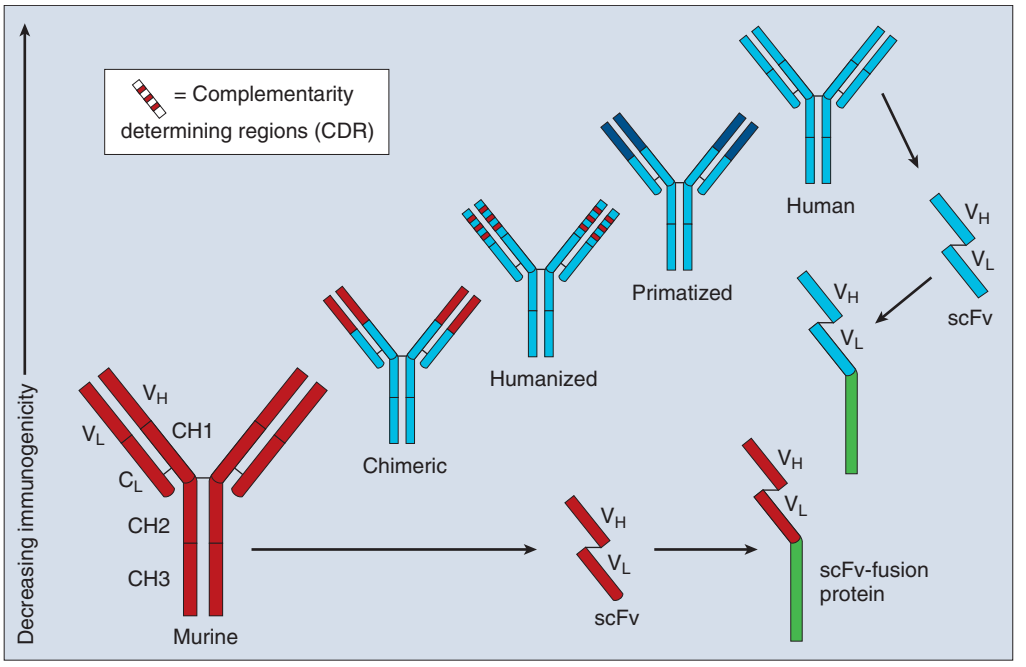


Figure 34-2 • Immunogenicity of MAb. CH1, CH2, and CH3, constant region domains of an IgG heavy chain; scFv, single chain variable fragment; V_H, variable region of the heavy chain; V_L, variable region of the light chain. *Red,* mouse; *blue,* human; *green,* recombinant protein to which scFv is genetically fused.

ALTERNATIVE TARGETS FOR ANTICANCER ANTIBODIES

Besides the ability to block receptors from interaction with their natural ligand, MAb can inhibit receptor dimerization or receptor interaction with coreceptors.[218] HER-2 is a ligand-less member of the ErbB receptor family that functions as a coreceptor with HER-1/EGFR, HER-3, and HER-4. MAb 2C4 sterically hinders the recruitment of HER-2 into HER ligand complexes and inhibits in vitro and in vivo growth of breast and prostate tumors. The humanized antibody Omnitarg is currently in clinical trial. Most of the MAb targeting effort has been focused on individual tumor cells, but alternative strategies directed at tumor neovasculature,[219] tumor stroma,[220] or tumor infiltrating T cells[221] are promising approaches. Bevacizumab (Avastin), a humanized IgG1 that is specific for vascular endothelial growth factor (VEGF) was effective for metastatic renal cancer[222,223] and, when combined with chemotherapy, for non-small-cell lung cancer,[224] metastatic CRC,[225] and metastatic breast cancer.[226] Furthermore, MAb can be made to inhibit homing of angiogenic progenitors (e.g., anti-VLA4 [Natalizumab][227] and anti-VEGF-R1[228]) or to block the VEGF-R2/KDR (e.g., IMC-1C11, chimeric anti-KDR).[229,230] Targeting tumor vasculature may have significant advantages over direct tumor targeting,[231] in that endothelial cells, unlike tumor cells, are less likely to acquire resistance. Another angiogenesis target is $\alpha V\beta 3$ integrin, which initiates endothelial proliferation, migration, and matrix remodeling.[232] In a phase I trial, chimeric IgG1 (MEDI-522) that is specific for $\alpha V\beta 3$[233] was well tolerated, and tumor perfusion was possibly modified. Ipilimumab (also known as MDX-010) is a fully human antibody against human CTLA-4, a molecule on T cells that attenuates their immunocompetence. Ipilimumab is currently being tested in metastatic melanoma as monotherapy or in combination with melanoma-peptide vaccine.[221]

WHAT IS THE FUTURE ROLE OF MAb AS A TREATMENT MODALITY?

Can One Size Fit All?

Human tumors and their response to MAb-based therapies are heterogeneous. Although MAb share common structures and properties, the successful translation of their antitumor activity into survival benefit in patients requires a much better appreciation of the clinical biology of each individual tumor type as well as an understanding of the fundamental biology of the antigens being targeted.

Is There an Optimal Time to Use MAb Therapy?

It is likely that MAb therapy is most beneficial at the time of minimal residual disease (MRD). Accurate and sensitive measures of MRD will provide objective indicators of tumor response to help guide clinicians to apply this modality more effectively.

What It the Future Role of Antibody Therapy in Treating Cancer?

As a rapidly expanding class of pharmaceuticals, MAb are now an important modality for cancer treatment. They have demonstrated antitumor activity in a broad spectrum of malignancies in the last two decades. The successful integration of MAb and immunoconjugates with other treatment modalities has the potential for achieving further improvements in symptom control and patient survival.

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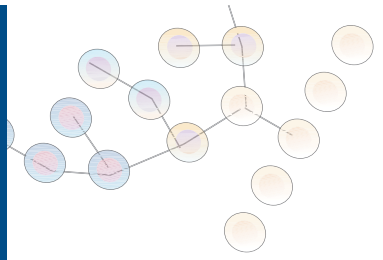
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35 Complementary and Alternative Medicine

James M. Metz and Heather Jones

SUMMARY OF KEY POINTS

- Complementary and alternative medicine (CAM) therapies are used by a significant number of cancer patients worldwide.
- Providing a nonthreatening environment for discussion of CAM will facilitate communication on this topic between physicians and patients.
- Many types of CAM may interact with conventional medications or cancer treatments to increase the toxicity or decrease the efficacy of the drug or therapy.
- Some CAM therapies have been shown to have side effects that mimic those of conventional cancer treatments.
- Physicians must warn patients about potential problems with CAM. They also should support those patients using those types of CAM that do not adversely affect conventional cancer treatment.
- A number of complementary therapies may be effective for stress reduction and combating pain or nausea.
- Health care providers must familiarize themselves with the most common CAM treatments used by patients with cancer so that informed discussions can occur.

INTRODUCTION

Complementary and alternative medicine (CAM) has infiltrated mainstream medical practices in recent years, driven mainly by patient desires to obtain these treatments. These therapies have gained increased exposure through television, radio, magazines, books, and the Internet. Most health care professionals have limited formal education on the subject and are unable to provide informed responses to questions about complementary and alternative methods. Patients' expectations of their health care team have expanded to include open discussions of CAM. They no longer accept labeling all of these CAM treatments by health care providers as ludicrous and unfounded. Numerous interactions with conventional medical therapies have been described in the scientific literature, so there are important medical reasons for physicians to understand the utilization of CAM. Medical professionals must be able to converse intelligently with the patient about CAM practices and to provide information about relevant dangers and hoaxes when appropriate. Health care providers also must learn to accept patients' use of alternative and complementary techniques so long as such modalities are safe.

Physicians must ask all patients under their care specifically about alternative and complementary medical practices that may be in use. Patients are more likely to discuss their adoption of these techniques openly when the physician provides a nonthreatening environment for discussion. Patients who have cancer are prime consumers and targets for alternative medical therapies. Many feel that they are in a desperate and hopeless situation. Many simply want to regain control over their lives, and use of CAM is an expression of this desire.

This chapter provides a general introduction to the topic of CAM and considers some of the more commonly used CAM therapies. Not every CAM modality in use is covered, because this would be beyond the scope of the discussion; rather, relevant information on commonly used therapies is presented to promote optimal physician-patient interactions whenever CAM treatments are discussed.

DEFINITION OF COMPLEMENTARY AND ALTERNATIVE MEDICINE

The terms *alternative medicine* and *alternative therapy* have become popular in recent years but do not accurately reflect or encompass the practices for which they are used. *Alternative* is the generally accepted term that refers to a diverse assortment of philosophies, theories, diagnostic, preventive, and therapeutic practices not generally viewed as arising from or belonging to the modern Western medical paradigm.[1] Other popular terms are *complementary, unconventional*, and *integrative medicine*. Each of these terms attempts to encompass the practice modalities not common to Western medicine. The terms *complementary medicine* and *integrative medicine* often are used to acknowledge the combination of these nontraditional treatment modalities with more conventional views and therapeutic approaches. Although some authors prefer to define alternative medicine as treatment approaches not amenable to combination with conventional therapy,[2,3] several other terms have been used to define this subject: *unconventional, unorthodox*, *nontraditional*, *holistic*, and *non-Western*.[1]

The National Institutes of Health (NIH) Office of Alternative Medicine established a Panel on Definition and Description, charging it "to establish a definition of the field of complementary and alternative medicine for purposes of identification and research; and to identify factors critical to thorough and unbiased description of CAM systems and practices that would be applicable to both quantitative and qualitative research."[4] The panel defined complementary and alternative medicine as follows: Complementary and alternative medicine is a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period. CAM includes all such practices and ideas self-defined by their users as preventing or treating illness or promoting health and well-being. Boundaries within CAM and between the CAM domain and the domain of the dominant system are not always sharp

Box 35-1. COMPLEMENTARY AND ALTERNATIVE MEDICINE AS DEFINED BY THE NATIONAL INSTITUTES OF HEALTH

In 1992, the National Institutes of Health (NIH) convened a meeting to discuss the major areas of alternative medicine and to direct future research activities.[1] As part of this meeting, the group defined the following seven fields of alternative therapy:

1. **Alternative systems of medical practice.** This field includes "folk" medicine and organized health care systems based on alternative practice. Examples include acupuncture, homeopathy, and naturopathy.
2. **Bioelectromagnetics.** Researchers in this field study how living organisms interact with electromagnetic fields. Magnetic field therapy is one example of bioelectromagnetics practice. It most often is used to treat osteoarthritis and nonunion of bone fractures.
3. **Diet and nutrition.** This field includes the use of special diets to improve health. Examples include the macrobiotic diet and orthomolecular medicine.
4. **Herbal remedies.** This field includes the use of herbs and plants to promote and improve health. Herbal therapy is considered to be the most popular alternative therapy used in the United States. It is used for many conditions.
5. **Manual healing methods.** Practitioners use touch and manipulation to promote and improve health. Examples include chiropractic therapy, massage therapy, and therapeutic touch.
6. **Mind-body interventions.** This form of therapy uses the interconnectedness of mind and body to improve health. Examples include psychotherapy, meditation, guided imagery, hypnosis, biofeedback, and prayer. Such interventions most commonly are used to treat nausea and vomiting (particularly for anesthesia- or chemotherapy-induced hyperemesis gravidarum) and postoperative dental pain.
7. **Pharmacologic and biologic treatments.** This field includes treatment with drugs and vaccines not accepted by mainstream medicine. Examples include the use of shark cartilage, EDTA for chelation therapy (for coronary artery disease), and apiotherapy.

EDTA, ethylenediaminetetra-acetic acid.

or fixed. Box 35-1 presents a list of CAM modalities defined by the NIH.

UTILIZATION OF COMPLEMENTARY AND ALTERNATIVE MEDICINE

Many studies have been performed to identify the utilization patterns of CAM throughout the world. This section addresses the worldwide use of CAM, which can be influenced by demographic factures such as culture, religion, race, geographic location, and gender of the patient. A number of questionnaire studies have suggested that a significant percentage of cancer patients are using CAM. Estimates range from 9% to 64%, depending on the definition of CAM and the cancer patient population studied.[5–10] Some evidence indicates that the use of these treatments within the general U.S. population increased during the past decade.[11] Also, studies suggest that many patients do not discuss their use of these treatments with their physicians.[8]

Risberg and colleagues evaluated 252 cancer patients in Norway and found a 45% likelihood (i.e., cumulative risk) of using CAM among patients under observation or cancer treatment.[5] Females were much more likely to use these therapies than males. Liu and associates evaluated 100 patients with advanced cancer receiving conventional cancer treatment in China; 64% were found to be using some form of CAM, mainly herbal therapies.[6] Begbie and colleagues evaluated 319 cancer patients in Australia and found that 22% used CAM treatments; 40% of the users did not discuss them with their physicians.[7] Downer and coworkers found that the 16% of 415 patients with cancer surveyed in England used CAM. The typical user of CAM tended to be younger, of higher socioeconomic status, and female.[8]

In the United States, the use of CAM also is prevalent. In a telephone survey of patients with cancer, 452 of 5047 (9%) admitted to using CAM techniques.[9] Mind-body interventions and diet therapies were the most common. A study from the University of Pennsylvania showed that 40% of patients with cancer undergoing radiation therapy were using CAM. However, only 7% admitted to using these therapies during the standard history and physical examination.[11] Only after the addition of a few directed questions regarding use of CAM did a majority of these patients reveal that they were using these therapies. Exercise and prayer were specifically excluded as CAM practices in this study. A recent study of patients with stage I and II breast cancer found that a complementary or alternative medical system was used by 57.3% of the patient population.[10] When exercise therapy was excluded from the analysis, 40% were using CAM. Younger age and increasing income and educational level were predictors of such use. The definition of CAM can vary significantly between studies, which affects the percentage utilization reported, as noted. Clearly, it is important to understand the precise definitions used in each study when comparisons are made.

Very limited information is available concerning the use of CAM therapies in the pediatric oncology population. An interview of the parents of 84 pediatric patients with cancer in The Netherlands found that 26 of 84 children (31%) had used or were using CAM.[12] Among these children, 19 of 26 (73%) had suffered a relapse before using these techniques. Fernandez and associates performed a study of pediatric oncology patients in British Columbia and found that 42% of the 366 respondents used some form of CAM treatment.[13]

CANCER PREVENTION AND COMPLEMENTARY AND ALTERNATIVE MEDICINE

A growing body of literature relating cancer prevention and CAM is available to the public. More than 50% of U.S. adults use some type of vitamin, mineral, or other micronutrient supplement.[14] Several studies indicate that users of dietary supplements believe that supplements can prevent or treat chronic diseases, such as cancer and cardiovascular disease, despite limited scientific support for the efficacy of such use.[15–18] Information about micronutrient supplements is becoming more common in the popular medical literature and is creating increased curiosity and a broader awareness. The explosion of the micronutrient supplement market is compelling physicians to become aware of dietary supplements. Whether or not they are used in clinical practice is a decision for the individual physician. In view of the increasing number of patients who are using micronutrient supplements, however, it is imperative that physicians have a good understanding of this topic (Box 35-2).

Antioxidants

Fruits and vegetables appear to be protective against the major cancers.[19] People who eat more fruits and vegetables that are rich in carotenoids or who have higher serum beta-carotene levels have a lower risk of cancer, according to randomized trials in human populations.[20] The antioxidant vitamins—vitamin A and related compounds such as beta-carotene, as well as vitamins C and E—are prominent components of many fruits and vegetables. Conjecture regarding the micronutrients responsible for this beneficial effect has been extensive because the antioxidant vitamins function as scavengers for DNA-damaging, mutagenic oxygen free radicals.

Box 35-2. WHY PATIENTS USE COMPLEMENTARY AND ALTERNATIVE MEDICINE

The complex trend of public awareness of and use of complementary and alternative medicine (CAM) has grown extraordinarily in the past decade. This seemingly insatiable desire for ancient philosophies and approaches to medical care by the general public seems particularly odd because it comes at a time of extraordinary technological and therapeutic advances. The physician should strive to understand what motivates a particular patient to seek CAM therapies before entering into a discussion with a patient—reaching this understanding can be quite challenging. The clinical literature for the most part has done an excellent job in documenting the incidence and patterns of CAM use but often has overlooked the more important question of why patients choose alternative modes of care. This motivation stems from a complex combination of social, cultural, philosophical, and personal factors that often differ among ethnic groups and disease types.

One reason for this phenomenon, no doubt, is the enormous increase in public access to worldwide information available on the Internet and from extensive media coverage. Commercial advertising and continuous exposure through the lay press, ranging from tabloid publications to magazines, medical journals, and books, have vigorously promoted the concepts of disease prevention and healing by unconventional means, striking a responsive (and highly lucrative) chord in a truly global population.

Another reason for the popularity of CAM is the escalating cost of modern allopathic medical care. New technologies have been developed at a record pace, producing many medical, surgical, and diagnostic innovations, most of which are unquestionably improvements but which also are very costly. The expense and the resulting rationing of these new modalities by managed care programs in an attempt to reduce the costs of medical care have placed them out of reach for a considerable segment of the population. The outcome appears to be the creation of a strong public desire for a wide range of CAM modalities to prevent and treat the full scope of human illness.

Other reasons sited for CAM use have included an affinity for a holistic or natural approach to healing, the need to manage side effects, dissatisfaction with the mindset of physicians, and an overall failure of conventional therapies to meet patient needs. Additional insight can be gained by reviewing patient assessments of CAM providers. Patients often praise CAM providers for the ability to define an illness, the amount of time provided for patient visits, continued involvement of the same provider over the course of treatment, and the attention to personality and personal experience. The satisfaction with treatments received often is not contingent on clinical improvement with regard to the presenting complaint.

Many patients are more informed about complementary and alternative therapies than their physicians are, a situation that, in itself, should encourage physicians to learn more about CAM. CAM therapies offer patients "a participatory experience of empowerment, and authenticity, when illness threatens their sense of intactness and relationship to their world."* Understanding what motivates patients may better enable physicians to enter into a dialogue with them and encourage a positive physician-patient relationship.

*Pappus S, Perlman A: Complementary and alternative medicine: the importance of doctor-patient communication. Med Clin North Am 2002;86:1–10.

Accumulating epidemiologic evidence suggests that a number of micronutrients may decrease the incidence of cancers of epithelial cell origin. These include vitamin A, vitamin C, vitamin E, and beta-carotene. Dietary deficiency of vitamins A, C, and E has been implicated in the development of cancers of the lung, breast, oropharynx, stomach, bladder, prostate, and colon.[21–26] Squamous tissues deficient in vitamin A exhibit metaplastic differentiation that can be reversed by administration of vitamin A and related compounds.[27] Additional evidence suggests that diets rich in vitamin A and related compounds not only diminish the risk but also are protective against the development of certain cancers. Whereas vitamin C appears to inhibit the formation of carcinogenic nitrosamines that have been associated with the development of gastric cancer, vitamin E inhibits mutagenesis and cell transformation mainly through its antioxidant function.[28] Nonetheless, the role of vitamins C and E in neoplastic development remains particularly unclear. Although vitamins C and E function as antioxidants, little evidence is available to support any direct role for these vitamins in the inhibition or reversal of neoplastic growth and development.

Several recent studies of dietary supplementation highlight the importance of clinical trials in defining benefit.[29] Both the CARET (beta-carotene and retinol) and the alpha-tocopherol–beta-carotene trials suggest that pharmacologic doses of beta-carotene *increase* the risk of lung cancer among smokers or those with asbestos exposure.[30,31] A large, four-arm clinical trial of multiple dietary supplements in 30,000 subjects in Linxian, China, demonstrated no significant effect on cancer incidence. However, those subjects who received a combination of selenium, beta-carotene, and alpha-tocopherol enjoyed statistically significant lower total and gastric cancer–specific mortality rates.[32]

Vitamin D, Calcium, and Selenium

Among the many minerals required for normal tissue development, calcium and selenium have received the most attention with regard to carcinogenesis. Laboratory data, as well as preliminary clinical data, suggest a role for calcium deficiency in the development of colon cancer. In epidemiologic studies, an inverse relationship also has been reported between vitamin E, vitamin D, and calcium supplementation and prostate cancer.[33] In addition, laboratory studies have shown that the active metabolite of vitamin D, 1,25-dihydroxyvitamin D (calcitriol), inhibits growth of both primary cultures of human prostate cancer cells and cancer cell lines; however, the mechanism by which cellular growth is inhibited has not been clearly defined.[34]

Recently, a large randomized trial of more than 1000 patients with a history of polyps showed that daily supplementation with 1.5 g of calcium reduced new adenomatous polyp formation by 20%.[35]

The Nutritional Prevention of Cancer Study by Clark and associates randomized 1312 patients to receive placebo or 200 μg of selenium per day and was designed to evaluate the effect of this supplement on risk of developing new basal cell and squamous cell skin cancers. In the analysis of the primary outcomes, selenium supplementation had no effect on reducing the incidence of these skin cancers. After preliminary analyses showed a reduction in total carcinoma, however, the protocol was modified in 1990 to add total and cancer mortality, as well as the incidence of lung, colon, rectal, and prostate cancers, as secondary endpoints. Analysis of these endpoints revealed a preventive effect for cancers of the lung, prostate, colon, and rectum, but no reduction in risk of breast or bladder cancer.[36]

Soybeans

Soy products are the primary food source for the isoflavone glycosides genistin and daidzin, which are metabolized by colonic microflora to the biologically active aglycones genistein and daidzein. These compounds, along with lignans, are generically named phytoestrogens and have structural similarities to estradiol. Evidence suggests that the consumption of diets rich in soybean products is associated with lower cancer mortality rates, particularly for cancers of the colon, breast, and prostate.[37–40]

The soy protein Bowman-Birk trypsin inhibitor (BBI), also found in other beans and peas, now in clinical trials, has been shown to suppress carcinogenesis in laboratory animals and in in vitro transformation systems.[40]

It is difficult to study the effects of micronutrient supplementation on the formation of cancers, in view of the inherent complexity of carcinogenesis. Information about the mechanisms of chemopreventive agents that inhibit carcinogenesis is still imperfect. Elucidation of how various dietary components inhibit carcinogenesis will be instrumental in the development of novel dietary chemopreventive agents in the future. Results from large trials such as the Women's Health Initiative Trial and the Selenium and Vitamin E Cancer Prevention Trial (SELECT) will provide a great deal of information regarding the effects of dietary modification and calcium, selenium, vitamin D, and vitamin E supplementation on breast, prostate, and colon cancer.

COMPLEMENTARY AND ALTERNATIVE MEDICINE MODALITIES AND THEIR LEGISLATION AND REGULATION

National Center for Complementary and Alternative Medicine

In 1990, Congress became aware of the rapidly developing interest in CAM in the United States. In 1991, the Office of Alternative Medicine (OAM) was established at the NIH but did not have formal status as a section or subsection. Initially, it was given an annual budget of approximately $2 million. The budget was increased to $20 million by 1997, and the OAM has since been given increased status by being renamed the National Center for Complementary and Alternative Medicine (NCCAM), with an annual budget of $50 million.[41] The charge of the NCCAM is to begin to appraise various CAM products as scientifically as possible through controlled studies. The NCCAM has thus far been slow in reporting results, no doubt at least in part because of the complex nature of conducting meaningful double-blind, clinical trials with CAM products. Numerous studies, however, are now in various stages of completion through the NCCAM and many other facilities throughout the world. At present, 13 institution-affiliated centers of research on CAM exist in the United States, and 75 medical schools in the United States are now teaching integrative medicine courses to their medical students.[41]

Herbal Medicine

Herbs have been used for medicinal purposes for thousands of years. Ancient Egyptians used herbs for the treatment of disease as early as 3000 BC. Almost one fourth of the current pharmacopoeia is derived from botanicals. Digoxin is derived from foxglove, aspirin is derived from willow bark, narcotics are derived from opium poppy, and birth control pills were developed from the Mexican yam. With the advent of modern medical science, people came to believe that synthetic ingredients were more effective than those found in nature, and the use of herbal remedies quickly diminished, especially in the United States. Currently available herbal preparations are sold mainly as nutritional products.[42]

Today, herbs are widely used in Europe and are again gaining popularity in the United States.[43] The most informative longitudinal data on use of herbal medicine derive from two Harvard surveys.[43,44] The results indicated that between 1990 and 1997, the use of self-prescribed herbal medicines within the U.S. general population increased from 2.5% in 1990 to 12.1% in 1997. During the same period, the proportion of persons consulting practitioners of herbal medicine rose from 10.2% to 15.1%. These survey studies estimated that in 1997, the entire U.S. population spent approximately $5 billion on herbal medicines. Most of this was out-of-pocket expenditure.[43–45]

Regulation of Herbals

The over-the-counter availability of herbal medicines fosters the notion that these medications are safe, and many casual users have inadequate knowledge about the use of these medications. Users often avoid discussing the use of these medications with their conventional care providers unless specifically asked.[46] These factors may set the stage for potential adverse drug reactions and interactions. Consumers in the United States are accustomed to products that have been tested and approved before sale. The U.S. Food and Drug Administration (FDA) functions to oversee the safety of foods, drugs, and medical devices sold in this country.

Most herbal products in the United States are considered dietary supplements and thus are not regulated as medicines and are not required to meet the standards for drugs specified in the Federal Food, Drug, and Cosmetic Act. In 1994 the Dietary Supplement and Health Education Act (DSHEA) was passed. This legislation had profound effects on the regulation and marketing of herbal products in the United States. Herbs or other botanicals could be sold as dietary supplements and were not subjected to the rigorous regulations that applied to medicines.[47] Herbal products may be produced without the assurance of compliance standards for good manufacturing practice (although such standards are being developed), and they are marketed without previous approval of their efficacy and safety by the FDA. According to the DSHEA, the manufacturer of a herbal preparation is responsible for the truthfulness of claims made on the label and must have evidence that the claims are supported, yet the DSHEA neither provides a standard for the evidence needed nor requires submission of the evidence to the FDA. Under the DSHEA, the manufacturer is permitted to claim that the product affects the structure or function of the body, so long as no claim is made of efficacy for the prevention or treatment of a specific disease, and provided that a disclaimer is supplied informing the user that the FDA has not evaluated the agent. Some of the claims on the labels of herbal products suggest that they can be used to treat disease, and supplementary materials, produced by persons other than the manufacturer, that overtly promote such use may be available where the herbal remedies are sold. According to the DSHEA, the manufacturer is responsible for controlling quality and safety, but if a concern about safety arises, the burden of proof lies not with the manufacturer but with the FDA, which has to prove that the product is unsafe.[48,49]

Several European countries have implemented guidelines for licensing herbal remedies. In Germany, such products can be registered as medicines on the basis of information in approximately 300 monographs on herbs ("positive" monographs with concise information about terminology, composition, uses, contraindications, side effects, drug interactions, dosage, mode of administration, and actions, and "negative" monographs explaining insufficient benefits or unacceptable risks).[50]

The European Commission (which governs the European Union) has recently publicized a draft directive on the licensing of traditional herbal preparations. If accepted, this proposal will require all members of the European Union to introduce a simplified procedure for these preparations so that they can receive a "traditional use" registration without the need to present data on efficacy from randomized trials.[49,51] The simplified licensing approach allows a premarketing assessment of the quality and safety of a product and facilitates postmarketing surveillance and product recalls.[49]

Generally, herbal products are not evaluated by the strict preclinical toxicology and pharmacology guidelines that are in place for conventional drugs. Instead, the focus of the clinical trials is on the efficacy of the products. A number of herbal formulations currently are undergoing clinical trials. The FDA has established a hotline for information about herbal products and one for reporting adverse effects.[47]

Acupuncture

Acupuncture has been practiced in China for more than 5000 years. Around the same time, acupressure, which uses similar points without needles, was developed in Japan. Acupuncture may be recommended by some practitioners for a variety of conditions, but abatement of pain or of nausea and vomiting is of greatest interest for cancer patients.

Acupuncturists use fine needles that range in length from 0.5 cm to several centimeters. The needles, usually made of stainless steel or copper, are placed approximately 5 mm deep and are gently manipulated by hand. The needles may be stimulated with a weak electrical current or by heat. Many patients describe a tingling sensation and feel a sense of heaviness in the area where the needles are placed.

The classic acupuncture teaching states that a life force called *qi* (pronounced "chi," to rhyme with "eye") dominates every organism and flows along interconnected meridians through the body and crosses at specific points. The meridians surface at various locations denoting the acupuncture points (these points are very similar for both acupuncture and acupressure). The opposing forces of *yin* and *yang* must be in balance before *qi* can get the body's vital functions to work normally; imbalance causes an accumulation of lactic acid in the muscles. Stimulating the acupoints dissipates the lactic acid and restores the *yin-yang* balance and the flow of *qi*.

To date, scientists in the Western world have found no evidence to support the existence of *qi*, *yin*, or *yang*. Bing and colleagues observed that stimulation of acupoints with needles activates the subnucleus reticularis dorsalis neurons that send projections to the dorsal horn of the spinal cord at all levels.[52] These investigators suggest that this anatomic structure may be involved in the modulation of pain. Grossman and Clement-Jones postulated that the release of endorphins within the nervous system may reduce the perception of pain.[53] Of interest, it also has been shown that the acupoints have a similarity in location to some of the anatomic sites used for local and regional anesthesia.[54]

Cancer Pain and Acupuncture

Owing to the widespread use of acupuncture and evolving scientific studies, in 1997, an NIH panel of experts issued a consensus statement for the use of acupuncture. According to this statement, clear evidence supports the effectiveness of acupuncture for the treatment of postoperative and chemotherapy-induced nausea and vomiting, nausea associated with pregnancy, and postoperative dental pain.[55]

In the palliative care setting, acupuncture is increasingly being used alongside conventional medical treatment for pain and symptom management.[56] Select evidence indicates that acupuncture effectively reduces acute perioperative and postoperative pain.[57–60] Despite numerous observational studies showing the effectiveness of the technique for chronic cancer pain relief, randomized controlled trials (RCTs) of acupuncture remain scarce. A recent review of the published data revealed only a single high-quality RCT for pain control in cancer,[61] by Alimi and colleagues.[62] This study showed statistically significant pain relief with auriculoacupuncture in patients with cancer compared with those in two control groups: a "nonpoint" needling control group and a noninvasive control group. Numerous observational and case series suggest that acupuncture may help relieve a variety of pain symptoms, including postsurgical and treatment-induced breast pain, often resulting in reduction in analgesic requirements and an improvement in mobility and circulation.[63–70]

Non-Pain Syndromes and Acupuncture

Nausea and vomiting are harrowing symptoms that commonly accompany cancer treatments. Numerous RCTs and reviews have been performed using the traditional point and have shown efficacy for postoperative nausea and vomiting and chemotherapy-related nausea and vomiting.[71,72] Fatigue is a commonly encountered debilitating symptom in cancer and may persist after successful cancer treatment.[73,74] A recent study concluded that acupuncture was worthy of further study in the treatment of fatigue following chemotherapy.[75] Studies indicate that pilocarpine-resistant xerostomia can be ameliorated by acupuncture.[76] Vasomotor symptoms and hot flashes secondary to cancer treatment and hormone manipulation also have been ameliorated by acupuncture.[5,77,78]

Regulation of Acupuncture

Acupuncturists can be certified in either of two ways: They can complete a formal, full-time educational program that includes both classroom and clinical hours, or they can participate in an apprenticeship program. Acupuncturists also must complete a "clean needle technique" approved course. Medical doctors with training in acupuncture also can obtain board certification. Certification for formally trained acupuncturists is through the National Certification Commission for Acupuncture and Oriental Medicine (NCCAOM). Medical doctors are certified through the American Academy of Medical Acupuncture and must possess a valid medical license. Currently, 37 of the 40 states that regulate acupuncturists require NCCAOM certification.

In response to petitions submitted by the acupuncture community, the FDA has reclassified acupuncture needles for general use from class III, the category in which clinical studies are required to establish safety and efficacy, to class II, a category that involves less stringent control by the FDA but does require good manufacturing and proper labeling. Manufacturers are required to label FDA needles for single use only. Use of acupuncture needles for clinical practice would be restricted to qualified practitioners as determined by state practice laws.[47]

Homeopathy

From the Greek words *homoios* ("like") and *pathos* ("suffering"), homeopathy is a system of medicine whose first tenet is the "principle of similars": A substance that can cause symptoms in a healthy person possibly can encourage self-healing in a person with an illness presenting with similar symptoms. This principle was developed into a practice of medicine in the nineteenth century by the renowned German physician Hahnemann. The theory of homeopathy is rooted in three of Hahnemann's principles: (1) the "law of similars," which states that a substance that can cause disease in a well person can cure similar symptoms in the diseased; (2) the "principle of the minimum dose," which states that by diluting a substance, its curative properties are enhanced and its side effects minimized; and (3) prescribing for the individual, which advocates basing treatment not only on the medical diagnosis but also the patient's temperament, personality, and emotional and physical responses.[58]

The principles of homeopathy are not well understood by the public or the medical profession, yet medical consumers are using homeopathic treatments in increasing numbers. In the United States and Europe, the sale of homeopathic medicines increased by 20% to 30% per year in the 1980s and 1990s.[80] A recent survey study revealed that many women who have breast cancer turn to alternative treatments in the hope of minimizing adverse reactions to treatment, rather than in the hope of a cure,[81] and use homeopathy for the reduction of treatment-related side effects. Two reviews identified 11 additional RCTs of homeopathy between 1997 and 2001.[82,83] These trials did not show any strong evidence that homeopathy was effective for any specific condition, and some of the better-designed trials had the least positive results. Even more recently, a comparative study of 100 placebo-controlled trials of homeopathy and conventional medicine found no specific effect for homeopathy when sources of bias were removed.[84]

Two meta-analyses have been published suggesting that homeopathic remedies are more effective than is placebo alone. However, both studies conclude that the current research and literature in the field do not meet the rigorous, scientific proof needed to establish

efficacy of homeopathy for specific clinical conditions.[85,86] More research is needed before homeopathy can be declared clinically useful for any one condition.

Regulation of Homeopathy

Although in other countries, homeopathic training and certification have been available for decades, the United States has not had full-time homeopathic schools or accredited professional education for more than 40 years.

Only three states—Arizona, Connecticut, and Nevada—license homeopaths. The scope of practice varies but includes the use of substances of animal, vegetable, or mineral origin given in microdoses and prepared according to homeopathic pharmacology. All three states use licensure as a means to authorize practice. These states require a DO or MD degree, as well as certification in the study of homeopathy. Arizona and Nevada have independent examining boards. In Delaware and New Hampshire, the practice of homeopathy is regulated by the state, although under no specific board. The Council of Homeopathic Education has implemented a voluntary certification process that includes a written multiple-choice examination, an oral examination, a videotaped interview, and 10 case reports. A person can be admitted to examination only after completion of a required curriculum and clinical supervision. Thus far, this certification process has not been recognized by the U.S. (or other) medical boards.

The FDA currently is attempting to establish guidelines for the regulation of homeopathic products. The FDA takes the position that homeopathic remedies, which are used in the treatment of disease, are by definition drugs and should be regulated. In recent years, the FDA has exempted homeopathic products from the regular drug-reviewing process if such drugs have been reviewed and approved by the Homeopathic Pharmacopeia of the United States.[47]

Massage

Massage therapy has had a long and well-known history, having been known to the ancient Chinese and Japanese and the Greeks, Romans, and Egyptians. The "laying on of hands" was the primary form of healing throughout history in places such as ancient Greece, where Hippocrates wrote that the "physician must be experienced in many things, most especially in rubbing."[87] Massage therapy is considered a form of medical treatment in several countries where it is covered by national health insurance, including China, Japan, Russia, and West Germany. In the United States, massage therapy still is considered a CAM modality. The popularity of massage therapy is growing. National and international massage therapy associations increased their membership by thousands of therapists during the 1990s.[88]

Regulation and Training for Massage

To become certified, massage therapists must complete a formal therapeutic massage bodywork program. They also may be considered for certification if they have training in anatomy, physiology, and kinesiology, as well as formal education and professional experience in bodywork or massage, or both. Massage provider practice acts for the regulation of massage exist in 22 states. Most statutes include directives for the treatment of soft-tissue or muscle, or both. Techniques may include, but are not limited to, friction, beating, and percussion. Types of health conditions treated, depending on the practice act, include maintaining good health, improving muscle tone, and reducing stress. Board certification is through the National Certification Board for Therapeutic Massage and Bodywork and is required in 20 of the 29 states that regulate massage therapists.[47,88]

Naturopathic Medicine

Benedict Lust, a German physician, introduced naturopathy to the United States. He used the term *naturopathy* (from *natur*, to indicate nature, and *pathy*, from homeopathy) to encompass all natural approaches to healing. Several healing modalities have been added to the healing module to arrive at modern naturopathy. Naturopathic medicine is far from being a single scientific discipline. The basic principle is that healing comes from within more than from without, and that medicine depends on the healing power of nature to cure (Table 35-1). Naturopathy employs various natural means to empower the patient to reach the ability to self-heal. The tools include lifestyle modifications, nutrition, dietetics, herbs, breathing, education, and hydrotherapy. In addition, naturopaths may elect to use a variety of healing modalities, including acupuncture, botanicals, homeopathy, massage, and Oriental medicine. Naturopaths are the "generalists" of the alternative medicine world. The emphasis of their practice is on prevention, education, and health maintenance.[89]

Table 35-1 Six Basic Principles of Naturopathic Medicine

Belief	Resultant Principle
The belief that the body has the inherent nature to heal itself	The healing power of nature underlies the ability to recover from illness or injury.
The belief that health and disease result from the interaction of a person's physical, mental, emotional, genetic, environmental, and social components	Treat the whole person.
The belief that the cause of disease, not merely the symptoms, should be treated	First, do no harm.
The belief that a physician's major role is to educate, empower, and motivate patients to take responsibility for their own health	Identify and treat the cause.
	Prevention is the best cure.
	The physician is a teacher.

Shealy CN, Thomas R (eds): The Complete Family Guide to Alternative Medicine. Rockport, Mass., Element Books, 1996.

Regulation and Training for Naturopathy

Naturopathic practitioners undergo a 4-year training program that includes therapies such as homeopathy, clinical nutrition, manipulation, herbal medicine, and hydrotherapy. Naturopaths often may have additional training in Chinese medicine (acupuncture and herbs). Naturopaths are licensed in 12 states. The naturopathic certification examination is administered by the North American Board of Naturopathic Examiners. Each state defines the scope of practice differently, using several adjunctive therapies including acupuncture, biofeedback, and nonprescription medications.[47,89]

Chiropractic

The term *chiropractic* is derived from two Greek words meaning "done by hand" and is defined as "the diagnosis, treatment and rehabilitation of conditions that affect the neuromuscular system."[89] Chiropractic care origins are in the manipulative health care modalities. It became an organized discipline approximately 100 years ago when Canadian Daniel David Palmer introduced it in the United States. The chiropractic system of health is based on two principles: a testable principle, that the structure and condition of the body influence how it functions and heals, and the untestable principle that the mind-body relationship is instrumental in maintaining health and affects the healing processes. Hence, the focus is on the body's ability to self-heal, on the nervous system's role in overall health, and on the interaction between body structure and the functioning of the nervous system. In the past decade, chiropractic care

gained measured acceptance and has developed into a treatment and wellness modality that is practiced by 55,000 licensed practitioners and used by roughly 10% of the U.S. population. A majority of visits to chiropractors in the United States are for back pain. According to some studies, chiropractic treatment is as beneficial for low back pain as treatment given by primary care providers, orthopedists, and physical therapists.[90,91] The evidence for the use of chiropractic for other conditions is less compelling.

Regulation and Training for Chiropractic Care

Chiropractic care is licensed in all 50 states, with 45 requiring insurers to include it in their plans. A large variation exists in the scope of practice; certain states restrict the practice to spinal manipulation, whereas others permit different procedures to be performed, such as acupuncture, electromyography, and laboratory diagnosis. The Council on Chiropractic Education (CCE) (www.cce-usa.org) has accredited 17 colleges of chiropractic medicine in the United States. Since 1974, chiropractic education has been established with a 4-year curriculum monitored by the CCE. Admission requirements differ from school to school, although a minimum of 2 years of college education and specific science courses are required by all.[47,92] Chiropractors must pass either a state licensing examination or an examination given by the National Board of Chiropractic Examiners.

Ayurveda

The word *Ayurveda* is derived from the Sanskrit *ayur*, meaning "long life," and *veda*, "knowledge." One of the world's oldest traditional healing systems, Ayurveda has been documented and practiced in India for thousands of years. Ayurveda is a holistic system that deals with all aspects of life: mind, body, and spirit. The ayurvedic practice is founded on the pooled wisdom of ancient Hindu saints and healers. Ancient Ayurveda was meant essentially to promote health, rather than fight disease.

A basic theory of Ayurveda states that everything in the material world is a sign of the unseen universe of energy or life force. The world was created from the unseen universe when the primordial sound created the five fundamental elements responsible for the material world: space, air, fire, water, and earth. These five elements manifest in the human physiology as three life energies called *doshas*. The three doshas are *vata* (space and air), *pitta* (fire and water), and *kapha* (water and earth). Each dosha, its subdivision, and underlying structures confer a particular characteristic and quality to each person. Health is a state of balance among the mind, body, and consciousness. Several factors can disturb this balance, including congenital and genetic factors, natural tendencies, habits, seasonal factors, and internal and external traumas. The imbalance produced in the doshas disturbs the life force, producing the disease state.

Diagnosis is based on identifying the exact quality and nature of the imbalance and correcting it. This is accomplished through a detailed history, inspection, and examination. Radial pulses (three superficial and three deep pulses, bilaterally) and tongue, nail, and eye examinations, among others, are important parts of the ayurvedic diagnostic examination. Treatment consists of amplifying or reestablishing the body's balance through a combination of interventions, including lifestyle changes, diet modifications, meditation, yoga, breathing exercises, massage, aromatherapy, herbs, and detoxification.[93] Studies have documented the favorable effects of regular meditation on reducing cardiovascular risk factors and stress. Further studies investigating the effects of the ayurvedic herbal products on a wide variety of conditions including cancer, aging, and health promotion are ongoing.[94]

Regulation and Training for Ayurveda

Ayurvedic medicine is the progenitor of several CAM disciplines. These include aromatherapy, homeopathy, and massage. There is no national standardization of training and credentialing of ayurvedic providers. A wide variance of training and experience exists among providers.

THE CANCER PATIENT AND POPULAR COMPLEMENTARY AND ALTERNATIVE MEDICINE THERAPIES

The tendency of CAM modalities to change and shift in popularity does not arise in response to new developments or randomized clinical trials; rather, particular therapies simply go in and out of vogue. Typically, a CAM therapy remains popular for a limited period of time, after which it is replaced by a new and usually nonvalidated CAM therapy. Popular CAM modalities that currently are used by cancer patients are discussed in this section under the categories developed by the NIH (see Box 35-1).

Mind-Body Techniques

The effectiveness of meditation, biofeedback, and yoga in stress reduction and in the control of particular physiologic reactions is well supported by accepted research. The belief that patients can use mental attributes and mind-body work to prevent or cure cancer has not been demonstrated in clinical studies.

Biofeedback

Biofeedback manipulates the body's physiologic responses that are normally controlled by the autonomic nervous system. A biofeedback therapist, of which there are over 10,000 in the United States, can teach a patient how to control many involuntary functions. Some patients learn to control their heart rate, blood pressure, muscle tension, and emotions.

Monitoring electrodes are placed on the body or scalp by the biofeedback therapist. The electrodes then are connected to a computer or polygraph, which will emit a noise or signal indicating the intensity or level of the process to be controlled. The patient is instructed to concentrate on influencing the signal. Specific mental exercises are carried out under the direction of the therapist. The patient is asked to visualize certain images that affect mood and in time may become able to identify which mental exercises change the signals. After a number of sessions (usually 8 to 10), the patient may be able to affect certain of the autonomic processes.

Researchers at Vanderbilt University performed a randomized study to evaluate the effectiveness of a combination of biofeedback and relaxation training for the reduction of side effects of chemotherapy.[95] Biofeedback reduced some indices of physiologic arousal but did not modify the side effects of chemotherapy. However, relaxation training was found to produce a decrease in nausea and anxiety during chemotherapy and a decrease in physiologic arousal after chemotherapy. The researchers concluded that the major benefit of biofeedback was the relaxation training that accompanies the instruction and not the biofeedback alone.

The potential benefit from biofeedback therapy for the cancer patient is relaxation and reduction of stress. This can undoubtedly improve quality of life and allows the cancer patient to take an active role in overall management. Biofeedback is a noninvasive procedure. A group of 10 sessions with a biofeedback therapist costs approximately $500. No specific reports in the medical literature have described side effects attributed to the use of biofeedback.

Guided Imagery

Guided imagery is a technique that relies heavily on the power of suggestion to create relaxing mental images. It is particularly useful for relieving stress and promoting serenity. Some patients find that it helps them cope more effectively with the impact of the diagnosis and the side effects of treatments.

In this technique, the therapist instructs participants to visualize a specific image. Sometimes the participant is asked to visualize a mass of cancerous cells being attacked by the immune system, chemotherapy, or radiation therapy. Many patients use guided imagery audiotapes that provide instruction on meditation exercises, guided relaxation, and visualization techniques. Some patients use these tapes while they are undergoing chemotherapy or radiation therapy, or en route to receive treatment.

Syrjala and colleagues evaluated relaxation and imagery training along with cognitive-behavioral coping skills for control of oral mucositis pain in patients undergoing bone marrow transplantation.[96] These investigators found that patients who received relaxation and imagery training reported less pain than the control groups. No benefit was obtained with the addition of cognitive-behavioral skills, however.

The goal of guided imagery is total relaxation. Patients learn breathing exercises to help them attain an "inner calm," or they try to modify their experience of anxiety or pain by imagining a pleasurable scene or situation. Some patients with cancer find the method effective in promoting relaxation and relieving anxiety. It must be emphasized, however, that no reliable evidence indicates any effect of this technique on disease progression or survival.

Guided imagery is a noninvasive therapy. Relaxation and guided imagery audiotapes cost approximately $10 to $20 and are available in local bookstores. Some patients prefer to visit a therapist for individualized training, which may be more expensive. No reports in the medical literature describe any side effects related to guided imagery.

Herbal Medicine and Biological Supplements

PC-SPES

PC-SPES (PC stands for "prostate cancer," and SPES is the Latin word for "hope") is a patented preparation of eight herbs[97] (Box 35-3). PC-SPES is the only herbal medicine for prostate cancer that has been subjected to clinical trials.

Four clinical trials of PC-SPES have been carried out in the United States and Germany.[98–101] These trials have been single-arm, phase I and II studies in patients with prostate cancer and have demonstrated prolonged decreases in prostate-specific antigen (PSA) levels in most of the men in the study. The side effect profile of PC-SPES has been suggestive of an estrogenic effect (i.e., breast tenderness, decreased libido, impotence, venous thromboses), and components of PC-SPES contain known phytoestrogens.[99]

The largest and most recently reported study was a phase II trial in 70 patients with prostate cancer.[101] Each patient received 320 mg of dried PC-SPES extract orally, three times a day. All androgen-dependent patients experienced PSA declines of 80% or more, and 26 patients (81%) experienced PSA decreases to undetectable levels. At 15 months, only one patient exhibited biochemical or objective progression. More than half of the patients with androgen-independent disease had a PSA response, with a median duration of response of 18 weeks. In the two androgen-dependent patients with positive findings on bone scans at study entry, one patient's follow-up scan revealed complete resolution of the osseous lesions, and the second patient's follow-up scan showed improvement but did not yield normal results. One patient had measurable disease and experienced complete resolution of a bladder mass seen on pelvic CT scan, accompanied by a decline in PSA from 8.9 ng/mL to an undetectable level. PC-SPES generally was well tolerated but was associated with a number of endocrine side effects, including decreased libido, erectile dysfunction, gynecomastia or mastodynia, and hot flashes.

Despite these encouraging results, a survival benefit for PC-SPES thus far has not been demonstrated. A worrisome possibility is that PC-SPES may decrease PSA levels while masking increases in tumor growth. PC-SPES also is associated with an increased risk of thromboembolic events.[102–104] Of enormous concern, PC-SPES was found to contain warfarin (and SPES, a more generic version for all cancers, to contain alprazolam), prompting the U.S. Food and Drug Administration (FDA) to issue a recall of both products in February 2002.[105]

Box 35-3. COMPONENTS OF THE HERBAL PREPARATION PC-SPES

Dendranthema morifolium Tzvel. (chrysanthemum)
Isatis indigotica
Glycyrrhiza glabra L.
Ganoderma lucidum
Panax pseudo-ginseng
Rabdosia rubescens
Saw palmetto
Scutellaria baicalensis Georgi (skullcap)

Hydrazine Sulfate

Cachexia remains a major problem in patients with advanced disease undergoing cancer treatment. There has been interest for a number of years in hydrazine sulfate for combating cachexia seen in cancer patients. Gold evaluated 84 patients with disseminated cancer and found that 59 of the 84 patients (70%) improved subjectively and 14 of the 84 (17%) improved objectively when receiving hydrazine sulfate. It was concluded that the compound may favorably influence nutritional status and clinical outcome in patients with disseminated cancer.[106]

Enthusiasm has been dampened by three prospective trials that showed no benefit when hydrazine sulfate was added to standard treatment regimens. Loprinzi and coworkers randomized 243 patients with non-small-cell lung cancer and 127 patients with advanced colorectal cancer to receive hydrazine sulfate or a placebo in addition to conventional anticancer regimems and showed no benefit with use of hydrazine sulfate.[107,108] Kosty and colleagues randomized 291 patients with advanced non-small-cell lung cancer to receive chemotherapy with or without hydrazine sulfate.[109] No benefit was found for pain control, cachexia, or survival in any of these studies. Hydrazine sulfate is not recommended for the treatment of any cancer-related symptoms, although it remains widely promoted on the Internet.

Shark Cartilage

Shark cartilage has gained increased popularity as the basis for an unconventional medical therapy (UMT) for the treatment and prevention of cancer. Shark cartilage was initially promoted by William Lane, PhD, in his book *Sharks Don't Get Cancer* and the follow-up book, *Sharks Still Don't Get Cancer*. In fact, however, tumors, including malignant tumors, do develop in sharks, in which thyroid and central nervous system neoplasms,[110,111] papillomas,[110–112] oral cavity cancers, adenomas of the liver, chondromas, and odontomas[110] have been observed.

Shark cartilage is purported to contain angiogenesis inhibitors. In fact, a modest antiangiogenic effect has been seen in vitro.[113] Shark cartilage is supplied in powder and capsule forms. It usually is taken orally but sometimes as an enema.

The television news program *60 Minutes* gave shark cartilage a huge boost a few years ago. The program reported a Cuban study of 29 patients with "terminal" cancer who were placed on shark cartilage; most "felt better" several weeks thereafter. "Feeling better" is not a reliable endpoint in a scientific study. The National Cancer Institute (NCI) performed a review of the study and found the data to be "incomplete and unimpressive."[114] The *60 Minutes* program allegedly refused to broadcast the findings of the NCI.

A small study on shark cartilage was reported at the American Society of Clinical Oncology in 1997.[115] Of the 58 patients with advanced cancer who were given shark cartilage for 12 weeks, not one objective complete response or partial response to shark cartilage was obtained. Only two patients reported significant improvement in the quality of life. Rigorous studies of shark cartilage are ongoing at a number of institutions, but no positive results have yet been published. It has been reported that shark cartilage can cause an elevation of values on liver function tests (LFTs) and frank hepatitis.[116] Patients on chemotherapy should be urged not to use shark cartilage enemas because of the risk of infection associated with chemotherapy-associated neutropenia.

Shark cartilage is relatively expensive. If it is taken as described by William Lane, the cost of the 16-week program is approximately $3000.

Mistletoe

Mistletoe (*Viscum album* L.) is one of the most commonly used CAM herbal medicines in Europe.[5,117–118] The active compounds identified in mistletoe are lectins (glycoproteins) and viscotoxins (proteins). The lectin component has in vitro immunostimulant activity and has been shown to increase the number of peripheral blood lymphocytes, as well as lymphocyte activity, in patients with gliomas.[119–121] The viscotoxins have been shown to have direct cytotoxic activity against certain cancer cell lines.[122]

Mistletoe has been used primarily as an adjuvant to conventional cancer therapies to manage micrometastatic disease. Various mistletoe products have been evaluated in several randomized, controlled clinical trials. An analysis of 11 of the randomized trials of mistletoe published in 1994 found that although 10 of these studies reported improved survival in the mistletoe treatment group, many of these trials had deficiencies in 5 or more of the 10 criteria of good methodology. These methodologic issues have led reviewers to question the validity of these studies and promoted demands for further well-defined studies.[123]

Recently, two well-designed prospective randomized trials have reported negative results. The effect of adjuvant treatment with mistletoe lectin-1, a standardized mistletoe preparation (Eurixor), was tested in a prospective, randomized clinical trial involving 477 patients with head and neck squamous cell carcinoma.[124] The European Organization for Research and Treatment of Cancer (EORTC) has completed a phase III randomized trial of adjuvant treatment with low-dose interferon-α versus interferon-γ versus mistletoe extract (Iscador M) versus no further treatment after curative resection of high-risk stage I or IIB malignant melanoma. No benefit was seen in disease-free survival or overall survival for patients receiving either Eurixor or Iscador.[124,125]

Ginseng (Panax Ginseng)

Ginseng has been touted as enhancing mental and physical strength. It may affect nitric oxide synthesis in the endothelial tissue of the lung, heart, and kidney.[126] In addition, effects on serotonin and dopamine may be responsible for its actions. Survey data indicate that breast cancer survivors seeking treatment for fatigue often turn to this drug for amelioration of fatigue.[127] A recent randomized, double-blind, placebo-controlled pilot trial was carried out by Kim and colleagues. Fifty-three patients were randomly assigned to receive sung ginseng 3000 mg a day or placebo. Quality of life was assessed using the World Health Organization Quality of Life Assessment and the General Health Questionnaire-12. The investigators concluded that ginseng did improve the quality of life scores of patients and that this intervention warranted further investigation.[128]

Adverse effects may include irritability, insomnia, and gastrointestinal disturbance. Ginseng may interact with oral anticoagulants, antiplatelet agents, corticosteroids, and hypoglycemic agents.[129]

Ginger

Several studies have demonstrated the efficacy of ginger for the treatment of nausea and vomiting. Most of the investigations involved pregnant women.[130–134] A randomized study of ginger for the amelioration of nausea caused by platinum-based chemotherapy showed that ginger is at least equivalent to the commonly used medication metoclopiramide and has less toxicity.[135]

Hoxsey Regimen and Essiac

The Hoxsey regimen, a herbal compound comprising pokeroot, burdock root, barberry root, buckthorn bark, and stillingia root, was used first in 1924 by Harry Hoxsey. The recipe was passed down to him by his grandfather, a farmer who observed a horse cure itself of cancer by eating certain plants. Despite decades during which no supporting data have been forthcoming, the Hoxsey formula remains popular and in use among patients with cancer.[80]

Essiac is one of the most popular herbal medicines in North America and is a mixture of four herbs given by a Native American healer to nurse Renee Caisse. ("Essiac" is Caisse spelled backward.) Despite a lack of systematic research or documentation of its value, Essiac is promoted and purchased for all forms of cancer.[135]

Diet and Nutrition

Macrobiotic Diet

Various dietary regimens have been promoted for both prevention and treatment of cancer. The macrobiotic diet was first described by George Ohsawa (1893–1966). He developed a diet consisting of 10 stages, with each stage more restrictive than the previous one. The final stage consisted of only rice and water. The American Medical Association and various governmental agencies have opposed the macrobiotic diet owing to its restrictive nature. In fact, a number of health problems and even deaths have been reported among persons who have followed the diet.[137]

The macrobiotic diet subsequently has been modified and is regaining popularity in the United States and generally consists of 50% to 60% whole grains, 20% to 25% vegetables, 5% to 10% beans and sea vegetables, and 5% soups. Some variations of the diet allow small amounts of fish. There may be alterations of the diet depending on the disease process.

The Kushi Institute in Massachusetts is a strong proponent of the macrobiotic diet. This institute teaches the macrobiotic diet and lifestyle. Specific foods for the individual cancer patient are recommended. Numerous testimonials supporting the effectiveness of the macrobiotic diet are provided, but no controlled studies have been performed to evaluate the Kushi Institute methods.

A number of nutritional deficiencies have been reported in association with the macrobiotic diet. Breast milk from mothers who follow the macrobiotic diet contains less vitamin B_{12}, calcium, magnesium, and saturated fatty acids than in the milk of mothers following "regular" diets.[138] Infants of mothers on the macrobiotic diet were found to have retarded growth, fat and muscle wasting, and slowed psychomotor development. Bone mineral content was evaluated in a study of adolescents who had followed a macrobiotic diet and compared with that in control patients without dietary restrictions.[139] The bone mineral content was found to be significantly lower in both boys and girls who had followed the macrobiotic diet. The study investigators suggest that this decreased bone density may hold important implications for fracture risk in later life. Machiels and associates reported a rare case of nutritional rickets in a young child due to the macrobiotic diet.[140]

Megadose Vitamin C: A Closer Look

The use of vitamin C for the treatment of cancer has been publicized for many years. Many continue to claim efficacy without strong scientific data to back these claims. Linus Pauling, PhD, and Ewan

Cameron, MD, claimed that high doses of vitamin C could significantly improve survival in cancer patients. The claim was based on the known antioxidant properties of vitamin C and some epidemiologic evidence that populations with high dietary intake of the vitamin have a decreased risk for development of some types of cancer. These scientists believed that much higher doses than the recommended daily intake of 60 mg/day of vitamin C were needed to prevent free radical damage within the body. Pauling and Cameron reported a study of 100 patients in the terminal stages of cancer treated with megadose vitamin C who had significantly improved survival when compared with historical controls.[141] It was recommended that patients with cancer take 10,000 mg of vitamin C daily on the basis of their research.

The study was plagued by significant design issues. The "terminal" patients in the vitamin C treatment group all came from Dr. Cameron's practice, whereas the historical controls were "terminal" patients who came from other sources in the geograhic region. It is conceivable that significant selection bias occurred between Dr. Cameron's patients given vitamin C and the patients of other physicians who were not offered any additional treatments.

Owing to the exceptional reputation of Nobel Laureate Dr. Pauling, investigators at the Mayo Clinic performed a prospective randomized study to evaluate vitamin C. Creagan and colleagues randomized 150 patients with advanced cancer to receive 10 g of vitamin C or a placebo.[142] No difference in symptoms, performance status, appetite or survival was found between the two groups. These investigators concluded that high-dose vitamin C had no therapeutic benefit.

Dr. Pauling criticized the design of the Mayo Clinic study, claiming the patients had poor performance status and too much prior treatment with chemotherapy. Based on his criticisms, a new trial was launched. Moertel and coworkers randomized 100 patients with advanced colorectal cancer in a double-blind study to receive high-dose vitamin C (10 g daily) or a placebo.[143] No patient received previous cytotoxic therapy, and all had good performance status. Again, vitamin C showed no advantage over placebo therapy with regard to disease progression, objective improvement in measurable disease, or survival. The researchers concluded that high-dose vitamin C therapy is not effective against malignant disease regardless of whether the patient has had any prior chemotherapy.

In a recent trial of oral supplementation with ascorbic acid (vitamin C, 6100 mg/d), DL-alpha-tocopherol (a form of vitamin E, 1050 mg/d), and beta-carotene (vitamin A precursor, 60 mg/d), patients who had stage IIIB or IV non-small-cell lung cancer were randomly assigned to chemotherapy with paclitaxel and carboplatin (72 patients) or to this chemotherapy regimen plus the supplements (64 patients). No significant survival differences were reported, with 1-year survival rates of 33% and 39% and 2-year survival rates of 11% and 16% in the chemotherapy and the combination treatment groups, respectively.[144]

The argument has been made that the inability to confirm Pauling's results may reflect the use of oral rather than intravenous vitamin C.[9,145] A 1.25-g dose of vitamin C given orally results in a mean plasma level of 135 µmol/L, whereas the same dose given intravenously results in a level of 885 µmol/L. The same study showed that the maximum tolerated oral dose of 3 g every 4 hours increased the plasma level to only 220 µmol/L, whereas the maximum tolerated intravenous dose of 50 g resulted in a plasma level of 13,000 µmol/L. The form of oral vitamin C also affects its bioavailability. A solution of vitamin C has an approximately 40% lower bioavailability than that of a slow-release formula.[146] Vitamin C intake also has been examined for the amelioration of toxicity associated with chemotherapy administration.

Weijl and colleagues[147] investigated the use of oral vitamin C, vitamin E, and selenium for the prevention of cisplatin-induced renal toxicity and ototoxicity. No significant overall effect was demonstrated, but a correlation with plasma levels of the vitamins and lower toxicity was observed. These investigators, however, concluded that poor compliance or inadequate supplementation may have confounded the results. Song and coworkers[148] investigated the use of an intravenous administration of 10 g vitamin C twice with a 3-day interval and an oral intake of 4 g vitamin C daily for a week. They then evaluated demographic data and assessed changes in patients' reported quality of life after the administration of vitamin C. Quality of life was assessed with the EORTC QLQ-C30 questionnaire. These researchers concluded that high-dose vitamin C therapy did indeed significantly improve quality of life scores.

Side effects of megadose vitamin C include diarrhea, formation of renal stones, iron overload, and gastrointestinal discomfort. Ardent supporters of megadose vitamin C remain, however, despite the strong scientific evidence refuting its use in the treatment of cancer. Based on the current scientific literature, megadose vitamin C is not recommended for the prevention or treatment of cancer.

COMPLEMENTARY AND ALTERNATIVE MEDICINE AND TOXICITIES

A multitude of potential interactions are possible between conventional cancer treatments and UMTs. Many such interactions are just beginning to be recognized by the medical establishment and reported in reputable scientific journals.[149,150] Both renal and hepatic function can be impaired by various UMTs.[151–156] Multiple biochemical pathways can be affected, including the lipoxygenase, cyclooxygenase, and cytochrome P-450 pathways.[112] Such effects may have an impact on drug concentrations in the body, resulting in increased toxicity or changes in effectiveness of chemotherapy and radiation therapy. Antioxidants may decrease the effectiveness of radiation therapy as a result of the scavenging of free radicals, which can damage DNA, leading to cell death.[157] Moreover, many of these therapies have their own side effects that can mimic those of conventional cancer treatments[158–177] (Tables 35-2 and 35-3). If the oncologist is not aware

Table 35-2 Potential Adverse Effects of Some Common Herbal and Other Alternative Medicines

Preparation/ Medication	Adverse Effect(s)
Ephedra species	Hypertension, tachycardia, stroke, seizures
St. John's wort	Depression, nausea, hypersensitivity reactions
Amygdalin (Laetrile)	Emesis, headache, dizziness, obtundation, dermatitis
Antineoplastons	Somnolence, confusion
Ginseng	Sedative, diarrhea, headache, hypertension, insomnia, nausea
Echinacea	Hypersensitivity reactions
Kelp	Hyperthyroidism
Saw palmetto	Urinary retention, headache, diarrhea, constipation, hypertension, nausea
Mistletoe	Local irritation, allergic reactions
Shark cartilage	Hepatitis, emesis, constipation
Ginkgo	Emesis, headache
Green tea	Insomnia, emesis, diarrhea, confusion
Hydrazine sulfate	Hepatorenal failure
Goldenseal (*Hydrastis canadensis*)	Uterine contractions

Data from references 163 to 179.

Table 35-3 Potential Interactions between Herbal Medicines and Conventional Drugs

Herb(s)	Drug(s)	Potential Interaction/Effect(s)
St. John's wort	Irinotecan, protease inhibitors, other drugs metabolized by cytochrome P-450	Reduced drug levels
	Cyclosporine	
	Oral contraceptives	
	Digoxin	
Hawthorn flower, devil's claw, licorice	Digoxin	Alters pharmacodynamics; drug levelmonitoring is prudent
Licorice	Potassium-sparing diuretics	Affects potassium levels
Kelp	Thyroxine	Iodine content of herb may interfere with thyroid replacement
Kava	Alprazolam	Additive sedative effects, coma
	Terazosin	
Evening primrose oil	Anticonvulsants	Lowered seizure threshold
Feverfew, garlic, ginseng, gingko, ginger, dong quai	Warfarin	Altered bleeding time
Yohimbe bark	Centrally active antihypertensive agents	Yohimbine may antagonize guanabenz and methyldopa through its α_2-adrenoceptor–antagonistic properties
Ginseng	Phenelzine sulfate	Headache, tremulousness, manic episodes
	Estrogens, corticosteroids	Additive effects

Data from references 163 to 176.

that a patient is using a particular UMT, signs or symptoms developing as a result of that UMT may be erroneously attributed to a conventional cancer treatment with established efficacy, which may then may be unnecessarily altered or discontinued.

Many forms of CAM are associated with no or minimal risk to a cancer patient; however, this is not true for all such therapies. It is well established that a variety of herbal medications may produce serious side effects. Quality control of these preparations can be a major concern. Issues include variability in biologic potency in different crops, the very realistic possibility of contamination (e.g., by fungal or bacterial organisms), and use of wrong plant species.[158] Herbal remedies may contain lead, arsenic, mercury, tin, or zinc, each of which can itself be toxic.[159]

Immunoaugmentative therapy (IAT) of Burton is based on balancing four protein components in the blood while strengthening the patient's immune system. The use of various organ extracts from cows and pigs is claimed to selectively suppress tumors and stimulate the immune defense cells.[160,161] No studies have shown clinical effectiveness of immunoaugmentative therapy; however, samples of infected material from patients who received IAT revealed evidence of hepatitis virus.[161]

New toxic effects of a variety of herbal preparations continue to be reported. Kava, for example, a widely publicized natural sleep medication, has been associated with severe liver dysfunction, leading to at least one case of hepatic failure and the requirement for a liver transplant.[167] Other herbal medications also have been shown to be associated with hepatotoxicity.[168]

Laetrile (amygdalin), derived from apricot and other fruit pits, one of the oldest CAM medications, continues to be marketed to the public.[178] Amygdalin had been used for centuries, but, in the 1950s it was elevated to new heights under the trade name Laetrile. Proponents of Laetrile claim that proper use of this substance can eradicate cancer entirely (www.worldwithoutcancer.com and www.sumeria.net/health/laetrile.html). Moertel and colleagues carried out a phase II clinical trial of Laetrile, along with vitamins A, C, E, and B complex and various minerals and pancreatic enzymes, in 178 patients with cancer not previously subjected to conventional cancer treatment and with good performance status. Only one patient, who had gastric carcinoma with cervical lymph node metastases, had a possible short-lived partial 10-week response. All others showed no signs of response. No evidence of disease stabilization was noted. Evaluation of toxicity revealed blood cyanide levels in the ranges known to kill animals and humans in several patients.[171] Studies have demonstrated that this drug can produce signs and symptoms of nausea, vomiting, headache, dizziness, and obtundation.[170,171]

To date, one of the gravest examples of the potential for harm associated with herbal medications is that of the development of renal failure and urothelial carcinoma in persons who used the Chinese herb *Aristolochia fangchi*.[179,180] As a result of a manufacturing error, this herb replaced another preparation (*Stephania tetrandra*) used in a weight-reducing pill. More than 40 people who took this pill experienced progressive renal failure, and almost 50% subsequently were found to have a urothelial cancer.[179]

Vitamin toxicities are uncommon but well defined. Megadoses of vitamin A can cause increased intracranial pressure and vomiting in children, and its chronic use in adults can lead to hypercalcemia.[181] Vitamin B complex overdose can lead to cardiovascular toxicity including arrhythmias, edema, vasodilation, and allergic reactions. Megadoses of niacin can cause cardiac toxicity with arrhythmia, as well as liver toxicity and peptic ulceration. Long-term high-dose toxicities include gouty arthritis, hyperglycemia, dry skin, and rashes. Vitamin B_6 in megadoses can cause peripheral neuropathies, with resulting numbness lasting for weeks. Vitamin C toxicities include the formation of renal stones.[182] High-dose vitamin E therapy can interfere with blood coagulation by antagonizing vitamin K and inhibiting prothrombin production. A recent study of vitamin E demonstrated an increased number of strokes in the vitamin E treatment group as compared with the control group.[183]

Both acupuncture and chiropractic medicine generally are quite safe; however, they too can be associated with irritating and more serious side effects.[184,185] Reported toxic effects of acupuncture include transmission of infectious agents through needle insertion; broken, forgotten, or misapplied needles; pneumothorax; transient hypotension; minor bleeding; contact dermatitis; and pain.[184] A small but finite risk of a cerebrovascular accident is always associated with cervical spinal manipulations.[185]

THE INTERNET AND COMPLEMENTARY AND ALTERNATIVE MEDICINE

The Internet has become a hotbed of CAM offerings and information over the past decade. However, patients must be advised to be extremely careful about where the information is being derived and what is being marketed over the Internet. Since the public introduction of the Internet in 1994, this computer resource has experienced exponential growth. In August 2002 it was estimated 64% of the U.S. population (177.6 million people) had access to the Internet.[186] This was increased from 56.5% of the population in October 2000.

Studies have been performed to specifically evaluate the use of the Internet by patients with cancer to obtain information about CAM. In a study of 921 patients presenting to radiation oncology centers in the United States, it was found 42% of those presenting to an academic medical center and 25% of those presenting to a community medical center were using the Internet to find cancer-specific information.[156] A questionnaire study from England showed that 24% of prostate cancer patients were using the Internet to obtain further health information.[187] A Canadian questionnaire study of patients with prostate cancer revealed that 35% of patients had used the Internet to obtain cancer-related information.[188] Another recent Canadian questionnaire study evaluated 191 cancer patients on the reliance on the news media and the Internet as sources of medical information.[189] This study showed that 50% used the Internet to obtain information and 7% used the Internet as their primary source of information. A study reporting on use of the Internet by 295 patients with prostate cancer in the United States showed that 32% were using the Internet to gather information.[190] Of interest, 58% of these patients used the Internet to search for information on CAM.

Many more patients probably are obtaining Internet-derived information from other people. As indicated by questionnaires placed on OncoLink (http://www.oncolink.upenn.edu), the cancer information resource from the University of Pennsylvania, many patients' friends and family members are using the Internet to obtain cancer-related information. Vordermark and colleagues used a questionnaire study to identify where patients were obtaining information.[191] Of 139 German radiation oncology patients, 12% had used the Internet to obtain information about their cancer, but an additional 15% received Internet-derived information about their cancer from friends or family members. Of note, only 24% discussed the information obtained from the Internet with their physicians.

Yakren and coworkers used a patient survey to analyze the use of media information, including that from the Internet, among cancer patients and their companions at Memorial Sloan-Kettering Cancer Center.[192] As indicated by the responses of the 443 patients who returned the completed surveys, 44% of the patients and 60% of the companions reported use of the Internet to obtain cancer-related information. This is very similar to the utilization rate of 41% for patients at the University of Pennsylvania Cancer Center.[11]

The identification of good Internet sites can be difficult for the nonmedical person searching for information on complementary and alternative medicine. The general public requested 30% of all PubMed searches performed in 1999. A study by Bernstam and associates evaluated the ability of a computer-literate lay user to perform multiple searches for various question types related to cancer on MEDLINE.[193] A blinded investigator then rated each search's relevancy. The computer user was then given a custom interface to help with the searches through MEDLINE. Overall, significantly higher precision was observed with use of the MEDLINE interface than with unaided novice searching. This finding emphasizes the need for the medical community to help guide patients' search for medically relevant information on the Internet. Although this study does not specifically evaluate Web searches, these results may be generalizable to patients looking for information on the Internet regarding CAM.

It can be a daunting task for the nonmedical person to objectively evaluate the quality of Internet sites, particularly those offering CAM. A recent study by RAND Health reported on the quality of health information on the Internet.[194] A variety of health Web sites were evaluated, including 20 major Web sites for breast cancer information. It was found that on average, two to four websites needed to be visited to find more than minimal coverage for at least 75% of the indicators for a topic. Although experts may be able to quickly evaluate the quality and appropriate coverage of a topic, as in the RAND study, this can be very difficult for the patient. Meric and colleagues found that popularity and traffic of breast cancer Websites do not always correlate with quality.[195] This finding again emphasizes the need for professionals to help guide the lay public to appropriate medical material on the Internet.

Most health care providers have experienced a visit from a patient entering the office with pages of CAM information printed from the Internet. Only a limited number of studies, however, have documented the use of the Internet to find information on CAM. A study from the University of Pennsylvania showed that 53% of cancer patients using the Internet were interested in finding information about CAM.[196] Most of these patients were doing so without their health care providers' knowledge. CAM therapies were purchased over the Internet by 12% of Internet users in this study. However, this study did not specifically evaluate the type of therapy purchased. Health care providers need to familiarize themselves with the therapies offered over the Internet in order to have an informed discussion with their patients regarding these treatments. Particular discussions should emphasize the potential side effects and interactions with conventional cancer treatments.[11] A typical search on Yahoo, one of the Internet search engines (http://www.yahoo.com), for "alternative and complementary medicine" reveals greater than 6.14 million different Web site matches. This is increased from 432,000 in 2004. Some of these Web sites provide credible information. Unfortunately, many are designed only to sell a specific product and give false or misleading information. It can be overwhelming for the average person without medical knowledge to sift through and understand the claims presented on many of these sites.

Some patients will ask their health care providers for recommendations on evaluating Web sites offering CAM information. It generally is recommended to start with sites managed by major academic centers and the government. These institutions maintain a level of quality outside of the Internet that typically is upheld on these Web sites in keeping with the general philosophies of these organizations. Patients also should be warned to be wary of sites designed to sell a specific product or treatment. Many of these sites do not give unbiased information and are designed strictly to generate revenue. Box 35-4 provides some suggestions to guide patients in evaluating Internet sites. Table 35-4 recommends selected Web sites with reliable information on CAM for the cancer patient and health care provider.

ALTERNATIVE MEDICINE CANCER CLINICS

Numerous cancer clinics promoting alternative medicine techniques have formed throughout the world. Many centers are transient, but

Box 35-4. EVALUATING MEDICAL WEBSITES

- **Accuracy of information:** Websites that post information that is not referenced, or articles that do not state authors and dates for content, should be avoided.
- **Availability of editorial staff:** An online resource should list the names of its editorial staff, the credentials of the people behind the resource. An address and email contact information also should be provided.
- **Qualifications of editorial staff:** Many online resources are run by people who are not qualified to provide medical advice. Fundamentally, there is nothing wrong with this, provided that it is clearly stated. In general, however, the best information is provided by health care professionals who are health care providers themselves. Much of what physicians, nurses, and other professionals are trained to do involves interacting with patients and providing information in the clearest, most appropriate manner.
- **Freshness of content:** Sites with content that is updated regularly are likely to be ones that are best managed and most up to date.
- **Disclosure of conflicts of interest:** Conflicts of interest should either be obvious or clearly disclosed to the users.
- **Price of information:** So far, very few online medical resources are charging for information. Although this may change in the future, open access to information with fees that are minimal should be the rule. If you are being charged for the information, make sure it is not information others are providing for free.
- **Confidentiality:** Most online medical resources will not respond to direct medical inquiries by users. This is due in part to concerns about patient confidentiality, and about accuracy of information either sent to or received by the patient. It is important to ensure that sites that require registration are not releasing contact data without permission.
- **Reputation:** Resources known to be run by reputable institutions are more likely to be providing more timely, accurate, and unbiased information.
- **Look and "feel":** Resources must balance between having an attractive resource and being able to provide the best possible information to users. Certainly, content rich in graphics is attractive, but if it is poorly organized, or if downloading it takes an inordinate amount of time, it may not be serving its primary purpose.
- **Navigation and searching:** Make sure a site is well organized and easy to navigate and has a good search engine.

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some have been established for quite some time and have a large following and have marketed their facilities to the general public. A complete enumeration is beyond the scope of this chapter, but none of the treatments offered by these facilities are known to have shown verifiable beneficial results when compared with conventional medical treatments. Nevertheless, case reports and testimonials abound. It is important that health care providers recognize that these treatments are being promoted to their patients through the Internet and print publications, and by word of mouth.

For example, Tijuana, Mexico, has long been a destination for patients seeking alternative medical therapies. The government has acted to close down a number of these centers at various times, but many continue to thrive. At any one time, some 50 to 70 alternative medicine clinics are in operation. It has been estimated that roughly 40,000 people travel to Tijuana in search of alternative treatments each year. Of these patients, 95% are from the United States. Many of these clinics operate in a hospital-type atmosphere, and patients stay for a number of days or weeks for their therapy. A few such clinics are strictly outpatient or day treatment centers.

The therapies offered in these centers range from simple dietary management to complex operative treatments. Some of these treatments are innocuous, whereas others may be quite dangerous. For instance, some patients are offered insulin-induced hypoglycemia therapy (IHT). Patients are given insulin to drop the blood glucose level to less than 40 mg/dL and then are infused with a glucose solution incorporating a diluted chemotherapy preparation. The rationale for this treatment is that "starving" cancer cells need more glucose and thus more readily take up the chemotherapy drugs, so no side effects develop.

Claims of benefit by these alternative medicine centers have not been substantiated by the outside medical establishment. As confirmed by our own observations in such centers, however, some patients with hormone-responsive tumors such as breast cancer and prostate cancer are receiving hormonal therapies. Also, as mentioned earlier, chemotherapy sometimes is offered along with the alternative treatments. This may account for some for the claims of response to these treatments.

These treatments generally constitute out-of-pocket medical expenditures, because these are not covered by medical insurance programs. Table 35-5 shows the estimated cost at some of the more popular centers offering alternative cancer treatments. Some of the prices do not include room and board. Many have added charges that may not become specified until the patient is seen and evaluated at the clinic. All require cash payment before treatment. Travel expenses are not included in the estimates.

Table 35-4 Selected Web Sites with Reliable Information on Complementary and Alternative Medicine

Organization	Web Address
American Botanical Council	http://www.herbalgram.org
American Cancer Society	http://www.cancer.org
M.D. Anderson Cancer Center	http://www.mdanderson.org/departments/cimer
Memorial Sloan-Kettering Cancer Center	http://www.mskcc.org/mskcc/html/11571.cfm
National Cancer Institute	http://www.cancer.gov/cancertopics/pdq/cam/cam-cancer-treatment/Patient
National Center for Complementary and Alternative Medicine	http://nccam.nih.gov
Office of Complementary and Alternative Medicine	http://www.cancer.gov/cam
OncoLink (University of Pennsylvania Cancer Center)	http://www.oncolink.org
Quackwatch	http://www.quackwatch.com

Table 35-5 Popular Unconventional Cancer Therapy Clinics

Clinic	Location	Type of Treatment	Duration of Therapy	Estimated Cost
Kushi Institute	Brookline, Massachusetts	Macrobiotic diet	1 week	$1,500*
Burzynski Clinic	Houston, Texas	Antineoplastins	6 months	$50,000†
Immuno-Augmentive Centre	Bahamas	Immuno-Augmentive	3 months	$13,100‡
Hosp de Baja California del Sol	Tijuana	Gerson Method	1 month	$20,000§
Bio Medical Center	Tijuana	Hoxsey Herbal	Variable	$3,800‖
Center for Cell Specific Therapy	Santo Domingo	Magnet Therapy	Variable	$20,000¶

*Based on published advertising on the Internet of $1,495 for 1 week. Private counseling sessions are an additional $225 each.

†Based on telephone quotation of intravenous therapy of $14,000 for the first month and $7,200 for each additional month, which averages 6 months in duration. Cost of the oral formula is $6,000 for the first month and $2,000 for each additional month.

‡Published advertising fee schedule from the Immuno-Augmentive Centre of $7,500 for the first 4 weeks and $700 per week thereafter, up to 8 additional weeks. Cost of supplies for home maintenance is $50 per week indefinitely.

§Based on published advertising on the Internet of $3,990 per week for basic charges, with a recommended stay of 1 month; ". . . actual costs for any individual will become evident only during the course of treatment."

‖Based on telephone quotation of $3,500 lifetime supply of Hoxsey Tonic, $300 to $400 for blood work, and $25 consultation fee.

¶Based on brochure from the Center for Cell Specific Therapy. All patients are charged $20,000 regardless of the length of treatment.

CONCLUSIONS

Many patients with cancer, as well as their friends and and family members, are searching for information regarding CAM. Health care providers must become educated on this topic so that they can appropriately guide these patients. CAM is here to stay, and patients need to be supported in their decision to use complementary therapies that are safe. Health care providers must warn patients of potential or known interactions with conventional medications and treatments when appropriate. Clinical trials evaluating CAM should be developed and encouraged. CAM needs to be held to the same stringent criteria as those in place for conventional treatment modalities.

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A. SYMPTOM MANAGEMENT AND PALLIATIVE CARE

36 Cancer Pain

Stuart A. Grossman and Suzanne Nesbit

SUMMARY OF KEY POINTS

Incidence

Major Presenting Symptom of Malignancies

- Affects more than 30% of patients undergoing antineoplastic therapy
- Moderate to severe pain occurs in over 70% of patients during the later phases of their illness
- Significantly affects quality of life
- Frequently managed poorly

Etiology of Complication

- Can be of nociceptive, neuropathic, or sympathetically maintained origin
- Due to direct tumor involvement (70%), evaluation or therapy (20%), or illness unrelated to the malignancy (<10%)

Evaluation of the Patient

- Determining the etiology of pain is key to appropriate therapy
- Treat pain aggressively during evaluation
- Fully evaluate the pain using a careful history and physical examination, validated pain assessment scales, and selected laboratory tests

Grading of the Complication

- Measurements of pain intensity using validated pain assessment scales
- Results should be recorded serially as an integral part of the medical record

Treatment

- 85% of patients can be well palliated using simple, inexpensive, "low-technology," oral analgesics
- Addition of appropriate adjuvant pain medications, alternate routes of opioid administration, antineoplastic therapy, nonpharmacologic approaches, neurostimulatory techniques, regional analgesia, and neuroablative procedures provides excellent palliation for nearly all patients with cancer pain

INCIDENCE

Facts

Pain is one of the most common and dreaded symptoms associated with cancer. It occurs in one-quarter to one-half of patients with newly diagnosed malignancies, in one-third of those undergoing treatment, and in more than three-quarters with advanced disease. Overall, 75% of patients with cancer experience pain severe enough to require treatment with opioids during their illness.[1] Unrelieved pain directly affects patients' daily activities, quality of life, and psychologic status. The importance of this symptom and the availability of excellent analgesic therapies make it imperative that health care providers be adept at the evaluation and treatment of cancer pain (Table 36-1).

Etiology

Pain in patients with malignancies is a complex and often recurring process that occurs from many causes. Ninety percent of pain in patients with cancer results from the tumor or its evaluation or therapy, whereas less than 10% is due to unrelated illnesses. In 70% of patients, pain develops from tumor invading or compressing soft tissue, bone, or neural structures. The common pain syndromes that result are listed in Table 36-2. The remaining 20% of cancer pain occurs from diagnostic and therapeutic procedures that these patients undergo in the process of evaluation and treatment.[2] Examples of these procedures include venipuncture, bone marrow aspiration and biopsy, endoscopy, lumbar puncture, invasive radiologic procedures, surgery, chemotherapy, and radiation therapy.

Surgery is a frequent cause of pain in patients with cancer and can consist of biopsy, removal, or debulking of a tumor or management of a complication of the tumor or its treatment, such as a small-bowel obstruction. These procedures are associated with postoperative pain and injury to local nerves, which can produce neuromas and chronic pain syndromes that are severe and difficult to manage. Surgically induced nerve injuries are most commonly seen after breast cancer surgery, thoracotomy, radical neck dissection, and limb amputation.[3] Postmastectomy syndrome occurs in 4% to 10% of all women undergoing this type of breast cancer surgery. It is most frequent in patients with postoperative complications or keloid formation and is characterized by a constricting, burning sensation in the posterior arm, axilla, and anterior chest. It can develop immediately after the procedure or months later and can be complicated by the secondary development of a frozen shoulder. Post-thoracotomy syndrome occurs after nerve injury secondary to rib retraction and typically presents as an aching, burning sensation in the incisional area with local tenderness, sensory loss, and occasional autonomic changes. Injury to local nerves after a radical neck dissection can produce tightness and burning dysthesias in the area of sensory loss and acute, lancinating pain. The loss of neck musculature from this surgery can also result in a "droopy shoulder," thoracic outlet syndrome, and suprascapular nerve entrapment.

Chemotherapy and radiation also produce significant pain in patients with cancer. Phlebitis, mucositis, hemorrhagic cystitis, and peripheral neuropathy are common complications of antineoplastic agents. Glucocorticoids, administered as a component of therapy, can cause aseptic necrosis of the hip, and severe perineal pain when given rapidly in high doses. Examples of radiation-induced pain include mucositis, local skin reactions, enteritis, proctitis, fibrosis with nerve

Table 36-1 Landmark Literature on Cancer Pain

Foley KM: N Engl J Med 1985;313:84–95. A consideration of changing attitudes toward the use of narcotic analgesics and novel methods of managing cancer pain.

WHO: Cancer Pain Relief, 1986. A guide to pain relief that also served to set cancer pain in context.

Twycross RG: Oncology 1988;2:35–43. An early review of the literature in cancer pain management offered a guide to drugs and dosages.

Cleeland CS, et al: N Engl J Med 1994;330:595–596. A study of 1308 cancer outpatients concluded that despite published guidelines for pain relief, many patients receive inadequate analgesia.

Grossman SA, Staats PS: Oncology 1994;8:93–107. A detailed look at state-of-the-art management of cancer pain.

Levy MH: N Engl J Med 1996;335:1124–1132. An in-depth review of the pharmacologic treatment of cancer pain.

Koshy RC, et al: Support Care Cancer 1998;6:430–437. A discussion of the complex issues involved in cancer pain management in developing countries.

NCCN: Guidelines for Adult Cancer Pain. Available at <http://www.nccn.org> First published in 1998, an expert consensus panel offers guidelines on currently accepted approaches to treatment.

Miaskowski C, et al: APS Clinical Practice Guidelines Series, No. 3, 2005. An updated guideline for the management of cancer pain in adults and children.

Smith TJ, et al: J Clin Oncol 2002;20:4040–4049. In this study, an implantable intrathecal drug delivery system improved pain control and survival in patients with refractory cancer pain.

From Grossman SA, Dunbar EM, Nesbit SA: Cancer pain management in the 21st century. Oncology 2006;20:1333–1340.

Table 36-2 Etiology of Pain in Cancer Patients

A. Direct tumor involvement (70%)
   1. Invasion of bone
   2. Invasion or compression of neural structures
   3. Obstruction of hollow viscus or ductal system of solid viscus
   4. Vascular obstruction or invasion
   5. Mucous membrane ulceration or involvement

B. Cancer-induced syndromes (<10%)
   1. Paraneoplastic syndromes
   2. Pain associated with debility (i.e., bedsores, constipation, rectal or bladder spasm)
   3. Other (i.e., postherpetic neuralgia)

C. Diagnostic or therapeutic procedures (20%)
   1. Procedure-related pain (i.e., bone marrow aspiration or biopsy, lumbar puncture)
   2. Acute postoperative pain or postsurgical syndromes (i.e., postmastectomy, postthoracotomy, postamputation syndromes)
   3. After radiation (i.e., injury to plexus or spinal cord, mucositis, enteritis)
   4. After chemotherapy (i.e., mucositis, peripheral neuropathy, aseptic necrosis)

D. Pain unrelated to the malignancy or its treatment (<10%)

From Grossman SA, Baumohl L: Evaluation and management of cancer pain. In Bone RC (ed): Current Practice of Medicine. Philadelphia, Current Practice, 1993, p 18.1.

entrapment syndromes, and radiation myelopathy. Electric shock-like sensations that accompany flexion of the neck (Lhermittes syndrome) can last for months after radiation to the spinal cord. Painful peripheral nerve tumors can also follow radiation therapy, especially in patients with neurofibromatosis.

Patients with malignancies are also predisposed to painful infections. Common examples include pneumonia, urinary tract infection, wound infections, candida esophagitis, oral or genital herpes, and herpes zoster.

Current Status of Cancer Pain Management

Studies from hospices and from World Health Organization demonstration sites suggest that 85% of patients with cancer pain can be well palliated using oral opioids. A wide array of effective options exist for the remaining 15% of patients. These include parenteral, transdermal, transmucosal, or intraspinal opioids, glucocorticoids, anti-inflammatory and adjuvant medications, antineoplastic therapies, and anesthetic and neurosurgical procedures.

Although proper use of available therapeutic approaches should result in excellent pain control in nearly 95% of patients with cancer pain, cancer pain remains grossly undertreated throughout the world.[4] In most countries, the unavailability of oral opioids is a major contributing factor.[5,6]

Even in countries such as the United States and the United Kingdom, where a wide range of opioid analgesics and routes of administration are available, studies suggest that cancer pain is undertreated. A survey of oncologists highlights their reluctance to assess pain routinely and prescribe appropriate analgesics. These findings prompted the creation of cancer pain initiatives in most states and the development of cancer pain guidelines and algorithms by the American Society of Clinical Oncology, the American Pain Society, and the U.S. Public Health Service's Agency for Health Care Policy and Research.[7–11] In addition, to improve the overall management of pain in the United States, the Joint Commission on Accreditation of Healthcare Organizations has recently set new standards for pain management that are required for continued accreditation.[12]

Barriers to the Provision of Adequate Analgesia

Many reasons have been cited for the inadequate treatment of patients with cancer pain in developed nations. Some of them relate directly to health care providers, including

- Failure to appreciate the intensity of the pain their patients are experiencing
- Reluctance to evaluate the etiology of the pain
- Lack of training in pain management
- Excessive concern regarding the regulatory oversight of opioid prescribing

One major barrier to the provision of adequate analgesia in patients with cancer is the failure of health care providers to appreciate the intensity of patients' pain. This occurs because pain is entirely subjective and can only be experienced and quantified by the patient. There are no pathognomonic findings on physical examination, and laboratory studies can be normal. Assessment of pain is further complicated by the complexities surrounding death and dying and the possibility that patients with chronic, severe pain might not appear or act uncomfortable. In one study examining health care provider perceptions of patient pain, pain intensity was quantitatively assessed using a visual analog scale in 103 consecutive patients admitted to the solid-tumor service of a large cancer center.[13] Each patient's primary care nurse, house officer, and oncology fellow rated his or her perceptions of their patient's pain intensity using the same pain rating instrument as the patient. The results (Fig. 36-1) demonstrate a lack of correlation between the patient's and the health care provider's perception of patient pain. Furthermore, the concordance between patient and health care provider pain intensity scores was

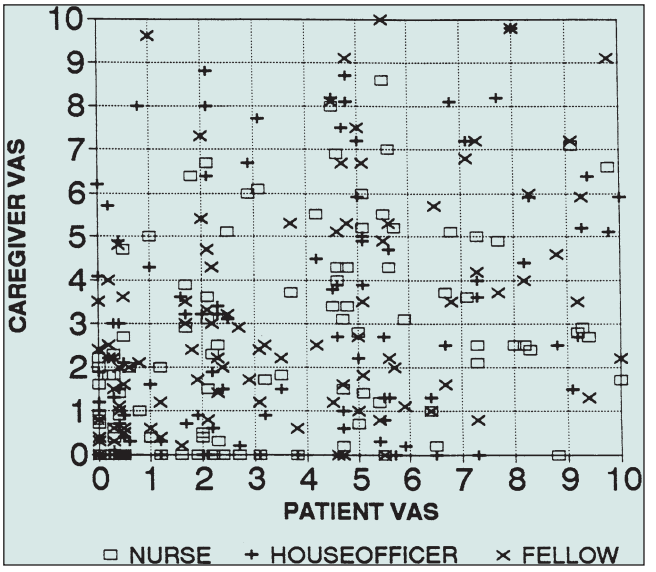


Figure 36-1 • Correlation of health care provider and patient perceptions of patient pain. (Data from Grossman SA, Sheidler VR, Swedeen K, et al: Correlation of patient and caregiver ratings of cancer pain. J Pain Symptom Manage 1991;6:53. Copyright U.S. Cancer Pain Relief Committee.)

highest when patients had no pain and lowest when the patients were experiencing severe discomfort. Similar results have been obtained in studies of patients with cancer and their next of kin and in burn patients.

There are many reasons why health care providers might be unaware of the pain their patients are experiencing. Because pain is entirely subjective, its presence and intensity must be communicated to health care providers by patients. Patients, however, might not discuss their pain if they expect cancer to be painful or if they are concerned about opioid addiction, tolerance, or side effects or about diverting their physician's attention from treating the tumor. In addition, they might be reluctant to admit to themselves or others that their pain has worsened, knowing that this could signify progression of the cancer. Health care providers also contribute to the lack of communication by neglecting to emphasize their interest or abilities in controlling pain and by failing to use validated pain assessment tools. Serial numeric pain ratings in the medical record will foster the necessary dialogue between patients and health care providers about pain management issues.

These issues are greatly magnified in children, the elderly, or individuals with a history of drug abuse. Children have special difficulty in communicating pain intensity, and their unique pain management needs have been relatively neglected. Special pain assessment tools are required, and the child's age and developmental level must be considered when planning assessment or interventions. Many elderly patients also find it difficult to communicate their discomfort to health care professionals, have multisystem disease, and are especially sensitive to the adverse effects of analgesics.[14] Those with cancer and a current or prior history of drug abuse often have difficulty finding health care providers who believe their reports of pain and who will provide the high doses of analgesics required in these opioid-tolerant individuals.[15]

Another barrier to the provision of adequate analgesia relates to the training of medical professionals. The principles of cancer pain management receive little attention in academic centers and relevant scientific societies. Medical school courses and textbooks typically focus on diseases rather than symptoms, and pain management issues are infrequently highlighted at rounds, educational conferences, or in the formal curriculum of those training to care for patients with cancer. These circumstances leave many health care professionals eager to concentrate on medical problems they feel competent to handle. In addition, the scarcity of research abstracts on cancer pain at the scientific meetings of physician oncologic societies reinforces the notion that pain control is a topic of limited importance.

The lack of training and emphasis on cancer pain management manifests in many ways, including physicians' lack of opioid-prescribing skills, failure to evaluate the etiology of cancer pain, and excessive concerns regarding the regulatory oversight of opioid prescribing. In one study, 81 physician trainees, given a hypothetical patient case that included performing opioid conversions, 75% calculated a dose that was only one-third the correct dose, and only 5% calculated the dose correctly.[16] Another study of experienced oncology nurses indicated that they lack the capacity to recognize physician orders that could result in serious over- or underdosing of opioids. These difficulties in calculating equi-analgesic doses have prompted the development of software to facilitate opioid conversions.[17]

Many physicians and nurses consider "cancer pain" a diagnostic entity that requires opioids, without a formal evaluation of the etiology of the pain. Although this approach can provide relief, it is often ineffective and can lead to indefensible medical practices. For example, progressive back pain in a patient with metastatic lung cancer can occur from a postobstructive pneumonia or tumor invasion of the esophagus, liver, spleen, pleura, pericardium, rib, vertebrae, intercostal nerves, brachial plexus, leptomeninges, or epidural space. Each of these diagnostic possibilities can be associated with a different therapeutic approach or sense of urgency. To provide opioids without evaluation would be an error in such a patient with an impending epidural cord compression. Furthermore, many common cancer pain syndromes might be better treated with therapies tailored to a patient's individual pain problem. These may include local radiation, nerve blocks, glucocorticoids, anticonvulsants, or surgery to maximize analgesia, minimize side effects, and improve quality of life.

Physicians, pharmacists, and nurses caring for patients with cancer must be willing to prescribe, dispense, and administer the opioids in doses required to alleviate their pain. Drug enforcement agencies often discourage opioid prescribing, however, in an attempt to reduce the illegal diversion of these drugs. Unfortunately, many health care professionals with limited knowledge and experience in the treatment of cancer pain react to the perceived threat of investigation by law enforcement agencies with dramatic decreases in opioid prescribing.[18] This perception further contributes to the undertreatment of patients with cancer pain.

EVALUATION OF THE PATIENT WITH PAIN

A comprehensive assessment of cancer pain is the first important step toward optimal pain relief.[2] This evaluation should provide the clinician with sufficient information to carry out the following tasks:

- Estimate the severity of pain.
- Form a clinical impression regarding the etiology of the pain.
- Determine the need for further diagnostic studies.
- Formulate therapeutic recommendations that take into account the patient's overall medical and psychosocial status (Table 36-3).

As with any serious medical condition, the assessment of cancer pain requires a detailed history, physical examination, and review of available records, laboratory data, and imaging studies. The special challenges associated with the assessment of cancer pain include the entirely subjective nature of pain, the complex multisystem involvement in patients with advanced malignancies, and the ever-changing clinical situation in this patient population.

A detailed pain history is the cornerstone of the assessment. This can be complex, because 75% of patients with advanced cancer have several concurrent painful sites, and nearly one-third have four or more separate pain problems.[19,20] Each distinct pain must be

Table 36-3 Components of a Comprehensive Assessment of Cancer Pain

I. Detailed history of current pain problem
  A. Catalogue of pain (number and locations)
  B. Information for each pain
    1. Intensity (0–10)
    2. Locations and radiation
    3. Onset and changes over time
    4. Temporal pattern (constant, intermittent, etc.) and quality (burning, etc.)
    5. Exacerbating and relieving factors
    6. Associated neurologic or vasomotor abnormalities
    7. Other associated factors
    8. How the pain interferes with the patient's life
    9. Current therapeutic modalities (schedule, efficacy, side effects)
    10. Prior therapeutic modalities (schedule, efficacy, side effects)
II. Oncologic history
  A. Histologic
  B. Presentation: date, stage, sites of involvement
  C. Antineoplastic therapies: dates, types, doses, toxicities, and response to each therapy
  D. Current sites of disease: stable, responding, or progressive
  E. Patient expectations and goals
III. Medical history—may be affected by pain therapies
  A. Coexisting diseases
  B. Medications and allergies
  C. Substance abuse history
  D. Other constitutional symptoms (i.e., anorexia, fatigue, sedation and other changes in mental status, nausea, vomiting, dysphagia, dyspnea, constipation, urinary and sexual function, depression, dry mouth, ability to take medications by mouth, presence of a central venous catheter)
IV. Personal and social history
  A. Background: age, educational, employment, marital, residential, religious, cultural, ethnic
  B. Current status: functional status, caregivers and their health and availability, support system
V. Physical examination
VI. Review of additional information
  A. Medical records, radiologic/laboratory studies
  B. Family members and physicians and/or nurses who know the patient and his or her illness
VII. Differential diagnosis
VIII. Recommendations regarding workup and therapy
IX. Reassessment

From Grossman SA: Cancer pain assessment: a continual challenge. Support Care Cancer 1994;2:105.

identified and characterized. Pertinent information should include its intensity, location, radiation, how and when it began, how it has changed over time, and what makes it better or worse. The quality of each pain, its temporal pattern, whether it is associated with neurologic or vasomotor abnormalities, how it interferes with the patient's life, and an account of the successes and failures of current and prior therapeutic modalities also provide valuable insight.

Many instruments have been developed to aid in pain assessment.[21] These attempt to characterize and quantify the quality and/or intensity of a patient's pain and represent the best available means to document the discomfort and to follow the results of therapy serially. Each instrument has its shortcomings, but several have been validated in patients with cancer pain and incorporated into clinical practice. Most contain a variant of the unidimensional visual analog scale and a schematic representation of the body for the patient to indicate where their pain is located. The McGill Pain Questionnaire is comprehensive, but too awkward and time-consuming for most oncology patients in a clinical setting.[22–24] The Wisconsin Brief Pain Inventory, which can be completed in 15 minutes, provides information on the characteristics, severity, and location of the pain, its interference with normal life functions, and the efficacy of prior therapy. The Memorial Pain Assessment Card can be completed in less than a minute and features scales for the measurement of pain intensity and pain relief.[25] It is also designed to provide insight into global suffering or psychologic distress. The Hopkins Pain Rating Instrument is a validated plastic version of the visual analog scale that obviates the need for the paper, pencil, ruler, and measurements associated with the standard visual analog scale.[26] This simplifies repeated pain intensity measurements, making it easier to reassess the efficacy of therapeutic endeavors on a continuing basis.[27]

A complete oncologic history is also essential, because 90% of cancer pain is related to the malignancy or cancer treatment. The histology, presentation, stage, sites of involvement, and natural history and the history of surgery, radiation, chemotherapy, and hormonal treatments will help shape a therapeutic approach. In addition, it is important to note whether the malignancy is responding to therapy, stable, or progressing. A general medical history is also helpful, because pain treatments can affect coexisting medical problems, exacerbate constitutional symptoms, interact with other medications, or be contraindicated because of allergies. For example, a patient with painful bone metastases and severe peptic ulcer disease would not be an ideal candidate for potent anti-inflammatory agents. Opioids can be problematic in patients with severe benign prostatic hypertrophy or severe obstructive pulmonary disease and carbon dioxide retention. Likewise, knowledge that a patient tolerates food or fluids poorly by mouth, has an indwelling venous access device, or admits to substance abuse might influence decisions about the best way to control that patient's pain. The patient's age, functional status, social support, education, residence, health insurance, finances, and religious and cultural background might also figure prominently in planning therapy. A careful neurologic and physical examination also provides important clues as to the etiology of the pain. Added insight can come from a review of available laboratory and imaging data, from medical records, and from discussions with family members and physicians who are familiar with the patient and his or her illness.

The history, physical examination, and review of other available data should provide the clinician with sufficient information to formulate a differential diagnosis for each of the patient's distinct pains and to make recommendations regarding the workup and therapy for each. Based on this initial impression, analgesic therapy should be initiated. The nature of the treatment prescribed might depend on the clinician's judgment regarding the origin of the pain. Somatic, visceral, neuropathic, and sympathetically maintained pain are each approached somewhat differently (Table 36-4). Prompt institution of therapy reassures patients that their pain will receive immediate attention, ensures patient comfort for diagnostic studies, and can provide information on the accuracy of the clinician's assessment. Excellent pain relief suggests an accurate initial diagnosis and appropriate therapy, whereas suboptimal control might prompt a new treatment approach or a search for a different etiology of the pain.

One of the most difficult aspects of cancer pain management is that the patient's clinical situation is rarely static. The patient's

Table 36-4 Classification of Cancer Pain

Type	Characteristics	Examples	Primary Therapies
Somatic	Constant, aching, gnawing, often well localized	Bone metastases	Treatment of tumor, anti-inflammatory agents, analgesics
Visceral	Constant, aching, often associated with nausea	Pancreatic cancer	Treatment of tumor, analgesics, nerve blocks
Neuropathic	Paroxysmal shocklike pain on top of a burning, constricting sensation	Plexopathy or postherpetic neuralgia	Treatment of tumor, analgesics, TENS, nerve blocks
Sympathetically maintained	Severe burning, squeezing, or constricting with local edema	Reflex sympathetic dystrophy	Sympathetic blockade, physiotherapy, adjuvant analgesics

TENS, transcutaneous electrical nerve stimulation.
From Grossman SA, Staats PS: The current management of pain in patients with cancer. Oncology 1994;8:93.

underlying malignancy, antineoplastic therapy, and psychosocial status change continually during the course of the illness. As a result, the etiology and intensity of each new or worsening pain must be reassessed. The toxicities of the analgesics should also be evaluated periodically, because they can affect quality of life substantially. If significant toxicities are recognized, alternate approaches with a lower toxicity profile can be attempted.

MANAGEMENT OF CANCER PAIN

Nearly 85% of patients with cancer pain can achieve good control of their pain with conventional oral medications. More aggressive or invasive therapies should provide pain relief to an additional 10% of patients, leaving only a small fraction of patients with cancer with inadequate relief. [28]

Pharmacologic Therapy

Pharmacologic approaches are the most commonly used treatments for cancer pain, because they are effective, safe, and usually inexpensive. These are classified as nonopioids, opioids, and adjuvant analgesics. Twenty years after the World Health Organization's analgesic ladder was introduced, it still provides a framework for analgesic prescribing.[29–31] Aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) are preferred for mild to moderate pain.[32] If these do not provide adequate analgesia, codeine, oxycodone, or hydrocodone will frequently provide excellent relief (Table 36-5). For persistent or severe pain, codeine (or its congener) is replaced by a potent opioid, such as morphine (Table 36-6). Drug substitution should be considered before an entire class of agents is abandoned, because patients frequently tolerate one NSAID or opioid better than another. In addition, patients with severe pain might need a strong opioid as initial therapy to ensure rapid pain relief.[33]

The site of action of the nonopioids is primarily the peripheral nervous system. These agents are not associated with physical dependence, tolerance, or addiction, and they have a maximum dose associated with analgesia. Many are available in combination with a weak opioid. The anti-inflammatory component of aspirin and of the NSAIDs and COX-2 inhibitors is often useful for patients with somatic pain from bone metastasis, inflammation, or mechanical compression of tendons, muscles, pleura, and peritoneum, and for nonobstructive visceral pain. Because some of these agents can affect platelet and renal function or act as antipyretics, they should be administered thoughtfully to patients receiving chemotherapy. COX-2 inhibitors allow NSAIDs to be used with less risk of gastrointestinal bleeding and platelet dysfunction. However, the mounting evidence of increased cardiovascular risk calls into question the overall safety of all NSAIDs. Caution must be exercised in using these agents in patients with a history risk of cardiovascular disease.[34–36] In addition, it is important to recognize that sustained high doses of acetaminophen can cause renal and hepatic damage, especially when combined with more than 2 ounces of alcohol per day or with other agents that cause liver damage or induce hepatic microsomes.

Most patients with moderate-to-severe pain rely primarily on opioid analgesics for the management of their cancer pain. The vast majority of patients can be managed with oral opioids. These are best given "around the clock" to keep pain under control. Although tolerance to these agents occurs, tumor progression is the most common reason for increasing opioid requirements. Tolerance can easily be overcome by raising opioid doses. Addiction is extremely rare in patients with cancer who are taking opioids for pain relief (Table 36-7). Most opioid side effects can be managed without excessive

Table 36-5 Opioids for Mild to Moderate Pain

Drug	Route	Equi-Analgesic Dose (mg)*	Peak Effect (hr)	Duration of Effect (hr)	Comments
Codeine	PO	200	0.5	3–6	Ceiling for analgesia reached at doses >240 mg/day orally.
	IV/IM	130	0.5	3–6	
Oxycodone	PO	30	0.5	3–6	No ceiling dose if given without fixed combinations; parenteral formulation not available.
Hydrocodone	PO	NA	0.5	4–6	Only available as fixed combination with acetaminophen or aspirin.
Propoxyphene	PO	NA	1.0	4–6	100 mg napsylate = 65 mg hydrochloride salt. Not recommended for treatment of cancer pain.

*Approximate potency relative to 10 mg of parenteral morphine.
Modified from Grossman SA, Gregory E: Cancer pain. In Kirkwood MT, Lotze MT, Yasko JM (eds): Current Cancer Therapeutics. Philadelphia, Current Medicine, 1994, p 290.

Table 36-6 Strong Opiates for Moderate to Severe Cancer Pain

Drug	Route	Equi-Analgesic Dose (mg)*	Duration of Effect (hr)	Comments
Oxycodone	PO	20	3–6	No ceiling dose if given without fixed combinations; parenteral formulations not available.
	PO SR		12	
Morphine	PO	30	4–6	Many oral formulations for individual patient needs.
	PO (SR)		8–12	
	IV/IM	10	3–5	
Hydromorphone	PO	7.5	3–4	Good choice for SQ due to potency.
	PR	(?)	Unknown	
	IV/IM	1.5	3–4	
Meperidine	PO	300	3–6	Not preferred due to CNS toxic metabolite that accumulates in renal failure.
	IV/IM	75	2–3	
Levorphanol	PO	4.0	6–8	Long $T_{1/2}$ (11 hr) necessitates slow dose titration. Drug accumulation may occur.
	IV/IM	2.0	6–8	
Fentanyl	TD	(?)	≥12	Short $T_{1/2}$ (<1 hr). TD dose titration difficult with depot in SQ adipose tissue. TD fentanyl 25 μg/hr ≈ 45 mg/day oral morphine.
	IV/IM	0.1	0.5–1.0	
Methadone†	PO	10	6–8	Despite long $T_{1/2}$ (15 to >150 hr), duration of analgesia is not prolonged; however, drug accumulation can result in toxicities. Caution is warranted when converting to methadone in patients with high opioid tolerance.
Oxymorphone	PO	10	7–9	Now available as immediate-release formulations.
	PO SR		12	
	IV	1	7–9	

IV, intravenous; PO, oral; SQ, subcutaneous; TD, transdermal; (?), unknown.

*Approximate potency relative to 10 mg of parenteral morphine. Caution: Cross-tolerance between opioids is incomplete. Use caution when performing equi-analgesic conversions. Titrate to clinical response.

†Ripamonti C, Groff L, Brunelli C, et al: Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol 1998;16:3216–3221; Moryl N, Santiago-Palma J, Kornick C, et al: Pitfalls of opioid rotation: substituting another opioid for methadone in patients with cancer pain. Pain 2002;96:325–328; Bruera E, Neumann CM: Role of methadone in the management of pain in cancer patients. Oncology 1999;13:1275–1282; Pereira J, Lawlor P, Vigano E, et al: Equianalgesic dose ratios for opioids: a critical review of proposals for long term dosing. J Pain Symptom Manage 2001;22:672–687; Bruera E, Sweeny C: Methadone use in cancer patients with pain: a review. J Pall Med 2002;5:127–138.

Modified from Grossman SA, Gregory E: Cancer pain. In Kirkwood MT, Lotze MT, Yasko JM (eds): Current Cancer Therapeutics. Philadelphia, Current Medicine, 1994, p 290, with permission.

difficulty (Table 36-8). Constipation should be anticipated and treated prophylactically.[37]

The opioids have their primary effect centrally, where they interfere with pain perception. They can be classified into three groups:

1. Morphine-like opioid agonists that bind competitively with μ and κ receptors (e.g., codeine, fentanyl, hydromorphone, morphine, oxycodone, and methadone)
2. Opioid antagonists that have no agonist receptor activity (e.g., naloxone)
3. Mixed agonists-antagonists (e.g., pentazocine and butorphanol) or partial agonists (e.g., buprenorphine).[38]

The mixed agonist-antagonist drugs have limited utility in cancer pain because of their side effect profiles and their propensity to induce opioid withdrawal in patients who have received opioid agonists. Proper opioid prescribing is critical to patients with cancer (Box 36-1), who often require high doses of opioids for long periods of time.[39]

Several classes of drugs that are used primarily for conditions other than pain have been found to be useful adjuvant analgesics in specific circumstances (Table 36-9). Antidepressants and anticonvulsants can be effective in neuropathic pain. Psychostimulants can decrease opioid-induced sedation. Glucocorticoids are effective anti-inflammatory agents and are also used to reduce pain associated with brain edema and epidural metastases. Muscle relaxants, anxiolytic, antispasmodic, and neuroleptic agents also are administered for specific indications.[40] Bisphosphonates reduce the incidence of skeletal complications, particularly in patients with myeloma and breast cancer.[41,42] Caution must be exercised in the use of adjuvant drugs that have sedative properties, in that the dose of opioids should not be compromised by the toxicities of these secondary agents.

Although the vast majority of outpatients can be managed with oral opioids, alternative routes of analgesic administration are sometimes needed. Subcutaneous, intravenous, transdermal, transmucosal, or intraspinal opioids can be delivered by intermittent bolus, continuous infusion, or a combination of both, as is frequently the case with patient-controlled analgesia. These alternative routes of administration should be considered when a patient has one of the following conditions:

- Intractable vomiting or bowel obstruction, making oral therapy impractical

Table 36-7 Important Definitions in the Treatment of Cancer Pain

PHYSICAL DEPENDENCE

- A normal physiologic response to chronic opioid administration characterized by development of the abstinence syndrome on abrupt withdrawal of opioids.
- A potential problem in virtually all patients receiving moderate to high doses of opiates.

TOLERANCE

- A normal pharmacologic response to chronic opioid therapy characterized by the development of a relative resistance to analgesic and other effects of the drug.
- Overcome by increasing the dose administered.

PSYCHOLOGICAL DEPENDENCE (ADDICTION)

- Abnormal behavior pattern characterized by an all-consuming desire to obtain opioids for reasons other than pain relief. This often occurs at the expense of the patient's physical, social, and environmental well-being.
- Extraordinarily rare in patients with cancer pain.
- Not to be confused with "pseudo-addiction," which is behavior commonly seen in patients who are undertreated and in pain attempting to obtain appropriate analgesia.

Definitions Related to the Use of Opioids for the Treatment of Pain 2001. (Available at http://www.ampainsoc.org; www.asam.org). Modified from Grossman SA, Gregory E: Cancer pain. In Kirkwood MT, Lotze MT, Yasko JM (eds): Current Cancer Therapeutics. Philadelphia, Current Medicine, 1994, p 290, with permission.

Table 36-8 Management of Common Opioid Side Effects

Side Effect	Management	Specific Agents
Constipation	Begin bowel program when initiating therapy.	Stool softeners
	Combinations of agents may be useful.	Irritants
		Bulk laxatives
		Lubricants
		Enemas
Nausea and vomiting	Treat with antiemetics, especially phenothiazine and anticholinergic agents.	Promethazine
		Prochlorperaxine
	Switch to another opiate.	Olanzapine
		$5HT_3$ antagonists
		Scopolamine
		Hydroxyzine
Sedation	Use of stimulants	
	Dextroamphetamine	
	Methylphenidate	
		Modafinil
Pruritus	Treat with antihistamines.	Hydroxyzine
	Consider another opiate, avoiding morphine.	
	Diphenhydramine	
Myoclonus	Switch to another opiate or lower opiate dose.	
	Benzodiazepines	
	Use of anxiolytics	
	Avoid meperidine, especially in patients with impaired renal function.	
Withdrawal symptoms	Taper dose by one-half every other day when discontinuing.	Clonidine

Modified from Grossman SA, Gregory E: Cancer pain. In Kirkwood MT, Lotze MT, Yasko JM (eds): Current Cancer Therapeutics. Philadelphia, Current Medicine, 1994, p 290, with permission; O'Mahony S, Coyle N, Payne R: Current management of opioid-related side effects. Oncology 2001;15:61–77; Cherny N, Ripamonti C, Pereira J, et al: Strategies to manage the adverse effects of oral morphine: an evidence-based report. J Clin Oncol 2001;19:2542–2554.

Box 36-1. MANAGEMENT APPROACH

Tenets of Opioid Prescribing

- Order opioids on a scheduled "around-the-clock" basis to optimize relief.
- Order an as-needed opioid to treat breakthrough or incident pain. For example, if a patient is taking morphine elixir, 100 mg orally every 4 hours, order an additional 25 to 50 mg of oral morphine elixir every 2 hours as needed for pain.
- Initiate a prophylactic bowel regimen at the same time opioids are prescribed. Patients usually require a combination of detergent and stimulant cathartics to treat opioid-induced constipation.
- Treat opioid-induced nausea and vomiting with aggressive antiemetic management. This includes giving patients antiemetics on an around-the-clock basis. Patients often become tolerant to this side effect several days after beginning opioids.
- Once baseline opioid requirements are determined, sustained-release opioid preparations can be used to reduce the number of pills taken each day.
- Teach the patient and family about the purpose and benefits of opioids to allay their fears about side effects and addiction. This instruction will improve patient compliance.
- Frequent assessment of pain relief is paramount during the opioid titration period. Titrate doses based on the patient's report of pain relief and/or the amount of as-needed opioid that has been required for patient comfort.
- Maximize the doses of one opioid before changing to another agent or route. Changes should be made primarily because of toxicities. For example, a patient taking 200 mg of controlled-release morphine every 12 hours and 200 mg of immediate-release morphine daily for breakthrough pain should have the dose of controlled-release morphine increased to 300 mg every 12 hours if he or she is not experiencing significant opioid side effects. This approach is more likely to be beneficial than beginning titration with subcutaneous or intravenous morphine or oral hydromorphone.
- Refer to equi-analgesic tables when initiating or changing a patient's analgesic regimen (see Tables 36-5 and 36–6).
- Avoid chronic administration of intramuscular or rectal opioids.
- Do not use chronic administration of meperidine, which can be associated with the accumulation of normeperidine, a neurotoxic metabolite.

- Ineffective pain relief despite titration to toxicity with several oral opioids
- Unacceptable toxicities to several oral opioids
- Such high opioid requirements that oral administration is impractical

The costs associated with these routes of opioid administration must be considered carefully. In addition, care must be taken not to transform the home unnecessarily into a complex health care setting.

Subcutaneous opioid injections administered through a butterfly or subcutaneous needle on a fixed schedule are used commonly by hospices as an effective, less expensive alternative to continuous intravenous or subcutaneous infusions. A transdermal system for opioid administration can be beneficial for some patients. Although transdermal fentanyl provides patients with continuous drug delivery, it does not eliminate the need for additional analgesics for breakthrough pain. The slow onset of action of fentanyl and the uncertainties associated in conversion from other opioids have led many to reserve transdermal fentanyl for patients with stable opioid requirements who do not have significant incidental pain.[43,44]

Oral transmucosal fentanyl citrate (OTFC) can be effective for patients with incident or breakthrough pain, for whom rapid onset and short duration of action are desired.[45] This opioid is available as a lozenge or a buccal tablet. When placed into the mouth, a portion of the fentanyl is absorbed rapidly through the oral mucosa, while the remainder is swallowed and absorbed through the gastrointestinal tract. The onset of analgesia can be as soon as five minutes. The optimal dose for this delivery system is found through titration and is not predicted by the around-the-clock dose of opioids. The effervescent transmucosal fentanyl tablet has a higher bioavailability than oral transmucosal fentanyl citrate, and the manufacturer recommends converting doses of the two products.[46]

Intraspinal opioids produce analgesia without blocking other sensory, motor, or sympathetic functions. These can be delivered into the epidural space through a tunneled external catheter or to the subarachnoid space or lateral ventricles using a totally implanted pump.[47] Because the total daily dose of intraspinal opioid is one-tenth to one-hundredth of parenteral opioid, it is associated with fewer systemic toxicities. Chronic epidural or intrathecal opioids are invasive, expensive, and frequently ineffective in patients requiring high doses of systemic opioids. Tolerance, pruritus, urinary retention, and nausea and vomiting occur in as many as 20% of patients receiving spinal opioids. Respiratory depression is unusual. The addition of low doses of anesthetic agents or agents such as clonidine to intrathecal and epidural opioids could add considerably to pain relief. Ziconotide, a selective N-type calcium channel blocker, is approved for intrathecal analgesia in patients with pain refractory to other treatments.[48] Intraspinal opioids are generally used after documentation of the failure of maximal doses of opioids through other routes.[49] Consensus guidelines are available to guide the practitioner with proper drug selections for intraspinal analgesia.[50]

Antineoplastic Therapy

Antineoplastic therapy can provide analgesia if it reduces the size of lesions invading or compressing normal tissues. Radiation therapy is the treatment of choice for most patients with local pain from tumor progression. It is frequently administered to patients with symptomatic bone, brain, epidural, and plexus metastases. Systemic radiopharmaceuticals such as strontium-89 and samarium are also used for the treatment of pain from bone metastases.[51] Chemotherapy can provide substantial pain relief in malignancies that respond to this therapeutic modality. Surgery can be effective in relieving pain from intestinal obstruction, pathologic fractures, and obstructive hydrocephalus.

Nonpharmacologic Therapy

Neurostimulatory techniques, such as transcutaneous electrical nerve stimulation, are safe, noninvasive, relatively inexpensive, and easily added to other analgesic approaches.[52] Transcutaneous electrical nerve stimulation could provide short-term benefits in patients with cancer, and a 2- to 4-week trial will often determine its clinical utility. Nonpharmacologic approaches such as progressive muscle relaxation, massage, use of heat or cold, guided imagery, biofeedback, hypnosis, and acupuncture are useful adjuncts to pain management.[53] Although psychotherapy is indicated for an associated depression, unrelieved pain can result in depression that is best treated with analgesic therapies.

Invasive Therapy

Although most cancer pain can be well controlled using the techniques listed in the foregoing discussions, some pain remains refractory, and some patients have persistent adverse effects from opioids despite aggressive therapy with psychostimulants, antiemetics, and laxatives. The side effects can be severe enough that patients might refuse to take sufficient medication to relieve their pain. Adding adjuvant medications, changing to another opioid, or using continuous intravenous or subcutaneous infusions to reduce "peak" levels might be helpful. In selected patients, regional analgesia or neuroab-

Table 36-9 Commonly Used Adjuvant Analgesics for Cancer Pain

Drug Category	Indications	Drugs	Common Toxicities	Comments
Antidepressants	Neuropathic pain	Amitriptyline Nortriptyline Desipramine	Sedation, dry mouth, constipation, postural hypotension, urinary retention	Begin with low doses (10–25 mg); increase dose every few days; expect to see pain relief within several days, mood elevation within several weeks.
Anticonvulsants	Neuropathic pain, myoclonic jerks	Phenytoin Carbamazepine Valproic acid Clonazepam Gabapentin	Drowsiness, dizziness, nausea, rash, bone marrow depression	Use loading dose with phenytoin; monitor platelets wth carbamazepine.
Psychostimulants	Opioid-induced sedation	Dextroamphetamine Methylphenidate Modafinil	Nervousness, irritability, insomnia, dizziness, dry mouth	Give early in the day to avoid insomnia; do not use if patient is already delirious or confused.
Corticosteroids	Spinal cord compression, increased intracranial pressure, visceral distention	Decadron Methylprednisolone Prednisone	Gastritis, insomnia, fluid retention, hyperglyceroximal myopathy, increased appetite	
Muscle relaxants	Muscle spasm	Diazepam Baclofen Methocarbamol Cyclobenzaprine	Sedation, dizziness, nausea, weakness, confusion	
Benzodiazepines	Muscle spasm, myoclonus, anxiety, insomnia	Diazepam Lorazepam Alprozolam Midazalam Temazepam	Sedation, delirium, hypotension, headache, respiratory depression	Not analgesics; synergistic effect with opioids can cause respiratory depression.
Antispasmodics	GI or bladder spasm	Diphenoxylate and atropine Loperamide Scopolamine patch Dicyclomine	Sedation, dry mouth, constipation	
Neuroleptics	Delirium, agitation, nausea and vomiting, hiccoughs	Methotrimeprazine Haloperidol Prochlorperazine Chlorpromazine	Sedation, orthostatic hypotension, confusion, extrapyramidal reactions	Useful for symptoms other than pain; methotrimeprazine has analgesic properties
Bisphosphonates	Bone pain	Pamidronate Zoledronic acid	Hypocalcemia, fever, GI disturbances, anemia	Delays time to painful skeletal events; also used with analgesics for bone pain.

GI, gastrointestinal.

lative procedures might permit the doses of pharmacologic agents to be reduced substantially. In particular, spinal metastases may be treated with minimally invasive therapies such as vertebroplasty, kyphoplasty, or radiofrequency ablation.[54] Neurosurgery has been shown to be the first-line therapy over radiation therapy in the management of a solitary spinal metastasis.[55] These invasive approaches should be considered under the following conditions:

- If significant pain persists at doses of analgesics that are associated with intolerable side effects
- If excessive toxicities result from opioid analgesics
- If a careful assessment suggests that a low-risk procedure is likely to result in excellent analgesia

Regional Analgesia

Regional analgesia can be achieved with long-acting local anesthetics that provide pain relief for 3 to 12 hours, neurolytic agents (alcohol or phenol) that produce analgesia for weeks to months, or opioids injected into the epidural or subarachnoid space (Table 36-10). Diagnostic blocks with local anesthetics are usually performed before neurolysis. This permits the anesthesiologist to determine the response to local therapy and allows the patient to decide whether the "numbness" that replaces the pain is tolerable. If the pain can be relieved temporarily with local anesthetics, alcohol or phenol can be injected into the subarachnoid or epidural space to destroy nociceptive fibers in the dorsal rootlets, thus simulating a surgical rhizotomy. Although

Table 36-10 Regional Anesthetic Techniques

	Types of Blocks	Examples	Indications	Comments
Local anesthetic blocks	Diagnostic	Intercostal nerve block	Determine etiology of pain and the response and side effects following local therapies.	Analgesic effect will last only hours.
	Treatment of sympathetically maintained pain	Stellate ganglion block	Sympathetically maintained pain	Repeated blocks might be needed.
	Trigger point injections	Trigger point injection	Myofascial pain syndrome	Repeated blocks might be needed.
Neurolytic (alcohol or phenol) blocks	Peripheral	Intercostal nerve blocks	Chest wall tumor	Pain relief usually lasts several months.
	Visceral	Celiac plexus block	Pancreatic cancer	Pain relief usually lasts several months.
	Neuraxial	Epidural	Pain localized to two or three dermatomes	Pain relief usually lasts several months
		Intrathecal neurolysis		

From Grossman SA, Staats PS: The current management of pain in patients with cancer. Oncology 1994;8:93, with permission.

injections of these neurolytic agents are commonly called "permanent blocks," pain relief usually lasts several months. Neurolytic blocks can be particularly useful in the thoracic region, where they are associated with few motor complications. In the cervical and lumbar regions, nearly 20% of patients develop motor and/or sphincter dysfunction, which can be permanent. In patients with pre-existing lower extremity paralysis, colostomy, or nephrostomy tubes—cases in which loss of motor or sphincter function might be less critical—lumbar neurolysis might be worthwhile. Other potential side effects of these procedures include hypotension, toxic reactions from accidental intravenous or subarachnoid administration, or pneumothorax after needle placement. Neurolysis is usually restricted to patients with a limited life expectancy, because it can produce a painful neuritis that becomes clinically apparent only months after the procedure.

Neurolytic blocks are used in selected patients who have localized or regional pain. Percutaneous celiac plexus neurolysis is an outpatient procedure associated with few risks; it alleviates pain originating in the pancreas, stomach, gallbladder, or other upper abdominal viscera in most patients. One randomized, prospective, double-blind trial comparing celiac plexus injections of alcohol or saline and systemic analgesic therapy in patients with unresectable pancreatic cancer showed greater pain relief with the block. Opioid consumption and quality of life were not statistically significant, however.[56] In other settings, it has been shown to decrease opioid requirements.[57,58] Although pain can recur months after a celiac block, subsequent blocks are often associated with excellent pain relief. Less commonly used neurolytic procedures include intercostal blocks (chest wall or rib pain), neuroaxial blocks (pain in two to three dermatomes), Gasserian ganglion neurolysis (pain in the anterior two-thirds of the head), brachial plexus blocks (for patients with pre-existing limb paralysis), and ganglion impar and superior hypogastric blocks (for lower abdominal and pelvic pain).

Neuroablative Procedures

Neuroablative procedures are performed infrequently on patients with cancer because of the success of more conservative approaches. The most commonly performed procedures are radiofrequency ablation and the open unilateral anterolateral cordotomy, percutaneous cordotomy, and commissural myelotomy. An open cordotomy is usually performed through a T2 or T3 laminectomy and produces excellent pain relief in the lower part of the body in 80% of patients. A 5% to 10% mortality rate and significant morbidity in an additional 15% of patients are reported for this procedure. Hemiparesis, urinary retention, sexual impotence, unmasking pain on the opposite side of the body, and late sensory abnormalities are not infrequent. Bilateral cordotomies are associated with higher complication rates. Percutaneous cordotomy is safer and provides excellent pain relief; however, pain recurs within 3 months in 50% of patients. A commissural myelotomy can be considered in selected patients who experience bilateral pelvic and perineal pain. This involves a laminectomy and surgical division of the crossing fibers of the spinal cord. Although it can result in pain relief with sphincter sparing, few neurosurgeons have extensive expertise with this procedure.

DIFFICULT-TO-MANAGE PAIN PROBLEMS

Difficult-to-manage pain problems are most common in patients with any of the following conditions:

- Pain of neuropathic origin
- Episodic or incidental pain
- Impaired cognitive or communicative skills
- A history of substance abuse

Referral to an experienced multidisciplinary cancer pain team can be helpful if initial attempts to control pain in patients with these underlying problems are unsuccessful.

Patients with Pain of Neuropathic Origin

Any injury to the peripheral or central nervous system can cause neuropathic pain. This is often characterized by paroxysms of shock-like pain on top of a burning or constricting sensation. Neuropathic pain in patients with cancer commonly arises from tumor invading or compressing peripheral nerve, nerve plexus, or spinal cord. It can occur as a result of surgery, radiation, or chemotherapy as exemplified by postmastectomy and post-thoracotomy syndromes, radiation-induced plexopathies, and chemotherapy-induced neuropathies.[59,60] Neuropathic pain also can accompany disorders that are unrelated to the tumor or its treatment, such as diabetes mellitus, nerve entrapment syndromes, and herpes zoster.

Providing adequate relief from neuropathic pain can be difficult even for the most experienced physicians. Although this pain might improve on opioids, it seems to respond less well to these agents than does nociceptive pain. Optimal therapy for neuropathic pain often depends on opioids used in combination with a variety of nonopioid "adjuvant" analgesics (see Table 36-9).[61] Tricyclic antidepressants have been studied most extensively in this situation. Although the most

convincing efficacy data is with amitriptyline, this agent is associated with significant anticholinergic effects and sedation. Other drugs in this class with a more favorable toxicity profile include desipramine and nortriptyline. Duloxetine, a serotonin and dual serotonin-norepinephrine reuptake inhibitor, has substantial effect in neuropathic pain.[62]

Anticonvulsants are also helpful in the management of neuropathic pain, particularly if the pain has lancinating qualities. The doses of these agents are similar to those used for the control of seizures. Care must be taken to avoid abrupt withdrawal, because this could induce seizures. Randomized controlled trials have demonstrated the efficacy and tolerability of gabapentin for the treatment of postherpetic neuralgia and painful diabetic neuropathy.[63] Other studies suggest that it might help in the management of neuropathic pain secondary to cancer or its treatment.[64] This agent is well tolerated, no drug-drug interactions have been identified, and the average effective dose is 1800 to 3600 mg/day. A newer anticonvulsant, pregabalin, has a mechanism of action and side effects similar to gabapentin. Maximum doses are achieved within 1 to 2 weeks, offering an advantage over gabapentin.[65] Reports support the use of carbamazepine, valproic acid, and diphenylhydantoin, although the myelosuppression associated with carbamazepine might compromise the ability to administer concurrent chemotherapy.

Systemically administered local anesthetics have been used for the treatment of neuropathic pain. Anesthetic creams that produce few systemic side effects are also available. Topical lidocaine patches are an effective means to contol neuropathic pain that is confined to a small area. Capsaicin, a neurotoxin that selectively destroys nociceptors, is also manufactured as a topical preparation and provides relief in some patients. If oral agents and topical creams are ineffective, afferent input can be reduced with transcutaneous electrical nerve stimulation or regional anesthetic techniques such as long-term epidural catheters or intrathecal pumps for the delivery of local anesthetics. Neurolytic blocks, more invasive neurostimulatory techniques, or even neurosurgical procedures might be indicated in extreme situations.

Patients with Episodic or Incidental Pain

It is widely recognized that some patients experience transient, but severe, exacerbations of their pain. These can be difficult to treat and are often very troubling to the patient. These exacerbations can occur as a result of an inadequate analgesic regimen. For example, a patient who receives opioids every 6 hours and has good relief for only 4 hours needs a change in regimen to ensure that opioid levels will not fall below the analgesic threshold after 4 hours. This change is best accomplished by providing the agent more frequently or by administering sufficient doses of a sustained-release preparation. Episodic pain associated with voluntary or involuntary movements poses a more difficult therapeutic problem. Examples of these "incidental pains" are seen in patients with pelvic metastases or pathologic fractures who have severe pain with walking or sitting, patients with rib metastases who experience stabbing chest pain with movement or coughing, or patients with esophageal, rectal, or bladder lesions with pain on swallowing, defecation, or urination, respectively. Involuntary precipitants can include bowel or ureteral distention. In a recent study of incident pain, nearly three-quarters was directly related to neoplastic lesions, 20% resulted from of antineoplastic therapy, and the remainder was unrelated to the tumor or its treatment.[66–68]

Proper management of these patients requires a comprehensive assessment to determine the origin of the pain. Therapy directed at the underlying etiologic factors is most likely to provide pain relief. Relieving a bowel obstruction, repairing or splinting a fracture, treating a local metastatic lesion with radiation therapy, or performing a neurolytic block for a painful rib lesion provides better analgesia than opioids. The frequency and severity of incidental pain might also be reduced significantly by anti-inflammatory agents or corticosteroids in bone or nerve compression pain and by anticonvulsants or tricyclic antidepressants in neuropathic pain. In addition, agents that reduce the frequency of precipitating events should be used. These include antitussives, laxatives, antiperistaltic drugs, or agents that reduce muscle spasms. Physiotherapy can be useful in musculoskeletal complications, and the cognitive and psychologic approaches can be helpful to patients with these pains. Rarely, patients require invasive anesthetic or neurosurgical approaches for relief of these transient but severe pains. Local anesthetic injections might predict whether a patient is likely to respond to chemical neurolysis or a destructive neurosurgical procedure. Continuous epidural anesthetics and opioids might also be helpful in carefully selected patients.

Many of the approaches listed in the foregoing discussion might not be effective, or even possible or advisable, in the context of a patient's illness. In such situations, opioids remain the mainstay of therapy. The baseline dose of opioid can be escalated until pain relief or intolerable side effects occur. Although this approach might produce relief, patients are often excessively sedated during the intervals between the severe pains. Alternatively, patients might elect to take supplemental analgesics (usually short-acting opioids) 30 to 60 minutes before they know a precipitating event is likely to occur. If the pain is unpredictable, the additional medications are taken as soon as the pain begins. The optimal timing of opioids for episodic pain is difficult to achieve. Episodic pain is characterized by a quick onset and short duration. Parenteral opioids, while having a faster onset of action than the oral route, are not practical in the home setting. Alternatively, the transmucosal fentanyl products may provide the best option. The doses of these supplemental opioids must be determined from the patient's baseline opioid requirements. It is common to begin with 5% to 10% of the total daily opioid dose ordered every 2 to 3 hours as needed. The dosing of transmucosal formulations, as previously mentioned, is determined through titration and not based on the baseline opioid requirement.[45,69]

Patients with Impaired Cognitive or Communicative Function

The difficulties that physicians and nurses have determining the intensity of pain in patients with cancer have been described previously in this chapter. Problems in conveying pain intensity are greatly magnified in patients who cannot communicate with their health care providers or who are cognitively impaired. These deficits complicate the assessment of both pain intensity and pain relief. Some patients are unable to speak the language of the health care provider, whereas others have severe neurologic deficits, such as an expressive aphasia. As previously noted, children and the elderly have special difficulty communicating pain intensity.[70] Patients with severe cognitive deficits present obvious problems in assessing an entirely subjective symptom. Delirious patients with cancer are often restless, moaning, and unable to convey the intensity, nature, or even location of their pain. These patients require a review of correctable factors contributing to the delirium. Neurologic events, infections, trauma, bladder distention, fecal impaction, hypoxia, or metabolic abnormalities are common. The patient's drug regimen should be simplified, and all agents with anticholinergic properties should be discontinued. If the patient is on an opioid, reducing the dose, switching agents, or using a continuous infusion or sustained-release preparation to avoid wide fluctuations in drug levels might result in improvement.[71]

Patients with a History of Substance Abuse

The principles of cancer pain assessment and management in patients with a current or prior history of drug abuse are similar to those for any patient with cancer pain.[15] These individuals should not remain in pain as a result of this complicating medical problem. Patients with a history of drug abuse, however, often have difficulty finding physicians who believe their reports of pain and who will provide the high doses of analgesics required in these opioid-tolerant individuals. As a result, they can become angry, frustrated, and more persistent in their

demands for opioids. This constellation of symptoms is also seen in patients who do not have a history of drug abuse but who have severe, untreated pain. Their preoccupation with obtaining analgesics is referred to as pseudo-addiction and tends to disappear rapidly with appropriate pain therapy.

A frank discussion of major issues relating to the proper use of opioid analgesics for pain management with the patient, the patient's family, and the drug counselor is important. Pain management agreements often help to ensure that all parties understand and agree to the same principles and plans for therapy. Oral agents are preferred, or regional pain management techniques that could limit the need for opioids can be considered. Opioids such as methadone might be prescribed in lieu of morphine or hydromorphone.

CONCLUSION

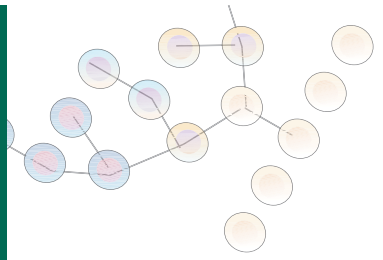
Pain is common in patients with cancer and remains one of the most feared aspects of this illness, despite the excellent therapies that are available to provide pain relief. Cancer pain commonly results from tumor compressing or invading soft tissue, bone, or nerves or from diagnostic or therapeutic endeavors. The key to optimal pain management rests with a thorough assessment of the patient's pain. This involves a determination of pain intensity, an evaluation of the etiology of the pain, a carefully considered therapeutic plan, and repeated assessments of pain relief after therapeutic interventions. The vast majority of cancer pain can be well controlled with therapies readily available to most physicians. These include nonopioid analgesics, opioid analgesics, adjuvant medications, antineoplastic therapies, nonpharmacologic approaches, and noninvasive neurostimulatory techniques. Regional anesthetic or neurosurgical approaches should be considered for selected patients who continue to experience pain after an adequate trial of the foregoing therapies or who have unrelenting toxicities from these agents. They should also be considered for patients whose pain suggests that an inexpensive, low-risk procedure is likely to result in excellent analgesia. Examples of such cases include pancreatic cancer pain and thoracic pain in a dermatomal distribution. Referral to an experienced multidisciplinary pain team might be required in situations that are known to pose special challenges in pain management. These include patients with neuropathic pain, episodic or incident pain, impaired cognitive or communicative capabilities, or a history of substance abuse.

Cancer pain remains undertreated despite evidence that a careful assessment of cancer pain and the appropriate use of available therapies should result in excellent relief in nearly 95% of patients. Providing optimal cancer pain relief tests the skills and commitment of physicians, nurses, and pharmacists, because the diagnostic, therapeutic, and social issues in these patients are complex and constantly changing. Meeting these challenges can be satisfying, because patients and family are grateful to find that pain can usually be alleviated. Furthermore, as noted in the American Society of Clinical Oncology's policy statement on cancer pain, "patients with cancer have a right to effective treatment of pain" and the "evaluation and treatment of cancer pain are an integral part" of each caregiver's responsibilities.[7]

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37 Rehabilitation of Individuals with Cancer

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SUMMARY OF KEY POINTS

- As cancer treatment improves, more patients are living longer with functional limitations, and quality-of-life (QoL) issues become as important as survival.
- Rehabilitation must be patient centered and goal oriented. It requires an interdisciplinary team with the active participation of the patient.
- Impairments, activity limitations, and participation restrictions from cancer dramatically affect QoL, but these are amenable to rehabilitation efforts.
- The focus of rehabilitation varies with the phase of the disease process.
- Important impairments include pain, fatigue, cognitive dysfunction, mood disorders, paresis, feeding difficulties, bone and soft tissue involvement, and bladder, bowel, and sexual dysfunction.
- Activity limitations can be ameliorated with training in activities of daily living (ADLs), exercise, and adaptive equipment.
- Participation in home, vocational, and recreational activities plays a critical role in QoL. Economic burdens, environmental barriers, and transportation problems often require attention.

INTRODUCTION

The National Cancer Institute Dictionary of Cancer Terms defines rehabilitation as "a process to restore mental and/or physical abilities lost to injury or disease, in order to function in a normal or near-normal way."[1] Rehabilitation is critical to improving quality of life (QoL) for cancer survivors, and maintaining dignity for those with terminal illness. Rehabilitation requires several components to be successful.

First, it must be *patient-centered*—that is, individualized to the patient's needs, desires, and situation. Health care providers always must remember that the patient is the captain of the rehabilitation team. Rehabilitation that fails to respect a patient's wishes will fail altogether. Most problems in rehabilitation occur when there are differences in the team's goals and those of the patient.

Second, it must be *goal-oriented.* Goals should be meaningful to the patient's QoL. They must be measurable and concrete, so that they are transparent to the patient and the caregivers. Goals also must be achievable. Health care providers must balance realism with hope in counseling patients about their goals.

Third, rehabilitation requires an *interdisciplinary team approach.* In traditional multidisciplinary medical teams, different health care professionals each individually set goals appropriate to their area of specialization. In interdisciplinary rehabilitation, the team members work toward common goals by fulfilling the responsibilities of not only their particular discipline, but also the added responsibility as a group toward fulfilling the patient's goals. Team members must demonstrate a high degree of communication skills, humility, and commitment.[2]

Finally, rehabilitation also requires the *active participation of the patient.* Rehabilitation is not something done *to* an individual; it must be done *with* the individual. It is not a passive process, and it requires individuals to take responsibility for *self-management* of their illness. Rehabilitation is largely an educational process for the patient and family members.

The World Health Organization has recently published an International Classification of Functioning, Disability and Health, which is meant to supplement the International Classification of Disease (ICD-10).[3] It lays out a series of definitions that are crucial to understanding the role of rehabilitation in improving QoL. Box 37-1 lists these definitions. In this chapter we will focus on *impairments, activity limitations,* and *participation restrictions* seen in cancer patients, and discuss how rehabilitation can ameliorate these disabilities.

EPIDEMIOLOGY OF CANCER DISABILITY

As a result of the tremendous progress in prevention, early detection, and treatment of cancer in the last quarter century, there has been a decline in mortality rates from cancer. However, the number of cancer survivors continues to grow, as more people are living longer with cancer because of the new advances in surgery, and in medical and radiation oncology.[4] The result is that increasing numbers of patients face more years with cancer-related disability.[5] Data from the National Health Interview Survey 2002 indicate that 11.3% of patients with cancer have difficulty with activities of daily living (ADLs) as compared with 3.8% of people without cancer in the United States.[6] Among prostate cancer patients, 15% have major difficulties with ADLs; among colon cancer patients, 35% have such difficulty, and the proportion rises to 40% among lung cancer patients.[7]

Even among 5-year cancer survivors, elderly women with a history of cancer had statistically significantly more problems with ADLs than age-matched controls.[8] Focus should be directed away from mere survival toward the preservation and improvement of QoL for these survivors. In Japan, for example, the number of breast cancer survivors with lymphedema, as well as chest wall, axilla, and arm pain is expected to double by 2020.[9]

Box 37-1. WORLD HEALTH ORGANIZATION INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY, AND HEALTH DEFINITIONS

Impairments: Problems in body function or structure such as a significant deviation or loss of a body part or organ system.
Activity limitations: Difficulties an individual may have in executing activities of daily life.
Participation restriction: Problems an individual may experience in involvement in life situations.

OUTCOME MEASURES FOR CANCER REHABILITATION

Cancer is a complex, chronic illness whose management requires vigilance and a comprehensive and preventive approach to illness and disability. To accomplish this, a systematic approach to patient evaluation throughout all the phases of the disease process is necessary (Table 37-1).

The major concerns of persons with cancer include their overall health, fitness, fatigue, emotional and social function, and pain,[10] which may vary during different phases of the disease. For example, in the initial staging phase, anxiety and disruption of routines may present the greatest challenges. During the treatment phase, the symptoms of fatigue, nausea, and sleep disruption may be the most significant problems.

In general, patient assessments should be tailored to which signs and symptoms are most likely to be associated with the current phase of the disease. Screening tools should include questions relevant to which problems are important to the patient and family, which are likely to be associated with disabilities and which are remediable or need palliation. Once treatments are initiated the care team must assess whether the treatments are effective and at what cost.

Many outcome measures have been developed for cancer patients and have been validated in this population—some for specific cancers, some for toxicity measures, some for specific age groups. In general, it is appropriate to select measures that are easy to use, standardized, and valid for the population and problems being addressed. The following measures are recommended:

- Impairment measures: range of motion, muscle testing (including grip strength), pain indices, fatigue measures, mood/affect
- Functional measures/disability measures: mobility (6- or 9-minute walk time), ADLs
- Health-related QoL/health status measures: SF36, Karnofsky, Eastern Cooperative Oncology Group (ECOG), Eastern Organization for Research and Treatment of Cancer–Quality of Life Questionnaire (EORTC-QLQ).

IMPAIRMENTS

Cancer, even when localized to—or arising from—one organ system, causes the loss of body function across many organ systems in individuals. The physician must obtain a comprehensive review of systems when evaluating a cancer patient, because this will help identify impairments to be addressed by the treatment team.[11] Delineating these impairments in individuals is the first step toward ameliorating them; this lies at the core of cancer rehabilitation.

Pain

Virtually every cancer patient experiences pain during the course of the illness; it can often become debilitating.[12,13] Pain severity correlates closely with function, as demonstrated in one study of 216 Chinese cancer patients with metastatic disease.[14] In that study patients with increasing severity of pain had poorer function, whereas those with mild, well-controlled pain functioned similarly to those without pain. The clinician should distinguish whether the pain is acute in onset or a chronic problem. Often it can be an acute exacerbation heaped upon a chronic underlying pain.

The etiology of pain in cancer patients is myriad and frequently has multifactorial causation. The pain may be visceral (arising from internal organs), somatic (from soft tissue, muscles, and/or bones), or neuropathic (from the central or peripheral nervous system). Visceral pain tends to be poorly localized. It is often described as "deep" and "cramping." Somatic pain, on the other hand, is usually well localized. It is often characterized as "sharp" or "stabbing," and is frequently worsened by weight bearing or movement. There is often point tenderness on examination. Neuropathic pain tends to radiate along dermatomal or peripheral nerve distributions. Patients frequently describe "burning" or "pins and needles." The pain tends to be unrelenting. There may be associated allodynia (pain with light stroking).

Pain often produces psychological distress in patients, which in turn exacerbates the pain.[15] Tishelman and colleagues studied symptoms among 400 patients newly diagnosed with inoperable lung cancer and reported that pain, breathing, and fatigue caused the most distress. They concluded, "Breathing and pain appeared to function as icons representing threats associated with lung carcinoma."[16] Thus, pain may cause the patient to fear disease progression and impending death.

Sadly, pain is often inadequately treated in cancer patients. As many as 50% to 80 % of nonhospice cancer patients receive inadequate analgesia.[17] Yet pain can be well controlled in more than three-quarters of cancer patients using multimodal treatment, according to one study of 2118 patients.[18] Treatments can include opioids,[19] adjuvant medications,[20,21] complementary therapy,[22] physical modalities, exercise,[23] behavior management,[15] injections, implantable opiate pumps,[24] radiation therapy,[25] and surgery.[26]

Table 37-1 Phases of Cancer Rehabilitation

Phase	Patient Needs	Symptoms	Impact
1. Evaluation and treatment planning	Education	Pain, anxiety, insomnia	Disruption of daily routines
2. Primary training	Education, acute care	Pain, fatigue, ROM, ↓ ambulation, ADL support	Daily routines, stamina (psychologic social function)
3. Post-treatment, recovery	Education, support, chronic care, healthy lifestyle	Pain, anxiety, depression, mobility, edema, fatigue, neuropathy, insomnia	Work, family, avocation, cosmesis
4. Recurrence	Education, support	Same as above; metastatic disease effects	Daily routines, work/play
5. End of life	Education, support	Pain, asthenia, depression	Dependence

Fatigue

Cancer-related fatigue (CRF) is a "persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning." (National Comprehensive Cancer Network [NCCN], http://www.nccn.org; American Cancer Society, http://www.cancer.org). This has been expanded to include concepts of "overwhelming and sustained exhaustion and decreased capacity for physical and mental work . . . not relieved by rest."[27] In addition, fatigue has been shown to affect negatively one's economic status,[28] and social and emotional status.[29]

CRF is correlated to treatment intensity[30] and can last well past completion of treatment. As many as 75% of cancer patients[31] have CRF. The likelihood of developing fatigue is increased with any cancer-related treatment (surgical, chemotherapeutic, or radiotherapeutic) and is also more likely to occur with comorbidities (e.g., hepatic, cardiac, renal, pulmonary) and other conditions (e.g., insomnia, inactivity, chronic pain, mood disorders).[32] Fatigue may persist beyond the treatment period.[33]

Treatment is frequently directed at varying the treatment protocol when possible and providing treatment holidays (Practice Guidelines NCCN for Cancer-Related Fatigue. http://www.nccn.org). It has been shown that improving quality of sleep is helpful, but increasing the amount of "rest" is not effective in reducing the symptoms of CRF.[34] Careful attention to comorbidities and their treatment will reduce CRF. Treatment of depression and chronic pain has been shown to improve symptoms.[35] Exercise has been shown to mitigate fatigue.[36]

Delirium and Cognitive Dysfunction

Delirium is a mental state in which a person is confused, disoriented, and not able to think or remember clearly.[1] The incidence in studies of advanced cancer patients ranges from 20% to 86%.[37] Delirium may be reversible in 50% of the cases with proper identification and management.[38] Delirium in cancer usually has multifactorial etiology. Accurate assessment is critical for effective treatment.[39] Direct involvement of the central nervous system by primary or metastatic tumors, especially with resultant cerebral edema, is the most readily apparent cause. However, distant tumor cytokine production may also play a role.[40] Liver metastasis may also elevate serum toxins, causing a metabolic delirium. Risk factors for the development of delirium in bone marrow transplant patients before transplantation include lower cognitive functioning, lower physical functioning, and higher blood urea nitrogen, alkaline phosphatase, and magnesium levels.[41]

Medications certainly play a large role in the development of delirium. In a study of 216 hospitalized cancer patients, corticosteroids, opioids, and benzodiazepines were most frequently associated with delirium.[42] A variety of other medications may also contribute: anticholinergics, anticonvulsants, antihistamines, dopamine agonists, metoclopramide, and selective serotonin reuptake inhibitors. A number of chemotherapy agents have also been implicated: methotrexate, isofamide, fluorouracil, vincristine, bleomycin, carmustine, cisplatin, and procarbazine. It is also important to remember that abrupt withdrawal of certain medications can cause delirium; these include benzodiazepines and muscle relaxants (especially Baclofen).

The clinician must also consider metabolic causes. Fever and sepsis often produce acute delirium. Dehydration and uremia frequently contribute. Electrolyte abnormalities—increased and decreased levels of sodium, calcium, and magnesium—are often associated with cognitive dysfunction. Hypoxia and hypoglycemia are additional possibilities that can be easily assessed.

Delirium may present as either a hypoactive or a hyperactive state. In hypoactive cases, dehydration frequently contributes to delirium. In hyperactive states, medication side effects (especially opioids and corticosteroids) and liver failure are often culprits.[37]

Management of delirium should always start with nonpharmacologic interventions. Family involvement may decrease anxiety and provide familiar surroundings. If family is unavailable to supervise the patient, a sitter may be necessary. Calm, simple communication should be used. Environmental changes should be used to minimize distractions (noise, lights, simultaneous conversations). Physical restraints tend to worsen the situation and should only be applied in extreme situations. The clinician should discontinue the use of unneeded medical devices such as intravenous lines and urinary catheters.

Pharmacologic intervention can be of help when there is agitation or hallucination. Haloperidol is considered to be the major tranquilizer of first choice.[21] Newer antipsychotics such as olanzapine may be helpful as well. Benzodiazepines are effective when there are convulsions or in cases of alcohol or sedative withdrawal, but they often worsen confusion in other causes of delirium. Methylphenidate has been used successfully in a small study (in cancer patients with hypoactive delirium (psychomotor retardation).[43]

Mood Disorders

Receiving a cancer diagnosis is stressful and frightening for most individuals. Initially patients may experience symptoms of shock, disbelief, denial, or despair as they struggle to accept and incorporate the reality of the diagnosis. Patients may also experience a variety of normal fears throughout their treatment course, including fears of disability, loss of societal roles, loss of control, loss of desirability, abandonment, and death. Overall, however, most patients cope successfully with cancer diagnosis and treatment and experience good long-term psychologic adjustment.[44] Many patients even describe positive changes in their lives related to their diagnosis, including positive changes in self-perception, interpersonal relationships, priorities, and goals.[45]

Although most patients cope well, a significant number do experience serious mood disorders. The average estimates of the prevalence of depression among cancer patients are from 15% to 25%.[46] The importance of correctly diagnosing and treating depression is underlined by research showing that depression is associated with poor compliance with medical care, longer hospitalizations, and higher mortality rates in patients with chronic illnesses.[47]

Anxiety is quite common in cancer patients and may be related to poorly controlled pain, abnormal metabolic states, or medication side effects. They may also develop post-traumatic stress disorder in response to cancer diagnosis and treatment. Post-traumatic stress disorder is an anxiety disorder that develops after an extremely stressful event, such as the development of a life-threatening illness. Within 5 years of diagnosis, between 10% and 15% of cancer survivors may meet criteria for post-traumatic stress disorder.[48]

Neurologic Impairments

A wide variety of impairments of nervous system function may result from cancer, either by direct effect at the primary or metastatic tumor site or secondarily as a consequence of surgical or radiation treatments. These impairments, regardless of the tumor's location, extent, or type, may significantly affect the individual's physical, social, vocational, and emotional capabilities. Important differences exist between the management of patients with cancer of the central nervous system and those with other types of acquired neurologic disability. Rehabilitation strategies must consider progressive, sometimes rapid, functional decline, toxic effects of cancer treatments, tumor recurrence, CRF, medical fragility, insurance and workplace discrimination, and psychologic and family issues associated with an often terminal disease. The interdisciplinary rehabilitation team is best equipped to handle the complexities of restorative care in these situations, and meet the patient's and family's goals of maximizing functional recovery and preserving QoL.

Hemiplegia

Tumors affecting brain tissue are either primary or metastatic in origin, with metastatic lesions composing roughly 50% of all

intracranial tumors.[49] Brain metastases occur in 20% to 40% of patients with cancer and their frequency has increased in recent years, probably as a result of improved detection and treatment.[50] Lung, breast, and skin (melanoma) are the commonest sources of brain metastases, and in as many as 15% of patients the primary site remains unknown.[51] In those with metastatic brain tumors, studies demonstrate that the three strongest prognostic factors are physical performance status, response to steroids, and evidence of systemic disease.[52] Brain tumors vary widely in aggressiveness and prognosis. To what extent tumor type or location has an impact on rehabilitation outcomes is not clear. However, one study found a tendency for greater gains for meningiomas and patients with left hemispheric lesions.[53] Brain tumor patients receiving inpatient acute rehabilitation show similar gains between those with metastatic origin and primary brain tumor.[53] However, functional gains were superior on initial presentation to rehabilitation as compared with those with recurrence of the cancer.[54] Brain tumor patients have been found in some studies to have shorter lengths of stay on acute rehabilitation units as compared with other noncancerous brain disorders,[49] possibly as a result of higher initial levels of functional independence on admission, fewer behavioral issues, better social support, and expedited discharge planning due to cancer-related prognostic factors. Despite increases in survival rates of patients with primary brain tumors and advances in treatment, survival is limited for many and must be considered with regard to the timing, duration, and types of rehabilitation interventions.[52] Statistics show the mean survival for glioblastoma multiforme patients with optimal treatment is about 1 year,[55] and that patients with brain metastases assessed as having the best prognosis survive only a mean of 7.1 months.[56]

Most patients with brain cancer have multiple impairments, depending on tumor location and size, and in those who have undergone surgery, the volume of tissue excised. In a study of patients with brain tumor undergoing acute rehabilitation, the most common neurologic deficits included impaired cognition (80%), weakness (78%), and visual-perceptual dysfunction (53%).[53] Rehabilitation efforts for brain cancer patients should focus on the patient's neurologic and functional status, coexisting medical problems, and tolerance of physical activity. As with patients with stroke or traumatic brain injury, goal setting should be appropriate to the individual's physical, cognitive, and behavioral status, and include early planning for post-acute rehabilitation care.

Specific rehabilitation measures for patients with brain cancer-related disability emphasize early attention to mobilization, including bed mobility, transfer training, and ambulation or wheelchair skills. Those patients presenting with unilateral leg weakness will benefit from a physical therapist assisting with progressive gait and balance training, and when necessary using an assistive device appropriate for the degree of stability required (single-point cane, four-pronged cane, or walker). Provision of an ankle-foot orthosis to control weakness and/or spasticity of ankle musculature is often needed. The risk of limb contracture—especially in ankle plantar flexion, wrist and finger flexion, and shoulder adduction and internal rotation—is increased in patients with weakness, particularly spastic hemiplegia. Early and regular stretching programs, along with appropriate limb positioning and supportive devices such as Multi Podus (LEEDER Group Inc., Miami, FL) boots are critical. Glenohumeral support and position in bed and wheelchair, the latter involving a lap table or arm trough, is key to preventing hemiparetic shoulder pain. A flaccid or significantly subluxed glenohumeral joint may require a humeral cuff or sling-type arm support, used judiciously so as to not promote a contracture in internal rotation and adduction. For individuals limited by unilateral arm weakness, an occupational therapist can provide adaptive equipment such as reachers, sock donners, or elastic shoelaces.

Additionally, attention should be given to other potential complications of reduced mobility including deep venous thrombosis and skin breakdown. Awareness among physicians of the risk of thromboembolism in brain tumor surgery patients may be insufficient,[57] highlighting the need to be vigilant in prophylaxis for deep venous thromboses. Seizures represent the most frequent medical problem encountered during rehabilitation for brain tumor patients, occurring in about 20% to 40% of patients with brain metastases.[58] Anticonvulsants are appropriate in patients with documented seizures and probably for short-term use perioperatively, but prophylactic use of these agents in patients with tumor but without seizures is generally not recommended.[59]

Paraplegia and Tetraplegia

Injuries to the spinal cord may be secondary to either traumatic or nontraumatic causes. Cancer-related spinal cord injury (SCI) incidence may actually exceed that from trauma and represents the most frequent type of nontraumatic SCI.[49] Symptoms consistent with SCI occur as a result of metastasis in as many as 5% of all cancer patients.[60] Symptoms such as weakness, sensory loss, and bladder and bowel sphincter dysfunction can be a consequence of either tumor compression on, or invasion of, the spinal cord or its vasculature, spinal instability from bony invasion, or secondary to the cancer therapy itself (radiation or surgery). Spinal metastases occur more commonly in the thoracic spine (70%), followed by the lumbosacral (20%) and cervical (10%) spine, and most often originate from primary tumors of breast (15%), lungs (10%), and prostate (10%). Lymphoma, myeloma, and primaries of unknown origin also metastasize to the spine, each accounting for around 10% of cases. The majority (95%) of metastatic spine involvement is extradural, arising from a vertebral body.[61] Primary tumors of the spinal cord such as meningiomas, neurofibromas, and gliomas are relatively rare. Spinal cord metastases produce a clinical syndrome characterized initially by pain in 90% of cases, followed by weakness, sensory loss, and sphincter dysfunction. Weakness is present in 74% to 76% of patients, autonomic dysfunction in 52% to 57%, and sensory loss in 51% to 53%.[62] Pain alone may persist for a month or more (average 6 weeks) before significant neurologic changes develop. Acute onset of back or neck pain in a patient with cancer should be considered as spinal metastasis until proven otherwise.

Positive results have been demonstrated following rehabilitation for individuals with disability from spinal cord tumors, with significant functional gains measured after inpatient rehabilitation.[54,63] For patients who retained some motor or sensory function, those with the most neurologic deficits were found to benefit most from inpatient rehabilitation. Factors that have been identified as better prognostic indicators for survival after inpatient rehabilitation include lymphoma, myeloma, breast and kidney tumor types, SCI as the presenting symptom, slow progression rate of neurologic symptoms, combined surgery and radiation treatments, partial bowel control, and partial independence with transfers on admission.[64]

As with traumatic injuries, dysfunction resulting from spinal cord tumor may be classified according to the level of motor and sensory impairment as well as the completeness of the involvement. However, nontraumatic SCI, which includes cancer etiology, differs from traumatic involvement. For spine tumor patients, McKinley and associates[65] found less severe neurologic impairment, greater likelihood of presenting with paraplegia than tetraplegia, and greater frequency of motor incomplete lesions than complete lesions.

Medical complications associated with recent SCI are common, potentially life-threatening, and require a vigilant and knowledgeable hospital staff. Comprehensive SCI care includes attention to ventilatory ability in those with high spinal levels of injury, and management of pain, autonomic dysreflexia, pulmonary and urinary tract infections, thromboembolic disease, bowel and bladder dysfunction, decubitus ulcers, limb contractures, and spasticity. Certain measures instituted immediately after onset of spinal cord dysfunction remain standards of acute care in this patient population. Prophylaxis for lower-extremity venous thromboses with low-molecular-weight heparin should be immediately initiated unless otherwise medically

contraindicated, and continued for at least the duration of the rehabilitation phase, and in cases of plegia or severe paresis, for a total of 3 months. Other areas of management that should be instituted early for those with loss of thoracic musculature include incentive spirometry and chest physiotherapy. Initiation of intermittent bladder catheterization every 4 to 6 hours when daily bladder volumes are less than 2 liters should be routine treatment, as well as instituting a bowel program with daily or every other day suppository or digital stimulation. Other key measures in early spinal cord care include prevention of skin breakdown in body areas commonly at risk (occiput, sacrum, greater trochanter, heels, and ischial tuberosities) including turning in bed every 2 hours, specialized pressure relief bed and wheelchair mattresses, and heel protectors. Additionally, at least daily limb range of motion should be initiated immediately after onset of the SCI. Patients with severe spinal cord dysfunction above T6 level are prone to developing autonomic dysreflexia—a significant increase in blood pressure above baseline, as a result of vasoconstriction from splanchnic sympathetic nerve stimulation by noxious stimuli below the level of the spinal lesion. If blood pressure remains significantly elevated, pharmacologic measures and intensive monitoring may be required.

Speech, Swallowing, and Nutrition

Disorders of speech and swallowing may be the result of direct tumor invasion of the oral cavity, larynx, pharynx, esophagus, or adjacent structures; secondary to surgical or radiation treatments; or consequent to cancers of the nervous system that affect pharyngeal or laryngeal control. Head and neck cancers constitute about 3% to 5% of all malignancies. Preservation of swallowing, having a natural airway, and intact speech are critical components that influence QoL in head and neck cancer patients. Among these, swallowing has been shown to have the largest impact on global QoL.[66]

Head and neck cancer and its treatment often results in major effects on nutrition, swallowing, and communication function. Depending on the tumor location, surgical excision and repair often impairs key articulatory, deglutitory, or airway-protective structures causing difficulty in speaking, transporting food, and maintaining a healthy airway. For example, deeply infiltrative cancerous lesions of the tongue requiring more than 50% tissue resection significantly impair speech and swallowing.[67] In one study, some surgical patients, depending on the extent of tissue resection, achieved functional swallowing and eating within 3 months of surgery, whereas for others significant impairment remained for as long as 9 months postoperatively.[68]

Postsurgical nutrition is initially via nonoral means (percutaneous endoscopic gastrostomy or nasogastric feeding tubes). However, prompt and early evaluation of oropharyngeal function is required before oral intake is resumed. The physical examination should include the neck, mouth, oropharynx, and larynx, and related neurologic function. As soon as feasible following surgery, oral-motor exercises are initiated with speech-language pathology focusing on strength, range of motion, and sensory awareness of the involved structures. Dysphagia assessment and treatment typically begin with a radiographic evaluation defining the nature of the patient's swallow dysfunction, with attention to alterations of the local anatomy. A videofluorographic swallowing study is particularly useful for identifying aspiration risk and for empirically testing therapeutic and compensatory techniques to eliminate food entry into the airway and promote successful and timely passage into the esophagus.

Swallowing strategies focus on prevention of aspiration and the efficiency and completeness of moving the food bolus through the oral, pharyngeal, and esophageal segments. Common interventions include modifying food texture, such as thickening liquids or blenderizing solid food, and/or altering head posture and swallowing behaviors. The latter may include techniques such as chin tuck to prevent laryngeal penetration, head rotation to reduce retention in the piriform sinus, enforced double or effortful swallows to reduced pharyngeal residue, or supraglottic swallow to optimize vocal fold closure and airway clearance.[69]

In the majority of head and neck cancer patients, impaired vocal communication occurs at some point during treatment. It is important to keep in mind that multiple conditions other than total laryngectomy can result in deficient phonation in cancer patients. These include copious secretions, localized edema, fibrosis and scarring, presence of a tracheostomy, glossectomy, loss of oral mobility from local tumor or trismus, and neurogenic pharyngeal or laryngeal paralysis. The patient with total laryngectomy lacks a source of voice production and must replace laryngeal function with an artificial larynx (electrolarynx), esophageal speech, or tracheoesophageal puncture voice restoration with a prosthetic surgical device.

Bone Tumors, Amputation, Bony Metastases

In 2007, about 2370 new cases of cancer of the bones and joints will be diagnosed. Skeletal tumors account for less than 0.2% of all cancers.[70] Soft-tissue and bony sarcomas are managed with amputation or limb-sparing procedures. Limb salvage procedures are increasing in frequency and are associated with long-term survival, local recurrence rates, and QoL equivalent to those of amputations, largely made possible by improved surgical techniques that preserve unaffected tissue, advances in endoprosthetic design and durability, soft-tissue reconstructive procedures, and radiation and chemotherapy effectiveness in controlling local and distal spread.[71]

Rehabilitation after limb-sparing procedures depends on the extent of soft-tissue and bony resection, and because of combined tumor resection, skeletal reconstruction, and soft-tissue and muscle transfers, may be more intensive than that following amputation. The planning process begins preoperatively, with the rehabilitation specialists providing evaluation of the individual's functional level before surgery and then projecting what the probable functional needs will be postoperatively. This includes instruction on mobility aids, orthotics for joint stabilization, as well as strengthening and endurance exercises in collaboration with the treating surgeon. The possible need for long-term limb bracing should be discussed if sacrifice of major nerves or muscles is required. Complex limb reconstruction requires an astute team to assess for possible complications during the recovery process. The majority of microsurgical complications occur within the first 24 to 36 hours after surgery, but that period may extend to as long as 1 or more weeks when the patient begins initial mobilization of the extremity after a period of bedrest. Complications may include arterial or venous microvascular thrombosis, hematoma, or flap dehiscence during ambulation. Splinting and wound dressing must be done with care to avoid problems associated with pressure on the flap. Although various strategies are used in mobilizing patients following reconstruction of the lower extremity, they often require a period of strict bedrest (as long as 7–10 days) to allow wound healing, control edema, and maintain limb alignment, followed by several days of dangling the extremity for short intervals. If this has been successfully achieved, physical therapy can begin with toe-touch ambulation with an assistive device such as a crutch or walker. Upright activity progresses to partial and full weight bearing depending on the patient's strength and degree of wound healing. After adequate healing has occurred, a pressure garment should be fitted so as to prevent or lessen the onset of lymphedema.[72]

Other lower limb-sparing procedures undertaken in this population may involve wide excision of portions of muscle, typically involving hip adductors, quadriceps, hamstrings, and gastrocnemius muscles. Leg elevation, active range-of-motion exercises, and compression garments to control edema are instituted as part a rehabilitation program following these procedures. Approximately 15% to 20% of sarcomas arise in the upper extremities, and are generally smaller in size and associated with better survival than those in the lower extremities, with whole muscle groups only rarely removed.[73,74]

However, major resections of tumors of the shoulder region can present significant challenges to the rehabilitation team, depending on the extent of tissue loss and neurologic involvement. Upper-extremity reconstructive procedures often require a sling or shoulder harness for support, with the goal to develop adequate strength and function of the hand and control edema through the use of low-stretch bandages. Early rehabilitation should avoid humeral motion, and range of motion after acute healing should not exceed 90 degrees of abduction, with adduction not permitted. To minimize contracture formation of the digits, the hand should be placed in a functional position with the wrist dorsiflexed at 30 degrees, the metacarpophalangeal joints flexed at 70 to 90 degrees, the interphalangeal joints extended, and the thumb abducted.[75] The salvaged limb becomes for the long term non–weight bearing and nonlifting. A shoulder mold can be fashioned that allows a more cosmetic clothing fit. For soft-tissue sarcomas involving the forearm extensor muscles or radial nerve removal, a cock-up splint to maintain wrist extension or a brace that incorporates a dynamic outrigger to substitute for weak or absent finger extension may be prescribed.

Tumor amputees differ from dysvascular and traumatic amputees in several important ways. Fatigue, anemia, nausea, and toxic effects of chemotherapy may diminish functional capacity. Wound healing may be delayed over irradiated areas and skin less tolerant of prosthetic wear. Cancer amputees typically have shorter residual limbs so as to obtain tumor-free margins. It is more common in this population to have more proximal sites of amputation, in that the primary pathology is often located at proximal sites, such as forequarter or shoulder disarticulation in the upper limbs or hemipelvectomy in the lowers.[61] Weight loss, muscle atrophy, and residual volume shifts, particularly during chemotherapy, may prolong the wait for a definitively fitted prosthesis. In these cases, the use of flexible, adjustable sockets to permit continued prosthetic wear and training has proven beneficial for patients with early postoperative fluctuations in stump size.[76,77]

If amputation is required the most functional level should be selected, allowing for as much residual limb length without sacrificing tumor control. For instance, a very short above-knee amputation can be accommodated with a prosthesis and is more energy efficient and functional than a more proximal hip disarticulation. Similarly, prosthetists are able to effectively fit short below-knee and below-elbow stumps, functionally superior to their above-elbow and above-knee counterparts.[78] Otherwise the rehabilitation of tumor amputees is similar to that for other patients, including the use of a multidisciplinary team, preoperative education for the family and patient about what to expect at different stages of preprosthetic and prosthetic training, and early initiation of exercises to improve strength and stamina. Rehabilitation often commences in the operating room when it is recommended that an immediate postoperative rigid dressing be fitted to the residual limb. Early use of rigid stump dressings have been shown in some studies to reduce time to delivery of the first definitive prosthesis, control stump edema and pain, reduce phantom limb sensation, help shape the residual limb, and speed incision healing.[79] Otherwise stump shrinker socks or elastic wraps are applied to control the shape of the residual limb. Proper positioning both in bed and in the wheelchair is necessary to prevent contracture formation and reduce edema in the residual limb, along with range-of-motion exercises and judicious use of splinting. Management of postoperative pain is critical, often requiring narcotics for the initial period. Desensitization techniques can help prepare the stump for acceptance of the prosthetic socket. Preprosthetic training includes upper-body strengthening and endurance exercises, and should include unipedal walking with appropriate assistive devices until weight bearing through the prosthetic leg is advised. The timing of fabrication of a permanent prosthesis will depend on the type and extent of the surgery as well as the status of other concurrent medical management, including chemotherapy.

The vast majority of skeletal cancer is of metastatic origin, with breast cancer being the most common primary source in women and prostate cancer in men. Other common primaries that metastasize to bone include lung, renal, and thyroid cancers.[80] The vertebrae, pelvis, femur, ribs, and skull are the most frequently involved sites of bone metastases, with the axial skeleton and the lower extremities, particularly the hip region, affected most frequently. One or more of the following problems may occur with bone metastasis: pain, hypercalcemia, pathologic fractures, myelosuppression, and spinal cord and/or nerve root compression with subsequent progressive immobility.

Bone metastases are a frequent source of cancer-related physical impairment that requires the active involvement of the rehabilitation team. Challenges for the treating team arise when metastatic bone lesions produce severe pain that limits function or imposes risks of fracture during therapeutic exercise or mobility. Factors that inform the therapeutic approach will include the degree of associated pain, lesion location, response to radiation therapy, neurologic compromise, and the presence or risk of fracture. The type of metastasis (lytic versus blastic) is also important, with lytic lesions considered more prone to fracture. The incidence of pathologic fracture among all tumor types is about 8%, with breast carcinoma responsible for the majority of these. Sixty percent of all long bone fractures involve the femur, with most of these involving the proximal portion.[81] Patients who are deemed at risk for a pathologic fracture should be made non–weight bearing to the affected structure, pending surgical consultation.

Rehabilitation for this patient population focuses on removal of weight bearing or immobilizing compromised bone through the provision of assistive devices and orthoses, strength and balance training, and modification of the patient's environment. Whenever possible, bedrest should be avoided, because it adds to general debility and further functional loss, as well as increasing the risks of hypercalcemia and thromboembolic disease. Depending on the severity and location of the lesion, mobility restrictions can range from non–weight bearing to weight bearing as tolerated. For complete non–weight bearing restrictions, assistive devices in the form of walkers or bilateral crutches are typically necessary. Single-point canes are used for patients with minimal balance deficits and smaller lesion size, but patients with larger, more symptomatic lesions should be advanced to a forearm (Lofstrandt)-type crutch, which permits a greater degree of weight support. It is critical to first rule out the coexistence of upper-extremity lytic lesions before prescribing assistive devices that require weight support through the arms. Bracing may reduce risk or symptoms of a pathologic fracture involving the upper extremities, and can facilitate use of the arms in functional activities. Those individuals with upper-limb lesions should be taught to minimize torsion and weight loading, and may benefit from an arm sling or humeral cuff support. In the spine, Jewett bracing to prevent spinal flexion, or a custom-molded clam-shell design to give stability in all directions can be prescribed. When more rigid bracing is not tolerated secondary to poor skin tolerance or discomfort, a thoracolumbar corset provides limited support and pain relief. Spinal bracing should extend several segments above and below the involved area of the spine.

Cancer patients suffering from pathologic fractures and associated functional deficits have been shown to make significant gains when admitted to an inpatient rehabilitation hospital unit.[82] It should be recognized that rehabilitation of patients with skeletal metastases has many inherent risks, and strategies to exercise these patients remain largely theoretical because of a lack of empiric data. However, the alternative to rehabilitation therapies is often bedrest, which carries its own set of potential complications, including muscle contractures, weakness and atrophy, osteoporosis, orthostatic hypotension, pressure sores, pulmonary infection, and increased risk of thromboembolic disease.

Soft-Tissue Impairments Associated with Cancer Diagnoses

Cancer and or its treatments can cause significant soft-tissue abnormalities. One of the most frequently observed is lymphedema, extremity swelling that results from disruption of the lymphatics following axillary or groin dissection. The prevalence of this in breast cancer patients has been reported to be 200,000 (10%),[83] or generally between 15% and 30%.[84] In the ALMANAC study,[85] the relative risks of any lymphedema and sensory loss for the sentinel lymph node biopsy group compared with the standard axillary treatment group at 12 months were less, as were drain usage, length of hospital stay, and time to resumption of normal day-to-day activities after surgery. Overall patient-recorded QoL and arm functioning scores were statistically significantly better in the sentinel lymph node biopsy group. Although the prevalence of limb edema is high following standard treatment, the treatment options for managing this have improved. The use of manual lymph drainage and compression garments is effective in controlling edema. When applied early in the course of treatment, before the development of significant volume increase (e.g., >250 mL increase in the arm), lymphedema can almost be reversed.[86]

The second, frequently seen soft-tissue complication of cancer treatment is frequently radiation induced. In the brain this causes gliosis, in the lung and gastrointestinal tract, fibrosis. Each is associated with significant inflammatory reaction and subsequent scarring. In the musculoskeletal system, muscle, fascia, and tendon all respond in a similar fashion. Long-term sequelae include fibrosis and contracture, eventually resulting in loss of muscle mass. This process is associated with vascular permeability and inflammation and release of proinflammatory cytokines (interleukins, transforming growth factor-β) and continues well past cessation of the radiation therapy.[87] The use of antifibrotic agents in the treatment of this problem has shown promise.[88]

Allogeneic bone marrow transplantation has prolonged life for many with hematologic malignancies. One of the complications of this procedure has been the rejection by the host of the transplanted, immunocompetent engrafted cells, called graft versus host disease. The immunologic reaction is often quite brisk, resulting in organ damage (fibrosis) to lung, liver, gastrointestinal tract, and notably skin and soft tissue. In the chronic form of graft versus host disease, limb edema, peau d'orange, fasciitis, and enthesitis can occur, resulting in significant loss of joint motion. There may be subsequent muscle atrophy secondary to disuse and associated loss of upper- and lower-extremity mobility.[89]

Bladder and Bowel Management

Loss of bladder or bowel control in cancer patients is often multifactorial and can be secondary to neurogenic causes, such as with brain or spinal cord tumors, can result from nonsurgical or surgical cancer therapies, or can occur as a direct effect of gastrointestinal or genitourinary tumors. Incontinence in this population may also be related to immobilization in bed, side effects of pharmacologic management, or diminished alertness and communication skills. This condition encompasses both medical consequences and QoL issues. Medical sequelae of loss of bladder and bowel function include renal infection and stone formation, skin ulceration, autonomic dysreflexia, fecal impaction, hemorrhoids, diverticulosis, and rectal prolapse. Loss of self-esteem, depression, and social isolation may develop. Incontinence after stroke, for instance, has been shown to be a strong predictor of mortality, dependency, and need for institutional care.[90] It is incumbent on the treating team to properly assess patients with fecal or urine incontinence and institute a management plan.

The formulation of a bowel management program should take into account the limitations of the patient's functional mobility and self-care skills, available family support and resources, and concurrent medical problems. Patient and family need to be educated on the long-term management of bowel dysfunction including the rationale, goals, and techniques of bowel management. This should include instruction in the safe use of assistive devices for bowel emptying, efficient and effective techniques for bowel emptying, and the importance of timing, regularity, and positioning in bowel evacuation.

Any destructive lesion or process above the conus medularis can lead to an upper motor neuron bowel pattern of dysfunction, characterized by fecal distention of the colon, overactive segmental peristalsis, underactive propulsive persistalsis, and a hyperactive holding reflex with spastic external anal sphincter constriction. The latter requires a mechanical (i.e., digital stimulation) or chemical (i.e., bisocodyl suppository) aid to trigger a reflex defecation. A lesion at the level of the conus medullaris, cauda equina, or inferior splanchnic or pudendal nerves affects the parasympathetic and somatic pudendal cell bodies. This condition results in a lower motor neuron lesion characterized by colonic slowing, constipation, fecal incontinence, and difficulty with emptying.[91] In such patients routine manual clearance of stool from the rectum may be necessary. Inactivity and debility associated with hospitalization for cancer management promotes the supine position, which inhibits effective bowel evacuation. Hospitalized cancer patients should also be placed on a consistent timed emptying program based on stimulating regular bowel evacuation, and where appropriate, the use of stool softeners, bulk-forming agents, and/or natural stimulants such as senna. Stimulation of the rectocolic reflex using manual stimulation and/or bisocodyl or glycerine suppository may induce bowel movement on a regimen basis. Taking advantage of the gastrocolic reflex with planning defecation after meals is also useful. Overactive intestinal motility with frequent stooling and/or diarrhea may require judicious use of medications to decrease peristalsis.

Management of bladder incontinence in cancer patients follows many of the same principles outlined previously for managing bowel incontinence. The patient should be taught to take responsibility wherever feasible for understanding and directing his or her bladder program. Patients with cancer involving bladder outlet obstruction such as with prostate cancer are at added risk of incomplete emptying, urinary stasis, hydronephrosis, and urinary tract infection. Certain commonly encountered medications may impair bladder control and function, including sedatives, muscle relaxants, opiates, calcium channel blockers, and antihistamines.

Voiding disorders in cancer patients may be a result of neurologic conditions, such as spinal cord tumor involvement, myelopathic consequences of radiation therapy, brain tumor, or lesions affecting sacral or pelvic nerve structures. Spinal cord lesions at suprasacral levels result in bladder dysfunction characterized by detrusor hyperreflexia and uncoordinated micturition with detrusor-sphincter dyssynergia. Tumors involving more caudal spinal regions including the conus medullaris, cauda equina, and S2 to S4 peripheral nerves will cause variable loss of parasympathetic and somatic nerve function, resulting in areflexia and loss of external sphincter function. Suprapontine lesions due to brain tumors may lead to uninhibited bladder contractions possibly secondary to loss of cerebral cortex inhibition at the sacral micturition center. Voiding dysfunction may also be classified functionally as failure to store urine due to bladder hyperreflexia, or insufficient sphincter outlet control, or due to failure to empty because of bladder hypo- or areflexia, or from inadequate sphincter opening (Table 37-2).

Sexual Function

Sexual function can be very important to cancer patients, yet it is seldom discussed by the patient and physician. In breast cancer, treatment often produces side effects of fatigue, nausea, diminished

Table 37-2 Functional Classification of Voiding Dysfunction and Management Options

FAILURE TO STORE

Reason: bladder hyperreflexia

Management options

1. Behavioral: timed voiding
2. Collection devices: condom catheters, intermittent catheterization, indwelling catheter (Foley or suprapubic)
3. Medications: anticholinergics, calcium channel blockers, botulinum toxin
4. Surgery: augmentation, continent diversion, denervation procedures

Reason: inadequate outlet pressure

Management options

1. Behavioral: timed voiding, pelvic floor exercises
2. Collecting devices: condom catheters, indwelling catheters, diapers
3. Medications: α-agonists, imipramine, estrogen cream
4. Surgery: implantable artificial sphincter, fascial sling, collagen and Teflon injections

FAILURE TO EMPTY

Reason: Detrusor hypo- or areflexia

Management options

1. Behavioral: timed voiding, bladder stimulation such as tapping; Valsalva and Credé's maneuver
2. Collecting device: condom catheter, indwelling catheter, diapers
3. Medications: cholinergic agonists
4. Surgery: Neurostimulation device

Reason: Inadequate outlet relaxation

Management options

1. Behavioral: anal stretch
2. Collecting device: indwelling catheterization
3. Medications: α-blockers, striated muscle relaxants, botulinum toxin
4. Surgery: sphincterotomy, pudendal neurectomy, bladder outlet surgery

vaginal lubrication, not to mention the significant body image changes from mastectomy.[92] A meta-analysis of 36 studies of sexuality in testicular cancer patients showed that problems were largely related to ejaculatory dysfunction, but, fortunately, rates of decreased sexual desire were low and may improve with time.[93] Erectile dysfunction is a common side effect of prostatectomy, and of hormonal and radiation therapy for prostate carcinoma.[94] Colorectal cancer surgeries often lead to sexual dysfunction in men.[95] Not surprisingly, gynecologic cancers often produce changes in vaginal sensation, structure, and lubrication.[96] On a positive note, however, of cancer patients who received brief sexual counseling, 63.5% reported improvement.[97]

ACTIVITY LIMITATIONS

With their multitudes of possible impairments, it is not surprising that many individuals with cancer have significant limitations in their activities. These limitations include reduced mobility and limited ability to perform ADLs. These often result from neurologic or orthopedic impairments but may also be related to fatigue. Communication and socialization skills may be negatively affected by cognitive deficits, by impairment of speech, or by depression and anxiety.

Activities of Daily Living

Basic ADLs include feeding, dressing, hygiene, and toileting. These ADLs are virtually universal to human dignity across world cultures. Impairments of upper-limb function play an obvious role in limiting performance of ADLs, but other impairments also can impede these functions. Cognition is critical to sequencing, awareness, and carryover in the performance of ADLs. Pain and fatigue can also limit the individual's ability to complete these tasks. Lower-limb impairments can limit standing and transferring, making it difficult to carry out dressing, hygiene, and toileting.

When individuals become disabled enough to require assistance with these skills, the burden generally falls on caregivers. In one study of 483 cancer patients at varying stages of their disease course, 18.9% had unmet needs in their ADLs as a result of lack of a suitable caregiver.[98] Among advanced-stage cancer patients the percentage of caregivers with a high level of psychologic distress varies from 41% to 62% directly depending upon the functional status of the patient.[99]

Rehabilitation efforts, particularly with the involvement of occupational therapy, can significantly reduce this burden on caregivers and enhance the QoL for cancer patients with disabling impairments.[100] Addressing functional loss from impairments of the upper limb, such as chemotherapy-related peripheral neuropathy of the hand[101] or radiation-induced brachial plexopathy,[102] can substantially improve performance of ADLs. To improve feeding independence among cancer patients with upper-limb neurologic dysfunction, Chinese researchers used positioning, feeding aid supports, and upper-limb supports, and significantly improved function over a 3-week treatment intervention.[103] Use of simple adaptive aids, such as a swivel fork,[104] can enhance function tremendously. Home-based occupational therapy interventions produce a high level of patient and caregiver satisfaction, reducing burden of care.[105]

Exercise for Cancer Patients

Patients with cancer diagnoses suffer from a variety of symptoms attributable to direct effects of tumor and/or their treatments. Some of the treatments—surgical, chemotherapeutic, radiotherapeutic, or biologic—can cause immediate and remote effects.

Typically the treatment substantially affects the neuromusculoskeletal system, resulting in functional loss and fatigue. The latter is reported to be one of the most distressing symptoms.[29,106]

Exercise is one of the most effective strategies for symptoms associated with cancer fatigue, sleep disruption, and abnormalities of mood, physical function, and QoL.[107] Rigorous meta-analyses, however, caution that these studies are subject to significant methodologic problems, such as small sample sizes, diverse forms of exercise, nonrepresentative samples (e.g., few African Americans and Hispanics; few advanced cancers, many breast cancer studies). Another significant methodologic problem is that the instruments used to measure fatigue, mood, and QoL are subjective, relatively insensitive, and inconsistent in measuring intensity, impact on daily routines, or state of satisfaction or well-being. This makes study comparability difficult. Nonetheless, meta-analyses[108] suggest that for adults with a variety of cancer diagnoses and receiving a variety of exercise interventions, exercise improves physical function, QoL, and cardiorespiratory fitness,[109] and decreases CRF.[110] The great majority of these studies use aerobic exercise, using ergometry and walking programs, and occasionally, aquatic therapies.[111]

Strengthening protocols, though not contraindicated, have not been thoroughly evaluated.[112]

Contraindications for exercise include: thrombocytopenia (<50,000 platelets/μL, no resistive exercise; <20,000 platelets/μL,

only ADLs and light activity); anemia (<8 g ADLs only; 8–10 g, light exercise as tolerated); bony metastatic disease (25% to 50% cortical involvement in long bone, partial weight bearing, avoid lifting; 0 to 25%, full weight bearing, no high-impact sports); pulmonary (50% to 75% forced expiratory volume in 1 second or carbon monoxide diffusing capacity, no aerobic exercise); cardiac (low ejection fraction or arrhythmia, consult cardiology; electrolytes (Na below 130 mEq/L, K below 3 mEq/L [correct the hypokalemia], Ca above 6 mEq/L [correct the hypercalcemia], no exercise). Relative contraindications are for tachycardia greater than 100 beats per minute and temperature of >99.5°F or >37.5°C.

Physical Modalities

Physical modalities may be used to control pain and improve range of motion, thus leading to better mobility. Most physical modalities have not been well studied in cancer patients because of the concern of exacerbating an underlying malignancy. Those that are generally believed to be safe include cryotherapy, biofeedback, iontophoresis (transdermal delivery of medication by electrical current), transcutaneous electrical nerve stimulation (TENS), and massage. Electrical stimulation, regardless of how it is delivered, is generally not done directly over a tumor site. The same is true for massage therapy and superficial heat. Deep heat (e.g., ultrasound and phonophoresis) is usually contraindicated in cancer patients. Spinal traction is contraindicated in those patients with spinal metastases or with significant osteoporosis.

Durable Medical Equipment

Durable medical equipment provides an important tool in improving the activity level of cancer patients. Durable medical equipment includes hospital beds, canes, walkers, wheelchairs, and motorized scooters. These can greatly enhance mobility when properly prescribed and when the patient is properly trained in their use. Wheelchairs should be individually fitted, because the wrong size can lead to skin breakdown[113] or make accessibility difficult, if it is too wide.

Oxygen tanks and supplies are also considered durable medical equipment. Oxygen supplementation can enhance endurance and cognition, and reduce dyspnea in patients with hypoxia due to lung cancers or metastases.[114]

PARTICIPATION RESTRICTIONS

Participation refers to the roles an individual plays in society. These roles can include family and social relationships as well as vocational and avocational pursuits, and they often require modes of transportation to accomplish. Cancer patients are often restricted in many of these functions.

Family and Social Relationships

Cancer can often draw a family together; however, it just as often leads to significant distress for families. Caregiver and patient coping styles significantly influence the level of strain in families.[115] Support groups can also be helpful, yet fewer than half of patients receive information about them, even in a large tertiary oncology center.[116] In one study of 121 cancer patients, caregiver QoL was significantly correlated to the social/family and functional dimensions of the patients' QoL; physical and emotional dimensions did not correlate.[117] Early, though, caregivers undergo significant psychosocial stress. There are also significant economic burdens on families.[118] Indeed cost considerations play a large role in patient decision making regarding cancer treatment, especially among the poor.[119]

Vocational Rehabilitation

Work disability following cancer diagnosis is a common occurrence. Short and coworkers[120] conducted phone interviews of 1433 cancer survivors at 1 to 5 years after diagnosis. More than half had quit work during their first year after cancer diagnosis, but fortunately three-quarters of those returned to work subsequently. A projected 13% had indefinite work disability. Survivors of central nervous system, head and neck, and stage IV blood and lymph malignancies had the highest risk of quitting work.

Fortunately U.S. laws in recent years have provided more protection to the cancer survivor returning to work.[121] These include the Americans with Disabilities Act, Family and Medical Leave Act, and the Health Information and Portability Act.[122] Nevertheless, a great deal of barriers still stand in the way of gainful employment for cancer survivors with disability.[4] These include ignorance of both employers and cancer survivors of their rights, discrimination, and limits on pre-existing conditions in health insurance benefits.[123]

Little is known about which medical impairments have the greatest impact on employability.[123] Undoubtedly, cognitive and communication deficits play a large role, as evidenced by the high work disability rates among survivors of central nervous system and head and neck malignancy.[120] Fatigue and pain are also likely to limit work participation. Spelten and colleagues studied 235 cancer survivors in the Netherlands.[124] Fatigue levels strongly predicted inability to return to work.

Participation in Recreation

Recreation is much more than fun and games; it is critical to physical and mental well-being. Fatigue, pain, weakness, depression, and other impairments will limit cancer survivors' participation in avocational pursuits. Health care providers and family members should encourage recreational activity for those with cancer. The benefits include improvements in fitness, musculoskeletal problems, immune system function, cognition and sleep. Physical activity reduces the risk of cardiovascular and cerebrovascular disease, as well as diabetes mellitus. It is also reduces the risk for several common cancers, which is relevant to cancer survivors who are already at risk for new primary cancers.[125] One study looked at 97 European youngsters attending a summer camp for adolescents living with cancer and diabetes.[126] Significant improvements were seen in self-esteem, self-efficacy, and anxiety. Adults benefit as well. For example, Tai Chi Chuan, an Asian mind-body practice, has been shown to have beneficial effects on cancer survivors in 11 small studies.[127]

Transportation

Cancer patients may be limited in their ability to drive, fly, or take public transportation. They may not have caregivers available to help with transporting them. This can become a major barrier to cancer treatment, which often involves frequent medical visits. Some patients forgo recommended treatments because of lack of adequate transportation.[128] Thus, it behooves physicians to explore with cancer patients any limits to their ability to get transportation.

Physicians are often leery to allow patients to drive while using opioids. However, Galski and associates showed that patients on chronic, stable, opioid analgesic therapy are safe to drive.[129] Patients with cerebral dysfunction due to tumor, paraneoplastic effects, or treatment side effects should be evaluated for driving safety before allowing them to return to the road. There are well-defined off-road driver evaluation tools available.[130]

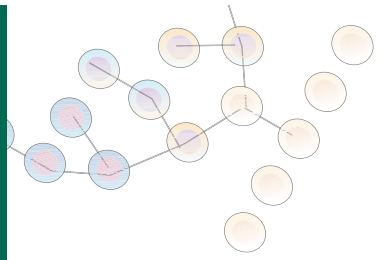
Air travel might be problematic for patients with brain tumors. There have been case reports of cerebral edema[131] and hemorrhage,[132] although it is unclear how frequently these events occur.

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38 Cachexia

Michael J. Tisdale

SUMMARY OF KEY POINTS

- The cachectic syndrome is defined by body weight loss of ≥10%, reduced food intake (≤1500 kcal/day). and systemic inflammation (C-reactive protein ≥10 mg/L).
- Patients with cachexia have a reduced quality of life, a lower activity level, and a reduced survival time.
- Anorexia is often associated with cachexia, but there might not be a cause-and-effect relationship because of the following:
  - Body composition change in cachexia is different from that in anorexia, with equal loss of muscle and fat.
  - There is selective loss of skeletal muscle in cachexia.
  - It is not possible to reverse the loss of skeletal muscle by nutritional supplementation or drug-induced appetite stimulation.
  - Resting energy expenditure is not uniformly increased in all cancer patients.
  - Levels of uncoupling protein 3 increased in muscle of cachectic patients. This could convert lipid released from adipose into heat.
- Factors involved in the loss of lipid from adipose tissue are the following:
  - Zinc α_2-glycoprotein by the induction of lipolysis and increased expression of uncoupling proteins.
  - Cytokine (TNF-α, IL-6, IFN-γ) inhibition of lipoprotein lipase, although TNF-α can also induce lipolysis and induce uncoupling proteins.
  - Futile energy cycles such as the Cori cycle and the triacylglycerol/fatty acid cycle.
- There is loss of skeletal muscle due to a depression of protein synthesis and an increase in protein degradation.
- Both calpain and the ubiquitin-proteasome proteolytic pathway are involved in the degradation of intact myofibrils.
- Factors involved in the loss of skeletal muscle are proteolysis-inducing factor (PIF), angiotensin II, and tumor necrosis factor-α.
- These factors stimulate increased expression of the ubiquitin-proteasome pathway by activation of the transcription factor NF-κB.
- Although other cytokines such as interleukins-6 and -8 are elevated in cachectic patients, there is less evidence for a direct role in atrophy of skeletal muscle.
- Pharmacologic management of cachexia may involve progestins, corticosteroids, eicosapentaenoic acid, β-hydroxy-β-methylbutyrate, or combination therapy.

INTRODUCTION

The word *cachexia* comes from the Greek *kakos hexis* and literally means "bad condition." In cancer patients, cachexia is a multifactorial syndrome characterized by a progressive loss of body weight with depletion of both adipose tissue and skeletal muscle mass. Cachexia is often, but not invariably, associated with anorexia as well as an elevated acute phase response. While patients are defined as cachectic when their body weight is 5% less than their preillness stable weight, weight loss alone does not identify the full effect of cachexia on physical function, and it is not a prognostic variable. However, by using weight loss (≥10%) together with reduced food intake (≤1500 kcal/day) and systemic inflammation (C-reactive protein ≥10 mg/L), it is possible to identify patients who have both adverse function and poor prognosis.[1]

The incidence of cachexia depends on tumor type, being highest in patients with pancreatic and gastric cancer and lowest in patients with breast cancer and non-Hodgkin's lymphoma. Overall weight loss occurs in 30% to 80% of cancer patients and is severe (>10% of initial body weight) in 15%.[2] Cancer therapies are also associated with the induction of anorexia and further weight loss. Patients with cachexia have a reduced quality of life, a lower activity level, and a reduced survival time.[2] Malnutrition also increases the risk of infections, treatment toxicity, and health care costs and decreases response to treatment.[3] A shorter survival time has been shown[4] to be independently associated with a weight loss of more than 8.1 kg in the previous 6 months and serum albumin levels less than 35 g/L. Weight loss often precedes tumor diagnosis and is often a presenting symptom.

ANOREXIA AND CACHEXIA

The association of anorexia with cachexia has led to the term *cachexia-anorexia syndrome*. Between 15% and 20% of patients are malnourished at the time of diagnosis, and for patients with advanced disease, this is up to 80% to 90%.[5] The tumor may cause reduced food intake, either directly, by interfering mechanically with the digestive tract, or indirectly, by producing inhibitory substances that act on peripheral receptors or in the hypothalamus. The principal biochemical mediators implicated in anorexia are (1) cytokines such as interleukin (IL)-1β, IL-6, IL-8, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and ciliary neurotrophic factor; (2) serotonin; (3) the hypothalamic neuropeptides neuropeptide Y (NPY) and corticotrophin-releasing factor; and (4) peptide hormones such as

insulin, glucagon, and leptin. Although the exact mechanism that triggers cancer anorexia is not known, it has been suggested to result from an imbalance between NPY (orexigenic) and pro-opiomelanocortin (anorexigenic) signals in the hypothalamus.[6] In anorectic tumor-bearing rats, the paraventricular concentration of serotonin was increased.[7] However, in a mouse cachexia model showing mild anorexia, hypothalamic NPY mRNA was significantly raised, suggesting that suppression of hunger might be due to tumor products that inhibit NPY transport or release or that interfere with neuronal targets downstream of NPY.[8]

In humans, cancer anorexia is not due to a dysfunction of leptin production.[9] The levels of leptin are dependent only on the total amount of adipose tissue present in the patient and decrease as adipose mass decreases. Also mean plasma ghrelin levels, a neuropeptide released from the stomach in response to fasting and which stimulates food intake, were found to be higher among cachectic than noncachectic patients,[10] suggesting that this is not involved in the anorexia.

Of the cytokines, most studies show elevations of IL-6, IL-8, and IL-10 but not TNF-α, IL-1β, IFN-γ, or ciliary neurotrophic factor in the serum of cachectic cancer patients.[11–13] IL-6 levels are independently associated with levels of C-reactive protein, which in turn has been linked with survival.[11] Patients with IL-6 levels greater than 5.2 pg/mL or IL-10 levels greater than 9.8 pg/mL had significantly lower survival times than patients with lower levels.[12] Higher IL-6, IL-10, and IL-8 levels were also associated with poor performance status and/or weight loss. Some studies have shown that IL-6 levels increase gradually during the early stages of cachexia and then show a sudden steep rise just before death.[13] The systemic inflammatory response, as evidenced by increased serum C-reactive protein, has been shown to be an important factor in the progressive nutritional decline of patients with non-small-cell lung cancer and is a prognostic factor independent of stage, performance status, and treatment.[4]

Despite the association of anorexia with cachexia, no studies have been able to prove a cause-and-effect relationship. Rather, anorexia might be a separate phenomenon from the chronic wasting syndrome, although it might contribute to the loss of fat mass. Pair feeding experiments in animals have shown that this did not lead to either the same extent of weight loss or the metabolic abnormalities that are found in tumor-bearing animals. Thus, the changes in cachexia resemble those found in infection and injury rather than those found in starvation. Thus, in starvation, adipose tissue is lost preferentially to lean body mass, while in cachexia both are lost to a comparable extent. Also in starvation, when adipose stores are depleted, both skeletal muscle and visceral proteins are lost to an equal extent, while in cachexia, there is a selective loss of skeletal muscle mass. It is not possible to reverse this loss of skeletal muscle mass by nutritional supplementation or by drug-induced appetite stimulation, although such treatments do lead to some repletion of the adipose mass. This suggests that tumor factors or host factors induced by the tumor might lead to loss of adipose tissue and skeletal muscle mass in cachexia.

CHANGES IN HOST TISSUES IN CACHEXIA

Adipose Tissue

Adipose tissue is the main source of energy for the body, and its loss could reflect an increase in resting energy expenditure. However, resting energy expenditure can be unchanged, increased, or decreased in relation to the predicted energy expenditure.[2] In patients with pancreatic cancer, when resting energy expenditure was increased in comparison with the predicted values for healthy individuals, both total energy expenditure and physical activity level were reduced,[14] as might be expected in malnourished subjects. Levels of mRNA for the uncoupling protein 3 (UCP-3) have been shown to be significantly higher in muscle of cancer patients compared with controls and with cancer patients who had not lost weight; this increased level could increase energy expenditure and thus contribute to weight loss.[15] Studies in both animals and humans support a role for UCP-3 in energy balance and lipid metabolism. Transgenic mice that overexpress UCP-3 in skeletal muscle are hyperphagic but weigh less than wild-type littermates, and there is a large reduction in adipose tissue mass.[16] Although UCP-1, found only in brown adipose tissue (BAT), is considered to be the principal UCP involved in decreasing the level of coupling of respiration to ADP phosphorylation, the low level of BAT in adult humans could mean that UCP-3 in muscle is of major importance.

Factors Involved in Loss of Adipose Tissue in Cachexia

Zinc α_2-Gylcoprotein

One of the principal mechanisms by which lipid is lost from adipose tissue in cachexia is through an increased lipolysis, and the UCPs might serve to utilize the excess lipid that is mobilized. Zinc α_2-glycoprotein (ZAG), a 43-kd glycoprotein, is overexpressed in cachexia-inducing tumors and acts as a lipid-mobilizing factor that stimulates lipolysis in adipocytes.[17] ZAG binds to the β_3-adenoreceptor and stimulates lipolysis through a cyclic AMP–dependent mechanism.[18] Administration of ZAG to mice caused a time-dependent decrease of body mass that was attributed entirely to a loss of body fat without an effect on food and water intake.[18] There was an increased expression of UCP-1 in BAT, which probably contributed to the loss of adipose tissue. Both the glucose utilization rate and the rate of lipid oxidation were increased by ZAG lipid-mobilizing factor, suggesting that it increased energy utilization.[19] Although ZAG was originally thought to be produced by the tumor, further studies[17] showed that it was expressed in both white adipose tissue (WAT) and BAT, suggesting that it was produced locally by adipocytes. Tumor-bearing mice with a 19% loss of body weight and a 61% loss of fat mass showed a tenfold increase in ZAG mRNA and protein in WAT and a threefold increase in ZAG mRNA and a 20-fold increase in protein in BAT. In contrast to ZAG, leptin mRNA was suppressed 33-fold, while the adiponectin mRNA level was unchanged. ZAG expression in both WAT and BAT has been shown to be induced by glucocorticoids,[20] suggesting a relationship between the elevated cortisol levels in cachectic cancer patients and induction of ZAG.

Cytokines

Cytokines such as TNF-α, IL-6, and IFN-γ are also capable of reducing adipose tissue mass. The primary mechanism is thought to be suppression of the clearing enzyme lipoprotein lipase (LPL), although there is evidence that TNF-α can directly induce lipolysis.[21] LPL is a rate-limiting enzyme that is responsible for the hydrolysis of circulating triglyceride-rich lipoproteins, such as chylomicrons and very low-density lipoproteins. It is bound to the luminal surface of capillary endothelium in adipose tissue and muscle, and the fatty acids that are generated are utilized by adipose tissue for the synthesis of triglycerides. Thus, inhibition of LPL would deplete adipose tissue of the basic building blocks for lipid synthesis required to maintain levels in the presence of lipolysis. In addition to the cytokines, there are still unidentified factors that can inhibit LPL, since a study of five human cancer cell lines that induced cachexia in nude mice showed that they exhibited LPL-inhibitory activity, which was not due to any of the known cytokines.[22] An unknown lipid mobilizing factor of molecular weight less than 1 kd and stable to heat was also identified. The induction of lipolysis by TNF-α requires prolonged incubation (12 to 24 hours), and although the mechanism involves cyclic AMP, as with ZAG,[18] this is through stimulation of mitogen-activated protein kinase and extracellular signal-regulated kinase rather than through stimulation of adenylate cyclase.[21] As with ZAG, TNF-α induces increased expression of UCPs, which can metabolize released fatty acids.

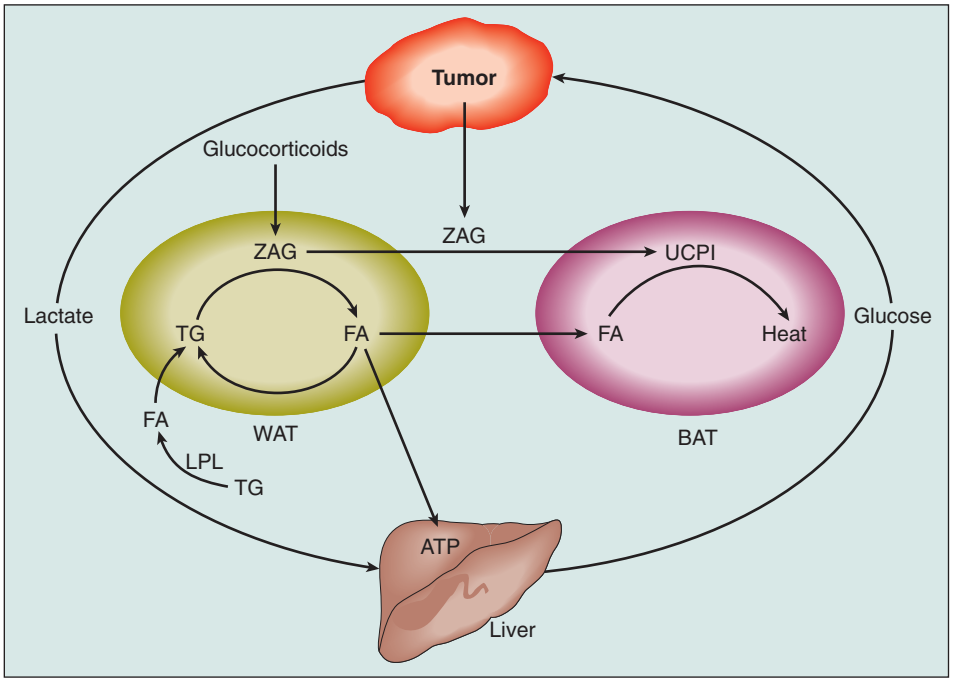


Figure 38-1 • Breakdown of adipose tissue and energy utilization in cachectic cancer patients. BAT, brown adipose tissue; FA, fatty acid; TG, triglyceride; WAT, white adipose tissue.

Futile Energy Cycles

Futile energy cycles also contribute to energy loss in cancer patients. One of the most important of these is the Cori cycle, which might account for an additional loss of energy of 300 kcal/day.[23] The Cori cycle involves utilization of the carbon skeleton of lactate to form glucose in the liver. Tumors consume large amounts of glucose and convert it to lactate, not because of mitochondrial dysfunction but because the oxygen tension is too low for the Krebs cycle and mitochondrial oxidative phosphorylation to operate. Thus, in effect, the liver consumes energy to convert lactate into glucose, which is converted back to lactate again by the tumor. In addition, in mice bearing a cachexia-inducing tumor, the triacylglycerol fatty acid substrate cycle is increased.[24] In this process, a high proportion of nonesterified fatty acids released from adipose tissue are immediately reesterified into triacylglycerol. The reason for the increased operation of this cycle is not known but could be related to a high rate of release of fatty acids combined with a low utilization rate. The interrelationship between tumor and host factors in WAT and BAT and energy-utilizing cycles such as the Cori cycle is shown in Figure 38-1.

Skeletal Muscle

Loss of muscle mass in cachexia leads to muscle weakness (asthenia), reduced respiratory function, and reduced immunity and is probably the most important factor contributing to the shortened survival time. Muscle atrophy is characterized by a decrease in protein content, fiber diameter, force production, and fatigue resistance. About half of the total muscle protein is myofibrillar protein, which is lost at a faster rate than other proteins during atrophy. Not all myofibrillar proteins are lost at the same rate. Thus, of the core myofibrillar proteins, there is selective loss of myosin heavy chain during muscle atrophy, while losses of actin, troponin, and tropomyosin remain constant.[25] Depending on the initiating signal, loss of myosin heavy chain can occur through an RNA-dependent or a proteasome-dependent process. A change in muscle myosin isoform expression has also been reported,[26] with a decrease in type I and an increase in type II (fast) isoform expression.

Muscle atrophy in cachexia is due to a depression in protein synthesis together with an increased rate of protein degradation. The depression of protein synthesis is due to a reduction in both RNA content and RNA activity, that is, the amount of protein synthesized per unit weight of RNA per hour. It has also been suggested that the balance of amino acids might not be correct for muscle protein synthesis because of the synthesis of acute phase proteins, which contain relatively high levels of sulfur amino acids. However, the situation must be more complicated than this, since nutritional supplementation alone is unable to reverse the muscle atrophy. This has been attributed to the high rate of protein degradation through an increased expression and activity of the ubiquitin-proteasome proteolytic pathway.[27,28] Protein substrates are marked for degradation by the attachment of a polyubiquitin chain by a series of enzymes: E1's ubiquitin-activating enzyme, E2's ubiquitin-conjugating enzymes, and E3's ubiquitin-protein ligases. Two muscle-specific E3s, MuRF1 and atrogin-1/MAFbx, have been identified[29,30] and are thought to act as critical components in muscle atrophy in cachexia. Protein degradation occurs in the 26S proteasome, a multisubunit proteolytic complex consisting of a central catalytic core (20S proteasome) and two terminal regulatory complexes (19S and 11S). The 19S regulatory complex plays a central role in the recognition and degradation of proteins by recruiting proteasomal substrates utilizing polyubiquitin chains and chaperone-like binding activities and by opening the access to the core of the 20S proteasome to promote degradation. The expression of mRNA for USP19, a 50-kd deubiquiting enzyme, was shown to be increased in skeletal muscle in a number of catabolic conditions, including cancer cachexia.[31] This suggests that it might play a role in the regeneration of free ubiquitin and might also be involved in post-translational processing of polyubiquitin.

The proteasome does not degrade intact myofibrils. Degradation of Z-band associated proteins, in particular titin and alpha-actinin, and release of myosin and actin from the myofibrils is mediated by the calcium-dependent enzyme calpain, which has been shown to be elevated in both skeletal muscle and heart during cancer cachexia in mice.[32] A diagram illustrating the factors involved in the degradation of myofibrillar proteins is shown in Figure 38-2.

The end-product of the ubiquitin-proteasome proteolytic pathway is oligopeptides, and these are degraded by the extralysomal peptidase tripeptidyl-peptidase II, together with various aminopeptidases, to form tripeptides and amino acids. In mice bearing a cachexia-inducing tumor, both proteasome proteolytic activity and tripeptidyl-

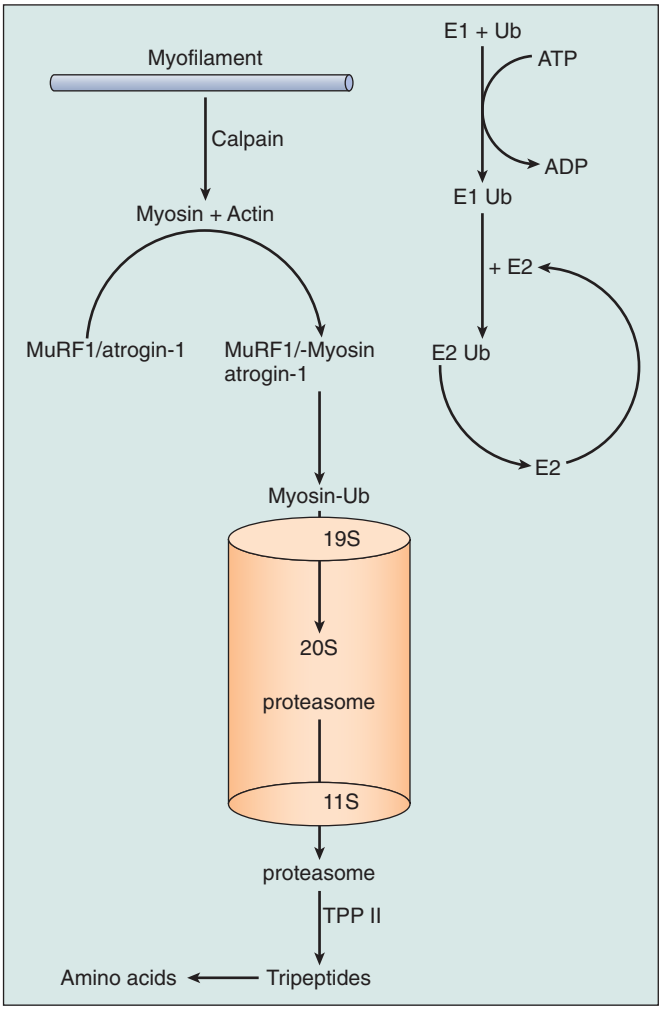


Figure 38-2 • Steps in the breakdown of myofibrillar proteins.

peptidase II activity were found to increase in parallel with increasing weight loss, suggesting that both activities are regulated in a parallel manner.[33]

Factors Involved in Loss of Skeletal Muscle in Cachexia

Proteolysis-Inducing Factor

Proteolysis-inducing factor (PIF) is a 24-kd sulfated glycoprotein produced by both primary and metastatic cachexia-inducing tumors, which induces muscle atrophy through a depression of protein synthesis and an increase in protein degradation. PIF acts both in vitro and in vivo to upregulate expression of both the mRNA and protein of the principal components of the ubiquitin-proteasome pathway including ubiquitin, E2, and proteasome subunits.[34] PIF also induces an increase in activity of tripeptidyl-peptidase II in parallel with the increase in proteasome activity.[33] The mechanism for induction of the ubiquitin-proteasome pathway by PIF involves activation of the transcription factor nuclear factor-κB (NF-κB), and inhibitors of this process, such as resveratrol, attenuated protein degradation induced by PIF in vitro, and muscle protein loss in mice bearing a cachexia-inducing tumor.[35] PIF also induces an increase in apoptosis in muscle cells in vitro,[36] although the importance of this in human cancer has been questioned for patients with a weight loss of less than 10%.[37] However, muscle loss is very small in patients with this degree of weight loss. In rabbits bearing the cachexia-inducing VX-2 tumor, the apoptotic index in skeletal muscle reached 54% to 56% when the loss of lean body mass reached 18%.[38] This suggests that further studies are required in humans at higher levels of weight loss.

Angiotensin II

The vasoconstrictor angiotensin II (Ang II) has also been shown to influence muscle mass by decreasing protein synthesis[39] and increasing protein degradation.[40] The latter effect occurs through the Ang II type 2 (AT_2) receptor by inducing an increased activity and expression of the ubiquitin-proteasome pathway. Like PIF, Ang II is capable of acting directly in vitro as well as in vivo, and as with PIF, induction of the ubiquitin-proteasome pathway occurs through the transcription factor NF-κB.[40]

Cytokines

TNF-α. TNF-α also inhibits protein synthesis and increases protein degradation in muscle, although most studies report that it is inactive when used alone in vitro but that its activity is enhanced when it is used with another cytokine, such as IFN-γ.[25] The induction of protein degradation by TNF-α is due to an increased expression of the ubiquitin-proteasome pathway. In rats bearing the Yoshida AH-130 ascites hepatoma, in which TNF-α plays a pivotal role in the pathogenesis of muscle wasting, treatment with pentoxyfilline, an inhibitor of TNF-α synthesis, prevented the depletion of muscle mass and significantly reduced the activity of both ATP-ubiquitin and the calpain-dependent proteolytic pathways.[41] As with PIF and Ang II, activation of NF-κB is important in the degradation of muscle proteins by TNF-α.[42] Activation of NF-κB by TNF-α in differentiating mouse myocytes has also been shown to inhibit their differentiation, by suppressing production of MyoD mRNA at the post-transcriptional level.[43] MyoD is a transcription factor that is essential for differentiation of skeletal muscle, as well as for repair of damaged tissue, and it may be important for replenishing atrophied muscle. These results suggest that TNF-α has the potential to induce muscle atrophy, although, as was previously discussed, most studies[11–13] have been unable to show elevations in the level of TNF-α in the serum of cachectic cancer patients. While the short half-life of biologically active TNF-α and formation of complexes with its soluble receptor contribute to the lack of detection, this does not explain why it can be detected in other wasting syndromes, such as cardiac cachexia.[44]

IL-6. Of the cytokines, IL-6 is the most closely correlated with the development of cachexia in cancer patients,[11–13] and has been shown to be independently associated with levels of C-reactive protein as a measure of the acute phase response.[11] IL-6 is thought to be the prime regulator of acute phase protein production in human hepatocytes, which has been correlated with a shorter survival time of cancer patients.[45] This possibly explains why IL-6 levels rise sharply before death.[13] In addition to induction by cytokines, IL-6 production in human hepatocytes is induced by PIF, through activation of the transcription factors NF-κB and STAT3.[46] Some human pancreatic tumors also produce IL-6.[47]

Despite the correlation of serum IL-6 levels with the development of cachexia there are doubts about whether it plays a direct regulatory role in muscle protein degradation.[48] Thus, IL-6 did not affect the rate of protein degradation in vitro in rat muscle preparations, and although it induced an acute phase response in mice, it did not induce cachexia and had no effect on the expression of ubiquitin transcripts in muscle. This suggests either that IL-6 is a marker of the cachexia process or that it acts in concert with known or unknown factors to induce muscle atrophy.

IL-8/IL-1β. While serum levels of IL-1β were not significantly elevated in patients with pancreatic carcinoma, levels of IL-8 were

significantly elevated and were correlated with weight loss.[12] Several studies have failed to demonstrate an effect on IL-1β on muscle protein breakdown in vitro, while the IL-1 receptor antagonist had no effect on protein hypercatabolism in rats bearing a cachexia-inducing tumor.[48] There are no reports on the ability of IL-8 to induce protein degradation in muscle. However, IL-8 is a potent angiogenic factor and might play a role in tumor proliferation.

Dystrophin Glycoprotein Complex Dysfunction

Skeletal muscle wasting has been linked to a dysfunctional dystrophin glycoprotein complex, a membrane structure that is associated with muscular dystrophy.[49] Muscles from tumor-bearing mice with cachexia showed reduced levels of dystrophin and increased glycosylation on dystrophin glycoprotein complex proteins. Dystrophin glycoprotein complex dysfunction was shown to mediate the induction of the E3 ubiquitin ligase MuRF1. Carcinoma patients with marked weight loss had large reductions in dystrophin compared to weight-stable healthy controls. These results suggest a similarity between cachexia and muscle dystrophy.

PHARMACOLOGIC TREATMENT OF CACHEXIA

Established Agents

Progestins

Megestrol acetate (MA) and medroxyprogesterone acetate (MPA) are two synthetic progestins derived from 17α-hydroxyprogesterone that have received an extensive evaluation for the treatment of cachexia.[50] These agents are used in the treatment of hormone-dependent tumors, and it was during the evaluation of their antitumor activity that an increase of body weight and appetite was observed, independently of objective response. The mechanism of action of these agents may be related to their glucocorticoid activity. They might stimulate appetite via NPY in the ventromedial hypothalamus,[51] or they might act in part by downregulating the synthesis and release of proinflammatory cytokines.

Maltoni and colleagues[50] reviewed 15 randomized clinical trials of progestin therapy. Dosages ranged from 160 to 1600 mg/day for MA and from 300 to 1000 mg/day for MPA. The pooled odds ratio for weight gain was 2.66, indicating that patients who were treated with progestins had more than twice the probability of gaining weight than did patients who were treated with placebo. However, the pooled odds ratio for appetite was somewhat larger.[4,23] Body composition studies of patients who gain weight with both MA and MPA have shown that the vast majority of the gained weight was adipose tissue and water and that there was no significant effect on fat free mass. This probably explains why the studies showed no improvement in the quality of life.[50] The duration of treatment in the studies was very short, lasting from 1 to 12 weeks, which probably overcame some of the side effects of therapy, which were significantly greater than were observed in the control arm. The side effects of long-term treatment (>12 weeks) are principally hypertension and edema resulting from water retention, as well as thromboembolic events. In a study of elderly men treated with MA (800 mg/day), there was an antianabolic effect on muscle with a significant reduction in thigh muscle cross-sectional area despite a significant increase in body weight.[52] Thus, administration of MA might actually accentuate the loss of lean body mass in cachectic cancer patients. It is surprising, therefore, that MA and MPA are the only agents that are routinely used for the treatment of weight loss in cancer anorexia and cachexia.

Corticosteroids

These include dexamethasone, prednisolone, and methylprednisolone. They induce a temporary effect on symptoms such as appetite, food intake, sensation of well-being, and performance status but show no beneficial effect on body weight. They tend to be used in patients in the end stages of cancer in an attempt to improve the quality of life.

Agents Undergoing Clinical Evaluation

Omega-3 Fatty Acids

Cold water fish such as mackerel, sardines, and salmon contain an oil under their skin containing omega-3 polyunsaturated fatty acids, the major components being eicosapentaenoic acid (EPA:20:5:) and docosahexaenoic acid (DHA; 22:6, ω3). Of the two fatty acids, only EPA has been shown to be effective in attenuating weight loss in a murine cachexia model.[53] Muscle mass is preserved and protein degradation suppressed through inhibition of the ubiquitin-proteasome pathway. EPA has been shown to attenuate the induction of the ubiquitin-proteasome pathway by PIF in murine myotubes by preventing activation of NF-κB.[54]

While most of the clinical studies have been carried out with fish oil, two studies have been carried out with EPA either as free acid[55] or as the propane diol diester.[56] Patients with pancreatic cancer and a median rate of weight loss of 2 kg/month who were administered EPA (6 g/day) showed weight stabilization over the 12-week study period.[55] However, in a placebo-controlled randomized study with EPA ester (2 or 4 g daily), patients with advanced gastrointestinal or lung cancer and with a mean weight loss of 18% showed no statistically significant improvement in survival, weight, or other nutritional variables.[56] A further uncontrolled study of fish oil capsules (supplying 4.7 g EPA/day) in patients with advanced malignancy and weight loss showed weight stabilization over a 1.2-month period.[57] When fish oil was combined with an energy- and protein-dense nutritional supplement, initial studies showed that patients gained 2 kg over a 7-week period and that this represented lean body mass.[58] However, in a randomized double-blind trial, intention to treat group comparisons indicated that omega-3 fatty acids did not provide a therapeutic advantage, mainly because of problems with compliance.[59] Post hoc analysis, however, showed a net gain of weight and lean tissue and improved quality of life in patients with measured increases in plasma EPA. In addition, total energy expenditure and physical activity level increased.[14] The increased physical activity level might reflect an improved quality of life. Interestingly, in a further randomized study, although fewer patients taking the EPA supplement gained 10% or more of baseline weight over a 3-month period than did patients taking MA, the percentage of patients with appetite improvement was similar in the two groups.[60] This suggests that EPA could also be used as an appetite stimulant. Further studies are required to confirm the anticachectic activity of EPA.

Thalidomide

Thalidomide is being evaluated for the treatment of cancer cachexia owing to its ability to promote weight gain in HIV-infected patients. Thalidomide has been shown to block NF-κB regulated genes through suppression of IκB kinase activity.[61] A small study with 10 patients with nonobstructing and inoperable esophageal cancer showed thalidomide (200 mg daily) to increase both body weight (1.29 kg) and lean body mass (1.75 kg), while an isocaloric diet caused a loss of both body weight and lean body mass.[62] A further study in 50 patients with advanced pancreatic cancer who had lost at least 10% of their body weight substantiated these results.[63] Thus, after 4 weeks, patients receiving thalidomide (200 mg daily) had gained an average of 0.37 kg in body weight and 1 cm^3 in arm muscle mass compared with a weight loss of 2.2 kg and arm mass of 4.46 cm^3 in the placebo group. After 8 weeks, patients on thalidomide had lost 0.06 kg in weight and 0.5 cm^3 in arm mass, while the placebo group had lost 3.62 kg and 8.4 cm^3, respectively. These results suggest that thalidomide has the potential to attenuate muscle wasting in cachexia.

β-Hydroxy-β-methylbutyrate

β-Hydroxy-β-methylbutyrate (HMB) is a metabolite of leucine formed by transamination to α-ketoisocaproate in muscle, followed by oxidation of the α-ketoisocaproate in the cytosol of the liver and possibly other tissues. HMB has been shown to attenuate the loss of body weight and skeletal muscle mass in mice bearing a cachexia-inducing tumor by attenuating the increased expression of the ubiquitin-proteasome pathway.[64] HMB acts like EPA to attenuate PIF-induced signaling pathways in muscle, leading to an increased proteasome expression by preventing activation of NF-κB.[65] Only a single clinical study has been reported on the effect of HMB in cancer cachexia.[66] This showed that HMB (3 g/day) in combination with L-arginine (14 g/day) and L-glutamine (14 g/day) produced a 0.95 kg gain in body weight in 4 weeks, whereas control subjects lost 0.26 kg. This gain was the result of a significant increase in fat free mass, and this was maintained over a 24-week study period. Further studies are required to confirm the clinical efficacy of HMB.

Combination Treatment

Evidence has been presented to indicate that oxidative stress plays an important role in age-dependent skeletal muscle atrophy.[67] Since an increase in oxidative stress has been observed in cancer patients, Mantovani and colleagues[68] administered vitamins A, E, and C (antioxidants), polyphenols, omega-3 fatty acids, α-lipoic acid, carboxycysteine, MPA, and a selective COX-2 inhibitor, with or without anti-TNF-α antibodies, to 25 cachectic cancer patients. Over a 4-month period, body weight was significantly increased from 51.3 to 58.1 kg together with lean body mass, appetite, grip strength, and quality of life. It is not certain which components of the treatment were responsible for the beneficial effect, since some have not been tested individually, but combination of agents attacking various components of the cachexia syndrome might be the way forward for improved clinical treatment of cachectic cancer patients.

In addition to these treatments there are a number of experimental agents that require clinical investigation:

- Adenosine 5′-triphosphate[69]
- Cyclooxygenase inhibitors (COX-1 and COX-2)[70]
- Interleukin-4[71]
- Interleukin-15[72]
- Ghrelin[73]
- Reseveratrol[35]
- Antibodies to parathyroid hormone–related protein[74]
- Melanocortin-4-receptor antagonists[75]
- Lipoxygenase inhibitors[76]
- Erythropoietin[77]
- β_2-adrenergic receptor agonists (e.g., formoterol)[78]

SUMMARY

Progress in basic science has improved our understanding of the cellular mechanisms underlying tissue wasting in cachexia and has provided new molecular targets for therapeutic drug development. Further studies on tumor and host factors involved in the cachectic process, together with their cellular receptors, will aid in drug design and provide rational drug combinations for therapy. Attention in clinical trials is moving away from appetite and total body weight to measurements of lean body mass and physical functioning, which are important factors in maintaining the quality of life. This is not to say that anorexia is not an important factor that needs attention. Feeding is an important social interaction and something in which the family can help in the treatment of severely malnourished patients. Advances in our understanding of neuropeptides and their relationship to cancer anorexia will lead to new developments in this field, although few have received rigorous clinical evaluation.

Nutritional therapy could prove to be synergistic with other types of agents. Thus, inhibitors of the activation of NF-κB, such as EPA, HMB, and thalidomide, might be expected to attenuate muscle protein degradation but not improve protein synthesis. This is borne out by clinical trials, which show attenuation of the loss of muscle mass but no marked increase in size. Certain amino acids, principally the branched-chain amino acids, are known to stimulate protein synthesis at the translational level and might be expected to be synergistic with agents targeting muscle protein degradation.

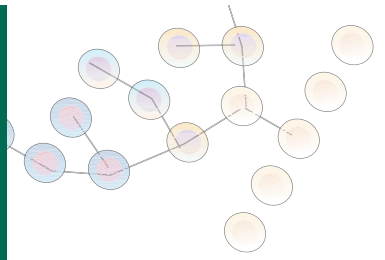
Cure of the cancer would of course abolish the need to treat cachexia. However, until this happens, there will be a need for palliative therapy to improve the quality of life of the cancer patient.

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39 Nausea and Vomiting

John D. Hainsworth

SUMMARY OF KEY POINTS

Incidence
- Most common chemotherapy-associated toxicities
- More frequent and severe with repetitive doses of chemotherapy
- Significant impact on quality of life and can influence patient compliance with treatment

Etiology of Complication
- Acute nausea and vomiting often mediated by activation of serotonin type 3 receptors in the gastrointestinal tract
- Mechanism of delayed nausea and vomiting (more than 24 hours after chemotherapy) unknown

Evaluation of the Patient
- Risk factors, including type of chemotherapy (drugs, doses, schedule), age, sex, and prior alcohol use, should be assessed before treatment.

Grading of Complication
- Episodes of vomiting should be recorded (number, duration, time to onset); severity of nausea can be graded using visual analog scale.

Treatment
- Optimal treatment provides complete control of acute nausea and vomiting in most patients receiving highly emetogenic chemotherapy regimens; only 15% of patients have severe nausea and vomiting.
- Treatment of delayed nausea and vomiting has recently improved with the introduction of aprepitant and palonosetron; however, as many as one-third of patients still experience this complication.

INTRODUCTION

Nausea and vomiting are common side effects associated with systemic chemotherapy, and are among the adverse effects most feared by patients.[1,2] Although these complications of treatment are usually self-limiting and seldom life-threatening, the deleterious effects on nutritional status and quality of life can be substantial. Many of the recently introduced targeted agents have less potential to produce nausea and vomiting. However, intensive combination chemotherapy continues to be the cornerstone of treatment for many types of cancer, ensuring that antiemetic therapy will continue to be an integral aspect of supportive care.

Antiemetic therapy has improved dramatically during the last 20 years. With optimum treatment, most patients receiving highly emetogenic chemotherapy do not experience any nausea or vomiting during the 24 hours after treatment.[3–11] However, delayed symptoms are more common and are often underestimated by treating physicians and nurses.[12] Accurate assessment of delayed nausea and emesis is essential in providing maximal intervention with recently available agents.

The identification of potent new antiemetics has been made possible by an improved understanding of the physiology of the emetic reflex. Critical assessment of the optimal use of new agents for patients receiving chemotherapy has been facilitated by the development of reproducible methods of assessing nausea and vomiting, and by the conduct of carefully designed, randomized clinical trials.

PHYSIOLOGY OF THE VOMITING REFLEX

The pioneering work of Borison and Wang[13] more than 40 years ago provided the basis for understanding the vomiting reflex. In studies using ablative techniques and electrical stimulation with microelectrodes (primarily in decerebrate cats), these investigators proposed the existence of two distinct sites in the brain stem believed to be critical for the control of emesis. The first of the sites, the so-called vomiting center, was thought to be located in the lateral reticular formation of the medulla. Electrical stimulation of this site triggered the vomiting reflex, whereas ablation prevented the vomiting induced by a variety of stimuli. The vomiting center was thought to be located adjacent to the other structures involved in the coordination of vomiting, including the respiratory, vasomotor, and salivary centers, and cranial nerves VIII and X. More recent studies have suggested that the "vomiting center" is actually not anatomically discrete but that the initiation of the vomiting reflex is controlled by a complex system of networks located in the nucleus tractus solitarius.[14,15] The networks in this area control complex patterns of motor activity such as the vomiting reflex and are more accurately described as "central pattern generators."

The second important center identified by Borison and Wang was the chemoreceptor trigger zone (CTZ), located in the area postrema at the ventral aspect of the fourth ventricle. This center, located outside the blood-brain barrier, is exposed to various noxious agents borne in the blood or cerebrospinal fluid. Although electrical stimulation of the CTZ does not produce vomiting, intimate connections to the vomiting center permit stimulation of this center after exposure to blood-borne toxins. Ablation of the CTZ abolishes vomiting induced by these agents.

Although these concepts have been retained and are integral to the current understanding of the vomiting reflex, several other important components have also been recognized. Input from the gastrointestinal tract, predominantly through afferent vagal fibers, is critical in initiating the vomiting reflex after ingestion of noxious

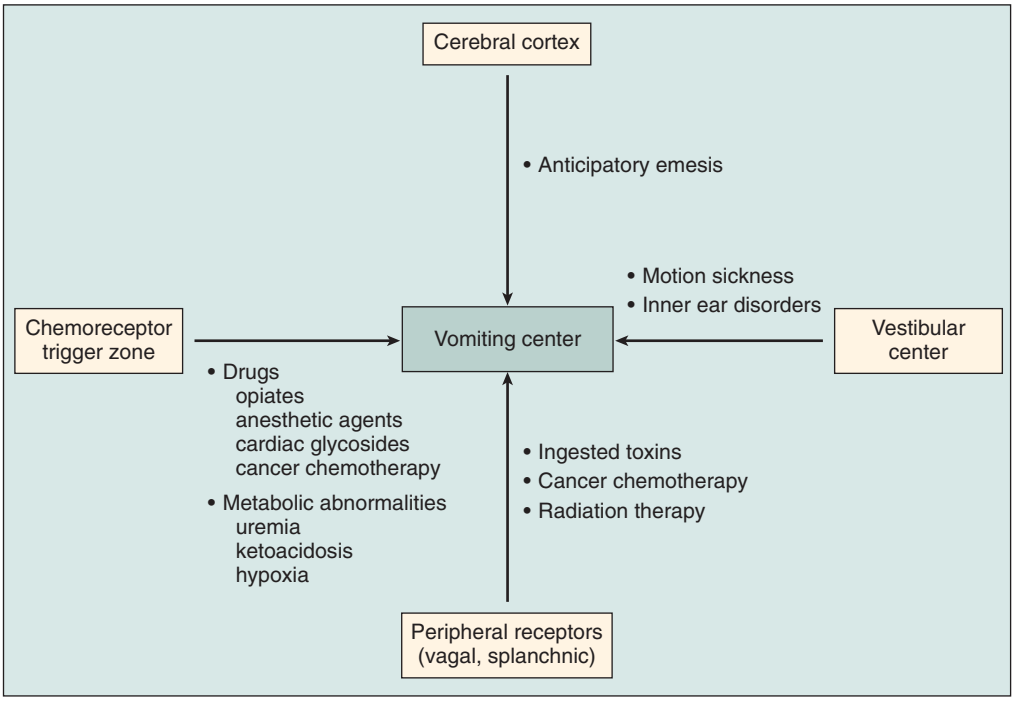


Figure 39-1 • Schematic diagram of the various pathways for initiation of the vomiting reflex. Clinical syndromes mediated by each mechanism are illustrated.

substances.[16] Incoming vagal afferents connect with the vomiting center directly; an intact CTZ is not essential when vomiting is initiated by this mechanism. It is now known that in addition to ingested substances, some blood-borne substances, including chemotherapeutic agents, can trigger the vomiting reflex through activation of the vagal afferent mechanism.

Two additional components of this complex system involve the vestibular apparatus and the higher brain stem and cortical structures. The vestibular system is involved primarily in initiating the vomiting reflex in motion sickness. Input from higher cortical centers seems to be critical in a variety of conditions, including anticipatory emesis seen for patients who have previously experienced chemotherapy-induced emesis. The various components of the vomiting reflex are illustrated diagrammatically in Figure 39-1, along with the clinical situations in which they are operative. Given the complexity of this system, it is not surprising that different pharmacologic approaches are necessary to control vomiting of different etiologies. Improved understanding of the neurochemistry of the emetic reflex has been important in developing antiemetics with new mechanisms of action. The initial focus of such investigation was the area postrema, where receptors for a large number of neuroactive agents have been identified.[17–19] Many of these neurotransmitters (e.g., dopamine, histamine, acetylcholine, norepinephrine, substance P) are in themselves emetogenic agents. The development of pharmacologic agents that block specific sets of receptors (e.g., dopamine, neurokinin-1) has resulted in the identification of valuable antiemetics, and it is likely that continued efforts in this area will be productive of additional valuable agents in the future.

In addition to neurotransmitters located in the CTZ, type 3 serotonin (5-hydroxytryptamine 3 or 5-HT3) receptors are present in large quantities on vagal and splanchnic afferents within the gastrointestinal tract.[20] These peripheral receptors are pivotal in the initiation of the acute nausea and vomiting caused by cisplatin and other strongly emetogenic chemotherapeutic agents; inhibition of this pathway by specific 5-HT3 receptor antagonists results in highly effective antiemetic therapy.[21]

CLINICAL FEATURES OF CHEMOTHERAPY-INDUCED EMESIS

Clinical Syndromes

Chemotherapy-induced nausea and vomiting can be subdivided into three distinct clinical syndromes, each having specific therapeutic implications. These syndromes and their clinical correlates are defined here; treatment approaches are considered later in the chapter. Because nausea and vomiting are common symptoms among patients with cancer, etiologies other than chemotherapy should also be considered. Among the diverse causes of nausea and vomiting among patients with cancer are intestinal obstruction, liver metastases, central nervous system involvement, and other medications (particularly narcotic analgesics). These etiologies should be considered especially when the time course or duration of nausea and vomiting is unusual for the known chemotherapy-induced syndromes.

Acute Nausea and Vomiting

Acute nausea and vomiting after the administration of chemotherapy occur within 24 hours after the chemotherapy dose. The nausea and vomiting during this phase are the most severe, hence the emphasis on therapeutic intervention during this phase. With most chemotherapeutic agents, acute nausea and vomiting begin 1 to 2 hours after intravenous administration. This delay in onset argues against a direct effect at the CTZ, which would be expected to produce emesis within minutes of intravenous drug administration. A peripherally mediated vomiting reflex, probably serotonin release from small intestinal mucosa, offers a better explanation of the delayed onset of emesis.[22] The onset of nausea and vomiting after the intravenous administration of cyclophosphamide is delayed even longer than with other agents, typically occurring 9 to 18 hours after administration of the drug.[23] The mechanism of cyclophosphamide-induced nausea and vomiting is unclear; the difference in the time of onset suggests that the mechanism might differ from that of other agents.

Delayed Nausea and Vomiting

Delayed nausea and vomiting occur 24 or more hours after chemotherapy administration. Although the severity is decreased in comparison with acute nausea and vomiting, the course can be more protracted, resulting in significant difficulties with hydration, nutrition, and performance status. Delayed emesis is most severe and frequent after administration of high-dose cisplatin; most patients treated with this drug experience some degree of delayed emesis, with onset most frequently 24 to 72 hours after chemotherapy.[24] In some patients onset can occur as late as 4 to 5 days after treatment, persisting for several days. Patients who have poor control of acute nausea and vomiting are more likely to experience delayed nausea and vomiting as well; however, delayed emesis can occur among patients who have complete emetic control during the first 24 hours after administration of chemotherapy.

The pathophysiology of delayed emesis remains unclear, but it seems likely that this syndrome is mediated centrally by different neurotransmitters. 5-HT3 receptor antagonists, which are highly effective in the prevention of acute emesis, have less activity in the treatment of delayed emesis. Conversely, the neurokinin-1 (NK-1) receptor antagonists, which block the action of substance P, have consistently shown activity against delayed emesis. Peripheral factors, including residual metabolites of chemotherapeutic agents or gastrointestinal mucosal damage, might also play a role.

Anticipatory Nausea and Vomiting

Anticipatory nausea and vomiting often occur among patients who have experienced poor control of emesis during previous courses of chemotherapy.[25] The onset can occur before or during chemotherapy administration. Because this is a conditioned response, certain associations with chemotherapy administration, such as the hospital environment or the oncologist's office, might trigger the onset of emesis.

Prognostic Factors

Multiple clinical factors that are important in determining the incidence and severity of chemotherapy-induced nausea and vomiting have been identified. These factors include the type of chemotherapy administered, certain patient characteristics, and the antiemetic regimen employed (Table 39-1).

Table 39-1 Determinants of Chemotherapy-Induced Nausea and Vomiting

CHEMOTHERAPY
Emetic potential of drug(s) used
Dose
Schedule of administration
Route of administration
PATIENT CHARACTERISTICS
Age
Gender
Alcohol use
Emesis control during prior chemotherapy
ANTIEMETICS
Dose
Schedule
Combination regimens
Route of administration

Chemotherapeutic Agents

The commonly used chemotherapeutic drugs are separated into five groups according to emetic potential in Table 39-2. Drugs in category 5 produce emesis in greater than 90% of patients, whereas drugs in category 1 produce emesis in fewer than 10%. The drugs that cause emesis most frequently also cause the most severe emesis. Emesis is most severe during the first 8 hours after onset, but with strongly emetogenic drugs patients are often ill throughout the 24-hour period after administration.

In general, the potential for acute nausea and vomiting increases with the dose of chemotherapy. Schedule of administration is also important with certain agents: Large intravenous bolus doses, or doses administered intravenously over a short period of time, are more likely to cause emesis than are smaller divided doses or continuous infusion.

The use of chemotherapeutic agents in combination increases the emetogenic potential of a treatment regimen. On the basis of the information in Table 39-2, Hesketh and colleagues[26] have proposed a model for predicting the emetogenic potential of a combination regimen (Table 39-3). As new combination regimens are introduced into clinical practice, application of this algorithm can result in optimum, cost-effective antiemetic therapy.

Patient Characteristics

Several patient characteristics are important predictors of the development and severity of acute chemotherapy-induced nausea and vomiting. These are age, gender, history of alcohol intake, and history of previous chemotherapy.

AGE. Data are conflicting regarding the effect of patient age on the severity of chemotherapy-induced nausea and vomiting. However, increasing evidence indicates that chemotherapy-induced emesis occurs more frequently in younger patients.[21,22] Fortunately, the best current antiemetic agents are effective and well tolerated by patients of all ages.

GENDER. Data from large prospective studies indicate that females have more severe and frequent chemotherapy-induced nausea and vomiting than males, even after controlling for chemotherapy regimen. In one study all patients received cisplatin-containing regimens and were treated with ondansetron; more women receiving high-dose cisplatin with either 5-fluorouracil or etoposide for lung cancer or head and neck carcinomas had poor control of emesis than did men receiving these same regimens (49% vs. 29%, respectively).[27]

HISTORY OF ALCOHOL INTAKE. Patients with a history of chronic alcohol intake (four to five mixed drinks per day) have more effective control of chemotherapy-induced nausea and vomiting when optimal antiemetics are used.[28,29] In a prospective study of 52 patients receiving high-dose cisplatin along with combination antiemetic therapy, 93% of those with a high alcohol intake experienced no emesis, as opposed to 61% of patients without this history.[28] It is important to emphasize, however, that the administration of highly emetogenic chemotherapy to these patients, in the absence of appropriate antiemetic therapy, still results in a high incidence of severe acute nausea and vomiting. The mechanism of the alcohol effect is unclear; it is possible, however, that various receptor sites are less sensitive among patients with a history of alcohol intake and that blockade of these receptors is relatively easy with appropriate antiemetics.

PREVIOUS CHEMOTHERAPY. Patients who have experienced poor control of emesis during previous chemotherapy are more likely to have unsatisfactory results with subsequent antiemetics.[27] The development of an anticipatory component to the nausea and

Table 39-2 Acute Nausea and Vomiting without Prophylactic Treatment with Commonly Used Chemotherapeutic Agents

Level	Frequency of Emesis (%)	Agent
5	>90	Carmustine >250 mg/m^2
		Cisplatin ≥50 mg/m^2
		Cyclophosphamide >1500 mg/m^2
		Dacarbazine
		Mechlorethamine
		Streptozocin
4	60–90	Carboplatin
		Carmustine ≤250 mg/m^2
		Cisplatin <50 mg/m^2
		Cyclophosphamide >750 mg/m^2 ≤1500 mg/m^2
		Cytarabine >1 g/m^2
		Doxorubicin >60 mg/m^2
		Epirubicin >90 mg/m^2
		Melphalan >50 mg/m^2
		Methotrexate >1000 mg/m^2
		Procarbazine (oral)
3	30–60	Arsenic trioxide
		Cyclophosphamide ≤750 mg/m^2
		Cyclophosphamide (PO)
		Doxorubicin 20–60 mg/m^2
		Epirubicin ≤90 mg/ m^2
		Hexamethylmelamine (PO)
		Idarubicin
		Ifosfamide
		Irinotecan
		Lomustine
		Methotrexate 250–1000 mg/m^2
		Mitoxantrone
		Oxaliplatin >75 mg/m^2
2	10–30	Cytarabine 100–200 mg/m^2
		Capecitabine
		Cetuximab
		Docetaxel
		Doxorubicin (liposomal)
		Etoposide
2 *(con't)*	10–30 *(con't)*	5-Fluorouracil <1000 mg/m^2
		Gemcitabine
		^{90}Y ibritumomab tiuxetan
		Methotrexate >50 mg/m^2 <250 mg/m^2
		Mitomycin
		Paclitaxel
		Panitumomab
		Sorafenib
		Sunitinib
		Temozolomide
		Topotecan
		Tositumomab/iodine-131 tositumomab
1	<10	Alemtuzumab
		Asparaginase
		Bevacizumab
		Bleomycin
		Bortezomib
		Chlorambucil (PO)
		Cladribine
		Denileukin diftitox
		Erlotinib
		Fludarabine
		Gemtuzumab ozogamicin
		Hydroxyurea
		Imitanib
		Melphalan (low dose, oral dosing)
		Methotrexate ≤50 mg/m^2
		Pentostatin
		Rituximab
		Thioguanine (PO)
		Trastuzumab
		Vinblastine
		Vincristine
		Vinorelbine

Adapted from Hesketh PJ, Kris MG, Grunberg SM: Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103–109.

vomiting is certainly one influence; whether additional influences are also involved is unknown.

Conduct and Interpretation of Clinical Antiemetic Trials

Because multiple patient characteristics and chemotherapy variables influence the incidence and severity of chemotherapy-associated nausea and vomiting, optimal design and interpretation of clinical trials with new antiemetics or new combination regimens requires that these factors be taken into account. Definitive demonstration of the superiority of an agent or regimen requires a large, randomized trial in which the comparison groups are matched with respect to the various patient characteristics and chemotherapy received. Patients should be receiving their initial dose of chemotherapy, so as to avoid the confounding effects of anticipatory emesis. Crossover trials are also difficult to interpret for this reason. Optimally, the treatment received should be double-blinded to avoid investigator or patient bias. Because effective regimens now exist for all subgroups of patients, new treatments should be compared with existing treatments; the inclusion of a "no-treatment" or placebo arm in a randomized trial is inappropriate. The completion of this type of large controlled randomized trial has hastened the improvement of antiemetic therapy and the rapid incorporation of new treatments into clinical practice.

Table 39-3 Formula for Estimation of Emetogenic Potential of Combination Chemotherapy Regimens

- Use Table 39-2 to assign emetic level to each agent in the regimen.
- Identify most emetogenic agent.
- When considering the other components of the regimen, use the following rules:

  Level 1 agents do not contribute to emetogenicity.

  Adding level 3 or 4 agents increases emetogenicity by one level per agent.

  Adding level 2 agents (regardless of number) increases emetogenicity by one level greater than the most emetogenic agent.

EXAMPLES OF ALGORITHM USE

Regimen	Emetogenic Level of Agents in Regimen	Emetogenic Level of Regimen
CMF	3 + 2 + 1	4
CAF	3 + 3 + 2	5
Paclitaxel/ carboplatin	2 + 4	5
CVP	3 + 1 + 1	3

A, doxorubicin; C, cyclophosphamide; F, 5-fluorouracil; M, methotrexate; P, prednisone; V, vincristine.

Adapted from Hesketh PJ, Kris MG, Grunberg SM: Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103.

When interpreting the results of antiemetic trials, special attention should also be given to the definitions of therapeutic response and the methods used to assess efficacy. Most trials measure the number of emetic episodes as the primary efficacy parameter, because this is an objective measurement. Some trials also measure various secondary efficacy parameters, including nausea, food intake, and overall patient satisfaction with treatment. Even when emesis is used to measure efficacy, comparisons between trials must be made with caution, as definitions of response have varied also. "Complete response," in various studies, has been defined as "no vomiting," "no vomiting and only mild nausea," or "no vomiting and no nausea" during the 24 hours after chemotherapy. Clearly, response rates can vary substantially, depending on the definition used. Standardization of response assessment would greatly aid in the interpretation of future trials.

TREATMENT OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Acute Nausea and Vomiting

Several families of drugs with antiemetic activities have been identified. Table 39-4 lists the classes of antiemetic agents in current use, in approximate order of antiemetic potency. Only the 5-HT3 receptor antagonists, the substituted benzamides, and the new class of NK-1 receptor antagonists show marked activity against highly emetogenic chemotherapy. Because no single agent is ideal, combination antiemetic regimens have been developed, which have further improved efficacy. Increased understanding of the mechanism of action of the various compounds has led to more rational development of combination regimens; in general, the most effective regimens use agents with different mechanisms of action.

5-HT3 Receptor Antagonists

The selective 5-HT3 receptor antagonists are the most effective family of antiemetics in the treatment of acute emesis. These agents block the serotonin type 3 receptors and are thought to exert their antiemetic activity primarily through peripheral blockade in the small intestine (see the preceding discussion). Before 2003, three agents in this class were available in the United States: ondansetron, granisetron, and dolasetron. All three of these drugs proved superior to high-dose metoclopramide (the previous standard) in the prophylaxis

Table 39-4 Antiemetic Agents: Recommended Dosing

Antiemetic Agent	Recommended Dose: Acute Emesis	Recommended Dose: Delayed Emesis
5-HT3 Antagonists		
Ondansetron	0.15 mg/kg or 8 mg IV; 12–16 mg PO	8 mg PO bid × 2–3 days
Granisetron	1 mg IV or PO	
Dolasetron	1.8 mg/kg or 100 mg IV; 100–200 mg PO	
Palonosetron	0.25 mg IV	
Neurokinin-1 antagonists		
Aprepitant		125 mg PO (or 115 mg IV) day 1, then 80 mg days 2, 3
Corticosteroids		
Dexamethasone	8 mg IV or PO	4–8 mg PO bid days 2–4
Dopamine antagonists		
Metoclopramide	2–3 mg IV prechemotherapy, repeat 2 hr after chemotherapy	20–40 mg PO qid days 2–5
Prochlorperazine	10 mg PO or IV every 3–4 hrs as needed	
Haloperidol	1–3 mg IV or PO every 2–6 hrs as needed	
Benzodiazepines		
Lorazepam	1–2 mg IV every 4 hrs as needed	
Cannabinoids		
Dronabinol	5–10 mg PO every 3–4 hrs as needed	

of cisplatin-induced emesis,[30–35] and all were superior to standard agents when used to prevent emesis associated with cyclophosphamide-based regimens.[36–38] Dose-ranging studies with all drugs demonstrated an efficacy plateau,[39–41] and multiple large randomized trials comparing these agents to one another showed equivalent efficacy.[3–11] For patients receiving high-dose cisplatin therapy, use of appropriate doses of any one of these three agents results in complete control of emesis in 50% to 70% of patients during the first 24 hours after administration of chemotherapy. Complete control of emesis ranges from 70% to 80% among patients receiving moderately emetogenic regimens, usually cyclophosphamide based (Box 39-1).

In July 2003 a new 5-HT3 receptor antagonist, palonosetron, was approved by the U.S. Food and Drug Administration for the prophylaxis of acute and delayed chemotherapy-induced nausea and vomiting. Compared with other 5-HT3 receptor antagonists, palonosetron has a higher receptor binding affinity and a longer half-life (approximately 40 hours). In two phase III randomized clinical trials palonosetron provided superior control of acute and delayed nausea and vomiting when compared with either ondansetron or dolasetron.[42,43] Both trials contained patients receiving moderately emetogenic chemotherapy, and most patients did not receive concurrent dexamethasone.

The adverse events produced by all available 5-HT3 receptor antagonists are essentially identical. Mild to moderate headache is the most frequently observed toxicity and is produced by all three drugs in approximately 20% to 30% of patients. Other adverse events, including constipation and diarrhea, are mild and uncommon.

Recommended intravenous and oral doses of the 5-HT3 receptor antagonist and other antiemetics are outlined in Table 39-4. For prophylaxis of acute nausea and vomiting, a single dose during the first 24 hours is as effective as multiple doses. Therefore, the use of additional doses of these agents for "breakthrough" vomiting during this time is to be discouraged, and the writing of "as needed" orders for these agents should be avoided. Oral preparations are available for all 5-HT3 receptor antagonists except palonosetron and have shown equivalent efficacy.[44–46]

Box 39-1. MANAGEMENT APPROACH

Chemotherapy-Induced Nausea and Vomiting

Antiemetic therapy for acute chemotherapy-induced nausea and vomiting should be based on the emetic potential of the chemotherapy regimen being used and should take into account individual patient risk factors (e.g., sex, age, history of alcohol use, previous emesis with chemotherapy). Excellent algorithms for the prediction of the likelihood of emesis with single chemotherapeutic agents or combination regimens have been developed.

For optimal control of acute nausea and vomiting, patients receiving chemotherapy with moderate or high emetogenic potential should receive prophylaxis with a 5-HT3 receptor antagonist plus dexamethasone. Palonosetron may offer modest advantage over other 5-HT3 receptor antagonists, particularly in patients receiving highly emetogenic regimens.

Patients receiving mildly emetogenic therapy should receive dexamethasone (8 mg intravenously or orally); a 5-HT3 receptor antagonist should be added with subsequent courses only if antiemetic control is inadequate. Patients with breakthrough nausea and vomiting should receive either prochlorperazine (10 mg orally or intravenously) or lorazepam (1 mg intravenously every 4 hours). Additional doses of 5-HT3 receptor antagonists or dexamethasone during the first 24 hours are usually ineffective.

Delayed nausea and vomiting occurs more than 24 hours after chemotherapy is administered and should be anticipated among patients receiving highly emetogenic regimens (particularly cisplatin or cyclophosphamide). These patients should routinely receive prophylaxis: aprepitant should be added to the antiemetic regimen, and palonosetron is the 5-HT3 receptor antagonist of choice.

Neurokinin-1 Receptor Antagonists

The NK-1 receptor is a component of the centrally mediated vomiting reflex that mediates the emetogenic action of substance P, a tachykinin contained in vagal afferents innervating the area postrema and nucleus tractus solitarii in the brain stem.[19] Several selective NK-1 receptor antagonists have shown antiemetic activity,[47,48] and one of these, aprepitant, is currently approved by the Food and Drug Administration for the prevention of acute and delayed chemotherapy-induced nausea and vomiting.[49–52] The most substantial contribution of this drug has been in the management of delayed emesis following moderately or highly emetogenic chemotherapy. In the pivotal randomized phase III study, patients treated with high-dose cisplatin received prophylaxis with either granisetron/dexamethasone or granisetron/dexamethasone plus aprepitant.[49] Patients who received aprepitant more frequently had no vomiting during the first 24 hours (93% vs. 67%; $P < 0.001$) and also during days 2 through 5 (82% vs. 33%; $P < 0.001$). Similar results have subsequently been obtained in patients receiving cyclophosphamide-containing regimens.[52] Side effects with aprepitant are mild and infrequent, and include fatigue, constipation, hiccoughs, and headache.

Substituted Benzamides

High-dose metoclopramide was the first drug to demonstrate substantial antiemetic activity among patients treated with high doses of cisplatin.[53] The mechanism of action was initially attributed to dopamine receptor antagonism. However, high-dose metoclopramide also inhibits the 5-HT3 receptors, probably a more important mechanism.[54] Today, high-dose metoclopramide is rarely used, as a result of the higher efficacy and lower toxicity of the selective 5-HT3 receptor antagonists.

The major side effects associated with high-dose metoclopramide are extrapyramidal reactions caused by dopamine receptor antagonism.[53,55] Acute dystonic reactions are the most dramatic adverse effects but are relatively uncommon in adults, occurring in only 2% to 5% of cases. Akathisia, though less dramatic, is a more common problem and often persists for several hours. Both adverse effects are more common in young patients. In most adults, these side effects are not difficult to control or prevent. Intravenous diphenhydramine quickly ends an acute dystonic reaction, and the addition of lorazepam to metoclopramide-containing regimens greatly reduces the incidence of extrapyramidal reactions.[56]

Corticosteroids

The antiemetic mechanism of action of the corticosteroids is unclear. Unlike most other antiemetics, there is no current evidence that neurotransmitter blockade is involved. The antiemetic activity of the corticosteroids has been confirmed in several trials, predominantly for patients receiving moderately emetogenic chemotherapy.[57,58] Corticosteroids that have been used as antiemetics include dexamethasone, methylprednisolone, and occasionally prednisone. Although no obvious differences in efficacy have been demonstrated among the corticosteroids, dexamethasone is almost universally used currently. A recent randomized dose-finding study identified a single 8-mg dose of dexamethasone before treatment as optimal.[59] Because of their moderate antiemetic efficacy, corticosteroids should be used as single agents only in the prophylaxis of mildly emetogenic chemotherapy. However, they consistently add to the effect of other antiemetics when used in combination (see the discussion later in this chapter), presumably because they have a different mechanism of action.

The adverse effects of short courses of corticosteroid are mild and infrequent. Additional caution must be used in treating patients with

diabetes mellitus or other conditions predisposing to difficulties with steroids. Occasional acute psychotic reactions have been observed.

Phenothiazines

The phenothiazines were the first family of agents to demonstrate substantial antiemetic activity and are thought to act primarily as antidopaminergic agents. Several of these agents, including prochlorperazine, promethazine, and thiethylperazine, are still used frequently. In 1963 a randomized, double-blind, placebo-controlled trial documented the superiority of prochlorperazine and thiopropazate to placebo in the control of nausea and vomiting induced by fluorouracil.[60] Efficacy has also been documented against other moderately emetogenic chemotherapeutic agents.[61] These agents are ineffective against highly emetogenic chemotherapy, however, and should currently be used only in combination with other more effective agents.[53] The side effects of the phenothiazines include sedation, akathisia, and, less commonly, acute dystonic reactions.

Benzodiazepines

Lorazepam is the only benzodiazepine that has found widespread use in antiemetic therapy. Direct antiemetic effects of lorazepam are minor; however, the sedative, anxiolytic, and amnesic effects have made this drug ideal for use in combination regimens.[62] Several trials have documented improved patient acceptance of lorazepam-containing combination regimens, even when the objective antiemetic efficacy increased only slightly.[56] The use of intravenous lorazepam often causes marked sedation lasting several hours, which limits its use in the outpatient setting. In addition, some patients experience confusion, amnesia, and transient enuresis.

Butyrophenones

The butyrophenones, haloperidol and droperidol, have antiemetic activity as a result of specific dopamine receptor blockade.[63,64] Common side effects of the butyrophenones include sedation, dystonic reactions, and akathisia; in addition, hypotension is occasionally encountered. Because the butyrophenones are less efficacious than the 5-HT3 receptor antagonists and high-dose metoclopramide, their use should be reserved for the occasional patient who achieves poor results with standard antiemetic treatment.

Cannabinoids

Anecdotal reports of reduced emesis among patients smoking marijuana during chemotherapy stimulated interest in the cannabinoids during the early 1980s. Several cannabinoids have been evaluated as antiemetics; at present dronabinol is the only commercially available agent in this class. This drug has antiemetic activity for patients receiving moderately emetogenic chemotherapy; in this setting, it has been more effective than prochlorperazine.[65] The mechanism of action of the cannabinoids is incompletely defined; a central nervous system site of action has been postulated because of the marked psychoactive properties of these agents. Clinical use of cannabinoids is limited because of their unfavorable toxicity profile in some patients. Frequent toxicities include dysphoria, hallucinations, vertigo, dry mouth, sedation, and disorientation. These side effects are more common in elderly patients. The cannabinoids should not be considered for first-line antiemetic therapy, because more effective and better tolerated agents exist. They should be considered for the occasional patient with mild to moderate nausea and vomiting who has either poor tolerance or poor response to other antiemetics.[66]

Combination Antiemetic Therapy

Because none of the antiemetic agents is ideal when used alone, a variety of combination regimens has been developed in an attempt to improve efficacy. The most successful combinations use drugs with different mechanisms of action and nonoverlapping toxicities.

The corticosteroids have been most extensively evaluated as "second drugs" in combination regimens because of their ease of administration, minimal toxicity, and different mechanism of action. When combined with the 5-HT3 receptor antagonists, dexamethasone has consistently improved antiemetic efficacy among patients receiving moderately or highly emetogenic regimens.[67–69] In a recent meta-analysis of randomized trials comparing various regimens with or without dexamethasone, complete protection from emesis was increased by 16% when dexamethasone was added to a 5-HT3 receptor antagonist.[70] The addition of dexamethasone to high-dose metoclopramide also improves antiemetic efficacy.[71] A single dexamethasone dose of 8 mg before therapy is as effective as higher doses or multiple dose schedules.[59] Therefore, a corticosteroid should be included in the prophylactic treatment of all patients receiving moderately or highly emetogenic chemotherapy, unless specific contraindications exist.

Aprepitant is also an agent with proven efficacy in combination regimens, usually as a third drug (added to a 5-HT3/dexamethasone combination). The addition of aprepitant reduces acute and delayed emesis in patients receiving moderately or highly emetogenic chemotherapy.[49–52] Aprepitant should be included in the prophylactic antiemetic treatment of all patients receiving highly emetogenic chemotherapy and should be considered in patients receiving moderately emetogenic chemotherapy who are at high risk for emesis (e.g. female, younger patients, emesis with previous chemotherapy). If aprepitant is not initially included in the antiemetic regimen, it should be added during subsequent cycles for patients who have poor control of emesis.

The addition of lorazepam to antiemetic regimens was common when high-dose metoclopramide was the major antiemetic agent, in large part as a result of the reduction of extrapyramidal side effects.[56] However, the contribution of lorazepam to current 5-HT3 receptor antagonist combinations is unclear, and sedation is consistently increased when lorazepam is added. The use of lorazepam should be considered only for patients with a high level of anxiety before treatment.

Anticipatory Nausea and Vomiting

Because anticipatory nausea and vomiting are conditioned responses, effective control of chemotherapy-induced nausea and vomiting prevents the development of this reflex and is therefore the best strategy for preventing this problem.[25,72] The highly effective combination regimens in current use have greatly decreased the prevalence of this problem. For patients in whom anticipatory nausea and vomiting develop, treatment with anxiolytics such as the benzodiazepines is sometimes effective.[62] In addition, various nonpharmacologic approaches, including hypnosis and behavioral modification, have shown some benefit for these patients.[25,73,74]

Delayed Nausea and Vomiting

Until recently, control of delayed nausea and vomiting was poor as compared with the control achieved during the first 24 hours after chemotherapy. The combination of metoclopramide (0.5 mg/kg four times daily for 4 days) and dexamethasone (8 mg twice daily for 2 days, then 4 mg twice daily for 2 days) was superior to dexamethasone alone in patients receiving cisplatin-based chemotherapy (35% vs. 11% control rate).[75] However, most patients did not have adequate control of emesis, and side effects were bothersome for some patients. Similarly, the contribution of the initial 5-HT3 receptor antagonists was modest, when compared with their excellent activity in treating acute nausea and vomiting. Oral ondansetron (8 mg orally twice daily, days 2–6) had modest benefit versus placebo,[76] but in other trials the efficacy of a 5-HT3 antagonist was not any better

than dexamethasone.[77,78] Despite these modestly effective interventions, a recent study showed that the rates of delayed nausea (54%) and vomiting (32%) remained substantial in patients receiving moderately or highly emetogenic chemotherapy.[79] Furthermore, 23% of patients with complete control during the first 24 hours had either nausea or vomiting during the delayed phase.

With the introduction of palonosetron and aprepitant, the treatment of delayed nausea and vomiting has improved substantially. Palonosetron, the newest 5-HT3 receptor antagonist, is more effective than either ondansetron or dolasetron in controlling delayed nausea and vomiting.[42,43] In patients receiving moderately emetogenic chemotherapy, a single dose of palonosetron (0.25 mg) provided complete control of delayed nausea and vomiting in 48%, as compared with 36% for dolasetron 100 mg.[42] Similar results occurred when palonosetron 0.25 mg was compared to ondansetron 32 mg (74% vs. 55% control of delayed emesis; $P < 0.001$).[43] The differences between palonosetron and the other 5-HT3 receptor antagonists are unexplained but may relate to the longer half-life of palonosetron or to the improved control of acute emesis.

The addition of aprepitant, the first NK-1 antagonist, has been even more important in controlling delayed nausea and vomiting.[49–52] When added to granisetron/dexamethasone in patients receiving cisplatin-based chemotherapy, aprepitant reduced the incidence of delayed emesis from 67% to 18% ($P < 0.001$).[49] Improvement also occurred when aprepitant was added to ondansetron/dexamethasone in patients receiving cyclophosphamide/anthracycline chemotherapy (complete control improved from 42.5% to 50.8%; $P = 0.019$).[52]

Currently, optimal management of delayed chemotherapy-induced nausea and vomiting requires prediction of high-risk patients and administration of the most effective antiemetic regimen, beginning with the first cycle of chemotherapy. High-risk patients include all patients receiving highly emetogenic chemotherapy regimens, and certain subgroups (e.g. young patients, females) receiving moderately emetogenic regimens. In these patients, palonosetron should be the 5-HT3 receptor antagonist of choice, and aprepitant should be added to the antiemetic regimen. Similar substitutions or additions should be made in other patients who experience delayed nausea or vomiting regardless of the chemotherapy regimen they are receiving.

Radiation-Induced Nausea and Vomiting

Radiation-induced nausea and vomiting are common with some types of radiation therapy and are related to the size of the radiation portal, the dose delivered, and the site of radiation. Radiation-induced emesis occurs acutely in more than 90% of patients receiving total-body irradiation. Among patients receiving conventional daily doses of radiotherapy (2 Gy/fraction), emesis develops within 2 to 3 weeks in about 50% of patients receiving an upper abdominal portal.[80] The mechanism of radiation-induced emesis remains unclear, but release of serotonin from the gastrointestinal enterochromaffin cells and subsequent involvement of the gastrointestinal 5-HT3 receptors and vagal afferent fibers is most likely.

Most of the antiemetic agents found active against chemotherapy-induced nausea and vomiting also have some activity against radiation-induced emesis; however, few randomized trials have been performed to identify an optimal regimen. Dexamethasone or ondansetron, used as single agents, were superior to placebo in patients receiving upper abdominal irradiation[81,82] or total-body irradiation.[83] With multifractionated courses, the use of daily dexamethasone is problematic; however, the addition of dexamethasone (4 mg orally daily, during the first 5 days only) to ondansetron (8 mg orally twice daily) improved results in patients receiving upper abdominal radiation therapy.[84]

Given the postulated mechanism of radiation-induced emesis and the available clinical data, it seems likely that the 5-HT3 receptor antagonists are the most active antiemetic agents in this setting. Routine prophylaxis for acute and delayed nausea and vomiting should accompany total-body irradiation. For patients receiving upper abdominal irradiation, in which the incidence of nausea and vomiting is lower, initial prophylaxis with phenothiazines or other less expensive agents might be a reasonable option. However, these patients should receive daily oral prophylaxis with a 5-HT3 receptor antagonist if emesis is uncontrolled with other agents; use of concurrent dexamethasone for the first 5 days should also be considered.

SUMMARY OF RECOMMENDATIONS FOR COMBINATION ANTIEMETIC THERAPY

Optimal selection of antiemetic therapy is based on the emetic potential of the planned chemotherapy regimen. The information presented in Tables 39-2 and 39-3 should be used to assign an emetic level to the chemotherapy agent or regimen being used. Optimal doses of all antiemetic agents are contained in Table 39-4.

All patients receiving regimens with emetic level 4 or 5 should receive routine prophylaxis for acute nausea and vomiting with a 5-HT3 receptor antagonist plus dexamethasone. Because all of these patients also have substantial risk for delayed emesis, aprepitant should be added, and palonosetron should be considered the 5-HT3 antagonist of choice. Patients receiving level 3 regimens are usually well controlled with a 5-HT3 receptor antagonist plus dexamethasone; routine prophylaxis for delayed emesis is not necessary. Patients receiving mildly emetogenic regimens (category 1 or 2) do not require routine use of a 5-HT3 receptor antagonist and are usually managed effectively with either dexamethasone alone (category 2) or no prophylactic antiemetic therapy (category 1).

FUTURE DIRECTIONS

Major improvements in antiemetic therapy during the past 20 years have resulted in complete protection from chemotherapy-induced nausea and vomiting in most patients receiving chemotherapy. A few patients (fewer than 20%) continue to have problems during the first 24 hours after treatment, and in most of these patients breakthrough nausea and/or vomiting occurs more than 16 hours after administration of chemotherapy. Delayed nausea and vomiting remain common, but therapy has improved markedly with the introduction of aprepitant and palonosetron.

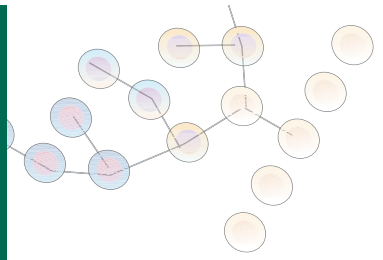
The evolution of standard chemotherapy for many types of cancer has had an impact on the antiemetic therapy required. Two highly emetogenic chemotherapeutic agents, mechlorethamine and dacarbazine, are now uncommon in clinical practice. More importantly, the use of cisplatin has declined greatly during the last several years mostly because of its replacement by carboplatin, a drug with a lower emetogenic potential. Many of the more recent cytotoxic agents (e.g., paclitaxel, docetaxel, gemcitabine, topotecan, vinorelbine) are mildly emetogenic agents. Increasing use of these new drugs has also fortuitously allowed the more effective control of chemotherapy-induced emesis. Finally, it is likely that future targeted agents, many of which will be administered orally, will not be associated with nausea or vomiting in most patients. Recent experience with several monoclonal antibodies (e.g., rituximab, trastuzumab, bevacizumab) and oral tyrosine kinase inhibitors (e.g., imatinib, erlotinib) confirms the low frequency of nausea, even in the absence of any prophylaxis.

Future improvement in antiemetic therapy will require continued improvement in understanding of this complex physiologic reflex, and identification of new mediators. Continued well-designed clinical trials are necessary to define the most effective—and the most cost-effective—ways of incorporating new agents into current antiemetic regimens.

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40 Oral Complications

Kostandinos Sideras, Charles L. Loprinzi, and Robert L. Foote

SUMMARY OF KEY POINTS

Incidence

- Mucositis is a major dose-limiting toxic effect of chemotherapy for solid tumors developing in 5% to 40% of patients.
- Mucositis develops in 70% to 100% of patients receiving high doses of chemotherapy with bone marrow rescue.
- Radiation therapy to the oral cavity frequently causes a host of oral complications, including mucositis, xerostomia, dental caries, tissue necrosis, and taste alterations.

Etiology of Complications

- Cytotoxic chemotherapy and radiation therapy cause oxidative stress and injury to oral cavity tissues, leading to upregulation of inflammatory cytokines, additional signaling and amplification of inflammatory pathways, and subsequent ulceration and healing.
- Treatment-induced myelosuppression may lead to secondary infections.
- Graft-versus-host disease (GVHD) is a further complication.

Prophylactic Measures

- The importance of instituting oral hygiene protocols in patients receiving chemotherapy is well established.
- Cryotherapy is the most conventional and easy to use preventative method, at least for 5-FU-based bolus therapy and appears to have implications for other chemotherapeutic regimens as well, such as edatrexate and high-dose melphalan therapy.
- The role of antibiotics, either topically or systemically, has not yet been established.
- Glutamine supplementation in the form of AES-15 (Saforis) has recently shown promise as a potentially effective agent.
- Palifermin, a keratinocyte growth factor preparation, has been approved by the FDA for use with high-dose chemotherapeutic regimens associated with high rates of mucositis and has shown promise in other settings as well
- Low-level laser therapy has shown promise, but its use is limited to centers that are able to support its use.
- Pretreatment dental care, good oral hygiene, and sophisticated treatment planning are recommended for patients receiving radiation therapy.

Treatment

- There is an overall lack of evidence regarding the efficacy of various agents in promoting healing of the oral mucosa after mucositis is established.
- Systemic analgesic therapy of mucositis pain with narcotic medications is well established and recommended.
- Antibiotics and/or antifungal medications should be given to patients with evidence of infection.
- In the palliative setting, various mouthwashes are widely used in clinical practice based on provider preference and experience. These mouthwashes most frequently contain combinations of diphenhydramine, viscous lidocaine, magnesium hydroxide/aluminum hydroxide, nystatin, and corticosteroids. The efficacy of these measures has not been adequately evaluated to date.
- Baking soda mouth rinses appear to be the most economical solution, although efficacy has not been clearly established.

INTRODUCTION

The oral cavity is a common site for chemotherapy-induced and radiation-induced toxicity. Manifestations of this toxicity include alimentary tract mucositis; secondary infectious complications induced by bacteria, fungi, and viruses; and graft versus host disease in patients receiving allogeneic bone marrow transplants. Although alimentary tract mucositis can involve the entire gastrointestinal tract,[1] it is most frequently manifested in the oral cavity as ulceration, pain, and bleeding. Mucositis leads to significant patient morbidity and decline in quality of life and limits the use of additional chemotherapeutic treatment. Moreover, the economic burden of this frequent oncologic complication is also considerable.[2,3] This chapter discusses the etiology, incidence, risk factors, prevention, and treatment of oral toxic effects of standard chemotherapy, intensive marrow-ablative chemotherapy, and radiation therapy. The prevention and treatment of graft-versus-host disease is beyond the scope of this chapter (see Chapter 32).

Pathophysiology of Mucosal Injury

It is currently accepted that the processes of mucosal injury and subsequent healing are not limited to the epithelium alone but involve all layers of the mucosa, including the extracellular matrix. A five-stage process has been postulated to explain the complex molecular, cellular, and histologic events that are associated with chemotherapy-induced mucosal injury[4] (Fig. 40-1). Oxidative stress related to chemotherapy is thought to be responsible for the first phase of mucosal injury (initiation phase). The second phase involves the upregulation of transcription factors and the generation of messenger signals (upregulation and message generation phase). In this stage, upregulation of NF-κ beta is thought to play a central role in the

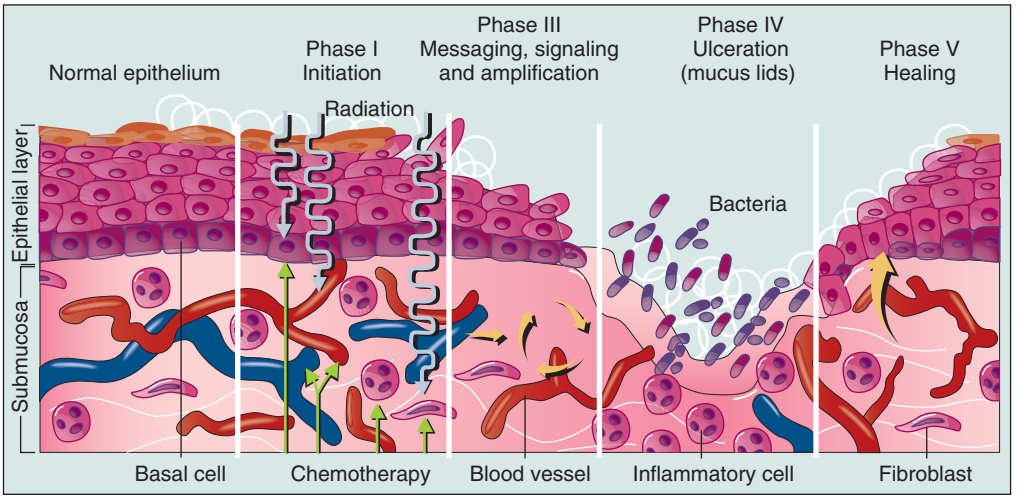


Figure 40-1 • Phases in the development of oral mucositis. (Adapted from Peterson DE: New strategies for management of oral mucositis in cancer patients. J Support Oncol 2006;4:9–13.)

subsequent upregulation of multiple proinflammatory cytokines, such as TNF-α, IL-1b, and IL-6. NF-κ beta is also thought to upregulate cyclooxygenese-2, which in turn is implicated in the upregulation of matrix metalloproteinase.[5] In addition to the sphyringomyelinase and ceramide pathways, fibronectin breakup and macrophage activation are other complex events that take place leading to further mucosal injury and apoptosis. The third phase of mucosal injury involves additional signaling and amplification of the previously discussed pathways, leading to the generation of additional proinflammatory cytokines (signaling and amplification phase). Up to this point, the biologically altered mucosa appears still to be anatomically intact. The fourth phase consists of the symptomatic phase of mucositis, involving mucosal ulceration, pain, and bleeding (ulceration phase). Bacterial superinfection and reduction in salivary gland function can complicate and amplify the mucosal injury at this stage. The fifth and final phase involves the healing of the mucosa, a process that depends on angiogenesis and on increased biological activity in the extracellular matrix (healing phase). In patients who are undergoing myeloablative chemotherapy, the healing phase might not begin until leukocyte recovery. It is important to understand that these phases do not necessarily follow a linear progression but may occur simultaneously at different locations.[4]

Mucositis Assessment

Multiple mucositis scales exist in clinical practice, differing in the level of objective and subjective information used. However, it is known that patient-provided data lead to the same conclusions as do clinician-determined data.[6] The WHO and NCI-CTC scales are the most commonly used ones and combine information from both the patient's signs and symptoms and the patient's functional status and ability to eat.[4]

ORAL COMPLICATIONS FROM CHEMOTHERAPY INCLUDING MYELOABLATIVE CHEMOTHERAPY

Incidence and Risk Factors

The type of chemotherapeutic agents that are used, the specific dose, route, and frequency of administration, and whether the chemotherapy is given as monotherapy or in combination with other agents and modalities of treatment significantly affect the degree of injury (Fig. 40-2).

Antimetabolites such as methotrexate and 5-FU, antitumor antibiotics such as doxorubicin, platinum agents such as cisplatin, purine analogs such as cytarabine, and topoisomerase inhibitors such as etoposide are most specifically associated with mucositis. Methotrexate and etoposide are secreted into the saliva thus enhancing mucosal toxicity. Irinotecan, although notorious for causing gastrointestinal mucositis in the form of diarrhea, has limited oral toxicity.

Regarding the time course of mucosal injury, 5-FU-induced mucositis is usually first noticed anywhere from 3 to 7 days after initiation of therapy. Incidence peaks at 7 to 12 days and diminishes by around 2 to 3 weeks (Fig. 40-3). With myeloablative chemotherapy for hematologic malignancies, mucositis severity can peak up to 18 days following initiation of therapy.[7]

Chemotherapy for the treatment of solid tumors leads to the development of mucositis in 5% to 40% of patients (5% to 15% grade 3 to 4).[8] Many modern treatment approaches have not solved this problem and, owing to their aggressiveness, are frequently more toxic.[9] A vast experience exists with 5-FU, the most commonly used drug to treat gastrointestinal malignancies. Although there has long been the belief that continuous administration of 5-FU carries a higher risk of mucositis than does bolus administration of 5-FU, a meta-analysis of trials failed to support this association.[10]

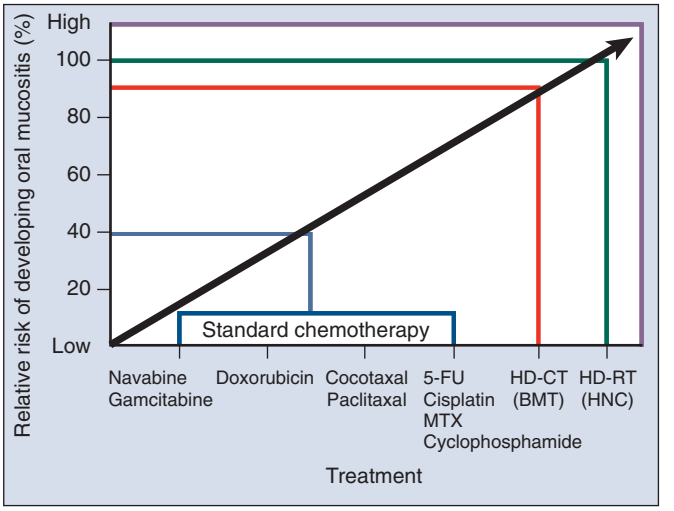


Figure 40-2 • Risk of mucositis according to type of cancer therapy. (Adapted from Peterson DE: New strategies for management of oral mucositis in cancer patients. J Support Oncol 2006;4:9–13.)

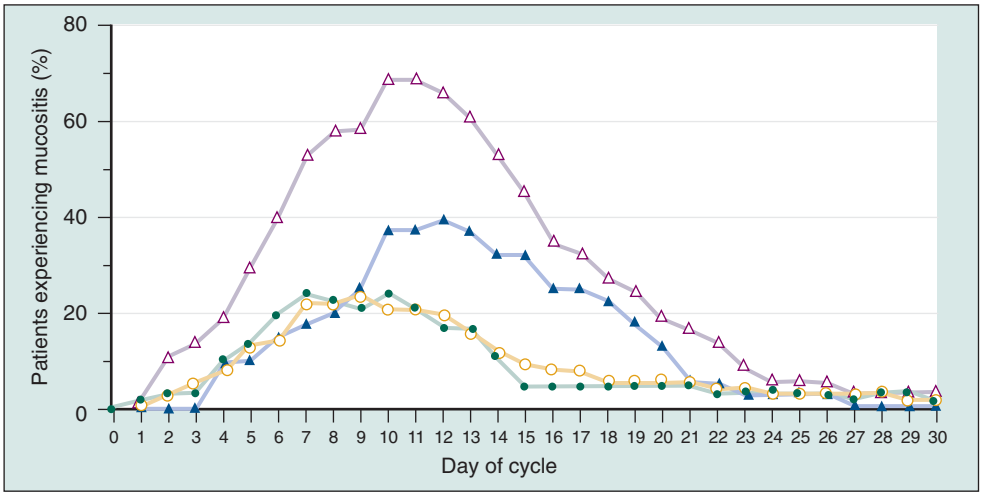


Figure 40-3 • Percentages of patients with mucositis for 30 days after initiation of 5-fluorouracil-based chemotherapy. These data come from two sequential randomized trials:[32,36] one that compared 30 minutes of oral cryotherapy (▲) with a control group (△) and one that compared 30 minutes of cryotherapy (○) with 60 minutes of cryotherapy (●).

When myeloablative chemotherapy is used, the incidence of mucositis increases to 70% to 100% (21% to 67% grade 3 to 4).[7,11] This appears to be especially true for induction regimens that contain high-dose melphalan.[7] When chemotherapy is used in combination with radiation therapy to treat cancer of the head and neck, the rate of mucositis approaches 90% to 100% of patients (43% grade 3 to 4).[12]

The role of age and gender in the development of mucositis has not yet been clearly defined, owing to conflicting reports.[13] There is also conflicting evidence on whether the type of bone marrow transplant (autologous versus allogeneic) or the use of total body irradiation in the conditioning regimen is related to the risk of mucositis.[13] On the other hand, poor oral hygiene, dental caries, periodontal disease, and high titers of herpes simplex virus (HSV) and positive cultures for *Candida tropicalis* are generally accepted to be risk factors.[13]

Finally, interpersonal variability in the development of mucositis been observed for years and could be due to the differences in metabolism of the chemotherapeutic drugs from person to person. A prime example consists of the drug methotrexate, which results in much higher degrees of mucositis[14] in patients with an inability to metabolize this drug.

Prevention of Chemotherapy-Induced Oral Complications

Effective means of preventing chemotherapy-induced oral complications would allow for an improved quality of life for patients receiving chemotherapy as well as a reduction of the rate of life-threatening infections that are thought to be originating from the oral mucosa. Theoretically, it might also improve the effectiveness of antineoplastic therapy by preventing treatment modifications during subsequent cycles and permitting more dose-intensive therapies. Several different methods have been proposed for preventing chemotherapy-induced oral complications (Box 40-1).

Oral Hygiene

Although generally there is insufficient evidence to suggest any one approach, there is enough collective evidence to recommend the institution of a comprehensive oral care protocol for patients receiving chemotherapy for solid tumors.[15] Multiple oral care protocols have demonstrated feasibility and tolerability, and some have shown a reduction in the severity of mucositis and an improvement in the patient's ability to cope with symptoms.[15] Such oral care protocols are usually implemented by nursing staff and involve various degrees of patient education. They can include cavity screening and dental consultations; basic oral care with tooth brushing, flushing, and rinsing; regular inspection of the oral cavity; and avoidance of substances such as smoking, alcohol, and spices.[16,17] The cross-study differences that are seen in two similar treatment arms illustrated in Figure 40-3 could be related to the use of nurse-directed oral care recommendations in the second study that were not used in the first study. Teeth extraction prior to chemotherapy for severe periodontal disease may also be reasonable to consider.[18]

Currently, there is a wide heterogeneity in the approach to mucositis prevention in the United States, and multiple different oral care protocols are available. The need for a more standardized approach is evident, including the institution of multidisciplinary teams.[19,20]

Regarding the oral care of myeloablative chemotherapy candidates, guidelines drafted by the Centers for Disease Control, Infectious Disease Society of America, and American Society of Blood and Marrow Transplantation in 2000 recommend a formal dental evaluation, with appropriate subsequent treatment, prior to initiation of any conditioning regimen. This includes appropriate treatment of caries, proper fitting of any dental prosthesis, and extraction of teeth with significant periodontal disease. These interventions should ideally be performed 10 to 14 days prior to any conditioning therapy. During therapy, oral hygiene should be maintained with rinses four to six times a day using either sterile water, normal saline, or sodium bicarbonate solutions, and patients should brush their teeth at least twice daily with a soft or ultra-soft tooth brush or a toothette (i.e.,

Box 40-1. PREVENTION OF CHEMOTHERAPY-INDUCED ORAL MUCOSITIS

The importance of instituting oral hygiene protocols in patients receiving chemotherapy is well established. Cryotherapy is the most conventional and easy-to-use preventive method, at least for 5-FU-based bolus therapy, and appears to have implications for other chemotherapeutic regimens as well, such as edatrexate and high-dose melphalan therapy. The role of antibiotics, either topically or systemically, has not yet been established. Glutamine supplementation in the form of AES-15 (Saforis) has recently shown promise as a potentially effective agent. The FDA has approved palifermin, a keratinocyte growth factor preparation, for use with high-dose chemotherapeutic regimens associated with high rates of mucositis, and it has shown promise in other settings as well. Low-level laser therapy has shown promise, but it is limited to centers that are able to support its use.

foam swab on a stick). Use of toothpaste is optional, and daily dental flossing should be done only by patients who are experienced in the technique, if it can be done without trauma. Orthodontic appliances and space maintainers can be removed during therapy, although if good tissue integrity and satisfactory daily oral hygiene are maintained, their use can continue during the initial conditioning phase.[21]

Antimicrobial Agents

In the past, microorganisms were hypothesized to play a central role in the pathogenesis of mucositis. This no longer is thought to be true. This is partly because topical and systemic antibiotics, to date, have failed to significantly affect the incidence and severity of mucositis and, as a result, are currently not recommended for routine use.[22] One explanation might be the general failure to significantly eradicate microbes from the oral cavity[23] or the possibility that alterations in the microbial flora by antimicrobial agents might make no difference or cause more harm.[22,24] Another explanation is that microorganisms might play a more complex and possibly a more minor role than was initially thought. It is currently suggested that instead of being involved in the initiation phase, they probably intensify the inflammatory process associated with the later phases of mucosal injury.[4,22] Nevertheless, what appears to be true is the association between the severity of mucositis and the incidence of sepsis and other infections, suggesting that microbes use the already damaged gastrointestinal mucosa as a portal of entry, thus increasing the risk of infectious complications.

Of all the antiseptics, chlorhexidine has been most extensively studied in multiple randomized trials, and the results have been mixed. Therefore, its regular use is not recommended.[15,25,26] Isenagan, a naturally occurring peptide with a broad antimicrobial spectrum, has also failed to show benefit.[27] Although one small placebo-controlled randomized trial has shown benefit for the prophylactic use of topical povidone-iodine, further study is needed before this agent is accepted in clinical use.[25] Regarding systemic antibacterial prophylaxis, data are also not convincing, and systemic antimicrobials therefore are not recommended at this time for the prevention of mucositis.[22,28,29]

Reactivation of HSV can be a significant complication in patients receiving myeloablative chemotherapy and frequently presents with oral ulceration. Although high titers of HSV and positive cultures for *C. tropicalis* have been reported as significant risk factors for the development of mucositis, routine surveillance cultures of oral tissues is not recommended.[30] On the other hand, HSV infection should be suspected if mucositis persists or appears to worsen, 2 or more weeks following transplantation. The guidelines of the Centers for Disease Control, Infectious Disease Society of America (IDSA), and American Society of Blood Marrow Transplantation (ASBMT) recommend testing for serum anti-HSV IgG prior to bone marrow transplant. However, prophylactic treatment with acyclovir is recommended only for seropositive allogeneic stem cell recipients. In this situation, its use is recommended only until engraftment, until mucositis resolves, or up to 30 days after the start of treatment. Prolonged treatment can be considered in patients with frequent recurrent HSV infections. Autologous seropositive recipients can also be potentially treated if significant mucositis is expected from the conditioning regiment. Valacyclovir and Foscarnet are not recommended for this indication.[21] Despite these recommendations, HSV is thought to have a marginal role in causing frank oral mucositis.[15]

Although antifungal medications are currently not recommended for the prophylaxis of oral candidiasis in patients receiving chemotherapy, there is evidence to suggest that prophylactic gastrointestinally absorbable or partially absorbable antifungal medications reduce the rate of oral candidiasis.[31]

Cryotherapy

5-FU-BASED CHEMOTHERAPY. Initially, a North Central Cancer Treatment Group randomized clinical trial demonstrated that oral cryotherapy can inhibit the development of bolus 5-FU-induced mucositis.[32] This has been independently validated by other investigators.[33–35] It is hypothesized that cryotherapy works by causing local vasoconstriction during periods of peak 5-FU blood concentration, thus decreasing the delivery of 5-FU to the oral mucosa. This therapy is administered by having the patient suck on crushed ice, starting 5 minutes prior to 5-FU administration and continuing for a total of 30 minutes. A longer duration of oral cryotherapy (60 minutes) does not appear to provide any additional benefit in this setting.[36]

EDATREXATE. Four small nonrandomized phase I and II trials have used 20 to 30 minutes of oral cryotherapy for prevention of mucositis in patients receiving edatrexate, a methotrexate analog with improved preclinical antitumor activity. Three out of the four trials have shown good tolerability of edatrexate when it is used with oral cryotherapy,[37–39] while one study showed high toxicity despite this preventive strategy.[40] Current guidelines recommend cryotherapy as an attempt to decrease mucositis in patients who are treated with bolus edatrexate.[15]

HIGH-DOSE MELPHALAN. At least five small prospective nonrandomized studies in patients receiving high-dose melphalan therapy have tested the efficacy of oral cryotherapy as compared to historical controls. Grade 3 mucositis developed in only 0% to 11% of patients treated with oral cryotherapy as compared to the incidence of mucositis in historical controls, which is observed in over 70% of patients.[41–45] In the only randomized placebo-controlled study, using room temperature normal saline as placebo, 40 patients were treated with cryotherapy or placebo for 30 minutes before and 6 hours after chemotherapy with high-dose melphalan. Grade 3 mucositis was experienced in 14% of patients receiving cryotherapy and in 74% of patients receiving normal saline.[46] Although the need for such prolonged administration of cryotherapy is questionable, owing to patient noncompliance and the probably equivalent efficacy of shorter administration, cryotherapy appears to be a promising strategy in lowering mucositis in patients receiving high-dose melphalan therapy, and it is currently recommended in this setting.[47] This evidence points to a possible role for cryotherapy in more diverse settings than was previously thought.

Antioxidants, Anticholinergics, and Coating Agents

In general, insufficient evidence exists regarding the effectiveness of antioxidant compounds such as tretinoin and vitamin E in preventing oral mucositis in patients receiving chemotherapy.[13] A small randomized trial of zinc sulfate reported a statistically significant benefit in preventing severe mucositis; more investigation is warranted before accepting this agent as standard practice.[48] There is also insufficient evidence to support the prophylactic use of Propantheline, an anticholinergic drug that is thought to reduce the amount of etoposide secreted in the saliva.[25] Mixed data exist on the role of sucralfate, a coating agent; therefore, sucralfate is not currently recommended for the prevention of oral mucositis.[25,26]

Anti-inflammatory Agents

Since inflammatory mediators appear to play a central role in mucositis development, the use of anti-inflammatory agents has been proposed as a method for preventing mucositis. However, cytokine inhibitors and anti-inflammatory agents have not yet proven to be efficacious.

Pentoxifylline, a TNF-α and IL-2 inhibitor, is currently not recommended in either the standard chemotherapy or bone marrow transplant setting.[15,25] Benzydamine mouthwash has been approved for radiation-induced mucositis in Europe and Canada and is currently being tested in the United States.[15,49] However, evidence regarding its use in prevention of chemotherapy-induced mucositis is weak, and it is currently not recommended in this setting.[25]

Amino Acids

Glutamine is a nitrogen-rich nonessential amino acid with a critical role in nucleotide synthesis, muscle function, and overall metabolic homeostasis. However, during periods of stress, it becomes a conditionally essential amino acid, and its stores can be significantly depleted, as is the case in patients with cancer.[50] Multiple trials to date have attempted to investigate the beneficial potential of different glutamine preparations through both the parenteral and oral routes, with mixed results.[50,51] Glutamine had been administered through the parenteral route, as part of total parenteral nutrition, or in intravenous infusions mixed with normal saline. It has also been administered as oral supplements and as swish and swallow mouthwash preparations. Overall, these trials have been small, and conclusions have been difficult to draw.

However, recent data have emerged regarding Saforis, an oral suspension form of L-glutamine with an enhanced delivery system. Three hundred and twenty-six breast cancer patients who developed grade ≥2 mucositis during the first cycle of treatment with an anthracycline-based regimen were treated with Saforis, 2.5 g/5 mL orally three times per day concurrent with their next chemotherapy dose, swished for 30 seconds and then swallowed, for at least 14 days, versus placebo. The results showed a reduction in the incidence of grade ≥2 mucositis in the subsequent cycle of chemotherapy by 11% (50% to 39%: $P = 0.03$), as well as a reduction in the subsequent severity of mucositis in the patients who were treated with Saforis.[52] In another trial, 197 patients undergoing bone marrow transplant and treated with glutamine via the swish and swallow method for 14 days had a significant reduction in the severity and duration of mucositis. This was true for the autologous transplant patients but not the patients receiving allogeneic transplants.[53] In summary, although glutamine is not yet officially recommended for the prevention of chemotherapy-induced oral mucositis, results of several studies are promising, and if subsequent data are confirmatory, recommendations could change.

Growth Factors

Growth factors, systemically or topically, are hypothesized to help prevent oral mucositis due to their potential to improve healing. Although the use of granulocyte colony stimulating factor and granulocyte macrophage colony stimulating factor (GM-CSF) has been associated with reduced mucositis in certain randomized trials, the data are inconclusive as yet (Cochrane).[25] A recent meta-analysis found a benefit for prophylactic treatment with systemic growth factors but not for topical preparations.[26] However, the results of the meta-analysis were largely dependent on one strongly positive study alone, and further evidence is needed.[54]

Topical keratinocyte growth factor, which is secreted by injured mucosal epithelium, may have a more localized healing effect in the oral cavity. The Food and Drug Administration (FDA) recently approved one such preparation, palifermin, for use in preventing mucositis induced by myeloablative chemotherapy. The recommendation was based on a study of 212 patients who were randomized to receive intravenous palifermin or placebo for three consecutive days immediately before the initiation of conditioning therapy. Grade 3 or 4 mucositis developed in 63 percent of patients in the palifermin group and 98 percent of patients in the placebo group.[55] Palifermin has shown benefit in at least two more trials. In a series of 59 patients undergoing hematopoietic stem cell transplantation 13% of patients receiving palifermin developed severe mucositis compared to 48% of patient who received standard care.[56] Palifermin was also tested in 64 patients with colorectal cancer who received 5-FU-based chemotherapy, and a significant reduction in severe mucositis score was seen, with 29% of patients receiving palifermin developing severe mucositis compared to 61% receiving placebo.[57] Although apparently effective, it constitutes an expensive option for mucositis prevention at this point. In addition, since in these studies, oral cryotherapy was not administered to either the patients who received 5-FU-based chemotherapy or the patients who received high-dose melphalan therapy, it would be interesting to examine how palifermin would fare in comparison to oral cryotherapy.

Low-Level Laser Therapy

Evidence is accumulating that low-level laser therapy might promote healing and reduction of pain in patients who are at risk for oral mucositis.[58,59] However, the expense, the need for specialized training and equipment, and the difficulty in interpreting and comparing the results from the various trials limit the widespread applicability of this approach at this time. Although no guidelines regarding its use exist yet, further investigation with large phase III randomized placebo-controlled clinical trials is encouraged.[15] Moreover, for centers that are able to support the necessary technology and training, this approach is recommended in an attempt to reduce the oral mucositis associated with myeloablative chemotherapy. In fact, low-level laser therapy is considered standard in some centers.[59]

Other Interventions

A variety of protocols include the prophylactic use of oral rinses and mouthwashes, such as normal saline, sodium bicarbonate solutions, and other mixtures. Although there is insufficient evidence to support their use, they constitute parts of various standard oral care protocols. Evidence does exist, however, that rinses that contain alcohol tends to worsen the symptoms of mucositis and therefore should be avoided. In a double-blind controlled trial in patients undergoing bone marrow transplantation, a benefit has been suggested for a neutral supersaturated calcium phosphate rinse (Caphosol) given in conjunction with fluoride when compared to fluoride rinsing alone.[60] Allopurinol mouthwashes, despite constituting standard clinical practice at some institutions the early 1990s, are currently not recommended, since at least two randomized clinical trials have convincingly shown no benefit.[25,61,62] Traumeel S, a homeopathic remedy, was tested as a mouthwash in a randomized placebo-controlled trial of 32 pediatric patients undergoing stem cell transplantation, and a statistically significant reduction in the incidence and severity of mucositis was reported. However, the study is not conclusive, and further investigation is under way. Finally, a double-blind randomized placebo-controlled trial of chamomile mouthwash has also failed to show benefit.[25,26]

Conclusion

The importance of instituting oral hygiene protocols in patients receiving chemotherapy is well established. Cryotherapy is the most conventional and easy-to-use preventive method, at least for 5-FU-based bolus therapy, and appears to have implications for other chemotherapeutic regimens as well, such as edatrexate and high-dose melphalan therapy. The role of antibiotics, either topically or systemically, has not yet been established. Glutamine supplementation in the form of AES-15 (Saforis) has recently shown promise as a potentially effective agent. The FDA has approved palifermin, a keratinocyte growth factor preparation, for use with high-dose chemotherapeutic regimens associated with high rates of mucositis, and it has shown promise in other settings as well. Low-level laser therapy has shown promise, but it is limited to centers that are able to support its use.

Treatment of Chemotherapy-Induced Oral Mucositis

Scant information is available regarding the effective treatment of chemotherapy-induced mucositis, despite a plethora of prescribed remedies (Box 40-2). Hence, initial treatment of established mucositis varies significantly among institutions, and different providers often prescribe remedies based on their individual experience and preference.[19] Among these many proposed treatments are various mouthwashes, coating agents, topical anesthetics or analgesics, anti-

Box 40-2. TREATMENT OF CHEMOTHERAPY-INDUCED ORAL MUCOSITIS

There is overall lack of evidence regarding the efficacy of various agents in promoting healing of the oral mucosa after mucositis is established. Systemic analgesic therapy of mucositis pain with narcotic medications is well established and recommended. Antibiotics and/or antifungal medications should be given to patients who have evidence of infection. In the palliative setting, various mouthwashes are widely used in clinical practice based on provider preference and experience. These mouthwashes most frequently contain combinations of diphenhydramine, viscous lidocaine, magnesium hydroxide/aluminum hydroxide, nystatin, and corticosteroids. The efficacy of these measures has not been adequately evaluated to date. Salt and baking soda mouth rinses appear to be the most economical solution, although efficacy has not been clearly established.

inflammatory agents, systemic narcotics, and topical and systemic growth factors.[15] These treatments are aimed at promoting the healing of the injured oral mucosa and thus limiting the severity and duration of ulcerations, as well as palliating the symptoms of oral mucositis.

General recommendations that are frequently given to the patients with established mucositis include the avoidance of spicy, coarse, hot, cold, or acidic foods or juices or medications or beverages containing alcohol and the encouragement of rather soft, moist foods and non-alcoholic beverages. Moreover, the treating physician should take care not to lose sight of the other important means of support for the cancer patient presenting with mucositis such as proper hydration, nutrition, infectious surveillance, and psychological support, all of which can significantly affect the patient's well-being and quality of life.

Mouthwashes

For patients with established mucositis, one of the first therapeutic measures that is frequently used consists of having the patients rinse their mouths every 2 to 4 hours with a solution of salt and baking soda (1/2 teaspoon salt plus 1/2 teaspoon baking soda in an 8-ounce glass of warm water). This is often soothing and is thought to be cleansing. Some centers use baking soda alone, since the addition of salt is thought to be too drying to the mucosa. In one multicenter study, 200 patients receiving standard chemotherapy, who followed a carefully planed oral hygiene protocol (PRO-SELF), were randomized to one of three different mouthwashes: salt and soda, chlorhexidine, or "magic" mouthwash (lidocaine, Benadryl, and Maalox). No significant differences were observed in time to cessation of the signs and symptoms of mucositis among the three regiments; salt and soda was the least costly.[63]

Mouthwashes, often referred to as "magic" or "miracle mouthwash," are usually topical preparations of analgesic, anesthetic, and coating agents, the composition of which varies across institutions. The most common ingredients are diphenhydramine, viscous lidocaine, magnesium hydroxide/aluminum hydroxide, nystatin, and corticosteroids.[64] Other ingredients include benzocaine, milk of magnesia, chlorhexidine, kaolin, and pectin.[15] Despite their widespread use, the general lack of evidence supporting their efficacy and tolerability does not allow presently any of these preparations to be included into formal guidelines.[15] Further study of these palliative mixtures however is strongly encouraged, given their overall availability, ease of administration, frequent use, and low cost.

Chlorhexidine mouthwashes are not recommended, since studies have failed to support the use of this agent for the treatment of established mucositis.[15] Coating agents, such as sucralfate, have also failed to show any benefit for the treatment of established chemotherapy-induced mucositis when tested in small randomized trials.[65]

Anti-inflammatory Agents

Anti-inflammatory agents in general have failed to find a role in the treatment of chemotherapy-induced mucositis.[66]

Growth Factors

It is hypothesized that GM-CSF, systemically or topically as a mouthwash, might stimulate proliferation of endothelial cells and promote keratinocyte growth, thus enhancing recovery of oral mucositis. However, studies have been limited and are of poor methodological quality.[65,67]

Systemic Analgesics

Oral mucositis pain can be severe and can significantly interfere with the quality of life of patients receiving chemotherapy. Management should follow the same aggressive guidelines that are used to treat pain in patients with cancer in general.[68] The use of patient-controlled anesthesia is effective and well established for treating mucositis pain, especially in the hematopoietic stem cell transplantation setting.[15]

Conclusion

There is overall lack of evidence regarding the efficacy of various agents in promoting healing of the oral mucosa after mucositis is established. Systemic analgesic therapy of mucositis pain with narcotic medications is well established and recommended. Antibiotics and/or antifungal medications should be given to patients who have evidence of infection. In the palliative setting, various mouthwashes are widely used in clinical practice based on provider preference and experience. These mouthwashes most frequently contain combinations of diphenhydramine, viscous lidocaine, magnesium hydroxide/aluminum hydroxide, nystatin, and corticosteroids. The efficacy of these measures has not been adequately evaluated to date. Salt and baking soda mouth rinses appear to be the most economical solution, although efficacy has not been clearly established.

RADIATION THERAPY

Mucositis

Etiology

The most troublesome acute reaction for patients who are receiving radiation therapy to the oral cavity is radiation-induced mucositis. Acute mucositis results from the loss of squamous epithelial cells owing to the sterilization of mucosal stem cells and the inhibition of transit cell proliferation. This leads to a gradual linear decrease in epithelial cell numbers. As radiation therapy continues, a steady state between mucosal cell killing and mucosal cell regeneration may occur because of an increased cell production rate from the surviving cells. Usually, however, cell regeneration cannot keep up with cell killing, and partial or complete denudation develops. This presents as patchy or confluent pseudomembranous mucositis. Healing eventually occurs when cells regenerate from the surviving mucosal stem cells. The loss of the epithelial barrier exacerbates insults from physical, chemical, and microbial agents. It has been reported that the oropharyngeal flora may contribute to radiation therapy–induced mucositis. However, which flora is involved and which step in the mucositis process may be prevented by eliminating the offending flora remain unknown. One hypothesis is that endotoxins produced by gram-negative bacilli are potent mediators of the inflammatory process.

The oral cavity mucosa, having a relatively high turnover rate, change early during a course of fractionated external-beam radiation therapy. With 200-cGy fractions per day, 5 days per week, mucosal erythema is typically noted within the first week or two of treatment. By approximately 2 to 3 weeks, the erythematous mucosa develops small whitish yellow patches called patchy pseudomembranous mucositis. These pseudomembranes represent collections of dead

surface epithelial cells, fibrin, and polymorphonuclear leukocytes on a moist background. This acute reaction is typically accompanied by oral discomfort. In many patients, the patchy mucositis becomes confluent by the third or fourth week of radiation therapy and can be associated with significant pain.

The severity of mucositis is related to the daily dose of radiation therapy, the total cumulative dose, the volume of irradiated tissue, and the use of concurrent radiation-sensitizing and/or mucositis-inducing chemotherapeutic agents. At fractions of 170 to 180 cGy daily, 5 days per week, the maximal reaction is typically intense erythema with occasional patchy mucositis. In this situation, the cell killing and repopulation of epithelial stem cells are in near equilibrium. If the daily dose is increased to 200 cGy or more, as in the case of altered fractionation schedules such as hyperfractionation (110 to 150 cGy twice a day) or accelerated fractionation (160 cGy two or three times a day or concomitant boost with 180 cGy in the morning and 150 cGy in the afternoon), and the treatment volume is large (the entire oral cavity), cell killing will exceed the proliferative capacity of the epithelial stem cells, and almost all patients will have confluent mucositis by the third week of radiation therapy. Mucositis first appears and is often most severe on the mucosa of the soft palate, tonsillar pillars, buccal mucosa, lateral border of the tongue, and pharyngeal walls. In contrast, mucositis less frequently involves the hard palate, gingival ridges, and dorsum of the tongue during a course of radiation therapy or, alternatively, only after very high doses or when administered with concurrent radiation-sensitizing chemotherapy. In patients with metallic dental restorations, a prominent mucositis frequently develops on the adjacent buccal mucosa and/or the lateral border of the adjacent tongue or both as a result of backscattering of low-energy electrons.

Symptoms of oral discomfort are usually maximal 3 to 4 weeks into the course of radiation therapy. Thereafter, symptoms usually plateau and may even diminish in patients who are treated with radiation therapy alone, even though treatment is continued. After external-beam radiation therapy, the mucous membranes normally heal within 4 to 6 weeks, although an occasional patient might require up to 12 weeks or even several months. The latter is particularly true of patients treated with concurrent radiation-sensitizing chemotherapy.

The mucositis that is produced by an interstitial radioactive implant typically appears 7 to 10 days after removal and is maximal approximately 2 weeks after removal. The mucositis generally heals by 6 weeks unless the implanted volume was large, in which case complete healing may require several months.

Radiation-induced oral mucositis can result in intense pain, which may substantially limit adequate hydration and nutrition, prevent proper oral hygiene, serve as a portal for infection, and affect speech. All these effects can significantly interfere with the general well-being of the patient and might tempt the treating physician to interrupt the course of treatment to permit resolution of the acute symptoms. At times, the treatment might be discontinued altogether before delivery of a potentially curative dose of radiation therapy.

Clinical and radiobiologic evidence shows that the protraction of overall treatment time adversely influences the radiocurability of certain human tumors, particularly squamous cell carcinomas of the head and neck region. The additional dose that is needed to compensate for a protracted course of radiation therapy has been attributed to an accelerated tumor clonogenic growth rate. Randomized clinical trials have demonstrated improved local control and survival when altered fractionation schemes that deliver conventional or higher doses of radiation therapy are used over a shorter-than-conventional period.[69] Therefore, a break in radiation therapy because of mucositis may lead to treatment failure.

Prevention and Treatment

In light of the serious deleterious effects that radiation-induced oral mucositis may have on a patient's well-being and the potential loss of tumor control that may result from an interruption or prolongation of treatment because of mucositis, measures for preventing mucositis are being investigated. Benzydamine hydrochloride 0.15% oral rinse, a nonsteroidal drug, that has analgesic, anesthetic, anti-inflammatory, and antimicrobial properties, is effective, safe, and well tolerated for prophylactic treatment of radiation-induced oral mucositis.[49,70] Nonetheless, benzydamine is not approved for this use in the United States, as the data are not convincing regarding its benefit and as some of the studies looking at it used an alcohol-based control arm (which should cause toxicity in patients getting radiation therapy) instead of an inert placebo substance.

Several controlled clinical trials have evaluated the combination of relatively nonabsorbable antibiotics (tobramycin, polymyxin E, and amphotericin B or bacitracin, clotrimazole, and gentamicin or iseganan) for patients undergoing radiation therapy to the oral cavity.[49,71–79] In total, these trials do not provide convincing data of sufficient clinical magnitude to recommend use of antimicrobial mouthwashes (chlorhexidine or benzydamine), antibiotic lozenges, or paste as part of standard practice. For a critical review, the reader is referred to an article by Sutherland and Browman.[80]

The inability to control mucositis-related pain can be frustrating for both the patient and the treating physician. Viscous lidocaine with 1% cocaine; dyclonine hydrochloride 1.0%; a mixture of kaolin-pectin solution, diphenhydramine, and saline; morphine; tricyclic antidepressants; a mucosa-adhesive water-soluble polymer film containing topical anesthetics and antibiotics; oral aloe vera; capsaicin lozenges; and a sodium-sucrose octasulfate oral rinse have all been evaluated, with mixed results.[81–86] Janjan and colleagues[87] reported improved pain management in patients undergoing radiation therapy for head and neck cancer with daily nursing intervention consisting of instructions on the use of mouthwashes and a three-step analgesic protocol consisting of acetaminophen, acetaminophen with codeine suspension, and liquid morphine for relief of mild, moderate, and severe pain, respectively. The physician promptly changed the prescribed analgesic regimen when the patient's symptoms changed. Patients who had daily nursing intervention reported fewer days of moderate and severe pain; had less pain throughout the day; and noted less disturbance in sleep, eating, and energy level. Daily review of a symptom survey by a radiation oncology nurse combined with a well-defined strategy for mouth care and analgesics appeared to improve pain management of radiation-induced oropharyngeal mucositis because of prompt attention to patient needs. Many narcotic pain medications come in a liquid formulation that is relatively easy to swallow or can be administered through a feeding tube. Fentanyl patches are also very effective for patients who cannot swallow. A topical morphine mouthwash might be a more effective treatment for mucositis pain than a commonly utilized "magic mouthwash" (lidocaine, diphenhydramine, magnesium aluminum hydroxide).[88]

Additional interventions for preventing or minimizing radiation-induced mucositis have been evaluated. One such intervention involves the use of a sucralfate suspension, an agent that appears to provide a protective barrier and may also have a cytoprotective effect. The latter may be mediated through prostaglandin release, resulting in increased mucosal blood flow, increased mucus production, increased mitotic activity, and a surface migration of cells. However, results from small double-blind, placebo-controlled, randomized prospective trials are contradictory.[89–95] Thus, the randomized trials of sucralfate for therapy-induced mucositis do not establish a role for sucralfate in clinical practice.

In an evaluation of another intervention, Maciejewski and colleagues[96] reported that painting the buccal mucosa with a 2% silver nitrate solution for several days before radiation therapy stimulates normal mucosa repopulation during radiation therapy, producing a significantly less severe mucosal reaction and faster mucosal healing after completion of radiation therapy. Low-energy laser therapy might also activate epithelial healing. A phase III, randomized, placebo-controlled trial to evaluate the efficacy of low-energy

helium-neon laser in the prevention of radiation-induced mucositis demonstrated significant reductions in severity and duration of oral mucositis associated with radiation therapy, even when combined with chemotherapy.[97] A double-blind, placebo-controlled, randomized trial of treatment with 40 mg of prednisone, beginning on day 8 of an accelerated course of radiation therapy, did not show a reduction in the intensity or duration of mucositis. However, there was a trend favoring prednisone in terms of shorter treatment interruptions and a significant reduction in overall treatment time.[98] Zinc sulfate, α-tocopherol, and intravenous L-alanyl-L-glutamine have been found to be effective in decreasing the severity of radiation-induced mucositis and oral discomfort in placebo-controlled prospective trials.[48,99,100] In an uncontrolled evaluation, orgotein, a Cu-Zn superoxide dismutase, demonstrated reduced acute toxicity associated with radiation therapy.[101] These unique approaches to the problem of acute mucositis deserve further study.

Other preliminary studies have investigated the direct application of a prostaglandin E_2 gel,[102] the use of oral glutamine,[103] and daily use of subcutaneous GM-CSF.[104] Results of pilot studies suggested that GM-CSF might be quite effective in the prevention and treatment of radiation-induced oral mucositis.[105–108] However, prospective randomized clinical trials have revealed no definite evidence that subcutaneously administered GM-CSF reduce the severity of radiation-induced mucositis.[109,110] On the other hand, some early murine mucosal and human clinical data suggest that keratinocyte growth factor might be efficacious in the prevention and treatment of radiation-induced mucositis.[55,111–113] This was previously reviewed in the section on prevention of chemotherapy-induced oral mucositis. A multicenter study of intravenous palifermin to reduce mucositis in patients with head and neck cancer receiving chemoradiotherapy is being conducted by the Radiation Therapy Oncology Group.

The radioprotector amifostine has been evaluated as a means of preventing radiation-induced acute mucositis. One small randomized clinical trial reported that amifostine reduced the severity of acute mucositis.[114] Unfortunately, larger randomized trials evaluating intravenous or subcutaneous amifostine in patients receiving radiation therapy alone or combined with chemotherapy have revealed conflicting results.[115–119] Nausea, vomiting, hypotension, and allergic and injection site reactions are common side effects of this drug. These side effects may be reduced by rapid intravenous push, optimal hydration of the patient, premedication with antiemetics, and subcutaneous administration. The questionable efficacy and significant toxicity are associated with remarkably increased costs.[120] In total, present data are insufficient to recommend amifostine at the current dose and schedules to prevent mucositis associated with radiation therapy.[121]

One should not forget the role that sophisticated radiation therapy treatment planning can have in limiting the volume of normal tissues that are irradiated and thereby reducing the severity of normal tissue reactions. Normal tissue reactions can be reduced in a substantial number of patients with head and neck cancer by the use of computed tomography-based target delineation, intensity-modulated radiation therapy and simple, custom-made, intraoral devices that are designed to exclude uninvolved tissues from the treatment portals or to provide shielding of tissues within the treatment area.[118,122,123] Patients with primary cancers of the oral cavity, oropharynx, paranasal sinuses, and salivary glands are the best candidates for the use of such devices. These intraoral stents can be very useful in excluding the mucosa of the tongue and the floor of the mouth when hard palate, nasal cavity, and paranasal sinus malignancies are being treated. These same stents can be useful in excluding the palate mucosa during treatment of the tongue or floor of the mouth. Shielding stents made with a lead alloy were found to be useful in treatment of well-lateralized tumors of the oral cavity, parotid gland, lip, and skin of the cheek. These shielding stents can decrease the amount of radiation that is delivered to the contralateral mucosa. More frequent use of electron-beam and/or sophisticated three-dimensional conformal, multibeam, wedged-pair, or oblique treatment plans will also help to exclude or minimize the radiation dose to uninvolved mucosa. Packing gauze between metallic dental restorations and mucosa of the lateral tongue and buccal area appears to be very beneficial in minimizing the dose from scattered radiation.

Given these data, what measures should be taken to prevent and treat mucositis in patients receiving radiation to the oral cavity? Standard practice often includes aggressive, good oral hygiene consisting of brushing teeth after each meal, using a soft toothbrush and baking soda toothpaste, and rinsing the mouth every 2 hours throughout the day with a half-strength hydrogen peroxide or alkaline solution. Patients should be instructed to avoid the use of irritating or abrasive substances such as commercial toothpastes and mouthwashes; tobacco; alcoholic beverages; extremely hot or cold drinks or foods; very spicy foods; acidic foods such as citrus fruits and their juices; and foods that are hard and coarse, such as pretzels, raw vegetables, potato chips, crackers, and hard bread. When discomfort develops, topical anesthetic agents can be used. As the pain progresses, use of systemic analgesics, including acetaminophen with codeine suspension or oral morphine sulfate elixir, might become necessary. Suspensions are preferred over elixirs because suspensions are formulated without alcohol. As Janjan and colleagues suggest,[87] daily intervention by a radiation therapy nurse or physician with prompt increases in doses of systemic analgesics appears to result in improved pain control, improved sense of well-being, and less weight loss.

The mucosa of patients undergoing radiation therapy to the oral cavity should be examined at least once a week, and antibiotic or antifungal medications should be prescribed as infections are documented. Clotrimazole troches, one dissolved in the mouth five times a day for 14 days, generally work well for oral candidiasis. However, if significant mucositis, altered taste, or xerostomia has developed, the troches might not be tolerated. In this situation, nystatin oral suspension or fluconazole in tablet or liquid form is often effective. Fluconazole is more effective than nystatin and might need to be given at a higher dose and/or for an extended period of time in patients who are receiving combined chemotherapy and radiation therapy due to infections with resistant species.[124,125]

Xerostomia

Etiology

The major salivary glands (parotid, submandibular, and sublingual) produce most of the salivary secretion (up to 80%). The rest of the saliva is produced by minor glands scattered throughout the oral cavity. It is estimated that the sublingual glands contribute only 2% to 5% of the salivary flow rate. Submandibular glands seem to be as important as, or more important than, parotid glands in the resting state, although parotid glands become the main contributors under stimulation.

When radiation therapy treatment fields include the major salivary glands, many patients will experience dryness of the oral mucosa during the first 1 or 2 weeks of treatment. Not only is the quantity of saliva reduced, but its composition and physical properties are changed as well. Drastic reductions of baseline and reflex production of alkaline and watery secretions of serous acini often persist after the completion of radiation therapy. Without appropriate management, this problem can lead to progressive deterioration of the teeth, mucosa, gingiva, and mandible.

The acute radiation response of serous salivary glands has been shown to be due to interphase killing of serous cells. Chronic atrophy of these glands is attributed to the death of the reproductive stem cells and damage to the fibrovascular stroma. A progressive reduction in salivary flow rates, pH, and secretory immunoglobulin A (IgA) with increasing doses of radiation therapy has been demonstrated. In 90% of parotid glands that receive less than 1000 cGy, there will be continued secretion of measurable quantities of saliva after stimula-

tion. This is reduced to 50% after administration of 3000 cGy, 19% after 5000 cGy, and 0% after 7000 cGy. In 94% of patients receiving doses of less than 5200 cGy, there may be recovery of secretion beginning 2 months after treatment with continual improvement of the salivary flow for up to 18 months. Doses exceeding 6400 cGy cause irreversibly depressed parotid function in the majority of glands. Patients who receive doses of more than 6400 cGy to one gland might have only slight dryness; however, patients with both glands irradiated will have severe problems with salivary flow and discomfort of dryness. Exclusion of more than 50% of both parotid glands from the direct radiation beam can prevent severe dryness when the rest of the major salivary glands are included in the field. There is a linear correlation between postradiotherapy flow ratio and parotid gland dose (5% loss of function per 1 Gy of mean dose) and a strong parotid volume dependency.[126] There is no threshold dose. Therefore, in radiation treatment planning, attempts should be made to achieve as low a mean parotid dose as possible. A mean dose below 39 Gy has a complication probability of 50%. Recovery of parotid function can be demonstrated at 6 months, 12 months, and 5 years after radiation therapy.[127,128]

Eisbruch and colleagues[129] and Blanco and colleagues[126] suggested that a mean parotid gland dose of ≤26 Gy should be a planning goal if substantial sparing of the gland function is desired. Using the Normal Tissue Complication Probability model, they found that the dose/volume/function relationships in the parotid glands are characterized by dose and volume thresholds, steep dose/response/function relationships when the thresholds are reached, and a maximal volume dependence parameter. Chao and colleagues[130] observed a correlation between mean parotid dose and the fractional reduction of stimulated saliva output at 6 months after the completion of radiation therapy. They also noted that responses to quality-of-life questions on eating and speaking functions were significantly correlated with stimulated and unstimulated saliva flow at 6 months. Therefore, sparing of the parotid glands should translate into objective and subjective improvement of xerostomia and quality of life in patients with head and neck cancer receiving radiation therapy. Eisbruch and colleagues[129] found that the degree of xerostomia was related to the degree of preradiation therapy xerostomia, the time since radiation therapy, and the mean dose to the major salivary glands (most notably the submandibular gland) and to the oral cavity. This would suggest that sparing of the oral mucosa with its minor salivary glands is an important goal in treatment planning to reduce the severity of radiation-induced xerostomia.

Prevention and Treatment

Treatment of radiation-induced xerostomia includes the avoidance of any drugs that might also decrease the flow of saliva and contribute to the discomfort of xerostomia. These drugs may include anorectic agents, anticholinergics, antidepressants, antihistamines, antihypertensives, antipsychotics, antiparkinsonian agents, diuretics, caffeine, nicotine, hypnotics, and sedatives. Patients should be advised to take frequent sips of water and suck on ice chips. Because chewing stimulates the flow of saliva, patients with residual salivary function may be helped by eating foods such as carrots or celery or by chewing sugarless or xylitol-containing gum. Patients with xerostomia are highly susceptible to dental caries and should not use sugar-containing foods or acidic foods or beverages to stimulate salivary flow. Commercial nonprescription solutions that are used to lubricate the oral tissues might be the only effective treatment for patients without functioning salivary gland parenchyma or for those whose salivary glands do not respond to stimulation. Virtually all lubricants can provide some short-term relief for patients with xerostomia. Some studies have indicated that salivary substitutes that contain carboxymethylcellulose or hydroxymethyl cellulose are more effective in relieving dryness than are water- or glycerin-based solutions. Some patients prefer mucopolysaccharide solutions. Xialine, a xanthan gum–based saliva substitute, has been shown to be no better than placebo in decreasing the effects of xerostomia, although a trend was seen in favor of Xialine for improving problems with speech and senses.[131] Various reports have suggested that acupuncture can subjectively (patient-completed xerostomia inventories) and objectively (unstimulated and stimulated salivary flow rates) reduce symptoms of xerostomia and improve salivary flow rates.[132–134]

For the treatment of established radiation-induced xerostomia, the following are recommended (Box 40-3):

- Pilocarpine: 5.0 mg, given orally three to four times a day, up to 10 mg three times a day maximum
- Artificial saliva (Mouthkote, Xerolube, Moistir, Salivert, Sage)
- Biotene products (gum, toothpaste, mouthwash)

Xerostomia primarily affects mastication and oral manipulation of dry, absorbent food material. Initiation and duration of the pharyngeal swallow do not appear to be affected. Patients with severe xerostomia may be helped by eating soft, bland foods, especially cool or cold foods with a high liquid content, such as ice cream, Popsicles, puddings, watermelon, and grapes. Solid foods can be made easier to swallow by adding gravies, sauces, melted butter, broth, mayonnaise, yogurt, or salad dressing. Dunking bread and other baked foods in milk or other liquids will make them easier to swallow. Some patients may find a pureed diet or a full-liquid diet easier to swallow than solid foods. Addition of a liquid high-protein supplement will help to ensure that patients are getting enough protein and calories. Hot, spicy, or acidic foods may be irritating and should be eaten with caution. Some patients find that a vaporizer or humidifier in the room or at the bedside helps to alleviate the discomfort of xerostomia. Frequent oral rinses with an alkaline solution may help to refresh the taste, moisten the mouth, and promote better hygiene.

Two large randomized, double-blind, placebo-controlled, multicenter clinical trials have documented the efficacy of oral pilocarpine (5.0 mg given orally three times a day) in relieving oral dryness; improving salivary flow, mouth comfort, and ability to speak; and reducing the need for oral comfort agents after head and neck irradiation. Adverse reactions are minimal, the most common being mild to moderate sweating, which is dose-related. Best results may require continuous treatment for more than 8 weeks.[135–137] Most patients report significant relief of symptoms of xerostomia and improvement in quality of life that do not appear to be dependent on previous radiotherapy dose/volume parameters, suggesting that oral pilocarpine acts primarily by stimulating ectopic salivary glands and can be of benefit for a whole range of patients with xerostomia of varying severity. Topical pilocarpine administration has shown results similar to those achieved with systemic treatment but with improved patient tolerance.[138]

One small retrospective trial and two small double-blind, placebo-controlled, randomized trials suggested that pilocarpine (5.0 mg given orally four times a day), started the day before or on the same day as radiation therapy, given concurrently with radiation therapy

Box 40-3. PREVENTION AND THERAPY OF RADIATION-INDUCED XEROSTOMIA

Prevention of radiation-induced xerostomia has been actively studied in the recent past. Results from the use of pilocarpine in this situation have been mixed, the largest placebo-controlled trial being negative. However, on the basis of results of clinical trials, the FDA has approved amifostine in the adjuvant setting as an agent that can attenuate the development of xerostomia. Nonetheless, the inconvenience and toxicity of this drug therapy limit its use in some practices. Intensity-modulated radiation therapy has been shown in a phase III trial to preserve salivary flow and improve quality of life in patients with early stage nasopharyngeal carcinoma.

and for 3 months after radiation therapy, results in a lower frequency of oral symptoms and xerostomia during treatment and afterward. It might not be necessary to continue the use after 3 months to maintain the benefit.[139–141] Two large placebo-controlled clinical trials conducted by Princess Margaret Hospital and the Radiation Therapy Oncology Group nonetheless failed to confirm these initial findings and did not demonstrate any reduction in the incidence or severity of radiation-induced xerostomia with prophylactic use of pilocarpine 3 days before radiation therapy, during radiation therapy, and for 3 months after completion of radiation therapy.[142,143]

Amifostine appears to protect the salivary glands from the effects of radiation therapy and might prove to be helpful in preventing or minimizing the effects of xerostomia and loss of taste.[114–116,119,144,145] Buntzel and colleagues,[114] Brizel and colleagues,[116,] Wasserman and colleagues,[144] Antonadou and colleagues,[115] and Jellema and colleagues[145] have all reported significant reduction in the severity of acute and chronic radiation-induced xerostomia with prophylactic use of amifostine as determined by non-placebo-controlled clinical trials. There was no evidence that amifostine interfered with the antitumor effects of radiation therapy as measured by local or regional control and overall survival. Jellema and colleagues compared no amifostine to amifostine three times weekly and five times weekly amifostine. Grade 2 or greater late xerostomia differed significantly at 6 months (74% for no amifostine, 67% for three times weekly, and 52% for five times weekly) but not thereafter. Patient-rated xerostomia deteriorated more in the patients who received no amifostine. There was no difference between three times weekly and five times weekly administration of amifostine. Nausea and emesis were common side effects with 28% of patients discontinuing the amifostine before the end of radiotherapy.[145] Subcutaneous administration of amifostine may be as effective as intravenous administration with less severe nausea, vomiting, and hypotension but more frequent cutaneous toxicity.[146] It is of interest to note the continued reduction in the incidence of grade ≥2 xerostomia, and increased unstimulated and stimulated saliva production at 12, 18, and 24 months in the patients not receiving amifostine. In addition, while the mean overall scores for the patient benefit questionnaire are improved significantly by amifostine at 12 months, there are no significant differences at 18 or 24 months.[144] A placebo-controlled phase III trial failed to confirm the radioprotective benefit of amifostine on salivary function following chemoradiotherapy.[118] Patient self-reported xerostomia questionnaire scores are a more accurate reflection of the severity of xerostomia, since physician-assessed scores underestimate the severity of xerostomia.[147] A small randomized trial demonstrated that amifostine might prevent deterioration of dental health.[148] The use of amifostine may be considered to decrease the incidence of acute and late xerostomia in patients undergoing fractionated radiation therapy in the head and neck region that includes the salivary glands.[121] The Food and Drug Administration has approved amifostine for use in the postoperative adjuvant setting.

In selected patients with cancers in the oropharynx, hypopharynx, or larynx, it has been reported that surgical transfer of a submandibular gland into the submental space can be successfully accomplished.[149] If patients require postoperative radiation therapy, the submandibular gland can more readily be excluded from the irradiated volume, thus preserving some saliva production. This process requires validation by controlled clinical trials.

Three-dimensional conformal and intensity-modulated radiation therapy has been shown in prospective uncontrolled and controlled phase III clinical trials to preserve parotid salivary flow and improve quality of life by reducing the dose to the parotid glands.[117,129,130,150,151] Altered fractionation radiation therapy schedules may also help to preserve salivary function. Leslie and Dische[152] evaluated the function of parotid glands in patients treated with three different radiation therapy schedules 9 or more months after completion of treatment. Twelve parotid glands that had received conventionally fractionated radiotherapy to a dose of 60 to 66 Gy showed a mean percentage flow of 20% and a significant decrease in saliva pH. Six glands that had received continuous hyperfractionated accelerated radiation therapy showed mean percentage flows of 65% with only slight and nonsignificant decreases in saliva pH. These results were attributed to the lower dose per fraction used, with subsequent greater repair of sublethal damage between treatment fractions.

Dental Caries

Etiology

Patients undergoing radiation therapy to the oral cavity have an increased incidence of caries because of the lack of saliva to cleanse the teeth and changes in the quality of the saliva. This promotes oral cavity colonization with a more cariogenic flora. In addition, the discomfort associated with xerostomia and persistent mucositis may result in poor oral hygiene with infrequent brushing, flossing, and oral rinses. Some patients may also alter their diet to include sugar-containing drinks and soft foods to help alleviate the effects of xerostomia. Rampant caries can occur, involving all tooth surfaces (including the cervical portion) after just a few months of xerostomia.

Prevention and Treatment

To prevent the development of dental caries (which may result in the need for extraction, soft-tissue necrosis, bone exposure, and osteoradionecrosis) after a course of radiation therapy, all patients should undergo a thorough dental evaluation before treatment. Nonsalvageable teeth should be extracted, and an alveolotomy and primary wound closure should be performed, if indicated. A thorough dental prophylaxis should be performed, including scaling, root cleaning, curettage, and polishing. Restorative dental procedures, including surgical endodontics, should be performed for salvageable teeth. A preventive regimen should be initiated, including plaque removal with the use of dental floss and thorough instructions for correct toothbrushing. Custom-made fluoride carriers should be fabricated, and a neutral 1.1% sodium fluoride gel should be applied to the teeth after breakfast and before bedtime for a period of 2 weeks, beginning as soon as possible after the initiation of radiation therapy. This may be reduced to one bedtime application for 1 month and then twice-weekly fluoride applications indefinitely. Some patients may require twice-daily application throughout their lifetime. The dosage of the fluoride should be modified according to the patient's history of dental caries and oral hygiene performance. Patients should also use a calcium phosphate remineralizing rinse immediately after fluoride applications. Combined fluoride and calcium formulations are available.

Edentulous patients should have their dentures evaluated, and ill-fitting dentures should be corrected. Patients should be discouraged from wearing their dentures until the mucosa is completely healed from the acute effects of radiation therapy (usually about 3 months).

After radiation therapy, patients should be seen every 3 months for frequent dental checkups. There is no concern regarding the additional X-ray exposure of dental films, because the dose is insignificant in comparison with the therapeutic dose that is given for the cancer therapy. All routine dental procedures can be performed without unusual precautions after a course of radiation therapy except radical periodontal treatment and extractions, which may lead to osteoradionecrosis if not done with special care. When extractions are required after a course of radiation therapy, it is best to remove one tooth at a time with as little trauma to adjacent tissues as possible and to wait until healing is complete before proceeding to further extractions. Prophylactic antibiotic coverage should be started 1 day before extraction and be continued until the site is completely healed. Some institutions favor the use of hyperbaric oxygen before extraction.[153] Primary closure of the wound should be carried out

over a smooth, bony surface so that no sharp spicules or ridges are left beneath the mucosa. Postradiation therapy tooth extractions carried out in this manner have a good chance of complete healing without the development of necrosis. When extreme root sensitivity occurs after radiation therapy, brushing fluoride onto the exposed root surface and using specially formulated commercially available toothpaste appears to decrease the sensitivity to some extent.

Soft-Tissue and Bone Necrosis

Etiology

The soft-tissue necrosis of oral cavity mucosa that occurs after high doses of radiation therapy may be attributed to the obliteration of small blood vessels or severe mucositis with ulceration. Irradiated epithelium is thinner than normal and appears pale and atrophic. It also has telangiectatic vessels. The irradiated mucosa is more susceptible to mechanical injury and to the noxious effects of alcohol and tobacco. Soft-tissue necrosis usually begins with breakdown of damaged mucosa, resulting in a small ulcer. Most soft-tissue necroses will occur within 2 years after radiation therapy. Occurrence after 2 years is generally preceded by mucosal trauma. The risk of soft-tissue necrosis is increased with larger fraction sizes, higher total doses, large volumes of irradiated mucosa, and the use of an interstitial implant.

Treatment

If recurrent cancer is not clinically suspected, biopsy should be avoided, because this may enlarge the area of necrosis. Topical anesthetics can relieve the discomfort associated with soft-tissue necrosis and allow the patient to eat normally. Antibiotics often provide pain relief, particularly when the ulceration is deep and infected. It is essential that the patient discontinue the use of alcohol and tobacco. If the area of necrosis is traumatized by dentures, the dentures should not be worn until healing is complete.

More than 90% of soft-tissue necroses will heal with conservative treatment, although in some instances, it might take many months. A small trial (consisting of 12 patients with 15 sites of late radiation necrosis of the soft tissues) has been conducted to evaluate the effect of pentoxifylline on healing radiation necrosis. The average duration of nonhealing before treatment with pentoxifylline was 30.5 weeks. With the institution of pentoxifylline (400 mg given orally three times a day), 13 of 15 necroses healed completely, and one partially healed an average of 9 weeks after treatment was started. All patients had pain relief.[154] Additional case reports and small clinical trials have suggested that the combination of pentoxifylline, tocopherol, and clodronate may be beneficial in preventing and healing severe osteoradionecrosis, radiation-induced trismus, radiation-induced ulcerated fibrosis, soft-tissue necrosis, and mucosal necrosis.[155–162] These results support further study of pentoxifylline in patients in whom soft-tissue necrosis develops after a course of radiation therapy.

The mandible and maxilla will tolerate rather high doses of radiation therapy without serious problems, as long as the tissues overlying the bone remain intact. If soft-tissue necrosis develops in the mucosa overlying the mandible or maxilla, the underlying bone may become exposed. This can lead to serious injury, resulting in bone necrosis (osteoradionecrosis). Compared with the maxilla, the gingiva of the mandible has a rather tenuous blood supply, placing the mandible at greater risk of exposure and necrosis. Most bone exposures will heal spontaneously after conservative treatment. Small areas of bone exposure (<1 cm) generally heal spontaneously after a period of weeks to months. Larger areas of bone exposure may persist for a long period and may lead to bone necrosis, followed by sequestration. If exposed, necrotic bone may become infected. The necrotic process may then extend to involve adjacent bone for a considerable distance. Severe necrosis can then develop and lead to orocutaneous fistulae and pathologic fractures.

If the bone is rough or protrudes above the level of the gingiva, an oral surgeon may remove it to promote healing. Local debridement of moderate-size necrosis can be performed by an oral surgeon if indicated. If the patient wears a denture, it should be withheld from use or relieved over the site of exposure. Pain is not a common symptom; if present, it can usually be controlled with analgesics. A local anesthetic can be applied with a cotton-tipped applicator if needed for pain control. Antibiotics frequently reduce infection and discomfort within a few days but should be continued for 2 to 3 weeks. Hyperbaric oxygen along with antibiotic therapy and local debridement may help promote healing. Mandibular resection should be reserved as the last resort for the patient with intractable pain, recurrence of severe infections, fracture, or trismus.

Most bone problems develop within 3 to 12 months after radiation therapy, but some risk persists for many years, especially if the patient undergoes dental extractions. Necrosis is most likely to occur after extraction of mandibular teeth, although this is infrequent if special precautions are taken. The edentulous patient has a lower overall risk for bone necrosis compared with the dentulous patient.

Patients who are at highest risk for osteoradionecrosis appear to be those with tumors involving the gingiva or bone; those who continue to smoke or drink or both after radiation therapy; and those who receive high doses of radiation therapy, large treatment volumes, large fraction sizes, and/or interstitial implants.

Taste Alterations

Loss of taste occurs rapidly early in the course of radiation therapy to the oral cavity. Most patients report that the sense of taste is essentially nonexistent by the third or fourth week of treatment. After the completion of radiation therapy, most patients report some taste improvement within 1 to 2 months. Full recovery of taste usually requires 2 to 4 months. In some patients, taste never returns to normal, at least in part because of xerostomia. Although some studies have suggested that zinc therapy may be useful in improving taste acuity, a randomized clinical trial did not show any benefit for zinc over a placebo.[163] Amifostine may protect against taste loss caused by irradiation.[114,116]

Trismus

Etiology

Trismus may be caused by fibrosis of the muscles of mastication after high-dose radiation therapy to the oral cavity or oropharynx, surgical scarring, and/or advanced carcinomas involving the pterygoid and/or masseter musculature. The temporomandibular joint itself is relatively resistant to ankylosis caused by radiation therapy, but the risk of injury increases if the joint is invaded by tumor. The use of large daily treatment fractions also appears to increase the risk of trismus.

Prevention and Treatment

High-energy x-ray beams and sophisticated multiple-field techniques should be used whenever possible to reduce the dose of radiation therapy to the temporomandibular joint and to the muscles of mastication. Patients who are treated with both surgery and radiation therapy have a greater risk for trismus than do patients who are treated with either modality alone. Patients who are at high risk for trismus and those in whom trismus has developed before treatment should perform jaw-stretching exercises daily in an attempt to increase the interarch or interincisor distance. A number of techniques are used, including commercially available jaw-stretching tools and less expensive stacked tongue blades, tapered corks, or clothespins. These devices are inserted between the teeth to increase the interincisor distance until slight pain is encountered. The exercises should be done for about 30 seconds every 2 hours. Additional tongue blades can be added, or a thicker aspect of the cork can be placed between

the teeth every few days to increase the interincisor distance and stretch the muscles of mastication.

Malignancy

The carcinogenic effect of ionizing radiation has long been recognized. The latent interval between radiation therapy and the development of cancer varies from several to many years. Kogelnik and colleagues[164] reviewed charts of 1163 patients treated for head and neck cancer at the M.D. Anderson Cancer Center who had survived a minimum of 5 years after treatment without having recurrent cancer. Follow-up for these patients ranged from 7.5 to 25.5 years. Patients were treated with surgery alone (337 patients) or radiation therapy with or without surgery (826 patients). The incidence of new cancers in the primary tumor site (1.8% versus 2.7%), within the immediate vicinity of the primary tumor (4.2% versus 3.1%), or at sites remote from the primary tumor but still within the oral cavity or pharynx (4.7% versus 5.7%) was very similar for patients treated with surgery alone and patients treated with irradiation with or without surgery, respectively. It was concluded that moderate or high-dose radiation therapy did not produce any new squamous cell carcinomas of the mucous membranes. Similar findings were reported from the Fox Chase Cancer Center[165] and the University of California, Los Angeles.[166]

The rarity of radiation-induced sarcomas, the long latent period before their development, and the difficulty in obtaining reliable long-term follow-up data make the task of estimating the true risk of this problem difficult. However, most series include one or two cases of radiation-induced bone sarcoma per 1000 5-year survivors. If one were to assume malignant induction in 1 patient of every 500 long-term survivors, then with an estimated 5-year survival rate of 40% for all patients with head and neck cancer who received radiation therapy, it is calculated that 1 case would be induced per 1250 patients treated. A review of the Mayo Clinic experience showed no difference in survival between patients with radiation-induced sarcomas of the mandible or maxilla and non-radiation-induced sarcomas of the same site (45% 5-year overall survival).

Because some patients with radiation-induced osteogenic sarcomas of the mandible or maxilla can be cured, the risk of dying from a radiation-induced sarcoma after a course of radiation therapy is minimal and is very similar to the risk of death that a patient accepts when undergoing chemotherapy, general anesthesia, general surgery, or major head and neck cancer surgery.

An association has also been noted between radiation therapy and thyroid tumors. The latent period is usually 10 to 30 years. Almost all reported cases have followed low doses of radiation therapy (<6 to 1500 cGy), well below the doses that are used for squamous cell carcinomas of the head and neck.. Doses greater than 2000 to 3000 cGy are associated with a very low risk of induction of thyroid neoplasia compared with lower doses. This is likely because higher doses of radiation therapy either completely destroy follicular cells or at least render the surviving cells incapable of division. Not all thyroid neoplasms that develop after radiation therapy are malignant, and many of the malignant neoplasms that do develop (papillary and follicular carcinomas) are readily curable with surgery. Thus, the risk of radiation-induced carcinoma should not be a major factor in determining treatment approaches for the typical patient with head and neck cancer.

Implementation of Prevention and Treatment of Radiation-Induced Oral Complications

Jansma and colleagues[167] surveyed all Dutch radiation therapy centers in which irradiation of patients with head and neck cancer is performed to determine which prevention and treatment regimens are used for oral sequelae resulting from head and neck radiotherapy. Survey questions included queries about screening, care before irradiation, care during radiation therapy, care during postradiation therapy, and the composition of the dental team who evaluated and treated the patients undergoing radiation therapy. Unfortunately, these investigators found a great diversity in the preventive approach to treatment of patients with head and neck cancer at Dutch radiotherapy institutes. Disturbing findings included a lack of well-defined guidelines in many centers, absence of a dental team at some centers, absence of an oral hygienist on some dental teams, and the observation that many patients were not referred to the dental team in a timely manner. The investigators recommend the development of a general protocol for the prevention of oral complications applicable at all head and neck cancer radiation therapy centers.[168] Similar deficiencies are probably present at the head and neck cancer radiotherapy centers within the United States. It is strongly recommended that dedicated teams be assembled to administer aggressive care to patients receiving radiation therapy to the oral mucosa. These teams should institute preventive measures and treat symptoms early in their course.

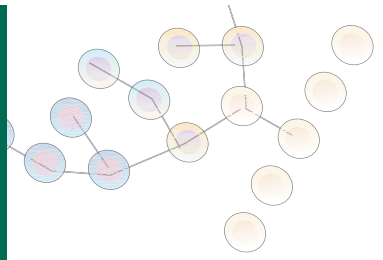
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41 Alopecia and Cutaneous Complications

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SUMMARY OF KEY POINTS

The human skin that serves as the interface between the living organism and the external environment is in fact the largest and most complex human organ. Its complexity is directly related to the myriad of specialized cells, tissue types, and structures that allow the skin to carry out many vital functions including maintenance of body temperature and protection against the ingress of infectious organisms and noxious chemicals, as well as the egress of vital tissue fluids. It is highly probable that the complex anatomy and physiology of the skin make it a major target of chemotherapy-induced toxicity.

Incidence

Cutaneous reactions are among the most common adverse drug reactions to occur in patients undergoing medical treatment for cancer. The incidence and severity of such reactions vary depending on the class of agent or agents, the route and frequency of administration, the dosage of drug or drugs given, and the specific tissue type involved. Some agents may cause toxicity only after the patient has been exposed to one more additional physical agent, such as ultraviolet light or x-ray emissions.

Etiology of Complication

Causes of adverse cutaneous reactions to cancer chemotherapeutic drugs are quite varied but tend to be characteristic and often unique to a particular agent or category of agents. Some reactions, such as those seen as a result of infiltration of drug during infusions, are caused by direct toxicity of the drug on any and all involved tissues. These reactions are often associated with regimens using the alkylating agents, the vinca alkaloids, and the antibiotics. Other reactions occur as a result of the specific tissue-targeted effect of an agent, such as alopecia associated with a variety of mitotic inhibitors, or the "pustular-like" eruption so commonly associated in epidermal growth factor receptor (EGFR)–targeted therapy. Cutaneous "hypersensitivity reactions" are also fairly common.

Evaluation of the Patient

Because the number and types of cutaneous reactions to cancer chemotherapy are large and quite variable, each having its own unique set of cutaneous and histopathologic findings, there are no well-established guidelines that may be commonly adhered to in patient evaluation. Patient skin signs and overall symptoms are one's best guides to evaluation and treatment. Histopathologic examination of skin specimens is often helpful as well.

Grading of the Complication

Unlike grading of complications in other organ systems, grading of cutaneous complications associated with cancer chemotherapeutic drugs has until recent years been poor, inconsistent, and often not addressed even in conjoint studies of a single agent. Interest in a more precise dermatologic examination and better grading of the severity of cutaneous eruptions has been stimulated by several recent reports that show a correlation between the extent and severity of the cutaneous eruption caused by a group of EGFR antagonists, and disease response and patient survival. It should be noted that at this point in time there is not universal acceptance of this concept (Table 41-1).

Treatment

Treatment approaches to the large variety of cutaneous responses to cancer chemotherapeutic drugs are as varied as there are reactions and teams of investigators addressing these reactions. To reduce patient morbidity and assure early initiation of the most appropriate treatment plan, it is most appropriate and beneficial to the patient to obtain dermatologic and surgical consultation, if needed, at the earliest stage of the reaction.

INTRODUCTION

As with other pharmacologic agents used in the treatment of human disease, the administration of most cytotoxic or cancer chemotherapeutic agents can result in toxic side effects. Moreover, as with other pharmacologic agents, toxicity is often manifested in the skin. Some toxic side effects occur at ordinary therapeutic drug dosages, whereas others occur as an extension of a therapeutic drug effect at higher dose levels. Toxic drug reactions in the skin may occur as idiosyncratic or allergic drug reactions.

Cancer chemotherapeutic drugs produce many common skin conditions, such as pruritus, urticaria, and angioedema. They also cause cutaneous reactions that are not shared by any other agent or class of agents—for example, the sclerotic effect that bleomycin can have on the skin.

A description of all the cutaneous reactions to cancer chemotherapeutic agents is beyond the scope of this book. Instead, we have elected to highlight a group of reactions that are fairly common and yet unique to cancer chemotherapy. Some reactions are associated with fairly severe sequelae and might direct the ultimate course of

Table 41-1 National Cancer Institute and Eastern Cooperative Oncology Group Grading System for Dermatologic Toxicities

Toxicity Grade	National Cancer Institute	Eastern Cooperative Oncology Group
1	Maculopapular rash or erythema and no associated symptoms	Maculopapular rash or erythema and no associated symptoms
2	Maculopapular eruption or erythema, associated pruritus, or other symptoms; <50% of body surface area coverage or localized desquamation or other lesions covering <50% of the body surface area	Scattered maculopapular eruption or erythema with pruritus or other associated symptoms
3	Symptomatic generalized erythroderma or macular, papular, or vesicular eruption or desquamation covering >50% of the body surface area	Generalized symptomatic macular, papular, or vesicular eruption
4	Generalized exfoliative dermatitis, ulcerative dermatitis	Exfoliative dermatitis or ulcerating dermatitis

chemotherapy; others might appear severe upon occurrence but can be treated symptomatically, with no effect on the outcome of the treatment regimen. For completeness, Table 41-2 lists the various categories of cancer treatment agents and the dermatologic conditions they may cause.

NONSPECIFIC REACTIONS

Alopecia

Of the myriad of drug-related cutaneous toxicities encountered by the cancer patient, alopecia is the most common.[1] Hair loss is an unfortunate side effect, because hair appearance often dictates a patient's self- and body image. Patients, especially females, receiving cancer chemotherapy often find alopecia psychologically and emotionally devastating. In fact, the occasional patient who is unable to cope with alopecia and the associated psychic trauma often opts to forgo potentially curative treatments.

Etiology

Systemic administration of a variety of cancer chemotherapeutic drugs can produce alopecia. Drug-induced inhibition of hair follicle stem cells within the hair matrix causes a reduction in the number and size of epithelial cells contained within the hair shaft. This results in a partially constricted and weakened hair shaft that is susceptible to breakage from trauma as minor as simple combing. Complete cessation of hair formation can also occur. Antineoplastic agents vary in their effects on hair matrix epithelium, hence their ability to induce alopecia. The degree of hair loss secondary to cancer chemotherapy is related to dosage, regimen, and route of administration. Drugs with a strong propensity to induce alopecia include doxorubicin, daunorubicin, cyclophosphamide, and etoposide.[2–5]

Some novel dosage formulations of standard chemotherapeutic agents may ameliorate the extent of alopecia; for example, liposomes coupled with doxorubicin and mitoxantrone have been shown to significantly decrease the extent of drug-induced alopecia.[6,7]

Clinical Manifestations

Chemically damaged and mechanically manipulated hair is more susceptible to the effects of chemotherapy.[8] Anagen effluvium (loss of hair during the proliferative or growth phase of its cycle) may begin 1 to 2 weeks after a single dose of chemotherapy but will be most noticeable after 1 to 2 months of continuous drug administration. It can also occur as late as 2 to 3 weeks after cessation of chemotherapy.[8] Alopecia associated with anagen effluvium is most pronounced and widespread on the scalp, because this site normally contains 60% to 85% of its hairs in the proliferating anagen phase. Repeated drug doses given over the course of 1 to 2 months ultimately synchronize with each follicle's matrix cells in anagen phase; total inhibition of cell replication follows, and alopecia results. The eyebrows, eyelashes, beard, groin, and axillary hairs have fewer hair follicles in the anagen phase at any one time; consequently, repeated doses over many more months are required to achieve significant alopecia in these areas. The onset of telogen effluvium (loss of hair during the resting phase of its cycle) occurs approximately 3 to 6 months after the start of chemotherapy.

Pathology

The normal scalp hair growth cycle consists of an anagen (growth) phase, a catagen (involution) phase, and a telogen (resting) phase. About 60% to 85% of scalp hairs are always in the anagen phase, 1% are in the catagen phase, and the remainder are in the telogen phase. Body hairs are not synchronized in such phases. During the anagen phase, germinative cells within the matrix of scalp hair have a cell replication time approximating 24 hours. Thus, scalp hair, by virtue of its content of highly proliferative matrix cells, is particularly susceptible to growth inhibition by chemotherapeutic drugs that inhibit cellular proliferation. Inhibition (anagen effluvium) ranges from partial to total. Patients with fewer anagen hairs are less sensitive to anagen effluvium induced by chemotherapy. Less commonly, certain drugs, such as recombinant interferon-α2b (IFN-α2b), can induce the anagen hair into the dormant telogen phase, which is followed by a period of total hair epilation.[9] Telogen effluvium can also occur in response to the emotional stress of chemotherapy or to an anemia associated with chemotherapy, principally iron deficiency anemia.

Differential Diagnosis

Most often, patients receiving cancer chemotherapy experience anagen effluvium; only a few experience telogen effluvium. Anagen effluvium alopecia usually persists throughout the period during which drug is given. Normally, hair returns shortly after drug administration ceases. There is always a temporal relationship to drug administration. Telogen effluvium results principally from psychic or bodily stress, high fever, nonmatrix toxic medication, or poor nutrition. Telogen effluvium is first noticeable about 3 to 6 months after insult and is temporary. Hair growth generally resumes, even as chemotherapy is continued.

Treatment and Outcome

It is important for the clinician to fully appreciate the negative emotional devastation that chemotherapy patients, particularly female, experience with rapid loss of hair. Strategies to ameliorate this experience include preparing patients mentally for such an event and constant reassurance that this effect is only temporary. Patients should receive early information on scalp hair care and on the availability and acceptable of wigs and other scalp covering.[10] In cooperation with the American Cancer Society, the Cosmetic Toiletries

Table 41-2 Chemotherapeutic Agents and Common Cutaneous Side Effects

Alkylating agents	Alopecia
	Neutrophilic eccrine hidradenitis
	Pigmentation reactions—depigmentation and hyperpigmentation
	Angioedema
	Extravasation necrosis
	Dysethesia and erythrodysesthesia (acral erythema)
	Radiation recall
	Reactivation erythema
Antimetabolites	Hyperpigmentation
	Dysethesia and erythrodysesthesia (acral erythema)
	Radiation recall
	Alopecia
	Extravasation necrosis
	Cutaneous flare
Plant alkaloids	Alopecia
	Dysethesia and erythrodysesthesia (acral erythema)
	Radiation recall
	Cutaneous "flare" (must be differentiated from extravasation necrosis; excellent prognosis)
	Hair and nail dystrophy
Antitumor antibiotics	Xerosis/scaling
	Radiation recall dermatitis
	Rash/urticaria
	Reversible total alopecia
	Hyperpigmentation of nail beds
	Onycholysis
	Acral erythema
	Flagellate erythema (bleomycin)
	Cutaneous ulceration
	Pseudo-dermatomyositis (hydroxyurea)
Topoisomerase inhibitors	Reversible alopecia
	Dermatitis
	Facial edema
	Acral edema
	Paronychial inflammations
	Perianal dermatitis
	Anal fissures
Biologics	Acneiform rash
	Vasculitis-like eruption
	Paronychial inflammation
	Exfoliation/desquamation
	Xerosis
	Capillary leak syndrome
	Pruritus
	Urticaria/angioedema
	Alopecia
	Skin fissures
	Sweet's syndrome

and Fragrances Association and groups of local beauticians have developed a highly successful image-building program called "Look Good, Feel Good." This program is available free of charge to cancer patients with alopecia and other cosmetic defects.

Prognosis

Chemotherapy-associated alopecia is usually temporary. Regrowth can be apparent 3 to 10 months after withdrawal of the offending medication and may occur during prolonged cycles of therapy. Permanent alopecia has been reported infrequently with high-dose busulfan, bone marrow transplantation, and high-dose chemotherapy using cyclophosphamide, thiotepa, and carboplatin.[11,12] Most patients experience some changes in the character of their regrown hair. These changes, which include alterations in color, texture, and type of hair shaft, are often transient.[13]

Prevention

Several different maneuvers have been used in an attempt to protect patients from chemotherapy-induced alopecia. These include physical modalities that may temporarily decrease scalp blood flow and drug contact time with the hair follicle—that is, use of scalp-cooling devices, such as the MSC cold cap system (Medical Specialties of California, London, UK), cooling fluid ring turbans, and cold air hoods that deliver cooling temperatures below 22°C. Each works to decrease the metabolic rate of matrix stem cells and blood flow to the follicle matrix.[14] Results using hypothermic devices has been encouraging.[15] Efficacy is increased during use of a chemotherapeutic agent that has a short half-life (e.g., adriamycin) and is given in low dose. Also, patients treated with rapidly administered combinations seem to benefit from scalp hypothermia.[13] Tumor metastases to the scalp have been reported after use of this technique. Other side effects include headaches, dizziness, nausea, vomiting, aversion to ice, cold feeling, and heavy feeling on the head.[16] It has been suggested that hypothermia is contraindicated in patients with leukemia, lymphoma, or highly metastatic neoplasms and for patients who have a tendency to develop migraine headaches. Folic acid can prevent alopecia when given with methotrexate.[8]

Imuvert has been shown to protect against alopecia induced by ara-C (cytarabine) and doxorubicin but not by cyclophosphamide. This protective effect is presumed to be mediated by interleukin-1 (IL-1). AS101, a new immune modulator, has also been stated to prevent chemotherapy-induced alopecia.[8]

Electrotrichogenesis, or the use of specific pulsed electrostatic fields, has shown promising results in preventing chemotherapy-induced hair loss. A pilot study of 13 patients undergoing treatment with cyclophosphamide, methotrexate, and 5-fluorouracil (5-FU) showed good hair retention without attributable side effects.[17] M50054, 2,2.-methylenebis (1,3-cyclohexanedione), a novel inhibitor of apoptosis, might be an effective agent in the future for preventing or reducing chemotherapy-induced alopecia.[18]

Cellulitis, Phlebitis, Extravasation Necrosis, and Various Flare Reactions

It has been estimated that local skin toxicity, other than alopecia, accounts for 2% to 5% of all adverse reactions from antineoplastic drugs. The extravasation of vesicant cancer chemotherapeutic agents remains one of the single most distressing causes of this complication. Local tissue injury occurs as intravenously administered agents irritate the lining of access veins during drug administration (phlebitis), or when a cytotoxic drug escapes the confines of the cutaneous vasculature and spreads throughout the surrounding tissues. A local inflammatory reaction (chemical cellulitis), or local tissue necrosis (extravasation necrosis) then occurs. Cellulitis and necrosis can involve skin alone or can extend to subcutaneous tissue, muscle, fascia, and tendons. Extravasation frequently occurs during use of subcutaneous indwelling vascular access devices.

Etiology

Clarification of the mechanism of local tissue injury after insult by chemotherapeutic agents awaits further investigation. It has been postulated that agents that produce highly alkaline, or acidic, hypertonic solutions are probable causes. Drugs that bind to DNA are considered the most frequent causes. Necrotic tissue reactions can continue for weeks and months after withdrawal of the inciting agent. There is support for the concept of tissue binding as a probable cause of local necrotic reactions. Other possible contributors include local chemical irritant reactions and maturation arrest induced in proliferating cells.

The list of agents causing severe local tissue toxicity include the vinca alkaloids, vincristine and vinblastine; the alkylating agents, mechlorethamine and mitomycin C; the anthracyclines, doxorubicin and daunorubicin; and the antibiotic dactinomycin.[19–23] Other drugs less likely to cause severe local toxicity include 5-FU, etoposide, bleomycin, cisplatin, mitoxantrone, paclitaxel, streptozocin, oxaliplatin, docetaxel, and doxil.[24–31]

Delayed skin ulcers have been reported to appear within a prior mitomycin C infusion site after a second treatment is given into a site on the opposite extremity.

Doxorubicin local tissue reactivity includes, in addition to necrosis and radiation "recall effect," a "venous flare" reaction.[32,33] The "venous flare" that occurs is characterized by a linear eruption in the skin overlying access veins of the infusion site. Erythema, edema, induration, pruritus, and tenderness overlie the area (Fig. 41-1). Superficial blisters and vesicles can appear. This reaction subsides without residual tissue damage within 48 hours after discontinuation of the infusion. It has been estimated that venous flares occur in up to 3% of all adriamycin infusions.

Clinical Manifestations

During infusions that lead to necrosis, patients complain of acute burning pain and swelling. Within 7 days after the infusion, patients complain of pain, edema, erythema, and induration at the site. Severely involved untreated sites develop clusters of vesicles and large blisters, followed by ulceration or the development of a large plaque with a necrotic center, or both (Fig. 41-2). Underneath the plaque, or ulcer, extensive areas of necrosis may be found. A hard black eschar ultimately forms. Peripheral to the eschar, erythema and swelling persist for weeks. Simultaneously with involvement of subcuticular tissue, there is joint stiffness, limitation of motion, neuropathy, and causalgia in the affected parts.



Figure 41-1 • Venous flare reaction overlying access vein of the forearm.



Figure 41-2 • Extravasation injury, late-stage lesion with a central eschar, beneath which lies an extensive area of subcutaneous necrosis.

Pathology

Bhawan and colleagues among others reported early and late histologic changes in the skin of patients with doxorubicin extravasation.[34] In an early lesion, before eschar formation, marked epidermal hyperplasia is observed. Individual necrotic keratinocytes are abundant. All other cell types show similar reactive responses. In a late lesion, beneath the area of ulcer formation, panepidermal, dermal, and subcutaneous tissue necrosis is seen. Lateral to the ulcer, there is marked epidermal hyperplasia. Fibroblasts and endothelial cells show signs of extreme reactivity. Lobular panniculitis best describes lesions of the subcutaneous fatty layers. Curiously, signs of acute inflammation are not usually described in old or new lesions.

Differential Diagnosis

Local tissue extravasation must be differentiated from the doxorubicin "venous flare" reaction. Radiation recall phenomenon can occur with infusions of doxorubicin, mitomycin C, and 5-FU.This reaction tends to occur at remote sites of previous radiation dermatitis.

Treatment

Conservative, nonsurgical measures are very effective for treating small (500 mm^2 or less), and medium-size (2000 mm^2 or less) areas of extravasation. Phlebitis and cellulitis often cause mild injury, heal with minimum residual effects, and require minimum treatment. Because less than one-third of all local extravasations proceed to blister and ulcer formation, there is considerable disagreement about the correct approach to management of local tissue toxicity.[35–37] Termination of the infusion is mandatory and is almost always followed by complete healing without residual defect in areas of phlebitis and cellulitis. Elevation and intermittent cooling of the affected part can accelerate healing.

In more severe reactions the general use of a number of frequently recommended local antidotes is frowned upon. At most extravasation sites, antidotal treatments have often made necrosis and ulceration worse. There is general agreement that the infusion should be terminated immediately if the patient complains of pain, burning, or stinging at the infusion site or if local swelling is observed. If the original infusion needle or catheter is patent, aspiration of extravasated fluid may be attempted. If the line is not patent it should be removed immediately.

Elevation of the involved extremity is recommended for at least 48 hours. Local heat applications are recommended if the vesicant is one of the vinca alkaloids.[37] Cooling of the extremity may be benefi-

cial after other vesicant injury, except that caused by the alkylating agents mechlorethamine and mitomycin C.[38,39]

Although routine use of surgery is not indicated, timing and the ultimate use of surgical intervention are of utmost importance. Surgical consultation should be sought immediately on suspecting extravasation injury. Persistent pain, erythema, and swelling, even in the absence of ulceration and eschar formation, require surgical consultation and are indications for surgical intervention even in the absence of ulceration and eschar formation. Severe blistering, ulceration, and persistent pain make surgical intervention mandatory. Inordinate delay of surgery permits active drug to infiltrate and cause injury to tissues far beyond the original site of extravasation. In such cases, delay might ultimately cause the need for more extensive surgery ranging far beyond skin and subcutaneous tissues.

Outcome

Morbidity associated with extravasation injury is high, but mortality is nonexistent. The degree of discomfort experienced by some patients is severe enough to cause voluntary termination of treatment. Others become litigious, losing confidence in their therapist. The injury accompanying extravasation has no effect on disease status; thus there is no reason to stop further treatments with a given agent. Unless extravasation occurs again, retreatment of the patient with the same agent is not associated with recurrence of necrosis.

Prevention

In every patient considered for treatment with a known vesicant, prevention of local tissue injury is paramount. Prevention begins with selection of the infusion site. Sites to be avoided at all costs are the dorsal surfaces of the hands and the antecubital fossae, as well as extremities that have been sites of extensive ablative surgery. The preferred site of infusion is the proximal forearm that has not been surgically compromised, and where a large amount of subcutaneous tissue overlies vital structures. If tissue-poor areas such as the dorsal surface of the hand are used, a subcutaneous flexible indwelling catheter is preferred over the standard intravenous needle. When multiple infusions are anticipated over a prolonged period, placement of subcutaneous reservoirs with long indwelling lines should be considered. Nevertheless, even indwelling devices are not foolproof; an extravasation incidence of 6.4% has been reported using these devices.[40]

Drugs should always be administered through a free-flowing intravenous line. Any hint of obstruction within the line calls for immediate termination of the infusion and an attempt at correcting the problem. Every attempt should be made to administer a solution that is as dilute as possible over the shortest period of time, preventing injury from concentrated drug and eliminating lengthy exposure of tissues to a toxic agent.

Palmar-Plantar Dysesthesia and Erythrodysesthesia Syndrome (Acral Erythema)

The true incidence of this reaction is unknown. Yet, on the basis of personal experience, the number of cases reported in the literature, and a reported incidence of 39% in a group of patients treated for acute myeloid leukemia using the CHA regimen (lomustine, doxorubicin, cytosine arabinoside), one would suspect that erythrodysesthesia is fairly common and is among the most frequently encountered cutaneous reactions to cancer chemotherapeutic agents.[41–43]

Etiology

Early reports described this reaction in patients with hematologic malignancies. Subsequent reports described the reaction in patients receiving continuous infusions of 5-FU in solid tumors. Hence, 5-FU became widely recognized as the offending agent in nearly all cases of palmar-plantar erythrodysesthesia. A considerable variety of chemotherapeutic agents and treatment regimens have since been associated—for example, capecitabine, cytosine arabinoside, doxorubicin, methotrexate, 6-mercaptopurine, hydroxyurea, etoposide, 5-fluoro-2-deoxyuridine, and various combinations of agents. There appear to be no age, sex, or racial predilections for susceptibility to this phenomenon. There is no known mechanism for the reaction pattern other than that it seems to be dependent on drug dose.

Clinical Manifestations

Weeks to months after beginning high-dose intravenous chemotherapy, dysesthesia and paresthesia, expressed as a tingling sensation in the hands and feet, herald the onset of the syndrome. Increasing discomfort (consisting of burning sensations, pain, and tenderness while holding objects and while walking) signals progression of disease. Pain with swelling and erythema develop within 2 to 4 days of onset. Reddening begins over thenar and hypothenar eminences and spreads to involve the entire palm and sole (Fig. 41-3A and B). Blanching and erythema also occur on the interarticular spaces, and erythema appears in the periungual areas. Swelling and severe pain occur even at rest. Eventually, many of the blanching areas become bullous. This typical pattern is commonly seen with cytarabine therapy. Desquamation followed by healing of the palms and soles occurs within several weeks (Fig. 41-4). In a few patients, erythematous scaling dermatoses develop on other body areas, together with nail disturbances, including onycholysis. Recall-induced palmar-plantar erythrodysesthesia syndrome has been described with a variety of chemotherapy regimens.[44]

Pathology

Pathologic findings in a small number of patients have been described as nonspecific, showing mild focal spongiosis of the lower epidermis, mild to moderate epidermal atypia, mononuclear cell infiltration of the superficial dermis, and mild vasculitis of small vessels. Mild focal vacuolar degeneration of the basal cell layer has also been described.[43] Immunofluorescent studies are negative.

Differential Diagnosis

ACRAL ERYTHEMA ASSOCIATED WITH ACUTE GRAFT-VERSUS-HOST DISEASE. Dermatitis of the palms and soles may occur as the earliest and only sign of acute graft-versus-host disease (GVHD). Dermatoses of GVHD usually occur within a period varying from 4 to 47 days after allogeneic bone marrow transplantation, but the onset of palmar-plantar lesions may be delayed by as long as 100 days. Unlike the spotty erythema of erythrodysesthesia that begins on thenar and hypothenar areas, acute GVHD palmar-plantar erythema presents with reddening of the dorsal aspects of the fingers and within periungual skin. Diffuse erythema of the hands and feet soon follows. Pruritus and tenderness of the palms and soles characterize acute GVHD, as opposed to severe pain and swelling associated with the palmar-plantar dysesthesia syndrome. Other findings associated with acute GVHD and acral erythema include nausea, vomiting, intractable diarrhea, and a severe rise in serum bilirubin levels. Both diseases can occur concurrently.[45]

ACRAL ERYTHEMA OCCURRING IN SEVERE LIVER DISEASE. Acral erythema with severe liver disease is a chronic abnormality and is not generally accompanied by pain, blistering, or desquamation of the skin. Liver abnormalities are profound, with elevated serum enzymes and serum bilirubin.

Treatment

Treatment has been quite variable. In some patients complete cessation of chemotherapy is mandatory, followed by simple but intensive topical care consisting of frequent wet dressings and topical applications of midrange-potency corticosteroids. Often this regimen is sufficient to clear the eruption. Pain, swelling, and blister formation



Figure 41-3 • **A** and **B,** Palmar-plantar dysesthesia and erythrodysesthesia. Early manifestation with prominent erythema and edema.



Figure 41-4 • Late manifestation of palmar-plantar dysesthesia showing palmar desquamation after clofarabine use.

clear within 1 week without residual effects. Many patients heal completely without therapeutic intervention.

In some patients a moderate reduction in chemotherapy dosage and intensive topical care allows continuation of infusion therapy. A return to the original chemotherapy dosage is usually associated with recurrence of skin disease.

In other patients cutaneous manifestations have been ignored, and treatment with the offending agent has been continued at presyndrome dose levels. Only symptomatic treatment measures were required. Successful treatment of a group of patients using daily oral dosages of pyridoxine during infusions has been noted. Its use has permitted continued treatment with high-dose infusions, without recurrence or worsening of the palmar-plantar dysesthesia syndrome, or adverse effects on disease response to chemotherapy.[46] The use of pyridoxine for prevention of dysesthesia is empiric. Topical 99% dimethyl sulfoxide has shown promising results for treatment of liposomal doxorubicin-induced palmar-plantar erthrodysesthesia.[47]

Outcome

Severe acral pain and blister formation can cause considerable morbidity and poor patient compliance. No matter how severe the process may appear, it has no effect on the patient's disease status. Most chemotherapists agree that acral dysesthesia is not life-threatening, yet it can cause sufficient discomfort to require withdrawal of drug or alteration in drug dosage.

Hyperpigmentation

A variety of patterns of hyperpigmentation have been described in association with cytotoxic agents. Cutaneous hyperpigmentation can be generalized or can occur in specific localized patterns. Mucous membranes, hair, teeth, and nails can be affected by changes in pigmentation produced by cancer chemotherapy.[48–50]

Etiology

Generalized hyperpigmentation has been described in association with busulfan, cyclophosphamide, bleomycin, 5-FU, mechlorethamine, hydroxyurea, daunorubicin, dactinomycin, doxorubicin, and procarbazine. Localized patterns of skin hyperpigmentation occur after administration of cyclophosphamide, thiotepa, bleomycin, doxorubicin, daunorubicin, 5-FU, vinca alkaloids, plicamycin, and paclitaxel. Mucosal pigmentation is seen after doxorubicin, 5-FU, cisplatin, and busulfan therapy. Nail pigmentation is produced by cyclophosphamide, bleomycin, doxorubicin, daunorubicin, 5-FU, and hydroxyurea. Alteration in hair pigmentation has been caused by methotrexate. Cyclophosphamide may also produce pigmentation of the teeth.

Increased pigmentation from cancer chemotherapy is due to increased deposition of melanin in the affected tissue; a similar mechanism is shown to occur when hyperpigmentation is produced by antimalarials, tetracyclines, or heavy metal therapy, and is not caused by an accumulation of drug or its byproducts. Melanin, a pigment product or polymer, is manufactured within the basal layer of the epidermis of skin, nails, and hair follicles by melanocytes. Melanocytes package the pigment into containers called melanosomes and distribute them to neighboring epithelial cells through tubular cytoplasmic extensions called dendritic processes. Alterations in baseline pigmentation can occur when there is an increase in melanin production, an increase in the size of melanosomes, or a change in the distribution of melanosomes within the epithelial cells of skin, nails, and hair. How chemotherapeutic agents act to produce increased pigmentation is unknown. They may act to increase pigmentation by a direct stimulatory or toxic effect on melanocytes and/or by slowing the turnover and transit rates of epithelial cells, thus allowing more time for the transfer of melanin to occur. Adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone (MSH) are central nervous system–produced polypeptides that stimulate overall pigmentation in humans. ACTH and MSH are known to produce generalized hyperpigmentation in Addison's disease after bilateral adrenalectomy and after parenteral administration. The role of these hormones in the normal regulation of human pigmentation is poorly understood. ACTH and MSH levels have been studied in patients with pigmentary abnormalities while receiving cytotoxic agents; no elevation of these hormones has been detected.[51,52]

Clinical Manifestations: Alkylating Agents

BUSULFAN. Busulfan can produce generalized brown hyperpigmentation that is accentuated on the face, trunk, and forearms. Hyperpigmentation may be accompanied by symptoms of fatigue, nausea, anorexia, and weight loss, resulting in a condition much like Addison's disease. In such patients, however, hyperpigmentation of mucous membranes and palmar creases is rarely observed, and there is no evidence of increased ACTH or MSH activity. Busulfan hyperpigmentation occurs in 5% to 15% of treated individuals. It resolves when the drug is discontinued.

CARMUSTINE. Carmustine has produced erythema followed by postinflammatory hyperpigmentation when it is spilled on the skin inadvertently, but parenteral use is not associated with pigmentary changes.

CYCLOPHOSPHAMIDE. Cyclophosphamide can cause generalized skin pigmentation (which could be photoaccentuated) in addition to localized pigmentation of the palms, soles, and nails. Nail pigmentation can be diffuse or can present as horizontal or longitudinal dark bands. On cessation of therapy, this pigmentation usually resolves as the nail grows. In one large series of patients treated with cyclophosphamide, the incidence of skin and nail pigmentation was less than 50%. There is a single report of a child in whom a persistent brown line developed on the teeth as a result of cyclophosphamide therapy.

MECHLORETHAMINE. Used topically in the treatment of mycosis fungoides, mechlorethamine produces diffuse hyperpigmentation. This problem can occur with or without clinical evidence of allergic or irritant contact dermatitis.

THIOTEPA. Given intravenously in high doses, thiotepa may cause discrete areas of hyperpigmentation corresponding to sites occluded by adhesive patches or tape. This effect might result from an enhanced local toxic effect of the drug, which is excreted in sweat.

Clinical Manifestations: Antibiotics

ACTINOMYCIN. Persistent serpentine surpravenous hyperpigmentation has been associated with actinomycin and vincristine chemotherapy.

BLEOMYCIN. Bleomycin causes several patterns of hyperpigmentation. These include a generalized darkening of the skin that includes the palmar creases and cuticles, and patchy pigmentation at pressure points that might be delayed in appearance over the elbows, shoulders, and buttocks. The most distinctive pattern seen in 30% or more of patients consists of linear or "flagellate" streaks on the trunk that appear to correspond to areas of pruritus and trauma (Fig. 41-5). Attempts to reproduce these lesions experimentally have met with variable success. Flagellate hyperpigmentation has its onset after 3 weeks of therapy and persists up to 5 months. Horizontal brown nail banding has also been observed.

DACTINOMYCIN. Intertriginous, trauma-induced, and diffuse hyperpigmentation have been associated with dactinomycin therapy.

DAUNORUBICIN. Chemically related to doxorubicin, daunorubicin has also been reported to cause skin and nail pigmentation, but with less frequency. Transverse pigmented nail bands and polycyclic pigmentation of the scalp have been reported.

DOXORUBICIN. Doxorubicin is associated with localized pigmentation of the nails, palms and soles, dorsa of the hands, face, and interphalangeal and palmar creases. Diffuse pigmentation also can occur. Intraoral pigmentation occurs on the buccal mucosa and tongue. Nail pigmentation can present as horizontal or longitudinal bands or in a diffuse manner. These changes are more common among black patients. MSH levels are not elevated in patients with doxorubicin-induced pigmentation.



Figure 41-5 • Bleomycin pigmentation. This is the most distinctive pattern of pigmentation following the administration of bleomycin. Erythematous, linear lesions often precede the appearance of increased pigmentation.

Clinical Manifestations: Mitotic Inhibitors

ETOPOSIDE. Hyperpigmentation occurs in occluded areas.

IFOSFAMIDE. Hyperpigmentation on the hands, feet, and occluded areas has been reported.

MITHRAMYCIN. Mithramycin has been associated with postinflammatory hyperpigmentation following intense flushing and facial edema.

PACLITAXEL. Causes localized hyperpigmentation.

PROCARBAZINE. Localized hyperpigmentation has been reported.

Clinical Manifestations: Antimetabolites

5-FLUOROURACIL. 5-FU causes uniform pigmentation in sun-exposed areas in 2% to 5% of patients. Localized hyperpigmentation can occur at previously irradiated sites. Many localized patterns of pigmentation in nonirradiated areas have also been described. Serpentine supravenous hyperpigmentation occurs over veins used for repeated 5-FU infusions even in the absence of phlebitis or thrombosis. Serpentine pigmented streaks and reticulate pigmentation on the back and buttocks have also been reported. Hyperpigmentation can present in stria distensae. Banded pigmentation over small joints of the hands, diffuse pigmentation of the palms, and macular pigmentation of the palms and soles have been described. Nail pigmentation can occur as transverse banding, and pigmentation of the oral mucosa can result after long-term therapy.

METHOTREXATE. Methotrexate has been reported to cause horizontal dark banding of the hair after intermittent therapy, similar to the "flag sign" of kwashiorkor.

Clinical Manifestations: Miscellaneous Drugs

CISPLATIN. Cisplatin has been reported to produce a gingival band of pigmentation similar to a "lead line." Hyperpigmentation at sites of pressure is common and is seen in as many as 70% of patients.

HYDROXYUREA. Hydroxyurea has caused generalized hyperpigmentation and scaling in patients receiving long-term maintenance therapy. Pigmentation is accompanied by partial alopecia, cutaneous and subcutaneous atrophy, and erythema of the face and hands. Multiple longitudinal pigmented nail bands have also been observed.

Pathology

Skin biopsy specimens have demonstrated a variety of alterations in both the amount of melanin present and its distribution within the epidermis. Melanin can also be seen in dermal macrophages. On occasion, melanocytes might be increased in number, are larger than normal, and might appear to have more dendritic processes.[53]

Differential Diagnosis

Diffuse generalized hyperpigmentation can be seen in Addison's disease or primary adrenal insufficiency, which could be caused by metastatic carcinomas or Hodgkin's lymphoma. Addison's disease is also characterized by constitutional symptoms of fatigue, anorexia, and malaise, which are noted commonly among patients receiving cancer chemotherapy. Pigmentation in Addison's disease usually involves the oral mucosa and is accentuated in skin folds and creases, on the areolae and genitalia, and in sun-exposed areas. ACTH levels are elevated, and there is an abnormal response to ACTH stimulation. These laboratory findings are not present in patients with hyperpigmentation due to cytotoxic drugs.

Patients with hemochromatosis, an iron storage disease, show diffuse bronze pigmentation. The acquired form can present in patients who have received multiple blood transfusions. Hepatomegaly is usually present. Hyperpigmentation is due primarily to melanin, but hemosiderin deposition can be present in the skin also. Serum iron levels are elevated, and saturation of transferrin is noted in patients with hemochromatosis. Generalized hyperpigmentation and melanuria can occur in patients with advanced metastatic melanoma.

Melasma is an acquired macular brown pigmentation of the face that becomes pronounced with sun exposure. It can be seen during pregnancy and in patients on oral contraceptive or phenytoin therapy. Multiple pigmented longitudinal nail bands can occur as a normal finding among dark-skinned individuals and can be seen in metastatic melanoma. These are caused by benign melanocytic hyperplasia, lentigos, or junctional nevi within the nail matrix. Diffuse brown nail pigmentation can be caused by drugs other than cytotoxic agents, such as antimalarials, phenothiazines, tetracyclines, psoralens, and gold salts.

Treatment and Outcome

Hyperpigmentation secondary to cytotoxic agents is primarily a cosmetic problem and does not affect the continuation of treatment. Some patients might suffer psychologic distress but should be reassured that cutaneous hyperpigmentation, though persisting for several months, usually resolves after cessation of treatment. Nail pigmentation also resolves as the nails grow after treatment is discontinued.

Prevention

Use of sunscreens and avoidance of excessive sun exposure might prevent accentuation of pigmentary changes.

Nail Disorders

In addition to pigmentary nail abnormalities, cytotoxic drugs may disturb normal nail growth to produce a variety of nail changes, including Beau's lines, transverse white bands, onycholysis, and brittle nails.

Etiology and Pathogenesis

Cytotoxic agents can cause a direct toxic effect on the mitotically active cells of the nail matrix, which, as noted in the discussion on alopecias, can lead to cessation of growth with incomplete formation of the nail plate and the formation of Beau's lines. Disruption of nail keratinocyte differentiation can produce an abnormal nail plate. Measurements of the distance between Beau's lines and transverse white bands have shown a temporal relationship between nail abnormalities and the sequence of drug administration.[54]

Signs and Symptoms

Beau's lines are transverse depressions of the nail plate produced by the temporary cessation of nail growth. Typically, all nails are affected, but Beau's lines are most readily visible on the thumbs. They are commonly observed after short, intense chemotherapy regimens.[54]

Multiple transverse white bands of all 10 fingernails can result from combination chemotherapy featuring a variety of agents that include cyclophosphamide, doxorubicin, vincristine, prednisone, bleomycin, methotrexate, procarbazine, carmustine, semustine, and cisplatin.[55]

Onycholysis, or separation of the nail plate from the nail bed, has been reported among patients receiving 5-FU and bleomycin.[56] Doxorubicin may cause onycholysis, subungual blistering, blistering of the soles, and subsequent callus formation.[57] Brittle nails have been reported secondary to the administration of 5-FU and hydroxyurea.

Differential Diagnosis

Beau's lines can be seen after many severe febrile illnesses, after myocardial infarction, and with Raynaud's syndrome, zinc deficiency, or

chronic dermatitis of the nail folds. Transverse white bands can sometimes be seen after an acute illness or after ingestion of arsenic, thallium, or fluoride. Onycholysis is common in psoriasis and fungal infections of the nail and secondary to trauma.

RADIATION-ASSOCIATED REACTIONS

Two types of reactions have been associated with the use of chemotherapeutic drugs and ionizing radiation: radiation enhancement and radiation recall. The resulting reactions correlate with the specific drug given and with the sequence of administration.

Radiation Recall

Radiation recall is an acute inflammatory cutaneous or organ reaction that develops within a previously irradiated site and after administration of a chemotherapeutic agent.[58] Involved organs may include skin and mucous membranes, lung, esophagus, gastrointestinal tract, central nervous system, bladder, and heart.

Etiology

Multiple drugs have been reported to cause radiation recall. The most common drugs known to cause this reaction are the cytotoxic antibiotics (dactinomycin, doxorubicin, daunorubicin, and bleomycin), the taxanes (paclitaxel, docetaxel), and methotrexate.[59]

Clinical Manifestations

Radiation recall may develop without clinically apparent antecedent radiation damage to the skin. Clinical manifestations usually develop within days after chemotherapy is given; however, the time interval between radiotherapy and the resultant radiation recall reaction can vary from several days to years. Mild reactions appear as erythema and edema followed by dry desquamation, similar to first-degree burns (Fig. 41-6). More severe reactions are associated with moist desquamation, painful blistering, weeping, and in the most severe cases, full skin necrosis and painful ulcerations. The severity of the cutaneous reaction seems to correlate with the time interval between radiation and chemotherapy, with the shortest time intervals resulting in more severe reactions.

Pathology

The pathogenesis of radiation recall is controversial. The severity of the radiation recall reaction is also related to the tissue at risk, type and dosage of drug, the radiation dose utilized, and the sequential relationship between the administration of radiation and the administration of the chemotherapeutic agent.[60,61]



Figure 41-6 • Radiation recall. This patient had small-cell cancer of the lung treated with radiation. Cyclophosphamide treatment some months later elicited erythema and desquamation within the portal of radiation. This lesion is now in the healing phase.

Differential Diagnosis

Radiation recall reaction could be difficult to differentiate from cytostatic drug recall of acute inflammation caused by ultraviolet light or other cutaneous irritants and infections. Areas that have experienced an acute or remote sunburn reaction or have been sites of previous irritation or infection can also become further inflamed during the administration of a chemotherapeutic agent. The resulting skin reaction does not differ from that noted as radiation recall.[62]

Treatment and Outcome

Mild cases of radiation recall, which are characterized by erythema, edema, and dry desquamation, are self-limiting. Cool compresses and lubricating creams or ointments provide symptomatic relief. In the more severe cases in which exudates and/or blisters predominate, wet to dry compresses should be used to promote drying. Upon cessation of exudates formation, moist wound healing strategies should be implemented. Infected sites should be cultured and treated.

Radiation-induced necrotic ulcers are slow to heal. They are poor candidates for grafting because neovascularization and fibroblastic repair is limited. Strategies that attempt to both limit the amount of exudates and provide for moist wound healing should be implemented. Topical corticosteroids have little effect in treatment of radiation recall injuries.[61]

Radiation Enhancement

Certain chemotherapeutic drugs, termed *radiation sensitizers,* potentiate or enhance the effect of ionizing radiation. The occurrence of radiation enhancement depends on drug delivery being concurrent with or following within 3 weeks of radiation therapy. Although radiation enhancement might be planned to increase tumor destruction, this technique often causes significant injury and morbidity in adjacent noncancerous tissues.

Etiology

Radiation sensitizers include gemcitabine, IFN-α2a, 13-*cis*-retinoic acid, doxorubicin, docetaxel, carboplatin, cisplatin, dactinomycin, methotrexate, 5-FU, bleomycin, and hydroxyurea.

These drugs interfere with the repair processes that allow sublethally damaged cells to recover from radiation injury. The degree of reaction depends on the type of drug and dosage, the radiation dosage, and the time interval between the delivery of radiation and drug.

Clinical Manifestations

The clinical manifestations of radiation enhancement fall into one of three patterns:

1. A mild reaction consisting of erythema, edema, and dry desquamation
2. A moderate reaction with moist desquamation, vesiculation, blister formation, and erosion
3. Severe necrotic ulcerative reactions that could result in residual skin hypopigmentation.

The affected sites are not limited to the radiation port but also involve contiguous skin.

Differential Diagnosis

Acute radiation-induced dermatitis may show clinical findings similar to those of radiation enhancement. However, they differ in time of occurrence following irradiation. Radiation dermatitis tends to occur within 1 to 3 weeks after radiation. Recall reactions occur weeks to months after irradiation.

Treatment and Outcome

Prognosis and treatment are dependent on the severity of the reaction and are similar to those described in the section on radiation recall reactions.

Reactivation Dermatitis

Cytostatic drugs frequently reactivate acute inflammation and exacerbate pre-existing eczema and other cutaneous diseases[63,64] (Figs. 41-7 and 41-8). IFN-α often exacerbates psoriasis and psoriatic arthritis.[65]

It is paradoxical that immunosuppressive agents can enhance cutaneous hypersensitivity reactions. Methotrexate blocks the induction of allergic contact dermatitis during the period of its administration, yet it can reactivate a positive patch test to 10% benzalkonium chloride solution.[63] Cyclophosphamide-treated guinea pigs can experience an enhanced allergic contact dermatitis when challenged with dinitrochlorobenzene.[66]

Although both topical and systemic administration of 5-FU can result in a seborrheic dermatitis-like eruption, this reaction does not appear to be reactivation but instead a de novo cutaneous adverse effect.[67]

Neutrophilic Eccrine Hidradenitis

Neutrophilic eccrine hidradenitis is an acute dermatosis associated with the administration of multiple chemotherapeutic agents including bleomycin, chlorambucil, cytarabine, daunorubicin, doxorubicin, mitoxantrone, vincristine, and topotecan.[68] Once considered rare and confined to adults receiving cytarabine for acute myeloid leukemia, it has been suggested more recently that the entity is more common than previously admitted. Not only has it been observed in children undergoing systemic chemotherapy, but neutrophilic eccrine hidradenitis has been reported in association with bacterial infections, acquired immunodeficiency syndrome, and a variety of medications.[69,70] It has been observed to occur in children and adults with several different malignancies and receiving a wide spectrum of systemic chemotherapeutic drugs. The clinical appearance is quite variable, yet the histopathologic picture remains characteristic.

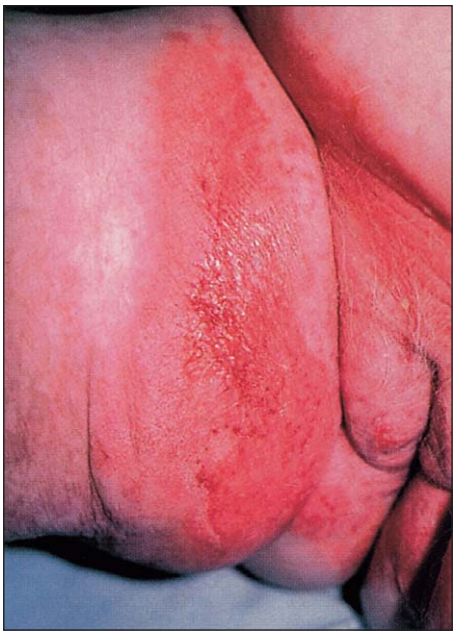


Figure 41-7 • Reactivation dermatitis. This elderly diabetic female had a previous history of a *Candida* infection of the groin several years before. Methotrexate administration on each of several occasions caused the development of a weeping erosive dermatitis.

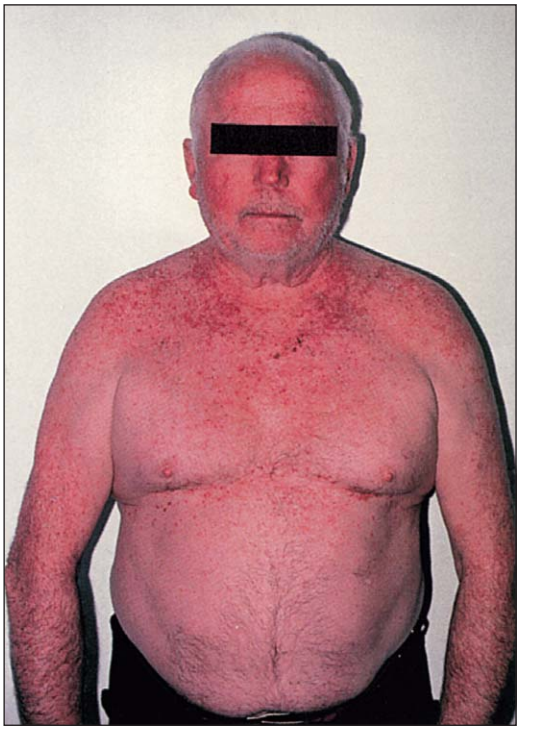


Figure 41-8 • Inflamed actinic keratoses secondary to the administration of systemic 5-FU.This patient had extensively photodamaged skin showing "activation" of previously unrecognized actinic keratoses. Red scaling papules and cutaneous ulcerations predominate.

Etiology

The primary histopathologic lesion in this disease is localized necrosis of the eccrine glands in the skin. Associated necrosis of apocrine glands has been reported. The mechanism whereby necrosis is induced is unclear.[71] The histologic picture, which is quite characteristic, tends to rule out hypersensitivity vasculitis as a cause. Necrosis caused by the accumulation of high concentrations of cytotoxic agents within the sweat glands cannot be excluded.

Clinical Manifestations

Affected patients present with a wide variety of cutaneous lesions. Tender erythematous to purpuric macules, papules, nodules, and plaques, some with dark central areas, will suddenly appear on any body area during active administration of a cytotoxic agent. Lesions might appear within 2 to 3 days of starting chemotherapy or may go unnoticed until weeks after chemotherapy has started. Some unusual presentations include periorbital edema with erythema and injection site reactions.[72] Usual manifestations include hyperpigmented plaques and painful edema of the ears. Spiking fevers often accompany the onset of cutaneous lesions.

In many patients, skin lesions begin to resolve within 7 to 21 days after onset despite continuous chemotherapy administration. Likewise, new lesions can appear days and weeks after resolution of an original outcropping or might recur with the reinstitution of a course of chemotherapy. New papules, plaques, and nodules also might develop within sites previously involved by initial lesions.

Pathology

Histopathologic changes within affected skin sites are quite characteristic for this disease. There is pronounced neutrophilic infiltration

of the dermis about and focally within the eccrine glands, resulting in focal epithelial necrosis and basilar vacuolization of eccrine epithelial cells. The neutrophilic infiltrate is heaviest in those glands demonstrating vacuolar changes and less intense around those glands showing intense necrosis. Neutrophilic infiltration of the coiled duct and straight duct may or may not be observed. Some secretory coil epithelial cells show marked nuclear pyknosis and cytoplasmic eosinophilia. Mucinous degeneration of the eccrine gland adipose tissue cuff, along with an infiltrate of lymphocytes, eosinophils, and neutrophils, may be present, as well as focal areas of hemorrhage within the dermis, mild to moderate spongiosis, and occasional vacuolization of the epidermis. In patients with active leukemia, abnormal or immature leukemia cells do not make up part of the tissue infiltrate.

Differential Diagnosis

Because neutrophilic eccrine hidradenitis is a fairly benign, self-limiting disease, it is imperative that it be differentiated clinically from other, more serious diseases that it might mimic. The variety of cutaneous lesions described in patients with neutrophilic eccrine hidradenitis could easily cause confusion with a fairly large number of clinical entities. Among these are leukemia cutis, cutaneous tumor metastases, erythema multiforme, vasculitis, drug hypersensitivity, sepsis (bacterial and fungal), Sweet's syndrome, and pyoderma gangrenosum. The localized nature of lesions associated with neutrophilic eccrine hidradenitis, and the temporal relationship of cutaneous lesions to the administration of chemotherapy, should aid clinically in differentiating neutrophilic eccrine hidradenitis from most diseases. Because the abnormal histopathologic picture presented by this disease is quite unique, histologic sampling of tissue is of importance.

The histologic differential diagnosis would include several entities involving necrosis of the eccrine gland, including bacterial sepsis with eccrine hidradenitis or other neutrophilic dermatoses; however, the well-trained pathologist, aided by the astute clinician, should combine to make a definitive diagnosis possible.

Treatment and Outcome

Neutrophilic eccrine hidradenitis is a benign, self-limiting disease that generally requires no treatment. The course or the disease does not appear to be influenced by chemotherapy protocols that often include high dosages of systemic corticosteroids. Within 7 to 10 days of origin, most lesions tend to resolve. Recurrent lesions appear to be less severe than preceding lesions and have been suppressed with concurrent dapsone administration.[73] In all patients described to date, healing occurs without residual scarring.

Prognosis

The prognosis for total recovery without sequelae is excellent.

Syringosquamous Metaplasia

Although it can present as a histopathologic finding in association with various other cutaneous conditions, syringosquamous metaplasia has become increasingly associated with the administration of a variety of chemotherapeutic agents and cancers.[74] It has been described in association with bleomycin, cytarabine, daunorubicin, doxorubicin, mitoxantrone, suramin, and docetaxel.[75]

Etiology

The exact etiology of syringosquamous metaplasia is unknown. It is presumed to be a reactive or inflammatory response of the eccrine duct epithelium to the offending agent.

Clinical Manifestations

During or soon after the administration of chemotherapy, there is the onset of nondescript erythematous papules, plaques, or vesicles. These may be generalized or localized and have been reported to occur only in the intertriginous areas.[76,77]

Pathology

The characteristic histopathology shows eosinophilic squamous metaplasia of the eccrine ducts within the dermis. Focal necrosis of the ductal epithelium has also been noted. The prominent neutrophilic infiltrate of neutrophilic eccrine hidradenitis is not present.

These pathologic changes are not specific and have been described in other disorders unrelated to chemotherapy.[77]

Differential Diagnosis

The differential diagnosis is extensive and includes neutrophilic eccrine hidradenitis; bacterial, viral, or fungal infections; erythema multiforme, metastatic disease; and drug hypersensitivity. Histopathology is necessary to differentiate among these various entities.

Treatment and Outcome

The eruption is benign and resolves spontaneously after cytotoxic treatment is discontinued.

REACTIONS TO BIOLOGIC RESPONSE MODIFIERS

The recent introduction of a group of agents referred to as biologic response modifiers in the treatment of cancer has led to the occurrence of a host of cutaneous reactions.

These powerful physiologic agents used in the setting of underlying malignancy, immunosuppression, other medications, and individual genetically determined host factors have precipitated a variety of specific and nonspecific cutaneous responses. These reactions are summarized in Table 41-2.

Cutaneous Reactions to Interleukin-2

Recombinant human IL-2, or T-cell growth factor, is a glycoprotein that exerts a wide variety of biologic effects on the immune system. It has found use in the treatment of advanced malignancies, including malignant melanoma, cutaneous T-cell lymphoma, renal cell carcinoma, advanced colorectal carcinoma, and advanced lymphoma.[78–83] IL-2 has been used after autologous bone marrow transplantation to prevent or reduce the high relapse rate of advanced hematologic malignancies.[84] In the clinical setting, IL-2 is often used in combination with other biologic response modifiers, including lymphokine-activated killer (LAK) cells and IFN-α.[84] IL-2 has also been used in complex with diphtheria toxin as a fusion protein (denileukin diftitox) for the treatment of malignancies characterized by a predominance of activated T and B cells and/or macrophages that express the IL-2 receptor.

IL-2 alone and in combination with LAK and IFN-α has produced a wide variety of toxicities, including one characteristic cutaneous eruption. It is estimated that 50% to 100% of patients treated with IL-2 alone or in combination with other biologic response modifiers will experience some form of cutaneous eruption.[85]

Etiology

Within 48 to 72 hours after the start of an infusion of IL-2 alone or in combination with another cytokine, patients develop a skin eruption of varying severity. The precise etiology is unclear, except it seems that cutaneous reactions occur more often when high doses of IL-2 (100,000 μg/kg) rather than low doses (30,000 μg/kg) are used.[85] There is no difference in rate of occurrence, whether bolus or continuous infusions are administered.

Thus far, no racial or sexual predominance has been observed. More than one-quarter of all patients treated with IL-2 develop a capillary leak syndrome, which, except for extensive edema, does not as yet seem to be entirely related to the development of cutaneous

lesions. Nearly all patients receiving IL-2 therapy develop fever and chills. These symptoms tend to occur almost immediately with the initiation of treatment. Gaspari and colleagues[85] have studied IL-2 cutaneous reactions extensively and have concluded that there is immunohistochemical and histologic evidence to support the presence of a cell-mediated immune response during IL-2 therapy. Other studies have implicated a possible role for nitric oxide, Fas ligand and perforin, and complement and other inflammatory mediators in affecting vascular permeability, resulting in a capillary leak syndrome.[86–88] It is likely that vascular leak syndrome occurs as a result of multiple mechanisms: cell-mediated damage, cytokine-mediated damage, inflammatory mediators, and modification of endothelial cell integrity and the extracellular matrix.[89]

Clinical Manifestations

Chills and fever along with transient cutaneous flushing occur during the first 24 to 48 hours of IL-2 administration. After 48 to 72 hours, persistent erythema associated with itching and a burning sensation develop, first on the malar aspects of the face and then on the neck and chest. In other patients, total body erythema (erythroderma) develops along with erythema and edema of the palms and soles (Fig. 41-9). If the use of IL-2 is combined with LAK cell infusions, it appears that the onset of the eruption might begin within 24 hours. Resolution of disease can occur within 2 to 3 days, when drug administration is stopped. Resolution is associated with continuing pruritus and desquamation of involved skin. There are other reports of erythema progressing to life-threatening bullous eruptions and toxic epidermal necrolysis-like lesions. Some investigators report that the histopathologic findings in these cases separate these patients from those suffering the most frequently observed IL-2 reactions. Erosions of the buccal mucosa, icterus, glossitis, and cutaneous erosions have also been described. A persistent but not progressive vitiligo-like depigmentation has been described after IL-2 and IFN-λ, plus carmustine, cisplatin, and dacarbazine treatment of malignant melanoma.[90]



Figure 41-9 • IL-2 cutaneous reaction. This patient's disease is characterized by intense facial redness, red swollen hands and feet, and a generalized macular eruption.

Pathology

Histopathologic findings thus far are nonspecific. Within the epidermis, foci of spongiosis, focal vacuolar basal cell degeneration, rare necrotic keratinocytes, and exocytosis of mononuclear cells are seen. In the dermis, mild papillary edema, mild to moderate perivascular mononuclear cell infiltrates, and occasional engorgement of blood vessels occur. These are nonspecific findings. Immunohistochemistry shows activated T cells within the epidermis and dermis with approximately equal numbers of major histocompatibility complex class I and II reactive cells.

Differential Diagnosis

Viral and bacterial exanthems, drug or phototoxic reactions, toxic shock syndrome, staphylococcal scalded skin syndrome, toxic epidermal necrolysis, and acute graft-versus-host reactions must be considered and ruled out with appropriate tests.

Treatment and Outcome

Cessation of treatment is followed 48 to 72 hours later with complete clearing of the skin and little or no residual effect except transitory hyperpigmentation.

Antihistamines given during drug administration and the application of emollients have shown some benefit in the relief of pruritus. The use of systemic glucocorticoids that could offer some immediate relief of symptoms is not indicated; glucocorticoids decrease IL-2 toxicity but might also reduce IL-2 efficacy.[91,92]

Cutaneous Reactions to Proteasome Inhibitors

Proteasomes exist as large multiprotein particles within the cytosol and cell nucleus and are responsible for regulation of protein expression and degradation of damaged or obsolete proteins within the cell. Proteasome inhibitors have been recently introduced as anticancer agents.[93–95] The ubiquitin-proteasome pathway is the major proteolytic system in eukaryotic cells. Some of the proteins regulated by this pathway are mediators of cell-cycle progression and apoptosis. These pathways are needed for the survival of all cells including cancer cells. Proteasomes allow the cell to progress through the cell cycle by such mechanisms as degrading cell-cycle regulatory proteins or regulating transcriptional factors such as nuclear factor-κB (NF-κB).[93]

It has been suggested that malignant cells are more susceptible to proteasome blockade than noncancerous cells.[94] Proteasome inhibitors fall into five classes: peptide aldehydes, peptide vinyl sulfones, peptide boronates, peptide epoxiketones, and beta-lactones. All except peptide boronates have been found unsuitable for clinical development.[93] Cutaneous toxicity has been variously described in from 20% to 30% of patients treated. Severity grade varies from 1 to 3.

Etiology

The proteasome inhibitor bortezomib, a peptide boronate, was approved for treatment of refractory multiple myeloma. Investigations are currently underway for treatment of non-Hodgkins lymphoma and a variety of solid tumors. It has been suggested that bortezomib's cutaneous toxicity occurs as an inflammatory response associated with delayed hypersensitivity, cell-mediated immune responses, vascular damage, or direct toxic reactions.[96] Enhancement of the release of pro-inflammatory cytokines may also be involved.[97]

Clinical Manifestations

In most patients described thus far cutaneous adverse reactions vary in severity and occurrence. An undefined "exanthem" consistent with a hypersensitivity reaction seems to be most common. It resolves spontaneously without treatment but recurs with additional treatment cycles.

At least 20% of patients develop lower extremity edema. An unspecified rash, pruritus, urticaria, sweating, dry skin, and eczema

appear commonly, whereas alopecia seems to be rare.[98] Red nodules or plaques on the trunk, and a generalized exanthem associated with ulceration and fevers may appear during the second to fourth treatment cycles; however, they can be seen in the first cycle.[98] Drug-induced Sweet's syndrome[98,99] and erythematous maculopapular eruptions that on biopsy display "leukocytoclastic vasculitis" have been seen in many patients.[97,100,101] It has been suggested that the development of vasculitis may be a possible surrogate marker of disease response.[101] A folliculitis-like eruption has also been described,[102] as has reactivation of latent varicella zoster virus.[103] Finally, a solitary paranasal plaque and eschar have been described.[104]

Pathology

Histology differs depending on the type of skin eruption. In patients with nodules, plaques, and exanthem, histology ranged from perivascular dermatitis to interstitial and interface dermatitis.[96] In those with leukocytoclastic vasculitis, perivascular neutrophilic infiltrates with fibrinoid necrosis is seen. In Sweet's syndrome there are diffuse neutrophilic infiltrates in the reticular dermis with papillary dermal edema. Leukocytoclastic nuclear debris is often seen interstitially, but true vasculitic changes are absent. In the folliculitis-like lesions, perivascular lymphoid infiltrates were seen.[102] In a solitary alar lesion, a superficial perivascular and interface dermatitis compatible with drug eruption was seen.[104]

Differential Diagnosis

Infectious exanthems and other eruptions due to medicines other than bortezomib must be considered. Sweet's syndrome must be distinguished from other reactions such as neutrophilic eccrine hidradenitis, pyoderma gangrenosum (bullous), erythema multiforme, vasculitis, and other infectious or neoplastic causes. Vasculitis must be distinguished from capillaritis, vasculopathy, and other inflammatory dermatoses such as Sweet's syndrome, urticaria, and erythema multiforme. Additionally, Sweet's syndrome and leukocytoclastic vasculitis can be due to several etiologies, and there do not seem to be any unique features suggesting bortezomib as the etiology.

Treatment and Outcome

In some cases lesions resolve without specific treatment, or with the use of oral corticosteroids and/or antihistamines.[96–98,100,102] Oral corticosteroids have been used prophylactically to prevent recurrence of lesions[96–98,102] or reduce the number and extent of lesions.[96] Antihistamines alone were not sufficient to prevent occurrence.

Histone Deacetylase Inhibitors

Histone deacetylase inhibitors (HDACs) have recently emerged as potential agents for use in cancer therapy.[105] Acetylation of histone proteins can affect gene activation. Histone deacetylases remove acetyl groups from histones leading to repression of gene transcription. Dysregulation of acetylation has been implicated in cancer development when genes involved in cell-cycle control or apoptosis are affected. HDACs are thought to work by allowing gene reactivation of tumor suppressor or apoptotic pathway genes leading to cell-cycle arrest or cell death.

Five classes of HDACs have been described. A few medications have been tested in phase I and II trials including depsipeptide, suberoylanilide hydroxamic acid, and MS 275.[105] Thus far, skin toxicity appears to be minimal. In two phase I trials for depsipeptide[106,107] it was noted that skin toxicities seem to be distinct from conventional agents. No alopecia or mucositis was noted. No sign of skin toxicity or bleeding was noted. Similarly, in a recent phase I study by Kelly and associates no cutaneous reactions were described for suberoylanilide hydroxamic acid.[108] Finally, another HDAC, MS-275, was evaluated in a phase I trial by Ryan and coworkers.[109] Cutaneous reactions were rare, with edema noted in four patients, and sweating and nail changes noted in one patient each. An allergic reaction was noted in one patient, but this was not further described. Further use of these medicines will better elucidate the adverse cutaneous effect profile.

Toll-like Receptor Agonists

Toll-like receptor agonists have emerged as other potential cancer medications.[110] There are 10 Toll-like receptors (TLRs) in humans that are expressed on cells of the innate immune system. Most signaling through these pathways results in the production of proinflammatory cytokines. Agonists have been found to drive adaptive immunity toward a Th1 response, which then targets tumor cells. In chronic lymphocytic leukemia, these agonists may enhance the activity of T cells and natural killer cells, and inhibit angiogenesis. TLR-7 and TLR-9 agonists in particular may lead to production of cytokines that render tumor cells more susceptible to killing. In this way they may be useful as adjuvant medications.

TLR-7 agonists, imidazoquinolines, are currently being studied (including S28690). There is minimal information available on cutaneous adverse effects of these medications. Imiquimod (Aldara) is also an imidazoquinoline that has been used topically for treatment of verruca and skin cancers. Topical use of this medication has been associated with systemic and cutaneous side effects. In recent trials itching, pain, and tenderness at the site of the application were the most common cutaneous complaints.[111] Other local reactions included scabbing, erosion, ulceration, erythema, and vesiculation.

Cutaneous Reactions to Epidermal Growth Factor Receptor Inhibitors

The EGFR (or ErbBl) is a 170-kd transmembrane protein that includes an extracellular ligand-binding domain and an intracellular protein tyrosine kinase.[112] Stimulation of this often overexpressed receptor in aberrant cell lines propagates pathways of cellular proliferation (including tumor growth, progression, and metastasis of human cancer); thus, EGFR therapeutic blockade has proven beneficial in treating a variety of solid tumors.[113] Two classes of EGFR inhibitors are currently in use: monoclonal antibodies that target the extracellular domain to inhibit ligand binding and induce receptor downregulation, and receptor tyrosine kinase inhibitors that competitively block receptor phosphorylation.[112] Dermatologic reactions are the most commonly reported toxicities with both classes. The most characteristic is an acneiform eruption reaction, which is seen in 50% to 90% of treated patients.[114]

Etiology

Within the first 2 weeks of treatment, a characteristic rash appears as an acne-like folliculitis, typically starting on the face, upper chest, back, and scalp but potentially extending to the extremities (Fig. 41-10). The descriptive term "acneiform" is commonly encountered in the literature, but it is important to emphasize that the pathophysiology of the primary lesion, a pustule, seems to be distinct from that of acne vulgaris.[115] The precise etiology is unclear. It has been postulated that inhibition of the EGFR pathway results in disruptions of normal development and maintenance of the hair follicle. Follicular rupture and an inflammatory reaction result.

Clinical Manifestations

There seems to be a drug-dosage relationship to the severity of the skin reaction. Severity is often rated 2 to 3. Most commonly the face is affected, including forehead, nose, nasolabial folds, cheeks, and chin.[115] There may be caudal progression of disease, but mucosa and acral surfaces are spared. Pustular lesions are primary, although erythema and cystic nodules have also been described.[115] The rash typically appears 1 to 3 weeks after onset of treatment, appearing maximal between weeks 3 and 5. It commonly resolves once treatment is



Figure 41-10 • EGFR typical eruption. **A,** Right breast with numerous pink acneiform papules and macules. **B,** Forehead with characteristic acneiform eruption of several pink papules and pustules some with crust. **C,** Bilateral forearms and dorsal hands with small pink papules and macules.

stopped but may persist for more than 12 weeks after cessation. Resumption of treatment may cause reappearance or worsening of the rash. Other than hyperpigmentation there are few residual effects.[116] Limited data suggest that patients with a skin rash of any grade may have a superior survival as compared with patients with no skin rash, and furthermore, there may be a trend toward improved survival with increasing grade of rash.[117] There is some evidence to suggest that the rash parallels saturation of receptor clearance and may be used as a measure of optimum biologic dose in those patients so affected.

Histopathology

Two primary reaction patterns have been identified: suppurative folliculitis with epithelial rupture and superficial perifollicular dermal inflammation with hyperkeratotic and ectatic infundibula.[114,115] The stratum corneum demonstrates compact orthokeratosis with focal parakeratosis and prominent follicular plugs. Also occasionally reported are basilar vacuolar degeneration, lichenoid patterns, and intradermal acantholysis.[115]

Treatment and Outcome

Depending on severity, which ranges from grade 1 to 4,[117] cutaneous toxicity, management may include drying agents, topical antibiotics and antiseptics, systemic antibiotics, topical retinoids, topical or systemic corticosteroids, or topical immunomodulatory agents. Secondary complications including *Staphylococcus aureus* infections and severe pruritus may occur and will require appropriate interventions.[116] Several published studies have even suggested that the severity of the skin eruption may parallel patient survival.[117]

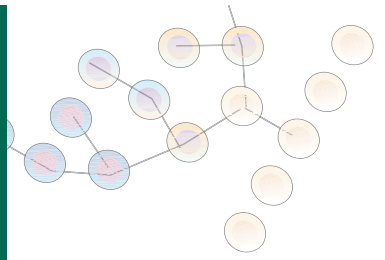
Other Dermatologic Side Effects of Anti-EGFR Therapy

Additional and less common cutaneous effects reported include nail bed infections and paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, onycholysis of nails, with the great toes and thumbs as the most commonly affected digits[114,115]; generalized exfoliation and desquamation; xerosis; pruritus; urticaria and angioedema (primarily with trastusumab); alopecia; skin fissures; and mild to moderate stomatitis and mucositis.[115] Treatment is primarily symptomatic.

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42 Lymphedema

Lance Wyatt and Julian Pribaz

SUMMARY OF KEY POINTS

Definition
- Lymphedema is the accumulation of protein-rich interstitial fluid within the skin and subcutaneous tissue.

Etiology and Classification
- Primary lymphedema is thought to be a genetically determined disease with expression at or shortly after birth (Milroy disease), puberty (lymphedema praecox), or after 35 years of age (lymphedema tarda).
- Secondary lymphedema occurs as a result of a precipitating cause.

Incidence
- The incidence of lymphedema is not known.
- The most common cause of secondary lymphedema worldwide is lymphatic filariasis.
- In Western countries the most common cause is damage to or removal of lymph nodes by surgery, radiotherapy, tumor invasion, or as the result of infection or inflammation.

Diagnosis
- Diagnosis is made in the majority of cases by history and physical examination; lymphoscintigraphy, computed tomography and magnetic resonance imaging may be needed.
- Soft, pitting edema generally begins distally and progresses proximally over months to years.

Goals of Treatment
- There is no cure for lymphedema.
- Goals of therapy are to (1) reduce fluid production and accumulation, (2) reduce associated complications, and (3) improve limb function and appearance.

Medical Treatment
- Skin care, extremity elevation, compressive garments, pneumatic compression pumps, noninvasive complex lymphedema therapy, and treatment of infection are the mainstays of medical therapy.

Surgical Treatment
- Surgery is a continuum of medical management and is performed for failure of medical management, gross extremity size and weight with impaired extremity function, severe skin changes, and/or recurrent lymphangitis (more than three episodes per year).
- Physiologic procedures attempt to restore lymphatic drainage.
- Excisional procedures remove lymph-producing as well as fibrosclerotic tissue and fat.

INTRODUCTION

Lymphedema is the accumulation of protein-rich interstitial fluid within the skin and subcutaneous tissue. Cases in which the etiology is unknown or that develop as a result of congenital lymphatic dysfunction are referred to as primary lymphedema. All forms of lymphedema that occur as a result of a precipitating cause are termed secondary lymphedema. No cure exists for lymphedema. The aims of therapy are to reduce fluid production and accumulation, to reduce associated complications, and to improve limb function and appearance.

ETIOLOGY AND CLASSIFICATION

The most commonly used classification categorizes the etiology of lymphedema as primary or secondary to some inciting event. Primary lymphedema, which is thought to be due to aplasia or hypoplasia of the lymphatics, has long been thought to be a genetically determined disease with expression at or shortly after birth (Milroy disease), puberty (lymphedema praecox), or after 35 years of age (lymphedema tarda). The time of onset may be related to the relative number of functioning lymphatics. It is generally thought that the fewer lymphatics the earlier the onset. The molecular basis for congenital primary lymphedema (Milroy disease) has been established as autosomal dominant with incomplete penetrance due to a mutation in the gene locus encoding VEGFR3.[1,2] This condition may be diagnosed prenatally.[3]

Lymphedema praecox, the most common form of primary lymphedema, is responsible for as many as 94% of cases in large reported series. The uncertainties of this condition derive from its unusual, unexplained features: female predominance (ratio of females to males is estimated to be 10 : 1), development around the time of menarche, more common involvement of the left leg, and rare upper extremity involvement. Estrogenic hormones have been implicated.[4] The edema typically is limited to the foot and calf. Lymphedema tarda, which develops later in life, accounts for fewer than 10% of cases of primary lymphedema. The precipitating cause often follows minor trauma or an inflammatory process (e.g., cellulitis) that can damage and possibly obstruct an already reduced number of lymphatics, tipping the balance in favor of lymphedema.

The most common cause of secondary lymphedema worldwide is lymphatic filariasis. In its most obvious manifestations, lymphatic filariasis, also known as elephantiasis, causes edema of the entire arm or leg; the genital regions (vulva, scrotum, breasts) also may be involved. Lymphatic filariasis is a significant cause of poverty in more than 80 countries in which it is endemic, primarily in Asia, Africa,

the Western Pacific, and the Americas. Approximately 90% of these infections are caused by *Wuchereria bancrofti*, with most of the remainder by *Brugia malayi* and *B. timori*. The major vectors for *W. bancrofti* are *Culex*, *Aedes* species, and *Anopheles* mosquitoes. The World Health Organization estimates that at least 120 million people are infected, with approximately 40 million disabled as a result of this condition.

In Western countries, damage or removal of lymph nodes by surgery, radiation therapy, tumor invasion, or as the result of infection or inflammation are the most common causes of secondary lymphedema. The onset of upper extremity edema following axillary lymph node dissection is probably the most common cause of lymphedema in the United States.[5] The incidence of lymphedema following breast cancer therapy ranges broadly depending on the definition of lymphedema, on type of therapy, and on time elapsed since therapy; however, an overall incidence rate of 25% has been reported. The incidence rate climbs to 38% among patients with axillary node dissection and radiation.[6] Changes in clinical practice, such as the use of sentinel lymph node biopsy rather than full axillary dissection in breast cancer treatment, may lead to a reduction of this rate. Studies have shown that, at least in the short term, the incidence of lymphedema is reduced in patients undergoing sentinel lymph node biopsy as compared with standard axillary dissection.[7,8] In the ALMANAC trial,[8] self-assessment among 954 patients randomized to each of these treatment groups, the relative risk self-reported of moderate to severe lymphedema within 12 months of surgery in the sentinal node biopsy group was 0.37 in comparison to the axillary dissection group. Furthermore, objective measurements of arm circumference were shown to be greater in the axillary dissection group at all sampling time points. The difference was statistically significant at 1, 3, and 6 months, but failed to meet that threshold at the 12-month measurement. No long-term results have yet been reported on the effect of sentinal node biopsy on the incidence of lymphedema, but studies are under way. Lymphedema of the lower extremity may occur after inguinal and pelvic lymph node dissection or irradiation, with a published frequency of 1% to 47%.[9,10]

Why do the vast majority of individuals not develop lymphedema after surgery, regional node dissection, malignancy, radiotherapy, trauma, inflammation, and infection? The capacity for compensation by collateral flow and regeneration of damaged lymphatics may explain whether lymphedema develops. Disrupted lymphatics are not reconnected during replantation or microsurgical free-tissue transfer. Temporary swelling of a re-implanted or transplanted part resolves without intervention. Radiocolloid lymphoscintigraphy with technetium-99m–antimony trisulfide colloid (Sb_2S_3) studies in individuals without lymphedema have demonstrated spontaneous regeneration or reconnection of lymphatics after free-tissue transfer.[11] These findings suggest that persons with lymphedema lack compensatory mechanisms necessary to prevent the development of lymphedema.

Lymphedema may be either genetic or syndromic. Turner's syndrome, Noonan's syndrome, and Hennekam syndrome are examples of syndromic lymphedema. Lymphedema-distichiasis syndrome, cholestasis-lymphedema syndrome, all forms of primary, and most forms of secondary lymphedema may be classified as genetic lymphedema. Individuals who manifest the disease at or shortly after birth may have a more severe form of lymphedema without sufficient compensatory mechanisms. The mildest forms of the condition may exist as a subclinical process, with expression only after an inciting event.

PATHOPHYSIOLOGY

Lymphedema is confined to the subcutaneous compartment; the deep muscle regions appear to be clinically uninvolved. Extravasation of protein-rich fluid occurs when lymphatic transport capacity is reduced because of reduced numbers of functioning lymphatics or increased lymphatic load. This high-protein edema causes a shift in Starling's equilibrium, resulting in the accumulation of more fluid. In time, low oxygen tension, decreased macrophage function, and the presence of increasing amounts of protein-rich fluid give rise to a chronic inflammatory state and gradual tissue fibrosis. In chronic lymphedema, a hypertrophy of adipose tissue also occurs, but the mechanism for this has not been elucidated. The high-protein edema serves as a medium for bacteria, and episodes of infection so characteristic of the condition lead to additional lymphatic sclerosis and further lymphatic transport dysfunction (Table 42-1).

Table 42-1 Pathophysiology of Lymphedema

REDUCED NUMBER OF LYMPHATICS BELOW CRITICAL LEVEL
Congenital lymphedema
Surgical ablation
Scar, radiation, infection
INCREASED LYMPHATIC LOAD
High-protein edema
Increased osmotic pressure
Inflammation
Perilymphatic scarring
Increased fatty deposition
PROGRESSIVE DETERIORATION
Increased volume
Induration
Fibrosis

DIAGNOSIS

In the vast majority of patients, diagnosis can be made by history and physical examination. The National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE, version 3) outlines the diagnostic and staging criteria for lymphedema related to malignancy (Table 42-2).[12] Edema generally begins distally and progresses proximally over months to years. Early in the course of lymphedema the accumulation of protein-rich interstitial fluid results in a soft, pitting edema. With time the chronic inflammatory state and accumulation of fat and gradual tissue fibrosis give rise to a nonpitting edema. Skin changes may occur, but ulceration is infrequent. Individuals with lymphedema may complain of fatigue or pressure in the extremity, but the complaint of pain should prompt the physician to search for an alternative cause. Lymphoscintigraphy with radiocolloids has been successful in delineating the anatomy of lymph vessels and in evaluating the dynamics of lymph flow. This technique has replaced lymphangiography, which may damage lymphatics and worsen lymphedema.[13] Lymphangiography is not recommended. Computed tomography and magnetic resonance imaging may be useful to rule out malignancy.

Edema from cardiac, renal, or hepatic insufficiency is distinguished from lymphedema by history and examination. Chronic venous insufficiency and postphlebitic syndrome are associated with aching discomfort and chronic pruritus.[14] Physical examination reveals hemosiderin deposits in the skin, dusky discoloration and venous engorgement with dependence, varicosities, and ulceration in advanced cases.

Myxedema of thyroid disease may be confused with lymphedema and develops when abnormal mucinous substances accumulate in the skin. Individuals with myxedema develop roughening of the skin of the palms, soles, elbows, and knees. These individuals also may have diminished sweat production, yellow-orange discoloration of the

Table 42-2 National Cancer Institute's Common Terminology Criteria for Adverse Events Staging and Diagnosis for Lymphedema

	GRADE				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Edema: head and neck	Localized to dependent areas, no disability or functional impairment	Localized facial or neck edema with functional impairment	Generalized facial or neck edema with functional impairment (e.g., difficulty in turning neck or opening mouth compared with baseline)	Severe with ulceration or cerebral edema; tracheotomy or feeding tube indicated	Death
Edema: limb	5% to 10% interlimb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection; pitting edema	>10% to 30% interlimb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	>30% interlimb discrepancy in volume; lymphorrhea; gross deviation from normal anatomic contour; interfering with ADL	Progression to malignancy (i.e., lymphangiosarcoma); amputation indicated; disabling	Death
Edema: trunk/genital	Swelling or obscuration of anatomic architecture on close inspection; pitting edema	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; interfering with ADL; gross deviation from normal anatomic contour	Progression to malignancy (i.e., lymphangiosarcoma); disabling	Death

ADL, activities of daily living.

National Cancer Institute: NCI common terminology criteria for adverse events v3.0 (CTCAE). Available at: http://ctep.cancer.gov/forms/CTCAEv3.pdf. Accessed 8 December 2006.

skin, thinning hair, and uneven nails. The process may be localized to the pretibial region in thyrotoxicosis[15] but is more generalized in hypothyroidism.

Lipedema is caused by the abnormal accumulation of fatty substances in the subcutaneous regions, typically between the pelvis and the ankle. The feet are spared, and the swelling is symmetric, bilateral, and often painful. The condition affects women or men with a feminizing disorder and arises within 1 to 2 years after the onset of puberty. Patients often have a propensity to bruising, possibly as a result of increased fragility of capillaries within the adipose tissue. Skin changes characteristic of lymphedema are not present, and consistent fat pads anterior to the lateral malleoli are found in individuals with lipedema.[16]

In the United States a frequent cause of lymphedema of both the upper and lower extremities is neoplastic disease. Individuals previously treated for neoplastic disease who develop new or worsening lymphedema must be evaluated for the recurrence of cancer. Malignant lymphedema often develops rapidly and results in intrinsic or extrinsic obstruction of lymph flow. Pain, generally absent in lymphedema, may be present (Fig. 42-1).[17]

Lymphangiosarcoma is an extremely rare tumor that initially appears as multiple blue-red subcutaneous nodules. In the upper extremity, it most frequently occurs in cases of chronic lymphedema after mastectomy (described by Stewart and Treves in 1948 and known as Stewart-Treves syndrome[18]). Lymphangiosarcoma seldom occurs in the lower extremity but may develop in the presence of lymphatic filariasis. The usual interval between mastectomy and the appearance of lymphedema is approximately 1 year; lymphangiosarcoma develops approximately 5 to 9 years after mastectomy. The reported incidence varies from between 0.07% and 0.45%.[19] Immunologic and electron microscopic studies suggest that these tumors arise from vascular endotheliocytes, despite the clinical appearance of arising from lymphatic vessels.

Why lymphangiosarcoma has a predilection for lymphedematous tissue is unknown. It has been shown that these tumors grow more



Figure 42-1 • A 59-year-old man with gross end-stage obstructive lymphedema after recurrent squamous cell cancer excision and irradiation. The limb was nonfunctional and was treated with amputation.

consistently in lymphedematous as opposed to non-lymph-rich tissue. Some have speculated that the presence of a local immune deficiency creates a climate for malignant degeneration. Lymphangiosarcomas develop multicentrically and spread rapidly. These are extremely aggressive, highly malignant tumors; limb-sparing procedures are not recommended. Amputation may be the only hope for survival. Prognosis for patients with lymphangiosarcoma is extremely poor, with 5-year survival reported in between 8.5% and 13.6% despite aggressive treatment.[19]

MEDICAL MANAGEMENT

The aim of all forms of management is to restore the balance between lymphatic load and transport capacity. No treatment option is completely and permanently curative. The patient must understand the chronicity of the condition as well as the patient's important role in controlling the edema and preventing complications.

Limb girth should be assessed at the initial visit and at regular intervals thereafter to provide an accurate determination of the effect of therapy. Various methods allow assessment of limb volume, and all are prone to error in reproducibility. Measuring tapes may be used, and circumferential measurements should be obtained from standard, regional landmarks (antecubital fossa, etc.; Table 42-3). The physician should recognize that measurements taken at various times of the day may yield different results; the girth of an extremity may increase throughout the day, because it is in a dependent position and subjected to the effects of gravity. Measurements of water volume displacement are more precise, but do not identify changes in a specific area of the limb (Fig. 42-2). Another useful modality to measure is the degree of limb tissue turgor; the degree of hardness or softness can be measured by a specially designed tonometer (Fig. 42-3).[20] Patients should be serially followed up by physical examination, with any combination of the following: circumferential measurements, volume displacement, tonometry, serial photography, lymphoscintigraphy, and patient survey.

Weight reduction and extremity elevation are important measures that decrease edema. The individual must elevate the affected extremity at night. A sling may be used for the upper extremity, and elevating the foot of the bed on 4- to 6-inch blocks is recommended for edema of the lower extremity.

Custom-fitted elastic compressive garments (sleeves or stockings) are often worn during the day to maintain limb volume. The length of the garment should match the extent of disease. A comfortable fit is essential to ensure compliance.

Intermittent pneumatic compression with multichamber pumps removes excess fluid from the involved limb and may be helpful if used early in the course of disease, before the development of fibrosclerotic tissue changes. These devices apply a sequential pattern of compression to the extremity, permitting a physiologic distal-to-proximal milking action of the lymphedematous limb.[21] Therapy is most effective if continued at regular intervals, and compressive garments should be worn between treatments. Cardiac failure, active infection, and deep venous thrombosis are contraindications to pump therapy.

Table 42-3 Measurement of Lymphedema

Linear: girth
Hand (foot)
Wrist (ankle)
15 cm below elbow (knee)
Elbow (knee)
15 cm above elbow (knee)
Volume
Water tank: volume displacement
Tonometry



Figure 42-2 • Volume measurement of the upper limb.

Noninvasive complex lymphedema therapy, which consists of manual lymph drainage, compressive bandaging, and physical therapy exercises, may be used with promising results.[22] Complex lymphedema therapy facilitates lymph drainage by recruiting collateral vessels so that the lymphedematous area can be drained into normally functioning lymphatic systems. Recent series have demonstrated therapeutic responses in compliant patients.[23,24]

Basic skin care is essential in the prevention of infection and may assist in preventing associated skin changes, including dermatitis,

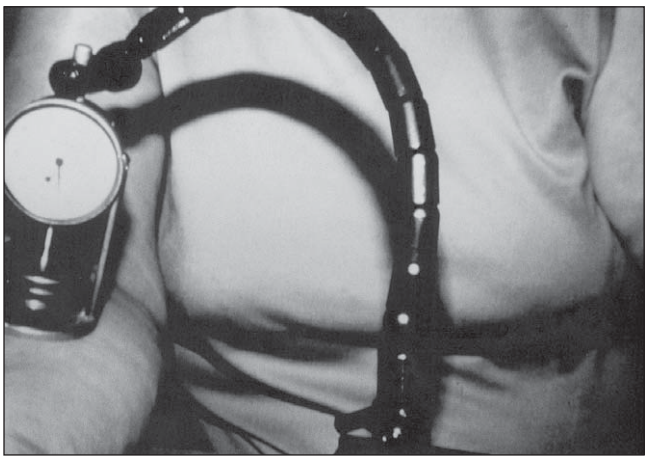


Figure 42-3 • Tonometry measurement of the upper limb.

Box 42-1. LYMPHEDEMA: MEDICAL THERAPY

Meticulous skin care
Weight reduction
Limb elevation
Exercise
Custom-fitted elastic compressive garments
Pneumatic compressive pump
Noninvasive complex lymphedema therapy
Treatment of infection
Diuretics (optional)
Heat (investigational)
Benzopyrones (investigational)
Dietary flavonoids (investigational)
Intra-arterial injection of lymphocytes (investigational)

hyperkeratosis, warty verrucosis, as well as breakdown of the epidermis and leakage of lymph fluid (lymphorrhea). Meticulous foot care for individuals with lower extremity lymphedema with daily use of a low-pH, water-based lotion will help to prevent fungal infections of the web spaces. Topical antifungal therapy is recommended for localized fungal infections, but invasive infection may require systemic antifungal therapy.

Aggressive and prompt treatment of lymphangitis and cellulitis is recommended to prevent the development of sepsis. It is thought that each bout of sepsis causes further sclerosis of existing lymphatics. Systemic antibiotic therapy targeted toward staphylococcal and streptococcal species for 5 to 7 days, combined with bedrest and extremity elevation, is suggested. Approximately 15% to 25% of patients will have recurrent lymphangitis and cellulitis, and these individuals may require long-term prophylactic antibiotic therapy.

Benzopyrones have been advocated in the treatment of lymphedema.[25] Benzo-α-pyrone (coumarin) is thought to have a stimulatory effect on macrophages and other elements of the immune system, enhancing proteolysis in breaking down large complex tissue proteins into peptides, which can be absorbed by the venous system. Although coumarin is used in mild cases of lymphedema outside of North America, its hepatotoxicity and studies showing a lack of efficacy in lymphedema have led North American experts to conclude that the risk-to-benefit ratio does not justify its use.[26] Parasitic infections involving *W. bancrofti*, *B. malayi*, and *B. timori* are initially treated with albendazole and ivermectin or albendazole with diethylcarbamazine. Antihistamine and/or anti-inflammatory agents are used to control the allergic reactions to the dying parasite.

Laser therapy,[27] hyperthermia,[28] and intra-arterial injection of lymphocytes[29] are investigational treatments purported to play a role in the management of lymphedema. Further evidence is needed to better clarify the role of these modalities in the management of lymphedema (Box 42-1).

SURGICAL MANAGEMENT

Numerous surgical procedures have been described for the treatment of lymphedema. None is curative, and quantitative, long-term data on outcome are sparse. Individuals must view surgery as a continuum of management; the physician must emphasize that surgery does not obviate the need for continued medical therapy.

It is estimated that approximately 10% of patients with lymphedema will need surgery.[30] Operative intervention has traditionally been recommended if medical therapy is ineffective in controlling lymphedema or preventing complications. Surgery also is recommended for impaired extremity function secondary to gross extremity size and weight, severe skin changes, and recurrent lymphangitis (more than three episodes per year; Box 42-2).

Box 42-2. LYMPHEDEMA: SURGICAL INDICATIONS

Failure of medical management
Excessive extremity size and weight, with functional impairment
Severe skin changes
Recurrent infection (more than three episodes of cellulitis or lymphangitis per year)

All procedures aim to reduce lymph fluid accumulation, halt the progression of disease, improve limb function, reduce bulk, improve appearance, and facilitate conservative therapy. Physiologic procedures attempt to re-establish lymphatic drainage, whereas excisional procedures debulk the limb, removing both fibrosclerotic and normal, lymph-producing tissue and fat. This distinction is blurred, in that many physiologically designed operations have excisional components; moreover, excisional procedures have an apparent physiologic effect.[31] Combinations of excisional and physiologic procedures also are commonly used to maximize the improvement in lymphedema (Box 42-3).

Physiologic Procedures

Physiologic procedures include lymphangioplasty,[30–37] pedicle flap procedures (omental transposition, enteromesenteric bridge),[38–41] and microsurgical anastomosis (lymph nodal-venous, lymphaticovenous, lympholymphatic shunts).[42–49]

Lymphatic Bridging

One of the earliest procedures for lymphedema was the subcutaneous implantation of silk threads (lymphangioplasty) advocated by Handley in 1908.[32] Many materials (rubber,[33] polythene,[34] polyvinylchloride[35]) have subsequently been used in the attempt to create drainage channels. This technique was abandoned because of the consistently high incidence of infection and extrusion of material.

Pedicle flap procedures juxtapose lymphatic-rich flaps and lymphedematous tissue to induce lymphatic communication and provide drainage. Initially, tube pedicles with a random blood supply were fashioned in multiple stages by Gillies and Fraser[50] and Mowlem.[51] These resulted in considerable scarring and poor function. Clodius and colleagues[52] found that skin flaps with an axial blood supply also contained axial lymphatics and allowed spontaneous lymphatic

Box 42-3. SURGICAL THERAPY

Physiologic
Lymphangioplasty
Omental transposition
Enteromesenteric bridge
Lymphaticovenous anastomoses
Lympholymphatic anastomoses

Excisional
Total skin and subcutaenous excision ("Charles procedure")
Buried dermal flap ("Thompson procedure")
Staged subcutaneous excision beneath flaps ("modified Homans' procedure")
Suction-assisted lipectomy

connections. He reported using these flaps to improve brachial neuritis and upper extremity lymphedema simultaneously (Fig. 42-4). Omentum and small bowel have also been used as pedicle flaps. These operations require celiotomy; hernia, adhesion formation, and bowel obstruction have been reported with these procedures (see Fig. 42-4).

The omental transposition operation depends on lymphatic connections developing between the omentum and lymphadematous tissue (Fig. 42-5). This was first used by Dick[53] in 1935 in two cases of scrotal lymphedema. The omentum is rich in lymphatics and can easily reach the chest and axilla, but when it has to be lengthened to reach farther into the upper or lower limb, many of the lymphatics may be divided. Goldsmith[39] reported long-term results but provided no objective data on the extent of extremity size reduction. The complication rate was high, and there was no clarification as to how many patients were followed up beyond 3 years (see Fig. 42-5).

Hurst and associates[41] followed up for 2.5 to 7 years eight patients who underwent the enteromesenteric bridge procedure. This operation, physically limited to individuals with proximal lymphatic obstruction at the level of the iliac or lower aortic nodes, also requires a celiotomy. Of patients in this series, 25% failed to improve and underwent a subsequent excisional procedure. Five patients were noted to improve clinically, but the authors provide no objective data.

Drainage into Deep Lymphatics

Thompson[54] proposed that a dermal wick of a lymphedematous tissue could be transposed deep to the muscle fascia, to allow bypass of lymph from superficial to deep lymphatics. The reported results may have been due to the excisional aspect of this procedure that accompanies the dermal wick. Sawhney[55] studied this procedure with radioactive serum albumin but was unable to demonstrate an increased uptake after dermal-wick procedures.

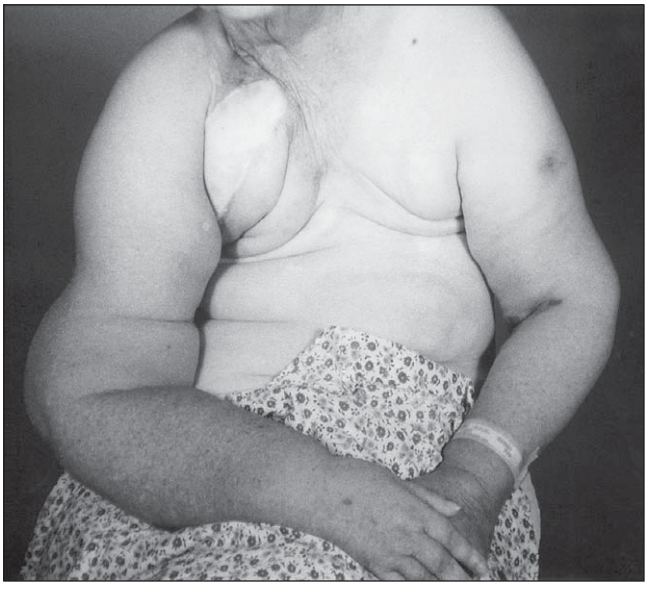


Figure 42-4 • Patient with lymphedema and brachial plexus neuropathy after right radical mastectomy and irradiation for breast cancer. She was treated with excision of dense axillary contracture, brachial plexus neurolysis, and latissimus dorsi myocutaneous flap to provide better coverage with well-vascularized tissue to the brachial plexus and also to help bridge obstructed upper limb lymphatics. Upper extremity volume decreased, and the arm felt subjectively softer and less heavy for this woman.

Microsurgical Procedures

Microsurgical procedures designed to reestablish lymphatic drainage to an affected extremity may be divided into three categories: (1) lymph nodal–venous shunts, (2) lymphaticovenous anastomoses (LVAs), and (3) lympholymphatic anastomoses.

Lymph Nodal–Venous Shunts

Lymph nodal–venous shunts involve anastomosis of a transected lymph node to a neighboring vein. This was first described by Neilubowicz and Olszewski.[56] These procedures have been used for lymphedema involving the male and female genitalia, and these authors have reported good results in 50% of the patients. However, Calnan and coworkers[57] found that these lymph node–venous anastomoses remained patent for only a limited time in individuals with lower extremity lymphedema, and by 3 months they were all obstructed. Unfortunately, obstructive lymphedema usually results after lymphadenectomy, and thus lymph nodes are typically not available for use in this type of anastomosis.

Lymphaticovenous Anastomoses

Because lymph eventually drains into the venous system via the thoracic duct, in cases in which obstruction to flow occurs, it makes intuitive sense that it should be possible to bypass a lymphatic obstruction by allowing the lymph to enter the venous system more peripherally. In obstructive lymphedema lymphatic pressure is higher than venous pressure,[58] which should theoretically keep the LVA patent.

One of the pioneers of microlymphatic research for treatment of obstructive lymphedema was O'Brien, working at St. Vincent's Hospital in Melbourne, with whom the senior author trained and subsequently worked. In the first results, reported in 1976, an 83% patency of LVA was achieved in nonlymphedematous dogs. Considerable work was involved in creating a canine chronic lymphedema model, and once this was achieved, extensive research in LVA, free microvascular nodal transfers, and free microvascular omental transfers followed.[59–61]

Concurrent with this basic research, clinical studies on individuals with obstructive lymphedema ensued. A 15-year study of 134 persons (116 females and 18 males) with established obstructive lymphedema from various causes and treated with LVA was reported in 1990.[45] Most patients (102) had lymphedema of the upper extremity, and 32, of the lower extremity. These individuals were all treated with LVA with or without additional reduction procedures. Of these patients, 90 were available for long-term follow-up (Tables 42-4 and 42-5): 52 patients had LVA only (mean, five anastomoses), and 38 patients had LVA plus segmental reduction (mean, 4.1 anastomoses). The results were graded both subjectively ("limb smaller and softer," "less weight," "more comfortable," "clothes fit better," etc.) and objectively with linear, volume, and tonometry measurements (see Tables 42-4 and 42-5)

Subjectively, 73% and 78% of these individuals reported improvement after LVA alone and LVA plus segmental reduction, respectively. Objectively, 42% had improvement after LVA alone, and 60% had improvement after LVA and reduction. Of the entire group, 58% reported fewer episodes of cellulitis. The results were generally better in the upper extremity compared with the lower extremity, a finding that other authors also reported.[49] Furthermore, of the persons who obtained postoperative improvement, none subsequently became worse. Of the remaining individuals whose condition did not improve, 12% reported no change in lymphedema, and in 46%, the lymphedema became gradually worse, as is the natural history of untreated lymphedema.[45]

The technique used in this series of patients involved performing multiple LVAs at multiple levels (wrist, medial forearm [upper calf], medial arm [leg]). In individuals who would benefit from a segmental reduction, this was done laterally (upper lateral arm,

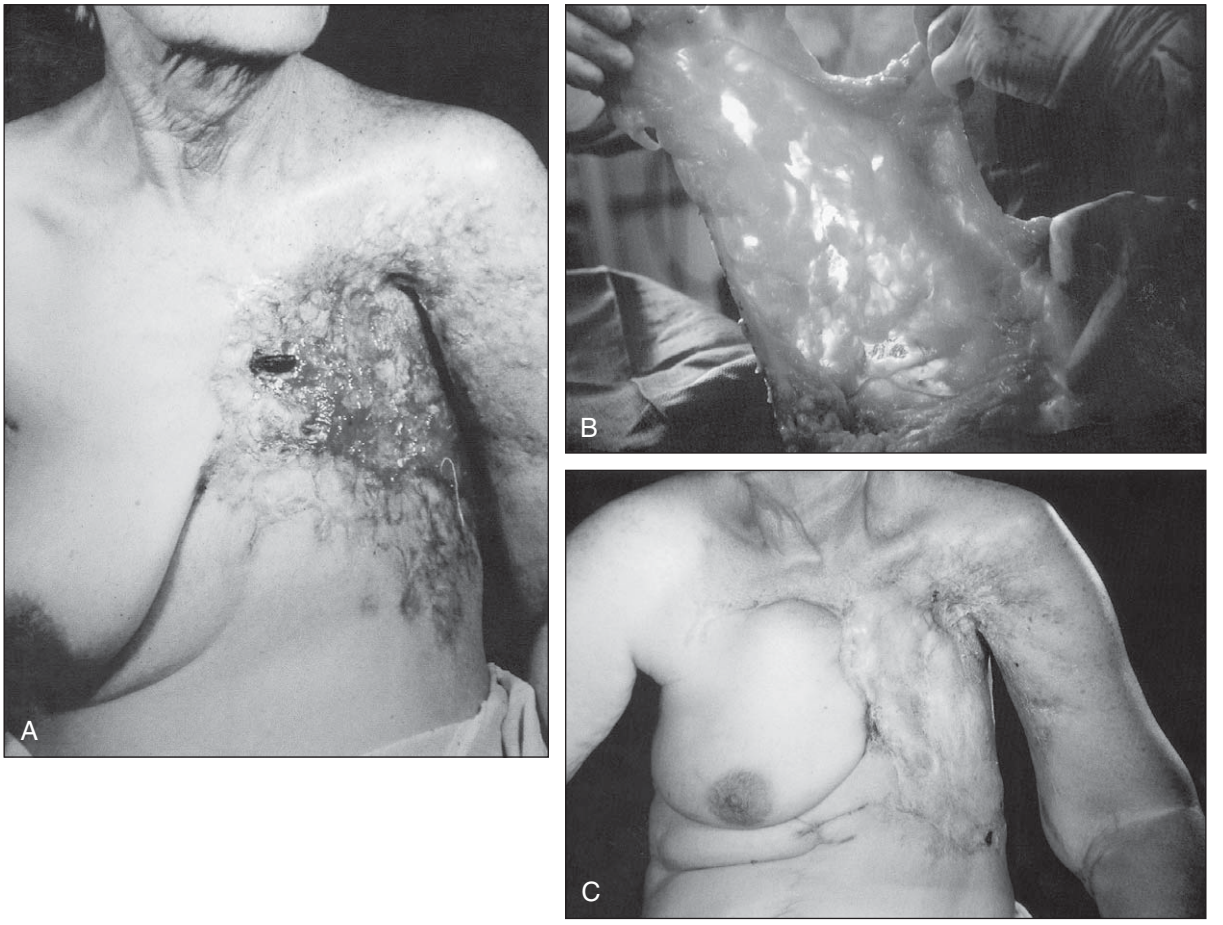


Figure 42-5 • **A,** A 79-year-old woman with radiation necrosis of the left chest wall and axilla after radical mastectomy and irradiation with upper limb lymphedema. **B,** Omental flap was raised and pedicled on right gastroepiploic vessels. The chest wall and axilla were debrided; the omentum was transferred to cover both the chest wall and axilla and to serve as a bridge for lymphatic drainage. **C,** Nine months after radical debridement, omental flap, and skin graft to chest wall and axilla, with some improvement in upper limb lymphedema.

lateral thigh). Patent blue dye was injected subdermally into the web spaces. A tourniquet was used, but the limb was not exsanguinated. With 4× loupe magnification, the subcutaneous tissues were carefully dissected to isolate the lymphatics, which appeared as beaded, blue, thin, fragile vessels measuring 0.3 to 0.5 mm in diameter. Adjacent veins also were located or transposed from adjacent areas to lie near the dissected lymphatics. The lymphatics and veins were tagged with loose silk loops. The anastomosis of the lymphatic to the vein was performed in end-to-end fashion with the operating microscope and 11-0 nylon suture on a 75-mm needle.

Table 42-4 St. Vincent's Lymphedema Experience*

LVA (134 patients)
116 females, 18 males
Average age 52 yr
102 upper limb, 32 lower limb
No suitable lymphatics (20 patients)

LVA, lymphaticovenous anastomosis.
*Surgery for obstructive lymphedema in 154 patients (1974–1988)
Adapted from O'Brien et al: Long term results after microlympyhaticovenous anastomoses for treatment of obstructive lymphedema. Plast Reconstr Surg 1990;85:562.

Table 42-5 St. Vincent's Lymphedema Experience*

	LVA Only	LVA and Reduction
Patients	52	38
No. of LVAs (mean)	5	4.1
Mean volume reduction (%)	44 (10–84)	44 (10–84)
Subjective improvement (%)	73	78
Objective improvement (%)	42	60
Objective no change (%)	12	16
Objective worse (%)	46	24
58% Reduction cellulitis upper limb		
• Better results than lower limb		
• Hand better than forearm		
• All patients who improved initially continued to do so		

LVA, lymphaticovenous anastomosis.
*Long-term follow-up in 90 of 134 patients (1974–1988).
Adapted from O'Brien et al: Long term results after microlympyhaticovenous anastomoses for treatment of obstructive lymphedema. Plast Reconstr Surg 1990;85:562.

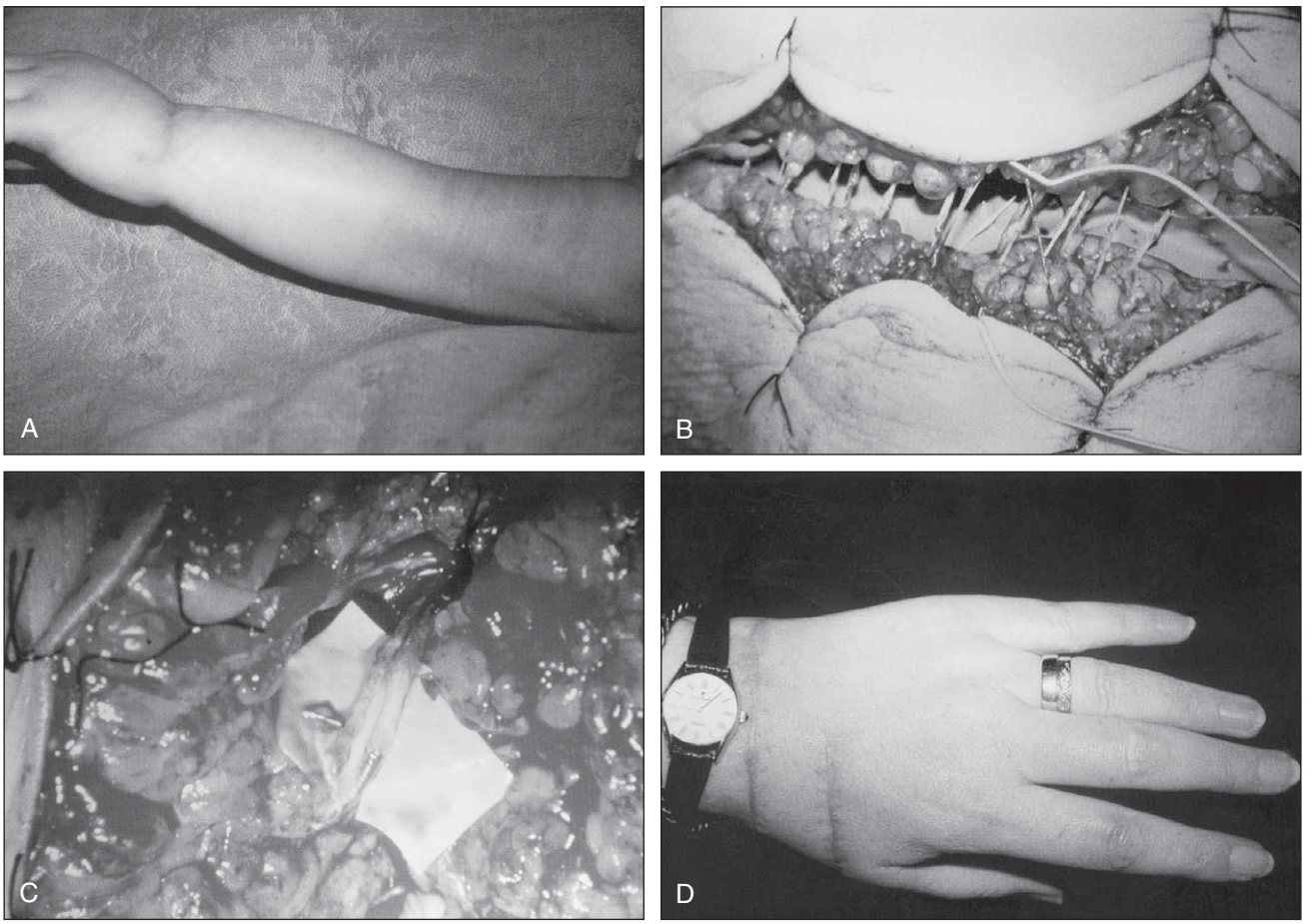


Figure 42-6 • **A,** Patient with lymphedema of upper extremity affecting hand and forearm. **B,** Patent blue dye has been injected into web spaces and lymphatics, and veins dissected out at wrist, proximal forearm, and arm levels. **C,** Magnified view. Typical lymphaticovenous anastomoses completed. This patient had a total of six anastomoses at three levels. **D,** Three months after surgery, with complete resolution of the lymphedema; this woman was able to wear her rings.

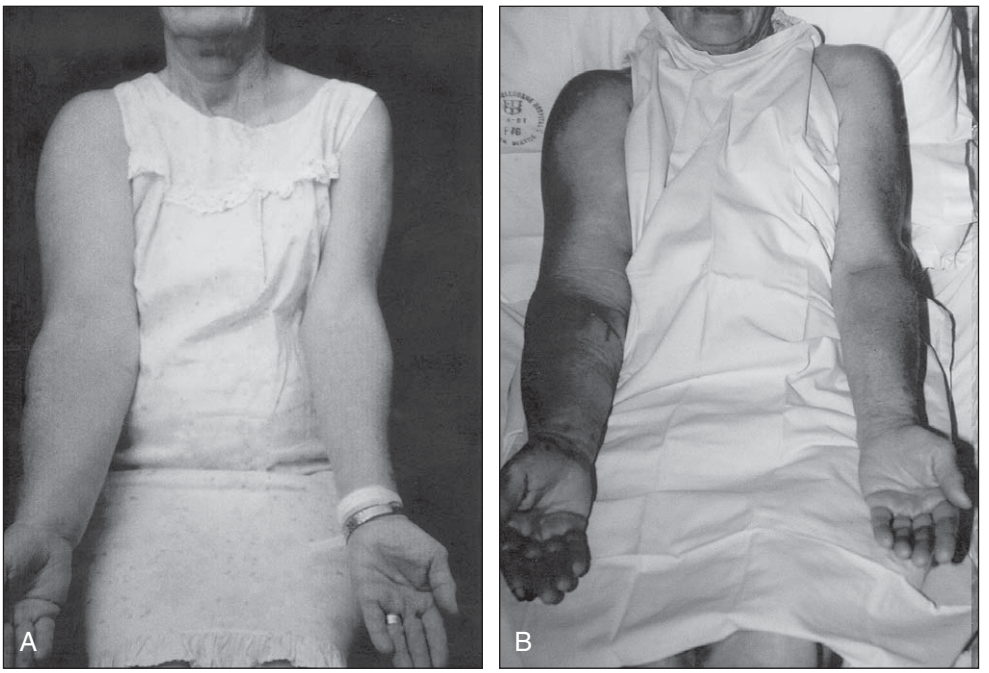


Figure 42-7 • **A,** Woman with lymphedema of right upper limb after mastectomy and irradiation. **B,** Six months after multiple-level lymphaticovenous anastomosis with smaller, softer limb.

Approximately four to six sutures were used per anastomosis. As many anastomoses as possible were performed at multiple levels (Figs. 42-6 and 42-7).

This type of surgery is very demanding, but a significant number of patients obtain subjective improvement, and approximately half obtain measurable objective improvement. Critics of this type of surgery argue that no easy way exists of knowing how many LVAs stay patent in the long term.[47,49]

Similar results have been reported by Huang and colleagues,[58] who reported excellent and good results in 79% of patients, most of whom had obstructive lymphedema of the lower limb resulting from filariasis.[58] Both Huang and O'Brien have found that the results are better when the duration of the edema is shorter, and Huang, but not O'Brien, found that the number of anastomoses performed was significant, whereas O'Brien's group did not find the same correlation.

Lymphaticolymphatic Anastomosis

Lymphaticolymphatic shunts bypass regional areas of lymphatic obstruction. Baumeister and associates[62] first reported this technique in 1981 and later reported his results in 55 patients in 1990. He believes that lymphaticolymphatic anastomoses are better than LVAs, because no increased back pressure is found, as can sometimes occur in higher venous pressure. He described the harvest of two to three lymphatic tracts from the anteromedial aspect of the thigh (adjacent to the saphenous vein).[62] In the lower extremity, these are pedicled from the normal limb to the lymphedematous limb, across the pubic area, and the lymphatics anastomosed to the dilated obstructed lymphatics on the involved side. For the upper extremity the lymphatic grafts are harvested and transferred as free grafts to bridge the obstruction across the axilla with the proximal anastomoses into a lymphatic trunk in the neck. In his series of patients Baumeister was able to show an 80% reduction in limb volume over a 3-year follow-up and also was able to demonstrate graft patency and improved transport index with lymphoscintigraphy. Better results were obtained in the upper limb (Fig. 42-8).[63]

Excisional Procedures

Excisional procedures include total skin and subcutaneous skin excision (erroneously referred to as the Charles procedure),[64–66] staged subcutaneous tissue excision (erroneously referred to as the Kondoleon operation),[67–72] and suction-assisted lipoplasty.[73–75] The buried dermal flap described by Thompson is an excisional procedure proposed to have a physiologic component.[76–79] Excisional procedures are suitable for both primary and secondary lymphedema.

Charles[64–66] described a surgical technique for the treatment of scrotal edema. The Charles procedure, however, has become an eponym for an operation in which the skin and subcutaneous compartment is completely excised and resurfaced with skin grafts.[64–66] Chronic ulceration, skin graft breakdown, and hypertrophic, unstable scarring have been consistently seen when split-thickness grafts are used.[65] Coverage with full-thickness grafts provides a more durable graft site, but graft breakdown and substantial scar formation also may occur.

Staged subcutaneous tissue excision was initially described by Sistrunk,[68] and modifications of the procedure have been reported by others, notably Homans.[69,70] This excisional approach removes significant amounts of skin and subcutaneous tissue, recognizing that the pathology of lymphedema is essentially limited to the superficial tissue compartment. The operation reduces the amount of subcutaneous tissue that produces lymph, and excisions of redundant skin also result in circumferential compression, which probably works in concert with muscular activity to facilitate the subdermal lymph drainage preserved within the flap. A recent study demonstrated long-lasting results for improvement in lower extremity lymphedema, regardless of cause, in a majority of patients treated.[71] This procedure has not been as effective for upper extremity lymphedema (Figs. 42-9 and 42-10). [64]

Although presented as a physiologically designed procedure, the buried dermal flap procedure described by Thompson[76] incorporates the excision of considerable amounts of tissue. In this procedure the subcutaneous compartment is buried in the deep subfascial area in an attempt to drain lymph. Radioactive iodinated human albumin clearance studies have been reported to support a physiologic improvement.[78] However, identical improvement in postoperative clearance was demonstrated in patients after skin and subcutaneous excision.[79] These findings could indicate that the reduction of the subcutaneous tissue improves overall function.

Suction-Assisted Lipectomy

Many authors have advocated the use of liposuction in both primary and secondary lymphedema to reduce the size of lymphatic extremities, as an alternative to segmental wedge excision, removing excess fluid and fat.[73–75] Most authors agree that individuals who will benefit most from this procedure are those who have lymphedema of short duration and have yet to develop the fibrosclerotic changes associated with long-standing disease. However, Brorson and colleagues[73,80,81] in Sweden have advocated a new concept in the management of upper extremity lymphedema in women after mastectomy. Brorson has made a distinction between the presence of edema fluid and the increased fatty deposition that is seen in individuals with chronic lymphedema. His hypothesis is that liposuction should address only the increased fatty deposit, and conservative methods should be used to treat the increased lymphatic fluid. He has rightly observed that individuals with chronic lymphedema have an increase in subcutaneous fatty deposition, a finding that has been greatly underappreciated by advocates of physiologic-type approaches to the management of lymphedema. Brorson's strategy has been to reduce the edema first, using compression therapy until all the pitting edema has subsided, and then proceed to extensive circumferential liposuction with a specially designed cannula. His experience thus far has been in lymphedematous upper extremities in women after mastectomy, and he has been able to achieve excellent long-term results with minimal complications. However, a mainstay of therapy after the surgery is ongoing controlled compression therapy, day and night, indefinitely. His studies have shown that the excess fat is permanently removed, and that there is no worsening of an already impaired lymph transport system.[73,80,81]

Heat Treatment

The Chinese have been able to demonstrate that the use of local limb hyperthermia also is a useful adjunct for the treatment of lymphedema. In 1984 Zhang[82] reported a regimen of heating the involved limb to 6°C to 7°C above normal for 1 hour per day for 20 days. He used three to four courses that were 7 to 10 days apart. Between treatments, bandaging was used to compress the limb. He reported a reduction in limb volume in two thirds of patients and a sixfold decrease in incidence of cellulitis.

The continuing debate on the most efficacious medical and surgical approach underscores the need for intensified research. Management of individuals with lymphedema suffers because of a lack of randomized, controlled prospective studies. Furthermore, no well-defined standards exist with respect to the definition of edema, documentation of results, and outcomes of therapy.

OUTCOMES

Little information exists on the economic outcome after surgery for lymphedema. This condition may manifest as recurrent infections, discomfort, functional impairment from increased extremity size and weight, musculoskeletal problems, psychosocial distress caused by cosmetic issues, and difficulty in carrying out activities of daily living.[83] However, patients should be informed that regional and Internet-based support groups exist, and individuals with lymphedema who are compliant with management regimens can decrease

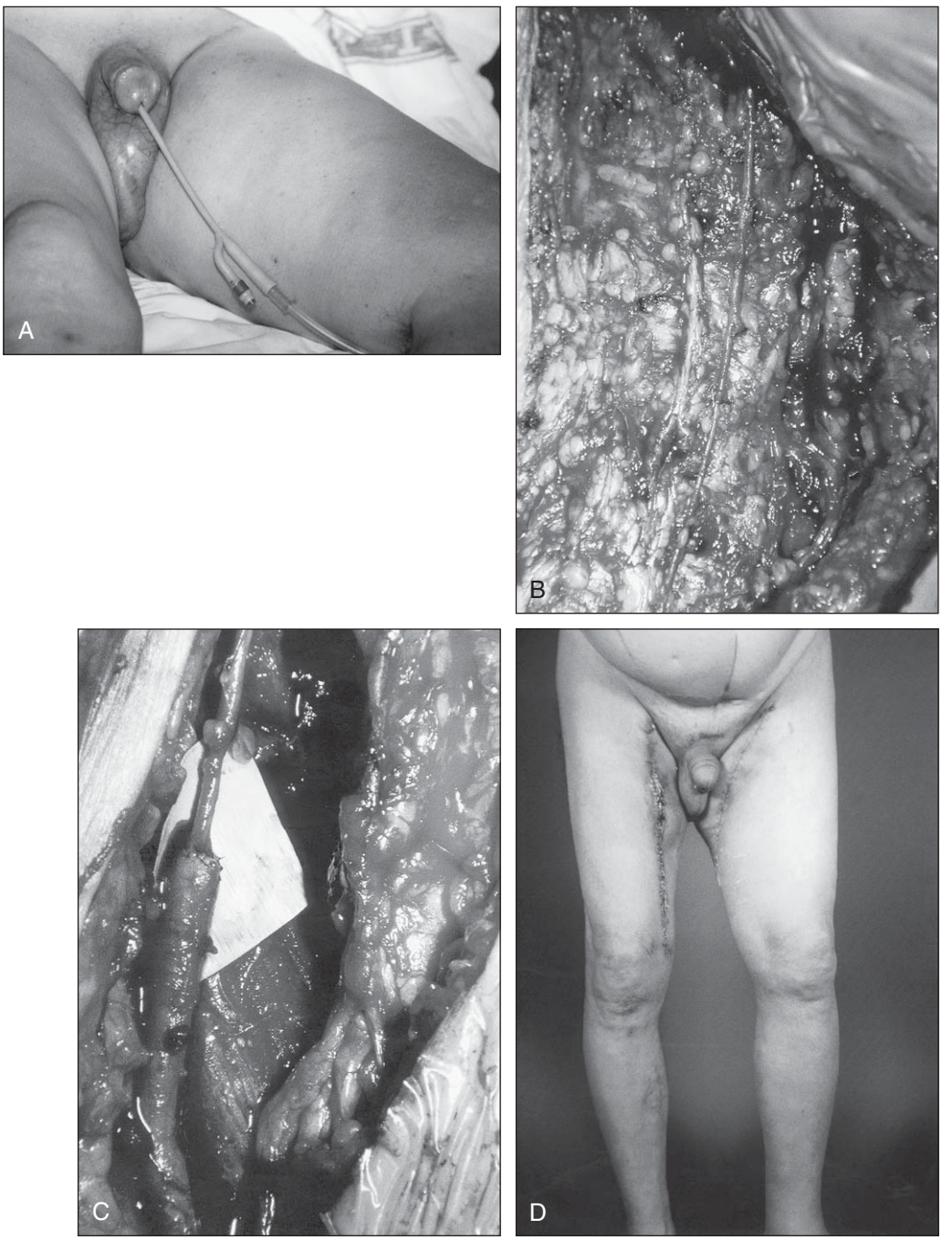


Figure 42-8 • **A,** Male with obstructive lymphedema of left leg and increased venous pressures on manometry in saphenous vein. **B,** Dissection of right saphenous vein and surrounding lymphatics and pedicled across the pubic area to the left thigh (groin superior). **C,** Venous and lymphatic anastomoses performed. (groin superior). **D,** Two months after surgery: improvement in lymphedema in left leg.

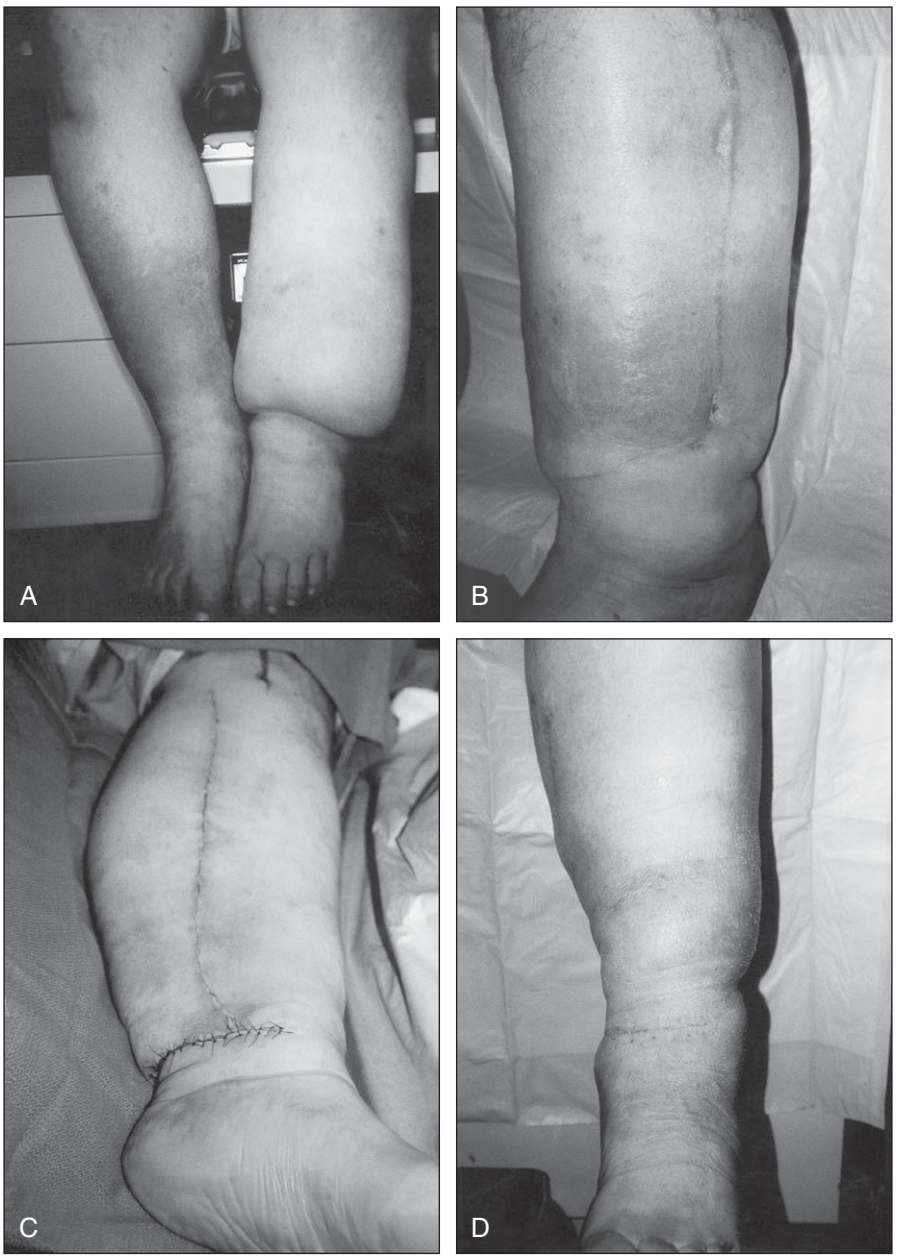


Figure 42-9 • **A,** A 45-year-old patient with lymphedema tarda of left leg, with lymphedema worse laterally. **B,** At 17 months after first excision on lateral aspect of left leg before medical excision. **C,** Intraoperative view after medial wedge excisions. **D,** Four years after surgery with stable leg.



Figure 42-10 • **A,** A 22-year-old man with gross primary lymphedema commencing in early puberty (lymphedema praecox). He was unable to wear normal clothes. **B,** Extended medial wedge excision of the thigh, knee, calf, and ankle. **C,** Intraoperative view of filled leg after excision of lymphedematous tissue. **D,** Immediate intraoperative result. **E** and **F,** Three months after second-stage lateral wedge excision: lateral **(E)** and anterior view **(F). G,** He was now able to wear normal clothes.

in-hospital stays; many will enjoy a normal or near-normal quality of life.

THE FUTURE

Those in whom lymphedema develops seem to be incapable of lymphatic generation or regeneration. Evidence suggests the presence of growth factors specific for the lymphatic system[84,85] and a capacity for lymphatic regeneration in individuals who do not have lymphedema.[11] Do those in whom lymphedema develops after some inciting event lack the mechanisms needed for lymphatic vessel repair? Or is there a deficit in the response to a growth factor(s), or is there a lack of growth factor(s)? We submit that a genetic etiology explains why, in a fraction of individuals who undergo similar procedures, this condition develops.

SUMMARY

The large number of medical therapies and surgical procedures that have been described in the treatment of lymphedema emphasize the discouraging fact that this condition remains incurable by any means. The severity of symptoms may vary from mild extremity swelling to serious disabling or life-threatening complications such as recurrent infections and rarely, lymphangiosarcoma. Most patients are diagnosed by history and physical examination alone and may be managed conservatively. If this is unsuccessful, and the individual has primary lymphedema, then a reduction procedure is all that is available. Traditionally, this has involved staged resection of skin and subcutaneous tissue. However, liposuction is gaining popularity, especially in relatively early cases in which the quality of skin is good and little fibrosis is found. In individuals with secondary or obstructive lymphedema that is not well controlled with conservative management, a physiologic procedure, often using multiple modalities (e.g., pedicle flaps plus LVAs or LVAs with or without segmental reduction or liposuction) has been the authors' preferred method of treatment (Fig. 42-11). Regardless of treatment modality, patient cooperation is critical for successful outcome. Future efforts should focus on clarifying the genetic etiology of lymphedema, with hope that a better understanding of the basis of disease will lead to more effective treatment strategies.

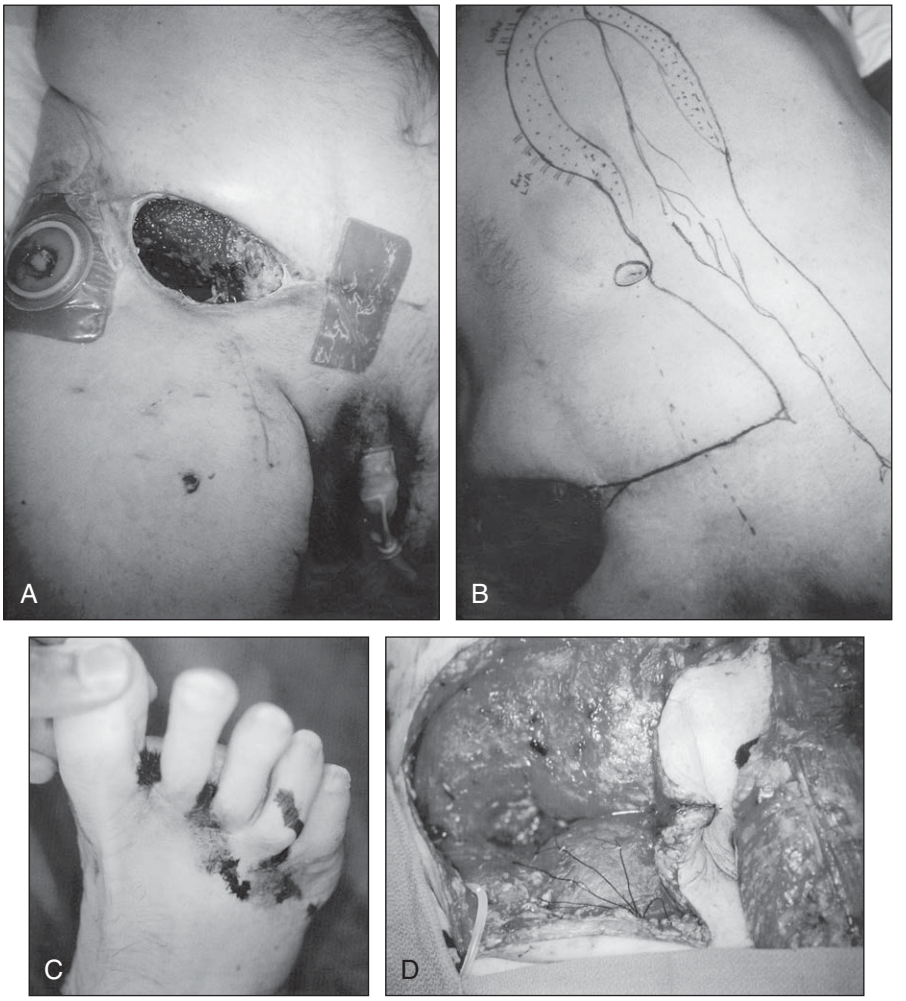
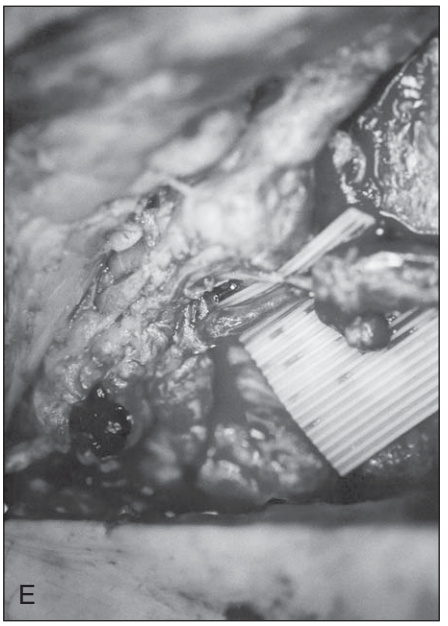


Figure 42-11 • **A,** A 74-year-old patient with chronic wound draining lymphatic fluid in right hip area, after radical excision of chondrosarcoma and irradiation. The right leg is lymphedematous. **B,** Design of contralateral vertical rectus abdominis musculocutaneous (VRAM) flap (based on superficial and deep inferior epigastric vascular pedicle). The lymphatic drainage into left groin is intact. Plan to dissect out multiple small venous channels at upper aspect of flap for lymphaticovenous anastomoses (LVAs). **C,** Methyl blue dye injected intradermally into web spaces for foot. **D,** Multiple dilated lymphatics dissected out in upper right thigh, marked with silk loops.

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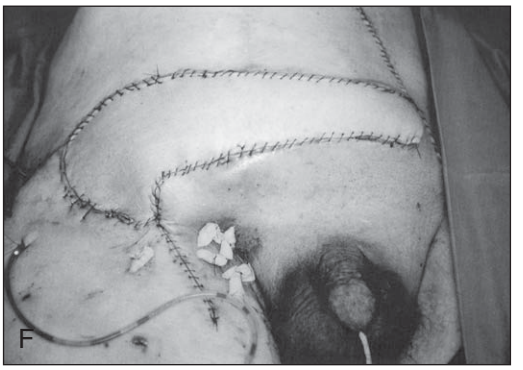


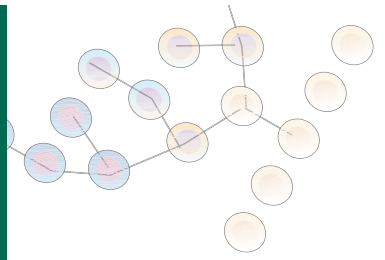


Figure 42-11, cont'd • **E,** The VRAM flap was transposed across the lower abdomen to the deficit in the right groin. Magnified view of two LVAs is shown. Four LVAs were performed from thigh lymphatics into small veins of distal (top) end of VRAM flap using 10-0 nylon suture. **F,** Immediate result after wound closure. **G,** Result at 11 months showing healed wound and reduced lymphedma.

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43 Fatigue

Victoria Mock

SUMMARY OF KEY POINTS

Incidence
- Fatigue may be a presenting symptom of malignancy or a signal of disease recurrence.
- Fatigue is the most prevalent symptom in patients with cancer.
- Fatigue affects more than 70% of patients who receive chemotherapy, radiation therapy, or biologic response modifier therapy.
- A significant level of fatigue occurs in more than 75% of patients with advanced cancer.
- Fatigue significantly reduces functional status.
- Fatigue significantly reduces quality of life.
- Fatigue in patients with cancer is often managed poorly.

Etiology of Complications
- The etiology of fatigue is usually multifactorial.
- Direct factors include the malignancy and cancer treatments.
- Contributing factors include pain, emotional distress, sleep disturbance, anemia, nutritional deficits, deconditioning, and comorbidities.
- Specific pathophysiologic mechanisms are unclear.

Evaluation of the Patient
- Screening should be done at the initial visit, at regular intervals, and as clinically indicated.
- Patients should be evaluated by means of focused history and physical examination, fatigue assessment, selected laboratory tests, and assessment of contributing factors.

Grading of the Complication
- Fatigue intensity should be measured with valid and reliable scales.
- Serial measurements should be recorded in the medical record for comparison.

Treatment
- Any identified contributing factors should be treated.
- Pharmacologic and nonpharmacologic should be added treatments according to the patient's clinical status (e.g., active cancer treatment, disease-free follow-up, or palliative care at end of life).

INTRODUCTION

Definition

Fatigue in patients with cancer, often referred to as cancer-related fatigue (CRF), has been defined by the National Comprehensive Cancer Network as a "distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning."[1]

Fatigue is a universal human experience that, in healthy individuals, is regarded as a basic protective mechanism against the depletion of body reserves of adenosine triphosphate and resulting exhaustion and possible tissue damage. Compared with the fatigue of healthy individuals, which resolves with adequate rest and sleep, the fatigue of patients with cancer often remains after a period of rest or sleep, is of greater magnitude and persistence, is more disruptive to activities of daily living, and has a more negative affective impact.[2] When patients with cancer were asked to describe their fatigue, responses revealed three major characteristics: physical sensations (59% of responses) such as weakness and decreased physical performance, affective sensations (29% of responses) such as sadness and diminished motivation, and cognitive effects such as difficulty concentrating and decreased problem-solving ability (12% of responses).[2]

CRF has been accepted as a diagnosis in the International Statistical Classification of Diseases, 10th Revision—Clinical Modification with the required criterion of "significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level" plus five or more criteria related to the impact of fatigue and present every day or nearly every day during 2 weeks of the previous month.[3] Although these criteria are promising in the diagnosis of CRF, they have been tested in only one study of cancer survivors, in which the prevalence of CRF was determined to be 17%.[3]

Incidence

CRF is the most prevalent unmanaged symptom reported by patients being treated for cancer, and it affects 70% to 100% of patients receiving cytotoxic chemotherapy, radiation therapy, stem cell or marrow transplantation, or treatment with biologic response modifiers.[4–8] Fatigue is a persistent, distressing symptom in 17% to 40% of patients who have completed treatment[3,9–11] and is a significant symptom in more than 75% of patients with metastatic disease.[12–14] The increasing prominence of CRF is related to both the increase in intensive multimodal cancer treatments, characterized by increased dose density and dose intensity, and better management of formerly predominant symptoms of pain, nausea, and vomiting. Patients report fatigue to be the most distressing symptom associated with cancer and its treatment, more distressing even than pain.[7,8]

Management of CRF is important for several reasons beyond its prevalence and the discomfort and distress that it causes. First, high levels of fatigue affect functional status and the ability to tolerate cancer treatment. Research reports indicate that fatigue can have a profound effect on functional status,[15,16] and it is uncertain whether

patients regain full functioning when treatment is over.[9] If fatigued patients cannot tolerate their cancer treatment or must choose between treatment and quality of life, control of their malignancy may be compromised.[6] In addition, high levels of fatigue affect patients' quality of life and interfere with their ability to engage in valued roles and activities.

DESCRIPTION OF FATIGUE

Etiology

Fatigue in patients with cancer is a complex and multifactorial phenomenon that may have a variety of causes and contributing factors. The exact mechanisms that are involved in its pathophysiology are unknown.[17,18]

Fatigue may be caused by the malignancy itself or by cancer treatment and treatment-related anemia.[19,20] Physiologic factors that are known to contribute to CRF are cachexia, deconditioning, and high levels of certain cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor-α.[21] Psychosocial factors that contribute to fatigue include anxiety, depression, and insomnia. Fatigue is also associated with high levels of other symptoms.[16] In fact, fatigue commonly occurs in the context of multiple symptoms and, in this context, is highly correlated with decreased functional status.[15]

Patterns of Fatigue

Patients with cancer frequently state that fatigue begins with cancer treatment or during the stressful diagnostic process. They report that fatigue continues during the course of active cancer treatment and declines when treatment is over.[18] The fatigue may persist after treatment at a higher-than-baseline level, and a significant percentage of disease-free survivors report disruptive levels of fatigue for years after treatment. For example, in a survey of 1957 survivors of breast cancer, one-third reported severe and persistent fatigue 3 years after diagnosis.[9]

Patterns of fatigue during the course of cancer treatments vary according to the type of treatment. Fatigue typically rises sharply after intravenous cytotoxic chemotherapy to a peak 48 to 72 hours later and drops to near-normal levels 3 weeks later, with a smaller peak occurring on days 10 to 14 with some regimens.[22,23] Studies have not shown substantial increases in fatigue during successive infusions.[24]

During radiation therapy for breast cancer, fatigue levels typically increase linearly over time to a maximum intensity during the fourth week of treatment and then plateau.[25] Levels of fatigue after radiation therapy return to normal in most patients within 3 weeks to 3 months[25] but are more likely to persist at high levels after chemotherapy. In a study of 322 patients with breast cancer in remission, post-treatment fatigue levels were highest in women who received chemotherapy in addition to radiation therapy and lowest in those who received radiation therapy only.[26]

EVALUATION

The National Comprehensive Cancer Network has developed guidelines for the evaluation and treatment of CRF on the basis of available research findings and clinical experience (see www.nccn.org for the most recent guidelines).[1] This multidisciplinary panel of experts in CRF developed an algorithm in which patients are screened regularly for fatigue by means of a brief screening instrument and are treated according to their level of fatigue and clinical status. The algorithm includes phases of screening, primary evaluation, intervention according to three levels of clinical status, and reevaluation (Fig. 43-1).

Progress in the management of CRF has been limited by several factors relating to screening. Patients are reluctant to report fatigue to health care professionals because they fear that their cancer therapy may be modified, doses may be reduced, or treatment may be stopped. Another reason patients give for not reporting CRF is that they believe that it is a symptom to be endured (like sleep problems or emotional distress), which they should be able to manage themselves. Many health care professionals are reluctant to screen for CRF because they are unaware of evidence-based treatments or because they are unaware of the distress and interference with function that accompany fatigue. The result is that fatigue in patients with cancer is underreported, underdiagnosed, and undertreated.[27]

The guidelines recommend that screening for the presence and severity of fatigue occur at the patient's initial contact with an oncology care provider, at appropriate intervals (including the follow-up period after treatment ends), and as clinically indicated. If the patient reports the presence of fatigue during screening, the fatigue should be quantified for future comparison. Although a variety of valid and reliable research instruments are available to measure the multiple dimensions of fatigue,[28] many are lengthy and burdensome for patients with CRF. The guidelines recommend measuring the intensity of fatigue by using a brief clinical instrument such as the 0 to 10 rating scale commonly used to measure pain. On the 0 to 10 scale, 1 to 3 is generally considered to be a mild level of fatigue; 4 to 6 is moderate; and 7 to 10 is severe. Although moderate levels of fatigue may cause distress and a reduction in activity level, severe fatigue levels are accompanied by a marked decrease in the ability to work and perform other activities of daily living.[29,30]

If the patient reports no fatigue or a mild level of fatigue, education should be provided regarding fatigue as a possible or common side effect of treatment, especially if the patient is embarking on a treatment regimen that is known to cause fatigue. A plan to reevaluate the fatigue level as cancer treatment proceeds is appropriate because fatigue levels commonly rise in later stages of treatment. Patients and family members who do not receive this information often interpret decreased energy as a lack of treatment effectiveness or even a progression of disease, and the fatigue becomes a major source of worry.

If the screening process reveals a moderate or severe level of fatigue (4 to 10 on the 0 to 10 scale), the clinician should perform a focused history and physical examination as part of the primary evaluation phase. This evaluation includes an assessment of the patient's current disease status to rule out recurrence or progression and a review of current medications. Many of the medications that are used during cancer treatment, such as antiemetics and narcotics, may interact to produce lethargy and fatigue. Other medications the patient may be taking for comorbidities, such as β-blockers for cardiac conditions, may contribute to worsening of fatigue.[31] The focused history should also include an in-depth fatigue assessment that evaluates the intensity and pattern of fatigue, the duration and changes over time, the exacerbating or alleviating factors, and interference with daily activities.[31]

An essential component of the focused history is an assessment of treatable factors that are known to commonly contribute to fatigue. The factors that have been identified by the National Comprehensive Cancer Network practice guidelines panel are pain, emotional distress, sleep disturbance, anemia, nutritional status, activity level, and comorbidities.[1] The guidelines recommend that these factors be assessed and treated as a first step in managing fatigue. Although these seven factors might not be the primary cause of the patient's fatigue, because they are known to increase the intensity as well as the distress of fatigue, treating these factors—if they are present—as an initial approach often reduces the fatigue to a tolerable level.

Numerous studies have shown that fatigue commonly clusters with pain, emotional distress, or sleep disturbance.[16,32,33] Depression, in particular, has been associated with fatigue.[34,35] Preliminary evidence suggests that the relationship between fatigue and depressive symptoms is mediated by functional status.[36] Anemia commonly occurs in patients with cancer as a result of the neoplastic process or myelosuppressive therapies. Hemoglobin levels below 9 g/dL are

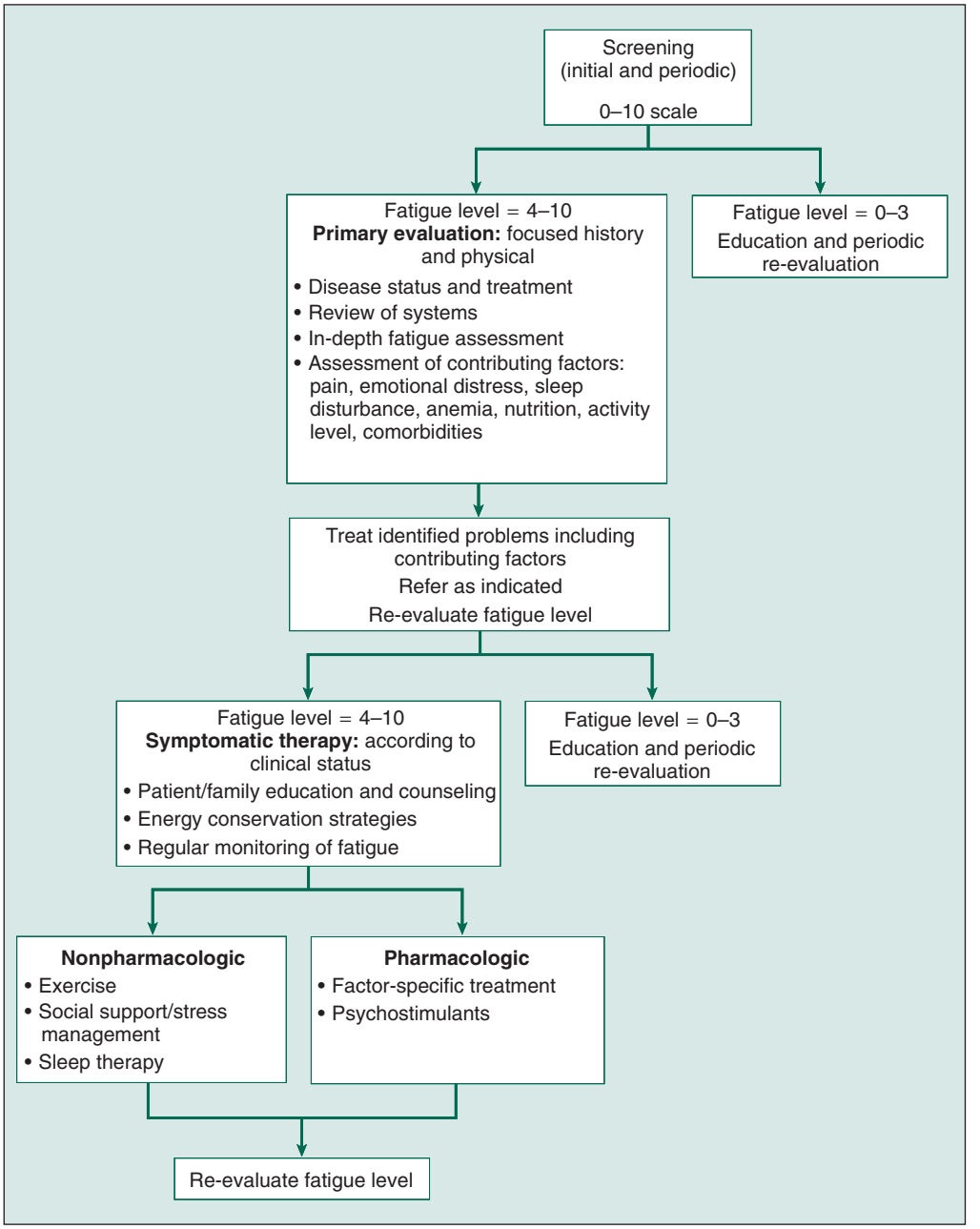


Figure 43-1 • Evaluation and management of cancer-related fatigue. (Adapted with permission from the National Comprehensive Cancer Network, Inc. Mock V, Atkinson A, Barsevick A, et al. NCCN [v.1.2003]. Cancer-related fatigue clinical practice guidelines in oncology. J Natl Comp Cancer Network 2003;1:308–331.)

often accompanied by severe fatigue, and improvements in energy are measurable with anemia correction to hemoglobin levels of 12 to 13 g/dL.[37]

Nutritional deficits related to anorexia, nausea, vomiting, diarrhea, or mucositis can lead to impaired protein synthesis, weight loss, muscle wasting, cachexia, weakness, and fatigue in patients with cancer.[38,39] Appropriate treatment with supplementation and correction of fluid and electrolyte imbalances provides nutrients that are necessary for energy. Consultation with a nutrition expert may be appropriate.

Patients with moderate to severe fatigue should be assessed for changes in their ability to tolerate exercise and other daily activities. A decrease in regular activity frequently accompanies cancer diagnosis and treatment. The resulting deconditioning can be ameliorated by a progressive increase in activity, which could decrease fatigue.

Noncancer comorbidities are important potential contributors to CRF. The status and current management of identified comorbidities should be evaluated, and more effective treatment should be instituted if the comorbidity is not optimally managed. Comorbidities that require evaluation include infections; cardiac, pulmonary, renal, hepatic, neurologic, and endocrine dysfunction; and hypothyroidism.[1]

If any of the seven contributing factors that are known to be associated with CRF are identified, they should be treated, and the fatigue should be reevaluated. If the patient continues to have moderate to severe levels of fatigue, treatment with nonpharmacologic and pharmacologic clinical interventions should be instituted in accordance with the patient's clinical status (e.g., receiving active cancer treatment, receiving disease-free long-term follow-up, or receiving palliative care at end of life). In many instances, a combination of approaches must be used to successfully reduce the fatigue and restore optimum functioning.

CLINICAL INTERVENTIONS

Interventions for the clinical management of CRF include both specific and general approaches. When an etiologic or contributing factor for CRF, such as anemia or insomnia, can be identified, it should be treated by using clinical practice guidelines as an initial approach to fatigue management. Guidelines provide "best care" information based on current evidence to support treatment. However, in many patients with cancer, no cause for fatigue can be readily identified beyond the disease and cancer therapies. In this situation, the approach to management is a general one.

Pharmacologic Therapy

Pharmacologic interventions include administration of erythropoietin alfa for chemotherapy-induced anemia, administration of medications for cause-specific treatments, such as antidepressants for depression, and thyroid hormone replacement for hypothyroidism. Corticosteroids have been shown to increase feelings of well-being and energy levels in some patients with advanced cancer,[40] and psychostimulants have been used on a limited basis to increase energy and decrease fatigue.

Anemia is a common cause of CRF; it occurs in a majority of patients receiving myelosuppressive chemotherapy.[41] Three community-based, nonrandomized, open-label studies[42–44] and two double-blind randomized trials comparing erythropoietin alfa[45,46] with placebo have shown a beneficial effect on CRF, transfusion requirements, and quality of life. Erythropoietin alfa is effective in subcutaneous doses of 10,000 U three times a week or 40,000 U weekly.[44] Crawford and colleagues[37] demonstrated that the incremental increase in the patient's quality of life was highest when the hemoglobin level rose from 11 to 12 g/dL. Research reports confirm the relationship between increases in hemoglobin during erythropoietin alfa treatment and quality-of-life improvements in patients with chemotherapy-related anemia.[37,47,48] These studies provide good clinical evidence for reduction of CRF by returning the hemoglobin level in the patient with cancer and anemia to a more normal value. Published guidelines support treatment with erythropoietin alfa.[19,49] It is important to note that although most patients with anemia report significant fatigue and there is good evidence of fatigue reduction with anemia correction,[50] the causes of CRF are multifactorial, and many cancer patients with cancer and fatigue are not anemic.

Aside from the treatment with erythropoietin alfa, there have been few controlled studies that have investigated pharmacologic therapy for CRF, although a few clinical reports have been published. Psychostimulants have been found to relieve fatigue in other chronic conditions such as human immunodeficiency virus infection,[51] but the data are limited regarding efficacy in CRF.

Methylphenidate has been found to be effective in reducing opiate-induced somnolence, acute depression, and cognitive dysfunction in the palliative care setting,[52] but a randomized trial in cancer patients found no difference between methylphenidate and placebo in reducing fatigue levels.[53]

Pemoline, a central nervous system stimulant similar to methylphenidate, has shown some effectiveness in relief of fatigue in patients with multiple sclerosis (46% response) but has not been tested in patients with cancer.[54] In addition, serious liver problems have been reported in some patients receiving this drug. Modafinil has been used to treat narcolepsy, and some reports suggest that it might be helpful in managing CRF,[55] but no clinical trials have been reported.

In summary, the evidence is strong for pharmacologic treatment for CRF in the case of erythropoietin alfa for correction of anemia, but evidence is insufficient to support the use of psychostimulants. More research is needed before recommendations can be made regarding the use of psychostimulants to manage CRF.

Nonpharmacologic Therapy

Nonpharmacologic interventions for CRF are notable in that they are effective, safe, and usually inexpensive; however, they have not been widely recognized for their efficacy, nor are they commonly included as standard of care for fatigue management. Nonpharmacologic treatments include alterations in activity and rest—including exercise, sleep therapy, and energy conservation—and psychosocial support programs and coping strategies to reduce stress.

Strong evidence from clinical trials supports the efficacy of exercise to manage fatigue in patients with cancer.[1] The theory that supports exercise as a treatment for CRF suggests that the combined effects of cytotoxic treatments and reductions in physical activity during lengthy, often debilitating treatments lead to a decreased capacity for physical performance. Thus, even ordinary activities are perceived as fatiguing. Regular exercise, even at a moderate level, can maintain and increase functional capacity and result in greater exercise tolerance as evidenced by increased cardiac output, reduced heart rate, and less fatigue as less energy is required to perform equivalent work (Box 43-1). If the patient has severe deconditioning, advanced disease, or significant comorbidities, referral to a rehabilitation program supervised by a physical therapist or specialist in physical medicine or rehabilitation is indicated.

The cumulative evidence from studies of exercise in patients with cancer who are receiving active cancer treatment, as well as in long-term survivors, demonstrates that this health-promoting activity has

Box 43-1. EXERCISE PRESCRIPTION FOR CANCER-RELATED FATIGUE

At the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, we have evaluated a moderate symptom-limited walking exercise program to manage cancer-related fatigue in patients with solid tumors who are beginning outpatient treatment with adjuvant chemotherapy or radiation therapy. After initial testing with more than 100 patients with breast cancer, we have extended the program to include patients with prostate and colorectal cancer.

On screening during the cancer therapy planning visits, we identify patients who do not have metastatic disease or comorbidities that would contraindicate a regular walking program. In consultation with the patient's oncologist and an exercise physiologist, our oncology nurses teach the walking exercise program to consenting patients. Patients are given an individually tailored exercise prescription to follow throughout their cancer treatment. The initial prescription is to walk briskly for 15 to 20 minutes per day on 5 to 6 days of the week at a moderate intensity (with a target heart rate range of 60% to 80% of maximum heart rate), but the regimen is modified according to the patient's age, physical condition, and planned cancer therapy. Each walking session begins and ends with 3 to 5 minutes at a slow pace as "warm-up" and "cool-down" periods to protect the heart. Patients progress, as tolerated, to a maximum of 30 minutes of walking on 5 to 6 days per week. Very debilitated or sedentary patients might need to begin by walking for 5- to 10-minute sessions twice daily until they can tolerate longer periods. We contact patients every 2 weeks to discuss their progress with the program and the side effects of cancer treatment. The exercise program is adjusted as indicated. Patients are taught how to exercise safely—including how to monitor pulse rate—and when to contact the oncology care team to report signs and symptoms (e.g., dizziness, chest pain). Patients are encouraged to walk with a family member or friend at a convenient location, such as in their neighborhood, at a shopping mall, or at a community exercise facility. The program is well accepted by patients, the cost is low, and walking is beneficial and safe. Our patients have experienced no adverse events that could be attributed to the exercise program.

many positive benefits and few risks for patients with cancer. Furthermore, a few cohort studies report significant improvements in survival related to increased levels of physical activity after cancer diagnosis.[56–58]

Four meta-analyses[59–62] and a number of systematic reviews[63–68] have addressed exercise as an intervention for cancer patients and survivors. The number of studies in the meta-analyses ranged from 14 to 35 depending on whether all types of trials or only randomized controlled trials were included. The reviewed studies examined the effects of various forms of aerobic exercise, resistance exercise, and combinations. They included supervised laboratory programs and home-based programs, both during cancer treatment and initiated after treatment. The majority of interventions consisted of aerobic exercise of moderate intensity (60% to 85%) of estimated maximal oxygen uptake (VO_2 max) 3 to 5 days per week for 20 to 30 minutes each day for less than 3 months' duration. All of the studies showed positive results for physical functioning, psychological well-being, and symptoms—including fatigue, difficulty sleeping, and nausea—as well as for health-related quality of life. Fatigue levels were found to be 40% to 50% lower in exercising subjects. Although no adverse events were reported in any of the studies, high-risk patients with serious comorbidities were excluded from participation. Adherence to exercise programs is a challenge for both healthy and chronically ill populations. In the studies of patients with cancer, adherence ranged from 60% to 80% in the home-based programs to 100% in laboratory studies, a marked contrast to the 50% dropout rate for healthy individuals who begin an exercise program.[69] Apparently, patients with cancer are sensitized to the potential beneficial effects of health-promoting activities.

The published exercise studies of patients with cancer have notable limitations.[70] The majority of the studies were samples of female patients with breast cancer, and ethnic diversity and age ranges were limited. Thus, the study results have limited generalizability to other cancer diagnoses, older individuals or children, and varied ethnic groups. Another limitation of the studies is that the exercise interventions were begun at a specific point in patients' cancer therapy—either the beginning or the end—regardless of their level of fatigue. There is limited information about the effectiveness and feasibility of initiating an exercise program for patients who already have high levels of fatigue and have difficulty performing activities of daily living. Current evidence indicates preventing CRF by initiating regular exercise early in the course of cancer treatment may be more effective than managing high levels of fatigue after it develops.[1]

Rest and Sleep

Oncology care providers commonly recommend additional rest and sleep to patients with cancer who report distressing levels of CRF.[71] Patients who use additional rest and sleep to manage fatigue report that it helps but does not relieve the symptom.[72] Several studies, in which actigraphy was used to measure activity and sleep, indicate that patients with cancer spend increased time resting and sleeping but that their pattern of sleep may be severely disrupted, with awakenings nearly every hour.[22,73] Frequent night awakenings were accompanied by lower levels of daytime activity, more daytime napping, and high levels of fatigue.[74] The potential for deconditioning resulting from reductions in activity during lengthy cancer treatments may be an important contributing factor to CRF. Although sleep disturbances have been identified as a neglected problem in oncology,[75] the relationship between sleep problems and CRF has been inadequately explored. Few studies in which a sleep intervention was tested in cancer patients have been published.[76]

Energy Conservation

Energy conservation is an intervention that utilizes planned management of personal energy resources to prevent their depletion. Strategies include priority setting, use of labor-saving devices, balancing periods of rest and activity, and delegating activities of lesser importance.[77] Energy conservation may be a particularly useful intervention for patients with advanced disease or those with significant weakness or debilitating fatigue. Although research is limited, results of a pilot study testing an energy conservation intervention has been published and indicates beneficial effects.[77]

Stress Reduction

Studies of psychosocial interventions aimed at stress reduction and improved coping have also demonstrated reductions in fatigue. Since both depression and anxiety may be characterized by fatigue, it has been proposed that CRF is a response to the stress of cancer diagnosis and treatment through activation of the hypothalamic-pituitary-adrenal axis.[17] Since it is also evident that high levels of fatigue may lead to emotional distress when valued roles and activities are affected, the precise relationship between emotional distress and fatigue is not clearly understood.

Psychosocial interventions tested include cognitive behavior therapy,[78] psychoeducational counseling,[79,80] a comprehensive coping strategy,[81] and stress management training.[82] The investigations were randomized controlled clinical trials with adequate sample sizes and included a variety of cancer populations. All studies demonstrated significant effects of the intervention on fatigue levels. A limitation of several of the studies was that fatigue was a secondary endpoint that was measured by either a single item or a subscale of an instrument used to measure emotional distress.

CONCLUSION

Fatigue is the most prevalent symptom reported by patients with cancer and the source of much distress for them. Fatigue may have profound effects on functional status and quality of life. However, clinical evaluation and management of this disturbing side effect of cancer and cancer treatment have been limited as a function of both patient and care provider barriers. Patients have been hesitant to report fatigue, and clinicians have been unaware of effective treatments.

Effective management of CRF begins with informed and supportive oncology care providers who perform initial and regular screening for fatigue and provide treatment as indicated by the patient's fatigue level. When the patient's fatigue levels are mild, education about fatigue is indicated. When fatigue levels are moderate or severe, the initial screening is expanded to include a focused evaluation of current disease and treatment status, review of body systems, and an in-depth fatigue assessment. The patient should be assessed for the presence of treatable contributing factors such as pain, emotional distress, sleep disturbance, anemia, nutritional deficits, decreased activity level, and unmanaged comorbidities. If any of these conditions are present, they should be treated as an initial step, and the fatigue should be reevaluated. If none of these factors are present or if fatigue levels remain moderate or severe, fatigue management strategies should be considered as appropriate for the patient's clinical status.

Evidence-based interventions for managing CRF include correction of anemia, moderate exercise regimens, and psychosocial support programs. A combination approach might be needed, and referral to other members of the multidisciplinary team should be considered. Although CRF is common and expected, it can be managed and does not need to be distressful and disruptive to quality of life.

Several important gaps exist in our knowledge of fatigue and fatigue management. These are reflected in the recommendations for future research presented in Box 43-2. However, evidence-based practice guidelines are available to guide clinical care of patients with CRF, and health care professionals are increasingly aware of the importance of addressing this distressing symptom.

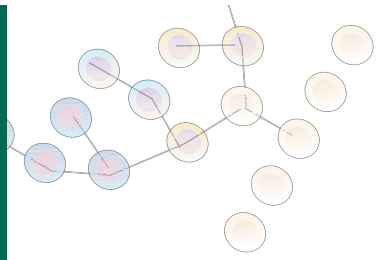
Box 43-2. RECOMMENDATIONS FOR FUTURE CANCER-RELATED FATIGUE RESEARCH

1. Additional intervention testing research, especially with pharmacotherapeutics, psychosocial interventions, sleep quality therapies, and conservation of energy approaches
2. Use of more rigorous research designs with larger sample sizes, control groups including healthy control subjects and attentional control subjects as appropriate, and greater standardization of interventions to facilitate replication and increase internal validity
3. Targeting of more diverse populations of patients with cancer and selection of diverse samples, especially with regard to ethnicity, socioeconomic status, age, and type of cancer diagnosis
4. Exploration of fatigue interventions in recurrent disease and palliative care
5. Use of more objective instruments and outcomes to increase validity and reliability (e.g., actigraphy to measure activity and sleep, biochemical markers for fatigue)
6. Theory-based research with a focus on elucidating the mediating mechanisms for every intervention to facilitate our understanding of cancer-related fatigue
7. Investigation of secondary outcomes of fatigue interventions such as quality of life, return to work, use of health care resources, sleep quality, mood state, and survival

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44 Caring for Patients at the End of Life

Janet L. Abrahm

SUMMARY OF KEY POINTS

- Physicians must be clear about prognosis, not overly optimistic.
- Patient decisions about resuscitation and entry into phase I trials should be predicated on receiving accurate prognostic estimates.
- A sense of purpose can be maintained by patients who work on completing legacies, reconciliation, saying goodbye, and making plans for support or care of bereaved survivors.

Distress

- Physical comfort is a prerequisite for exploring other sources of distress; consultation with anesthesia pain or palliative care specialists can be useful.
- Depression can be ameliorated even in the last weeks of life; delirium can be mistaken for pain and may be exacerbated if treated with increases in opioid medication alone.
- Problematic relationships can create open wounds as painful as any physical injury.
- Families with young children are in special need of counseling and support.
- Ongoing losses (in physical attractiveness or physical or mental function or of roles in family, community, or workplace) contribute to spiritual and existential distress. Life reviews and reconnection with sources of spiritual support, including religious rituals, can help.

Hospice Care

- Hospice is the gold standard of care at the end of life. Hospice teams are multidisciplinary (M.D., R.N., social worker, chaplain, volunteers), but the referring physician remains in charge of the plan of care. Hospice programs provide care in the home, including all medications and durable medical equipment related to the terminal diagnosis. Patients need not have signed a "Do Not Resuscitate" order to enroll.
- Barriers to hospice referral include physician and patient reluctance to accept a terminal prognosis (i.e., less than 6 months); current inadequate reimbursement for palliative therapies; and physician, family, and patient misconceptions about entry criteria and services provided.

Grief and Bereavement

- The intensity of a survivor's grief depends on the characteristics of the mourner, the nature of the death, and societal and cultural factors.
- Skillfully communicating the diagnosis and terminal prognosis; providing emotional, psychological, and spiritual support and physical comfort; helping families to resolve outstanding issues; and making the death as peaceful as possible are all measures that diminish the suffering of the survivors.
- Survivors appreciate ongoing communication with the patient's physician. The formal bereavement program that hospice programs offer takes place during the first year after the patient's death. The program includes descriptions of typical manifestations of grieving and offers of counseling, support groups, and services of remembrance.

INTRODUCTION

When cure or even prolongation of life is no longer possible, oncologists have one last task remaining: to provide expert care to patients at the end of life and support for their families.[1] Despite physical comfort, patients can experience profound suffering from any of the following causes:

- Difficulty in maintaining personal dignity
- Losses of significant aspects of who they were at home, in the community, or in the workplace
- Lack of closure in important relationships
- Feelings of spiritual alienation
- Inability to discern the meaning in their lives[2]

When those problems are addressed, patients have the chance to attain transcendence, a sense that who and what they have been will persist long after they have died.[3,4] Through collaborations with psychiatry, nursing, social work, and chaplaincy, oncology clinicians can promote physical comfort, social functioning, and psychological and spiritual well-being.[5,6] We need never say, "There is nothing more I can do."

Patients rely on us to help them achieve a comfortable death that follows a time when goodbyes have been said, legacies have been established, and relationships have been brought to an acceptable closure. Their families need us to minimize the patient's suffering, obtain expert palliative care consultation when needed, and communicate clearly and often with them. Currently, however, such care is the exception rather than the rule.[7,8] This chapter provides an outline for oncology clinicians who wish to provide excellent care at the end of life and includes discussions of communication with patients and their families, approaches to ameliorating distress at the end of life, hospice care issues, manifestations of grief and bereavement, and suggestions for supporting bereaved survivors.

COMMUNICATION NEEDS OF PATIENTS AND FAMILIES

Timely, truthful, compassionate communication among patients who are dying, their families, and their physicians is needed to dispel fears (e.g., of unrelieved pain or of abandonment), to promote feelings of autonomy and control, to set goals of care, and to enable patients and families to be prepared for what is to come. The vast majority of patients (80% to 98%) want to be able to do the following:

- Name a proxy to make health care decisions
- Know what to expect as their physical condition deteriorates
- Put their financial affairs in order
- Know that the doctor is comfortable talking about death and dying
- Feel that the family and they themselves are prepared for their death
- Have funeral arrangements in place
- Have treatment preferences, especially about resuscitation, in writing[9]

Families want to be able to say goodbye and be present when the death occurs, talk about their fears, and talk about the death with the clinicians.[10] Bereaved survivors are more likely to have a major depressive disorder if they feel that they have not been prepared for the death.[11] For patients and survivors to be prepared, physicians must be clear about prognosis.

The cultural norms of medicine, however, favor optimism over accuracy in delivering prognosis.[12] Physicians might assume that patients will ask when they are ready for the information. There are no data, however, on how often patients with advanced refractory disease ask about their prognosis. Moreover, patients are known to be reticent about raising other important topics—such as uncontrolled pain or their wishes regarding resuscitation—with their physicians.[13,14] Physicians might also worry that giving a truthful prognosis will eliminate hope.

Through a truthful prognosis, however, patients with far-advanced disease can be helped to reframe what it is they are hoping for in the time that remains. Most patients hope for time to say goodbye and to bring closure to their lives. Even patients with far-advanced disease want to work on their legacies. Some dictate letters to be opened at significant events (e.g., graduations, weddings); others might want to narrate a scrapbook. Most want time at least for a personal, private review of who they were, what they did, and the difference they made.

Further, patients need to decide whether it still makes sense for them to be resuscitated. The likelihood of bad functional or cognitive outcomes affects their decisions, as does their understanding of their prognosis.[15] It is important, therefore, to tell a patient who has widely metastatic cancer that resuscitation has very limited efficacy.[16–19] We also need to tell their caregivers, because they, too, are usually unaware that the patient is incurable or that the patient would benefit from hospice care until they hear it directly from their physician.[20] It is equally important to correct mistaken impressions of patients who really have only weeks or months to live. Patients who think that they have a greater than 10% chance of surviving 6 months, for example, usually want to be resuscitated. Only patients who think that they have a less than 10% chance of surviving for 6 months overwhelmingly choose comfort care and do not want to be resuscitated.[21]

Conversations about life-support preferences and those in which news of relapse or progression must be delivered take a significant emotional toll on the clinicians who conduct them, especially those in busy practices in which many such talks are needed each week. Using straightforward communication strategies such as the S-P-I-K-E-S protocol can enhance the effectiveness of the communication both for the clinician and the patient and family who are receiving the bad news.[22]

Table 44-1 Dignity Psychotherapy Question Protocol

Can you tell me a little about your life history, particularly those parts that you either remember most or think are the most important?
When did you feel most alive?
Are there specific things that you would want your family to know about you, and are there particular things you would want them to remember?
What are the most important roles (e.g., family, vocational, community service) you have played in life?
Why are they so important to you, and what do you think you accomplished in those roles?
What are your most important accomplishments, and what do you feel most proud of?
Are there particular things that you feel still need to be said to your loved ones, or things that you would want to take the time to say once again?
What are your hopes and dreams for your loved ones?
What have you learned about life that you would want to pass along to others?
What advice or words of guidance would you wish to pass along to your _____ (son, daughter, husband, wife, parents, other[s])?
Are there words, or perhaps even instructions, you would like to offer your family to provide them with comfort or solace?
In creating this permanent record, are there other things that you would like included?

Chochinov HM: Dignity-conserving care—A new model for palliative care: Helping the patient feel valued. JAMA 2002;287:2253.

Communication with dying patients must also be culturally effective and extend to include psychosocial and spiritual needs, addressing loss, dignity, and the need for meaning.[4,5,23,24] Clinicians who are not experienced in such conversations might find it helpful to use the questions crafted by experts in this field (Table 44-1).[5,23–25]

DISTRESS

Dying patients might experience problems of a physical, psychological, social, or spiritual nature. These patients define quality of life at the end of life as including physical comfort, a sense of control and dignity, relieving burden on their loved ones, strengthening and completing relationships with significant others, and avoiding prolongation of the dying process.[26] To provide high-quality care, therefore, oncologists need to collaborate with an interdisciplinary team such as that provided by palliative care and hospice programs. In 2006, the specialty of Hospice and Palliative Medicine was recognized by the American Board of Medical Specialties, and ACGME-approved training started in 2007. Physicians and nurses trained as palliative care practitioners address all dimensions of distress, including communication, decision making, management of complications of treatment and the disease, symptom control, psychosocial care of patients and their families, and care of the dying.[27]

Physical Causes

In the last days to weeks before death, a significant percentage of people exhibit or experience one or more of the following:

- Fatigue or pain (70%)
- Restlessness/agitation/delirium or noisy or moist breathing (60%)
- Urinary incontinence or retention (50%)

Table 44-2 Treatment of Common Physical Problems in the Last Days of Life

Problem	Agent(s)	Routes, Doses
Pain (continuous)	Morphine, hydromorphone	IV/SC infusion
	Fentanyl	Transdermal
	Morphine, oxycodone	SL oral concentrates
Pain (intermittent)	Morphine, oxycodone	SL oral concentrates
	Fentanyl	Buccal lozenge
"Death rattle"	Scopolamine	Transderm Scop patch 1–3 every 3 days
	Hyoscyamine	0.125–0.25 mg SL 3–4 times daily
	Glycopyrrolate	0.1–0.2 mg IV 3–4 times daily
Anxiety	Lorazepam	0.5–2 mg SL; every 2 hours
	Clonazepam	0.5–2 mg twice daily PO
Depression	Methylphenidate	2.5–5 mg PO every morning or every morning and noon
Delirium (mild)	Haloperidol	1–5 mg PO, PR or 0.5–3 mg SC, IV, every 2–12 hours
	Chlorpromazine	12.5–50 mg PO, IV, PR every 4–8 hours
	Olanzapine	2.5–5 mg PO or SL every hour or bid
Agitated delirium/or palliative sedation for refractory symptoms	Midazolam	0.4 mg–1 mg load; 0.4–1 mg/hr IV initial dose
		Rebolus and titrate as needed to target symptom/sign relief
	Pentobarbital	1–3 mg/kg IV load; 1–3 mg/kg/hr IV drip
		120–200 mg PR every 4 hours
	Lorazepam	0.5–1 mg/hr IV
	Propofol	2.5–5 μg/kg/min IV
Dyspnea (anxiety)	Lorazepam	1 mg SL, PO every 2 hours
Dyspnea (other)	Morphine	5–10 mg PO/PR every 2 hours; 1–3 mg IV every hour
	Chlorpromazine	25–50 mg PO, IV, PR every 4–12 hours
Nausea	Lorazepam/metoclopramide or haloperidol	Compounded suppositories with desired agents (depending on presumed cause of nausea) every 6 hours PR

IV, intravenous; PO, oral; PR, per rectum; SC, subcutaneous; SL, sublingual.

Data from Abrahm JL: A Physician's Guide to Pain and Symptom Management in Cancer Patients, 2nd ed. Baltimore, Johns Hopkins University Press, 2005 p. 408; and Cowan JD, Palmer TW: Practical guide to palliative sedation. Curr Oncol Rep 2002;4:242–249.

- Dyspnea (20%)
- Nausea and vomiting (10%)[28]

Most of the physical problems that dying patients experience can be controlled by using a limited number of medications given by the rectal, transdermal, or, if necessary, parenteral route (Table 44-2).

Pain Control

If oncologists use World Health Organization guidelines for cancer pain relief, 50% of their patients near death will experience no pain, 25% will experience mild to moderate pain, and only 3% will experience severe pain.[29] Patients require close monitoring, and both opioids and nonopioid adjuvants are usually required. For patients who are unable to take pills, buccal, sublingual, transmucosal, or rectal opioids are usually effective.[30–32] There are no data on the absorption of transdermal opioids newly placed in patients near the end of life. Concentrated morphine or oxycodone oral solutions (20 to 40 mg/mL) can be given hourly or every 2 hours and are often satisfactory. Rectal administration of sustained-release opioid preparations are not FDA approved, but studies indicate that morphine absorption from a sustained-release preparation placed in the rectal vault is equivalent to that from oral administration,[33] while absorption from a sustained-release oxycodone preparation is increased by ~30%.[34] If pain is a new problem and the patient is opioid-naive, institute therapy with 15 to 30 mg sustained-release morphine every 12 hours.

Adjuvants can also be given rectally or subcutaneously.[31] Patients who have previously benefited from oral nonsteroidal anti-inflammatory drugs (NSAIDs) can receive rectal indomethacin; patients on a stable glucocorticoid dose for bone or nerve pain can receive subcutaneous dexamethasone or specially prepared dexamethasone suppositories. Rectal doxepin can replace oral tricyclic antidepressants.

Pain control must be maintained as death approaches. If the calculated opioid dose is too large to be delivered by sublingual, transdermal, or rectal routes, if pain relief does not seem to be satisfactory using any of these routes, or if the routes are unacceptable to the patient or the caregiver, use a subcutaneous or intravenous opioid infusion.

Although pain relief is the goal in dying patients, the family is sometimes concerned that the opioid is "killing" the patient. If the patient's respiratory rate declines, the family might mistakenly think that the patient is oversedated. Unlike patients who are in less advanced stages of their illness, the normal respiratory rate in terminal patients is about six to twelve breaths a minute. If the rate falls to fewer than six breaths per minute, reducing the dose of the opioid by 25% is usually effective; naloxone is almost never indicated in such situations.

Death Rattle

Pooling of secretions in the hypopharynx of dying patients causes the loud rasping sounds referred to as the "death rattle." Patients are usually unaware of these loud respirations, but they can be very distressing for families. Reposition the patient to a lateral recumbent position and, if needed, add hycosamine (0.125 mg three or four times daily sublingual [Levsin SL]), glycopyrrolate (subcutaneously 0.2 mg every 4 to 8 hours or 0.6 to 1.2 mg per day by subcutaneous or intravenous infusion), or scopolamine in a transdermal patch.[35]

Dyspnea

The prevalence of cancer-related dyspnea in dying patients is approximately 70%.[36] These patients benefit from the same symptomatic therapies that are recommended for patients with less advanced disease. Any opioid that is being used for pain control can also be used to ameliorate the patient's dyspnea. Aggressive treatment of panic due to perceived breathlessness includes an oral or parenteral opioid (e.g., morphine 5 to 10 mg orally), rectal or parenteral chlorpromazine, or parenteral midazolam for refractory panic.

Xerostomia

Although patients are unlikely to be thirsty or hungry, they might have dry mouths caused by opioids.[37] Rehydration is not indicated to relieve this symptom because there is no difference in the reports of thirst or dry mouth between dehydrated and normally hydrated dying patients, and no controlled studies have shown that rehydration is effective.[38] Providing parenteral hydration increases distress, causing nausea and vomiting from increased gastric secretions; dyspnea from ascites, upper airway secretions, and pulmonary edema; and pain from ascites and peripheral edema.[37] Moistening the mouth with swabs or offering sips of water, ice chips, or fruit-flavored ice usually ameliorates the xerostomia.

Exsanguination

Massive hemoptysis, hematemesis, hematochezia, or exsanguination from a tumor eroding into a major vessel is rare but can be horrifying for professional caregivers, family members, or friends to observe. If the patient is likely to develop such a complication, ensure that there are dark-colored sheets, towels, and blankets available to mask the blood. Consider insertion of a peripherally inserted central catheter line in patients who have no indwelling venous access device to ensure emergency intravenous access for patient sedation. Appropriate medications should be on hand, either on the hospital unit or in the home. If the patient is enrolled in a hospice program, the nurse can provide instruction for administering prefilled syringes of morphine, to be given intravenously when possible, or a benzodiazepine. Midazolam (Versed) can be given intramuscularly or intravenously; diazepam or lorazepam (e.g., Ativan) can be given rectally. When the event occurs, the patient is placed bleeding side down, in the Trendelenburg position if possible, and given midazolam for anxiety and opioids if there is dyspnea or pain.

Psychological Causes

According to Dr. Susan Block, "grief, sadness, despair, fear, anxiety, loss and loneliness are present, at times, for nearly all patients facing the end of their lives."[39] They need "good communication and trust among patient, family, and clinical team, the ability to share fears and concerns, as well as meticulous attention to physical comfort and psychological and spiritual concerns."[39] The elements of a thorough discussion of the patient assessment (which includes "developmental issues; meaning and impact of illness; coping style; impact on sense of self; relationships; stressors; spiritual resources; economic circumstances; physician-patient relationship" can be found in Dr. Block's review.[39]

Anxiety

Anxiety in dying patients can arise from physical or psychological disorders.[40] Sepsis, hypoxia, metabolic abnormalities, withdrawal from opioids, selective serotonin reuptake inhibitors (SSRIs), or benzodiazepines, drug reactions (e.g., akathisia from metoclopramide or paradoxical agitation from benzodiazepines), and uncontrolled pain all can present as anxiety. Patients with panic disorders, agitated depression, phobias, or adjustment disorders also can present with anxiety.

Nonspecific pharmacologic treatments usually include benzodiazepines (e.g., the short-acting lorazepam, 0.5 to 2 mg every 2 hours as needed, or long-acting clonazepam, 0.5 to 2 mg orally twice daily), SSRIs, and, when there is evidence of delirium, neuroleptics (e.g., haloperidol, 1 to 5 mg orally or 0.5 to 3 mg intravenously every 2 to 12 hours, or olanzapine, 2.5 to 5.0 mg at bedtime or twice daily). Opioids with or without benzodiazepines are useful for patients whose anxiety is due to dyspnea.[41] Nonpharmacologic treatments, such as relaxation training, hypnosis, supportive psychotherapy, and counseling, are also very effective.[40]

Depression

Terminally ill patients who answer, "Yes," to the screening question "Are you depressed?" are likely to be diagnosed as depressed in a more comprehensive evaluation.[42] To explore the subject further, clinicians can try to determine whether the patient exhibits hopelessness, a sensation of helplessness, or guilt or reports being a burden to caregivers. Clinicians can ask, "How do you see your future? What do you imagine is ahead for yourself with this illness? What aspects of your life do you feel most proud of? Most troubled by?"[43] The clinician can serve as a therapeutic agent by listening actively and by providing support for both the patient and the family. For depressed patients who have only a few weeks to live but can still take oral medications, methylphenidate (2.5 to 5 mg orally at 8:00 A.M. and noon, initial dosing) can provide rapid symptomatic improvement.[44] For those with 4 weeks or more to live, an SSRI should also be included.

Delirium

Delirium (hypoactive, hyperactive, or mixed) has been reported in up to 88% of dying patients.[45] Hypoactive delirium can be confused with depression, and agitated delirium can be confused with uncontrolled pain, especially in dying patients.[46,47] Patients with hypoactive delirium might appear withdrawn, paranoid (e.g., fearing that the caregiver is trying to poison them with medications), or sad, and careful mental status testing with tools such as the Folstein Minimental or "draw a clock with the hands indicating a time of 10 minutes to 2" might demonstrate significant cognitive impairment. Patients with agitated delirium may cry out, be restless, and pick at clothes or bedsheets. Patients with any type of delirium can experience insomnia and daytime somnolence, nightmares, agitation, irritability, distractibility, hypersensitivity to light and sound, anxiety, difficulty in concentrating or marshaling thoughts, fleeting illusions, hallucinations and delusions, emotional lability, attention deficits, and memory disturbances.[48] It is therefore important to treat the delirium even among patients without overt agitation.

The etiology of delirium among patients with advanced cancer is often multifactorial.[45] Medical causes include metabolic abnormalities (hypercalcemia, hyperglycemia, and uremia), malnutrition, dehydration, hypoxia, fever, infection, bladder outlet obstruction, obstipation, uncontrolled pain, hepatic failure, primary brain tumor, and brain metastases. Medications—especially opioids, benzodiazepines, NSAIDs, and high-dose corticosteroids—often contribute to delirium. Substitution of another opioid might help to reverse the delirium.[49] A comprehensive psychiatric evaluation (which can be done at home by appropriately trained clinicians) can differentiate delirium from anxiety, minor depression, anger, dementia, and

psychosis.[48] Among patients who are very near the end of life, the burden of the evaluation might exceed the benefit of finding a specific, reversible cause. Empiric therapy that controls the delirium might suffice. Discussion with the patient's health care proxy can help to clarify the best course of action. Treatment protocols for delirium are included in Table 44-2.

AGITATION IN THE DYING PATIENT

Almost half of the patients who are actively dying of cancer show signs of restlessness and agitation. They might toss and turn, moan, have muscle twitching or spasm, and be awake only intermittently. Some are suffering from unresolved spiritual or social problems. The approach to assessment and treatment of agitated dying patients involves, sequentially, nonpharmacologic symptomatic therapy, an evaluation for reversible causes and treating those that are found, and empiric symptom management (Fig. 44-1). Whenever a treatment resolves the agitation, it should be continued, and the patient should be reassessed. In rare cases, patients with agitation require sedation. The aggressiveness of the evaluation and the nature of the treatments that are given should be guided by the patient's goals and the burdens and benefits of each intervention. The site of care (hospital, nursing home, home) need not be the deciding factor in the decision about which palliative assessment and therapies to offer.

Many patients' agitation responds to nonspecific, nonpharmacologic measures, such as adjusting the lighting, decreasing extraneous noise in the room, playing favorite music, gently touching the patient, or having family and friends read to, pray with, or quietly talk with the patient. A visit from one of the hospital chaplains can be comforting. A visit from an estranged family member or friend, reassurance that loved ones are well cared for and are prepared for the patient's departure, and family permission to "let go" can have significant impact.

If these measures are not effective, the family and caregivers should weigh the burdens and benefits of searching for reversible causes. Those such as a full bladder, a fecal impaction, poorly cleared secretions, pain, or side effects from opioids or other medications are usually easy to detect and correct. Metabolic disturbances leading to delirium and pulmonary processes causing hypoxia or anxiety could require invasive maneuvers that do not seem appropriate. When a specific cause is found, decisions can be made regarding the burden and benefits of specific versus symptomatic treatment. The patient's condition and goals, for example, dictate whether a patient who has dyspnea from a large pleural effusion should undergo a thoracentesis or simply receive opioids. If correction of one specific cause does not resolve the agitation, resume the search, as appropriate, for another one.

If no specific cause is detected or if the search for specific causes is felt to be inappropriate, empiric therapies based on the likeliest process(es) causing the distress should be tried. Empiric treatment for delirium, pain, hypoxia, and anxiety often relieves the agitation. If the agitation persists, sedation will be required (see Table 44-2).

Social Causes

Family concerns can weigh heavily on dying patients. Practical concerns are often the easiest to resolve, although a major concern of dying patients is the burden they feel they are imposing on their loved

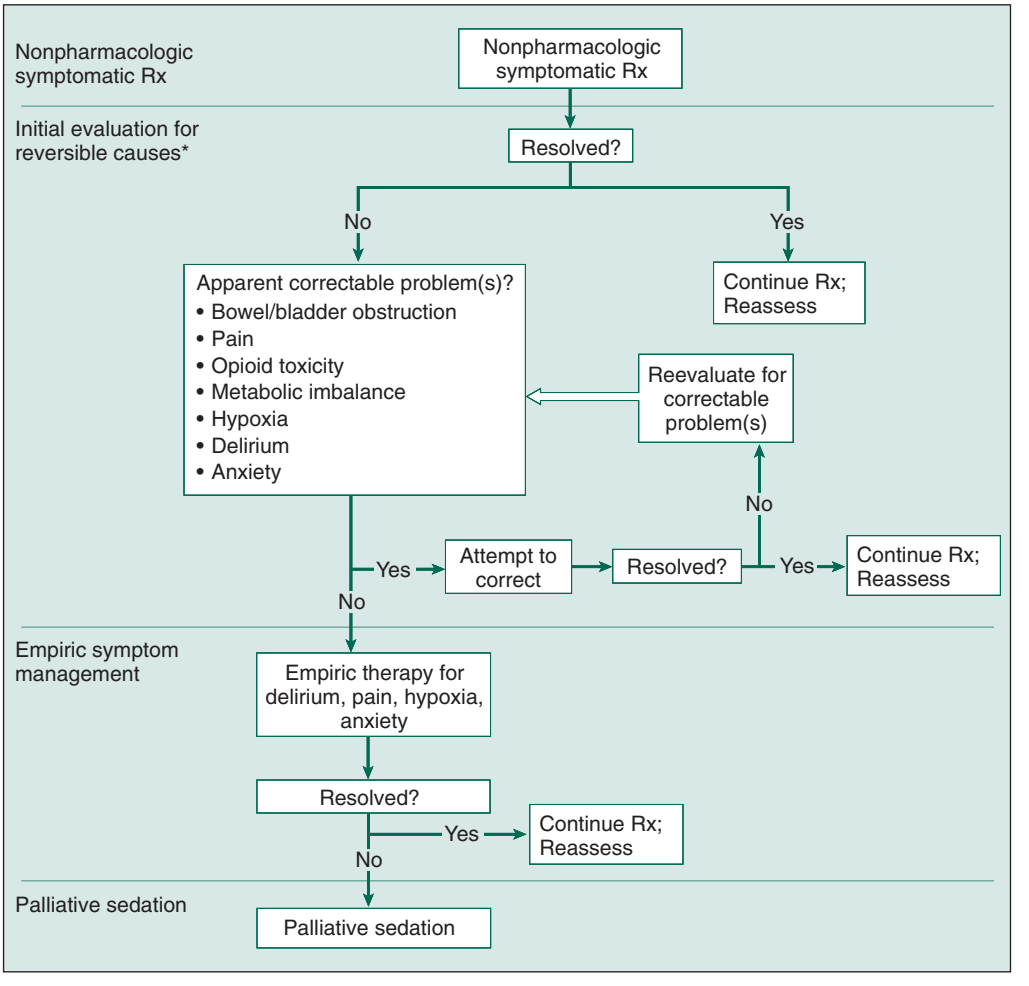


Figure 44-1 • Treatment of agitation in the last days. *Guided by patient/family wishes, burden/benefit.

ones.[26] They also want to strengthen and complete their relationships. For this reason, problematic relationships can create open wounds that are as painful as those from any physical injury. Dr. Ira Byock offers five simple phrases ("The Five Things") that encompass the subjects people can benefit from discussing with those they love: "Forgive me; I forgive you; thank you; I love you; and goodbye."[3] Many patients and families find it difficult to say these phrases or discuss these subjects. Social workers, chaplains, psychologists, and psychiatrists can be of great help in facilitating these conversations and bringing peace to a dying patient and to the soon-to-be-bereaved family members.

Families of dying patients face an extraordinary number of challenges. They must cope with their own losses, organize and pay for home care, and care for the family members who are not ill. They are best helped by the following measures:

- Patient comfort
- Communication with health care providers
- Help with caregiving and meeting financial and social costs
- Maintaining stability
- Adapting to change
- Support for their grief and upcoming bereavement[50–52]

Oncology clinicians can help by simplifying medication regimens and planning for emergencies that can be foreseen.[53] See also Box 44-1 for suggestions about how oncologists can address some of the family's needs. Social workers collaborate with the patient's primary oncology team to provide most of the support, explain the benefits of hospice and other needed services, and arrange family access to them.

Families with young children are in special need of counseling and support. Guidelines for clinicians who work with these parents and their children include six steps (which are described in detail in the reference provided):

1. Learn about the children.
2. Maximize the child's support system.
3. Facilitate honest communication about the illness.
4. Address common questions.
5. Prepare for hospital visits.
6. Say goodbye.[54]

Cultural Considerations

To avoid communication difficulties, physicians and nurses should explore with patients and families what they feel are appropriate context and structure of end-of-life discussions (Box 44-2).[55] Non-Hispanic whites and African Americans, for example, differ in many areas: who they want present (immediate family only versus extended family, friends, and pastor); having durable power of attorney or

Box 44-1. ADDRESSING THE NEEDS OF THE CAREGIVER

During the last weeks to months of the patient's life, office visits become impractical. Regular contact by telephone, supplemented, when possible, by one or more home visits, retains the connection that patients and families need with their primary treatment team. Clinicians also can promote continuity and minimize feelings of abandonment by collaborating with the home care or hospice nurses and, as requested, with the social workers who are part of the home care team. Praising the family caregivers for the work they are doing, helping them to anticipate upcoming problems and make contingency plans, and checking in with them at regular intervals promote timely identification and, when possible, resolution of new problems.

Many family members and medical trainees have never seen anyone die an expected death outside an intensive care unit. The clinician who is familiar with the dying process can be a crucial source of information and comfort. For inpatients, the clinician works with the nursing team that is caring for the patient and also serves as an attentive observer striving to provide maximum comfort. I make at least two visits a day to stable patients to monitor their comfort through reports from nursing and family, to answer questions, and to educate professional and family caregivers as to what they should expect in the last days.

Patients who were formerly alert and communicative usually become less so. They are apparently still comforted by the touch and voices of those they love and might even emerge from what seemed to be an insensible state to greet a welcome newcomer. I tell families that to me, it is as though the patient lives in a house with many rooms, a mansion. As they come closer to dying, the patient moves farther and farther back in the house, and it is more and more effort for them to greet callers at the front of the house. But the callers are still welcome, as are their voices and conversation. I ask families to let patients know they have arrived and then to add that patients should not feel obliged to speak to them. Patients can also be asked to provide a hand squeeze or other sign of recognition. With close family, I discuss the "Five Things" (see the section of the chapter entitled "Social Causes") and suggest that they find the time to share with the patient any of those sentiments they feel would be appropriate.

I reassure families that we know that dying patients are rarely hungry or thirsty and that moistening the mouth is all that is needed. If necessary, I review the burdens of hydration (see the section entitled, "Xerostomia"). I also explain about Cheyne-Stokes breathing and that it does not indicate that the patient is gasping for breath. I also ask them to feel free to let us know if the patient seems uncomfortable or develops noisy breathing, as we want to address any source of discomfort as rapidly as possible. I offer the services of chaplaincy, and I am alert to whether a social worker would be helpful, if chaplains and social workers are not already involved. Many family members do not know that this kind of help is available to them in the hospital.

If the family has not done so already, I urge them to choose a funeral home and make all the necessary arrangements before the patient has actually died, to free themselves of that task when the death occurs. Families often ask how they will know that the patient is dying. I ask them to look for a marked decrease in urine output (in a foley bag or diapers), cooling of the arms and legs, and new pallor or mottling of the skin. Some patients develop fecal incontinence as they die, so if hospice is not involved and the patient is at home, I alert the family to this possibility.

Supporting the Ward Personnel and the House Staff

To decrease potential feelings of guilt and anxiety, I review with all team members the history of the illness, the limits of the treatments that remain, the burdens of those treatments, and, when appropriate, the limits the patient has placed on further supportive measures. I also remind them that despite our best efforts, patients still die and that it is no one's fault. I also suggest things they can do that will enhance the patient's last days and that will further the healing process of the survivors.

During the hospitalizations that lead to death and after the death itself, I try to dispel any misconceptions they have about their "fault" for the death and to praise the work they did to make the dying as comfortable as possible. This kind of support goes a long way toward enabling young physicians and ward staff to recover from the pain they experience when a patient dies and to allow themselves to feel a sense of satisfaction for a job well done.

Box 44-2. KEYS TO A SUCCESSFUL FAMILY MEETING

One of an oncology clinician's hardest tasks is conducting a successful family meeting when the burden of disease-directed therapies exceeds the benefits. While chemotherapy or radiation might no longer offer benefit, it is never true that "there is nothing more we can do for you." The following steps increase the chance that the meeting will enhance communication among clinicians, patients, and family members; relieve concerns of abandonment; enhance trust; and provide a conversational template for the tough times to come.

1. Schedule a pre-meeting (actual or virtual) and consider:
   - A. Who needs to be there (which family members, which members of the clinical team)?
   - B. What is the realistic prognosis or functional goal for the patient?
   - C. Who will run the meeting? How can others help (e.g., the palliative care clinicians, the social worker)?
   - D. Who will stay with the patient and family to debrief?
2. During the meeting
   - A. Everyone must be seated.
   - B. Introduce everyone present.
   - C. **ASK**–tell–ask
     - i. How do you think you (or "the patient") is/are doing?
     - ii. What changes have you seen in the last (days, weeks, months)?
     - iii. What are you hoping for? And what else? And what else?
     - iv. What are you most concerned about? What are your worst fears?
     - v. How can we help?
   - D. ask–**TELL**–ask
     - i. Answer their questions.
     - ii. Provide key medical information, but **AVOID** giving medical details that obscure the big picture.
       - a. Example: The (disease) is clearly progressing despite our best efforts. In my best judgment, s/he has only (days, weeks, months) of good time left. S/he may well live longer, but this is the time when s/he will have the most energy, think the most clearly, and be most him/herself.
     - iii. **STOP TALKING**
       - a. Counting silently to 20 helps.
     - iv. Respond to their grief.
   - E. ask–tell–**ASK**
     - i. What do you still want to accomplish during your life?
     - ii. What might be left undone if you were to die today?
     - iii. What legacy do you want to leave to your family?
     - iv. What do you want your children and grandchildren to remember about you?
     - v. How can we help **NOW?**
3. After the meeting
   - A. Review with your team how everyone is doing.
   - B. Make a plan for who will follow up next with the family.
   - C. Success is measured by how much they trust you and how little they feel abandoned. Feeling bad is normal and expected, both on your part and theirs; that does not mean that you were not successful.

living will in place and interest in knowing about hospice programs[56] (more common in non-Hispanic whites[55–57]); and what the focus and tempo of the discussion should be (concerns about prognosis, irreversibility of the illness, quality of life, financial concerns and medical choices versus spiritual concerns, lack of trust, concerns about "do not resuscitate" orders and hospice, allowing adequate time for decisions and not feeling pressure to make them).[57,58] More patients who are not of non-Hispanic white or African-American descent prefer to have surrogates informed of their prognosis and make treatment decisions for them. Some patients from Asian, Bosnian, or Italian-American cultures might perceive frank communication about a serious illness or prognosis as "at a minimum, disrespectful, and more significantly, inhumane."[55] It is therefore important to determine from the patient whether the patient or his or her designees are to be involved in these discussions and to respect that choice as the exercise of that patient's autonomy. Every effort should be made to provide a qualified translator in conversations about prognosis and goals of care where the clinician is not a fluent speaker of the patient's language.[55]

Spiritual and Existential Causes

Dying patients also can suffer from spiritual and existential concerns. As cancer advances, patients face ongoing losses in terms of normal appearance and physical and mental function; roles in the family, community, or workplace; control, autonomy, and privacy.[2] Suffering arises when the illness robs patients of something fundamental to who they are, and consequently, each person's sources of suffering are unique. For example, although loss of mobility might be irrelevant to someone whose major avocation is reading, it can be devastating to an avid golfer. Young patients in particular search for the meaning in their existence, their illness, and their premature deaths. Counseling, including life reviews ("What have you been most proud of in your life? What surprised you most? What has made you happiest? What do you wish you could have done better or differently?") may help dying patients to find a context and a meaning for their lives.

Some patients seem to blame themselves for their illness, even though scientific evidence does not support their belief. The concern could arise from a much larger sense of guilt about the patients' sense of failure to live the lives they should have lived. Other patients—those with uncontrolled pain, for example—might feel that God is testing or punishing them. They search their consciences for a transgression so dreadful that it deserved such punishment.[59] A mental health professional or chaplain might be able to provide reassurance or to help patients develop strategies to right the wrongs they feel that they caused. Even dying patients can be provided hope that in the absence of a cure, they will still be able to heal these wounds.

Religious rituals can be an important source of comfort and healing to dying patients and their families.[59] Even in a hospital setting, therefore, every effort should be made to identify and accommodate these spiritual practices. Appropriate hospital or community religious leaders should be welcomed as part of the patients' care team and should be assisted in performing the necessary rites after the patient dies.

Palliative Sedation for Refractory Symptoms

Sedation is considered when, despite expert evaluation and management, a patient who is near death continues to experience intolerable physical, psychological, or spiritual-existential distress.[60] Fewer than 5% of patients need palliative sedation; those who do most commonly suffer from refractory pain, cough, dyspnea, seizures, or delirium. The doses of opioid, benzodiazepine, or neuroleptic that are needed to control the symptom(s) sedate the patient. In other cases, the request for sedation for refractory symptoms arises when psychological or spiritual-existential concerns coexist with physical problems. Expert palliative care and pastoral consultation, evaluation by a psychiatrist, and discussions among the health care team, the patient, and the family members should be undertaken before

palliative sedation is administered. Most often, all the people concerned reach a consensus on the need for and acceptability of sedation as a means of achieving symptom control. Obtaining formal informed consent, either from the patient or from the health care proxy, is recommended.

Medications that are used to produce the sedation that relieves the distressing symptom(s) include opioids, neuroleptics, intravenous benzodiazepines, and subcutaneous or intravenous barbiturates (see Table 44-2).[61] Intravenous hydration or enteral or parenteral nutrition can be provided if they meet the goals set by the patient and family. They are rarely used in imminently dying patients whether or not the patients are sedated, as these patients are rarely suffering from hunger or thirst.[37]

HOSPICE CARE

Hospice care can be an enormous source of comfort to families of dying patients and professional caregivers, particularly those who have never witnessed a "natural" death. The team members have "been there," can explain what is likely to happen, and can provide expert symptom management during the last hours to days. Hospice care might also decrease the risk of death of surviving elderly widows.[62]

American patients, however, are generally very resistant to accepting a terminal prognosis.[63,64] To enroll in hospice, patients must acknowledge their 6 months prognosis, relinquish further curative therapy, and give informed consent. These requirements and common misconceptions about hospice care (Table 44-3) can be serious obstacles to enrollment in hospice programs.[65]

Table 44-3 Common Misconceptions about Hospice

- *Patients enrolling in hospice must choose not to be resuscitated.* Patients do not have to relinquish resuscitation to enroll in hospice. After they and their families fully understand the implications of the resuscitation, most patients elect not to be resuscitated.
- *Patients enrolled in hospice lose their primary physicians.* The referring attending physician continues to direct and approve all the patient's care.
- *Hospice patients cannot be hospitalized and remain enrolled in hospice.* Any hospice patient can be admitted to an acute, inpatient level of care to control a distressing symptom. Hospices can admit patients to contract beds in acute care hospitals or to their own inpatient facilities.
- *Hospice patients cannot participate in research projects while enrolled in hospice.* Hospice patients have the right to participate in research studies. Hospice ethics and research committees usually evaluate the burden vs. the benefit of the research on the patient, family, and hospice staff.
- *Hospice nursing personnel do not provide sophisticated care.* Hospice personnel provide expert palliative care that requires astute assessment and expert intervention tailored to the patient and family goals.
- *Patients can "use up" their hospice eligibility, so it is important not to enroll them too soon.* Patients are initially certified for three months of service, after which their physician and the hospice medical director are asked to recertify them indefinitely, at two-month intervals. Patients who choose to revoke the hospice benefit to seek life-prolonging therapies may choose to re-enroll if their goals change.
- *Patients must have a live-in caregiver to enroll in hospice.* With appropriate safeguards (e.g., "lock-boxes" to provide access in emergencies, and daily phone contact) hospice care can be safely provided to patients who "live alone."

Financial Considerations

The hospice benefit (under Medicare) is a managed care, capped reimbursement program that reimburses a hospice program a per diem rate based on the patient's level of care (approximately $130 per day for routine or respite care, approximately $500 per day for inpatient acute care). In skilled nursing facilities, patients are receiving Medicare benefits for skilled care and cannot retain these and simultaneously enroll in the hospice Medicare benefit. If they choose a hospice program, either a Medicaid program or their families must pay the room and board costs in the nursing home. Medicaid, private insurance, and health maintenance providers reimburse the hospice at various rates; with the last, services must be approved through the plan's case manager. Aggressive palliation using chemotherapy or radiation is often prohibitively expensive for small to moderate-size hospices, given this reimbursement schedule. Individual hospices must decide both which treatments are consistent with their philosophy and which they can afford. Most hospices must secure additional funding from grants and donations to provide the mandated services.

Further, the majority (80%) of the services a hospice program delivers must, by law, be to patients at home. Fewer than 1% of patients who are enrolled in hospice programs die in hospitals. Although the hospice program provides some help, the majority of the patient's care at home must be provided by family or friends or by privately paid professional caregivers. Therefore, some patients will not be able to stay at home even with the maximum help that hospice personnel and volunteers can offer.

Clinical Care Provided

Patients in hospice programs are cared for by medically directed, interdisciplinary teams that include the referring physician, the hospice medical director, a nursing director of patient services, an office administrator, a nurse, a social worker, a bereavement counselor, a home health aide, a chaplain, and volunteers. The core team also can request additional consultations from physicians, registered dietitians, or occupational, speech, or physical therapists (Table 44-4).

Levels of Care

Hospice programs provide a continuum of care, from home to the inpatient setting. Whereas most patients are cared for in their homes,

Table 44-4 Medicare-mandated Hospice Services

PRACTITIONERS AVAILABLE

Medical director, nurses, social workers, home health aides, chaplains, volunteers, administrative personnel, medical consultations, occupational therapy, physical therapy, speech therapy, bereavement counseling

PALLIATIVE TREATMENT OF TERMINAL ILLNESS

Prescription medications

Durable medical equipment and supplies

Oxygen

Radiation and chemotherapy

Laboratory and diagnostic procedures

OTHER BENEFITS

Transportation when medically necessary for changes in level of care

When needed, continuous care at home or in a skilled nursing facility or inpatient setting

Respite care (care in a nursing facility that provides a "respite" for the caregivers)

Medicare Hospice Regulations: 42 Codes of Federal Regulations, Part 418, 1993.

all Medicare-certified hospices, as stated in the 1983 federal regulations, are required to provide four levels of care: routine, continuous, inpatient, and respite. They also provide bereavement care both to support family members who are experiencing "anticipatory grief" before the patient's death and to communicate with and support the bereaved for the year after the death.

Routine care services are offered seven days a week, 24 hours a day. In addition to the patient's nurse, there is always an on-call registered nurse to provide phone support and make home visits when necessary. The registered nurse monitors the patient's comfort and works with the referring physician to adjust the treatment regimen as needed. Occupational, speech, or physical therapy and home health aides are provided as required. As death approaches, the patient's registered nurse reviews the dying process and provides the family or the inpatient or long-term care facility personnel with written materials that explain how they can determine that death is imminent. The nurse also describes the signs and symptoms of dying, instructs the family in emergency procedures, and is available for support while the patient dies.

Social workers offer support and family counseling and identify those who are at risk for a particularly painful bereavement period. They engage the patient and family in advance care and funeral planning and in completion of living wills and durable powers of attorney, provide applications for financial aid or waivers, and help to identify financing for additional home health care. They assist patients in making plans for their survivors (e.g., guardianship for children) and in completing life reviews; they often work alongside the chaplain to facilitate family reconciliation.

The team chaplain also offers home visits or coordinated care with the patient's own clergy. Chaplains are of help even to nonreligious patients who have spiritual or existential sources of distress (e.g., loss of hope, loss of connection or of love, a need for forgiveness or to forgive, or a need to identify the meaning of their lives).

Volunteers, who are usually available 2 to 4 hours a week, help families in nonclinical areas. A hospice medical director works with the team and the patient's primary physician to optimize symptom management.

Continuous home care is provided for patients who require continuous symptom management and for whom the home care setting remains appropriate. Patients with, for example, unrelieved cough, dyspnea, pain, or delirium can receive 24-hour nursing services until the problem is brought under control. Home visits from a hospice medical director can also be provided.

If the patient's symptoms cannot be controlled at home, inpatient care is offered. Orders are written by inpatient unit personnel and inpatient staff provide the care. The hospice team, however, continues to be responsible for the plan of care. Team members visit the patient as they would visit an outpatient, and the hospice medical director provides consultation as needed. The referring physician remains the primary physician and can bill for services under Medicare Part B.

Respite care is available generally for 5 days every month in a community skilled or intermediate nursing facility with which the hospice has a contract. The goal of the respite is either to provide a rest for the caregiver or to remove the patient to an adequate facility when the home is temporarily inadequate to meet the patient's care needs.

Medications and Treatments Provided

Hospice programs provide 95% of the cost of prescription drugs related to the terminal diagnosis and necessary for its palliative treatment (and many waive the other 5% if there is no insurance coverage). They also provide all durable medical equipment, supplies, and oxygen for needs related to the terminal diagnosis; laboratory and diagnostic procedures related to the terminal diagnosis; and transportation when this is medically necessary for changes in the patient's level of care (see Table 44-4).

GRIEF AND BEREAVEMENT

Survivor's grief is a "process of experiencing the psychological, behavioral, social, and physical reactions to the perception of loss," and it is distinguishable from the anxiety and depression that survivors might also be experiencing.[66,67] The intensity of a survivor's grief is based on the characteristics of the mourner himself or herself, the nature of the death, and societal and cultural factors. Rando writes that being very attached to or very dependent on the deceased, having a great deal of ambivalence in one's feelings toward the deceased, having a personal history of clinical depression, or having difficulty with previous losses all can exacerbate the grief.[66] Recent studies of psychiatric outpatients confirmed the association between attachment and dependence and severity of grief but also found that having more ambivalence predicted for less grief.[68] Sudden or accidental death, suicide, or homicide magnify the grief.[66] The perception of a violent death is associated with major depression in the survivors, but religious rituals, a good support system, and involvement with hospice programs for more than 3 days decrease depression.[69,70]

Each bereaved person's loss is unique, as are the experiences and manifestations of grief and mourning. Many people manifest typical symptoms of grief, some of which become less persistent as the people rebuild their lives.[66,67,71,72] Recurrent intense symptoms typically occur at the anniversary of the death of the patient but can occur at unpredictable times, sparked by any type of reminder of the deceased. Although there are no rigid stages through which bereaved survivors pass, there are some typical manifestations of grief.

At the time of death, survivors appear numb, confused, or dazed and usually express some form of denial as the reality of the death intensifies.[73] Behavior can range from uncontrolled shrieking to an unnerving calm.

In the weeks and months that follow, pain intensifies as the absence of the person who has died asserts itself repeatedly. Mourners yearn for the one who is dead and experience repeated pangs of intense grief; denial is replaced by disorganization, depression, disinterest, and despair.[72] Survivors commonly experience the feelings, behaviors, physical symptoms, spiritual concerns, and thoughts listed in Box 44-3.

As the roles the deceased played in the marriage, the family, and the community become apparent to the survivors, they grieve each loss as they learn to cope with the increasing responsibilities. It is very difficult for people to move beyond loss if they never allow themselves to feel it in some way that is appropriate for them. Family obligations and unspoken strictures against demonstrations of grief can further impair a survivor's ability to experience the pain of the loss adequately. Putting those feelings away to deal with later or denying their existence only prolongs or inhibits the grieving process.

Often by a year or two after the loss, survivors accommodate to it.[66] They tacitly acknowledge the changes that must be made if they are ever to resume old relationships and responsibilities or to establish new ones and risk recurrent loss. Accommodation involves realizing that loving someone new need not mean betraying the memory of the person who has died.[66]

About 10% to 20% of survivors, however, suffer either from depression and/or from "complicated grief." Patients with depression have "symptoms of sadness, impassivity, and psychomotor retardation,"[74] but they do not yearn for the deceased and they can accept the death. Depressed survivors benefit from counseling and consideration of pharmacologic treatment.[74,75] Patients with complicated grief disorder, in contrast, have grief that causes serious functional impairments. They do have profound yearning for the deceased, as well as "numbness, feeling that part of oneself has died, assuming symptoms of the deceased, disbelief, or bitterness."[74,76] These patients are at increased risk of medical and psychiatric illness[77] and should

Box 44-3. WHAT YOU CAN EXPECT WHEN SOMEONE CLOSE TO YOU DIES

Grief is associated with feelings, thoughts, and physical symptoms that include the following:

Common Feelings/Behaviors
- Fear or anxiety
- Anger or guilt
- Depression or despair
- Separation or longing
- Sudden wave of mental pain
- Confusion or inability to concentrate or make decisions
- Tearfulness or crying
- Sighing
- Restlessness
- Yearning
- Helplessness
- Relief
- Disbelief
- Hope

Spiritual
- Sense of the deceased's presence
- Faith may be strengthened, altered, or abandoned

Common Physical Symptoms
- Decreased or increased appetite
- Decreased energy; weakness of muscles
- Nausea and diarrhea
- Decrease or increase in sex drive
- Inability to sleep or sleeping too much
- Feeling something stuck in the throat
- Tightness in chest, breathlessness
- Increased sensitivity to noise
- Vivid dreams
- Dry mouth

Common Thoughts
- Preoccupation with "if only," "what if," and with memories
- "Who am I now?"

Most people find that their grief lasts anywhere from 6 months to 2 years. However, remember that each person is a unique individual, and for some people, much more time is needed before the pain lessens.

What You Can Do
1. Allow yourself to feel the loss and to grieve over it.
2. Realize that your grief is unique.
3. Expect yourself to have some negative feelings.
4. Accept the help of others and let people know how they can help.
5. Give yourself time alone.
6. Exercise.
7. Read books about feelings of grief and the process of recovery.
8. Talk to others about your loss.
9. Attend community support groups.
10. Most important: Understand that it is very likely that your pain will lessen.

What It Is Better Not to Do
1. Try not to make major changes.
2. Resist withdrawing from social activities.
3. Avoid excessive smoking or drinking.

When You Should Call Us
- If you have any questions or would like further information.
- If you feel that you would like professional counseling.
- If you need our help.

Abrahm JL, Cooley ME, Ricacho L: Efficacy of an educational bereavement program for families of veterans with cancer. J Cancer Ed 1995;10:207–212.

Box 44-4. SAMPLE OFFICE-BASED BEREAVEMENT PROGRAM

At the Time of Death
Family members are often in a state of shock; their moods can swing widely from feeling numb to feeling distraught. This volatility can be frightening, so our staff explains that this reaction is normal and that they should not worry about controlling themselves.

If I am sad, I cry with the family; if family members need to talk things over, I ask leading questions that help them share their feelings. Most families want to review the circumstances of the death, to assure themselves that the patient did not suffer and that everything that could have been done was done. I always try to find something for which I can praise them (e.g., their care of or their advocacy role for the patient) and add how lucky the patient was to have had them there when he or she needed them. If I cannot do this in person, I try to offer as much support as I can by telephone.

Initial Follow-up Call
We next call the family within 24 to 48 hours of the death to offer our condolences and our help. During this call, we offer comfort and provide a listener for a reiteration of the story of the death and the meaning of it for the bereaved. If necessary, we again reinforce the normality of the wide emotional swings or other symptoms of acute grief that they might have been experiencing. We listen empathetically and indicate our continued support. We end the conversation by asking whether we can keep in touch, and we let them know we will call again in about a month. We also send a condolence letter. If the family was involved with hospice, we remind them that the hospice team is still available to them.

Four to Six Weeks
About a month after we send the letter, we call again and offer to send a variety of materials we think would be helpful. These include a list of feelings and physical signs commonly experienced by those who are grieving and what to do or not to do about them (see Box 44-3).

We also include a list of support groups in the family's area, including those hosted by the hospice, because talking about their loss with skilled bereavement counselors or others who have suffered the same losses can help their recovery. Groups such as Widow-to-Widow, or, for parents who have lost a child, Compassionate Friends or Candlelighters (www.candle.org) provide much needed help with rebuilding a life.

Other Contacts
Because this has been shown to be a time of most need for bereaved families, we call again at six months and repeat our offer of various materials. We also participate in the once- or twice-yearly memorial services held by our cancer center and by the hospices who cared for our patients and their families. And, because we anticipate recurrence of grief, we send a letter at the first anniversary of the person's death, and we send a "Holiday letter" a few weeks before Thanksgiving letting them know that they are still in our thoughts and would welcome a call.

Our staff finds the process very rewarding. I have noticed that as I speak to the survivors at longer and longer intervals and begin to remember the patients as they were before the terminal stages, it helps me achieve closure and makes it easier for me to move on.

Abrahm JL, Cooley ME, Ricacho L: Efficacy of an educational bereavement program for families of veterans with cancer. J Cancer Ed 1995;10:207–212.

be referred for psychiatric or spiritual counseling. Survivors with a history of attachment disorders (e.g., childhood abuse, childhood separation anxiety) or an aversion to lifestyle changes, who are unprepared for the death and unsupported after it, are at higher risk of developing "complicated grief." Additional risks include a "dependent, close, confiding" relationship with the deceased.[74] There is no randomized control trial of a pharmacotherapy that is effective for the extreme grief symptoms,[73,74] but a new effective psychotherapy has been developed specifically for this disorder that is superior to standard interpersonal psychotherapy.[78]

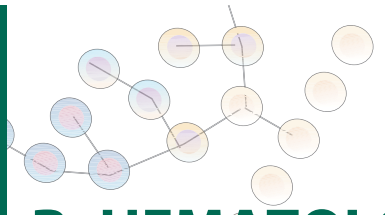
Skillfully communicating the diagnosis and terminal prognosis; providing emotional, psychological, and spiritual support and physical comfort; helping families to resolve outstanding issues; and making the death as peaceful as possible are all measures that diminish the suffering of the survivors. Survivors who feel unprepared for the patient's death have a higher risk of developing complicated grief.[69]

After the patient dies, survivors appreciate ongoing communication with the patient's physician.[75] When a formal bereavement program is offered, it usually takes place during the first year after the patient's death. After the formal program ends, the bereaved are welcome to continue to participate in any bereavement activities that have been meaningful to them (Box 44-4). Survivors who experience severe grief symptoms or depression should be referred for formal assessment and consideration of pharmacologic treatment.[75,79] Unfortunately, although the depression often responds to standard therapy, there is no widely accepted effective therapy for the symptoms of extreme grief.[75]

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B. HEMATOLOGIC PROBLEMS

45 Disorders of Blood Cell Production in Clinical Oncology

John Glaspy

SUMMARY OF KEY POINTS

- Anemia is very common in oncology patients and is multifactorial.
- Many patients with cancer have in part the anemia of chronic disease.
- The anemia of chronic disease is associated with decreased absorption of oral iron and decreased ability to access storage iron pools.
- Iron-restricted erythropoiesis may limit the efficacy of erythropoietic agents for the treatment of anemia in these patients and can be overcome with parenteral iron.
- Treatment of anemia in cancer patients reduces transfusions and improves quality of life.
- The safety of increasing hemoglobin levels to greater than 13 g/dL is not established, and the target hemoglobin level during treatment should be 12 g/dL.
- Neutropenia in oncology is usually due to treatment.
- Myeloid growth factors can be used to reduce infection risk in patients in whom the risk is unacceptably high, and this is preferable to delaying or reducing the dose of chemotherapy when cure is the intent.
- There are new agents for the stimulation of platelet production in clinical development.

INTRODUCTION

Disorders of blood cell production, usually manifest as anemia, leucopenia, or thrombocytopenia, are both very common and enormously important in the clinical practice of oncology. Under ordinary conditions in the healthy adult, blood cell production is extraordinarily prolific, with daily outputs in the range of 2×10^{11} erythrocytes,[1] 5×10^{10} neutrophils,[2] and 2.5×10^{11} platelets,[3] as well as substantial numbers of lymphocytes, macrophages, antigen-processing cells, eosinophils, and basophils. With more than 5 million blood cells produced every second under ordinary conditions, the mitotic yield of normal bone marrow is greater than that of almost any malignancy, where the production of a similar number of new cells would result in a daily increase of tumor cell burden of more than 0.25 kg per day. It is not surprising therefore that among the most common unintended consequences of cancer treatments with antimitotic mechanisms of action are clinically important degrees of anemia, neutropenia, or thrombocytopenia.

The rate of blood cell production is both tightly regulated and highly variable. Under conditions of either increased destruction of cells, such as bleeding, hemolysis, or immune destruction of platelets, or demand for increased numbers of cells, such as infection, production rates of appropriate cells increase several fold. The regulation of this dynamic system is complex[4] but for practical purposes can be conceived of as involving an interaction between a pool of pluripotent hematopoietic stem cells, capable of both infinite self-renewal and differentiation into mature blood cells and regulatory factors, including both a well-characterized set of glycoprotein hematopoietic growth factors and a less well-understood group of inhibitory factors. Cancer and its treatment are very often associated with profound perturbations in this system controlling blood cell production. Understanding this biology is key to rational intervention and optimal care of the oncology patient.

DISORDERS OF RED CELLS

Anemia

Pathophysiology

Anemia is common in cancer patients[5,6] and is often multifactorial, with frequent contributors including: bleeding, general malnutrition, iron, folate or vitamin B_{12} deficiency, hemolysis, myelosuppressive chemotherapy, radiation to marrow-bearing bones, and the anemia of chronic illness. In addition to these factors, for B-cell malignancies and solid tumors extensively involving the marrow, disruption of the normal interactions of hematopoietic progenitor cells and endothelial and connective tissue stromal cells in the marrow microenvironment may play an important role. For patients with secretory multiple myeloma, renal insufficiency is a frequent and often unrecognized factor in the anemia. Finally, for patients with myelodysplasia and myeloid malignancies, the hematopoietic stem cells themselves are reduced in number and/or dysfunctional.

It has been recognized for some time that, in patients with chronic inflammatory illnesses including cancer, a diminished endogenous erythropoietin (EPO) response to anemia is frequently observed.[7] More recently, it has been shown that inflammation is frequently associated with increased production of the iron-regulatory peptide, hepcidin, by the liver.[8–11] Hepcidin binds to and inactivates the iron transporter, ferroportin, impairing both absorption of dietary iron and access to storage iron pools.[12,13] These discoveries strongly suggest that iron-restricted erythropoiesis may occur despite the presence of what are believed to be adequate iron stores and be more common in patients with cancer than has been previously suspected. Our current understanding of the biology of anemia in cancer patients is shown in Figure 45-1.

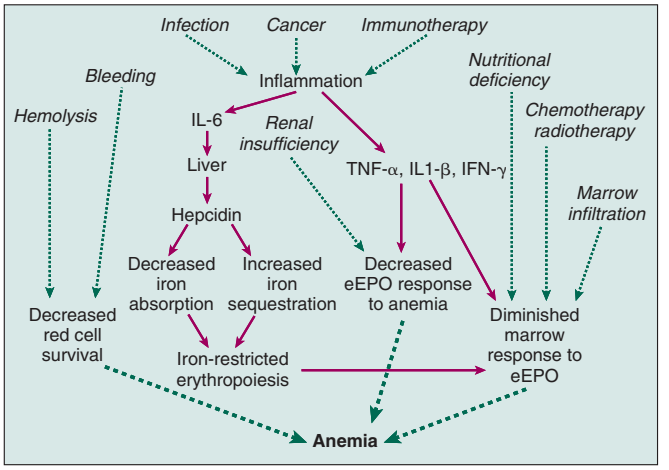


Figure 45-1 • The pathophysiology of the anemia frequently observed in cancer patients. Type I acute-phase cytokines decrease the endogenous EPO response to anemia and suppress the effects of EPO on the marrow. Type II acute-phase cytokines induce hepcidin production in the liver, which decreases iron availability to erythropoiesis through decreased gastrointestinal absorption and accessibility of storage iron in reticuloendothelial cells. Other common factors include marrow suppression through disruption of the normal microenvironment, the myelosuppressive effects of chemotherapy, and nutritional deficiencies other than iron. Renal insufficiency is particularly common in patients with multiple myeloma and patients treated with cisplatin chemotherapy. eEPO, endogenous erythropoietin; IFN-γ, interferon γ; IL1-β, interleukin-1β; IL-6, interleukin-6; TNF-α, tumor necrosis factor α.

Management

It is surprising how frequently the anemia observed in cancer patients is due, at least in part, to reversible factors, such as iron loss through bleeding or previously unsuspected vitamin B_{12} deficiency. In one recent study, 5% of cancer chemotherapy patients being considered for inclusion in an erythropoiesis-stimulating protein (ESP) clinical trial were found on screening evaluation to have serum vitamin B_{12} concentrations below normal.[14] Historically, the only available treatments for the remaining patients with cancer and anemia were red cell transfusions and successful treatment of the underlying malignancy. Because of the well-known risks associated with transfusions and the need to conserve a limited blood supply, specific anemia treatment was limited to those patients with profound degrees of anemia (hemoglobin [Hb] levels 8 g/dL or lower) or severe cardiovascular symptoms, such as chest pain or dypsnea at rest.

The key regulator of red cell production is the glycoprotein hormone EPO. The cloning, development and introduction into clinical use of recombinant human EPO represented a watershed in anemia management. Two preparations of recombinant ESPs are currently available in the United States, epoetin alfa and the hyperglycosylated recombinant EPO, darbepoetin alfa,[15] which has a longer half-life. In randomized, placebo-controlled trials, both epoetin alfa[16–20] and darbepoetin alfa[21,22] have been shown to reduce red cell transfusion rates in patients with cancer receiving chemotherapy, and both agents are approved by the U.S. Food and Drug Administration (FDA) for this indication.

It had long been known that even mild and moderate degrees of anemia can impair function and limit productivity in otherwise healthy adults.[23] When ESPs became available and were applied to the treatment of patients with renal failure, it was shown that quality of life and productivity improved when Hb levels increased and that this relationship continued to hold even at Hb levels well above the traditional transfusion threshold.[24–27] Comparisons of data gathered during ESP treatment of anemic dialysis patients to those from anemic cancer patients suggested that the impacts of anemia and the benefits of treatment in terms of improved quality of life and energy level were quite similar in the two settings.[28] Analyses of the relationship between Hb level and energy, activity, and overall quality of life observed in large, uncontrolled series of cancer patients during treatment for anemia with epoetin alfa suggested that larger incremental increases in these patient-reported outcomes were observed with Hb increases from 11 to 12 g/dL than with any other 1-g increase.[29] Two large surveys had demonstrated that fatigue is common and often the dominant symptom in cancer patients in the United States, limiting function and quality of life.[30,31] When analysis of data from randomized trials confirmed that ESP therapy for anemia is associated with improvements in fatigue in cancer patients,[16,20,32–46] a second goal of ESP therapy beyond transfusion prevention emerged: maintenance of functionality and relief of fatigue. Although no ESP is currently approved by the FDA for relief of fatigue in anemic cancer patients, in clinical practice these agents are used with both goals in mind.

Both ESPs are currently used for the treatment of anemia in patients with cancer receiving chemotherapy, and randomized trials to date have failed to demonstrate that either agent is superior in terms of transfusion prevention or fatigue reduction when used at starting doses of epoetin alfa of 40,000 U/week and darbepoetin alfa of 200 μg every 2 weeks.[47,48] Recently, it has been shown that darbepoetin alfa is effective for the treatment of chemotherapy-associated anemia when given every 3 weeks at doses of either 300 μg[49] or 500 μg[50]; every-3-week dosing on the same day as chemotherapy seems to be as effective as asynchronous dosing.[51] Studies using initial weekly dosing followed by every-3-weekly epoetin alfa at a dose of 120,000 U have demonstrated that it is also feasible to administer this agent every 3 weeks for at least a portion of the treatment period; trials exploring less frequent dosing of this agent throughout the treatment period are in progress.[52] There is little evidence that higher doses of either ESP results in improved outcomes for cancer patients, and although it is common practice to increase doses in hyporesponsive patients, this practice has never been studied and its benefit, if any, is unknown.

It is important to bear in mind that weeks are usually required before ESP therapy increases Hb levels, and there is still a role for red cell transfusion for acute intervention in severe anemia and ominous symptoms such as chest pain and dypsnea at rest. The relatively slow onset of ESP effects has important implications for the optimal utilization of ESPs in the management of chemotherapy-induced anemia. Theoretically, when intervention with an ESP is withheld until the Hb level is less than 10 g/dL, some responsive patients will require transfusions for acute management of severe anemia before they respond to treatment. Several trials have now prospectively addressed the issue of early versus late intervention, and taken in aggregate the results strongly suggest that later intervention is associated with a substantial increase in transfusion risk.[53] Moreover, later intervention will probably result in more fatigue for cancer patients. Both of the recently developed guidelines by the National Comprehensive Cancer Network[54] and the European Organization for Research and Treatment of Cancer (EORTC)[55] support the initiation of treatment when Hb levels fall to 11 g/dL, especially when symptoms such as fatigue are manifest and continued chemotherapy is contemplated.

Once ESP treatment is initiated, it should be continued, with doses adjusted to maintain a Hb level of approximately 12 g/dL. The safety of targeting higher Hb levels has not been demonstrated (see later discussion). This titrated treatment should be continued until the chemotherapy is completed and Hb levels remain in the target range without ESP support.

Problems of Iron

When therapy with recombinant EPO is given to patients with the anemia of renal failure, an increase in platelet count is observed in some patients. Although this was initially believed to reflect an effect of EPO on megakaryocyte growth and development, it has been

shown to be due to inadequacy of iron supply to the marrow.[56] When patients are treated with ESPs, evidence of iron-restricted erythropoiesis can develop, even in the presence of apparently adequate body iron stores.[57] This phenomenon, thought to be due to an inability to mobilize storage iron rapidly enough to support the accelerated erythropoiesis associated with ESP treatment, has been termed functional iron deficiency to distinguish it from the more familiar absolute iron deficiency reflective of diminished total body iron stores. The limited quantity of oral iron that can be absorbed on a daily basis, coupled with the poor gastrointestinal tolerance of and consequently patient compliance with oral iron makes parenteral iron an attractive option for reversing functional or absolute iron deficiency during ESP therapy. For patients receiving ESPs for the anemia of chronic renal failure, treatment with parenteral iron has become a frequent adjunct that appears to enhance response and/or decrease the ESP dose required.[58] Although earlier preparations of iron dextran were associated with infrequent but potentially life-threatening anaphylactic reactions, the newer low-molecular-weight dextran preparations and the iron salts ferric gluconate and ferric sucrate are relatively safe.[59–61] A summary of the available parenteral iron preparations and practical aspects of their administration is contained in Table 45-1.

As noted previously, chronic illness such as cancer is associated with diminished absorption of oral iron and decreased accessibility of body iron stores (see Fig. 45-1) When patients with this anemia of chronic illness receive ESP therapy, it would be expected that the increased iron demand of the erythron would frequently result in functional iron deficiency. It is therefore surprising how few studies are available addressing the potential of parenteral iron to improve the response to ESPs in anemic cancer patients. In one randomized trial, iron dextran, given either as a weekly fixed dose containing 100 mg of elemental iron or as a single total dose infusion, was associated with a significantly better response to epoetin alfa than that observed with either oral iron or no iron support.[62] Similar results have been reported in trials using ferric gluconate[14] and darbepoetin alfa. These data strongly suggest that parenteral iron will play a substantially greater role in the future in the management of anemia in cancer patients.[63,64]

The most formidable challenge to rational iron support during ESP treatment of the cancer patient is the reliable detection of iron-restricted erythropoiesis in this patient population. The anemia of chronic illness is associated with reductions in serum iron and iron-binding capacity and with increases in serum ferritin levels, rendering transferrin saturation and ferritin determinations less reliable indicators of adequate iron delivery to the marrow or of body iron stores.[65] Serum levels of soluble transferrin receptors are normal in patients with the anemia of chronic disease and increased in patients with iron deficiency anemia and therefore might be useful in distinguishing the two conditions[66]; however, this laboratory parameter is not yet widely available. Moreover, soluble transferrin receptor levels are increased by ESP treatment and fluctuate during the chemotherapy cycle, making their future usefulness for monitoring iron supply to the marrow in anemic cancer chemotherapy patients during ESP therapy less promising. Similar limitations may apply to the use of the transferrin receptor-to-ferritin ratio.[67–69] Two parameters that can be reliably determined using flow cytometric techniques available in some hemogram autoanalyzers include the percentage of hypochromic red cells[70–72] and the reticulocyte hemoglobin content.[71,73–77] The relationship of these parameters to iron delivery to the marrow is not affected by the inflammatory milieu of chronic illness, ESP therapy, or chemotherapy, and both have been shown to be useful in guiding iron therapy in patients with renal failure receiving ESP therapy. When the proportion of red cells with a Hb concentration of less than 28 g/dL exceeds 5%, it can be concluded that there has been significant iron restriction of erythropoiesis over the preceding 2 weeks. Although the usefulness of the test is limited in the presence of macrocytosis, when the reticulocyte Hb content is less than 29 pg, iron-restricted erythropoiesis has occurred during the preceding 2 days. Until these two tests are more widely available and validated for monitoring iron supply during ESP therapy for chemotherapy-associated anemia, it is prudent to consider parenteral iron therapy whenever the transferrin saturation is less than 25% to 30% or when the response to ESP therapy is inadequate. If the percentage of hypochromic red cells or reticulocyte Hb content is available, these values can be integrated into the evaluation. An algorithm for the

Table 45-1 Summary of Available Parenteral Iron Preparations

Preparation	Brand Name	Administration
Low-molecular-weight dextran	Infed	Anaphylactic reactions have been reported, and an intravenous test dose of 0.5 mL infused over ≥30 sec is recommended before the first dose. Intravenous doses containing ≤100 mg elemental iron (2 mL) can be given at a rate of ≤50 mg (1 mL) per minute as frequently as daily. Infusion of the total dose (TDI) calculated as $$\text{dose (mL)} = 0.0442\ (\text{desired Hb} - \text{observed Hb}) \times \text{LBW} + (0.26 \times \text{LBW})$$ is feasible in one session.* Premedication with corticosteroids will decrease the frequency of myalgia and arthralgias following TDI.†
High-molecular-weight dextran	Dexferrum	Similar to low-molecular-weight dextran, although reported rates of adverse drug reaction are greater[60,61] and the use of this preparation with ESP therapy in cancer patients cannot be supported.
Ferric gluconate complex	Ferrlecit	A test dose is not required. TDI is not feasible because of a high frequency of adverse events when doses of >10 mL (125 mg iron) are given in a single session. Doses of up to 125 mg can be diluted in 100 mL of normal saline and infused intravenously over 1 hour, or the solution can be pushed undiluted at a rate of 1 mL (12.5 mg) per minute.
Iron sucrose	Venofer	A test dose is not required. TDI is not feasible, although doses of up to 400 mg can be administered by slow infusion over 3 hours. Doses of 100–200 mg can be given by slow intravenous push over 5 min. Alternatively, 100 mg can be diluted in 100 mL of normal saline and infused intravenously over 15 min or more.

ESP, erythropoiesis-stimulating protein.

*Auerbach M, Witt D, Toler W, et al: Clinical use of the total dose intravenous infusion of iron dextran. J Lab Clin Med 1988;111:566–570; and Auerbach M, Winchester J, Wahab A, et al: A randomized trial of three iron dextran infusion methods for anemia in EPO-treated dialysis patients. Am J Kidney Dis 1998;31:81–86.

†Auerbach M, Chaudhry M, Goldman H, Ballard H: Value of methylprednisolone in prevention of the arthralgia-myalgia syndrome associated with the total dose infusion of iron dextran: a double blind randomized trial. J Lab Clin Med 1998;131:257–260.

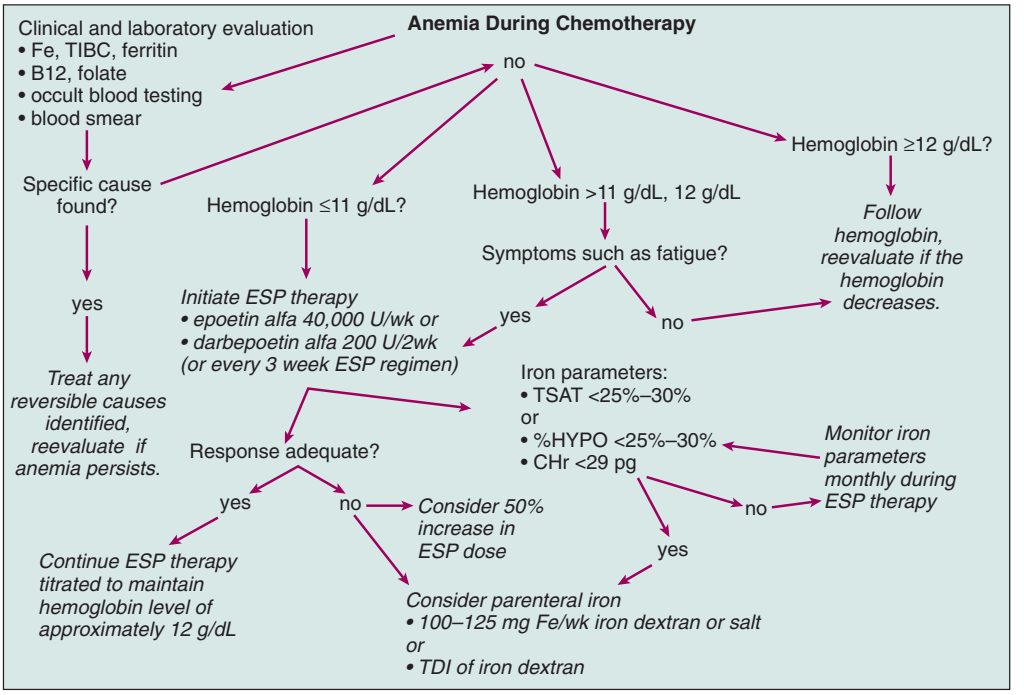


Figure 45-2 • An approach to the treatment of anemia in cancer patients. CHr, reticulocyte hemoglobin content; ESP, erythropoiesis-stimulating protein; Fe, serum iron; %HYPO, percentage of hypochromic red blood cells; TDI, total dose infusion; TIBC, total iron-binding capacity; TSAT, transferrin saturation (Fe/TIBC).

management of anemia during cancer chemotherapy is shown in Figure 45-2.

Safety of Erythropoiesis-Stimulating Proteins in Oncology

Erythropoietic agents are generally well tolerated, although there are three issues regarding their safety that merit consideration on the part of the oncologist. First, shortly after the introduction of a new formulation of epoetin alfa in Europe and Canada, an increase in pure red cell aplasia was noted in chronic renal failure patients receiving ESP therapy.[78] This complication was found to be caused by autoantibodies to EPO apparently developed in response to a subtle alteration in tertiary structure of the recombinant molecule and cross-reactive with endogenous EPO. With changes in the storage and handling of recombinant EPO, the incidence of red cell aplasia has diminished,[79] and it did not occur in patients with cancer receiving ESP therapy, possibly as a result of either the short duration of treatment in this setting or the immunosuppressive effects of chemotherapy. However, this episode has implications for the development of generic EPO preparations and serves to emphasize the importance of correct and careful storage and handling of these agents.

Recent meta-analysis of randomized, placebo-controlled trials of ESPs administered to patients with cancer during chemotherapy has demonstrated an increase in the incidence of thrombotic events in patients receiving these agents.[80,81] The overall relative risk of thrombosis associated with ESPs is 1.5 to 1.9, but it appears that, rather than the incremental risk being spread evenly over all patient groups, it is greater in patients with gynecologic malignancies and those receiving combined radiotherapy and chemotherapy treatment regimens.[82,83] The mechanism by which ESP therapy affects thrombosis risk is unknown; significant correlations of thrombotic events with Hb level, rate of Hb rise, or ESP dose have not been observed with sufficient consistency to permit a conclusion that the increased risk is due, in whole or in part, to altered blood rheology. The increase in diastolic blood pressure that can occur with the initiation of ESP treatment suggests the possibility of a direct effect on vasculature, and there is some biochemical evidence of endothelial cell and platelet activation during ESP treatment in humans.[84] There is in vitro evidence that ESPs may synergize with endogenous thrombopoietin in inducing platelet activation[85] and that platelets may be activated through interaction with young red blood cells.[86] Further studies are needed, both to elucidate the mechanism(s) of ESP-induced thrombosis and to establish rational approaches to prediction and prevention.

Recently, in two randomized trials of recombinant EPO used to prevent, rather than to treat, anemia in patients with breast cancer receiving chemotherapy[87] or with head and neck cancer undergoing radiation therapy,[88] an increase in the rate of tumor progression has been observed in the EPO-treated patients. Although there were methodologic issues in both trials, the results must be taken seriously until additional, better powered tumor progression and survival studies currently underway are completed and the final results are available. Meta-analyses of randomized, controlled trials of ESP treatment during cancer chemotherapy have not shown an increase in tumor progression or a decrease in overall survival in anemic patients treated with ESPs.[89–92] For the present, there is no evidence of decreased survival or enhanced tumor progression when anemic cancer patients receive ESPs. Until there is a much better understanding of the safety of erythropoietic agents used to prevent anemia or to normalize Hb levels in these patients, these practices cannot be condoned and a target Hb level of 12 g/dL is prudent in clinical practice.[93]

It is important to bear in mind that anemia is associated with cellular hypoxia, especially in tumor cells,[94–100] and that tumor cell hypoxia has been associated with both enhanced mutation rates and selection of more apoptosis-resistant or invasive phenotypes[97,101–117] and with resistance to both radiation[103,118–123] and chemotherapy.[124–126] Anemia is an independent negative prognostic factor across a wide range of malignancies[127]; although this is an association rather than a demonstrated cause-and-effect relationship, the observation does serve to underscore the potential importance of rational anemia management to optimal cancer care and outcomes. One critical issue that remains to be addressed is the "optimal" Hb level for cancer patients. The vasculature of solid tumors is more tortuous and disorganized than that in normal tissues; just as tumor cell oxygenation drops off more rapidly as Hb levels fall below 12 g/dL,[97,128,129] there is some evidence that oxygenation may decline again as Hb levels rise above 13 g/dL, because of the altered rheology of blood in tumor vessels.[98–100,130] If tumor cell hypoxia is an important driver of tumor progression and resistance to treatment, it may be deleterious to

patients to allow Hb levels to fall below 11 to 12 g/dL or to increase them to levels much greater than 13 g/dL. This hypothesis will be very difficult to test in clinical trials, but the answer is obviously essential to rational oncology care aimed at optimizing outcomes.

Several recent publications have reported on the detection of EPO receptor (EPO-R) protein in human cancer cells.[131–134] These studies have used immunohistochemistry with polyclonal rabbit antisera. Recent work has demonstrated that these antisera reagents also bind tumor-associated proteins other than EPO-R and are therefore not specific.[135] The issue of the potential of ESPs to directly induce proliferation or apoptosis resistance in human cancers is obviously a very important one and merits more attention in future work rigorously addressing both the specificity of techniques used in EPO-R detection and the functionality of any true EPO-R found. Thus far, in vitro work with human cancer cell lines and in vivo studies using human tumor xenografts have not consistently demonstrated any effect of ESPs on cancer cell proliferation or tumor progression.[136,137]

Polycythemia

Paraneoplastic polycythemia is an uncommon syndrome observed in a variety of human cancers[138] including renal cell carcinoma,[139,140] hepatocellular cancers,[141–143] Wilms' tumor[144,145] and, rarely, other malignancies.[146–149] The mechanism is usually ectopic production of EPO,[147,148,150–152] although increased EPO levels are not always observed[139] and other mechanisms, such as ectopic renin secretion, have been suggested.[149] In renal cell carcinomas, in which inactivating mutations of the von Hippel-Lindau gene are common, accumulation of hypoxia-inducible factor, the transcription factor driving EPO gene expression, occurs, causing polycythemia.[140] In most cases of paraneoplastic polycythemia, Hb levels are only modestly elevated, presumably as a result of compensatory decreases in EPO production by the normal kidney. Rarely, polycythemia can be severe, with hematocrit levels exceeding 50% and/or the development of symptoms such as fatigue, headache, visual blurring, and dyspnea. In these cases, it is prudent to rule out other causes of polycythemia, including hypoxemia and coexisting myeloproliferative disorders, before treating the patient with phlebotomy or surgical removal of tumor.[139]

DISORDERS OF WHITE CELLS

Neutropenia

Pathophysiology

By far the most common cause of neutropenia in oncology practice is the relatively straightforward myelosuppressive effects of cytotoxic chemotherapy and radiation treatment. Because of their relatively short life spans, neutrophil counts are particularly sensitive to the effects of recently administered chemotherapy, and nadirs of these counts are frequently observed 7 to 10 days following the administration of chemotherapy. Less commonly, antibodies to neutrophils, bone marrow infiltration with disruption of normal marrow stromal function, and splenic sequestration can play a role. Neutropenia is a critically important problem in oncology practice for two reasons. First, neutropenia is the major factor driving the risk of life-threatening infections, one of the most serious and costly toxicities of cancer treatment.[153] Second, neutropenia frequently results in substantial reductions in the delivered dose intensity of chemotherapy, causing even patients with curable malignancies to receive less than the planned, optimal antitumor treatment. For both reasons, good neutropenia management is essential in oncology care.

Although there are several glycoproteins with effects on neutrophil precursor cells including interleukin-3, granulocyte-macrophage colony-stimulating factor (GM-CSF), and macrophage colony-stimulating factor, granulocyte colony-stimulating factor (G-CSF) seems to be the primary regulator of basal and emergency neutrophil production[154–158] as well as mature neutrophil function.[2,159–161] GM-CSF plays a critical role in pulmonary homeostasis,[162–165] and a defect in this function seems to be involved in the pathogenesis of pulmonary alveolar proteinosis.[165–167] There are also negative regulatory factors of neutrophil production that are less well understood, including neutrophil elastase[168] and the *src* family kinases.[169] Neutropenia can also result from decreased neutrophil survival associated with immune destruction, sequestration, consumption at sites of infection, and the effects of inflammatory cytokines such as tumor necrosis factor.[170]

Management

PREVENTION OF INFECTION. There are two effective strategies for the prevention of infection during myelosuppressive chemotherapy: the administration of myeloid growth factors and prophylactic antibiotics. Prophylactic antibiotics have the advantage of being less costly and the disadvantage of selection of resistant bacteria. There are three myeloid growth factor preparations currently in use in clinical practice in the United States: recombinant G-CSF (filgrastim), pegylated recombinant G-CSF (pegfilgrastim), and recombinant GM-CSF (sargramostim). In randomized, controlled clinical trials in patients receiving myelosuppressive chemotherapy for nonmyeloid malignancy, filgrastim, administered as a daily subcutaneous injection at doses of 5 μg/kg, commencing the day following chemotherapy and continued until resolution of the white blood cell nadir (usually 10–12 days of treatment), has been consistently associated with a reduction in the duration of neutropenia and in the incidence of febrile neutropenia across all cycles of chemotherapy.[171–174] The results with sargramostim, usually administered at a daily subcutaneous dose of 250 μg/kg, have been less consistent, with some trials suggesting reduction in febrile neutropenia across all planned cycles,[175,176] others not demonstrating an impact on febrile neutropenia,[177–179] and some demonstrating an effect on febrile neutropenia only during the first chemotherapy cycle.[180,181] There are some studies suggesting that the myeloid growth factor can be started later during the chemotherapy cycle or given on less than a daily basis to conserve resources.[182,183] However, in the best-powered randomized trial that has been carried out addressing the issue of late initiation of myeloid growth factor treatment, initiating filgrastim treatment once neutropenia was established was not effective in reducing infection risk.[184] There are data suggesting that a daily G-CSF dose of 2 μg/kg may be as effective as 5 μg/kg in shortening the duration of neutropenia following standard dose chemotherapy.[185]

Pegfilgrastim has a longer half life than filgrastim, particularly following the administration of chemotherapy.[186] Because pegfilgrastim is cleared by neutrophils and their precursors, its half-life is prolonged by chemotherapy, and in this setting the drug is "self-regulating" with levels persisting through the postchemotherapy nadir and until the neutrophil count begins to recover. In randomized, placebo-controlled trials in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy, pegfilgrastim given as a once-per-cycle subcutaneous dose on the day following the completion of chemotherapy was at least as effective as daily filgrastim in shortening the duration of neutropenia and reducing the incidence of febrile neutropenia.[187–189] In these comparative trials, pegfilgrastim was not associated with more toxicity, and specifically bone pain was not reported more frequently with pegfilgrastim. In a randomized, placebo-controlled trial involving patients with metastatic breast cancer, pegfilgrastim was associated with a reduction in the risk of febrile neutropenia.[190] In prior studies of myeloid growth factors, the incidence of febrile neutropenia in the control group had been relatively high, at approximately 40% or greater, and myeloid growth factor treatment was associated with a 50% reduction in this risk. In the placebo-controlled trial of pegfilgrastim, the incidence of febrile neutropenia in the control group was approximately 20%, and pegfilgrastim treatment was associated with a 95% reduction in risk. This

demonstration of efficacy of myeloid growth factor therapy at lower risks of febrile neutropenia has resulted in a change in practice guidelines, acknowledging the potential of myeloid growth factors to reduce lower risks of infection.[191,192] The issue of the cost effectiveness of myeloid growth factors used to prevent febrile neutropenia remains controversial.[193–197] Largely because of its increased convenience for patients, pegfilgrastim has become the most frequently used myeloid growth factor for the reduction of infection risk during chemotherapy. The increasing popularity of every-2-week chemotherapy regimens for the treatment of early breast cancer and lymphoma made it necessary to document the safety and efficacy of pegfilgrastim with every-2-week chemotherapy. Pegfilgrastim seems to be both safe and effective when used in this setting.[198] When chemotherapy and myeloid growth factors are administered on the same day, it is possible that myeloid progenitors will be recruited into the cell cycle while cytotoxic chemotherapy is still in their environment, with myeloid growth factors having the paradoxic effect of increasing myelosuppression.[199] Because it would be more convenient for patients, there has been an interest in exploring the administration of pegfilgrastim and chemotherapy on the same day. At the time of this writing, the preliminary results of studies of synchronous pegfilgrastim and chemotherapy are conflicting, and the safety and efficacy of this approach has not been documented. In practice, it remains prudent to administer pegfilgrastim the day following the completion of chemotherapy.

In approaching the decision to administer myeloid growth factors during chemotherapy, it is appropriate for the clinician to assess the patient's risk factors for infection, including the chemotherapy regimen being used, the patient's functional status and comorbidities, age, and the presence of open wounds.[200,201] If the risk of serious infection with the planned chemotherapy is unacceptably high, it is appropriate to use a myeloid growth factor. If the chemotherapy is being given every 2 weeks or less frequently, pegfilgrastim at a fixed dose of 6 mg administered on the day following the completion of chemotherapy is appropriate management.

Myeloid growth factor therapy is associated with both an increase in neutrophil numbers and enhanced function of mature neutrophils.[202] In animal models of sepsis, the addition of G-CSF to antibiotic treatment results in improved outcomes as compared with antibiotics alone.[203] It is therefore logical to investigate the combination of antibiotics and myeloid growth factors for the prevention of infection in chemotherapy patients at particularly high risk for infection. In one large randomized trial, the addition of filgrastim to prophylactic antibiotics (ciprofloxacin and roxithromycin) for patients receiving cancer chemotherapy was associated with a reduction in infection risk as compared with antibiotics alone,[204] although the authors raise questions regarding the cost-effectiveness of filgrastim in this setting.[205] The clinician has two options in the managing a cancer chemotherapy patient at risk of infection: prophylactic antibiotics[206] and myeloid growth factors. For patients in whom the risk of infection remains unacceptably high despite prophylactic antibiotics, the addition of myeloid growth factor therapy will further reduce risk.

TREATMENT OF ESTABLISHED NEUTROPENIA OR NEUTROPENIC INFECTION. As noted previously, the initiation of myeloid growth factors treatment late in the chemotherapy cycle, after neutropenia has already occurred, may shorten the duration of neutropenia but is not associated with a meaningful reduction in infection risk.[184] There have been several randomized trials of myeloid growth factors for the treatment of chemotherapy patients with established febrile neutropenia who have not been receiving prophylactic myeloid growth factor.[207–212] Taken in aggregate, these studies document that treatment with either filgrastim or sargramostim probably shortens the duration of severe neutropenia, but for the typical patient with uncomplicated febrile neutropenia this hematologic effect does not translate into significant clinical benefit in terms of reduction in the duration of hospitalization or parenteral antibiotic use. For the exceptional patient who is quite ill and in whom a modest reduction in the duration of neutropenia may be expected to be of benefit, the initiation of myeloid growth factor treatment is prudent. For these patients, either filgrastim at a dose of 5 to 10 μg/kg per day or sargramostim, 250 to 500 $\mu g/m^2$ per day is a reasonable treatment approach.

USE OF MYELOID GROWTH FACTORS TO MAINTAIN CHEMOTHERAPY DOSE INTENSITY. When chemotherapy is being given with the intention to cure or significantly prolong life, substantial dose reductions may compromise those therapeutic goals. Studies of charts from community oncology practices suggest that the administered dose intensity of both adjuvant breast cancer chemotherapy[213] and lymphoma treatment[214] are frequently substantially lower than the published and planned regimen, suggesting that chemotherapy dose reductions and delays are common, even when cure is the therapeutic goal. In these and other studies, myeloid growth factor treatment use was highly variable between practitioners,[215] and these agents were usually not used to maintain dose intensity. Myeloid growth factors can be used to enhance the delivered dose intensity and support the administration of full chemotherapy doses on time in these settings.[216–219] In clinical practice, when there is good evidence that a given chemotherapy regimen administered in full, planned doses given on time produces an improvement in cure rate or survival, it is prudent to use myeloid growth factors rather than dose delays or reductions to manage bone marrow tolerance and infection risk.

Leukocytosis

Leukocytosis occurs in oncology practice as a result of myeloid growth factor treatment, as a result of marrow involvement with tumor with a leukoerythroblastic pattern in the peripheral blood smear, or, rarely, as a paraneoplastic syndrome. In patients with squamous cell carcinomas, a paraneoplastic leukocytosis with hypercalcemia with or without cachexia and thrombocytosis can occur[220–225] The pathophysiology of this syndrome seems to be production of parathyroid hormone-like peptides coupled with G-CSF.[226–229] Isolated production of G-CSF can occur in any tumor and produce a neutrophilic leukocytosis[230–232]; in fact, this factor was initially discovered and isolated from the conditioned medium of a human bladder cancer cell line. In general, paraneoplastic leukocytosis does not require specific therapy; knowledge of its existence is primarily important in aiding the clinician in differential diagnosis.

DISORDERS OF PLATELETS

Thrombocytopenia

Pathophysiology

The primary regulator of the platelet count in humans is thrombopoietin,[233,234] a glycoprotein that is produced primarily in the liver and cleared primarily by platelets and their precursors. Thrombopoietin induces growth and development of megakaryocytes[235]; levels fluctuate with changes in platelet count due to variations in clearance. Interleukin-11 induces a modest increase in platelet counts but is not required for thrombopoiesis[236–240]; its primary constitutive role seems to be the maintenance of female fertility.[234,241] Thrombocytopenia that is encountered in oncology practice may be due to the effects of chemotherapy, particularly with agents such as bortezomib, gemcitabine, or ifosfamide, or after multiple cycles of treatment, liver disease with decreased thrombopoietin levels, immune destruction, particularly in patients with lymphoid malignancies or infection with the human immunodeficiency virus, and sequestration. Occasionally, patients with underlying collagen vascular diseases present with thrombocytopenia due to autoantibodies directed against the thrombopoietin receptor.[242,243]

Management

The mainstay of management has been the use of platelet transfusion to treat severe thrombocytopenia and/or bleeding patients, and treatment of the underlying cause. Recombinant interleukin-11, oprelvekin, has been shown to accelerate platelet recovery following chemotherapy and to reduce platelet transfusion burden in transfusion-dependent chemotherapy patients.[244–247] Oprelvekin is approved by the FDA for this indication. However, toxicities of this agent are substantial and include: fluid shifts, cardiac arrhythmias, optic neuropathy, and the potential for anaphylaxis; these toxicities have limited the usefulness of this drug in oncology practice. Oprelvekin is administered at a dose of 50 μg/kg per day, as a daily subcutaneous injection, commencing the day following chemotherapy and continuing until the nadir has past and the platelet count has returned to 50,000 cells/μL; the drug should be stopped 2 days before the next chemotherapy dose is given. For patients with significant renal impairment, the daily dose is reduced to 25 μg/kg/day.

The cloning of human thrombopoietin was met with hope that this would represent a safer platelet growth factor for clinical practice. Both a full-length clone (rTPO) and a truncated, pegylated preparation, megakaryocyte growth and differentiation factor (MGDF)[234,238,248] were introduced into clinical trials. Therapy with either rTPO[249–252] or MGDF[253–256] was associated with an increase in platelet counts and a reduction in the duration of postchemotherapy thrombocytopenia, without fluid shifts or arrhythmias. Unfortunately, some patients treated with MGDF developed antibodies to thrombopoietin,[257] resulting in sustained thrombocytopenia, and the development of this molecule was discontinued in the United States. For reasons that are less clear, the development of rTPO has not been completed and therefore neither agent is available for prescription in this country. However, the potential of a thrombopoietin receptor agonist to provide oncologists with a rational, safe, and effective platelet growth factor was demonstrated.

Recently, two promising thrombopoietin receptor agonists have been introduced into clinical trials. AMG 531 is a peptibody that has no sequence homology with human thrombopoietin.[258–261] Eltrombopag is an orally bioavailable member of a new class of small molecule thrombopoietin receptor agonists.[262] Neither agent would be expected to induce antibodies to thrombopoietin, and the initial results with both drugs suggest that they will be both safe and effective in increasing platelet counts.

It has been shown that immune thrombocytopenic purpura is associated with a relative thrombopoietin deficiency,[263–270] presumably because of increased clearance of this factor by the expanded platelet precursor pool.[271,272] It would therefore be expected that therapy with a thrombopoietin receptor agonist would increase platelet counts in immune thrombocytopenic purpura, and treatment with MGDF has been shown to do so.[273] Both AMG 531 and eltrombopag have shown promising results in the treatment of immune thrombocytopenic purpura.[261,274] They are also being developed for the treatment of thrombocytopenia associated with liver disease, chemotherapy, and myelodysplasia. An approach to the thrombocytopenic patient in oncology practice is shown in Figure 45-3.

Thrombocytosis

When thrombocytosis is encountered in oncology practice, it is most often due to functional or absolute iron deficiency, infection or inflammation, or hyposplenism. As noted previously, thrombocytosis can occur in conjunction with leukocytosis and hypercalcemia, as a paraneoplastic syndrome, usually occurring in patients with a squamous cell malignancy. Rarely, it can occur as an isolated paraneoplastic syndrome,[275] or as a coexisting myeloproliferative disorder such as essential thrombocytosis or polycythemia vera. In most instances the thrombocytosis does not require specific intervention. Platelet counts exceeding 800 to 1,000 cells/μL warrant a workup for a myeloproliferative syndrome, and if one is present, consideration should be given to antiplatelet therapy.

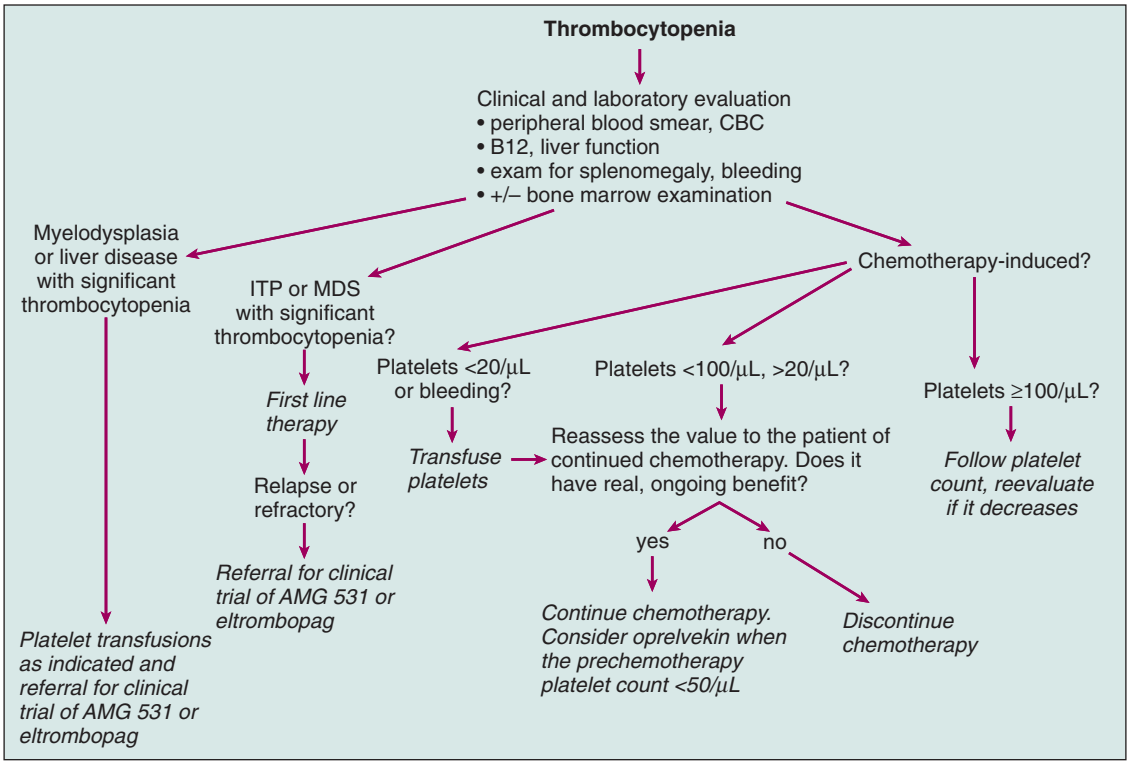


Figure 45-3 • An approach to the evaluation and treatment of thrombocytopenia in the cancer patient. B12, vitamin B_{12}; CBC, complete blood count; ITP, idiopathic thrombocytopenic purpura; MDS, myelodysplastic syndrome.

ACQUIRED MARROW FAILURE STATES

Myelodysplastic Syndrome

This syndrome is quite common in oncology practice, and usually presents as a clinically significant cytopenia. The reader is referred to Chapter 105 for a complete discussion of this topic. It is important to consider in the differential diagnosis of anemia, thrombocytopenia, or leukopenia, especially in patients who are elderly or have been treated in the past with cytotoxic chemotherapy. For the anemia that occurs in these patients, both recombinant EPO[276–285]and darbepoetin alfa[286–289] have been shown to increase Hb levels or reduce transfusion requirements in 30% to 60% of patients with low or intermediate-1 stage disease. There is some evidence that coadministration of a myeloid growth factor may enhance the erythropoietic response,[290–297] although the cost-effectiveness of this approach has been questioned.[298] It is reasonable to treat a patient with either transfusion-dependent or symptomatic anemia, who has an IPSS low or intermediate-1 stage MDS with and ESP alone or an ESP with a myeloid growth factor, and to continue this therapy if it is effective in improving clinical status and not associated with increasing thrombocytopenia or the percentage of circulating blasts.

In early clinical trials, myeloid growth factors were shown to increase the neutrophil counts[299–304] and improve neutrophil function[305,306] in neutropenic patients with MDS. Myeloid growth factors have also been used to support myelosuppressive therapy for MDS.[307,308] There is not sufficient data available to support the long-term administration of myeloid growth factors to patients with MDS, except to support the treatment of anemia. Short-term administration of myeloid growth factors to support myelosuppressive therapy or to transiently increase neutrophil counts during an infection is reasonable.

A persistent vexing problem in these patients is transfusion-dependent thrombocytopenia, and it is hoped that one of the new thrombopoietin receptor agonists will be useful and become established in this setting.

Acute Nonlymphocytic Leukemia

Patients with acute nonlymphocytic leukemia (AML) develop prolonged and profound cytopenias during induction and consolidation chemotherapy. The reader is referred to Chapter 105 for a complete discussion of this topic. The mainstay of blood cell support in this setting has been and remains transfusion of red cells and platelets. There was initial concern regarding the safety of administering hematopoietic growth factors in this setting, because of the logical concern that they may stimulate or protect the malignant clone of cells.

The initial studies of a myeloid growth factor in this setting suggested that the treatment was safe and may have promise in shortening the duration of neutropenia, the main driver of morbidity during AML treatment.[309] Subsequent studies shown that treatment with a myeloid growth factor during induction and consolidation treatment does not compromise remission rates and shortens the duration of neutropenia, with some benefit to patients, particularly those from vulnerable populations such as the elderly.[310–312] Attempts to utilize myeloid growth factors to recruit AML cells into cycle and enhance their sensitivity to chemotherapy have met with mixed results.[307,313,314]

CONGENITAL MARROW FAILURE STATES

Congenital and Cyclic Neutropenia

The congenital neutropenias are the only congenital marrow disorders for which specific treatment of the cytopenia other than transfusion has established benefit. These are rare disorders, usually diagnosed in childhood, but occasionally mild cases of cyclic neutropenia are identified in young adults. The administration of filgrastim to these patients has been shown to lead to sustained improvements in neutrophil counts and infection risk in some patients with congenital neutropenia and most patients with cyclic neutropenias.[315–317] Patients with severe congenital neutropenia frequently require relatively high doses of filgrastim,[318] and long-term treatment could be a financial burden. Fortunately, filgrastim for these patients can currently be obtained through the Chronic Neutropenia Registry (http://depts.washington.edu/registry/). For the subset of these patients with severe congenital neutropenia, with the prolonged survival that filgrastim has supported has come the development of acute leukemia in some patients. Current data suggest that these leukemias are occurring in a clone that is unresponsive to G-CSF, suggesting that they are not caused by the filgrastim treatment but instead are occurring with a higher frequency because of the prolonged survival of patients at risk for evolution to leukemia.[319–323]

CELLULAR TREATMENT OF CYTOPENIAS

Until the development of hematopoietic growth factors, the mainstay of treatment for anemia and thrombocytopenia was transfusion, and this was reserved for severe cases. Transfusions are still the preferred treatment for patients in need of a rapid increase in these blood counts. The risks of transfusion include infections (hepatitis viruses, human immunodeficiency virus, malaria, and prion-mediated illness), nonhemolytic allergic reactions, and transfusion-associated graft versus host disease. For red cell transfusions, added risks include acute and delayed hemolytic transfusion reactions and iron overload. For platelets, repeated transfusions can be associated with allo-immunization, limiting the life span and clinical benefit of future platelet transfusions. Limiting the side effects of these transfusions is an important part of oncology practice; key strategies include: (1) Transfuse only when medically necessary (Hb < 8 g/dL or severe anemia symptoms, platelets <20,000 cells/μL, or bleeding). (2) Discontinue all chemotherapy that is not associated with a benefit that more than offsets the risk of transfusions. (3) Limit the numbers of blood donors to whom the patient is exposed (use of single-donor platelets for instance). (4) Use white cell filters whenever possible. (5) Use irradiated blood products, especially when transfusing patients who have received bone marrow transplants or transfusing blood from related donors.

When granulocyte transfusions were initially attempted before the development of myeloid growth factors, they were unsuccessful, as a result of the relatively low dose of granulocytes that could be harvested and to the transmission of cytomegalovirus infection to compromised recipients. More recent trials of granulocyte transfusions harvested from filgrastim-treated donors have yielded promising results,[324,325] although in the postmarrow transplant setting human lymphocyte antigen incompatibility may limit the benefit.[326] It is reasonable to consider granulocyte transfusions, if the institution has the capability, in the acute management of neutropenic patients who have infection that is not responding to antibiotics and who are not expected to recover granulopoiesis in the near future.

Therapy with myeloid growth factors is associated with the mobilization of progenitor cells into the peripheral blood progenitor cells which can be harvested by leukapheresis. As compared with traditional bone marrow, autologous peripheral blood progenitor cells used to support high-dose chemotherapy are associated with more rapid engraftment.[327–332] Use of peripheral blood progenitor cells has made it possible to modify the dose of progenitor cells given and aided attempts to manipulate the graft.[333–336] Engraftment following these transplants is sufficiently rapid that the benefit of additional myeloid growth factor given during this recovery phase is relatively small, though safe and probably cost-effective.[337–339] The use of peripheral blood progenitor cells as an alternative to marrow is feasible in the allogeneic transplant setting as well.[340–351] Finally, myeloid growth factors can be used to mobilize and harvest dendritic cell precursors for cancer vaccine applications.[352]

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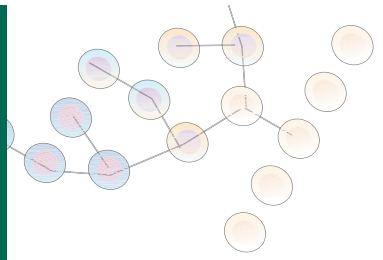
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46 Diagnosis, Treatment, and Prevention of Cancer-Related Venous Thrombosis

Steven R. Deitcher

SUMMARY OF KEY POINTS

- Venous thrombosis has an incidence of approximately 15% in cancer patients.
- Venous thrombosis has been identified in up to 50% of cancer patients at autopsy.
- Cancer patients with venous thrombosis at diagnosis have a worse prognosis.
- Cancer patients are more likely to have large, proximal, persistent, and recurrent venous thromboses.
- Venous thrombosis can complicate the management of any and all types of cancer.
- Malignant tumors can cause venous stasis, vascular injury, procoagulant accumulation, natural anticoagulant deficiency, and impaired endogenous fibrinolysis.
- Plasma markers of coagulation activation do not predict development of thrombosis but can assist in prognosis determination.
- Cancer-associated venous thrombosis is likely underdiagnosed because of inadequate physician suspicion, underutilization of proper objective tests, and the asymptomatic nature of many thrombotic events.
- Clinical diagnosis alone lacks sensitivity and specificity for acute venous thrombosis.
- Diagnostic imaging studies such as duplex ultrasound and lung scintigraphy may provide more false-positive and false-negative results in cancer patients.
- Cancer patients might not respond to or benefit from standard approaches to venous thrombosis management, as do patients without cancer.
- Tendencies toward thrombocytopenia, osteopenia, malnutrition, brain metastasis, hepatic metastasis, and bleeding all complicate thrombosis care in cancer patients.
- Cancer patients are more likely to manifest heparin resistance and warfarin failure and to have limited venous access to support therapeutic anticoagulant monitoring.
- Low-molecular-weight heparins are safe and effective for the short- and long-term management of venous thrombosis in cancer patients.
- Low-molecular-weight heparins are associated with lower recurrent thrombosis rates than is oral warfarin during up to 6 months of anticoagulation therapy.
- Low-molecular-weight heparins may affect survival in subgroups of cancer patients with and without venous thrombosis.
- Diagnosis should be sought by using duplex ultrasound with magnetic resonance venography, computed tomography, and venography reserved for confirmation.
- D-dimer testing is likely less sensitive and less specific in cancer patients.
- Low-molecular-weight heparins are likely to be the best drugs to minimize recurrence rates without significantly increasing bleeding complication rates.
- It is prudent to continue anticoagulation for a minimum of 6 months and until all cytotoxic therapy has been completed and no evidence of active cancer is found.
- Duplex ultrasound and venography are the mainstay of upper extremity thrombosis diagnosis.
- Upper-extremity thrombosis should be treated like lower-extremity thrombosis, with the exception of catheter-related thrombosis, which may require catheter removal.
- Helical computed tomography (CT) and lung scintigraphy are both means of objectively diagnosing pulmonary embolism. Helical CT is preferred when the chest radiograph is not normal.
- Pulmonary embolism should be treated in a similar fashion and on the basis of the same principles as lower extremity deep venous thrombosis.
- The risks of thrombolysis should be reserved for patients with hemodynamically unstable pulmonary embolism.
- Incidental findings of intra-abdominal vein thrombosis on standard CT scans should be confirmed by a more appropriate diagnostic method.
- Treatment should be the same as that for lower-extremity deep venous thrombosis.
- Superficial venous thrombosis may herald the diagnosis of cancer and should be treated with local measures such as warm compresses and analgesics.
- Patients with superficial thrombophlebitis may harbor asymptomatic deep venous thrombosis, so screening duplex ultrasound is recommended.
- Inferior vena cava filters should be reserved for patients with acute lower extremity or pelvic thrombosis who have a contraindication to anticoagulation or documented anticoagulation failure.
- Inferior vena cava filters may reduce the incidence of all pulmonary embolism in the short run after diagnosis of a deep vein thrombosis but may also increase the risk of recurrent deep vein thrombosis in the long run.
- Greater attention to prevention would reduce our need to provide thrombosis treatment to this challenging population of at-risk patients.
- Pharmacologic prophylaxis is safe and effective in a wide range of surgical and medical oncology patients and settings.

INTRODUCTION

Venous thromboembolic disease (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a common but often underdiagnosed and underappreciated clinical problem in oncology that results in significant patient morbidity and mortality. Timely and accurate diagnosis of VTE is imperative because of the unacceptable outcomes associated with a misdiagnosis. VTE diagnosis based on clinical grounds alone is unreliable, so physicians should select an appropriate objective diagnostic test to confirm or refute their clinical suspicions. Compression duplex ultrasound remains the first-line imaging test for both suspected upper and lower extremity DVT. Magnetic resonance venography (MRV) is a valid alternative when ultrasound is inconclusive. Helical (spiral) computed tomography (CT) and ventilation-perfusion (V/Q) lung scintigraphy remain the first-line imaging modalities for suspected acute PE. Spiral CT is preferred in cases of obvious pulmonary or pleural-based disease. Indeterminate initial studies should prompt performance of additional tests, possibly including the "gold standard": contrast venography and pulmonary angiography. Evidence to date suggests that D-dimer assays might be unreliable in excluding VTE in cancer patients.

Standard VTE treatment practices, including the use of intravenous unfractionated heparin (UFH) for initial anticoagulation, oral warfarin for chronic anticoagulation, and the prescription of only 3 to 6 months of total therapy, might not be optimal in the setting of active cancer and ongoing anticancer therapy. Challenges of VTE management in cancer patients include heparin resistance due to excess circulating acute-phase proteins, increased recurrence rates during and after standard-intensity warfarin therapy, limited venous access to support therapeutic monitoring, and anticoagulation intensity-independent increased bleeding rates during anticoagulation. Bleeding during anticoagulation is of particular concern in patients with disease- or chemotherapy-related thrombocytopenia, central nervous system (CNS) involvement with cancer, and recent invasive procedures. Low-molecular-weight heparins (LMWHs) have been shown to be at least as effective and safe for initial anticoagulation compared with UFH in patients with acute VTE and have gained popularity in the setting of VTE in cancer. The recently approved synthetic antifactor Xa pentasaccharide, fondaparinux, may also be an acceptable option in the cancer patient. LMWHs and fondaparinux have the advantage of less nonspecific protein binding, subcutaneous weight-based dosing without the need for monitoring in most cases, and less heparin-induced thrombocytopenia. Recent trials demonstrated efficacy superiority of select LMWHs in place of oral warfarin for long-term anticoagulation in the cancer patient.

The challenges of proper VTE diagnosis and treatment in the cancer patient are best averted by expanded use of VTE-prevention modalities. Trials have shown that medically ill patients have a high risk of VTE similar to that of high-risk surgical patients. LMWHs and fondaparinux have emerged as the premier pharmacologic agents for VTE prevention. Extended prophylaxis beyond acute-care hospitalization has a role in minimizing the total risk of VTE development. Newer oral agents may improve on the efficacy, safety, and convenience of LMWH-based prophylaxis.

This chapter addresses the diagnosis, treatment, and prevention of VTE specifically in the cancer patient population.[1–3] The potential for anticoagulant therapy to enhance cancer patient survival and the role of anticoagulants that are in development to affect cancer patient care also are addressed.

EPIDEMIOLOGY OF CANCER-ASSOCIATED VENOUS THROMBOEMBOLISM

The incidence of clinically apparent (i.e., symptomatic) VTE in cancer patients has been reported to be approximately 15%, with reported incidence rates ranging from 3.8% to 30.7%.[4,5] This is in comparison to an age-adjusted VTE incidence of 2.5% in the general population.[6] The wide range of reported incidence rates likely reflects differences in patient tumor histology, investigator level of VTE clinical suspicion, and VTE confirmation methods. Nonetheless, studies have uniformly demonstrated a higher incidence of VTE in patients with cancer of a specific organ compared with those with benign diseases of the same organ. In a Scandinavian retrospective study of more than 63,000 patients hospitalized for acute VTE, 18% had been diagnosed with cancer before the VTE.[7] A large Medicare registry study revealed that cancer patients were diagnosed with VTE at the time of initial hospitalization at a higher rate than were patients admitted for nonmalignant disorders.[8]

The risk of postoperative DVT in cancer patients after general surgery is as high as 36% and exceeds that of noncancer surgical patients by 1.5- to 3.6-fold.[9] VTE detection rates as high as 50% in autopsy series have been reported but might still not represent the true magnitude of VTE-related illness in cancer.[10] Limiting factors in the proper antemortem detection of VTE in cancer patients include an inadequate index of suspicion by many clinicians and idiosyncrasies of VTE diagnostic modalities, as will be described later.[2] The former is exacerbated by the fact that VTE is often asymptomatic, and even when symptoms are present, they are often nonspecific or mistakenly attributed to the underlying malignancy itself.

NATURAL HISTORY OF CANCER-RELATED VENOUS THROMBOEMBOLISM

Thrombosis may be a presenting feature of occult malignancy, a life-threatening component of early or advanced cancer, a harbinger of cancer recurrence, and a complication of anticancer therapy itself. Patients with cancer diagnosed at the time of acute VTE detection have a greater likelihood of distant metastases at the time of diagnosis compared with individuals without concomitant VTE [44% versus 35.1%; prevalence ratio: 1.26; 95% confidence interval (CI): 1.13 to 1.40] and significantly lower 1-year survival rates (12% versus 36%; $P < 0.001$).[7] VTE presentations in the cancer patient include symptomatic DVT, PE, superficial thrombophlebitis, central venous access device–associated thrombosis, arterial thrombosis, and nonbacterial thrombotic endocarditis. Asymptomatic VTE, although often viewed as clinically insignificant, can evolve into symptomatic VTE, and both may be particularly deleterious in the cancer patient by promoting vascular endothelial growth factor expression.[11] VTE is likely to be a common proximate cause of death in patients with solid tumors.

The natural history of VTE in the cancer patient differs significantly from that in the noncancer patient. Cancer patients are more likely than noncancer patients to present with proximal DVT.[12] Cancer patients have been shown to present with a greater initial thrombus burden, to experience greater clinical deterioration despite anticoagulant therapy, and to have less venographic improvement in response to standard treatment when compared with noncancer patients.[12]

The perception of many physicians has been that cancer patients have a greater propensity toward recurrent VTE, both during and after completion of a course of antithrombotic therapy.[13] Recent studies have substantiated the high risk of recurrence. A population-based retrospective study of 404 individuals showed that people with cancer have a twofold to threefold increased risk of recurrent VTE.[14] Antineoplastic therapy further accentuated the risk of recurrence in the cancer patient population. The 5-year cumulative incidence of recurrent VTE was 21.5% in a prospective cohort study of 738 consecutive patients with a first or second DVT.[15] The relative risk of recurrence was 1.97 in patients with cancer. Another prospective study reported an overall VTE recurrence rate of 10.3% in 58 patients with cancer compared with 4.7% in 297 patients without cancer.[16,17] The fact that cancer patients had a higher recurrence rate while

reportedly "therapeutically" anticoagulated suggests that the usual target international normalized ratio (INR) range of 2.0 to 3.0 might not be therapeutic at all. Prandoni and colleagues[18] recently reported a 20.7% (95% CI: 15.6–25.8) 12-month incidence of recurrent VTE in cancer patients with VTE compared with a 6.8% (95% CI: 3.9–9.7) 12-month incidence of recurrence in noncancer patients with VTE. The greatest risk of recurrent VTE was observed in patients with genitourinary tract, gastrointestinal tract, and lung cancers and predominantly during the first month of anticoagulation.[18]

A recent analysis of malignancy status-specific and INR range-specific VTE recurrence rates revealed that patients with VTE and malignancy ($n = 261$) have an overall thromboembolism recurrence rate of 27.1 events per 100 patient years compared with 9 recurrent events per 100 patient years in individuals with VTE and no malignancy.[19] In both patient populations, the rate of VTE recurrence was greatest during periods when the INR was 2.0 or less (the lower boundary of the target INR range). Patients without cancer had 15.9 recurrent events per 100 patient years during such periods of suboptimal warfarin anticoagulation, whereas patients with underlying malignancy had a VTE recurrence rate of 54 events per 100 patient years during similar periods of inadequate anticoagulation. Thus, it can be surmised that cancer patients are exquisitely sensitive to periods during which the INR is less than a target level of 2.0 to 3.0.

Venous thrombosis has been traditionally associated with aerodigestive tract adenocarcinomas involving the pancreas, stomach, and lungs. A closer look at DVT and PE incidence rates for different tumor histologic types, though, reveals that ovarian carcinoma, primary brain tumors, and lymphomas are among the four tumor types with the highest VTE rates.[8] This is of particular interest, considering that hematologic malignancies such as lymphoma have traditionally been viewed as coagulation-inert histologic types and management of malignancy-associated VTE has traditionally been viewed as the sole domain of the solid tumor medical oncologist. Thrombosis can affect the clinical course of all histologic types, of all stages, of all grades, and during any and all treatments.

Table 46-1 Venous Thromboembolic Event Risk Factors in Cancer Patients

TUMOR-ASSOCIATED PROCOAGULANT MECHANISMS IN THE CANCER PATIENT
Extrinsic vascular compression and invasion
Tissue factor production
Cancer procoagulant production
Sialic acid residue support of nonenzymatic factor X activation
Promotion of tissue factor production by monocytes and endothelial cells
Accentuated platelet activation and accumulation
Expression of phosphatidyl serine, which supports prothrombinase and tenase activity
Inflammation-mediated increases in factor VIII, fibrinogen, and von Willebrand factor
Impaired endogenous fibrinolysis due to excess levels of plasminogen activator-inhibitor 1
Acquired deficiencies of natural anticoagulants
NONTUMOR-ASSOCIATED PROCOAGULANT MECHANISMS IN THE CANCER PATIENT
Central venous access devices
Antineoplastic agent–induced platelet activation and endothelial cell damage
Antiangiogenesis therapy
Anthracycline-induced congestive heart failure
Immobility

CANCER-ASSOCIATED HYPERCOAGULABILITY

Different tumors of different extent, in different patients, with different comorbidities, and different inherited hypercoagulable states likely promote the development of VTE by different combinations of tumor-associated and non-tumor-associated procoagulant mechanisms (Table 46-1). Solid tumor–mediated extrinsic vascular compression and invasion can obstruct venous return, resulting in blood flow stasis, endothelial cell injury, and coagulation activation.[1] Tumor cells can directly promote thrombin generation by producing tissue factor, expressing the coagulation factor X activator known as cancer procoagulant, and by displaying surface sialic acid residues that can support nonenzymatic factor X activation. Tumor cells also can indirectly promote thrombin generation by eliciting tissue factor expression by monocytes and endothelial cells. Selected tumors may mediate an accentuation of platelet activation and accumulation, whereas other tumor cells may express surface phospholipid species such as phosphatidyl serine, which can support prothrombin and factor X activation.

Malignancy-associated inflammation can result in increased concentrations of acute-phase proteins such as factor VIII, fibrinogen, and von Willebrand factor. Whether in the setting of active malignancy or in otherwise normal patients, elevations of these acute-phase proteins are associated with an increased risk of thrombosis.[20] Tumor-associated increases in plasminogen activator inhibitor-1 can result in impaired endogenous fibrinolysis.[21] Malignancy-associated acquired deficiencies of natural anticoagulant proteins such as protein S have been described.[22] Baseline profiling of cancer patients with acute VTE found elevated levels of factor VIII, von Willebrand factor, plasminogen activator inhibitor-1, and the dilute Russell viper venom time (a specific lupus anticoagulant assay) in 17%, 71%, 34%, and 36% of patients, respectively. Deficiency of protein C, protein S, and antithrombin were found in 36%, 56%, and 6% of patients, respectively.[3] This study underscored the multifactorial pathogenesis of cancer-associated thrombosis. The variation between different cancer patients with regard to their hypercoagulable tendencies makes specific prognostic testing for cancer-associated thrombosis challenging and of limited clinical usefulness.

Although coagulation-marker testing may fall short of being able to predict which cancer patients are most apt to develop VTE, such testing might assist in prognosis determination. Beer and colleagues[23] performed a prospective evaluation of the predictive value of coagulation-activation markers for survival in cancer patients. They quantified thrombin-antithrombin complex, prothrombin fragment 1+2 (F1+2), D-dimer, fibrin monomer, and fibrinopeptide A. In general, patients with active malignancy, those with active adenocarcinoma, those with extensive disease, and those who died during follow-up (mean: 17 months) had significantly higher marker levels. A comparison of first and fourth quartiles in active cancer patients revealed significant odds ratios of death for fibrin monomer, thrombin-antithrombin complex, D-dimer, F1+2, and fibrinopeptide A of 4.1, 2.8, 2.7, 2.4, and 2.4, respectively.[23]

Non-tumor-derived VTE risk factors in the cancer patient include central venous catheters and antineoplastic agents themselves. Central venous catheters are the major risk factor for upper-extremity DVTs in the cancer patient population and can precipitate superior vena cava (SVC) thrombosis and SVC syndrome.[24,25] These DVTs may result in PE, cause catheter dysfunction, and serve as a nidus for catheter-related infection.[26] Antineoplastic agents themselves, including cytotoxic chemotherapy, selective estrogen-receptor modulators, antiangiogenic agents, and especially combinations of these drugs, are associated with an increased risk of VTE.[1,27] Thalidomide, an

immunomodulating and antiangiogenic agent, has been linked to VTE in patients with multiple myeloma, especially when combined with anthracycline antineoplastic drugs. Theorized mechanisms of antineoplastic agent-induced hypercoagulability are varied and have not been completely elucidated. Medical complications of cancer and its therapy (including congestive heart failure, major infection, pathologic fractures, extended immobility, and pre-existent VTE) can exacerbate the tendency to venous thrombosis. Common inherited risk factors for VTE such as factor V Leiden and prothrombin G20210A have not been found to be more prevalent in cancer patients with thrombosis than in the general population.[3]

CHALLENGES OF VENOUS THROMBOEMBOLISM DIAGNOSIS IN CANCER PATIENTS

Selection of the most appropriate and effective treatment for a patient's cancer depends on a timely and accurate assessment of tumor histology, disease stage, and patient performance status. In similar fashion, prescription of the most appropriate and effective treatment for a cancer patient's disease- or treatment-associated VTE is dependent on a timely and accurate diagnosis. Failure to surpass a minimum threshold of anticoagulant intensity [activated partial thromboplastin time (aPTT) >1.5 times control for intravenous UFH] within 24 hours of acute DVT diagnosis is associated with a markedly increased risk of late thrombosis recurrence.[28] It thus makes sense that patients with acute DVT in whom a proper diagnosis is significantly delayed should have similar suboptimal outcomes. Classification of venous thromboses as superficial versus deep and distal versus proximal, differentiation between acute and remote thrombotic events, and distinction between a venous filling defect and extrinsic vessel compression are required to ensure that patients are appropriately treated.

It has long been recognized that the diagnosis of DVT and PE made on clinical grounds alone is notoriously unreliable. The severity of limb edema and pain is often unrelated to the location and extent of DVT, whereas the symptoms of PE vary depending on the degree and extent of vessel occlusion, as well as on a patient's cardiopulmonary reserve. The classically described Homans' sign (calf discomfort triggered by passive dorsiflexion of the foot) has been found in only 8% to 60% of symptomatic patients with confirmed DVT and in up to 40% of symptomatic individuals without DVT.[2] Half of the patients with clinically suspected DVT do not have the diagnosis confirmed by objective testing.[2] Data from the Prospective Investigation of PE Diagnosis (PIOPED) Study revealed that dyspnea, pleuritic chest pain, cough, and lower-extremity edema, among other symptoms, were present in similar frequencies (30%–70%) among patients with or without angiographically confirmed PE. In cancer patients, the clinical diagnosis of DVT or PE is unlikely to be more accurate and may be even less accurate.

VTE is often asymptomatic or minimally symptomatic, and even when symptoms are present, they are nonspecific and can be easily attributable to the underlying malignancy. Surveys have shown that constitutional symptoms such as weakness and fatigue occur in 50% to 70% of patients in hospice or palliative care,[2] whereas dyspnea and cough occur in 25% to 50% of such patients and in more than 40% of patients with advanced cancer, respectively. The incidence of upper-extremity (UE) edema due to lymphedema in women after axillary lymph node dissection and/or radiotherapy for breast cancer has been reported to range from 6% to 30%.[2] In a series of more than 2000 palliative care patients with different types of pain syndromes, 22% and 11% had lower-extremity (LE) and UE pain, respectively.[2] None of these symptoms is unique to a particular disorder, and the etiology may be related to the underlying malignancy itself, a venous thrombotic complication, or both. Likewise, worsening dyspnea in a patient with primary or metastatic lung cancer; limb edema in a patient with bulky pelvic, axillary, or mediastinal tumor or adenopathy; and abdominal pain after colectomy or abdominal hysterectomy in patients with colon cancer or uterine cancer are a few examples in which VTE may mimic, be confused with, or be coexistent with the underlying disease. Therefore, awareness that VTE is a common complication of cancer and possession of a high index of suspicion are necessary to avoid missing a diagnosis of DVT or PE.

Compared with noncancer patients, those with cancer have a greater risk of bleeding while receiving oral anticoagulant therapy and a threefold to sixfold higher rate of recurrent VTE.[18,19] Therefore, the diagnosis of DVT and PE should not be made on clinical grounds alone, and objective diagnostic confirmation is mandatory. Failure to make a timely diagnosis of VTE can result in significant morbidity and mortality because of recurrent VTE, whereas empirical anticoagulation therapy without a confirmed diagnosis may expose the cancer patient to unnecessary and potentially avoidable risk in the absence of any tangible benefit. With the exception of cases of superficial thrombophlebitis, any signs and symptoms that are suggestive of VTE should be used not as diagnostic endpoints, but simply as a compelling reason to pursue further testing.

Although the methods that are used to confirm the diagnosis of DVT or PE in noncancer and cancer patients are the same, particular features of the underlying malignant disease may, in some circumstances, reduce the accuracy of those diagnostic methods. The presence of direct tumor invasion of blood vessels or extrinsic venous compression by a bulky tumor or adenopathy, as well as rare primary vascular tumors, may all lead to false-positive diagnoses of DVT. Likewise, primary pulmonary artery tumors and compression of a pulmonary artery or vein by tumor or adenopathy may result in impaired regional pulmonary perfusion. This might be interpreted as "high probability" or "indeterminate" for PE on V/Q lung scanning (V/Q scan) or can lead to interpretative pitfalls on helical (spiral) CT. Prior radiation therapy to the chest wall also might lead to false-positive perfusion defects on V/Q scan, whereas fluctuating platelet counts might impair the ability of nuclear scintigraphy methods to detect LE-DVT. Moreover, increased baseline D-dimer levels in some cancer patients and impaired endogenous fibrinolysis in others might at least in part explain the limitation of D-dimer assays in excluding VTE in this population. Thus, an understanding of the limitations inherent in the various diagnostic modalities and of the circumstances in which these modalities may result in false-positive and false-negative diagnosis are of the utmost importance. Because the cancer population may be subject to a higher rate of nondiagnostic, false-positive, and false-negative noninvasive tests than are patients without cancer, it is possible that many cancer patients will require more than one diagnostic test to prove or rule out conclusively a diagnosis of DVT or PE.

Historically, the diagnostic approach to DVT and PE has shifted from purely clinical (insensitive and nonspecific) and angiography-based (invasive) to being dependent primarily on noninvasive or minimally invasive imaging techniques. These newer methods are less accurate to detect calf, pelvic, and intra-abdominal DVT, as well as PE in the subsegmental branches of the pulmonary artery. As a consequence, a number of clinical management models have been reported and validated.[2,29] These models combine clinical assessment (pretest probability of DVT or PE) with noninvasive imaging tests and D-dimer assays, with the goal of reducing the need for repeated or invasive confirmatory tests but without compromising patient safety. The majority of patients who were included in these studies had a low-to-moderate pretest VTE risk, and the combination of a low pretest risk with a negative imaging test and a normal D-dimer has been shown to exclude DVT or PE safely. However, in these studies, patients with high pretest clinical probability of VTE and a negative or indeterminate initial test result almost invariably went on to undergo additional testing, including invasive studies.

Given the high incidence of VTE and the impact of such a diagnosis on cancer patients, it is our opinion that all patients with active cancer should be considered as having a "high pretest probability" or "high clinical suspicion" in models that rely on pretest clinical assessment. In addition, management models that include currently available D-dimer assays as part of the risk assessment should not be used to aid in the diagnosis of VTE in the cancer population for reasons that will be discussed later in this chapter.

CHALLENGES OF VENOUS THROMBOEMBOLISM TREATMENT IN CANCER PATIENTS

DVT and PE warrant prompt institution of antithrombotic therapy to effectively prevent thrombus propagation, embolization, and recurrence; to ameliorate patient symptoms; and to allow thrombus organization, plasmin-mediated lysis, and restoration of venous patency.[30] Specific therapy and duration of therapy in the cancer patient depend on thrombus location (e.g., iliofemoral DVT versus calf DVT), thrombus extent (e.g., massive PE versus subsegmental PE), underlying thrombosis "trigger" (e.g., major abdominal surgery versus thalidomide-based therapy for multiple myeloma), and patient comorbidities (e.g., self-limited thrombocytopenia and hemorrhagic brain metastases). Despite the special attention afforded the cancer patient with regard to other disease-related complications, such as hypercalcemia, nausea, fatigue, and pain, the recommended and most commonly used treatment of VTE in patients with active cancer is not significantly different from the regimens that are prescribed to VTE patients without malignancy. Ideally, unique features of individual cancer patients, the natural history of VTE in cancer patients, and cancer patient response to various anticoagulant agents should be noted and should affect our approach to VTE treatment in this group.

Heparin Resistance

Cancer patients, like others with acute illness and inflammatory processes, have a propensity toward heparin resistance. "True" heparin resistance causes inadequate anticoagulant and antithrombotic responses from what would otherwise be perceived as an adequate dose of heparin. Some have deemed a requirement of more than 35,000 units of heparin per 24-hour period, regardless of patient weight, to reflect this form of heparin resistance.[31] With true heparin resistance, both a measurement of anticoagulant activity such as the aPTT and a measurement of antithrombotic activity such as the antifactor Xa activity assay demonstrate inadequate degrees of heparin activity. True heparin resistance most likely results from the nonspecific binding of heparin to mononuclear white cells, vascular endothelial cells, and acute-phase protein such as histidine-rich glycoprotein, vitronectin, and platelet factor-4, resulting in an inadequate quantity of free or antithrombin-bound heparin.[1] Another potential cause of heparin resistance in the cancer patient is disseminated intravascular coagulation–associated antithrombin deficiency.

Cancer patients can also manifest an "apparent" heparin resistance characterized by dissociation between the aPTT and heparin assays.[31] In these patients, the aPTT may be normal or near normal, while the antifactor Xa activity assay reveals a heparin activity level within the therapeutic range of 0.3 and 0.7I U/mL. Simply escalating the dose of heparin to achieve the desired aPTT without checking a heparin assay can result in a pronounced bleeding risk. Dissociation between the aPTT and heparin concentration likely reflects elevated levels of factor VIII that can shorten the in vitro aPTT without affecting the antithrombotic actions of the drug.

Warfarin Failure

Warfarin failure is the term that is often used to describe the development of an objectively documented recurrent VTE, despite an apparently stable INR between 2.0 and 3.0. Such an event suggests that this degree of anticoagulation was insufficient to neutralize the sum of hypercoagulable stimuli in a given individual. Warfarin failure must be distinguished from early thrombus extension during the initial period of acute parenteral anticoagulation. Underlying cancer, because of its potent prothrombotic nature, is often suspected in the setting of warfarin failure. Patients with VTE and known cancer are at an increased risk for recurrent thrombosis compared with noncancer patients.[12,14,15,18,19,32] This may reflect cancer-associated hypercoagulability in excess of warfarin-induced anticoagulation or reflect less ability to keep cancer patients within the target INR range. Cancer patients have been shown to spend less time (43.3%) within the target INR of 2.0 to 3.0 than do control noncancer patients (56.9%) during standard warfarin anticoagulation.[1] It is likely that cancer patients spend approximately 30% of their time with an INR of 2.0 or less and 30% of their time with an INR of 3.0 or more. The remaining time is probably spent in transit between these out-of-target extremes. As Hutten and associates have shown,[19] cancer patients are at a particularly high risk for recurrent VTE when the INR is 2.0 or less. An increased frequency of therapeutic monitoring does not necessarily improve outcome in cancer patients with VTE.[1,17]

Malnutrition

Cancer patients can experience periods of excess catabolism, anorexia, corticosteroid-induced appetite stimulation, antimicrobial therapy, parenteral nutrition, and compromised hepatic function.[33] Each can affect either vitamin K supply or metabolism and thus vitamin K antagonist (i.e., warfarin) therapy. These often unpredictable aspects of the cancer patient may contribute to the greater degree of INR instability during oral warfarin therapy. An increasing number of cancer patients are relying on over-the-counter dietary supplements and herbal preparations to compensate for malnutrition, alleviate symptoms, and complement traditional anticancer therapy. Unfortunately, these preparations may contain vitamin K, vitamin K analogs, or compounds that are known to affect warfarin anticoagulation (e.g., Ginkgo biloba). Reliance on acetaminophen-containing narcotic and nonnarcotic analgesics also can affect the toxicity of oral warfarin.[34]

Thrombocytopenia

Thrombocytopenia in the cancer patient can develop for a multitude of underlying reasons. Some patients have decreased platelet production secondary to myelosuppressive chemotherapy or marrow infiltration by tumor. Others have peripheral consumption of platelets due to hypersplenism associated with Hodgkin's disease and lymphoproliferative disorders or congestive splenomegaly due to thrombosis and/or portal hypertension associated with extensive hepatic metastases. Other patients experience peripheral platelet destruction due to autoimmune clearance associated with low-grade non-Hodgkin's lymphomas and chronic lymphocytic leukemia, whereas others have consumption due to disseminated intravascular coagulation. Thrombocytopenia that develops during heparin administration for VTE prevention or treatment should be considered heparin-induced thrombocytopenia (HIT) until proven otherwise.[35] Detection of HIT in patients with pre-existent cancer-associated thrombocytopenia can be difficult. Because cancer patients may possess antiheparin:platelet factor-4 antibodies even in the absence of clinical HIT, testing should be reserved for the patient with new thrombocytopenia that develops during or shortly after a heparin exposure and without another possible explanation.[3]

The safety of administering systemic anticoagulation for any duration of time in patients with thrombocytopenia is likely dependent on the etiology and degree of thrombocytopenia, the presence or absence of concomitant platelet hypofunction, the location of primary and metastatic tumors, platelet transfusion responsiveness, and the

anticipated duration of thrombocytopenia. No exact cutoff value has been established below which it is uniformly unsafe to administer heparin, LMWH, or oral anticoagulation. The fact that diverse cutoff values of 20,000/μL, 50,000/μL, and 100,000/μL are often used reflects a lack of physician consensus about the bleeding risk associated with thrombocytopenia and a wide range of comfort levels with anticoagulation in this setting. Recent cancer-associated VTE treatment trials comparing long-term dalteparin and enoxaparin with standard warfarin anticoagulation used minimum platelet counts of 75,000/μL and 50,000/μL, respectively, as study inclusion criteria.[3,36] On the basis of thromboelastographic assessment of hematologic malignancy patients, some patients with chemotherapy-induced thrombocytopenia may even have evidence of overwhelming hypercoagulability.[37]

Bleeding Tendencies

Contemporary evidence on the risk of anticoagulation-related hemorrhage in cancer patients remains conflicting; primarily retrospective studies support a greater bleeding risk in cancer patients, and mainly prospective cohort studies suggest that the risk is no greater than that in noncancer patients. The true risk most likely depends on the temporal relationship between anticoagulation and major invasive and surgical procedures, concomitant thrombocytopenia or antiplatelet medication consumption, and the location and vascularity of cancerous lesions. Erosive, friable endobronchial, gastrointestinal, and genitourinary lesions are more likely to be prone to bleed during anticoagulation than at baseline. As in the noncancer population, older cancer patients and those with anemia, diabetes, recent myocardial infarction, renal insufficiency, history of stroke, and history of gastrointestinal bleeding are most likely at a greater risk for warfarin-associated bleeding.[38,39]

A large, retrospective, population-based study from the Mayo Clinic demonstrated that malignancy was associated with major bleeding with a relative hazard ratio of 4.26 (95% CI: 1.61–11.33) in univariate analysis and 4.07 (95% CI: 1.53–10.87) in multivariate analysis.[40] A recent retrospective analysis of 1303 patients enrolled in two large randomized, prospective trials comparing intravenous UFH with subcutaneous LMWH for initial VTE management also demonstrated a greater likelihood of major bleeding in patients with VTE and cancer.[19] The incidence of bleeding was 4.2, 2.1, and 13.3 events per 100 patient years in all patients, noncancer patients ($n = 1039$), and cancer patients ($n = 264$), respectively. The bleeding rate correlated with anticoagulation intensity in the noncancer patients but was independent of INR level in the cancer patient group. The major limitation of this study was the small total number of major bleeding events ($n = 12$). One small, prospective study revealed an odds ratio of 2.4 for bleeding in cancer patients with VTE compared with noncancer patients with VTE.[41] A recently published study revealed that the 12-month cumulative incidence of major bleeding in cancer patients treated for symptomatic DVT was 12.4% (95% CI: 6.5–18.2) compared with 4.9% (95% CI: 2.5–4.1) in treated noncancer patients ($P = 0.015$).[18] Two other prospective studies have shown that the overall and major bleeding rates noted in DVT patients with and without cancer were not significantly different. Prandoni and coworkers[16,17] reported major bleeding rates of 3.4% and 3.0%, respectively, in VTE patients with and without cancer during the first 3 months of oral anticoagulation. Overall bleeding rates in the same groups were 8.6% and 9.8%, respectively.

A recently published analysis, the largest study to date, suggests that the risk of major bleeding in cancer patients receiving oral warfarin after acute VTE is increased approximately sixfold and independent of the INR intensity.[19]

Osteopenia and Lytic Skeletal Lesions

Cancer patients, those affected by multiple myeloma and breast carcinoma in particular, are often plagued by osteopenia, lytic skeletal lesions, and pathologic fractures. Immobility as a result of chronic bone pain and fractures may promote DVT. Prolonged administration of UFH can result in osteopenia and osteoporosis in up to 30% of noncancer patients, is associated with a 1% to 2% incidence of vertebral fracture, and certainly has the potential to exacerbate cancer-associated bone loss.[42] Experimental models have demonstrated simultaneous increases in osteoclast activity and decreased osteoblast activity in response to UFH exposure. Less osteoclast activation is observed in response to LMWH exposure.[43]

Primary and Metastatic Central Nervous System Tumors

Patients with primary brain tumors and metastatic CNS lesions are at an increased risk for developing VTE and are viewed by many as having an absolute contraindication to systemic anticoagulation.[44] CNS hemorrhage is of particular concern in patients with highly vascular brain metastases, such as those from choriocarcinoma, melanoma, and renal cell carcinoma. VTE in these cancer patients may prompt the placement of an inferior vena cava (IVC) filter instead of systemic anticoagulation. Controlled CNS metastases (i.e., after radiation therapy) are often viewed as being less prone to bleed. Available limited data from several series suggest that the risk of spontaneous intracranial bleeding in patients with primary brain tumors (mainly glioblastoma multiforme) and CNS metastases might not be greater in those who receive anticoagulant therapy compared with those not receiving anticoagulant therapy.[45] A major limitation of these reports is that most studied patients received prophylactic, and not treatment, intensity of UFH or warfarin. Careful dosing and frequent therapeutic monitoring are imperative, especially in patients receiving concomitant phenytoin therapy. In the ONCENOX study, six patients with primary CNS cancer, CNS lymphoma, or CNS metastases were treated per protocol without developing minor or major bleeding or a recurrent VTE.[3,46]

Limited or Compromised Venous Access to Support Therapeutic Monitoring

Initial management of acute VTE with continuous infusion UFH requires short-term but consistent intravenous access and frequent phlebotomy for therapeutic monitoring. With regard to oral warfarin, a narrow therapeutic index and wide intraindividual and interindividual variations in degree of anticoagulation achieved with a particular dose warrant frequent therapeutic monitoring and dose adjustment. Both UFH and warfarin therapeutic monitoring are associated with cost, patient inconvenience, and patient discomfort. Because of fluctuations in nutritional status and unpredictable fluctuations in the INR in cancer patients, frequent INR monitoring (once to twice weekly) might be required. The need for frequent phlebotomy and intravenous-access insertion can result in a cancer patient having limited to no usable peripheral veins. Venous sampling via central venous catheter for therapeutic monitoring may result in false prolongations of the aPTT and prothrombin time due to sample contamination.

Persistent Hypercoagulability

Active residual cancer of any extent and active anticancer therapy of any form represent persistent hypercoagulable states. The magnitude of the prothrombotic stimulus may actually intensify with time as disease burden and metastases mount. As in other persistent hypercoagulable states, including congenital deficiencies of natural anticoagulants and chronic antiphospholipid antibodies, active malignancy and ongoing therapy should prompt an extended duration of anticoagulant therapy.

CANCER PATIENT RESPONSE TO LOW-MOLECULAR-WEIGHT HEPARINS

Several prospective, randomized, controlled trials have demonstrated the efficacy and safety equivalency of intravenous, aPTT-adjusted, UFH and subcutaneous, weight-based LMWH for the treatment of acute LE-DVT.[47–51] The major advantage of subcutaneous LMWH is that it can be self-administered at home, without the need for therapeutic monitoring. This translates into a significant reduction in mean hospital length of stay compared with UFH initial therapy (1.1 versus 6.5 days).[47] Patients may be begun on LMWH in the hospital and then discharged in an accelerated fashion to continue the bridging to oral warfarin or may be treated exclusively in the outpatient setting. A reduction in length or avoidance of hospitalization may be of particular importance in immunocompromised cancer patients who are prone to nosocomial infections. LMWH treatment does require once- or twice-daily subcutaneous injection but does not require phlebotomy for therapeutic monitoring in the majority of patients. Cancer patients might be even more adept and accepting of subcutaneous injections than are noncancer patients because of experience with self-administered hematopoietic growth factor therapy.

LMWHs are associated with less HIT than is UFH, especially in heparin-naive patients.[52] This statistic makes LMWHs particularly attractive for VTE prevention and treatment in cancer patients with disease- and chemotherapy-related thrombocytopenia in whom HIT detection may be hindered by pre-existent low platelet counts. LMWHs are associated with less osteopenia in animal models and could offer a theoretical treatment advantage in cancer patients with osteolytic lesions.[43] Osteoporosis, though, has been reported with long-term LMWH use, and an increase in spontaneous fracture has been described during long-term LMWH exposure in pregnant women.[42]

LMWHs display less nonspecific binding to acute-phase plasma proteins, platelets, mononuclear leukocytes, and endothelial cells.[51] Active cancer patients treated with LMWHs are thus theoretically less likely to experience true heparin resistance. LMWHs also have been shown to promote a small but significantly greater degree of thrombus regression and restoration of venous patency than does UFH.[12] Disadvantages of LMWHs include the inability to be completely reversed by protamine sulfate in the event of bleeding or unanticipated surgery. LMWH accumulation in patients with severe (creatinine clearance: <30 mL/min) renal insufficiency precludes its predictable use in cancer patients with renal failure.

Two early meta-analyses of randomized controlled clinical trials comparing LMWHs with UFH in patients with acute DVT demonstrated a reduction in short-term mortality in cancer patients treated with LMWH (relative risks: 0.44 and 0.33, respectively).[53,54] More recent meta-analyses demonstrated an overall survival advantage in VTE patients treated with LMWHs compared with UFH.[55,56] Much of this observed advantage was derived from a single trial comparing tinzaparin with UFH.[49,57] A total of 97 cancer patients were included in the analysis, 47 of whom received tinzaparin. Death rates at 3 months were 10.6% in those randomized to tinzaparin and 28% in those who received UFH ($P = 0.041$).[49] Proposed mechanisms for the survival advantage include tumor growth retardation, metastasis prevention, tumor neovascularization inhibition, and fatal VTE prevention.[58] If real, the survival advantage associated with LMWH is likely due to a combination of effects. Properly powered prospective randomized trials are needed to confirm the meta-analysis and preclinical experimental observations.

Kakkar and associates[59] reported on a randomized, placebo-controlled trial of dalteparin, 5000 anti-Xa units daily, in patients with advanced solid tumor malignancy without evidence of underlying thrombosis, with the primary objective of determining effect on survival at 1 year. The Kaplan-Meier survival estimates at 1, 2, and 3 years after randomization were 42%, 19%, and 13%, respectively, for placebo and 45%, 27%, and 21%, respectively, for the dalteparin group ($P = 0.29$). Although no significant early impact on survival was seen, a post hoc analysis of those surviving more than 17 months demonstrated survival estimates at 2 and 3 years after randomization of 56% and 37%, respectively, for placebo versus 77% and 59%, respectively, for dalteparin ($P = 0.04$).[59] A recent analysis of the impact of dalteparin on survival in patients with thromboembolism reported no difference in mortality at 12 months between those treated for 6 months with dalteparin and those treated with oral warfarin (56% versus 58%).[60] A post hoc subgroup analysis suggested that long-term treatment-intensity dalteparin might reduce mortality in cancer patients with nonmetastatic disease and acute VTE compared with oral anticoagulation with warfarin (20% versus 35%). In a double-blind study in 302 patients with metastatic or locally advanced solid tumors, 6 weeks of subcutaneous nadroparin resulted in a median survival of 8 months in comparison to 6.6 months in those treated with placebo.[61] The major benefit from the nadroparin was observed in the prespecified subgroup of patients with a life expectancy of greater than or equal to 6 months at enrollment.[61] In a study of 84 patients with limited or extensive stage small cell lung cancer randomized to chemotherapy alone versus chemotherapy plus once-daily dalteparin 5000 U for 18 weeks, both progression-free survival (10 months versus 6 months) and overall survival (13 months versus 8 months) were longer in the chemotherapy plus LMWH arm ($P = 0.01$ for both).[62] Larger-scale trials are needed to confirm these findings.

LMWH preparations differ in manufacturing methods, mean molecular weight, molecular weight distribution, effect on tissue factor pathway inhibitor expression, and possibly clinical effect. In part, for these reasons, LMWHs should not be viewed as interchangeable, and favorable data on one preparation do not necessarily apply to any other.

LOWER-EXTREMITY DEEP VENOUS THROMBOSIS MANAGEMENT

Diagnosis of Lower-Extremity Deep Venous Thrombosis in Cancer Patients

The LE deep venous segments that can be affected by thrombosis include, in ascending order from the ankle, the paired calf veins (posterior tibial, anterior tibial, peroneal, gastrocnemius, and soleal), the popliteal, superficial femoral, deep femoral (profunda femoral), common femoral, and external and common iliac veins. The superficial and deep femoral veins converge to form the common femoral vein in the proximal thigh. Despite its terminology, the superficial femoral vein is actually a deep vein, not a superficial vein; isolated superficial femoral vein thrombosis should therefore be treated as a DVT and not viewed as a superficial thrombophlebitis. Currently available diagnostic methods for the objective diagnosis and exclusion of lower-extremity DVT include several imaging techniques and biochemical assays (Table 46-2). Although contrast venography remains the gold standard method for lower-extremity DVT diagnosis, duplex ultrasound is the most appropriate initial diagnostic test owing to the combination of accuracy, noninvasiveness, short examination time, portability of newer equipment, and lower cost.

Contrast Venography

Contrast venography has the ability to outline the deep venous system after the injection of radiopaque contrast medium into a dorsal foot vein. A central deep venous access (e.g., popliteal or common femoral vein) is usually necessary for adequate opacification of the pelvic (iliac) veins.[2] Available contrast agents include ionic and nonionic iodinated aromatic-acid salts of varying osmolality and CO_2. CO_2 may provide an uneven intravascular distribution but is not nephrotoxic and is quite inexpensive to use. The presence of a constant intraluminal filling defect in at least two distinct projections is the

Table 46-2 Tests for the Diagnosis or Exclusion of Upper and Lower Extremity Deep Venous Thrombosis

Contrast venography
Duplex ultrasound
Impedance plethysmography
Venous-phase helical computed tomography
Magnetic resonance venography
[^{125}I]-fibrinogen scan
[^{99m}Technetium]-apcitide scintigraphy
D-dimer semiquantitative and quantitative assays

most reliable diagnostic criterion for acute DVT.[63] Nonfilling of one or more venous segments proximal to the site of injection, abrupt termination of the column of contrast at a constant site, and the presence of flow in collateral veins are indirect signs that can be caused by artifacts. Artifacts can result from improper contrast administration and flow artifacts, particularly at the common femoral vein level, when nonopacified blood from the deep femoral vein mixes with opacified blood from the superficial femoral vein.[2]

The greatest limitations of venography are primarily related to its invasiveness and need for intravenous injection of contrast medium. The procedure also requires meticulous technique as well as experienced radiologists to avoid misinterpretation of inadequate studies. Unsuccessful venograms have been reported in 2% to 20% of examinations, because of either inadequate technique with failure to outline a venous segment properly or inability to perform the test,[2] and interobserver disagreement ranges from 4% to 21%.[63] Although the deep femoral (profunda) vein is visualized only 50% of the time, isolated deep femoral vein DVT appears to be very rare.[2] Indeterminate findings also may result from the lack of visualization of the calf veins, which may occur because of nonfilling of the calf veins either because of improper test technique or occlusive DVT.[2] Other limitations include the fact that examinations cannot be performed at the bedside and are restricted to the limb where venous access has been gained.

Complications of contrast venography include postprocedure DVT in approximately 2% to 10% of examinations and superficial thrombophlebitis at the site of contrast injection.[2] Rare complications include tissue necrosis due to extravasation of contrast during injection and hypersensitivity reactions.

Nonfilling of the iliac veins during contrast venography in cancer patients with known or suspected pelvic masses neither rules in nor rules out DVT. Such finding may be due to DVT, extrinsic venous compression by tumor, or both. In one study, 51% of all high-grade non-Hodgkin's lymphoma patients who were diagnosed with VTE also had concomitant pelvic venous compression by bulky lymphadenopathy.[2] In this situation of nonvisualization of the pelvic veins, an alternative imaging method, such as CT or magnetic resonance imaging (MRI), should be considered to assess for the presence of extrinsic vascular compression.[2]

Duplex Ultrasound

A venous duplex ultrasound study combines real-time B-mode ultrasound with pulsed-color Doppler flow imaging. The former provides direct visualization of the vessels and surrounding tissues, whereas the latter detects blood flow when the emitted ultrasound energy is reflected by red blood cells and sensed at a different frequency (Doppler shift).[2] The lower-extremity deep venous segments that can routinely be examined by duplex ultrasound include the very distal external iliac, common femoral, superficial femoral, popliteal, and calf veins.

The diagnosis of DVT with duplex ultrasound relies on a combination of the following findings: vein noncompressibility, vein dilatation, visualization of echogenic intraluminal material, and lack of spontaneous and augmented blood flow.[2,64] The most widely used and reliable, validated criterion is lack of vein wall compressibility on B-mode ultrasound. The other criteria are relatively inaccurate when applied individually. Most important, however, the use of these criteria in combination does appear to increase the accuracy of the examination.[65]

Although the sensitivity and specificity of compression duplex ultrasound for acute femoropopliteal DVT have been reported to be quite high in symptomatic patients (92%–100% and 94%–100%, respectively), this method lacks adequate sensitivity when used for screening of asymptomatic individuals.[2] In addition, duplex ultrasound has been reported to lack adequate sensitivity (36%–95%) for the detection of calf DVT, despite comparable specificity (89%–100%).[2,65] A number of conditions can impair the ability of duplex ultrasound to detect calf vein thrombi, such as edema, large calf size, and the presence of open wounds, surgical bandages, or even large collateral veins, all of which lead to a high rate (10% to 40%) of inadequate examinations that impair interpretation.[2] This technical inadequacy is the likely explanation for the lower sensitivity of duplex ultrasound to detect calf DVT. Two studies comparing the sensitivities of all (adequate plus inadequate) calf examinations versus adequate-only examinations have shown sensitivities that increased from 73% and 85% to 95% and 99%, respectively.[2] In addition, the use of color Doppler has been shown to facilitate the localization and visualization of the calf veins, yielding fewer indeterminate examinations than venography in patients with isolated calf DVT.[2] Lack of color Doppler examination might explain the lower accuracy in early studies. Visualization of the calf veins by duplex ultrasound also has been enhanced by the use of an intravenous contrast agent, which in a small series led to reduction in the number of inadequate calf vein examinations from 55% to 20%.[66] Contrast ultrasound has the potential to improve the accuracy of this diagnostic modality even further.

The advantages of duplex ultrasound include the facts that it is noninvasive and that bilateral examinations can be performed in a timely fashion. Unlike venography, duplex ultrasound might also increase the overall diagnostic yield of calf examinations because of its ability to detect extravascular pathology, such as hematomas and Baker's cysts.[2]

Pitfalls of duplex ultrasound include the risk of false-positive incompressibility of the distal superficial femoral vein at the level of Hunter's (femoral) canal; the risk of setting the color gain inappropriately high, leading to "color-blossoming" that might obscure nonocclusive DVTs; and the potential to miss a DVT diagnosis in patients with duplicate venous systems or with the rare cases of isolated deep femoral DVTs.[2]

An important limitation of duplex ultrasound is the inability to perform compression maneuvers adequately in the veins above the inguinal ligament (common iliac and proximal external iliac veins). The lowest accuracy of duplex ultrasound was reported by a study that attempted to visualize and interpret iliac vein compression maneuvers routinely.[65] Although these venous segments may be visualized and interrogated for the presence of spontaneous blood flow and normal respiratory phasicity, these criteria are insensitive because normal flow may be present in cases of nonocclusive DVT. Only the distal 3 cm of the external iliac veins could be adequately visualized by one study, partial visualization of the external and common iliac veins being accomplished in 79% and 47% of the examinations, respectively.[2] Therefore, a negative LE duplex ultrasound does not rule out iliac vein thrombosis, whereas attempts to diagnose iliac vein DVT by compression ultrasound alone may lead to a number of false-positive DVT diagnoses. Conversely, the use of Doppler flow

imaging may assist in the diagnosis of pelvic vein DVT or extrinsic compression: In a study of 37 cancer patients with leg edema and negative compression ultrasound, a 100% correlation was found between a monophasic waveform in the common femoral vein by spectral Doppler and the presence of either more proximal, not directly visualized DVT or extrinsic pelvic venous compression by a mass.[67] However, this finding does not differentiate iliac DVT from extrinsic venous compression by tumor.

A controversial issue is the need for bilateral LE duplex ultrasound in patients with unilateral LE symptoms. Six studies have shown rates of isolated DVT in the asymptomatic, contralateral leg ranging from 0% to 5%, with another 2% to 22% of patients having bilateral DVT despite unilateral symptoms.[2,68,69] One study that was performed exclusively in cancer patients found that 1% of patients had DVT in the asymptomatic contralateral leg, and an additional 7% had bilateral DVT.[68] A further study that used bilateral duplex ultrasound examinations in patients with unilateral symptoms found that eight (53%) patients who had DVT in the asymptomatic limb had active cancer, and in seven of those eight patients, symptoms developed in the previously asymptomatic limb during the first month of anticoagulation therapy.[69] Of these seven, four were diagnosed with a new DVT in a previously unaffected venous segment, but three were found not to have a new DVT, illustrating the relevance of detecting symptomless DVT in the cancer population.[69] Lack of documentation of acute DVT in an asymptomatic limb could negatively affect patient management by leading to a false diagnosis of recurrent VTE and "warfarin failure" in future duplex ultrasound examinations. Thus a cancer patient should always undergo bilateral duplex ultrasound examinations for suspected LE-DVT, even if the symptoms are unilateral.[2]

Another limitation of duplex ultrasound is that the accuracy of compression maneuvers to detect recurrent DVT is uncertain. The ability to distinguish acute from remote (chronic) DVT is hampered by the fact that 50% of patients with prior LE-DVT will have some degree of residual vein obstruction.[2] Old, organized thrombi may appear hyperechoic and heterogeneous sonographically, but this might not help to differentiate acute from remote DVT.[64] Unless the new DVT is found in a previously normal venous segment, compression ultrasound could be unreliable. Although serial duplex ultrasound evaluation of vein diameters and comparison with prior ultrasound measurements has been proposed as an alternative means of diagnosing recurrent DVT (with an incremental increase in vein diameter being attributed to recent DVT),[70] this method has not been validated by a large-scale prospective comparison with contrast venography. It also is unclear whether the same protocol would be as useful in cancer as in noncancer patients.

Contrast-Enhanced Computed Tomography

CT has not been validated as a method for DVT diagnosis (i.e., no accuracy studies have been performed comparing it with the gold standard contrast venography, no interobserver variability has been formally assessed, and no validation (outcome) studies have been performed).[2,71] Therefore, it should not be routinely used for this purpose. However, because cancer patients frequently undergo body CT as a component of initial tumor staging, assessment of cancer recurrence and surveillance, or a workup for persistent fever, physicians are frequently faced with the dilemma of an incidental finding of filling defects involving the pelvic veins or common femoral veins. In this situation, it is imperative that the diagnosis be confirmed by a validated method, such as duplex ultrasound or contrast venography.[2]

The use of combined helical CT pulmonary angiography with CT venography (venous phase CT) of the pelvis and proximal legs has been studied as a means to detect DVT in patients with suspected PE.[2] The examination starts 2 to 4 minutes after contrast is injected for helical CT of the chest, and images are obtained either at 4- to 5-cm intervals or contiguously from the diaphragm to the ankles. Criteria for acute DVT include visualization of a filling defect in an opacified vein, a nonopacified segment between normally opacified proximal and distal segments, venous dilatation (when compared with the contralateral side), and venous wall ring enhancement. The sensitivity and specificity range from 71% to 100% and 87% to 100%, respectively, when compared with duplex ultrasound.

Advantages of helical CT venography include its ability to visualize the IVC, portal, ovarian, and renal veins, as well as the soft tissues, to detect the presence or absence of intra-abdominal DVT and concomitant extrinsic venous compression.[72] No formal studies have been performed to assess the usefulness of this modality in differentiating acute from chronic DVT, although possible signs of chronicity include venous wall calcification and "shrunken" vessels. A disadvantage of helical CT venography is that it requires the use of iodinated contrast and if contiguous image acquisition is used the effective radiation dose is exponentially increased. This possibility has led some to state that the use of this technique should be limited in individuals younger than 30 years.[2]

False-positive DVT diagnoses have occurred because of flow artifacts, particularly at the level of the calf and pelvic veins and also because of muscle hematomas and abscesses.[72] False-negative findings have occurred in cases of extensive bilateral DVTs, in which no normal vein enhancement in either limb is seen, so no contralateral normal vein is present for comparison, and a case of a thrombosed left-sided IVC that was misinterpreted as necrotic lymph nodes.

Although observational and accuracy studies of helical CT venography do exist, no comparisons with venography and no clinical outcome studies have been performed. The appropriateness of this technique in cancer clinical practice is unclear at this time.

Magnetic Resonance Venography

Magnetic resonance angiography (MRA) to evaluate the venous system (MRV) can be performed with time-of-flight and phase-contrast techniques. The most commonly used is an axial, two-dimensional time-of-flight technique based on standard two-dimensional gradient-echo imaging, with or without gadolinium enhancement.[2] The observed signs of acute DVT as seen by MRV include total obstruction of the vein and venous dilatation, as well as the presence of a rim of increased signal intensity surrounding the thrombus. Although one study suggested that the pattern of rim enhancement was useful in differentiating acute from chronic DVT, no correlation with contrast venography was performed.[73]

MRV has been shown to be as accurate as duplex ultrasound for diagnosing LE-DVT in three prospective studies that compared the two methods with contrast venography (100% sensitivity, 95%–100% specificity). False-positive diagnoses occurred in patients with extrinsic compression of the iliac veins. The method is less accurate when evaluating for calf DVT.

Advantages of MRV include the lack of need for intravenous iodinated contrast and the ability to assess for the presence of extrinsic venous compression when combined with soft tissue-weighted MRI and the fact that, unlike duplex ultrasound, MRV can routinely visualize the pelvic veins.[74] Disadvantages include cost and lack of wide availability.

Nuclear Scintigraphy

Activated platelets expressing glycoprotein IIb/IIIa (GP IIb/IIIa) that become incorporated into acute evolving venous thromboses serve as the physiologic target for [^{99m}technetium]-apcitide (AcuTect) in the diagnosis of LE-DVT. A phase III prospective clinical trial in 280 patients who underwent both [^{99m}Tc]-apcitide scintigraphy and contrast venography demonstrated an overall sensitivity and specificity of 76% and 73%, respectively, for imaging acute LE-DVT.[75] Higher sensitivity and specificity (91% and 84%, respectively) were seen in

patients with their first DVT event and signs and symptoms of less than 3 days' duration, and false-negative diagnoses occurred more frequently in patients with calf DVT.[75] Because [^{99m}Tc]-apcitide is a functional rather than anatomic diagnostic imaging method, it has the theoretical potential to discern acute from chronic (without activated platelets) thrombus. In cancer patients, thrombocytopenia of any etiology and tumor-associated platelet activation likely limit the usefulness of this technique for the diagnosis of acute LE-DVT.

[^{125}I]-Fibrinogen leg scanning was used mostly in the 1970s and early 1980s for the diagnosis of acute LE-DVT. It was highly sensitive (90%) for calf DVT but insensitive (60%–80%) for DVT involving the proximal veins because the isotope is a relatively low gamma emitter and because the bladder frequently contained radioactive urine. The use of this method has largely been abandoned because of its attendant risk of transmissible viral diseases and the wide availability of duplex ultrasound. In addition, [^{125}I]-fibrinogen leg scanning was never used alone for the diagnosis of acute DVT because it can take up to 72 hours to become positive. Other radiolabeled peptides under investigation for DVT diagnosis include [^{99m}Tc]-DMP 444 and [^{99m}Tc]-FDB (fibrin domain of fibronectin). A radiolabeled antibody targeted against the DD domain of fibrin also is under development.

D-Dimer

D-dimer is a cross-linked degradation product resulting from the plasmin-mediated lysis of cross-linked fibrin. Three readily available techniques are used to assay D-dimer: enzyme-linked immunosorbent assays (ELISA), plasma-based latex agglutination, and whole-blood hemagglutination (WBA) assays. Qualitative latex agglutination assays are relatively inexpensive to perform, widely available, and rapidly performed but are not sufficiently sensitive to exclude VTE. Both ELISA and WBA assays have been prospectively studied in clinical management trials and found to have high negative predictive values in outpatients with suspected VTE.[2] These studies suggest that lack of D-dimer elevation combined with a negative noninvasive imaging test reliably excludes LE-DVT, but D-dimer elevation alone neither rules in nor rules out thrombosis. In general, these D-dimer assays are excellent screening tests for VTE, but the negative predictive value of the WBA D-dimer assay has been shown to be lower in cancer patients (78.9%) than in those without cancer (96.5%).[76] Thus, it is not as useful for excluding VTE in cancer patients. Conversely, false-negative D-dimer results have been described in cancer patients with PE and baseline impaired endogenous fibrinolysis due to excessive levels of plasma plasminogen activator inhibitor-1.[21] More recently, however, both a subgroup analysis of a retrospective cohort study and a prospective cohort study showed that the negative predictive value of a new latex agglutination assay remained high and reliably excluded DVT in cancer patients.[77,78] However, confidence intervals in the latter study were somewhat wide; therefore, additional studies are needed to determine whether the D-dimer assay is truly reliable in excluding DVT in the cancer population.[78] Until conclusive evidence from larger studies is available, D-dimer assays should not be used to exclude VTE in cancer patients.

Lower-Extremity Deep Venous Thrombosis

Patients with clinically suspected LE-DVT or an incidental finding of DVT on CT should be initially evaluated with duplex ultrasound. A nondiagnostic ultrasound examination should prompt further evaluation with contrast venography. If the patient is known to have a pelvic mass and has either no opacification of the pelvic veins by venography or a monophasic Doppler signal during sonographic interrogation of the common femoral vein, MRV or CT should also be considered to rule out concomitant extrinsic venous compression. Given the high rate of VTE recurrence and "warfarin failure" in cancer patients, it is advisable to pursue contrast venography in cases of suspected DVT recurrence in which the duplex ultrasound does not detect a new DVT in a previously normal segment. Unfortunately, however, venography also has limitations in diagnosing recurrent DVT involving previously involved venous segments, and neither MRV nor CT has been validated or conclusively shown to differentiate acute from chronic DVT reliably.

Treatment of Lower-Extremity Deep Venous Thrombosis in Cancer Patients

General guidelines for VTE management have been published elsewhere.[30,79] Specific, evidence-based guidelines for VTE management in the cancer population are lacking. Analysis of recently completed and ongoing clinical trials could provide the basis for future detailed guidelines. In the meantime, cancer patients with VTE should be treated in a manner that takes the previously described unique features, subgroup analyses of prospective, randomized VTE treatment trials, and recently completed LMWH trials into account (Box 46-1).

Box 46-1. DEEP VENOUS THROMBOSIS ANTICOAGULANT TREATMENT IN THE CANCER PATIENT

Initial Phase Anticoagulant

- Acute treatment with a parenteral agent (unfractionated heparin or low-molecular-weight heparin) should be initiated in the inpatient or outpatient setting.
- Intravenous unfractionated heparin should initially be dosed on the basis of patient weight and adjusted to achieve an activated partial thromboplastin time that corresponds to an antifactor Xa activity level of 0.3 to 0.7 U/mL.
- Subcutaneous low-molecular-weight heparins should be dosed on the basis of patient weight, avoided in individuals with calculated or actual creatinine clearance rates less than 30 mL/min, and not monitored in the majority of cases.
- When using enoxaparin sodium for initial phase anticoagulation, I prefer to use 1 mg/kg twice daily instead of 1.5 mg/kg once daily.
- I prefer using a low-molecular-weight heparin rather than unfractionated heparin to facilitate outpatient management and because of evidence suggesting a possible survival advantage.

Subacute Phase Anticoagulant: Up to 6 Months

- Subacute management can consist of oral warfarin with a target international normalized ratio (INR) between 2.0 and 3.0 or once daily subcutaneous low-molecular-weight heparin without therapeutic monitoring.
- Warfarin therapy requires a minimum of 4 days overlap with the parenteral agent used for initial phase anticoagulant and can be difficult to maintain between an INR of 2.0 and 3.0 because of variable nutrition, concomitant medications, and hepatic dysfunction.
- I favor low-molecular-weight heparin because of excellent patient compliance, reduced on-treatment thrombosis recurrence rates, and a possible survival advantage.

Chronic Phase Anticoagulant: Beyond 6 Months

- Patients with persistent hypercoagulability from their malignancy, anticancer therapy, antiphospholipid antibody, or underlying inherited prothrombotic state such as deficiency of a natural anticoagulant have their subacute phase therapy extended until the persistent hypercoagulable state has resolved or completed.
- Attenuated intensity therapy with warfarin (INR 1.5 to 2.0) and low-molecular-weight heparin (primary prophylaxis intensity) are not recommended for patients with active malignancy and those receiving anticancer therapy.

Initial Anticoagulation Therapy

The mainstay of pharmacologic therapy for VTE in all patients remains anticoagulation. Initial (acute-phase) therapy typically consists of parenteral UFH or LMWH for a minimum of 4 days and until a stable, target intensity of warfarin treatment has been achieved.[79] Treatment with UFH or LMWH should be begun as soon as possible after VTE diagnosis unless an absolute contraindication exists. Whenever possible, therapy should actually begin as soon as VTE is suspected and even before diagnostic tests are obtained. A delay in achieving a therapeutic intensity of initial parenteral therapy may negatively affect a patient's long-term VTE recurrence rate.[28,80] Weight-based initial dosing of UFH (80-U/kg bolus followed by 18 U/kg/hr) with subsequent dose adjustments based on a standardized nomogram achieves a therapeutic aPTT within 24 hours of treatment commencement.[81] Because of problems with heparin resistance, greater than usual doses of UFH may be required in the cancer patient.

LMWH may be preferred for both initial inpatient and outpatient treatment of acute VTE in the stable cancer patient for the safety, efficacy, and survival reasons already discussed. The optimal LMWH preparation, dose, and dosing frequency remain to be determined. Acute DVT treatment safety and efficacy data exist for enoxaparin, 1.5 mg/kg once daily, and enoxaparin, 1.0 mg/kg twice daily, in cancer patients.[82] No statistically significant difference in VTE recurrence rate was observed between patients randomized to initial treatment with intravenous UFH, once-daily enoxaparin, and twice-daily enoxaparin. Of the 47 cancer patients randomized to the twice-daily dosing (total daily dose of 2.0 mg/kg), 3 (6.4%) developed recurrent VTE compared with 6 (12.2%) of the 49 cancer patients allocated to once-daily dosing (total daily dose of 1.5 mg/kg). This trend has led many physicians to advocate twice-daily dosing of enoxaparin for initial VTE treatment in cancer patients. The observed difference probably reflects the difference in total daily dose rather than an inherent inadequacy of once-daily dosing. This fact is important to note in considering the use of once-daily LMWHs such as tinzaparin and dalteparin. Tinzaparin, 175 IU/kg once daily, has an excellent safety and efficacy track record in cancer patients.[49] Dalteparin is given at a dose of 200 IU/kg up to a maximal dose of 18,000 IU once daily. Whether these or higher total daily doses of these two agents given as divided twice-daily injections in cancer patients would be superior to the standard dosing is not known. Concerns about underdosing cancer patients weighing more than 90 kg with standard-dose dalteparin might be justified.

Despite the excellent safety profiles of LMWHs in cancer and noncancer patients alike, initial inpatient UFH treatment may be preferred in patients who are at very high risk for bleeding and in those who are likely to require urgent invasive procedures. Such patients include those with recent surgery, gastrointestinal lesions, any past gastrointestinal or neuraxial bleeding, significant anemia, and marked thrombocytopenia. At present, cancer patients with severe renal dysfunction and most weighing more than 120 kg should be treated with adjusted-dose, monitored UFH. On the basis of a recent pharmacokinetic analysis in obese patients up to 165 kg, tinzaparin appears to be able to be dosed on the basis of actual weight without dose adjustment.[83] Patients with nonhemorrhagic CNS primary tumors or metastatic CNS lesions and VTE should be considered for anticoagulation, preferably begun in the hospital. The randomized study of enoxaparin sodium alone versus initial enoxaparin sodium followed by warfarin for a 180-day period as secondary prevention of venous thromboembolic events in patients with active malignancy (ONCENOX) trial enrolled six patients with confirmed CNS malignancy, all of whom were treated exclusively in the outpatient setting and in none of whom did recurrent VTE or bleeding complications develop.[3] Patients with hemorrhagic CNS lesions are probably best treated with IVC filter placement.

Subcutaneous fondaparinux, 7.5 mg once daily, has been shown to be as safe and effective as subcutaneous enoxaparin for the initial treatment of patients with acute DVT and adjusted-dose intravenous UFH for the initial treatment of patients with acute PE.[84,85] Specific data in patients with active cancer and VTE have not been published.

Chronic Anticoagulation Therapy

Chronic-phase anticoagulation for VTE has traditionally consisted of oral warfarin dosed to achieve an INR between 2.0 and 3.0. Cancer patients with lupus anticoagulants and baseline elevated prothrombin times may require alternative warfarin therapeutic monitoring in place of the INR.[86] Chromagenic factor X activity assays or assessment of individual vitamin K-dependent factor activity levels on dilute plasma samples are acceptable alternatives. Warfarin therapy can be started as soon as a therapeutic-intensity aPTT has been achieved with UFH or an initial weight-based dose of LMWH has been given. Bolus dosing of warfarin does not help to achieve a stable, target INR faster and might actually delay achievement of a stable INR and prolong hospitalization.[87] Initial dosing with 2.5 to 7.5 mg per day (based on patient weight and nutritional status) seems prudent. Frequent (weekly) INR monitoring might not actually facilitate a more stable INR in cancer patients but still seems prudent. Warfarin therapy alone is contraindicated in the setting of acute thrombosis because of the inherent delay in achieving therapeutic anticoagulation and the theoretical transient exacerbation of hypercoagulability caused by a rapid reduction in protein C functional activity.[87] This warfarin-induced paradoxical hypercoagulability may contribute to warfarin-induced limb gangrene in patients with HIT and to warfarin-induced skin necrosis and may be particularly troublesome in patients with hypercoagulability of malignancy.

Warfarin Failure

Patients in whom objectively confirmed recurrent VTE develops during periods of subtarget INR (≤2.0) should be restarted on treatment-intensity UFH, LMWH, or fondaparinux until a stable INR between 2.0 and 3.0 is achieved. Patients in whom objectively confirmed recurrent VTE develops despite an INR between 2.0 and 3.0 (warfarin failure) can either be treated with UFH or LMWH until a higher intensity of oral anticoagulation (INR: 3.0–4.0) is attained or be switched to primary long-term therapy with LMWH.[32,88] LMWH therapy is gaining popularity in patients with warfarin failure because of the challenges of warfarin therapy regulation at any target intensity, and data from early randomized trials suggest efficacy and safety comparability to warfarin.[1] The optimal long-term anticoagulation dose of any LMWH is not known and may be less than the dose used during initial VTE treatment. The ONCENOX trial evaluated the feasibility, safety, and efficacy of long-term enoxaparin at 1.5 mg/kg once daily and 1.0 mg/kg once daily based on this supposition.[3] In the event of warfarin failure followed by LMWH or fondaparinux failure, adjusted-dose, subcutaneous direct-thrombin inhibitor therapy with lepirudin should be considered.[89,90]

Long-Term Anticoagulation Therapy with Low-Molecular-Weight Heparin

Each of the three commercially available LMWHs in the United States has been recently studied as a substitute for oral warfarin in the management of cancer patients with acute VTE (Table 46-3).[3,36,91,92] In the randomized trial of long-term dalteparin LMWH versus oral anticoagulant therapy in cancer patients with VTE (CLOT), 8.0% of LMWH-treated patients experienced recurrent VTE during 6 months of treatment compared with 15.8% of those treated with warfarin (target INR: 2.5).[36] In the ONCENOX trial, in 3.3% of the patients treated for 180 days with one of the two once-daily doses of enoxaparin, recurrent VTE developed, compared with 6.7% of those treated with warfarin (target INR: 2.0–3.0).[3] In

Table 46-3 Long-Term Low-Molecular-Weight Heparin Therapy in Cancer-Associated Venous Thromboembolic Events

	VTE Recurrence Rate (%)	
	LMWH	**Warfarin**
CLOT (dalteparin)[36]	27/336 (8.0)	53/336 (15.8)
LITE (tinzaparin)[91]	6/101 (5.9)	11/105 (10.5)
CANTHANOX (enoxaparin)[92]	2/67 (3.0)	3/71 (4.2)
ONCENOX (enoxaparin)[3]	2/61 (3.3)	2/30 (6.7)
Total	37/565 (6.5)	69/542 (12.7)

the comparison of LMWH and warfarin for the secondary prevention of VTE in patients with cancer (CANTHANOX) trial, in 3.0% of the patients treated for 3 months with enoxaparin, 1.5 mg/kg once daily, recurrent VTE developed, compared with 4.2% of those treated with oral warfarin.[92] In the cancer subgroup of the randomized trial evaluating long-term LMWH therapy for 3 months versus intravenous heparin followed by warfarin sodium (LITE), in 5.9% of those treated with tinzaparin, recurrent VTE developed, compared with 10.5% of those treated with heparin followed by warfarin.[91] Major bleeding rates were not statistically different between the treatment groups in these clinical trials. These studies support the use of once-daily subcutaneous LMWH in place of oral warfarin in cancer patients with acute VTE to minimize recurrent VTE rates.

Duration of Anticoagulation

With regard to the optimal duration of anticoagulation in patients with VTE in the setting of cancer, it seems prudent to treat for a minimum of 6 months and at least until all cancer therapy has been completed and the patient has been deemed to have no residual malignancy. Residual malignancy constitutes a persistent hypercoagulable state, which typically warrants long-term anticoagulant treatment. Warfarin therapy itself has been shown to improve survival in patients with extensive-stage small cell lung carcinoma and a longer duration of oral anticoagulation (6 months versus 6 weeks) after acute VTE has been shown to reduce the risk of developing genitourinary tract cancers.[93,94]

The recently published study of long-term, low-intensity warfarin therapy for the prevention of recurrent VTE (PREVENT) demonstrated a 64% reduction in recurrent VTE without increased risk of major bleeding compared with placebo when warfarin with a target INR of 1.5 to 2.0 is prescribed to patients after completion of a standard course of anticoagulation for idiopathic VTE.[95] This study specifically excluded patients with known active malignancy and therefore should not be applied to this population.

UPPER-EXTREMITY DEEP VENOUS THROMBOSIS MANAGEMENT

Diagnosis of Upper-Extremity Deep Venous Thrombosis in Cancer Patients

The UE deep venous segments that can be affected by thrombosis include, in ascending order from the elbow, the brachial, axillary, subclavian, and brachiocephalic veins, as well as the SVC. Similar to LE-DVT, the prevalence of confirmed DVT is less than 50% among symptomatic patients who are suspected of having UE-DVT.[25] Therefore diagnostic confirmation by an imaging method is mandatory. In general, the same modalities that are used for the diagnostic approach of LE-DVT apply for patients with suspected UE-DVT. However, no formal studies of helical CT venography, nuclear scintigraphy, or impedance plethysmography have been performed to diagnose DVT in the upper extremities, and as was previously discussed, D-dimer assays should not be considered reliable for the exclusion of DVT in a patient with cancer.

Contrast Venography

A number of anatomic variants and the converging nature of the central venous anatomy in the UE can lead to flow turbulence artifacts that can complicate the interpretation of UE venography.[2] In addition, because the technique is usually performed by contrast injection in an antecubital vein, it does not visualize the internal jugular veins, which can be easily visualized by duplex ultrasound. Similar to its applicability in the lower extremities, the single most reliable criterion for acute DVT is the presence of a constant, intraluminal filling defect in at least two different projection views. The complications related to the use of contrast medium are infrequent and similar to those described for LE-DVT. However, no data are available on the incidence of DVT after venography in the UEs.

Duplex Ultrasound

The internal jugular, subclavian, axillary, and brachial veins can be routinely visualized in the neck and arms. However, the medial two thirds of the subclavian veins are not easily compressible because of their anatomic location behind the clavicles.[2] In addition, it is not technically feasible to perform compression maneuvers at the level of the brachiocephalic veins and the SVC; in fact, the right brachiocephalic vein and the SVC are usually not visualized by ultrasound examination. Even if these segments of the subclavian veins and left brachiocephalic veins are visualized, duplex ultrasound has not been validated for the detection or exclusion of DVT in these locations because the diagnosis cannot be established by the compression method. Rather, DVT in those locations is suggested by indirect Doppler-flow criteria, such as lack of diameter change with inspiration and incomplete color filling of the lumen, and by the presence of echogenic material on B-mode ultrasound imaging.[2]

The sensitivity and specificity of duplex ultrasound for the diagnosis of acute symptomatic axillosubclavian DVT range from 96% to 100% and from 94% to 100%, respectively.[2,25,96,97] Studies of the accuracy associated with other sonographic criteria than vein compressibility have been found to possess a lower sensitivity of 50% to 73%.[96] The presence of an indwelling catheter in an UE vein has been shown not to alter significantly the Doppler-flow dynamics compared with the contralateral vein that does not have a catheter in place. Nevertheless, duplex ultrasound appears to be unreliable as a screening method to diagnose asymptomatic, catheter-related UE-DVT.

Other Imaging Modalities

Neither contrast-enhanced CT nor MRV has been validated in evaluating the UEs, including the SVC. CT is not an ideal method because the convergence of the central veins in the upper chest is frequently associated with flow artifacts. Thus, the diagnosis of any suspected SVC or innominate DVT found by CT should ideally be confirmed by contrast venography. No studies have reported on the use of helical CT venography for central chest veins.

Two early studies (28 and 25 arms examined, respectively) correlating MRV with contrast venography for the diagnosis of acute axillary-subclavian DVT found a sensitivity and specificity of 80% and 100%, respectively.[98,99] However, in one study, the sensitivity for nonocclusive DVT was quite low (20%) in comparison with the one for occlusive DVT (80%).[98] Nevertheless, MRV appears to be very accurate in detecting conditions that may be associated with UE or central chest vein extrinsic compression or stenosis. Two studies in

selected patients with UE central venous abnormalities showed 100% correlation between 3D, gadolinium-enhanced MRV, and contrast venography for detecting SVC and brachiocephalic vein stenosis or compression.

Treatment of Upper-Extremity Deep Venous Thrombosis in Cancer Patients

Central venous catheter–associated DVT has been described in up to 56% of patients with indwelling catheters.[100] These "UE" DVTs may result in SVC thrombosis, SVC syndrome, and PE. The true risk of PE from central venous catheter–associated thromboses is often debated. Prandoni and coworkers and Bernardi[25] reported a 36% rate of PE complicating UE DVT; Monreal and colleagues[101] reported a 16% rate of PE in this setting. Ault and Artal,[102] in contrast, suggested that PE is uncommon in patients with central venous catheters based on a lack of any PE in 33 of their patients with DVT due to peripherally placed central catheters. In patients with symptomatic central venous catheter–related DVT and a functional catheter, line removal is often unnecessary. Anticoagulation management following the same guidelines as for LE-DVT in the cancer patient is recommended. Continuation of anticoagulation for the life of the catheter seems reasonable. This management approach allows uninterrupted cancer treatment and prevents the need for additional vascular-access surgery. Central venous catheter–related DVT in conjunction with a dysfunctional catheter usually warrants anticoagulation and line removal. Thrombolytic therapy followed by anticoagulation may alleviate thrombosis-related symptoms more quickly and completely than anticoagulation alone. Randomized trials comparing thrombolysis with anticoagulation for central venous catheter–associated DVTs are lacking.

PULMONARY EMBOLISM MANAGEMENT

Diagnosis of Pulmonary Embolism in Cancer Patients

Currently available tests for the diagnostic confirmation or exclusion of PE include various imaging methods and blood-based biochemical assays (Table 46-4). Although many believe that pulmonary angiography is no more accurate than helical CT, pulmonary angiography remains the gold standard diagnostic test for PE. However, helical CT and V/Q lung scanning are the most appropriate initial tests because they are noninvasive and widely available.

Pulmonary Angiography

Pulmonary angiography is typically performed via common femoral vein access (or internal jugular or brachial vein) and can include selective catheterization of either or both the right and left main pulmonary arteries. The pulmonary vascular tree is then visualized after an injection of iodinated contrast medium.

On the basis of clinical-outcome studies, the sensitivity and specificity of pulmonary angiography have been estimated to be 98% and 97%, respectively.[2,30,103] The specificity of pulmonary angiography approaches 100% when a filling defect or abrupt "cut-off" of a pulmonary artery branch is present.[103] Ancillary findings that may be present but are not specific for PE include abnormal distribution of flow to the different lobes, delayed venous return, and partially opacified, tortuous vessels.[103] The accuracy of the test is not influenced by the presence of chronic obstructive pulmonary disease.[103] In the PIOPED study, interobserver disagreement occurred more often for the exclusion of PE (17%) than for PE confirmation (8%) by pulmonary angiography.[104] Experts agreed 98%, 90%, and 66% of the time on the presence of lobar, segmental, and subsegmental PE, respectively.[105]

Complications reported with pulmonary angiography include minor and major complications as well as death. These three endpoints were observed in 5%, 1%, and 0.5%, respectively, of 1111 patients who underwent pulmonary angiography in the PIOPED study.[105] A review of more than 7000 patients undergoing pulmonary angiography revealed a 0.1% death rate with the procedure.[106]

Table 46-4 Tests for the Objective Diagnosis or Exclusion of Pulmonary Embolism

Pulmonary angiography
Ventilation-perfusion lung scintigraphy
Helical (spiral) computed tomography
Magnetic resonance angiography
D-dimer semiquantitative and quantitative assays

Ventilation and Perfusion Lung Scintigraphy

V/Q lung scanning combines ventilation and perfusion nuclear medicine imaging techniques. The ventilation (V) study involves the inhalation of a radioactive gas (e.g., xenon), which provides an image of all ventilated portions of the lung. The perfusion (Q) study consists of an intravenous injection of [^{99m}Tc]-labeled macroaggregated human serum albumin particles with the patient in supine position, and the particles become trapped in approximately 0.1% of the pulmonary capillary bed.[103] Any obstruction to arterial flow is viewed as an area of hypoperfusion and is called a "perfusion defect" on gamma-camera images. The presence of multiple segmental perfusion defects increases the test specificity for PE.[103] On the basis of the presence and extent of matched (absence of both perfusion and ventilation) and unmatched (absence of perfusion but preserved ventilation) defects, the V/Q scan can be interpreted by using PIOPED published criteria as either normal or low probability, intermediate probability, or high probability for PE.[104,107]

Because they provide indirect evidence of PE, V/Q scans are most clinically useful when considered in combination with an assessment of pretest clinical suspicion.[104] On the basis of PIOPED data, a normal V/Q scan essentially rules out clinically significant PE, and a high-probability V/Q scan alone has a high positive predictive value (88%) for PE, with 96% of patients with high pretest clinical suspicion and a high-probability V/Q scan having PE documented by pulmonary angiography.[104] Only 4% of patients with both low-probability V/Q scan and low clinical suspicion had PE on angiography.[104] Low- and intermediate-probability scans are now considered together as being "indeterminate" scans.

A plain chest radiograph is necessary before interpretation of a V/Q scan. Pleural effusions, bullous disease, pulmonary infiltrates or masses, and atelectasis have been associated with a higher frequency of indeterminate-probability scans and with a lower positive predictive value of high-probability findings.[103]

V/Q scan has the advantage of not using iodinated contrast. Its greatest limitation as a diagnostic tool for PE is that it provides a definitive result in a minority of patients. In the PIOPED series, only 13% had a normal study, and 14% had a high-probability scan.[104] Therefore, it can be expected that as many as 73% of all patients undergoing a V/Q scan will have a nondiagnostic, indeterminate scan that warrants further testing such as pulmonary angiography to confirm or exclude PE. In addition, it has been demonstrated that the rates of nondiagnostic V/Q scan findings increase significantly, from 21% to 63% in patients without chronic obstructive pulmonary disease to 46% to 91% in those with chronic obstructive pulmonary disease and from 9% in patients with normal chest radiographs to 48% in patients with abnormal chest radiographs.[108,109]

Pitfalls in the interpretation of V/Q scintigraphy may represent a significant problem in the cancer population, particularly when primary or secondary (metastatic) pulmonary involvement is present. Patients with a history of PE may have a high-probability V/Q scan that does not reflect a new, acute event but rather the remnants of old PE.[103,104] False high-probability scans may occur as a consequence of an abnormal perfusion scan due to pulmonary artery invasion or compression, regional hypoventilation secondary to bronchial compromise, pulmonary vein obstruction by hilar masses or adenopathy, and pulmonary leukostasis, which have been described in lymphoma, osteosarcoma, neuroblastoma, lymphangitic carcinomatosis, lung carcinoma, carcinoid, left atrial leiomyosarcoma, metastatic renal cell carcinoma, pulmonary artery sarcomas, and acute myelogenous leukemia.[2] Areas of V/Q mismatch also have been described as a result of prior radiation therapy to the chest in patients with breast and lung carcinoma.[2,110]

Helical (Spiral) Computed Tomography Angiography

Contrast-enhanced spiral CT is performed by scanning a distance of 10 to 12 cm from the aortic arch to 2 cm below the inferior pulmonary veins during a single 30-second breath hold while the pulmonary vasculature is opacified by the automated injection of iodinated contrast medium. Technical parameters such as collimation, rate and timing of contrast administration, and scanning delay, as well as breathing, motion artifacts, and even central venous catheters, can influence the timing and quality of opacification of the pulmonary arteries, thus having the potential to compromise the quality of the study.[2,103] The rate of studies that are inadequate for interpretation ranges from 2% to 13%.[2,108]

Spiral CT has an overall sensitivity of 53% to 100% and specificity of 78% to 100% for the diagnosis of PE.[2,30] These rates approach 95% to 100% for the central and segmental pulmonary arterial branches, but are lower (sensitivity: 53% to 63%) for PE involving the subsegmental branches. The accuracy of helical CT is highly influenced by, and dependent on, the equipment being used. Earlier CT scanners included 5-mm collimation that resulted in an effective section thickness of 6.57 mm and imaging reconstruction at 3-mm intervals.[2,111] Many currently available CT scanners include 2- to 3-mm collimation, resulting in effective section thickness of 2 to 4 mm and improved visualization of the subsegmental arterial bed. The newest-generation multislice CT scanners allow subsecond scanning with 1.25-mm collimation, 1.25-mm section thickness, and image reconstruction at 0.6-mm intervals. Although these modern scanners also have been shown to improve visualization of subsegmental arteries significantly, two recent studies disagreed on whether this improved visualization led to higher detection rates of subsegmental PE.[112,113] In addition, the use of workstations for image viewing and primary interpretation has been shown to increase the detection of PE by 25% in comparison to hard-copy image viewing.

Studies with the highest frequency of isolated subsegmental PE, and hence the lowest spiral CT sensitivity, have been reported in patients who also had nondiagnostic V/Q scans, and studies have shown that the prevalence of subsegmental PE ranges from 6% to 36%.[2,114] Whether subsegmental PE is clinically relevant and should definitively be detected remains a controversial matter. A total of six prospective management studies have been performed with spiral CT in patients with indeterminate V/Q scan findings.[115–120] In five of these studies, patients with a negative helical CT also underwent LE duplex ultrasound, anticoagulation being held after a negative result. Follow-up periods ranged from 3 to 6 months, and rates of recurrent VTE ranged from 2% to 4%. The only study that withheld anticoagulation on the basis of a negative helical CT alone reported a 1% rate of VTE recurrence in patients with low pretest probability for PE. Because these studies did not rely on a negative CT alone before withholding anticoagulation and because the sensitivity of helical CT is low in patients with nondiagnostic V/Q scans, the current evidence is insufficient to rely on a negative helical CT alone to justify withholding anticoagulation and even to support the hypothesis that subsegmental PE is not clinically significant.

The major advantages of spiral CT include the rapid nature of data acquisition and the lower percentage of nondiagnostic studies due to its ability to evaluate vascular as well as nonvascular intrathoracic structures simultaneously and provide an alternative diagnosis that either suggests or supports the final clinical diagnosis in 26% to 67% of examinations.[2] Although some studies have suggested that the presence of such alternative diagnoses adequately excludes PE, other studies have shown that the frequency of alternative diagnoses was the same in patients with and without confirmed PE.[121] Therefore, even the presence of an alternative explanation of the patient's symptoms does not necessarily imply that it is safe to withhold anticoagulation, and pursuit of pulmonary angiography might still be appropriate in such patients.

Magnetic Resonance Angiography

MRA is a promising technique in patients with suspected PE, particularly with the use of 3D, gadolinium-enhanced imaging.[2,103,122] The sensitivity and specificity of MRA for the detection of PE are 50% to 100% and 95%, respectively.[122,123] The sensitivity is less than 50% for subsegmental PE, and overall accuracy is highly dependent on the technique and experience of the interpreting physicians.[123] In cases of suspected pulmonary artery sarcoma, MRI appears to be more useful than CT because the presence of gadolinium enhancement suggests tumor instead of thrombus.

Echocardiography

The sensitivity and specificity of the transesophageal echocardiogram for the detection of central pulmonary artery PE range from 76% to 97% and from 77% to 100%, respectively, when compared with helical CT.[124] However, the sensitivity for peripheral PE is lower.[124] Echocardiography currently appears to be most useful in assessing patients who are hemodynamically unstable, are unable to undergo helical CT or V/Q scan, and need to have a workup initiated at the bedside.

Pulmonary Embolism Diagnosis in Cancer Patients

When a cancer patient is suspected of having PE, a chest radiograph should be performed to exclude other conditions that might require immediate intervention, such as a central line–related tension pneumothorax, pulmonary hemorrhage, and malignant pleural effusion. However, the chest radiograph should not be used as a means of supporting or refuting the need for specific diagnostic testing for PE. Helical CT is probably best indicated when the chest radiograph is abnormal and in individuals with known pulmonary disease. Alternatively, if the chest radiograph is normal, a V/Q-scan approach also is appropriate, but it is important that physicians clearly establish and document their pretest clinical suspicion of PE. Otherwise, PIOPED probability criteria may not be applicable. Regardless of the initial diagnostic approach, an indeterminate or negative initial test result should be followed by a duplex ultrasound of the legs and possibly of the arms as well, particularly in patients with symptoms of pain and swelling or who have an indwelling catheter. A positive duplex ultrasound does not confirm PE, but detection of acute DVT will prompt and justify systemic anticoagulation. In the cancer patient who is suspected of having PE, the combination of a nondiagnostic helical CT or V/Q scan with the absence of acute DVT by duplex ultrasound warrants the performance of pulmonary angiography. In this clinical setting, the risks of pulmonary angiography are sufficiently low and are outweighed by the benefits. Pulmonary angiography also is indicated in the setting of a normal spiral CT alone, particularly with a high pretest suspicion.

Treatment of Pulmonary Embolism in Cancer Patients

Most cancer patients with symptomatic PE should be treated with anticoagulation by following the same guidelines for treatment that are applied to DVT.[1,51,85,125] Initial inpatient intravenous UFH is recommended in symptomatic patients with extensive PE. Some patients, including cancer patients, with PE may derive benefit from thrombolytic therapy to degrade actively the thrombus obstructing the pulmonary vasculature. Clear indications for PE thrombolysis are debated.[126] Thrombolysis has been demonstrated to improve survival in patients with massive PE plus shock and is probably indicated in these patients regardless of cancer status. When compared with anticoagulation alone, thrombolytic therapy results in more rapid thrombus lysis, an early improvement in pulmonary blood flow, and improvement of right ventricular function.[127] However, these improvements in cardiopulmonary function alone have not resulted in decreased mortality in stable patients without significant hemodynamic compromise.[128,129] Thrombolysis is contraindicated in any cancer patient with significant transfusion-refractory thrombocytopenia, active bleeding, and CNS lesions.

INFERIOR VENA CAVA AND INTRA-ABDOMINAL DEEP VEIN THROMBOSIS MANAGEMENT

Diagnosis of Inferior Vena Cava and Intra-abdominal Deep Vein Thrombosis in Cancer Patients

Many cancer patients undergo serial imaging with CT as a means of assessing cancer-therapy efficacy, disease stage or progression, and nonspecific abdominal symptoms. Incidental findings of what appears to be a DVT should not affect patient treatment and prompt the placement of an IVC filter. Prompt and proper diagnostic imaging is especially needed in such a situation.

Contrast Venography

Popliteal or common femoral vein access is the most appropriate approach for performance of contrast cavography. Access through an internal jugular vein might be necessary in some circumstances. Contrast venography is the reference standard to show the presence or absence of IVC or renal vein thrombosis conclusively, and the same criteria that are used to diagnose LE- and UE-DVT by venography apply to the IVC. However, in cancer patients not all intraluminal filling defects represent thrombus, and the distinction between intravascular tumor and thrombus might require further investigation with CT or MRI and, in some selected cases, with transvenous catheter-guided biopsy. Likewise, if the column of contrast does not opacify the IVC, CT or MRI is indicated to assess for the presence of extrinsic compression or invasion by tumor. The diagnosis of portal, mesenteric, or ovarian vein thromboses by venography is more challenging because of limited ability to perform selective contrast injections.

Duplex Ultrasound

No studies have validated the use of duplex ultrasound for the detection of IVC thrombosis (i.e., duplex ultrasound has never been compared with the gold standard contrast venography, nor has it been subject to accuracy or management studies in this setting). Although visualization of the IVC and interrogation of its lumen for Doppler-flow measurements have been described in studies that imaged the IVC before IVC filter placement,[2,130] compression maneuvers are not technically feasible in the abdomen, and the indirect signs of impaired flow and loss of flow phasicity are not specific for IVC thrombosis. Moreover, duplex ultrasound cannot differentiate IVC thrombus from tumor, except in cases of suspected portal vein invasion by tumor. In this setting, color Doppler ultrasound can be a reliable diagnostic tool.[131]

Contrast-Enhanced Computed Tomography

CT remains a nonvalidated method to assess for the presence of thrombus in the IVC. Indirect signs that have been described in cases of IVC thrombosis include IVC enlargement, reduced IVC lumen density compared with that of the aorta, and rim enhancement. However, these signs may occur as a result of contrast flow phenomena mimicking an intraluminal filling defect and also have been described in patients with renal cell or adrenal cortical carcinoma extending into the renal veins and IVC, producing a "tumor thrombus."[132–136] Although spiral CT venography has been shown to visualize the intra-abdominal veins accurately, no formal studies have been published. Any incidental finding of an IVC or renal vein "filling defect" by CT should ideally be confirmed by venography and not prompt the initial placement of an IVC filter.

The previously mentioned features also are used in the diagnosis of portal and mesenteric vein thrombosis by CT.[137] These signs are of little value in a patient with a history of portal vein thrombosis who is suspected to have a recurrent event. Although the true sensitivity of contrast-enhanced CT in diagnosing portal vein thrombosis is unknown, its specificity has been suggested to be quite high. The presence of cavernous transformation—a "masslike" network of collateral veins—is suggestive of remote portal vein thrombosis.[137]

Only one retrospective case series pertaining to the diagnostic imaging of ovarian vein thrombosis in cancer patients has been published.[138] In this small study, none of the six patients with ovarian DVT had the related CT findings of uterine enlargement and other pelvic masses that are typically described in larger series of patients with puerperal ovarian DVT. Similar to portal DVT, these indirect CT signs are not useful in a patient with a history of ovarian vein thrombosis, because at least half of the patients will not have normalization of the original CT findings after 3 months to 2 years after the index event.[139]

Magnetic Resonance Venography

MRV is currently considered the diagnostic method of choice for diagnosing IVC, renal, and portal vein thrombosis, particularly when spin-echo and cine MRI techniques are used in combination. In a small series of 26 patients with puerperal ovarian DVT, MRV had 100% sensitivity and specificity.[139] Spin-echo MRI may help to differentiate acute from chronic thrombus on the basis of differences in patterns of signal intensity.[140]

Artifacts created by flow phenomena may cause signal voids at the junction of the renal vein and the IVC because this is an area of slow and convergent blood flow. This can lead to a false-positive diagnosis of IVC thrombosis.[141] MRI also is limited in distinguishing true portal DVT from tumor invasion of the portal vein unless an adjacent mass is seen.

The rare IVC leiomyosarcoma appears to be equally demonstrated by CT or MRI, although MRI is superior because it seems to be capable of differentiating tumor (homogeneous, intermediate signal intensity on T_1-weighted images, and high signal intensity on T_2-weighted images) from thrombus (hyperintense on T_1- and T_2-weighted images).[142–144]

Treatment of Inferior Vena Cava and Intra-abdominal Deep Venous Thrombosis in Cancer Patients

No specific guidelines exist for the treatment of IVC and other intra-abdominal DVT in the cancer patient or noncancer patient. Whether to use standard anticoagulant therapy as is used for proximal LE-

DVT or catheter-directed thrombolytic therapy depends on the extent of thrombosis, patient symptoms, and patient bleeding risk. Patients with acute, complete IVC occlusion may develop significant bilateral LE swelling and pain and are at risk for phlegmasia cerulean dolens (venous limb gangrene). Such patients could benefit most from pharmacologic or mechanical thrombolysis. Long-term anticoagulation is likely warranted.

SUPERFICIAL THROMBOPHLEBITIS MANAGEMENT

Diagnosis of Superficial Thrombophlebitis in Cancer Patients

Superficial venous thrombophlebitis (SVT) is the only manifestation of venous thromboembolic disease that does not require objective diagnostic imaging. The diagnosis can be made clinically by the detection of a palpable tender cord in the course of a superficial vein; the induration of the vein is usually associated with erythema of the overlying skin. The clinical differential diagnosis includes sarcoidal granulomas, Kaposi's sarcoma, and lymphangitis.

Duplex ultrasound should be considered to rule out concomitant DVT, particularly when the greater or lesser saphenous veins are involved. The most common location for progression from SVT to DVT to occur is at the junction between the greater saphenous vein (a superficial leg vein) and the common femoral vein (a proximal deep leg vein). Proximity of an SVT to the junction between the involved superficial vein and its connection to the deep venous system does not seem to affect the likelihood of PE. The rates of DVT in patients with clinical signs and symptoms of isolated SVT have been reported to range from 6% to 57%, and the rates of symptomatic PE have been reported to range from 4% to 10%.[145–150]

Trousseau's syndrome or migratory thrombophlebitis was initially described in patients with mucin-secreting carcinoma of the gastrointestinal tract. It is unclear whether the "thrombophlebitis" in many of the reported cases was manifested as SVT or DVT. The SVT related to Trousseau's syndrome typically was first seen as multiple tender nodules, which progressed to form palpable cords, usually involving the bilateral LEs and, on occasion, the UE veins and the abdominal wall veins as well.

Treatment of Superficial Thrombophlebitis in Cancer Patients

Typically, nonsteroidal anti-inflammatory drugs and warm compresses are adequate treatment for SVT symptom control. When the deep system is involved or symptomatic pulmonary embolism is diagnosed, standard anticoagulant therapy is indicated. Because of the reported high rate of progression from SVT to DVT, many physicians treat SVT with anticoagulants for a variable time. Anticoagulants such as UFH and LMWH may help to relieve symptoms related to vessel inflammation but are probably best reserved for individuals with recurrent SVT or documented DVT. Serial ultrasound to detect meaningful SVT progression seems prudent in selected cases such as those with SVT already at the saphenofemoral junction.

INFERIOR VENA CAVA FILTERS

IVC filters are often placed in cancer patients with acute VTE, especially in the settings of thrombocytopenia, active bleeding, and CNS malignancy.[151–154] Limitations to IVC filters include technical difficulties during insertion, insertion-site hemorrhage or thrombosis, caval thrombosis, and obstruction below the filter, filter change of position (migration or tilting), caval erosion and perforation, and filter failure.[154] IVC filters obviously play no role in the management of UE-DVT. SVC filter placement has been shown to be technically feasible, but outcome data are lacking.[155] A recent study published by Decousus and associates[155] addressed the impact of IVC filter placement on PE prevention and DVT recurrence rate. All patients had proximal DVT, and all received anticoagulation. Placement of an IVC filter conferred a significant benefit in preventing PE within the first 12 days after DVT, with PE developing in 4.8% of patients without filters compared with 1.1% of patients with filters ($P = 0.03$). At 2 years' follow-up, however, the benefit was no longer statistically significant with regard to symptomatic PE prevention. Moreover, at 2 years, those patients with prophylactic filter placement had a higher risk of DVT recurrence than did those who did not have a filter placed (20.8% versus 11.6%; $P = 0.02$).[155] These findings underscore the need for caution in placing filters, especially when patients are receiving cancer treatment with a curative intent, and long-term survival is contemplated. When a filter is placed because of a transient contraindication to anticoagulation, appropriate pharmacologic therapy should be commenced once the contraindication has passed.

VENOUS THROMBOSIS PREVENTION IN THE CANCER PATIENT

The relation between cancer and clinical thrombosis has been recognized for more than 150 years. The concept of and an appreciation of thromboprophylaxis have been widely accepted, primarily in the surgical setting, for more than 25 years. However, only in the last decade has the widespread application of thromboprophylaxis to patients with cancer begun to receive significant attention from the medical community. One of the observations driving this level of interest is the expanding body of data suggesting that the connection between thrombosis and cancer may well be bidirectional.

In the not-too-distant past, the prevailing opinion was that cancer caused thrombosis and that, although it was a regrettable complication, thrombosis did not significantly affect the overall clinical course of the patient with cancer. The interactions between cancer and thrombosis might not be as simple as that. Take the time-honored observation that in an inordinate number of patients with idiopathic VTE, cancer develops in the subsequent several months[156] and extend the follow-up for several years, and one finds that the rate of malignancy continues to increase inordinately in this population for at least 6 years, with no evidence of a plateau developing in the curve.[157] Although it is conceivable that some aspect of an occult malignancy (even one that does not become clinically apparent for 6 years) promotes thrombosis, it is equally conceivable that some pathophysiologic element related to the thrombosis itself promotes the development or progression of the cancer. If this were true, then it would logically follow that alterations in the biology of thrombosis might alter the likelihood of subsequent malignancy.

Data from randomized clinical trials support this hypothesis. Patients who received oral warfarin secondary prophylaxis for 6 months after an idiopathic VTE had a lower rate of subsequent malignancy over the ensuing 6 years than did patients who were randomized to receive only 6 weeks of anticoagulation.[157] Not only does it appear that thrombosis might, through mechanisms unknown, predispose to the development of cancer, but the presence of thrombosis[158] or even evidence of activation of coagulation without overt thrombosis[23] also is associated with more aggressive behavior of the associated malignancies. This body of data, taken to its logical conclusion, allows the development of a hypothesis that thromboprophylaxis could be used for both primary prevention of and treatment of some forms of cancer. Add to this the facts that standard anticoagulation treatment of acute VTE is less efficacious and more toxic in cancer patients than in noncancer patients (see the previous sections) and that the risk of death from PE might be higher in cancer patients than in noncancer patients,[1] and it becomes clear that prevention of thrombosis is clinically important in patients with cancer.

To date, the available data on thromboprophylaxis specifically in cancer patients is derived mainly from studies whose major endpoints included the incidence of any (primarily asymptomatic) DVT rather than more meaningful endpoints such as disease progression, fatal PE, and survival. However, with meta-analysis, heparin thromboprophylaxis that was successful in preventing asymptomatic DVT in patients without cancer has been shown to prevent both symptomatic DVT and fatal PE.[159] Therefore, it is reasonable to infer that any intervention that prevents asymptomatic DVT also prevents clinically significant thromboembolic disease in patients with cancer. Data discussed earlier also raise the possibility that thromboprophylaxis in the cancer patient could modify the course of the malignancy in a favorable direction. Consequently, comments in the remainder of this section are based on the assumption that thromboprophylaxis (operationally defined as any intervention that prevents asymptomatic DVT) is clinically useful and should be used in cancer patients in several common, clinically defined situations.

Thromboprophylaxis in Surgical Oncology

Most studies of surgical thromboprophylaxis, such as those focusing on elective joint replacement, have not differentiated between patients with and without underlying malignancy. Consequently, the quantitative risk added by the presence of cancer to each and every type of surgical procedure is unknown. Despite this, the American College of Chest Physicians Consensus Conference on Antithrombotic Therapy categorizes any patient older than 40 years undergoing any major surgery in the setting of active or prior cancer as being in the "highest risk" group of patients, with an estimated risk of proximal DVT of 10% to 20% and fatal PE of 0.2% to 5.0% without thromboprophylaxis.[160]

Two basic methods of thromboprophylaxis have been widely studied in surgical patients: mechanical and pharmacologic. For practical purposes in surgical oncology, mechanical forms of prophylaxis are limited to external pneumatic compression (EPC) boots, whereas pharmacologic methods are limited to heparin-related compounds.

EPC has been found to provide a modest degree of efficacy in surgical oncology, ultrasound-defined failure rates varying from 1% in gynecologic oncology patients[161] to 14% in cancer patients undergoing orthopedic procedures.[162] Assuming that they are applied correctly 100% of the time, EPC boots are a cost-effective form of prophylaxis during and after high-risk gynecologic oncology procedures.[163] Unfortunately, the assumption of proper application of EPC devices 100% of the time is generally incorrect in practice, rates of 33% being more common.[164] In evaluation of the efficacy of EPC in gynecologic surgery, the presence of cancer has been found to be an independent risk factor for failure, with a relative risk of DVT of 4.9 compared with noncancer patients.[165] EPC as the sole method of prophylaxis is not recommended for the "highest risk" patients[160] and should not be relied on for most surgical procedures performed on cancer patients.

Heparin and heparin-related compounds form the mainstay of pharmacologic methods of thromboprophylaxis, although other medications, such as oral direct thrombin inhibitors and factor Xa inhibitors, could begin to play a major role in the future. The efficacy of UFH and its derivatives has been studied primarily in noncancer patients undergoing surgery. The first major investigation of the efficacy of heparin in curative cancer surgery was a prospective, randomized, double-blind study comparing subcutaneous UFH, 5000 units three times daily, with subcutaneous enoxaparin, 40 mg once daily, begun 2 hours before surgery.[166] Contrast venography within 24 hours of the last drug injection (10 ± 2 days) was scheduled to be performed in all patients. Of 1116 randomized patients, 319 UFH-treated patients and 312 enoxaparin-treated patients were evaluable. Total VTE, symptomatic DVT, and any DVT were detected in 18.2%, 1.9%, and 17.6%, respectively, of the UFH-treated patients and in 14.7%, 1.3%, and 14.4%, respectively, of the enoxaparin-treated group. These rates of thrombosis are more than twice those generally seen in noncancer patients undergoing general surgery receiving the same medications and evaluated with the same endpoints.[160] As the data demonstrate, most detected thromboses were asymptomatic (any DVT minus symptomatic DVT). To deal with the high failure rate of pharmacologic thromboprophylaxis in this group of patients, two different, and not mutually exclusive, approaches could be taken: (1) find a way to improve in-hospital efficacy and/or (2) find a way to prevent these asymptomatic thrombi from propagating and posing a risk of death after hospital discharge. The first approach might be accomplished by combining mechanical and pharmacologic methods of prophylaxis. This approach has been shown to be valid in noncancer patients by using EPC and graduated-compression stockings combined with UFH or LMWH[167,168] and has shown promise in patients undergoing craniotomy for brain tumors.[169] The second approach might be accomplished by extending the duration of thromboprophylaxis sufficiently that the asymptomatic thromboses fail to propagate, fail to embolize, and successfully undergo spontaneous thrombolysis. This approach has been recently found to be valid as well.

A similar group of patients undergoing planned curative open surgery for abdominal or pelvic cancer were all given enoxaparin, 40 mg once daily for 6 to 10 days, and subsequently randomized to 21 additional days of enoxaparin at the same dose or 21 days of placebo.[170] Bilateral venography was performed between days 25 and 31 after surgery, and patients were clinically followed up for a total of 3 months after surgery. A total of 501 patients were randomized with 332 patients included in the efficacy analysis. The group that was randomized to enoxaparin had a 4.8% rate of any DVT at 4 weeks compared with 12.0% in the placebo group ($P = 0.02$). The majority of detected DVTs were asymptomatic and involved calf veins. Approximately 1.5% of patients in both groups had clinically apparent VTE in the 2 months of follow-up with no prophylaxis (an annualized rate of 9%, roughly 90 times that of the normal population).[170] A recent clinical outcome-based study of venous thrombosis following cancer surgery reported that 40% of confirmed thrombotic events occurred more than 21 days after the operation.[171] In patients undergoing high-risk abdominal surgery, including cancer surgery, postoperative subcutaneous fondaparinux was at least as effective as perioperative subcutaneous dalteparin in preventing venous thromboembolism.[171] In the 1408 evaluated subjects in the PEGASUS study who underwent cancer surgery, 4.7% of those who were randomized to fondaparinux were diagnosed with postoperative venous thrombosis compared to 7.7% of those who were randomized to dalteparin.[172] Taken in total, these data suggest that the following scheme should be strongly considered for all cancer patients undergoing major surgery:

- All should be given combined EPC and prophylactic-intensity LMWH or fondaparinux during hospitalization (unless contraindicated by renal insufficiency or a history of heparin-induced thrombocytopenia)
- All should be considered for prophylactic dose anticoagulation for 3 weeks after hospitalization (with the same caveats)
- Extended thromboprophylaxis with prophylactic anticoagulation should be considered for those with continuing risk factors for VTE, such as chemotherapy, infection, paralysis, and use of central venous catheters

Prevention of Central Venous Access Device–Associated Deep Venous Thrombosis

The quantitative scope of the problem of central venous catheter–related UE, internal jugular, and thoracic vein thrombosis (a clinical entity distinct from catheter dysfunction due to a fibrin sheath or small, nonocclusive tip thrombosis) depends on the method of detection. The incidence ranges from 2.4% to 35% if only symptomatic

events are considered and from 36% to 66% if surveillance venography is used to detect all thromboses.[160,173–176] Because of the reported incidences of catheter-associated thrombosis, cancer patients with central venous catheters should always be considered as being at high risk for DVT.[160] These thrombi are not benign, having at least a 25% incidence of asymptomatic PE.[177] Given that PE is a significant cause of death among cancer patients, central venous catheter–related DVT must be considered a potentially lethal problem.

In addition to their shared relation with PE, central venous catheter–related DVTs also pose clinical problems that are different from those seen with LE-DVT. As with leg vein DVT, not all central venous catheter–related thromboses undergo complete physiologic thrombolysis. An unknown fraction undergo organization and remain as a permanent obstruction to the involved veins. These organized thrombi prevent insertion of subsequent catheters at that vascular site, such as at the time of tumor relapse, from 14% to 30% of the time.[175] Central venous catheter–related thrombi also can be a nidus for infection. The risk of sepsis in patients with central venous catheter–related DVT is 2.62 times that of patients with catheters but without thrombosis.[178]

By consensus, the gold standard for determining the efficacy of any method of thromboprophylaxis is the randomized clinical trial using contrast venography-documented thrombosis as an endpoint.[160] Studies using purely clinical endpoints are generally not used in this context. Relatively small studies that examined fixed, low-dose warfarin and fixed-dose subcutaneous LMWH have demonstrated successful catheter-related DVT prevention.[173,177] Reported rates of thrombosis in the active therapy groups were in the 6% to 10% range. Neither study showed toxicity with these methods of prophylaxis, although while receiving antibiotic therapy, patients taking fixed, low-dose warfarin often had sufficiently long prothrombin times that a bleeding risk was probable.[174] During times of acute illness, especially when antibiotics are used, prothrombin time monitoring is recommended in patients receiving low-dose warfarin for thromboprophylaxis. Despite the results of small, provocative studies, larger-scale and more rigorously executed studies of low-dose oral warfarin and LMWHs have failed to demonstrate greater thromboprophylactic activity than placebo.[179–181] In fact, these recently reported studies demonstrated much lower thrombosis rates than were previously reported. This might reflect improvements in catheter material and placement. At this time, routine prescription of thromboprophylaxis in cancer patients with indwelling central venous catheters is not recommended.[160]

Prevention of Central Venous Access Device–Associated Thrombotic Occlusion

Very little work has been directed at finding methods of prevention of central venous catheter thrombotic occlusion. Thrombotic occlusion can manifest as the inability to infuse, inability to withdraw, or a combination of the two, known as *total occlusion.* The methods that are used to prevent central venous catheter–associated DVT have not been evaluated for efficacy in prevention of catheter obstruction. Although it is widely held that heparin flushing and meticulous catheter care prevent this problem, no experimental data support this contention. Heparin flushing of catheters does, however, increase the risk of HIT in this already hypercoagulable population. Fortunately, a readily available and highly effective therapy is available for patients who are experiencing thrombotic catheter obstruction. Thrombolytic therapy with low-dose recombinant tissue–type plasminogen activator instilled into the obstructed catheter has roughly a 90% likelihood of restoring catheter function at 4 hours.[182,183] Consequently, in the face of limited data on efficacy, infrequent but potentially severe toxicity, and highly effective salvage therapy, routine flushing of catheters with UFH to prevent occlusion cannot be recommended. Flushing of catheters with normal saline after each use is suggested as a preferable alternative to heparin flushing.

The only parameter that has been found to affect rates of thrombotic catheter occlusion is the anatomic location of the catheter tip. Catheters whose tips have been placed in the innominate vein have an inordinate incidence of thrombosis, especially compared with those whose tips are in the lower portion of the SVC or right atrium. Use of intraoperative guide-wire measurement or alternative techniques to ensure that the catheter tip is placed in the lowest third of the SVC is recommended.

Thromboprophylaxis during Chemotherapy

Chemotherapy is an independent risk factor for both VTE[1,184,185] and death within 1 week of VTE,[159] above and beyond that conferred by the presence of cancer alone. Unfortunately, the absolute risk of VTE that is conferred has been studied in only a relative few of the many chemotherapy regimens used to treat the wide spectrum of known malignant diseases. The absolute risk of VTE varies from 1.3% per year with tamoxifen only to 7.9% per year with tamoxifen combined with CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) as adjuvant therapy for breast cancer[1,27] to as much as 43% during shorter-duration therapy of a variety of malignancies with thalidomide-containing regimens.[186] The 0.1% per year risk in the general population pales in comparison to these rates of VTE.

Despite the growing recognition of chemotherapy as a risk for VTE, little has been done to evaluate the role of primary thromboprophylaxis. The only trial to evaluate prophylaxis formally was done in the setting of systemic therapy for randomized breast cancer patients on active therapy with either warfarin, 1 mg daily for the first 6 months, followed by adjusted-dose warfarin to achieve an INR between 1.5 and 1.9 or placebo. The study compared the rates of clinically detected VTE over a mean of 6 months.[187] Active therapy reduced the incidence of VTE from 4.4% to 0.7%, with no differences in the rates of major bleeding complications. This intervention did not increase the costs of medical care for these patients.[188] Secondary prophylaxis (prevention of recurrence after the initial episode of VTE) by using warfarin in therapeutic doses has been effective in a limited number of patients taking thalidomide, suggesting that standard methods of thromboprophylaxis may be effective in a spectrum of chemotherapy regimens. In short, this phenomenon of chemotherapy-related VTE has not been given the attention it deserves, given the potential scope of the problem. Despite this, because of the low toxicities of current thromboprophylactic measures, it seems reasonable to consider either warfarin in doses to prolong the INR to 1.5 to 1.9 or prophylactic doses of LMWH for patients receiving chemotherapy regimens associated with a meaningful increased risk of VTE.

Thromboprophylaxis for the Hospitalized Cancer Patient

Being sufficiently ill to require hospitalization for any reason is associated with a 100-fold increase in the risk of VTE[189] and an 18-fold increase in the risk of death within 1 week of VTE[159] compared with community residents. Patients who have been hospitalized for medical illness account for almost 23% of all cases of VTE.[185] Hospitalization for medical illness complicating cancer further increases the risk of VTE.[185,190] Patients with cancer who have been hospitalized for nonsurgical illness account for almost 30% of all cases of VTE,[184] making this population a prime target for the use of thromboprophylaxis.

Thromboprophylaxis has not been studied specifically in medically ill cancer patients. Inferences must be made from studies of a wide spectrum of patients with medical illnesses, some of whom have cancer. In this population, meta-analysis has shown that thromboprophylaxis with UFH or LMWH is associated with a more than 50% reduction in symptomatic DVT and PE without an increase in bleeding complications.[191] The first prospective, randomized, controlled trial of thromboprophylaxis in this group of patients using the

gold standard of contrast venography endpoint randomized 866 patients (14% of whom had cancer) to receive either placebo or one of two doses of enoxaparin (20 mg daily or 40 mg daily) during their hospitalization.[192] At the time of discharge, DVT had developed in approximately 15% in the placebo group and in the group randomized to receive 20 mg of enoxaparin daily but only in 5.5% in the group randomized to 40 mg of enoxaparin daily, a risk reduction of more than 60% that was highly statistically significant. This population of medically ill patients was at high risk of bleeding complications. As a group, 1.3% experienced major hemorrhage during their hospitalization (a median of 7 days). The use of enoxaparin was not associated with an increase in this basal rate of major hemorrhage. This therapy was associated with a small increase in the cost of hospitalization but could actually be cost effective if one considers the savings from not having to treat as many new VTEs.[193] These data strongly suggest that all hospitalized cancer patients receive thromboprophylaxis with an LMWH unless contraindicated by either severe renal insufficiency or a history of HIT.

Chemotherapy-related thrombocytopenia, intracranial malignancy, and gastrointestinal lesions have been perceived by some physicians as contraindications to the use of prophylactic doses of LMWH. Whereas no data formally evaluate the safety of prophylactic LMWH in these high-risk situations, inferences can be made from several sources. Patients undergoing elective neurosurgery, including surgery for intracranial malignancy, have an incidence of bleeding similar to that of hospitalized medical patients (approximately 2%–3%).[169,194] This rate of bleeding was not increased with the use of 40 mg of enoxaparin daily.[194] Patients undergoing curative abdominal and pelvic surgery for cancer do not have an increased rate of bleeding complications with the use of this dose of enoxaparin.[166] From these data, it appears that the use of prophylactic doses of LMWH is unlikely to pose an additive risk of bleeding over that inherent with the underlying disease. Consequently, unless the extent of the intracranial or gastrointestinal disease or the degree and duration of thrombocytopenia are great, these comorbidities pose only a relative, and probably small, contraindication to the use of pharmacologic thromboprophylaxis. In situations in which this type of prophylaxis is perceived to be contraindicated, use of EPC and/or periodic ultrasound surveillance[195] is strongly recommended.

In the previously mentioned thromboprophylaxis trial,[192] all patients were monitored for the development of symptomatic VTE for 3 months after discharge. In approximately 1% of the patients, symptomatic DVT or PE developed during this time, which is roughly 40 times the incidence of VTE in the general population. This incidence is similar to that seen in the 3-month follow-up of patients undergoing curative surgery for cancer,[170] in which prolonged use of enoxaparin after discharge has been shown to be safe and effective in prevention of DVT. These data suggest that the risk of VTE does not end as the patient passes out through the doors of the hospital but continues for a protracted period. Extended thromboprophylaxis, as used in cancer surgery, should be strongly considered, especially in patients whose in-hospital cancer therapy has not been completely curative.

FUTURE PROSPECTS

As more and more oncologists become aware of the importance and challenges of clinical thrombosis in patients with malignancy, we will likely see more attention paid to earlier venous thrombosis diagnosis, optimization of acute and chronic venous thrombosis management, and greater compliance with thromboprophylaxis recommendations. We hope that venous thrombosis will be viewed less as simply a nuisance during the care of cancer patients and more as a major source of patient morbidity, treatment delay, and mortality.

Continued improvements in duplex ultrasound, CT, and MRI are expected. The ability to scan the pulmonary vasculature, abdominal vasculature, pelvic veins, and lower extremities with one contrast injection and one imaging session will likely be perfected. This will provide a more comprehensive approach to thrombosis confirmation and will limit intravenous contrast exposure. Nuclear medicine scans that are capable of whole-body thrombus imaging are on the horizon and might even assist with the detection of occult malignancy in patients with an initial idiopathic VTE. Integration of diagnostic algorithms into one's oncology practice could assist the busy clinician with decision making in the case of suspected DVT and PE.

Continued interest in developing improved strategies to treat VTE specifically in the cancer patient is anticipated. Further reduction in both thrombosis recurrence rates and bleeding rates is needed. Prospective clinical trials are needed to support the long-term anticoagulation of the cancer patient with thrombosis. In particular, optimal management of women with thrombosis and the need for years of adjuvant hormonal therapy for breast cancer must be clarified. Despite excellent compliance with daily subcutaneous LMWH for up to 6 months of VTE therapy, newer oral anticoagulants could make long-term anticoagulation more palatable to all patient populations. Newer oral compounds might prove to be effective for primary and secondary venous thromboprophylaxis specifically in the cancer patient. Careful assessment for hepatic toxicity will be required before use in cancer patients who are prone to liver metastases and those receiving hepatically metabolized chemotherapeutic agents. Further research into the anticancer and survival prolongation properties of selected anticoagulants might identify a particular agent or class of agents as being ideal in cancer patients in general or in those with specific responsive tumor histologies.

Prevention will continue to be of paramount importance. It is always easier and less potentially toxic to prevent thromboses with low doses of anticoagulation than to treat life-threatening thromboses with longer courses of higher doses of the same drugs. Ongoing research attempting to link thrombosis with accelerated tumor neovascularization, growth, and metastases may highlight the importance and value of aggressive primary thrombosis prevention in all cancer patients. Time and significant research efforts will tell.

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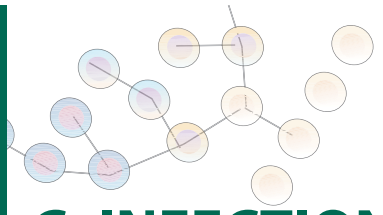
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C. INFECTIONS

47 Infection in the Patient with Cancer

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SUMMARY OF KEY POINTS

- Risk assessment is an important tool for evaluation and treatment in the patient with cancer who has fever and neutropenia. Patients who are expected to have neutropenia lasting more than 7 days, including those undergoing allogeneic stem cell transplantation or therapy for acute leukemia, are considered to be at high risk for infectious complications. Most patients with solid tumors will have neutropenia lasting less than 7 days and are considered to be at low risk.
- Other risk factors for infection in patients with cancer, besides chemotherapy- and disease-related neutropenia, are presence of indwelling catheters, comorbid medical conditions such as diabetes or chronic obstructive pulmonary disease, recent surgery, malnutrition, and cellular and humoral immune defects from underlying tumor and its treatment.
- Fever during neutropenia necessitates immediate evaluation, assessment of risk as high or low, appropriate cultures, and prompt institution of empirical broad-spectrum antibacterial therapy with a defined regimen that covers *Pseudomonas aeruginosa* and enteric gram-negative organisms, as well as common institutional pathogens. Gram-positive–active agents are not a standard component of the empirical treatment regimen for fever and neutropenia.
- Antibiotic prophylaxis with levofloxacin has been shown to decrease fever and infection in high-risk patients with acute leukemia or those undergoing stem cell transplantation, with neutropenia (<1000 neutrophils/mm^3) lasting more than 7 days, although no morality benefit has been consistently shown.
- Posaconazole prophylaxis reduces the incidence of invasive fungal infections and mortality in patients undergoing induction for acute leukemia and reduces fungal infections in patients treated for higher-grade graft-versus-host disease (GVHD). Voriconazole has been shown equivalent to fluconazole for prevention of fungal infections in allogeneic stem cell transplant recipients.
- Newer agents used to treat a variety of lymphoproliferative disorders (e.g., alemtuzamab, purine analogs) result in prolonged suppression of cellular immunity and predispose to certain infections; patients receiving these agents may benefit from prophylaxis against opportunistic infections.
- An epidemic strain of *C. difficile* has emerged as a major cause of morbidity and mortality in many centers, and fluoroquinolone use is a risk factor. Metronidazole is recommended for mild disease, but oral vancomycin should be given for more severe symptoms of *C. difficile* infection.
- Numerous antifungals may be used for empirical antifungal therapy after 4 to 7 days of broad-spectrum antibiotics in patients who are still febrile; however, some debate continues regarding whether all patients definitely require empirical antifungal therapy. A high-resolution computed tomography (CT) scan of the chest may identify possible mold infections and guide antifungal management.
- Patients scheduled for allogeneic hematopoietic stem cell transplantation (HSCT) should be screened for evidence of latent herpesvirus and hepatitis virus infections, and prophylaxis instituted accordingly.

INTRODUCTION

Numerous disease-related and chemotherapy-induced factors render the patient with cancer at increased risk for infection.[1,2] These include the type of cancer (solid tumor versus a lymphoma or acute leukemia), depth and duration of neutropenia, and impairments in cellular function caused by cytotoxic or immunosuppressive drugs; breaches in the integument from surgical procedures, presence of indwelling plastic venous catheters, or mucositis of the gastrointestinal tract secondary to chemotherapy; and comorbid conditions such as malnutrition, deconditioning, or medical problems such as chronic obstructive lung disease or diabetes. In recent years, it has become clear that prevention, diagnosis, and management strategies for infectious complications in patients with cancer are greatly influenced by overall immunosuppression status, as reflected by the cumulative burden of these risk factors. Nonetheless, neutropenia remains a critical risk factor for infection in these patients, and the oncologist must be informed of the most appropriate methods for managing fever and other possible infections during neutropenia.

This chapter addresses current standards for the management of fever during neutropenia and also highlights contemporary guidelines for the prevention and treatment of common infectious complications in patients with cancer.

INFECTION RISK FACTORS

Neutropenia as a Risk Factor for Infection

The association between neutropenia and increased infection risk initially was demonstrated by Bodey and colleagues in 1966 in a study of leukemic patients undergoing cytotoxic therapy.[3] The data show that the frequency of infectious complications is inversely related to the degree and duration of neutropenia (Fig. 47-1). Infection risk starts to increase when the absolute neutrophil count

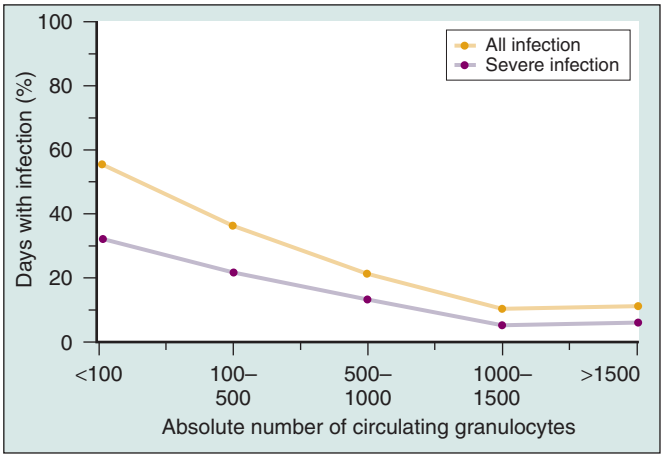


Figure 47-1 • Relationship between neutrophil count and infection in patients with acute leukemia.

(ANC) decreases to less than 1000 cells/mm^3 and increases dramatically when it is less than 500 cells/mm^3. Fewer than half of the neutropenic patients who become febrile will have an identified infection. In roughly 10% to 20% or more of patients with neutrophil counts less than 100 cells/mm^3, a bloodstream infection will develop. More than 50% of all episodes of fever and neutropenia represent *fever of undetermined origin* (FUO), with no identifiable infection source on physical and radiographic examination and cultures.[3,4] In addition to the depth of the ANC nadir, the duration of neutropenia also is an important determinant of both infection risk and infection type. Brief durations of neutropenia, particularly for less than 7 days, are associated with a rapid and favorable response to empirical antibiotic therapy. Fever often may be of unknown origin during this early phase of neutropenia, but if a causative pathogen is identified, bacteria and viruses predominate. A neutrophil count persistently less than 500 cells/mm^3 for more than 7 days is associated with greater risk for infection-related morbidity and mortality and is the setting in which *Aspergillus* and other invasive fungal infections most often occur. Other pathogens that may cause infection during the course of prolonged neutropenia (i.e., after 7 days) include antibiotic-resistant bacteria, *Candida* species, and other molds. Deaths during neutropenia usually are due to these subsequent infections. Overall mortality rates during fever and neutropenia are less than 1% for low-risk patients and approximately 5% for those with more prolonged duration of neutropenia.[5–9]

In addition to cytotoxic chemotherapy, other cases of neutrophil deficiency include bone marrow incompetence occurring as a result of myelodysplastic syndrome, or secondary to crowding out of normal granulocytic precursors by tumor cells. "Functional neutropenia" due to impaired neutrophil microbicidal activity may arise as a consequence of underlying disease such as leukemia or therapies such as steroids. In these instances, ineffective neutrophil killing leaves the patient highly vulnerable to infection despite seemingly normal peripheral white blood cell counts.

Other Risk Factors for Infection

Disruption of integumentary, mucosal, and mucociliary barriers by cytotoxic therapies provides opportunities for invasion by colonizing bacteria on the skin, gastrointestinal tract, or mucous membranes.[10] Shifts in normal colonizing microbial flora at these sites occur as a result of chemotherapy, antibiotic use, and nosocomial exposures, leading to increased colonization with gram-negative and antibiotic-resistant pathogens. Indwelling catheters create a significant breach in host defense, permitting direct access of skin flora and other pathogens to blood or subcutaneous tissue. Tumor growth can disrupt normal anatomic structures, and cancer surgery may result in anatomic alterations and wounds, providing local sites for pathogen entry.

Underlying diseases and cancer therapies also play important roles in infection risk. For example, hypogammaglobulinemia often complicates chronic lymphocytic leukemia (CLL) or multiple myeloma, so that patients are at increased risk for severe pneumococcal infections or *Haemophilus influenzae* or *Neisseria meningitidis* infection. In contrast to patients with solid tumors, those with acute leukemias are more likely to have overwhelming sepsis or invasive fungal infections because of prolonged periods of profound neutropenia related to the underlying leukemia. Patients with acute lymphocytic leukemia, Hodgkin's disease, or non-Hodgkin's lymphoma (NHL) typically have defects in cell-mediated immunity that predispose them to development of *Pneumocystis jirovecii* pneumonia (PCP), cryptococcal disease, or infections with intracellular organisms such as *Salmonella* or *Listeria*.

Steroid therapy induces a broad immunosuppressive effect, including impaired chemotaxis and killing by neutrophils, impaired T-cell function, and alterations in skin and mucosal barriers. Long-term or high-dose steroid therapy is a significant risk factor for invasive fungal infections in particular (i.e., *Aspergillus* and *Cryptococcus*), as well as *P. jiroveci* (usually seen with tapering of the steroid regimen). Such therapy also may predispose affected patients to development of bacterial infections and *Mycobacterium tuberculosis* reactivation. High-dose cytosine arabinoside therapy causes mucositis that may predispose to life-threatening streptococcal bacteremias.[11] Fludarabine and alemtuzumab cause prolonged suppression of CD4$^+$ lymphocytes and attendant susceptibility to infections with *Listeria*, *P. jiroveci*, and herpesviruses, as well as bacterial infections.[12,13] Temazolomide with radiation, given for glioblastoma, also is associated with increased susceptibility to *P. jiroveci*, as well as profound myelotoxicity.[14]

SOURCES OF INFECTION

Colonization by pathogenic bacteria, fungi, or viruses generally is a prerequisite for infection. Accordingly, endogenous bacterial and fungal flora and latent herpesvirus infections account for a majority of initial infections in the neutropenic patient with cancer.[11,15,16] These include skin colonizers such as *S. aureus* and coagulase-negative staphylococci, viridans streptococci, and herpes simplex from the oropharynx, and gram-positive bacteria as well as enteric gram-negative bacteria from the gut. *Candida albicans* infections often are derived from the skin or the gastrointestinal or female genital tract. Latent infections that may reactivate during immunosuppression include those due to herpes simplex or varicella-zoster virus, Epstein-Barr virus (EBV), and cytomegalovirus (CMV), as well as hepatitis B and C viruses, *M. tuberculosis*, and *Toxoplasma gondii*.

Exogenous sources of infection often are found in the hospital and home environments. Contaminated blood products, hospital equipment, water sources, and nosocomial spread of organisms from health care workers represent less common, albeit significant sources of infection. Common nosocomially spread infections include those due to *C. difficile*, respiratory viruses, vancomycin-resistant enterococci, and other multiresistant bacteria. Water sources such as faucets and shower heads have been implicated in the spread of *Legionella*. Outbreaks of infection related to intravenous solutions have been well documented with *Klebsiella* and *Enterobacter*.[17–19]

Foods can be a potential infection source, particularly unwashed fruits and vegetables. Neutropenic patients generally are advised to avoid raw foods of this type unless measures are taken to peel or thoroughly wash them. Potted plants, mulch, and excavation and building or renovation sites have been identified as sources of *Aspergillus* and other molds that may cause disease.[20]

APPROACH TO FEVER IN THE NEUTROPENIC PATIENT

Fever often is the only reliable sign of significant underlying infection in the neutropenic patient. No specific clinical features, such as hypotension or chills, or magnitude of the increase in body temperature can accurately distinguish between fever due to an infection and that due to a noninfectious cause. Nor are laboratory tests such as determination of C-reactive protein and procalcitonin considered specific or rapid enough to be relied on.[21] Therefore, all febrile neutropenic patients should receive empirical broad-spectrum antibiotics, ideally within 1 hour of presentation. Although a clinically or microbiologically documented source of fever is not found in most patients with fever and neutropenia, the rapid initiation of empirical antibiotic therapy remains an important standard of care for all patients in this setting. The choice of specific antibiotic regimens, however, depends on an assessment of the patient's infection risk during neutropenia, which is in turn dependent on duration of neutropenia, underlying cancer, and comorbid medical conditions. Conditions and findings that may alter the empirical antibiotic regimen are shown in Table 47-1.

DEFINITIONS

Guidelines for evaluating antimicrobial therapy for fever and neutropenia have been developed by the Infectious Diseases Society of America (IDSA) and the National Comprehensive Cancer Network (NCCN):[2,22] *Fever* is defined as a single temperature measurement of

Table 47-1 Approach to Management of Fever and Neutropenia

History and Physical Findings	Indicated Modifications in Antimicrobial Coverage or Diagnostic Test
Fever during neutropenia	*Empirical antibiotic regimen*: See text.
	If the patient is on antibiotic prophylaxis, then empirical therapy must be based on an agent of a different class from that for prophylaxis (e.g., if the patient is on fluoroquinolone-based prophylaxis, then switch to a beta-lactam–based regimen).
Hypotension, signs of sepsis	*Broad-spectrum antimicrobial coverage*: A triple-antibiotic regimen (e.g., carbapenem plus vancomycin plus an aminoglycoside) is recommended.
	If cultures are negative for gram-positive organisms, consider discontinuing vancomycin after 3 days.
Fever that is persistent or recrudescent on or after day 5 of antibiotic therapy	*Empirical antifungal therapy*: Add amphotericin B product, an echinocandin, or voriconazole if the patient is not already on prophylaxis with a mold-active agent. CT scan of the chest may help identify fungal infection.
	Consider CT scan of the chest and frequent galactomannan testing during neutropenia to guide preemptive treatment, as an alternative strategy to empirical antifungal treatment.
Severe oral or esophageal mucositis	Send swab for viral (HSV) culture.
	Add antiviral coverage (if not already being given).
	Consider antiviral resistance to prophylaxis if esophagitis occurs late in the course of neutropenia.
	Add antifungal agent for possible *Candida* esophagitis.
	Switch streptococcal coverage to vancomycin.
	Esophagoscopy may be indicated.
Catheter exit site or tunnel erythema, tenderness, or discharge or cellulitis at any site	Culture any discharge.
	Add vancomycin.
	For tunnel infection (erythema and tenderness 2 cm above exit site), catheter removal and surgical débridement generally are required.
Possible anaerobic infection	Add metronidazole to broad-spectrum antibiotics.
Abdominal pain, especially right lower quadrant, suggestive of neutropenic enterocolitis	Perform CT scan of affected area.
	Supportive care: Avoid surgical intervention if possible in a neutropenic patient.
Oropharyngeal or neck or soft-tissue swelling	
New pulmonary infiltrate	Bronchoscopy (with or without biopsy) is the preferred method for evaluating new infiltrates in the high-risk patient.
	Nodular: Add mold coverage with voriconazole, posaconazole, or amphotericin B preparation.
	Alveolar: Broaden gram-negative coverage and add *Legionella* coverage (quinolone or macrolide).
	Interstitial: Send specimen for diagnostic studies for both respiratory viruses and herpesviruses, particularly CMV.
	Review patient history for risk factors for tuberculosis or infection with endemic fungi.
Upper respiratory symptoms of coryza, congestion during fall/winter	Send nasal wash or swab for respiratory virus culture and rapid antigen tests for RSV and influenza virus.
Hemorrhagic cystitis	Indicated studies include urine viral culture and BK virus PCR assay.

CMV, cytomegalovirus; CT, computed tomography; HSV, herpes simplex virus; PCR, polymerase chain reaction; RSV, respiratory syncytial virus.

38.3° C (101° F) or greater, in the absence of other obvious causes; a temperature of 38° C or greater for an hour or longer is considered to represent a "febrile state" that also requires prompt evaluation and intervention in the setting of neutropenia.[2,22] *Neutropenia* is defined as an absolute neutrophil count (ANC) less than 1000 cells/mm^3 in some centers but more often is designated by a neutrophil count of less than 500 cells/mm^3, which is a level associated with a much higher risk for infection. For practical purposes, an ANC less than 500 cells/mm^3, or a count that is anticipated to fall below that level within 48 hours, constitutes a state of neutropenia.

Rarely, a neutropenic patient who is afebrile may exhibit signs or symptoms of infection (e.g., abdominal pain, severe mucositis, perirectal pain) and should be considered to have an active infection. The concomitant administration of corticosteroids also may initially blunt the fever response. With afebrile neutropenic patients who show signs or symptoms suggestive of an infection, empirical antibiotics should be started immediately because of their increased risk for serious invasive infections.

INITIAL EVALUATION

The initial evaluation should be directed toward determining the possible sites of infection and causative organisms and assessing the patient's level of risk for infection-related complications. A thorough site-specific review of systems is essential. Pertinent history includes recent antibiotic therapy, recent surgery or other invasive procedures such as biopsies or catheter placement, and possible exposure to infections from close contacts and household members, foods, animals, or travel.

The physical examination should focus on common potential sites of infection. Worthy of emphasis in this regard is that the manifestations of infection are muted in the absence of inflammatory cells. Careful examination of the oropharynx may reveal ulcers, or plaque-like lesions may be due to herpes or thrush, and specimens for appropriate tests should be sent for evaluation. Catheter sites require careful assessment for erythema, tenderness, or discharge. With bacterial cellulitis of the skin or perirectum, induration and erythema may be minimal; pimples or pustules are uncommon without neutrophils to create pus. Similarly, few respiratory signs or symptoms may be noted, and auscultation of the lungs may reveal few adventitial sounds, but an infiltrate may be seen on radiographs. A urinary tract infection may not be associated with dysuria. Gastrointestinal tract mucositis due to cytotoxic chemotherapy can lead to sore throat, oral ulcers, and diarrhea that are indistinguishable from the signs and symptoms of infection. Abdominal pain in neutropenic patients may signify a wide variety of problems, including intestinal tumor necrosis and neutropenic enterocolitis, both of which can result in intra-abdominal catastrophe or sepsis.

Initial laboratory evaluation should include a complete blood count and differential white cell count to determine the degree of neutropenia, liver and renal function tests, oxygen saturation determination, and urinalysis. Chest radiography should be performed routinely at presentation with fever and neutropenia, but initial findings may be minimal in neutropenic patients with pneumonia. Two blood culture samples, each consisting of 20 to 40 mL of blood, should be obtained from febrile, neutropenic patients.[4] An adequate volume of blood taken for culture will enhance the chances of recovering a pathogen.[23]

The usefulness of taking blood samples from both a vascular catheter and a peripheral vein has been confirmed, and this strategy is now standard practice in evaluation. Dual-site blood cultures may help determine whether the catheter is a source of infection if the differential time to positivity between catheter- and venipuncture-derived cultures is less than 2 hours.[24] One study, however, revealed that in patients with cancer, catheter-drawn blood culures without concomitant peripheral cultures have very good negative predicitve value and fairly good sensitivity (89%) and specificity (95%), albeit with low positive predictive value; accordingly, a positive result—especially for a common contaminant such as coagulase-negative staphylococci—requires careful clinical interpretation.[25] Quantitative blood cultures are rarely used because of their expense.

Cultures of any suggestive sites of infection should be performed: Diarrheal stools should be tested for the presence of *C. difficile* toxin, specimens from oral or perineal lesions suspected to harbor herpes simplex virus (HSV) should be sent for viral cultures, and nasal wash or swab specimens for culture for respiratory viruses should be obtained in patients with suggestive signs or symptoms during the winter season.

Risk Assessment

Risk assessment should be performed as part of the initial evaluation in an effort to predict the probability that a patient is at high or low risk for serious complications during a febrile episode.[2,22,26–33] The assessment of a patient's risk is driven largely by the duration of neutropenia expected to occur as a consequence of chemotherapy, and by certain historical and physical characteristics of the neutropenic patient who presents with fever (Table 47-2). Clinical features in low-risk patients include neutropenia anticipated to last less than 7 days, absence of serious medical comorbidity, and outpatient status at onset offever.[2,5,6] Typically, low-risk patients are those receiving chemotherapy for solid tumors or consolidation therapy for leukemia. These patients may be eligible to receive treatment outside of the traditional hospital setting or receive initial empirical therapy with oral antibiotics. Clinical features in high-risk patients generally include expected duration of neutropenia of 7 days or longer and presence of serious medical comorbidity. These patients may be recent recipients of allogeneic hematopoietic stem cell transplants or patients with acute leukemia not in remission, or with neutropenia secondary to induction therapy or other conditions such as aplastic anemia. Additionally, non-neutropenic patients with graft-versus-host disease (GVHD) treated with significant doses of corticosteroids also are considered to be at high risk for infections, particularly those due to encapsulated bacteria and invasive molds. Recipients of autologous hematopoietic stem cell transplants seem to be at intermediate risk for infections, even though prolonged (longer than 7 days) durations of neutropenia are likely in these patients. Similarly, patients with lymphoma or CLL and recipients of purine analog therapy (e.g., fludarabine) or those undergoing mini-allogeneic transplantation may be considered to be at intermediate risk for severe infection because they tend to have only brief periods of neutropenia, or none at all, but they may acquire significant impairments of cellular immunity that make them susceptible to certain types of infections. Although many clinicians rely on the criteria shown in Table 47-2, an important point is that these criteria are derived from clinical observations from numerous trials, rather than from a risk assessment algorithm.[2] The Multinational Association of Supportive Care in Cancer (MASCC) has put forth a set of validated clinical prediction rules that can distinguish high- from low-risk patients with substantial accuracy (see Table 47-2).[8,29] This prediction model has recently been validated, and the use of the MASCC prediction criteria is encouraged to distinguish between low- and high-risk patients.[33]

Once risk categorization has been assigned and after pertinent historical data have been acquired, physical examination and radiographic studies have been performed, and appropriate culture specimens have been obtained, then empirical antibiotics should be started promptly in the patient with fever and neutropenia. Preferably, these tasks should be completed within 1 or 2 hours, at most.

EMPIRICAL ANTIBIOTIC THERAPY: GENERAL PRINCIPLES

Numerous clinical trials over the last 3 decades have failed to demonstrate the clear superiority of one empirical antibiotic therapy

Table 47-2 Risk for Infectious Complications after Cytotoxic Chemotherapy: Clinical Features Defining Risk Status and Risk Prediction in Patients with Fever and Neutropenia

GENERAL CLINICAL FEATURES IN HIGH- VERSUS LOW-RISK PATIENTS

High risk

- Neutropenia anticipated to extend to or beyond 7 days
- Presence of any comorbid medical problems including but not limited to
  - Hemodynamic instability
  - Oral or gastrointestinal mucositis that interferes with swallowing or causes severe diarrhea
  - Abdominal pain or perirectal pain of new onset
  - Nausea and vomiting
  - Diarrhea (passage of six or more loose stools daily)
  - Neurologic or mental status changes of new onset
  - Intravascular catheter infection, especially catheter tunnel infection
  - New pulmonary infiltrate or hypoxemia, or underlying chronic lung disease
- Evidence of hepatic insufficiency (defined as aminotransferase values greater than 5 times normal values) or renal insufficiency (defined as a creatinine clearance less than 30 mL/min).

Low risk

- Neutropenia expected to resolve within 7 days
- Absence of any medical comorbidity as listed in high-risk criteria
- Adequate hepatic function and renal function

MASCC PREDICTION TOOL FOR DETERMINING HIGH AND LOW RISK FOR SERIOUS MEDICAL COMPLICATIONS

Characteristic	Weight (No. of Points)*
Age <60 years	2
Outpatient status	3
Clinical status at presentation	
No severe burden of febrile neutropenia	
No or only mild symptoms	5
Moderate symptoms	3
No hypotension: systolic blood pressure >80 mm Hg	5
No dehydration requiring parenteral fluids	3
Medical history, underlying disease, and/or comorbidity	
No chronic obstructive pulmonary disease	4
Solid tumor or hematologic malignancy without previous invasive fungal infection	4

MASCC, Multinational Association for Supportive Care in Cancer.

*If relevant, points are added to yield a sum score. If the score is >20, the patient is predicted to be at low risk (<10%) for the development of serious medical complications during the course of febrile neutropenia.

Adapted from IDSA Guidelines 2007.

regimen over all others. Effective and reliable regimens, however, are characteristically bactericidal for gram-negative pathogens, particularly *P. aeruginosa*, even in the absence of neutrophils. Several antibiotic approaches are acceptable, but an important point is that the final choice of a specific regimen will depend on the patient's risk factors for infection, the specific sites that may be sources of infection, and the prevailing institutional flora.

Monotherapy with a broad-spectrum antipseudomonal agent such as an extended-spectrum antipseudomonal cephalosporin (e.g., cefepime, ceftazidime), or piperacillin-tazobactam or a carbapenem (e.g., imipenem-cilastatin, meropenem), constitutes a standard approach to the management of fever and neutropenia in patients with cancer. [2,22,30–39] The choice of agent should be based on a review of local institutional bacterial susceptibility patterns. Some institutions routinely use combinationt therapy with either (1) an aminoglycoside plus either an extended-spectrum antipseudomonal cephalosporin or piperacillin-tazobactam or (2) ciprofloxacin plus an antipseudomonal penicillin. No clear benefit of combination therapy over montherapy has been demonstrated, and increased renal toxicity has been observed with aminoglycoside use.[39,40] In an era of increasing bacterial resistance, however, circumstances may arise in which initial empirical antibiotic combinations are advisable.[41] With the possibility of infection due to methicillin-resistant *S. aureus*, for example, addition of vancomycin is prudent. If a pneumonia is identified at the outset, then adding an antipseudomonal fluoroquinolone (i.e., ciprofloxacin or levofloxacin) ensures a broadened spectrum against potentially resistant gram-negative or atypical pathogens, as well as "atypical" organisms such as *Legionella*.[42]

INITIAL EMPIRICAL ANTIBIOTIC THERAPY

For patients who have been determined to be at low risk for developing infection-related complications during the course of neutropenia, oral ciprofloxacin plus amoxicillin-clavulanate (or clindamycin for patients who are allergic to penicillin) is an effective alternative to intravenous monotherapy, as indicated by several large randomized studies.[30–32] High-dose ciprofloxacin or ofloxacin oral monotherapy has been evaluated in small trials, but the evidence does not currently support the routine use of these fluoroquinolones for monotherapy in low-risk patients with fever and neutropenia.[43–46] Ciprofloxacin as a single agent does not provide adequate coverage for certain gram-positive organisms (e.g., *S. aureus*, alpha-streptococci), and therefore should never be used without an additional antibiotic directed toward those pathogens. Levofloxacin oral monotherapy has not been adequately studied.

Patients who are assessed as being in a high-risk category for complications during fever and neutropenia should receive intravenous antibiotics, as outlined earlier, in the inpatient setting. The choice of specific regimen is highly dependent on institutional profiles of pathogen susceptibility and on potential infection sites in a specific patient.

Use of Vancomycin or Other Gram-Positive Agents

Vancomycin or another agent with activity against drug-resistant gram-positive pathogens is not routinely recommended for inclusion in the initial empirical regimen, despite a predominance of gram-positive pathogens isolated in febrile neutropenic patients.[47] The dilemma is that a small proportion of infections caused by gram-positive pathogens can be fulminant, so some clinicians are anxious to use these agents. Regardless, a large, prospective, randomized trial from the European Organization for Research and Treatment of Cancer failed to show a clinical advantage for using a vancomycin-containing regimen over one that did not contain vancomycin, in adults with fever and neutropenia.[48] A major concern with widespread routine empirical use and prolonged courses of vancomycin has been the emergence of vancomycin-resistant organisms, especially

enterococci, associated with these practices. To limit the spread of vancomycin resistance, the Hospital Infection Control Practices Advisory Committee of the Centers for Disease Control and Prevention has issued guidelines to limit vancomycin use.[49] These guidelines include specific clinical situations that may justify initial use of vancomycin therapy in febrile, neutropenic patients with cancer (Table 47-3). Other agents active against gram-positive pathogens include daptomycin, quinupristin-dalfopristin, and linezolid. The use of these drugs should be similarly limited to distinct indications, rather than broadly applied. Caution is advised with use of these agents because each has significant adverse effects; of note, linezolid may cause myelosuppression when used for a prolonged course.

Documented serious, clinically apparent infections that are likely to be caused by gram-positive pathogens, such as cellulitis or obvious catheter-related infections, should be treated with vancomycin or another gram-positive–active agent. Many catheter-related bloodstream infections are caused by coagulase-negative staphylococcal isolates, which have high-level beta-lactam antibiotic resistance. Increasingly, *Staphylococcus aureus* also is being seen as a community-acquired pathogen.[50] If the patient is known to be colonized with methicillin-resistant *S. aureus*, then vancomycin should be added to the initial regimen until blood and other cultures are proved negative for this organism. Substantial mucosal damage increases risk for infection with viridans streptococci, of which 18% to 29% of are beta-lactam–resistant.[51–55] High-dose cytarabine or intensive therapy that damages oropharyngeal mucosal barriers has been associated with an increased risk of such overwhelming sepsis due to viridans streptococcal infections. Prophylaxis with ciprofloxacin or trimethoprim-sulfamethoxazole (TMP-SMX) also has been associated with an increased risk of gram-positive infections, particularly those due to viridans streptococci.[51–54] Viridans streptococcal breakthrough infections also have been observed with levofloxacin prophylaxis.[55,56]

Presence of hypotension or septic shock in a neutropenic patient necessitates very broad empirical antibiotic coverage, including the use of a gram-positive–active agent, until culture results are available. If a vancomycin (or other gram-positive–active agent) is added initially for empirical coverage, its use should be reassessed in 2 or 3 days. If a drug-resistant gram-positive pathogen cannot be identified, empirical vancomycin therapy should be discontinued.[49]

Table 47-3 Appropriate Use of Gram-Positive–Active Antibiotics in the Neutropenic Cancer Patient

VANCOMYCIN OR ANOTHER GRAM-POSITIVE–ACTIVE ANTIBIOTIC

Clinical situations for which addition of vancomycin or another gram-positive–active antibiotic is recommended include the following:

- Clinically apparent, serious catheter-related infection (e.g., tunnel or port pocket infection, any other skin or soft-tissue infection)
- Blood culture positive for gram-positive bacteria before final identification and susceptibility testing
- Known colonization with methicillin-resistant *Staphylococcus aureus* (MRSA)
- Hypotension or septic shock without identified pathogen (i.e., clinically unstable patient)
- Risk factors for viridans streptococcal bacteremia, including severe mucositis (typically associated with high-dose cytarabine and with TMP-SMX or fluoroquinolone prophylaxis)

OTHER AGENTS FOR USE WITH KNOWN VANCOMYCIN RESISTANCE

Linezolid, quinupristin-dalfopristin, or daptomycin may be used in very selected clinical situations in which vancomycin-resistant pathogens (e.g., VRE) are identified or in patients for whom use of vancomycin is not a clinical option.

GRAM-POSITIVE–ACTIVE ANTIBIOTICS FOR GRAM-POSITIVE INFECTIONS ONLY

Vancomycin or other gram-positive–active antibiotic should be discontinued in 2 to 3 days if no resistant gram-positive infection is identified.

TMP-SMX, trimethoprim-sulfamethoxazole; VRE, vancomycin-resistant enterococci.

Initial Empirical Therapy for Patients Who Are Clinically Unstable

Patients who have hypotension when with fever and neutropenia, or those who have a history of *P. aeruginosa* colonization or invasive disease, should receive multidrug therapy with an antipseudomonal beta-lactam (cephalosporin, carbapenem, or penicillin, depending on local susceptibilities) plus an aminoglycoside or ciprofloxacin, and vancomycin or other gram-positive active agent. Broad coverage is warranted in view of the high mortality rate in neutropenic patients with the systemic inflammatory response syndrome.[2,22]

Subsequent Modifications of Empirical Antibiotic Regimens

No empirical antibiotic regimen initially administered for fever and neutropenia can be expected to cover all possible infections that may occur during the course of neutropenia. Therefore, modifications of the initial regimen—additions or changes of antimicrobials—sometimes are required. An important consideration in the management of cancer-related infection is that the mean time to defervescence for febrile patients with neutropenia who receive appropriate initial antibiotic therapy ranges from 2 to 7 days.[5,6] Therefore, at least 3 to 4 days of the initial antibiotic regimen should be given to otherwise stable patients, regardless of continued fever, to determine effectiveness. For patients with a documented infection, it is important to note that tissue-based infections such as pneumonia may take longer to respond to antimicrobial therapy.[7]

Patients with a fever persisting beyond 4 days of initial antimicrobial therapy, and without an identifiable site or source of infection, should undergo reassessment of their initial antimicrobial therapy. Any change in antimicrobials should be based on the patient's clinical status, results of examination and cultures, and also the likelihood of early marrow recovery. Although fever resolution may be slow, persistent fever may suggest a nonbacterial infection, a bacterial infection that is resistant to empirical antibiotics, the emergence of a secondary infection, a closed-space infection, inadequate antimicrobial serum levels, or drug fever. A careful search for these etiologic conditions should be made. Frequent and arbitrary antibiotic changes for persistent fever, in an otherwise stable patient, are to be discouraged, however. The clinically stable patient with persistent fever may be safely watched without altering the initial antibacterial therapy. If vancomycin was started earlier, it should be discontinued if the patient does not meet the criteria for its use.[49] Addition of vancomycin, without specific indications, in a blind effort to suppress persistent fever after empirical antibiotics have been started, has not been shown to be effective.[57] If the fever persists beyond 4 to 7 days, a change in antibiotic regimen or initiation of empirical antifungal therapy should be considered.

For the patient who is persistently febrile and clinically unstable, a change in antibacterial antibiotics may be needed. The addition of increased gram-negative bacillary coverage often is recommended. The addition of vancomycin should be considered if the patient's clinical situation justifies its use, as indicated in Table 47-3. If fever

persists or is recrudescent beyond 4 to 7 days of empirical antibiotic therapy, empirical antifungal therapy probably should be initiated because the risk of invasive fungal disease increases with prolonged neutropenia.

Empirical Antifungal Therapy

Empirical antifungal therapy traditionally is started when neutropenic patients demonstrate continued or recrudescent fever after 4 days or more of an empirical antibacterial regimen. The empirical use of amphotericin B in early studies during the 1970s and 1980s actually failed to demonstrate an effect on defervescence or overall survival; however, a reduction in breakthrough fungal infections was noted.[58–60] Since then, in an attempt to reduce toxicity, numerous comparative studies have demonstrated that liposomal amphotericin B, amphotericin B lipid complex, itraconazole, and caspofungin are noninferior to, albeit less toxic than, amphotericin B desoxycholate for empirical therapy.[61–67] It is likely that the other echinocandins (anidulafungin, and micafungin) also are effective in this setting, but they have not been formally studied. In one large randomized trial, voriconazole failed to fulfill criteria for noninferiority in comparison with the comparator amphotericin preparation.[68] Breakthrough fungal infections, however, were less frequent in patients receiving voriconazole. Accordingly, many clinicians accept voriconazole as appropriate for empirical antifungal therapy. Itraconazole has been demonstrated to have efficacy in this setting as well, but concerns about liver and cardiac toxicities have discouraged use of this drug.[61,67]

Whether all patients with persistent fever require empirical antifungal therapy, and when it should be started, are subjects of longstanding debate. Invasive fungal infections are now relatively infrequent during neutropenia with the advent of more effective antifungal prophylaxis and the use of colony stimulating factors to abbreviate duration of neutropenia. Furthermore, it is clear that fever is a nonspecific surrogate marker for fungal infection. Patients who are not receiving antifungal prophylaxis but who have persistent or recurrent fever after 4 to 7 days of appropriate empirical antibiotics, and without prospect for imminent neutrophil recovery, may be candidates for empirical antifungal therapy. For patients not on antifungal prophylaxis, candidemia is the greatest concern, and persistent fever may be the only manifestation. An amphotericin B preparation, caspofungin, itraconazole, and voriconazole, or even fluconazole, are considered acceptable choices. If the patient is already receiving fluconazole prophylaxis, certain non-*albicans* species of *Candida*, including *C. glabrata* and *C. krusei*, and mold infections such as invasive aspergillosis must be considered, because fluconazole has reduced activity against these *Candida* species and lacks activity against molds. At present, no data are available to guide the use of empirical antifungal therapy in patients already receiving antimold prophylaxis, such as with voriconazole, posaconazole, or an echinocandin. In all cases, symptoms and signs of invasive fungal pneumonia or sinusitis should be sought; the workup may include CT scans of chest or sinuses (or both), with follow-up nasal endoscopy or bronchoalveolar lavage as indicated. Biopsy and culture of any suspected lesions should be pursued aggressively in order to make a definitive mycologic diagnosis that can guide therapy.

CT scan of the chest is increasingly used to evaluate the possibility of invasive aspergillosis in patients with prolonged fever and neutropenia; in one study, 90% of those with proven active disease showed radiographic abnormalities by CT.[69] Macronodules with or without a halo sign are characteristic of invasive aspergillosis, the halo sign being an especially important early clue.[70] Other manifestations include nodular, wedge-shaped, peripheral, multiple, and cavitary lesions. An air-crescent sign generally is a late finding. Initiation of antifungals on the basis of finding a halo sign has been associated with significantly better response to therapy and improved survival.[71,72] In a recent pilot study, Maertens and colleagues used intensive monitoring for clinical symptoms and signs, serial galactomannan testing (see later on), and early CT scanning to identify a group of patients with persistent fever while on fluconazole prophylaxis in whom antimold therapy did not appear to be required.[73] These data, as well as increasing clinical experience, have lead some experts to suggest withholding empirical antifungal therapy if the patient is clinically stable and has no clinical or chest CT scan signs of fungal infection, no *Candida* or *Aspergillus* organisms are recovered from any site, and neutrophil recovery is imminent. A high-resolution chest CT scan may be a useful screening tool in patients with persistent fever and neutropenia; any abnormalities should be investigated with nasal endoscopy or bronchoalveolar lavage; biopsy and culture of any suspected lesions should be pursued aggressively in order to make a definitive diagnosis, and an antimold agent should be started.

The serum galactomannan assay specifically detects *Aspergillus* organisms but not other common fungal pathogens.[74] Sensitivity varies widely in different patient populations. A recent meta-analysis reported sensitivities of 58% to 65% and specificities of 65% to 95% in patients with hematologic malignancies or HSCT.[75] Many conditions affect the performance of the galactomannan assay, especially the use of concomitant piperacillin-tazobactam (false-positive) or antimold antifungal agents (false-negative). Although prospective serial galactomannan monitoring may be useful for pateints at high risk for *Aspergillus* infections, routine use in low-risk patients is not advised.[74,75] Furthermore, a single negative test result is of little value in ruling out invasive aspergillosis, although a positive result in concert with abnormalities on the chest CT scan makes the diagnosis highly probable. Galactomannan testing of bronchoalveolar lavage fluid appears to be very sensitive and specific for identifying invasive aspergillosis, as confirmed in early studies.[76,77]

Duration of Antibiotic Therapy

It generally is recommended that empirical antibiotic therapy continue until recovery of the ANC to more than 500 neutrophilic cells/mm^3 on one occasion, so long as the patient is clinically stable. In a stable patient who remains febrile despite return of counts, it usually is safe to discontinue antimicrobials and look for a source of fever. In patients who are afebrile and clinically stable but have continued neutropenia, some clinicians recommend a 2-week course of antibiotics, at a minimum, and then stopping, with close observation.[2,22]

Documented infections should be treated for a minimum duration of 7 to 14 days with an antibiotic regimen that is narrowed and directed toward any organisms that have been documented microbiologically. Most experts prefer to continue antibiotics at least until the ANC returns to more than 500 cells/mm^3. A longer course is given if clinically necessary, regardless of neutrophil recovery.

For low-risk patients who typically have brief periods of neutropenia, some groups of investigators have examined stopping antibiotics before the ANC reaches 500 cells/mm^3. With a clear and steady increase in the ANC or, alternatively, in the absolute phagocyte count (APC = PMNs + bands + monocytes), it appears that discontinuing antibiotics before a count of 500 neutrophilic cells/mm^3 is achieved-generally is safe so long as no complicating comorbid conditions are present.[78–83]

ADJUNCTIVE THERAPIES

Hematopoietic Growth Factors

Prophylactic use of hemopoietic growth factors is common in the setting of intensive chemotherapy regimens such as stem cell transplantation. Treatment of fever or infection with growth factors, however, is not standard practice. No consistent benefit has been demonstrated in terms of morbidity (duration of fever and use of antimicrobial) or mortality among several randomized controlled trials of growth factors added to antibiotics at the time of fever during

neutropenia.[84–86] Both the IDSA[22] and the American Society of Clinical Oncology (ASCO)[86] guidelines do not recommend the routine use of growth factors in treatment for febrile neutropenic patients. Therapy with colony stimulating factors, however, could be considered for severely neutropenic patients who have serious uncontrolled infections such as bacterial sepsis, pneumonia, severe cellulitis or sinusitis, systemic fungal infections, hypotensive episodes, or multiorgan dysfunction secondary to sepsis.

Granulocyte Transfusions

Granulocyte transfusion may potentially increase the response to antimicrobial therapy in selected cases of uncontrolled fungal or gram-negative infection during prolonged neutropenia. Granulocyte colony stimulating factor use in donors has increased the granulocyte yield approximately fourfold. Multiple recent studies have shown that granulocyte transfusions can be helpful in controlling severe infections progressing despite the use of appropriate antibiotics, with a response rate of 40% to 80%.[87] Variability in results is a consequence of patient characteristics. This benefit is limited to a limited patient population, because the incidence of prolonged yet reversible neutropenia is relatively low. Rare adverse events associated with granulocyte transfusions include transmission of CMV, alloimmunization associated with fever, graft-versus-host reactions if granulocytes are not irradiated, and progressive platelet refractoriness.

INFECTIONS IN THE PATIENT WITH CANCER

Bacteremia

Bloodstream infections occur in about 10% to 20% of febrile patients during neutropenia, most often when neutrophil counts are less than 100/mm^3.[4–7] The risk of bacteremia is related to the depth of neutropenia, the presence of gastrointestinal mucositis or of an indwelling catheter, or the concomitant presence of a specific site of infection such as pneumonia or soft-tissue process. A majority of bacteremias are due to gram-positive organisms, with coagulase-negative staphylococci and streptococci predominating. Gram-negative pathogens, including *Escherichia coli*, *Enterobacter*, *Klebsiella*, and *Pseudomonas aeruginosa*, are important albeit less frequent pathogens (see Table 47-3).

A classification system for bacteremias in febrile neutropenic patients has been developed by Elting and colleagues, based on size and presence of associated tissue involvement.[7] Complex bacteremias were those associated with deep-tissue infections of the lung, the liver or spleen, the kidney, the colon, bone and joints, veins and heart, meninges, soft tissues with necrosis, or affected skin or soft tissue, wound, or cellulitis greater than 5 cm in diameter. Simple bacteremias were associated with less tissue involvement (bacteruria, otitis, pharyngitis, affected area of soft tissue less than 5 cm in diameter). The prognostic significance of complex infection associated with bacteremia on survival was dramatic. At 21 days, 20% of patients with complex infections were dead, compared with only 5% of patients with simple bacteremias ($P < 0.0001$). Profoundly neutropenic patients with simple bacteremias had a much higher response rate to antibiotics than that noted in patients with complex bacteremias (94% versus 70%; $P < 0.0001$). The median time to defervescence for patients with simple bacteremias was half that observed for patients with complex bacteremias (2.5 days versus 5.3 days; $P < 0.0001$).

With increasing incidence of MRSA in hospitals and the community, it is recommended that vancomycin be added to standard empirical antibiotic coverage if gram-positive cocci in clusters are isolated from a blood culture, pending identification.[15,41,50] Vancomycin-resistant enterococcus (VRE) also is common in high-risk cancer patients at some institutions. If gram-positive cocci in chains are identified in blood cultures in settings where VRE is prevalent, then empirical addition of an antimicrobial active against VRE (e.g., linezolid, daptomycin) is prudent, pending definite identification and susceptibility profile. Gram-negative bacteremias in the neutropenic patient are associated with high mortality unless treated promptly and with appropriate antibiotics.[88–90] A variety of resistance mechansims are evolving among gram-negative organisms. Therefore, if gram-negative rods are isolated in blood cultures during fever and neutropenia, an aminoglycoside or a fluoroquinolone should be added to empirical therapy regimens to ensure coverage of resistant strains until a full susceptibility report is available.

Pulmonary Infections

Pulmonary infections are associated with the greatest morbidity and mortality, even when a specific pathogen is not identified. Approximately 25% of all febrile episodes in the neutropenic patient, and 50% of documented infections, are pneumonias.[91–93] Numerous infectious and noninfectious causes of pulmonary infiltrates are found in cancer patient with cancer who has fever and neutropenia.[87] Noninfectious causes include the underlying disease itself, radiation therapy, drug toxicity, pulmonary hemorrhage, and leukostasis. Infectious involvement of the lungs may be caused by bacteria (pneumococci, members of Enterobacteriaceae, *Pseudomonas* spp., *Legionella* spp.), fungi (*Candida*, *Aspergillus*, *Fusarium* spp.), viruses (influenza virus, parainfluenza virus, respiratory syncytial virus [RSV], CMV, HSV), and protozoa (*Toxoplasma*, *Cryptococcus*, *Strongyloides*).

Auscultatory abnormalities in the chest may be minimal or absent, and the chest radiograph appears normal at the onset of clinical manifestations in 30% of neutropenic patients with subsequently identified pneumonia.[92] A CT scan of the chest is essential to better define a pulmonary process. Neutropenia will decrease the diagnostic advantage normally provided by the sputum examination, because purulent sputum production is rare in this setting. Bronchoalveolar lavage will increase the diagnostic yield, especially for *P. jiroveci*, viruses, and bacteria. The yield for molds such as *Aspergillus* with this procedure has been mostly in the range of 50% for suspected cases, so a negative result on bronchoalveolar lavage sampling does not rule out an invasive fungal process. Polymerase chain reaction (PCR) assay or galactomannan testing of lavage fluid may increase these yields, although these tests are not currently available commercially.[76,77] If the clinical picture, radiographic appearance, and findings on lavage fluid analysis are nondiagnostic, a thoracoscopic or CT-guided lung biopsy should be considered if the patient's platelet count is adequate.

The radiograph appearance of a pulmonary infiltrate may give clues to the etiology (Table 47-4).[93] Focal lesions are suggestive of bacterial etiology and should be treated accordingly with broad-spectrum antibiotics. Nodular lesions, particularly those with surrounding areas with a ground-glass appearance (i.e., halo lesions), are suggestive of mold infection—such as with *Aspergillus*. This is of particular concern in the two patient groups that are at particularly high risk for mold infection: patients with GVHD on high-dose steroids and patients with prolonged neutropenia, such as those undergoing induction treatment for acute myelogenous leukemia. In these types of patients, even minimal symptoms of low-grade fever, pleuritic chest pain, or nasal stuffiness should prompt an immediate CT scan of the chest and sinuses to look for signs of invasive aspergillosis.

A diffuse interstitial picture is suggestive of a noninfectious etiology such as pulmonary edema or diffuse alveolar damage; or it may represent an atypical pneumonia, such as that due to *Legionella*, community respiratory viruses (e.g., parainfluenza virus, RSV, influenza virus), or *Mycoplasma*, or opportunistic infections such as *P. jiroveci* and CMV infection in the susceptible host (see later). Addition of a fluoroquinolone or a macrolide will cover most atypical bacterial

Table 47-4 Pulmonary Infiltrates and Their Association with Specific Infectious and Noninfectious Disorders

Radiologic Sign	Potential Etiologic Disorder(s)
Interstitial infiltrates	Pulmonary edema
Diffuse alveolar damage	Idiopathic pneumonia syndrome
	Respiratory virus infection: RSV, parainfluenza virus, influenza virus, adenovirus, enterovirus
	Herpesvirus infection: CMV, HSV, VZV, HHV-6
	Pneumocystis pneumonia
Focal airspace disease	Bacterial pneumonia
	Fungal pneumonia
Nodules	Fungal pneumonia (aspergillosis)
	Nocardia infection
	Legionella infection
	Septic bacterial emboli
	Mycobacterial infection (with cavitation)
	EBV lymphoproliferative disorder
	Relapsed malignancy
	Pulmonary embolism (pleura-based)
Halo sign or air-crescent sign	Aspergillosis

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HHV, human herpesvirus; HSV, herpes simplex virus; RSV, respiratory syncytial virus; VZV, varicella-zoster virus.

pathogens. For PCP, TMP-SMX at high doses (15 to 20 mg/kg per day) is standard treatment. CMV pneumonia requires initial treatment with intravenous ganciclovir plus administration of intravenous immunoglobulin as an adjuvant treatment.[94]

Pneumonia in a patient undergoing treatment for cancer is considered a health care-associated process. Accordingly, the empirical antimicrobial regimen is directed toward a range of pathogens. Current guidelines from the American Thoracic Society specify a combination of an antipseudomonal beta-lactam agent (cefepime, ceftazidime, a carbapenem, or piperacillin-tazobactam) plus vancomycin or linezolid plus an antipseudomonal fluoroquinolone or aminoglycoside.[95]

Fungal Infections

Fungal infections are due to yeast or mold pathogens. *Candida* organisms typically may colonize the gastointestinal tract and are the most common yeast pathogens in cancer patients. The spectrum of disease caused by *Candida* spp. ranges from mild mucocutaneous lesions (e.g., thrush) to disseminated deep tissue involvement (e.g., hepatosplenic candidiasis). An episode of candidemia probably precedes all tissue-invasive infections. Not all candidemias are clinically or microbiologically detected, however, and end-organ disease may be the first manifestation of invasive candidiasis. Blood cultures lack sensitivity for *Candida* and are positive in only approximately half of the patients with invasive disease.[96]

Neutropenia, the presence of an indwelling venous catheter, and chemotherapy-associated gastrointestinal mucosal injury are important risk factors for invasive candidiasis, rendering patients with cancer at especially high risk. *Candida*-related mortality rates of 33% to 75% are reported in these patients.[97] Because of the difficulty in diagnosing this infection and the associated high mortality, any blood culture found to grow even a single colony of *Candida* must be regarded as a sign of true infection, and the patient should receive therapy. Clinical signs of candidemia may range from fever alone to fulminant sepsis. Approximately 15% of neutropenic patients will have pustular skin lesions. *C. albicans* accounts for about half of the cases, but non-*albicans* species, especially *C. glabrata* and *C. krusei*, are increasing in incidence. Of note, these species are somewhat resistant and fully resistant, respectively, to fluconazole.

Catheter-related candidemia should be treated with antifungal therapy, and the catheter should be removed in most cases.[24] Determining if candidemia arises from a central venous catheter or the gut in a patient with neutropenia or gastrointestinal GVHD can be challenging. For a patient who has candidemia and a tunneled central venous catheter infection, the decision about its removal should be based on the likelihood of catheter-related candidemia. Factors indicating catheter-related candidemia include (1) isolation of *Candida parapsilosis* from blood samples; (2) quantitative blood cultures showing, in blood drawn through the catheter, five times the number of colonies isolated from blood drawn from a peripheral vein; (3) differential time to positivity (longer than 2 hours) for blood samples drawn from a percutaneous site, compared with that for samples drawn through the catheter; (4) candidemia in a patient who is receiving hyperalimentation through the catheter; and (5) persistent candidemia while receiving systemic antifungal therapy.[93] Catheter removal is strongly encouraged under any of these circumstances.[24,98–100]

The availablity of echinocandins (e.g., caspofungin, micafungin, anidulafungin) and newer-generation triazoles (posaconazole and voriconazole), combined with increasing prophylactic use of antifungals in certain populations (e.g., those with acute leukemia or GVHD) and the emergence of resistant *Candida* species in some institutions, has changed the treatment paradigm for candidemia. Some non-*albicans* species (e.g., *C. glabrata*) may have reduced susceptibility to fluconazole. In institutions with higher rates of these organisms, empirical treatment with an echinocandin (e.g., caspofungin, micafungin, anidulafungin) or a later-generation triazole (e.g., voriconazole or posaconazole) is appropriate pending identification when a yeast is identified in the blood. Candidemia that develops during prophylaxis with an azole should be treated with an echinocandin or a amphotericin B preparation. Complications of fungemia may include endocarditis, endophthalmitis, vertebral osteomyelitis, and hepatosplenic candidiasis.[101]

Aspergillus spp. are the most common mold pathogens in patients with cancer, but they are seen almost exclusively in two specific settings: during periods of prolonged neutropenia or in patients with GVHD after allogeneic transplantation. As discussed earlier (under Pulmonary Infections), the vast majority of *Aspergillus* and other mold infections occur in the lung, whereas fewer organisms disseminate to sinuses, skin, or abdominal organs.[102,103] Dissemination to brain occurs in approximately 5% of patients. Unfortunately, the sensitivity of diagnostic tests used to diagnose invasive aspergillosis remains very poor, and delay in diagnosis is all too common, contributing to poor outcome.[104] The CT scan has become an essential diagnostic tool for earlier diagnosis of invasive aspergillosis, with characteristic lesions such as nodules, the halo sign and the crescent sign having high predictive value for the diseasee.[69–72] Despite some improvements in antifungal therapy in recent years, invasive aspergillosis is still associated with an at least 50% mortality rate in patients with cancer.[102,103] Voriconazole has been shown to be superior to amphotericin B for for the treatment of proven or probable invasive aspergillosis, and it is now the agent of choice.[105] The use of combination therapy for invasive *Aspergillus* infections is an attractive approach that has scientific merit in that combinations of echinocandins with azoles or amphotericin B formulations have produced positive results both in vitro and in aspergillosis animal models.[106,107]

On the basis of a few small retrospective studies, combination antifungal treatment appears to be safe and has promising efficacy.[106,108] One recent open-label trial suggested that oral posacon-

azole was associated with a 42% response rate in patients who are refractory to or intolerant of conventional therapy for *Aspergillus* infection, although this is not better than results seen with voriconazole.[109] The enhanced efficacy of two- or three-drug antifungal combinations for invasive aspergillosis remains unproved, pending a prospective comparative clinical trial. Many clinicians, however, are anxious to employ combination therapy in an effort to improve the dismal outcomes for invasive aspergillosis.

Fusarium is notable for causing tender, red skin nodules and positive blood cultures for mold in approximately half of the cases.[110] Infection with any of the zygomycetes (*Mucor*, *Rhizopus*, *Rhizomucor*) is characterized by later onset (after day 90 of transplant) and a longer median duration of survival. Sinus disease with erosion through tissue planes is a feature of zygomycete infections but also may occur with *Aspergillus* infection. The mortality rate is approximately 80% for transplant recipients with proven infection. In up to 60% of those colonized, progression to invasive infection will occur.[111] Other, less common molds, including *Fusarium*, *Scedospoarium*/*Pseudaollescheria*, and *Trichosporon*, appear to be more susceptible to voriconazole than to amphotericin B. Of note, however, one report recently indicated successful treatment of *Fusarium* infection with a combination of both agents.[112]

An increased incidence of infection with voriconazole-resistant molds such as *Rhizopus* or *Mucor* species has recently been described. This increase is hypothesized to be related to more frequent use of voriconazole prophylaxis in high-risk cancer patients.[113,114] Use of amphotericin B products has been standard therapy for infections due to these pathogens, but the recently approved triazole posaconazole has potent in vitro activity against the zygomycetes and has quickly become an important drug in battling infections with these molds. Furthermore, it is available in an oral formulation and has less toxicity than that observed with amphotericin products. Posaconazole has not been evaluated as a first-line agent for treatment of zygomycoses, but reports of its use in salvage therapy are promising.[100] Patients in whom pulmonary lesions with radiologic characteristics suggestive of mold infection (e.g., halo sign, as noted earlier) develop despite voriconazole prophylaxis should receive treatment for zygomycoses with amphotericin B or posaconazole pending microbiologic or histologic diagnosis. Aggressive and repeated surgical débridement is a critically important adjunct to the treatment of zygomycoses of the sinuses.[111]

Hepatosplenic candidiasis is a form of chronic disseminated candidiasis that almost exclusively affects patients undergoing leukemia induction or stem cell transplantation.[101] It generally manifests only on recovery from neutropenia, as persistent fevers unresponsive to antibacterial agents. Patients may have right upper quadrant tenderness and demonstrate a variety of other gastrointestinal signs and symptoms. Consistent laboratory findings include marked elevation of alkaline phosphatase, with normal or mildly elevated bilirubin and transaminases, and a rebound leukocytosis after neutrophil recovery. Blood cultures are almost always negative for fungal growth, as are liver biopsy specimens. Suspected hepatosplenic candidiasis is confirmed by the presence of multiple characteristic well-defined lesions in the liver or spleen, and occasionally in the kidneys on CT scan or ultrasound examination. A prolonged course of therapy, initially with amphotericin B or a lipid formulation and then with fluconazole for a number of months, has been advocated. Echinocandins also may be effective.[100] For patients with acute leukemia and hepatosplenic candidiasis, repeated cycles of chemotherapy may be given once the infection is stabilized, and the antifungals are continued through the courses of cytotoxic therapy.

Gastrointestinal Infections

Upper Gastrointestinal Tract

Mucositis of the oral cavity and alimentary mucosa is a common consequence of cytotoxic cancer therapies. Disruption of the gastrointestinal mucosa causes erosions and inflammation that can provide a portal of entry for colonizing organisms. Esophageal symptoms of odynophagia, dysphagia, and retrosternal or epigastric discomfort do not point to a specific etiology, and it often is difficult to discriminate between drug-induced and infection-induced mucositis. The most common organisms causing local oral or esophageal infection are herpes simplex virus and *Candida* spp., although gram-negative and anaerobic bacteria rarely are responsible. The treatment of presumed esophagitis during a period of neutropenia often is based on the empirical administration of antacids or systemic antifungal or antiviral therapy with acyclovir. For patients who do not respond to empirical therapy with these agents, careful upper endoscopy may be considered to obtain a more precise diagnosis based on direct visualization of the lesions, as well as on tissue biopsy for histopathologic and microbiologic examination. Of note, esophageal endoscopy may be associated with substantial morbidity in patients who are profoundly neutropenic or thrombocytopenic, and it often is advisable to wait until counts recover before proceeding.

Lower Gastrointestinal Tract

Enteritis, clinically manifested by diarrhea, is common in cancer patients. Diarrhea may be due to chemotherapy-induced mucositis or infection-induced. *C. difficile* is the most common pathogen to cause diarrhea in the cancer patient. Over the past few years, the emergence of an epidemic strain of *C. difficile* has resulted in a dramatic increase in the incidence and severity of *C. difficile* infection at many centers.[115,116] The epidemic strain is resistant to fluoroquinolones, and use of this class of antibiotics has been implicated as a risk factor in institutional outbreaks.[117] Because of an increased rate of failure of oral metronidazole noted in recent studies, some experts recommend oral vancomycin for patients with evidence of severe disease (e.g., white blood cell count above 20,000 cell/μL, shock, renal failure, need for transfer to the intensive care unit),[115] and some advocate the addition of metronidazole. For patients unable to tolerate oral therapy (because of ileus or toxic megacolon, for example), intravenous metronidazole and vancomycin adminstered by nasogastric tube or by enema should be considered. Colectomy may be necessary in seriously ill, nonresponding patients. Relapse rates are high.[118] Although no proven approach is recognized, a slowly tapering course of oral vancomycin or metronidazole over 6 weeks often is used for patients with multiple relapses. Outpatients must be alerted to the possibility of recurrence so that retreatment can be instituted quickly.

Other bacterial causes of diarrhea are uncommon in patients with cancer unless exposure to such pathogens has occurred. CMV infection can cause protracted or hemorrhagic diarrhea, especially in children or in patients undergoing allogeneic HSCT. Adenovirus may cause severe diarrhea in allogeneic transplant recipients, and stool culture techniques and plasma PCR assay aid in diagnosis.

Typhlitis, also known as neutropenic enterocolitis, is a unique and potentially life-threatening syndrome occurring in febrile neutropenic patients, particularly those with leukemia or who have had intensive cytotoxic therapy.[119–122] Abodominal pain, especially in the right lower quadrant, often with attendant rebound tenderness, and decreased bowel sounds, fever, and diarrhea are typical presenting features. Typhlitis may be limited to the cecum but can involve the entire intestine. CT scan is the diagnostic study of choice and usually demonstrates thickening of the bowel wall, sometimes with pneumatosis coli.[122] *C. septicum*, *P. aeruginosa*, enteric gram-negative organisms, and anaerobes are the most common pathogens associated with this syndrome. *C. difficile* occasionally is associated with typhlitis, so treatment for *C. difficile* infection (i.e., with oral vancomycin or metronidazole) should be included in the initial antibiotic regimen for typhlitis, along with a broad-spectrum intravenous antimicrobial cocktail. Severe sepsis, bowel perforation, and hemorrhage may accompany or follow typhlitis. Therapy consists of nasogastric suction, bowel rest, intravenous fluids, and broad-spectrum antibiot-

ics to cover gram-negative organisms and anaerobes (e.g., piperacillin/tazobactam, a carbapenem). Antifungal agents also should be part of the initial treatment regimen for typhlitis. In approximately 5% of patients with typhlitis, complications develop that require surgical intervention, including uncontrolled sepsis, lower gastrointestinal tract bleeding, and perforation.[121]

Perirectal infection occurs primarily in patients with acute leukemia and especially among those with monocytic and myelomonocytic leukemia, although it is relatively uncommon. The usual symptoms are fever, pain on defecation, and persistent rectal discomfort. Although anaerobes are thought to play a role in these infections, the associated bacteremias are most likely to be caused by *P. aeruginosa*, *E. coli*, and other enteric gram-negative bacteria. Therapy consists of broad-spectrum antibiotics, warm compresses, and stool softeners. Although few abscesses develop in the absence of neutrophils, some patients will benefit from surgical incision and drainage.

Central Nervous System Infections

In the patient with cancer who demonstrates new mental status changes, focal neurologic signs, or neck stiffness, evaluation for central nervous system (CNS) infection is necessary, because infection is a common cause of neurologic complications.[123] The initial evaluation begins with cerebral magnetic resonance imaging (MRI) or contrast-enhanced CT, followed immediately by lumbar puncture. Empirical treatment with antibacterials with adequate CNS penetration, such as cefepime or meropenem at high doses, is indicated. Of note, neutropenic patients may have few white cells in the cerebrospinal fluid (CSF), even in the setting of meningitis. Impaired T-cell function (e.g., corticosteroids, purine analogs, GVHD, alemtuzamab) but not neutropenia is a risk factor for *Listeria* meningitis. Ampicillin should be added if *Listeria* infection is suspected in a patient with T-cell impairment. Patients with varicella-zoster virus (VZV) or HSV meningoencephalitis may have suggestive skin lesions; if such infection is suspected, then acyclovir 10 mg/kg every 8 hours should be added and a CSF sample sent for PCR testing for both viruses. Cryptococcal meningitis often manifests with subtle mental status changes over several days, and very low CSF cell counts often are seen; serum and CSF crytococcal antigens are senstive diagnostic tests. False-positive test results at low titers may occur in patients with plasma cell dyscrasias. Treatment is with amphotericin B preparations combined with 5-fluorocytosine (monitor for thrombocytopenia, leucopenia, and diarrhea) initially. A repeat spinal fluid examination must be done after 2 weeks of therapy to determine if the CSF is culture-negative; if it is, then the patient may be switched to oral fluconazole. Heavily immunosuppressed patients (e.g., recent recipients of allogeneic HSCT, patients with chronic extensive GVHD) are at risk for meningoencephalitis from reactivation of pathogens such as HHV-6, EBV, or *T. gondii*, although such cases are very rare. CSF PCR assay for these specific herpesviruses or *Toxoplasma* is used to make the diagnosis; CSF culture typically is negative. Ganciclovir or foscarnet generally is used to treat HHV-6 infection. *T. gondii* reactivations often are rapidly fatal despite combination therapy with pyrimethamine and sulfadiazine or clindamycin treatment.[124]

Patients with ring-enhancing CNS lesions may have infection with bacteria, *Toxoplasma*, *Nocardia*, mycobacteria, or fungal organisms, including cryptococci. Post-transplantation lymphoproliferative disorder (PTLD) and other malignancies also may manifest as mass lesions. Typically, a brain biopsy is required to make the diagnosis if obvious concurrent infection at a more accessible site is not present (e.g., *Nocardia* growth from blood cultures or conincident diagnosis of pulmonary invasive *Aspergillus* infection). First-line therapy for CNS nocardiosis includes high-dose TMP-SMX (15 to 20 mg/kg daily) given in three or four divided doses, usually in combination with a second agent such as meropenem. Sensitivity testing should be performed to further refine therapy.

Treatment of CNS mold infections (other than those due to with zygomycetes) should include voriconazole, which attains CSF and brain tissue levels of approximately 22% and 100%, respectively (as indicated by data for a small number of samples).[125] The alternative treatment for CNS mold infection (intraventricular amphotericin accompanied by systemic amphotericin) is very toxic and very rarely used. Limited information suggests that posaconazole may be an effective agent for treatment of CNS fungal infections caused by *Cryptococcus neoformans* and invasive molds.[126]

Vascular Access Devices

Indwelling venous access devices are commonly required in cancer patients for the administration of chemotherapy, blood products, and parenteral nutrition, as well as for withdrawal of blood for therapy monitoring and microbiologic evaluation. Infection is a common complication of venous access devices. The risk of infection varies with the device used, duration of placement, and extent of the patient's immunosuppression. Local signs and symptoms, such as erythema and tenderness, are unreliable indicators of catheter infection even in the immunocompetent patient. The evolution of these signs over time, however, is suggestive of infection. Venous access device infections are categorized as entry site infections, tunnel or pocket infections, and catheter-associated bloodstream infections.[24,127]

Entry-site infections can be treated effectively with appropriate antimicrobial therapy, without the need for catheter removal. Tunnel (i.e., erythema, induration or tenderness beyond 2 cm from the entry site) and pocket infections necessitate catheter removal, as well as the immediate initiation of an empirical antimicrobial therapy that includes vancomycin to cover methicillin-resistant *S. aureus*, until culture results are available.

It often is difficult to determine whether a bloodstream infection is related to the venous access device because frequently, no evidence of local catheter inflammation is seen. Recently, however, the concept of "*differential time to positivity*" has been used to distinguish venous access device–related infections from other types of infection, as follows: If the times at which blood cultures become positive (by machine detection in the clinical microbiology laboratory) are more than 2 hours apart for simultaneously obtained catheter and peripheral vein blood cultures, the catheter is then strongly implicated as the source of infection.[127] Although this differentiation may help determine whether a catheter can be retained or must be removed, most indwelling catheter-related infections will respond to antimicrobial therapy alone, without catheter removal. Certain exceptions are notable: Catheter removal is advisable for patients with bloodstream infections caused by fungi (yeasts and molds) and nontuberculous mycobacteria (*M. chelonae*, *M. fortuitum*, *M. abscessus*). For other bacteria, the decision concerning the need for catheter removal will depend on the severity of the clinical picture, the degree of immunosuppression, and the availability of an alternative vascular access site in a given patient. *S. aureus* may cause endocarditis, and the value of the transesophageal echocardiography in the setting of any *S. aureus* bloodstream infections has been well demonstrated to determine duration of therapy.[128] In general, if blood cultures remain positive despite appropriate antimicrobial therapy for more than 48 hours, or if the patient is clinically unstable, the catheter should be removed independent of the etiology.

Viral Infections

The incidence of herpes simplex virus (HSV) reactivation infections has been reduced with the widespread use of acyclovir prophylaxis. Reactivations not involving the CNS are treated with lower doses of intravenous acyclovir (e.g., 5 mg/kg every 8 hours) or similar drugs given orally, whereas VZV infections are treated with higher doses (e.g., intravenous acyclovir 10 mg/kg every 8 hours or oral valacyclovir 1000 mg every 8 hours). Acyclovir resistance is very uncommon among cancer patients. HSV infections that break through acyclovir

prophylaxis, however, should be considered to be acyclovir-resistant until viral sensitivity testing can be performed, and consideration should be given to initiating treatment with foscarnet or cidofovir. Reports of acyclovir-resistant varicella are extremely rare.[129]

Patients at highest risk of CMV reactivation include recipients of allogeneic bone marrow transplants in the early period after engraftement (i.e., days 30 to 100 after transplantation) during which invasive CMV disease will develop in approximately 2% of patients.[130] Also, patients receiving alemtuzumab and those receiving high-dose corticosteroids for GVHD are at high risk. Universal prophylaxis and preemptive strategies using ganciclovir or valganciclovir have markedly reduced the incidence of CMV disease in these patient groups.[131] Asymptomatic CMV viremia or "CMV syndrome" (fever, leukopenia) without end-organ disease is common in the absence of universal prophylaxis, and is often a trigger for starting an antiviral preemptively, as described later.

End-organ CMV disease most commonly involves the lungs, gastrointestinal tract, or liver.[132,133] Definitive diagnosis requires histopathologic evidence, but compatible clinical findings (e.g., colonic ulcers, interstial pattern on chest radiography) in the setting of CMV viremia diagnosed by PCR or antigen testing is suggestive of invasive disease. CMV treatment is initiated with induction doses of the antiviral agent for at least 2 weeks, followed by a variable course of maintenance dosing, which is one-half the induction dose. The total duration of treatment depends on clinical response, the results of viremia or antigenemia assays that reflect viral replication activity, and the patient's overall state of immunosuppression. Intravenous ganciclovir generally is used for the initial antiviral course (induction dose of 5 mg/kg every 12 hours, maintenance dose of 5 mg/kg once daily) when end-organ disease is documented, although some centers are increasingly using oral valganciclovir in patients who can reliably absorb the drug. The valganciclovir dose in patients with normal renal function is 900 mg twice daily for at least a 2-week induction and then 900 mg once daily to complete 1 to 3 months of treatment. Foscarnet and cidofovir are options, albeit somewhat toxic, for patients who are intolerant of or unresponsive to ganciclovir or valganciclovir.

When the end-organ manifestation of CMV infection is pneumonitis, intravenous immune globulin (IVIG) given at a dose of 500 mg/kg typically is added on an every-other-day basis for the duration of induction.[94,132] When CMV infection manifests in an end organ other than the lungs, the use of IVIG is not so clearly delineated. For other end-organ manifestations of CMV disease, IVIG can be added if the patient's total immunoglobulin G (IgG) level is below 400 mg/dL. No clear advantage favors CMV hyperimmune globulin over regular IVIG.[94,132]

HHV-6, a virus acquired by 95% of humans during childhood, reactivates asymptomatically in up to 50% of patients after allogeneic HSCT.[134,135] Clinical disease is uncommon but may include interstitial penumononitis, encephalitis, rash, cytopenias, and delayed engraftment.[134,135] PCR assay performed on plasma, tissue biopsy material, or CSF can be useful in suggesting HHV-6–associated disease. HHV-6 has 60% DNA homology with CMV, and treatment of documented infection usually is initiated with induction doses of foscarnet or ganciclovir, although responses are variable and it is unclear which drug is more effective.[136]

Respiratory syncytial virus (RSV) and influenza virus infections generally are seasonal; parainfluenza and adenovirus infections may occur year round. Upper respiratory infections may progress to pneumonia, with mortality rates between 6.6% and 80% in heavily immunosuppressed patients.[137,138] A neuraminidase inhibitor commonly is used to treat influenza and may prevent progression from upper respiratory infection to pneumonia, but prolonged shedding and the development of resistance may occur.[139] Inhaled ribavirin reduces RSV shedding, but clinical efficacy has not been demonstrated[140]; furthermore, difficulty of administration and occupational exposure issues limit use of this agent.

Adenovirus may cause pneumonia, colitis, hemorrhagic cystitis, hepatitis, or disseminated disease with a sepsis-like presentation in patients undergoing allogeneic HSCT.[141] Asymptomatic reactivaton is common in adults, but rising levels of viremia or isolation from multiple sites has been associated with an increased risk of severe disease. No standard treatment has been validated, but cidofovir (1 mg/kg three times a week or 5 mg/kg weekly) has been associated with a reduction in levels of viremia.[142]

Reactivation of BK virus in the uroepithelium may lead to hemorrhagic cystitis in the allogeneic transplant recipient, and quantitative PCR assay for BK virus in urine and plasma may be helpful both diagnostically and in assessing response to treatment.[143,144] Low-dose cidofovir (1 mg/kg weekly) has been used for treatment, but its efficacy is unknown.[145]

PREVENTION OF INFECTIONS IN SELECTED RISK GROUPS

General guidelines for prevention of infections are shown in Table 47-5.

Low-Risk Patients

Patients categorized at low risk for complications during fever and neutropenia include most with solid tumors. These patients are at lower risk for serious infections, so they do not generally require any prophylaxis against bacteria, fungi, or viruses. Although one recent large randomized study demonstrated that levofloxacin prophylaxis led to a statistically significant decrease in febrile episodes, hospitalizations, and possible infections in a group of largely low-risk patients (e.g., those with breast cancer, testicular cancer, or small cell lung cancer), the reductions seen were of marginal clinical significance. Consequently, this practice is discouraged by most experts.[146–148] The absolute risk reduction for a first febrile episode was only 4.4%, documented infections were rare, and mortality was unaffected by prophylaxis.[147] Concerns for antimicrobial resistance and for increasing incidence of severe *C. difficile* with widespread fluoroquinolone use are also reasons to limit the use of these agents. Furthermore, because fluoroquinolone-based outpatient treatment of fever during neutropenia is an option for many low-risk patients, routine fluoroquinolone prophylaxis in these patients would eliminate that attractive possibility. Routine fungal or viral prophylaxis also is not required for low-risk patients, with the exception of HSV prophylaxis in patients with a history of HSV reactivation.

Patients who receive autologous transplants may be considered to be at intermediate risk for severe infections in that the associated period of neutropenia is relatively long, often at least 10 days, but they typically experience few complications. The role of prophylaxis in these patients varies with the center and the preparative regimens used; consistent recommendations are lacking.

Patients with Acute Leukemia

Patients undergoing induction or consolidation therapy for acute leukemia have a prolonged period of neutropenia, and the use of routine antibacterial prophylaxis during the period of neutropenia has been controversial. A recent large trial randomized patients with expected duration of neutropenia longer than 7 days to receive either treatment with 500 mg of levofloxacin daily or placebo. Among patients with acute leukemia, a reduction in febrile episodes, microbiologically documented infection, and bacteremia was observed with levofloxacin treatment; however, no mortality benefit was seen.[149] A meta-analysis of clinical trials of fluoroquinolone prophylaxis in high-risk patients did show a survival advantage.[150] The NCCN curently recommends antibacterial prophylaxis with a fluoroquinolone (levofloxacin preferred) for patients with acute leukemia with expected duration of neutropenia of greater than 7 days.[2] Potential problems

Table 47-5 Prophylaxis for Selected Risk Categories

Risk Category	Bacterial	Duration	Viral*	Duration	Fungal	Duration	PCP†
Most solid tumors	None	—	None‡	Neutropenic period	None	—	None
Acute leukemia/MDS	Fluoroquinolone	Neutropenic period	HSV, VZV	Neutropenic period	Posaconazole	Neutropenic period	Only patients with ALL
Autologous HSCT (neutropenic period)	None	—	HSV, VZV	Neutropenic period and 30 days after	Fluconazole	Neutropenic period	For 90–180 days after transplantation
Allogeneic HSCT	Penicillin	Minimum 1 year after transplantation	HSV, VZV, CMV	HSV and VZV during neutropenia, some centers continue for up to 1 year, CMV monitoring to day 100 minimum	Fluconazole (some centers use mold-active agent)	75 days after transplantation	For at least 6 months after transplantation
GVHD	Penicillin	Until resolution of GVHD and off immunosuppression	HSV, VZV, CMV	Until resolution of GVHD and off immunosuppression	Posaconazole	Until off significant immunosuppression	Until resolution of GVHD
Alemtuzumab	None	None	HSV, VZV, CMV	At least 2 months and $CD4^+$ ≥100 cells/μL	Consider	None	At least 2 months and CD 4^+ ≥200 cells/μL
Purine analogs§	None	None	HSV, VZV	At least 2 months	None	None	At least 2 months and $CD4^+$ ≥200 cells/μL

ALL, acute lymphoblastic leukemia; CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HSV, herpes simplex virus; MDS, myelodysplastic syndrome; PCP, *Pneumocystis* pneumonia; VZV, varicella-zoster virus.

*HSV or VZV prophylaxis with acyclovir, valacyclovir, or famciclovir; see text (under Prevention of Infections in Selected Risk Groups) for CMV prophylaxis strategy.

†Agents used for PCP prophylaxis include trimethoprim-sulfamethoxazole, dapsone, atovaquone, and inhaled pentamidine.

‡HSV prophylaxis for patients with a history of HSV reactivation.

§Fludarabine, cladribine, pentostatin.

associated with routine antibacterial prophylaxis include *C. difficile* colitis, fungal superinfections, and the development of antimicrobial resistance.

Similarly, in patients with acute leukemia, a recent trial suggested a morbidity and mortality benefit with the use of antimold prophylaxis with posaconazole. This trial, conducted in more than 600 patients with acute leukemia or myelodysplastic syndrome, randomized patients to prophylaxis with itraconazole, fluconazole, or posaconazole until recovery from neutropenia and complete remission of disease were obtained.[151] Patients who received treatment with posaconazole experienced significantly fewer invasive mold infections and had a survival benefit. Based on this data, posaconazole should be considered the agent of choice for antifungal prophylaxis in neutropenic patients with acute leukemia. Many centers use voriconazole for this purpose because its activity against *Aspergillus* spp. also is potent, but no comparative study has been done to show equivalence of voriconazole and posaconazole for this purpose.

HSV reactivations in seropositive cancer patients are frequent after chemotherapy and are associated with increased mucosal damage, resulting in increasing pain, limitation of the patient's ability to maintain oral hydration and nutrition, and an increased risk of bacterial and fungal superinfections. Therefore, HSV prophylaxis with acyclovir, valacyclovir, or famciclovir is recommended during the period of neutropenia for patients with acute leukemia. Although VZV reactivation is less common than HSV reactivation, life-threatening disseminated disease may occur, and the foregoing agents will serve as prophylaxis for this pathogen as well. CMV disease is not common in this population, and no routine preventive strategy is required. With the exception of patients with acute lympocytic leukemia (ALL), routine prophylaxis against PCP is not required.

Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation

Bacterial infections may cause over 25% fevers in the pre-engraftment phase of allogeneic HSCT, so antibacterial prophylaxis (usually with a newer fluoroquinolone) is often used during this period[152] (Fig. 47-2). This practice has been shown to reduce the incidence of infections, particularly those due to gram-negative organisms, in other high-risk groups (see earlier section), but has not been consistently associated with a decrease in mortality.[149,150] Because of the risk of resistant organisms and *C. difficile* infection, some centers choose not to use routine prophylaxis for allogeneic transplant recipients.[153,154] After engraftment, prophylaxis against encapsulated organisms is indicated. Penicillin prophylaxis has decreased the incidence of infection-related morbidity and mortality from *S. pneumoniae*, *H. influenzae* type b, and *N. meningitidis* significantly. Prophylaxis generally is discontinued 1 or 2 years after transplantation, or later if immunosuppression is ongoing at the 2-year point. Prophylaxis with TMP-SMX (or atovaquone, dapsone, or aerosolized pentamidine, if intolerant) for 6 months after transplanation is indicated to prevent PCP.

Fluconazole prophylaxis has been clearly demonstrated to prevent candidemia and hepatosplenic candidiasis among allogeneic transplant recipients, with treatment generally continuing to day 75 after transplantation.[155–158] Fluconazole, however, does not have activity against yeasts such as *C. glabrata* (some strains) and *C. krusei*, or molds such as *Fusarium*, *Aspergillus*, and the zygomycetes. Some centers use prophylaxis with a mold-active agent such as voriconazole in high-risk patients (i.e, mismatched or matched unrelated donor transplants), and a recent trial demonstrated voriconazole to be equivalent to fluconazole for the prevention of fungal infections when administered for the first 100 days (180 days for those receiving prednisone at a dose of ≥1 mg/kg/day or for recipients of T-cell depleted grafts with $CD4^+$ counts <200 at day 100) after transplant.[159]

Prevention of CMV disease after allogeneic HSCT can be effectively accomplished using either universal prophylaxis or preemptive therapy with ganciclovir or valganciclovir.[160,161] The preemptive strategy employs weekly or twice-monthly blood antigenemia or PCR viral load monitoring tests to guide initiation of antivirals, whereas universal prophylaxis involves providing the drug to all patients at risk (all but seronegative donors and recipients). A majority of transplant recipients will initially manifest CMV reactivation silently; this typically is detected by the weekly monitoring test before the development symptoms (e.g., fever) or end-organ disease. Severe end-organ disease can occur if subclinical reactivations are not treated. The preemptive strategy is preferred to universal CMV prophylaxis for two reasons: First, it decreases exposure to this marrow-toxic drug, and, second, allowing for some low-level replication of CMV, recovery of CMV-specific immunity may be enhanced. Both strategies, however, appear to shift the timing of CMV reactivations to later (after day 100, when monitoring often stops) in the postengraftment course, after it is discontinued in those transplant recipients at higher risk.[159] Strategies for preemptive therapy vary; typically, intravenous valganciclovir or ganciclovir is administered at induction dosing for 7 to 14 days and then reduced to maintenance dosing if reduction in viremia or antigenemia is observed.[162] Treatment may be continued for 2 to 3 weeks after a negative result on a viremia or antigenemia test, and then weekly monitoring is resumed. In most centers, weekly monitoring is continued for at least 100 days, and longer if immunosuppression for GVHD is needed.

For patients seropositive for HSV and VZV, most centers use antiviral prophylaxis with acyclovir or an equivalent agent (valacyclovir, famciclovir) during the neutropenic period, and some continue for up to a year to prevent VZV reactivation. These agents should be stopped if a patient is receiving ganciclovir or valganciclovir.

Vaccination after allogeneic HSCT should be initiated once cellular immunity is thought to be reconstituted. Typically, this occurs at approximately 1 year after transplantation, provided that the patient is not on continued immunosuppression for GVHD. Table 47-6 shows a standard vaccination schedule for after allogeneic transplantation.

Patients with Graft-versus-Host Disease

GVHD and its treatment result in significant suppression of the cell-mediated immune system and high risk of certain infections. The use

Table 47-6 Vaccine Schedule after Hematopoietic Stem Cell Transplantation

Vaccine	12 mo	14 mo	24 mo
INACTIVATED-ORGANISM VACCINES			
Begin reimmunization at 1-year anniversary visit.			
Diphtheria, tetanus, pertussis*	×	×	×
Haemophilus influenzae type b conjugate	×	×	×
Hepatitis B	×	×	×
Pneumococcal 23-valent	×		Optional
Inactivated polio	×	×	×
Influenza	Seasonal if >6 months after transplantation		
LIVE-VIRUS VACCINES			
Reimmunize at 2-year anniversary visit if no active graft-versus-host disease or immunosuppressive therapy.			
Mumps-measles-rubella			×
Varicella			×

*One of these three boosters should be the Tdap tetanus–diphtheria–acellular pertussis vaccine.

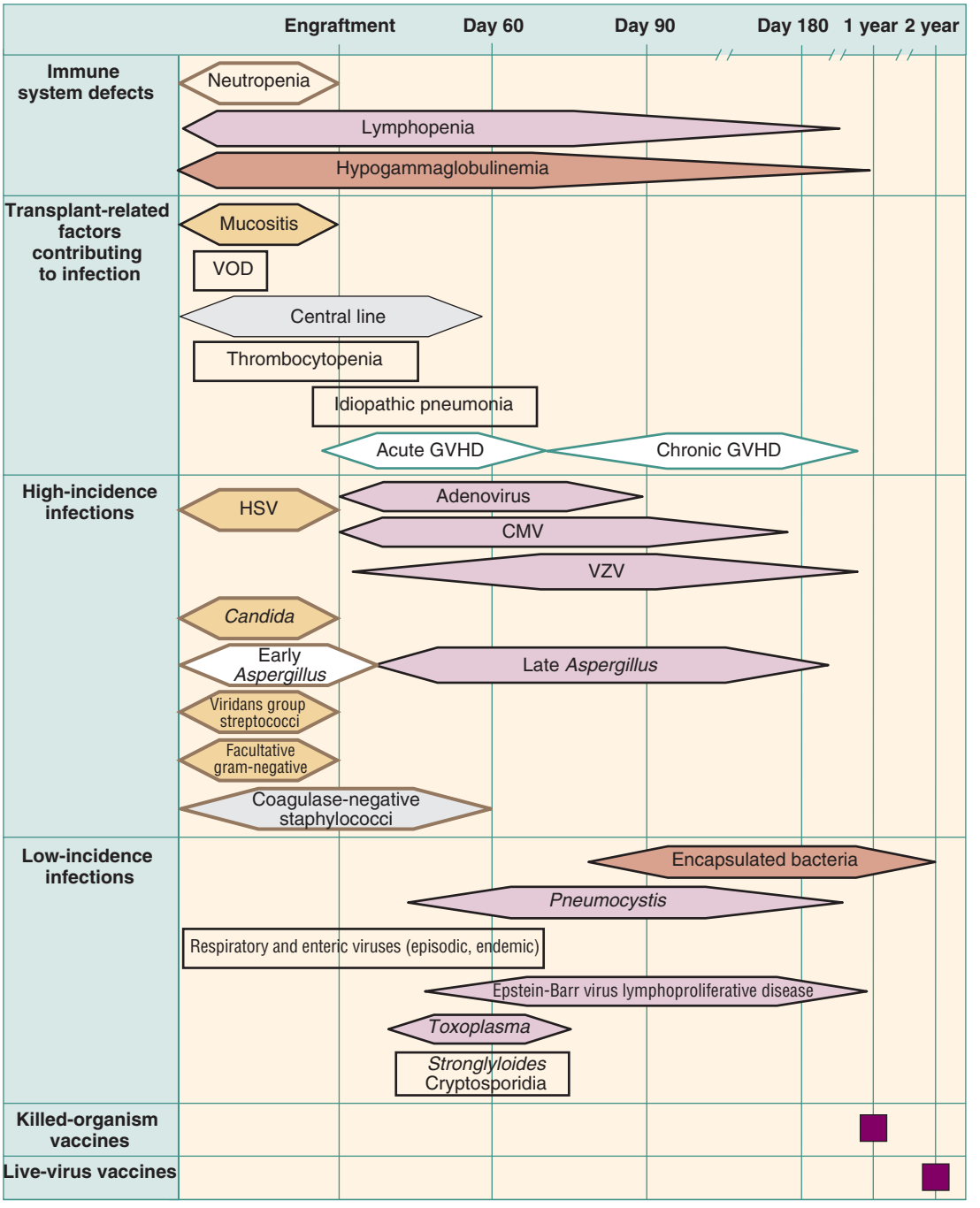


Figure 47-2 • Phases of predictable immune suppression with characteristic opportunistic infections among allogeneic hematopoietic stem cell transplant recipients. CMV, cytomegalovirus; GVHD, graft-versus-host disease; HSV, herpes simplex virus; VOD, veno-occlusive disease; VZV, varicella-zoster virus.

of penicillin to prevent infection with encapsulated organisms (e.g., *Streptococcus pneumoniae*) is widely accepted,[2,161] despite the fact that *S. pneumoniae* is increasingly resistant to this agent.

Although invasive mold infections, particularly invasive aspergillosis, constitute a serious threat during GVHD, few studies have evaluated fungal prophyalxis until recently. A large randomized trial comparing the new triazole posaconazole with fluconazole in patients with grade II or IV acute GVHD or chronic extensive GVHD has now demonstrated a reduction in overall breakthrough invasive fungal infections including invasive *Aspergillus* infections.[163] No effect on mortality was observed, however. Based on this trial, the NCCN recommended posaconazole prophylaxis in patients who are undergoing immunosuppressive treatment for severe GVHD.[2] Posaconazole currently is available only as an oral suspension that must be taken three times daily with a high-fat meal, which is critical for adquate absorption of the drug. Patients with GVHD of the gut may not be able to tolerate this regimen. Voriconazole and echinocandins are potential alternatives but are not well studied for prophylaxis in this setting.

Antiviral prophylaxis with acyclovir or an equivalent drug (e.g., valacyclovir, famciclovir) is widely used to prevent HSV- or VZV-related disease. Most centers have adopted a preemptive monitoring approach, as discussed previously (see earlier section, Patients Undergoing Allogeneic Hematopoietic Stem Cell Transplantation) to

decrease the incidence of CMV-related disease. TMP-SMX or an alternative agent for intolerant patients (e.g., dapsone, inhaled pentamidine, atovaquone) is routinely used as prophylaxis against PCP while patients remain on immunosuppression.

Prophylaxis with Other Immunosuppressive Therapies

Alemtuzumab (Campath) has been used with increasing frequency in patients with a variety of lymphoproliferative disorders, with the primary effect being prolonged suppression of cellular immunity. In one study of patients with B-cell CLL, the median time to reach a $CD4^+$ count greater than 100 cells/μL was 4 months, and the median $CD4^+$ count was less than 25% of baseline at 9 months.[164] A high frequency of CMV reactivation and bacterial infections has been reported during alemtuzumab therapy, and opportunistic infections similar to those seen in patients with late-stage AIDS (e.g., PCP, progressive multifocal leukoencephalopathy, cryptococcosis, disseminated histoplasmosis, cerebral toxoplasmosis) also have been described.[165,166] Prophylaxis against PCP with TMP-SMX or an alternative agent should be given for at least 2 months after completion of alemtuzumab therapy and probably should be continued until the $CD4^+$ count is above 200 cells/μL. Weekly monitoring for CMV infection (i.e., antigenemia or PCR) should be instituted until a $CD4^+$ cell count is greater than 100 cells/μL, and positive results should be treated (see Viral Infections). Acyclovir or an equivalent agent also should be considered throughout the course of cellular immunosuppression to reduce the risk of HSV or VZV reactivation. Although serious bacterial and fungal infections also appear to be increased with alemtuzumab, it is thus far unclear what type of prophylaxis should be undertaken in these patients.[167]

Purine analogs (e.g., fludarabine, cladribine, pentostatin) also cause a depletion of T-cell populations and an increased risk of opportunistic infections compared with traditional therapy with alkylating agents. The rate of opportunistic infection varies considerably, but patients who have received previous therapy, partially or nonresponding patients, and patients receiving other agents (e.g., alkylating agents, corticosteroids) are at higher risk for such infections.[12,168] Prophylaxis against PCP for 2 months and until the $CD4^+$ count is above 200 cells/μL is recommended. Antiviral prophylaxis with acyclovir or an equivalent drug should be considered in these higher-risk patients. The role of antifungal prophylaxis with fluconazole or a moldactive agent in this population is unclear.

PRETRANSPLANTATION MEASURES TO PREVENT INFECTION

Pretransplantation Serostatus Blood Work

The serostatus of herpesviruses (HSV, VZV, CMV, and EBV) that may be present in latent form in the body should be checked before transplantation to determine if the patient is at risk for reactivation. Current testing of both donor and recipient before the transplant-preparative regimen begins includes not only herpesvirus antibodies but also hepatitis virus panels, human T-cell lymphotrophic virus (HTLV-I and HTLV-II) antibodies and human immunodeficiency virus (HIV), and syphilis serology.

The only test result that could lead to immediate cancellation of the transplantation procedure would be a positive result on HIV testing in a patient not known to be seropositive. If the screening test for HIV is positive from either the donor or the recipient, a Western blot study should be completed to confirm the result before informing the affected person of the screening test result. Any time a positive HIV test result is conveyed to a patient, appropriate counseling must be provided.

Several serostatus test results, if positive, would not constitute an indication to cancel the transplant but would lead to a different action plan.[169] If the indirect screening test for syphilis, such as the rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test, yields a positive result, confirmed by a direct test, the fluorescent treponemal antibody (FTA) test, then the patient should receive high-dose penicillin treatment for 10 to 14 days.

Hepatitis B (core antibody, surface antibody, and surface antigen) and C serologic studies are performed in donor and recipient before transplantation; if results are positive, viral load testing should be performed. Hepatic dysfunction from either hepatitis B or C after transplant can lead to life-threatening liver complications.[170–172] Hepatitis occurs within months or the first few years after transplantation in approximately 20% of HBsAg recipients, whereas cirrhosis developing over a period of many years usually is due to hepatitis C.[173] A hepatitis virus-infected person may serve as a donor if no alternative donor is available or if the intended recipient is already seropositive. The risk of transmission is lowest when a hepatitis B- or hepatitis C-positive donor has an undetectable viral load. Accordingly, donors found to have high viral loads on testing for hepatitis B or C should receive treatment with appropriate antivirals to reduce viral loads before transplantation and before donation, in conjunction with hepatology consultation.[174,175] Similarly, transplant recipients with serologic evidence of previous infection with hepatitis B or C, or those who receive cells from a seropositive donor, should have viral load levels monitored before and after transplantation and also may require treatment. Agents with activity against hepatitis B virus include lamivudine, tenofovir, and entecavir. Hepatitis C currently is treated with pegylated (PEG) interferon and ribavirin, with acceptable safety profiles and cure in up to 50% of patients.[176] Regarding hepatitis C, no evident correlation exists between hepatitis C genotype and type or severity of liver disease after transplantation.[177]

CMV, HSV, and VZV serologic studies are routinely performed before transplantation. If either the donor or the recipient is seropositive, a prevention strategy as presented earlier is used. If both the recipient and the donor are CMV-seronegative, seroconversion with blood products is possible, so CMV-seronegative or filtered blood products should be used.[178,179] Patients seropositive for HSV or VZV (or with a reliable history of chickenpox) receive prophylaxis as discussed. VZV-seronegative patients should receive varicella-zoster immune globulin (VZIG) prophylaxis within 96 hours of significant exposure.[160] If VZIG is not available, most experts would treat with acyclovir or valacyclovir for 3 weeks.

Knowing the EBV serostatus before transplantation is not mandatory because 95% of adult patients can be assumed to be seropositive for this virus. EBV-driven PTLD occurring as a consequence of EBV reactivation is in the differential diagnosis for any space-occupying mass after transplantation, but this usually occurs several months after the neutropenic phase.[180] Major risk factors for the development of PTLD include primary EBV infection after transplantation in a seronegative recipient, the use of antithymocyte globulin or anti-CD3 monoclonal antibodies for immunosuppression, and CMV primary infection or reactivation.[181–183] Mismatched or unrelated donor stem cell grafts or T-cell–depleted grafts also are associated with an increased risk for PTLD. Although the incidence of PTLD after allogeneic HSCT is as low as 0.5% in patients without major risk factors, it increases to 22% in patients with three or more risk factors. Routine monitoring of EBV viral load appears to be of limited value after transplantation, however.[184]

Historically, 15% of patients receiving transplants in the United States are seropositive for *T. gondii*, but this percentage may be higher in European centers.[185] The risk of reactivation among seropositive patients is 2%, for an overall incidence of less than 1% of transplant recipients.[185,186] Because serologies for *T. gondi* may be unreliable after transplantation, serologies should be obtained prior to transplant because this information can be useful in evaluating patients who later develop syndromes (e.g., CNS mass lesion) compatible

with toxoplasmosis. It is likely that low-dose sulfa-based regimens such as those used to prevent PCP also are effective in preventing *Toxoplasma* infection.[186,187]

Environmental Measures to Prevent Infection during and after Transplantation

Handwashing or, preferably, the use of alcohol-based hand-rub disinfectant is the mainstay of infection prevention in the hospital or clinic.[188] Persons entering the patient room to perform examination or touch the patient (including visitors as well as health care workers) should wash or disinfect their hands outside the room.[16] During respiratory virus season, infection control teams will often add extra signs to doorways and in other areas of the wards to remind visitors of the importance of handwashing. Staff and visitors without control of body secretions should not be permitted to have direct patient contact. It should be stressed, however, that routine use of gown, gloves, and masks is not required in the presence of a neutropenic patient.

Some infectious situations necessitate use of special isolation procedures.[16] Contact isolation (gloves, gowns) is indicated for encounters with patients with adenovirus, methicillin-resistant *S. aureus*, or *C. difficile* infection. Droplet precautions are added to contact precautions for respiratory virus or varicella infection. Carriers of vancomycin-resistant enterococci are placed in contact isolation until they meet federally determined criteria for discontinuation of isolation, including a negative result on culture from the original site of positive culture, if the site is still available for culture (as in wound or urine), plus three consecutive negative results on culture of rectal swabs taken at least 1 week apart.[189]

High-efficiency particulate air (HEPA) filtration has replaced laminar air flow as the means of prevention of infection through ventilation in most transplant centers.[16] With at least 12 air exchanges per hour, HEPA filters are capable of removing particles larger than 0.2 mm in diameter, such as mold spores. In addition, it is recommended that room air pressure be maintained continuously above that of the corridor (i.e., positive-pressure environment). These environmental measures are recommended for allogeneic transplant recipients; it does not appear that autologous transplant recipients require this level of protection. For individual patients, such as those who will receive T-cell–depleted transplants, "upgrade" to a laminar air flow environment may be considered. Not all centers, however, continue to maintain laminar air flow patient rooms, and the use of these facilities remains controversial.[16]

Patients may ask if portable HEPA filters should be purchased for the home or apartment that will be occupied after hospitalization is over. In the broadest sense, this extra measure can be recommended on an individual basis, but if portable HEPA filters are used, then they should be obtained for each of the rooms that the patient will occupy during the day and night, and each unit should be sized for the individual room.

Review of Commonsense Measures That Will Assist in the Prevention of Infection

After transplantation, questions often arise about the infectious potential of diet, travel, exposure to crowds, and pets.[160] Diet should be reviewed so that both provider and patient recognize whether the patient is taking any restricted foods or herbal supplements.[160] Patients may not realize that such supplements fall in the same category with medications, and that most herbal supplements need to be discontinued after transplantation.[190]

Food-borne infections constitute an increasingly difficult problem in the United States. Ground meat products must be cooked thoroughly so that bacteria distributed onto meat in the grinding process, such as *E. coli* O157 : H7, are killed. Any fruits or vegetables that cannot be peeled must be washed thoroughly before being eaten, and patients should be aware that salad bars are associated with occasional transmission of *Salmonella*, *Shigella*, and *E. coli* infections.[191,192] Food products that inherently contain infectious organisms should be avoided, including undercooked eggs (*Salmonella*), miso soup (*Aspergillus*), and soft cheeses or unpasteurized dairy products (*Listeria*) or blue cheeses (molds). Yogurt containing *Lactobacillus* has been found to cause lung infection rarely, possibly after aspiration events.[193]

No particular restrictions apply to travel, but strategies to minimize transmission of infectious diseases have been summarized.[160] Some social situations, such as sitting in a crowded movie theater or classroom, increase the risk of acquiring a viral illness. Turning away from people who are coughing or sneezing, or even quickly donning a mask, may be helpful in preventing transmission of infection in the first months after transplantation, until immunosuppression is stopped. Patients should be instructed to practice appropriate infection prevention by handwashing as soon as possible after being close to someone with a cold. In view of recent outbreaks of infection with noroviruses (Norwalk-like viruses) on cruise ships, and other types of outbreaks (e.g., staphylococcal infection) commonly associated with the close living quarters typical with this type of vacation, cruise ships should not be high on the list for vacation choices.[194,195]

Healthy dogs and cats are considered acceptable pets. The immunosuppressed patient, however, should avoid any contact with used cat litter, including "scooping" the litter box, because of potential *Toxoplasma* cyst exposure. Similarly, the patient should not play in sandboxes, because these areas may be used by outdoor cats as litter boxes. Because reptiles of many sorts have been reported to be infected with *Salmonella*, the patient should not touch these animals or the inside or outside of their aquarium homes. The heated water of tropical fish tanks may carry *Mycobacterium marinum*. *Cryptococcus* and *Chlamydia psittaci* can be transmitted from large pet birds.

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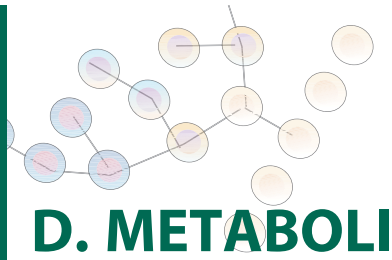
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D. METABOLIC AND PARANEOPLASTIC SYNDROMES

48 Hypercalcemia

A. Ross Morton and Allan Lipton

SUMMARY OF KEY POINTS

Incidence
- Hypercalcemia is a major metabolic complication associated with malignant disease.
- It occurs in approximately 10% of patients with cancer.
- It has a specific predilection for squamous carcinoma of the bronchus, carcinoma of the breast, and multiple myeloma.
- It is frequently recognized late and managed poorly.

Etiology of Complication
- Parathyroid hormone-related protein (PTHrP) produces hormonal and paracrine effects.
- Factors released by, or in response to, metastases in bone (receptor activator of nuclear factor-κB ligand [RANKL], PTHrP, transforming growth factor-α, tumor necrosis factor, interleukin-1 [IL-1], and others) cause paracrine effects.
- Final common pathway is osteoclastic bone resorption.
- It is aggravated by renal functional abnormalities or renal effects of PTHrP, or both.

Evaluation of the Patient
- Determination of the stage of disease and subsequent antineoplastic options provides a logical approach to management.
- Patient symptomatology is more relevant than the absolute calcium level.
- The total calcium concentration must be corrected for serum albumin concentration.
- Close attention to volume status and renal function are mandatory.
- Causes of hypercalcemia other than malignancy should be considered.

Grading of the Complication
- Patients with symptoms due to their hypercalcemia should be treated as severely affected irrespective of the absolute calcium level.
- A corrected serum calcium of less than 3.0 mmol/L is considered mild, 3.0 to 3.5 mmol/L is moderate, and greater than 3.5 mmol/L is severe.

Treatment
- Antitumor therapy should be implemented for best long-term results.
- Consideration should be given to active palliation in the face of advanced disease when antitumor options are exhausted.
- Extracellular fluid volume should be expanded to induce a calciuresis.
- Antiresorptive therapy (bisphosphonates with or without calcitonin) should be considered as first-line therapy.

INTRODUCTION

Hypercalcemia is one of the most common metabolic complications of malignancy. Even though it occurs in approximately 8% to 10% of patients with malignant disease, the diagnosis is frequently delayed. A knowledge of the tumor types associated with hypercalcemia, the mechanisms generating the hypercalcemia, and the symptom constellation will lead to prompt diagnosis, timely and appropriate intervention, and amelioration of morbidity.

Hypercalcemia in association with malignant disease was first reported by Zondek and colleagues in 1924,[1] and the first review of a large series was by Gutman and coworkers in 1936.[2] Since then, the syndrome has become increasingly well recognized and characterized. The frequency with which hypercalcemia occurs varies considerably with tumor type, but it is most commonly seen in association with squamous carcinoma of the bronchus, carcinoma of the breast, and multiple myeloma. It is of considerable interest that some tumors that frequently metastasize to bone—for example, small-cell carcinoma of the lung, carcinoma of the prostate, and some other common tumors, such as adenocarcinoma of the colon and stomach—are infrequently associated with hypercalcemia.

ETIOLOGY

Before we discuss the possible etiologies of hypercalcemia in malignant disease, a short review of normal calcium homeostasis is appropriate. (For a more extensive review see Ramasamy.[3]) The adult human body contains approximately 1 kg of calcium, of which all but 10 g is lodged in bone. Most of the extraosseous calcium is found in the extracellular fluid, but the minute concentrations present in cells (10^{-8} to 10^{-7} M) are vital to normal cellular function and control. The total body calcium is dependent on the balance between calcium intake and calcium loss. Figure 48-1 demonstrates the normal calcium metabolism.[4] The normal dietary calcium intake is approximately 1 g per day (25 mmol). Absorption of dietary calcium is incomplete (25% to 50%), and in healthy individuals it is approximately 300 mg (7.5 mmol per day). Bone represents an enormous reservoir of calcium, yet very little transfer of calcium (on the order of 500 mg or 12.5 mmol per day) occurs between bone and the plasma in health. When net calcium balance is zero, the body is required to excrete approximately 150 mg (3.75 mmol) of calcium daily. The kidney filters large amounts (10 g or 250 mmol) of calcium daily. Of this amount, 65% is reabsorbed in the proximal convoluted tubule, 25%

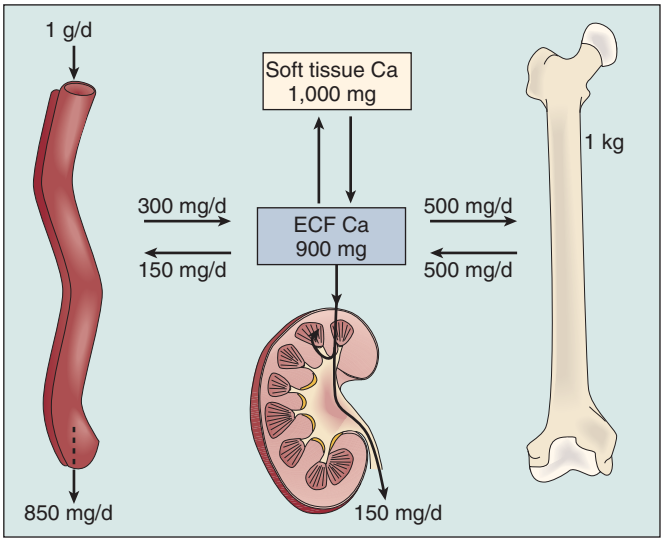


Figure 48-1 • Normal calcium homeostasis. ECF, extracellular fluid. (From Mundy GR: Calcium Homeostasis: Hypercalcemia and Hypocalcemia. Martin Dunitz, London, 1990, p 2, with permission.)

in the ascending limb of the loop of Henle, and a variable amount in the distal convoluted tubule. Calcium reabsorption in the proximal tubule is independent of hormonal control but is closely linked to the reabsorption of sodium, a phenomenon that has important consequences in, and implications for, the treatment of hypercalcemia. Calcium reabsorption from the distal tubule is enhanced in the presence of parathyroid hormone (PTH), and it is at this site that the fine-tuning of calcium homeostasis occurs. The maximal reabsorptive capacity of the kidneys is limited to about 600 mg per day (15 mmol per day); thus, bone resorption can increase by approximately 150% over bone formation before the renal clearance mechanisms are overwhelmed.

The total plasma calcium consists of free plasma calcium (which amounts to approximately 50% of the total) and calcium bound to albumin (and occasionally to other proteins, including paraproteins), which varies with the level of plasma proteins but accounts for approximately 40% of the total. The remaining 10% is in complex with ions such as bicarbonate and citrate (Fig. 48-2). In physiologic terms, the plasma free (or "ionized") calcium carries the greatest

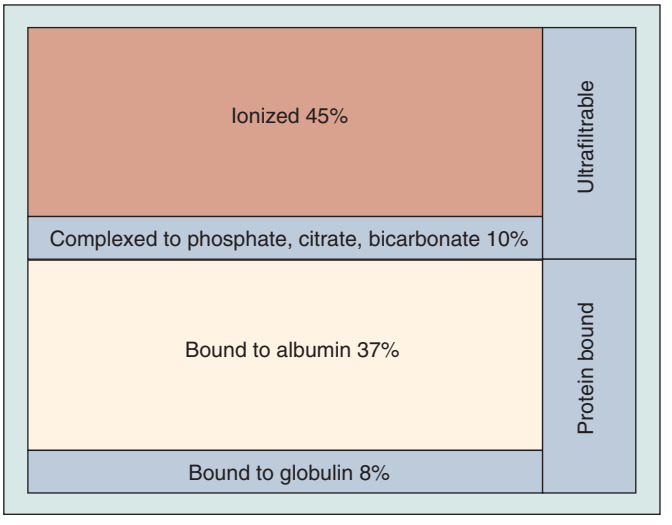


Figure 48-2 • The constituents of total calcium within the serum.

significance. Direct measurement of the plasma free calcium is possible using ion-selective electrodes, but for the most part, total plasma calcium is measured. Because there is a reasonable correlation between serum albumin and serum calcium, algorithms have been suggested to "correct" the total plasma calcium for albumin concentration. Although no algorithm is 100% specific or sensitive for the detection of all true cases of hypercalcemia, the following equation has the merits of accuracy and simplicity.

$$\text{Ca (corrected)} = \text{Ca (measured)} + (0.8 \times [4 - \text{albumin concentration}])$$

Conventional units

$$\text{Ca (corrected)} = \text{Ca (measured)} + (0.02 \times (40 - \text{albumin concentration}))$$

SI units

The serum level of ionized calcium is tightly controlled. The major hormonal determinant of ionized calcium is PTH. This hormone brings about its effects by altering calcium resorption from bone, calcium reabsorption in the kidney, and, via stimulation of formation of active vitamin D (1,25-$(OH)_2D_3$), calcium absorption from the gastrointestinal tract. The active form of circulating PTH is a polypeptide containing 84 amino acid residues; however, only the first 34 amino acid residues are required for activity related to calcium homeostasis. Several larger C-terminal fragments of PTH are found in circulation (most notably in the presence of renal insufficiency). The role of these peptides, and particularly the large PTH(7–84) fragment (which has been postulated to have antagnositic properties to PTH(1–84), which is secreted from the parathyroid glands during hypercalcemia) remains controversial. An excellent review on the topic of PTH has been written by Potts.[5]

PTH release and, to a lesser extent, formation is under the control of the calcium-sensing receptor (CaSR) which is located on the external cell membrane of parathyroid chief cells. This receptor is a G-protein coupled receptor with a large extracellular domain, responsible for calcium binding, seven transmembrane domains, and a smaller intracellular domain responsible for signal transduction. Stimulation of the CaSR by even mild changes in ionized calcium level results in a rapid and profound change in the secretion of PTH as well as more delayed effects on PTH formation.[6]

The parathyroid glands also manufacture the hormone calcitonin. Although pharmacologic doses of calcitonin have effects on plasma calcium levels when given acutely, there remains considerable controversy over its true physiologic role,[7] because in both the absence of calcitonin (following total thyroidectomy) and in the presence of large circulating amounts (seen in medullary carcinoma of the thyroid), gross disturbance of calcium balance is extremely rare.

An understanding of normal calcium homeostasis makes it clear that there are three potential mechanisms that can cause hypercalcemia of malignancy. Calcium can be mobilized from bone in quantities sufficient to overwhelm the renal excretory mechanism, renal reabsorption of calcium can be inappropriately increased (or excretion can be decreased), and gastrointestinal absorption of calcium can be enhanced.

TYPES OF HYPERCALCEMIA OF MALIGNANCY

Humoral Hypercalcemia of Malignancy

In 1980, Stewart and colleagues[8] described a series of 50 patients with hypercalcemia and malignant disease. In their extensive metabolic evaluation they were able to characterize the patients into two groups dependent on their excretion of nephrogenous cyclic adenosine monophosphate (cAMP). Patients with high nephrogenous cAMP shared other features with primary hyperparathyroidism, including a

lowered renal phosphate threshold. There were, however, significant differences between these groups in terms of fasting urinary calcium excretion, 1,25-$(OH)_2D_3$ concentrations, and immunoreactive PTH levels. They concluded that urinary nephrogenous cAMP was a useful marker for identifying hypercalcemia of malignancy associated with a humoral factor—so-called humoral hypercalcemia of malignancy (HHM)—but that this factor was not native PTH.

Parathyroid Hormone-related Protein

Advances in molecular biology, in association with the failure to detect circulating immunoreactive PTH in patients with hypercalcemia, cast increasing doubt on the role of native PTH in HHM. In 1983, Simpson and colleagues,[9] using complementary DNA probes to PTH messenger RNA (mRNA), failed to demonstrate the production of PTH mRNA in many of the tumors considered as prime candidates for ectopic PTH secretion.

In 1987, Burtis and associates,[10] Moseley and coworkers,[11] and Strewler and colleagues[12] published descriptions of a polypeptide hormone isolated from tumors that are associated with the hypercalcemia of malignancy. The primary structure of these peptides shows considerable N-terminal homology with native PTH (Fig. 48-3) and has led to the terminology PTHrP. Although PTHrP is the main humoral factor in patients with hypercalcemia of malignancy, there is increasing information on its normal physiologic roles.[13] Furthermore, PTHrP seems to be under the control of the CaSR, where, in the case of malignant disease, hypercalcemia sensed by the CaSR may actually *increase* the elaboration of PTHrP, thus aggravating the vicious cycle of hypercalcemia. This has led to the suggestion that high calcium levels may actually have a pro-malignant potential mediated by the CaSR, and at least in part due to the actions of PTHrP. This topic has been extensively reviewed by Chattopadhyay.[14]

Vitamin D-linked Hypercalcemia

In the majority of patients with hypercalcemia, levels of 1,25-$(OH)_2D_3$, the active metabolite of vitamin D, are suppressed. Normal vitamin D metabolism is closely controlled at the level of 1α-hydroxylation of 25-hydroxyvitamin D_3 in the proximal convoluted tubules of the kidney. The renal tubular 1α-hydroxylase is stimulated by increased levels of PTH and hypophosphatemia, inhibited by hyperphosphatemia, and decreased in activity as PTH levels fall.

In addition to the well-known association of hypercalcemia in sarcoidosis, abnormal vitamin D metabolism, characterized by a substrate-dependent conversion of 25-hydroxyvitamin D_3 to 1,25-$(OH)_2D_3$, has been described in association with lymphomas. Indeed about half of lymphoma patients presenting with hypercalcemia have abnormal amounts of 1,25-$(OH)_2D_3$, whereas the remainder have elevated concentrations of PTHrP. It seems that the cells responsible for the activation of vitamin D are macrophages in close proximity to the lymphoma cells.[15]

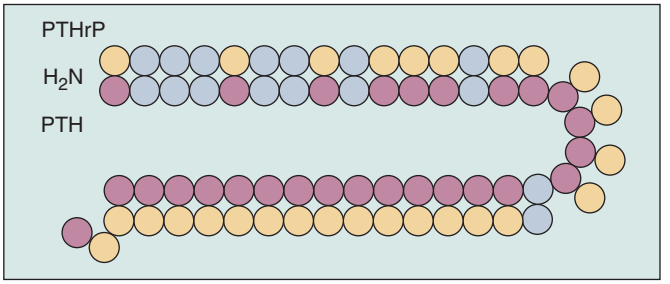


Figure 48-3 • Sequence homology between PTHrP (1–34) and PTH (1–34). Blue circles indicate identical amino acids between the polypeptides; purple and yellow circles indicate that the corresponding amino acids are not identical.

It has become apparent that as many as 50% or more of patients with adult T-cell lymphoma have hypercalcemia. Evidence suggests that the mechanism of hypercalcemia in this lymphoma type is due to overexpression of the receptor activator of nuclear factor-κB ligand (RANKL; see later discussion) in the malignant T cells. Recent work by Okada and associates points to the role of macrophage inflammatory protein-1α as the RANKL-inducing agent, as well as having a recruiting effect on osteoclast precursors.[16]

The role of pharmacologic doses of active vitamin D and its analogs in the treatment of malignant disease is increasing. The major early drawback to this therapy has been the development of drug-induced hypercalcemia. More recently the introduction of intermittent dosing, the combination with dexamethasone or bisphosphonates, and the promise of less calcemic analogs seems to be circumventing this problem. (See reviews.[17,18])

Local Osteolytic Hypercalcemia

In the presence of a large bony metastatic burden, calcium is mobilized from the skeleton by the action of osteoclasts. The osteoclasts seem to be stimulated by local factors produced by the tumor cells. Tumor types in this category (carcinoma of the breast, multiple myeloma, lymphoma, and leukemia) rarely produce hypercalcemia in the absence of significant bony involvement, but it must be remembered that local and humoral factors can interact to aggravate bone destruction.

Multiple Myeloma

Bone resorption, osteopenia, and hypercalcemia are characteristic features of patients with multiple myeloma. The neoplastic cells are in close proximity to bone by the very nature of the condition. Many factors responsible for local osteolysis have been identified, produced by, or in response to, myeloma cells in the marrow. Collectively, these have been called osteoclast-activating factors. They include IL-1, IL-6, IL-11, PTHrP, hepatocyte growth factor, tumor necrosis factor, macrophage inflammatory protein-1α, among others (reviewed by Yeh and Berenson[19]).

The identification of the cytokine system involving RANKL, the target of this polypeptide (receptor activator of nuclear factor-κB [RANK]), and the controlling inhibitor osteoprotegerin (OPG) that acts as a soluble decoy receptor, has represented a major breakthrough in the understanding of local control of bone cell biology (reviewed by Hofbauer[20]). Essentially, RANKL, normally produced by osteoblasts, is responsible for osteoclast differentiation and function. In patients with multiple myeloma the RANK/RANKL/OPG system is deranged. Multiple myeloma cells in the bone marrow increase the presence of RANKL either by direct secretion or by stimulating stromal cell production. Furthermore, there is depression of OPG availability, both at the level of protein systhesis, and after OPG has been secreted as a result of binding to CD-138 (syndecan-1) elaborated by multiple myeloma cells.[21]

The picture of hypercalcemia in multiple myeloma is further complicated by the various renal defects that are a feature of at least 20% of patients with this condition. The major impact is a reduction in glomerular filtration rate, which decreases the kidneys' ability to excrete a calcium load.

Carcinoma of the Breast

It is generally considered that hypercalcemia is uncommon in patients with carcinoma of the breast in the absence of widespread osseous metastases. Bony destruction is again mediated by stimulated osteoclasts. It has been suggested that breast cancer cells themselves might be capable of resorbing bone, but this does not seem to be a major mechanism. Breast cancer cells are able to produce or induce a number of factors in the local bone microenvironmant that could act at a local level to enhance osteolysis (including transforming growth factor-α, IL-8, IL-11, and prostaglandins—particularly of the E series).

Despite this, it is also clear that not all cases of hypercalcemia in carcinoma of the breast are wholly dependent on metastatic disease. Indeed, one of the original tumor types from which PTHrP was isolated was breast cancer.[10] In an early study of 98 women with varying degrees of breast cancer, Bundred and coworkers[22] noted elevated PTHrP levels in 12 of 13 hypercalcemic patients. Furthermore, tumor staining for PTHrP was positive in 22 of 25 patients who had bone metastases and later developed hypercalcemia.

It has become increasingly clear that cell-cell interaction between breast cancer cells and the local bone cells has much to do with the maintenance of the metastatic phenotype in bone. Local production of PTHrP by breast cancer cells can increase osteoclast development and recruitment via RANKL. Enhanced bone resorption can release stored factors including insulin-like growth factor-1 and transforming growth factor-β. These substances support the growth of the malignant cells. Osteoclastic mobilization of calcium increases tumor production of PTHrP (mediated in part by the CaSR), resulting in a vicious cycle. Cellular cross-talk as it relates to bone metastases has been elegantly reviewed by Yoneda and Hiraga.[23]

Special Cases

Pseudohypercalcemia

The phenomenon of psuedohypercalcemia is a rare condition in which excess calcium bound to nonalbumin plasma proteins results in an elevated total serum calcium concentration. These proteins are usually monoclonal proteins associated with multiple myeloma and benign monoclonal gammopathy.[24] The ionized calcium concentration is normal under these circumstances, but correction formulas using albumin give falsely abnormal results.

Multiple Endocrine Neoplasia

The multiple endocrine neoplasia (MEN) syndromes are a group of disorders associated with hyperfunction of two or more endocrine glands. Hyperparathyroidism or parathyroid hyperplasia is a feature of both MEN-1 and MEN-2. Hypercalcemia is usually mild and frequently asymptomatic. The role of parathyroidectomy is unclear in MEN-1 and MEN-2B, but the association with medullary carcinoma of the thyroid in MEN-2A means that it will more frequently be undertaken in this condition. The fact that the hyperplastic parathyroid glands display the CaSR renders them susceptible to treatment using calcimimetics (see later discussion).

Tamoxifen-Linked Hypercalcemia

Hypercalcemia in association with the use of estrogen or antiestrogen therapy for carcinoma of the breast has been recognized for more than 50 years. The severity of the hypercalcemia is variable, but it can be fatal. The mechanism by which tamoxifen and similar agents cause hypercalcemia is unclear. Cell culture studies suggest that prostaglandins could be the main mediators of the response.[25] A role for prostaglandins would be compatible with the clinical picture of a tamoxifen "flare," which, in addition to the hypercalcemia, is frequently associated with bone pain.

EVALUATION OF THE PATIENT

That malignancy is the cause of hypercalcemia is usually not hard to establish. Nonetheless, careful consideration of other causes of hypercalcemia is warranted for all patients. The differential diagnosis of isolated hypercalcemia is a long one (Table 48-1). It is worth noting, however, that immobilization is common in patients with cancer, that primary hyperparathyroidism is not a rare disease, and that the iatrogenic causes of hypercalcemia are easily remedied. An excellent review of rarer causes of hypercalcemia has been written by Jacobs and Bilezikian.[26]

Table 48-1 Causes of Hypercalcemia (Other Than Malignant Disease)

Type	Cause
Endocrine	Hyperparathyroidism
	Hyperthyroidism
	Addison's disease
Iatrogenic	Immobilization
	Vitamins A and D
	Thiazide diuretics
	Lithium
Other	Paget's disease of bone
	Granulomatous disease

Clinical Findings

The syndrome of hypercalcemia of malignancy is often overlooked because many of the symptoms are nonspecific or vague and are ascribed to the underlying malignant process or to its therapy. The symptoms of hypercalcemia are protean. Only parts of the old dictum of "stones, bones, abdominal groans, and psychic moans" used in the description of the symptoms due to primary hyperparathyroidism hold true.

Gastrointestinal symptoms are present in nearly all affected individuals. Nausea, anorexia, and vomiting are early symptoms, but they can easily be confused with the side effects of tumor treatment or with symptoms produced directly by the tumor itself. By inducing dehydration and hence aggravating the hypercalcemia, these complications set up a vicious cycle. Constipation is common, and complete ileus can occur at severely raised calcium levels. Cramping abdominal pains, such as those seen in primary hyperparathyroidism, are encountered occasionally, but acute pancreatitis or peptic ulceration complicating the hypercalcemia of malignancy is extremely rare.

The major effect of hypercalcemia on the kidney is to impair renal concentrating ability. Urine, dilute compared with plasma, is excreted in large volume. As the hypercalcemia and the polyuria persist, volume depletion ensues, with a resultant fall in the glomerular filtration rate. Further impairment of the kidney's ability to handle the abnormal calcium load occurs, and the hypercalcemia is aggravated. Tubular damage continues and manifests as acquired renal tubular acidosis, glycosuria, and aminoaciduria. An important consequence of the tubular malfunction is a natriuresis. This results in a sodium loss that aggravates the hypercalcemia, in that the mechanisms for conserving sodium and calcium within the kidney are similar. A syndrome akin to nephrogenic diabetes insipidus occurs, and polydipsia is therefore an early feature. Unfortunately, the gastrointestinal symptoms of anorexia and vomiting overcome the thirst, and intense dehydration can occur. Nephrocalcinosis and nephrolithiasis require hypercalcemia of a prolonged duration and are therefore atypical of the syndrome.

Neuropsychiatric symptoms of apathy, depression, and fatigue are frequently overlooked and ascribed to the underlying neoplasm. Muscle weakness itself can be profound and can confine the patient to bed. This immobility leads to further calcium mobilization and enhances the hypercalcemia. As hypercalcemia continues to worsen, confusion and finally coma supervene. Focal neurologic symptoms, including ataxia, which resolve on normalization of the serum calcium, also can occur but are rare.

Pruritus is a well-recognized, if infrequent, complication of hypercalcemia, as are various irritating eye symptoms. Their frequency in malignant hypercalcemia is less than in primary hyperparathyroidism.

Bone pain is a frequent symptom of both malignant disease and hypercalcemia. Clearly, this might in part be related to the presence of metastases within bone causing areas of increased intramedullary pressure, ischemia, or microfractures, but the symptom is also present in the absence of demonstrable metastatic disease.

The syndrome of hypercalcemia of malignancy therefore presents insidiously, with anorexia, fatigue, apathy, and polyuria, but it can progress rapidly to obtundation and death.

Laboratory Investigations

From a practical point of view, a few well-chosen, simple investigations are all that are required to aid in the diagnosis, therapy, and monitoring of patients. From the academic point of view, these and less readily available investigations can enhance the understanding of the hypercalcemic process in any given individual.

A complete blood count and estimation of the platelet count are required. Measurements of serum electrolytes, blood urea nitrogen, and creatinine are mandatory. Because of the importance of protein binding on the "free" calcium concentration, serum albumin should always be measured with the serum calcium, and a correction formula (such as the one given previously) should be used. In asymptomatic patients with hypercalcemia and multiple myeloma, a serum ionized calcium should be obtained.

Renal function and the response of the serum calcium to therapy should be monitored daily until the calcium concentration normalizes, and weekly thereafter unless circumstances necessitate more frequent investigation.

Biochemical clues to the presence of HHM due to PTHrP include hypophosphatemia, hyperchloremia, and a mild metabolic alkalosis, although these could not be considered diagnostic. Urinary excretion of calcium is high, as is urinary cAMP. The renal phosphate threshold is low, indicating a renal phosphate leak, and significant hypophosphatemia can result following treatment of the hypercalcemia. Assays for PTHrP are available but currently have limited clinical application in the setting of hypercalcemia of malignancy.

Serum immunoreactive PTH is low or undetectable unless the primary site of malignancy is the parathyroid gland itself, or primary hyperparathyroidism coexists. Vitamin D metabolites are also frequently low in most cases of hypercalcemia, even though PTHrP is capable of stimulating renal 1α-hydroxylase. Measures of osteoblastic function, such as alkaline phosphatase and bone γ-carboxyglutamate (gla) protein (osteocalcin), have little to offer in the diagnosis or management of hypercalcemia.

Radiographs and isotope bone scans might be pertinent for prognostication and follow-up but do not help delineate the cause of the hypercalcemia, nor are they useful in predicting the response to therapy.

GRADING THE COMPLICATION

Although it is possible to grade hypercalcemia according to mild, moderate, and severe categories on the basis of a biochemical value, it is important to note that the development and severity of symptoms do not seem to be strictly related to the serum calcium level. As a general rule, patients with symptoms readily related to hypercalcemia should be treated as severe cases, regardless of the objective degree of elevation of the calcium level. A frequently made but poorly understood observation is that patients with tumor-induced hypercalcemia often have greater symptomatology for any given rise in calcium level as compared with patients with primary hyperparathyroidism. Our approach to the treatment of hypercalcemia of malignancy is based on the following classification of hypercalcemia. It is worth noting that many variables other than the serum calcium level affect the logical choice for therapy.

Mild Hypercalcemia

Patients in this group are asymptomatic and have a serum calcium level of less than 3.0 mmol/L. The abnormality is frequently detected as part of the routine biochemical workup in patients with tumor types known to predispose to hypercalcemia. These individuals are therefore usually outpatients. Although urgent management of the hypercalcemia is not indicated, several considerations must be borne in mind. The natural history of tumor-induced hypercalcemia is for the condition to worsen. A reevaluation of the current antineoplastic regimen and response to treatment is warranted, because the development of hypercalcemia might be an early indication of a diminishing response to therapy. The development of any intercurrent insult to the kidneys is likely to precipitate more severe hypercalcemia. Intercurrent insult includes both any situation in which volume depletion could occur, and the introduction of nephrotoxic agents, such as nonsteroidal anti-inflammatory agents.

Moderate Hypercalcemia

In asymptomatic patients with a serum calcium of 3.0 to 3.5 mmol/L, the situation is more serious. Although this level of calcium might not be life-threatening, little is required to tip the scales toward a more serious problem.

Severe Hypercalcemia

All patients with symptoms attributable to hypercalcemia should be treated as an acute medical emergency. Furthermore, patients with a serum calcium concentration (corrected for albumin) greater than 3.5 mmol/L require urgent treatment.

TREATMENT

The serum calcium concentration can be reduced in almost all patients with tumor-induced hypercalcemia. A variety of antihypercalcemic regimens remains in common use, although the wide therapeutic index and high success rates of the newer bisphosphonates have resulted in their use as first-line management in the majority of cases. Although it has been possible to target osteoclast-mediated bone resorption in a fairly specific way, the same cannot be said for enhanced renal tubular calcium reabsorption or gastrointestinal calcium absorption. The introduction of calcimimetic agents has provided a specific therapy in relationship to parathyroid carcinoma with hypersecretion of PTH.

Selection of therapy should be geared to a knowledge of the individual tumor type (and hence, to the probable mechanism underlying the hypercalcemia) and to the status of the patient's renal function and bone marrow reserve. Any specific antineoplastic therapy that can be used, be it surgical, radiotherapeutic, or chemotherapeutic, will be a powerful adjuvant to antihypercalcemic therapy. An excellent clinical review has been published by Stewart.[27]

Ethical Considerations

The first decision is whether or not to treat this complication. Unless specific antitumor therapy is available, the majority of patients who develop hypercalcemia of malignancy are in the last few weeks of their lives. A recent review of aerodigestive squamous cancer demonstrated a median survival of 35 days and a 2-year mortality of 72%[28] (pulmonary cancers were under-represented in this study at 12% of the total). Similarly, hypercalcemia was predictive of early death in patients presenting with multiple myeloma.[29] Thus, it can be argued that treatment is not indicated for all cases of hypercalcemia associated with malignancy. For some, however, the use of an effective, safe treatment to ameliorate the substantial morbidity of hypercalcemia and to allow patients to return home is clearly warranted.

General Considerations

The best treatment is one directed specifically and effectively at the underlying malignant disease. Early mobilization is a laudable but often unachievable goal in patients with advanced malignant disease. Thiazide diuretics should be avoided because they promote renal tubular calcium reabsorption.

Although dietary restriction of calcium seems intuitively appropriate, gastrointestinal calcium absorption is low in most cases of hypercalcemia associated with malignant disease. A notable exception is among patients whose tumors are associated with a substrate-dependent 1α-hydroxylase, which allows continued production of calcitriol. Patients taking supplemental vitamin D and vitamin A (β-carotene) should be advised of the hypercalcemic effects of these agents.

Extracellular Fluid Volume Expansion

Most patients with hypercalcemia of malignancy have significant depletion of fluid volume (on the order of 5 to 10 L) due to the combined effects of anorexia, vomiting, and nephrogenic diabetes insipidus. In this state, the glomerular filtration rate is reduced, and the response by the proximal convoluted tubule is to increase sodium retention. Concomitantly, proximal tubular resorption of calcium is also increased. The aim of fluid replacement in these circumstances should be to induce a state of mild fluid overload. Restoration of a normal circulating blood volume restores the glomerular filtration rate and increases the fractional excretion of calcium. Further salt loading, on the other hand, induces natriuresis and concomitant calciuresis. Care must be taken to avoid severe congestive cardiac failure in elderly patients or in patients with poor cardiac reserve. Because of the hypoalbuminemia that frequently accompanies advanced malignant disease, dependent edema is to be expected during volume expansion. Care must also be taken to ensure an adequate intake of free water. In the presence of severe hypercalcemia, a resistance to the distal tubular actions of antidiuretic hormone may predispose obtunded patients to significant hypernatremia. After restoration of euvolemia, a maintenance infusion of 3 L/day of 0.9% saline solution will induce continued natriuresis and calciuresis. Patients should be encouraged to drink freely. During such aggressive fluid management, other electrolyte abnormalities are likely to be uncovered or precipitated. Despite impaired renal function, both hypokalemia and hypomagnesemia are frequent findings, and appropriate supplementation could be required.

Although serum calcium can be expected to fall while a patient is on this regimen, restoration of normocalcemia is unlikely. Failure to restore normal fluid balance, however, will greatly detract from the success of subsequent therapeutic measures.

Calciuretic Therapy

Aside from the calciuretic effects of saline overload, two other agents are commonly used to induce renal calcium wasting: furosemide and calcitonin.

Furosemide

Furosemide is a diuretic agent whose main site of action is in the thick ascending limb of the loop of Henle (thus making this agent a loop diuretic), where it completely and reversibly inhibits the $Na^+/K^+/2Cl^-$ cotransporter. In the euvolemic and volume-expanded state, the fractional excretion of calcium can be increased by as much as 30% by loop diuretics. If a patient is volume depleted, however, enhanced proximal tubular sodium and calcium resorption can obviate this response. Thus, the potential exists for loop diuretics to aggravate hypercalcemia if adequate attention is not paid to fluid volume status. In the initial report of the effectiveness of this treatment, the regimen involved the administration of doses of furosemide in the region of 100 mg every 2 hours. Therapy this aggressive would require the facilities of an intensive care unit to ensure adequate fluid monitoring. Although substantial reductions in the serum calcium can be achieved, a rationale for the use of this treatment for other than acute situations is lacking, in that the primary cause of the hypercalcemia—increased bone resorption—is not affected. Given the risks of severe electrolyte disturbances and the availability of potent antiresorptive medication, loop diuretics should be reserved primarily for situations of fluid overload rather than using them as antihypercalcemic agents.

Calcitonin

The renal actions of calcitonin are complex. The calciuretic effect seems to be due to inhibition of calcium reabsorption in the distal tubules. This, in turn, is dependent on an adequate delivery of calcium to the distal nephron, a situation that is compromised by the extracellular fluid volume depletion in hypercalcemia. This renal tubular effect is rapid, however, and the administration of calcitonin can be of great value as an adjunct to more potent antiresorptive therapies.

Antiresorptive Therapy

Given that bone resorption is increased in the majority of cases of hypercalcemia of malignancy, the best treatment after that designed to combat the tumor itself is one directed at bone resorption. The osteoclasts represent the final common pathway for bone resorption in both humoral and local osteolytic hypercalcemia. The following agents, which inhibit osteoclast function, not surprisingly are highly effective antihypercalcemia treatment.

Bisphosphonates

The bisphosphonates are a class of compounds—structural analogs to pyrophosphate—in which the P-O-P bond is replaced by a P-C-P bond stable to enzymatic cleavage. Figure 48-4 shows the structure of some of the available bisphosphonates compared with the structure of pyrophosphate. Pharmacokinetic and pharmacodynamic studies of bisphosphonates indicate that these compounds are absorbed poorly from the gastrointestinal tract after oral administration. Diet has a profound effect on gastrointestinal absorption, reducing the effective bioavailability of the drugs to zero if taken with food.

Although bisphosphonates have a significant physicochemical effect, preventing the formation and dissolution of calcium compounded with phosphate, it has become clear that the major clinical mechanisms of action relate to inhibition of farnesyl pyrophosphate synthase in the case of aminobisphosphonates, and incorporation into adenosine triphosphate–containing compounds resulting in inhibition of cell function in nonaminobisphosphonates. Both mechanisms promote apoptosis in osteoclasts, whereas the aminobisphosphonates also inhibit osteoclast recruitment.[30]

There are strong data to support the use of the intravenous bisphosphonates zoledronic acid (4 mg over 15 minutes), pamidronate (60 to 90 mg over 2–4 hours), ibandronate (4 mg over 1 hour), and clodronate (1500 mg over 4 hours) in the management of hypercalcemia of malignancy. Favorable studies have been reported when comparing bisphosphonates with placebo, calcitonin, glucocorticosteroids, and mithramycin (plicamycin; see an extensive review in Ross and colleagues[31]).

In studies comparing bisphosphonates, pamidronate proved superior to edtironate and clodronate.[32] A pooled analysis of two studies involving 287 patients demonstrated a significantly better response rate for zoledronic acid (4 mg and 8 mg) as compared with pamidronate (90 mg).[33] The complete response rate for both zoledronic acid doses (defined as normocalcemia at day 10) was similar (88.4% for patients given 4 mg; 86.7% for patients given 8 mg), whereas the response rate for pamidronate was 69.7%. Although these studies confirmed the superiority of zoledronic acid to pamidronate in the sample population, it should be noted that the response rate to

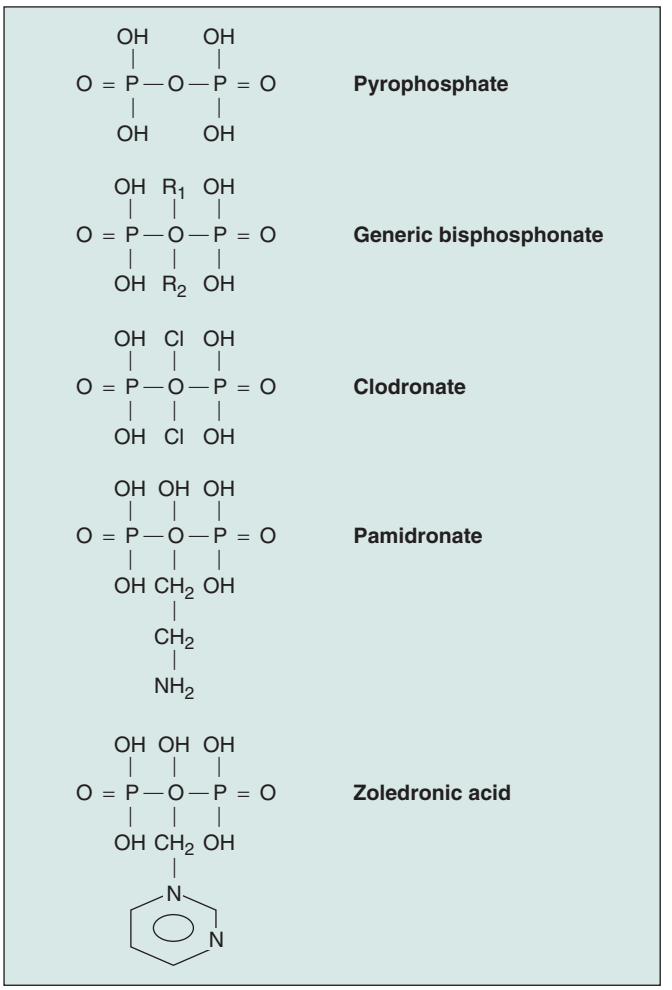


Figure 48-4 • Structural formulas of commonly studied bisphosphonates in relation to the generic bisphosphonate and to pyrophosphate.

pamidronate was lower than has been reported in previous trials. A comparative study between ibandronate and pamidronate has shown that the former is at least equal to the latter in terms of biochemical response and possibly associated with a longer time to recurrence of the hypercalcemia.[34]

The primary mechanism in the generation and maintenance of hypercalcemia in malignant disease is enhanced bone resorption. However, tumors secreting PTHrP also have a significant influence on renal calcium handling, which would not be influenced directly by bisphosphonate therapy. In a review of 147 patients with hypercalcemia of malignancy and available measurement of PTHrP, it was found that, although the hypercalcemia responded well to intravenous ibandronate, the renal tubular calcium index changed only slightly, confirming that the majority of the action of the bisphosphonates was to limit enhanced bone resorption. Although patients with those tumor types associated with higher PTHrP (lung, upper respiratory tract) had the greatest risk of recurrence of their hypercalcemia, this was not statistically associated with PTHrP levels.[35]

The duration of response to bisphosphonates is difficult to determine and varies considerably among individuals. Elucidation of the duration of response is also compounded by the high mortality in this group of patients due to their tumors and by the introduction of specific and effective antineoplastic therapy for patients with cancers such as breast and multiple myeloma. Median time to relapse in the studies comparing zoledronic acid with pamidronate was 30 to 40 days with zoledronic acid and 17 days with pamidronate.[33] Unfortunately, it is not possible to predict the length of time that any specific patient will remain normocalcemic.

In general, bisphosphonate therapy is well tolerated. An acute inflammatory reaction (so-called first-dose effect) with low-grade pyrexia, bone pain, and myalgias is noted in 10% to 30% of patients. The use of rapid intravenous infusions of clodronate and etidronate has been associated with deterioration in renal function in patients with previously diminished renal reserves. Renal dysfunction has been noted with pamidronate (often in the setting of frequent use at doses higher than recommended). The observation of more frequent renal abnormalities in patients receiving 8 mg zoledronic acid has led to the recommendation that 4 mg be the starting dose. Hypophosphatemia sufficient to require supplementation is seen with effective management of hypercalcemia in the setting of bisphosphonate use. The mechanisms of phosphate imbalance are unclear but may include pre-existing nutritional deficiency aggravated by volume expansion, renal phosphate wasting in association with PTHrP activity, and increased native PTH activity as normocalcemia (or even mild hypocalcemia) follows therapy. Osteonecrosis of the jaw has been associated with the use of aminobisphosphonates in the long-term management of skeletal morbidity from cancer and (infrequently) nonmalignant conditions.[36] According to our current understanding of the condition, this side effect would be considered rare after a single treatment for hypercalcemia of malignancy. Infrequently, eye findings including uveitis and scleritis have been associated with aminobisphosphonate use. The management of bisphosphonate side effects has been the subject of a recent review.[37]

Gallium Nitrate

Hypocalcemia was noted as a side effect of therapy among patients receiving gallium nitrate for the management of lymphoma.[38] Thereafter, its effectiveness as an antihypercalcemia agent was confirmed by Warrell and associates[39] The exact mechanism of action of gallium is unknown, although it is clear that urinary calcium excretion is reduced. By implication, bone resorption is reduced, although no histologic changes were noted in explants of fetal long bones exposed to this agent.

Gallium nitrate requires intravenous administration. The best-investigated regimens involve sequential 5-day infusions of 200 mg/m^2/day. At this dose, the drug is relatively free of side effects, although caution is required if other nephrotoxic agents (e.g., aminoglycosides) are being used. Clinical trials using gallium nitrate have shown a superior response (in terms of normalization of calcium and duration of normocalcemia) when compared with calcitonin, etidronate, and pamidronate. Gallium nitrate is effective in tamoxifen-induced hypercalcemia, and it has also been suggested that it may be more effective in cancers associated with higher levels of PTHrP (see review[40]).

The major drawback with this therapy is the need for 5 days of infusion, as compared with the shorter duration of therapy for the bisphosphonates.

Therapy Directed against Humoral Factors

Calcimimetics

Calcimimetics are agonists at, or modulators of, the CaSR. These receptors are abundant on normal parathyroid gland tissue but are also present on malignant parathyroid tissue. A well-documented case report using an allosteric modulator of the CaSR (rendering the receptor more sensitive to the effects of high calcium) showed improved control of hypercalcemia in a patient with parathyroid carcinoma.[41] Parathyroid carcinoma is a rare cause of hypercalcemia of malignancy, and it is equally rare for tumors to manufacture ectopic PTH, thus the clinical impact of calcimimetics in the area of hypercalcemia of malignancy is likely to be limited. Indeed, the effect

of pharmacologic modulation of the CaSR in nonparathyroid cancers is unclear but has the potential to be detrimental by increasing the production of PTHrP as described previously.

Humanized Antibodies to PTHrP

In a murine model antibodies directed against PTHrP were effective in reversing the HHM and improving nutritional status.[42] No human clinical trials have been reported.

Osteoprotegerin and Denosumab

As described previously, OPG, a soluble receptor belonging to the tumor necrosis factor receptor superfamily, is thought to act as a modulator of osteoclast differentation and function by acting as an inhibitory (or decoy) receptor for the polypeptide RANKL. OPG has been shown to reverse hypercalcemia induced by several factors, including IL-1, tumor necrosis factor-α, PTH, PTHrP, and $1,25(OH)_2D_3$, in a mouse model of HHM.[43,44] No human clinical trials in hypercalcemia of malignancy have been reported, although a phase I study using an Fc-OPG construct showed potent antiresorptive effects (including hypocalcemia) of this agent in patients with bone metastases related to myeloma or breast cancer.[45]

Denosumab is a human monoclonal antibody directed against RANKL. It has been shown to reduce markers of bone resorption in patients with multiple myeloma and breast cancer who had normal corrected calcium levels and bony metastases. Mild reductions in calcium levels were seen with this agent, but they were transient.[46] No human data on hypercalcemia of malignancy have been reported.

Potential advantages of these agents include their subcutaneous route of administration and lack of renal side effects. Concerns have been raised about the potential for the development of inactivating antibodies with prolonged use. It is unclear whether human trials specific to hypercalemia of malignancy will occur with these agents.

Other Therapies

The widespread acceptance of bisphosphonates as first-line therapy for the hypercalcemia of malignancy because of their effectiveness, ease of use, and reasonable safety profile has resulted in a dramatic reduction in the use of alternate therapies.

The antitumoral antibiotic mithramycin (plicamycin) has a direct toxic effect on osteoclasts and is effective at restoring normocalcemia in approximately 80% of treated patients. Despite myelotoxicity and exacerbation of renal dysfunction, it remains a useful agent in cases of resistance to bisphosphonates.

Calcitonin has both calciuretic and antiresorptive actions and thus would seem to be an ideal antihypercalcemic agent. The antiresorptive effects of calcitonin are related directly to osteoclast toxicity and possibly to inhibition of new osteoclast recruitment. When used as a single agent, calcitonin's hypocalcemic effect is modest at best, and resistance to the effects of calcitonin develops rapidly. Calcitonin can be used in combination with more powerful antiresorptive agents. Under these circumstances a rapid and enhanced hypocalcemic effect has been documented. In cases of life-threatening hypercalcemia, or when neurologic symptoms are a major feature, we recommend the use of 8 MRC (Medical Research Council) units/kg given intramuscularly every 6 hours for 1 or 2 days in association with an intravenous bisphosphonate. This regimen has the advantage of combining the rapid calciuretic effect of calcitonin with the powerful, prolonged antiresorptive effect of the bisphosphonate.[47]

As discussed previously, prostaglandins (notably prostaglandin E_2) have potent bone-resorbing effects in relationship to certain tumor types. Thus it was hoped that a significant subset of patients might be found who would respond to prostaglandin synthesis inhibitors such as indomethacin. Although well-characterized case reports have shown a good response to these agents, in general they are ineffective for the treatment of tumor-induced hypercalcemia.

Glucocorticoids are commonly used in the management of tumor-induced hypercalcemia despite significant evidence that their usefulness is limited. The mechanism of any hypocalcemic effect produced by these agents is unclear. In patients with multiple myeloma and lymphoid malignancies, glucocorticosteroids may form part of the antineoplastic regimen, thus reducing production of those factors responsible for the hypercalcemia. Furthermore, because glucocorticosteroids block absorption of calcium from the gut, they can be expected to be useful for patients with vitamin D–mediated hypercalcemia where gastrointestinal absorption of calcium is enhanced.

Hemodialysis using a dialysate bath free of calcium can be used in the emergency treatment of hypercalcemia and would be particularly useful in the setting of renal insufficiency, which would preclude aggressive fluid expansion.

Long-Term Treatment

For patients for whom no antitumor therapy is available, long-term survival is unusual. By implication, there are few good long-term studies on the management of hypercalcemia, and most results are anecdotal. Individualization of therapy is the rule. Patients should be advised to drink an adequate volume of fluid (2 to 3 L daily) and to maintain their mobility as long as possible. They should be reminded of the symptoms of hypercalcemia and urged to report for treatment early should those symptoms arise. Table 48-2 shows suggested maintenance treatments for the hypercalcemia of malignancy. It is noteworthy that the effectiveness of antihypercalcemia therapy with bisphosphonates seems to wane with repeated treatments.[48]

The importance of palliative care cannot be overemphasized in the management of these unfortunate individuals.

A logical therapeutic regimen for the acute management of tumor-induced hypercalcemia is shown in Box 48-1. This regimen represents one approach to this problem. Other equally valid regimens are possible, and individualization of regimens is mandatory for long-term therapy.

Table 48-2 Options for Long-term Management of Hypercalcemia of Malignancy

Agent	Dose	Frequency*
Intravenous zoledronic acid	4 mg over 15 min	Every 2–3 weeks
Intravenous pamidronate[†]	60–90 mg over 2–4 hr	Every 2–3 weeks
Oral pamidronate[‡]	200–1200 mg	Daily
Oral clodronate[§]	3200 mg	Daily
Oral etidronate[¶,‖]	20 mg/kg	Daily
Oral phosphate	2–3 g	Daily
Corticosteroids	Variable	Daily
Multiple myeloma		
Carcinoma of the breast		
NSAIDs	Variable	Daily

NSAIDs, nonsteroidal anti-inflammatory drugs.

*Suggested frequencies and doses may be altered to suit individual patients.

[†]Dodwell DJ, Howell A, Morton AR, et al: Infusion rate and pharmacokinetics of intravenous pamidronate in the treatment of tumour-induced hypercalcemia. Postgrad Med J 1992;68:434–439.

[‡]Thiébaud D, Portmann L, Jaeger PH, et al: Oral versus intravenous AHPrBP (APD) in the treatment of hypercalcemia of malignancy. Bone 1986;7:247–253.

[§]Chapuy MC, Meunier PJ, Alexandre CM, Vignon EP: Effects of disodium dichloromethylene diphosphonate on hypercalcemia produced by bone metastases. J Clin Invest 1980;65:1243–1247.

[¶]Ringenberg QS, Ritch PS: Efficacy of oral administration of disodium etidronate in maintaining normal serum calcium levels in previously hypercalcemic cancer patients. Clin Ther 1987;9:318–325.

[‖]Hasling C, Charles P, Mosekilde L: Etidronate disodium in the management of malignancy-related hypercalcemia. Am J Med 1987;82:51–54.

Box 48-1. MANAGEMENT OF HYPERCALCEMIA OF MALIGNANCY

The most effective way to control the hypercalcemia of malignant disease is by therapy aimed at eradicating or reducing the tumor burden. Chemotherapy, radiation therapy, and surgical therapy all have roles to play. In the absence of effective antitumor therapy, the patient's general condition and immediate prognosis should be used to guide the decision to embark on aggressive antihypercalcemic therapy, active palliation, or both. The introduction of agents with high efficacy and few side effects has broadened the oncologist's options.

Our practice is to discuss treatment options with the patients and their families, emphasizing that the drugs used to control the hypercalcemia have little or no impact on the progression of the underlying cancer but will help the symptoms of the hypercalcemia. Volume expansion with 0.9% saline is begun immediately. The rate is determined by the state of hydration of the individual patient as assessed by the clinician. An infusion of intravenous bisphosphonate (zoledronic acid or pamidronate) is begun at the same time as saline volume expansion. In the presence of severe hypercalcemia and neurologic symptomatology, calcitonin 8 MRC units/kg intramuscularly every 6 hours is used in conjunction with the bisphosphonate.

Biochemical response is rapid. The serum calcium can be expected to fall after 24 hours. Most patients reach a nadir calcium value in 5 to 7 days. We maintain natriuresis by continuing the saline infusion until normocalcemia is reached. Volume overload, as shown by an elevation of the jugular venous pressure, the development of a fourth heart sound, pulmonary congestion, or peripheral edema, is treated with furosemide, which has the added benefit of inducing calciuresis. Care is taken to avoid volume depletion during use of the diuretic. Close attention is paid to renal function and electrolyte balance, because hypokalemia, hypomagnesemia, and hypophosphatemia are common sequelae of this treatment approach. Failure to respond to bisphosphonate therapy is a poor prognostic feature, but alternative antiresorptive therapy can be attempted (gallium nitrate, plicamycin).

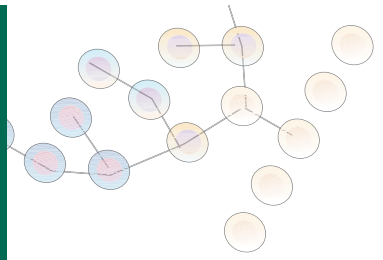
In the absence of effective antitumor therapy, hypercalcemia is almost certain to recur if the patient survives long enough. The duration of normocalcemia is variable, and further antihypercalcemic therapy must be individualized. Patients are advised to maintain a high fluid intake (3 L daily). Corrected calcium concentration is determined weekly. We treat patients again with intravenous bisphosphonate therapy when the corrected serum calcium exceeds 2.7 mmol/L and at regular intervals thereafter. Repeat treatment is performed on an outpatient basis when possible. The dose of bisphosphonate is based on the last dose that reversed the hypercalcemia.

Often the malignant process is at such an advanced stage that death occurs within a few weeks of the development of hypercalcemia. Because of this, we involve palliative care early in the management of hypercalcemic patients.

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49 Hyponatremia

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SUMMARY OF KEY POINTS

Incidence
- Hyponatremia is a common problem in many malignancies.
- It occurs in at least 30% of patients in hospitalized, outpatient hospital, and community-based care settings.
- Hyponatremia is present in 10% to 30% of patients with small cell lung cancer.

Etiology
- Hyponatremia has many causes; primary extrarenal sodium loss associated with several medications, as well as cardiac, renal, and hepatic dysfunction. However, diarrhea, vomiting, and hemorrhage are the most common.
- The syndrome of inappropriate antidiuretic hormone (SIADH) is associated with several malignancies, particularly small cell lung cancer.
- Pseudohyponatremia is associated with hyperglycemia, hyperproteinemia, or hyperlipidemia.
- Water overload at surgery, low-sodium intravenous fluids, or polydipsia are other causes.
- Additional causes include edematous states such as malignant peritonitis, heart failure, hepatic tumor, or cirrhosis.
- Thyroid and adrenal deficiencies can result in hyponatremia.
- Renal sodium loss is mediated by diuretics or natriuretic peptides (with central nervous system tumors or injury), the effect of arginine vasopressin (AVP) on the distal tubules, and the renin-angiotensin-aldosterone system.

Evaluation of the Patient
- Start by assessing plasma osmolality and extracellular fluid (ECF) volume.
- SIADH is a common cause but must be a diagnosis of exclusion.

Grading of the Complication
- Many patients are asymptomatic.
- Sodium concentrations below 125 mEq/L and those developing rapidly are most likely to be symptomatic.
- Symptomatic hyponatremia is a medical emergency.

Treatment
- Isotonic saline (0.9%) is an appropriate fluid for most patients.
- Correction of sodium should occur slowly and at a rate that approximates its development; 10 to 12 mEq/L over the first 24 hr is considered safe.
- Overly rapid correction is associated with severe neurologic morbidity.
- Hypertonic saline is appropriate only in symptomatic patients with very low sodium concentrations; discontinue once serum sodium becomes 120 to 125 mEq/L.
- Water restriction is the primary approach to SIADH.

INTRODUCTION

Hyponatremia is among the most common electrolyte disturbances faced in clinical medicine. Recent reports show 30% to 43% of a group of hospitalized, ambulatory hospital, and community-based care patients had hyponatremia (serum sodium below 136 mEq/L), and an additional 3% to 6% had concentrations of 126 mEq/L or less.[1,2] This is particularly sobering in light of the substantial morbidity and mortality that can be associated with hyponatremia. Current studies suggest that the mortality associated with hyponatremia in hospitalized patients is as high as 27%, in comparison with 9% in other patients.[3] Even relatively mild and presumably "asymptomatic" hyponatremia (128 ± 3 mEq/L) is associated with attention deficits and a high incidence of accidental falls and injury.[4] Among patients with cancer, clinical experience suggests that the overall incidence of hyponatremia is perhaps even higher than in other populations. This is because many tumors predispose to the development of hyponatremia (i.e., small cell lung cancer with an incidence as high as 30%) as well as the influences of polypharmaceutical treatments, and chronically ill, debilitated patients.[5]

Sodium (Na^+) is the dominant ion of the extracellular fluid (ECF) and thus the prime contributor to osmolality. Sodium and water balance are tightly linked, and disturbances of one are also generally reflected in the other. This balance is the result of many homeostatic feedback loops that revolve around protection of intravascular volume. Components of this integrated homeostatic system include the hypothalamic osmoreceptors; the adrenals (via the renin-angiotensin-aldosterone cascade); the cardiac, glomerular, and carotid baroreceptors; and changes in renal tubular permeability to water and sodium in response to antidiuretic hormone (ADH, or arginine vasopressin), and natriuretic peptides released from the heart and brain. Thus, there are many paths to hyponatremia.

Definitions

Hyponatremia and hypernatremia are conditions of altered tonicity. To put the physiology of the problem into perspective, it is important to understand the difference between osmolality and tonicity. Osmolality is the concentration of all particles in a fluid. Particles are either "effective" or "ineffective" osmoles. Ineffective osmoles are solutes

that can cross the cell membrane freely and distribute equally in the intracellular fluid (ICF) and ECF yet produce no net movement of water. Examples of physiologically ineffective osmoles include urea and ethanol; their addition to the ECF produces no change in osmolality, because they equilibrate rapidly with the ICF.

Solutes that do not cross the membrane freely or that are kept predominantly to one side by a transporter are referred to as effective osmoles. Only effective osmoles contribute to tonicity. In the physiologic setting, sodium is the major effective osmolar solute. It is relatively restricted to the ECF and is thus the major determinant of ECF tonicity. Other examples of physiologically effective osmoles are glucose and mannitol, two large molecules that are also relatively restricted to the ECF. Potassium and a host of organic compounds that are dominantly restricted to the intracellular milieu are the major osmolar solutes of the ICF and the major determinants of ICF tonicity. Despite the differences in tonicity of these compartments, the osmolality of the ECF and ICF are quite similar as a result of water movement. Even so, the distribution of water in these two spaces is not at all similar; 60% to 75% of total body water resides within the ICF and the remainder in the ECF. Within the ECF, approximately 65% is apportioned to plasma, and the rest is interstitial fluid between cells.

OSMOLAR HOMEOSTASIS: CONTROL OF WATER AND SODIUM

From the perspective of sodium, the job of the osmoregulatory system is to prevent either hyper- or hyponatremia and the secondary movement of water that can change cell volume and disrupt function. Under normal circumstances, plasma osmolality is kept within a relatively constant osmolar range of 275 to 290 mOsmol/kg. The maintenance of this narrow range is primarily the result of ADH, thirst, and renal function.

ADH provides the most sensitive control mechanism. Changes in serum osmolality of as little as 1% to 2% can be sensed by the hypothalamic osmoreceptors and can trigger ADH secretion from the posterior pituitary.[6] At the renal level, ADH acts on receptors in the collecting ducts to initiate a passive reabsorption of water. The threshold for ADH release occurs at a plasma osmolality of 280 to 290 mOsmol/kg; below 280 mOsmol/kg, the secretion of ADH is suppressed.[4,5] Although there is a roughly linear rise in ADH with increases in osmolality, a plateau in its effect occurs at an osmolality of 295 mOsmol/kg or greater. Thus, there is a limit to the ability of ADH to reduce hypertonicity.

Another group of osmoreceptors located in the anterior hypothalamus stimulate thirst; this group is recruited at or near the serum osmolality where ADH begins to show its plateau in effect. Thirst can also be recruited by changes in plasma volume sensed by carotid and cardiac baroreceptors.

Carotid baroreceptors responding to a decrease in effective blood volume can also stimulate ADH release. The sensitivity of this system is significantly less than that of the hypothalamic osmoreceptors, and a change in vascular volume of 8% to 10% or more is required to initiate this nonosmotic stimulus for ADH release. In situations characterized by decreased effective circulating volume or arterial vasodilation (e.g., in anthracycline-induced congestive heart failure, sepsis, or third-space fluid accumulations from malignant ascites or hepatic cirrhosis), nonosmotic baroreceptor-mediated stimulation of ADH can override the osmotic suppression of ADH release that would otherwise be expected as a result of the expanded hypotonic ECF space.[6] The net result can be a spiraling decrease in sodium as more water is retained, and effective volume continues to decline even further.

Although most osmoregulation is affected by water as described previously, sodium also has an active regulatory mechanism. Reabsorption of sodium in the renal tubule is the dominant mechanism of regulation; under normal conditions, about 70% of filtered sodium is reabsorbed. Active excretion of sodium also occurs and is mediated through the actions of a group of related natriuretic peptides that inhibit sodium reabsorption.[7,8] The best described of these, atrial and brain-derived natriuretic peptides, are released from cells in the atrial chambers in response to central volume overload or from the brain as a result of injury. Although there remains much to be learned about the complex physiologic effects of these peptides, their actions in medullary collecting tubules and their inhibitory effect on the renin-angiotensin-aldosterone system result in a sodium diuresis.

Cellular Adaptations to Hyponatremia

In response to hypotonic conditions, water moves from the ECF into the ICF causing an expansion of cell volume that, if unopposed, would eventually lead to cell lysis. Normally, the Na^+,K^+ ATPase pump in the cell membrane maintains cell volume by pumping out the small amounts of sodium that "leak" into cells in exchange for potassium. In the setting of acute hypotonicity, additional mechanisms must come into play; cells adjust initially by losing sodium, potassium, and chloride across stretch-activated membrane channels. However, this process reaches its limit within several hours. In the setting of more slowly developing or chronic hypotonic states, loss of intracellular organic molecules is part of the compensation process.[9,10] In the reverse setting of hypertonicity, adaptations include new synthesis and an increased concentration of these organic osmoles. Because this change requires several days to be complete, these adaptations are not effective in acute events.

The brain is particularly sensitive to changes in tonicity. Hypotonic stresses that lead to cell swelling are tolerated poorly in the central nervous system (CNS) because of the constraints that the skull places on increased volume. The most feared change is increased intracranial pressure; coma and death can occur with as little as a 10% increase in brain volume. Another debilitating and potentially lethal complication is the osmotic demyelination syndrome. This is an uncommon but devastating result of an overly rapid correction of hyponatremia, which leads to demyelination in the pons and extrapontine white matter.[11,12] Thus, both the initiating process and the interventions for hyponatremia can be associated with significant morbidity and mortality.

HYPONATREMIC STATES

Hyponatremia is defined as a serum sodium less than 135 mEq/L. Although hyponatremia is seen most frequently in association with a low plasma osmolality (hypotonic hyponatremia), it also can occur in settings of high or low osmolality. Similarly, hyponatremia can also be associated with normal, increased, or decreased ECF. Identification of the probable etiology and proper approach to hyponatremia begins with evaluating plasma osmolality and ECF volume (Fig. 49-1). In the sections that follow, hyponatremia is characterized and and addressed by these parameters. A graphic representation of many hyponatremic states is shown in Figure 49-2.

Pseudohyponatremia

There are two situations in which sodium can be fictitiously low as a result of the presence of substances that alter the volume of plasma water in which sodium is measured.

Pseudohyponatremia is common in the setting of hyperglycemia or the use of some other restricted solute that causes high plasma osmolality. These situations cause a shift of water from the ICF to the ECF, resulting in sodium dilution. As a general rule, each 100 mg/dL increase in glucose reduces serum sodium by 1.6 mEq/L. The presence of some other nonglucose, active substance (e.g., mannitol) is identified by finding a 10-point or greater difference in the measured vs. the calculated osmoloality (Box 49-1). This "osmolar gap" can also be increased in azotemia and in ethanol and methanol intoxications. Although the plasma osmolality is increased by the

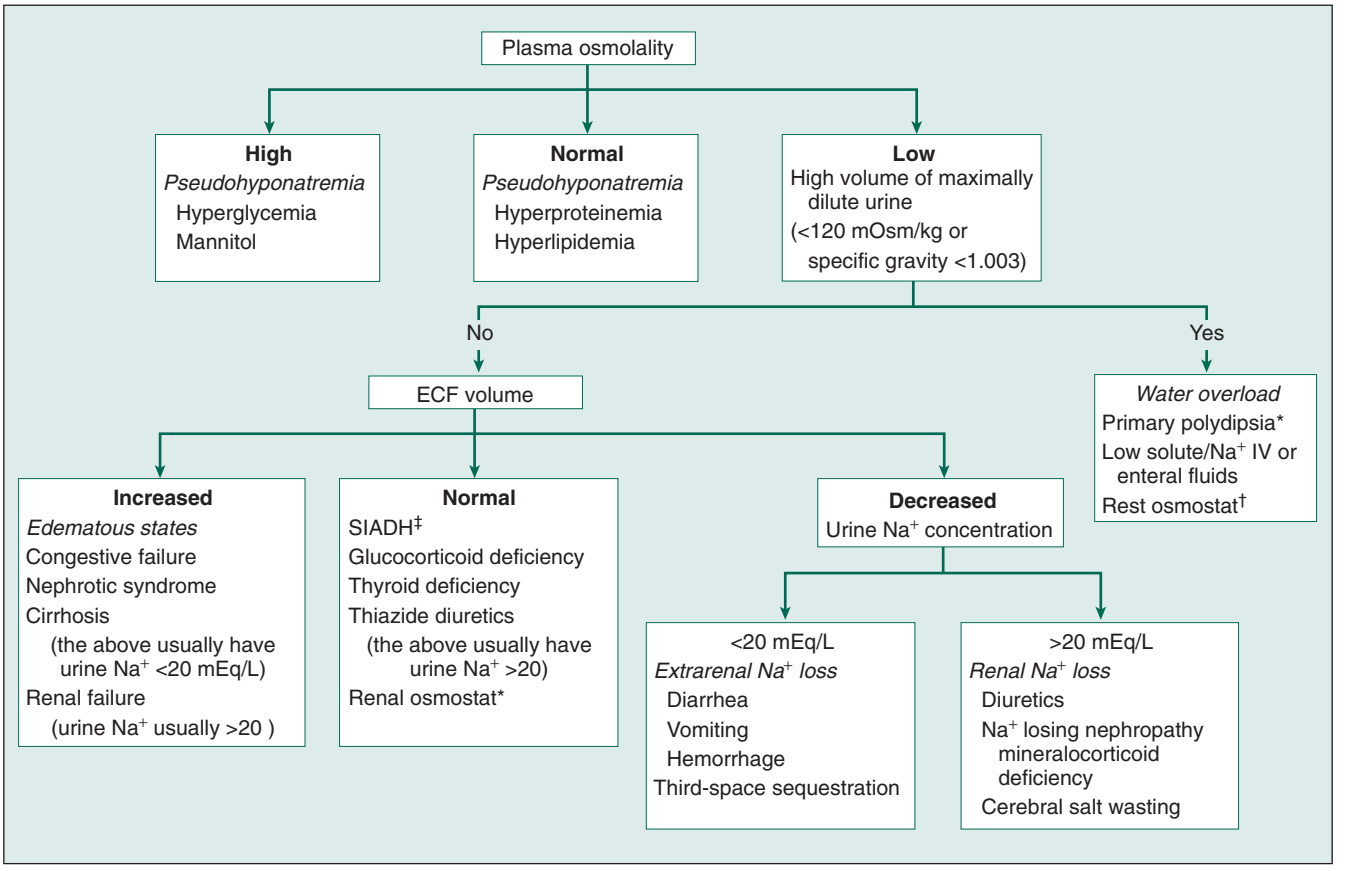


Figure 49-1 • A clinical algorithm for determining causes of hyponatremia using plasma osmolality and extracellular fluid volume. *May be accompanied by increased AVP in some patients. †Rest osmostat usually associated with low plasma osmolality and normal ECF volume. ‡See Table 49-1 for associated etiologies.

addition of these ineffective osmolar substances, there is no shift in water; the true sodium is normal.

Pseudohyponatremia also can occur as a result of an increase in relatively high-molecular-weight substances, such as occurs with Bence-Jones proteins in multiple myeloma or in hyperlipidemia. In these situations, plasma osmolality is normal, but the volume of plasma in which sodium is measured is expanded as a result of compensatory water shifts into the ECF. Thus, if sodium is normalized to the volume of sampled plasma, it will be reported as artificially low. However if sodium is measured using an ion-selective electrode that measures sodium only in the aqueous phase of plasma, its concentration will be reported as normal. Thus, it is important to know how a given laboratory determines sodium concentration.

Patients with pseudohyponatremia are not at risk for complications of low sodium and do not require sodium correction. Their true plasma sodium is normal.

Hypotonic Hyponatremia

Hyponatremia in the setting of hypotonic plasma (hypotonic hyponatremia) is the most common type of low serum sodium and represents a process in which there is an excess of water in relation to sodium.[13,14] Several potential causes of this problem are outlined in the ensuing discussion and summarized in Table 49-1. Most such situations are also characterized by the relative inability to excrete water. Although many patients might be "asymptomatic," even mild hyponatremia is now known to be associated with increased morbidity.[2] Perhaps the most dangerous situation is when hyponatremia develops fairly rapidly (within 48 hours) and in which rapid changes in osmolality may lead to serious and potentially deadly neurologic sequelae.

Hypovolemia

Hyponatremia developing in the setting of either decreased ECF or hypovolemia is a result of both sodium loss and water loss. As adaptations to volume loss occur, however, a relative excess of water over sodium develops.

The most common causes of decreased ECF are a result of extrarenal fluid losses such as diarrhea, vomiting, or third-space sequestrations of body fluid, as in malignant peritonitis. The net effect of these problems is the stimulation of ADH secretion and thirst in an effort to enhance water retention and restore ECF volume. The decreased circulating volume, renal hypoperfusion, and ADH-mediated water retention combine to limit renal water excretion and produce dilutional hyponatremia. The hyponatremia could be made worse by the concomitant depletion of potassium in severe diarrhea or vomiting and by the secondary migration of sodium into cells to compensate. Because the major pathology in these situations is nonrenal, these patients should have a low urine sodium excretion. As a rule of thumb, a urine sodium of less than 20 mEq/L suggests renal sodium conservation. The management of these patients is primarily saline volume expansion. Potassium may be added as necessary.

Hyponatremia associated with the use of thiazide diuretics is a result of sodium, potassium, and volume depletion. Secondary water retention can occur as a result of ADH response to volume loss. Urine sodium is characteristically elevated (>20 mEq/L) in these patients, reflecting increased renal sodium loss. This form of hyponatremia is characterized by hypovolemia or euvolemia with little decrease in effective plasma volume. In contrast, the loop diuretics (e.g., furosemide) rarely cause significant hyponatremia, because they inhibit

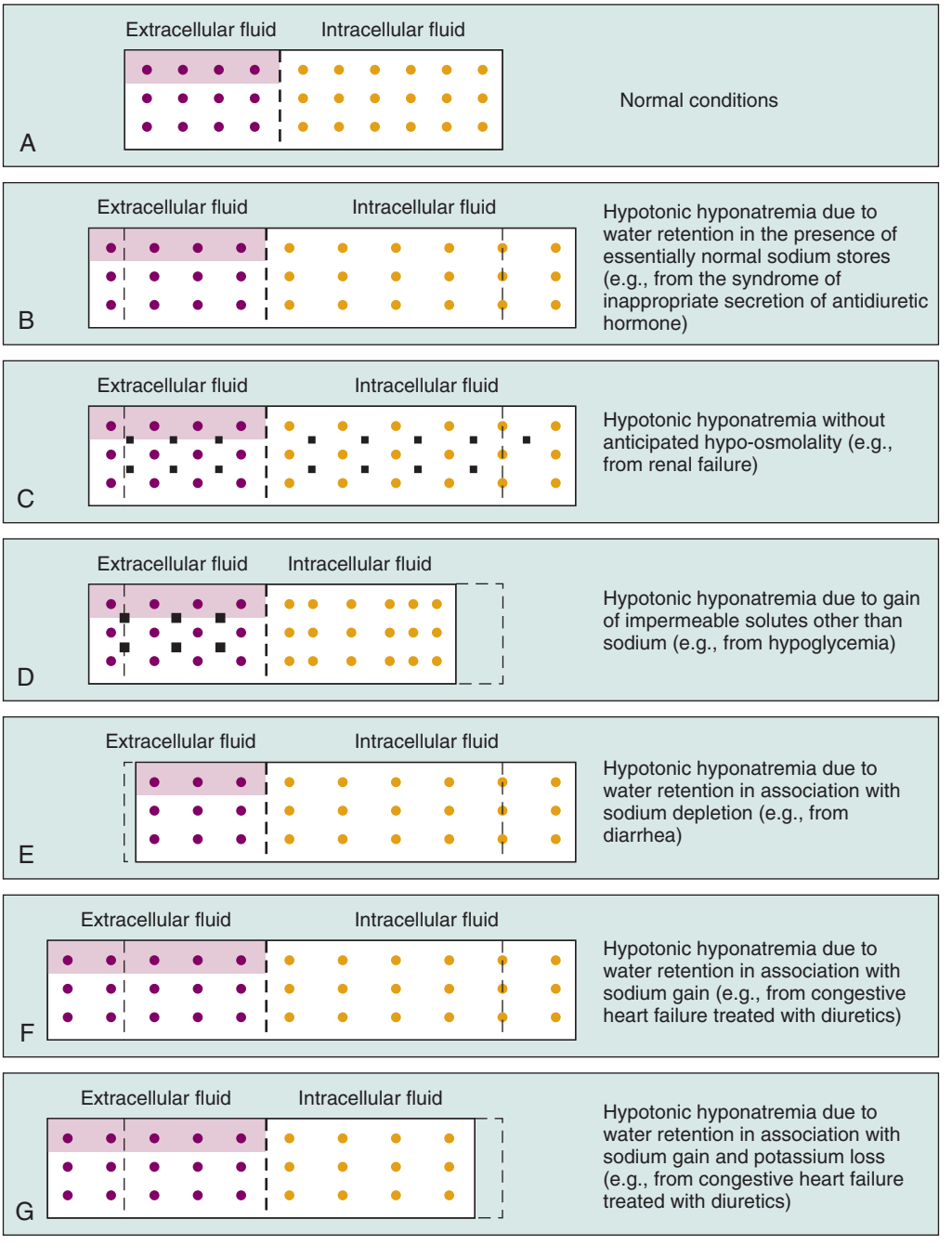


Figure 49-2 • Extracellular and intracellular fluid (ECF, ICF) compartments under normal conditions and during states of hyponatremia. **A,** Normally the ECF and ICF make up 40% and 60% of total body water, respectively. **B,** With the syndrome of inappropriate secretion of antidiuretic hormone, the volumes of ECF and ICF expand (although a small element of sodium and potassium loss, not shown, occurs during inception of the syndrome). **C,** Water retention can lead to hypotonic hyponatremia with the anticipated hypo-osmolality in patients who have accumulated ineffective osmoles, such as urea. **D,** A shift of water from the ICF compartment to the ECF compartment, driven by solutes confined in the ECF, results in hypertonic (translocation) hyponatremia. **E,** Sodium depletion (and secondary water retention) usually contracts the volume of ECF but expands the ICF compartment. At times, water retention can be sufficient to restore the volume of ECF to normal or even above normal levels. **F,** Hypotonic hyponatremia in sodium-retentive states involves expansion of both compartments but predominantly the ECF compartment. **G,** Gain of sodium and loss of potassium in association with a defect of water excretion, as they occur in congestive heart failure treated with diuretics, lead to expansion of the ECF compartment but contraction of the ICF compartment. In each panel: *red circles,* sodium; *yellow circles,* potassium; *large squares,* impermeable solutes other than sodium; *small squares,* permeable solutes; *broken line,* cell membrane; *shading,* intravascular volume.

Box 49-1. CALCULATED PLASMA OSMOLALITY (mOsm/kg)

$$2 \times ([Na] + [K] + BUN/2.8 + glucose/18$$

Note that measured osmolality is generally 10 mOsm/kg higher than calculated osmolality because of the effect of minor solutes such as magnesium, calcium, protein, phosphates, and amino acids. Normal osmolality is 287 ± 4, with a normal range extending from 280 to 290 mOsm/kg.

sodium reuptake and reduce renal interstitial tonicity, which, in turn, limits passive water reabsorption. The management of these patients involves cessation of diuretic medication and volume expansion with saline.

Another cause of hypotonic hyponatremia is salt wasting associated with renal dysfunction.[13,14] This can occur as a result of obstructive uropathy from abdominal and retroperitoneal tumors, loss of renal structure as in polycystic disease, or tubular damage associated with interstitial nephritis. The latter can occur as a result of several chemotherapeutic agents (especially cisplatin, aminoglycosides, or amphotericin) or infection, all of which can limit sodium reabsorption and diminish free-water excretion. As expected, urine sodium is high (>20 mEq/L) in these situations. The management of these situations relies on addressing the underlying problem and on replacing volume with saline.

Table 49-1 Causes of Hypotonic Hyponatremia

ASSOCIATED WITH HYPOVOLEMIA

Extrarenal sodium loss

Diarrhea, vomiting, hemorrhage, fluid sequestration (third space), excessive sweating

Renal sodium loss

Diuretics, *osmotic diuresis (use of mannitol with cisplatin over multiple days)*

Renal tubular acidosis

Salt-losing nephropathy

Interstitial nephritis, urinary tract obstruction, Bartter's syndrome

Hormonal

Adrenal insufficiency (mineralocorticoid deficiency; most common as a late effect of cranial irradiation)

Cerebral salt wasting syndrome

Edematous states

Congestive heart failure, nephrotic syndrome, *malignant ascites,* cirrhosis, renal failure

ASSOCIATED WITH EUVOLEMIA

Distal tubule diuretics

Loop diuretics (furosemide, ethacrynic acid)

Hypothyroidism (early effect of cranial and/or craniospinal irradiation)
adrenal insufficiency (glucocorticoid deficiency; most commonly a late effect of cranial irradiation)

SIADH

Cancer

Small cell carcinoma of lung, Hodgkins disease, leukemia, lymphoma, adenocarcinoma of pancreas and duodenum, breast, and many others

CNS lesions

Tumor, stroke, subarachnoid bleed, hemorrhage, infection

Selected drugs

Opiates, phenothiazines, vincristine, cyclophosphamide, ifosfamide, cisplatin, carbamazipine, tricyclics, NSAIDs, selective serotonin reuptake inhibitors, desmopressin, nicotine, chlorpropamide

Increased intrathoracic pressure

Mediastinal tumor, positive pressure ventilation, pneumonia

Reset osmostat*

Trauma, *pain, and stress (postoperative state)*

AIDS

ASSOCIATED WITH HYPERVOLEMIA

Primary polydipsia†

Excessive dilute or sodium-free irrigants during surgery

Tap water enemas

AIDS, acquired immunodeficiency syndrome; AVP, arginine vasopressin; CNS, central nervous system; NSAIDs, nonsteroidal anti-inflammatory drugs; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Common cancer-associated causes are *italicized.*

*Normal volume accompanied by low plasma osmolality.

†May also be accompanied by decreased water excretion as a result of AVP stimulation.

Hypervolemia

In the disease states listed in this discussion, hyponatremia develops even though total body sodium is generally increased. This is a result of physiologic adaptations to disease that cause an even larger increase in total body water (particularly in the ECF), thus driving sodium down.

Congestive heart failure, ascites associated with malignant peritonitis or cirrhosis, and nephrotic syndrome are edematous states with increased ECF. Despite the edema, however, these diseases are usually associated with decreased effective circulating volume. In these situations, atrial and carotid baroreceptors stimulate ADH release and volume expansion as a compensatory (but physiologically inappropriate) event.[6,13] The management of these situations is centered on improving effective circulating volume by addressing the underlying problem and restricting both sodium and water.

Hypotonic hyponatremia occurring in the setting of volume expansion can also develop in patients with renal failure.[13,14] Accumulation of ineffective osmols (e.g., urea) leads to increased osmolality in both the ICF and ECF, with consequent water retention and an increase in the volume of both compartments. Thus, a dilutional hyponatremia occurs in the setting of increased ECF. As with the edematous states described previously, management is centered on treatment of the primary disease (dialysis) and on restriction of both sodium and water.

Hyponatremic states that are a result of excessive water intake, such as psychogenic polydipsia or low-sodium intravenous or enteral fluids, are examples of hypotonic hyponatremia in the setting of increased ECF.[13,14] Although renal water excretion is usually normal in these patients, the volume of water intake overwhelms the normal ability of the kidney to excrete the maximum of 26 L/1.73 m^2 per day of free water. A moderate to significantly increased ECF usually accompanies these problems. Characteristic of these states is the excretion of large volumes of maximally dilute urine, indicating intact renal function. Depending on how rapidly the problem has evolved, the degree of hyponatremia, and the presence of symptoms, treatment is aimed at net water loss or sodium replacement.

Isovolemia

Patients who develop hyponatremia in the setting of normal or near-normal ECF volume generally have a modest increase in water relative to sodium. This condition generally signals the syndrome of inappropriate antidiuretic hormone secretion (SIADH).[6,15] It is noteworthy, however, that increased ADH by itself is generally insufficient to cause significant hyponatremia; water intake is necessary for the dilutional effect to occur. Although SIADH is often classified as an isovolemic hyponatremia because of the lack of edema and overt signs of volume expansion, most patients have expansion of their ECF, diminished urine output and weight gain. Despite the hyponatremia, an atrial natriuretic peptide-mediated natriuresis can occur in response to the volume expansion. This, and the diminished sodium reabsorption associated with volume expansion, further decrease plasma sodium and limit the formation of edema. Eventually, a new equilibrium between sodium intake and excretion occurs, such that intake and output are matched. Thus, attempts to correct SIADH with the addition of sodium alone are rarely successful; water restriction remains the primary method of management in asymptomatic patients. SIADH is a diagnosis of exclusion. To make the diagnosis, the following criteria should be met:

- Other causes of hyponatremic hyponatremia, particularly hormone deficiencies (e.g., thyroid and adrenal) and a reset osmostat are absent (see related topics covered later in this chapter).
- The patient should be clinically isovolemic or only mildly hypervolemic. The presence of edema or clinical volume overload is not compatible with SIADH.

- The plasma osmolality should be 280 mOsm/kg or less. Higher osmolality does not support the "inappropriate" nature of ADH secretion.
- Urine osmolality must be greater than plasma (≥500 mOsm) and urine sodium must be in excess of 20 to 30 mEq/L; concentrations of 40 mEq/L or greater are not uncommon.

SIADH is associated with a wide variety of clinical settings (see Table 49-1). The most common cause in clinical oncology is the ectopic production of ADH by tumor. Although small cell anaplastic carcinoma of the lung is the most frequent cause, several other neoplasms also can be associated with the problem (see Table 49-1).[1,2] Even though serum ADH is increased in as many as 40% of patients with small cell lung carcinoma, the clinical manifestations may occur in only 10% of such patients. The latter have latent SIADH, which might become evident only in the setting of water loading. It should be noted that ectopic ADH secretion is not steady, nor is it usually at a level that approaches the maximal release by the hypothalamus. Thus, an episode of volume depletion still can produce a nonosmotic ADH release.

Several pharmaceutical products, including several antineoplastic compounds, are also associated with SIADH. Most notable among these is vincristine, which has been associated with acute and severe SIADH. The problem generally develops 2 to 3 days after vincristine administration, is associated with increased ADH levels, and can persist for days to weeks. High-dose (2 g/m^2) cyclophosphamide is also capable of inducing hyponatremia through direct renal tubular effects and possible enhancement of ADH activity.[13] In contrast to hyponatremia due to vincristine, the hyponatremia associated with cyclophosphamide occurs within several hours of administration, and is not associated with ADH secretion. Curiously, we have not identified SIADH associated with the use of ifosfamide, which is structurally similar to cyclophosphamide. Ifosfamide has, however, been associated with significant renal toxicity and a Fanconi-like tubulopathy characterized by the wasting of multiple electrolytes, glucose, and protein. The platinating agents, cisplatin and (less commonly) carboplatin, have also been associated with hyponatremia, although the mechanisms of these agents are probably related in part to direct renal toxicity and not to SIADH. Several other drugs listed in Table 49-1 also can cause SIADH.

The management of SIADH depends on how rapidly the problem has evolved and the degree of hyponatremia; it must include treatment aimed at the underlying disease process. In the asymptomatic patient with SIADH who has a serum sodium greater than 125 mEq/L, water restriction is the primary mode of management. The use of furosemide is appropriate for patients who do not respond well to fluid restriction alone. In the symptomatic patient, partial correction with 3% hypertonic saline and furosemide is indicated (see ensuing discussion).[13,16] Even in these cases, however, treatment must eventually rely on water restriction.

Cerebral salt wasting (CSW) is a cause of hyponatremia associated with intracranial disease or injury.[7,17] It is important to differentiate this process from SIADH, which it can closely resemble and for which it is often mistaken. The approaches to treatment for CSW and SIADH are quite different from one another. CSW is mediated by not yet fully defined physiologic circumstances and is characteristically associated with volume depletion rather than the isovolemic or modestly expanded state of SIADH. At a basic level, primary CNS tumors, subarachnoid hemorrhage, and increased intracranial pressure all seem to be associated with the release of natriuretic peptides from brain, cardiac foci, or both, causing a sodium diuresis and ECF volume loss. Water restriction, the typical approach to SIADH, is contraindicated in CSW, which requires both volume and sodium replacement.

Reset Osmostat

Resetting of the hypothalamic osmostat is generally associated with chronic hyponatremia and has been seen in a variety of malignancies as well as in cachexia, malnutrition, and pregnancy.[6,18] Another common setting is in patients with hypothalamic tumors or hypothalamic injury from trauma or surgery. The mechanism seems to be one in which the set point for ADH release is adjusted downward. Such individuals might have stable plasma sodium concentrations in the range of 125 to 135 mEq/L and are generally asymptomatic. Treatment is unnecessary and even if attempted is generally unsuccessful, because thirst and ADH maintain sodium at the new set point. In isolation, this is a relatively benign problem unassociated with neurologic sequelae. In association with other central water and sodium problems, however (e.g., diabetes insipidus or loss of thirst that could accompany hypothalamic/pituitary tumor or injury), a reset osmostat can become a challenge.

HYPONATREMIA IN ASSOCIATION WITH HORMONE DEFICIENCIES

Hyponatremia also can occur in the setting of a number of primary or secondary hormone deficiencies, such as hypothroidism or hypocortisolism.[7,8,16] Although these are generally associated with a euvolemic state, hypervolemia may occur also. It is important to keep the hyponatremia associated with these deficiencies in mind, because they can be slow to evolve after organ injury and can easily be mistaken for SIADH.

Although the mechanism of hyponatremia in hypothyroidism is not fully understood, the relatively low cardiac output, a decrease in renal perfusion, impaired water excretion, and ADH secretion all seem to be involved. Patients with milder forms of hypothroidism might be euvolemic and have only modestly decreased sodium. Settings commonly associated with hypothyroidism occur in those patients who have received head and neck or craniospinal irradiation. It can take 1 to 2 years for clinically evident hypothyroidism to develop after such events. The treatment of this problem relies largely on thyroid replacement. In patients with advanced disease, temporary sodium, with or without water restriction, may also be helpful.

In the setting of adrenal insufficiency, hyponatremia can be a result of mineralocorticoid deficiency, glucocorticoid deficiency, or both. The mechanisms of hyponatremia in these two settings are entirely independent of each other. Primary and metastatic tumors to the adrenal can reduce both hormones. Isolated glucocorticoid deficiency can occur as a result of hypothalamic or pituitary tumors, surgery, or CNS radiation therapy. Of note, central adrenocorticotropic hormone regulation is relatively radioresistant and generally requires doses exceeding 50 Gy and typically has a 3- to 5-year latency before becoming evident. Glucocorticoid deficiency is generally characterized by hyponatremia in the setting of normal or modestly expanded ECF. Cortisol is necessary for maximum urinary dilution and free water excretion, thus a deficiency results in water retention from increased permeability in the renal collecting tubules. This action seems to be independent of ADH, in that patients with panhypopituitarism who are given cortisol replacement soon exhibit diabetes insipidus. In the setting of an otherwise intact hypothalamic/pituitary axis, cortisol deficiency is also associated with some increase in ADH secretion. Thus, management might require not only cortisol replacement but also desmopressin acetate to control the diabetes insipidus that cortisol has "unmasked."

In mineralocorticoid deficiency the renin-angiotensin system is compromised, and there is generally a contraction of effective circulating volume because of diminished capacity by the kidney to reabsorb sodium. In response to diminished volume, baroreceptor-mediated ADH release and water retention can drive sodium lower.

SYMPTOMS AND MANAGEMENT OF HYPONATREMIA

Most patients with hyponatremia are relatively asymptomatic, and treatment can be aimed at the underlying disease. Symptomatic hyponatremia should be considered a medical emergency. In the

absence of infections and issues related to tumors, congestive failure, and the other edematous states, the symptoms associated with hyponatremia depend on the depth of the sodium concentration and the rapidity of its onset. When hyponatremia develops within a matter of several hours as a result of an acute hypotonic volume load, neurologic findings related to evolving cerebral edema dominate. Those patients in whom hyponatremia develops over an extended period (≥48 hr) might have only mild lethargy, muscular symptoms, and anorexia even though their serum sodium might be the same or even lower than that of patients who develop the problem acutely.

Mild symptoms characterized by vomiting, malaise, and even agitation are usually seen in patients with sodium concentrations above 125 mEq/L. As sodium falls further, muscle cramps and weakness, as well as neurologic symptoms including lethargy, headache, and confusion can occur. Sodium levels below 120 mEq/L are associated with seizures and coma.

In all but the unequivocal acute volume overload state and patients with neurologic signs, it is wise to assume that hyponatremia is a chronic process that has developed over several days. The rationale for this assumption is that chronic hyponatremia must be corrected slowly. Too rapid a correction is associated with severe, life-threatening CNS complications from osmotic demyelination syndrome.

Osmotic demyelination is related to an overly aggressive sodium correction. Rapid but relatively modest degrees of sodium correction can cause ECF to appear hypertonic to the cell (even though sodium is still low). Thus, correction should be limited to no more than 12 mEq/L in 24 hr and 18 to 24 mEq/L in 48 hr.[5,12,19] It should be noted that there is typically a delay of 2 to 4 days (and sometimes as long as 6 days) before the signs of brain injury and demyelination occur. Thus, it is possible to see patients improve initially but have a subsequent neurologic decline some days after the start of correction. Patients with acute hyponatremia have significantly less risk of developing this problem than do those with chronic hyponatremia.[16]

Treatment of Asymptomatic Hyponatremia

Hypovolemic hyponatremia is generally associated with the symptoms of volume depletion, and these patients are not at risk for the neurologic complications related to cerebral edema that accompany acute hyponatremia. They might, however, be subject to osmotic demyelinating syndrome associated with rapid sodium correction. The management of patients with mild hypovolemic hyponatremia from chronic renal sodium loss or overuse of diuretics is best performed by giving isotonic (0.9%) saline or, if tolerated, oral salt tablets. A rate of correction aimed at no more than 12 mEq/L per day over a period of 2 to 3 days is generally sufficient.

In the isovolemic hyponatremias that commonly result from SIADH, treating the underlying disease, stopping any potentially offending drugs, and water restriction are the methods of choice. Rigorous restriction of free water to as little as 30% to 70% of maintenance needs might be necessary and could take 2 to 3 days to become effective. The often attempted use of isotonic saline at a lower than maintenance rate is a doomed strategy, because an isotonic load is excreted quickly with little or no net change in serum sodium. In patients who do not tolerate or who are noncompliant with water restriction or in whom furosemide is contraindicated or ineffective, democycline may be used to induce a nephrogenic diabetes insipidus-like state with increased free-water excretion. Lithium carbonate can produce the same result but is generally not well tolerated.

In relatively asymptomatic hypervolemic hyponatremic patients, modest fluid restriction, sodium restriction, and the use of a loop diuretic to promote renal free-water excretion are appropriate measures. These measures will be ineffective, however, without management aimed at the underlying edematous disease state.

Box 49-2. SODIUM DEFICIT

[Desired Na – measured Na] × 0.6 body weight (kg) = mEq of Na^+ needed.*

*Use 0.5 in elderly and frail.

Treatment of Acute Symptomatic Hyponatremia

Acute hyponatremia—most frequently the result of volume overload with hypotonic fluids—generally manifests by the presence of some neurologic findings as a result of evolving cerebral edema. These patients generally have a serum sodium below 120 mEq/L and are generally hospitalized individuals with iatrogenic hyponatremia (Box 49-2). Common characteristics include: menstruating women (who are more susceptible than males), excessive hypotonic intravenous fluids, recent use of diuretics, particularly thiazides, or seratonin reuptake inhibitors, which can lead to SIADH. Another group are patients who have undergone transurethral prostatectomy with excessive absorption of hypotonic fluids across the organ bed, and those with colonoscopic preparation–induced losses.[12] The goal of treatment for these patients should be to raise the serum sodium sufficiently to stop any seizure activity and to correct cerebral edema; changes in serum sodium of as little as 5% can diminish cerebral edema, and increases of as little as 3 to 6 mEq/L can stop most seizures.[13] With this in mind, a rate of correction of about 1 to 1.5 mEq/hr during the first 4 to 6 hr is often sufficient to manage the acute neurologic problems. Anticonvulsants might be necessary for those with seizures. This initial correction might use 3% hypertonic saline (Box 49-3). Acute, symptomatic hyponatremia is the only condition in which the use of a hypertonic saline solution is unequivocally an appropriate intervention. Although patients with acute hyponatremia have a lower risk of osmotic demyelination than those who develop low sodium on a more chronic basis (>48 hr), the use of hypertonic saline should be limited to achieving an initial increase of 3 to 6 mEq/L or a serum sodium of 120 to 125 mEq/L. After the initial period of correction, the rate of sodium rise should be limited to 0.5 mEq/L using 0.9% (isotonic) saline. Correction rates of 10 to 12 mEq/L during the first 24-hr period and 18 mEq/L over the first 48 hr are safe.[5,12,19]

The addition of furosemide during the initial correction period has been advocated as a method of encouraging free-water excretion by the kidney. Furosemide diminishes interstitial renal medullary tonicity, impairs urinary concentrating ability, and leads to a hypotonic urine with a concentration of about 0.45% saline (75 mEq/L). Although this often seems to be helpful, it should probably be limited to a single dose, thus minimizing too rapid a correction. Furosemide is particularly useful in a frail patient with diminished cardiac reserve, in whom the use of hypertonic saline could incite congestive failure.

Management of Chronic Hyponatremia and SIADH

The management of these patients relies on treating the underlying disease. Examples include the treatment of malignancies, hormone replacement, removal of drugs associated with SIADH, providing adequate sodium (and water) needs for patients receiving enteral feeding, and compensating for disordered thirst. Preventive measures, such as the preference for the use of isotonic saline in "at risk" patients

Box 49-3. SODIUM CONTENT OF COMMON INTRAVENOUS SOLUTIONS

Solution	Na^+ (mEq/L)	Na^+ (mEq/mL)
3% saline	513	0.513
0.9% saline	154	0.154
Ringer's lactate	130	0.130

(malignancy, chemotherapy, positive pressure ventilation, and other states noted in Table 49-1) who require hydration, are equally important. It is important to remember that correction of chronic hyponatremia must be executed slowly to avoid the potential of osmotic demyelination. Asymptomatic patients who have slowly developed sodium concentrations as low as 105 to 110 mEq/L have been corrected successfully using an initial rate of 0.5 mEq/L/hr or less to bring them to serum levels of 120 mEq/L. After this, the rate of correction may be liberalized, keeping in mind the risk factors for demyelination noted earlier. Although it is permissible to initiate treatment with 3% saline solutions in these severely hyponatremic patients, the need to do so and the potential risks of too rapid a correction in a relatively asymptomatic patient suggest isotonic saline as a safer alternative. For unstable patients and those with neurologic symptoms, the approach to treatment should be similar to that noted earlier for acute symptomatic hyponatremia, but at a slower pace; a planned initial rise in sodium of 4 to 6 mEq/L over 12 hr, followed by a more gradual correction at a rate not to exceed 12 mEq/L during the first 24 hr, is considered safe (including the initial 4- to 6-mEq/L correction). During the second 24 hr, the rate of correction should be even more gradual than for the acutely symptomatic patient. A rate of 0.5 mEq/L or less, with the plan of limiting sodium rise to no more than 18 mEq/L over the initial 48 hr, is appropriate. Some authors suggest an even slower rate of correction, limiting sodium rise to no more than 8 mEq/L in any 24-hr period.[13] Furosemide may be used during the initial correction phase but should probably be limited to a single dose to minimize too rapid a correction, particularly in the setting of hypertonic saline use.

A more challenging situation is that of a patient with severe hyponatremia associated with a malignancy. Such patients should have at least a partial correction to a serum sodium above 125 mEq/L (and preferably above 130 mEq/L) before proceeding with chemotherapy and hydration.

A caution is that the correction of a hypovolemic hyponatremia associated with excessive use of thiazide diuretics might occur more rapidly than anticipated. As volume is replaced, these patients might quickly regain the ability to excrete a hypotonic urine that could cause an unintended acceleration of sodium correction. Likewise, other hypovolemic patients are at risk for rapid correction. As their volumes are expanded and the nonosmotic stimulus of ADH decreases, accelerated sodium correction can occur. Again, the use of isotonic rather than hypertonic saline for correction, as well as frequent evaluations of volume and sodium status, limits the potential for too rapid a rate of correction.

An important, more elegant and selective treatment of hyponatremia is now emerging as a result of the development of antagonists to the renal arginine vasopressin (ADH) receptors. Some amount of impaired water excretion is common in virtually all the hypervolemic and isotonic hyponatremic states. Thus, antagonists to the renal AVP receptors (V2 receptor antagonists; tolvapatan and conivaptan) which mediate free-water reabsorption from the distal tubules can promote free-water excretion. These agents have no effect on the excretion of sodium or other electrolytes; the effect is pure aquaresis. Though not yet in common use outside of the management of congestive heart failure, these agents will undoubtedly become a part of the primary treatment of hyponatremias, as adjuvants or replacements for management by water restriction.[20–22]

EXAMPLE CASES

Postoperative Symptomatic Hyponatremia

A 56-year-old woman who had an uncomplicated resection of a breast tumor 48 hr ago is reported by her family to be more lethargic and somewhat confused compared with the day before. She has a tonic-clonic seizure that is controlled rapidly with lorazepam. Serum chemistries reveal a serum sodium of 115 mEq/L, a serum potassium of 3.3 mEq/L, and a serum osmolality of 245 mOsm/kg. Her urine osmolality is 125 mEq/L, and urine sodium is 20 mEq/L. On examination, she has a heart rate of 90 beats/min, is normotensive, and has no peripheral edema. Her preoperative weight was 65 kg. Based on the foregoing data, a probable diagnosis is hypotonic hyponatremia in what seems to be a euvolemic patient. The differential diagnosis includes SIADH from the pain and stress of surgery and/or from the use of morphine for postoperative discomfort, or dilutional hyponatremia from hypotonic volume overload. SIADH would be expected to be associated with a more concentrated urine and a urine sodium well in excess of 20 mEq/L. Her record indicates that she received 2.5 L of D5W during surgery. Additionally, it is noted that she has had several glasses of water over the last 12 hr, the exact amount unknown. The highly dilute urine, the relatively low urine sodium in the setting of a low serum osmolality, and her history are characteristic of acute hypotonic fluid overload. Because the patient is symptomatic, the initial plan should be to increase her serum sodium by 3 to 6 mEq/L over the course of 3 to 6 hr. Based on her weight and gender, the appropriate factor for determining the volume of ECF in need of correction is 0.5, thus giving a volume of 32.5 L (0.5×65 kg). An initial correction of 5 mEq/L over the course of 6 hr is planned using 3% saline. The total amount of sodium needed is 163 mEq (32.5 kg × 5 mEq/L). Given over 6 hr, this equates to 27 mEq/hr. Using 3% saline, which contains 0.513 mEq/mL of sodium, her hourly fluid rate becomes

$$\frac{27 \text{ mEq Na}}{0.513 \text{ mEq Na/mL 3\% saline}} = 53 \text{ mL/hr for 6 hr}$$

If furosemide is given at the start of the initial correction, the time to correction might be somewhat longer as a result of both free-water and sodium loss (furosemide produces a roughly 0.45% saline diuresis). Thus, sodium should be monitored every 2 hr, and the infusion rate should be adjusted accordingly (Box 49-4).

At the end of the initial 6 hr the serum sodium is 119 mEq/L, and there have been no further seizures. The patient remains unresponsive, however. Based on this, an additional 5 mEq/L sodium correction is planned. Even though patients with acute volume overload are not at high risk for osmotic demyelination associated with rapid correction, it is wise to assume that the problem occurred slowly to minimize the potential for development of this condition. Thus, the second-phase correction should be done at a much slower rate of 0.5 mEq/L/hr, with the goal of not exceeding a total correction of more than 12 mEq/L over the first 24 hr. Another 163 mEq of sodium will be required (32.5 kg × 5 mEq/L) over the next 18 hr. Because the patient is still unresponsive, it is appropriate to use 3% saline for correction. The hourly rate of correction now changes to 163 mEq/18 hr, or 9 mEq/hr. Using 3% saline, this becomes

$$\frac{9 \text{ mEq Na}}{0.513 \text{ mEq Na/mL 3\% saline}} = 17 \text{ mL/hr for 12 hr}$$

At the end of 24 hr, the patient's serum sodium is 125 mEq/L, and she is somewhat lethargic but arousable. At this point, it is appropriate to switch to isotonic saline (0.9%) for further correction. The goal is now to continue correction, limiting the total amount of correction in the first 48 hr to 18 mEq/L. Thus, an additional 8 mEq/L of sodium will be given over the second 24-hr period, for

Box 49-4. CALCULATING THE RATE OF FLUID ADMINISTRATION

Na^+ deficit/Na^+ mEq/L = rate (mL/hr)

a total of 260 mEq of sodium (8 mEq/L × 32.5 L) or 11 mEq/hr. Using isotonic saline, the rate becomes

$$\frac{11 \text{ mEq Na}}{0.513 \text{ mEq Na/mL 3\% saline}} = 39 \text{ mL/hr}$$

At the end of the first 48 hr the patient's serum sodium is 132 mEq/L, and she is alert and responsive. Further correction with 0.9% saline at a rate of no more than 0.5 mEq/L/hr over the next 12 to 24 hr will result in a normal serum sodium having been achieved over a period of time long enough and at a slow enough rate to minimize the potential for CNS demyelination.

Hypotonic Hyponatremia Associated with Euvolemia

A 72-year-old man with recently diagnosed small cell lung carcinoma is noted to have become increasingly confused and lethargic over the last 72 hr. He has not yet started chemotherapy. Notably, he has been on replacement therapy for hyperthyroidism for several years. His wife is not sure whether he has been taking his thyroid replacement over the last several days. Laboratory evaluation reveals a serum sodium of 112 mEq/L, serum potassium at 3.6 mEq/L, and a serum osmolality of 225 mOsm/kg. The urine osmolality is 590 mOsm/kg. His blood pressure and heart rate are normal, and there is no evidence of edema, suggesting that he is euvolemic. His urine sodium is 50 mEq/L. His weight is 66 kg. Although the temptation to make the diagnosis of tumor-related SIADH is strong, this must be a diagnosis of exclusion. Other possible causes of euvolemic hypotonic hyponatremia include overuse of a diuretic and glucocorticoid or thyroid deficiency (see Fig. 49-2). He has not been taking any diuretics, and cortisol deficiency seems unlikely because his potassium is normal and he has been an otherwise healthy, active man except for recent events. Although known to have primary hypothyroidism, it is unlikely that missing 2 to 3 days of replacement therapy would put him at risk for hyponatremia. Thus, tumor-related SIADH is the most likely diagnosis. He is given 1 L of normal saline (0.9%), and 2 hr later his serum sodium is 110 mEq/L and his urine osmolality remains at 590 mOsm/kg. Although this might initially be surprising, recall that patients with SIADH have a relatively fixed urine osmolality due to tonic ADH secretion, and they retain the ability to excrete sodium despite their hyponatremia. Thus, the net effect of isotonic saline was to produce further dilution of serum sodium, as a concentrated sodium-containing urine is excreted, leaving a relative free-water gain.

The approach to this symptomatic patient involves raising his sodium to a level of 120 mEq/L and then restricting free water. The goal is to provide an initial sodium increase of 3 to 6 mEq/L. Knowing that the hyponatremia has developed over a period of at least 72 hr based on the patient's history, the rate of correction should be similar to minimize the potential for osmotic demyelination, for which he is at significant risk. Based on this information, the goal is an increase in serum sodium of no more than 10 to 12 mEq/L over the first 24 hr at a rate of no more than 0.5 mEq/L/hr. Because he is an elderly man, the factor for determining his total body water is 0.5, thus making his total ECF volume 33 L (0.5 × 66 kg). Although the use of isotonic saline is often a better plan for correcting hyponatremia in patients who have developed the disorder chronically, 3% saline is acceptable for this patient because he is symptomatic.

Raising his sodium by 10 mEq/L to 120 mEq/L over the next 24 hr requires 10 mEq/L of sodium by 23 L, for a total of 230 mEq of sodium.

$$\frac{230 \text{ mEq Na}}{0.51 \text{ mEq/mL/3\% saline}} = 450 \text{ mL 3\% saline at 19 mL/hr}$$

This correction rate is only 0.4 mEq/L/hr and within the guidelines for minimizing the risk of osmotic demyelination discussed earlier in the chapter. Also, keep in mind that the rate of correction should be limited to 18 mEq/L within the first 48 hr. If furosemide is used at the start of the initial correction, the rate of correction might even be somewhat slower, as noted in the previous case example. At 24 hr, the patient's serum sodium is 119 mEq/L; he is lethargic but arousable and less confused, and the objective of bringing his sodium close to 120 mEq/L has been achieved. If he had not been clinically improved, it might have been prudent to increase his sodium another 5 mEq/L over the next 12 hr, to about 125 mEq/L. At this point, with signs of improvement in the patient and a serum sodium of 119 mEq/L, it is appropriate to begin water restriction, limiting water and anything that becomes water at body temperature (e.g., gelatin and ice cream) to 1 L/day. Over the next 48 to 72 hr, one should expect to see his sodium increase to 130 mEq/L or more. At this point, it is appropriate to begin management of his tumor.

Hyponatremia with Diminished Extracellular Fluid

A 12-year-old 50-kg male underwent resection of a large temporal lobe tumor 48 hr previously; the tumor has been associated with significantly increased intracranial pressure. He is irritable but lucid, complaining of leg cramps; he has a moderate hypotension of 100/60 mm Hg and a moderate sinus tachycardia of 120 beats/min and has developed significantly increased urine output of 6 mL/kg/hr over the last 12 hr. Serum chemistries reveal a sodium of 124 mEq/L, potassium of 4.5 mEq/L, blood urea nitrogen (BUN) of 17, and creatinine of 1.2. His serum osmolality is 300 mOsm/kg, urine osmolality is 350 mOsm/L, and urine sodium is 155 mEq/L. Review of his record shows that he received 0.5 g/kg dose of mannitol before surgery and 1 L of normal saline during surgery. Over the last 24 hr he has been drinking ad lib and seems to have increased thirst. His examination suggests some degree of hypovolemia, and the elevated urine sodium is compatible with either a primary salt-wasting process or SIADH. The urine sodium and moderate urine concentration are not consistent with diabetes insipidus. The latter is unlikely given his increased serum osmolality, excessive urine output, and signs of hypovolemia. A hypovolemic hyponatremia characterized by excessive renal sodium loss in a neurosurgical setting is characteristic of cerebral salt wasting.

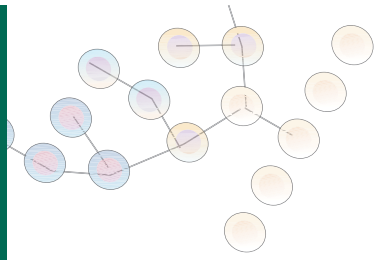
Recognizing that the serum sodium has probably developed acutely and is likely to quickly drop even further given the amount of sodium he is excreting and the fact that he is developing some mild symptoms (irritability and muscle cramps), the decision is to make a partial correction of his sodium to diminish the potential of more severe symptoms. At the same time, his hypovolemia must be treated, and his ongoing losses must be replaced. The plasma volume for this adolescent male is 30 L (0.6 × 50 kg). Because the sodium loss has been rapid, the decision is taken to raise his sodium by 4 mEq/L over 6 hr. Thus, a total of 120 mEq of sodium over 6 hr will be needed at a rate of 20 mEq/hr using 3% saline.

$$\frac{20 \text{ mEq Na}}{0.513 \text{ mEq Na/mL 3\% saline}} = 39 \text{ mL/hr}$$

Simultaneously, it is necessary to replace his urine output, volume for volume, with isotonic saline. To this it is necessary to add an amount calculated to represent his current volume deficit with the intent of correcting it over 24 hr. After 24 hr, the patient appears euvolemic with a normal blood pressure and heart rate. Having replaced his volume deficit, it is now prudent to decrease the rate of isotonic saline correction to match urine output. The natriuresis continues for several days, but isotonic saline keeps the serum sodium at 138 mEq/L. At this point the patient is stable, is able to drink, and appears to have a normal thirst. He can be discharged on oral NaCl supplements approximating his renal sodium loss. Two weeks later he appears well, and his urine output has diminished to 3 mL/kg/day. He is on a normal diet, and urine osmolality has increased to 550 mEq/L with 50 mEq/L of sodium. The serum sodium is 138 mEq/L. At this point NaCl supplements are stopped, and the patient's serum sodium remains normal.

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50 Tumor Lysis Syndrome

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SUMMARY OF KEY POINTS

Incidence and Epidemiology

- The exact incidence of tumor lysis syndrome is unknown; incidence in high-grade non-Hodgkin's lymphoma is approximately 40%.
- Tumor lysis syndrome is most commonly associated with acute lymphocytic leukemia and "high-grade" non-Hodgkin's lymphoma; however, it has been observed in a variety of hematologic and solid malignancies.
- Tumor lysis syndrome has been observed with the administration of chemotherapy, corticosteroids, radiation, hormonal agents, and biologic response modifiers. Tumor lysis syndrome can rarely occur spontaneously before the initiation of therapy.

Etiology

- Tumor lysis syndrome results from the spontaneous release of intracellular ions and metabolites from malignant cells before or after the initiation of cytotoxic therapy.
- The body's inability to handle the increased concentrations of ions and metabolites results in the characteristic metabolic abnormalities associated with tumor lysis syndrome, including hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and/or uremia.
- The metabolic disturbances associated with tumor lysis syndrome can lead to life-threatening complications including arrhythmias, acute renal failure, and sudden death.

Evaluation of the Patient

- Patients with tumors with a high proliferative rate and sensitivity to cytotoxic therapy, large tumor masses, pre-existing renal insufficiency, and high serum lactate dehydrogenase levels are at highest risk for the development of tumor lysis syndrome.

Management and Treatment

- Recognition of patients at risk for the development of tumor lysis syndrome is the most important management issue.
- Establishing central venous access and administration of intravenous fluids and allopurinol or rasburicase should begin before the initiation of tumor therapy.
- Alkalinization of urine with sodium bicarbonate or acetazolamide is not recommended.
- Prompt initiation of hemodialysis may aid in the reversal of severe complications associated with renal failure and metabolic abnormalities.

INTRODUCTION

Tumor lysis syndrome (TLS) describes the metabolic derangements that occur from rapid tumor breakdown associated with the initiation of cytotoxic therapy of malignancy in both children and adults. The syndrome is characterized by a tetrad of abnormalities including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia; it should be considered an oncologic emergency.[1–5] The abrupt release of intracellular ions, nucleic acids, proteins, and their metabolites results from the rapid destruction of malignant cells and the release of their intracellular contents into the extracellular space after the initiation of therapy. Cell lysis can overwhelm the body's normal homeostatic mechanisms and cause severe metabolic disturbances that require immediate clinical intervention (Fig. 50-1).

TLS has been primarily observed in patients with acute lymphocytic leukemia and high-grade non-Hodgkin's lymphomas, in particular Burkitt's lymphoma. However, TLS has also been recognized in a variety of other malignancies, both hematologic and solid. These malignancies share the characteristics of a high proliferative rate and a relative sensitivity to cytotoxic therapy.[6–14] Other hematologic malignancies associated with TLS include acute myeloid leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, and low-grade and intermediate-grade non-Hodgkin's lymphomas. TLS has also been reported to occur in a number of solid tumors such as breast cancer, ovarian and testicular cancer, neuroblastoma, and small cell carcinoma of the lung.[15–24]

The overall incidence of TLS is not well established and has only been closely studied in high-grade non-Hodgkin's lymphomas.[25] In a retrospective study of 102 patients with high-grade non-Hodgkin's lymphoma, the incidence of TLS was reported to be 42% as determined by serial laboratory testing. The incidence of clinically significant TLS was only 6% in the same group of patients. Part of the difficulty in obtaining the true incidence of TLS is that there is no unifying definition or grading system. Recent proposals define TLS by both laboratory (LTLS) and clinical (CTLS) criteria and use these criteria to develop a grading system (Tables 50-1 through 50-3).[1,2,5]

The development of TLS is not limited to the administration of chemotherapy alone. Reports of TLS have been associated with the administration of radiation therapy, corticosteroids, hormonal agents, biologic response modifiers, monoclonal antibodies, and more recently, the low-molecular-weight inhibitor, imatinib mesylate, better known as Gleevec.[15,20,24,26–41] TLS is not limited to systemic administration of agents; it has been observed with intrathecal administration of chemotherapy and with chemo-embolization. It is extremely important clinically to note that TLS can occur spontaneously, before the initiation of any intervention. The identification of

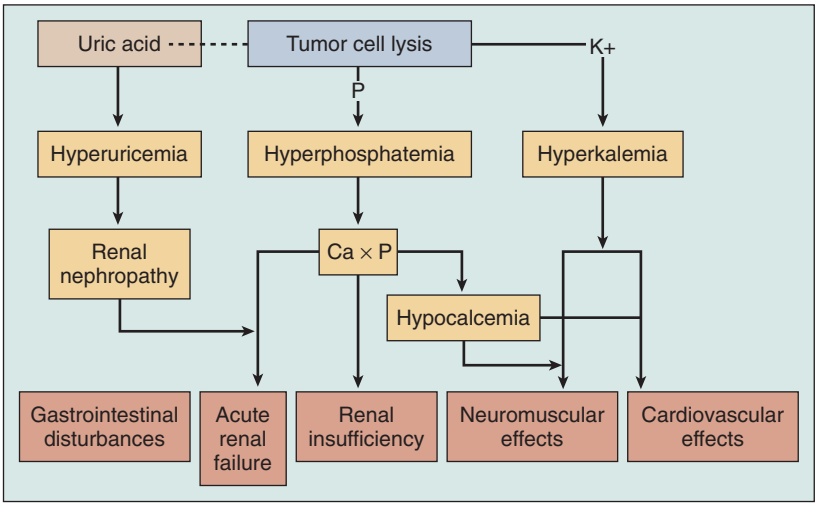


Figure 50-1 • Schematic of the metabolic abnormalities associated with the development of tumor lysis syndrome and the clinical complications stemming from these metabolic derangements.

patients at risk for the development of TLS is the most important aspect of management, so that prophylactic measures can be initiated before the initiation of therapy. Most of the complications can be readily managed when they are recognized early; however, delay in recognition and initiation of treatment of TLS can be life-threatening. In addition, a recent cost analysis looking at acute renal failure, length of stay, and total cost demonstrated that those patients who went on to develop acute renal failure requiring dialysis had up to two to three times the length of stay and more than five times the cost.[42,43]

PATHOPHYSIOLOGY

The majority of agents that are used in the treatment of malignancies are dependent on the proliferative rate of malignant cells for their activity. In tumors with a high proliferative rate, a relatively large mass, and a high sensitivity to cytotoxic agents, the initiation of therapy often results in the rapid release of intracellular anions, cations, and the metabolic products of proteins and nucleic acids into the bloodstream. The increased concentrations of uric acid, calcium, phosphates, potassium, and urea can overwhelm the body's natural mechanisms to process and excrete these materials and result in the clinical spectrum associated with TLS.

Hyperuricemia and its associated complications are the most frequently recognized manifestations of TLS, and more importantly, predispose to many of the other clinical derangements. Hyperuricemia results from rapid release and catabolism of intracellular nucleic acids. Purine nucleic acids are catabolized to hypoxanthine, then xanthine, and finally to uric acid by xanthine oxidase. In humans, who lack urate oxidase, uric acid is the final endpoint of purine catabolism (Fig. 50-2). Uric acid clearance is renal, and in normal circumstances approximately 500 mg of uric acid are excreted through the kidneys each day. Uric acid has a pKa of 5.4 to 5.7 and is poorly soluble in water. At normal concentrations and at physiologic blood pH, more than 99% of uric acid is in the ionized form.[44] The concentration of uric acid has been noted to be elevated in patients with acute leukemias and lymphomas before the initiation of therapy.[45] The high concentrations of uric acid increase the risk for urate crystal precipitation in the renal collecting ducts and distal tubules, which are sites of urinary acidification.[46,47] General clinical manifestations of hyperuricemia include nausea, vomiting, diarrhea, and anorexia. Uric acid crystal precipitation within renal tubules results in a decline in glomerular filtration and the subsequent development of acute renal failure. The risk of acute renal failure caused by uric acid precipitation may be increased by dehydration, which is often present at the time of diagnosis; ureteral obstruction by tumor; a history of renal insufficiency; and the possible need for nephrotoxic antibiotics, such as aminoglycosides, in patients with active infections. If the hyperuricemia results in acute obstructive uropathy, other clinical manifestations may include hematuria, flank pain, hypertension, azotemia, acidosis, edema, oliguria, anuria, lethargy, and somnolence.

Table 50-1 Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Uric acid	≥8.0 mg/dL or 25% increase from baseline
Potassium	≥6.0 mEq/L or 25% increase from baseline
Phosphorous	≥6.5 mg/dL (children)
	≥4.5 mg/dL (adults) or 25% increase from baseline
Calcium	≤7.0 mg/dL or 25% decrease from baseline

Laboratory tumor lysis syndrome (LTLS) is defined as either a 25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration and a hypouricemic agents(s).

Modified from Hande and Garrow (1993).

(This research was originally published in Cairo MS, Bishop M: Tumour lysis syndrome: New therapeutic strategies and classification. Br J Haematol 2004;127:3–11. © Blackwell Publishing Ltd.)

Table 50-2 Cairo-Bishop Definition of Clinical Tumor Lysis Syndrome

1. Renal failure (creatinine*: ≥1.5 ULN† [age >12 yr or age adjusted])
2. Cardiac arrhythmia/sudden death*
3. Seizure*

Clinical tumor lysis syndrome (CTLS) assumes the laboratory evidence of metabolic changes and significant clinical toxicity that requires clinical intervention. CTLS is defined as the presence of laboratory tumor lysis syndrome (LTLS) and any one or more of the above-mentioned criteria.

*Not directly or probably attributable to a therapeutic agent (e.g., rise in creatinine after amphotericin administration).

†Patients will be considered to have elevated creatinine if their serum creatinine is 1.5 times greater than the institutional upper limit of normal (ULN) below age/gender defined ULN. If not specified by an institution, age/sex ULN creatinine may be defined as: >1 <12 years, both male and female, 61.6 µmol/L; ≥12 <16 years, both male and female, 88 µmol/L; ≥16 years, female, 105.6 µmol/L; ≥16 years, male, 114.4 µmol/L.

Modified from Hande and Garrow (1993).

(This research was originally published in Cairo MS, Bishop M: Tumour lysis syndrome: New therapeutic strategies and classification. Br J Haematol 2004;127:3–11. © Blackwell Publishing Ltd.)

Table 50-3 Cairo-Bishop Grading System for Tumor Lysis Syndrome

	Grade 0*	Grade I	Grade II	Grade III	Grade IV	Grade V
LTLS	–	+	+	+	+	+
Creatinine†‡	≤1.5 × ULN	1.5 × ULN	>1.5–3.0 × ULN	>3.0–6.0 × ULN	>6.0 ULN	Death§
Cardiac arrhythmia‡	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g. defibrillator)	Life-threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock)	Death§
Seizure‡	None	—	One brief generalized seizure; seizure(s) well controlled by anti-convulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive or difficult to control (e.g. status epilepticus, intractable epilepsy)	Death§

Clinical tumor lysis syndrome (CTLS) requires one or more clinical manifestations along with criteria for laboratory tumor lysis syndrome (LTLS).
Maximal CTLS manifestation (renal, cardiac, neuro) defines the grade.
*No LTLS.
†Patients will be considered to have elevated creatinine if their serum creatinine is 1.5 times greater than the institutional upper limit of normal (ULN) below age/gender defined ULN. If not specified by an institution, age/sex ULN creatinine may be defined as: >1 <12 years, both male and female, 61.6 µmol/L; ≥12 <16 years, both male and female, 88 µmol/L; ≥16 years, female, 105.6 µmol/L; ≥16 years, male, 114.4 µmol/L.
‡Not directly or probably attributable to a therapeutic agent (e.g. rise in creatinine after amphotericin administration).
§Attributive probably or definitely to CTLS.
(This research was originally published in Cairo MS, Bishop M: Tumour lysis syndrome: New therapeutic strategies and classification. Br J Haematol 2004;127:3–11. © Blackwell Publishing Ltd.)

Hyperphosphatemia results from the rapid release of intracellular phosphates from malignant cells, which may contain as much as four times the amount of organic and inorganic phosphates as normal cells.[1–5,25] Initially, the kidneys are able to respond to the increased concentration of phosphorus from tumor lysis by increased urinary excretion and decreased tubular absorption of phosphorus. Eventually, however, the tubular transport mechanism becomes saturated and is unable to maintain normal serum phosphorus concentrations. The development of hyperphosphatemia may be further exacerbated by acute renal insufficiency associated with uric acid precipitation, resulting in obstructive uropathy or other complications of tumor therapy. Hyperphosphatemia can lead to the development of acute renal failure after precipitation with calcium in renal tubules during TLS. Hyperphosphatemia may be associated with nausea, vomiting, diarrhea, lethargy, and seizures. More importantly, hyperphosphatemia may result in tissue precipitation of calcium-phosphate crystals, resulting in hypocalcemia, metastatic calcification, intrarenal calcification, nephrocalcinosis, nephrolithiasis, and additional acute obstructive uropathy. The serum concentration of calcium rapidly decreases as precipitation with phosphate occurs. Hypocalcemia is one of the most serious clinical manifestations of TLS and has been associated with the development of severe muscle cramping, tetany, and cardiac arrhythmias. In addition to the kidneys, other tissues such as muscle may be sites of precipitation of calcium and phosphorus.[8]

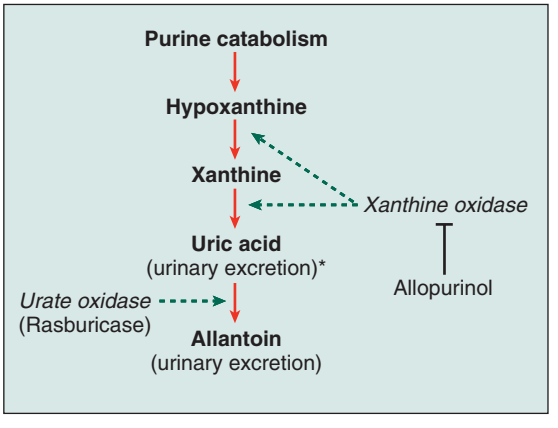


Figure 50-2 • Mechanism of action: rasburicase and allopurinol. Depicted is the pathway of purine catabolism. Rasburicase is a recombinant form of urate oxidase, an enzyme that converts uric acid to allantoin. Allopurinol in comparison acts by inhibiting the endogenous enzyme xanthine oxidase, thereby inhibiting formation of uric acid. *A normal endpoint of purine metabolism in humans. (This research was originally published in Goldman SC, Holcenberg JS, Finklestein JZ, et al: A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 2001;97:2998–3003. © The American Society of Hematology.)

Hyperkalemia may also be a life-threatening consequence of TLS.[8,37,48] Hyperkalemia results from the kidneys' inability to clear the massive load of intracellular potassium released by lysed tumor cells. General clinical manifestations of hyperkalemia may include nausea, anorexia, vomiting, and diarrhea. More specific complications include neuromuscular and cardiac abnormalities. Neuromuscular signs and symptoms may include muscle weakness, cramps, paresthesias, and possible paralysis. Cardiac manifestations may include asystole, ventricular tachycardia or fibrillation, syncope, and possible sudden death.[1–5,25]

Increases in blood urea nitrogen and creatinine levels occur as a result of renal impairment associated with acute uric acid crystal nephropathy, calcium-phosphate crystals and nephrocalcinosis, or a combination of both, leading to an acute obstructive uropathy syndrome. A correlation with the pretreatment serum lactate dehydrogenase (LDH) concentration and the development of azotemia has been reported, and the blood urea nitrogen level will generally rise in parallel with the rise in the serum phosphorus concentration. Acute clinical manifestations may include uremia resulting in nausea, vomiting, and lethargy; oliguria or anuria leading to fluid retention; edema, hypertension, congestive heart failure, metabolic disturbances, and exacerbations of hyperphosphatemia and/or hyperkalemia (see previous discussion); flank or back pain; hematuria; and severe acidosis. Extreme elevations in blood urea nitrogen concentrations can

result in a platelet function defect, cellular immunodeficiency, and inflammatory pericarditis.[49,50] Furthermore, acute obstructive uropathy may precipitate acute renal failure (anuria), confusion, somnolence, seizures, and/or coma.

TREATMENT

The management of TLS can be classified into preventative and immediate treatments. The ability to prevent TLS is highly dependent on the immediate recognition of patients at risk for its development (Table 50-4). Patients at high risk include those with tumors with a high proliferative rate, large tumor masses including elevated leukocyte counts, extensive adenopathy and splenomegaly, preexisting renal insufficiency, and elevated levels of phosphorus, uric acid, or both before the initiation of therapy (Table 50-5). The elevation of the serum LDH level before the initiation of therapy has also been associated with the recognition of patients at risk for TLS.[1,2,4] Cytotoxic therapy should be delayed in patients at high risk for development of TLS until prophylactic measures can be initiated. Unfortunately, a delay in therapy is not possible for many patients because of the aggressive nature of their underlying malignancy. In this clinical situation, a decision must be made regarding the relative risks in the delay of tumor therapy versus the risk of development or exacerbation of TLS and its associated complications including acute renal failure.[51,52] Regardless of time constraints, the patient should have reliable venous access and be treated in an intensive care or oncology special care unit with personnel who are trained and familiar with the complications associated with TLS. The unit should have, at a minimum, the capability of continuous cardiac monitoring and preferably the capacity for hemodialysis.

The patient's vital signs, weight, urinary output, and fluid intake must be carefully monitored. Serum creatinine, blood urea nitrogen, sodium, potassium, calcium, phosphorus, LDH, and uric acid concentrations should be determined before therapy and every 4 to 6 hours for the first 48 to 72 hours after the initiation of tumor therapy. The LDH concentration serves as an excellent marker for tumor proliferation and response to therapy. Patients should have a baseline electrocardiogram and continuous cardiac monitoring until the completion of treatment. Ideally, all patients should receive intravenous hydration 24 to 48 hours before the initiation of tumor therapy.[4,53]

Table 50-4 Risk for Tumor Lysis Syndrome by Tumor Type

Burkitt's lymphoma	Frequent cases
Lymphoblastic lymphoma	
Acute leukemia	
Large cell lymphoma	
Low-grade lymphoma treated with chemotherapy, radiotherapy or steroids	Recognized complication but few occurrences
Breast carcinoma treated with chemotherapy or hormonal therapy	
Small cell lung carcinoma	
Seminoma	
Neuroblastoma	
Low-grade lymphoma treated with interferon	Case reports only
Merkel's cell carcinoma	
Medulloblastoma	
Adenocarcinoma of the gastrointestinal tract	

Table 50-5 Initial Management of Patients at Risk for Tumor Lysis Syndrome

1. Identification of the patient at risk (see Table 50-4).
2. Admit to intensive care or hematology/oncology unit.
3. Alert dialysis team of existence of patient and potential emergent need of assisted renal support.
4. Establish adequate venous access.
5. Perform baseline electrocardiogram and continuous cardiac monitoring.
6. Determine baseline and serial WBC, serum LDH, uric acid, Na^+, K^+, creatinine, BUN, phosphorous, and Ca^{++} levels. Repeat every 4–6 hours.
7. Provide intravenous hydration with hypotonic or isotonic saline solution at 2500 to 3000 mL/m^2/24 hours.
8. Given allopurinol, 300 mg/m^2/day orally, or rasburicase, 0.20 mg/kg/day intravenously, over 30 minutes for up to 3 days.

Intravenous hydration, preferably with a hypotonic or isotonic saline solution at 2500 to 3000 mL/m^2/24 hr, should ideally begin 24 to 48 hours before the initiation of therapy and continue for 48 to 72 hours after completion of chemotherapy. Care must be taken to prevent severe hyponatremia, especially when hypocalcemia is present, because the risk of seizures is increased. A hypotonic saline solution should be used when the urinary sodium concentration is less than 150 mEq/L, to reduce the risk of uric acid supersaturation. The rate and amount of fluid is dependent on each patient's cardiovascular function. Administration of mannitol may be considered if sufficient diuresis cannot be achieved with intravenous hydration alone. A test dose of 200 to 500 mg/kg may be given intravenously and discontinued if an appropriate increase in urine output is not observed. Careful attention must be given to the administration of both intravenous fluids and mannitol to avoid fluid overload and the potential for congestive heart failure.

In addition, it is necessary to administer a hypouricemic agent, either allopurinol or rasburicase, before the initiation of therapy. Allopurinol is a potent inhibitor of xanthine oxidase and blocks the conversion of hypoxanthine and xanthine to uric acid.[47] Whereas hypoxanthine is more soluble than uric acid is at physiologic pH, xanthine is less soluble than uric acid. This may result in the formation of xanthine crystals in the kidney and lead to obstructive uropathy. Although allopurinol prevents new uric acid formation, it does not reduce the amount of uric acid already present. Thus allopurinol requires administration for 2 to 3 days before the serum uric acid concentration begins to fall and therefore needs to be initiated 2 to 3 days before the initiation of cytotoxic therapy. Allopurinol is generally given at a dose of at least 300 mg/m^2/day.[54] Allopurinol is known to interfere with the degradation of 6-mercaptopurine, 6-thioguanine, and azathioprine through inhibition of the P450 pathway; thus, the dose of allopurinol should be reduced 50% to 75% in patients receiving these chemotherapeutic agents. Allopurinol should be used with caution in patients with underlying renal insufficiency, because it can cause a syndrome consisting of rash, hepatitis, eosinophilia, and worsening renal function. A previous limitation of allopurinol has been the requirement for administration by the oral route. For some critically ill patients or young infants who may be unable to tolerate oral medications during the prevention or treatment of TLS, there is an intravenous preparation of allopurinol available.[53,55] Previously, urine alkalinization was recommended to increase uric acid solubility and promote uric acid excretion in patients treated with allopurinol. However, alkalinization is not currently recommended because of the risk of decreasing ionized calcium concentrations, decreasing phosphate excretion, and increasing serum phosphate concentrations.

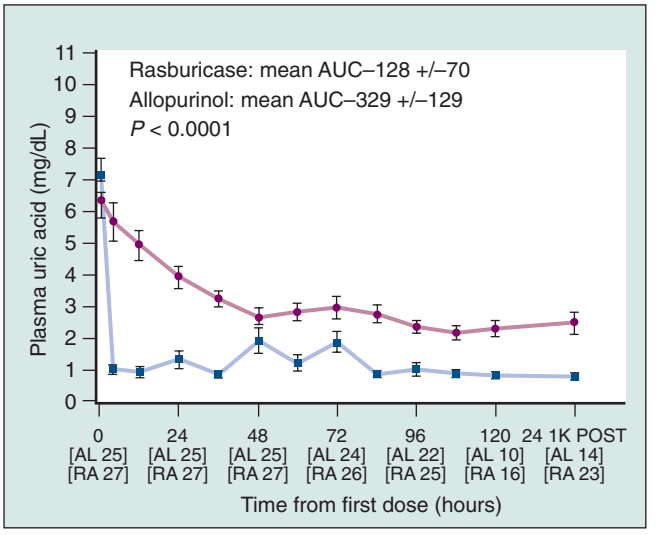


Figure 50-3 • Mean (± SE) plasma uric acid concentrations over time for all patients. Squares denote patients who received rasburicase ($n = 27$) and stars allopurinol ($n = 25$). The 24-hour post levels reflect 24 hours after the last dose of study drug. Patients who received rasburicase demonstrated more rapid decline and maintained lower plasma uric acid levels throughout the study period. The area under the serial plasma uric acid concentration curve (AUC) through the first 96 hours of therapy was significantly less for patients receiving rasburicase ($P < 0.0001$). (This research was originally published in Goldman SC, Holcenberg JS, Finklestein JZ et al: A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood 2001;97:2998–3003. © The American Society of Hematology.)

An alternative to inhibiting uric acid formation by competitively inhibiting xanthine oxidase is to promote the catabolism of uric acid to allantoin by uric acid oxidase. Allantoin is 5 to 10 times more soluble in the urine than uric acid. Urate oxidase is an endogenous enzyme commonly found in many mammalian species but not in humans. Urate oxidase, extracted from *Aspergillus flavus,* has been demonstrated to rapidly and significantly reduce uric acid levels in patients at high risk for TLS. Recently, the gene encoding urate oxidase was identified and expressed in yeast to yield large quantities of the pure recombinant form of urate oxidase (rasburicase).[54,56–63] In a multicenter trial, 52 pediatric patients with hematologic malignancy at high risk for TLS were randomly assigned to receive allopurinol or rasburicase. Uric acid levels significantly decreased by 85% with rasburicase as compared with 12% with allopurinol within 4 hours of drug administration (Fig. 50-3).[64] Pui and colleagues administered rasburicase IV at doses up to 0.2 mg/kg in 131 pediatric patients with newly diagnosed leukemia or lymphoma. They found a rapid drop in uric acid levels from 9.7 to 1 mg/dL within 4 hours of treatment in patients with hyperuricemia and further reductions to 0.5 mg/dL within 24 hours after rasburicase administration. Serum phosphorus and creatinine concentrations also decreased significantly within 1 to 3 days.[65] The same investigators went on to review data on 173 children and 72 adults with malignancy who were treated with rasburicase. All patients had a dramatic decrease in uric acid concentration with median post-treatment concentrations of 0.5 to 0.7 mg/dL. There were very few adverse reactions after administration, and all of these were mild, making this an excellent therapeutic option.[66,67] Coiffier and associates investigated the safety and efficacy of rasburicase in 100 adult patients with non-Hodgkin's lymphoma over a 1-year period. Of these patients, 66% had elevated LDH levels and 11% were hyperuricemic with concentrations higher than 7.56 mg/dL. Rasburicase was given to all subjects and uric acid levels then measured at 4 hours. All of the patients responded to rasburicase with normalization of uric acid, and none exhibited increased creatinine levels or required dialysis.[56]

Attempts should be made to correct fluid overload, dehydration, and electrolyte and acid-base abnormalities, and to establish adequate urinary output before the initiation of therapy. Hyperkalemia should be treated expediently with standard measures such as the administration of sodium polystyrene sulfonate, a potassium-binding resin, at a dose of 15 to 60 g/day given orally or rectally. There should be little hesitation about initiating hemodialysis to correct this electrolyte abnormality. Aluminum hydroxide, given orally or through a nasogastric tube at a dose of 15 mL (50–150 mg/kg/24 hr) every 4 to 6 hours, should be used to treat hyperphosphatemia. The degree of tumor lysis declines after the first 48 to 72 hours of treatment, and a decline in the serum LDH level serves as an excellent marker for a decrease in tumor lysis. However, close monitoring of the patient should continue until treatment is completed.[1,2,54] Treatment of asymptomatic hypocalcemia is generally not recommended. In patients with symptomatic hypocalcemia, intravenous calcium gluconate (50–100 mg/kg per dose) may be administered to correct the clinical symptoms; however, this may increase the risk of calcium and phosphorus deposition and acute obstructive uropathy.

For patients who have acute renal failure, significant uremia, or severe electrolyte abnormalities associated with TLS, the general consensus is that hemodialysis should be initiated as soon as possible. Continuous hemofiltration has been used to correct fluid overload and electrolyte abnormalities associated with TLS in children.[68] The failure to promptly initiate hemodialysis for acute renal failure may turn a potentially reversible clinical situation into an irreversible one (Table 50-6).

CONCLUSIONS

Successful management and treatment of TLS is highly dependent on the prompt identification of clinical and laboratory characteristics, signs, and symptoms of patients at risk. Establishment of vascular access and the initiation of prophylactic measures, especially hydration and administration of allopurinol or rasburicase, are vital. The early recognition and treatment of metabolic abnormalities usually prevents the severe and life-threatening complications associated with TLS.

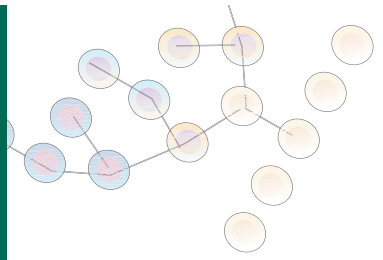
Table 50-6 Approach to the Management and Treatment of Tumor Lysis Syndrome

	Decreased Urinary Output (< 50 mL/h)	Hyperkalemia	Uremia	Hypocalcemia	Hyperuricemia	Hyperphosphatemia
Primary intervention	Mannitol challenge	K^+ binding resin	Diuretic	Cautious replacement	Allopurinol or rasburicase	Aluminum hydroxide (200–500 mg/kg)
Clinical manifestation	Renal insufficiency or fluid overload	Arrhythmia	Pericarditis or platelet dysfunction	Arrhythmia or tetany	Renal insufficiency	Renal insufficiency
Secondary intervention	Hemodialysis	Treat arrhythmia	Hemodialysis	Treat arrhythmia	Hemodialysis	Hemodialysis

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51 Paraneoplastic Neurologic Syndromes

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SUMMARY OF KEY POINTS

- The paraneoplastic neurologic syndromes include an extensive group of disorders that can affect any part of the central or peripheral nervous system.
- Evidence indicates that many of these syndromes have an immunopathogenesis and are mediated by immunologic responses triggered by the presence of a cancer.
- Antibodies directly mediate some disorders of the neuromuscular junction and peripheral nervous system, such as myasthenia gravis, the Lambert-Eaton myasthenic syndrome, and neuromyotonia. For these disorders and a few paraneoplastic neurologic syndromes of the central nervous system, immunotherapy may result in neurologic improvement. However, for most paraneoplastic neurologic syndromes of the peripheral and central nervous system the response to any type of therapy is, in general, disappointing. The physician's main concern should be to rule out other diagnostic entities and to uncover the presence of the associated neoplasm.
- The treatment approach should be aimed at the tumor, because stabilization and, less often, improvement of neurologic symptoms after tumor treatment have been reported for almost all syndromes. In a few cases, depending on the syndrome and if the patient is in the early stages of the neurologic disease, treatment with immunosuppression may have some effect on the paraneoplastic neurologic syndrome.

INTRODUCTION

Clinically significant paraneoplastic neurologic syndromes occur in fewer than 1% of all cancer patients. Paraneoplastic syndromes may affect any part of the neuraxis. In some, a single cell type, such as the Purkinje cells in paraneoplastic cerebellar degeneration (PCD), is predominantly involved, whereas in others any neuron of the central or peripheral nervous system may be affected, as occurs in paraneoplastic encephalomyelitis (PEM) and sensory neuropathy (PSN). Due to this variable distribution of pathological involvement, patients with these disorders may present with symptoms of unifocal or multifocal involvement of the nervous system.

Most paraneoplastic neurologic syndromes are thought to have an immunopathogenesis. One hypothesis is that the expression of neuronal antigens by the tumor triggers an immune response against the tumor that affects the nervous system. An immune-mediated pathogenesis has been demonstrated for the Lambert-Eaton myasthenic syndrome (LEMS).[1] Patients with LEMS have serum antibodies against voltage-gated calcium channels that are expressed by the tumor, which usually is a small cell lung cancer (SCLC). These antibodies block the entry of calcium necessary for the release of quanta of acetylcholine and result in neuromuscular weakness. Removal of the serum antibodies results in improvement of symptoms. In paraneoplastic myasthenia gravis (MG), a thymoma triggers an immune response against the acetylcholine receptor at the postsynaptic level of the neuromuscular junction, resulting in weakness and fatigability.[2] A similar antibody-mediated mechanism directed against voltage-gated potassium channels has been reported in paraneoplastic neuromyotonia.[3] Antibodies directed to mGluR1 and voltage-gated calcium channels may be pathogenic in a small subgroup of patients with paraneoplastic cerebellar degeneration.[4] Autonomic dysfunction, sometimes associated with cancer, may result from immunity to the nicotonic acetylcholine receptor.[5]

Aside from these syndromes and cancer-associated and melanoma-associated retinopathy (CAR, MAR), the immune origin of other paraneoplastic neurologic disorders has not been proven but is supported by a number of findings[6]:

- Patients with these disorders have high titers of antibodies that react with antigens restricted to the nervous system and tumor.[7,8]
- The antibodies are specific markers of characteristic syndromes and tumors and are produced intrathecally.[9,10]
- Similar antibodies are not found in other inflammatory disorders of the central nervous system (CNS) associated with neuronal destruction, or with tumors that do not express the specific antigen.
- A pathogenic effect of antibodies has been shown in animals for some of these disorders (anti-Hu and paraneoplastic gut dysmotility and anti-amphyphysin and paraneoplastic stiff-man syndrome).[11,12]
- Recent data indicate that in some paraneoplastic neurologic disorders of the CNS in which the antibodies target cell surface rather than intranuclear antigens, the antibodies may mediate the neurologic dysfunction.[13,14]

For some paraneoplastic syndromes of the CNS, circumstantial evidence suggests that T-cell-mediated mechanisms play a major pathogenic role. Autopsies of patients with paraneoplastic syndromes of the CNS show intense inflammatory infiltrates of mononuclear cells, including CD4+ and CD8+, which predominate in the areas of the nervous system that are symptomatic.[10,15] The mechanism whereby CD4+ or CD8+ cytotoxic T-cells recognize antigens expressed in neurons which normally lack expression of the antigen presenting MHC class I and II molecules is unknown.

Identification of the paraneoplastic origin of a patient's symptoms is important because in more than two thirds of patients the neurologic symptoms develop before the cancer is detected. Because similar

Table 51-1 Immune Associations in Paraneoplastic Neurologic Disorders

Antibody	Syndrome	Most Common Tumor Association(s)
Anti-Hu	PEM/PSN	SCLC
Anti-Yo	PCD	Ovary, breast
Anti-Ma	Brainstem encephalitis/PCD	Several
Anti-Ma2	Limbic/brainstem encephalitis	Testicular
Anti-Ri	Opsoclonus-ataxia	Breast, gynecologic
Anti-Tr	PCD	Hodgkin's lymphoma
Anti-amphiphysin	Stiff-man syndrome	Breast, SCLC
Anti-CV2/CRMP5	PEM/PCD, peripheral neuropathy, uveitis	SCLC, several
Anti-recoverin	Retinopathy	SCLC
Anti-bipolar cells of retina	Retinopathy	Melanoma
Anti-NMDAR	Limbic encephalitis, seizures, psychiatric symptoms	Teratoma
Anti-VGCC*	LEMS, PCD	SCLC
Anti-AChR*	Myasthenia gravis	Thymoma
Anti-VGKC*	Peripheral nerve hyperexcitability	Thymoma, others

*These antibodies may occur with or without a cancer association and therefore are not markers of paraneoplasia.

AChR, acetylcholine receptor; CRMP, collapsin response-mediator protein; LEMS, Lambert-Eaton myasthenic syndrome; NMDAR, N-methyl D-aspartate receptor; PCD, paraneoplastic cerebellar degeneration; PEM, paraneoplastic encephalomyelitis; PSN, paraneoplastic sensory neuropathy; SCLC, small-cell lung cancer; VGCC, voltage-gated calcium channel; VGKC, voltage gated potassium channel.

disorders may occur without cancer, the diagnosis of the paraneoplastic origin of a disorder depends heavily on the index of suspicion. This is based in part on the syndrome, since some syndromes have a paraneoplastic origin more frequently than others. For example, the likelihood that LEMS or subacute cerebellar degeneration in a middle-aged or elderly patient is paraneoplastic is probably more than 50%.[16] In contrast, subacute sensory neuropathy or dermatomyositis probably is paraneoplastic in origin in less than 20% of patients.[17,18] In most paraneoplastic syndromes, symptoms develop acutely or subacutely and may resemble a viral process. Symptoms evolve over weeks or months and then stabilize, differentiating them from the more chronic and progressive degenerative diseases of middle age and adulthood.

The finding that some paraneoplastic neurologic syndromes of the central or peripheral nervous system are associated with specific antineuronal antibodies has had a major impact on the ability to diagnose and manage these disorders.[19] These antibodies serve as markers of the paraneoplastic origin of neurologic symptoms and as markers for the presence of specific types of tumors (Table 51-1). Criteria have been proposed to facilitate the diagnosis of paraneoplastic disorders that take into consideration the type of neurologic syndrome, the detection of an associated tumor, and the presence or absence of paraneoplastic antibodies[20] (Box 51-1 and Fig. 51-1).

PARANEOPLASTIC SYNDROMES OF THE CENTRAL NERVOUS SYSTEM

Paraneoplastic Encephalomyelitis

Patients with PEM develop symptoms of multifocal involvement of the nervous system resulting in several syndromes that may occur in isolation or in various combinations.[21,22] These include limbic encephalitis, cerebellar degeneration, brainstem encephalitis, myelitis, and sensory and autonomic neuropathies.

Paraneoplastic encephalomyelitis has been described in association with many tumors, but in 70% of patients the underlying tumor is an SCLC. Most tumors are diagnosed within 2 years of the first neurologic presentation. Most patients with PEM and SCLC have high titers of anti-Hu antibodies in their serum and CSF, as do some patients with PEM associated with other types of cancer.[8,23] Antibodies to CV2/CRMP5, with or without anti-Hu antibodies, also occur at a lower frequency and most commonly are associated with thymoma.[21,24] A subset of patients with PEM and antibodies to CV2/CRMP5 also develop paraneoplastic chorea and uveitis.[25]

The onset of symptoms in PEM is subacute. Sensory neuropathy is the most common initial manifestation, followed by brainstem and limbic encephalopathy.[21,26,27] The progression of symptoms usually is relentless, or, less frequently, intermittent, until stabilization. Spontaneous improvement is rare but has been described in patients with limbic encephalitis.[28] For most patients the neurologic deficits are severe and incapacitating. Respiratory or autonomic failure due to neurologic dysfunction is commonly the cause of death.[26]

About one third of patients with PEM develop symptoms of cerebellar and/or brainstem dysfunction.[8,21,29] Motor weakness, muscle atrophy, and fasciculations are found in 20% of patients with PEM.[26] When spinal cord involvement predominates, a diagnosis of subacute motor neuron dysfunction or atypical motor neuron disease may be entertained until other areas of the nervous system become involved.[30,31] Autonomic dysfunction affects about 30% of patients. Symptoms include orthostatic hypotension, gastrointestinal paresis, and pseudo-obstruction.[32,33] Hypothermia, hypoventilation, sleep apnea, and cardiac arrhythmias may be the cause of sudden death in these patients.

About 75% of patients with anti-Hu-associated PEM develop an asymmetric pansensory neuropathy, called *paraneoplastic sensory neuronopathy* (PSN; see later discussion).[21,26] Often associated with painful dysesthesias, PSN results from inflammation of the dorsal root ganglia and neuronal degeneration. For patients in whom motor weakness and a sensory neuropathy develop subacutely, the initial diagnosis may be that of acute inflammatory polyneuritis (Guillain-Barré syndrome).[34]

Limbic Encephalitis

Symptoms of paraneoplastic limbic encephalitis may develop alone but more often are found in association with brainstem dysfunction, cerebellar symptoms, or PSN (see Paraneoplastic Encephalomyelitis).[26]

Box 51-1. DIAGNOSTIC STRATEGIES

The diagnosis of a paraneoplastic neurologic syndrome is relatively straightforward for patients who develop symptoms of a well-defined syndrome that typically is associated with cancer. The specificity of paraneoplastic antineuronal antibodies for paraneoplastic neurologic syndromes or some types of cancer makes them useful diagnostic tools. Therefore, in the right clinical context, the detection of a paraneoplastic antibody in the serum or cerebrospinal fluid (CSF) helps to establish the diagnosis and focus the search of the neoplasm. If the detected antibody usually does not associate with the patient's neurologic syndrome, other etiologies for the neurologic dysfunction should be considered. Similarly, if the detected cancer is not the histologic type typically found in association with the patient's antibody (e.g., anti-Yo with lung cancer rather than breast or ovarian cancer), the presence of a second neoplasm should be suspected. A search for another neoplasm definitely is indicated if the tumor cells do not express the target antigen of the paraneoplastic antibody. If paraneoplastic antibodies are present but a cancer is not discovered, the patient should be assumed to harbor an occult neoplasm unless proven otherwise. Whole-body positron emission tomographic scans may detect tumors that escape detection by other standard imaging methods. In patients with a history of cancer or who have recently gone into tumor remission, the development of a paraneoplastic neurologic syndrome frequently heralds tumor recurrence.

The diagnosis of paraneoplastic neurologic syndromes is more difficult in patients who develop less characteristic symptoms (e.g., brainstem dysfunction, myelopathy), especially if no antibodies are found in the serum or CSF. In this case and if other non-cancer-associated etiologies have been ruled out, analysis for serologic markers of cancer (e.g., carcinoembryonic antigen, CA-125, CA-15-3, prostate-specific antigen) may provide evidence for the presence of cancer. The CSF may show evidence of inflammation with pleocytosis, elevated protein concentration, intrathecal synthesis of immunoglobulin, and oligoclonal bands. Immunoelectrophoresis may disclose M-proteins in serum or urine, suggesting a plasma cell dyscrasia. A skeletal survey to rule out lytic or osteosclerotic myeloma should be considered for patients with peripheral neuropathy associated with a monoclonal gammopathy. CT of the chest is the study of choice to demonstrate a suspected lung cancer. Due to the common association of breast and gynecologic cancers with paraneoplastic disorders, mammogram and pelvic CT scan or ultrasound should be carried out in all women with a suspected paraneoplastic neurologic syndrome. Symptoms of limbic and brainstem encephalitis should cause men to be examined with testicular ultrasound and young women to be checked for an ovarian teratoma that may appear as a benign cyst. Whole-body PET scans are useful when other tests are negative. The best approach to treating paraneoplastic neurologic syndromes is to discover and treat the tumor promptly and provide supportive care for the neurologic deficits with symptomatic treatment and physical therapy.

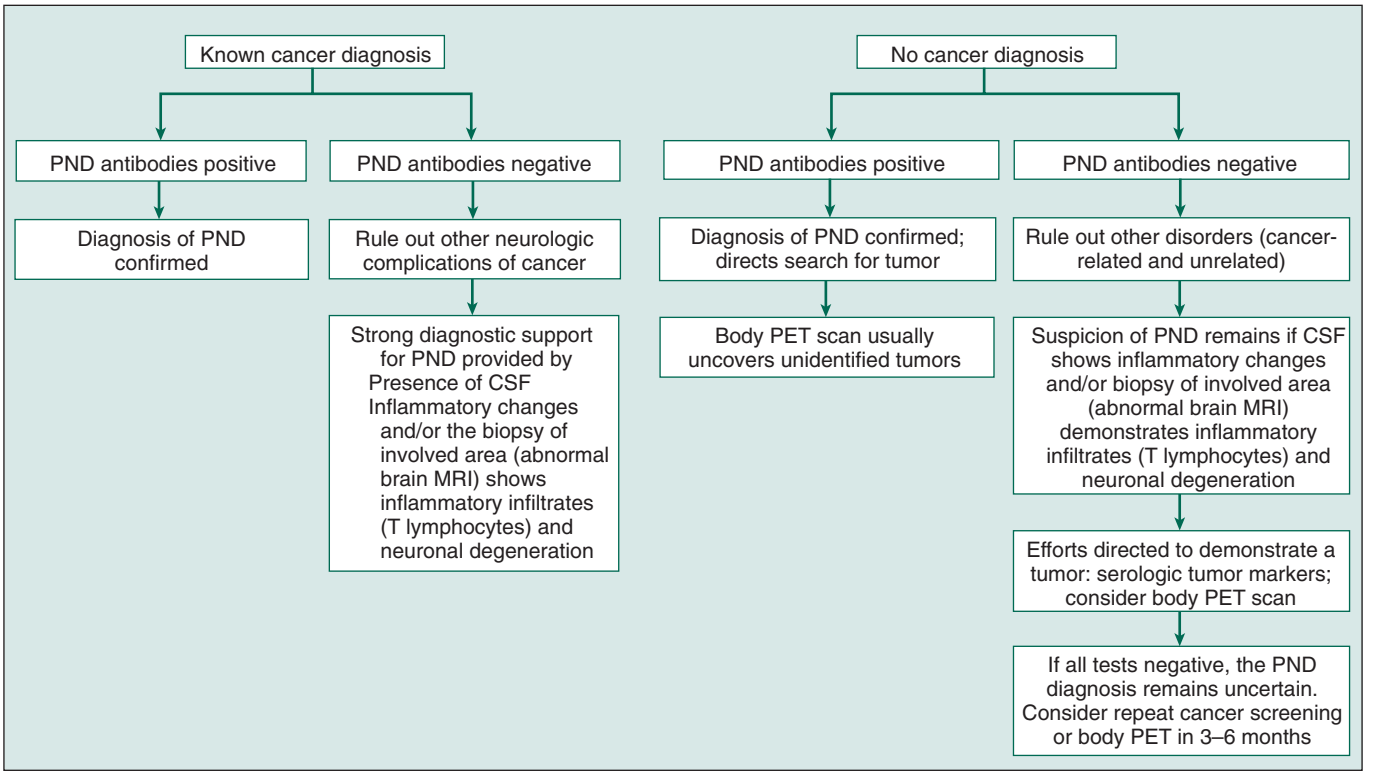


Figure 51-1 • Approach to the patient with a suspected paraneoplastic neurologic disorder (PND) of the central nervous system (CNS). CSF, cerebrospinal fluid; PET, positron emission tomography.

The most common underlying tumor is SCLC, followed by testicular cancer. Regardless of the tumor type, the neurologic dysfunction usually precedes the diagnosis of cancer.

The most characteristic finding is short-term memory deficits with relative preservation of other cognitive functions.[35,36] Memory deficits often become evident after several weeks of depression, personality changes, irritability, and seizures. Partial complex temporal lobe seizures with or without motor involvement of face and extremities are common. Some patients develop signs of diencephalic-hypothalamic dysfunction, including drowsiness, hyperthermia, hyperphagia, and, less frequently, pituitary hormonal deficits. The disorder may resemble a viral encephalitis or a rapidly developing dementia due to a primary neurodegenerative disorder.

Paraneoplastic limbic encephalitis is one of the few paraneoplastic neurologic disorders in which neuroimaging may be useful. Typical MRI findings include unilateral or bilateral mesial temporal lobe abnormalities best seen on T2-weighted and FLAIR images (Fig. 51-2).[28,37,38] On T1-weighted sequences, the temporal–limbic regions may be hypointense and sometimes may enhance with contrast injection. Patients with herpes simplex encephalitis may have similar MRI findings in the early stages of the disease. However, these patients usually develop prominent signs of edema and mass effect involving one or both inferomedial temporal lobes, inferior frontal lobes, and cingulate gyrus often associated with gyral enhancement and signs of hemorrhage.[39,40]

The major pathological findings are from the hippocampus, parahippocampal gyrus, cingular cortex, insular cortex, and diencephalon.[36] Almost all patients have mild abnormalities in other areas of the nervous system in a pattern of distribution resembling PEM, suggesting that paraneoplastic limbic encephalitis should be regarded as PEM with predominant involvement of the limbic structures.

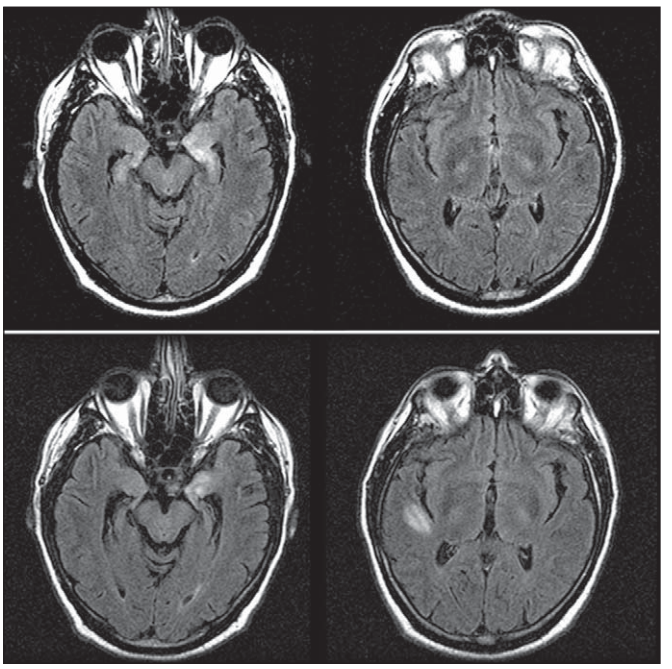


Figure 51-2 • MRI abnormalities in a patient with limbic encephalitis. Fluid-attenuated inversion recovery (FLAIR) sequences of two MRI studies of a patient with paraneoplastic limbic encephalitis associated with a papillary thyroid carcinoma that was confined to the thyroid gland. *Upper panels,* Bilateral hyperintensity of the medial aspect of the temporal lobes (hippocampi) is seen, with the left greater than the right. *Lower panels,* Another MRI obtained 6 months later shows atrophy of the hippocampi and new signal abnormality in the right posterior insular region. The patient had severe short-term memory loss that did not significantly change between the two MRI studies.

Antineuronal antibodies, when present in serum and cerebrospinal fluid (CSF), facilitate the diagnosis of PLE and often allow for early detection of the associated tumor. In patients with SCLC, the anti-Hu antibody is present in about 50% of cases with predominant or isolated symptoms of limbic encephalitis.[41] A few patients have been reported with limbic encephalitis and anti-CV2 antibodies. In these patients the underlying tumors are SCLC and thymoma.[42] Limbic encephalitis in association with antibodies to voltage-gated potassium channel antibodies is paraneoplastic in about 20% of patients; the most common cancers are thymoma and SCLC.[43]

Anti-Ma2 antibodies may be found in the serum and CSF of patients with limbic and/or brainstem encephalopathy. These patients usually have testicular cancer (either seminomatous or nonseminomatous germ cell tumors), but other tumors have been reported.[10] Patients with anti-Ma2 antibodies often have additional involvement of the hypothalamus and brainstem and are more likely to have abnormal MRI findings than are other patients with paraneoplastic limbic encephalitis.[44]

A paraneoplastic limbic encephalitis recently has been described in young women with ovarian teratoma (in one patient the tumor was a teratoma of the mediastinum). All patients had serum and CSF antibodies to the NR1/NR2 subunits of the NMDA receptor that are highly enriched in hippocampus. These patients often present with acute change in behavior and personality, with delusional thinking, paranoid thoughts, and aggressive behavior, and may be misdiagnosed with acute psychosis, or suspected malingering or drug abuse. Others can have a picture more typical of limbic encephalitis with short-term memory loss and seizures. Most will progress to decreased level of consciousness, with autonomic dysfunction and central hypoventilation, requiring prolonged ventilatory support.[14,45]

When limbic encephalitis is part of PEM or PSN, it usually responds poorly to treatment. Symptom stabilization or improvement may occur if the tumor is recognized and treated early.[10,22,46] A study of patients with SCLC and paraneoplastic limbic encephalitis suggested that the presence of anti-Hu antibodies was associated with a decreased likelihood of improvement.[41] In contrast, about 35% of patients with limbic encephalopathy associated with antibodies to Ma2 improve with immunotherapy and treatment of the tumor (most of these 35% have a testicular germ-cell tumor).[47] The encephalitis of patients with antibodies to NR1/NR2 subunits of the NMDA receptor and teratomas usually responds to removal of the tumor and corticosteroids, intravenous immunoglobulins (IVIg), or plasma exchange.[45]

Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) is characterized by the subacute development of rapidly progressive cerebellar dysfunction, which stabilizes after a few months, leaving the patient severely disabled.[48] Postmortem studies demonstrate near or total loss of Purkinje cells with relative preservation of other cerebellar neurons, and Bergmann astrogliosis (Fig. 51-3). Almost every type of tumor has been reported in association with PCD; the most common neoplasms are gynecologic tumors, breast and lung cancers, and lymphomas.[49,50] In about 60% of patients the neurologic symptoms precede detection of the tumor.

Presenting symptoms of PCD include dizziness, visual problems, nausea, vomiting, and dysarthria. Within days or even hours the patient develops ataxia of gait and of the extremities, usually accompanied by dysphagia. Some patients with PCD who have gynecologic or breast tumors have serum and CSF antibodies called anti-Yo that react with 34- and 62-kd proteins expressed by Purkinje cells and the underlying tumor.[51] Other patients develop PCD that is not associated with anti-Yo antibodies. Some of these patients have PCD in

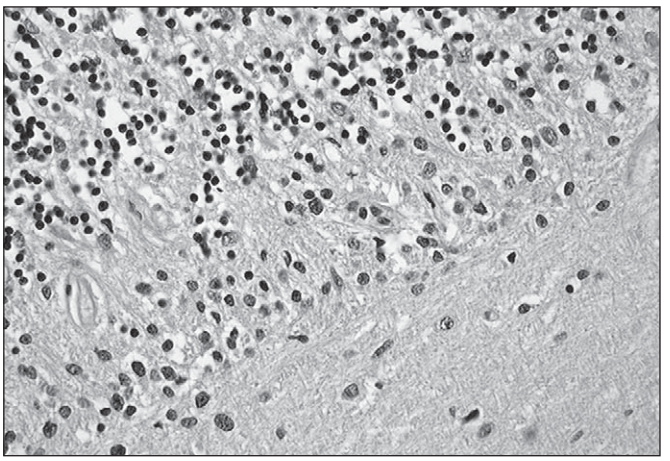


Figure 51-3 • Paraneoplastic cerebellar degeneration. Section of cerebellum from a patient with adenocarcinoma of the ovary and paraneoplastic cerebellar degeneration associated with anti-Yo antibodies. Note the Bergmann gliosis and the absence of Purkinje cells, which normally are located between the granular cell layer *(top left)* and the molecular cell layer *(bottom right).*

association with Hodgkin's disease, in which case an antibody called anti-Tr usually is found (Fig. 51-4).[52]

For patients with SCLC, PCD may develop in association with LEMS.[49,53] Because LEMS symptoms often are treatable, suspicion of LEMS should prompt an appropriate investigation with electrophysiologic testing or measurement of antibodies directed against P/Q type voltage gated calcium channels. Recent studies demonstrate that these antibodies also are present in some patients with SCLC and PCD without symptoms of LEMS.[4]

A distinctive clinical syndrome occurring predominantly in women is characterized by the subacute onset of ataxia and opsoclonus.[54] The ataxia predominates in the trunk, causing severe gait difficulty and frequent falls. In half of these patients the neurologic symptoms develop before the tumor is diagnosed. The tumor usually

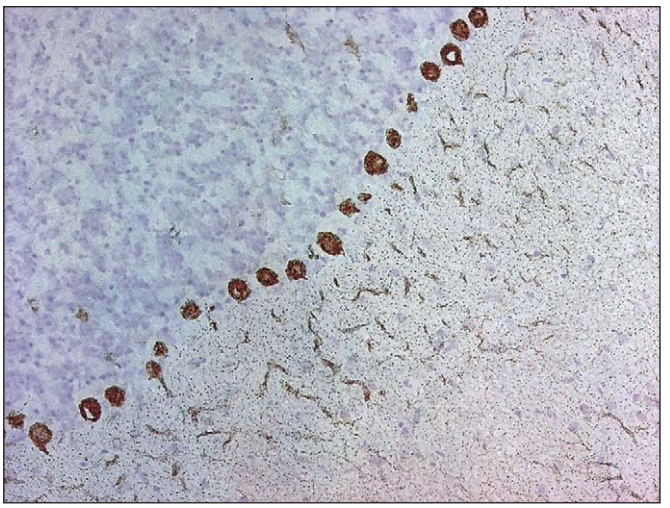


Figure 51-4 • Detection of an anticerebellar antibody (anti-Tr) in the serum of a patient with paraneoplastic cerebellar degeneration. A frozen section of rat cerebellum incubated with the serum of the patient shows a characteristic dot-like reactivity with the cytoplasm of Purkinje cells and molecular layer of the cerebellum. This antibody, known as anti-Tr, is a specific marker of paraneoplastic cerebellar degeneration associated with Hodgkin's lymphoma.

is a breast cancer or, less frequently, gynecologic cancers or SCLC. The serum and CSF of these patients contain an antibody called anti-Ri, which is expressed by neurons and the associated tumor.[54,55]

In patients with SCLC, the development of PCD may be the presenting symptom of PEM. In such cases, anti-Hu or anti-CV2/CRMP5 antibodies usually are present, and the patients eventually develop signs and symptoms of multifocal neurologic disease. Patients whose symptoms remain restricted to the cerebellum and who do not harbor anti-Hu antibodies may have antibodies to voltage-gated calcium channels.[56]

One subset of patients develop PCD in the setting of brainstem dysfunction. These patients have serum and spinal fluid antibodies against Ma1 and Ma2 proteins expressed in neurons and spermatogenic cells of testis. These patients have a variety of associated cancers, including those of the lung, breast, parotid, colon, and testis.[57]

Most patients with PCD do not improve, although there are isolated reports of improvement with treatment of the tumor, corticosteroids, IVIg, plasma exchange, rituximab, or cyclophosphamide.[58–60]

Motor Neuron Syndromes

The existence of paraneoplastic motor neuron dysfunction is based on reports of patients with typical amyotrophic lateral sclerosis (ALS) who improved after treatment of the underlying tumor, suggesting more than a coincidental relationship.[61,62] In patients with cancer and symptoms of motor neuron disease the most common neoplasms are carcinoma of the lung, breast, kidney, and lymphoma. For these patients, the neurologic syndrome and laboratory studies are similar to those seen in typical patients with ALS.

Patients with PEM may develop symptoms resembling motor neuron disease.[26,30] These patients almost always develop signs of involvement of other areas of the nervous system, which, along with the presence of the anti-Hu antibody, helps to rule out typical ALS.

Patients with Hodgkin's and non-Hodgkin's lymphoma may develop a subacute lower motor neuronopathy.[63] Typically, these patients have a subacute, progressive, painless, and asymmetric involvement of the extremities, with the legs more affected than the arms. In contrast to typical ALS, fasciculations are rare, bulbar muscles usually are spared, and upper motor neuron signs are absent. Examination of the CSF is normal or shows mildly increased proteins, and electrophysiologic studies demonstrate denervation with normal or mild slowing of motor nerve conduction velocities. Neurologic stabilization or spontaneous improvement may occur. Paraneoplastic subacute lower motor neuronopathy must be distinguished from the lower motor neuron dysfunction that patients may develop after radiation therapy of the spinal cord.[64]

Peripheral Nerve Hyperexcitability and Stiff-Man Syndrome

Peripheral nerve hyperexcitability (PNH) is characterized by muscle cramps, stiffness, myokymia, and delayed muscle relaxation (neuromyotonia) due to spontaneous and continuous muscle fiber activity of peripheral nerves. It often is found in association with a sensorimotor polyneuropathy and has been described most often in patients with thymoma and SCLC.[3,65] An autoimmune etiology for neuromyotonia is supported by the presence of serum antibodies that interfere with the function of voltage-gated potassium channels.[66] Electrophysiologic studies reveal large numbers of bizarre, high-frequency motor unit discharges during voluntary contraction that persist during relaxation, in contrast to patients with stiff-man syndrome (discussed in the following paragraph), who have continuous but relatively normal motor unit activity.[67] Treatment with phenytoin, carbamazepine or plasma exchange may be effective in some patients.

The stiff-man syndrome is an unusual disorder characterized by progressive muscle stiffness, aching, muscle spasms, and rigidity. The stiffness develops over a period of months and is most prominent in the paraspinal muscles and lower limbs. The muscle spasms are painful and are triggered by a variety of stimuli. They are severe enough to produce limb deformities and fractures.[68] There are no other associated neurologic abnormalities; the CSF may show oligoclonal bands, and increased IgG index and neuroradiologic studies are usually normal. The tumors most commonly involved include breast cancer, SCLC, thymoma, and Hodgkin's disease. A subset of patients with paraneoplastic stiff-man syndrome and breast cancer or SCLC have antibodies that react with amphiphysin, a neuronal synaptic protein.[68–70] When stiff-man syndrome occurs in patients who do not have cancer, the disorder is associated with antibodies against glutamic acid decarboxylase (GAD).[71–73] These patients usually develop diabetes and other endocrine deficits. Treatment of the tumor and use of corticosteroids may result in improvement. Patients with nonparaneoplastic stiff-man syndrome respond to IVIg, and this approach may be useful for patients with the cancer-associated syndrome.[74,75] Drugs that enhance GABA-ergic transmission (e.g., diazepam, baclofen, sodium valproate, tiagabine, vigabatrim) improve symptoms of most patients.

A rare disorder seen in patients with cancer is progressive encephalomyelitis with rigidity.[72,76] In this disorder, most often associated with SCLC, patients usually develop brainstem dysfunction, rigidity, and spinal myoclonus due to widespread dysfunction of the CNS. The cervical portion of the spinal cord is affected most commonly.[77]

Paraneoplastic Opsoclonus-Myoclonus

Opsoclonus is a disorder of ocular motility characterized by the presence of spontaneous, arrhythmic, large-amplitude conjugate saccades occurring in all directions of gaze without a saccadic interval.[78] In patients with cancer, opsoclonus can have a paraneoplastic origin, in which case it often is associated with myoclonus of head, trunk, or extremities (paraneoplastic opsoclonus-myoclonus). The differential diagnosis includes viral, toxic, metabolic, and vascular disorders.

In children, paraneoplastic opsoclonus-myoclonus is a well-known complication of neuroblastoma.[79,80] In half of the patients, the opsoclonus precedes diagnosis of the neuroblastoma, but it also may develop after tumor diagnosis, during remission, or at recurrence. The onset is subacute, with frequent fluctuations of symptoms; in some patients symptoms may resolve spontaneously. Treatment with corticosteroids, adrenocorticotropic hormone, plasma exchange, IVIg, or rituximab, or treatment of the tumor, results in improvement in one half to two thirds of patients.[81] Despite an initial response, about 60% of patients are left with permanent neurologic deficits, including language and cognitive dysfunction.[82]

Paraneoplastic opsoclonus-myoclonus also has been described in adult patients with cancer. Most have an underlying SCLC, although there are individual case reports associated with other tumors, including carcinoma of the uterus, fallopian tube, breast, bladder, thyroid, thymus, chondrosarcoma, and Hodgkin's disease.[78,83–85] A small number of women with breast cancer, anti-Ri antibodies, and opsoclonus have been reported.[54,86] Patients with anti-Ri antibodies often have other symptoms, suggesting a more diffuse involvement of the brainstem, whereas patients without anti-Ri antibodies tend to have limb or truncal myoclonus and encephalopathy.

Compared to the idiopathic form of opsoclonus-myoclonus, from which patients often recover, paraneoplastic opsoclonus-myoclonus in adults has a more severe clinical course, even when aggressively treated with IVIg or corticosteroids. For those patients who develop an associated encephalopathy, one series noted improved outcomes when the tumor (usually SCLC) was identified and treated promptly.[87] Currently, no immunologic markers have been found that identify most cases of adult or pediatric paraneoplastic opsoclonus-myoclonus. Recent studies have found a high incidence of autoimmune responses to a variety of neuronal autoantigens but did not identify a specific antibody marker.[88,89]

Paraneoplastic Syndromes of the Visual System

In patients with cancer, visual symptoms and blindness usually are related to metastatic infiltration of the optic nerves by tumor and neurotoxicity from chemo- and radiation therapy.[90–93] Paraneoplastic visual syndromes can result from retinopathy and optic neuritis. Paraneoplastic optic neuritis is very rare, and while it may develop in isolation, it usually is associated with PEM.[94] The onset is subacute with painless bilateral visual loss.[95,96]

The paraneoplastic retinopathies are a heterogeneous group of syndromes including CAR and MAR. These two syndromes have specific clinical, electrophysiologic, and pathological characteristics and distinct immunologic associations. Patients with cancer-associated retinopathy develop acute or subacute visual loss due to degeneration of the retinal photoreceptor or ganglion cells.[97,98] The onset usually is unilateral, but progresses to become bilateral over days or weeks. Initial symptoms include photosensitivity, light-induced glare, color vision deficits, intermittent visual obscurations, and central or ring-like scotomas. For most patients the underlying tumor is SCLC, but a few case reports have been associated with breast or gynecologic cancers. Visual symptoms usually precede diagnosis of the tumor. Visual evoked responses usually are normal, but electroretinograms demonstrate reduced or flat responses to photopic and scotopic stimuli, suggesting dysfunction of cones and rods. Examination of the CSF may reveal a mild pleocytosis; neuroimaging studies are normal.

The serum of some patients with CAR contains antibodies that react with antigens expressed by photoreceptors and ganglion cells. The most common antibody is against recoverin, a 23-kd photoreceptor calcium-binding protein,[99] and the presence of antirecoverin antibodies indicates that the associated tumor almost always is an SCLC.[100] These antibodies cause apoptotic retinal cell death, suggesting a direct pathogenic role.[101] Other antigens that are targets of immune responses in some patients include tubby-like protein 1 and the photoreceptor-specific nuclear receptor (PNR).[102,103] The role of the latter antibodies in the pathogenesis of the retinopathy is unknown, but it is of interest that mutations of the PNR gene have been identified in a cohort of patients with enhanced S-cone syndrome, a disorder of retinal cell fate that progresses to retinal degeneration.[104,105] This finding suggests a mechanism whereby antibodies interfere with autoantigen function, resulting in retinal cell death.

Melanoma-associated retinopathy has been described in patients with metastatic cutaneous melanoma. These patients present with acute visual loss, years or months after the diagnosis of the metastatic disease,[106,107] and have serum antibodies that target unidentified proteins localized in the bipolar cells of the retina.[108,109] The electroretinogram shows selective loss of the photopic "b" wave with relative preservation of the "a" and "d" wave forms. Intraocular injection of serum from patients with MAR reproduces the retinal abnormalities, demonstrating that the antibodies are pathogenic.[107]

For both CAR and MAR, the visual loss usually is irreversible. Treatment with immunosuppression, plasma exchange, or corticosteroids is mostly ineffective, but in rare cases may result in symptom stabilization.[110,111]

PARANEOPLASTIC SYNDROMES OF THE PERIPHERAL NERVOUS SYSTEM

Paraneoplastic Sensory Neuronopathy

Paraneoplastic sensory neuronopathy (PSN) resulting from dorsal root ganglia dysfunction may develop in isolation but most often is

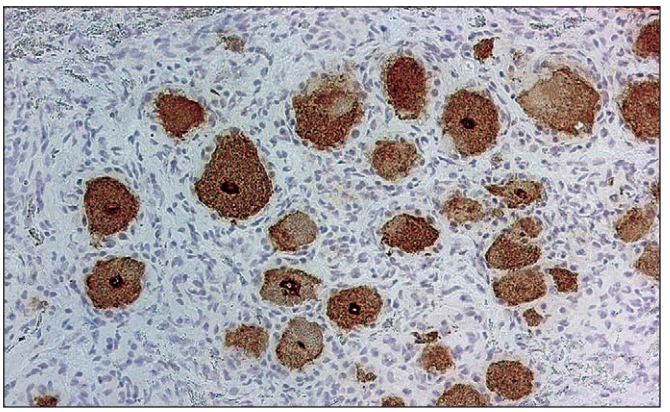


Figure 51-5 • Detection of an antineuronal antibody (anti-Hu) in the serum of a patient with paraneoplastic sensory neuronopathy. A frozen section of rat dorsal root ganglion incubated with the serum of the patient shows intense immunolabeling of the neurons, with reactivity predominantly involving the nuclei. This antibody, known as anti-Hu, usually is associated with paraneoplastic sensory neuronopathy (or dorsal-root ganglionitis) and encephalomyelitis. Patients with anti-Hu antibodies usually harbor a small cell lung cancer.

a fragment of PEM.[26] Patients typically develop asymmetric pain and paresthesias that can mimic radiculopathy or multineuropathy.[112] Symptoms usually progress over weeks or months to involve other extremities and, sometimes, the trunk.[26] Cranial nerves may be affected, resulting in loss of taste, facial numbness, and sensorineural deafness. Eventually, there is severe involvement of all modalities of sensation, resulting in pseudo-athetotic movements of the hands, a debilitating sensory gait ataxia, and neuropathic pain that are difficult to control.

In more than 80% of patients with PSN the associated tumor is SCLC. Sensory symptoms usually precede diagnosis of the tumor. Electrophysiologic studies confirm the isolated or predominant involvement of the sensory nerves, but in some patients the motor conduction velocities may be affected.[113] These patients had evidence of both demyelination and axonal degeneration in association with loss of neurons in the dorsal root ganglia, and circulating anti-CV2/CRMP5 antibodies in association with anti-Hu antibodies.

Patients who develop PSN as a component of PEM often have anti-Hu antibodies, and the associated cancer almost always is an SCLC (Fig. 51-5).[21,26] In patients with PSN without anti-Hu antibodies, associated cancers include SCLC, non-SCLC lung tumors, and breast cancer. Except for the detection of anti-Hu antibodies in patients with SCLC, laboratory studies of patients with PSN are nonrevealing. The CSF may show increased proteins and a mononuclear pleocytosis.

There is no specific treatment for PSN. Studies have suggested that patients with PSN associated with SCLC and anti-Hu antibodies whose tumors responded to therapy were more likely to have stabilization of improvement of the PSN compared with those whose tumors were not treated or did not respond to treatment.[21,22] Some patients may have partial improvement with corticosteroids. The effects of IVIg, cyclophosphamide, and rituximab are unclear.[60,114,115]

Sensorimotor Neuropathies

Many patients with cancer, particularly those with advanced disease and significant weight loss, develop signs and symptoms of peripheral neuropathy. In most patients, an identifiable cause such as a nutritional deficit, hepatic or renal failure, the use of chemotherapeutic agents, or leptomeningeal metastases can be found. Mononeuropathies and plexopathies in patients with cancer most often are secondary to compression of nerves by tumor or hemorrhage and infarction secondary to leukemic infiltration.[116,117] A paraneoplastic brachial neuritis may occur with increased frequency in patients with Hodgkin's disease.[118,119] The clinical presentation is similar to that of brachial neuritis observed in patients without cancer, with the initial pain complaints followed by the development of paresthesias and weakness.

A subacute or chronic sensorimotor neuropathy may occur with any malignancy but most commonly is associated with lung cancers.[116,120] The onset usually follows the cancer diagnosis but may precede it by several months or years. Lower extremities are predominantly involved, with symptoms spreading proximally over the course of the disease with rare involvement of cranial nerves. Weakness occurs late, and most patients have slowly progressive disease.

An acute rapidly progressive sensorimotor polyneuropathy can be seen in association with Hodgkin's lymphoma.[121] The syndrome is clinically indistinguishable from Guillain-Barré syndrome (GBS). A similar syndrome also has been reported in patients with solid tumors. Treatment is the same as for patients with idiopathic GBS and includes plasma exchange and IVIg. There is evidence, however, that cancer-associated GBS has a worse outcome than GBS alone.[122]

Approximately 10% of patients with multiple myeloma will develop a clinically significant neuropathy. The neuropathy, most often sensorimotor, commonly precedes diagnosis of the myeloma and is slowly progressive.[123] Treatment of the myeloma usually does not alter the course of the neuropathy. Other causes of peripheral nerve or nerve root involvement include deposits of amyloid and root compression by spine metastases.

Osteosclerotic myeloma represents about 3% of all cases of myeloma. More than 50% of patients with osteosclerotic myeloma develop a predominantly motor paraneoplastic peripheral neuropathy, which often is the initial presentation of the myeloma.[124] The clinical picture is similar to that of chronic inflammatory demyelinating polyneuropathy.[125] Resection or radiation of the sclerotic lesions, or chemotherapy, often results in neurologic improvement.[123]

Ten percent of patients with Waldenström's macroglobulinemia develop a peripheral neuropathy with predominant sensory involvement. In some, the monoclonal IgM has activity against myelin-associated glycoprotein or gangliosides.[126]

The POEMS syndrome (*p*olyneuropathy, *o*rganomegaly, *e*ndocrinopathy, *m*onoclonal proteinemia, and *s*kin changes) is a rare disorder that can develop in association with all forms of myeloma but is seen predominantly with osteosclerotic myeloma.[125,127,128] Patients develop a severe, symmetric, sensorimotor neuropathy that is associated with muscle atrophy.

Castleman's disease is a rare disorder that overlaps with POEMS. Patients commonly develop neuropathies, including a painful sensorimotor neuropathy, a chronic relapsing sensorimotor neuropathy, and a predominantly motor neuropathy.[129] Treatment of the Castleman's disease along with plasma exchange or immunosuppression may result in improvement of the neuropathy.[130]

Vasculitic Neuropathy

Paraneoplastic vasculitis may be systemic or confined to nerve and muscle. When systemic, the small vessels of the skin commonly are affected, and the most commonly associated tumors are lymphomas and leukemias.[131,132] A paraneoplastic microvasculitis of the muscle and nerve without systemic vasculitis has been reported in older patients with solid tumors, particularly carcinoma of the prostate, kidney, lung, endometrium, and lymphoma.[133] These patients develop symptoms of symmetric or asymmetric painful sensorimotor neuropathy. As a result of the muscle vasculitis, patients can develop proximal muscle weakness. The diagnosis is suggested by the presence of elevated proteins in CSF and an elevated erythrocyte sedimentation rate and is confirmed by biopsy of nerve and muscle. This disorder may respond to corticosteroids and cyclophosphamide or other types of immunosuppression.

Autonomic Neuropathy

Paraneoplastic autonomic neuropathy usually occurs as a component of other disorders, such as LEMS and PEM, but it may occur rarely as the predominant symptom.[26] Patients with paraneoplastic autonomic neuropathy can develop several life-threatening complications, such as gastrointestinal paresis with pseudo-obstruction, cardiac dysrhythmias, and postural hypotension. Additional symptoms include dry mouth, erectile dysfunction, anhidrosis, and sphincter dysfunction. Paraneoplastic autonomic neuropathy has been reported in association with several tumors, including SCLC, cancer of the pancreas, cancer of the testis, carcinoid tumors, and lymphoma. When the autonomic dysfunction is a component of PEM, serum anti-Hu and anti-CV2/CRMP5 antibodies may be positive. Serum antibodies to ganglionic acetylcholine receptors have been reported, but they also may occur without a cancer association.[134]

PARANEOPLASTIC SYNDROMES OF THE NEUROMUSCULAR JUNCTION

Myasthenia Gravis

Myasthenia gravis (MG) results from an immune response directed against the acetylcholine receptor at the neuromuscular junction. Thymic abnormalities are reported to occur in approximately 75% of patients with MG. Of these, 15% have microscopic or gross evidence of thymoma, and 85% have evidence of thymic hyperplasia. Patients develop weakness of the extremities and the ocular and bulbar muscles; a few patients have pure ocular involvement.[2,135] The most common presenting signs are ptosis and intermittent diplopia. Proximal muscles tend to be more affected than distal muscles, and muscle atrophy is rare. Deep tendon reflexes are preserved. Pain usually is not reported, although some patients complain of paresthesias. Aspiration secondary to dysphagia and ventilatory paralysis secondary to respiratory muscle involvement may be causes of death.[136]

The initial approach to treatment should be directed at the underlying tumor. Additional therapeutic strategies, including symptomatic treatment (i.e., anticholinesterase drugs), immunomodulation (e.g., plasma exchange, IVIg), and immunosuppression (e.g., corticosteroids, azathioprine) are similar for patients with and without cancer.

Lambert-Eaton Myasthenic Syndrome

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of the neuromuscular junction in which the presence of autoantibodies against P/Q type voltage-gated calcium channels results in a defect in the presynaptic quantal release of acetylcholine.[137–139] Approximately 60% of patients with LEMS have an associated SCLC.[16] In most patients (70%), the neurologic symptoms develop before the tumor diagnosis is made; in 25% of patients the symptoms develop at the same time the tumor is diagnosed.[140]

Patients present with lower extremity weakness, increased fatigability, and difficulties walking, rising from a chair, or climbing stairs. Some patients report a brief increase in muscle strength following a period of activity. Nerve conduction studies show a very-low-amplitude compound muscle action potential that increases progressively (>200%) in response to fast rates (20–50 Hz) of repetitive stimulation or after a short period of maximum voluntary contraction (Fig. 51-6). Detection of antibodies against the P/Q type voltage gated calcium channel currently is used as a serologic test for LEMS.[138]

At least 50% of patients have evidence of autonomic dysfunction, such as dry mouth, impotence, constipation, or impaired sweating.[16,141,142] Mild and usually transient cranial nerve dysfunction occurs in most patients.[143] Although rare, respiratory muscle weakness may occur, even to the point of requiring assisted ventilation. In contrast to MG, where the deep tendon reflexes usually are spared, in LEMS they are reduced or absent, especially in the lower extremities. In some patients, LEMS may develop in association with PCD or PEM.[4,49]

When LEMS is associated with cancer, most patients will have neurologic improvement with combined cancer treatment and therapy directed to LEMS. The latter includes medications that increase the presynaptic release of acetylcholine and immunomodulation. The use of 3,4-diaminopyridine results in moderate to marked neurologic improvement in 80% of patients.[144] If 3,4-diaminopyridine is not available, a combination of pyridostigmine and guanidine may be beneficial.[145] Plasma exchange and IVIg are useful for treating patients with severe weakness.[146] Neurologic improvement occurs within days or weeks but is transient. For patients who are refractory to these treatments, long-term immunosuppression with prednisone or azathioprine may be effective. Patients whose neurologic symptoms relapse should be evaluated for tumor recurrence.

PARANEOPLASTIC MYOPATHIC SYNDROMES

Polymyositis–Dermatomyositis

About 9% of patients with polymyositis develop cancer. Since the neoplasm often is diagnosed several years before or after diagnosis of the polymyositis, this may represent a coincidental occurrence and casts doubt on the role of cancer in the pathogenesis of the neurologic disorder.[17] In contrast, 15% of patients with dermatomyositis develop cancer, and in most patients the tumor is diagnosed by the time the myopathic symptoms develop.[17] Cancer of the breast, lung, ovary, and stomach are the most commonly associated tumors.

Clinical symptoms are similar for patients with and without cancer.[147] Patients with dermatomyositis may present with a reddish or purplish skin rash that often precedes the onset of proximal muscle weakness. Serum creatine kinase levels usually, but not always, are elevated. Respiratory muscle weakness may lead to ventilatory failure and contribute to death. Other symptoms include arthralgias and muscle contractures, myocardial inflammation leading to congestive

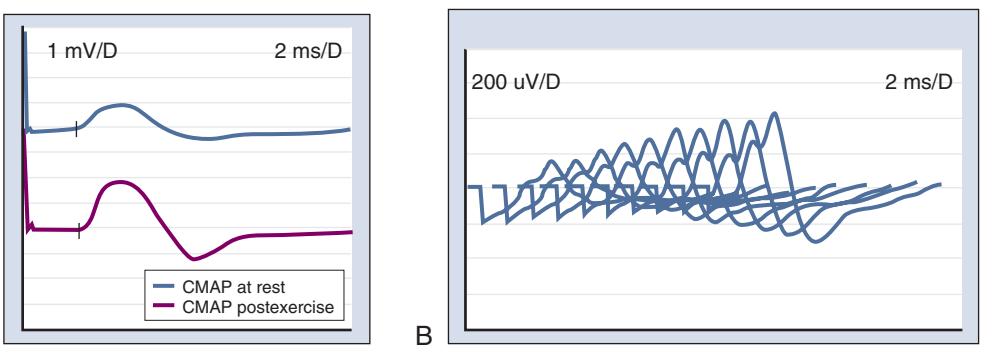


Figure 51-6 • Electrophysiologic study of a patient with small cell lung cancer and the Lambert-Eaton myasthenic syndrome. **A,** Facilitation of the compound motor action potential (CMAP) after 10 seconds of maximal voluntary contraction. **B,** Progressive increase of the CMAP amplitude with high-frequency repetitive stimulation. These are the classic electrophysiologic findings in patients with LEMS.

heart failure, and interstitial lung disease.[148] Reflexes and sensory examination usually are normal.

Several autoantibodies have been identified in patients with polymyositis and dermatomyositis. Jo-1 antibodies are identified in a group of patients with either disorder and are associated with interstitial lung disease.[149,150] Antinuclear antibodies typical of other connective tissue diseases also can be detected.[151] There are no specific markers indicative of the paraneoplastic origin of dermatomyositis. Dermatomyositis and polymyositis usually respond to corticosteroids and other types of immunosuppression (e.g., azathioprine). High-dose IVIg has proved to be effective for dermatomyositis.

Acute Necrotizing Myopathy

Acute necrotizing myopathy has been described in patients with cancer of the lung, bladder, breast, and gastrointestinal tract.[152] Patients present with symmetric weakness of the extremities associated with pain and a marked increase of serum muscle enzymes. Symptoms rapidly progress to involve pharyngeal and respiratory muscles, often resulting in death. The electrophysiologic studies are consistent with myopathy, and pathology studies demonstrate extensive muscle necrosis with little or no inflammatory infiltrates. It has been suggested that acute necrotizing myopathy represents a severe and more rapid form of polymyositis, but this remains unproven.[153]

Treatment and Prognosis

In general, paraneoplastic syndromes of the CNS have a subacute, progressive course that results in severe deficits or death in weeks or months.[26,51] Spontaneous improvement has been observed in some patients with opsoclonus-myoclonus, mostly children with neuroblastoma,[154] or patients with PCD associated with Hodgkin's disease,[52,155] subacute motor neuronopathy,[63] and sensorimotor neuropathies, which usually fulfill the criteria of acute or chronic GBS.[121,156,157] Progression to severe disability is seen less often in the neuromuscular disorders that develop after the diagnosis of the tumor, such as some sensorimotor neuropathies. A few patients with anti-Hu-associated sensory neuronopathy, and patients with PCD, particularly those without anti-Yo antibodies, may have a mild, indolent clinical course or even stabilize with only moderate neurologic deficits.[49,158] A classification of the paraneoplastic neurologic disorders by expected treatment response is given in Table 51-2.

Improvement of neurologic symptoms after tumor treatment has been reported for almost all the paraneoplastic syndromes.[159] However, the actual impact of antineoplastic therapy on the paraneoplastic symptoms is difficult to assess. This is due, in part, to the low incidence of neurologic paraneoplastic syndromes and the lack of effective treatment for some neoplasms. The rapid and apparently irreversible neuronal damage that is characteristic of many paraneoplastic symptoms may allow potentially effective treatments to arrest, but not reverse, the neurologic symptoms. Despite these limitations in assessment, some patients with limbic encephalitis have neurologic improvement, which appears to relate to tumor treatment. In particular, limbic encephalitis in young men with anti-Ma2 antibodies and germ cell tumors and young women with anti-NR1/NR2 antibodies and teratomas improves with treatment of the tumor and immunotherapies.[28,45]

For those paraneoplastic disorders of the peripheral nervous system associated with pathogenic antibodies (e.g., MG, LEMS, neuromyotonia), removal of the antibodies,[160] treatment of the tumor (removing the source of antigen), or immunosuppression often is effective.[161] For other paraneoplastic disorders, the symptoms sometimes evolve independently of the course of the tumor. An exception is osteosclerotic myeloma, in which treatment of the myeloma can result in dramatic improvement of an associated sensorimotor neuropathy.[162–164] Immunosuppressive treatments including corticosteroids, IVIg, and plasma exchange have been used in paraneoplastic syndromes that appear to result from immune-mediated mechanisms.[159,165] These include demyelinating sensorimotor neuropathies, vasculitic neuropathy,[166] and dermatomyositis.[167,168] In these disorders, clinical improvement can be expected after treatment, because the area of the nervous system involved is not irreversibly damaged. Large series examining plasma exchange and IVIg in paraneoplastic disorders of the CNS have not shown any significant benefit.[169,170] There are, however, individual case reports of improvements.[87,171–173]

Table 51-2 Treatment Response of Paraneoplastic Neurologic Disorders

Disorder	Treatment
DISORDERS THAT USUALLY RESPOND TO TREATMENT	
Myasthenia gravis	Tumor, plasmapheresis, IVIg, immunosuppression
Lambert-Eaton myasthenic syndrome	Tumor, plasmapheresis, IVIg, 3,4-diaminopyridine
Dermatomyositis	Corticosteroids, IVIg, immunosuppression
Opsoclonus/myoclonus (pediatric)	Tumor, corticosteroids, ACTH
Limbic encephalitis with anti-Ma2 antibodies and testicular tumors	Tumor, corticosteroids, IVIg
Encephalitis with anti-NMDAR antibodies and ovarian teratoma	Tumor, corticosteroids, plasmapheresis, IVIg, cyclophosphamide
Carcinoid myopathy	Tumor, cyproheptadine
Neuropathy (osteosclerotic myeloma)	Tumor, radiation
DISORDERS THAT MAY RESPOND TO TREATMENT	
Vasculitis (nerve/muscle)	Corticosteroids
Opsoclonus/myoclonus (adults)	Tumor, corticosteroids, protein A column, clonazepam, diazepam, baclofen
PCD (Hodgkin's disease)	Tumor
Opsoclonus/ataxia (anti-Ri associated)	Corticosteroids, plasmapheresis
Guillain-Barré (Hodgkin's disease)	Tumor, plasmapheresis, IVIg
Stiff-man syndrome	Tumor, corticosteroids, diazepam, baclofen, IVIg
Neuromyotonia	Plasmapheresis

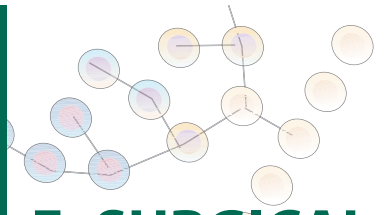
ACTH, adrenocorticotropic hormone; IVIg, intravenous immunogbbulin; NMDAR, N-methyl D-aspartate receptor; PCD, paraneoplastic cerebellar degeneration.

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E. SURGICAL PROBLEMS

52 Establishing and Maintaining Vascular Access

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SUMMARY OF KEY POINTS

- More than 750,000 vascular access devices are used in the United States each year.
- Placing the catheter tip in the superior vena cava or inferior vena cava provides large lumen and high flow.
- Types of central access systems are traditional central line for short-term use, tunneled central lines for long-term use, surgically implanted infusion ports, and peripherally inserted central catheters (PICC lines).
- Three questions to ask in selecting a catheter system are: (1) What device best meets the patient's therapy needs? (2) How is the device most safely inserted and maintained? (3) What are the likely immediate and long-term complication risks?
- Vascular access devices can be placed using a number of anatomic sites to access the superior vena cava or inferior vena cava: subclavian vein, internal jugular vein, external jugular vein, and femoral vein.
- Insertion can occur via Seldinger technique (closed) or by operative exposure of vein (open) technique.
- Complications include vascular laceration, arterial puncture, pneumothorax (2%), hemothorax, and air embolus (overall placement complications should be <5%).
- Long-term complications include catheter exit site or tract infection, catheter-associated sepsis, cardiac arrhythmias, catheter colonization, catheter thrombus (~30%), fibrin sheath, extravasation, occluded catheter, and shearing of catheter.
- Factors that increase the risk of catheter-associated infection include prolonged duration of indwelling time, multiple-lumen catheters, femoral or internal jugular vein locations, non-catheter-related bacteremia (neutropenic patient), number of times the system is accessed, difficult catheter placement, and poor technique in catheter or port-site care.

INTRODUCTION

During the course of disease, many patients with cancer require intravenous chemotherapy, frequent blood sampling, transfusion of blood products, or total parenteral nutrition. Many of these intravenously administered therapies—especially chemotherapies—are inflammatory to small peripheral veins. Over the past three decades, techniques for obtaining and maintaining central vascular access have been developed and refined. Managing the treatment of patients with cancer requires a thorough familiarity with the special use of vascular access devices. This chapter provides a review of the pros and cons of various devices, insertion methods, and catheter maintenance techniques.

Although it would be ideal to base vascular access decisions on solid clinical information, few randomized controlled trials have examined the clinical controversies that are involved with chronic vascular access for the patient with cancer. In addition, many of the larger studies regarding central vascular access were performed in the inpatient intensive care unit (ICU) setting. Comparing ICU patients with patients with cancer who receive chemotherapy or weekly blood draws on an outpatient basis could lead to inaccurate conclusions. It is important, however, to review the available randomized trials, a number of carefully performed retrospective analyses, and pertinent ICU literature to address some of the questions concerning vascular access for the patient with cancer.

When managing a patient who requires vascular access for treatment of a malignancy, there are three important questions: (1) What device will best meet this patient's therapeutic needs? (2) How can we most safely insert and maintain central venous access? (3) What are the immediate and delayed complications of vascular access procedures that are unique to the oncology patient population?

CHOOSING THE RIGHT DEVICE

Clinical oncologists use the vascular access devices that are discussed in this chapter to aspirate blood and centrally infuse agents into central veins, such as the superior vena cava (SVC) or the inferior vena cava. Many chemotherapeutics and parenteral nutrition formulations act as vesicants to the venous intima, causing inflammation and thrombosis of smaller veins. By infusing this type of product into the higher-flow, less thrombogenic cardinal veins, the durability and safety of vascular access can be extended, and patient comfort can be enhanced significantly.

Percutaneous Central Lines

Traditional central lines are placed by using the Seldinger technique, which is described in detail later in this chapter. The subclavian vein, internal jugular vein, or femoral vein is cannulated percutaneously, and the catheter is placed by using guide-wire assistance. There is a very short distance between the skin and the catheter's entry point into the vein. Theoretically, this proximity to skin flora increases the risk of subsequent central line infection.

These central lines are in common use throughout most hospitals for oncology patients, for critically ill patients who require central access, or for any patients who require infusions that are poorly

tolerated via peripheral intravenous access. Such central lines provide excellent short-term access to the central venous system. In general, percutaneous central lines are considered only for short-term use, and after the first 7 to 10 days, percutaneous central lines have a markedly higher incidence of infection despite optimal skin entrance site dressing techniques. Obviously, prolonged patient neutropenia and episodes of bacteremia could result in shorter life spans of such catheters.

Patients could benefit from these traditional central venous catheters if the patients require a relatively short course of infusion or need a bridge to placement of a more long-term catheter. Meticulous sterile dressing changes are an absolute necessity for outpatients who need short-term therapy via these lines. Patients without the resources or dexterity to care for percutaneous central lines are at a prohibitively increased risk of line infection, bacteremia, or thrombotic event and should be provided with a long-term form of central access. Certain comorbid conditions (e.g., burns, open wounds near the line site, or tracheostomy) preclude placement of this type of vascular access.

Surgically Tunneled Central Lines

Most oncology patients need a long-term form of central venous access rather than a traditional central line. Surgically tunneled central lines were developed to increase the distance between the skin entrance site and the puncture of the vein. The hypothesis was that by increasing this distance, the life span of the central access would be increased by decreasing the incidence of infection and thrombosis. Tunneled central lines are commonly referred to by the name of the first brand marketed, Hickman. Other examples include Broviac, Quinton, and Groshong (Fig. 52-1). These polymeric silicone rubber venous access catheters are placed via a subcutaneous tunnel that is described in detail later in this chapter. Clinical studies have supported the hypothesis that increasing the distance between the catheter exit site in the skin and the hole in the vein decreases the incidence of externally derived infection.[1,2] Studies suggest that the incidence of bloodstream infections associated with tunneled catheters is approximately 1 to 2 per 1000 catheter days.[3] The frequency of bacteremia among nontunneled catheters has been reported at between 1.0 and 13.0 per 1000 catheter days.[4]

A Dacron cuff 3 to 4 cm from the exit site encourages scar formation to fix the catheter in place. This exaggerated scarring eliminates the need for long-term sutures holding the catheter in place to the skin. Avoiding these fixation sutures can decrease the incidence of stitch reactivity and associated localized skin infections. One drawback of this type of central access device is the inconvenience of placing and removing the lines. In most instances, surgeons insert these lines in the operating room under local anesthetic and intravenous sedation. Therefore, these procedures require coordination of the patient, the surgeon, the anesthesia staff, and the operating room staff. They are also more uncomfortable to remove than are nontunneled lines owing to the Dacron cuff scar reaction. Removal requires intravenous sedation and local anesthesia but can be accomplished outside of the operating room.

Surgically Implanted Infusion Ports

Implantable ports consist of a small injection reservoir with a self-sealing membrane; they are placed entirely beneath the skin. There is no external catheter. An internal catheter runs from the reservoir into the subclavian or internal jugular vein to provide central access. The internal catheter is essentially identical to those used for tunneled central lines. A noncoring (Huber) needle can pass directly through the skin into the reservoir for infusion or aspiration.[5] The self-sealing rubber cap on the reservoir prevents leakage from the reservoir after withdrawal of the Huber needle. The gauge of the noncoring needle—not the catheter—typically limits flow through the port system (Fig. 52-2). The ports can also be used for continuous drug infusion, as shown in Figure 52-3.

The theoretical concern that bacteria more easily traverse the short distance between the skin and the "neo-vein" or reservoir and cause increased rates of infection does not prove true.[6–11] Sterile technique and site care lead to an infection risk comparable to that of tunneled catheters. With adequate care, the rate of infection could be fourfold to fivefold less than that for tunneled catheters.[3] The low rates of infection and extravasation make infusion ports ideally suited for patients with cancer who need long-term single-lumen access and a low-maintenance catheter. Experience has shown, however, that patients with prolonged periods of neutropenia or significant risk of cutaneous eruptions might not be good candidates for port devices. The visible lump of the port could bother extremely thin patients; however, the port is hidden from plain view in most people.

Long-Line Central Access

Also known as a peripherally inserted central catheter (PICC line), this vascular access device is becoming increasingly popular. The catheter is inserted into a brachial, cephalic, or antecubital vein and advanced into the subclavian vein or higher. Successful placement

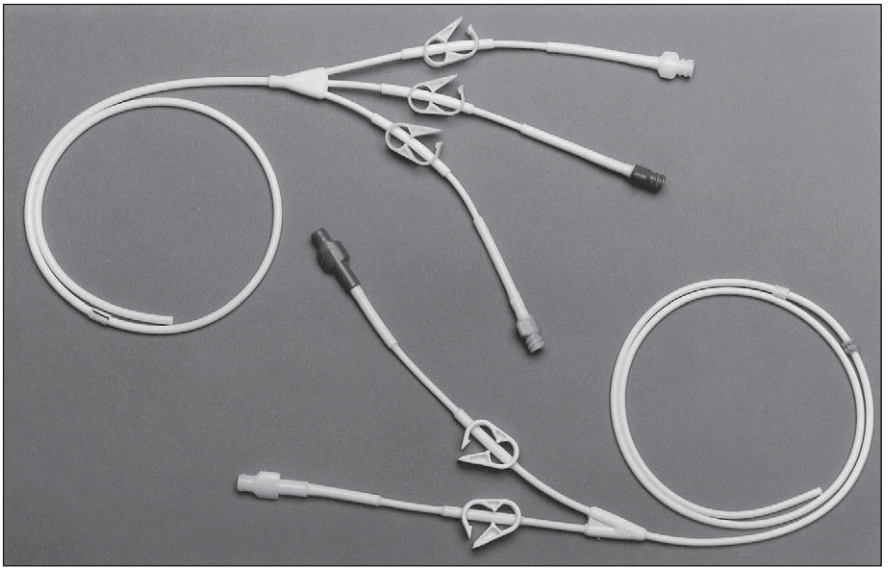
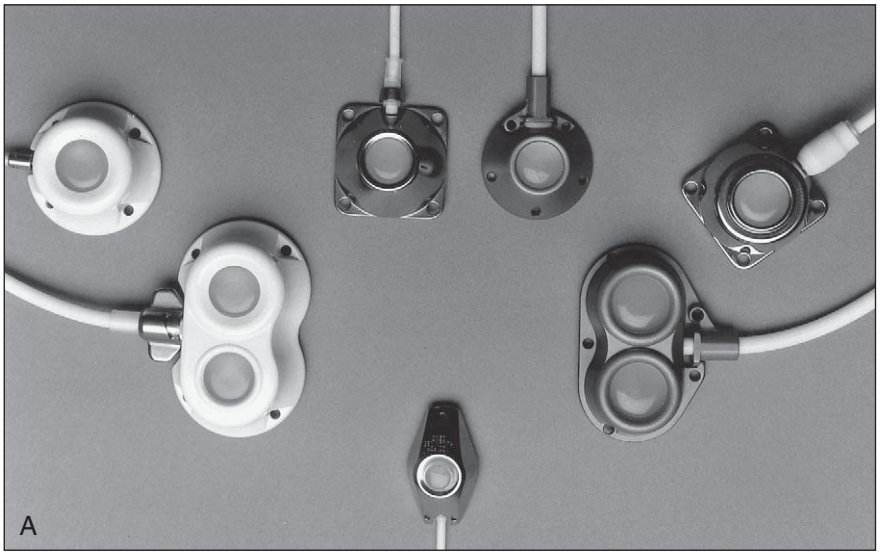


Figure 52-1 • Examples of standard double- and triple-lumen Hickman catheters. The double-lumen catheter has both the standard Dacron cuff and an additional antibacterial barrier cuff.



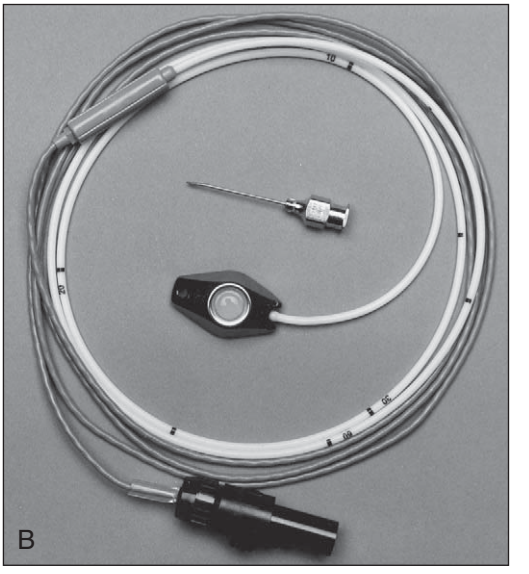


Figure 52-2 • **A,** Examples of implantable infusion devices: Low-profile titanium ports (*top center*), peripheral access port used in the arm (*bottom center*), single and dual polysulfone-titanium ports (*left*), single- and double-lumen standard profile ports (*right*). **B,** Peripheral access catheter for placement of a small port in the forearm. This system utilizes a fluoro-free thermosensor (gray wire) initially inside the white silicon catheter. An external wand over the chest determines the site of catheter top placement.

rates of 75% might be improved by the addition of ultrasound guidance.[12–14] These lines can be placed simply and easily in the outpatient office setting and are well tolerated by patients, with minimal risk. Many oncology patients have poor arm veins after multiple peripheral infusions and are therefore poor candidates for this technique. The 50% risk of catheter-related thrombosis is the greatest drawback to more widespread use of PICC lines in oncology patients. This problem is secondary to the presence of a long length of catheter within the vein and to the catheter tip in the relatively low flow subclavian vein. Advancing the catheter tip into the SVC can reduce the incidence of thrombosis by more than half.[15] Accurate placement of the catheter tip in the SVC can be complicated by the large displacement of the catheter tip (up to 8 cm) with normal arm range of motion.[16]

INSERTING VASCULAR ACCESS DEVICES

Providing patients who are undergoing treatment for cancer with appropriate vascular access requires not only a thorough knowledge of available devices but also technical expertise in the procedures for placing these catheters. Although these procedures are sometimes viewed as routine, the risks of poor technique can be devastating for the patient. Before undertaking the procedure, one should carefully consider everything from choosing the site of insertion to selecting the dressing to be used at the end of the procedure (Table 52-1).

Choosing Insertion Location

Vascular access devices can be placed by using a number of different access points, including the internal jugular, subclavian, external jugular, and femoral veins. The vast majority of catheters that are used for long-term vascular access in patients with cancer are placed in the internal jugular and subclavian veins. We will limit this discussion to these most common access sites.

The most frequent site for insertion of vascular access devices in the oncology population is the subclavian vein. Clavicular fracture or previous median sternotomy can alter the anatomy of this location. For a patient with such a history, an alternative site should be considered. Even for patients with standard venous anatomy, the acute angle at the confluence of the subclavian and internal jugular veins at the brachiocephalic vein can complicate the passing of the guide wire into the SVC. There is a higher incidence of pneumothorax, hemothorax, and catheter malposition among inexperienced operators, and there is a higher incidence of vein stenosis with

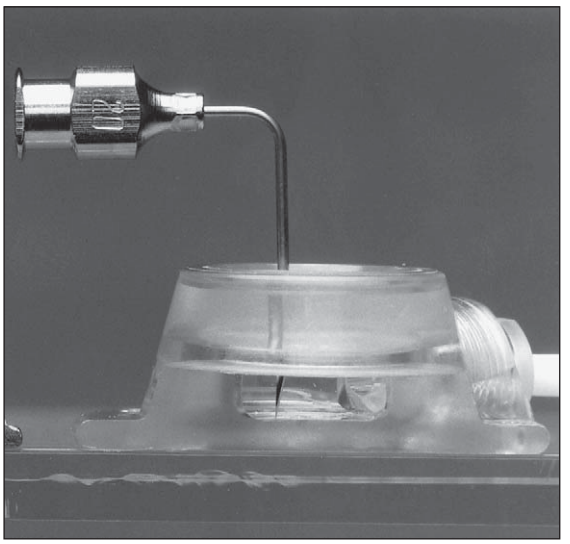


Figure 52-3 • Placement of a deflected point (Huber) needle in a port. The lower portion of the port has been cut away to show the needle tip in the reservoir. This example of a bent needle shows how the needle can be taped and secured at the skin surface for protracted infusion using an external pump.

subclavian vein placement than with internal jugular placement.[17–19] A subclavian artery puncture during line placement can be difficult to control, owing to the position of the artery posterior to the clavicle. A catheter placed on the anterior chest wall is more comfortable and easier to cover with clothing, however, than is a line in the neck. Additionally, some authors have concluded that with lines that are in place for more than 4 days, the risk of line infection is less for subclavian catheters than for internal jugular catheters.[17,18]

In many ways, the internal jugular vein is the ideal location with regard to ease of placement of a central catheter. The path of the guide wire during placement is straight, thereby limiting many guidewire complications and catheter malposition. In the event of carotid artery puncture, arterial bleeding can be controlled safely with the application of direct pressure. This advantage is especially important in the thrombocytopenic patient. The incidence of central venous occlusion is decreased, which could be important for patients who are likely to need an arteriovenous fistula for hemodialysis in the future. Unfortunately, patients often complain of pain with neck and shoulder movements after placement of an internal jugular catheter.

Preparing to Place the Vascular Access Device

Adequate preparation for placing a central venous catheter for oncology patients includes several steps before the actual line insertion. The surgeon must make several decisions that can limit the incidence of both immediate and delayed complications and ensure optimal line function.

Studies suggest that providing a single dose of prophylactic antibiotic to cover common skin flora before inserting the vascular access device reduces central line infection. It is difficult, however, to determine how this small benefit affects antibiotic resistance and subsequent infections. Using central venous catheters impregnated with antibiotics could be more effective in dealing with infectious complications and will be discussed later in this chapter.[20,21]

Table 52-1 General Guidelines for Catheter and Port Use

Type	Advantages	Uses	Dressings	Flushing	Comments
Central line	Placed at bedside Easy removal One or multiple lumens Can change over wire	Hospital use only	Sterile transparent dressing Change dressing twice weekly	5 mL heparinized saline (10 units/mL) in each lumen daily or after each use	Antibiotic ointment may promote resistance
PICC catheter	Safe to insert and remove	1 week to 6 months of IV access	Transparent antimicrobial foam dressing Change every 6 days	3 mL heparinized saline bid or after each use	Flush and draw blood slowly to avoid catheter migration
Hickman catheter	Multiple sizes and lumens Tunneled under skin	Continuous infusion therapy Long-term access	Newly placed: antimicrobial dressing for 7 to 10 days Gauze or transparent dressing changed 2 times per week	5 mL heparinized saline daily or after each use	Clean with chlorhexidine during dressing change After 4 weeks may clean with antimicrobial soap
Groshong catheter	Slit valve requires no heparin flushes Smaller, more flexible catheter	Single- or double-lumen catheter for long-term use			
Port	Completely under skin Minimal care	One lumen access and low maintenance	None	5 mL heparinized saline daily or after each use 20 mL saline after blood draw Monthly flush with 5 mL heparinized saline (100 units/mL)	Clean with chlorhexidine before use, access with noncoring needle Use no needle >20 gauge to access EMLA cream helpful

A sterile surgical field with mask, gown, cap, gloves, and a large sterile drape should be used to minimize the risk of line infection.[22] The skin of the entire anterior neck and chest should be prepared with chlorhexidine, which is superior to povidone-iodine or alcohol in limiting line infections.[23–26]

The choice to use ultrasound guidance to identify the vein during cannulation should be addressed before beginning the procedure. Less experienced operators will likely benefit from the use of ultrasound guidance as an adjunct to the anatomic landmarks technique.[13,27] Ultrasound can decrease the incidence of arterial puncture and placement failure. Although a few reports in the literature exist regarding the advantage of these techniques, such superiority is often judged when compared with high rates of complications using the landmark approach as the control group.

The operator must also decide where to position the catheter tip within the central vein. Clearly, catheters that are positioned with the tip in the right atrium will function longer as a source for aspirating blood samples than will those with the tip positioned in the SVC.[28,29] A case review of thrombosed catheters documents that the position of the tip of the catheter at the time of thrombosis seems to be the most important contributing factor.[30–33] The closer the catheter tip is to the right atrium, the lower is the frequency of thrombosis and infection. The risk of a catheter tip in the right atrial position is primarily that of cardiac arrhythmias when the tip is near the tricuspid valve. An additional risk of right atrial catheter placement is right atrial thrombus or right atrial erosion.[32] These risks have led the Food and Drug Administration to publicly warn operators to avoid placement of the catheter tip within the right atrium. Instead, the catheter tip should sit at the junction of the SVC and the right atrium.

Insertion Technique

After informed consent is obtained, a rolled towel is placed directly under the vertebral column at the shoulders to extend the clavicles. A peripheral line is established, and the patient is connected to an EKG monitor and a pulse oximeter. Intravenous sedation is typically established by using small doses of benzodiazepines. The fluoroscopy operating table and patient are placed in the Trendelenburg position. The skin of the neck and entire upper anterior thorax is prepared, and sterile drapes are positioned. The skin and deep tissues are anesthetized with 1% lidocaine using a 25-gauge needle for the skin followed by a 22-gauge needle for the anticipated insertion tract (Fig. 52-4A).

For subclavian vein puncture, the site of skin puncture is usually 1 cm below the angle of the lateral third of the clavicle. The long insertion needle, as depicted in Figure 52-4A, is slowly inserted below the clavicle, aiming for a point approximately one fingerbreadth above the sternal notch. During insertion, a small amount of negative pressure is maintained on the syringe. With experience, the physician develops a feel for the actual puncture of the vein, and when this occurs, the syringe fills easily with venous blood.

As the position of the needle is being carefully maintained, the syringe is removed, and the guide wire is inserted (Fig. 52-4B). If the patient experiences discomfort in the neck, the guide wire is partially withdrawn. Turning the patient's head away from the site of insertion and exerting a downward pull on the ipsilateral arm could facilitate entrance of the catheter or guide wire into the SVC. Cardiac ectopy indicates that the guide wire has entered the right atrium, and the wire should be withdrawn slightly.

Fluoroscopy may be used to pass the wire when difficulty is experienced. The correct position of the catheter is confirmed by fluoroscopy or chest x-ray before the catheter is secured with a 3–0-nylon suture at the skin exit site. The tip of the catheter is positioned 1 cm above the SVC-atrial junction when the patient is in the Trendelenburg position. A chest x-ray is obtained to document the absence of pneumothorax and accurate placement of the catheter within the SVC.

When it is necessary to use the veins in the neck, the right internal jugular provides more direct access to the SVC and right atrium. In this case, the patient's head is turned to the opposite side. The insertion site is located just lateral to the carotid artery and approxi-

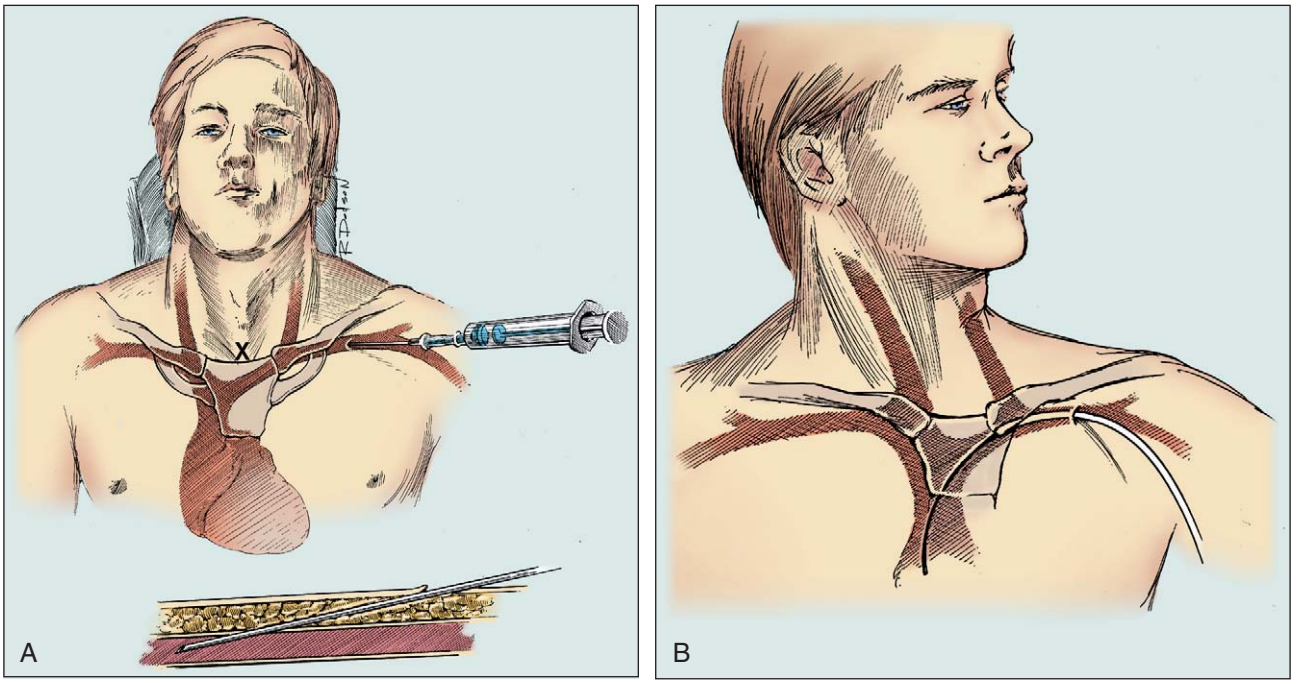


Figure 52-4 • **A,** Placement of a catheter using the Seldinger technique. The long insertion needle is shown entering the vein through skin and subcutaneous tissues. **B,** Demonstration of a catheter passing over the guide wire.

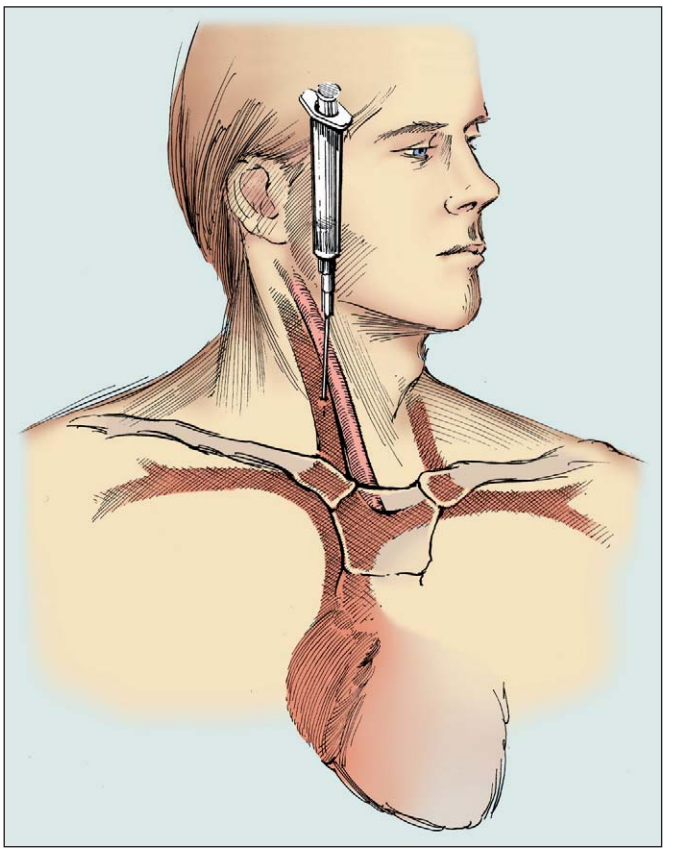


Figure 52-5 • Demonstration of catheter insertion technique when utilizing a vein in the neck (right internal jugular).

mately two fingerbreadths above the head of the clavicle. Another useful landmark for the insertion site is the angle formed by the sternal and clavicular heads of the sternocleidomastoid muscle (Fig. 52-5).

Placement of a permanent Silastic catheter, such as a Hickman, is depicted in Figure 52-6. Placement of the introducing needle and guide wire is as described in previous figures except that a 1-cm incision is made before insertion of the introduction needle. A prophylactic antibiotic is given before the procedure. It is often beneficial to provide the patient with intravenous sedation.

A second 1-cm incision is placed lower on the anterior chest, usually at the level of the fourth or fifth interspace. The skin and subcutaneous tissues are first anesthetized with 1% lidocaine. The projected course of the tunneled catheter is also infiltrated with lidocaine. A tunneler is passed from the lower incision to the upper incision, where the guide wire is exiting. A heavy suture is tied to the end of the tunneler and brought down through the tract. The suture is tied to the end of the catheter and used to pull the catheter up through the tract, securing the cuff 3 to 4 cm from the skin exit site. The catheter is trimmed to the correct length that will position it about 1 cm above the SVC-RA junction with the patient in Trendelenburg position. This location is approximately four fingerbreadths below the sternal notch.

Care is taken to cut the catheter squarely and smoothly. An introducer and a tear-away sheath are passed over the guide wire into the vein (Fig. 52-7). A slight rotary motion facilitates the introduction of the sheath and avoids crimping. To avoid developing a false passage, the guide wire should be withdrawn occasionally as the introducer is inserted. The guide wire is then removed, and a syringe is attached to the introducer to confirm that blood can be aspirated. The introducer is removed, and the thumb is used to control bleeding or air intake through the sheath. It is important to have the catheter tip poised to insert as the introducer is removed. The passage of the catheter could meet some resistance as it is passed between the clavicle and first rib.

Fluoroscopy or a chest x-ray is obtained to confirm correct positioning and the absence of pneumothorax. The catheter is aspirated and flushed to confirm function. Care should be taken to avoid any angulations of the catheter through the subcutaneous tract, especially at the bend toward the subclavian vein. The incision below the clavicle is closed with a subcutaneous absorbable suture. The catheter is secured at the exit site with a 3-0 nylon suture, which is maintained for approximately 3 weeks to allow the fibrous tissue ingrowth into the subcutaneous cuff. The exit site is covered with a sterile gauze dressing.

Similar techniques apply to the use of neck veins. The catheter is tunneled over the clavicle, the exit site being the same as for subclavian vein placement. When other sites are required (e.g., the femoral vein with the catheter tip in the inferior vena cava), direct cut-down exposure of the saphenous vein or other large femoral branch is preferred.

Figure 52-8 illustrates the placement of an implanted injection port. A 1-cm incision is placed below the clavicle at the site planned for subclavian venipuncture. A second, 3-cm incision is placed lower on the chest in a position that provides a relatively flat surface and stability for the port chamber. Local anesthesia is 1% lidocaine with 1 : 200,000 epinephrine. A subcutaneous pocket just large enough to accommodate the port is dissected inferior to the incision. Ideally, the level of this pocket is over the underlying pectoral fascia. The skin coverage needs to be thick, but the port must be percutaneously accessible. A tunneler is passed subcutaneously from the pocket through the infraclavicular incision. A suture is tied to the tunneler and brought down through the tract. The suture is tied to the end of the port catheter and used to pull the catheter through the tract to the intraclavicular incision. Care should be taken to position with a gentle curve and to avoid catheter angulation. The port is secured in the pocket with three sutures of 0-prolene. It is necessary to anchor the port adequately to prevent flipping or rotation of the device.

The guide wire is inserted as described, and the dilator and sheath are passed over it. The catheter is cut to the desired length. The dilator and guide wire are removed, and the catheter is inserted through the sheath as described. The incision for the port pocket is closed with interrupted 3-0 absorbable sutures placed in the subcutaneous layer. The skin is approximated with a running subarticular 4-0 absorbable suture. A transparent nonpermeable dressing is used at the port incision.

Open insertion methods are quite safe in a skilled surgeon's hands. The major complication of the open technique is the possibility of air embolus during the actual catheter insertion. This is most likely to occur in patients who are hypovolemic, cachectic, or unable to tolerate positioning in Trendelenburg position. An air embolus happens most frequently when the internal jugular vein is used, and extreme care with the use of the purse-string suture around the insertion site and venous occlusion with vascular clamps should limit the possibility of introduction of air into the vascular system. With open direct surgical placement, although it takes considerably longer than the closed Seldinger technique, complications should be much lower than 5%.[33–35] In the Hopkins series, the open method results in a complication rate of less than 1%. Although this is a safer technique, it requires more training, more experienced operative personnel, and larger incisions. Any patient who has had repeated problems with closed insertions should be approached in an open fashion, however, as this is the most controlled and safest format for that patient. Sometimes, previous operations or radiation therapy in the region of the cardinal veins makes the open operative approach more difficult, but generally such problems are limited.

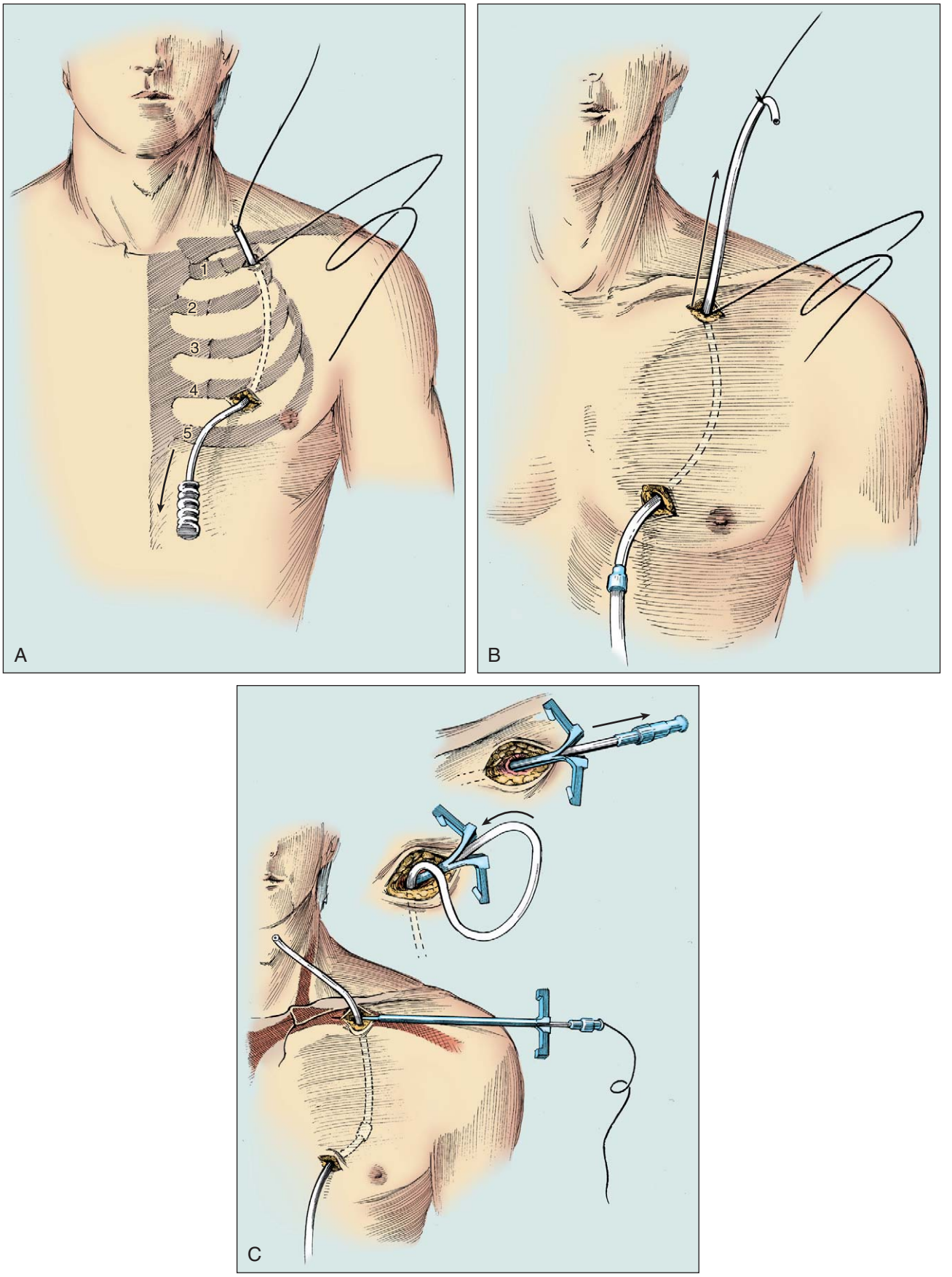


Figure 52-6 • **A,** Placement of a permanent Silastic catheter (such as a Hickman). The first and second incision sites are shown, as is the path of the tunneler. **B,** The catheter is pulled through the tract by using a heavy suture. The catheter cuff is secured 3 to 4 cm from the skin exit site. **C,** The catheter is trimmed and positioned 1 cm below SVC-RA junction. The introducer and tear-away sheath are shown passing over the guide wire. The catheter is inserted into the sheath, and the sheath and introducer are removed.

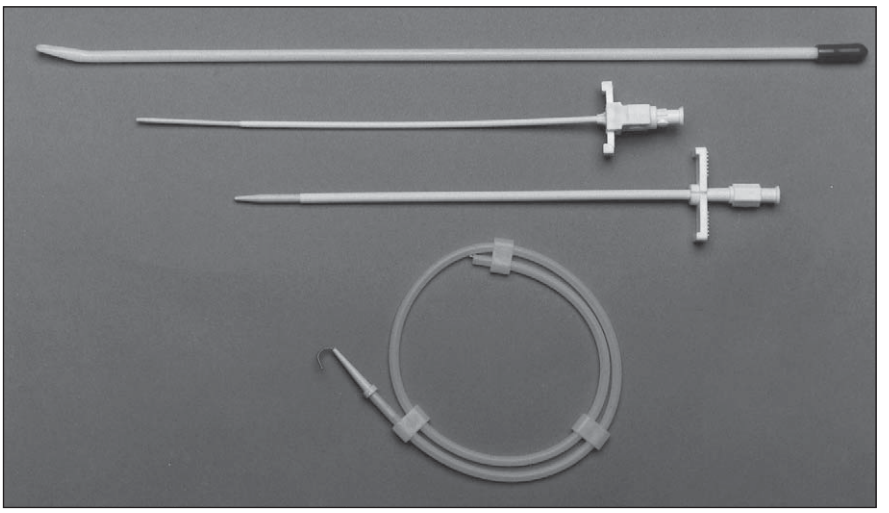


Figure 52-7 • Example of an introducer kit. The kit includes a guide wire and introducer (dilator) with tear-away sheath (two different sizes shown). The upper, longer blunt object is a tunneler, which is included in some kits.

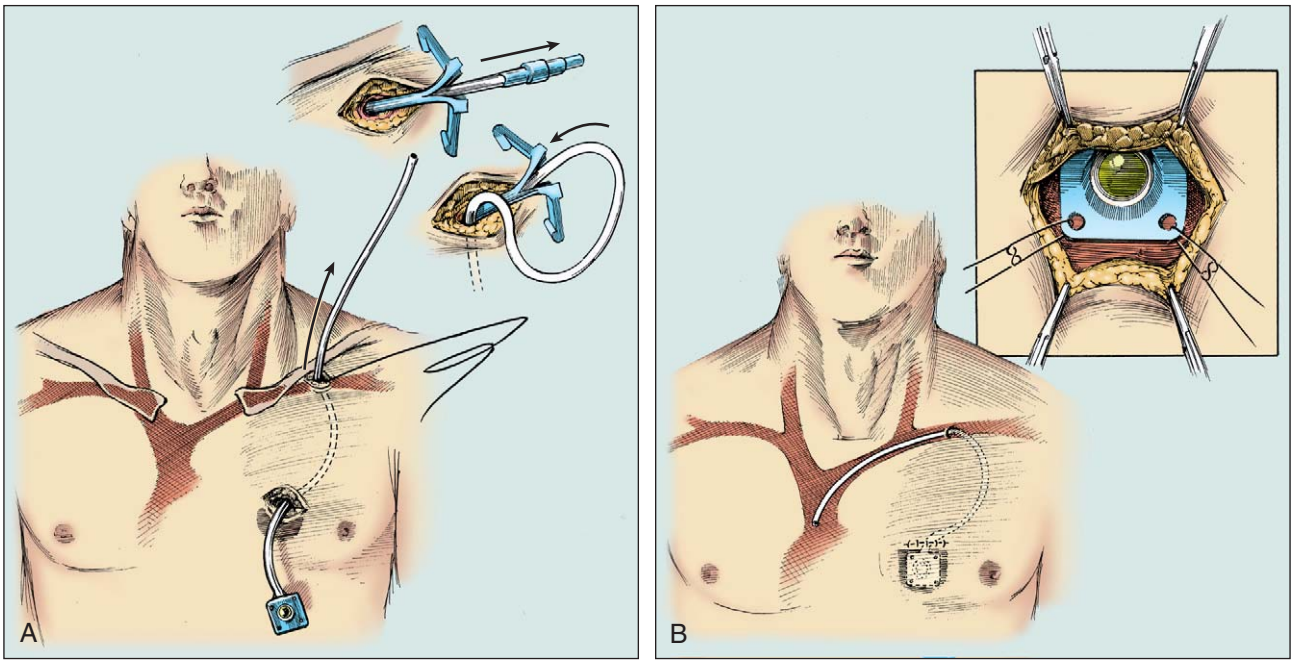


Figure 52-8 • **A,** Placement of an implanted injection port. First and second inclusion sites are shown, as is dissected pocket to accommodate port. **B,** Demonstration of placement of a port into a subcutaneous pocket.

COMPLICATIONS OF VASCULAR ACCESS DEVICES

When complication rates are examined as a whole, certain patient factors, catheter factors, and operator factors seem to predict the occurrence of complications. Patient-related factors that predict higher complication rates include the presence of multiple comorbid conditions, atherosclerosis, abnormal anatomy, thrombocytopenia, immunocompromise, prior radiation therapy to insertion area, recent myocardial infarction, and patient restlessness.[36] In addition, multiple-lumen or stiffer catheters carry increased risks of complications.[37–40] Factors related to the person performing the insertion of the catheter also influence risk of complications. Risk increases if the operator has inserted fewer than 50 central venous catheters, if more than two tries at cannulating the vein are required, or if the insertion of the catheter is difficult.[16,41,42] Risk factors for specific complications are discussed in the sections that follow.

Immediate Complications

Pneumothorax

Published complication rates for pneumothorax after jugular vein central line placement are approximately 0.5% and up to four times higher for subclavian vein procedures.[16,37,38,43] The risk of this technical complication can be reduced dramatically among experienced operators or physicians who have experienced supervisors.[36]

Bleeding

Many patients with cancer are at increased risk of bleeding complications owing to thrombocytopenia, uremia, other platelet dysfunction,

or anticoagulant therapy. Bleeding complications are associated most frequently with thrombocytopenia.[39] For patients with platelet counts less than 50 or International Normalized Ratio greater than 2.0, we consider administration of platelets or fresh-frozen plasma. Experienced physicians should perform these procedures with access to ultrasound guidance if necessary.

Cardiac Arrhythmias

Disruptions in the normal cardiac conduction pathway can be caused by contact between the catheter and the right atrium. Most of these arrhythmias are short-lived and self-limiting.[16] These problems are more common with insertion of pulmonary artery catheters than with catheters that are typically inserted for oncologic vascular access. They are associated with more significant sequelae in patients who have recently suffered a myocardial infarction or who have a history of left bundle branch block.[40,44]

Delayed Complications

Infectious Complications

Infectious complications are the most common complications of long-term vascular access devices in the oncology patient population. Two factors make the interpretation of this relatively well-studied topic challenging. First, many of the large randomized controlled trials that have studied central line infections have concentrated on ICU patients. The ICU population has different risk factors and susceptibilities from those of the outpatient population of people with cancer. Nevertheless, by carefully reviewing the available data, we can make some conclusions regarding the pathogenesis, prevention, and treatment of line-related infections among oncology patients. In studies of ICU patients with central lines, factors that predispose to line infection have included malignancy, neutropenia, extended duration of indwelling time, and coincident parenteral nutrition. All of these factors can contribute to the incidence of infection among patients with vascular access for oncologic treatment.[45,46]

Second, the confusing terminology regarding line-related infections can make the literature on this topic difficult to interpret. *Local infection* is a positive culture at the catheter insertion site. *Catheter colonization or infection* is the positive culture of a segment of removed catheter. *Catheter-associated bacteremia* is evidenced by a positive blood culture from a site other than the catheter and the positive culture of a segment of removed catheter with the same pathogen.

Understanding the pathophysiology of catheter-associated bacteremia can help to limit the incidence of this complication. Up to 50% of catheter-associated bacteremia is caused by coagulase-negative staphylococcus. This common skin flora can colonize the catheter during insertion or later. A thrombus that forms at or along the catheter tip can become a nidus for bacterial proliferation, with resultant bacteremia. Thrombosis significantly increases the risks of colonization and infection.[47] Bacteria can also be introduced into the bloodstream by hub contamination, by hematogenous seeding from another focus of infection, and, rarely, by the infusate itself.

Factors that increase the risk of catheter infection include prolonged indwelling time, multiple-lumen catheters, femoral or internal jugular vein location, difficult catheter placement, and non-catheter-related bacteremia.[45,48] As was mentioned previously, nontunneled catheters are at increased risk of catheter infection compared with tunneled catheters, and totally implantable devices are even less susceptible than tunneled catheters.[49,50]

Multiple-lumen catheters have demonstrated higher infection rates than single-lumen catheters. The addition of each lumen exponentially increases incidence of infection.[51–54] There are two possible explanations for this observation. First, the increased internal lumen diameter of the line is associated with a higher thrombosis rate and accumulation of loose thrombus at the catheter tip. Thrombosis causes more breaking of the line and more line manipulation when attempting to declot, leading to subsequent infection. Second, the multiple ports invite multiple interruptions of the line for access and result in a greater likelihood of introduction of bacteria. Despite their greater risk of iatrogenic infection, multiple-lumen catheters have great appeal for patients who need multiple simultaneous infusions of incompatible drugs. Very strict nursing guidelines must be followed in the management of multiple-lumen catheters to prevent iatrogenic infections and thrombosis.[55,56]

Diagnosis and management of catheter-related infection differs between nontunneled and tunneled catheters. However, some diagnostic principles apply to both tunneled and nontunneled catheters. Routine surveillance blood cultures should not be performed. When a catheter-related infection is suspected due to fever, chills, or purulence around the catheter site, percutaneous and catheter blood samples should be submitted for culture.[57–60] Qualitative culture with continuously monitored differential time to positivity compares the time to positivity for catheter blood cultures to percutaneous peripheral-blood cultures. This technique has demonstrated excellent specificity and sensitivity for detecting catheter-related infection in tunneled catheters.[61,62]

In most patients with nontunneled central venous catheters, the line should be removed if the patient demonstrates signs of site infection or sepsis or if blood culture results from the catheter and percutaneous blood samples are positive.[61,62] Seven to 10 days of narrow-spectrum antibiotic therapy is generally recommended. In certain cases of clinically stable patients with a single episode of coagulase-negative staphylococcus, a trial of antibiotic therapy might salvage the catheter.[53] For any patient with persistent bacteremia despite antibiotic therapy and removal of the infected catheter, a thorough investigation of possible septic sources, such as endocarditis or septic thrombus, is warranted.

Tunneled catheters or infusion ports should be removed in cases of sepsis, complicated infections, tunnel tract infections, or port abscesses.[63] A thorough evaluation confirming the surgically implanted catheter as the source of infection should precede the removal of any of these vascular access devices. In the absence of complicated infection, catheter salvage could be indicated. Antibiotic lock therapy is a reasonable approach for attempting to salvage lines with common coagulase-negative staphylococcus, *Staphylococcus aureus,* or gram-negative bacilli intraluminal infections. This therapy consists of instilling the catheter lumen with high concentrations of antibiotics and leaving them there for several days.[64–67] If salvage therapy fails, a new tunneled catheter can be placed after removing the infected catheter, treating with an appropriate course of antimicrobial therapy, and repeating blood cultures with negative results.

Catheter Thrombus

Thrombus of central vein access devices predisposes to both line malfunction and line infection. The most common site of thrombus formation with prolonged indwelling central catheters is where the catheter enters the vein. At this point, a fibrin sleeve progresses distally toward the tip of the catheter. The precipitating event is likely local trauma from line insertion with subsequent endothelial damage and disruption of intraluminal laminar flow. The venous intima exposed to blood flow activates the coagulation cascade. Understanding this pathophysiology helps to explain why difficult line placements often lead to shorter catheter survival and increased rates of infection.

The incidence of central venous catheter-related thrombus as demonstrated by ultrasound is greater than 30% for catheters that are in place longer than 7 days.[68] This problem typically presents as progressive difficulty in flushing the catheter. A change in posture or the Valsalva maneuver could allow aspiration of blood. Occasionally, thrombosis can present as extremity edema. This can be especially devastating after axillary nodal resection or axillary irradiation. Management of a nonfunctioning catheter is discussed later.

Acute line obstruction can also be caused by precipitation of incompatible medications. Common offenders include total

Table 53-2 Management of a Suspected Clot

Complications	Cause	Gravity Flow Observation	Corrective Action
Fibrin sheath*	Fibrin collects on the tip or encases the catheter	Excellent in all positions but no blood return in any position	May be declotted following the declotting procedure
Occluded catheter*	Fibrin and platelets collect inside catheter	Inability to infuse solutions and draw blood	May be declotted following the declotting procedure; drug precipitate cannot be corrected with tPA or heparin

*These are the only two instances in which it is safe to declot after checking the chest x-ray for proper placement.

parenteral nutrition, etoposide salts, lipid emulsions, calcium salts, antibiotics, and sodium bicarbonate. Infusion of a solution specifically matched to the precipitated material might flush the line.[69]

Extravasation

Extravasation is defined here as the leaking of infusate into the subcutaneous tissue surrounding a central venous catheter. This complication can be caused by needle displacement from an implanted port, a defect in the catheter tubing, or withdrawal of the catheter from the vein due to inadequate fixation. Additionally, "backtracking" can occur when the catheter is partially occluded and infusate tracks up along the fibrin sleeve and into the subcutaneous tissue. Findings that are suggestive of extravasation include sudden swelling at the line site, increased patient discomfort during infusion, and sudden loss of blood return.[70]

Clavicular–First Rib Compression

This infrequently discussed complication may occur up to 1% of the time in long-term indwelling catheters.[71] When the subclavian vein is cannulated more medially than usual in the narrow space between the clavicle and first rib, the line can be compressed between the first rib and the clavicle. Patients who report difficulty infusing while in the sitting position or when the ipsilateral arm is elevated or abducted should be suspected of this compression. This malposition can be observed on chest x-ray as kinking of the line over the first rib. The catheter can break free and embolize if the line is not promptly removed. An interventional radiologist using a percutaneous retrograde femoral catheterization approach can retrieve an embolized section of catheter.

MANAGEMENT OF NONFUNCTIONING CATHETERS

When a central venous catheter does not return blood or infuse solution, the malfunction should be assessed systematically to maximize catheter durability and to minimize the incidence of catheter-related complications. The first step in this assessment is reviewing the most recent chest x-ray to confirm appropriate placement. The next step is checking for gravity flow. Connecting a bag of normal saline to gravity flow and asking the patient to change position, cough, and breathe deeply will demonstrate whether flow is positional. If the catheter is patent to gravity flow, lower the bag below the catheter and assess for blood return. With this information, one can make a decision as to whether to remove, reposition, or declot the catheter (Tables 52-2 and 52-3).

Two conditions are appropriate for thrombolysis of the catheter with alteplase or tissue plasminogen activator (TPA): fibrin sheaths and intraluminal thrombus occlusions. Contraindications for declotting procedures include high bleeding risk and known recent or current episode of bleeding.

Catheter malfunction caused by fibrin sheaths usually demonstrates good gravity flow and no blood return because the sheath acts as a one-way valve, allowing outflow but not inflow through the catheter. When intraluminal fibrin and platelets occlude the catheter, the catheter will demonstrate neither gravity flow nor return, regard-

Table 52-3 Management of an Unknown Clot

Complications	Cause	Gravity Flow Observation	Corrective Action
Do not attempt to declot any of the following conditions.			
Malposition	Catheter cut short and abutting vessel wall	Positional; no blood return in any position	Must be removed; do not attempt declot, which may erode vessel wall
Pinch-off syndrome	Insertion site too close to first rib and clavicle	Excellent when lying down but absent when standing	Must be removed to avoid catheter breakage
Transverse catheter	Catheter crosses into opposite subclavian	Positional flow, slow blood return, position noted on chest x-ray	Interventional radiology can reposition via femoral vein access
Arrhythmia	Catheter in right atrium	Positional; position noted on chest x-ray	Catheter must be pulled back into SVC or removed
Flipped up	Catheter tip in jugular vein; can occur in association with vomiting or coughing	Positional, blood return may be positional, patient complaint of tinnitus or headache with catheter flushing, position noted on chest X-ray	Interventional radiology may be able to reposition if catheter not cut too short
Major vessel thrombus	External thrombus within vessel due to insertion trauma	No change; good blood return; arm, hand, or neck swelling	Documentation of thrombus with ultrasound or venogram, treatment with thrombolytics after consultation with hematology

less of any positional changes. If the caregiver is convinced that the catheter malfunction fits one of these categories and appropriate catheter position is confirmed on chest x-ray, catheter thrombolysis is indicated. Contrast venography is not necessary before using TPA to open nonmechanical catheter occlusions.

Techniques for declotting catheters vary from institution to institution but follow the same general principles. We recommend instilling 500 μg of TPA and allowing the infusate to dwell for 1 hour. If patency is not restored after 1 hour, instill an additional milligram of TPA and allow the infusate to dwell for another hour. Using a very similar technique, the authors of the Cardiovascular Thrombolytic to Open Occluded Lines Trial (COOL-2) studied nearly 1000 patients with occluded central venous catheters. These patients in a predominantly oncology population did not undergo prethrombolysis contrast studies. No deaths or major bleeding episodes were directly attributable to the thrombolysis. More than 87% of the catheters were opened with the TPA. At 3-month follow-up, nearly 75% of the catheters were still patent.[72] A similar study in the oncologic population reported a success rate greater than 80%.[73]

VASCULAR ACCESS DEVICE MAINTENANCE

The risk of complications with a long-term vascular access device does not end with insertion of the device. Proper care and maintenance of each type of central catheter can dramatically reduce the incidence of catheter-related bacteremia, catheter thrombosis, and line failure.[74] Maintenance is performed not only by qualified staff of oncology centers but also by patients and family members in the outpatient setting. In Table 52-1 and Box 52-1, we have detailed our recommendations for central catheter care after a thorough review of the best available literature.

SUMMARY

Patients and physicians have a large variety of vascular access devices from which to choose, and no individual catheter is the ideal solution for all clinical situations. By understanding the strengths and weaknesses of each catheter system, insertion site, and maintenance technique, we hope to minimize the morbidity associated with these commonly used devices. Clearly, having a great deal of experience in placing vascular access devices in the oncology population minimizes the number of problems. Line care is the joint responsibility of the health care team and can be a major source of patient morbidity if each and every member of the oncology team does not maintain the highest quality of care.

More than 750,000 vascular access devices are used in the United States each year. We must continue to conduct clinical studies to make the safest, most cost-effective choice for each cancer patient.

Box 52-1. PROBLEM SOLVING IN CATHETER USE

Troubleshooting Guidelines

If a catheter does not have a blood return or will not infuse solution, perform the following troubleshooting techniques to diagnose the problem before proceeding with the declotting procedure:

1. Connect a flush bag of NS or D5W to the catheter and open the roller clamp to allow the fluid to flow to gravity.
2. Have the patient change position, take deep breaths, and cough while the drip rate is observed.
3. When the fluid infuses at the fastest rate, lower the bag and observe for a blood return.
4. If a blood return is observed, use the catheter as indicated, making a note that it is positional.
5. If no blood return is observed in any position, if gravity flows freely in all positions, and if the last chest x-ray verifies that the catheter tip is in the SVC, proceed to declot the catheter with a likely fibrin sheath obstruction.
6. If the x-ray shows that the catheter tip position is questionable, obtain a dye study to verify the exact location of the catheter tip, integrity of the catheter, and flow of solution.

Declotting Procedure

See the preceding guidelines before proceeding to declot, as follows:

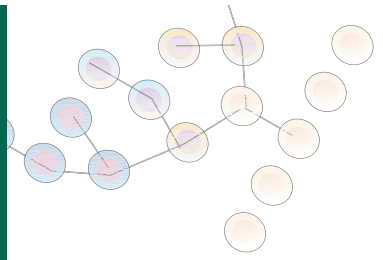
1. Using a 1-mL syringe, create a vacuum by aspirating back on the plunger (at the hub) and clamp. Repeat once.
2. Instill 2 mL 1 : 1000 U heparin solution (in each lumen) and let dwell for 1 hour. Assess for a blood return.
3. If the line remains clotted, instill the appropriate amount of alteplase to fill the catheter (listed following) using the same technique as with the heparin.
4. Let dwell for 30 minutes to 1 hour and then assess for a blood return.

Catheter Type	Alteplase (mL)
Central line, 14 gauge	0.7
Central line, 16 gauge	0.5
Hickman, 12 F	1.6
Hickman, 10 F	1.3
PICC	0.5
Groshong	1.6
Plasmapheresis	1.4

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53 Acute Abdomen, Bowel Obstruction, and Fistula

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SUMMARY OF KEY POINTS

Gastrointestinal Perforation
- Perforation affects approximately 20% of patients with acute abdominal emergencies.
- Bowel perforation can be due to spontaneous tumor rupture, tumor necrosis secondary to chemotherapy, radiation therapy, drugs (e.g., steroids), or inflammatory conditions.
- Operative intervention is mandated unless the patient's overall prognosis is poor.

Gastrointestinal Bleeding
- Bleeding affects approximately 15% of patients with acute abdominal emergencies.
- Bleeding is more commonly seen in patients with leukemia or lymphoma who are undergoing chemotherapy.
- Endoscopy is critical to identify the source of bleeding and can even be therapeutic.
- Nonoperative therapy is successful for many patients.

Neutropenic Enterocolitis
- Also termed *necrotizing enterocolitis,* neutropenic enterocolitis typically affects the terminal ileum, cecum, and ascending colon in patients with chemotherapy-induced neutropenia.
- Most patients respond to conservative management with broad-spectrum antibiotics and bowel rest.
- Surgical intervention should be considered for perforation, uncontrolled sepsis, or persistence of symptoms despite correction of neutropenia.

Bowel Obstruction
- Obstruction affects approximately 40% of patients with cancer who experience acute abdominal emergencies.
- One fourth to one third of patients who require surgical intervention have a benign cause of their obstruction.
- Partial bowel obstruction can initially be treated nonoperatively, which is successful 25% of the time.
- Clinical suspicion of bowel ischemia or complete obstruction mandates urgent surgical intervention.

Fistulae
- Presenting symptoms rarely match those of intra-abdominal malignancy and more commonly represent complications after surgery or radiation therapy or both.
- Fistulae occur most often as a result of treatment of gynecologic malignancies.
- Medical management consisting of nutritional support and bowel rest allows spontaneous closure of most enterocutaneous fistulae.
- Causes for persistence of a fistula include undrained infection, luminal obstruction distal to the fistula, prior radiation, epithelialization of the fistulous tract, cancer within the tract, presence of a foreign body, and malnutrition.

INTRODUCTION

General surgical problems in the cancer patient require special attention. This chapter reviews common abdominal complications and emergencies that are encountered in patients with a cancer diagnosis. In some cases, these problems might not be related to the cancer itself. For other patients, clinicians must be cognizant of the potential complications associated with progression or treatment of disease. The management of cancer patients has undergone significant changes with the increasing utilization of multimodality therapy. Combined approaches, including surgery, radiation therapy, chemotherapy, and immunotherapy, are now commonplace. Topics having to do with the "acute abdomen" include intestinal obstruction, gastrointestinal (GI) bleeding, and perforation. Other related presentations, such as gastrointestinal inflammatory conditions and fistulae, are also reviewed in this chapter. In addition, unique abdominal problems that are seen in patients undergoing bone marrow transplantation (BMT) are covered.

ACUTE ABDOMEN: GENERAL CONSIDERATIONS

The classic general surgery approach to a patient with acute abdominal pain entails identification of a potentially life-threatening problem and evaluation for emergency exploratory laparotomy. In patients with cancer, the etiology of acute abdominal pain may be directly related to a malignant process, but seemingly unrelated processes must be considered as well. Some GI cancers can present as abdominal emergencies that require surgical intervention. Problems that require surgical consultation include obstruction, perforation, hemorrhage, inflammatory processes, and other miscellaneous problems such as fistulae (Box 53-1).[1,2] In a recent prospective analysis of over 1000 consecutive palliative procedures in patients with cancer, over 50% were performed on the GI system, with obstruction and bleeding making up over 75% of the presenting symptoms. Interestingly, surgical intervention resulted in symptom resolution in over 80% of patients.[3] The decision to intervene with surgical therapy is often

Box 53-1. ACUTE ABDOMINAL EMERGENCIES IN CANCER PATIENTS

- Obstruction
- Hemorrhage
- Perforation
  - Ruptured tumor
- Bowel perforation
- Inflammatory conditions
  - Cholecystitis
  - Appendicitis
  - Pancreatitis
  - Neutropenic enterocolitis

difficult because of abnormal physiologic responses to injury and inflammation, complications associated with previous cancer therapies, and competing risks due to extent or stage of the underlying cancer. In some instances, medical management or utilization of palliative measures make up the mainstay of therapy.

Abdominal pain is the most common symptom in the patient with an acute abdomen. In patients with a diagnosed intra-abdominal malignancy who are undergoing chemotherapy and/or radiation therapy, abdominal pain must be investigated carefully. Care must be taken not to automatically attribute these complaints to cancer progression. Important considerations in the evaluation of the patient with an acute abdominal process include hemodynamic stability and deterioration of symptoms during the course of examination and workup. Patients taking corticosteroids or who have an altered sensorium warrant special attention because of a potentially unreliable physical examination. Other abdominal complaints, such as vomiting, distention, lack of flatus, and fever, should raise the examiner's index of suspicion that an emergent problem is present.

On physical examination, tenderness to palpation is the most common finding. Peritonitis almost invariably produces tenderness as a localized or diffuse finding, since abdominal pain is transmitted by both visceral and somatic sensory pathways. There is no substitute for a thorough history and physical examination. A careful and thoughtful differential diagnosis is important in directing the course of subsequent evaluation and action. Laboratory tests and diagnostic imaging studies can help to narrow the nature of the problem. Standard laboratory studies should include a complete blood count and electrolyte panel. Leukocytosis will normally be evident if an intra-abdominal infection is present. Unfortunately, chemotherapy-induced neutropenia or immunosuppression might prevent the white cell count from adequately reflecting an inflammatory process. Liver function studies and a serum amylase are helpful in patients with upper abdominal complaints when hepatobiliary or pancreatic etiology is suspected. Patients with evidence of GI bleeding require serial hemoglobins to assess the severity and magnitude of the bleeding; thrombocytopenia and coagulopathy should be corrected when possible.

If an intra-abdominal process is suspected and time permits, diagnostic imaging with plain abdominal films, ultrasonography, and/or computed tomography (CT) could be helpful in making a more definitive diagnosis. With increasing sophistication of CT studies, their importance in identification of abdominal processes, including free fluid, free air, intestinal pneumatosis, portal venous gas, transition points for gastrointestinal obstruction, and localization of abdominal inflammatory processes, is well defined.[4] Importantly, rapid tumor progression and/or metastases can often be assessed at the same setting. Localization of the bleeding source by endoscopy or arteriography can be helpful, and these can often be used as therapeutic modalities as well.

Ultimately, the surgeon must make the determination as to whether the patient has an acute abdominal process that requires surgical intervention. Decisions to operate on acutely ill patients with cancer are difficult and often require a high level of surgical decision making. Due consideration must be given to the stage and prognosis of the cancer itself, since the surgeon's ability to offer a procedure with curative intent versus palliation only may alter the decision-making process. The role of palliative procedures has increased tremendously, with as many as 6% to 21% of cancer operations being classified as palliative in nature.[3,5–6] Even without curative intent, surgeons have a great deal to offer in terms of symptom relief and overall improvement in quality of life. However, attempts at successful palliation must be balanced with inappropriately aggressive attempts, which may carry unacceptable rates of morbidity and mortality.

GASTROINTESTINAL PERFORATION

Perforation of the GI tract mandates operative intervention unless the patient's condition is judged to be extremely poor. Excluding iatrogenic causes of bowel perforation, the causes of perforation can be categorized into the following subgroups: spontaneous tumor rupture or erosion into bowel, drug-induced or associated perforations, and inflammatory conditions. GI tract cancers may present with perforation as the precipitating event, but this is rare and associated with high mortality rates. Primary colon cancers can present as localized perforations or can cause obstruction with subsequent perforation. The perioperative mortality rate following presentation with colon cancer perforation, either at or proximal to the tumor site, ranges from 17% to 48%.[7] Even after accounting for stage, patients tend to have a poorer prognosis.

Spontaneous perforation of GI tumors is more common in patients with lymphomas involving the gastrointestinal tract, although this diagnosis is rare. Large malignant retroperitoneal lymphomas, renal cell carcinomas, and testicular cancers metastatic to aortocaval nodes can invade the adjacent duodenum and cause perforation. Patients with GI lymphomas can have symptoms at presentation or can develop symptoms related to regression of their primary tumor during treatment with chemotherapy and/or radiation therapy. Perforation or bleeding from treatment-induced tumor lysis occurs in approximately 3% and 5% of patients, respectively. Although resection of larger, higher-grade GI lymphomas can be associated with increased morbidity, the mortality rate is greater than 50% when surgical intervention is urgently required for perforation or bleeding in the setting of neutropenia and thrombocytopenia.[8–10]

Surgical management of bowel perforations varies with the site and etiology. Infectious causes of perforation, such as colitis secondary to cytomegalovirus or *Clostridium difficile,* have been described but are rare. Treatment includes proper control of the infection and usually necessitates resection with possible enteric diversion. For gastric perforations secondary to benign ulcers, surgical intervention is indicated. For perforated duodenal ulcers, various surgical options can be employed, depending on the patient's underlying disease and clinical status (e.g., hemodynamic stability). Small bowel perforations should be resected with primary anastomosis if possible. Colonic perforations, especially in the setting of the unprepped bowel and in the immunosuppressed patient, should be treated with resection and diversion. One-stage procedures to include primary anastomosis in these situations must be used cautiously and are generally not advised. Aggressive supportive care with control of intra-abdominal infection and sepsis are paramount in the immediate perioperative period.

GASTROINTESTINAL BLEEDING

The true incidence of significant gastrointestinal (GI) bleeding in patients with cancer is not well defined. An estimated 10% to 15% of patients with abdominal emergencies requiring operative intervention had abdominal hemorrhage, most of them secondary to intralu-

minal bleeding.[1] Patients with lymphoma or leukemia treated with combination chemotherapy regimens can experience GI tract bleeding. While a GI tumor itself could be the source of bleeding, differential diagnosis should include non-tumor-related sources as well. The most common causes of upper GI tract bleeding in patients with cancer are peptic ulcer disease or stress ulceration and complications of anticoagulation or thrombocytopenia.[2,11–12] Rates are likely to be lower in clinical practice, given the availability and increasingly widespread use of H2-receptor blockers and proton pump inhibitors.[13] Other, less common, causes of bleeding include Candida esophagitis, Mallory-Weiss mucosal tears, hemorrhage from inflammatory conditions (e.g., neutropenic enterocolitis), or radiation-associated complications (e.g., arterial-enteric fistulae, radiation enteropathy).

The pathogenesis of upper GI bleeding can be multifactorial. Gastritis or peptic ulcers can be associated with a variety of agents, such as aspirin, alcohol, steroids, indomethacin, or phenylbutazone. Chemotherapeutic agents can depress platelet production as well as damaging or irritating the mucosal surfaces. While the correlation between thrombocytopenia and bleeding is well described, it is difficult to predict which patients might develop transfusion-requiring bleeding or life-threatening hemorrhage. Overall, the incidence of bleeding is low, with one group reporting bleeding episodes with 9% of chemotherapy cycles.[12,14] The vast majority of episodes were mild (e.g., epistaxis), but major hemorrhage (including GI bleeding) was seen in approximately 3% of cycles. In that study, administration of certain chemotherapy agents (cisplatin, carboplatin, carmustin, and lomustine) was noted to be significantly related to bleeding episodes:. Others have more recently reported thrombocytopenia, hemorrhage, and hemolysis with oxaliplatin.[15] Prophylactic platelet transfusions should be considered on a case-by-case basis, especially if bleeding has occurred previously.

Hepatic arterial infusion of fluorodeoxyuridine utilizing an implanted pump for the treatment of liver tumors has been reported to result in a significant incidence of upper GI toxicity with biliary sclerosis, gastritis, peptic ulcers, and intra-abdominal bleeding due to catheter displacement.[16–18] Other unusual causes of bleeding include hemobilia secondary to presence and/or treatment of hepatobiliary tumors. Arterial-enteric fistulalization may result in severe intraluminal hemorrhage, and operative management should be approached with joint vascular surgery consultation. Communication with vascular structures should always be considered in previous surgical sites and areas of prior radiation treatment.

Intra-abdominal hemorrhage is usually seen as a result of tumor rupture (Fig. 53-1), but spontaneous splenic rupture in patients with hematologic malignancies can be seen as well. Rapid tumor necrosis with subsequent hemorrhage has been reported during chemotherapy and is most commonly seen in patients with GI lymphomas. The incidence of significant GI bleeding in this patient population secondary to tumor lysis from therapy is approximately 5%.[19] Surgical resection of GI lymphoma before systemic or radiation therapy could be beneficial for lesions that are amenable to resection with minimal morbidity.

Treatment of upper GI tract bleeding requires defining its source. Early endoscopic examination should be performed for diagnosis. In most patients, nonoperative treatment is successful. Supportive measures with antacids, proton pump inhibitors, and blood products will control the bleeding in most patients with gastritis or ulceration. Endoscopic injection with sclerosing agents or endoscopically guided use of coagulative laser or electrocautery can sometimes control bleeding from isolated ulcerations or tumors. If medical management fails to stop bleeding from erosive gastritis or if there is intractable bleeding necessitating ongoing packed red cell transfusion, operative management should strongly be considered. Indications to proceed with surgery should also be predicated on the patient's quality of life and disease prognosis. For erosive gastritis, total or near-total gastrectomy is the most effective means of controlling hemorrhage but is associated with a high morbidity and mortality because of the underlying

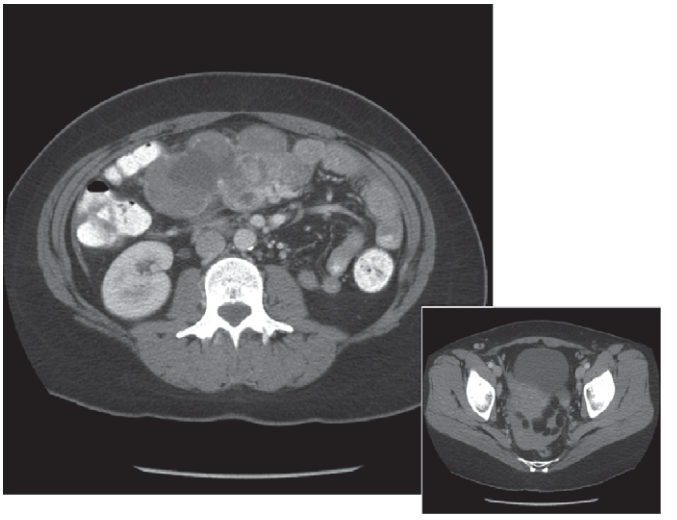


Figure 53-1 • Intra-abdominal hemorrhage from gastrointestinal stromal tumor (GIST). CT scan of the abdomen demonstrating a 10.5-cm proximal jejunal GIST on initial presentation with intra-abdominal perforation and subsequent hemorrhage (*inset photo,* blood in the pelvis).

medical condition of these patients. Bleeding from duodenal ulcer disease in a patient with cancer is probably best treated by oversewing the ulcer and performing a truncal vagotomy with pyloroplasty. When extensive bleeding occurs from a tumor, operative resection might be the only recourse.

Lower GI tract bleeding is infrequently seen from primary cancer sites. Endoscopy, radionuclide imaging, or mesenteric angiography might be required to identify the source. Colonoscopy should be performed as the initial diagnostic study for lower GI bleeding, followed by consideration of upper GI endoscopy. Brisk bleeding can make endoscopic examinations difficult. For GI bleeding at a rate greater than 1 mL/minute, selective mesenteric arteriography might be the most accurate method for localization. Technetium-labeled red blood cell scans can be helpful in localizing the site of hemorrhage when bleeding is more intermittent. Small bowel sources should be entertained if upper and lower endoscopic examination is negative. Primary small bowel tumors (e.g., carcinoids, adenocarcinomas, gastrointestinal stromal tumors) and metastatic lesions (e.g., melanoma, lung) to the small bowel may initially present with an episode of lower GI bleeding. Bloody diarrhea can be seen as a sequelae of radiation treatment for rectal cancer. Radiation enteropathy resulting in bleeding can usually be managed nonoperatively, but in the setting of acute hemorrhage, resection with intestinal diversion might be required.

Operative management of lower GI bleeding is necessary when modalities such as vasopressin infusion or embolization are not indicated or are unsuccessful. In poor-risk patients, these nonoperative therapies are associated with a definitive risk of bowel infarction. Prior localization of the bleeding source is necessary to identify the segment of bowel to resect. When it is not possible to localize the source of colonic bleeding either preoperatively or intraoperatively with inspection or on-table endoscopy, subtotal colectomy should be performed.

ADVERSE EVENTS WITH CYTOTOXIC AGENTS LEADING TO BLEEDING OR PERFORATION

Special consideration should be given to patients receiving targeted molecular therapy agents. Bevacizumab (Avastin), a monoclonal antibody targeting the vascular endothelial growth factor (VEGF)

receptor, has been shown to significantly improve overall and progression-free survival rates in patients with metastatic colorectal cancer when used with combination chemotherapy compared to chemotherapy alone[20,21] Results of these randomized trials have led to the widespread use of bevacizumab in patients with metastatic colorectal cancers and in selected patients with other solid-organ cancers. Because this drug targets tumor angiogenesis, rare but serious complications, such as bowel perforation, can occur in about 1.5% of patients during treatment.[22] Risk factors for perforation are difficult to define but include longer length of treatment, prior radiation, carcinomatosis, and bowel inflammation from entities such peptic ulcer disease, tumor necrosis, diverticulitis, and chemotherapy-induced colitis.[20,22] Bowel perforation can occur at sites that are not affected by malignant disease; perforations were reported in 8% of patients treated with gemcitabine and bevacizumab for pancreas cancer.

Another targeted molecular agent associated with bowel perforation and gastrointestinal bleeding is imatinib (Gleevec), a tyrosine kinase receptor inhibitor that is commonly used in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors (GIST). In an early Phase II study of metastatic and/or unresectable GISTs, 5% of patients had hemorrhages into the GI tract or tumor sites.[23] Some of the cases might have been related to tumor rupture. However, episodes were not correlated to imatinib dosing, tumor burden, treatment duration, or platelet count.

With the expanding indications for use of immunotherapeutic agents such as interleukin-2 (IL-2) for metastatic melanoma and renal cell cancer, clinicians should be alert to occasional cases of colonic infarction and perforation.[24] The causes of these perforations are unknown, but it has been postulated that they arise from impaired perfusion due to hypotension, tissue edema, and vasoconstriction secondary to the use of pressor agents. A recent report suggests that bowel perforation might be more commonly seen when IL-2 is used in combination with anti-CTLA 4 antibody and that association can be seen in conjunction with autoimmune colitis.[25]

Bowel necrosis with perforation has been described with the use of cytosine arabinoside. In 50 patients treated for leukemia, seven patients were found to have bowel necrosis and peritonitis at autopsy.[26] Paclitaxel (Taxol), which is commonly used to treat patients with ovarian, breast, and non-small-cell lung cancers, has also been reported as a chemotherapeutic agent that can cause bowel perforation unrelated to tumor lysis.[27] In patients with advanced ovarian cancer, this is a rare but serious complication, and its presentation is associated with a 43% mortality rate.[28] Noncytotoxic drugs are the presumed cause of perforation when bowel wall injury cannot be associated with tumor necrosis or other specific factors in patients with cancer who are undergoing drug therapy. Immunosuppressed patients have a blunted inflammatory response and may have a more subtle presentation of GI perforation. The drugs that are most commonly implicated are corticosteroids, which can give rise to ulcers and perforations in various portions of the GI tract.

INFLAMMATORY CONDITIONS IN THE CANCER PATIENT

Increasingly, aggressive chemotherapeutic regimens are being employed in the treatment of patients with cancer. These treatments can expose patients to life-threatening complications related to bone marrow suppression and neutropenia. The incidence of acute illnesses necessitating surgical intervention in the setting of the neutropenic patient with cancer is approximately 7%.[29] Unique inflammatory abdominal problems in patients with cancer receiving aggressive therapies are reviewed in this section.

Neutropenic Enterocolitis

Neutropenic enterocolitis is a clinicopathologic syndrome that involves the gastrointestinal tract of patients receiving chemotherapy for hematologic and solid malignancies. The clinical condition has been given a variety of names in the past, including typhlitis, ileocecal syndrome, and necrotizing enteropathy. Most commonly seen in pediatric patients who are undergoing treatment for leukemia, neutropenic enterocolitis is still a relatively rare occurrence in adults, with an incidence of less than 5% in this patient population.[30–32]

The pathophysiologic basis of this clinical entity has not been established clearly and is undoubtedly multifactorial. Neutropenic enterocolitis characteristically affects the terminal ileum, cecum, and ascending colon in patients with chemotherapy-induced neutropenia. Although any part of the GI tract can be involved, the cecum appears to be the most severely affected, with mucosal ulceration, gangrene, and perforation. The presence of microorganisms such as *Clostridium difficile, Pseudomonas, Escherichia coli, Klebsiella,* and *Candida* in areas of necrotic bowel and in blood cultures suggests that enterocolitis is primarily an infectious process in an immunocompromised host. The invasion of bacteria itself can cause further necrosis of the bowel wall, leading to full-thickness infarction and perforation of the intestine.

The clinical presentation of neutropenic enterocolitis is extremely variable, and there are no specific criteria on which to make the diagnosis. Furthermore, the symptoms are nonspecific and can be similar to those of a number of other GI processes. Affected patients typically present with fever, abdominal pain and distension, and diarrhea. Abdominal tenderness is frequently localized to the right lower quadrant but can also be diffused. Peritonitis suggests intestinal perforation. Portal venous gas, low serum bicarbonate levels, and generalized peritonitis are ominous findings and suggest a poor outcome.[33,34] A right lower quadrant mass might be palpable, indicating a dilated cecum or a focal inflammatory phlegmon or abscess. Advanced cases can present with systemic sepsis and multiorgan failure.

No specific laboratory or radiologic findings are diagnostic for neutropenic enterocolitis. Pneumatosis intestinalis is often seen and is not itself an indication for surgical intervention.[35] The initial treatment for neutropenic colitis is supportive, with the administration of broad-spectrum antibiotics, nasogastric decompression, intravenous fluids, bowel rest, and serial abdominal examinations.[36] In most patients, these measures are sufficient, and symptoms resolve after correction of the neutropenia. Surgical intervention is rarely helpful, but sound surgical judgment should be exercised in determining which patients require an operation (Box 53-2). Specific situations that dictate surgery include uncontrollable GI bleeding, intestinal perforation, and deteriorating clinical course on medical management.

Appendicitis

Other intra-abdominal inflammatory conditions, such as appendicitis, can be indistinguishable from neutropenic enterocolitis in patients receiving chemotherapy. In large series of children with leukemia or other malignancies, the incidence of appendicitis has been reported to be between 0.2% and 2%, which is equivalent to the incidence in the general pediatric population.[37] Typically, acute appendicitis presents with right lower quadrant pain and localized tenderness. "Classic"

Box 53-2. CONDITIONS FOUND AT SURGERY IN NEUTROPENIC PATIENTS WITH CANCER UNDERGOING EMERGENCY LAPAROTOMY

- Neutropenic enterocolitis
- Bowel perforation
- Hemorrhage (e.g., tumor site, gastritis, gastric ulcers)
- Other (appendicitis, cholecystitis, incarcerated hernia, etc.)
- No disease

symptoms and clinical findings of appendicitis can be followed by a CT scan to confirm diagnosis.[38] Whereas the treatment of neutropenic enterocolitis is primarily medical, the treatment of acute appendicitis is surgical. Nonoperative management of appendicitis (e.g., intravenous antibiotics with interval appendectomy) is associated with high mortality in patients with leukemia. Delay in treatment results in a higher incidence of perforation, peritonitis, and death. Appendectomy is the treatment of choice for appendicitis. Cases that are complicated by perforation or abscess formation could necessitate the placement of drains, and the surgical incision should be left to close by secondary intention.

Pancreatitis

Pancreatitis in the patient with cancer is likely to be caused by the same factors that are implicated in the general population, such as gallstones or alcohol abuse. However, pancreatitis can also be a complication of either medical or surgical therapy. Primary adenocarcinoma of the pancreas is seldom a cause of acute pancreatitis. Metastases to the pancreas have been reported from a variety of tumors, including renal cell carcinoma, melanoma, some types of soft tissue sarcoma, and cancers of the prostate, breast, and lung. However, the vast majority of these metastases are asymptomatic.

Pancreatitis is a recognized complication of a number of antineoplastic chemotherapeutic agents, although the drug with which it is most commonly reported is L-asparaginase. Other antineoplastic drugs that are known to induce pancreatitis are corticosteroids, didanosine, and, less commonly, cytarabine, cisplatin, interleukin-2, vincristine, methotrexate, mitomycin C, cyclophosphamide, doxorubicin, and ifosfamide.[39,40] The clinical course of patients with chemotherapy-induced pancreatitis is most often mild and self-limiting but can progress to necrotizing pancreatitis or pseudocyst formation. Pancreatitis is also a complication of other cancer treatments. Associated procedures, such as endoscopic retrograde cholangiopancreatography, pancreatectomy, or splenectomy, can also result in pancreatitis. Transarterial embolization of the liver for primary or metastatic tumors can cause pancreatitis by misperfusion of chemotherapeutic agents.

The clinical presentation of pancreatitis includes epigastric pain, nausea, vomiting, generalized ileus, tachycardia, and fever. The diagnosis is usually confirmed by elevations in the serum amylase and lipase levels. CT of the abdomen with intravenous contrast is useful to confirm the presence of pancreatic inflammation or phlegmon and to document necrosis or pseudocyst. The treatment of pancreatitis is generally supportive and includes bowel rest, hydration, and intravenous hyperalimentation. If possible, the causative agent should be eliminated or discontinued, if it can be identified. Necrotizing pancreatitis warrants consideration of pancreatic debridement if there is overwhelming infection.

Perianal and Perirectal Infections in Patients with Cancer

The exact pathogenesis of perianal infections in the patient with cancer is not well defined, though most patients have an underlying neutropenia or immunosuppression. Many patients have a history of pre-existing anorectal problems, including previous perianal or perirectal abscesses, fistula in ano, anal fissures, or hemorrhoids. Once established, the infection can spread into the ischiorectal fossa, supralevator space, retroperitoneum, or perineum. Perianal and perirectal infections develop most frequently in patients with acute leukemia who are being treated with chemotherapy but can also be encountered in some patients with solid tumors or following BMT. In most series in the literature, the incidence of perianal infections in patients with leukemia is between 2% and 8%.[41,42]

The most common presenting symptoms are perianal pain and fever. On examination, the perianal region could be erythematous, indurated, and extremely tender to palpation. Often, an abscess does not develop owing to the patient's profound neutropenia or immunosuppression. Spontaneous drainage of an abscess can result in ulceration, purulent discharge, or bleeding. Spread of the infection in the perineum can lead to a fulminant necrotizing fasciitis. The initial course of therapy is administration of broad-spectrum antibiotic and supportive measures such as sitz baths, warm compresses, stool softeners, and analgesics. Most patients can be managed successfully using a nonoperative approach. However, early surgical intervention for complete drainage of pus and debridement of necrotic tissue may be required and should not be delayed when indicated.

INTESTINAL OBSTRUCTION

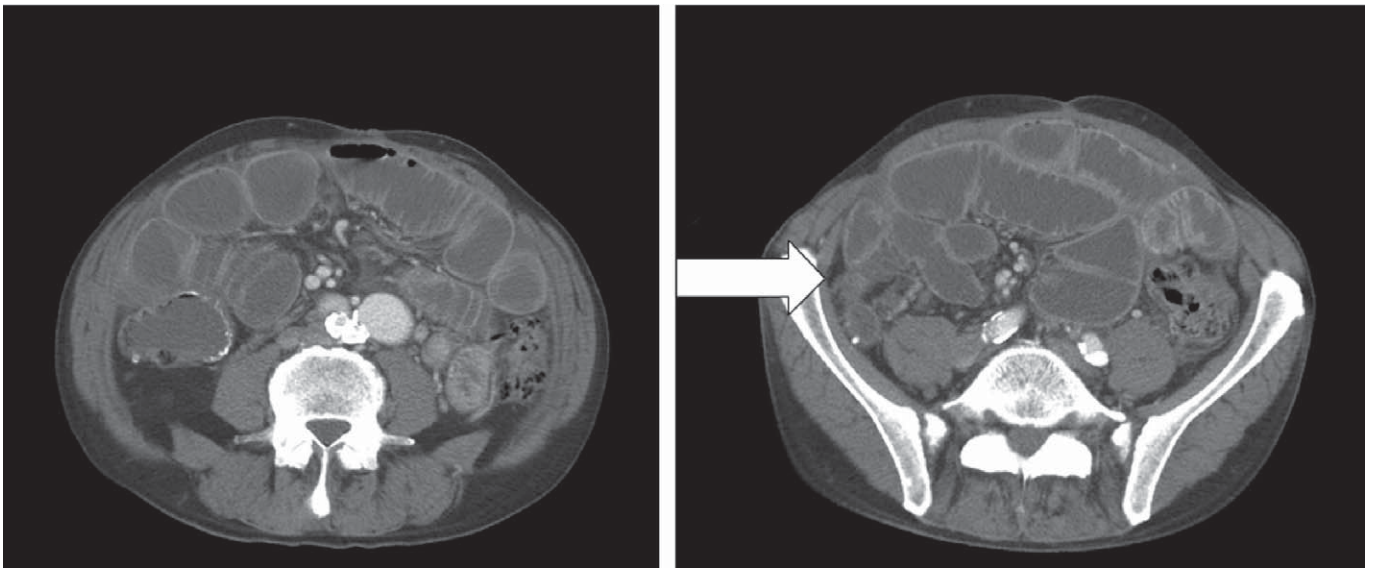
Complete or partial obstruction of the GI tract is a common problem in patients with cancer.[43] Typical presentation includes abdominal pain, nausea, and vomiting. Intestinal obstruction is one of the most common indications for emergency laparotomy.[1,3] Intestinal obstruction can occur at any site along the GI tract, and symptoms are often dictated by the level of obstruction. Initial symptoms may be identical to those of adynamic ileus, a condition that needs to be distinguished from obstruction. Adynamic ileus in patients with cancer can be related to chemotherapeutic agents or can be secondary to other metabolic problems. Vincristine sulfate and the vinca alkaloids are known to produce peripheral neuropathies and a paralytic ileus. Drug-induced ileus is estimated to occur in 10% of patients receiving these agents and could be due to their neurotoxic effects.[44] Clinical presentation and radiologic studies are very helpful in differentiating adynamic ileus from a mechanical obstruction. With an adynamic ileus, generalized small bowel and colonic distension is apparent on plain films without the multiple air-fluid levels and absence of colonic gas that are seen with mechanical obstruction. Cross-sectional imaging with CT is now the adjunctive study of choice, since it can provide information simultaneously about the presence, level, severity, and cause of obstruction.[4,45]

Therapeutic options include nasogastric decompression with bowel rest (e.g., NPO with intravenous fluid support). Adjunctive treatment with analgesics, antiemetics, somatostatin, or motility agents have been used with varying success. Patients with a history of previous malignancy who present with bowel obstruction should be treated like any other patient with intestinal obstruction.[43] In the case of a first presentation with obstructive symptoms, the etiology is benign (e.g., due to adhesions or herniation) in up to one third of patients. Many patients who require laparotomy to treat their obstructions are found to have benign disease, and some even have a new primary malignancy.[46] Given a good baseline performance status, surgical exploration for benign causes of obstruction have a high rate of success.

Recurrence of cancer, either locally or as diffuse peritoneal disease, is a more common problem and, unfortunately, is more difficult to treat. Surgical intervention is required if bowel strangulation and infarction are suspected because of fever, leukocytosis, and localized peritoneal tenderness. Radiographic evidence of complete bowel obstruction with loss of air in the distal large bowel and absence of flatus may likewise prompt an urgent laparotomy. Patients with partial obstructions can be managed expectantly. Further evaluation to include CT scan or other contrast studies may be helpful in delineating level(s) or extent of obstruction (Fig. 53-2).

Successful nonoperative management of malignant bowel obstruction is reported in up to 29% of cases; however, recurrent episodes of obstruction are commonplace.[43] Operative mortality and successful intervention rates for patients with cancer undergoing exploratory laparotomy for intestinal obstruction are difficult to measure, since patient selection bias tends to skew the reported results. The extent of disease and failing performance status are associated with high perioperative morbidity and mortality.[43,47] Even with early relief of symptoms, durability of palliation can be short.

Retrospective studies have identified presence of ascites and multiple sites of obstruction as factors predictive of unsuccessful surgical



A B

Figure 53-2 • Small bowel obstruction in a patient with metatstatic appendiceal carcinoma. **A,** CT scan of the abdomen demonstrating a widely patent–stapled anastomosis from a prior right colectomy; **B,** Decompressed bowel distal to the point of obstruction *(arrow).* Findings at laparotomy were consistent with intractable bowel obstruction due to adhesions from small tumor implants.

intervention. Conversely, long disease-free interval, good nutritional status (albumin >3.0 mg/dL), and good performance status are predictive of successful laparotomy. However, each patient must be approached on an individual basis, and it is of paramount importance to combine surgical decision making with basic principles of palliative care in forming a treatment plan. The reported results of surgical treatment for intestinal obstruction in this patient population vary significantly. The site of the primary tumor may also influence the clinician's approach to management, since the natural history of a cancer should also be taken into account.

Stomach and Duodenum

The most common causes for upper GI obstruction involving the stomach or proximal duodenum in patients with cancer are benign peptic ulcer disease, primary carcinoma of the gastric antrum, and gastric outlet obstruction secondary to an upper GI, pancreatic, or biliary tract cancer. Symptoms due to obstruction at this level include nonbilious vomiting, postprandial pain, and epigastric fullness. On physical examination, a succussion splash or palpable mass is present in approximately one third of cases, reflecting ascites and tumor burden. Endoscopy is helpful for defining the site and cause of upper GI obstruction.

Benign, obstructive ulcer disease is uncommonly seen in the modern era of H2-receptor blockers and proton pump inhibitors. Operative therapy is generally required after initial stabilization with fluid resuscitation and nasogastric decompression in uncontrolled cases. Vagotomy with pyloroplasty is the treatment of choice, particularly for patients with cancer who might be debilitated. For obstructing primary gastric carcinomas, a curative resection with gastrojejunostomy reconstruction is recommended if the patient is stable and if the procedure is technically feasible. In cases of advanced disease, gastrostomy tube placement, with or without gastrojejunostomy (intestinal bypass), may be the best course of action. When gastric outlet obstruction is due to an unresectable pancreatic or biliary tract neoplasm, prognosis is typically poor owing to the extent of disease. Creation of a gastrojejunostomy via an open or laparoscopic approach can be considered for bypassing the obstruction and maintaining gastrointestinal continuity, but outcomes are not uniform. Many patients have poor emptying of stomach contents even with a mechanically patent anastomosis. Therapeutic endoscopic options are in their infancy, and success has been seen with endoscopically deployed metal endoluminal stents. This procedure is gaining widespread acceptance, and reports show 70% relief of symptoms with low complication rates. Common complications include perforation (0% to 15%) and stent migration (0% to 40%).[43,48] In patients with concomitant biliary obstruction from a cancer in the head of the pancreas, an endoscopic retrograde cholangiopancreatography can be performed at the same setting to accomplish biliary stenting with plastic or metal prostheses.

Small Intestine

Most malignant obstructions of the small intestines are a result of metastatic deposits from other cancers; primary tumors of the small bowel are rare. The most common malignancies that give rise to obstructive metastatic deposits are intra-abdominal tumors, such as colorectal, ovarian, pancreatic, and gastric cancers.[49] Carcinomatosis with resultant malignant bowel obstruction from appendiceal primaries (including pseudomyxoma peritonei) are seen less commonly. Symptoms of small bowel obstruction include crampy abdominal pain, distension, nausea, and vomiting. Physical examination usually reveals percussion tympany and high-pitched bowel sounds. Plain films of the abdomen reveal multiple air-fluid levels within the small intestine. A contrast study of the large bowel should be performed to determine whether distal obstruction is present, as carcinomatosis can involve multiple sites. If a partial small bowel obstruction is diagnosed (e.g., presence of gas in the large bowel), then nonoperative management is generally recommended.

During an exploratory laparotomy when intestinal bypass is being considered, it is preferable to perform the simplest procedure with maximal conservation of bowel length. Ileostomy or colostomy might be unavoidable, depending on the level of obstruction. At least one third of patients with symptomatic relief of malignant small bowel obstruction experience recurrence of the obstruction at a later point in time. Survival after bypass surgery for malignant obstruction is often short, and is a marker of advanced malignancy.

Colon and Rectum

Obstruction of the colon and rectum occurs approximately half as frequently as small bowel obstruction in the cancer patient population. Large bowel obstruction is more often a result of malignancy (i.e., primary or recurrent tumor) than of benign causes such as volvulus or diverticulitis. Symptoms include vomiting, crampy abdominal pain, bleeding, lack of flatus or stool, or change in bowel habits. Flat and upright abdominal films are important in the initial assessment of these patients. Follow-up contrast studies are helpful in delineating the site of obstruction.

Initial treatment should consist of nasogastric tube decompression and fluid resuscitation. If a total colonic obstruction is present, dilation of the proximal colon can lead to perforation of the cecum, especially if a competent ileocecal valve is present. Cecal dilation of 12 to 14 cm is associated with a high risk of perforation, and a decompressive procedure should be performed urgently to avoid this complication. A diverting colostomy may be the surgical therapy of choice if there is evidence of peritoneal carcinomatosis. If the obstruction is related to a primary colon cancer, resection with primary anastomosis or ostomy should be performed. Obstructive tumors of the rectum are often a harbinger of locally advanced primary rectal tumors or recurrent carcinomas after a previous low anterior resection. These tumors are often associated with evidence of distant metastatic disease or a high local recurrence rate if resection is performed. Therapeutic endoscopy with colonic stenting offers an alternative to surgical diversion, providing excellent palliation and allowing an elective procedure to be performed following bowel decompression and other treatments if necessary. There is no apparent difference in long-term survival rates with stents compared to an emergent operation.[50]

Palliation Issues in Bowel Obstruction

Heterogeneity of patient populations, coupled with lack of evidence-based medicine in this area, makes appropriate patient selection one of the biggest challenges in palliative surgery. End-stage cancer patients are diverse in multiple facets: symptoms experienced, tumor biology, extent of underlying disease, previous treatments received, type of palliative procedure performed, and psychosocial circumstances, to name a few. Deterioration of a patient's general medical condition can make operative treatment of bowel obstruction prohibitive or inappropriate. A patient might also wish to avoid further operative interventions in the face of terminal disease. In these patients, optimal medical management should be considered to help alleviate suffering from abdominal pain, nausea, vomiting, and dehydration.

Because of the nature of the underlying disease process, surgical resection and/or bypass might not yield durable palliation. Proper patient selection is paramount to successful palliative efforts. Recent series have reported effective palliation in up to 80% of patients with obstruction.[3] Another approach that has been described for the therapy of these patients is the use of a decompressive gastrostomy tube in conjunction with either enteral or parenteral fluids. Management of malignant bowel obstruction has to be coordinated with end-of-life care in some patients. Time to mortality with malignant bowel obstruction is short; small series report mean durations of survival ranging from 35 to 64 days regardless of intervention.[43,48,51,52]

GASTROINTESTINAL PROBLEMS FOLLOWING BONE MARROW TRANSPLANTATION

Evaluation of acute abdominal complaints in patients who have had BMT represents a major diagnostic challenge for the surgeon. Virtually all patients who have undergone BMT will experience gastrointestinal problems at some point in the post-transplant period; these can include nausea, vomiting, alterations in liver function tests, diarrhea, and abdominal pain.[39] Such findings in an acutely ill patient following BMT may herald a broad spectrum of acute abdominal processes. There are, however, several disease entities that are unique to the BMT patient, and these warrant special consideration.

There are three common causes of abdominal complaints in the BMT patient that are unique:

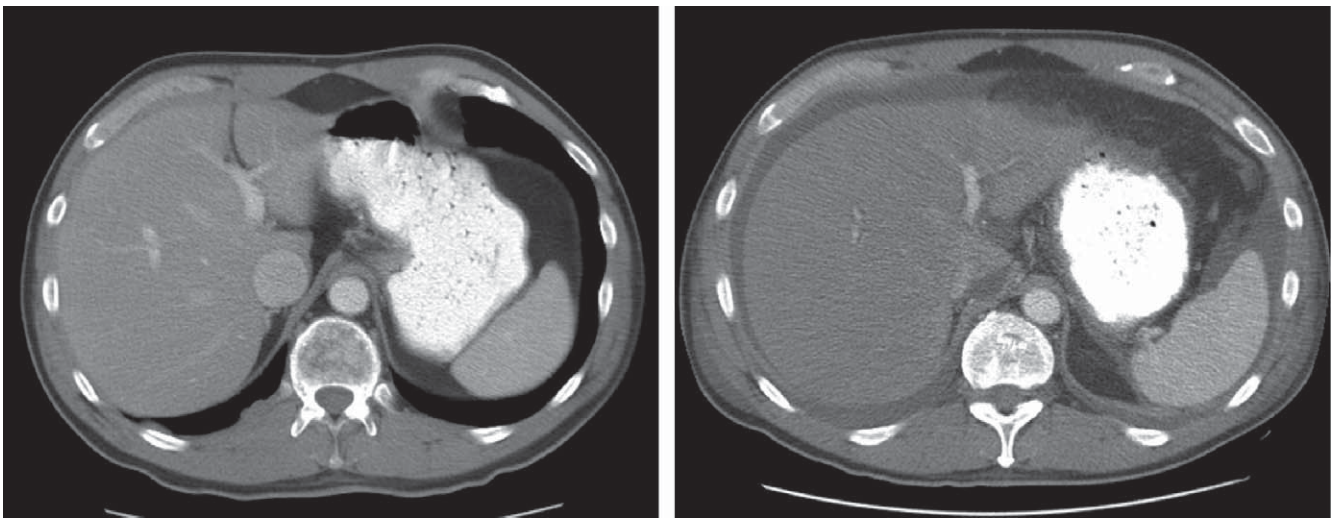
1. High-dose induction chemotherapy or chemoradiation therapy given before transplantation
2. Acute intestinal graft-versus-host disease (GVHD) in recipients of allogeneic transplants
3. Infections of the gut that occur before bone marrow recovery

The post-transplant period at which each of these potential complaints becomes problematic differs. Injury to the gastrointestinal tract and liver after high-dose chemotherapy and radiation is usually present by day 10; the process is transient and usually resolves after several weeks. Acute GVHD appears between 2 and 8 weeks after allogeneic BMT, while chronic GVHD is manifest from 3 to 15 months after BMT. In patients receiving HLA-mismatched marrow, the onset of acute GVHD could be as early as 7 days. Lower GI tract involvement with acute GVHD is characterized by diarrhea and abdominal cramping and is often severe in its presentation. GVHD affecting the upper GI tract is characterized by anorexia, dyspepsia, nausea, and vomiting. Biopsies of affected portions of the GI tract for histologic examination are diagnostic, though diagnosis is often made on clinical grounds. Immunosuppression with combination therapy is the cornerstone of treatment.

Infections of the gut caused by bacteria and fungus are most often seen before post-transplant day 30, while viral infections are usually seen after 30 days, although there are reports of late (5 months to 1 year) reactuation of varicella zoster infection associated with acute abdominal pain, hepatitis and pancreatitis, or disseminated disease. Mortality rates are from 50% to 100%.[53,54]

GVHD is a process in which donor T-cells react to recipient cells; it develops in 30% to 50% of patients receiving allogeneic grafts.[55,56] Despite the prominence of intra-abdominal organs and symptoms in the manifestations of GVHD, it is rare that surgical intervention is necessary. The most common indications for abdominal surgery in patients with GVHD are gastrointestinal bleeding and obstruction.[56,57] Perforation of the bowel is uncommon. The finding of pneumatosis intestinalis on abdominal radiography has been reported to be present in as many as 18% of BMT patients with acute GVHD;[58] the majority of these cases do not require operation.[54,59–61] Although usually an indication for surgery, free air in the peritoneal cavity need not be associated with a frank bowel perforation, and there are reports of managing this problem without an operation.

Another intra-abdominal complication of BMT that presents with abdominal pain is venoocclusive disease (VOD) of the liver.[39,62] The etiology of VOD is thought to be damage to the endothelium of hepatic venules and centrilobular hepatic necrosis, leading to fibrosis and occlusion of the central hepatic veins. VOD is associated with significant mortality. The differential diagnosis of VOD is lengthy and includes any disorder that could result in right upper quadrant pain, jaundice, or ascites. A partial list would include such disorders as hepatitis, drug- or parenteral nutrition-induced liver dysfunction, acute cholecystitis, cholangitis, or liver abscess; careful work-up should be undertaken. The diagnosis of VOD can usually be made on clinical signs, liver biopsy being reserved for patients in whom the diagnosis is not certain (Fig. 53-3). Because of underlying hematologic disorders, liver biopsies are associated with acute bleeding and must be performed with care. The treatment of VOD is supportive, with emphasis on maintaining intravascular volume and renal



A B

Figure 53-3 • Venoocclusive disease following bone marrow transplant. **A,** CT scan of the abdomen demonstrating no abnormalities of the liver. **B,** Following allogeneic peripheral stem cell transplant for refractory large B-cell lymphoma, this patient developed increasing fatigue, abdominal distention, and elevated liver function tests. CT scan showed new findings of ascites and low-density diffusion of the liver. Subsequent laparoscopic biopsy of the liver confirmed venoocclusive disease.

perfusion while limiting the amount of sodium and extravascular fluid accumulation.

In summary, BMT has become a proven and accepted treatment for a number of hematologic and solid malignancies. Transplant-related complications, such as GVHD and VOD, remain a major cause of morbidity and mortality. The presentation and sequelae of both these disease entities present difficult diagnostic and management challenges for the clinician. Although the management of GVHD and VOD is primarily medical, surgical consultation could be required for evaluation of abdominal pain and distension, nausea, vomiting, diarrhea, hyperbilirubinemia, or other gastrointestinal complaints. An understanding of the manifestations of these complications, together with vigilant clinical evaluation, is paramount to determine when surgical intervention is necessary in this complex patient population.

FISTULAE

A fistula is an abnormal connection between two epithelialized surfaces, and fistula formation is an important complication of cancer and its treatment. Fistulae that complicate cancers have been reported between the stomach and pericardium, the biliary and bronchial trees, the portal and systemic circulations, and the alimentary canal and vascular system, to name a few. This overview concentrates on the more routine fistulae connecting the skin, alimentary canal, and genitourinary tract in various combinations.

Fistulae are seen as complications in patients with cancer because multiple risk factors for fistula development are often present in these patients.[63] Fistulae are rarely the presenting symptom of an intra-abdominal malignancy; they most often present as complications during or after treatments. Most clinicians agree that contributing factors include prior abdominal surgery, inflammatory bowel disease, use of radiation therapy, cancer, malnutrition, and intra-abdominal sepsis. Unfortunately, many of these factors are prevalent in patients with cancer and are not often reversible. Despite the use of total parenteral nutrition, enteral nutrition, antibiotics, and highly sophisticated bioengineered wound care adjuncts, mortality and morbidity rates from gastrointestinal fistulae remain high. Although mortality rates as low as 7% are reported, numbers in the range of 10% to 30% are more representative.[64,65] The exact incidence of GI fistula formation in patients with cancer is not known but is likely quite low.

Enterocutaneous fistulae commonly occur in patients who have received radiation therapy. Direct invasion with subsequent tumor necrosis can result in an abnormal connection between viscera and the skin. Ischemic necrosis secondary to neoplastic vascular invasion or secondary to small vessel occlusion from host reaction and sclerosis likewise can lead to fistula formation. Finally, tumor-induced perforation with abscess and subsequent erosion can result in fistula formation. This latter mechanism is particularly troublesome, as it can lead to diagnostic confusion and can complicate management. Ionizing radiation could have both acute and chronic effects on the GI tract. The acute effects—a result of the depletion of rapidly proliferating mucosal cells causing diarrhea, nausea, vomiting, abdominal pain, and GI tract bleeding—are generally self-limiting. However, chronic radiation damage can become evident as early as 1 month after radiation therapy, or it might not be clinically apparent for as long as 30 years after treatment.[66,67] Although radiation injury to the bowel can arise as a complication in as many as 15% of patients receiving treatment to abdominal fields, fistulae occur more rarely. Factors related to the incidence of radiation-induced injury include the total radiation dose and fractionation, the sensitivity of exposed normal organs within the radiation port, anatomic considerations, the presence of comorbid conditions, and concomitant administration of other drugs.

Bowel tolerance of radiation therapy is limited. The small bowel, stomach, and colon are the least tolerant organs, with a maximum tolerated dose of 45 Gy. The greater the amount and extent of exposure to the radiation beam, the greater is the risk of injury.[68] Factors that tend to fix the bowel in a single location, such as postoperative adhesions, increase the likelihood of radiation enteritis. Pre-existent large-vessel atherosclerosis and small-vessel diabetic vasculopathy can increase sensitivity to radiation injury. Finally, the effects of many chemotherapeutic agents—especially doxorubicin, 5-fluorouracil, gemcitibine, and mitomycin-C—can potentiate the effects of radiation therapy, increasing its toxicity. In this regard, pyrimidine analogs

such as bromodeoxyuridine and iododeoxyuridine are being studied as tumor-selective radiation sensitizers.[69] Many techniques have been developed to limit GI tract exposure to radiation, including the use of shielding and conformal mapping techniques as well as intra-operative radiation therapy, whereby normal visceral structures can be better shielded from the radiation ports.[70]

Fistulae that complicate cancer generally occur during active treatment or subsequent follow-up. To reduce the risk of fistula formation following surgical procedures, adherence to good surgical principles and techniques is thought to be helpful. Systemic antibiotics might help to prevent complications (including fistulae) in these situations. Intra-operative risk factors for fistula formation include active infection, extensive adhesions, creation of serosal injuries, prior radiation therapy, prior fistulization, and presence of ischemic tissue. Thorough drainage of all intra-abdominal infection and debridement of all devitalized and ischemic tissue can reduce the incidence of fistulae. Protection of sites of anastomosis or extensive dissection could also be important, particularly in the previously irradiated abdomen. Vascularized flaps, including serosa, omentum, and muscle, have all been described to fill soft tissue defects and exclude small bowel from areas of dissection.[71] Many investigators have demonstrated the relationship of nutritional status to operative morbidity and mortality, including fistulae. In patients with cancer who developed postoperative gastrointestinal fistulas, an albumin level of less than 3.0 g/dL was a poor prognostic factor for fistula closure.

GI fistulae occur commonly during the treatment of gynecologic malignancies. Although less common, they also occur in the settings of bladder and rectal cancer. Postoperative irradiation after the extensive pelvic operations exposes the bowel to high doses of ionizing radiation. Fistulae resulting from the treatment of other cancers are much less common.

A number of factors decrease the likelihood of spontaneous closure of a fistula. The most common are undrained infections and luminal obstruction distal to the fistula. Other factors include prior radiation or chemotherapy, epithelialization of the fistula tract, cancer within the tract, granulomatous disease (e.g., inflammatory bowel disease or mycobacterial infection) within the fistula, presence of a foreign body, and malnutrition. Although predictive of morbidity due to fistulae, fistula output does not necessarily appear to be related to the probability of spontaneous fistula closure. Given proper nutritional support and attention to these factors, as many as 60% of GI fistulae can close spontaneously.[64,65]

Complications that are routinely encountered with GI fistula include fluid and electrolyte disorders, sepsis, malnutrition, and impaired skin integrity. The frequency and severity of these complications relate to the daily volume of fistula output and to the composition of the output. High-output fistulae (>1 L/day) tend to originate more proximally in the GI tract. Because of the specialized composition of gastric juice, bile, and succus pancreaticus, these more proximal fistulae not only tend to lead to dehydration but also are more prone to cause electrolyte and acid-base imbalances. Low-output fistulae generally originate more distally in the alimentary canal, resulting in low-volume outputs that are generally isotonic. For these reasons, the classification of fistulae according to their daily output volume can help to predict the likelihood and kinds of complications to be expected.

Resuscitation of patients with GI fistulae follows the principles of general fluid and electrolyte assessment and management. A urinary catheter and, if necessary, central venous pressure monitoring are quite helpful. Specific fluid, electrolyte, and acid-base disturbances, organ dysfunction, and nutritional status should be identified with the initial bloodwork and treated appropriately. Subsequent diagnostic and therapeutic maneuvers must await completion of the resuscitation phase, so these issues must be dealt with promptly, over the initial 12 to 48 hours after presentation.

Patients who exhibit signs of sepsis must be evaluated aggressively to identify the source. Intra-abdominal and perifistular abscesses are common and must be identified quickly. Thorough physical examination (including digital examination of the rectum, vagina, stomas, and wounds) is absolutely necessary. CT scanning of the abdomen and pelvis using intravenous and enteric contrast and contrast in the rectum, fistula tract, and drainage tubes is often the most enlightening radiologic study (Fig. 53-4). Any undrained foci of infection must be addressed aggressively and drained either percutaneously or operatively. Once the acute electrolyte imbalances have been corrected and the fistula output has stabilized, intravenous fluid and nutritional infusions may be combined to simplify fluid management. Definitive treatment of fistulae ultimately requires the reestablishment of normal skin integrity; macerated skin and large open wounds complicate and delay spontaneous or operative closure. Techniques such as sump drainage, stoma bag application, and barrier protection of the skin using special adhesives or pastes should be used liberally.

Malnutrition either pre-exists or will develop in nearly all patients with GI fistulae unless specific, aggressive nutrition support is initiated early in the treatment course. Either enteral or parenteral nutrition support can generally be started as soon as the initial resuscitative and stabilization measures have been accomplished. Formal nitrogen balance studies and indirect calorimetric measurement of energy expenditure are the gold standards for adjusting protein and calorie intake to meet needs. Once requirements have been determined, the route of administration that is chosen depends on overall patient status and the nature of the fistula. In general, early initiation of parenteral nutrition is helpful to ensure adequate support without delay. Subsequent aggressive attempts should be made to meet some or all of the patient's nutritional requirements enterally.

Fistulae can be managed appropriately only when their anatomic features are well defined. Reversible causes for fistulae failing to close spontaneously must be identified. Careful examination of the fistula with appropriate biopsies is necessary to rule out epithelialization or the presence of cancer. Generally, the entire GI tract should be investigated with radiographic contrast studies to rule out distal obstruction, to determine the origin of the fistula accurately, and to identify all involved organs and poorly drained associated abscesses. A fistulogram, obtained in the presence of an experienced surgeon, can provide valuable anatomic information and can help in the formulation of surgical plans. In patients with cancer, a thorough search for recurrent and metastatic disease is also important.

In patients who are stable and in whom no factors preventing spontaneous fistula closure are present, a trial period of nonsurgical management is generally indicated. The availability of parenteral and enteral nutrition support programs should be coordinated with home care services to allow for spontaneous closure. In some patients, adequate stabilization cannot be achieved. Ongoing fistula output or sepsis in these patients precludes nutritional repletion, adequate skin care, and protection of end-organ function. In this setting, early operation is mandatory.

The operative goals for treating intestinal fistulae are to effect excision of the fistula tract and associated diseased tissue, restore continuity of the GI tract, and prevent recurrent fistulae. Use of vascularized omental, mesenteric, bowel, or muscular flaps to fill inflamed cavities and protect anastomoses is often helpful and should be planned for in conjunction with appropriate consultants preoperatively. The definitive operation is a good opportunity to simplify subsequent management of the patient through the insertion of enteric tubes for feeding and GI drainage. Bypass of fistulae can be a useful palliative technique when definitive resection is technically impossible or is thought to be associated with prohibitive morbidity.



Figure 53-4 • Arterioenterocutaneous fistula. Patient with a multiply recurrent high-grade liposarcoma of the spermatic cord treated with radical surgical resection and radiation therapy. After the most recent surgery, the patient developed an enterocutaneous fistula that was managed conservatively. He later presented with brisk bleeding from the fistula and per rectum. **A,** CT scan of the pelvis demonstrating recurrent tumor and tract *(arrows)* of enterocutaneous fistula. **B,** Arteriogram with contrast extravasation from the left external iliac artery and communication of the bowel *(arrow).*

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F. LOCAL EFFECTS OF CANCER AND ITS METASTASIS

54 Superior Vena Cava Syndrome

David H. Johnson, Janessa Laskin, Anthony Cmelak, Steven Meranze, and John Robert Roberts

SUMMARY OF KEY POINTS

Etiology
- Superior vena cava (SVC) syndrome is usually due to neoplastic process—predominantly primary lung carcinoma, with a disproportionate number of patients having small cell histology; non-Hodgkin's lymphoma and metastatic tumors are the next most common.
- SVC syndrome can be iatrogenic—sometimes seen as a complication of central venous line or cardiac surgery.

Anatomy and Physiology
- Junction of the brachiocephalic veins forms the thin-walled, low-pressure SVC, which is subjected to obstruction from a variety of mediastinal components.
- External compression often precedes direct tumor invasion or thrombus formation.
- The SVC has an extensive collateral network.

Clinical Features
- Usual symptoms are head "fullness," dyspnea, cough, and chest pain, typically with insidious onset.
- More severe symptoms are infrequent, and life-threatening, neurologic symptoms are rare.
- Diagnosis is based on clinical findings.

Evaluation
- Chest radiograph typically shows mediastinal widening; a mass is often seen in the region of the SVC.
- Small-dose cavagrams can be safely accomplished to define exact location and routes of collateral flow.
- Computed tomography (CT) scanning identifies the mass and collateral flow and is the most helpful study to guide treatment.
- Treatment of an identified mass before histologic diagnosis is rarely justified unless prior diagnosis is established.
- Methods used to define histology are sputum cytology, bronchoscopy, lymph node biopsy, thoracentesis, percutaneous biopsy, mediastinoscopy, and thoracotomy; previously reported high risks associated with these procedures are not borne out in current data.

Treatment
- Radiation therapy with or without chemotherapy is the preferred treatment in most malignant causes of SVC obstruction, particularly small cell lung cancer (SCLC) and non-Hodgkin's lymphoma.
- Radiation therapy fractionation schedule depends on tumor histology, stage, prognosis, patient's general condition, and whether obstruction is acute or subacute.
- Surgery is usually reserved for selective patients with benign causes of obstruction and consists of a bypass procedure.
- Percutaneously placed, self-expanding intravascular wire stents provide an option or adjunct to other procedures in the palliative treatment of patients (usually with malignant disease).

INTRODUCTION

Obstruction of the superior vena cava (SVC) may occur as an acute or subacute process producing a syndrome with characteristic features including facial edema and plethora, dilation of chest wall and neck veins, mild to moderate respiratory difficulty, and, less commonly, conjunctival edema, central nervous system complaints such as headache, or, more rarely, visual disturbances and signs of altered states of consciousness.[1–4] The first recorded description of SVC obstruction (SVCO) occurred in 1757 when William Hunter described the entity in a patient with syphilitic aortic aneurysm.[5] For nearly two centuries thereafter, nonmalignant processes such as aortic aneurysms, syphilitic aortitis, or chronic mediastinitis due to tuberculosis were the predominant etiologic factors.[1,3,6,7] However, these diseases are now quite rare, and cancer has become the leading cause of SVCO primarily because of the rapid increase in the incidence of bronchogenic carcinoma after World War II.[1,3,6,8–10] Although SVCO was once considered a medical emergency, it is now well established that patients with SVCO rarely experience immediate, life-threatening complications.[6,11–13] Consequently, in cases in which a diagnosis is not known, it is appropriate to proceed with a biopsy to establish the underlying cause, because optimal management is dependent on etiology.[14]

ANATOMY AND PATHOPHYSIOLOGY

The SVC is formed by the junction of the brachiocephalic veins, which in turn are formed by the joining of the internal jugular and subclavian veins. Thus, the SVC represents the major drainage system of venous blood from the head, neck, arms, and upper thorax.[15] The right and left brachiocephalic veins join at about the level of the sternal angle to form the SVC. The SVC descends on the right side of the ascending aorta and empties into the right atrium, with its distal 2 cm lying within the pericardial sac (Fig. 54-1).

Because of its mediastinal location surrounded by several rigid structures including the sternum, trachea, pulmonary artery, right main-stem bronchus, and numerous lymph nodes, the SVC is particularly vulnerable to obstruction. Despite being a relatively large

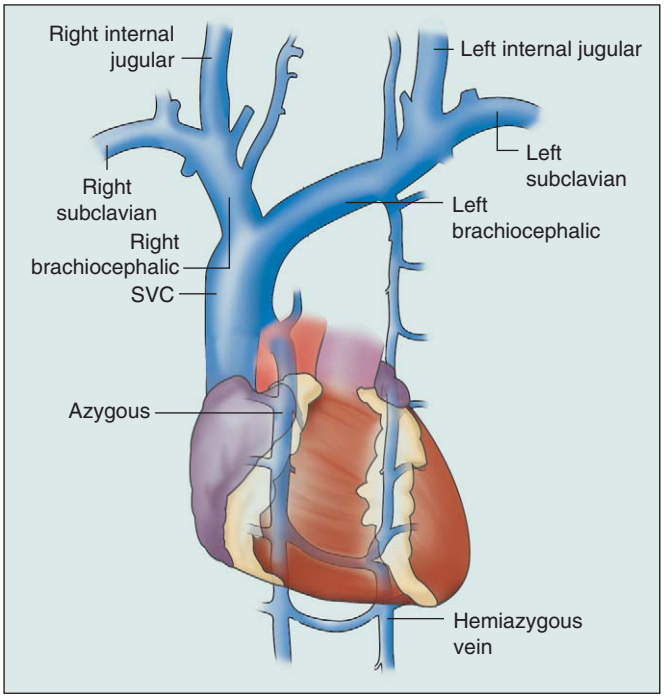


Figure 54-1 • Normal anatomy and drainage pattern of the superior vena cava.

vessel, its thin vascular walls and low intravascular pressure contribute to the ease with which the SVC can be obstructed.[15] SVCO can be caused by external compression due to tumor or by lymph nodes enlarged by inflammation or metastases (Fig. 54-2). SVCO also can be caused by direct tumor invasion or by a thrombus. Secondary thrombus is reported to occur in up to 50% of cases[2] and may contribute to the lack of response to appropriate therapeutic maneuvers.

The azygous vein represents an important collateral system of the SVC and is formed by the junction of the right subcostal and right ascending lumbar veins. Additional routes of collateral flow include the mammary, vertebral, lateral thoracic, paraspinous, and esophageal vessels. The azygous vein ascends through the posterior and superior mediastinum, arches over the hilum of the right lung, and ends in the SVC. Fortunately, extensive anastomoses are formed between the SVC, azygous, and vertebral systems, providing multiple routes of collateral blood flow. Therefore, an obstruction of the SVC above the orifice of the azygous vein is better tolerated than is blockage below this level, because blood can be diverted through chest-wall veins into the thoracic and iliac veins and enter the heart by way of the inferior vena cava and azygous systems.[9,15,16] Blood from the head and neck also can return to the heart via the vertebral plexus. If the SVC is obstructed between the azygous vein and the heart, the only route of blood return is via the inferior vena cava.

ETIOLOGY

Since the middle part of the 20th century, cancer has been the principal cause of SVCO, with bronchogenic carcinoma accounting for up to 85% of cases (Table 54-1).[1–3,8,11,17–21] The two most frequent lung cancer histologic types associated with SVCO are small cell and

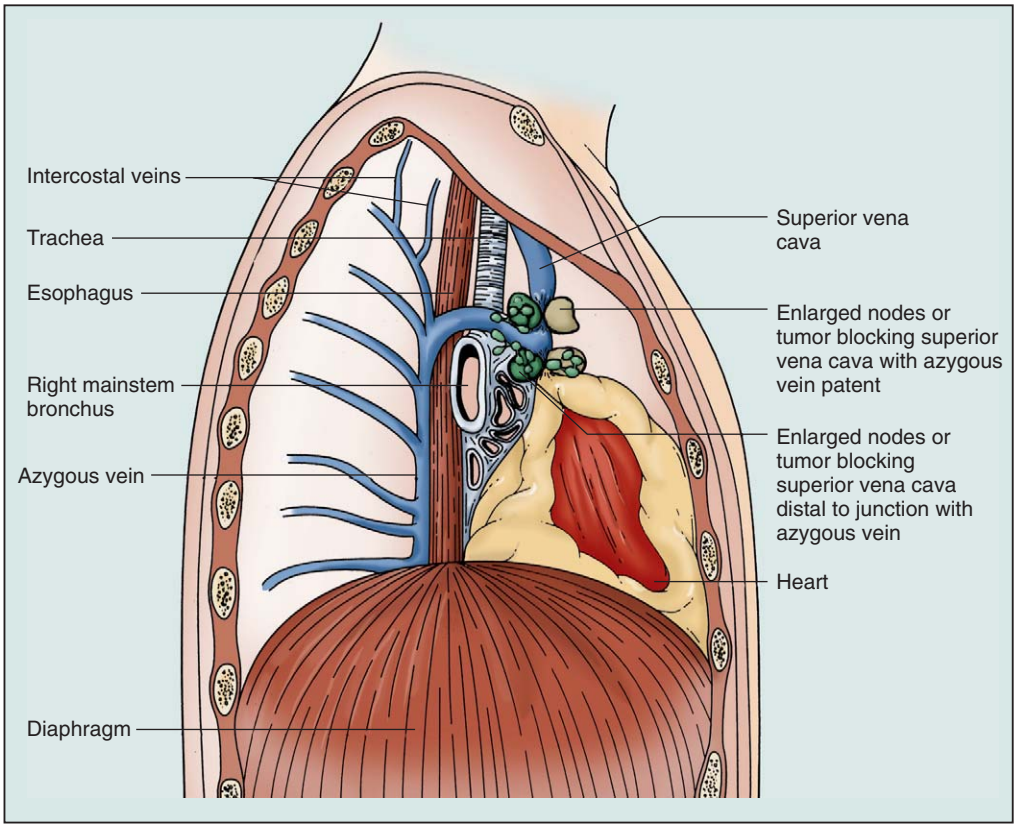


Figure 54-2 • Lateral view of the thorax with superior vena cava obstruction.

Table 54-1 Causes of Superior Vena Cava Syndrome

	Parish et al	Yellin et al	Lochridge et al	Davenport et al	Bell et al	Armstrong et al	Scarantino et al	Little et al
Total patients	86	63	66	35	159	125	60	42
Lung cancer	45	30	52	26	129	99	36	35
Non-small cell	33	26	44	6	64	57	23	28
Small cell	12	4	8	20	65	42	13	7
Lymphoma	8	13	8	1	3	18	8	3
Metastases	12	4	4	4	4	8	4	3
Thymoma/Thyroid	2	4	—	1	—	—	—	1
Benign	19	11	2	—	2	—	—	—
Biopsy not done	—	—	—	3	21	—	12	—

Data compiled from references 1–3, 11, 17–19, and 21.

squamous cell carcinoma.[1,15,22–24] Although small cell lung cancer (SCLC) accounts for just 15% to 20% of newly diagnosed lung cancers, it is the underlying cause of up to 65% of all cases of SVCO.[6,9,22,25,26] The tendency of SCLC to occur centrally within the lung, as well as its high incidence of mediastinal lymph node metastases, most likely accounts for this consistent observation. Although lung cancer is the leading cause of SVCO, the incidence of this syndrome in patients with lung cancer ranges from 3% to 30%, with most series tending toward the lower figure.[4,12,27]

Non-Hodgkin's lymphoma is the second most common cause of SVCO.[3,6,28,29] Perez-Soler and colleagues[29] identified 36 cases among 915 lymphoma patients treated at the M.D. Anderson Cancer Center (University of Texas, Houston). SVCO was most commonly observed with diffuse large cell and lymphoblastic lymphomas.[29] The frequency of mediastinal presentations with the latter histologic types may account for this association, because up to 65% of patients with lymphoblastic lymphomas are first seen with a mediastinal mass. The incidence of SVCO in these categories of non-Hodgkin's lymphoma is reported to be 7% and 20%, respectively.[29]

Metastatic cancers account for approximately 5% to 10% of SVCOs (see Table 54-1).[1,3,8,11,18,21,30–32] The most common primary tumor sites are, in approximate order of frequency: breast cancer, germ cell malignancies, and gastrointestinal cancers. Less common primary sites include sarcomas (including primary sarcomas of the great vessels),[33–35] transitional cell carcinoma, prostate cancer, and melanomas.[32] However, virtually any cancer capable of metastasizing to the mediastinum can result in SVCO.

Nonmalignant causes of SVCO account for up to 5% of cases. An increasingly common benign cause of SVCO is central venous catheter-induced thrombosis, which may occur with cardiac pacemakers, LaVeen shunts, hyperalimentation lines, and Swan-Ganz catheters, as well as those used for chemotherapy administration.[8,36–43] SVCO seems to be more common when the tip of the catheter is placed in the left subclavian vein in the upper part of the vena cava.[40] The incidence of catheter-related thrombosis may be reduced with the administration of very-low-dose warfarin (1 mg/day) before insertion of the catheter and continuation afterward.[44,45] Additional rare benign causes of SVCO include chronic mediastinitis secondary to histoplasmosis, retrosternal goiters, *Nocardia* infection, and congestive heart failure.[3,46–50]

In children, SVCO is most frequently related to iatrogenic causes secondary to cardiovascular surgery for congenital heart disease or ventriculoatrial shunts for hydrocephalus.[51–53] The most common malignant causes of SVCO in children are non-Hodgkin's lymphoma, acute lymphoblastic leukemia, Hodgkin's disease, neuroblastomas, and yolk sac tumors.[51,53]

CLINICAL FEATURES

Although the duration of symptoms may range from a few days to several weeks, a majority of patients have symptoms of 4 weeks' duration or less.[1] The physical findings accompanying SVCO are diagnostic (Fig. 54-3). Patients frequently complain of a sense of head "fullness," mild dyspnea, cough, chest pain, and occasionally dysphagia (Table 54-2).[1,3,13,21,25,53] Less frequently arm edema, stridor, upper body cyanosis, and neurologic symptoms (e.g., headaches or lethargy) may occur. All symptoms may be aggravated by positional changes, particularly those associated with lowering of the head, for example bending to put on shoes.

The prospect of catastrophic neurologic events has led to the characterization of SVCO as an "oncologic emergency."[4,9,53] However, experimental studies in dogs as well as several recent reviews have conclusively demonstrated that life-threatening neurologic symptoms such as seizures, syncope, or coma rarely occur.[6,8,13,14,16]

RADIOGRAPHIC FINDINGS AND DIAGNOSTIC STUDIES

Imaging Studies

A standard chest radiograph is the first radiographic procedure performed when SVCO is suspected, with the most common abnormality being mediastinal widening. Typically, a mass is found in the superior mediastinum, right hilum or perihilar region, or right upper lobe[3,4]; however, a normal chest radiograph is not inconsistent with the diagnosis of SVCO.[3]

A contrast-enhanced chest computed tomography (CT) scan provides visualization of extravascular and intravascular tumor, as well as thrombus formation within the SVC, and also demonstrates collateral flow.[54–61] A CT diagnosis depends on diminished or absent contrast opacification of central venous structures such as the innominate vein or the SVC inferior to the obstruction, and opacification of collateral venous routes,[59] especially anterior subcutaneous collaterals (Fig. 54-4).[54] Because dilution of the contrast medium by unopacified blood or the displacement of blood by laminar flow may simulate an intraluminal filling defect, both criteria must be present for the diagnosis of SVCO to be made.[59] The anatomy defined by CT scan may help to guide a fine-needle aspiration biopsy or another diagnostic procedure if a histologic diagnosis has not been previously established. The current-generation helical CT scans also have been used to diagnose SVCO with results that correlate well with regular contrast CT scans.[58] In addition, helical scans can potentially reveal more information regarding the site and extent of disease

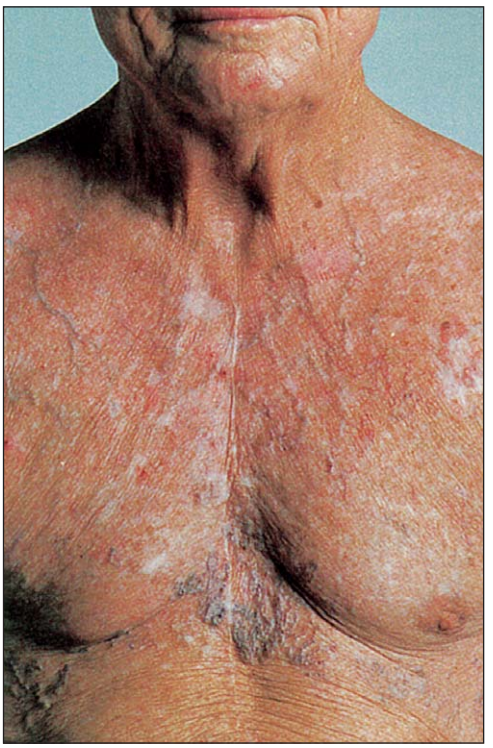


Figure 54-3 • A patient with characteristic venous dilation and facial edema.

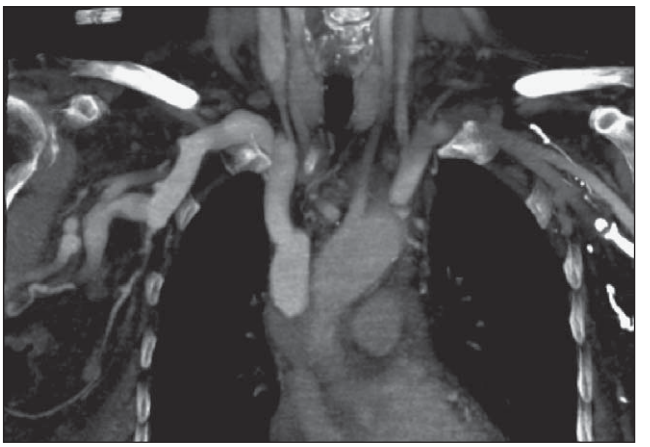


Figure 54-4 • Chest computed tomography venogram scan of a patient with superior vena cava obstruction. Note the abrupt blockage of contrast dye indicative of the superior vena cava obstruction.

and the collateral pathways involved, as well as define soft-tissue abnormalities.

Contrast venacavograms may still play an occasional role in determining management strategy, particularly when surgical bypass or stenting is being considered.[62] Current techniques using low-osmolarity contrast involve the positioning of a small catheter in the desired vascular location under fluoroscopic guidance with injection of only small amounts of contrast dye necessary to define the pattern of venous flow and degree of SVCO.[62] Collateral circulation is usually identified readily, and complications are uncommon. Cavography also is possible by using nuclear medicine techniques.[63–66]

In the majority of cases of SVCO, a contrast CT scan will be the most useful radiographic study; noncontrast studies are of limited value, because the vessels are difficult to distinguish. However, occasionally other imaging studies may also provide helpful data.[56,57] For example, transesophageal echocardiography can be used to distinguish thrombus formation from extrinsic compression of the SVC.[67] Single-photon emission CT has been used to identify obstruction of the SVC by an intravascular metastasis from an adenocarcinoma.[68]

DIAGNOSTIC APPROACH

In the absence of a known cause of SVCO, every effort should be made to obtain a histologic diagnosis before the initiation of any therapy (Box 54-1) for two reasons.[6,8,13,14] First, a definitive diagnosis is necessary to plan therapy, and second, even a brief course of radiation therapy before establishing a diagnosis can make histologic diagnosis difficult or even impossible.[14,69,70]

The least invasive diagnostic technique should be performed initially, followed by more invasive procedures as necessary (Box 54-2). Procedures commonly used to establish a tissue diagnosis include

Table 54-2 Signs and Symptoms of Superior Vena Cava Obstruction

	Parish et al	Yellin et al	Lochridge et al	Maddox et al	Bell et al	Armstrong et al	Scarantino et al	Little et al
Total patients	86	63	66	56	159	125	60	42
Suffusion	69	54	55	49	62	56	55	35
Dyspnea	54	19	55	—	112	69	47	22
Cough	47	13	46	—	11	29	11	26
Pain	17	4	—	—	20	19	—	—
Dysphagia	10	4	1	—	—	16	6	3
Syncope	6	—	2	—	6	—	—	—
Arm edema	3	20	—	19	13	49	—	—
Stridor	1	—	22	—	1	—	—	—
Neurologic	2	—	23	—	0	0	—	—
Hemoptysis	—	5	—	—	—	—	—	5

Data compiled from references 1, 3, 11, 17–19, 21, and 31.

Box 54-1. HISTOLOGIC CONFIRMATION OF UNDERLYING CAUSE OF SUPERIOR VENA CAVA OBSTRUCTION

In most cases the distinction between carcinoma and lymphoma is readily accomplished with routine hematoxylin and eosin stains. Special studies sometimes required to distinguish these entities include the following:

1. Immunoperoxidase stains
   a. Common leukocyte antigen; positive in lymphoma, negative in carcinomas
   b. Epithelial membrane antigen or keratin; positive in carcinomas, negative in lymphomas
   c. Surface immunoglobulins; positive in B-cell lymphomas, negative in carcinomas
2. Electron microscopy
   a. Desmosomes and intracellular junctions typical of carcinomas
   b. Microvilli typical of adenocarcinomas
   c. Dense-core granule (neurosecretory) present in neuroendocrine tumors (e.g., small cell lung cancer)
   d. Transformed lymphocytes, identified from a paucity of organelles, abundant free ribosomes, prominent nucleoli, and occasional presence of nuclear blebs

Immunoperoxidase studies can usually be obtained relatively quickly and are most helpful in distinguishing a lymphoma from a carcinoma. However, expensive pathology studies are avoided unless necessary to help guide therapeutic decisions.

Box 54-2. APPROACH TO PATIENTS WITH SUPERIOR VENA CAVA OBSTRUCTION

Diagnosis is established by physical examination and clinical presentation (see text).

- Respiratory status should be assessed promptly. Only patients in extremis should be treated urgently with radiation without a histologic diagnosis. Emergency radiation therapy is necessary in fewer than 5% of all SVCO cases. Stent insertion can also be considered as first-line therapy for patients with malignant cases of SVCO.
- Diagnostic evaluation should proceed with least invasive procedures performed initially followed by more invasive procedures as needed to obtain histologic diagnosis:
  - Chest radiograph
  - Sputum cytology
  - Thoracentesis with cytologic evaluation of fluid
  - Node biopsy if palpable node is present, avoid fine-needle aspiration if lymphoma suspected
  - Fiberoptic bronchoscopy
  - Mediastinoscopy
  - Thoracostomy
  - Evaluation may vary depending on the age and sex of the patient.
- In older adults (i.e., ≥50), the most common cause of SVCO is lung cancer; lymphoma or metastatic cancer are less common and benign processes are uncommon.
- In young adults (<50 years old), the most common cause of SVCO is lymphoma (usually large cell lymphoma or lymphoblastic lymphoma; rarely Hodgkin's disease); lung cancer or rare thoracic malignancy are less common, and germ cell cancer (almost never in females) and benign causes all uncommon. The preceding evaluation should be modified to include the following studies before more invasive procedures:
- Serum tumor markers (i.e., β-human chorionic gonadotropin, α-fetoprotein, lactate dehydrogenase)
- Bone marrow aspiration and biopsy

sputum cytology, bronchoscopy, lymph node biopsy, thoracotomy, and mediastinoscopy, although the diagnosis is sometimes obtained through other means such as thoracentesis and percutaneous lung biopsy with or without ultrasound guidance.[6,17,71–73] The complication rate of invasive procedures in the face of SVCO is fairly modest. Schraufnagel and associates[13] reviewed the outcome of 93 invasive procedures in 62 patients with diagnostic problems, and none of the procedures, including bronchoscopies and mediastinoscopies, was associated with a fatal outcome. Yellin and coworkers[21] performed 27 invasive diagnostic procedures in 63 patients with SVCO. No mortality or major bleeding episodes were observed, and diagnostic material was obtained in 89% of patients. Ahmann[6] reported that complications of bronchoscopy and lymph node biopsies are virtually nonexistent and that contrast studies, such as nuclear medicine venography, are remarkably safe in the presence of SVCO. Of the various invasive procedures used to obtain tissue in patients with SVCO, mediastinoscopy seems to be the most risky. However, even this procedure has a relatively low complication rate. Mineo and colleagues[73] reviewed the outcome of 80 patients who underwent diagnostic mediastinoscopy for SVCO by a single surgeon over a 23-year period. Five patients had significant bleeding, but only one required an urgent sternotomy, and no perioperative mortality was recorded. A definitive diagnosis was made in all of the patients; therefore, mediastinoscopy should be considered if less invasive procedures are unsuccessful at determining a diagnosis (Table 54-3).[17,72,74,75]

Special pathologic studies may be needed to establish a diagnosis when routine histologic assessment is unclear or available tissue is scant. Other laboratory studies such as serum tumor marker (e.g., β-human chorionic gonadotropin and α-fetoprotein) determination may be useful in selected cases. For example, the presence of an

Table 54-3 Diagnostic Procedures, Yield, and Complication Rate in Superior Vena Cava Obstruction

Procedure	No. Performed	No. Diagnostic	Complications
Sputum cytology	30	8	0
Bronchoscopy	84	39	1
Thoracotomy	22	21	0
Mediastinoscopy	132	124	13
Lymph node biopsy	44	30	0
Bone marrow	13	3	0

Data compiled from references 13, 21, 31, 55, 73, 75, and 147.

elevated β-human chorionic gonadotropin and/or an abnormal α-fetoprotein in a young male patient with SVCO is virtually diagnostic of an underlying germ cell malignancy. In the latter situation, no further workup is needed before initiation of chemotherapy.

The diagnostic yield from various noninvasive and invasive procedures ranges from approximately 20% for cytologic studies to virtually 100% with thoracotomy and mediastinoscopy (see Table 54-3).[73,75] Although these findings may reflect publication bias, the existing data argue against the need for immediate irradiation without a histologic diagnosis in most cases. In rare circumstances, a definitive tissue diagnosis cannot be made in a timely manner. In such cases it is appropriate to proceed with radiotherapy or placement of an endovascular stent, because either therapy is effective for most underlying causes of SVCO. Prudence dictates that prolonged attempts to establish a histologic diagnosis should be discouraged in the presence of severe dyspnea due to tracheal compression or rapidly progressive neurologic symptoms. Furthermore, in circumstances in which SVCO occurs in an individual with an established diagnosis of cancer or other known cause, an attempt to reestablish the histology of the underlying cause clearly is not a productive exercise.[13]

TREATMENT

Radiotherapy

Radiotherapy is the most commonly used treatment modality for SVCO after a malignant etiology has been established. Three factors must be considered before radiation delivery: (1) dose fractionation (fraction size and timing), (2) total dose to be delivered, and (3) volume to be irradiated, or "field size."[9]

Dose Fractionation

Considerable controversy is found in the radiation oncology literature over the past 40 years regarding fractionation in patients with SVCO. Before 1960, treatment of SVCO generally consisted of low-dose (i.e., 50–100 cGy) fractions to avoid inducing "radiation edema," which was assumed to cause further compromise of SVC patency and worsen associated symptoms.[76] In reality, however, the fear of producing further SVC compromise by radiation-induced edema was largely unfounded, and symptoms previously ascribed to radiation edema were predominantly due to inadequately treated tumor, causing progressive obstruction.[23]

Rubin and associates[23] undertook a retrospective comparison of a high-fraction regimen (400 cGy/day) with historical controls treated with lower fraction schedules (200 cGy/day). They noted more prompt relief of facial swelling after an initial high-dose-per-fraction schedule. The apparent superiority of high-dose-per-fraction regimens in providing faster symptom relief has been corroborated in several other retrospective nonrandomized studies.[1,2,13,14,16,19,22,77] In contrast, Perez and colleagues[4] found the high-dose-per-fraction regimen only slightly better than conventional fractions. It is our belief that for the management of potentially curable patients, 300-cGy fractions for the first 2 to 3 days is reasonable therapy for those experiencing rapidly progressive and distressing SVCO. Thereafter, the daily fraction size can be safely reduced, and the total dose adjusted to compensate for the number of initial high-dose fractions. Patients with subacute SVCO treated with curative intent should be managed with conventional (e.g., 200 cGy) fractions throughout their treatment course. Effects on surrounding normal tissues treated to tolerance doses are more predictable with standard fractions. Appropriate oblique fields with spinal cord shielding can later be used to boost the target volume.

In patients with extrathoracic disease who are treated with palliative intent, total radiotherapy doses will probably be lower, and the use of higher fraction sizes (e.g., ≥300 cGy) for the entire course of radiation is appropriate. With two hypofractionated regimens with 8-Gy fractions, Rodrigues and associates[77] concluded that 24 Gy given once weekly in 8-Gy fractions using spinal cord sparing after the first fraction produced better relief of symptoms, more durable responses, and better median survival than did 16 Gy given in 1 week.

Total Dose

In the individual with SVCO, the planned total radiation therapy dose should take into account the specific type and extent of underlying malignancy and normal tissue tolerance. Other considerations include prognosis and performance status, the speed at which SVCO symptoms developed, and whether chemotherapy is to be included in the treatment program. The radiation oncologist must also decide if the goal of treatment is curative or palliative and treat accordingly. If radiation alone is to be used for the curative treatment of lymphoma in adults, 3600 to 4400 cGy is commonly recommended.[78,79] More commonly, however, combined-modality treatment is given, and total radiation dose can then be reduced.[80] In SCLC, typically 4500 cGy twice daily or 6000 cGy given daily with concomitant chemotherapy is recommended,[81,82] and for non-SCLC, 6000 cGy to 7000 cGy is usually used sequentially or, more commonly, simultaneously with chemotherapy.[83,86]

Field Size

Radiation field size is determined by the extent of disease, baseline pulmonary reserve as determined by pulmonary function tests and split perfusion-ventilation scans, and the type of chemotherapy, if any, the patient will receive. Toxicity of treatment, in particular radiation pneumonitis, pericarditis, and fibrosis, can carry significant morbidity and mortality if severe. Mortality from severe radiation pneumonitis approaches 50% in some reports.[87] Therefore, efforts to minimize radiation field size carry considerable importance in the treatment of SVCO. Risk of pneumonitis is a function of many patient- and treatment-related factors: pretreatment performance status, gender (women more likely than men), forced expiratory volume in 1 second, low PaO_2 (<80 torr), mean lung dose, and volume of lung irradiated to 20 Gy.[88–90] To reduce the risk of pulmonary and cardiac toxicity, some groups have used induction chemotherapy followed by thoracic irradiation with a reduced treatment volume. With bronchogenic carcinoma, retrospective and prospective studies have shown that the postchemotherapy tumor volume can be treated without significantly compromising local control or survival.[91,92] In addition, CT scan-based treatment planning, particularly with intensity-modulated radiation therapy, provides better assurance of the target volume and allows a reduction in the lung volumes irradiated.[93–96] Volumes should be constricted if high total doses are used (>4000 cGy) or if methotrexate, mitomycin C, doxorubicin, or bleomycin is used concomitantly.

Patients with lymphoma will need chemotherapy for control of systemic as well as local disease. Fraction size and total dose to the spinal cord should be carefully considered in these patients who may subsequently undergo a bone marrow transplant requiring total body irradiation.

Response to Radiotherapy

Clinical response of SVCO signs and symptoms to various radiotherapeutic dose-fractionation schedules is high (Table 54-4).[2,11,19,21,31] Radiographic and postmortem pathologic studies, however, indicate that reestablishment of vena cava patency is rare, and therefore collateral flow rather than therapeutic intervention may be responsible for symptomatic improvement. Ahmann[6] reported the response to radiation therapy for SVCO based on a literature review of more than 90 publications since 1934. Overall, approximately 50% to 70% of treated patients achieve symptomatic improvement within 2 weeks of initiation of therapy. In circumstances in which serial venograms

Table 54-4 Clinical Response of Superior Vena Cava Obstruction to Radiation Therapy

Author	No. of Patients	Response Rate (%)	Recommendation
Yellin et al[20]	23	78	SVCO not emergency; obtain biopsy before RT
Armstrong et al[11]	125	78 to 83	Use initial 4-Gy fractions
Maddox et al[29]	14	64	Chemotherapy and RT are equally effective
Scarantino et al[18]	60	86	Use initial high-dose RT fractions
Davenport et al[1]	35	91	Use initial 4-Gy fractions
Howard[23]	253	86	Use 30-Gy total dose

RT, radiation therapy; SVCO, superior vena cava obstruction.
Data compiled from references 2, 11, 19, 24, and 31.

were obtained, normal venous flow through the SVC was rarely observed after completion of radiation therapy.[19,24,97] In some instances, complete obstruction remained despite clinical improvement in the patient's signs and symptoms.[19,24,97]

SVC patency after radiation also has been assessed in autopsy studies.[6,12] After radiotherapy, the SVC usually is not sufficiently patent to allow adequate blood flow through the vessel. Ahmann's literature review[6] found that among 99 postmortem examinations of which most patients had achieved symptomatic relief after radiation therapy, only 14 patients had complete or partial SVC patency. Although autopsy studies may be less reliable than venography obtained in living patients, these results are entirely consistent with reported radiographic data. Although radiotherapy is associated with improvement or relief of clinical signs and symptoms in most patients, the majority of patients do not actually achieve any measurable increase in vena cava blood flow. The development of collateral blood flow probably contributes to the clinical improvement in some patients and is the sole reason for improvement in others. Thus, the literature does not support the traditional dogma that emergency irradiation is needed in all patients with SVCO.

Chemotherapy

Small Cell and Non-Small Cell Lung Cancer

SVCO has been reported to occur in 7% to 12% of SCLC patients at diagnosis.[26,31,98–101] With rare exception,[31] the literature indicates that the presence of SVCO has little impact on the prognosis of SCLC patients, provided that therapy is appropriately instituted.[26,98,101,102] Even in the presence of SVCO, chemotherapy (with or without thoracic radiotherapy) is the preferred initial treatment of SCLC.[103] The choice of treatment is dictated by the patient's stage and performance status. Those with limited-stage disease, good performance status, and no contraindication to cisplatin are best treated with cisplatin plus etoposide and concurrent chest irradiation.[82] In extensive-stage disease, it is reasonable to proceed with chemotherapy alone—either cisplatin-based therapy or a cyclophosphamide-based regimen in those in whom excessive hydration is to be avoided.[26,98,99,101,102] Alternatively, carboplatin can be substituted for cisplatin if there is a need to avoid aggressive hydration.[104] A majority of patients will experience partial or complete resolution of signs and symptoms within 7 days of initiation of treatment, and in most series, complete resolution of symptoms has occurred within 2 weeks. Although the rapidity of symptom resolution suggests that a direct treatment effect on tumor regression is the principal cause of symptom improvement, the development of collateral drainage undoubtedly plays an equally significant role, as noted earlier. Thoracic radiotherapy does not cause transient worsening of symptoms. Although SVCO reoccurs in approximately 25% of patients, reinstitution of therapy with salvage chemotherapy alone, radiotherapy alone, or a combination of these modalities has resulted in the prompt resolution of symptoms in most cases.[24] Unfortunately, sequential thoracic radiotherapy on completion of chemotherapy has not resulted in a reduction in the incidence of SVCO relapse.[105]

Chemotherapy alone also has been used for the treatment of SVCO in non-SCLC with positive results.[106] However, because of their innate chemotherapy resistance this approach is less effective with non-small cell tumors, and thus radiotherapy or combined-modality therapy remains the preferred initial treatment.[90] Unlike SCLC, the presence of SVCO in non-SCLC seems to have a negative impact on the prognosis of patients with locally advanced disease.[106]

Non-Hodgkin's Lymphoma

Although symptoms can be well controlled with radiotherapy, chemotherapy alone also can effectively palliate the symptoms of SVCO in non-Hodgkin's lymphoma.[29] However, because lymphoma is usually a systemic process and death is rarely due to localized disease, radiotherapy should never be used in isolation except when dealing with recurrent disease. Local recurrences tend to occur primarily in patients with large mediastinal masses and large cell histologic types.[29] Therefore, local consolidation with radiotherapy after a few cycles of chemotherapy can be justified in patients with large cell lymphoma and mediastinal masses larger than 10 cm.[29] Conversely, in lymphoblastic lymphoma, recurrences are uniformly systemic, obviating the need for radiotherapy in this histologic type of non-Hodgkin's lymphoma.[29] As in SCLC, the optimal chemotherapy regimen for treatment for lymphoma-associated SVCO has not been determined and is dictated to a much greater degree by the underlying histologic type, further underscoring the need to establish a tissue diagnosis before institution of therapy. It should be noted that a fine-needle aspiration is insufficient for a complete diagnosis and characterization of a lymphoma and should not be relied on as the sole diagnostic procedure. Lymphoblastic lymphoma is more aggressive than large cell lymphomas and generally requires more aggressive chemotherapy.[54,107,108]

SURGERY

Surgery generally plays a limited role in the management of the patient with SVCO, although reconstruction of the obstructed SVC may be indicated in highly selected patients.[58,109–112] Surgical intervention is reserved most often for patients with SVCO due to a benign cause such as granulomatous disease, aortic aneurysm, or retrosternal goiter.[113] When symptomatic malignant obstruction is refractory to radiotherapy, chemotherapy, or both, and when anticipated survival approaches 6 months, operation may be considered. Surgical intervention also may prove beneficial in the setting of recurrent SVCO after chemotherapy and radiation, and when caval thrombosis is the primary problem and fails to improve symptomatically with anticoagulants or thrombolytic therapy.[95,114–116]

Surgical bypass of the obstructed SVC may be accomplished with synthetic grafts (Dacron or Goretex), autologous pericardium, or autogenous vein graft, with preference for the later because of a better

potential for long-term patency.[109–112,117,118] The spiral vein graft, initially described by Doty and associates,[110,119] is constructed by using the saphenous vein, which is slit longitudinally and wrapped around a stent (usually a chest tube) of the desired diameter. The edges of the vein are joined by using continuous suture, resulting in a large-bore conduit. The bypass is constructed between the brachiocephalic or left internal jugular vein and the right atrial appendage. Long-term relief of symptoms may be achieved.[112,119,120] When SVCO is the result of a primary tumor of the SVC or right atrium, resection (with cardiopulmonary bypass) and reconstruction is recommended. These tumors may be relatively slow-growing sarcomas (angiosarcomas or leiomyosarcomas), and long-term palliation is sometimes possible.[33–35,121]

Stents

Percutaneously placed, self-expanding intravascular wire stents can offer an attractive adjunct to other procedures in the palliative treatment of patients with SVCO in the presence or absence of an underlying malignant disease.[122] These devices have been placed before radiotherapy, during the course of radiotherapy or chemotherapy, and after maximum-tolerance radiation therapy.[20,123–140] This percutaneous treatment option offers the ability to increase the lumen diameter of the SVC and does not usually require general anesthesia (Fig. 54-5). Complete symptom relief is often obtained within 24 to 48 hours in 75% to 95% of patients, depending on the underlying cause of SVCO and type of stent deployed. Dyspnea seems to be the least likely symptom to improve, whereas facial and upper body edema improve within 48 hours in virtually all patients.[123] Possible complications include acute thrombosis, retroperitoneal hemorrhage, and death due to cardiac arrhythmias, and reocclusion may occur (especially in the absence of anticoagulant therapy).[126–128] Because all currently available expandable stents have a metallic composition, their presence may preclude or limit serial follow-up with magnetic resonance imaging. This point should be taken into account before this course of treatment is chosen.

Venous access is accomplished through a femoral, jugular, or subclavian vein. It is necessary to traverse the obstruction with a guide wire to allow deployment of the stent, and in many cases, a preplacement venous angioplasty is indicated. The presence of acute thrombosis superimposed on the chronic SVCO may indicate the need for preprocedure thrombolytic therapy. Although thrombolytic therapy is associated with a known risk of hemorrhage, it may minimize the risk of thromboembolization and permit greater accuracy of stent placement.[122,139] Careful consideration should be given to a preprocedure cerebral CT scan to help rule out the presence of cerebral metastases before the use of thrombolytic therapy.[139]

Whereas a variety of metallic stents is currently available, most reports address one or more of three general device designs, the Gianturco-Rösch (sometimes referred to as the "Z-stent"; Cook, Bloomington, IN), Wallstent (Schneider, Plymouth, MN), and Palmaz stent (Johnson & Johnson Interventional Systems, Warren, NJ). No rigorous comparisons of outcomes have been made among the various stent designs. Each has particular qualities with respect to flexibility and radial strength, which may make one or another particularly well suited under certain clinical circumstances. Although the Wallstent and Z-stent are "self-expanding" devices, balloon dilatation may be required after stent insertion to provide a clinically adequate effect.[141]

Technical and clinical success and long-term venous patency have been demonstrated by several trials summarized in Table 54-5.[122,134–140,142] The overall complication rate is relatively low,

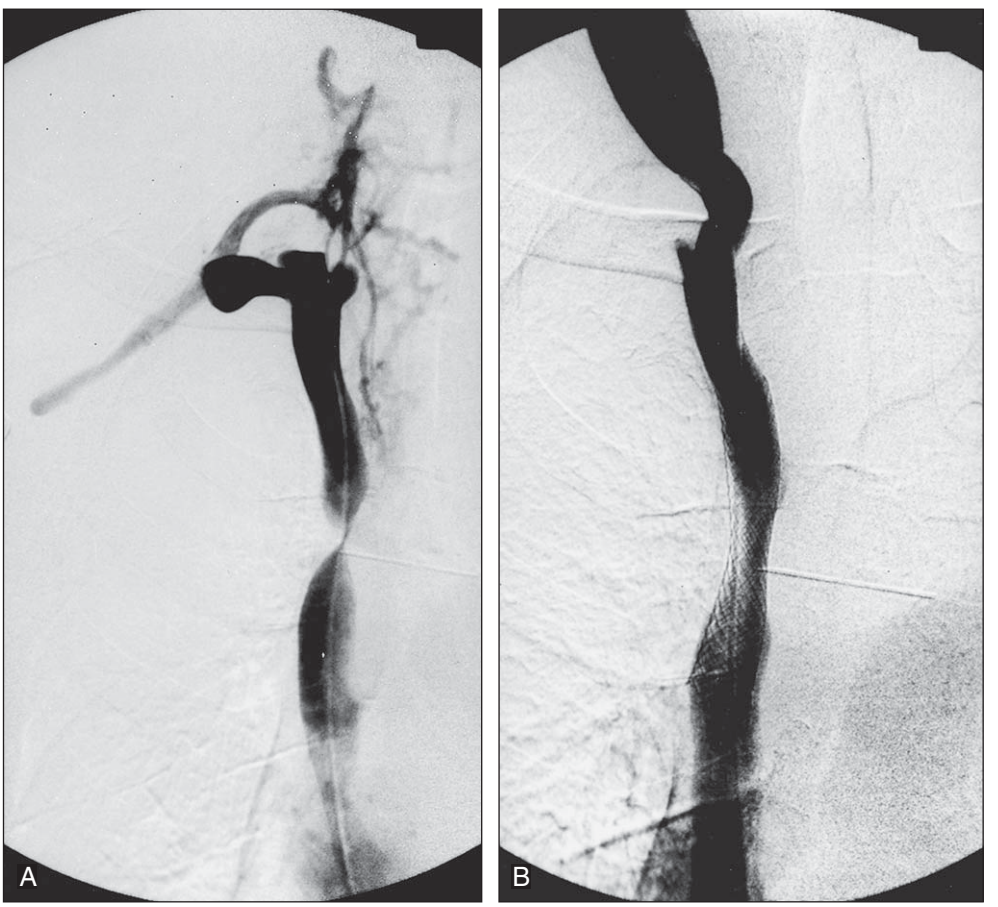


Figure 54-5 • **A,** A 60-year-old man after radiotherapy for lung cancer with recurrent superior vena cava obstruction. **B,** Placement of a Wallstent resulted in immediate relief of symptoms. Radiograph at 6-month follow-up.

Table 54-5 Evaluation of Intravascular Stents

Author	No. of Patients	Primary Patency Rate (%)	Clinical Success (%)	Overall Complication Rate (%)
Kee et al[128]	51	95	78	10
Smayra et al[141]	30	74	100	7
Chatziioannou et al[147]	18	100	89	0
Lanciego et al[142]	52	92	100	25
De Gregorio Ariza et al[146]	82	93	95	0
Miller et al[143]	23	100	83	13
Thony et al[144]	26	83	90	4
Nicholson et al[145]	76	100	90	9
Urruticoechea et al[148]	52	100	90	10

Data compiled from references 122, 134–140, and 142.

although considerable variation is found in the reporting of complications, in that some studies include reocclusion as a complication.[136] The majority of the more serious complications involve graft migration. Many patients require more than one stent either to maintain SVC confluence with adjacent vessels or because the vascular lesion is too extensive to be covered by a single stent. Close follow-up is required to monitor venous patency, and stent occlusion can generally be alleviated by a second procedure.

A discrepancy exists in the literature regarding balloon dilation before stent placement. Some studies advocate routine balloon dilation before stent insertion, whereas others limit such dilations to situations necessitated by very tight stenoses.[122,134,135,137] The suggestion is that immediate stenting without dilation traps endothelial clots, thus helping to prevent distant embolic events.[135] Other series reported improved patency rates with balloon angioplasty after stent placement.[140] Some believe that this variation in practice may relate to the type of stent used.

Considerable variation also exists regarding routine anticoagulation after stent placement. Chatziioannou and coworkers[136] recommend oral anticoagulation therapy with coumarin "for life." Kee and colleagues[122] recommend continuous oral anticoagulation for all of their patients with an underlying malignancy. In both the studies of Lanciego and associates[134] and Chacon Lopez-Muniz and coworkers,[123] patients were initially given anticoagulation with heparin and warfarin; however, over time their standard of practice changed to recommend antiplatelet agents alone, with seemingly no adverse effects. Thony and colleagues[140] treated a few selected patients with heparin for up to 3 days after the procedure and otherwise recommend aspirin therapy for 3 months after stent placement. This shift in practice may reflect parallel studies of anticoagulation for coronary artery stents. As no standard recommendations exist now, the risks and benefits of full anticoagulation versus antiplatelet agents must be weighed for individual patients.[143]

Although no randomized trials have been done, two studies directly compared the results of endovascular stenting with radiation with or without chemotherapy for malignant SVCO. Tanigawa and associates[144] reported the results of 33 patients treated with radiation therapy or stents. These patients were selected for a specific therapy and not randomized. Of the 23 patients who underwent a stenting procedure, 11 had undergone ineffective radiation therapy for their obstructions. The majority of patients in the stent group and all 10 of the patients who received radiation therapy had a primary lung cancer. Symptom relief was seen in 78% of the stent group overall: 75% of those who had not had previous therapy and 82% of those who had received prior radiation. Although the rate of improvement (80%) in clinical signs and symptoms in patients who were treated with radiation therapy was similar, the median time to respond was longer at 5.5 days compared with 24 to 48 hours after stenting. No difference was found in the overall survival between the two treatment groups. These authors suggested that stenting be considered first-line therapy and certainly indicated after an ineffective trial of radiation. Nicholson and colleagues[139] reported their experience with malignant SVCO of 76 patients treated with stent insertion and compared the results retrospectively with those of 25 similar patients who had been treated with radiation therapy for malignant SVCO. Of the 76 patients, 26 were treated with stents alone, and the remainder were treated with chemotherapy or radiation before or after stent placement. The report of Nicholson and colleagues confirms the more rapid resolution of clinical symptoms in the stent group versus the radiation-alone group; however, it should be noted that the radiation group was examined retrospectively. The mean asymptomatic time was significantly longer in the stent group at 21.8 weeks compared with 11.7 weeks in the radiation-only group. Although 83% of patients treated with a stenting procedure continued to have minor symptoms of swelling or venous distention, major symptoms were relieved in all 76 patients. In addition, more than 90% of patients in the stent group died without a recurrence of their SVCO symptoms compared with only 12% in the radiation-only group. The figures for the stent group include the patients who were treated with additional therapy, although the trends are the same for the 26 patients who were only stented. Poststent venography was performed on 19 patients. Interestingly, although they were all asymptomatic, seven of these patients had a reoccluded SVC, suggesting that collateral vessels play a significant role in symptom relief. This finding is consistent with the reocclusion after radiation therapy noted in autopsy studies.[6,13]

Although a definite role exists for stents in malignant SVCO, the results of endothelial stent placement for benign causes are more mixed, and few long-term follow-up data are available.[141] Life expectancy for patients with malignant disease is often limited, but the same may not be true with benign SVCO, and therefore in these patients, long-term patency is a critical consideration. The underlying cause of the initial SVCO and the likelihood of recurrence may be more relevant in these situations. Technical success and symptom relief have been reported, primarily for venous catheter-induced SVCO.[137] The gold standard for benign SVCO remains surgical bypass, although, given the variability and rarity of this condition, no studies have been done comparing these two modalities.

Although endovascular stents may provide more rapid relief of symptoms, they are not designed to treat the underlying cause of the obstruction, whereas radiation, chemotherapy, and surgery may function both palliatively and therapeutically. No randomized trials are likely to compare treatments for SVCO, because the goals of each therapeutic modality are somewhat different. However, many studies report that stented patients experience a rapid and almost complete resolution of the symptoms associated with SVCO.[123,126,134,135,137,138,140,144]

For this reason, several recent studies advocated stent placement as first-line therapy for patients with malignant causes of SVCO.[138,142–144,147] Stent insertion should not interfere with subsequent radiation or chemotherapy and may allow symptom relief while further therapy is being planned and initiated.[145]

SUPPORTIVE MEASURES

Few medical measures are of proven benefit in the management of SVCO, other than therapy directed at the underlying cause. General recommendations include bedrest, head-of-the-bed elevation, and oxygen administration.[9,21] These therapies are designed to reduce venous pressure and cardiac output. Diuretics also have been advocated without clear evidence of efficacy, although they are thought to lessen edema.[9] Steroids also are sometimes administered without good documentation as to their efficacy. These agents have been advocated for their putative benefit in lessening the likelihood of radiation-induced edema. However, in experimental systems, little inflammation or edema has been observed with irradiation.[74] Anticoagulation and thrombolytic therapy may be of benefit when the underlying cause is an indwelling catheter, but otherwise they have not been shown to alter the course of recovery.[32,37,39,109] Furthermore, because anticoagulation may impair diagnostic efforts, it should be avoided until a clear indication for its use is identified.

Survival in the face of SVCO is dependent on the underlying cause and proper treatment.[1,11,29,146] Overall, median survival is around 6 months and is clearly related to the underlying cause. One-year survival may range from as little as less than 1% in non-SCLC to more than 40% in patients with non-Hodgkin's lymphoma.[1,11]

SUMMARY

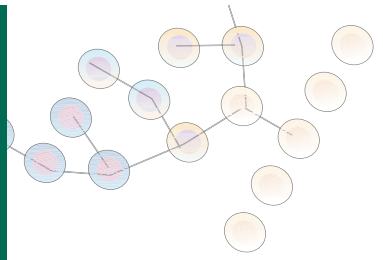
SVCO is usually not a true oncologic emergency, except in rare situations in which a patient experiences respiratory compromise secondary to tracheal obstruction. Administration of irradiation before histologic confirmation of the underlying cause can lead to inappropriate therapy and should be discouraged. Excessive concern about the risk of invasive procedures in the face of SVCO is likewise without foundation. Numerous reports have demonstrated the relative safety of bronchoscopy, thoracentesis, lymph node biopsy, and similar invasive procedures. In the past 5 years, numerous studies have demonstrated the palliative benefit of endovascular stent placement, particularly for malignant causes of SVCO. Stent placement does not preclude the use of additional therapy such as chemotherapy or radiation. In experienced hands, the procedure has a low rate of complications and often provides rapid and lasting relief of symptoms. Depending on availability, endovascular stenting should be considered early in the treatment of SVCO and certainly when a different primary therapy has failed. In many institutions, radiotherapy remains the treatment of choice, with exceptions made for those causes known to be relatively sensitive to chemotherapy (e.g., SCLC or non-Hodgkin's lymphoma).

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55 Spinal Cord Compression

Daniel M. Sciubba, Ali Bydon, and Ziya L. Gokaslan

SUMMARY OF KEY POINTS

Incidence
- Spinal cord compression is diagnosed in more than 30% of all patients with disseminated cancer, and roughly 5% to 10% of all patients experience cord dysfunction.
- Back pain is the most common presenting complaint and almost always precedes neurologic dysfunction.
- Spinal cord compression has a devastating effect on quality of life and is frequently diagnosed late.

Etiology
- Compression occurs from epidurally located tumor or from bony fragments generated by pathologic fractures.
- Constant compression leads to spinal cord arterial compromise, venous occlusion, vasogenic edema, and demyelination with subsequent clinical deterioration.

Evaluation
- Any new or worsening back pain in a cancer patient mandates urgent radiographic evaluation.
- Unfortunately, no characteristics of back pain can safely differentiate cord compression from other benign or malignant spinal diseases.
- Any evidence of myelopathy may signal impending catastrophic loss of cord function.
- A scout sagittal magnetic resonance imaging (MRI) view of the entire spine or a scanning MRI is the most rapid and cost-effective means of diagnosis and should be the first procedure performed.

Treatment
- Corticosteroids, conventional radiation therapy, and decompressive surgery are the mainstays of treatment.
- Although treatment of metastatic spinal lesions is considered palliative, aggressive medical and surgical treatment can significantly improve pain, neurologic function, and quality of life.

INTRODUCTION

Spinal metastases have long been a significant source of morbidity in patients with systemic cancer. Regional pain, pathologic compression fractures, deformity, and spinal cord compression with ensuing neurologic compromise are problems that commonly must be managed in both the patient with advanced cancer and the patient with isolated metastatic vertebral disease. In regard to metastatic epidural spinal cord compression (MESCC), data from the 1970s from Gilbert and colleagues and from Greenberg and colleagues showed that a significant proportion of patients entering the hospital in an ambulatory state left with varying degrees of paresis and paralysis.[1,2] Specialists from that era emphasized the need for earlier diagnosis and improved treatment.[3] Unfortunately, proposed diagnostic algorithms relied heavily on the only available diagnostic tool at the time: myelography.[4] Early opposition existed for using such an invasive test on neurologically intact cancer patients with new onset back pain; however, Rodichok and colleagues demonstrated that roughly 60% of patients with new back pain, abnormal findings on a plain spinal radiograph, and normal findings at neurologic examination who underwent myelography were shown to have epidural cord compression.[4,5] Since that time, diagnosing spinal cord compression prior to clinically apparent neurologic dysfunction has remained paramount in the management of metastatic vertebral disease. Early diagnosis and early, aggressive treatment are the hallmarks of current treatment.

Currently, roughly 30% of patients with cancer develop symptomatic spinal metastases during the course of their illness, and up to 90% of cancer patients have metastatic lesions within the spine at the time of death.[6] With advances in the treatment of systemic oncologic disease, patient survival has increased over the last few decades. This increase, combined with improved imaging modalities of the neurologic and musculoskeletal systems (magnetic resonance imaging [MRI], bone scintigraphy, etc.), will undoubtedly increase the incidence with which physicians encounter spinal metastases. As a result, it is essential that individuals with cancer and those caring for them understand not only the myriad ways in which spinal metastases present, but also the means by which they are currently diagnosed and managed. In this chapter, the authors attempt to address these issues using an evidence-based approach from the most recently compiled literature. In addition, we propose a simple algorithm to aid in deciding which patients are ideally treated medically and which patients could benefit from surgery.

EPIDEMIOLOGY

Over 1.4 million new cases of cancer are diagnosed annually in the United States,[7] and roughly 500,000 of these patients die annually from metastatic disease.[8] Metastases to the skeletal system occur third in frequency behind metastases to the lungs and liver.[9,10] Within the skeletal system, the spinal column is the most commonly affected site. Cadaver studies have shown that as many as 30% to 90% of

terminal cancer patients possess metastatic disease to the spine.[11–15] Although it is estimated that only roughly 10% of cancer patients develop *symptomatic* spinal secondaries,[16] the prevalence of spinal metastases is likely to increase as survival rates for many cancers improve.

The highest incidence of clinically detected spinal metastases occurs during midlife (40 to 65 years of age), which corresponds to the period of increased cancer risk.[17] Primary breast, lung, and prostate represent the most common histologies metastatic to spine, reflecting both their higher prevalences and their tendencies to metastasize to bone.[18,19] A slightly higher incidence in men is related to the slightly higher incidence of prostate cancer over breast cancer.[17] However, as adjuvant treatment for breast cancer improves overall survival, this dissimilarity could vanish.

PATHOPHYSIOLOGY

Figure 55-1 shows the relevant anatomy of the spinal cord, spine, and associated structures and the location of metastatic lesions in these areas. Lesions that cause spinal cord compression usually first invade the epidural space, most often as direct extension of metastatic disease from the vertebral body. Spine metastases are thought to arise by various mechanisms, often predicated on the biologic behavior of the primary.

- *Hematogenous spread.* As the most common means of malignant tumor spread to the skeleton, such dissemination likely occurs by both venous and arterial routes. Batson's venous plexus is the longitudinal network of valveless veins that course parallel and juxtaposed to the spinal column. This plexus communicates with multiple venous systems (spine, vena cava, portal, azygous, intercostals, pulmonary, renal), and the flow direction within the plexus may be variable owing to changes in intrathoracic and intra-abdominal pressures. In this way, tumors in multiple sites of the major body cavities could deposit tumor cells in the spine.[20] Owing to the significant blood flow to the vertebral bodies, the arterial system also is effectively able to deliver tumor cells to these well-perfused bones.[21] Although less common, hematogenous dissemination of tumor cells may also lead to direct metastasis to the cord (intramedullary) or to the epidural space itself.
- *Direct extension.* Primary tumors located in paravertebral soft tissues can often extend into the vertebral column via intervertebral foramina. Lung cancer, for instance, may become locally aggressive and invade the thoracic spine, while prostate, bladder, and colon cancer may invade the lumbar and sacral spine.[20]
- *Cerebrospinal fluid (CSF) spread.* Such spread is usually conferred by "shedding" of tumor cells from cerebral or cerebellar metastatic lesions, often following surgical manipulation of brain metastases.[22]

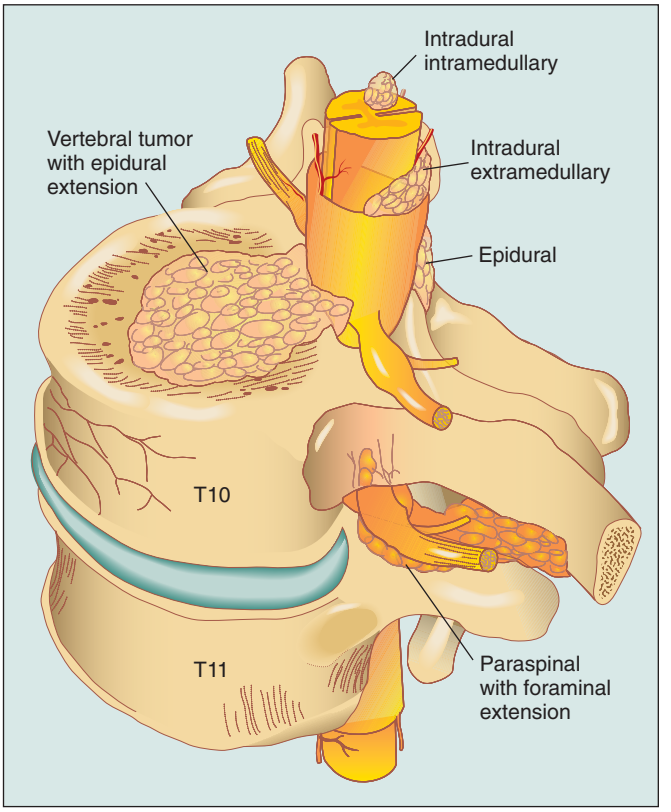


Figure 55-1 • Locations of metastatic lesions of the spine: vertebral body, epidural space, neural foramen, intradural space, and within the spinal cord itself.

After a malignant lesion has begun to grow in the epidural space, it is unclear how or at what point spinal cord compression (as may be seen on MRI or myelogram) leads to clinically apparent spinal cord compromise. Animal models demonstrate that at least three mechanisms may be at play.[23–25] First, direct pressure on the neural structures of the cord may result in subsequent demyelination. Second, compression may also lead to arterial insufficiency with subsequent neural degeneration. Finally, compression may cause venous blockage with secondary vasogenic edema due to disruption of the blood–spinal cord barrier. Interestingly, results of various animal experiments have shown that the spinal cord can tolerate prolonged pressure if the onset of the pressure is slow and the neural degeneration is not irreversible.[26–28] Along these lines, Rades and colleagues found that slower clinical progression of neurologic symptoms before diagnosis led to improved outcome,[29] emphasizing again that early diagnosis is a key to successful management.

CLINICAL EVALUATION

Back Pain

Significant back pain will likely affect over 80% of Americans at some point in their lives.[30] Because the overwhelming majority of such patients suffer from noncancerous musculoskeletal pain, the presenting complaint of back pain may divert many physicians away from patients who will ultimately harbor underlying spinal metastatic disease. However, in roughly 10% of patients with cancer, symptomatic spinal metastases may be the initial presentation.[31] In addition, when vertebral lesions are discovered, pain ends up being the most common presenting symptom, occurring in approximately 83% to 95% of patients.[3,18,32] As a result, a cancer patient who reports back strain from a particular event still needs very close attention and follow-up care.[33]

Three classic pain syndromes affect patients with spinal metastases: local, mechanical, and radicular pain. Patients often present with a combination of these pain syndromes. *Local pain* is usually described by patients as a persistent "gnawing" or "aching" pain emanating from the region of the spine that is affected by metastatic disease. It is hypothesized that growth of the metastatic tumor, most commonly located in the posterior vertebral body, leads to periosteal stretching and/or a local inflammatory process that stimulates the pain fibers within the spinal periosteum. In such patients, percussion over the spinous process may elicit local tenderness. Such pain usually responds well to steroid administration.[34]

Mechanical pain, also known as axial back pain, is aggravated by movement, activity, or simply increasing weight-bearing forces on the spinal segment affected. Spinal metastases that result in vertebral body damage (e.g., deformity, fracture) may result in spinal instabil-

ity, which likely results in muscle, tendon, ligament and/or joint capsule strain and ensuing symptoms of mechanical pain. Unfortunately, such discomfort is usually refractory to narcotics and steroids but responds to recumbency, bracing, and/or internal stabilization. *Radicular pain* may occur when spinal lesions compress or irritate an exiting nerve root, yielding pain in the dermatomal distribution of the involved root that is often described as "sharp," "shooting," or "stabbing." Interestingly, *dysesthetic/neuropathic pain* may also arise when patients have intradural extramedullary disease, creating pain that may be described as an "intense, burning" sensation.[22]

Motor and Autonomic Dysfunction

The second most common presenting complaint of patients with vertebral metastases is motor dysfunction, which can manifest as myelopathy and/or radiculopathy. Although less common than the presentation of pain alone, in patients with MESCC, roughly 60% to 85% of such patients are weak at the time of diagnosis.[2,3,18] In addition, patients often have some level of bladder, bowel, and/or sexual dysfunction related to the MESCC that they will not readily offer to the physician unless an inquiry is made. Bladder dysfunction is the most common autonomic finding and commonly correlates with the degree of motor dysfunction.[8] Although the rate of clinical progression is variable, patients with motor dysfunction inevitably progress to complete paralysis in the absence of intervention.[35] In addition, severe autonomic dysfunction with urinary retention, constipation, and loss of control of bowel or bladder function is a late and particularly ominous finding because full paraplegia can follow within hours.[33]

Neurologic status at the time of diagnosis, particularly motor function, has been shown to correlate with prognosis from MESCC,[21,36] thus reinforcing the concept that diagnosis prior to the development of a neurologic deficit is of paramount importance. Unfortunately, since complaints of chronic back pain in the general population are extremely common,[30] it is likely that a delay in diagnosis of vertebral metastasis occurs frequently in patients who complain merely of new-onset back or neck pain. Levack and colleagues reported, in a study of 319 cancer patients, that a median of 2 months passed from the onset of pain, as reported to their primary care providers, until the diagnosis of metastatic spinal cord compression.[37] For this reason, new-onset back or neck pain in a patient with known cancer must be considered spinal metastatic disease until proven otherwise. Moreover, thoracic pain is less common than is pain originating from the mobile cervical and lumbar regions, where degenerative disease is the precipitating cause of pain; thus, pain in the thoracic region should raise a high level of suspicion for the likelihood of cancer.

Sensory Dysfunction

Sensory disturbances such as anesthesia, hypesthesia, and/or parasthesia typically occur in correlation with motor dysfunction both in location and time of onset. In this way, patients with myelopathy may elicit a sensory level across the chest or abdomen, while patients with radicular pain or weakness may complain of sensory abnormalities in the same dermatomal distribution as their motor dysfunction. Notably, patients with MESCC of the thoracic cord may present complaining only of discomfort around the chest, described as if they were being restricted by a "tight shirt" or "corset," similar to the symptoms of patients with thoracic transverse myelitis.

DIAGNOSIS

In patients with known or suspected malignancy who present with back pain, the first step is a neurologic examination (Fig. 55-2). If the presence of an abnormal finding is in question, assistance should be sought from a neurologist. Any sign of myelopathy should lead to a prompt MRI of the entire spine with institution of high-dose dexamethasone therapy before the patient is sent to the MRI suite. Since a single bolus of steroid is unlikely to cause any significant side effects, waiting for confirmation of spinal cord compression before instituting administration of steroids is almost never warranted.[38]

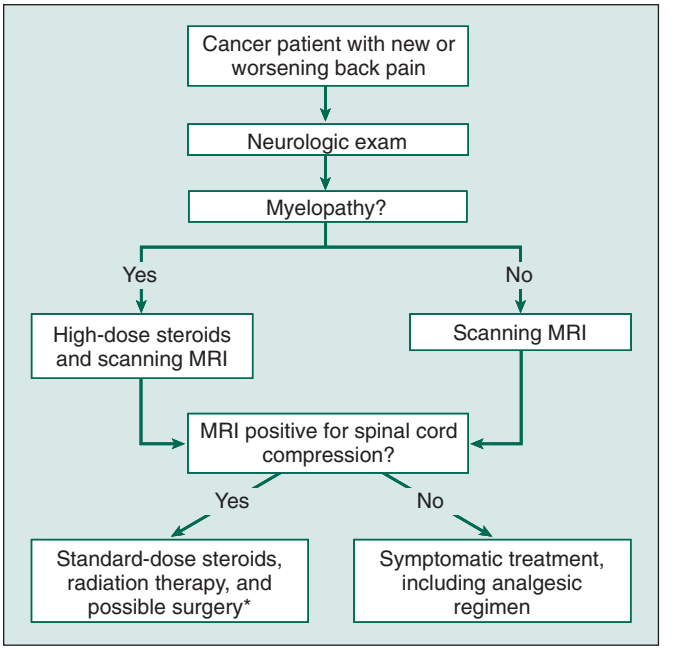


Figure 55-2 • Flowchart for initial workup of patient with suspected spinal metastatic disease. *See Figure 55-3.

In the absence of an abnormal neurologic examination, imaging for spine tumors may include any combination of plain radiographs (with or without myelogram), computed tomography (CT) (with or without myelogram), MRI, nuclear scintigraphy, and positron emission tomography. Although MRI is currently the gold standard for imaging spine tumors and epidural disease, patients may often provide other images that were requested by primary or emergency physicians.

Plain Films

Plain radiographs have long been the first course of imaging obtained for patients with spine pain, mainly owing to ease of use and relatively low cost. They serve mainly as a screening test by revealing lytic or sclerotic areas of bone, pathologic compression fractures, deformity, and/or paraspinal masses. The major proportion of spinal metastatic lesions are osteolytic, but up to 50% of the bone must be eroded before there is a noticeable change on plain radiographs.[39] Notably, osteoblastic/sclerotic lesions most often result from carcinoma of the breast or prostate.[40]

Bone Scan

Bone scanning or nuclear scintigraphy is sensitive for identifying increased metabolic activity throughout the entire skeletal system. Thus, whereas plain films might not detect tumor-induced radiographic changes until 30% to 50% or more of the vertebral medullary space has been replaced,[41] bone scans may reveal the lesion at an earlier stage.[42] However, such scans may detect increased metabolic activity associated with spinal inflammation and infection, leading to overall decreased specificity. In addition, nuclear scintigraphy currently has poor imaging resolution, necessitating correlation with CT or MRI to exclude benign processes and to plan possible operative intervention.[43] Positron emission tomography scanning with

^{18}F-fluorodeoxyglucose is now more commonly used for whole-body metastatic surveys and as a staging technique in patients with known systemic cancer.[44] However, as with nuclear scintigraphy, poor spatial resolution in positron emission tomography necessitates concomitant use of CT or MRI.

Computerized Tomography

CT imaging provides precise representation of the normal osseous anatomy and the extent of tumor involvement within the bone. In combination with myelography, it also provides the most accurate view of compressed neural elements. In this way, it may be extremely useful in determining whether cord compression is secondary to tumor expansion into the canal or whether osseous fragments from a pathologic fracture are the cause of compression. Furthermore, CT imaging is ideal for surgical planning, for which understanding of the regional osseous anatomy may direct the type and extent of spinal instrumentation.

Magnetic Resonance Imaging

MRI is considered the gold standard imaging modality for assessing spinal metastatic disease.[45–47] MRI is more sensitive than standard radiographs, CT, and bone scans in detecting primary malignant bone tumors and metastatic lesions in the spine.[48,49] Such sensitivity is due to the fact that MRI allows for superior resolution of soft-tissue structures such as intervertebral discs, spinal cord and nerve roots, meninges, and paraspinal musculature. Moreover, MRI provides clarity at the osseous–soft-tissue interface, yielding accurate anatomic detail of bony compression or invasion of neural and paraspinal structures.

When a patient has either local or radicular back pain with no evidence of myelopathy, a scanning MRI should be ordered.[50] This study involves a series of T_1-weighted sagittal images extending from the cervical spine to the sacrum. If metastatic lesions of bone are found, the procedure is converted to a more comprehensive set of images. This method is a faster and more cost-effective approach to early diagnosis of spinal cord compression.[50] The comprehensive MRI protocol should include T1- and T2-weighted images and contrast-enhanced studies that provide axial, sagittal, and coronal reconstructions.[51] Owing to the high signal intensity of fat within bone marrow on T1-weighted images, fat suppression techniques are useful in evaluating osseous lesions that enhance with contrast.[51] Diffusion-weighted imaging may be helpful in distinguishing between benign and pathologic compression fractures.[52]

Angiography

This advanced imaging modality is ordered by the neuroradiologist and/or neurosurgeon once the diagnosis of a spine tumor has been made. In patients with spinal metastases that are suspected to result from highly vascular primary tumors, such as renal cell carcinoma, thyroid carcinoma, angiosarcoma, leiomyosarcoma, hepatocellular carcinoma, and neuroendocrine tumors (pheochromocytoma, paraglanglioma),[53] angiography may provide diagnostic and have therapeutic benefit. If the lesions are considered for surgery, preoperative knowledge of vascular supply may prove invaluable. In addition, angiography might allow preoperative embolization of the spinal lesion, leading to decreased blood loss with operative resection.[54] Such intraoperative blood loss can influence the surgeon's ability to visualize an adequate view of the surgical field, thus affecting achievement of complete resection. In addition, significant blood loss may be associated with life-threatening hemorrhage intraoperatively, longer operating times, intraoperative complications, postoperative hematomas, and wound breakdown. In patients who are not candidates for surgery, embolization may be effective as primary treatment for the lesion.[55]

Percutaneous Spine Biopsy

Although imaging modalites have improved vastly over the last two decades, acquisition of tissue is not uncommonly needed for diagnosis. If surgery is not indicated up front and no other systemic lesions can be found, percutaneous image-guided biopsy may be indicated. Improved CT fluoroscopy and needle biopsy systems provide relatively easy access to most lesions with success rates approaching 90%. The majority of such procedures are now done in the outpatient setting.[56,57]

TREATMENT

Treatment of spinal metastases is primarily palliative. As a result, goals of treatment are centered on pain relief, maintenance or restoration of spinal stability, and preservation of neurologic function. Although in rare circumstances, patients may be cured with radical surgical excision (e.g., solitary renal cell carcinoma spinal metastasis),[58] patient variables, including age, tumor burden, life expectancy, and functional status, overwhelmingly influence the choice of therapeutic options. The three traditional mainstays of therapy have been corticosteroids, radiation therapy, and surgery. In the following paragraphs, we will provide the most current treatment paradigms involving each of these modalities and describe how technologic advances (e.g., bisphosphonates, radiosurgery, percutaneous vertebroplasty, aggressive decompressive surgery) have increased the armamentarium against metastatic spine disease and have consequently improved outcomes (Fig. 55-3).

Hormonal Therapy, Chemotherapy, and Medical Therapy

Chemotherapeutic agents can be classified into antitumor drugs and drugs that minimize the secondary effects of the tumor.[59] Except in cases of chemosensitive tumors, such as Ewing's sarcoma and neuroblastoma, antitumor drugs continue to have a limited role in the treatment of spinal metastases. On the other hand, drugs that are used to prevent or ameliorate the effects of spinal tumors (e.g., corticosteroids, bisphosphonates, analgesics) are widely accepted.

The three most common primary tumors that metastasize to the spine are breast, prostate, and lung cancers.[18,19] Unfortunately, although lung cancer is still the leading cause of cancer mortality in the United States, the median survival of patients with lung cancer metastatic to bone disease is reportedly between 3 and 9 months. As a result, most patients die of progressive disease before skeletal complications become a large problem.[60] In most prostate and breast cancers, on the other hand, lesions may be sensitive to hormonal manipulation.[59] Estrogen agonists/antagonists, such as tamoxifen, and aromatase inhibitors, such as letrozole, have been shown to be effective for breast cancer. For prostate cancer, androgen deprivation is the mainstay of treatment with GnRH agonists and/or flutimide.

Chemotherapy is usually given to patients with prostate and breast cancer when hormonal agents become ineffective. Breast cancer is often chemotherapy sensitive, and the most effective agents include doxorubicin and the taxanes. Although prostate cancer is considered less responsive to chemotherapy, some agents have demonstrated effectiveness, such as mitoxantrone, prednisone, vinblastine, and the taxanes. Multiple myeloma responds to combinations of mephalan and prednisone as well as infusioned vincristine and adriamycin.[59]

Corticosteroids

Corticosteroids are the mainstay of pharmacologic therapy for pain associated with vertebral metastases and for the acute neurologic deterioration that often accompanies MESCC. Corticosteroids decrease tumor-associated inflammation (analgesia effect), decrease spinal cord edema (improving short term neurologic function), and may be

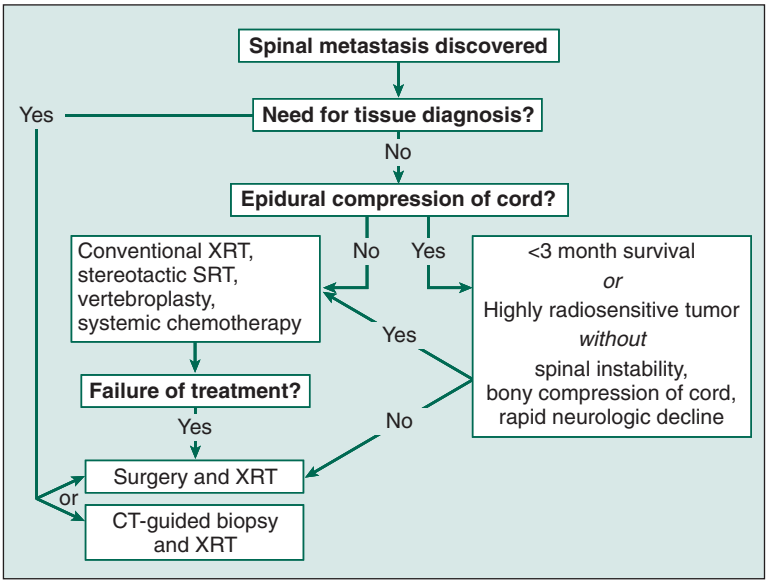


Figure 55-3 • Flowchart for management of spinal metastatic disease.

directly oncolytic, as with lymphoma, multiple myeloma, and breast cancer.[3] Experimental animal models have confirmed the clinical observations that those treated with dexamethasone have improvement in motor function faster than in untreated controls.[61–63] Memorial Sloan-Kettering Cancer Center has popularized a high-dose regimen: a loading dose of 100 mg dexamethasone followed by 6 mg given four times a day (total dose 24 mg),[2,38,64] a regimen that is based on studies demonstrating a dose-response benefit of dexamethasone.[62] However, there is no current optimal dosing regimen for corticosteroids used with MESCC, and no consensus data are available to recommend high-dose steroids (96 mg/day) versus low-dose steroids (16 mg/day). For instance, Vecht and colleagues compared initial doses of 10 mg IV bolus versus 100 mg IV bolus but showed no outcome differences regarding pain, ambulation, or bladder function.[65]

As was stated previously however, if a metastatic spine lesion is suspected, there are minimal drawbacks to starting high-dose dexamethasone in anticipation of an MRI scan. In patients presenting without obvious myelopathy, lower doses of steroids may be started, such as 4 mg every 6 hours or a bolus of 10 mg awaiting MRI.[38] Whatever dose is initiated, however, tapering of the steroid should begin during the course of radiation therapy.[66] By reducing the dose by one third every 3 to 4 days, the steroid course will be almost completely tapered by the end of radiation treatment.[33] Long-term use of corticosteroids, on the other hand, may be fraught with serious clinical side effects. Higher doses of steroids are rarely needed beyond the first 48 to 72 hours or even beyond the initial bolus. Therefore, if neurologic symptoms continue to progress with either the standard or high-dose regimen, prompt surgical intervention may be indicated.[33] In addition, recrudescence of symptoms during the steroid taper may be an indication for increasing the steroid dose or considering surgical decompression.

Bisphosphonates

This class of drugs suppresses bone resorption by inhibiting osteoclastic activity. In this way, bisphosphonates may reduce the risk of pathologic fracture,[67] relieve local pain secondary to lytic lesions,[68] and lower malignancy-associated hypercalcemia. Although most of the clinical trials on bisphosphonates have been conducted in patients with metastatic breast cancer and multiple myeloma, small studies on patients with other metastatic carcinomas have demonstrated benefit.[59]

Analgesia

Poorly managed cancer pain contributes to depression, anxiety, and fatigue.[69] Unfortunately, undertreatment of pain in cancer patients persists despite significant efforts by clinicians to improve delivery of analgesics. The American Pain Society Quality of Care Committee Consensus Statement in 1995 delineated the high prevalences of unrelieved pain across clinical settings with specific regard for cancer pain.[70] The World Health Organization has outlined a three-step system for the treatment of progressively severe pain using nonopioid analgesics, opioid analgesics, and adjuvant medications.[71] First-line agents should be nonopioid analgesics, such as acetominophen, aspirin, and other nonsteroidal anti-inflammatory drugs, which are often efficacious for bone pain. If pain is not controlled, an opioid analgesic should be added. If pain remains uncontrolled, a strong opioid analgesic should then be prescribed. At all levels of this ladder, adjuvant drugs may be added to treat specific types of pain.[72] Specifically, corticosteroids have been shown effective for use in spine tumor pain. In addition, neuropathic pain may respond to anticonvulsant medications (e.g., gabapentin, lamotrigine, carbamazepine), the 5% lidocaine patch, opioid analgesics, and tricyclic antidepressants.[73]

Conventional Radiation Therapy

Conventional radiation therapy (XRT) plays an important role in the palliative treatment of all spinal metastases with the goals of obtaining pain relief, preventing pathologic fractures or vertebral collapse, and avoiding progression or allowing reversal of neurologic dysfunction. Indications for XRT include radiosensitive tumors (lymphoma, multiple myeloma, small cell lung carcinoma, seminoma of testes, neuroblastoma, Ewing's sarcoma); expected survival less than 3 months; inability of patient to tolerate an operation; and multilevel or diffuse spinal involvement.

XRT is typically administered to spinal lesions over a 10- to 14-day course with a total radiation dose of 25 to 50 Gy.[74–76] The standard radiation portal involves the diseased level with a 5-cm margin, which effectively includes two vertebral bodies above and below the target.[77] Local vertebral tumor control is directly proportional to radiation dose delivered to the area, and the primary factor that limits radiation to the spine is the relatively low tolerance of the spinal cord for radiation damage. Unfortunately, conventional XRT

lacks the precision to deliver large single-fraction doses of radiation to the spine near radiosensitive structures such as the spinal cord; therefore, the actual treatment dose that is delivered is often far below the optimal therapeutic dose.[78–80] Allowing greater radiation doses to reach just the specifically targeted treatment volume, as is the potential with stereotactic radiosurgery, may increase tumor control while minimizing the risk of spinal cord injury.

Surgical Approaches and Techniques

As a result of improvements in chemotherapy, radiation therapy, and hormonal therapy with concurrent increases in survival time for many patients with metastatic spine disease, many clinicians have advocated aggressive surgical decompression and stabilization for symptomatic lesions.[81] Effective techniques to achieve dorsal and ventral spinal stabilization have become more widely available in the last two decades, allowing surgeons to achieve adequate decompression and tumor resection with acceptable morbidity. The ability to correctly identify appropriate candidates for surgical intervention requires an understanding of the anatomy of the tumor and its surrounding structures, the biomechanical changes created by vertebral metastases, and the characteristics of the specific histopathology that may affect surgical resection.

Biomechanical Considerations

The vertebral body has been shown with biomechanical studies to support up to 80% of the axial load from above.[82] Since the vertebral body is the most common site of metastatic growth, destructive lesions in this area can have a significant impact on the load-bearing capacity of the spine. Such capacity is directly associated with tumor size, cross-sectional area of the remaining intact body, and bone mineral density. Windhagen and colleagues have shown that pathologic fracture can be accurately predicted (in cadaveric spines) by calculating the product of the remaining intact vertebral cross-sectional area and the bone mineral density.[83] Taneichi and colleagues studied 53 patients with osteolytic metastases and found that impending collapse was predicted by 50% to 60% involvement of the vertebral body in the thoracic spine and 35% to 40% involvement in the thoracolumbar/lumbar spine.[84] As a result, axial loading most commonly creates a compression fracture or a burst fracture with structurally significant lesions. Conversely, invasion and disruption of the posterior spinal elements, such as the facet joints, may predispose patients to dislocation and translational deformity. However, because these dorsal elements are less commonly affected by metastases, such structural pathology is unusual.

Surgical Anatomy and Histopathology Affect Resection

In general, the surgical approach is dictated by the segment of spine that is involved with tumor (cervical, thoracic, lumbar, sacral), the location of the tumor within the spine segment (anterior, posterior, right, left, or circumferential to neural elements), tumor histology, and the type of spinal reconstruction or stabilization required after tumor resection. In addition, patients with hypervascular tumors (e.g., renal cell carcinoma, thyroid carcinoma, hepatocellular carcinoma) may benefit from preoperative embolization to minimize intraoperative blood loss.

Metastatic tumors that cause epidural cord compression typically arise from the vertebral body and extend dorsally; thus, anterior approaches commonly provide the greatest ability to decompress the spinal cord. The cervical spine can be approached easily both anteriorly and posteriorly, and the accompanying reconstructive instrumentation is also familiar to most surgeons. In the thoracic spine, the upper segments (T1 to T4) may be particularly challenging to access, possibly requiring a combination of an anterolateral cervical approach with a sternotomy and/or thoracotomy to decompress the anterior cord.[85] To avoid encountering the great vessels and aortic arch, thoracic levels T5 to T10 are ideally approached via a right-sided thoracotomy unless the bulk of the extravertebral tumor is on the left side.[86] Approaches to the thoracolumbar junction (T11 to L1) may require a combined thoracotomy and retroperitoneal approach, while decompression at the L2 to L4 levels can occur via a retroperitoneal or transperitoneal/transabdominal approach. Disease that is limited to L5 is most commonly treated with posterior decompression and stabilization. Sacral lesions may require posterior alone approaches or transperitoneal entry into the pelvis for anterior-posterior approaches.

Adequate decompression of the spinal cord from a lone posterior approach is challenging but possible. Several authors have advocated bilateral transpedicular or costotransversectomy approaches to decompress the ventral aspect of the spinal cord.[87–92] Reconstruction of the anterior and middle columns of the spine may then be achieved with polymethylmethacrylate (PMMA) secured with Steinman pins[88,89] or a chest tube,[87] titanium mesh cages,[93] or expandable titanium cages.[90–92] One potential criticism of such approaches is that the spine is severely destabilized from such procedures. Specifically, since the normal posterior elements are generously resected to remove the diseased anterior elements, there is potentially increased surgical morbidity and a lower chance of successful biologic osseous fusion owing to the large gap that is created between neighboring bone surfaces.

In general, vertebral body resection for tumor with successive reconstruction/stabilization is now most commonly performed via an anterior approach with subsequent vertebral column reconstruction (distractible of mesh titanium cage) and anterolateral plating. Supplemental posterior stabilization with pedicle screw instrumentation is advocated in those with significant damage to the posterior elements from tumor or from tumor removal surgery, significant kyphosis, or lesions at the thoracolumbar junction and in patients with two or more adjacent vertebrectomies (Fig. 55-4). Lone posterior approaches should likely be reserved for patients with contraindications to anterior approaches (e.g., transthoracic approach in patients with severe lung disease), owing to the severely destabilizing characteristics of such procedures.

Metastatic Epidural Spinal Cord Compression Treatment

Metastatic epidural spinal cord compression (MESCC) is defined as radiographic evidence of an epidural metastatic lesion that is causing displacement of the spinal cord from its normal position in the spinal canal. This condition occurs in roughly 5% to 10% of cancer patients and in up to 40% of patients who have concurrent nonspinal bone metastases.[94–96] The result is approximately 25,000 annual cases of symptomatic MESCC in the United States.[8] Traditionally, treatments for patients with MESCC have included corticosteroids, surgery, and XRT. Historically, surgical options were limited to decompressive laminectomy. Unfortunately, laminectomy procedures frequently did not address the primary site of spinal cord compression, which is the ventral vertebral body. Tumor in this area often causes intrinsic instability of the anterior column of the spine. Laminectomy procedures, which are destructive to the posterior spinal elements, may thus further destabilize the spine and worsen a patient's pain and neurologic status.[87,97] For this reason, combined with improved spinal instrumentation, aggressive surgical decompression with instrumented stabilization has become mainstream.

A review of the literature from 1964 to 2005 by Witham and colleagues regarding articles related to radiation therapy and surgical management for MESCC has shown improved outcomes concurrent with evolution toward more aggressive decompressive surgery and more extensive surgical stabilization (Table 55-1).[98] Review of articles investigating neurologic function following XRT alone in patients with MESCC revealed that a mean of 36% of patients improved and a mean of 17% worsened. Review of articles investigating neurologic function in patients treated with laminectomy with or without XRT

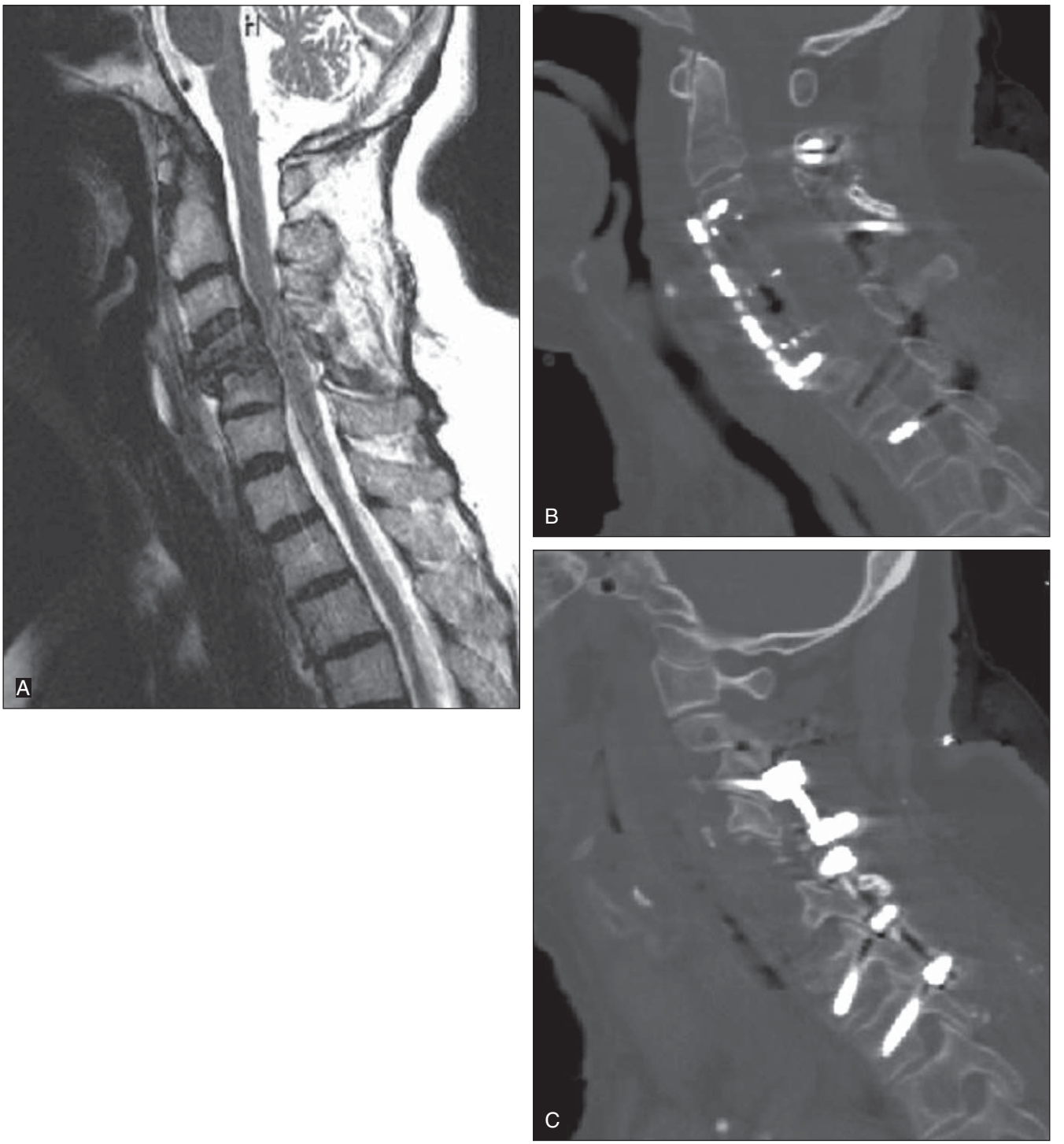


Figure 55-4 • Images from a patient with metastatic breast cancer undergoing surgical decompression and fusion. **A,** T2-weighted sagittal MRI image of the patient showing destructive and compressive lesion in the cervical spine. Postoperative sagittally reconstructed CT images showing anterior cages and plate (**B**) and posterior rods and screws (**C**).

Table 55-1 Review of the Literature for Treatment of Metastatic Epidural Spinal Cord Compression

	Improved Neurologic Function (mean)	Surgical Mortality (mean)
XRT alone	36%	N/A
Laminectomy, +/– XRT	42%	6%
Laminectomy, spinal stabilization, +/– XRT	64%	5%
Anterior decompression, spinal stabilization, +/– XRT	75%	10%

N/A, not applicable; XRT, radiation therapy.

Witham TF, Khavkin YA, Gallia GL, et al: Surgery insight: current management of epidural spinal cord compression from metastatic spine disease. Nat Clin Pract Neurol 2006;2:87–94.

showed results similar to those of the XRT alone series, with improved neurologic function in a mean of 42% of patients and worsened function in a mean of 13% of patients. Notably, surgical morbidity and mortality (mean surgical mortality of 6%) did occur in the laminectomy series compared to the nonsurgical XRT series. Interestingly, in the series of articles involving patients undergoing stabilization procedures performed in conjunction with posterior decompressive procedures, functional outcomes were improved, with a mean motor improvement in 64% of patients. In this series, pain relief was achieved a high percentage of the time (mean: 88%) with a mean mortality rate that was comparable to that of laminectomy alone (5%). Moreover, in the series of articles involving patients undergoing stabilization procedures concurrent with *anterio*r decompression to the spinal cord, functional neurologic improvement was even more remarkable (mean: 75%) with only a slight increase in surgical mortality (mean: 10%).

Recently, a randomized, prospective clinical trial of direct decompressive surgical resection and XRT versus XRT alone for MESCC was conducted by Patchell and colleagues (Table 55-2).[99] Both groups of patients received a total radiation dose of 30 Gy delivered in 10 fractions. The intent of surgery in all cases was spinal cord decompression, removal of as much tumor as possible, and spinal stabilization. Results showed a statistically significant difference in the post-treatment ambulatory rate in the surgery group of 84% (42 of 50) compared to the XRT alone group 57% (29 of 51) ($P = 0.001$). In addition, post-treatment ambulatory patients retained the ability to walk significantly longer in the surgery group than in the XRT group (median of 122 days versus 13 days, $P = 0.003$). Regarding patients who were ambulatory prior to treatment, 94% (32 of 34) in the surgery group continued to be ambulatory compared to 74% (26 of 35) in the XRT group ($P = 0.024$). In addition, 62% (10 of 16) of the patients in the surgery group who were nonambulatory prior to treatment regained the ability to ambulate compared to only 19% (3 of 16) in the XRT group ($P = 0.012$).

Most important, Patchell and colleagues demonstrated that survival time, maintenance of continence, muscle strength (ASIA scores), and functional ability (Frankel scores) were all significantly improved in the surgery group relative to the XRT alone group. Specifically, median survival in the surgery group was 126 days relative to 100 days in the XRT group ($P = 0.033$). Thus, Patchell and colleagues concluded that selected patients with MESCC treated with surgery and XRT possess a modest improvement in survival time, maintain the ability to ambulate longer, and recover the ability to ambulate more frequently than those treated with XRT alone.

On the basis of such results, basic recommendations can be made regarding indications for XRT alone versus surgery and XRT. Indications for lone XRT include MESCC secondary to highly radiosensitive tumors (lymphoma, myeloma, small cell lung carcinoma) *without* spinal instability, significant bony compromise of the spinal canal, or rapidly progressive neurologic decline. Lone XRT could also be indicated in patients with life expectancy less than 3 months. Indications for surgery include MESCC secondary to radio-resistant tumors or those that recur despite XRT, rapid neurologic deterioration during XRT, spinal instability, epidural cord compression from bone, or a need for tissue diagnosis (see Fig. 55-3). Solitary lesions with indolent courses, such as renal cell carcinoma in the absence of additional systemic metastases, may be considered for en bloc tumor resection with total spondylectomy in hope of a cure.[88,100–105]

Spinal Stereotactic Radiosurgery

Although spinal stereotactic radiosurgery (SRS) is a relatively new radiation treatment option for spinal metastases and therefore has not undergone rigorous, long-term investigation, it may have advantages over conventional XRT for the treatment of MESCC. The most common delivery systems are modified linear accelerators (Novalis, BrainLAB Inc., Chicago, IL) and a robotic linear accelerator (CyberKnife, Accuray, Sunnyvale, CA). In these systems, stereotactic

Table 55-2 Results of a Randomized, Prospective Trial Comparing Radiation Therapy Alone to Surgery and Radiation Therapy Combined

	Post-treament Ambulatory Rate	Post-treatment Retention of Ambulation (days)	Ambulatory Prior to Treatment Who Maintained Ambulation	Nonambulatory Prior to Treatment Who Regained Ambulation	Mean Survival (days)
XRT alone	57%	13	74%	19%	100
Surgery and XRT	84%	122	94%	62%	122

XRT, radiation therapy.

Patchell RA, Tibbs PA, Regine WF, et al: Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet 2005;366:643–648.

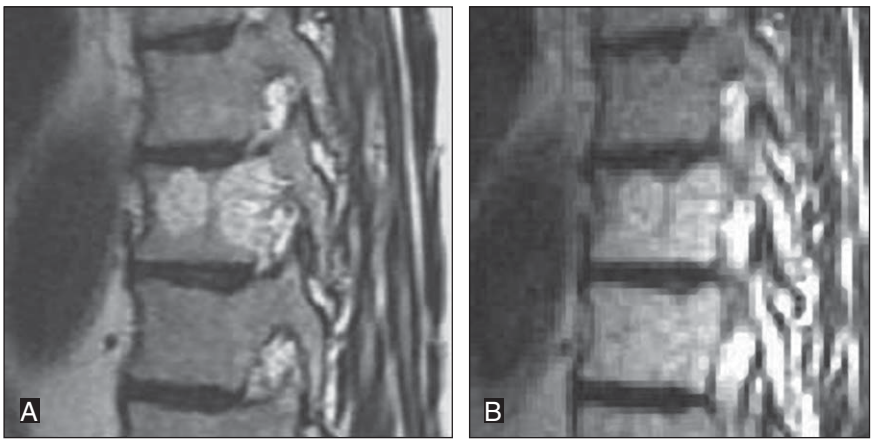


Figure 55-5 • Contrast-enhanced T2-weighted sagittal MRI images showing stable size of metastatic prostate lesions in the T9 vertebra before (**A**) and 5 months following stereotactic spinal radiosurgery (**B**). (Borrowed with permission from Jack Rock, M.D.)

localization provides precise convergence of multiple, "fractionated" radiation beams onto the targeted lesion. Because fractionation allows the normal tissues to optimally tolerate the radiation exposure, spinal SRS and intensity-modulated radiotherapy permit accurate delivery of radiation while minimizing radiation exposure to normal tissues.[74] Total doses typically range from 8 to 18 Gy, and SRS can be administered in one or two sessions in an outpatient setting.

A number of studies involving SRS for MESCC have provided encouraging results. Degen and colleagues presented the outcomes of patients with MESCC who were treated with Cyberknife to treat 58 spinal metastatic lesions that were documented as durable at 1 year follow-up.[106] Of the patients who presented with a neurologic deficit, 31% improved, 47% were unchanged, and 22% worsened. In this same study, a significant improvement in pain was noted, and quality of life was maintained with relatively limited treatment morbidity. Interestingly, there was 100% tumor control for metastatic lesions treated with SRS that had not undergone previous irradiation. In another recent study by Gerszten and colleagues involving CyberKnife radiosurgery for spinal lesions, axial and radicular pain improved in 74 of 79 patients who were symptomatic before treatment.[107] Potential limitations of SRS include the inability to address spinal instability or deformity secondary to metastatic spine disease and the inability to treat large lesions safely, owing to its associated highly concentrated radiation dose. In addition, SRS is still largely viewed as an experimental treatment modality for MESCC. Nonetheless, spinal SRS could prove to be an effective and indispensable weapon in the arsenal against metastatic spine disease (Fig. 55-5).

Percutaneous Vertebroplasty and Kyphoplasty

Traditionally, extensive, multifocal metastatic disease of the spinal column was treated by conventional XRT combined with conservative measures such as bed rest, bracing, corticosteroids, and analgesia. However, successful XRT often does not provide pain relief for up to 2 weeks, and bone strengthening is not seen for up to 4 months if it occurs at all.[108] Although originally developed for the treatment of painful vertebral hemangiomas, percutaneous vertebro/kyphoplasty has now become an effective treatment for the painful, pathologic fractures of metastatic spine disease.

Percutaneous injection of PMMA cement into a pathologically collapsed vertebral body has been shown to be effective for the treatment of pain.[109] Although it is assumed that such techniques minimize mechanical pain via cement-augmented structural support, it is possible that the cement itself possesses analgesic properties within the vertebral body.[110] Vertebroplasty is characterized by direct injection of PMMA into the vertebral body (Fig. 55-6). Kyphoplasty, on the other hand, involves first placing an expandable balloon into the vertebral body. Once inflated, the balloon creates a cavity for the subsequent injection of PMMA. It is postulated that kyphoplasty might actively improve kyphotic deformity of the spine with such balloon expansion.

Exact indications for vertebro/kyphoplasty in relationship to metastatic spinal disease are evolving. The technique is safe and effective for treating intractable pain secondary to vertebral fractures. A relative contraindication to vertebro/kyphoplasty is epidural spinal cord compression; however, when combined with XRT, such procedures can result in dramatic pain relief for poor surgical candidates. For instance, Fourney and colleagues presented 97 procedures in patients with intractable pain secondary to pathologic vertebral body fractures and noted moderate to complete pain relief in 84%.[109] Although rare, complications of such procedures are related to leakage or misdirection of PMMA outside the confines of the vertebral body, leading to spinal cord/root compression or PMMA pulmonary emboli via cement injection into the spinal venous plexus.[111]

CONCLUSIONS

Although management paradigms for patients with metastatic disease of the spine can appear complicated, involving multiple modalities and multiple specialties, technologic advances have allowed many patients to be treated more aggressively, often resulting in improved outcomes. Innovations in spinal fixation devices have permitted surgeons to decompress the spine more adequately, leading to improved functional outcomes. Specifically, a randomized, prospective trial has demonstrated that treatment with the combination of surgery followed by radiation leads to a greater likelihood of regaining and maintaining ambulation after treatment. In addition, improving imaging modalities and focused radiation therapies, such as spinal stereotactic radiosurgery, appear to target lesions of the spine more precisely while minimizing damage to neighboring structures. In this way, spinal metastatic disease, albeit classically managed with palliative care, might eventually be approached with intent to cure for a large proportion of patients.

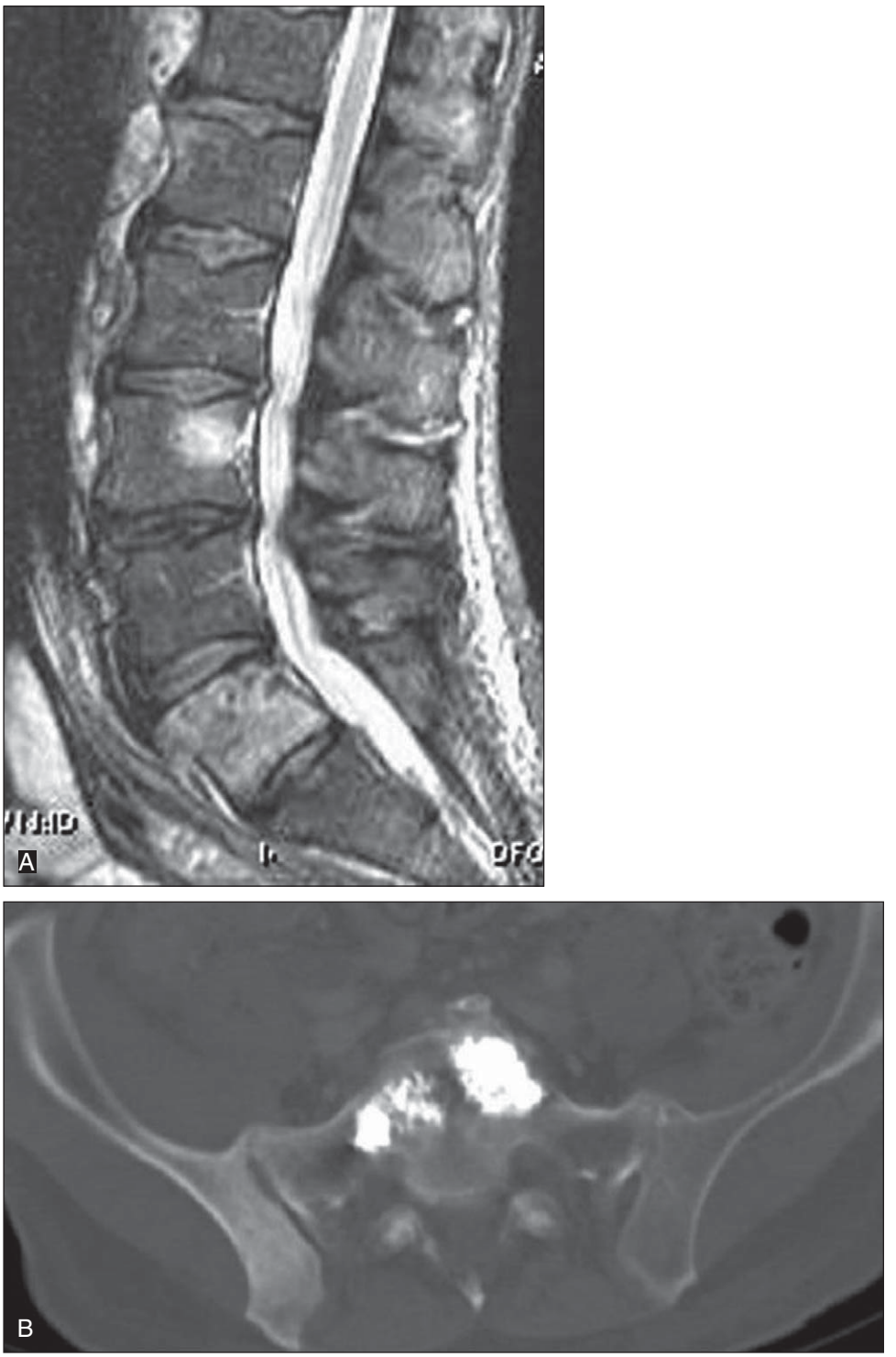
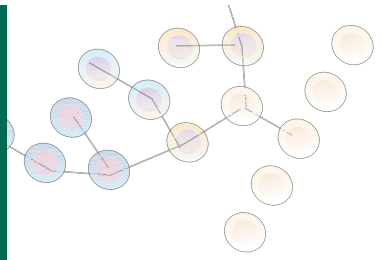


Figure 55-6 • Images from patient with metastatic non-small-cell lung cancer. **A,** T2-weighted sagittal MRI showing metastasis in a lumbosacral vertebral body. **B,** Axial CT image following percutaneous vertebroplasty.

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56 Brain Metastases and Neoplastic Meningitis

Penny K. Sneed, Norbert Kased, Kim Huang, and James L. Rubenstein

SUMMARY OF KEY POINTS

Epidemiology

- Central nervous system metastases are common, affecting up to 25% of cancer patients.
- Most central nervous metastases involve the brain; less often, the dura, leptomeninges, skull base, or cranial nerves may be affected.
- The terms *neoplastic meningitis* and *carcinomatous meningitis* refer to the dissemination of cancer cells within the leptomeningeal space.
- The most frequent primary tumor types that give rise to brain metastases are lung cancer, melanoma, breast cancer, and renal cell carcinoma.

Diagnosis

- Brain metastases are best detected with contrast-enhanced magnetic resonance imaging (MRI) and generally appear as enhancing, well-circumscribed lesions with surrounding vasogenic edema. Biopsy or resection might be indicated to confirm the diagnosis, particularly in a patient with a single lesion and no cancer diagnosis or no known metastatic disease.
- Neoplastic meningitis often eludes early detection because meningeal enhancement is visible on MRI in only about 50% of cases and cerebrospinal fluid cytology may be negative initially in 40% to 50% of cases.

Prognosis

- The most important factors predicting for longer survival of patients with brain metastases include age less than 65 years, good performance status, control of the primary tumor, and lack of extracranial metastases.

Treatment

- The most standard treatment for brain metastases is whole-brain radiotherapy (WBRT), though patients with good prognosis who have a limited number of brain metastases might benefit from more aggressive therapy, such as surgery (especially for a single brain metastasis) or radiosurgery, with or without adjuvant WBRT. After WBRT alone, at least 60% of symptomatic patients improve significantly, and the median survival time is typically 3 to 6 months, with one third to one half of the patients dying of brain metastases and the rest dying of systemic disease. About 24% of brain metastases have a complete response to WBRT, and another 35% of lesions have a partial response, but the 1-year actuarial local control probability may be as low as 15%. Among patients with newly diagnosed brain metastases who are selected for surgery or radiosurgery with or without WBRT, the median survival time is approximately 9 to 11 months. One-year actuarial local control is about 35% for surgery alone, 85% for surgery and adjuvant WBRT, and 75% to 90% for radiosurgery with or without adjuvant WBRT. However, the increased local control that is achievable with surgery plus WBRT or with radiosurgery may only be meaningful in patients likely to live at least 6 or 12 months from the standpoint of their extracranial disease. Chemotherapy is not generally used as a primary treatment for brain metastases, but it has some efficacy on its own, and there is increasing interest in combining drugs with WBRT.
- Intrathecal chemotherapy plays a major role in the management of neoplastic meningitis, alone or in combination with radiotherapy. Because craniospinal radiotherapy causes significant acute toxicity as well as long-lasting myelosuppression, neoplastic meningitis may be managed by using intrathecal chemotherapy combined with more limited radiotherapy, such as a lumbar field for gross disease in the cauda equina, skull base fields for cranial nerve involvement, or WBRT in patients with hydrocephalus stemming from diffuse brain leptomeningeal involvement.

INTRODUCTION

Central nervous system (CNS) metastases result from the intracranial spread of tumor cells that originate outside of the CNS. Most CNS metastases involve the brain parenchyma, dura, or leptomeninges; less commonly, metastases involve the base of skull, cranial nerves, or dural sinuses. This chapter deals with both parenchymal brain metastases and leptomeningeal metastases, also known as neoplastic or carcinomatous meningitis.

BRAIN METASTASES

Epidemiology

Brain metastases appear to be more common than primary malignant brain tumors, though the exact incidence is unknown. In a Memorial Sloan Kettering Cancer Center autopsy series, 24% of cancer patients had CNS metastases, and 15% had brain metastases,[1] and in a Roswell Park Memorial Institute autopsy study of 216 melanoma

patients, 55% had brain metastases.[2] One population-based study in the Netherlands reported by Schouten and colleagues found that 8.5% of 2724 patients with melanoma or lung, breast, colorectal, or renal cell carcinoma developed brain metastases. The 5-year cumulative incidence of brain metastases was 7.4% in patients with melanoma and 16.3%, 9.8%, 5.0%, and 1.2% for patients with lung, renal cell, breast, or colorectal carcinoma, respectively.[3] Barnholtz-Sloan and colleagues calculated the population-based incidence of brain metastasis within the Metropolitan Detroit Cancer Surveillance System. In this cohort, 16,210 patients were found to have brain metastases, representing 9.6% of all lung, melanoma, breast, renal, and colorectal cancer patients diagnosed from 1973 to 2001. Lung and melanoma were the primary sites with the highest rates at 19.9% and 6.9%, respectively, and 5.1% of breast cancer patients, 6.5% of renal cancer patients, and 1.8% of colorectal cancer patients developed brain metastases.[4] It has been theorized that the incidence of brain metastases may be increasing as a result of improvements in cancer management leading to longer survival times and increased sensitivity of lesion detection made possible by contrast-enhanced, high-resolution magnetic resonance imaging (MRI), although Schouten and colleagues found no evidence of an increasing incidence of brain metastases over the period from 1986 through 1995.[3]

The most common primary tumors responsible for brain metastases are lung cancer (making up approximately 40% to 50% of cases), breast cancer (15%), melanoma (10%), and unknown primary (5% to 10%), followed by renal cell carcinoma, colorectal cancer, gynecologic cancers, and other miscellaneous tumors.[5,6] Brain metastases may arise from any primary cancer, but certain tumors such as melanoma and carcinomas of the lung, kidney, and breast have a predilection for spread to the CNS. By contrast, some tumors rarely metastasize to the brain, such as prostate, oropharyngeal, and skin carcinomas. In children, the most common solid malignancies responsible for brain metastases are sarcomas, neuroblastoma, and germ cell tumor.[7]

Cancer can spread to the brain at various points in the course of disease. Synchronous brain metastases, found within 1 month of the primary cancer diagnosis, occur in up to one third of patients,[3] including cases in which brain metastases are responsible for a patient's presenting signs or symptoms. More commonly, however, brain metastases are discovered after the diagnosis of cancer, often after other systemic metastases have developed, at a median of less than 1 year after diagnosis of lung cancer and at a median of 2 to 3 years after diagnosis of melanoma, breast cancer, gynecologic cancer, or renal cell carcinoma.[6] Overall, the median time from primary diagnosis to diagnosis of brain metastases is 12 months.[6]

Pathophysiology

Brain metastases arise primarily from arterial hematogenous spread to the brain, with tumor cells tending to become trapped where blood vessels decrease in caliber at the gray/white matter junction and the distalmost vasculature (the border zones or "watershed" zones between arterial territories).[8] Metastatic cells then adhere to the endothelial cells, penetrate into the brain parenchyma, and proliferate. Larger aggregates of tumor cells that gain access to the venous circulation are filtered out in lung capillaries before entering the systemic arterial circulation, but individual tumor cells may pass through the lung to lodge in the brain. Tumor emboli may also break off from lung metastases or primary lung cancers to travel to the brain via the arterial circulation. It has also been theorized that cells from pelvic or abdominal cancers may gain access to the posterior fossa or leptomeninges through Batson's vertebral venous plexus without passing through the lungs.[5] Intracranial spread may also occur via direct extension from bone or dural metastases or perineural extension along cranial nerves. The distribution of metastases is roughly proportional to the relative blood flow to different regions; approximately 80% of brain metastases are located in the cerebral hemispheres, 10% to 15% in the cerebellum, and 1% to 5% in the brain stem.[5,6] Posterior fossa metastases appear to arise disproportionately from pelvic or abdominal primary tumors.[5]

Most brain metastases are very well circumscribed. Although there may be extensive associated edema, the tumor cells do not tend to infiltrate into surrounding brain tissue, in contrast to primary malignant brain tumors. Most brain metastases are solid, but they can appear cystic because of necrosis, keratin deposits in squamous cell carcinoma, or mucin secretion from adenocarcinoma. Brain metastases may be hemorrhagic, particularly from melanoma, renal cell carcinoma, choriocarcinoma, and, less frequently, bronchogenic carcinoma.[9] The pathologist can easily identify well-differentiated metastases, but immunohistochemistry or electron microscopy might be needed to help make the diagnosis of metastatic versus primary brain neoplasm and to suggest the likely site of origin of poorly differentiated metastases.

Single brain metastases are more common than multiple metastases in patients with renal cell, gastrointestinal, or unknown primary cancers.[6] In the era of computed tomographic (CT) imaging, about 50% of brain metastasis patients had a single brain lesion.[5] By MRI criteria, the actual percentage of brain metastasis patients with a single lesion might be lower than this, because contrast-enhanced MRI is more sensitive than CT is[10] and because triple-dose gadolinium is more sensitive than is single-dose gadolinium-enhanced MRI.[11] Of note, the term *solitary brain metastasis* implies that a single brain metastasis is the only known site of metastatic disease, whereas the term *single brain metastasis* refers to a single cerebral lesion without implying whether or not there are extracranial metastases.

Clinical Presentation

The possibility of brain metastases should be suspected in any cancer patient who develops new neurologic signs or symptoms. Two thirds of cancer patients who are found to have brain metastases at autopsy had experienced neurologic symptoms from the metastases,[12] and only 10% of a series of 729 patients diagnosed by CT or MRI from 1973 through 1993 were asymptomatic.[6] The most common presenting symptoms are headache (24% to 53%), focal weakness (16% to 40%), altered mental status (24% to 31%), seizures (15% to 16%), and ataxia (9% to 20%).[6,13] Symptoms may worsen gradually from a growing tumor and the associated edema. Less often, acute neurologic symptoms may occur from hemorrhage into a brain metastasis. Again, the histologic types with the greatest propensity to produce hemorrhagic brain metastases include melanoma, renal cell carcinoma, and choriocarcinoma.

Diagnosis

It is widely accepted that MRI is the best diagnostic test to detect brain metastases. Standard imaging includes T2-weighted and pre- and post-gadolinium-enhanced T1-weighted sequences; a postcontrast fluid-attenuated inversion-recovery sequence is also helpful in visualizing small metastases near cerebrospinal fluid (CSF) spaces (Fig. 56-1). Gadolinium-enhanced MRI is much more sensitive than either non-enhanced MRI or contrast-enhanced CT imaging.[10,14] In one study, 17 of 55 patients (31%) with a single metastasis based on contrast-enhanced CT imaging were found to have multiple metastases on contrast-enhanced MRI.[15] The sensitivity of MRI is improved by using triple-dose gadolinium (0.3 mmol/kg instead of 0.1 mmol/kg gadoteridol) to increase contrast enhancement[11] and by using contiguous axial 3-mm slices without skips and coronal three-dimensional spoiled gradient echo recovery volume imaging so that small lesions are not missed between slices. Functional imaging techniques such as positron emission tomography, magnetic resonance spectroscopy, and perfusion and diffusion MRI may aid in distinguishing metastatic lesions from necrosis, primary brain tumor, or nonmalignant processes.[16–18]

The differential diagnosis of an enhancing or hemorrhagic intracranial lesion includes brain metastasis, primary brain tumor, CNS

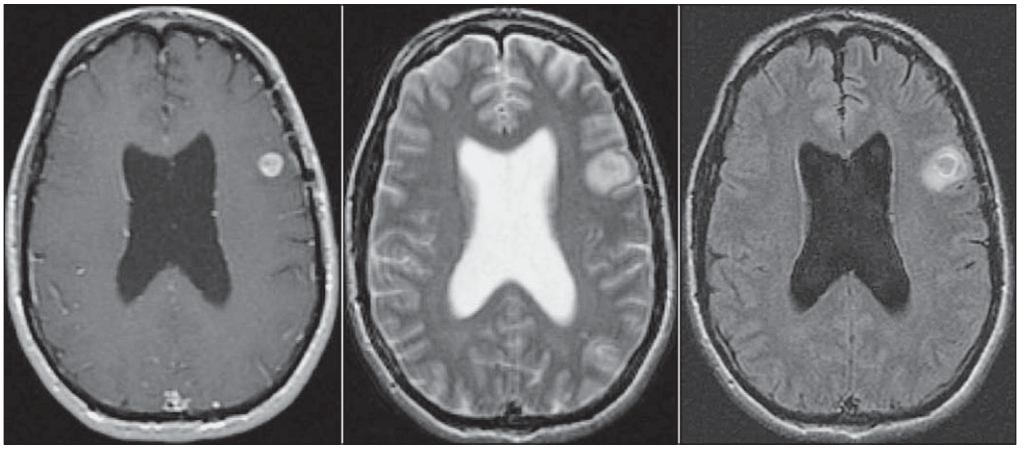


Figure 56-1 • Typical appearance of a brain metastasis on magnetic resonance imaging. The lesion is well circumscribed and brightly enhancing on the postcontrast T1-weighted image (*left*). Both edema and cerebrospinal fluid show up as increased signal on the T2-weighted image (*center*). Both the metastasis and the surrounding edema appear bright on the postcontrast fluid-attenuated inversion-recovery image, while the cerebrospinal fluid signal is suppressed (*right*).

lymphoma, abscess, encephalitis, cerebral infarct or hemorrhage, progressive multifocal leukoencephalopathy, tumefactive demyelinating disease, and radiation necrosis. Factors that aid in making a diagnosis based on imaging include characteristic appearance, a known cancer diagnosis, and multiplicity of lesions. However, a biopsy can be warranted if there is doubt about the diagnosis or if a single brain lesion is seen in a patient with a history of cancer but no other known metastatic disease, because management and prognosis may vary widely depending on the diagnosis. In a study reported by Patchell and colleagues that required biopsy or surgery before WBRT, 11% of 54 patients with a single brain lesion that was thought to be a metastasis turned out to have a glioblastoma, low-grade astrocytoma, abscess, or inflammatory process.[19] A stereotactic biopsy series in 100 patients with multifocal brain lesions and no known primary cancer diagnosed malignant gliomas in 37% of patients, primary CNS lymphoma in 15%, brain metastases in 15%, low-grade gliomas in 12%, infectious processes in 10%, and ischemic lesions in 6%.[20]

Prognostic Factors

In general, brain metastases are associated with a poor prognosis. In the pre-CT era, the median survival time of patients with symptomatic brain metastases was approximately 1 to 2 months without treatment,[21–23] 2 to 2.5 months with corticosteroid therapy,[24] and 3 to 6 months with WBRT.[25–27] Despite some major advances in cancer diagnosis, cancer treatment, and brain imaging, the overall survival time of unselected patients with brain metastases treated with WBRT has remained at 3 to 6 months since the 1950s.[6,28–30] The majority of patients with brain metastases have or will soon develop disseminated systemic disease and overall survival is often determined by the extent and activity of the extracranial disease. In patients with a relatively short life expectancy, the treatment goal is to achieve rapid palliation and a neurologic symptom-free remission interval that is commensurate with the life expectancy. However, long-term survival or cure is possible in a small proportion of patients with brain metastases, and patients with a longer life expectancy from the standpoint of their extracranial disease might benefit from more aggressive therapies that will yield more durable control of their brain metastases.

Two large series of brain metastasis patients evaluated for prognostic factors are summarized here. Lagerwaard and colleagues studied 1292 patients with CT-diagnosed brain metastases who were treated at Daniel den Hoed Cancer Center in Rotterdam from 1981 through 1990.[31] The overall median survival time was 3.4 months, and the most important patient and tumor characteristics that were prognostic for longer survival time included better performance status, limited versus extensive systemic tumor activity, and normal serum lactate dehydrogenase level, followed by lesser factors, including breast cancer versus other primary sites, age less than 70 years, and 1 to 2 versus 3 or more brain metastases.[31] Gaspar and colleagues identified three prognostic groups using a recursive partitioning analysis (RPA) of over 1100 evaluable patients enrolled in three consecutive Radiation Therapy Oncology Group (RTOG) trials conducted from 1979 through 1993.[32] The median survival time was 7.1 months for the subgroup with the best prognosis, RPA class 1, consisting of patients less than 65 years old with a Karnofsky performance status (KPS) of at least 70, controlled primary tumor, and no extracranial metastases (Table 56-1). The subgroup with the poorest prognosis, RPA class 3, including patients with KPS less than 70, had a median survival time of only 2.3 months; and the median survival time was 4.2 months for the remaining patients who made up RPA class 2 (see Table 56-1).[32] The prognostic value of these RPA classes has been validated in 569 patients with single or multiple brain metastases who were treated with radiosurgery with or without adjuvant WBRT, with median survival times of 14.0 to 15.2 months for RPA class 1, 7.0 to 8.2 months for RPA class 2, and 5.3 to 5.5 months for RPA class 3 (see Table 56-1).[33] Similarly, two groups reported median survival times of 13.4 to 25.4 months for RPA class 1, 5.9 to 9.3 months for RPA class 2, and 1.5 to 4.5 months for RPA class 3 patients treated with radiosurgery alone,[34,35] and three surgical series found median survival times ranging from 10.9 to 21.4 months for RPA class 1, 9.0 to 9.9 months for RPA class 2, and 6.0 to 8.9 months for RPA class 3 patients who underwent surgical resection with or without adjuvant WBRT (see Table 56-1).[36–38]

Treatment

The symptoms resulting from brain metastases may be ameliorated with corticosteroids or osmotic therapy for the peritumoral edema or with anticonvulsants for seizure control. Direct antitumor therapies include surgery, radiotherapy (external beam radiotherapy, radiosurgery, and brachytherapy), chemotherapy, and molecular targeted drugs.

Corticosteroids

Corticosteroid therapy is generally instituted in symptomatic patients as soon as brain metastases are diagnosed, to help alleviate symptoms

Table 56-1 Median Survival Time by Radiation Therapy Oncology Group Recursive Partitioning Analysis Class

	RPA Class 1		RPA Class 2		RPA Class 3	
Treatment	**No. of Patients**	**MST (Months)**	**No. of Patients**	**MST (Months)**	**No. of Patients**	**MST (Months)**
WBRT alone[32]	236	7.1	765	4.2	175	2.3
RS alone initially[34]	23	25.4	74	5.9	20	4.2
RS alone initially[35]	15	13.4	65	9.3	21	1.5
RS alone initially[33]	39	14.0	197	8.2	29	5.3
RS + upfront WBRT[33]	64	15.2	222	7.0	9	5.5
Surgery + WBRT[36]	26	14.8	63	9.9	36	6.0
Surgery ± WBRT[37]	26	10.9	69	9.8	—	
Surgery ± WBRT[38]	50	21.4	208	9.0	13	8.9

MST, median survival time; RPA, recursive partitioning analysis; RS, radiosurgery; WBRT, whole-brain radiotherapy.

until the brain metastases and edema improve from specific antitumor treatment. Corticosteroids reduce the permeability of leaky tumor blood vessels and thereby reduce the mass effect and edema caused by brain metastases.[39] The most commonly used steroid is dexamethasone because of its relatively low mineralocorticoid activity, often using a loading dose of 10 mg followed by 4 mg every 6 hours. Lower doses (2 to 4 mg twice daily or 2 to 4 mg three times a day) may be adequate in many situations, and higher doses might rarely be needed. Patients commonly improve within hours after the first dose, attaining maximal benefit after approximately 3 to 7 days. After patients become asymptomatic or reach maximal benefit, the dose should be gradually tapered and either discontinued or maintained at the lowest dose level needed to manage symptoms. If headaches recur or neurologic symptoms worsen during the course of the taper, the dose should be increased as needed, and then the taper should proceed more gradually. Occasional patients develop steroid withdrawal symptoms of depression, fatigue, nausea, or poor appetite, necessitating reinstitution of low-dose dexamethasone and a gradual taper schedule in the low-dose range. Steroids have numerous adverse effects, particularly with long-term use. Common short term side effects include insomnia, increased appetite, fluid retention, mood changes, acne, and exacerbation of diabetes, and some of the serious long-term side effects include significant weight gain, steroid myopathy, immunosuppression, and aseptic necrosis of the femoral heads. Of note, steroid myopathy can cause fairly profound weakness in large proximal muscles, making it difficult for patients to get up and walk; this dysfunction may be mistaken as a sign of progression of CNS metastases and as an indication to continue or increase steroids when it is actually a complication of steroid therapy.

Anticonvulsants

Seizures are very unlikely to occur from infratentorial metastases but may be triggered by supratentorial metastases. About 15% of patients with brain metastases present with seizures and 30% to 40% experience seizures at some point in their disease course.[40] Any patient with brain metastases who experiences a seizure should be started on an anticonvulsant such as phenytoin, carbamazepine, or levetiracetam, but prophylactic anticonvulsants are not generally recommended because prospective and retrospective studies have failed to demonstrate a benefit for prophylactic anticonvulsants in patients with brain metastases.[39–41] Also, anticonvulsants can have adverse side effects or cause serious allergic reactions, such as Stevens-Johnson syndrome. It is important to note that certain anticonvulsants, such as phenytoin, can reduce the efficacy of corticosteroids and can activate the cytochrome P450 enzyme system.[42] This latter property can affect patients who are undergoing chemotherapy by altering the metabolism of some chemotherapeutic agents, thus requiring chemotherapy dose adjustment.

External Beam Radiation Therapy

The most standard treatment for brain metastases consists of WBRT covering the entire intracranial contents with shielding of the eyes (Fig. 56-2). The benefits of WBRT were first described in the 1950s and 1960s. In these early studies, significant symptomatic improvement was noted in about 60% of patients, and the median survival time ranged from about 3 to 6 months with WBRT[25–27] compared with an expected median survival time of 1 to 2 months without treatment.[21–23]

SELECTED RANDOMIZED TRIALS OF WHOLE-BRAIN RADIOTHERAPY ALONE. The RTOG has conducted multiple large phase III randomized trials of WBRT since 1970 (Table 56-2). The first two trials, which compared various WBRT fractionation schemes in over 1800 patients who were treated from 1971 through

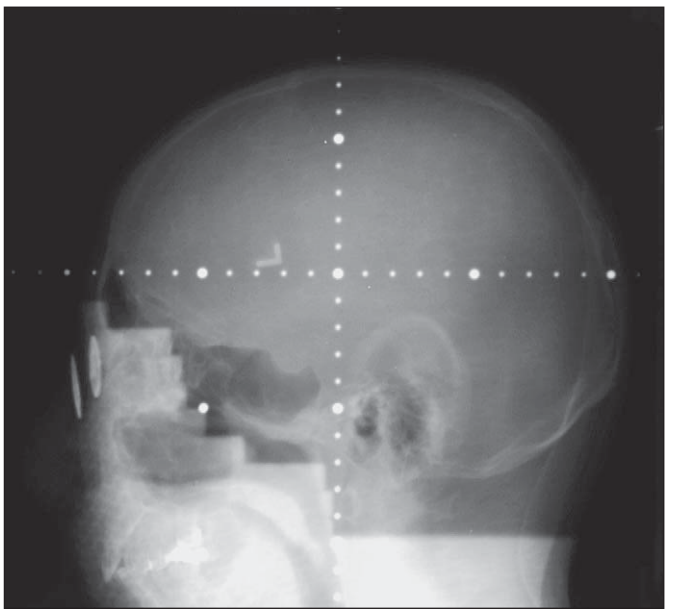


Figure 56-2 • Double-exposed portal image of a typical whole-brain radiotherapy field, showing radiation covering the entire brain with blocking of the eyes and other extracranial structures.

Table 56-2 Selected Randomized Trials of Whole-Brain Radiotherapy Alone for Brain Metastases

Protocol	Years	No. of Patients	Fractionation Scheme	Median Survival Time (Months)
RTOG 6901[28,43]	1971–1973	233	30 Gy/10 fractions/2 weeks	4.8
First study		217	30 Gy/15 fractions/3 weeks	4.1
		233	40 Gy/15 fractions/3 weeks	4.1
		227	40 Gy/20 fractions/4 weeks	3.7
RTOG 7361[28,43]	1973–1976	447	20 Gy/5 fractions/1 week	3.4
Second study		228	30 Gy/10 fractions/2 weeks	3.4
		227	40 Gy/15 fractions/3 weeks	4.1
RTOG 6901[44]	1971–1973	26	10 Gy/1 fractions/1 day	3.4
RTOG 7361[44]	1973–1976	33	12 Gy/2 fractions/2 days	3.0
Ultra-rapid				
RTOG 7606[29]	1976–1979	130	30 Gy/10 fractions/2 weeks	4.1
"Favorable patients"		125	50 Gy/20 fractions/4 weeks	3.9
RTOG 9104[30]	1991–1995	213	30 Gy/10 fractions/2 weeks	4.5
Accelerated hyperfractionation		216	54.4 Gy at 1.6 twice daily	4.5

RTOG, Radiation Therapy Oncology Group.

1976, gathered a wealth of data.[28,43] Complete or partial response of specific neurologic symptoms was observed in 60% to 90% of symptomatic patients; 47% to 52% of patients improved to a higher neurologic function class; the median duration of improvement was 10 to 12 weeks; and 75% to 80% of patients' remaining survival time was spent in an improved or stable neurologic state. The overall median survival times were 18 weeks (4.1 months) in the first study and 15 weeks (3.4 months) in the second study, and brain metastases were reported to be the cause of death in 49% or 31% of the patients, respectively. There were no significant differences in symptomatic response rates, duration of response, or survival time according to the treatment regimen: 40 Gy in 20 fractions, 40 Gy in 15 fractions, 30 Gy in 15 fractions, 30 Gy in 10 fractions, or 20 Gy in 5 fractions.[28,43] With the ultrarapid fractionation schemes that were tested by the RTOG (10 Gy in one fraction or 12 Gy in 2 fractions; see Table 56-1), there was some concern that irradiation might have led to herniation and death within 48 hours of treatment in a small number of cases, and time to neurologic progression was shorter than that with more protracted regimens.[44,45] Both of these findings agreed with conclusions of a Memorial Sloan Kettering Cancer Center evaluation of 15 Gy in 2 fractions over 3 days compared with 30 Gy in 15 fractions.[46] Two later RTOG trials failed to show any advantage of 50 Gy in 20 fractions or 54.4 Gy at 1.6 Gy twice daily over 30 Gy in 10 fractions (see Table 56-1),[29,30] further solidifying 30 Gy in 10 fractions over 2 weeks as the most frequently used WBRT treatment regimen. Other common treatment regimens include 35 to 37.5 Gy at 2.5 Gy per fraction, 40 to 50 Gy at 2.0 Gy per fraction, and 45 to 50.4 Gy at 1.8 Gy per fraction. Shorter regimens may be selected for patients with a shorter life expectancy or when WBRT is delaying chemotherapy that is needed to treat systemic disease, and smaller fraction size may be selected in patients with longer life expectancy on the basis of a suspicion that this might give less risk of late neurotoxicity.

RESPONSE AND LOCAL CONTROL. Neider and colleagues studied CT response of brain metastases to WBRT (30 Gy in 10 fractions).[47] By lesion, the complete response rate was 24%, and the partial response rate was 35%. The overall (complete plus partial) response rates were 81% for small cell carcinoma, 65% for breast cancer, 56% for squamous cell carcinoma, 50% for nonbreast adenocarcinoma, 46% for renal cell carcinoma, and 0% for melanoma. Absence of necrosis and smaller volume were associated with improved response rate; complete response rates were 39% for solid metastases, 15% for those with less than 50% necrosis, and 11% for those with at least 50% necrosis, and 52%, 39%, 17%, 20%, 5%, and 0% for lesion volumes up to 0.5 mL, 0.6 to 1.0 mL, 1.1 to 3.0 mL, 3.1 to 6.0 mL, 6.1 to 10.0 mL, and more than 10 mL, respectively.[47] In another study by the same group, there was a suggestion that a higher response rate was obtained with 40 at 2 Gy per fraction with or without a partial brain boost to 50 or 60 Gy compared with 30 Gy at 3 Gy per fraction.[48] For the WBRT-only arm of a recent RTOG trial of WBRT with or without radiosurgery, the complete response rate was 8%, the partial response rate was 54%, the stable disease rate was 22%, and the progression rate was 17% among 78 patients with imaging follow-up.[49] Data on long-term local control of brain metastases after WBRT alone are limited and highly variable. The 1-year actuarial local control probability by patient ranged from 0% to 14% in the WBRT-only arms of randomized trials reported by Kondziolka and colleagues[50] and Patchell and colleagues[19] but as high as 71% in the WBRT-only arm of the RTOG randomized trial of WBRT with or without radiosurgery.[49]

PARTIAL BRAIN RADIOTHERAPY. Partial brain radiotherapy can be considered for a single metastasis in lieu of WBRT, but it is generally not advisable in that it would complicate or preclude later WBRT if needed (unlike radiosurgery, which delivers much more focal radiation dose). Caution is advised when postoperative radiotherapy to the posterior fossa alone is contemplated because cerebellar metastases appear to be associated with an increased risk of leptomeningeal dissemination after resection.[51,52] On the other hand, partial brain radiotherapy might be useful for treating recurrent brain metastases that are not suitable for resection or radiosurgery.

TOXICITY OF WHOLE-BRAIN RADIOTHERAPY. Acute toxicity of WBRT includes hair loss, fatigue, and modest skin reaction in essentially all patients and mild acute ototoxicity in some patients. The skin reaction resolves by several weeks, and fatigue improves gradually over one or several months. Hair generally regrows by 6 months following WBRT, but alopecia may be permanent in a central strip on the top and back of the head from the reduced skin

sparing of tangential radiation beams. In the minority of patients who are long-term survivors after WBRT, there is a risk of late hearing loss, retinopathy if the retina was included in the radiation field, and permanent neurocognitive toxicity. DeAngelis and colleagues reported an 11% risk of severe radiation-induced dementia among 1-year survivors after resection of a single brain metastasis followed by postoperative WBRT to 20 to 40 Gy using high-dose daily fractions.[51] A separate report from the same group described 12 patients cured of brain metastases who developed severe radiation-induced dementia with associated ataxia and urinary incontinence.[53] Imaging with CT showed atrophy, ventricular dilatation, and hypodense white matter. The WBRT fractionation schemes included mostly mixtures of 3- or 4-Gy fractions with 5- or 6-Gy fractions, but two of the affected patients had received the standard regimen of 30 Gy in 10 fractions.[53] Nieder and colleagues reported a 42% 2-year actuarial probability of symptomatic mild, moderate, or severe late radiation toxicity in patients who were treated with resection of a single brain metastasis followed by WBRT to 30 Gy in 10 fractions or 40 Gy in 20 fractions, but no details were provided regarding the nature of the toxicity.[54] Among 112 patients on the WBRT-only arm of a recent RTOG randomized trial, Andrews and colleagues reported four grade 1, one grade 2, one grade 3, and one grade 4 late central neurologic toxicities; two grade 1, two grade 2, and one grade 3 late ototoxicities; and eleven grade 1 and four grade 2 chronic skin toxicities.[49] This RTOG trial did not include formal neurocognitive testing, but it is becoming more common to incorporate baseline and follow-up neurocognitive testing into prospective trials in patients with brain metastases.

Surgery

Surgery has important roles to play in certain subsets of patients: confirming the diagnosis when needed (as discussed in the section on Diagnosis); relieving mass effect from a large, symptomatic lesion (Fig. 56-3); improving the likelihood of durable local control for a single metastasis; and salvaging a failing metastasis after prior therapy. Surgical resection may also be useful for lesions with considerable peritumoral edema despite steroids or for lesions that are causing refractory seizures, even if the lesion is sufficiently small that radiosurgery would be a therapeutic option.[55] Resection of brain metastases has become safer with advances in neuroimaging and neurosurgery, such as image guidance, preoperative and intraoperative functional mapping, and intraoperative ultrasound and MRI.[56]

RANDOMIZED TRIALS OF WHOLE-BRAIN RADIOTHERAPY WITH OR WITHOUT SURGERY. Three prospective, randomized trials have been performed to evaluate the addition of surgery to WBRT (Table 56-3). In the trial reported by Patchell and colleagues, 48 patients with a single brain metastasis were randomized to biopsy and WBRT versus resection and WBRT to 36 Gy in 12 fractions.[19] Patients who underwent resection had significantly improved local control (80% versus 48% for resection and WBRT versus biopsy and WBRT; $P < 0.02$), duration of functional independence (median: 38 weeks versus 8 weeks, $P < 0.005$), and survival (median: 40 weeks versus 15 weeks, $P < 0.01$). Factors that were associated with longer survival included younger age, no extracranial disease, surgical resection, and a longer interval from primary diagnosis to brain metastasis diagnosis.[19]

A trial that was performed in the Netherlands randomized 63 evaluable patients with a single brain metastasis to surgery plus WBRT versus WBRT alone (40 Gy at 2 Gy twice daily; see Table 56-3).[57] Patients on the surgery arm of the trial had longer functionally independent survival (median: 7.5 months for surgery and WBRT versus 3.5 months for WBRT alone, $P = 0.06$) and longer survival time (median: 10 months versus 6 months, $P = 0.04$). The survival benefit was seen only in patients without active extracranial disease, in whom the median survival time was 12 months for surgery and WBRT versus 7 months for WBRT alone ($P = 0.02$); the median survival time was 5 months for patients with active extracranial disease regardless of the treatment arm. Older age (over 60 versus 60 years or younger) was also confirmed as an important unfavorable prognostic factor ($P = 0.003$; hazard ratio = 2.74).[57]

A third trial failed to show a benefit for surgery in addition to WBRT (30 Gy in 10 fractions over 2 weeks; see Table 56-3).[58] The median survival times were 5.6 months among 41 patients randomized to surgery with WBRT versus 6.3 months among 43 patients randomized to WBRT alone (4 of whom had surgery before WBRT and 6 of whom had surgery after WBRT). There was no difference in duration of functional independence between the two treatment arms. The authors concluded that further trials and/or a meta-analysis was indicated,[58] but overall, these studies and previous nonrandomized experience[59–61] support the use of surgery in addition to WBRT in patients with good performance status, controlled extracranial disease, and a single brain metastasis.

RANDOMIZED TRIAL OF SURGERY WITH OR WITHOUT WHOLE-BRAIN RADIOTHERAPY. Postoperative WBRT may help to prevent recurrence at the resection cavity and to prevent the appearance of new brain metastases by treating any microscopic metastases elsewhere in the brain and any dissemination of tumor cells as a result of the surgery. Following up on multiple retrospective studies that suggest a benefit for postoperative WBRT after resection of a brain metastasis, Patchell and colleagues performed a randomized trial (see Table 56-3).[62] Ninety-five adults were randomized to observation versus postoperative WBRT to 50.4 Gy in 28 fractions after complete resection of a single brain

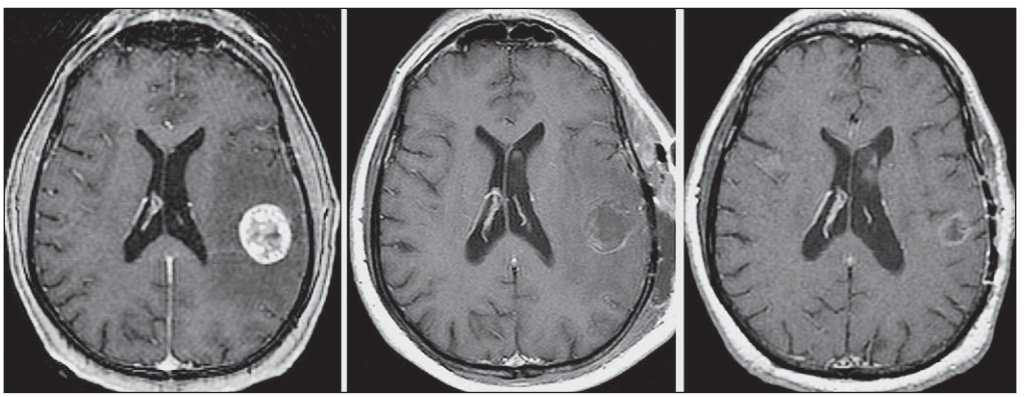


Figure 56-3 • Preoperative (*left*), immediate postoperative (*center*), and 2-month postoperative (*right*) contrast-enhanced T1-weighted magnetic resonance images of a single metastasis treated with surgical resection.

Table 56-3 Randomized Trials of Surgery or Radiosurgery and Whole-Brain Radiotherapy for Brain Metastases

First Author (Years)	Treatment	No. of Patients	Patients with Extracranial Disease (%)	Median Local FFP (Months)	Median Functionally Independent Survival (Months)	Median Survival (Months)
Patchell[19] (1985–1988)	Biopsy + WBRT	23	83	4.8	1.8	3.4
	Surgery + WBRT	25	76	>13.6	8.7	9.2
	(36 Gy/12 fx)			($P < 0.0001$)	($P < 0.005$)	($P < 0.01$)
Noordijk[57] (1985–1990)	WBRT	31	68	—	3.5	6
	Surgery + WBRT	32	69	—	7.5	10
	(40 Gy at 2 Gy BID)			—	($P = 0.06$)	($P = 0.04$)
Mintz[58] (1989–1993)	WBRT	43	84	—	—	6.3
	Surgery + WBRT	41	73	—	—	5.6
	(30 Gy/10 fx)			—	(P = NS)	($P = 0.24$)
Patchell[62] (1989–1997)	Surgery	46	65	6.2	8.0	9.9
	Surgery + WBRT	49	63	>12.0	8.5	11.0
	(50.4 Gy/28 fx)			($P < 0.001$)	($P = 0.61$)	($P = 0.39$)
Kondziolka[50] (1985–1988)	WBRT	14	71	6	—	7.5
	WBRT + RS	13	62	36	—	11.0
	(36 Gy/12 fx)			($P = 0.0005$)	—	($P = 0.22$)
Andrews[49] (1996–2001)	WBRT	167	69	[71% 1-year LC]	—	5.7
	WBRT + RS	164	68	[82% 1-year LC]	—	6.5
	(37.5 Gy/15 fx)			($P = 0.013$)	—	($P = 0.136$)
Aoyama[90] (1999–2003)	RS	67	43	[73% at 1 year]	[27% at 1 year]	8.0
	WBRT + RS	65	37	[89% 1-year LC]	[34% at 1 year]	7.5
	(30 Gy/10 fx)			($P = 0.002$)	($P = 0.53$)	($P = 0.42$)

FFP, freedom from progression; fx, fractions; LC, local control; NS, not significant; RS, radiosurgery; WBRT, whole-brain radiotherapy.

metastasis. The observation arm had a significantly increased risk of local failure (46% for observation versus 10% for WBRT), distant brain failure (37% versus 14%), and any brain failure (70% versus 18%); shorter time to local failure (median: 27 weeks versus more than 52 weeks [6.2 months versus more than 12 months]; $P < 0.001$; hazard ratio: 6.03); and shorter time to any brain failure (median: 26 weeks versus more than 70 weeks [6.0 months versus more than 16.1 months]; $P < 0.001$; hazard ratio: 4.94). Patients who were randomized to observation were more likely to die neurologic deaths (44% versus 14%; $P = 0.003$) but, interestingly, had similar duration of functional independence (median: 35 weeks [8.0 months] for observation versus 37 weeks [8.5 months] for WBRT; $P = 0.61$) and similar survival time (median: 43 weeks versus 48 weeks [9.9 months versus 11.0 months]; $P = 0.39$).[62] Topics that were not addressed in the report included the use or success of salvage therapy and acute and late toxicity of WBRT and salvage therapies.

SURGERY FOR MULTIPLE METASTASES. Surgical resection may also be used successfully to manage selected patients with more than one brain metastasis. Bindal and colleagues reported a median survival time of 14 months among 26 patients with multiple brain metastases who underwent resection of all of their brain lesions in a single operation, identical to the survival time of matched patients who had had resection of a single metastasis.[63] The complication rate was 9% per craniotomy, the 30-day mortality rate was 4%, and only 6% of symptomatic patients worsened, while 83% improved and 11% remained stable.[63] A different group describing results of surgery and WBRT had noted significantly poorer survival among 18 patients with multiple brain metastases compared with 28 patients with a single metastasis, but apparently, only one patient with multiple metastases had undergone gross total resection of all (two) metastases, and this patient survived 46 months.[64] In a recent series, Paek and colleagues reported a median survival time of 8 months after surgery for approximately 103 patients with a newly diagnosed single metastasis versus 11 months after surgery for 46 patients with newly diagnosed multiple brain metastases (only 9 of whom had multiple brain metastases resected). Most patients received postoperative WBRT.[65]

TOXICITY OF SURGERY. The morbidity and mortality associated with surgical resection of brain metastases have decreased over the years as techniques have improved. Lang and colleagues estimated the 30-day mortality rate to be about 4% to 5% after surgery for brain metastasis (essentially identical to the 30-day mortality rate in patients who were managed with WBRT alone).[56] The most common types of postoperative morbidity include wound infection, hemorrhage, meningitis, pneumonia, deep venous thrombosis, and pulmonary embolism, which occur in about 10% to 15% of patients on average.[56,66] Most patients are symptomatic preoperatively; one surgical series reported that 0% to 13% of patients worsened neurologically, 65% to 84% improved, and 11% to 22% remained stable after resection of single or multiple brain metastasis.[63] Paek and colleagues recently reported outcomes in 208 patients who underwent resection of one ($N = 191$) or multiple ($N = 17$) newly diagnosed ($N = 149$) or recurrent ($N = 59$) brain metastases at a single institution using modern neurosurgical techniques.[65] The 30-day mortality rate was 1.9%, with two deaths from hemorrhage in the resection cavity, one from pulmonary embolism secondary to deep venous thrombosis, and one from bowel perforation with sepsis. The median hospital

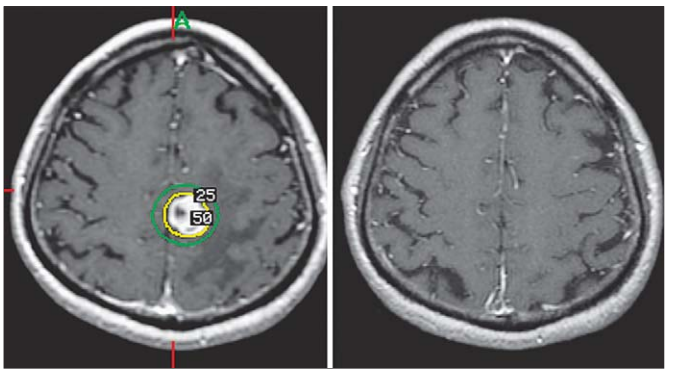


Figure 56-4 • Postcontrast T1-weighted magnetic resonance imaging of a brain metastasis shown on the day of radiosurgery with superimposed 50% and 25% isodose contours (*left*) and follow-up imaging 11 months later, showing near complete response (*right*). A dose of 17.5 Gy was prescribed at the 50% isodose contour.

stay was 3 days after surgery, and KPS improved postoperatively in 33%, remained stable in 61%, and decreased in 6% of patients.[65]

Radiosurgery

Radiosurgery implies the delivery of carefully targeted, very focal radiation to one or more intracranial targets, usually using a specially adapted linear accelerator[67] or a gamma knife.[68] A stereotactic frame may be applied prior to the procedure under local anesthesia to help allow very precise targeting. Multiple beams or arcs provide for very steep falloff of dose outside of the target or targets, minimizing dose to surrounding normal brain tissue, but a thin shell of tissue around the target receives a potentially damaging dose of radiation (Fig. 56-4). Because the risk of radiation injury increases with increasing volume, lower doses are generally prescribed for larger target volumes, and radiosurgery targets tend to be limited to about 2.5 to 3 cm in diameter.

RETROSPECTIVE RESULTS OF RADIOSURGERY. Table 56-4 summarizes results of selected retrospective series of radiosurgery for single or multiple newly diagnosed or recurrent brain metastases treated with or without adjuvant WBRT.[69–83] For median target volumes ranging from 0.9 to 7.5 mL and median prescribed doses ranging from 15.0 to 27.0 Gy in a single fraction, the crude local control rates were 85% to 96% and the 1-year actuarial local control probabilities were 82% to 94% by lesion, with a 0% to 17% risk of symptomatic radiation necrosis (average risk, 4%). In most of the series, the median survival times ranged from 7 to 11 months.

RADIOSURGERY DOSE-RESPONSE RELATIONSHIPS. An RTOG dose escalation trial in patients with recurrent primary or metastatic brain tumors concluded that the maximum tolerated doses of single fraction radiosurgery (without WBRT) were 24 Gy for tumors 2 cm or less in maximum diameter, 18 Gy for tumors 2.1 to 3.0 cm, and 15 Gy for tumors 3.1 to 4.0 cm.[84] A dose-response analysis specifically in newly diagnosed or recurrent brain metastases 2 cm in diameter or smaller found crude local control rates of 91% using a radiosurgery dose less than 20 Gy ($N = 46$), 99% using a dose of 20 Gy ($N = 158$), and 96% using a dose higher than 20 Gy ($N = 24$) when radiosurgery was combined with planned WBRT. Because the risk of complications was 1.9% for radiosurgery doses of 20 Gy or less and 5.9% for doses above 20 Gy, the authors concluded that 20 Gy was the optimal radiosurgery dose for metastases 2 cm or less in diameter. Of note, the crude local control rates were 97% for radiosurgery with WBRT versus 87% for radiosurgery without planned WBRT ($P = 0.0001$).

On the basis of a data set of 518 newly diagnosed or recurrent brain metastases treated with radiosurgery with or without WBRT at

Table 56-4 Results of Radiosurgery with or Without Whole-Brain Radiotherapy for Newly Diagnosed or Recurrent Brain Metastases

First Author	No. of Metastases/ No. of Patients	Mean or Median Dose	Median Target Volume	Local Control by Lesion (%)	Median Survival Time (Months)	Necrosis (%)
Single metastases						
Auchter[69]	122/122	17.0 Gy	2.7 mL	86*/85†	12.9	0
Flickinger[70]	116/116	17.5 Gy	—	85*	11	4
Simonova[71]	237/237	21.5 Gy	7.5 mL	95*	9	2.5
Single or multiple metastases						
Deinsberger[72]	161/110	18.3 Gy	3.1 mL	89*	12.4	2
Flickinger[73]	229/157	16.0 Gy	3.0 mL	89*	10	1
Fukuoka[74]	>215/130	>25 Gy	5.5 mL	≥96*	8	5
Gerosa[75]	1307/804	20.6 Gy	4.8 mL	94†	13.5	—
Goodman[76]	682/258	18.5 Gy	1.7 mL	82†	9.1	—
Joseph[77]	189/120	26.6 Gy	5.3 mL	94*	7.4	17
Kihlstrom[78]	235/160	27.0 Gy	4.5 mL	94*	7	5
Moriarty[79]	643/353	15.0 Gy	2.5 mL	88†	10.5	3–6
Petrovich[80]	1305/458	18 Gy	0.9 mL	87†	9	4.7
Pirzkall[81]	311/236	20 Gy	—	92*	5.5	2
Sansur[82]	411/193	20 Gy	—	82 by patient	7.5	2
Young[83]	669/250	—	—	91*	7	<4

*Crude.
†1-year actuarial.

the University of California, San Francisco,[76] the 1-year actuarial local freedom from progression probabilities were 88%, 75%, and 29% for doses of 18 Gy or more, 15.0 to 17.9 Gy, and less than 15.0 Gy, respectively, and 92%, 83%, 69%, and 37% for maximum target diameters 1.0 cm or less, 1.1 to 2.0 cm, 2.1 to 3.0 cm, and more than 3.0 cm, respectively. A study of 126 lesions in 80 patients who were treated with linac radiosurgery at the University of Chicago found 1-year local control probabilities of 50%, 97%, and 90% for prescribed doses of 10 to 13.99 Gy, 14 to 17.99 Gy, and 18 Gy or more, respectively, and 67%, 94%, and 93% for minimum tumor doses of 12 Gy or less, 12.1 to 18 Gy, and more than 18 Gy, respectively.[85]

RANDOMIZED TRIALS OF WHOLE-BRAIN RADIOTHERAPY WITH OR WITHOUT RADIOSURGERY. The first reported randomized trial of WBRT (30 Gy in 12 fractions) with or without a radiosurgery boost (16 Gy) was performed in patients with a KPS of at least 70 and two to four brain metastases less than or equal to 2.5 cm in diameter, at least 5 mm from the optic chiasm.[50] The study accrued only 27 patients because of early stopping rules based on a significant difference in brain control between the two arms. Compared with WBRT alone, radiosurgery plus WBRT yielded significantly improved time to local failure (median: 36 months versus 6 months; $P = 0.0005$) and time to any brain failure (median: 34 months versus 5 months; $P = 0.002$). However, survival was not significantly different for the two arms (median: 7.5 months for WBRT versus 11 months for WBRT plus radiosurgery; $P = 0.22$; see Table 56-3). Multiple patients who failed WBRT alone underwent salvage radiosurgery.[50]

A recent RTOG trial randomized 331 patients with KPS of at least 70 and one to three newly diagnosed brain metastases to WBRT (37.5 Gy in 15 fractions) with or without a radiosurgery boost within 1 week after WBRT from 1996 through June 2001.[49] Treatment arms were fairly well balanced comparing WBRT alone to WBRT plus radiosurgery, with KPS of 90 to 100 in 63% versus 57%, age less than 65 years in 60% versus 66%, primary disease controlled or absent in 75% versus 77%, extracranial metastases in 69% versus 68%, and a single brain metastasis in 56% versus 56% of patients, respectively. The radiosurgery treatment arm had significantly improved KPS at 6 months ($P = 0.033$), decreased steroid use at 6 months ($P = 0.016$), and improved actuarial local control (with 1-year local control probabilities of 71% for WBRT alone versus 82% for WBRT + radiosurgery; $P = 0.013$). Although survival was not significantly different between the two groups overall (5.7 months for WBRT alone versus. 6.5 months for WBRT + radiosurgery; $P = 0.136$; see Table 56-3), there was a statistically significant difference in survival for patients who had a single metastasis (4.9 months for WBRT alone versus 6.5 months for WBRT + radiosurgery; $P = 0.039$).[49]

RADIOSURGERY WITHOUT WHOLE-BRAIN RADIOTHERAPY FOR NEWLY DIAGNOSED BRAIN METASTASES. Because of concern about potential late toxicity of WBRT, multiple groups have tried managing patients using radiosurgery alone initially, followed by later salvage surgery, radiosurgery, WBRT, or chemotherapy as needed,[33,35,81,86–89] and one prospective, randomized trial of radiosurgery alone versus radiosurgery plus WBRT has been reported to date (see Table 56-3 and the following section).[90] Retrospective comparisons of radiosurgery alone initially to radiosurgery with upfront WBRT are summarized in Table 56-5. Survival was similar for radiosurgery alone initially versus radiosurgery with upfront WBRT for three of five studies (~5 months versus ~6 months;[81] 11.3 months versus 11.1 months;[86] and 8.2 months versus 8.6 months[33]); in one study, median survival time was thought to be shorter in the WBRT group because of worse prognostic factors in this group,[87] and in the fifth study, there was a trend toward longer survival time in patients who were treated with RS + WBRT versus RS alone.[89] Multivariate analyses adjusting for known prognostic factors confirmed that the omission of upfront WBRT had no influence on survival time.[33,81,86,87] Local control was slightly worse for

Table 56-5 Nonrandomized Comparisons of Radiosurgery Alone Initially to Radiosurgery Plus Upfront Whole-Brain Radiotherapy for Single or Multiple Newly Diagnosed Brain Metastases

First Author (Years)	Treatment	No. of Patients	Single Brain Metastasis (%)	Extracranial Disease (%)	1-Year Local FFP	Median Brain FFP (Months)	Median Survival (Months)
Pirzkall[81] (1984–1997)	RS	158	76	68	89%	—	~5
	RS + WBRT	78	71	67	92%	—	~6
					($P = 0.13$)	—	(P = NS)
Sneed[86] (1991–1997)	RS	62	58	74	71%	8.3 (19.8*)	11.3
	RS + WBRT	43	33	65	79%	15.9 (18.1*)	11.1
					($P = 0.30$)	($P = 0.008$; 0.31*)	($P = 0.80$)
Chidel[87] (1989–1998)	RS	78	74	—	~62%	9.2	10.5
	RS + WBRT	57	60	—	~75%	35.1	6.4
					($P = 0.034$)	($P = 0.027$)	—
Sneed[33] (1989–1998)	RS	268	63	70–71	—	—	8.2
	RS + WBRT	301	58	64–68	—	—	8.6
							($P = 0.93$)
Wang[89] (1990–2000)	RS	130	59	—	—	—	15.4
	RS + WBRT	83	40	—	—	—	20.9
							($P = 0.12$)

FFP, freedom from progression; NS, not significant; RS, radiosurgery; WBRT, whole-brain radiotherapy.
*Median brain FFP and *P* value allowing for successful salvage therapy.

radiosurgery alone initially, with 1-year actuarial local freedom from progression probabilities of 89% versus 92%,[81] 71% versus 79%,[86] and approximately 62% versus 75%.[87] Because of a much greater risk of developing new brain metastases when upfront WBRT was omitted, brain freedom from progression was significantly shorter for radiosurgery alone initially (median: 8.3 months versus 15.9 months[86] and 9.2 months versus 35.1 months).[87] In one series, the median brain freedom from progression allowing for salvage therapy was 19.8 months for radiosurgery alone initially versus 18.1 months for radiosurgery with upfront WBRT, and only 26% of radiosurgery-alone patients ultimately received WBRT.[86] Among 101 patients with one to three brain metastases who were treated with radiosurgery alone, Lutterbach and colleagues reported 1-year local brain, distant brain, and overall brain freedom from progression rates of 91%, 53%, and 51%, respectively; parameters that were associated with longer overall brain freedom from progression included single brain metastasis and an interval greater than 2 years from primary tumor diagnosis and diagnosis of brain metastases.[35]

RANDOMIZED TRIAL OF RADIOSURGERY WITH OR WITHOUT WHOLE-BRAIN RADIOTHERAPY. Aoyama and colleagues recently reported the first prospective, randomized trial comparing radiosurgery alone ($N = 67$) to WBRT plus radiosurgery ($N = 65$).[90] Patients with KPS of at least 70 and one to four brain metastases less than 3 cm in diameter were accrued at 11 institutions from 1999 through 2003. The WBRT dose was 30 Gy in 10 fractions, and the radiosurgery-alone doses were 22 to 25 Gy for lesions up to 2 cm and 18 to 20 Gy for lesions over 2 cm, with a 30% dose reduction when radiosurgery was combined with WBRT. Age, KPS, and extracranial disease activity were not significantly different between the two groups. Endpoints were measured from the date of randomization. The median survival times were similar for the two groups (8.0 months for radiosurgery alone versus 7.5 months for WBRT + radiosurgery; $P = 0.42$). Intracranial control was significantly lower in the radiosurgery-alone arm, with 1-year local control probabilities of 73% versus 89% ($P = 0.002$), 1-year freedom from new brain metastasis probabilities of 36% versus 58% ($P = 0.003$), and 1-year overall brain freedom from progression probabilities of 24% versus 53% ($P < 0.001$) for radiosurgery alone versus WBRT + radiosurgery, respectively. The majority of new brain metastases were asymptomatic. Salvage therapy for brain metastases was given in 29 patients on the radiosurgery-alone arm versus 10 patients on the WBRT + radiosurgery arm. There was no significant difference in functional independent survival (27% versus 34% at 1 year; $P = 0.53$) or neurologic preservation (70% versus 72% at 1 year; $P = 0.99$) for radiosurgery alone versus WBRT + radiosurgery, respectively. Deterioration of neurologic function occurred in 21 radiosurgery-alone patients and in 22 WBRT + radiosurgery patients; the deterioration was attributed to new or original brain metastases in 18 radiosurgery-alone patients versus 13 WBRT + radiosurgery patients. Leukoencephalopathy occurred in 2 radiosurgery-alone patients versus 7 WBRT + radiosurgery patients, and it was symptomatic in 3 of the 9 patients. The authors concluded that radiosurgery alone "could be a treatment option, provided that frequent monitoring of brain tumor status is conducted."[90]

RADIOSURGERY COMPARED WITH SURGERY. Radiosurgery has potential advantages over surgery in that it is less invasive and can more easily address inaccessible or multiple lesions. In addition, the border zone between the metastasis and normal brain tissue may receive sufficient radiation dose to decrease the risk of local recurrence. The two major disadvantages of radiosurgery are that it is generally applicable only to lesions less than about 2.5 to 3.0 cm in diameter and that it results in slow tumor shrinkage over weeks or months rather than relieving mass effect immediately.

In the absence of data to date from prospective, randomized trials, several authors have compared results cited in the literature for surgical patients with their own results for similar subsets of radiosurgery patients. Auchter and colleagues[69] reported a four-institution experience of radiosurgery and WBRT in 122 adults who met selection criteria similar to those used in randomized trials of WBRT with or without surgical resection: KPS of at least 70 and newly diagnosed, surgically resectable single brain metastases with "nonsensitive" histology (excluding lymphoma, leukemia, multiple myeloma, small cell lung cancer, and germ cell tumors) and no urgent indication for resection. Local control was achieved in 86% of lesions with a 1-year actuarial local control probability of 85%, a median duration of functional independence of 10.1 months, and median survival time of 12.9 months (see Table 56-4), comparable to the results of the surgery + WBRT arms of the randomized trials reported by Patchell and colleagues[19] and Noordijk and colleagues[57] (see Table 56-3).

Three other retrospective comparisons of radiosurgery and surgery are summarized in Table 56-6, with somewhat differing results.[66,91,92] Bindal and colleagues reported 61% versus 87% crude local control rates for radiosurgery (with or without WBRT) versus surgery (with or without WBRT) and median survival times of 7.5 months versus 16.4 months, respectively.[91]

In another retrospective study, Muacevic and colleagues compared outcomes for patients with single metastases less than or equal to 3.5 cm in diameter who were treated with radiosurgery alone (56 patients) or surgery with WBRT (52 patients). One-year local freedom from progression probabilities were 83% for radiosurgery versus 75% for surgery with WBRT ($P = 0.49$); new brain metastases developed in 11 (20%) of the radiosurgery patients versus 6 (12%) of the surgery-plus-whole-brain-radiotherapy patients, but salvage radiosurgery was successful in all 6 radiosurgery patients who were offered salvage therapy. Median survival times were 8.0 months after radiosurgery versus 15.6 months after surgery with WBRT. Death rates from neurologic causes and complication rates were similar for the two treatment approaches, and steroid requirements tended to be less among the radiosurgery patients.[66]

A third retrospective study compared patients with single metastases who were candidates for either surgery or radiosurgery. Most patients received adjuvant WBRT in conjunction with radiosurgery (23 patients) or surgery (74 patients). Pretreatment performance status was worse in the radiosurgery group. Crude local control rates were 100% versus 85% ($P = 0.02$), and 1-year survival probabilities were 56% versus 62% for radiosurgery versus surgery, respectively (univariate $P = 0.15$; multivariate $P = 0.62$ with adjustment for age, performance status, and systemic disease status). Short-term and long-term complications occurred in 0% versus 13.5% and 17.4% versus 17.6% of radiosurgery and surgery patients, respectively.[92]

Because of the difficulties in overcoming selection bias and other confounding factors in retrospective studies, a prospective, randomized trial is underway to better compare radiosurgery versus surgery for single brain metastases.

TOXICITY OF RADIOSURGERY. Acute complications of radiosurgery occur in about 10% of patients, including seizures, headaches, exacerbation of pre-existing neurologic deficits, nausea, and hemorrhage.[66,86,93] Early delayed and late complications may include transient perifocal edema responding to a short course of steroids in 7% to 18% of patients[66,81,93] or symptomatic radiation necrosis in an average of 4% of patients (see Table 56-4), causing headaches, seizures, or neurologic deficits. Symptoms usually respond to steroids, but surgery might be needed if a patient requires a prolonged course of steroids, tolerates steroids poorly, or remains symptomatic on steroids or if there is uncertainty as to whether a lesion represents progressive tumor versus radiation necrosis.

Brachytherapy

Brachytherapy, the insertion of radioactive sources directly inside a tumor or tumor bed, allows delivery of a high dose of radiation to the target volume with a steep falloff of dose outside of the intended

Table 56-6 Nonrandomized Comparisons of Radiosurgery with and Without Whole-Brain Radiotherapy to Surgery with and Without Whole-Brain Radiotherapy for Single Newly Diagnosed Brain Metastases

First Author (Years)	Treatment	No. of Patients	Single Brain Metastasis (%)	Extracranial Disease (%)	Local FFP (%)	Median Survival (Months)
Bindal[91] (1991–1994)	RS ± WBRT	31	77	42	61*	7.5
	Surgery ± WBRT	62	74	52	87*	16.4
					($P = 0.0001$)	($P = 0.0018$)
Muacevic[66] (1990–1997)	RS alone	56	100	—	83%†	8.0
	Surgery + WBRT	52	100	—	75%†	15.6
					($P = 0.49$)	($P = 0.19$)
O'Neill[92] (1991–1999)	RS ± WBRT	23	100	74	100%	56% 1-yr
	Surgery ± WBRT	74	100	55	85%	62% 1-yr
					($P = 0.020$)	($P = 0.15$)

FFP, freedom from progression; RS, radiosurgery; WBRT, whole-brain radiotherapy.
*Crude.
†1-year actuarial.

region owing to the fact that dose intensity decreases with the square of the distance from point sources and also decreases because of attenuation in tissue. Temporary brachytherapy has been applied to brain metastases by using high-activity sources, often within afterloading catheters inserted under stereotactic guidance into gross tumor or a resection cavity or using a balloon within a resection cavity inflated with radioactive liquid. Permanent brachytherapy is generally accomplished by lining a tumor bed with low-activity radiation sources intraoperatively after gross total resection of a metastasis. Results of brachytherapy for brain metastases are summarized in Table 56-7.[94–99] In patients who were treated for recurrent brain metastases, crude local freedom from progression rates ranged from 60% to 95%, and median survival times ranged from 6 to 13.9 months. Among patients who were treated for newly diagnosed brain metastases, local freedom from progression rates ranged from 80% to 95% and median survival times ranged from 9.2 to 17 months (except for an outlier median survival time of 68.2 months in 5 patients). The incidence of symptomatic radiation necrosis ranged from 0% to 30%, with an average of about 9%.

Chemotherapy

Chemotherapy has generally been considered to be relatively ineffective for brain metastases, presumably because the blood-brain barrier prevents adequate access of chemotherapy to these tumors. However, some chemotherapeutic agents partially or even readily cross the blood-brain barrier, and the fact that brain metastases enhance with contrast on CT or MRI is proof that the blood-brain barrier is broken down within metastases. The chemosensitivity of the primary tumor is another critical factor in determining the potential efficacy of chemotherapy for brain metastases.[100] The responsiveness of brain

Table 56-7 Results of Brachytherapy for Newly Diagnosed or Recurrent Brain Metastases

First Author (Years)	Technique/ Isotope	No. and Type of Patients	Adjuvant WBRT Given?	Crude Local FFP (%)	Median Survival (Months)	Necrosis (%)
Bernstein[94] (?–1994)	Temporary I-125	10 recurrent	No	60	10.5	30
Bogart[95] (1991–1996)	Permanent I-125	15 new	No	80	14	0
McDermott[96] (1979–1994)	Temporary	5 new	Yes (4/5)	—	68.2	10
	I-125	25 recurrent	No	—	13.9	
Ostertag[97] (1982–1992)	Temporary	38 new	Yes	89	17	0
	I-125	34 new	No	91	15	
		21 recurrent	No	95	6	
Rogers[98] (2001–2003)	GliaSite	54 new	No	82–87	9.2	17
Schulder[99] (1987–?)	Permanent	1 new	No	82	9	15
	I-125	12 recurrent	No			
Huang, K. (1997–2001)*	Permanent	19 new	No	95	12.0	16
	I-125	21 recurrent	No	90	7.3	19

FFP, freedom from progression; I-125, iodine-125-labeled; WBRT, whole-brain radiotherapy.
*Unpublished data from the University of California San Francisco.

metastases to chemotherapy is similar to that of the primary tumor and extracranial metastases. Primary small cell lung carcinoma (SCLC), lymphoma, germ cell tumors, and breast cancer are relatively chemosensitive[101] while non-small-cell lung carcinoma (NSCLC) and melanoma are less chemosensitive.

TRIALS ASSESSING CHEMOTHERAPY FOR BRAIN METASTASES FROM A VARIETY OF PRIMARY SITES. Chemotherapy with cisplatin at 100 mg/m^2 on day 1 and etoposide at 100 mg/m^2 on days 4, 6, and 8 every 3 weeks was used as the primary treatment in a phase II study of 22 breast cancer patients with brain metastases, resulting in a 23% complete response rate and a 32% partial response rate.[102] This regimen was then used as first-line therapy in a prospective study conducted from 1986 to 1993 by a nine-institution group; 116 patients with recently diagnosed, previously untreated brain metastases from breast cancer, NSCLC, or melanoma were enrolled, and 107 were evaluable.[103] None of the melanoma patients achieved an objective response, but among the breast and lung cancer patients, the complete response rates were 13% and 7%, respectively, and the partial response rates 25% and 23%, respectively. The median duration of response was 7 to 8 months; the median overall time to progression was 3.9 months for breast and lung cancer patients; and the median survival times were 7.1 months for breast cancer patients, 7.4 months for lung cancer patients, and 3.9 months for melanoma patients.[103] Data were not collected on further therapy given after chemotherapy. Another group examined a similar two-drug regimen using intra-arterial carboplatin plus intravenous etoposide in 27 patients with brain metastases from a variety of primary tumors and were able to achieve a 54% response rate (25% partial response, 25% complete response, and 4% "minor" response).[104]

There has also been interest in temozolomide (TMZ), an oral alkalating agent that crosses the blood-brain barrier. Several studies have assessed the efficacy of TMZ in patients with brain metastases. At Memorial Sloan Kettering Cancer Center, 41 patients with recurrent or progressive brain metastases were treated with TMZ at 150 to 200 mg/m^2 daily for 5 days, repeated monthly. The partial response rate was 5%, 37% of patients had stable disease, and the median survival time was 6.6 months.[105] Another group used a similar regimen in 27 heavily pretreated patients with brain metastases. Of the 24 evaluable patients, the authors reported only one partial response and four cases of disease stabilization, with an overall median survival time of 4.5 months.[106] TMZ has also been used concurrently with other agents. Christodoulou and colleagues administered TMZ at 150 to 200 mg/m^2 daily for 5 days combined with cisplatin at 75 mg/m^2 on day 1 every 28 days in 32 patients with brain metastases. The overall median survival time was 5.5 months. Although nine patients had a partial response (six with breast cancer, two with melanoma, and one with NSCLC), only one patient (with NSCLC) had a complete response, and five patients had disease stabilization.[107] Concurrent TMZ and liposomal doxorubicin has also been investigated; one group reported three complete responses and four partial responses in a cohort of 19 patients given this regimen.[108]

Various studies have examined the use of TMZ in conjunction with radiation therapy. In one phase II randomized trial, 48 evaluable patients were randomized to either WBRT alone or WBRT + TMZ. There were seven complete responses and seven partial responses for the WBRT alone group versus nine complete responses and 14 partial responses in the combined modality group, with median survival times of 7.0 months for WBRT versus 8.6 months for WBRT + TMZ.[109] A later phase II trial randomized 82 patients to receive either WBRT alone ($N = 41$) or WBRT with concurrent TMZ ($N = 41$) and found no significant differences in response rates or survival. The authors did, however, report a significant difference in progression-free survival at 90 days (54% for WBRT alone versus 72% for WBRT and TMZ). They noted that their patients had more aggressive disease and were more heavily pretreated than those in the aforementioned study by Antonadou and colleagues.[110] TMZ is also discussed in the following sections in the context of brain metastases from individual primary sites.

CHEMOTHERAPY FOR BRAIN METASTASES FROM PRIMARY NON-SMALL-CELL LUNG CARCINOMA. Several trials have assessed the response of brain metastases from primary NSCLC after treatment with various systemic agents. Combined carboplatin and etoposide was used in a study of 30 patients with brain metastases from primary lung cancer (18 NSCLC, 12 SCLC); three patients had complete responses (all SCLC), while seven had partial responses (four SCLC, three NSCLC).[111] Concurrent cisplatin and teniposide yielded three complete responses and five partial responses among 23 patients with brain metastases from primary NSCLC.[112] Other regimens that have been studied in patients with brain metastases from NSCLC include vinorelbine, gemcitabine, and carboplatin (with 15% complete response and 30% partial response in 20 patients)[113] and paclitaxel and cisplatin combined with either vinorelbine or gemcitabine (resulting in a 38% objective response rate among 25 patients).[114] Fujita and colleagues used an alternative three-agent regimen of cisplatin, ifosfamide, and irinotecan with rhG-CSF support in 30 patients and were able to achieve a 50% partial response rate, although no patient had a complete response.[115] Two other groups have studied the efficacy of TMZ as a single agent in this context, one group reporting no objective treatment response in 12 patients[116] and another group achieving two complete responses and one partial response among 30 patients.[117]

The use of concomitant systemic chemotherapy and WBRT for brain metastases from NSCLC has also been studied by several groups. In a large phase III trial of 176 patients with brain metastases from NSCLC, Robinet and colleagues examined the use of cisplatin and vinorelbine in conjunction with either early or delayed WBRT. Neither cohort demonstrated significantly different response rates, survival, nor treatment-related toxicities.[118] One recent phase III trial examined outcomes in 42 patients with brain metastases from NSCLC treated either with WBRT alone or with concurrent carboplatin. Neither objective response rates (10% [WBRT alone] versus 29% [WBRT + carboplatin]) nor survival (4.4 months [WBRT alone] versus 3.7 months [WBRT + carboplatin]) were significantly different, and the trial closed early because of poor accrual.[119] The efficacy of TMZ and cisplatin followed by WBRT was studied in 50 patients with brain metastases from primary NSCLC in a recent phase II study; only 2% of patients achieved a complete response, while 10% had partial responses for their cerebral lesions.[120]

CHEMOTHERAPY FOR BRAIN METASTASES FROM SMALL CELL LUNG CARCINOMA. Given the relative chemosensitivity of SCLC, brain metastases from this primary tumor type could theoretically be expected to respond to systemic chemotherapy. Twelves and colleagues examined this concept in an early study of 19 patients with symptomatic brain metastases from SCLC initially treated with cyclophosphamide, vincristine, and etoposide without upfront WBRT. On imaging follow-up, eight patients had a partial response, and one had a complete response.[121] Korfel and colleagues examined the efficacy of topotecan in a phase II study of 30 pretreated, relapsed patients with symptomatic brain metastases from SCLC. Of the 30 patients, 10 achieved an objective response (three complete responses and seven partial responses).[122] In another small study, carboplatin's efficacy as a second-line agent was investigated in 20 patients with recurrent or progressive brain metastases from primary SCLC. Nineteen of the 20 patients were evaluable, with two patients exhibiting a complete response and six showing a partial response.[123]

The use of teniposide, an agent that is known to be active against SCLC, was examined in a phase II study of 80 patients with brain metastases from primary SCLC; 33% of patients had an objective response to chemotherapy (6 had a complete response, and 20 had a

partial response).[124] In a large phase III study also examining the use of teniposide, Postmus and colleagues randomized 120 patients with brain metastases from primary SCLC to receive either teniposide alone ($N = 60$) or concurrently with WBRT ($N = 60$). The teniposide + WBRT cohort had a significantly better response rate (18 complete responses, 16 partial responses) compared to the teniposide-alone arm (5 complete responses, 8 partial responses), although median survival times were not different (3.5 months [WBRT + teniposide] versus 3.2 months [teniposide alone]).[125]

CHEMOTHERAPY FOR BRAIN METASTASES FROM MELANOMA. As was noted earlier, melanoma is relatively insensitive to systemic chemotherapy. The efficacy of various agents in treating patients with brain metastases from primary melanoma have been studied, largely without success. The study by Franciosi and colleagues, as discussed previously, reported no treatment response in melanoma brain metastases treated with cisplatin and etoposide.[103] One group reported only a 12% response rate (with two complete responses and two partial responses) and a median survival time of 4.5 months among 34 melanoma patients with brain metastases treated with sequential dacarbazine and fotemustine.[126] Another group examined fotemustine as a single agent in a subset of patients with brain metastases from primary melanoma within a larger study. Of the 36 patients who had cerebral metastases from primary melanoma, none had a complete response, while 9 patients had a partial response.[127] Mornex and colleagues studied two groups of patients with brain metastases from melanoma; one group was treated with fotemustine alone ($N = 39$), and the other was treated with fotemustine and WBRT ($N = 37$). The authors reported five partial responses—two in the fotemustine-alone group and three in the combined-therapy arm—with no significant differences in median survival time (2.7 months versus 3.4 months, respectively).[128]

TMZ has also been studied in patients with metastatic brain lesions from primary melanoma. One multicenter phase II study examined TMZ alone in 151 patients, none of whom had received any prior radiation therapy. Thirty-four patients, however, had received prior systemic chemotherapy. In the 117 chemotherapy-naive patients, one patient had a complete response and seven had a partial response. In the 34 previously treated patients, there were no complete responses, and only one patient had a partial response. For the entire patient cohort, median survival was only 3.2 months.[129] TMZ was used concurrently with carboplatin in 11 patients with brain metastases from melanoma in a small phase I study; none of these patients achieved an objective response.[130] Another study sought to assess TMZ with concurrent WBRT in 31 patients with no prior radiation therapy. Only one patient had a complete response, and two had partial responses. The median survival time was 6 months.[131]

CHEMOTHERAPY FOR BRAIN METASTASES FROM BREAST CANCER. Aside from the small cohorts of breast cancer patients within the broader studies discussed previously,[102–104,106,107] other groups have focused specifically on patients with brain metastases from breast cancer. Rosner and colleagues examined the efficacy of several multiagent regimens in a group of 100 patients with brain metastases from primary breast cancer. The overall objective response rate was 50% (10 complete responses and 40 partial responses) with the authors reporting a median survival time of 39.5 months, 10.5 months, and 1.5 months for the complete responders, partial responders, and nonresponders, respectively.[132] Another group examined three-agent regimens of either cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) (used in 20 patients) or cyclophosphamide, doxorubicin, and 5-fluorouracil (CAF) (used in two patients). Two patients (one using the CMF regimen and the other using the CAF regimen) had complete responses, while 10 patients had partial responses (nine using the CMF regimen and one using the CAF regimen).[133]

Follow-up and Salvage Therapy

In patients who are doing reasonably well from the standpoint of their systemic disease, we recommend follow-up MRI every 3 months after treatment for brain metastases to detect new, progressive, or recurrent brain metastases that might need to be addressed with salvage therapy. Of note, a contrast-enhancing lesion that is seen after high-dose external beam radiation, radiosurgery, or brachytherapy could represent radiation necrosis rather than recurrent tumor, and additional analyses might be needed before considering retreatment.[134] The same therapeutic options that are available for newly diagnosed brain metastases may be considered for new, progressive, or recurrent metastases, although the type of previous therapy that was given may influence therapeutic options at recurrence. In general, retreatment options include WBRT, radiosurgery (especially for lesions less than about 3 cm in diameter), surgery (especially for a single large or symptomatic progressive lesion), perhaps with permanent brachytherapy to help prevent local recurrence, and chemotherapy. If repeat WBRT is given, lower doses and smaller fraction sizes are generally used, such as 20 to 25 Gy in 10 fractions or 30 Gy at 1.0 Gy twice daily. Results are similar to those reported for a first course of WBRT, with symptomatic improvement in 42% to 75% of patients and median or mean survival time of 3.2 to 5 months after reirradiation.[135–137]

NEOPLASTIC MENINGITIS

Dissemination of cancer cells into the leptomeningeal space is an extremely serious complication that affects approximately 5% of patients with cancer. With incremental improvements in outcomes in systemic cancer, the incidence of metastatic disease to the leptomeninges appears to be on the rise. Neoplastic meningitis presents significant diagnostic and therapeutic challenges; early diagnosis can be elusive, and effective control for leptomeningeal carcinoma is usually difficult to achieve. With current therapies, the median survival time is 3 to 6 months.

Epidemiology

Virtually any type of cancer can disseminate into the leptomeningeal space. Acute leukemias and intermediate- or high-grade lymphomas are common causes of neoplastic meningitis. Among solid tumors, melanoma and small cell carcinoma exhibit the strongest propensity for leptomeningeal dissemination; up to 25% of patients with metastatic disease from these diagnoses develop this complication. Ultimately, between 2% and 5% of breast cancer patients develop carcinomatous meningitis. Leptomeningeal dissemination has also been documented in less common neoplasms, such as sarcomas, squamous cell carcinomas, and germ cell tumors. Primary tumors of the CNS such as medulloblastoma or ependymoma often seed the leptomeningeal space as well.[138–142]

Pathophysiology

The biologic basis for dissemination and multifocal seeding of the leptomeninges by malignant cells is not well understood. Several distinct pathways have been proposed: (1) most obviously as a consequence of drop metastases that may occur during resection of metastatic foci within the brain, especially after resection of posterior fossa tumors; (2) by direct extension from the cerebrum; (3) by infiltration through arachnoid vessels or the choroid plexus following hematogenous dissemination of the tumor; (4) by direct extension along peripheral nerves to the subarachnoid space or perivenous spread from the bone marrow within the skull; (5) by extension along perineural or perivascular lymphatics; and (6) from subependymal or choroid plexus metastases with subsequent escape into the CSF.[143] Spread of tumor cells along the meningeal surface is facilitated by bulk CSF flow. In turn, meningeal deposits may also invade

parenchyma as well as cranial or spinal nerve roots. The most frequently affected regions of the CNS are the basilar cisterns, the posterior fossa, and the cauda equina, where gravity promotes deposition of circulating cells.

Clinical Presentation

Leptomeningeal dissemination of cancer elicits several distinct neurologic presentations. (1) Local tumor infiltration in the brain or spinal cord may cause headache; alterations in mental status; cranial nerve deficits causing diplopia, hearing loss, decreased taste, problems with swallowing, and hoarseness; and incontinence, lower motor neuron weakness, and back or radicular pain. (2) Metabolic dysfunction caused by disturbances in regional blood flow in the affected nervous tissue may cause seizures, isolated neurologic deficits, including strokelike symptoms, and even generalized encephalopathy. (3) Obstruction of normal CSF flow pathways by focal tumor deposits may cause increased intracranial pressure and hydrocephalus.[138–142,144]

Diagnosis

CSF Evaluation

A high index of suspicion is required to make an early diagnosis of neoplastic meningitis; this ultimately requires a detailed examination of CSF. Routine measurements include opening pressure, cell count, differential, protein, glucose and direct cytologic evaluation of the CSF.[138] Patients with carcinomatous meningitis typically have elevated CSF opening pressure, increased CSF protein, and decreased CSF glucose.[145] While the CSF is abnormal in terms of protein or glucose concentration in most patients with neoplastic meningitis, cytologic evaluation of the CSF, the gold standard, is an insensitive test, especially initially; 40% to 50% of patients with neoplastic meningitis have negative CSF cytology on initial lumbar puncture.[138] While repeat CSF cytologic evaluations over time will increase diagnostic sensitivity, the eventual conversion to positive cytology usually occurs in pace with neurologic deterioration secondary to overt tumor progression. Because of the importance of early diagnosis and intervention, there has been significant effort to identify surrogate biomarkers for CNS and leptomeningeal metastases. For example, in the early 1980s, Posner's group demonstrated that the tumor antigen carcinoembryonic antigen as well as the enzymatic activity of β-glucuronidase could be detected in the CSF of patients with brain and leptomeningeal metastases.[146] The presence of these markers was shown to precede clinical detection of neoplastic meningitis and to rise and fall in parallel with the clinical course. Several other biomarkers have been examined in patients with carcinomatous meningitis from a variety of primary tumors, including lactate dehydrogenase, β-human chorionic gonadotropin, alkaline phosphatase, vascular endothelial growth factor, myelin basic protein, creatinine kinase, and others. The utility of these biomarkers is still under investigation.[145] The use of other diagnostic tools such as polymerase chain reactions, fluorescence in situ hybridization, immunohistochemical examinations of the CSF, and cytogenetic analysis may also enhance detection.[147]

Radiologic Features

The most frequent radiographic presentation is hydrocephalus without an identifiable mass lesion. Leptomeningeal contrast enhancement is suggestive of neoplastic meningitis (Fig. 56-5) but may also be seen after lumbar puncture and with infection, inflammatory disease, trauma, subdural hematoma, or changes occurring post craniotomy.[138] The enhancement pattern may be focal (including tumor nodules) or diffuse.[147] While gadolinium-enhanced MRI is more sensitive than CT in identifying leptomeningeal enhancement, only approximately 50% of patients with neoplastic meningitis and spinal symptoms have abnormal imaging studies.[138]

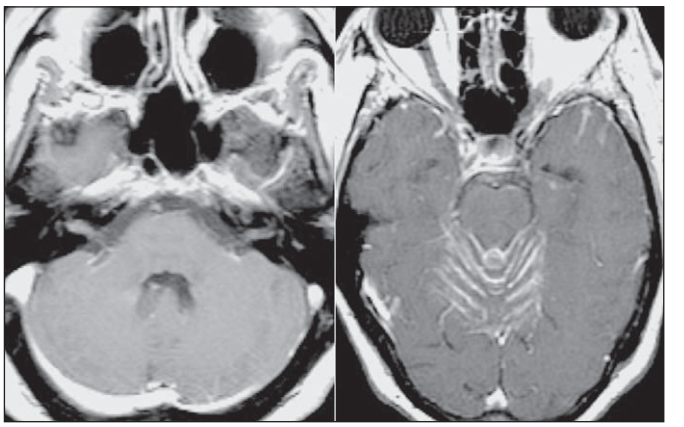


Figure 56-5 • Leptomeningeal enhancement on postcontrast T1-weighted magnetic resonance imaging from carcinomatous meningitis. Note the enhancement of the acoustic nerves (*left*) and cerebellar folia (*right*).

Treatment

Current therapeutic goals for most patients with neoplastic meningitis are to prevent further neurologic deterioration, to cytoreduce leptomeningeal tumor burden, and to prolong survival. Typically, untreated carcinomatous meningitis is associated with an advanced stage of systemic disease, often with concomitant parenchymal brain metastases and with anticipated survival time of 4 to 6 weeks. Because of the inefficient regenerative capacity of the CNS, early aggressive intervention is critical to preserve neurologic function. Therapeutic intervention relies on traditional approaches with radiation and/or chemotherapy with the goal of treating the entire neuroaxis.

Radiation Therapy

Radiation therapy is the most effective means of palliation with the focus on symptomatic sites and regions where imaging studies have demonstrated bulk disease. There is substantial acute toxicity of craniospinal axis irradiation, with nausea, vomiting, marked fatigue, and myelosuppression. There is also a long-duration negative impact on bone marrow function, compromising the safe administration of subsequent myelosuppressive chemotherapy. One strategy is to selectively apply external beam irradiation to symptomatic sites of disease and to rely on intrathecal chemotherapy to suppress the remainder of the disease in the neuroaxis. For example, in patients who present with cranial nerve deficits, one approach is to treat only the base of the skull with radiation. In patients who present with cauda equina syndrome, external beam irradiation may be directed to the lumbosacral spine. Patients who present with seizure or hydrocephalus caused by extensive cranial leptomeningeal disease may best be palliated with whole-brain irradiation.[139–142]

Intrathecal Chemotherapy

The most reliable means of administering intrathecal chemotherapy is to use an implanted subcutaneous reservoir and ventricular catheter (Ommaya device). While subarachnoid injections of chemotherapy result in high local CSF concentrations, studies of administration by lumbar administration suggest that 10% to 15% of lumbar punctures fail to completely deliver all of the drug to the subarachnoid space.[142] In addition, retrospective analysis suggests that intraventricular administration may result in prolonged remission in patients with leptomeningeal leukemia compared with administration by lumbar puncture.[148] Chemotherapeutic agents administered into the ventricle are carried through the neuroaxis by bulk CSF flow. CSF flow abnormalities are common in patients with leptomeningeal metastases, who frequently present with hydrocephalus and increased intracranial pressure as a result of disease that

impedes CSF flow. Radionuclide ventriculography in patients with neoplastic meningitis has demonstrated that as many as 70% have ventricular outlet obstruction, abnormal flow in the spinal canal, or impaired flow over the CSF convexities.[149] These CSF flow abnormalities may be reversed with local irradiation. Because of the potential risk of irreversible neurotoxicity from high sustained concentrations of intrathecal chemotherapy, a CSF flow study is recommended for every patient beginning intrathecal chemotherapy via a ventricular catheter.[139,140]

Methotrexate and cytarabine are the most widely used agents for intrathecal chemotherapy. Intraventricular injection of methotrexate results in therapeutic concentrations (more than 1 μmol) that persist for up to 48 hours; serum levels peak at approximately 0.1 μmol and fall more slowly. Treatment of active neoplastic meningitis typically consists of twice weekly intrathecal therapy until CSF clears followed by weekly and then monthly maintenance therapy unless there is disease progression. The combination of twice weekly methotrexate plus radiation results in an approximate 50% rate of disease stability or clinical improvement. Response should be assessed both in the ventricle and in the lumbar sac, where cytology is more likely to be positive. Intrathecal methotrexate can cause myelosuppression as well as mucositis, toxicities that can be attenuated by leucovorin. Leucovorin does not efficiently cross the blood-brain barrier in amounts that are sufficient to interfere with intra-CNS effects of methotrexate.

Cytosine arabinoside is also commonly used but may have less efficacy in the treatment of neoplastic meningitis. Cytosine arabinoside is inactivated by deamination by the enzyme cytidine deaminase. Low CNS levels of this enzyme result in relatively slow deamination of cytosine arabinoside within the brain and CSF, resulting in an extended half-life in the CNS compartment.[142] Thiotepa, a cell cycle–nonspecific alkylating agent, is another commonly used intrathecal drug.[147] Other intrathecal agents that have been studied in this context include mafosphamide,[150] topotecan,[151] etoposide,[152] interferon-α,[153] and 5-fluoro-2′-deoxyuridine.[154] Further investigation of these agents is warranted.

Treatment-Related Toxicity

Placement of an intraventricular catheter is associated with less than a 1% risk of perioperative hemorrhage. Extended use of the device is associated with at least a 5% risk of infection, usually with *Staphylococcus epidermidis* or *S. aureus*. Impaired CSF flow of chemotherapy secondary to obstruction may result in seizures as well as acute arachnoiditis, characterized by nausea, vomiting, and mental status changes. For this reason, many practitioners will obtain a radionuclide CSF flow study before initiation of intra-Ommaya chemotherapy. Ultimately, the most significant toxicity associated with the treatment of leptomeningeal carcinomatosis is the development of a necrotizing leukoencephalopathy. This is most common in patients who have received intrathecal methotrexate following cranial irradiation. Initial findings are radiographic changes, usually symmetric abnormalities in white matter. Many of these patients subsequently develop progressive dementia that can progress to substantial debility and to death.[142]

Systemic Chemotherapy and New Approaches

A significant fraction of contrast-enhancing tumor that is visualized on neuroimaging studies is theoretically accessible by systemic chemotherapy, which is able to reach this fraction of tumor supplied by an abnormally permeable neovasculature. However, water-soluble chemotherapy drugs are limited by the intact blood-brain barrier, and systemic therapy fails to treat microscopic, nonenhancing disease both in brain parenchyma and in the subarachnoid space. One exception is in the use of high-dose systemic administration of methotrexate, which results in therapeutic levels in the CSF for a longer duration than the intrathecal route; this therapeutic strategy has been shown to be active in neoplastic meningitis both in lymphoma and in solid tumors. Moreover, systemic administration of methotrexate at high doses overcomes the problems associated with CSF flow obstruction, which can compromise subarachnoid administration. However, because high-dose methotrexate administration requires detailed inpatient monitoring of fluid status, urine alkalinization, and renal function, systemic administration of methotrexate at high doses is not appropriate or practical for all patients.[155]

Finally, in the current era of targeted therapeutics, there is increasing interest in the application of biologic therapies in the leptomeningeal compartment, particularly small molecule inhibitors of signal-transducing molecules such as protein kinases or monoclonal antibodies against tumor-associated cell surface molecules. There is increasing evidence that when these agents are administered systemically, they penetrate the leptomeningeal space inefficiently. For example, relatively low CSF levels of monoclonal antibodies that target CD20 in B-cell lymphomas or of small molecules that inhibit the bcr-abl tyrosine kinase have been documented after systemic administration.[156,157] Direct intra-CSF administration of monoclonal antibodies and immunotoxins is an area of current early-phase investigation in the treatment and/or prophylaxis of neoplastic meningitis.[156,158] A recent phase I dose escalation study formally evaluated the safety and efficacy of intrathecal administration of an anti-CD20 antibody in 10 patients with recurrent CNS and intraocular lymphoma.[159] Responses were identified in patients with meningeal, parenchymal, and intraocular disease, and a successor study of intraventricular rituximab plus methotrexate is under way. Another group reported promising results of targeted iodine-131-radiolabeled monoclonal antibodies administered to 52 patients with neoplastic meningitis.[160] Various case reports have also documented responses to trastuzumab, a humanized antibody directed to HER2, in patients with leptomeningeal carcinomatosis from HER2-overexpressing primary breast cancer.[161,162]

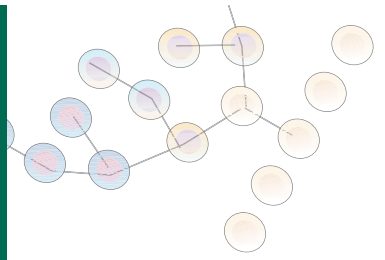
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57 Bone Metastases

Robert E. Coleman and Ingunn Holen

SUMMARY OF KEY POINTS

Incidence
- A major cause of (often prolonged) morbidity in cancer
- Especially prevalent in breast and prostatic cancer

Causes
- Osteolytic damage is mediated largely by stimulation of osteoclasts via tumor-derived cytokines; intermediary cells, including immune cells and osteoblasts, are involved.
- The vertebral-venous system of vessels is a significant anatomic pathway for metastatic spread to the skeleton.

Diagnosis
- Differential diagnosis includes osteoporosis, degenerative disease, and Paget's disease.
- The isotope bone scan is a sensitive test to detect the presence of skeletal pathology but gives little information about its nature.
- Structural information on skeletal damage from metastatic bone disease is best obtained by skeletal radiography supplemented by computerized tomography or magnetic resonance imaging.

Evaluation of the Patient
- An assessment of patients' symptoms and activity status is essential.
- Skeletal radiography assesses response to treatment, but the information is delayed and the method insensitive.
- Early indications of response of bone metastases to treatment can be obtained by monitoring biochemical markers, including the bone isoenzyme of alkaline phosphatase, osteocalcin, and pyridinium cross-linking amino acids.
- Isotopic bone scanning is not useful in monitoring response to treatment.

Treatment
- Antitumor treatments, such as radiation therapy, endocrine therapy, cytotoxic chemotherapy, targeted biologic agents, and radioisotope therapy have a role in the multidisciplinary palliative treatment of metastatic bone disease.
- The bisphosphonates are inhibitors of osteoclast activity and have become important agents for the treatment of metastatic bone disease, because they relieve symptoms, allow bone healing, and delay complications.

Complications
- Complications include pain, impaired mobility, pathologic fracture, spinal cord compression, cranial nerve palsies, nerve root lesions, hypercalcemia, and suppression of bone marrow function.
- Bisphosphonates in combination with intravenous rehydration constitute the treatment of choice for hypercalcemia.
- Orthopedic surgery has an important role in the treatment and prophylaxis of pathologic fractures and spinal decompression and stabilization in the relief of spinal cord compression.

INCIDENCE

Primary Tumors Leading to Bone Metastases

Primary bone cancer occurs predominantly among children and adolescents and is rare. By contrast, secondary bone cancer—particularly from carcinomas of the breast, lung, prostate, kidney, and thyroid—is common. The incidence of bone metastases from different primary sites recorded in postmortem studies is summarized in Table 57-1. Although the variability in these metastatic patterns is probably related to molecular and cellular biologic characteristics of both the tumor cells and those of the tissues to which they metastasize, other factors, such as vascular pathways and blood flow, are also important.[1]

Given the high prevalence of carcinomas of the breast, bronchus, and prostate, these cancers probably account for more than 80% of cases of metastatic bone disease. The distribution of bone metastases is predominantly to the axial skeleton—particularly the spine, pelvis, and ribs—rather than to the appendicular skeleton, although lesions in the humeri and femora are also common.

Breast cancer, the most common malignancy in women of western Europe and North America and which, in the areas of its highest incidence, accounts for some 10% of all cancers, is the tumor most often associated with metastatic bone disease. Because of the long clinical course this disease potentially can follow even after metastases have developed, morbidity from bone deposits presents a major problem for health care systems. Approximately 70% of patients dying from breast cancer will have radiologic evidence of skeletal metastases before death, and bone is the first metastatic site in over 40% of those with distant relapse. Median survival after first relapse in bone is around 2 years, and significantly longer than is seen after first relapse in visceral sites such as the liver.[1] Although the management of metastatic visceral disease has improved in recent years, the prognosis following visceral relapse remains poor, whereas bone metastases can be a protracted problem over many years. Favorable factors for a longer survival after first relapse in bone are low histologic grade, positive estrogen receptor status, long postoperative disease-free interval, and lack of development of extraosseous disease.[2]

There is increased interest in personalized medicine whereby biologic factors are utilized to predict the probability or distribution of

Table 57-1 Incidence of Skeletal Metastases from Autopsy Studies

Primary Tumor	No. of Studies	Incidence (%) of Bone Metastases	
		Median	Range
Breast	5	73	47–85
Prostate	6	68	33–85
Thyroid	4	42	28–60
Kidney	3	35	33–40
Bronchus	4	36	30–55
Esophagus	3	6	5–7
Gastrointestinal tract	4	5	3–11
Rectum	3	11	8–13

Modified from Coleman RE: Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006;12(Suppl): 6243–6249.

recurrence. The association between estrogen receptor expression and bone metastasis has been appreciated for 20 years.[1] However, more recently, other markers, especially the noncollagenous bone proteins, have been suggested as predictors of bone recurrence. These have included bone sialoprotein (BSP), which in addition to being apparently predictive of bone metastasis in breast cancer,[3] may be relevant in other tumors with a propensity to metastasize to bone.[4] Parathyroid-related peptide (PTHrP) is expressed by a very high proportion of breast cancers in bone,[5] and it was previously suggested that immunohistochemical determination of PTHrP expression by the primary tumor might be a useful predictive test. However, long-term follow-up of a large cohort of patients with PTHrP assessment of the primary tumor has indicated that this is not the case with PTHrP positivity associated with a better prognosis and a lower incidence of metastasis.[6]

Gene expression profiling has identified genetic signatures that are strongly associated with prognosis,[7,8] possibly outperforming conventional panels of clinical and pathologic criteria. However, the risk of metastasis per se does not necessarily predict for metastasis to specific sites. Recently, a 69-gene signature was described that was specifically predictive of metastasis to bone as opposed to metastasis in other sites.[9] The set of genes expressed suggested involvement of the fibroblast growth factor receptor pathway in the process of metastasis to bone. Subsequently, a classifier of 31 genes was constructed that was able to predict all tumors relapsing in bone with a specificity of 50%. Much more work is required to confirm the utility of genetic profiling in clinical management, but this approach holds much promise.

The skeleton is by far the most common site of metastatic disease in prostatic cancer. Unlike breast cancer, in which radiologically the lesions frequently show a mix of osteoblastic and osteolytic appearances, osteosclerotic disease predominates in prostatic cancer. Nevertheless, computed tomography (CT) often identifies lytic areas within these ostensibly sclerotic lesions. Histologic and biochemical studies also have demonstrated increased bone resorption in metastatic prostatic cancer.[10] As in breast cancer, metastatic bone disease in prostatic cancer can follow a relatively long course. For example, patients of good performance status and bone-only disease affecting the axial skeleton have a median survival of about 53 months, compared with 30 months for those with additional visceral disease and only 12 months for poor-performance status patients with both bone and visceral disease.[11]

Several studies have attempted to correlate the extent of skeletal metastatic involvement with survival in patients with advanced prostate cancer. A system based on the number of lesions identified by bone scintigraphy was predictive for survival,[12] and a bone scan index to quantify the extent of skeletal involvement by tumor more accurately has been developed.[13] It is based on the known proportional weights of each of the 158 bones derived from the so-called "reference man," a standardized skeleton in which postmortem-based individual bone weights were reported for the average adult. The bones were considered individually and assigned a numeric score representing the percentage involvement with tumor multiplied by the weight of the bone. In an analysis of outcomes according to the bone scan index in 191 patients with androgen-independent prostate cancer, patients with low, intermediate, or extensive skeletal involvement had median survivals of 18.3, 15.8, and 8.1 months, respectively.[13]

In lung cancer, the incidence of bone metastases identifiable at the time of primary diagnosis is highest in the small cell variety and lowest with squamous cell tumors, but at autopsy the incidence of bone metastases is similar for all four main histologic types of lung cancer (squamous cell, small cell, large cell anaplastic, and adenocarcinoma) at about 30%. Survival from primary diagnosis of lung cancer is poor, and fewer than 10% of patients are alive after 5 years. Once metastatic disease is evident, most patients die within a few months. Bone metastases from lung cancer are usually of the osteolytic type, but because of the poor survival prospects, morbidity from them is much less of a long-term health care problem than for either breast or prostatic cancers.

CAUSES

Mechanisms of Metastases

The predominant distribution of bone metastases in the axial skeleton, in which most of the red bone marrow is situated, suggests that the slow blood flow at these sites could assist in the attachment of metastatic cells. Contrast this, for example, with the circulation in the kidneys, which accounts for a high proportion of cardiac output and in which metastatic disease is extremely rare. Furthermore, the high incidence of bone metastases in prostate and breast cancers, without corresponding lesions in the lungs, is assumed to in part reflect the circulation of tumor cells through the vertebral-venous plexus, which parallels, connects with, and provides bypasses for the portal, pulmonary, and caval system of veins and so provides a pathway for the spread of disease between distant organs.[14] However, these anatomic characteristics do not account adequately for metastatic patterns. It seems likely that molecular properties of both the malignant cells and those of the tissue in which metastases develop are of critical importance.

Pathogenesis

Bone Remodeling

Bone is a highly specialized connective tissue comprising an unmineralized (osteoid) matrix composed predominantly of type I collagen; and a mineralized component of hydroxyapatite crystals, which encloses the marrow space containing a variety of marrow-residing cells (osteoblasts, osteoclasts, bone marrow stromal cells, immune cells, stem cells, adipocytes, fibroblasts, endothelial cells), platelets, fat, and interstitial fluid. During childhood and adolescence, bone is constantly shaped and remodeled, with peak bone mass being reached in early adulthood. Bone turnover continues throughout life, with up to 20% of the skeleton undergoing remodeling at any time so as to replace damaged bone and maintain skeletal integrity. The total duration of a remodeling cycle in young adults is estimated to be around 200 days. This process is essential for providing bone strength and is responsive to mechanical stress.[15]

Bone resorption is mediated by the osteoclast, a multinucleated giant cell derived from granulocyte-macrophage precursors, whereas bone formation is carried out by osteoblasts, derived from mesenchy-

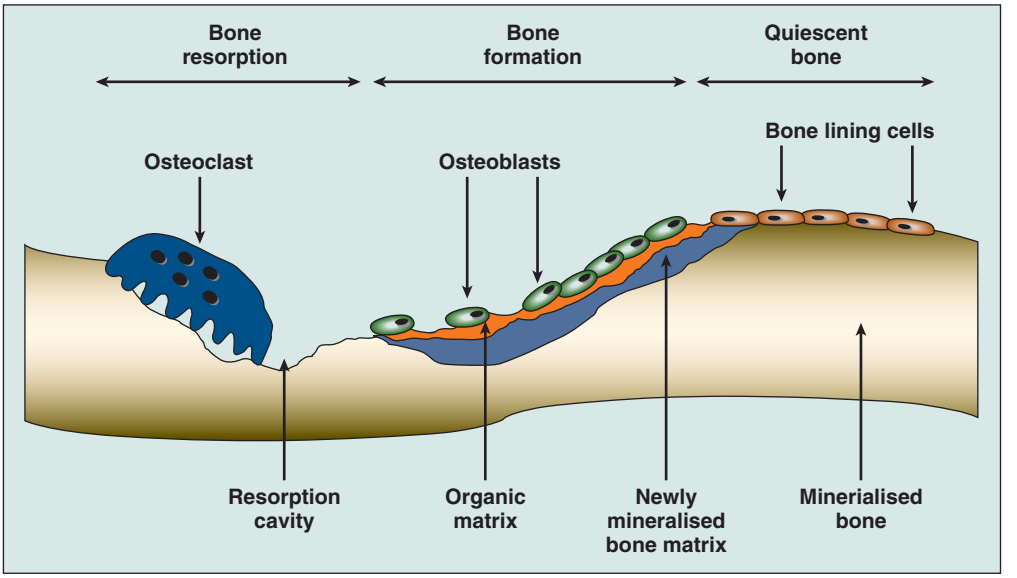


Figure 57-1 • Schematic diagram illustrating the normal bone remodeling cycle. Osteoclasts attracted to a site of fatigued bone create an erosion cavity. Osteoblasts are attracted and synthesize the organic matrix, which will fill the resorption cavity. The new bone is then remineralized to complete the remodeling process.

mal fibroblast-like cells. In a healthy individual, bone resorption and bone formation are coupled and perfectly balanced in location, time, and amount. Bone remodeling is regulated by complex interactions between hormones, paracrine growth factors, and cytokines, and involves interactions between osteoclasts and osteoblasts as well as other cell types present in the bone microenvironment (Fig. 57-1).

The presence of tumor cells in metastatic bone disease leads to disruption of the fine-tuned balance between bone formation and bone resorption, either causing excess bone resorption (as associated with lytic bone lesions) or increased levels of bone formation (as in osteosclerotic bone lesions). In many cases there are mixed lesions, comprising both lytic and sclerotic features (Fig.57-2). In the late stages of cancer, tumor masses may also damage the skeleton by compression of vasculature and consequent ischemia.

Tumor Cell–Bone Cell Interactions

Malignant cells secrete factors that stimulate osteoclastic activity both directly and indirectly, as reviewed by Mundy[16] and recently by Siclari and colleagues,[17] and the importance of interactions between malignant cells and the bone microenvironment in the development of bone metastases has been the focus of intensive research. Factors produced by tumor cells that cause increased bone resorption include prostaglandin-E and a variety of cytokines and growth factors, such as transforming growth factor (TGF) α and β, epidermal growth factor, vascular endothelial growth factor, tumor necrosis factor, and interleukins-1, -6, -8, and -11.

Several proteolytic enzymes are proposed to be involved in the early phases of formation of bone metastases, including matrix metalloproteinase (MMP)-2 and -9 and cathepsin K.[18] Normal bone trabeculae are lined by a thin layer of uncalcified matrix, which protects the calcified bone from osteoclastic activity, and the action of proteolytic enzymes might be a prerequisite for osteoclastic bone resorption. In addition, MMPs are involved in bone metastases formation both through their ability to degrade basement membrane and facilitate tumor cell dissemination, but also by causing release of growth factors and cytokines bound to the bone matrix, thereby supporting further tumor cell proliferation.[19] Malignant cells might also increase bone resorption by stimulating tumor-associated immune cells to

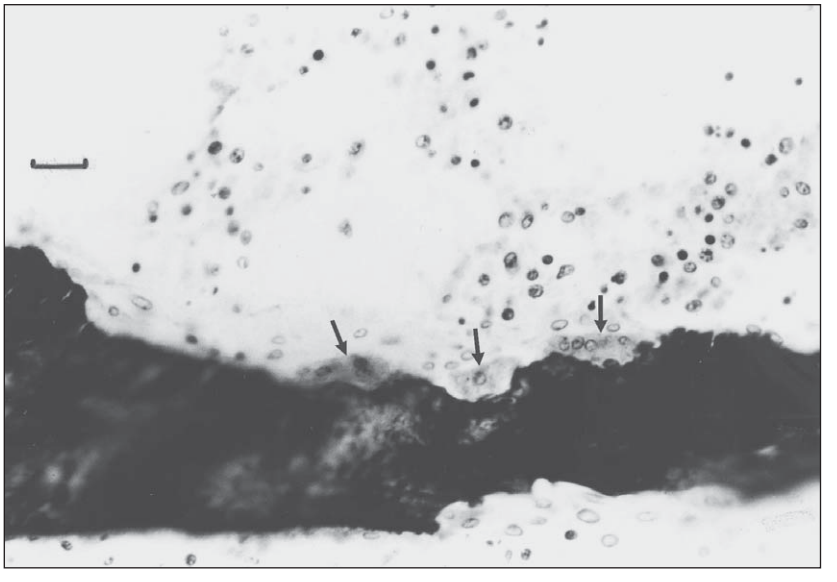


Figure 57-2 • Histologic section showing resorption lacunae on a bone trabeculum. Multinuclate osteoclasts (*arrows*) are resorbing bone in close association with mononuclear hematopoietic cells. The bar represents 20 mm. (From Boyce BF: Normal bone remodeling and its disruption in metastatic bone disease. In: Rubens RD, Fogelman I [eds]: Bone Metastases—Diagnosis and Treatment. London, Springer Verlag, 1991, p 14.)

release osteoclast-activating factors. It has been shown that human melanoma cells produce a factor that stimulates macrophages to release tumor necrosis factor and interleukin-1 in vitro. Furthermore, purification of a cytokine-releasing factor from medium conditioned by melanoma cells has identified it as granulocyte-macrophage colony-stimulating factor, which activates osteoclastic bone resorption.[20] The complex interaction between tumor cells, osteoblasts, osteoclasts, and associated immune cells is summarized in Figure 57-3.

In addition to the local paracrine factors just described, osteoclastic activity can also be stimulated in malignant disease by systemic factors, particularly PTHrP. This peptide is immunologically distinct from PTH, but the two hormones have significant homology at the N terminus of the molecule, which is necessary for osteoclast stimulation. Ectopic production of this hormone, particularly in lung cancer, is a cause of osteoclastic bone resorption and hypercalcemia even in the absence of bone metastases.

The importance of PTHrP in the pathogenesis of osteolysis induced by metastatic breast cancer has been elegantly elucidated.[21] In bone metastases, the secreted PTHrP acts in a paracrine manner to stimulate osteoclastic bone resorption. Not only does this lead to skeletal damage, but it also seems to confer a selective growth advantage on the tumor cells. This results from the release of factors for tumor growth from bone during the osteolytic process. Hence, a vicious circle is established in which the growth of metastatic cells is potentiated, leading to enhanced osteolysis and secretion of additional growth factors to stimulate tumor cell proliferation.[17] This paracrine activity occurs even in the absence of hypercalcemia or increased circulating PTHrP levels. PTHrP stimulates osteoclastic resorption by increasing osteoblast and stromal cell production of receptor activator of nuclear factor-κB (RANK) ligand.[20] RANK ligand binds to its receptor, RANK, on osteoclast lineage cells, resulting in differentiation to mature osteoclasts and stimulation of osteoclast activity. In the normal bone environment, osteoblast secretion of osteoprotegerin (OPG) neutralizes RANK ligand, thus terminating its stimulatory effects on osteoclasts. The MCF-7 estrogen-dependent breast cancer cell line has been found to decrease osteoblastic OPG messenger RNA levels, thus enhancing osteoclast formation.[22] This imbalance is further compounded by release of TGF-β and insulin-like growth factor from resorbing bone, which further promotes tumor production of PTHrP, thus promoting a perpetuating cycle of osteolytic bone destruction.

Tumor cells might also have direct cell-to-cell interaction with bone marrow cells. One study recently found that prostate cancer cells are able to express a soluble form of RANK ligand, a finding that implies a direct ability of prostate cancer cells to affect bone resorption.[23,24]

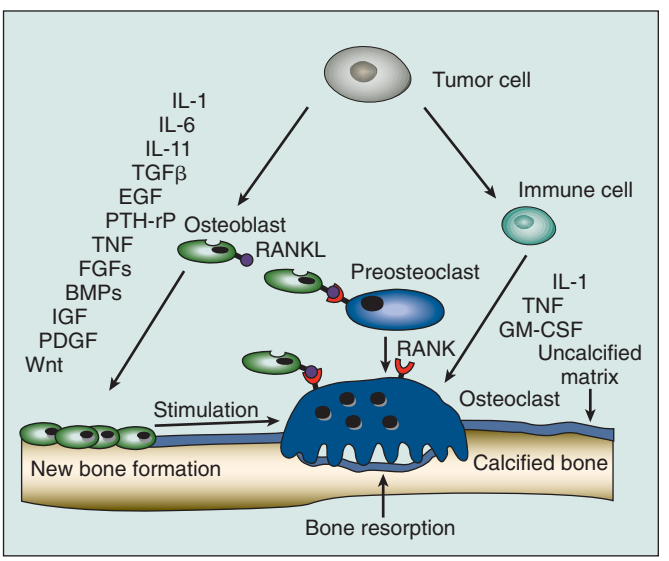


Figure 57-3 • Diagrammatic summary of the cellular and molecular interactions involved in bone resorption and new bone formation in metastatic disease of the skeleton. BMPs, bone morphogenetic proteins; EGF, epidermal growth factor; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IGF, insulin-like growth factor; IL-1, interleukin 1; IL-6, interleukin 6; PDGF, platelet-derived growth factor; PTH-rP, parathyroid hormone-related protein; TGF, transforming growth factor (α and β); TNF, tumor necrosis factor.

Sclerotic Bone Metastases

Although osteolytic disease is usually most evident at sites of bone metastases, osteosclerosis sometimes can predominate, particularly in prostatic cancer. Prostate cancer, in contrast to breast cancer, tends to cause osteoblastic lesions in bone, leading to dense, sclerotic-looking metastases on plain radiographs, and osteoblast growth factors, such as TGF-β and platelet-derived growth factor, have been purified from prostatic tumor cells. One of the factors that might be involved in prostatic bone lesions is the growth factor endothelin-1 (ET-1), which is produced by prostate cancer cells. Circulating levels have been found to be increased in patients with osteoblastic bone metastases from androgen-refractory prostate cancer, compared with patients whose cancer is confined to the prostate and normal controls.[25] ET-1 has been found to stimulate osteoblast activity in animal models and to inhibit osteoclast activity, whereas antagonists of endothelin have been found to inhibit bone formation in vivo.[26] Furthermore, a recent study found that ET-1 production by prostate cancer cells is reduced by androgens but is stimulated in androgen-insensitive prostate cancer cells by factors (such as TGF-β).[27] This finding is clinically relevant, because metastatic prostate cancer typically develops androgen resistance. It is possible that PTHrP is also involved in the pathogenesis of prostate cancer bone metastases, because coexpression of PTHrP and its receptor has been found in both the primary tumor and in bone metastases of patients with prostate cancer.[28]

Evidence from morphometric studies and measurement of urinary markers of osteolytic bone resorption has led to the hypothesis that initially, osteoclastic bone resorption is important in prostate cancer, followed by intense osteoblastic activity.[29] This might not necessarily always be the case, however. A recent study found that the prostate cancer cell line PC-3 implanted into tibia of SCID mice caused osteolytic lesions, possibly through secretion of RANK ligand.[30] When another prostate cancer cell line (LAPC-9) was used, however, osteoblastic lesions developed even when no osteoclasts were present. Therefore, in this study the authors concluded that osteoclastic activity might not be a prerequisite for the formation of osteoblastic lesions.

There is an increasing interest in the role of the osteoblasts in bone metastases, and it has recently been established that the Wnt signaling system plays a key role in bone development and turnover.[31] Subsequent studies have found that several molecules in this system are implicated in the development of bone metastases.[32] In prostate cancer, tumor-derived Wnt induces osteoblastic activity in bone metastases, which in the early stages of disease may be counteracted by the presence of the Wnt agonist DKK1 (an inhibitor of osteoblast differentiation), thereby favoring lytic lesions. In the later stages of progression of prostate cancer bone metastases, the balance between Wnt and its inhibitors is suggested to be shifted toward Wnt, favoring osteoblastic lesions.

In myeloma bone disease, bone marrow stromal cells are important for the pathogenesis of multiple myeloma. Interleukin-6 seems to be an important growth and survival factor for myeloma cells and for conferring resistance to treatment with dexamethasone, a commonly used treatment for multiple myeloma. Barille and colleagues

also found that matrix metalloproteinases (MMPs), known to be important in normal and malignant remodeling, contribute to the pathogenesis of myeloma. Bone marrow stromal cells secrete interstitial collagenases (MMP-1) and gelatinase A (MMP-2). MMP-1 initiates bone resorption, degrading type I collagen, which becomes a substrate for MMP-2.[33] Malignant plasma cells have been found to upregulate MMP-1 and activate MMP-2.[34]

Dysregulation of the Wnt signaling system has also been implicated in myeloma bone disease, where the production of DKK1 by myeloma cells is reported to be associated with the presence of lytic bone lesions.[35]

DIAGNOSIS

Differential Diagnosis

Metastatic involvement of the skeleton typically affects multiple sites and causes pain, bony tenderness, and increasing disability. The diagnosis is often straightforward but occasionally can be difficult to make, and confusion with benign pathology is particularly a problem for elderly patients, in whom degenerative disease and osteoporosis are common. Particularly difficult clinical situations include elderly women with painful collapsed vertebrae who have a past history of breast cancer and in whom it can be difficult to distinguish osteoporotic collapse from metastatic destruction, and elderly men with prostatic cancer and pelvic pain with sclerotic radiologic changes in the pelvis attributable to either metastases or Paget's disease of bone.

In all cases, appropriate imaging tests are necessary and must be interpreted in conjunction with the clinical picture, information from measurement of biochemical markers of bone metabolism, and—when appropriate—serum tumor markers. Occasionally, bone biopsy under radiologic control or at open operation is necessary. Table 57-2 summarizes the typical clinical, radiologic, bone scan, and biochemical abnormalities of the more common skeletal pathologies.

Diagnostic Methods

Skeletal Radiography

A skeletal radiogram indicates the net result of bone resorption and repair. To be recognized on a plain radiograph, a destructive lesion in trabecular bone must be greater than 1 cm in diameter, with loss of approximately 50% of the bone mineral content. When radiography is used as the primary investigation for bone metastases, such as in multiple myeloma, a skeletal survey is performed. On the basis of the usual distribution of metastases, this normally includes radiograms of the lateral skull and cervical spine, anteroposterior and

Table 57-2 Clinical, Radiologic, and Biochemical Features of Common Skeletal Disorders That May Mimic Bone Metastases

Diagnosis	Clinical Features	Radiologic	Biochemical
Bone metastases	Pain common	Bone scan very rarely completely normal	Alkaline phosphatase usually elevated
	Usually multiple sites	Discrete lytic or sclerotic lesions on radiographs	Increased urinary markers of bone resorption
	Axial skeletal involvement typical	Fracture/vertebral pedicle destruction	Hypercalcemia common
		Soft tissue extension on CT/MRI	
Degenerative disease	Elderly	Spinal involvement results in symmetric increased tracer uptake on scan	Usually normal
	Limb involvement common	Radiograms usually confirmatory	
	Pain and stiffness		
	Long history		
Osteoporosis	Elderly female	Normal scan unless recent fracture or vertebral collapse	Usually normal serum parameters
	Painless unless fracture or vertebral collapse	Diffuse osteopenia on radiograms	Slight elevation of urinary indices
		Normal marrow on MRI	No hypercalcemia
Paget's disease of bone	Elderly	Diffuse involvement of bone on scan	Alkaline phosphatase greatly elevated
	Bone deformity common	Sclerotic expanded appearance on radiograms	Increase in urinary hydroxyproline excretion
	Involved site warm due to increased blood flow		Hypercalcemia very rare
	Skull often involved and enlarged		
Traumatic fractures	History of trauma usual	Intense linear uptake on scan	Usually normal
	Spontaneous rib fractures after chest wall irradiation common	Rib lesions typically aligned, not randomly distributed	
		No evidence of destruction around fracture site on radiographs (unless radiation induced)	

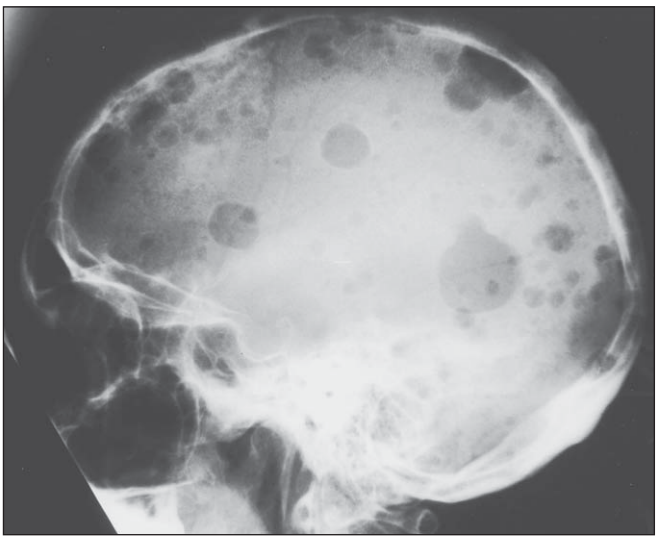


Figure 57-4 • Lytic metastases in the skull.



Figure 57-5 • Sclerotic metastases in the pelvis.

lateral thoracic and lumbar spine, and anteroposterior pelvis and chest radiograms taken at low KVp to visualize the ribs optimally.

It is the predominance of lysis or sclerosis that gives rise to the characteristic radiographic appearances of bone metastases. When bone resorption predominates, focal bone destruction occurs, and bone metastases have a lytic appearance. Conversely, in bone metastases characterized by increased osteoblast activity and associated with a fibrous stroma (e.g., in prostate cancer), the lesions appear sclerotic. Even when one element predominates, both processes are greatly accelerated in the affected bone. Though probably a general phenomenon, this is most apparent in the appropriately termed "mixed" lesions, seen most commonly in breast cancer, in which both lytic and sclerotic components are clearly visible.

Lytic metastases are the most common type arising from breast, lung, thyroid, renal, melanoma, and gastrointestinal malignancies (Fig. 57-4). There is thinning of trabeculae, and the margins are usually ill defined, representing regions of partially destroyed trabeculae between the central destruction and the radiologically normal bone. The width of the margin reflects the aggressiveness of the lesion, with a narrow zone of transition in the less aggressive lesions. If the metastasis is in the medulla, there could be endosteal scalloping, whereas cortical lesions produce subperiosteal scalloping or a focal cortical defect.

Sclerotic metastases are usually from prostate cancer but also arise from breast, lung, and carcinoid tumors (Fig. 57-5). Excessive new bone formation gives rise to thickened, coarse trabeculae, which usually appear on radiograms as nodular, rounded, fairly well-circumscribed sclerotic areas. Sometimes, less well-defined, mottled, irregular areas of increased bone density occur, which can coalesce to produce a diffuse sclerotic appearance to the skeleton.

Radionucleotide Bone Scan

The radionuclide bone scan provides quite different information from the skeletal radiogram. The bone-seeking radiopharmaceutical is absorbed onto the calcium of hydroxyapatite in bone, a reaction that is influenced by osteoblastic activity and skeletal vascularity, with preferential uptake of tracer at sites of active bone formation. The bone scan, therefore, reflects the metabolic reaction of bone to the disease process, whether neoplastic, traumatic, or inflammatory. When bone metastases develop, there is usually sufficient increase in blood flow and reactive new bone formation to produce a focal increase in tracer uptake, often before bone destruction can be seen radiologically, and with the exception of patients with multiple myeloma, the bone scan is a more sensitive technique than plain radiograms for the detection of skeletal pathology. Lesions in the pubis, ischium, and sacrum may on occasion be obscured on the bone scan as a result of bladder activity, and not all established metastases may be visualized.

A bone scan is generally performed by acquiring multiple images of the skeleton 3 to 4 hours after the intravenous injection of ^{99m}technetium-labeled methylene-diphosphonate. If a lesion is identified, particularly when solitary, further investigation is necessary. A suggested protocol for investigation is shown in the accompanying algorithm (Fig. 57-6). Appropriate plain radiographs of a focal lesion should be obtained in the first instance. If these are normal and

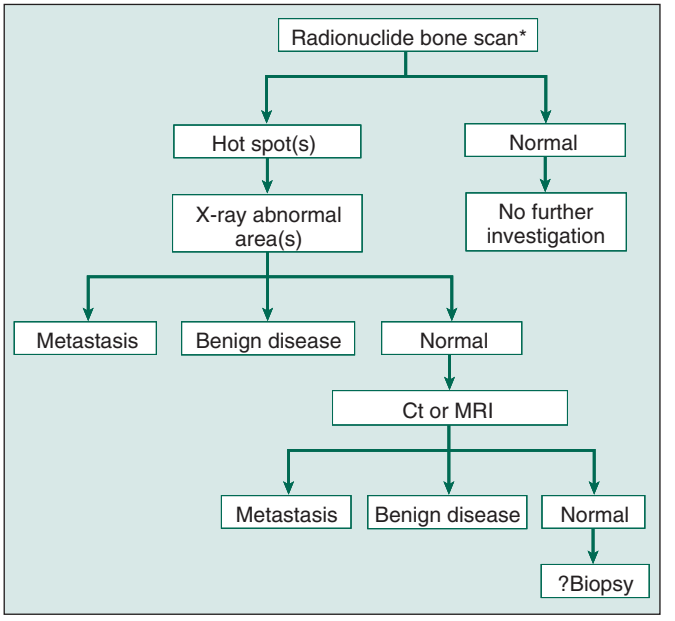


Figure 57-6 • Diagnostic methods for the investigation of a patient with possible bone metastases. *Patients with multiple myeloma are best investigated by performing a skeletal survey.

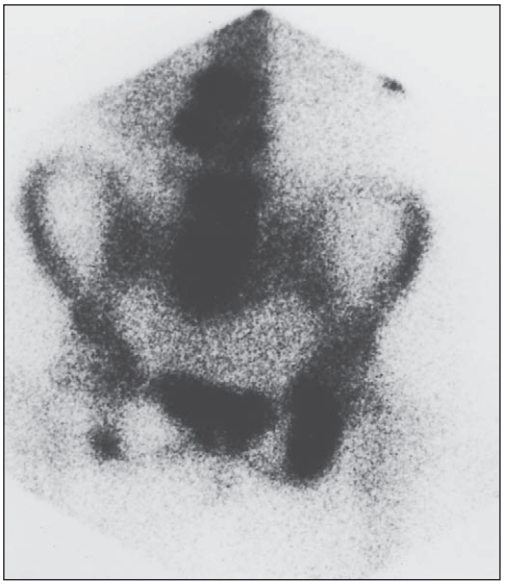


Figure 57-7 • Radionuclide bone scan appearances of metastases in the lumbar spine and pelvis.

clinically a metastasis is likely, then CT or magnetic resonance imaging (MRI) of the area could be diagnostic.

Although bone scan appearances are nonspecific, recognizable patterns of bone scan abnormalities might suggest a specific diagnosis. Metastases are usually multiple, irregularly distributed foci of increased tracer uptake that do not correspond to any single anatomic structure (Fig. 57-7). Generally, they affect the axial skeleton, but metastatic disease can involve the appendicular skeleton, and approximately 7% of patients have involvement of the distal skeleton, the proportion increasing in certain tumor types such as renal cell carcinoma.[36] Although bone metastases are usually multiple when diagnosed, as many as 20% of women with breast cancer present with a solitary hot spot on the bone scan with or without pain.[37]

Because detection of a lesion depends on the presence of a focal increase in osteoblast activity, a false-negative scan will occur when there is pure lytic disease. This is typical of multiple myeloma, which is best investigated radiographically but also can occur in other tumors when there are rapidly growing lytic lesions. In extreme cases, where there has been significant bony destruction, a photon-deficient area (cold spot) can develop (Fig. 57-8). Sclerotic metastases, on the other hand, are generally clearly visualized on the bone scan, the only exception being very slow-growing metastases, in which the alteration in metabolic activity is so subtle that it might not be distinguishable from normal background activity.

When there are extensive skeletal metastases, the focal lesions might coalesce to produce diffusely increased uptake—the so-called "super scan" of malignancy (Fig. 57-9). This occurs most often in prostatic cancer but also is seen in other tumors, such as breast cancer. An increase in the contrast between bone and background soft tissue and faint or absent renal images are the typical appearances.

Computed Tomography

A CT scan produces images with excellent soft-tissue and contrast resolution. Bony destruction and sclerotic deposits are well shown (Fig. 57-10), and any soft-tissue extension of bone metastases is demonstrated clearly. CT is most appropriate for diagnosing spinal metastases, but because the whole spine cannot be scanned readily, CT is normally reserved for assessment of patients with positive bone scans and negative radiograms in an attempt to clarify the pathology.

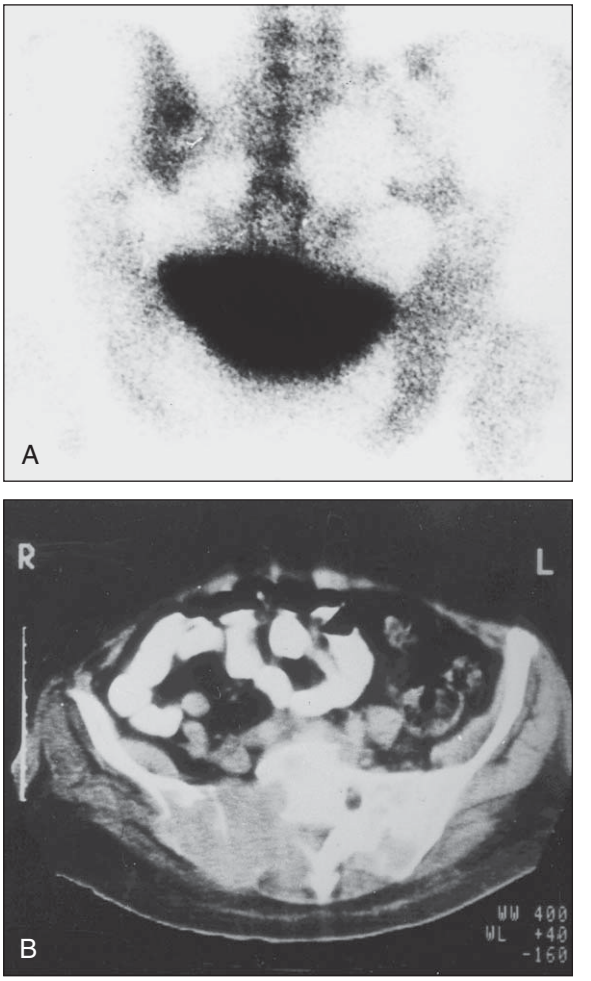


Figure 57-8 • **A,** Photodeficient (cold lesion) in the sacrum resulting from a rapidly progressive destructive bone metastasis as demonstrated by CT scan slice taken through the lesion **(B).**

Magnetic Resonance Imaging

MRI has the advantage over CT of providing multiplanar images that permit (as one example) imaging of the entire spine in the sagittal plane (Fig. 57-11). The solid constituents of cortical bone give no signal on MRI and appear black, whereas the high water content of fat and bone marrow results in strong signals, making these tissues appear white. This signal is variable depending on the pulse sequence used. Detection of bone metastases by MRI depends on differences in MR signal intensity between tumor tissue and normal bone marrow. Metastatic tumor is therefore visualized directly, in contrast to the indirect changes observed by x-ray or radionuclide bone scanning. Like CT, MRI has proved useful for evaluating patients with positive bone scans and normal radiograms and for elucidating the cause of a vertebral compression fracture. MRI is excellent for demonstrating bone marrow infiltration and has also been reported to be more sensitive than the bone scan for the early detection of metastases.[38]

Positron Emisssion Tomography

Scanning with ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) provides the opportunity to visualize function. However, its role in the identification of bone metastases is far from clear. FDG has the advantage of demonstrating all metastatic sites, and in the skeleton it is assumed that its uptake is directly into tumor cells. For bone metastases from breast and lung cancer, FDG-PET has similar sensitivity, though poorer specificity, than the isotope



Figure 57-9 • "Super scan" of malignancy. Note absent renal images and diffuse uptake of tracer throughout the skeleton.



Figure 57-10 • CT scan image through the right shoulder showing mixed lytic and sclerotic disease.

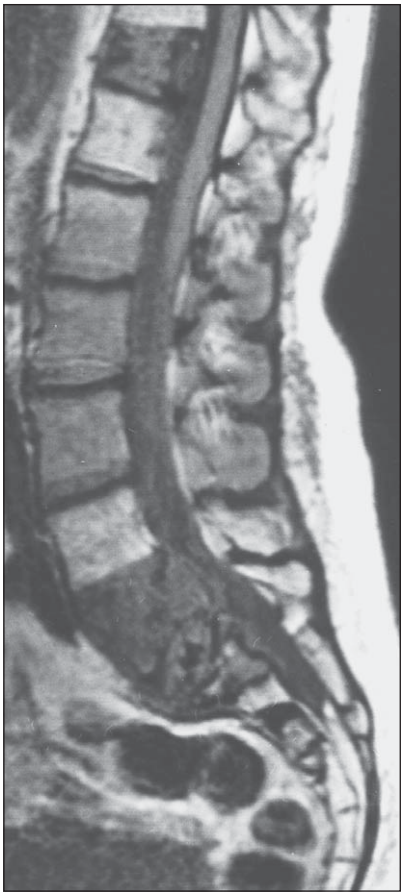


Figure 57-11 • T1-weighted magnetic resonance image of spine with metastases in T11 and L5 appearing darker than normal marrow. (From Richards MA: Magnetic resonance imaging. In: Rubens RD, Fogelman I [eds]: Bone Metastases—Diagnosis and Treatment. London, Springer Verlag, 1991, p 91.)

bone scan. However, the evidence is inconsistent, with several studies suggesting that FDG-PET is less sensitive than conventional imaging in breast cancer. There is convincing evidence that FDG-PET is less sensitive than the bone scan for prostate cancer, whereas for multiple myeloma FDG-PET it is clearly better than the bone scan, presumably because FDG is identifying marrow-based disease at an early stage.[39]

Biochemical Markers of Bone Metabolism

The effects of tumor cells on bone cell function can influence serum and urinary levels of biochemical markers of bone metabolism. In recent years, the number of available markers and the clinical relevance has increased rapidly; their value in the diagnosis of bone metastases has been studied in several tumor types.

Bone Formation Markers

BONE ALKALINE PHOSPHATASE. Bone alkaline phosphatase (BALP) hydrolyzes pyrophosphate, thereby removing an inhibitor of osteogenesis while creating the inorganic phosphate that is required for generation and deposition of hydroxyapatite.[40] This enzyme is secreted as a "bud" from the osteoblast cell membrane to the bone matrix vesicles, allowing bone mineralization to proceed.

There are several alkaline phosphatase isoforms secreted by the various organs into the serum. Predominant isoforms originate from bone, liver, intestine, and placenta. Because of these wide sources of activity, limited information may be obtained from a total alkaline phosphatase measurement. However, the bone-specific isoform (BALP) is a relatively specific marker for osteogenesis. Elevated BALP levels occur in Paget's disease, renal rickets, bone cancer, osteomalacia, and celiac disease. In addition, BALP may be increased in patients with liver diseases because it is normally cleared from the serum by the liver.[41]

OSTEOCALCIN. Osteocalcin is the major noncollagen protein in the bone matrix.[42] It is produced by osteoblasts, odontoblasts, and hypertrophic chondrocytes, and is thought to function as a localization site for hydroxyapatite crystals during bone matrix synthesis. Both osteolysis and osteogenesis release osteocalcin into the serum, from which it is eliminated via renal clearance and degradation.[42] Therefore, osteocalcin levels might reflect overall bone metabolism, not just osteogenesis. Detection of serum or plasma osteocalcin may be impaired by high lipid levels because of osteocalcin-lipid binding. Moreover, multiple isoforms exist in the circulation, and current assays have a limited ability to detect them all. Urinary osteocalcin levels may also be assayed, but, because of recovery and degradation, urinary osteocalcin levels typically reflect only basal bone turnover instead of acute changes in bone metabolism.[42]

PROPEPTIDES OF PROCOLLAGEN TYPE I. Collagen type I composes approximately 90% of the organic bone matrix. Extracellular processing occurs before the final collagen fibril assembly wherein the N-terminal (N-terminal propeptide of procollagen type 1 [PINP]) and C-terminal (C-terminal propeptide of procollagen type 1 [PICP]) regions are generated in a 1 : 1 ratio with collagen and released into the serum. Therefore, levels of PINP and PICP may reflect the level of osteogenesis. However, type I collagen is synthesized is some other tissues, which may contribute to the serum PINP and PICP levels. Serum PICP levels have been correlated with bone formation, and decreased levels have been reported after bisphosphonate therapy or hormone replacement therapy. Both PINP and PICP are removed by the liver, but PINP can also be deposited directly into bone and has been found to constitute 5% of the noncollagenous protein in bone.[43] However, recent reports have suggested that PINP has greater diagnostic validity than PICP, and in a multivariate Cox analysis, PINP was shown to be an independent predictive factor for survival in patients with prostate cancer.[44]

Bone Resorption Markers

CALCIUM. Resorption of bone releases calcium, hydroxyproline, and collagen fragments into the circulation. These are cleared by the kidney and excreted largely unchanged into the urine. Serum calcium measurements are performed routinely, but changes within the normal range give little guide to disease activity. Hypocalcemia is seen when osteoblastic metastases predominate; this is more typically associated with prostate cancer but does sometimes occur in advanced breast cancer.

Urinary calcium excretion is a more sensitive indicator of alterations in calcium homeostasis. The molar ratio of calcium to creatinine in an early morning urine sample collected after an overnight fast is a convenient, reproducible method of quantifying calcium excretion. The problem with urinary calcium is that it is not a specific resorption inhibitor but only reflects the net effects of bone formation and resorption and is influenced by diet, the circulating levels of both PTH and PTHrP, and the concomitant administration of drugs such as bisphosphonates (which influence bone resorption independently of any tumor-related effects). Urinary calcium excretion is not increased significantly in the majority of patients with metastatic bone disease, a finding that reflects the effects of bone formation and the renal handling of calcium.

HYDROXYPROLINE. Urinary hydroxyproline excretion is a conventional parameter for measuring bone resorption in benign bone disease; it indicates matrix destruction more specifically but has been generally unreliable in the assessment of metastatic bone disease as a result of contributions from both diet and soft-tissue destruction by metastases.[41]

PYRIDINOLINE AND DEOXYPYRIDINOLINE. Pyridinoline (PYD) and deoxypyridinoline (DPD) are produced from the post-translational modification of lysine and hydroxylysine. They stabilize mature type I collagen in all major connective tissues, cross-linking the telopeptide domain of one collagen fibril to the helical region of an adjacent one. During bone resorption, PYD and DPD are released from bone in approximately a 3 : 1 ratio as free molecules or attached to collagen fragments. They are not recovered by the bone and are excreted via the kidneys with no known metabolic degradation. Urinary excretion is closely related to the rate of bone resorption. Although PYD and DPD are present in other tissues, bone is the major reservoir and has a higher turnover than most connective tissues. In fact, DPD is found almost exclusively in bone. However, the contribution from soft tissues may make these markers less accurate than other markers, especially in the case of PYD.

C-TELOPEPTIDE AND N-TELOPEPTIDE. C-telopeptide (CTX) and N-telopeptide (NTX) are the C-terminal and N-terminal peptides, respectively, of mature type I collagen with the cross-links attached and are released during bone resorption.[6] Degradation products of collagen are of various sizes that may undergo additional breakdown in the liver or kidney to their constituent amino acids and cross-links (PYD and DPD) and are excreted in the urine. However, osteoclast-derived fragments are different from those formed in nonskeletal tissues. The cross-linked peptide is primarily attached as an $\alpha 2$ isoform for NTX from bone and as an $\alpha 1$ isoform from other tissues. The CTX peptide exists as α or β isoforms, with β isoforms found more often in mature bone.[41]Assays for NTX utilize an antibody to the $\alpha 2$ chain and are usually performed on urine samples. However, urinary results must be adjusted for urine dilution, which may add to measurement variability. Urinary CTX measurements have poor precision at concentrations lower than 200 μg/L, so serum or plasma samples are often used. Serum CTX measurements utilize an antibody to the β isoform.

PYRIDINOLINE CROSS-LINKED C-TERMINAL TELOPEPTIDE OF TYPE I COLLAGEN. PYD cross-linked C-terminal telopeptide of type I collagen (ICTP) is another metabolic product of mature type I collagen resorption. Increased levels of serum ICTP correlate well with bone resorption levels in patients with either high or low bone turnover.[44] Serum ICTP level increases of as much as 20% have been reported in patients with osteolytic metastases.[45] Indeed, ICTP levels are elevated in lung cancer patients with bone metastases compared with patients without bone metastases, and in multiple myeloma patients with negative radiograms but positive MRI results.[45,46] Immunochemical characterization of serum ICTP reveal that cathepsin K–mediated bone resorption cleaves the collagen at the antigenic site, and the resulting ICTP fragment is not detected by the assay.[45] However, MMP-mediated release leaves the antigenic site intact, and in this situation the resulting ICTP fragment is detectable. These results explain why the current assay for ICTP is insensitive to physiologic changes in bone turnover such as those induced by estrogen or bisphosphonate treatment but a potentially useful marker in skeletal metastases.

TARTRATE-RESISTANT ACID PHOSPHATASE SERUM TYPE 5b. Tartrate-resistant acid phosphatase serum type 5b (TRAcP-5b) is secreted by osteoclasts after they have attached to the bone surface. The enzyme then enters the circulation where it is inactivated and degraded and active enzyme levels in the circulation

reflect recently released enzyme as a result of bone resorption. TRAcP-5b has been suggested as a useful marker for bone resorption. However, some studies have suggested that TRAcP-5b may reflect osteoclast numbers rather than activity.[47]

BONE SIALOPROTEIN. BSP is a noncollagenous bone matrix protein secreted by osteoclasts and is part of the small integrin-binding ligand N-linked glycoprotein (SIBLING) family. It is secreted by other cells and is present in all mineralized tissues. Elevated serum BSP levels have been reported in patients with prostate cancer, breast cancer, and colon cancer.[48] In fact, BSP levels in patients with bone metastases secondary to prostate cancer were an independent prognostic factor for survival.[49] Elevated serum BSP levels have also been reported in patients with multiple myeloma.[50]

Osteoclastogenesis Markers

RECEPTOR ACTIVATOR OF NUCLEAR FACTOR-KB LIGAND/OSTEOPROTEGERIN. RANK and the RANK ligand (RANKL) are required for osteoclastogenesis. OPG is a soluble decoy receptor that binds RANKL, thereby blocking stimulation of osteogenesis. RANKL exists as two isoforms: a membrane-bound form and a shorter soluble form. In patients with bone metastases secondary to breast cancer, prostate cancer, or lung cancer, both OPG and RANKL were not significantly elevated compared with patients without bone metastases.[51] However, among patients with multiple myeloma, serum levels of soluble RANKL and the RANKL/OPG ratio were elevated and correlated with markers of disease activity.[52]

Bone Markers as Predictive and Prognostic Indicators

Because commonly used radiographic methods do not detect bone metastases in the very early stages of development, the question arises whether serial measurements of bone markers might identify the impending development of bone metastases. Thus far, data relating to this question are sparse. However, once bone metastases have developed, bone markers can provide useful prognostic information. Clinical evidence of correlations between bone marker levels and patient outcomes have been recently reported from retrospective analyses of several large trials in patients with bone metastases.[10,53] Elevated on-study bone marker levels correlated with negative clinical outcomes in patients with metastatic prostate cancer, lung cancer, or other solid tumors.

Specifically, patients with elevated urinary NTX levels either at baseline or at their most recent assessment had an approximate twofold increase in their risk of disease progression and an approximate two- to threefold increase in their relative risk of skeletal-related events (SREs) compared with patients with low NTX levels. Among patients with prostate cancer, elevated NTX levels were associated with a 4.6-fold increased risk of death, and a 2.7-fold increased risk of death was observed in patients with lung cancer or other solid tumors compared with those with low NTX. In contrast, BALP levels were not a consistently strong prognostic indicator.

NTX levels have also been shown to provide valuable prognostic information in a larger analysis of patients receiving bisphosphonate treatment for bone metastases from a wide range of solid tumors and multiple myeloma.[53] Among patients with solid tumors, elevated NTX levels were associated with a significant twofold increased risk of disease progression ($P < 0.001$). Furthermore, elevated NTX levels were associated with a significant four- to sixfold increased risk of dying on study in all patients except those with multiple myeloma ($P < 0.001$ for all).

EVALUATION OF THE PATIENT

A variety of treatments, including radiotherapy, endocrine treatment, chemotherapy, and bisphosphonates, are used for the treatment of metastatic bone disease, and evaluation of their effects is important for both routine clinical practice and research. The current imaging methods used to assess response to these treatments are qualitative and routinely include plain radiographs, radionuclide bone scans, and, in particular situations, CT scans. Assessing the response of bone metastases to therapy is notoriously difficult; the events in the healing process are slow to evolve and quite subtle, with sclerosis of lytic lesions only beginning to appear 3 to 6 months after the start of therapy. Bone is the only site of metastatic disease that has separate criteria for evaluation of response to treatment, based on bone repair and destruction rather than on changes in tumor volume. A complete review of the bone radiographs since the start of treatment is necessary to evaluate response—a slow and tedious process.

Assessing response to treatment in bone is more difficult than evaluation of disease in viscera and soft tissues, where tumor measurements can usually be taken. This difficulty results in reports of lower response frequencies to systemic treatments in the skeleton compared with other sites of disease. Complete response in nonosseous sites affected by breast cancer occurs in 10% to 20% of patients, but a complete response in bone with return of normal trabecular pattern or resolution of sclerotic metastases is very rare. Although a low rate of complete response might represent some biologic phenomenon of site-specific resistance, this is unlikely, and the discrepancy in response frequency is almost certainly a reflection of the insensitivity of the assessment methods. Consequently, patients with metastatic disease confined to the bone are frequently excluded from many therapeutic trials, and patients with widespread metastatic disease (including bone) rely on the changes observed in soft tissue or visceral disease to judge response to treatment.

Although we recognize that the changes seen on serial radiograms remain the "gold standard" for evaluating response to therapy, new methods of assessing response are needed, both to improve patient management and to evaluate specific treatments. Several alternatives or adjuncts to assessment based on plain radiograms have been suggested. None is ideal, each having advantages and disadvantages as outlined in the following sections.

Assessment of Symptoms and Activity Status

The relief of symptoms is the principal aim of palliative therapy and rationally should be the most important marker of response to treatment. The use of pain as a marker of response in clinical trials has not found universal acceptance, however, and there is still no single internationally accepted pain questionnaire in oncology, although the Brief Pain Inventory is frequently used in clinical trials. Subjective response to treatment for bone disease requires information on pain intensity, analgesic consumption, and mobility.[54]

Quality-of-life assessment is now an important aspect of clinical trials methodology and, notwithstanding all the difficulties of analysis and interpretation, well-validated generic tools such as the Functional Living Index in Cancer patients (FLIC) and the EORTC QOL-C30 questionnaire can provide useful information on subjective response to treatment in the routine clinical setting. A specific quality-of-life tool for patients with bone metastases is currently under development by an international consortium.

Imaging of Bone Metastases

Radiologic assessment of response is based on radiographic evidence of bone healing. It is generally accepted that sclerosis of lytic metastases with no radiologic evidence of new lesions constitutes tumor regression (a partial response). Confounding factors include the appearance of sclerosis in an area that was previously normal on the radiogram. This could represent progression of a new metastasis but could also indicate a response, reflecting a radiographic example of the healing flare phenomenon within a lesion that was present at the start but was not destructive enough to be radiographically visible. Interpretation is further complicated by variations in film exposure and by the effects of overlying bowel gas. The evaluation of response

in osteosclerotic lesions is even more difficult, with most patients with sclerotic metastases eventually classified as either "no change" in response to therapy or unassessable. Here, decisions about the efficacy of treatment have to be based on symptomatic response or (when present) on change in extraskeletal disease.

Although the plain radiogram remains the assessment tool for judging response in clinical trials, it is clearly an inadequate technique. This lack of precision for radiographic assessment of response is exemplified by the observation that, in terms of survival, patients with radiographic evidence of sclerosis (partial response) and those with no change in radiographic appearance for at least 3 months have a similar outcome.[55]

The use of bone scanning for assessment of response to therapy has always been contentious; when lytic metastases predominate, it is often unreliable. A reduction in the intensity and number of lesions (hot spots) on the bone scan was previously considered to represent response, and progressive disease was assumed if an increase in intensity or number of hot spots was seen. This interpretation is too simplistic, however. After successful therapy for metastatic disease, the healing processes of new bone formation cause an initial increase in tracer uptake (akin to callus formation), and scans performed during this phase are likely to show increased intensity and number of hot spots. After treatment for 6 months, the bone scan appearances might improve, as the increased production of immature new bone—the cause of the hot spots—eventually ceases and isotope uptake gradually falls. This "deterioration" followed by subsequent "improvement" in the bone scan appearances after successful therapy has been termed the flare response and is now a well-recognized phenomenon in both breast and prostate cancers (Fig. 57-12). Conversely, a reduction in isotope uptake can occasionally be seen in rapidly progressive disease, when overwhelming bone destruction allows little chance for new bone formation, sometimes culminating in a photon-deficient (cold spot) lesion on the bone scan.

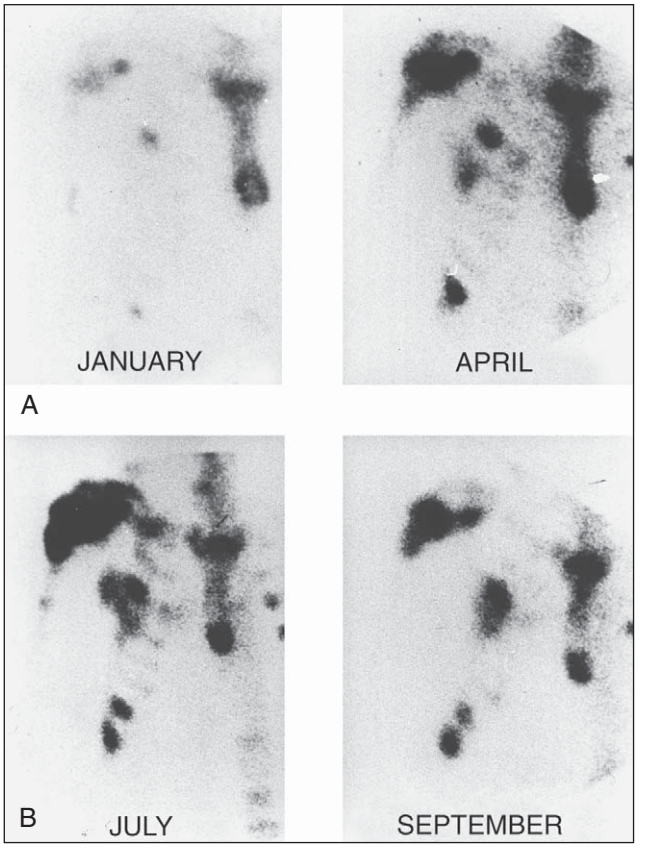


Figure 57-12 • **A,** CT appearances of metastases in a lumbar vertebra. **B,** Evidence of bone healing 2 months after irradiation.

Bone scanning in advanced disease should certainly be interpreted with great caution when performed within 6 months of a change in therapy; it is most useful for restaging at the time of relapse, to identify sites for radiologic assessment, and to bring to the attention of the clinician those sites at risk of pathologic fracture where prophylactic surgery could be indicated.

CT evaluation is effective for diagnosing metastases, particularly in the spine, but it is also occasionally valuable as a parameter of response to metastatic disease. Metastatic lesions that are considered to be representative of the metastatic process (target lesions) and suitable for serial examination with a standard window width and level appropriate for bone are optimum for selection. If required, a region of interest can be defined and the spectrum of Hounsfield values within it calculated by the computer. Changes in the spectrum with time can be determined, with a shift to the right (more positive) indicating replacement of lytic bone (which has a low Hounsfield value) by new sclerotic bone (which has a relatively high Hounsfield number).

CT evaluation is particularly useful for assessing areas that are poorly visualized on plain radiographs (e.g., the sacrum) and might permit assessment of sclerotic bone disease. Within sclerotic metastases, areas of osteolysis are usually present and can be identified by CT. Sclerosis of this lytic component would suggest response to treatment, whereas new areas of lysis appearing within a sclerotic region probably represent progression of disease.

The use of MRI for monitoring response to treatment is not used routinely, and in many parts of the world limited equipment availability makes MRI unlikely to be suitable for routine use. As in primary bone tumors, however, MRI could have a role for detailed evaluation of a specific lesion, for example before surgery.

The role of PET scanning in assessment of response remains uncertain.[56] Uptake of ^{18}F-FDG is related at least in part to function within the tumour and in theory could be useful just as it has been shown to be in the early assessment of soft-tissue tumours.

Tumor Markers

In breast cancer, unlike the germ cell malignancies, there is no highly specific tumor marker for either diagnosis or monitoring of disease. Some breast tumors, however, do produce tumor antigens that can be detected by radioimmunoassay. The most widely studied are carcinoembryonic antigen, which is elevated in 50% to 80% of patients with metastatic breast cancer, and CA 15-3, which is elevated in 60% to 90% of cases with advanced disease. Dynamic changes must be interpreted with caution. Although some patients show the expected increase in markers with progression and decrease in markers with regression, others who respond show an initial surge in tumor marker followed later by the expected decline.

Using an index derived from carcinoembryonic antigen and CA 15-3 in combination with erythrocyte sedimentation rate, a study in patients with metastatic breast cancer found a significant correlation with clinical assessment of response using Union Internationale Contre Cancer (UICC) criteria at 2, 4, and 6 months after systemic endocrine treatment.[57] A multicenter evaluation of the same index confirmed that changes in the markers were in line with and often predated therapeutic outcome criteria for both remission and progression.[58]

Prostate specific antigen (PSA). is a marker of prostatic pathology and can be elevated in any prostate disease: benign prostatic hypertrophy, prostatitis, and cancer. The highest tissue production occurs in prostate cancer, and PSA has proved useful in the early diagnosis, staging, and follow-up of patients.[59] The level of PSA is dependent on the volume of cancer, the volume of benign prostatic hypertrophy in the prostate, and the differentiation of the tumor, with less production of PSA from poorly differentiated tumors. PSA levels usually

decline after androgen deprivation therapy (ADT) and provide a reliable guide to response; elevations of PSA usually antedate other clinical evidence of progression by at least 12 months.[60]

Biochemical Assessment of Response

The stimulation of osteoclast function that results in osteolysis and disruption of the normal coupling between osteoblast and osteoclast function leads to changes in a variety of biochemical parameters. When treatment is prescribed for a patient with bone metastases, the effects of that treatment on the tumor cell population will influence bone cell activity. These changes can be appreciated within the first few weeks of starting effective therapy; for this reason, biochemical markers that reflect the rates of bone formation and resorption, respectively, might provide an early assessment of response to treatment (Table 57-3).

Hypercalcemia is usually indicative of progressive disease, and this is certainly the case if the hypercalcemia has developed more than a few weeks after the start of a new systemic treatment. Rarely, hypercalcemia can be a manifestation of the tumor flare, occurring within a week or so of starting tamoxifen, and in this case it might herald a response to treatment.[61]

More recently, attention has turned to the possible use of collagen cross-link measurements for the assessment of response in bone. Walls and colleagues[62] studied the collagen cross-links PYD and DPD in 36 patients with breast cancer with bone metastases. In women who developed progressive disease, both markers increased and preceded radiologic evidence by a median of 2 months. By contrast, in women who responded to hormone therapy, the markers did not change significantly.

Similarly, Vinholes and associates[63] studied 37 patients with newly diagnosed bone metastases from breast cancer. NTX levels were significantly lower than baseline values ($P = 0.05$) at 1 and 4 months in responding patients, compared with values for patients with progressive disease. Furthermore, a greater than 50% increase in NTX excretion correctly predicted disease progression in 78% of patients. In a larger, more recent study, 97 evaluable patients with metastatic bone disease from a variety of primary sites were followed during systemic therapy to correlate marker changes with response to treatment.[64] Good correlations of urinary NTX, ICTP, and BALP changes with response were observed, with a rise in NTX of greater than or equal to 52% having the highest positive predictive value (71%) for identifying progression of disease.

Although it is now well accepted that bone-targeted systemic therapy—particularly the use of the bisphosphonates—can reduce morbidity of skeletal metastases of breast cancer substantially, the optimization and timing of these therapies remains to be established. Bone markers potentially offer a powerful and relatively simple tool to assist the clinician in developing the most appropriate treatment strategies. Moreover, there is a prospect of using bone markers to tailor treatment to the individual patient.

There is evidence that the individual pretreatment values of a bone marker, particularly NTX, correlate with response to treatment. In patients with metastatic bone pain treated with pamidronate, the baseline values of NTX were significantly higher ($P < 0.02$) in nonresponding patients compared to clinical responders.[65] This study also showed that normalization of bone resorption markers correlated with response to treatment. Clinical benefit, as indicated by an improvement in a pain score, was seen only among those patients achieving a normal bone resorption rate after administration of pamidronate. No response was seen in the patients with persistently elevated levels. This suggested that the aim of bisphosphonate therapy should be to produce a fall in marker levels, preferably into the normal range. A subsequent study has shown that this principle may be extended to the use of bone markers to distinguish between the benefits of different bisphosphonates.[66] In one study, 51 patients were allocated randomly to treatment with either oral clodronate, intravenous clodronate, or intravenous pamidronate. Symptomatic response was more frequent in the pamidronate group than in patients receiving clodronate, and this was reflected by a correspondingly greater decrease in the bone resorption markers CTX and NTX.

The ability of bisphosphonate therapy to reduce the frequency of skeletal complications also seems to be correlated with a reduction in bone resorption markers. Retrospective analyses of large randomized trials with zoledronic acid have shown that among patients with solid tumors, elevated NTX levels despite treatment were associated with a significant two- to threefold increased risk of skeletal complications ($P < 0.001$).[53]

Table 57-3 Biochemical Markers of Bone Resorption and Formation

Resorption	Formation
URINE	**SERUM**
Calcium	Alkaline phosphatase
Hydroxyproline	Osteocalcin
PYD	PICP
DPD	PINP
NTX	
Crosslaps	
Free DPD	
Free PYD	
Galactosyl hydroxylysine	
SERUM	
Calcium	
ICTP	
Galactosyl hydroxylysine	

DPD, deoxypyridinoline; ICTP, type I collagen C telopeptide; NTX, N-telopeptide of type I collagen; PINP, N-terminal propeptide or type I procollagen; PICP, C-terminal propeptide or type I procollagen; PYD, pyridinoline.

TREATMENT

In general, the treatment of bone metastases is aimed at palliating symptoms, with cure only rarely a realistic aim (e.g., in lymphoma); treatment varies depending on the underlying disease. External beam radiotherapy, endocrine treatments, chemotherapy, and radioisotopes are all important. In addition, orthopedic intervention may be necessary for the structural complications of bone destruction, and some patients with bone metastases develop hypercalcemia requiring specific treatment (see Chapter 48). Optimal management requires a multidisciplinary team that includes not only medical and radiation oncologists, orthopedic surgeons, general physicians, radiologists, and nuclear medicine physicians, but also palliative medicine specialists and the symptom control team.

A schema for the management of bone metastases is shown in the accompanying algorithm (Fig. 57-13). Treatment decisions depend on whether the bone disease is localized or widespread, the presence or absence of extraskeletal metastases, and the nature of the underlying malignancy. Radiotherapy is frequently relevant throughout the clinical course of the disease. Resistance to systemic treatments can be expected to develop, necessitating periodic changes of therapy in an effort to regain control of the disease.

External Beam Radiation Therapy

Shortly after the discovery of x-rays by Roentgen in 1895, radiation therapy was tried as an empiric treatment for bone metastases, and

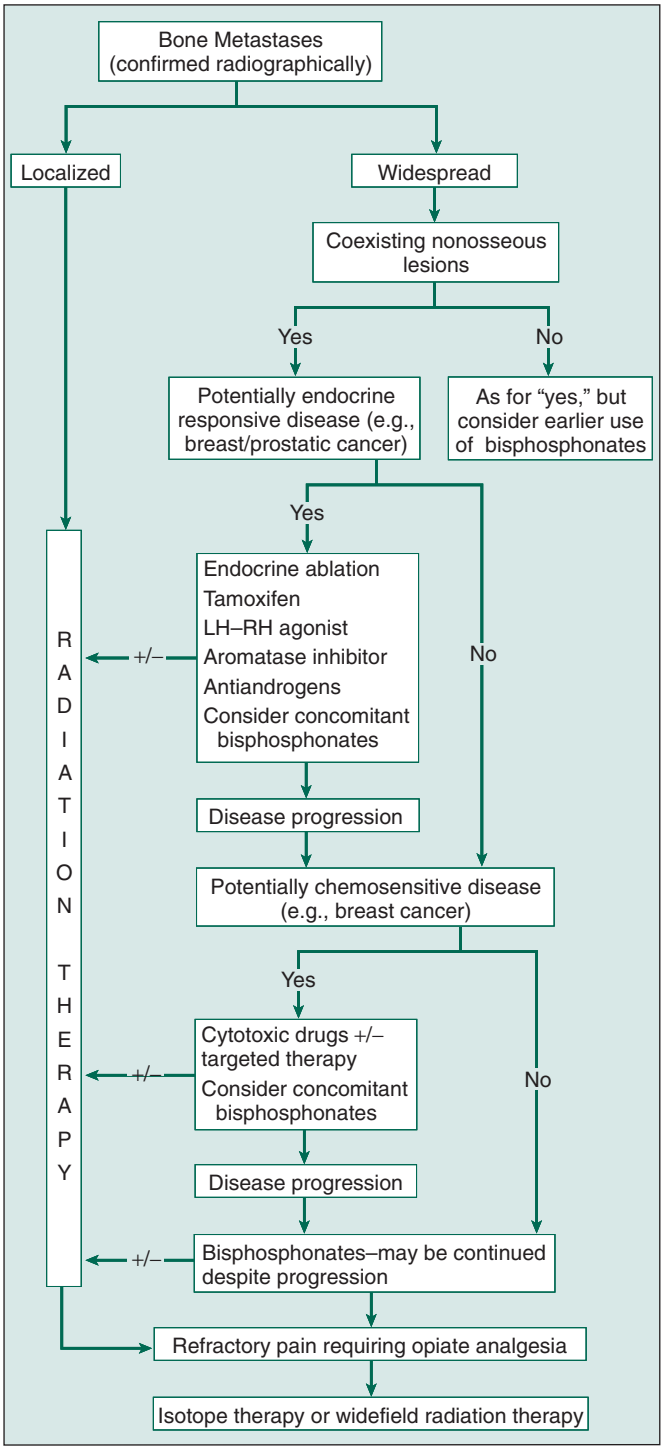


Figure 57-13 • Treatment of bone metastases.

relief of bone pain was observed. Since these early reports, radiotherapy has become established as the treatment of choice for the palliation of painful single sites.

Most treatments for bone pain use an external beam of ionizing radiation, either γ-rays or x-rays. Opposing anterior and posterior fields are used to produce an even dose distribution across the volume to be treated. Although surface anatomy can be used to localize the treatment area, use of a treatment simulator is preferable for accurate localization, particularly if treatment of adjacent areas is likely in the future.

Irradiation of bone can result in a number of pathologic changes that can include atrophy, osteitis, necrosis, and sarcomatous change. Postmortem studies have provided some insight into the structural effects of irradiation on bone-containing metastases. Initially, there is degeneration and necrosis of tumor cells, followed by a proliferation of collagen. Subsequently, a rich vascular fibrous stroma is produced, within which intense osteoblast activity lays down new woven bone. This is then gradually replaced by lamellar bone, and the intratrabecular stroma is repopulated by bone marrow tissue. Radiologically, it can be seen that recalcification of lytic areas begins 3 to 6 weeks after irradiation, with maximum recalcification occurring 2 to 3 months after the time of irradiation.

There is no doubt that local irradiation is effective for bone pain. Overall, response rates of around 85% are reported, with complete relief of pain achieved in one-half of patients.[67] Pain relief usually occurs rapidly, with more than 50% of responders showing benefit within 1 to 2 weeks. If improvement in pain has not occurred by 6 weeks or more after treatment, it is unlikely to be achieved.

Traditionally, treatment techniques and doses have varied considerably between different centers, with prolonged fractionated treatments preferred in North America and single treatments or short fractionation schedules most frequently utilized in Europe. A considerable number of randomized trials have been performed comparing different fractionation schedules. No particular approach seemed to be superior in terms of pain relief. American practice is influenced by the studies by the Radiation Therapy and Oncology Group. A variety of dose fractionation schedules were used ranging from 15 Gy in five fractions to 40.5 Gy in 15 fractions in a prospective randomized study of more than 1000 treatments for metastatic bone pain. An overall response rate of 90% was observed, with approximately half of responders maintaining pain relief until death. Median duration of pain relief in the complete responders was 12 to 15 weeks. The complete response rate was 35% after 40.5 Gy in 15 fractions, compared with a response rate of only 28% after 25 Gy in five fractions ($P = 0.0003$).[68] In Europe several trials have shown no difference in outcome between fractionated treatment and a single treatment, notably a large Dutch trial of 1157 patients with painful bone metastases who were randomized to receive either a single fraction of 8 Gy or a treatment schedule of six fractions of 4 Gy each.[69] No statistically significant differences in pain response, analgesic consumption, treatment side effects, or quality of life were identified. A meta-analysis of eight trials comparing single versus multiple fractions revealed similar response rates; 1011 of 1391 (73%) treated with a single fraction and 958 of 1321 (73%) who received multiple fractionation achieved a symptomatic response.[70] Hence, accumulating evidence strongly favors single-fraction radiotherapy as the treatment of choice for many patients with painful bone metastases.

The option of retreatment of a painful site requires careful review of previous treatment fields, dose, and fractionation to ensure that normal tissue tolerance, particularly of the spinal cord, is not exceeded. When higher radiation doses are administered, retreatment may be precluded; targeted radioisotope therapy is an alternative approach in such patients. After a single 8-Gy fraction, however, retreatment is usually possible, with more than 50% of patients with recurrence of bone pain responding to a second 8-Gy treatment—a finding that further supports the move occurring in many centers toward single-fraction treatments for routine palliation of metastatic bone pain.

When there are multiple scattered sites of painful bone metastases, wide field/hemibody irradiation is an alternative to treating each site individually with local irradiation. Using single fractions of 6 to 7 Gy to the upper hemibody and 6 to 8 Gy to the lower hemibody, pain relief is reported in about 75% of patients, often occurring rapidly and sometimes within 24 to 48 hours of treatment.[67] Hemibody irradiation is inevitably more toxic than localized external beam treatment. Virtually all patients who receive lower hemibody irradiation suffer gastrointestinal toxicity with nausea and diarrhea, requiring premedication with intravenous hydration, steroids, and antiemetics

to reduce these effects. The serious toxicities of hemibody irradiation are bone marrow suppression and radiation pneumonitis. Significant bone marrow suppression is seen in about 10% of patients receiving a single half-body treatment and in most patients who have sequential upper and lower hemibody treatment; these developments often compromise the use of subsequent chemotherapy. Radiation pneumonitis is both dose- and dose-rate-dependent; the occasional cases that do occur are difficult to treat and can be fatal.

Targeted Radioisotope Therapy

The therapeutic use of radioactive-labeled tracer molecules is currently an area of considerable interest and research. The principles of the technique are well established after decades of experience with iodine-131 (^{131}I) for the treatment of follicular thyroid cancer. Targeted radiotherapy has theoretic advantages over external beam radiotherapy in that the radiation dose is delivered specifically to the tumor and normal tissues are spared unnecessary irradiation. Theoretically, it should also be possible to administer high doses of radiation to the tumor on a recurrent basis if necessary. Despite the theoretic attractions of radioisotope therapy, however, technical difficulties have limited the use of therapeutic radiopharmaceuticals thus far.

Therapeutic radionuclides have characteristics different from those used for diagnostic purposes. Ideally, radionuclides for therapy should have a fairly long half-life, allowing adequate accumulation of the radiopharmaceutical within the target tissue. The γ-particle emission should be small to reduce unwanted radiation to nontarget tissues, but present in sufficient amounts to permit localization of the radionuclide by gamma camera imaging. Predominantly α- or β-emitting radionuclides are the most suitable, but, apart from ^{131}I, they have been very expensive to produce. Although many α- and β-emitting radionuclides exist, relatively few have been evaluated clinically.

Because follicular carcinoma of the thyroid commonly metastasizes to bone, the treatment of bone metastases with ^{131}I is now well established, and excellent results can be obtained. In patients with a significant uptake of ^{131}I into the metastases, long-term palliation is usually possible. Treatment is generally well tolerated, although some patients develop a radiation reaction in the salivary glands. More important, however, is the 1% to 2% incidence of radiation-induced leukemias.[71]

Neuroblastomas, and tumors of neuroectodermal origin in general, frequently metastasize to bone. Some 90% of these neoplasms incorporate the radiopharmaceutical ^{131}I-meta-iodo benzyl guanadine (^{131}I-MIBG), and this has now been used to treat many children with metastatic neuroblastoma. Bone marrow suppression is often severe, and ideally, bone marrow harvesting should be performed as a precautionary measure on patients with extensive bone metastases.

^{131}I-MIBG has also been used therapeutically to treat bone metastases from malignant pheochromocytoma, medullary carcinoma of the thyroid, and carcinoid tumors with limited success. Between one-third and one-half of patients achieve symptomatic benefit, but long-term remissions are rare.

Strontium-89 (^{89}Sr) is a β emitter that imitates calcium and is taken up preferentially at sites of new bone formation. It has been shown to localize at the sites of prostatic bone metastases, with greater accumulation occurring in the metastatic lesions than is observed in normal bone.[71,72] The biologic half-life of strontium in metastases is long compared with that of normal bone, with whole-body retention of ^{89}Sr treatments ranging from 11% to 88% depending on the degree of skeletal involvement. The radiation dose to individual vertebral metastases from a single 150-MBq dose of ^{89}Sr has been shown to vary from 9 Gy to 92 Gy depending on the extent of metastatic spread. Of great clinical importance is the low dose of radiation to the bone marrow, which is only about one-tenth of that to the bone metastases.

The selective β-particle irradiation provides pain relief in up to 80% of patients, with 10% to 20% becoming pain free.[72] On average, the response lasts for 6 months, with only mild hematologic toxicity. Several randomized clinical trials have been performed. These have included a double-blind, placebo-controlled trial of ^{89}Sr, with active therapy clearly superior in terms of pain relief ($P < 0.01$).[72] ^{89}Sr has also been compared with conventional radiotherapy (hemibody or local) for the palliation of bone metastases from prostatic cancer. ^{89}Sr was at least as effective as external beam radiotherapy in achieving palliation and seemed also to delay or prevent the development of new sites of pain.

Samarium-153 (^{153}Sm) is both a β- and a γ-ray emitter, making it suitable for combined therapy and imaging. It has a short half-life (46 hours) and, linked to ethylene diamine tetramethylene phosphonate (EDTMP) for use as a radiopharmaceutical, concentrates preferentially in skeletal metastases. Clinical reports indicate that ^{153}Sm-EDTMP can provide excellent palliation of pain in both breast[73] and prostate cancer.[74] The short half-life also makes ^{153}Sm-EDTMP suitable for repeated treatments.

Rhenium-186, an investigational radiopharmaceutical, which is also a β- and a γ-ray emitter, in complex with hydroxyethylidene diphosphonate is used therapeutically. Studies suggest encouraging clinical results with a 70% response rate.[75] Bone marrow toxicity is mild and reversible, making the compound potentially suitable for repeated administration. However, comparative studies of this agent with other therapeutic radionuclides are needed before its clinical role can be defined clearly.

Most recently the bone-seeking, α-particle-emitting radiopharmaceutical Alpharadin $^{223}RaCl_2$ (radium chloride) has been developed. In addition to effective palliation of bone pain, early results suggest an antiumor effect with declines in PSA levels in a population of patients with advanced prostate cancer.[76]

Systemic Therapy

Systemic therapy for bone metastases can be directed against the tumor cell to reduce both cell proliferation and, in consequence, the production of cytokines and growth factors. Alternatively, systemic treatment is directed toward blocking the effect of these substances on host cells. Chemotherapy, biologically targeted agents, endocrine treatments, and bone-seeking isotopes have direct antitumor effects, whereas agents such as the bisphosphonates and denosumab are effective by preventing host cells (primarily osteoclasts) from reacting to tumor products. Systemic therapy, therefore, has either direct or indirect actions.

In general, the systemic treatment for metastatic bone disease is the same as that available for other metastatic manifestations of the malignancy. Treatment must therefore be discussed according to tumor type. Breast and prostate cancers are the most important, first because there are effective (albeit palliative) systemic treatments available, and second because these two tumors represent the majority of patients with bone metastases. For a fuller discussion of systemic cancer management, the relevant site-specific chapters should be consulted.

Breast Cancer

For breast cancer, endocrine therapy is the treatment of choice for the initial treatment of metastatic disease. Exceptions to this are when visceral disease is so extensive and/or aggressive that it is inadvisable to wait 6 to 8 weeks for a possible response—for example, when there are lymphangiitic pulmonary metastases or liver metastases with compromised hepatic function. In these two situations, cytotoxic chemotherapy is the initial treatment of choice.

Hormones act predominantly on cancer cells that express high-affinity binding proteins (receptors) for estrogen and progesterone (PgR). These hormone-receptor complexes, in turn, act on the cell nucleus to mediate the specific cell response of the hormone.

Significant (>50%) tumor shrinkage (a complete or partial objective response) after endocrine treatment occurs in one-third of unselected patients but is more likely among those with either steroid-receptor-positive tumors, a long disease-free interval from diagnosis to relapse, or bone or soft tissue metastases rather than visceral disease.

Selection of specific endocrine treatment for patients is based on menopausal status. Premenopausal patients are now usually treated with a combination of tamoxifen and ovarian ablation, the latter achieved by the use of LHRH agonists, surgical bilateral oophorectomy or in some centres ovarian irradiation. For postmenopausal patients the choice of agents is large with aromatase inhibitors, tamoxifen, fulvestrant, and progestogens the most frequently used. Although in general the median duration of response to endocrine therapy is around 15 months, prolonged responses to first-line hormone treatments lasting several years are not uncommon in patients with bone metastases.

Numerous recent developments in cytotoxic and biological treatments are of relevance to the patient with metastatic bone disease. Patients with disease progressing after endocrine therapy, and those with rapidly progressive life-threatening disease or those who are known to have estrogen receptor- and progestogen receptor-negative tumors, should be considered for cytotoxic chemotherapy. This is usually combined with trastuzumab in patients with tumors overexpressing the HER2neu growth factor receptor. Objectively responding patients usually gain relief of symptoms (including bone pain) and might become able to resume their previous activities.

Responses among women with bone metastases are nearly always only partial, with a median duration of response of 9 to 12 months. The precise choice of drugs and schedule of administration to obtain the best results is not yet certain and vary from one patient or clinical problem to another. The anthracyclines (doxorubicin and epirubicin) and the taxanes (docetaxel and paclitaxel) are particularly active but at full doses are sometimes too toxic for elderly or frail patients. Chemotherapy can be especially hazardous for patients with extensive bone disease because of both poor bone marrow tolerance after replacement of functioning marrow by tumor and the effects of previous irradiation. In view of this, regimens with relatively little myelotoxicity are usually preferable. The use of hematopoietic growth factors may be required to permit chemotherapy to be administered safely.

Prostate Cancer

In prostate cancer, bone is the dominant site for metastatic disease and in many patients is the only symptomatic problem. The appearances on plain radiography are predominantly osteoblastic and because of this, radiologic response is notoriously difficult to evaluate. Nevertheless, at least 80% of prostate tumors show some degree of hormone responsiveness.

Worldwide, the luteinizing hormone-releasing hormone (LHRH) agonists are the most commonly used form of endocrine therapy, although surgical castration remains a first-line treatment in some parts of the world. Stilbestrol is no longer appropriate first-line therapy because of its feminizing effects and cardiovascular risks. The role of combined endocrine therapy causing total androgen blockade (LHRH + antiandrogen) and the timing of endocrine interventions have, and continue to be, areas of intense clinical trial investigation.

Patients with advanced prostate cancer tend to be elderly and often of poor performance status. Because of this and the presence of widespread bone involvement, their tolerance of toxic chemotherapy regimens is often poor, and this has significantly limited the use of this treatment modality. Until recently there was little evidence that cytotoxic drugs prolonged survival for patients with advanced prostate cancer. Mitoxantrone and prednisone has been shown in a randomized trial to provide better palliation of symptoms and improved quality of life compared with that achieved with prednisone alone.[77] More recently, docetaxel has been shown to be an active cytotoxic agent in endocrine-resistant prostate cancer and is able to improve median survival by about 3 months. Cautious use of this agent in appropriate patients is now recommended.[78]

Other Tumors

Skeletal morbidity is a major problem in multiple myeloma, and either widespread lytic metastases or diffuse osteopenia can occur. Around 50% of patients respond to chemotherapy, with a reduction in paraprotein levels and subjective improvement. Alkylating agents, anthracyclines, vinca alkaloids, and the corticosteroids are the most frequently prescribed first-line agents. Despite the subjective improvement that is seen, bone healing is rare, with lytic lesions persisting despite control of the disease for months or years. Survival in multiple myeloma has been shown to be improved by the selective use of high-dose chemotherapy with bone marrow or peripheral blood stem cell support, and this is part of standard first-line treatment in fit patients under the age of 65.[79] Newer agents including thalidomide and related analogs, bortezomib, and arsenic trioxide provide many more options that have transformed the clinical course of multiple myeloma in recent years into that of a chronic disease.

Bone involvement in curable malignancies is uncommon. In patients with germ cell tumors, bone involvement is an adverse prognostic feature, but despite this, cure with chemotherapy is usual. Bone involvement at diagnosis in lymphoma is relatively uncommon. When localized it does not significantly affect the prognosis in Hodgkin's disease but does carry an adverse prognosis in non-Hodgkin's lymphoma. Curative therapy is still possible, however, and there is no evidence that bone represents a "sanctuary site."

Chemotherapy is of only limited and temporary benefit in relatively chemotherapy-resistant solid tumors such as non–small cell lung cancer or melanoma. Patients with skeletal metastases from these tumors derive most benefit from local palliative radiotherapy and bisphosphonates. Alternative (and more effective) systemic treatment approaches are urgently needed for many of these maligancies. Biologic agents, especially the angiogenesis inhibitors sorafinib and sunitinib, are showing great promise in renal cell cancer, and small molecules and antibodies are being developed at a rapid pace across a range of tumors.[80]

Bisphosphonates

In the last two decades the bisphosphonates have become established as a valuable additional approach to the range of current treatments. All bisphosphonates are pyrophosphate analogs, characterized by a P-C-P containing central structure rather than the P-O-P of pyrophosphate, and a variable R′ chain that determines the relative potency, side effects, and the precise mechanism of action.[81] The P-C-P backbone renders bisphosphonates resistant to phosphatase activity and promotes their binding to the mineralized bone matrix. The structures of the commonly used bisphosphonates are illustrated in Figure 57-14.

After administration, bisphosphonates bind avidly to exposed bone mineral around resorbing osteoclasts, leading to very high local concentrations of bisphosphonate in the resorption lacunae (up to 1000 mM). During bone resorption, bisphosphonates are internalized by the osteoclast, where they cause disruption of several biochemical processes involved in osteoclast function, ultimately leading to apoptotic cell death. These include destruction of the cytoskeleton, disruption of the sealing zone at the bone surface, and loss of the ruffled border across which the hydrolytic enzymes and protons necessary for bone dissolution are normally secreted. The molecular mechanism of action of the bisphosphonates are now established, with nitrogen-containing bisphosphonates having been shown to inhibit enzymes of the mevalonate pathway, which are responsible for events that lead to the post-translational modification of a number of proteins including the small guanosine triphosphatases such as Ras and Rho.[81] Non-nitrogen-containing bisphosphonates, such as

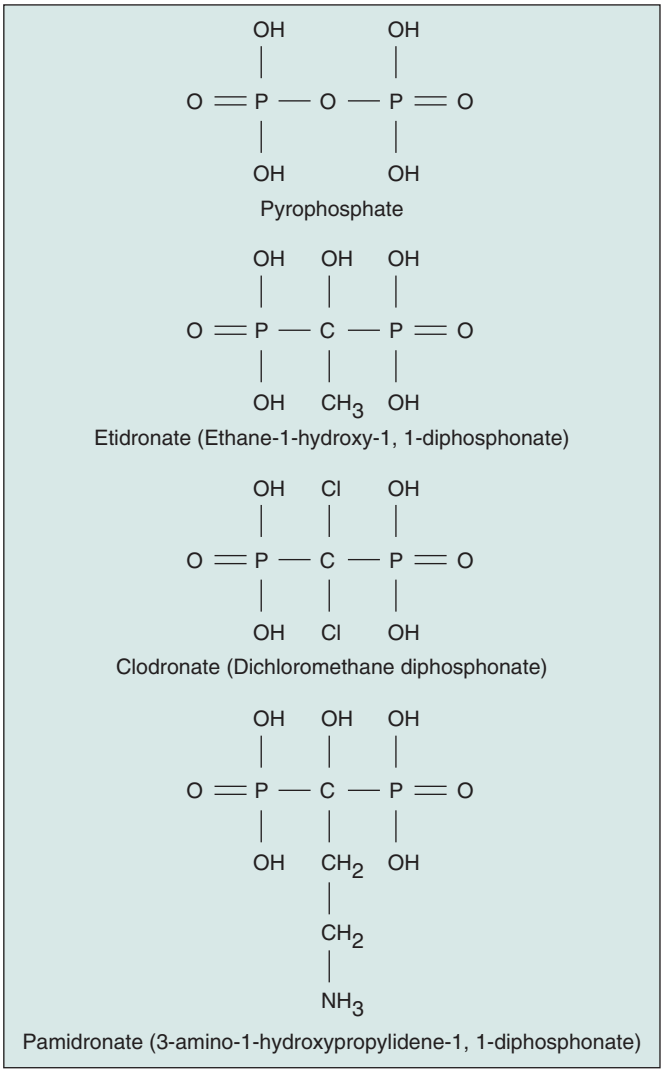


Figure 57-14 • Structural formulas of commonly used bisphosphonates in relation to pyrophosphate.

clodronate, have been found to induce osteoclast apoptosis through the generation of cytotoxic adenosine triphosphate analogs.[82] Recent studies also suggest that bisphosphonates could have direct apoptotic effects on tumor cells, and that this effect may be enhanced by combination with other anticancer agents.[83]

After intravenous administration of a bisphosphonate, approximately 25% to 40% of the injected dose is excreted by the kidney, and the remainder is taken up by bone.[84] All bisphosphonates suffer from poor bioavailability when given by mouth. They must be taken on an empty stomach, because they bind to calcium in the diet and can cause gastrointestinal toxicities such as nausea, vomiting, indigestion, and diarrhea.[85]

Irrespective of the mechanism(s) of action, bisphosphonates have been used successfully in the treatment of conditions characterized by increased osteoclast-mediated bone resorption, such as Paget's disease of bone or osteoporosis. In oncology they have become the standard treatment for tumor-induced hypercalcemia and a valuable, new form of medical therapy for bone metastases.[86]

Rationale for the Wider Use of Bisphosphonates

As indicated previously, it is now generally accepted that osteoclast activation is the key step in the establishment and growth of bone metastases. Biochemical data indicate that bone resorption is of importance not only in classic "lytic" diseases such as myeloma and breast cancer but also in prostate cancer, with values of resorption markers in the latter at least as high as those seen in breast cancer and other solid tumors.[10,53] As a result, the osteoclast is a key therapeutic target for skeletal metastases irrespective of the tissue of origin.

Bisphosphonates to Prevent Skeletal Morbidity and Relief of Bone Pain

Although radiotherapy is the treatment of choice for localized bone pain, many patients have widespread, poorly localized bone pain, whereas others experience recurrence of bone pain in previously irradiated sites. The bisphosphonates provide an additional treatment approach for the relief of bone pain across a range of tumor types, and the effects seems to be independent of the nature of the underlying tumor or radiographic appearance of the metastases, with sclerotic lesions responding similarly to lytic metastases.[87]

Additionally, based on the results of large randomized controlled trials conducted in the late 1990s, the bisphosphonates became the standard of care for the treatment and prevention of skeletal complications associated with bone metastases in patients with breast cancer and multiple myeloma. More recently, they have demonstrated benefits in patients with bone metastases secondary to other cancers including prostate cancer,[88] lung cancer,[88] and other solid tumors (Table 57-4).[89,90]

BREAST CANCER. The greatest experience with bisphosphonates is in the management of bone metastases from breast cancer, and the value of the agents is now undisputed.[91]

Oral Bisphosphonates. The absorption of bisphosphonates from the gut is poor, variable, and dramatically inhibited by food intake. To make matters worse, the absorbed fraction of oral bisphosphonates decreases even further when the absolute ingested amount is lower; thus, the more potent bisphosphonates are even less well absorbed than etidronate and clodronate. Nevertheless, both oral clodronate and ibandronate have been shown in randomized trials to have some clinical efficacy (see Table 57-4).[92,93]

Paterson and coworkers randomized 173 patients with bone metastases from breast cancer to receive either clodronate capsules, 1600 mg daily, or placebo capsules of identical appearance in addition to appropriate anticancer treatment(s).[92] In the patients who received clodronate, there was a significant reduction in skeletal morbidity (219 vs. 305 events per 100 patient years). Most of the benefit was accounted for by a reduction in hypercalcemic episodes and the incidence of vertebral fractures, with no significant effect on nonvertebral fractures, radiotherapy requirements, changes in antitumor therapy, or survival.

Oral ibandronate is the newest and most potent oral agent and is available in Europe and many other countries outside North America. A film-coated formulation of ibandronate has been developed that has been shown to produce a dose-dependent reduction, at doses that are generally well tolerated, in both urinary calcium and collagen cross-link excretion.[93] Phase III placebo-controlled trials of the oral formulation have been completed. The endpoint of a significant reduction in the proportion of patients experiencing a SRE was not met. However the skeletal morbidity rate was significantly less with ibandronate, and the investigators concluded that the activity of oral ibandronate is similar to other bisphosphonates.[94] This new oral agent has obvious attractions to both patients and health care providers, but the place of ibandronate cannot be clearly defined until comparative data with other bisphosphonates are available.

Intravenous Bisphosphonates. In the first randomized study of intravenous pamidronate, Conte and associates[95] randomized 295 patients with breast cancer and bone metastases to chemotherapy

Table 57-4 Effects of Bisphosphonates on Skeletal Morbidity: Results of Randomized Trials

Agent and Route	N	Results	Investigator
BREAST CANCER			
Clodronate 1600 mg PO vs. placebo	173	Reduced SMR 305 vs. 219 events/100 woman years ($P < 0.001$)	Paterson[92]
Pamidronate 45 mg IV vs. control	295	Increased time to bone progression 168 vs. 249 days ($P = 0.02$)	Conte[95]
Pamidronate 90 mg IV vs. placebo	382	Reduced proportion experiencing SRE 65% vs. 46% ($P < 0.001$) Delay in first SRE 7.0 vs. 13.1 months ($P = 0.0005$)	Hortobagyi[97]
Pamidronate 60 mg IV vs. control	401	Median time to skeletal progression 9 vs. 14 months ($P < 0.01$)	Hultborn[96]
Pamidronate 90 mg IV vs. placebo	374	Reduced proportion experiencing SRE 67% vs. 56% ($P = 0.027$) Delay in first SRE 6.9 vs. 10.4 months ($P = 0.049$)	Theriault[98]
Ibandronate 2/6 mg IV vs. placebo	467	Reduced SMR with 6-mg dose, 2 mg ineffective SMR 2.18 vs. 1.61 ($P = 0.03$)	Body[104]
Zoledronic acid 4 mg IV vs. placebo	227	Reduced proportion experiencing SRE 50% vs. 30% ($P = 0.003$) Reduced SMR by 43% ($P = 0.016$)	Kohno[101]
MULTIPLE MYELOMA			
Agent and Route	**N**	**Results**	**Investigator**
Clodronate 1600 mg PO vs. placebo	350	Improved 2-year progression-free survival 24% vs. 12% ($P < 0.05$)	Lahtinen[105]
Pamidronate 90 mg IV vs. placebo	392	Reduced proportion experiencing SRE 24% vs. 41% ($P < 0.001$)	Berenson[107]
Clodronate 1600 mg PO vs. placebo	614	Less skeletal morbidity and pain on progression	McCloskey[106]
MULTIPLE MYELOMA AND BREAST CANCER			
Agent and Route	**N**	**Results**	**Investigator**
Zoledronic acid 4/8 mg IV vs. pamidronate 90 mg IV	1648	Zoledronic acid (4 mg) showed clinical activity equivalent to that of pamidronate (90 mg) In breast cancer patients, 43% had a SRE with 4 mg zoledronic acid, compared with 45% with pamidronate. In myeloma, 47% of patients had a SRE with zoledronic acid and 49% with pamidronate	Rosen[102,103]
PROSTATE CANCER			
Agent and Route	**N**	**Results**	**Investigator**
Clodronate (4 × 520) mg oral vs. placebo	311	Reduction in number of SREs vs. placebo not significant (49% vs. 41%, P = NS)	Dearnaley[110]
Pamidronate 90 mg IV vs. placebo	378	Number of SREs equal in pamidronate and placebo arms, $P = 1.0$	Small[112]
Zoledronic acid 4/8 mg vs. placebo	643	Proportion of patients experiencing at least one SRE during the study was 25% lower in the zoledronate arm than in the placebo arm ($P = 0.021$)	Saad[88,113]
OTHER TUMOR TYPES			
Agent and Route	**N**	**Results (Bisphosphonate vs. Placebo/Control)**	**Investigator**
Zoledronic acid 4/8 mg vs. placebo	773	Significant delay to time of first skeletal event in Zoledronic acid arm compared with placebo ($P = 0.023$) Significant reduction in proportion of patients having an event (47% vs. 38%, $P = 0.039$)	Rosen[89]

SRE, skeletal related event; SMR, skeletal morbidity rate.

with or without intravenous pamidronate, 45 mg every 3 weeks (a dose intensity of pamidronate that is now considered suboptimal). Blinded, extramural review of serial radiographs was performed and identified a 48% increase in the median time to progression in bone in favor of the patient group who received pamidronate (249 vs. 168 days, $P = 0.02$). The other major endpoint of this trial was bone pain. A marked improvement in pain was seen more often in the pamidronate group (44% vs. 30%, $P = 0.025$), indicating that intravenous pamidronate adds to the symptom relief achieved by chemotherapy alone. Similar results were reported in a Scandinavian trial, in which 401 patients receiving chemotherapy for advanced breast cancer were randomly allocated to receive either an intravenous pamidronate infusion (60 mg every 4 weeks) or a placebo infusion of the same dose intensity of pamidronate that was given in the Conte study.[96]

Subsequently, the results of two double-blind, placebo-controlled trials of 90 mg pamidronate infusions every 3 to 4 weeks in addition to cytotoxic or endocrine treatments for patients with breast cancer and lytic bone metastases established bisphosphonate treatment as the standard of care in breast cancer.[97,98] These two studies were of similar design, with the exception of the systemic anticancer treatment at study entry. As in all subsequent bisphosphonate trials the primary endpoint of these studies was the influence of pamidronate on the number of patients experiencing SREs as well as the time to first SRE and the rate of SREs as determined by either a simple annual rate or more complex multiple event analysis techniques. SREs were defined as

- Occurrence of pathologic long bone and vertebral fractures
- Development of spinal cord compression
- Need for radiation for pain relief or to treat or prevent pathologic fractures or spinal cord compression
- Requirement for surgery to bone
- Episodes of hypercalcemia of malignancy

In the chemotherapy study,[97] 382 patients received either pamidronate 90 mg or placebo every month in combination with systemic chemotherapy. The median time to the SRE was significantly longer in the pamidronate group than in the placebo group (13.1 vs. 7.0 months, $P = 0.005$), and the proportion of patients in whom any SRE occurred was significantly lower (43% vs. 56%, $P = 0.008$). Benefits were maintained for at least 2 years. Pain, analgesic use, and Eastern Cooperative Oncology Group (ECOG) performance status were monitored throughout the study period. Because there was inevitably a tendency for the underlying cancer to progress during the study period, there was an overall deterioration in mean performance status, pain, and analgesic consumption. The deterioration, however, was significantly less in the pamidronate group for all of these endpoints. Quality of life was also better maintained in the pamidronate group. Survival was similar in other treatment groups.

In the endocrine study, 374 patients were randomized to receive hormone therapy with pamidronate 90 mg or placebo every month.[97] As in the chemotherapy study, pamidronate reduced the number and rate of SREs. The time to first SRE (excluding hypercalcemia of malignancy) was 6 months for the placebo group and 10 months for those receiving pamidronate ($P < 0.049$). The benefits of pamidronate were slower to appear than in the chemotherapy study, but again the effect was maintained for at least 2 years. The effects on pain and analgesic consumption were even more clearly evident in this study. Again, there was no difference in survival by treatment group.

Zoledronic acid is the most potent bisphosphonate available. A phase I study of 30 patients with hypercalcemia indicated that dose levels as low as 0.02 mg/kg (1–2 mg total dose) were effective in achieving normocalcemia.[99] Following a dose-finding, phase II study of zoledronic acid at doses of 0.5 g, 2 g, and 4 mg zoledronic acid given on a 4-weekly schedule, 4 mg zoledronic acid was selected for phase III evaluation.[100] A placebo-controlled trial of zoledronic acid was performed in Japan.[101] In this study, Kohno and coworkers randomly assigned women with bone metastases from breast cancer to treatment with zoledronic acid ($n = 114$) or placebo ($n = 114$) every 4 weeks. After 1 year, the percentage of patients with at least one SRE (excluding hypercalcemia of malignancy) was significantly reduced by 20% by zoledronic acid (29.8% vs. 49.6% for placebo; $P = 0.003$). Zoledronic acid also significantly delayed the time-to-first SRE ($P = 0.007$) and reduced the risk of SREs by 41% in multiple event analysis ($P = 0.019$) compared with placebo.

Elsewhere in the world zoledronic acid was compared to pamidronate in a randomized, double-blind, phase III trial.[102] The trial was designed as a noninferiority trial, in which the primary efficacy variable was the proportion of patients experiencing at least one SRE. A group of 1130 patients with advanced breast cancer and at least one metastatic bone lesion were randomized to receive either 4 mg zoledronic acid or 8 mg zoledronic acid via a short intravenous infusion, or 90 mg pamidronate via a 2-hour infusion. Treatments were administered every 3 to 4 weeks. Initially, zoledronic acid was administered as a 5-minute infusion in 50 mL of 0.9% saline or 5% dextrose. This was amended to a 15-minute infusion in 100 mL of saline or dextrose because of concerns over renal toxicity. Similarly, the 8-mg dose of zoledronic acid was reduced to 4 mg because of continuing concerns over renal safety.

After 25 months of follow-up, the reduction in the overall proportion of patients with a SRE and the skeletal morbidity rate were similar in patients receiving zoledronic acid and pamidronate. However, zoledronic acid 4 mg reduced the risk of developing skeletal complications (including hypercalcemia of malignancy) as determined by multiple event analysis by an additional 20% compared with pamidronate in the overall population ($P = 0.025$).[103] Thus, the risk of skeletal complications with zoledronic acid is approximately one-half the rate experienced in the prebisphosphonate era (Fig. 57-15). All markers of bone resorption or formation decreased from baseline to the end of the study, but at all time points the urinary marker of bone resorption NTX was significantly less in the zoledronic acid 4-mg group than in the pamidronate group. Median overall survival was similar at approximately 2 years in the study groups. The most common adverse events were bone pain, nausea, fever, and fatigue, and as with the other adverse effects, they occurred generally with a similar frequency in each group. The incidence of renal dysfunction among the patients receiving 4 mg zoledronic acid (given on the 15-minute schedule) was indistinguishable from that for the pamidronate patients.

Ibandronate is another highly potent amino-bisphosphonate that is licensed in Europe for the treatment of hypercalcemia of malignancy, the treatment of metastatic bone disease, and the prevention

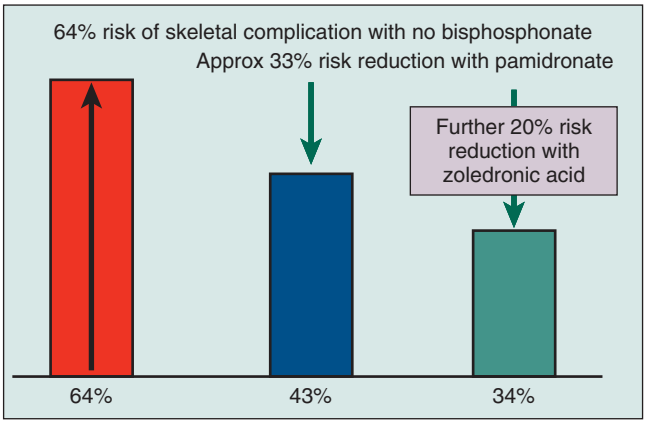


Figure 57-15 • Incremental improvement in the risk of skeletal-related events with use of pamidronate and more recently zoledronic acid in the treatment of bone metastases from breast cancer.

and treatment of osteoporosis. A phase III placebo-controlled trial of monthly infusions in breast cancer has shown a significant reduction in skeletal-related morbidity with ibandronate 6 mg.[104] Additionally, improvements in pain and quality of life were clearly demonstrated at this dose. However, as with the oral formulation, the clinical value of intravenous ibandronate is unclear until comparative trials with established bisphosphonates are completed.

MULTIPLE MYELOMA. Multiple myeloma is typically characterized by a marked increase in osteoclast activity and proliferation. This excessive resorption of bone can be detected histomorphometrically at an early phase in the development of the disease, and this itself could, through the release of interleukin-6 by the osteoclasts, play a contributory role to the growth of myeloma cells in bone. Bisphosphonates could thus be of great benefit in these patients.

ORAL BISPHOSPHONATES. In a randomized, placebo-controlled trial of 350 patients with newly diagnosed myeloma, it was demonstrated that 2.4 g of clodronate daily for 2 years results in a significant reduction in the proportion of patients developing progression of osteolytic bone lesions (24% vs. 12%). There was only a mild, albeit significant, effect on the incidence of bone pain, however, and no effect on the occurrence of fractures or overall survival.[105] Another randomized, placebo-controlled trial of 614 patients evaluated the efficacy of 1600 mg daily of clodronate given from the time of diagnosis. Treatment with clodronate was associated with a 50% decrease in the proportion of patients with severe hypercalcemia (5.1% vs. 10.1%, $P = 0.06$) and a reduction in reported nonvertebral fractures (6.8% vs. 13.2%, $P = 0.04$). Additionally, a 30% reduction in the number of vertebral fractures (80 vs. 146, $P = 0.012$) was observed in a subset of patients with serial spine radiograms available for review.[106]

INTRAVENOUS BISPHOSPHONATES. In the last 10 years, intravenous bisphosphonates have become routine clinical management for most patients with multiple myeloma. This followed the very clear results demonstrated in a 21-month placebo-controlled trial of pamidronate 90 mg conducted in 392 patients.[107] The proportion of patients developing SRE(s) was significantly lower in the group receiving pamidronate than the group receiving placebo (24% vs. 41%, $P < 0.001$). Quality-of-life scores, performance status, pain scores, the incidence of pathologic fractures, and the need for radiotherapy were all favorably influenced by pamidronate therapy.

Zoledronic acid has also been evaluated in multiple myeloma; 450 patients with advanced myeloma were included in a randomized trial comparing zoledronic acid with pamidronate.[102] No significant differences between the two agents were identified. Of the patients treated with zoledronic acid 4 mg, 50% experienced one or more SREs, compared with 54% in the group receiving pamidronate. The risk of an SRE was 7% lower with zoledronic acid, but this difference was not statistically significant.[103]

Intravenous ibandronate has been investigated in a randomized trial; however, the 2-mg dose chosen was unfortunately inactive and not statistically different from placebo.[108] It is now known that a dose of ibandronate 6 mg is required to reduce skeletal morbidity from metastatic bone disease.[104]

PROSTATE CANCER. Bisphosphonates have been shown to reduce biochemical markers of bone resorption in patients with osteoblastic bone lesions that are associated with advanced prostate cancer. Additionally, several phase II studies have assessed bone pain and analgesic use with some benefit in these acute endpoints.[86] However, these trials were statistically underpowered to detect significant effects on skeletal complications, and the results were not sufficiently convincing to lead to either regulatory approval for or widespread use of bisphosphonates for metastatic bone disease in prostate cancer. Furthermore, until recently, randomized, placebo-controlled trials of bisphosphonates had failed to demonstrate a significant reduction in skeletal complications from bone metastases in patients with advanced prostate cancer.

ORAL BISPHOSPHONATES. In a study of 57 patients with hormone-refractory prostate cancer and bone pain at study entry, Smith[109] concluded that etidronate had no significant effects on pain levels or analgesic usage over and above placebo. The Medical Research Council in the United Kingdom performed a phase III trial of oral clodronate (Loron, 1040 mg twice daily) in 311 men with metastatic bone disease from prostate cancer.[110] A slight reduction in the proportion of patients receiving clodronate who experienced a SRE, an improvement in time to progression and increased median survival were observed, but none of these differences was statistically significant.

INTRAVENOUS BISPHOSPHONATES. A more recent clinical trial involving 208 patients investigated both pain and analgesic usage. In this study, intravenous clodronate was added to a background treatment of mitoxantrone and prednisolone. The study also included objectively measurable skeletal complications as clinical endpoints. No significant differences between clodronate and placebo were seen.[111]

Pamidronate has also been studied in 236 patients with prostate cancer and bone metastases treated with intravenous pamidronate (90 mg) or placebo every 3 weeks for 9 months. This trial assessed bone pain as the primary endpoint and included an assessment of SREs as a secondary endpoint. Patients in this trial had very advanced disease (median baseline PSA = 97.8 ng/mL in the pamidronate group), very high levels of bone resorption, and substantial bone pain at study entry. Pamidronate did not reduce the incidence of SREs and had only a slight effect on bone pain.[112]

Despite the failure of all other bisphosphonates, zoledronic acid was investigated in patients with advanced prostate cancer to determine whether the increased potency of this compound would translate into improved clinical benefit. In this study, 643 patients with hormone-refractory prostate cancer and documented bone metastases were randomized to receive either placebo or zoledronic acid at a dose of 4 mg or 8 mg administered every 3 weeks.[88] In the 8-mg arm, the dose was reduced by a protocol amendment to 4 mg because of concerns over renal safety, and conclusions on the efficacy of this cohort are difficult to make. Zoledronic acid was significantly more effective than placebo across all primary and secondary endpoints. The zoledronic acid 4 mg treatment group experienced significantly fewer SRE(s) (33% vs. 44% with placebo; $P = 0.021$). Furthermore, there were consistent reductions in the proportion of patients with each type of skeletal complication, including nonvertebral fractures. Zoledronic acid also prolonged the time to first skeletal complication by more than 4 months ($P = 0.011$). Zoledronic acid 4 mg remained superior to placebo when fractures were excluded, indicating that the beneficial effect was not simply as a result of the prevention of osteoporotic fractures. Using the Andersen-Gill multiple-event analysis, it was calculated that zoledronic acid 4 mg reduced the overall risk of skeletal complications by 36%.[113] Zoledronic acid reduced bone pain at all time points. Despite the favorable effects on skeletal morbidity, however, there were no significant effects on disease-related endpoints such as time to progression and survival. Treatment was generally well tolerated, and in particular the risk of renal function deterioration in patients treated with zoledronic acid 4 mg via a 15-minute intravenous infusion was found to be similar to that of placebo-treated patients. The only adverse events that occurred at increased frequency with zoledronic acid were fatigue, anemia, myalgia, and pyrexia.

OTHER TUMORS. Until recently there had only been anecdotal reports of the use of bisphosphonates in other tumors associated with bone metastases. The pathophysiology of bone metastases is broadly similar in all tumor types, however, and bisphosphonates could thus be expected to be of value in preventing skeletal morbidity, especially

if metastatic bone disease was a patient's dominant site of disease. As part of the development program for zoledronic acid, a phase III randomized, placebo-controlled trial was performed in the management of bone metastases from solid tumors other than breast or prostate cancer.[89] The study found that 4 mg of zoledronic acid significantly reduced the proportion of patients with at least one SRE (39% vs. 48%, $P = 0.039$) and significantly prolonged the time to the first SRE compared with placebo (314 days vs. 168 days, respectively, $P = 0.021$). This is a particularly important result in a population of patients with a very short median survival time (6 months). Overall, zoledronic acid reduced the risk for SRE(s) by about 30% (hazard ratio 0.693 vs. placebo, $P = 0.003$). Of particular note was a 58% reduction in the risk of an SRE in the subgroup of patients with renal cell cancer accompanied by an apparent increase in time to progression and overall survival, albeit in an unplanned subset analysis.[90]

Optimum Use of Bisphosphonates in Metastatic Bone Disease

Criteria need to be determined regarding when in the course of metastatic bone disease bisphosphonates should be started and stopped.[114,115] Because of the logistics and cost of delivering monthly intravenous infusions for all patients with metastatic bone disease, certain empiric recommendations on who should receive treatment are needed.[116] These should take into account the underlying disease type and extent, the life expectancy of the patient, the probability of the patient experiencing a SRE, and the ease with which the patient can attend for treatment (or be treated by a domiciliary service).

Consensus guidance recommendations indicate that all patients with multiple myeloma[116] and radiologically confirmed bone metastases from breast cancer[117] should receive bisphosphonates from the time of diagnosis and continued indefinitely. The development of an SRE is not necessarily a sign of treatment failure or signal to stop treatment; evidence is now available to confirm that bisphosphonates delay second and subsequent complications, not just the first event. However, a recent report suggested that switching to zoledronic acid may be an appropriate option in breast cancer patients in whom pamidronate or clodronate therapy proves unsatisfactory. Clemons and colleagues conducted a phase II clinical trial involving 31 patients with breast cancer who had experienced progressive bone metastasis or SREs while on pamidronate or clodronate therapy. Subjects were switched to monthly administration of zoledronic acid 4 mg. After 8 weeks, 13 of 31 subjects (42%) reported a reduction in pain ($P < 0.001$). The switch to zoledronic acid was also associated with significant reductions in urinary markers of bone turnover ($P = 0.008$).[118]

Bisphosphonate treatment—specifically zoledronic acid—is also appropriate for patients with endocrine-resistant metastatic bone disease from prostate cancer. Patients with other tumors and symptomatic metastasis to bone should be considered for bisphosphonate treatment if bone is the dominant site of metastasis, especially if the prognosis is reasonable (longer than 6 months). Patients with renal cell cancer particularly seem to benefit from treatment.

Despite the obvious clinical benefits of bisphosphonates, it is clear that only a proportion of events is prevented, and some patients do not experience a skeletal event despite the presence of metastatic bone disease. It is currently impossible to predict whether an individual patient needs or will benefit from a bisphosphonate. Overall, bisphosphonates reduce the frequency of skeletal events by 25% to 40%; however, bisphosphonates are a relatively costly additional intervention in cancer care that is now potentially applicable to a very large proportion of patients with advanced malignancy. The cost effectiveness of routine long-term treatment has been questioned, and prioritization of bisphosphonate use is essential.[119,120]

A report on the use of the bone resorption marker NTX suggests that biochemical monitoring could be useful to identify patients at high risk of skeletal complications. In this study of 121 patients with bone metastases, monthly measurements of urinary NTX were made during treatment with a range of bisphosphonates.[121] All SREs, hospital admissions for control of bone pain, and deaths during the period of observation were recorded. NTX was strongly correlated with the number of SREs and/or deaths ($P < 0.001$). Patients with NTX values above 100 nmol/mmol creatinine were many times more likely to experience an SRE or death than those with NTX below this level ($P < 0.01$). Thus, a more cost-effective use of bisphosphonates, particularly in patients with additional extensive visceral metastases or solid tumors associated with a short life expectancy, might be to reserve them until patients have raised NTX levels, and to adjust the dose and schedule to maintain a normal rate of bone resorption. Randomized trials to assess this approach are planned.

Uncertainty remains about the appropriate duration and schedule of treatment. Bone marker–directed therapy is under evaluation in randomized clinical trials, and the value of maintenance therapy after 1 to 2 years of treatment may become clear from the Optimize trial ongoing in the United States. Long-term, full-dose monthly intravenous treatment is associated with the development of osteonecrosis of the jaw (a hitherto rarely encountered problem characterized by painful bone destruction, secondary infection, and delayed healing in the mandible and or maxilla).[122] The risk of osteonecrosis of the jaw is related to duration of treatment at around 1% per year on therapy.[123] Good dental hygiene and pretreatment restorative treatment are recommended to reduce the risk of this unpleasant complication of treatment.[124]

New Targeted Therapies in the Treatment of Metastatic Bone Disease

As our understanding of the signaling mechanisms between bone cells themselves and bone cells and tumor cells increases, several targeted agents have entered clinical development. These include inhibition of RANKL, cathepsin K (an osteoclast-derived enzyme that is essential for the resorption of bone), PTHrP, and Src (a key molecule in osteoclastogenesis). Of all these, inhibition of RANKL seems the most promising.

Denosumab is a fully human monoclonal antibody that binds and neutralizes RANKL with high affinity and specificity, thereby inhibiting osteoclast function and bone resorption. Denosumab could potentially be used to treat bone loss caused by bone metastases, multiple myeloma, or osteoporosis. Following a single subcutaneous dose, denosumab caused rapid and sustained suppression of bone turnover in postmenopausal women with low bone mass,[125] as well as in multiple myeloma and breast cancer patients.[126] A subsequent dose-finding phase II study has defined a dose and schedule for phase III development of 120 mg four times weekly. Currently a broad program in metastatic disease, treatment-induced bone loss, and bone metastasis prevention studies are underway.

Protecting the Skeleton

Prevention of Bone Metastases

Bone is the most frequent site of distant relapse, accounting for around 40% of all first recurrences.[1] In addition to the well-recognized release of bone cell-activating factors from the tumor, it is now appreciated that release of bone-derived growth factors and cytokines from resorbing bone can both attract cancer cells to the bone surface and facilitate their growth and proliferation.[127] Inhibition of bone resorption could therefore have an effect on the development and progression of metastatic bone disease and is an adjuvant therapeutic strategy of potential importance.

Encouraging animal studies with a variety of animal tumor models and a range of bisphosphonates have shown inhibition of bone metastasis development and a reduction in tumor burden within bone.[128] More recently, several clinical trials have been reported using the relatively low-potency oral bisphosphonate, clodronate. In the largest study, 1079 women with primary operable breast cancer were randomized to receive either clodronate 1600 mg daily or placebo for 2

years in addition to standard adjuvant systemic treatment. With a median follow-up time of 5 years, a modest reduction in the frequency of bone metastases in the patients treated with clodronate (63 [12%] vs. 80 [15%] patients) was seen.[129] There was no significant effect on non-bone recurrence (112 [21%] vs. 128 [24%] patients), but patients randomized to the clodronate arm had a higher probability of survival (82% vs. 77%, $P = 0.047$).

In a second study, Diel and colleagues[130] studied 302 patients with breast cancer selected on the basis of immunocytochemical detection of tumor cells in the bone marrow, a known risk factor for the subsequent development of distant metastases. Patients received appropriate adjuvant chemotherapy and endocrine treatment. The incidence of osseous metastases was significantly lower in the clodronate group, and there was also a large, somewhat unexpected, reduction in the incidence of visceral metastases in the clodronate group. Survival was significantly extended. These results have subsequently been updated and show similar results, although the striking effect on extraskeletal visceral relapse is no longer statistically significant.[131] A third study produced conflicting results; the overall 5-year survival was significantly lower in the clodronate group (70% vs. 83%, $P = 0.009$). although there were some prognostic imbalances favoring the control group that may explain this unexpected result.[132]

A definite adjuvant role for bisphosphonates will require the results from much larger randomized studies. The National Surgical Adjuvant Breast Project has completed accrual ($n = 3300$) to a placebo-controlled trial of oral clodronate in stage I to III breast cancer in an attempt to resolve the value or otherwise of adjuvant clodronate. Similarly a large trial of adjuvant zoledronic acid ($n = 3360$) in stage II/III breast cancer has completed accrual. First efficacy results from these studies are not expected before 2008. It is hoped that the added potency of zoledronic acid might have beneficial effects, not only through the inhibition of bone resorption, but also through direct effects on tumor cells in the bone marrow. There is increasing evidence, from a range of cell line and animal model experiments, that zoledronic acid can inhibit tumor cell adhesion and invasion.[133] Additionally, zoledronic acid promotes apoptosis both directly and, more importantly, a schedule-dependent synergy with chemotherapy.[134] These effects are mediated through the mevalonate pathway, using the same molecular pathway that aminobisphosphonates exploit to inhibit osteoclast function. Finally, there are experimental data from animal models indicating that zoledronic acid can suppress angiogenesis.[135]

Effects of Cancer Treatments on Skeletal Health

There are now increasing numbers of long-term survivors from cancer who have received combination chemotherapy, radiotherapy, and hormonal cancer treatment. Many of these individuals are at increased risk of osteoporosis, largely because of the endocrine changes induced by treatment. There might also be clinically relevant, direct effects of cytotoxic drugs on bone. Cancer treatment-induced bone loss is a particularly important long-term problem for women with breast cancer and men receiving ADT.[136] Peak bone mass minus the bone loss associated with age and estrogen deficiency are the main determinants of osteoporotic fracture risk. However, other factors, including genetics, lifestyle, concomitant medication, and nutrition, influence the risk for bone loss.

Bone Loss in Breast Cancer

Cancer treatment-induced bone loss is an increasingly recognized complication in women receiving long-term estrogen-reducing therapies. Estrogen is known to be critical in the maintenance of normal bone mass in women. After menopause a reduction in bone mineral density (BMD) occurs, with the loss most pronounced during the first 3 years, when the rate can be as high as 5% annually, before reducing to a rate of about 0.5% annually thereafter. In the adjuvant setting, all third-generation aromatase inhibitors have demonstrated increased loss of BMD, which may lead to osteoporosis and skeletal complications.[136] In fact, spinal function is negatively affected by bone loss regardless of detectable fractures. Compared with naturally occurring bone loss, aromatase inhibitor-associated bone loss may result in greatly increased BMD loss at 1 year, with rates averaging 5% to 6% in the immediate postmenopausal period.[136]

Several clinical trials have demonstrated increased fracture rates in postmenopausal women with breast cancer receiving aromatase inhibitors.[137] However, a significant proportion of this excess rate of fractures may be due to the absence of the bone-protective effects of tamoxifen. Tamoxifen is known to have a modest estrogenic effect on bone, at least in postmenopausal women, and placebo-controlled trials, for instance in the breast cancer prevention setting, have shown a modest reduction in fracture incidence compared with placebo. Furthermore, in a study of breast cancer patients who received either letrozole or placebo as extended adjuvant therapy, although more patients in the letrozole group had fractures after 5 years, the difference did not reach significance.[138]

A few studies have evaluated women with breast cancer and a treatment-induced premature menopause. Saarto and colleagues[139] studied the effect of clodronate 1600 mg in 148 premenopausal women receiving adjuvant chemotherapy for breast cancer. They observed that rapid bone loss occurred in the women who became amenorrheic after chemotherapy (6% and 2% losses at 2 years in the spine and hip, respectively). Among those receiving clodronate, however, the bone effects of chemotherapy-induced premature menopause were attenuated (2% loss and 1% gain at 2 years in the spine and hip, respectively). In a comparison of risedronate with placebo in a postmenopausal group of patients receiving tamoxifen, Delmas and associates[140] observed an approximate 2.5% increase in BMD at the lumbar spine and femoral neck in the risedronate group compared with the group receiving placebo.

Intravenous bisphosphonate administration is used widely in oncology in the treatment of metastatic disease and could be an attractive option for preventing bone loss in a cancer population. Among patients with breast cancer, 6-monthly zoledronic acid has also been shown to reverse the bone loss induced by a combination of the LHRH analog goserelin plus further estrogen suppression with anastrozole. In this study, the mean loss of bone in the lumbar spine over 3 years in the absence of a bisphosphonate was 17%. However, the bone loss was abrogated by administration of 6-monthly zoledronic acid.[141]

In older postmenopausal women the strategy of immediate 6-monthly zoledronic acid alongside aromatase inhibitor therapy has been compared with initiation of bone protection treatment if osteoporosis or significant bone loss occurs on treatment. The difference in lumbar spine BMD at 1 year was approximately 5%.[142]

Bone Loss in Prostate Cancer

Many men with prostate cancer are at risk of developing osteoporosis, largely because of the ADT they receive for their cancer. ADT may be achieved either by bilateral orchiectomy or, increasingly, by use of a gonadotropin-releasing hormone agonist. These treatments are being introduced earlier and earlier in the course of the disease with the result that men may experience many years of androgen suppression. ADT results in substantially reduced serum concentrations of testosterone (to less than 5% of normal level) and estrogen (to less than 20% of normal level).

It might be expected that androgen deprivation would lead to increased bone loss and increased fracture rate. As yet there seem to have been no large prospective studies of the relationship between fracture rate and ADT, but retrospective studies indicate a significantly increased fracture rate with an estimated 10-year probability of fracture at around 40%.[143] As the potential scale of the problem is being realized, attention is not only focusing on measuring bone density in such patients to assess those at risk, but also on therapeutic options such as bisphosphonates to prevent or treat

therapy-related bone loss in prostate cancer. Pamidronate given on a 3-monthly schedule has been shown to prevent loss in BMD in patients with locally advanced prostate cancer.[144] A multicenter prospective study has evaluated the potent bisphosphonate, zoledronate, in locally advanced or recurrent prostate cancer.[145] At 1 year, in the zoledronic acid arm, BMD increased by 5.3% at the lumbar spine and 1.1% in the total hip. In the placebo arm the BMD decreased by 2% in the lumbar spine and 2.8% in the total hip.

COMPLICATIONS OF BONE METASTASES

Bone metastases cause considerable morbidity: pain, impaired mobility, hypercalcemia, pathologic fracture, spinal cord or nerve root compression, and bone marrow infiltration. In two large randomized trials that included patients with breast cancer and multiple myeloma receiving chemotherapy, the mean skeletal morbidity rates (number of skeletal events per year) in the absence of bisphosphonates were 3.5 and 2.0, respectively, indicating that a skeletal event occurs in metastatic bone disease from breast cancer on the average of every 3 to 4 months and in multiple myeloma every 6 months.[97,107] Despite the clinical importance of metastatic bone disease and the huge expenditure on medical care for skeletal complications, however, there has until recently been relatively little thought given as to how best to coordinate clinical management and deliver optimum care for patients with bone metastases.

Extensive infiltration of the bone marrow by metastatic disease causes leukoerythroblastic anemia and pancytopenia predisposing to infection and hemorrhage. Radiotherapy, often needed for the treatment of bone metastases, can exacerbate this problem, which in turn can compromise the ability to give chemotherapy effectively. Animal experiments have shown that cytotoxic drugs can interfere with osteoblastic function and new bone formation, but the clinical significance of these findings is unknown. Other iatrogenic factors might also aggravate morbidity from bone metastases including corticosteroids and endocrine ablation.

Bone Pain

Bone pain is the most common type of pain from cancer and a significant problem in both hospital and community practice. Pain is usually the presenting symptom and is caused by a variety of factors, including periosteal stretching, compression or infiltration of nerve roots, reflex muscle spasm, and the local effects of cytokines. Features of bone pain are that it is often poorly localized, has a deep, boring quality that aches or burns, and is accompanied by episodes of stabbing discomfort. It is often worse at night, being little helped by sleep and not necessarily relieved by lying down. There is often disturbance of the highly innervated periosteum—possibly giving this pain its neurogenic-like qualities and adding to its intractability.

Spinal instability is the cause of back pain in 10% of patients with cancer.[146] This instability can cause excruciating pain that is mechanical in origin. The patient is comfortable only when lying still, and any movement reproduces severe pain. Consequently, the patient might not be able to sit, stand, or walk. Because the pain is mechanical in origin, radiation therapy or systemic treatment cannot help; the only solution is stabilization of the spine. Stabilization requires major surgery, with risks of significant morbidity and mortality, but with careful selection of patients, excellent results can be obtained.

Hypercalcemia of Malignancy

Hypercalcemia (see also Chapter 48) is another emergency associated with metastatic bone disease. Its clinical features include nausea, vomiting, dehydration, and confusion. Although malignant hypercalcemia is usually associated with demonstrable bone metastases, this is not always the case. Hypercalcemia causes a number of signs and symptoms, which vary considerably from patient to patient. These are often nonspecific, affecting many systems in the body, and can be mistaken for symptoms of the underlying cancer or associated treatment if there is not an astute awareness of the possibility of hypercalcemia. If untreated, a progressive rise in serum calcium leads to deterioration in renal function and level of consciousness. Death ultimately ensues as a result of cardiac arrhythmias and renal failure.

It is now clear that various mechanisms are involved in the pathogenesis of malignant hypercalcemia. These include increased bone resorption (osteolysis) and systemic release of humoral hypercalcemic factors. Bone metastases are common but not invariably present. In some tumors, such as squamous cell cancers, humoral mechanisms are dominant, increasing both renal tubular calcium reabsorption and phosphate excretion. In others—multiple myeloma and lymphoma, for example—osteolysis predominates, whereas in breast cancer both osteolysis and humoral mechanisms seem to be important.

Doubt about the etiology of hypercalcemia in patients with cancer is unusual, but nonmalignant causes must be considered, particularly in the absence of metastases. In the community, hyperparathyroidism is the most common cause of hypercalcemia and may be encountered also in patients with cancer. Measurement of PTH using a modern, specific radioimmunoassay is worthwhile if there is any doubt about the diagnosis; levels of PTH tend to be low or undetectable in malignancy and inappropriately high in hyperparathyroidism.

Intravenous bisphosphonates, in conjunction with rehydration, are now established as the treatment of choice for hypercalcemia. Approximately 70% to 90% of patients will achieve normocalcemia, resulting in relief of symptoms and improved quality of life. Zoledronic acid is the most effective bisphosphonate for the acute treatment of this metabolic emergency.[147]

Pathologic Fractures

Metastatic destruction of bone reduces its load-bearing capabilities, resulting initially in trabecular disruption and microfractures and, subsequently, in total loss of bony integrity. Rib fractures and vertebral collapse are the most common occurrences, resulting in loss of height, kyphoscoliosis, and a degree of restrictive lung disease. The most severe disability, however, is caused by fracture of a long bone or epidural extension of tumor into the spine.

The incidence of pathologic fracture in patients with bone metastases is somewhat uncertain and is dependent on whether rib and vertebral fractures are included and the method of evaluation. In recent series in which regular skeletal surveys were performed the annual risk of a pathologic fracture (in the absence of bisphosphonates) was between 20% in prostate cancer[85] and 40% in breast cancer.[97] Not all of these fractures are symptomatic, and undoubtedly some are due to treatment-induced osteoporosis rather than metastatic infiltration, but nevertheless structural damage to bone is clearly extremely common in metastatic bone disease. Paterson and colleagues,[92] who systematically reviewed serial radiographs in patients participating in a clinical trial of oral clodronate, showed that a woman with bone metastases from breast cancer can expect to experience an average of 1.3 vertebral and 0.4 nonvertebral fractures a year.

The probability of developing a pathologic fracture increases with the duration of metastatic involvement and is therefore, somewhat paradoxically, more common in those patients with bone-only disease who have a relatively good prognosis. A retrospective analysis of 859 patients with bone metastases from breast cancer showed that those with bone-only disease had almost a fourfold increase in the incidence of subsequent pathologic long-bone fractures compared with patients who also had concomitant liver metastases. This finding was attributed to the different survival outcomes between the two groups; the median survival from diagnosis of bone metastases for patients with bone-only disease was 2.2 years, compared with 5.5 months for those with concomitant liver disease.[148] The study also showed that scintigraphic evidence of metastases in the femora and humeri at the

time of diagnosis significantly predicted an increased risk of future fractures.

Because the development of a fracture is so devastating to a patient with cancer, increased emphasis is now being placed on attempts to predict metastatic sites at risk of fracture and the use of prophylactic surgery and long-term administration of bisphosphonates to reduce fracture risk. Assessment of patients with symptomatic bone metastases by a specialist orthopedic and/or spinal surgeon should be a much more frequent component of multidisciplinary management than has been the case until now.

Fractures are common through lytic metastases and weight-bearing bones, the proximal femora being the most commonly affected sites. Damage to both trabecular and cortical bone are structurally important, but it is the relevance of cortical destruction that is most clearly appreciated. Several radiologic features that could predict imminent fracture have been identified. Risk factors that have been taken into account include pain, the anatomic site of a lesion, its radiologic characteristics, and its size. Although intensity of pain, which is difficult to quantify, is not clearly associated with fracture risk, pain that is exacerbated by movement seems to be an important factor in predicting impending fracture. Presumably, such functional pain indicates diminution in the mechanical strength of a bone and in one series was followed invariably by fracture.

As far as radiologic appearances are concerned, there is a general consensus that lytic lesions carry a much higher risk of fracture than either mixed or osteosclerotic lesions. Accordingly, a particularly high fracture rate is found in association with metastases from lung cancer. Given the poor prognosis of this tumor, however, such fractures rarely lead to prolonged disability. By contrast, in breast cancer, which follows a much more protracted course, pathologic fracture is a major cause of prolonged disability.

Radiologic assessment also yields information about the size of a lesion and the extent to which the bone is destroyed. When less than two thirds of the diameter of a long bone is affected, pathologic fracture is relatively unusual but above this limit the fracture rate increases markedly, with an incidence of approximately 80% for such lesions. A practical scoring system incorporating anatomic, radiographic, and symptom-related factors has been described to give valuable guidance in the selection of patients for prophylactic fixation.[149]

Prophylactic internal fixation is usually the treatment of choice for such lesions, followed by radiotherapy to inhibit further tumor growth and avoid further bone destruction. It is easier to stabilize a bone while it is still intact, and the rehabilitation and convalescence are shorter and easier. Providing the lesion is irradiated, there is no evidence to suggest that surgery increases the risk of disseminating tumor cells either locally or into the circulation. Indeed, there is some experimental evidence that pathologic fractures are associated with an increased incidence of pulmonary metastases and that prophylactic stabilization decreases this incidence. If a given patient is not fit for surgery, radiotherapy and avoidance of weight-bearing activity are indicated.

Before surgery, a radionuclide bone scan and radiographs of the entire length of the affected bone should be obtained. These measures ensure that any other metastases that might subsequently develop into a pathologic fracture are also stabilized and included in the radiotherapy field. A pathologic fracture at the edge of a plate or of an intramedullary nail, particularly when fixed with methylmethacrylate, is more difficult to treat than if there were no implant in the bone.

Pathologic fractures are not necessarily a manifestation of terminal disease, and primary internal stabilization followed by radiotherapy are usually the treatments of choice, and certainly the only modalities likely to both restore mobility and relieve pain. Untreated pathlogic fractures rarely heal, and although radiotherapy might achieve local tumor control, bony union remains unlikely. Radiotherapy inhibits chondrogenesis (a prerequisite for fracture healing), and with large areas of bone destruction there could be insufficient matrix remaining for adequate repair.

The type of internal stabilization chosen depends on the site of the lesion, and the range of stabilization devices and custom-made prostheses increases year on year. When feasible, closed intramedullary nailing is preferred; however, at the end of the long bones, intramedullary nailing alone is inadequate, and alternative techniques are necessary. It is essential that the internal stabilization provide sufficient strength to allow unsupported use of the limb and for the legs to bear weight. Fulfilling this demand could require supplementation with methylmethacrylate (which is inserted into the tumor cavity with the implant fixed across the methylmethacrylate while still soft) and bridging normal bone above and below the lesion.

Pathologic femoral neck fractures do not unite despite internal fixation, and this situation requires replacement arthroplasty. Careful preoperative assessment of the pelvis and femur is necessary, and for this, CT scanning or MRI is often helpful. If there is no metastatic involvement of the acetabulum, a hemiarthroplasty could be all that is required. If the acetabulum is involved, however, total-replacement arthroplasty is indicated, and sometimes pelvic reconstruction is necessary. Many patients have metastases in the distal femur together with proximal involvement, and for these patients, a long-stemmed femoral prosthesis is recommended.

For humeral fractures, internal fixation is also useful, providing more rapid and greater pain relief compared with conservative treatment. Although patients with a very short life expectancy can be managed adequately with conservative treatment, those patients expected to survive longer than 3 months are best managed by internal fixation to ensure pain relief and restoration of function. Replacement arthroplasty could be necessary if the proximal humerus is involved, but most pathologic fractures of the humerus can be treated by intramedullary nailing.

Occasionally, patients present with an isolated metastasis in the distal skeleton. If on careful evaluation there is no other evidence of dissemination of the tumor, resection of the lesion should be considered. Local resection and prosthetic replacement are usually possible, but occasionally, amputation is indicated.

Spinal Instability

Spinal instability can cause excruciating pain that is mechanical in origin and not relieved by radiotherapy or systemic treatment. As with pathologic fractures of long bones, stabilization is required for pain relief and involves major surgery, which is associated with significant morbidity and mortality. There are several methods for spinal stabilization, but in general, the posterior approach is technically easier and allows stabilization of a larger area of the spine. With careful selection of patients, excellent results can be obtained. An associated neurologic deficit is not a contraindication to these procedures.

Percutaneous vertebroplasty and kyphoplasty, a new approach to treating spinal pain and instability, involves injecting an acrylic polymer into a diseased vertebral body. The technique was developed initially for the treatment of painful vertebral hemangiomas, and considerable experience with it has been obtained in the treatment of osteoporotic compression fractures. Its use has now been extended to the treatment of malignant spinal disease.[150,151] The technique provides effective pain relief, which is achieved more rapidly than with radiotherapy, and it confers the added benefit of providing structural support to the spinal column, thus reducing the risk of vertebral collapse and instability. Although generally a safe procedure, vertebroplasty can be complicated by leakage of the polymer, which predisposes to spinal cord or nerve root compression. The risk of this is less with kyphoplasty.[151] The technique seems to have the potential for wider use, particularly among patients with limited vertebral disease and those for whom major surgical spinal stabilization procedures are unsuitable.

Compression of the Spinal Cord or Cauda Equina

Compression of the spinal cord or cauda equina in patients with metastatic disease of the spine is a medical emergency necessitating prompt diagnosis and treatment (see also Chapter 55). Its causes include pressure from an enlarging extradural mass, spinal angulation after vertebral collapse, vertebral dislocation after pathologic fracture, or, rarely, pressure from intradural metastases. The most common primary tumors producing this complication, in decreasing order of frequency, are carcinoma of the breast, lung cancer, prostatic cancer, lymphoma, and renal carcinoma.

Back pain is the most common initial symptom of spinal cord compression; two types of pain can occur—local spinal or radicular. Radicular pain varies with the location of the tumor, being common in the cervical (79%) and lumbosacral (90%) regions and less common with thoracic lesions (55%). Both local spinal and radicular pain are experienced close to the site of the lesion identified at myelography. Motor weakness, sensory loss, and autonomic dysfunction are all common at presentation of spinal cord or cauda equina compression.

The development of back pain in a patient with cancer, coincident with an abnormality on a plain spinal radiogram, should serve as a warning for the possible development of spinal cord compression. Compression of the spinal cord or cauda equina can occur in association with spinal stability or in isolation. When there is a greater than 50% vertebral collapse, compression of the spinal cord becomes more likely. The keys to successful rehabilitation are early diagnosis, high-dose corticosteroids, rapid assessment, and urgent referral for either decompression and spinal stabilization or radiotherapy. Neurologic recovery is unlikely if the spinal compression is not relieved within 24 to 48 hours.

In a retrospective analysis of 70 patients with spinal cord compression secondary to breast cancer, the most frequent symptom was motor weakness (96%), followed by pain (94%), sensory disturbance (79%), and sphincter disturbance (61%).[152] Of these 70 patients, 91% had at least one symptom for more than 1 week. The ability to walk was maintained by 96% of those ambulant before therapy. In those unable to walk, 45% regained ambulation, with radiotherapy and surgery equally effective. Median survival was 4 months. The most important predictor of survival was the ability to walk after treatment. These findings stress the importance of prompt presentation, diagnosis, and treatment and suggest that earlier diagnosis and intervention should improve outcome.

The choice between surgical decompression and radiotherapy depends on a variety of clinical features. Surgical decompression is indicated for patients with recent onset of symptoms and with progressive paraplegia and urinary retention of less than 30 hours' duration. The site of compression should be localized to no more than two or three vertebral segments, and the patient should have a life expectancy of at least several weeks. For patients in whom the paraplegia has been established for several days or urinary retention has been present for more than 30 hours, surgical decompression rarely results in the recovery of bladder or motor function. Radiotherapy is indicated for those who are either unfit for surgery or do not meet the criteria for surgical decompression.

Several studies in the past suggested that surgical decompression had no advantage over radiotherapy.[153] It should be appreciated, however, that these studies compared dorsal laminectomy—an outdated and now inappropriate procedure—with irradiation. However, surgical decompression should be followed by spinal stabilization. More recently a randomized trial was performed that compared modern surgical techniques with radiotherapy. Patchell and associates randomized 101 patients to surgery plus radiotherapy or radiotherapy alone. Significantly more patients in the surgery group (42/50, 84%) than in the radiotherapy group (29/51, 57%) were able to walk after treatment (odds ratio 6.2 [95% confidence interval 2.0–19.8] $P = 0.001$). Patients treated with surgery also retained the ability to walk significantly longer than did those with radiotherapy alone (median 122 days vs. 13 days, $P = 0.003$). Thirty-two patients entered the study unable to walk; significantly more patients in the surgery group regained the ability to walk than patients in the radiation group (10/16 [62%] vs. 3/16 [19%], $P = 0.01$). The need for corticosteroids and opioid analgesics was also significantly reduced in the surgical group.[154] Therefore, the choice of management should be decided on an individual basis, and there are undoubtedly patients who will benefit greatly from appropriate and prompt surgical management.

SUMMARY

The management of bone metastases requires an experienced multidisciplinary team to ensure timely diagnosis and the appropriate integration of local and systemic treatments. The effects of tumor cells on bone cell function (especially on osteoclast activity) underpin the rationale for the use of bisphosphonate treatment to reduce skeletal morbidity. These bone-specific treatments are now an accepted part of routine clinical management. Additionally, the disruption of bone remodeling results in release of collagen fragments, which seems to have value in predicting skeletal events, prognosis, and monitoring of response.

Further developments in our understanding of the pathophysiology of bone metastases can be expected to provide new therapeutic strategies. Already, improved knowledge of the signaling molecules involved in regulating osteoclast function—notably OPG and RANK ligand—has led to the development of highly active targeted therapies for bone diseases, including cancer and other novel therapeutic approaches in clinical development. Over the next 5 years several of these compounds can be expected to gain regulatory approval, and ultimately combinations of bone-targeted therapies may be recommended to further reduce the clinical burden of metastatic bone disease.

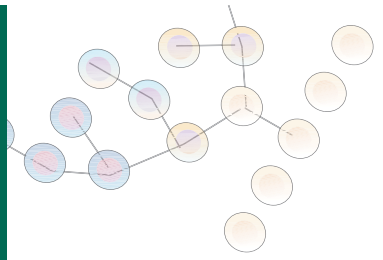
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58 Lung Metastases

Valerie W. Rusch

SUMMARY OF KEY POINTS

Incidence
- Lungs are the second most common site of metastases.
- Lungs are the sole site of metastasis in 80% of patients with sarcoma and in 2% to 10% of patients with carcinoma.

Etiology
- Hematogenous spread
- Lymphangitic spread in carcinomas can occur early or late in the natural progression of all cancers.
- It is not well understood why lung metastases take several years to develop.

Evaluation
- Few lung metastases are symptomatic; only 15% to 20% of patients complain of cough or pain. All patients with isolated pulmonary metastasis from extrathoracic malignancy should be evaluated for the possibility of resection.
- Initial imaging studies should consist of a plain chest radiograph followed by computed tomographic (CT) examination to predict resectability. Newer imaging modalities, such as ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI), have not been shown to be as accurate or cost effective as CT.
- CT is unable to distinguish reliably between malignant and benign lesions.
- CT differs from the final pathology report in 42% of cases.
- CT underestimates the number of malignant lesions in 25% of cases.
- The accuracy of radiologic imaging is only 37%, underestimating the number of lesions by 39% and overestimating them by 25%, for patients undergoing bilateral exploration.

Prognostic Factors
- Number of metastases
- Disease-free interval (<36 months or >36 months).
- Histology/organ site of primary tumor

Surgical Treatment
- First described case of pulmonary metastasectomy was by Weinlechner in 1882.
- Alexander and Haight described the first series of patients; 12 patients remained disease-free for 1 to 12 years.
- General guidelines that should be met before undertaking a resection include the following:
  - Control of the primary tumor, or ability to resect the primary tumor
  - Ability to resect metastatic disease completely
  - Ability of the patient to withstand the extent of pulmonary resection required to remove all gross tumor
  - Absence of extrathoracic metastasis
  - Absence of better alternative treatment
- The location of metastases determines the extent and type of resection:
  - Peripheral metastasis—parenchymal sparing
  - Central metastasis—lobectomy or pneumonectomy
  - Solitary endobronchial metastasis—lobectomy, sleeve lobectomy, or pneumonectomy
- Ensure that all grossly palpable tumors are resected with clear margins.
- More radical resection (lobectomy, pneumonectomy) does not increase survival.
- Bilateral metastases and recurrence of pulmonary metastases are not contraindications to resection and should not deter resection in lesion(s) that can be removed completely.

INTRODUCTION

The first described case of pulmonary metastasectomy was reported in 1882 by a German surgeon named Weinlechner, who removed two incidental pulmonary nodules during a chest wall resection for sarcoma.[1] In 1939 Barry and Churchill[2] reported the first long-term survivor from pulmonary metastasectomy, a patient with metastatic renal cell cancer. Their patient survived 23 years after surgery. Subsequently, Alexander and Haight described the first series of patients undergoing pulmonary metastasectomy and its correlation to survival.[3] Twelve patients in their study remained free of disease for 1 to 12 years. Most important, from this early study came the first generally accepted criteria for pulmonary metastasectomy:

- The primary tumor should be completely removed.
- There should be no evidence of extrapulmonary disease.
- The patient should be able to tolerate the planned operation from the standpoint of overall medical condition.

Subsequently these criteria were modified by other authors to reflect our improved understanding of the management of pulmonary metastases. Current additional criteria include the following:[4]

- Control of the primary tumor, or ability to resect the primary tumor completely simultaneous with resection of metastasis
- Ability to resect metastatic disease completely
- Ability of the patient to tolerate the extent of pulmonary resection required to remove all gross tumor

Table 58-1 Prognostic Factors after Pulmonary Metastasectomy

Disease-free interval
Mediastinal lymph node metastases
Number of pulmonary nodules
Tumor doubling time
Size of pulmonary nodules
Bilateral disease
Surgical margins
Histologic subtype

- Absence of extrathoracic metastasis
- Absence of better alternative treatment

Although these criteria are widely used, there are continued attempts to refine the selection of patients for pulmonary metastasectomy.

Several prognostic factors that are not universal across all tumor histologies have been reported to affect outcome after pulmonary metastasectomy (Table 58-1). The largest series of pulmonary metastectomies reported to date is from the International Registry of Lung Metastasis, which analyzed 5206 cases.[5] The overall 5-year survival after pulmonary metastasectomy without stratifying for tumor type was 36%. Factors associated with better prognosis included a long disease-free interval, complete resection, and a small number of lung nodules. A staging system based on these prognostic factors was proposed (Fig. 58-1).

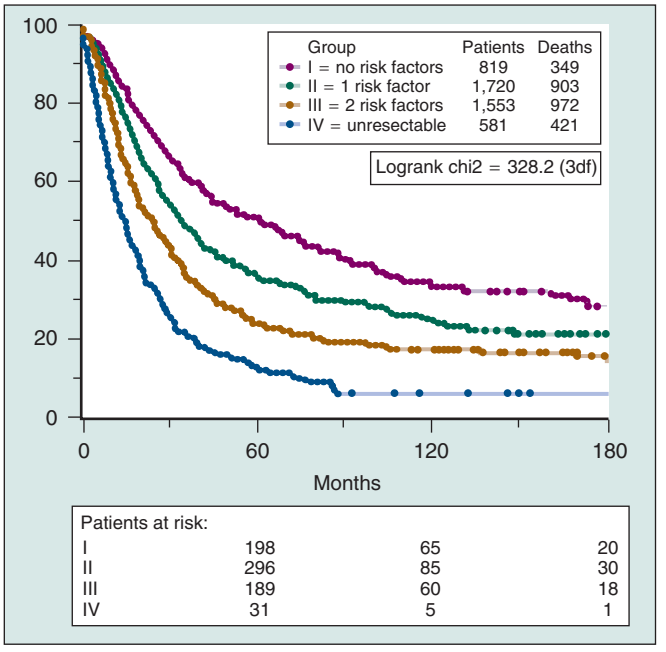


Figure 58-1 • Survival of the four prognostic groups based on the analysis of 5206 patients entered into the International Registry of Lung Metastases. Group I includes patients who had completely resectable disease with a single metastasis and a disease-free interval after resection of the primary tumor (DFI) of 36 months or more; group II, patients who had completely resectable disease with multiple metastases *or* a DFI of less than 36 months; group III patients who had completely resectable disease with multiple metastases *and* a DFI of less than 36 months; and group IV patients with unresectable disease. (From Pastorino U, Buyse M, Friedel G, et al: Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 1997;113:37.)

The role of surgery in the treatment of pulmonary metastases will continue to evolve as better systemic therapies become available. Currently, only a minority of patients with metastatic disease from any source are candidates for pulmonary metastasectomy; however, improved imaging studies and the widespread use of computed tomography (CT) might detect more patients who have small-volume pulmonary metastases and are therefore candidates for metastasectomy. A current perspective of the evaluation and treatment of patients with isolated lung metastases is presented in this chapter.

DIAGNOSIS

Few patients with pulmonary metastasis are symptomatic. It is estimated that only 15% to 20% of patients present with cough or nonspecific chest pain and even fewer still with hemoptysis. Traditionally, chest radiography has been the most commonly used and cost-effective modality for screening patients for metastasis from extrathoracic malignancy. The most frequent radiographic appearance of a pulmonary metastasis is a peripherally located, well-circumscribed nodule (Fig. 58-2).[6,7] Several less common radiographic characteristics have also been described. Cavitating lesions are associated with a differential diagnosis that includes benign, infectious, and malignant causes (Fig. 58-3). When malignant, cavitary lesions are usually squamous cell carcinomas. The frequency of cavitation in metastatic nodules is approximately 4%; however, squamous cell malignancy is responsible for 69% of these lesions. Spontaneous pneumothorax also can occur with metastatic lung lesions and is thought to be caused by cavitation and erosion into a bronchiole wall. Spontaneous pneumothorax is most frequently seen in patients with sarcoma. It is said that a spontaneous pneumothorax in a patient with history of a sarcoma should prompt an evaluation for possible occult metastatic lung lesions. Calcification of pulmonary nodules is usually related to a benign process such as a hamartoma; however, metastatic lesions of many types (especially osteogenic sarcoma) are known to produce calcification (Fig. 58-4).[6,7] Calcification in metastatic lesions are thought to be produced by several processes in different tumor types, including bone formation in osteogenic sarcoma, mucinous calcification of adenocarcinomas, or dystrophic calcification of lesions such as synovial sarcoma or giant cell tumors of the bone.[6] Hemorrhage around lung nodules is also seen more frequently in benign lung lesions (e.g., fungal or mycobacterial infections) and is visualized as a halo around the lung nodule. This can also be seen in metastatic lesions and should raise the suspicion for metastasis in patients with a history of malignancy.

Computed Tomography

The use of CT as an adjunct to plain film radiography for the diagnosis of pulmonary metastases has increased dramatically during the last decade. This has been facilitated by the development of high-speed helical scanners. It is clear that CT is able to visualize more lesions than chest radiography.[5,8–17] Chang and coworkers[11] reported that when compared with conventional radiography, CT was able to visualize nearly twice as many nodules.[18] CT is not able to distinguish reliably between malignant and benign lesions, however. McCormack and colleagues[8] retrospectively studied 144 patients who had both a chest x-ray and a CT to identify metastatic lesions. The CT results differed from the final pathology reports in 42% of cases, with CT scan underestimating the number of malignant nodules in 25% of patients. Pastorino and associates[5] reported results of imaging on 2988 patients undergoing pulmonary metastasectomy. The overall accuracy of radiologic assessment of the number of metastatic nodules was 61%, underestimating metastasis in 25% of patients. Interestingly, in those patients (1134) who had bilateral exploration, the accuracy of imaging was only 37%, underestimating the number of lesions in 39%, overestimating in 25%. The accuracy and sensitivity of CT also depends on the size of the lesions (Table 58-2): the larger

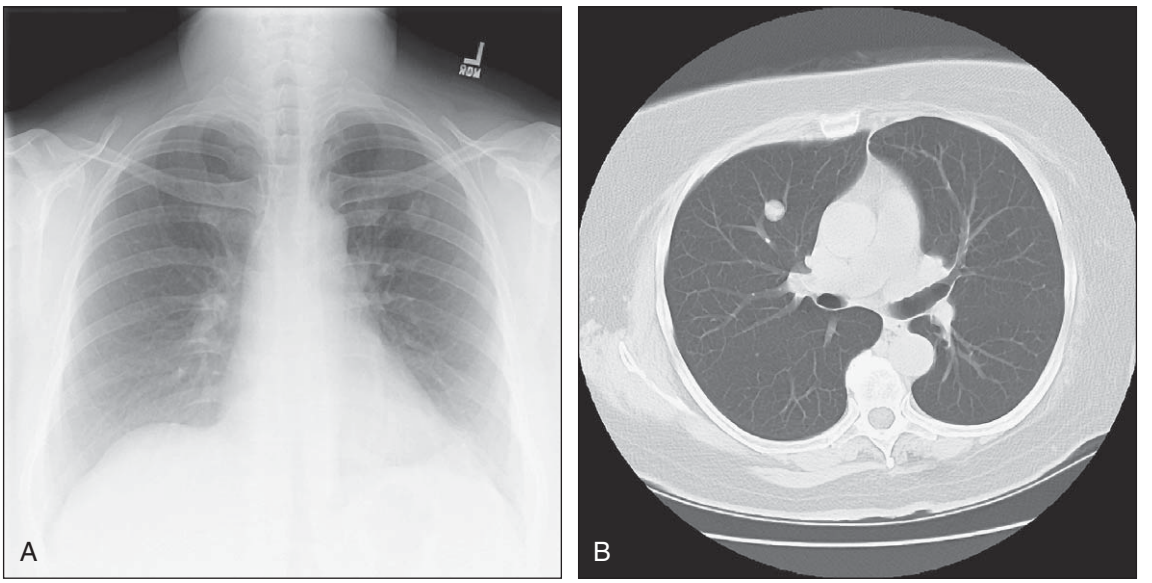


Figure 58-2 • Two patients with metastatic sarcoma demonstrating typical findings of well-circumscribed peripheral lesions. **A,** Plain chest radiograph. **B,** Computed tomographic image.

the lesion, the greater the sensitivity and accuracy. Munden and colleagues[14] reported on the clinical significance of pulmonary lesions less than 1 cm in diameter, finding malignant pulmonary lesions in 81% of patients with a history of malignancy. Multiple authors have described the ability of CT to detect a greater number of pulmonary nodules, while acknowledging a decreasing specificity of identifying malignant nodules with this diagnostic tool.[11,15] Therefore, not all small pulmonary nodules in patients with a history of cancer can be assumed to represent metastatic disease. Currently, there are no established guidelines for the routine screening for pulmonary metastases. Many institutions still use periodic chest radiography as the only imaging modality to rule out pulmonary metastasis. Other authors suggest that the use of CT for routine screening is indicated in groups of patients whose primary tumors have an unusually high propensity to spread to the lungs.[13,16] As the quality and speed of CT scanning progresses, it will probably become the sole screening tool for identifying pulmonary metastases.[11,15]

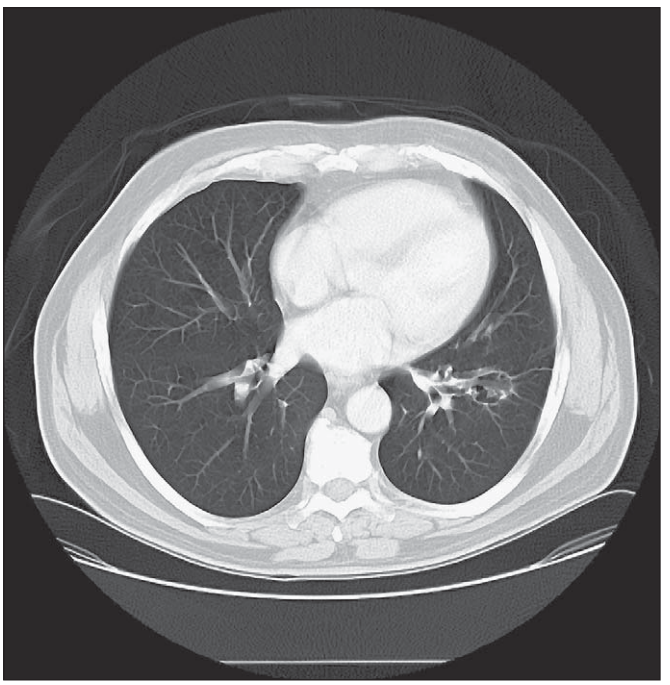


Figure 58-3 • Chest CT scan demonstrating cavitary lesion in a patient with metastatic colorectal cancer.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) provides the benefits of reduced radiation exposure (of particular interest for cases involving younger patients) and the ability to detect lesions at lung-mediastinal interfaces. MRI has not gained wide acceptance as a screening tool, however, mainly because of its increased time constraints and cost. Further technical considerations that are unfavorable include motion-related artifacts and an inability to detect calcified lesions. Kersjes and colleagues[19] performed a study comparing MRI and helical CT in the detection of pulmonary metastasis and showed MRI to have an overall accuracy of 84%. For lesions smaller than 5 mm, however, the sensitivity of MRI was only 36%. The routine use of MRI is currently not advocated as a screening tool for patients with pulmonary metastasis.

Nuclear Imaging

Imaging with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is being used more frequently to assist in the staging of primary tumors. Most often, this is used at the time of diagnosis to rule out distant metastasis but is occasionally used to assess response to therapy. Currently FDG-PET is not used as a screening tool to identify pulmonary metastasis, but multiple authors support the eventual use of this modality as a screening tool.[20,21] Dose and associates[21] studied 50 patients with breast cancer who had FDG-PET evaluation to determine presence of metastatic disease. FDG-PET had a sensitivity of 78.6% in identifying pulmonary metastasis as compared with conventional chest radiography, which had a sensitivity of 41.6%.[21] Other authors report that FDG-PET may not be superior to conventional imaging techniques in identifying pulmonary metastasis from bone and soft-tissue sarcomas.[22,23] Lucas and coworkers[22] studied 62 patients with soft-tissue sarcoma who had FDG-PET during initial evaluation. The sensitivity of FDG-PET in detecting lung metastasis was 86.7% as compared with 100% for CT, leading the authors to conclude that CT is a superior imaging tool

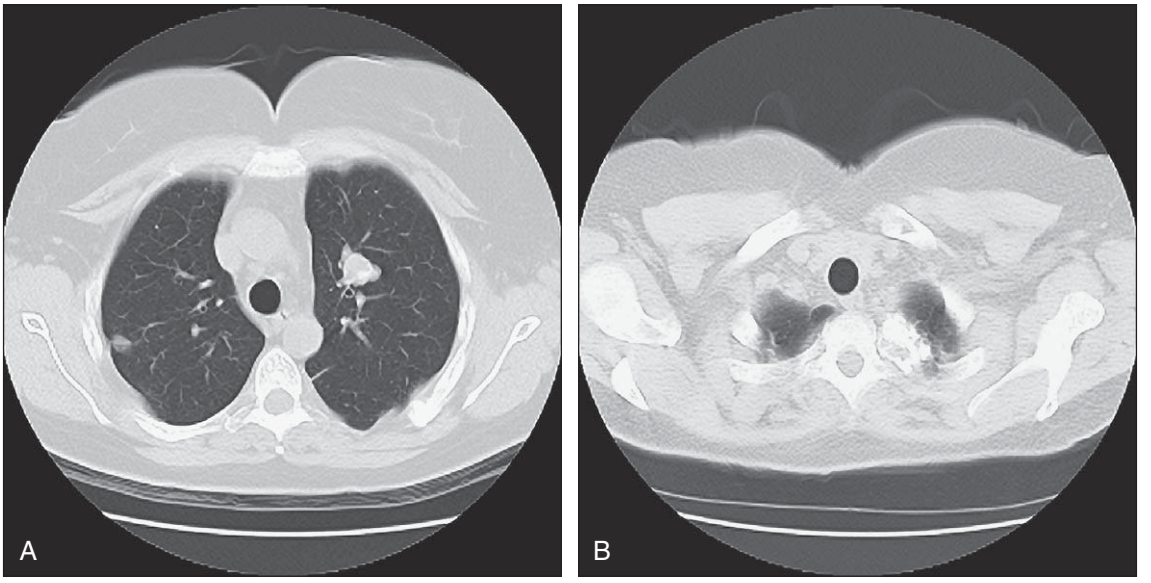


Figure 58-4 • **A** and **B,** Chest CT scans of patient with metastatic osteosarcoma demonstrating the presence of calcifications in metastatic lesions.

Table 58-2 Detection of Pulmonary Metastasis by Computed Tomography

Year	Author	No. of Nodules	Sensitivity for Small Lesions	Sensitivity for Larger Lesions
1998	Waters et al[18,*]	144	44% (≤5 mm)	91% (>5 mm)
1999	Diederich et al[9]	90	69% (≤6 mm)	95% (>6 mm)
2002	Margaritora et al[10,†]	188	48% (≤6 mm)	87% (>6 mm)

*Canine model
†High-resolution CT group

Table 58-3 Surgical Approaches to Resection of Pulmonary Metastases

Surgical Approach	Advantages	Disadvantages
Unilateral Disease		
Posterolateral thoracotomy	Superior exposure and palpation of lung	Painful, large incision
Videothoracoscopy (VATS)	Less painful	Inability to palpate, poor ability to detect deep lesions
Bilateral Disease		
Clamshell thoracotomy	Excellent bilateral exposure	Painful; sacrifice of both internal mammary arteries
Simultaneous bilateral thoracotomies	One hospital stay/procedure	Painful
Staged (sequential) bilateral thoracotomy	Allows technically complex procedures	Two hospitalizations and procedures
Median sternotomy	Bilateral exposure, less painful	Poor exposure to posterior lung fields

for identifying these lesions. Further study is warranted to determine the true benefit, if any, of using FDG-PET as a routine screening tool for identifying patients with pulmonary metastasis. Because PET is currently unable to detect sub-centimeter lung lesions reliably, it is likely that CT will remain the most sensitive imaging modality.

SURGICAL APPROACHES TO LUNG METASTASIS

The goal of pulmonary metastasectomy is to achieve complete resection of all visible and palpable tumors in the lung. The surgical approach is dictated by the extent and location of disease and by the patient's performance status. There are several approaches available depending on the size, number, and location of the lesions. The advantages and disadvantages of these approaches are outlined in Table 58-3.

The standard approach to the patient with disease localized to one hemithorax is a unilateral posterolateral thoracotomy. The thorax is usually entered through the fifth intercostal space. Several variations of this include muscle-sparing incisions, axillary incisions, or an anterior thoracotomy. All of these approaches allow full visual inspection and manual palpation of the entire lung.

During the past decade, the use of video-assisted thoracoscopy (VATS) has been described for pulmonary metastasectomy. This

approach is controversial, however.[24–28] McCormack and colleagues[25] performed a prospective study evaluating the role of VATS to treat pulmonary metastasis. Eighteen patients had preoperative CT followed by VATS resection of all visible and CT-detected lesions. All patients then immediately underwent thoracotomy with resection of any additional lung nodules. Additional malignant lesions were found in 56% of patients after attempted VATS resection of the nodules found on preoperative imaging. The authors concluded that this high failure rate of CT and VATS warranted closure of the study before the intended 50 patients could be enrolled. Recently, other authors have advocated the use of VATS for patients with a solitary pulmonary metastasis. Mutsaerts and associates[24,28] described their experience with 20 patients undergoing either VATS or thoracotomy for resection for single pulmonary metastasis. The 5-year survival and recurrence rates seemed to be similar to those seen with thoracotomy.[28] Other authors have described localization methods using radiotracer injection to help identify small or deeply located lesions during VATS resections.[26] Currently, the practice in our institution is to use VATS primarily for the diagnosis of metastatic disease, or as a therapeutic procedure in highly selected patients for whom thoracotomy may be a higher risk procedure. Thoracotomy or other open procedures remain our preferred approach to pulmonary metastasectomy because of the prognostic importance of complete resection and the potential for missing small metastases by VATS. However, a VATS approach may be appropriate for patients with one or two metastases clearly defined on high-quality imaging studies.

The approach to bilateral disease is more variable, but the principles remain the same. Median sternotomy, "clamshell" thoracotomy (bilateral anterior thoracotomy with transverse sternotomy), sequential bilateral thoracotomies, and simultaneous bilateral posterolateral thoracotomies are used as standard surgical approaches to the resection of bilateral metastases.[29–31] In general, resection of bilateral metastases is preferably done as a single operation. Sequential thoracotomies are performed only when the anatomic location of a lesion requires a complex or extensive operation, or when the patient's comorbidities dictate a more conservative approach to management.

In contrast to primary lung cancers, pulmonary metastases require only a local excision with a surrounding rim (1–2 cm) of benign lung tissue. This is accomplished most frequently by wedge resection performed by precision electrocautery or with a stapling instrument (Fig. 58-5). Segmentectomy, lobectomy, or pneumonectomy are used less commonly. It is important to note that survival after metastasectomy is not increased by a more radical resection such as lobectomy or pneumonectomy. These procedures might be required technically to remove the lesion, however, and should be applied to do so if needed. The most important principle of these techniques is a clear margin of resection.

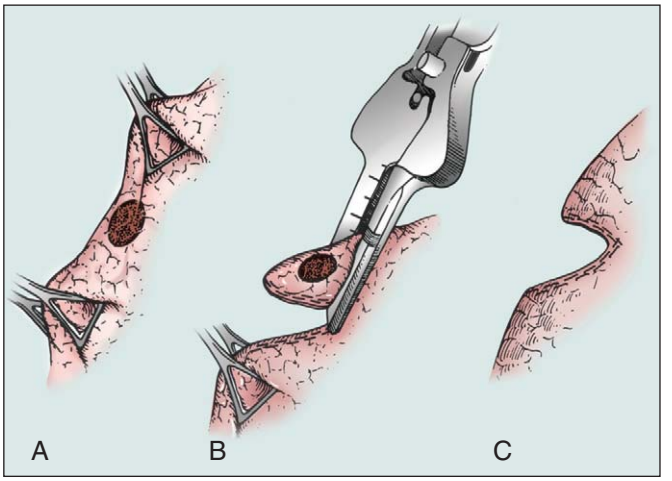


Figure 58-5 • **A–C,** Method of wedge resection by using a stapling device. This technique is most suitable for peripherally located metastases adjacent to the fissures or edges of the lung. (From Rusch VW: Surgical techniques for pulmonary metastasectomy. Sem Thorac Cardiovasc Surg 2002;14:4.)

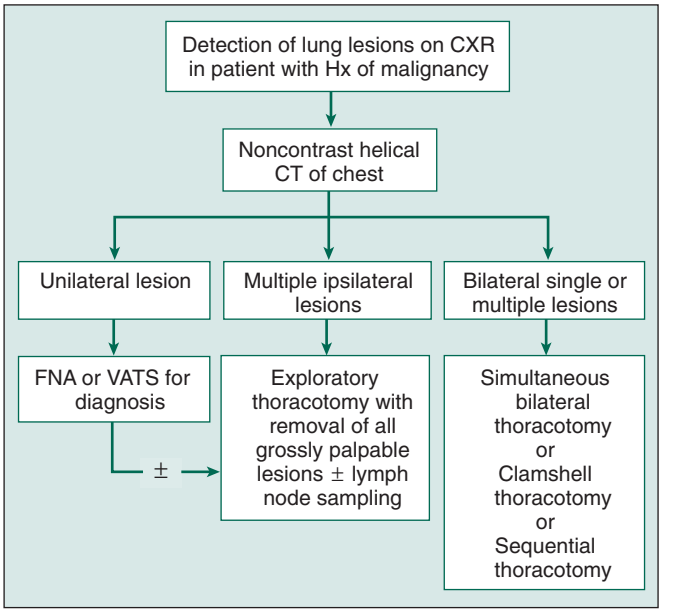


Figure 58-6 • Management algorithm for patients with isolated pulmonary metastasis from extrathoracic malignancy. CXR, chest radiography; FNA, fine-needle aspiration; Hx, history; VATS, video-assisted thoracoscopy.

The risk of resection of pulmonary metastasis using standard wedge resection is very low, with mortality generally 1% or less. Complications include bleeding, infection in the wound, or pneumonia and prolonged air leak. More extensive resections such as lobectomy or pneumonectomy carry only slightly higher morbidity rates, and these operations are very well tolerated by most patients.

The preoperative evaluation for these patients is similar to those undergoing lung resection for any other cause (Fig. 58-6). Pulmonary function testing should be obtained for all patients to assure that the volume of lung resection will not compromise overall respiratory function. Thorough evaluation of underlying cardiovascular disease should also be undertaken, with preoperative stress testing as clinically indicated.

PULMONARY METASTASECTOMY FOR SPECIFIC TUMOR TYPES

Colorectal Cancer

It is estimated that 10% to 25% of patients with primary colorectal tumors will have detectable metastases at the time of diagnosis.[32] Despite advances in adjuvant therapy and surgery, 50% of all patients with colorectal cancer will develop some form of metastasis during their lifetimes.[33] Approximately 15% of patients having curative resection of their primary colorectal tumor will develop distant metastasis, including metastasis to the lung.[34] Pulmonary metastasis can occur even with favorable primary tumor characteristics. Okumura and coworkers[35] reported that 26% of pulmonary metastectomies were performed in patients with Duke's A or B primary colorectal cancer. Since Blalock[36] reported the first pulmonary metastasectomy for colorectal cancer in 1944, several authors have reported their experience regarding overall survival and prognostic factors. The 5- and 10-year survival rates range from 30% to 40% and 27% to

Table 58-4 Survival of Patients Undergoing Pulmonary Metastasectomy for Colorectal Cancer*

Year	Author	Number	5-Year Survival (%)	10-Year Survival (%)
1992	McAfee et al[37]	139	30.5	N/A
1996	Okumura et al[35]	159	40.5	27.7
1998	McCormack and Ginsberg[38]	287	40.0	32.0
2001	Zink et al[39]	110	32.6	N/A
2002	Saito et al[40]	165	39.6	37.2

*Studies represent analysis of 100 patients or more.

37%, respectively (Table 58-4).[37–40] It is clear from the literature that pulmonary metastasectomy for colorectal cancer is associated with long-term survival, especially when a complete resection is performed. McCormack and associates[41] reviewed 144 patients who underwent pulmonary metastasectomy for colorectal cancer and showed that survival for patients who underwent complete resection was approximately 40% at 5 years, whereas incomplete resection was associated with a poor prognosis.

As for other primary tumors, studies evaluating the disease-free interval, the number of lesions (multiple vs. single), and the presence of lymph node involvement have shown these to be significant prognostic factors after pulmonary metastasectomy for colorectal cancer.[35,37–46] Colorectal cancer is also unique in the fact that the serum tumor marker carcinoembryonic antigen (CEA), used as a marker for follow-up, has been shown to be a prognostic indicator for patients with pulmonary metastases.[37–46]

There is some disagreement as to whether single, ipsilateral metastases are associated with a better prognosis than either multiple ipsilateral or bilateral metastases. The presence of bilateral metastases was previously thought to be a contraindication to metastasectomy. Recently, though, several authors have reported that the survival for patients with bilateral lesions is not significantly reduced as compared with patients who have multiple ipsilateral lesions.[38,43] Although a solitary metastasis might be associated with a better prognosis than multiple metastases (either unilateral or bilateral), the main criteria used to select patients with multiple lesions is whether removal of these lesions is technically feasible and removal of the volume of lung parenchyma does not seem to compromise the patient's lung function to a significant extent.

CEA levels are elevated in 40% to 70% of patients before pulmonary metastasectomy. Most authors report elevated CEA levels to be an adverse prognostic factor.[39,40,44,45,47] The reason for this is unclear, although it has been postulated that the presence of CEA may promote adhesion or attachment of tumors cells or could be due to undetected extrathoracic metastasis.[48] Although an elevated CEA is not used currently to exclude patients from resection, it could be useful to consider this in the context of other known prognostic factors. For instance, a patient who rapidly develops pulmonary metastases after resection of the primary tumor, and who has multiple lung nodules and an elevated CEA level, might be treated initially with chemotherapy instead of going directly to pulmonary metastasectomy.

Hilar or mediastinal lymph node metastases occur in 1% to 28% of patients with colorectal pulmonary metastasis.[35,40–43,45] Saito and colleagues[40] reported that 20 of 138 (14.5%) patients who underwent lymph node sampling had positive nodes. The 5-year survival was 48.5% for the patients without hilar or mediastinal lymph node metastasis, vs. 6.2% at 4 years for the patients with lymph node metastasis. More recently, Welter and associates[49] reported that 28 of 169 patients undergoing resection of colorectal pulmonary metastases had hilar or mediastinal nodal metastases. Nodal metastases had a highly significant adverse impact on survival. Okumura and coworkers[35] performed systematic lymph node dissection on 100 patients with colorectal pulmonary metastasis. Fifteen of these patients had positive lymph nodes with a 5-year survival of 6.7% as compared with a 50% survival for those with negative lymph nodes, indicating that complete lymph node dissection does not increase survival. The routine use of mediastinal lymph node dissection in patients with pulmonary metastases seems to be the exception rather than the norm. The presence of malignant lymph nodes could indicate a group of patients otherwise thought to be disease-free who might benefit from additional adjuvant therapy. We favor doing mediastinal lymph node sampling or dissection in these patients. Although these procedures might not have a therapeutic effect, they certainly provide important prognostic information.

Previously, the presence of both liver and lung metastases from colorectal cancer was thought to be a contraindication to metastasectomy. Synchronous or metachronous lung and liver metastasis occurs in approximately 5% of patients with colorectal cancer. Headrick and colleagues[50] reported 5- and 10-year survivals of 30% and 16%, respectively, for 58 patients who underwent resection of both liver and lung metastases from colorectal cancer. Decreasing morbidity and mortality rates for liver resection now make resection of both lung and liver metastases a viable option in carefully selected patients.

Bone and Soft-Tissue Sarcoma

Bone and soft-tissue sarcomas compose a histologically diverse group of tumors accounting for 1% of all adult malignancies, with approximately 6600 cases occurring in the United States annually.[51,52] Metastasis will occur in 25% to 70% of patients with localized disease, and 10% will present with metastasis upon diagnosis.[52] Isolated pulmonary metastases occur in up to 20% of sarcoma patients during the course of their disease, with the lung being the site of failure after treatment in up to 90% of cases.[53,54] Factors associated with an increased risk of pulmonary metastasis include high tumor grade, primary tumor size greater than 5 cm, lower extremity site, and histologic subtype.[53] The lack of effective systemic therapy for most soft-tissue sarcomas makes surgical resection the best treatment for pulmonary metastases. Several studies have shown that the complete resection of pulmonary metastases is associated with long-term survival.[5,51,53,55] Billingsley and coworkers[51] reported that the 3-year actuarial survival was 46% in patients who had complete resection as compared with 17% ($P < 0.001$) for those with incomplete resection of pulmonary metastasis. The cumulative 5-year survival for patients with bone and soft-tissue sarcomas after pulmonary metastasectomy ranges from 31% to 40% (Table 58-5).[5,51,55–57]

The histologic subtype of sarcoma influences both the development of pulmonary metastasis and overall survival. High-grade, undifferentiated, and alveolar soft-part sarcomas produce pulmonary metastasis in approximately 60% of patients.[51] Tumors that are high grade and histologic variants, such as liposarcoma, malignant fibrous histiocytoma, and malignant peripheral nerve tumor, have all been reported to be unfavorable prognostic factors.[51,53,58] Longer disease-free interval, fewer lesions, and unilaterality have also been reported to be favorable prognostic factors.

Table 58-5 Survival of Patients Undergoing Pulmonary Metastasectomy for Bone and Soft-Tissue Sarcomas*

Year	Author	Number	5-Year Survival (%)
1995	Choong et al[55]	214	40
1996	van Geel et al[56]	255	38
1997	Pastorino et al[5]	1917	31
1999	Billingsley et al[51]	138	37

*Studies represent analysis of 100 patients or more.

The incidence of hilar or mediastinal lymph node metastasis in patients with lung metastasis from sarcoma is 2%.[5] This low propensity for lymph node involvement is also a feature of primary sarcomas. Therefore, it seems that routine mediastinal lymph node sampling or dissection is unlikely to offer significant prognostic information or therapeutic benefit.

The rate of recurrence after pulmonary metastasectomy for sarcoma ranges from 45% to 83%; however, the role of repeat resection of pulmonary metastases has been studied by few authors.[53,57–60] Weiser and associates[61] reported experience from Memorial Sloan-Kettering Cancer Center in 86 patients who underwent repeat resection of pulmonary metastases for soft-tissue sarcoma. The 5-year survival after undergoing at least two operations for pulmonary metastasectomy was 36%. Patients who had a complete repeat resection had a median survival of 51 months, as compared with 6 months in those who could not be completely repeat resected. Poor prognostic indicators for repeat resection included three or more nodules, lesions greater than 2 cm in size, and high-grade primary tumors. This study strongly suggested a benefit for repeat or multiple procedures for clearance of pulmonary disease in carefully selected patients.

Pulmonary metastases from osteosarcoma occur most frequently in pediatric patients and respond better to chemotherapy than do soft-tissue sarcomas. Pulmonary metastasectomy within the context of a multimodality therapy program is a well-accepted approach to treatment and is associated with a 5-year survival of approximately 30%. Response to chemotherapy, the disease-free interval from resection of the primary tumor, and the number of metastases and complete resection are reported to influence overall survival.[62–64]

Melanoma

Patients with metastatic melanoma have an especially poor prognosis. The most common sites of metastasis from melanoma are the lungs, distant subcutaneous tissue, and distant lymph nodes, with isolated lung metastasis occurring in 1.9% to 11% of patients.[65,66]

Table 58-6 Survival of Patients Undergoing Pulmonary Metastasectomy for Malignant Melanoma

Year	Author	Number	5-Year Survival (%)
1985	Thayer et al[70]	18	11.1
1990	Karp et al[68]	22	4.5
1991	Gorenstein et al[66]	54	25.0
1995	Tafra et al[67]	106	27.0
1998	Ollila et al[72]	45	15.6
2002	Dalrymple-Hay et al[20]	121	22.1

Tafra and coworkers[67] reported their experience with 106 patients with metastatic melanoma who underwent pulmonary metastasectomy. Sixty-five of these patients underwent a complete resection. Although the benefit of a complete (vs. an incomplete) resection on survival could not be demonstrated in a univariate analysis, a multivariate analysis found that surgical resection (vs. no operation) was associated with a significantly better survival ($P = 0.0001$). Other authors have reported that complete resection is associated with prolonged survival.[68,69] Overall, the 5-year survival rates after resection of pulmonary metastasis from malignant melanoma vary from 4.5% to 27% (Table 58-6).[20,66–68,70–72] This wide range of values probably reflects the relatively small numbers of patients included in some studies. Prognostic factors that have been reported include operation, number of nodules, prior immune therapy, histologic type, disease-free interval, and tumor-doubling time.[20,65–72] Harpole and colleagues[69] reported on a large series of patients who had pulmonary metastases from melanoma. Of the total of 945 patients, 112 (11.8%) underwent pulmonary metastasectomy. Histologic type (nodular and acral lentiginous lesions), high Clark level, and thicker primary tumors were significantly associated with pulmonary metastasis. The overall 5-year survival in this group was 4%. Patients who had a complete resection had a significantly higher median survival rate as compared with those who had only partial resection, although all patients who underwent operations survived longer than those who had no operation. An analysis of the subset of patients who had a solitary metastasis found that patients who underwent resection had a significantly better median survival than patients managed nonsurgically. Important prognostic factors after surgery included complete resection, a long disease-free interval from treatment of the primary tumor to the diagnosis of the pulmonary metastasis, treatment with chemotherapy, and the total number of nodules. These data suggest that appropriately selected patients with metastatic melanoma confined to the lungs can benefit from pulmonary metastasectomy.

Renal Cell Carcinoma

Barry and Churchill[2] performed the first pulmonary metastasectomy from renal adenocarcinoma in 1938. Approximately 30% of patients with renal cell carcinoma will present with metastasis, and approximately 30% to 50% of patients with initially localized tumors will develop distant metastases.[73] One-half of patients who have a radical nephroureterectomy will develop pulmonary metastases later and only 16% of these patients will have disease confined to the lung.[74,75] The 5-year survival of patients with unresected metastasis is approximately 2.7%.[76] The 5-year survival after resection of isolated pulmonary metastasis is reported to range from 36% to 44% (Table 58-7).[75–79] Several prognostic factors for survival have been identified, including complete resection, the disease-free interval between primary tumor treatment and metastasis, the number of metastases, and the presence or absence of lymph node metastases.[75,76,78]

Pfannschmidt and associates[76] reported one of the largest series of pulmonary metastasectomy for renal cell cancer; they found that complete resection was possible in 78% of patients and that these patients had a 5-year survival of 41.5% vs. 22.1% for those with incomplete resection. This survival rate of 22.1% in incompletely resected patients was better than that for patients who had no resection at all.

Hilar and mediastinal lymph node metastases are seen in 22% to 30% of patients with metastatic renal cell cancer.[75,76] Fourquier and colleagues[75] and Pfannschnidt and associates[76] performed systematic mediastinal lymph node dissection on 50 and 191 patients, respectively. Both studies found that the presence of lymph node involvement was associated with a poorer survival. Although it is unknown whether lymph node dissection is therapeutic, it offers important prognostic information and should probably be performed in these patients.

Table 58-7 Survival of Patients Undergoing Pulmonary Metastasectomy for Renal Cancer*

Year	Author	Number	5-Year Survival (%)
1994	Cerfolio et al[79]	96	36
1997	Fourquier et al[75]	50	44
1999	Friedel et al[77]	77	39
2002	Pfannschmidt et al[76]	149	42
2002	Piltz et al[78]	105	40
2006	Marulli et al[101]	59	53

*Studies represent analysis of 50 patients or more.

Synchronous metastases are traditionally thought to be a relative contraindication to resection. The true incidence of synchronous versus metachronous metastases is in renal cell cancer is unclear, although in reported series of resected patients, synchronous lesions are less frequent and are thought to indicate a worse prognosis.[75,76] On the other hand, Fourquier and colleagues[75] examined survival in completely resected patients with synchronous lung metastases. Although the overall survival rate was lower in patients with synchronous lesions (48% vs. 20%), this was not statistically significant and again appeared to offer a survival benefit relative to no resection at all.

The recent development of more effective systemic therapy for renal cell cancers through the use of antiangiogenesis agents may alter the need or indications for pulmonary metastasectomy. This is an evolving area of cancer management, and the impact of these drugs on pulmonary metastasectomy warrants study.

Head and Neck Cancer

Approximately 60,000 new cases of head and neck cancer occur each year in the United States.[80] The potential for metastatic spread is dependent on the stage of the primary tumor, with the rate of lung metastasis ranging from 4.3% to 25.1%.[81] Head and neck tumors and especially squamous cell cancers have a predilection for metastasizing to the lung, which is often the only site of metastasis.[82] The diagnosis of lung nodules in these patients becomes even more challenging when one realizes that 10% to 40% of lung nodules in these patients are actually second primary lung tumors.[83] There are few effective systemic therapy options for the treatment of lung metastasis from head and neck tumors, leaving surgical resection as the most viable option. The estimated 5-year survival after pulmonary metastasectomy in these patients ranges from 29% to 59% (Table 58-8).[80,81,83,84] The wide range of survival rates may be related to the heterogeneous histologic groups reported in most series. Squamous cell tumors of head and neck origin have a worse prognosis than their glandular counterparts such as thyroid, adenoid cystic, and mucoepidermoid tumors.[80,81,84] Liu and coworkers[80] reported on 83 patients undergoing pulmonary metastasectomy from head and neck tumors. In their series the 5-year overall survival for squamous cell tumors was 34% as compared with 64% for tumors of glandular origin ($P = 0.14$). Bilateral metastasis and recurrence of metastasis are not contraindications to resection and have not been shown to be adverse prognostic factors at this time.

Germ Cell Tumors

Germ cell tumors compose only 1% of cancers but are the most common neoplasm in men aged 15 to 35 years. The vast majority of these tumors arise in the testis, with an annual incidence of 5 cases per 100,000.[85] The survival of patients with germ cell tumors has increased dramatically during the past 30 years because of cisplatin-based chemotherapy.[85] Monitoring of treatment and recurrence has been made possible by the use of sensitive tumor markers, including α-fetoprotein and human chorionic gonadotropin.

Table 58-8 Survival of Patients Undergoing Pulmonary Metastasectomy for Head and Neck Cancer

Year	Author	Number	5-Year Survival (%)
1992	Finley et al[83,*]	18	29
1996	Wedman et al[84]	21	59
1997	Nibu et al[81]	32	32
1999	Liu et al[80]	83	50

*Included only patients with squamous cell carcinoma metastasis.

Pulmonary metastasis at the time of presentation in these patients is common, approaching 50% in patients with retroperitoneal disease.[86] Residual masses after chemotherapy are present in approximately 50% of patients and could contain viable malignancy, mature teratoma, or only fibrosis and/or necrosis.[86] Surgical resection of these lesions is crucial to identifying which of the preceding components is present, to predicting outcome, and to determining if any further therapy is warranted. The estimated 5-year survival rate after pulmonary metastasectomy ranges from 59% to 77% (Table 58-9).[85–87] The most significant prognostic factor is the presence of viable tumor cells in the resected specimen. Liu and coworkers[85] reviewed the experience at Memorial Sloan-Kettering Cancer Center over a 28-year period of 157 patients undergoing pulmonary metastasectomy for germ cell tumors. After resection, viable tumor was found in 70 patients (44.5%), necrosis in 47 patients (29.9%), and mature teratoma in 40 patients (25.4%). Survival was significantly poorer in those patients with viable tumor cells (43% over 10 years) as compared with those patients with necrosis/fibrosis (86% 10-year survival) or mature teratoma (84% 10-year survival).[85] The presence of mature teratoma in a specimen did not significantly worsen prognosis. The inability to make an accurate determination of the presence or absence of viable tumor cells in all residual lesions after treatment for germ cell tumors mandates that all of these lesions be resected to determine overall prognosis and potential for further therapy.

More recently, Kesler and colleagues[88] reported the results of resection in 134 patients with either lung or mediastinal metastases. The overall survival at 5 years was 42.3%. Older patient age, lung rather than mediastinal metastases, and the number of metastases (four or more) adversely influence survival.

Breast Cancer

Breast cancer is the most prevalent cancer among women in the United States, with approximately 100,000 cases occurring annually.[89] Approximately 15% to 25% of patients with metastatic disease will have their disease confined to the thorax. The data regarding

Table 58-9 Survival of Patients Undergoing Pulmonary Metastasectomy for Germ Cell Tumors

Year	Author	Number	5-Year Survival (%)
1998	Cagini et al[86]	141	77
1994	Anyanwu et al[87]	104	59
1998	Liu et al[85]	157	68
2005	Kesler et al[88]	134	42.3

pulmonary metastasectomy are controversial, with most studies analyzing the outcome of encompassing small groups of patients treated over several decades. The largest series reported to date is by Friedel and colleagues[90] from the International Registry of Lung Metastases. They reported on 467 patients undergoing pulmonary metastasectomy for breast cancer. Complete resection of all metastasis was possible in 84% of patients. The 5-year overall survival was 38% in patients with complete resection, as compared with 18% of patients with incomplete resection ($P = 0.0009$). A long disease-free interval and fewer lesions were associated with a longer survival in this group.[90] McDonald and associates[91] reported on 60 patients undergoing pulmonary metastasectomy for breast cancer and failed to show a survival benefit for surgical management. Because breast cancer also frequently progresses to extrathoracic disease and is sensitive to current systemic therapies, pulmonary metastasectomy is rarely an appropriate treatment option. Indeed breast cancer is an example of the evolution of the role of pulmonary metastasectomy. Before the advent of effective hormonal and chemotherapy, pulmonary metastasectomy was commonly performed for breast cancer with metastases confined to the lungs. Surgery is now infrequently considered for treatment.

Nonsurgical Approaches to Lung Metastasis

Two therapeutic options are emerging as potentially effective alternatives to resection in selected patients with lung metastases: stereotactic body radiation therapy (SBRT) and radiofrequency ablation (RFA). SBRT is a method for delivering focused radiation to a tumor while excluding tissues not grossly involved with the tumor. It is usually delivered as high-dose hypofractionated treatment over just a few days and is therefore an attractive option for patients who have advanced disease or who may also require chemotherapy within a short interval of local therapy. Several small series now report excellent local tumor control rates with low toxicity (Table 58-10). Small, solitary peripheral tumors have been considered the ideal target for SBRT, although some series include patients with larger tumors, multiple lesions, or tumors that include the midline and the hilum.[92] The length of follow-up after SBRT is relatively short in most series,

Table 58-10 Published Treatment Concepts and Results of Stereotactic Radiotherapy of Targets in Thorax

Author	No. of Patients	No. of Targets	Average No. of Targets (per patient)	Median Lesion Volume (range)	Central Tumor Dose (Gy)/ No. of Fractions	Isodose Treated (%)	Crude Local Control (%)	Median Follow-up Time in Months (range)	Acute Toxicity (Grade 1–2) (%)	Acute Toxicity (Grade 3–5) (%)
Blomgren et al, 1998[102]	13	17	1.3	48 mL (3–198)	21–66/1–3	66	94	8.2 (3.5–25)	NA	NA
Uematsu et al, 1993[103]	45	66	1.5	2.5 cm (0.8–4.8)	38–94/5–15	80	97	11 (3–31)	11	0
Wulf et al, 2001[104]	26	27	1	57 mL (5–277)	45/3	65	85	8 (2–33)	22	8 (Grade 5)
Nakagawa et al, 2000[105]	15	22	1.5	Chest wall 40 mL (5–126), Central lung 4.5 mL (0.8–13)	15–45/1* 18–25/1*	NA	95	10 (1–82)	100 (Grade 1)	0
Uematsu et al, 2001[106]	50	50	1	3.2 cm (0.8–5)	38–75/5–10	80†	94	36 (22–66)	—‡	0
Nagata et al, 2002[107]	40	43	1.1	12.6 mL (0.5–39)	40–48/4	100	94	18 (3–29)	95 (Grade 1)	0
Hara et al, 2002[108]	19	23	1.2	4 mL (1–16)	23–36/1	100	79	13 (3–24)	5 (Grade 2)	5 (Grade 3)
Onimaru et al, 2003[109]	45	57	1.3	2.6 cm (0.6–6)	48–60/8	100	88	18 (2–44)	2.2 (Grade 2)	2.2 (Grade 5)
Hof et al, 2003[110]	10	10	1	12 mL (5–19)	19–26/1	100	80	15 (8–30)	70 (Grade 1)	0
Lee et al, 2003[111]	28	34	1.2	41.4 mL (4.4–230)	30–40/3–4	100	91	18 (7–35)	100 (Grade 1)	0
Timmerman et al, 2003[112]	37	37	1	22.5 mL (1.5–157)	24–60/3	100	84	15.2 (2–30)	95 (Grade 1–2)	5 (Grade 3)
Wulf et al, 2004[113]	61	71	1.2	17 mL (1–277)	33–56/1–3	66–80	92	9–11 (2–61)	7	0
Okunieff et al, 2006[92]	49	125	2.6	4.7 mL (0.1–125)	50/10	100	94	18.7 (4–61)	41 (Grade 1–2)	2 (Grade 3)

NA, not available.
*Only tumor peripheral dose reported. All but one patient also received 20–40 Gy fractionated radiation.
†Prescribed doses were 30–60 Gy. The isodose line used varied and for this table it was assumed to be 80% based on the examples published.
‡"Most" patients had Grade 1. No patients experienced toxicity greater than Grade 1.
From Okunieff P, Petersen AL, Philip A, et al: Stereotactic body radiation therapy (SBRT) for lung metastases. Acta Oncol 2006;45:808–817.

and there are no randomized trials comparing SBRT to surgical pulmonary metastasectomy. The optimal total radiation dose and dose per fraction, and the need for respiratory gating during treatment, are not yet fully defined.[93]

RFA is a thermal energy system delivered via percutaneous needle placed under imaging guidance into a tumor. RFA causes tumor destruction by coagulation necrosis. There is even less experience with RFA than with SBRT for the treatment of pulmonary metastases. Currently most institutions limit the use of RFA to peripheral tumors less than 5 cm in size. However, local recurrence rates of up to 50% are reported, and serious complications including hemorrhage, pneumothorax, severe pleuritic pain, and effusions occur with RFA. Long-term follow-up data in large numbers of patients are lacking.[94–97]

Both SBRT and RFA are potentially promising alternatives to surgical pulmonary metastasectomy in selected patients. However, well-designed prospective clinical trials are needed to define the indications for these nonsurgical approaches along with the associated risks and long-term outcome. Certainly, either of these modalities may be appropriate options for patients who are not surgical candidates.

Other Investigational Approaches to Lung Metastases

Two additional approaches have been investigated for the treatment of unresectable pulmonary metastases: isolated lung perfusion (ILP), and transpulmonary chemoembolization.[98,99] ILP is an extension of the technique of isolated organ perfusion originally developed for limb perfusion of patients with malignant melanoma or sarcoma. First developed by Johnston and coworkers[100] in 1983, ILP requires surgical exploration via thoracotomy or median sternotomy, isolation and cannulation of the pulmonary artery and veins, and chemotherapy perfusion of the isolated lung. However, clinical trials in humans have shown that ILP can be associated with significant pulmonary toxicity. The technical complexity and potential morbidity of this approach to treatment have prevented widespread acceptance of ILP. It remains an investigational treatment modality that should only be used within the context of clinical trials.[98]

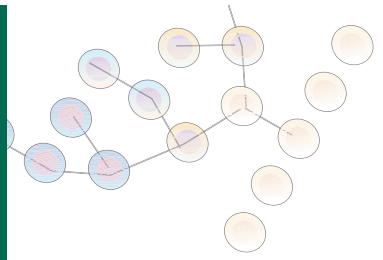
Transpulmonary chemoembolization is a method of delivering chemotherapy to the lung without surgery. Selective percutaneous image-guided catheterization of segmental pulmonary arteries is performed with a balloon catheter that occludes blood inflow. Chemotherapy is injected into the segmental pulmonary artery, which is then occluded by a second injection of microspheres. In a small trial involving 23 patients, Vogl and colleagues[99] performed transpulmonary embolization of 26 lung metastases. Tumor regression was observed in 8 patients and tumor stabilization in 6 patients. Treatment was well tolerated with only minor complications. Though clearly an investigational approach to treatment, transpulmonary chemoembolization seems to warrant further study for patients with unresectable pulmonary metastases.

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59 Liver Metastases

Nancy Kemeny, Margaret Kemeny, and Laura Dawson

SUMMARY OF KEY POINTS

Incidence

- Liver metastases are most frequently seen in patients with colorectal cancer (CRC; nearly 15% of patients presenting and an additional 60% developing subsequent spread); they are less common in patients with breast cancer (4% of initial failures), lung cancer (15%), and melanoma (24%).

Etiology

- The liver has a rich blood supply from both the hepatic artery and the portal vein; metastases can reach the liver from any organ, but the direct passage of blood from the gastrointestinal tract to the liver via the portal circulation plays a critical role in explaining the high rate of liver metastases from these sites.

Detection

- Contrast computed tomography (CT) and magnetic resonance imaging (MRI) can detect approximately two-thirds of liver metastases.
- CT angiography, CT portography, and intraoperative ultrasound seem to have increased sensitivity as compared with standard techniques.
- Positron emission tomography (PET) is more useful to detect extrahepatic disease.
- Of laboratory tests, carcinoembryonic antigen (CEA) can be useful for patients with metastatic CRC to the liver.

Treatment

Hepatic Resection

- There is general agreement that surgical resection is the treatment of choice for patients with one to three metastases from CRC, producing a 5-year survival of about 30%.
- Significant advances in surgical technique include the ability to perform metastasectomies (rather than formal lobectomies) and total vascular exclusion.
- The liver is the chief site of relapse after hepatic resection (50% of all patients).
- Prognostic variables that influence survival after hepatic resection include the presence of extrahepatic disease, the stage of the primary colon cancer, the time interval between primary and the development of hepatic metastases, and the number of metastases and positive margins.
- The use of adjuvant hepatic artery infusion (HAI) after liver resection has produced positive results in two American trials. There is a clear decrease in hepatic recurrence with adjuvant HAI.

Systemic Chemotherapy

- The objective response rate with intravenous chemotherapy is improving, with response rates of 40% to 50% among patients with breast cancer, gastric cancer, and now even colon cancer.

Hepatic Artery Infusion

- Eight randomized trials demonstrate a higher response rate for HAI than for systemic infusion (42% to 64% vs. 0 to 38%, respectively). Survival advantage is difficult to interpret: two large U.S. studies allowed a crossover from systemic therapy to HAI after tumor failure. New CALGB study without crossover showed a survival advantage. The chief toxicity of HAI is biliary enzyme elevations in 40% and biliary sclerosis in 5% to 35% of patients.

Hepatic Artery Embolization

- Embolization could play a role in highly vascular tumors (neuroendocrine tumors and hepatocellular carcinoma, HCC).
- Embolization agents include Gelfoam, lipiodol, and degradable starch microspheres.
- Embolization is rarely useful for patients with metastatic CRC.
- Chemoembolization involves the local entrapment of drug in the embolization agent in an attempt to provide a prolonged exposure of the tumor to drug locally, with less systemic exposure.

Ablative Techniques

- Cryosurgery involves destruction of tissue using a freezing probe.
- Limitations include the difficulty of controlling freezing and the typical requirement for laparotomy.
- Radiofrequency ablation involves destruction by frictional heat and can be used percutaneously but is rarely good for lesions larger than 3 cm.

Absolute Ethanol Injection

- Ethanol is injected into the tumor under ultrasound guidance and could be of use for small HCCs.

Radiation

- Whole-liver external-beam irradiation therapy alone is limited by the occurrence of radiation hepatitis to about 30 Gy in 15 fractions.
- Parts of the liver can be treated to far higher doses using yttrium-90 (^{90}Y) microspheres, interstitial brachytherapy, and external-beam irradiation therapy guided by three-dimensional treatment planning.

INTRODUCTION

Not so long ago an oncology textbook would not have devoted an entire chapter to liver metastases. Oncologists were so pessimistic about the appearance of such metastases that "no treatment" was often the recommendation. Enormous changes have occurred, so that now, diagnosing liver metastases early can lead to effective treatment and even cure for a growing percentage of patients.

The liver is the primary site of metastases for many malignant neoplasms. Gastrointestinal malignancies are especially prone to spread to the liver because of its portal venous drainage. Extra-abdominal tumors such as bronchogenic carcinoma, breast cancer, and malignant melanoma often spread hematogenously to the liver.

For gastrointestinal tumors, differences are seen in the natural history of the hepatic metastases. In some circumstances, hepatic metastases are a sign of disseminated disease. When gastric and pancreatic cancers metastasize to the liver, the mean survival is short, and widespread metastases often exist, so that radical measures such as hepatic resection or hepatic artery infusion (HAI) are rarely appropriate. In contrast, for colorectal cancer (CRC) the liver might be the sole site of metastatic disease, and a sizeable number of these patients might have isolated liver metastasis. In this setting, progress has been significant in the areas of hepatic resection, regional chemotherapy, and radiation therapy as discussed in this chapter.

For nongastrointestinal tumors, metastases to the liver are less common as the initial site of relapse. Although breast, lung, and melanoma are the main extragastrointestinal cancers to metastasize to the liver, initial isolated metastases in the liver occur in 4%, 15%, and 24% of these patients, respectively.

Treatment of these types of metastases varies according to the sensitivity of the tumor type to chemotherapy. Those that are more sensitive to antineoplastic agents might benefit from systemic therapy or aggressive regional approaches (breast), whereas those that have limited response to chemotherapy (such as melanoma) may be approached regionally in the setting of a clinical trial. Special care must be exercised in choosing patients for regional therapy who do not have CRC, because diseases such as breast cancer and melanoma are rarely confined to the liver.

The last 20 years have witnessed new and more accurate methods of detecting and quantifying liver metastases, more advanced surgical techniques facilitating hepatic resection, and biologic advances that have increased the spectrum of available regional therapies. This chapter discusses advances in detection and treatment of liver metastases.

DETECTION

The need for early and accurate detection of liver metastases has become more critical as the guidelines for resectability of liver metastases have become more liberal. Furthermore, ablative therapies and conformal radiation therapy are more likely to control unresectable liver metastases detected at an earlier stage, with a lower burden of disease. The most common imaging modalities for liver metastases imaging and their usefulness are described in the sections that follow.

Imaging Techniques

Computed Tomography

Computed tomography (CT) has been used for more than 20 years to image hepatic metastases. Modern CT scanners are capable of rapid scanning and high-resolution three-dimensional images of the liver that can be acquired during one breath hold.[1] Projection and reformatted views can be useful when assessing the proximity of liver metastases to the vessels. CT images are routinely evaluated by two window levels to maximize detection of lesions. A soft-tissue window (width of 300–500 Hounsfield units) is used for the initial examination of the liver and adjacent abdominal architecture. A second setting with a narrow window and a lower width (100–150 Hounsfield units) is then used to evaluate the liver, because this setting increases contrast differences between the normal liver parenchyma and abnormalities.

Noncontrast Computed Tomography

Contrast CT is sometimes not possible because of contrast allergic reactions or renal impairment. Although the sensitivity and specificity of noncontrast CT is far reduced as compared to contrast CT, it may help in identifying hypervascular metastases (especially carcinoid tumors, islet cell tumors, and renal cell carcinomas) or visualizing calcifications or hemorrhage. Noncontrast CT often fails to distinguish hypovascular tumors from the liver parenchyma. Nonenhanced blood vessels may also appear as low-attenuation masses and be confused with metastases.[2]

Contrast Computed Tomography

Intravenous contrast is infused over approximately 2 min, with repeat imaging acquired during the infusion to capture the different enhancing phases of tumors. The two most useful phases for hepatic metastases are the arterial phase (25-sec delay) and portal venous phase (60-sec delay). During portal venous imaging, the liver parenchyma enhances and hypovascular metastases, such as those from CRC, appear as filling defects.[2] Most metastases are seen best in the portal venous phase, but some are best seen in delayed venous and occasionally arterial phases. Hypervascular liver metastases may be missed with CT, because very vascular metastases may enhance to the same degree as normal liver parenchyma. Delayed contrast CT, referring to scanning 4 to 6 hr after contrast injection, is most useful as an adjunct to increase the sensitivity and accuracy of contrast CT, because malignant lesions usually do not retain contrast and appear as hypodense areas within the enhanced normal liver parenchyma.[2]

Computed Tomography Angiography and Portography

The rapidity with which multidetector CT scanners can acquire images makes possible imaging of the entire liver during the peak of the bolus of intravenous contrast, supporting CT angiography and portography.[3] This noninvasive imaging can provide images of hepatic vasculature of superb quality, avoiding catheter angiography. This technique is useful to detect vascular anomalies that may help in planning of hepatic resection or hepatic arterial chemotherapy. Most often, imaging is acquired during an arterial phase and a portal venous phase.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) exploits differences in magnetic properties of atomic nuclei to produce images. When placed in a magnet, protons have a nuclear spin that aligns with the magnetic field and give off radiowaves (MR signal) on returning to equilibrium. As the chemical environment changes, there is a change in the frequency of the signal, and the image. Differences in the time to return to equilibrium (relaxation times) are exploited in MRI, using T_1- and T_2-weighted pulse sequences. Most commonly, axial imaging is used for liver metastases imaging; however, coronal or sagittal views can define better a tumor's proximity to adjacent vessels. The most common pulse sequences used for liver metastases imaging are a T_1- or T_2-weighted spin echo. The T_1 images generally show metastases as low-intensity lesions, whereas in T_2-weighted images, metastases are of high signal intensity (Fig. 59-1). T_2-weighted sequences are generally superior for detection and characterization of liver masses. Benign cysts and hemangiomas usually appear homogeneous and bright, whereas metastatic lesions are less bright and more heterogeneous.[2,4] Although MRI inherently provides for soft-tissue contrast, contrast agents, such as gadolinium (Gd) chelates, can improve diagnostic accuracy. Similar to CT, MR angiography can be used as a

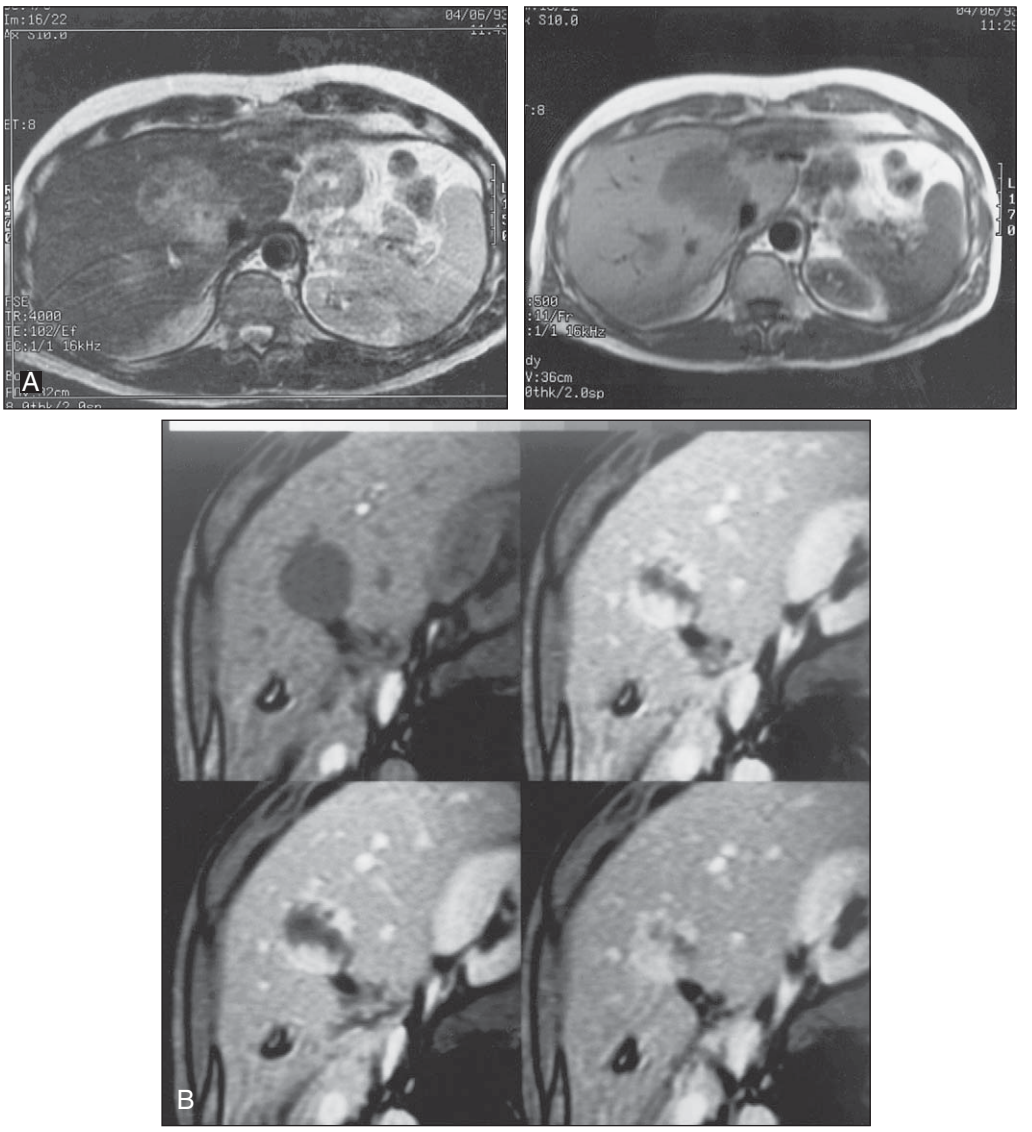


Figure 59-1 • **A,** T_2-weighted spin-echo image (*left*); T_1-weighted spin echo image (*right*). In T_2-weighted images the metastases are areas of high signal intensity. In T_1-wieghted images metastases have a low intensity. **B,** Dynamic gadolinium-enhanced MRI demonstrating peripheral nodular enhancement in a hepatic hemangioma. Enhancement increases as the study advances over time from upper left to lower left and then to upper and lower right.

noninvasive method to evaluate hepatic vasculature. Novel MR contrast agents have the potential for improving detection of liver metastases.[5] Advantages of MRI include the lack of radiation exposure to the patient and the low frequency of reactions to contrast agents. MRI is particularly useful for patients with contraindications to iodinated contrast, and MRI can detect hypervascular lesions that are not well visualized on CT. Limitations of MRI include inherent warping and the time required for imaging, which may lead to artifacts in patients who cannot hold their breath. Parallel imaging allows for high-resolution imaging of the entire liver within one breath hold, with the potential for more sophisticated sequences (such as diffusion-weighted imaging and MR spectroscopy) to improve liver metastases detection in the future.

Ultrasonography

Ultrasonography (US) relies on sound waves to generate an image. US is most commonly used for screening for metastases because of its wide availability and lack of the need for radiation exposure. It is most useful in detecting superficial liver metastases in small patients. Contrast-enhanced US, using intravascular microbubble contrast agents, has shown similar accuracy for liver metastases detection compared to CT and MR.[6] An advantage of contrast-enhanced US is the potential for characterization of liver lesions based on morphologic evaluation as well as temporal vascular enhancement pattern.[7] During the portal venous phase, benign lesions typically enhance more than the liver, whereas malignant lesions enhance less.[8] Expertise in contrast-enhanced US is not yet widespread.

Intraoperative US can also be useful at detecting small, deep hepatic metastases not palpable. In a study of 84 patients undergoing colon resection, intraoperative US detected 14 hepatic metastases that were missed on surgical palpation.[9] In a similar study, intraoperative US detected seven nonpalpable lesions in 70 patients.[10]

Positron Emission Tomography

Positron emission tomography (PET), in which a radioactively labeled tracer is administered to the patient and the scanner collects

the emitted positron radioactivity to generate an image, allows imaging of cellular processes (such as cellular proliferation (^{18}F-labeled thymidine), hypoxia (^{18}F-labeled Miso), and blood flow ([^{15}O]water) to be visualized. The majority of clinical experience has been with fluorodeoxyglucose ([^{18}F]FDG), which images cellular glucose metabolism. A limitation of PET scans of the liver is that they are acquired over many breathing cycles, leading to blurring due to respiratory motion and lower spatial resolution as compared with CT. This has driven the development of dual-modality scanners capable of CT and PET scanning. Scanners capable of respiratory sorting are also being developed.

FDG PET scans have been done to stage patients before resection of liver metastases[11–13] and to evaluate response to treatment.[14] In one study, 6 of 34 liver metastases treated with chemoembolization demonstrated persistent FDG PET activity, which led to further treatment.[15] FDG PET has also been found to be useful in diagnosing peritoneal recurrences in patients with elevated serum carcinoembryonic antigen (CEA), with a sensitivity and accuracy for peritoneal disease detection of 88% and 78%, respectively (as compared with 38% and 44% for CT).[16] In patients with colorectal liver metastases staged planned for resection, Ruers and colleagues found that 10 of 51 patients (20%) had a change in treatment plan due to unresectable metastases or extrahepatic metastases detected on FDG PET.[12] Other studies have also demonstrated a change in treatment resulting from FDG PET scans obtained before planned liver resection in 20% to 58% of patients.[13,17–19] In contrast, 15 out of 52 pathologically proven liver metastases were missed with FDG PET in another study, emphasizing that FDG PET cannot be the sole method used to evaluate liver metastases. Five-year survival of a series of 100 patients with liver metastases, imaged with FDG PET and treated with hepatic resection, was 58% (46% to 72%), demonstrating excellent outcomes in well-selected patients.[20] A continuing Canadian randomized trial of PET versus no additional imaging in resectable liver metastases, funded by the Ontario Clinical Oncology Group (OCOG), has the potential to more clearly define which patients with liver metastases planned for resection are most likely to have a change in treatment and benefit from PET scans obtained before resection (personal communication, Steven Gallinger, Toronto, March 2007).

Comparison of Modalities

Many studies have compared imaging modalities for the detection of liver metastases. A German study[21] prospectively compared dynamic CT with MRI and US in 75 patients with known gastrointestinal tumors before exploratory laparotomy. Ninety-five liver metastases were detected in 32 patients.[22] Of the 95 lesions, 68% were detected by CT, 63% by MRI, and 53% by US. Another prospective study involving 69 patients came to the same conclusion, and also demonstrated the superiority of MRI T_2-weighted images over T_1.[23] Other studies have shown improved detection of liver tumors with MRI,[24,25] and differences in the shape and size of hepatic metastases depending on which CT or MR sequence is used for imaging.[26] Overall, CT scans and MRI seem to have similar sensitivity and specificity for detection of liver metastases using state-of-the-art techniques at experienced centers.

Noncontrast external US has a lower rate of accuracy for liver metastases detection as compared with contrast CT or MRI. A unique study of US before liver transplantation allowed the accuracy to be determined pathologically.[27] Only 36 of 80 tumors in 34 patients were detected, indicating a sensitivity of 45%. The majority of lesions not detected were smaller than 1 cm. Contrast-enhanced US has demonstrated similar accuracy for liver metastases detection compared to CT and MRI.[6]

FDG PET can detect disease not seen on CT or MRI in patients with liver metastases.[12,13,28] In a comprehensive review of the literature,[11] the sensitivity and specificity of FDG PET for hepatic disease detection were 88% and 96% and for extrahepatic disease detection were 92% and 85%, respectively, as compared to 83% and 84% for hepatic disease and 61% and 91% for extrahepatic disease in CT. The management was changed based on FDG PET scans in 32% of cases on average. Overall, most studies have confirmed increased sensitivity of FDG PET as compared with MRI and CT, with increased sensitivity on a per-patient analysis as compared with a per-lesion analysis.[5] FDG PET is less sensitive for detection of small liver metastases (less than 1–2 cm) than state-of-the-art MRI or CT.[5,29,30]

At present, the standard of care for imaging of hepatic metastases is helical multiphasic intravenous contrast CT scan, with MRI or contrast-enhanced US alternatives for patients with contraindications to CT contrast. For patients whose treatment plan includes resection, extra imaging should be considered to help best select patients with liver-confined metastases.

Differential Diagnosis for Liver Metastases

The majority of liver metastases enhance on the portal venous phase of imaging. Arterial and portal venous phase imaging, using CT, MRI, or US, can help in distinguishing malignant from benign lesions and hepatic metastases from primary cancers. However, several benign lesions cannot always be reliably distinguished from metastases. Hemangiomas may be confused with highly vascular tumors and cysts. Dynamic Gd-enhanced MRI can help distinguish hemangiomas from tumors. Hemangiomas can also be mistaken for metastases in noncontrast CT scans and on portal phase contrast CT (see Fig. 59-1). Although portal phase contrast CT is sensitive in detecting small hepatic lesions, it has a high false-positive rate because benign lesions such as hemangiomas, cysts, adenomas, or flow artifacts may be confused with metastases. Technetium-99 (^{99m}Tc) red blood cell scintigraphy is the most specific noninvasive test to diagnose hepatic hemangioma (Fig. 59-2).[31] Table 59-1 lists some lesions that may be confused with liver metastases and suggests the tests to differentiate among those entities. A rare entity that can on occasion be confused with metastases is focal fatty infiltration of the liver (Fig. 59-3). This may be seen in patients receiving hyperalimentation. MRI is helpful for distinguishing these lesions.

Biochemical Laboratory Tests

Unlike imaging techniques, the laboratory tests that are available for liver function assessment are not very sensitive. The basic liver function tests include the alkaline phosphatase, bilirubin, albumin, prothrombin time, lactate dehydrogenase (LDH), and serum transaminases. For patients who have metastatic colon cancer, CEA is also extremely useful (see Fig. 59-3). Several studies have looked at the usefulness of these tests to detect liver metastases, especially metastases from CRC.[32–34] CEA remains the most sensitive test for CRC, but even this test can be normal in the presence of liver metastases, especially with minimal hepatic disease. In a prospective study at the City of Hope Hospital (Durante, CA, USA) in patients with metastatic liver disease deemed resectable by CT, the average alkaline phosphatase and LDH levels were within normal limits, whereas CEA was elevated in 73% of the patients.[35] Serum LDH is useful as a prognostic indicator, with high serum LDH denoting a poorer survival.[36]

HEPATIC RESECTION

Because of recent advances in techniques for liver surgery, hepatic resection for metastatic disease has become increasingly safe and used more frequently in treatment over the last two decades. Hepatic resection of metastases was first attempted just before World War II. Experience gained from trauma centers during the war led to the emergence of techniques applicable to resection of metastatic hepatic lesions. In recent years many new devices have helped in the technical aspects of the surgery and in the overall safety of the procedures.

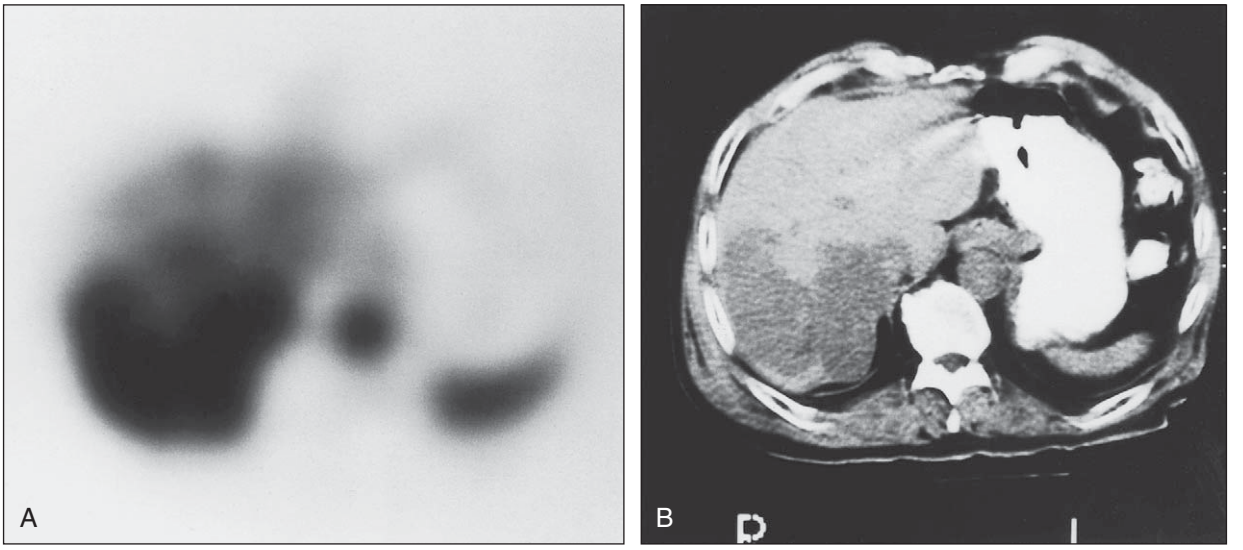


Figure 59-2 • Hepatic hemangiomas. **A,** Transaxial single-photon-emission computed tomography (SPECT) image obtained 2 hours after injection of ^{99m}Tc-labeled red blood cells. Normal blood activity is seen in the liver, and increased blood pooling activity is seen in the aorta and spleen (which is normal). There is a large area of increased blood pooling activity in the posterior section of the right lobe of the liver that corresponds to an area of reduced attenuation on the CT scan. **B,** The CT scan is obtained from the same plane as the SPECT scan. An increase in blood pooling activity with an increase in intensity from earlier images is specific for hemangioma.

In the last few decades hepatic resections have gone from formal lobectomies to resections along nonanatomic lines. Metastasectomies, or removal of the tumor plus a rim of normal hepatic tissue, can be done rather than a formal lobectomy. With the greater familiarity of the hepatic anatomic segments of Couinaud (Fig. 59-4),[37] current resections are more frequently being performed along these lines especially with the use of intraoperative US. These segment divisions cannot be seen by the naked eye on the surface of the liver but can be mapped out with the help of intraoperative US. In the modern operating room the use of intraoperative US is a necessary skill for the operating surgeon. This technique allows for both a reduction in the amount of normal liver removed and resection of disease from both lobes.

Table 59-1 Benign Liver Lesions That May Be Confused with Malignancy

Technique	Benign Lesions	Malignancy
MRI (T_2-weighted)	Vessels	Small metastatic lesions
	Hemangiomas	Highly vascular tumor (islet cell, renal, carcinoid)
	Cysts	Cystic tumors
	Cysts	Highly vascular tumors (islet cell, renal, carcinoid)
CT	Fatty infiltration	Metastases
	Fatty infiltration	Hepatocellular cancer
	Nonenhanced vessels	Metastases
	Adenoma	Abscess
CTP	Hemangioma	Metastases
	Cysts	
	Adenoma	
	Flow artifacts	
Angiography	Focal nodular hyperplasia Hemangioma	Metastases

CT, computed tomography; CTP, CT portography; MRI, magnetic resonance imaging.

Several new devices have been introduced to help with the resection itself. Probably the most commonly used device is the cavitron ultrasonic aspirator, which allows dissection of the liver parenchyma without entering the bile ducts. A new technique for dividing the parenchyma is the multiprobe bipolar radiofrequency device, which was introduced in 2004. This device uses radiofrequency waves to coagulate vessels and bile ducts in the liver parenchyma before dividing the tissue.[38] Other devices are available, but in the end it depends on the operating surgeons and their own techniques, which vary from center to center. No clear advantage has been established for one product over the other.

The operative technique of total vascular exclusion for hepatic resections involving tumors near to the vena cava was introduced in the 1980s by surgeons from the liver transplant community. With this technique the vena cava is cross-clamped in two areas (suprahepatic and subhepatic), and the porta hepatis is also occluded.[39,40] In Bismuth and associates'[41] report on 54 patients using total vascular exclusion, the average duration of cross-clamping was 46 min, and the average operating time was 6 hr. The transfusion requirements were low, and no intraoperative deaths occurred. The application of vascular occlusion seemed to be useful for tumors close to the vena cava or for large central tumors. Again, it is a technique to be used in special circumstances by surgeons who are familiar with the procedure.

The use of the autotransfuser, a technique pioneered in trauma patients, had been avoided initially for patients with malignancies because of fear that tumor cells might be disseminated into the bloodstream with this instrument. Prospective studies on patients undergoing hepatic resection for tumors have not shown this to be true.[42,43] Animal studies also support the concept that metastatic cells are organ specific and would not disseminate if introduced into the bloodstream. Because of these studies, many centers are using the autotransfusers during hepatic resection and reducing the need for multiple blood transfusions.

Another technical advance for hepatic surgery has been the use of fibrin glue, which can aid in sealing the large, raw surfaces of the liver left after major resections.[44]

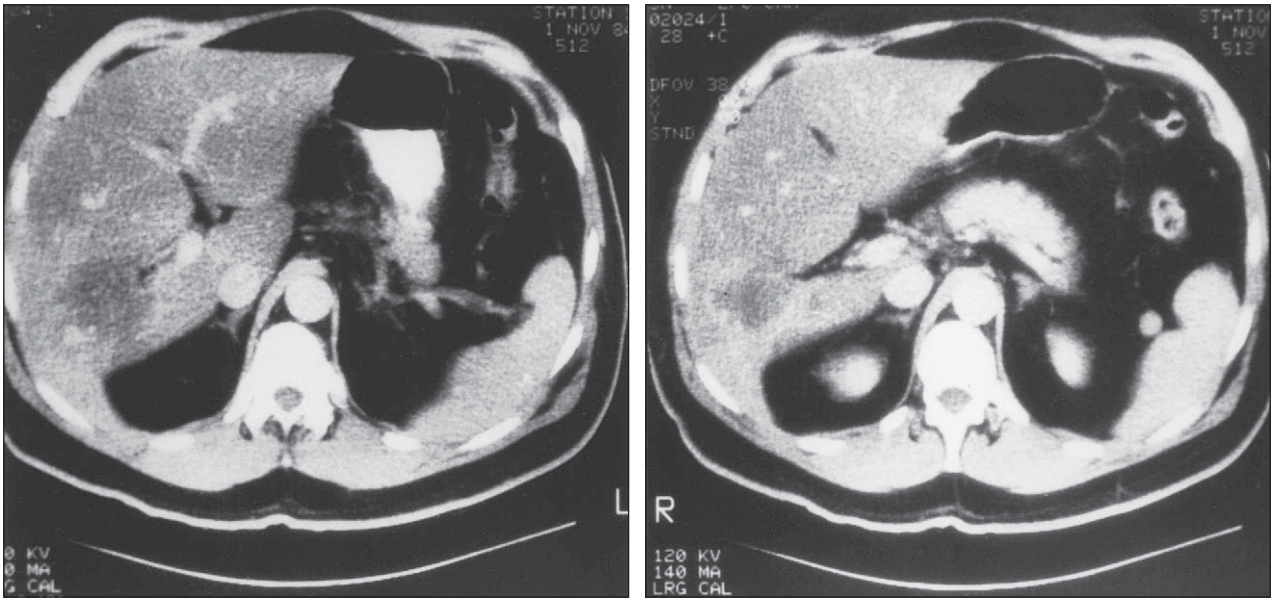


Figure 59-3 • Fatty infiltration. This lesion was thought to represent metastatic disease; surgery revealed it was only fatty replacement.

The question of drainage after hepatic resection has been addressed prospectively in a study that showed no difference in complications in the drained group versus the undrained group. When the data are analyzed more carefully, however, it becomes clear that patients with lobectomies or greater did benefit from drains, whereas those patients with smaller resections did not need drains placed.[45,46] However, this study was done before the advent of fibrin glue, which may reduce the need for drains.

In general, a major surgery such as a liver resection has been reserved for a situation in which the operation can be curative. Experience has shown that the resection of colorectal metastases to the liver can be curative in at least one-quarter of patients with certain requirements. The curability by resection of liver metastases from other primary cancers is not quite as clear. The resection of metastases from other gastrointestinal malignancies, such as stomach and pancreas, has been disappointing because of the aggressive nature of these tumors by the time they become metastatic.[47,48]

The performance of liver resections for metastatic disease from a breast cancer is controversial. Liver metastases from gastrointestinal tumors can be considered regional spread, but for the metastases to go from the breast to the liver requires release of the tumor cells into the systemic circulation. Thus, the concept that the liver could be the only site of spread is harder to prove, and as a result, curative intent is more difficult to achieve. Most of the literature about hepatic resections for breast cancer metastases has come from France. In a recent publication one hospital retrospectively reviewed their experience in 108 patients from the time of 1984 to 2004. Twenty-three (21%) of the patients were found to be unresectable at laparotomy because of intra-abdominal metastases or hepatic lesions that were technically not resectable. Of the 85 patients who had a liver resection, 38% had a solitary metastasis, 32% had two or three lesions, and 31% had more than three lesions. The metastases were small with an average size of 2.8 cm. The median follow-up of the patients was 38 months, with a median survival of 32 months. Only 18 patients were alive after 5 years. A multivariate analysis of factors showed only response to chemotherapy, the absence of extrahepatic metastases, and a clear margin at resection correlated with survival.[49]

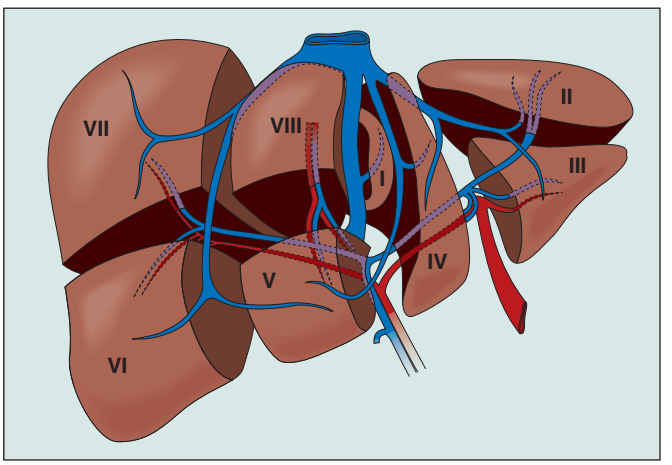


Figure 59-4 • Couinaud's eight hepatic segments. (From Iwalsuki S, Sheahan DG, Starzl TE: The changing face of hepatic resection. Curr Probl Surg 1989;25:281.)

Another Parisian team reported their experience from 1988 to 1997 with 49 liver resections for metastatic breast cancer. They reported no mortality and a morbidity of 11.5%. The 1-, 2-, and 3-year survival rates were 86%, 79%, and 65%, respectively. Recurrence in the remaining liver was seen in 49% of the patients at 3 years after resection. Recurrent disease anywhere in the body was seen in 63.8% of patients at 3 years after the resection. The only factor that correlated with survival was the disease-free interval between diagnosis of the primary breast cancer and the appearance of the liver metastases, with a 3-year survival of 45% if the liver metastases appear in less than 4 years after the primary breast cancer versus a 3-year survival of 82% if the breast cancer was more than 4 years from the appearance of the liver metastases.[50]

Another study from Paris reported on a smaller number of resections of solitary hepatic metastases from breast cancer.[51] Of the 32 patients with isolated liver metastases, 27 were found to have actual metastatic disease, whereas 5 had benign disease. Six of the 27 had diffuse disease that was not amenable to resection, whereas of the 21 who underwent hepatic resection, the average survival time was 26 months. For both of these studies there is no way of judging the usefulness of hepatic resection versus chemotherapy for these patients. It is interesting to note that the more recent study has a superior

survival time. This could signify several factors, including better drugs and improved selection. That the disease-free survival (DFS) is still quite low, however, emphasizes that even with strict patient selection, the chance of cure with a liver resection is quite limited, but real. Thus patients who have metastatic disease to the liver due to breast cancer need to be screened carefully before they are offered resection as a therapeutic option. Issues such as other sites of metastatic disease, response to chemotherapy, and disease-free interval between breast cancer and liver metastases all must be considered before hepatic resection.

Gastrointestinal neuroendocrine tumors frequently metastasize to the liver but their growth is often slow, and patient survival can be prolonged even without surgical intervention. Both the rarity of these tumors and their prolonged course make them poor candidates for prospective trials. Thus, the role of hepatic resection for metastatic neuroendocrine tumors can only be evaluated in a retrospective manner. At the Mayo Clinic, over a 20-year period from 1970 to 1990, only 37 patients with hepatic metastases from a neuroendocrine tumor had a resection (17 curative resections and 20 palliative resections).[52] Eleven of the 17 patients with curative resections were alive 1 to 92 months after surgery (median 19 months) without evidence of disease. Of the 20 patients who underwent palliative resection, 1 died in the postoperative period, 8 died of disease 9 to 76 months after resection, and 19 patients had some relief of symptoms. The authors concluded that resection is reasonable in cases in which the bulk of tumor can be removed and the patients are symptomatic. A second report from the Mayo Clinic reviewed their hepatic resections for neuroendocrine tumors from 1984 to 1992, with a total of 74 cases.[53] Because this is a report from the same institution and there is some overlap of the time period, clearly many more resections were done in the later years (1990–1992) than in the two decades before. The study included patients whose primary tumors were either completely resected or potentially completely resectable. Patients with carcinoid syndrome were injected with subcutaneous somatostatin preoperatively. Most patients[54] had nonanatomic resections, although 36 had a lobectomy or greater. The mortality rate was 2.7%, and the morbidity was 24.3%. Overall survival at 4 years was 73%, with a mean follow-up of 2.2 years. All of the 12 patients who died had tumor progression. There was no significant survival difference among those patients who had curative resections (that is, removal of all gross disease) versus those who had palliative resections. Symptom relief was seen in 90% of patients. The authors concluded that resection should precede hepatic arterial occlusion and systemic chemotherapy, because it provides an excellent response rate and good survival. Other studies with considerably fewer patients also support this conclusion.[55–57]

A review of the literature in 2002 reported on 227 patients with hepatic surgery for metastatic malignancies. The operative mortality for the 212 patients with carcinoid tumors was 2.3% and morbidity was 71%. The overall 5-year survival was 71%, and when looking at only the metastatic islet cell tumors, the survival was even higher at 82%. Symptomatic relief from carcinoid syndrome was 86% with a duration of 4 to 120 months. Some discussion of ablative techniques was offered, but only with very preliminary results. The analysis of these sorts of data suggest that for selected patients liver resection is safe, appropriate, and can result in long-term survival and relief from endocrinopathy symptoms. Guidelines for resection include the preoperative assessment that the primary and metastatic disease is completely resectable (Box 59-1).[59]

The other noncolorectal tumors metastatic to the liver that have been resected enough to have reported studies are the sarcomas. The largest retrospective review comes from M.D. Anderson Cancer Center with 66 patients having liver surgery for metastatic sarcoma. The mean size of the lesions was 3.9 cm and mean number of lesions was 3. The majority of patients had a gastrointestinal stromal tumor (GIST) (36 patients), 18 had a leiomyosarcoma, and the rest had various other sarcomas. Thirty-five patients had resection, 13 patients had radiofrequency ablation (RFA), and 18 patients had the combination of resection and RFA. The operative mortality and morbidity were 4.5% and 15.2% respectively. The recurrence rates were high with 85% of patients, with RFA recurring, 89% with the combination of resection and RFA recurring, and 57% of patients with resection only recurring (statistically better for this group). The 5-year DFS and overall survival were 16% and 27%, respectively. The article discussed the issue of the GIST tumors and the targeted therapy with Gleevec (imatinib mesylate). The authors felt that resection was still recommended for the GIST tumors, because the rate of complete response with imatinib mesylate was only around 5%, and the bulk of the patients progressed after 2 years on treatment. The conclusions of the report were that although recurrence is high, hepatic resection in selected patients is indicated and will lead to longer survival.[60]

The group at Memorial Sloan-Kettering (MSKCC) reviewed their experience with hepatic resections for sarcomas in the period from 1982 to 2000. There were 331 patients with liver metastases from a variety of primary sarcomas, 56 of whom had a hepatic resection. Thirty-four of the 56 patients had a GIST. Ten of the 56 patients have actually survived for 5 years, but only 2 are disease free. The disease-specific survival rate for 3 and 5 years was 50% and 30%, respectively. The patients with GIST had the same survival as those with other types of sarcoma. The time interval (less than or greater than 2 years) between the appearance of the primary sarcoma and that of the liver metastases had a significant influence on survival and was the only independent prognostic variable in a multivariate analysis.[61]

An analysis of hepatic resection for leiomyosarcomas from Germany reported a 40-month median survival in patients who had all tumor removed with negative margins. The conclusions from this study, similar to the other reports, were that hepatic resection for leiomyosarcomas could be done safely and in selected cases could prolong survival. Most of the other reports in the literature about resection of hepatic metastases from sarcomas are anecdotal, with far fewer patients in each study.[62,63]

The use of hepatic resection for metastases from melanoma is moderately rare as seen in a report from two major melanoma centers, where 1750 patients with hepatic metastases from melanoma were identified and only 34 of them had a surgical exploration with the intent to resect the tumor from the liver. Of the 34 patients explored, 24 went on to hepatic resection and 18 of them actually had a resection with curative intent. The median DFS and overall survival in the 24 patients with resection were 12 months and 28 months, respectively. When this was compared with the 6-month overall median survival in the 899 patients with hepatic metastases treated

Box 59-1. SURGICAL GUIDELINES FOR HEPATIC RESECTION

The existence of extrahepatic intra-abdominal metastases should be excluded before attempting a hepatic resection. Because the periportal lymph nodes are the most common site for intra-abdominal extrahepatic metastases, biopsy samples from them should be taken and sent for frozen section. If extrahepatic disease is present the hepatic resection should not be carried out.

The extent of a hepatic resection can span from one small nodule to a trisegmentectomy by which 75% of the liver is removed. The assessment of patients for trisegmentectomy is very difficult, because no tests are currently available to delineate accurately which patients can survive with a 75% loss of liver mass. In general, however, if a patient has cirrhosis, an extensive resection is discouraged. Debilitated (poor performance status) patients are not good candidates for major hepatic resection. Age alone should not preclude a patient's eligibility for hepatic resection.

nonoperatively, it was significantly better. The two major contributors to improved survival seemed to be longer disease-free interval between the primary melanoma and the development of hepatic metastases, and limited hepatic disease that could be completely removed. For the select patients who would fit these criteria—and obviously there are not many—they seemed to benefit from hepatic resection.[64]

Unlike these other primary tumors, the data on the resection of colorectal metastases to the liver has been advancing exponentially over the last 30 years. In the United States, there are more than 50,000 patients each year with liver metastases from CRC. The rate of resection of these metastases has been increasing because of the expanding patient eligibility criteria. In the last decade there have been several retrospective reviews of resection of hepatic metastases from colorectal primaries—some with more than 1000 patients—that have added to the knowledge of which patients will benefit from resection.[54,65–69] In the two largest series, the 5-year survival for patients with one to three metastases who had a resection was 30% or greater.[65,66] Because of the strong feeling over the last three decades that resection was the optimal treatment for patients with one to three metastases, no randomized study of resection versus any other treatment has been performed. Two early studies compared the survival of matched historical control patients who underwent resection with those who had solitary hepatic lesions but did not undergo surgery.[70,71] In both studies, not 1 of the 120 patients without resection survived for more than 3 years, whereas 30% of the resected patients survived for 5 years, underscoring the rationale for resection of solitary lesions.

The retrospective series from MSKCC reviewed their experience with 1001 liver resections in patients with colorectal metastases from the years 1985 to 1998.[65] Because the study was reported in early 1999, there were many patients who did not have a 5-year follow-up; in fact; the median follow-up of survivors was 32 months, which might not be long enough to tell us which patients would survive to 5 years. The median number of liver tumors was two, with 517 patients having solitary lesions and 330 having two or three lesions (Table 59-2). The operative mortality was 2.8%. The 3-, 4-, and 5-year survival rates were 89%, 57%, and 37%, respectively; however, only 24.6% of patients resected before 1994 are 5-year survivors. The number of tumors removed (one or greater than one), the size of the tumors removed (greater or less than 5 cm), the preoperative CEA level (greater or less than 200 ng/mL), the extent of resection (less than or greater than a lobectomy), the resection margin in the hepatic specimen (negative or positive), and the presence of extrahepatic disease all were highly significant univariate and multivariate predictors of postsurgical survival. From these data, a clinical risk score was devised using five clinical criteria: the nodal status of the primary CRC, the disease-free interval from the primary CRC to the development of liver metastases, the number of hepatic tumors, the prehepatic resection CEA level, and the size of the hepatic tumors. Each criterion was given 1 point if the inferior condition existed, and then the points were added to give the score. The 5-year actuarial survival for a clinical risk score of zero was 60% as compared with a 14% survival for a score of 5. This gives surgeons a good insight into the prognostic expectations, but the score was not really intended for exclusion of patients from resection.

Another large series was a multi-institutional report from France reviewing 1568 patients who underwent resection of liver metastases from CRC (Table 59-3).[66,72] Like the previous report, this study also looked at the effect of numerous prognostic indicators on overall survival after liver resection and then combined seven indicators into a prognostic scoring system. In this study, the 5-year survival among patients who had a resection of four or more lesions was 14% as compared with 30% for three or fewer nodules ($P = 0.001$). Both large studies, together with others, emphasize that the resection of more than four hepatic lesions results in significantly fewer cures, whereas for patients with one to three metastases, agreement exists that resection is worthwhile and can offer at least a 30% 5-year survival.[65–70,72–76]

The French series found that one of the most significant prognostic variables was the stage of the primary lesion. For patients with CRC and negative lymph nodes (stage II), the 5-year survival after hepatic resection was 35% as compared with 26% for patients with mesenteric lymph node involvement ($P < 0.001$). Other studies addressing the issue of stage are listed in Table 59-4.[73,76–80] In the French study, preoperative serum carcinoembryonic antigen (CEA) was also significant; patients with a CEA value of less than 5 had a 2-year survival of 70%, as compared with a 56% 2-year survival for patients whose CEA was above 30. For patients with tumor nodules smaller than 5 cm, survival was 30% as opposed to 26% for larger nodules ($P = 0.002$). The age of the patient was not found to be significant in this study or others.[81] The time between the primary tumor and the development of liver metastases in this and other studies was significant for prognosis if the time periods were divided to include at least the first year with the synchronous lesions (Table 59-5).[76–80]

Table 59-2 Five-Year Survival after Hepatic Resection of Colorectal Cancer Metastases Based on Number of Lesions Resected

		No. of Metastases (% of 5-Year Survival)			
Study Group	**No. of Patients**	**1**	**2–3**	**>1**	**>3**
Memorial Sloan Kettering[65]	441	44			
	510			28	23
France[63]	1350	30			
	183		30		14
Mayo Clinic[68]	187	31			
	70				
	23		29		9
Italy[72]	134	20			
	78			17	
Hepatic Registry[73]	789	37	37		18
Liver Met Survey[49]	2122		42*		26

*<3.

Table 59-3 Prognostic Variables in the Multi-Institutional Study from France

Prognostic Values	5-Year Survival (%)	*P* Value
Age		
< 60 yr	28	0.06
>60 yr	27	
Tumor size		
<5 cm	30	0.002
>5 cm	26	
Stage of primary		
Dukes B	35	0.001
Dukes C	21	
Disease-free interval		
<2 years	26	0.002
>2 years	32	
No. of nodules resected		
<4	30	0.0001
>3	14	
Resection margin		
>1 cm	32	0.0006
<1 cm	16	
CEA		
<5	70*	0.0001
>30	56*	

CEA, carcinoembryonic antigen.
*2-year survival (%).
Data from Nordlinger B, Guigiet M, Vallant JC, et al: Surgical resection of colorectal carcinoma metastases to the liver. Cancer 1996;77:1254–1262.

There have been conflicting reports about the importance of the margin of resection when removing hepatic metastases. Although the cutoff used in the French study was different from that used in the Memorial study, the margin of normal hepatic tissue around the resected metastases was significant. For those patients with a margin greater than 1 cm, 32% of patients survived for 5 years, as opposed to a 16% survival for those with a margin less than 1 cm ($P = 0.006$). A report from Germany in 1991, however, showed no significant difference in survival among over 170 patients relative to their margins of resection.[80] This study assigned the margins to three groups: 1–4 mm, 5–9 mm, and greater than 10 mm. More recent studies support this study by showing that if there is no margin of clearance between the tumor and normal liver parenchyma, patients do worse, but whenever there is a margin, the difference between 1 mm, 10 mm, or greater is not significant (Table 59-6).[40,41] These data are understandable from a pathologic standpoint, because these tumors tend to be firm nodules with pushing borders and even a small margin would remove all of the tumor, whereas a positive margin would leave cells behind. This would not be true for primary hepatocellular carcinomas (HCCs), as they can have more diffuse, infiltrative borders.

The French authors created a scoring system by using these seven variables, giving one point for each bad variable and two points for a CEA value over 30.[66] A 2-year survival of 79% was calculated for patients with a score of 0 to 2 points, 60% if they had scores of 3 to 4 points, and 43% if they scored 5 to 7 points.[66] These prognostic scoring systems from the French study and the Memorial study are valuable tools to estimate patients' survival after a resection. For patients with poorer prognoses, other therapies might be added to surgery to try to improve their chances.[66,72]

Although recent studies have suggested that resection of four or more lesions can result in 5-year survivals equivalent to those after resection of one to three lesions, these reports must be examined with caution. A report of 98 patients with hepatic resection of four or more colorectal metastases reported an actuarial survival of 33%. Yet the median follow-up was only 33 months, which is too short for patients with liver resections. The DFS for these patients was 12 months, and 83% of the patients had recurrence. Of this whole group there were only seven actual 5-year survivors, and all of them have recurrent disease. One important point from this article is that the worst survival was seen in patients whose disease was progressing while receiving neoadjuvant therapy before the liver resection.[82]

The Liver Met Survey is an international Internet-based registry that has entered 2122 patients. The 5- and 10-year survivals are 42% and 26%. The 5-year survivals for three or fewer nodules and more than three nodules were 48% and 24% ($P = 0.0001$). Another variable that affected survival concerned whether the tumor was unilateral or bilateral. In this review, preoperative chemotherapy did not benefit patients with solitary metastases (5-year survival of 45% vs. 58%), whereas for patients with more than five metastases, 5-year survivals were 22% and 12% for patients with and without previous chemotherapy.[83]

Table 59-4 Survival after Hepatic Resection Based on Stage of Primary Colorectal Cancer

Study Group	No. of Patients	Dukes Stage	No. of Patients	5-Year Survival (%)	*P* Value
Milan[77]	95	B	29	47	0.02
		C	50	24	
United States[73]	789	B	226	47	0.001
		C	317	23	
Paris[78]	97	B	39	52	NS
		C	58	53	
Rotterdam[79]	117	B	53	26	NS
		C	54	11	
Erlangen[319]	173	B	49	53	0.01
		C	119	32	
Italy[76]	212	B	69	32	0.001
		C	116	11	

Table 59-5 Survival after Hepatic Resection Based on Synchronicity of the Hepatic Lesions and the Primary Colorectal Cancer

Study Group	No. of Patients	Synchronous	No. of Patients (in each group)	5-Year Survival (%)	*P* Value
Milan[77]	95	Yes	28	31	NS
		No	67	28	
Rotterdam[79]	117	Yes	38	15	NS
		No	79	22	
Erlangen[319]	173	Yes	85	32	0.05
		No	88	45	
Heidelberg[320]	122	Yes	48	2	0.01
		No	74	16	
United States[73]	789	Yes	259	27	
		1–12 mo	206	31	
		>12 mo	333	42	0.02
Paris[78]	97	Yes	35	52	NS
		No	62	52	
Italy[76]	212	Yes	85	18	NS
		No	113	22	

A group from Paris reporting on surgery for patients who had been downstaged by chemotherapy also found that if the tumors' pathologic response to chemotherapy was less than complete necrosis, the survival after resection was significantly decreased ($P = 0.002$).[84] This group of patients with more than four lesions and progressing disease should probably not be candidates for surgical resection. The use of the PET scan may help increase the survival of patients with liver resections from colorectal primaries because of improved selection of patients. A study of 100 patients who were shown to have disease confined to their liver by PET scan reported a 5-year survival of 58%. PET scan is believed to detect unsuspected tumors in 25% of patients who would have otherwise been considered to have only resectable hepatic metastases. This was not a randomized study, so it is difficult to determine if the PET scan alone was responsible for this improved survival over the usual 30% 5-year survival. However, it may be prudent at this time to perform a PET scan before taking patients to liver resection, so that those who have incurable disease will be spared major surgery.[85]

The issue of trying to downstage patients with unresectable liver metastases and then proceed to liver resection is becoming more relevant as newer and more effective chemotherapy agents are being introduced. A report from Paris followed 1104 patients with liver metastases from colorectal primaries considered to be unresectable. Of these patients, 138 (13%) were downstaged sufficiently to go on to surgery. Eighty percent of these patient developed tumor recurrence, 72% of which involved the liver. DFS was 17% at 5 years. These numbers reflect that the overwhelming majority of patients will not be downstaged by chemotherapy sufficiently for resection, and even those that are do not fare particularly well.[84]

Several studies have addressed the issue of extrahepatic intra-abdominal metastases at the time of hepatic resection. In most instances, surgeons do not proceed with liver resection in the presence

Table 59-6 Significance of Hepatic Resection Margin

Institution	Margin of Resection	No. of Patients	5-Year Survival (%)	*P* Value
Erlangen[80]	0–4 mm	67	23	NS
	5–9 mm	40	29	
	>10 mm	65	39	
Mayo[69]	0–1 mm	17	29	NS
	1–10 mm	123	30	
	>10 mm	31	36	
	None	24	17	
Pittsburgh[68]	0–10 mm	92	25	
	>10 mm	95	29	
	None	17	0	0.006
Memorial[321]	1–10 mm	248	43	
	>10 mm	113	43	
	None	65	17	0.00003

Table 59-7 Recurrence after Hepatic Resection

Author	No. of Patients	No. of Recurrences	No. of Liver Only	No. of Liver and Extrahepatic	No. of Extrahepatic Only
Van Ooijen et al[79]	117	69	20 (29%)	14 (21%)	34 (50%)
Codi et al[77]	93	69	28 (41%)	13 (19%)	28 (41%)
Hohenberger et al[320]	122	80	17 (21%)	55 (69%)	8 (10%)
Hughes et al[75]	607	424	148 (27%)	154 (27%)	106 (28%)
Rees et al[322]	89	61	25 (41%)	9 (15%)	27 (44%)
Fong et al[321]	465	235	96 (41%)	16 (7%)	123 (52%)

of extrahepatic metastases. In the series from New York, 88 patients with extrahepatic disease were included.[19] More than half of these patients had direct extension into other organs such as the diaphragm. Only 10 patients had positive portal nodal disease. Looking at all 88 patients with extrahepatic disease, the 5-year actuarial survival was 18%. The breakdown between those with discontinuous disease or direct extension was not made. In the Mayo Clinic report on hepatic resections in patients with extrahepatic disease, none of the 22 patients survived for 5 years, and only 1 survived for 3 years.[86] In the Hepatic Registry, of the 61 patients with extrahepatic involvement undergoing hepatic resection, none had a 5-year DFS.[74] These data support the view that hepatic resection in the presence of noncontiguous extrahepatic intra-abdominal disease, with the exception of a local recurrence, is rarely curative and, in general, is inadvisable.

For extrahepatic disease not in the abdomen, the usefulness of resection could be different for disease in the lungs, especially solitary lesions in the lung. A recent study from the Mayo Clinic reviewed their experience with resection of both hepatic and pulmonary metastases from colorectal primaries. There were 58 patients, with no operative mortalities and a 5-year survival rate of 30%. These authors believed that the resection of both lung and liver of selected cases was justified.[87]

Relapse rates after liver resections are described in Table 59-7. In the larger studies it seems that approximately 40% of patients who have hepatic resections will have recurrent disease in the liver as the first sign of the relapse. Of the 69 patients who had relapse in the Milan study, 28 (41%) had relapse in the liver only, 19 (28%) had only extra-abdominal relapse, 9 (13%) had intra-abdominal extrahepatic relapse, and 13 (19%) had relapse in both the liver and at an extrahepatic site.[49] Although extrahepatic failure is of concern, the liver remains the main site of relapse, appearing in more than 60% of patients.

Because of the increased use of hepatic resection for metastatic liver disease, the incidence of repeat hepatic resection has also increased. Approximately 10% of patients who have had a hepatic resection can have a repeat resection (Table 59-8). A study from Paris of 116 patients who underwent repeat hepatic resection reported a low operative mortality of 0.9% and a 3-year survival of 33%.[54] Of the patients who underwent repeat hepatic resection, 55% had recurrence in their liver after this operation. There were 170 patients in a registry report who had repeat hepatic resections with a 5-year survival of 26%, which was comparable to the 5-year survival for the original hepatic resection.[88] A recent study from MSKCC reviewed 126 second liver resections for recurrent colorectal metastases; the 5-year actuarial survival was 34%, with 19 actual 5-year survivors. The operative mortality was 1.6%, and morbidity was 28%.[89] A study of recurrence among these patients revealed a liver recurrence in 67% of the patients. Repeat hepatic resection, when feasible, can be done safely, and the outcome is comparable to that for the original hepatic resection.[90] Thus, if patients have isolated liver metastases (preferably solitary lesions) after hepatic resection, they should be candidates for repeat resection.

The place for ablation of liver metastases whether by radiofrequency (RF) heating or cryotherapy freezing has not yet been delineated adequately. Because extensive reporting on resection has indicated an expected 30% 5-year survival for patients with one to three hepatic metastases from colorectal primaries, the use of ablation in this setting cannot be warranted until a randomized study has shown that the two therapies are equivalent. A retrospective study from M.D. Anderson Cancer Center analyzed a series of 418 patients with liver-only metastases from colorectal primaries, of whom 57 had RF only. The overall recurrence rate and the liver recurrence rate were both significantly higher for the RF group over the resection-only group, with a liver recurrence of four times greater in the RF group. The overall survival and DFS was also significantly better in the resection group. A multivariate analysis continued to show RF as a significant factor in poor prognoses. Interestingly, 31 patients with solitary tumors were treated with RF (we are not told why this happened), and these patients had significantly worse survival than the patients with resection of solitary lesions ($P = 0.025$). The group of patients who had RF alone when compared with those 70 patients with chemotherapy alone had a significantly improved survival.[91] A subsequent report from the same group of investigators compared RF to resection for patients with solitary colorectal metastases. The hepatic recurrence rate was much higher in the RF group than in the

Table 59-8 Survival after Repeat Hepatic Resections for Colorectal Metastases

Author	No. of Patients	Operative Mortality (%)	Survival (%)		
			2-Year	3-Year	5-Year
Nordlinger et al[54]	116	0.9	57	33	
Petrowsky et al[89]	126	1.6		51	34
Fernandez-Trigo et al[88]	170			37	26
Que et al[323]	21			50	

resection group, 37% as compared with 5%, respectively. The 5-year recurrence-free survival and overall survival were 40% and 50% as compared with 0% and 0% for resection versus RF, respectively. The conclusions are obvious: resection is the preferred method for treatment of solitary metastases whenever possible.[92]

Synchronous Liver Metastases

The question of whether liver metastases can safely be resected at the time of resection of the primary colorectal carcinoma is still uncertain. Small metastases seen at the time of laparotomy for the primary lesion can easily be resected. When patients are evaluated for their primary and are found to have a large burden of metastatic disease, a question may be whether a simultaneous resection of the primary tumor and the metastases should be done, or whether preoperative chemotherapy should be offered. Bolton and Fuhrman reported a 12% operative mortality with simultaneous surgeries that increased to 24% if the surgery included a major liver resection.[93] Nordlinger reported a 7% mortality for simultaneous resections compared with 2% for staged resections ($P = 0.01$).[94] Tanaka and coworkers, Martin and colleagues, and Weber and associates, on the other hand, reported that operative mortality and morbidity were comparable whether staged or simultaneous procedures were done.[95–97] It is the practice in many institutions to do a simultaneous resection with right colon primaries or when single synchronous metastases are found in the liver, and staged resections for rectal primaries or for patients with multiple liver metastases.[98] Some advocate systemic chemotherapy first, followed by resection of liver first, and then resection of the colon[99] or simultaneous resection.[100]

Adjuvant Therapy after Liver Resection

Despite the high curative resection rate of hepatic resections, the recurrence of metastases is around 70%, with 50% recurring in the liver. The use of hepatic artery infusion (HAI) of chemotherapy after liver resection was studied in a small prospective randomized fashion at the City of Hope Medical Center.[101,102] The patients with solitary metastases all had resection of their tumors, and half received postoperative continuous HAI of fluorodeoxyuridine (FUDR). For the six patients who had resection only, their median time to failure was 8.7 months, and three of the six metastases recurred in the liver. For the five patients with resection plus pump, none had recurrence in the liver, and their median time to failure was 30.7 months. There was no difference in median survival between the two groups.

At MSKCC, 156 patients were randomized after liver resection to either HAI with systemic chemotherapy (HAI + SYS) or systemic chemotherapy alone (SYS). Chemotherapy was administered for 6 months. The endpoint of this study was 2-year survival. HAI therapy used was FUDR and dexamethasone (Dex), and the systemic therapy was 5-fluorouracil (5-FU) and leucovorin (LV) or continuous infusion of 5-FU. Patients were stratified by type of previous chemotherapy or no chemotherapy and the number of liver metastases (one, two to four, more than four). Two-year survival was increased in the group receiving HAI + SYS (86%) versus 72% for SYS ($P = 0.03$).[103A] Median survival is presently 68.4 months for the HAI + SYS group and 58.8 months for the group receiving SYS alone. With a median 10-year follow-up, the 10-year survivals are 41% and 27%, respectively (Fig. 59-5).[104] Hepatic DFS is clearly better for the HAI + SYS group, with a median survival not reached, as compared with 32.5 months with SYS alone ($P = 0.003$; Fig. 59-6). Overall, DFS is also increased significantly (31.3 and 17.2 months for the HAI + SYS vs. SYS alone [$P = 0.02$]; Fig. 59-7). Toxicity was increased in the combined group, with increased diarrhea and increased liver function test abnormalities. A total bilirubin greater than 3 mg/dL occurred in 18% of patients receiving HAI and in 2% of the SYS group.[103]

The Eastern Cooperative Group (ECOG) and the Southwestern Oncology Group (SWOG) conducted a randomized study of hepatic resection alone versus resection followed by 4 cycles of HAI-FUDR

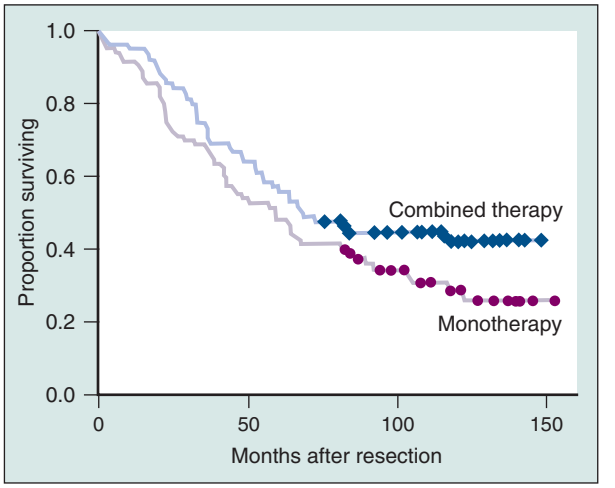


Figure 59-5 • Survival curve. Combined modality treatment: HAI FUDR + systemic 5-FU/LV. Monotherapy: systemic 5-FU/LV.[104]

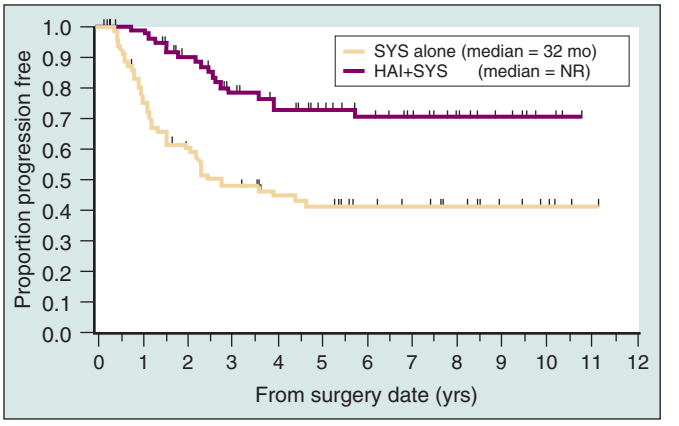


Figure 59-6 • Hepatic progression-free survival. HAI (FUDR/dex) + SYS (5-FU/LV) versus SYS (5-FU/LV) alone. $P < 0.0001$.[104]

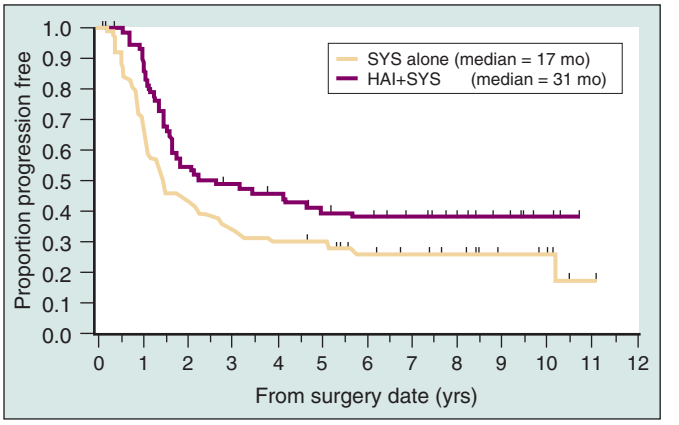


Figure 59-7 • Progression-free survival. HAI (FUDR/dex) + SYS (5-FU/LV) versus SYS (5-FU/LV) alone. $P < 0.02$.[104]

and 12 cycles of systemic infusion of 5-FU. Only patients with three or fewer metastases were enrolled in the study. The study was powered to answer the question of whether HAI would increase DFS. Of the 109 patients randomized, only 75 are actually in the study, because several patients were excluded because of extrahepatic disease, unresectable disease, or no tumor. Four-year liver recurrence-free survival was 67% in the chemotherapy group and 43% in the control group ($P = 0.03$). Median survival was 63.7 months for the chemotherapy group and 49% for the control group.[105] The endpoint was obtained with a 4-year DFS of 46% with HAI + SYS and 25% for the control group ($P = 0.035$).

A German cooperative group enrolled patients from 26 different centers and entered 226 patients into a study of resection followed by adjuvant hepatic arterial therapy with 5-FU and LV via a port as compared with a control group receiving no chemotherapy after resection. Although 113 were entered into the hepatic arterial group, only 87 were treated. Only 64% had chemotherapy data available, and only 30% completed treatment. At an 18-month interim analysis, the relapse rate was 33% in the group receiving adjuvant therapy and 36% in the group treated with resection alone. If one looks only at those who were treated, the median survival was 44.8 months from the treated group versus 39.7 months in the control group.[106]

A randomized study from Greece used intraoperative randomization to regional mitomycin C, 5-FU/LV with interleukin-2 via a hepatic arterial catheter with the same drugs via a systemic route versus systemic therapy alone. The 2-year survivals in 122 patients were 80% and 71%, and 5-year survivals were 73% and 60%, in the regional-plus-systemic versus systemic-alone groups, respectively ($P = 0.004$).[107] Five-year hepatic-free recurrence was also significantly increased in the regional-plus-systemic group at 82% versus 49% in the systemic-alone group ($P < 0.001$). Table 59-9 summarizes survival data of the randomized studies and the disease-free survival from these studies.

Tono and coworkers[108] randomized 19 patients to continuous infusion of 5-FU, 500 mg per day for 4 days via HAI for 6 weeks. Although this is a small study, there was an increase in 3-year DFS, 66.7% for the regional group and 20% for the control group ($P = 0.045$). The 5-year survivals were 77.8% for the regional group versus 50% for the control group.

In a nonrandomized study comparing two groups of patients in Japan,[109] the survival was increased with the use of adjuvant regional therapy after hepatectomy for colon cancer. The 5-year survivals were 23% using surgery alone, and 57% when adjuvant chemotherapy with 5-FU, doxorubicin, and mitomycin C were given after surgery. In another nonrandomized study from Japan,[110] 58 patients who had radical resection of metastatic colorectal carcinoma could select whether they wanted HAI + systemic, or systemic alone after surgery. The 5-year survival was significantly increased for the HAI + systemic group at 59%, as compared with 27% for the systemic-alone group ($P < 0.001$), as was hepatic recurrence at 7% versus 57% ($P < 0.001$). In another small study, 4-year survival was 100% as compared with 47% for the HAI and control groups, respectively ($P = 0.05$).[111]

Studies are now testing the new systemic chemotherapeutic agents with HAI as adjuvant therapy after liver resection. A phase I study at MSKCC with systemic CPT-11 (irinotecan) and HAI FUDR/Dex had a 2-year survival of 89% and a 5-year survival of 58%.[112] Another trial using escalating systemic doses of oxaliplatin (Oxali)/5-FU/LV and HAI therapy,[113] with a minimum follow-up time of 26.9 months, had a 2-year survival of 98%. At the Mayo Clinic, FUDR + Dex has been added to systemic Oxali and capecitabine. Presently, the 2-year survival is 86%.[114]

Ongoing studies to address the usefulness of adjuvant therapy after liver resection include the National Surgical Adjuvant Breast and Bowel Project study of HAI + systemic Oxali + capecitabine versus systemic Oxali + capecitabine alone. A trial at MSKCC is

Table 59-9 Randomized Trials of Adjuvant Therapy and Studies after Liver Resection: HAI versus SYS or Control

		2-YEAR SURVIVAL (%)		5-YEAR SURVIVAL (%)	
Author	**No. of Patients**	**HAI**	**SYS or Control**	**HAI**	**SYS or Control**
Kusonoki et al[110]	58	80	71	73	60
MSKCC[103]	156	86	72	57	48
Lorenz et al[106]	201*	60	62	50	30
ECOG[105]	75†	70	65	60	35‡
Lygidakis et al[107]	122	92	75	73	60
Asahara et al[111]	38	100	60	100	47§

		DISEASE-FREE SURVIVAL				
		2-YEAR (%)		5-YEAR (%)		
Studies	**No. of Patients**	**HAI**	**SYS**	**HAI**	**SYS**	***P* Value**
MSKCC[104]	156	55	40	40	30	0.02
ECOG[105]	75	60	40	40	20#	0.03
Lorenz et al[106]	186	Median 20/12.6#				NS
Lygidakis et al[107]	122	66	48	60	35	0.0002
Tono et al[108]	19	75	30	60	20	0.045

*Treated patients, not everyone randomized.
†Patients entered in study, not everyone randomized.
‡Updated figures.[107]
§4-year survival.
#No treatment in control arm.

addressing the question of the safety of bevacizumab (Bev) given with HAI + systemic therapy after liver resection in a randomized study of HAI and systemic therapy with or without bevacizumab. Few studies have evaluated the utility of systemic therapy after liver resection. In the ENG study (EORTC/NCIC CTG/GIVIO), 128 patients were randomized to receive 5-FU and LV chemotherapy for 8 weeks versus no further therapy (control) after liver or lung resection. There were no significant differences in DFS or survival between the two groups. The 4-year survivals were 57% and 47% for the treated and control groups.[115] A European intergroup study (FFCD) randomized 173 patients to systemic 5-FU/LV versus no further treatment. The 5-FU and LV were given by the bolus method on a monthly schedule. Two-year DFS was 50.4% for those receiving chemotherapy and 38.1% for the control group ($P = 0.058$). Negative prognostic factors were synchronous disease, multiple metastases, stage III tumor, preoperative hypertension, postoperative complications, and an elevated preoperative CEA. Two- and five-year survivals were 81% and 51% for the chemotherapy group and 82% and 41% for the control group. A trial combining these two studies to increase power demonstrated a DFS of 27.9 versus 18.8 months ($P = 0.058$) and overall survival of 62.2 versus 47.3 months ($P = 0.095$) for the chemotherapy versus surgery-alone groups, respectively. Patient characteristics in this study included one metastasis in 68% of patients, and more than 1 year disease-free interval in 57% of patients. This clearly can affect results, as seen in their own analysis, where DFS was 27 months for one metastasis and 16.8 months for two or more metastases ($P = 0.036$), and survivals were 64.5 and 40 months for one or more than two metastases, respectively. In the MSKCC adjuvant therapy of HAI + systemic 5-FU/LV after liver resection study, the patients had worse baseline characteristics, with 36% of patients having only one metastasis, whereas 19% had more than four metastases, and only 20% had a disease-free interval longer than 1 year.[103]

The efficacy of systemic CPT-11 in posthepatic resection was addressed in 29 patients of whom 62% had only one metastasis, 79% had a disease-free interval longer than 1 year, and 62% had a surgical margin larger than 1 cm. Their median DFS was 45 months, and 2-year survival was 85%.

Adjuvant therapy following resection has also been attempted in HCC. In patients with HCC, a randomized study compared hepatic arterial injection of epirubicin and oral 1-hexycarbamoyl-5-fluorouracil (HCFU) to no further treatment in 57 patients after liver resection of HCC.[116] There was no significant difference between the two groups, and the authors believed that the chemotherapeutic agents chosen might not have been appropriate. Postoperative adjuvant therapy could compromise survival if the treatment is not effective, because it suppresses host immunity. In a small randomized study of intravenous epirubicin with hepatic arterial iodized oil and cisplatin compared to no further treatment after liver resection for HCC, the DFS was shorter in the treated group. There was an increase in extrahepatic metastases in the treated group.[117]

Factors that inhibit hepatic carcinogenesis might be more useful as adjuvant therapies for HCC. Retinoic acid inhibits chemically induced hepatocarcinogenesis in rats, spontaneous HCC in mice, and the production of α-fetoprotein in human hepatoma cell lines. In a study by the Hepatoma Prevention Study Group, 89 patients were randomized to polyphenolic acid (acyclic retinoid) or placebo for 12 months after liver resection. The polyphenolic group had a significant reduction in recurrent or new hepatomas ($P = 0.04$). The drug also improved overall survival, but not significantly.[118]

SYSTEMIC CHEMOTHERAPY

Responses of liver metastases to systemic chemotherapy are variable but usually reflect the response of the primary tumor. Most studies of systemic therapy do not differentiate patients who have only liver metastases, making it difficult to draw conclusions about the usefulness of systemic chemotherapy to treat liver metastases. In some cases, however, the response rates of liver metastases are well documented.

In breast cancer, liver metastases represent a poor prognostic indicator, with median survival of 10 months in some series.[119] Visceral metastases, including liver metastases, have been reported to have fewer estrogen-positive receptors. Insulin-like growth factors are present in the liver and the lung and could be important to the growth and motility factors for breast cancer and lung cancer.[120] In looking at prognostic factors that predict response, patients with liver metastases were the ones who tended to respond the least.[121] Carter's[122] review of single agents (5-FU or cyclophosphamide) demonstrated a 20% response in liver metastases vs. 32% and 27% in soft-tissue and osseous metastases, respectively. The combination of halotestin, prednisone, and 5-FU produced objective responses in 26 of 52 patients (50%) with liver metastases from breast carcinoma.[84] Although combination chemotherapy has substantially improved the response rates obtained in treating breast cancer, liver metastases still have a lower response rate than soft-tissue or pulmonary disease. In a Southwest Oncology Group study of 262 patients, 41 of 88 patients (47%) with liver metastases responded, as compared with 110 of 154 patients (71%) without liver involvement ($P = 0.001$).[123] There is a suggestion that taxoids might be more effective against liver metastases.[124]

For metastases from gastric carcinoma, one of the more commonly used regimens (5-FU, doxorubicin, and mitomycin C) produces a mean response of 35%, whereas for those with hepatic metastasis, the response rate was 28%.[125] The cumulative response for liver metastases was 34%, while the overall mean response rate was 36% for combination chemotherapy in the treatment of gastric carcinoma.[126]

For patients with CRC, the liver is the most common site of dissemination, with as many as 70% of patients with metastatic disease developing liver metastases.[127] Several new agents are now available, among which are irinotecan (CPT-11) and oxaliplatin (Oxali).[128,129] Randomized trials using CPT-11 with 5-FU/LV versus 5-FU/LV alone[130,131] produced an increase in response rate and survival. When CPT-11/5-FU/LV (IFL) was compared to Oxali + 5-FU/LV (FOLFOX), the response rate was increased from 35% to 45%, and the survival was increased from 15 to 19.5 months for the IFL and FOLFOX groups, respectively.[132] When 5-FU was changed to infusion FOLFIRI (CPT-11/5-FU/LV) it became more effective and produced results that are similar to FOLFOX.[133] In the last few years, targeted agents have become available: Bev, a monoclonal antibody to vascular endothelial growth factor and cetuximab (C225), an antibody to epidermal growth factor receptor. The addition of Bev to IFL[134] increased response rates and survival (35% to 45%, and 15.6 to 19.5 months, for IFL vs. Bev + IFL, respectively). For almost four decades, the 2-year survival for metastatic colorectal patients treated with 5-FU or 5-FU + LV was 25%; with these new agents, 2-year survival has moved up to 30% to 39%, with a marked improvement in overall survival from 12 to 20 months.

When does one start systemic chemotherapy for patients with metastatic disease to the liver from breast, gastric, or colon cancer? For patients with colon or gastric cancer who are asymptomatic and have a small volume of disease (<20% of the liver involved with tumor and not resectable), three studies suggest that earlier treatment increases survival and increases the time with good performance status.[135–137] If the patient has rapidly progressive disease or is symptomatic, chemotherapy should be initiated immediately. One should have a baseline CT scan and laboratory values before starting treatment. To assess response, scans should be repeated at 2- to 3-month intervals to evaluate whether the tumor is responding, and therapy should be continued.

Hepatic Arterial Chemotherapy

The rationale for hepatic arterial chemotherapy has an anatomic and pharmacologic basis (Table 59-10):

1. Liver metastases are perfused almost exclusively by the hepatic artery, whereas normal hepatocytes derive their blood supply both from the portal vein and minimally from the hepatic artery.[138]
2. Certain drugs are mostly extracted by the liver during the first pass through the arterial circulation. This results in high local concentrations of drug with minimal systemic toxicity. Ensminger and coworkers[139,140] demonstrated that 94% to 99% of FUDR is extracted by the liver during the first pass, compared with 19% to 55% of 5-FU. This makes FUDR an optimal drug for hepatic arterial chemotherapy. The pharmacologic advantages of various chemotherapeutic agents for HAI are summarized in Table 59-11. Newer drugs, such as CPT-11 and etoposide, do not show an advantage when given by HAI.[141]
3. Drugs with a steep dose-response curve will be more useful when given by the intrahepatic route, because a large dose can be given regionally.
4. Drugs with a high total-body clearance are more useful for hepatic infusion. If a drug is not cleared rapidly, recirculation through the systemic circulation diminishes the advantage of hepatic arterial delivery.[142]
5. The liver is often the first and only site of metastatic disease. The theory of the stepwise pattern of metastatic progression states that hematogenous spread occurs first via the portal vein to the liver, then from the liver to the lungs, and then to other organs.[143,144] Thus aggressive treatment of metastases confined to the liver (resection and/or hepatic infusion) could yield prolonged survival for some patients.

Table 59-10 Rationale for Hepatic Artery Infusion[152]

- Liver metastases are perfused by the hepatic artery. Normal liver is primarily supplied by the portal vein.
- Certain drugs have high hepatic extraction.
- The liver is often the first site of metastases; eliminating liver metastases would prevent extrahepatic disease.
- Many drugs have a steep dose-response curve.
- Drugs with a high total-body clearance are more effective.

Table 59-11 Drugs for Hepatic Arterial Infusion

Drug	Estimated Half-life (min)	Increase on Exposure by HAI
5-FU	10	5- to 10-fold
FUDR	<10	100- to 400-fold
BCNU	<5	6- to 7-fold
Mit C	<10	6- to 8-fold
Cisplatin	20–30	4- to 7-fold
Adriamycin (doxorubicin hydrochloride)	60	2-fold

BCNU, bischloroethyl nitrosourea or carmustine; 5-FU, fluorouracil; FUDR, 5-fluoro-2-deoxyuridine; HAI, hepatic arterial infusion; Mit C, mitomycin C.

Regional hepatic arterial therapy can be done by using either a hepatic arterial port or a percutaneously placed catheter connected to an external pump or to a totally implantable pump. Early studies with percutaneously placed hepatic artery catheters produced high response rates, but clotting of the catheters and the hepatic artery, as well as bleeding, led physicians to abandon this method (Table 59-12). The development of a totally implantable pump allowed long-term HAI with good patency of the catheter and the hepatic artery and a low incidence of infection. One study compared three groups relative to placement of the hepatic artery catheter:

1. Surgical placement of a hepatic artery catheter
2. Percutaneous placement of the hepatic artery catheter
3. An operative implantable reservoir connected to the hepatic artery catheter

The reported ability of each technique to administer chemotherapy for the three groups of patients was 31, 25, and 115 days, respectively.[145] Several trials using the implantable pump produced high response rates with good survivals (Table 59-13).

Randomized Studies

It is difficult to assess the impact of hepatic infusional therapy on tumor response and patient survival without a prospective

Table 59-12 Hepatic Artery Infusion with External Pump

Investigators	No. of Patients	Drug	Response (%)	Catheter Complications or Bleed (%)
Tandon et al[324]	122	5-FU 25 mg/kg × 9 days	65	42
Ansfield et al[325]	419	5-FU 25 mg/kg × 4 days	55	21
Watkins et al[326]	184	5-FU 25 mg/kg × 10 days	71	28
Cady and Oberfield[327]	55	FUDR 20 mg/kg	67	39
Smiley et al[328]	166	5-FU 25 mg/kg × 4 days	25	30
New studies				
Metzger et al[160]	30	5-FU 2 g × 5 days	57	33
Denck[329]	50	5-FU 6 g × 3 days	58	5
Schlag et al[330]	33	5-FU 1 g × 5 days	27	20
Rougier et al[331]	43	5-FU 1 g weekly	56	65
Arai et al[332]	32	FU 1000 × 5 hrs every week	78	25
		Mit C 10–12 mg/m^2 every 6 weeks		

5-FU, 5-fluorouracil; FUDR, 5-fluoro-2-deoxyuridine; Mit C, mitomycin C.

Table 59-13 Hepatic Arterial FUDR Infusion with Internal Pump: Responses

Investigator	No. of Patients	Prior Chemotherapy (%)	PR (%)	Decrease in CEA (%)	Median Survival (mo)
Niederhuber et al[333]	70	45	83	91	25
Balch and Urist[334]	50	40	—	83	26
Kemeny et al[335]	41	43	42	51	12
Shepard et al[336]	53	42	32	—	17
Cohen et al[337]	50	36	51	—	—
Weiss et al[338]	17	85	29	57	13
Schwartz et al[339]	23	—	15	75	18
Johnson et al[340]	40	—	47	—	12

CEA, carcinoembryonic antigen; FUDR, 5-fluoro-2-deoxyuridine; PR, partial response.

randomized study comparing it with systemic chemotherapy. In such studies, patients would have to be stratified for parameters known to influence tumor response rates and patient survivals, such as performance status, extent of liver involvement, and initial LDH level.

The influence of the extent of liver involvement on survival has been demonstrated by many investigators. The median survival for patients with less than 20% involvement was greater than 20 months, whereas survival was only 6 months for those with more than 60% involvement (Fig. 59-8).[146] The influence of certain laboratory parameters on tumor response and patient survival was evaluated at MSKCC, where the initial LDH level proved to be the most significant factor.[147] Patients whose initial LDH and CEA levels were normal had a median survival of 32 months as compared with only 8 months for those with abnormal values (Fig. 59-9).

In a randomized study at MSKCC, patients were stratified by percentage of liver involvement and baseline LDH. All patients underwent exploratory laparotomy for pump placement; patients with extrahepatic disease were excluded from entry. Both groups received a 14-day continuous infusion of FUDR, but the dose was lower in the systemic group than in the HAI group. In patients randomized to systemic therapy, crossover from systemic therapy to HAI was permitted. Of the 99 evaluable patients, partial responses were seen in 53% and 21% of the HAI and systemic groups, respectively ($P = 0.001$). Of the patients who crossed over from systemic to HAI therapy, 25% had a partial response after the crossover and 60% had a decrease in CEA levels. The median survivals for the HAI and systemic groups were 17 and 12 months, respectively ($P = 0.424$). The interpretation of survival is difficult, because 60% of the systemic

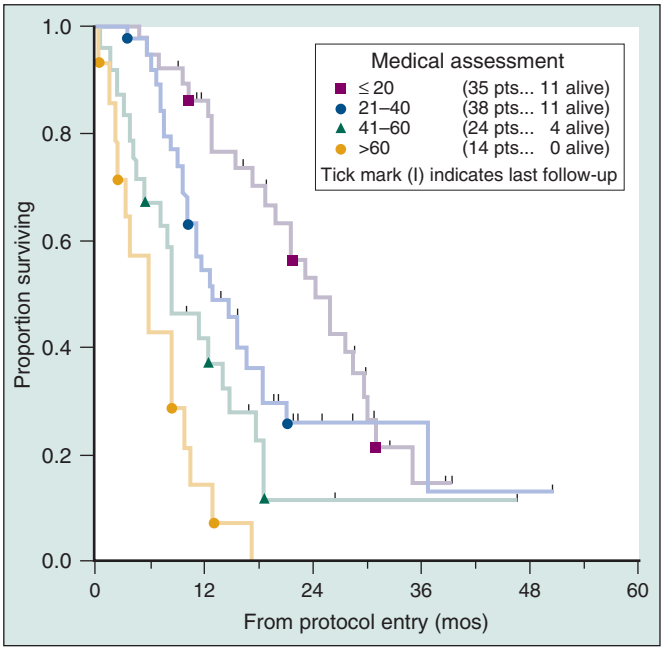


Figure 59-8 • Survival distributions by percentage of liver involvement (medical assessment). The median survival was 25 months for patients with less than 20% involvement vs. 6 months for patients with greater than 60% involvement. (From Kemeny N, Daly J, Oderman P, et al: Prognostic variables in patients with hepatic metastases from colorectal cancer: importance of medical assessment of liver involvement. Cancer 1989;63:742.)

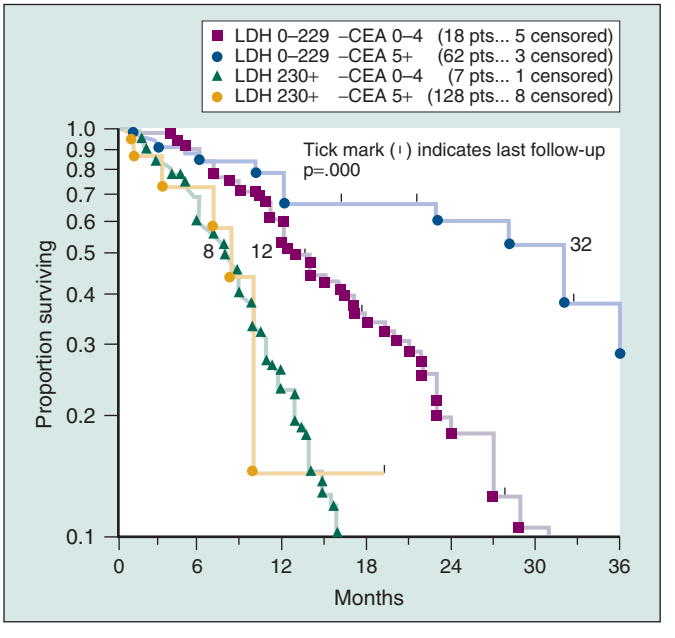


Figure 59-9 • Metastatic colorectal carcinoma (survival). Survival curves based on initial LDH and CEA levels. The median survival of patients with normal LDH and CEA levels at initiation of chemotherapy was 32 months, whereas it was 8 months if both values were abnormal ($P < 0.001$). (From Kemeny N, Braun DW: Prognostic factors in advanced colorectal carcinoma: the importance of lactic dehydrogenase, performance status, and white blood cell count. Am J Med 1983;74:786.)

patients crossed over. Those who did not cross over had a median survival of 8 months, as compared with 18 months for those who crossed over to HAI ($P = 0.04$). Randomized studies are outlined in Table 59-14.

A similar randomized study conducted by the Northern California Oncology Group also used FUDR infusion in both the HAI and systemic groups. A total of 114 patients were stratified by extent of liver involvement, baseline bilirubin values, and performance status. Of the 117 eligible patients, 42% responded to HAI and 10% to systemic therapy ($P < 0.001$). The median times to progression were 401 and 201 days for the HAI and systemic groups, respectively ($P = 0.009$), whereas median survivals were 503 days and 484 days, respectively. Although a crossover design was not built into the study, 43% of the patients on systemic therapy eventually received HAI, which could have obscured survival differences between the two groups.

A National Cancer Institute (NCI) study compared HAI with systemic infusion of FUDR.[148] In 64 patients, the response rates were 62% and 17% for the HAI and systemic groups, respectively ($P < 0.003$). Interpretation of survival data is difficult, because 34% of the HAI group never received chemotherapy, and 38% of the HAI group had positive portal lymph nodes. The 2-year survival was 47% in the HAI group compared with 13% in the systemic group ($P = 0.03$).

Another small study conducted by the Mayo Clinic (69 patients) compared HAI FUDR with systemic bolus 5-FU for 5 days.[123] Objective tumor response was observed in 48% and 21% of patients in the HAI and systemic groups, respectively ($P = 0.02$), and times to hepatic progression were 15.7 and 6 months, respectively ($P = 0.001$). Survival was similar in the two groups (12.6 and 10.5 months, respectively). Forty-eight percent of the HAI groups either were not adequately treated or had extrahepatic disease.

In a French trial of 163 patients randomized to HAI of FUDR versus systemic-bolus 5-FU, the patients were stratified by extent of liver involvement and baseline LDH levels.[118] The response rates were 49% and 14% in the HAI and systemic groups, respectively. Median times to hepatic progression were 15 and 6 months, and median survivals were 14 and 10 months for the HAI and systemic groups, respectively. The 2-year survival was 22% for HAI and 10% for the systemic group ($P < 0.02$).

In a similar study done in England, 100 patients were randomized to HAI FUDR or systemic 5-FU (which was given to symptomatic patients only).[149] Quality of life and survival were improved significantly for the HAI group. Median survival was 405 days versus 198 days for the HAI and systemic groups, respectively ($P = 0.03$).

The German Cooperative Group on Liver Metastases randomized 168 patients in a multicenter trial to one of three treatment groups: HAI of FUDR, HAI of 5-FU/LV, and systemic 5-FU/LV.[150] The median times to progression were 5.9, 9.2, and 6.6 months, and median survivals were 12.7, 18.7, and 17.6 months, respectively. Tumor response rates were 43.2%, 45%, and 19.7%, and development of extrahepatic disease was 40.5%, 12.5%, and 18.3%, respectively. It should be pointed out that only 70% of patients randomized to HAI of 5-FU/LV and 68.5% randomized to HAI of FUDR were actually treated.

The Medical Research Council/European Organization for the Research and Treatment of Cancer (MRC/EORTC) Colorectal Cancer Groups conducted a randomized trial of intravenous versus HAI administration of 5-FU/LV for 290 patients. Median and 2-year survival rates were 13.4 months and 23% in the intravenous arm as compared with 14.7 months and 20% in the HAI arm; however, 37% of patients allocated to the HAI arm did not receive the assigned treatment.[151]

The Cancer and Leukemia Group B (CALGB)[152] trial differs from the 135 other HAI studies in that it included the use of Dex in the HAI arm.[153] In patients, HAI FUDR + Dex + LV was compared to systemic-bolus 5-FU/LV. No crossover was allowed. The HAI group had a significant increase in survival of 24.4 months versus 20 months in the systemic group ($P = 0.0034$; Fig. 59-10). The time to hepatic progression was better in the HAI arm (9.8 months vs. 7.3 months in the systemic group; $P = 0.034$) but the time to extrahepatic progression was better in the systemic arm (14.8 months versus 7.7 months in the HAI group; $P < 0.029$). There was an improved quality of life in the HAI group, especially physical functioning, measured at 3 and 6 months ($P = 0.024$).

There are differences between the CALGB study[152] and the European studies, which could explain differences in outcomes. The CALGB study used pumps instead of ports, and HAI therapy included FUDR with Dex to decrease toxicity.[153] Survival was based on intent to treat in all three studies, and the actual number of patients treated was much lower in the European studies, 66% in the German study and 63% in the English study, whereas it was 86% in the CALGB study. The CALGB study did demonstrate that regional therapy alone can improve survival over systemic 5-FU/LV with a survival similar to that which is seen utilizing the new agents.

Table 59-14 Randomized Studies of Intrahepatic versus Systemic Chemotherapy for Hepatic Metastases from Colorectal Cancer

		Response (%)			Survival (mo)		
Group	**No. of Patients**	**HAI**	**SYS**	***P* Value***	**HAI**	**SYS**	***P* Value***
MSKCC[341]	162	52	20	0.001	18*	12	
NCOG[342]	143	42	10	0.0001	16.6	16	
NCI[148]	64	62	17	0.003	20	11	
Consortium[343]	43	58	38	NS	—	NS	
City of Hope[102]	41	56	0				
Mayo Clinic[344]	69	48	21	0.02	12.6	10.5	
French[345]	163	49	14	NS	15	11	0.02
English[135]	100	50	0	0.001	13	6.3	0.03
German[150]	168	43	20	0.019	12.7	18	
CALGB[152]	134	43	27	0.02	24.4	20	0.0034

HAI, hepatic artery infusion; NS, not stated; SYS, systemic chemotherapy.
*Only significant *P* values reported.

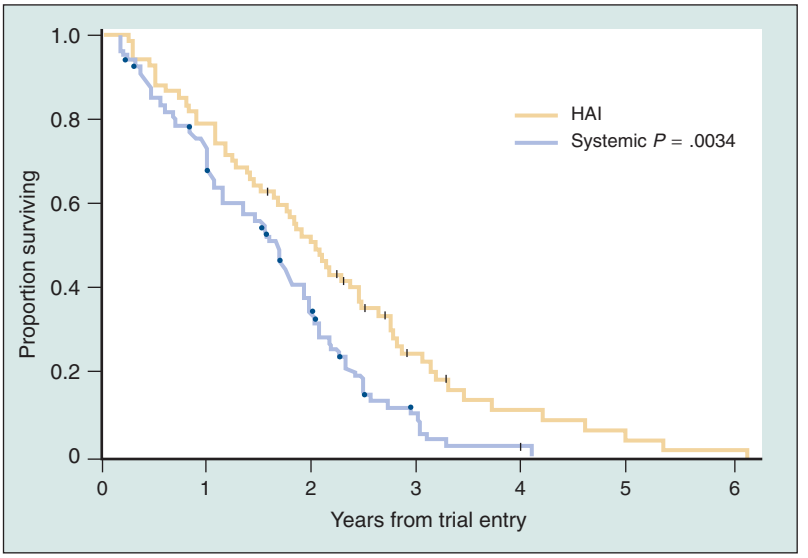


Figure 59-10 • Kaplan-Meier overall survival by treatment arm for all patients entered.

Randomized studies of HAI therapy versus the new therapies have not yet been done.

A meta-analysis combining the results of seven trials supports the use of HAI of FUDR in the treatment of nonresectable liver metastases from CRCs.[154] A significantly better local response rate of 41% was achieved with HAI of FUDR compared with a 14% response rate for systemic 5-FU. In addition, median survival time was increased in patients treated with HAI—16 months versus 13 months for those treated with 5-FU.

New Approaches to Decrease Hepatic Toxicity

The hepatic toxicity induced by HAI of FUDR could be related to portal triad inflammation, which could lead to ischemia of the bile ducts. Therefore, hepatic arterial administration of Dex might decrease biliary toxicity. In patients with established hepatobiliary toxicity from HAI, Dex promotes resolution of liver function abnormalities. In a randomized study of FUDR with Dex as compared to FUDR alone, there was a trend toward decreased bilirubin elevation in patients receiving FUDR + Dex compared with the group receiving FUDR alone (9% vs. 30%, respectively; $P = 0.07$).[153] Although the addition of Dex was not associated with a significant increase in the amount of FUDR that could be administered, the response rate was increased by 71% for the FUDR + Dex group as compared with 40% for the group receiving FUDR alone ($P = 0.03$). Survival was also improved: 23 months for patients receiving FUDR + Dex as compared with 15 months for those receiving FUDR alone ($P = 0.06$)

The use of circadian modification of HAI with FUDR is another method to decrease hepatic toxicity. In a nonrandomized study at the University of Minnesota, a comparison of constant (flat) infusion to circadian-modified hepatic arterial FUDR infusion was conducted.[155] The group with circadian modification received 68% of each daily dose between 3:00 PM and 9:00 PM. The patients with circadian modified infusion tolerated almost twice the daily dose of FUDR, with a decrease in hepatic toxicity compared with patients receiving flat infusions, but the study was not a prospective randomized study.

Another approach to decrease toxicity from HAI is to alternate drugs such as HAI FUDR with hepatic arterial 5-FU. A weekly hepatic arterial bolus of 5-FU does not cause hepatobiliary toxicity; however, it frequently produces treatment-limiting systemic toxicity or arteritis. Stagg and colleagues[156] used alternating HAI of FUDR (for 7 days) followed by a hepatic arterial bolus of 5-FU (weekly for 3 weeks every 35 days). The response rate was 51%, and median survival was 22.4 months. In contrast to the experience with single-agent HAI of FUDR, no patient on the alternating plan has had treatment terminated because of drug toxicity. Davidson and associates,[157] using a similar alternating regimen on 54 patients, produced a 54% response rate, with 3.5% of patients developing biliary sclerosis. Patt and coworkers,[158] using HAI of 5-FU and interferon in 5-FU- and LV-refractory patients, produced a 33% response rate with a median survival of 15 months and no hepatobiliary toxicity.

Warren and colleagues,[159] using weekly HAI 5-FU infusion and systemic LV, produced a 45% response rate in 31 patients without hepatic toxicity and mild systemic toxicity. Metzger and colleagues[160] treated 30 patients with an infusion of 5-FU + mitomycin C; the courses were repeated every 6 weeks. The median survival was 18 months, with a 57% partial response rate. No patients developed sclerosing cholangitis, but mucositis and leukopenia were seen. Catheter complications occurred in 33%, which led to premature termination of treatment in one-third of the patients. Schlag and associates,[161] using HAI of 5-FU via a surgically placed port connected to an external pump, reported a 27% partial response in 33 patients and a median survival of 14 months. Hepatobiliary toxicity was seen in only 5% of the patients. Table 59-15 lists some of the studies using 5-FU and other agents by this technique.

Methods to Increase Response Rate and Decrease Extrahepatic Disease

The potential benefit of multidrug hepatic arterial therapy has been evaluated. A randomized trial of a three-drug regimen (mitomycin C, bischloroethyl nitrosourea, and FUDR) compared to FUDR alone was conducted in 67 patients with disease progression after previous treatment with systemic chemotherapy.[162] The overall response rate and survival were similar. The response rates in both groups were higher than would be expected with a second systemic regimen after failure of first-line treatment. For patients who had been treated previously for metastatic disease, the response rate was 48% for the three drugs as compared with 24% for FUDR alone ($P = 0.03$).

HAI FUDR/Dex + mitomycin C[163] administered through the pump side port produced a 70% response rate in previously treated patients with a median survival of 19 months from the start of HAI therapy after progression on systemic FU/LV.

Sixty-four patients were treated with FUDR and LV by HAI. The overall response rate was 62%, but 15% of patients developed biliary sclerosis. The toxicity of the combination was higher than that of FUDR alone, but the survival was improved: 86% of the patients

Table 59-15 Hepatic Arterial Therapy: 5-FU Plus Other Agents

Investigator	No. of Patients	Dose (mg/m²)	Response (%)	Median Survival
Cortesi et al[346]	109	5-FU 500 × 5 Cisplatin 24 × 5	46	16
Warren et al[159]	31	5-FU 1500 × 24 hr LV 400 weekly × 6	48	17
Sugihara[347]	58	5-FU 360 × 7 then 100 × 7 days	50	11
Kerr et al[348]	43	LV 200 5-FU 400 then 5-FU 1800 × 22 hr	36	—
Howell et al[349]	40	LV 200 5-FU 400 then 5-FU 1600–22 hr every 2 wk	46	19
Patt et al[350]	48	IFN 5 mu 5-FU 1000 × 5 hr every wk	33	15
Borner et al[351]	28	5-FU 750 × 5 days	50	

were alive at 1 year, 62% at 2 years, 33% at 3 years, and 10% at 5 years after treatment.[164]

To further increase response rate without an increase in toxicity, the combination of FUDR, Dex, and LV was tested.[165] The response rate was 78% in previously untreated patients, with only 3% of these developing sclerosing cholangitis. The median survival was 24.8 months, and the 1- and 2-year survivals were 91% and 57%, respectively. In patients who had received previous chemotherapy, the response rate was 52%.

The use of systemic therapy + HAI might produce a decrease in extrahepatic disease. In Safi and coworkers' study[166] comparing FUDR (0.2 mg/kg/day for 14 of 28 days) with a combination of intra-arterial FUDR (0.21 mg/kg/day) and intravenous FUDR (0.09 mg/kg/day) given concurrently for 14 of 28 days, the response rates were 60% for both arms of the study. The incidence of extrahepatic disease, however, was 56% for the group receiving intra-arterial/intravenous treatment compared with 79% for those receiving HAI alone ($P < 0.01$). There was no difference in survival between the two groups ($P = 0.08$).[135] In Lorenz and colleagues,[150] study of 52 patients, combined HAI/intravenous did not increase survival or decrease the development of extrahepatic disease (60% and 62% for HAI/intravenous vs, HAI alone, respectively). Wanebo and colleagues[167] used continuous-infusion 5-FU and LV for 14 days alternating with intrahepatic FUDR, Dex, and LV. Two other studies produced median survivals of 12 and 18 months administering HAI FUDR + systemic 5-FU.[168,169]

A phase I study of HAI FUDR combined with systemic irinotecan[170] in previously treated patients (45% had previous CPT-11) reported a response rate of 74%, a TTP of 8.1 months, and a median survival of 20 months. Thirteen of the sixteen patients with previous CPT-11 exposure responded to this regimen. Systemic Oxali + 5-FU/LV or Oxali + CPT-11 with concurrent HAI FUDR/Dex in 36 previously treated patients (74% had received prior CPT-11) produced response rates of 86% with a median survival of 36 months, and a 1-year survival of 80%.[171]

Toxicity of Hepatic Arterial FUDR Infusion

Most trials of HAI given via an internal implantable pump use FUDR or 5-FU. A summary of the toxicities encountered is listed in Table 59-16. Myelosuppression, nausea, vomiting, and diarrhea do not occur with HAI of FUDR. If diarrhea does occur, shunting to the bowel should be suspected.[172] The most common problems with HAI FUDR are hepatic toxicity and ulcer disease (Box 59-2).[173] Hepatobiliary toxicity is the most problematic toxicity seen with HAI FUDR. Most studies point to a combined ischemic and inflamma-

Table 59-16 Hepatic Arterial FUDR Infusion with Internal Pump: Toxicities

Investigators	No. of Patients	Gastritis (%)	Ulcer (%)	SGOT (%)	Bilirubin (%)	Diarrhea (%)	Biliary Sclerosis (%)
Niederhuber et al[333]	70	56	8	32	24	—	—
Balch and Urist[334]	50	—	6	23	23	0	—
Kemeny et al[335]	41	29	29	71	22	0	5
Shepard et al[336]	53	—	20	49	24	—	—
Cohen et al[337]	50	—	40	10	25	—	—
Weiss et al[338]	17	50	11	80	23	23	—
Schwartz et al[339]	23	53	—	77	20	10	—
Johnson et al[340]	40	—	8	50	13	–0	5
Kemeny et al[175]	31	17	6	47	—	–8	29
Hohn et al[342]	61	35	2	0	78	11	29

SGOT, serum glutamic-oxaloacetic transaminase.

Box 59-2. DOSE MODIFICATION FOR HEPATIC TOXICITY

SGOT	Bilirubin	Alkaline Phosphatase	FUDR Dose Reduction (%)
<2 × baseline	—	—	80
3 × baseline	or 1.5×	or 1.5×	50
>3 × baseline	or 2×	or 2×	Hold

Baseline is day 1 or previous FUDR dose. If elevations continue on reduced doses, decrease duration of FUDR to 1 week. If bilirubin is >2 mg/dL, do not repeat treatment for 2 months. If bilirubin levels return to and remain normal, use 25% of the previous FUDR dose for 1 week.

tory effect on the bile ducts as the etiology of this complication. The bile ducts derive their blood supply almost exclusively from the hepatic artery and thus are undoubtedly perfused with high doses of chemotherapy.[174]

Clinically, biliary toxicity manifests as elevations of serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, and bilirubin. Elevation of SGOT is an early manifestation of toxicity; elevation of alkaline phosphatase or bilirubin is evidence of more severe damage. In the early stages of toxicity, hepatic enzyme elevation returns to normal when the drug is withdrawn and the patient is given a rest period, whereas in more advanced cases it does not resolve.

In patients who develop jaundice, endoscopic retrograde cholangiopancreatography (ERCP) might demonstrate lesions resembling idiopathic sclerosing cholangitis in 5% to 29%.[175] Because the ducts are sclerotic and nondilated, sonograms usually do not show dilation. In some patients, the strictures are more focal and usually worse at the hepatic duct bifurcation; drainage procedures either by ERCP or by transhepatic cholangiogram could be helpful.[176] Duct obstruction from metastases should first be excluded by CT of the liver.

Close monitoring of liver function tests is necessary to avoid the biliary complications. If serum bilirubin rises to 3 mg/dL or higher no further treatment should be given until the bilirubin returns to normal, and then only after a long rest period to prevent the development of sclerosing cholangitis. With proper monitoring, this complication occurs in less than 10% of patients.

Severe ulcer disease results from inadvertent perfusion of the stomach and duodenum with drug via small collateral branches from the hepatic artery and can be prevented via careful dissection of these collaterals at the time of pump placement. Even without radiologically visible perfusion of the stomach, however, mild gastritis and duodenitis still can occur. HAI 5-FU causes less biliary problems and more arteritis (Box 59-3).[156]

Box 59-3. INTRAHEPATIC THERAPY MANAGEMENT OF TOXICITY

Ulcer: Denude vessels that supply stomach and duodenum
Hepatitis: Monitor SGOT, alkaline phosphatase; decrease or hold dose for enzyme elevations.
Biliary sclerosis: Monitor liver enzymes, document by ERCP; if present, do not repeat treatment even if enzymes normalize.
Cholecystitis: Remove gallbladder.
Diarrhea: May be misperfusion or very extensive liver disease (repeat hepatic flow scan).

Complications of Hepatic Artery Infusion Pump Placement and Use

Incomplete or extrahepatic perfusion is usually a surgical problem. It is necessary to mobilize the entire gastroduodenal artery and ligate all branches supplying the stomach, duodenum, bile duct, or pancreas. The postoperative ^{99m}Tc macroaggregated albumin perfusion scan, when compared with the liver scan, can show incomplete perfusion of the liver from either an accessory or replaced hepatic artery not detected preoperatively or an incompletely isolated hepatic artery that is supplying vessels to the pancreas or gastrointestinal tract. These abnormalities can be assessed by performing a side port pump injection (Box 59-4). (Most implantable pumps have a main chamber with a central port in which the drugs, such as FUDR, are placed for constant infusion. These pumps also have a side port that bypasses the main chamber and goes directly into the main catheter.) Often an accessory left hepatic artery arising from the left gastric artery, or an accessory right hepatic artery arising from the superior mesenteric artery, has not been identified. In such instances it might be possible to embolize the accessory vessel, which will allow collateral flow to develop from the main hepatic artery. A common technical error during catheter insertion is placing the catheter too far from the junction of the gastroduodenal artery and hepatic artery. The segment of gastroduodenal artery that is continuously exposed to full-dose chemotherapy will eventually thrombose. There is a learning curve for both the surgeons and the medical oncologists. In one series, technical complications were seen in 37% of patients with inexperienced surgeons and in 6.6% of patients with experienced surgeons.[177]

Hepatic Arterial Infusion: Conclusions

HAI has several advantages. From a pharmacologic standpoint, HAI is more effective than systemic therapy, in that higher drug levels are achieved at the sites of metastatic disease. Utilizing agents with high hepatic extraction virtually eliminates the systemic toxicity observed with "standard" chemotherapy.

Should every patient with unresectable liver metastases and no extrahepatic disease undergo HAI? Hepatic arterial therapy produces higher response rates compared with systemic therapy. Older randomized studies with crossover design did not prove a survival advantage. In ten randomized trials, the response rate was higher using HAI compared with systemic therapy (see Table 59-14). The time to hepatic progression was significantly longer in the HAI groups as

Box 59-4. TECHNICAL ASPECTS OF PUMP INSERTION

1. Rule out extrahepatic disease by colonoscopy, chest radiograph, or CT scan of abdomen and pelvis.
2. Intraoperatively, biopsy samples should be taken from portal lymph nodes to rule out extrahepatic disease.
3. Celiac and superior mesenteric artery arteriography should be done to identify arterial anatomy of liver and vessels to stomach and duodenum and pancreas.
4. Portal vein must be patent.
5. Place catheter into gastroduodenal artery, not directly into hepatic artery, which could lead to thrombosis; secure catheter with nonabsorbable ties.
6. Identify and ligate branches to pancreas and duodenum.
7. Check whole-liver perfusion with 5 mL of fluorescein through side port.
8. Postsurgery macroaggregated albumin scan should be performed through side port of pump to check perfusion of the liver and to ensure no extrahepatic perfusion.

Table 59-17 Randomized Studies of HAI versus SYS: Time to Hepatic Progression

Group	No. of Eligible Patients	(MO) HAI	SYS	*P* Value
MSKCC[341]	99	9	6	
NCOG[342]	117	13	6.7	
Mayo Clinic[344]	64	15.7	6	
France[345]	163	15	6	
CALGB[152]	135	9.8	7.3	.034

HAI, hepatic arterial infusion; SYS, systemic chemotherapy.

compared with the systemic groups (Table 59-17). The randomized pump studies do not evaluate the issue of survival clearly, for the following reasons: (1) In some studies a crossover was allowed; (2) the number of patients was small; (3) positive portal nodes were included in the HAI-treated groups. Recent HAI trials demonstrate median survivals of 24 to 36 months. Therefore, in a patient with extensive hepatic disease (30% to 60% liver involvement) who can tolerate an operation, hepatic arterial therapy combined with systemic chemotherapy or systemic chemotherapy alone can be used as the first treatment. Patients who start with systemic therapy and whose tumor fails to respond can then still undergo HAI therapy (Fig. 59-11). Table 59-18 lists trials using HAI therapy after progression on systemic therapy. In institutions in which physicians are not familiar with placement of the hepatic arterial catheter and the pump or with the management of patients on regional infusion, systemic chemotherapy is a reasonable option.

Because the liver is often the initial site of metastatic disease in patients with CRC, early intensive therapy with surgical resection or intrahepatic infusion (or both) at a time when the tumor burden is small might prevent the progression of metastases to other sites. Although hepatic arterial therapy is applicable to only a minority of patients with metastatic CRC (those with only hepatic metastases), it might be the best available therapy for these patients.

In the future, molecular markers could help determine the optimal type of treatment. In one small study, patients with low thymidylate synthetase levels had a fourfold greater chance of responding after 5-FU-based infusion.[178] In another study, patients with mutated p53 had a shorter survival.[179]

The use of HAI for other tumor types has not been studied as extensively. Some of the breast studies using HAI are shown in Table 59-19. Most of these studies are on patients whose tumors are failing to respond to systemic therapy, and yet response rates of 50% or greater are seen in five of the eight studies.

Trials have been done using HAI therapy for cholangiocarcinoma and HCC (Tables 59-20 and 59-21). At MSKCC, HAI therapy alone produced a partial response of 47% in cholangiocarcinoma and 28% in HCC.[180] Yoshikawa and associates, using HAI, epirubicin, pararubicin, and carboplatin, had an objective response of 35.4% and 2-year survival of 30% in 319 patients.[181]

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy has been evaluated as a way to decrease hepatic tumor burden for the purpose of proceeding with hepatic resection. Although no randomized prospective trial has been completed testing this as a treatment strategy, the results of a retrospective analysis have been presented, and the results seem promising.

Giacchetti and colleagues[182] conducted a retrospective review of 151 patients with unresectable liver-only metastases from CRC who were treated with 5-FU/LV and Oxali followed by attempted liver resection. The criteria used to define unresectability were as follows: (1) more than four liver metastases (30%), (2) single tumor larger than 5 cm (34%), (3) tumor in both hepatic lobes, (4) invasion of the intrahepatic vascular structures, and (5) high percentage of liver involvement (>25% liver involvement; 48%). Their analyses revealed that of this group, 77 patients (51%) became resectable after neoadjuvant therapy. The 5-year survival rate for the 77 patients who underwent hepatic resection was 50%, progression-free survival was 17 months, and 72% had relapsed within a median of 12 months.[182,183] Adam and coworkers,[84] from the same group, reviewed the records of 1104 patients with unresectable disease who received mainly FOLFOX as neoadjuvant therapy; 12.5% became resectable and the 5-year survival of these patients was 34%, similar to what could be obtained with patients who were initially resectable.

Several trials were designed to address resectability rate after chemotherapy that varied with patient selection. The Mayo Clinic trial considered patients to be unresectable if they had (1) involvement of all three major hepatic veins, portal vein bifurcation, or the hepatic vena cava; (2) involvement of the main right or main left portal vein and the main hepatic vein of the opposite lobe; (3) disease requiring more than a right or left trisegmentectomy; or (4) six or more metastatic lesions distributed diffusely in both lobes of the liver. In patients treated with preoperative Oxali/5-FU/LV, 38% of 44 became suitable for resection, but after resection, 73% recurred in the liver. Median survival was 26 months.[184] A retrospective review of these data demonstrated that 10% of patients were actually resectable before neoadjuvant therapy.

Pozzo and colleagues treated 40 patients with unresectable disease, meaning: (1) six metastases or three per lobe, (2) size larger than 5 cm for one lesion if six metastases were present, (3) contiguity with two hepatic veins, inferior vena cava or liver hilum with neoadjuvant FOLFIRI.[185] Thirty-two percent underwent liver resection with a DFS of 28 months. Other trials evaluating neoadjuvant chemotherapy are in Table 59-22.

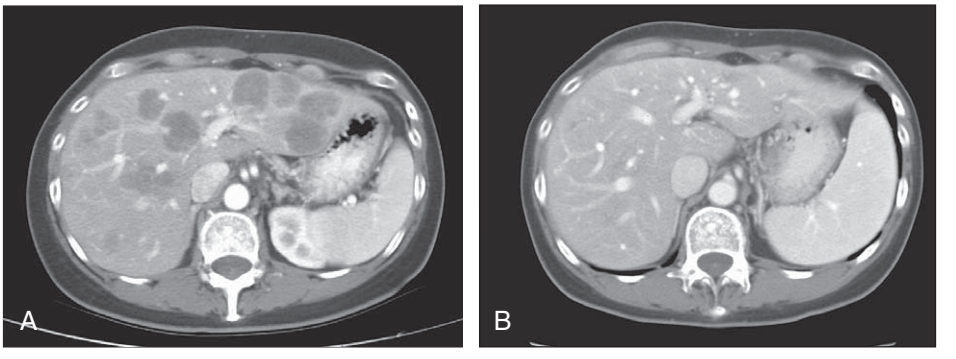


Figure 59-11 • **A,** Patient's CT before treatment, demonstrating massive liver involvement. **B,** Patient's CT after hepatic arterial therapy, showing an excellent partial response after HAI FUDR and LV.

Table 59-18 Hepatic Arterial Infusion in Previously Treated Patients: Second-Line Therapy

Regimen	No. of Patients	Partial Response (%)	1-Year Survival (%)
HAI alone			
FUDR alone[352]	49	67	33
FUDR + Mit C+ BCNU[352]	45	70	47
FUDR + LV + Dex[166]	29	66	52
Mit + FUDR + Dex[164]	37	77	65
CPT-11[353]	10	33	—
5-FU/LV + Cisplatin[354]	28	48	58
HAI + SYS			
FUDR + Dex + SYS–CPT-11[171]	56	74	84
FUDR + Dex + SYS–Oxali[171]	36	80	86
Oxali + SYS–FU/LV[355]	22	68	—
Oxali + SYS–FU/LV[356]	28	64	85
FUDR alone[340]			

BCNU, bischloroethyl nitrosourea or carmustine; CPT-11, irinotecan; Dex, dexamethasone; 5-FU, 5-fluorouracil; FUDR, 5-fluoro-2-deoxyuridine; HAI, hepatic arterial infusion; LV, leucovorin; Mit C, mitomycin C; Oxali, oxaliplatin; SYS, systemic chemotherapy.

Table 59-19 Hepatic Arterial Infusion for Breast Cancer*

Investigators	No. of Patients	Drugs	Partial Response (%)	Survival (mo)
Fraschini et al[357]	34	Cisplatin + vinblastine	33	11
Estape et al[358]	16	VP-16–cytoxan	50	16
Fraschini et al[359]	25	Vinblastine	52	11†
Fraschini et al[360]	26	Cisplatin	19	11
Maral et al[361]	15	Mit C + FUDR	53	18‡
Arai et al[362]	56	FU + doxo + Mit C	81	12.5
Tada et al[363]	45	Doxo + Mit C	37	7.5

FU, 5-fluorouracil; FUDR, fluorodeoxyuridine; Mit C, mitomycin C.
*Most studies consist of patients whose tumor progressed after previous systemic chemotherapy.
†Mean survival only for responders.
‡Some patients in study also had colon cancer.

Table 59-20 Biliary Tract Carcinoma—Hepatic Arterial Infusion Trials

Study	No. of Patients	Therapy	Response Rate (%)	Median Survival
Warren[364]	15	HAI Doxorubicin	60	NR
Makela and Kairaluoma[365]	27	HAI Mit C	48	14 mo
Melichar et al[366]	32	HAI 5-FU/FA ± Cisplatin	NR	14 ± 17 mo
Cantore Update[367]	26	HAI Epirubicin/Cisplatin	35	NR
		Systemic 5-FU IVCI		
Danso[180]	23	HAI FUDR	47	NR

Rougier and associates treated 23 patients with cetuximab and FOLFIRI, and seven (30%) became resectable.[186] Oxali/Irinotecan (CPT-11) + HAI in 44 clearly unresectable patients enabled 35% to become resectable (56% even though the majority had received this after second- or third-line therapy). The median survival of the entire group is 36 months, and median survival for the resected group has not been reached. In a Japanese study, 51 patients with unresectable disease were treated with HAI/5-FU and systemic UFT. The 3- and 5-year survivals were 58% and 42% for the resected group. In Italy, 244 patients were randomized to FOLFIRI or FOLFIRI + Oxali (Folfoxiri). In patients with only liver metastases, the resection rate was 12% and 36% for the FOLFIRI and Folfoxiri regimens, respectively.[187]

In making decisions about the timing of liver resection and pre- or postoperative chemotherapy, there are several considerations. The advantages and disadvantages are listed in Table 59-23. For patients

Table 59-21 Hepatic Artery Infusion Chemotherapy Trials in Hepatocellular Carcinoma

Study	No. of Patients	Treatment	PR (%)	Median OS
Okudaet al[368]	31	HAI cisplatin, 5-FU	29	NR
Shildt and Baker[369]	30	HAI FUDR, Dox, Strepto	10	NR
Fazio et al[370]	30	HAI Mit C, Cisplatin, 5-FU	11	8.6 mo
Patt et al[158]	29	HAI FUDR, LV, Dox, cisplatin	41	15 mo
Wellwood et al[371]	28	HAI FUDR	54	NR
Carr and Dvorchik[372]	26	HAI cisplatin	42	NR
Cheng et al[373]	16	HAI cisplatin	19	NR
Urabe et al[374]	15	HAI MTX, 5-FU, cisplatin, IFN	47	NR
Atiq et al[375]	10	HAI FUDR, Mit C, IFN	50	14.5 mo

Dox, doxorubicin; 5-FU, 5-fluorouracil; FUDR, 5-fluoro-2-deoxyuridine; HAI, hepatic artery infusion; IFN, interferon; Mit C, mitomycin C; LV, leucovorin; MTX, methotrexate; Strepto, streptozotocin.

Table 59-22 Prospective Trials Evaluating Neoadjuvant Systemic Chemotherapy for Unresectable Disease: Respectability Rate

Investigator	Treatment	No. of Patients	Resectability Rate (%)
Wein[376]	Oxali + FU/LV	53	11
Pozzo[185]	FOLFIRI	40	27.5
Alberts[184]	FOLFOX	42	33
Gaspar[377]	FOLFOX	37	27
Quenet[378]	Oxali/CPT-11/FU/LV	34	37.5
Abad[379]	Oxali/CPT-11/FU	47	30
Falcone[380]	Oxali/CPT-11/FU	39	30
Falcone[380]	FOLFIRI	42	12
Ho[381]	FOLFIRI	40	10
Masi[382]	FU/LV/Oxali + CPT-11	74	26
Wein[383]	FU/LV	53	11
Rougier[384]	Cetuximab + CPT-11/FU/LV	23	30

Table 59-23 Pros and Cons of Preoperative Chemotherapy

PROS

- Decrease size
- Control micrometastatic disease
- Assessment of chemotherapy activity
- Better chemotherapy tolerance
- Surrogate marker for success of liver toxicity

CONS

- Liver toxicity
- Steatosis
- Sinusoidal dilatation
- Risk of progression or growth of new sites
- Clinical response may make surgery more difficult
- Secondary splenomegaly
- Selection of resistant clones

with borderline resectability, chemotherapy can be done first but only for short periods of time, and as soon as response is noted, surgery should be performed. Adam reported prolonged chemotherapy (>12 cycles) was related to longer hospital stays after liver resection.[188] For clearly unresectable disease, patients should enter protocols that are addressing the question of how best to decrease liver metastases to allow resection. In patients with synchronous CRC, there are those who advocate for simultaneous resection of both the primary and the metastatic disease, those who recommend chemotherapy first,[189,190] and those who state both surgeries can be done simultaneously.

Supporting the concept of controlling micrometastatic disease, the Liver Met Survey group found patients with more than five metastases survived longer if they were given neoadjuvant chemotherapy, with a 5-year survival of 22% versus 12% ($P = 0.07$) for the preoperatively treated and preoperatively nontreated groups, respectively. In another retrospective review at MSKCC, preoperative chemotherapy did not improve survival. In a review of 230 patients who received HAI + systemic therapy after liver resection,[191] the median survivals for patients who did or did not receive preoperative (neoadjuvant) therapy were 63 and 115 months, respectively($P = 0.26$).

If metastases that disappear on CT remain viable, preoperative chemotherapy may be a disservice. In a review by Benoist and coworkers on 586 treated patients,[192] 38 patients had disappearance

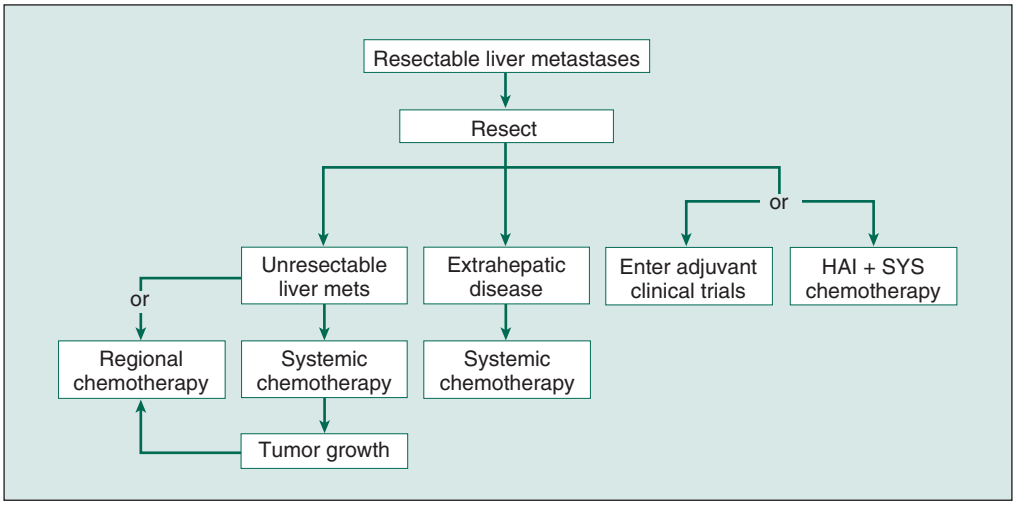


Figure 59-12 • Treatment of liver metastases.

of at least one lesion on CT. Pathologic examinations of sites with a complete response showed that in 11 of 15 (80%) there were viable tumor cells. Areas that could not be found were closely followed, and in 23 of 41 sites (47%), tumor reoccurred.

As use of preoperative chemotherapy increases, reports are emerging about liver toxicity from preoperative chemotherapy. There is an increased incidence of steatosis, sinusoidal abnormalities, venoocclusive disease, and steatohepatitis. In the Rubbia-Brandt and colleagues[193] report on 153 patients undergoing liver resection, 51% of the 87 patients who have received chemotherapy before resection had sinusoidal dilation and 78% who had prior Oxali showed striking sinusoidal alterations, with venoocclusive fibrosis in 48%. Kooby and associates reported on 325 patients with fatty livers undergoing resection at MSKCC and found that those treated with preoperative chemotherapy were more likely to have steatosis (66%), with marked steatosis being an independent predictor of complications following hepatic resection.[194] Vauthey and coworkers reported a 20% incidence of steatohepatitis in patients receiving preoperative CPT-11 versus 4.4% in those who received no preoperative chemotherapy, and an 18.9% incidence of sinusoidal dilation in those receiving preoperative Oxali versus 1.9% in those receiving no preoperative chemotherapy. Patients with steatohepatitis had an increased 90-day mortality, 14.7% versus 1.6% ($P = 0.001$).[195]

Is neoadjuvant chemotherapy useful for resectable liver metastases? The EORTC study is looking at preoperative and postoperative FOLFOX versus observation. They have randomized 364 patients to (1) six cycles of FOLFOX before and after surgery or (2) surgery alone.[196] Presently, in the group receiving preoperative chemotherapy, 7.7% progressed before surgery and 11% were not able to undergo resection. It is too early to look at the DFS and survival. For clearly resectable disease, until we know more from these studies, surgery should be done first, followed by adjuvant therapy. Figure 59-12 provides a treatment algorithm for liver metastases.

HEPATIC ARTERIAL EMBOLIZATION

Because both hepatic metastases and primary liver tumors derive their blood supplies from the hepatic artery, hepatic arterial ligation (HAL) and embolization have been used to reduce the tumor's blood supply.[197] In most hepatic tumors, HAL produces only a transient benefit because of the rapid development of collateral vessels. In vascular neuroendocrine tumors, HAL produces objective tumor reduction, whereas in colon metastases (which are typically less vascular), minimal regression occurs.

The development of a collateral blood supply might be minimized by injecting vasoocclusive particles into the hepatic artery (hepatic artery embolization, HAE), which also provides the opportunity for retreatment, because only the microvasculature is occluded.[103] In one study of 61 individuals with liver metastases from colorectal carcinoma, patients were randomized to HAE, HAL + microspheres (HAE), or no further treatment. The median survivals were 8.7, 13, and 9.6 months, respectively, suggesting that embolization or ligation alone had no effect on survival for patients with CRC.[198] Gerard and colleagues[199] randomized 67 patients to HAL alone versus HAL and portal vein infusion of 5-FU. The median survival in both groups was 12 months; among patients whose median extent of liver involvement was 30%, only one patient responded. Both studies suggest that this technique is not useful for CRC.

HAE has a definite role in highly vascular tumors, such as neuroendocrine tumors of the liver.[200] These tumors usually grow slowly, and a reduction in tumor bulk can result in significant palliation. Ajani and associates[201] treated 22 patients who had islet cell carcinoma with HAE using polyvinyl alcohol particles (Ivalon) and gelatin sponge particles (Gelfoam). The median survival in this study was 33 months from initiation of embolization (range, 1 month to 72 months); 12 patients had a partial response associated with subjective improvement and decrease in hormone levels. Other studies using HAE are listed in Table 59-24; all demonstrate an improvement in symptoms and a decrease in hormone levels. Gelfoam (size 1–2 mm), one of the agents used for embolization, does not lead to peripheral vascular occlusion and has an inconsistent duration of occlusion (due to absorption), whereas Ivalon (size 150–500 μm), a smaller particle, allows for more peripheral occlusion and is not absorbable, allowing for a more persistent arterial occlusion.[201–203] A collagen particle (Angiostat; size 20–250 μm) and a biodegradable albumin microsphere (Spherex; size 15–40 mm) are currently being tested, especially in combination with chemotherapy.

Interference with hepatic blood flow can exacerbate the underlying liver disease and can be dangerous in patients with portal venous thrombosis, which is present more often in patients with primary liver tumors than in those with metastatic disease. In a study by Carr and coworkers,[204] four patients with HCC had reversal of tumor-induced portal vein thrombus. The researchers obtained objective responses in 22 of 35 patients (63%) using Spherex (biodegradable) starch microspheres, doxorubicin, and cisplatin. There is clear evidence that arterial embolization causes antitumor effects, but some randomized studies have not shown increased survival.[205]

Table 59-24 Neuroendocrine Tumors

Investigators	Agent	No. of Patients	Biochemical or Symptomatic Response (%)	Tumor Response (%)
Hepatic artery ligation				
Martin et al[206]		8	76	
Moertel[207]		10	70	
Melia et al[208]		6	50	17
Hepatic artery embolization				
Carrasco et al[202]	Gelfoam	23	87	—
Ajani et al[201]	Ivalon + Gelfoam	22	60	
Marlink et al[203]	Gelfoam	10	100	90
Maton et al[385]	Lyodura	13	76	—

Complications of Embolization

The complications of embolization are nausea, vomiting, fever, pain, and changes in liver function tests (Table 59-25). Problems less commonly encountered include the following: injury of the gallbladder by retrograde flow through the cystic artery, ischemic necrosis of the bowel by embolization of one of the vessels to the intestinal tract, pancreatic infarction and pancreatitis by embolization of one of the pancreatic vessels, and dyspnea by embolization of the lungs.[201–203,206–208]

In neuroendocrine tumors responding to HAE, rapid cell death can result in tumor lysis syndrome with symptomatic hyperuricemia, leading to uric acid nephropathy and oliguria. Vigorous hydration and prophylactic allopurinol might prevent this problem. In carcinoid tumors, HAE could cause a life-threatening carcinoid crisis from the rapid release of hormones from tumor cells. Somatostatin analogs may be given, either before the procedure or if a carcinoid crisis should occur.[209] To avoid some of the serious complications of HAE, patients with cirrhosis, portal vein occlusion, and biliary tract obstruction are usually excluded.

Table 59-25 Complications and Management of Hepatic Arterial Embolization

COMPLICATION
Pain
Fever
Nausea and vomiting
↑WBC ↑LDH ↑SGOT
Cholecystitis
Hepatic gas formation and abscess
Renal insufficiency
Ileus
PRE-EMBOLIZATION
Hydration
Allopurinol
Somatostatin (only in neuroendocrine carcinomas)*
Analgesics just before procedure
POSTEMBOLIZATION
Analgesics
Follow WBC, LDH, SGOT, creatinine
Treat by appropriate measures nausea, fever, abscess, infection, ileus

LDH, lactate dehydrogenase; SGOT, serum glutamic-oxaloacetic transaminase; WBC, white blood cell count.

*150–250 mg SC, every 6–8 hrs before procedure.

CHEMOEMBOLIZATION

An extension of the work with embolization is chemoembolization. This process involves a local entrapment of drug in the embolization agent and provides a prolonged exposure of the tumor to the drug locally with less systemic drug circulation. A nonrandomized study by Daniels and colleagues[210] suggested that the addition of chemotherapy to the embolic agent (angiostat) produced an increase in response rate over the embolic agent alone. In a study by Venook and associates,[211] 51 patients with unresectable HCC were treated with Gelfoam and a mixture of three drugs—doxorubicin, mitomycin C, and cisplatin—given via a percutaneous hepatic artery catheter. Twelve (24%) had a partial response, and tumor liquefaction was noted in 70% of patients on CT, with a more than 50% reduction in α-fetoprotein in 68% of patients. Using this technique and the same drugs, these investigators also treated liver metastases from neuroendocrine tumors. In 12 patients with a median liver involvement of 60%, 33% had a partial response with a reduction in hormone levels.[160] Median survival from treatment initiation was 7 months (range 3 months to 3 years). Lipiodol has been found to remain selectively in the primary and secondary liver cancers when injected into the hepatic artery, allowing visualization of tumors as small as 4 mm.[161] Thus, Lipiodol can be used to deliver either chemotherapy or local radiation by combining with an agent such as iodine-131 (^{131}I).[212]

Chemoembolization is rarely used for CRC, because median survivals are usually not increased; average survival is approximately 9 months.[213] Adding systemic therapy to hepatic chemoembolization could improve results. In one trial using regional cisplatin in a polyvinyl alcohol suspension with systemic 5-FU, the partial response rate was 40%, and median survival was 19.3 months.[214]

Another form of chemoembolization is to enclose the chemotherapeutic agents in a microsphere.[215] Degradable starch microspheres injected intra-arterially are trapped in an extracapillary network formed in liver metastases.[215,216] Drug dissolved in the microsphere suspension is retained in the blood vessels of the target organ as long as the blood flow is blocked and then gradually releases the chemotherapeutic agents, resulting in a longer duration of tumor exposure to the drug. The most appropriate agents for microspheres would be those that, like mitomycin C, are preferentially toxic to cells under hypoxic conditions. Another useful drug to use with microspheres is doxorubicin. In a rabbit study, the mean tumor drug

level was significantly higher when this drug was used with the microsphere compared with doxorubicin alone, whereas hepatic uptake of the drug by normal tissue was similar in the two groups.[217] Monoclonal antibodies can also be attached to the microspheres.[218]

Radioembolization attempts have been made using glass microspheres containing ^{90}Y, a β-emitter with tissue penetrance of 2.5 mm. Andrews and coworkers[218] reported 5 of 23 responses with yttrium embolization. A study of ^{131}I- labeled lipiodol administered to 20 patients (15 HCC, 5 metastatic) produced an α-fetoprotein drop in 11 of 12 patients and a response in 9.[219] The response rates for radioembolization of metastatic tumors are far less than those reported for treatment of primary HCC, perhaps because most metastatic tumors except for neuroendocrine primaries are far less vascular than HCC.

Arterial embolization is commonly used for HCC. Responses and increase in time to tumor progression have been documented.[205,220–222] Meta-analysis showed an increase in survival with chemoembolization compared with conservative management.[223]

CRYOSURGERY

Cryosurgery is an in situ destruction of tissue using subzero temperatures. The rapid freeze/thaw of tissues results in cellular damage and death. One advantage of cryosurgery is the ability to use local treatment without sacrificing normal tissue. Among the difficulties with this technique are defining the full extent of the tumor and the inability to monitor the amount of freezing, and thus the possibility of overtreatment of surrounding vulnerable normal tissue. Two technical developments have improved the use of cryosurgery:

1. Cryoprobes cooled by liquid nitrogen allow more precise freezing, even within the liver.
2. Intraoperative ultrasound allow precise placement of the cryoprobe and more accurate monitoring of the freezing process.

Cryosurgery has been used intraoperatively but also can be used percutaneously. In a series of 32 patients with liver tumors (24 with CRC), 28% remained free of disease for 5 to 60 months.[224] In another series using intraoperative cryosurgery on 18 patients who had metastatic CRC with 1 to 12 lesions, Onik and coworkers[225] reported that 4 patients had complete remission with a median survival of 28 months, whereas 14 patients were considered inadequately treated and had a 21-month median survival.

Weaver and colleagues[226] treated 47 patients with cryosurgery with occasional operative resection. The number of metastases ranged from 1 to 12. The 2-year survival was 62%. Morris and Ross,[227] reporting on 67 patients, noted that 75% of patients undergoing cryosurgery had an increase in CEA by 6 months later. Occasionally, the surgeon feels that all disease has been destroyed but, as seen by this study's PET results after cryosurgery, tumor can still be present even though the surgeon feels that no disease has been left behind.

The 2-year survival after cryosurgery varies from 72% to 12%. The Boston series reported the highest survival, which might reflect the type of patient being selected for cryosurgery (i.e, lesser extent of disease and a smaller number of metastases).[228] Adam and associates[229] reported a 2-year survival rate of 50% for patients with colorectal metastases as compared with 67% for patients with HCC. They reported a local recurrence rate of 44% for the colorectal patients. Because local recurrence is high, the use of HAI after cryosurgery could be useful. One small, nonrandomized study doubled survival with the use of HAI after cryosurgery.[230] Other trials are now evaluating the use of HAI with or without systemic therapy. In a series of 185 nonrandomized patients, 71 received adjuvant CPT-11 and/or HAI of FUDR after cryosurgery. Two-year survival was 75% for patients receiving postcryosurgery therapy as compared with 35% if no adjuvant therapy was given.[231] Cryoablation can also be used after hepatic resection with close margins or to remove central lesions. Cryoprobes can be used as a handle to assist in segmental resections. An ice ball is produced with 1-cm margins around the tumor; then the probe is used for traction so that a segmental resection can be performed.[232]

The addition of cryosurgery to conventional surgical procedures was evaluated by Seifert and coworkers[118] in a randomized study. Those receiving surgical procedures plus cryosurgery had similar survival but an increase in liver recurrence for the cryo group.

Cryosurgery does involve some technical issues, including the following:

- Adequate hydration before surgery, because myoglobinuria and tumor lysis can occur.
- Attention to bile ducts, because biliary fistula can occur.
- Two freeze/thaw cycles are preferred.
- The probe should not be pulled or twisted vigorously, because that could cause cracking.[233]

Complications include hepatic cracking secondary to the thermal stresses that occur during rapid freezing; these are usually associated with hemorrhage, which could require packing. Other complications include biliary fistula requiring percutaneous drainage (which occurred in one patient) and myoglobinuria, resulting in acute tubular necrosis.

Published data do not support the use of cryosurgery in patients with resectable disease outside of a clinical trial.[234]

RADIOFREQUENCY ABLATION AND MICROWAVE COAGULATION

Just as tumors can be destroyed by cold, they can also be destroyed by heat. Techniques such as RFA and microwave coagulation (MC) have been used to destroy tumors. RFA involves placing within the tumor a small electrode, which is used to deliver energy to the tissue. The radiofrequency current generates ionic agitation, which is converted into frictional heat and results in breakdown of proteins and cellular membranes. The larger tumors can be destroyed by cryoablation. For RFA, tumors must be less than 4 or 5 cm in size. During the ablation, a hyperechoic area is formed around the tip of the needle, which corresponds to the area treated. It is sometimes difficult to evaluate whether all tumors have been treated. One of the advantages of RFA as opposed to cryoablation is that it can be performed percutaneously, because the probes are 10 mm in length. Solbiati and colleagues[235] treated 109 patients with colorectal metastases. He found a local control of 70%. Recurrence was significantly more frequent among patients with lesions larger than 3 cm. New metastases developed in 50% of patients, and survival rates were 67% and 33% at 2 and 3 years, respectively.[235] Bilchik and associates[236] proposed an algorithm for unresectable hepatic neoplasms, using cryosurgery for larger lesions and radiofrequency for tumors smaller than 3 cm, because local recurrences occurred in 38% of those receiving RFA and only in 17% of patients receiving cryosurgery. Among the most useful situations in which to use RFA is for patients with HCC who also have cirrhosis. Curley and coworkers[237] presented a series of 110 patients with cirrhosis who received RFA for HCC, with no recurrences occurring in 50%.

Cancer cells could be more sensitive than normal cells to heat due to the decreased vasodilation capacity of the neurovascular bed.[238] MC was initially developed for coagulation. When microwaves are applied to living tissue, they act mainly on the watery component. Using a probe to deliver 80-watt output for a 30-sec duration creates a column of coagulated area of 10 mm. In 19 patients with HCC, 28 of 31 nodules underwent complete tumor ablation. Ten of the 19 patients are still free of disease (follow-up, 14–64 months). Advocates of this therapy suggest that MC does not have inhomogeneous distribution within the tumor as seen with percutaneous ethanol injection therapy (PEIT).[239] MC is useful only in very small tumors (<3 cm). Both

modalities (MC and PEIT) might be more useful if combined with embolization. Lesions near hilar structures are not good candidates for MC, but lesions adjacent to hepatic veins can be treated.

A Italian study on 423 patients treated with RFA reported 3- and 5-year survivals of 47% and 24%, respectively,[240] which is similar to surgical series. In a series of 25 patients where resection was not performed because the lesion was close to a major vessel, the 3-year survival with RFA alone was 52%.[241] Elias and colleagues used RFA instead of repeat resections for the treatment of recurrence after liver resection in 47 patients. They found that this increased the percentage of local cures and decreased the need for resection.[242] Livraghi and associates evaluated the role of RFA in 88 patients who were waiting for resection. Fifty-three patients had complete tumor ablation by RFA, and 16 (30%) remained tumor-free. Among these 53 patients with complete ablation, 98% were spared surgical resection—44% because they remained tumor-free and 56% because they developed additional metastases. Lesions in 35 patients (40%) demonstrated local tumor recurrence, and 15 developed unresectable disease.[243]

In the Cleveland Clinic 135 patients received RFA because they were not good candidates for surgical resection, and the median overall survival was 28.9 months. Predictors of survival included size of the lesion and baseline CEA values. There was a median survival of 38, 34, and 21 months for lesions smaller than 3 cm, 3 to 5 cm, and larger than 5 cm, respectively ($P = 0.03$). Median survivals of 34 and 16 months were seen with CEAs of less than 200 ng/mL versus greater than 200 ng/mL, respectively ($P = 0.01$). In the Cox proportional hazards model, only the size of the largest lesion (>5 cm) was found to be a significant predictor of survival.[244] Other studies have reported size as an important predictor of recurrence.[245]

At M.D. Anderson Cancer Center 348 patients with liver metastases from CRC were treated for cure: 190 had resection only, 101 had RFA and resection, and 57 had RFA alone. Recurrences were lowest with resection: 52% versus 64% for RFA and resection, and 84% for the RFA alone. Liver-only recurrence after RFA was 44%. Four-year survival was 65% for resection, 36% for resection and RFA, and 22% for RFA alone.[91] A multivariate analysis of these patients found the type of procedure (i.e., resection, RFA and resection, or RFA alone) influenced survival, with the RFA-alone group having the lowest survival. Of course, RFA was usually a component of therapy when resection was not possible, especially in cases where the anatomic distribution of tumors made complete resection impossible. Therefore, this is not a true comparison of RFA versus resection. However, 3-year survival for patients with one metastasis treated by resection or RFA was 80% versus 40%, respectively, suggesting RFA cannot replace resection.

The combination of RFA and HAI may be useful. In an M.D. Anderson study on 50 patients, 32% remained tumor-free at a 20-month median follow-up. Recurrence at the site of RFA was seen in 10% and new liver metastases in 30%.[246] Kainuma and coworkers treated nine patients with bilobar disease with RFA and regional chemotherapy with 5-FU, doxorubicin, and cisplatin.[247] The local recurrence rate was 55%, and 2-year survival was 39%. Martin and colleagues treated 21 patients with RFA and HAI FUDR. With a median followup time of 24 months, the median survival is 30 months.[248]

RFA has been used in other tumor types. In a Chinese series on 240 patients with HCC and 44 patients with liver metastases treated with RFA, patients with liver metastases had a higher extrahepatic recurrence ($P = 0.019$) and shorter DFS ($P = 0.007$). Patients with multiple liver metastases had a higher local and extrahepatic recurrence[249] in neuroendocrine tumors. RFA can relieve symptoms in 95% of patients.[250,251] Livraghi and associates reported on 24 breast cancer patients whose liver lesions were treated with RFA, and 10 patients are still alive and free of disease with a median follow-up time of 10 months.[252]

Toxicity from RFA is clearly outlined in a series on 312 patients that included liver abscesses (7), portal vein thrombosis (3), pleural effusion (5), colon perforation (1), and renal insufficiency (1).[253]

In conclusion, RFA may have a role during surgical resection when one side of the liver is resected and small disease exists on the other side that cannot be resected. In patients who have undergone a resection and develop a small recurrence, percutaneous or laparoscopic RFA can be used if the lesion can be reached easily and is not close to large vessels. The presence of blood vessels near the tumors causes conduction of thermal energy away from the tumor and spares killing the tumor near the blood vessel.[254] Whether these techniques are more useful than chemotherapy, or should be used in combination with chemotherapy, are not known; the EORTC are exploring the use of RFA and chemotherapy versus chemotherapy alone.

PERCUTANEOUS ETHANOL INJECTION

PEIT was first performed in 1983 in Japan. Ultrasound guidance is used to place up to 30 mL of absolute ethanol into the lesion.[255] In patients with primary hepatoma, this treatment produced 5-year survivals of 43% for small lesions. Suzuki and coworkers[256] assigned 42 patients with HCC less than 3 cm to three groups—(1) chemolipiodolization, (2) chemolipiodolization followed by gelatin sponge transcatheter embolization (TAE) or (3) PEIT—and demonstrated a decrease in local recurrence with PEIT. Local recurrences at 1 year were 61%, 29%, and 20% for groups 1, 2, and 3, respectively. Shiina and colleagues[257] reported a 10-year survival of 66% using PEIT on single hepatocellular lesions smaller than 2 cm. In pooled data on 11,000 patients with HCC from Japan, 3-year survival for surgical resection, PEIT, or embolization was 58%, 53%, and 20%, respectively. Other researchers, however, report a higher recurrence rate after PEIT as compared with surgical resection. The size of the lesion also affects outcome. In an Italian study on 26 patients with metastatic disease, 13 of 15 patients with lesions smaller than 2 cm had responses, whereas among the 6 patients with lesions larger than 4 cm, no response was seen.[257] Yamamoto and associates[258] randomized 100 patients to TAE versus TAE + PEIT. The 3-year survival was 20% for the TAE group and 50% for the TAE + PEIT group, respectively ($P = 0.05$). This technique was also useful for treating small neuroendocrine tumors, possibly because they are highly hypervascular. At present, the technique needs further study to determine where it fits into the therapeutic armamentarium and whether it will increase survival for patients with metastatic liver tumors. Pending further study, it seems that PEIT and cryosurgery could be applicable to patients with small metastatic lesions who cannot undergo surgical resection. Whether these techniques will be more beneficial than regional hepatic arterial therapy is not clear, because they only treat visible disease and do not deal with possible small metastases that are not visible.

ISOLATION PERFUSION

To administer high drug concentrations locally, the liver can be isolated by clamping the hepatic arteries, vena cava, and portal vein and then placing a catheter in the hepatic artery to perfuse the liver. A catheter in the retrohepatic vena cava drains the liver, and extracorporeal filters allow removal of chemotherapeutic agents and simplify the technique of isolated perfusion. With a double-balloon inferior vena cava catheter, doses as high as 5,000 mg/m^2 of 5-FU and 120 mg/m^2 of doxorubicin have been administered. An initial trial using 30 mg/m^2 of mitomycin C produced venoocclusive disease in four of the nine patients.[259] With the use of melphalan (L-PAM), toxicity was decreased, and with doses of 30 mg/kg, complete responses were seen in 2 of 9 patients.[260] Hyperthermic isolation perfusion of tumor necrosis factor and melphalan is being investigated. Melphalan (1.5 mg/kg) and tumor necrosis factor (1 mg) over 60 min of hyperthermic infusion produced a 75% response rate.[261]

GENE THERAPY

Tumors largely restricted to the liver (primary or metastatic) can potentially be treated by gene therapy. The gene transfer agents can be injected locally or via the hepatic artery. One trial involves the use of an adenovirus vector carrying the wild-type *p53* gene. Alteration in p53 function is present in more than half of all malignancies, and reexpression of wild-type p53 can result in apoptosis and in tumor shrinkage in rodents. A phase I study of recombinant adenovirus encoding wild-type p53 administered via the hepatic artery produced no responses in 19 patients.[262] Transgene expression in tumor tissue was seen in patients receiving the highest dose levels. Other gene therapies involve the use of prodrug genes to convert innocuous drugs into active chemotherapeutic agents (cytosine deaminase converts 5-fluorocytosine to 5-FU).[263]

To deliver directed immunotherapy, Rubin and coworkers[264] injected *HLA-B7* gene on a liposomal vector into liver tumors. No responses were seen in 15 patients in the phase I study, but plasmid DNA was detected in 14 of 15 patients. Another concept being evaluated is to have cells express a gene such as thymidine kinase and then kill the cells by use of a ganciclovir, which is converted by thymidine kinase to an active metabolite.[263]

RADIATION THERAPY

In this section, the evolving role of radiation therapy for liver metastases will be reviewed. The first experience in using radiation therapy for liver metastases was with external-beam whole-liver radiotherapy (with and without systemic or regional chemotherapy), in which the doses that could be delivered safely were not high enough to eradicate metastases. More recently, technologic advances in radiation treatment planning allow high-dose radiation therapy to be delivered conformally around liver metastases safely, with the potential for eradication of disease and cure, in appropriately selected patients. Other types of radiation have also been used to treat liver metastases including brachytherapy and hepatic arterial delivery of ^{90}Y-tagged microspheres. Here, the experience following whole-liver irradiation, conformal radiation therapy, brachytherapy, and hepatic arterial ^{90}Y for treatment of liver metastases will be reviewed.

Whole-Liver Irradiation

The approach of using whole-liver irradiation for metastases is limited by the low tolerance of the whole liver to irradiation, with doses required to be less than 30 Gy over 3 weeks to avoid liver toxicity. Several clinical trials of whole-liver irradiation for liver metastases have established the safe whole-liver doses that can be delivered in a variety of fractionations.[265,266] The duration of response and survival rates tend to be short[267–269] (Table 59-26). In contrast, low-dose whole-liver irradiation can produce palliation of painful liver metastases in the majority of cases.[266,269,270]

In an attempt to improve on the poor outcomes following whole-liver irradiation alone, whole-liver irradiation has been combined with systemic or regional chemotherapy. The most widely used drugs in this effort have been the fluoropyrimidines because of their activity against CRC and their radiation-sensitizing properties.[271–273] The results of some of these trials are summarized in Table 59-27. In general, the response rates and survival rates following combined-modality therapy seem to be superior to those obtained following whole-liver irradiation alone. Selection bias may be at least partially responsible for this effect. A recent study demonstrated that whole-liver radiation (20 Gy in 10 fractions) does not improve the efficacy of 5-FU for patients who have diffuse liver metastases.[274]

Conformal Radiation Therapy

Technical advances in liver cancer imaging, radiation planning, methods to account for breathing motion during radiation delivery and image guidance at the time of radiation delivery (Figs. 59-13 and 59-14) have made it possible to deliver high-dose radiation safely to focal liver metastases, while sparing irradiation of the uninvolved liver, using a variety of radiation fractionation schedules.[275] In most studies, higher doses of radiation have been associated with more durable local control rates than lower doses, regardless of the fractionation schedule.[276–278]

Since the late 1980s at the University of Michigan, a series of phase I/II trials for patients with unresectable intrahepatic cancer have investigated dose-escalated conformal radiation therapy delivered concurrently with hepatic arterial chemotherapy (predominantly floxuridine [0.2 mg/kg/day]). In one of the first studies, the objective response rate of 22 patients with unresectable CRC liver metastases, treated with as much as 72.6 Gy at 1.5 Gy twice daily, was 50% (2 complete remission, 9 partial response, 11 stable disease),[279] with a median survival of 20 months. Similar results were obtained in subsequent studies,[280] including the most recent study in which the prescription dose was individualized based on the volume of liver irradiated and risk of toxicity, allowing higher doses (as much as

Table 59-26 Results of Treatment of Metastatic Cancer to the Liver Treated with Whole-Liver Irradiation Alone

Reference	Histology*	Dose (Gy/No. of Fractions)	No. of Patients	Response (% Total)	Median Survival (mo)	Hepatitis† Toxicity
Borgelt et al[266]	38% Colorectal	21–30/7–19	103	55‡	3	0
RTOG 76-05						
Leibel et al[269]	48% Colorectal	21/7 (± misonidazole)	187	80‡/7§	4	0
RTOG 80-03						
Phillips et al[267]	56% GI	≈20–37.5/8	36	72‡	ND	1
Prasad et al[268]	33% Colorectal	≈25/16	27	70‡	4	0
Russell et al[265]	60% Colorectal	27/15	53		4	0
RTOG 84-05		30/20	69	ND	4	0
		33/22	51		4	2

GI, gastroimestinal; ND, not determined.
*Predominant histology.
†Number of patients with ≥ grade 3 radiation hepatitis.
‡Subjective decrease in pain.
§Objective (CT scan).

Table 59-27 Results of Treatment of Metastatic Cancer to the Liver Treated with Whole-Liver Irradiation with Chemotherapy

Reference	Dose (Gy/Fractions)	Chemo	Route	No. of Patients	Response (% Total)	Median Survival (mo)	Hepatic* Toxicity
Ajlouni et al[309]	21–30/14–20	FUDR	IAH	10	30†	9	0
Byfield et al[310]	15–30/12‡	FUDR	IAH	28	ND	9	1
Friedman et al[311]	13.5–21/5–7	5-FU, Dox	IAH	22	48†	>3	1
Herbsman et al[312]	25–30/15	FUDR	IAH	13	70§	16	0
Lawrence et al[313]	33/22	FUDR	IAH	19	39†	7	0
	36/24			13	ND	ND	3
Lokich et al[314]	19.5–30/10–12	5-FU or FUDR	IAH	12	63§	ND	0
McCracken et al[206]	19.5/13	5-FU, Mito C	IAH	13	(adjuvant)	ND	1
Raju et al[315]	21/1.5	FUDR or FU	IAH or IV¶	12	83§	14	0
Rotman et al[316]	≈22.5–32.3/15	5-FU	IV	27	83§	6	0
Sherman et al[317]	15–30/7–10	5-FU or Pro ± HU ± Cy ± 5-FU	IV	50#	90§	4	0
Webber et al[318]	25/10	FUDR	IAH	25	72§	12	0
Wiley et al[319]	25.5/17	5-FU	IAH	19	37†	6	0
Volberding et al[320]	21/7	5-FU, Dox, MTX	IAH	27	33†	7	0

Cy, cyclophosphamide; Dox, doxorubicin; 5-FU, 5-fluorouracil; FUDR-fluorodeoxyuridine; HU, hydroxyurea; IAH, intra-arteria hepatic infusion; IV, intravenous infusion; Mito C, mitomycin C; MTX, methotrexate; ND, not determined; Pro, procarbazine.

*Number of patients with ≥ grade 3 radiation hepatitis.

†Objective response (CT or radionuclide scan documenting 50% decrease in bidimensional proudct).

‡Split-course therapy.

§Subjective response (e.g., decrease in pain).

¶FUDR (IAH) in four patients, 5-FU IV in eight patients.

#Includes 19 patients who received RT only.

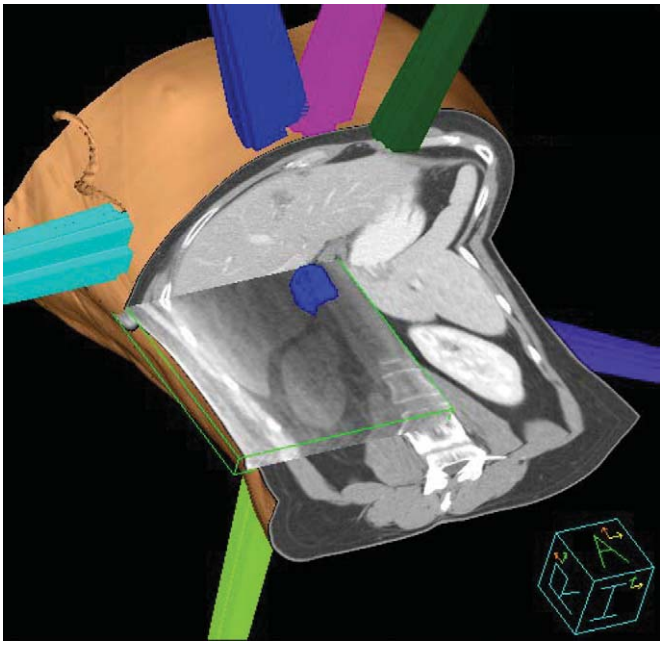


Figure 59-13 • Planning CT showing multiple liver metastases (in *blue*), treated with multiple radiation beams. Insert is a cutout of a verification CT obtained in the radiation treatment position immediately before therapy, registered to the planning CT scan.

90 Gy at 1.5 Gy twice daily) to be delivered safely to more patients. The median survival of 47 patients with liver metastases (median diameter ~10 cm) treated on this study was 17.2 months.[277]

Stereotactic body radiation therapy (SBRT), referring to a limited number of high-dose fractions delivered very conformally to targets, using biologic doses of radiation higher than those used in standard fractionation, has also been used to treat liver metastases.[278,281–287] Safety of 1- to 10-fraction SBRT has been described in several retrospective series and more recently confirmed in prospective dose escalation studies (Table 59-28). Blomgren and colleagues from Sweden first reported a response rate of 43% for 14 liver metastases treated with 20 to 45 Gy in one to four fractions,[262] with a prolonged time to maximal response (e.g., maximal response at 16 months for a 13-cm liver metastases). No liver toxicity was seen in patients with metastases, but hemorrhagic gastritis was seen in one patient. In an update in 1998, the local control rate was 95% with a mean survival of 17.8 months for 21 liver metastases.[288] SBRT (20 Gy × 2 or 15 Gy × 3) has also been used safely in patients with recurrent liver metastases following hepatic resection for CRC metastases, with no serious toxicity and local control 13 to 101 months following surgery.[289]

A prospective study of escalated single-fraction SBRT (14 Gy to 26 Gy) did not find a maximal tolerated dose in 60 liver tumors (56 metastases) with a median tumor size of 10 mL (1–132 mL) and found an actuarial local control rate of 81% at 18 months following SBRT.[281,290] SBRT delivered in three fractions (37.5 Gy total) has also been reported to be safe in small liver metastases, with 2-year local control and survival rates of 61% and 41%, respectively.[282,291] A North American prospective study confirmed the safety of three-fraction SBRT in 18 patients with 25 tumors of maximal diameter 6 cm.[278] A Canadian prospective study has shown the feasibility of delivering six-fraction SBRT using an individualized dose allocation approach as first described by the Michigan group, for liver cancers ranging from 3 to 3,000 mL.[292]

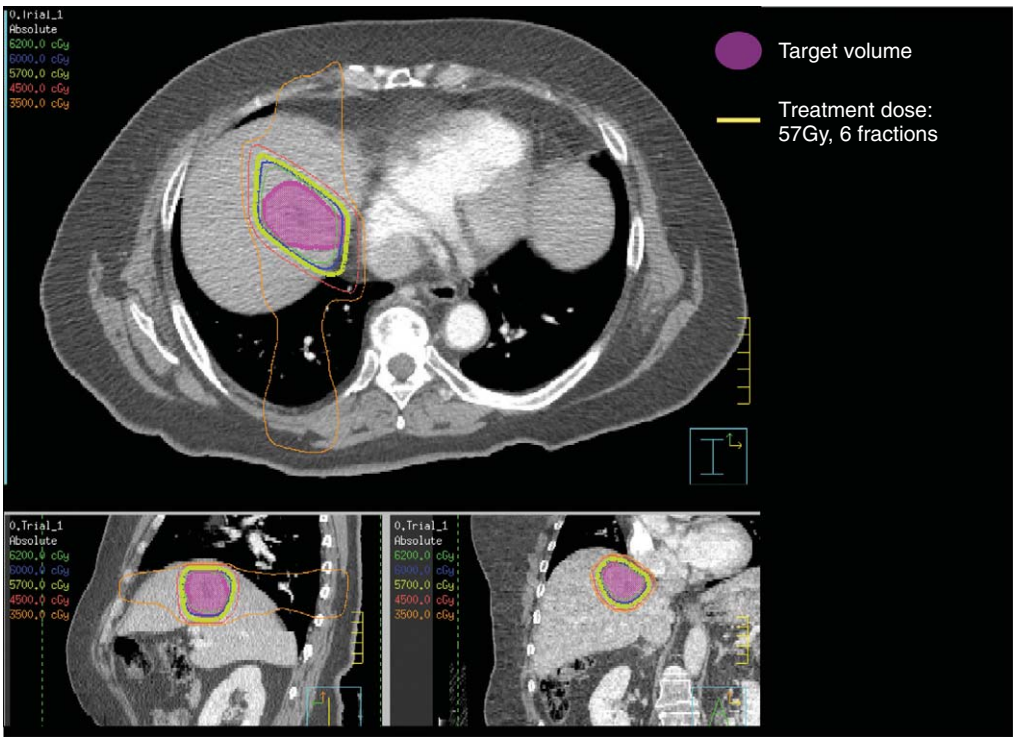


Figure 59-14 • Conformal radiation dose distribution, with the treatment isodose 57 Gy in six fractions, conforming to the target volume (*pink*).

More recently, outcomes following SBRT for 174 liver metastases from colorectal, pancreatic, breast, and lung cancer in 69 patients were reported.[285] The median dose delivered was 48 Gy (range 30–55 Gy) at 2 to 6 Gy per fraction. The local control was 76% and 57% at 10 and 20 months, respectively, with an overall medial survival of 14.5 months. No grade 3 toxicity was reported. Based on this experience, 10-fraction SBRT is being studied in a Radiation Therapy Oncology Group study that is now open.

Brachytherapy

High-dose radiation can also be delivered to focal liver metastases, with maximal sparing of dose to uninvolved liver, using interstitial brachytherapy, in which radiation is delivered from radioactive sources placed within or near the tumor.[293–297] High-dose-rate iridium-192 afterloaded to applicators placed at the time of laparotomy was used to deliver 20 to 30 Gy in 2 to 13 settings, with an actuarial local control rate of 26% at 26 months and two complete responses seen in lesions subsequently biopsied.[296] Iodine-125 seed implants, which deliver low-dose-rate irradiation (less than ~0.15 Gy/hr) over several months also have been used to treat liver metastases, with 10 of 11 tumors controlled at 1 year.[295] More recently, CT-guided placement of iridium-192 for liver metastases has been shown to be feasible in a phase II study[294] of 20 patients with liver cancers (19 metastases, 1 cholangiocarcinoma) unsuitable for thermal ablation. The mean tumor diameter was 7.7 cm (5.5–10.8 cm) for peripheral lesions and 3.6 cm (2.2–4.9 cm) for hilar cancers. The dose delivered ranged from 12 to 25 Gy. Two serious complications were observed. One patient had an intrahepatic hemorrhage on removal of the brachytherapy sources. Another patient developed obstructive jaundice 14 days after brachytherapy and subsequent elevated bilirubin and liver failure 9 months later, perhaps associated

Table 59-28 Selected Results of Liver Metastases Treated with Conformal or Stereotactic Radiation Therapy

Reference	No. of Patients	Tumor Type		Dose, No. of Fractions	Local Control		Survival	
		Mets	Other		%	Time	%	Time
Ben-Josef et al[277]	47	47+		<90 Gy, <60	95			17. 2 mo median
Blomgren et al[281]	23	14	9	20–45 Gy, 1–4	NR			NR
Herfarth et al[290]	37	60		15–26 Gy, 1	81	18 mo		
Wulf et al[291]	23	23		30 Gy, 3	61	24 mo	41	24 mo
Schefter et al[278]	18	25	1	36–60 Gy, 3	NR			NR
Mendez Romero et al[286]	25	34	11	37.5 Gy, 3	82	24 mo	50	24 mo
Katz et al[285]	69	174		30–55 Gy, 5–15	57	20 mo	37	20 mo

NR, not reported.

with biliary injury from high-dose radiation. Mild increases in liver enzymes and bilirubin without clinical symptoms were common. The 1-year tumor control rates were 40% and 71% for the large peripheral and small hilar lesions, respectively, with an overall 1-year survival rate of 83%.[294] Interstitial brachytherapy is a highly specialized method of delivering very conformal radiation for liver metastases, only available at a few centers worldwide.

Hepatic Arterial Radioisotopes

Another method of delivering high-dose radiation to liver metastases is by infusing radiolabeled glass or resin microspheres into the hepatic artery (sometimes referred to as selective internal radiation therapy). Although a variety of radioisotopes have been investigated in this setting, the available commercial products for liver cancer use ^{90}Y. ^{90}Y is a pure β-emitter with a half-life of 64.5 hr and an average electron range of approximately 2.5 cm and an effective pathlength of 5.3 mm (meaning that 90% of the energy is deposited within a 5.3-mm radius of the microsphere). ^{90}Y is incorporated into stable glass microspheres (TheraSphere, MDS Nordion Inc., Ottawa, Canada) or resin-based microspheres (SIRTex Medical, Inc., Lane Cove, New South Wales, Australia) which are infused into the hepatic artery as a form of regional therapy for well-vascularized liver tumors.[298–304] A typical prescribed dose is 120 to 150 Gy, where the microspheres are primarily deposited at the periphery of the metastases.[305] A reduction in CEA and radiographic responses are common following hepatic arterial ^{90}Y microspheres for liver metastases. Hepatic arterial ^{90}Y microspheres have been combined safely with regional 5-FU.[300]

A randomized trial comparing the combination of hepatic arterial ^{90}Y microspheres and hepatic arterial floxuridine to hepatic arterial floxuridine alone was conducted in 74 patients with unresectable liver confined colorectal metastases who underwent implantation of an HAI pump and chronic floxuridine in 12-day cycles at 4-week intervals. The patients were randomized to receive a single dose of ^{90}Y microspheres through the hepatic artery within 4 weeks of surgery versus no other therapy. The overall response rate and median time to progression were increased in the group receiving ^{90}Y microspheres (44% vs. 18% [$P < 0.01$] and 16 months vs. 10 months [$P < 0.001$], respectively), with a trend toward an improvement in overall sur-vival (17% vs. 7% 3-year survival).[299] This randomized trial demonstrated that irradiation of metastases improves outcomes over hepatic arterial chemotherapy alone. However, the response rate for hepatic arterial floxuridine in this study was substantially less than typically reported (see earlier in this chapter), and confirmatory studies are warranted.

Challenges associated with hepatic arterial delivery of ^{90}Y include the lack of understanding of dosimetry, the requirement for specialized interventional radiology expertise, and the potential for a radiation hazard associated with lost radioisotopes.

Liver Tolerance to Irradiation

In the early 1960s it was found that doses greater than 30 Gy at 2 Gy per fraction to the whole liver led to an unacceptable risk of liver toxicity. Eight fractions of 2.25 Gy to the whole liver was found to be safe, but a small increase in fraction size to 3.5 Gy was reported in 1973 to be associated with an unacceptable rate of liver toxicity (8 of 25 patients).[306,307] The tolerance of the liver to whole-organ irradiation does not seem to be substantially altered by the concomitant use of fluoropyrimidines. In contrast, whole-liver irradiation in combination with alkylating agents or mitomycin C is associated with an increased risk of liver toxicity.[308–310] Liver toxicity following irradiation has historically been referred to as "radiation hepatitis" and more recently termed "radiation-induced liver disease" (RILD),[308] because there is no evidence of hepatitis on pathologic examination.This complication is a clinical syndrome consisting of anicteric ascites and painful hepatomegaly, occurring in the absence of disease progression, usually within 3 months following a course of radiation therapy. Laboratory evaluation demonstrates a marked elevation of alkaline phosphatase out of proportion to the modest increases in the transaminases. Although the majority of patients recover from RILD, it may progress to liver failure and death.[308] The pathophysiology of RILD is not well understood. Pathologically, venoocclusive disease, similar to that seen following bone marrow translation, is seen.

Partial liver radiation therapy was first reported in 1965 by Ingold and associates, who safely delivered as much as 55 Gy to parts of the liver.[311] Others confirmed that high-dose radiation therapy could be delivered safely, as long as a substantial portion of the normal liver was spared. Conformal radiation planning permits portions of the liver to be treated with doses of radiation far higher than what the entire liver can tolerate so long as a sufficient volume of uninvolved liver can be spared from irradiation, similar to how a surgeon can resect a substantial fraction of the liver if the remaining liver is functional. Conformal radiation treatment planning allows the fraction of uninvolved liver irradiated to be quantified. Theoretical models have been proposed to estimate the volume dependence of normal tissue tolerance—referred to as normal tissue complication probability (NTCP) models.[312–315] Such an NTCP model has been used to describe the partial liver tolerance of 203 patients treated with conformal hyperfractionated radiation therapy and hepatic arterial floxuridine (17 of whom developed RILD). This analysis found that that mean liver dose can provide an estimate of the risk of RILD occurring, with a 5% risk of toxicity following 32 Gy and 37 Gy in 1.5 Gy twice daily for patients with primary liver cancer and metastases, respectively.[316]

The partial volume tolerance of the liver to hypofractionation or SBRT has not been well established, partially in that the majority of clinical SBRT experience has not required large liver volumes to be irradiated. Guidelines used in SBRT planning include sparing of 30% and 50% of the liver from 12 Gy and 7 Gy, respectively, for three- and one-fraction SBRT),[283] and ensuring that at least 700 mL of uninvolved liver receives less than 15 Gy in three fractions.[278] Dawson and coworkers have shown the feasibility of using an NTCP model for allocation of six-fraction SBRT in over 80 patients,[292] with a wide range of liver volumes irradiated.

The safe delivery of high-dose ^{90}Y to small volumes seems consistent with the partial volume estimates from conformal radiation and SBRT series, where the upper limit on the dose of radiation that can be delivered to an effective liver volume irradiated of 20% or less has not been established. The lack of a validated dose distribution in ^{90}Y treatment makes partial liver tolerance analysis challenging for ^{90}Y therapy.

Extrapolation of NTCP models and partial liver tolerances to different centers must be done with caution, because the results may not be valid for different patient populations treated with different treatments. The partial liver tolerance to irradiation, especially in diseased livers and following SBRT and ^{90}Y, should be measured and validated in prospective studies.

FUTURE DIRECTIONS

Although it is becoming established that radiation therapy, delivered using conformal radiotherapy, SBRT, brachytherapy, or ^{90}Y microspheres, can be used safely to treat liver metastases with the potential for sustained local control, recurrences outside the irradiated volume are not infrequent, providing a rationale for combining radiation therapy with other therapies. One possibility would be to combine radiation therapy with repeated cycles of modern hepatic arterial and systemic chemotherapy. More potent radiation tumor sensitizers could also be explored. Studies of targeted therapies combined with radiotherapy should be considered, given the radiation sensitization properties of many targeted agents and survival gains observed following the combination of radiation and targeted agents in other clinical sites.[317] Conversely, normal-tissue radiation protectors, as well as more technologic advances, may allow higher doses to be delivered

to more tumors safely. For instance, the free-radical scavenger amifostine protects the normal liver (but not tumor) from radiation in preclinical studies.[318] It is hoped that these approaches will permit a greater fraction of patients to benefit from high-dose therapy and will increase local control in patients with localized unresectable intrahepatic cancers.

CONCLUSIONS

Liver metastases, especially from colorectal primaries, are treatable and potentially curable. Imaging techniques such as CT, MRI, and sonography have advanced in recent years and have led to increased sensitivity and specificity in the diagnosis of liver metastases. When properly applied, the techniques are nearly as sensitive as surgical exploration in the detection of hepatic lesions and in differentiating benign from malignant processes.

Liver surgery has improved greatly in the past two decades. Dissections along nonanatomic lines have permitted the resection of multiple lesions that might previously have been considered unresectable. The new technique of vascular exclusion might improve the safety of major hepatic resections. Resection of solitary hepatic metastases or up to two to four metastases from CRC should be regarded as the best treatment for this condition.

Noninvasive approaches to liver metastases such as cryosurgery, chemoembolization, radiofrequency ablation, or alcohol injections are available. The usefulness of these techniques compared with surgery or regional therapy is being investigated.

For focal liver metastases unsuitable for or refractory to surgery or other ablative approaches, external-beam conformal radiation therapy, SBRT, or brachytherapy may be used to attempt to locally control disease. Hepatic arterial ^{90}Y-irradiation can be used safely to treat patients with diffuse metastases, with normal bilirubin levels. The optimal timing of radiation and chemotherapy has not been established, and there is rationale for investigating the combination of simultaneous regional or systemic therapies with radiation therapy in future studies.

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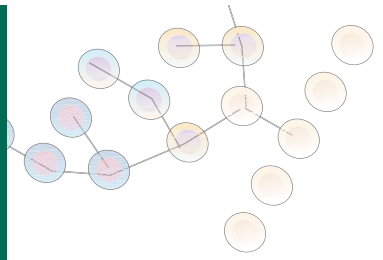
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60 Effusions

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SUMMARY OF KEY POINTS

Malignant Pleural Effusion

Background
- Common complication of cancer
- Frequently seen with breast and lung cancers and lymphoma
- Often asymptomatic

Incidence
- Presenting sign of malignancy in about one-half of patients who develop an effusion
- Approximately 40 cases of malignant pleural effusion diagnosed for every 10,000 hospital admissions

Diagnosis
- Exudative effusions (high protein, lactate dehydrogenase, or cholesterol) are very concerning for malignancy.
- Cytology is the gold standard.
- If an exudative effusion exists but is undiagnosed by other means, video-assisted thorascopic surgery (VATS) should be used for evaluation of the pleura.

Evaluation
- Cytology should be evaluated by an experienced pathologist.
- Low pH (<7.3) is associated with burden of disease, less likelihood of response to pleurodesis, and decreased survival.

Treatment
- Asymptomatic effusions can be monitored.
- Systemic chemotherapy can be effective in stable patients.
- For patients symptomatic from their effusions, effective options include systemic therapy for patients with very responsive disease (e.g., hematologic malignancies, germ cell tumors, breast cancer, small cell lung cancer) or repeated thoracentesis.

For patients requiring frequent thoracentesis or who rapidly redevelop effusions, options include the following:
- Pleurodesis with talc (favored), doxycycline, or bleomycin
- Pleurodesis with placement of a drainage catheter only
- VATS with mechanical abrasion
- Open surgical procedure in highly selected patients

For patients refractory to pleurodesis, options include Denver-type drainage catheter or clinical trial

Malignant Pericardial Effusion

Background
- Less common complication of cancer than pleural effusion or ascites
- Frequently seen with breast and lung cancers and lymphoma
- Size of effusion not correlated with symptoms; rather, acuity of collection and compliance of pericardium most associated with tamponade physiology
- Often a preterminal event

Incidence
- It is found in 2% to 30% of patients with cancer at autopsy.
- Only about 10% to 20% of patients with pericardial metastases develop tamponade.

Diagnosis
- Cytology is the gold standard but not very sensitive.
- Consider malignancy, comorbidities, and side effects of treatment (e.g., mediastinal radiation) in the differential diagnosis of a pericardial effusion in a cancer patient.

Evaluation
- Cytology should be evaluated by an experienced pathologist.
- Pericardial biopsy could be required if cytology is negative.
- Patients should be evaluated for clinical signs of cardiac tamponade (hypotension, signs of low cardiac output, abnormal pulsus paradoxus).
- Electrocardiogram should be evaluated for low voltages and electrical alternans.
- Echocardiogram should be obtained for all patients.

Treatment
- Asymptomatic effusions can be monitored.
- Systemic chemotherapy might be effective for stable patients, even those with solid tumors.
- Those with hypotension/clinical instability should proceed to emergent pericardiocentesis and placement of pericardial drainage catheters.
- Stable patients requiring drainage should undergo subxiphoid pericardiostomy.
- Open procedures or pericardial sclerosis should be saved for refractory patients.

Malignant Ascites

Background
- Common complication of cancer
- Frequently seen with ovarian cancer (most common cause), gastrointestinal malignancies, and carcinoma of unknown primary
- Rarely life-threatening

Incidence
- Accounts for approximately 10% of all patients with ascites
- Often (about 50% of the time) can be a presenting feature of malignancy

Diagnosis
- Ascites with low serum-to-ascites-albumin gradient is concerning for malignancy rather than portal hypertension.
- Cytology is the gold standard.

Evaluation
- Cytology should be evaluated by an experienced pathologist.
- Patient should be assessed for symptoms and probable response to systemic chemotherapy.

Treatment
- Asymptomatic ascites can be monitored.
- For patients symptomatic from their ascites, effective options include:
  Diuresis with spironolactone/furosemide
  Repeated paracentesis as needed
- Patients with moderate long-term survival can be considered for either percutaneous tunneled drainage catheter or peritoneovenous shunt.

MALIGNANT PLEURAL EFFUSIONS

A malignant pleural effusion is a common complication of cancer and is encountered frequently by oncologists and other physicians caring for such patients. Their effects can range from causing no symptoms to being markedly symptomatic. Treatments must be tailored appropriately (Fig. 60-1).

Collections of pleural fluid are likely to be directly related to tumor involvement of the pleura. For the patient with cancer, diagnostic accuracy in the assessment of pleural effusion is of the utmost importance. In many instances, the existence of a malignant pleural effusion drastically alters the treatment modalities that a patient will ultimately undergo; likewise, it drastically alters the likelihood of curing a patient with cancer. Nevertheless, many patients with cancer might have undergone surgery, have had radiation, or have other possible reasons for an effusion; there could therefore be alternative, benign reasons for an accumulation of pleural fluid. With this in mind, it is important to determine the appropriate cause of an effusion to provide optimal care.

Etiology and Pathogenesis

Pleural Space

The pleural space is a real space completely surrounding the lung up to the hilar root; the visceral pleura covers the lung and interlobar fissures, and the parietal pleura covers the chest wall, diaphragm, and mediastinum. The small amount of normal physiologic pleural fluid allows transmission of the breathing effort from the lung to the chest wall, thereby allowing respiration to occur. With the aid of a lavage technique in humans, each normal lung has been found to have approximately 0.13 mL pleural fluid/kg body mass (approximately 7 mL per lung).[1,2]

Under normal conditions the body is highly efficient in controlling the amount of pleural fluid present; a 10-fold increase in the production rate of fluid results in only a 15% increase in pleural fluid volume.[3] Malignant effusions are caused by both increased entry and decreased exit of fluid. Increased fluid entry seems to be the principal abnormality, because there are multiple pathways and channels of fluid resorption. Among patients whose effusion reaccumulates rapidly after drainage, it is likely that the patient has mainly an increased production of fluid. Exit blocks probably account for a small number of patients (5% to 10%) with a malignant effusion and most often appear as a transudate upon analysis.[4] In evaluating the cause of an effusion, it is helpful to classify effusions according to their mechanism (Table 60-1).

The molecular biology of pleural effusions has begun to be understood, with vascular endothelial growth factor (VEGF) emerging as a major role player.[5] Because it induces endothelial vasodilation and enhances the permeability of the mesothelium 50,000 times more potently than histamine, VEGF is thought to be a major, if not the most important, cytokine in the etiology of effusions.[6] It might one day be part of the diagnostic evaluation of effusions. Novel approaches that use anti-VEGF mechanisms will probably be evaluated once this is better understood.[7]

Incidence

More than a million pleural effusions occur each year, with about one-half arising from congestive heart failure (CHF). About one-fifth of effusions are malignant, but malignancy is the most common cause of symptomatic effusions. Under-reporting in most series might also be a significant issue. The causes of malignant pleural effusions are shown in Table 60-2 and reflect the incidence of cancers in general, with lung and breast cancers at the top of the list.[8–14]

Diagnosis and Evaluation of a Pleural Effusion

Pleural effusions are apparent on a chest radiograph when a volume of 200 mL or greater of fluid is present.[15] Oncologists' patients can be generally subdivided into those with clear advanced disease and probable malignant pleural effusion and those who have a history of malignancy but in whom the effusions may or may not be malignant. Among patients with advanced cancer, there is often no question as to whether the effusion is directly related to the malignancy, or the question is unimportant in terms of the patient's overall clinical management. In such a case, one can simply observe asymptomatic patients. For the patient in which an effusion could be malignant, however, accurate diagnosis becomes imperative for patient care and management, and one must consider all alternative causes in the etiology of the effusion. These include the possibility of other coexisting illnesses (e.g., CHF, infection), consequences of treating a prior malignancy (e.g., sequelae of prior surgery, radiation, or chemotherapy), and the possibility that the effusion is indeed malignant. Most locally advanced solid-tumor malignancies are considered incurable if the effusion is malignant, and treatments and goals of treatment will thus become dramatically different. In some cases, however, such as for childhood tumors (e.g., Ewing's sarcoma) or germ cell tumors, patients might remain curable but treatment plans can become radically different. Hematologic malignancies (e.g., lymphomas) might be upstaged, and this step might or might not affect

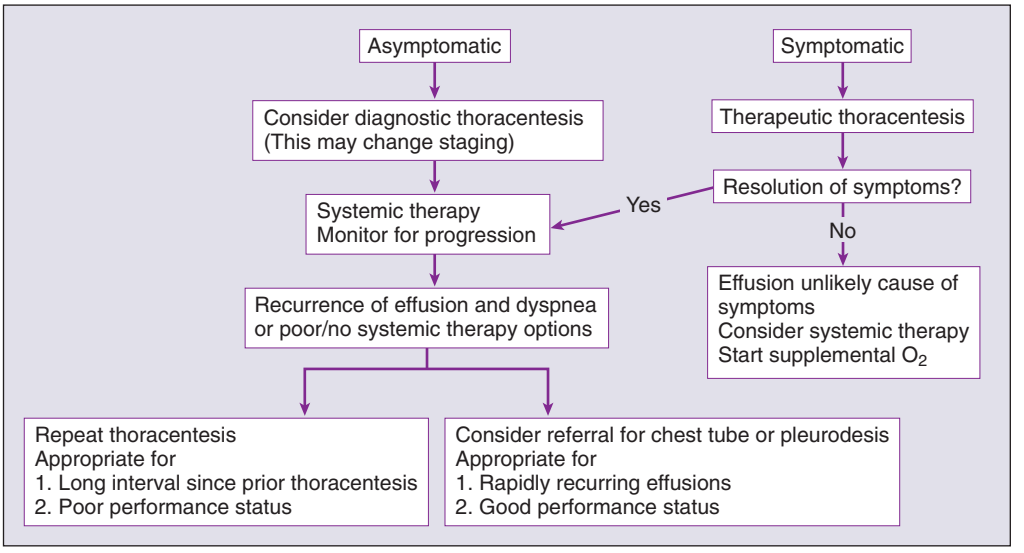


Figure 60-1 • Treatment approach to malignant pleural effusions.

Table 60-1 Differential Diagnosis of Pleural Effusion by Mechanism

INCREASED PERMEABILITY OF CAPILLARIES/LYMPHATICS
Malignancy
Metastatic malignancy
Intrathoracic malignancy (lung cancer)
Malignant mesothelioma
Infection
Bacterial, viral, fungal, mycobacterial, mycoplasmal, parasitic empyema
Pulmonary embolism
Connective tissue disorders
Drug induced (nitrofurantoin, procarbazine, amiodarone)
Esophageal rupture
Pancreatitis
Uremia
Postradiation
Collagen vascular disorders
Rheumatoid arthritis, systemic lupus erythematosus, Wegener's granulomatosis, polyarteritis nodosa, Churg-Strauss syndrome
Dressler's syndrome (postmyocardial infarction syndrome)
Subdiaphragmatic abscess
Systemic capillary leak syndrome/adult respiratory distress syndrome
Vascular trauma
Postsurgical (including thoracic and abdominal surgeries)
Sarcoid
Yellow-nail syndrome
Myxedema
INCREASED VENOUS HYDROSTATIC PRESSURE
Congestive heart failure
Superior vena cava syndrome
Massive pulmonary embolism
INCREASED LYMPHATIC PRESSURE
Malignancy
Metastatic malignancy
Lymphoma
Sarcoidosis
Chylothorax
Post–lymph node irradiation
Meig's syndrome
Peritoneal dialysis
DECREASED ONCOTIC PRESSURE
Hypoalbuminemia (often from cancer cachexia)
Hypoproteinemia
Cirrhosis
Nephrotic syndrome
Glomerulonephritis
ALTERED INTRAPLEURAL DYNAMICS
Trapped lung (infection, malignancy)
Atelectasis

Table 60-2 Malignant Neoplasms Associated with Pleural Effusion

Cause	No.	Percent
Total malignant effusions	1283	100
Lung cancer	450	35
Breast cancer	256	20
Lymphomas and leukemia	256	20
Unknown primary (adenocarcinoma)	154	12
Unknown primary (all types)	95	7
Gastrointestinal tract	90	7
Reproductive tract	70	5
Genitourinary tract	66	5
All other*	39	3

*Includes causes of malignant effusion (each less than 1%): endocrine, head and neck cancer, mesothelioma, soft-tissue sarcoma, bone cancer, and myeloma.

the planned treatments. Lung cancer, the most common etiology of malignant effusions, can cause effusions both via direct involvement of pleura by tumor with increased fluid production and by decreased exit via lymphatic blockage. Patients with non-small-cell lung cancer and transudative effusions on multiple evaluations of their pleural fluid are, in fact, considered early stage and are usually treated with curative intent, as if the effusion were caused by lymphatic blockage and not direct involvement of the pleura. Those with exudative effusions are considered to have advanced disease, even if malignant cells cannot be found, and are treated in a palliative manner. Patients with small cell lung cancer with exudative effusions are considered to be "extensive stage" because the field cannot be covered in a single, tolerable radiation port; these patients are treated in a palliative manner with chemotherapy alone. Patients with other nonmalignant reasons for effusions (e.g., large amount of ascites and cirrhosis or CHF) may be observed, but the physician should have a low threshold for reevaluation should clinical conditions change (e.g., a new fever or new shortness of breath) or if the effusion fails to resolve with appropriate measures.[16]

History and Physical Examination

Patients with pleural effusions usually present with dyspnea, chest pain, cough, or orthopnea. Other symptoms, such as hemoptysis, fever, and dysphagia, might also occur but are less common. Physical examination usually demonstrates dullness to percussion, decreased or absent breath sounds, and absence of fremitus. As a result of atelectasis of the adjacent lung, one can often hear crackles at the superior borders of the effusion. Both sides should be listened to equally to determine whether the effusion is unilateral or bilateral. Bilateral, symmetric effusions might be more associated with volume overload states such as CHF, although this is a nonspecific finding. The examination should also be alert for signs of systemic infection or other clues about the etiology of the effusion.

Radiologic Evaluation

The use of a chest radiograph to evaluate a suspected pleural effusion is the most valuable and easiest tool. Lateral views should be obtained along with posterioanterior views, because the latter miss as much as 500 mL of fluid hidden behind the dome of the diaphragm. At least 75 mL of fluid is needed to obscure the posterior costophrenic angle; up to 175 mL of fluid is required to obscure the lateral costophrenic angle. If the effusion reaches the fourth rib, 1000 mL is present; as little as 10 mL can be seen on a decubitus film. In terms of sampling

for thoracentesis, a general rule of thumb is that an effusion that is thicker than 1 cm on a decubitus film is large enough for sampling by thoracentesis.[17] Computed tomography (CT) scanning is even more accurate in detecting small effusions, including as little as 2 mL of fluid. The volume of the fluid present can best be determined radiographically by using three-dimensional reconstruction.[18] Neither magnetic resonance imaging (MRI) nor CT scan can distinguish transudates from exudates accurately, although both can be helpful in evaluating the pleural contents for masses, nodules, and pleural-based thickening once the fluid is removed.[19] Ultrasound is useful in evaluating for the presence of an effusion and as a guide during thoracentesis. Ultrasound also may aid in distinguishing an exudate (echogenic) from a transudate (anechoic), although this finding is not definitive.[20]

Thoracentesis

Among patients with an effusion that requires evaluation, the radiograph should be evaluated to determine whether the effusion is loculated. If the effusion is not free-flowing on the decubitus film and is therefore loculated or if the volume is insufficient to attempt a safe, unguided thoracentesis, ultrasound guidance should be used.[21,22] When obtaining fluid, samples should be collected into tubes containing heparin to prevent clot formation; cloudy fluids should be centrifuged before the analysis described shortly.[23] Relative contraindications to thoracentesis include a skin infection at the site of needle insertion, an abnormal coagulation profile (prothrombin time or partial thromboplastin time >1.8 times normal, platelets <25,000/mm^3, or creatinine >6 mg/dL), or uneasiness of the operator in performing the procedure.[24] Mechanical ventilation does not seem to increase the risk of pneumothorax, but there could be a higher likelihood of developing a tension physiology if a pneumothorax does occur.[25] Complications of the procedure include pain, bleeding (hemothorax or hematoma), infection, splenic or hepatic laceration, seeding of the needle tract with tumor, or, most commonly, pneumothorax.[26] Studies show that in thoracenteses performed by trained physicians, pneumothoraxes occur approximately 10% of the time, with a much higher rate when performed by trainees.[16,25] Small pneumothoraxes can be observed in nonventilated patients, whereas larger ones might require chest tube decompression. Although chest radiograph is often obtained after thoracentesis, it is not required for patients who are clinically asymptomatic after the procedure (absence of cough, chest pain, shortness of breath, and a normal lung examination), who do not experience aspiration of air, and for whom only one needle pass was used during the procedure.[27] The use of a therapeutic thoracentesis is discussed shortly.

Evaluation of Fluid: Transudates and Exudates

Fluids are classified as either transudates or exudates. Transudates arise from a disturbance in the hydrostatic or colloid forces across a barrier and have low protein and cellular contents. By definition this is a noninflammatory process without pleural disease. A classic example of a transudative effusion is one due to CHF. Transudates may be thought of as volume overload states and are in general benign. Exudates, on the other hand, are formed by active secretion, inflammation, leakage, or permeability of a lymphovascular barrier and have a high cellular or protein content. They have a broader list of potential causes, can be more serious in their effects, and mandate a more thorough evaluation. In reality, most effusions that will be referred to an oncologist will be exudative in nature, because transudative effusions often present with a known systemic disease—for example, heart failure, cirrhosis, or nephrotic syndrome.

Dividing effusions into one of these two categories is conceptually useful in classifying patients with unknown effusions. In 1972 Richard Light published what has become the classic criteria for the biochemical classification of a pleural effusion and now is commonly known as Light's criteria.[28] According to this system, the values of lactate dehydrogenase (LDH) and protein are measured both in the pleural fluid and in serum, and the effusion is classified as an exudate if any one or more of the following three criteria are met:

1. Ratio of pleural protein to serum protein greater than 0.5
2. Pleural LDH greater than two-thirds of the upper limit of normal for the serum reference range
3. Ratio of pleural LDH to serum LDH greater than 0.6

Criterion number 2 reflects a modification from the original published manuscript to account for the wide variation in the normal range of LDH in various reference laboratories.[23,29] A recent reevaluation of Light's criteria comes from Keller, demonstrating that Light's criteria have an overall sensitivity for an exudate of near 100%, but a specificity of only approximately 80%.[30]

Cholesterol

The level of cholesterol is higher in exudative than transudative effusions for unclear reasons. Costa and colleagues were able to demonstrate that a cholesterol concentration greater than 45 mg/dL and an LDH greater than 200 IU/L in the pleural fluid alone identified exudates with a very high sensitivity (99%) and specificity (98%) without the requirement for a serum sample.[29] Using a pleural cholesterol to serum cholesterol ratio threshold of 0.3, Valdes and associates were able to provide fewer misclassifications than when applying Light's criteria.[31] In short, the level of cholesterol in pleural fluid seems useful in distinguishing exudates from transudates.

Optimal Testing

Light's criteria have stood the test of time and are the most widely regarded. A meta-analysis of eight studies including 1448 patients was unable to define an optimal diagnostic technique.[32] Based on these results, a 21st-century version of Light's criteria, modified only slightly from Light's original work by the addition of cholesterol as a marker, could be suggested as the best means of determining an exudate. According to these updated criteria, a patient can be said to have an exudate if any of the following criteria are met[32]:

- Pleural fluid protein greater than 2.9 g/dL
- Pleural fluid cholesterol greater than 45 mg/dL
- Ratio of pleural fluid LDH to serum LDH greater than 0.6

The aforementioned meta-analysis demonstrated no superior combination (paired or triplet) to any one of these single tests. In most cases, particularly in the presence of obvious, known cancer, one should not have to delve beyond these criteria in the initial evaluation of a pleural effusion.

Other Testing

There are other situations in which a specific test might not differentiate between an exudate and a transudate but still might be helpful in differential diagnosis. However, although these tests are useful, they are not 100% specific but merely provide the clinician with some general clues that must be evaluated further.

VISUAL EVALUATION. The first step in the evaluation of pleural fluid is visual observation as it is removed. Strawlike fluid is more likely to be benign and transudative in nature. Fluid containing puslike material is more likely to be infective in nature. Bloody fluid is related to causes such as pulmonary infarction, malignancy, or a postoperative state. In general these clues can be helpful, but no diagnosis can be made definitively.

pH. In a diagnostic thoracentesis, pleural fluid pH should always be measured. For proper analysis, pleural fluid should be collected into a single syringe and a sample then transferred to a smaller, heparinized syringe for analysis.[33]Analysis should be via a blood gas machine, not on litmus paper, because the latter is unreliable and not an acceptable alternative.[34] Normal pleural fluid pH ranges from 7.60 to 7.64.

In one study, 46 patients with a pleural fluid pH less than 7.30 all had an exudate and one of the following six diagnoses: malignancy, empyema, collagen vascular disease, tuberculosis, esophageal rupture, or hemothorax.[35] Furthermore, patients with known malignant effusions and a pH less than 7.30 have a worse prognosis, shorter mean survival, poorer response to tetracycline pleurodesis, and a high rate of finding malignant cells on initial fluid cytology.[36] It should be remembered that patients with a parapneumonic effusion with either a pH less than 7.3 or gross pus should be considered for chest tube placement for drainage. The reader is referred to other texts for the management of empyemas.

CELL COUNT AND CYTOLOGY. Cell counts are often obtained on pleural fluids but are rarely useful or diagnostic. Very high nucleated cell counts (>50,000 per milliliter) are associated with complicated parapneumonic effusions and empyema but rarely are diagnostic.[16] Because most cells are normally neutrophils or monocytes, a predominance of lymphocytes (>50%) should make one more seriously entertain the idea of a carcinomatous pleural effusion, and greater than 85% lymphocytes should make one entertain the diagnosis of lymphoma, sarcoidosis, chylothorax, rheumatoid pleurisy, or yellow nail syndrome.[16,37] An increase in pleural fluid eosinophilia (>10% of nucleated cells) might be associated with benign disease (hemo- or pneumothorax), but also can be associated with all types of malignancy.[38] The presence of mesothelial cells is not helpful in terms of diagnosis.[37,39]

Pleural fluid cytology is the simplest and most definitive method of diagnosing a malignant effusion. The sensitivity depends on the type of malignancy, extent of disease, and experience of the cytopathologist. Fluids should be concentrated first for optimal detection of malignancy.[40] In general, the sensitivity is on the order of 62% to 90% and, as the gold standard, pleural fluid cytology is virtually 100% specific in the hands of an expert cytopathologist.[41] If an effusion demonstrates carcinoma and breast cancer is a diagnostic possibility, the cytologic specimen can be stained for estrogen and progesterone receptors as a means of both diagnosis and selection of potential treatment. In short, the presence of an abnormal cell population should prompt a further workup for the aforementioned causes, including malignancy.

Other tests have been evaluated in numerous studies as a means to refine the diagnosis of pleural effusions. For example, an elevated adenosine deaminase concentration has a high association with tuberculosis.[42] Elevated lipids (triglycerides) can be associated with a chylothorax and obstruction of the thoracic duct by any number of means, including malignancies.[43] In clinical experience, this and other tests (e.g., creatine kinase, LDH isoenzyme analysis, β_2-microglobulin, albumin, ferritin, lysozyme, and others) are rarely used, are rarely associated with malignancy, and are therefore discussed elsewhere.[23] Other tests including tumor markers (carcinoembryonic antigen [CEA], CA 19-9) have also been evaluated for use in determining the etiology of effusions but have not been found to be sensitive or specific.

Evaluation of a Suspected Malignant Effusion

Although most malignant effusions occur among patients with known cancers, they can be the first indication of the presence of malignancy in as many as 30% of patients.[44] In some patients an effusion often can be the only site of a potential malignancy after a thorough evaluation. Once a patient has been diagnosed with an exudative effusion, a malignant cause must be high on the list of differential diagnoses. A thorough history and complete physical examination must be performed, with careful attention to any potential causes or risk factors of malignancy. Once this evaluation takes place, the physician must gather some definitive evidence to institute appropriate evaluation. Frequently, such evidence involves consultation between the patient's primary physician and either a pulmonologist or an oncologist. Many clues about the etiology of the effusion are obtained with the performance of further evaluations, such as chest radiographs, CT scans, or mammograms. Alternatively, cytologic evaluation of an exudative effusion can reveal the presence and type of malignancy directly.

It is important to keep in mind the most common malignancies that cause effusions. Not surprisingly, a majority of these are caused by lung cancer. Breast cancers and lymphomas also cause a significant number of these, with approximately one-third of all malignant pleural effusions being caused by other types of malignancies (see Table 60-2).[45] Appropriate evaluations should be performed as indicated (e.g., careful breast examination and mammogram in women with effusions; particular attention for lung cancer among patients with a history of smoking). It should be noted that there is a recently established entity, primary effusion lymphoma. This is found in patients positive for the human immunodeficiency virus; it is associated with human herpesvirus 8 infection and has a pathogenesis similar to Kaposi's sarcoma.[46] This syndrome also can include pericardial effusions and ascites. Patients with mesothelioma often have a history of asbestos exposure and show evidence of both effusion and pleural thickening on CT scan. These patients can be considered for CT-guided biopsy of the appropriate areas, which is often effective in making a diagnosis.[47] A small percentage will be diagnosed with carcinoma of unknown primary, whose management, usually via chemotherapy, is also discussed in Chapter 98. Even after an extensive evaluation, results can be nondiagnostic, and the patient must undergo further evaluation to determine the etiology of the effusion because no other cause has been identified although malignancy is still suspected. These further evaluations will now be discussed.

Closed Pleural Biopsy

These refer to blind, percutaneous biopsies of the parietal pleura using a special needle, such as a Cope's needle. Unfortunately, among patients with a cytology-negative malignant effusion, the yield of this procedure is only about 7%.[48] Novel approaches to this procedure, such as the use of brushings or a Tru-cut needle, might ultimately prove to be better diagnostically, but the procedure is currently rarely used in such situations because of its poor yield.[49,50]

Thoracoscopy

Video-assisted thoracoscopic surgery (VATS) is the most commonly used procedure for thoracoscopy in the United States and is usually performed by thoracic surgeons. This procedure, using several ports and trochars, requires general anesthesia with single-lung ventilation and many single-use disposable instruments.[51] Although VATS is well tolerated, it does have some risks and carries with it a significant expense, due to general anesthesia and the requirement for expensive instruments. On occasion, it requires conversion to an open procedure if there are significant adhesions or if there are undue risks noted with the insertion of a thoracoscope.[45] Single-lung ventilation is also required and might be difficult for patients with significant lung disease.

With these techniques, fewer than 10% of malignant pleural effusions go undiagnosed, and thus thoracoscopy of some sort has become part of the evaluation algorithm when necessary if other methods fail.[52] Interestingly, a recent technique uses a semi-rigid pleuroscope, which is similar to bronchoscopes currently in use by pulmonologists but easier to use. These can be used to drain and pleurodese effusions and might ultimately decrease the need for VATS in diagnosing potentially malignant effusions if comparison studies demonstrate its effectiveness.[53]

Treatment

For most malignancies, the existence of a malignant effusion places the patient into a noncurable, advanced staging category, but one

that is often treatable nonetheless. In light of this a palliative approach is often the mainstay of therapy, with several important exceptions that will be addressed in the discussion that follows. For patients with relatively small effusions that do not cause a high degree of dyspnea or impairment of functional status, consideration of systemic therapy of the malignancy, usually chemotherapy, is indicated. If, on the other hand, dyspnea is a primary concern, immediate management of the effusion is necessary. Unfortunately, for many patients with advanced disease, chemotherapy might not be able to provide rapid enough resolution of dyspnea or other symptoms, and thus one must use mechanical means of reducing the effusion. First and foremost, the clinician should consider the individual patient's situation, with particular attention to overall prognosis, prior therapies (if any), age, and performance status. The physician must also weigh the likelihood of progression of other systemic disease during the time required for resolution of an effusion. For patients with large effusions who are in the terminal stage of their disease, supplemental oxygen with hospice referral might be the only appropriate intervention.

Systemic Therapy in Specific Malignancies

Many advanced solid tumors do not respond well to chemotherapy, so primary management of the effusion is often required. There are notable exceptions. Small cell lung cancer is unlikely to be curable, but effusions from this cause respond well to chemotherapy.[54,55] Testicular and other germ cell neoplasms are not only responsive but also very curable, even at an advanced state, and thus early systemic treatment should be used if at all possible.[56] Even patients with advanced germ cell tumors have good responses and should be considered for aggressive systemic therapy. Breast cancer might respond well to hormonal therapy or chemotherapy, particularly among patients who have not received prior systemic therapy. Mesothelioma is a unique tumor that arises directly from pleural or peritoneal surfaces. Effusions are often associated with the tumor and are not included in the staging system. Patients amenable for aggressive local therapy, even with an effusion, should be considered for such therapy. Effusions from hematologic malignancies, such as lymphoma, are often highly responsive to systemic chemotherapy. Treatment of effusions related to hematologic malignancies are generally focused on treatment of the disease as a whole rather than treatment directed at the effusion directly. Because patients with solid-organ tumors and advanced disease have relatively poor responses to chemotherapy overall, early direct management of the effusion among patients with dyspnea should be considered at the outset for patients who are unlikely to achieve rapid responses to chemotherapy.

SYSTEMIC CHEMOTHERAPY AND EFFUSIONS. It should be remembered that the pharmacokinetics of drugs in the presence of effusions are poorly understood, because drug might accumulate in effusions and only slowly redistribute throughout the body. Methotrexate is a classic example of this phenomenon. Methotrexate is slowly released from all of the "third spaces," and those of large volumes (ascites, pleural effusions, or anasarca) might dramatically prolong the terminal half-life and lead to potential increased toxicity.[57] There are no direct guidelines for the use of methotrexate or other chemotherapies when large effusions exist, but the clinician should consider drainage of the effusion before the use of methotrexate, or the use of alternative therapies. Patients with pleural effusions receiving new chemotherapy agents should be monitored closely for treatment-induced toxicity.

Effusion-Targeted Therapy

THERAPEUTIC THORACENTESIS. Therapeutic thoracentesis might serve as the main or sole therapy for management of an effusion in many patients. Thoracentesis, unlike other procedures, might permit rapid relief of symptoms without need of hospitalization. If systemic disease is a significant concern, thoracentesis might allow for a window of opportunity in which to gain control over a patient's symptoms before systemic chemotherapy is given. Similarly, it might also allow for palliation of symptoms for those patients with far advanced disease.

Therapeutic thoracenteses are performed similarly to diagnostic procedures. Although a pneumothorax usually occurs when air leaks into the pleural space through the needle, it can also occur if the visceral pleura is lacerated with the needle. The latter complication may be avoided if a plastic catheter is threaded through the needle, directed inferiorly, and the needle is then removed; this procedure minimizes the chances that a pneumothorax will occur via perforation when the visceral and parietal surfaces become opposed after fluid removal. If a pneumothorax occurs the leak usually seals itself quickly, but closure can be hastened by having the patient lie on the affected side, which decreases the pressure gradient between the alveoli and the pleural space.[58] The volume of pleural fluid that can be removed safely is unknown. One study by Light and coworkers demonstrated that pleural fluid removal could be considered safe as long as pleural fluid pressure does not decrease below −20 cm H_2O.[28] Because most clinicians do not measure pleural pressure, current recommendations are that no more than 1.0 to 1.5 L of fluid be removed at any one time, and that amount only if there are no signs of any adverse events such as dyspnea, pleural pain, or cough, which are indications of the rapid restoration of a strong negative pleural pressure. Patients with contralateral mediastinal shift can have larger amounts of fluid removed safely, because these adverse events are unlikely to occur. Rapid reexpansion might bring on the phenomenon of reexpansion pulmonary edema, which is due to the rapid restoration of capillary permeability through unknown mechanisms; this can occur when air or fluid is removed from the pleural space.[58] Patients with ipsilateral mediastinal shift are unlikely to obtain significant relief from thoracentesis, because this condition indicates a large amount of either trapped lung or mainstem bronchial occlusion.[46]

There have been no randomized or comparison trials examining the use of repeated thoracentesis compared with the use of other procedures. It is also difficult to predict the length of time within which an effusion might recur; some patients have rapid recurrence (within days), whereas others might have recurrence over a period of weeks. Most oncologists and pulmonologists often make an initial attempt at a therapeutic thoracentesis to allow immediate symptomatic relief and time for systemic therapy to take effect, as well as to gauge the extent to which a pleural effusion causes dyspnea. For patients whose effusions recur rapidly, more invasive procedures might be required; those whose effusions recur more slowly might be managed solely with repeat thoracentesis.

RADIATION THERAPY. In general, radiation of the hemithorax, as a means of controlling an effusion, is contraindicated in most patients with malignant pleural effusions. This is because of the high incidence of radiation pneumonitis that is likely when a sufficient dose of radiation is given to large areas potentially involved with malignant effusions.[59] Certain situations, such as lymphatic obstruction from focal areas of lymphadenopathy (which may arise in lymphoma or in lung cancer), might benefit from radiation applied to these specific areas. Radiation doses are dependent on the nature of the malignancy.

CHEMICAL PLEURODESIS. Pleurodesis is intended to achieve a "symphysis between the parietal and visceral pleura, in order to prevent accumulation of either air (pneumothorax) or fluid (pleural effusion) in the pleural space,"[60] and malignant pleural effusions are the largest indications for pleurodesis.[60,61] The mechanism by which this symphysis occurs is poorly understood, but in general it depends on pleural irritation to cause a cycle of inflammation, activation of the pleural coagulation cascade, fibrin placement and fibroblast recruitment, and, finally, collagen deposition that ultimately results in the fusion of both pleural surfaces.[60,62,63] Nevertheless, the exact

mechanisms and factors that influence pleural sclerosis and effect pleurodesis are not well known and require further research. Many agents have been used in the past with various success rates reported; much of this information is based on personal and anecdotal experiences. These agents include, as a minimum list

- Talc
- Tetracycline
- Minocycline
- Doxycycline
- Quinacrine
- Mepacrine
- Bleomycin
- Mitomycin
- Thiotepa
- Nitrogen mustard
- 50% glucose and water
- Interferon-α
- Interferon-γ
- Iodopovidone
- Radioactive colloidal gold
- Autologous blood
- Fibrin glue
- Bacille Calmette-Guérin
- Silver nitrate
- Killed *Corynebacterium parvum*[60]

The exact mechanism by which these agents effect pleurodesis probably differs slightly from one agent to another, but all lead to a final common pathway that activates the pleural coagulation cascade and the appearance of a fibrin network that yields a symphysis between the two surfaces.[61–63] The various agents have different properties and methods of administration.

METHOD OF PLEURODESIS. It should be recalled that patients must demonstrate that symptoms (usually dyspnea) respond to drainage of the pleural fluid, because patients with malignancy often have numerous reasons for dyspnea—pulmonary metastases, anemia, pulmonary embolus, trapped lung, or poor gas exchange—and might be unlikely to benefit from a resolution of the effusion. Thus, it is important for patients to undergo a trial of therapeutic thoracentesis initially rather than proceed directly to chest tube drainage. At the time that pleurodesis is performed, the effusion must be drained. For successful sclerosis, there should be evidence of complete lung reexpansion after initial drainage. Traditionally one gauged the optimal time for sclerosis when there was minimal pleural fluid drainage (<150 mL per day), but this seems to be less relevant for success in sclerosis than does the confirmation of complete radiologic lung reexpansion.[64]

Traditionally chest tube drainage has been performed with a standard-size (24–32 Fr) chest tube. Tubes in this size range are associated with a great deal of pain and discomfort. More recent work has supported the use of smaller bore (8–16 Fr) catheters. A prospective, randomized study of 18 patients found improved comfort and no difference in success or complication rates when small-bore catheters were used.[65] Small-bore tube placement is an emerging standard of care.[66]

Sclerosing Agents

TETRACYCLINE/DOXYCYCLINE. Tetracycline was the most widely used sclerosing agent until it was discontinued by the manufacturer in 1992, although it might still be available in some countries.[67,68] Doxycycline has been recommended as a replacement, but there are no direct studies comparing the two agents. Historical comparisons demonstrate similar success rates with doxycycline compared with tetracycline, both on the order of 80% to 85%.[69,70] Most studies and investigators have used 500 mg of doxycycline mixed in 50 to 100 mL of sterile saline, and the primary complication is pain related to the doxycycline, requiring either narcotics or conscious sedation.[45,69,70]

TALC. Talc is currently the most widely used, the best studied, and probably the most controversial sclerosing agent. A major advantage of talc is the cost; the average wholesale price for the amount of talc typically used for pleurodesis procedures is less than $1.00. Sterilization of the talc raises the cost to between $5 and $20, dependent on the methods used, and it remains sterile for at least a year on pharmacy shelves.[71] The cost of talc is therefore significantly less than for any of the other agents used. Talc may be introduced via slurry (i.e., mixed with saline) in the chest tube used to drain the effusion, or insufflated (poudrage) with a bulb syringe or atomizer at the time of a thoracoscopic drainage procedure. (Thoracoscopy will be discussed shortly.)

In 1994 Kennedy and Sahn reviewed all the published series using talc as a pleurodesis agent and found a 91% success rate (659 of 723 patients) for pleurodesis, with success judged by various clinical and radiologic findings.[72] Doses of talc ranged widely, from 1 to 14 g per procedure. There was no difference between poudrage and slurry. Animal studies suggest that concomitant use of steroids can decrease the efficacy of talc pleurodesis, and a small study in humans demonstrated a small, not statistically significant decreased response to talc slurry when steroids were used.[73,74] Although these studies are not conclusive, steroids should be discontinued or the dose reduced as much as possible before pleurodesis procedures when talc or any pleurodesis agent is used.

Adverse effects from talc are variable. Pain ranging from nonexistent to severe is not uncommon; there is an overall reported incidence of 7%.[75] Fever, up to 102°F, occurs within the first 12 hours and can last up to 72 hours.[16,75] Empyema is an occasional complication, more often with talc slurry than with poudrage. Cardiovascular complications (e.g., arrhythmia, chest pain) have been noted, but it is difficult to assess whether these are a result of the talc pleurodesis procedure itself or the patients' comorbidities.[72,74]

Pulmonary complications constitute the largest and most significant group of complications associated with talc pleurodesis. Acute respiratory distress syndrome (ARDS), pneumonitis, and respiratory failure all have been reported after pleurodesis with talc.[75,76] The mechanisms by which talc might produce acute lung injury are unclear. One hypothesis is that the pneumonitis is related to the systemic absorption of talc; this is supported by the findings of Rinaldo and colleagues[77] and others who were able to demonstrate talc particles both in bronchoalveolar lavage fluid after talc pleurodesis and in virtually every organ at autopsy of one patient.[76–79] One of the most concerning studies comes from Rehse and associates,[80] who found that in a series of 78 patients, 33% developed respiratory complications or death after talc pleurodesis, and 9% developed ARDS rates that are significantly higher than those previously reported. Some investigators feel that the incidence of pulmonary complications is related to the dose of talc used for pleurodesis. Talc pleurodesis is still commonly used, however, and the relative merits of this in comparison to other methods are fiercely debated among experts and will be discussed later in this chapter.[78,81]

BLEOMYCIN. Bleomycin has been studied since the 1970s for its use as a sclerosing agent.[82,83] The recommended dose for intrapleural administation is 60 U or 1 U/kg body weight, and is often reduced to 40 U/kg in the elderly.[84] Administration and its side effects are similar to those with talc pleurodesis, with pleuritic pain, rigors, fever, and mild nausea as the main concerns.[84] Although it also is used commonly as a chemotherapeutic agent, only 40% is systemically absorbed from the pleural cavity, and bleomycin is not myelosuppressive when used in pleurodesis.[82] Several studies report mixed results for bleomycin compared with other agents. A large meta-analysis (1168 patients) from Walker-Renard and coworkers[85] demonstrated a 54% success rate with bleomycin versus a 67% success

rate with tetracycline and its derivatives (doxycycline, minocycline) and a 93% success rate with talc. Zimmer and colleagues,[86] in a subsequent prospective randomized trial, did not demonstrate a statistically significant difference in efficacy between talc (90% successful) and bleomycin (79% successful, $P = 0.388$). Patz and associates[84] directly compared bleomycin and doxycycline with a small-bore catheter and likewise did not find any statistically significant difference between the two agents. It is important to note that there are large cost differences between the different agents. In the aforementioned study by Zimmer and coworkers, the cost of the bleomycin was $955 per patient, compared with only $12 per patient for talc.[86]

PLEURODESIS WITHOUT THE USE OF AGENTS. Interestingly, two studies demonstrated that one could obtain relatively effective pleurodesis with thoracoscopy and chest tube placement for several days without instillation of a pleurodesis agent; these studies demonstrate a combined 62% success rate among 61 total patients.[87,88] Talc insufflation at the time of thoracoscopy does indeed increase the success rate to more than 90% of patients, however.[72] The fact that one can achieve decent pleurodesis and modest success rates without the use of any pleurodesis agent highlights our relatively poor understanding of the mechanism of pleurodesis and suggests that irritation of any sort can in fact lead to sclerosis and symphysis of the two pleural membranes. One potentially superior alternative to simple chest tube placement is to perform mechanical abrasion of the pleura. There are, however, no large series evaluating mechanical abrasion at the time of thoracoscopy for effectiveness, nor any comparing mechanical abrasion with any other techniques.[78,79] Mechanical abrasion can be performed with a thoracoscope (usually VATS) or via an open procedure. Pleural abrasion, in conjunction with bleb stapling, has been shown to be effective in preventing recurrent pneumothorax as a method of sclerosis in this nonmalignant entity.[89]

PREDICTING THE EFFECTIVENESS OF PLEURODESIS. It has been stated that low pleural fluid pH can identify patients who might experience a low likelihood of success with pleurodesis.[61] Low pH is thought to be a marker of increased metabolic activity of intrapleural tumor, and as such it represents a larger tumor burden.[36] Large tumor burdens might prevent apposition of the pleural membranes. Heffner and colleagues[90] reanalyzed individual patient data from both published and unpublished studies in 2000. Their analysis of 433 patients demonstrated that pleural fluid pH was the only independent predictor of pleurodesis failure, with an odds ratio of 4.46 when pleural fluid pH was lower than 7.28. A pH value of 7.15 or lower had a positive predictive value of 45.7% for pleurodesis failure. Although pH certainly helps predict pleurodesis failure, it is only of modest benefit in predicting outcome in individual patients, in that even those patients with a low pH in the analyzed studies had a greater than 50% success rate with pleurodesis. Because of these limitations, fluid pH should only be considered as an additional piece of information, not as a means to totally rule out pleurodesis.

Surgical Options Including Shunts

There are several surgical procedures—parietal pleurectomy, decortication, and pleuropneumonectomy—that may be attempted for management of a malignant pleural effusion. These procedures carry with them major morbidities, and they have proven to be no better than pleurodesis alone.[91] Surgical palliation might, however, be an option for some patients, particularly those who fail chemical pleurodesis, patients with loculated effusions, or those with large tumor rinds on the pleural surface. VATS permits direct visualization of the entire pleural surface, the potential for mechanical abrasion of the pleural surface, and removal of some adhesions and loculations. Talc poudrage via insufflation may be performed, and a pleuroperitoneal shunt may be inserted as well.[92] Surgical intervention should also be considered if lung reexpansion does not occur promptly after removal of an effusion via chest tube drainage; failure to reexpand suggests a rind of malignant tissue surrounding the lung, which may be further confirmed by a radiograph demonstrating a large effusion without mediastinal shift.[91] If such a cortex is seen at the time of VATS, it may be removed by conversion of the VATS to an open thoracotomy. This procedure might make pleurodesis and the restoration of a trapped lung possible. There is, however, a perioperative mortality of 12% associated with open procedures for decortication in these situations; therefore, this choice of procedure must be limited to an appropriate patient population.[91] Pleuroperitoneal shunts have a complication rate of approximately 12%, which is manifested mainly by shunt occlusion requiring replacement.[93] Peritoneal seeding of intrathoracic malignancy is a potential hazard but has not been definitively studied.[91]

Intrapleural Therapy

The rationale of intrapleural therapy is very appealing: Agents given directly into the pleural space can be directly toxic to tumor cells or are stimulants of the immune system that would ultimately be cytotoxic to tumor cells, thereby causing resolution of an associated malignant effusion. It should be noted that it is difficult to separate the cytotoxic effects of intrapleural therapy from pleural irritation to determine whether resolution of an effusion is due to cytotoxicity or pleurodesis. Bleomycin is a classic example of this phenomenon in that it is used as a sclerotic agent but also posseses antineoplastic activity. Intrapleural therapy, particularly chemotherapy, offers hope for patients who have a malignancy confined to the pleural space (e.g., mesothelioma) or for patients who have a higher disease burden in this location compared with other sites. A similar approach of locally directed chemotherapy has been used with particular success in the abdominal cavity, in cases of intraperitoneal chemotherapy for ovarian cancer.

Most agents that have been tried over the years have had limited success, and thus the idea of intrapleural therapy is still highly experimental. In terms of cytotoxic chemotherapy, many agents have been tried, including intrapleural 5-fluorouracil (5-FU), mitomycin, cisplatin, cytarabine, doxorubicin, and etoposide.[85] Shoji and associates[94] recently reported their phase II results using repeated intrapleural chemotherapy with an implantable access system (an infuse-a-port, similar to that used for subcutaneous venous access), placed by a VATS procedure. Patients received biweekly 5-FU and cisplatin. Such a system was used previously for the administration of interferon-γ in the treatment of malignant mesothelioma by Driesen and coworkers[95] and allows for repeated, easy administration of intrapleural drugs with minimal catheter-related toxicity. There was virtually no systemic toxicity, not even of the type that is usually associated with systemic therapy of these drugs, although the doses (5-FU 250 mg, cisplatin 10 mg) were far less than those typically used intravenously. Because of this observation, such a system warrants further testing as a method of both pleurodesis and treatment (neither of which was an endpoint in this dose-finding trial), particularly for tumors sensitive to agents that can be given intrapleurally.

As described in virtually all of these reports, the success rates with these cytotoxic agents are less than those seen with talc, doxycycline, and even intrapleural bleomycin. There is the potential for systemic absorption, and consequently potential associated systemic toxicity from such agents. The costs of antineoplastic agents are much higher than those for doxycycline and talc. Because talc is well studied, inexpensive, effective, and readily available, it would be difficult to find a superior agent for use solely in the treatment of effusions; for these reasons, intrapleural therapy still remains experimental excepting the use of agents that cause pleurodesis.

Long-Term Drainage Catheters

For some patients, effective pleurodesis will not be attainable. In others, the life expectancy could be too short to justify such invasive procedures or minor surgeries (such as VATS), but control of the effusion is still important. Therefore, other effective means for the

palliation of pleural effusions are necessary. This need ultimately led to the development of the Denver Pleurx system (Denver Biomaterials Inc., Golden, CO), the only tunneled catheter approved by the U.S. Food and Drug Administration (FDA) for pleural effusion management.[96]

The details of the Denver catheter are described in detail elsewhere, but it consists primarily of a 15.5 Fr silicone catheter with side holes and a polyester cuff that induces fibrosis along the tunnel; fibrosis decreases the risks of dislodgement, infection, and pericatheter leakage.[96] There is a proximal hub that prevents air entry or fluid egress, and it is capped when not in use. The catheter is usually placed into a free-flowing effusion or large locule under local anesthesia at the bedside. After initial drainage of no more than 1500 mL, drainage usually is performed every other day by the patient, family member, or a visiting nurse. The tube may be removed if three drainages in a row are scant and imaging shows no reaccumulation of fluid, suggesting spontaneous pleurodesis. The pivotal, approval trial for the FDA in 1999 compared the Denver catheter with doxycycline sclerotherapy.[97] Quality-of-life benefits were the same for the two groups, and there was a greater improvement in dyspnea with the Denver catheter; hospitalization was shorter in the catheter group (1 day vs. 6.5 days), and spontaneous pleurodesis developed in 46% of catheter placements, but effusions did recur 13% of the time. Sclerotherapy may be given through the catheter as well. Catheter complications occur about 15% to 20% of the time and include poor drainage requiring replacement, external catheter migration, tumor tracking along the catheter route, and infection (pleural fluid and skin). A recent report demonstrates symptomatic benefit (but not pleurodesis) for 91% of patients with trapped lung or multiloculated effusions.[96] The Denver Pleurx system is likely to offer significant benefit to all patients with pleural effusion and might allow many stable patients to undergo drainage and sclerosis on an outpatient basis.

Approach to Management

This subject is not without controversy, particularly with respect to the method of pleurodesis. Surgeons are likely to favor a surgical approach, such as VATS or thoracoscopy with pleurodesis attempts using talc or pleural abrasion, whereas pulmonologists and oncologists are likely to favor chest tubes and talc. Newer approaches with smaller chest tubes allow for outpatient management of pleural effusions in a more stable patient population. Cost considerations are important as well; surgical approaches can add significant expense because of operating room time and the involvement of anesthesiologists, although some of these expenses can easily be recovered by quicker hospital discharges and elimination of complications. Certain physicians have strong feelings one way or the other based on their interpretations of the literature and their personal experiences; well-performed clinical trials are difficult to conduct in these situations and are unlikely to occur. For example, because of the low, but very real incidence of ARDS (and mortality) associated with the use of talc that has not been seen with the use of any other agents, some clinicians feel that intrapleural talc should never be used; others recommend talc as long as lower doses (2–5 g) are used, although ARDS can be associated even at these doses.[76,78,79,82] Because many patients achieve pleurodesis through the presence of a chest tube alone, that sole measure might be sufficient for a good percentage of patients, and certainly a trial of this can be considered in stable patients. Although one general approach is shown in the algorithm, the overall scheme needs to be individualized for the patient, with one physician (usually the medical oncologist) as the coordinator to ensure optimal outcomes.

PERICARDIAL EFFUSION

Malignant pericardial effusions are much less common than both ascites and pleural effusions. They are often an event that occurs with end-stage disease, and patients are often switched to a purely palliative mode on discovery of a malignant pericardial effusion, particularly if tamponade or near-tamponade physiology is present. Because primary intracardiac tumors are exceedingly rare, the most common cause of pericardial effusions is tumor metastatic to the heart or pericardium. About one-third of patients with end-stage lung or breast cancer have evidence of pericardial metastases and/or effusion present at autopsy, although only a small number of these are symptomatic. Figure 60-2 provides a treatment approach to malignant pericardial effusions.

Etiology and Pathogenesis

The pericardial space normally contains a tiny amount of fluid that serves to reduce friction, maintain position of the heart in the pericardium and mediastinum, and provide a barrier against infection. Malignant cells obtain access to the space either by direct invasion from an adjacent tumor in the lung or mediastinum or by hematogenous or lymphatic spread. Retrograde progression of disease through the lymphatic channels draining the heart and pericardium results in a majority of effusions.[98] The potential space in the pericardial cavity is much less than in other potential areas of fluid accumulation (abdomen, lungs), and, depending on the compliance of the pericardium and the acuity of fluid collection, symptoms can develop rapidly. Furthermore, because even a small amount of fluid that develops rapidly can compress the heart and thus impede diastolic filling, malignant pericardial effusions are often difficult to manage and tend to carry a grim prognosis.

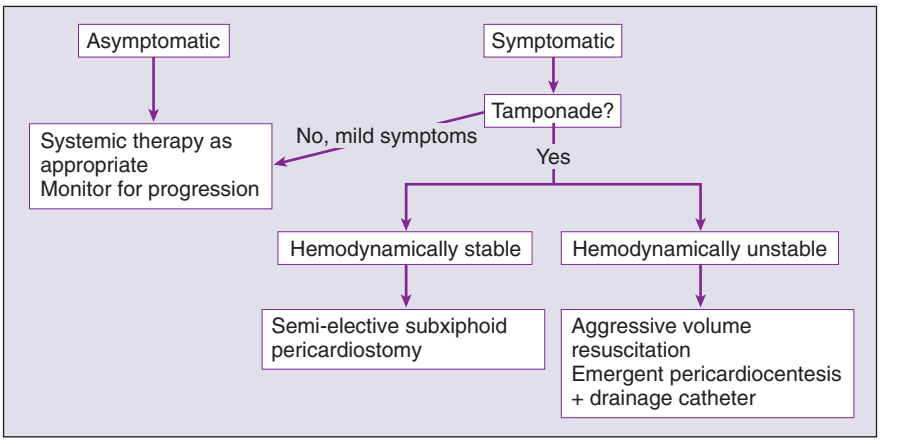


Figure 60-2 • Treatment approach to malignant pericardial effusions.

Clinical Presentation

The most common clinical manifestations of pericardial effusion are dyspnea, cough, chest pain, orthopnea, palpitations, tachypnea, tachycardia, and edema. Physical examination might show signs of a low-output cardiac state (coolness of the extremities, diaphoresis), jugular venous distention, distant heart sounds, narrowed pulse pressure, a pericardial friction rub, and a pulsus paradoxus. Pulsus paradoxus can be measured at the bedside using a sphygmomanometer that is deflated very slowly. During deflation, the first Kortokoff sounds are heard only during expiration and subsequently throughout the respiratory cycle. The difference in systolic pressures at which the Kortokoff sounds are heard between inspiration and expiration quantifies the pulsus paradoxus, which is normally no more than 10 mm Hg. Classically, Ewart's sign (dullness at the left infrascapular area due to bronchial compression by a large effusion) may be seen, but it is rarely observed in practice.[99] Electrocardiography might show low-voltage complexes across all leads (especially when compared with a prior study) and electrical alternans. Electrical alternans is considered a pathognomonic sign of pericardial tamponade; it is caused by a pendulum-like swinging of the heart in a fluid-filled pericardial cavity, but it is seen in less than 3% of cases.[100] Low voltage is defined as a total amplitude of the QRS complexes in each of the limb leads of 5 mm or less. Sinus tachycardia is often seen as well but has many other causes.

Diagnosis and Evaluation

A patient with a pericardial effusion, like a patient with pleural effusion, should be classified according to the likelihood of the effusion being malignant. The causes of pericardial effusions are shown in Table 60-3 and should be considered for all patients, because benign effusions clearly portend much better prognoses than malignant ones. Most effusions among patients with advanced cancer will, in fact, be due to that malignancy. An autopsy series of 3314 patients found that cardiac metastases occur in 10% of patients dying of cancer.[101]

Table 60-3 Major Differential Diagnosis of Pericardial Effusion by Etiology

Noninfectious
Malignancy (usually metastatic)
Myocardial infarction associated (Dressler's syndrome)
Uremia
Myxedema (rare cause of tamponade physiology)
Trauma (penetrating or nonpenetrating)
Chylopericardium
Acute idiopathic
Rheumatic fever
Collagen vascular disease (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, Wegener's granulomatosis)
Postsurgical (cardiac and intrathoracic)
Drug induced (procainamide, hydralazine, phenytoin, doxorubicin, isoniazid)
Infectious
Viral (coxsackievirus, echovirus, mumps, adenovirus, hepatitis, human immunodeficiency virus)
Bacterial (pneumococcus, streptococcus, staphylococcus)
Tuberculous
Fungal (histoplasmosis, coccidiomycosis, candida, particularly in immunosuppressed patients)

Many patients with malignant effusions have known advanced cancer, and therefore, there is little diagnostic dilemma. In those patients in whom advanced cancer is unlikely, a more thorough evaluation should be done.

Unfortunately, malignant pericardial effusion is often difficult to definitively diagnose.[100,102] Lymphatic obstruction by tumor might cause blockage without direct involvement of malignant cells in the pericardium, thereby making the usual gold standard test, cytology, unhelpful. Other causes such as prior radiation also can cause a pericardial effusion and should always be considered in a patient with such a history to avoid mistakenly classifying a patient as having advanced cancer.

Electrocardiogram and physical examination can be performed with particular attention to the aforementioned findings. Chest radiograph can show a water bottle-shaped pericardium or an enlarged silhouette. Echocardiogram should be performed, emergently if there are clinical signs of tamponade, and to assess the hemodynamic impact of an effusion; this test can detect a volume of fluid as little as 15 mL. Fluid first appears as a lucent space between the pericardium and epicardium, visible only during systole and behind the left ventricle; once reaching 25 to 50 mL, it may be seen throughout the cardiac cycle. Once the effusion can separate the pericardium from the epicardium, the pericardial image becomes stationary; once it extends behind the atrium, atrial wall motion is markedly increased. When tamponade physiology is reached, the echo-Doppler shows compression of the right side of the heart, increased respiratory variation of mitral and tricuspid inflow velocity, and right atrial and ventricular collapse during diastole. Assessment of tamponade should be based on clinical and imaging evidence, not just on the volume of fluid present. CT scan is also sensitive for diagnosing an effusion. It can detect as little as 50 mL of pericardial fluid and, similar to an echocardiogram, can give an idea of intracardiac masses.[103] MRI also can provide direct imaging of the pericardium.[104] Both of these tests can give some clues as to the nature of the fluid (bloody, serous, chylous), but they rarely provide clinically useful information. If there is a small, questionable effusion present, MRI can differentiate between a small effusion and epicardial fat. Because of the frequency with which oncology patients receive CT scans and MRIs, these studies often identify an effusion, prompting a further evaluation. Cardiac catheterization of the left and right sides of the heart can be used to confirm tamponade physiology (demonstrated by equivalence of pressures across all chambers) and improvement of these pressures after pericardiocentesis. However, this is usually not necessary.

Pericardiocentesis

Pericardiocentesis is usually performed with a 16- to 22-gauge needle (often a spinal needle) attached to a syringe inserted at roughly a 45-degree angle below the xiphoid process cephalad toward the tip of the left scapula. The needle is generally attached to an electrocardiograph machine during the procedure. Advancement into the myocardium usually reveals an injury pattern on the electrocardiogram. Although this procedure is usually performed semi-electively, pericardiocentesis occasionally must be done in an emergent setting, where removal of as little as 50 mL of fluid can improve hemodynamic status.[105] Complications include ventricular perforation, arrhythmias, and pneumothoraxes, and range from 5% to 20%. Complications are less likely (about 2%) when echocardiography is used to delineate the size and location of the fluid with respect to normal cardiac structures.[106] Among patients who are clinically unstable, with tamponade physiology and hypotension, vigorous volume resuscitation should be performed to increase cardiac filling pressures and cardiac output, even if signs of heart failure, such as edema or lung rales, are seen.[107]

Pericardial Fluid Evaluation

The evaluation of a patient with effusion depends on several characteristics. For those patients with small effusions and advanced

malignancy found incidentally on imaging, nothing needs to be done except a good physical examination and monitoring. For patients with a suspicion of cancer, or those patients who are symptomatic due to tamponade physiology, attempts at diagnosis and therapy should be made. Pericardial effusion is rarely the initial manifestation of malignancy. Two studies demonstrated that 7% of patients presenting with a pericardial effusion were ultimately given a new diagnosis of malignant disease.[108] Patients with no history of cancer who present with an effusion and absence of tamponade or significant clinical symptoms should be managed in a cautious, noninvasive manner. This approach usually includes treatment with anti-inflammatory therapy (such as nonsteroidal anti-inflammatory drugs) for potential idiopathic pericarditis for a period of 1 to 2 weeks.[108] Such management should be undertaken in cooperation with an experienced cardiologist. In terms of evaluating pericardial fluid, however, there are no specific guidelines for classifying an effusion as a transudate or exudate, or to further delineate the etiology of the effusion with criteria such as LDH, protein, glucose, pH, or cell count, as there are with pleural effusions. Interestingly, the best predictor for the behavior of a pericardial effusion of unknown etiology is from the clinical history of the patient. In a study of 322 patients from Sagrista-Sauleda and colleagues,[109] a large effusion with clinical signs of inflammation (two or more of the following: chest pain, fever, diffuse ST segment elevation, or friction rub) had a likelihood ratio of 20 for an idiopathic effusion, and those patients with tamponade without inflammation had a likelihood ratio of 2.9 for a malignant effusion.

It is worth repeating here that pericardial fluid, unlike pleural fluid, cannot be classified as a transudate or exudate. Nevertheless, aspirated fluid should be sent for cell count, cultures (if there is a possibility of infectious etiology), and cytology. The sensitivity of cytology for malignant pericardial disease varies widely, from 50% to 90%.[100,102] Reasons given for false-negative cytology include limited cellularity in the specimen, shrouding by blood, or the absence of an expert cytopathologist. Interestingly, DNA diploidy obtained from flow cytometry has been found to correlate with benign cytology, and aneuploidy is associated with malignant cytology but is not sensitive enough to be definitive.[110] It is uncommon for pericardial fluid cytology to provide the first diagnosis of a malignancy. In one study of 47 pericardial fluid specimens, only 10 were positive for malignancy, and none of these represented the first diagnosis of a malignancy in a patient.[111] It is imperative, however, that the physician realize that a negative cytology does not exclude malignant pericardial disease. By the same token, patients with a history of cancer could have an effusion for other reasons, particularly radiation.[112] One should be cautious, then, in providing the diagnosis of a malignant effusion (and usually advanced, incurable malignancy) unless definitive cytologic evidence is seen. For patients with a negative cytologic specimen but suspected malignancy, pericardial biopsy may be performed. Prospective studies have demonstrated a 5% to 20% positive yield for diagnostic pericardial biopsy specimens.[108] This is probably due to the blind nature of the biopsies and to the practice of taking biopsy specimens from the parietal pericardium, whereas the principal site of malignant involvement is the visceral pericardium, site of the epicardial lymphatics. The positive yield is much higher (54%) for biopsies performed during therapeutic (subxiphoid pericardiostomies) procedures; although there might be some selection bias, therapeutic procedures allow the pericardium to be visualized more directly and thus permit more accurate biopsy site selection.[108]

Pericardioscopy is a relatively new technique available in specialized centers that allows endoscopic inspection, aimed biopsies, and drainage of both pericardial surfaces, and can even be used to obtain epicardial biopsy specimens.[113] An expansion of this technique, using a perDUCER catheter, can be used for endocardial biopsies and thus far has been used for diagnosing and managing patients with nonmalignant pericarditis. This technique, however, also allows for guidewire and catheter placement, by which intrapericardial therapy may be administered. Ultimately, this technique might be expanded for use in evaluating and managing malignant pericardial etiologies.[114]

Treatment and Management

Asymptomatic malignant effusions do not require therapy. Volume depletion should be avoided, because adequate right ventricular preload is essential to allow sufficient cardiac output. For symptomatic patients pericardiocentesis may be performed, either as initial therapy or to allow stabilization until a more definitive procedure can be performed. Unfortunately, as many as three quarters of patients have recurrence and require treatment.[115]

Chemotherapy

A limited number of patients might benefit from systemic chemotherapy if such options are available (i.e., if they are expected to be chemotherapy responsive), or if a delay in treatment increases the risk of significant systemic progression. Such chemotherapy-sensitive tumors include leukemias, lymphomas, germ cell tumors, and even breast cancer. Although there might be reluctance on the physician's part to treat a malignant pericardial effusion with chemotherapy because of the feeling that even moderate effusions could become life threatening, there is ample evidence in the literature to support the use of chemotherapy in many circumstances. There are reports of successful resolution of effusions for patients with chronic myelomonocytic leukemia with hydroxyurea or chemotherapy.[116] Vaitkus and associates[115] reviewed the experience of treatment of 46 patients, mostly with breast cancer or lymphoma, who had malignant pericardial effusions treated with chemotherapy (38 of 46 patients initially having undergone therapeutic pericardiocentesis), and reported that systemic chemotherapy prevented recurrence in 67% of these patients. A special entity, primary cardiac lymphoma, although it responds to traditional chemotherapeutic regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), is not responsive to radiotherapy and carries a poor prognosis, probably due to myocardial infiltration and tissue necrosis that might precede or result from chemotherapy.[117] Several researchers have reported pericardial effusions from leukemias with the presence of blast cells in the pericardial fluid, which were treated with emergent pericardiocentesis (because of tamponade) and immediate chemotherapy with good outcomes.[118] Other primary cardiac tumors, such as sarcoma and intrapericardial pheochromocytoma, tend not to be as responsive to chemotherapy, so control of the effusion should be the initial focus.[119] Vaitkus and coworkers[115] also reviewed the experience of 54 patients treated with radiotherapy and found that this procedure was successful two thirds of the time, mainly in cases of hematologic malignancies and breast cancer (93% and 71% success rates, respectively) although 45% of patients with other solid tumors also had successful control. It should be noted, however, that radiotherapy might induce scarring or fibrosis that makes further interventions more difficult, so this procedure should be saved for end-stage patients declining other interventions. Those patients with physiology demanding immediate intervention should have some sort of drainage performed, whereas those that are stable and potentially chemotherapy responsive should be considered for chemotherapy.

Percutaneous Tube Pericardiostomy

For patients not amenable to systemic therapy for whatever reasons, percutaneous drainage is performed. Because the rate of fluid reaccumulation is very high, prolonged catheter drainage is often used in addition to pericardiocentesis. This is now common practice, because it allows a more complete drainage than that attainable by pericardiocentesis alone. After the pericardiocentesis, a guide wire is left in place, and a pigtail catheter is placed via the Seldinger catheter-over-a-guide wire technique. The catheter is left in place for several days and is not removed until the drainage is less than 20 to 30 mL per 24-hour period, at which point the catheter is removed. There is a

small risk of infection with a catheter remaining in place for several days.[120] The catheter should be subject to intermittent rather than continuous drainage to maintain catheter patency. With this technique, however, there is still a relatively high likelihood that the fluid will reaccumulate unless other steps are taken. Unless the patient has a very short life expectancy (which still might require a repeat drainage) or, in the physician's mind, the patient has a tumor from which one would expect a response from chemotherapy, other interventions will be required.

Surgical Approaches

SUBXIPHOID PERICARDIOSTOMY (SUBXIPHOID PERICARDIAL WINDOW). The subxipoid pericardial window, first reported by Napoleon's surgeon, Larrey, in 1829,[121] is now the most common surgical procedure for pericardial effusions. The procedure may be performed under local anesthesia with intravenous sedation; a small incision is made from the xiphoid process caudally for approximately 5 cm, and the xiphoid is either bisected or resected. After dissection to the pericardium, adhesions and masses are identified, a 2- to 4-cm^2 piece of pericardium is resected, and a drainage tube is placed. The drainage tube remains in place for several days, which could allow for sclerosis simply by acting as a pericardial irritant.[122] Allen and colleagues[123] retrospectively compared the experience of 117 patients who underwent either percutaneous catheter drainage with ultrasound or fluoroscopic guidance ($n = 23$), or subxiphoid pericardiostomy ($n = 94$). Complication rates were 17% in the percutaneous drainage group and 1% in the pericardiostomy group, with 4% mortality and a 30% recurrence rate in the percutaneous drainage group, compared with 0% mortality and 30% recurrence in the pericardiostomy group. In the percutaneous group, pigtail catheters remained in place for an average of 4.2 days, and mediastinal drainage was maintained for 5 days in the surgical group, so there was minimal difference in the number of days hospitalized. The advantages of the surgical group come with the caveat that the 23 patients who underwent percutaneous drainage did so because they were deemed to be too hemodynamically unstable to undergo a surgical procedure, and thus bias could account, at least in part, for the advantages of subxiphoid pericardiostomy. For all patients in this study, the median survival time of those patients having a malignant pericardial effusion was a paltry 2.2 months, with 13.8% of patients having a 1-year survival. No patients who underwent pericardiostomy developed constrictive pericarditis. For patients who are hemodynamically stable, the subxiphoid pericardiostomy can and should be considered in lieu of percutaneous catheter drainage.

ALTERNATIVE SURGICAL TECHNIQUES. Before the revival of the subxiphoid pericardial window, alternative surgical techniques had been used, including sternotomy and pericardiectomy or creation of a window via thoracotomy or VATS.[124,125] Initially, the experience of Piehler and associates[124] with 145 patients suggested that the extent of pericardial resection affected the recurrence rate, thus favoring open surgical drainage rather than the easier subxiphoid pericardiostomy. Several recent studies, however, have demonstrated no difference between the open or VATS procedures and subxiphoid pericardiostomies.[126,127] Vaitkus and coworkers[115] reported a decreased number of further pericardial complications when subxiphoid pericardiostomies instead of open pericardiectomies were performed. There is a much lower incidence of postoperative complications (including pneumonia, thrombosis, arrhythmia, respiratory failure) after subxiphoid pericardial drainage compared with transthoracic pericardial resection (10% vs. 50%, respectively).[126,127] VATS offers a minimally invasive technique for treatment of effusions but still requires general anesthesia and the ability to tolerate single-lung ventilation, so it offers little advantage over subxiphoid pericardiostomy. It should therefore be saved for situations in which the subxiphoid approach fails, in which a VATS approach would assist with evaluation or treatment of simultaneous lung pathology, or in which a larger specimen of pericardium is required for clearer observation and evaluation of an undiagnosed effusion.[127,128] A pericardial-peritoneal shunt with a Denver-type catheter and pump, similar to that used in pleural effusions, has been used for some patients with success, but its use should be limited to patients whose effusions are refractory to other management techniques.[128]

PERCUTANEOUS BALLOON PERICARDIOTOMY. Percutaneous balloon pericardiostomy is an extension of a percutaneous pigtail catheter, except that a balloon-dilating catheter (20 mm diameter and 3 cm length) introduced over a guide wire creates a nonsurgical pericardial window. Ziskind and colleagues[129] provided the results from the first 50 patients treated with this technique. The procedure was considered successful in 46 of the 50 patients, with two patients requiring early operation for a bleeding vessel and persistent drainage and two patients requiring late drainage for recurrent tamponade. Minor complications included fever, thoracentesis, requirement for chest tube placement, and pneumothorax. The most significant complications were the development of pleural effusions requiring drainage. Subsequent studies have reported up to 100% success rates.[130,131] Long-term outcome from these patients was still poor, with a mean survival time of 3.3 months. The procedure has been slow to gain acceptance because of the need for specialized training and equipment but could become a more popular option as interventional radiologists become adept in this technique.

INTRAPERICARDIAL SCLEROSING AGENTS AND CHEMOTHERAPY. For pericardial effusions, as for pleural effusions, sclerosing agents may be used, and in general, do work.[132] Maher and associates[133] reported their experiences with 93 patients who underwent pericardial fluid drainage, followed by sclerosis with either doxycycline or tetracycline. A median of three instillations was required and was able to control the effusion 88% of the time. Shepherd and colleagues[134] reported similar results (75% success rate). The most common complaints with this procedure are pain (intrapericardial lidocaine should be injected before the sclerosing agent) and arrhythmias. Bleomycin has been compared with doxycycline in a prospective, randomized study showing equal efficacy and less pain; therefore, it should probably be considered instead of doxycycline as the sclerosing agent of choice.[135]

The use of direct intrapericardial instillation of chemotherapy and biologic therapy has been examined in several settings with limited data. For pericardial as for pleural effusions, it is somewhat difficult to determine whether intrapericardial chemotherapy functions because of tumor cytotoxicity or pericardial irritation leading to sclerosis, because the physiology and mechanisms of sclerosis are poorly understood. Imamura and coworkers[136] looked at the use of OK-432 (a heat-treated lyophilate of *Streptococcus pyogenes* A3) instilled directly into the pericardium after fluid drainage. All 10 patients in this study achieved complete control of the pericardial effusion, 7 of the 10 with only one treatment, for an average of 10.8 months. Complications were primarily fever and chest pain. Hypotension was also seen and was thought to be a result of rapid fluid reaccumulation in several patients. Moriya and associates[137] explored the use of intrapericardial carboplatin in 10 patients with advanced non-small-cell lung cancer; 8 patients showed complete regression of the effusion with minimal toxicities and minimal systemic distribution of the carboplatin. Cisplatin is the best-studied therapy, with overall success rates of 67% to 87%.[138] One of the earliest studies on the use of cisplatin comes from Fiorentino and colleagues, who gave five patients intrapericardial cisplatin (50 mg over 5 minutes 5 days in a row, with courses repeated every 2–3 weeks if there was fluid recurrence).[138] There was a 60% complete response rate in the effusion. Side effects were limited to mild nausea with no hematologic or renal toxicities. Kawashima and colleagues[139] gave intrapericardial aclarubicin to five patients with pericardial tamponade secondary to malignant effusions; in four of the five, physicians were able to

remove the pericardial catheter, and two of the five patients experienced a complete remission of the pericardial effusion. All patients demonstrated disappearance of the malignant cells from the pericardial space, with no cytopathologically demonstrable pericardial recurrence. Mitoxantrone and interferon have also been used, with similar results.[140,141] With intrapericardial use, however, there is a significant risk of pain, a requirement for multiple instillations, and a possibility of constrictive pericarditis for patients with a prolonged survival. Because of these limitations the use of pericardial sclerosis is declining, and intrapericardial chemotherapy remains highly experimental.

Summary

Malignant pericardial effusion is a dreaded complication of malignancy, indicative of advanced disease in most cases. The oncologist should take care to ensure that advanced disease is in fact present, and that the effusion has no other etiology in a patient who has a history of cancer. Management should be focused on immediate resuscitation and control of life-threatening symptoms. Asymptomatic patients with cancer and an effusion can be managed conservatively and observed with either repeat careful physical examination or serial echocardiograms. If there is a strong likelihood of tumor response to chemotherapy, or if chemotherapy is absolutely required (e.g., in cases of lymphoma or life-threatening systemic disease), it should be started as soon as possible. If emergent pericardiocentesis is required, it should be performed with placement of a percutaneous pigtail catheter. For patients who are clinically more stable but unable to be treated adequately with systemic chemotherapy, one could consider either percutaneous drainage or subxiphoid pericardiectomy under local anesthesia, with probably similar results; the latter demonstrates a lower rate of recurrence and is the procedure of choice. Such a management approach has been validated in several studies.[123,142] Use of other techniques, such as VATS, percutaneous balloon pericardiotomy, sclerosis, or intrapericardial chemotherapy offers new potential options for these patients should primary therapy fail.

ASCITES

Malignant ascites is a frequent occurrence in the patient with malignancy and is usually an indication of peritoneal carcinomatosis. Like malignant pericardial and pleural effusions, it is often a harbinger of advanced disease. It accounts for 10% of cases of ascites, and 1-year survival is less than 10%.[143]

Etiology and Pathogenesis

The peritoneal membrane contains lymphatics, which serve to collect fluid, proteins, cells, and other substances and return them to the systemic collection. There is a specialized anatomic feature, the stomata, which are relatively open connections that connect the abdominal cavity to submesothelial lymphatics and that are the sites of most lymphatic drainage of the abdomen.[144] Fluid accumulations, as in the pleural and pericardial cavities, can occur if there is overproduction or decreased drainage of fluid. Studies in adults have demonstrated that increased fluid production is a major cause of ascites among patients with peritoneal carcinomatosis.[145] Animal models in which mice were given intraperitoneal injections of tumor cells have demonstrated that obstruction to lymphatic flow can cause ascites as well, and this has been confirmed using lymphoscintigraphy in humans.[146,147] VEGF, an angiogenesis factor expressed by most tumors (including those that spread to the peritoneum), has been demonstrated in vivo to cause increased fluid production and to influence the development of ascites.[148–150] VEGF is probably the single biggest mediator of ascites production. Interleukin-2, tumor necrosis factor, interferon-α, and matrix metalloproteinases have also been implicated as factors contributing to the formation of ascites.[151–153] Intraperitoneal protein accumulation decreases the difference between plasma and peritoneal oncotic pressures and subsequently decreases filtration into the lymphatics.[154] Free fluid flow into the abdomen therefore increases. Fluid protein concentration can reach oncotic pressures similar to that reached in peritoneal dialysis, which is very effective in causing ultrafiltration.[155] The most common tumors that cause ascites are those of gastrointestinal and pelvic organs; the single most common is ovarian cancer.

Diagnosis and Evaluation

Many patients with malignant ascites have small amounts of fluid first noticed on imaging studies, such as those done for staging or evaluation after therapy or for another complaint. Symptoms resulting from large amounts of fluid usually include abdominal distention (such that trousers no longer fit properly), early satiety, nausea, vomiting, an increase in weight, edema, and shortness of breath. Physical examination in the evaluation of ascites is notoriously difficult, especially among obese patients with lesser amounts of fluid. The physical examination has been shown to be from 50% to 94% sensitive and from 29% to 82% specific, with ultrasound being the gold standard.[156] Physical examination can demonstrate a fluid wave, shifting, or flank dullness. The absence of flank dullness is the most accurate predictor against ascites, but one requires 1500 mL of fluid to be present to notice flank dullness. If there is suspicion of ascites in any patient, ultrasound is the easiest, fastest, and cheapest method of ascertaining a diagnosis of ascites; one series demonstrated that as little as 100 mL of fluid can be demonstrated on an ultrasonogram.[157] Radiologic studies such as CT or MRI can also give clear-cut evidence of ascites, but these are usually not necessary as part of the first-line evaluation. Plain-film radiograms can show a ground-glass appearance to the abdomen, loss of detail, haziness, or floating bowel on supine films but is nonspecific. Figure 60-3 gives a treatment approach to malignant ascites.

For many patients with known malignancy, the presence of ascites will not alter management, because advanced disease is already present. For some patients, particularly those without a known malignancy, the detection of ascites requires an appropriate evaluation to determine the etiology. For these patients, the differential diagnosis includes CHF, alcoholic cirrhosis, cirrhosis due to hepatitis B or C, previous abdominal surgeries, nonalcoholic steatohepatitis, and other

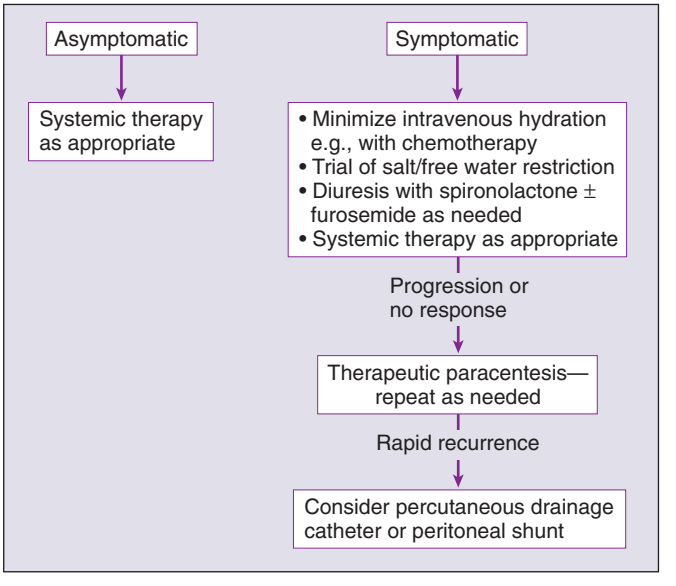


Figure 60-3 • Treatment approach to malignant ascites.

causes of increased portal venous pressure. It should be remembered that patients with a history of cirrhosis have a predilection for hepatocellular carcinoma.

In most cases of ascites in which malignancy is a possibility, cross-sectional imaging, such as with a CT scan, should be performed to seek a primary tumor site, hepatic metastases, or other evidence of peritoneal seeding. Women in particular should have either an ultrasonogram or CT scan to evaluate the ovaries. After this, a diagnostic abdominal paracentesis is indicated. Ultrasound may be used during the procedure to localize ascites and minimize the risk of injury to abdominal organs (particularly the liver and intestine).[157] After local anesthesia, an 18-gauge needle attached to a 25- to 50-mL syringe is inserted into a site indicated by ultrasound or into the areas percussed as dull in the flanks, if sufficient fluid is present. If cytology is required, several liters of fluid can be obtained using vacuum bottles. Even among patients with coagulopathies (such as cirrhosis), the risk of developing a hematoma is only 1% and that of causing peritonitis or hemoperitoneum is 0.1%; therefore, one can usually proceed without the use of clotting factors or platelets.[158] Patients on therapeutic anticoagulation should have their anticoagulation withheld for several days before paracentesis.

Visualization of the fluid can provide some useful clues; clear fluid is usually associated with cirrhosis. Infected fluid is cloudy. Milky fluid can indicate chylous ascites and should be sent for triglyceride evaluation. Such fluid often has triglyceride levels greater than 200 mg/dL and often as high as 1000 mg/dL. Some studies have demonstrated that the most common cause for chylous ascites is malignancy, although others have found cirrhosis as the primary cause.[159,160] Either way, if chylous fluid is found it should heighten the physician's attention to the potential for malignancy. Heterogeneously bloody fluid is associated with a traumatic tap, whereas homogeneously bloody fluid indicates prior bleeding (i.e., a nontraumatic tap) and could indicate malignancy. Ascites is bloody in up to one half of patients with hepatocellular carcinoma and in 22% of all patients with malignant ascites.[161] Spontaneous bacterial peritonitis (SBP) does not tend to develop to the extent that it does among patients with cirrhotic ascites, unless there has been previous surgery or a previous paracentesis. All patients should be evaluated for signs of SBP (including fever and abdominal pain), and a cell count on the ascitic fluid should be done; a polymorphonuclear cell count greater than 250 per cubic millimeter should prompt the use of empiric antibiotics in appropriate situations.[158]

The first and most important step in the evaluation of the patient with ascites of unknown etiology is to differentiate those causes arising from portal hypertension (usually cirrhosis) from other causes (including malignancy). The best test for this determination is the serum-to-ascites albumin gradient, which is the difference between serum albumin and ascitic fluid albumin. Low-protein ascites is usually from portal venous hypertension. A gradient equal to or greater than 1.1 g/dL indicates portal hypertension with 97% accuracy, whereas a lower gradient (high-protein ascites) indicates a lack of portal hypertension and possibly the presence of a malignancy.[160] The classical division of ascitic fluids into transudates and exudates using LDH, protein, and their serum-to-ascites ratios, akin to pleural effusions, has been shown to be not as useful. Total protein is not particularly useful for diagnosis of malignant ascites, although a value of less than 1 g/dL is useful in predicting a patient's increased risk for SBP.[162] This range of values is usually seen in cirrhotic patients. A glucose value below 50 mg/dL has been associated with malignancy but also can be indicative of infection.[27] An ascites-to-serum ratio of LDH greater than 1 indicates that the enzyme is actively being produced in the ascitic fluid and suggests malignancy, but not as specifically as with a pleural effusion. Triglyceride levels should be obtained in milky ascites but might or might not be particularly helpful. Other chemistries and cultures should be obtained if diagnoses other than malignancy are entertained.[143,158] Siddiqui and associates[163] have demonstrated that fibronectin is up to 100% sensitive and specific as a marker of malignant ascites in a small study of only 12 patients with malignant ascites; others feel that this test is not helpful, and it is not used routinely.[164]

The detection of tumor cells by cytology remains the gold standard for the detection of malignancy. For patients with peritoneal carcinomatosis due to cellular exfoliation into the ascitic fluid, malignant cells can be detected nearly 100% of the time.[161] On the other hand, patients with liver metastases and portal venous obstruction, chylous ascites from lymphomas and lymphatic obstruction, or hepatocellar carcinoma, might not have a positive ascitic fluid; the overall sensitivity for cytology is therefore on the order of 40% to 75% when 500 mL of fluid is obtained.[163,165] To increase the detection of tumor cells and differentiate mesothelial cells from malignant cells, immunohistochemistry for cytokeratin, vimentin, leukocyte common antigen, S100, CEA, HMB45, and other markers may be performed on the cytologic specimen. A small study by Loewenstein and coworkers[166] has shown that an elevated CEA level in ascitic fluid is a good marker for malignancy, although this has not been well validated and requires further evaluation. Elevated serum or ascites CA-125 and CEA levels certainly should prompt a careful evaluation for malignancies, particularly for ovarian cancer in women with highly elevated CA-125, although neither marker is specific for any particular malignancy (or even malignancies in general) and might reflect only intra-abdominal pathology rather than malignant disease.[154] No known studies have correlated levels of CA-125 and CEA with the likelihood of a malignancy, but one would expect higher levels of tumor markers to have a greater association with malignancy.

Women with only ascites and no evidence of primary malignancy on cross-sectional imaging present an interesting situation. These patients should undergo laparoscopic evaluation, at which time biopsy samples are taken from both ovaries, ascitic fluid is sampled, and random biopsies are performed throughout the abdomen. If ovarian carcinoma or adenocarcinoma consistent with ovarian carcinoma is seen, the procedure is converted to a laparotomy; it has been shown that aggressive surgical debulking to minimal residual disease improves response, survival time, and response to aggressive chemotherapy (usually taxane- and platinum-based) among patients with ovarian carcinoma. Such an approach can lead to a long disease-free interval and significant long-term survival. Even small, low-grade ovarian tumors, with the primary tumor not seen on imaging, can lead to diffuse peritoneal contamination, and hence, to the development of ascites.[167,168] Some patients might have papillary serous carcinoma of the peritoneum, which arises from the peritoneal surface but shares a common histogenesis with ovarian tissue and also might be difficult to detect on cross-sectional imaging. It is important to remember that patients with ovarian cancer with ascites are classified as only stage III, and hence this rather large subgroup should be treated aggressively whenever possible. Papillary serous carcinoma of the peritoneum should be treated in a fashion similar to ovarian carcinoma.[169] Laparoscopy should be performed diligently. In a study from van Dam and colleagues[170] of 104 women with advanced ovarian cancer who underwent laparoscopy for diagnosis, 58% of patients had tumor implanted at the trocar site when only the skin was closed at the conclusion of the procedure, but in those in whom all abdominal wall layers were closed, only 2% had such implantation. For patients with ascites, there is a risk of prolonged fluid drainage at trocar placement sites. In one study, 2 of 92 patients developed peritonitis and died after undergoing laparoscopic procedures in these circumstances.[171] For a more detailed discussion of the diagnosis and management of ovarian carcinoma, the reader is referred to Chapter 93.

Management

As with pleural and pericardial effusions, it is important to distinguish the appropriate situations in which to treat malignant ascites. Small amounts of ascites can be tolerated very well or not even

noticed. On the other hand, when symptoms such as dyspnea, abdominal pain, fatigue, anorexia, or early satiety arise, treatment can be required. The most worrisome sign is dyspnea, which can arise either from an inordinate amount of weight being carried by the patient or by compression of the pleural cavity leading to a decrease in total lung capacity. Clearly, the overall clinical status of the patient should be taken into account when making these treatment decisions. In light of the fact that ascites does not usually pose a life-threatening situation, and that the disease might respond well to systemic therapy in instances such as ovarian cancer, systemic chemotherapy can be considered front-line therapy. For other situations, such as pancreatic cancer, because responses to therapy are much less frequent, one would consider an early direct approach to control of the fluid. Certainly, in either case, because most techniques to manage fluid (e.g., diuresis, paracentesis) are relatively easy and performed on an outpatient basis, one could combine systemic chemotherapy with these other options.

Fluid Balance Management

Intravascular fluid that leaks into nonvascular compartments, also known as third spacing, results in decreased renal blood flow and consequently to sodium and water retention by the kidney, which ultimately leads to the propagation of further third-spacing of fluids. The use of fluid management techniques to manage malignant ascites is controversial. Because tumors that arise from peritoneal seeding are not caused by pressure gradient shifts, some feel that management using diuretics and salt management techniques that affect renal handling of excess fluid and sodium are useless, whereas others believe they can be effective.[172,173] One can attempt dietary restriction of sodium to less than 2 g/day and also restrict free water intake to help decrease the amount of ascites. Unfortunately, to the patient with advanced malignancy, this strategy can prove overly burdensome, particularly when the patient is undergoing other treatments such as chemotherapy. At a minimum, however, the physician should restrict intravenous hydration as much as possible when chemotherapy is being administered.

The next step in this mode of management is the use of diuretics, which offers a noninvasive mechanism to help maintain fluid balance. The advantage of this approach is that it can be done easily on an outpatient basis with oral medications, and it is even possible for patients to perform minor self-adjustments in medication after instruction, which also restores to patients a degree of control over their own health. A distal tubule diuretic such as spironolactone is usually used first. Such agents act on the distal nephron, thereby minimizing the chances for compensation by more distal renal elements. More important, it works at the site of the renin-angtiotensin-aldosterone axis, which is upregulated due to decreased renal perfusion when significant third-spacing occurs, as in ascites. Doses start at approximately 25 to 50 mg/day and can go as high as 200 mg/day. Painful gynecomastia can result, and if this proves bothersome, amiloride is an alternative. Spironolactone alone often is insufficient and not immediate in its effects. In such cases, furosemide (usually starting at 20 mg/day and titrated to much higher doses) has been used for either a short period or, commonly, in combination. Razis and associates,[174] along with others, however, have pointed out that loop diuretics such as furosemide are minimally effective, if at all, in the management of ascites. The maximal ascitic reabsorption rate is 930 mL/day, and patients should therefore be instructed to weigh themselves daily and allow no more than a 0.5 to 1 kg/day loss in weight; in the presence of peripheral edema, slightly more weight can be lost per day.[144] Overdiuresis can result in hypotension, volume depletion, azotemia, and electrolyte abnormalities (particularly hyperkalemia with spironolactone, hypokalemia with furosemide), and thus patients should be monitored closely. Patients should be instructed to monitor their weights between physician visits and even to modify the doses of diuretics used when certain weight goals are met.

Unfortunately, although diuretics initially are used by many physicians for the control of ascites and certainly are easy to administer, they are not very effective.[175] Malignant ascites is usually not very responsive to diuresis because the pathogenesis is usually not related to increased portal pressure, as it is in cirrhosis, but rather is related to increased fluid production from the presence of tumor cells in the peritoneum.[176] In the rarer cases in which massive hepatic metastases are present and portal hypertension is the etiology of ascites, patients are much more likely to respond to diuretics.[177] Pockros and coworkers[176] confirmed this, finding that patients with a large amount of hepatic metastases (and hence elevated portal venous pressure) had a serum-to-ascites-albumin gradient similar to cirrhotics and were more likely to respond to diuretics, whereas those patients with peritoneal carcinomatosis were less likely to respond to diuretic management of ascites. Although there are no direct comparative studies, it is because of these clinical experiences that diuresis is used much less frequently than paracentesis as a means of controlling ascites.[175]

Paracentesis

Paracentesis is the most frequently used and most effective management approach to malignant ascites, but its effects are only temporary.[175] Large-volume paracentesis can improve shortness of breath and early satiety quickly. Because one removes the fluid and not the cause of the fluid, however, there is rapid redistribution to the peritoneal cavity. Because of this, large-volume paracentesis can result in intravascular volume depletion, hypotension, azotemia, and other consequences of dehydration.[144] Colloidal volume expansion has been tried as a means to prevent these sequelae. In a randomized trial in cirrhotics by Gines and colleagues,[178] 105 patients receiving large-volume paracentesis were randomly assigned to receive albumin or not. Patients not receiving albumin were more likely to show signs of hemodynamic deterioration, worsening renal function, and hyponatremia (20.8% vs. 3.8%). Most of these patients, however, simply had laboratory abnormalities, because no advantages in clinical morbidity or survival ever have been demonstrated in this or any other study.[158] Further, a 5-L paracentesis would require approximately 50 g of albumin at a cost of up to several thousand dollars and would change a quick procedure into either a day-long one or one requiring an overnight hospital stay, which is not easily justified for patients with advanced malignancies in the absence of proven benefit.[7] Because of this, the use of any colloidal expanders is difficult to justify.

Complications of repeated paracentesis include bleeding, pain, the induction of peritonitis, and bowel perforation. The presence of loculated ascites can make adequate removal of fluid to provide a symptomatic benefit nearly impossible, and it can increase the risk of the procedure. Ultrasound guidance should be used to decrease the risk of complications.

Peritoneovenous Shunting

Peritoneovenous shunting, introduced by LeVeen for alcoholic liver disease, is effective in malignant ascites.[179] Because patients with intractable and debilitating ascites have a median survival of only 6 to 33 weeks and could probably be managed more easily with repeated paracentesis, patients selected for shunting should have an expected survival of several months requiring frequent paracentesis, as demonstrated by repeated recurrence of the ascites after drainage.[180] The device consists of a long, perforated tubing inserted in the peritoneal cavity, a tubing that inserts into the superior vena cava, and a one-way valve that connects the two. There are two types of shunts, the LeVeen shunt and the Denver shunt; the latter has a one-way pump that can be used by the patient or physician to clear debris in the shunt or valve. On inspiration, intrathoracic pressure is lowered and the one-way valve opens, allowing a baseline pressure difference between the thoracic cavity and abdominal cavity to increase by 3 to 5 cm H_2O from its baseline difference of 5 to 15 cm H_2O, causing fluid to flow across the pressure gradient and drain into the superior

vena cava. Placement of the shunt can be done under local anesthesia, with two to three separate incisions made. Parsons and associates demonstrated no survival or quality-of-life advantage when peritoneovenous shunting was compared with repeated paracentesis.[177] Peritoneovenous shunting is effective in controlling ascites between 62% and 88% of the time.[181,182] Early studies demonstrated a large number of pump failures due to occlusion (up to nearly two thirds), but more recent studies have demonstrated lesser rates of occlusion.[179,181,183] The manual pump present in the Denver device for clearing blockages has not demonstrated an advantage in the maintenance of shunt patency.[181] Flushing the pump and administration of thrombolytic agents might be able to restore patency and avoid pump removal and replacement in instances of pump failure.

Patients with ascites that is cytologically negative for tumor cells have a much longer shunt life than those patients with cytologic evidence of malignancy; this is probably due to sludging of the pump system with more viscous tumor cells or debris in the latter case. Immediately after placement of the pump, CHF can result from a rapid increase in intravascular volume from infusion of a large amount of ascitic fluid; this risk can be minimized by performing a large-volume paracentesis just before the procedure. Coagulopathy—specifically, disseminated intravascular coagulation (DIC)—is common when the pumps are used in cirrhotic patients, but not in those with malignant ascites (rate of 4%).[184] DIC probably arises as a result of fibrinolytic activity of ascitic fluid, and fibrinolytic activity is decreased in patients with malignant ascites.[185] Those patients with malignant ascites and good preshunt hepatic function seem to be at an even particularly low or negligible risk for DIC.[186,187] Widespread dissemination of tumor cells from the peritoneum to the lungs has been demonstrated in several studies.[179,183,187] The clinical significance of additional tumor emboli among patients with advanced refractory malignancy, although it represents a major potential complication of shunt placement, is unclear. Infection also remains a concern, but the incidence of shunt-induced peritonitis is much lower among patients with malignant disease than among those with cirrhosis, probably because of the higher levels of protein and immunoglobulin in the ascites.[162]

With significant potential complications and alternatives available, Souter and coworkers[183] suggest the following criteria for patients who should be considered for shunt placement:

- The goal of care is palliative.
- Expected survival is longer than 3 months.
- The rate of fluid reaccumulation is rapid after large-volume paracentesis.
- There is no loculation.
- Accumulated fluid is not bloody or viscous, which could lead to early shunt dysfunction.

Patients with peritonitis or those not able to handle large, rapid fluid shifts (patients with significant cardiac or renal dysfunction) would also not be candidates for shunt placement.

Drainage Catheters

External drainage catheters offer a different method for palliation of ascites, namely a route available for repeated drainage that does not require repeated needle insertion. Patients are therefore offered the ability to perform repeated paracentesis without increased morbidity and discomfort, possibly at home by themselves or with minimal assistance. Several different methods are available; most use vascular ports inserted into the peritoneum, tunneled catheters, or other similar devices to allow drainage after catheter access.[188–190] The best-described uses of this method are from Lomas and colleagues,[191] in which a patient with malignant ascites had 1 L of fluid removed per day for 3 months with a Tenckhoff catheter, and that from Belfort and associates,[192] in which 17 patients were implanted with a 20 Fr silastic tube with a Dacron cuff at the peritoneal surface, all of whom did well with repeated removal of ascites.[193] A disadvantage of repeated drainage of ascites via any means is that, among patients who do survive and undergo a number of procedures, there is a large amount of protein loss, particularly when compared with peritoneovenous shunting, in which the fluid is rerouted to the vascular system and protein might be retained. The most impressive protein loss seen comes from the Lomas and coworkers study,[191] in which the average albumin level fell from 2.8 g/dL to 1.8 g/dL. Other series, however, have demonstrated much smaller decreases in albumin level, especially when high-protein diets were used. If one considers that these patients have advanced, refractory malignancy, protein and albumin loss due to repeated drainage is probably not all that significant but should still be monitored.[189,192] There is a risk of infection with superficial catheters; in the aforementioned study by Belfort and colleagues,[192] in which patients were given cuffed catheters, 47% of patients (8 of 17) developed positive ascitic fluid surveillance cultures, and 12% (2 of 17) required removal due to "significant infection." In a study using a tunneled catheter (the Denver Pleurx catheter), 0 of 10 patients developed infections requiring catheter removal.[189] Although no comparison studies have been done with peritoneal catheters, randomized studies involving other catheter systems clearly have demonstrated decreased infection rates when catheters had their cuffs placed subcutaneously in a tunnel rather than at the surface.[192] Percutaneous catheters therefore remain an option for some patients, although they are not used frequently.

Surgery

Sugarbaker[194] has been an advocate of peritonectomy, in which various parts of the peritoneum, omentum, and some intra-abdominal organs are removed as a method of tumor cytoreduction (akin to debulking of ovarian cancer, which has now become a standard of care) in preparation for intraperitoneal chemotherapy. This approach has been used for patients with peritoneal carcinomatosis with the chemotherapy tailored toward the nature of the malignancy. Studies have shown modest success with this procedure in increasing survival time and in the prevention of the development of malignant ascites, but its use in the treatment of ascites has not been well evaluated.[195,196] It is likely to be of minimal use, because patients with advanced, malignant ascites often have chemotherapy-refractory disease and have too much systemic disease to benefit from cytoreduction; removal of ascites alone as palliation can usually be accomplished through much easier means. The role of intraperitoneal chemotherapy in the prevention of the development of ascites is intriguing, however, and is discussed next.

Intraperitoneal Therapy

Direct intraperitoneal therapy has been tried for quite some time in an attempt to deliver higher doses of chemotherapy locally with minimal systemic absorption and distribution.[197] Intraperitoneal therapy has been used to treat both ascites and intra-abdominal malignancies, such as ovarian cancer. Patients with disease responsive to chemotherapy are most likely to benefit from this procedure. In this manner, the intraperitoneal administration of cisplatin has been well studied, because ovarian cancer is one of the most common intra-abdominal tumors with a predilection for causing ascites and is very responsive to systemic cisplatin chemotherapy. Simultaneous administration of intravenous thiosulfate might decrease systemic absorption of cisplatin. Several investigators have found that intraperitoneal administration of cisplatin is indeed effective for control of intra-abdominal ovarian cancer, with perhaps better efficacy than that given intravenously.[198] The complexity of these procedures, their limited availability, and the fact that many or most patients who present with intractable ascites have already undergone numerous treatments and are probably resistant to chemotherapy, limits the role for intraperitoneal therapy in the management of ascites except in some special situations such as ovarian cancer and, of course, in clinical trials. It is important for the role of intraperitoneal chemotherapy immediately after initial surgical exploration for malignancy

to be examined further to determine whether it produces a survival advantage or a reduction in the rate of development of malignant ascites.

Summary

The level of aggressiveness that one undertakes in the management of ascites is highly dependent on the overall clinical status of the patient. For those patients with chemotherapy-sensitive tumors who are not heavily pretreated, chemotherapy should be an early step in management, particularly in cases of ovarian and hematologic malignancies. Although diuretic therapy probably does not have much of an effect, one can consider an early trial, in that it is relatively easy to carry out and can be particularly helpful for patients with increased portal pressures due to massive hepatic metastases. For those patients with a limited life expectancy but a large amount of ascitic fluid causing symptoms, paracentesis on an as-needed basis should be used, with the caveat that recurrence of the effusion is virtually assured and repeat paracentesis required unless other steps are taken. Intraperitoneal therapy of many types can be considered where available, particularly for ascites due to ovarian cancer or in the setting of a clinical trial. Patients who are likely to live a long time without chemotherapy-responsive tumors should be considered for a shunt or catheter drainage device, or for any available clinical trial.

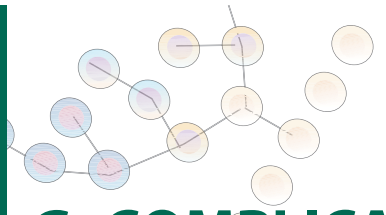
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G. COMPLICATIONS OF THERAPY

61 Neurologic Complications

Mark R. Gilbert

SUMMARY OF KEY POINTS

Incidence of Chemotherapy- and Radiation Therapy-Induced Neurotoxicity

- The actual incidence of treatment-related neurotoxicity is unknown, but the frequency is increasing.
- Improvements in supportive care, but not neuroprotective regimens, have allowed dose escalation for many drugs, so neurotoxicity often is the dose-limiting factor.
- Increased survival from cancer has resulted in an increasing prevalence of late-onset neurotoxicity.
- Newer treatments directed at tumors in the central nervous system often result in neurotoxicity, particularly with therapies administered directly into the brain.

Etiology of Neurotoxicity

- Direct effects on neurons, myelin, and supporting glial cells have been implicated.
- Effects on neuronal cytoskeleton and axonal transport, neuronal metabolism, and neurotransmitter function are the most commonly hypothesized mechanisms of toxicity. Alterations in specific ion channels have been reported in some cases of chemotherapy-induced peripheral neuropathy.

Evaluation of the Patient

- In general, chemotherapy or radiation toxicity should be considered a diagnosis of exclusion.
- Specific diagnostic tests do not exist for treatment-induced toxicity from most agents and regimens in use.
- The diagnosis often is made by recognition of a neurotoxic syndrome temporally related to treatment and by exclusion of other causes of neurologic dysfunction.

Grading of the Complication

- Grading scales are of limited value for monitoring individual patients and are used only for study populations.
- More refined grading for management is a component of neurologic and neuropsychologic testing.

Treatment

- With most neurotoxic syndromes, specific treatment is not available.
- Prevention or reduction of risk often is possible with proper monitoring or treatment planning.
- New agents are under development for management or prevention of neurotoxicity, but careful testing is required to ensure that the antineoplastic effect is not compromised.

INTRODUCTION

The neurotoxic effects of cancer chemotherapeutic agents and radiation therapy are of increasing importance in the management of patients with cancer. Although the exact incidence of treatment-related neurotoxicity is unknown, the frequency is certainly increasing. Several factors are known to be responsible for this increase in incidence of treatment-related neurotoxicity.

First, recent advances in supportive care allow the use of much higher doses of chemotherapeutic agents. For example, administration of granulocyte or granulocyte-macrophage colony-stimulating factors allows use of drug doses that previously would have caused severe bone marrow suppression. Unfortunately, similar factors for prevention of development of neurotoxicity do not exist. In initial studies of paclitaxel, a novel antitubulin agent, myelosuppression was dose-limiting. Use of colony stimulating factors has allowed dose escalation, but the development of severe peripheral neuropathy has been described in many patients receiving these higher doses.[1,2] Similarly, nephrotoxicity and myelosuppression limited dose escalation of cisplatin in the past. Innovative hydration schemes and the availability of colony stimulating factors have reduced the risk of these toxicities. Dose escalation has resulted in severe neurotoxicity and ototoxicity, now considered the dose-limiting toxic effects.[3]

Second, improvements in cancer treatment have increased the duration of survival from many malignant diseases. As a consequence, treatment-related neurotoxicity with a long latency between treatment and onset of symptoms is being recognized with increasing frequency. Childhood acute lymphoid leukemia often was fatal until recognition of the central nervous system (CNS) as a sanctuary for leukemia cells. Treatment of cerebrospinal fluid (CSF) with direct administration of methotrexate and use of cranial irradiation resulted in a marked increase in long-term remission and cure. This treatment of the CNS, however, also caused delayed neurotoxicity. Severe dementia developed in some patients, and many others experienced a decline in cognitive function years after completion of treatment.[4–8] Similarly, combined-modality treatment using both whole-brain irradiation and chemotherapy with high-dose methotrexate has markedly improved survival over that achieved with radiation therapy alone. A marked increase in leukoencephalopathy, however, has been observed with this combination regimen, particularly in the elderly.[9]

Third, newer agents, including biologic response modifiers, and novel routes of administration designed specifically to target the nervous system for management of brain metastases or primary brain tumors are very likely to result in an increase in neurotoxicity. Likewise, chemical disruption of the blood-brain barrier to improve drug delivery to brain tumors has led to a marked increase in neurotoxicity compared with that with standard systemic administration. Results of animal studies have demonstrated that chemical opening of the blood-brain barrier results in a marked increase in exposure of normal brain parenchyma to chemotherapy with a much smaller increase in delivery to the tumor.[10] Implantation of carmustine

(BCNU)-impregnated polymer wafers into the resection cavity has shown a survival benefit for patients with glioblastoma but with an increase in the incidence of brain necrosis and infection.[11]

Continued improvement in cancer treatment will result in prolonged survival and an increased rate of cure. Therefore long-term morbidity, particularly development of irreversible neurotoxicity, is a critical concern. This chapter discusses the agents most commonly responsible for neurotoxicity, describes the differential diagnosis for and evaluation of patients with neurologic dysfunction, and addresses management and prevention of chemotherapy- and radiation therapy-induced neurotoxicity.

SPECIFIC AGENTS

Cytosine Arabinoside

Cytosine arabinoside (ara-C), or cytarabine, can cause a wide range of neurotoxic effects. The toxicity that develops depends on the route of administration and the dose used.

Cerebellar Toxicity

Systemic administration of high-dose (greater than 1 g/m^2) intravenous ara-C can cause acute cerebellar toxicity.[12–15] Onset of neurologic symptoms generally is acute and often is noticed during administration of a multiday regimen.[12,13,16] Patients exhibit evidence of global cerebellar dysfunction, which manifests as truncal, limb, and gait ataxia; dysarthria; and nystagmus. In some cases, permanent cerebellar dysfunction results; in others, a mild cerebellar syndrome develops that resolves promptly after completion of the chemotherapy.[12,13]

Patients with irreversible cerebellar damage have a characteristic and selective loss of Purkinje cells in the cerebellum.[15] The pathogenesis of the specific cellular damage is unknown, and no pathologic findings have been described in the cerebella of patients who have recovered from transient cerebellar dysfunction.

The incidence of irreversible cerebellar toxicity with high-dose ara-C regimens has been reported to be 8% to 20%. Factors reported to affect the likelihood of development of cerebellar toxicity include size of current dose, cumulative dose, age (persons older than 50 years are at higher risk), and renal status (renal dysfunction with impaired drug clearance is associated with increased risk).[13,14,17,18] Whether patients in whom reversible cerebellar dysfunction develops with previous treatment are at higher risk for permanent dysfunction is unknown.

Encephalopathy

Acute encephalopathy, often accompanied by seizures, occurs less frequently than cerebellar dysfunction in patients receiving high-dose intravenous ara-C.[13] In most cases, somnolence and lethargy completely resolve soon after completion of chemotherapy. Patients with persistent encephalopathy usually have had additional medical problems, such as severe infection.[18] In addition, leukoencephalopathy that is clinically and pathologically indistinguishable from the leukoencephalopathy associated with methotrexate has been reported as a late complication of high-dose intravenous ara-C administration and with administration of ara-C directly into the CSF.[13]

Spinal Cord Toxicity

Direct administration of ara-C into the lumbar thecal space has been reported to cause myeloradiculopathy.[19–23] Patients exhibit evidence of both spinal cord and nerve root dysfunction. This complication is uncommon, usually being found only after an extensive course of intrathecal chemotherapy. In many instances, patients have received both intrathecal ara-C and methotrexate.[24,25] Neurologic signs typically are noticed days to weeks after treatment, although myelopathy may develop within minutes of administration. In most cases, loss of neurologic function progresses slowly over days, and only one half of patients demonstrate improvement or achieve full recovery.

Several hypotheses have been proposed for the mechanism of chemotherapy-induced myelopathy. Focal damage from injection of hyperosmolar solution,[26] barbotage from injection,[27] and direct toxic effects of chemotherapy on the spinal cord parenchyma[20] are the most common proposed mechanisms of subacute myelopathy. Histologic examination of the spinal cord shows focal areas of necrosis, most marked along the periphery of the spinal cord.[20,21,24] Microscopic examination shows axonal swelling with accompanying demyelination.[20,21,24] A newer formulation of ara-C uses a liposomal preparation. Although the pharmacokinetics of drug delivery in the CSF is improving, an increase in the incidence of arachnoiditis has been observed, and isolated cranial nerve palsies may be more frequent. With chemotherapy-induced spinal cord injury, myelin basic protein levels in the CSF may be elevated before marked neurologic damage occurs.[24,25] For patients with early symptoms, such as paresthesia, back pain, or Lhermitte's sign, the level of myelin basic protein in the CSF should be measured. If the level is elevated, further lumbar administration of chemotherapy should be avoided.[25]

Other Neurotoxicity Associated with Cytosine Arabinoside

Peripheral neuropathy has been reported after administration of high-dose ara-C.[28] In this report, symmetrical sensorimotor polyneuropathy developed 2 weeks after completion of treatment. Nerve biopsy demonstrated axonal damage with patchy regions of demyelination. In addition, a case of reversible parkinsonism has been reported after administration of high-dose ara-C.[13] Onset of tremor, bradykinesia, and mask-like facies were observed 3 weeks after completion of treatment. Treatment with carbidopa-levodopa provided only transient improvement. All parkinsonian features, however, resolved over 12 weeks.

L-Asparaginase

Cerebrovascular Events

Cerebrovascular events caused by L-asparaginase-induced coagulopathy constitute the most common form of neurotoxicity associated with L-asparaginase treatment. Both thrombotic and hemorrhagic strokes have been reported in patients receiving L-asparaginase.[29–31] Thrombosis of cerebral venous sinuses also has occurred in patients receiving this agent. The clinical manifestations of sinus thrombosis usually are acute and severe headache, nausea, and vomiting caused by the rapid increase in intracranial pressure. Changes in level of consciousness occur most frequently with sagittal sinus thrombosis with bilateral cerebral hemisphere involvement. Although most patients with sinus thrombosis demonstrate acute and rapidly progressive changes in neurologic function, some patients experience only headache and mild neurologic dysfunction.[29]

Patients in whom neurologic symptoms develop during L-asparaginase therapy should be evaluated with either head computed tomography (CT) or magnetic resonance imaging (MRI). MRI usually is preferred because it often depicts sinus thrombosis by absence of a flow void in the venous sinus. MRI also depicts early signs of ischemic brain injury, particularly on diffusion-weighted imaging, and punctate hemorrhages also may be seen.

Neuropsychiatric Effects

Less frequently, L-asparaginase treatment has been associated with development of neuropsychiatric symptoms,[32] most notably depression, delusions, hallucinations, disorientation, and altered level of consciousness. In the series described by Holland and colleagues,[32] 5 of 19 patients with acute leukemia experienced psychiatric symptoms. The onset of symptoms occurred 2 to 19 days after treatment, and the symptoms resolved completely in three patients who lived longer than 6 weeks. Neuropathologic analysis of the brains in two cases revealed leukemic infiltration. The combination of leukemic involvement of the CNS and treatment-induced depletion of L-

asparagine and L-glutamine in the brain has been proposed as a possible factor contributing to development of psychiatric symptoms.

Busulfan

Busulfan administration has been reported to cause generalized tonic-clonic seizures.[33] This reaction has been reported with high-dose treatment as a preparative regimen for bone marrow transplantation. Prophylactic treatment with anticonvulsants, particularly phenytoin, has been shown to reduce the risk of seizures.[34]

Methotrexate

Methotrexate can cause acute, subacute, or chronic neurotoxicity.

Acute Neurotoxicity

Administration of high-dose intravenous methotrexate (dosage greater than 3 g/m^2) has been associated with development of acute encephalopathy characterized primarily by somnolence, confusion, and seizures.[5,35] Although the pathogenesis of this syndrome is unknown, laboratory studies with rats have shown profound metabolic alteration in the brain after intravenous administration of high-dose methotrexate.[36] In these experiments, a widespread decrease in glucose utilization and protein synthesis was found. In similar studies, folinic acid (leucovorin) markedly diminished these metabolic effects,[37] a finding that suggested a possible role for leucovorin in decreasing the severity of methotrexate-induced somnolence syndrome. Although the somnolence and confusion that occur with acute methotrexate toxicity resolve completely, evidence shows that patients in whom this syndrome develops are at greater risk for chronic methotrexate-induced neurotoxicity.[38] Cases have been reported in which, despite resolution of the clinical symptoms, white matter changes persist on MR images.[39]

Subacute Toxicity

Subacute methotrexate-induced neurotoxicity generally develops weeks after methotrexate administration and occurs most frequently in patients who also have received cranial radiation.[5] Transient inhibition of myelin formation is thought to be the mechanism of toxicity. The syndrome is completely reversible over weeks, and corticosteroid treatment may accelerate recovery.

Chronic Neurotoxicity

Chronic methotrexate neurotoxicity is known as leukoencephalopathy. This syndrome develops months to years after methotrexate administration and has been seen after both intravenous and intrathecal administration of methotrexate.[4–8,40–50] Cranial radiation therapy, particularly when it precedes methotrexate administration, greatly increases the risk of leukoencephalopathy.[5,51] In addition, elevated CSF methotrexate concentration has been associated with an increased risk of neurotoxicity.[42] Younger patients are at higher risk for leukoencephalopathy.[52,54] Clinically, patients show progressive loss of cognitive function and focal neurologic signs, which may progress to profound dementia, coma, or death.[4–6,8,43] Some patients experience seizures as a consequence of widespread neuronal injury. No treatment is known, and the neurologic deficits generally are irreversible. Brain imaging with MRI or CT often shows large areas of abnormalities in cerebral white matter (Fig. 61-1). Elevated levels of myelin basic protein in CSF have been reported in patients with progressive neurologic dysfunction from methotrexate-induced leukoencephalopathy.[44]

Neuropathologic examination shows wide areas of coagulative necrosis with swollen axonal cylinders and demyelination.[4,40,45] Regions with vascular changes, particularly microangiopathic calcifications, are characteristic.[46,49,54] The pathogenesis of leukoencephalopathy is unknown, but results of laboratory studies with brain explant cultures suggest that the primary injury may be neuronal (axonal), and the characteristic demyelination may be a secondary phenomenon.[55]

Spinal Cord Toxicity

Chemotherapy-induced myelopathy is an uncommon toxicity of intrathecal treatment with methotrexate.[56–60] Myelopathy generally de-

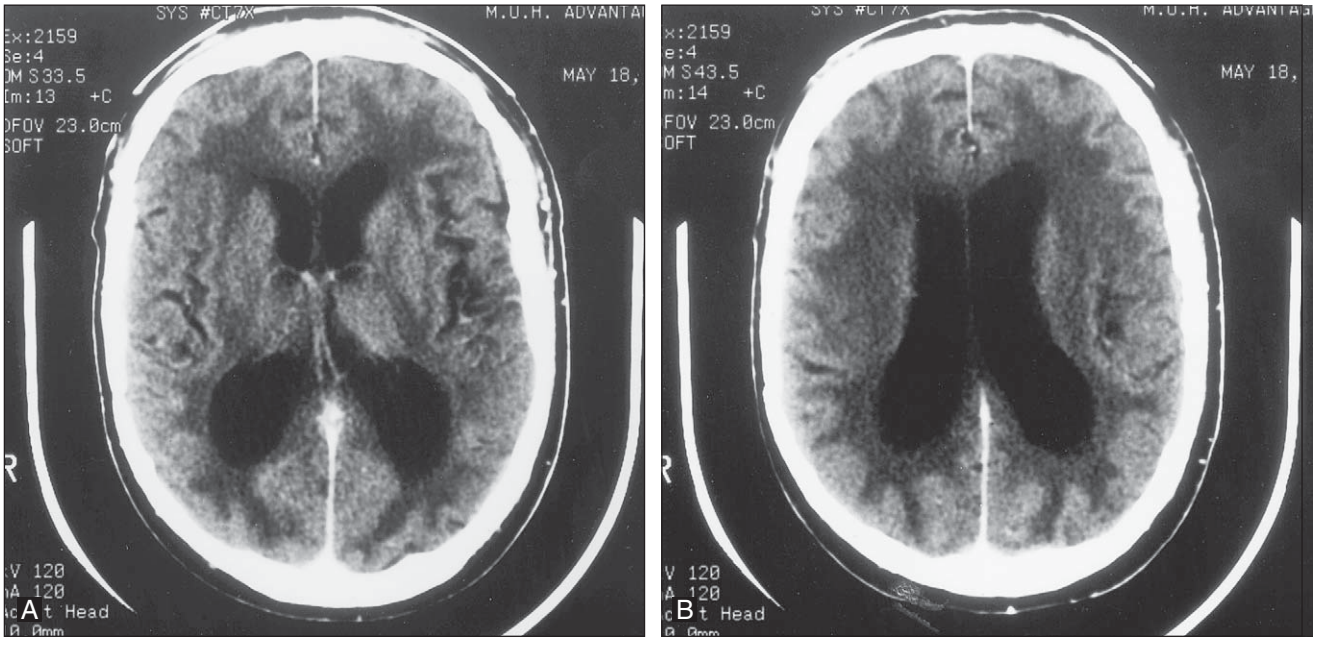


Figure 61-1 • Methotrexate-induced leukoencephalopathy. The patient was a 63-year-old man with meningeal lymphoma who underwent whole-brain radiation therapy. Several months later, his meningeal lymphoma recurred and was treated with intrathecal methotrexate. Progressive dementia developed. **A** and **B,** CT scans obtained 6 months after completion of intrathecal chemotherapy. Widespread destruction of white matter and diffuse atrophy are evident.

velops only after extensive intrathecal treatment. Both methotrexate and ara-C have been associated with myelopathy. The clinical syndrome of methotrexate-induced myelopathy is identical to that with ara-C (see earlier under "Cytosine Arabinoside"). Loss of neurologic function may be progressive; only approximately one half of patients experience either complete or partial recovery. The onset of symptoms generally is subacute. Symptoms develop over days to weeks, usually beginning days to weeks after administration of chemotherapy. The histologic findings are identical to those with ara-C-induced myelopathy.

Vinca Alkaloids

Treatment with vinca alkaloids, particularly vincristine, commonly is associated with neurotoxicity.

Peripheral Neuropathy

Peripheral neuropathy is the toxicity associated most frequently with vincristine and correlates with the cumulative dose of the drug.[61–66] Loss of deep tendon reflexes occurs in nearly all patients who receive several vincristine treatments. Distal sensorimotor polyneuropathy develops with continued treatment.[62,64,66] The predominant neurologic finding is loss of pain and temperature sensation in a stocking-and-glove distribution. Motor and vibration or proprioceptive loss usually is milder and occurs later with continued treatment.

The mechanism of toxicity is unknown but probably is related to the effects of the vinca alkaloids on microtubules. Vinca-induced disruption of axonal microtubules causes marked disarray of the axonal cytoskeleton and formation of neurofilamentous masses[65,67–71] and reversible neurofilament-containing crystalloid inclusions.[72] These effects are very likely to influence axonal transport, which depends on microtubules as the transport mechanism.[73] In patients with underlying neuropathy, such as diabetic neuropathy or Charcot-Marie-Tooth disease, vinca-induced neuropathy may be severe even with low cumulative doses.[74] Severe, even life-threatening neuropathy has been reported after administration of as little as 2 mg to patients with Charcot-Marie-Tooth disease (hereditary motor sensory neuropathy type 1), and evidence suggests that patients should be screened for this disorder before administration of vincristine.[74–76] Previous radiation treatment of peripheral nerves also increases the neurotoxic effects of vincristine.[77]

In addition to peripheral neuropathy, autonomic neuropathy and cranial nerve palsy have been reported. Autonomic neuropathy most commonly manifests as gastrointestinal dysmotility (obstipation or constipation). In severe cases, paralytic ileus and intestinal perforation have resulted.[66,78] Less frequently, orthostatic hypotension develops as a consequence of autonomic involvement. Vincristine-induced mononeuropathy involving the femoral nerve has been reported. Vincristine can cause cranial nerve palsies, affecting the optic (II), oculomotor (III), trigeminal, abducens, facial, acoustic, and vagus nerves.[62,66,79,80] In addition, patients occasionally report facial pain with vincristine treatment, possibly due to a transient effect on the trigeminal nerve or ganglion.[66]

Central Nervous System Effects

Vincristine has been reported to cause encephalopathy, coma, and seizures.[81–85] These effects are rare and reversible. The underlying mechanism is unknown in most cases, although in some reports these neurologic effects have been attributed to vincristine-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH) and hyponatremia.[84,86–89] The mechanism of SIADH is unknown, but serum antidiuretic hormone levels are elevated.

Other Toxicity Associated with Vinca Alkaloids

Quadriplegia with vincristine treatment has been reported, in one case in association with Guillain-Barré syndrome.[90–92] The time of onset of has been variable. In some patients, quadriparesis develops soon after vincristine treatment, whereas in others, it occurs several weeks after treatment. In most instances, the weakness is partially reversible.[90]

Myopathy has occurred with vincristine therapy.[61,93] No clinical correlate has been found in cases in which histopathologic examination of muscle tissue has revealed spheromembranous degeneration.

Cisplatin

Peripheral Neuropathy

The most common neurotoxicity associated with cisplatin is peripheral neuropathy. The neuropathy predominantly involves the large sensory fibers, which mediate vibration and proprioceptive function. Deep tendon reflexes are lost because of toxic effects on the large myelinated sensory fibers, which provide the afferent arm of the reflex arc. Involvement of motor function generally is mild and is seen only in patients with severe sensory neuropathy. Development of neuropathy is dose-related. The earliest signs are detected when the cumulative dose exceeds 300 mg/m^2.[94] Schedule of administration may be a significant factor, because the reported incidence of neuropathy has been higher in patients receiving treatment on 5 consecutive days than in patients on a regimen with a shorter dosing schedule but the same cumulative dose.[95–97] Continued treatment with cisplatin in patients with neuropathy can result in severe sensory ataxia, which often impairs ambulation. The neuropathy is partially reversible, and patients with mild impairment generally are more likely to experience full recovery.[96] A longitudinal study confirmed there is often a delay in the onset of neuropathy. Eleven percent of the patients had neuropathy at the end of treatment, but the incidence had increased to 65% 3 months later. One year later, most of the patients had recovered, only 17% having persistent symptoms.[98]

The pathogenesis of cisplatin-induced neuropathy is unknown. Neuropathologic studies have shown involvement of the large sensory fibers with regions of axonal swelling and myelin breakdown and, in more severe cases, axonal loss.[99] The spinal cord shows almost exclusive involvement of myelinated axons in the dorsal columns—a finding consistent with the clinical features of vibratory and proprioceptive loss.[100] Platinum concentration in peripheral nerve and spinal ganglia was 20 times greater than in brain from patients at autopsy.[98] This finding may explain the predilection of cisplatin for sensory fibers and sparing of the CNS.

Spinal Cord Toxicity

Cisplatin treatment has been associated with the development of Lhermitte's sign, which is an electric shock-like sensation down the spine or into the extremities with neck flexion.[101,102] The phenomenon most commonly is associated with spinal cord demyelinating lesions in multiple sclerosis. A similar mechanism, cisplatin-induced demyelination, may be the cause in patients with this syndrome. Most patients achieve full recovery, although, as with recovery from cisplatin-induced neuropathy, improvement may take several months.

Other Neurotoxicity Associated with Cisplatin

Other neurotoxic effects reported with cisplatin include optic neuropathy, seizures, encephalopathy, and cortical blindness.[103] These complications of treatment are rare. Patients with optic neuropathy may have prolonged vision loss and demonstrate pallor of the optic disk.[104,105] The reported cases of seizures and cortical blindness have been self-limited, all patients recovering fully.[106–108] The cause of the seizures and cortical blindness from cisplatin treatment is unknown but may be similar to that in toxicity from other heavy metals (lead, thallium), although endovascular injury has been proposed as a possible mechanism.[103,107] Many of these patients have white matter abnormalities on brain MRI, consistent with posterior reversible encephalopathy syndrome (PRES; see later under "Dementia and Encephalopathy"). A syndrome also has been described in which patients experience focal neurologic deficits and seizures after intra-

venous administration of cisplatin. In these patients, findings on brain MRI were normal. One patient experienced recurrence of encephalopathy with cisplatin rechallenge, and a second patient died of status epilepticus. At autopsy, the brain of the latter patient showed only focal gliosis.[109]

Toxicity Associated with Intra-arterial Administration

Intra-arterial administration of cisplatin causes focal toxicity. Administration into the internal carotid artery can cause severe retinal toxicity.[110,111] Supraophthalmic administration can cause focal areas of brain parenchymal necrosis with resulting seizures and neurologic impairment.[111]

Ototoxicity

Ototoxicity is a dose-related effect of cisplatin. Patients receiving more than 200 mg/m^2 are at high risk for the development of hearing loss.[112] Hearing loss, particularly when it is moderate to severe, often is permanent.[112,113] Results of most studies suggest that patients with underlying hearing loss are at greater risk for functional hearing loss, although a small series found no relation to previous hearing loss.[112,114,115] Additional risk factors include age older than 46 years and previous cranial radiation therapy involving the ears or temporal lobes.[113,114] Patients with normal hearing lose high-frequency hearing first, but with continued treatment, hearing may be lost in all frequency ranges.[112] A rapid screening audiogram technique has been developed to monitor patients undergoing cisplatin treatment.[115] Postmortem pathologic examination of cochleae from patients with cisplatin-induced ototoxicity reveals extensive loss of the outer hair cells and less effect on the inner hair cells.[112]

Oxaliplatin

Oxaliplatin has been shown to cause two distinct types of neuropathy: acute and chronic.[116] The acute neuropathy syndrome may begin during oxaliplatin infusion or up to 1 to 2 days after completion of treatment. Patients experience paresthesia and dysesthesia of the hands and feet, jaw tightness, and a sensation of loss of breathing without respiratory distress. The last syndrome has been called pharyngolaryngodysesthesia.[117] Dysesthesias constitute the most prominent symptom, although many patients describe pain that is more like muscle spasms of the jaw, tongue, and extremities. Some patients are unable to relax a tensed muscle, such as a grasp, during these episodes. The incidence of acute neuropathy increases with continued dosing, and an increased incidence also has been noted with higher dosing regimens. Overall, acute, severe (grade 3 or 4) neurotoxicity has been estimated to occur in 10% of patients with the initial dose, but that increases to 50% by the ninth cycle of treatment.[118] Most patients experience some resolution of symptoms, but most have residual neuropathic symptoms up to 6 months after treatment cessation. The pathogenesis of acute oxaliplatin neuropathy is thought to be related to drug-induced alterations in voltage-gated Na^+ channels.[119]

The development of chronic neuropathy from oxaliplatin is related to cumulative dose, with most studies reporting early neuropathy noted after a total dose of greater than 540 mg/m^2. As with cisplatin, chronic oxaliplatin peripheral neuropathy affects large caliber sensory nerves, with the resultant loss of proprioceptive function as the predominent clinical manifestation. Additionally, the Lhermitte's-like phenomenon described with cisplatin also has been reported with oxaliplatin.[120] The chronic neuropathy may abate over several months after the cessation of treatment, although some reports suggest that symptoms may persist in a small percentage of patients for longer than 5 years.[121]

Cyclophosphamide

Cyclophosphamide can indirectly cause metabolic encephalopathy and seizures. High-dose cyclophosphamide can result in SIADH.[122–125] Unrecognized, this syndrome can lead to severe hyponatremia, coma, and seizures. Although not reported in the literature in association with cyclophosphamide-induced SIADH, rapid correction of hyponatremia can result in central pontine myelinolysis, which is irreversible loss of the central pontine pathways.[126] A locked-in syndrome may develop, or a chronic vegetative state can result from central pontine myelinolysis.

Ifosfamide

The most common manifestation of neurotoxicity associated with ifosfamide is encephalopathy. Severe ifosfamide-induced encephalopathy has been reported in children and adults.[127–131] Neurologic deterioration usually begins within hours of administration of ifosfamide.[127,129,131] Confusion, hallucinations, and aphasia are the most common initial signs. Progression to coma generally is rapid. Some patients also exhibit clinical evidence of seizure activity or myoclonus with intermittent twitching of the extremities.[127,130] Electroencephalography (EEG) shows severe slowing with delta wave activity and can display evidence of seizure activity.[127,130] In most cases, encephalopathy completely resolves over several days after cessation of therapy, although in one study, investigators found persistent mental status changes in some patients 10 weeks after treatment.[132] A recent study of 60 patients reported the incidence of ifosfamide neurotoxicity to be 26%.[133] Several risk factors have been reported to predispose patients to development of neurotoxicity from ifosfamide. These factors include low serum albumin concentration,[131] high serum creatinine concentration, pelvic cancer,[134] and previous treatment with cisplatin.[135] A recent report, however, could not confirm any risk factor except age, with an increased incidence of encephalopathy in younger patients.[133] Ifosfamide treatment has been associated with an extrapyramidal syndrome characterized by choreoathetosis, blepharospasm, and opisthotonic posturing.[136] These abnormalities resolved over several days.

5-Fluorouracil

Cerebellar Toxicity

5-Fluorouracil (5-FU) causes acute cerebellar dysfunction. Patients experience moderate to severe gait ataxia, scanning speech, appendicular ataxia marked by severe dysmetria, and often nystagmus.[137–140] These neurologic abnormalities resolve completely within several days after completion of therapy. The incidence of cerebellar toxicity has been reported to be 3% to 7% and correlates with dose and the interval between treatments.[141]

Neuropsychiatric Symptoms

Organic brain syndrome has been reported with 5-FU treatment.[142] Confusion and disorientation develop without evidence of cerebellar dysfunction. In one patient, retreatment with 5-FU resulted in a similar episode of mental deterioration. Oculomotor disturbances, specifically vergence disturbances characterized by diplopia on viewing distant objects, were reported in two patients.[143] A possible association of 5-FU treatment with recurrent acute toxic neuropathy also has been reported.[144]

Other Neurotoxicity Associated with 5-Fluorouracil Treatment

Several cases have been reported of multifocal inflammatory leukoencephalopathy associated with use of 5-FU and levamisole in adjuvant therapy for colon carcinoma.[145] Affected patients have a subacute neurologic syndrome characterized by focal neurologic findings and cognitive dysfunction. MRI shows widespread patchy white matter lesions that enhance with administration of gadolinium (Fig. 61-2). Histopathologically these lesions are characterized by an intense inflammatory infiltrate with extensive loss of myelin, but the axons generally are spared. Complete recovery occurs over weeks after cessation of 5-FU and levamisole administration. The benefit of corticosteroid treatment is uncertain in accelerating

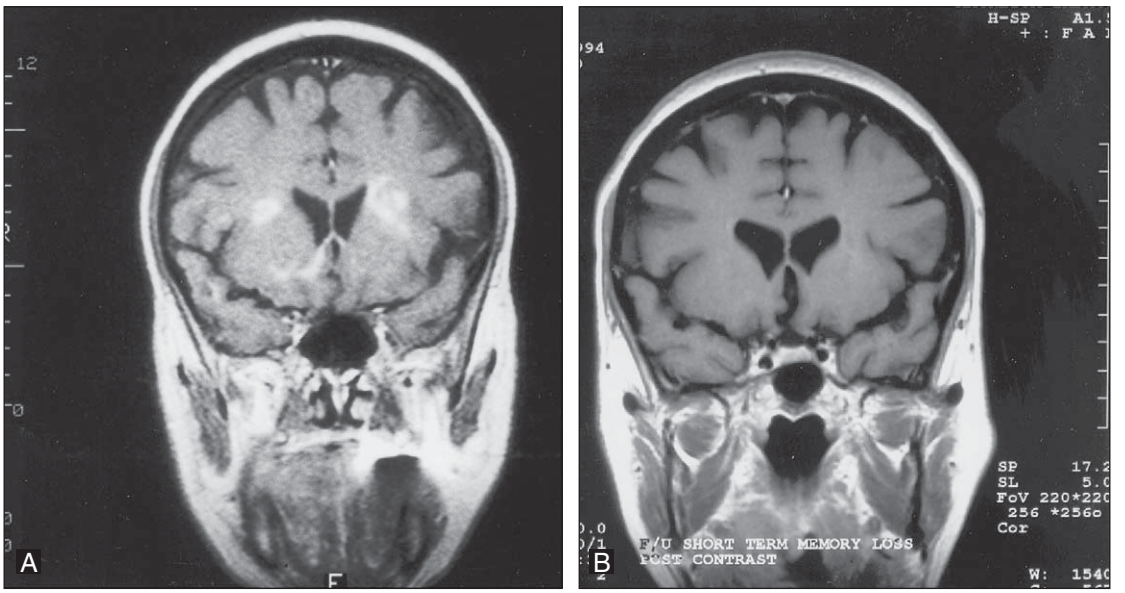


Figure 61-2 • Levamisole–5-fluorouracil (5-FU) multifocal inflammatory leukoencephalopathy. The patient was a 54-year-old woman in whom progressive encephalopathy and focal neurologic signs developed 4 months after initiation of adjuvant therapy with levamisole and 5-FU for colon carcinoma. **A,** Several white matter lesions are present, many of which enhanced with administration of gadolinium–ethylenediaminetetra-acetic acid (EDTA). **B,** Six months later, the patient had fully recovered. Resolution of the enhanced lesions is evident.

recovery. The pathogenesis of this idiosyncratic reaction is unknown, although levamisole can affect blood-brain barrier function, and this effect may be potentiated by 5-FU. Recognition of this treatment-induced leukoencephalopathy can be important, because the clinical presentation and MRI findings can be misinterpreted as brain metastasis. There are isolated reports of encephalopathy with single-agent therapy with 5-FU and recently reports of encephalopathy and coma with use of capecitabene, the oral prodrug of 5-FU.[146–148]

Fludarabine

Fludarabine can cause somnolence and a mild peripheral neuropathy at low doses.[149] At high doses, white matter changes, particularly in the occipital lobes and brainstem, have been reported.[150] Encephalopathy and cerebellar signs are common with this leukoencephalopathy. Progressive symptoms eventuating in coma and death have been reported. Pathologic evaluation has shown necrotic changes in the involved white matter.[150] The risk of development of progressive multifocal leukoencephalopathy, due to an infection with the JC virus, may be increased with fludarabine treatment. Diagnosis requires biopsy of involved brain or polymerase chain reaction testing of CSF.[151]

Nitrosoureas

Central Nervous System Toxicity

Nitrosoureas, most commonly carmustine (BCNU), can cause encephalopathy characterized by a progressive decline in cognitive function, development of seizures and coma, and death.[152–154] This complication most commonly is observed with intracarotid or supraophthalmic arterial delivery of nitrosourea, although a similar syndrome has been reported in patients who receive very high-dose intravenous carmustine treatment.[155] Histopathologically the toxicity associated with intra-arterial therapy is characterized by necrosis, regions of demyelination, edema, and axonal loss limited to the region perfused by the intra-arterial therapy. Because the predominant changes have been seen in the white matter, the condition is called *leukoencephalopathy*, indistinguishable from the changes seen with methotrexate and ara-C treatment. Similar pathologic changes are seen with high-dose intravenous carmustine, but both cerebral hemispheres are involved.[155] In addition, focal brain necrosis has been reported with intra-arterial nitrosourea treatment. This toxicity is thought to be a consequence of "streaming" of the drug along the vessel wall, without mixing with arterial blood.[156] This stream of concentrated drug may flow into a small branch of the artery. A small region of brain (or tumor) thus receives an enormous dose of drug, and focal necrosis results.

A biodegradable polymer containing BCNU has been shown effective in the management of recurrent malignant glioma. The BCNU-impregnated polymer also has been approved for treatment of newly diagnosed glioblastoma. This treatment usually is followed by conventional external beam radiation therapy.[157] This combination may increase the incidence of treatment-associated necrosis. The wafers are placed into the tumor cavity after surgical resection. Results of clinical trials indicate that the local therapy is well tolerated, although an increase in peritumoral edema necessitates a temporary increase in corticosteroid dose, and there are reports of treatment-associated necrosis.[158]

Retinal Toxicity

Retinal toxicity has been reported with intracarotid administration of nitrosoureas, particularly carmustine.[111,159] This retinopathy is painful and often results in permanent vision loss. Infusion above the ophthalmic artery eliminates this toxicity but may increase the likelihood of streaming (see preceding discussion, "Central Nervous System Toxicity").

Procarbazine

Early reports of procarbazine use describe neurotoxicity, both peripheral and CNS toxicity, as common side effects of treatment.

Peripheral Neuropathy

The peripheral neuropathy described with procarbazine use most commonly is described as paresthesia, often subjective and generally

transient. The incidence of paresthesia ranges from 2% to 20%; this variability may be related to dose or treatment schedule.[160–162]

Central Nervous System Toxicity

Signs of CNS depression, ranging from mild drowsiness to profound stupor, have been reported.[160,162] This toxicity worsens with use of phenothiazine to control emesis and may be related to the monoamine oxidase inhibitor-like qualities of procarbazine. No report has discussed the use of dietary restrictions in patients receiving procarbazine. CNS depression was reported to occur in 14% to 33% of patients in these series.[160–162]

Paclitaxel and Docetaxel

Paclitaxel and docetaxel are novel antineoplastic agents that bind to tubulin and promote formation and stabilization of microtubules.[144,163,164] In phase I and II testing of paclitaxel, myelosuppression was the dose-limiting toxicity. Since colony stimulating factors (e.g., granulocyte macrophage and granulocyte colony stimulating factors) have become widely available, however, peripheral neuropathy has become the dose-limiting toxicity.[1,2] The neuropathy is predominantly sensory, particularly affecting small-caliber (pain and temperature) sensory fibers.[165] The effect on motor fibers and large-caliber sensory fibers (vibration and proprioception) is less severe. Nerve conduction studies of large myelinated nerve fibers show evidence of both axonal injury and demyelination.[165] Neuropathy generally occurs at doses greater than 200 mg/m^2, and symptoms develop 1 to 3 days after treatment. Although much of the neurologic dysfunction reverses over several weeks, continued treatment causes progressive neurologic toxicity. The peripheral neuropathy associated with docetaxel appears to be similar to that with paclitaxel in preliminary reports, although in a randomized trial, the incidence and severity were less with docetaxel.[166,167] Peripheral neuropathy also is being reported with other microtubule-stablizing agents such as the epothilones.[168]

In one series, transient encephalopathy was reported to occur within hours of administration of standard doses of paclitaxel. All patients had undergone previous brain radiation therapy, and all recovered within hours.[169] Acute encephalopathy was reported to occur in six patients receiving a very high intravenous dose of paclitaxel (greater than 600 mg/m^2). Encephalopathy developed between 7 and 23 days after treatment. Three patients recovered; the other 3 patients died of progressive coma. Autopsy revealed generalized white matter atrophy.[170] Chronic neurocognitive changes also have been reported with extensive administration of taxanes.[171]

Tamoxifen

Tamoxifen can cause reversible retinal dysfunction at the conventional antiestrogen doses used for breast cancer therapy.[172–174] At higher doses, reversible encephalopathy with delusions, somnolence, and cerebellar dysfunction has been reported.[175–177]

BIOLOGIC RESPONSE MODIFIERS

Interleukin-2

Central Nervous System Toxicity

The vascular leak associated with intravenous interleukin-2 (IL-2) administration can result in encephalopathy and coma.[178] A high percentage of patients receiving both systemic IL-2 and lymphocyte-activated killer (LAK) cells experience encephalopathy or a neuropsychiatric syndrome.[178] In most cases, severe but reversible cognitive impairment occurs. In the presence of an intracranial mass lesion, the increase in brain edema leads to an asymmetrical shift in the brain, resulting in herniation. In a single case report, development of multifocal white matter lesions was associated with intravenous administration of IL-2. The lesions resolved completely over several months.[179] Another case report described fatal leukoencephalopathy associated with IL-2 treatment.[180]

Toxicity Associated with Interleukin-2 Treatment

In one series of five patients, the development of neuro-ophthalmic complications was temporally associated with intravenous IL-2 treatment.[181,182] Reported abnormalities included transient scotomata, diplopia, amaurosis fugax, and visual field cuts.

Interferons

Systemic administration of interferon affects both the CNS and the peripheral nervous system.

Central Nervous System Toxicity

Confusion, lethargy, mood changes, and loss of cognitive function are the most common CNS effects associated with use of interferons.[183–185] Encephalopathy, with perseveration and aphasia, also has been reported,[184] as has a parkinsonian syndrome with bradykinesia, mask-like facies, and micrographia.[186] In addition, major depression has been described with use of interferon-α (IFN-α).[187] The neurologic effects of interferon are dose-related, but they are more severe in patients with underlying neurologic abnormalities.[188] Although the neurotoxic effects of interferon therapy usually resolve completely within a few weeks, some patients may exhibit persistent behavioral changes.[183] Intraventricular administration of IFN-α caused severe neurologic toxicity in one study. Effects ranged in severity from headache and confusion to coma. Additional side effects of intraventricular administration included parkinsonism, hearing loss, and seizures.[189]

Peripheral Nervous System Toxicity

Mild peripheral neuropathy manifesting as paresthesia has been reported with interferon use,[184] as has a case of brachial neuritis in a patient with underlying neuropathy.[190]

Thalidomide and Lenalidomide

Thalidomide has both immunomodulatory and antiangiogenic properties, has shown significant activity in multiple myeloma, and is being evaluated in the management of several other cancers.[191] Somnolence, the predominant side effect, is dose-related, and the drug can be titrated in most patients to a level of tolerance. Peripheral neuropathy is treatment-limiting. The neuropathy has been characterized as sensory-motor axonal polyneuropathy manifesting as painful paresthesia or numbness.[192] Severity of symptoms correlates with cumulative dose. Nerve biopsy and examination reveal distal axonal degeneration and demyelination. A longitudinal study in patients with dermatologic disease confirmed the high incidence of neuropathy (25% in this study) and the association with daily dosing.[193] Early studies of lenalidomide indicate that peripheral neuropathy may occur in a small percentage of patients.[194] The available data are insufficient to determine if the incidence will be less than with thalidomide.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF) that has shown activity in a wide variety of cancer types including colon, lung, and renal cell cancers and glioblastoma. Exacerbation of hypertension is a commonly reported toxicity and may be related to the development of PRES, described in detail later on.[195,196]

Sorafenib

Sorafenib is an oral agent that is a RAF kinase inhibitor that inhibits VEGF receptors 2 and 3 and platelet-derived growth factor

receptor-β. Hypertension is a common toxicity with this agent, and as with bevacizumab therapy, reports of PRES are now emerging.[197]

Bortezomib

Bortezomib is a proteosome inhibitor that has demonstrated activity in multiple myeloma. Peripheral neuropathy, predominantly a sensory neuropathy, initially was reported during early phase I trials. A prospective study evaluated the occurrence of neuropathy in a group of 256 patients with refractory myeloma treated with standard dosing schedules of bortezomib.[198] The incidence of neuropathy was estimated to be approximately 35%, and neuropathy was more common in patients receiving bortezomib at 1.3 mg/m^2 than in those dosed at 1.0 mg/m^2. Cumulative dose also correlated with severity of the neuropathy, as did the presence of neuropathy before initiation of treatment. Most patients experienced either partial or complete resolution with cessation of treatment.

RADIATION NEUROTOXICITY

Radiation neurotoxicity is becoming an increasingly important and recognized complication of cancer therapy. New therapeutic strategies for systemic cancer and for CNS metastasis have improved survival, uncovering a greater incidence of late, chronic toxicity from radiation and combined chemoradiotherapy treatments. Advances in technology, such as radiosurgery and brachytherapy, allow local dose intensification of radiation treatment for brain tumors. Furthermore, advances in development of radiosensitizers will increase the effects of radiation therapy on tumor and surrounding normal tissue.

Central Nervous System Effects

Cranial radiation therapy can cause acute, subacute, and chronic neurotoxicity. Volume of brain treated, total dose, and dose fraction are the most important determinants of toxicity, although some variation in patient susceptibility is apparent.

Acute Toxicity

Acute toxicity manifests as rapid onset of alteration in level of consciousness. This disorder generally occurs within weeks of initiation of cranial radiation therapy.[199] Acute toxicity is most common in patients receiving whole-brain radiation therapy. The pathogenesis is unknown, and most patients experience complete recovery of neurologic function.

Early-Delayed Toxicity

Early-delayed toxicity is noticed weeks to 3 months after completion of radiation treatment.[200] Most commonly, patients have drowsiness, nausea, headaches, ataxia, and worsening of underlying neurologic dysfunction. Complete resolution is expected, although rare patients have an idiosyncratic reaction with widespread brain necrosis.[201] The pathogenesis of early-delayed toxicity is unknown, but the reaction has been speculated to be related to reversible demyelination. CT reveals decreased attenuation in the cerebral white matter; MRI reveals increased signal intensity in white matter on T_2-weighted images.

Recently, early treatment-related brain injury has been reported with the use of concurrent daily temozolomide with external beam radiation in patients with glioblastoma.[202] Changes are seen on brain imaging studies that emulate tumor growth with increasing edema and an increase in uptake of contrast material. These changes, now referred to as "pseudo-progression," may reflect an increase in blood-brain barrier breakdown that is the consequence of an augmentation of radiation effect from the coadministration of chemotherapy.

Chronic, Late Radiation Injury

Chronic, late radiation injury usually appears 9 months to 2 years after completion of radiation treatment, although some patients have experienced onset of symptoms 10 years after treatment.[201,203] Patients exhibit focal areas of radiation necrosis or evidence of diffuse radiation injury. The incidence of each type of injury depends on the dose of treatment, fractionation schedule, and area of treatment.[204,205] Focal necrosis often manifests as focal neurologic deficits, such as hemiparesis or aphasia. Global signs such as obtundation can occur when the localized necrosis causes increased intracranial pressure and herniation. Similarly, focal necrotic regions can cause seizures. Pathologic examination of the necrotic region reveals vascular injury to the small arteries and arterioles and evidence of coagulative necrosis, with destruction of all elements of the nervous tissue.[45] Treatment is directed at decreasing edema and mass effect. Patients generally respond to corticosteroids.[206] Surgical resection, if feasible, can be curative.

Diffuse Injury

Diffuse injury manifests as global neurologic dysfunction, with personality change, confusion, and lethargy, and can progress to dementia, obtundation, or coma.[200,205] Diffuse white matter changes are found on CT or MRI, manifesting as low attenuation on CT scans and high signal intensity in the periventricular and subcortical white matter on T_2-weighted and proton density MR images.[207–209] Mass effect and focal neurologic signs are not common, although late in the course, seizures and motor dysfunction can occur. The main risk factors for diffuse injury include the volume of brain treated, concurrent or adjuvant chemotherapy directed at the CNS, and use of short-course, high-dose-fraction regimens. The incidence is difficult to determine, but reports have shown neurologic and imaging changes in 32% to 50% of patients subjected to radiation therapy.[208–210]

The pathogenesis of diffuse radiation injury is not known, although distinctive neuropathologic changes have been described. The most prominent pathologic finding is vascular changes in the small arteries and arterioles. Hyalinization of the vessel walls with occlusion is common.[205,209] In addition, areas of necrosis, gliosis, and demyelination are found. No established treatment is recognized. Corticosteroids may provide transient relief of associated edema but do not alter the course of the syndrome.

Necrotizing Leukoencephalopathy

Necrotizing leukoencephalopathy is the most severe form of neurologic toxicity associated with radiation therapy. It is most common when CNS-directed chemotherapy is combined with radiation therapy. This syndrome is described earlier in the discussion of methotrexate-associated toxicity. The incidence of leukoencephalopathy is much greater in patients who receive chemotherapy after cranial radiation therapy than in patients receiving either treatment alone, or in those receiving chemotherapy before the initiation of radiation therapy.[211,212]

Mineralizing angiopathy has occurred in pediatric patients receiving both intrathecal methotrexate and radiation therapy.[211] The changes frequently are diagnosed as dystrophic calcifications during neuroradiologic examinations. Histopathologic analysis reveals deposits of calcium in small blood vessels, often with surrounding regions of necrotic brain. The clinical significance of these changes is uncertain.

Cranial radiation therapy has been associated with a wide spectrum of endocrinologic effects.[213] Most of these effects are attributed to damage to the hypothalamic-pituitary axis. These effects are generally dose dependent and may manifest several years after completion of the radiation treatment. Results of several studies have suggested differing vulnerability among the various endocrine loops.[214] Growth hormone deficiency and stimulation of precocious puberty have occurred at doses as low as 18 Gy.[215] Deficiency of gonadotropins, thyroid-stimulating hormone, and corticotropin usually results only when the hypothalamic-pituitary axis receives more than 40 Gy.[216] Similarly, hyperprolactinemia occurs most often in young

women receiving more than 40 Gy of radiation therapy. Careful long-term monitoring of these patients is critical.[217] Appropriate replacement therapy or prolactin suppression treatment should prevent sequelae.

Radiation Myelopathy

Several distinct syndromes have resulted from the effects of radiation injury to the spinal cord: an acute syndrome manifesting as paraplegia or quadriplegia; early transient myelopathy; delayed progressive myelopathy; and an anterior horn, lower motor neuron syndrome.

The acute syndrome is rare with today's dosing schedules. Case reports state that weakness evolves over a few hours or days.[218] The syndrome probably is caused by acute necrotizing radiation injury due to rapidity of onset and failure of neurologic recovery.

The early transient form appears 6 to 12 weeks after treatment.[219] Most patients exhibit Lhermitte's sign—an electrical shock-like sensation down the spine with neck flexion. No neurologic deficits are found, and the symptoms resolve spontaneously over several weeks. Transient demyelination is hypothesized to be the cause of the symptoms.

Delayed progressive radiation myelopathy is the most common radiation therapy-induced spinal cord disorder, although it is relatively rare. Signs and symptoms generally develop 6 months to 1 year after completion of radiation therapy, although some data suggest that the latent period may be as long as 18 months to 2 years.[220] The clinical picture may vary from patient to patient. Some patients have monoplegia, others paraplegia or quadriplegia. Sensory symptoms are generally more severe than motor symptoms. Some patients have Brown-Séquard syndrome. Progression may take several years.[218] The pathogenesis is thought to be similar to that of delayed neurotoxicity after cranial radiation therapy (see earlier discussion).[218,219] Pathologic examination reveals rarefaction of spinal cord white matter with small areas of necrosis. Degeneration of myelin sheaths and loss of oligodendrocytes have been noted. Other causes of spinal cord dysfunction need to be excluded, including intramedullary tumor or infection, multiple sclerosis, vitamin B_{12} deficiency, sarcoidosis, and Lyme disease. There is no treatment, and most patients experience progressive neurologic dysfunction over months to years.

Lower motor neuron syndrome occurs after spinal cord radiation therapy. Patients exhibit pure motor signs of weakness, atrophy, and fasciculations.[218] The syndrome manifests 3 months to 2 years after radiation treatment and is similar to polio. The pathogenesis is unknown. Hypotheses include loss of anterior horn cell neurons and radiation-induced injury to motor nerve roots. No treatment except supportive care exists.

Peripheral Nerve Toxicity

Peripheral nerves are relatively resistant to the effects of radiation therapy. Early effects, developing within 2 days of a single large-fraction treatment in an experimental animal system, include changes in vascular permeability of the nerve, changes in bioelectrical activity, and abnormal microtubule assembly in the axon.[221] Late changes include fibrosis in the nerve sheath and angiopathic changes in the small arterioles providing the vascular supply to the nerve.[222] Use of large (greater than 25 Gy) single doses or extended fractionated treatment to a very high total dose (greater than 80 Gy) is thought to be necessary for injury to the peripheral nerve. Similar changes have been found for some cranial nerves.

Brachial and lumbar plexopathies warrant a separate discussion. These syndromes result from radiation injury to the nerve fibers in the plexus. Brachial plexopathy is most common, caused by axillary radiation therapy for breast cancer.[223] Lumbar plexopathy is more commonly associated with pelvic external-beam radiation therapy, although local radioactive seed implantation (brachytherapy) may result in local nerve damage.[221]

The diagnosis of radiation plexopathy can be difficult and requires excluding tumor infiltration as the cause of the symptoms. This process is most difficult with brachial plexus dysfunction and in patients with apical lung cancer or metastatic breast cancer. The distinguishing features in comparing radiation with tumor brachial plexopathy have been described extensively.[223] None of the criteria are absolute, although tumor infiltration is more likely to be painful and involve the lower nerve roots (C7–T1) than is radiation injury, which is less likely to cause severe pain and generally involves higher roots (C5 and C6). Acute reversible radiation injury to the brachial plexus has been described. This condition often is painful, although the pain generally is mild. Patients experience weakness and atrophy in a C6–T1 distribution. Spontaneous recovery is typical.

Radiation has been reported to accelerate vascular injury, causing segmental obstruction of the subclavian artery.[224] This condition usually is painless. The motor and sensory loss evolves quickly, without subsequent progression or improvement.

Lumbosacral plexopathy is less common than radiation-related brachial plexopathy.[225] Onset of signs and symptoms usually is delayed until at least 1 year after radiation treatment. Pain is usual and mild. The pathogenesis is uncertain, although fibrosis causing nerve compression and ischemia is a likely cause. The diagnosis of radiation-related lumbosacral plexopathy is made by excluding tumor infiltration. Imaging (MRI or CT) often is useful, although in select cases, surgical exploration is indicated.

Muscle Injury from Radiation Treatment

Muscle is thought to be relatively resistant to the effects of radiation therapy, although results of several studies have suggested that at higher doses (greater than 50 Gy), significant late toxicity may occur.[222] Early effects are uncommon, symptoms generally are found after 1 year, and the onset of changes has been reported as late as 10 years after radiation therapy. Signs and symptoms include muscle contractures, loss of function, pain, extremity edema, and pathologic fractures. The synergy of the toxic effects with those of chemotherapy is uncertain, although most patients have received both modalities of treatment.[222] No treatment other than conservative measures including physical therapy is helpful.

DIFFERENTIAL DIAGNOSIS

Dementia and Encephalopathy

Acute Encephalopathy

A common neurologic problem in patients with cancer is acute encephalopathy.[226] The differential diagnosis includes an extensive array of potential causes. Most commonly, however, acute encephalopathy is caused by toxic or metabolic derangement. Frequent causes include narcotic effects, electrolyte abnormalities, hypoxia, and renal or hepatic dysfunction. Neoplastic meningitis frequently manifests as mental status changes as a result of increased intracranial pressure, seizures, or infiltration of the cortex through the Virchow-Robin spaces surrounding surface blood vessels. Likewise, brain metastasis can cause an acute change in mental status when a sudden increase in tumor size (often hemorrhage) results in a rapid change in intracranial pressure or when tumor-induced seizures occur. A paraneoplastic syndrome, limbic encephalitis, can manifest as a progressive dementia, which often is subacute. This paraneoplastic syndrome most frequently is associated with small cell lung cancer, but it has been described in association with other tumors. Patients often are found to have serum anti-Hu antibodies, also a feature of paraneoplastic sensory neuropathy.[227–229]

Cancer treatment can directly or indirectly cause acute encephalopathy. High doses of intravenous methotrexate or ara-C can cause reversible encephalopathy, often accompanied by lethargy.[5,13,35] Results of studies with animals and with patients in which positron

emission tomography was used after high-dose methotrexate showed temporary reduction in brain metabolic activity in both glucose utilization and protein synthesis.[36,230] Folinic acid (leucovorin) administration improved metabolic activity in laboratory studies.[37] Other agents known to cause encephalopathy include vincristine, ifosfamide, procarbazine, fludarabine, paclitaxel, cisplatin, and L-asparaginase. The immunostimulant levamisole combined with 5-FU causes reversible encephalopathy and has been associated with a demyelinating condition known as multifocal inflammatory leukoencephalopathy.[145] The hormonal agent tamoxifen has been reported to cause encephalopathy at high doses. Biologic response modifiers such as the interferons and interleukins commonly cause reversible encephalopathy, although permanent neurologic sequelae may result from prolonged use of interferon.[183,184] Radiation therapy can cause an acute syndrome manifesting as lethargy that generally is reversible.

PRES has been seen most frequently with use of the immunomodulators cyclosporine and tacrolimus, but cisplatin, gemcitabine, and combination chemotherapy regimens also have been associated with the syndrome. More recently, drugs that modulate the VEGF pathway, such as bevacizumab and sorafenib, have been associated with PRES. The clinical manifestations are encephalopathy, cortical blindness, and variable loss of other higher cortical functions, such as aphasia and apraxia. Brain imaging with CT and MRI reveals characteristic patchy white matter changes (Fig. 61-3). The pathogenesis of the syndrome is unknown, although hypertension and hypomagnesemia have been associated. Full recovery has occurred with cessation of treatment or adjustment of the dose of the immunosuppressant.[231–235]

Many chemotherapeutic agents provoke a change in mental status by causing secondary metabolic derangement. Cyclophosphamide and vincristine can stimulate SIADH.[89,90,123,124] The resulting hyponatremia can lead to seizures and encephalopathy. Hyponatremia secondary to cisplatin-induced salt-wasting nephropathy can cause the same neurologic problems. Treatment with L-asparaginase, corticosteroids, and streptozocin can lead to glucose intolerance. Left untreated, this condition can result in nonketotic hyperosmolar coma. Many chemotherapeutic agents can cause hepatic and renal dysfunction with consequent development of secondary neurologic symptoms.

Chronic Encephalopathy and Dementia

Dementia, or chronic progressive loss of cognitive function, most commonly is associated with treatment directed at the CNS. Leukoencephalopathy, characterized histologically by white matter changes consisting of axonal swelling and loss with regions of demyelination, is the classic chronic or late neurotoxic syndrome.[4,6] Cognitive changes are first noticed 6 months to 2 years after completion of treatment and often are progressive, leading to profound dementia, coma, or death.[4–6,8,43] Intrathecal chemotherapy with methotrexate, ara-C, or thiotepa is most closely associated with leukoencephalopathy, although a similar syndrome occurs with high-dose intravenous methotrexate and ara-C and with intra-arterial chemotherapy (with BCNU or cisplatin).[236,237] Previous treatment with cranial radiation therapy significantly increases the risk of leukoencephalopathy.[5,52] Cranial radiation therapy alone can cause leukoencephalopathy, although the incidence increases markedly when radiation therapy is combined with chemotherapy. Other agents such as ifosfamide can cause prolonged encephalopathy and are associated with acute toxicity.[132]

Diagnostic Evaluation

A thorough search for a treatable underlying cause of encephalopathy should be undertaken in all affected patients. The diagnosis of chemotherapy-induced encephalopathy is made by excluding other potential causes. The order of diagnostic tests is dictated by the findings on the physical and neurologic evaluations. Patients with focal neurologic abnormalities need early imaging studies (CT or MRI), although certain metabolic disorders (e.g., hypoglycemia) can manifest as focal neurologic deficits. A metabolic evaluation, including measurement of electrolytes, renal and liver function tests, measurement of oxygenation, serum calcium and magnesium, serum ammonia, and possibly thyroid and adrenal function testing, should be performed for most patients. Careful review of prescribed and over-the-counter medications may provide critical information. In some cases, blood and urine toxicology screening may be necessary. EEG often is helpful in directing the evaluation by indicating the presence of structural abnormalities (e.g., periodic localizing epileptiform discharges or focal slowing) or may indicate a global metabolic process (e.g., diffuse slowing with D waves or triphasic waves in hepatic encephalopathy). Patients in subclinical status epilepticus may have encephalopathy; in these cases, the EEG findings are diagnostic. Lumbar puncture often is needed to exclude infectious or neoplastic meningitis. In most cases, head MRI or CT should be performed before lumbar puncture to look for a mass lesion in the brain that would make lumbar puncture unsafe. The search for the underlying cause often is revealing. One group of investigators reported uncovering the cause of encephalopathy in 31 of 37 patients.[226]

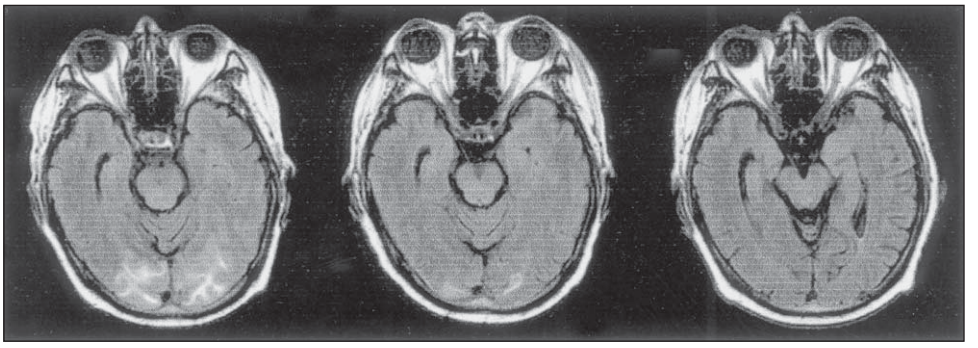


Figure 61-3 • Posterior reversible encephalopathy syndrome. The patient was a 47-year-old man with acute monocytic leukemia who had undergone allogeneic bone marrow transplantation and was receiving tacrolimus. He presented with headache, nausea, and vomiting. **A,** Magnetic resonance fast fluid-attenuated inversion recovery (FLAIR) image shows changes consistent with the syndrome. The patient's symptoms resolved within days of cessation of tacrolimus treatment. **B** and **C,** Repeated magnetic resonance images show resolution of the posterior abnormalities.

Table 61-1 Chemotherapeutic Agents That Cause Seizures

Agent	Route of Administration	Comment(s)
L-Asparaginase	Intravenous	Associated with cerebrovascular events
Bevacizumab	Intravenous	Associated with PRES
Busulfan	Oral	Bone marrow transplantation–preparative regimen
Cisplatin, oxaliplatin	Intravenous	Rare; may be associated with cortical blindness, PRES
Cytosine arabinoside	High-dose intravenous (acute)	Late with leukoencephalopathy
Ifosfamide	Intravenous	Associated with encephalopathy
Methotrexate	High-dose intravenous (acute)	Late with leukoencephalopathy
Metronidazole	Intravenous, oral	
Nitrosoureas	Intracarotid or supraophthalmic arterial	Often associated with focal brain necrosis
Sorafenib	Oral	Associated with PRES
Vincristine	Intravenous	

PRES, posterior reversible encephalopathy syndrome.

Seizures

Clinical Manifestations and Differential Diagnosis

The differential diagnosis for seizures in cancer patients includes an extensive list of possible causes. Causal factors can be broadly classified into toxic-metabolic and structural causes. Metabolic factors include hepatic and renal failure resulting from tumor growth or treatment toxicity, electrolyte abnormalities such as hypercalcemia from bone destruction or parathyroid hormone effect, hypomagnesemia from chemotherapy (cisplatin) or excessive vomiting, hyponatremia from SIADH or salt-wasting nephropathy (cisplatin), hypoxia, hyperglycemia from pancreatic failure (streptozocin), and glucose intolerance (corticosteroids). Several chemotherapeutic agents are known to be the direct cause of seizures (Table 61-1).

Structural causes of seizures include brain metastasis, dural metastasis, and meningeal carcinoma. Ischemic and hemorrhagic vascular events also may provoke seizures. A tumor-induced hypercoagulable state may greatly increase risk of stroke or venous sinus thrombosis.[238] A similar hypercoagulable state can be seen with L-asparaginase treatment. The paraneoplastic syndrome marantic endocarditis often results in cerebrovascular events, as can infectious endocarditis, a potential complication of treatment-induced neutropenia.[188] Cisplatin can cause vasospasm of the intracranial vessels, producing a stroke.[239] Furthermore, immunocompromised patients are at greater risk for CNS infection (including bacterial and fungal meningitis), brain abscess, and viral encephalitis (including progressive multifocal leukoencephalopathy).

Diagnostic Evaluation

The type of seizure dictates the initial evaluation. Focal seizures more commonly are associated with structural brain lesions, although metabolic disorders can precipitate focal seizures if an underlying structural problem is present. Generalized seizures may be the consequence of structural or metabolic processes or both.

The diagnostic evaluation generally involves a metabolic evaluation similar to that described for encephalopathy. Electrolyte imbalances, such as hyponatremia, hypomagnesemia, hypocalcemia or hypercalcemia, hyperglycemia, and hyperphosphatemia, are possible metabolic causes. Similarly, hepatic and renal dysfunction increase the likelihood of seizures, particularly in a patient with an underlying structural brain lesion. Most patients with cancer who experience a seizure require an imaging study of the brain (CT or MRI). These studies should be performed both with and without the administration of contrast material. EEG may be helpful in recognizing (or ruling out) ongoing seizure activity, in confirming the diagnosis of seizure if the event was not witnessed or not accompanied by tonic-clonic activity, or possibly in localizing a focal lesion or process. For example, EEG in patients with herpes encephalitis often demonstrates bitemporal periodic localizing epileptiform discharges, even before abnormalities are seen on MR images. Lumbar puncture may be needed to evaluate for infectious and neoplastic meningitis. Lumbar puncture should be performed after brain imaging, except in patients with suspected bacterial meningitis, in whom obtaining the scan would delay lumbar puncture and administration of antibiotic therapy.

The diagnosis of chemotherapy-induced seizures is made after other causes are excluded. For most chemotherapeutic agents, seizures develop acutely, either during or immediately after treatment. Seizures often are accompanied by encephalopathy. In most instances, the prognosis for recovery from the acute episode is good. Unfortunately, when seizures develop as a component of chronic or delayed neurotoxicity (leukoencephalopathy), the prognosis is poor, and neurologic dysfunction often progresses. In such instances, the seizures are a manifestation of widespread brain destruction.

Cerebellar Dysfunction

Clinical Manifestations and Differential Diagnosis

Cerebellar dysfunction in patients who have cancer occurs most commonly with metastatic spread to the cerebellum or brainstem. Meningeal carcinoma occasionally causes cerebellar signs by infiltrating cerebellar pathways. Patients with structural cerebellar lesions often show asymmetrical dysfunction, which can be useful in differentiating this condition from drug-induced cerebellar toxicity. Paraneoplastic cerebellar degeneration is is characterized by subacute progressive loss of cerebellar function.[228,240,241] Patients usually have symmetrical loss of all cerebellar function and exhibit appendicular and truncal ataxia, nystagmus, and scanning speech. This paraneoplastic syndrome occurs most commonly with lung cancer but also has been associated with gynecologic cancers and Hodgkin's disease. Many patients have antibodies in the serum, designated anti-Yo, that bind to cerebellar tissue, specifically Purkinje cells, and cross-react with tumor tissue.[240]

5-FU and ara-C can cause cerebellar toxicity from specific irreversible damage to the cerebellar Purkinje cells. The result is truncal ataxia, unsteady gait, dysarthria, and nystagmus.[12–15,137–144] The dysfunction usually is symmetrical. MRI findings immediately after chemotherapy are normal, but cerebellar atrophy often is detected at MRI months later.

Diagnostic Evaluation

Patients with cerebellar dysfunction should undergo MRI with and without gadolinium enhancement in an evaluation for metastatic lesions. In addition, the MRI findings may suggest the presence of neoplastic meningitis if enhancement is observed in the subarachnoid space. Patients with no evidence of brain metastasis need lumbar puncture to evaluate for neoplastic meningitis. Examination for the presence of serum anti-Yo antibodies should be performed, particularly in patients who have malignant lesions associated with this paraneoplastic syndrome.

In patients with only appendicular ataxia, the possibility of sensory ataxia must be kept in mind. The presence of sensory ataxia suggests the presence of severe sensory neuropathy, such as paraneoplastic sensory neuronopathy, dorsal column dysfunction from a structural lesion (e.g., epidural cord compression), or metabolic abnormality (e.g., vitamin B_{12} deficiency).

Cranial Neuropathy

Clinical Manifestations and Differential Diagnosis

Cranial neuropathy in patients with cancer most commonly indicates the presence of meningeal carcinoma, tumor involvement of the bones of the cranial base with encroachment of neural foramina, or rarely, brainstem metastasis.[242] Chemotherapy-induced cranial neuropathy is rare. Vincristine can cause cranial nerve palsy; extraocular eye movement abnormalities are most common.[62,66,79,80] Intraventricular administration of drugs and of biologic response-modifying agents can cause transient cranial nerve palsy, often due to abnormalities in CSF circulation.[243]

In both neoplastic meningitis and drug-induced cranial nerve palsy, the seventh (facial) cranial nerve most commonly is affected. Unfortunately, there is little to differentiate the clinical manifestations of drug-induced nerve palsy from those of neoplastic meningitis. Both conditions can involve several cranial nerves, be indolent in onset, and demonstrate spontaneous resolution. Therefore, examination of the CSF is critical in the care of patients with suggestive signs and symptoms. In addition to neoplastic meningitis, tumor encroachment on neural foramina at the skull base from bone metastasis can cause cranial nerve palsy, as can small intraparenchymal lesions (tumor, infarct, or hemorrhage), although such lesions are rare.

Diagnostic Evaluation

In the care of patients with cranial nerve palsy, serial examinations of the CSF often are needed to determine whether tumor cells are present. Evaluation of the bones of the skull base with thin-section CT helps determine the presence of metastatic bone lesions. MRI of the brainstem is performed to evaluate for intraparenchymal lesions, although in most instances, other brainstem signs are present, in which case this test should be part of the initial evaluation.

Optic Neuropathy and Ocular Toxicity

Clinical Manifestations and Differential Diagnosis

Optic neuropathy can be seen in patients with neoplastic meningitis, lymphoma, or leukemia with infiltration of the optic nerve.[244,245] In addition, compression from cranial base tumors can cause similar loss of vision. Optic neuritis, characterized by unilateral or bilateral loss of vision, has been reported as a rare paraneoplastic syndrome associated with small cell lung cancer.[246] Loss of vision often is accompanied by photosensitivity and papilledema. Antiretinal antibodies have been found in the serum of affected patients. Retinopathy most commonly is associated with intracarotid administration of nitrosoureas and cisplatin.[112,113,158,159] High concentrations of drug flow into the ophthalmic artery, which supplies the retina, causing severe pain and often complete loss of vision. Newer techniques, allowing administration above the ophthalmic artery, have reduced the incidence of this local toxicity.

Intravenous cisplatin administration has been associated with optic disk swelling and optic neuropathy.[104,105] This reaction is idiosyncratic, and the mechanism is unknown.

Diagnostic Evaluation

Chemotherapy-induced retinopathy from intra-arterial administration occurs soon after treatment and is rarely difficult to diagnose. Optic neuropathy from cisplatin is more indolent, and other causes must be considered, such as isoniazid, chlorpropamide, or ethambutol toxicity or paraneoplastic optic neuropathy. Optic nerve tumors and frontal lobe mass lesions can cause optic atrophy, although they are uncommon causes of isolated optic atrophy. MRI or CT may be helpful.

Spinal Cord Toxicity

Clinical Manifestations and Differential Diagnosis

The most common cause of spinal cord dysfunction in patients is epidural cord compression, either from direct extension of bone metastasis or from paravertebral spread through the intervertebral foramina. Intramedullary tumor and extramedullary intradural tumors can have myelopathic manifestations.[247] Similarly, epidural abscess and hematoma can be clinically indistinguishable from epidural tumor. Encephalomyelitis is a frequently described paraneoplastic syndrome associated with several types of tumors, particularly small cell lung cancer.[248] A rare paraneoplastic myelopathy has been described with lung cancer, renal cell carcinoma, and Hodgkin's disease. This syndrome is characterized by subacute progression of spinal cord dysfunction, usually in the thoracic region, although damage occasionally occurs at several levels. Pathologic examination reveals segmental necrosis.

Lumbar intrathecal administration of methotrexate and ara-C can result in focal myelopathy.[19–25] Symptoms and signs appear hours to days after treatment and can include sensory loss, upper and lower motor neuron dysfunction, radiating pain (similar to Lhermitte's sign), and bowel and bladder incontinence. The myelopathy may be transient or progressive; complete irreversible paraplegia usually is seen with progressive dysfunction. Myelopathy also has been reported with spinal radiation therapy. A rare, acute syndrome develops over days. The more common chronic myelopathy with radiation therapy develops months after completion of treatment.

Diagnostic Evaluation

The diagnostic evaluation of patients with spinal cord dysfunction is directed by findings on physical examination and the history. Rapid progression of symptoms suggests the presence of a rapidly growing tumor causing cord compression, epidural hematoma, or abscess. This finding warrants emergency evaluation with MRI. Early loss of bowel and bladder function or a suspended sensory level suggests the presence of an intramedullary lesion, best visualized by contrast-enhanced MRI.

Evidence of chemotherapy myelopathy may include edema on MRI and elevated myelin basic protein levels in CSF. The diagnosis of chemotherapy myelopathy often is made on the basis of temporal association with intrathecal treatment in the absence of other potential causes. Neoplastic meningitis can mimic spinal cord compression and requires CSF examination for diagnosis.

Peripheral Neuropathy

Clinical Manifestations and Differential Diagnosis

Peripheral neuropathy is a common paraneoplastic syndrome. Mild sensorimotor neuropathy is the most common neuropathy in patients with cancer.[249] The cause is unknown, but the condition is a distinct entity, separate from the diffuse weakness associated with cachexia. Rare pure motor and pure sensory paraneoplastic neuropathies also have been described. Sensory neuronopathy, most common with small cell lung cancer, causes severe sensory loss.[250,251] The intense

Table 61-2 Agents That Cause Peripheral Neuropathy

Agent	Comment(s)
Bortexomib	Primarily sensory, dose- and cumulative dose–related
Cisplatin	Large sensory fiber (vibration, proprioception); dose- and cumulative dose–related; dose-limiting
Cytosine arabinoside	Rare, symmetrical sensorimotor polyneuropathy
Interferons	Transient paresthesia
Oxaliplatin	Large sensory fiber (vibration, proprioception); dose- and cumulative dose–related; dose-limiting; acute hyperexcitability syndrome
Paclitaxel, docetaxel	Dose-related sensorimotor; dose-limiting
Procarbazine	Transient paresthesia
Thalidomide, lenalidomide	Sensory-motor axonal polyneuropathy; incidence related to duration and dose of treatment
Vincristine	Frequent; dose-related; autonomic and sensorimotor; exacerbated in patients with underlying neuropathy; dose-limiting

inflammatory reaction and neuronal destruction in the dorsal root ganglia have led to use of the term *dorsal root ganglionitis*. Some patients are found to have anti-Hu antibodies in serum.[228,251] Motor neuronopathy manifests as isolated lower motor neuron loss.[252] This syndrome has been found in both patients with Hodgkin's lymphoma and those with non-Hodgkin's lymphoma. The pathogenesis of this pure motor syndrome is unknown. Other causes of neuropathy that should be considered are diabetes, thyroid dysfunction, vitamin B_{12} deficiency, and alcoholic neuropathy.

Several cancer chemotherapeutic agents cause peripheral neuropathy. These are listed in Table 61-2. The peripheral neuropathy secondary to chemotherapy is temporally related to administration for most agents. Cisplatin is an exception, and delayed neuropathy occurs in some patients.

Carcinomatous meningitis can manifest as multilevel radiculopathy, initially mimicking peripheral neuropathy. Likewise, brachial and lumbar plexopathy from tumor infiltration or radiation therapy can mimic neuropathy, but careful neurologic examination determines the localized nature of the process.

Diagnostic Evaluation

The evaluation of a patient with neuropathy depends on the results of the neurologic examination. Determination of the components of the peripheral nervous system involved is critical in guiding evaluation. Pure motor loss in a patient with lymphoma strongly suggests the presence of a paraneoplastic process, although CSF analysis should be performed to exclude Guillain-Barré syndrome. Likewise, the presence of pure sensory neuropathy involving both small and large sensory fibers suggests dorsal root ganglionitis. Pure large-fiber sensory neuropathy is most common with cisplatin treatment. Nerve conduction testing and electromyelography (EMG) may be helpful in determining whether the process is axonal or demyelinating. Some patients should undergo lumbar puncture to exclude carcinomatous meningitis, or evaluation for Guillain-Barré syndrome.

Myopathy

Clinical Manifestations and Differential Diagnosis

Myopathy is a rare symptom in cancer, usually being the consequence of treatment. Dermatomyositis and polymyositis are paraneoplastic syndromes characterized by inflammatory myopathy and by the presence and the absence of a rash, respectively.[253,254] Dermatomyositis and polymyositis have been associated with many tumors, most commonly lung and gastrointestinal tumors. Patients have an elevated serum creatine kinase (CK) level. Although myopathy is a rare complication of chemotherapy, it has been described with use of paclitaxel and vincristine.[63,86,255]

Interferon and other biologic response-modifying agents can cause myalgia, but no evidence of muscle dysfunction or breakdown is found on histopathologic examination of muscle biopsy specimens. Cisplatin and other agents that induce electrolyte abnormalities (e.g., hypomagnesemia) can cause muscle cramping.

Diagnostic Evaluation

For patients with clinical evidence of myopathy, serum CK should be measured before EMG is performed. An elevated CK level suggests active muscle destruction, as in polymyositis or dermatomyositis or with use of paclitaxel or vincristine. Measurement of electrolytes (e.g., magnesium, potassium) may be useful. In patients with loss of strength or with muscle pain, EMG and muscle biopsy may be necessary.

GRADING OF NEUROTOXICITY

None of the uniform grading systems of neurotoxicity are suitable for use in serial clinical evaluations. The most commonly used neurotoxicity measures are based on the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE)—Neurology, as shown in Table 61-3. Although these toxicity tables are useful in the evaluation of groups of patients, they are not suitable for monitoring the clinical status of individual patients. Standard neurologic testing with careful recording is best suited for individual patient care. The techniques required for performing an in-depth neurologic evaluation are reviewed in classic neurology textbooks.[256,257] Quantitative measures of mental status function, motor examination results, and sensory function have been published.[258–260]

TREATMENT

No specific treatment exists to prevent or reverse neurotoxicity from most chemotherapeutic agents and regimens in use. Therefore, the focus should be on monitoring for development of toxicity so that treatment can be modified before the development of severe dysfunction. Rational treatment guidelines for minimizing neurotoxicity are needed.

Prevention

The key to prevention of permanent neurologic damage is to initiate a system for monitoring for toxicity. For example, patients receiving intrathecal chemotherapy are at risk of chemotherapy-induced myelopathy, an often irreversible toxicity. These patients may report vague neurologic symptoms or radicular back pain during the course of treatment that may be an early sign of neurologic damage. Findings at neurologic examination may not indicate loss of function, but

Table 61-3 National Cancer Institute Common Terminology Criteria for Adverse Events: Neurologic Toxicities

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Navigation note: ADD is graded as Cognitive disturbance.						
Navigation note: Aphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Apnea	Apnea	—	—	Present	Intubation indicated	Death
Arachnoiditis/ meningismus/ radiculitis	Arachnoiditis	Symptomatic, not interfering with function; medical intervention indicated	Symptomatic (e.g., photophobia, nausea), interfering with function but not interfering with ADLs	Symptomatic, interfering with ADLs	Life-threatening; disabling (e.g., paraplegia)	Death
Also consider: Fever (in the absence of neutropenia, defined as ANC $<1.0 \times 10^9$/L); Infection (documented clinically or microbiologically) with grade 3 or 4 neutrophils (ANC $<1.0 \times 10^9$/L)–*Select*; Infection with normal ANC or grade 1 or 2 neutrophils–*Select*; Infection with unknown ANC–*Select*; Pain–*Select*; Vomiting.						
Ataxia (incoordination)	Ataxia	Asymptomatic	Symptomatic, not interfering with ADLs	Symptomatic, interfering with ADLs; mechanical assistance indicated	Disabling	Death
Remark: Ataxia (incoordination) refers to the consequence of medical or operative intervention.						
Brachial plexopathy	Brachial plexopathy	Asymptomatic	Symptomatic, not interfering with ADLs	Symptomatic, interfering with ADLs	Disabling	Death
CNS cerebrovascular ischemia	CNS ischemia	—	Asymptomatic, radiographic findings only	Transient ischemic event or attack (TIA) ≤24 hr duration	Cerebral vascular accident (CVA, stroke), neurologic deficit >24 hr	Death
Navigation note: CNS hemorrhage/bleeding is graded as Hemorrhage, CNS in the Hemorrhage/Bleeding category.						
CNS necrosis/cystic progression	CNS necrosis	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADLs; medical intervention indicated	Symptomatic and interfering with ADLs; hyperbaric oxygen indicated	Life-threatening; disabling; operative intervention indicated to prevent or treat CNS necrosis/ cystic progression	Death
Cognitive disturbance	Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part-time basis indicated	Severe cognitive disability; significant impairment of work/ school/life performance	Unable to perform ADLs; full-time specialized resources or institutionalization indicated	Death
Remark: Cognitive disturbance may be used for ADD.						
Confusion	Confusion	Transient confusion, disorientation, or attention deficit	Confusion, disorientation, or attention deficit interfering with function, but not interfering with ADLs	Confusion or delirium interfering with ADLs	Harmful to others or self; hospitalization indicated	Death
Remark: Attention Deficit Disorder (ADD) is graded as Cognitive disturbance.						
Navigation note: Cranial neuropathy is graded as Neuropathy–cranial–*Select*.						
Dizziness	Dizziness	With head movements or nystagmus only; not interfering with function	Interfering with function, but not interfering with ADLs	Interfering with ADLs	Disabling	—
Remark: Dizziness includes disequilibrium, lightheadedness, and vertigo.						
Also consider: Neuropathy: cranial–*Select*; Syncope (fainting).						

Table 61-3 National Cancer Institute Common Terminology Criteria for Adverse Events: Neurologic Toxicities—cont'd

		GRADE				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Navigation note: Dysphasia, receptive and/or expressive, is graded as Speech impairment (e.g., dysphasia or aphasia).						
Encephalopathy	Encephalopathy	—	Mild signs or symptoms; not interfering with ADLs	Signs or symptoms interfering with ADLs; hospitalization indicated	Life-threatening; disabling	Death
Also consider: Cognitive disturbance; Confusion; Dizziness; Memory impairment; Mental status; Mood alteration–*Select*; Psychosis (hallucinations/delusions); Somnolence/depressed level of consciousness.						
Extrapyramidal/involuntary movement/restlessness	Involuntary movement	Mild involuntary movements not interfering with function	Moderate involuntary movements interfering with function, but not interfering with ADLs	Severe involuntary movements or torticollis interfering with ADLs	Disabling	Death
Navigation note: Headache/neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, postinfectious neuralgia, or painful neuropathies) is graded as Pain–*Select* in the Pain category.						
Hydrocephalus	Hydrocephalus	Asymptomatic, radiographic findings only	Mild to moderate symptoms not interfering with ADLs	Severe symptoms or neurological deficit interfering with ADLs	Disabling	Death
Irritability (children <3 years of age)	Irritability	Mild; easily consolable	Moderate; requiring increased attention	Severe; inconsolable	—	—
Laryngeal nerve dysfunction	Laryngeal nerve	Asymptomatic, weakness on clinical examination/testing only	Symptomatic, but not interfering with ADLs; intervention not indicated	Symptomatic, interfering with ADLs; intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening; tracheostomy indicated	Death
Leak, cerebrospinal fluid (CSF)	CSF leak	Transient headache; postural care indicated	Symptomatic, not interfering with ADLs; blood patch indicated	Symptomatic, interfering with ADLs; operative intervention indicated	Life-threatening; disabling	Death
Remark: Leak, cerebrospinal fluid (CSF) may be used for CSF leak associated with operation and persisting >72 hours.						
Leukoencephalopathy (radiographic findings)	Leukoencephalopathy	Mild increase in subarachnoid space (SAS); mild ventriculomegaly; small (± multiple) focal T_2 hyperintensities, involving periventricular white matter or <1/3 of susceptible areas of cerebrum	Moderate increase in SAS; moderate ventriculomegaly; focal T_2 hyperintensities extending into centrum ovale or involving 1/3 to 2/3 of susceptible areas of cerebrum	Severe increase in SAS; severe ventriculomegaly; near total white matter T_2 hyperintensities or diffuse low attenuation (CT)	—	—
Remark: Leukoencephalopathy is a diffuse white matter process, specifically NOT associated with necrosis. Leukoencephalopathy (radiographic findings) does not include lacunae, which are areas that become void of neural tissue.						
Memory impairment	Memory impairment	Memory impairment not interfering with function	Memory impairment interfering with function, but not interfering with ADLs	Memory impairment interfering with ADLs	Amnesia	—
Mental status*	Mental status	—	1–3 points below age and educational norm in Folstein Mini-Mental Status Exam (MMSE)	>3 points below age and educational norm in Folstein MMSE	—	—
Mood alteration–*Select*: • Agitation • Anxiety • Depression • Euphoria	Mood alteration–*Select*	Mild mood alteration not interfering with function	Moderate mood alteration interfering with function, but not interfering with ADL; medication indicated	Severe mood alteration interfering with ADLs	Suicidal ideation; danger to self or others	Death

Continued

Table 61-3 National Cancer Institute Common Terminology Criteria for Adverse Events: Neurologic Toxicities—cont'd

		Grade				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Myelitis	Myelitis	Asymptomatic, mild signs (e.g., Babinski's or Lhermitte's sign)	Weakness or sensory loss not interfering with ADLs	Weakness or sensory loss interfering with ADLs	Disabling	Death
Navigation note: Neuropathic pain is graded as Pain–*Select* in the Pain Category.						
Neuropathy: cranial–*Select* • CN I Smell • CN II Vision • CN III Pupil, upper eyelid, extraocular movements • CN IV Downward, inward movement of eye • CN V Motor–jaw muscles; Sensory–facial • CN VI Lateral deviation of eye • CN VII Motor–face; Sensory–taste • CN VIII Hearing and balance • CN IX Motor–pharynx; Sensory–ear, pharynx, tongue • CN X Motor–palate; pharynx, larynx • CN XI Motor-sternomastoid and trapezius • CN XII Motor–tongue	Neuropathy: cranial–*Select*	Asymptomatic, detected on exam/testing only	Symptomatic, not interfering with ADLs	Symptomatic, interfering with ADLs	Life-threatening; disabling	Death
Neuropathy: motor	Neuropathy–motor	Asymptomatic, weakness on exam/testing only	Symptomatic weakness interfering with function, but not interfering with ADLs	Weakness interfering with ADLs; bracing or assistance to walk (e.g., cane or walker) indicated	Life-threatening; disabling (e.g., paralysis)	Death
Remark: Cranial nerve *motor* neuropathy is graded as Neuropathy: cranial–*Select*. *Also consider*: Laryngeal nerve dysfunction; Phrenic nerve dysfunction.						
Neuropathy: sensory	Neuropathy–sensory	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Sensory alteration or paresthesia (including tingling), interfering with function, but not interfering with ADLs	Sensory alteration or paresthesia interfering with ADLs	Disabling	Death
Remark: Cranial nerve *sensory* neuropathy is graded as Neuropathy: cranial–*Select*.						
Personality/behavioral	Personality	Change, but not adversely affecting patient or family	Change, adversely affecting patient or family	Mental health intervention indicated	Change harmful to others or self; hospitalization indicated	Death
Phrenic nerve dysfunction	Phrenic nerve	Asymptomatic weakness on exam/testing only	Symptomatic but not interfering with ADLs; intervention not indicated	Significant dysfunction; intervention indicated (e.g., diaphragmatic plication)	Life-threatening respiratory compromise; mechanical ventilation indicated	Death
Psychosis (hallucinations/delusions)	Psychosis	—	Transient episode	Interfering with ADLs; medication, supervision or restrains indicated	Harmful to others or self, life-threatening consequences	Death
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, Babinski's sign, ↓ fine motor coordination)	Pyramidal tract dysfunction	Asymptomatic, abnormality on exam or testing only	Symptomatic; interfering with function but not interfering with ADLs	Interfering with ADLs	Disabling; paralysis	Death

Table 61-3 National Cancer Institute Common Terminology Criteria for Adverse Events: Neurologic Toxicities—cont'd

		GRADE				
Adverse Event	**Short Name**	**1**	**2**	**3**	**4**	**5**
Seizure	Seizure	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADLs	Seizures in which consciousness is altered; poorly controlled seizure disorder, with breakthrough generalized seizures despite medical intervention	Seizures of any kind which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death
Somnolence/ depressed level of consciousness	Somnolence	—	Somnolence or sedation interfering with function, but not interfering with ADLs	Obtundation or stupor; difficult to arouse; interfering with ADLs	Coma	Death
Speech impairment (e.g., dysphasia or aphasia)	Speech impairment	—	Awareness of receptive or expressive dysphasia, not impairing ability to communicate	Receptive or expressive dysphasia, impairing ability to communicate	Inability to communicate	—
Remark: Speech impairment refers to a primary CNS process, not neuropathy or end organ dysfunction.						
Also consider: Laryngeal nerve dysfunction; Voice changes/dysarthria (e.g., hoarseness, loss, or alteration in voice, laryngitis).						
Syncope (fainting)	Syncope (fainting)	—	—	Present	Life-threatening consequences	Death
Also consider: CNS cerebrovascular ischemia; Conduction abnormality/atrioventricular heart block–*Select*: Dizziness; Supraventricular and nodal arrhythmia–*Select*; Vasovagal episode; Ventricular arrhythmia–*Select*.						
Navigation note: Taste alteration (CN VII, IX) is graded as Taste alteration (dysgeusia) in the Gastrointestinal category.						
Tremor	Tremor	Mild and brief or intermittent but not interfering with function	Moderate tremor interfering with function, but not interfering with ADLs	Severe tremor interfering with ADLs	Disabling	—
Neurology—Other (Specify)	Neurology—Other (Specify)	Mild	Moderate	Severe	Life-threatening; disabling	Death

ADD, attention deficit disorder; ADLs, activities of daily living; ANC, absolute neutrophil count; CNS, central nervous system; CT, computed tomography.
*Folstein MF, Folstein SE, McHugh PR: Mini-mental state: a practical method for grading the state of patients for the clinician. *J Psychiatr Res* 1975;12:189–198.
From http://ctep.cancer.gov/forms/CTCAEv3.pdf, published August 9, 2006; accessed September 10, 2007.

an elevated CSF myelin basic protein level indicates that with subsequent treatment, the risk of myelopathy is high.[24,25]

Vincristine treatment can cause peripheral neuropathy. Some patients exhibit autonomic neuropathy out of proportion to the sensorimotor neuropathy. The autonomic dysfunction can lead to intestinal dysmotility, ileus, and viscus perforation. Therefore, all patients undergoing vincristine chemotherapy should be carefully evaluated for the development of abdominal symptoms. Obstipation from vincristine would mandate avoiding further vincristine treatment.

Modification of Drug Dosing or Order

In certain treatment regimens, altering the order of the drugs administered can result in a marked decrease in the risk of neurotoxic complications. The risk of methotrexate-induced leukoencephalopathy after therapy for meningeal leukemia or carcinoma is reduced if the chemotherapy treatments, particularly intrathecal chemotherapy, precede cranial radiation therapy.[5] The reason for this schedule-dependent toxicity is unknown. It has been suggested that radiation opens the blood-brain barrier, thereby increasing exposure of the brain to subsequent chemotherapy effects. Other regimens in which dose order seems important include combination chemotherapy with cisplatin and ifosfamide. Patients receiving cisplatin before ifosfamide are at greater risk for ifosfamide-induced encephalopathy.[135]

Despite concern for synergistic neurotoxicity, certain regimens have been shown not to cause excessive neurotoxic effects. For example, a phase I study of paclitaxel and cisplatin included frequent neurologic examinations as a critical component.[261] Despite the well-recognized effects of both drugs on the peripheral nervous system, minimal overlapping toxicity occurred. Cisplatin treatment caused dose-related loss of vibratory sensation, whereas paclitaxel treatment correlated with loss of peripheral motor function. These findings underscore the importance of including careful neurologic testing as a component of phase I and II trials of new drugs and combination therapies.

Protective Agents

Interest continues in developing agents that either block development of certain chemotherapy-induced neuropathies or help reverse toxicity. Published reports of studies of neuroprotection during chemotherapy have recently been reviewed.[262] In the former category, the agent ORG 2766 has been reported to protect against cisplatin neuropathy. This drug, a synthetic analog of corticotropin, was tested in a double-blind, placebo-controlled trial in which patients with

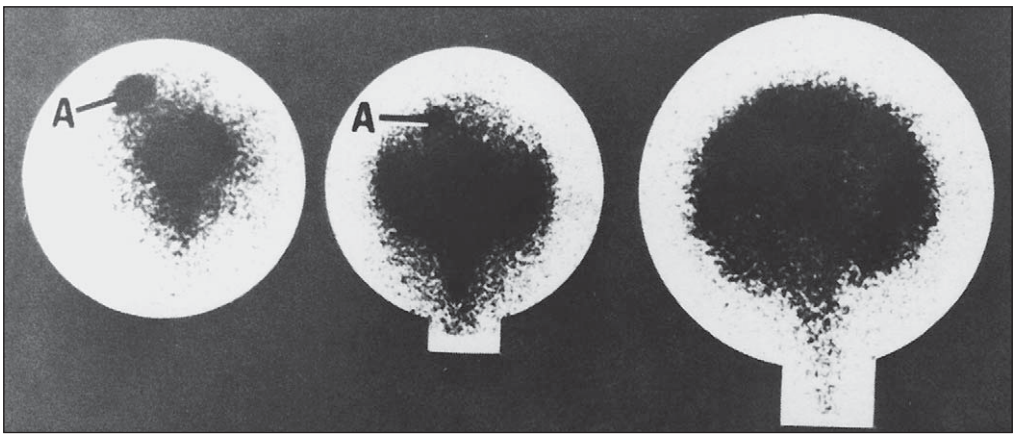


Figure 61-4 • Normal cerebrospinal fluid indium 111–diethylenetriaminepenta-acetic acid (DTPA) flow scan. Anterior cortical views immediately after injection *(left)*, at 4 hours *(middle)*, and at 24 hours *(right)*. A, reservoir.

ovarian cancer underwent intensive cisplatin therapy. A dose-related protective effect was found.[30] Although the mechanism of action is unknown, results of laboratory studies suggest that ORG 2766 works synergistically with trophic factors (e.g., nerve growth factors) to promote nerve regeneration.[263,264] Results of a study conducted with a tissue culture model suggested that corticotropin fragments may have a direct cellular protective role.[265] Amifostine, an organic thiophosphate, protects normal cells from the effects of radiation. Amifostine has been tested as a neuroprotectant with paclitaxel therapy in two phase III studies: A study of non-small-cell lung cancer found a reduction in incidence of radiation esophagitis but not in paclitaxel-induced neuropathy.[266] In a second study of ovarian cancer, the incidence of grade 3 and grade 4 peripheral neuropathy was significantly reduced.[267] Glutamine also has been evaluated as a neuroprotectant for the peripheral nervous system.[268] In a study with a small group of patients, the incidence of peripheral neuropathy among patients receiving paclitaxel plus glutamine (10 g orally, three times a day for 4 days after paclitaxel) was compared with the incidence when paclitaxel was given alone.[268] A statistically significant reduction in severe neuropathy was found in the glutamine treatment group, with significant decreases in the incidence and severity of dysesthesia, motor weakness, worsening of gait, and impairment of activities of daily living. Acetyl-L-carnitine has been reported to lessen neuropathic symptoms in patients receiving paclitaxel or cisplatin.[269] Alpha-lipoic acid, a broad-spectrum antioxidant, reportedly may help ameliorate symptoms from docetaxel and cisplatin or oxaliplatin neuropathy. Leucovorin may be helpful in reversing acute methotrexate-induced encephalopathy and somnolence.[37] The administration of methylene blue has been reported to accelerate recovery from ifosphamide-induced encephalopathy.[270] There is no known therapy for chemotherapy-induced leukoencephalopathy once brain injury has developed.

The acute neuropathic syndrome associated with oxaliplatin has generated special interest because of the painful nature of this toxicity. Various treatments including infusions of calcium gluconate, oral gabapentin, oral carbamazepine, intravenous amifostine, and intravenous glutathione have been used to prevent the development of this complication.[113,271] Infusions of calcium gluconate and alpha-lipoic acid also have been used to treat the acute neuropathy once it has developed.

Recognition of Groups at High Risk for Development of Neurotoxicity

Certain patients are at high risk for the development of treatment-related neurotoxicity. Patients with underlying peripheral neuropathy (e.g., Charcot-Marie-Tooth disease, diabetic neuropathy) have been reported to be much more susceptible to development of severe neuropathy, including potentially fatal autonomic neuropathy.[272,273] Such patients need careful monitoring with immediate cessation of treatment if autonomic dysfunction develops. Similarly, in patients in whom peripheral neuropathy may be a component of the cancer, such as multiple myeloma, the use of a neurotoxic agent such as bortezomib may increase the likelihood and severity of neuropathy.[194]

Patients with meningeal tumors (carcinoma, leukemia, lymphoma) often require extensive intrathecal chemotherapy. An intraventricular reservoir often is placed for this purpose. Before the reservoir system is used to administer chemotherapy, it is essential that correct placement and normal CSF flow be confirmed. This procedure is most readily performed by injecting indium 111-labeled albumin into the lateral ventricle through the reservoir system.[274,275] Not only does this test help confirm catheter placement, but also monitoring the flow of tracer at 6, 24, and 48 hours helps determine the presence of abnormalities of clearance from the ventricular system or drug resorption at the arachnoid granulations. Figure 61-4 shows normal CSF flow and resorption of tracer through the arachnoid granulations. By contrast, Figures 61-5 and 61-6 show poor outflow from the lateral ventricles persisting 24 hours after contrast injection. Poor clearance of drug markedly increases the neurotoxicity of intraventricular treatment. Patients with poor ventricular outflow may

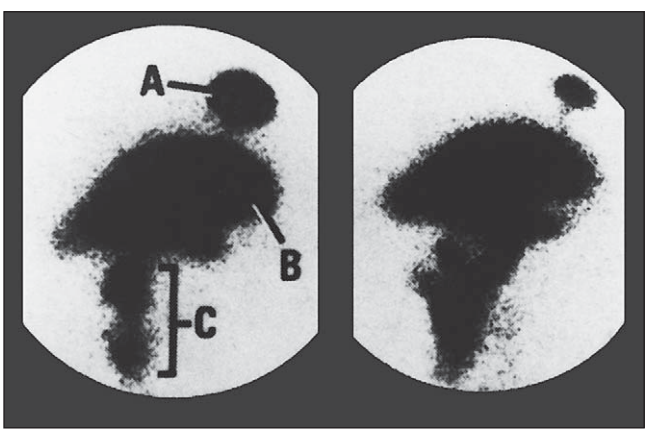


Figure 61-5 • Ventricular outlet obstruction, lateral cortical view. Scans immediately after injection *(left)* and hours later *(right)*. The reservoir (A), lateral ventricles (B), and fourth ventricle (C) are visible.

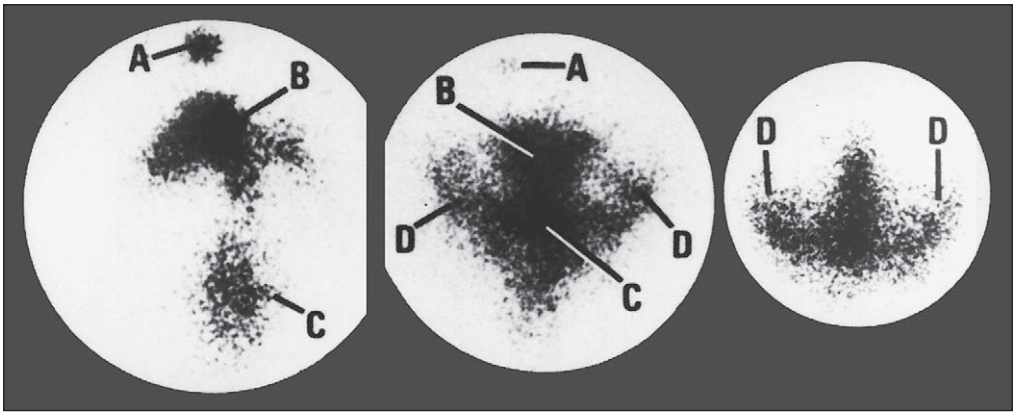


Figure 61-6 • Obstruction of flow over cortical convexities. Scans immediately after injection *(left)*, at 4 hours *(middle)*, and at 24 hours *(right)*. Visible are the reservoir (A), lateral ventricles (B), fourth ventricle (C), and tracer rising over the low portion of the cortical convexities (D).

need local radiation therapy for restoration of normal flow before instillation of chemotherapeutic agents.

Irreversible ototoxicity from cisplatin administration is more severe in patients with underlying hearing loss. Hearing loss with cisplatin also may be accelerated when the inner ear region and temporal lobe are included in the irradiated field.[118] Radiation treatment before or after cisplatin administration can cause this synergistic ototoxicity.

CONCLUSIONS

The incidence of chemotherapy-induced neurotoxicity is increasing as a consequence of advances in supportive care, use of higher doses of drugs, newer treatments targeted at the CNS, and prolonged patient survival, which allows toxicities with long latencies to become evident. The diagnosis of treatment-associated neurotoxicity is made after other diagnostic possibilities are excluded and when the pattern of toxicity is consistent with recognized neurotoxic effects. In most cases, options for management of treatment-associated neurotoxicity are limited. The optimal strategy is early recognition of neurotoxicity, careful monitoring of patients at increased risk for toxicity, and modification of regimens to avoid synergistic toxicity when possible. Future directions should include investigation of the mechanisms of toxicity and development of techniques for protecting the nervous system without altering the antineoplastic effect of treatment.

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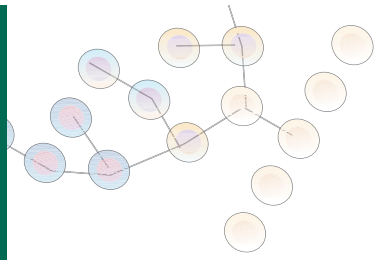
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62 Pulmonary Complications of Anticancer Treatment

Mitchell Machtay

SUMMARY OF KEY POINTS

Radiation Pneumonitis

Risk Factors

- Older age
- Lower performance status
- Lower baseline pulmonary function
- Large radiation volume treated with more than a "threshold" dose (it is frequently debated what this threshold dose is; the range is from 5 to 20 Gy)
- Cumulative radiation dose
- Lower lobe primary tumor
- Levels of cytokines such as TGF-β and interleukin-6

Diagnosis

- The most predominant symptoms are dyspnea and hypoxia, especially on exertion.
- Fever (usually low grade), cough, pleuritic chest pain, and other pulmonary symptoms are also common.
- Diffusing capacity of the lung for carbon dioxide is the most sensitive value during pulmonary function testing.
- Interstitial or ground-glass infiltrate usually, but not always, corresponds well to the irradiated volume.
- Findings at bronchoscopy are relatively unremarkable (bronchial lavage may reveal lymphocytosis).
- Pulmonary embolism, infection, and progressive tumor must be ruled out. These conditions can coexist with radiation pneumonitis.
- Response to corticosteroids is usually rapid.

Treatment

- The best treatment is prevention. Patients must be selected carefully for thoracic radiation, and irradiated volumes must be limited.
- Corticosteroids are very useful in the management of acute and subacute pneumonitis (although they have no prophylactic or therapeutic value in the management of long-term radiation fibrosis).
- Consultation with a pulmonologist is necessary.
- Oxygen is administered as indicated to prevent hypoxia.
- High doses of corticosteroids (60 mg/day of prednisone) with slow tapering are needed for severe grade 2 or any grade 3 radiation pneumonitis.
- If prolonged corticosteroid treatment is anticipated, prophylaxis against corticosteroid complications is needed. These measures include gastrointestinal prophylaxis, diet and pharmacologic management of hyperglycemia, infection prophylaxis, and osteoporosis prophylaxis.
- Antibiotics, bronchodilators, diuretics, and anticoagulation are administered as indicated for coexisting cardiopulmonary illnesses.

Drug-Induced Lung Injury

Risk Factors

- Usually, bleomycin, nitrosoureas, and mitomycin or combinations of several potentially pneumotoxic agents that on their own may only have modest pneumotoxicity (e.g., gemcitabine and weekly docetaxel)
- Bone marrow transplantation
- Concurrent or recent thoracic radiation therapy
- Lower baseline pulmonary function

Diagnosis

- Dyspnea and hypoxia are predominant, but a wide range of possible symptoms exists.
- Interstitial or ground-glass infiltrate usually is diffuse throughout both lungs and may be worse in the lower lobes.
- Findings at bronchoscopy are relatively unremarkable (bronchial lavage may reveal lymphocytosis).
- Pulmonary embolism, infection, and progressive tumor must be ruled out and may coexist with drug-induced lung injury.
- Injury is usually (but not universally) corticosteroid responsive; less likely to respond well to steroids than radiation pneumonitis but more likely to respond well than late radiation fibrosis.

Treatment

- When the diagnosis is suspected, the suspected causative agent should be discontinued.
- Consultation with a pulmonologist is necessary.
- Oxygen is administered as indicated to prevent hypoxia. (Note that high FiO_2 levels may be dangerous in bleomycin-related pneumonopathy).
- High doses of corticosteroids (≥60 mg/day of prednisone) with slow taper may be needed for severe grade 2 or any grade 3 pneumonitis.
- If prolonged corticosteroid treatment is anticipated, prophylaxis against corticosteroid complications entails gastrointestinal prophylaxis, diet or pharmacologic management of hyperglycemia, infection prophylaxis, and osteoporosis prophylaxis.
- Antibiotics, bronchodilators, diuretics, and anticoagulation are administered as indicated to manage coexisting cardiopulmonary illnesses.

INTRODUCTION

Although relatively uncommon, pulmonary disorders are among the most feared complications of anticancer therapy. Many cancer patients are elderly and/or suffering from one or more underlying comorbidities; therefore, a relatively minor challenge to the lungs can result in respiratory failure and death.

The two major categories of pulmonary complications are radiation pneumonopathy and drug-induced pneumonopathy. These conditions do not include other major categories of pulmonary disease in cancer patients, such as pulmonary embolism, infection (community-acquired, atypical, and aspiration pneumonia), and anatomic complications of tumor and/or medical-surgical interventions, such as pulmonary hemorrhage and fistula. Radiation therapy or chemotherapy can contribute to these multifactorial problems of the respiratory system.

Radiation pneumonopathy and drug-induced pneumonopathy share several important features, most notably that they are usually processes of the interstitium of the lung and thus can cause marked impairment of gas exchange and dyspnea. Corticosteroids are the mainstay of management of both types of pneumonopathy but at best may provide a only a temporary symptomatic improvement and at worst can cause life-threatening infections or other complications. Better techniques for avoiding treatment-related pneumonopathy—and better therapy for established pneumonopathy—will come only from improved understanding of and intervention against the complex molecular processes that cause and maintain these pathologic states.

PULMONARY TOXICITY OF THORACIC RADIATION THERAPY

Thoracic radiation is probably the most important cause of pulmonary toxicity in oncology. Lung toxicity from radiation is a clinically relevant issue for lymphoma, breast cancer, bone marrow transplantation (BMT), esophageal cancer, and lung cancer. Figure 62-1 illustrates a typical case of radiation pneumonitis and its sequelae.

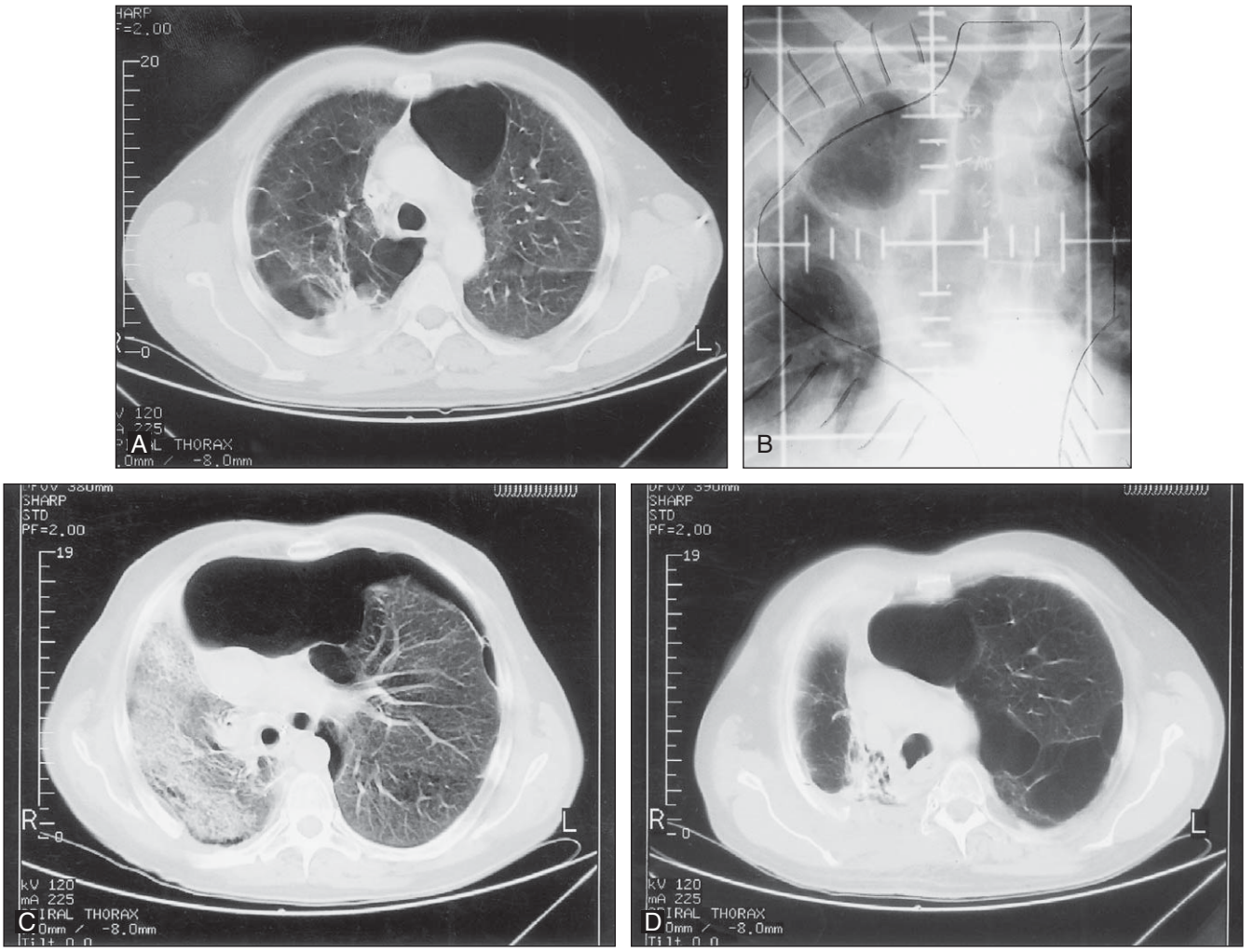


Figure 62-1 • Case example of radiation pneumonopathy. **A,** Diagnostic computed tomographic (CT) scan shows signs of advanced chronic obstructive pulmonary disease with bullous disease in an elderly man who had dyspnea and chest pain. Posteriorly located adenocarcinoma of the lung was found and clinically staged $T_3N_0M_0$. **B,** Radiation simulation image. The patient underwent gross total surgical resection but was found to have positive tumor margins and received radical radiation therapy to the chest. **C,** CT scan. Approximately 6 weeks after radiation therapy, progressively severe dyspnea developed, culminating in profound dyspnea necessitating hospitalization. Grade 3 acute radiation pneumonitis in the right lung was found with left-sided pneumothorax. The patient was treated with steroids, antibiotics, and a Pleurx catheter. **D,** CT scan. Approximately 1 year later, the patient's condition was stable with no evidence of recurrent cancer. The patient had discontinued steroid therapy but needed intermittent oxygen therapy for radiation fibrosis of the right lung.

The mechanisms behind radiation-induced lung injury remain poorly understood despite decades of study. A detailed review of the histopathologic and molecular events occurring in radiation pneumonopathy is beyond the scope of this chapter; several excellent reviews have been published in the last decade.[1–3] Irradiation damages endothelial cells, epithelial cells (particularly surfactant-producing type II pneumocytes), and reticuloendothelial cells within the lung through several mechanisms, including apoptosis and induction of stress response genes. It is now generally agreed that cytokines, such as transforming growth factor beta (TGF-β), play a major role in promoting radiation pneumonopathy, including development of long-term fibrosis.[4,5] It can be difficult histopathologically (or molecularly) to differentiate established radiation lung injury from other forms of end-stage lung disease, such as idiopathic pulmonary fibrosis, drug-induced injury, or even very advanced chronic obstructive pulmonary disease. Traditional clinical understanding of radiation lung injury recognizes two distinct syndromes: radiation pneumonitis and radiation fibrosis of the lung. Radiation pneumonitis is characterized by intense interstitial inflammation and alveolar exudate. It develops over several weeks to months after irradiation and (if the host/patient survives) resolves within 6 to 12 months. Radiation pulmonary fibrosis, in contrast, generally does not begin until several months after radiation therapy but progresses relentlessly over years. Radiation pneumonitis usually responds well to corticosteroids; in fact, a dramatic response to steroids helps to distinguish this disorder from other diagnoses. In contrast, corticosteroids do not influence the progression of radiation pulmonary fibrosis.

In most cases, radiation lung injury is confined to the regions of the lung within the radiation field or portal. This conventional wisdom has been challenged by several researchers who have found evidence of "out-of-field" radiation injury, which may be manifested in a syndrome similar to bronchiolitis obliterans with organizing pneumonia (BOOP).[6] In the most severe cases, diffuse acute respiratory distress syndrome can result from partial lung irradiation even with steroid treatment.[7] Autoimmunity has been hypothesized as a mechanism of out-of-field radiation lung injury, with the possibility that localized lung damage triggers diffuse lymphocyte-mediated hypersensitivity against pulmonary self antigens.[8]

Radiation lung injury may have any of a variety of clinical and radiographic presentations, but the hallmark symptom is generally dyspnea out of proportion to other findings. The most common imaging finding is an interstitial infiltrate corresponding to the radiation portals, but it is not unusual to find consolidation, nodularity, or even pleural effusions. The extent of radiographic findings does not necessarily correlate with the extent of symptoms or the patient's clinical course.[9] This problem can make the differential diagnosis among recurrent/progressive cancer, infection, and radiation lung injury extremely difficult, particularly in patients with lung cancer. Positron emission tomography with fluorodeoxyglucose may be helpful for differentiating recurrence from radiation toxicity, although intense radiation pneumonitis and even actively developing fibrosis causes elevated fluorodeoxyglucose uptake.[10]

Incidence of Radiation Lung Injury and Predictive Factors

The most important factor influencing development of clinically relevant radiation lung injury is the volume of lung irradiated; this issue is extensively discussed in the radiation oncology literature.[11–15] In radiation oncology, the lung is considered a parallel-architecture organ, meaning that destruction of very small portions of it should not cause overall organ dysfunction. In contrast, other organs, such as the spinal cord, are considered series-architecture organs, in which destruction of one region will lead to irreversible dysfunction downstream from that injury.[16]

Irradiation of the entire lung volume (bilateral lungs) is uncommon today, except as part of total body irradiation for selected BMT conditioning regimens. As reviewed by Sampath and colleagues, the therapeutic index for whole-lung irradiation is extraordinarily narrow and highly dependent on total dose, fractionation, partial lung transmission shielding, and dose rate[17]; a typical dose of 12 Gy total body irradiation has approximately 11% rate of severe pneumonitis, compared with approximately 2% when lung transmission shielding is used to reduce the lung dose to 6 Gy. At the other extreme, irradiation of small lung volumes rarely results in radiation pneumonitis. For example, in tangential irradiation of the breast (after lumpectomy) or chest wall (after mastectomy), the risk of clinically significant radiation pneumonitis is approximately 1%, increasing to approximately 5% with the addition of irradiation of the regional (axillary/supraclavicular) nodes.[18–20] Furthermore, radiation pneumonitis after small-volume thoracic radiation therapy such as this may be relatively mild and usually resolves completely.

Understanding the true incidence of radiation pneumonopathy is complicated by limitations of the historical and current standards for defining and grading this illness.[19] The traditional scoring system developed by the Radiation Therapy Oncology Group (RTOG), which dates back to the early 1970s, is shown in Table 62-1.[20,21] This system is no longer endorsed by major academic centers or organizations because of its several limitations[22]; however, understanding of this system is important because most modern publications rely on it. Among the limitations of the RTOG scoring system are that grade 1 radiation lung injury is almost certainly

Table 62-1 Traditional Scoring System for Radiation Lung Injury Based on the Radiation Therapy Oncology Group

Grade	(Acute) Radiation Pneumonopathy (Within 90 Days of Start of XRT)	(Late) Radiation Pneumonopathy (>90 Days After Start of XRT)
1	Mild, dry cough; dyspnea on significant exertion	Asymptomatic (e.g., slight radiographic findings only) or mild symptoms (e.g., dry cough).
2	Dyspnea on minimal exertion and/or persistent cough (requiring narcotics)	Moderate symptomatic fibrosis and/or pneumonitis (severe cough), fever, patchy radiographic appearances
3	Obvious severe radiation pneumonitis with dyspnea at rest and/or severe cough unresponsive to narcotics. Oxygen and/or steroids are indicated.	Severe symptomatic fibrosis/pneumonitis with dense radiographic changes
4	Life-threatening respiratory insufficiency requiring continuous oxygen/mechanical ventilation	Life-threatening respiratory insufficiency requiring continuous oxygen/mechanical ventilation
5	Death	Death

RTOG, 2000 #497;RTOG, 2000 #498.

underreported and that the distinction between grade 2 and grade 3 toxicity is highly subjective. Furthermore, the RTOG has in the past arbitrarily divided toxicity scales into early versus late on the basis of a 90-day cutoff point from the start of radiation therapy; this is inappropriate for many types of complex radiation injuries such as pneumonopathy. The new Common Terminology Criteria (CTCv3) for adverse events has been adopted for current and future studies.[23,24] The CTCv3.0 definitions and grading for selected pulmonary events are shown in Table 62-2. There have been numerous changes to the scoring criteria in the pulmonology section, and sep-

Table 62-2 CTCv3.0 Selected Common Terminology Criteria for Adverse Events Related to the Lung

Event	Grade 1	Grade 2	Grade 3	Grade 4
Acute respiratory distress syndrome	N/A	N/A	Present; intubation not required	Present; intubation required
Aspiration	Asymptomatic ("silent")	Symptomatic (e.g., altered eating habits, coughing/choking episodes); medical intervention required	Clinical or radiographic signs of pneumonia; unable to aliment orally	Life-threatening aspiration pneumonia
Atelectesis	Asymptomatic	Symptomatic (e.g., dyspnea, cough), medical intervention indicated (e.g., bronchoscopy)	Severe; operative intervention (e.g., stent, laser) indicated	Life-threatening respiratory compromise
Carbon monoxide diffusion capacity (DLCO)	90% to 75% of predicted value	74% to 50% of predicted value	49 % to 25% of predicted value	<25% of predicted value.
Cough	Symptomatic, nonnarcotic medication used	Symptomatic, requires narcotics	Symptomatic and significantly interfering with sleep or activities of daily living	N/A
Dyspnea	Dyspnea on exertion but able to walk up one flight of stairs without stopping.	Dyspnea on exertion, unable to walk one flight of stairs or one city block without stopping	Dyspnea with activities of daily living	Severe dyspnea at rest; intubation/ventilator indicated
FEV1	90% to 75% of predicted value	74% to 50% of predicted value	49% to 25% of predicted value	<25% of predicted value
Fistula	Asymptomatic (imaging findings only)	Symptomatic; medical management	Symptomatic; invasive management indicated	Life-threatening consequences (e.g., requiring multiple thoracotomies)
Hypoxia	N/A	Decreased O_2 saturation with exercise (<88% pulse oximetry)	Decreased O_2 saturation at rest; continuous oxygen therapy indicated	Life-threatening; intubation/ventilator indicated
Pleural effusion (nonmalignant)	Asymptomatic	Symptomatic, requiring intervention such as diuretics or 1 to 2 therapeutic thoracenteses	Symptomatic requiring supplemental oxygen, >2 thoracenteses and/or chronic indwelling catheter and/or pleurodesis	Life-threatening (e.g., causing hemodynamic instability and/or intubation/ventilator indicated)
Pneumonitis/pulmonary infiltrates	Asymptomatic (imaging finding)	Symptomatic but not interfering with activities of daily living	Symptomatic, interfering with activities of daily living; O_2 indicated	Life-threatening; intubation/ventilator indicated
Pneumothorax	Asymptomatic (imaging finding)	Symptomatic, requiring intervention (e.g., hospitalization for observation or temporary chest tube)	Sclerosis and/or operative indication required	Life-threatening (e.g., causing hemodynamic instability and/or intubation/ventilator indicated)
Prolonged intubation (following elective surgery/intubation)	N/A	Extubated within 24 to 72 hours postoperatively	Extubated >72 hours	Tracheostomy indicated
Pulmonary fibrosis	Minimal imaging findings, estimated % of total lung volume that is fibrotic is estimated <25%	Estimated % of total lung volume that is fibrotic is 25% to 49%	Dense widespread infiltrates/consolidation with estimated % of total lung volume that is fibrotic 50% to 75%	Estimated % of total lung volume that is fibrotic is >75%; honeycombing

Note that this is an abbreviated/abridged version of the CTCv3; the complete version can be found at ctep.cancer.gov/forms/CTCAEv3.pdf.

Note that as with the older scoring systems, grade 5 (not shown) is death, and grade 0 is the absence of the particular toxicity. Note that for some adverse events, Grades 1 to 2 (mild to moderate) might not be applicable (e.g., ARDS); conversely, for some adverse events, Grade 4 (life-threatening) might not be applicable (e.g., cough).

Table 62-3 Selected Clinical Studies of the Incidence and Severity of Radiation Pneumonopathy

Study	Patient Population	Rate of Grade 2 Pneumonopathy (%)	Rate of Grade 3+ Pneumonopathy (%)	Comments
LUNG CANCER STUDIES				
Byhardt et al.[120]	388 patients treated with chemo-RT.	NS	17	2-dimensional, large-field XRT. Grade 3 RP 20% with concurrent chemo-RT versus 10% with sequential chemo-RT
Keller et al.[121]	488 patients with postoperative RT ± concurrent chemo	NS	3.5	Moderate (50 Gy) XRT dose; high performance status population.
Turrisi et al.[122]	417 patients (limited stage small cell cancer) with concurrent chemo-RT	12	5	No difference between once daily and twice a day XRT
Wang et al.[13]	223 patients treated with 3-D XRT + concurrent chemo	NS	32	Higher rate than other studies may reflect the use of actuarial statistics and CTCv3 definition
Hope et al.[123]	219 patients treated with high-dose 3-D XRT.	12	11	Strong association of RP with tumor location, lung DVH characteristics
STUDIES IN CANCERS OTHER THAN LUNG CANCER				
Lind et al.[124] (breast cancer)	613 patients with breast cancer		NS	RP was significantly more common with regional nodal irradiation
Yu et al.[125] (breast cancer)	189 patients with breast cancer randomized between different chemo regimens prior to RT	5	<1	High rate (24% to 39%) of radiographic changes but low rate of clinical RP
Hughes-Davies et al.[126] (Hodgkin's disease)	172 patients with bulky intrathoracic Hodgkin's disease	14	NS	1% fatal toxicity
Koh et al.[26] (Hodgkin's disease)	64 patients with Hodgkin's disease	3	<1	RP associated with larger lung volume irradiated
Cooper et al.[127] (esophageal cancer)	117 patients with esophageal cancer treated with chemo-RT	NS	4	
Ishikura et al.[128] (esophageal cancer)	139 patients with esophageal cancer treated with chemo-RT	2	2	Radiation-induced cardiac complications and/or pleural effusions were more common than RP

arate scales are no longer used for early and late radiation therapy-related events.

Despite limitations of the scoring systems for radiation lung injury, some clinical studies provide insight into the complex relations among volume of lung irradiated, regions of lung irradiated, radiation dose, and host factors. Table 62-3 summarizes the literature on this topic. Most clinical radiation oncology studies have focused on the concept of the dose-volume histogram (DVH), in which percentage of total lung irradiated is plotted against radiation dose. The concept of DVH and V20 is shown in Figure 62-2. With modern radiation planning software integrating findings at computed tomography (CT), DVHs are easy to generate. However, there is no consensus on how to interpret these plots. Some researchers suggest that the most relevant information obtained from DVHs is the V20 (percentage of total lung volume irradiated to more than 20 Gy (conventionally fractionated radiation therapy); others recommend

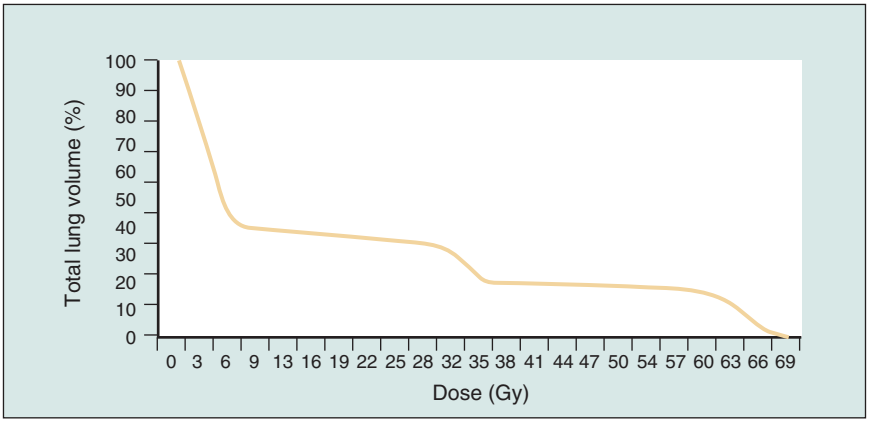


Figure 62-2 • Graphic representation (*yellow curve*) of dose-volume histogram for total lung volume irradiated to a nominal dose of 63 Gy in a patient with lung cancer. In this case, the V20 (the percentage of total lung volume receiving >20 Gy) is approximately 36%, which is considered a moderate-risk dose level for clinical radiation pneumonopathy.

emphasizing V30 (percentage of total lung volume irradiated to >30 Gy), V13, V5, and so on. Other researchers recommend using mean lung dose or complex formulas based on multiple parameters of the DVH curve to predict radiation pneumonitis. Retrospective studies conducted with moderate to large samples of patients with analyzable DVHs and clinical courses consistently show that lung toxicity is associated with lung DVH characteristics that reflect large volumes of irradiated lung. However, studies have not clearly defined a safe lung DVH in therapy for lung cancer. It is clear that irradiation of a smaller lung volume results in less pneumonopathy; a randomized trial showed that the incidence of radiation pneumonitis was significantly reduced from 29% to 17% with the use of "involved-field" radiotherapy, despite the use of higher tumor radiotherapy doses in the involved field arm.[25]

One flaw with the use of DVH analysis to predict radiation pneumonopathy is that the DVH is based solely on anatomic data, with no consideration of lung physiology or the patient's underlying health. In a DVH, every cubic centimeter of lung tissue is considered to have the same physiologic utility to the patient. This might be accurate for relatively young and healthy individuals such as Hodgkin's disease patients, who have a modest risk of radiation pneumonopathy,[26] but is almost certainly wrong for elderly smokers with cancer of the lung or esophagus. Among lung cancer patients, a higher risk of radiation pneumonopathy is seen for lower-lobe cancer treatment.[15,27] Nuclear medicine scans such as lung ventilation/perfusion scans may therefore be a useful adjunct to radiation planning.[28] Although radiation dose-volume parameters are the major predictor of radiation pneumonopathy, other factors are important. Some of these are treatment-related factors, including daily radiation fraction size[29] and the use of concurrent chemotherapy. The issue of chemotherapy has been particularly controversial and difficult to study. It appears that neoadjuvant chemotherapy before radiotherapy does not greatly affect the risk of radiation pneumonopathy. However, concurrent chemoradiotherapy probably increases the risk significantly; the maximum tolerated dose of localized radiotherapy with concurrent chemotherapy for non-small-cell lung cancer is generally considered to be 74 Gy.[30] Higher doses are achievable with radiotherapy alone.[14,31] A combination of concurrent radiotherapy and gemcitabine appears to have a particularly high rate of radiation pneumonopathy, and extreme caution is advised for this combination.[32] Several other drugs, most notably the anthracyclines (e.g., doxorubicin), methotrexate, and bleomycin, should be considered contraindicated during thoracic radiotherapy. Concurrent thoracic radiotherapy plus a taxane (paclitaxel or docetaxel) is a commonly used and generally safe combination, although it has been suggested that the risk of radiation pneumonopathy might be slightly higher than expected from historical series based on older chemo-RT regimens, particularly with weekly taxane schedules.[33,34] It may be especially prudent to use three-dimensional radiotherapy techniques and to carefully analyze lung DVH parameters in patients who are receiving a concurrent taxane.

Nontreatment factors that appear to be predictive of radiation lung injury have been studied. Not surprisingly, pretreatment performance status has been shown to correlate with development of clinical radiation pneumonopathy.[35] Underlying pretreatment pulmonary function is probably an important factor as well,[36] although study results have been inconsistent.[37,38] This might be because in many cases, poor pretreatment pulmonary function is due to effects of the cancer itself, in which case an effective treatment (such as radiotherapy) may substantially improve rather than harm pulmonary function.

Diagnosis and Management of (Acute and Subacute) Radiation Pneumonitis

With modern, conformal, multifield radiation therapy, it is no longer possible to simply look for pathognomonic rectangular infiltrates on a chest radiograph. A patient who has recently undergone radiation treatment and has dyspnea or other pulmonary symptoms of greater than grade 1 intensity should undergo CT scanning, in some cases with high-resolution CT imaging. CT angiography may also be indicated to rule out pulmonary embolism. Imaging will typically reveal an interstitial infiltrate and/or ground-glass appearance, which can be very difficult to distinguish from an infection. Suspected moderate to severe radiation pneumonopathy should be evaluated by a pulmonologist for consideration of bronchoscopy to rule out infection, particularly if fever is present.[39]

Pulse oximetry or arterial blood gas testing should be performed to assess the need for supplemental oxygen. Pulmonary function testing, especially the diffusion capacity of the lung for carbon monoxide (DLCO) test, is useful as part of the diagnostic workup, in particular to assess the severity of gas-exchange dysfunction. Spirometric parameters of pulmonary function are frequently reversible after radiation pneumonopathy, while DLCO abnormalities are less likely to improve.[40] The tests and procedures to be considered in evaluation of cancer patients with suspected pneumonopathy are summarized in Table 62-4. This workup should be considered appropriate for either suspected radiation-related or chemotherapy-related pneumonopathy.

If the clinical manifestations and test results are consistent with grade 2 or greater radiation pneumonitis, administration of corticosteroids should be instituted in most cases. Controlled randomized trials of corticosteroids for radiation pneumonitis have not been conducted with human subjects. However, the efficacy of corticosteroids has been well established in nonrandomized clinical studies[41] and in preclinical models.[42] There is no single "standard" dose schedule for steroid therapy for radiation pneumonopathy; the exact schedule must be tailored to the individual patient. In general, for severe (grade 3) radiation pneumonitis, prednisone approximately 1 mg/kg/day is indicated for 2 weeks. Brief hospitalization for intravenous administration of steroids may be indicated. Early onset of radiation pneumonitis following the completion of radiotherapy may predict a more virulent course and therefore might require a more aggressive management approach.[7] Moderate radiation pneumonitis (grade 2) may be effectively managed with somewhat lower initial doses of steroids (e.g., 0.5 to 0.75 mg/kg/day of prednisone); however, the patient must be evaluated frequently to ascertain that his or her condition is not progressing to grade 3 or worse radiation pneumonitis. After several weeks, the dose should be tapered gently, by approximately 10 mg every 2 weeks. It is not unusual for patients to have a symptomatic relapse in the setting of steroid taper.[43] If relapse occurs, it is important to rule out concomitant infection. If the diagnosis of recurrent radiation pneumonitis is confirmed, the steroid dose should be increased and titrated accordingly.

With these guidelines, the typical patient with grade 3 or intense grade 2 radiation lung injury will take steroids for approximately 2 to 4 months. Some patients need steroids for considerably longer, although the benefit after 6 months is dubious (when radiation pneumonitis has generally resolved and might be superseded by fibrosis). At the outset, the physician should explain to the patient the potential need and implications of longer-term steroid use. A proton-pump inhibitor or histamine$_2$-blocker should be prescribed to counteract gastritis. Consideration should be given to evaluation for, and medical prophylaxis against, osteoporosis. Patients should be counseled about exercise (as tolerated by their pulmonary symptoms) and diet to minimize problems with steroid-induced hyperglycemia and muscle wasting. Blood chemistry values, including fasting glucose, liver function tests, and albumin, should be checked periodically. If a diuretic is being used with steroids, it is important to check serum electrolyte levels frequently.

It is uncertain whether a low-dose "prophylactic" antibiotic should be prescribed. In any given patient with interstitial pneumonitis after thoracic radiotherapy, it can be very difficult to entirely rule out a concomitant infection, particularly if bronchoscopy or other invasive

Table 62-4 Evaluation of the Cancer Patient with Pulmonary Symptoms (Especially Dyspnea) and Suspected Radiation or Chemotherapy Pneumonopathy

Study	Rationale
Basic, minimal workup	
CT of chest, preferably both with and without contrast	Assess extent/appearance/location of infiltrates/effusions; correlate with radiation therapy and/or surgical data. Rule out recurrent/progressive cancer and/or other etiologies for dyspnea.
Pulse oximetry	Assess degree of hypoxia and possible need for supplemental oxygen.
Pulmonary function testing (spirometry and DLCO)	Assess extent and type of pulmonary function (radiation/drug pneumonitis is a restrictive pattern, with DLCO often markedly abnormal compared with baseline levels).
CBC/diff; chemistry panel	Rule out leukocytosis and/or leucopenia (possible signs of infection), anemia, hepatic and/or renal insufficiency (all factors that can lead to pulmonary distress).
Extended workup (if diagnosis is in question and/or if there is possibility of coexisting cardiorespiratory problems)	
High-resolution pulmonary-embolus protocol CT scan, V/Q scan and/or pulmonary angiogram	Rule out pulmonary embolism.
Electrocardiogram	Rule out cardiac ischemia and/or dysrhythmia.
Blood test for B-type natriuretic peptide (BNP)	Rule out CHF.
Arterial blood gas testing	More accurate measure of oxygenation than pulse oximetry; measurement of pH and CO_2 levels.
Blood cultures	Rule out sepsis and/or endocarditis.
Bronchoscopy	Rule out infection (particularly if atypical infection is suspected) and assess for possible recurrent cancer.
PET/CT scan	Assessment of status of the cancer; possible role as adjuvant form of imaging the extent of lung injury.
Open lung biopsy (e.g., thoracoscopic biopsy)	Definitive diagnosis but high-risk procedure. Avoid if diagnosis is highly likely and response to steroids is good.

Notice that chest x-ray is not a sufficiently sensitive or specific test to warrant inclusion in this table.

diagnostic procedure was not done.[39] In light of the profound lymphopenia that most patients have after chemoradiation therapy and steroid treatment (as with typical concurrent paclitaxel-radiation therapy regimens), it might be appropriate to prescribe an every-other-day dose of trimethoprim-sulfamethoxazole (Bactrim) when starting high-dose steroids.[44,45] If findings at chest CT suggest the presence of coexistent active infection, broader and more intense antibiotics are indicated. The patient should undergo bronchoscopy if there is no improvement after several days of steroid and antibiotic therapy.

The prognosis of grade 1 to 2 radiation pneumonitis is relatively good with meticulous supportive care and the use of steroids as needed. Grade 3 radiation pneumonitis, however, at least in lung cancer patients, has a much worse prognosis.[7,13] It is uncertain whether this is the direct result of radiation pneumonitis or coexisting problems, including tumor recurrence and infection.

It is uncertain how to manage radiation pneumonopathy that is refractory to steroids and/or in the patient who has severe contraindications to steroids. There have been case reports of the use of antirheumatic medications such as cyclosporin,[46,47] but there is little scientific evidence to support their use.

As described in the following sections, patients with radiation pneumonitis should receive supportive care based on careful and frequent assessment of their symptoms and risk factors for further complications of their illness.

Management of (Chronic and Late) Radiation Pulmonary Fibrosis

Although radiation pneumonitis usually is relieved with steroids, radiation pulmonary fibrosis is not. Some patients undergoing steroid therapy for radiation pneumonitis eventually start to experience worsening pulmonary function. This decline may be caused by pulmonary fibrosis but also may be caused at least in part by disorders such as infection, cardiac problems, and pulmonary embolism, and reevaluation is indicated. If it has been more than 6 months since the patient has undergone radiation therapy and/or chemotherapy, increasing the steroid dose is unlikely to yield benefit.

Management of radiation pulmonary fibrosis is supportive. Emphasis is on administration of oxygen, management of acute infection, bronchodilator therapy if needed, gentle diuresis if needed, and maximization of the other components of tissue oxygen delivery (e.g., cardiac and blood pressure medications and correction of anemia). Acute episodes of radiation pneumonitis may still occur, particularly if the patient receives a "radiation recall" type of drug; therefore, steroids might be needed periodically. It is unknown whether pulmonary rehabilitation programs involving exercise and weight maintenance are helpful for radiation pulmonary fibrosis. Patients who are disabled or immobilized owing to their pulmonary insufficiency might benefit from DVT prophylaxis. Tobacco should be strictly avoided.

Trials of Prevention or Management of Radiation Pulmonary Fibrosis

As is shown in Table 62-5, results of studies have suggested that prophylactic administration of amifostine during thoracic radiation therapy ameliorates radiation pneumonopathy.[48,49] However, these data are based on preclinical data supporting the role of amifostine as a protective agent against radiation pulmonary fibrosis. However, at this time, the routine use of amifostine is not standard, since the "positive" studies were relatively small, while a larger confirmatory study was disappointing.[50] In addition, amifostine is logistically and financially difficult to deliver and is associated with its own toxicities

Table 62-5 Randomized Trials of the Effect of Amifostine on Radiation Pneumonopathy after Radiation Therapy (± Chemotherapy) for Lung Cancer

Study	Patients/Characteristics	Amifostine Dose	Grade 2+ RP Without Amifostine (%)	Grade 2+ RP with Amifostine (%)
Antonadou et al.[129]	97 patients with Stage III NSCLC treated to 55 to 60 Gy without chemo	340 mg/m^2/day	43	9 ($P = 0.001$)
Antonadou et al.[130]	73 patients with stage III NSCLC treated to 55 to 60 Gy + chemo	300 mg/m^2/day	56	19 ($P = 0.002$)
Komaki et al.[131]	53 patients with Stage III NSCLC treated to 69.6 Gy + chemo	500 mg twice per week	16*	0* (Grade 3) ($P = 0.02$)
Movsas et al.[50]	205 patients with Stage III NSCLC treated to 69.6 Gy + chemo	500 mg four times per week	27	27

NSCLC, non-small cell lung carcinoma; RP, radiation pneumonopathy.
*Grade 3 RP.

(nausea, fatigue, skin rash). Its effectiveness is likely highly correlated with dose and schedule, and amifostine has no known role or rationale as a treatment once radiation has been completed.

Other nonspecific antioxidants have been studied as means of decreasing radiation fibrosis, although they are not necessarily specific for the lung.[51–53] Gene therapy to deliver antioxidants to the lung is under study. Researchers from the University of Pittsburgh have developed a system in which the gene for the potent antioxidant enzyme manganese superoxide dismutase can be transfected into a plasmid and administered by inhalation.[52] This approach, still highly experimental, might offer a treatment without the systemic effects that amifostine and steroids induce.

The use of angiotensin-converting enzyme inhibitors, particularly captopril, has shown promise in preclinical rodent studies.[57] The mechanism of efficacy is unclear and might be related to the beneficial vasodilatory effects of these drugs on small blood vessels or might be due to antioxidant activity. One ongoing RTOG trial is testing the potential efficacy of captopril versus usual supportive care for lung cancer patients who are receiving radiation therapy and are thought to be at significant risk of radiation pneumonopathy. Increased understanding of the cytokine-based mechanisms of radiation lung injury may offer opportunities for intervention.[53,54] Because TGF-β is thought to be the dominant profibrotic cytokine and perhaps even a cause of radiation pneumonitis, attempts are underway to develop molecules with anti-TGF-β activity. As one example, keratinocyte growth factor, which is FDA-approved for amelioration of bone marrow transplant-associated mucositis, is under study in preclinical models of radiation fibrosis.[55]

Other Forms of Radiation-Induced Lung Injury

There is increasing recognition that high-dose radiation can contribute to other serious problems within the lung. One of the most feared complications is bronchopleural fistula, a postoperative complication that is significantly increased by the use of preoperative radiation therapy or chemoradiotherapy and is very difficult to manage.[56,57] Patients who receive neoadjuvant chemoradiation for stage III lung cancer should be considered for additional bronchial stump reinforcement (e.g., intercostal muscle flap) at the time of surgery in an effort to minimize this risk.

Endobronchial brachytherapy for palliation of obstructive endobronchial malignant tumors is associated with an approximately 10% risk of severe pulmonary complications, including massive hemoptysis and bronchial stenosis.[58] It often is difficult to differentiate the contribution of irradiation to these serious events from the contribution of the tumor itself. It should be noted that with the recent significant increase in external beam radiotherapy doses, similar complications are occasionally seen without brachytherapy as well.[59] It is likely that radiotherapy dose per fraction and the use of concurrent chemotherapy increase the risk of these understudied types of complications. As is shown in the case example in Figure 62-1, radiation lung injury can be associated with pneumothorax, perhaps as a result of radiation fibrosis causing increased traction on the lung as well as direct radiation injury to the pleura.[60]

PULMONARY TOXICITY OF SYSTEMIC ANTICANCER THERAPIES

Many chemotherapy drugs can cause pulmonary toxicity, the incidence ranging from less than 1% to more than 30%. The drugs that are most associated with pulmonary toxicity are bleomycin, methotrexate, cytosine arabinoside, mitomycin, and the nitrosoureas (especially carmustine [BCNU]). Table 62-6 is a broad categorization of anticancer therapies into high, moderate, and low risks of pneumotoxicity, although any individual patient may experience severe lung problems from any agent.

Unlike thoracic radiation therapy, which usually affects only the portion of lung within the radiation field, systemic agents often cause diffuse pneumonopathy. Although it is relatively rare in comparison with radiation pneumonopathy, chemotherapy-induced lung injury can be extremely intense and can even have a higher fatality rate than radiation pneumonitis. As with radiation pneumonitis, corticosteroids are commonly used and may be effective, particularly in early stages of injury. It is particularly important to rule out alternative and concurrent diagnoses (see Table 62-4). Unlike radiation injury, drug-induced lung toxicity can occur in a time frame during which it is possible to discontinue the offending agent. A review of some of the systemic agents associated with pulmonary toxicity follows.

Bleomycin

Bleomycin is the chemotherapy drug most commonly associated with lung damage. The reported incidence ranges from 3% to 40%.[61,62] This drug is used predominantly in the management of Hodgkin's disease and germ cell tumors, cancers that occur mainly in younger patients with less underlying pulmonary comorbidity than lung cancer patients. There are a number of similarities between bleomycin pneumonopathy and radiation pneumonopathy, including two patterns of disease (pneumonitis and fibrosis). As with radiation, the clinical manifestations of bleomycin lung toxicity usually occur weeks to months after the initiation of treatment. The infiltrates can be diffuse or limited to basilar and subpleural aspects of the lungs.[63] A

Table 62-6 Anticancer Therapies Categorized by Risk of Pneumotoxicity

Highly pneumotoxic agents (risk of pulmonary SAE probably >5%)	Bleomycin; BCNU; mitomycin; interleukins. Bone marrow transplantation (with or without TBI). Large-volume thoracic radiation therapy (e.g., T_4N3 lung cancer). Surgical resection for lung cancer.
Moderately pneumotoxic agents (risk of pulmonary SAE probably 1% to 5%)	Methotrexate; busulfan; melphalan; CCNU/MeCCNU; cyclophospamide; ifosfamide; fludarabine; gemcitabine; paclitaxel/docetaxel. Small-volume thoracic radiation therapy (e.g., breast cancer). Non-lung cancer oncologic surgery.
Uncommonly pneumotoxic agents (risk of pulmonary SAE probably <1%)	5-FU; capecitabine; cisplatin/carboplatin; doxorubicin; actinomycin-D; etoposide; topotecan/irinotecan; vincristine/vinblastine; vinorelbine; temozolomide; tamoxifen; aromatase inhibitors for breast cancer. Hormonal therapies for prostate cancer; steroids.
Pneumotoxicity risks present but of uncertain frequency	Anti-EGFR agents (e.g., ZD-1839); monoclonal Antibodies (e.g., anti-VEGF MoAb_; imatinib (Gleevac).

BCNU, carmustine; CCNU, lomustine; EGFR, epidermal growth factor receptor; 5-FU, 5-fluorouracil; MeCCNU, semustine; MoAb, monoclonal antibody; SAE, serious adverse event; TBI, total body irradiation; VEGF, vascular endothelial growth factor.

nodular pattern occasionally occurs, mimicking cancer progression. Imaging other than CT scanning is investigational, although there are reports of abnormal fluorodeoxyglucose-PET scan results in bleomycin pneumonopathy.[64]

As in radiation pneumonopathy, dyspnea is the primary symptom of bleomycin lung toxicity, although, as is the case with radiotherapy, other symptoms such as cough and fever often occur as well. Pulmonary function testing shows a restrictive pattern; DLCO is frequently abnormal. DLCO should be measured before bleomycin is started and periodically between cycles. A significant decrease in DLCO should prompt consideration of discontinuation of this drug. Although there is no consensus on what represents a "significant decrease" in DLCO, some investigators have conservatively used a criterion of a 20% decrease to warrant discontinuation of bleomycin.[65]

There appears to be an association between cumulative bleomycin dose and risk of pneumonopathy. Again, there is no consensus regarding the absolute maximum cumulative bleomycin dose for an individual patient; values of 300 to 400 mg maximum have been suggested.[61,66] (A typical cumulative dose of bleomycin from six cycles of ABVD (Hodgkin's disease) is approximately 120 mg/m^2.) Again, however, it must be stressed that occasionally life-threatening or even fatal pneumonopathy can occur with cumulative bleomycin doses less than 100 mg. Another important predictive factor (in addition to age and dose) for bleomycin pneumonopathy appears to be renal insufficiency,[61,66] which is particularly concerning in patients who are receiving nephrotoxic agents such as cisplatin. Other possible risk factors may include concomitant use of a colony-stimulating factor,[67] combined treatment with radiotherapy, and concomitant delivery with gemcitabine.[69,70] Exposure to high oxygen concentrations, as part of operative anesthesia, has been associated with potentiation of bleomycin pneumonopathy, particularly in animal models,[71] and in some cases led to acute respiratory distress syndrome.[72,73] Extreme caution is advised when supplemental oxygen is being electively prescribed for bleomycin-treated patients, especially those who are currently undergoing or recently finished bleomycin (less than 12 months) and/or have documented bleomycin pneumonopathy.[74]

Bleomycin pneumonitis is rarely fatal; one study estimated a lethality risk of about 3%, with a suggestion that older age was associated with a higher risk for death.[75] Most patients achieve complete or near-complete recovery.[75–79] Corticosteroids may have some benefit,[61,76,80] although the data are not as clear as those for radiation pneumonitis. Some cases of steroid-responsive bleomycin pneumonitis/fibrosis may represent early hypersensitivity, BOOP-like events. After bleomycin chemotherapy, cancer survivors may have significant declines in pulmonary function for approximately 6 months, but by 2 years after chemotherapy, few have significant respiratory dysfunction.

Antimetabolites

Methotrexate, which is commonly used in therapy for rheumatoid arthritis as well as for cancer, is the antimetabolite drug that is most commonly linked to pulmonary injury. It can cause interstitial pneumonitis similar to that caused by bleomycin and other drugs.[81–84] Steroid therapy may be indicated for severe cases.

Gemcitabine has become one of the most commonly used chemotherapy drugs for solid tumors, including lung cancer. When gemcitabine is used as a single agent in previously untreated cancer patients, the risk of significant pulmonary toxicity is small, although it is associated with an occasional severe respiratory insufficiency that may be related to capillary leak syndrome.[85] However, increasing data suggest that combinations of gemcitabine with other agents may severely potentiate those agents' pneumonopathy (see discussion in previous sections regarding thoracic radiotherapy and bleomycin), in particular, the combination of gemcitabine with taxanes.[86,87] Steroid therapy can be a useful adjunct to supportive treatment.[77] Gemcitabine may also be associated with radiation recall pneumonitis, even a year or more after thoracic radiation therapy. Gemcitabine radiation recall reaction appears to be more likely to affect parenchymal organs such as the lung than the more common dermatologic radiation recall reactions associated with other chemotherapeutic agents.[78]

Fludarabine is now commonly used to manage hematologic malignant disease, including chronic lymphocytic leukemia, and, like other antimetabolite drugs, is relatively well tolerated. In approximately 8% of cases, fludarabine causes pulmonary toxicity characterized by fever and interstitial pneumonitis.[79,88] Although this syndrome is probably steroid responsive, it is critical to rule out opportunistic infection given the patient population usually treated with this drug.

Alkylators and Nitrosoureas

Alkylators and nitrosoureas are frequent components of conditioning regimens for BMT, a procedure that is associated with a high rate of pulmonary toxicity. It is difficult to isolate the effect of these drugs in this setting, in which many other insults to the lung often occur, but it is likely that they contribute, particularly at BMT dose intensity.[85,86] Results suggest that pulmonary toxicity from BMT with whole-body irradiation-containing regimens is similar to that from regimens without whole-body irradiation.[89,90] This underscores the relationship between high-dose alkylator therapy and pneumonopathy.

In the non-BMT setting, classic alkylators, such as cyclophosphamide, ifosfamide, and melphalan, have occasionally been associated with interstitial pneumonitis and acute or subacute dyspnea that may

be steroid responsive.[91,92] However, these drugs have caused long-term pulmonary fibrosis, even several decades after treatment.[91]

For nitrosoureas such as BCNU, pulmonary injury is considered a dose-limiting toxicity and has been well studied.[93] The predominant problem with these agents is pulmonary fibrosis, which appears to be chronic and dependent on dose and patient age.[94–96] In one study, BCNU pulmonary fibrosis in patients treated for glioma was rare at cumulative doses less than 960 mg/m^2.[96] The association between other nitrosoureas and pulmonary toxicity is not commonly reported but does occasionally occur.[97–109] The pulmonary fibrosis that is caused by nitrosoureas does not appear to be steroid responsive. The unpredictable and untreatable nature of nitrosourea-induced pneumonopathy has recently limited the use of these drugs in several settings.[98]

Anthracyclines and Other Antitumor Agents

Essentially every cytotoxic chemotherapy has been associated with pulmonary toxicity. Case reports and/or literature reviews can be identified even for drugs that are rarely associated with pneumonopathy, such as vinorelbine,[99] paclitaxel,[100] and oxaliplatin.[101] Response to steroids has been variable. Several other agents, however, deserve special mention.

The antibiotic chemotherapy drug mitomycin is well known as a potentially pneumotoxic agent that can cause noncardiogenic pulmonary edema, pneumonitis, and pleural effusion. Toxicity is difficult to predict and not clearly dose related[102–111] but is estimated to occur in 5% of patients or more.[103] In a prospective study of patients treated with mitomycin, 28% of patients tested had significant (>20%) declines in DLCO, and 5% had grade 3+ lung toxicity.[103–112] Mitomycin-induced pulmonary toxicity appears to be steroid responsive.[104]

Anthracyclines are vital drugs for the treatment of breast cancer among other malignancies; while they are associated with significant cardiac risk (which can mimic pulmonary toxicity), they rarely independently cause pneumonopathy. However, the combination of anthracyclines such as doxorubicin with thoracic radiotherapy can be highly toxic. For example, a randomized trial of concurrent versus sequential chemoradiotherapy (including doxorubicin) for small cell lung carcinoma was closed early because six fatal cases of pneumonopathy developed among 82 patients who were treated concurrently.[105] There may be a risk of radiation recall-like reactions in patients receiving doxorubicin after high-dose thoracic radiation therapy, at least in the vulnerable lung cancer population.[106]

Like the anthracyclines, the taxanes (paclitaxel and docetaxel) are widely used solid tumor antineoplastics. Docetaxel seems to be more associated with pneumonopathy than does paclitaxel. The risk of pneumonitis appears to be schedule-related, with a significantly higher risk with the use of weekly (versus every 3 weeks) docetaxel.[107] This contrasts with the nonpulmonary toxicities of this drug, which appear to be lessened with the weekly schedule.[107] Docetaxel has also been associated with enhancement of radiation pneumonopathy in lung cancer patients.[108] The combination of paclitaxel plus radiotherapy following anthracycline-based chemotherapy might not be feasible in breast cancer patients owing to pulmonary toxicity[109] despite the relatively modest amounts of lung in the irradiated field. As was noted previously, the combination of taxanes with gemcitabine appears to result in a significant risk of pneumonopathy[78] and should be used with extreme caution in patients with underlying lung disease.

Biologic Agents

Increasingly, cytotoxic therapies such as chemotherapy and/or radiotherapy are being replaced or supplemented by "biologic" agents that kill or inhibit cancer cells through highly specific pathways independent of direct DNA damage. Many of these drugs are still very new, and their toxicity profiles are still being generated. Therefore, data regarding pulmonary toxicity of these agents are incomplete.

Immunomodulatory anticancer agents are one of the oldest classes of biologic therapies. Pneumonopathy associated with interleukins or interferons occasionally occurs,[110] as well as a syndrome of noncardiogenic pulmonary edema, which differs from typical drug-induced interstitial pneumonitis.[111] Noncardiogenic pulmonary edema is generally reversible with steroids and supportive care and rarely progresses to fibrosis.

Several randomized trials suggested that the addition of interferon to conventional lung cancer therapy increased the risk of pneumonopathy.[112,113]

Targeted therapies against signal transduction pathways have become a heralded advance in several hematologic and solid tumor types. Most of these drugs have not been studied extensively enough to fully characterize their pulmonary risks. Two agents that have been well studied are the oral tyrosine kinase inhibitors (against the intracellular portion of the epidermal growth factor receptor) gefitinib and erlotinib (Fig. 63-3). These agents are associated with an uncommon but sometimes very severe syndrome of interstitial pneumonitis. This pneumonitis appears to be more common in the Japanese population, with a reported incidence of about 3%.[114] In a placebo-controlled trial of patients with advanced lung cancer, erlotinib was not associated with an increased risk of serious pulmonary adverse events.[115]

The risk of pneumonopathy from targeted therapies does not appear to be limited to the lung cancer population. Imatinib, used for several types of hematologic malignancies and gastrointestinal stromal tumors, has been associated with interstitial pneumonitis as well.[116] The anti-CD20 antibody Rituximab has been rarely implicated in pneumonopathy.[117]

At this time, there are no specific contraindications to the use of signal transduction inhibitory agents based on pulmonary risk;



Figure 62-3 • Case example of drug-induced interstitial pneumonitis that was presumed to be related to erlotinib. This patient previously underwent chemotherapy and right pneumonectomy but developed recurrent disease. Erlotinib was started, but the patient developed progressive dyspnea 1 month later. CT scan revealed interstitial pneumonitis of the (remaining) left lung. Erlotinib was discontinued, and steroids were started, but the patient soon thereafter died of progressive cancer.

however, current protocols call for the drugs to be discontinued if thoracic imaging reveals evidence of interstitial pneumonitis.

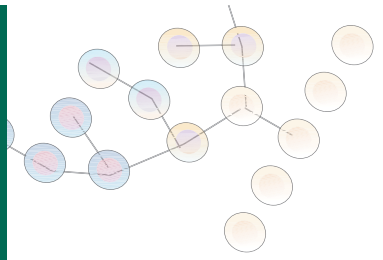
A final category of potentially pneumotoxic drug agents are the antiangiogenic compounds. These are relatively rarely associated with typical drug-induced pneumonitis.[118] However, the prototype antibody against VEGF, bevacizumab, has been associated with life-threatening pulmonary hemorrhage. This seems to be more associated with centrally located squamous cell lung carcinomas and might be related to rapid tumor response resulting in bronchovascular fistula. Further studies and means of predicting who is at risk for this devastating complication and how to avoid it are necessary in order to advance the use of this class of agents.[119]

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63 Cardiac Effects of Cancer Therapy

James L. Speyer, Boris Kobrinsky, and Michael S. Ewer

SUMMARY OF KEY POINTS

Incidence

Cardiomyopathy/Congestive Heart Failure

- Anthracyclines: 5% to 20% of patients receiving cumulative doxorubicin more than 450 mg/m^2, higher in children
- Other antineoplastics (mitoxantrone, cyclophosphamide): less than 2%
- Trastuzumab
- Imatinib
- Lapatinib
- Sunitinib
- Radiation therapy: common 5 to 20 years after single anteroposterior port

Arrhythmias

- Paclitaxel: less than 1%
- Dihydroazacytidine
- Interleukin-2, interleukin-6
- Interleukin-11
- Rituximab
- Arsenic trioxide

Myocardial Ischemia

- Radiation therapy
- 5-Fluorouracil (5-FU): 1% to 4.5% with infusion schedules
- Capecitabine

Pericardial Disease

- Radiation therapy: effusions in 6% to 30% of patients receiving radiation therapy to the chest, constriction in 2% of patients receiving radiation therapy to the chest with current techniques
- Cardiac tamponade
- Busulfan

Fluid Retention

- Docetaxel, interleukins, interferons, tumor necrosis factor, cytokines, granulocyte-macrophage colony-stimulating factor, monoclonal antibody (CD20)
- Dasatinib
- All-*trans* retinoic acid

Hypertension

- Bevacizumab

Hypotension

- Rituximab
- All-*trans* retinoic acid
- Bortezomib
- Paclitaxel
- INF
- Denileukin diftitox

Endocardial Fibrosis

- Busulfan

Etiology of Complications

- Anthracycline-induced cardiomyopathy
- Her2 signaling pathway and decreased repair
- Radiation-induced cardiomyopathy
- Radiation-induced myocardial ischemia
- Decreased systemic vascular resistance

Diagnosis

- Clinical cardiac symptoms—New York Heart Association Classification
- Hemodynamics—Bristow Staging Score
- Radionuclide scans—serial scans including baseline
- Endomyocardial biopsy—Billingham Histopathologic Scoring System
- Doppler echocardiography—pericardial effusion/constriction, left ventricular systolic/diastolic dysfunction
- Troponin
- Natriuretic peptide

Treatment

Cardiomyopathy/Congestive Heart Failure

- Sodium and fluid restriction
- Diuretics
- Afterload reduction (angiotensin-converting enzyme inhibitors)
- Angiotensin receptor blocking agents
- Beta blockers
- Discontinue offending agent

Risk Reduction with Anthracyclines

- Anthracyclines: limit dose (e.g., doxorubicin: <450 mg/m^2); use less toxic analogs
- Alteration of dose schedule
- Unique delivery systems (e.g., liposomes)
- Pegylated liposomal doxorubicin
- Blocking agents (dexrazoxane: ICRF-187, ADR 529) (Zinecard)

Radiation-Induced Pericardial Disease

- Acute pericarditis: nonsteroidal anti-inflammatory drugs, steroids
- Constriction: pericardiectomy

INTRODUCTION

The cardiac side effects of cancer therapies include the entire breadth of cardiac pathology. They provide a considerable challenge to the clinician because they produce signs and symptoms of disease that are not specific to treatment and their differential diagnosis therefore includes a broad spectrum of other etiologies. The sequelae of the tumors being treated, underlying cardiac disease, and effects of nononcologic interventions can affect the heart in ways that often cannot be distinguished clinically from the cardiac effects of cancer treatment. These factors make the diagnosis, assessment, and clinical course of the cardiac effects of cancer therapy especially challenging. Despite these considerations, it is clear that dysrhythmias, ischemia, congestive heart failure (CHF), peripheral vascular disease, and pericardial disease can be caused by a variety of cancer therapies and the various combinations of agents and modalities that are used in the treatment of malignancy.

A variety of approaches can be used to effectively evaluate patients with these side effects. The patient with cancer who presents with

cardiac problems can be approached by considering all known side effects associated with the therapy or therapies that he or she is receiving or has received in the past. Alternatively, the entire spectrum of treatment-related, as well as nontreatment-related, causes of the patient's cardiac presentation can be considered. Because the latter approach is closer to the usual clinical process of differential diagnosis, this chapter is organized in that manner. However, to consider side effects by therapeutic agent and modality, a summary is organized according to the effects of specific agents (Table 63-1).

In the cancer patient, a complex of interactions result from specific agents or modalities, causing damage through different pathophysiologic mechanisms, such as ischemia, free radical myocardial damage, radiation damage, alterations in conduction, and other factors that increase myocardial stress such as increased work, wall stress, and underlying ischemia. These may be modulated by cardiac repair mechanisms or strategies to reduce stress on the heart. Drugs that reduce cardiac repair or add to cardiac work or wall stress may in turn increase cardiac toxicity and worsen a patient's condition. In the

Table 63-1 Cardiovascular Complications of Cancer Therapies

Chemotherapy Drugs		Biologic Response Modifiers	
Therapy	**Complications**	**Therapy**	**Complications**
Anthracyclines (e.g., doxorubicin)	Cardiomyopathy	IFN-α	Hypotension
	CHF*		Tachycardia
	Dysrhythmias	IFN-β	Hypotension
Epirubicin	Pericardial effusion	TFN-γ	Hypotension
Anthrapyrazoles	Cardiomyopathy	Interleukin-1α	Hypotension
	CHF	Interleukin-2	CHF
Mitoxantrone	Cardiomyopathy		Hypotension
	CHF*		Dysrhythmias
Cyclophosphamide	CHF		Ischemia
	Hemorrhagic myocarditis*	Interleukin-4	Myocarditis
	Pericardial effusion	Interleukin-6	Dysrhythmias
Ifosfamide	CHF	Interleukin-11	Atrial dysrhythmias
5-Fluorouracil	Myocardial ischemia*	TNF	Hypotension*
	Cerebrovascular ischemia	GM-CSF	Hypotension
Vinca alkaloids	Angina		Pericardial effusion
	Raynaud phenomenon	Monoclonal Ab to CD20	Hypotension
Dihydro-5-azacytidine	Dysrhythmias		Angina
	Pericardial effusion		Dysrhythmias
Paclitaxel (Taxol)	Dysrhythmias	Radiation therapy	CHF
	ECG changes		Coronary artery disease*
	Ischemia		Pericarditis*
Docetaxel (Taxotere)	Fluid retention		Pericardial effusion
Cisplatin	Raynaud phenomenon*		Constriction*
Bleomycin	Raynaud phenomenon*		
Taxol + doxorubicin	Cardiomyopathy		
Thalidomide in combination	Thromboembolic events		
Trastuzumab	CHF		
Lapatinib	CHF		
Imatinib	CHF		
Dasatinib	Fluid retention		
	Dysrhythmias		
Sunitinib	Decrease in LVEF		
Arsenic trioxide	Dysrhythmias		
All-*trans* retinoic acid	Fluid retention, hypotension		
Capecitabine	Myocardial ischemia		
Rituximab	Dysrhythmias		
Bortezomib			

Ab, antibody; CHF, congestive heart failure; ECG, electrocardiographic; IFN, interferon; GM-CSF, granulocyte macrophage colony-stimulating factor; TNF, tumor necrosis factor.
*Significant effect.

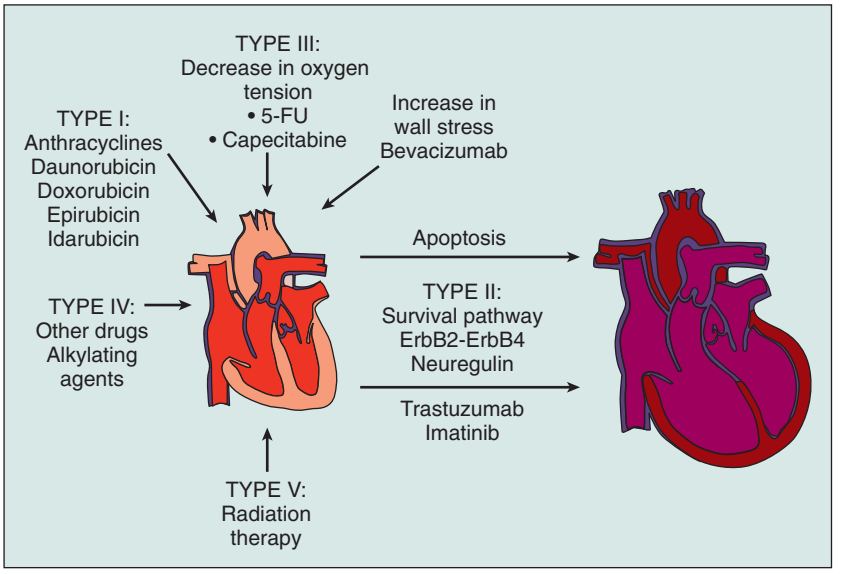


Figure 63-1 • Mechanisms of cardiac toxicity and repair with proposed modified classification system.[1,78]

case of some newer anticancer treatments, these drugs may cause additive or synergistic damage. Ewer and Lippman[1] have proposed a classification schema that indicates different types of myocyte damage leading to CHF with different pathophysiologic mechanisms and different clinical courses. A schematic model of these interactions as well as other sources of cardiac stress depicts multiple sources of cardiac stress and repair (Fig. 63-1).

Finally, as with all potentially negative effects of treatment, the clinician needs to balance the potential risk or negative impact on the patient with the potential benefit. Simply withholding treatment may eliminate the risk of a side effect but deprive the patient of a potentially beneficial therapy. At times, this may be the correct approach. At other times, giving treatment with judicious monitoring and appropriate toxicity reduction may on balance benefit the patient more.

CONGESTIVE HEART FAILURE

Previously, the major emphasis in drug-induced cardiac toxicity has been on anthracycline-induced damage because of the widespread use of these drugs, their unique mechanism of action and pathologic appearance, and clinically relevant toxicity. While anthracyclines remain an important part of any discussion of cardiac toxicity, the recent introduction of many new agents with activity, especially in cell-signaling pathways, makes consideration of treatment-related cardiac effects more complex and clinically important. The mechanisms by which these drugs inhibit tumor cell growth may also be involved in the normal response to stress by cardiac myocytes and can result in clinical toxicity alone or in combination with other drugs or sources of cardiac stress (e.g., traztuzumab, lapatinib, imatinib). Others may have direct cardiac toxicity.

Anthracyclines

Chemotherapy that incorporates an anthracycline antibiotic is a significant cause of CHF in cancer patients who are treated with these agents (Table 63-2). The anthracyclines are of special interest, in part because CHF resulting from these agents can progress to death. We now are able, in large part, to prevent the potentially deadly aspects of CHF from anthracycline use. Most information relating to anthracycline-induced cardiomyopathy is derived from studies with doxorubicin and, to a lesser extent, with daunorubicin. However, other clinically available drugs of this class also have been associated with clinically indistinguishable cardiotoxic effects.

Cardiac biopsy specimens have demonstrated that the dose-related cardiomyopathy that is associated with anthracyclines is biventricular. Retrospective studies indicate that the incidence of clinically recognizable congestive failure with doxorubicin is 7% to 15% in patients who have received a cumulative dose greater than 450 to 500 mg/m^2 without cardioprotection (Fig. 63-2).[2,3] Above this dose the incidence of clinical CHF rises more steeply. (Cumulative cardiotoxic doses associated with the use of other anthracyclines vary, but the shape of the curve that plots cumulative dose against the likelihood of CHF is similar for all anthracyclines that have been studied.) Caution must be exercised in evaluating patients who are receiving anthracyclines, because this cardiomyopathy is variable, and instances of CHF have been observed at lower cumulative doses.[4] The actual incidence of clinical CHF may be higher than was reported in retrospective trials.[5,6] Prospective clinical trials suggest that when patients are observed closely, the number who develop early signs of CHF at cumulative doses of 450 mg/m^2 may exceed 25%. The cardiotoxic effects of anthracyclines probably start with the first dose. Each subsequent administration constitutes a sequential stress superimposed on existing cardiac injury that may have resulted from prior doses of anthracyclines or from other causes. In addition, nonanthracycline-related stress or damage occurring months or years later finds the heart with pre-existing damage and adds a cumulative burden or sequential stress.[7] Other chemotherapy drugs (e.g., trastuzumab) that

Table 63-2 Anthracyclines and/or Anthraquinolones and Cardiotoxicity Associated with Cardiomyopathy in Clinical Use

Doxorubicin (Adriamycin)
Daunorubicin (Daunomycin)
4′Epidoxorubicin (Epiadriamycin/Epirubicin)
4′Deoxydoxorubicin (Esorubicin)
Demethoxydaunorubicin (Idarubicin)
Pegylated doxorubicin (Doxil)
Liposomal daunorubicin (Daunosome)
Mitoxantrone (anthracycline analog)
TLC D99 (Myocet)

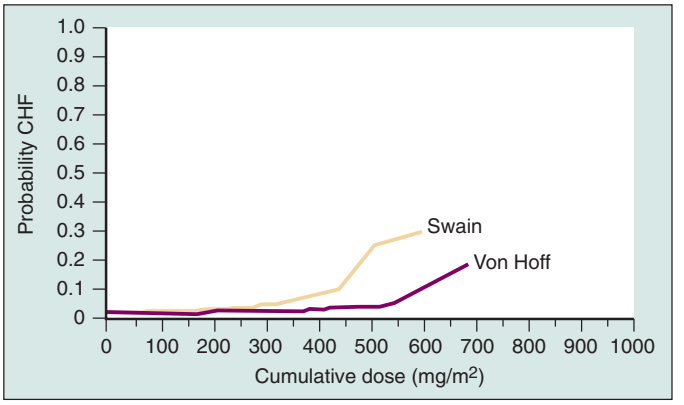


Figure 63-2 • Incidence of clinical congestive heart failure according to cumulative dose of doxorubicin. (Data from Swain SM et al, Personal communication. Studies 88001, 88002, 88006; von Hoff et al, 1979.)

may have a collateral effect of decreasing cardiac repair mechanisms can increase anthracycline toxicity (see later discussion).

Factors associated with an increased risk of anthracycline-induced chronic cardiomyopathy are derived from retrospective studies in adults.[2] They include age greater than 70 years, exposure to ionizing radiation to the chest wall, and pre-existing cardiac disease or risk factors. Prior cardiac risk factors include active CHF, history of myocardial infarction within the preceding year, hypertension, aortic stenosis, diabetes mellitus, and prior exposure to anthracyclines. The relative contributions of each of these factors are not well defined, and when an individual patient has more than one risk factor, the damage can be increased considerably. One possible common denominator among these entities is increased wall stress; any condition that results in increased wall stress warrants heightened scrutiny and efforts to mitigate the cardiotoxic effects of anthracyclines. Children are a subset of patients who are at increased risk for developing anthracycline cardiac toxicity with a different clinical course and some difference in mechanism (see later discussion).

The natural history of the cardiomyopathy from anthracycline use varies. In some patients, it worsens despite maximal medical therapy and can lead inexorably to death. Other patients are left with permanent reduction in left ventricular ejection fraction (LVEF) and persistent symptoms of CHF. Still others can experience gradual improvement in symptoms and LVEF,[8] perhaps owing in part to compensation and myocardial remodeling.

Pathophysiology

Anthracycline-induced cardiomyopathy is the result of a series of repeated chemical injuries to the myocardium (possibly with some recovery) that gradually impair cellular defenses, resulting in cell damage with decreased contractility and, eventually, cell death. This is consistent with the gradual onset, variability of course, risk factors for increased susceptibility, and laboratory and pathologic findings of the cardiomyopathy that results from use of these drugs.

The common mechanism for anthracycline cardiomyopathy appears to be via free radical damage. Reduction of the quinone groups on the B ring of the anthracene structure (Fig. 63-3) results in a semiquinone radical before further reduction to the alcohol (e.g., doxorubicinol). Interaction with oxygen yields free radical oxygen (O_2*). Further reaction of the semiquinone with H_2O_2 yields the OH^- radical. These reactions can proceed in either an iron-independent or iron-dependent fashion.[9]

Formation of an Fe^{3+}-doxorubicin complex can catalyze these reactions, greatly enhancing free radical generation. An Fe^{3+}-doxorubicin DNA complex has been demonstrated, which results in increased cell destruction. Free radicals can cause damage at a variety of intracellular sites, including the nuclear envelope, cell membrane, mitochondria, DNA, and sarcoplasmic reticulum.[9,10] In the myocyte, damage to the sarcoplasmic reticulum produces a decrease in bound calcium, which results in decreased contractility by its action on the actin-myosin complex. Free Ca^{2+} also may activate proteases within the heart, causing myofibrillar damage.

Anthracycline-induced free radical damage is not confined to the myocardium. It may indeed play some role in tumor cell killing, although this is primarily thought to be related to other mechanisms (e.g., DNA intercalation, inhibition of topoisomerase II).

The susceptibility of myocardial cells to free radicals may be explained in part by differences in cellular defenses. Of the primary cellular enzymatic defenses against free radicals—superoxide dismutase, catalase and glutathione peroxidase—only superoxide dismutase is unaffected by doxorubicin. In some mammalian systems, myocytes contain very low catalase compared to other cells, such as liver cells.[11] Furthermore, doxorubicin can decrease cellular glutathione peroxidase. The complete translation of the observations from the rodent system to humans is not clear.

In clinical practice, the anthracyclines appear to have a mechanism of activity similar to that just described. The mechanisms do not, however, fully explain the cardiac effects of the related anthracene compounds (e.g., mitoxantrone). In isolated myocyte models, specific inhibitory agents (dexrazoxane) inhibit anthracycline-induced cardiac damage but not that of mitoxantrone, suggesting that some other mechanism for cardiac toxicity also might exist.[12] In a spontaneously hypertensive rat model, though, dexrazoxane inhibits both doxorubicin and mitoxantrone-induced cardiac toxicity.[13] Some investigators have suggested that in addition to the preceding mechanism,

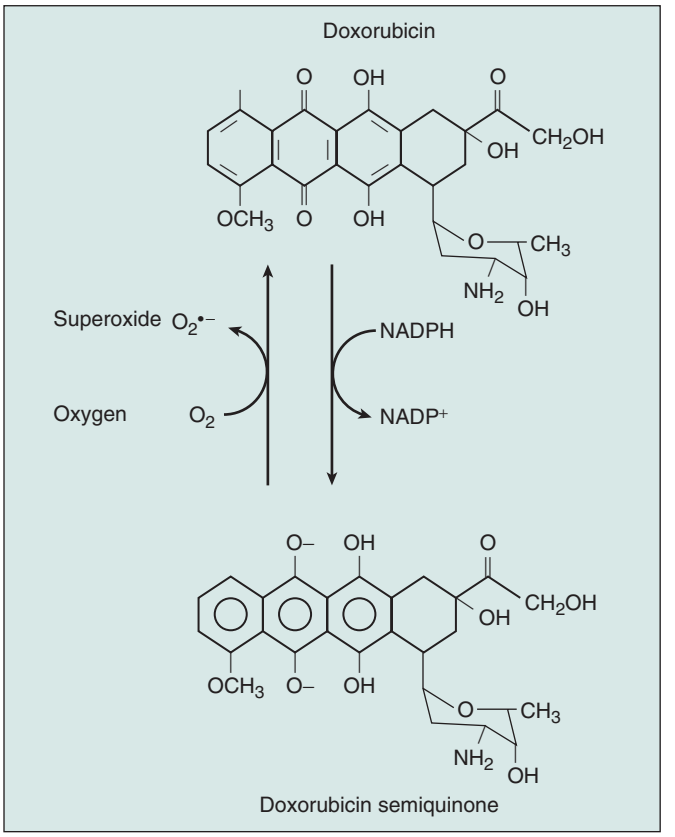


Figure 63-3 • Redox cycling of doxorubicin by flavin-centered reductases. (From Muggia FM, Green MD, Speyer JL [eds]: Cancer Treatment and the Heart. Baltimore, Johns Hopkins University Press, 1992, p 12.)

cardiac damage in children is due at least in part to interference with cell growth.[14]

Diagnosis

Patients may present with any or all symptoms of CHF, including decreased exercise tolerance, dyspnea, or signs of pulmonary and circulatory congestion. In our experience, sinus tachycardia and an inability to return promptly to basal cardiac rate after exertion in an otherwise oncologically stable patient are the earliest sign of myocardial toxicity and usually predate more classic symptoms of heart failure. These can be graded by the well-established system for grading CHF.[15] A system of staging anthracycline-induced hemodynamic changes in humans was developed by Bristow.[16] Severity is most frequently indicated by LVEF (absolute value and decrease during treatment) and clinical findings, often using the New York Heart Association classification of CHF.

Determination of LVEF by either cardiac ultrasound or gated radionuclide scanning techniques is used to assess anthracycline cardiac toxicity. However, changes in systolic function often are seen in cancer patients, and they might not be related to anthracycline-associated damage. Such changes may occur as a consequence of anemia, the extent of tumor burden, and a variety of metabolic aberrations that might or might not be related to the malignancy or its treatment. One way to monitor patients with echocardiography or nuclear imaging is to obtain a baseline study prior to therapy and then obtain values at intervals as the cumulative dose increases. At high cumulative doses, it might be desirable to make more frequent observations. Scans are examined for sequential changes in wall motion as well as LVEF. Any decrease in LVEF, including those that remain within the "normal" range as well as those that decrease to a clearly abnormal value, could indicate anthracycline damage.[17] Careful monitoring with multiple gated acquisition (MUGA) scans may permit treatment with greater cumulative doses of doxorubicin than an empiric stopping dose of 450 to 500 mg/m^2.[3,5,17,18] Serial determinations might, however, result in premature abandonment of an important therapy because of false-positive results on an ultrasound or MUGA scan. It is important to bear in mind that the likelihood of CHF follows an exponential curve, that early toxicity can be difficult to quantify, and that an additional two or three cycles of chemotherapy may expose patients to life-threatening cumulative dosages. Decreases in the absolute value of LVEF by 10% to 20% or to less than the lower limit of normal for the laboratory may warrant discontinuation of therapy. The key is that a decrease in LVEF usually precedes the development of clinical CHF and that termination of drug therapy might stop the progression of the biochemical process before clinical symptoms became apparent. Algorithmic validation of this approach has been published and supports this approach, but it is not fail-safe. When exceeding of recommended cumulative dosages can be anticipated, cardioprotective strategies are clearly appropriate.

Although MUGA scans have been used in most adult investigational studies and for clinical follow-up, Doppler echocardiography is also a useful tool for both preanthracycline evaluation of the heart (allowing assessment of underlying valvular and pericardial pathology as well as myocardial systolic and diastolic function) and clinical follow-up during treatment. Newer computer-assisted echocardiographic technologies, including automated border detection-derived quantification of cardiac volumes and LVEF, could make nuclear quantification modalities (which require radioisotopes) obsolete in patients whose hearts can be imaged ultrasonically.[19] Doppler evaluation of diastolic parameters, including rates of isovolemic relaxation and rapid filling, can be useful in the early detection of anthracycline-induced myocardial dysfunction.[20] Echocardiography has been used extensively in children, in whom the shorter periods of time needed to acquire data are helpful. In patients with cardiac dysrhythmias, the rhythm disturbance can interfere with cardiac gating, and echocardiography offers advantages. Patients who have received radiation to the left side of the chest can be difficult to study with cardiac ultrasound and often are better candidates for nuclear imaging.[21]

Myoscint scans may complement MUGA scans. In trials using Myoscint scans, a monoclonal antibody to cardiac myosin is tagged with iodine 131, which may provide more direct evidence of myocardial damage and overcome some of the lack of specificity of MUGA scans. These scans have been used as an adjunct to MUGA scans in a randomized trial of epirubicin and dexrazoxane. To date, neither the parameters of diastolic dysfunction nor any of the newer nuclear imaging techniques have been sufficiently sensitive to replace MUGA scans.[22]

Measurement of cardiac troponins is a highly sensitive method of detecting myocardial cell injury in acute coronary syndromes and has led investigators to study the applicability of such measurements to assessing anthracycline-induced myocardial cell damage. Elevated serum troponin T levels in children receiving doxorubicin for acute lymphoblastic leukemia (ALL) have been demonstrated to predict the echocardiographic findings of left ventricular dilatation and left ventricular wall thinning months later.[23] In at least one series,[24] troponin I levels rose in anthracycline-treated patients before deterioration in LVEF was visible by MUGA scanning. Troponin I levels were elevated and correlated with a fall in LVEF in breast cancer patients receiving high-dose chemotherapy with and without anthracyclines.[25] Markers of cardiac damage have not yet been demonstrated to help in making clinical decisions to continue or stop the administration of anthracyclines. The level of B natriuretic peptide, a measure of CHF, has also been used to monitor anthracycline-induced cardiac damage.[26,27]

Anthracyclines cause a unique pattern of histologic damage, as was originally demonstrated in animal models and confirmed by endomyocardial biopsies in humans (Table 63-3). A continuum of change is well described, from dilation of vacuoles to mitochondrial swelling, myofibrillar dropout, and, ultimately, cell death.[28] The changes that are seen on endomyocardial biopsy appear to parallel the clinical findings, and there is a good correlation with the clinical

Table 63-3 Histopathologic Scale of Doxorubicin Cardiomyopathy*

Grade 0	Within normal limits
Grade 1	Minimal numbers of cells (<5% of total number of cells per blocks) with early change (early myofibrillar loss or distended sarcoplasmic reticulum)
Grade 1.5	Small group of cells involved (5% to 15% of total number), some of which have definite change (marked myofibrillar loss or cytoplasmic vacuolization)
Grade 2	Groups of cells (16% to 25% of total number), some of which have definite change (marked myofibrillar loss or cytoplasmic vacuolization)
Grade 2.5	Groups of cells involved (26% to 35%), some of which have definite change (marked myofibrillar loss or cytoplasmic vacuolization)
Grade 3	Diffuse cell damage (>35% of total number of cells) with marked change (total loss of contractile elements, loss of organelles, mitochondrial, and nuclear degeneration)

*Other grading scales that may incorporate an intermediate grade of 0.5 are sometimes encountered. The individual defined grades are uniform between these various scales. (Mackay B, Ewer M, Carrasco CH, Benjamin RS: Assessment of anthracycline cardiomyopathy by endomyocardial biopsy. Ultrastruct Pathol 1994;18:203–211.)

Adapted from Billingham ME, Mason JW, Bristow MR, Daniels JR: Anthracycline cardiomyopathy monitored by morphologic changes. Cancer Treat Rep 1978;62:865.

examination and results of MUGA scans.[29] The consistency of these findings among nonmammalian species has provided the basis for a number of animal models of anthracycline cardiomyopathy.[30]

The principal advantage of endomyocardial biopsy is the relative specificity of the test. The procedure is usually done by performing a right heart catheterization and using a specially designed bioptome to obtain a number of small tissue fragments from the interventricular septum. These are fixed for routine histologic examination using hematoxylin and eosin or are fixed in glutaraldehyde for examination under the electron microscopic. The procedure is usually performed on an outpatient basis, and in experienced hands, the incidence of serious complication is less than 1%.[31]

The disadvantages of endomyocardial biopsy include the necessity for special expertise in obtaining and interpreting the biopsies, the cost, and the possible, though low, risk of complications. In the modern clinical setting, it is unusual to need biopsies for arriving at appropriate medical decisions, but the biopsy still has a role in clinical investigation.

Decreasing Anthracycline Cardiotoxicity

Risk Reduction

The most obvious way to reduce risk is not to administer the medication at all or to discontinue it. Current approaches to risk reduction include changes in dose and schedule, use of analogs, new delivery systems, and specific blocking agents. Dose adjustment can be achieved by limiting anthracycline doses in patients at increased risk for toxicity or by empiric limitation of cumulative doses of doxorubicin to 400 to 450 mg/m^2. Both of these approaches have merit, but neither prevents toxicity in all patients. Moreover, limiting therapy or discontinuing therapy prematurely could deprive patients who are not experiencing toxicity of therapy from which they are continuing to benefit. As has been noted, a combination of dose restriction with careful cardiac monitoring may offer the safest practical approach to patients receiving doxorubicin.[5] However, such strategies do have some risk of both suboptimal tumor management and cardiotoxicity.

Dose Schedule Changes

Alterations in the dose schedule of anthracyclines are based on the hypothesis that chronic cardiac toxicity is related primarily to peak drug concentration, whereas the antitumor effect is more related to total drug exposure (concentration time, or area under the curve). Clinical trials of weekly schedules versus those in which the drug is given every 21 days support this hypothesis: Weekly schedules resulted in decreased clinical toxicity[1] and improved endomyocardial biopsy scores.[32] Extending this approach to continuous infusion maximizes the reduction in plasma drug concentration while still maintaining oncologic effect. Several studies have demonstrated decreased cardiac toxicity with prolonged continuous infusions (e.g., 24 to 96 hours) compared with standard rapid infusion schedules.[33] The cardiac toxicity is less when measured by clinical examination, MUGA scan, or cardiac biopsy without apparent loss of antitumor efficacy. While all of the studies demonstrate that continuous infusion schedules clearly reduce cardiac toxicity, they do not totally prevent it. They do, however, allow significantly higher cumulative dosages to be administered with acceptable cardiotoxicity. In the case of doxorubicin, for example, approximately 900 mg/m^2, or twice the usual cumulative dosage, can be given when the drug is administered by 96-hour continuous infusion. Mucositis is the factor that limits the duration of infusional regimens to a maximum of 96 hours. Continuous infusion schedules have not been universally accepted, in part because of the increased cost and the necessity for long-term or implantable access lines and infusion pumps.

New Delivery Systems

Liposomal drugs may permit more specific organ targeting of anthracyclines, thereby producing less systemic and cardiac toxicity. The drug can be incorporated into a variety of liposomal drug preparations.[34,35] Initial activity was reported in Kaposi's sarcoma for daunorubicin[34] and doxorubicin.[35] More recently, activity also has been reported in ovarian cancer and breast cancer. In animal models, the pegylated liposomal preparation of doxorubicin, Doxil, is less cardiotoxic than is the free drug. In one trial, patients who were treated with the pegylated doxorubicin (Doxil) had lower cardiac biopsy scores (0.5 versus 2.25) than did controls who were treated with the standard doxorubicin protocol.[36,37] Similar reductions in cardiac toxicity, as measured by biopsy score, were reported in a group of 29 women with breast cancer who were being treated with TLC D-99 liposomal doxorubicin, a new pegylated preparation.[38] Pegylated liposomal doxorubicin (PLD) consists of STEALTH technology-based liposomes containing doxorubicin HCL in an aqueous core. Liposomes are covered by surface-bound methoxypolyethylene glycol that is covalently linked to liposome phospholipids, utilizing the process called pegylation.[39] PLD takes advantage of its stable pegylated cover to be protected from enzymatic and phagocytic degradation. The small size of liposome (100 nm) enables drug preferential penetration through the compromised tumor vasculature and accumulation in tumors, thereby producing less systemic toxicity and less cardiac toxicity. In a phase III study of 509 women with metastatic breast cancer, 18.8% of patients in the doxorubicin arm developed decline in LVEF versus 3.9% of patients (all of them asymptomatic) in the PLD arm. Overall risk of cardiotoxicity was significantly higher in the doxorubicin arm than in the PLD arm (HR = 3.16, $P < 0.001$). Pegylated liposomal doxorubicin demonstrated efficacy comparable to that of doxorubicin (overall survival was 21 months for PLD versus 22 months for doxorubicin).[40] Other unique delivery systems that have not had significant clinical impact include starch microspheres,[41] albumic microspheres,[42] and lipiodol.[43]

Analogs

Analog development holds the promise of good antitumor activity with decreased cardiac toxicity. Many anthracyclines that are in clinical use (e.g., epirubicin and esorubicin) have been shown to produce less cardiac toxicity in preclinical animal models and were developed as potentially less cardiotoxic compounds than doxorubicin. Although this is still an important avenue of research, it has not yet resulted in a major reduction in clinical cardiac toxicity when the drugs are administered at equimyelotoxic doses.[44] Twenty-five of 261 patients who received more than 600 mg/m^2 of epirubicin (with single doses of epirubicin 45 to 90 mg/m^2 day 1 and day 8 q 28 days) developed CHF (10%), including seven who died of cardiac toxicity.[44] In a later analysis, the same group reported that 59% of patients who had received 850 to 1000 mg/m^2 of epirubicin exhibited a 25% fall in ejection fraction 3 years after the completion of epirubicin, and 20% developed symptoms of CHF. Therapy with angiotensin-converting enzyme (ACE) inhibitors reversed the clinical symptoms in most, but not all, cases.[45] Biopsy studies have been limited but suggest some cardiac protection over the native compound.[46] Some degree of cardiac toxicity indicated by a change in LVEF or development of clinical CHF was observed in patients receiving adjuvant therapy[46] with high doses (epirubicin 200 mg/m^2 and cyclophosphamide 4 g/m^2)[47] or in combination with paclitaxel,[48] although in all of these, the incidence of clinical CHF was low. In the Canadian trial that compared FEC (5-fluorouracil [5-FU], epirubicin, and cyclophosphamide) to CMF (cyclophosphomide, methotrexate, and 5-FU), there was no clinical cardiac toxicity in the 351 patients in the FEC arm; one of the 359 patients in the CMF arm did show cardiac toxicity, however.[44]

Blocking Agents

Differences in the biochemical mechanisms of antitumor activity and cardiac toxicity provide a potential avenue of selectively inhibiting or preventing the adverse effect. Targets for this approach include agents that prevent free radical generation or salvage free radicals. Several free radical scavengers, including α-tocopherol (vitamin E),[49] N-

acetyl cysteine,[50] coenzyme Q-10,[51] and prenylamine,[52] have been tested as selective cardiac protectors with negative or inconclusive results. Dexrazoxane (Zinecard) is the one drug that has been approved for this use and is clearly cardioprotective. The compound is a bisdioxopiperazine that is hydrolyzed intracellularly to form a bidentate chelator, similar in structure to EDTA; it effectively binds intracellular iron. The putative mechanism of cardioprotection is that dexrazoxane strips Fe^{2+} from the iron-doxorubicin complex, thereby preventing free radical generation (Fig. 63-4). Randomized trials in patients with breast cancer[18] and small cell lung cancer[53] indicate that dexrazoxane can reduce doxorubicin-induced cardiac damage as measured by clinical examination, MUGA scan or endomyocardial biopsy. Dexrazoxane's limiting toxicity of myelosuppression did not add significantly to the toxicity of the regimens. Conflicting results for its effect on antitumor activity have been reported, but most trials indicate no negative effects.[5] However, a possible increase in early disease progression in one large study has led to some concern.[54] Additional trials have suggested that the drug affords cardioprotection in breast cancer without interfering with antitumor efficacy.[55–57] Furthermore, analysis of randomized trials in breast cancer suggests that even when dexrazoxane is added after the sixth course of chemotherapy (300 mg/m^2), there is significant cardioprotection while maintaining the antitumor activity of the regimen. This concern has led to limitation of its approval to metastatic disease after patients have received doxorubicin alone.[58] While these analyses argue for the use of this agent in the management of breast cancer, it is now clear that anthracyclines cause cardiac damage considerably earlier than had been previously appreciated, and protection after multiple cycles of chemotherapy might not represent the optimal approach to cardioprotection.[59] Coadministration of dexrazoxane with a less cardiotoxic doxorubicin analog could offer the best future means of reducing anthracycline-related cardiac toxicity. Of interest, dexrazoxane has been shown in animal systems to protect against the cardiotoxic effects of epidoxorubicin but may have less effect with mitoxantrone.[12] Clinical testing of dexrazoxane in combination with epidoxorubicin has been shown in randomized trials in women with breast cancer to protect against cardiac toxicity without inhibiting antitumor activity,[60] and these results have been extended to sarcoma treated with high-dose epirubicin.[22]

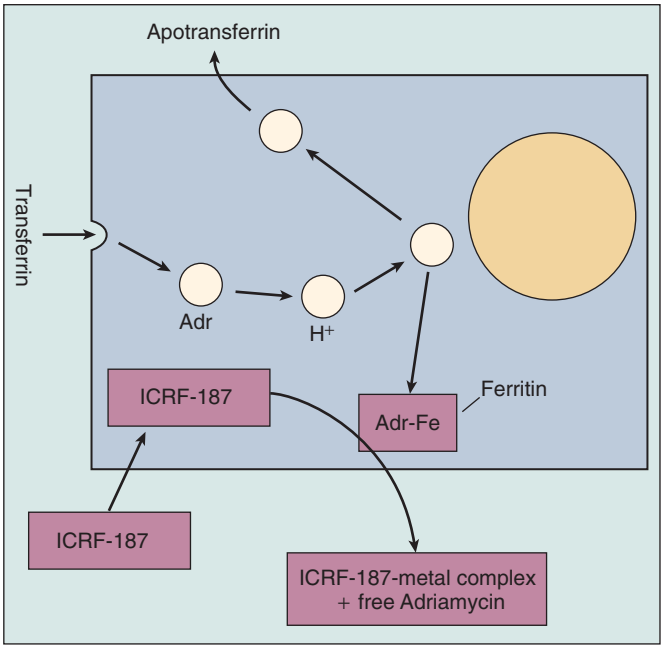


Figure 63-4 • Proposed mechanism for ICRF-187 inhibition of doxorubicin Fe complex formation. (From Muggia FM, Green MD, Speyer JL [eds]: Cancer Treatment and the Heart. Baltimore, Johns Hopkins University Press, 1992, p 27.)

Pediatrics

Overall, children are at increased risk for developing cardiac toxicity. In a large retrospective cohort study (Childhood Cancer Survivor Study), 10,397 survivors of childhood cancer were followed for a median of 17 years; the relative risk of grade 3 or 4 CHF was 15.1 (95% CI: 4.8 to 47.9); that of coronary artery disease was 10.4 (95% CI: 4.1 to 25.9 to 3.5).[61]

Children are particularly sensitive to treatment with anthracyclines. It occurs at relatively lower cumulative doses and appears to increase over time. In a study of 830 children treated in the Netherlands, the incidence of CHF with a median of 8.5 years follow-up was 2.5%, rising to 5.5% at 20 years. Higher cumulative doses were associated with greater risk, 9.8% in children who received greater than 300 mg/m^2.[62] Longitudinal studies by Lipshultz and colleagues in 115 pediatric leukemia patients (median follow-up: 11.2 years) also indicated that cumulative anthracycline dose is the most important risk factor. However, many children developed significant changes in cardiac function at lower doses (228 mg/m^2); 59% showed increased afterload, and 23% showed decreased contractility.[63] Younger age at treatment, radiation exposure, female sex, and tumor type are also risk factors.[64]

The pathophysiology of anthracycline cardiac damage in children appears to be a product of both direct myocyte damage and a progressive loss in heart muscle mass leading to decreased contractility. In the leukemia studies, the reduction in fractional shortening *z*-scores (related to impaired contractility and increased afterload) was progressive at more than 12 years follow-up.[63] Treatment is similar to that with adults. Enalapril and ACE inhibitor may delay the pathologic process but do not prevent it.[64] Dexrazoxane (Zinecard) however can prevent or significantly reduce anthracycline cardiac toxicity. It was first reported by Wexler in a group of children with pediatric solid tumors.[65] In a larger randomized trial involving 206 children with ALL receiving doxorubicin, cardiac injury measured by rise in troponin T levels was observed in 21% of children receiving dexrazoxane versus 50% in those receiving doxorubicin alone ($P < 0.001$). Moreover, there was no evidence that dexrazoxane compromised the treatment efficacy. At 2.5 years, the event-free survival and continuous complete remission rates were 83% and 81%, respectively, for both groups.[66]

Other Causes of Congestive Heart Failure

Chemotherapy

TRASTUZUMAB. Trastuzumab (Herceptin) and possibly related compounds are the chemotherapeutic agents that are most associated with CHF other than the anthracyclines. Although the signs and symptoms of heart failure are the same, the clinical course and pathophysiologic mechanism may be quite different. Combinations of trastuzumab with other cardiotoxic agents, including the anthracyclines, may cause additive or synergistic toxicity. The monoclonal antibody to Her2/neu receptor, trastuzumab, is widely used in breast cancers that overexpress Her2/neu. The significant reduction in risk of recurrence when applied in the adjuvant setting means that many more patients will be receiving this drug. Cardiac toxicity was reported in the single-agent phase II trial reported by Cobleigh and coworkers.[67] In the pivotal stage III trial in metastatic disease that led to initial drug approval, an unexpectedly high incidence of cardiac toxicity was observed: 27% when an anthracycline and cyclophosphamide were combined with trastuzumab compared with 8% with the chemotherapy alone. A similar though smaller effect (13% versus 1%) was observed when paclitaxel was combined with trastuzumab. It should be noted that all of the patients who were treated with paclitaxel had received prior anthracyclines.[68] Seidman and colleagues reviewed the records of 1219 patients in seven trastu-

zumab trials.[69] They report an incidence of cardiac dysfunction of 3% to 7% with trastuzumab alone, 27% with anthracycline and cyclophosphamide, and 13% with paclitaxel. Further data from prospective trials are still necessary to better quantify the contribution of trastuzumab to chemotherapy-induced toxicity.[70] In the NSABP B31 adjuvant breast cancer trials, 3-year cumulative incidence of grade 3 and 4 toxicities were reported in 4.1% of patients receiving trastuzumab after doxorubicin and cyclophosphamide followed by paclitaxel chemotherapy compared to 0.8% of patients who received chemotherapy alone.[71] Additional questions that are being addressed in several large trials include the relative effects of the duration and sequence of trastuzumab therapy combined with chemotherapy. The addition of carboplatin to paclitaxel and trastuzumab does not appear to increase cardiac toxicity,[72] nor does the combination of vinorelbine and trastuzumab.[73,74] Cardiac observations with combinations of trastuzumab and gemcitabine, capecitabine, and other drugs are underway. The lesser cardiotoxic potential of liposomal doxorubicin led to a recently completed a trial of 30 patients with metastatic breast cancer who were treated with PLD in combination with trastuzumab. In this relatively small study, 10% of patients developed asymptomatic decline in LVEF of at least 15%. No symptomatic CHF was observed.[75] Trastuzumab-induced cardiac toxicity differs from anthracycline cardiac toxicity in the following ways:

- It is not dose related.
- It is usually reversible. In one report, 79% of patients responded to medical management, yet some also recover without specific treatment.
- Many patients can be successfully rechallenged after a return of cardiac function to normal without symptom recurrences or further deterioration on LVEF.
- It does not present with the same ultrastructural changes on endomyocardial biopsy.
- The biochemical mechanisms of damage are different.

In recognition of these important differences, Ewer and Lippman have proposed a classification system of chemotherapy-induced CHF that divides anthracycline-induced cardiac damage (type I) from trastuzumab damage (type II).[1] We propose further revising this system to include other causes of cardiac damage in cancer patients (see Fig. 63-1).

There is increasing knowledge about the mechanism of trastuzumab cardiac toxicity that points to a role of inhibition of normal cardiac repair pathways. This would explain the increased toxicity when trastuzumab is combined with doxorubicin and might suggest additive toxicity with other sources of cardiac stress. Her2 heterodimerizes to Her4, leading to autophosphorylation of the Her2 tyrosine kinase domain.[76] This complex, which is the antitumor target of trastuzumab, is also active in cardiac repair. The complex is activated by neuregulin 1, which is secreted in paracrine fashion by cardiac endothelial cells that are under stress.[76] Activation of the complex leads to multiple downstream effects that in turn lead to hypertrophy of cardiac myocytes in vivo. In mice, deletion of Her2 results in a dilated cardiomyopathy.[77] Chien proposed a model in which various types of cardiac stress such as mechanical strain, anthracyclines, or hypoxia trigger two competing pathways of cardiac myocyte survival (mediated by neuregulin-1 or gp 130 cytokines) or apoptosis. The clinical outcome depends on which process prevails. In this model, treatment with trastuzumab blocks the survival pathway by preventing Her2/Her4 heterodimerization, thus shifting the balance to apoptosis. The result is decreased cardiac contractility and CHF.[78]

LAPATINIB. Oral lapatinib (Tykerb) is a small molecule dual selective inhibitor or ErbB1 (EGFR) and ErbB2 (Her2/neu) tyrosine kinases. In part because of the cardiac effects of trastuzumab, cardiac function has been carefully monitored in early clinical trials. Isolated cases of clinical CHF with reduction in LVEF were reported in early phase I and II trials. In a retrospective analysis from 3500 patients from all reported trials, Perez and colleagues reported a 1.3% incidence of asymptomatic CHF and a 0.1% incidence of symptomatic CHF. Because of the possibility of interactions with other agents, cardiac toxicity is still carefully monitored in current trials of this agent.[79]

MITOXANTRONE. Mitoxantrone was developed primarily as a noncardiotoxic analog of the anthracyclines. It is an anthracendione that lacks the amino sugar that is common to anthracyclines. Data from collected single-agent studies and two randomized studies indicate that mitoxantrone may result in a congestive cardiomyopathy but at a lower incidence than doxorubicin when equimyelotoxic doses are compared.[80] The incidence of cardiotoxicity at cumulative doses of greater than 160 mg/m^2 is about 5%, although the incidence of clinical CHF is less than 2%. The clinical presentation is similar to that seen with doxorubicin. The diagnostic evaluation and endomyocardial biopsy changes are similar to those seen with doxorubicin. The biochemical mechanism of damage is not clear. Prior therapy with doxorubicin increases the risk of mitoxantrone cardiac toxicity; changing from one anthracycline to another or to an analog might not protect from cardiotoxicity. As was stated previously, the mechanism of cardiac toxicity might not be the same as for doxorubicin.

PHOSPHORAMIDE MUSTARDS. High-dose intravenous cyclophosphamide infusion (120 to 240 mg/kg over 1 to 4 days) has been associated with CHF and death from hemorrhagic myocarditis.[81,82] In contrast to that from anthracyclines, cardiac toxicity from cyclophosphamide is acute and is not related to the cumulative dose. Mortality is high in the face of fulminant hemorrhagic myocarditis. The majority of patients who are treated with high-dose cyclophosphamide will demonstrate a decrease in QRS voltage and a decrease in systolic function, which often are asymptomatic and reversible. Postmortem studies and an experimental animal model suggest that the loss of systolic function is due to direct endothelial injury resulting in capillary microthrombosis and interstitial fibrin deposition.

IFOSFAMIDE. Ifosphamide also has been associated with the development of CHF in a dose-dependent fashion. In one series of 52 patients receiving a high dose (10 to 18 g/m^2) as part of high-dose chemotherapy with ABMT, 9 patients (17%) developed CHF (8 severe enough to require admission to the intensive care unit) at a mean of 12 days (range: 6 to 23 days) after therapy.[83] Most of these patients received prior doxorubicin, raising the possibility of sequential stress. Of interest, autopsy data (endomyocardial biopsies were not performed) did not reveal hemorrhagic myocarditis.

INTERLEUKIN-2. The major cardiovascular effects of interleukin-2 (IL-2) include hypotension (secondary to decreased peripheral vascular resistance), dysrhythmias, and ischemia. Primary myocardial suppression is also suggested by a decrease in LVEF and an increased end-diastolic volume. This results from inadequate cardiac compensation in the face of changes in peripheral resistance.[84]

IMATINIB. Imatinib (Gleevec), an oral agent small molecule that competes for BCR-ABL, C-KIT, PDGFR, and ABL-2 protein kinase-binding sites by impeding protein kinase phosphorylation and activation of downstream kinases, has significant activity in chronic myeloid leukemia (CML) and some activity in ALL and gastrointestinal stromal tumor and may also have cardiac side effects. Although no cardiac events were noted in a series of 553 CML patients receiving imatinib,[85] two cases of CHF with elevated BNP levels were reported in patients with gastrointestinal stromal tumor,[86] and 10 patients (8 CML, 1 ALL, 1 myelofibrosis) with CHF were reported by Kerkela and colleagues[87] In two patients, pathologic whorls suggestive of toxic myopathy (but different from anthracycline effects) were observed on endomyocardial biopsy. A murine model with imatinib revealed

similar findings and a dilated cardiac myopathy. There is controversy about the extent of this problem. The mechanism of imatinib toxicity, if it exists, is probably through a type II mechanism (see Fig. 63-1). The actual incidence or significance of these findings is a matter of debate but has led to a cautionary warning by the manufacturer.[88]

SUNITINIB. Sunitinib (Sutent) is an oral agent and a small molecule that inhibits PDGFR, VEGFR, KIT, FLT3, CSF-1R, and RET tyrosine kinases that are important for tumor cell growth, survival, metastases, and angiogenesis. In two studies of 169 patients with metastatic renal cell carcinoma who failed prior cytokine-based therapy, the drug showed that 14% of patients had declines in LVEF below normal level. In the first study, 4.7% of patients had a LVEF drop of 20% or more with no reported symptoms.[89] In addition, grade 3 hypertension was reported in 6%. In the second study, one patient developed dyspnea.[90] However, in another study of 207 patients with gastrointestinal stromal tumor, there were no cases of decrease in LVEF or CHF.[91] At this time, the drug maker recommends stopping sunitinib in the event of clinical heart failure and interrupting and/or reducing the dose in asymptomatic patients with an LVEF drop of less than 50% or in those with LFEV more than 20% below baseline.[92]

OTHER COMBINATIONS. Combinations of chemotherapeutic agents have been reported to cause varying degrees of CHF. When doxorubicin was first combined with paclitaxel, an 18% incidence of CHF was reported with cumulative doxorubicin doses of 400 mg/m^2.[93] Not all investigators reported this high rate, however.[94] When the paclitaxel was initially administered as a 24-hour infusion, increased plasma and tissue concentrations of doxorubicin and the doxorubicinol metabolite were observed. Limiting the doxorubicin dose and allowing for an interval between doxorubicin and paclitaxel administration reduced the incidence of CHF to 4.7% of 657 patients, with a higher incidence of 25% in patients who received more than 440 mg/m^2.[95] Combinations of doxorubicin with docetaxel have not been associated with increased cardiac toxicity. In a randomized trial comparing doxorubicin and docetaxel with doxorubicin and cyclophosphamide in 429 women with breast cancer, CHF was not increased (3% versus 4%), and the decline in LVEF—30 points from baseline—was less (1% compared with 6%).[96] The incidence of CHF has been reported to be 6% for the combination of epidoxorubicin and paclitaxel.[97] Several trials have raised the possibility of increased cardiac toxicity when doxorubicin is combined with high-dose cyclophosphamide[98] in the transplant setting.

Radiation

Radiation to the myocardium can cause interstitial myocardial fibrosis. This occurs through capillary damage, organization of fibrinous exudates with microcirculatory damage, and fibrosis.[99] Echocardiography and MUGA scans can help to differentiate primary myocardial damage from the pericardial damage that often occurs in the same patients.[100] Repeated doses or very high radiation doses (>6000 cGy) are associated with a greater risk of radiation damage. Biventricular dysfunction is common, although usually asymptomatic, occurring 5 to 20 years after radiation therapy. This is especially likely in patients who have been treated through a single anteroposterior port.[101] As a result of advances in radiotherapy techniques, clinically significant radiation-induced myocarditis is rare; presumably, the rates of late dysfunction will become less frequent as well.

Serial large retrospective reviews suggest that radiation therapy to the heart leads to increased mortality. Breast cancer cohorts in which the radiation dose to the heart varies depending on whether the cancer was in the right or left breast provide evidence for assessing this toxicity. In a meta-analysis of 40 trials from the 1980s of more than 19,000 women with breast cancer who were treated with radiation, the Early Breast Cancer Trialists Collaborative Group (2000) found an increased mortality from cardiovascular disease.[102] However, a more recent study with up to 15 years of follow-up of more then 15,000 breast cancer patients who were treated with more modern heart-sparing techniques revealed no excess in cardiac disease among those who were treated for left-sided versus right-sided breast cancer.[103] In another retrospective study of 27,283 patients, there was a progressive 6% yearly decline in ischemic heart disease hazard of death in patients with left-sided breast cancer versus right-sided breast cancer who were treated with radiation after 1979.[104] In the largest data analysis of 308,861 women from U.S. Surveillance Epidemiology and End Results, 115,165 of whom had been treated by radiation, Darby and colleagues found progressive decrease in the cardiac mortality ratio (left versus right tumor) from 1.42 after 10 to 14 years for those irradiated in 1972 to 192 to 1.27 after 10 years for those irradiated in 1983 to 1992.[105] Harris and colleagues studied long-term side effects (median follow up of 12 years) of radiation therapy of 961 breast cancer patients treated with right-side versus left-side heart irradiation with lower volume of heart exposure techniques used in University of Pennsylvania since 1977. Although "there was no difference in overall mortality from any cardiac cause," the authors found a 6.4% cumulative risk of cardiac death for the left-sided irradiation versus 3.6% for right-sided irradiation at 20 years.[106] The new methods of radiation therapy, such as tomotherapy, intensity-modulated radiation therapy, mixed electron/photon beams, respiratory gating,[107] and prone accelerated partial breast irradiation,[108] have a potential of further decrease of radiation-caused cardiac mortality and morbidity.

Increased caution must be exercised, however, when radiation therapy is combined with doxorubicin therapy or possibly other cardiotoxic drugs because there appears to be a synergistic toxic effect on the myocardium. This can occur even if the two therapies are separated by long time periods. Prior radiation is a well-recognized risk factor for developing doxorubicin toxicity.[109] Conversely, radiation can cause a sudden decrease in ventricular function in a patient who either is receiving or has received doxorubicin. There are insufficient data to assess a possible interaction between radiation and trastuzumab therapy.

Therapy

Treatment of all cardiomyopathies is similar, regardless of their etiology (Box 63-1). Ceasing treatment with the offending agent is of prime importance, and changing from one agent to another, especially when an anthracycline is involved, will not protect from further cardiotoxicity. Fluid and sodium restriction and the use of diuretics may provide some relief in acute situations. Afterload reduction with agents such as ACE inhibitors is clearly beneficial, and in stable patients, beta-adrenergic blockers such as carvedilol appear to be of significant benefit.[110] Clinical improvement in anthracycline-induced CHF has been demonstrated, as has improvement in LVEF as measured by serial MUGA scans.[17,111] In an animal model, treatment with angiotensin II receptor blockers may also be of benefit.[112] Currently, no therapy is available that can reverse the damage done to the injured myocardium; and dexrazoxane, despite its mechanism of protection in the acute stage of cardiac damage, would not be expected to repair existing damage. Early treatment of significant cardiac dysfunction may mitigate the progression of disease. Digitalis can improve symptoms but probably does not extend life.

CONGESTIVE STATES ASSOCIATED WITH OTHER CANCER TREATMENT

General considerations of fluid and electrolyte management should be carefully considered in administering anticancer treatment. Possible fluid overload states can result from intensive hydration regimens (e.g., for cisplatin) or with transfusion. Patients with anemia and low serum albumin are more susceptible to high output states. Malignant pleural and pericardial effusions, as well as ascites or

Box 63-1. DOXORUBICIN-INDUCED CARDIOMYOPATHY

Monitoring

- Physical examination is the best way to monitor patients for doxorubicin-induced cardiomyopathy (e.g., sinus tachycardia is a nonspecific early sign), with radionuclide scans or echocardiograms at baseline, 300 mg/m^2, 450 mg/m^2, and each 100 mg/m^2 thereafter.
- Patients who are at increased risk—for instance, those who have had prior treatment with anthracyclines, are older than 70 years of age, have had prior chest radiation therapy, or have pre-existing cardiac disease—might need to be observed more closely. Therapy should be withheld if the left ventricular ejection fraction falls to less than 0.45 or to 0.2 below baseline. (Other investigators have used a fall of 0.15 as the cutoff for discontinuing therapy.)
- Most centers still use endomyocardial biopsy as the confirmatory tool. Biopsy should be considered in patients with a cumulative dose of 450 mg/m^2 or more, and therapy should be withheld in any case if the Billingham biopsy score is 2 or greater.
- Cardiac troponin C and I are under investigation for monitoring purposes.

Cumulative Dose Limitation

If monitoring strategies are in place, most patients who are thought to be benefiting from therapy can be safely treated to doses exceeding 450 mg/m^2.

Dosage Schedule Modification

The incidence of cardiomyopathy may be decreased by modifying the dose schedule. For example, intravenous bolus schedules may be adjusted by dividing the 21-day dose into three weekly doses or a continuous infusion schedule in which the full dose is given over 72 to 96 hours through central catheters with portable infusion pumps.

Cardioprotection

Dexrazoxane (ICRF-187: ADR 529), a chelating agent that binds intracellular iron and prevents free radical production, has been shown in clinical trials to markedly reduce the incidence and severity of cardiomyopathy.

Treatment

- The first step in treatment is to stop the doxorubicin and then not to use it again in the future. As with other cardiomyopathies, fluid intake is limited.
- Sodium, diuretics, afterload, and cautious use of afterload reduction, especially with angiotensin-converting enzyme inhibitors, may result in clinical improvement.
- The course can vary, ranging from improvement to steady worsening with biventricular failure and death as the outcome.

intrathoracic malignancies, can cause external compression of the heart with resulting symptoms of CHF. Thyroid dysfunction sometimes is identified in cancer patients and responds to the usual therapeutic interventions.

DYSRHYTHMIAS

Dysrhythmias are commonly seen in the course of treatment of malignancies. The entire spectrum of supraventricular and ventricular bradydysrhythmias and tachydysrhythmias can be seen in cancer patients for a variety of reasons that might or might not be related to the cancer or its treatment. These include intracardiac or paracardiac tumor, electrolyte imbalance, fever, and hyperadrenergic states. Dysrhythmias related to therapy may, in turn, be related to coronary or myocardial disease resulting from anticancer therapy or to the direct dysrhythmogenic effects of the anticancer therapy itself.

Radiation injury has been implicated in the development of sinus node dysfunction, atrioventricular block, and conduction disturbances below the bundle of His.[113]

Occasional dysrhythmias have been reported with the anthracyclines. While these usually occur in the setting of the drug-induced cardiomyopathy, the dysrhythmias are not a prominent part of the clinical picture. Sinus tachycardia, however, is exceedingly common in patients with an anthracycline-induced cardiomyopathy and may be the earliest sign of the cardiomyopathic effect of anthracyclines. Supraventricular dysrhythmias also may occur with the development of pulmonary venous hypertension. Ventricular dysrhythmias occur in the setting of left ventricular failure. Sudden death, however, remains rare.

Arsenic trioxide (Trisenox), an important agent for treatment of acute promyelocytic leukemia, has been reported to cause cardiac arrhythmias associated with QT interval prolongation[114] as well as complete atrioventricular block.[114,115] QT prolongation can be a risk factor for torsade de pointes, a life-threatening form of ventricular arrhythmia.[116] The prevalence of QT prolongation increased from 14.4% at baseline to 68% of treated patients in one study.[114] However, in the same study, analysis of 99 patients and 1189 electrocardiographic recordings suggests that QT prolongation may be a reversible effect, provided that careful patient cardiac evaluation is done before and during therapy as well as detection and timely correction of electrolyte abnormalities. Indeed, only 2 patients out of 99 developed significant arrhythmias.[114] Rare deaths have been reported; female gender and African extraction may be risk factors, but further study is needed. Reports are anecdotal.

Taxol has been implicated in the development of dysrhythmias. A 30% incidence of asymptomatic bradycardia has been observed with this agent; however, the bradycardia seldom requires termination of the agent. In addition, atrioventricular block of varying degrees, bundle branch block, and ventricular tachycardia have been described[117] and may require specific therapy. Supraventricular tachycardias were reported in 8 of 41 (20%) patients receiving therapy with dihydro-5-azacytidine, an investigational pyrimidine, for mesothelioma.[118]

Interleukin-11 (Neumega) is used for the reduction of chemotherapy-induced thrombocytopenia. In one trial, 6 of 58 patients (10%) developed symptomatic dysrhythmias.[119] Five patients had atrial fibrillation, and one patient had atrial flutter. The authors speculated that these effects might have been secondary to fluid retention.

Dysrhythmias also have been reported with the monoclonal antibody to CD20 (Rituximab).[120]

Nonspecific dysrhythmia is common in cancer patients and might be due to fluid and electrolyte shifts associated with vomiting, as well as hyperadrenergic states that may accompany anemia and a variety of other factors. Most of these rhythm disturbances can be managed with correction of the underlying abnormality and do not require specific antidysrhythmic therapy.

MYOCARDIAL ISCHEMIA

A variety of ischemic syndromes have been ascribed to oncologic therapy. Much of the data is anecdotal, however, as there is a high incidence of coronary artery disease in the population in which cancer is also common. Chemotherapy may shift a previously stable oxygen

supply and demand balance in favor of an increased demand in the face of a fixed supply that results in the ischemic syndrome. The clinical picture is further confused by the high incidence of intercurrent intrathoracic malignant disease, anemia, fever, and infections and concomitant treatment with other drugs, all of which can affect the balance. Furthermore, the malignancy itself may cause chest pain in a patient with noncritical ischemic disease.

There is, however, convincing evidence that thoracic radiation therapy is associated with the development of coronary artery disease.[121] In addition to the very substantial body of evidence that radiation causes small vessel damage, which ultimately leads to myocardial fibrosis and cardiomyopathy, there also are data that implicate radiation therapy in the development of epicardial (particularly ostial) coronary artery disease.[121,122] The original data came largely from case reports of myocardial ischemia and infarction in young adults (without other risk factors for coronary atherosclerosis) following mediastinal radiation therapy. Two basic pathologic mechanisms have been implicated. The first relates to the direct effects of radiation on the endothelial cells of epicardial coronary arteries, leading to accelerated atherogenesis. The second—and more typical—pathology is that of severe medial and adventitial fibrosis, perhaps mediated through radiation damage to the vasa vasorum. Typically, this vessel fibrosis is associated with a paucity of the intimal lipid deposition that characterizes atherosclerotic lesions.[123–125] With newer cardiac-sparing radiation therapy techniques, the likelihood of cardiac damage has been reduced.

Fluoropyrimidines are the most commonly chemotherapy drugs associated with myocardial ischemia. The largest number of cases of ischemia that have been ascribed to anticancer therapy are associated with treatment with 5-FU.[126] Several case reports called attention to this possible association. There have been isolated reports of patients with normal coronary angiography who developed typical symptoms and electrocardiographic evidence of ischemia after 5-FU infusion, but a review of over 1000 patients receiving 5-FU revealed an incidence of cardiac toxicity of 4.5% in patients in whom coronary disease was known to predate treatment compared to an incidence of 1.1% in those not known to have coronary artery disease prior to therapy. Thus, it was not surprising that an early prospective analysis was not convincing for a causative role of this drug in the development of angina or myocardial infarction. In a prospective series of 910 patients,[127] however, 5 patients (0.55%) developed signs and symptoms that were consistent with coronary artery spasm. All five patients had ST segment elevation and ventricular dysrhythmias. Four had documented infarction, and two had cardiac arrests, leading to the hypothesis that there might be 5-FU- or metabolite-mediated increases in coronary vasomotor tone. Coronary artery spasm as a mechanism for 5-FU-associated ischemia could explain the increased incidence of ischemia in patients with underlying coronary disease as well as in those with angiographically normal coronary vessels. Nitrates and calcium blockers may be protective. There is some suggestion that the association of 5-FU with myocardial ischemic events is more striking in patients who are treated with continuous infusion therapy.[126] The association is more common in patients who are receiving concomitant radiation therapy[128] or treatment with cisplatin.

Capecitabine (Xeloda), an oral prodrug for 5-FU, has also been associated with cardiac toxicity. In a review of 832 patients, incidence was similar to that with 5-FU (3% for all toxicities and 1% for grades 3 to 4). Individual cases of myocardial infarction, angina pectoris, myocardial ischemia, myocarditis, and tachycardia were described.[129] It is possible that combination with oxaliplatinum may increase this toxicity. In combined data from two trials of 153 patients, cardiac toxicity was observed in 6.5% of patients; 4.6% were ischemic.[130]

Although the vinca alkaloids also have been reported to precipitate angina and myocardial infarction,[131] this observation is strictly anecdotal.

PERIPHERAL VASCULAR DISEASE

Raynaud phenomenon has been described in patients receiving cisplatin-based therapy.[132] It also has been described after therapy with vinblastine, vincristine, and bleomycin. These may be similar in mechanism to other ischemic syndromes (e.g., coronary ischemia or cerebral vascular ischemia), which have been described with these agents as well as 5-FU. Increased thromboembolism has been observed when thalidomide is combined with doxorubicin[133] and with gemcitabine and infusional 5-FU.[134] A similarly high incidence of thromboembolic events was reported with the combination of gemcitabine, cisplatin, and SU5416.[135] As is the case for radiation-induced coronary artery disease, clinically significant occlusive lesions in other arteries, such as the carotids,[136] have been reported following irradiation.

PERICARDIAL DISEASE

Most pericardial disease presenting in cancer patients may be attributed to the underlying malignancy, the most common malignancies being melanoma, breast cancer, and lung cancer. Patients may have metastatic disease to the pericardium or obstruction of lymphatic or venous flow, producing a pericardial effusion. Even in patients without clinically manifest disease, asymptomatic pericardial effusions are common. Pericardial effusions have been ascribed to the anthracyclines[137] as well as cyclophosphamide[138] and dihydro-5 azacytidine.[118] With the exception of irradiation, pericardial manifestations of cancer treatment are seldom troublesome. Interestingly, in series in which pericardial effusions were reported with doxorubicin or cyclophosphamide, most patients ultimately went on to demonstrate evidence of myocardial toxicity from the drugs. Isolated pericarditis was rare.

There have been case reports of high-dose busulfan causing cardiac tamponade in children with thalassemia[139] and a report of busulfan-related endocardial fibrosis.[140]

FLUID RETENTION

Docetaxel (Taxotere), an active taxane analog of paclitaxel (Taxol), has broad antitumor activity but is associated with fluid retention in some patients. Severe fluid retention and CHF are rare. This syndrome is progressive with more treatment cycles. It does not appear to be of cardiac or renal origin. Premedication with steroids substantially reduces this problem.[141]

Dasatinib (Sprycel) is an oral agent that is active in 14 of 15 imatinib-resistant BCR-ABL tyrosine kinase mutants and inhibits other tyrosine kinases such as SRC, C-Kit, and PDGFR. In a study of 84 CML and Ph^+ ALL patients, 15% of patients developed pleural effusion, 19% developed peripheral edema, 14% developed pulmonary edema, and 7% developed pericardial effusion.[142] Also in studies of patients with leukemia, dasatinib caused QT prolongation in nine patients, three of whom (<1%) had QTcF greater than 500 msec.[143] Therefore, special attention should be paid to correction of hypokalemia and hypomagnesemia prior to dasatinib treatment as well as to patients with known QT prolongation and patients who are taking other medicines that can cause QT prolongation.[143]

All-*trans* retinoic acid, an oral agent that overcomes promyelocyte retinoic acid receptor maturation block caused by a t(15,17)-related protein, has become an important part of acute promyelocytic leukemia treatment. The drug causes retinoic acid syndrome,[144] which consists of respiratory distress, hypoxemia, weight gain, pleural and pericardial effusions, pulmonary infiltrates, fever, hypotension, and acute renal failure, after a median of 11 days (2 to 47 days) in approximately 25% of treated patients.[145] The treatment is high-dose dexamethasone given as soon as the syndrome is suspected[144] and temporary discontinuation of all-*trans* retinoic acid, depending on the clinical situation.

RADIATION-INDUCED PERICARDIAL DISEASE

Pericardial disease is a well-known side effect of thoracic radiation therapy. Effusions have been reported in 6% to 30% of patients receiving radiation therapy to the chest using older radiation techniques.[146] Since the 1960s, there have been numerous reports of patients who had received high-dose mediastinal radiation for the treatment of lymphoma and ultimately developed pericardial disease. Similar reports ascribing pericardial disease to radiation therapy for breast cancer also appeared in the late 1960s.

The clinical spectrum of radiation-induced pericardial disease is wide. Acute pericarditis occurs in 10% to 15% of patients with Hodgkin's disease who receive more than 4000 rads to the mediastinum.[147] The clinical onset of symptoms related to the pericarditis is anywhere from 0 to 85 months after therapy, with a peak occurring between 5 and 9 months. The acute pericarditis may be symptomatic, with the patient experiencing chest pain and fever and the physician noting a pericardial friction rub. However, acute pericardial inflammation probably is often asymptomatic. In any event, the acute pericarditis usually resolves spontaneously. In symptomatic patients, treatment with nonsteroidal anti-inflammatory drugs (including aspirin) or corticosteroids is probably warranted.[148]

The acute effects of radiation on the pericardium appear to be due to an increase in capillary permeability in the pericardium resulting in a fibrinous exudate. Ultimately, fibrosis and calcification can occur. Fewer than half of symptomatic and asymptomatic patients with acute pericarditis will go on to develop chronic pericardial disease or tamponade. Constrictive pericarditis has been described anywhere from 2 to 20 years after radiation. Signs of constriction may include a pericardial knock, Kussmaul's sign, peripheral edema, and evidence of bowel edema or hepatic congestion. The pericardium might appear thickened on a thoracic CAT scan or an echocardiogram. The diagnosis of constrictive physiology can almost always be confirmed by Doppler echocardiography. In such patients, pericardiectomy might be warranted; however, the surgery is often difficult and carries significant morbidity and mortality.

Radiation-induced pericardial disease depends on the extent to which the heart has received radiation and the dose of radiation delivered to the heart. With current techniques in mediastinal radiation, including the use of modern megavoltage equipment and the delivery of divided radiation to the anterior and posterior thorax with a subcarinal shell and intensity-modulated radiation therapy, it is likely that the incidence of pericardial disease has been significantly decreased, perhaps to the range of 2% to 2.5%.[149]

CARDIOCIRCULATORY EFFECTS OF BIOLOGIC RESPONSE MODIFIERS

Bevacizumab (Avastin) is a recombinant monoclonal humanized IgG1antibody that selectively interacts with vascular endothelial growth factor (VEGF) and competitively inhibits its binding to VEGFR-1 (Flt-1) and VEGFR-1 (KDR/Flk-1) endothelial cell surface receptors, thereby disrupting microvascular proliferation and metastasis of tumors. Bevacizumab showed its activity as an adjunct to cytotoxic drug combination and is approved for use in colon, lung, and breast cancer. An 8% to 18% incidence of grade 3 or 4 hypertension was found in many phase I and II studies.[150] In the phase III trial, there was an 11% incidence of grade 3 hypertension in the group of 393 patients who were treated with bevacizumab in combination with irinoitecan and 5-FU/leucovorin (B/IFL), as compared to the 2.3% in the group of 397 patients who were treated with IFL alone. Hypertension was successfully controlled with ACE inhibitors, diuretics, and other antihypertensive medications.[151] Rarely, the drug must be discontinued; the blood pressure might remain elevated despite treatment interruption.

Recombinant technology has made a number of new agents available for clinical trial. They have a variety of side effects. In some cases, these adverse effects may actively be the molecular indicator of a variety of cellular interactions. Hypotension and tachycardia are observed with a number of agents. With interferon-alpha, these have been reported in 6% to 14% of patients.[152] It is difficult in these studies to separate changes in blood pressure from dysrhythmias or ischemic events. Hypotension is a more consistent feature of interferon,[153] although fewer patients have received other biologic therapies.

Hypotension (along with dysrhythmias, ischemia, and decreased contractility) is a major side effect of interleukin-2 and was observed to occur in more than 70% of patients in the early IL2/LAK trials.[154] The primary mechanism appears to be decreased vascular resistance.[84,155] In the early days of therapy, patients develop increased heart rate, increased cardiac index, and decreased left ventricular stroke volume work index, peripheral vascular resistance, and mean arterial blood pressure. The clinical presentation is similar to that of septic shock, with a vascular leak syndrome, fluid retention, and noncardiogenic pulmonary edema. The mechanism may be similar to that of septic shock, with induction of cytokines and effector cells and the release of vasoactive agents. Reductions in dose and continuous infusion schedules have lessened these toxicities[156–158] but also may decrease the antitumor effects.[159] In one study,[160] oral L-carnitine appeared to decrease these complications. IL-2 toxicity often requires intensive-care management, support with pressors, and, at times, ventilatory support.

Hypotension also has been described with tumor necrosis factor,[161] granulocyte macrophage colony-stimulating factor,[162] interleukin-11,[119] and monoclonal antibodies.[117] With tumor necrosis factor, the hypotension often is dose-limiting.[161] With granulocyte macrophage colony-stimulating factor, it is observed at high doses and is associated with a capillary leak syndrome and decreased peripheral resistance.[162] The mechanism with these two agents is not as well defined, nor is the clinical problem as acute as it is with IL-2. Hypotension also has been reported with interleukin-1 in phase I trials.[163]

The possibility of cardiac toxicity was raised in early trials of interleukin-4, especially when one patient was found to have biopsy-proven myocarditis.[164] Interleukin-6 has been associated with cardiac dysrhythmias.[165] Syncope or near-syncope was reported in 6 of 58 patients in a trial of IL-11 (5 patients at the 50-mg/kg level and 1 patient in the in placebo group). Six patients also had documented dysrhythmias.[119]

Changes in peripheral vascular resistance and hypotension may be generalized effects of biologic therapies. Further elucidation of their mechanisms and management is required.

The complexities of bone marrow transplantation have led to cardiac toxicity in a number of patients. In a series of 170 patients who were monitored prospectively, life-threatening pericardial effusions or cardiac arrest were observed in fewer than 2% of cases.[166] Decreased ejection fraction was observed in 17 patients. In a retrospective study of 138 patients treated with high-dose therapy and stem cell rescue, cardiotoxicity occurred in 17 patients. It occurred more frequently in patients with lymphoma and breast cancer.[167] It is difficult, however, to determine which of the many drugs used in the regimen, particularly the chemotherapy induction, is responsible for these changes.

LONG-TERM EFFECTS OF CHEMOTHERAPY

One additional caution must be raised. As an increasing number of patients are long-term survivors of childhood cancers, adult patients who received adjuvant therapy without disease recurrence, or long-term survivors of more advanced adult malignancies, unanticipated cardiovascular effects may be observed. Long-term observation and study of these patients are necessary. Identification of such effects may bring into question the overall risk-benefit ratio of the

original treatment. In a long-term (median: 10.2 years) follow-up study of 992 males in the United Kingdom who had been treated with chemotherapy or radiation for testicular cancer, the incidence of cardiac events (angina, chest pain, or myocardial infarction) was increased when compared to controls treated with orchiectomy alone (chemotherapy alone: rate ratio = 2.59; radiation therapy: RR 2.40; and chemotherapy plus radiation: rate ratio = 2.78). Neither the radiation fields nor the specific chemotherapeutic agent (bleomycin, vinblastine, cisplatin, or carboplatin) fully explained these findings.[168]

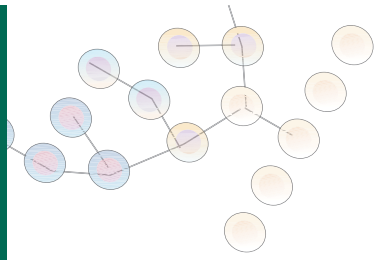
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64 Reproductive Complications

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SUMMARY OF KEY POINTS

- Reproductive complications secondary to cancer or its treatment are expected to increase as the number of cancer survivors increases.

Cancer-Related

- Oligospermia is present in more than 50% of patients with Hodgkin's disease and testicular cancer.
- Patients with baseline oligospermia are more likely to become infertile following treatment.

Treatment-Related Complications

- Surgery
- Radiation therapy
- Hormonal therapy
- Chemotherapy and bone marrow transplantation

Surgery

- Prostatectomy and other pelvic surgeries are associated with erectile dysfunction; retroperitoneal dissection is associated with retrograde ejaculation.
- Nerve-sparing surgery improves potency and decreases retrograde ejaculation rates in patients with prostate, testicular, and rectal cancers.
- Gynecologic surgery can have a direct impact on sexual function by altering the normal female genital anatomy.
- Altered body image can have a profound impact on sexual function.

Radiation Therapy

- Prepubertal testicles and ovaries are more resistant to the effects of radiation.
- Testicular spermatogenesis is affected by doses as low as 15 cGy, and complete aspermia may occur with a dose of 600 cGy.
- Leydig cell dysfunction occurs at doses exceeding 2000 cGy.
- Ovarian function is more resistant to the effects of radiation. The effects are age related, with a significantly increased risk of permanent menopause in patients older than 40 years at dosages exceeding 150 to 400 cGy.
- Erectile dysfunction occurs by 2 years from treatment in 60% to 80% of prostate cancer patients receiving external beam radiation radiations. The majority are attributed to vascular insufficiency.

Hormonal Therapy

- Gonadotropin-releasing hormone (GnRH) agonists and antagonists result in medical castration with resultant loss of libido and impotence.
- Antiandrogen therapy results in a lesser degree of impotence compared to GnRH analogs in the treatment of prostate cancer.

Chemotherapy and Bone Marrow Transplantation

- Alkylating agents are associated with the highest rates of infertility.
- Doses and duration of treatment are directly associated with risk of infertility.
- Risk of infertility and amenorrhea is related to age, dose, and duration of therapy.
- Prepubertal males and females have the highest tolerance for chemotherapy. Normal puberty has been reported in both genders.
- Premature ovarian failure is age-related, the highest risk being in patients older then 40 years. The younger the female, the lower is the risk of amenorrhea and the higher are the chances that menstruation will resume on completion of chemotherapy.
- High doses of alkylating agents such as cyclophosphamide greater than 7.5 g/m^2 are likely to be associated with abnormal sperm count in children. Doses greater than 9 g/m^2 are associated with prolonged infertility. The mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) regimen that is used in Hodgkin's disease is particularly associated with male infertility. In some males, fertility recovered several years after completion of therapy.
- Females who resume menstruation after treatment are at higher risk of early menopause.
- Radiation therapy during bone marrow transplantation conditioning results in male infertility and a high rate of premature ovarian failure. Bone marrow transplantation without radiation has been associated with a high rate of fertility preservation in females treated before puberty or at a very young age.

Cancer and Pregnancy

- Cancer complicates 1 in every 1000 pregnancies.

Chemotherapy

- The highest risk of congenital abnormalities is during the first trimester of pregnancy and is especially common with antimetabolites such as methotrexate.
- Data available from leukemia and breast cancer patients suggest that chemotherapy during the second and third trimesters of pregnancy results in normal offspring. No long-term complications have been identified.

Radiation Therapy

- Risks are highest during organogenesis period (first trimester).
- Mental retardation and microcephaly may occur with second-trimester and early third-trimester exposure.

Prevention and Treatment

- Sperm cryopreservation should be discussed with all males who undergo potentially sterility-inducing treatments.
- Use of GnRH analogs may have a protective effect on ovarian function, but no protective effects on spermatogenesis have been established yet. Their use is considered experimental.
- Gonadal shielding and ovarian transposition ameliorate the effects of radiation on gonadal function.
- Assistive reproductive technologies and alternative methods of sperm collection have resulted in successful pregnancies for couples with severe male infertility secondary to cancer or its treatment.
- The use of sildenafil has reestablished potency in a large number of patients with surgery- or radiation-induced erectile dysfunction.

INTRODUCTION

Advances in the treatment of cancer have resulted in marked improvements in survival and cure rates, causing the number of cancer survivors to rise.

Cancer patients often suffer acute and long-term complications related to cancer and its treatment. Insults to reproductive health constitute an often overlooked dimension. Sexual dysfunction and infertility can have a major impact on patient well-being, interpersonal relationships, and family planning.

Attention to reproductive health issues and patient involvement in treatment planning early in the course of the disease and its treatment are key. This review focuses on the reproductive complications of cancer and its treatment.

REPRODUCTIVE PHYSIOLOGY

Gonadal Form and Function

The ovary produces mature fertilizable eggs as well as sex steroids and reproductive/gonadal peptides. These activities are carried out in an integrated manner by the different compartments of the ovarian functional unit, the follicle. The granulosa cells are the source of the sex steroids estradiol and progesterone as well as the peptides inhibin, activin, and follistatin. De novo synthesis of progesterone by the theca cells is dependent on an abundant supply of cholesterol. Granulosa cells also produce progesterone independently.[1] Estrogen biosynthesis, by contrast, requires cooperation of both the granulosa and the theca-interstitial cells. Precursor steroids (mainly androstenedione) synthesized in the theca cells are transferred across the basement membrane of the follicle to the granulosa cells, where they are aromatized to estrogens. The peptides inhibin, activin, and follistatin are expressed in various tissues, including the ovary and anterior pituitary.

Humans have approximately one million follicles at birth. During the reproductive years, typical cyclic follicular recruitment, selection, and dominance eventually deplete the ovary of follicles, leading to cessation of ovarian function and menopause.

In males, the testes secrete androgenic hormones and produce mature spermatozoa. These two processes are highly interrelated and regulated by multiple factors. Much like the ovary, compartments of the testes serve different functions. The seminiferous tubules consist of Sertoli cells that support the developing sperm and germ cells and are the sites for spermatogenesis. The interstitial or Leydig cells are essential for testosterone synthesis. Testosterone is transported from the Leydig cells to the seminiferous tubules, where it enhances spermatogenesis. Testicular hormones are responsible for the induction of male genitalia development during embryogenesis.

Hypothalamic-Pituitary-Gonadal Axis

The main regulators of testicular and ovarian function are the gonadotropins, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). The biosynthesis and secretion of gonadotropins are modulated by an interplay of hypothalamic factors: gonadotropin-releasing hormone (GnRH), intrapituitary factors (pituitary peptides—activin and follistatin), and feedback by gonadal factors.[1] Gonadotropin expression is controlled by the hypothalamus primarily through the action of GnRH. GnRH is produced in the medial basal hypothalamus and released in a pulsatile fashion to the anterior pituitary, where it binds to plasma membrane receptors on the gonadotropes and stimulates release of FSH and LH. Depending on the reproductive stage, estrogens can either increase or decrease gonadotropin production. Increased levels of estrogen in females or testosterone in males downregulate gonadotropin secretion. However, increased levels of estrogens at the time of LH surge exert a positive feedback effect. In addition to steroid hormones, the gonadal proteins activin, inhibin, and follistatin modulate release of FSH.[2] Inhibin decreases and activin stimulates gonadotropin function. Follistatin also inhibits FSH but is less potent than inhibin.

Regulatory effects of gonadotropins on the ovaries and testes are similar. In the testes, LH interacts with high-affinity receptors on the plasma membrane of the Leydig cells and, through a cAMP-activated series of steps, stimulates the synthesis of the enzymes of testosterone production. The epithelium of the seminiferous tubules is the primary site of action of FSH. FSH binds to cell surface receptors of the Sertoli cells, stimulating the synthesis of androgen-binding proteins and aromatase enzyme complex that convert testosterone to estradiol. LH and FSH effects on the ovaries strongly resemble those in the testes. Activation of gonadotropin receptors on the plasma membranes of the granulosa and theca cells stimulates the adenylate cyclase system, inducing the regulation of female steroid hormone production and follicular maturation.[3]

DIRECT EFFECTS OF CANCER ON REPRODUCTIVE FUNCTION

Although this chapter concentrates on the impact of cancer therapy on reproductive function, it is important to note that cancer can have important direct effects on sexual and reproductive function.

Gonadal tumors can result in reproductive dysfunction secondary to gonadal germinal tissue destruction as well as to aberrations in hormonal balance. Ovarian sex cord–stromal tumors are often associated with hormonal effects such as precocious puberty, amenorrhea, virilizing symptoms, or postmenopausal bleeding. Male sex cord tumors may be associated with precocious puberty, feminization syndrome, and gynecomastia. Reproductive organ cancers and other cancers involving the pelvis may have direct anatomic interference with coitus or indirect interference secondary to pain. Females with invasive vulvar and vaginal cancers and advanced cervical cancers often present with postcoital bleeding or dyspareunia. Males with testicular cancer may have diffuse testicular pain, swelling, and tenderness that interfere with intercourse. Penile cancer usually presents as a penile sore or mass, but when neglected, it can result in ulceration, bleeding, or secondary infection, which can interfere with coitus.

Central nervous system damage by primary or metastatic cancer or indirectly through paraneoplastic involvement can have a considerable impact on reproductive function. Pituitary prolactin-secreting adenomas are commonly associated with impotence in men and amenorrhea and galactorrhea in women. Other pituitary adenomas can affect reproductive function by destroying LH- and FSH-producing gonadotropes. Craniopharyngiomas and other metastatic cancers can directly invade the pituitary gland and produce hypothalamic-pituitary dysfunction. Metastatic disease that affects the hypothalamus-pituitary axis will also lead to reproductive dysfunction. Paraneoplastic syndromes are an infrequent but well documented cause of reproductive dysfunction. Ectopic adrenocorticotropic hormone secretion (e.g., small cell lung cancer) can result in Cushing-like disease including amenorrhea. Other neurologic paraneoplastic syndromes can have a direct impact on reproductive function through the involvement of the autonomic system such as in Lambert-Eaton syndrome or indirectly by resulting in personality changes such as in limbic encephalitis.[4]

Testicular cancer and Hodgkin's disease are among the most common diseases affecting young men of reproductive age, and both are associated with an increased rate of infertility.

Men with Hodgkin's disease may have pretreatment impairment of spermatogenesis. A recent study of patients with Hodgkin's disease reported that 47% had abnormal semen analysis.[5] In this study, semen quality correlated significantly with the hemoglobin level but not with disease stage or fever. In another study of 158 patients with Hodgkin's disease, elevated erythrocyte sedimentation rate and advanced disease stage were associated with poor semen quality.[6] The association between testicular cancer and abnormalities of spermato-

genesis is even more pronounced. The degree of spermatogenic abnormalities in these patients is greater than can be attributable to local tumor effect or the degree of systemic involvement. A recent study found that sperm count was lower in 83 patients with testicular germ cell cancer (15×10^6/mL versus 48×10^6 mL) compared with healthy men.[7] Histologic investigations have revealed a high prevalence of dysfunctional spermatogenesis even in the contralateral testicle that is uninvolved with cancer.[8] An increased risk of testicular cancer has also been observed in men presenting with an abnormal semen analysis and infertility. Infertile men with abnormal semen analyses have a 20-fold higher incidence of testicular cancer compared to the general population.[9] The specific links between the pathologic events that cause infertility and testicular cancer remain unclear.

EFFECTS OF CANCER THERAPY ON SEXUAL AND REPRODUCTIVE FUNCTION

Surgery

The surgical treatments that have the most significant impact on reproductive function are those involving the pelvis. These include radical prostatectomy, radical cystectomy, rectal cancer surgery, orchiectomy and retroperitoneal dissection, and radical hysterectomy.

Prostate Cancer

Erectile dysfunction in patients undergoing radical prostatectomy is commonly seen after surgery.[10–13] Steineck and colleagues randomized 376 patients to radical prostatectomy versus watchful waiting; the incidence of erectile dysfunction was significantly higher in the surgical group (80%) versus the observation group (45%).[14] Identification and sparing of the neurovascular bundles that carry cavernous nerves is associated with a significant improvement in potency rate following radical prostatectomy.[15] Bilateral nerve-sparing surgeries are considerably more effective in maintaining erection compared to unilateral nerve-sparing surgeries. Potency rates following bilateral sparing surgery at 3 years were 76% compared to 30% with unilateral sparing surgery in previously potent patients younger than 60 years of age. The rates of potency are lower in older patients and in patients with known erectile dysfunction prior to surgery.[16]

Testicular Cancer

Retroperitoneal lymph node dissection (RPLND) frequently damages the sympathetic nerves that innervate the seminal vesicles and the bladder neck. This leads to loss of seminal vesicle emission or emission without bladder neck closure (retrograde ejaculation).[17,18] In the series reported by Hartmann and colleagues, patients who had received more than one modality of treatment (such as chemotherapy or radiation therapy and RPLND) had the highest incidence of infertility.[19] Six out of 29 patients who underwent bilateral RPLND in this series suffered from dry ejaculation. A selective RPLND, as described by Donohue and colleagues, results in the sparing of a unilateral sympathetic chain and preservation of antegrade ejaculation.[20] Jacobsen and colleagues reported preserved antegrade ejaculation in 89% of patients undergoing a RPLND after chemotherapy.[21]

Rectal Cancer

Conventional rectal surgery is associated with high rates of impotence and retrograde ejaculation, likely owing to the damage of the pelvic autonomic parasympathetic and sympathetic nerves by blunt dissection. Williams and colleagues described the outcomes of 78 patients who underwent abdominoperineal resection or low anterior resection. Two thirds of patients who underwent abdominoperineal resection had impaired sexual function compared to 30% of patients who underwent low anterior resection.[22] Total mesorectal excision is a standard procedure in rectal cancer surgery. This technique requires sharp dissection of the mesorectum and emphasizes autonomic nerve preservation, resulting in a lower rate of local recurrences and a higher rate of potency preservation. A comparison of sexual outcomes of patients with conventional surgery and mesorectal excision showed that the ability to have intercourse dropped from 75% to 13% in the conventional surgery arm compared to a drop from 67% to 29% in the total mesorectal excision group.[23] Limited information is available about sexual dysfunction in women with rectal cancer. One study reported that 39% of sexually active women and 62% of all women treated for rectal cancer had Female Sexual Function Index scores that were considered abnormal despite the use of nerve-sparing surgery at the reporting institution.[24] Physical factors such as vaginal stenosis, urinary and fecal incontinence, and dyspareunia have a significant impact on female sexual function, and issues such as low libido, decreased vaginal lubrication, and body image concerns also contribute.

Other Surgeries

Gynecologic surgeries can alter sexual function directly by affecting the anatomy of the female genital tract. In a large Swedish study, patients who had been treated with radical hysterectomy were compared to controls matched for age and geographic region. The researchers found no difference in sexual desire or orgasm between the groups. Patients who had been treated with radical hysterectomy reported statistically significant differences in vaginal lubrication, vaginal length, and vaginal elasticity compared with controls.[25] In contrast, a recent publication found that women who had been treated with radical hysterectomy resembled their age- and race-matched peers who have never had a cancer diagnosis or hysterectomy in sexual well-being.[26] While sexual problems occur with considerable frequency in breast cancer patients and often extend beyond the acute phase of treatment, several prospective studies show no difference in quality-of-life outcomes or sexual functioning for breast cancer survivors on the basis of surgical treatment.[27,28] The use of breast-conserving treatment (versus mastectomy) is not predictive of sexual health after mediating variables are controlled in the analysis.[29]

Radiation Therapy

Radiation therapy affects reproductive function through direct effects on the pituitary, hypothalamus, gonads, uterus, and penile arterial and nerve supplies.

Central Nervous System Effects on Reproductive Function

Mounting evidence suggests that cranial irradiation reduces fertility and sexual function in survivors of childhood cancer. External irradiation to the brain can cause damage to the hypothalamus and impair its function; pituitary cells are more resistant to irradiation. Pituitary dysfunction secondary to irradiation is attributed to disturbance in the hypothalamic-pituitary axis. Hypopituitarism develops slowly after brain irradiation and can be associated with an increase in prolactin levels.[30] The hypothalamic-pituitary function was studied in 31 patients with nasopharyngeal tumors treated with primary radiation therapy (4000 to 6000 cGy).[31] All patients had normal baseline pituitary function. At 1 year from treatment, elevations in thyroid-stimulating hormone and blunted LH response to luteinizing hormone-releasing hormone (LHRH) suggest an abnormality in the pulsatile release of LHRH in males. Three females developed amenorrhea in association with elevated prolactin levels.[31] A dose-dependent response has been suggested, with thyroid-stimulating hormone and gonadotropin abnormalities more commonly seen with brain irradiation doses exceeding 3000 cGy.[32] A recent multicenter study of 593 long-term survivors of acute lymphoblastic leukemia disclosed an increased rate of infertility among children treated with whole-brain radiation.[33] The study suggests that cranial irradiation affects fertility by disrupting gonadotropin secretion. The fertility of female survivors who were treated around the time of menarche was significantly lower than that of sibling controls (rate ratio = 0.59).

Fertility in male patients who received cranial radiation doses of 2400 cGy before the age of 9 years was one third that of controls (rate ratio = 0.35). Survivors who were treated at other ages did not have fertility deficits. This suggests a window period in which normal gonadotropin function is most essential for gonadal maturation.[33] This study also shows that reproductive dysfunction can occur at lower doses of brain irradiation (1200 to 2400 cGy) than was previously suggested.

Radiation Effects on Testicular Function

The testis is one of the most radiosensitive tissues; very low doses of radiation cause significant impairment of testis function. Damage may be caused by direct irradiation of the testis or, more commonly, from scattered irradiation during treatment of adjacent targets. Permanent Leydig cell dysfunction occurs with a dose of 2000 to 3000 cGy. Therapeutic irradiation (2400 cGy) to the testes in patients with acute leukemia causes Leydig cell dysfunction, which is manifested by low testosterone levels or a poor testosterone response to gonadotropins.[33,34] Spermatogenic elements are much more sensitive to radiation than are Leydig cells. Radiation doses as low as 15 cGy transiently suppress spermatogenesis, and doses higher than 600 cGy permanently destroy the germinal elements.[35] Berthelsen evaluated the effects of adjuvant irradiation for seminoma on gonadal function. Retroperitoneal and ipsilateral iliac irradiation resulted in an estimated 200- to 1300-cGy scatter to the unaffected contralateral testicle.[36] Two thirds of patients developed azoospermia, and it took a median of 540 days from the end of treatment before spermatozoa were again found in semen samples. A median of 1250 days passed before the pretreatment sperm count was reached. Sperm counts were low (median: 6×10^6 per ejaculate) up to 5 years after treatment, and serum FSH was elevated (median: 61 IU/L).[36] The time to sperm count recovery is dose dependent at least in the range of 19 to 148 cGy.[37] There is no evidence of an increase in post-treatment congenital abnormalities, and the post-treatment conception rate was 60% to 70%.[36]

Radiation Effects on Ovarian Function

The ovaries of prepubertal children and adolescents, with their greater number of follicles, are relatively resistant to therapy-induced damage. Irradiation that does not involve the pelvis usually does not result in ovarian failure, while individuals who are treated with abdominal, pelvic, or spinal irradiation are at an increased risk of developing ovarian failure, especially if both ovaries are within the field. The effect of radiation on the ovaries is dose-dependent. Recent studies suggest that the LD_{50} (the radiation dose that is required to kill 50% of oocytes) is less than 2 Gy.[38] The ovaries of younger individuals are less sensitive to damage from radiation than are those of older adults.[39] While a radiation dose of 6 Gy is sufficient to result in permanent ovarian failure in women older than 40 year old, higher doses in the range of 1 to 20 Gy result in permanent ovarian failure in the majority of patients who are treated in childhood.[40]

Pelvic Radiation as a Cause of Reproductive Dysfunction

Radiation therapy is commonly employed as definitive treatment for patients with localized or locally advanced prostate cancer. Although the etiology of erectile dysfunction after definitive radiation therapy for prostate cancer is likely to be multifactorial, mounting evidence suggests that the arteriogenic mechanism is more important in this setting then the cavernosal mechanism. Maintenance of normal erection requires both vasodilation of penile arteries (arteriogenic element) and concomitant relaxation of the corporal smooth muscles (cavernosal element). Duplex ultrasonography can assess arteriogenic function by measuring peak penile blood flow and cavernosal function by measuring distension of the corpora cavernosa in the setting of normal penile flow.[41] Duplex ultrasonography in prostate cancer patients with radiation therapy-induced erectile dysfunction confirmed a 63% rate of arteriogenic dysfunction.[41] This contrasts with prostatectomy-induced erectile dysfunction, in which only 32% had arteriogenic dysfunction while 52% had cavernosal dysfunction.[41] Erectile dysfunction is frequently seen after external beam radiation for prostate cancer and increases in frequency with time. Potency and age prior to treatment are risk factors for erectile dysfunction following completion of therapy. Data from one institution on 802 patients before and after treatment for prostate cancer show that only 15% of patients (24.5% of whom were previously potent) who elected radiation therapy had normal erectile function at a median of 53 months of follow-up.[42] Others have shown higher rates of potency, especially when erectile dysfunction prior to radiation is accounted for. In 290 prostate cancer patients treated with radiation, 62% and 42% of those who were potent before treatment maintained potency at 12 and 24 months, respectively.[43] Potency rates drop further with time. Conformal radiation therapy limits the radiation field while delivering a high dose of radiation to the prostate and may be associated with a lower degree of impotence.[44,45] Mantz and colleagues described a 5-year potency rate of 53% among 287 prostate cancer patients who were treated with 6000 to 7200 cGy conformal radiation therapy.[45] The use of brachytherapy in the treatment of prostate cancer has also been associated with a lower incidence of impotence. Prostate brachytherapy as monotherapy was associated with 5- and 6-year potency rates of 76% and 52%, respectively, among previously potent patients.[46,47] The addition of external beam radiation or antiandrogen therapy to brachytherapy decreases the rates of potency substantially.[46,47]

Pelvic radiotherapy for cervical carcinoma is associated with vaginal atrophy, shortening, or agglutination, making intercourse difficult or impossible for these women.[48] In addition, patients often become menopausal as a result of pelvic radiation. Women who have been treated with pelvic radiation report severe sexual dysfunction despite the fact that their desire for sexual intimacy is similar to that of controls. At 2 years of follow-up, Jensen and colleagues reported 85% of women having no interest in sex, 55% having dyspareunia, and 50% having vaginal shortening. These problems were very significant in comparison to the women's own premorbid sexual function and age-matched controls.[49]

Abdominal and pelvic radiation therapy may be part of therapy for management of Wilms' tumor, pelvic rhabdomyosarcoma, and Ewing sarcoma of the pelvis or spine. Young patients exposed to flank radiation (20 to 30 Gy) may have preservation of ovarian function. If women do conceive after this degree of abdominal radiation, there is a significant risk of preterm delivery, low-birth-weight infants, and infants that are small for gestational age compared to controls.[50] Other data suggest a particularly high risk of preterm delivery and low birth weight but no congenital malformations in women who conceive within 1 year after completion of irradiation implying uterine or hormonal defects as the cause of these abnormalities.[51]

Hormonal Therapy

Ablative hormonal therapy is often used in patients with androgen- or estrogen-sensitive tumors. The most common applications are prostate cancer and breast cancer.

Gonadotropin-Releasing Hormone Agonists and Antagonists

Leuprolide and goserelin are two potent GnRH analogs that are commercially available in the United States. These two analogs are much more potent in stimulating gonadotropin release than is GnRH. Initial treatment with GnRH agonists results in an LH and FSH surge with resultant gonadal steroid synthesis stimulation. However, after 10 to 14 days of continuous exposure to GnRH analogs, GnRH receptors on gonadotropin cells in the pituitary are downregulated, resulting in inhibition of LH/FSH release and gonadal suppression. Following prolonged GnRH analog therapy, testosterone and estrogen levels are suppressed to castrate levels. In males, this is usually associated with substantial loss of sexual desire

and marked decrease in frequency, magnitude, duration, and rigidity of nocturnal erections.[52] Treatment exceeding 2 years results in atrophic testes, which might not recover even if GnRH is discontinued.[53] In females, the use of GnRH in the adjuvant treatment of breast cancer is associated with an increased rate of sexual dysfunction, but the symptoms are usually reversible on discontinuation of therapy.[54]

Antiandrogens

Antiandrogens bind to and block the activity of androgen receptors. Androgen receptor blockage is associated with a rise in FSH/LH and a resultant rise in serum testosterone.[55] Antiandrogens, such as flutamide, bicalutamide, or nilutamide, are commonly used in the management of prostate cancer either with LHRH analogs or following LHRH agonist/antagonist failure. When combined with LHRH analogs, antiandrogens do not add to the incidence of gynecomastia (12% to 13%) or hot flashes (60% to 64%) and do not affect the incidence of impotence, which is universal in these patients.[56] High-dose bicalutamide has been evaluated as monotherapy in patients with advanced prostate cancer. While some studies suggest comparable clinical activity, there is significantly less impotence and loss of libido with antiandrogen monotherapy.[57] Recent reports, however, suggest that the ability to maintain potency while receiving antiandrogen monotherapy is limited. A study evaluating flutamide as monotherapy in 147 previously untreated prostate cancer patients resulted in 22% preservation of sexual activity and 20% preservation of morning erection at 2 to 6 years from start of therapy.[58] The median time to loss of morning erections and sexual activity was 12.9 and 13.7 months, respectively.[58]

Endocrine Therapy and Breast Cancer

Tamoxifen, a selective estrogen receptor modulator, is a commonly prescribed adjuvant hormonal therapy. Tamoxifen has estrogenic effects in bone and endometrium and antiestrogenic effects in breast tissue. This results in an antitumor effect while maintaining bone density. In premenopausal women, the hypothalamus perceives the antiestrogen effect as a state of estrogen deficiency, thus resulting in an increase in LH and FSH and hyperestrogenemia. In postmenopausal women, in whom FSH and LH are elevated and estrogen levels are depressed, tamoxifen reduces gonadotropin secretion.

Treatment with tamoxifen following primary therapy for breast cancer is associated with a high incidence of hot flashes (20% to 50%); less information is available on the incidence of sexual function.[59] Tamoxifen does not make a significant contribution to sexual dysfunction in women greater than age 50,[60] and in a randomized study that examined only premenopausal women, patients receiving tamoxifen alone did not report worse sexual function.[61]

Aromatase inhibitors are increasingly being used as the standard hormonal therapy for postmenopausal women with breast cancer and are successful in increasing distant and overall disease-free survival as well as preventing contralateral breast cancer compared with tamoxifen. Aromatase inhibition results in a marked decrease in estrogen synthesis, leading to minimal levels of circulating estrogen. Aromatase inhibitors such as anastrozole and letrozole are associated with a lower incidence of hot flashes and have been generally better tolerated than tamoxifen. In a recently published report of the quality-of-life measurements of postmenopausal women participating in the ATAC trial (anastrozole [Arimidex] or tamoxifen alone or in combination), patients reported diminished libido (34% versus 26%) and dyspareunia (17% versus 8%) significantly more frequently with anastrozole than with tamoxifen treatment.[62]

Chemotherapy

Effects in Men

Many anticancer drugs, particularly alkylating agents, are gonadotoxic. Though the ultimate assessment of germinal cell function is the attainment of fatherhood, multiple confounding factors exist that make this endpoint difficult to interpret. Therefore, most studies focus on semen analysis and biochemical markers of fertility for practical reasons.

Cyclophosphamide treatment frequently results in testicular dysfunction. In a series of 116 males treated with cyclophosphamide alone, 52 (45%) had evidence of testicular dysfunction.[63] The incidence of gonadal dysfunction increases with the total dose of cyclophosphamide, occurring in over 80% of postpubertal patients receiving more than 300 mg/kg.[64] Cisplatin disrupts spermatogenesis in a dose-dependent fashion. A threshold level of 600 mg/m^2 has been identified, above which significant impairment of spermatogenesis is seen.[65]

Combination chemotherapies containing alkylating agents are far more fertility-impairing than are nonalkylating combinations. The majority of men who are treated with mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) become severely oligospermic or azoospermic, and testicular biopsies confirm germinal aplasia.[5,66] Procarbazine has significant effects on testicular spermatogenesis, and its effects are often irreversible. Non-procarbazine-containing regimens such as cyclophosphamide, vincristine, and prednisone are usually associated with only transient FSH elevations and oligospermia.[67] Chapman and colleagues followed 64 patients with Hodgkin's lymphoma treated with mechlorethamine, vinblastine, procarbazine, and prednisone.[68] Only 4 out of 64 who were treated with the procarbazine-based regimen recovered spermatogenesis after a median follow-up of 51 months.[68] Comparison of the procarbazine-containing regimen MOPP to ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine, dacarbazine) in patients with Hodgkin's disease revealed a considerably higher azoospermia with MOPP (100%) than in ABVD (35%). Recovery of azoospermia rarely occurred with MOPP and occurred in the majority of patients receiving ABVD.[69] Dose-dependent infertility is clearly evident in Hodgkin's disease patients receiving combination chemotherapy. Azoospermia occurred considerably less often in patients receiving two cycles of MOPP compared to six cycles.[70]

Combination chemotherapy in testicular cancers is associated with FSH elevation and oligospermia. These findings are complicated further by the fact that the majority of testicular cancer patients have abnormal spermatogenesis prior to initiation of therapy. Cisplatin-based regimens are associated with suppression of spermatogenesis following completion of therapy. In 89 patients who were normospermic prior to chemotherapy, the postchemotherapy count was normospermic in 64%, oligospermic in 16%, and azoospermic in 20%. There was clear evidence for recovery beyond 1 year, and the probability of spermatogenesis increased to 48% at 2 years and 80% by 5 years.[71] Testicular cancer patients with pretreatment oligospermia or with persistent FSH elevation at 2 years from treatment are unlikely to recover normal spermatogenesis following treatment.

Effects in Women

Follicular growth and maturation are affected by chemotherapy. Histologic evaluation of ovaries among women who have been treated with cytotoxic chemotherapy show fibrosis and follicular destruction.[72,73] Premature ovarian failure is a common result of chemotherapy and is dependent on patient age, drug dose, and the duration and type of chemotherapy administered. Alkylating agents are strongly associated with ovarian dysfunction. Daily cyclophosphamide treatment for durations exceeding 1 year are associated with amenorrhea in females younger than 40 years of age.[74,75] Most series report a 50% or higher incidence of amenorrhea within 1 month of starting cyclophosphamide.[76] Younger females are more tolerant of the effects of chemotherapy and have a better chance of resuming menstruation after completing chemotherapy. In assessing the effects of adjuvant CMF (cyclophosphamide, fluorouracil, and methotrexate) on reproductive function in breast cancer patients, Mehta

and colleagues reported a median of 5.5, 2.3, and 1.1 months to onset of amenorrhea in patients younger then 35, 35 to 45, and older than 45 years, respectively.[77] In another study among patients 30 to 40 years of age, a mean dose of 9.3 g of cyclophosphamide was associated with amenorrhea, while patients older than 40 years required a median dose of 5.2 g.[78] A median of 20.4 g was required before the onset of amenorrhea in patients less then 30 years of age.[78] Menses resumed in 50% of those younger than 40 years, while it rarely occurred in females older than 40 years of age.[78] Treatment with the alkylating agent melphalan resulted in amenorrhea in 73% of patients between 40 and 49 years of age compared to 22% in patients younger then 40 years of age.[79] Similar results have been described with other alkylating agents, such as busulfan and chlorambucil. Younger women have a larger number of oocytes in reserve and thus a lesser likelihood of experiencing permanent ovarian damage after alkylating agent chemotherapy in comparison to older females. Other nonalkylating chemotherapies, such as antimetabolites, bleomycin, vinca alkaloids, and daunorubicin, are not a frequent cause of amenorrhea.

Combination chemotherapies have been evaluated more extensively as a cause of premature ovarian failure. Doxorubicin-based regimens in the adjuvant treatment of breast cancer resulted in a 96% frequency of amenorrhea in women 40 to 49 years of age compared to 0% among women 30 years or younger.[80] These regimens frequently incorporated other alkylating agents. Data collected from patients who were treated with MOPP for Hodgkin's disease similarly confirm the importance of age at the time of treatment.[81] Treating lymphoma patients with regimens that do not include procarbazine (e.g., ABVD) results in a lower incidence of premature menopause.[67,82] The importance of age and chemotherapy intensity has been stressed by a survey of 96 female patients who had been treated with combinations of ifosfamide, methotrexate, cisplatin, etoposide, and doxorubicin for localized osteosarcoma. The study evaluated the incidence of treatment-related amenorrhea and post-treatment fertility.[83] All 24 patients who were treated at a prepubertal age developed menarche at a median age of 13 years. After menarche, 16 had normal menses, and 8 had permanent irregular cycles.[83] Sixty-eight patients (11 to 43 years) were postpubertal on initiation of chemotherapy. Sixty-nine percent of these developed amenorrhea, typically after one cycle of therapy. A four-drug regimen was associated with amenorrhea in 89% of patients, while a three-drug regimen was associated with amenorrhea in only 53%. Amenorrhea was also related to age; 19 of 51 patients younger then 20 years maintained menses through chemotherapy versus only 2 of 17 in patients who were older then 20 at time of treatment. The majority regained menstruation on completion of chemotherapy. Among 22 patients who married after treatment, 20 patients became pregnant at a median age of 27 years. None of the pregnancies resulted in congenital anomalies.[83]

The duration of combination chemotherapy is also of paramount importance in induction of amenorrhea. Treatment of premenopausal women with a combination of cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone resulted in amenorrhea in 55% of patients who were treated for 12 weeks and in 83% of patients who were treated for 36 weeks.[84]

Effects in Children

EFFECTS OF CHEMOTHERAPY ON TESTICULAR FUNCTION IN BOYS. The prepubertal testes are more resistant to the effects of chemotherapy than are the adult testes. This relative resistance might be due to the nonproliferative status of the prepubertal germinal layer. Although it can take years, a certain degree of spermatogenesis recovery occurs in most boys who receive a total dose of cyclophosphamide of less then 10 g.[85] Gonadal function was assessed in 17 male survivors of childhood sarcomas who were treated with vincristine, actinomycin, and cyclophosphamide with or without doxorubicin.[86] Only two patients who received less than 7.5 g/m^2 of cyclophosphamide had normal semen analysis. All patients who received more than 7.5 g/m^2 had abnormal semen analysis, and all 5 out of 5 who received more than 25 g/m^2 had azoospermia more than 5 years after therapy.[86] Most patients (15 out of 16) maintained a normal testosterone level.[86] MOPP therapy leads to a considerably higher rate of testicular damage, presumably secondary to the added effect of procarbazine. Nine out of 19 prepubertal patients receiving MOPP or cyclophosphamide-based therapy (exceeding 9 g of cyclophosphamide) were sterile at a median of 9 years of follow-up.[87] Pubertal alkylating therapy might be more detrimental to gonadal function than in the prepubertal setting. In a cohort of 12 prepubertal and pubertal patients receiving MOPP therapy, all pubertal patients developed irreversible azoospermia, while two prepubertal patients were able to recover spermatogenesis. Pubertal treatment with MOPP was also associated with a high incidence of gynecomastia in association with low-normal testosterone levels and elevated LH and FSH.[88]

EFFECTS OF CHEMOTHERAPY ON OVARIAN FUNCTION IN GIRLS. The majority of prepubertal girls and adolescent females who receive standard combination chemotherapy will retain or recover ovarian function during the immediate post-treatment period. Prepubertal ovaries are relatively resistant to the effects of chemotherapy in comparison with postpubertal ovaries. However, histologic examination and ultrasound examination of the ovary following cancer therapy have revealed a decreased number of ovarian follicles compared to age-matched controls.[89] Menopause appears to be triggered when the number of ovarian follicles drops below a threshold, and a reduction in the population of follicles resulting from cancer therapy could result in premature menopause.[90]

Most prepubertal females who received MOPP therapy for Hodgkin's disease achieved normal puberty and were subsequently able to carry normal pregnancies.[91,92] Treatment of females with acute leukemia with a multidrug regimen of prednisone, vincristine, methotrexate, and 6-mercaptopurine with or without cyclophosphamide resulted in ovarian failure in only one of 17 prepubertal females.[93] Byrne and colleagues evaluated retrospectively fertility rates in childhood and adolescent cancer survivors.[94] In their comparison of 2283 survivors and 3270 siblings controls, there was no apparent effect of alkylating-agent therapy administered alone (relative fertility: 1.02), and only a moderate fertility deficit was evident when alkylating-agent therapy was combined with radiation below the diaphragm (relative fertility: 0.81) among women. The overall relative fertility in women was 0.93, which compared favorably to men's relative fertility of 0.76.[94] Childhood cancer therapy has also been associated with an increased risk of early menopause. In a large cohort of childhood cancer survivors, the principal risks for early menopause were treatment after the onset of puberty, treatment with radiotherapy below the diaphragm, and alkylating agents.[95] Survivors who were diagnosed after puberty and treated with radiation therapy below the diaphragm were 8.5 times more likely to reach menopause in their twenties. The average age for menopause in survivors who were treated with both an alkylating agent and radiation therapy below the diaphragm was 31 years.[95]

High-Dose Chemotherapy (Bone Marrow Transplantation)

Effects in Females

Gonadal dysfunction after high-dose chemotherapy is dependent on age, sex, type of conditioning regimen, and previous therapy. In women, increased age and treatment with an alkylating conditioning regimen including total body irradiation (TBI) result in a high rate of ovarian failure. In 144 women who were transplanted for leukemia after TBI and cyclophosphamide, amenorrhea was present for 3 years following transplantation in all women. Only nine patients eventually recovered their ovarian function.[96] The likelihood of recovering

ovarian function decreased by a factor of 0.8 per year of age.[96] TBI enhances the risk of ovarian failure. Ovarian failure usually occurs within 3 months of TBI. A single nonfractionated dose of 10 Gy is likely to result in more damage to the ovary and a lower chance of ovarian recovery than is a fractionated 12-Gy total dose.[96] Recovery of ovarian function is more likely with chemotherapy-only conditioning regimens but is usually limited to females younger than 30 years of age. In a conditioning regimen of cyclophosphamide of 200 mg/kg, all females 26 years of age or younger recovered their ovarian function, while only 5 out of 16 women over age 26 did so.[96] In another report on patients with non-Hodgkin's lymphoma, who were treated with consolidation high-dose chemotherapy (cyclophosphamide, carmustine, and etoposide), 9 out of 56 patients were able to conceive despite receiving a total dose of 10,800 mg/m^2 of cyclophosphamide.[97] Pregnancies were limited to females younger then 29 years of age; no birth defects were reported.[97] The addition of busulfan to cyclophosphamide is rarely associated with ovarian recovery, even in younger patients.[98]

Bone marrow transplantation may also be complicated by graft-versus-host disease. When severe, graft-versus-host disease can cause vaginal strictures and adhesions that interfere with intercourse.[99]

Effects in Males

The majority of males transplanted with or without TBI have marked elevations in their LH and FSH. Testosterone levels may be depressed but are usually maintained in the normal range, reflecting adequate compensatory reaction by Leydig cells to the rise in LH. Infertility is the rule in adults and young males receiving high-dose chemotherapy with or without TBI, reflecting the relative sensitivity of the germinal component to chemotherapy and/or radiation therapy relative to Leydig cells. Decreased libido has been reported in bone marrow transplantation patients. This is probably multifactorial and results from psychological stress, mild suppression of testosterone levels, and vascular and neurologic damage. Testosterone levels were found to be in the low normal range in a study of 24 males with features of hypogonadism and erectile dysfunction following transplantation.[100] While supplementation with testosterone resulted in an improvement in libido, there was no clear beneficial effect on erectile dysfunction.[100] Doppler studies in these patient confirmed evidence of cavernosal arterial insufficiency and strongly correlated with prior TBI therapy.[100,101]

Effects in Children

Permanent ovarian failure is less commonly seen in prepubertal females than in adults. A combination of high-dose chemotherapy and TBI is associated with a higher incidence of ovarian failure than chemotherapy alone. Sarafoglou and colleagues reported a median age of 8.6 years for prepubertal females with acute leukemia treated with bone marrow transplantation (TBI-based regimen) who developed ovarian failure.[102] The median age for prepubertal females who went on to enter puberty was 6.1 years.[102] Even in those who enter puberty, normal uterine maturation is impaired, and the endometrium is atrophic secondary to radiation therapy. Supplementation with hormone replacement improves mucosal thickness, but the total volume of the uterus remains contracted.[103] Long-term follow-up of childhood acute leukemia survivors reveals that TBI is indeed the most important factor in development of gonadal failure. In 77 survivors of leukemia, three groups of treatment were identified: chemotherapy, chemotherapy and cranial irradiation, and chemotherapy and TBI.[104] Forty-four out of 44 patients who were treated with chemotherapy entered and progressed through puberty without sex hormone supplementation. Only one of 18 of patients who were treated with chemotherapy and cranial irradiation developed early amenorrhea accompanied with elevated gonadotropin levels. Eight of 15 patients who were treated with chemotherapy and TBI developed gonadal failure (3 men and 5 women), requiring long-term sex hormone supplementation.[104]

CHEMOTHERAPY AND RADIATION DURING PREGNANCY

Cancer complicates 1 in 1000 pregnancies.[105] The most frequent cancers during pregnancy are cervical cancer, breast cancer, melanoma, ovarian cancer, thyroid cancer, and leukemia.[106] As more women defer childbearing into their thirties and beyond, more cancers are expected to be diagnosed during pregnancy. Chemotherapy has an essential role in the management of many of these tumors. The timing and selection of chemotherapeutic agents should be optimized to maximize the clinical benefit to the patient while minimizing the risk to the fetus (Box 64-1).

Fetal Stage of Development and Pregnancy Outcome

The most important factor influencing fetal outcome in cancer patients who are treated during pregnancy is the stage of fetal development on initiation of treatment. The first trimester is the most susceptible period. The blastocyst is relatively resistant to teratogens for the first 2 weeks because it lacks an established circulation. Following implantation but prior to organogenesis, the blastocyst may exhibit damage from chemotherapy resulting in abortion or may survive without manifesting any abnormalities. Organogenesis begins in the fifth gestational week and continues until the eighth week. During organogenesis, the stem cell population is limited, and damage from chemotherapy may result in major defects. Exposure to chemotherapy during the first trimester may result in a malformation rate of 10% to 20% compared to an estimated rate of 3% in the general population.[107] By the thirteenth week of gestation, all organs have developed, with the exception of the brain and gonads.[108] Exposure to chemotherapy on completion of organogenesis (second and third trimesters) is thus unlikely to result in major birth defects but may result in fetal growth retardation. Treatment of patients with hematologic malignancies and breast cancer during the second and third trimesters has not been associated with any increase in the rate of congenital anomalies.[109–111]

Effects of Different Classes of Chemotherapy on Pregnancy Outcome

Different classes have varying teratogenic potential. Alkylating agents and antimetabolites appear to have a greater potential of causing a

Box 64-1. CHEMOTHERAPY AND RADIATION DURING PREGNANCY

The risk of congenital anomalies is highest for first-trimester exposure and is most commonly associated with antimetabolites such as methotrexate. Decision making should be individualized, and decisions regarding termination or continuation of pregnancy should take into consideration the risks to the mother and the fetus. In first-trimester pregnancies that require initiation of chemotherapy, termination of pregnancy should be considered. In patients who elect to proceed with pregnancy, the choice of chemotherapy should take into account the risks of congenital malformations. Treatment of patients with hematologic malignancies and breast cancer during the second and third trimesters has not been associated with an increased rate of congenital anomalies. A delay in chemotherapy for a few weeks or until delivery for third-trimester pregnancies can be considered if the mother's outcome is unlikely to be compromised. Delivery induction for gestations of more then 32 weeks is another acceptable option for third-trimester pregnancies.

Radiation therapy should be avoided at all stages of pregnancy. First- and second-trimester exposures are associated with congenital abnormalities, and third-trimester exposure can result in cognitive dysfunction.

detrimental effect than do antitumor antibiotics, platinum analogs, and vinca alkaloids.[112]

Alkylating Agents

Fetal abnormalities have been reported from first-trimester exposure to cyclophosphamide, chlorambucil, and busulfan.[113–117] No definite causal relationship is available with other agents, such as thiotepa, melphalan, and dacarbazine, but exposure data in the first trimester for these compounds are limited.

Antibiotic Agents

No definite causal relationship with congenital malformations has been documented with dactinomycin or bleomycin. There have been reports of normal children born to patients exposed during the first, second, and third trimesters.

Antimetabolites

Methotrexate is known for its teratogenic effects and has been used as an abortifacient. Congenital anomalies have been described with first-trimester use. Malformations include severe skull abnormalities, heart defects such as dextroposition, and digital anomalies.[118,119] Exposure starting as late as 11 weeks has been associated with anomalies.[119] 5-Fluorouracil may be similarly associated with congenital anomalies when administered in the first trimester. One case of multiple congenital anomalies including radial dysplasia, absent digits, and hypoplasia of multiple organs has been reported in a first-trimester exposure.[120] Cytarabine has been commonly used in second- and third-trimester pregnancies in hematologic malignancies without a reported increase in congenital defects. First-trimester exposure has been associated with congenital abnormalities, including microtis and auditory canal atresia, lobster claw hand and other digital anomalies, and lower-extremity defects.[121,122] Other studies have reported normal pregnancy outcome in first-trimester exposures.[123] There is currently no information on pregnancy outcomes in patients who have been treated with the newer antimetabolite gemcitabine.

Anthracyclines

First-trimester exposures have been associated with normal and abnormal fetal outcomes. Imperforate anus, rectovaginal fistula, and microcephaly have been described following first-trimester exposure to doxorubicin.[124]

Vinca Alkaloids

Definite fetal anomalies secondary to vinca alkaloids have not been reported. Sporadic anomalies have been reported in patients receiving combination therapy. Several pregnancies with exposure to vinca alkaloids during the first trimester of pregnancy have resulted in normal neonates.[107,125]

Platinum Analogs

Ten pregnant women with cancer have been reported who received cisplatin during the second or third trimester.[126] None of the neonates demonstrated any congenital anomalies, but fetal growth was restricted in 50% of pregnancies.

Taxanes

Limited information is available on the clinical effects of taxanes on pregnancy. There has been one report of an ovarian cancer patient treated during the third trimester of pregnancy with carboplatin and paclitaxel without any adverse events in the newborn.[127] Treatment of a case of metastatic breast cancer with docetaxel during the second and third trimesters of pregnancy resulted in a normal healthy newborn.[128]

Topoisomerase II Inhibitors

Etoposide has not been reported to cause congenital malformations. However, fetal marrow suppression manifesting as severe neonatal anemia and leukopenia has been reported in a patient treated for leukemia.[129]

In general, chemotherapy has not been associated with an increased risk of congenital malformations if administered in the second or third trimesters, but an increased incidence of growth restriction and premature birth has been noted. An increased risk of congenital anomalies has been associated with treatment in the first trimester. Doll and colleagues reported a 15% incidence of fetal malformations in association with first-trimester chemotherapy exposure versus 1.3% for second- and third-trimester exposures.[130] This risk is apparently highest for antimetabolites, especially methotrexate. If cancer occurs in the first trimester and systemic cytotoxic therapy is clearly indicated, termination of the pregnancy should be considered. Delay in chemotherapy until it can be given more safely in the second and third trimesters should be considered if the outcome for the mother is not at risk. The long-term effects on progeny have not been adequately evaluated for different chemotherapeutic agents. Anecdotal data suggest that most offspring who are exposed in utero exhibit normal physical and mental development. Eighty-four children who were born to patients with hematologic malignancies and were exposed to chemotherapeutic agents in utero were followed for a median of 18.7 years.[131] In all the children who were studied, the learning and educational performances were normal, and no congenital, neurologic, or psychological abnormalities were observed. There was no apparent increase in malignancies. Some of these individuals became parents during the period of follow-up. Twelve second-generation offspring were evaluated, and all of them were normal.[131]

Targeted Therapy

Several newer agents have been developed to target specific growth receptor, antigens, or kinases that are essential for cell growth and development. Two commercially available agents are the anti-Her2/neu antibody trastuzumab and the anti-CD-20 antibody rituximab. Reproductive data in monkeys using 25 times the human equivalent of trastuzumab did not show any evidence of teratogenicity. However, trastuzumab diffuses through the placental circulation, and acute or long-term effects on human progeny have not been evaluated. Rituximab has not been evaluated extensively in reproductive animal models. A 29-year-old patient with diffuse large cell lymphoma was treated during her second and third weeks of pregnancy with a combination of rituximab and CHOP therapy.[132] She delivered a healthy female newborn at 36 weeks.

Imatinib is now a standard therapy for patients with chronic myeloid leukemia. A series of 19 pregnancies involving 18 patients (10 females and 8 males) who conceived while receiving imatinib for the treatment of chronic myeloid leukemia was recently reported. All female patients discontinued therapy immediately on recognition of pregnancy. There were three spontaneous abortions, including two of the ten pregnancies in female patients. In addition, two (13%) of the 16 babies who were born from these parents had congenital abnormalities (one baby with hypospadias, one with mild rotation of the small intestine). Given the constraints of the small series, this could represent a higher-than-expected frequency of congenital abnormalities. At present, the recommendation is for patients on imatinib to practice effective barrier forms of birth control and to discontinue imatinib if pregnant or lactating.[133]

Immunomodulators

Limited data are available on the effects of interferons and interleukins on pregnancy. In animals, interferon-α and interleukin-2 have abortifacient and embryolethal effects. More than 20 case reports of pregnancy during interferon-α treatment in all three trimesters have been reported.[134–136] None of the cases were associated with congenital anomalies, but growth retardation and premature births were more frequent than expected.[136]

Effects of Radiation Therapy on Pregnancy Outcome

Human data regarding the effects of radiation on fetal outcome is limited to accidental exposure and to nuclear disaster victims. Similar to chemotherapy, the effects seem to be most pronounced during the period of organogenesis. During the period of 8 to 25 weeks of pregnancy, the central nervous system is particularly sensitive to the effects of radiation. The most comprehensive review of clinical effects of pelvic radiation therapy was reported by Dekaban.[137] Pelvic irradiation up to 3 weeks following conception did not result in severe congenital anomalies, although a considerable number of embryos may have been resorbed or aborted.[137] Irradiation between weeks 4 and 11 led to the development of severe congenital anomalies in many organs. Exposure between weeks 11 and 16 led to anomalies of the eye, skeleton, and genital organs; stunted growth; microcephaly; and mental retardation.[137] Exposure between 16 to 20 weeks was associated with mild microcephaly, mental retardation, and stunted growth. Later exposures were unlikely to cause structural abnormalities.[137]

Data from survivors of the atomic bombs in Hiroshima and Nagasaki suggest a dose-dependent effect of radiation on congenital anomalies, a dose of 50 cGy resulting in a 40% risk of microcephaly. Doses in excess of 10 cGy may result in cognitive impairment, and higher exposures result in further exacerbation of mental retardation. In utero radiation exposure also results in an increased risk of carcinogenesis with an estimated 6% risk of cancer by age 15 per Gy of exposure.[138]

Radiation therapy should be avoided during pregnancy because of the significant physical, functional, and mental dysfunction that can result from exposure in the first and second trimesters. Even in cases such as breast cancer, in which breast irradiation is given with abdominal shielding, the estimated fetal exposure with 5000 cGy to the primary tumor is 14 to 18 cGy. This is well above the proposed threshold for microcephaly and mental retardation.[139]

PREVENTION

Modifying the treatment and its timing as discussed previously may reduce reproductive complications, but care must be taken not to compromise treatment efficacy, and detailed discussions with patients are mandatory (Box 64-2).

Retroperitoneal nerve-sparing dissections result in significant improvements in potency rates after radical prostatectomy. Similar results are reported in rectal surgeries with nerve-sparing dissection. Alternative chemotherapeutic regimens with low gonadal toxicity potential should be considered when possible. The substitution of ABVD therapy has resulted in similar or better efficacy in the treatment of Hodgkin's lymphoma and a lower rate of ovarian and testicular failure.

Unfortunately, most cancer diagnoses have limited options of treatment, and the choice of a regimen with a low potential for gonadal toxicity is often not feasible. Spermatogenesis and follicular growth and maturation are particularly sensitive to the effects of chemotherapy because of their high mitotic rate. Thus, treatment interventions that suppress germinal function during administration of cytotoxic therapy may limit the gonadal toxicity. GnRH analogs have been shown to inhibit spermatogenesis in various animals and in humans. The use of GnRH analogs has been reported to protect rat testes from chemotherapy and radiation.[140,141] However, treatment of testicular cancer and Hodgkin's disease patients with LHRH analogs has failed to show any protective effects against the development of azoospermia.[142–144] Effective inhibition of spermatogenesis may require several weeks of hormonal manipulation with GnRH analogs. Treatment with GnRH analogs for several weeks prior to initiation of chemotherapy is often not feasible clinically and may account for the failure of previous studies to show a protective effect on gonadal function.

Box 64-2. PREVENTION AND TREATMENT OF SEXUAL AND REPRODUCTIVE DYSFUNCTION OF CANCER THERAPY

Prevention

The best prevention is the selection of equally effective treatments but with lower toxicities. Treatment of Hodgkin's disease with ABVD rather than MOPP will often result in fertility preservation. Bone marrow-conditioning regimens that do not incorporate total body radiation should be considered in bone marrow transplant patients. Ovarian and testicular suppression with GnRH analogs has not been shown conclusively to protect gonadal function and should be limited to clinical studies.

All males who are contemplating future fatherhood and for whom either chemotherapy that has been associated with infertility (such as alkylating agents) or pelvic radiation is planned should be offered sperm banking. Oocyte banking and ovarian cryopreservation continue to be investigated in females and have not yet been standardized. In vitro fertilization with embryo cryopreservation may represent another alternative for females who are undergoing gonadal-toxic treatments.

Treatment

Treatment involves hormonal replacement for patients with premature ovarian failure and low testosterone levels. Estrogen replacement ameliorates menopausal symptoms, including hot flashes, vaginal dryness, and dyspareunia. Vaginal-directed estrogen therapy can improve local vaginal symptoms in patients with relative contraindications to systemic estrogen replacement. For patients with a history of breast cancer, nonhormonal vaginal moisturizers and lubricants remain the first line of therapy.

Testosterone replacement in men improves the libido and reduces hot flashes and can improve potency in severe androgen deficiency cases. Impotence secondary to surgery or radiation therapy may be successfully treated with sildenafil. This agent should be avoided in patients with significant cardiovascular illness and is contraindicated in patients who are receiving nitrates. Sildenafil therapy should be considered as a first-line pharmacologic therapy in impotent patients with normal testosterone levels and in whom psychosocial etiologies are not suspected.

Assisted reproductive technologies such as intrauterine insemination, in vitro fertilization, and ICSI should be considered as options for restoring fertility in couples who have difficulty conceiving after cancer therapy.

Similar attempts to protect the ovaries from cytotoxic chemotherapy by suppressing cycling through GnRH analogs and oral contraceptives have been made. A small study of patients with Hodgkin's disease receiving alkylating agent-based chemotherapy and oral contraceptives showed that five of six patients resumed normal menstrual function at 26 months.[145] Other studies of oral contraceptives and GnRH analogs failed to show any protective effects in patients with Hodgkin's disease in comparison with controls.[143,146] However, one prospective study in patients with lymphoma showed a significant protection against ovarian failure with cotreatment with GnRH analogs.[147] Eighteen patients with lymphoma were treated with a monthly injection of depot GnRH agonist starting prior to chemotherapy and continuing for a maximum of 6 months. Most of these patients (15 of 18) were treated with the MOPP/ABVD combination chemotherapy followed by mantle field irradiation in 10 patients. This group of prospectively treated lymphoma patients was compared to a matched control group of 18 women. Only 39% of the patients receiving chemotherapy alone resumed spontaneous ovulation in

comparison with 94% of those receiving GnRH analogs along with chemotherapy.[147,148]

Other means of protection from radiation effects include gonadal shielding. In females receiving pelvic radiation, transposition of the ovaries might be one alternative to avoid radiation damage. Transposition of one or two ovaries can be done at the time of laparotomy or laparoscopically. Spontaneous pregnancy rates after ovarian transposition are low, presumably because of the distorted tubo-ovarian anatomy secondary to the procedure itself or the local therapy (radiation) to the pelvic area.[149]

TREATMENT

Treatment of reproductive complications aims at relieving the symptoms related to gonadal failure and providing assistance in achieving reproduction. This section focuses on hormone replacement, treatment measures for impotence, and reproductive assistance technologies.

Hormonal Replacement

Premature ovarian failure results in the sudden onset of menopausal symptoms secondary to an abrupt decrease in estrogen levels. Sexual symptoms related to ovarian failure include vaginal atrophy, thinning of vulvar tissue and the vagina, decreased vaginal lubrication and elasticity, mood swings and irritability, and hot flashes. Estrogen replacement therapy (in combination with progesterone in patients without hysterectomy) can reverse most of these symptoms and should be discussed with all patients with iatrogenic ovarian failure. Risks, including increased rate of cardiovascular and cerebral accidents, and benefits such as osteoporosis prevention should be addressed prior to initiation of therapy.[150] Hormonal replacement therapy in breast cancer patients continues to be an area of concern because of the theoretical potential of promoting tumor growth. However, no reports have yet shown a detrimental effect of estrogen replacement in this cancer population. Patients who are not candidates can be treated symptomatically with vaginal moisturizers (e.g., Replens) and water-based lubricants (e.g., K-Y liquid). Vaginal-directed estrogen therapy with an Estring vaginal ring, estrogen creams, or Vagifem tablets have also resulted in improvements in symptoms of vaginal dryness and dyspareunia and a decrease in the incidence of urinary tract infections.

Male hypogonadism secondary to chemotherapy and radiation therapy is associated with loss of libido, hot flashes, and impotence. Testosterone replacement as a depot injection or in a transdermal formulation may restore sexual function in those instances.[151,152]

Management of Erectile Dysfunction

The advent of sildenafil citrate (Viagra) marks an important milestone in the treatment of male impotence. The physiologic mechanism of penile erection involves the release of nitrous oxide in the corpus cavernosum during sexual stimulation. Nitrous oxide results in an increase in cyclic guanosine monophosphate, which in turn results in corpus cavernosum smooth muscle relaxation and allows an increase in blood flow. Sildenafil improves the ability to achieve and maintain an erection by blocking the degradation of cyclic guanosine monophosphate.

Sildenafil leads to successful intercourse in prostate cancer patients with erectile dysfunction after prostatectomy, external beam radiation, or brachytherapy. Response rates typically range between 70% and 80%.[153–156] The ease of oral administration and the efficacy of this agent have made it the most commonly prescribed agent for erectile dysfunction.[157] Because sildenafil potentiates the hypotensive effects of nitrates, prescribers should ensure that patients taking sildenafil do not have any significant cardiac history and are not receiving any concomitant nitrate medications. Alternative therapies include penile injections, vacuum devices, or intraurethral suppositories. These are more cumbersome to the patient and are associated with high dropout rates.[158] In refractory situations, surgical intervention with penile implants may be considered.

Assisted Reproductive Technologies

Once germinal testicular aplasia or premature ovarian failure occurs secondary to cancer therapy, the damage might be irreversible. Unless sperm or embryonic banking is performed prior to treatment, these patients will not be able to parent their own biological children. This issue has not been given adequate attention, and its importance to patients has long been overlooked. A survey of 904 men diagnosed with cancer revealed that 51% of men wanted children in the future.[159] Only 60% of men recalled being informed about infertility, and only 51% had been offered sperm banking.[159] Lack of prior discussion about sperm banking with patients was the most common reason for failing to bank sperm.[159]

Several advances in reproductive technologies allow for fertility preservation in patients who are undergoing gonadal toxic therapies. Intrauterine insemination is accomplished by selecting washed sperm with high motility and injecting them directly into the uterus at the time of ovulation. This procedure requires cryopreservation of 5 to 10 million normal sperm. In vitro fertilization with embryo transfer involves culturing the aspirated oocytes and spermatozoa in vitro, followed by the transcervical replacement of the embryo into the uterine cavity. With in vitro fertilization with embryo transfer, the number of sperm required is 0.5 to 1 million.[160] Intracytoplasmic sperm injection (ICSI) involves the injection of a single sperm into the cytoplasm of the oocyte with transcervical placement of the embryo into the uterine cavity. ICSI reduces the criteria for sperm cryopreservation theoretically to the presence of one motile sperm. This makes almost any male cancer patient who is not completely azoospermic a candidate for sperm cryopreservation. Even in patients with complete ejaculatory azoospermia, testicular sperm extraction followed by ICSI and embryo cryopreservation might represent an option for fertility preservation.[161,162] Testicular sperm extraction is typically achieved by obtaining open biopsies of testicular tissues with or without microdissection.[163] ICSI is now performed in 60% to 80% of assisted reproductive procedures in some metropolitan U.S. areas and is the procedure of choice for couples with a male infertility factor. In patients for whom sperm is stored or extracted successfully, successful pregnancy rates in the range of 30% are expected.[162,164] Transrectal electroejaculation is yet another viable method for sperm collection for the purpose of cryopreservation or in vitro fertilization in patients with retrograde ejaculation.[165] Other options of sperm collection in patients with retrograde ejaculation are insemination by using sperm-rich urine (after masturbation) or bladder washings. Successful reports of insemination by using these collection methods have been reported, using techniques ranging from intrauterine insemination to ICSI.[166]

Oocyte cryopreservation has been associated with few pregnancies. Low pregnancy yield as well as the need to delay chemotherapy to achieve appropriate follicular stimulation limits the use of this technique for female fertility preservation. Ovarian tissue cryopreservation is a novel technique that is under investigation. The procedure involves oophorectomy and cryopreservation prior to the initiation of cancer treatments. On completion of cancer-directed therapy and when conception is planned, the frozen banked ovarian tissue is thawed and autotransplanted in the patient. Successful ovulation after autotransplantation has been reported, and the procedure continues to be under investigation.[167] Another option for fertility preservation involves in vitro fertilization and embryo cryopreservation prior to initiation of treatment. The technique is cumbersome and expensive, can delay the initiation of effective chemotherapy, and constitutes an ethical dilemma.

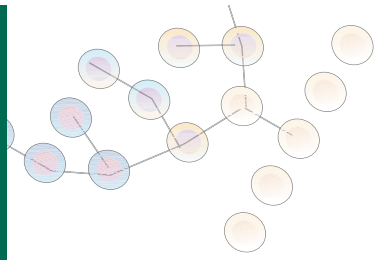
For patients who are unable to conceive secondary to uterine or cervical abnormalities attributed to the cancer or its treatment, in vitro fertilization with implantation in a surrogate has been described.[168]

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65 Endocrine Complications

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SUMMARY OF KEY POINTS

Introduction

- Endocrine dysfunction may directly result from cancer or as a consequence of cancer therapy (surgery, radiation, chemotherapy, biologic agents, and hormone therapy). Endocrine dysfunction may be an intentional consequence or an adverse effect of antineoplastic therapy.
- Hypopituitarism with clinically significant deficiencies of growth hormone, thyrotropin, gonadotropin, and corticotrophin may result from radiation (cranial or total body irradiation), surgery, or chemotherapy.
- Thyroid dysfunction from neck irradiation, immune therapy (interleukin-2), and small molecule inhibitors such as sunitinib may result in either hyperthyroidism or hypothyroidism.
- Gonadal dysfunction following surgery, radiotherapy, or chemotherapy results in disruption of puberty, infertility, and premature menopause.
- Adrenal dysfunction from chemotherapy (ketoconazole, aminoglutethimide) may result in glucocorticoid or mineralocorticoid deficiency.
- Pancreatitis and occasionally pancreatic exocrine or endocrine deficiencies may result from chemotherapy (L-asparaginase and streptozotocin).

Diagnostic Considerations

- A detailed history along with a complete physical examination is the key to the diagnosis. Locations of primary as well as metastatic tumor along with past and current therapies are necessary elements of evaluation.
- Signs and symptoms such as delayed or precocious puberty, fatigue, weight loss or gain, amenorrhea, orthostatic hypotension, hyperpigmentation, or electrolyte abnormalities should prompt consideration of unrecognized endocrine dysfunction.
- When one hormonal deficiency is identified, others should be sought.

Evaluation and Treatment

Hypothalamic-Pituitary Axis

- Basal serum hormone concentrations are usually sufficient; however, dynamic testing might be required to diagnose partial deficiencies.
- Patients often have multiple, concurrent hormone deficiencies. Replacement therapy should be started as soon as possible.

Thyroid

- Primary hypothyroidism is characterized by low free thyroxine (T4) level and elevated thyroid-stimulating hormone (TSH), while central hypothyroidism is associated with low free T4 and inappropriately normal or low TSH levels. Replacement with levothyroxine is indicated and highly effective.
- Hyperthyroidism is caused by increased T4 and/or T3 (tri-iodothyronine) levels with a low serum TSH level. Treatment options include surgery, radioiodine ablation or antithyroid medications (propylthiouracil). Rarely, hyperthyroidism may be associated with production of TSH-like substances by germ cell or choriocarcinoma. Management in these instances involves thyroid suppression and treatment of the primary tumor.

Adrenal

- Low- or high-dose corticotrophin test can distinguish between central and primary causes of adrenal insufficiency. Acute adrenal insufficiency is a medical emergency and should be treated by immediate parenteral glucocorticoid replacement and supportive care. Chronic insufficiency is treated by oral glucocorticoid supplement with or without mineralocorticoid.

Syndrome of Inappropriate Antidiuretic Hormone Secretion

- Hyponatremia is classically associated with cyclophosphamide and vinca alkaloids. Measurement of serum and urine osmolality, renal function tests, and assessment of volume status of a patient are the key to diagnosis. Treatment involves fluid restriction and increased salt intake. Refractory cases might need loop diuretics, doxycycline, or newer vasopressin receptor blockers.

INTRODUCTION

Endocrine dysfunction is an increasing cause of morbidity in cancer patients. Improved cancer therapies and new agents with endocrine side effects are primarily responsible for the increase. For example, the Childhood Cancer Survivor Study showed that one or more endocrine conditions were reported in 43% of childhood brain tumor survivors.[1] Timely recognition and management of endocrine dysfunction are essential to prevent further morbidity and impairment of quality of life in cancer patients. Table 65-1 outlines the causes of endocrine dysfunction in this population. Appropriate evaluation and treatment of common endocrinopathies are discussed in the latter sections of this chapter. A special section is included on surveillance of childhood cancer survivors for detection of late endocrine

Table 65-1 Causes of Endocrine Dysfunction in Patients with Cancer

- Direct product of hyperplastic/neoplastic endocrine tissue
- Iatrogenic
  - Postsurgical
  - Postradiation
  - Postchemotherapy
  - Postbiologic agents
  - Intentional hormone ablation therapy (e.g., for breast and prostate cancer)

Table 65-2 Risk Factors Associated with Increased Incidence of Radiation-Induced Endocrine Dysfunction

Radiation dose >30 Gy
Total body irradiation
Cranial irradiation
Age (children more sensitive)
Prior pituitary compromise by tumor/surgery
Length of follow-up

complications of various cancer therapies. Tumors of endocrine origin and neuroendocrine tumors are discussed in relevant sections of this textbook.

ROLE OF SURGICAL THERAPY

Historically, surgery has been used as a means of disrupting normal endocrine function with therapeutic intent.[2] Response rates of 15% to 30% were reported after hypophysectomy or adrenalectomy in advanced breast cancer.[3,4] However, these procedures resulted in significant morbidity, including hypoadrenalism and hypopituitarism, requiring lifelong replacement therapy. For premenopausal women, ovarian ablation by surgical oophorectomy remains a therapeutic option in metastatic and adjuvant settings. These surgical procedures have been largely supplanted by pharmacologic agents such as luteinizing hormone-releasing hormone agonists along with aromatase inhibitors (inhibit adrenal steroidogenesis) to attain functional castration.[5,6] Orchiectomy is considered a therapeutic option for men with metastatic prostate cancer.[7]

Normal pituitary function may be altered by surgical resection of a pituitary tumor or by injury to the pituitary stalk disrupting the hypothalamic-pituitary axis. In the former case, anterior pituitary hormones are primarily affected; in the latter case, both the anterior and posterior pituitary hormones are affected.

Similarly, resection of a tumor involving other endocrine glands may result in deficiencies of hormones secreted from these glands: thyroid (hypothyroidism), parathyroids (hypoparathyroidism), pancreas (diabetes mellitus), ovaries (hypogonadism), testes (hypogonadism), or adrenals (hypoadrenalism). Unilateral gland resection rarely results in noticeable hormone deficiencies. Extensive neck surgery and irradiation for advanced head and neck cancers may result in parathyroid hormone deficiency. This might be due to interference with the vascular supply of the parathyroids. Permanent hypoparathyroidism can result inadvertently from total thyroidectomy; the reported incidence is up to 40%.[8] Subtotal removal of parathyroid glands as a part of therapy for parathyroid hyperplasia can also cause hypoparathyroidism. It is often possible to preserve parathyroid function by careful surgical technique and/or by autotransplanting the parathyroid tissue to another part of body.

ROLE OF RADIATION THERAPY

Endocrine organs may be intentionally or unavoidably exposed to ionizing radiation during treatment for malignancy, and high-dose radiation may result in endocrine dysfunction. Table 65-2 lists factors that are known to be associated with a high risk of endocrine dysfunction following radiation. Assessment of late effects of radiation may be difficult and subjective. Various groups have attempted to develop a scoring system to standardize toxicity reporting and description. An example is the LENT-SOMA (Late Effects on Normal Tissue–Subjective, Objective, Management and Analytic) to grade radiation-induced toxicity to the hypothalamic-pituitary axis and thyroid.[9] These scales grade the radiation-induced side effects on these organs exposed to irradiation in a manner similar to common toxicity criteria grading of adverse effects. Newer scales have been designed by the European Organization Treatment of Cancer and Radiation Therapy Oncology Group to grade toxicities related to radiation.[10] The late toxicity assessment of a treatment might depend on the toxicity scale used. The LENT-SOMA scale seems to be the most accurate scale so far.[11,12]

Hypothalamic-Pituitary Axis

Anterior pituitary dysfunction can result from irradiation of nasopharyngeal, extracranial, or primary brain tumors, especially those involving the pituitary. Total body irradiation as part of a bone marrow transplant preparative regimen[13] and prophylactic cranial radiation in patients with acute lymphoblastic leukemia can also cause hypopituitarism.[14] Approximately 19% of patients have a deficiency in one or more anterior pituitary hormones as early as 2 years after cranial irradiation for nasopharyngeal carcinoma.[15]

Data indicate that the hypothalamus is more radiosensitive and is damaged by lower doses of cranial radiation than is the pituitary.[16] Secondary pituitary atrophy evolves with time owing to impaired secretion of hypothalamic regulatory factors or direct radiation-induced damage. This necessitates prolonged follow-up and yearly testing of pituitary function in patients who have received cranial irradiation. The frequency, rapidity of onset, and severity of endocrine abnormalities correlate with the total radiation dose delivered to the hypothalamic-pituitary axis, the fraction size, younger age at irradiation, prior pituitary compromise by tumor and/or surgery, and the length of follow-up.[17]

Somatotrophes (cells that secrete growth hormone) are the most vulnerable to radiation damage; hence, growth hormone deficiency (GHD) is the most commonly seen endocrine dysfunction, following cranial irradiation. GHD may occur in isolation following irradiation of the hypothalamic-pituitary axis with doses less than 30 Gy. The clinical manifestations of GHD are most evident in the growing child: reduction in growth velocity and short stature. Some data suggest that children are more sensitive to radiation effects than are adults.[18] Although poor linear growth is very common in children with GHD, it is not universal or immediately apparent. Several studies suggest that the slowing of growth might not occur for the first year or two after onset of GHD. In postpubertal individuals, GHD is associated with a decrease in muscle mass along with an increase in adiposity.[19]

The hypothalamic neurons secrete gonadotropin-releasing hormone (GnRH) in pulses that are necessary for normal secretion of gonadotropins from the pituitary. This GnRH-pulse generation is affected differentially by the dose of radiation that is received. Abnormalities in gonadotrophin secretion are dose-dependent. Precocious puberty can occur after a radiation dose less than 30 Gy in girls and in both sexes equally with a radiation dose of 30 to 50 Gy.[20,21]

Radiation-induced precocious puberty might be caused by damage to inhibitory GABAergic neurons, leading to disinhibition and premature activation of GnRH neurons.[22] Higher-dose irradiation (>30 Gy) is associated with delayed sexual maturation due to gonadotropin deficiency from damage to GnRH secretory neurons.[23]

Deficiency in other pituitary hormones is less common. Five years after treatment, a study of 251 patients who had been treated for pituitary disease with external radiotherapy described an incidence of thyroid-stimulating hormone (TSH) deficiency of 9% at 20 Gy, increasing to 52% at 42 to 45 Gy.[24] A similar trend for incidence of adrenocorticotrophic hormone (ACTH) deficiency relation was seen. Hyperprolactinemia can be seen after high-dose radiotherapy (>40 Gy) and has been described in both sexes and all age groups but is most common in young women.[25] Constine and associates[26] described a 50% frequency of hyperprolactinemia in 32 patients who were treated with radiation for brain tumor with doses ranging from 39.6 to 70.2 Gy. Other investigators reported rates of 20% after treatment for nasopharyngeal carcinoma. Hyperprolactinemia can cause pubertal delay or arrest in children, galactorrhea and/or amenorrhea in women, and decreased libido and impotence in adult males.

Radiation-induced anterior pituitary hormone deficiencies are irreversible and progressive but are treatable with appropriate hormone replacement therapy. Careful surveillance and close follow-up with an endocrinologist are warranted.

Thyroid

Irradiation of the thyroid may produce hypothyroidism, Graves disease, silent thyroiditis, benign nodules, and thyroid cancers.[27] Hancock and colleagues described their experience with thyroid disease among patients treated with irradiation with or without chemotherapy for Hodgkin's disease at Stanford University.[28] Of 1787 patients, 1677 received irradiation to the thyroid. At 26 years of follow-up, the actuarial risk of thyroid disease was 67%. Hypothyroidism developed in the majority of the patients (47%). The risk of Graves disease was 7 to 20 times higher than that for normal subjects. The risk of thyroid cancer was noted to be 15.6 times the expected risk for normal subjects. The association between thyroid cancer and radiation is discussed in further detail in Chapter 75. These data remind clinicians to follow thyroid function closely in patients who have been treated with upper mantle or cervical irradiation. Similar results were noted in the Childhood Cancer Survivor Study with an evaluable cohort of 1791 (959 males) Hodgkin's disease survivors. Among patients with Hodgkin's disease, the risk of hypothyroidism at 20 years from the time of diagnosis in those treated with 45 Gy or more was 50%.[29] Total dose of irradiation received has been shown to correlate with the incidence of hypothyroidism in many studies.[27–30] There is controversy regarding the effect of age at the time of irradiation, gender, and association with the prior use of lymphangiograms.[27,29]

Radiation-induced thyroid dysfunction is thought to be caused by damage to small thyroid vessels and to the glandular capsule. Focal and irregular follicular hyperplasia, hyalinization, and fibrosis beneath the vascular endothelium, lymphocytic infiltration, single and multiple adenomas, and thyroid carcinomas are histomorphologic features that are described in such patients.[27,28]

A rare complication of external neck irradiation is acute radiation thyroiditis.[30] It is more commonly associated with therapeutic doses of radioiodine for thyroid diseases. Patients typically present with fever, pain in the anterior cervical region, and transient hyperthyroidism. Hyperthyroidism with a clinical picture that resembles Graves disease may be seen after neck irradiation for Hodgkin's disease.[31] The incidence is uncertain owing to the small number of cases reported. The clinical picture is characterized by diffuse thyroid enlargement, suppressed TSH, high levels of thyroid hormones, and development of thyroid autoantibodies. Ophthalmopathy, with or without overt hyperthyroidism, may be seen and is thought to be related to autoantibodies, similar to Graves disease.[32]

Parathyroid Glands

There are several studies that link prior head and neck irradiation and hyperparathyroidism.[33,34] Cohen and colleagues[35] followed a cohort of patients who were treated with radiation to the tonsils before the age of 16 years. Among the 2923 patients, 32 patients were found to have clinical hyperparathyroidism. This is a 2.5-fold to 2.9-fold increase compared with the general population in the same age group. There is a long latency period (>25 years) between exposure and onset of hyperparathyroidism. Clinical presentations vary from asymptomatic increases in serum parathormone levels and hypercalcemia to disabling metabolic bone disease or nephrolithiasis. Individuals with a history of head and neck radiation should be monitored with calcium levels periodically (every 1 to 2 years) and indefinitely.[36]

ROLE OF SYSTEMIC THERAPY

Chemotherapy is not widely recognized to contribute to endocrine dysfunction; however, many data indicate to the contrary. Effects of systemic chemotherapy on ovarian and testicular function are discussed in Chapter 64.

Hypothalamic-Pituitary Axis

In children, chemotherapeutic agents alone may disrupt growth hormone (GH) secretion even in the absence of cranial radiation. Roman and colleagues studied growth and GH secretion in 60 children who were in complete remission after treatment with chemotherapy and surgery for solid tumors.[37] They observed growth hormone deficiency in 45% of those studied and found that these children were more likely to have received high doses of chemotherapy (actinomycin D), but they could find no correlation with the duration of treatment, length of follow-up, tumor type, sex, or age. Depending on the intensity of chemotherapy, significant height loss can be detected in 40% to 70% of patients at 6-year follow-up.[38] Adjuvant chemotherapy can also aggravate growth failure in children with brain tumors receiving craniospinal radiation.[39]

Rose and colleagues reported hypothalamic dysfunction in patients with non–central nervous system tumors who received chemotherapy but did not receive cranial irradiation or traumatic brain injury.[40] Of 31 identified patients, GHD was identified in 15 (48%), central hypothyroidism in 16 (52%), and pubertal abnormalities in 10 (32%) patients. GHD and hypothyroidism were coexistent in eight patients (26%). Overall, 81% ($n = 25$) had GHD, hypothyroidism, precocious puberty, or gonadotropin deficiency.

The syndrome of inappropriate antidiuretic hormone (SIADH) secretion may result from the effects of many chemotherapeutic agents, either by potentiation of antidiuretic hormone (ADH) effect or by increased ADH secretion. The most commonly implicated agents are vinca alkaloids and cyclophosphamide. The vinca alkaloids are reported to stimulate the central release of ADH from the neurohypophyseal system,[41] whereas alkylating agents enhance renal tubular sensitivity to ADH.[42] Regardless of the mechanism, the result is an increase in water reabsorption by the distal tubules of the kidney, leading to volume expansion and dilutional hyponatremia. Many case reports also implicate platinum agents,[43] vinorelbine,[44] taxanes,[45] and methotrexate.[46] Clinically significant hyponatremia may occur with administration of these agents. Management requires fluid restriction and, at times, salt replacement.

Thyroid

Clinically evident thyroid dysfunction is rarely associated with the use of standard chemotherapy agents. However, a growing body of

literature points to the increased prevalence of endocrine dysfunction after bone marrow transplantation, which may be seen following high doses of chemotherapy in absence of any radiation. There are reports of thyroid dysfunction in nearly 50% of allogeneic bone marrow transplant recipients treated with busulphan and cyclophosphamide alone.[47] Thyroid dysfunction may present as low T3 syndrome (free T4 normal, TSH normal, and free T3 below normal), chronic thyroiditis, and transient subclinical hyperthyroidism or hypothyroidism. Chemotherapy may potentiate radiation-induced damage to normal tissue. Among 32 patients treated for medulloblastoma in childhood, Paulino found that 18 patients developed hypothyroidism after a median time of 41 months after irradiation. Hypothyroidism was reported in 10 of the 12 patients (83%) who received 23.4 Gy plus chemotherapy (vincristine, *N*-[2-chloroethyl]-*N′*-cyclohexyl-N-nitrosourea [CCNU], cisplatin, or cyclophosphamide) and 6 of 10 (60%) of those who received 36 Gy plus chemotherapy (vincristine, CCNU, prednisone) versus only 2 of the 10 (20%) of those who received 36 GY radiation alone.[48]

Aminogluthemide, now an infrequently used drug to disrupt adrenal and peripheral steroid hormone synthesis, inhibits cholesterol conversion to pregnenolone. It causes thyroid dysfunction after long-term use due to blockade of iodination of tyrosine.[49] Figg and associates reported that 9 of 29 men who were treated with aminogluthemide for metastatic prostate cancer had clinical and biochemical evidence of hypothyroidism.[50]

Chemotherapeutic agents can also interfere with circulating thyroid hormones, thereby altering their free blood levels. 5-Fluorouracil increases total T3 and T4 levels, but free T4 index and TSH remain normal, indicating increased levels of thyroxine-binding globulin or enhanced binding capacity.[51] L-Asparaginase causes transient thyroxine-binding globulin deficiency by diminishing hepatic synthesis and also inhibits TSH secretion from the pituitary, resulting in decreased total T4 as well as free T4 levels.[52] Transient hyperthyroidism after L-asparaginase therapy for acute lymphoblastic leukemia has also been observed.[53] These thyroid function abnormalities are mild and short-lived and generally do not require specific therapy.

In postmenopausal women, tamoxifen therapy is associated with changes in thyroid hormone concentrations, though patients may remain clinically euthyroid.[54] Mamby and colleagues undertook a randomized, placebo-controlled trial with tamoxifen 10 mg orally, twice daily, with 14 patients in each group.[55] Thyroid function test assessment before and 3 months after initiation of therapy was done. Serum thyroid-binding globulin increased, as did T4 uptake and T4 levels in the tamoxifen-treated group compared to placebo. TSH levels and free thyroxine index remained unchanged; patients were clinically euthyroid and did not require treatment.

Adrenal

A method of medically ablating or reducing adrenal function was sought for a number of years as an alternative to surgical resection of the adrenal glands. Surgical adrenalectomy was used primarily for the treatment of advanced breast cancer. Aminoglutethimide and ketoconazole both suppress adrenal function. These drugs appear to have their effect through their ability to inhibit important cytochrome P-450 isozymes, which are necessary for adrenal steroid synthesis.[56,57] Aminoglutethimide, at doses of 1000 to 1500 mg/day, and ketoconazole, at doses of 800 to 1200 mg/day, produce adrenal insufficiency in 30% to 40% of patients. Although standard glucocorticoid treatment is generally required in these patients during treatment, mineralocorticoid replacement is usually not required. The antiadrenal effects of ketoconazole and aminoglutethimide are reversible with treatment discontinuation. Full recovery within 1 to 2 weeks is usual.

Mitotane (1-dichloro-2-[o-chlorophenyl]-2-[p-chlorophenyl]-ethane), is an oral chemotherapeutic agent that is used to treat adrenal carcinoma based on its potent antiadrenal effects.[58] It is used primarily to treat adrenal hyperfunction associated with adrenal carcinoma or ectopic production of corticotrophin. It has been reported to result in sustained remission for some patients with metastatic adrenal carcinoma with long-term administration.[59] Although the mechanism of action is incompletely understood, adrenal necrosis and permanent adrenal insufficiency can result, necessitating lifelong glucocorticoid administration.

Pancreas

Pancreatic exocrine or endocrine insufficiency attributable to chemotherapy is uncommon. Acute pancreatitis has been described as a complication of L-asparaginase therapy and can be fatal.[60] Although rare, several cases of diabetes mellitus have been associated with L-asparaginase therapy.[61] Hyperglycemia is usually transient and responds to intravenous fluids and drug discontinuation. A plausible mechanism may be inhibition of protein synthesis by L-asparaginase leading to interference with insulin production.[62] High triglyceride levels have been associated with L-asparaginase use, though it is not clearly associated with incidence of pancreatitis in these patients. Knoderer and colleagues retrospectively described 33 patients (13%) with asparaginase-associated pancreatitis in a cohort of 254 patients over a 5-year period.[63] Twelve cases were noted after *Escherichia coli* asparaginase, and 20 cases were noted after PEG-asparaginase therapy. The incidence of pancreatitis was found to be independent of the individual or cumulative asparaginase dose. The interval to pancreatitis diagnosis was longer for PEG-asparaginase than for *E. coli* asparaginase ($P = 0.02$). Patients who received prednisone ($P = 0.02$) and daunomycin ($P = 0.006$) were more likely to develop pancreatitis than were those who received dexamethasone ($P = 0.04$). Use of other chemotherapy agents was not observed to have a significant effect on the incidence of pancreatitis.

High-dose cytarabine can rarely result in pancreatitis. Siemers and colleagues described two patients with evidence of pancreatitis among 30 patients treated with cytarabine.[64] Prior therapy with L-asparaginase was found in another small series of patients who received cytarabine and developed pancreatitis.[65]

Streptozotocin is a nitrosurea that is used primarily for the treatment of pancreatic endocrine tumors. In preclinical models, streptozotocin causes beta cell necrosis and insulin-dependent diabetes in many species.[66] Mild glucose intolerance has been described in patients receiving this agent; however, specific treatment is rarely required.[67]

Androgen ablation therapy may also be associated with diabetes. Keating and colleagues showed an increased incidence of diabetes in prostate cancer patients receiving GnRH agonist. A potential mechanism is the increase in body fat mass associated with hypogonadism, which results in insulin resistance.[68]

ROLE OF BIOLOGIC AGENTS

Biologic agents are increasingly important in cancer treatment, and various endocrine complications are being recognized with the use of these agents.

Immune therapies may cause thyroid dysfunction. Atkins and colleagues[69] were the first to describe an association between therapy with recombinant interleukin-2 and thyroid abnormalities. Interleukin-2 therapy is known to be associated with both hypothyroidism and hyperthyroidism, though the former is more common.[70] In Atkins and colleagues' original report, seven patients (21%) had laboratory evidence of hypothyroidism, a decline in the serum thyroxine concentration and serum free thyroxine index, and an increase in the serum TSH concentration 6 to 11 weeks after treatment.[69] All five symptomatic patients had borderline or elevated serum antimicrosomal antibody titers after treatment; two had serum antibodies to thyroglobulin. Five of the seven patients with hypothyroidism (71%) but only 5 of the 27 euthyroid patients (19%) had evidence of tumor regression ($P < 0.02$). Fifteen patients (47%) became hypothyroid with high serum TSH levels within 60 to 120 days after the

start of treatment. The proposed mechanism is autoimmune with development of antithyroid antibodies. Proposed mechanisms are that either the interleukin-2 treatment itself triggers autoreactive B-cell clones or cellular and/or cytokine-mediated thyroid destruction leads to activation of autoreactive B-cell clones.

Hypothyroidism is a recognized complication of tyrosine kinase inhibitors. Sunitinib maleate is an oral tyrosine kinase inhibitor that was recently approved for the treatment of gastrointestinal stromal tumors and renal cell carcinoma. Desai and colleagues reported hypothyroidism in patients undergoing sunitinib therapy.[71] One potential mechanism may be sunitinib-induced destructive thyroiditis through follicular cell apoptosis. Sunitinib is also a RET/PTC tyrosine kinase inhibitor that is involved in pathogenesis of papillary thyroid cancer and perhaps affects normal thyroid function as well.

Imatinib also interacts with thyroid hormone replacement and results in increased TSH levels in hypothyroid individuals who are on levothyroxine therapy. However, it does not appear to have a direct effect on the thyroid but alters the levels of thyroxine binding protein.[72] Berman and colleagues reported hypophosphatemia and associated changes in bone mineral metabolism in patients taking imatinib for either chronic myelogenous leukemia or gastrointestinal stromal tumors.[73] Patients were found to have high levels of urinary phosphate and markedly decreased serum levels of osteocalcin and N-telopeptide, indicative of reduced bone turnover. Imatinib inhibits platelet-derived growth factor receptor, which in a rat model has been demonstrated to have a critical role in skeleton development.

Interferon-beta (IFN-β) and interferon-alpha (IFN-α) may both increase ACTH, prolactin, growth hormone, and cortisol levels in patients.[74] An assessment of IFN-α-induced endocrine stimulation in patients with myeloproliferative disorders revealed that on day 1 of therapy, a significant stimulation of the hypothalamic-pituitary axis was apparent, an effect that disappeared by the third week of therapy.[75] The acute stimulatory effect of IFN-α on cortisol release appears to be mediated by the release of hypothalamic corticotropin-releasing hormone. There are reports of alterations in the levels of sex hormones during IFN therapy, and male sexual dysfunction has been noted.[76]

Clinicians should keep in mind that there are limited data regarding the effects of many new agents and one must be alert to endocrine dysfunction in patients receiving such drugs.

EVALUATION AND TREATMENT OF COMMON ENDOCRINE DYSFUNCTION

A detailed history, including treatment history and physical examination, should be done in any patient who is suspected of having endocrine dysfunction. Evaluation should be directed by this information and the location and type of tumor. The initial approach to the diagnostic workup is outlined in the following sections. Endocrinology consultation should be sought for more complex and multisystem involvement. Table 65-3 shows a brief outline of evaluation of common endocrine disorders. The workup for gonadotropin deficiency and hormone replacement is discussed in detail in Chapter 64.

Hypothalamic-Pituitary Axis Disorders

Growth Hormone Deficiency

EVALUATION. The assessment of pituitary GH production is difficult because GH secretion is pulsatile and serum GH levels are often low between the pulses. Therefore, measurement of a single serum GH level is of limited use in diagnosing GHD. Serum insulin-like growth factor (IGF-1) and IGF binding protein-3 (IGFBP-3) concentrations may be measured as a surrogate marker for GH production, and further evaluation is indicated if these results are below the mean for normal children of the same age. An IGF-1 level below 84 ng/mL using the Esoterix assay reportedly is highly indicative of GHD.[77] Confirmation can be done by GH secretion provocative tests.

According to the consensus guidelines for the diagnosis and treatment of adults with GH deficiency, the insulin hypoglycemia test is the gold-standard GH provocative test.[78] According to the Food and Drug Administration, GHD is diagnosed if the maximum stimulated serum GH concentration is less than 5.1 μg/L (polyclonal radioimmunoassay) or less than 2.5 μg/mL (immunochemiluminescent assay).[79] Even though reliable, this test requires strict monitoring. The insulin hypoglycemia test is contraindicated in debilitated patients, those with cardiovascular or cerebrovascular disease, and those with a history of seizure, abnormal electroencephalogram (EEG), or history of brain surgery.[77–79] In these patients, the combined arginine/GHRH stimulation test may be used. The arginine stimulation test involves intravenous infusion of 0.5 g/kg body weight (to a maximum of 30 g) of arginine given over 30 minutes and measuring serum growth hormone level at 0, 30, 60, 90, and 120 minutes. Though historically the insulin hypoglycemia test was considered the gold standard for GHD, the arginine-GHRH test is much safer, is 95% sensitive and 91% specific (at a cutoff of 4.1 μg/L), and has essentially replaced the former.[80]

The diagnosis of GHD in childhood is a complex process that requires clinical and growth assessment combined with biochemical tests and radiologic evaluation. GHD may be an isolated finding or a component of multiple pituitary hormone deficiency. In a child

Table 65-3 Diagnostic Evaluation of Common Endocrine Disorders

Disease	History	Signs	Screening	Confirmatory Tests
GH deficiency	Fatigue, poor stamina, hypoglycemia	Slow growth velocity, delayed puberty, truncal fat distribution	IGF-1, IGFBP-3, and bone maturation	Insulin hypoglycemia test, arginine, L-dopa, clonidine
Hypothyroidism (primary or secondary)	Fatigue, cold intolerance, weight gain, cognitive dysfunction, mental retardation, constipation, growth failure, dry skin, depression, menstrual disturbances	Slow movement and slow speech, delayed relaxation of tendon reflexes, bradycardia, coarse skin, periorbital edema, macroglossia	Free T4, TSH, and bone maturation	TSH surge
Hyperthyroidism	Hyperactivity, tremors, diarrhea, sweating, weight loss, heat intolerance	Atrial fibrillation, lid lag, proptosis, goiter	Free T4, T3, and TSH	Radioiodine uptake scan
Adrenal insufficiency (primary or secondary)	Dehydration, hyperpigmentation, weakness, fatigue	Electrolyte disturbance, hypotension, nausea, vomiting	Early morning serum cortisol level	Low- or high-dose ACTH stimulation test

with clinical criteria for GHD, a peak GH concentration less than 10 mg/L has traditionally been used to support the diagnosis after a provocative GH test.[81] Supportive evidence is indicated by very short height (more than 2.5 standard deviations below the mean height for normal children of the same age), delayed bone age, poor growth velocity (less than twenty-fifth percentile), and a predicted adult height substantially below the mean parental height.[77] IGF-I/IGFBP-3 levels and GH provocation tests should be done after hypothyroidism has been excluded as a cause of slow growth. Great care should be taken in using insulin or glucagon provocative tests in a young child, and testing should be monitored by an experienced team.

TREATMENT. Children with proven GHD should receive GH therapy as soon as possible after diagnosis. The goal of therapy is to maximize height attained before puberty. The usual starting dose of GH is 25 to 50 μg/kg/day, administered subcutaneously in the evening.[72,73] Each dose produces a pharmacologic level of GH for approximately 12 hours. Evaluation of the growth response and adjustment of GH dose should occur every 4 to 6 months, and assessment should include measurement of height, weight, and arm span. GH dose is increased as weight gain occurs to maintain a stable dose per kilogram of body weight. Serum IGF-1 measurements are recommended yearly. If IGF-1 increases above the upper limits of normal for age and gender, the GH dose should be decreased.

GH therapy in adults is approved by the Food and Drug Administration only if there is evidence of hypothalamic or pituitary disease and a subnormal serum GH response to a provocative test. The goal of the therapy is to improve muscle and cardiac function, restore normal body composition, and improve serum lipids. The usual starting dose for adults between 30 to 60 years of age is 300 μg/day; the dose is increased every 1 to 2 months by 100 to 200 μg/day, guided by clinical response and measurement of serum GH levels.[77,78]

Hyperprolactinemia

EVALUATION. The presenting symptoms of hyperprolactinemia include amenorrhea, galactorrhea, impotence, and infertility. The diagnosis of hyperprolactinemia is made by a random serum prolactin level measurement. Dynamic testing of the lactotrophin reserve with thyrotropin-releasing hormone is not useful because it does not differentiate between the different causes of hyperprolactinemia.[82] Hypothyroidism must also be ruled out as a cause of clinical findings, and careful review of medications should be done to rule out drug-induced hyperprolactinemia.

TREATMENT. Dopamine released from hypothalamic nerve endings acts as a prolactin inhibitory factor, and dopaminergic agonists are useful in the treatment of hyperprolactinemia. Commonly used agents include bromocriptine and cabergoline. The most common side effects of these drugs are nausea, postural hypotension, and mental fogginess. Less common side effects include nasal stuffiness, depression, Raynaud phenomenon, alcohol intolerance, and constipation. The usual starting dose is 0.25 mg of cabergoline twice a week or 1.25 mg of bromocriptine once a day. The doses can be increased on the basis of serum prolactin level and the side effect profile.

Thyroid Disorders

EVALUATION. Primary hypothyroidism is characterized by a high serum TSH (normal range: 0.5 to 5 mU/L) concentration and a low serum free T4 concentration (normal range- 0.8 to 1.8 ng/dL). Secondary hypothyroidism is characterized by a low serum T4 concentration and a serum TSH concentration that is not appropriately elevated.[83] To distinguish between pituitary and hypothalamic causes of hypothyroidism, thyrotropin-releasing hormone stimulation test and/or imaging studies of the sellar and suprasellar region should be done. Patients who are diagnosed with central hypothyroidism should also be evaluated for coexistent adrenocortical, gonadal, posterior pituitary, and, in children, growth hormone function. As was noted previously, patients with cranial irradiation or traumatic brain injury are at high risk for panhypopituitarism.

Primary hyperthyroidism is associated with low TSH and high free T4. Graves disease is associated with uniformly high 24-hour radioiodine uptake, while toxic adenoma is associated with focal high uptake. If free T4 and T3 are high with a normal or high TSH in a clinically hyperthyroid patient, pituitary magnetic resonance imaging should be done to look for a pituitary mass (TSH-secreting adenoma).

TREATMENT. Thyroid hormone replacement with levothyroxine (T4) is usually sufficient. The goal of therapy is to attain normal TSH (in primary hypothyroidism) and free T4 levels (in secondary hypothyroidism). The average replacement dose of T4 in adults is approximately 1.6 μg/kg body weight per day. Treatment with liothyronine (T3) may be required in patients with no response to levothyroxine therapy or in patients with myxedema coma.

Thyroid ablation with surgery, radioiodine, or pharmacologic agents (propylthiouracil, methimazole) should be considered in patients with hyperthyroidism. Beta blocker therapy is used as a clinical adjunct in most patients. The goal of therapy is to keep the TSH and T3 and T4 in the normal range. Surgery is indicated primarily in patients who have large or obstructive goiter.

Syndrome of Inappropriate Antidiuretic Hormone

EVALUATION. SIADH is characterized by hyponatremia, a low plasma osmolality, an inappropriately elevated urine osmolality (above 100 mosmol/kg), and a high urinary sodium concentration (usually above 40 mEq/L). Other supportive findings include low BUN and serum uric acid concentration, normal plasma creatinine concentration, normal acid-base and potassium balance, and normal adrenal and thyroid function.[84]

TREATMENT. Water restriction is the mainstay of therapy in asymptomatic hyponatremia and in chronic SIADH. Severe, symptomatic, or resistant hyponatremia requires the administration of salt tablets or hypertonic saline administration. A loop diuretic (such as furosemide once or twice a day) may be used to enhance the effect of fluid reduction, since it directly interferes with the countercurrent concentrating mechanism by decreasing sodium and chloride reabsorption in the medullary portion of the loop of Henle.[85] In patients who remain refractory, demeclocycline (300 to 600 mg twice a day) or lithium may be used.[86] These drugs act on the collecting tubule cell to diminish its responsiveness to ADH, thereby increasing water excretion. ADH receptor antagonists are being evaluated that are selective for the V2 (antidiuretic) receptor and may thus reverse the hyponatremia. Conivaptan blocks V2 and V1a receptors and is available in parenteral form.[87]

Hyperparathyroidism

EVALUATION. Primary hyperparathyroidism is characterized by elevated parathormone level and hypercalcemia. Supportive findings include low serum phosphate level, an increase in 24-hour urinary calcium excretion, a decrease in serum calcitriol and 25(OH) cholecalciferol, and an increase in biochemical markers of bone turnover (collagen cross-links, osteocalcin, bone-specific alkaline phosphatase). Patients may present with classic symptoms of the disease (nephrolithiasis or bone disease), or they may have nonspecific symptoms such as fatigue, weakness, mild depression, vague abdominal pain, and constipation.

TREATMENT. Patients should be advised to avoid factors that can aggravate hypercalcemia, including thiazide diuretic and lithium carbonate therapy, volume depletion, prolonged bed rest or inactivity, and a high-calcium diet (>1000 mg/day). Daily vitamin D intake

of 400 to 600 IU daily should be maintained, as vitamin D deficiency stimulates parathormone secretion and bone resorption and therefore is deleterious in patients with primary hyperparathyroidism. Surgical removal of the parathyroid glands remains the mainstay of therapy in most patients. Medical therapy involves estrogen plus progestin, bisphosphonates, or raloxifene. These drugs inhibit bone resorption and increase bone density and possibly lower serum calcium concentrations in patients with hyperparathyroidism. Calcimimetics and vitamin D analogs act by suppressing parathyroid hormone release and counteract the effects of hyperparathyroidism at the level of the parathormone receptor. Calcimimetics are currently being studied for primary and secondary hyperparathyroidism.[88]

Adrenal Disorders

EVALUATION. There is controversy about the optimal biochemical approach to diagnosis of corticotropin deficiency. In moderate to severe corticotropin deficiency, the early morning serum cortisol levels are consistently less than 250 nM. A corticotropin stimulation test may be used to confirm the diagnosis. Both low-dose (1 μg) and high-dose (250 μg) corticotropin stimulation tests are useful to distinguish primary from pituitary (secondary) causes of adrenal insufficiency. Serum cortisol levels are measured at 0, 30, and 60 minutes after intravenous administration of corticotropin. If corticotropin and adrenal secretion are normal, the serum cortisol levels should increase to 20 mg/dL or higher. In patients with severe corticotropin deficiency, the serum cortisol response will be lower or absent as a result of adrenal atrophy. Primary adrenal insufficiency is characterized by low response to both low-dose and high-dose corticotropin stimulation tests. Acute adrenal crisis is an oncologic emergency. Electrolyte disturbances such as hyponatremia, hyperkalemia, azotemia, hypercalcemia, and hypoglycemia are common.

TREATMENT. Adrenal insufficiency requires glucocorticoid supplementation and at times mineralocorticoid supplementation. Pituitary or isolated ACTH deficiency is not characterized by mineralocorticoid deficiency. Patients with symptomatic adrenal insufficiency should be treated with hydrocortisone or cortisone in the early morning and afternoon. The usual initial oral dose is 25 mg of hydrocortisone (15 mg in the morning and 10 mg in the afternoon). This may be decreased over time, with the goal of using the minimal effective dose to prevent weight gain and osteoporosis.[89] Patients with primary adrenal insufficiency require mineralocorticoid replacement with fludrocortisone (0.05 to 2 mg orally each day).

Box 65-1. TREATMENT OF ACUTE ADRENAL CRISIS

1. Check airway, breathing and circulation, and baseline vital signs. Establish intravenous access with a large-gauge needle.
2. Assess serum electrolytes, glucose, and random plasma cortisol and ACTH levels.
3. Replace intravascular volume with isotonic saline (at least 2 to 3 liters), and maintain hydration.
4. Intravenous corticosteroid administration preferably with dexamethasone (4 mg intravenous every 8 hrs) intravenously. Hydrocortisone 100 mg IV every 6 hours may be used but can interfere with ACTH stimulation test.
5. Treat underlying causes of the adrenal crisis (e.g., infection).
6. Perform a short ACTH stimulation test to confirm the diagnosis of adrenal insufficiency if the patient does not have known adrenal insufficiency.
7. Begin mineralocorticoid replacement with fludrocortisone (0.1 mg by mouth daily) after volume replacement.

Box 65-2. YEARLY SURVEILLANCE FOR ENDOCRINE DISORDERS IN CHILDHOOD CANCER SURVIVORS

1. Detailed history and physical examination, including accurate height and weight measurements (arm span measurement if unable to assess height)
2. Determination of bone age (radiograph of left hand and wrist) in children who are growing too fast or too slowly
3. Ascertainment of Tanner stage of pubertal development and interpretation of whether the pubertal status and rate of progression are appropriate for chronologic age
4. Measurement of IGF-I and IGFBP-3 levels in children who are growing too slowly (to assess for GHD)
5. Measurement of serum LH, FSH, and sex hormone levels (testosterone or estradiol) in children with delayed or interrupted progression of puberty
6. Measurement of free T4 and TSH levels

During periods of stress, patients with adrenal insufficiency require higher-than-usual doses of hydrocortisone, and in severe illness, they might require intravenous high-dose hydrocortisone therapy due to acute adrenal crisis. Box 65-1 outlines a treatment algorithm for acute adrenal crisis, which should be treated as an oncologic emergency.

SURVEILLANCE OF CHILDHOOD CANCER SURVIVORS

With improved therapy for most childhood cancers, there is an increasing population of childhood cancer survivors.[90] Such individuals are at risk for long-term endocrine complications related to the tumor and/or the treatment received. The risk of a particular endocrinopathy depends on the tumor location and the dose and duration of radiotherapy and chemotherapy received. Box 65-2 depicts a summary of recommended yearly surveillance in childhood cancer survivors for endocrine complications.[91] Close follow-up should be performed every 4 to 6 months if the initial tests are normal but the child remains symptomatic.

Children typically exhibit catch-up growth and weight gain after completion of therapy. Some children transiently develop breast buds corresponding to this period of newly improved nutrition. These children should be examined every 3 to 6 months to evaluate for precocious puberty. Assessment of Tanner stage of pubertal development is useful to assess for precocious or delayed puberty. Further testing should be guided by the physical findings.

Surveillance for adrenocortical deficiency is indicated primarily for high-risk patients such as those who received cranial irradiation in excess of 40 Gy. There is controversy regarding how long the surveillance should be carried out. The surveillance is guided largely by the pattern of growth and development. If normal growth and pubertal development are attained, the surveillance can be stopped.

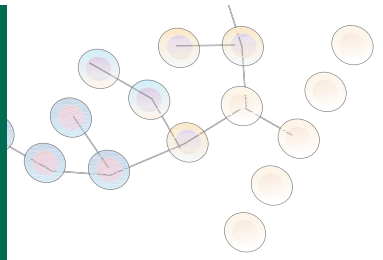
CONCLUSION

Endocrine disorders are common in patients with cancer and are related primarily to cancer therapy. Careful clinical examination and yearly surveillance should be done in cancer survivors. A high degree of clinical suspicion is necessary in patients who are on newer therapies with which there is limited experience. Most endocrine disorders are readily treatable, and an accurate diagnosis should be pursued aggressively.

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66 Second Malignant Neoplasms

John P. Plastaras, Daniel M. Green, and Giulio J. D'Angio

SUMMARY OF KEY POINTS

Epidemiology

- Pediatric patients who survive their primary cancer are at increased risk of developing a new malignancy.
- The magnitude of this risk is modulated by several factors, including the patient's genetic susceptibility, the type of surgical procedure used for removal of the tumor, the use of radiation therapy as part of the treatment plan, the chemotherapeutic agents that are employed, the severity of immune suppression that is present at the completion of all treatment, and environmental exposures.
- The potential risk of a second malignant process following treatment of adults should not lead to therapeutic compromises when treatment, often aggressive, is of known benefit.

General Recommendations

- All former cancer patients should remain under a physician's care indefinitely.
- All former cancer patients should undergo frequent physical examinations (preferably by a physician or other specifically trained health care worker who is familiar with the problem of therapy-induced malignancy).
- Physicians should counsel cancer survivors regarding the potential for the adverse effects of tobacco use, including the potential to interact with the adverse effects of their prior therapy, such as irradiation of the oropharynx, esophagus, and/or lungs.

Specific Recommendations

- Plain radiographs should be obtained for patients who have been irradiated whenever local pain occurs in a previously irradiated bone.
- Patients who have received irradiation to volumes that include the breast, uterine cervix, or intestine should undergo routine evaluation with available screening tests, such as mammography, Pap smear, and stool examination for the presence of occult blood.
- Annual mammography should be initiated no later than 10 years after breast irradiation.
- Careful physical examination of irradiated patients will facilitate the early identification of thyroid nodules and skin cancer.
- All patients who have been treated with an alkylating agent, procarbazine, or a topoisomerase II inhibitor, should have a complete blood count every 6 to 12 months for a minimum of 12 years after diagnosis.
- Presence of macrocytosis and/or cytopenia should prompt evaluation of the bone marrow.

INTRODUCTION

Second malignant neoplasms (SMNs) develop in patients as a result of genetic and iatrogenic factors and their interplay. The therapies that are employed are different for children and adults because of the differences in the primary cancers that are encountered. Primary cancers in adults are usually of epithelial origin, unlike the embryonal and sarcomatous neoplasms encountered at earlier ages. In addition, some of the cancers that are encountered in adults are the result of therapies they received for nonmalignant conditions that were treated when they were children. This discussion therefore has been divided into two parts according to the age group being considered.

CHILDREN AND ADOLESCENTS

SMNs are a recognized complication of successful treatment of children and adolescents for cancer. The frequency of these had been reported to be 1.9% at 10 years after diagnosis, 5.0% to 12.0% at 25 years after diagnosis, 3.3% to 4.9% at 25 years after diagnosis among 3-year survivors, 3.2% to 12.0% at 20 years after diagnosis among 5-year survivors, and 4.2% to 7.8% at 25 years after diagnosis among 5-year survivors.[1–8] These series differed with respect to the time period during which the patients were treated, the completeness of follow-up, and the treatment exposures that the patients experienced. SMNs are a major threat to the long-term survivors of childhood cancer, in whom they are looming ever larger as a cause of death. Moller and colleagues reported results of a survey in the Nordic countries, where the proportions of deaths from second tumors increased from 3% to 22% between 5 and 10 years and 20+ years.[9] In fact, Lawless and colleagues found SMNs to be more often the cause of death than was relapse of the primary tumor.[10] In their single-institution study, they found that SMNs were the leading cause of death (39%) in 15+-year survivors; greater than the rates for primary cancer (21%) and cardiac (16%) deaths. Increasingly, the data suggest that although specific exposures (whether to a particular chemotherapeutic agent or to ionizing radiation) might be linked to the occurrence of a new malignancy, the most important factor in the pathogenesis of many SMNs could well be the patient's genetic susceptibility. We will review the genetic and treatment factors that have been associated with the occurrence of SMNs and discuss the follow-up and evaluation of the successfully treated pediatric cancer patient.

Genetic Factors

The importance of genetic predisposition to the occurrence of a SMN has been demonstrated most clearly in patients with hereditary

retinoblastoma. Among 1604 1-year survivors of retinoblastoma in Boston and New York City between 1914 and 1984, 961 had the hereditary form of the disease.[11] The cumulative percentage of those who developed a SMN was 51.0% (±6.2%) 50 years after retinoblastoma diagnosis, compared with 5.0% (±3.0%) among those with nonhereditary retinoblastoma (Fig. 66-1A). Among patients with hereditary retinoblastoma, the cumulative percentage that developed SMNs was 58% among those whose treatment included radiation therapy (RT), compared with 26.5% among those whose treatment did not include RT (Fig. 66-1B). Kleinerman and colleagues[12] updated this series to focus on secondary sarcomas and found that there was a significantly increased risk of sarcomas within the RT field as well as an increased risk outside of the RT field, with a 13% cumulative risk of sarcoma 50 years after RT. Leiomyosarcomas were frequently diagnosed over 30 years later, indicating that older carriers remain at risk. Fletcher and colleagues[13] described the long-term risks of SMNs in retinoblastoma survivors born before 1950, a group that was not routinely treated with high-dose RT. The cumulative incidence of SMNs from age 25 to 84 was 69% in the hereditary cases and 48% in the sporadic cases, but the majority were epithelial cancers and not sarcomas. These studies indicate that retinoblastoma carriers have both an inherent risk of other SMNs and a RT-dependent risk of secondary sarcomas, which affects how these patients should be followed into adulthood.

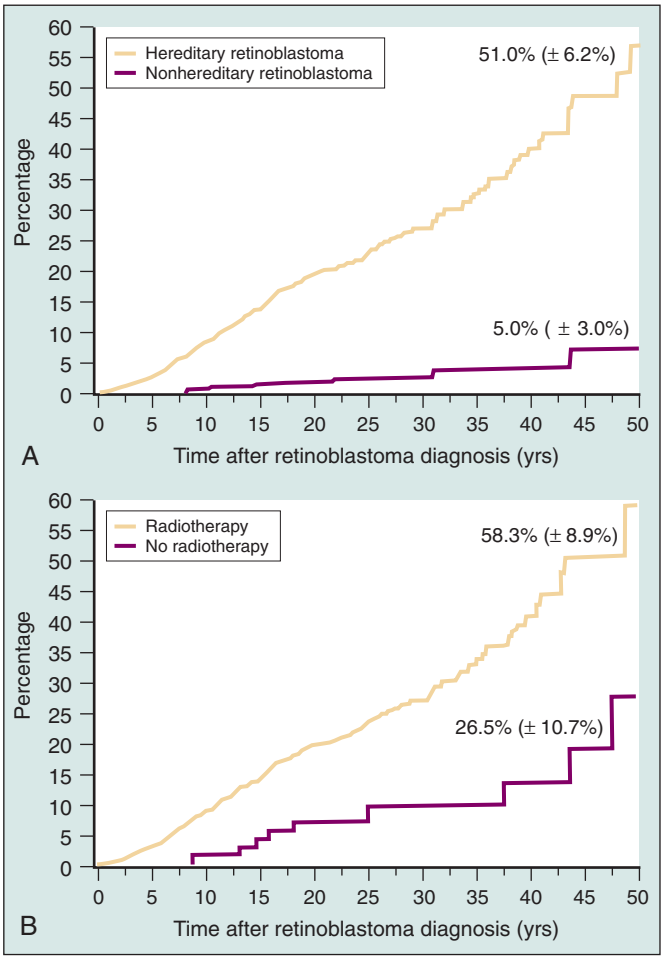


Figure 66-1 • **A,** The cumulative incidence of second malignant tumors is increased in children with familial retinoblastoma. **B,** The cumulative risk of second malignant tumors is increased in children with familial retinoblastoma who are treated with radiation therapy. (Data from Wong GL, Boice JD Jr, Abramson DH, et al: Cancer incidence after retinoblastoma: radiation dose and sarcoma risk. JAMA 1997;1262:278.)

Li-Fraumeni syndrome consists of sarcoma diagnosed in the proband before age 45 years, with additional cancers (frequently soft-tissue sarcoma or breast cancer) diagnosed in other children and young adults within the family.[14] The genetic defect in some families with the Li-Fraumeni syndrome was demonstrated to be a mutation within the p53 gene.[15–18] Because the pattern of first and second malignant tumors in some patients with SMNs resembles the distribution that is observed within some families with Li-Fraumeni syndrome, a series of patients with SMNs was evaluated for the occurrence of mutations at this locus. Mutations were identified in 5.1% of 59 patients who were examined.[19,20] Pediatric patients with cancer who have neurofibromatosis have a relative risk of 8.1 of developing a SMN compared with pediatric patients with cancer who do not have neurofibromatosis.[21] Future research could demonstrate that neurofibromatosis type 1 patients who develop SMNs have coexistent germline p53 mutations.

Treatment Factors

Surgery

Surgical procedures can increase the risk of subsequent malignancy. Adenocarcinoma of the colon has been reported in several patients after ureterosigmoidostomy. The incidence of adenocarcinoma in these patients was approximately 9.9 per 1000, compared with an incidence rate of 9.9 per 100,000 in the general population.[22] The majority of reported patients have undergone this procedure for treatment of exstrophy of the bladder. The median interval between ureterosigmoidostomy and the diagnosis of colon carcinoma was 22 years.[23]

Radiation Therapy

The risk of various SMNs has been linked to the use of both RT and chemotherapy.[8,24,25] As treatment of childhood malignancies has intensified over the past several decades, the cure rate has increased, but so has the risk of SMNs.[8] In the cohort of 13,136 patients from the Childhood Cancer Survivor Study, 59% of the nonbreast, nonskin, nonthyroid SMNs occurred within RT fields.[26] A European case-control study of 4581 survivors by Guerin and colleagues demonstrated a radiation dose-response for the excess risk of SMNs that best fit a linear model of 0.13 per Gy.[24] This study also noted that the relative risk of SMN was increased when chemotherapy and RT were delivered concomitantly.

Patients who receive neck irradiation for malignant diseases are at risk for the subsequent occurrence of thyroid malignancies. These have been reported after treatment of patients with medulloblastoma, acute lymphoblastic leukemia, and Hodgkin's disease (HD).[27–29] The incidence of thyroid cancer in survivors of HD was 0.8% (1 in 119) among children who were treated at Stanford University.[30] Malignant thyroid tumors occurred at lower RT doses than did benign lesions.[31] Ron and colleagues reported that a linear-exponential model fit the dose-response data for thyroid cancer after treatment for childhood cancer better than a linear model did.[32]

This finding is consistent with the data of Upton, who demonstrated that the dose-response relationship for some radiation-induced experimental tumors was quadratic rather than linear.[33] These data led Gray to hypothesize that the shape of the dose-response curve was the sum of two radiation-induced processes: mutation induction and cell death.[34] Radiation-associated SMNs in other sites, however, have been fit to linear models (see later discussion).

Central nervous system tumors, including meningiomas and gliomas, have been reported with increasing frequency after direct or incidental irradiation of the brain, which is not surprising when the occurrence of brain tumors in children treated with low doses of RT for tinea capitis is recalled. Neglia and colleagues[35] reported that the excess radiation-associated risk for secondary gliomas was 6.8 and

that for meningiomas was 9.9. There was a linear dose response, with a steeper slope for meningiomas (1.1) than for gliomas (0.3; Fig. 66-2). The excess risk for gliomas was greatest in children who were irradiated before age 5. Other researchers have confirmed the increased risk of central nervous system tumors in children whose treatment for acute lymphoblastic leukemia included cranial irradiation.[36] In children with neurofibromatosis type 1, there was a threefold relative risk of second nervous system tumors after RT for optic pathway gliomas compared to unirradiated patients.[37]

Genetic loci associated with the occurrence of Wilms' tumor have been identified on chromosomes 11, 17, and 19.[38–40] Some patients have germline mutations in WT1, the only Wilms' tumor-associated gene that has been sequenced.[41,42] Li and associates reported that the frequency of SMNs in a cohort of successfully treated Wilms' tumor patients was 6% 20 years after diagnosis.[43] SMNs were diagnosed only in irradiated patients. Breslow and colleagues reviewed the occurrence of SMNs among patients entered on the National Wilms Tumor Studies.[44] The cumulative risk of SMN was 1.6% 15 years after diagnosis (Fig. 66-3). The relative risk of developing SMN was increased in patients who had received RT, the relative risk increasing with increasing radiation dose. Administration of doxorubicin increased the relative risk at each level of radiation exposure.[44] Other researchers have reported a cumulative frequency of SMN after treatment for Wilms' tumor at 3.9% at 20 years, with a relative risk of 11.0.[45] Patients with bilateral Wilms' tumor were not at increased risk for SMNs, according to the National Wilms Tumor Study Group analysis.[44]

Sarcomas of bone have been reported both in patients with hereditary retinoblastoma and in those who survive other types of childhood cancer. The cumulative risk of SMN in bone was estimated to be 2.8% among 9170 patients who were evaluated but was 14.1% among those with retinoblastoma and 22.1% among those who had

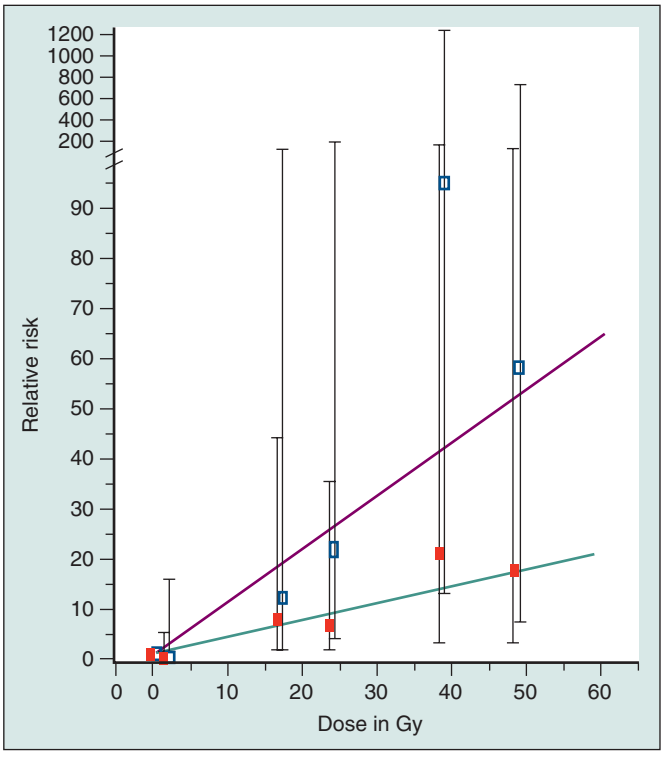


Figure 66-2 • The risk of subsequent glioma (*closed squares*, *purple line*) and meningioma (*open squares*, *blue line*) increases with radiation dose. (Data from Neglia JP, Robison LL, Stovall M, et al: New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98:1528.)

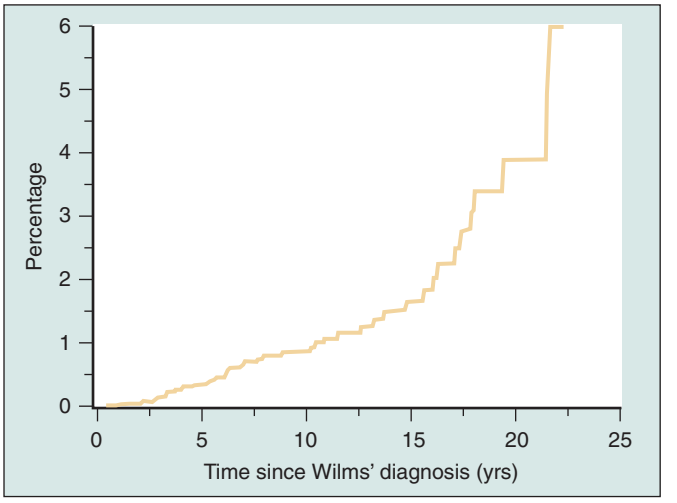


Figure 66-3 • Children who have been successfully treated for Wilms' tumor have a significant risk of developing a second malignant tumor. (Data from Breslow NE, Takashima JR, Whitton JA, et al: Second malignant neoplasms following treatment for Wilms' tumor: a report from the National Wilms Tumor Study Group. J Clin Oncol 1995;13:1851.)

been treated for Ewing sarcoma (ES) at 20 years after diagnosis (Fig. 66-4).[46] The relative risk was 2.7 among patients whose treatment had included RT; the relative risk increased with increasing RT dose and more intensive use of alkylating agents.[46] Other researchers reported a relative risk for osteosarcoma of 88–1515 in patients who had been treated for retinoblastoma; the relative risk rises to 800 after treatment for ES.[3,47] Hawkins and colleagues calculated the cumulative frequency of bone cancer in previously irradiated childhood cancer survivors as 0.5% among those who were not treated for retinoblastoma and as 7.2% among those who were treated for heritable retinoblastoma.[48] A dramatically high risk of sarcoma of bone after treatment of ES was observed in a multi-institutional study.[49] The cumulative frequency of a SMN in ES patients who were treated successfully was 9.2% at 20 years after diagnosis, and that of a secondary sarcoma was 6.5%. No secondary sarcomas developed in patients who had received less than 48 Gy.[49] A case-control study of bone sarcoma as a SMN found no difference in relative risk between patients treated with orthovoltage and megavoltage RT.[46] A decreased risk might have been expected because of the lower absorbed doses in bone after high-energy RT. Successfully treated patients are at risk of developing carcinomas (e.g., of the skin) within prior RT treatment volumes given at a very early age.[50]

Irradiation of breast tissue increases the risk of breast cancer, as was demonstrated in women who were exposed to diagnostic radiograph for pulmonary tuberculosis and survivors of the atomic bomb detonations in Hiroshima and Nagasaki.[51,52] The reported relative risks of breast cancer in girls who were treated for HD have varied widely. The largest study with the longest follow-up reported a relative risk of 11.5.[53] In this large, population-based study of 383 HD survivors, all 16 women who developed breast cancer had supradiaphragmatic irradiation. The cumulative risk of breast cancer at 25 years was 9.9% for all HD patients and 12.2% for those who were treated with supradiaphragmatic RT.

Total body irradiation, a component of most preparative regimens for allogeneic bone marrow transplantation for malignant diseases, is associated with a cumulative risk for the occurrence of a second solid neoplasm of 6.1% at 10 years after treatment.[54]

Hormone Therapy

Growth hormone (GH) treatment is necessary for the management of some children who received cranial irradiation as part of their

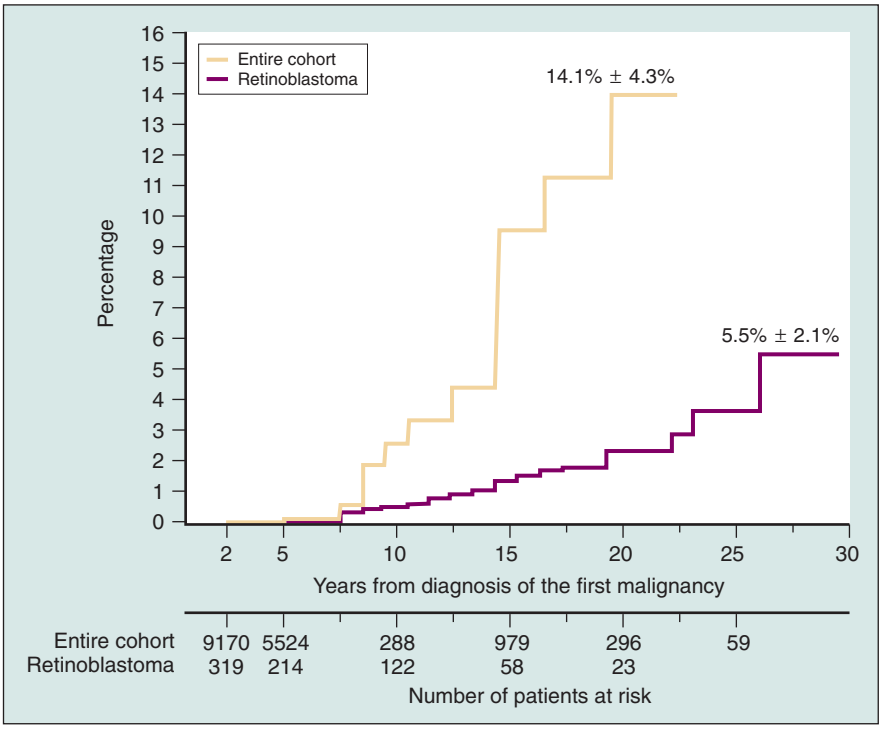


Figure 66-4 • The cumulative incidence of bone sarcoma as a second malignant tumor is increased in children who were treated for retinoblastoma compared with those who were treated for other forms of childhood cancer. (Data from Tucker MA, D'Angio GJ, Boice JD Jr, et al: Bone sarcomas linked to radiography and chemotherapy in children. N Engl J Med 1987:317:588.)

therapy for acute lymphoblastic leukemia or brain tumors. The question of whether use of GH increases the risk of second cancers was addressed in the Childhood Cancer Survivor Study cohort.[55] Using a time-dependent Cox multivariate model, the authors found that GH increased the risk of SMNs by 2.1, which was less than previous estimates. The majority of SMNs were intracranial, especially meningiomas. Although the use of radiation was taken into account in their model, the radiation dose was not, so it is possible that the need for GH was a surrogate for radiation dose. The possible risk identified by these two studies must be weighed in the context of the substantial benefits that accrue to these patients as the result of GH therapy, including improved linear growth and bone mineral accretion.

Chemotherapy

The significance of prior treatment with chemotherapy in the pathogenesis of SMNs was first evaluated in detail in cohorts of adults who had been treated successfully for HD. The risk factors for the occurrence of SMNs in pediatric patients after treatment for HD have been evaluated less thoroughly.

Bhatia and coworkers reported that the cumulative risk of developing any SMN after treatment for HD in childhood was 7% at 15 years after diagnosis.[56] The risk of developing non-Hodgkin's lymphoma (NHL) was 1.1%, and the risk of developing any type of leukemia was 2.8% at 15 years after diagnosis. The investigators found that the relative risk of leukemia was proportional to the alkylating agent dose score, that is, the cumulative dose of those drugs. The actuarial risk of developing acute myelogenous leukemia 10 years after diagnosis was 11% among pediatric patients treated at Stanford University with low-dose (2500 cGy) RT and MOPP (nitrogen mustard [M], vincristine [O], procarbazine [P], and prednisone [P]) chemotherapy, which has an alkylating agent dose score of 2.[57] The risk was 1.1% 15 years after diagnosis among pediatric patients treated with involved or extended field RT and various chemotherapy regimens that did not contain nitrogen mustard (vincristine, prednisone, doxorubicin, with or without procarbazine; cyclophosphamide, vincristine, prednisone, procarbazine, or methotrexate).[58]

Other investigators have studied the risk of developing SMNs after various chemotherapeutic agent exposures. Tucker and colleagues reported that prior treatment with an alkylating agent increased the risk of developing bone cancer or leukemia (Fig. 66-5) as SMN.[46] De Vathaire and coworkers demonstrated that dactinomycin increased the risk of a bone or soft tissue SMN (relative risk: 8.7).[59] Garwicz and associates reported that treatment with classical alkylating agents (nitrogen mustard, cyclophosphamide, lomustine), nonclassical alkylating agents (procarbazine), vinca alkaloids (vinblastine, vincristine), or prednisone each increased the relative risk of SMN.[21] Only procarbazine increased the relative risk of SMN when it was included in a two-factor multivariate model.[21] Klein and colleagues reported an increased relative risk for SMN with higher doses of several agents, including cyclophosphamide (RR 6.3 for doses >8000 mg/m^2), cisplatinum (relative risk: 2.8 for doses >435 mg/m^2), and 6-mercaptopurine (relative risk: 4.5 for doses >5000 mg/m^2).[60] Neglia and associates reported that treatment with an anthracycline (relative risk: 1.51 for doses of 101–300 mg/m^2; relative risk: 1.44 for doses >300 mg/m^2) or epipodophyllotoxin (relative risk: 2.78 for doses >4001 mg/m^2) did not demonstrate an increased relative risk with increasing alkylating agent dose score or cisplatinum exposure.[6]

The epipodophyllotoxins have been identified as important leukemogens. Pui and coworkers reported the risk of secondary acute myelogenous leukemia (AML) as 4.7% at 6 years after diagnosis among patients treated for acute lymphoblastic leukemia.[61] The risk was substantially higher (19.1%) among patients with T-cell leukemia. These investigators subsequently demonstrated that the risk of secondary AML in this population was related to the administration of epipodophyllotoxins, with the cumulative frequency of AML being 12.3% among those who were treated twice weekly and 12.4% among those who were treated weekly, compared with a frequency of 1.6% among those who were treated with the drug less frequently or not at all (Fig. 66-6).[62]

The risk of secondary leukemias after the treatment of solid pediatric tumors has been linked to treatment with radiation, epipodophyllotoxins, and vinca alkaloids.[25] The onset of secondary leukemia

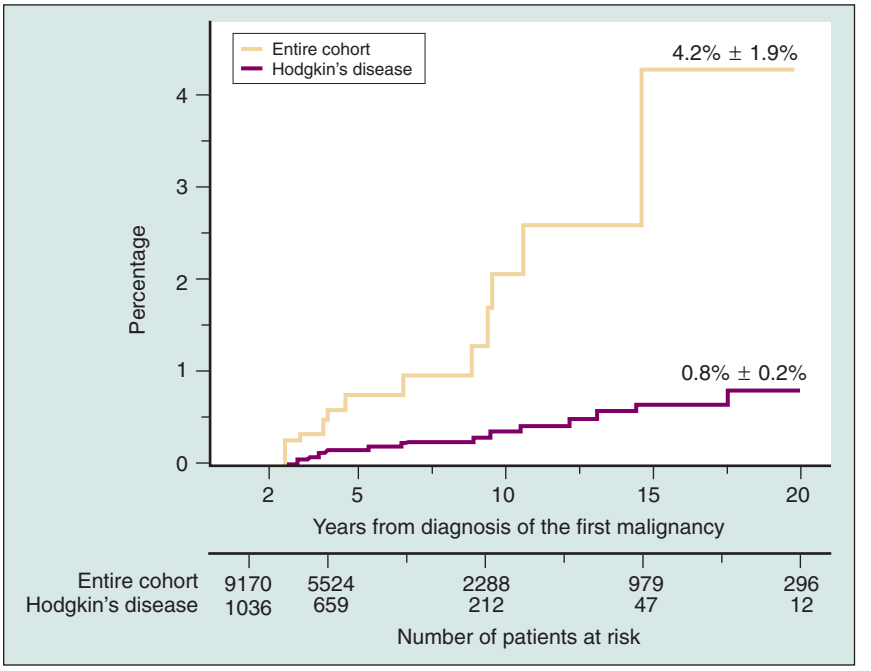


Figure 66-5 • The cumulative incidence of leukemia as a second malignant tumor is increased in children who were treated for Hodgkin's disease compared with those who were treated for other forms of childhood cancer. (Data from Tucker MA, Meadows AT, Boice JD Jr, et al: Leukemia after therapy with alkylating agents for childhood cancer. J Natl Cancer Inst 1987;78:459.)

is generally considered an early event, but Haddy and coworkers noted peaks in the first 10 years and again after 20 years.[25] The risk of secondary AML depends on the cumulative dose of drug administered and the schedule of administration; the frequency was reported to be 0% among germ cell tumor patients who were treated with less than 2000 mg/m^2, 5.9% among childhood acute lymphoblastic leukemia patients who were treated with 1800 to 9900 mg/m^2, 11.3% among germ cell tumor patients who received more than 2000 mg/m^2, and 18.4% among pediatric NHL patients who received 4200 to 5600 mg/m^2.[63–65] Hawkins and associates reported an increased risk of secondary leukemia with increasing cumulative dose of epipodophyllotoxin.[66]

The carcinogenic potential of the anthracycline doxorubicin was suggested by the results of a previous case-control study of risk factors for leukemia as a SMN. Increasing doxorubicin dose was found to be associated with an increasing relative risk of leukemia as a SMN after adjustment for the cumulative dose of alkylators given concomitantly.[67] More recently, prior treatment with anthracyclines or epipodophyllotoxins has been shown to increase the risk of therapy-related acute promyelocytic leukemia and of secondary leukemia or myelodysplasia.[68,69] Patients who received 1.2 to 6.0 g/m^2 of epipodophyllotoxin had a relative risk of developing leukemia of 3.9, whereas those who received more than 170 mg/m^2 of anthracycline had a relative risk of developing leukemia of 3.0.[68] This finding is of

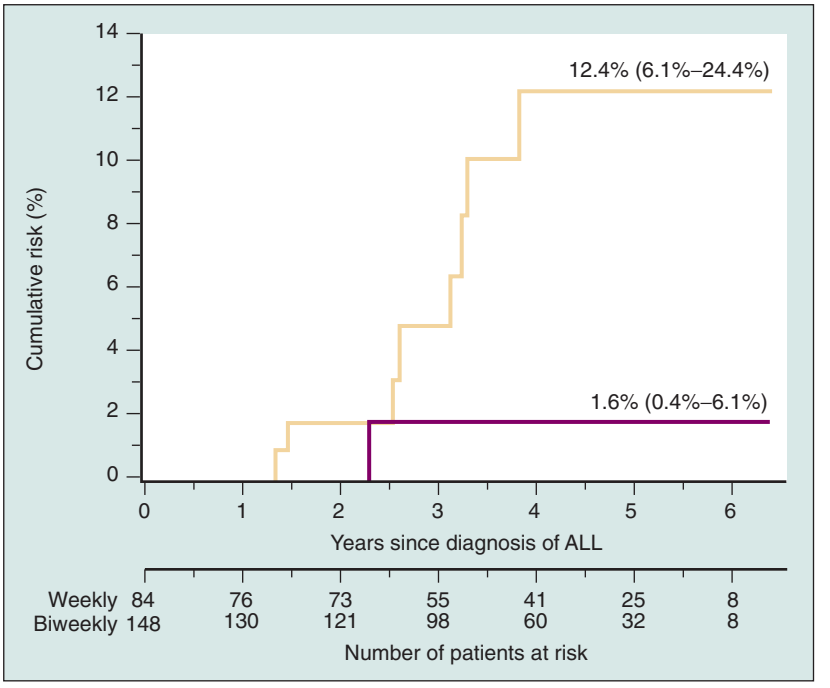


Figure 66-6 • The cumulative incidence of acute myelogenous leukemia after treatment for acute lymphoblastic leukemia is increased among children whose therapy includes weekly epipodophyllotoxin. (Data from Pui C-H, Behm FG, Raimondi SC, et al: Secondary acute myeloid leukemia. N Engl J Med 1989;321:136.)

interest, as doxorubicin is now known to have topoisomerase II as one of its targets—the same target as that of the epipodophyllotoxins. A case-control study of risk factors for bone sarcoma as a SMN did not identify any effect of doxorubicin therapy on the risk of developing such SMNs.[46] An analysis of risk factors for any SMN in a large cohort of pediatric patients with cancer demonstrated that treatment with doxorubicin was the only factor that was identified (other than treatment with carmustine) that increased the risk of a SMN. (This finding apparently extended the earlier suggestion that doxorubicin was leukemogenic.[2]) The evidence in adults will be reviewed later in the chapter.

The leukemogenicity of topoisomerase II inhibitors could be related to the high degree of specificity of these agents for specific DNA targets, including the myeloid-lymphoid leukemia gene and the acute myeloid leukemia 1 (AML1) gene.[70–72]

Although most studies of carcinogenicity of chemotherapeutic agents have focused on the development of leukemia after treatment, it is clear that solid tumor induction is also possible after exposure to one or more chemotherapeutic agents. The best example of this is the occurrence of solid SMNs in genetically predisposed retinoblastoma patients who were treated only with cyclophosphamide after enucleation.[73] As our ability to identify genetically predisposed patients improves, our understanding of the apparent anomaly of solid tumor induction after systemic exposure to a carcinogenic agent will increase.

Immune Suppression

Immune suppression is a component of allogeneic bone marrow transplantation. To prevent graft-versus-host disease, antithymocyte globulin can be administered to the recipient, or the bone marrow can be manipulated to remove T cells. These manipulations and bone marrow transplantation from an unrelated bone marrow donor increase the risk of Epstein-Barr virus-associated B-cell lymphoproliferative disorder. The cumulative incidence rates at 10 years after bone marrow transplantation were 11.3% among those who were treated with antithymocyte globulin, 11.4% among those who received T-cell-depleted bone marrow, and 2.3% among those who received bone marrow from unrelated donors.[74]

Recommendations

Survivors of childhood cancer are at increased risk of developing a new malignancy. The magnitude of this risk is modulated by several factors, including the patient's genetic susceptibility, the type of surgical procedure that is employed for removal of the tumor, the use of RT as part of the treatment plan, the chemotherapeutic agents that are employed, the severity of immune suppression present at the completion of all treatment, and environmental exposures.[75]

All former patients should remain under a physician's care indefinitely and should undergo frequent physical examinations, preferably by a physician or other health care worker who is familiar with the problem of therapy-induced malignancy.

Patients who have been irradiated should have plain radiographs obtained whenever local pain occurs in a previously irradiated bone. Patients who have received irradiation to volumes that include the breast, uterine cervix, or intestine should undergo routine evaluation with available screening tests, such as mammography, Pap smear, and stool examination for the presence of occult blood. Annual mammography should be initiated no later than 10 years after breast irradiation. Careful physical examination of irradiated patients will facilitate the early identification of thyroid nodules and skin cancer.

All patients who have been treated with an alkylating agent, procarbazine, or a topoisomerase II inhibitor should have a complete blood count every 6 to 12 months for a minimum of 12 years after diagnosis. The presence of macrocytosis and/or cytopenia should prompt evaluation of the bone marrow.

The adverse health consequences of tobacco use, including carcinogenesis, are well documented. Unfortunately, childhood cancer survivors are only slightly less likely to use tobacco.[76,77] Physicians should counsel childhood cancer survivors about the potential for the adverse effects of tobacco use to interact with the adverse effects of their prior therapy, such as irradiation of the oropharynx, esophagus, and/or lung.

ADULTS

Genetic Factors

Travis provides an excellent, comprehensive overview and update of research concerning SMNs focusing on solid tumors in the adult age group.[78] She stresses that several factors besides chemotherapy, RT, and their interplays need to be considered. For example, the complex potential interactions of alkylating agents, RT, and tobacco smoking are developed extensively in her discussion of lung cancers as SMNs, especially in HD patients. She points out the additional variable in HD patients (i.e., impaired immunologic responses), so that data derived from long-term survivors of HD cannot be extrapolated with confidence to patients with other SMNs. Studies of second cancers can help point to common genetic mechanisms. For example, a study of secondary pancreatic cancers showed an increased propensity of pancreas cancer to occur not only after tobacco-associated cancers, but also after breast cancer (male and female) and ovarian cancer, which are associated with BRCA2 mutations.[79]

The potential importance of immunodeficiency in the appearance of SMNs was the hypothesis explored by Hemminki and coworkers in an imaginative epidemiologic investigation.[80] They noted that skin cancers and NHLs were the most frequent malignant lesions to appear in immune-deficient patients (e.g., in renal transplant patients who were given needed post-transplant immune-suppressing agents). Using the Swedish nationwide database, they found 4301 secondary skin cancers and 1672 NHLs in a period of about 40 years among 10.2 million survivors of a primary cancer. The researchers found increased risks—up to 12-fold depending on patient sex and primary tumor site—for these two neoplastic entities. These results suggest that immunodeficiency could play a role in the appearance of SMNs.

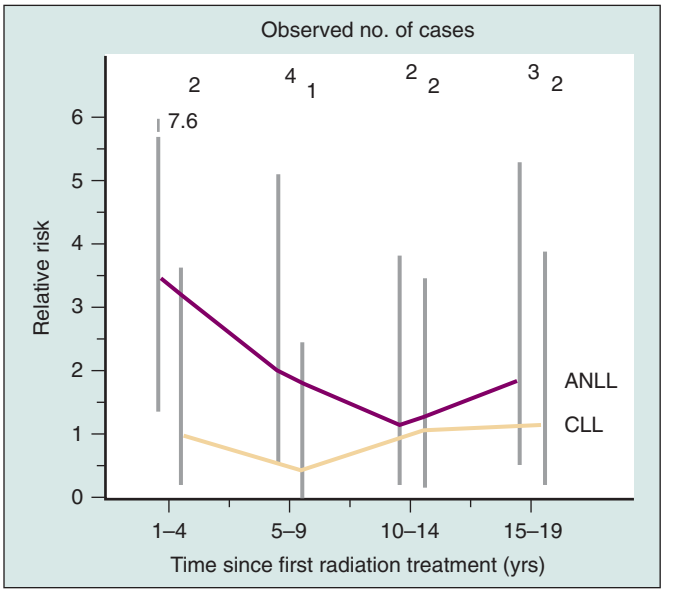


Figure 66-7 • Schematic illustration of risk factors for second primary cancers. ANLL, acute nonlymphoblastic leukemia; CLL, chronic lymphoblastic leukemia. (Data from Storm HH: Second primary cancer after treatment for cervical cancer. Later effects after radiotherapy. Cancer 1998;61:679.)

Several sites of primary tumors in both males and females were encompassed in their study, making therapy-induced immunosuppression unlikely. This conclusion points to possible underlying genetic factors as contributory influences (Box 66-1).

The importance of the Li-Fraumeni syndrome as a risk factor for cancer in young adults has been discussed previously.[75] Cancer families provide evidence supporting laboratory studies of the genetic bases of adult cancers. Cancer predisposition genes for breast cancer (BRCA1, BRCA2), colon cancer (MSH1, MSH2, APC, DCC), malignant melanoma (CDK2), and renal cell carcinoma (RCC) have all been identified.

Box 66-1. EVALUATION FOR PATIENTS AT RISK FOR SECOND MALIGNANT NEOPLASMS

Risk Factors
- Treatment with radiation therapy, an alkylating agent, and/or a topoisomerase II inhibitor
- History of hereditary retinoblastoma (unilateral with a positive family history or bilateral)
- Carrier of ataxia-telangiectasia
- Postsurgical chronic lymphedema
- Ureterosigmoidostomy
- Estrogen treatment

History
- Pain in any previously irradiated area
- Bruising
- Gum bleeding
- Pallor
- Easy fatigability
- Breast lump
- Cough
- Chest pain
- Hemoptysis
- Blood in stool
- Constipation
- Tenesmus
- Hematuria
- Increased urinary frequency/incontinence
- Difficulty voiding
- Intermenstrual bleeding

Physical Examination
- Pallor
- Petechiae
- Chronic skin ulceration
- Presence of lump (mobility, tenderness, consistency)
- Asymmetric breath sounds
- Nodule in prostate
- Abnormal uterine cervix

Evaluation
- Plain radiographs of any painful area or mass in a previously irradiated area
- Stool examination for occult blood (any patient who received any abdominal irradiation)
- Pap smear
- Urine cytology (in any patient with hematuria and a history of bladder irradiation and/or treatment with a cyclophosphamide or ifosfamide)
- Mammogram
- Additional tests as indicated by the history and physical examination

At the clinical level, carriers of the ataxia-telangiectasia gene (ATM) are more likely to develop cancer; Swift and colleagues estimate a 3 to 4 excess relative risk of cancer in male and female carriers.[81] Female breast cancer was the most frequent cancer reported (excess risk of about 5) and was more likely to occur in those exposed to ionizing radiation. Little and coworkers compared the relative risks of developing post-therapeutic irradiation SMNs to those among Japanese survivors of the atomic bomb blasts.[82] They found the relative risks of developing leukemia or lung, bone, or ovarian cancer to be higher among the Japanese survivors than among treated patients. Neither chemotherapy nor underlying genetic factors seemed to play a role in their results.

The cytogenetics of SMNs have been the subject of intensive investigation. Le Beau and associates described characteristic abnormalities of chromosome 5(del (5q)) and 7(del (7q)) in patients with treatment-associated acute myeloid leukemia.[83] (The terms *acute myeloid leukemia* [AML] and *acute nonlymphoblastic leukemia* will be used interchangeably in this discussion. In most cases, the term that is used will be the one employed by the authorities being cited.) Detourmignies and colleagues found t(15;17) in treatment-associated acute promyelocytic leukemia (t-APL) and the other forms of acute myeloid leukemia (t-AML), the same translocation as is found in those diseases de novo.[84] In addition, t(8;21), t(9;11) and inv[16] were found in t-APL and other t-AMLs. They tend to arise in patients with solid tumors, have short latent periods, and are associated with prior therapy with drugs that inhibit topoisomerase II. Cytogenetic evaluations of solid SMNs have demonstrated chromosome 22 deletions in meningiomas and deletions in chromosomes 10 and 17 in malignant astrocytomas.[85,86] These cytogenetic findings could have important implications regarding early identification and early treatment of SMNs.

Treatment Factors

Surgery

In adults, perhaps the most common SMN ascribed to surgery is angiosarcoma in a lymphedematous structure (Stewart-Treves syndrome), a complication that has been described most often after radical mastectomy.[87] The tumors tend to arise in the edematous arm rather than in irradiated areas.[88] Marchal and coworkers conducted a survey of breast angiosarcomas that develop in women who were treated with breast-conserving techniques.[89] They found 9 cases among almost 20,000 women but found no conclusive evidence linking therapy as a causative factor.

Radiation Therapy

Lindsay and colleagues have reviewed the factors involved in radiation carcinogenesis.[90] Breast, thyroid, bone, soft tissues, and organs and tissues that are prone to develop SMNs after RT given in childhood are also vulnerable to radiation oncogenesis when treatment is given during the adult years (Fig. 66-7). The dose-response relationship has classically been described as bell-shaped: an initial increase with low and moderate radiation doses to a peak followed by a rapid decrease at higher doses due to killing of the vulnerable cells. The observed rate for second cancers after radiation of Hodgkin's disease has been higher than predicted, and Sachs and Brenner proposed a model using normal cell repopulation to account for high cancer rates after higher radiation doses.[91] Precise RT dose-response relationships remain murky, in part owing to limited data about the true RT doses at observed SMN sites.

LYMPHOMA. Survivors of Hodgkin's disease are at increased risk for a variety of cancers, especially lung, colorectal, and breast cancer, all of which were more common in those who were treated with chemotherapy and radiation.[92] In fact, a leading cause of death among long-term survivors of HD is second cancer. Treatment of HD has served as a model for therapeutic radiation-induced carcinogenesis,

especially the risk for breast cancer.[91,93,94] Wendland and colleagues studied secondary breast cancers in 8036 females with HD from Surveillance, Epidemiology and End Results (SEER) registries. Second breast cancers were seen in 2.3%, and the standardized incidence ratio was 1.9 for women treated with RT.[94] Interestingly, the breast cancer-free survival curves crossed for irradiated and nonirradiated patients. There was a paucity of early breast cancers in the radiated group, but an increased incidence over time. This was modeled best with a nested proportional hazard model, possibly owing to a therapeutic effect on pre-existing tumors combined with induction of latent tumors. Travis and colleagues[93] studied 3817 female 1-year survivors of HD and noted an age- and dose-dependent cumulative risk of breast cancer development that was lower in patients who were treated with alkylating agents. In their model, women who were treated at age 25 would have an estimated cumulative absolute risk of breast cancer of 1.4% by age 35, 11% by age 45, and 29% by age 55. Projections from these studies should be taken with caution, however, owing to decreases in the dose and volume radiated in the modern era.

A SEER study of 77,876 patients with NHL showed that irradiated patients had a similar risk of SMNs compared with unirradiated patients (relative risk: 1.04).[95] The SMN types differed, with more sarcomas, breast cancers, and mesotheliomas occurring in irradiated patients. Younger patients had an increased relative risk for SMNs, which was more pronounced in irradiated patients.

BONE AND SOFT TISSUE. The largest follow-up study of second cancers in patients with soft-tissue sarcoma primaries (N = 6,671) comes from the Swedish Family-Cancer Database, which identified 650 second cancers (9.7%).[96] The median time to second cancer was 7 years, and the standardized incidence ratio was 1.42 (95% CI: 1.31 to 1.53). The most common second cancer was another soft-tissue sarcoma. Although 10 of 39 were at the same primary site, the majority occurred at different anatomic sites. A weakness of this database is the lack of treatment information, so Ji and colleagues did a reverse analysis, which showed an increased rate of second soft-tissue sarcomas after any primary tumor as well (1.92, 95% CI: 1.78 to 2.07).[96] This suggests that factors other than treatment, such as genetic predisposition and environmental risk, also play an important role.

Lagrange and coworkers reported 80 radiation-associated sarcoma cases collected by a consortium of French cancer centers.[97] The median dose of RT was 50 Gy (range: 9 to 110 Gy) delivered to adults (median age: 44 years) for a variety of primary diagnoses. Of the histologically proven secondary sarcomas, 70% were bone and 30% were soft-tissue sarcomas, osteosarcomas and malignant fibrous histiocytomas predominating among them. Unlike the earlier study by Tountas and colleagues,[98] these authors could not demonstrate a correlation with increasing dose. The outcomes were poor despite aggressive treatment based largely on surgical maneuvers.

HEAD AND NECK. In the head and neck, second primary tumors are commonly observed as a result of premalignant field changes due to environmental risk factors, such as tobacco. A multicentric, case-control study of laryngeal and hypopharyngeal cancers showed an average second cancer rate of 2.1% per year. A higher risk was associated with tobacco, alcohol, and butter consumption, whereas citrus fruit consumption was protective.[99] An attempt has been made to prevent second cancers with antioxidant therapy in a randomized, placebo-controlled trial.[100] Unfortunately, α-tocopherol did not lower the overall recurrence/second cancer rate and actually increased the rate in the first 3.5 years.

In an analysis of 326 consecutive patients with nasopharyngeal carcinoma who were treated with definitive RT, 5.2% developed second primary cancers at a rate of 1% per year.[101] Only about one third of these were in-field, and there was not an association with the total prescribed dose. The only second tumors that occurred after 5 years were within the radiation field, supporting the concept of a lag time for radiation-induced solid cancers.

GYNECOLOGIC. Storm reviewed the frequency of SMNs in a cohort of 24,970 Danish women with invasive cervical cancer and 19,470 who had carcinoma in situ followed for 30 or more years.[102] Taken together, there was an increased relative risk of 1.9 in irradiated patients who survived 30 or more years, representing an excess of 64 cases per 10,000 women annually (see Fig. 66-7). Werner-Wasik and coworkers analyzed the frequency and patterns of SMNs in women with cervical cancer and came to a different conclusion.[103] They found 11 SMNs among 10 of the 125 women with FIGO stage I and II cervical carcinoma who received RT in a recent 10-year period (1980 to 1990). All of the SMNs were outside the fields of irradiation, and none of the women had received chemotherapy. The researchers concluded that the increased relative risk of a SMN might be genetically based, as the administered treatments did not appear to be factors. The Werner-Wasik report again emphasizes the need to consider the multiple possible contributing factors to oncogenesis (see Fig. 66-7).

Sturgeon and associates found an excess of SMNs among women with vulvar or vaginal cancers.[104] Most of the SMNs were smoking-related (lung, upper airways) or in patients infected with the human papillomavirus, which is known to be associated with cancers of the genital tract. A related observation by Hemminki and Dong is of interest; they found an increase in anal cancers in both women with cervical cancer and their husbands, implicating human papillomavirus in the etiology of anal cancer.[105]

Hall and colleagues found an increased risk of ovarian cancer as a SMN in certain sets of women.[106] These were women younger than 50 years of age with melanoma or cancer of the colon, breast, cervix, uterine corpus, or ovary. The relative risks ranged from about 5 to almost 20.

Bergfeldt and coworkers could not substantiate a reputed increase in breast cancers among women with ovarian cancer.[107] Their case-control study from a pool of 5060 Swedish women led them to conclude that increased surveillance (mammography) of surviving patients with ovarian cancer was not warranted. Travis and associates likewise attributed secondary breast cancers to factors other than therapy, although they attribute soft-tissue, bladder, and rectal malignancies to RT and leukemia to chemotherapy.[108]

Buiatti and colleagues reported a population-based study of second primary cancers.[109] They considered only the 463 metachronous SMNs that developed among the 19,252 adults with primary cancers of the colon, rectum, lung, stomach, and female breast who constituted the study population. Significantly higher risks of developing another cancer were found in patients under 65 years of age. Associations of three types were found:

1. Between primary rectal and secondary kidney cancers
2. Between colon and later ovarian malignancies
3. Between female breast and subsequent rectal cancers, although cancer in the opposite breast constituted the highest risk in this group

No correlations were made between the treatments that were used for the primary tumor and the secondary cancer. This report, together with that of Werner-Wasik and associates,[103] highlights the fact that SMNs should not all be assumed to have an iatrogenic basis.

GENITOURINARY TRACT. The incidence of second neoplasms resulting from RT for prostate cancer is controversial. Movsas and associates found no increase in the risk of SMN among 543 of their patients when compared with a matched set of 18,135 men derived from the Connecticut Tumor Registry.[110] Most of the SMNs developed outside the RT fields and were associated with lifestyles that were predisposing to cancer. Johnstone and colleagues also found no definite increase.[111] Groups using the SEER database have found

conflicting results.[112–115] In comparison to patients who were treated only with surgery, there was a small but significantly increased risk of in-field tumors, especially bladder and rectal cancers, following RT.[112,113] However Moon and colleagues also found an increased risk of second cancers outside the field and in men who were treated with transurethral resection of prostate alone.[115] These results suggest the researchers did not adjust for all relevant factors. In fact, when Cox modeling was used and adjusted for attained age, no significant excess risk from RT was found.[114,116]

SMNs occurring in men with testicular cancers have been studied by several investigators. Wanderas and associates found an increased risk of second germ cell cancer, usually of the same histology, among 2201 patients, the risk being highest among men younger than 30 years of age at first diagnosis.[117] More SMNs than expected were found by Ruther and colleagues in their multicenter collection of men with pure seminomas.[118] These included both nontesticular and testicular SMNs. Other researchers, who have studied larger numbers of patients, have documented increased relative risks for gonadal and nongonadal carcinomas of 1.2 to 2.3. Higher risks were recorded for leukemia (relative risk: 2.4) and soft-tissue sarcomas (relative risk: 3.0).[119] The SMNs tended to develop in irradiated fields.

Travis and coworkers showed that men who were treated for testicular cancer had a persistent increased risk of second cancers (relative risk: 1.9) in a large cohort study of 40,576 survivors.[120] SMNs of the lung, colon, bladder, pancreas, and stomach accounted for almost 60% of the excess cancers. The risks of cancer 40 years after treatment were 36% for seminomas and 31% for nonseminomas compared to 23% for the general population to age 75. Richiardi and associates also found an elevated risk of second cancers with a standardized incidence ratio of 1.65 compared to population controls in a cohort of 29,511 patients with testicular cancer.[121] Interestingly, they found a markedly increased risk of myeloid leukemia, especially in nonseminomas that were diagnosed after 1990 (standardized incidence ratio: 38). The elevated risk in these patients could be due not only to genetic and environmental factors, but also to outdated RT techniques in which extended fields were used even for early-stage disease.[122]

BREAST CANCER. After a diagnosis of breast cancer, the risk of second cancers is increased in general in comparison to population controls. A study of 335,191 women with either invasive or noninvasive breast cancer revealed a second primary rate of 12% for women who were diagnosed before age 50 and 17% for women who were diagnosed over age 50.[123] Noteworthy is the fact that the standardized incidence ratios for second cancers actually decreased with age, suggesting that genetic mechanisms play a role. The patterns of second cancers, namely, second breast, bone, colorectal, sarcoma, leukemia, lung, ovarian and thyroid cancer, have a shared pattern of risks with BRCA1, BRCA2, p53, and PTEN mutations.[123] In a study of 491 female carriers of either BRCA1 or BRCA2 mutations, the risk of contralateral breast cancer was 29.5% at 10 years, with BRCA1 carrying a higher hazard than BRCA2.[124] Studies of second malignancies after male breast cancer have similarly shown increased rates compared to population controls, especially breast, gastrointestinal, and prostate cancers, but unlike female breast cancer, the risks increased over time.[125,126]

In women who had been treated uniformly with wide local excision, axillary dissection, and postoperative irradiation, the cumulative 10-year SMN rate was 16% in the 1253 women who were reviewed, about half of whom had second breast malignancies.[127] A 20-year analysis of 1801 similarly treated women showed a contralateral breast cancer rate of 15.4%, the majority (83%) of which were the invasive type.[128]

The contralateral breast does receive some radiation dose during breast RT. It is in the range that is known to be carcinogenic, especially in young women.[129] A case-control study of 41,109 women with breast cancer showed an attributable contralateral breast cancer risk of only 2.7% from prior irradiation.[130] Some of the more important variables that were considered in the analyses are shown in Table 66-1. An increase in relative risk was observed in irradiated women surviving 10 or more years, but only in those who had been treated when under 45 years of age (relative risk: 1.85). The risk among this sample increased with increasing RT dose, the analyzed range extending from 1.99 Gy to 4 Gy, and the relative risks from 1.54 to 2.35, respectively ($P = 0.003$).

The use of adjuvant RT appears to increase the risk of both contralateral breast and other cancers (skin, lung, colon, and esophagus) in some,[131–134] but not all studies.[135] Additional evidence for an increased risk of esophageal cancer after breast cancer has been found in population-based studies.[136,137] This may be attributable to the radiation field that was used to include the internal mammary nodes. Although the absolute risk from RT of breast cancer is small, the doses to the contralateral breast and mediastinum can and should be reduced by using modern RT techniques.

NERVOUS SYSTEM. Jones conducted an extensive retrospective analysis of brain tumors occurring in patients after RT for pituitary lesions, a unique group that receives relatively high doses of RT for nonmalignant lesions.[138] He concluded that the risk of RT oncogenesis in adults is low after small-field RT in the doses usually used for the control of pituitary disorders. When both irradiated and unirradiated adults with pituitary tumors who developed regional fibrosarcomas, gliomas, and meningiomas were compared, the role of therapeutic RT in the genesis of such SMNs became questionable. Erfurth and associates not only find no clear evidence implicating RT, but also again raise the possibility that underlying genetic factors are responsible.[139]

LEUKEMIA. The risk of secondary leukemia is greatest within the first several years after radiation, whereas the risk for solid tumors generally becomes evident thereafter. Although relatively rare, an excess absolute risk of AML was detected in patients who have been treated for HD.[140] The excess risk was greatest in the first 10 years after treatment and subsequently remained elevated. In cervical cancer patients, Storm described a significantly increased relative risk of acute nonlymphoblastic leukemia (relative risk: 3.5), manifest in the early postirradiation years but not of chronic lymphoblastic leukemia (CLL).[102] The relative risk decreased by the 10th year after diagnosis, and the incidence approximated that of the general population by the 15th year after diagnosis. This was unlike the experience with solid tumors, in which relative risks continued to increase with time.

Table 66-1 Relative Risk of Contralateral Breast Cancer after Radiation Therapy

Age at Treatment (10-Year Survivors)	No. Exposed	Total No.	Relative Risk (95% Confidence Interval)
<45 yrs old	45	143	1.85 (1.15–2.97)
>45 yrs old	55	298	1.08 (0.74–1.57)

Data from Boice JD, Harvey EB, Blettren M, et al: Cancer in the contralateral breast after radiotherapy for breast cancer. N Engl J Med 1992;326:781.

Intensity-Modulated Radiotherapy and Proton Radiotherapy

Technological advancements in RT over the past several decades have led to safer, more tolerable treatment. Intensity-modulated radiotherapy (IMRT) has been popularized in recent years owing to the ability to shape the irradiated volume in three dimensions. This permits both a limitation of doses to adjacent normal structures and an increase in the dose to critical diseased sites that need a boost, allowing for dose escalation opportunities. A disadvantage of IMRT is higher integral body doses, resulting both from the spreading of a low dose to a greater volume and from longer treatment times with the attendant increase in incidental irradiation due to machine head leakage. Higher integral doses have led to concerns about a possible increased risk of fatal SMNs; indeed, these have been calculated to be 1.7% for conventional treatment compared to 2.1% for IMRT.[141] These worries were echoed by Hall, who also pointed out a potentially increased risk of SMNs from proton RT due to neutron contamination of the proton beam.[142] Proton RT has the advantage of no exit dose, but the most common method of proton field generation, passive scattering, is associated with a higher level of neutron contamination. Active scanning proton RT has less neutron contamination than passive scattering and is predicted to deliver a lower integral dose than photon IMRT. Hall's neutron contamination calculations and SMN risk for passive scattering proton RT were widely criticized as being based on outdated equipment.[143] The point still stands, however, that active scanning proton RT may provide the best conformality with the lowest risk of SMNs, despite a very high price tag.[144]

Radionuclide Therapy

Unlike external beam RT that is aimed to a particular site, radionuclide therapy is delivered intravenously and any localization is a result of specific affinities. Although the use of radioimmunotherapy for lymphoma with radiolabeled anti-CD20 antibodies is on the rise, the most experience with radionuclide therapy has been with I-131 for thyroid cancer. In a pooled European cohort of patient with primary thyroid cancers, patients who were treated with I-131 were found to have an increased incidence of bone, soft-tissue, colorectal, and salivary gland cancers.[145] A multinational record linkage study of 39,002 patients with primary thyroid cancer demonstrated an increased risk of second cancers both after and before treatment for the thyroid cancers.[146] A similar observation was seen in both the SEER database and a cohort from Leiden University Medical Center, indicating that common genetic and environmental risk factors are probably more important than I-131 causation.[147,148]

Chemotherapy

LEUKEMIA–LYMPHOMA. Most of the SMNs reported after chemotherapy have been AML or NHL. The alkylating agents were the first to be implicated in the etiology of these SMNs and remain the most frequently implicated agents.[149,150] Subsequently, the leukemogenicity of the nitrosoureas was recognized.[151] Greene and colleagues estimated the increased relative risk of AML in patients with brain tumors who had been given carmustine to be about 25.[152] More recently, other agents have been associated with AML. These include the epipodophyllotoxins, the platinum compounds, and their combinations.[25,153]

AML that developed in women with ovarian cancer who had been given alkylating agents was one of the first iatrogenic chemotherapy-related SMNs to be reported in convincing numbers.[150] The relative risk reported by Reimer and associates was more than 170 for women who received alkylating agents compared with those who did not. That estimate was updated by Greene and colleagues, who found a relative risk of 110 and the excess risk of acute nonlymphoblastic leukemia to be 5.8 cases per 1000 women per year.[154] Melphalan and chlorambucil were the two agents that were most strongly implicated (relative risks of 122 and 159, respectively), the risk of leukemia being dose-related.

Kaldor and coworkers published an international case-control study in 1990 of women with ovarian cancer and reported increased risks of leukemia in those who had received cyclophosphamide, chlorambucil, melphalan, thiotepa, or dihydroxybusulfan (treosulfan) as single agents.[155] The relative risks, which increased with larger administered doses, ranged from 2.2 for low-dose cyclophosphamide to 23.0 for chlorambucil and melphalan and 33.0 for treosulfan in high doses as defined by the researchers. The risk estimates were relative to those of women who received only RT or surgery, no increased leukemia risk being identified in patients who had RT alone. The risk of leukemia was also increased in patients who were treated with the combination of doxorubicin and cisplatin. Kaldor and coworkers concluded that at least one of the two drugs was leukemogenic.[155] The controversies that are engendered by large-scale studies of this kind are reflected in the editorial that accompanied the article and the brisk correspondence that followed.[156,157]

Travis and associates underscore these issues by their findings regarding the 4402 10-year survivors among the 32,251 women with ovarian cancer on whom they collected data.[108] They found 1296 SMNs rather than the expected 1014 in such a cohort, the cumulative risk at 20 years of follow-up being 18.2% versus the 11.5% expected in the general population. Although leukemias appeared to be related to chemotherapy and cancers in infradiaphragmatic sites appeared to be related to RT, there were also increased risks of tumors in other sites—for example, breast cancer and ocular melanoma—that are not obviously related to the treatments that were used. Travis and associates therefore postulated genetic or other factors that predispose to ovarian cancer as being responsible.[108] In this way, they echo the surmises of Werner-Wasik and colleagues concerning the genetic bases of SMNs that develop in women with cervical cancer.[103]

Fisher and coworkers reviewed the extensive experience that had accumulated in women who were treated for breast cancer following the protocols of the National Surgical Adjuvant Breast and Bowel Project (NSABP).[158] Using data from the SEER registry for comparison, they reported a relative risk of 24.0 for AML among all patients who were treated with surgery and chemotherapy. The risk was found to be 39.3 among patients under 50 years of age compared with a relative risk of 19.9 among those age 50 or older. The relative risks of AML were 2.6 among all women who were treated with surgery only and 10.3 among those who were treated with surgery and RT. These data confirm the leukemogenicity of melphalan, the alkylating agent that was employed in the chemotherapy trials conducted by the NSABP.[155] Curtis and associates reported the relative risks for acute nonlymphoblastic leukemia or myelodysplastic syndrome of 10.0 and 17.4 among unirradiated and irradiated patients with breast cancer, respectively, who were treated with an alkylating agent.[159]

Greene reviewed the evidence concerning the carcinogenicity of cisplatin in animals and humans and provided a concise survey of the oncogenic potential of other chemotherapeutic agents that are in common use in adults with cancer.[153] He pointed out that cisplatin has many of the properties of an oncogene and is carcinogenic in animal systems, where its effects can be reversed by MESNA (2-mercaptoethane-sulfonate). The evidence implicating cisplatin as a leukemogene in humans is found in situations in which it has been used together with etoposide or doxorubicin. It is not clear whether cisplatin is a cofactor in leukemogenesis when used with other drugs or whether these other drugs, rather than cisplatin, are responsible.

AML, usually of French-American-British M5 morphology, which has a characteristic translocation that involves 11q23, has been detected in patients who were given topoisomerase II inhibitors.[160,161] The anthracyclines, epipodophyllotoxins, and dactinomycin are such inhibitors.[161] Detourmignies and colleagues implicated inhibitors of topoisomerase II in their report of therapy-associated acute promyelocytic leukemia (t-APL).[84] They pointed out that the same translo-

cation, t(15;17), can be identified in both de novo and treatment-related acute promyelocytic leukemias that develop after therapy with drugs of this class.

van Leeuwen provided an extensive analysis of AML and myelodysplasia that developed after cancer treatments of various kinds and at different ages.[162] In general, the findings authoritatively confirm the observations of others in that chemotherapy was found to be more leukemogenic than was irradiation, and the latent periods for the appearance of nonlymphatic leukemias after therapy with topoisomerase II inhibitors and with alkylating agents tended to be short (<5 years) and long (5 to 10 years), respectively. There has been a recent report of a 23-year interval between treatment of HD and the appearance of secondary erythroleukemia. This was attributed to the alkylating agents that were used as part of the HD therapy.[163] van Leeuwen's detailed analyses by original tumor type, treatments employed, and age factors are worthy of careful reading by students of this problem.[162]

SOLID TUMORS. Solid tumors are not often associated with anticancer drugs. Greene listed four breast carcinomas among the few solid tumors that appeared in cisplatin-treated women without there being a convincing causative relationship.[153] A dose-effect relationship between alkylating agent treatment and the occurrence of secondary bone sarcomas was identified in children, and there have been several reports of urothelial carcinomas in adults who were treated with cyclophosphamide.[164] Although the data of Fairchild and coworkers[165] and others[166] suggested that cyclophosphamide was not a significant etiologic factor for bladder cancer, Travis and associates reported a relative risk of 4.5 of bladder cancer among patients with NHL who were treated with cyclophosphamide.[167] The relative risk increased with increasing cumulative dose, being 6.3 for cumulative doses of 20 to 49 g and 14.5 for cumulative doses of 50 g or more. Topical nitrogen mustard has been held responsible for the appearance of skin cancers in patients with mycosis fungoides treated in that way.[168]

HODGKIN'S DISEASE. There is a voluminous literature concerning the leukemias, NHLs, and solid tumors that are encountered in adults with HD, often with conflicting reports. The major focus here will be placed on two recent comprehensive analyses of the solid tumor and leukemia risks.[169,170]

Dores and colleagues assessed the relative and absolute excess risks of site-specific SMNs in long-term HD survivors.[169] They analyzed data from 32,591 HD patients, including 1111 25-year survivors, and found 1726 solid tumors among those patients. Cancers of the lung, gastrointestinal tract, and female breast were the most frequently observed. The actuarial SMN rate among 25-year survivors was approximately 20%, the risk being about the same in all age groups. Of interest was an apparent decrease in SMN risk after the 25th year of survival. Brusamolino and coworkers reviewed the leukemia risk in HD survivors.[170] Their 1659-patient sample was analyzed according to age, splenectomy, combined modality therapy, and cumulative drug doses, especially of alkylating agents, including nitrosourea derivatives. The overall actuarial risk of leukemia at 15 years was 4.2%, with two peaks. These occurred at 3 and 8 years after initiation of therapy, and the curve flattened at 12 years. The risks after RT alone, chemotherapy alone, and combined modality treatments were 0.3%, 2.8%, and 5.4%, respectively. Risks were higher among patients who had received extended field RT, lomustine, or mechlorethamine. Neither age nor splenectomy proved to be a significant independent variable. No leukemias were found in patients who were treated with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine).

SECONDARY NON-HODGKIN'S LYMPHOMA. The cumulative incidence rate of secondary NHL among HD patients increased during the first 5 years after treatment before reaching a plateau. These findings were not correlated with any specific treatment or combinations of therapies. Swerdlow and colleagues[171] suggest that immunosuppression could be a contributing factor to the occurrence of secondary NHL in HD patients, most if not all of whom have long been known to be immunologically impaired at diagnosis.[172]

Immunosuppression

Immunosuppressive drugs and the human immunodeficiency virus have been linked to lymphomas and other tumors.[173,174] Kinlen and associates were among the first to conduct a systematic study of cancers appearing in patients who had been given immunosuppressants.[173] In 1979, they reported an increase in the risk of NHL (especially in the brain) in renal transplant recipients (relative risk: 58.6). A large study of SMNs in patients with either primary or secondary NHL showed bidirectional effects with several potentially virally linked cancer sites, suggesting a role for immune suppression. Bone marrow transplantation entailing iatrogenic immunosuppression has also been linked to SMNs.[175–177] Curtis and colleagues[175] reported that bone marrow transplant survivors are at risk of developing solid tumors with the passage of time. Their analyses were based on 20,000 bone marrow transplant recipients; many different types of SMNs were encountered, including brain and thyroid tumors. These developed only in patients who had been given brain and total body irradiation. The highest risk was in young children (<10 years of age). In contrast, a smaller cohort of 926 patients with long follow-up showed that recipients over 40 years of age and those with female donors were at higher risk of SMNs, and there was no impact from total body irradiation.[176]

Hosing and associates discussed the risks of myelodysplastic syndrome and acute myelogenous leukemia (AML) after therapy.[178] They studied almost 500 patients with NHL who received high-dose chemotherapy and autologous stem cell transplantation and found 22 patients with myelodysplastic syndrome or AML. The risk was highest among patients who received total body irradiation together with cyclophosphamide and etoposide.

Prolonged immunosuppression is associated with the appearance of skin cancers. Liddington and coworkers reported cutaneous carcinomas (mostly of the squamous cell type) in renal transplant patients and estimated the increase in risk to be approximately 100-fold.[179]

Hormones

Hormones and hormonal manipulations have been held responsible for oncogenesis. Various second tumors have been reported in men with prostatic cancer who were treated with estrogens. These include breast cancers, hepatomas, and desmoids.[180–182] In women, the use of oral contraceptives that emphasize the estrogenic component has been held responsible for the subsequent appearance of endometrial cancer. Thus, female patients with cancer who are managed by hormonal manipulations or women who use hormone-based contraceptives may be at an increased cancer risk.[183]

Recommendations and Conclusions

The recommendations that were made previously for children apply equally to adults, suitably modified for the age group. In adults particularly, for whom the prognosis often is worse than that for children, the potential risk of a second malignant process should not lead to therapeutic compromises when treatment, often aggressive, is of known benefit. Further SMN research must take into fuller account possible contributory genetic, immunologic, environmental, and other factors beyond which drugs and what RT doses were used.

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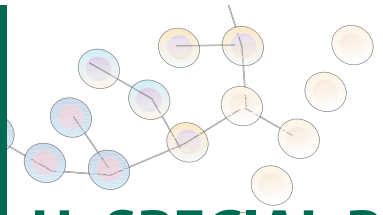
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H. SPECIAL POPULATIONS

67 Cancer in the Elderly: Biology, Prevention, and Treatment

Lodovico Balducci and Claudia Beghé

SUMMARY OF KEY POINTS

Incidence

- Cancer in the older person is increasingly common.
- Data on prevention and management of cancer in the older person are limited.

Epidemiology of Aging and Cancer

- The older population continues to expand as a result of reduced mortality and birth rates. Currently, 60% of all malignancies occur in persons aged 65 and older, and this proportion is expected to rise to 70% by the year 2030. Although cancer-related mortality is declining among younger persons, it is increasing among the oldest ones.
- Of special interest, cancer appears to affect mainly older persons who are otherwise healthy and would have lived longer were it not for the cancer.

Aging and Carcinogenesis

The association of cancer and age may be explained by three mechanisms that are not mutually exclusive:

1. Carcinogenesis is a time-consuming process, the end-product of which, cancer, is more likely to develop at an advanced age.
2. Aging is associated with molecular changes that mimic carcinogenesis; older cells are primed to the effects of environmental carcinogens.
3. Aging is associated with environmental phenomena such as immune senescence or proliferative senescence that favor the development of cancer.

Aging and Cancer Biology

The biology of common malignancies such as breast cancer, ovarian cancer, non-Hodgkin's lymphoma, and acute myelogenous leukemia (AML) may change with age. In some cases, the tumor may become more indolent, whereas in others, it becomes more aggressive. Two mechanisms underlie these changes:

1. The biology of the tumor cells (e.g., the prevalence of MDR1 in AML increases after age 60, associated with a worse prognosis).
2. The aging of the patient: An age-related increase in circulating concentrations of interleukin-6 (IL-6) may favor the growth of lymphomas, whereas hormonal senescence may inhibit the growth of breast cancer.

Assessment of the Older Person

- Aging involves a progressive shortening of life expectancy and reduction in the functional reserve of multiple organ systems.
- Personal and social resources to cope with stress may become more limited.
- Reduced life expectancy and reduced stress tolerance lessen the benefits and enhance the risks of medical intervention.
- A comprehensive geriatric assessment (CGA), evaluating the patient's function, comorbidity, cognition, nutrition, medications, and living resources, is a currently available, reliable instrument for predicting life expectancy and the risk of treatment-related complications.
- The CGA may unveil pre-existing situations or conditions such as undiagnosed disease, poor nutrition, depression, or lack of adequate social support that are remediable and may influence the outcome of treatment.
- A number of laboratory tests, including assays of circulating levels of IL-6 and D-dimer, and tests of physical performance may complement the CGA.

Cancer Prevention

- Older persons may be primary candidates for chemoprevention of cancer, but none of the current chemopreventive agents have demonstrated efficacy definitively.
- Screening asymptomatic patients for cancer of the breast and of the large bowel appears to be reasonable when the life expectancy is 5 years or longer.

Cancer Treatment

- *Surgery*: Age by itself, up to 100 years, does not appear to increase the surgical mortality rate, although the risk of surgical complications and length of postoperative hospitalization increase with age. Age is a definitive risk factor for death related to emergency surgery.
- *Radiation therapy*: Tolerance for radiation therapy seems to remain high, even for persons aged 80 and older.
- *Cytotoxic chemotherapy*: The main pharmacologic changes of age include decreased excretion of drugs and of their active metabolites from the kidneys; decreased volume of distribution of water-soluble drugs, which may in part be accounted for by anemia; increased susceptibility to myelodepression, mucositis, and peripheral and central neuropathy; and cardiomyopathy. The National Cancer Center Network (NCCN) has issued the following guidelines for the management of older cancer patients:
  1. Dose adjustment according to the individual patient's glomerular filtration rate (GFR), for persons aged 65 and older
  2. Prophylactic use of filgrastim or pegfilgrastim for patients aged 65 and older treated with combination chemotherapy of dose intensity comparable to that of the cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) regimen
  3. Maintenance of hemoglobin levels of 12 g/dL or greater

INTRODUCTION

The progressive aging of the population is an epidemiologic hallmark of our times. People 65 years of age and older represented 12% of the U.S. population in 1990; the percentage in this age group is expected to grow to 20% by 2030.[1] The segment of the older population undergoing the most rapid growth is that older than 85, the so-called oldest old.

Aging is the most important risk factor for cancer. The incidence of common malignancies increases with age—in fact, currently more than 60% of all neoplasms occur in persons aged 65 and older[2] (Fig. 67-1), and this proportion is expected to increase to 70% by 2030. Today, cancer is the main cause of death among persons up to the age of 85.[2] Clearly, improved cancer control involves effective management of cancer in older adults.

This chapter explores the association between cancer and aging, the influence of aging on cancer biology, and prevention and treatment of cancer in older persons, after reviewing the biologic and clinical aspects of aging. This information is presented as a frame of reference allowing the practitioner to estimate risks and benefits of preventive and therapeutic interventions in each patient.

BIOLOGY OF AGING

Molecular and Cellular Biology

Cellular aging observed in vitro (in the culture plate or test tube) is associated with a number of molecular events, of which some may favor and others may inhibit the development of cancer. Formation of DNA adducts, DNA hypermethylation, and point mutation[3] mimic the early stages of carcinogenesis, are associated with activation of oncogenes and inhibition of antiproliferative genes, and may prime the aging cell to the effects of environmental carcinogens, which explains, in part, the association between cancer and age. Other changes, including a progressive reduction in telomere length and telomerase activity[4] and activation of the *P14* antiproliferative gene, encoding the CDK16 inhibitor, are contrary to those observed in neoplastic cells.[5] Of special interest are age-related abnormalities in protein synthesis, with reduced activity of DNA-repairing and drug-metabolizing enzymes, which may both accelerate carcinogenesis and enhance the complications of cytotoxic chemotherapy in normal tissues.[6]

Paradoxically, proliferative senescence may enhance the risk of cancer, because the senescent cells lose the ability not only to replicate

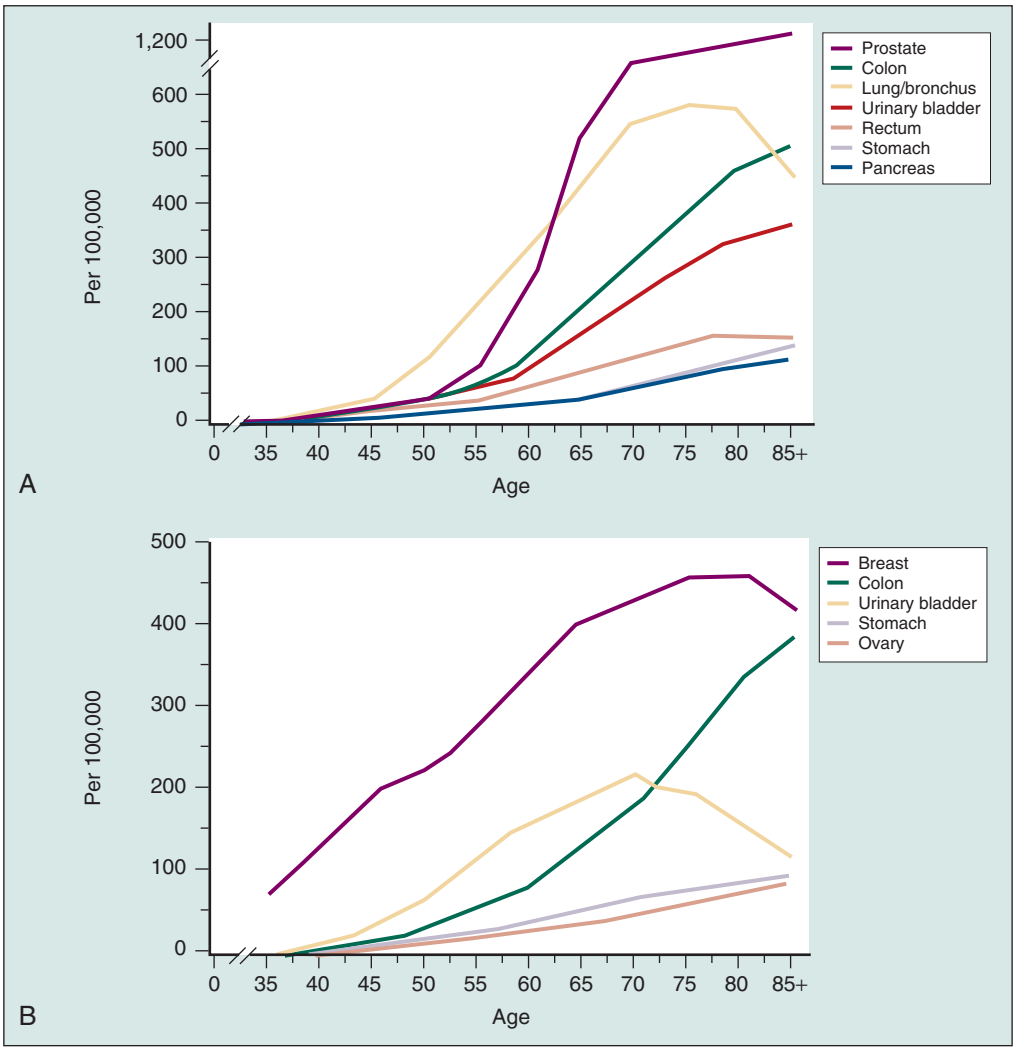


Figure 67-1 • Incidence of different neoplasms with age. **A,** Men. **B,** Women.

themselves but also to undergo apoptosis—thereby acquiring immortality and its inherent risks.[7,8] Proliferative senescence also is associated with the production of tumor growth factors and of proteolytic enzymes that may favor metastatic spread.[7,8]

Physiology of Aging

Aging involves a progressive reduction in the functional reserve of multiple organ systems, with reduced tolerance of stress, including cancer and cancer treatment. The mechanisms may include increased prevalence of chronic diseases[9]; progressive accumulation of catabolic cytokines, including the interleukins IL-6 and IL-10 and tumor necrosis factor in the circulation[10]; and reduction in the stem cell reserve of different tissues.[11] Catabolic cytokines appear to be pivotal in physiologic aging: Their accumulation is associated with increased prevalence of geriatric syndromes,[12] increased risk of mortality and functional decline,[11] and a generalized catabolic status.[13]

From the standpoint of cancer treatment, the most significant changes include gastrointestinal, renal, hepatic, hematopoietic, and mucosal changes, which may alter the pharmacokinetics of antineoplastic agents and may increase the risk of complications from cancer treatment.

BIOLOGIC INTERACTIONS OF CANCER AND AGING

Aging may affect tumor biology at two levels: carcinogenesis and tumor growth.

Aging and Carcinogenesis

The association of aging with carcinogenesis may be explained by at least three mechanisms: duration of carcinogenesis, increased susceptibility of aging tissues to environmental carcinogens,[3] and changes in body environment, including proliferative senescence[7] and immune senescence.[14] Both experimental and epidemiologic findings support the theory that aging tissues are more susceptible to environmental carcinogens. Several murine tissues, including cutaneous, hepatic, lymphatic, and nervous tissues, have been found to be more likely to develop cancer after exposure to carcinogens if they are obtained from older animals.[3] In humans, the incidence of some cancers, such as nonmelanomatous skin cancer and prostate cancer, increases geometrically with age, suggesting enhanced carcinogenesis.[2] In addition, the incidence of some neoplasms, including non-Hodgkin's lymphomas,[15] anaplastic astrocytomas, and glioblastoma multiforme,[16] has increased several-fold among older adults during the past 30 years, suggesting that older persons may be more susceptible than younger ones to new environmental carcinogens. In the Italian city of Trieste, Barbone and coworkers found that the incidence of lung cancer after exposure to environmental pollutants increased in relation to the patient's age at the time of exposure.[17] The increased susceptibility of older people to environmental carcinogens indicates that primary cancer prevention, including elimination of environmental carcinogens and chemoprevention, may be particularly effective in this population. This is a new concept, directly opposed to common wisdom, which has held that preventive interventions are less efficacious for older persons.

Aging and Tumor Growth

Aging may influence tumor growth at two levels, the neoplastic cell itself and the host environment in which the tumor grows. It is reasonable to expect a concentration of more indolent tumors among older persons (Fig. 67-2), by a process of natural selection. This is certainly the case with breast cancer, because the prevalence of well-differentiated, hormone receptor-rich tumors increases with age.[18]

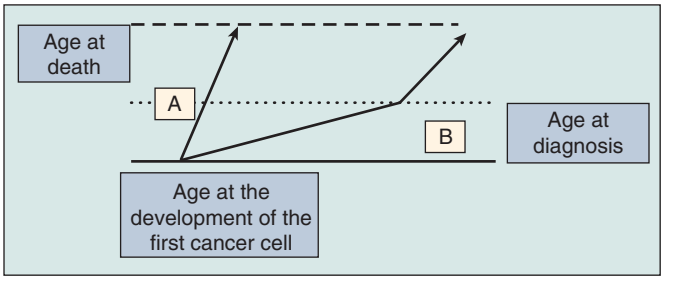


Figure 67-2 • The prevalence of more indolent tumors may increase with age for a process of natural selection. In this diagram, two persons start developing cancer, both at the age of 35 years. One cancer (A) is very aggressive and will manifest at age 37 and cause death at age 39. The other (B) is very indolent, will not manifest until age 65, and will not cause the patient's death until age 75. By a process of natural selection, by which the bearers of more aggressive tumors die earlier, a higher prevalence of indolent tumors can be expected among older persons.

The influence of the tumor host on cancer growth was demonstrated in a now-classic experiment by Ershler and coworkers, who demonstrated that the same loads of Lewis lung carcinoma and of B16 melanoma were associated with shorter survival and higher incidence of metastasis in younger animals than in older animals.[19] In successive studies, these investigators demonstrated that the tumor growth rate seemed to decrease for poorly immunogenic and increase for highly immunogenic tumors as the host age increased, highlighting the influence of immune senescence on tumor growth. In humans, Kurtz and colleagues demonstrated a reduction in the growth rate of primary breast cancer among older women, related directly to the degree of mononuclear cell reactions.[20] This observation suggested that immune senescence may mitigate tumor growth in poorly immunogenic tumors.

The clinical behavior of several human malignancies may change with the age of the patient.[21] Table 67-1 reveals that the biology of both the tumor cell and the tumor host may influence the change in prognosis. Another important observation is that in some instances, the prognosis becomes worse with age, in contrast with the generally held view. In any case, age by itself should not be considered a prognostic factor. If it is true that approximately 80% of breast cancers in women aged 70 and older are rich in hormone receptors, the converse also is true: 20% of cancers in women in this age group are not rich in hormone receptors, and appropriate treatment may require the use of cytotoxic chemotherapy. If MDR1 is present in 67% of patients older than 60 years with AML, it also is true that 33% of these patients have a disease responsive to chemotherapy and potentially curable. Each case should be treated on its own merits on the basis of an estimate of risks and benefits.

CLINICAL EVALUATION OF THE OLDER PATIENT

The benefit of cancer prevention and cancer treatment may be reduced and the risk enhanced in the older person, owing to a simultaneous reduction in life expectancy and in the tolerance of medical interventions. The basic questions of geriatric oncology include the following:

- Is the patient going to die with cancer or of cancer?
- Is the patient going to suffer the consequence of cancer during his or her lifetime?
- Is the patient able to tolerate cancer treatment?
- What are the long-term consequences of cancer and cancer treatment in older persons?

Table 67-1 Age and Changes in Cancer Prognosis

Neoplasm	Age-Related Changes in Prognosis	Mechanism(s)
Acute myelogenous leukemia[73]	Worse with age	Neoplastic cell
	Increased resistance to chemotherapy	Increased prevalence of MDR1-expressing cells
	Increased mortality during induction	Increased prevalence of stem cell leukemia
Non-Hodgkin's lymphoma[21]	Worse with age	Tumor host
	Decreased duration of complete remission	Increased circulating concentration of interleukin-6
Breast cancer[20]	More indolent disease	Neoplastic cell
		Increased prevalence of hormone receptor-rich, well-differentiated tumors
		Tumor host
		Decreased production of sex hormones
		Immune senescence
Celomic ovarian cancer[21]	Worse with age	Unknown
	Decreased remission duration	
	Decreased survival	
Non-small cell lung cancer[21]	Better prognosis with age	Unknown
	Presentation at an earlier stage	

The issue of long-term consequences has become highly relevant as the percentage of older cancer survivors has increased. For example, the Cancer Acute Leukemia Group B (CALGB) recently reported that the risk of adjuvant chemotherapy-related acute leukemia increases with age and may be as high as 1.7% for women 65 and older.[22]

The life expectancy and functional reserve of the older person may be estimated with a comprehensive geriatric assessment (CGA; Table 67-2) to determine the patient's level of functioning and to identify any coexisting medical conditions (e.g., comorbidity, geriatric syndromes, polypharmacy, malnutrition) and the social resources available to ensure compliance with and safety of cancer treatment.[23] In addition, the CGA may unearth unsuspected conditions that interfere with the treatment of cancer, including malnutrition, polypharmacy, cognitive and emotional disturbances, and inadequate social support.[23–25]

General Principles of Geriatric Assessment

In general geriatrics, the CGA has succeeded in reducing the rates of functional dependence and of admission to the hospital and to adult living facilities.[23,24] In geriatric oncology, the CGA may unearth conditions that may compromise cancer treatment. In a pilot study involving 15 women aged 70 and older with early breast cancer, the performance of the CGA resulted in, on average, an additional 17.2 interventions per patient.[26] Three studies exploring the effects of CGA in older cancer patients demonstrated some degree of functional dependence in approximately 70% of those patients; some degree of comorbidity in more than 70%; and dementia, malnutrition, and depression in approximately 20%.[27–29]

The CGA also helps the practitioner to make a gross estimate of the patient's life expectancy and expected tolerance of treatment. Life expectancy declines with the degree of functional dependence and also with the seriousness of comorbid conditions and geriatric syndromes.[30,31] One group of researchers have devised a "frailty index," based on functional deficit, comorbidity, and social support, from which they calculate the functional rather than chronologic age of each patient.[32] This instrument may become particularly useful for the classification of older patients with cancer enrolled in clinical theapy trials. Two studies demonstrated that the risk of chemotherapy-induced myelosuppression increased for patients who were dependent in some instrumental activities of daily living (IADLs).[33,34]

Thus, the CGA provides a common language for use in the classification of older patients undergoing cancer treatment or enrolled in clinical trials. A recurrent term that needs clarification is

Table 67-2 Comprehensive Geriatric Assessment and Clinical Implications

Assessment Component	Clinical Implication(s)
Functional status	
Activities of daily living (ADLs) and instrumental activities of daily living (IADLs)	Relation to life expectancy, functional dependence, and tolerance of stress
Comorbidity	
Number of comorbid conditions and comorbidity indices	Relation to life expectancy and tolerance of stress
Mental status	
Folstein Mini-Mental Status Examination	Relation to life expectancy and functional dependence
Emotional condition	
Geriatric Depression Scale (GDS)	Relation to life expectancy; may indicate motivation to receive treatment
Nutritional status	
Mini Nutritional Assessment (MNA)	Reversible condition; possible relationship to survival
Polypharmacy	Risk of drug interactions
Geriatric syndromes	
Delirium, dementia, depression, falls, incontinence, spontaneous bone fractures, neglect and abuse, failure to thrive, vertigo	Relation to survival and functional dependence

frailty, which commonly is associated with aging. At a recent consensus conference supported by the National Institute on Aging and the American Geriatrics Society, frailty was defined as a syndrome with multiple causes and involving multiple organ systems, characterized by increased vulnerability to stress and associated with sarcopenia, increased concentration of inflammatory cytokines in the circulation, and decreased motility and decreased ability to perform complex movements.[35] The conference recognized the existence of multiple signs of frailty and agreed to adopt for the time being the definition of the frail phenotype that emerged in the Cardiovascular Health Study (CHS).[36] On the basis of five parameters: weight loss of at least 10 pounds over 6 months, reduced energy levels, difficulty in initiating movements, reduced gait speed, and decreased strength of the hands, the CHS recognized three phenotypes with different life expectancy and risk of functional dependence. These phenotypes are (1) *fit*, with no abnormalities; (2) *pre-frail*, with one or two abnormalities; and (3) *frail*, with three or more abnormalities. It is worthy of emphasis that the definition of frailty will evolve with better insight in the biology of this syndrome. In the meantime, the CHS classification also may be helpful for classification of patients enrolled in clinical trials.

CLINICAL ASPECTS OF GERIATRIC ASSESSMENT

Function

Function is assessed on the basis of performance status (PS), activities of daily living (ADLs), and IADLs. The ADLs include transferring, bathing, dressing, eating, toileting, and continence; dependence in one or more of these functional areas, with the exception of continence, is associated with a 2-year mortality rate of approximately 40%.[23–25,37] The IADLs are those activities necessary to maintain an independent life, including use of transportation, shopping, and the ability to take medications, to provide one's own meals, to use the telephone, to manage personal finances, and to take care of laundry and housecleaning. Dependence in one or more IADLs (with the exceptions of laundry and housecleaning) is associated with a 2-year mortality rate of 16%[23–25,37] and a 50% risk of developing dementia within 2 years.[38] In addition, dependence in IADLs is associated with increased risk of neutropenia from cytotoxic chemotherapy.[33,34] In two prospective studies, functional dependence and PS appeared poorly correlated; consequently, it is recommended that they be evaluated independently.[27,28]

Comorbidity

Comorbidity is an independent cause of mortality for older patients with cancer[9] and may be associated with reduced tolerance of cancer treatment. The best way to assess comorbidity is still being investigated. Satariano and Ragland identified seven conditions associated with reduced life expectancy and demonstrated that the risk of mortality increased with the number of comorbid conditions.[39] Other investigators have devised comorbidity scales that take into account the degree of severity of each condition. Of these, the Cumulative Index of Related Symptoms–Geriatrics (CIRS-G) proved in some studies to be the most sensitive.[40] Another advantage of the CIRS-G is that its final score may be translated into the score of another scale in common use in epidemiologic studies, Charlson's scale.

Anemia is of special interest among the comorbid conditions[41] because its incidence and prevalence increase with age. Anemia is an independent risk factor for death and for myelosuppression from cytotoxic chemotherapy,[42] is a main cause of fatigue and functional dependence,[41] and may be associated with congestive heart failure and dementia.[41] An unsolved question is what level of hemoglobin defines anemia. Of special interest is the finding by the Women's Health and Aging Study that hemoglobin levels lower than 13.4 g/dL were an independent risk factor for death among 556 home-dwelling women aged 65 and older, evaluated on a prospective basis for a period of 8 years.[43] Similar findings were reported in the CHS.[44] In patients with cancer, anemia was associated with reduced survival and increased risk of functional dependence.[45]

Geriatric Syndromes

Geriatric syndromes include a number of conditions typical, if not specific, of aging, such as dementia, depression, delirium, incontinence, vertigo, falls, spontaneous bone fractures, failure to thrive, and neglect and abuse. Geriatric syndromes are associated with reduced life expectancy.[23–25] To be considered a geriatric syndrome, the condition must interfere with the affected person's daily life. Dementia must be moderate to severe; delirium must occur as a result of medications or organic diseases that do not commonly affect the central nervous system (e.g., urinary or upper respiratory infections); incontinence must be complete and irreversible; and falls must occur at least three times a month, or the fear of falling must prevent regular activities such as walking. Depression is of special interest because it is associated with decreased life expectancy, even when it is subclinical.[46] Depression also interferes with treatment compliance and in many cases may be fully reversible by medication. A simple 15-item questionnaire, the Geriatric Depression Scale 15 (GDS 15), speedily and reliably identifies persons with subclinical depression and is part of the CGA.[46]

Social Resources

Pivotal among the social resources ideally available to the older patient is the home caregiver. The ideal caregiver should be able to recognize and manage emergencies, to support the patient physically and emotionally, to mediate conflicts among family members, and to act as spokesperson for the family with the health care provider.[47] Under the best circumstances, the caregiver is the practitioner's best ally in ensuring compliance with treatment and smooth interactions with the patient. For this reason, it behooves the practitioner to participate in the selection, training, and support of the caregiver. In reality, the caregiver of an older person often is an older spouse with health problems of his or her own, or a married daughter who needs to balance her caregiving duties with other family and work responsibilities.

Nutrition

The prevalence of protein-calorie malnutrition increases with age. Isolation, depression, economic restriction, and reduced appreciation of hunger may all contribute to insufficient food intake, and chronic diseases and inflammatory cytokines may impede the synthesis of new proteins.[35] The Mini Nutritional Assessment (MNA) is a simple nutritional screening test used worldwide that identifies patients who are malnourished and those at risk of becoming malnourished, thereby permitting the prevention and early reversal of malnutrition.[48]

Polypharmacy

The prevalence of polypharmacy increases with age and, among cancer patients aged 70 and older, has been found to be as high as 41%.[23–25] The problem of polypharmacy exemplifies a common problem of elderly patients in developed countries: the absence of a primary care provider.[49] According to a recent study, more than 50% of people 70 years of age and older in the United States, Canada, and Israel, although attending multiple specialty clinics, lacked a primary care physician.

Other Forms of Geriatric Assessment

The CGA is the standard form of geriatric assessment, but it may be complemented by laboratory data and by so-called proofs of physical performance levels (Box 67-1).

Box 67-1. ASSESSMENT OF OLDER PERSONS: SCREENING TESTS

The comprehensive geriatric assessment (CGA) is time-consuming. A number of provisions that save office time may render its use more cost-effective. Proposed strategies include the following:

- Home assessment, in which questionnaires are mailed to the patient at home and completed before the office visit. The advantage is reduction of the visit time. Disadvantages include dependence on self-reported function and comorbidity, inability to self-assess cognition, and, in a significant proportion of patients, inability to complete the questionnaire.
- Administration of screening tests before the visit, with a more complete CGA then performed for patients for whom screening gives a positive result. The Vulnerable Elderly Survey 13 (VES 13), one of the best-validated screeing tests, can be completed in less than 1 minute. This is our favorite approach because it saves time and has been validated with functional and survival outcomes. Potential disadvantages include disagreement among clinicians on a cutoff score above which the result is considered positive and lack of a way to provide information about comorbidity, nutrition, cognition, and emotional disorders.
- Use of laboratory tests or physical performance tests to identify patients at risk for death and disability. This approach is promising but needs validation and should be considered at present to be in clinical trials.
- An additional issue is the age at which screening should begin. We have selected the age of 70 years, because previous studies have shown that the steepest increase in prevalence of age-related changes is seen between the ages of 70 and 75.

Laboratory Markers of Aging

The recognition that the concentration of catabolic cytokines in the circulation increases with age and usually is correlated with the presence of geriatric syndromes prompted a number of studies aimed at establishing whether these substances may predict functional dependence and decreased survival. In a recent study, Cohen and coworkers demonstrated that increased concentrations of either IL-6 or D-dimer were associated with a 50% increase in the risk of functional dependence and death.[50] When the concentration of both substances was elevated (with values in the upper quartile), however, the risk increased more than threefold.

Tests of Physical Performance

Difficulty in performing some activities is considered a predictor of functional dependence and disability. Of particular interest, a study has shown that the risk of mortality and functional dependence in older persons can be predicted by the "get up and go" test.[51] In this test, the patient is asked to get up from an armchair and walk 10 feet forward and then back to the chair. Both inability to get up without using the chair arms and requiring more than 10 seconds to walk the distance are highly predictive of functional decline.

Issues Related to Geriatric Assessment

A number of issues related to the application of the CGA in clinical practice merit further study. Among these are the questions of which patients should undergo a CGA, who should perform the test, and whether the complete test is always necessary.

Who should undergo a CGA? In three prospective studies of patients with cancer aged 70 and older, the CGA unearthed a number of conditions that were reversible and could interfere with cancer treatment.[27–29] On the basis of these findings, the NCCN recommended some form of CGA for all patients with cancer aged 70 and older.[25]

Who should perform the CGA? Ideally, the CGA should be performed by a primary care provider at periodic intervals, and the results should be part of the patient's permanent record. Any physician involved in the management of older patients should be familiar with the principles of CGA and its interpretation.

Is a full CGA necessary in all patients? Because the CGA is time-consuming, more cost-effective alternatives have been explored. Their value has not yet been determined. These include the use of a screening instrument to identify patients at high risk for functional dependence,[25] including questionnaires and tests of physical functioning.[1] The problem with both of these, however, is that they do not provide any direct assessment of comorbidity, depression, cognition, and social resources. Another interesting approach, proposed by Ingram and coworkers, involved sending to the patient's home a package including questionnaires about function, comorbidity, depression, and social resources.[29] The CHS assessment appears to be one of the most suitable ways to classify older patients involved in clinical trials: It is simple to execute, time-saving, and widely accepted and has been validated in a population of 8500 subjects.[37] For persons classified as prefrail and frail, a more in-depth assessment may be in order.

CANCER PREVENTION IN OLDER PERSONS

Some aspects of aging favor and others interfere with cancer prevention. Because the incidence of cancer increases with age, the elderly presumably would be the population most likely to benefit from cancer prevention. At the same time, reduced life expectancy and decreased tolerance of chemopreventive therapy may lessen the benefits of some types of prevention. The study of cancer prevention in older persons is complicated by a lack of general agreement on what represents a meaningful endpoint: Should it be reduction in cancer-related mortality, as commonly accepted in prevention trials, or should it instead be an improvement in quality of life, in view of the limited life expectancy for this population?[52] This section provides a brief review of the evidence supporting chemoprevention and early detection of cancer among older persons.

Chemoprevention

At least three groups of substances, the selective estrogen receptor modulators (SERMs), the retinoids, and the nonsteroidal anti-inflammatory drugs (NSAIDs), have demonstrated cancer preventive activity in randomized clinical trials,[53] but these substances are used to only a limited degree in current clinical practice for cancer prevention. The SERM tamoxifen has a number of potential adverse side effects, including endometrial cancer, deep vein thrombosis, strokes, and vasomotor and genitourinary manifestations of menopause, the incidence of which increases with age.[53] In a decision analysis, Gail and coworkers calculated that tamoxifen may be beneficial for women aged 70 if their risk of developing breast cancer over 5 years is as high as 7% and if they do not present other contraindications to the drug; the threshold of risk at which this agent may be beneficial increases with the age of the patient.[54] Recently it was shown that raloxifen was as effective as tamoxifen in preventing breast cancer and had fewer side effects.[55]

Older persons may be ideal candidates for inclusion in future studies of chemoprevention in view of their increased risk of cancer, but none of the current options for chemoprevention appear to be optimal.

Screening and Early Detection

Because the prevalence of common cancers increases with age, the positive predictive value of screening tests might be expected to

increase as well.[52] At the same time, older persons have in general undergone screening for common cancers earlier in life. Previous examinations may have eliminated all prevalence cases and minimized the diagnostic yield of subsequent examinations.

Breast Cancer

Most of the randomized controlled studies on breast cancer detection have established that serial mammograms reduce by 20% to 30% the cancer-related mortality rate among women aged 50 to 70.[56] The benefits of mammography after age 70 have been suggested by three reports. A historically controlled cohort study, the Nijmegen study, showed a reduction in cancer-related mortality up to age 75[57]; a retrospective study of the Survey Epidemiology and End Results (SEER) data showed a more than twofold decrement of breast cancer-related mortality for women aged 70 to 79 who had undergone at least two mammograms after age 70[58]; and another retrospective analysis of the same data showed that women older than 70 who had not undergone screening mammography presented with breast cancer at a more advanced stage than that typical for women who had been screened.[59]

An important question is the role of clinical examination of the breast (CBE). The Canadian study suggested that CBE may be as effective as screening mammography in women aged 50 to 60,[60] and the Breast Cancer Detection Demonstration Project (BCCDP) showed that mammography was superior to CBE only in the diagnosis of ductal carcinoma in situ (DCIS).[61] The CBE appears particularly attractive for older women who undergo multiple clinic visits in the course of the year, because it may be performed with no additional cost and inconvenience.

Colorectal Cancer

Early detection of cancer of the large bowel reduces cancer-related mortality among persons aged 50 to 80, but controversy lingers concerning the most appropriate screening strategy.[52] According to a decision analysis by Frazier and associates, full colonoscopy every 10 years is more cost-effective than yearly examination of the stool for fecal occult blood or more frequent flexible rectosigmoidoscopy.[62] A more recent decision analysis by Lin and colleagues[63] claiming that colonoscopy in persons aged 80 and older has negligible benefit may be misleading: These researchers failed to take into account individual life expectancy and functional reserves, which are highly diverse at that age. Virtual colonoscopy, which appears to be as sensitive as endoscopy, may be a more comfortable alternative for older persons.

Prostate Cancer

The value of screening asymptomatic men for prostate cancer with serial determinations of prostate-specific antigen (PSA) level, and the most cost-effective screening strategies, are controversial.[53] If screening is instituted, it should be continued up to age 75, because a Swedish study has demonstrated that radical prostatectomy reduces prostate cancer-related mortality in men up to age 75.[64]

Other Cancers

No benefits of screening women older than 60 for cervical cancer have been recognized if the women have undergone regular Papanicolaou examinations of the cervix earlier in life[53] and have had normal results. Interest in screening ex-smokers for lung cancer has been renewed by the demonstration that helical (spiral) computed tomography is able to detect small and curable cancers.[52] This approach remains controversial but may be of particular interest in older persons, because the incidence of lung cancer is increasing after age 80, probably because smoking cessation has resulted in a decrease in early coronary deaths and an increase in indolent lung cancers.[65]

Clearly, early detection of breast and colorectal cancer may reduce mortality among older persons and may improve their quality of life. It appears reasonable to institute some form of screening for persons whose life expectancy is 5 years or longer, because the initial benefits of screening are seen after 5 years.

CANCER TREATMENT

Surgery

Although surgical mortality and the risk of other surgical complications increase with the age of the patient, elective surgery appears to be safe in general, even in patients older than 80 years.[66] Persons 70 years of age and older are substantially more vulnerable to the complications of emergency surgery, especially surgery related to the digestive tract. In this population, regular screening for colorectal cancer may minimize the incidence of emergency surgery. A number of recent advances in surgery and anesthesia have rendered cancer surgery even safer for older persons. These include more limited surgical excisions (e.g., transanal resection of rectal cancer) and the use of anesthetic agents with a shorter half-life and minimal respiratory suppression.[67]

Radiation Therapy

Two large patient series from Europe and one from the United States attest to the feasibility and safety of radiation therapy in patients of all ages.[68–70] Combined chemotherapy and radiation therapy in the management of cancers of the head and neck, the esophagus, the bladder, and the lung also appear to be well tolerated up to the age of 80 at least. Among the newer radiation techniques, brachytherapy and high-dose intraoperative irradiation are of special interest for treatment in older patients: Brachytherapy minimizes the risk of complications to normal tissues, and intraoperative radiation eliminates the inconvenience of serial visits. Data on use of hyperfractionated radiation in older patients are wanted. Among the complications of radiation therapy, mucositis is of special concern in older patients, because age is associated with a more limited reserve of mucosal stem cells and increased proliferation of epithelial superficial cells[71]—two conditions that predispose older persons to more prolonged and severe mucositis. With cancer of the upper airway or upper digestive tract, in which the risk of mucositis is highest, nutritional management is essential and may involve prophylactic insertion of a percutaneous endoscopic gastrostomy tube.[70]

Cytotoxic Chemotherapy

Age is associated with changes in the pharmacokinetics and pharmacodynamics of cytotoxic drugs and increased susceptibility of certain organ systems to therapeutic complications.[71] The pharmacokinetic changes of major interest involve absorption, renal excretion, and volume of distribution of drugs.

The intestinal absorption of nutrients decreases with age, secondary to a reduction in the absorbing surface area, in the splanchnic circulation, and in gastric motility and secretions,[72] but the bioavailability of oral agents (e.g., capecitabine) does not appear to be compromised. Oral drugs are particularly appropriate for older patients because of the convenience of administration and adjustability of doses.

A progressive reduction in GFR is an almost universal consequence of aging, and it may lead to a more prolonged half-life of medications that are excreted from the kidneys (e.g., methotrexate, bleomycin, carboplatin) and of active and toxic metabolites of drugs excreted through other avenues.[71] These metabolites include daunorubicinol and idarubicinol, responsible for approximately 80% of the activity of the parent compounds,[71] and arauridine, responsible for the cerebellar toxicity of high-dose cytarabine.[71] Dose adjustment of these agents to the patient's GFR may improve tolerability.

The volume of distribution (Vd) of a drug is determined by the body composition and the concentrations of serum albumin and of hemoglobin.[71] Hemoglobin is important because most antineoplastic

agents are bound to red blood cells. In the presence of anemia, the free concentration in plasma and toxicity of these substances in the circulation increase.[43] Correction of anemia may then ameliorate the toxicity of chemotherapy. Among the pharmacodynamic changes associated with age, the most significant are the increased prevalence of multidrug resistance, abnormal intracellular metabolisms of drugs, and abnormal repair of DNA damage. Multidrug resistance may be caused by increased expression of the *MDR1* gene, as is the case in acute myelogenous leukemia[73]; increased prevalence of anoxic tumor cells; and resistance to apoptosis.[71] Abnormal drug metabolism and delay in DNA repair may enhance the toxicity of these agents.[6]

Myelosuppression and mucositis are particularly common and severe complications of cytotoxic chemotherapy. The risk of neutropenia and neutropenic infections with moderately toxic chemotherapy (such as the CHOP regimen—cyclophosphamide, doxorubicin, vincristine, and prednisone) increases with age and appears to be particularly marked after age 70; fortunately, hematopoietic growth factors in pharmacologic doses prevent this complication in 50% to 75% of people older than 70 years of age.[74] Neutropenic infection is potentially fatal and may occur after the first course of treatment—a fact that prompted the recommendations to use growth factors prophylactically in patients aged 65 and older.[75]

The risk of mucositis also increases with age, and this complication may be fatal if not treated promptly.[76] A keratinocyte growth factor, undergoing clinical trials, appears promising for the prevention of mucositis.[77] Other interventions to ameliorate this complication include substitution for intravenous fluorinated pyrimidines by capecitabine, which is associated with a lower risk of mucositis, and ensuring adequate hydration for older people in whom diarrhea or severe dysphagia develops.

Targeted Treatment

Treatments targeted to specific tumor components or tumor functions have substantially reduced the risk of therapeutic complications in older patients with cancer.[78] Some words of caution are in order, however:

- In many cases, these compounds are more a complement of than an alternative to cytotoxic chemotherapy. The most noticeable exceptions to this rule are imatinib, desatinib, and nilatinib.
- A number of complications of these agents may be particularly burdensome to older patients, including the risk of hypertension with bevacizumab; the risk of skin reactions with cetuximab, panitumab, and most small molecule inhibitors of receptor tyrosine kinase; and the risk of myelotoxicity related to lenalidomide and radioimmunotherapy.

Hormonal Treatment

Overall, hormonal treatment of cancer is considered much safer than cytotoxic chemotherapy, and the ongoing tendency is to institute chemical castration for PSA "relapses" in prostate cancer. This approach, however, may have a multiple unwanted effects in older men, including osteoporosis, bone fractures,[79] fatigue, anemia, diabetes, and coronary artery disease.[80]

PRACTICAL DECISIONS RELATED TO THE MANAGEMENT OF OLDER PATIENTS

Informed decision making is the key to effective and safe treatment of older patients with cancer. Any oncologic decision has two components: the person and the neoplasm. For example, cytotoxic chemotherapy is rarely indicated in a woman aged 90 or older with stage 1 or 2 breast cancer, in view of the negligible benefit and the substantial risk of treatment. Extermann and coworkers demonstrated that adjuvant chemotherapy is beneficial to an 80-year-old woman when her chances of dying of breast cancer are only about 30%, if a 1% reduction in breast cancer-related mortality is desirable; in a 90-year-old woman, however, the risk of dying of breast cancer must be close to 70% to justify the use of chemotherapy.[81] Chemotherapy seems definitively indicated if the same patient has a chemotherapy-responsive disease that may shorten her survival, such as large cell non-Hodgkin's lymphoma. The algorithm presented in Figure 67-3 depicts a useful frame of reference for the use of chemotherapy in older patients. The two points that deserve emphasis are (1) the rapidly evolving classification of older patients with cancer and (2) the likelihood that chemotherapy may represent the best option for palliation in frail patients. Several agents with minimal toxicity, including capecitabine at low doses, weekly taxanes, gemcitabine, and vinorelbine, may be used safely in these patients.[35]

NATIONAL AND INTERNATIONAL INITIATIVES RELATED TO CANCER AND AGE

The issues of cancer in the older person have been well recognized throughout the Western world and have prompted a number of important responses.

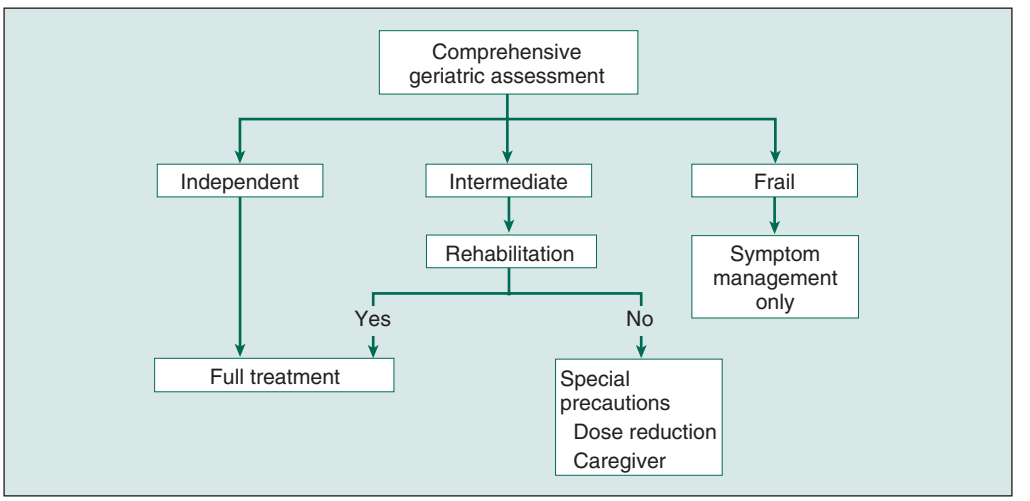


Figure 67-3 • Treatment algorithm for the use of chemotherapy in older persons with cancer.

Governmental Responses

The National Cancer Institute, in cooperation with the National Institute on Aging, has held a number of conferences related to cancer and aging. As a consequence of these conferences, six to eight program grants (P20) for the development of geriatric programs within comprehensive cancer centers have been offered. In addition, a number of requests for proposals for the study of management of cancer in the older person have been offered.

All major cooperative groups in the United States and Europe now have a committee or subcommittee whose aim is promotion of enrollment of older patients with cancer into existing clinical trials and promotion of clinical trials devoted to older persons.

Professional Associations and Private Foundations

The American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO), and the European Society of Medical Oncology (ESMO) have dedicated special scientific and educational sessions to the issues of cancer and aging. ASCO also has developed a special curriculum on cancer and age. Of the private foundations, the Hartford Foundation merits special mention: This body has founded, through ASCO, 12 3-year fellowships for special training in geriatric oncology.

A number of industry-funded cooperative efforts for studying the management of cancer in the elderly also have been developed, including the Geriatric Oncology Consortium in the United States, the Geriatric Radiation Oncology Group (GROG) in Italy, and the Italian Group of Geriatric Oncology (GioGER), which, although it originated in Italy, incorporates the effort of several European countries.

Practice Guidelines

In 1999 the NCCN established a panel for the issuance of guidelines for the management of older patients with cancer. The first set of guidelines (Table 67-3) was published in 2000.[52] These guidelines are based on the available clinical evidence, reviewed in this chapter, and are intended to be used as a frame of reference for clinical practice and as a building block to accommodate emerging data. Other associations, including the EORTC and the Canadian Cancer Institute, are preparing their own guidelines.

Table 67-3 Guidelines for Management of the Older Person with Cancer Established by the National Cancer Center Network

1. All patients aged 65 and older should undergo some form of geriatric assessment before institution of treatment.
2. With compounds that are excreted through the kidneys, or that give origin to active and toxic metabolites excreted through the kidneys, the dose should be adjusted to individual GFRs in persons aged 65 and older. Dose escalation can begin if no evidence of toxicity is encountered.
3. Patients aged 65 and older undergoing moderately toxic chemotherapy (of dose intensity comparable to that of CHOP) should receive prophylactic growth factors (G-CSF or pegylated G-CSF).
4. Hemoglobin levels should be maintained at 12 g/dL or greater with epoietin.
5. Patients aged 65 and older experiencing grade 3 or 4 mucositis should be hospitalized for aggressive fluid resuscitation.

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; G-CSF, granulocyte colony stimulating factor; GFR, glomerular filtration rate.

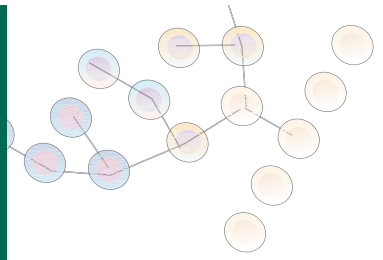
CONCLUSIONS

The scope of geriatric oncology includes changes in tumor and patient biology as well as comprehensive evaluation of the older person aimed at establishing life expectancy, treatment tolerance, risk of cancer-related complication, and need for rehabilitative intervention. Biologic changes and CGA are the two poles of preventive and therapeutic interventions. Treatment-related guidelines may help establish a uniform approach to older cancer patients and thus facilitate the interpretation of clinical data. A number of initiatives developed during the past 5 years promote clinical research in older patients with cancer and promise to fill the current gaps in clinical evidence. In no circumstances does age alone represent a contraindication to effective cancer treatment.

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68 Special Issues in Pregnancy

Andrew Grigg

SUMMARY OF KEY POINTS

- Cancer complicates 1 in 1000 pregnancies; the most common malignancies are breast and cervical cancer, lymphoma, and melanoma.
- There is no evidence that pregnancy alters the clinical behavior of cancer, but cancer often is advanced at diagnosis owing to the overlap of symptoms with those of a normal pregnancy.
- Important factors in management include assessment of gestational age, maternal staging with limited exposure to ionizing radiation, the urgency for therapy, and the impact of therapy on maternal prognosis and fetal outcome.
- Physiologic changes in pregnancy affect the metabolism of chemotherapy drugs, but there are few practical guidelines about how dosing should be adjusted to take this into account.
- Alkylators and antimetabolites should be avoided in the first trimester, but these agents and other cytotoxics are generally not contraindicated in the second and third trimesters.
- The scheduling of chemotherapy should be planned to minimize the risk of complications at the time of delivery.
- There is no evidence that exposure to chemotherapy results in long-term adverse effects on physical or intellectual development, and there is no increased risk of malignancy in surviving children.
- Therapeutic radiation jeopardizes fetal outcome and should be reserved for the postpartum period when possible.
- Subsequent pregnancy after cancer diagnosis and effective therapy is usually possible.

INTRODUCTION

This chapter focuses on the issues related to the care of cancer diagnosed during the gestational period. Cancer is the second leading cause of death in women between the ages of 20 and 39 and complicates 1 in 1000 pregnancies. The most common cancers diagnosed in pregnant patients are those that are seen in nonpregnant women of similar age: breast, cervix, lymphoma, and melanoma.[1] Although pregnancy is associated with immunologic tolerance, there is no evidence of an increased incidence of cancer or of more aggressive behavior of malignancies that are diagnosed during pregnancy. However, many cancers in pregnancy are diagnosed at an advanced stage, often because symptoms of the malignancy overlap with those that are experienced in a "normal" pregnancy.

FETAL DEVELOPMENT AND PHYSIOLOGY

The three phases of fetal development are implantation, organogenesis, and growth. The implantation phase lasts from conception to 2 weeks and often ends in a spontaneous abortion after exposure to a toxic stimulus. Organogenesis occurs between 2 and 7 to 12 weeks; noxious stimuli at this time may lead to organ dysgenesis, resulting in fetal malformation or death. The growth phase occurs from the second trimester to term; toxic stimuli to the mother and fetus may result in fetal growth retardation, which can be associated with abnormal brain development and subsequent learning difficulties. However, as will be discussed, this has not been demonstrated to be a significant clinical concern in women receiving chemotherapy during the second and third trimesters.

As most chemotherapy drugs are uncharged, lipophilic, of low molecular weight, and minimally protein bound, they cross the placenta to the fetal circulation. The placenta is the primary portal of exit of waste products and toxins from the fetus. However, the metabolites are generally more polar than is the parent compound, might not cross the placenta as easily, and hence may accumulate in fetal tissues or amniotic fluid. The fetal liver can metabolize drugs as early as 7 to 8 weeks of pregnancy, but the extent to which fetal liver and kidneys participate in drug elimination is minimal.[2]

MATERNAL PHYSIOLOGY: RELEVANCE TO CHEMOTHERAPY AND SURGERY

Pregnancy induces a number of important physiologic changes that cause significant alterations in the metabolism and efficacy of commonly used medications (Box 68-1). However, few data exist to guide physicians in adjustment of drug dosing (see the section on chemotherapy dosing).

Physiologic changes in pregnancy also affect surgical treatment and planning. Pregnancy is accompanied by increased plasma volume and dilutional anemia, reduced mean arterial pressure, increased oxygen consumption, and a narrow respiratory reserve. Cardiac output is increased by 30% to 50% as early as the second trimester, but in the supine position, the gravid uterus can compress the inferior vena cava, resulting in decreased venous return and reduction in cardiac output. Fetal development or viability may be jeopardized by hypotension and hypoxemia. Nevertheless, surgery can usually be performed safely during pregnancy; there is a small but increased risk

Box 68-1. PHYSIOLOGIC CHANGES IN PREGNANCY THAT MAY AFFECT THE METABOLISM AND EFFICACY OF CHEMOTHERAPY AGENTS

- Alteration of drug absorption due to delayed gastric emptying and gastrointestinal mobility
- Increased plasma volume leading to dilutional anemia, increased volume of distribution, and decreased peak plasma concentration of drugs
- Increased enterohepatic circulation leading to increased drug bioavailability
- Enhanced hepatic oxidation enhancing drug clearance
- Altered levels of plasma proteins altering the pharmacokinetics of drugs with significant protein binding
- Increased glomerular filtration resulting in enhanced drug clearance

of low birth weight and spontaneous abortion but no increased risk of fetal malformation.

DIAGNOSTIC RADIOLOGY FOR STAGING

The practitioner who is responsible for the radiologic examination must take all reasonable steps beforehand to advise the pregnant patient of the potential risks to the embryo or fetus that are associated with in utero exposure.

Radiation can be divided into ionizing and nonionizing radiation. Ionizing radiation has the ability to penetrate tissue and damage cellular DNA, resulting in mutation and ultimately affecting the development and viability of the fetus. Numerous studies of radiation exposure after atomic bomb detonations in Japan confirmed that this effect is dependent on dose and stage of fetal development at the time of exposure (Table 68-1).[3] Fetal abnormalities after exposure to excessive ionizing radiation include microcephaly, eye malformation, and growth retardation.[4] The American College of Obstetricians and Gynecologists has published recommendations for imaging during pregnancy that state that 5-cGy exposure to the fetus is not associated with any increased risk of fetal loss or birth defects.[5] Radiation exposure is well below this for most procedures except for the maximum dose with CT scanning of the abdomen and pelvis (Table 68-2). A more relevant concern is an increased risk of childhood cancer. After a gestational age of 3 to 4 weeks, the number of excess cancer cases (leukemia and solid tumors) up to age 15 years following radiation in utero is estimated to be 1 in 17,000 per 0.1 cGy. The baseline cancer risk in the first 15 years is about 1 in 650, so a fetal dose of 2.5 cGy will approximately double the risk; however, this represents an excess lifetime fatal cancer risk of less than 0.5%.

Table 68-2 Typical Ranges of Fetal Doses Following Common Diagnostic Procedures

Examination	Mean Dose (cGy)	Maximum Dose (cGy)
CONVENTIONAL X-RAY		
Abdomen	0.14	0.42
Chest	<0.01	<0.01
Cervical spine	<0.01	<0.01
Lumbar spine	0.17	1.0
Pelvis	0.11	0.4
Thoracic spine	<0.01	<0.01
COMPUTED TOMOGRAPHY		
Abdomen	0.8	4.9
Pelvis	2.5	7.9
Chest	0.006	0.096
Cervical spine	<0.01	
Brain	<0.005	<0.005
NUCLEAR MEDICINE		
99m Tc bone scan (phosphate)	0.33	0.46
67 Ga tumors and abscesses	—	1.2
131 I thyroid metastases	—	2.2

The radiation doses have been estimated from surveys conducted in the United Kingdom for a range of diagnostic radiology.

Ultrasound and Magnetic Resonance Imaging

Ultrasound is accepted as being safe in pregnancy and can be particularly useful in assessing the breasts and liver. Magnetic resonance imaging (MRI) does not expose the patient to ionizing radiation, and there has been no indication that MRI during pregnancy has produced deleterious effects. Hence, MRI may be used in pregnant women if other nonionizing forms of diagnostic imaging are inade-

Table 68-1 Estimates of Threshold Doses for Effects Following Fetal Radiation in Utero

	Minimal Dose (mGy)		
Age (in weeks)	**Death**	**Gross Malformations**	**Mental Retardation**
0 to 1	No threshold at day 1; 100 thereafter	No threshold at day 1?	Analysis of Japanese data suggest a dose related reduction of about 3 IQ points per 10 cGy for children irradiated in utero from 8 to 15 weeks post fertilization. The threshold is ill defined and may lie between 6 and 30 cGy
2 to 5	250 to 500	200	
5 to 7	500	500	
7 to 21	>500	Very few observed	
To term	>1000	Very few observed	

quate or if the examination provides important information that would otherwise require exposure to ionizing radiation (e.g., fluoroscopy, CT). Contrast agents such as gadolinium cross the placenta and are contraindicated. MRI of the abdomen is limited by motion artifact of the bowel.

Position Emission Tomography Scanning

Pregnancy is a relative contraindication to positron emission tomography (PET) scanning but termination is not generally recommended if a patient is found to be pregnant after a PET scan. After a PET/CT scan, a representative dose is 8 mGy (PET) and 0.3 cGy (CT). The dose to the fetus may be higher owing to close proximity of the mother's bladder, where fluorodeoxyglucose is excreted.

TERATOGENICITY OF CHEMOTHERAPY

The U.S. Food and Drug Administration (FDA) has defined risk categories for all drugs based in part on the evidence in animals of fetal harm (Table 68-3). The majority of chemotherapeutic agents are Category D. Extrapolation of teratogenic and mutagenic effects of chemotherapeutic agents from animals to human organogenesis is difficult, however, because of differences in susceptibility between species.[6] The timing of fetal drug exposure is critical. Drugs that are administered with one week of conception may produce a spontaneous abortion or a healthy fetus. During the first trimester, when organogenesis occurs, drugs may produce congenital malformations and/or result in spontaneous abortion. Other factors that may influence the probability of teratogenesis include the frequency of drug administration, duration of exposure, synergistic effects of multiple drugs, radiation, and individual genetic susceptibility.

Most human data about chemotherapy during pregnancy involve small series or case reports, which are prone to reporting bias. There is limited specific or systemic information about the teratogenicity of individual cytotoxics or modern multiagent chemotherapy regimens, particularly in the first trimester. Many reported malformations have occurred after exposure to multiple agents, making it difficult to apportion blame to a single causative agent. Interpretation of these data should be tempered by the reality that the overall incidence of major congenital malformations is approximately 3% of all births, the incidence of minor malformations may be as high as 9%, and between 10% to 15% of all pregnancies result in a miscarriage or spontaneous abortion.[7] Extrapolation from older data might also not be appropriate, as many of these drugs (e.g., alkylating agents such as nitrogen mustard and busulfan and antimetabolites such as aminopterin) are now rarely used. Limited experience in the first trimester with regimens such as adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) and cyclophosphamide, adriamycin, vincristine, and prednisolone (CHOP) suggests low rates of teratogenicity.[8] In the second and third trimesters, drugs extremely rarely cause significant malformations but could impair fetal growth and development, probably mainly indirectly due to maternal ill-health. The available literature suggests that learning or behavioral problems (functional teratogenesis) do not result from chronic prenatal chemotherapy exposure. Overall, the use of systemic antineoplastic therapy alone appears to be accompanied by significantly lower risk than is commonly appreciated.

SPECIFIC CHEMOTHERAPY DRUGS

Table 68-4 details the available experience on the use of some of the more commonly used chemotherapy drugs in animals and at various stages of pregnancy, in humans, together with the FDA category.[9–34] The recommendations are those published by Briggs and colleagues,[9] with some additional comments from the author. An excellent review by Cardonick and Iacobucci is recommended.[35]

Antimetabolites

Methotrexate is widely distributed, including into fluid spaces such as amniotic fluid, and is closely associated with fetal abnormalities when given during the first trimester, characterized by cranial dysostosis, hypertelorism, micrognathia, limb deformities, and mental retardation.[20] However, methotrexate does not uniformly cause malformations, and there may be a critical dose above which fetal malformations occur.[21] Exposure to methotrexate in the latter trimesters has not been associated with significant malformations,[9] but its elective use at this time, particularly in high dose, is still not recommended.

5-Fluorouracil (5-FU) was associated with multiple congenital malformations in the fetus of a patient who was found to be pregnant at week 14 after she began receiving chemotherapy for colon cancer at week 12 and hence is not recommended for use during the first trimester.[36] Cytosine arabinoside, alone and in combination with other drugs, during the first trimester has also been associated with congenital anomalies.[18]

Alkylating Agents

Alkylating agents are commonly used in the treatment of lymphoma, acute lymphocytic leukemia, and breast cancer. Among 47 at-risk pregnancies, six malformations were reported when alkylating agents were used in the first trimester, usually as part of combination

Table 68-3 Food and Drug Administration Risk Categories for Drugs Administered During Pregnancy

Category	Description
A	Controlled studies in women do not show risk to the fetus during the first trimester; there is no evidence of risk in late trimesters, and the possibility of fetal harm is remote.
B	Animal reproduction studies have not shown a fetal risk, but there are not controlled studies in pregnant women; or animal reproduction studies have shown an adverse effect (other than a decrease in fertility), but this has not been confirmed in controlled studies in women in the first trimester (no evidence of a risk in later trimesters).
C	Studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal, or both), and there are no controlled studies in women, or studies in animals and women are unavailable. Drug should be given only if potential benefit justifies the risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (if the drug is needed in a life-threatening situation for which other safer drugs are not available).
X	Studies in humans and animals have shown fetal malformations; there is evidence of fetal risk based on human experience or both. The risk of use in a pregnant woman clearly outweighs any potential benefit. This drug is contraindicated in women who are or may become pregnant.

Table 68-4 Summary of and Recommendations[9] for Chemotherapy Drug Experience in Pregnancy

Drug	First Trimester	Second Trimester	Recommendations	Risk Category	Author Comment
Alkylators in general[10]	Inadequate data; teratogenic in animals	Case reports without apparent fetal harm	Contraindicated in first trimester	D	
Anthracyclines	Teratogenic in rats; little human data as single agent	No reports of specific fetal abnormalities; idarubicin associated with neonatal cardiomyopathy[11]	Contraindicated in first trimester	D	Doxorubicin preferred
Bleomycin	Teratogenic in rats; use in combination not associated with fetal malformations	Use in combination has not been clearly associated with fetal abnormalities	Not specified	D	Oxygen during delivery may aggravate pulmonary toxicity[12]
Cisplatin	Teratogenic in animals; little human data	Case reports suggest safety[13,14]	Contraindicated in first trimester	D	
Corticosteroids	Associated with nonsyndromic orofacial clefts[15]	Repeated exposure to dexamethasone may increase leukomalacia and neurodevelopmental abnormalities[16]	Potential maternal benefit outweighs embryo/fetal risk	C: second/third trimester D: first trimester	
Cyclophosphamide	Yes: cyclophosphamide embryopathy[17]	Main concern is neonatal myelosuppression	Contraindicated in first trimester	D	
Cytarabine	Yes: limb abnormalities[18]	Main concern is maternal myelosuppression and sepsis with secondary effects on the fetus	Not specified; relatively contraindicated in first trimester	D	
Etoposide	Teratogenic in animals; no human data	IUGR and myelosuppression when used in aggressive combination regimens	Not specified	D	
Imatinib	Limited data; malformations reported[19]	Limited data suggest safety	—	D	Consider in second or third trimester if poor disease control
Methotrexate	Yes: methotrexate embryopathy;[20] minimal risk at 6 to 8 weeks post-conception at doses ≥10 mg/week[21]	Neonatal myelosuppression; accumulates in ascitic fluid	Contraindicated at all stages	X	
Rituximab	Not teratogenic in animals; limited data suggest no adverse effects[22,23]	Limited case reports suggest safety[24–28]	—	C	Benefit outweighs risk in most circumstances
Taxanes	Teratogenic in animals; no human data	Reports suggest no significant risk to the fetus[29,30]	Not specified		Consider in second/third trimester if clear maternal benefit
Trastuzumab	No fetal harm in monkeys	One report of reversible anhydramnios[31]	—	B	Not contraindicated but use with caution
Vinca alkaloids	Teratogenic in rats, but limited human data suggest relatively safe[8,32–34]	No reports of specific fetal abnormalities	Not specified	D	Vinblastine has been recommended as single agent in HL in first trimester

Refer to text for additional comments.
Briggs GG, Freeman RK, Yaffe ST: Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk, 7th ed. Philadelphia, Lippincott Williams and Wilkins, 2005.

therapy.[10] Cyclophosphamide is clearly teratogenic in animals, with similar malformations noted in different species. A distinct and similar embryopathic phenotype in humans has been described after exposure to cyclophosphamide as a single agent, with one dose (20 mg/kg) during the sixth week after conception.[17] Second- and third-trimester exposure has not been associated with malformations. Other alkylating agents, such as thiotepa and dacarbazine, are teratogenic at high doses in rats, but little is known about their effects in humans apart from case reports of lack of side effects when used in the second trimester or beyond. Exposure to chlorambucil during the first trimester has been reported to cause renal aplasia, cleft palate, and skeletal abnormalities.[37]

Platinum

A number of case reports documenting platinum use after the first trimester have not noted any congenital malformations.[13,14]

Vinca Alkaloids

Although vinblastine is highly teratogenic in animal models, the literature suggests that its use in the first trimester may be relatively safe. No congenital malformations were reported in 11 pregnancies that were exposed to vincristine, three being in the first trimester.[32] Vinorelbine, vinblastine, and vincristine had been used during the latter trimesters without fetal harm.[8,31,34]

Anthracyclines

There is little information about the effects of these drugs in pregnancy as single agents; malformations have been reported when they are used in combination regimens in the first trimester. Idarubicin is more lipophilic, which favors placental transfer, and has been associated with neonatal cardiomyopathy.[11]

New Agents

There are minimal human data with respect to the following:

- Topoisomerase-1 inhibitors such as topotecan (used in ovarian and small cell lung cancer) and irinotecan (used for colorectal cancer and non-small-cell lung cancer)
- Ertotinib, an epidermal growth factor receptor tyrosine kinase inhibitor that is used in metastatic lung and pancreatic cancer
- Bevacizumab, a humanized monoclonal antibody with an antiangiogenic effect that is used for metastatic colorectal cancer. Because it is teratogenic in rabbits (according to Roche product information), consistent with a crucial role of angiogenesis during normal fetal development, bevacizumab should not be administered to pregnant women.
- Oxaliplatin. This is embryotoxic in animals, classified as a Category D drug and is not recommended for use in pregnancy.
- Capecitabine is an oral drug akin to 5-FU used in bowel and breast cancer. This is embryotoxic in animals, classified as a Category D drug, and is not recommended for use in pregnancy.

Miscellaneous Agents

Granulocyte colony-stimulating factor (G-CSF) is not teratogenic in rats, and no congenital malformations or toxicities attributable to G-CSF have been reported in humans.[9] G-CSF is a Category B drug and should not be withheld in pregnancy if there is a significant potential benefit to the mother.

5-Hydroxytryptamine-3 (5HT3) antagonists, such as ondansetron, are widely used to prevent and treat chemotherapy-induced nausea and vomiting. These drugs are not teratogenic in animals, and the small number of reports of ondansetron for hyperemesis gravidarum and chemotherapy in pregnancy suggest effectiveness and safety. 5HT3 antagonists have been classified as Category B drugs in pregnancy.[9] Aprepitant (Category B) is an effective antiemetic for delayed nausea after chemotherapy. Animal studies have not revealed harm to the fetus after exposure to aprepitant (according to Merck, Sharp and Dohme product information), but there are no data on its use in pregnant women.

Recombinant human erythropoietin (Category C) does not cross the human placenta and does not appear to present a major risk to the fetus,[9] and the benefit of its appropriate use for maternal anemia appears to outweigh any known or potential risks.

CHEMOTHERAPY IN PREGNANCY: OVERVIEW

An overview of the approach to treatment is detailed in Figure 68-1.

First Trimester

Patients should be counseled that the incidence of teratogenicity as a result of exposure to a particular chemotherapy drug or a drug combination in the first trimester is not well established. Counseling regarding the effects of chemotherapy needs to be performed using as much information as possible, which may involve asking the relevant pharmaceutical company for updated information. In addition, for many malignancies, there is no evidence either way that delaying chemotherapy from the first trimester until the completion of fetal organogenesis early in the second trimester adversely affects the

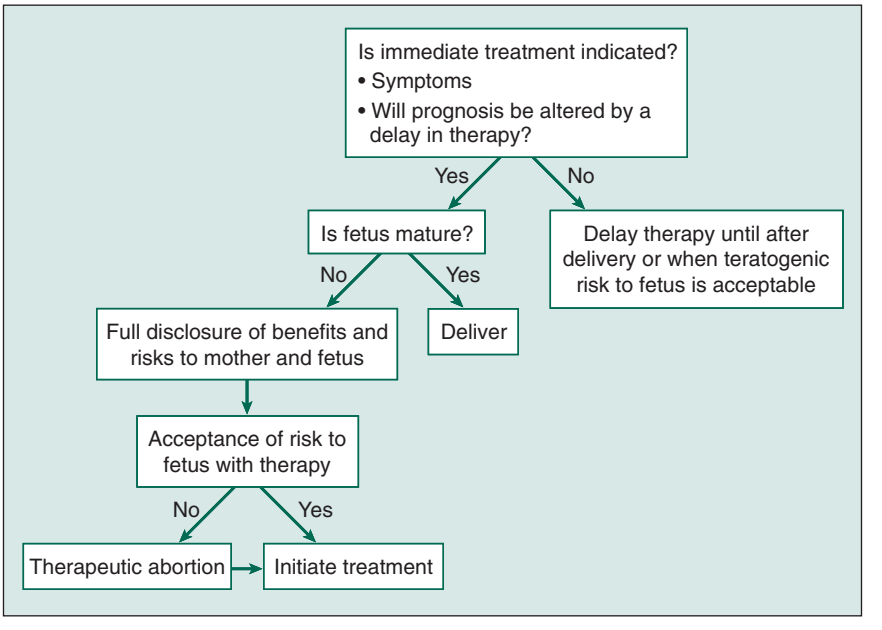


Figure 68-1 • Overview of the treatment approach to cancer in pregnancy.

ultimate outcome. A therapeutic abortion is usually recommended for cancers diagnosed in the first trimester that require urgent multiagent chemotherapy. There are multiple factors, such as desire to avoid termination, risk of delay, and interim use of truncated chemotherapy protocols with drugs with a low probability of teratogenicity, that need to be considered in each patient.

Second and Third Trimesters

The administration of most chemotherapeutic agents in the second and third trimesters has not been associated with specific adverse effects on the fetus; hence, in general, chemotherapy-based treatment of the underlying malignancy at this stage of pregnancy should not be delayed and should follow the same guidelines as for nonpregnant women. The main risk to the fetus appears to be secondary to neutropenic sepsis, anemia, and nutritional deficiency in the mother.[35] The parents can be assured that long-term studies have shown that in the absence of chemotherapy-embryopathy, children who are exposed to chemotherapy in utero are not different physically or intellectually from matched controls, and there is no suggestion of a significantly increased risk of malignancy in the neonate (i.e., transferred from the mother) or in long-term follow-up.[8]

Chemotherapy Dosing

An anecdotal observation of fewer chemotherapy-related side effects during antenatal treatment compared with identical chemotherapy postpartum has been reported,[35] consistent with physiologic changes in pregnancy leading to lower plasma levels and reduced area under the concentration × time curve. Pharmacokinetic studies have not been done. Accordingly, particularly when given with curative intent, chemotherapy doses should not be empirically dose-reduced. A practical approach, particularly in curable hematologic malignancies such as Hodgkin's lymphoma in which low hematotoxicity is an independent prognostic factor for a poorer treatment outcome, may involve regular blood counts with individualized dose adjustments (up or down) according to the level of myelosuppression.[38]

SPECIFIC MALIGNANCIES

Breast Cancer

The incidence of breast cancer during pregnancy is estimated to be 1 in 3000.[39] Women with a genetic predisposition to breast cancer, particularly BRCA2 mutations, might be overrepresented in this group.[40] Despite its long-term protective effect on the development of breast cancer, pregnancy itself may temporarily increase the risk of disease, again particularly in women with BRCA2 mutations. Breast cancer in pregnancy is more likely to be advanced (almost 50% stage IV, with lymph node involvement in 65%), is thought to reflect a delay in diagnosis as the physiologic breast changes of pregnancy may mask a malignant mass, and possibly involves a higher incidence of Her-2/neu positivity and a lower incidence of estrogen receptor positivity (there is conflicting literature) than breast cancer in nonpregnant women.[40–42] The majority are poorly differentiated infiltrating ductal adenocarcinomas. However, stage-specific survival is similar to that of nonpregnant patients.[43,44] Placental metastases of breast cancer have been reported, but rarely, and there are no reports of fetal involvement.[45]

The principles of diagnosis are similar to those for nonpregnant women. Mammography is safe, as there is negligible radiation dose to the fetus with abdominal shielding, but may be associated with high false-positive rates. Ultrasonography can distinguish solid from cystic masses. Gadolinium-enhanced MRI of the breast is contraindicated. Fine needle aspiration biopsy is acceptable, but accurate interpretation requires an experienced pathologist who is aware that the woman is pregnant. If nondiagnostic, solid masses should be subject to excisional biopsy. Safe staging procedures include a chest x-ray and MRI without contrast. A chest CT scan is not contraindicated (see the section on radiology), but a MRI of the thorax is preferred. Bone evaluation if required, can be with a modified bone scan with maternal hydration and frequent voiding to limit fetal radiation exposure from radionuclides in the adjacent maternal bladder.[46] The serum alkaline phosphatase level rises physiologically during pregnancy and is not useful as an indicator of bony secondaries.

National Comprehensive Cancer Network Guidelines for the treatment of nonmetastatic breast cancer during pregnancy are available and are reproduced in Figure 68-2. International expert recommendations have also been published recently.[47] Treatment should not be unnecessarily delayed, as delay may result in significantly worse disease-free survival. Therapeutic abortion does not appear to alter maternal survival.

Considerations and selection of optimal local therapy are similar to that recommended in non-pregnancy-associated breast cancer. Breast and axillary surgery during any trimester appears to be reasonably safe for the mother and associated with minimal fetal risk. Axillary lymph node dissection is important, as nodal metastases are common and nodal status affects the choice of adjuvant therapy. At present, sentinel lymph node biopsy has not been systematically evaluated and is not generally recommended.[47] Therapeutic radiation has been contraindicated during pregnancy, as this is calculated to expose the fetus to 10 cGy in early pregnancy and 200 cGy in late pregnancy, which are above the acceptable limits;[39] however, this view has recently been questioned.[48] Accordingly, mastectomy is a consideration in early gestation when radiation therapy is significantly delayed. Breast-conserving surgery is an option in the second or early third trimester with neoadjuvant chemotherapy or by itself late in the third trimester.

Adjuvant chemotherapy should be delayed to beyond the first trimester. FAC (5-FU, adriamycin, cyclophosphamide) during the second or third trimesters has not been associated with spontaneous abortions or fetal abnormalities; methotrexate is usually avoided.[49] Tamoxifen is contraindicated owing to its association with spontaneous abortion, birth defects, fetal death, and, in pregnant rats, breast cancer in female offspring.[47] International guidelines suggest avoiding taxanes and dose-dense anthracyclines during pregnancy owing to the paucity of data, although the limited literature has not demonstrated any adverse fetal effects with taxanes that are administered beyond the first trimester.[29,30] Trastuzumab (herceptin), a pregnancy category B drug, is a monoclonal antibody that blocks the human epidermal growth factor receptor Her-2/neu and that in combination with adjuvant chemotherapy has been shown to improve disease-free and overall survival for early-stage Her-2 positive breast cancer.[49] Reports have demonstrated either no adverse effect or reversible anhydramnios in women who are exposed to trastuzumab in the first trimester.[31,50,51] Consideration should be given to the use of trastuzumab and/or taxane compounds beyond the first trimester if there is a strong likelihood of maternal benefit.

There is no evidence that a future pregnancy worsens the prognosis with respect to recurrence; in fact, on early follow-up, pregnancy may lower the risk of death.[52] However, most oncologists advise women to wait two to three years before another pregnancy, as the risk of recurrence is highest during this time. Recent literature has highlighted the impact of chemotherapy regimen, age, and time since treatment on ovarian function after breast cancer treatment in premenopausal women.[53]

Cervical Cancer

Cervical cancer is the most common malignancy diagnosed during pregnancy (1 in 750) probably owing to routine Papanicolaou screening.[54] Unlike other malignancies in pregnancy, cervical cancer is often detected early because of this; advanced cervical cancer is rarely encountered. Symptoms such as vaginal bleeding or discharge may overlap with those of pregnancy. Human papillomavirus is involved

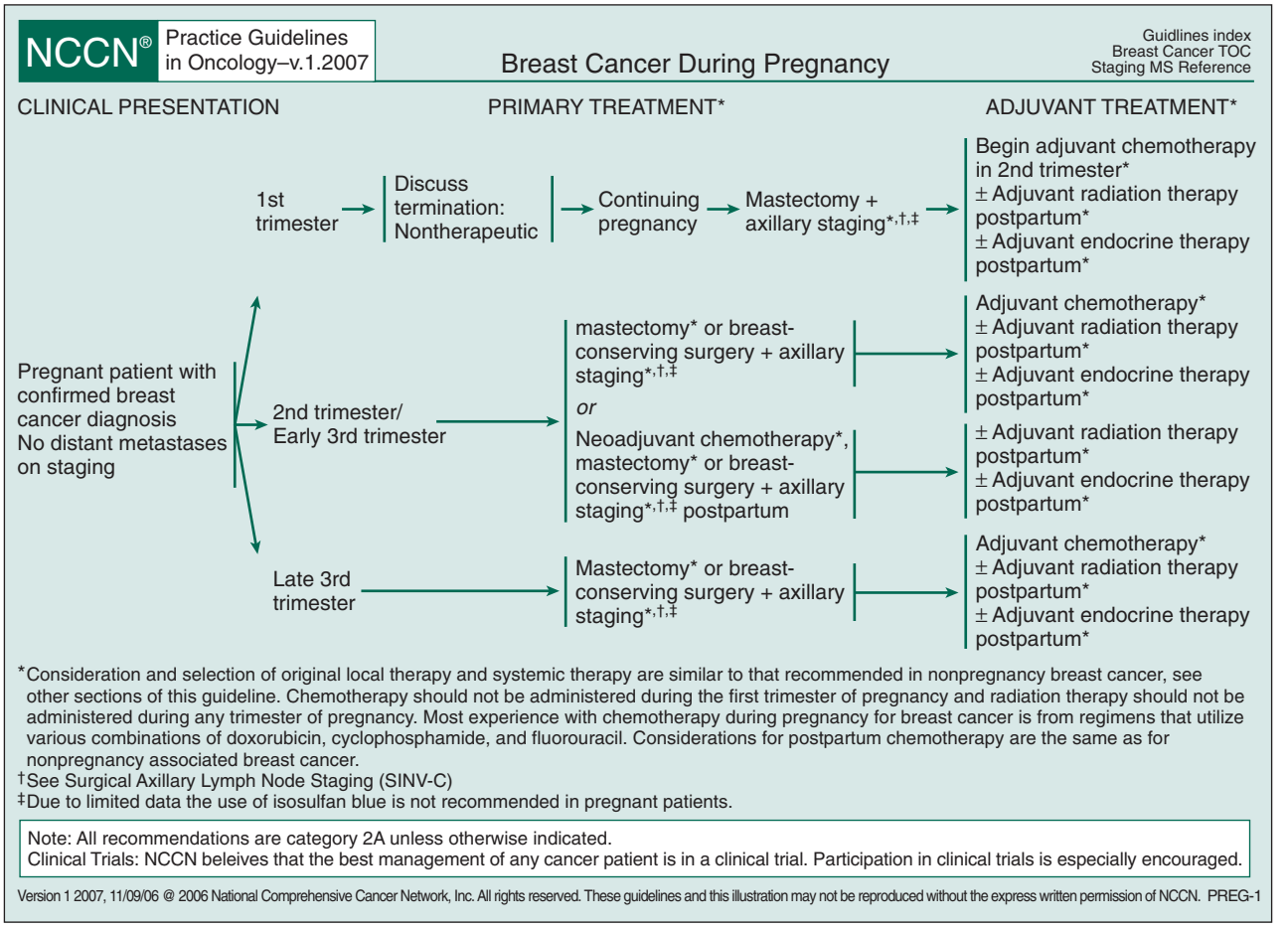


Figure 68-2 • National Comprehensive Cancer Network Guidelines for the treatment of nonmetastatic breast cancer during pregnancy. (Reproduced with permission from The NCCN 1.2007 Breast Cancer During Pregnancy Clinical Practice Guidelines in Oncology. Available at: www.nccn.org. Accessed December 2006. To view the most recent complete version of the guidelines, go online to www.nccn.org.)

in most cervical cancers. There is no evidence that the relative immunosuppressive state of pregnancy modifies the aggressiveness of human papillomavirus infection.[55] Cone biopsies may result in significant hemorrhage and fetal death and should be done only if necessary for diagnosis of invasive malignancy.[56]

Management recommendations differ according to disease stage. There is evidence that delay of treatment of early-stage cancer until fetal maturity in a desired pregnancy is not deleterious to the mother. An algorithm of treatment options for early-stage cancer at less than 20 weeks gestation has been described.[55] If advanced disease is diagnosed and the fetus is viable, then delivery by cesarean section is recommended, followed by commencement of therapy. Neoadjuvant chemotherapy is a consideration if treatment needs delay for fetal indications. If the fetus is not viable and stage IIB–IVA disease is detected, treatment should be directed with curative intent. Chemoradiation should be initiated promptly, which will lead to abortion of the fetus.

Melanoma

While overall there is a male preponderance, age-specific incidence rates are higher among females until age 40 years, leading to speculation that some causes may be hormonally driven.[57] However, there is no clear evidence that exogenous hormone use increases the risk,[58] that the incidence of melanoma is higher in pregnancy,[59] or that pregnancy influences the prognosis.[60] Treatment principles are similar to those for the nonpregnant patient. An approach to the management of pregnant women with high-risk melanoma has been published.[61] Melanoma is the most common malignancy associated with transplacental metastases to the fetus. With placental involvement, the fetal risk of melanoma metastasis is approximately 22%, with a high fatality rate in affected infants.[62]

Ovarian Cancer

Invasive epithelial ovarian cancer is uncommon during pregnancy, the majority of cases being diagnosed early owing to frequent use of pelvic ultrasound and generally having germ cell or low malignant potential histology.[63,64] Surgical staging and treatment of ovarian neoplasms include debulking surgery, including omentectomy, lymph node and peritoneal biopsy, and assessment of peritoneal washings. Germ cell tumors are typically treated with bleomycin, etoposide, and cisplatin; experience with these agents in the latter trimesters of pregnancy with this combination is limited but has been associated with prematurity and ventriculomegaly in one report.[65] Low malignant potential neoplasms are treated with surgery alone. Invasive epithelial ovarian cancer is treated with postoperative chemotherapy consisting of platinum and paclitaxel; the safe use of this combination in the second trimester has been reported.[13,66]

Gestational Choriocarcinoma

Gestational choriocarcinoma is a highly malignant vascular neoplasm of the cytotrophoblast and syncytiotrophoblast that readily

metastasizes. Choriocarcinoma can be preceded by any gestational event; most arise after a hydatiform mole or a spontaneous abortion or after a normal pregnancy. Diagnosis concurrent with a normal pregnancy is extremely rare.[67] A scoring and risk factor system for gestational choriocarcinoma from the International Federation of Gynecology and Obstetrics (FIGO) has been published; chemotherapy recommendations depend on the FIGO risk score.[68] In tumors that are diagnosed after pregnancy, a high cure rate can be achieved with single-agent chemotherapy (usually methotrexate) for low-risk disease, but responses are lower in high-risk disease, for which multiagent chemotherapy is the treatment of choice.[69] However, the cure rate for choriocarcinoma concurrent with pregnancy is poor. Simultaneous choriocarcinoma in the mother and infant is rare but may be curable in both if recognized and treated early.[70]

Colorectal Cancer

About 300 cases of colorectal cancer during pregnancy have been reported; underlying risk factors such as hereditary or familial syndromes and long-standing inflammatory bowel disease are likely to be particularly relevant in this younger age group.[71] Unlike the general population, in which only 20% to 25% of colon cancers occurs in the rectum, a higher incidence of rectal presentation may result from increased local symptoms from rectal compression by the pregnant uterus or more frequent rectal or pelvic examinations. Sigmoidoscopy is safe. While the safety of colonoscopy during pregnancy is not well established, the limited literature suggests no increase in adverse outcome to the mother or children.[71] Abdominal ultrasound is safe, but CT scanning of the abdomen and pelvis, especially in the first trimester, is problematic (see the section on radiology). Of note, ovarian metastases occur in 25%,[71] and serum BHCG may be elevated owing to ectopic production by the cancer cells.[72]

Surgical recommendations are complex and are well summarized in a recent review.[71] Adjuvant chemotherapy with 5-FU or related drugs such as capecitabine is contraindicated in the first trimester. Later trimester exposure to 5-FU has not been associated with increased fetal loss or development abnormalities but with intrauterine growth retardation and prematurity. Delaying adjuvant chemotherapy is an option, but whether the beneficial effect is maintained is unclear. Preoperative or postoperative radiotherapy is contraindicated during pregnancy. Survival is generally poor, owing to late presentation and advanced pathologic stage, but is no different from that in the general population when stratified for pathologic stage.[73]

Thyroid Cancer

The most common presentation is that of an asymptomatic nodule. The outcome does not appear to be affected by pregnancy.[74] Recommendations include delaying surgery to the second trimester for tumors that are diagnosed early in pregnancy and, if required, administration of radioiodine after delivery, as it might cause cretinism in the fetus.[75] Conventional chemotherapy is not particularly effective in resistant disease.

Other Cancers

Gastrointestinal pancreatic and hepatic cancers are very rare in pregnant women, except for gastric cancer in Japan. Delays in diagnosis are common. A detailed review of these malignancies in pregnancy has recently been published.[76]

Genitourinary malignancies are rare, although the risk of renal cell cancer may be increased by pregnancy.[77] Lung cancer has a poor prognosis in pregnancy,[14] and metastasis of small cell carcinoma from mother to fetus has been reported.[14,78] Sarcomas are rare in pregnancy. There appears to be no interaction between pregnancy and the natural history of osteogenic carcinoma.[79] Successful delivery of chemotherapy to the mother has been reported for Ewing's sarcoma.[80]

HEMATOLOGIC MALIGNANCIES

Hodgkin's Lymphoma

Hodgkin's lymphoma, with an incidence of 1 : 1000 to 1 : 6000, is the most common lymphoma in pregnancy.[81] Reasonable options for staging in pregnancy include a CT scan of the neck and chest with MRI of the abdomen and pelvis.

The majority of patients who are found to have Hodgkin's lymphoma during pregnancy do not require immediate intervention. Asymptomatic or minimally symptomatic patients can be followed carefully, with treatment reserved for threatening or more symptomatic disease; many patients can carry the pregnancy to term without any treatment becoming necessary.[34]

Options for symptomatic disease that is diagnosed in the first trimester include single-agent chemotherapy or multiagent chemotherapy with or without a prior therapeutic abortion. There are no large studies of the teratogenic effects in the first trimester of commonly used regimens such as ABVD, although the limited literature has not demonstrated any adverse effect.[8,35] Vinca alkaloids, anthracyclines, bleomycin, and steroids appear to be relatively safe in the first trimester, but alkylators such as cyclophosphamide and dacarbazine may be teratogenic. Options that have been proposed include ABV or vinblastine alone.[34,35] Mantle field radiotherapy for supradiaphragmatic disease has not been associated with adverse fetal effects, as the estimated fetal dose after uterine shielding is below the threshold for major congenital malformations.[81] Nevertheless, it is rarely indicated, and its use during pregnancy cannot be considered standard, as there is a lack of reliable clinical data on late effects.

Multiagent chemotherapy such as ABVD appears to have minimal fetal risk when administered during the second or third trimester, with only one minor malformation in 10 patients treated with ABVD ($n = 9$) or ABV ($n = -1$) (E. Cardonick, personal communication).[35] An option is single-agent vinblastine, which almost always induces some disease regression and allows disease control until after delivery, at which time multiagent chemotherapy can be delivered.[34] These alternatives—that is, (1) prompt potentially curative chemotherapy with protocols such as ABVD after counseling that there does not seem to be an increased risk of congenital birth defects or of significant long-term neurologic sequelae or (2) minimizing fetal risk by delay of definitive therapy until after delivery—need to be discussed in each case, considering factors such as symptoms and aggressiveness of the tumor. Supradiaphragmatic radiation is problematic in the third trimester, as fetal exposure is increased owing to uterine proximity.

The role of allogeneic stem cell transplantation for Hodgkin's lymphoma is controversial, but this approach is occasionally used in patients with relapsed disease after an autograft. In the absence of a histocompatible sibling, alternative sources of allogeneic stem cells include marrow, peripheral stem cells, or cord blood from an unrelated donor. Cryopreservation of umbilical cord blood at delivery is an issue that might need to be addressed in some patients with high-risk disease.[82]

Non-Hodgkin's Lymphoma

Aggressive non-Hodgkin's lymphoma (NHL) in pregnancy is rare, with an incidence of approximately 1 in 100,000. Indolent NHL usually does not require immediate therapy.[82] The NHL that is most likely to require treatment in pregnancy is CD20 positive diffuse large B cell NHL. These lymphomas are usually aggressive and advanced at diagnosis in pregnancy with a higher incidence of breast, uterine, cervical, and ovarian involvement, perhaps related to increased vascularity.[81] The current standard therapy is CHOP-rituximab, with consideration of the addition of involved field radiotherapy for localized disease.[83]

Treatment delay is rarely advisable in the first trimester but may be a consideration in some patients with relatively indolent disease

clinically. A recommended option has been a therapeutic abortion followed by standard chemotherapy.[81] However, experience with CHOP-based regimens in the first trimester suggests the risk of teratogenicity is low; Aviles reported no adverse fetal outcome 17 mothers with aggressive NHL treated in the first trimester with CHOP-bleomycin or similar regimens.[8] This suggests that CHOP-based chemotherapy, preferably without an alkylator initially, is a reasonable consideration during the first trimester when treatment is required without delay and termination is not acceptable. Prompt administration of CHOP-rituximab chemotherapy is recommended in the second trimester. Reduced intervals between cycles (e.g., each 2 weeks versus the standard 3 weeks) is commonly used in nonpregnant women[84] but is not currently advised in pregnancy, as there are no data on this approach.

An important issue is the safety of rituximab during pregnancy. This agent has been shown in a number of randomized studies to improve outcome in aggressive CD20+ NHL and represents a major therapeutic advance.[83] Administration of rituximab during organogenesis in monkeys had no obvious adverse effect on embryo or fetal development apart from the expected pharmacologic effect of B cell depletion, as IgG is known to cross the placental barrier.[85] The available literature in human pregnancy is limited. Two reports of exposure to rituximab without chemotherapy in the first trimester have described delivery of healthy, normal babies with no immunologic deficits.[22,23] Four reports of CHOP (or CHOP-like)-rituximab chemotherapy in the second trimester described delivery in all cases of healthy babies with subsequent normal immunologic reconstitution.[24–27] Two babies had detectable rituximab levels at birth with severe B lymphopenia but subsequently achieved normal immunologic status at 3 to 4 months without infectious sequelae in the interim.[26,27] One report of rituximab in the third trimester described no toxicity apart from asymptomatic transient neonatal neutropenia.[28] The approved product information states that rituximab should not be given to a pregnant woman unless the potential benefit outweighs the potential risk. A reasonable position is to recommend rituximab as part of combination chemotherapy during pregnancy, as in the author's opinion, the available evidence suggests that the maternal benefits outweigh the fetal risk.

Acute Leukemia

The presence of acute leukemia and/or its treatment has been associated with increased incidence of premature birth, stillbirths, and intrauterine growth retardation, particularly early in pregnancy.[35] Contributing factors other than chemotherapy include sepsis, anemia, and disseminated intravascular coagulation. Treatment is generally required without delay, irrespective of gestational age, as delay may increase both fetal and maternal mortality.

The most common acute leukemia in adults is acute myeloid leukemia, for which the usual chemotherapy is cytarabine (with at least one high-dose course) and an anthracycline such as daunorubicin or idarubicin. Acute lymphoblastic leukemia in adults is less common; induction treatments are less standard and more complex than in acute myeloid leukemia but generally include cyclophosphamide, vincristine, adriamycin, and steroids. Consolidation treatments in acute lymphoblastic leukemia characteristically include high-dose methotrexate. The risk of teratogenicity appears to be confined to the first trimester, particularly with methotrexate, other antimetabolites, thioguanine, and alkylating agents.[35] Cytarabine has been associated with limb malformations after first trimester exposure.[18] Other chemotherapy drugs such as vincristine, anthracyclines, and prednisolone appear to be relatively safe. Aviles and colleagues reported the outcome of 29 pregnancies that were complicated by acute leukemia: acute myeloid leukemia in 19 patients and acute lymphoblastic leukemia in the remainder.[8] All were treated with standard antileukemic protocols; 11 received chemotherapy during the first trimester. No congenital abnormalities were observed, there was no evidence of intrauterine growth retardation, and no excess of complications was seen in long-term follow-up in the children.

General principles of management include the following:

- In the first trimester, a therapeutic abortion is probably the recommendation of choice, particularly in acute myeloid leukemia, owing to concern of the teratogenicity of the optimal chemotherapy. Methotrexate is absolutely contraindicated.
- In the second and third trimesters, it is reasonable to treat with standard regimens without inducing an abortion, as there are no convincing data that the relevant chemotherapy is teratogenic at this time. However, the mother needs to be counseled about the fetal risks from maternal sepsis, anemia, and coagulopathy. High-dose methotrexate is inadvisable, and the administration of high-dose cytarabine is arguably best deferred until after birth, as there is minimal experience with this schedule during pregnancy.
- If possible, delivery should be scheduled not to coincide with severe neutropenia and thrombocytopenia. It is recommended to maintain platelets at greater than 30 to 50×10^9/L, especially around time of delivery, to allow for regional anesthesia and to maintain hemoglobin at greater than 9.8 g/dL, as perinatal complications increase as the hemoglobin declines.[82,86] Neonatal blood counts should be checked at delivery. Neonates are at risk of transient myelosuppression and cardiomyopathy after administration of idarubicin.[11]

- Following are some specific points:
  - Use of prednisolone rather than dexamethasone is recommended owing to concern of repeated fetal exposure to dexamethasone and adverse neurologic sequelae.[82] Steroids may increase the risk of diabetes owing to increased insulin resistance in pregnancy.
  - L-Asparaginase is commonly used in acute lymphoblastic leukemia protocols. Limited experience suggests this drug does not pose a major risk to the fetus when used beyond the first trimester. However, L-asparaginase has been associated with thromboembolism related to reduced levels of antithrombin III.[87] The risk may be higher in pregnancy, which is a hypercoagulable state. Consideration should be given to prophylactic infusion of antithrombin III concentrates if L-asparaginase is administered during pregnancy or in the first 6 weeks thereafter.
  - Acute promyelocytic leukemia is optimally treated with all-*trans*-retinoic acid, usually in combination with an anthracycline.[88] Retinoic compounds are teratogenic in animals, which has led to FDA approval of a centralized pregnancy risk management program for isoretinoin preparations. First trimester acute promyelocytic leukemia should be managed with a therapeutic abortion followed by chemotherapy that includes all-*trans*-retinoic acid. However, there are a number of reports of safe and effective use of all-*trans*-retinoic acid in the second trimester and beyond.[89,90] Arsenic is another agent active in acute promyelocytic leukemia. There are no data on the effect of therapeutic doses of arsenic in pregnancy, but epidemiologic studies in women with chronic exposure to arsenic found in drinking water reported an increase in stillbirths and an increase in spontaneous abortions.[91] These observations would argue strongly against the use of arsenic in pregnancy at any stage.

Chronic Leukemias

Of the chronic leukemias, chronic myeloid leukemia (CML) is the condition that is most likely to require treatment in pregnancy. Imatinib is now the treatment of choice in newly diagnosed CML.[92] Imatinib is teratogenic in rats (but not rabbits) during organogenesis at ≥100 mg/kg, doses that are equivalent to >800 mg/day in adults based on body surface area.[93] Defects include exencephaly, encephalocele, and skull bone abnormalities with fetal loss in all animals. Postimplantation loss occurred at doses ≥45 mg/kg, approximately

equivalent to 400 mg/day. The product information from Novartis recommends that imatinib not be used in pregnancy.

A recent publication reported on 180 cases of women who were exposed to imatinib during pregnancy.[17] Timing of exposure by trimester was known in 146 cases; of these, 71% involved exposure in the first trimester. Outcome data were known for 125 cases (63%): normal live infant ($n = 63$; 50%), elective termination ($n = 35$; 28%, including three following identification of fetal abnormalities), fetal abnormality ($n = 12$; 10%), and spontaneous abortion ($n = 18$; 14%). The fetal abnormalities included bony defects similar to those seen in animal models as well as an excess incidence of exomphalos. No data was presented on crucial issues such as the relationship of dose to the incidence and nature of fetal abnormalities or whether abnormalities were confined to first trimester exposure.

The MD Anderson group reported the outcome of CML in 10 women in whom imatinib was discontinued immediately after pregnancy was identified.[94] Six patients had an increase in Philadelphia-positive metaphases during pregnancy. All resumed imatinib after the abortion or birth, and nine achieved complete hematologic remission with varying levels of cytogenetic response with a median follow-up of 18 months (5 to 40 months).

Within the caveats of this limited experience, the following guidelines are suggested:

- In the first trimester, cease imatinib immediately. Counsel that there might be an increased risk of spontaneous abortion and fetal abnormalities, although the risk is probably not high enough at 400 mg/day to recommend termination of the pregnancy. There is no meaningful experience at doses in excess of 400 mg/day. Monitor CML, and institute treatment with leukapheresis or interferon if therapy is required. Interferon is thought to be safe in all trimesters.[95] Hydroxyurea is teratogenic at high doses in animals but has not been associated with major malformations in human pregnancies, even with first trimester exposure.[96] Consider reintroduction of imatinib at 400 mg/day in the second and third trimesters if CML is poorly controlled with these other measures and the mother's health is compromised.
- In the second and third trimesters, cease imatinib and commence interferon if therapy is required, but consider resumption as described previously.
- Postpartum, resume imatinib as quickly as practical. It should not be administered to women who are breast-feeding.

OTHER CONSIDERATIONS

Therapeutic Abortion

The decision by the mother or parents whether to continue with the pregnancy or to have a therapeutic abortion will depend on ethical, moral, and religious issues as well as the medical situation. Some of the parental considerations include willingness to assume a possible risk of fetal toxicity either directly from chemotherapy or radiation or indirectly from maternal complications of therapy, the impact on prognosis of delaying effective chemotherapy until the second trimester if a termination is not performed and there is unwillingness to accept risks to the fetus of chemotherapy in the first trimester, overall maternal prognosis and the ability to care for the child, and the effect of treatments on future fertility.

Therapeutic Radiation

Radiation therapy is commonly used in the treatment of patients with breast cancer, cervical cancer, and lymphoma, and systemic iodine 131 is often used for treatment of thyroid cancer. The use of radiation therapy is addressed in the sections devoted to these cancers. Radiation is extremely important for palliation of cancer-related symptoms and has been carefully used during pregnancy without fetal harm.

Subsequent Pregnancy

There is no evidence that a subsequent pregnancy increases the risk of recurrence of any malignancy in the mother, including hormone-responsive breast cancer, or the risk of fetal anomalies. Standard practice has been to defer pregnancy for 2 to 3 years, as the relapse risk is highest during this period, but recommendations need to be individualized on the basis of each patient's circumstances.

Transfer of Maternal Disease to the Fetus

Placental involvement has been documented, albeit rarely, in a variety of malignancies, but only a handful of cases of active transfer of malignancy to the fetus have been described; most have been melanoma. It is reasonable to counsel the mother that, apart perhaps from melanoma, the risk is minimal.

CONCLUSION

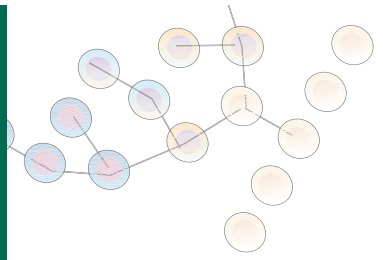
The care of the pregnant woman with cancer is complicated by unique issues such as the teratogenicity of staging procedures as well as chemotherapy and radiotherapy, the altered maternal physiology affecting drug metabolism, the impact of treatment on subsequent fertility, and the emotional trauma experienced by the mother (and her partner) in making decisions about the well-being of herself and the unborn child. Appropriate management of these issues necessitates the coordinated effort of a multidisciplinary team including hemato-oncologists, surgeons, nurses, psychologists, obstetricians, and pediatricians.

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69 HIV-Associated Malignancies

Richard F. Ambinder and Nina D. Wagner-Johnston

SUMMARY OF KEY POINTS

Incidence

- Non-Hodgkin's lymphoma, Hodgkin's lymphoma, and Kaposi's sarcoma (KS) all occur with increased incidence in human immunodeficiency virus (HIV)-infected patients.
- KS occurs in HIV-infected patients who also are infected with KS herpesvirus (KSHV). Outside of Africa and some Mediterranean populations, KS occurs mainly in men who have sex with men.
- Lymphoma (non-Hodgkin's and Hodgkin's) occurs in all HIV risk groups. These neoplasms tend to be aggressive and extranodal and to manifest at an advanced stage. Burkitt's and Hodgkin's lymphomas tend to occur in patients with higher $CD4^+$ counts (typically greater than 200/mm^3), whereas primary central nervous system lymphoma tends to occur in patients with very low $CD4^+$ counts (typically less than 50/mm^3).

Etiology and Pathogenesis

- KS is always associated with KSHV; immunocompromise, inflammatory cytokines, and perhaps the HIV TaT protein contribute to pathogenesis.
- Lymphoma in HIV-infected patients is associated with Epstein-Barr virus (EBV) in approximately half of the cases; immunocompromise, chronic antigen stimulation, and perhaps inflammatory cytokines and chemokines contribute to pathogenesis.

Evaluation of Patients with Kaposi's Sarcoma

- Determination of $CD4^+$ T-cell count and HIV load is the first step in evaluation.
- Biopsy is indicated to confirm diagnosis.
- Computed tomography (CT) scan of chest and abdomen also is indicated.
- Gastrointestinal endoscopy is performed if clinically indicated

Treatment of Kaposi's Sarcoma

- Highly active antiretroviral therapy (HAART) and treatment of opportunistic infections sometimes are associated with regression of KS.
- If disease is symptomatic or rapidly progressive, or with visceral involvement, systemic therapy with liposomal anthracycline or paclitaxel is instituted; all patients should be receiving *Pneumocystis* prophylaxis. Hematopoietic growth factors and antifungal and anti-herpesvirus prophylaxis or treatment also are appropriate for most patients receiving cytotoxic chemotherapy.
- If disease is indolent and antiretroviral therapy has just been initiated or major changes have been made, observation may be appropriate.
- For a few lesions, topical therapy, injection of lesions, or radiation therapy may be adequate treatment.
- For systemic disease, interferon, thalidomide, or experimental therapy should be considered.

Evaluation of Patients with Lymphoma

- Determination of $CD4^+$ T-cell count and HIV load is the first step in evaluation.
- Assessment for signs of tumor lysis also is indicated.
- Extranodal presentations of lymphoma are common, as are constitutional symptoms (especially with Hodgkin's lymphoma).
- Staging for systemic lymphoma should include testing lactate dehydrogenase levels; imaging of chest, abdomen, and brain; bone marrow biopsy; and lumbar puncture.
- Positron emission tomography (PET) scans with fluorodeoxyglucose (FDG) labeling should be interpreted with extreme caution because HIV infection, inflammation associated with opportunistic infection, and immune reconstitution syndrome all are associated with FDG activity.

Treatment of Lymphoma

- Allopurinol and hydration constitute the first step in treatment, even before staging is complete.
- Chemotherapy (with cyclophosphamide, hydroxydaunomycin (doxorubicin), vincristine (Oncovin), and prednisone (CHOP) plus rituximab or etoposide, Oncovin, doxorubicin, cyclophosphamide, and prednisone (EPOCH) plus rituximab for non-Hodgkin's lymphoma, and doxorubicin (Adriamycin), bleomycin, vincristine, and dacarbazine (ABVD) or the Stanford V regimen for Hodgkin's lymphoma) is standard treatment.
- Intrathecal prophylaxis is appropriate for patients with Burkitt's or Burkitt's-like lymphoma, for patients with bone marrow involvement of non-Hodgkin's lymphoma, and for patients with EBV-associated non-Hodgkin's lymphoma. Either cytarabine or methotrexate can be used for this purpose.

Cytotoxic Therapy for Cancer

- *Pneumocystis* prophylaxis is given regardless of $CD4^+$ count.
- Antifungal and anti-herpesvirus infection prophylaxis or treatment also is indicated.
- In HAART-naive patients, antiretroviral therapy should be initiated shortly after cytotoxic chemotherapy begins when associated nausea is controlled.
- Patients with relapsed lymphoma may be appropriate candidates for high-dose therapy with stem cell rescue.

INTRODUCTION

In 1981, the first cases of *Pneumocystis carinii* pneumonia in gay men were reported.[1] Shortly thereafter, KS, primary central nervous system lymphoma, and Burkitt's lymphoma also were recognized in gay men. In 1983 human immunodeficiency virus (HIV-1) was cultured from the lymph node of a patient.[2] The origins of the HIV/AIDS (acquired immunodeficiency syndrome) epidemic remain obscure, but by 2006, the impact of the epidemic was staggering. Nearly 40 million people worldwide were infected with HIV, and the annual death rate was approximately 3 million, making HIV the fourth leading cause of death worldwide.[3] In North America, approximately 1.4 million people are infected, and almost half a million have died. Among patients with access to antiretroviral therapy, however, AIDS-related mortality has dramatically declined. This chapter reviews aspects of HIV infection and the diagnosis and management of KS, AIDS-associated lymphoma, and Hodgkin's lymphoma.

HIV INFECTION

The virus is transmitted sexually, parenterally, and vertically.[4] Worldwide, heterosexual transmission is most common. Condoms reduce the risk of transmission, and male circumcision reduces the risk of female-to-male HIV transmission.[5] The highest risk of sexual transmission is associated with receptive anal intercourse. In the United States, men who have sex with men are the largest HIV risk group. Injection drug use also is a major contributor to the epidemic. Health care workers are at risk, but barrier precautions, safer needle devices, attention to safe practices, and related technical innovations have reduced exposure.[6]

HIV is associated with a spectrum of disease from asymptomatic to profoundly immunocompromised. HIV RNA levels are important predictors of the rate of progression, whereas $CD4^+$ T-cell counts are markers of immunologic status. In patients who do not receive treatment, the plasma HIV load reaches a fairly constant level within about 6 months of primary infection. The host cytotoxic T-cell response is one determinant of this "set point." Some diseases are specifically associated with low $CD4^+$ T-cell counts. For example, *Pneumocystis* pneumonia typically occurs in patients with counts of less than 200 cells/mm^3, and primary brain lymphoma typically is diagnosed in patients with counts of less than 50 cells/mm^3.[7]

A variety of constitutional signs and symptoms are common in HIV-infected patients, even in the absence of opportunistic infection or malignancy. These include anorexia, nausea, vomiting, and weight loss. Persistent fever, however, always requires a search for opportunistic infections. Typically this investigation involves a chest radiograph, sinus CT scan, blood cultures for bacteria and atypical mycobacteria, and serum cryptococcal antigen test. Neurologic problems include AIDS dementia complex, HIV myelopathy, and various peripheral neuropathies.

Opportunistic infections that commonly occur in HIV-infected patients include *Pneumocystis* pneumonia (the agent of which is now called *Pneumocystis jiroveci*), chronic sinusitis, oral and esophageal candidiasis, herpes simplex infections, shingles, cytomegalovirus retinitis, and enterocolitis associated with *Campylobacter*, *Salmonella*, *Shigella*, adenovirus, cytomegalovirus, or any of various protozoans (*Cryptosporidium*, *Entamoeba histolytica*, *Giardia*, and others). A variety of infections manifest in the central nervous system, including toxoplasmosis, progressive multifocal leukoencephalopathy, and cryptococcal meningitis. Skin infections with molluscum contagiosum and dermatophytic fungi also are common. Several of these infections can be prevented with appropriate prophylaxis[8] (Table 69-1).

Antiretroviral therapy generally is recommended for all patients with acute HIV infection or within the first 6 months after seroconversion.[9–11] In addition, antiretroviral therapy is recommended for all patients with symptomatic AIDS, thrush, or unexplained fever and patients with $CD4^+$ T-cell counts below 200/mm^3. For asymptomatic patients with $CD4^+$ T-cell counts above 200/mm^3, many clinicians would initiate therapy only in those with higher viral loads. Drugs approved for the suppression of viral replication include nucleoside analog reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and an inhibitor of fusion of the viral envelope with $CD4^+$ T cells.[12] In parallel with the treatment of chemotherapy-responsive malignancies, combination antiretroviral therapy with two or more agents appears to be the most effective way to suppress viral replication and to reduce the emergence of resistant virus. Use of non-nucleoside reverse transcriptase inhibitors is associated with rapid mutations to high-level resistance, so these agents should never be used alone. Use of protease inhibitors sometimes is associated with lipodystrophy, a disorder associated with fat redistribution. The only available envelope fusion inhibitor, enfuvirtide, is a parenteral drug and approved solely for resistant virus. A convenient guide to the medical management of HIV infection, which is updated regularly, can be found at the Johns Hopkins AIDS Service website (http://hopkins-aids.edu/publications/publications).

Table 69-1 Prophylaxis of Opportunistic Infections

$CD4^+$ T-Cell Count	Indicated Prophylaxis
Less than 200/mm^3	*Pneumocystis* pneumonia (PCP)* prophylaxis with TMP-SMX, dapsone, or aerosolized pentamidine.
Less than 100/mm^3	Toxoplasmosis prophylaxis in patients who are seropositive for *Toxoplasma gondii*. TMP-SMX administered for PCP prophylaxis also protects against toxoplasmosis. A variety of other agents are available for use in patients not receiving TMP-SMX.
Less than 50/mm^3	*Mycobacterium avium* complex (MAC) infection prophylaxis. The drug of choice is either clarithromycin (daily) or azithromycin (weekly).

TMP-SMX, trimethoprim-sulfamethoxazole.
*I.e., *Pneumocystis jiroveci* infection.

KAPOSI'S SARCOMA

Epidemiology

Before AIDS, KS was a rare disease recognized in older men of Eastern European or Mediterranean descent, in parts of Africa where it often occurred in children, and in organ transplant recipients.[13] Among AIDS patients, KS is the most common cancer. The risk of development of KS for an HIV-infected patient in the pre-HAART era was estimated to be greater than 1000 times the risk in the HIV-uninfected population.[14] With antiretroviral therapy, the incidence has diminished substantially.[15,16] The risk of KS is not evenly distributed among HIV risk groups. KSHV, also referred to as human herpesvirus-8 (HHV-8), is a required cofactor.[13] In contrast with most human herpesvirus infections, which are ubiquitous, KSHV infection is uncommon in most populations worldwide. Rates of infection are higher in central and southern Africa and intermediate in Mediterranean and Eastern European countries.

Men who have sex with men are at especially high risk for acquiring KSHV infection.[17] Sexual transmission may be inferred from several studies, but the precise mode of transmission remains poorly understood. By contrast, patients who acquire HIV infection through nonsexual blood-borne exposure (from intravenous drug use or transfusion of blood or blood products) are at lower risk for KSHV infection and for the development of KS. Among persons who are seropositive for KSHV and HIV, the sequence of exposure is an

important risk factor for the development of KS.[18] When KSHV seroconversion follows HIV seroconversion, the risk of developing KS is higher. Presumably this reflects the impact of HIV on establishing an effective primary immune response to KSHV.

Pathogenesis

KS lesions are composed of spindle-shaped cells between collagen bundles, neovascular slit-like spaces, extravasated erythrocytes, hemosiderin-laden macrophages, and an infiltrate of plasma cells, lymphocytes, and other inflammatory cells.[19] Spindle cells show nuclear pleomorphism in the later stages. Lesions begin in the dermis and progress from macular to plaque to tumor stage. In the early macular stage, spindle cells form irregular slits and clefts. Nuclear atypia and mitoses are absent. In the plaque stage, the entire dermis is involved, and extravasated erythrocytes and hemosiderin-laden macrophages appear. With progression to the tumor stage, spindle cells come to predominate. Nuclear atypia and mitoses are present.

Spindle cells probably are of lymphatic endothelial origin. KS may begin as a polyclonal inflammatory lesion and only sometimes progress to clonal neoplasia. Immunohistochemistry and in situ hybridization studies show that KSHV is present in spindle cells and some of the cells of the inflammatory infiltrate. KSHV is invariably present in KS lesions.[20] Electron microscopy shows evidence of viral production in some cells in KS lesions (Fig. 69-1), but spindle cells generally are latently infected (Fig. 69-2). Several viral genes are implicated in aspects of regulation of cellular growth, apoptosis, immune regulation, and angiogenesis.[21] Curiously, many of the genes with functional properties suggesting that they may play a role in transformation are lytic cycle genes and are not expressed in most of the spindle cells of KS lesions. These include the viral interferon regulatory factors (v-IRFs), an antiapoptotic protein viral Bcl-2 (v-Bcl-2), viral interleukin 6 (v-IL-6), a G protein-coupled receptor (GPCR), and K1, a transmembrane glycoprotein with transforming properties. The viral proteins that are expressed in latently infected spindle cells are LANA (latency-associated nuclear antigen), a nuclear protein required for maintenance of the viral episome; v-CyC, a cyclin-D homolog that may disrupt usual pathways of cell cycle inhibition; and v-FLIP (viral FLICE-like inhibitory protein—FLICE being Fas-associated protein with death domain [FADD]-like interleukin-1α–converting enzyme), an antiapoptotic protein that blocks death signals and may induce survival signals. KSHV LANA may recruit de novo DNA methyltransferases, an integral feature in the development of cancer.[22] The molecular biology of the virus and its role in transformation are discussed further in Chapter 11.



Figure 69-1 • Electron micrograph showing herpesvirus particles budding from spindle cells in a Kaposi's sarcoma lesion. (Courtesy of Jan Orenstein.)

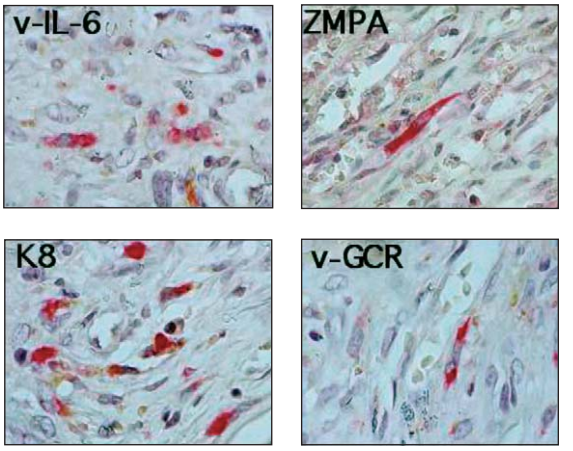


Figure 69-2 • Kaposi's sarcoma herpesvirus (KSHV) antigens in spindle cells of a nodular KS lesion. Immunohistochemical studies show punctate nuclear LANA *(brown spots)* in many cells, with v-GPCR expression *(red cytoplasm)* in a few scattered lytic cells with nuclei that are devoid of LANA. LANA, latency-associated nuclear antigen; v-GPCR, viral G protein-coupled receptor; v-IL-6, viral interleukin-6.

The immune system seems to play a determining role in the pathogenesis of KS. In organ transplant recipients, reduction or withdrawal of immunosuppression is often associated with tumor regression.[17] The virus itself expresses a number of genes that modify immune function. Viral genes modulate the actions of interferon and downregulate the display of major histocompatibility complex (MHC) class I and natural killer (NK) cell receptor ligands.[23–25] Cytotoxic T-cell responses to viral lytic antigens are readily detected in KSHV-seropositive individuals but are diminished in HIV-infected persons.

Cytokine dysregulation associated with HIV infection may specifically enhance the proliferation of this neoplasm. In vitro interleukin-6, tumor necrosis factor-α, interleukin-1β, interleukin-8, and various chemokines will stimulate proliferation of KS-derived cells. The HIV TaT protein may activate the RAS/ERK MAPK and JAK/STAT pathways, leading to lytic cycle replication of KSHV.[26,27] Opportunistic infections often precede the presentation or an exacerbation of KS. Although both phenomena may reflect a deterioration of underlying immune status, several investigators have suggested that altered cytokine and inflammatory mediator production in association with opportunistic infection may have a direct impact on KS pathogenesis.[28]

Clinical Aspects

KS lesions typically arise on the skin or mucous membranes as flat deep purple plaques (Fig. 69-3). These plaques may progress to form nodules. Many parts of the body may be involved, and the clinical problems associated with KS vary as a function of location. Lesions generally are not pruritic or painful (except occasionally when they involve the plantar surface of the feet). The most frequent sites of disease are the skin, mucous membranes, lymph nodes, and gastrointestinal tract. Skin lesions most commonly appear on the legs and face (especially the nose and ears) and often are symmetrically distributed. The oral hard palate also is commonly involved. KS virtually never involves brain parenchyma.

KS lesions have a distinctive appearance that is highly suggestive with regard to diagnosis. Other entities, however, occasionally are confused with KS. Among them is bacillary angiomatosis, a benign

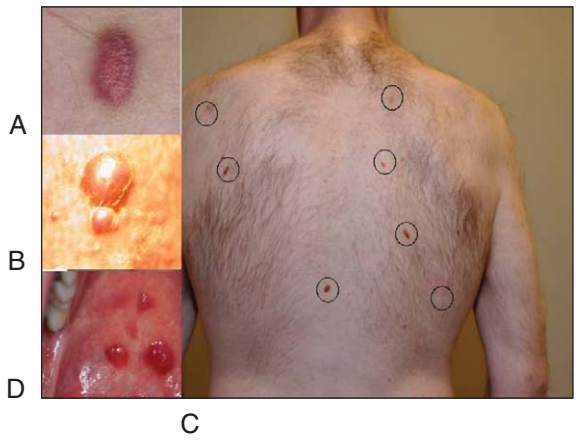


Figure 69-3 • Kaposi's sarcoma lesions. **A,** Plaque lesion. **B,** Nodular lesions. **C,** Near-symmetrical distribution of lesions on the trunk. Lesions are circled. **D,** Lesions on the hard palate.

disease associated with a slow-growing, fastidious, gram-negative bacillus and treated with antibiotic therapy.[29] Bacillary angiomatosis often is associated with systemic symptoms such as fever, chills, and headache. Therefore, a biopsy generally is indicated to confirm the diagnosis. This most commonly is a punch biopsy of a skin lesion, but at times lymph node biopsy, transbronchial or other endoscopic biopsy, or pleural biopsy is required. Once the diagnosis has been established, visualization of a characteristic lesion by bronchoscopy without biopsy or characteristic CT findings (flame-shaped hemorrhages) generally are regarded as adequate to diagnose pulmonary KS (Fig. 69-4). Gallium scan may be useful in differentiating pulmonary KS from *Pneumocystis* pneumonia, because the inflammatory infiltrates in *Pneumocystis* pneumonia are gallium-avid and KS lesions are not. On the other hand, KS lesions usually are thallium-avid.

Lesion location is an important determinant of symptoms. Facial lesions are particularly likely to be cosmetically disturbing. Lesions of the lower extremities often lead to lymphatic obstruction with painful edema. Pulmonary lesions often are associated with dyspnea (but rarely with hemoptysis). Gastrointestinal lesions may be associated with pain, cramping, diarrhea, and bleeding or may be entirely asymptomatic.

Staging and Prognosis

Standard tumor-node-metastases (TNM) staging has not proved particularly useful for KS, partly because KS is a multicentric disease and partly because the status of HIV disease is of overriding importance.



Figure 69-4 • Computed tomographic scan of the chest shows a nodular lesion with characteristic flame-like appearance adjacent to the right upper bronchus. (Courtesy of Elliot Fishman.)

The AIDS Clinical Trials Study Group (ACTG) developed a staging system specifically for KS occurring in HIV-infected persons.[30] Devised in the era before the introduction of HAART, this system classified patients as "good risk" or "poor risk" according to the extent of tumor (confined to skin or minimal disease versus edema, ulcers, and extensive oral, visceral, or gastrointestinal invasion), immune status as measured by $CD4^+$ T-cell count ($\geq 200/mm^3$, $<200/mm^3$), and evidence of HIV-associated systemic symptoms; it proved to be a reasonable predictor of survival. When the ACTG staging system was re-evaluated in patients receiving HAART, immune status was no longer associated with an increased risk of death, even when the $CD4^+$ cutoff point was lowered to $100/mm^3$ or less.[31]

Suppression of HIV replication with antiretroviral therapy sometimes is associated with remission.[32,33] It has been noted that some protease inhibitors have direct antiangiogenic effects, but regimens that do not include protease inhibitors appear equivalent with regard to clinical outcome of antiretroviral-naive HIV-infected patients with KS.[34] KSHV copy number does not correlate well with clinical response in patients receiving liposomal doxorubicin.[35]

Therapy

Management of HIV and Opportunistic Infection

HAART has profoundly altered the survival of patients with KS. The Multicenter AIDS Cohort Study showed an 81% reduced risk of death for patients with KS who received HAART.[33] The only form of KS clearly implicated in directly causing the death of patients is pulmonary KS. In the era before HAART, KS was associated with a 90% mortality rate attributable to disease progression. In patients receiving HAART, KS is associated with a 47% mortality rate.[36]

The impact of antiviral therapy may be multifaceted. Restoration of immune function must be of major importance, but antiviral therapy also may reduce exposure to HIV proteins such as TaT and a variety of inflammatory cytokines associated with opportunistic infections also thought to play a role in KS progression. Thus, therapy begins with ensuring that the antiretroviral regimen has been optimized and that opportunistic infections have been treated (Box 69-1). In the absence of rapidly progressing disease (more than 10 new lesions in the past month), lymphedema, or symptomatic visceral or cosmetically disfiguring disease, it often is appropriate to wait several months to assess the full impact of the initiation of antiretroviral therapy before systemic therapies are instituted.

Systemic Therapy

Interferon-α is active in a subset of patients.[37] The mechanism of action may involve antiviral, immune modulatory, antiproliferative,

Box 69-1. TREATMENT OF KAPOSI'S SARCOMA

- *Treatment with liposomal anthracycline*: Liposomal doxorubicin is administered at a dose of 20 mg/m^2 intravenously every 2 to 3 weeks. Granulocyte colony stimulating factor (G-CSF) is used as needed. Once a maximum response is attained, treatment is discontinued.
- *Treatment with paclitaxel*: Paclitaxel is administered at 100 mg/m^2 infused over 3 hours every 2 weeks. G-CSF is routinely used. Once a maximum response is attained, treatment is discontinued.
- *Treatment with interferon-α*: Therapy begins at 1 million units/per day, with dose escalation as tolerated up to 9 million units per day over a period of 2 months. Interferon treatment is associated with flu-like symptoms of fevers, chills, myalgias, and fatigue. These symptoms typically diminish and tolerance improves with time. Night-time administration and adjuvant use of acetaminophen and nonsteroidal anti-inflammatory medications improve the tolerability of the regimen. Patients who respond or whose disease is stable are continued on treatment until disease progression.

or antiangiogenic properties. Uncertainties with regard to mechanism notwithstanding, interferon-α has demonstrated beneficial activity in the treatment of KS. In combination with protease inhibitor-based antiretroviral therapy, interferon can be safely administered at 5 million IU per day.[38] Dose-limiting toxicities are neutropenia and malaise. Time to interferon response of 8 to 12 weeks precludes its use in patients with very symptomatic or aggressive disease. On the other hand, responses often are long-lasting, particularly complete responses (CRs). This period is longer than the response duration typically associated with cytotoxic chemotherapy. Furthermore, even patients with widespread disseminated disease can have complete clinical responses.

Although a variety of single agents and combinations of agents have been studied in the past, single-agent therapy with a liposomal anthracycline or with paclitaxel is now the standard of care. Liposomal formulation of anthracyclines leads to altered pharmacokinetic profiles. Thus, liposomal doxorubicin has a prolonged plasma half-life and achieves increased concentration in tumor tissues and decreased concentration in normal tissues.[39] In phase III trials, liposomal doxorubicin and liposomal daunorubicin have been shown to be at least as effective as and less toxic than combination regimens including nonliposomal anthracyclines.[40,41] Liposomal anthracyclines generally are well tolerated, with myelosuppression as the major limiting toxicity. A "hand-foot" syndrome occasionally is seen and often responds to steroids.[42] Alopecia is rare, and cardiotoxicity is very rare.

Paclitaxel is an active agent for treatment of refractory KS.[43–45] In an initial trial, patients with advanced KS received 135 mg/m^2, escalated to 175 mg/m^2 every 3 weeks. The response rate was 71.4%. Responses were seen in all four assessable patients who had previously received anthracycline therapy for KS and in patients with pulmonary KS. In a subsequent study, patients in whom one or more chemotherapy regimens, including combination chemotherapy and chemotherapy with liposomal daunorubicin, had failed to provide benefit, received treatment with paclitaxel 100 mg/m^2 every 2 weeks.[45] Of these patients with poor prognosis, in whom the median CD4$^+$ T-cell count was 5/mm^3, 53% responded. The same regimen in treatment-naive patients yielded an overall response rate of 70%. Alopecia, nausea, vomiting, myalgias, and myelotoxicity often requiring growth factor support are common toxicities.

Thalidomide also shows activity against KS.[46,47] Regimens studied include daily doses of 100 mg for 8 weeks, dose escalation beginning at 200 mg daily to tolerance, and treatment with 200 to 600 mg daily.[48,49] Sedation, depression, fever, rash, and neurologic toxicity have all been reported. The antineoplastic activity of thalidomide is poorly understood. Thalidomide inhibits tumor necrosis factor (TNF) production, alters T-cell response, and modulates T_H1 cytokine production. Although only a minority of patients respond, its oral availability and toxicity profile make it an attractive alternative for patients who do not require immediate responses and in patients who cannot tolerate myelosuppressive regimens.

Several other agents have been reported to have promising results. Administration of interleukin-12 to patients whose KS was progressing despite antiretroviral therapy led to partial response or CR in 71% of patients in a phase I pilot study.[50] Two oral therapies have also been reported to be active against KS in small series: Imatinib induced regression of tumor in HIV-infected patients,[51] whereas substitution of rapamycin therapy for other immunosuppression modalities was associated with regression in renal transplant recipients.[52]

Local Therapies

Local therapies are appropriate for patients with a few lesions and slowly progressive disease. For example, a patient with maximally suppressed HIV-1 infection and indolent but cosmetically disturbing facial lesions may benefit from local treatment. Local therapy avoids immunosuppression associated with cytotoxic chemotherapy but does nothing to interrupt or slow systemic progression and the appearance of new lesions. Alitretinoin (9-*cis*-retinoic acid) is administered as a topical gel.[53] Four to 8 weeks of therapy typically are required before responses are seen. Responses occur even in patients with low CD4$^+$ T-cell counts. Irritation at the site of gel application is common. Intralesional injections with vinblastine, interferon, and sodium tetradecyl sulfate all have a high response rate, but regrowth is common.[54,55] Similarly, liquid nitrogen is effective for the treatment of small lesions, particularly on the face.[56] Radiation therapy is an effective and widely used local treatment.[56–59] Response rates generally are between 80% and 90%. A variety of dosing schedules have been used. In a randomized study, three radiation regimens were compared: 8 Gy delivered in 1 fraction, 20 Gy in 10 fractions, and 40 Gy in 20 fractions. Each treatment scheme led to flattening of lesions. As might be expected, the highest dose was associated with the greatest chance for complete clearing of lesions and the longest duration of benefit. Thus, single fractions are most appropriate for patients with very short life expectancy and to provide symptomatic rather than cosmetic relief. The conjunctiva, oral pharynx, and other sensitive tissues require different doses and fractionation schemes than those used with most cutaneous lesions.

Antiherpesvirus Agents

In vitro ganciclovir and foscarnet are active in inhibiting lytic KSHV replication.[60] Several studies have demonstrated a decreased incidence of KS in patients with HIV who received either ganciclovir or foscarnet regimens but not acyclovir.[61–64] Thus, of potential interest to researchers is the possibility that agents with similar in vitro activity may block the development of KS. By contrast, these agents appear to have no activity in the treatment of established KS.[65] Presumably, the resistance of established KS to such treatments reflects the predominantly latent state of the viral genome in tumors.

LYMPHOMA

Epidemiology

Both non-Hodgkin's and Hodgkin's lymphomas occur with increased incidence in patients with HIV infection, although the increase in non-Hodgkin's lymphomas is much greater, and only aggressive B-cell non-Hodgkin's lymphomas have been formally recognized as AIDS-defining illnesses. In contrast with the situation with KS, lymphomas occur in all HIV-infected populations and show no marked predilection for men who have sex with men or other particular risk groups. Early data from cancer and AIDS registries in the United States showed that the relative risk of development of non-Hodgkin's lymphoma within 3.5 years of another AIDS diagnosis was 165-fold compared with that in persons without AIDS.[66] Particular types of lymphoma showed a much more dramatic increase in incidence. Thus, brain lymphoma was increased 3600-fold in comparison with the general population.[67] The risks for high-grade diffuse immunoblastic and Burkitt's lymphomas were increased 652-fold and 261-fold, respectively. The risk for Hodgkin's lymphoma in HIV-infected persons is increased 5- to 10-fold.[68–70]

With HAART, the overall incidence of lymphoma is decreasing, with the most marked decrease occurring in primary brain lymphoma.[71–74] The length of time with HIV infection before diagnosis of lymphoma is increasing, as is the CD4$^+$ T-cell count at the time of diagnosis. Of interest, the incidence of Hodgkin's lymphoma has increased in the past decade beginning with the availability of HAART.[68,75,76]

Histology and Pathogenesis

The spectrum of lymphomas in the general population includes indolent and aggressive, follicular and diffuse, B- and T-cell tumors, and Hodgkin's and non-Hodgkin's histologic types. In patients with

HIV infection, the increased incidence of lymphomas is mainly an increase in aggressive B-cell tumors with diffuse architecture and in Hodgkin's lymphoma.[73,77] Diffuse immunoblastic, Burkitt's (and Burkitt's-like), and diffuse large B-cell lymphomas each account for approximately one third of the total of non-Hodgkin's lymphomas. Polymorphic lymphoproliferative disorders such as those seen in transplant recipients also have been described.[78] Surface markers characteristic of B cells (CD19, CD20, CD22) generally are expressed, with the notable exception of primary effusion lymphomas. The latter often exhibit an indeterminate phenotype with expression of lymphoid activation markers.[77] Mixed cellularity is the most common Hodgkin's lymphoma subtype in the HIV-infected population, whereas lymphocyte-predominant Hodgkin's lymphoma is quite rare.[70,79–81]

The Epstein-Barr virus (EBV) genome is present in approximately half of lymphomas that arise in HIV-infected patients. In contrast with KSHV, EBV is a ubiquitous virus. EBV has a tropism for B lymphocytes and mediates growth transformation of primary B cells into long-term-proliferating lymphoblastoid cell lines. It is associated with lymphoma across the spectrum of immunocompromised patients, including patients with congenital immunodeficiency and transplant recipients. The molecular biology of the virus and its role in transformation are discussed further in Chapter 11. Particular anatomic sites and particular histologic types are especially likely to be EBV-associated. Primary brain lymphomas and lymphomas with central nervous system involvement are virtually always EBV-positive in patients with AIDS[82–84] (Fig. 69-5). Lymphomas with immunoblastic features, primary effusion lymphomas, plasmablastic oral lymphomas, and Hodgkin's lymphoma usually also are EBV-associated.[77,79] Curiously, although EBV was discovered in African Burkitt's lymphoma and nearly 100% of endemic Burkitt's lymphomas are EBV-associated, AIDS-associated Burkitt's or Burkitt's-like lymphoma is the histologic type least frequently associated with EBV (20% to 30%).[77]

Burkitt's lymphomas occur earlier in the course of HIV disease than do diffuse immunoblastic or diffuse large cell lymphomas.[73] In one series, the median $CD4^+$ T-cell count in patients with Burkitt's lymphoma was 270/mm^3, whereas it was 99/mm^3 for diffuse immunoblastic and diffuse large cell lymphomas.[85] Among patients with lymphoma as an AIDS-defining event, Burkitt's lymphoma accounted for 47% of lymphomas occurring as the first manifestation of AIDS, whereas it accounted for only 13% of non-Hodgkin's lymphomas that developed after another AIDS-related event. Isolated extranodal lymphomas were histologically diffuse immunoblastic or large cell types (97%) and were associated with a median $CD4^+$ T-cell count of 70/mm^3. Primary central nervous system lymphomas represent the extreme end of this spectrum and are associated with a particularly low $CD4^+$ T-cell count.[83] It has been suggested that HAART has changed the character of lymphomas occurring in HIV-infected patients, with a shift away from lymphomas of postgerminal center origin.[86]

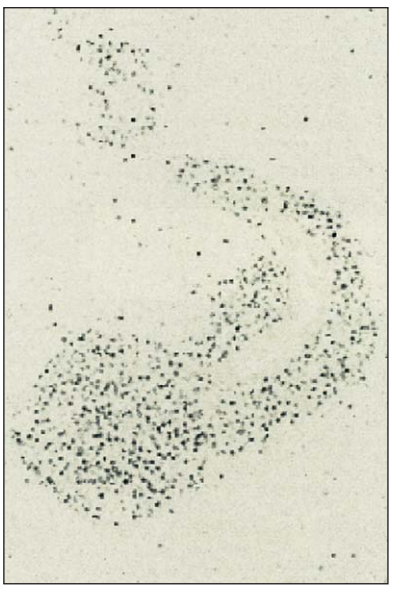


Figure 69-5 • In situ hybridization demonstrating the presence of Epstein-Barr virus (EBV) RNA in brain lymphoma. Tumor cells are clustered around a vessel.

Clinical Aspects

Advanced stage, extranodal disease, and constitutional symptoms frequently are seen in patients with HIV-associated lymphoma.[87–89] Approximately 90% of patients have some extranodal involvement, and in 30%, all disease is extranodal. The gastrointestinal tract is a particularly frequent site of extranodal involvement. Sites not generally involved by lymphoma, such as heart, common bile duct, and rectum, exhibit such involvement in patients with AIDS. Similarly, brain and skin may be involved by Hodgkin's lymphoma at presentation in HIV-infected patients. Pleural, pericardial, or peritoneal cavities may harbor lymphomatous effusions in the absence of any "solid" tumor mass.

Constitutional symptoms are much more common in association with lymphoma in HIV-infected patients than in other patients. As in patients with KS, the presence of such symptoms in patients with lymphoma should prompt a search for opportunistic infections. In contrast with the KS situation, however, even after opportunistic infections are excluded, constitutional symptoms are common. Biopsy is required for the diagnosis of lymphoma, with the possible exception of primary central nervous system lymphoma, as discussed later.[90] CT or magnetic resonance imaging (MRI) of the chest and abdomen often is useful in identifying lesions likely to yield diagnostic material. Gastrointestinal tract lesions occasionally will be detected only by endoscopy. Persistent generalized lymphadenopathy is common in patients with HIV infection, but asymmetrically enlarged nodes should always be biopsied. A finding of benign hyperplasia on biopsy and examination of an enlarged node does not exclude the possibility of lymphoma elsewhere, and several biopsies may be required to establish a diagnosis. Even in the absence of cytopenias, bone marrow biopsy sometimes will yield a diagnosis (Fig. 69-6). Bone marrow-only presentations of Hodgkin's lymphoma are not uncommon.

The location of the pathologic lesion is important in determining the type of biopsy to be performed. Lesions in the brain or other organs devoid of lymphoid tissue are adequately assessed by needle biopsy. Lymph nodes are best assessed by excisional biopsy, which allows assessment of architecture. Failure to identify a clonal population by flow cytometry or other molecular diagnostic techniques does not exclude lymphoma. Clonality could not be demonstrated in a sizable percentage of lymphomatous lesions in a San Francisco series; whether its absence reflected technical artifact or distinctive pathogenesis was not clear.[91]

Staging of non-Hodgkin's lymphomas in patients with AIDS requires that the brain be imaged by MRI or CT. In addition, in patients with EBV-positive tumors and in patients with Burkitt's, Burkitt's-like, or immunoblastic lymphomas, a diagnostic lumbar puncture is indicated. An initial dose of an appropriate agent for prophylactic intrathecal chemotherapy (cytosine arabinoside or methotrexate) often is administered at the time of the diagnostic lumbar puncture.

Although brain lymphomas are common in patients with HIV infection, toxoplasmosis is the most common cause for an intracranial mass lesion.[92] Ring-enhancing unifocal or multifocal lesions are

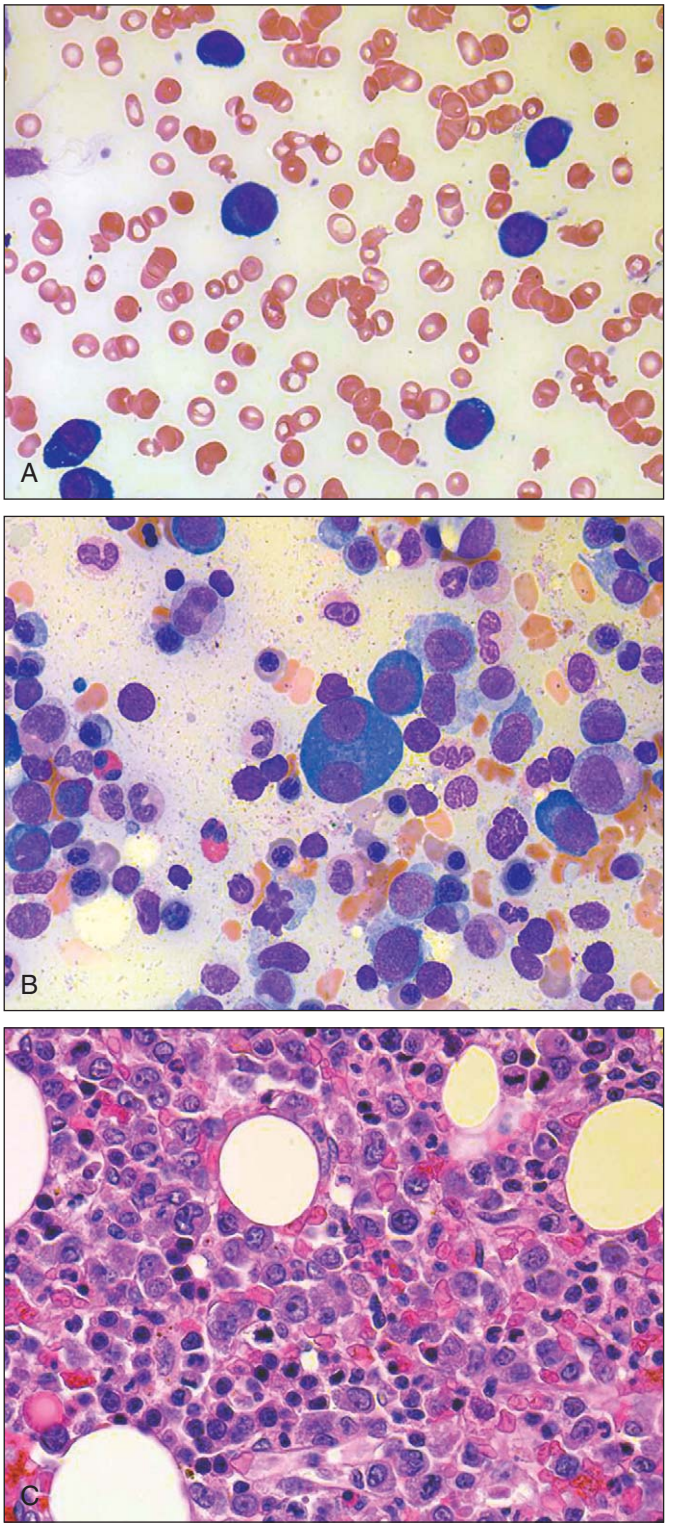


Figure 69-6 • Plasma cell leukemia in a patient with human immunodeficiency virus infection. **A,** Peripheral blood smear. **B,** Aspirate. **C,** Bone marrow biopsy.

common in both diseases. Yet biopsy sometimes is associated with morbidity and even death, particularly in patients with lymphoma.[93] Thus, rather than prompt biopsy of suspicious lesions, empirical treatment for presumed toxoplasmosis is standard in seropositive patients. Biopsy is pursued only if a patient fails to respond to toxoplasmosis therapy or if evidence of progression is observed over a 2-week therapeutic trial.

A variety of approaches to differentiate neoplastic from non-neoplastic lesions have been explored.[94–98] Recent studies of diffusion-weighted MRI have shown significant overlap in apparent diffusion coefficients between lymphoma and toxoplasmosis lesions, thereby limiting its utility in distinguishing between the two entities.[99,100] PET with [^{18}F]fluoro-2-deoxyglucose (FDG) seems promising in accurately differentiating between lymphoma and infectious intracranial lesions, although the literature is not recent and includes relatively few cases.[101] Single-photon emission computed tomography (SPECT) with thallium 201 generally correctly identifies patients with primary central lymphoma but occasionally mislabels patients with infectious lesions as having such neoplasms.[96–98]

A nonradiographic approach to diagnosis of primary brain lymphoma involves polymerase chain reaction (PCR) assay for EBV DNA in cerebrospinal fluid.[102,103] Although PCR analysis occasionally will detect EBV DNA in cerebrospinal fluid in other settings, such as acute infectious mononucleosis with neurologic manifestations, viral DNA rarely is detected in the cerebrospinal fluid of HIV-infected patients without lymphoma.

The established International Prognostic Index (IPI) factors of age, tumor stage, lactate dehydrogenase level, together with Eastern Cooperative Oncology Group (ECOG) performance status and number of extranodal sites, are confirmed to be significant variables in AIDS-related non-Hodgkin's lymphoma in the era of HAART.[104,105] Failure to attain complete remission also has been shown to predict shorter survival. $CD4^+$ cell counts below 100/mm^3 also were prognostic for poor outcome when analyzed prospectively; of interest, however, in a retrospective analysis, $CD4^+$ counts less than 100/mm^3 predicted shorter survival only in the pre-HAART era. The response to antiviral therapy has emerged as the most important prognostic factor.[74]

Therapy

Patients with HIV infection often have very aggressive, rapidly proliferating tumors. Attention to the possibility of tumor lysis syndrome with prompt assessment of renal function, serum electrolytes, and hyperuricemia is critical. Patients should always be started on allopurinol and aggressively hydrated, even before the staging evaluation is complete (Box 69-2). Rapid assessment and treatment can be critically important in patients with aggressive lymphomas.

Before the routine use of *Pneumocystis* prophylaxis and hematopoietic growth factors, lymphoma regimens in AIDS patients were associated with a high treatment-related mortality rate.[106]

Box 69-2. TREATMENT OF NON-HODGKIN'S LYMPHOMA

- Treatment is with standard-dose CHOP: cyclophosphamide (750 mg/m^2), doxorubicin (50 mg/m^2), vincristine (Oncovin; 1.4 mg/m^2), prednisone (100 mg/day for 5 days)—repeated every 3 weeks. A maximum of six cycles are given. Granulocyte colony stimulating factor is routinely prescribed. Dose adjustments are made for toxicity.
- Patients with Epstein-Barr virus-associated lymphoma, except Hodgkin's lymphoma, or with Burkitt's or Burkitt's-like lymphoma receive intrathecal prophylaxis with 12 mg of methotrexate and 100 mg of hydrocortisone administered five times during the first two cycles of systemic chemotherapy.
- Patients with lymphomatous meningitis receive whole-brain irradiation and intrathecal chemotherapy (three times per week until clear; the interval of treatments is then tapered to once a week for a month and then once a month for a total of 6 months), until the cerebrospinal fluid (CSF) demonstrates clearance of lymphoma.

A randomized trial of standard versus reduced-dose therapies showed that reduced-dose therapies did not compromise overall or disease-free survival but were associated with a decrease in the percentage of patients in whom severe toxicities developed.[107] In profoundly immunocompromised patients, the antitumor effects of cytotoxic chemotherapy had to be balanced against associated myelosuppressive and immunosuppressive effects. With the advent of improved prophylaxis of opportunistic infections, highly effective antiretroviral therapy, and perhaps some change in the character of the tumors emerging in such patients, the outlook for these patients has improved significantly.

A first question addressed in the era of HAART was the safety of the combination of antiretroviral therapy and cytotoxic chemotherapy. Data from retrospective series and from trials combining cytotoxic chemotherapy regimens with antiretroviral regimens have been published.[108,109] Although some interactions have been reported with altered clearance rates of serum concentrations of cyclophosphamide, doxorubicin, and indinavir, adverse interactions have been modest, with the exception of regimens that include zidovudine. Additional studies have suggested increased toxicity with the combination of chemotherapy and some of the protease inhibitors, known potent inhibitors of the cytochrome P-450 system. When saquinavir was combined with an infusional regimen of cyclophosphamide, doxorubicin, and etoposide (CDE), mucositis was observed in 67% of patients, a significantly higher rate than that seen with didanosine plus CDE.[108,110] Decreases in day 10 and day 14 neutrophil counts in patients receiving CDE with protease inhibitor-containing HAART compared with those who received HAART without protease inhibitors also are described, with grade 3 and 4 infections requiring hospitalization occurring in 48% versus 25% of patients, respectively.[111] Infusional regimens have attracted a great deal of interest. CDE administered as a 96-hour infusion combined with HAART has yielded impressive results in a multi-institutional study.[112] Of 98 analyzable patients, those who received the infusional therapy and HAART had a median overall survival time of almost 14 months, whereas those who received the same infusional therapy and only a single antiretroviral agent (didanosine) had a median survival time of approximately 7 months. Combination of the regimen with rituximab yielded a CR rate of 70% and a significant increase in estimated overall survival rate (64% at 2 years).[113] This study and another trial evaluating rituximab combined with CHOP (i.e., cyclophosphamide, vincristine, doxorubicin, and prednisone) chemotherapy have raised concerns that rituximab may increase the risk of severe and life-threatening infection.[114] Further evaluation of this strategy should proceed with caution. A different continuous infusion regimen used in a single-institution study also yielded impressive results.[86] The EPOCH chemotherapy regimen (i.e., cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone) given by continuous infusion yielded a 92% disease-free survival time of 53 months. These survival outcomes represent a dramatic improvement over what was reported in cooperative group trials from the pre-HAART era. Whether the improved survival reflects changing pathogenesis of lymphoma in HIV-infected patients, improved antiretroviral therapy following lymphoma therapy, the use of continuous infusion, or the particular choice of agents is not clear.

One of the complexities of infusional chemotherapy relates to possible metabolic interactions with antiretroviral agents. The possibility of important, possibly adverse interactions led the investigators studying one of the infusional therapies to not initiate antiretroviral therapy until the conclusion of cytotoxic chemotherapy.[86] Viral load increased modestly during therapy and plateaued between cycles 4 and 6. At 3 months after starting or restarting antiretroviral therapy, viral loads declined to below baseline. There was no evidence that therapy led to the emergence of antiviral resistance. To the contrary, resistance mutations became transiently undetectable during therapy. $CD4^+$ T-cell counts decreased but recovered to baseline within 6 to 12 months. *Pneumocystis* prophylaxis probably should be administered to all patients undergoing intensive chemotherapy regardless of $CD4^+$ T-cell count, whereas *Mycobacterium avium* complex prophylaxis is administered only to patients with $CD4^+$ T-cell counts below 50/mm^3.[87]

Most patients with HIV infection and Hodgkin's lymphoma present with advanced-stage disease. Thus, combination chemotherapy is virtually always the mainstay of therapy (Box 69-3). The ABVD regimen (i.e., doxorubicin, bleomycin, vinblastine, and dacarbazine) was studied by the AIDS Clinical Trials Group in the era before HAART.[115] With the advent of HAART, the CR rate has nearly doubled. In a recent retrospective series of 62 patients with advanced Hodgkin's lymphoma treated with ABVD and HAART, 54 (87%) achieved a CR with 5-year event-free survival (EFS) and overall survival (OS) probabilities of 71% and 76%, respectively.[116] The Stanford V regimen[117] with concomitant HAART was evaluated in a phase II study. Of 59 patients subjected to this regimen, 81% achieved a CR. At a median follow-up of 17 months, the estimated 3-year disease-free survival (DFS) and OS rates were 51% and 68%, respectively.[118]

A variety of salvage therapies have been evaluated, often with disappointing results.[88] ESHAP (etoposide, methylprednisolone, cisplatin, and high-dose cytarabine) chemotherapy is a commonly used regimen.[119] Increasingly, high-dose therapy with autologous peripheral stem cell transplantation is being used as consolidation.[120,121] Time to engraftment, infectious complications in the post-transplantation period, and conditioning regimen complications are similar to those seen in patients without HIV infection. High-dose therapy with peripheral stem cell transplantation is rapidly becoming established as the appropriate salvage strategy for patients with chemotherapy-responsive relapse of either Hodgkin's or non-Hodgkin's lymphoma.

What should be regarded as "standard therapy" for AIDS-associated lymphoma? Except in the most immunocompromised patients, standard-dose lymphoma therapy including doxorubicin is appropriate. Among the chemotherapy regimens that might be considered as standard are CHOP, CDE, and EPOCH. Rituximab has been almost universally added to these regimens.[113,114,122,123] One study suggested that rituximab therapy may be associated with an increased incidence of fatal bacteremia, but this has not been confirmed by other studies.[114] The optimal integration of antiretroviral therapy with chemotherapy remains uncertain, but long-term lymphoma-free survival can be achieved with concomitant or delayed antiretroviral therapy. Patients who experience relapse and are in good condition are appropriate candidates for salvage and may benefit from high-dose therapy with stem cell rescue or other aggressive interventions.

Whole-brain radiation therapy has been the mainstay of treatment for brain lymphomas (Box 69-4).[124,125] Retrospective studies show tumor responses, improvement in quality of life, and longer survival with treatment, but long-term survival is rare. Small series with high-dose methotrexate or ganciclovir and zidovudine have been reported.[126–128] In a retrospective analysis of the impact of HAART on survival in patients with primary central nervous system lymphomas, 6 of 7 patients who received HAART were alive, versus 0 of 18 patients who received no treatment, at a median follow-up time of 667 days ($P = 0.0007$).[129]

Box 69-3. TREATMENT OF HODGKIN'S LYMPHOMA

- Treatment is with standard-dose ABVD—doxorubicin (Adriamycin; 25 mg/m^2), bleomycin (10 units/m^2), vinblastine (6 mg/m^2), dacarbazine (375 mg/m^2)—administered on days 1 and 15.
- A maximum of six cycles are given. G-CSF is routinely prescribed.
- Dose adjustments are made for toxicity.

Box 69-4. APPROACH TO PATIENTS WITH AIDS-ASSOCIATED BRAIN LYMPHOMA

- In the presence of characteristic lesion(s) on magnetic resonance imaging and thallium or positron emission tomography studies, detection of Epstein-Barr virus DNA by polymerase chain reaction assay in cerebrospinal fluid is diagnostic of brain lymphoma. In patients in whom lumbar puncture is contraindicated, brain biopsy is required for diagnosis.
- Treatment is with radiation therapy.

OTHER MALIGNANCIES IN PATIENTS WITH HIV INFECTION

With HAART, the spectrum of malignancies in HIV-infected patients has been changing.[130] Non-AIDS-defining cancers have been reported with increased incidence, including those most common in the general population (lung cancer, colon cancer, skin cancers) as well as multiple myeloma and related plasma cell disorders, anal cancer, and cervical cancer. Lung and colon cancers may be indistinguishable from those appearing in the general population. Plasma cell dyscrasias in this population are quite distinctive, however. They are EBV-associated and often manifest with visceral or leukemic involvement.[131] Although cervical cancer has been recognized by the Centers for Disease Control and Prevention as an AIDS-defining illness, an excess of cervical cancer attributable to HIV infection remains to be conclusively demonstrated.[87,132] Some evidence, however, suggests that HIV-infected women with cervical cancer are more likely than non-HIV-infected women to have advanced disease at presentation and exhibit a higher recurrence rate. Furthermore, cervical intraepithelial neoplasia occurs more frequently in women with HIV infection. Anal cancer occurs with a 40- to 80-fold excess in people with AIDS compared with the general population. Receptive anal intercourse also is a well-established risk factor for this cancer, and the relative contributions of HIV infection and behavior have not been fully defined. Leiomyosarcomas in visceral organs occur with dramatically increased frequency in patients with HIV infection, particularly pediatric patients, but remain rare. The approach to treatment of these disorders does not differ from that in the non-HIV-infected population or has yet to be defined, although clearly, cognizance of the special risks associated with chemotherapy is important.

CURRENT OUTLOOK

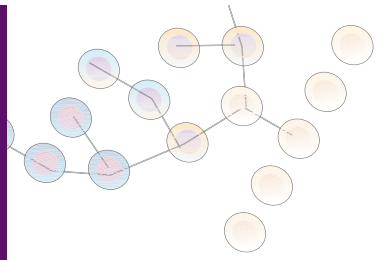
With an improved prognosis for patients with HIV infection as a result of advances in supportive care and antiretroviral therapy, the neoplastic complications of HIV infection grow in importance. In the early days of the epidemic, the treatment of malignancies with curative intent might have been regarded as only marginally important in patients who were otherwise doomed to a short survival by virtue of their retroviral infection. For an increasing number of patients, however, HIV infection is most appropriately viewed as a chronic disease that requires a collaborative and multidisciplinary effort on the part of primary care and subspecialty providers, and the nihilism of the past should be replaced by a cautious optimism. It is now clear that durable remissions will translate into long-term survival in patients whose HIV load can be suppressed to very low or undetectable levels. The challenge that remains is to further develop specific therapies for HIV-associated malignancies and to integrate these approaches with the growing armamentarium of antiretroviral therapies.

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70 Cancer of the Central Nervous System

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SUMMARY OF KEY POINTS

Incidence

- An estimated 43,800 new primary tumors of the central nervous system (CNS) were diagnosed in the United States in 2005, of which 18,500 were malignant.
- Approximately 85% of all primary CNS tumors are intracranial; the remainder occur in the spinal axis. An estimated 3410 new childhood (ages 0 to 19 years) primary benign and malignant brain tumors were diagnosed in 2005.
- Primary CNS malignancies account for 1% of all adult cancers and 2% of all adult cancer deaths. Among children 14 years of age or younger, primary CNS malignancies account for approximately 23% of all cancers and 26% of deaths due to cancer.

Pathology and Classification

- Taking all age groups into account, histologic types of CNS tumors include meningiomas (30%), glioblastomas (20%), other astrocytomas (9%), nerve sheath tumors (8%), pituitary adenomas (6%), oligodendrogliomas (4%), ependymomas (2%), and embryonal tumors including medulloblastomas (2%).
- Among children 14 years or younger, histologic tumor types include pilocytic astrocytomas (21%), glioblastomas (3%), other astrocytomas (11%), ependymomas (7%), oligodendrogliomas (2%), embryonal tumors including medulloblastomas (19%), craniopharyngiomas (3%), and germ cell tumors (4%).
- Most brain tumors are supratentorial; notable exceptions include brainstem gliomas, cerebellar pilocytic astrocytomas, medulloblastomas, and ependymomas that involve the posterior fossa.
- Glioblastoma (World Health Organization [WHO] grade IV astrocytoma) and brainstem gliomas in children carry the poorest prognosis. Pilocytic astrocytomas carry the best prognosis.

Clinical Manifestations

- *General signs and symptoms:*—from mass effect, increased intracranial pressure (ICP), edema, or shift or destruction of surrounding brain tissue—may include changes in personality and cognitive function, headaches, nausea, vomiting, seizures, and papilledema.
- *Focal signs and symptoms* may include focal seizures, visual changes, speech abnormalities, gait abnormalities, and cranial nerve deficits.
- Posterior fossa tumors often compress the fourth ventricle, causing hydrocephalus, and frequently manifest with ataxia and intractable nausea and vomiting.
- Brainstem gliomas often manifest with a combination of cranial nerve palsies and "long tract" signs such as hemianesthesia or hemiparesis coupled with ataxia in cases with cerebellar involvement.
- Pineal region tumors (germ cell tumors, pineocytoma, and pineoblastoma, as well as gliomas of this region) may compress the aqueduct of Sylvius, causing hydrocephalus. Compression of the pretectal area produces Parinaud's syndrome, with paralysis of upgaze, ptosis, and loss of pupillary light reflexes, along with retraction-convergence nystagmus.

Diagnostic Studies

- Magnetic resonance imaging (MRI) with gadolinium contrast is the most sensitive technique.
- Computed tomography (CT) scanning is good for visualizing intratumoral calcifications and bone erosion but poor at visualizing the posterior fossa.
- Positron emission tomography (PET) may help discriminate between tumor recurrence and radiation necrosis.
- Magnetic resonance (MR) spectroscopy may help distinguish high-grade tumor from low-grade tumor or radiation necrosis.

Therapy

- For most brain tumors, tissue diagnosis is required (an exception may be selected brainstem gliomas).
- Treatment for brain tumors is highly dependent on histologic type. For many tumors (e.g., gliomas, meningiomas, primitive neuroectodermal tumors [PNETs], ependymomas), maximal surgical resection that is safely feasible is the primary treatment.
- For some tumors (e.g., glioblastomas, PNETs, germ cell tumors), radiation therapy is an essential adjunct treatment after surgery.
- For some tumors (e.g., acoustic neuromas, glomus tumors), either irradiation or surgery can offer successful control; the decision between the two is based on assessment of side effects.
- Chemotherapy is assuming an increasingly important role in the management of many brain tumors (e.g., glioblastomas, germ cell tumors, anaplastic oligodendrogliomas, PNETs, CNS lymphomas).

INTRODUCTION

The different histologic types of CNS tumors are shown in Table 70-1. Meningiomas, glioblastomas, and astrocytomas constitute more than half of all CNS tumors. The frequency of different histologic tumor types varies with age, as shown in Figure 70-1. The incidence of all brain tumors is highest in the 75- to 84-year-old group. The incidence of meningiomas increases with increasing age, whereas for gliomas and pituitary adenomas, the incidence increases with age but then declines at the highest age category (see Fig. 70-1A). Certain histologic types, such as germ cell tumors, medulloblastomas, and pilocytic asctrocytomas, are far more common in children than in adults (Table 70-2; see Fig. 70-1B).

For most patients with primary CNS tumors, the initial therapy usually is operative. Radiation therapy often is an important component of treatment after surgery, but for management of malignant disease, chemotherapy has had an expanding role. A great deal of knowledge has been amassed over the past 2 decades regarding the biology of brain tumors, which with time should lead to improved treatments.

EPIDEMIOLOGY

An estimated 43,800 new cases of primary CNS system tumors were diagnosed in the United States in 2005.[1] Approximately 18,500 were malignant, representing 1.35% of all cancers diagnosed that year.[2] Malignant CNS tumors caused approximately 13,000 deaths in 2005.

On the basis of data provided by the Surveillance, Epidemiology, and End Results (SEER) Program, Deorah and colleagues[3] found that the incidence of brain cancer increased until 1987, when the annual percentage of change reversed direction. The elderly experienced an increase in brain cancer until 1985, but their rates were stable thereafter. Overall, however, the incidence of glioblastoma has been increasing, with survival unchanged over the past 2 decades.

Ionizing radiation is one of the few factors shown to have a strong association with the development of brain tumors. Exposure to ionizing radiation represents the most important exogenous risk factor for childhood brain tumors. Prenatal diagnostic x-ray exposure increases the risk of childhood brain tumors,[4] and various reports describe the occurrence of gliomas, meningiomas, and other brain tumors in children who received radiation therapy to the head for tinea capitis and for prior malignancies.[5–8] A dose of 1 to 2 Gy of radiation, used to treat tinea capitis in Israeli children, was associated with an increased risk of developing brain tumors—specifically, meningiomas, gliomas, and nerve sheath tumors.[9] A dose-response correlation in the induction of brain tumors was seen with a relative risk of 3.0 at a dose of 1 Gy. Tumors developed at least 6 years after irradiation, with a mean interval greater than 15 years. Even lower doses of radiation delivered with ^{226}Ra used to treat hemangiomas in Swedish infants (mean dose to brain of 7 cGy) were found to be associated with an excess risk of intracranial tumors, including pituitary adenomas, gliomas, meningiomas, and nerve sheath tumors.[10]

A large amount of data has been accumulated on the incidence of brain tumors in patients who received cranial irradiation for the treatment of acute lymphoblastic leukemia (ALL). The estimated cumula-

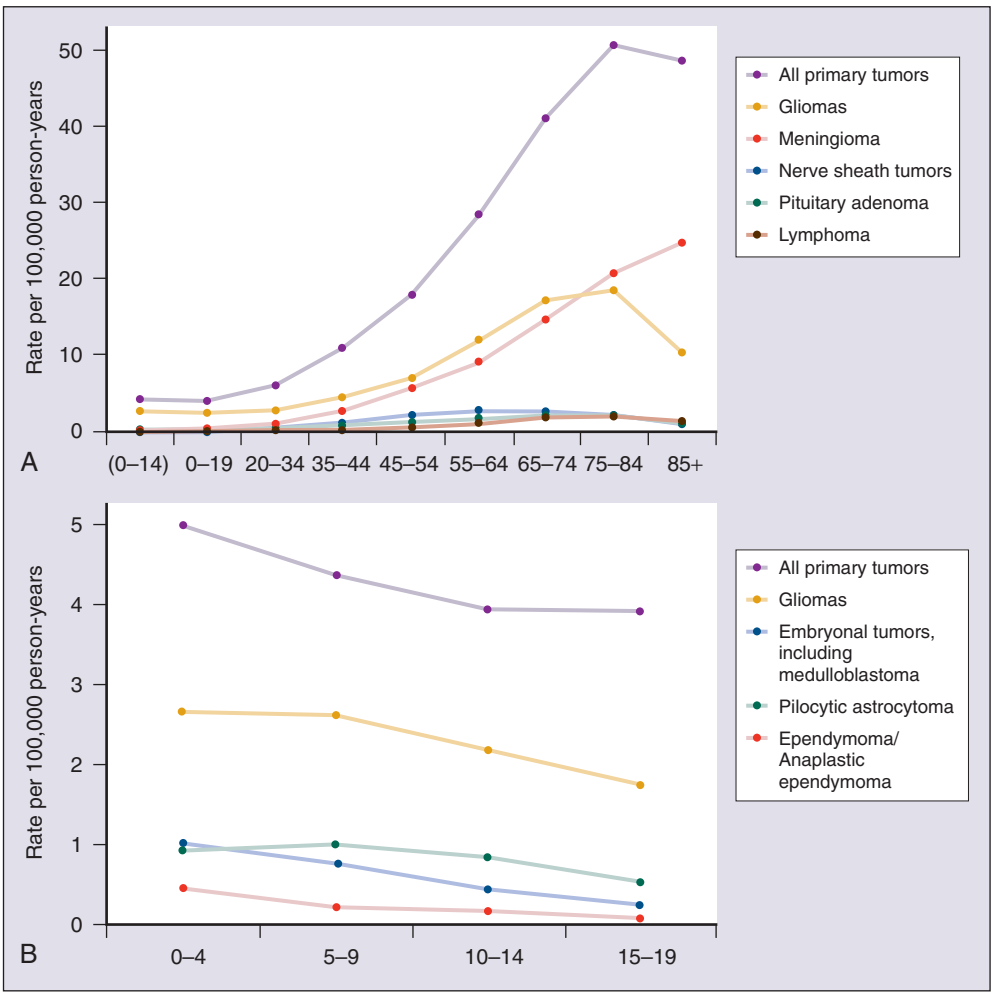


Figure 70-1 • Age-specific incidence of primary CNS tumors by histologic type. **A,** Selected histologic types among all age groups. **B,** Selected histologic tumor types in children. (Data from Central Brain Tumor Registry of the United States [CBTRUS]: Primary Brain Tumors in the United States Statistical Report, 2005–2006. Hinsdale, IL, CBTRUS, 2006. Data were collected between the years 1998 and 2002.)

Table 70-1 Primary Central Nervous System Tumors: Cell of Origin and Distribution by Histologic Type

Histologic Tumor Type	Cell of Origin	Frequency (%) In All Age Groups*	Frequency (%) Among Young Adults†
Meningioma	Arachnoidal fibroblast	30.1	13
Glioblastoma	Astrocyte	20.3	5.9
Other astrocytomas	Astrocyte	9.8	17.7
Ependymoma	Ependymocyte	2.3	4.6
Oligodendroglioma	Oligodendrocyte	3.7	8.9
Embryonal tumors, including medulloblastoma	Embryonal	1.7	2.8
Pituitary adenoma	Pituitary	6.3	13
Craniopharyngioma	Cells from Rathke's pouch	0.7	1.3
Nerve sheath	Schwann cell	8.0	9.4
Lymphoma	Lymphocyte	3.1	2.8
All others		13.9	20.8
Choroid plexus papilloma or carcinoma	Choroid epithelial cell		
Hemangioblastoma	Endothelial cell		
Germ cell tumor	Primitive germ cell		
Pineocytoma	Pineal parenchymal cell		
Chordoma	Notochordal remnant		

*Frequency among all patients with primary brain and CNS tumors ($N = 63,698$). Gliomas (glioblastomas, astrocytomas, oligodendrogliomas) and ependymomas and neuroepithelial tumors account for 40% of all tumors and 78% of malignant tumors.

†Frequency among young adults (20 to 34 years of age) with primary brain and CNS tumors ($N = 5741$).

Data from Central Brain Tumor Registry of the United States (CBTRUS), 2005–2006.[1]

tive risk of secondary malignant brain tumors after childhood ALL therapy is 0.5% at 10 years after completion of therapy.[11] In a study from St. Jude's Children's Hospital, the actuarial 20-year probability of developing a brain tumor in these patients was 1.4%.[12] The probability of developing a high-grade glioma was greater in children younger than 5 years of age at diagnosis than in those 6 years of age or older (1.08% versus 0.45%; $P = 0.045$). An apparent dose-response correlation was observed: The 20-year risk of developing a brain tumor was 3.2% in patients who received greater than 30 Gy, versus 1.03% in those who received 21 Gy or less ($P = 0.015$). No CNS malignancies were seen in patients who did not receive cranial irradiation. The latency between irradiation and the diagnosis of a brain tumor ranged from 5.9 to 29 years (median, 12.6) but was longer for meningiomas (median, 19 years) than for high-grade gliomas (median, 9.1 years). Very similar results regarding the frequency of brain tumors, latency, and dependence on prior cranial irradiation were seen in studies from the German BFM (Berlin-Frankfurt-Munster) group[13] and the Children's Cancer Study Group (CCSG).[14] The types of brain tumors that have been reported in these series include gliomas, meningiomas, and medulloblastomas. Patients who received cranial irradiation for ALL also often received intrathecal chemotherapy. It has been suggested that cranial irradiation and intrathecal chemotherapy may work synergistically to increase the incidence of glial tumors.[15,16]

Table 70-2 Primary Central Nervous System Tumors of Childhood: Distribution by Histologic Type

Histologic Tumor Type	Frequency (%) Age 0–14 Years ($N = 4214$)	Frequency (%) Age 15–19 Years ($N = 1241$)
Pilocytic astrocytoma	20.9	14.0
Glioblastoma	2.8	3.2
All other astrocytomas	10.5	11.4
Ependymoma	7.0	4.6
Oligodendroglioma	2.0	4.0
Embryonal tumors, including medulloblastoma	16.8	6.7
Pituitary adenoma	0.8	10.1
Craniopharyngioma	3.1	2.7
Germ cell tumor	3.9	6.8
All others	32.1	36.6

Gliomas account for 56% of all tumors and 67% of all malignant tumors in children 0 to 14 years of age and for 45% of all tumors and 68% of all malignant tumors in those 15 to 19 years of age.

Data from Central Brain Tumor Registry of the United States (CBTRUS) 2005–2006.[1]

Viruses can induce brain tumors in animals in the experimental setting; however, no conclusive data point to viruses as a cause of brain tumors in humans (reviewed by Berleur and Cordier[17]). Although many chemicals can induce brain tumors in laboratory animals, no definitive associations have been found in humans. For example, *N*-nitroso compounds, which commonly are present in foods, are known to be neurocarcinogenic in animals. Oxidants in the environment can cause DNA damage, so it has been hypothesized that antioxidants, such as vitamin E, found in certain foods may protect against the development of cancers. Epidemiologic studies, however, have provided mixed support for the idea that the intake of *N*-nitroso compounds, antioxidants, or specific nutrients in foods can influence the risk of developing brain tumors (reviewed by Berleur and Cordier[17]).

Also lacking is conclusive evidence that occupational exposure to industrial chemicals leads to the development of brain tumors,

Table 70-3 Hereditary Syndromes Associated with Brain Tumors

Syndrome	Associated CNS Tumors	Gene	Chromosomal Locus	Defective Protein and Normal Function
Neurofibromatosis type 1	Optic pathway gliomas, meningiomas, neuromas	*NF1*	17q11–12	Neurofibromin; GTPase-activating protein (GAP) that negatively regulates Ras
Neurofibromatosis type 2	Bilateral acoustic neuromas, meningiomas, gliomas	*NF2*	22q12	Merlin; related to membrane cytoskeleton linker protein 4.1 superfamily
Tuberous sclerosis	Cerebral hamartomas	*TSC1*	9q34	Hamartin
	Subependymal giant cell astrocytoma (SEGA)	*TSC2*	16p13	Tuberin; associates with hamartin; both are involved in signaling downstream of Akt
von Hippel-Lindau syndrome	Hemangioblastomas	*VHL*	3p25–29	VHL protein; degrades HIF1a
Li-Fraumeni syndrome	Malignant gliomas	*TP53*	17p13	p53; maintains genomic stability
Cowden's syndrome	Meningiomas	*PTEN*	10q23	PTEN; lipid phosphatase, counters PI_3 kinase activation
Gorlin's syndrome (nevoid basal cell carcinoma syndrome)	Medulloblastomas	*PTCH*	9q22	Cell surface receptor; regulates normal brain development
Turcot's syndrome	Medulloblastomas	*APC*	5q21	APC; part of β-catenin/Wnt signaling pathway
	Malignant gliomas	*hMLH1*	3p21	Involved in mismatch repair
	Malignant gliomas	*PMS2*	7p22	Involved in mismatch repair
Familial retinoblastoma	Pineoblastomas	*RB*	13q14	Rb protein; regulates entry into S phase
Ataxia-telangiectasia	CNS lymphoma	*ATM*	11q22–23	ATM protein; involved in DNA damage sensing
Multiple endocrine neoplasia syndrome 1 (MEN-1)	Pituitary adenomas	*MEN1*	11q13	Menin

APC, adenomatous polyposis coli; ATM, ataxia-telangiectasia mutated; CNS, central nervous system.

although a number of studies have suggested such a link (reviewed by Wrensch and coworkers[18]). Some of the chemicals that can induce brain tumors in laboratory animals, such as polycyclic aromatic hydrocarbons, can do so only when administered by direct contact or transplacentally, but not by inhalation or dermal contact; the latter two modes of exposure are more relevant in the occupational setting. Specific chemicals that have been examined include cosmetics containing *N*-nitroso compounds, organic solvents, chemicals used in the manufacture of synthetic rubber, formaldehyde, phenols, polycyclic aromatic compounds, polyvinyl chloride, and pesticides. Vinyl chloride can induce brain tumors in rats; however, a recent review found that the association in humans is inconclusive.[19] Bohnen and Kurland reviewed studies examining the incidence of brain tumors in agricultural workers exposed to pesticides and found that the results were inconclusive.[20] A large meta-analysis of studies examining workers in the petrochemical industry found no increased risk of brain tumors in this population.[21]

Recently a great deal of interest has emerged in a possible association between use of cellular telephones and the risk of brain tumors. In a case-control study, Inskip and coworkers were unable to show a correlation between the duration of cell phone use and the development of gliomas, meningiomas, and acoustic neuromas.[22] Other large case-control studies also have failed to find any association between cell phone use and the risk of developing brain tumors.[23–25] Nevertheless, some still claim that there is a link between cell phone use and brain tumors.[26]

Other factors that have been analyzed for their possible relationship to the development of brain tumors include a history of head trauma and injury, drugs and medications, allergies, seizures, smoking and alcohol consumption, and exposure to power-frequency electromagnetic fields. None of these factors, however, have been shown to be conclusively important (reviewed by Wrensch and associates[18]).

Most brain tumors represent sporadic cases; however, familial clustering has been noted. It is estimated that hereditary syndromes account for 2% of childhood brain tumors, although this may be an underestimate because hereditary syndromes may go undiagnosed in a number of cases.[27] Some hereditary syndromes known to be associated with brain tumors are listed in Table 70-3 (reviewed by Kimmelman and Liang[28]). Some of the associations are extremely strong. Nearly 70% of all optic pathway gliomas occur in patients with neurofibromatosis type 1 (NF-1), and acoustic neuromas commonly occur in patients with NF-2. In addition, hereditary immunosuppression disorders such as Wiskott-Aldrich syndrome, as well as treatment-associated immunosuppression as in organ-transplant recipients, or exogenous immunosuppression as in human immunodeficiency virus (HIV) infection, are known to be associated with an increased risk of primary CNS lymphoma.

TUMOR BIOLOGY

In the past decade, the field of oncology has seen explosive growth in elucidation of basic biologic processes. Normal cells have constraints in their ability to grow; for example, their growth generally is inhibited when they contact other cells. Tumor cells, by contrast, have sustained genetic mutations that allow them to overcome these constraints. Some of these changes allow them to proliferate in the absence of external cues. Other genetic changes allow them to invade adjacent normal tissues. Still other mutations allow tumor cells to induce angiogenesis and develop their own blood supply.

Cell Proliferation

Normal cells rely on growth factors secreted in their local environment to stimulate their growth. Many CNS tumors, however, have developed the ability to express their own growth factors along with the respective receptors, resulting in an autocrine loop that allows for self-stimulation.[29] Platelet-derived growth factor receptor-α (PDGFR-α), for example, is overexpressed in all grades of astrocytomas, but

only higher-grade tumors overexpress the ligands PDGF-A and PDGF-B.[30] Insulin-like growth factors and their receptors both are expressed in brain tumors including gliomas and meningiomas.[31] The epidermal growth factor receptor (EGFR) is amplified or overexpressed in 50% of glioblastomas,[29] and expression of transforming growth factor-α (TGF-α), a ligand that binds to this receptor, is increased in many gliomas.[32,33] Both scatter factor (also known as hepatocyte growth factor [HGF]) and its receptor c-Met are expressed in gliomas, with the highest level of expression seen in the most malignant tumors.[34]

As a result of increasing expression of receptors and ligands, increased signaling occurs in many brain tumors, resulting in activation of many different pathways that are important in proliferation (reviewed by Rao and James[32]). The best-studied of these pathways is the microtubule-associated protein (MAP) kinase pathway, which involves Ras and Raf. Another pathway that has attracted much attention recently is the phosphoinositide-3 (PI_3) kinase pathway, which leads to activation of Akt. Mutation of *PTEN*, which occurs in 30% to 40% of glioblastomas, also can lead to increased Akt activation in these tumors.[35]

Ras activation commonly is seen in human astrocytomas and neurofibromas despite the fact that these tumors rarely contain Ras mutations. In astrocytomas, Ras activation probably occurs through activation of growth factor receptors such as EGFR and PDGFR.[36] Other mechanisms of activation of aberrant G proteins have been identified in other CNS tumors (reviewed by Woods and coworkers[37]). In NF-1, loss of expression of neurofibromin, an inactivator of Ras, is seen (see Table 70-3). This loss of neurofibromin leads to the increased Ras activation seen in NF1-associated astrocytomas. Pituitary adenomas often show activation of the α subunit of the large heterotrimeric Gs protein, resulting in mitogenic signaling.

Cell proliferation is intimately tied to cell cycle regulation. For many cancers, mutations in two different pathways are important for deregulating the cell cycle. The first of these is the p16/Cdk4 or Cdk6/cyclin D/Rb pathway. The second is the p21/p53/Mdm2/$p19^{ARF}$ pathway. Mutations in both of these pathways are common in many brain tumors, particularly gliomas.

Invasion

Many brain tumors, particularly gliomas, display an invasive phenotype, with infiltration of tumor cells into surrounding tissues, making a cure very difficult to achieve. In fact, tumor recurrence was reported in one case even after the drastic measure of taking out the entire hemisphere in which a glioma was located.[38] Numerous molecules associated with invasion have been found to be upregulated in gliomas, including tenascin-C, secreted protein acidic and rich in cysteine (SPARC), various integrins, and matrix metalloproteinases (reviewed by Demuth and Berens[39]).

Angiogenesis and Hypoxia

For a tumor to grow beyond a certain size, it must develop a blood supply. The process of angiogenesis is described in detail in Chapter 8. A number of growth factors are known to be important in angiogenesis. The most prominent of these is vascular endothelial growth factor (VEGF), which is overexpressed in many brain tumors. In one study, increasing VEGF expression correlated with increasing malignant grade in astrocytomas, oligodendrogliomas, and ependymomas.[40] This study also found that increased expression of the VEGF receptors Flt-1 and KDR in tumor vasculature was found to correlate with increasing VEGF expression and malignant grade. Growth factors other than VEGF that may play a role in angiogenesis in gliomas include members of the TGF-β family, PDGF, placenta growth factor, basic fibroblast growth factor, and scatter factor/hepatocyte scatter factor (HSF).[41] Angiogenesis can also be negatively regulated by factors such as thrombospondins 1 and 2 (TSP1 and TSP2). TSP1 is positively regulated by p53, so loss of p53, which commonly occurs in gliomas, can lead to decreased TSP1 expression and increased angiogenesis.[41]

Angiogenesis is particularly prominent within glioblastomas. One of the characteristic features of these tumors is endothelial proliferation and neovascularization. A variety of growth factors that can increase angiogenesis are expressed by glioblastomas, foremost being VEGF. VEGF, also known as vascular permeability factor (VPF), is a potent inducer of capillary permeability. The high levels of VEGF expression in glioblastoma may be responsible for the edema associated with these tumors. Some evidence indicates that genetic changes common to glioblastomas, such as EGFR activation and *PTEN* mutation, may contribute to high levels of VEGF expression, perhaps through activation of the PI_3 kinase pathway.[42–44]

Despite expressing high levels of VEGF, glioblastomas contain significant regions of hypoxia, which may be a cause of treatment resistance. Hypoxia has been shown to be present in malignant gliomas by both polarographic needle electrode measurement[45,46] and binding of the 2-nitroimidazole EF5.[47] Hypoxia as measured by needle electrodes was not prognostic for survival.[46,47] The latter study, however, found a correlation between more rapid tumor recurrence and hypoxia as measured by EF5 binding.

The presence of hypoxia in glioblastomas is consistent with the histologic features commonly seen in these tumors, including the presence of pseudopalisading necrosis and proliferative blood vessels. It has been proposed that pseudopalisades seen within glioblastomas represent a wave of tumor cells actively migrating away from central hypoxia that arises secondary to vaso-occlusion and intravascular thrombosis.[48] It may seem counterintuitive that hypoxia can persist in the presence of high VEGF levels and robust neovascularization; however, the explanation may be that although hypoxia may stimulate VEGF and the formation of new vessels, many of these vessels are nonfunctional and do not transport oxygen well.

Stem Cells

The stem cell hypothesis proposes that a small fraction of cells with stem cell properties are the source of renewal of the tumor and determine a tumor's behavior. Such stem cells have been identified in human brain tumors and express the neural precursor marker CD133.[49,50] A number of strategies may be used to target these stem cells.[51] It recently has been demonstrated that these stem cells may be relatively radioresistant as a result of overexpression of DNA damage repair proteins including the checkpoint kinases Chk1 and Chk2.[52] The cells may be made more radiosensitive by using specific inhibitors of Chk1/Chk2. Piccirillo and colleagues showed that $CD133^+$ glioblastoma stem cells have a functional bone morphogenic protein (BMP) receptor pathway.[53] By exposing mice implanted with orthotopic glioblastomas to BMP4, they were able to cause the $CD133^+$ cells to differentiate toward glial cells and reduce tumor growth. These two strategies potentially may be used to target stem cells in glioblastomas. Another potential strategy is to target the tumor stroma, which provides a specialized niche for tumor cells. Calabrese and associates showed recently that stem cells in brain tumors occupied a perivascular niche and can be targeted by using antiantiangiogenic therapy.[54]

CLINICAL PRESENTATION

Pathophysiology of Signs and Symptoms

Parenchymal brain tumors produce clinical signs and symptoms by three main mechanisms, each of which has important implications for therapy: (1) Infiltration along nerve fiber tracts is typical of low-grade astrocytomas and oligodendrogliomas. The first clinical manifestation may be a single seizure. Normal brain tissue may be present within areas appearing abnormal on MRI, and functional mapping may be necessary for safe resection of these slowly growing tumors.[55–58]

(2) Displacement of brain tissue with production of vasogenic edema is typical of cerebral metastases. Such tumors sometimes can be resected or irradiated focally with less risk to adjacent normal brain tissue than is the case with infiltrating tumors. (3) Rapidly growing aggressive tumors such as high-grade astrocytomas may enlarge as a mass and also destroy surrounding neuropil to such an extent that surgical resection, although helpful for the reduction of mass effect and ICP, may not alleviate local symptoms and signs.

Intracranial neoplasms tend to produce progressive symptoms. Location and rate of growth determine both general and specific localizing symptoms and signs. Thus, a patient with a low-grade glial tumor may have seizures for many years or may exhibit behavioral alteration for many months before developing focal signs. With a more aggressive glial neoplasm, headache and focal signs may develop over a few weeks. Acute apoplectic onset is associated with hemorrhage or the development of hydrocephalus.

Brain tumor symptoms may be general, localizing, or falsely localizing. *General symptoms* include headache, lethargy, nausea, vomiting, and vague balance difficulties. These symptoms tend to be manifestations of increased ICP from a combination of expanding tumor volume and the production of associated vasogenic cerebral edema. Tumors also may cause raised ICP by obstruction of the ventricular system or blockage of the venous sinuses. Abrupt headache and exacerbation of neurologic signs may accompany the plateau waves of sudden increased ICP.

Sustained ICP in excess of 200 mm H_2O causes brain shifts that can displace brain tissue through fixed intracranial openings, producing life-threatening herniation syndromes[59] (Fig. 70-2; Table 70-4). The *uncal herniation syndrome* is caused by tumors arising in the lateral aspect of the brain, most commonly the temporal lobe. The earliest, most consistent sign of uncal herniation is a unilaterally dilated pupil due to compression of the ipsilateral third cranial nerve. This is followed by extraocular movement abnormalities consistent with an oculomotor palsy. The posterior cerebral artery may be compressed against the tentorium, leading to homonymous hemianopia. Brainstem compression can cause contralateral hemiapresis or, on occasion, ipsilateral hemiparesis. This is a result of compression of the contralateral cerebral peduncle against the edge of the tentorium, causing what is known as Kernohan's notch phenomenon.[60] Patients with uncal herniation initially may be awake, but progression to obtundation, coma, and death may occur rapidly, within hours.

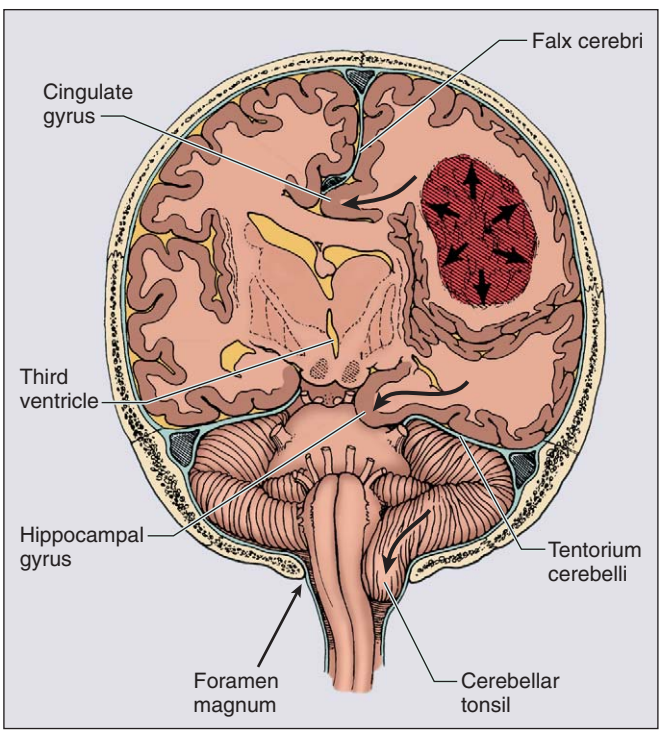


Figure 70-2 • Intracranial herniation syndromes evoked by supratentorial masses. The tumor and its edema *(arrows)* have produced the following *(curved arrows)*: cingulate gyrus herniation under the falx cerebri; diencephalic herniation across the midline compressing the ipsilateral ventricle and producing the hydrocephalus in the contralateral ventricle; hippocampal gyrus herniation through the tentorial notch compressing the posterior cerebral artery and brainstem, and herniation of the cerebellar tonsils through the foramen magnum (Adapted from Plum F, Posner JB: The Diagnosis of Stupor and Coma, 3rd ed, Philadelphia, FA Davis, 1980.)

The *central herniation syndrome* results from tumors that arise along the midline axis of the brain, especially those deep in the basal ganglia and thalamus regions. The initial signs and symptoms are due to diencephalic compression. The first evidence for this syndrome often is an alteration in the level of alertness and behavior. Some patients become agitated; others become very drowsy. Hemisensory or hemiparetic deficits and periodic Cheyne-Stokes respirations may develop in these patients. Initially with diencephalic compression, pupils are small (1 to 3 mm), but as the syndrome progresses and the midbrain and upper pons are compressed, the pupils dilate moderately and fix at midposition (3 to 5 mm). As the syndrome progresses, patients become progressively lethargic and apathetic and may develop Cushing's signs of hypertension and bradycardia due to direct compression of the hemodynamic control nuclei within the brain stem.[61,62]

Tonsillar herniation may be caused by an expanding mass in the posterior fossa, the region of the brain between the tentorium and the foramen magnum. This results in the cerebellar tonsils being pushed through the foramen magnum. The syndrome is characterized by posterior headache, vomiting, stiff neck, and sometimes opisthotonic posturing. Other features may include dysconjugate eye movements and syncope with cough or sudden postural change. Frequently, these patients complain of visual dysfunction due to progressive papilledema affecting visual acuity. As a result of direct compression of the medulla and its respiratory center, irregular breathing and acute apnea may develop in these aptients. Further compression of the brainstem can lead to Cushing's signs of hypertension and bradycardia. Tumors in the posterior fossa may also completely obstruct the fourth ventricle, leading to an obstructive hydrocephalus, which, if left untreated, will manifest as a central herniation syndrome. From a clinical standpoint, tonsillar herniation can be very difficult to diagnose. Patients often are agitated at the onset of the syndrome and frequently are sedated with narcotics, which only further compromises respiratory function, with the potential for a fatal outcome.

These herniation syndromes can rapidly progress from the onset of symptoms to death. They can be precipitated by medical procedures. Lumbar puncture may lead to tonsillar herniation, and ventriculostomy may result in upward herniation in which the brainstem is forced up through the tentorial notch. A high index of suspicion is required in order to successfully diagnose and treat this condition by emergency intubation and administration of appropriate therapy (see later under Treatment of Brain Tumor Symptoms).

General Signs and Symptoms

Headache results from traction on pain-sensitive structures of the intracranial contents including the large cerebral vessels, the dura and meninges, the venous sinuses, and cranial nerves V and IX. Headache is the most common symptom of a brain tumor and occurs in approximately 50% of patients at some time during the course of the illness.[63] Headache more frequently accompanies rapidly growing than slowly growing tumors. Tumors located in neurologically noneloquent brain areas such as the nondominant frontal and temporal lobes may manifest with headache as the sole clinical manifestation. The "classic" brain tumor-associated headache often is worse in the

Table 70-4 Important Clinical Syndromes in Patients with Brain Tumors

Syndrome/Signs and Symptoms	Localization and Pathogenesis	Common Tumor Type(s)
Obstructive hydrocephalus		
Headache, papilledema	Posterior fossa	Medulloblastoma, ependymoma, astrocytomas
Nausea, vomiting	Third ventricle compressed with growth of tumor or cyst	
Ataxia, stiff neck		
Communicating hydrocephalus		
Headache/pressure waves	Arachnoid granulation	Meningeal gliomatosis, any primary or metastatic tumor type
Gait apraxia	Scarring from treatment, hemorrhage, or infection	
Venous sinus thrombosis	Sinus	Meningioma
Uncal herniation		
Pupil dilation, oculomotor palsy	Temporal lobe herniates through tentorial notch, leading to compression of posterior cerebral artery, contralateral peduncle, midbrain	Any tumor type
Heminiaopia		
Ipsilateral hemiparesis		
Coma		
Central herniation		
Lethargy, small pupils	Diencephalic compression	Any tumor type
Cheyne-Stokes respiration		
Tonsillar herniation		
Posterior headache	Cerebellar tonsil herniates into foramen magnum	Posterior fossa tumor (astrocytoma, ependymoma, medulloblastoma)
Stiff neck		
Opisthotonos		
Pituitary apoplexy		
Headache, diplopia	Hemorrhage into pituitary	Pituitary adenoma, meningioma, craniopharyngioma
Third nerve palsy		
Hypotension		

morning and lateralized to the affected side of the brain. Brain tumor-associated headache may be worsened by coughing or straining. A majority of patients with brain tumors, however, do not have these classic symptoms but instead have headaches that are deep, aching, and difficult to distinguish from tension-type headache. As a general rule, headaches from posterior fossa tumors are localized to the back of the head or neck, whereas headaches from tumors of the anterior and middle cranial fossas may be referred to the forehead or eye, at times being misconstrued as "sinus" headache.

Brain tumor-associated cognitive changes initially may be subtle and frequently are misdiagnosed as depression or, in the older patient, age-associated forgetfulness or early Alzheimer disease. The patient may complain of additional nonspecific signs and symptoms such as fatigue, concentration problems, irritability, and loss of interest in usual activities. Frontal lobe tumor location is the most common site for tumors producing these symptoms as the initial manifestation of neoplasm. Hypomania and psychosis are less common cognitive symptoms and when occurring as the presenting symptoms usually are associated with temporal lobe tumors.

Roughly paralleling cognitive decline and of poor localizing value by themselves, several other symptoms may emerge. Dysphagia is a common complaint, and caregivers may note that the cognitively impaired patient seems to take a long time to chew and swallow. Oral candidiasis is a potential complicating issue in patients on long-term corticosteroid therapy and appropriate treatment should be instituted. Similarly, incontinence tends to parallel the degree of cognitive impairment. Urinary retention may occur in patients with bifrontal brain disease or with spinal cord problems. Opiate medications may exacerbate the urologic problems.

Seizures occurring for the first time in adults are more likely to be due to focal brain pathology, particularly neoplasms, than seizures occurring in childhood. Intracranial tumors produce both generalized tonic-clonic seizures, secondarily generalized tonic-clonic seizures, and partial, localization-related seizures. The tumors that are most likely to manifest with seizures are slowly growing astrocytomas and oligodendrogliomas or oligoastrocytomas. Seizures occur at some time in 25% to 50% of patients with brain tumors.[64–66] Tumors in the cortical and subcortical cerebral hemispheres, particularly the insula, are the most likely to produce seizures. Such seizures may be more difficult to control than those of idiopathic epilepsy and many patients require more than one antiepileptic drug (AED; see later under Treatment of Brain Tumor Symptoms). Seizure frequency may increase during radiation treatment and continue at an increased frequency for several months thereafter because of localized swelling.

Papilledema, swelling of the optic nerve head with engorgement of retinal veins, usually indicates raised ICP. In the pre-CT and MRI era, papilledema was a more frequent finding in brain tumors than it is today, because diagnosis now occurs earlier in the disease course. Currently, papilledema is seen in less than 20% of patients at presentation, down from 59% in the report by Huber.[67]

The development of papilledema is dependent on the location of the tumor and the rate of growth. Papilledema is more common in patients with infratentorial tumors than in those with supratentorial tumors. Other papilledema-producing tumor areas include the third ventricle, cerebral aqueduct, and fourth ventricle. Thus, in adults, medulloblastomas, glial tumors of the cerebellum, hemangioblasto-

mas, and tumors of the cerebellopontine angle are most commonly associated with papilledema.

Vomiting, with or without nausea, may occur as a result of direct simulation of emetic centers in the floor of the fourth ventricle. This mechanism explains the nausea and vomiting seen with raised ICP, particularly when the rise in pressure has been rapid and is associated with hemorrhage or herniation. Patients with posterior fossa tumors frequently experience nausea and vomiting. More commonly, however, nausea is a nonlocalizing symptom, so the differential diagnosis must include adverse drug reactions from AEDs, analgesics, or other concurrent medications and gastritis from high-dose corticosteroid treatment.

Localizing Signs of Intracranial Tumor

Focal clinical signs of intracranial tumor reflect the location of the mass and its associated vasogenic edema, which often is of much greater volume. This chapter does not provide a detailed discussion of every possible localizing sign but rather focuses on the general principle of neurologic localization and the specific emergent syndromes that should be recognized because of their localizing and management importance (summarized in Table 70-4).

Disorders associated with *frontal lobe lesions* include early impairment of intellectual function and language function if the dominant frontal lobe is involved. Patients with bilateral frontal tumors appear to lack initiative and spontaneity—a state called *abulia*. Such patients may have an impaired gait with difficulty initiating walking. Personality changes include inattentiveness, apathy, and depression, as well as the less common disinhibition and inappropriate affect leading to socially inappropriate behaviors. As tumors enlarge to involve the motor cortex, contralateral motor problems, such as hemiparesis or monoparesis, may develop in these patients.

Receptive language, auditory discrimination, and memory all are important functions of the dominant temporal lobe. Patients with *nondominant temporal lobe tumors* may have seizures involving visual, olfactory, or gustatory hallucinations. Deep temporal tumors may cause a contralateral visual field cut (superior quadrantanopia).

The parietal lobe is demarcated form the frontal lobe by the central sulcus. Parietal lobe functions include tactile perceptions, integration of sensory, visual, and auditory information and visual discrimination in the inferior contralateral quadrant. When tumor involves the nondominant *parietal lobe*, inattention to the deficit (anosognosia) may be a prominent feature of the presentation.

Tumors in the occipital lobes cause a contralateral quadrantic or hemianopic defect, sometimes with sparing of central macular vision.

Tumors of the brainstem cause a great many focal deficits early in their course. Typically, a combination of cranial nerve palsies and long tract signs such as hemianesthesia or hemiparesis coupled with ataxia reflecting cerebellar involvement give a clue to the localization. Patients with brainstem tumors experience difficulty with swallowing and speech articulation. They are at risk for aspiration.

Cerebellopontine angle tumors such as acoustic neuromas impair function of the eighth cranial nerve and produce unilateral hearing loss, tinnitus, and, later, vertigo. Involvement of adjacent cranial nerves VII and V leads to facial palsy and facial anesthesia. Later cerebellar dysfunction reflects tumor growth in this area.

Tumors of the pituitary and suprasellar region produce endocrinologic abnormalities either by hormonal production by secretory adenomas or by impingement on hypothalamic-pituitary connections. Visual defects reflect chiasmatic involvement. The most common pituitary region field defect is a bitemporal hemianopia.

Pineal region tumors (germ cell tumors, pineocytoma, and pineoblastoma, as well as gliomas of this region) may compress the aqueduct of Sylvius, causing hydrocephalus. Compression of the pretectal area produces a characteristic syndrome (Parinaud's syndrome) with paralysis of upgaze, ptosis, and loss of pupillary light reflexes, along with retraction-convergence nystagmus.

Many primary tumors are capable of *diffuse infiltration of the meninges*. Gliomas, lymphomas, and oligodendrogliomas all may invade the subarachnoid space, producing a meningeal reaction that may mimic chronic infection. They produce variable cranial nerve and spinal root dysfunction and diffuse headache, and sometimes lead to communicating hydrocephalus. Elevated cerebrospinal fluid (CSF) protein, low CSF glucose, and positive results on cytologic studies are the diagnostic hallmarks.

On occasion, the clinician will be faced with symptoms that appear to give a clue to the patient's tumor site but in fact are *false localizing symptoms*. Abducens nerve (cranial nerve VI) palsies may reflect brainstem involvement but commonly are a nonlocalizing sign of raised (or, much less commonly, low) ICP. Ocular pain is of little localizing value because it may reflect any of the structures innervated by the first division of the fifth cranial nerve. Thus, eye pain may reflect any process in the anterior or middle cranial fossa. Diplopia may result from cranial nerve invasion by brainstem or leptomeningeal tumor but also can be caused by excess levels of AEDs.

Posterior head pain may reflect posterior fossa disease but also may come from the upper cervical segments, and spinal cord tumor or caudal extension of a primary brainstem tumor should be considered if the patient presents with pain in the occiput. Another sign of cervical cord disease is bilateral upper limb weakness or numbness.

Gait disorders pose another potential hazard for falsely localizing signs and symptoms. A frontal lobe gait ataxia may mimic basal ganglia or even cerebellar disease. The affected patient walks slowly, with a wide-based gait, and seems to have difficulty initiating movements. Proximal leg weakness may reflect spinal metastases from intracranial or systemic tumor, but probably the most common cause of proximal leg weakness is corticosteroid-induced myopathy.

Treatment of Brain Tumor Symptoms

Acute Raised Intracranial Pressure

The most immediate life-threatening syndromes are the herniation syndromes, but rapid increase in vasogenic edema also mandates aggressive treatment of evolving neurologic signs and symptoms. If the patient is rapidly deteriorating, intubation and hyperventilation aiming for a PCO_2 of 25 to 30 mmHg are required. Mannitol is administered intravenously in a loading dose of 1 to 2 g/kg, followed by 0.5 to 1 g/kg every 6 hours as needed to control ICP. Mannitol may be transiently effective, but a rebound pressure increase sometimes develops after 24 to 48 hours. Intravenous dexamethasone in a loading dose of 20 mg followed by 6 to 10 mg every 4 to 6 hours is appropriate to start as initial treatment as well. Electrolytes and glucose levels must be monitored, and gastritis prophylaxis is required. Acute neurosurgical interventions include ICP monitoring devices and ventricular drainage or tumor decompression in cases of obstruction. Fluid management requires avoidance of hyponatremia.

Chronically Increased Intracranial Pressure

Dexamethasone in doses of 8 to 40 mg per day repairs the "leaky" blood-brain barrier of tumor vasculature. Controlling the edema helps to control headache, nausea, and seizures as well. Chronic raised ICP can cause visual loss, so careful ophthalmologic follow-up evaluation with visual field assessment is essential. Acetazolamide therapy for symptomatic plateau waves has been useful for some patients with raised ICP from intracerebral or leptomeningeal tumor.[68]

In the doses required to treat cerebral edema, corticosteroids produce many adverse effects. These range from the easily managed gastritis symptoms and glucose intolerance to insomnia, steroid psychosis, intractable hiccoughs, and disabling myopathy. The psychosis may readily respond to reduction of steroid dose and addition of neuroleptics. Treatment of the steroid myopathy, however, will require weeks of physical therapy with attempts at steroid reduction.

Anecdotal reports suggest that substitution of a nonfluorinated steroid such as methylprednisolone for fluorinated steroids such as dexamethasone may help reverse the weakness.[69]

Many brain tumor patients remain on corticosteroids for prolonged periods. They are thus susceptible to infection, particularly with *Pneumocystis jiroveci*, which carries a 50% mortality rate. Among solid tumors primary and metastatic brain tumors have the highest rate of *Pneumocystis* infection that occur in 2% of patients and prove fatal to 40% of these.[70] The mean duration of steroid therapy before infection was seven months with a mean dexamethasone equivalent dose of 1 to 2 mg per day.[71] In view of these statistics chemoprophylaxis with one tablet twice daily of trimethoprim-sulfamethoxazole twice weekly should be given to patients with brain tumors who are on corticosteroids longer than 4 weeks.

With long-term use of corticosteroids, an adrenal insufficiency state may develop in these patients, manifested by lethargy, hypotension, electrolyte imbalance, and diffuse weakness on steroid withdrawal. Intercurrent systemic stressors such as surgery or systemic infection may lead to serious hypotension. Chronic glucocorticoid supplementation with hydrocortisone 10 to 20 mg per day is essential for these patients.[72,73]

Seizures

Neuro-oncologists often find themselves working closely with epileptologists as they seek to control seizures with minimal side effects. Because brain tumor patients frequently require corticosteroids, analgesics, anxiolytics, and antiemetics, drug-drug interactions make epilepsy management complex.

The potential interaction of AEDs with other medications required for brain tumor patients has led to reconsideration of prophylactic use of antiseizure drugs. Cytochrome P-450 enzyme-inducing drugs such as phenytoin and carbamazepine may interact with numerous chemotherapeutic agents, as well as newer biologic agents such as tyrosine kinase receptor inhibitors (as discussed later under General Principles of Chemotherapy), reducing levels achieved and diminishing efficacy. AEDs also may increase the corticosteroid dose required for effective vasogenic edema treatment. For those patients with low-grade gliomas who may be on AEDS for many years there is also the risk of teratogenesis and osteoporosis.

A rash develops in approximately 20% of patients with gliomas treated with phenytoin or carbamazepine and cranial irradiation; the most serious and sometimes life-threatening reaction, the Stevens-Johnson syndrome, occurs in a few patients. This reaction is seen in the setting of hypersensitivity to AEDs unmasked during the taper of high-dose corticosteroids. The mechanism may be depletion of suppressor T cells by radiation, allowing emergence of the hypersensitivity syndrome.[74,75] Treatment is controversial, but often the corticosteroid dose is doubled as AEDs are withdrawn abruptly.

In view of all of the potential hazards of AEDs, it is worthwhile to consider whether their prophylactic use is justified in the brain tumor population. A controlled prospective study of patients with brain tumors addressing the question of prophylaxis for epilepsy showed an overall incidence of 26% with no difference in the seizure rate between patients taking AEDS and those without prophlyaxis.[76] A second study involving 100 patients with brain tumors confirmed the lack of efficacy of AEDs in preventing seizures or altering survival outcome in this clinical setting.[77] These findings are consistent with those of Foy and colleagues, who conducted a prospective trial in 276 patients who had undergone craniotomy (not all of whom had tumors) who were randomized postoperatively to receive phenytoin, carbamazepine, or no treatment. No difference in the incidence of seizures (37%) or postoperative complications was found among the groups.[78] For all of these reasons, a practice parameter published by the Quality Standards Subcommittee of the American Academy of Neurology concluded that no benefit could be established for routine prophylactic use of AEDs in patients with brain tumors.[79]

Table 70-5 Adverse Effects of Antiepileptic Drugs: Special Issues in Patients with Brain Tumors

Drug	Potential Adverse Effect(s)
Oxcarbazepine	Hyponatremia (confusion, seizures)
Gabapentin	Sedation, ataxia, weight gain
Depakote	Weight gain, platelet dysfunction
Topiramate	Memory/word-finding problems, weight loss
Zonisamide	Sedation
Levetiracetam	Psychosis, irritability, lethargy

Even after the acute phases of successful tumor treatment, epilepsy management may continue to be a major issue in quality of life for long-term survivors of low-grade brain neoplasms. A particularly dangerous late consequence of chronic antiepileptic therapy with phenytoin, carbamazepine, and phenobarbital is osteoporosis; therefore, long-term survivors should be screened regularly with dual-energy x-ray absorptiometry (DEXA) scans.

In the last 20 years, several AEDs have been introduced that offer new choices for brain tumor patients and the possibility of limiting side effects while achieving excellent seizure control. Of the newer agents, levetiracetam is emerging as an excellent choice in brain tumor patients as its level is not affected by chemotherapy drugs and it does not alter the metabolism of any chemotherapeutic agents. The clinician must be familiar with some side effects specific to these drugs (summarized in Table 70-5) in order to diagnose symptoms accurately, eliminate the offending drug, and avoid unnecessary diagnostic and therapeutic interventions.

Deep Venous Thrombosis

Deep venous thrombosis is extremely common in patients with brain tumors, with a reported incidence of 28% to 45%.[80,81] Among these patients, those with gliomas and meningiomas are at the highest risk for thromboembolism, which is a common cause of fever of unknown origin in this population. Alterations in fibrinolysis, immobility, paresis, tumor necrosis factor, steroids and neurosurgical procedures all combine to make brain tumor patients a high-risk group. Many of these patients receive vena cava filters because of the perceived risk of hemorrhage into their intracranial tumors. Retrospective studies, however, have suggested a very low risk of hemorrhage and in addition have demonstrated an incidence of complications of vena cava filters of greater than 60% in this patient group. Complications included pulmonary embolism, filter thrombosis, and postphlebitic syndrome.[82] Low-molecular-weight heparins have a good safety profile in the neurosurgical population.[83] Prophylaxis with enoxaparin 40 mg subcutaneously daily plus external compression stockings has been found to be superior to compression stockings alone for the prevention of venous thromboembolism after neurosurgery.[84,85] Although no absolute guidelines are available, most neurosurgeons would be reluctant to institute full anticoagulation in these patients within 3 weeks of surgery. A subset of patients with late white matter changes due to radiation therapy, like patients with extensive ischemic leukoaraiosis, may be at special risk for brain hemorrhage while on heparin.

DIAGNOSTIC IMAGING

Lumbar Puncture

Lumbar punctures are not commonly employed for the diagnosis of brain tumors. With primary gliomas the yield from CSF cytology at

initial diagnosis is extremely low. Leptomeningeal metasases occur in 4% to 15% of patients with solid tumors, most commonly from breast, lung, melanoma (reviewed by Taillibert and coworkers[86]). Hematologic malignancies also commonly involve the meninges. Leptomeningeal seeding from supratentorial malignant gliomas is usually an end stage finding. Patients with leptomeningeal tumor frequently present with signs and symptoms such as focal cranial nerve neuropathies, paresis of one or more limbs, headaches, and lethargy, which would be more expeditiously evaluated with a brain MRI study.

Skull X-Ray Studies

Plain films of the skull have been used in the past to determine evidence of mass effect due to shift of the calcified pineal gland. This has been largely replaced with the modern use of computed tomography and magnetic resonance imaging. Plain radiographs of the skull are still useful for evaluating skull lesions such as dermoids and epidermoids as well as eosinophilic granulomas. These are primary lesions of the skull which frequently can be best seen with plain skull x-ray films. Epidermoid and dermoid tumors of the bone are congenital tumors derived from ectopic epithelium. These are benign lesions but can grow to be quite large and are usually painless, causing deformity of the skull. Eosinophilic granulomas may be associated with Hand-Schüller-Christian disease, a triad of diabetes insipidus, exophthalmos, and bone lesions usually found in the skull. Other primary bone lesions that can be found on plain skull films include multiple myeloma and plasmacytoma. Bone foramen abnormalities occurring in the skull include fibrous dysplasia and Paget's disease. Fibrous dysplasia can be cystic or sclerotic and usually occurs in the anterior middle fossa. This can cause proptosis of the eye and compression of the cranial nerves exiting the middle fossa causing pain and entrapment syndromes. Paget's disease is benign but thought to be a premalignant condition causing similar symptoms to fibrous dysplasia due to thickening of the bone at the skull base constricting neural foramen. Occasionally meningiomas can grow selectively into the bone rather than into the intracranial compartment. This causes thickening of the bone with compression syndromes as previously described causing proptosis of the eye, constriction of neural foramen causing cranial nerve deficits and more commonly, complaints of headache syndromes. Due to the thickening and sclerotic changes seen in the latter three disease states, these lesions are frequently evaluated with plain skull radiographs as part of the workup.

Computed Tomography

A CT scan usually is the first study obtained when a patient presents with a neurologic complaint. CT scans can be obtained quickly in most hospitals as a screening tool. Hemorrhagic lesions can be seen as a result of the increased density of blood. Infarcts will manifest acutely as edematous tissue and can be confused with tumors, especially low-grade gliomas, which may not enhance with contrast agents. Iodinated contrast agents are useful to differentiate the tumor from the surrounding edematous brain tissue, because the contrast agent is able to leak out of the vascular space into the tumor owing to breakdown of the blood-brain-barrier. The pattern of ring enhancement of tumors may be difficult to distinguish from the ring enhancement of a cerebral abscess, though brain tumors are far more common than brain abscesses in the United States. CT images have limitations at the skull base due to volume averaging artifact as the x-ray beam slides over uneven bone ridges. This makes it difficult to interpret findings in the skull base and in the posterior fossa (the region between the tentorium and the foramen magnum). CT scans are still the study of choice in patients who cannot undergo magnetic resonance imaging (MRI), such as those with implanted pacemakers, defibrillators, or other metal devices that prevent imaging by MRI.

Magnetic Resonance Imaging

MRI has become the study of choice for evaluating brain tumors. The high degree of definition of the anatomy of the brain as well as the absence of bony artifacts seen in CT scans has enabled magnetic resonance imaging (MRI) to provide exceptional images of the tumor. Localization of the lesion is precise as an MRI is done in three planes. The study of choice for evaluating brain tumors is MRI with and without contrast. Much like CT scan contrast, the MRI contrast agent gadolinium is able to penetrate into the tumor because of breakdown in the blood-brain barrier and subsequent "leak." This enables the tumor site to become white on the T1 weighted images. Gadolinium enhancement can be crucial in identifying leptomeningeal disease as thickened areas of the dura, as well as "sugar coating" the brain itself.

Multiple sequences may be obtained from the MRI scans that highlight different properties of both the brain and the tumor. Of particular interest are the T_2-weighted and fluid-attenuated inversion recovery (FLAIR) images showing the vasogenic edema created by the tumor. Evaluating this edema pattern is very important in assessing the degree of mass effect. The volume of edematous brain may represent the true limits of a glioma tumor, because tumor cells are present in the nonenhancing tissue surrounding the enhancing tumor.[87] This provides the rationale for extending the irradiated zone in standard external beam radiation therapy to include the edematous volume of brain plus a margin of 1 to 2 cm. Presence of an edema pattern extending into the corpus callosum implies direct tumor invasion into the corpus callosum. The extremely compact fiber tracts passing through the corpus callosum will not allow edema fluid to pass through, so any edema seen is created by local tumor infiltration. This point is very important to keep in mind in assessing extent of tumor.

Endothelial proliferation with neovascularity is a hallmark of malignancy in brain neoplasms. MRI perfusion imaging can be performed in combination with conventional MRI examinations to determine the extent of neovascularity. Correlation between regional cerebral blood volume and grade of malignant glioma appears to be very good. In particular, this is especially helpful in distinguishing grade III from grade IV malignant gliomas.[88,89] It has been noted that anaplastic astrocytomas with gadolinium enhancement show a higher vascularity index than that in tumors without gadolinium enhancement. Perfusion imaging may enable monitoring of the antiangiogenic effects of treatment in brain tumors. Perfusion imaging appears to be useful in assessing benign tumors such as meningiomas to determine the vascularity of these tumors, which may be associated with progression.[90]

MRI techniques have been utilized to identify areas of brain activity in real time. This functional MRI technique has become quite useful in identifying regions of eloquent brain adjacent to tumors.[91,92] By identifying language and motor areas adjacent to tumors one can determine the degree of aggressive surgical resection that can be carried out and also the best way to preserve this functional activity.[93] Functional MRI scans are being imported into frameless stereotaxy units that are used for intraoperative surgical planning.[94] By using discrete motor, sensory, language or visual paradigms, the relevant part of the cortical brain can be activated for identification of functional activity. The one limitation to functional MRI scanning is that it does not identify subcortical white matter tracts that are activated by the investigated activity.

A great deal of interest has centered on the capability of routine clinical MRI scanners to perform MR spectroscopy (MRS) as a technique to evaluate molecular components of a defined voxel within the brain tissue. Today's smaller voxel sizes allow a much greater degree of selectivity in evaluating components of a tumor. MRS has been applied quite extensively to malignant gliomas, for which the most important molecular components are *N*-acetylaspartate (NAA), creatine, choline, and a combined peak of lipids and lactate.[95] MRS

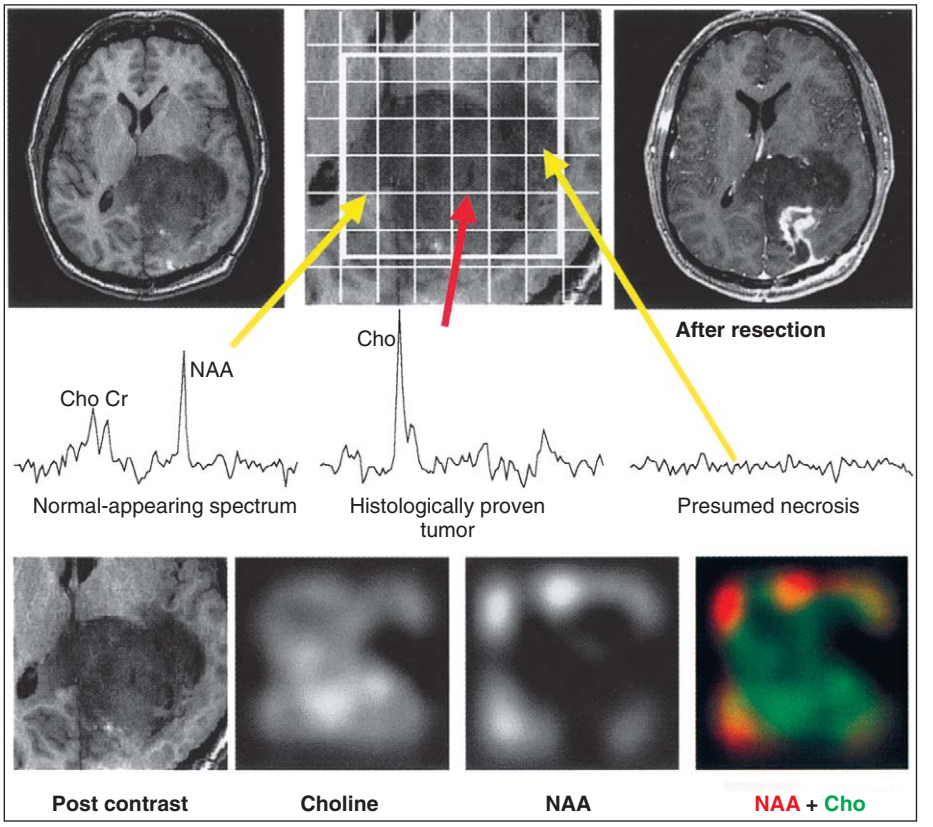


Figure 70-3 • MRI/MRS studies of WHO grade II oligoastrocytoma. Axial T_1-weighted post-gadolinium MRI on day before surgery *(top left panel)* shows area of hypodensity that does not enhance (bottom left panel). MRS *(middle panel)* shows area of high choline (Cho; 1.8 times greater than adjacent brain) and low NAA levels, as well as a smaller region of no significant metabolite levels, which is presumed necrosis. The resection was limited to a region of elevated choline with no significant NAA. Cr, creatine; NAA, *N*-acetyl aspartate; WHO, World Health Organization. (From Vigneron A, Bollen A, McDermott M: Three-dimensional magnetic resonance spectroscopic imaging of histologically confirmed brain tumors. Magn Res Imaging 2001;19:93.)

can be useful in diagnosis in that malignant gliomas exhibit a higher choline peak relative to creatine, and a lower NAA peak, with increasing grade of malignancy (Fig. 70-3). An additional peak beyond the NAA peak identifies lipids and lactate, which also constitute markers of malignancy and can be seen both in primary gliomas and metastatic tumors. MRS can be used to determine whether a region of enhancement in a previously treated tumor represents active tumor or radiation necrosis. MRS has been used to follow treatment effects over an extended period of time. Most useful has been the development of the multivoxel technique, in which large areas of the brain can be mapped with individual small voxels so that it is possible to determine small areas of active tumor within a large region of brain.

MRI has the capability to specifically identify vascular structures such as major arteries and veins. MR angiography (MRA) and MR venography (MRV) can be useful in evaluating major vessels at the base of the skull for skull base tumors. The quality of MRA and MRV has been steadily improving, and both of these techniques provide a noninvasive means for evaluating these vascular structures without the need for angiography.

Positron Emission Tomography

PET imaging uses a radioactive isotope, ^{18}F-fluorodeoxyglucose (FDG), to image metabolism of glucose in the brain. Because glucose is the sole fuel for brain tissue this metabolic imaging allows visualization of brain physiology. PET scans will be positive in glioblastoma, primary CNS lymphoma, oligodendroglioma, and malignant meningioma owing to the high uptake of FDG.[96] Anaplastic astrocytomas and oligodendrogliomas, meningiomas, and metastatic tumors show variable FDG uptake; low-grade gliomas and radiation necrosis show little to no FDG uptake (Figs. 70-4 and 70-5).

Intraoperative Ultrasound Examination

In general, brain tumors are echogenic, so real-time ultrasound studies can be used for localization. Ultrasound examination can be used to identify normal intracranial structures such as the ventricles, the falx, and the tentorium. Exact tumor localization is necessary because of the limited operative exposure to the brain. The ultrasound transducer can be applied to the dura surrounding the brain or placed directly on the brain tissue. Ultrasound examination can be quite useful in finding large brain tumor cysts, which can cause herniation of the brain during surgery. With accurate localization of the cyst by this means, a needle can be inserted to drain the cyst, thereby rapidly decompressing the brain.

SURGERY: GENERAL CONSIDERATIONS

The successful resection of a brain tumor requires removing the tumor only, without injuring surrounding normal brain. The approach to removal of brain tumors follows the mantra of real estate agents: "location, location, location." Deep tumors that are in noneloquent regions of brain can be easily accessed and removed, whereas superficial tumors may not be easily resectable owing to their location within extremely eloquent brain tissue.

The goals of surgery are (1) to establish the histology of the lesion; this is frequently better performed through a craniotomy with a more aggressive debulking of the tumor, rather than a simple stereotactic biopsy, so that there is no question of sampling error; (2) to debulk the mass effect of the tumor to correct a neurologic deficit and to prevent imminent death in patients with large tumors and early herniation syndromes; and (3) to debulk the tumor to increase efficacy of radiation therapy and chemotherapy, which produce the best response rate when they are used with minimal tumor burden.

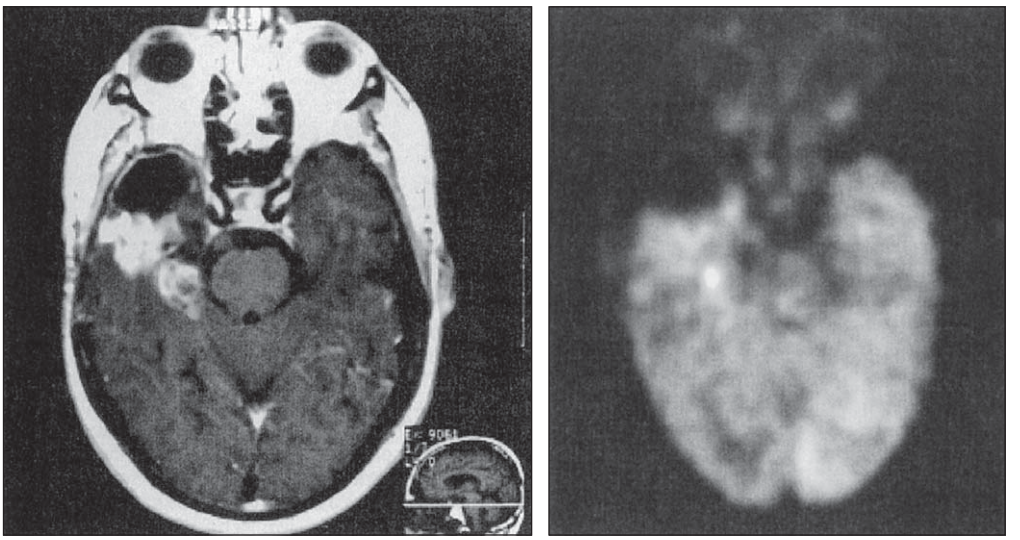


Figure 70-4 • Positron emission tomography (PET) scan of recurrent glioma. The patient had undergone surgical resection of an anaplastic oligodendroglioma 15 months earlier. Areas of contrast enhancement on T_1-weighted magnetic resonance imaging (MRI) scan *(left panel)* have high fluorodeoxyglucose (FDG) accumulation, consistent with recurrent high-grade tumor on the co-registered FDG-PET image *(right panel)*. (From Hagge RJ, Wong TZ, Coleman RE: Positron emission tomography. Brain tumors and lung cancer. Radiol Clin North Am 2001;39: 874.)

Establishing a tissue diagnosis is extremely important for therapeutic and prognostic considerations. Frequently, the histologic diagnosis may be straightforward; however, a category of tumors exists that manifest as mixed gliomas, in which tissue sampling can induce errors in diagnosis.[97] A limited biopsy specimen may show a solitary cell type, but further examination of a more extensive specimen may reveal the presence of other components. This is particularly important when the other components identified may change the histopathologic interpretation from a grade II glioma to an anaplastic grade III glioma. Noninvasive means of establishing tissue diagnosis have been pursued, primarily through the use of MRS.[98,99] Significant progress has been made to determine histologic diagnosis of tumors with MRS; however, MRS is still not specific enough to form the basis for major therapeutic decisions. Histopathologic determination remains the gold standard.

The most common presenting manifestations in patients with glioma are headache and seizures.[100] Debulking large tumors will reduce the dural stretch, decreasing headaches. The incidence of seizures in patients with malignant gliomas can be decreased by at least 75% with attempts at gross total resection.[101] Recovery from other neurologic deficits manifesting as hemiparesis, visual field loss, or aphasia, for example, will depend on whether the impaired brain tissue is simply compressed by the tumor mass or whether the tumor itself has directly destroyed these neural tracts. In the former case, but not the latter, debulking the tumor will help relieve the patient's symptoms.

As a result of liberal use of CT and MRI scans, herniation syndromes with brain tumors, as noted earlier under Pathophysiology of Signs and Symptoms (in the clinical presentation section), are uncommon presentations. Occasionally, however, patients present with central or uncal herniation syndromes from late-stage brain tumors. These patients need to have an emergency CT or MRI scan and undergo rapid evaluation for possible surgery for reduction of mass effect as a life-saving measure.

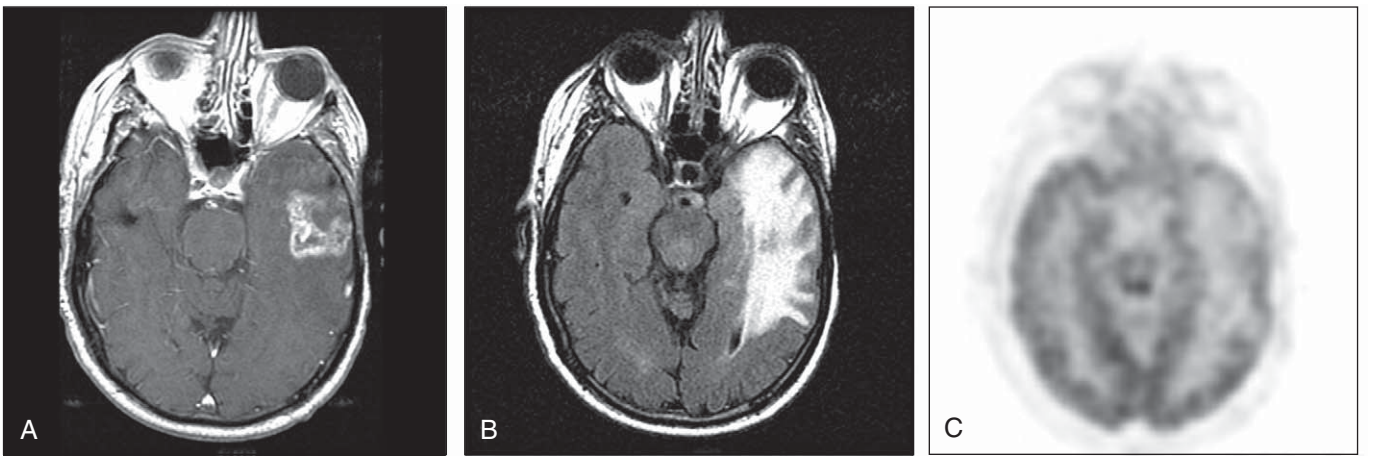


Figure 70-5 • Positron emission tomography/magnetic resonance imaging (PET/MRI) studies showing radiation necrosis of the brain. The patient had had a recurrence of a basal cell carcinoma involving the skin overlying the zygoma and the left periauricular region, with extension into the temporalis muscle. He underwent surgical resection, but because of perineural invasion, he received radiation therapy at a dose of 6400 cGy postoperatively to the tumor bed. Approximately 2 years later, he presented with aphasia and confusion. **A,** T_1-weighted post-gadolinium MRI showed a ring-enhancing mass in left temporal lobe, a finding highly suggestive of malignancy. **B,** FLAIR MRI showed extensive edema. **C,** An ^{18}F- fluorodeoxyglucose (FDG) scan, however, showed patchy areas of hypometabolism within the anterior and lateral aspects of the left temporal lobe—findings consistent with radiation effect, not malignancy. The patient underwent surgery with resection of the lesion, which confirmed it to be radiation necrosis without any evidence of malignancy.

Another rationale for maximal debulking is to reduce the tumor burden by one or two log orders of cells. Such cytoreduction is perfomed in the hope of increasing efficacy of both radiation therapy and chemotherapy for these tumors.

RADIATION THERAPY: GENERAL CONSIDERATIONS

Radiation is commonly used to treat many different types of brain tumors. The radiation oncologist must decide on many factors in the treatment plan for an individual patient, including treatment volume, dose, and fractionation. Treatment techniques including three-dimensional conformal therapy, stereotactic radiotherapy, and intensity-modulated radiation therapy (IMRT) are being used in a majority of patients presenting with brain tumors. Proton therapy, which has increasing availability in the United States, may be used for specific cases, especially for tumors at the skull base.

Radiation Therapy: Technical Details

Treatment planning starts with a review of the MRI scan to identify the target volumes. The appropriate volume to be irradiated varies according to the tumor type. Most brain tumors including gliomas and meningiomas are treated with focal radiation to the lesion plus a margin. The actual abnormality seen on imaging studies is termed the *gross tumor volume* (GTV). Additional tissue surrounding the GTV that is thought to potentially contain tumor cells is included in the *clinical target volume* (CTV). For some tumors such as glioblastomas, which can be highly infiltrative, the CTV includes the area of edema as demonstrated on the FLAIR or T_2 sequences plus a 1.5- to 2.0-cm margin. For other tumors that do not infiltrate, such as meningiomas, pituitary adenomas, acoustic neuromas, and craniopharyngiomas, the CTV typically would be much tighter than that used for glioblastomas. An additional volume is included around the CTV to take into account day-to-day setup error and to allow for buildup of dose, resulting in the *patient treatment volume* (PTV). Treatment planning proceeds by placing the patient on a CT simulator, generally in the supine position. Multiple immobilization devices are available, including thermoplastic masks, bite blocks, and systems that include motion tracking devices. After the CT scan is obtained, a previously obtained MRI scan can be fused onto the treatment planning system to better define the target volumes. In addition to the tumor, normal structures including the optic nerves, chiasm, cochlea, and brainstem often are drawn as areas to limit the radiation dose. Computerized treatment planning is then used to generate radiation beams and dose distributions.

Most brain tumors are treated with focal radiation therapy; however, for some tumors, such as PNETs and metastatic germ cell tumors of the CNS, it may be necessary to include the entire craniospinal axis in the irradiated zone. In such cases, a special technique must be used. For craniospinal irradiation, the optimal patient position is prone. This facilitates daily setup and treatment, with the spinal canal included in one or two fields entering from the patient's back and the entire cranial contents included in opposed lateral fields. Because abutting fields are used to encompass the entire craniospinal axis, the possibility exists for overlap between fields, resulting in a potential overdosage to part of the spinal cord. Therefore, great care must be taken during the setup of these fields. In many institutions, a technique termed *feathering* is used in which the matchlines between fields are changed periodically to ensure that an overdose or underdose does not occur in the same region of the spinal cord throughout the entire treatment.

Stereotactic Radiotherapy

Stereotactic radiotherapy is a technique for delivering high-dose radiation to a target volume with very tight margins, thereby sparing surrounding normal tissues. This technique can be implemented in a number of ways using various devices, including (1) a Gamma Knife machine, which contains 201 fixed cobalt sources that converge to a single point; (2) a conventional linear accelerator ("linac") outfitted with additional hardware so that it can deliver focused radiation, generally using between 3 and 5 arcs; and (3) delivery of charged particles such as protons, which, because of their physical properties, deposit energy in a narrower region than is possible with x-rays.

Stereotactic radiation can be delivered in a single large fraction. When this is done, the technique is termed *stereotactic radiosurgery*. Despite of its name, no surgery is performed. A sterotactic headframe often is screwed to the skull. In adults, this can be done using local anesthesia, but in children, conscious sedation or general anesthesia must be used. The headframe allows for localization of the tumor in a three-dimensional coordinate system and also immobilizes the head during treatment, thereby allowing for delivery of radiation with precision to a very tightly defined volume. For linear accelerator-based radiosurgery, the patient has a CT scan performed with the headframe in place. At our institution, MRI with gadolinium contrast is performed before placement of the headframe. The MRI images are then fused to the CT images, and a treatment plan is devised that targets the lesion while minimizing dose to normal structures. For Gamma Knife radiosurgery, an MRI-compatible headframe is placed before a contrast-enhanced MRI scan is obtained for use in target definition. The doses of radiation that are used in stereotactic radiosurgery range from 10 to 24 Gy and are based on the histologic tumor type and the volume of tissue irradiated. The doses used are based on the likelihood of tumor control and the risk of developing radiation necrosis.[102] The choice between a Gamma Knife and a linear accelerator is based on availability. Generally, Gamma Knife doses are prescribed to the 50% isodose line, and those with linear accelerator-based therapy, to the 80% isodose line.

Stereotactic radiotherapy also can be delivered in a fractionated regimen over several days or weeks. Of course, in this instance a headframe that is screwed into the skull cannot be used. Therefore, relocatable headframes have been developed. These headframes use custom-made moldings conforming to the patient's occiput and a bite block to maintain a precise and reproducible fit day to day.

A large experience has been accumulated with the use of stereotactic radiotherapy, in either a single fraction or a fractionated regimen, for the treatment of intracranial metastases, arteriovenous malformations, and primary brain tumors. The use of this modality to treat arteriovenous malformations is beyond the scope of this chapter, and its use in treating intracranial metastases is covered in Chapter 56. The use of stereotactic radiotherapy techniques for the treatment of meningiomas, pituitary adenomas, and acoustic neuromas is discussed in greater detail in the corresponding sections in this chapter.

Delivery of charged particles including protons has been used to treat brain tumors. Because of their physical properties, protons result in more limited dose to normal tissues than is possible with conventional x-rays. Only six centers in the United States have protons or other charged particles available for medical treatment, although a number of new facilities have recently been opened, and additional sites are in the planning phase.

Intensity-Modulated Radiation Therapy

The technique of IMRT uses multiple segmented fields with inverse treatment planning algorithms. In addition to defining the doses to be delivered to the GTV, CTV, and PTV, dose constraints are placed on normal structures to limit their radiation exposure. Constraints include the maximum dose to the entire structure and limits to a portion of the structure, as well as the maximum point dose within the structure. The most common mechanism of delivering this dose is use of multiple fields, typically 5 to 9, with use of a multileaf collimator to divide each field into multiple beamlets. From 50 to more

than 100 beamlets may be used. Most modern radiation departments have access to this technique.

Adverse Effects after Irradiation of the Brain or Spine

Acute and Early Delayed Effects after Cranial Irradiation

A variety of adverse effects may follow irradiation of the CNS (reviewed by Schultheiss and associates[103]). These effects can be divided into acute, which occur during the treatment; delayed early, which occur within a few months of radiation; and late, which occur months to years later.

Acute effects of cranial irradiation include fatigue, nausea, headaches, anorexia, and alopecia. Patients often complain of fatigue, not just with cranial irradiation, but with irradiation to other regions of the body, and as a result they often need to sleep longer than usual or take naps during the day. Patients may experience nausea within hours after the administration of the radiation and headaches during the course of treatment. Nausea usually is well controlled with antiemetics such as ondansetron or granisetron. Nausea and headaches are thought to be caused by radiation-induced edema and can be ameliorated with corticosteroids. In patients receiving craniospinal radiation, the nausea and anorexia may be compounded by the radiation that the upper gastrointestinal tract receives as an exit dose from the spinal field. Hair loss generally starts after the scalp has received 20 to 30 Gy. It generally is not permanent, but regrowth of hair may take months, and the new hair often is thinner than the original or even of a different color. In areas that receive a high dose of radiation, especially with tangentially directed fields, alopecia may be permanent. Other acute side effects of cranial irradiation may include accumulation of cerumen in the ear canals and serous otitis media.

The most common delayed early effect from radiation is the somnolence syndrome which is characterized by excessive drowsiness, nausea, and irritability.[104] If it occurs, it generally does so one to three months after radiation has been completed. This syndrome is thought to be due to transient, diffuse demyelination. It usually is seen after whole-brain irradiation for ALL but also can develop after limited-field irradiation for brain tumors. The syndrome resolves spontaneously, but steroids can shorten its duration. Delayed early effects occurring after cranial irradiation also can take the form of focal neurologic signs due to intralesional reactions related to tumor response or perilesional reactions related to edema or demyelination.

Brain Necrosis and Neurocognitive Deficits Following Cranial Irradiation

The pathophysiology of late effects from CNS irradiation is poorly understood. Some of the effects may be caused by degenerative changes in the supporting glial cells, whereas others may be caused by vascular changes due to endothelial cell loss and capillary occlusion.

One of the most serious late effects of cranial irradiation is brain necrosis, which may cause significant and persistent neurologic injury.[105,106] Second, it may produce progressive cerebral edema and mass effect requiring prolonged corticosteroid use or surgery. Third, it may be confused with tumor growth, resulting in the inappropriate use of antitumor therapies. The onset of radiation necrosis includes behavioral changes—lethargy and dementia, headache and papill-edema, and seizure. Clinical signs and symptoms are usually identified from 2 to 3 years after irradiation, although confirmed cases been detected as early as 9 months and as late as 16 years after completion of radiation therapy. The signs and symptoms are strongly related to the site of radiation necrosis; however, the most common clinical signs are focal motor deficits. Radionecrosis often is difficult to distinguish from recurrent tumor by CT or MRI, which may show increased signal intensity on T_2-weighted images and contrast enhancement on T_1-weighted images.[107] As discussed earlier (in the "Diagnostic Imaging" section), and as shown in Figure 70-5, however, PET scanning with FDG may help distinguish viable tumor from necrotic tissue.[108–110] Surgical exploration often is necessary not only to establish a diagnosis but also as a therapeutic intervention to remove the region of necrosis. Histopathologically, the changes seen in radiation-induced necrosis generally are limited to the white matter and include focal coagulative necrosis and demyelination.[111] Accurate data regarding the incidence of brain necrosis based on CT and MRI findings come from a randomized trial of irradiation for low-grade gliomas.[112] In this study, the 2-year actuarial incidence of brain necrosis was 2.5% for patients receiving 50.4 Gy and 5% for those receiving 64.8 Gy.

Neurocognitive deficits often are observed after cranial irradiation, especially in young children. Many of the sequelae appear several years after treatment of children with brain tumors, which mandates long-term follow-up. Sequential assessments of neurocognitive function demonstrated progressive deterioration during 6 years after radiotherapy in children with ALL treated with 18 Gy of whole-brain irradiation.[113] Numerous studies of neurocognitive function in children after whole-brain irradiation for ALL have been performed.[114–118] In summary, these findings show that whole-brain irradiation can lead to decline in neurocognitive function, an effect that appears to be greater in younger children and with higher doses of radiation (24 Gy) but can be seen after 18 Gy.[113] It also is possible that an interaction between methotrexate (intrathecal or high-dose systemic) and whole brain irradiation causes these late effects.[118]

Another treatment complication associated with cranial radiotherapy is leukoencephalopathy. This most is often associated with intravenous or intrathecal methotrexate and cranial irradiation.[105,119] Young age also is an important risk factor; however, leukoencephalopathy can affect all age groups. Histologically, multifocal white matter destruction with loss of myelin can be seen, especially in the periventricular regions; MRI scans show these periventricular abnormalities. CT scans also may reveal the presence of intracerebral microcalcifications due to mineralizing microangiopathy. The clinical expression of leukoencephalopathy ranges from mild evidence of white matter injury on neuroimaging studies to severe necrotizing leukoencephalopathy with profound neurologic impairment and, in some cases, death. Mild or subclinical cases are more common than severe necrotizing leukoencephalopathy. The bulk of the experience comes from children who received 24 Gy of whole-brain radiation along with high doses of intravenous and intrathecal methotrexate. The frequency of leukoencephalopathy is low in patients who receive cranial radiotherapy and intrathecal methotrexate or cranial irradiation and intravenous methotrexate but may be as high as 45% in patients who receive all three treatments.[120] In general, methotrexate is most toxic when given during or after radiation.

Although the major portion of the literature on neurocognitive function after cranial irradiation concerns children, some data on adults are available. Taphoorn and colleagues found no significant differences in neurocognitive function between patients with low-grade gliomas who received radiation (45 to 63 Gy) and those who did not.[121] In another retrospective study, young adults with low-grade brain tumors treated with 54 to 56 Gy of radiation to limited fields often showed a transient, early delayed drop in neuropsychological performance at 6 months; however, the risk of long-term cognitive dysfunction was low, at least up to the age of 4 years.[122]

In an NCCTG randomized study of 64.8 versus 50.4 Gy for treatment of low-grade gliomas,[112] data regarding cognitive performance were collected prospectively. Analysis of these data with a median follow-up time of 7.4 years in survivors showed that the vast majority of patients with normal baseline findings on the Mini-Mental Status Examination (MMSE) maintained these after radiotherapy.[123] Patients with abnormal MMSE results before radiotherapy were more likely to have an improvement in cognitive abilities than deterioration after receiving radiotherapy. Armstrong and coworkers

conducted prospective, comprehensive, longitudinal neuropsychological testing on 26 adult patients with low-grade supratentorial brain tumors, mostly gliomas, who had received radiotherapy.[124] Nine patients underwent testing at 6 years after radiotherapy. No declines were noted on most neurocognitive tests. Seven of the 37 neuropsychological tests showed improvement over 6 years. However, declines emerged only after 5 years on selected tests of cognitive function such as visual memory.

On the basis of these and other studies, one recent review on the neurocognitive effects of radiotherapy on patients with low-grade gliomas came to the conclusion that the weight of evidence suggests only sporadic, limited neurocognitive damage from focal radiotherapy at the doses usually prescribed.[125] These patients do not appear to suffer from widespread cognitive impairment or dementia.

Cranial irradiation can result in arterial vascular problems such as vessel obliteration or narrowing, resulting in a stroke-like syndrome.[126] These complications are rare, but when they occur they are more likely to happen after irradiation of the parasellar region.

Endocrine Deficits after Cranial or Spinal Irradiation

Endocrine problems are common after cranial irradiation, particularly in children.[127–129] Such problems include growth hormone deficiency and thyroid and gonadal dysfunction.

The hypothalamus is more radiosensitive than the pituitary gland and is responsible for endocrine dysfunction at lower doses. At higher doses (greater than 40 Gy), however, both the anterior pituitary gland and the hypothalamus contribute to endocrine dysfunction. Of all the hormones, growth hormone is the most likely to show deficiency following irradiation. Growth hormone deficiency is seen in a majority of children who have received whole-brain irradiation. One study found that in children with ALL given 24 Gy to the whole brain, 56% developed growth hormone deficiency, whereas no such problems were seen in children given 18 Gy, at least 4 years later.[130] The latency of onset is dose-dependent, being shorter with higher doses.[131] Growth may be further impaired by spinal irradiation, which directly affects vertebral body growth center.

Precocious puberty may also occur after relatively low doses, on the order of 18 Gy.[132] Deficiencies in the other hormones, such as gonadotropins, TSH, and ACTH, are rare after doses below 40 Gy, however.[128] Thyroid dysfunction is common in patients with brain tumors treated with high-dose radiotherapy.[133] Constine and associates studied endocrine function in 32 patients with brain tumors not involving the hypothalamic-pituitary region who received 39.6 to 70.2 Gy to this region.[134] Hypothalamic or pituitary hypothyroidism developed in 65% of the patients. Fourteen of 23 (61%) postpubertal patients had evidence of hypogonadism as manifested by oligomenorrhea or low estradiol levels or low testosterone levels. Half of the patients had mild hyperprolactinemia. Subtle abnormalities in adrenal function were seen in 35% of patients.

In patients receiving craniospinal radiation, hypothyroidism also may occur secondary to exit dose to the thyroid gland. In a study of radiation therapy for brain tumors not involving the hypothalamic-pituitary axis from the Christie Hospital in Manchester, the incidence of hypothyroidism was 15% or 33% ($P = 0.013$), respectively, for patients receiving cranial or craniospinal irradiation.[135] The mean spinal dose was 29 Gy, and the exit dose to the thyroid gland ranged from 10 to 15 Gy.

Optic Neuropathy after Cranial Irradiation

Irradiation of tumors that are close to the optic nerves or chiasm may result in sufficient dose to these structures that optic neuropathy is a concern. Two major classes of optic neuropathy are recognized: anterior optic neuropathy and retrobulbar optic neuropathy.[136] The former is thought to be due to vascular injury affecting the nerve head inside the globe anterior or adjacent to the lamina cribrosa. This is associated with swelling of the optic head, in contrast with retrobulbar optic neuropathy, which is due to more proximal injury to the optic nerve. Diagnostic criteria for retrobulbar optic neuropathy include (1) visual loss (monocular or binocular) accompanied by corresponding visual field defects, (2) funduscopic examination often showing a pale optic disc but without edema, (3) onset 6 months to several years after radiation therapy that delivered a significant dose to the optic nerve-chiasm, and (4) no radiologic evidence of visual pathway compression.[137] MRI scans may show pathologic contrast enhancement of the region of the optic nerve-chiasm that received a high dose of radiation.[138]

Parsons and colleagues examined radiation-induced optic neuropathy in patients receiving radiation treatment for primary extracranial head and neck tumors at the University of Florida.[136] Of 215 optic nerves at risk, these investigators found anterior optic neuropathy in 5 nerves and retrobulbar optic neuropathy in 12. No injuries were observed in 106 optic nerves that received less than 59 Gy. The 15-year actuarial risk of optic nerve neuropathy after 60 Gy more was 11% when daily fractions less than 1.9 Gy were used, versus 47% when 1.9 Gy or more was used.

The foregoing data suggest that the optic nerve-chiasm tolerance is at least 59 Gy; however, the University of Florida population did not include patients with intracranial tumors compressing the optic nerve-chiasm. It is possible in the latter situation that the tolerance of the optic nerve-chiasm is lower as a result of ischemic injury. In some patients with pituitary adenomas or craniopharyngiomas treated with irradiation, optic neuropathy developed after doses as low as 45 to 50 Gy, although in many of these cases the daily fraction size was greater than 2 Gy.[137,139,140] On the basis of these results, most investigators currently recommend limiting the optic chiasm-nerve dose to 50 Gy in 1.8- to 2-Gy fractions in the treatment of pituitary adenomas or craniopharyngiomas. For other brain tumors requiring higher doses, most radiation oncologists would try to restrict the optic nerve-chiasm dose to 54 Gy or lower. Adherence to these guidelines should keep the risk of radiation-induced optic neuropathy extremely low (1% or less) but unfortunately will not completely eliminate it.

Second Malignant Neoplasms Developing after Cranial Irradiation

Second malignant neoplasms including malignant gliomas and meningiomas remain relatively uncommon consequences of radiation therapy for brain tumors.[6,141] Recent reports raise concerns that the addition of adjuvant chemotherapy may increase the risk of second malignancies in long-term survivors of childhood brain tumors.[15,16] This may be especially true after prolonged use of alkylating agents and etoposide with or without irradiation.

Myelopathy after Spinal Irradiation

A delayed early effect that can be seen after irradiation of the cervical spine is Lhermitte's syndrome, which is characterized by an electric shock-like sensation precipitated by forward neck flexion.[142] The symptoms typically start weeks to a few months after completion of radiation therapy. They are maximal at first but abate with time, without the development of any objective signs. The paresthesias most commonly occur in the lumbosacral region but also can involve the upper and lower extremities and the upper back. This transient form of Lhermitte's syndrome can occur after doses of radiation well within accepted spinal cord tolerance and is not associated with any permanent late sequelae. The pathogenesis is thought to involve an inhibitory effect on oligodendrocytes that results in transient reversible demyelination. A more ominous form of Lhermitte's syndrome can manifest after a longer latency period after completion of radiation therapy (at least a year), which then progresses to chronic radiation myelopathy.

Chronic myelopathy is the most catastrophic late effect that can occur after spinal cord irradiation. Nearly half of the affected patients will die from complications.[143] A biphasic distribution in the latency

period from irradiation to the onset of myelopathy has been observed. The early peak is from 12 to 14 months, and the second peak, from 24 to 28 months. The pathologic insults that lead to myelopathy include damage to oligodendroglial cells, causing demyelination and white matter necrosis, and death of endothelial cells, resulting in vascular injury. In some patients, partial neurologic dysfunction develops; others progress to complete paraplegia or quadriplegia. No clinical or radiologic findings are pathognomonic for radiation-induced myelopathy. Therefore, the diagnosis usually is made by a combination of (1) neurologic abnormalities corresponding to a level just below the irradiated region, (2) a history of spinal cord irradiation with a high total dose (greater than 45 Gy) at least 6 months before the onset of signs and symptoms, (3) MRI findings of increased signal intensity on T_2-weighted images in the irradiated region,[144] and (4) exclusion of other etiologic factors. The MRI findings in spinal cord myelopathy can mimic tumor recurrence with gadolinium enhancement on MRI (Fig. 70-6).

The probability of developing chronic radiation myelopathy is dependent not only on the total dose delivered to the spinal cord but also on the fraction size. It is now well recognized that larger fraction sizes are associated with more severe later effects. This correlation was not always appreciated, however, and many of the cases of chronic myelopathy described in the literature occurred in patients who received 40 to 60 Gy to the cord in large daily fractions (2.45 to 5 Gy) (as described by Schultheiss and associates[103]). Using standard fraction sizes (1.8 to 2 Gy per day), a commonly observed limit for dose to the spinal cord is 45 Gy. In a study of the incidence of myleitis after irradiation of the cervical cord, Marcus and Million found that of 1112 patients, only 2 (0.18%) developed chronic radiation myelopathy.[145] Two out of 471 patients (0.42%) receiving between 45 and 50 Gy developed this complication. Myelitis developed in none of the 442 patients who received between 40 and 45 Gy and none of the 75 who received greater than 50 Gys. The investigators' conclusion was that even with doses of up to 50 to 55 Gy to the cervical cord, the likelihood of developing chronic myelopathy was extremely low. Even if the spinal cord dose is limited to 45 Gy, myelitis may still develop. This report cited published cases in which myelitis developed with doses less than 45 Gy or even less than 40 Gy, given in 1.8- to 2-Gy daily fractions. Such cases, however, are extremely rare, with an estimated risk of 0.2% or less for the development of chronic myelopathy at this dose.[103]

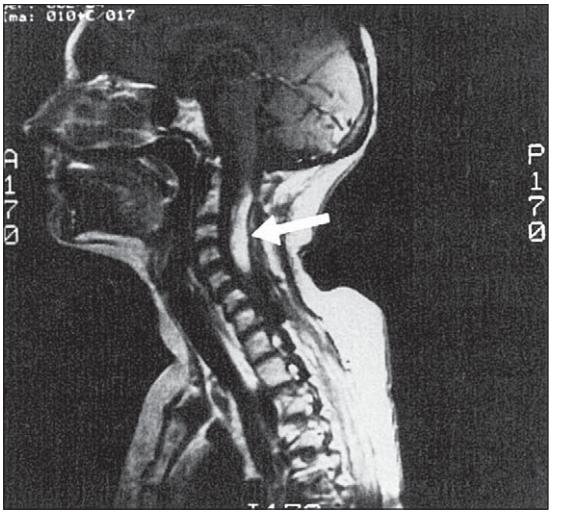


Figure 70-6 • Magnetic resonance imaging (MRI) in a patient with radiation necrosis of the spinal cord. The patient received 45 Gy of radiation to the cervical cord (C1 to C6) for grade II astrocytoma of the cord. Four years later she presented with weakness of the upper extremities. T_1-weighted post-gadolinium MR image showed enlargement of the cervical cord and enhancement *(arrow)*, thought to be consistent with recurrence. The patient received chemotherapy without improvement and eventually died as a result of respiratory failure. Autopsy of the spinal cord showed chronic radiation changes and necrosis of the cervical cord but no evidence of recurrent tumor. (From Phuphanich S, Jacobs M, Murtagh FR, Gonzalvo A: MRI of spinal cord radiation necrosis simulating recurrent cervical cord astrocytoma and syringomyelia. Surg Neurol 1996;45:363.)

GENERAL PRINCIPLES OF CHEMOTHERAPY

Chemotherapy of brain tumors involves many of the same problems as chemotherapy for systemic cancer, including lack of specificity, intrinsic or developing cellular resistance, intolerance of normal tissue to drug toxicity, synergistic toxicity between chemotherapy and radiation therapy, and systemic toxicity. Brain tumor therapy also is associated with specific problems of drug delivery across the blood-brain or blood-tumor barrier. Cerebral edema may impede drug delivery, and corticosteroids that effectively treat the edema may "repair" tumor vessels and impede the delivery of chemotherapy to the tumor. Thus, a recurring disappointment in clinical chemotherapy trials has been the failure to translate promising preclinical chemotherapy findings into meaningful improvement in patient survival.

Further complicating assessment of chemotherapy in brain tumor patients is the observation that corticosteroids also often reduce MRI contrast enhancement and relieve symptoms, making it difficult to distinguish chemotherapy effect from corticosteroid effect.[146] Further confusion may arise when neuroimaging documents enlargement of mass after stereotactic radiosurgery that may progress over many months. Because PET scanning may not reliably distinguish radiation necrosis from tumor progression, the results of concurrent chemotherapy may be ambiguous.[146] Conventional MRI response criterion of 25% to 50% reduction in contrast-enhancing tumor, therefore, may not always be a true measurement of chemotherapeutic efficacy. Radiation therapy also may result in endovascular changes, making access to the brain more difficult for chemotherapeutic agents. Attempts to circumvent this problem by administering chemotherapy before irradiation remain an area of active investigation.

Clinical criteria for chemotherapeutic success are similarly confusing. Performance status, measured in many clinical trials by the Karnofsky Performance Scale (KPS), is affected by tumor site, presence of seizures, and adverse effects of AEDS and steroids. Thus, appropriate measurement of chemotherapeutic efficacy should not be median survival alone. Median progression-free survival or 6-month progression-free survival and reduction in seizure frequency, corticosteroid requirement, and focal deficits all are parameters that must be measured. For long-term survivors, cognitive impairment and other serious acute and chronic neurologic toxicities of cytotoxic chemotherapy and newer molecular strategies factor into the assessment of chemotherapeutic program efficacy.

Finally, chemotherapy of primary brain tumors for the past 20-some years has been designed on the assumption that the problem is one of local control, with few recurrences outside the original tumor site.[147] With longer survivals and better local tumor control, however, however, a higher rate of multicentric cerebral and even leptomeningeal disseminated disease has been noted among patients with high-grade glial tumors, and oncologists may need to design future systemic regimens with these considerations in mind.

An important consideration in the chemotherapy of brain tumors is the ability of the drugs to cross the blood-brain barrier. This physiologic barrier defines the restricted transport between blood and the CNS of water-soluble, ionized molecules larger than about 200 daltons. The blood-brain barrier is formed by the endothelial cells of brain capillaries, with some contribution from astrocytes. Brain capillaries differ from capillaries elsewhere in the body by the presence of tight intercellular junctions. The brain's extracellular or intersititial fluid is an ultrafiltrate essentially identical to CSF. Capillaries of the

choroid plexuses are fenestrated, allowing access of large protein molecules into the plexus stroma. The epithelial cells separating stroma from CSF, however, have apical tight junctions. The brain lacks a lymphatic system.

These features of the blood-brain barrier and the blood-CSF barrier exclude entry of large molecules such as proteins and limit entry of smaller molecules to their ability to cross the lipid bilayer of cells. Lipid-soluble molecules such as nicotine, ethanol, heroin, and the alkylating agent BCNU (carmustine) pass readily across the blood-brain barrier. Another function of the blood-brain barrier may be that of pumping out chemicals potentially harmful to the brain. P glycoprotein, a blood-brain barrier protein, is present in the membrane of some brain tumor cells and serves to reduce the intracellular concentration of several chemotherapeutic agents.[148] The P glycoprotein is encoded by a gene responsible for a form of resistance to chemotherapy: the *MDR1* gene (for *m*ulti*d*rug *r*esistance).[149] Numerous studies have linked the expression of P glycoprotein with resistance to topoisomerase inhibitors including VP-16 (etoposide), VM-26 (teniposide), camptothecin, and other drugs such as paclitaxel and their derivatives. In preclinical studies in nude mice bearing human glioblastoma implanted tumors, coadministration of P glycoprotein inhibitors such as valspodar (SDZ PSC-833) resulted in marked improvement in access of paclitaxel and 90% reduction in tumor volume.[150] Not all malignant gliomas contain tumor cells that express P glycoprotein, and the expression in such cells does not correlate with tumor grade. Little evidence links the expression of *MDR1* gene to patient response to specific chemotherapeutic drugs.[151,152]

Another mechanism involved in glioma cell BCNU resistance is O^6-methylguanine DNA-methyltransferase (MGMT) expression. MGMT repairs nitrosourea-induced DNA damage by catalyzing the transfer of a methyl group from the O^6 position of guanine to its own molecule through a cysteine acceptor site. Not all BCNU-resistant glioma cell lines overexpress this enzyme, but the presence of MGMT recently has been shown to correlate with survival in patients with glioblastomas treated with nitrosoureas. Patients who had high levels of MGMT had a median survival period of 9 months, versus 15 months for those with low levels of MGMT. Administration of MGMT inhibitors resulted in increasing the cytotoxic effects of BCNU.[153]

Quantitative examination of the blood-brain barrier and the brain-tumor barrier has resulted in new avenues of investigation for brain tumor chemotherapy. Methotrexate entry into brain tumors can be enhanced by intra-arterial delivery, but the use of hyperosmolar mannitol for this purpose results in a far greater increase of drug entry into normal brain tissue than into tumor. Human and rat studies of BCNU, cisplatin, and other agents after blood-brain barrier disruption in both primary glial tumors and primary CNS lymphoma have demonstrated significant toxicity.[154,155] Attempts to deliver BCNU and other drugs intra-arterially have been largely abandoned because of unfavorable survival compared with that for patients who received intravenous treatment; the poor outcomes were due in large part to marked cerebral and ocular toxicity.[156–158]

The blood-brain barrier in brain tumors is impaired in many pathologic states, including traumatic injuries, infections, ischemia, and neoplasms. In brain tumors, the degree to which the tight endothelial cell junctions of the blood-brain barrier are disrupted and vascular permeability is thereby increased varies within even a single tumor. The persistence of a relatively intact barrier impedes entry of some water-soluble chemotherapeutic agents into areas of tumor, leading investigators to look for methods of opening the blood-brain barrier that are less toxic than intra-arterial mannitol. Another method of opening the barrier has been with the agent RMP-7, a bradykinin analog. On the basis of earlier promising studies in rat tumors in which intravenous RMP-7 selectively increased uptake of carboplatin into tumors, a randomized controlled trial of intravenous carboplatin and RMP-7 versus carboplatin and placebo was conducted in patients with recurrent malignant glioma. No significant differences were found in median survival times, median time to progression, or findings on neuropsychological, functional independence, or quality of life assessments. The use of RMP-7 had no effect on the pharmacokinetics or toxicity of carboplatin.[159]

SUPRATENTORIAL GLIOMAS

Clinical Considerations

Patients with supratentorial gliomas may present with general signs and symptoms such as changes in mental status, seizures, headaches, papilledema, and nausea and vomiting, as listed earlier under Clinical Presentation. They also may have focal signs and symptoms, dependent on tumor location, as discussed previously.

The past few decades have seen a change in clinical presentation with supratentorial low-grade astrocytomas. In the pre-CT era, patients often presented with headaches, papilledema, and motor weakness (as described by Vertosick and coworkers[160] and in the references cited in their report). In more recent series, however, in which CT or MRI scans were performed routinely, at least two thirds of patients presented with seizures, and very few had other signs or symptoms.[160–162] A possible explanation is that in the pre-CT era, many of these patients would have been placed on antiseizure medication and would not have been diagnosed with a brain tumor until their tumor grew large enough to cause signs and symptoms of increased ICP.

A history of seizures also is extremely common in patients with oligodendrogliomas, occurring in 70% to 90% of cases. The duration of symptoms can be prolonged. In a study by Ludwig and coworkers, 55% of patients had symptoms for longer than 1 year before diagnosis, and 37% had symptoms for longer than 3 years.[163] A few patients had symptoms for 10 to 15 years before diagnosis.

Low-grade astrocytomas decrease in frequency with increasing age. Their incidence is highest between the ages of 20 and 40 years and decreases in patients older than 50. Oligodendrogliomas display a similar age-related frequency. Conversely, high-grade astrocytomas, including glioblastomas, increase in frequency with increasing age (after the age of 60 years; see Fig. 70-1).

Pathologic Classification of Supratentorial Gliomas

Astrocytomas arise from astrocytes, the supporting cells of the central nervous system. Glial fibrillary acidic protein (GFAP) is expressed in the cytoplasmic processes that extend from the astrocytes; therefore, antibodies against this protein can be used in immunohistochemical studies. Over the years, many different histopathologic staging systems have been used. Kernohan devised a four-tiered system that classified tumors into grade 1, the slowest-growing tumors, through grade 4, the most malignant tumors.[164] A three-tiered system including astrocytoma, anaplastic astrocytoma, and glioblastoma, developed by Ringertz, was used in many cooperative trials.[165]

More recently, Daumas-Duport and Scheithauer, reviewing cases from the Mayo Clinic and Sainte-Anne's Hospital in Paris, devised a system using the presence of nuclear atypia, mitoses, endothelial proliferation, and necrosis to grade tumors from 1 through 4.[166] This system led to a better discrimination of outcome for patients who underwent treatment at the Mayo Clinic than did the Kernohan system.

The most widely used system today for classification of astrocytomas is the WHO system.[167] Grade I is reserved for pilocytic tumors, which are the most benign in terms of histology, generally curable with surgery alone. Because they are more common in children than in adults, they are discussed in greater detail later under Childhood Brain Tumors. The remaining categories are grade II (diffuse astrocytomas), grade III (anaplastic astrocytomas), and grade IV (glioblastomas).

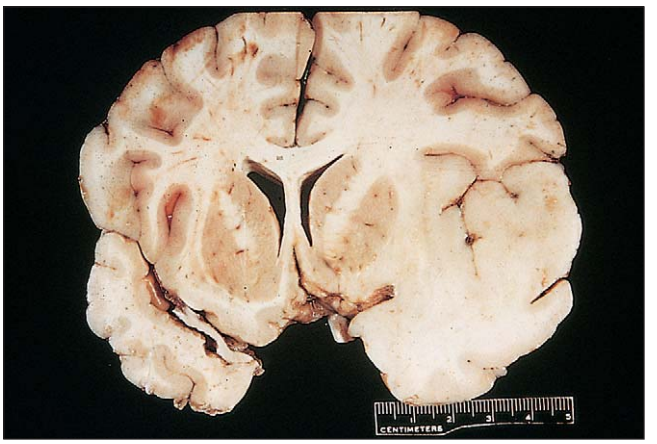


Figure 70-7 • Diffuse low-grade astrocytoma, gross specimen. WHO grade II astrocytoma arises diffusely and infiltrates the right frontal lobe. Gross determination of the tumor's boundaries is almost impossible, but the tumor is evident as an ill-defined area of enlargement, with loss of distinction between the gray and white matter. (Maher EA, McKee AC: Neoplasms of the central nervous system. In Skarin AT [ed]: Dana-Farber Cancer Institute Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 405)

Diffuse astrocytomas (grade II) are poorly defined, gray tumors that expand the parenchyma and obliterate normal gray matter–white matter boundaries[168] (Fig. 70-7). Microscopically there are increased numbers of irregularly distributed astrocytes with mildly atypical nuclei (Fig. 70-8A). Tumor cells can be seen infiltrating into normal brain tissue at some distance from normal tissue. Diffuse astrocytomas often are classifed into one of three subtypes: fibrillary, which is the most common subtype, protoplasmic, or gemistocytic.[169] Fibrillary astrocytomas are composed of tightly interlacing bundles of small, spindle-shaped cells amid a predominantly fibrillar matrix. Gemistocytic astrocytomas contain plump cells with distinct, round pink cytoplasm arranged on a more delicately interlacing fibrillar matrix, whereas protoplasmic astrocytomas are composed of small, round, regular cells with indistinct cytoplasmic boundaries arranged on a loosely fibrillar stroma.

Microscopically, anaplastic astrocytomas (WHO grade III) are distinguished from grade II tumors by their greater cellularity, increased nuclear pleomorphism, and of most importance, mitotic activity (see Fig. 70-8B). In both these and grade IV glioblastomas, tumor cells can be seen infiltrating into surrounding normal brain tissue, often at a great distance from the primary tumor mass. Histologically, glioblastomas are distinguished from anaplastic astrocytomas by the presence of endothelial proliferation or necrosis (Fig. 70-9). The necrosis can form a serpentine pattern referred to as "pseudopalisading," in which tumor cells crowd around the edges of the necrotic region. The presence of necrosis is of particular importance in grading gliomas and has been associated with shorter

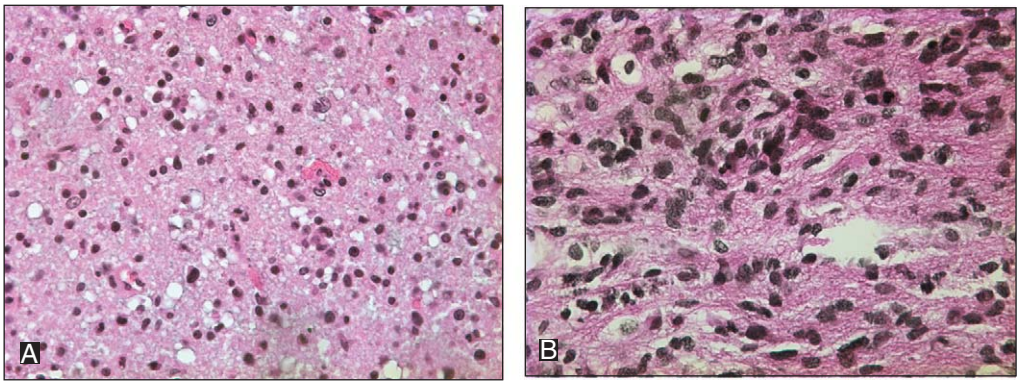


Figure 70-8 • Histologic appearance of low-grade astrocytoma versus anaplastic astrocytoma. **A,** Low-grade astrocytoma (WHO grade II) shows low cellularity, slight nuclear pleomorphism, no endothelial proliferation, and no necrosis. **B,** Anaplastic astrocytoma (WHO grade III) shows increased cellularity, pleomorphism, and mitotic activity compared with the grade II tumor in **A.** Anaplastic astrocytoma also lacks endothelial proliferation and necrosis. (Courtesy of Dr. Daniel Skovronsky, Department of Pathology, University of Pennsylvania School of Medicine.)

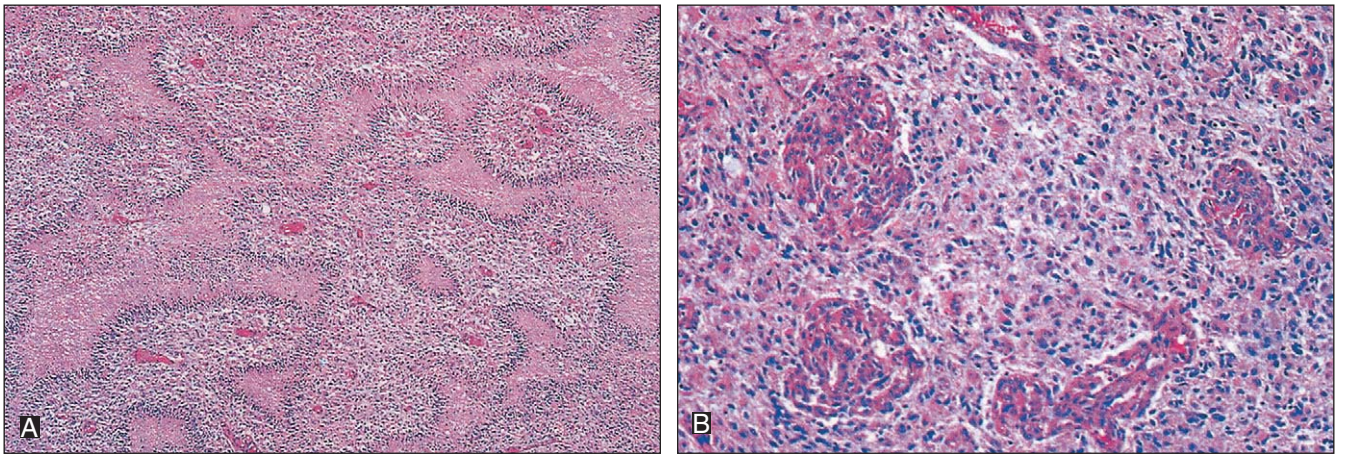


Figure 70-9 • Glioblastoma (grade IV astrocytoma): histologic appearance. **A,** Pseudopalisading cells surrounding regions of necrosis. **B,** Endothelial proliferation, which in this case has reached dramatic proportions, with the formation of tangled clusters of neovascular channels, often referred to as "glomeruloid" blood vessels because of their resemblence to renal glomeruli. (From Maher EA, McKee AC: Neoplasms of the central nervous system. In Skarin AT [ed]: Dana-Farber Cancer Institute Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 406.)



Figure 70-10 • Glioblastoma: gross specimen. The tumor appears as a necrotic, hemorrhagic infiltrating mass. (From De Girolami U, Anthony DC, Frosch, MP: The central nervous system. In Cotran RS, Kumar V, Collins T [eds]: Robbins' Pathologic Basis of Disease, 6th ed. Philadelphia, Saunders, 2003, p 1344.)

survival.[170] Grade IV glioblastomas show areas of hemorrhage, necrosis, and cystic change on gross examination[172] (Fig. 70-10). Glioblastomas can manifest with multicentric disease, but this occurs in less than 5% of cases as determined at autopsy of patients with untreated tumors.[147]

In addition to pathologic grading by morphology, techniques have been developed to measure cell kinetics based on the idea that faster-growing tumors are more malignant. These include immunohistochemical staining using antibodies directed against Ki-67 (MIB-1) or proliferating cell nuclear antigen (PCNA). Another technique involves calculation of an S phase fraction by measuring the incorporation of bromodeoxyuridine (BUdR) or iododeoxyuridine (IUdR) into tumor cells after intravenous injection of the agent. The predictive power of all three of these techniques has been compared with that for clinical parameters.[171] Problems with application of these methods remain, so they are not routinely used, but they offer some promise as a means of providing prognostic information independent of histology. Likewise, it is very possible that immunohistochemical stains for genetic changes found in glial tumors also will be used in the future to assess prognosis.

The different grades of astrocytoma carry very different prognoses. With WHO grade I (pilocytic) astrocytomas, a cure rate greater than 90% after surgical resection alone can be expected. By contrast, with WHO grade IV tumors, the median survival period is 1 to 2 years, even after aggressive combined-modality therapy. With WHO grade III tumors, long-term survival rates on the order of 20% are usual, but the median survival period is approximately 2 years. WHO grade II tumors carry a better prognosis than grade III tumors; nevertheless, recurrence with a higher-grade tumor is common with grade II tumors, although this may take 6 to 8 years to occur.

Most oligodendrogliomas occur in the cerebral hemispheres (80%), but they can occur in the lateral and third ventricles. Oligodendrogliomas arise from oligodendrocytes, which produce myelin. They often involve the subcortical white matter, with extension into the cerebral cortex. On gross examination, oligodendrogliomas often are soft and gelatinous and better circumscribed than astrocytomas.[168] They frequently contain calcifications. Despite their gross appearance suggesting that they are contained, they can infiltrate surrounding tissues, including the subarachnoid space and leptomeninges,

Owing to fixation artifact, oligodendrogliomas appear microscopically as sheets of cells with nuclei surrounded by a clear halo of cytoplasm, giving the cells the appearance of a "fried egg" (Fig. 70-11A). Unlike astrocytomas, oligodendrogliomas lack fibrillary cytoplasmic processes. Calcifications are present in 90% of these tumors. A common finding is a network of capillaries, lending a "chicken wire" pattern. The current WHO classification for oligodendrogliomas is a two-tiered system of grade II (oligodendroglioma) and grade III (anaplastic oligodendroglioma).[167] Features suggestive of anaplasia include cytologic atypia and increased mitotic activity (see Fig. 70-11B). Two other features, microvascular proliferation and pseudopalisading necrosis, when present in an oligodendroglial tumor would classify it as a grade III tumor, in contrast with an astrocytic tumor, in which these features would make it a glioblastoma (grade IV). The prognosis with anaplastic oligodendrogliomas is less favorable than with low-grade tumors, but they are much more sensitive to chemotherapy than their astrocytoma counterparts, as discussed in detail later on. In the Mayo Clinic series, the 5- and 10-year survival rates and median survival period for low-grade oligodendrogliomas were 75%, 46%, and 9.8 years, respectively, versus 41%, 20%, and 3.9 years for high-grade tumors.[172]

Distinct from oligodendrogliomas are mixed gliomas or oligoastrocytomas. According to the WHO classification, this latter category includes tumors that show "a conspicuous mixture of two distinct neoplastic cell types resembling the tumor cells in oligodendroglioma and diffuse astrocytoma."[167] The two components may be in different regions or diffusely mixed together. This definition is vague in that an oligodendroglioma with a very small astrocytic component may be classified by some pathologists as a pure oligodendroglioma but by others as a mixed oligoastrocytoma. In the WHO classification, these tumors are subdivided into oligoastrocytomas (grade II) and anaplastic oligoastrocytomas (grade III). Grading of these tumors is very difficult because the two components often differ in grade. In particular, it is problematic how to classify a tumor that has oligodendroglioma-like regions in a background that otherwise appears to be a glioblastoma. Some experts have referred to these as glioblasto-

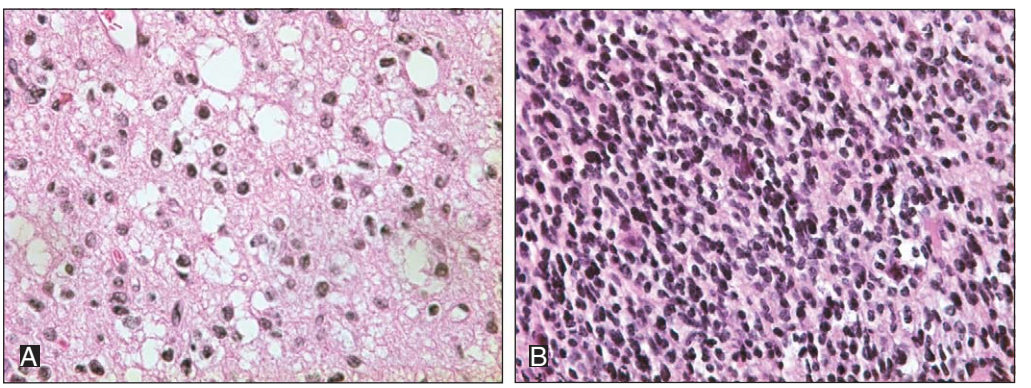


Figure 70-11 • Histologic appearance of oligodendroglioma versus anaplastic oligodendroglioma. **A,** In WHO grade II oligodendroglioma, oliogodendrocytes are uniform cells with small, round nuclei and a characteristic perinuclear halo ("fried egg" cells). **B,** Grade III oligodendroglioma shows cytologic atypia and increased mitotic activity compared with the tumor in **A.** (Courtesy of Dr. Daniel Skovronsky, Department of Pathology, University of Pennsylvania School of Medicine).

mas with oligodendroglioma component, which may carry a better prognosis than that for ordinary glioblastomas.[173]

Overall, patients with oligodendrogliomas have a better prognosis than patients with astrocytomas.[112] Oligoastrocytomas might be expected to have an intermediate prognosis, and in some series this is the case. For example, in the Mayo Clinic experience, the 5- and 10-year survival rates and the median survival period were 46%, 17%, and 4.7 years for low-grade diffuse astrocytomas, compared with 73%, 49%, and 9.8 years for low-grade oligodendrogliomas.[174] The respective figures for patients with oligoastrocytomas were in between, at 63%, 33%, and 7.1 years. In the University of California at San Francisco series, however, 5- and 10-year survival rates for patients with pure oligodendrogliomas and with oligoastrocytomas were identical.[175] The discrepancy between these series may be due to the difficulty in categorizing these tumors, and to interinstitutional differences in pathologic interpretation.

Imaging of Supratentorial Gliomas

WHO grade I (pilocytic) astrocytomas show enhancement on CT and MRI scans. By contrast, WHO grade II astrocytomas typically are poorly defined, hypodense or isodense lesions on CT scans that do not enhance. Either localized or homogeneous enhancement, however, can be seen in up to 30% to 40% of cases, with calcification in 5% to 10% of cases.[162,176] MRI shows low signal intensity on T_1-weighted images and high signal on T_2-weighted images (Fig. 70-12A and B). Grade III anaplastic astrocytomas and grade IV glioblastomas generally enhance with contrast although in one study, enhancement was not seen in 40% of the former and in 4% of the latter (see Fig. 70-12C and D).[177] The region of enhancement typically has a ring-like appearance surrounding an area of necrosis. The perimeter of the enhancing region does not define the border of the tumor, and malignant cells may be present beyond this. T_2-weighted MRI images show abnormalities that are more extensive than those seen on a contrast-enhanced CT scan or T_1-weighted MRI scan. In one study in which stereotactic biopsy findings were correlated with radiologic findings in patients with gliomas, isolated tumor cells often were found as far away as the region showing increased signal intensity on T_2-weighted images.[87]

At least 50% of oligodendrogliomas show calcifications, which can be appreciated on plain films of the skull as well as on CT scans.[178] Enhancement of oligodendrogliomas can be seen on CT and MRI scans, but this often is mild and poorly defined.

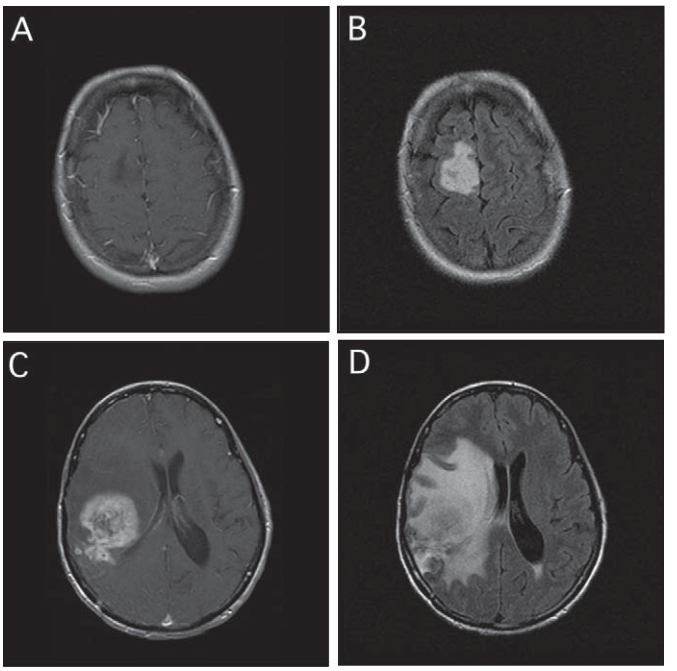


Figure 70-12 • Magnetic resonance imaging: low-grade astrocytoma versus glioblastoma. **A,** WHO grade II astrocytoma: T_1-weighted post-gadolinium axial image shows no enhancing mass; however, a region of hypodensity is seen. **B,** Corresponding FLAIR image of the tumor in **A** shows abnormality consistent with edema. **C,** WHO grade IV glioblastoma: T_1-weighted post-gadolinium axial image shows the presence of a large mass compressing the right lateral ventricle. A rim of enhancement with central necrosis is typical of these tumors. **D,** Corresponding FLAIR image of the tumor in **C** shows extensive peritumoral edema. FLAIR, fluid-attenuated inversion recovery; WHO, World Health Organization.

Genetics of Supratentorial Gliomas

Genetic Changes in Astrocytomas

The p53 pathway frequently is disrupted in all grades of astrocytomas. This can occur by mutation of p53 itself, by overexpression of MDM2, which degrades p53, or by mutation or deletion of $p14^{ARF}$, which positively regulates p53 by inhibiting MDM2 expression. In one study, the p53 pathway was disrupted by one of these mechanisms in 67% of diffuse astrocytomas, 72% of anaplastic astrocytomas, and 76% of glioblastomas.[179] Therefore, disruption of the p53 pathway appears to be an early event in the genesis of astrocytomas. It is possible that mutation of p53 in low-grade astrocytomas leads to genomic instability that sets the stage for additional mutations that lead to the formation of higher-grade tumors. The p53 gene (*TP53*) is located on the long arm of chromosome 17 (17p), which frequently is lost in both low-grade and high-grade astrocytomas, suggesting that p53 is the target for this genetic change (reviewed by Ichimura and coworkers[180]).

The Rb pathway, which regulates the G_1/S transition, commonly is disrupted in high-grade astrocytomas. This can occur through deletion or mutation of *RB* itself; deletion or mutation of *CDKN2A*, which encodes the cyclin-dependent kinase inhibitor p16; deletion or mutation of *CDKN2B*, which encodes the cyclin dependent kinase inhibitor p15; or amplification of the *CDK4* gene. Ichimura and coworkers noted that one of these changes had occurred in 67% of glioblastomas and 21% of anaplastic astrocytomas, but in none of 15 low-grade astrocytomas.[181] These findings suggest that progression to a higher grade glioma is facilitated by deregulation of the G_1/S transition.

Loss of heterogosity (LOH) of 13q and 9p has been identified in high-grade astrocytomas, and these deletions may lead to alterations in the Rb pathway. LOH of chromosome 13 occurs in 30% to 40% of higher-grade astrocytomas.[180] The Rb gene (*RB*), which maps to 13q14, is the likely target of this deletion. *CDKN2A* is located on 9p21, and this chromosomal region is homozygously deleted in at least 30% to 40% of glioblastomas and in approximately 10% of anaplastic astrocytomas, but never in diffuse astrocytomas.[180] Because two different gene products, CdkN2A and $p14^{ARF}$, both are transcribed from a single locus on 9p21, deletion of this region leads to simultaneous disruption of both the Rb and p53 pathways.

Astrocytic tumors also frequently display high-level expression of PDGF ligands and receptors.[30] Most studies have found that the PDFG-α receptor is overexpressed in 60% to 90% of low- and high-grade astrocytomas. By contrast, overexpression of the ligand PDGF-A or -B is not very common in low-grade gliomas but is seen in higher-grade tumors, suggesting that this growth factor participates in an autocrine loop in these tumors.[30]

Genetic Changes in Glioblastomas

Approximately 80% of all glioblastomas develop without any prior history of a glioma and are termed primary glioblastomas. The clinical history usually is short, on the order of months, and the patients tend to be older, with a median age of 55 when diagnosed. These

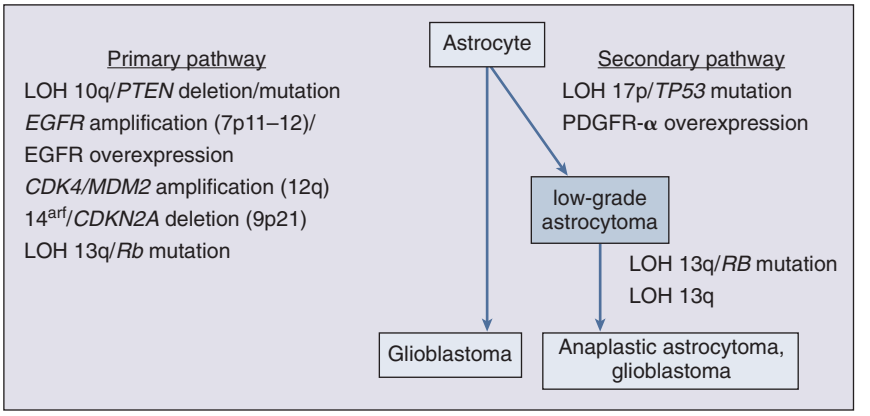


Figure 70-13 • Molecular alterations during "gliomagenesis." Two pathways for the development of glioblastomas have been described. In the secondary pathway shown, the patient has a history of a prior lower-grade astrocytoma, whereas in the primary pathway, no such history exists. The Rb/p16/Cdk4 pathway is disrupted in primary and secondary glioblastomas to a similar extent with LOH 13q/*RB* mutation and *CDK4* amplification. However, 9p/*CDKN2* deletion, another means of disrupting the Rb pathway, is seen more commonly in primary glioblastomas. These three changes targeting the Rb pathway appear to be mutually exclusive. *EGFR,* epidermal growth factor receptor; LOH, loss of heterozygosity; PDGFR-α, platelet-derived growth factor receptor-α.

tumors tend to be large with lots of edema, central necrosis, and ring enhancement. In 20% of the cases, the patient has an antecedent history of a lower-grade glioma (grade II or III), generally 5 to 10 years previously. These secondary glioblastomas tends to arise in younger patients, with a median age of 40 years.

The genetic changes seen in primary and secondary glioblastomas are very different[182–188] (Fig. 70-13). Primary glioblastomas often show homozygous deletions of the *CDKN2A*/*p14*^{ARF} locus on 9p21 (in 30% to 40% of cases) or amplification of *CDK4* and *MDM2* on 12q13–15 (in 8% to 13% of cases).[180] Either of these sets of genetic changes will cause disruption of both the p53 and Rb pathways.

EGFR amplification, leading to overexpression, is seen in approximately 35% of primary glioblastomas, rarely in anaplastic astrocytomas, and never in diffuse astrocytomas.[29] Another 15% of primary glioblastomas overexpress EGFR without amplification. Approximately half of glioblastomas with *EGFR* amplification express a mutant form of the receptor.[183] The most common mutant is known as ΔEGFR or EGFRvIII, which is missing exons 2 to 7, resulting in an in-frame deletion of 801 base pairs of the coding sequence of the extracellular domain.[183,184] This particular mutant form of EGFR is constitutively activated and cannot be downregulated. Its expression in glioblastoma cells has been associated with increased proliferation, decreased apoptosis, and increased tumorigenicity and invasion in vivo.[184] Even in glioblastomas that overexpress wild-type EGFR, which is not constitutively active, the ligands EGF and TGF-α often are coexpressed, which may activate an autocrine loop that allows for self-stimulation.[29]

Up to 90% of primary glioblastomas exhibit deletion of 10q, on which is located the tumor suppressor gene *PTEN*.[186] The retained *PTEN* allele is mutated in approximately 50% of tumors with 10q loss, leading to complete loss of functional PTEN protein. Therefore, the incidence of *PTEN* mutation in glioblastoma is at least 45%.[180] One study suggested a potential association between lower PTEN levels and shorter survival in patients with glioblastomas, although this did not reach statistical significance.[187] *PTEN* mutations have been found in anaplastic astrocytomas, although at a much lower frequency than in glioblastomas.[188] This study found the presence of *PTEN* mutations in anaplastic astrocytoma to be a powerful prognostic factor portending a poorer outcome.[188]

In contrast with primary tumors, secondary glioblastomas rarely display EGFR amplification.[189–191] Secondary glioblastomas have loss of 10q, but they do not have mutations of the retained *PTEN* gene.[190] Both the p53 and Rb pathways generally are disrupted in secondary glioblastomas, as is the case with primary glioblastomas; however, the mechanisms tend to be different. Both wild-type p53 alleles are lost in more than half of all secondary glioblastomas, generally one allele by deletion and the second by mutation. By contrast, p53 mutations rarely are seen in primary glioblastomas (occurring in less than 10% of cases).[189,191] The Rb pathway is disrupted in secondary glioblastomas, often through loss of both wild-type alleles.[180] Secondary glioblastomas may also show disruption of the p53 and Rb pathways through promoter methylation of CdkN2A and p14^{ARF}.

Genetic Changes in Oligodendrogliomas and Oligoastrocytomas

Two chromosomal abnormalities frequently are seen in oligodendrogliomas: deletion of 1p and deletion of 19q. Oligodendrogliomas exhibit LOH at 19q in up to 88% of cases and LOH at 1p in up to 100% of cases.[192] LOH of 1p and 19q is common in both grade II and III oligodendrogliomas, so these changes probably occur early during tumorigenesis.[193,194] By comparative genome hybridization, loss of 1p and 19q is found in 79% and 74%, respectively, of oligodendrogliomas but in only 25% and 30% of oligoastrocytomas.[192] Finer mapping indicates that the regions of interest lie in 1p36 and 19q13, although the specific genes have not yet been identified. Some evidence suggests that AOs with 1p or 19q deletions respond much more favorably to chemotherapy than tumors without these losses.[195] This is discussed in greater detail later on (under Chemotherapy for Newly Diagnosed Anaplastic Oligodendrogliomas). A correlation also has been found between oligodendroglioma location and the presence of these genetic alterations. Anaplastic oligodendrogliomas arising from frontal, parietal, or occipital lobe were more likely to contain 1p or 19q deletions than those arising in temporal lobe, insula, or diencephalon.[196]

Although 1p and 19q losses are the most common genetic abnormalities in oligodendrogliomas, other mutations have been reported. In one genetic analysis of 446 CNS tumors, *TP53* mutations and homozygous deletions of *CDKN2* were identified in 5% and 11%, respectively, of oligodendrogliomas. The same mutations were seen in 37% and 15%, respectively, of oligoastrocytomas.[197]

Surgery for Supratentorial Gliomas: Extent of Surgical Resection

The role of extent of surgical resection in the treatment of gliomas has been controversial for many years.[198–200] Virtually all of the reviews in this subject area have been retrospective; therefore, they are subject to significant selection bias. It is likely that patients with the most favorable, easily resectable lesions within noneloquent brain regions have tended to undergo aggressive resections, whereas those with deeper lesions in more eloquent brain regions have been selected for stereotactic biopsy to minimize surgical morbidity. Some experts have advocated maximal resection for gliomas, reasoning that this approach is associated with improved survival.[201] A possible explanation for this outcome may be that fewer cells are left behind that need to be eradicated with irradiation and chemotherapy.

Other investigators have advocated stereotactic biopsy alone as the preferred mode of histological diagnosis in the treatment of patients

with gliomas.[199,202] Stereotactic biopsy affords a histological diagnosis with a low complication rate (2% to 5%). However, stereotactic biopsy may lead to an inaccurate pathologic diagnosis. In a review of data for 81 consecutive patients initially diagnosed with stereotactic biopsy who subsequently underwent a craniotomy, Jackson and colleagues showed that the histopathologic classification based on stereotactic biopsy findings was incorrect in 38% of the patients.[198] This represented sampling error in these patients, 96% of whom underwent biopsy at outside institutions. Despite the fact that these were tumors located in eloquent brain and previously treated by neurosurgeons, gross total resection could be achieved in 57% of these patients once they reached a major tertiary care hospital (M.D. Anderson Cancer Center, Houston, Texas). Major complications were seen in only 12.3% of the patients undergoing aggressive craniotomy for resection of the malignant glioma located in eloquent brain.

To specifically address the role of aggressive resection of gliomas in prolonging survival, Lacroix and coworkers performed a retrospective multivariate analysis of outcomes for 416 patients using prospectively collected data.[200] Postoperative volumetric MRI scans were obtained on all patients so that a blinded neuroradiologist was able to determine extent of resection given as a percentage of the original tumor. Patients with a resection of 98% or more of the tumor volume had a median survival period of 13 months, versus 8.8 months for patients with a less than 98% resection. Also found to be significant were age, KPS score, and extent of tumor necrosis. Even when statistical analysis controlled for these other three factors, extent of resection remained a significant variable.

Navigation during Surgery

Intraoperative MRI scanners have allowed for real-time evaluation of the extent of tumor resection. Imaging of relevant anatomy can be performed during surgery with MRI in order to provide real-time feedback regarding the surgical resection. Schulder and colleagues reviewed the cases of 93 patients who underwent neurosurgery aided by a low-field intraoperative MRI scanner.[203] These investigators found that surgery was directly affected by imaging in 51% of the operations. Second lesions not otherwise evident on the initial preoperative scan were seen in 21 patients, and in another 14 patients unnecessary dissection was avoided as a result of real-time imaging. Intraoperative MRI scanners with field strengths of 1.5 T are being used not only for anatomic imaging but also for perfusion imaging and MR angiographic imaging. Frameless stereotactic units have been available for many years, allowing for downloading preoperative MRI scans to an intraoperative computer workstation to create a three-dimensional reconstruction of the images. The patient's head can be directly referenced to the images for precise intraoperative localization to less than 2 mm. Investigators have been able to import both PET and functional MRI data into the frameless stereotaxy units to map out functional brain during surgery.[94,204]

Intraoperative cortical and subcortical mapping has been used to define eloquent brain during resection of gliomas.[205,206] Intraoperative cortical mapping has enabled neurosurgeons to become more aggressive with tumors located within eloquent brain regions. This application is especially useful with low-grade gliomas that occur immediately adjacent to motor and speech areas. Cortical mapping may be done with the patient lightly anesthetized but awake enough to respond to questions so that speech areas can be mapped.

Complications of Surgery

A recent analysis by the Glioma Outcome Project reviewed perioperative complications and neurologic outcomes for patients who underwent craniotomy for the diagnosis and treatment of gliomas.[207] The Glioma Outcome Project was a prospectively compiled database capturing information on 788 patients. Of these, 499 underwent either a first or second craniotomy for treatment of their malignant glioma, and the remaining 289 patients underwent stereotactic biopsy only. No difference was found in the characteristics of the patients who underwent first or second craniotomy. Analysis of the perioperative symptoms, however, revealed that patients undergoing a second craniotomy had a higher incidence of altered level of consciousness and papilledema, whereas those undergoing a first craniotomy had a higher incidence of headache. The incidence of depression was higher in patients undergoing a second craniotomy: 11% in the group undergoing the first craniotomy versus 20% in the patients undergoing a second craniotomy. This difference may reflect the presence of a chronic disease state. The rate of systemic infections also was higher in patients undergoing a second craniotomy at 4.4%, versus zero in patients undergoing a first craniotomy. This is not unexpected, because these patients frequently have been heavily pretreated with radiation therapy and chemotherapy, as well as long-term steroid use, causing significant immunosuppression. Evaluation of postoperative neurologic status showed that neurologic status was the same or better in 92% of the patients undergoing their first craniotomy, whereas this rate dropped to 82% in patients undergoing their second craniotomy. Nevertheless, the overwhelming majority of patients are benefited by a debulking procedure to reduce neurologic deficits. As has been shown in multiple other studies, the most important preoperative factor associated with good neurologic outcome has been KPS score. Those patients with higher KPS scores fared better with surgery than did patients with lower scores. This finding is a reflection of degree of neurologic injury. The Glioma Outcome Project is perhaps the only prospectively collected database for evaluating outcomes of surgery in the treatment of malignant gliomas. The analysis of these data reveals that the incidence of further neurologic deficit with craniotomy is only 8% in patients undergoing their first operation, versus 18% in patients undergoing a second craniotomy for resection of a malignant glioma. In view of the severity of the disease, this is certainly an acceptable risk. Of greater importance, they are objective prospectively obtained data showing improvement in neurologic outcome with aggressive debulking surgery. An important point is that these data were compiled from participating institutions, and the decision for surgery was left to the discretion of the surgeon; therefore, certainly selection bias obtained in terms of who underwent radical surgery versus stereotactic biopsy. The investigators do not discuss the frequency of tumors in eloquent versus noneloquent brain. Nevertheless, findings of this study are representative of the general practice of surgical neuro-oncology throughout the nation.

Convection-Enhanced Delivery

Local therapy for gliomas has been an intriguing concept because of the anatomically limited nature of the disease. Gliomas do not metastasize outside of the CNS and frequently recur within a 2-cm margin of the previous resection.[147] Simple diffusion will work for small molecules and some forms of chemotherapy. With the advent of biologic modifying agents with large molecular weights, however, another development has been convection-enhanced delivery—that is, pressure-driven delivery of drugs directly into the brain tissue, causing a gradient to induce bulk flow into the interstitial space of the brain, thereby distributing macromolecules across a distance measured in centimeters, rather than millimeters. Use of this technique to deliver two such agents has been described. The first agent is a conjugate of transferrin and a mutant *Diphtheria* toxin infused into patients with malignant gliomas.[208] The investigators reported at least a 50% reduction in tumor volume in 9 of 15 patients. The second clinical trial administered a conjugate of IL4 with *Pseudomonas* exotoxin for patients with recurrent malignant gliomas.[209] This study was a safety and toxicity trial and has been carried forward using IL-13 into the recently concluded Phase III Randomized Evaluation of CED (Convection Enhanced Delivery) of IL13-PE Compared to Gliadel Wafer with Survival Endpoint Trial (also known as the PRECISE Trial). The survival data for this study are not available at this time. The preclinical and some of the clinical studies using convection-enhanced delivery show excellent distribution through-

Box 70-1. MANAGEMENT OF SUPRATENTORIAL ASTROCYTOMAS

- **Grade I (pilocytic) astrocytomas:** Surgery is curative. If residual tumor is seen on postoperative imaging, the patient should undergo a second craniotomy to resect the entire tumor. Radiation therapy and chemotherapy have limited usefulness for treatment of these tumors.
- **Grade II (low-grade) astrocytoma:** Surgery is the mainstay of therapy for tumors in noneloquent regions of brain. In patients younger than 40 years of age who undergo gross total resection, no additional therapy is given. In patients younger than 40 with incomplete resection and patients older than 40 with or without complete resection, adjunctive treatment with radiation therapy (54 to 60 Gy) is indicated.
- **Grade III astrocytoma (anaplastic astrocytoma) and grade IV gliomas (glioblastoma):** Surgery is required to establish tissue diagnosis, preferably with debulking as well. Chemotherapy is begun with temozolomide during radiation therapy and continued for six cycles after completion of the radiation regimen. The radiation dose generally is 60 Gy. Tumor tissue is sent for analysis of *O^6-methylguanine DNA-methyltransferase (MGMT)* promoter activity. Temozolomide is offered to all patients, however, regardless of promoter methylation status.

out the brain, and the agent has been reported to pass through normal brain to reach a second site of tumor, with excellent drug delivery to the second tumor site.[208] Box 70-1 summarizes the recommended approach to management of supratentorial gliomas.

Radiation Therapy for Supratentorial Gliomas

Radiation Therapy for Low-Grade Gliomas

Numerous retrospective reports have been published on the use of radiation therapy for low-grade gliomas (summarized by Leighton and associates[210]). These studies are plagued with a myriad of problems, making them inconclusive. In order to contain sufficient patient numbers, most of these reports span decades, sometimes going back as far as the 1940s. Obviously, before the advent of CT scans, accurate treatment planning would have been difficult, as would good radiologic follow-up to document relapses. Before the 1960s, radiation was given using orthovoltage machines, which do not have the capability to deliver treatment to deep tissues. The doses given to some of the patients would be considered inadequate by today's standards. In these studies, immediate postoperative radiation often was given to patients with poor prognostic features, thereby potentially skewing the results in favor of observation.

The results of these retrospective studies have largely been superseded by the results of three randomized trials, two from the European Organization for Research and Treatment of Cancer (EORTC) and one from the North Central Cancer Treatment Group (NCCG; Table 70-6). The EORTC 22844 trial randomized adults with supratentorial low-grade astrocytomas, oligodendrogliomas, or mixed oligoastrocytomas to receive either 45 Gy or 59.4 Gy of radiation after surgery.[211] The NCCG study was similar except that patients were randomized to receive either 50.4 or 68.4 Gy after surgery.[112] Patients underwent a range of surgical procedures, including biopsy and subtotal or gross total resection. Neither study showed any benefit to the higher dose in terms of overall survival or progression-free survival. If anything, the NCCG study showed a worse survival in patients receiving the higher dose of radiation (64.8 Gy). The 5-year survival rate in both studies ranged from 58% to 72%.

The EORTC also performed study 22845, in which patients who underwent surgical treatment for astrocytomas, oligodendrogliomas, or mixed oligoastrocytomas were randomized to receive either adjunctive irradiation in a dose of 54 Gy or no upfront radiation therapy.[212] Patients in the latter group had the option of receiving radiation if progression of disease was observed. No difference was seen in overall survival between the early radiotherapy and observation groups (see Table 70-6: 5-year survival rate, 68% versus 66%; median survival period, 7.4 versus 7.2 years). A statistically significant advantage, however, was observed in the patients who received radiation in terms of progression-free survival (55% versus 35% at 5 years; median time to progression, 5.3 versus 3.4 years; $P < 0.0001$). The absence of any difference in survival has supported the position of experts who advocate delaying radiation. Conversely, those favoring upfront radiation in the treatment of low-grade gliomas have cited the improved progression-free survival in the irradiated group, and the fact that at 1 year, seizures were better controlled in the radiation treatment arm.

These randomized trials confirmed the importance of certain prognostic factors in low-grade gliomas. In the NCCG trial, three prognostic factors—histologic subtype, patient age, and tumor size—were consistently associated with overall survival in multivariate analysis.[112] The 5-year survival rates for patients with oligodendroglioma-predominant tumors and those with astrocytomas were 74% and 56%, respectively ($P = 0.0001$); for patients younger than 40 years of age and those ≥40 or older, 77% and 60%, respectively ($P = 0.025$); and for preoperative tumor size less than 5 cm and 5 cm

Table 70-6 Results of Treatment for Low-Grade Gliomas: Selected Randomized Trials

Study	Years	Histologic Type	Treatment Protocol	No. of Patients	5-Year Survival	5-Year PFS
Karim et al[211]	1985–1991	9% A, grade 1	45 Gy	171	58%, $P = 0.94$	47%, $P = 0.73$
EORTC 22844		60% A, grade 2	59.4 Gy	172	59%	50%
		22% O				
		9% mixed				
van den Bent et al[212]	1986–1997	2% A, grade 1	Observation	157	66%, $P = 0.87$	35%, $P < 0.0001$
EORTC 22845		60% A, grade 2	54 Gy	154	68%	55%
		25% O				
		10% mixed				
Shaw et al[112] NCCTG	1986–1994	32% A or mixed (A > O)	50.4 Gy	101	72%, $P = 0.48$	55%, $P = 0.65$
		68% O or mixed (O > A)	64.8 Gy	102	65%	52%

A, astrocytoma; EORTC, European Organization for Research and Treatment of Cancer; NCCTG, North Central Cancer Treatment Group; O, oligodendroglioma; PFS, progression-free survival.

or greater, 81% and 61%, respectively ($P = 0.008$). In the EORTC 22844 study, the extent of resection had a great impact on overall survival: Patients who had greater than 90% of their tumor removed did much better than those who underwent a biopsy. Multivariate analysis of data from the two EORTC trials confirmed that astrocytoma histology, age older than 40 years, and preoperative size greater than 6 cm all were unfavorable prognostic factors but also uncovered a few others, such as tumor crossing midline and the presence of neurologic deficits before surgery.[213]

On the basis of these randomized trials, it is evident that in adults with low-grade gliomas, no difference in survival is achieved whether radiation therapy is given postoperatively or delayed until recurrence. Therefore, a reasonable management strategy would be observation in a patient with a completely resected low-grade glioma. Many investigators, however, still advocate radiation after complete resection in older patients (older than 40 years) or after incomplete resection. The standard dose is 54 Gy given in 1.8-Gy fractions over 6 weeks. It is common to treat the MRI-defined gross tumor volume (GTV) with a 1.5- to 2-cm margin.

Radiation Therapy for High-Grade Gliomas

The earliest randomized trial to demonstrate that radiation therapy was beneficial in the treatment of high-grade gliomas was conducted by the Brain Tumor Study Group (BTSG 69-01)[214] (Table 70-7). Patients were randomly assigned to one of four groups: supportive care, whole-brain radiation therapy (WBRT), BCNU, or WBRT plus BCNU. The role of BCNU is discussed further under Chemotherapy for Gliomas later on. This BTGS trial clearly showed a benefit for radiation alone versus supportive care with a median survival for 9 months versus 3.5 months and a 1-year survival rate of 24% versus 3% ($P = 0.001$). On the basis of this trial, radiation therapy has remained an essential component in the treatment of high-grade gliomas. A second randomized trial from the Scandinavian Glioblastoma Study Group confirmed the efficacy of radiation using a lower dose of WBRT (45 Gy) compared with supportive care (see Table 70-7).[215]

The results from BTSG 69-01 and two successive BTSG studies were pooled together to examine dose response.[216] The original studies were all randomized, but patients were not randomly assigned to different radiation doses; therefore, the analysis of dose was a retrospective one. With this caveat kept in mind, the study showed a benefit to using 60 Gy versus 50 Gy (median survival, 10.5 versus 7 months; $P = 0.004$). The Medical Research Council in Great Britain performed a randomized study examining dose in radiation treatment for high-grade astrocytomas.[217] After surgery patients were randomly assigned to receive either 45 or 60 Gy of radiation. The treatment volumes used in this study were very generous but less than for whole-brain levels. Among patients receiving 45 Gy, irradiation was mostly to the entire supratentorial region. Among those who received the higher dose, a dose of 40 Gy was delivered to volumes similar to those in the first group, followed by an additional 20 Gy to the tumor volume with a 1-cm margin.

The current standard of care in RTOG studies is to define the initial volume as the preoperative lesion with edema as seen on T_2-weighted MR images with a 2-cm margin. This volume is treated to 46 Gy, followed by a boost to the gadolinium-enhancing lesion seen on T_1-weighted images with a 2.5-cm margin to 60 Gy.

By pooling the results of three RTOG studies and using a nonparametric recursive partitioning technique, Curran and associates identified several significant prognostic factors for survival in patients with high-grade gliomas: histologic type, KPS score, age, neurologic function, and duration of symptoms.[218] Patients could be placed into groups I through IV with different outcomes on the basis of these factors.

Data have been accumulated regarding the radiologic response of high-grade astrocytomas to radiation therapy. In one multicenter trial, patients had CT scans done at several points in management: (1) preoperatively, (2) at the end of radiation therapy, (3) 6 to 8 weeks after the end of radiation therapy coinciding with the start of chemotherapy, (4) 8 weeks after the first course of chemotherapy, and then (5) every 3 to 4 months.[219] The radiation dose consisted of 44 Gy to the whole brain, followed by 14 Gy to the tumor volume. Twenty-two of 63 evaluable tumors (35%) responded to irradiation, defined as showing a decrease in the enhancing tumor volume by 25% or more. The vast majority of responding tumors, 20, showed a response by the end of radiation therapy. In two tumors, the response occurred between the end of radiation and the start of chemotherapy (8 weeks later). Three tumors (5%) progressed by the end of radiation therapy. Complete disappearance of the enhancing mass was extremely rare, occurring in only three tumors (5%). Response was more common in patients with anaplastic astrocytomas (11 of 21, or 52%) than in those with glioblastomas (11 of 42, or 26%), although this difference did not reach statistical significance.

Because of the poor survival of patients with high-grade astrocytomas, numerous strategies have been tried to improve the results with irradiation. These efforts fall into two main classes: first, increasing radiation dose, and second, modulating the radiation response. Doses higher than 60 Gy have been used, but to no avail. The RTOG 74-01–ECOG 1374 trial randomized between 60 Gy WBRT and a total dose of 70 Gy (60 Gy WBRT followed by a 10-Gy boost) but showed no improved survival with the additional dose (see Table 70-7).[220] Hyperfractionation also has been used to try to increase the total dose. In the Brain Tumor Cooperative Group (BTCG) study 77-02, patients who were randomly assigned hyperfractionated WBRT (66 Gy in 1.1-Gy twice-daily fractions) with BCNU showed no difference in survival compared with those who received conventional WBRT (60 Gy).[221] In RTOG trial 90-06, patients were randomized to receive either 60 Gy in conventional fractionation or 72 Gy in a hyperfractionated regimen (1.2 Gy twice daily). No differences were found in survival between the two groups.[222]

Radioactive implants also have been used to increase dose locally to the tumor bed. Single-institution data suggested improved outcome with this approach over conventional radiotherapy.[223] In the BTCG 87-01 trial, patients were randomized to receive either an ^{125}I seed implant (60 Gy) or no implant at surgery (see Table 70-7). Thereafter, patients received 60 Gy via external beam radiation. Remarkably, no survival benefit was found for use of 120 Gy delivered with brachytherapy and external beam irradiation.[224] In a trial conducted at the Princess Margaret Hospital, patients underwent surgery followed by 50 Gy of external beam radiation and then were randomized to either receive an ^{125}I implant (60 Gy) or not.[225] This study too showed no improvement with an implant.

An implantable balloon has been developed for the delivery of brachytherapy. This implantable balloon (Gliasite) comes in several sizes to fit the diameter of the resection cavity. After resection of the tumor, the balloon is placed in the cavity and filled with x-ray contrast medium. The catheter is attached to the balloon and then is brought out through the skull, and an infusion port at the end of the catheter is attached to the skull. A liquid form of ^{125}I (Iotrex), specifically developed for use in the Gliasite, can then be used to fill the balloon 2 to 3 weeks after insertion. Dwell times range from 2 to 5 days, based on the calculated dose of radiation, following which the Iotrex is withdrawn from the balloon via the infusion port. Loading and unloading of the Iotrex are done percutaneously. Patients can be sent home with appropriate radiation safeguards (personal communication, Allen Sills, MD, Memphis, Tennessee); alternatively, the patient is kept in the hospital with the appropriate radiation isolation precautions. This device provides brachytherapy directly to the resection cavity, with minimal exposure of unaffected brain to the radiation source. The device is used for treatment of primary gliomas as well as metastatic tumors. The dose for recurrent gliomas is 60 Gy at 1 cm and for metastatic lesions 60 Gy at 0.5 cm. Use of the Iotrex has yielded significant improvements in quality of life and tumor control.[226,227]

Table 70-7 Results of Treatment for High-Grade Astrocytomas: Selected Randomized Trials Focusing on Radiation and Radiation Modifiers

Study	Years	Gliomas (%)	Treatment Protocol	No. of Patients	Median Survival (mo)	18-Month Survival (%)	Comment(s)
Walker et al[232]	1969–1972	90	Supportive care	31	3.5	0	RT superior to supportive care (P = 0.001)
BTSG 69-01			BCNU	51	4.6	4	
			RT (60 Gy WBRT)	68	9	4	
			RT (60 Gy WBRT) + BCNU	72	8.6	18	RT + BCNU superior to supportive care (P = 0.001)
Kristiansen et al[215]	1974–1978	—	Supportive care	38	5.2	0	RT superior to supportive care
SGSG			RT (45 Gy WBRT)	35	10.8	13	
			RT (45 Gy WBRT) + Bleo	45	10.8	13	
Bleehen and Stenning[217]	1983–1988	—	RT (45 Gy)	144	—	11	60 Gy superior to 45 Gy (P = 0.04)
			RT (60 Gy)	299	—	18	
Chang et al[220]	1974–1979	80	RT (60 Gy WBRT)	148	9.9	19	No difference between any groups
RTOG 74-01			RT (60 Gy WBRT) + 10 Gy boost	105	8.4	22	No improvement with 70 Gy
			RT (60 Gy WBRT) + BCNU	165	10.0	29	
			RT (60 Gy WBRT) + DTIC + MeCCNU	136	9.8	26	
Curran et al[218]			RT (60 Gy) + BCNU			13.2	No improvement with HFX
RTOG 90-06			RT (72 Gy HFX) + BCNU			11.2	For patients <50 yr, median survival better with standard fractionation
Selker et al[224]	1987–1994 (10% AA)	85	^{125}I implant (60 Gy) + BCNU + RT* (60.2 Gy)	137	17	56	No improvement with implant
BTCG 87-01			RT* (60.2 Gy) + BCNU	133	14.8	44	
Laperriere et al[225]	1986–1996	92	RT (50 Gy) + BCNU	69	13.2		No improvement with implant
PMH			RT (50 Gy) + BCNU + ^{125}I implant (60 Gy)	71	13.8		
Nelson et al[231]	1979–1983	83	RT + BCNU	146	12.4	34	No improvement with misonidazole
RTOG 79-18			RT + Miso + BCNU	147	10.7	27	
Prados et al[230]	1994–1997	0†	RT (60 Gy) + PCV	134	—	74	Preliminary: no improvement with BUdR
RTOG 94-04			RT (60 Gy) + BUdR + PCV	134	—	62	
Souhami et al[229]	1994–2000	100	RT (60 Gy) + BCNU	186 (total in both arms)	14.1	22 (2 yr)	Preliminary; no improvement with radiosurgery boost
RTOG 93-05			Radiosurgery boost + RT (60 Gy) + BCNU		13.7	18 (2 yr)	

AA, anaplastic astrocytoma; BCNU, carmustine; Bleo, bleomycin; BTCG, Brain Tumor Cooperative Group; BUdR, bromodeoxyuridine; DTIC, dacarbazine; HFX, hyperfractionation; MeCCNU, sem ustine; Miso, misonidazole; PCV, procarbazine, cisplatin, vincristine; RT, radiation therapy; RTOG, Radiation Therapy Oncology Group; SGSG, Scandinavian Glioblastoma Study Group; WBRT, whole-brain radiation therapy.

*During the early part of the study, external beam radiation was given to whole brain to a dose of 43 Gy, followed by a boost to the tumor volume for an additional 17.2 Gy. From May 1989, WBRT was dropped, and the entire dose was restricted to tumor volume.

†All patients in this trial had AAs.

Another means of increasing dose to the tumor region after conventional radiation therapy has been stereotactic radiotherapy. Single-institution studies have shown improved results with this approach—for example, from the Joint Center for Radiation Therapy at Harvard.[228] This approach was tested in the RTOG study 93-05, in which patients in the control group received standard fractionated radiotherapy (60 Gy in 30 fractions) with BCNU chemotherapy, whereas patients in the experimental group received a radiosurgery boost (15 to 24 Gy) before external beam radiation therapy. Preliminary results in abstract form from this trial indicate no benefit for the radiosurgery boost (see Table 70-7).[229]

Numerous agents have been tried in combination with radiation in attempts to improve survival. Conventional chemotherapy is discussed later under Chemotherapy for Gliomas. Halogenated

pyrimidine analogs are incorporated preferentially into dividing cells, with substitution of pyrimidine for the thymidine in DNA, sensitizing cells to double-strand breaks. In vitro, this can lead to radiosensitization by preventing the repair of double-strand breaks. The halogenated pyrimidine BUdR has been studied in a randomized trial. Prados and associates randomized patients with anaplastic astrocytomas to receive radiation therapy and chemotherapy with procarbazine, CCNU (lomustine), and vincristine (the PCV regimen), with or without the radiosensitizer BUdR, which was given as a 96-hour infusion concurrently with the radiation.[230] No difference in survival was found, however.

Glioblastomas are thought to have regions of hypoxia that can lead to radioresistance. Therefore, agents that are hypoxic cell sensitizers have been used in conjunction with radiation (see Table 70-7). The hypoxic cell sensitizer misonidazole was tested in RTOG trial 79-18 but was not found to lead to an improvement in survival.[231] Misonidazole also showed no benefit in another randomized trial, BTSG 77-02.[221]

The one agent that has clearly been shown to be of benefit when combined with radiation is the alkylating agent temozolomide. The results with this drug for treatment of glioblastomas are discussed next.

Chemotherapy for Gliomas

Chemotherapy for Newly Diagnosed High-Grade Astrocytomas

The role of chemotherapy in the treatment of high-grade astrocytomas has been investigated for more than 30 years. The earliest prospective brain tumor chemotherapy clinical trials were performed by the BTCG/Brain Tumor Study Group (BTSG) investigators. In BTSG 69-01, Walker and colleagues found that median survival was not significantly prolonged in patients receiving carmustine (BCNU), but at 18 months, 19% of patients reciving chemotherapy, radiation therapy, and surgery were alive, compared with 4% of those treated with radiation therapy and surgery alone.[232] In BTSG 75-01, Green showed that the addition of chemotherapy to surgery and radiation therapy significantly increased mean survival from 40 weeks to 50 weeks and increased the percentage of patients surviving 18 months to 24%.[233] In these and most studies of chemotherapy as adjuvant therapy for high-grade astrocytoma, the benefit was greater in patients with anaplastic astrocytoma than in those with glioblastoma.

Another well-studied and frequently used chemotherapy regimen is combination therapy with procarbazine, CCNU, and vincristine (i.e., PCV). Although initial reports suggested a survival advantage for patients with anaplastic astrocytoma receiving PCV over those receiving BCNU, subsequent meta-analysis of four studies failed to confirm this finding.[234] The PCV regimen clearly is more toxic as a result of myelosuppression and peripheral neuropathy and has been replaced by temozolomide.

The introduction of temozolomide has dramatically altered the treatment of high-grade gliomas. Temozolomide is an oral alkylating agent whose levels are not affected by AEDs or other hepatic enzyme-inducing drugs. Toxicity with this drug is relatively mild, with good CNS penetration. The pivotal study conducted jointly by the European Organization for Research and Treatment of Cancer (EORTC) trial 22981–26981, and the National Cancer Institute of Canada (NCIC) trial CE.3 confirmed the usefulness of temozolomide and radiation in newly diagnosed glioblastomas.[235] This study randomized 573 patients to receive 60 Gy of standard fractionated radiation or the same radiation regimen with daily temozolomide at 75 mg/m^2 followed by six cycles of adjuvant temozolomide (150 to 200 mg/m^2 for 5 days during each 28-day cycle). The patients in the radiation plus temozolomide arm had a statistically significant improvement in survival over those in the radiation only arm ($P < 0.001$; Fig. 70-14A). At follow-up evaluation at a median of 28 months, the median survival periods in the two arms were 12.1 and 14.6 months, respectively. The 2-year overall survival rates were 10.4% and 26.5%, respectively.

Hegi and coworkers subsequently evaluated the status of the epigenetic silencing of the MGMT DNA repair gene (*MGMT*) by promoter methylation in patients enrolled in this trial.[236] Two hundred six of the patients enrolled in EORTC 22981–26981–NCIC CE.3 had samples in which MGMT promoter methylation could be assessed. The MGMT promoter methylation occurred in 45% of these cases, and this was found to be an independent favorable prognostic factor regardless of treatment ($P < 0.001$). Patients with a methylated MGMT promoter had better survival than those without (see Fig. 70-14B). The median and 2-year survival rates for patients receiving radiation versus radiation and temozolomide based on MGMT promoter methylation status are shown in Table 70-8. Even among patients with unmethylated MGMT, a trend toward increased survival is recognized for those receiving temozolomide. These data have made irradiation plus adjuvant temozolomide the standard of care for all patients with glioblastoma regardless of *MGMT* status. The relative contributions of oral daily temozolomide during radiation versus after radiation are not clear, and the optimal dose of temozolomide to inhibit MGMT activity has not been established and is the subject of ongoing trials. In the current RTOG trial, patients with newly diagnosed glioblastoma are randomized to receive standard chemoradiation therapy followed by 12 rather than 6 monthly cycles of adjuvant temozolomide at standard dosing, or, alternatively, dose-intensive temozolomide (21 days on and 7 days off).

Table 70-8 Results of Treatment for Glioblastomas Stratified by MGMT Promoter Status: EORTC Trial 22981-26981 and NCIC Trial CE.3

	MGMT Promoter Status/Treatment*			
Study Result	**Unmethylated ($N = 114$)**		**Methylated ($N = 92$)**	
Median overall survival (mo)	12.2	($P < 0.001$)	18.2	
	Radiation only ($N = 54$)	**Chemoradiation ($N = 60$)**	**Radiation only ($N = 46$)**	**Chemoradiation ($N = 46$)**
	11.8	12.7	15.3	21.7
2-year survival	1.9%	13.8%	22.7%	46%
	($P = 0.06$)		($P = 0.007$)	

EORTC, European Organization for Research and Treatment of Cancer; MGMT, O^6-methylguanine DNA methyltransferase; NCIC, National Cancer Institute of Canada.
*Either radiation therapy only or chemotherapy plus radiation therapy.
Adapted from Hegi ME, Diserens AC, Gorlia T, et al: *MGMT* gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997.

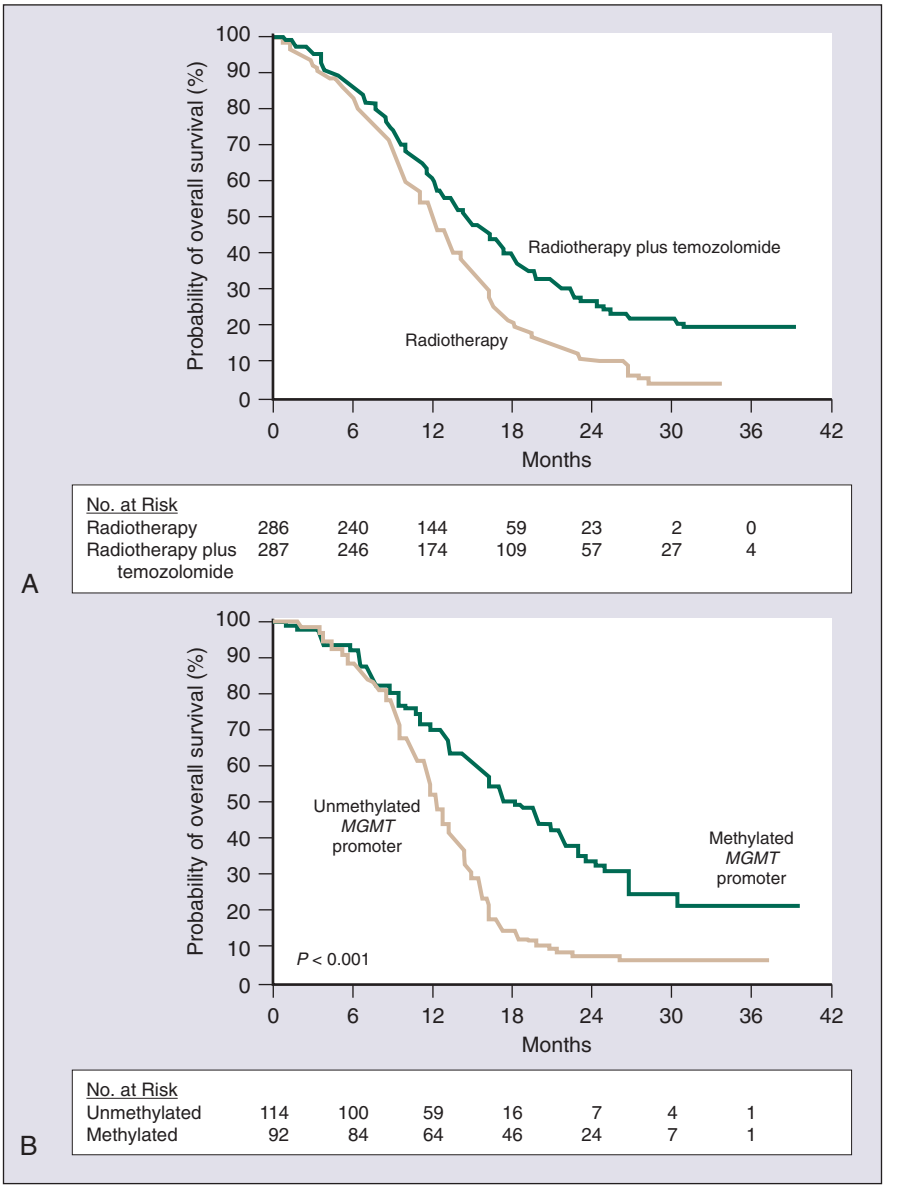


Figure 70-14 • Survival of patients with glioblastoma based on temozolomide administration or *MGMT* status. Patients enrolled in the EORTC trial 22981–26981 and NCIC trial CE.3 were randomized to receive radiotherapy alone or radiotherapy plus temozolomide. **A,** Kaplan-Meier estimates of overall survival according to treatment group. The hazard ratio for death among patients who received temozolomide, compared with those who received radiotherapy alone, was 0.63 (95% confidence interval, 0.52 to 0.75l; $P < 0.001$). **B,** In a subset of the patients enrolled on the trial in **A,** the methylation status of the MGMT (O^6-methylguanine DNA methyltransferase) gene promoter was assessed. The curves in **B** represent Kaplan-Meier estimates of overall survival according to MGMT promoter methylation status. The difference in survival between patients with a methylated MGMT promoter (92 patients, 65 of whom died) and those with an unmethylated MGMT promoter (114 patients, 105 of whom died) was highly significant ($P < 0.001$ by the log-rank test), indicating that the MGMT promoter methylation status has prognostic value. In the group of patients with a methylated MGMT promoter, a risk reduction of 55% (hazard ratio for death, 0.45; 95% confidence interval, 0.32 to 0.61) was determined, as compared with the patients with an unmethylated MGMT promoter. (**A,** From Stupp R, Mason WP, van den Bent MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987. **B,** From Hegi ME, Diserens AC, Gorlia T, et al: *MGMT* gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997.)

Even though the cited data on temozolomide were generated in patients with glioblastomas, many oncologists have extrapolated these findings to anaplastic astrocytomas and have used this agent concurrently with radiation in this setting. Of note, however, some experts have questioned whether concomitant temozolomide should be considered standard therapy in patients with anaplastic gliomas in the absence of randomized data.[237]

Chemotherapy for Recurrent High-Grade Astrocytomas

Patients with high-grade astrocytomas in whom initial therapy with radiation and temozolomide fails to provide benefit are candidates for participation in phase I/II trials. Such trials include drugs as well as a radiolabeled antibody that is infused directly into the tumor. In patients for whom some interval has elapsed between initial temozolomide therapy and failure, retreatment with low-dose daily temozolomide may be tried. Any benefit from chemotherapy for recurrent disease must be measured against the roughly 4- to 5-month median survival after repeat surgical removal of recurrent high-grade astrocytic tumors.

Some patients with recurrent high-grade astrocytomas are offered re-resection with use of either Gliasite (covered earlier under Radiation Therapy for High-Grade Gliomas) or Gliadel (intracavitary biodegradable BCNU wafers). A placebo-controlled multicenter study in 22 patients reported a median survival period of 31 weeks in patients receiving BCNU polymers, compared with 23 weeks in the patients receiving placebo polymers.[238] The use of Gliadel is limited to those patients who can have meaningful re-resection of tumors that are relatively well circumscribed, unilateral, and in noneloquent brain locations—a situation not typical for a majority of anaplastic astrocytic tumors.

Gliadel wafers also have been used in patients with newly diagnosed high-grade gliomas. In one large study, 240 patients received either BNCU or placebo wafers at the time of primary surgical resection and then underwent external beam irradiation of their tumor. Median survival in the BCNU wafer group was 13.9 months, versus 11.6 months in the placebo group. This modest survival advantage may have been partly outweighed by a higher incidence of adverse effects in the BCNU group, including CSF leak and significant

vasogenic edema.[239] Several institutions have reported a high rate of perioperative craniotomy infection after wafer placement.

Irinotecan, a topoisomerase I inhibitor, has been the subject of several studies in patients with recurrent malignant astrocytoma. A respectable 10% to 15% objective imaging response rate has been achieved after thrice-weekly infusions.[240] In two other studies seeking maximal tolerated dose, a marked effect of concomitant enzyme-inducing AEDs was found. Patients taking cytochrome P-450-inducing AEDs achieved lower levels of the active metabolite SN-38 (7-ethyl-10-hydroxycamptothecin) than those measured in patients not receiving AEDs.[241] Subsequent and ongoing irinotecan studies have stratified patients according to AED use.

Chemotherapy for Low-Grade Astrocytomas

Chemotherapy for low-grade astrocytomas usually is reserved for those patients whose unresectable tumors are progressively symptomatic. Radiation therapy traditionally has been used as a first-line treatment for progression. Potential toxicity of any proposed therapy for low-grade gliomas must be balanced against the long natural history. Particularly in younger patients and in those whose tumors have an oligodendroglial component, median survival periods may approach 10 years, with 5-year survival rates of 75% or higher.[178] Indeed, some investigators have argued that quality of life considerations, with particular attention to cognitive status, dictate a prolonged "wait and see" policy in patients with suspected low-grade glioma.[242] Some variants of low-grade glial tumors cary a more ominous prognosis and for the rare situation of multicentric gliomatosis cerebri, chemotherapy may be a reasonable first-line approach. A recent case report documents both MRI and MRS improvement in this usually untreatable condition.[243] Potential considerations in the use of alkylating agents for patients with low-grade astrocytomas should include the risks of hematologic malignancies (5% at 5 years) and sterility. When the astrocytoma contains a portion of oligodendroglial cells, an increasingly common practice is to recommend chemotherapy, but the percentage of oligodendroglial cells required to convey chemosensitivity to the entire mass is unknown. Molecular genetic analysis of oligoastrocytomas has suggested an inverse correlation between 1p or 19q deletions and p53 mutations, rarely occurring in the same tumor (see earlier under Genetics of Supratentorial Gliomas).[194] Tumors with 1p or 19q deletions tend to have a predominant oligodendroglial component. It remains to be seen if patients with low-grade tumors can be reliably selected for chemotherapy on the basis of these criteria.

Examination of quality of life outcomes must factor into recommendations for chemotherapy and radiation therapy. The trend over the last 30 years has been for increasing survival times, with a majority of patients receiving only surgery as a first course of treatment.[244] Patients who have a low risk of progression—those who are younger than 40 years of age with tumors less than 4 cm in diameter and who have undergone gross total resection—have an overall 5-year survival rate of 94%, with a progression-free 5-year survival rate of 50%. For these patients, close observation seems indicated.

The Radiation Therapy Oncology Group (RTOG) recently completed trial 9802 for histologically confirmed low-grade gliomas (Fig. 70-15). Patients who had undergone total resection and were younger than 40 years of age (low-risk group) were managed by observation. The remaining patients were randomized to receive either radiation therapy alone (54 Gy) or radiation therapy followed by six cycles of PCV chemotherapy. The results have been reported in abstract form.[245] For the low-risk patients who were observed, overall survival (OS) at 2- and 5-years was 99% and 94%, respectively, with a median follow-up time of 4 years. Progression-free survival (PFS) at 2- and 5-years was 82% and 50%, respectively. For the high-risk patients who were randomized to RT versus RT + PCV, there was no difference in OS or PFS between the two groups. OS at 2- and 5-years was 87% and 61% (RT alone) versus 86% and 70% with RT + PCV ($P = 0.72$)."

The RTOG currently has a trial (3302) open that is a phase II study for patients with high-risk low-grade gliomas that uses daily temozolomide for 12 cycles.

Chemotherapy for Newly Diagnosed Anaplastic Oligodendrogliomas

Over the past decade, increasing evidence has accumulated to confirm that anaplastic oligodendrogliomas and possibly anaplastic oligoastrocytomas are special types of malignant gliomas that are sensitive to chemotherapy. Although the molecular markers of chemosensitivity, allelic loss of 1p and 19q, have been shown to have prognostic significance in multiple studies, the reason for oligodendroglial chemosensitivity remains unknown. Zlatescu and colleagues have made the clinically interesting observation that allelic loss of 1p and 19q is related to tumor location and extent of tumor spread in the brain.[196] Anaplastic oligodendrogliomas located in the frontal, parietal, and occipital lobes were significantly more likely to harbor 1p or 19q loss than are histologically identical tumors arising in the temporal lobe, insula, or diencephalon. Frontal tumors tend to have greater bilateral diffuse spread, and investigation of the biologic significance of these growth and invasion differences eventually may have implications for management strategies.

In the first large study of chemotherapy for anaplastic oligodendrogliomas, Cairncross and the National Cancer Institute of Canada conducted a multicenter phase II trial of intensive PCV chemotherapy (i.e., procarbazine, CCNU, and vincristine) using higher doses of the first two drugs than are found in the standard PCV regimen.[246] This study included new or recurrent anaplastic oligodendrogliomas and reported a 75% overall response rate, with 38% complete responses. Time to tumor progression was at least 16.3

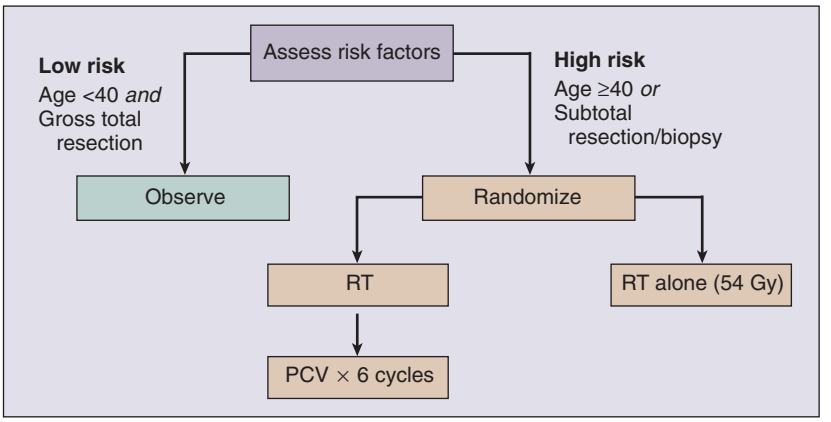


Figure 70-15 • Schema for RTOG/Intergroup 9802 protocol for treatment of low-grade gliomas. Protocol was open to patients with histologically verified WHO grade II astrocytoma, oligodendroglioma, or oligoastrocytoma. The study was closed to accrual in June 2002. Results have been reported only in abstract form. CCNU, vincristine; PCV, procarbazine; RT, radiation therapy.

months for the entire eligible group and at least 25.2 months for complete responders.

Two randomized trials have been conducted comparing radiation only with radiation plus PCV chemotherapy in patients with newly diagnosed anaplastic oligodendrogliomas or anaplastic oligoastrocytomas.[247,248] In RTOG 9402, patients were randomized to receive radiation only or up to four cycles of intensive PCV chemotherapy followed by radiation.[248] In EORTC 226951, patients were randomized to receive radiation only or radiation followed by six cycles of standard PCV chemotherapy.[247] The two studies showed remarkably similar results. In both studies, the addition of PCV chemotherapy improved progression-free survival but not overall survival. Patients with combined 1p and 19q loss showed a much better survival than that observed for patients with intact 1p and 19q; however, even in this chemotherapy-sensitive subgroup, the addition of PCV did not improve overall survival.

The PCV regimen has significant hematologic toxicity, and given its lack of survival benefit in anaplastic oligodendrogliomas in these randomized phase III trials, there has been a movement toward temozolomide, which is much better tolerated. In spite of a lack of randomized data with temozolomide in anaplastic oligodendrogliomas, many oncologists are currently using this drug concomitantly with radiation, extrapolating from the experience with glioblastoma.[235]

Chemotherapy for Recurrent Anaplastic Oligodendroglioma and Oligoastrocytoma

Most patients with recurrent AOs who received PCV at initial presentation are currently being treated with temozolomide at relapse. Several small trials have shown the safety and efficacy of temozolomide following prior PCV therapy (Table 70-9).[249–251] An open label phase II trial of temozolomide in 47 patients with anaplastic oligodendroglioma or anaplastic oligoastrocytoma who relapsed after radiation and PCV chemotherapy demonstrated an objective response rate of 43%, median PFS of 7.5 months and 34% rate of disease-free survival at 12 months.[251] In another phase II multicenter trial that included patients with anaplastic oligodendroglioma or anaplastic oligoastrocytoma, a response rate was seen in 26% of patients who had previously received PCV therapy and in two out of three chemotherapy-naive patients.[249] A short time to tumor progression appears to be a bad prognostic factor for response to both first-line PCV chemotherapy and temozolomide.

Brandes and associates recently reported on 67 patients with recurrent anaplastic oligodendroglioma or anaplastic oligoastrocytoma treated with temozolomide at the time of disease progression.[252] All patients had received surgery and radiotherapy, and none had received prior chemotherapy. The overall response rate was 46% and was higher in those with anaplastic oligodendroglioma than in those with anaplastic oligoastrocytoma (62% versus 25%; $P = 0.003$). Combined 1p and 19q loss (present in 48% of patients) significantly correlated with response rate ($P = 0.04$), time to progression ($P = 0.003$), and overall survival ($P = 0.0001$). By contrast, only a borderline correlation was found between MGMT promoter methylation (present in 69% of assessable patients) and overall survival ($P = 0.09$).

Chemotherapy for Low-Grade Oligodendrogliomas and Oligoastrocytomas

Temozolomide has been used in patients with low-grade oligodendrogliomas or oligoastrocytomas that have recurred. The EORTC conducted one study using temozolomide for patients who had received PCV chemotherapy and irradiation for their initial disease,[253] and another study for patients who had received surgery and irradiation without chemotherapy initially.[254] These studies showed 25% to 53% response rates, respectively, to temozolomide (see Table 70-9). Loss of 1p has been correlated with response to temozolomide for first-line chemotherapy in patients with recurrent oligodendrogliomas.[255,256]

Therapy for Elderly Patients with Malignant Gliomas

Elderly patients with malignant gliomas have a poorer outcome than that for younger patients. Brandes and coworkers evaluated the role of surgery, radiation therapy, and chemotherapy for the treatment of newly diagnosed glioblastoma in patients older than 65 years of age.[257] These investigators found that the main predictive factor in evaluating this treatment was perioperative KPS score. The higher the KPS score, the better the patient fared, regardless of the treatment. Patients were stratified into group A (surgery with radiation therapy to a dose of 59.4 Gy), group B (surgery, radiation therapy, and PCV chemotherapy), and group C (surgery, radiation therapy, and temozolomide). The median time to disease progression was significantly better in group C patients. Overall survival was better in group C, but this did not reach statistical significance. Hematologic toxicity was higher in patients on a PCV regimen than in those receiving temozolomide.

Another study evaluated the role of debulking craniotomy versus stereotactic biopsy in the treatment of malignant gliomas in patients older than 65 years of age.[258] Patients in this study were randomized to undergo either stereotactic biopsy or craniotomy for debulking of the tumor. Patients were evaluated with an intention to treat analysis. The median survival period was 171 days after craniotomy versus 85 days after biopsy. The difference was not statistically significant; however, this finding did suggest that patients undergoing a more aggressive craniotomy survived longer. Time to deterioration was 105 days in the craniotomy group and 72 days in the biopsy group. This increased time to deterioration corresponds with maintenance of

Table 70-9 Results of Treatment for Recurrent Low-Grade and Anaplastic Oligodendroglioma and Oligoastrocytoma: Temozolomide-Based Chemotherapy Regimens

Study	Tumors Treated	No. of Patients	CR/PR/SD	MTP (mo)	6/12-Month PFS	MST(mo)
Yung et al[250]*	AA, AOA, AO	111	8%/27%/26%	5.4	46%/24%	13.6
Chinot[251]	AO, AOA	47	15%/28%/40%	7.5	NR/34%	8.8
van den Bent et al[249]	AO, AOA	30	10%/21%/28%	NR	44%/27%	7
Brandes et al[252†]	AO, AOA	67	25%/21%	12	NR/50%	31
van den Bent et al[253†]	O, OA	38	53% (CR + PR)	10.4	71%/40%	NR
van den Bent et al[254]	O, OA	28	25% (CR + PR)	8.0 (in responders)	29%/11%	NR

AA, anaplastic astrocytoma; AO, anaplastic oligodendroglioma; AOA, anaplastic oligoastrocytoma; CR, complete response; MTP, median time to progression; MST, median survival time; NR, no response; O, oligodendroglioma; OA, oligoastrocytoma; PFS, progression-free survival; PR, partial response; SD, stable disease.

*This study also included AA and is included here for comparison. Patients with AOA and AO had better survival than those with AA.

†In these reports, none of the patients had received any prior chemotherapy before being placed on temozolomide at relapse.

quality of life during this time period. Both groups of patients tolerated the radiation therapy well.

On the basis of these results, it appears that patients with malignant gliomas older than 65 may still benefit from aggressive therapy if they have a reasonable performance status. Therefore, old age alone should not be a criterion for minimizing therapy. An abbreviated radiotherapy regimen may be considered in older patients with a poor performance status. Roa and associates randomized patients with glioblastoma older than the age of 60 to receive a standard course of radiation (60 Gy in 30 fractions over 6 weeks) or a shorter course (40 Gy in 15 fractions over 3 weeks).[259] Overall survival times measured from randomization were similar at 5.1 months for standard RT versus 5.6 months for the shorter course ($P = 0.57$). The survival probabilities at 6 months were also similar, at 44.7% for standard RT versus 41.7% for the shorter course.

Quality of Life after Therapy for Gliomas

Quality of life issues are paramount in treatment for patients with gliomas. Taphoorn and coworkers found that drowsiness, fatigue, memory deficits, and concentration problems were more common complaints in patients with low-grade gliomas than in control patients with hematologic malignancies. An analysis of quality of life was performed in patients participating in an EORTC trial of randomization to either 59.4 or 45 Gy for low-grade gliomas.[211] This analysis found that patients receiving the higher dose complained of more fatigue and insomnia immediately after radiotherapy and poorer emotional functioning 7 to 15 months after institution of therapy.[260]

The EORTC/NCIC performed a quality of life study as part of a randomized trial of radiation versus radiation plus temozolomide for patients with glioblastoma.[261] The study investigators found that health-related quality of life measures (fatigue, overall health, social function, emotional function, future uncertainty, insomnia, and communication deficit) did not deteriorate by a clinically meaningful amount in either treatment group over time after treatment, and even improved for some parameters. Furthermore, the addition of the temozolomide regimen to radiotherapy did not negatively affect health-related quality of life. Notwithstanding these results, patients with malignant gliomas face enormous stresses. They face the same burdens of dealing with a terminal disease as patients with breast cancer, lung cancer, and other malignancies, but they have unique perspectives in that they are uniformly concerned about the potential for damage to the brain and the effect of cognitive function. These patients not only have to deal with concepts of dying and leaving behind their families and friends but also have a constant worry about being in a persistent vegetative state and being a burden to their families. Measurement of quality of life is important to elucidate the impact of available treatments on the disease: The goal is to improve survival, but not at the sacrifice of quality of life.[262]

New Approaches to Therapy of Gliomas

The disappointing results with conventional cytotoxic chemotherapy have led to efforts to find more effective and better-tolerated therapies. The challenge of neuro-oncology is to develop new compounds or procedures of gene transfer that specifically target the molecular alterations of glioma tumor cells and restore normal gene expression, cell cycle regulation, and apoptosis.[263] Significant progress is likely to come from some combination of cytotoxic chemotherapy with biologic agents directed at genetic alterations specific to brain tumors, such as growth factor receptors. Receptors are tempting targets because they are extracellular and easily accessible to drugs or antibodies. A number of agents targeted to the EGFR receptor and the vIII variant are being tested. These EGFR inhibitors have shown limited utility in the clinic with brain tumors. These inhibitors may be effective only in patients with tumors that have a susceptible target. In one study, patients who had received treatment with gefitinib or erlotinib were analyzed for expression of EGFR, the deletion mutant EGFRvIII, and the tumor suppressor gene *PTEN*. Tumors that coexpressed EGFRvIII and PTEN were most likely to respond to EGFR kinase inhibitors.[264]

Receptor tyrosine kinases (RTKs), such as PDGF and insulin-like growth factor (IGFR) receptors, regulate cell proliferation and differentiation. Deregulated RTK signaling frequently is found in human astrocytic tumors. In addition, gefitinib and erlotinib, mentioned earlier, and other inhibitors of RTKs have been evaluated in malignant glioma including imatinib mesylate. Other agents target farnesyl transferase, histone deacetylase, rapamycin (mTOR), protein kinase C, and the ubiquitin-proteosome pathway. In general, small early trials have been disappointing, although the agents were well tolerated. Most are metabolized through the cytochrome P-450–CYP3A4 system, and significant dose modifications are necessary in patients with brain tumors who are taking enzyme-inducing AEDs.

Because gliomas produce specific angiogenic peptides such as VEGF (see the molecular genetics section earlier in this chapter) to stimulate new blood vessel formation, angiogenesis inhibitors are a logical drug development target. Hypoxic areas within gliomas may stimulate angiogenesis and promote invasiveness of glial cells.[265] Many of these changes in gene expression are mediated by hypoxia-inducible factor-1 (HIF-1). Many antiangiogenic agents directed against VEGF, VEGFR, and other targets are in clinical trials. Bevacizumab, a humanized monoclonal antibody against VEGF, showed a 63% radiologic response rate in patients with recurrent high-grade gliomas.[266]

The transfer of genetic material to tumor cells to make them more susceptible to chemotherapy, or to reverse the alterations that sustain the neoplastic phenotype, has been studied in several centers. Gene therapy strategies include transfecting antioncogenes or drug-activating enzymes to glioma cells. The most extensively studied system is the "suicide gene therapy" with herpes simplex thymidine-kinase (HSV-tk) gene inserted into a replication defective murine retrovirus. Murine fibroblasts are engineered to produce these recombinant retroviruses, which are injected into gliomas, infecting the proliferating tumor cells and making them produce thymidine kinase. The tumor cells then are susceptible to the antiherpes drug ganciclovir, while nondividing brain cells are not infected. Clinical studies using this promising approach have been disappointing because of poor tumor cell transfection efficiency, although some long times to tumor progression have been reported.[267–269] A prospective controlled trial in patients with newly diagnosed glioblastoma showed no improvement in survival or time to tumor progression when intraoperative HSV-tk therapy and standard radiation therapy were compared with surgery and irradiation alone.[270] Adenoviral and adeno-associated viral vector genes are being studied as well. A phase I study of stereotactic injection of an adenovirus vector to transfer wild-type p53 gene is among the early clinical trials now under way that involve viral vectors to replace tumor suppressor genes.[271]

Other translational strategies that have moved to small preliminary human trials include glutamine depletion with phenylacetate and 13-*cis*-retinoic acid (CRA), a metabolite of beta-carotene that acts to promote differentiation.[272] Yung and colleagues administered CRA orally, but although toxicity was acceptable, the results were not better than with temozolomide as a single agent.[273]

Another strategy involves drugs that inhibit autophagy, such as hydroxychloroquine, which in a single-institution phase II trial resulted in more than doubling of overall median survival.[274] A phase II trial in patients with newly diagnosed glioblastoma will incorporate chemoradiation therapy with temozolomide and adjuvant temozolomide in addition to chronic daily hydroxychloroquine.

Biologic response modifiers that stimulate or restore the immune system include monoclonal antibodies, interferons, and interleukins. Inhibitors of TGF-β2, a cytokine that promotes invasion and angiogenesis, have been shown to inhibit glioma growth in vitro.[275]

Despite effective neuroimaging and earlier diagnosis, advances in the understanding of cellular events that underlie progression of brain tumors, a steady stream of novel agents, and suggestive preclinical

animal studies, clinical trials have proved disappointing. Because of the heterogeneity of malignant glial tumors, treatment strategies probably will require synergistic combinations of cytotoxic agents and noncytotoxic specific molecular methods, with the hope that genetic profiling eventually will help pinpoint appropriate choices for individual patients.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

Histopathologic Features

Primary CNS lymphoma (PCNSL) has been known previously by many other names, including "reticulum cell sarcoma," "diffuse histiocytic lymphoma," and "microglioma." The cell of origin is the B lymphocyte, and PCNSL is therefore a high-grade non-Hodgkin's B-cell neoplasm, usually diffuse large cell or large cell immunoblastic type. A frequent finding is perivascular clusters of lymphocytes, and T-lymphocyte infiltrates are common in immunocompetent patients.[276] Although the Epstein-Barr virus genome has been found in HIV-infected patients with PCNSL, no consistent confirmation of viral etiology of PCNSL has been possible among immunocompetent patients. Human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) was reported in over 50% of both normal and immunocompromised patients with PCNSL.[277] Human T-cell lymphotropic virus type 1 (HTLV-1) and hepatitis C virus have not been associated with PCNSL.

Only 1% to 3% of PCNSLs are of T-cell origin. The incidence of T-cell PCNSL appears to be higher in Japan than in the United States.[278] Primary T-cell lymphoma has been diagnosed in both immunocompromised and immunocompetent patients. A younger age at diagnosis for T-cell lymphomas has been suggested, and presentation as an infratentorial lesion appers to be more frequent, with one third to one half of reported cases in the cerebellum or brainstem.[279] T-cell lymphoma may appear as a large cystic mass on MRI. The prognosis for T-cell PCNSL may be worse than that for comparably staged B-cell tumors. Authors of published case reports suggest that this tumor should be treated aggressively with regimens used for the more common B-cell lymphomas.[280]

Tumor Biology

PCNSL arises in the brain leptomeninges, spinal cord, or eyes and rarely spreads outside the central nervous system. Its predilection for the periventricular white matter gives rise to the characteristic neuroimaging appearance of a hyperdense mass on unenhanced CT or a hypointense appearance on long TR-weighted MRI. Three fourths of immunocompetent patients have a solitary enhancing mass lesion at presentation. After contrast administration, most bulky masses of PCNSL enhance, most often homogeneously but occasionally in a ring-like pattern (Fig. 70-16). PCNSLs, however, appear to be diffusely infiltrative at the time of presentation. These areas of disease are not visible on neuroimaging studies because they are behind a relatively intact blood-brain barrier. Postmortem correlates with findings on MRI performed shortly before death show widespread microscopic infiltration in areas that appear normal on the MRI scan.[281] Therefore, PCNSL can be classified as stage 1E disease and should be considered for treatment purposes to be a *whole-brain disease*.

Until the 1980s, PCNSL was considered a rare tumor, accounting for approximately 2% of CNS malignancies in immunocompetent patients and 1% to 2% of all lymphomas.[282] The demographics of the disease have changed, however, both among immunocompetent patients and among those with HIV infection and organ transplant recipients. The incidence of PCNSL among immunocompetent persons has increased 25-fold to 51 cases per 10 million by 2000. Among immunocompetent patients with PCNSL, median age at diagnosis is 55 years, and males outnumber females by 2 : 1. Among patients with AIDS, the median age is 35 years, and 95% of HIV-infected patients with PCNSL are male.[283] Among organ transplant recipients, the peak incidence of PCNSL is at 6 months after transplantation, a period much shorter than in the pre-cyclosporine transplantation era.

Recent data from the Surveillance, Epidemiology, and End Results (SEER) program show an overall decline in total PCNSL incidence rates, from a peak of 102 per million in 1995 to 51 in 1998, a decrease largely attributable to decline in the disease in males younger than 59 years of age. The annual rate among patients older than 60 has remained unchanged since 1994.[284] The decline in the younger male population with PCNSL reflects the advent of effective antiretroviral therapy and a declining incidence of PCNSL in the HIV-infected population.[285] This chapter discusses PCNSL and its treatment in the immunocompetent population.

Clinical Diagnosis and Staging

The most common clinical presentation is one of progressive focal symptoms. Seizures also may occur. Less commonly, progressive cognitive decline without focal symptoms leads to the diagnosis. Several variant clinical presentations are possible in the immunocompetent population: primary ocular, meningeal, or relapsing-remitting disease; intravascular malignant lymphomatosis with stroke-like onset; or

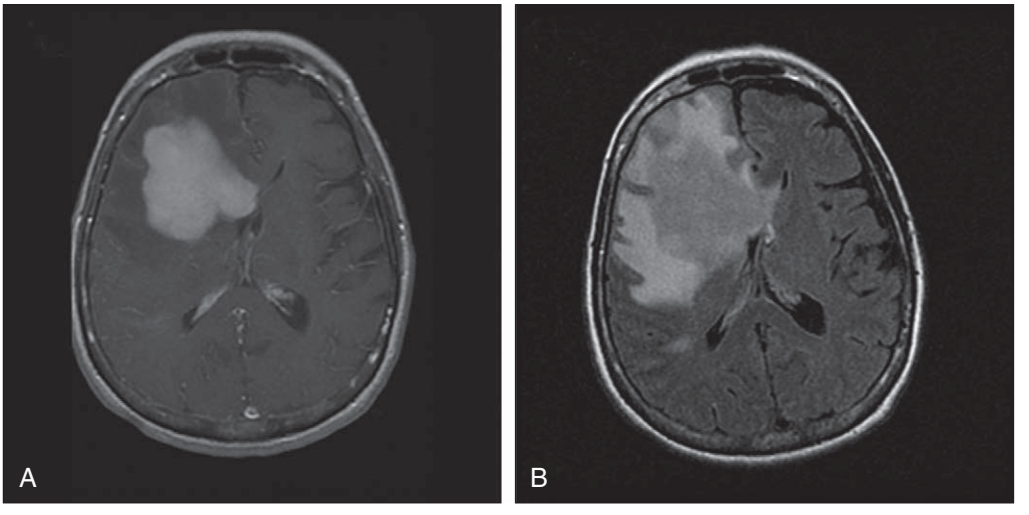


Figure 70-16 • Central nervous system lymphoma seen on magnetic resonance imaging. **A,** T_1-weighted post-gadolinium axial image shows a homogeneously enhancing frontal mass compressing the ventricles. **B,** Corresponding fluid-attenuated inversion recovery (FLAIR) image shows extensive peritumoral edema.

neurolymphomatosis with both peripheral and CNS involvement. Considerations in the differential diagnosis for PCNSL include high-grade glial tumor, CNS metastases, neurosarcoidosis, and tumefactive multiple sclerosis. Spinal cord PCNSL is very rare. Ocular lymphoma may be the first manifestation of the disease or its relapse. Patients with ocular lymphoma have a 50% to 80% chance of developing cerebral lymphoma.

Initial evaluation of patients with suspected PCNSL should include a thorough physical examination to exclude possible extraneural sources of lymphoma. Neurologic evaluation is directed at clarification of the extent of CNS disease. Extraneural sites are uncommon in patients without prior known lymphoma, and extensive abdominal and pelvic studies usually are not warranted. Chest x-ray studies should be performed, and blood tests should include a complete blood count (CBC) and liver function tests, as well as HIV testing. Gadolinium-enhanced spinal MRI should be performed, because bulky nodular disease sometimes can be seen in the leptomeninges.

Ophthalmologic consultation for slit-lamp examination is a critical part of the workup, because up to 10% to 15% of patients with PCNSL will have vitreous involvement at the time of diagnosis, and half of these will have no visual symptoms. Lumbar puncture should be performed if not contraindicated because of the intracranial mass location(s). Glucose and protein determinations, cell count, and flow cytometry should be performed. Recent reports of molecular diagnosis of PCNSL by the demonstration of monoclonality by amplification of the rearranged IgH genes by polymerase chain reaction (PCR) to the CDR-III region raises the possibility of definitive diagnosis even with few cells present in the CSF.[286] In several cases, however, the PCR analysis was negative even when conventional cytologic findings were suggestive of malignancy. In another study, monoclonal patterns in the CSF were found in 77% of biopsy-proven cases, with no false positives among control subjects.[287] At present, however, it is premature to base clinical therapeutic decisions on these promising early findings.

When the foregoing procedures fail to confirm the diagnosis, the surgical procedure of choice is a stereotactic brain biopsy. Aggressive surgical resection does not improve survival and may cause deterioration owing to the deep location of many PCNSLs. It is most important to try to *withhold corticosteroids* from patients during initial evaluation and surgical confirmation. Corticosteroids repair the blood-brain barrier and also have a direct cytolytic effect on B-cell lymphomas. Although the patient's clinical symptoms may abate with early institution of corticosteroids, with frequent nearly complete resolution of MRI-enhancing abnormalities, diagnosis will be compromised, and corticosteroids will have to be withdrawn in order to proceed with definitive biopsy confirmation. Recent interest has focused on immunohistochemical definition of morphologic markers of prognostic significance on the biopsy material (Fig. 70-17). Braaten and colleagues studied the expression of BCL-6 antigen in PCNSL and found that the presence of this antigen predicted a median survival of 101 months, compared with 14.7 months in patients without this marker.[288] Other groups of investigators, however, have found that the marker correlates with a negative prognosis, so clinical decisions cannot be made on the basis of early immunohistochemistry studies.[289]

Treatment

PCNSL is an aggressive disease for which median survival in immunocompetent patients is only 3 months without treatment. Increasing age and poor performance status are important negative prognostic variables. The goal of treatment is to eradicate both contrast-enhancing mass lesions and microscopic infiltration of brain, spine, leptomeninges, and vitreous. Treatment must be designed to maximize efficacy but also to minimize toxicity to the brain. Optimal treatment has not been established. The reason for the lack of standardized treatment protocols is the relatively small number of patients and the absence of a phase III randomized trial.[290] In the past 15 years, however, steady increases in median survival have been achieved in patients with PCNSL. Five-year survival rates on the order of 40% are now being reported by many groups of investigators, with median survival periods of 3 to 4 years.[291–293]

Radiation treatment alone led to median survival periods of 18 months in early clinical trials, with only 3% to 4% 5-year survival rates.[294,295] Chemotherapy was first used as an adjunct to radiation therapy more than 20 years ago after methotrexate was found to be effective in the treatment of systemic lymphoma. Twelve studies totaling more than 450 patients have established the efficacy of multiple chemotherapeutic regimens. Initially, most were used along with or after a course of whole-brain radiation therapy. The most commonly used drugs have been methotrexate, cytarabine, and cyclophosphamide. The first two agents have been administered intravenously and intrathecally. Extension of median survival periods for up to 4 years with combined regimens was achieved in the mid-1990s. The most frequently used combined regimen involved administration of intravenous methotrexate at doses ranging from 3.5 to 8 g/m^2 every 10 to 14 days for three cycles, followed by whole-brain radiation therapy to a dose of 40 to 50 Gy, with subsequent administration of cytarabine 3 g/m^2 for three cycles. DeAngelis and colleagues reported a 58% complete response rate, with additional 36% rate of partial responses and progression-free median survival for 24 months.[296] A worse prognosis was associated with age older than 60 years (survival for 50.4 months versus 21.8 months). With improved survival, however, severe delayed neural toxicity has developed in increasing numbers of patients. At 18 months, 15% to 50% of patients who had received combined radiation therapy and chemotherapy were found to have extensive white matter abnormalities, with consequent severe cognitive decline.[297–299] Age and pre-existing white matter disease due to hypertension may be relative risk factors.[295,300] This complication typically begins from 4 months to several years after treatment.[297] Recognition of the serious sequelae of

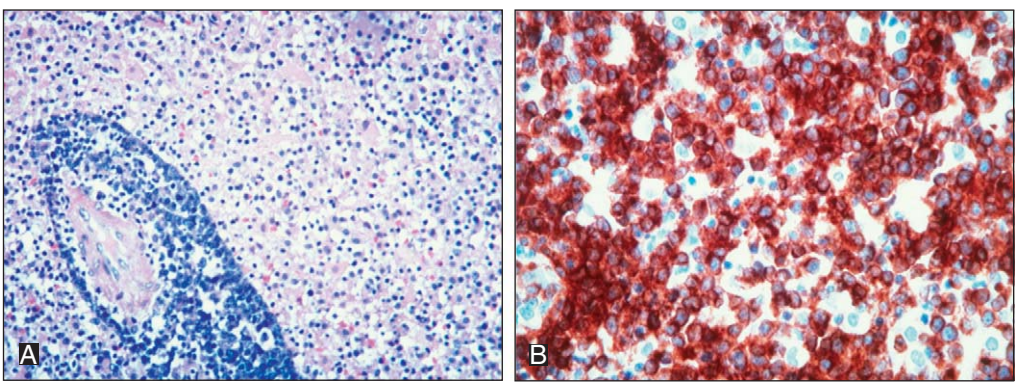


Figure 70-17 • Central nervous system lymphoma: histologic features. **A,** High-grade B-cell lymphoma with dense perivascular lymphocytic cuffing. (Hematoxylin and eosin staining.) **B,** Dense staining with CD20 (a B-cell marker) in the same specimen as in **A.**

combined radiation therapy and chemotherapy led to attempts to provide chemotherapy as the sole modality for treatment of newly diagnosed PCNSL. Initial response rates to chemotherapy vary from 50% to 100%, with duration of response between 12 and 44 months. Typical of the successes of many clinical trials are the results of Cher and colleagues, who reported complete responses in 17 of 19 patients receiving methotrexate alone, with an event-free median survival period of 32 months and overall survival period of 53 months.[301] Therapeutic levels of methotrexate can be achieved in the CSF after intravenous drug administration, making it possible to achieve clearance of malignant cells from the CSF without intrathecal administration.[302]

Attempts to improve on the results of methotrexate have included a variety of other multidrug chemotherapy regimens. Standard regimens effective in the treatment of comparable systemic non-Hodgkin's lymphomas (CHOP, CHOD, or MACOP-B) are not effective for PCNSL.[303–306] Attempts to disrupt the blood-brain barrier with hyperosmolar intra-arterial mannitol do not provide additional survival benefit beyond that achieved with intravenous methotrexate-based regimens.[307]

Many neuro-oncologists, therefore, have concluded that high-dose methotrexate should be offered to all patients as the first-line agent for treatment of PCNSL.[308] However, there are dissenting opinions. Herrlinger and colleagues recently reported only a 29.7% complete response rate with intravenous methotrexate while 37.8% of their patients progressed, and they revisit the question of whole brain radiation therapy as a first-line treatment for PCNSL.[309] Most centers, however, have based their therapy on methotrexate regimens. Long-term follow-up of patients who achieved durable remissions for more than 1 year suggests that chemotherapy alone is associated with a low risk of neurotoxicty even in the elderly, although MRI may show significant areas of clinically asymptomatic leukoencephalopathy.[310–312] The neuropsychological outcome after chemotherapy alone for primary CNS lymphoma is quite good, whereas increasing numbers of studies document progressive dementia, sometimes with gadolinium-enhancing lesions on MRI, as early as several months after combined-modality treatment.[313–315] Autopsy studies have confirmed not only widespread "pan-brain" infiltrative lymphoma but extensive vascular changes and leukoencephalopathy in patients who received radiation with or without chemotherapy.[316]

The following recommendations apply to immunocompetent patients only. The goal of treatment is to achieve a complete response while avoiding irradiation of normal brain. Patients with AIDS-related PCNSL require individualized treatment based on their immune status and presence of concurrent infections.[317] Transplant recipients similarly require an initial attempt at reduction of immunosuppression, and their treatment also must be tailored to the extent of organ dysfunction due to the primary disease process and concurrent therapy.

No firmly established dose for methotrexate has been confirmed; doses in excess of 3.5 g/m^2 have been shown to achieve satisfactory CSF drug levels. Figure 70-18 presents an algorithm for the diagnosis and management of PCNSL at the Hospital of the University of Pennsylvania; the recommended approach to management of these

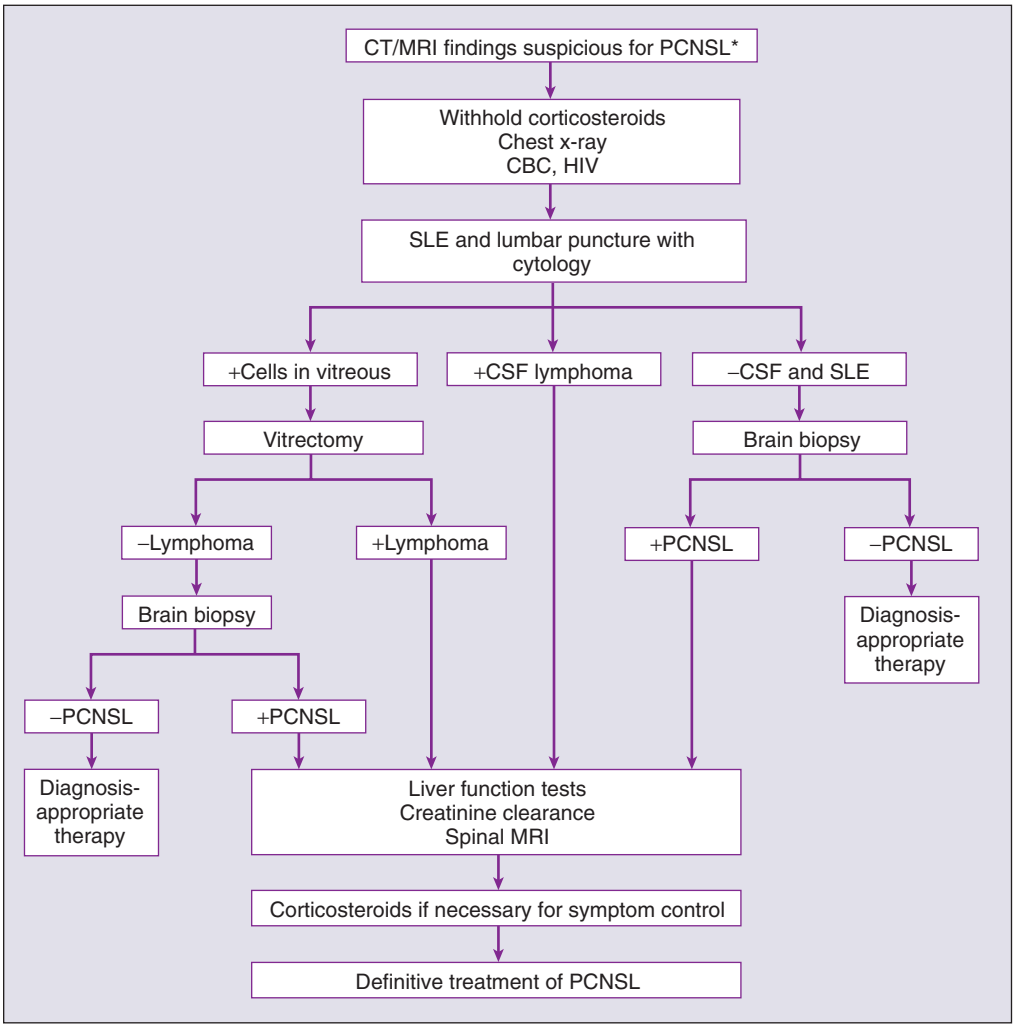


Figure 70-18 • Algorithm for diagnosis and management of primary central nervous system lymphoma (PCNSL) at the University of Pennsylvania. CBC, complete blood count; CSF, cerebrospinal fluid; CT, computed tomography; HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; SLE, slit-lamp examination. *Enhanced scan demonstrating periventricular lesions with homogeneous enhancement.

Box 70-2. MANAGEMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA AT THE UNIVERSITY OF PENNSYLVANIA

- Primary central nervous system lymphoma (PCNSL) is a non-Hodgkin's B cell lymphoma arising in the brain, leptomeninges, spinal cord, or eyes. It should be regarded as a whole-brain disease; it rarely spreads outside the nervous system.
- Optimal treatment of PCNSL is not yet fully established, but experience acquired during the past decade with various combinations of radiation therapy and chemotherapy suggests that initial induction treatment should be attempted with a methotrexate-based intravenous chemotherapy regimen and that concurrent intrathecal chemotherapy is not necessary. Median survival times longer than 40 months have been reported with methotrexate monotherapy, with significantly less cerebral white matter toxicity and its clinical correlate of cognitive decline, than seen in earlier protocols that included cranial irradiation.
- Intravenous methotrexate 8 g/m^2 every 14 days for up to 8 cycles is used for induction therapy, followed by 11 monthly cycles of methotrexate at the same dose in patients in whom a complete response is attained. Leucovorin rescue also is given, and concurrent corticosteroids and antiepileptic drugs as indicated are prescribed.
- Adequate delivery of chemotherapy to microscopically infiltrated areas of brain protected by the blood-brain barrier remains a significant challenge, and recurrence at multiple cerebral sites remains a problem for which effective therapy remains to be developed.
- Retreatment of a prior complete responder at relapse with the foregoing intensive methotrexate regimen is feasible. Alternatives include whole-brain radiation therapy, cytarabine, and investigational regimens using temozolomide or rituximab.

tumors is summarized in Box 70-2; and Figure 70-19 presents an algorithm for treatment of these tumors. Patients with PCNSL receive methotrexate 8 g/m^2 every 14 days for up to 8 cycles. The calculated dose is diluted in 500 mL of 5% dextrose in water (D_5W) and given intravenously over a 4-hour period. Patients achieving a complete response will receive 2 additional doses of methotrexate at 14-day intervals, followed by 11 monthly doses of methotrexate 8 g/m^2 so long as a complete response is maintained. MRI scans are obtained monthly during induction therapy and at 3-month intervals during maintenance therapy. The methotrexate protocol involves close clinical monitoring, adjustment of intravenous fluid, and calcium leucovorin rescue, in addition to frequent monitoring of urine pH, renal function, and methotrexate levels.

Contraindications to methotrexate therapy include allergy to methotrexate; inability to achieve adequate hydration because of cerebral edema, or cardiac or pulmonary problems; and concurrent immunosuppressive treatment. Patients should not have received prior cranial irradiation. Patients with renal dysfunction resulting in a creatinine clearance of less than 50 mL/min or serum creatinine level greater than 2 mg/dL should not receive methotrexate. Patients with significant ascites or pleural effusions may experience delayed methotrexate clearance because of third space accumulation.

Calcium leucovorin rescue therapy should begin 24 hours after the *start* of methotrexate infusion. The dose is adjusted according to methotrexate levels. Any dose of leucovorin greater than 50 mg should be given intravenously. If the plasma concentration of methotrexate at 24 hours is greater than 10^{-5} M, 100 mg/m^2 of leucovorin is given intravenously every 6 hours until rescue is achieved and continued at 25 mg intravenously or orally every 6 hours until the methotrexate plasma concentration is less than 10^{-7} M. In most patients, the methotrexate concentration clears to this level by 72 hours after the infusion.

Patients with an established PCNSL diagnosis may receive concurrent corticosteroid therapy to alleviate symptoms. Concurrent use of salicylates or other nonsteroidal anti-inflammatory drugs or sulfonamide medications is prohibited for at least 1 week before the initiation of methotrexate therapy. Many patients with PCNSLs will remain on corticosteroids for extended periods. The combination of corticosteroids and methotrexate may lead to a low CD4$^+$ count, and

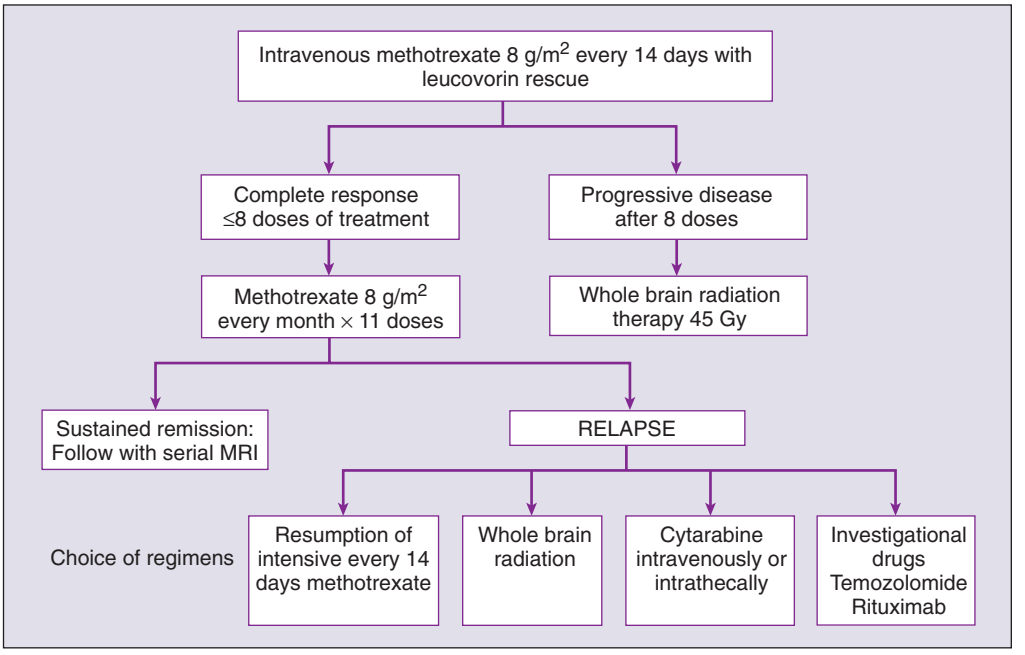


Figure 70-19 • Algorithm for definitive treatment of primary central nervous system lymphoma. MRI, magnetic resonance imaging.

these patients will be at risk for *Pneumocystis jiroveci* pneumonia. Like patients with other brain tumors, patients with PCNSL should receive prophylaxis with trimethoprim-sulfamethoxazole two or three times per week, with discontinuation of this drug 1 week before institution of methotrexate therapy.[318] Concurrent AED therapy is acceptable, and management of nausea associated with chemotherapy does not differ in this population from that for other patients receiving comparable regimens.

The management of progressive or recurrent PCNSL is not yet well established. Age and performance status of the patient must be taken into account. In general, greater than 25% enlargement of previous areas of gadolinium contrast enhancement, the appearance of new lesions, or the appearance of malignant cells in the CSF, vitreous, or, rarely, elsewhere in the body constitutes treatment failure. Cher and colleagues have reported that for patients who have completed their maintenance therapy, return to a more intensive methotrexate dosage regimen may lead to a second complete response.[301] For patients who have progressed through therapy, other chemotherapeutic agents such as cytarabine given intravenously or intrathecally may be considered. At relapse or in the case of failure to achieve complete response after 8 cycles of methotrexate, many treating physicians would consider palliative radiation therapy. The immediate palliation of progressive signs and symptoms is a realistic goal but must be weighed against the possibility that survival will be extended enough to allow emergence of late cognitive neurotoxicity. At most centers, whole-brain irradiation to 40 to 45 Gy in 20 doses is given over 4 to 5 weeks.

After initial diagnosis, surgical intervention usually has little place in treatment. The need for intrathecal chemotherapy, however, may mandate placement of an Ommaya reservoir. Development of communicating hydrocephalus with or after treatment of meningeal lymphoma may require shunting.

Parenchymal treatment failure is the most common pattern of relapse. Ocular, meningeal, and late rare extra-CNS relapses (breast, abdominal wall, bone, lymph nodes) have been described and may be seen with increasing frequency as patients survive longer. Temozolomide is under investigation as an agent for treatment of progressive PCNSL. Rituximab, a monoclonal antibody against the B cell-specific CD20 antigen, has been demonstrated to be effective against various non-Hodgkin's lymphomas, but CSF drug levels attained with intravenous therapy are not high.[319] Attempts to circumvent this problem have involved intraventricular administration through an Ommaya reservoir, with some early reports indicating total clearing of tumor cells with leptomeningeal lymphoma.[320] Whether rituximab will clear parenchymal masses is not clear. Intensive chemotherapy followed by hematopoietic stem cell rescue using a regimen of cytarabine and etoposide has been reported to give a complete response rate of 70%, with a median progression-free survival period of 3 years.[321] Several of the patients in the reported study, however, had intraocular lymphoma only.

MENINGIOMA

Clinical and Pathologic Considerations

Meningiomas account for approximately 30% of all intracranial tumors (see Table 70-1). The male-to-female ratio is 1 : 2, with the incidence increasing with age and reaching a peak in the seventh decade.[322] These tumors arise from arachnoidal cells in the meninges, not the brain parenchyma; therefore, they are extra-axial. They produce signs and symptoms by compressing normal tissues. The locations of meningiomas in two large series are shown in Table 70-10.[322,323] The specific signs and symptoms depend on the anatomic location of the meningioma. For example, meningiomas arising from the cerebral convexity can cause altered mentation and seizures, whereas those arising from the suprasellar region are likely to cause loss of vision, bitemporal hemianopia, and optic atrophy.

Table 70-10 Meningiomas: Distribution by Anatomic Location

	FREQUENCY (%*)	
Tumor Location	**Series 1***	**Series 2†**
Convexity	34	21
Parasagittal	22	17
Sphenoid ridge	17	16
Lateral ventricle	5	—
Tentorium	4	—
Cerebellar convexity/posterior fossa	5	14
Parasellar	3	12
Intraorbital	2	2
Cerebellopontine angle	2	—
Olfactory groove	3	10
Foramen magnum	1	—
Clivus	1	—
Spine	—	8
Other	1	—

*Of 179 cases reported by Rohringer and associates[322]; this series included only cases of intracranial meningiomas, none of the spine.

†Of 225 cases reported by Mirimanoff and coworkers.[323]

Numerous potential etiologic agents for meningiomas have been investigated, including radiation, trauma, viruses, occupational exposure, diet, and exposure to sex hormones (reviewed by Longstreth and colleagues[324]). Only ionizing radiation, however, has been strongly implicated in the pathogenesis of these tumors—for example, after scalp irradiation for tinea capitis (as discussed previously under Epidemiology).[9] Some relationship with breast cancer may exist, because the likelihood of developing a meningioma after developing breast cancer, or breast cancer after meningioma, is higher than in the general population.[325]

Deletions of chromosome 22 are frequent in meningiomas. The likely target of this chromosomal deletion is the *NF2* gene, which is mutated in patients with neurofibromatosis type 2 (NF-2). One of the tumor types commonly seen in these patients is meningioma.[326] The *NF2* gene also appears to have an important role in the pathogenesis of sporadic meningiomas. One study found *NF2* mutations in 60% of sporadic meningiomas, all of which had lost one copy of chromosome 22.[327] However, 40% of meningiomas have neither allelic loss of chromosome 22 nor *NF2* gene mutation; therefore, a second tumor suppressor gene probably is linked to the development of meningiomas.

Grossly, meningiomas appear as rounded masses, well circumscribed in contour, with a well-defined dural base that can be easily separated from the underlying brain tissue (Fig. 70-20). Often these tumors extend into the adjacent bone. Histologically, several different subtypes of benign meningiomas are recognized, including syncytial, fibroblastic (fibrous), transitional (mixed), psammomatous, microcystic, and papillary; however, these distinctions carry little prognostic significance.[169] Of more importance prognostically is whether the meningioma is benign, which it is in 90% of the cases.[322] Features of atypical meningiomas are focal isolated necrosis, prominence of nucleoli, and mitotic figures with high cell density.[169] Malignant meningiomas are characterized by invasion into adjacent normal brain tissue. In one large study based on data from the U.S. National Cancer Data Base (NCDB), the overall 5-year survival rates in patients with benign, atypical, and malignant meningiomas were 70%, 75%, and 55% respectively.[328]

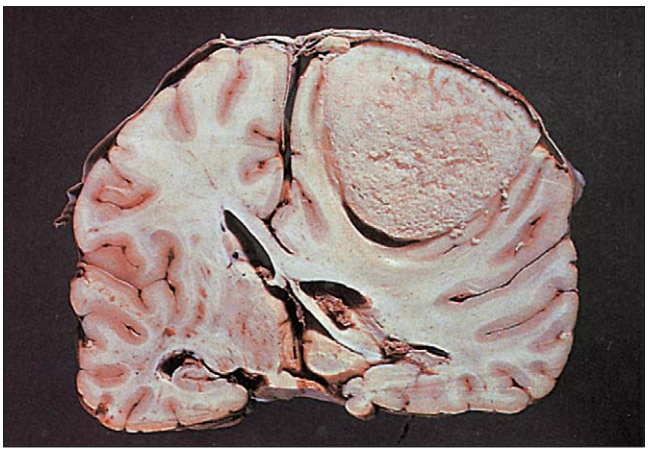


Figure 70-20 • Meningioma: gross specimen. A large-convexity meningioma severely displaces the underlying tissue downward and laterally, creating a midline shift and resulting in marked ventricular compression. (From Maher EA, McKee AC: Neoplasms of the central nervous system. In Skarin AT [ed]: Dana-Farber Cancer Institute Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 420.)

Meningiomas have a distinctive appearance on radiologic studies. On MRI, most meningiomas are isointense with gray matter on T_1-weighted scans and enhance intensely with gadolinium[329] (Fig. 70-21). Peritumoral edema is evident in 60% of meningiomas, and associated bony changes, either destruction or hyperostosis, are seen in 20%. The bony changes are better visualized on CT scans than with MRI.[329] Within the tumor may be seen calcifications, central necrosis, or pseudocysts.

Surgery and Conventional Radiation Therapy for Meningiomas

In a classic paper describing the outcome in 225 patients with meningiomas treated with surgery as the sole modality at Massachusetts General Hospital, Mirimanoff and associates found progression-free survival rates of 93%, 80%, and 68% at 5, 10, and 15 years, respectively, for those who underwent a total resection versus 63%, 45%, and 9% for those who underwent a subtotal resection ($P < 0.0001$).[323] In general, lower rates of progression were seen with sites associated with higher resectability rates. For example, meningiomas in the convexity, 96% of which underwent total resection, had a 5-year recurrence or progression rate of 3%, versus 34% for lesions in the sphenoid ridge, which had only a 28% rate of total resection. These results suggested that surgery alone was inadequate therapy for meningiomas if total resection could not be achieved. In a subsequent study from Massachusetts General Hospital, Miralbell and coworkers reported on 17 patients who underwent subtotal resection of a meningioma followed by radiation therapy.[330] Their 8-year progression-free survival rate was 88%, which was much better than the 48% rate calculated for the cohort of patients with subtotal resections who did not receive postoperative radiation.

Another retrospective study from the University of California at San Francisco reached similar conclusions regarding the improvement in local control with postoperative radiation therapy in patients who have undergone a subtotal resection.[331] This series included mostly patients with benign meningiomas. A much poorer outcome was observed for patients with malignant meningiomas than for those with benign meningiomas (5-year progression-free survival rate of 89%, versus 48%; $P = 0.001$).[331]

The foregoing studies all have used conventional fractionated radiation therapy, usually to doses ranging from 50 to 60 Gy of radiation via conventional fractionation and delivery techniques. Most investigators today would recommend approximately 54 Gy for benign meningiomas after incomplete resection and up to 60 Gy for meningiomas that have atypical or malignant features.



Figure 70-21 • Meningioma. Axial T_1-weighted post-gadolinium magnetic resonance image shows an extra-axial enhancing mass that compresses the underlying brain tissue.

Stereotactic Radiation Techniques for Meningiomas

Substantial experience with use of stereotactic techniques in the treatment of meningiomas has been accumulated. One of the centers with extensive experience with this technique is the University of Pittsburgh: In a long-term follow-up study of 99 patients with meningiomas treated with Gamma Knife stereotactic radiosurgery from 1987 to 1992 with 9 to 25 Gy (median marginal dose of 16 Gy), the total rate of failure was 11% at 63 to 120 months after stereotactic radiosurgery.[332] A majority of meningiomas showed a decrease in size by MRI with time. At years 4 to 6, 69% of cases showed a decrease in size by MRI scan; by years 8 to 10, this number had increased to 88%.

The Mayo Clinic and the Brigham and Women's Hospital also have reported rates of local control on the order of 89% in benign meningiomas with use of Gamma Knife- and linear accelerator-based stereotactic radiosurgery.[333,334] Follow-up remains short, however, with a median duration of 31 to 40 months. Furthermore, in both of these series, patients with atypical or malignant features did poorly. In the Mayo Clinic series, the 5-year local control rates were 93%, 68%, and zero for benign, atypical, and malignant meningiomas, respectively ($P < 0.0001$). Despite the goal to deliver an extremely conformal dose, stereotactic radiosurgery can cause significant complications. Rates of complications, often involving cranial nerves, have been reported in the 5% to 13% range.[332–334] With the reduction in radiation dose used to treat meningiomas, however, this complication rate has decreased.

A large experience has been reported for use of stereotactic radiosurgery for treatment of cavernous sinus meningiomas. Because of their location, surgical resection can cause significant complications, particularly cranial nerve morbidity and resulting extraocular muscle paralysis.[335] A number of institutions have reported high local control rates, in the 91% to 98% range, using marginal doses that typically range from 12 to 18 Gy, but with very short follow-up (median, 2 to 3 years).[336–338] The current standard dose delivered with stereotac-

tic radiosurgery or Gamma Knife for treatment of these tumors is a marginal dose of 14 Gy. Furthermore, cranial nerve V appears to be sensitive to single high-dose fractions, because the incidence of trigeminal nerve dysfunction has ranged from 4% to 11% in these series when higher doses are used.

In an effort to decrease late effects, fractionated stereotactic radiotherapy (FSRT) also has been used to treat meningiomas. At the University of Heidelberg, a dose of 56.8 Gy was given in 1.8-Gy daily fractions, delivered using a relocatable headframe, for treatment of large base-of-skull meningiomas.[339] At a median follow-up time of 35 months, the 5-year progression-free survival rate was 94% for 180 patients with benign meningiomas but 78% for those with atypical features. Another instance in which the fractionated technique has been used instead of conventional stereotactic radiosurgery is for treatment of optic nerve sheath meningiomas, because of the potential risk of optic nerve injury with a single large dose of radiation. One group of investigators reported using FSRT with 50 to 54 Gy in 1.8-Gy fractions to treat these tumors.[340] Of 22 optic nerves with vision before FSRT, 20 nerves (92%) demonstrated preserved vision, and 42% manifested improvement in visual acuity and/or visual field at follow-up.

A nonrandomized comparison of conventional (nonstereotactic) fractionated radiotherapy versus Gamma Knife radiosurgery for selected patients with cavernous sinus meningiomas was reported by Metellus and coworkers.[341] Thirty-eight patients received fractionated radiotherapy, and 38 had Gamma Knife radiosurgery. Both groups fared well, with progression-free survival rates of 94.7% and 94.4%, respectively. Permanent morbidity was seen in 2.6% of patients in the first group and in none in the second group. These results suggest that in selected patients, Gamma Knife radiosurgery can be performed with little late morbidity.

In summary, numerous reports have described the use of stereotactic techniques for delivering radiation to meningiomas as an alternative to surgery or after subtotal resection. In view of the long natural history of these tumors, however, much longer follow-up will be needed to adequately evaluate these modalities.

Medical Therapy for Meningiomas

A number of agents, including hydroxyurea, interferon-α, tamoxifen, and mifepristone (RU-486), have been reported to be provide modest benefit in patients with recurrent meningiomas.[342] Isolated reports have indicated reduction in the size of meningiomas with hydroxyurea[343] and RU-486.[344,345] Other studies have not always reported regression, although in some cases, treatment with either of these agents appears to halt the growth of the tumor or to ameliorate the patient's symptoms, or both.[346–348] Box 70-3 summarizes the recommended approach to management of meningiomas.

Box 70-3. MANAGEMENT OF MENINGIOMAS

- Meningiomas are extra-axial tumors that arise from dura; common locations are cerebral convexity, parasagittal falx, and sphenoid ridge.
- A very long natural history is characteristic, mandating prolonged follow-up.
- Greater than 90% of these tumors are benign; the remainder exhibit atypical histologic features or frank invasion of brain parenchyma.
- Primary treatment is surgical, if feasible.
- Radiation therapy is reserved for tumors that are incompletely resected, recur after surgery, are inaccessible to surgical resection, or have atypical or invasive features.
- The standard radiation dose has been approximately 54 Gy for benign meningiomas and up to 60 Gy for those with atypical or invasive features.
- Stereotactic radiation therapy techniques have been used; however, follow-up is still short in these studies.
- Anecdotal reports exist of responses to medical therapy (hydroxyurea and antiestrogen and antiprogesterone agents).

PITUITARY ADENOMA

Clinical and Pathologic Considerations

Pituitary adenomas make up 10% to 15% of all intracranial tumors. They arise from the anterior lobe of the pituitary gland. The pituitary gland and stalk normally are isointense with brain on T_1-weighted MRI scans. The gland and stalk, however, intensely enhance after contrast administration because of the absence of a blood-brain barrier. Pituitary adenomas generally are seen as hypointense foci on T_1-weighted MRI scans and do not enhance with gadolinium.[349] Other abnormalities that can appear as a hypointense, nonenhancing lesion in the pituitary include pars intermedia cysts, metastases, infarctions, and epidermoid cysts and abscesses.

Asymptomatic pituitary adenomas were found in 1.5% to 27% of autopsy cases and in 10% of normal adult volunteers by MRI scanning. Symptomatic pituitary adenomas are much less common. These tumors can give rise to signs and symptoms through secretion of hormones or by compression of nearby structures, causing neurologic disturbances such as headaches, bilateral bitemporal hemianopia from compression of the optic chiasm, and cranial nerve palsies from invasion into the cavernous sinus. Adenomas also can cause hypopituitarism from compression of the pituitary stalk.

Many investigators have studied the genetics of pituitary adenomas. Patients with multiple endocrine neoplasia type 1 (MEN-1) are predisposed to developing pituitary adenomas as well as parathyroid and pancreatic islet tumors (reviewed by Thakker[350]). Anterior pituitary tumors occur in 30% of patients with MEN-1, most commonly prolactinomas but also nonfunctional and growth hormone (GH)- and adrenocorticotropic hormone (ACTH)-secreting tumors. *MEN1* mutations are not commonly found in sporadic pituitary adenomas; however, one gene that is mutated in a substantial proportion of pituitary adenomas is that encoding the α subunit of the guanosine triphosphate (GTP)-binding protein Gs.[351] Mutation of this gene leads to constitutive activation of the cyclic adenosine monophosphate (cAMP) pathway. The mutated form of this gene is called *gsp* and is present in 10% to 40% of GH-secreting adenomas.[351]

At one time, pituitary adenomas were classified according to their staining characteristics (basophilic, eosinophilic, chromophobe). Today, however, they are classified according to secretion of hormones. In one series of 684 patients with pituitary adenomas who underwent surgery, prolactinomas were the most common (43%), followed by nonsecreting tumors (30%)[352] (Table 70-11). Thyroid-stimulating hormone (TSH)-secreting tumors were rare in this series (2 of 684), as they are in others.

Adenomas also are classified on the basis of size as either macroadenomas (greater than 1 cm in diameter) or microadenomas. Nonsecreting adenomas generally are macroadenomas at the time of diagnosis because they usually come to medical attention fairly late, when they are causing neurologic symptoms due to mass effect. The same is true for gonadotropin-secreting adenomas, which are inefficient producers and secretors of hormones. GH-secreting adenomas and prolactinomas in men often are macroadenomas at the time of diagnosis, probably because their clinical effects evolve over time and often are ignored early on. Because the same pituitary stem cell can produce both GH and prolactin, many patients have adenomas that secrete both hormones. Prolactinomas in women and ACTH-secreting adenomas usually are microadenomas at diagnosis. Prolactinomas in women commonly cause amenorrhea and galactorrhea. ACTH-secreting adenomas often cause dramatic clinical signs and symptoms associated with hypercortisolism that rapidly bring patients to medical attention. ACTH-secreting pituitary adenomas also can

Table 70-11 Pituitary Adenomas: Clinical Presentation by Endocrine Secretion

Type	Frequency* (%)	Signs and Symptoms	Typical Size at Diagnosis
Prolactinoma	43	*Women*: Amenorrhea, galactorrhea	*Women*: Microadenoma
		Men: Impotence, hypopituitarism	*Males*: Macroadenoma
Nonsecreting gonadotropin	30	Hypopituitarism	Macroadenoma
GH-secreting	17	Gigantism in children	Macroadenoma
		Acromegaly in adults	
ACTH-secreting	7	Cushing's syndrome	Microadenoma
		Nelson's disease	
TSH-secreting	<1	Hyperthyroidism	Can be microadenoma; often macroadenoma owing to delayed diagnosis

ACTH, adrenocorticotropic hormone; GH, growth hormone; TSH, thyroid-stimulating hormone.
*Among 684 cases reported by Oruckaptan and colleagues.[352]

be seen in approximately 25% of patients who have undergone bilateral adrenalectomies for Cushing's syndrome secondary to loss of negative feedback control by cortisol on the hypothalamus. In a majority of these patients, hyperpigmentation develops as a result of ACTH hypersecretion. This is termed *Nelson's syndrome*, and in this setting the pituitary tumors usually are very large and often are difficult to completely resect.[353]

Surgery for Pituitary Adenomas

The current therapy for most pituitary adenomas, excluding prolactinomas, involves surgery. For nonsecreting tumors, which tend to be large and manifest with neurologic signs and symptoms, surgery offers rapid decompression of the visual pathways. For hormonally active tumors, surgery leads to a rapid drop in hormone secretion. The current preferred technique is the transsphenoidal approach, which was popularized by Harvey Cushing in the early 1900s. It then fell out of favor but regained popularity in the 1960s.[354] Transsphenoidal resection is fairly safe, with a mortality rate less than 1%.[355] The most common complications arising from this surgery are nasal septum perforation, anterior pituitary insufficiency, postoperative diabetes insipidus (which usually is transient), and CSF leak sometimes leading to meningitis.[355] Much rarer complications include carotid artery injury and loss of vision. A recent variation of this approach has been to use an endoscope through the nostril to gain access to the pituitary transsphenoidally, thereby eliminating the need for conventional skin incisions and further improving postoperative recovery.[356] The transsphenoidal approach is used in more than 90% of pituitary operations. It is appropriate for resection of microadenomas, enclosed macroadenomas with symmetrical suprasellar extension, and even some invasive adenomas. If the pituitary adenoma is very fibrous or exhibits significant extension into the middle cranial fossa, however, a transsphenoidal resection may be impossible, and it may be necessary to perform an intracranial operation.

The success of surgery alone in curing adenomas depends on the size of the tumor. In a review of transsphenoidal resection for GH-secreting adenomas, in most series hormonal normalization was seen in 67% to 91% of microadenomas but in only 48% to 65% of macroadenomas.[357] ACTH-secreting adenomas, which generally are less than 1 cm at diagnosis, show a normalization of hormones following resection in 75% to 96% of cases in most surgical series (reviewed by Ludecke and coworkers[358]). TSH-secreting adenomas are rare compared with other pituitary adenomas, and when diagnosed they are often large. Normalization of TSH after resection of these tumors has varied widely in different series, ranging from 33% to 86%.[359]

The results of surgery for hormone-inactive adenomas are harder to document because the criteria for surgical success are less well defined. Clinical improvement can be seen even without total removal of the tumor. Series in which CT or MRI scans were performed a few months after surgery show a wide range of gross complete resection rates for these tumors, from 28% to 84%.[360–362] A review of several surgical series showed that the likelihood of normalization of visual fields after surgery ranged from 16% to 53% and that visual field improvement occurred in 26% to 70% of cases.[363]

Medical Therapy for Pituitary Adenomas

Although surgical resection and radiation therapy are effective therapies for prolactinomas, the primary treatment for these tumors currently is medical.[364] This is due to the availability of drugs that can suppress prolactin secretion and shrink these tumors. Surgical resection and radiotherapy are still used for the treatment of prolactinomas in the minority of patients who fail to respond to drugs or who cannot tolerate them.

Clinical manifestations of prolactinomas differ between the sexes. In premenopausal women, oligomenorrhea or amenorrhea and galactorrhea are extremely common. Infertility also may be the presenting sign, and women often have decreased libido. Estrogens have a marked stimulatory effect on prolactin synthesis and secretion; therefore, pregnancy can stimulate the growth of these tumors. In men and postmenopausal women, these tumors generally are asymptomatic until they are large enough to compress nearby structures, causing signs and symptoms such as visual deficits, headaches, and panhypopituitarism. Chronic hyperprolactinemia leads to decreased libido and impotence in 90% of men. Galactorrhea is uncommon in men but can occur in 10% to 20% of cases. The problems with reproductive and sexual function are due to inhibition of pulsatile gonadotropin secretion.

Secretion of prolactin by the lactotroph cells in the anterior pituitary gland is negatively regulated by dopamine produced by the hypothalamus. Therefore, dopamine agonists such as bromcriptine stimulate dopamine secretion by the hypothalamus and inhibit prolactin secretion by the lactotrophs. Administration of bromocriptine has been the standard therapy for prolactinomas for decades. This agent has been shown to decrease tumor size and normalize prolactin levels in 70% to 90% of patients. Bromocriptine also restores ovulation and menses and improves visual fields in a similar percentage of cases. Tumor shrinkage and decrease in prolactin levels can take anywhere from days to weeks to months to occur. Unfortunately, the action of bromocriptine is reversible; therefore, when the drug is discontinued, regrowth of the tumor with increase in the prolactin

level usually is seen. Therefore, lifelong administration is the rule, and many patients can tolerate prolonged treatment for years. Bromocriptine has been used prophylactically during pregnancy to reduce symptomatic tumor enlargement. Of note, however, 10% to 20% of patients experience side effects such as nausea, vomiting, dizziness, postural hypotension, and headaches. In patients who have limiting toxicity with bromocriptine or whose tumor fails to respond to this drug, newer dopamine agonists such as lisuride, pergolide mesylate, cabergoline, and tergulide have been used with some success (reviewed by Nomikos and coworkers[365]).

A few drugs are now available for the treatment of endocrine hypersecretion in pituitary tumors other than prolactinomas. For GH-secreting adenomas, somatostatin analogs such as octreotide and lanreotide have been shown to reduce GH levels in more than 90% of patients, with almost complete suppression in half.[366] Synthetic agents that block GH binding to its receptor or growth hormone-releasing hormone to its receptors in the pituitary are being used experimentally. In general, these drugs are not being used for first-line therapy in patients with GH-secreting adenomas but rather are indicated in patients in whom surgery has been unsuccessful.

TSH-secreting adenomas often are very large at diagnosis, making complete surgical resection difficult. Because these tumors express somatostatin receptors, octreotide and lanreotide can decrease tumor size and decrease TSH secretion.[366]

Radiation Therapy for Pituitary Adenomas

Radiation therapy also is highly effective in controlling pituitary adenomas. Nowadays, however, it is rarely given as sole treatment for newly diagnosed pituitary adenomas. In contrast with surgery, radiation therapy will not result in a rapid reversal of neurologic signs and symptoms or a rapid drop in hormonal secretion. Radiation therapy usually is reserved for patients who either have residual disease after surgery or have a recurrence after surgery. Radiation therapy occasionally is used as the sole primary therapy in patients who have a medical condition that makes their tumor inoperable.

The overall 10-year control rate using radiation therapy is on the order of 85% to 95% based on a number of large retrospective series.[367–371] In a study from the University of Heidelberg, in 138 patients with pituitary adenomas who received radiation as initial therapy or after recurrence, the overall local control was 95% with a mean follow-up time of 6 years.[369] Likewise, in a study from the University of Florida with a median follow-up time of 9.2 years, the overall local control rate at 10 years was 93%.[367] Ninety-eight patients in this series had surgery and radiotherapy as initial therapy, and their 10-year local control was 95%. This was comparable to the 10-year local control rate of 90% for the 23 patients who had radiotherapy alone for newly diagnosed adenomas, but better than the 80% control rate seen in 20 patients who received radiation for a recurrence after their initial surgery ($P = 0.03$). Similar findings regarding improved local control in patients receiving surgery and radiation "up front" compared with those receiving radiation at recurrence were obtained from the Princess Margaret Hospital study that examined 160 patients with hormonally inactive pituitary adenomas.[368] Pituitary adenomas can occur in the pediatric population, although they are much less common than in adults. In one study in 11 patients aged 19 or younger with pituitary adenomas, treatment consisted of surgery plus radiation or radiation only.[372] At a median follow-up time of 15.6 years, only two had failed to respond to treatment.

In the foregoing studies, local control refers to lack of disease progression, clinically and radiologically. In many patients who have hormone elevations at the outset, however, complete normalization may not be achieved after radiation therapy. In the University of Heidelberg series, of 68 patients with hormonally active pituitary adenomas, 52% of patients showed some reduction in their hormonal overproduction, but only 38% demonstrated complete normalization.[369] Furthermore, in patients who had a response, it often took years, in some cases up to 9 years. A study from the Princess Margaret Hospital specifically analyzed data for 145 patients who received radiation for hormonally active pituitary adenomas.[370] The progression-free survival rate was 96% at 10 years; however, the actuarial long-term biochemical remission rate was only 40%. Radiation is thus highly effective in preventing pituitary adenomas from growing; however, it is far less effective in normalizing hormone levels in patients with hormonally active tumors.

Late Effects after Pituitary Irradiation

In the foregoing series, the median doses ranged from 45 to 50 Gy.[367–370] In the University of Heidelberg study, a statistically significant dose-response relationship was found in favor of a dose of 45 Gy or less.[369] One of the worrisome potential late effects of using higher total doses is the possibility of radiation-induced optic neuropathy. In some series, visual problems develop in a few patients after radiation, presumably as a result of optic nerve damage, but such complications are uncommon, ranging in frequency from 0.7 to 2%.[367,369,370] As discussed earlier (under "Adverse Effects after Irradiation of the Brain or Spine"), the risk of optic nerve-chiasm injury is dependent on both total dose and dose per fraction. At the doses commonly used to treat pituitary adenomas (45 to 50 Gy), the risk of radiation-induced optic neuropathy with standard fractionation (1.8 to 2 Gy per day) is very low but not zero.

Doses of 45 to 50 Gy to the pituitary gland carry a substantial risk of causing hypopituitarism. In patients who did not have hormonal deficiencies at the start, the risk of developing insufficiency of a given hormone ranged from 10% to 30% in the series discussed earlier.[367–370] It is likely that in half of all patients who received radiation doses of 45 to 50 Gy, deficiency of at least one pituitary hormone will develop 5 years after radiotherapy. This is an ongoing risk after radiation therapy, however, and can occur many years later; therefore, patients must be monitored indefinitely for this complication.

Second malignant neoplasms are always a concern in patients who receive radiation and who are expected to be long-term survivors. In an analysis of 334 patients with pituitary adenomas treated at the Royal Marsden Hospital with surgery and radiation therapy (median dose of 45 Gy), a secondary brain tumor (two astrocytomas, two meningiomas, one meningeal sarcoma) developed in 5 patients, for an actuarial risk of 1.3% at 10 years and 1.9% at 20 years.[373] The relative risk for developing a second tumor compared with the incidence in the normal population was 9.3. A report from the Princess Margaret Hospital presented similar conclusions. In a series of 306 patients with pituitary adenomas treated with irradiation, gliomas of the brain developed in 4 patients, with a latency of 8 to 15 years. The relative risk compared with risk in the normal population was 16, with an actuarial risk of 1.7% at 10 years and 2.7% at 15 years.[374]

Stereotactic Radiation Techniques for Pituitary Adenomas

A number of institutions have reported using stereotactic means of delivering radiation to pituitary adenomas, both in fractionated and single-dose regimens. Investigators have used FSRT with 45 to 50 Gy in 1.8-Gy daily fractions delivered using relocatable stereotactic headframes.[375,376] Stereotactic radiosurgery also has been used, with single fractions ranging from 10 to 27 Gy.[375–377] The local control rates using these techniques has been reported to be greater than 90%; however, the length of follow-up in these studies is too short to allow definite conclusions to be drawn.

The rationale for using single large doses is the contention that the interval to normalization of hormonal levels is shorter with this approach than with conventionally fractionated radiation therapy. Yoon and colleagues reported that 11 of 13 patients with prolactino-

Box 70-4. MANAGEMENT OF PITUITARY ADENOMAS

- Pituitary adenomas are extremely common as an incidental finding (in up to 10% of normal volunteers by magnetic resonance imaging screening).
- These tumors may become symptomatic, when the patient comes to medical attention, because of hormone secretion, compression of nearby structures causing neurologic symptoms, or compression of the pituitary stalk, leading to hypopituitarism.
- These tumors are classified by size as microadenomas (1 cm or less in diameter) or macroadenomas.
- Initial therapy for most prolactinomas is with a dopamine agonist (e.g., bromocriptine, lisuride, pergolide), which usually decreases prolactin levels and shrinks the tumor.
- Initial therapy for most other pituitary adenomas is transsphenoidal surgical resection, which is safe and leads to rapid reversal of neurologic signs and symptoms. Surgery normalizes hormone levels in most patients with microadenomas.
- Radiation therapy currently is reserved for treatment of residual disease or recurrence after surgery, or for patients who are not eligible for surgery because of medical reasons. In patients with elevated hormones, normalization of levels after radiation therapy may take years. A dose on the order of 45 Gy in 180-cGy daily fractions should offer good control with extremely low risk of optic neuropathy.

mas had normalization of their hormone level within 1 year.[377] Mitsumori and associates found that the average time to normalization with stereotactic radiosurgery was 8.5 months, versus 18 months with FSRT (45 Gy in 1.8-Gy daily fractions).[376] Pouratian and associates reported on 23 patients with prolactinomas that had failed to respond to medical and surgical treatment and then were treated with Gamma Knife radiosurgery.[378] Subsequently, a normal prolactin level was attained in 26%, by an average time of 24.5 months. Remission was significantly associated with the patient's being off a dopamine agonist at the time of irradiation. Box 70-4 summarizes the recommended approach to management of pituitary adenomas.

ACOUSTIC NEUROMA

Clinical and Pathologic Considerations

Acoustic neuroma has many other names; in addition to neuromas, these tumors also are referred to as neurilemmomas, neurinomas, neurofibromas, schwannomas, and nerve sheath tumors. They are benign tumors that most commonly originate from cranial nerve VIII, usually in the vestibular region of the internal auditory foramen, where the nerve acquires a Schwann sheath. For this reason, these tumors also are sometimes called *vestibular schwannomas*. Neuromas can affect other cranial nerves, such as the trigeminal nerve and nerves in the jugular foramen region; however, these are much less common than acoustic neuromas.[379,380]

Acoustic neuromas account for 8% to 10% of all primary intracranial tumors, generally affecting people in the fifth decade of life. These tumors characteristically grow very slowly. Early on, they are asymptomatic, but with enlargement, they lead to progressive hearing loss and tinnitus.[381] The hearing loss typically is in the conversational range. As the tumor expands and compresses cranial nerve VIII, it may cause vertigo and unsteadiness of gait. With growth into the cerebellopontine angle, cranial nerves V and VII may be compressed, resulting in otalgia, facial numbness, facial palsy, and change in taste. With continued growth, brainstem compression and obstruction of the fourth ventricle may develop, causing hydocephalus. Because signs and symptoms can arise insidiously, a progressive hearing loss and gait unsteadiness may evolve over years in some patients before the tumor is diagnosed.

Patients with NF-2 often have bilateral acoustic neuromas; in fact, this finding is diagnostic for NF-2.[326] Acoustic neuromas in patients with NF-2 contain mutations in the *NF2* gene and chromosome 22 deletions. Sporadic unilateral acoustic neuromas arising in patients without NF-2 also are associated with chromosome 22 deletion and *NF2* mutation.[382,383]

Surgery for Acoustic Neuromas

Traditionally, acoustic neuromas have been treated by surgical resection. A number of different approaches can be taken, including the suboccipital approach, the translabyrinthine approach, and the middle fossa approach.[384] Some centers strongly favor one approach over the others, but many surgeons make a decision on a case-by-case basis. The translabyrinthine approach is the only procedure that inherently sacrifices hearing in the course of the procedure; therefore, it generally is not used in patients who have some residual useful hearing.[385] Hearing preservation is possible but not guaranteed with either the suboccipital or middle fossa approach. In one series of patients who underwent a resection using the suboccipital approach with an attempt to preserve hearing, 18 of 46 (39%) patients who had good preoperative hearing maintained good hearing after surgery.[386] The middle fossa approach is indicated in patients who have useful hearing and have tumors entirely contained within the internal auditory canal. In one series using this approach, total tumor removal was achieved in 98% of the cases, with hearing preservation in 59%.[387] Approximately 89% of patients maintained normal or near-normal facial nerve function.

Catastrophic complications such as brainstem stroke, postoperative cerebellar hemorrhage, or death are rare after surgery for acoustic neuromas.[388] Two other serious complications that are more common are CSF leak, which can lead to meningitis, and cranial nerve VII palsy. Some surgical teams feel that CSF leak and damage to the facial nerve are more likely with the suboccipital approach than the translabyrinthine approach; however, both complications have been described with both approaches.[385,389] In an effort to decrease damage to the facial nerve, many surgeons routinely perform intraoperative electromyographic monitoring.[388] Persistent headaches that last for months to a year are more common after surgery using the suboccipital approach, presumably as a result of aseptic meningitis from contamination of the subarachnoid space with bone dust when the internal acoustic canal is drilled intradurally.[384]

Radiotherapy for Acoustic Neuromas

Radiation therapy often is effective in cases in which total resection cannot be performed. In a series from the University of California at San Francisco, postoperative radiation therapy (at a dose greater than 45 Gy) decreased the recurrence rate after subtotal resection from 46% (6 of 13 patients) to 6% (1 of 11 patients) ($P = 0.01$).[390] Radiation therapy also is effective in controlling acoustic neuromas that are not surgically resected. Proton beam therapy has been used to deliver single large radiation fractions to acoustic neuromas. In the Massachusetts General Hospital series, 68 patients received a dose of 12 Gy to the tumor margin. With a median follow-up time of 44 months, the 5-year actuarial control rate was 84%.[391]

Single large doses of radiation delivered using stereotactic radiosurgery also have been used. The University of Pittsburgh has accumulated one of the largest experiences with this approach. An analysis of their first 5 years of using Gamma Knife radiosurgery with a 12- to 20-Gy marginal dose showed a 98% local control.[392] Of patients with normal function of cranial nerves VII and V before radiosurgery, however, 15% and 16%, respectively, developed some dysfunction afterward. Furthermore, of patients with useful hearing before radiosurgery, only 47% maintained the same level of hearing. Other institutions also found high local control rates, along with

high rates of cranial nerve V and VII dysfunction, after single large stereotactic doses using either a Gamma Knife machine[393] or a linear accelerator.[394] On the basis of their initial results, the investigators at the University of Pittsburgh changed their policy by decreasing the marginal dose and using MRI scans for treatment planning purposes.[395] From 1992 to 1997, 190 patients underwent Gamma Knife radiosurgery delivering 11 to 18 Gy to the margin of the tumor (median dose, 13 Gy). With a median follow-up time of 30 months, the 5-year actuarial tumor control rate was 97%, and 71% of patients retained useful hearing. The 5-year rates for developing facial weakness and facial numbness were 1% and 2.7%, respectively.[395]

In order to potentially reduce late effects, a number of institutions have started using FSRT. Both hypofractionation (25 Gy in 5-Gy fractions, 30 Gy in 3-Gy fractions, 21 Gy in 7-Gy fractions)[396,397] and conventional fractionation with 54 to 58 Gy in 1.8- to 2-Gy fractions[398,399] or 36 to 44 Gy in 1.8-Gy fractions[400] have been used. Although the follow-up is very short in some of these series, the control rates have ranged from 97% to 100%, with a useful hearing rate ranging from 72% to 85% and low rates of cranial nerve V and VII dysfunction. Although the jury is still out on use of single-dose stereotactic radiosurgery versus FSRT for acoustic neuromas, the experience at Jefferson University Hospital strongly favors the latter. Patients have received treatment with either Gamma Knife stereotactic radiosurgery (12-Gy marginal dose) or FSRT (50 Gy in 2-Gy fractions) in a nonrandomized fashion. The rates of cranial nerve V and VII preservation were equally high in both groups (93% to 98%), as were the local control rates (97% or better). A significant difference, however, was found in the rates of serviceable hearing (33% for Gamma Knife stereotactic radiosurgery versus 81% for FSRT).

As indicated by the foregoing findings, radiation therapy can be a useful alternative to surgery to control the growth of acoustic neuromas. Undoubtedly, however, debate will continue regarding the merits of one treatment over the other, as well as the optimal radiotherapy technique. Although the previous discussion centered on the treatment of acoustic neuromas, some evidence indicates that SRS is effective in controlling the growth of trigeminal neuromas and alleviating trigeminal neuralgia, as either an alternative or adjunct to surgery.[401]

CEREBELLAR HEMANGIOBLASTOMAS

Clinical and Pathologic Considerations

Hemangioblastomas are low-grade vascular tumors that constitute 1% to 2% of intracranial tumors. They usually occur in the cerebellar hemispheres and vermis, although they can involve the pons, medulla, and spinal cord. Most cases occur sporadically, but 20% occur as part of the familial von Hippel-Lindau syndrome.[402] Patients with this syndrome have a germline mutation in the *VHL* gene. Tumors that these patients develop have sustained a mutation in the second *VHL* allele, leading to loss of VHL protein function and resulting in stabilization of the HIF-1α protein under normoxic conditions. Stabilization of HIF-1α leads to constitutive high levels of expression of target genes including VEGF (vascular endothelial growth factor) (reviewed by Kaelin[403]). For this reason, the tumors seen in patients with von Hippel-Lindau syndrome are highly vascular. Other abnormalities seen in these patients include retinal angiomas, renal cell carcinomas, and cysts involving many organs such as the pancreas, kidney, lungs, and liver. Pheochromocytomas also may develop in these patients, who often display erythrocytosis as a result of increased erythropoietin production. Sporadic hemangioblastomas, which occur in patients not suffering from von Hippel-Lindau syndrome, also contain mutations in the *VHL* gene in at least 20% of cases.[404]

Patients with cerebellar hemangioblastomas often present in the third decade of life. Presenting manifestations stem from cerebellar dysfunction, increased ICP, and involvement of nearby cranial nerves. These signs and symptoms include headaches, nausea, vertigo, diplopia, tinnitus, ataxia, and poor coordination.[405] The lesion is well visualized by CT scanning or MRI. Angiography, which generally is performed before surgery, shows the highly vascular nature of these tumors.

Histologically, hemangioblastomas show numerous capillary and sinusoidal channels lined with endothelial cells. A cystic component often is present; the cyst is filled with xanthochromic, proteinaceous fluid, with a vascular nodule in the cyst wall. In one series, 6 of 19 patients (32%) had a solid lesion without a cystic component.[406] Lesions of this type are more likely to originate in the brainstem.

Therapy for Cerebellar Hemangioblastomas

The primary therapy for most patients with these tumors is surgical resection, if this can be done safely. If a cyst is present, it is drained; then the solid component is dissected and removed. If the tumor involves the brainstem, however, surgery may be extremely risky, with the potential for massive hemorrhage or extensive postoperative edema leading to death.[406] Surgical resection historically has been associated with high local control rates. In one series, recurrence was noted in only 13 of 112 patients (12%) after surgery.[405] In 6 patients, disease recurred in the original tumor bed, after incomplete removal, and in 10 patients, recurrence was in a different site or in the same site after gross total resection.

For patients with unresectable or incompletely resected hemangioblastomas or for those whose tumors are medically inoperable, radiation therapy usually is given. In a series from the Mayo Clinic, 27 patients received radiation treatment, 6 because of microscopic positive margins after surgery and 20 for gross residual disease.[407] In patients with gross residual disease, the rate of local control was 57% for those who received 50 Gy or more but only 33% for those receiving less than this dose. In four of the six patients with microscopic residual disease, this protocol achieved local control. For all 27 patients, the overall 15-year survival rate was 58%, and the relapse-free survival rate was 42%. Sung and associates also found that patients who received a higher dose (40 to 55 Gy) had a superior survival compared with those who received 20 to 36 Gy.[408] On the basis of these results, therefore, it would be reasonable to use approximately 50 Gy in patients requiring radiation therapy.

Radiosurgery has been used for cerebellar hemangioblastomas. In a study from three institutions, 38 hemangioblastoma lesions in 22 patients were treated stereotactically, with single fractions ranging from 12 to 20 Gy (median, 15.5 Gy).[409] The vast majority of these tumors had not undergone gross total resection. With a median follow-up time of 24.5 months, the 2-year actuarial overall survival rate was 88% and the 2-year progression-free survival rate was 86%.

CHORDOMAS AND CHONDROSARCOMAS INVOLVING THE BASE OF THE SKULL

Clinical and Pathologic Considerations

Chordomas constitute less than 0.1% to 0.2% of all intracranial tumors. They arise along the path of the primitive notochord, which stretches from the tip of the dorsum sellum to the coccyx. Fifty percent of chordomas arise from the sacrococcygeal region, but a third arise from the base of skull, most commonly the clivus but occasionally the petrous bone. Chordomas rarely metastasize. Grossly, they are extradural, often multilobulated and pseudoencapsulated. They may have a consistency that can range from extremely soft to woody or cartilaginous. Histologically, nests and cords of large vacuolated epithelioid cells can be seen within a myxoid stroma. There is a chondroid subtype that contains areas with a hyaline-appearing stroma. Previously, it was thought that the chondroid subtype might have a more favorable outcome than the typical chordoma; however, this has not been substantiated in recent studies.

In a report from the Mayo Clinic, diplopia was the most common symptom followed by headaches, ptosis, retro-orbital pain, and neck pain. Cranial deficits were very common, especially cranial nerve VI, although deficits of cranial nerves III, IV, V, IX, X and XII also were seen.[410] In the same study, MRI was demonstrated to be the best modality for demonstrating the entire extent of cranial chordomas and the involvement of adjacent structures. These tumors typically appear hypointense (black) on T_1-weighted images and hyperintense (white) on T_2-weighted images. Other possibilities to be considered in the differential diagnosis for a clival lesion are metastasis, myeloma, osteochondroma, meningioma, and chondrosarcoma.

Low-grade chondrosarcomas often are lumped together with chordomas. The former arise from primary mesenchymal cells or embryonal rests of cartilaginous matrix. Chondrosarcomas are composed of either hyaline cartilage or myxoid cartilage, or a mixture of the two. The myxoid variant may be confused with chordoma.

In one large series of chondrosarcomas of the base of the skull, 6% arose from the sphenoethmoid complex, 28% from the clivus, and 66% from the temporo-occipital region.[411] Chordomas and low-grade chondrosarcomas have a similar radiologic appearance. Together they account for almost all primary malignant bone tumors arising from the base of the skull. Both rarely metastasize; however, they can result in significant morbidity from local invasion or can be fatal. Even though they are treated similarly, low-grade chondrosarcomas appear to have a better prognosis than chordomas, as discussed next.

Therapy for Chordomas and Chondrosarcomas Involving the Base of the Skull

Surgery is almost always performed when a chordoma or chondrosarcoma in the base of skull is suspected, both to establish a diagnosis and to alleviate symptoms. The surgery often is performed jointly by a neurosurgeon and a head and neck surgeon. Complete resection can be curative, but this is often not possible because of the extent of disease. In a series of 60 patients (46 with chordomas, 14 with chondrosarcomas) from the University of Pittsburgh, the tumors were treated primarily with surgery.[412] Approximately 67% underwent total or near-total resection, and 20% received postoperative radiation because of radiologic evidence of residual tumor. The 5-year recurrence-free survival rates were 65% for patients with chordomas and 90% for those with chondrosarcomas ($P = 0.09$). Two common problems following surgery were the development of CSF leakage and new cranial nerve deficits, which occurred in 30% and 80% of cases, respectively.

In a series from the Mayo Clinic, 51 patients with intracranial chordomas were treated with subtotal resection (78%) or biopsy (22%); 76% received postoperative radiation (median dose 50 Gy).[413] However, in spite of this extra treatment, the 5-year actuarial disease-free survival was only 33%. The most important factor for survival on multivariate analysis was young age. Those less than 40 years of age had a 10-year actuarial survival of 63% versus 11% for those greater than 40. The use of postoperative radiation did not improve overall survival but did show a trend toward improved disease-free survival, especially in patients younger than 40 years old.

Because tumors in the base of skull are near critical structures within the brain, there has been a growing use of radiation techniques that can deliver doses to a tightly conformal treatment volume, such as stereotactic radiation and proton beam therapy. Some reports have described using both stereotactic radiosurgery (SRS) to deliver single large fractions[414] and fractionated sterotactic radiotherapy (FSRT).[415] In one series, 45 patients (37 with chordoma and 8 with chondrosarcoma) received fractionated radiation using a stereotactic headframe but with conventional fractionation (1.8 Gy per day) to a total median dose of approximately 65 Gy.[415] Among the patients with chondrosarcomas, the local control was 100% at 5 years. In patients with chordomas, however, local control rates were only 50% at 5 years and 40% at 8 years.

Some experts consider fractionated proton beam therapy to be the treatment of choice for incompletely resected skull base chondrosarcomas and chordomas, although the availability of facilities that can deliver such treatment is very limited. The advantage of proton beam therapy is that, unlike conventional x-rays, protons have a very sharp fall-off in dose. Proton beam therapy has been used since the 1970s at Massachusetts General Hospital. In a report from that institution, 200 patients with chondrosarcomas of the skull base were treated with surgery followed by radiation.[411] A gross total resection was achieved in only 5% of patients. Radiation was delivered using a combination of x-rays and proton beam therapy to a dose of 64.2 to 79.6 cobalt-gray-equivalents (median dose, 72.1 C-G-E in 38 fractions). The 10-year local control and progression-free survival rates were 98% and 99%, respectively. By contrast, the experience with almost 300 patients with skull base chordomas treated in a similar manner was not nearly as good, with 5- and 10-year progression-free survival rates of 70% and 45%, respectively.

GLOMUS TUMORS OF THE BASE OF THE SKULL

Clinical and Pathologic Considerations

Glomus tumors are low-grade tumors of neural crest origin arising from the paraganglionic (glomus body) cells; therefore, they are also referred to as nonchromaffin paragangliomas. Becase they are thought to be associated with chemoreceptor tissue, they are also known as chemodectomas. Glomus tissue is found along the vagus nerve, the glossopharyngeal nerve, and the jugular ganglion. Glomus tumors are often divided into those arising in the soft tissue of the neck (glomus vagale and carotid body) and those involving the temporal bone or base of skull (glomus jugulare and glomus tympanicum). Only the latter group will be discussed in this chapter as they often have intracranial extension and are managed by neurosurgeons.

Glomus jugulare tumors originate from the jugular bulb in the skull base, whereas glomus tympanicum tumors arise from the middle ear cavity along the nerve of Jacobsen (cranial nerve X) or Arnold (cranial nerve IX). In one series, 57 of 75 (76%) patients with glomus tumors of the head and neck region had glomus jugulare tumors, whereas 11 of 75 (15%) had glomus tympanicum tumors.[416] In this series, otologic signs and symptoms were common in patients with both of these tumors. Conductive hearing loss and/or tinnitus occurred in the majority of these patients. Over a third had bleeding from the ear, ear pain, a polyp visible in the ear canal and/or a mass behind the tympanic membrane. Cranial nerve impairments were also very common, specifically cranial nerve VII in patients with glomus tympanicum tumors and cranial nerves V, VI, VII, VIII, IX, X, XI, and XII in patients with glomus jugulare tumors.

CT and MRI often are diagnostic with these tumors. Cerebral angiography will demonstrate the extremely vascular nature of these tumors and generally is performed immediately before surgery.

Therapy for Glomus Tumors of the Base of the Skull

The therapy for glomus tumors is very controversial, with some experts strongly advocating surgery and others strongly advocating irradiation. When surgery is performed, it generally preceded by embolization to reduce the subsequent operative time and blood loss. Surgery for glomus tumors involving the base of the skull usually is performed jointly by a neurosurgeon and a head and neck surgeon, often using a combined suboccipital and transtemporal approach. The results with surgery in the modern era have been excellent, with local control rates ranging from 83% to 95% (reviewed by Hinerman and coworkers[417]). The main complications after surgery have been cranial nerve palsies, especially the facial nerve, and CSF leak.

An extensive literature regarding radiation treatment for glomus tumors has been accumulated. In a series of 46 patients with glomus

tumors treated with radiation at doses ranging from 35 to 66 Gy at the Royal Marsden Hospital, the 10-year local control rate was 90%, with a median follow-up time of 9 years.[418] Some late relapses occurred, so the 25-year local control rate dropped to 73%. In two patients, both of whom had received 64 Gy or more, a facial nerve palsy developed as a late complication. In a series from the University of Florida, 53 patients with temporal bone glomus tumors (46 with jugulare and nine with tympanicum tumors), most of whom had no prior therapy, received radiation therapy at doses ranging from 37.7 to 60 Gy (median dose, 45 Gy).[417] The 10-year local control rate was 92%, with a median follow-up time of 15 years. On the basis of their experience, the investigators recommended 45 Gy in 1.8-Gy fractions when radiation was used. Their review of the literature showed local control rates ranging from 83% to 100% in series using radiation therapy for temporal bone glomus tumors. A few reports have described stereotactic radiosurgery using single large fractions (20 to 25 Gy)[419,420]; the follow-up is short, however, and this modality cannot be considered to be a standard treatment for this disease.

Therefore, both surgery and irradiation can offer excellent local control for glomus tumors. The decision between the two often is based on consideration of treatment complications. It may be reasonable to use primary resection for early-stage base of skull glomus tumors in which the risk of surgical complication should be low and to reserve radiation therapy for patients with large tumors or with incomplete surgical resections.

PINEAL REGION TUMORS

The pineal gland is located adjacent to the cerebral aqueduct and brainstem. Therefore, tumors in this location frequently obstruct the posterior aspect of the third ventricle and aqueduct of Sylvius, causing acute hydrocephalus with headaches, papilledema, nausea, vomiting, diplopia, and lethargy. As tumors grow anteriorly, the midbrain tegmentum and quadrigeminal plate are compressed resulting in Parinaud's syndrome: paralysis of upward gaze, diminished pupillary response to light and retractory or convergence nystagmus.

In the United States and Europe, tumors of the pineal region account for less than 0.5% to 1% of all intracranial tumors.[421] In Japan, however, they account for 3% of all intracranial tumors. Tumors in this location are much more common in childhood and account for 3% to 11% of intracranial tumors in this age group.[422]

In series from the United States and Europe, roughly a third of all pineal region tumors are germ cell tumors, a majority of which are germinomas.[421,423] In Japan, germ cell tumors comprise a larger percentage of all pineal region tumors because germinomas are much more common than in the West. Because germ cell tumors occur most commonly in the second decade of life, they are discussed in the section on childhood brain tumors. Approximately a third of pineal region tumors are of glial origin, mostly astrocytomas, but also glioblastomas, oligodendrogliomas, and ependymomas. These tumors are managed in a similar manner as for their counterparts in other parts of the brain, as discussed elsewhere in this chapter.

Pineal parenchymal tumors (PPTs) account for slightly less than a third of all pineal region tumors. A little less than half of PPTs are pineocytomas; the other half are pineoblastomas. Pineocytomas are histologically benign neoplasms composed of well-differentiated pineal parenchymal cells. These tumors generally affect young adults and rarely disseminate. In one study, the 5-year actuarial survival rate for nine patients with pineocytomas was 86%.[424] After resection, all of these patients received local field radiotherapy to a dose greater than 50 Gy without craniospinal irradiation.

By contrast, pineoblastomas consist of embryonal cells indistinguishable from those characteristic of PNETs in other CNS sites, tend to disseminate through the CSF, and have a much poorer prognosis than pineocytomas. Pineoblastomas are rare in adults,[425] generally occurring in the first 2 decades of life. Management of these pineoblastomas is similar to that of other supratentorial PNETs, as discussed later under Childhood Brain Tumors. A small percentage of PPTs (less than 10%)—mixed pineocytoma-pineoblastoma tumors or PPTs of intermediate differentiation—do not fit either of the two categories.[426] These tumors, like pineoblastomas, have the capacity to seed the CSF; therefore, some experts have recommended craniospinal irradiation for management in such cases.[426] In one study, the 5-year survival rate for patients with PPTs excluding pineocytomas (15 pineoblastomas, 2 mixed PPTs, 4 PPTs with intermediate differentiation) was 49%.[424] A multicenter retrospective study examining adults with PPTs found that those with tumors of intermediate differentiation had a better outcome than those with pineoblastomas: 10-year survival rates of 72% versus 23%, respectively ($P = 0.001$), and rates for control of spinal disease at 10 years of 81% and 50% ($P = 0.04$).[425]

TUMORS OF THE SPINAL AXIS

Clinical and Pathologic Considerations

Tumors of the spinal cord are far less common than intracranial tumors, accounting for only 15% of all CNS tumors. The distribution of histologic types of tumors involving the spinal axis is different from that of tumors affecting the brain (Table 70-12).[427] For example, neuromas (schwannomas) account for almost one fourth of all spinal axis lesions but are very uncommon in the brain. Most spinal axis tumors are intradural, although chordomas are extradural (see Table 70-12). Clinically these tumors manifest in one of three ways: (1) radicular pain secondary to compression or infiltration of spinal cord roots, causing a knife-like sensation along the nerve distribution; (2) sensorimotor deficits dependent on the level of the tumor, characterized by muscle weakness, paresthesias (pain and temperature abnormalities contralateral to the side of muscle weakness; and (3) central syringomelia with destruction of the central gray matter causing motor neuron destruction and muscle wasting, loss of pain and temperature sensation with preservation of touch.

The imaging modality of choice for spinal tumors is MRI.[428] Both meningiomas and schwannomas are intradural but extramedullary. The signal intensity of meningiomas on T_1- and T_2-weighted images is similar to that of the normal cord whereas for neuromas the signal is increased on T_2-weighted images. Meningiomas typically enhance with gadolinium. Spinal cord ependymomas and astrocytomas generally are intramedullary tumors. The exception is ependymoma involving the conus medullaris, which is not actually an intrinsic tumor of the spinal cord. Ependymomas and astrocytomas of the spinal cord have a similar appearance on MRI. T_1-weighted images show an enlarged spinal cord extending for several vertebral body segments. Both astrocytomas and ependymomas may have cysts that are visible on MRI. T_2-weighted images show increased signal intensity in the region of the tumor, with accompanying adjacent edema. Both tumor types typically enhance with gadolinium although there are rare

Table 70-12 Primary Spinal Axis Tumors: Distribution by Histologic Type

Tumor	Location	Frequency (%)
Meningioma	Intradural; extramedullary	42
Schwannoma	Intradural; extramedullary	22
Ependymoma*	Intradural; intramedullary	15
Astrocytoma	Intradural; intramedullary	11
Other		6

*Ependymomas of the spinal cord are intramedullary, but myxopapillary ependymomas of the cauda and filum terminale are intradural but extramedullary.

Data from Los Angeles County, 1972–1985 (reported by Preston-Martin[427]).

exceptions. The gadolinium enhancement in ependymomas tends to be very homogenous with clear demarcation of the upper and lower extent, unlike astrocytomas, in which the true extent often is underestimated by MRI. Because they arise from cells in the central canal, ependymomas are centrally located and expand circumferentially. In contrast, astrocytomas can originate from anywhere in the spinal cord. The differential diagnosis of these tumors includes various nonmalignant conditions such as multiple sclerosis, transverse myelitis, and infarction of the cord. Hemangioblastomas are much less common than astrocytomas or ependymomas. They show enlargement of the spinal cord with multiple cysts. One or more intensely enhancing nodules may be present in the cyst wall.

Chordomas Involving the Spinal Axis

Chordomas involving the base of the skull have been discussed earlier; however, these tumors also can involve the sacrum or the mobile spine. Unlike the other histologic tumor types listed in Table 70-12, chordomas are extradural tumors. Radiation therapy has been used but with poor results. In a series from the Princess Margaret Hospital, 48 patients with chordoma (23 of the sacrum, 5 of the mobile spine, and 20 of the base of the skull) received radiation therapy, most immediately after initial diagnosis but some after local failure after surgery.[429] Survival rates were 54% at 5 years and 20% at 10 years, and patients with nonclival disease did just as poorly as patients with clival disease.

In patients with chordomas of the sacrum or spine who are able to undergo a radical resection, there is a reasonable chance for long-term local control and cure. In a series from the Sahlgrenska University Hospital in Sweden, 39 patients (30 involving the sacrum, 9 involving the mobile spine) underwent surgery as the primary treatment.[430] Most patients presented with pain, but many also had neurologic symptoms. En bloc surgical resection was performed in 35 cases. The final surgical margins were negative for tumor in 23 patients but only marginal or positive in 16. With a mean follow-up time of 8.1 years, 23 patients (59%) were found to be disease-free at the time of last follow-up evaluation. Local recurrence was seen in 17 patients (44%), and distant metastases in 11 (28%). The estimated 10- and 15-year survival rates were 64% and 52%, respectively.

Spinal Meningiomas

Meningiomas are the most common spinal axis tumor (see Table 70-12). They are associated with neurofibromatosis 2, as are their intracranial counterparts.[326] The prognosis with surgery is excellent. In a large series of meningiomas from MGH treated with surgery alone, 18 (8%) involved the spine (see Table 70-12).[323] No failures were observed at 5 years, and a 13% recurrence rate at 10 years. In a report from the Milan Neurologic Institute, the crude recurrence rate was 6% in 150 patients with spinal meningiomas who had a complete tumor resection versus 17% in the 6 patients who underwent subtotal resection.[431] Of 80 patients who had undergone a total resection at the Cleveland Clinic, only one relapsed, at 8 years.[432] Even the seven patients who had a subtotal resection did well, with only two relapsing, one at 13 and one at 16 years. These findings indicate that patients with these tumors do very well after total resection. In the event of subtotal resection, radiation therapy should be considered, as in the case of intracranial meningioma.

Spinal Schwannomas

Schwannomas (neuromas) arise from the Schwann sheath, which covers the extramedullary axons of the nerve roots. They are evenly distributed throughout the cervical, thoracic, and lumbar regions but are uncommon in the sacral region. The lesions are benign and well encapsulated; therefore, total surgical resection usually is possible and is curative.

Spinal Cord Ependymomas

Although spinal cord ependymomas are less common than meningiomas and schwannomas involving the spinal axis (see Table 70-12), they account for 60% of all intramedullary tumors. They occur more frequently in the middle adult years and are rare in children. Because of their central location within the spinal cord, ependymomas often manifest with dysesthesias followed by progressive motor dysfunction but without objective evidence of sensory dysfunction.[433] A variety of histologic subtypes have been described, including cellular (the most common), epithelial, fibrillar, malignant, and myxopapillary. The last subtype is seen only in the filum terminale or the conus medullaris and is, therefore, technically not an intramedullary tumor.

Spinal cord ependymomas have a more favorable outcome than that noted for intracranial ependymomas. The primary treatment for these tumors is surgery. Although not usually encapsulated, benign spinal cord ependymomas generally do not infiltrate adjacent normal tissue. Therefore, the surgeon usually can find a plane between tumor and normal tissue, allowing for gross total resection, which is associated with a very low rate of recurrence. In one series of 38 patients with spinal cord ependymomas who underwent a gross total resection, none had recurred after a mean follow-up time of 24 months.[433] In another series, of 11 patients with spinal ependymomas who underwent gross total resection, only one patient required a second operation for recurrent tumor.[434] By contrast, of 13 patients who underwent a subtotal resection, continued tumor growth led to a second operation in 5 patients and death in 1 patient.

It is hard to assess the role of postoperative radiation for this tumor because of the limited number of retrospective studies with small numbers of patients. Generally postoperative radiation has been given to patients who had a subtotal resection. In a review of 11 series using surgery followed by postoperative radiation for spinal ependymomas, both the 5- and 10-year survival rates ranged from 60% to 100% with most of the series showing 5-year survival rates in the 80% to 90% range and local relapse rates from 13% to 33%.[435] In two of the largest series from the Princess Margaret Hospital[436] and the Royal Marsden Hospital/Atkinson Morley's Hospital,[437] patients with high-grade tumors had a much higher relapse rate than those with low-grade tumors. In both of these series, when failures occurred, they were usually local.

Based on the limited data available, it is difficult to make strong recommendations. However, for benign ependymomas that are totally resected, there does not appear to be a need for postoperative radiation. For incompletely resected benign ependymomas, it would be reasonable to give 45 to 50 Gy to the tumor bed. For high-grade ependymomas, some would advocate giving all patients postoperative radiation, regardless of the extent of surgical resection. The actual volume that should be irradiated is unclear. High-grade spinal ependymomas have been reported to fail intracranially. This has led some to advocate craniospinal radiation,[436] although there is little evidence that the addition of cranial irradiation adds any benefit.[437] If one considered craniospinal irradiation for a high-grade spinal ependymoma, a reasonable dose would be 36 Gy followed by a boost to the primary tumor bed to a dose of 50 to 54 Gy.

Spinal Cord Astrocytomas

Astrocytomas are slightly less common than ependymomas in the spinal cord, accounting for approximately 40% of all intramedullary spinal tumors. Most spinal astrocytomas are low-grade; in adults only 10% to 15% are high-grade. In children, high-grade astrocytomas are even less common, but pilocytic astrocytomas are seen. As with ependymomas, the initial therapy for astrocytomas of the cord is surgical resection. Astrocytomas tend to be more infiltrative than ependymomas, however, making it difficult to find a plane of resection between tumor and normal cord in order to perform a total resection.

Spinal astrocytomas have a poorer prognosis than spinal ependymomas. In a study from Hokkaido University, of 13 patients with astrocytomas and 22 ependymomas, the five-year actuarial survival rate for the two groups were 50% and 96%, respectively ($P = 0.007$). The histologic grade of the astrocytoma has as significant influence on prognosis. In a series from the Mayo Clinic, of 43 pilocytic astrocytomas and 25 diffuse fibrillary astrocytomas, the 10-year survival rates were 81% and 15%, respectively.[438] In a series from the University of California at San Francisco, 12 patients with low-grade spinal astrocytomas had a relapse-free survival of 53% whereas the 3 patients with high-grade tumors all died within 8 months.[439] The 5-year survival for patients with low-grade astrocytomas has been in the 55% to 79% range in other series[440,441]; however, for high-grade astrocytomas, it is rare to have survivors at 5 years, with a median survival period of 1 year or less.[441,442]

As with spinal astrocytomas, it is hard to conclusively demonstrate that postsurgical radiation improves outcome; however, generally it has been given to patients who have had a subtotal resection. Most investigators have used 45 to 50 Gy to local fields for low-grade astrocytomas. High-grade astrocytomas have been known to recur with CNS dissemination, leading some to recommend craniospinal irradiation. However, in spite of such aggressive therapy, these tumors still recur.

There are no strong data supporting the use of chemotherapy for spinal cord astrocytomas. However, nitrosureas and other agents used in intracranial astrocytomas have been used with anecdotal reports of efficacy (reviewed by Balmaceda[443]).

Miscellaneous Intramedullary Tumors

Of the 10% of intramedullary spinal cord tumors that are not ependymomas or astrcocytomas, there is a mixture of uncommon tumors including hemangioblastomas, ependymomas, and gangliogliomas (reviewed by Miller and McCutcheon[444]). Although exceedingly rare, there are reports of primary intramedullary germ cell tumors and PNETs.[443,445]

Hemangioblastomas are benign vascular lesions associated with von Hippel-Lindau disease in 10% to 30% of cases, as is the case for their cerebellar counterpart (discussed in the Cerebellar Hemangioblastomas section). They typically occur in men in their fourth decade of life. Most of these tumors appear as an enhancing tumor nodule within a cyst or syrinx. Because they have well-defined margins, surgical resection usually provides a cure, although care must be taken to avoid excessive bleeding of these vascular tumors.[446]

Subependymomas are benign well-circumscribed lesions that affect men between 30 and 60 years of age. Subependymomas typically are avascular and well demarcated from the normal cord, enhancing the feasibility of complete surgical resection. Gangliogliomas generally are benign tumors that have neuronal differentiation. They usually are seen intracranially, but tumors in the spinal cord have been reported. The primary treatment for these tumors is complete surgical resection; however, this approach is associated with a significant risk of recurrence. In one series of 30 spinal gangliogliomas, the 5-year actuarial survival rate was 84%, but the 5-year event-free survival rate was only 36%.[447]

CHILDHOOD BRAIN TUMORS

Primary CNS tumors are the most common solid tumors and the leading cause of cancer-related morbidity and mortality in children.[448] CNS neoplasms constitute 24% of all malignancies in children younger than 14 years of age in the United States. An estimated 3410 new cases of childhood (age 0 to 19 years) primary benign and malignant brain tumors were diagnosed in 2005.[1] Of these, 2330 were estimated to be in children younger than 15 years. The annual age-adjusted incidence rate is currently approximately 3.9 per 100,000 children.[449,450] During the period 1973 through 1994, the reported incidence of primary malignant brain tumors among children in the United States increased by 35%.[450] This increase may be due to improved detection and reporting facilitated by the availability of high-resolution neuroimaging.[451]

These observations also raise serious concerns that environmental factors may play a substantial causative or contributory role. Despite these concerns, epidemiologic studies investigating maternal nutritional intake, childhood diet, childhood exposure to electromagnetic fields, and parental occupational exposure have not established direct links between these factors and the development of childhood brain tumors.[452–455] As noted earlier in the section on epidemiology, however, strong data support a connection between cranial irradiation in childhood and the subsequent development of brain tumors.

Hereditary factors are estimated to be primarily responsible for approximately 2% of childhood brain tumors.[27] Nearly 70% of all optic pathway gliomas occur in patients with neurofibromatosis type 1 (NF-1),[456] and almost all childhood vestibular schwannomas occur in patients with NF-2. Hereditary immunosuppression disorders, as seen in Wiskott-Aldrich syndrome and ataxia-telangiectasia, as well as treatment-associated immunosuppression, as in organ transplant recipients, or exogenous immunosuppression, as in HIV infection, are known to be associated with an increased risk of primary CNS lymphomas.[457–459]

Primitive Neuroectodermal Tumors

PNETs constitute 23% of pediatric CNS tumors and are the most common malignant brain tumor in childhood.[453] When located in the cerebellar vermis, the site of approximately 85% of all CNS PNETs, these tumors usually are called *medulloblastomas*. Other common locations include the pineal region (pineoblastoma, 10%) and supratentorial regions (5%).[460–462] The nosology of these tumors is the subject of long-standing controversy among neuropathologists. Rorke has suggested that they be grouped together as primitive neuroectodermal CNS tumors (i.e., PNET) on the assumption that they each arise from neoplastic transformation of pluripotent uncommitted neuroectodermal precursors.[463,464] For cerebellar medulloblastoma (i.e., PNET/MB), recent evidence supports the hypothesis that that these tumors arise from disordered cerebellar granular cell development.[465] The cells of origin for pineal and supratentorial PNETs have not been identified; however, microarray studies demonstrate different patterns of gene expression for medulloblastoma, pineal, and supratentorial PNETs.[466]

A variety of cytogenetic and molecular genetic abnormalities have been observed in childhood PNETs. The most common, observed in 40% to 50% of cases, is a deletion of the short arm of chromosome 17, typically resulting in the formation of an isochromosome i(17q).[463] Putative tumor suppressor locations have been identified on 17p and 9q. Multivariate analysis has not clearly identified a clinical prognostic significance for 17p deletion either altering clinical outcome or associated with higher metastatic stage.[467] A putative tumor suppressor locus located on the long arm of chromosome 9 has been identified in 10% to 18% of PNETs.[468,469] The locus for nevoid basal cell carcinoma syndrome (Gorlin's syndrome) has been mapped to this region of chromosome 9. The gene responsible for nevoid basal cell carcinoma syndrome is the human homologue of the *Drosophila* Patched-encoding gene (*PTCH*).[470] It encodes a cell surface receptor that, among other functions, regulates normal brain development by repressing transcription of genes encoding members of the transforming growth factor-β (TGF-β) and Wnt families of signaling proteins.[471] Sonic hedgehog is a PTCH ligand that has many functions as an oncoprotein in mammalian tumors.[472] The incidence of PNET/MB among patients with nevoid basal cell carcinoma syndrome is reported to be approximately 4%.[473] Mutations in *PTCH* have been identified in nearly 12% of sporadic PNET/MBs,[474] and one PNET/MB was shown to contain a mutation in the Sonic hedgehog gene.

These observations indicate that multiple genes in the Sonic hedgehog PTCH signaling pathway contribute to PNET tumorigenesis.

The clinical presentation with PNET/MB is dominated by signs and symptoms of obstructive hydrocephalus and increased ICP: headache, nausea, and vomiting; drowsiness and other behavior changes; and ataxia. These clinical characteristics often are indistinguishable from those of other posterior fossa tumors, including ependymoma and cerebellar astrocytoma. To differentiate posterior fossa tumors, computer-based neural networks combining data from neuroimaging studies (Fig. 70-22A–C) and patient characteristics have been successfully used. In a series of 33 children with posterior fossa tumors, an experienced neuroradiologist was able to correctly predict the tumor type in 73% of cases, whereas the neural networks using different datasets had 95% accuracy.[475]

Preoperative management includes the assessment and treatment of increased ICP. Patients with papilledema and significant visual impairment require emergency placement of an external third ventricle drain, followed immediately by tumor resection. Prolonged delay between ventricular drainage and tumor resection significantly increases the risk of transtentorial upward herniation. For patients with less severe signs and symptoms of increased ICP, corticosteroids and acetazolamide (Diamox) may be used to relieve symptoms, reduce tumor swelling, and permit further surgical planning.

Surgical treatment of PNET/MB has three objectives. First, sufficient tissue must be obtained to permit accurate histopathologic diagnosis. Second, tumor removal should be complete or near-complete, because complete tumor removal favorably influences prognosis.[476] Third, every effort should be made to reestablish normal CSF flow. A majority of children with PNET/MB will not need a permanent ventriculoperitoneal shunt. The incidence of tumor dissemination to the abdomen by ventriculoperitoneal shunt is extremely low.[477]

Two postoperative syndromes may complicate the clinical course of patients with PNET/MB and other posterior fossa tumors. Aseptic meningitis may occur in up to 5% of patients undergoing posterior fossa surgery and is not limited to those with PNET/MB. Fever and meningismus, ranging in intensity from mild to severe, develop 5 to 10 days after surgery. Although this complication may occur more frequently in patients with large postoperative pseudomeningoceles under tension, no clinical features have been found to reliably distinguish this presumed chemical meningitis from bacterial meningitis. Therefore, CSF analysis and culture are essential. If no infectious etiology is identified, this complication may be effectively treated with corticosteroids. A second syndrome, that of cerebellar mutism after resection of posterior fossa tumors, was noted in the early 1980s.[478,479] This condition is far more common than was originally reported and occurs in up to 15% of children with large midline cerebellar tumors.[480] Complete or near-complete loss of speech often is accompanied by severe lower cranial nerve, cerebellar, and motor abnormalities as well as visual disturbances.[481] Cerebellar mutism typically manifests 1 to 4 days after surgery and may be more frequent in cases of aggressive surgical pursuit of PNET/MB adherent to or invading the brainstem. Most patients with this syndrome recover functional speech during a period of several weeks to months from onset, although it is common to have significant residual dysfunction in speech, lower cranial nerve conduction, and motor coordination.

The need for adjuvant therapy in PNET/MB is determined by postoperative staging for prognostic risk factor assessment. The most important clinical prognostic factor is metastatic stage, followed by postoperative residual tumor volume, tumor location, and patient's age at diagnosis.[476,482,483] PNET/MB commonly is associated with seeding of the spinal cord (Fig. 70-23). Accordingly, three tumor staging studies are important for PNET/MB: (1) neuraxis staging evaluation by spinal MRI (performed preoperatively or 10 to 14 days after surgery) to identify metastatic tumor aggregates; (2) CSF cytologic examination (performed intraoperatively or 10 to 14 days after surgery) to identify leptomeningeal tumor spread; and (3) postoperative neuroimaging to assess residual tumor. On the basis of these studies, patients with PNET/MB can be classified into two risk-for-recurrence groups—standard risk and high risk. Standard-risk patients must have no evidence of metastatic disease, 1.5 cm or less of residual tumor, be older than 3 years at diagnosis, and have primary tumor located in the posterior fossa only.[484] High-risk patients have one or more of the following conditions: evidence of leptomeningeal tumor spread; greater than 1.5 cm of residual tumor; age younger than 3 years at diagnosis; or primary tumor location outside the posterior fossa.

Clinical prognostic factors alone are not sufficient to distinguish a low-risk from a standard-risk group. Furthermore, a potentially very-high-risk group of patients may benefit from therapy regimens significantly different from those for standard- or high-risk PNET/MB. It is unlikely that additional clinical prognostic factors will be identified, and the identification of biologic prognostic factors will facilitate a more sensitive and specific stratification of patients to risk-adopted therapies. Accordingly, biologic studies of large, representative and relatively homogeneously treated PNET/MBs are of great interest. Independent retrospective studies of patients with childhood PNET demonstrate that tumor expression of the neurotrophin receptor TrkC is a potent biologic prognostic factor.[485,486] Other candidates include HER2/HER4 coexpression,[487] GFAP expression,[488] *MYC* amplification,[469] and PDGFR expression.[489] Larger prospective studies are planned to determine if these new biologic factors will supplement, or supplant, the significance of clinical factors.

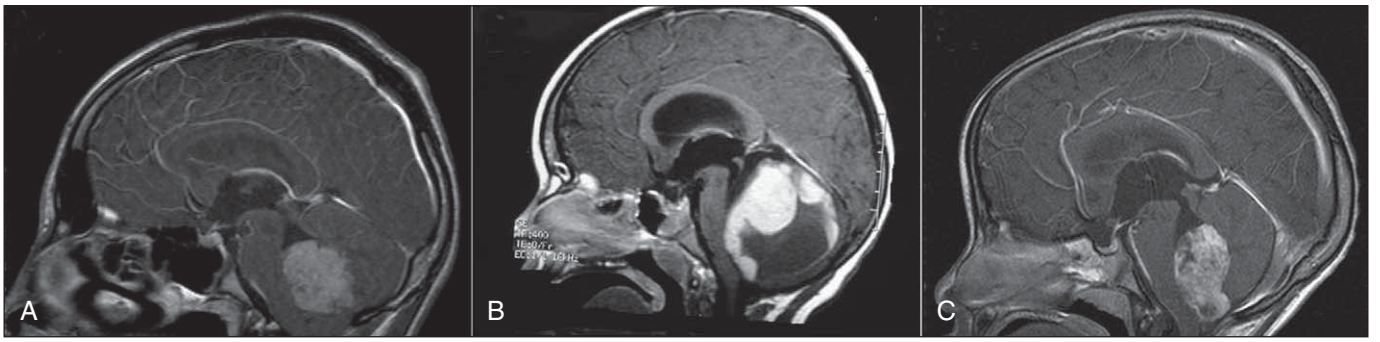


Figure 70-22 • Posterior fossa tumors. Sagittal T_1-weighted post-gadolinium magnetic resonance imaging of three different posterior fossa tumors: **A,** Medulloblastoma shows homogeneous contrast enhancement without evidence of cyst formation. **B,** Cerebellar pilocytic astrocytoma shows prominent cyst or multicyst formation, with one or more contrast-enhancing mural nodules. **C,** Ependymoma arising from the floor of the fourth ventricle shows a heterogeneous contrast enhancement pattern and extends inferiorly to the upper cervical spinal cord. Note that the pilocytic astrocytoma shows intense enhancement despite being a low-grade glioma (WHO grade I).

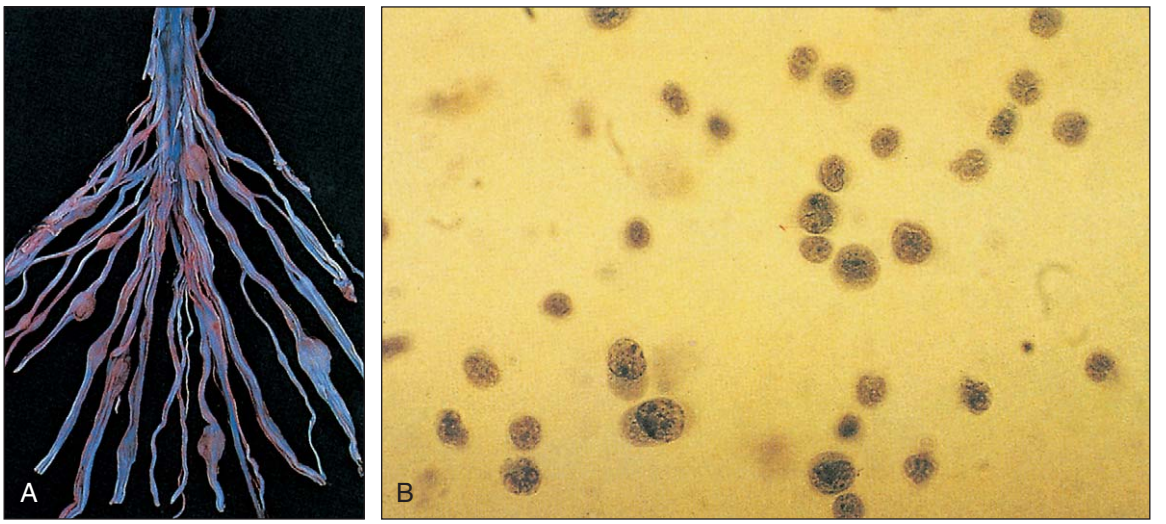


Figure 70-23 • Disseminated medulloblastoma. **A,** "Studding" of caudal nerve roots from spinal arachnoid spread of tumor. **B,** Malignant cells identified on cytologic examination of cerebrospinl fluid. (From Maher EA, McKee AC: Neoplasms of the central nervous system. In Skarin AT [ed]: Dana-Farber Cancer Institute Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 415.)

Treatment approaches for PNET/MB are determined by assignment of the patient to either a standard- or a high-risk category. Four general trends have emerged. Patients in the high-risk category receive 36 Gy of radiation to the craniospinal axis and chemotherapy. Patients in the standard-risk category are eligible for treatment with less intensive approaches, including reduced craniospinal irradiation (e.g., 2400 cGy) to decrease the risk of significant treatment-associated toxicities. Infants and children younger than 3 or 4 years of age may be given intensive chemotherapy alone to postpone or avoid the neurotoxic effects of radiation on developing brain. Newer protocols combine systemic and intrathecal chemotherapy with conformal radiation therapy to the tumor bed. For recurrent tumors, the introduction of high-dose chemotherapy followed by peripheral blood stem cell (PBSC) rescue may offer some hope for retreival, especially for patients with minimal residual disease before high-dose chemotherapy. Nevertheless, the prognosis for recurrent PNET/MB remains very poor.

Radiation therapy is the mainstay of PNET/MB treatment. Cumulative local tumor doses should be approximately 56 Gy. Doses less than 50 Gy have been shown to be less effective.[490] Radiation should be delivered to the entire craniospinal axis, regardless of the tumor metastatic stage.[491] Treatment with craniospinal irradiation (to a dose of 36 Gy) and local boost radiotherapy (for a total dose of 54 Gy) without adjuvant chemotherapy results in long-term disease control in approximately 60% of children with PNET/MB.[492] After whole-brain radiotherapy, however, many children will have significant long-term neurocognitive sequelae, including a demonstrable drop in overall intelligence. This decline in intelligence is influenced by age at irradiation and dose used. Silber and colleagues reported that patients who received a dose of 36 Gy to the whole brain scored 8.2 points less on intelligence quotient (IQ) testing than those with 24 Gy, and 12.3 points less than those who received 18 Gy.[493] Older age at the time of irradiation was associated with less decline in subsequent IQ score.

Serious long-term side effects of radiotherapy on the developing nervous system prompted efforts to reduce the dose of craniospinal radiation therapy in nonmetastatic PNET/MB. The lowest craniospinal radiotherapy doses reported, 18 Gy in 10 fractions, with 50.4 to 55.8 Gy to the posterior fossa tumor bed, has been used in combination with vincristine during irradiation and subsequent vincristine, CCNU, and cisplatin.[494] Ten patients between 18 and 60 months of age, and without evidence of tumor dissemination, received treatment according to this approach. With a median follow-up time for living patients of 6.3 years, the survival rate at 6 years was 70% ± 20%. The three patients who relapsed all were found to have spinal metastases, in association with brain or posterior fossa recurrence. These data suggest that a subset of patients with these tumors can be cured with chemotherapy and reduced doses of craniospinal irradiation.

The optimal dose of craniospinal radiation therapy remains uncertain. A prospective single-arm study reported the use of 23.4 Gy for craniospinal radiation therapy, standard local radiotherapy (55.8 Gy), and adjuvant vincristine, CCNU, and cisplatin chemotherapy given during and after radiotherapy.[495] After 3 years, the progression-free survival rate for 68 children aged 3 to 10 years with nondisseminated PNET/MB treated with this approach was 86% ± 4%.

Prospective studies demonstrate that chemotherapy has an important role in the treatment of high-risk PNET/MB. PNET/MB are responsive to a variety of chemotherapeutic agents, including cisplatin, cyclophosphamide, vincristine, CCNU, and busulfan.[496] Incorporation of cisplatin, CCNU and vincristine into a postirradiation chemotherapy regimen for high-risk patients resulted in 5-year survival rates in excess of 80%.[497] Of note, this survival rate was significantly higher than survival rates for standard-risk patients treated with radiation therapy alone (i.e. historical controls). This and other single-institution studies have provided strong support for the use of effective adjuvant chemotherapy for all PNET/MB patients.

High-dose chemotherapy (HDCT) with peripheral blood stem cell (PBSC) rescue is a therapeutic strategy that has shown encouraging results in the treatment of relapsed PNET/MB.[498] In children with recurrent PNET/MB, Kalifa and associates used a high dose busulfan-thiotepa regimen.[499] Of 28 patients evaluable for tumor response, complete tumor resolution was obtained in 36%, a partial response in 39%, and no response in 25%. Finlay and colleagues reported a series of 23 patients with recurrent PNET/MB.[500] The chemotherapy consisted of carboplatin, thiotepa, and etoposide followed by PBSC rescue. Three patients died of treatment-related toxicities. Overall, 7 of the 23 patients (30%) remained free from tumor recurrence at a median follow-up of 54 months after HDCT. These results are better than previously reported phase II trial results. Prospective collaborative national and international studies will determine different HDCT regimens that not only aim at maximiz-

Box 70-5. MANAGEMENT OF MEDULLOBLASTOMAS AND PRIMITIVE NEUROECTODERMAL TUMORS

- Medulloblastoma and related primitive neuroectodermal tumor (MB/PNET) constitute the most common malignant childhood brain tumor.
- Surgical objectives include gross total resection to establish diagnosis, restore cerebrospinal fluid (CSF) flow, and improve survival.
- Postoperative staging should be undertaken in all patients and should include magnetic resonance imaging (MRI) of the brain within 24 hours of surgery, an MRI study of the entire spine 10 to 14 days after surgery, and CSF cytologic studies 10 to 14 days after surgery. These studies determine subsequent risk-based treatments.
- Standard-risk patients must meet *all* of the following criteria: age older than 3 years, cerebellar location, little or no residual tumor (less than1.5 cc), and *no* evidence of metastatic tumor spread. All other patients are considered to be in the high-risk category.
- Treatment in standard-risk patients consists of lower-dose craniospinal RT to doses of approximately 24 Gy in 1.8-Gy daily fractions, tumor doses of approximately 55.8 Gy, and less intensive chemotherapy.
- MB/PNET in high-risk patients is treated with craniospinal irradiation to doses of approximately 36 Gy in 1.8-Gy daily fractions, tumor irradiation to doses of approximately 55.8 Gy, and intensive chemotherapy.

ing survival but also address toxicity and quality of life. Box 70-5 summarizes the recommended approach to management of medulloblastomas and primitive neuroectodermal tumors.

Low-Grade Astrocytomas of Childhood

Low-grade gliomas-astrocytomas occur throughout the brain and spinal cord. The predominant histologic subtype for cerebellar astrocytomas is pilocytic, whereas optic pathway or hypothalamic low-grade gliomas are more commonly fibrillary in appearance. Optic pathway or hypothalamic gliomas may be classified by location as follows: (1) those anterior to but not involving the chiasm, (2) chiasmal tumors with extension posteriorly along the optic radiations, and (3) chiasmal-hypothalamic tumors for which the initial site of tumor growth cannot be determined.

Optic Nerve Gliomas Anterior to the Chiasm

Optic nerve gliomas anterior to the chiasm manifest with symptomatic and progressive visual loss or proptosis, or both. Their appearance on CT and MRI studies usually is sufficiently diagnostic that routine biopsy is not necessary. Meningiomas of the optic nerve sheath often can be distinguished from optic nerve gliomas on the basis of neuroimaging characteristics. Optic nerve gliomas should be treated conservatively. Progressive tumor growth together with severe visual dysfunction justifies surgical resection of the nerve. Surgical resection is curative, and no further therapy is required. As a rule, optic nerve gliomas anterior to the chiasm do not invade the chiasm itself. For patients with progressive tumor growth and functional vision, radiation therapy is rarely indicated, and current chemotherapy is similar to that for chiasmal gliomas, discussed next.

Chiasmal and Chiasmal-Hypothalamic Gliomas

Chiasmal and chiasmal-hypothalamic gliomas constitute 60% to 85% of all optic pathway-hypothalamic tumors. These tumors, especially very large chiasmal-hypothalamic glioma, often come to medical attention before the age of 5 years with signs and symptoms of visual loss and hydrocephalus. Older children are more likely to present with symptoms, which include those of endocrinopathies and behavioral changes. Children younger than 2 years of age may present with a diencephalic syndrome characterized by frequent vomiting, anorexia, and failure to thrive.[501] In children with chiasmal tumors involving the optic nerve, the diagnosis frequently is made on the basis of radiographic criteria alone. Especially in children with NF-1, diffuse enlargement of the optic chiasm, with extension posteriorly along the optic radiations to the geniculate bodies and beyond, may be sufficiently characteristic to permit reliable diagnosis. Surgical biopsy with histologic confirmation is advisable for large globular tumors with hypothalamic involvement. Although diagnostic confusion is not common, these tumors may have a clinical and neuroimaging appearance similar to that of solid craniopharyngiomas or germ cell tumors.

Most chiasmal and chiasmal-hypothalamic gliomas are not "cured" by currently available surgical approaches, radiation therapy, or chemotherapy. The slow and often erratic growth of these tumors has led some experts to conclude that most of these "benign" tumors will eventually be fatal.[502] In the past decade, the development of more effective chemotherapy strategies makes this conclusion far less certain, and a majority of patients remain alive without progressive tumor growth in excess of 10 years. In most cases, the decision to initiate treatment is based on clinical or radiographic evidence of tumor growth from serial observations, rather than automatically initiating treatment at the time of tumor diagnosis. Patients with severe visual loss or clear historical evidence of rapid clinical worsening represent exceptions to this approach. Whereas some patients show significant changes in visual acuity or neuroimaging scans within weeks or months of initial diagnosis, many others remain clinically stable for months or years without interval treatment.

For patients who retain a degree of useful vision, chiasmal and chiasmal-hypothalamic gliomas cannot be completely resected. Surgical debulking of large chiasmal-hypothalamic gliomas, however, is increasingly recognized to provide rapid relief of symptoms caused by mass effect and hydrocephalus, delay the need for radiation therapy in young children, result in years of clinical stability without tumor growth, and improve the effectiveness of subsequent radiation therapy.[503,504]

Local involved-field radiation therapy has been shown to be effective in arresting tumor growth and causing tumor shrinkage.[505,506] Complete tumor regression is rare after irradiation, however. Because more than 90% of patients with optic pathway-hypothalamic gliomas survive longer than 10 years,[505,507] the late effects of radiation therapy, including neurocognitive problems, endocrinopathy, optic nerve injury, and radiation-induced second neoplasms, are important considerations. These issues have stimulated the investigation of alternative treatment approaches, including chemotherapy.

Chemotherapy has a defined role in the treatment of optic pathway-hypothalamic gliomas. In a large multi-institutional trial of carboplatinin and vincristine, 60% of the patients with progressive low-grade glioma had a significant reduction in tumor volume, and another 30% of patients had tumor stabilization.[508] A different regimen developed at University of California at San Francisco included procarbazine, 6-thioguanine, dibromodulcitol, CCNU, and vincristine. This treatment protocol resulted in prolonged periods of disease stabilization with a median time to tumor progression of 132 weeks in children with low-grade gliomas.[509] For younger children, particularly those younger than 5 years of age, the use of chemotherapy delays or obviates the need for radiation therapy, thereby reducing or eliminating the neurologic morbidity associated with radiation therapy in young children. Currently used chemotherapy regimens for optic pathway tumors generally are well tolerated, can be administered in the outpatient setting, and are not associated with a high incidence of serious late effects. Because of the successful outcomes with chemotherapy in younger children, the use of chemotherapy to treat these tumors in older patients has been attempted. It remains to be proved, however, whether the duration of

progression-free survival for patients treated with chemotherapy is comparable to that for radiotherapy.

The incidence of optic pathway tumors in patients with NF-1 is markedly higher than in the general population. Up to 15% of children in whom the diagnosis of NF-1 is confirmed will be found to have optic pathway tumors when they undergo screening neuroimaging.[510] Most optic nerve gliomas in patients with NF-1 are anterior to the optic chiasm. In slightly more than half of all children with radiographically identifiable optic pathway tumors, however, signs or symptoms directly related to their tumors ultimately developed. When studied systematically, these tumors appear to behave in a more indolent fashion than their counterparts in children who do not have NF-1. However, low-grade gliomas in children with NF-1 are notoriously erratic in their natural history. At times, these tumors appear to undergo rapid growth and then spontaneously arrest. Treatment of anterior optic nerve glioma is necessary only with significant symptomatic tumor progression. Consequently, routine screening neuroimaging of asymptomatic patients is unwarranted.[456] Because optic pathway tumors nearly always arise in children younger than 10 years of age, all younger children with NF-1 should undergo yearly ophthalmologic evaluation and annual assessment of growth to monitor for signs of precocious puberty.

As with their non-NF-1 counterparts, management of children with NF-1 and optic pathway glioma is dependent on the location of the tumor. Anterior optic pathway gliomas do not invade the chiasm in NF-1 patients and are managed according to the clinical symptoms. Chiasmatic optic pathway gliomas are watched closely for neuroimaging or clinical evidence of tumor progression. Progressive chiasmal tumors are treated with chemotherapy strategies associated with a relatively low incidence of second malignancies (e.g., carboplatin and vincristine). Use of nitrosoureas in children with NF-1 is associated with an increased risk of myeloid leukemia. In addition, a pervasive concern remains that use of radiation therapy in this patient population with an increased incidence of glial brain tumors will result in an unacceptably high incidence of treatment-induced secondary brain tumors. The challenge for the future is to determine the most appropriate treatment for each patient, based on rate of tumor progression, age, prior therapy, and visual and endocrine status.

Cerebellar Astrocytomas

Cerebellar astrocytomas of childhood typically are pilocytic or low-grade fibrillary on histopathologic examination. Malignant gliomas of the cerebellum in childhood are extremely rare. The survival rate is determined by the extent of resection, not by histological features. Use of radiation therapy is limited to those cases of recurrent astrocytoma that cannot be resected because of extensive invasion into the cerebellar peduncles or brainstem. Cerebellar astrocytomas have, arguably, the best prognosis of any brain tumor, with 10-year survival rates approaching 100%.[511] If postoperative MRI shows resectable tumor (see Fig. 70-20B), reexploration may be indicated to achieve complete resection.

Ependymoma

Childhood intracranial ependymomas represent approximately 5% to 10% of all childhood brain tumors (see Table 70-2) and behave primarily as localized, relatively noninvasive neoplasms that originate from the ventricular ependymal linings. Nearly 70% of childhood ependymomas are located in the posterior fossa arising from the floor of the fourth ventricle (see Fig. 70-22C). The remaining 30% are located in supratentorial periventricular regions. The classic histologic feature of ependymomas is the perivascular pseudorosette. Two general histologic classifications have been described. *Well-differentiated* ependymomas are moderately to highly vascular, with low mitotic indices and little cellular pleomorphism or evidence of necrosis. *Malignant* ependymomas exhibit higher mitotic rates, substantial cellular atypia, and prominent necrosis. The rare "ependymoblastoma" is best classified as a PNET with histologic evidence of ependymal differentiation and treated in a fashion identical to that for the PNETs. The role of standard histologic classification in prognosis is controversial; however, growing evidence suggests that biologic factors identified in tumor specimens, such as Erb receptor expression, may provide greater prognostic accuracy.[512]

The primary challenge in ependymoma treatment is local control, because metastatic disease at initial diagnosis or first relapse is uncommon.[513,514] Surgical resection of these tumors often is difficult, and complete removal is achieved in less than 50% of the patients. Ependymomas often are located close to brainstem structures, which increases the risk of morbidity when complete resection is attempted. Several studies confirmed the critical role of a radical surgical resection in patients with newly diagnosed ependymomas.[515,516] Five-year progression-free survival rates range from 50% to 70% after complete surgical resection and from zero to 30% after incomplete resection.[517–519] Better survival is noted in children who have undergone complete resection. The frequency of gross total resections has been increased by sophisticated technologies including ultrasonic tissue dissociators, argon lasers, and robotic localizing devices; by experience of the surgeon with childhood tumors; and by the intent and preoperative plan to perform a radical surgical resection.[520] The availability of intraoperative neuroimaging may provide immediate confirmation of the degree of resection and allow the surgeon to reoperate, immediately, if necessary.[521] For patients with residual tumor after initial surgery, re-resection immediately after the postoperative MRI study reveals residual tumor remains an option. Alternatively, deferral of second surgery until the child recovers and receives chemotherapy or radiotherapy may be considered.

Involved-field radiotherapy represents standard therapy for children older than 3 years who have intracranial ependymomas. Conventional radiation therapy doses range from 54 to 56 Gy. Controversial aspects of radiation therapy for ependymomas include treatment volume and the necessity for craniospinal irradiation. On the basis of published reports that indicated a significant risk of CSF seeding, craniospinal irradiation initially was recommended.[522] In subsequent studies, neuraxis relapse in ependymoma occurred in less than 5% of cases.[513] Routine staging for relaps includes postoperative MRI of the brain to characterize the extent of resection. MRI of the spine, as well as lumbar puncture to evaluate CSF cytology, is critically important to therapeutic planning. In the absence of disseminated disease at diagnosis, the pattern of relapse is local in the vast majority of cases and is not influenced by the delivery of craniospinal irradiation. Therefore, prophylactic craniospinal irradiation is no longer recommended. Currently evaluated strategies to enhance local tumor control in patients with residual or progressive disease include radiosurgery-based techniques.[523]

The role of chemotherapy in the treatment of ependymoma is controversial, because these tumors are considered to be relatively chemotherapy-resistant. In a study of 19 children with newly diagnosed ependymoma, a 74% 5-year progression-free survival rate was reported in children with postoperative residual tumor treated with radiation therapy and platinum-based chemotherapy.[524] This rate was higher than published results for radiotherapy alone for this group. On the basis of this finding, current clinical trials use chemotherapy for patients whose postoperative imaging studies are positive for residual tumor. For patients with recurrent ependymoma, options for further therapy other than re-resection are few; usually, maximal irradiation has already been administered, and high-dose chemotherapy is of modest benefit in only a minority of patients.[525,526] Therefore, management consists largely of symptom control and palliation.

Brainstem Glioma

Gliomas of the brainstem, distinctly uncommon in adults, represent a major tumor group in childhood. In past years, brainstem tumors

were considered to represent a single entity, uniformly fatal despite the most intensive therapies. Nevertheless, some children had continuous progression-free survival in excess of 5 years[527]; a larger number of children, however, died from progressive tumor within 18 months. To distinguish good- from poor-risk groups, investigators evaluated neuroimaging characteristics and biopsied these tumors.[527] Results from these studies identified two major classes of brainstem gliomas: (1) diffuse intrinsic brainstem gliomas, typically centered in the pons and upper medulla, which carry a uniformly poor prognosis, and (2) focal brainstem gliomas, typically located in the upper midbrain or lower medulla, which are associated with a substantially better prognosis.

Factors responsible for the initiation and progression of brainstem and supratentorial gliomas in children are poorly understood. Although a model of tumor progression has been proposed for gliomas in adults, it is unlikely that this model is applicable to gliomas in younger children. Malignant transformation from low-grade astrocytoma to malignant glioma is distinctly uncommon in children. The genetic pathways leading to primary (de novo) glioblastoma of pediatric patients appear to be different than those of adult patients, as reflected by the comparatively low frequency of *EGFR* amplification (6%) and *CDKN2A* deletion (19%) and the absence of *MDM2* amplification in childhood glial tumors.[528]

Diffuse Intrinsic Brainstem Gliomas

Diffuse intrinsic brainstem gliomas constitute more than 70% of all brainstem neoplasms. Their MRI characteristics include diffuse infiltrative enlargement of the pons and rostral medulla[529] (Fig. 70-24). T_1-weighted MRI sequences usually show mass effect and reduced signal intensity compared with normal brain. T_2-weighted MRI sequences often reveal regions of high signal intensity representing tumor infiltration with rostral extension into the midbrain and brachium pontis and lateral extension into the cerebellar peduncles. Brainstem enlargement may be unilateral and often is asymmetrical on diagnosis. The fourth ventricle usually is distorted; however, obstructive hydrocephalus is distinctly uncommon at initial presentation. The clinical presentation of diffuse pontomedullary brainstem gliomas classically involves one or more of the following abnormalities: (1) cranial nerve palsies, typically VI and VII; (2) ataxia; and (3) long tract signs, including hyperreflexia and extensor plantar responses. The prediagnostic symptomatic interval often is less than 3 months.



Figure 70-24 • Diffuse pontine glioma. Sagittal fluid-attenuated inversion recovery (FLAIR) magnetic resonance image shows diffuse infiltration of the pons by tumor.

The impetus for biopsy and autopsy studies of these tumors arose from efforts to correlate histopathologic features with clinical outcome. The brainstem is among the most eloquent brain structures, thereby reducing surgical accessibility. These studies showed that a limited surgical procedure, either stereotactic or open biopsy, can be accomplished safely with acceptable risk of morbidity.[530] Information obtained at biopsy, however, was not found to be a uniformly accurate predictor of clinical outcome, possibly because of the difficulty of obtaining a sufficiently large, representative sample.[531] In many centers, current management for these tumors avoids routine diagnostic biopsy when the clinical and neuroimaging features typical of diffuse pontomedullary brainstem gliomas are identified. Diagnostic biopsy is clearly indicated for brainstem mass lesions with an unusual MRI appearance or associated with a highly atypical clinical course. Examples of these circumstances include that of the young child with a several-year history of slowly progressive clumsiness and facial asymmetry who may have a ganglioglioma of the brainstem and the case of the child with the acute onset of facial weakness, ataxia, fever, and CSF pleiocytosis who may have a focal brainstem encephalitis.

In general, no established role is recognized for the routine resection of diffuse intrinsic brainstem gliomas. Early in the clinical course, tumor cells infiltrate widely throughout brainstem structures but still permit neurologic function to remain at normal or near-normal levels. Consequently, removal of tumor is likely to result in severe neurologic deficits. Some diffuse pontomedullary brainstem gliomas may have a cystic projection in a dorsal or lateral direction. These surface projections may provide a limited opportunity for tumor resection. It is uncommon, however, that more than 50% of the tumor can be removed, and limited debulking is unlikely to improve progression-free or total survival.

Diffuse pontomedullary brainstem gliomas are among the least responsive and most treatment-resistant childhood solid tumors. Conventional radiation therapy consists of 54 to 60 Gy, delivered using an involved-field irradiation protocol, administered in single daily fractions of approximately 1.8 to 2 Gy. This approach results in a median survival time of 9 to 13 months from diagnosis.[531] Despite encouraging single-institution reports suggesting prolonged progression-free survival for children with gliomas treated with hyperfractionated radiation therapy in which total radiation doses reached 78 Gy, larger cooperative trials failed to demonstrate a therapeutic advantage for this approach.[532–534] Radiation implants (i.e., brachytherapy) are not appropriate for these tumors, and the role of stereotactic radiosurgery has not been evaluated.

Chemotherapy trials for diffuse pontomedullary brainstem gliomas have yielded similarly disappointing results. Pre-irradiation single-agent or combination chemotherapy infrequently produces objective (i.e., radiographic) response rates that exceed 25%.[531] Furthermore, it is unlikely that even these limited response rates translate into significantly longer total survival. A phase III trial using CCNU, vincristine, and prednisone after radiation therapy failed to show a survival advantage over use of radiation therapy alone.[535] The use of more aggressive chemotherapy strategies including high-dose chemotherapy followed by PBSC reinfusion results in relatively brief-duration responses and few instances of significant tumor reduction lasting 12 months or longer.[536] Accordingly, it is difficult to support the routine use of chemotherapy in brainstem gliomas outside the setting of well-structured clinical trials.

Dorsally Exophytic Tumors

Dorsally exophytic tumors arise from the floor of the fourth ventricle. Although eventually the tumor often completely fills the ventricle, patients may have few if any neurologic signs for years before the development of signs and symptoms of obstructive hydrocephalus. MRI demonstrates a well-demarcated lesion, hyperintense on T_2-weighted images and hypointense on T_1-weighted images but enhancing with gadolinium (Fig. 70-25). Usually these tumors are low-grade fibrillary or pilocytic astrocytomas that are amenable to surgical resec-



Figure 70-25 • Dorsally exophytic brainstem glioma. Sagittal T_1-weighted post-gadolinium magnetic resonance image shows an intensely enhancing lesion filling the floor of the fourth ventricle, attached only at the floor at the level of the pontomedullary junction. Enhancement is characteristic of juvenile pilocytic astrocytomas. (From Halperin EG, Constine LS, Tarbell NJ, Kun LE: Pediatric Radiation Oncology, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 1999, p 99.)

tion. If substantial surgical tumor removal is achieved, often no adjuvant treatment is necessary and the patient can be managed with close observation using serial MRI scans. Use of local radiation therapy or chemotherapy is limited to the uncommon cases of malignant dorsally exophytic gliomas or the occurrence of significant tumor growth after surgery.[537]

Cervicomedullary Tumors

Cervicomedullary tumors occupy the inferior two thirds of the medulla and the upper portion of the cervical spinal cord. These histologically low-grade gliomas tend to extend from their cervicomedullary center in conformance with anatomic boundaries.[538] In contrast with midbrain tumors, intratumoral cysts are uncommon. The prediagnostic symptomatic interval may extend for several years. Surgical resection of these tumors is indicated with clinical or radiographic evidence of tumor growth. Although near-total resection is possible, the poorly defined interface between tumor and normal brainstem often precludes complete surgical removal of these tumors. Long-term follow-up studies indicate that many patients will not have evidence of growth for more than 5 years. When tumor growth is observed, its rate often is extremely slow, and malignant transformation has not been documented. As with the dorsally exophytic tumors, use of radiation therapy or chemotherapy is limited to those few cases in which progressive symptomatic tumor growth is observed and cannot be controlled by surgical approaches alone.

Cystic Nodular Brainstem Tumors

Cystic nodular brainstem tumors may be located in any region of the brainstem but most often are noted in the midbrain.[527] These tumors have a radiographic appearance identical to that of their cerebellar counterparts, and their histologic features typically are those of a juvenile pilocytic astrocytoma. Surgery is appropriate treatment for those symptomatic patients with unequivocal evidence of tumor growth on neuroimaging studies. When possible, resection of the mural nodule usually is curative. In cases in which the major portion of the tumor is in the ventral midbrain, surgical options are limited to a diagnostic biopsy, and treatment consists of radiation therapy or chemotherapy. Long-term survival for patients with these tumors often is in excess of 5 to 10 years, and a conservative management approach often is advisable.

Adult Brainstem Gliomas

As discussed previously, brainstem gliomas are much rarer in adults than in children. They account for less than 2% of all adult brain tumors.[539] In one study of 48 adults with brainstem gliomas, the overall median survival period was 5.4 years and the 3-year survival rate 66%.[540] The study investigators categorized them into three different groups. The most frequent type (in 48% of cases) occurred in young adults and resembled the diffuse pontine glioma of childhood in terms of clinical and radiologic presentation. The overall outcome (median survival of 7.3 years) was much better than that for pediatric diffuse pontine gliomas, however. This may be because in adults, many of these tumors were low-grade gliomas (in 9 of 11 patients who underwent biopsy, the tumor was found to have benign histologic features). The other common tumor type (in 31%), which occurred in elderly patients, showed ring-like contrast enhancement and was associated with a median survival period of only 11 months. Tumors in this category that were biopsied were found to be high-grade gliomas. The third group (8%) consisted of focal tectal gliomas, which affected young adults and had a favorable outcome.

The conclusion that adults with this disease have a better prognosis than children also was reached in a study from the Memorial Sloan-Kettering Cancer Center of 19 adult patients with brainstem gliomas. The investigators found the median survival period to be 54 months and the 5-year survival rate to be 45%.[541]

Intracranial Germ Cell Tumors

Germ cell tumors constitute 12.5% to 16% of all childhood tumors in Japan but only 3% to 11% in United States and Western European countries.[542] A majority are located in the pineal region and approximately a third in the suprasellar region. The clinical presentation of tumors involving the pineal region and the differential diagnosis for these tumors are discussed earlier under Tumors of the Spinal Axis. The clinical presentation with suprasellar germ cell tumor includes panhypopituitarismus, diabetes insipidus, and visual disturbances with usually long prediagnostic symptomatic intervals, often exceeding 1 year.

The neuroimaging characteristics of germ cell tumors, suprasellar or pineal, do not provide sufficient differentiation between germ cell tumor histologic types to render biopsy unnecessary.[542,543] The diversity of tumor types in the suprasellar or pineal region underscores the importance of adequate biopsy samples for accurate diagnosis. Small samples obtained from stereotactic biopsy may not identify mixed tumor types. Therefore, an open surgical biopsy approach, when possible, is preferred. Knowledge of histologic type influences surgical management. Complete resection is curative for well-differentiated teratomas. By contrast, chemotherapy and radiation therapies are ineffective with this tumor. The extent of surgical resection may be less important for germinomas, which are exquisitely sensitive to chemotherapy and radiation therapy, or for the malignant nongerminomatous germ cell tumors, which frequently spread throughout the CSF and are less responsive to irradiation and chemotherapy.

Histologic type also influences radiation treatment planning. Germinomas are very radiation sensitive. Of purely historical interest, 10- to 30-Gy "diagnostic" doses of radiation have been administered to unbiopsied suprasellar or pineal region tumors. If significant tumor reduction was observed, it was assumed to be a germinoma, and radiation therapy was continued to doses ranging from 40 to 56 Gy. This strategy is unacceptable in modern clinical practice for several reasons. Patients with mature teratoma and other radioresistant tumors are likely to receive unnecessary treatment. Furthermore, nongerminomatous or mixed germ cell tumors may respond briskly to radiotherapy but treatment tumor volume may then be insufficient

Table 70-13 Cerebrospinal Fluid and Serum Tumor Markers for Germ Cell Tumors

Tumor	AFP	β-HCG
Germinoma	–	±
Nongerminomatous GCT		
Embryonal carcinoma	±	±
Yolk sac tumor	++	–
Choriocarcinoma	–	++
Teratoma, mature	–	–
Teratoma, immature-malignant	±	±
Mixed germ cell tumor	±	±

AFP, alpha-fetoprotein; β-HCG, β-human chorionic gonadotropin.

Adapted from Kretschmar CS: Germ cell tumors of the brain in children: a review of current literature and new advances in therapy. Cancer Invest 1997;15:187.

for subsequent craniospinal radiotherapy if required. Finally, growing evidence indicates that patients with nongerminomatous or mixed germ cell tumors benefit from a combination of chemotherapy and radiotherapy.

Identification of nongermanomatous or mixed germ cell tumors may be facilitated by evaluation of specific markers in blood or CSF. Alpha-fetoprotein (AFP) is produced initially by the fetal yolk sac and later by hepatocytes. Detection of elevated levels of AFP in a patient with a CNS tumor implies the presence of primitive yolk sac elements[542] (Table 70-13). β-Human chorionic gonadotropin (β-HCG) is a marker for germ cell tumors with syncytiotrophoblast activity. Although pure germinomas may express relatively low levels of β-HCG, choriocarcinomas produce the highest levels of this hormone (see Table 70-13). β-HCG expression is not a marker of metastasis or tumor size. Placental alkaline phosphatase (PLAP) is another marker that has been found to be elevated in patients with germ cell tumors.[544] Its diagnostic use lies more in immunohistochemistry. PLAP immunostaining is positive and diagnostically definitive for germinomas.[542]

Craniospinal irradiation is clearly indicated in cases of documented leptomeningeal metastasis from germinoma; however, its use in patients with normal findings on CSF examination and spinal MRI is controversial. In a series from the University of Pennsylvania in which 39 patients with biopsy-proven germinomas all received craniospinal irradiation, regardless of extent of disease, no relapses occurred over a median follow-up time of 7.1 years, and the 10-year survival rate was 97%.[545] Of note, however, other institutions using more limited radiation fields with or without chemotherapy for biopsy-proven germinomas also have reported 5-year survival rates exceeding 90%.[546,547]

In contrast with germinomas, nongerminomatous germ cell tumors (choriocarcinoma, embryonal carcinoma, yolk sac tumors, and malignant teratomas) have a high incidence of leptomeningeal metastasis,[548] and craniospinal radiation therapy is an important component of the overall treatment plan with these tumors. Well-differentiated teratomas generally are unresponsive to radiation, and use of radiation therapy is limited to unresectable recurrent or progressive teratomas in many centers. For these cases, stereotactic radiosurgery may prove to be of greater therapeutic benefit.

Chemotherapy has an important role in the treatment of many germ cell tumors. Germinomas appear to be as sensitive to chemotherapy as they are to radiation.[549,550] Chemotherapy has been used effectively for germinomas in three settings: (1) chemotherapy without radiation therapy; (2) chemotherapy followed by reduced-dose radiation therapy for tumors with incomplete tumor response; and (3) chemotherapy after radiation therapy for tumors with incomplete tumor response. Malignant nongerminomatous germ cell tumors carry a considerably worse prognosis than that for pure germinomas.[547] Accordingly, in patients with nongerminomatous germ cell tumors,intensified chemotherapy and multimodality therapeutic strategies have been used in an attempt to improve survival.[551] A study of postoperative pre- and postradiation chemotherapy for patients with nongerminomatous germ cell tumor, but no metastases, reported a 4-year progression-free survival rate of 74%.[552]

Craniopharyngioma

Craniopharyngiomas constitute 6% to 10% of all childhood brain tumors and represent one of the three major tumor groups frequently found in the suprasellar region. These tumors probably arise from embryonic epithelial cell rests in the region of Rathke's cleft. Radiographically, their appearance typically includes a cystic or multicystic component, as well as a solid component (Fig. 70-26). Calcifications are present in a majority of cases. Craniopharyngioma cyst fluid, similar to that of a Rathke's cleft cyst, is viscous, with a high cholesterol content. Rupture of the cyst contents during surgical removal is well known to produce an intense chemical meningitis.

The clinical presentation with craniopharyngiomas is similar to that with other suprasellar tumors. The primary age at onset is in the first decade of life; however, presentation before the age of 2 years is uncommon. Approximately 25% of craniopharyngiomas are detected in the third decade or later. The primary signs and symptoms include visual dysfunction; headache; optic pallor; endocrinopathies, including growth failure and diabetes insipidus; and behavioral or learning dysfunction. On the basis of these findings, preoperative assessment of patients with suspected craniopharyngioma should include a thorough visual examination and endocrine evaluation.

Surgical removal of craniopharyngiomas is the primary therapeutic modality.[553] Complete surgical resection obviates the need for further therapy in a majority of cases. When postoperative MRI and intraoperative visual assessment show no evidence of tumor, the rate of recurrence is less than 20%; a majority of recurrences occur within the first 2 years after surgery.[554] The overall surgical approach to craniopharyngiomas, however, remains the subject of considerable disagreement. Gross total resection often is achieved at the expense of panhypopituitarism and behavioral and neuropsychological dysfunction that often severely affects the patient's quality of life.[555–557]

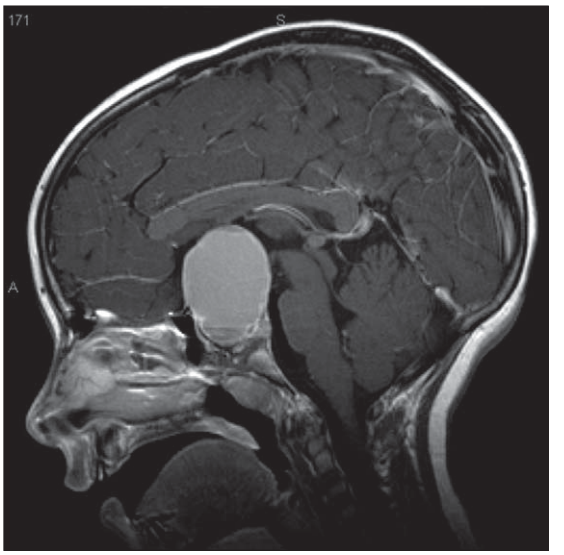


Figure 70-26 • Craniopharyngioma. Midline sagittal T_1-weighted post-gadolinium magnetic resonance image shows an enhancing cystic suprasellar mass.

An alternative surgical strategy involves planned incomplete resection followed by radiation therapy. Radiation therapy represents standard treatment for patients with residual craniopharyngioma.[558–560] Less than 50% of patients with known postoperative residual tumor who do not receive radiation therapy will survive for 10 years. By contrast, those who receive local field radiation, typically at doses of 50 to 56 Gy, have disease-free survival rates of approximately 80% at 10 years. More recent studies suggest that quality of life may be better for these patients than for children managed with aggressive surgical resection alone.[559]

No established role for chemotherapy in the treatment of craniopharyngioma is recognized. In patients whose tumor recurs after external beam irradiation with primarily a cystic component, a technique that may be useful is the instillation of colloidal β-emitting radionuclides, such as ^{32}P or ^{90}Yt.[561] This technique also has been used in some patients as first-line therapy.

Brain Tumors in Infants

Approximately 20% of childhood brain tumors occur in infants and young children before the age of 3 years. Unfortunately, the survival outcomes in this age group have been significantly less favorable than in older children, both overall and for specific tumor types.[562] These children also are at increased risk for substantial radiation-related neurotoxicity, including mental retardation, growth failure, and leukoencephalopathy.[563,564] Therefore, primary postoperative chemotherapy approaches have been adopted with the aim of postponing or even avoiding radiation therapy. Between 1976 and 1988, 17 children younger than 3 years of age with PNET/MB or ependymoma underwent treatment with a multiagent chemotherapy regimen consisting of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP).[565] Radiotherapy was reserved for treatment of recurrent disease. Eight of 12 children with PNET/MB and 2 of 5 children with ependymoma survived, and those children who did not require radiation therapy showed normal height and intellectual ability. Although a subset of infant PNET/MB can be cured by chemotherapy alone,[563,566] expectations that the use of intensive multiagent chemotherapy will improve outcomes for these children have not been realized. Ongoing cooperative group studies are testing chemotherapy dose intensification, addition of intrathecal chemotherapy, and earlier introduction of more limited radiation therapy, with restriction of treatment volumes and use of conformal techniques to minimize exposure of normal tissue.

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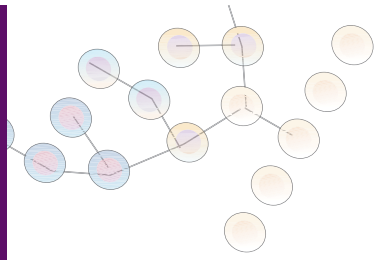
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71 Eye, Orbit, and Adnexal Structures

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SUMMARY OF KEY POINTS

Incidence
- Primary ocular (eye) and ophthalmic (eye and adnexae) tumors are relatively uncommon.
- The most common primary ocular tumors are choroidal melanoma and retinoblastoma. The most common adnexal tumors are lymphoma, rhabdomyosarcoma, optic nerve glioma, and epithelial and melanocytic malignancies of the eyelid and conjunctiva, respectively.
- Many systemic diseases can involve the eye and adnexae, especially breast and lung cancers, as well as lymphoma and leukemia.

Etiology
- The etiology of most ophthalmic tumors is unknown.
- Retinoblastoma is the prototypical model of a genetically transmissible tumor via loss of a tumor suppressor gene.
- Squamous tumors of the lids and conjunctiva are associated with sun exposure, immunosuppressed states, and viral infections.
- Ocular and orbital metastases are unexpectedly frequent; approximately 25% of ocular metastases are discovered at an occult stage.

Diagnosis
- Intraocular tumors can be directly visualized, greatly facilitating diagnosis, but the biopsy is not easy and is limited to special circumstances.
- For intraocular tumors, a combination of funduscopic examination, intravenous angiogram, ultrasonography, and CT/MRI imaging can yield diagnostic accuracies over 90%–95%.
- Orbital and adnexal tumors are diagnosed by CT/MRI imaging and biopsy.

Treatment
- Intraocular tumors are treated with local modalities such as external beam irradiation, brachytherapy, and photocoagulation, with or without chemotherapy. If useful vision cannot be preserved in the tumor-containing eye, the eye is enucleated.
- Orbital malignancies are frequently treated by radiation/chemotherapy, but exenteration may be necessary in far-advanced sarcomas.
- Eyelid and conjunctival malignancies are managed by local excision, with or without topical chemotherapy; cryotherapy; or irradiation.
- Metastatic malignancies may be palliated by external beam irradiation.
- Because radiation is widely utilized in treatment of ophthalmic malignancies, radiation toxicity is an exceedingly important issue in management protocols. Ophthalmic tissue components range from extremely radiosensitive tissues, such as the lens, to radioresistant tissues, such as the retina and the optic nerve.

INTRODUCTION

In today's practice of oncology, the role of radiation therapy is vast. As with other oncologic subspecialties, the practice of ophthalmic oncology would be impossible without the use of radiation for imaging and therapeutic purposes.[1] A practical approach to a discussion of ophthalmic tumors—as with tumors of other anatomic regions—is to consider neoplastic conditions of the major structures with primary involvement: the globe, the conjunctiva and eyelids, and the orbit. Because the tumors and tumor-like conditions of these structures are exceedingly diverse, only the common entities that are encountered in daily practice are addressed in this chapter (Tables 71-1 to 71-4).

Retinoblastoma is a much more radiosensitive tumor than uveal melanoma; however, for both of these intraocular neoplasms, radiation treatment, in one form or another, is an indispensable management tool for today's ocular oncologist. Radiation also is used for the treatment of rarer types of intraocular tumors such as juvenile xanthogranuloma, ocular or central nervous system (CNS) lymphoma, multiple myeloma, leukemias, and some metastatic tumors.[2]

One large group of conjunctival, eyelid, and orbital tumors that respond to radiation therapy, alone or in combination with chemotherapy, are the lymphoproliferative neoplasms. In contrast with lymphoid lesions, epithelial tumors of the conjunctiva and the eyelids—including basal cell carcinoma, squamous cell carcinoma, and melanoma—are not very responsive to radiation, and severe ophthalmic complications may develop after radiation treatment. In this group of tumors, certain types of malignancies, such as sebaceous gland carcinoma, pose considerable therapeutic challenges in that although the tumor is radiation sensitive, the therapy results in substantial adverse effects in the eye. In most instances, ocular oncologists avoid this treatment modality. Accordingly, use of irradiation usually is limited to treatment for the advanced stages of these tumors, primarily for palliation.

In orbital tumors other than lymphoproliferative lesions, radiotherapy has been successfully used for rhabdomyosarcoma and, with less rewarding results, for other mesenchymal malignancies. Epithelial tumors of the lacrimal gland, sebaceous gland tumors, and histocytic tumors occasionally respond well to radiation treatment. Primary tumors of the optic nerve, including optic nerve glioma and meningioma, also benefit from radiation treatment. In the advanced stages of aggressive sarcomas, radiation treatment also may be used as an adjunct to surgery and chemotherapy.[3]

Finally, some of the idiopathic inflammatory conditions of the orbit, including Graves disease and pseudotumor of the orbit, also may be treated with radiation.[4,5]

Table 71-1 Malignant Intraocular Neoplasms

PRIMARY MALIGNANT TUMORS OF THE GLOBE
Uveal melanoma*
Primary intraocular lymphoma (PIOL)*
Medulloepithelioma
Rhabdomyosarcoma
Leiomyosarcoma
Neuroepithelial adenocarcinoma
Retinoblastoma*

SECONDARY MALIGNANT TUMORS OF THE GLOBE
Conjunctival/skin carcinoma*
Orbital sarcoma
Lacrimal gland carcinoma

METASTATIC TUMORS OF THE GLOBE
Carcinoma*
Neuroblastoma
Melanoma
Carcinoid tumor
Leukemia/lymphoma*

*Relatively common tumor; discussed in text.

Table 71-2 Malignant Conjunctival Neoplasms

ATYPICAL REACTIVE LYMPHOID HYPERPLASIA INVOLVING CONJUNCTIVA

PREMALIGNANT LESIONS OF CONJUNCTIVA
Actinic keratosis*
Carcinomatous intraepithelial neoplasia
Primary acquired melanosis (PAM)*

PRIMARY MALIGNANT TUMORS OF CONJUNCTIVA
Squamous cell carcinoma*
Mucoepidermoid carcinoma*
Melanoma*
Sebaceous gland carcinoma*
Lymphoma*
Kaposi's sarcoma*

SECONDARY MALIGNANT TUMORS OF CONJUNCTIVA
Uveal melanoma
Orbital sarcomas
Eyelid malignancies*
Lacrimal drainage system malignancies
Retinoblastoma*

METASTATIC TUMORS OF CONJUNCTIVA
Distant carcinomas
Leukemia

*Relatively common tumor; discussed in text.

Table 71-3 Malignant Eyelid Neoplasms

PREMALIGNANT LESIONS OF EYELIDS
Actinic keratosis*
Lentigo maligna*
Juvenile xanthogranuloma*

PRIMARY MALIGNANT TUMORS OF EYELIDS
Basal cell carcinoma*
Bowen's disease*
Squamous cell carcinoma*
Melanoma*
Sebaceous gland carcinoma*
Kaposi's sarcoma
Malignant skin appendage tumors
Merkel cell carcinoma

SECONDARY MALIGNANT TUMORS OF EYELIDS
Uveal melanoma
Orbital sarcomas

METASTATIC TUMORS OF EYELIDS (exceptionally rare)

*Relatively common tumor; discussed in text.

This chapter summarizes the specifics of radiation therapy and other recommended modalities for the management of the ophthalmic neoplasms commonly encountered in clinical practice (for discussion of other, rare ocular and periocular tumors, the reader is referred to ocular oncology textbooks and review references[6–10]). First, however, the effects of radiation on each of the major tissues and structures of the eye are reviewed.

RADIATION TOXICITY IN THE EYE

The eye is a complex organ composed of structures with widely variable radiation sensitivity. Its different components range from extremely radiosensitive tissues, such as the lens, to radioresistant tissues, such as the retina and the optic nerve.[11] The variations in radiation effect on the eye are dependent not only on tissue sensitivities but also on the methods of radiation delivery. Today, a majority of ophthalmic radiotherapy protocols involve the use of external beam radiation therapy (EBRT); indications for brachytherapy are fewer. With EBRT, radiation is delivered as photons (gamma rays or x-rays) or particles (e.g., protons and neutrons), primarily with linear accelerators.[12,13] Newer techniques of radiation delivery improve the rates of ocular toxicity. For example, proton-photon accelerated fractionated radiation (AFR) allows the delivery of treatment doses to advanced tumors of the nasal cavity and paranasal sinus, with tolerable eye complication rates.[14] Modern EBRT techniques such as stereotactic fractionated radiation therapy (SFRT), photon EBRT, and carbon ion boost appear to allow safe delivery of high target doses to patients with locally advanced orbital malignancies. Although the ocular toxicity rates are reported to be reduced compared with the historical neutron therapy data, the follow-up periods are limited because of limited survival of these patients.[15,16]

From the standpoint of radiation toxicity, the eye and periocular tissues can be divided into several zones: external eye (conjunctiva, cornea and the tear layer); anterior intraocular components (iris, anterior chamber angle, and lens), posterior intraocular components (retina, choroid, and optic disc), eyelid, orbital soft tissues, hypothalamus, and pituitary gland.

Table 71-4 Malignant Orbital Neoplasms

LESIONS WITH CLINICALLY MALIGNANT BEHAVIOR
Langerhans cell tumors*
Non-Langerhans cell tumors*
Atypical lymphoid hyperplasia*
Meningioma of optic nerve*
PRIMARY MALIGNANT TUMORS OF ORBIT
Lymphoma*
Lacrimal gland carcinomas*
Rhabdomyosarcoma*
Primitive neuroectodermal tumors
Malignant peripheral nerve sheath tumor
Alveolar soft part sarcoma
Melanoma
Osteosarcoma
Fibrosarcoma
Leiomyosarcoma
Chondrosarcoma
Liposarcoma
Glioma of optic nerve*
SECONDARY MALIGNANT TUMORS OF ORBIT
Eyelid malignancies*
Conjunctival malignancies*
Uveal melanoma*
Retinoblastoma*
Lacrimal drainage system malignancies*
Paranasal sinus and nasal carcinoma*
Brain tumors
METASTATIC TUMORS OF ORBIT
Distant carcinomas (e.g., breast, lung, gastrointestinal tract)*
Neuroblastoma*
Leukemia (granulocytic sarcoma)
Carcinoid tumor
Metastatic melanoma

*Relatively common tumor; discussed in text.

External Eye

Most of the tissues of the external eye, including the epithelium of the conjunctiva, cornea, glandular excretory ductules, and lacrimal drainage apparatus, have the same sensitivity as that of skin, because these structures are lined with epithelial cells, which are characterized as vegetative intermitotic cells (VICs). During the acute phase of radiation (within 6 months), fractional doses of 20 Gy cause erythema and edema of the eyelid skin and conjunctiva; if the dose is high enough, keratinization of the epithelium also takes place. The tear layer becomes thinner and irregular secondary to edema of the parenchyma of the lacrimal and meiobomian glands and goblet cells. Also, the damage to the epithelial cells of glandular ductules reduces the inflow of tears. Disruption of the tear layer is a serious matter, causing problems ranging from a scratchy sensation and mild visual distortion to severe external eye infections and cornea-sclera melt, which may even lead to perforation. Among its other functions, the tear layer possesses bactericidal properties because it contains immunoglobulins and lysozomes; it also flushes away foreign materials and bacterial debris from the external eye into the lacrimal drainage system. When the composition and the quantity of the tear layer are distorted by radiation-induced changes, both of these antibacterial properties are lost. As the orthovoltage dose approaches 40 to 50 Gy, a confluent mucositis appears. At this stage, lacrimal gland secretions are reduced and thickened, and the external eye may become infected. During this period, photophobia also may be noted.

In the subacute period, ranging from 6 to 24 months, telangiectasias may develop in the skin and the conjunctiva, and the dryness worsens. The cornea demonstrates few structural changes until fractionated doses are in the range of 50 Gy; at this point, superficial punctate keratitis may develop. The cause of corneal damage also is twofold: (1) the direct toxicity of ionizing radiation on its epithelial cells and stromal collagen and (2) drying of the ocular surface. Punctate keratitis, which develops during the acute stages owing to focal epithelial erosion and edema, becomes worse. Along with epithelial changes, the corneal sensation diminishes for weeks to months. During the subacute phase, scarring of the cornea may advance if deep keratitis was present during the acute period. Further scarring may lead to vascularization and thinning of the stroma, which in turn may lead to total opacification or perforation.[17] Medical and surgical management of radiation keratopathy may be difficult owing to poor wound healing.

It would be an error to underestimate the consequences of the dry eye syndrome and to send the patient home with artificial tears and antibiotic or steroid eyedrops or ointments. The management of dry eye should be directed by an ophthalmologist who is familiar with current treatments for radiation toxicity, which range from simple supplementation with artificial tears to complex surgical interventions. The scope of this chapter does not allow a detailed discussion of dry eye management; the reader is referred to recent reviews.[18,19]

The sclera maintains the structural integrity of the anterior eye as well as that of the posterior eye. The sclera consists of thick, irregular collagen bundles, and it is less affected by ionizing radiation than the cornea.[20] No scleral radiation damage has been reported after EBRT at doses up to 60 Gy. High scleral brachytherapeutic doses (e.g., in excess of 600 Gy), however, can cause melting of the sclera.[21] In practice, strontium 90 (^{90}Sr) and ruthenium 106 (^{106}Ru) are more likely to deliver much higher scleral doses than is either iodine 125 (^{125}I) or palladium 103 (^{103}Pd) during plaque radiation therapy of intraocular tumors.[22]

Anterior Intraocular Components

The iris is located behind the cornea and in front of the lens and extends into the ciliary body. The iris and ciliary body are composed of fibroblasts, smooth muscle, vessels, and columnar pigmented and nonpigmented epithelial cells. Many of these cells are reverting postmitotic cells and therefore are quite resistant to radiation. Iritis has been reported with a single dose of 10 to 20 Gy, but severe anterior uveitis is not observed until higher doses of 30 to 40 Gy (in 10-Gy fractions) are given, and then appears only after 6 to 8 weeks. Radiation iritis may be followed by secondary glaucoma. Dry eye-related corneal ulceration also may exacerbate iritis and secondary iris neovascularization.[23] Localized iris atrophy has been noted after brachytherapy for iridociliary melanomas but not after EBRT for orbital tumors.[24,25]

Among the anteriorly located intraocular tissues, the crystalline lens is uniquely susceptible to radiation injury. The lens is an avascular protein structure covered by an elastic tissue capsule. The anterior surface of the lens has a layer of epithelial cells that do not show much mitotic activity; these cells behave as reverting postmitotic cells. Near the equator of the lens, however, the epithelial cells divide regularly and thus behave as VICs. Formation of cataracts is the most frequently encountered delayed radiation effect in the mammalian

eye. It is known that DNA damage and abnormal protein cross-linking lead to development of opacities within the lens protein; however, the exact mechanism of the DNA damage by radiation is not known.[26] Some practitioners postulate that cell membrane permeability changes are caused by radiation, whereas others hypothesize that radiation changes the activity of certain enzymes of the lens cortex.[27] The thermal damage also should be taken into account as a cataractogenic influence because heat cannot be dissipated effectively in the avascular lens tissue.

The best clinical description of radiogenic cataracts has been reported by Cogan and associates[28] (Fig. 71-1). The development of radiation opacity begins in the posterior subcapsular zone when small granules turn into small vacuoles as they enlarge to 3 to 4 mm within months; a central clear area may be identified during development. If this opacity progresses, a hard, central, circular plaque of highly reflective material develops at the posterior pole. As the posterior opacity becomes denser, a faint anterior subcapsular cataract containing interspersed vacuoles and occasional fine striations may be seen. When the changes progress slowly over several years and the entire lens becomes opacified, it can no longer be distinguished from other types of mature cataract.

The development of radiation opacity is dose, time, and age dependent (Fig. 71-2). Significant variation, however, is observed among persons who receive the same dose. The lenticular opacities do not always interfere with vision; clinically significant cataract development usually requires higher doses and longer postradiation times. The latent period for production of cataracts from the time of exposure is on average 2 to 3 years but may range from 6 months to 3 decades.

In Merriam and Focht's classic study, a large series of patients undergoing EBRT for ocular and orbital malignancies was studied from the standpoint of cataract formation.[29] The higher the absorbed dose, the shorter the latent period to cataract fomation. Single doses of 2 Gy or fractionated doses of 4 Gy result in the formation of posterior lens opacities but rarely in significant visual impairment. A dose of 7.5 Gy, however, invariably causes clinically significant cataract formation. A similar incidence has been noted with 14 to 21.5 Gy given over a period of 1 to 3 months. Merriam and Focht concluded that a given dose of radiation becomes less likely to produce a cataract when it is fractionated over a longer period. Fractionation of the radiation dose delays the onset and decreases the incidence of cataract development and slows its progression, as does the use of partial and total shielding of the equatorial areas of the lens.[30]

Because of treatment-related toxicity, studies increasingly focus on long-term complications secondary to hematopoietic stem cell transplantation in survivor populations. Gurney and coworkers recently reported an incidence of cataracts of 36% at 15 years after transplantation; cataracts developed only in those patients who received total-body irradiation as a conditioning regimen or head irradiation before transplantation.[31] Of 4000 cancer survivors, 4% had cataracts. Cataracts were a frequent occurrence in survivors of hematologic diseases (chronic leukemia, 17%; myeloma, 13%; acute leukemia, 9%; and lymphoma, 7%).[32] Cataracts that develop as a late effect following hematopoietic stem cell transplantation are related to either the transplantation process or the transplantation-preparative regimen. Problems related to the transplantation process include delayed recovery of the immune system and chronic graft-versus-host disease (GVHD). Chronic GVHD manifests between 3 and 14 months after transplantation in approximately 20% of matched sibling transplant recipients and in 40% of matched unrelated donor transplant recipients. Cataracts develop secondary to total-body irradiation or prolonged corticosteroid use. Cataracts developing after fractionated radiation do not impair the vision significantly enough to be removed.[33]

Another concern with radiation toxicity is the ocular exposure during modern imaging procedures. Although the great majority of CT scanners deliver lower than the threshold dose for development of cataracts, nevertheless the potential exists for delivery of higher doses.[34]

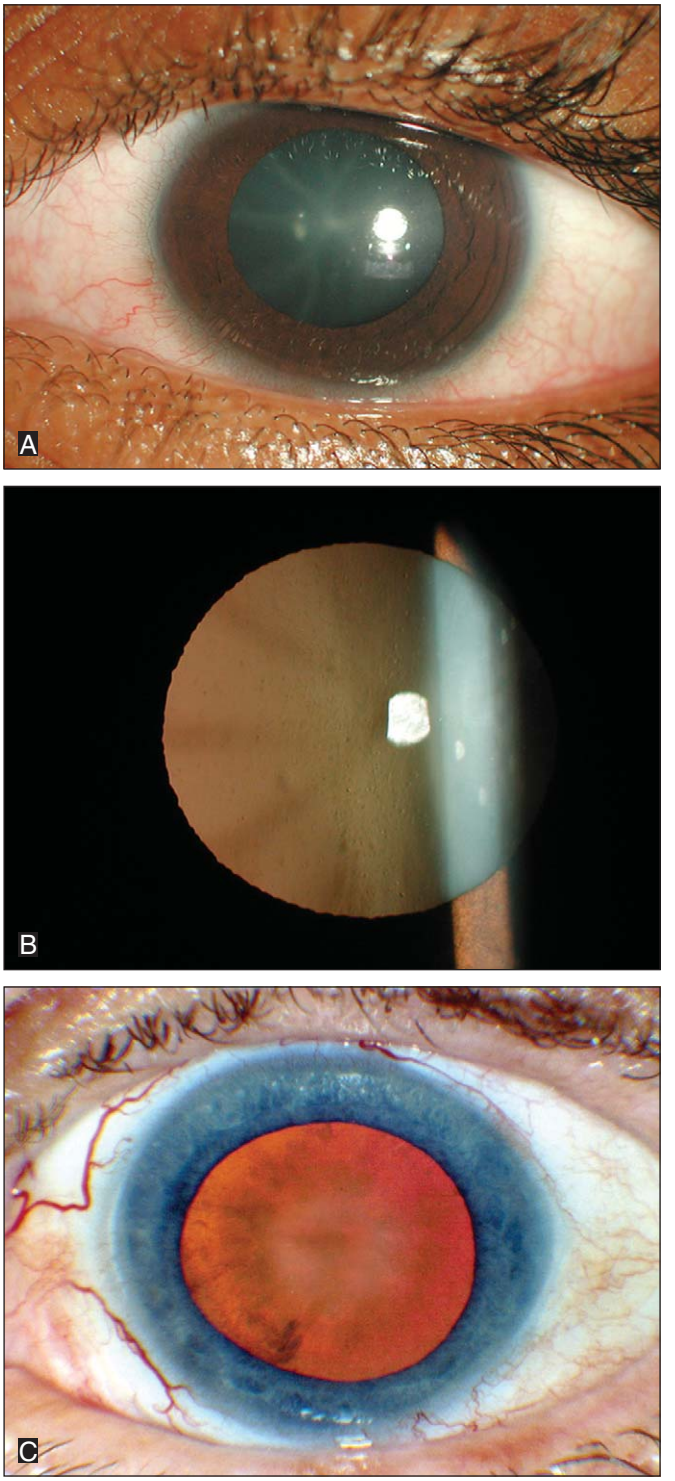


Figure 71-1 • **A–C,** Slit-lamp appearance of radiation cataracts.

It has been reported that comprehensive imaging in patients with stroke may result in radiation exposure up to local doses of 490 mGy. Although critical doses for organ damage (e.g., cataract formation or hair loss) are not reached, physicians need to be aware of possible radiation-induced complications, particularly with repetitive examinations.[35] For decades, it has been known that in utero exposure to radiation, particularly during the first trimester, can result in cataract formation, as well as pigmentary degeneration of

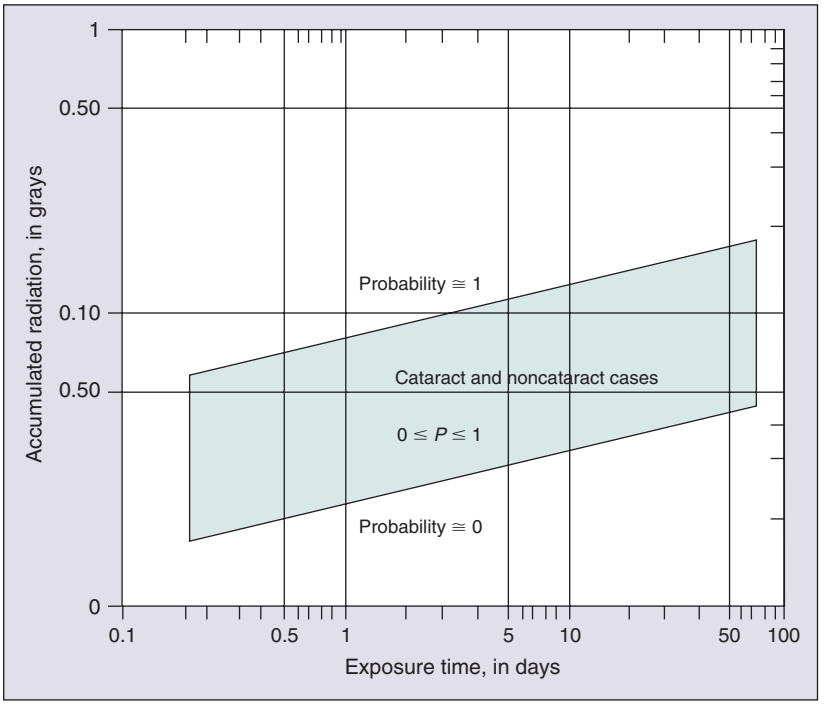


Figure 71-2 • Influence of radiation dose and exposure time on cataract formation in humans. (Data from Mettler FA, Moseley RD: Medical Effects of Ionizing Radiation. Orlando, FL, Grune & Stratton, 1985, p 138.)

the retina or microphthalmia.[36] Bateman indicated that doses in the range of 3 to 5 Gy delivered during the first half of the pregnancy are quite damaging to the neurons of the developing retina, although as the neurons mature, they become much more radioresistant.[37] Long-term topical and systemic administration of corticosteroids is well known to induce formation of posterior subcapsular cataracts. In humans and experimental animals, even a low dose of radiation given with steroid treatment accelerates the development of lenticular opacities.[38]

Posterior Intraocular Components

The retina, choroid, and optic nerve are composed of relatively radioresistant tissues. At common therapeutic dose levels, acute effects of irradiation are rare; however, at doses higher than 50 Gy, acute retinal edema may occur, although this effect usually is transient (Fig. 71-3).

Chronic radiation damage to posterior ocular tissues usually is the result of disruptions in the vascular supply and is primarily a form of microangiopathy. Because of the radiation damage to vascular endothelial cells, abnormal vascular permeability occurs, and vascular lumina are narrowed or obliterated. Owing to vascular disruption, the nerve fiber layer becomes ischemic, with the potential for the development of infarcts, exudates, and hemorrhages. The retinal vascular changes include totally occluded "ghost" vessels, vascular sheathing, microaneurysm formation, increased tortuousity, retinal telangiectasis, and eventually neovascularization (see Fig. 71-3). The associated abnormal vascular permeability may impair vision secondary to macular exudates, often in a circinate pattern. Vascular occlusions of both the arterial and venous circulation may occur. Radiation retinopathy in the macula causes vision loss and blindness. Serious hemorrhagic complications may result from fragile vasculature and the neovascular tufts, leading to a hemorrhagic retinitis or a vitreous hemorrhage. Organized vitreous hemorrhage and associated fibrovascular proliferations may produce a traction retinal detachment followed by phthisis bulbi. Characteristic alterations also occur in the retinal pigment epithelium (RPE), leading to pigmentary mottling over large areas and extensive RPE cell atrophy. Occasionally, large areas of chorioretinal thinning are so pronounced that the sclera can be clearly visualized beneath this layer on ophthalmoscopic examination. Typically, onset of radiation retinochoroidal disease is between 6 months and 3 years after treatment; in some patients, however, the disease develops after much longer periods.[39] It has been reported that retinal damage may be produced by EBRT at doses as low as 15 Gy but is more common after EBRT at fractionated doses of 30 to 35 Gy. (At total fractionated doses of 70 to 80 Gy, retinopathy would occur in 85% of eyes.) Diabetes and chemotherapy, when combined with irradiation, seem to have an additive effect on progression of retinopathy. An associated papillitis often is seen with radiation retinopathy.

Both anterior ischemic optic neuropathy and posterior vascular occlusions can occur in the optic nerve, leading to visual loss (see Fig. 71-3). Radiation optic neuropathy can temporarily cause decreased vision, with later improvement over several months. This entity involves the anterior optic nerve and is characterized acutely by hyperemia and disc edema. Peripapillary hemorrhages and subretinal fluid also may be present. With EBRT, the mean total fractionated dose causing this effect is 55 Gy, with a range of 36 to 72 Gy. The mean latent period after radiotherapy is 19 months (5 to 36 months). Optic atrophy may be found secondary to ganglion cell degeneration or after a direct vascular insult.[40,41]

In a long-term study of optic nerves that received a radiation dose greater than 60 Gy, the 15-year actuarial risk of optic neuropathy was 11% when fraction size was less than 1.9 Gy per day, compared with 47% for larger fractions.[42]

Eyelid and Orbital Tissues

Main eyelid changes associated with EBRT include acute erythema, depigmentation, atrophy, telangiectasias of the eyelid skin, and loss of eyelashes; ectropion and entropion also are seen.[43,44] Radiation typically travels through the skin and other structures of the eyelids on its way to treat orbital tumors. Eyelid skin behaves like skin of other sites, but it is thinner. The first reaction is erythema (typically seen at 2 to 4 weeks after initiation of treatment), followed by dry and moist desquamation. Erythema, or reddening, usually is transient and subsides rapidly. Eyelid and periorbital skin erythema occurs if a single dose of 6 to 8 Gy is given and may not be identified until 1 to 2 days after irradiation. The higher the radiation dose, the more quickly the erythema develops. Erythema increases during the first week and usually fades during the second week. It then may return

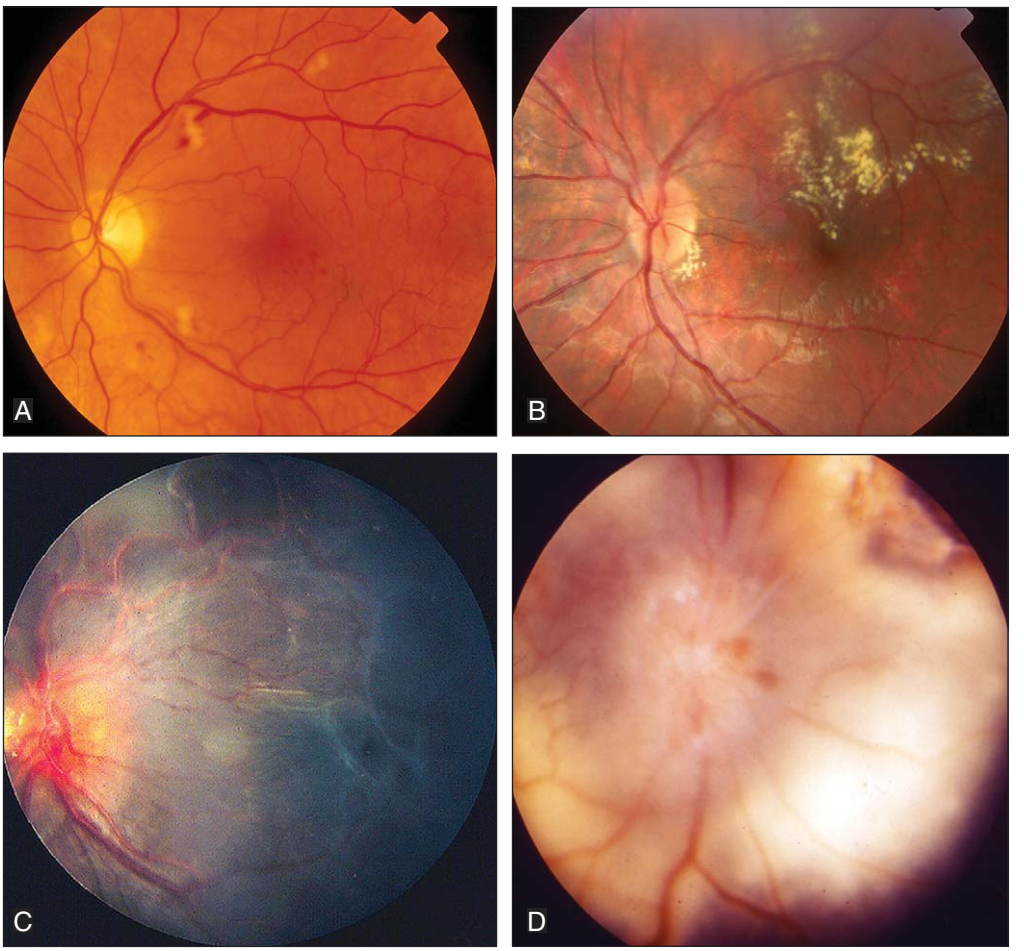


Figure 71-3 • **A,** Acute radiation toxicity with focal intraretinal hemorrhages and cotton-wool spots. **B** and **C,** Chronic radiation toxicity of the fundus with hard exudates, edematous and necrotic retina, infarcted choroid, and vascular changes ranging from tortuosity and engorgement (**B**) to diffuse atrophy ("silver-wire vessels") (**C**). **D,** Acute papillitis secondary to external beam irradiation for treatment of retinoblastoma. (**A** and **B,** Courtesy of Dr. Edward Chaum, Memphis, TN.)

2 to 3 weeks after the initial insult and last for 20 to 30 days. The early reddening presumably is due to release of vasoactive amines. The second phase of erythema is due to vessel damage; thermographic studies demonstrate increased blood flow during the first 2 to 3 months. Desquamation usually is healed by the time treatment has ended because compensatory regeneration occurs in the basal layer of the skin. Moist desquamation is more common after doses of 50 to 60 Gy (in 1.8- to 2.2-Gy daily fractions) given over 5 to 6 weeks, and also more common where superficial lesions break the skin. Healing typically is slow and may take up to 4 weeks. No radiation-related scar usually results unless an unusually high dosage is used or a complication such as secondary infection occurs.

Scarring can result in entropion or ectropion of the eyelids. Slowly progressive skin alterations may lead to depigmentation and telangiectasias.[1] The accessory glands around the eye (including Moll, meibomian, and lacrimal glands) contain reverting or fixed postmitotic cells; the ductal epithelium for some of these glands contains VICs as well. Thus, the excretory ducts, particularly in the meibomian glands, are relatively sensitive to direct effects of radiation, as are the equatorial regions of the optic lens and the basal cell layer of the cornea. Meibomian glands are of about the same radiosensitivity as that of hair follicles, but sweat glands are somewhat more resistant.

With EBRT, temporary loss of hair occurs in about 3 weeks with 3 to 5 Gy. Hair begins to return during the second month, and regrowth continues for up to 1 year. Single doses of 7 Gy may cause permanent epilation, with a latent period of less than 3 weeks. Not all body areas have the same radiation epilation sensitivity. The scalp and beard are most sensitive, with less sensitivity in the eyebrow and then the eyelashes. Eyelash loss may be incomplete or complete, depending on the dose and dose rate. It may occur with as little as 10 Gy but can be permanent with as little as 30 Gy. A radiation dose of 50 Gy has been used to achieve permanent epilation in patients with trichiasis and secondary corneal disease.

Doses in the range of 30 to 40 Gy can be delivered to the entire orbit without functional effect on the main lacrimal gland. On the other hand, evidence of histopathologic atrophy of the lacrimal gland has been reported with single doses of 20 Gy and after 50 to 60 Gy given over a 6-week period.[45] Although the mesenchymal tissues of the orbit including the extraocular muscles, fibroconnective tissue, and fat are rather resistant to radiation, orbital deformity leading to fascial asymmetry remains a major problem, particularly in children younger than 6 to 8 years of age who receive a tumor dose of approximately 50 Gy[46] (Fig. 71-4).

Another very serious side effect of orbital EBRT is that it increases the incidence of multiple primary malignancies in patients with retinoblastoma and other childhood malignancies such as rhabdomyosarcoma, Ewing's sarcoma, Hodgkin's lymphoma, and Wilms' tumor.[47–49] Acute leukemias also have been reported among the patients who survive retinoblastoma.[50] When the relative risk of death was calculated, it was found to exceed the expected rates for malignant tumors of bone and soft tissues by 300-fold, for melanoma by100-fold, and for brain tumors by about 25-fold.[51] At 40 years of follow-up, the cumulative mortality rate for all second primary malignancies was approximately 25% (expected 1.3%) for bilateral tumors and 1.5% (expected 1.1%) for unilateral disease. In the patients with bilateral retinoblastoma, radiotherapy further increases the risk of death. Early detection and management of these tumors are very difficult.



Figure 71-4 • A patient who underwent orbital exenteration and external beam irradiation for unilateral retinoblastoma. Note the deformity of the left socket and ulceration of the skin posteriorly.

Hypothalamus and Pituitary Gland

Hypothalamic and pituitary dysfunction with growth hormone deficiency with height loss is commonly seen in children irradiated for optic nerve glioma.[52,53]

INTRAOCULAR TUMORS

The most commonly encountered malignancies in adults and children—uveal melanoma, metastatic tumors to the eye including leukemia, intraocular lymphoma, and retinoblastoma—are reviewed in this section.

Uveal Melanoma

Uveal melanoma is the most common primary malignancy of the eye, but it comprises only 5% of all melanomas in the body.[54] Up to 85% of ocular melanomas are uveal (primarily choroidal) in origin. The annual incidence of this tumor is approximately 4 per million population in the United States; this incidence is similar to that reported from European countries. The most recently reported male-to-female ratio is 4.9:3.7.[55]

Pathogenesis

Approximately 98% of cases of uveal melanoma occur in the white population. This racial predisposition to uveal melanoma has been explained on the basis of susceptibility of the white persons to the oncogenic effects of sunlight. Although this hypothesis is convincing for skin melanoma, the evidence with regard to uveal melanoma is conflicting.[56] It is well known that intraocular melanoma develops as a result of the proliferation of uveal melanocytes, but the knowledge regarding this tumor's molecular pathogenesis is rather limited. It seems conceivable that these cells are intrinsically resistant to apoptosis because of constitutive Bcl2 expression. Hypothetically, the main event in the neoplastic conversion of the uveal melanocyte appears to be the inhibition of the Rb pathway. Genetic alterations that subvert the Rb and p53 pathways probably occur early, allowing the altered melanocytes to reenter the cell cycle and proliferate. The proliferation of the melanocytes may then become arrested by other tumor suppressor mechanisms, resulting in a dormant nevus; most of the nevi are permanently arrested at this stage. For further growth to occur, activation of a "malignant switch," such as a reinhibition of the p53 pathway, may be necessary subsequent to another genetic shift.[57] Recently, a gene expression-based classification of uveal melanomas that predicts metastatic death has been reported, which may represent a breakthrough in current understanding of the molecular pathobiology of this neoplasm and may lead to major changes in management protocols for uveal melanoma. According to this scheme, class 1 tumors carry a low risk and class 2 tumors a high risk for metastatic death.[57,58]

Table 71-5 Classification of Uveal Melanomas by Size

	Tumor Size		
Dimension	**Small**	**Medium**	**Large**
Diameter (mm)	<10	10–15	>15
Height (mm)	<2	2–5	>5

Clinical Features

Most patients remain asymptomatic unless the tumor involves the macula by means of direct extension, secondary retinal detachment, or macular edema. Large, anteriorly located tumors may induce lenticular astigmatism, cataract, or glaucoma. The typical posterior lesion is an elevated, brown, oval, dome-shaped choroidal mass (Table 71-5). These tumors occasionally may be amelanotic. The presence of orange lipofuscin pigment at the level of the RPE is characteristic of choroidal melanoma (Fig. 71-5). Mushroom-shaped eruption of the tumor through Bruch's membrane also is highly characteristic of melanoma.

Many conventional and newer imaging techniques, including fundus photography, Optomap (Optos, Marlborough, MS), intravenous angiography with or without indocyanine green, A- and B-scan ultrasonography, three-dimensional scan ultrasonography scanning, color Doppler imaging, ultrasound biomicroscopy (using higher-frequency ultrasound), optical coherence tomography (OCT), computed tomography (CT), and positron emission tomography (PET), may be used for diagnosis and treatment of choroidal melanoma. The most useful techniques are fundus photography, A- andB-scan ultrasonography, and intravenous fluorescein angiography (IVFA). Ultrasonography is the most important diagnostic modality in evaluation for suspected choroidal melanoma. Standardized A-scan ultrasonography can reliably differentiate the low-to-medium internal tumor reflectivity with a high initial scleral spike (positive angle kappa sign) of melanomas from medium-to-high internal tumor reflectivity of metastatic tumors and the high internal reflectivity of choroidal hemangiomas and osteomas (Fig. 71-6).

Fine-needle aspiration and incisional biopsy occasionally may be valuable procedures for diagnosis of choroidal tumors of unknown origin. The relatively high frequency of postoperative complications and the potential risk of dissemination of tumor cells underline the importance of careful case selection. In the great majority of cases, the diagnosis of melanoma is based on clinical and imaging information.[59]

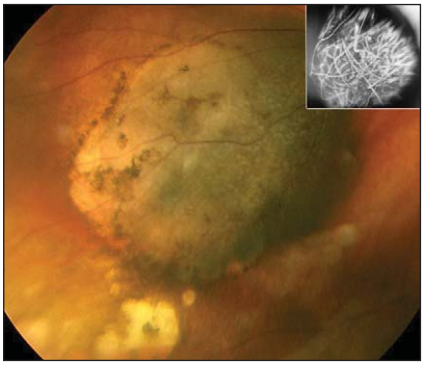


Figure 71-5 • Funduscopic appearance of pigmented choroidal melanoma as a dome-shaped elevation; orange pigment partly covers its surface. *Inset*: Intravenous fluorescein angiography of the tumor depicts diffuse vascularity.

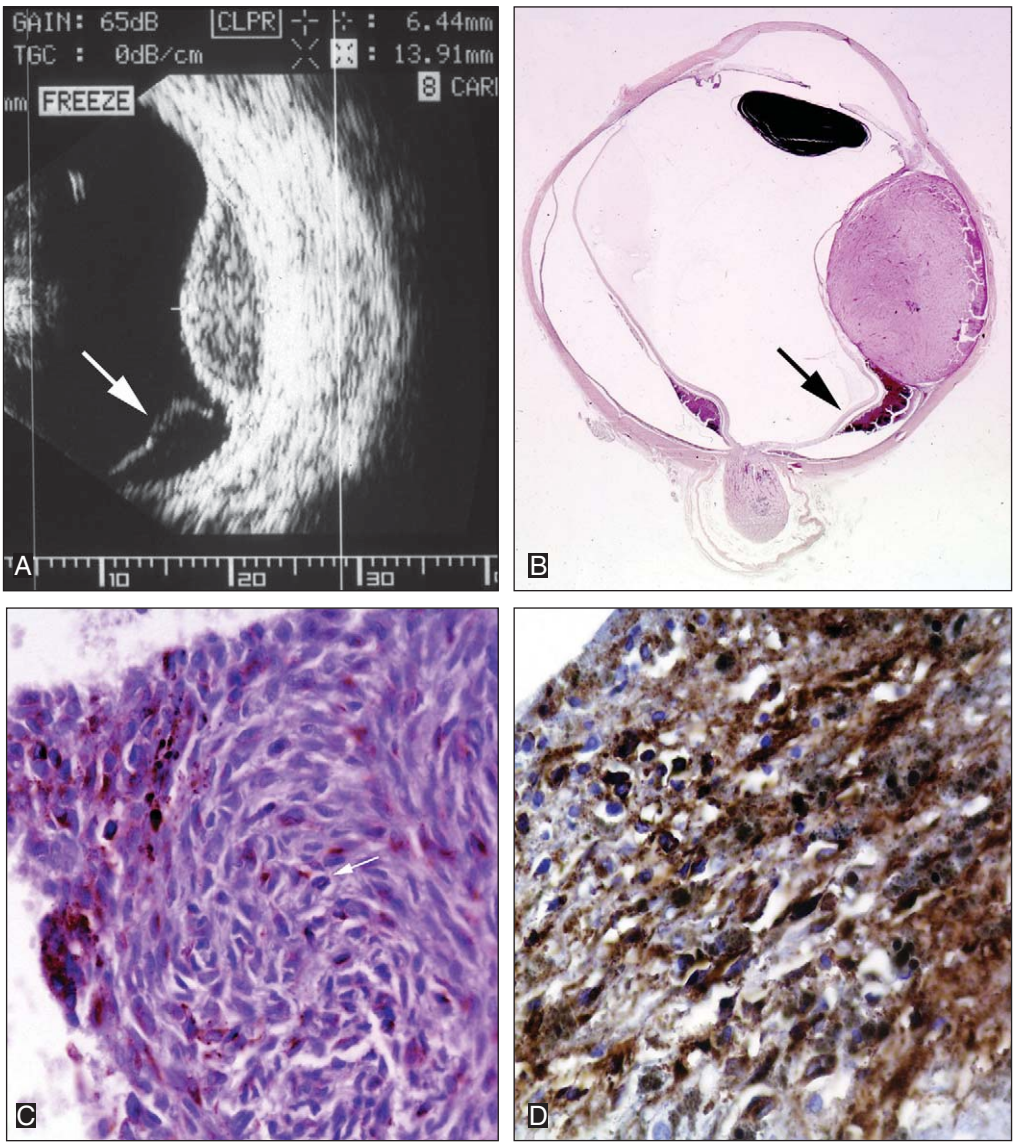


Figure 71-6 • **A,** B-scan ultrasonographic appearance of choroidal melanoma with inferior retinal detachment (*white arrow*). **B,** The low-power histopathologic appearance of a choroidal melanoma with corresponding inferior retinal detachment (*black arrow*) is similar to that of the tumor in **A**. **C** and **D,** Histopathologic detail of a mixed, spindle and epithelioid cell choroidal melanoma in hematoxylin-eosin and Melan A stains, respectively. Numerous pleomorphic epithelioid tumor cells and mitotic figures are present (*white arrow*).

These tumors metastasize primarily to the liver. Usually within 15 years after the initial diagnosis of posterior uveal melanoma, metastasis develops in approximately 50% of the patients. Clinically evident metastatic disease at the time of initial presentation, however, is very rare, so if early metastasis is present, it is subclinical in most cases. The traditional means of metastasis detection has been screening with liver function tests and chest radiographs. Currently, however, the value of whole-body PET/CT in screening for metastatic choroidal melanoma has been emphasized. Liver enzyme levels can be normal in the presence of PET/CT abnormalities, but false-positive results on up to 5% of these assays also are possible.[60] The main disadvantages of PET/CT imaging are the high cost and the sometimes limited availability, but from the standpoint of sensitivity, this approach is superior to the conventional methods of screening for detection of metastatic disease.

Orbital extension of uveal melanoma is another major potential problem with these tumors.[61] Transscleral extension and invasion of the adjacent soft tissues usually occur with large choroidal melanomas composed of epithelioid cells, but occasionally medium-sized tumors of mixed cell type also may invade extraocular structures to a limited degree. Intraocular melanoma is known to leave the eye through emissarial channels, extend onto the scleral surface, and disseminate into the orbital soft tissues (Fig. 71-7). It has been reported that approximately 10% of patients with ciliochoroidal melanomas have extrascleral extension at the time of enucleation.[62] In the early stages of the extrascleral extension, the tumor manifests as a nodular formation, but as it grows, it may be widespread and extend into the meninges, into the optic nerve, and to the lumina of the orbital vasculature (see Fig. 71-7).

With continued growth, the mass effect of the retrobulbar melanoma will result in proptosis, extraocular motility disturbance, congestion, and chemosis. The eye and the periorbita may be painful and tender to palpation, masquerading as an inflammatory condition such as endophthalmitis.[63] Once extraocular extension is clinically suspected, the patient should be investigated with ultrasonography, CT scan, or MRI. Although the diagnosis of intraocular melanoma usually is made by indirect ophthalmoscopy, intravenous fluorescein angiography, and ultrasonography, in cases of suspected orbital extension, imaging with CT scan or MRI is more helpful. A particularly helpful feature of melanoma in MRI is based on the signal characteristics of the melanin. Melanin produces stable free radicals, which create a paramagnetic proton relaxation enhancement, which leads in turn to shortening of T_1 and T_2 relaxation times. The melanoma thus manifests with moderately high signal intensity on T_1-

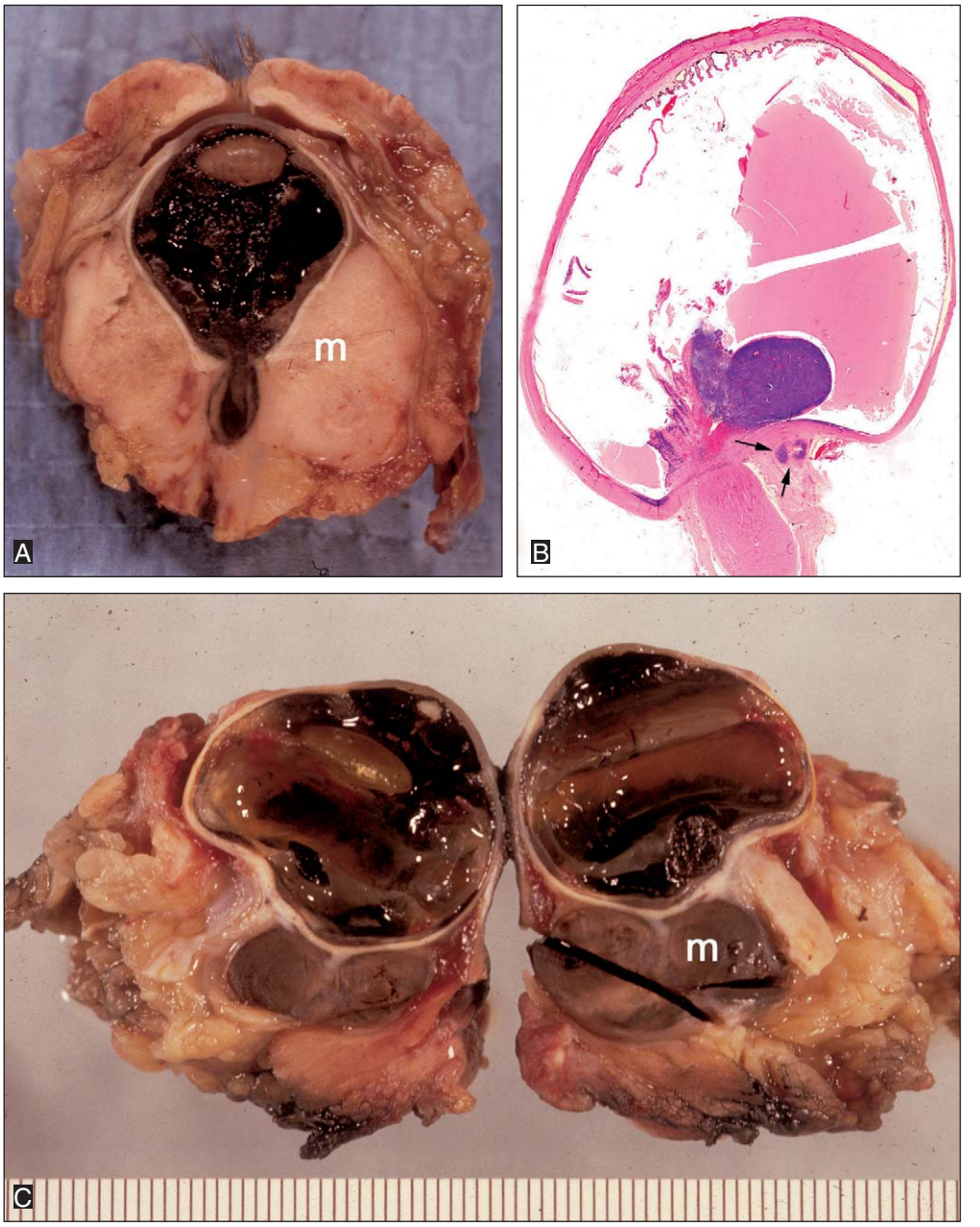


Figure 71-7 • Orbital extension of choroidal melanoma. **A,** The tumor (m) extends into the optic nerve as well as into the orbital soft tissues. Note that it is amelanotic in the orbit but densely pigmented in the optic nerve. **B,** The low-power histopathologic appearance of a juxtapapillary melanoma extending into orbital soft tissues (*arrows*). **C,** The orbital component of this melanoma (m) is as densely pigmented as the intraocular primary tumor.

weighted images and a moderately low signal intensity on T_2-weighted images.[64]

It has been reported that secondary orbital melanoma originating from the choroid can be treated with brachytherapy with some success when the extraocular extension consists of a single nodule that is less than 3 mm in diameter.[63] In cases in which the melanoma nodule is greater than 3 mm in diameter, enucleation is performed to remove the melanoma nodule encased by normal-appearing orbital fat, and secondary EBRT is given. With larger and more invasive tumors, total or partial exenteration is done.[65] In general, extraocular extension, particularly orbital extension, is an indicator of poor prognosis, with a 5-year mortality rate of approximately 55%.

Differential Diagnosis

Other pigmented and nonpigmented mass lesions of the choroid may be clinically confused with choroidal melanoma. Such lesions include nevus, metastatic tumors, choroidal hemangioma, and other benign and malignant tumors; inflammatory lesions; and hemorrhages.[66,67]

Management

The primary objective of any treatment for uveal melanoma is to prevent extraocular direct spread or metastases (Box 71-1). Maintenance or recovery of good vision is rather secondary, for the reason that almost all forms of current therapy lead to vision-impairing complications. The choice among the wide range of therapeutic modalities is based on the patient's age and general health, tumor location and size, the extent of the tumor, the patient's preferences regarding vision and globe preservation, and the risk of metastases. The current belief is that patients in whom metastatic uveal melanoma develops already have micrometastases at the time their intraocular tumors are first detected. Detection of micrometastases is very important, because the outlook with existing therapies for detectable

Box 71-1. MANAGEMENT OF CHOROIDAL MELANOMA

Observation
- Monitoring should include tumor photography, intravenous fluorescein angiography, ultrasonography, and optical coherence tomography.
- Observation with careful follow-up is appropriate management when the tumor is asymptomatic, without signs of growth, and is less than 10 mm in diameter and less than 2 mm in height.

Surgical Excision (External Eyewall Resection)
- Excision is appropriate management when the tumor does not involve the posterior pole and is less than 15 mm in diameter.
- Good initial vision may be retained.
- Surgical excision has limited application today because of high rates of early and late complications.

Radiation Therapy
- Brachytherapy or external beam irradiation with charged particles can be used.
- Irradiation is appropriate management for tumors less than 15 mm in diameter and less than 10 mm in height.
- Radiation therapy can be used when preservation of vision is possible or if the patient has only one seeing eye.
- Ocular retention is possible in up to 90% of the cases, with preservation of vision in more than 50% of eyes.
- Survival rates in patients with medium-sized melanomas treated with brachytherapy are not different from those with enucleation.

Enucleation/Exenteration
Indications for this modality include the following:
- Eyes with no vision potential
- Eyes in which irradiation will unequivocally lead to vision loss
- Eyes with recurrence after irradiation or surgical treatment
- Eyes containing melanoma with significant extraocular extension (secondary external beam irradiation may be required)
- Eyes with complications (e.g., neovascularization, pain)

metastatic lesions is dismal; however, treatment of micrometastases promises to be more effective.[57]

At the initial presentation, approximately 30% the tumors are too large for treatment with current eye salvage techniques. Patients with these tumors are managed with primary enucleation. The remaining 70% of tumors are treated with radiation therapy delivered in different forms.[68] The proportion of cases treated by radiotherapy in the United States increased gradually from 2% to 28% over the last 25 years.[69] Brachytherapy frequently is used for tumors 3 to 8 mm in thickness or less than 16 mm in basal diameter[70] (Table 71-6; Fig. 71-8). Irradiation of tumors greater than 10 mm in height or 16 mm in diameter usually leads to serious radiation-related toxicity of the retina and the optic disc. Tumors adjacent to or surrounding the optic nerve also can be treated with brachytherapy, but this strategy increases the chance of nerve and macular radiation toxicity.[71] ^{125}I is the most frequently used radioactive source used in the United States because of its accessibility, relatively long half-life, good tissue penetration, and ease of shielding. The current treatment delivery design includes use of a lead or gold shield with radioactive seeds set within a silicone holder inside the plaque template.

The Collaborative Ocular Melanoma Study (COMS) trial has demonstrated that survival rates in patients with medium-sized melanomas treated with brachytherapy are not statistically different from those for patients whose eyes were enucleated. A mean local control rate of approximately 90% has been reported after approximately 4 years of follow-up. Complication rates and visual outcomes are associated with tumor dose, dose rate, and tumor location and size (patients with larger tumors have worse outcomes). Specifically, maculopathy and papillopathy are more likely to occur in patients with tumors that are near or adjacent to the optic disc or macula. The data from the COMS trial indicate that outcomes for eyes with medium-sized tumors treated with brachytherapy and with enucleation, as determined by Kaplan-Meier analysis, included 5-year rates of all-cause mortality of 18% and 19%, respectively. The 5-year rates of metastasis were 9% after brachytherapy and 11% after enucleation.[72] Studies of juxtapapillary tumors have demonstrated similar rates of metastatic disease.[73] In small choroidal melanomas, on the other hand, the 5-year melanoma-specific mortality rate after ^{125}I plaque radiotherapy has been reported to be approximately 4%.[74]

The COMS trial also reported a 17% incidence of visual acuity of 20/200 or worse by 1 year, and 43% by 3 years after plaque therapy of medium-sized choroidal melanomas.[75] By the fifth year of follow-up, a 10% risk of treatment failure, defined as extrascleral extension, continued growth of the tumor, or recurrence of a tumor that initially responded to radiation, was noted. Although excellent tumor control was achieved in 90% of patients, the visual acuity in 63% of eyes had deteriorated to 20/200 or worse.[76]

Within 12 years after enrollment in the COMS, 45% of the patients were alive and clinically cancer free. Five-, 10-, and 12-year rates of death with histopathologically confirmed melanoma metastasis were 10%, 18%, and 21%, respectively, in the ^{125}I brachytherapy group and 11%, 17%, and 17% in the enucleation group. Older age and larger maximum basal tumor diameter were the primary determinants correlating with melanoma metastasis and death.[77]

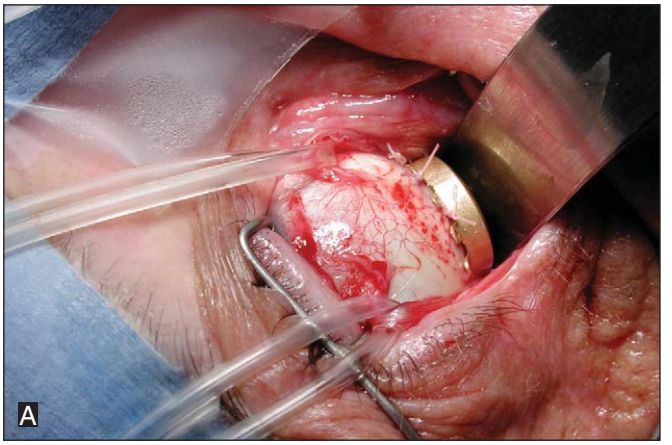
It has been reported that final visual acuity after brachytherapy is dependent on the patient's age, systemic medical problems, and initial visual acuity; tumor location and size; presence or absence of subretinal fluid; and the type of isotope used. Visual acuity was best preserved in eyes with small tumors and those with tumors located away from the optic disc and fovea.[78]

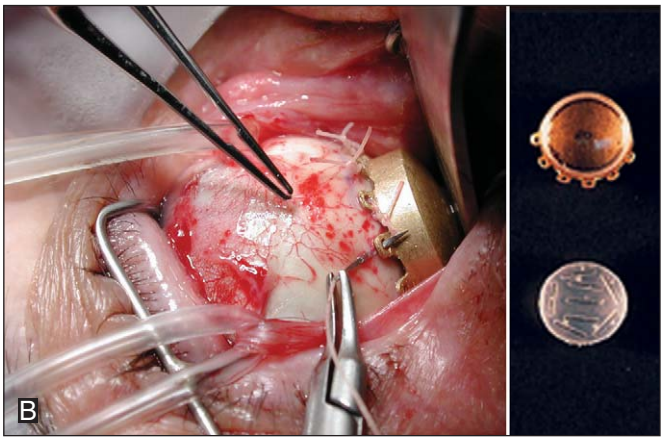
The other major radiation delivery system for the treatment of choroidal melanoma is proton beam radiation therapy (PBRT).[79] Although a theoretical advantage of PBRT is the capability focusing the radiation onto the lesion, the efficacy in terms of tumor control and complications is similar to that for brachytherapy.[80] With current PBRT techniques, an approximately 95% local control rate has been achieved. Long-term preservation of eyes is dependent on tumor size and thickness, as is the case with plaque therapy. In one report, approximately 84% of eyes were retained at 15 years.[80,81]

A number of new radiation delivery systems for the treatment of choroidal melanoma are in the process of evolution.[82] The ideal new scheme should be noninvasive and should be less radiotoxic to the eye than PBRT and plaque radiotherapy, while ensuring therapeutic dose delivery as accurate as proton or plaque techniques. It also should allow fractionation of the dose as is used in proton treatment. New techniques, which include gamma knife radiosurgery, linear accelerator-based radiosurgery, and robot-controlled linear accelerator radiosurgery (CyberKnife, Accuray Inc., Sunnyvale, CA), thus far

Table 71-6 Radionuclides Commonly Used in Plaque Brachytherapy for Ocular Tumors

Radionuclide	Half-life
Cobalt 60	5 years
Iodine 125	60 days
Ruthenium 106	366 days
Palladium 103	17 days





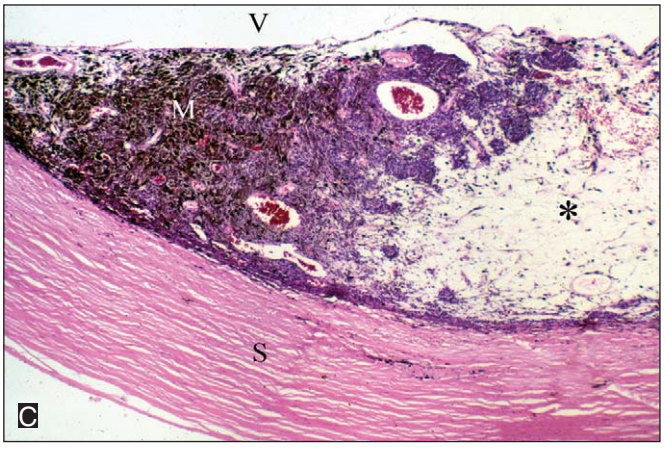


Figure 71-8 • **A** and **B,** Surgical insertion of the brachytherapy iodine-25 plaque. *Inset* with **B**: The gold plaque and silicone radioactive seed carrier. The histopathologic picture (**C**) depicts the partial response (asterisk) of choroidal melanoma to radiation; viable tumor (M) can be seen on the *left*. V, vitreous; S, sclera.

have been found to be less effective than conventional delivery systems for the treatment of choroidal melanoma.[83]

Data from the COMS also have revealed that preoperative EBRT before the enucleation of the eyes containing large choroidal melanomas offers no protection against metastatic disease.[84] Other forms of treatment for uveal melanoma—surgical excision of the tumor and laser therapy—have limited applications.

Eye wall resection surgery is done to conserve the eye with as much useful vision as possible when radiotherapy is unlikely to give a satisfactory result, or if extensive retinal detachment develops after radiotherapy. Even in the best hands, however, this kind of surgery is associated with many vision-threatening complications.[85,86] Laser therapy has always been considered to be an attractive potential treatment method for management of choroidal melanoma; however, its applications, even with modern technology, have been limited. At present, the most effective form of laser treatment for uveal melanoma is transpupillary thermal therapy (TTT). TTT is performed with an 810-nm-wavelength laser delivered through a slit-lamp biomicroscope or with an indirect ophthalmoscope. Usually, the eye is anesthetized with a retrobulbar block, and the beam is delivered with use of a lens. The depth of tumor necrosis created by the laser beam is directly correlated with elevations in temperature ranging from 45° to 60° C and exposure time varying from 1 to 10 minutes; but even in the best of circumstances, tumors thicker than 3 mm cannot be effectively treated with TTT. Despite the availability of the aforementioned different treatment modalities, the overall 5-year survival rate for this tumor is still high, ranging from approximately 75% to 85%.[87]

Metastatic Tumors to the Eye

Today, metastatic tumors to the uvea are considered to be the most common type of intraocular neoplasia (Fig. 71-9). The vascular tissue of the posterior choroid is the most likely site for ocular metastasis. Presenting signs and symptoms include metamorphopsia, diminished central vision, and visual field defects. Serous retinal detachment represents the most frequent clinical presentation; pain typically is absent. The diagnostic workup for metastatic lesions is similar to that for choroidal melanoma, with particular use of ophthalmoscopy, IVFA, and ultrasonography. OCT also is useful in the evaluation of secondary RPE changes and in follow-up assessment of lesions after treatment.[88]

Metastatic tumors may originate from a variety of different primary sites, with breast and lung carcinomas being the most common primary malignancies. Treatment options include systemic therapy, EBRT, plaque brachytherapy, PBRT, photodynamic therapy, TTT, and other types of laser photocoagulation[89] (Box 71-2). The selection of the treatment modality depends on the size and location of the tumor, as well as on the life expectancy and preference of the patient. Overall prognosis for patients with metastatic tumors of the choroid is poor. Median survival is approximately 12 months. Palliative treatment for patients with metastatic tumors of the choroid has proved to be effective both in improving visual acuity and in maximizing quality of life.

Another pathologic condition of the eye secondary to neoplasia elsewhere in the body is cancer-associated retinopathy (CAR), an uncommon paraneoplastic retinopathy, most commonly associated with small cell lung cancer, in which antibodies are directed against retinal antigens.[90] Clinical findings typically include bilateral visual loss and electroretinographic abnormalities in the absence of actual metastatic disease in the eye. Visual symptoms may precede diagnosis of the systemic malignancy or ocular metastases.

Ocular Leukemia

Ophthalmic infiltration by acute leukemia is rare.[91] With developing curative advances, the survival of patients with acute leukemia has been considerably prolonged. This has led to an increase in the variability of ocular presentations in the form of side effects of the treatment and the ways leukemic relapses are being first identified as an ocular presentation. Leukemia may involve many ocular and adnexal tissues, including the conjunctiva, cornea, sclera, anterior chamber, iris, lens, vitreous, retina, choroid, and optic nerve, either by direct infiltration or as a result of secondary toxicity due to chemotherapy and radiation therapy (Fig. 71-10). Ocular involvement also may develop in the GVHD reaction seen in patients undergoing stem cell transplantation or occurring as the result of increased susceptibility

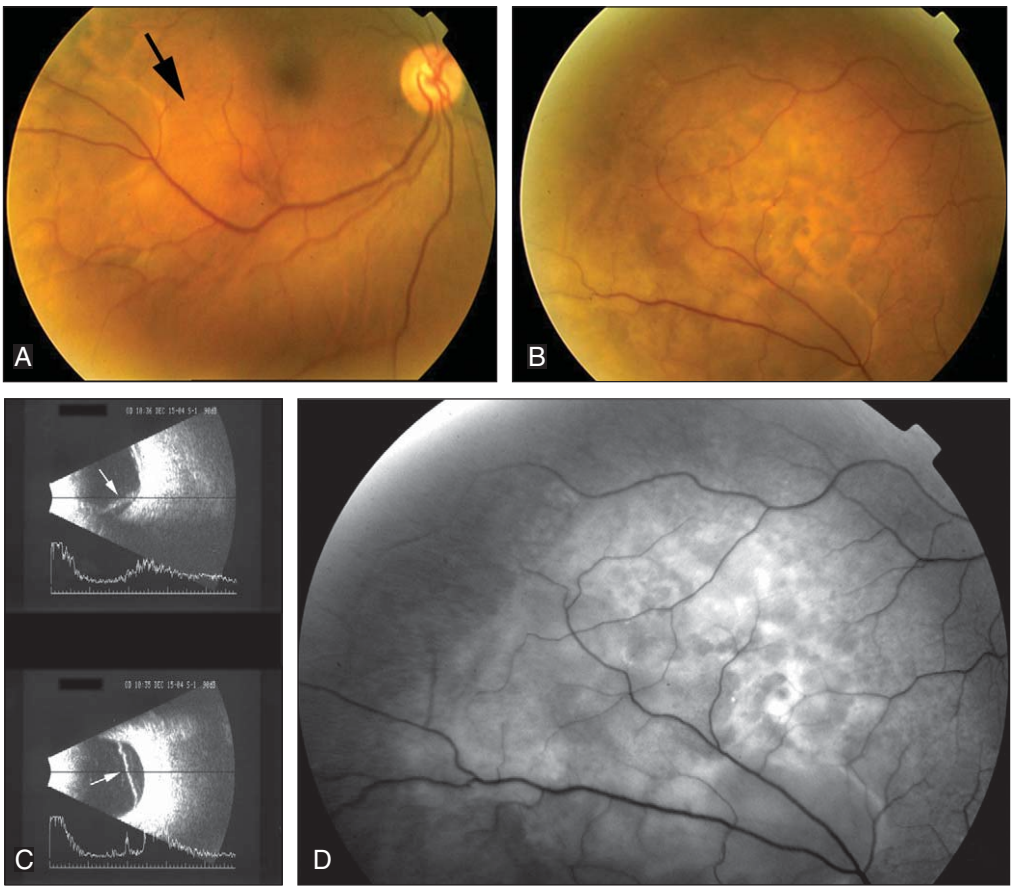


Figure 71-9 • Funduscopic and B-scan ultrasonographic appearance of metastatic breast carcinoma to choroid. **A,** Elevated, nonpigmented mass (*black arrow*). **B** and **D,** Funduscopic and intravenous fluorescein angiography appearance of irregular, flat infiltrates of choroidal metastasis. **C,** The B-scans reveal flat metatastatic lesions and overlying retinal detachments (*white arrows*).

to infections due to immunosuppression in patients with leukemia.[92,93] Early diagnosis and treatment are essential to prevent visual deterioration. Chemotherapy and EBRT are the main modalities of treatment in ocular and orbital leukemia; irradiation may provide more prompt resolution of vision-threatening symptoms.[94]

Box 71-2. MANAGEMENT OF INTRAOCULAR METASTASES

Diagnosis

- Choroidal metastasis should be considered in any patient with cancer who presents with new visual complaints, especially those with breast or lung primaries.
- Indirect ophthalmoscopy shows characteristic multiple, yellowish, low-lying lesions with poorly delineated margins.
- In 10% to 20% of patients, the eye finding is the presenting complaint and precedes the diagnosis of the known primary neoplasm.

Treatment

- Radiation should be given to the eye with metastatic lesions through a lateral field (30 to 40 Gy over 2 to 4 weeks).
- The contralateral eye should be carefully followed to assess for metastatic disease. If no evidence of metastasis is found, treatment fields should avoid this eye as much as possible; if metastases develop later, the fellow eye can then be treated.
- Simultaneous brain metastases should be ruled out.

Intraocular Lymphoma

Primary intraocular lymphoma (PIOL) is a rare subset of intraocular primary CNS lymphoma (PCNSL), in which lymphoma cells invade the eye. PCNSL is an aggressive form of non-Hodgkin's lymphoma typically associated with a worse prognosis than for other extranodal lymphomas with similar histologic characteristics. At least 95% of PCNSLs are of large B-cell histology, the most common subtype of non-Hodgkin's lymphoma. At the time of ocular diagnosis, CNS involvement may or may not be present. The incidence of this tumor has increased over the past several years in immunosuppressed as well as in immunocompetent patients.[95]

Pathogenesis

Some evidence indicates that chronic antigenic stimulation may result in the development of PIOL.[96] The immunophenotype of PIOL is $CD79a^+$, $CD20a^+$, $PAX\text{-}5^+$, $BCL\text{-}2^+$, and $OCT2^+$; the only documented chromosomal translocation is t(14;18), with rearrangements being reported in 56% of the patients.[97]

Clinical Features

In most cases of PIOL, the patient presents with uveitis-like symptoms including pain, blurred vision, and vitritis (Fig. 71-11). It is a common neoplastic masquerade syndrome involving the eye. Its protean ocular manifestations, plus in many cases the initial positive response to steroid therapy for presumed uveitis, may delay proper diagnosis and treatment. A high index of suspicion is essential; prompt tissue biopsy with cytologic and laboratory workup is indicated in any patient in whom PIOL is likely.

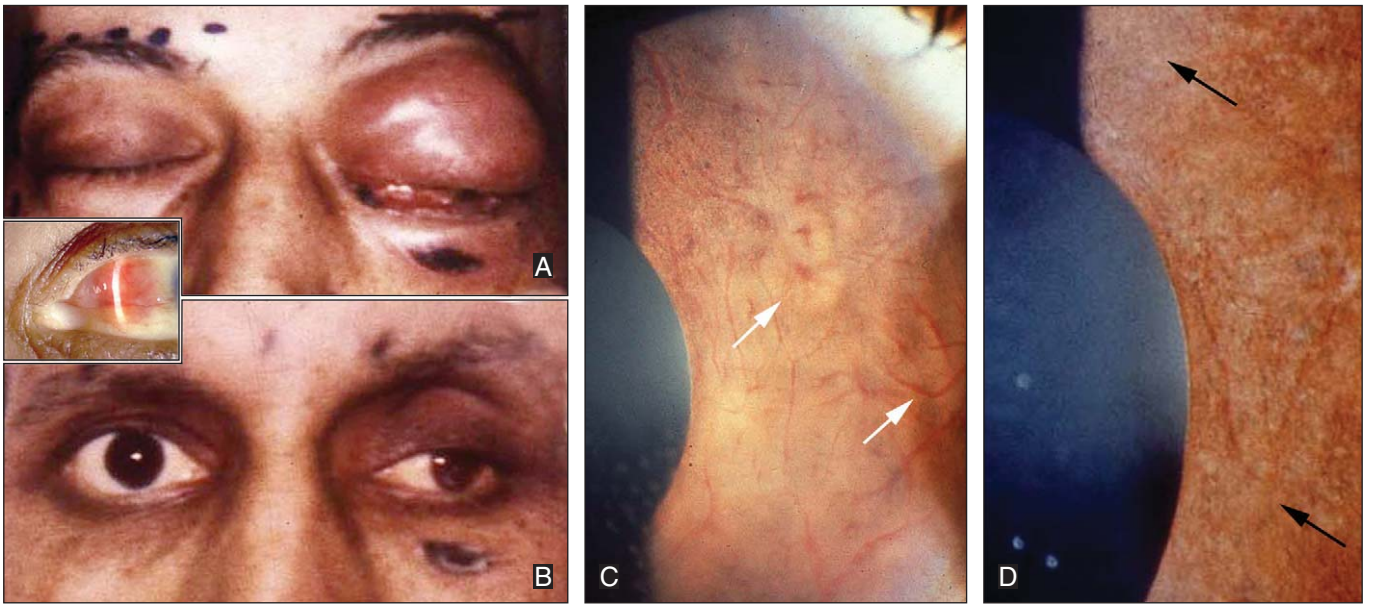


Figure 71-10 • **A** and **B,** The clinical appearance of orbital and iris involvement of acute myeloblastic leukemia (AML) before (**A**) and after (**B**) radiation treatment. *Inset*: Conjunctival "salmon patch" lesion of chronic lymphocytic leukemia (CLL). **C,** Pretreatment photograph of the iris with engorged tortuous blood and focal whitish infiltrates of leukemic cells within the stroma (*white arrows*). **D,** Scarred areas of iris (*black arrows*) after radiation treatment.

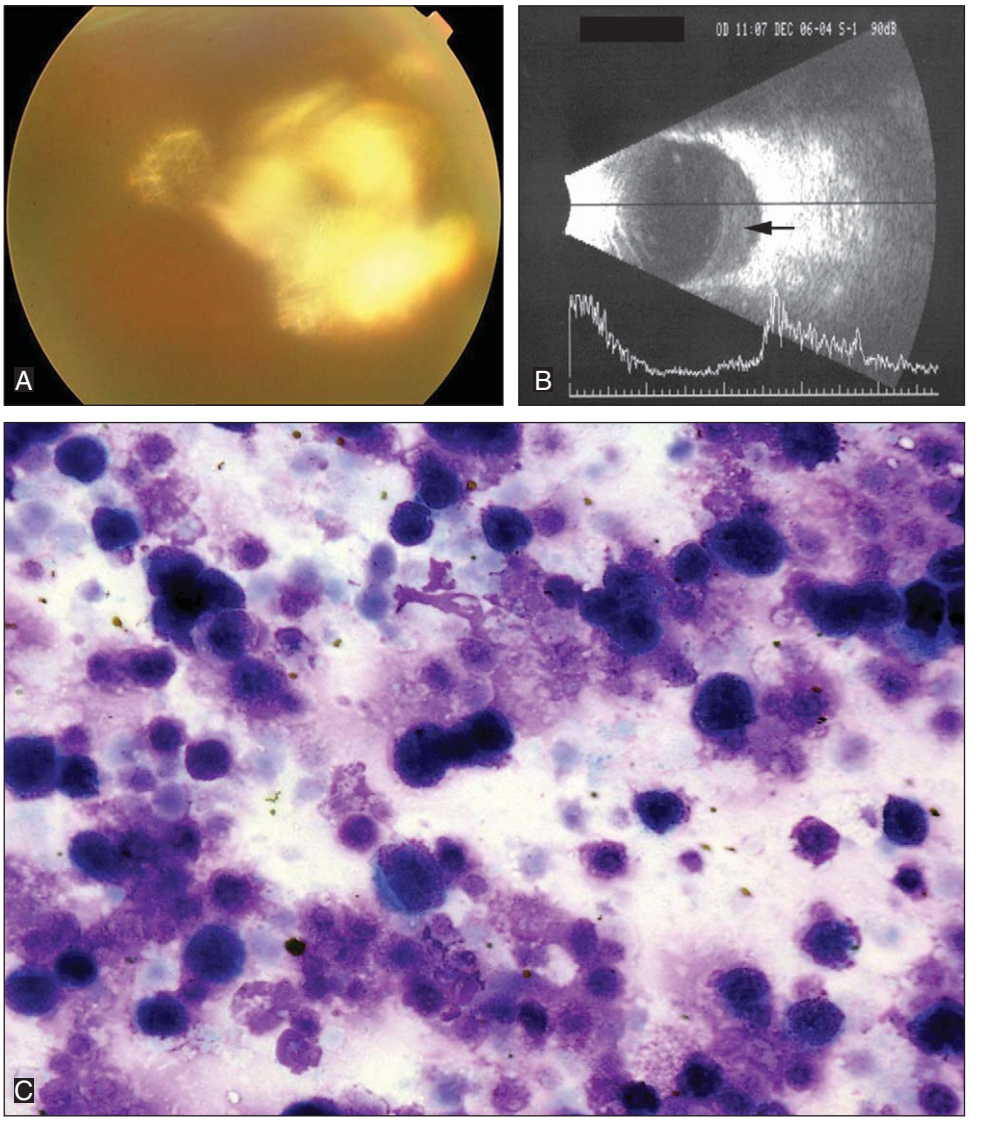


Figure 71-11 • Intraocular lymphoma. **A,** Fundus appearance of hazy vitreous with the yellowish plaque-like lesions of intraocular lymphoma. **B,** Combined A- and B-scan showing the tumor infiltrate in vitreous (*arrow*). **C,** Atypical lymphocytes within the cellular debris retrieved by vitreous tap.

Differential Diagnosis

Recent advances in the diagnosis of PIOL are due primarily to improved laboratory methods of processing vitreous specimens for cytologic studies and availability of immunocytologic investigation for lymphoid cells, flow cytometry, cytokine evaluation, and molecular analysis. Because PIOL has a nonspecific presentation, considerations in the differential diagnosis should include infectious and noninfectious causes manifesting with vitreitis or subepithelial infiltration, as well as paraneoplastic syndromes including CRMP-5 optic neuropathies. Because the treatment is prolonged and is associated with significant systemic and ocular complications, tissue diagnosis is important.[96]

Management

Treatment of PIOL may include EBRT and systemic chemotherapy with high-dose methotrexate-based regimens, as well as intraocular injections of methotrexate and rituximab (anti-CD20 antibody). In cases in which the vitreous cells persist after systemic chemotherapy, methotrexate may be given intravitreally thereafter; this is an effective, repeatable, and safe treatment.[98] Ocular remissions typically are sustained for years, but recurrence is possible. EBRT, which usually is delivered with high-energy photons, causes the production of free radicals, which target the DNA of the tumor cell. Today, EBRT to the eye and CNS is being used less often to treat this disease. Prognosis is poor owing to CNS involvement.

Retinoblastoma

Retinoblastoma, the most common intraocular neoplasm of childhood, is reported to have an incidence of approximately 6 in 100,000 live births, accounting for approximately 10% of cancers during the first year of life. Approximately 300 new cases are diagnosed annually in the United States.[99,100] Approximately one third of cases of retinoblastoma are bilateral tumors.[101] This neoplasm, primarily a disease of early childhood, has been detected even in fetal life.[102,103] It also may rarely occur in children older than 5 years of age and more rarely in young adults.[104]

Pathogenesis

Retinoblastoma is the prototypical model of hereditary neoplasms; it develops as a result of mutational inactivation of both alleles of the retinoblastoma gene (*RB1*).[105] This gene is mapped to chromosomal band 13q14. The *RB*-encoded protein (pRb) is a tumor suppressor that plays a pivotal role in negative control of the cell cycle and in tumor development. It has been shown that pRb is responsible for a major G_1 checkpoint, blocking S-phase entry and cell growth. Loss of pRb functions may induce cell cycle deregulation and so lead to a malignant phenotype. Gene inactivation of pRB through chromosomal mutations is one of the principal reasons for retinoblastoma development.[106] Functional inactivation of pRb by viruses also is documented in many malignancies, including cervical cancer, mesothelioma, and Burkitt lymphoma.[107]

The two-mutation model of Knudson (the "two-hit" hypothesis) dictates that the development of retinoblastoma is caused by two corresponding chromosomal mutations. In hereditary retinoblastoma, the initial occurrence, or "hit," is a germinal mutation that is inherited to be present in all the child's cells. The second hit occurs sometime during development and, if it occurs in a somatic cell such as the primitive photoreceptors, then the tumor develops. Therefore, in hereditary cases of retinoblastoma, all cells in the body are predisposed to neoplastic development, because germline mutation (the first hit) takes place in all cells of the body. This predisposition also may help to explain the high incidence of multiple nonocular tumors, such as sarcomas, lymphomas, and brain, seen in patients with hereditary retinoblastoma.

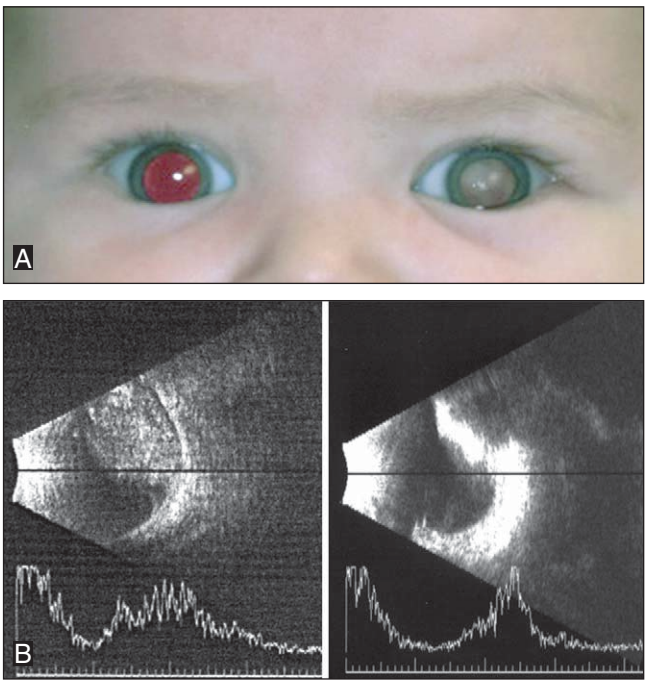
On the other hand, in most cases of unilateral sporadic retinoblastoma, the two hits occur during development of the retina, and both are somatic mutations. Theoretically, the rest of the body carries no higher risk for the development of other tumors, because affected persons have a normal chromosomal pattern in cells elsewhere in the body. It is well known that survivors of hereditary retinoblastoma have an increased risk for multiple malignant and benign neoplasms, especially soft-tissue sarcomas.[108] Some reports indicate a greater than 10-fold increase in overall mortality in patients with retinoblastoma compared with the general population, because of second malignancies.[109] For practical purposes, a child with retinoblastoma has approximately a 5% chance of developing another malignancy during the first 10 years of follow-up, 20% during the first 20 years, and 25% within 30 years. Survivors of hereditary retinoblastoma revealed a statistically significant increase of leiomyosarcoma and other soft-tissue sarcomas that persists decades after their initial diagnosis. These patients should undergo lifelong medical monitoring for sarcomas.[110] The 30-year cumulative incidence of nonocular tumor development is approximately 30% for those patients with retinoblastoma treated with EBRT, compared with approximately 10% for those patients who did not receive radiation. It has been reported that among patients with retinoblastoma treated with radiotherapy, an increased incidence of soft-tissue sarcomas, especially leiomyosarcomas, are found in the radiation field, as well as outside the field of radiation.[110]

Morphologically and clinically, hereditary and nonhereditary tumors generally are indistinguishable. The most important differences are that hereditary retinoblastoma usually occurs at a younger age and is more likely to be bilateral and multicentric. Although approximately one third of cases of retinoblastoma are inherited, only about 5% of patients in newly diagnosed cases present with a family history. Patients with bilateral tumors and those with a positive family history can be safely assumed to have a germinal mutation for the *RB* gene; for practical purposes, these patients are at a 50% risk of transmitting the *RB* gene to their offspring by autosomal dominant transmission. The gene is approximately 80% penetrant, so clinical expression will be seen in approximately 40% of these patients' children; some offspring may be merely carriers of the gene, without development of clinical manifestations of the tumor. Approximately 15% of unilateral tumors develop by germinal mutations that, by chance, affect only one eye. The remaining 80% to 85% of unilateral tumors are due to somatic mutations that involve only the retina; in such cases, the disease is not passed on to future generations.

Clinical Features

Leukocoria, or cat's eye reflex (seen in 55% of cases), and strabismus (seen in 20%) are the most common presenting signs of retinoblastoma in children in Western countries[111,112] (Fig. 71-12). Retinoblastoma also may manifest with atypical features such as uveitis, vitreous hemorrhage, and orbital cellulitis, particularly in older children.[104] An important point is that invasive treatment and vitrectomy should be avoided in these children until the possibility of underlying retinoblastoma is excluded.[113]

The most dependable way of diagnosing retinoblastoma is by means of dilated indirect ophthalmoscopic examination performed with the patient under general anesthesia (EUA); tumor, if present, is recognized as a characteristic whitish gray mass within the eye[114] (Fig. 71-13). Dilated fundus examination also permits identification of multifocal tumor or vitreous seeding. Currently this examination is made even more rewarding with the digital image capture and storage capability of the wide-angle fundus visualization systems, which include Retcam 120 (Massie Research Laboratories, Dublin, CA), Optomap (Optos, Marlborough, MS), and Panoret-1000 (CMT Medical Technologies Inc., Valley Stream, NY). The risk of general anesthesia is balanced by the benefit of improved survival of the patient and preservation or maximization of vision. The currently recommended schedule for surveillance among persons in whom a nongermline mutation is proved by genetic screening may perhaps be relaxed in the future, but in today's clinical practice, multiple



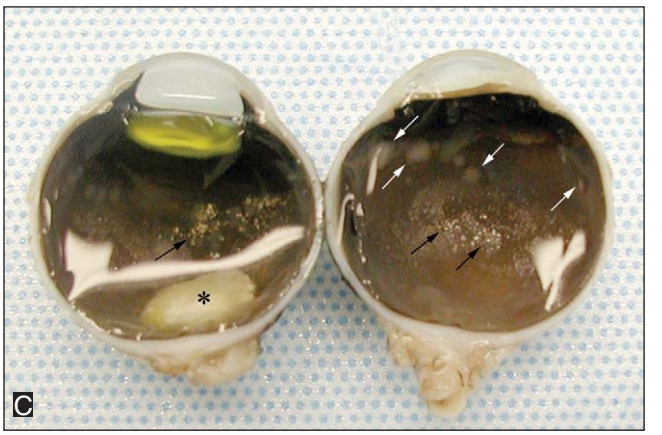
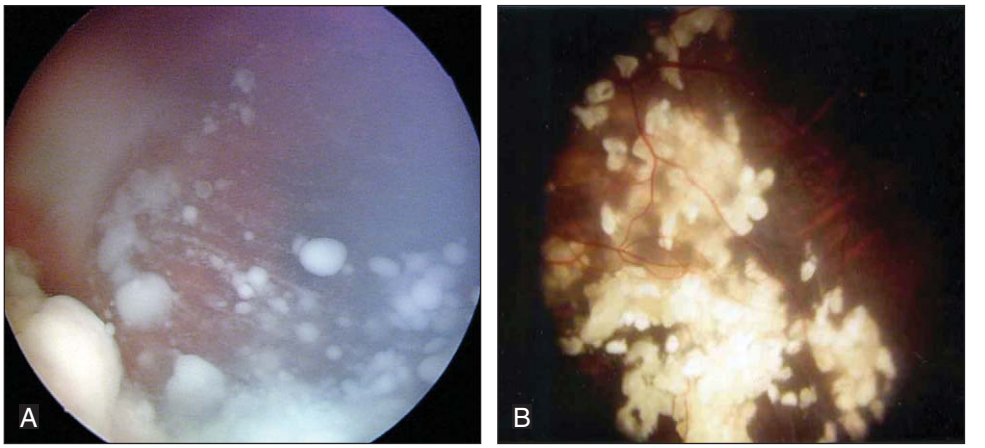


Figure 71-12 • Retinoblastoma. **A,** Leukocoria in the left eye. **B,** A- and B-scan appearance of preradiation (*left*) and postradiation (*right*) treatment of a large retinoblastoma mass. **C,** Postenucleation appearance of partially regressed retinoblastoma (*asterisk*). *White arrows* show multiple recurrent lesions. *Black arrows* show extensively calcified intraocular seeds after radiation treatment.



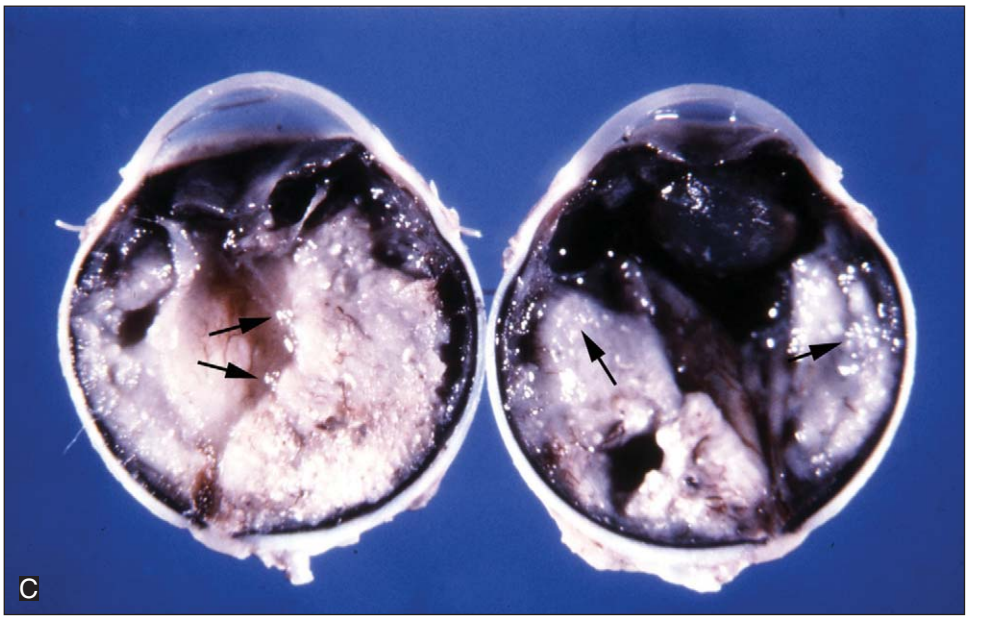


Figure 71-13 • **A,** Retinoblastoma with extensive intravitreous seeding. **B,** Totally calcified vitreous seeds after radiation treatment. **C,** *Black arrows* on the pathology specimen show partially regressed, calcified retinoblastoma after external beam irradiation.

EUAs within the first 5 years of life is the standard of care. Additional tests, although not always necessary, may be performed to confirm the diagnosis, but ocular biopsy in retinoblastoma is not done for histopathologic confirmation because of the fear of carrying tumor cells to extraocular tissues.[115]

Ocular A- and B-scan ultrasonography or CT may demonstrate a solid intraocular tumor with characteristic calcifications. CT also may be required to exclude a concomitant primitive neuroectodermal tumor (PNET) in the midline (i.e., the so-called trilateral retinoblastoma, which consists of bilateral retinoblastomas and concomitant pineal PNET).[116–118]

Spontaneous regression of retinoblastoma is an exceptionally rare occurrence. If the tumor is not treated, it will rapidly enlarge to occupy the entire globe and extend into adjacent orbital, periorbital, and intracranial tissues[119] (Fig. 71-14). The most common routes of extension are by direct infiltration of the optic nerve or sclera and spread via the choroid.[120] The risk of neural spread depends on the level of the invasion of tumor cells into the optic nerve. Mortality rates of up to 85% and 70% have been reported if tumor cells have reached the surgical transaction margin of the optic nerve and posterior to the lamina cribrosa, respectively. Additional routes of spread include dispersion of the tumor cells through the subarachnoid space into the CNS, lymphatic dissemination of the tumor anteriorly into the conjunctiva and eyelids, and hematogenous metastases to distant organs such as the bone, liver, and brain.

MRI can be particularly helpful in those cases with possible extension into the optic nerve or choroid; fat suppression and gadolinium contrast techniques constitute the best imaging choice[121] (see Fig. 71-14). If imaging provides evidence of tumor outside the eye, a metastatic workup should be pursued.[122] Metastatic disease is rarely suspected at the time of initial presentation, and the usual tumor staging studies such as bone marrow biopsy, lumbar puncture, radionuclide bone scan, or PET usually are not performed. In the usual case of endophytic retinoblastoma in which the optic nerve can be seen, the morbidity associated with metastatic screening tests outweighs their likely value.[123] Symptoms and signs of metastatic disease may include weight loss, vomiting, headache, neurologic impairment, orbital mass, or enlarged neck nodes.[124] Preoperative bone scan is not justified in patients with intraocular disease even when it is advanced. Bone scan should be done only in patients with documented extraocular metastatic disease.[125]

The Reese-Ellsworth classification, still the most widely used retinoblastoma organization system, is based on intraocular tumor staging and globe salvage prediction after EBRT; survival is not taken into account in this categorization.[126] A newer proposed organization for the disease, the International Intraocular Retinoblastoma Classification (the "ABC classification"), is more suitable to current management senarios for this tumor.[127,128] This classification stages intraocular tumors according to their prognosis after chemoreduction and adjuvant focal therapy. It consists of five groups—A, B, C, D, and E—in descending order of favorable prognosis (Table 71-7).

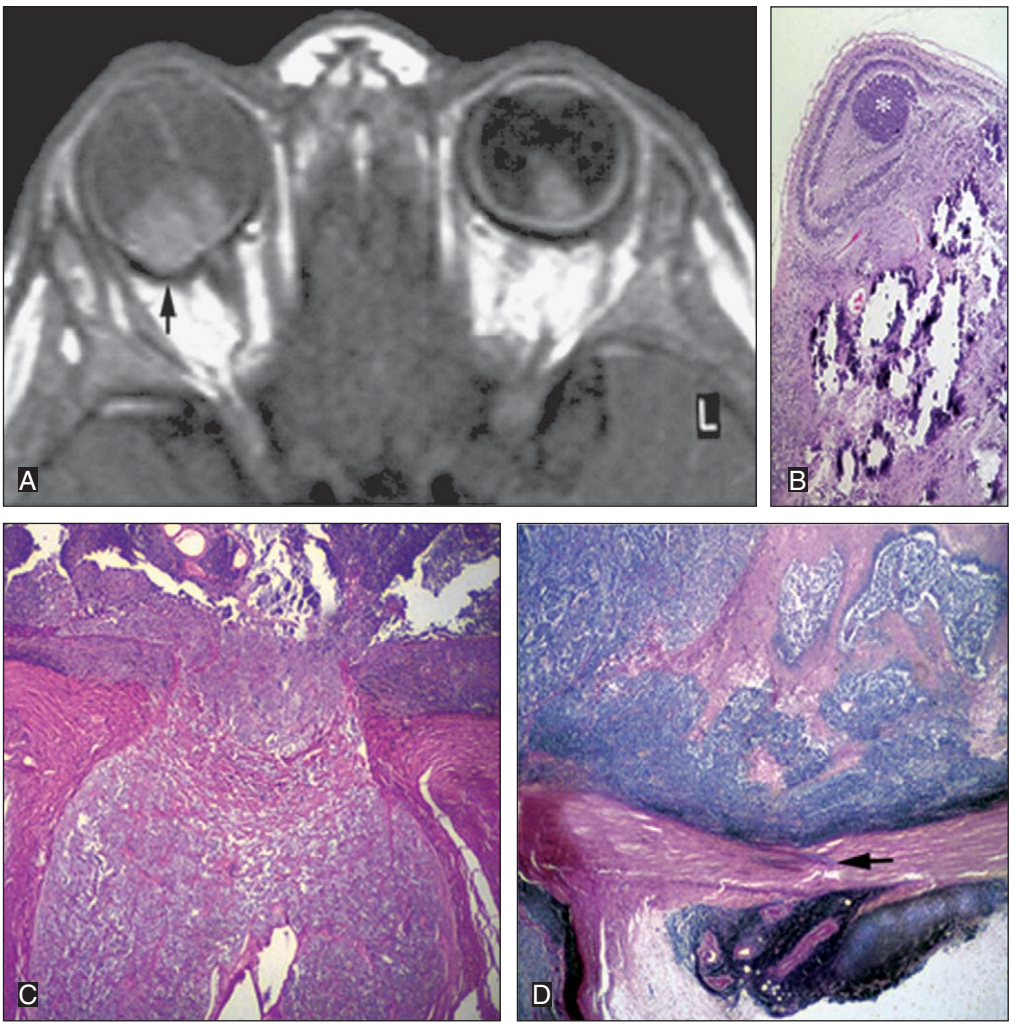


Figure 71-14 • A, T_1-weighted axial magnetic resonance image shows the extraocular extension of retinoblastoma into the orbit (*black arrow*). **B,** Contrasting histopathologic appearance of viable (*asterisk*) versus calcified tumor after external beam irradiation. **C** and **D,** Images reveal extension of the tumor into the optic nerve and then to the orbital soft tissues through scleral blood vessels (*black arrow*).

Table 71-7 International Intraocular Retinoblastoma Classification

Group	Quick Reference	Specific Features
A	Small tumor	Retinoblastoma ≤3 mm*
B	Larger tumor	Retinoblastoma >3 mm *or*
	Macula	Macular retinoblastoma location (≤3 mm to foveola)
	Juxtapupillary	Juxtapupillary retinoblastoma location (≤1.5 mm to disc)
	Subretinal fluid	Additional subretinal fluid (≤3 mm from margin)
C	Focal seeds	Retinoblastoma with
		Subretinal seeds ≤3 mm from retinoblastoma
		Vitreous seeds ≤3 mm from retinoblastoma
		Both subretinal and vitreous seeds ≤3 mm from retinoblastoma
D	Diffuse seeds	Retinoblastoma with
		Subretinal seeds >3 mm from retinoblastoma
		Vitreous seeds >3 mm from retinoblastoma
		Both subretinal and vitreous seeds 3 mm from retinoblastoma
E	Extensive retinoblastoma	Extensive retinoblastoma occupying >50% globe *or*
		Neovascular glaucoma
		Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space
		Invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, anterior, chamber

*Refers to 3 mm in basal dimension or thickness.

Differential Diagnosis

Other causes of leukocoria such as Coats disease, persistent hyperplasic primary vitreous, retinopathy of prematurity, *Toxocara* endophthalmitis, large retinal detachments, and rarely unilateral congenital cataracts may be confused with retinoblastoma.[129,130] Most of these pathologic conditions can be differentiated easily from retinoblastoma with today's advanced diagnostic technologies. Coats disease, however, may still be a problem when it presents in young children. MRI or IVFA can be helpful, particularly when Coats' disease with retinal detachment is in the differential diagnosis.[131,132]

Management

Retinoblastoma is now considered a "curable" tumor if it is diagnosed early. Early treatment of the disease is effective at a reasonable cost, saving both life and vision. Undertaken at a late stage, however, treatment is very costly, with poor outcome, particularly for vision. This underlines the call for early diagnosis and the importance of public and professional awareness of this deadly disease.[133] The hereditary form is associated with increased risk of second nonocular primary malignancies that are even more lethal than the retinoblastoma itself.[134]

Management of retinoblastoma should be tailored to the individual patient. All parameters should be taken into account, including the size, location, and laterality of the tumors; threat of metastases; risks for second malignancies; and projected visual prognosis. Today's treatment methods include chemotherapy (i.e., chemoreduction) with intravenous carboplatin, etoposide, and vincristine; subconjunctival carboplatin injection; TTT; cryotherapy; laser photocoagulation; plaque brachytherapy; EBRT; and enucleation or exenteration[135] (Fig. 71-15). In general, eyes classified as group A are treated with cryotherapy or laser photocoagulation, or both. Eyes classified as group B or C typically receive chemoreduction; unilateral cases without seeding may be managed with plaque brachytherapy. Eyes with diffuse vitreous seeding (group D) are treated with either chemoreduction, EBRT, or enucleation, depending on the laterality of the disease. Chemoreduction usually reduces tumor volume by more than 50% within a few weeks and dries out most of the retinal detachment. The choice of antimetabolic agents, dosage, and the duration of treatment will vary from one hospital to another; however, most centers make use of vincristine, carboplatin, and an epipodophyllotoxin (etoposide or teniposide).[136] The tumor-related disadvantage of chemoreduction is the recurrence of vitreous or subretinal seeding or appearance of new crops of retinoblastomas elsewhere (in approximately one fourth of cases) in the eye after the discontinuation of therapy.[137] A permanent response is almost never achieved with chemoreduction alone, so the response to this treatment should be monitored closely and other focal therapies should be implemented before the recurrent tumor gets a chance to reach a large size. Also, chemoreduction is not without its systemic side effects, such as

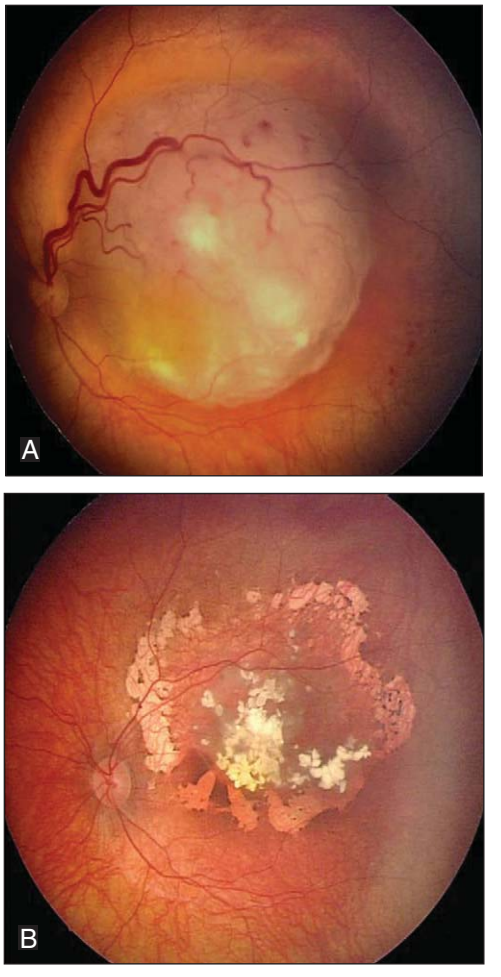


Figure 71-15 • **A** and **B,** Prechemoreduction and postchemoreduction appearance of a large solitary retinoblastoma nodule.

bone marrow suppression, loss of hair, and, possibly more serious, long-term complications such as development of second malignancies. Final data on chemoreduction are not yet available.

Plaque radiotherapy is a form of brachytherapy in which a radioactive seed carrier (i.e., plaque) is surgically sutured over the wall of the eye at the base of a tumor focus for transscleral irradiation (see Fig. 71-8). Placement of radioactive plaques (^{125}I, ^{106}Ru) is limited to tumors measuring approximately less than 15 mm in cord diameter and 8 mm in thickness and can be used for the primary treatment of medium-sized tumors. When a retinoblastoma focus reaches these sizes, however, it usually breaks down, with seeding into the vitreous and subretinal spaces. Therefore, the plaques more often are used as a secondary measure after other forms of treatment. Currently, the most widely used plaque is the ^{125}I plaque, which delivers unidirectional low-energy gamma rays that can be shielded well. The old cobalt 60 plaques have been largely abandoned because their high-energy gamma rays cannot be shielded effectively. When plaque radiotherapy is given in cases with extensive subretinal or vitreous seeding, it has a high failure rate.[138] On the other hand, when this method is used as a primary treatment of RB, it provides long-term tumor control in almost 90% of cases. It also is very effective in those eyes in which a focus of RB recurs after chemoreduction. Of note, although plaque radiotherapy is much safer than EBRT in terms of local radiation toxicity, it may lead to localized radiation effects such as radiation vasculopathy, maculopathy, or papillopathy, depending on the location of the lesion.

EBRT is no longer considered to be first-line conservative treatment owing to its important long-term side effects. It may still be needed, however, in advanced bilateral disease or for control of recurrent tumors inaccessible to focal treatment methods. The customary total radiation dose is 40 to 50 Gy, delivered in fractions of 1.8 Gy through a lateral or anterior port. The use of other delivery techniques for external beam irradiation such as stereotactic conformal radiotherapy and accelerated proton beam irradiation are not commonly used in retinoblastoma.

The other form of treatment to be taken into account for retinoblastoma is enucleation. Although enucleation has become less common with early diagnosis and better alternative therapies for this tumor, it remains the treatment of choice for advanced disease in eyes with no visual potential or with high risk of metastasis. For unilateral tumors, enucleation is required in approximately two thirds of cases.[139] This stems from the fact that most cases of unilateral sporadic retinoblastoma are detected by the affected child's parents, who notice leukocoria or strabismus when the disease is advanced.[140] For those patients with less advanced unilateral disease, chemoreduction with focal consolidation of each focus of tumor with thermotherapy or cryotherapy or the use of plaque brachytherapy is helpful. The great majority of group E cases are managed by enucleation or more extensive surgical procedures such as exenteration with or without EBRT to the socket and adjuvant chemotherapy. Children with dissemination of retinoblastoma to the CNS or metastatic disease remain incurable and die of progressive disease despite the aggressive treatment.[124,141]

CONJUNCTIVAL TUMORS

Conjunctival tumors comprise neoplasms originating from cells of all germ layers, including epithelial, melanocytic, glandular tissue, vascular, and other soft tissue elements, and other cells.[142] This section covers only the commonly encountered malignancies, including melanoma, squamous cell carcinoma, and Kaposi's sarcoma.

Conjunctival Squamous Cell Carcinoma

Squamous cell carcinoma is the most frequently encountered malignancy of the conjunctiva; the incidence of this tumor varies, ranging from 0.025 to 3.5 per 100,000 population, depending on the geographic location.[143,144] The mean age of affected patients is approximately 60 years. Although this tumor is considered to be a low-grade malignancy, local extension into the globe and underlying eyelid structures may be seen. Regional and distant metastases are rare, but the tumor may show local aggressiveness.[145]

Pathogenesis

The etiology of conjunctival squamous cell carcinoma is multifactorial, involving such factors as age, fair pigmentation, ultraviolet light exposure, and exposure to human papillomavirus (HPV). Ultraviolet radiation is considered to be the most important cancerogenic factor for conjunctival squamous cell carcinoma.[146]

In the past, HPV infection and impairment of p53 function have been identified as frequent events in conjunctival squamous cell carcinoma.[147] Recent studies, however, indicate that the role of HPV in the pathogenesis of conjunctival and eyelid tumorigenesis may be auxiliary. The p53 protein probably is involved in the development of conjunctival and eyelid carcinomas, owing to its frequent presence in both benign and malignant neoplasms of the eyelids.[148,149]

It seems that human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) and other forms of immunosuppression-related conjunctival squamous cell carcinoma and virus-associated tumors are increasing in Africa and elsewhere in the world. Recent studies have described conjunctival tumors that behave more aggressively and are seen in younger patients.[150,151]

Clinical Features

The most common presenting signs and symptoms of conjunctival squamous cell carcinoma are redness and irritation of the eye with or without foreign body sensation. The bulbar conjunctiva, particularly the limbus, is the frequent site for the occurrence of a slow-growing, elevated pinkish gray lesion with a pearly or gelatinous appearance with surrounding feeding vessels. Similar to squamous epithelial neoplasms elsewhere in the body, conjunctival tumors evolve through morphologic advances of dysplasia, to carcinoma in situ, to the invasive stage (Fig. 71-16). The degree of dysplasia in these lesions cannot be determined by clinical examination; therefore, it is absolutely necessary that they be biopsied and examined histopathologically.[152,153] Although most lesions manifest as a localized mass formation, atypical presentations of squamous cell carcinoma as a diffuse growth or a masquerade lesion mimicking scleral keratitis or scleromalacia also have been reported.[154] Both carcinoma in situ and the invasive form are considered to be low-grade malignancies that are locally invasive but rarely manifest with distant metastases. Once the neoplasm breaks through the basement membrane of the conjunctival epithelium and invades the subepithelial tissues and episclera, however, it behaves in a locally aggressive fashion.[155] Although squamous cell carcinomas are slowly growing tumors, under certain conditions they are known to extend into the underlying structures, including the globe and the orbit[156] (see Fig. 71-16).

Differential Diagnosis

Conjunctival squamous cell carcinoma should be differentiated from pingueculum or pterygium, foreign body granuloma, and other tumors of the conjunctiva such as lymphoma, melanoma, and metastatic tumors.

Management

The treatment of of conjunctival squamous cell carcinoma varies depending on the age and the extent of development. The management of superficial disease (carcinoma in situ, superficially invasive tumor) include surgical excision of the lesion with lamellar scleral keratoconjunctivectomy and cryotherapy.[157,158] Although other treatments and immunotherapy with dinitrochlorobenzene and photodynamic therapy have been used, most of these regimens do not offer

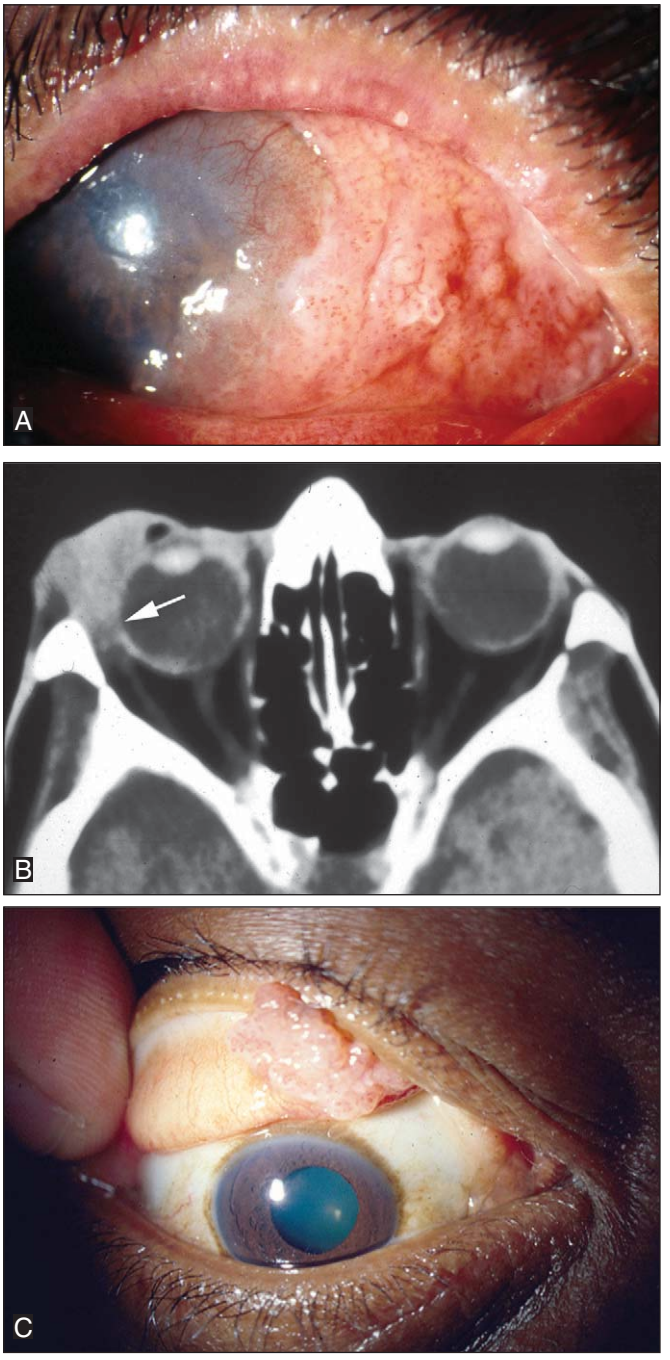


Figure 71-16 • **A** and **B,** Slit-lamp photograph and axial computed tomographic scan showing advanced-stage conjunctival squamous cell carcinoma originating from bulbar conjunctiva. Notice that the tumor extends into the orbital soft tissue laterally (*white arrow* in **B**). **C,** Squamous cell carcinoma originating from a conjunctival inverted papilloma of tarsal conjunctiva of the upper eyelid.

a very good prognosis.[159] Topical chemotherapy with mitomycin C and 5-fluorouracil has been reported to yield good results in superficial cases. A literature review reported that the use of mitomycin C, 5-fluorouracil, and interferon alfa-2b offers tumor regression rates for carcinoma in situ and squamous cell carcinoma ranging from 80% to 96%. Side effects of keratitis, redness, and irritation occurred most often with mitomycin C, followed by 5-fluorouracil and interferon alfa-2b.[160,161] Radiation treatment with brachytherapy and EBRT may be considered in recurrent cases with or without globe invasion.[162] Current knowledge of the efficacy of EBRT is limited; however, proton beam therapy may be considered as a possible alternative to enucleation for the treatment of invasive conjunctival squamous cell carcinoma, although it has serious side effects.[163]

Conjunctival Melanoma

Conjunctival melanoma is a rare ocular malignancy, with an estimated incidence of 5 cases per 1 million population annually; the incidence of melanoma is much lower in the nonwhite population, but the tumor may be seen exceedingly rarely.[164,165] Although conjunctival malignant melanoma is a rare disease, it is life-threatening, and complete tumor excision and other treatments are mandatory to prevent local recurrence and metastasis.

Pathogenesis

Conjunctival melanoma originates from dendritic melanocytes of the basal layer of the conjunctival epithelium. It is estimated that about 20% of conjunctival melanomas arise from pre-existing nevi, another 70% develops from primary acquired melanosis (PAM), and the rest is considered to develop de novo without a pre-existing lesion.

Conjunctival melanoma refers to the development of excessive melanocytic pigmentation as either an epithelial or a subepithelial lesion. Grayish blue subepithelial lesions occur congenitally and do not become malignant. PAM usually develops in the later decades of life and may be due to simple hyperplasia of conjunctival melanocytes, or to atypical melanocytic hyperplasia, which eventually progresses to malignant acquired melanosis and melanoma.

Clinical Features

Clinically, PAM areas form unilateral, tannish brown or black, flat, localized or patchy lesions (Fig. 71-17). Clinical experience indicates that approximately one third of these lesions may eventually become melanomas, but the process is slow, usually taking several decades.[166] Malignant PAM lesions appear as darkly pigmented, irregularly thickened, nodular foci, arising within pre-existing flat lesions. The rapid growth, high vascularity, spontaneous bleeding, and fixation to underlying tissues of melanomas differentiate malignant transformation from benign PAM and cyst-containing nevi. Any long-standing conjunctival nevus that suddenly changes in size, color, or overall appearance should be excised for histopathologic examination.

In early stages, conjunctival melanoma lesions are not deeply invasive into the underlying tissues, and surgical excision is easy. With growth of the tumor, however, fixation to underlying structures may occur, and eventually the tumor invades the lacrimal drainage system, globe, or orbit.[167] Survival time after primary diagnosis of conjunctival melanoma averages approximately 6 years, with death ensuing from postregional metastasis within a median of approximately 12 months. Regional metastasis after treatment is associated with a poor prognosis.[168,169]

Differential Diagnosis

The significant issues in the differential diagnosis lie in distinguishing between ordinary PAM and PAM with atypia, and between a nevus and conjunctival melanoma. Other masses such as conjunctival lymphoma, carcinoma, and granulomatous lesions also are seen occasionally. In most instances, the biopsy findings are conclusive. An anterior uveal melanoma with extrascleral extension may manifest as an epibulbar pigmented tumor mass; this should not be confused with conjunctival melanoma. If the clinical findings are suggestive, a high-resolution echographic examination with A and B scans or MRI will be helpful.

Management

Current management for early conjunctival melanoma is surgical excision under frozen section control whenever possible, followed by

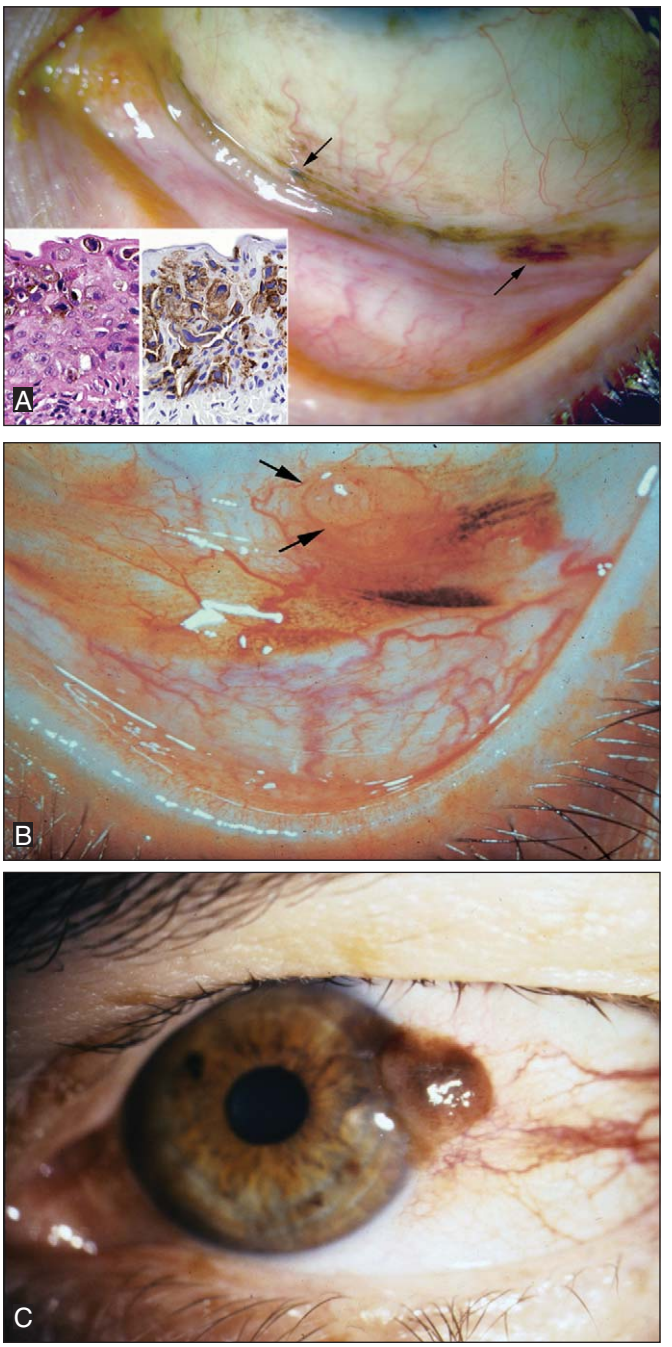


Figure 71-17 • Conjunctival pigmented lesions. **A,** Recurrent primary acquired melanosis (PAM) (*arrows*). *Inset*: The histopathologic appearance of the atypical melanoctes in hematoxylin-eosin and Melan-A stains. **B,** Transition of PAM to elevated but not pigmented lesions of conjunctival melanoma (*arrows*). **C,** Pigmented conjunctival melanoma at the limbus.

alcohol epitheliectomy and cryotherapy to the margins of excision. With larger tumors, the surgical technique should include wider and deeper excision for melanomas on the surface of the eye. Enucleation or exenteration should be considered for tumors with ocular or orbital invasion. In patients with large tumors, the regional lymph nodes should be biopsied for staging purposes. Some histopathologic features observed in the biopsy indicate the likelihood of recurrent and disseminated tumor. These include invasive melanoma thickness more than 0.8 mm, lack of inflammatory cell response at the invasive front, five or more mitotic tumor cells per 10 high-power fields (HPFs), and involvement of orbital soft tissues with melanoma and positive lateral and deep margins of the excisional biopsy. With one or more of these findings, the patient should undergo clinical evaluation every 2 to 3 months for 1 to 2 years to detect recurrent tumor. Recurrent cases should be evaluated for regional lymph node involvement and metastatic disease.

Once the tumor extends into the orbit, local resection of the lesion is no longer feasible and exenteration may be indicated. According to some physicians, exenteration should only performed for tumors involving the fornices or extending to the eyelid skin and for tumors which do not respond to EBRT. Recent investigation of regional lymph node metastasis in conjunctival melanoma performed with sentinel lymph node mapping and biopsy indicate that preauricular lymph nodes are most commonly involved. The sentinel lymph node biopsy may be used as a piece of information in decision making for exenteration. Other clinical features reported as predictive of orbital extension of conjunctival melanoma include visual acuity of 20/200 or worse, extralimbal location, amelanotic tumors, caruncular lesions, and tumors that manifest with histopathologic invasion deeper than 1 mm. Paridaens and coworkers reported mortality rates between 33% and 50% for melanomas thicker than 1-mm invasion despite exenteration.[170] The same investigators indicated that invasion of the lymphatics, blood vessels, and sclera, as well as the incomplete excision at the time of initial treatment, indicated very poor outcomes.

Topical mitomycin treatment also shows considerable promise, particularly in the treatment of diffuse PAM with atypia. Long-term data are lacking, however.[171,172]

Although radiotherapy has been tried on conjunctival melanomas, these tumors are not very responsive to radiation, and EBRT may lead to various complications. Proton beam irradiation can serve as an alternative therapy to exenteration in cases of conjunctival melanoma with a large, diffuse, or multilocular growth pattern.[173] In extended tumors, ocular surface toxicity can result after therapy. Some physicians suggest that brachytherapy may offer better therapeutic outcomes with these tumors.[174]

Kaposi's Sarcoma of the Conjunctiva

With the advent of the HIV/AIDS epidemic, the incidence of conjunctival or eyelid Kaposi's sarcoma has increased, with development of these tumors in approximately 10% of HIV-infected male patients.[175] This rate varies among patient populations, however. An important point is that Kaposi's sarcoma is a multifocal disease, affecting, for example, the skin, mucous membranes, lung, and gastrointestinal tract; dissemination of the lesions carries significant morbidity and mortality.

Clinical Features

Conjunctival tumors appear as flat or slightly elevated, dark reddish plaques or larger, circumscribed nodular masses (Fig. 71-18). These mass lesions can cause local irritation, chemosis and lid edema, trichiasis, ptosis, and visual problems.

Pathogenesis

Current evidence suggests that Kaposi's sarcoma is not a true tumor but rather represents a dysregulation of the inflammatory response. It is associated with viral infections, and the lesion's growth depends on numerous cytokines and growth factors, including the *tat* gene from the HIV genome.[176]

Differential Diagnosis

Conjunctival lesions may be confused clinically with pyogenic granuloma, hemangioma, subconjunctival hemorrhage, and inflamed pinguecula or bacillary angiomatosis from *Bartonella henselae* infection. Eyelid lesions may be confused with melanocytic tumors.

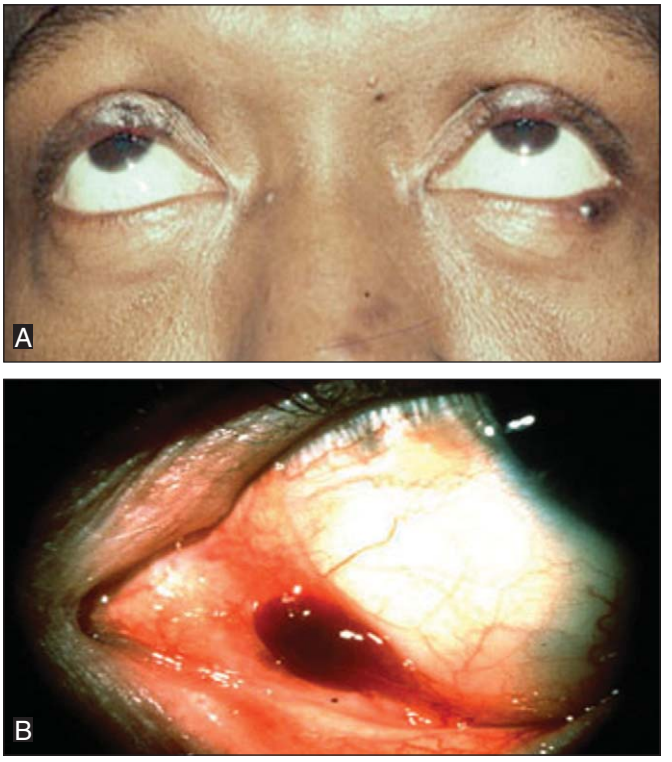


Figure 71-18 • Multiple foci of skin, eyelid, and conjunctival Kaposi's sarcoma in a patient with acquired immunodeficiency syndrome.

Management

Because of their apparent location, many lesions are discovered early and can be observed without treatment. Others can be surgically removed with 1- to 2-mm margins, but recurrence is common. Cryotherapy and local injections of antimetabolites and immunomodulators such as interferon-α and human chorionic gonadotropin have been reported to be effective in some patients. If the systemic antiretroviral therapy has favorably affected the course of HIV infection with normalized $CD4^+$ levels, the associated Kaposi's sarcoma may regress.[176]

Radiotherapy also has been used effectively to treat ophthalmic Kaposi's sarcoma, but it is associated with numerous side effects and a high recurrence rate. It has been reported that a single dose of 800 cGy is a safe and effective palliative therapy for ophthalmic Kaposi's sarcoma.[177] Conjunctival and eyelid Kaposi's sarcomas seem to be more radiosensitive when compared with these tumors in other cutaneous sites, with a higher remission rate; an approximately 95% remission rate was reported with use of single doses ranging from 10 to 20 Gy.[178]

EYELID TUMORS

Eyelid tumors originate from many tissue components, including skin, glandular structures, vascular and other mesenchymal elements, lymphoid tissue, and other types of cells. This section covers the commonly encountered malignancies, including basal cell carcinoma, squamous cell carcinoma, sebaceous gland carcinoma, and melanoma.

Basal Cell Carcinoma of the Eyelid

Basal cell carcinoma accounts for greater than 90% of malignant eyelid tumors.[179] It rarely metastasizes, but may lead to significant morbidity and mortality by invading contiguous structures around the eye and the orbit. The mortality rate from basal cell carcinoma is approximately 10%, which is due mostly to intracranial extension. The typical patient is an elderly person who has been exposed to actinic radiation. Despite its prevalence in adults, it is extremely rare in children.[180]

Pathogenesis

The factors accounting for the development of basal cell carcinoma are complex and still not completely understood. Ultraviolet light (UV) exposure is a major influence, but its relationship to clinical phenotype is not yet clear. In addition, immunosuppression has been shown to be a significant risk factor.[181] UV radiation not only induces DNA damage in epidermal cells but also interferes with the pattern of the apoptosis process in the epidermis. Excessive UV exposure can mutate the p53 tumor suppressor gene, leading to the loss of its repair function and thus creating an apoptosis resistance. If the DNA damage is not repaired or the damaged cells are not eliminated by apoptosis, the result is uncontrolled proliferation and eventual formation of basal cell carcinoma. An additional pathway has also been identified for tumor formation.[182] A number of hereditary syndromes including basal cell nevus syndrome of Gorlin-Gotz,[183] linear unilateral basal cell nevus,[184] Rombo syndrome,[185] and Bazex syndrome[186] are associated with basal cell carcinoma.

Clinical Features

The most common sites for basal cell carcinomas on the eyelids are, in order of frequency, the lower eyelid, the medial canthus, the lateral canthus, and the upper eyelid. Four main subtypes of this tumor are recognized, each with a different clinicopathologic pattern and with distinct biologic behavior: nodular ("rodent ulcer"), sclerosing (morphea-like type), superficial, and basosquamous.

The nodular subtype accounts for 75% of all tumors. This lesion usually begins as a small translucent papule. As it gets larger, it forms a zone of central necrosis and ulceration as the tumor outgrows its blood supply. The periphery of the tumor is raised with pearly margins and the vessels course over the surface.

The morphea-like, or sclerosing, subtype is a plaque-like lesion that accounts for 15% of all basal cell carcinomas and is responsible for a majority of tumors invading the orbit. It may be difficult to diagnose and delineate, because the margins are clinically indistinct. Morphea-like basal cell carcinomas are characterized by deep invasion into the deeper tissues and loss of the eyelashes. The superficial subtype may appear as a scaly area that resembles chronic dermatitis, which may be difficult to differentiate from an inflammatory lesion.

The basosquamous subtype of basal cell carcinoma, which manifests with squamous differentiation, may not be clinically distinguishable from the nodular type. Biologically, however, it behaves in a more aggressive fashion, with perineural invasion and distant metastatic potential. Long-standing basal cell carcinomas may develop necrotic changes and manifest as cysts.[187]

Orbital invasion may develop with all subtypes of basal cell carcinoma, although it is more common in the diffuse morphea-like type. Delay in diagnosis and incomplete excision of the initial tumor are critical factors in the development of orbital invasion.[188] The most common presentation of orbital basal cell carcinoma is as a mass lesion and incomitant strabismus. Perineural spread, although more commonly reported with squamous cell carcinoma, can also occur in basal cell carcinoma and should be suspected if the patient complains of burning or stinging pain, numbness, or formication.

Differential Diagnosis

Basal cell carcinoma may mimic all other types of skin tumors and inflammatory conditions, including keratoacanthoma, sebaceous gland carcinoma, amelanotic malignant melanoma and metastatic tumors, and granulomas and fungal infections of the eyelids.

Management

Complete surgical excision monitored with frozen-section control of the margins of the lesion offers the lowest tumor recurrence rate.[189]

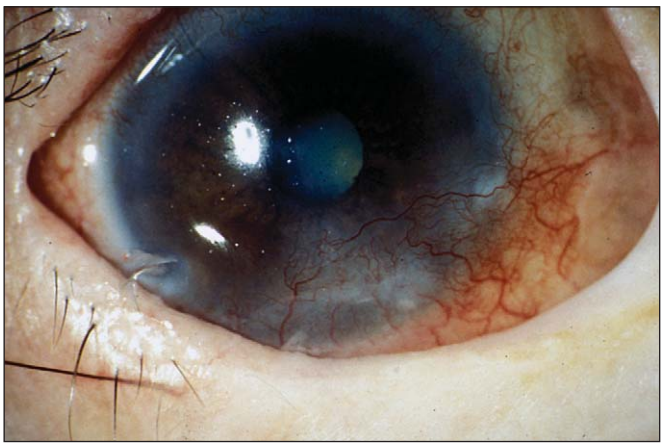


Figure 71-19 • Eyelid and external eye complications after radiation treatment of basal cell carcinoma. Although the tumor was successfully eradicated, conjunctiva and cornea were scarred, with neovascularization. Radiation cataract also is seen through the pupil. The lower eyelid shows loss and misdirection of the cilia secondary to irradiation. Also, the eye was extremely dry.

Reports from tertiary care hospitals indicate approximately 25% of initially incomplete excisions lead to recurrent tumors in approximately 5% of patients.[190]

In many cases with orbital invasion, cure is possible only with exenteration. If the patients cannot undergo or refuse exenteration, other treatment modalities including EBRT may be offered. Radiotherapy is a useful measure, although in light of the significant recurrence rate, it is not to be recommended as an effective initial treatment. EBRT also causes significant complications in the eye and eyelids[191] (Fig. 71-19). Brachytherapy with ^{125}I has been reported as an alternative to exenteration and EBRT for orbital invasion by the tumor.[192] Results appear to be better for untreated tumors than for incompletely excised tumors or tumors recurring after surgery.[193]

Squamous Cell Carcinoma of the Eyelid

Squamous cell carcinoma is the second most common form of skin cancer. It represents less than 2% of all eyelid malignancies.[194,195] A majority of patients (75%) with squamous cell carcinoma are older than 60 years of age. The distinct male predominance (65% versus 35%) probably represents increased occupational sunlight exposure by men rather than a genetic predisposition. It tends to occur in fair-skinned persons with a history of exposure to UV light. The incidence of developing invasive squamous cell carcinoma increases with increasing proximity to the equator.

The incidence of squamous cell carcinoma has been on the rise for the last 3 to 4 decades. The annual incidence in the United States is approximately 100 per 100,000 population; Australia has the highest incidence of SCC in the world, with an annual incidence of approximately 200 per 100,000 population.[196]

The squamous proliferations of the eyelid and periorbital skin manifest with a spectrum of premalignant lesions, carcinoma in situ and invasive squamous cell carcinoma. Premalignant lesions are defined as dysplastic epidermal changes that harbor the potential for transformation into invasive squamous cell carcinoma. These lesions include actinic (solar) keratosis, epidermal dysplasia, radiation dermatoses, and xeroderma pigmentosum.

Pathogenesis

Squamous cell carcinoma may arise from a precancerous condition or de novo. The mechanism of UV-induced photocarcinogenesis appears to involve the inactivation of the p53 tumor suppressor gene, as with basal cell carcinoma. It is a potentially fatal neoplasm that can metastasize to regional lymph nodes and also exhibit aggressive local spread. Other predisposing factors for the development of squamous cell carcinoma are Bowen disease; solar keratosis; keratoses resulting from arsenic, tar, or irradiation[23]; xeroderma pigmentosum; therapeutic ultraviolet light treatments such as psoralen plus ultraviolet A (PUVA); fair skin; immunosuppression; and chronic inflammation.[197,198]

Clinical Features

The lower lid is the most common site for squamous cell carcinoma, accounting for approximately 60% of lesions; the upper lid is the least common site.

Carcinoma in situ and actinic solar keratosis are similar clinically, although the average size of carcinoma in situ is larger than average actinic keratosis. Carcinoma in situ manifests as erythematous scaly patches or small placoid lesions, which may or may not show increased pigmentation.[199] Actinic keratosis may occasionally manifest as a nodular lesion. Left alone, all cases of carcinoma in situ develop into invasive squamous cell carcinoma, but the exact incidence of malignant transformation in actinic keratosis is not definitely known.

Once the epidermal neoplastic proliferation violates the epidermal-dermal interface and extends into the subepidermal tissues, the tumor is known as "invasive" squamous cell carcinoma, which may manifest as plaques, large ulcerated lesions, or papillomas. Squamous cell carcinoma is the second most common malignancy of the eyelid and periorbital skin. Invasive squamous cell carcinoma usually occurs in the sun-exposed skin areas of elderly persons with lightly pigmented skin. The most common histologic subtype of invasive tumors is the well-differentiated kind. High incidence rates of peripheral nerve involvement (25%) and orbital invasion (45%) have been reported.[200] Squamous cell carcinoma of the eyelid and periorbital skin is a malignant tumor with potential of invasion into the full thickness of the lid, underlying globe, and orbit. It also may spread into regional lymph nodes and to distant viscera. Regional lymph node metastasis is detected in approximately 5% of cases at initial examination. Some studies indicate that the overall rate of regional lymph node metastasis in patients with squamous cell carcinoma of the eyelid or periocular skin may be as high as 25%.[201]

Patients with squamous cell carcinoma require long-term follow-up because of the risk of new skin cancer formation. It has been reported that new foci of nonmelanotic skin cancer developed in about 60% of the patients every 3 years. The main risk factor for new cancer formation is the number of previous skin cancers that a patient had; those who had three or more cancers were at significantly greater risk than those with fewer than three.[202]

Differential Diagnosis

Periocular squamous cell carcinoma manifests with variable clinical features ranging from plaque-like scaly lesions to nodular growths.[203] Occasionally, the tumor may be totally or partially covered by pearly keratin or may show central or peripheral ulcerations.

The wide variation in clinical appearances of squamous cell carcinoma presents great difficulty in differentiating these lesions from basal cell carcinoma; approximately 30% are clinically diagnosed as basal cell lesions at presentation.[204] Other malignancies, such as sebaceous gland carcinoma and deep fungal infections, also should be considered in the differential diagnosis for squamous cell carcinoma.

Management

Before decisions regarding specific treatment, the patient with squamous cell carcinoma should undergo careful workup to assess for orbital and ocular invasion, as well as intrasinusoidal and intracranial extension of the tumor. Consultation with a medical oncologist is in order, to rule out distant metastasis. Orbital ultrasonography and cranial CT and MRI may be very useful to determine the extent of the tumor before any treatment preferences are selected. PET and radionuclide scans and microdissection of the sentinel

lymph nodes also may be helpful to determine the extent of the disease.[205]

Some physicians firmly believe that all in situ and invasive squamous cell carcinomas should be treated with surgical excision.[206–208] If surgical treatment is not feasible, radiation therapy, carbon dioxide laser, or cryotherapy may be considered alternative treatment modalities. The essence of surgical treatment is to obtain tumor-free margins either with conventional frozen-section control or using the Mohs microsurgery technique (Fig. 71-20). Although the Mohs technique has been very popular lately, the rates of tumor cure it offers are not distinctly different from those achieved with conventional frozen-section monitoring.[209,210] Five-year survival rates greater than 95% have been reported with use of Mohs microsurgical excision for primary and recurrent squamous cell carcinoma.[211]

These surgical techniques, however, are mostly reliable with surface tumors; once the tumors extend into the orbit, both methodologies become unreliable. If the tumor extends into the underlying soft tissues and bone, it is extremely difficult to remove surgically with tumor-free margins. Squamous cell carcinoma with bone involvement also responds poorly to radiotherapy.

Squamous cell carcinoma is responsible for approximately 10% of carcinomas involving the orbit, mainly as a result of direct spread from surrounding tissues. Like orbital invasion by basal cell carcinoma, invasion by squamous cell carcinoma tends to result from a delayed diagnosis, inadequate prior treatment with surgery or irradiation, and frequent recurrences. When perineural spread has extended to the orbit and beyond to the base of the skull or the cavernous sinus, the prognosis is extremely guarded. Radical surgery may be attempted to be followed by radiation but only after extensive consultation with the patient and the family.

On the other hand, some physicians believe that radiotherapy also offers high tumor regression with good cosmesis in squamous cell carcinoma as well as in basal cell carcinoma with local control rates of 75% and 91%, respectively. Recurrent tumors after other therapies are controlled by irradiation less effectively.[212,213] The radiation treatment techniques employed to treat squamous cell carcinoma of the lids and the underlying structures include use of superficially penetrating orthovoltage x-rays, superficially penetrating electrons, or more deeply penetrating megavoltage x-rays and implantation of radioactive sources depending on the location and the extent of the tumor. The radiation is delivered over 1 to 7 weeks, depending on the site, size, and cosmetic requirements. Irradiated skin cancers may continue to regress for weeks after the end of therapy. Desquamation with erythema and peeling of the epidermis at the treatment site commonly develops, which may be more severe in the eyelids because of the thinness of the skin.[214]

The radiation fields usually include surrounding margins of normal-appearing skin to incorporate microscopic extension of tumor. It has been reported that the extent of microscopic extension of tumor beyond the grossly visible lesion averages approximately 5 mm, and a margin of 10 mm is required to provide a 95% chance of obtaining clear resection margins. The extent of the microscopic tumor correlates well with the size of the gross lesion.[215]

The advantages of radiation treatment include relative sparing of normal tissue with good cosmetic outcome, cure rates comparable to surgical treatment, and avoidance of hospitalization and surgery in elderly, debilitated, or anticoagulated patients or those in whom medical conditions make the tumor inoperable. The potential for complications and side effects such as alopecia and more serious ocular toxicity, particularly in upper lid lesions, and rarely occurring soft tissue and bone necrosis, also should be taken into account. The risk of complications is related to tumor size. Complications develop in approximately 5% of the patients with skin lesions smaller than 1 cm, but in up to 15% of patients who have lesions larger than 5 cm.[216]

Brachytherapy has also been recently advocated for fascial squamous cell carcinomas that pose problems of surgical reconstruction with a claim to provide a high level of local control and good cosmetic results. The results were particularly better for untreated tumors than for incompletely excised tumors or tumors recurring after surgery.[217] Topical and systemic chemotherapy and immunotherapy have limited applications in advanced cases.

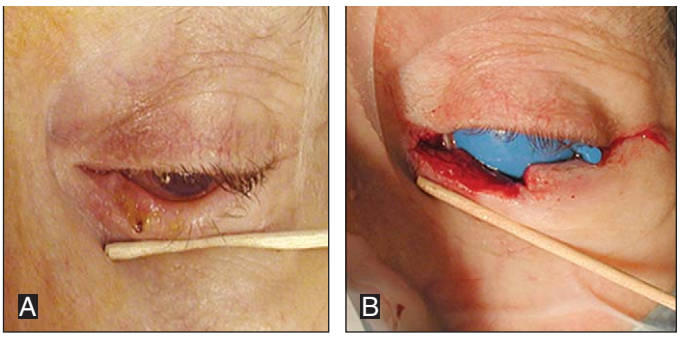


Figure 71-20 • **A,** Preoperative appereance of squamous cell carcinoma of the lower eyelid. **B,** The appearance of the eyelid tissue defect at the end of excision under frozen section control. Note that although the tumor appears to be innocuous, the extent of the invasion is far greater than could be appreciated on clinical examination alone.

Sebaceous Gland Carcinoma of the Eyelid

Sebaceous gland carcinoma is a relatively rare eyelid adenocarcinoma that originates from the meibomian or Zeis glands, or both, or from the sebaceous glands in the eyebrow or carbuncle.[218] Sebaceous gland carcinoma accounts for approximately 5% of all malignant eyelid tumors. It affects mainly elderly patients in the sixth to seventh decades of life and is encountered predominantly in women; no explanation is evident for its predilection for females. It is seen more often in the upper eyelid than in the lower, probably because meibomian glands are more abundant in the upper lid.[219]

Pathogenesis

Development of sebaceous gland carcinoma has been reported in patients who underwent irradiation for facial acne, hemangioma, or eczema, regardless of their age. Moreover, eyelid sebaceous carcinoma developed in children with hereditary retinoblastoma who received EBRT in their teenage years. It has been reported recently that sebaceous gland carcinoma also may be seen in younger age groups of immunosuppressed patients.[220]

Clinical Features

The tumor initially appears as a tarsal nodule in approximately 40% of the cases and as a diffuse thickening of the eyelids in 60%. The mean duration of symptoms or signs before diagnosis is approximately 2 years. The diffuse tumors usually simulate blepharoconjunctivitis. In patients who present with a chronic inflammatory condition, sebaceous gland carcinoma often exhibits "pagetoid" spread or conjunctival intraepithelial invasion. Of those with diffuse conjunctival involvement, the superior tarsal and conjunctiva and fornix are involved in almost all cases. Direct orbital invasion occurs in about 10% to 15% of the cases (Fig. 71-21). Another point to keep in mind is that sebaceous gland carcinoma may be associated with Muir-Torre syndrome, which is a rare genodermatosis of autosomal dominant inheritance associated with mutations in mismatch repair proteins, which predispose affected patients to GI and genitourinary tract malignancies.[221] Almost half of the patients with sebaceous gland carcinoma have been reported to have additional visceral neoplasms.[222]

Differential Diagnosis

Known as a masquerader, sebaceous gland carcinoma may mimic other benign and malignant conditions such as chronic blepharoconjunctivitis or chalazion, as well as squamous cell carcinoma, often

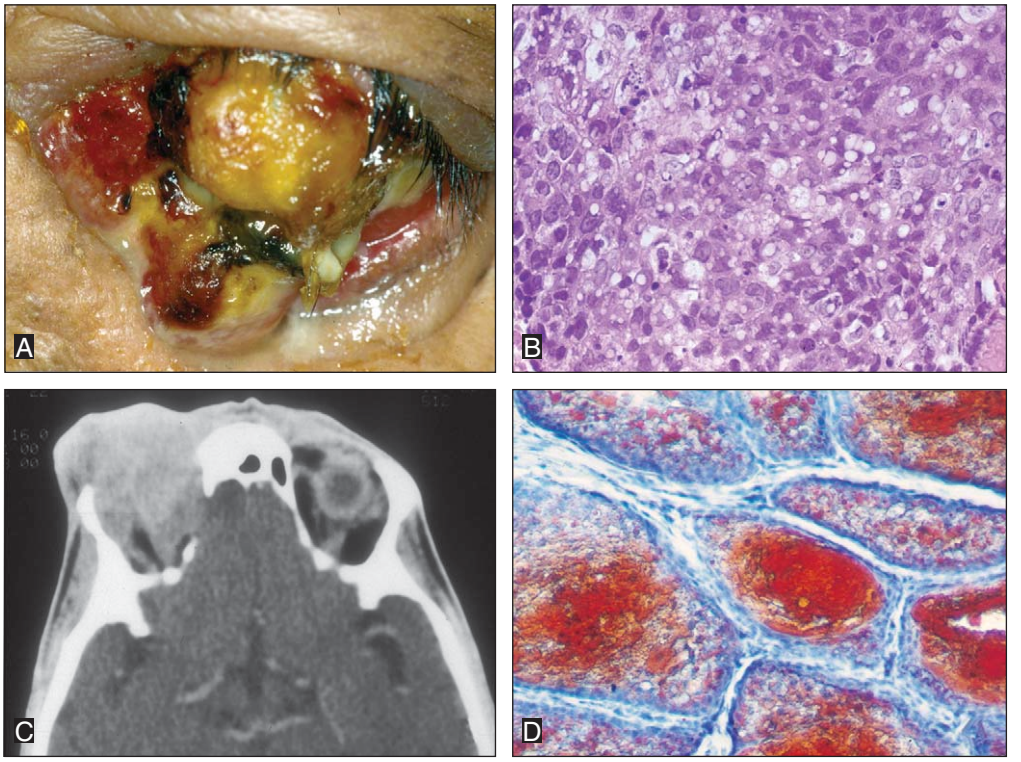


Figure 71-21 • Sebaceous gland carcinoma. **A** and **C,** External photograph and axial computed tomographic scan showing massive growth of the tumor anteriorly and posteriorly into the orbital soft tissues and bone. **B** and **D,** Histopathologic appearance of the tumor, with infiltration of markedly pleomorphic tumor cells with mitotic figures. In better-differentiated areas of the tumor, positive staining with oil red O is seen (**D**).

resulting in delayed diagnosis, which can lead to higher morbidity and mortality.[223,224] Sebaceous gland carcinoma should be considered in any unilateral chronic inflammatory condition of the eyelids in the elderly.

Management

Treatment should be individualized on the basis of the extent of the tumor and the specific needs of the patient.[225] If the lesion is diffuse and without a nodular component, multiple mapping biopsy specimens should be obtained and submitted for histopathologic examination, with fixation of permanent slides. Currently, the mainstay of treatment of tumors without orbital involvement has been wide local excision, with monitoring of margins with both permanent and frozen sections.[226] In a majority (75%) of the cases, the initial treatment method is surgical excision with or without cryotherapy. In cases with orbital involvement, exenteration often is warranted.

Topical antimetabolites, brachytherapy, and EBRT also are used in some cases. EBRT with an appropriate delivery system is reported to be a curative treatment for eyelid sebaceous cell carcinoma when a radiation dose greater than 55 Gy is used.[227] Moreover, brachytherapy should be considered for patients seeking an alternative to surgical excision.[228] Some sebaceous gland carcinomas present a challenge to surgical excision because of the cosmetic and functional impairment. According to some experts, interstitial radiation with ^{19}Ir may very well be an effective alternative treatment to surgical excision.[229] Treatment complications include symblepharon formation, irregular eyelid and conjunctival scarring, and eyelid malpositions as the result of multiple surgical procedures, cryotherapy, and radiation of the eyelids and conjunctiva.

TUMORS OF THE ORBIT

A variety of tumors and pseudotumors can involve the orbit. Approximately two thirds are benign and one third are malignant. The percentage of malignant tumors increases with age because of the higher incidence of lymphoma and metastasis in the elderly.[230]

Tumors that most commonly are treated with radiation are covered in this section; for more extensive literature coverage, the reader is referred to ophthalmic oncology and orbit textbooks.[2,4–7,231–233]

Orbital Lymphoma

Lymphoproliferative tumors are the most common primary orbital neoplasms in adults yet constitute only approximately 2% of all lymphomas.[234] Lymphoid tumors constitute approximately 10% of all orbital tumors. A majority of orbital lymphomas are of the non-Hodgkin's type and are seen mostly in adults during the fifth and the seventh decades of life.

Pathogenesis

Malignant lymphoma is diagnosed when diffusely arranged populations of immature and mitotically active lymphocytes are found in the orbit. Monoclonal populations of B cells confirmed by immunohistochemical studies, with prominent nucleoli, chromatin margination, nuclear membrane irregularities, and cellular atypia are histologic hallmarks of this disease.[235]

Different theories regarding the pathogenesis of lymphomas have been proposed. Although no specific agents have yet been identified, new trends hypothesize an infectious etiology. A possible seasonal variation for a greater incidence of lymphomas also has been suggested.[236]

A higher risk of lymphoma has been noted in patients with rheumatoid arthritis or those on anti-inflammatory drug therapy.[237] The relationship between viruses and lymphomas, particularly Epstein-Barr virus (EBV) and Hodgkin's lymphoma, has been described.[238]

Clinical Features

Orbital lymphomas usually are unilateral, with a predilection for the superior and anterior orbits, but also may be seen in both orbits. The patient usually presents with a painless proptosis of insidious onset, downward displacement of the globe, a palpable nontender orbital mass, with or without exraocular motility problems, and ptosis.

Imaging studies usually confirm the presence of a mass. On CT, lymphomas appear homogeneous in texture, are isodense to muscle, and show mild enhancement with contrast. A diffuse or well-defined orbital mass with molding to the globe, optic nerve, and orbital bones strongly suggests the diagnosis of orbital lymphoma; molding usually is associated with indolent histology, whereas bone destruction is associated with aggressive histology (Fig. 71-22). MRI commonly reveals intermediate signal intensity on T_1- and T_2-weighted images and moderate signal intensity with gadolinium enhancement.[239]

In the orbit, the distinction between "primary" and "secondary" orbital lymphoma is to some extent arbitrary. Primary lymphomas are considered to be limited to the orbit. Thus, by definition, "primary" orbital lymphomas are stage I. In secondary orbital lymphomas, the orbit is considered as a secondary extranodal site of involvement. In these cases, the systemic disease is either known previously or it is diagnosed at the same time as the discovery of orbital lymphoma.[240] With application of the more advanced diagnostic tools such as PET, bone marrow biopsy, and monoclonal antibodies for detecting small foci of systemic lymphoma as part of the staging workup, it appears now that the incidence of truly "primary" orbital lymphoma is lower than was suggested in the past.[241]

Lacrimal gland lymphomas, which are considered in the category of orbital lymphomas, are B-cell tumors that develop in older adults. A majority of these tumors have mucosa-associated lymphoid tissue (MALT) characteristics and carry a favorable prognosis.[242]

Accurate histopathologic evaluation is the most critical diagnostic step in the management of orbital lymphomas.[243] Ideally, the biopsy tissue should be delivered to the laboratory fresh (without preservatives) and sterile. Current laboratory workup for lymphoma includes immunohistochemistry, flow cytometry, cytogenetics, and molecular studies.[241] Approximately 85% to 90% of orbital lymphomas are categorized as diffuse, low-grade proliferations of small, monoclonal B-cell lymphocytes. The remaining 10% to 15% have follicular or nodular characteristics. Lesions displaying high mitotic activity are most likely to be associated with extraorbital, systemic disease; follicular lesions with germinal centers are more likely to be indicative of localized disease.[244] The advances in the detection of monoclonal antibodies, which identify surface antigens on lymphoid cells, led to the classification of lymphomas based on their immunophenotype. In addition, the chromosomal and molecular characteristics of lymphomas are now studied routinely and correlated with their clinical behavior. The Revised European-American Classification of Lymphoid Neoplasms (REAL) is the most recently and widely used diagnostic classification system and is based on morphology, immunophenotype, genotype, and clinical features of the lymphoma[245] (Table 71-8). In this classification, lymphomas are grouped as indolent, aggressive, and highly aggressive types.[246]

A thorough staging workup with a complete history and physical examination, including gastrointestinal endoscopy, orbital and systemic imaging, barium studies of the gastrointestinal tract, and morphologic studies, is necessary for patients with orbital lymphoma in order to recognize systemic disease.[247] PET has replaced bone and gallium scans for detecting small foci of lymphoma throughout the body because of its high sensitivity.[248] PET/CT is another new and useful tool for the diagnosis and staging of orbital lymphoma.[249] Today, the Ann Arbor Staging System most commonly is used to assign a stage for lymphomas (Table 71-9).

Differential Diagnosis

So long as the orbital lymphoma is associated with a conjunctival component, which presents a salmon-colored "fish flesh" appearance, the differential diagnosis is not difficult. Pure orbital tumors, however, may mimic other localized or diffuse space-occupying masses in the orbit, including some inflammatory conditions such as Graves' disease and idiopathic orbital inflammation.

Management

Current treatment of lymphoma is based on the use of EBRT or systemic chemotherapy, or both, for the treatment of primary orbital lymphomas.[250,251]

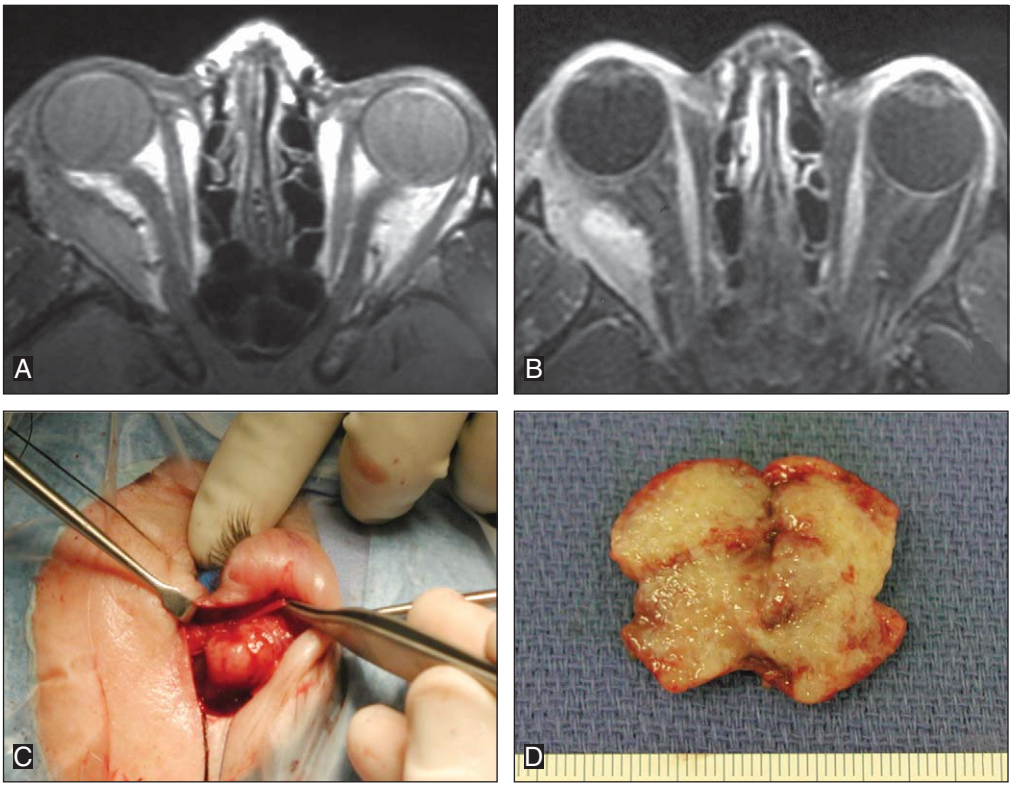


Figure 71-22 • Lymphoma. **A** and **B,** B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type depicted on T_1- and T_2-weighted axial magnetic resonance images. **C,** Intraoperative appearance of the well-encapsulated, firm tumor located in the lateral orbit. **D,** The "fish flesh" gross appearance of the cut surface of the tumor.

Table 71-8 Revised European-American Classification of Lymphoid Neoplasms

INDOLENT LYMPHOMAS
Follicular lymphoma
B-CLL/small lymphocytic lymphoma
Lymphoplasmacytic lymphoma
Marginal zone lymphoma (nodal and/or extranodal)
T/NK large cell granular lymphocyte leukemia
T-CLL
AGGRESSIVE LYMPHOMAS
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Peripheral T-cell lymphoma (unspecified)
Peripheral T-cell lymphoma (angioimmunoblastic, angiocentric)
T/NK cell, hepatosplenic, intestinal T-cell lymphoma
Anaplastic large cell lymphoma
HIGHLY AGGRESSIVE LYMPHOMAS
Precursor T- or B-cell lymphoblastic leukemia/lymphoma
Burkitt and Burkitt-like lymphoma
Adult T-cell leukemia/lymphoma

CLL, chronic lymphocytic lymphoma; NK, natural killer.

The therapeutic approach should be individualized for each patient based on the histologic classification and staging of the disease. Lymphomas are radiosensitive; although EBRT at a 30-Gy dose may be successful in controlling local orbital disease in a majority of patients with low-grade indolent lymphoma, intermediate-grade lymphomas are more appropriately treated with higher doses of up to 40 Gy.[252,253] Some reports have stated that with localized mucosa-associated lymphoid tissue (MALT)-type lymphomas, excellent control and prognosis can be achieved even after lower doses (15 to 25 Gy) of radiation.[254]

Distant relapse has been observed in approximately 25% of patients with low-grade lymphoma and 50% of those with higher grade lymphomas. For orbital lymphomas, the risk of distant relapse is significant with radiotherapy alone.[255] In patients with more aggressive orbital lymphoma for which widespread systemic involvement is likely, combining systemic chemotherapy with local radiation treatment is a safer approach[256] (Fig. 71-23).

Table 71-9 Ann Arbor Staging System for Lymphoma

Stage	Description
I	Single lymph node region or lymphoid structure (e.g., spleen or Waldeyer ring)
II	Two or more lymph node regions on the same side of the diaphragm OR localized involvement of an extranodal lymphoid structure AND of one or more lymph node regions on same side of diaphragm
III	Lymph nodes on both sides of diaphragm ± extranodal sites
IV	Two or more extranodal sites or liver or bone marrow

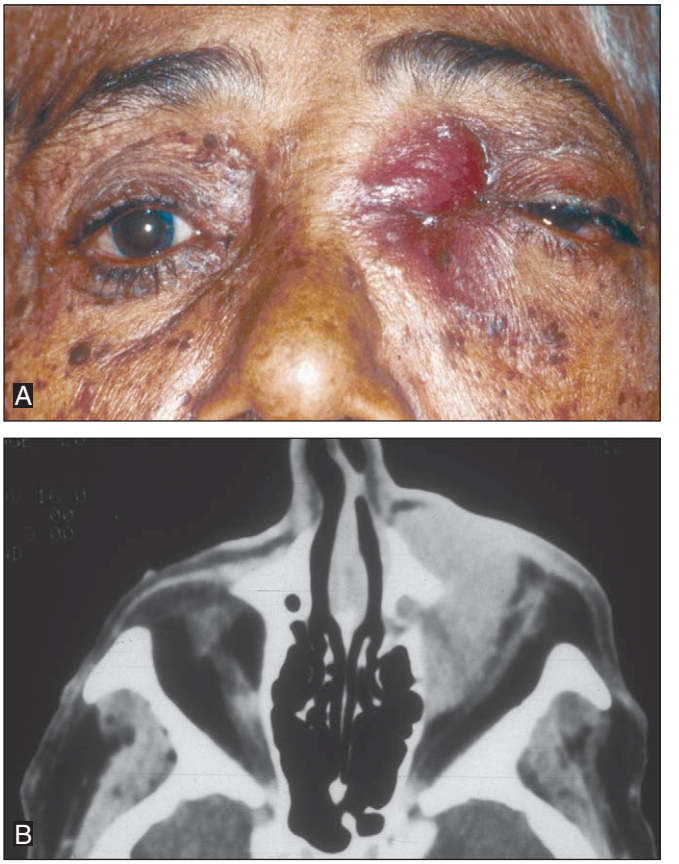


Figure 71-23 • **A,** Large cell lymphoma of the orbit, with involvement of the skin, underlying soft tissues, and bone. **B,** The invasion of bone is not a typical feature of orbital lymphoma but may be seen in long-standing cases or in more malignant types of lymphoma.

Low-dose external beam irradiation (at a dose of 20 Gy) also is used with good results in orbital pseudotumor (idiopathic orbital inflammatory disease) as well.[257] This regimen is recommended in patients with moderate to severe active orbital inflammation but contraindicated in young and diabetic patients because of the risk of secondary malignancies and aggravation of diabetic retinopathy.[258]

In most patients, radiotherapy for primary orbital lymphoma induces minimal acute ocular toxicity, but long-term follow-up can document the usual ocular side effects, including dry eye syndrome and occasionally cataracts.[259] A cumulative dose of 16.5 Gy or higher is likely to lead to formation of lens opacities. Adequate shielding can decrease the risk of cataract formation, but shielding usually does not prevent dry eye syndrome, which frequently occurs after EBRT for orbital lymphoma. Severe radiation vasculopathy of the retina and optic nerve does not commonly occur with the typical total dose used for orbital lymphoma.

Newer approaches in radiation delivery, such as conformal therapy, promise isodose delivery to tumors with minimal ocular radiation toxicity.[260]

Chemotherapy usually is indicated for the more aggressive histologic subtypes of orbital lymphoma and may have potential for subsequent or existent disseminated disease. Combined chemotherapy and radiation therapy may be an appropriate option for intermediate- to high-grade lymphomas. The rationale for combined-modality therapy originates from observations that systemic relapse is common after EBRT alone. Relapse-free 5-year survival rates of approximately 95% for stage I lymphomas and 75% for stage II disease have been reported.[261]

Low-grade lymphomas are very sensitive to both single-agent chemotherapy, such as cyclophosphamide, and combination chemotherapy, which usually is with a doxorubicin-containing regimen such as cyclophosphamide, doxorubicin (i.e., hydroxydaunomycin), vincristine, and prednisone (CHOP) or cyclophosphamide, vincristine, doxorubicin (Adriamycin), and dexamethasone (CVAD).

Recent reports have suggested that monoclonal antibody therapy also may be effective in the treatment of low-grade non-Hodgkin's lymphomas. The availability of active monoclonal antibodies has altered the treatment paradigms for patients with non-Hodgkin's lymphomas. Many patients do not respond, however, and almost all of those who do eventually relapse and require conventional treatment.[262–264] Thus the search for more effective treatment alternatives has led to the development of radioimmunotherapy (RIT). RIT entails the administration of a monoclonal antibody in combination with a radioactive ligand.[265] Beta particles emitted by commonly used radioisotopes are tumoricidal over a distance, allowing eradication of antigen-negative tumor cells by radioactive "crossfire" from neighboring antigen-positive antibody-coated cells. This additional mechanism for tumor lysis leads to more effective treatment than is possible using the nonradioactive antibody. Monoclonal antibodies labeled with radionuclides have become an important therapeutic tool in the treatment of patients with non-Hodgkin's lymphomas. RIT is an attractive option because of the inherent radiosensitivity of most NHLs. Yttrium 90 ibritumomab tiuxetan and ^{131}I tositumomab are two radioimmunoconjugates currently available for clinical use. Toxicities primarily include myelosuppression, with a potential risk of treatment-associated myelodysplastic syndrome and acute myelogenous leukemia. Further development of RIT may be expected to lead to a prolongation of survival for patients with non-Hodgkin's lymphoma.[266,267]

Lacrimal Gland Tumors

The lymphomas and pseudotumors of the lacrimal gland, which are two to three times more common than its epithelial neoplasms, are discussed earlier under "Orbital Lymphoma." Although many carcinomas, including malignant mixed tumor, acinic cell carcinoma, mucoepidermoid carcinoma, and others, develop in the lacrimal fossa, the primary epithelial malignancy of the gland is adenoid cystic carcinoma, which accounts for approximately half of the epithelial malignancies.[268,269]

The mean age at presentation in patients with adenoid cystic carcinoma is approximately 40 years, with a range of 7 to 80 years. A bimodal peak of distribution has been noted in the fourth and the sixth decades of life.

Pathogenesis

It has been proposed that allelic loss for microsatellite markers at 1p36 may be a common and an early event in formation of adenoid cystic carcinomas.[270]

Histopathologically, adenoid cystic carcinoma manifests in five different patterns: cribriform ("Swiss cheese"), basaloid, sclerosing, comedocarcinomatous, and ductal, in order of frequency. The Swiss cheese pattern has been associated with longer survival. The basaloid pattern may be seen more frequently in patients older than 40 years and is associated with a poor prognosis.[271] Perineural invasion of the peripheral nerves frequently is observed in exenteration specimens, accounting for the symptoms of pain and numbness.

Clinical Features

Lacrimal gland carcinomas typically manifest with upper eyelid fullness and rapidly developing downward and medial displacement of the globe with diplopia. In later stages of the disease, proptosis may be associated with pain and visual loss. Adenoid cystic carcinoma extends perineurally and into adjacent bone; therefore, periorbital pain and rarely numbness are associated with this tumor.[272]

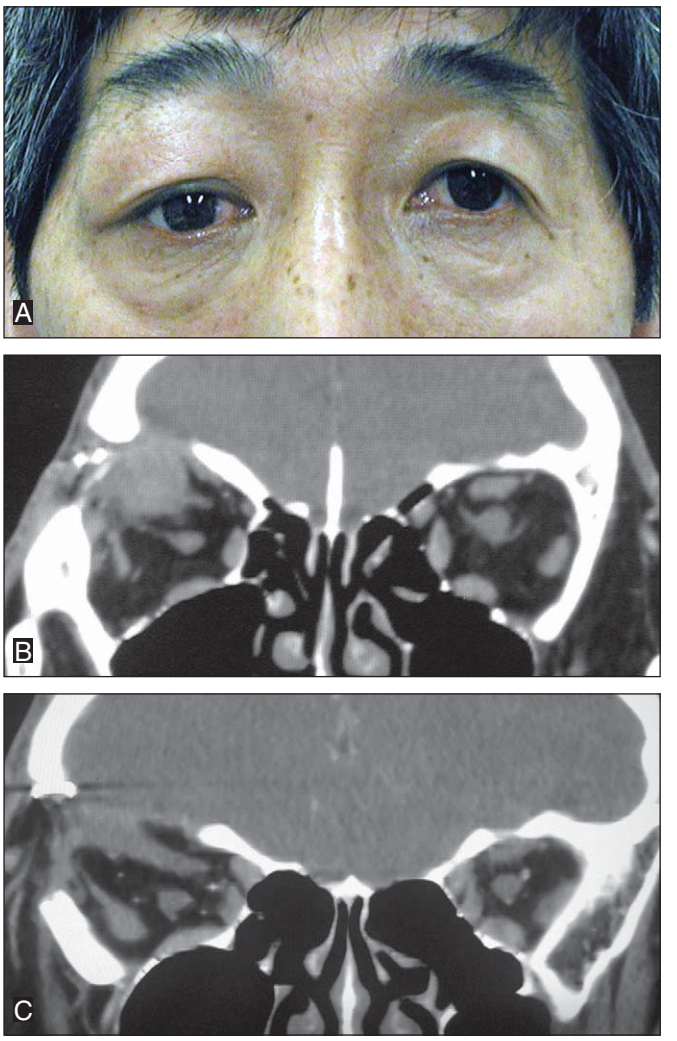


Figure 71-24 • Adenoid cystic carcinoma of the lacrimal gland. Mild proptosis of the right eye is present (**A**), but the destruction of the bony orbit seen on the computed tomographic scans is extensive (**B** and **C**). (Courtesy of Dr. Yoon-duck Kim, Republic of South Korea.)

On high-resolution CT, an elongated mass is seen to extend along the lateral orbital wall, with expansion of the lacrimal fossa with bone invasion. Calcifications more commonly are seen in malignant tumors. Immediate tumor biopsy is indicated in such cases. High-resolution CT typically shows a round or irregular mass lesion extending along the lateral orbital wall with expansion of the lacrimal fossa and bony invasion (Fig. 71-24). Contrast enhancement helps to reveal involvement of the dura and intracranial extension.

MRI will reveal the tumor as hypointense on the T_1-weighted images and hyperintense on the T_2-weighted images with contrast enhancement. This diagnostic modality also is useful for assessing invasion by tumor into the cavernous sinus and brain.

Differential Diagnosis

Acute onset of swelling, periorbital pain, chemosis, or an erythematous indurated lid indicates an inflammatory process. CT or MRI may reveal a diffuse glandular enlargement with irregular margins, frequently demonstrating contrast enhancement and no bone changes. Most cases of bacterial dacryoadenitis resolve rapidly with appropriate systemic antibiotics. Idiopathic acute inflammation can be treated with a short course of corticosteroids. Failure to respond to treatment over a few weeks should prompt incisional biopsy, because acute and

subacute inflammatory episodes may be related to an underlying carcinoma.

As mentioned, orbital lymphoproliferative lesions are another common cause of glandular enlargement. It is characterized by an insidious and painless onset in a slightly older patient and often can be bilateral. Imaging shows that most lymphoid tumors mold themselves around existing orbital structures, such as the globe and the bony orbit, without eroding bone or enlarging the orbit.

When painless swelling in the upper lid without inflammatory symptoms and signs manifests more than 12 months, benign mixed tumor (pleomorphic adenoma) should be suspected. Most patients with malignant epithelial tumors present with painful swelling in the upper eyelid in less than 1 year. Imaging of pleomorphic adenomas usually shows a rounded, well-circumscribed mass with expansion of the lacrimal fossa without invasion of overlying bone. Biopsy of pleomorphic adenoma should be avoided. If biopsy is done before excision, the 5-year recurrence rate is estimated to be 30%, and many recurrent tumors undergo malignant transformation.

Management

Surgical tumor removal with postoperative radiotherapy constitutes the most common treatment for adenoid cystic carcinoma. The surgical techniques of tumor removal include local resection, en bloc removal, exenteration, and orbitectomy. Even with very radical surgical approaches, the survival rate with this tumor does not go beyond 20% at 10 years, and the median survival period is 5 years.[273] Patients usually die of intracranial spread. Orbitectomy with bone removal may help to achieve local control in advanced cases of adenoid cystic carcinoma of the lacrimal gland, but such surgery does not decrease the risk of distant metastases.[274] The use of brachytherapy has been tried in patients with adenoid cystic carcinoma, yielding reasonably good results.[275] The long-term results are unknown, however. The preliminary data suggest that intra-arterial cytoreductive chemotherapy (IACC) is potentially effective in improving local disease control and overall disease-free survival in lacrimal gland adenoid cystic carcinoma. Intracarotid cisplatin and intravenous doxorubicin were used before and after exenteration and irradiation, with long-term survival periods of 9.5 and 7.5 years, respectively.[276] Adenoid cystic carcinoma also is known to grow slowly and to exhibit recurrence and metastasis years after the initial treatment.

Orbital Rhabdomyosarcoma

Rhabdomyosarcoma makes up approximately 5% of all cancers in the pediatric population, but it is significant in ocular oncology as the most common malignant mesenchymal orbital tumor of childhood.[277]

Orbital tumors account for about 15% of the cases of rhabdomyosarcoma; males are more often affected than females, and the mean age at diagnosis is 8 years. A confirmed or unclear history of trauma frequently is associated with the clinical presentation of the tumor.[278]

Pathogenesis

Rhabdomyosarcoma, which is considered to originate from primitive mesenchymal cells, manifests in various histopathologic forms that usually differ among age groups. These lesions appear to be separate biologic entities as well as morphologic categories, with embryonal tumors manifesting genetic lesions related to loss of heterozygosity and aberrant parental imprinting, alveolar tumors containing fusions between *PAX* and *forkhead* genes, and pleomorphic tumors showing an accumulation of genetic lesions similar to those with other adult high-grade sarcomas.[279,280] Infants and young children tend to have embryonal tumors, adolescents and young adults tend to have alveolar tumors, and older adults tend to have pleomorphic forms, although some overlap is recognized. A fusion-positive rhabdomyosarcoma has a distinct molecular signature, which may lead to successful genetic testing for diagnosis and staging in the near future.

Clinical Features

The most characteristic presenting feature of orbital rhabdomyosarcoma is its rapid onset and progression with proptosis and displacement of the globe.[281]

Rhabdomyosarcoma should always be suspected whenever the clinical presentation is that of a rapidly progressive unilateral exophthalmos in a child (Fig. 71-25). Signs and symptoms depend on the site and histologic type of the tumor. With posterior tumors, rapid development of edema of the optic disc and loss of color vision, choroidal folds, and some degree of ophthalmoplegia are characteristic. When the tumor is situated in the inferior and anterior regions of the orbit, it often causes chemosis and edema of the eyelids and motility limitation.

The histopathologic types of rhabdomyosarcoma in the orbit consist primarily of embryonal and alveolar tumors. The embryonal type is the most common; the alveolar is less common and carries the worst prognosis.[282,283] Tumor locations within the orbit usually correlate with histologic type: Embryonal and differentiated tumor types more commonly are located in the superior and superonasal regions, whereas the alveolar type originates from the mid- and posterior orbit. CT and MRI play important roles in the preoperative evaluation to determine the location and size of the tumor and also in evaluating residual or recurrent disease on follow-up examinations.[284,285] Intracranial and sinonasal invasion are rather uncommon



Figure 71-25 • **A** and **B,** Two children with superiorly (**A**) and inferiorly (**B**) located rhabdomyosarcomas in left and right orbits, respectively.

at presentation, whereas changes in the adjacent bone frequently have been reported.[284] CT depicts a moderately well-delineated, homogeneous orbital mass isodense to the extraocular muscles, which often shows enhancement after contrast administration (Fig. 71-26). On MRI, on T_1-weighted images, the tumor may appear isointense to hyperintense with respect to the extraocular muscles and hypointense with respect to orbital fat. Proton density and T_2-weighted images are not very distinct. On T_1-weighted, contrast-enhanced images, rhabdomyosarcoma exhibits moderate to marked enhancement, to a degree that its highly vascular internal architecture may resembles that of a capillary hemangioma.[286]

Differential Diagnosis

Considerations in the clinical differential diagnosis for rhabdomyosarcoma include most disorders that lead to rapidly developing proptosis in childhood, including orbital cellulitis, vascular tumors, Burkitt tumor, and metastatic tumors, particularly neuroblastoma in younger patients. The differential diagnosis has become simpler than in previous years because of the use of myogenic factors in immunohistochemistry studies, nevertheless, in some cases, it may still be challenging. Diagnosis and management of orbital rhabdomyosarcoma require close collaboration among the radiologist, the ophthalmologist, and the medical and radiation oncologists.[287]

Management

No matter how typical the clinical imaging features are, the ultimate diagnosis, staging, and the management plan are based on the histopathologic diagnosis. If the tumor is located within the posterior orbit, excision biopsy or open core biopsy should be performed; fine-needle aspiration biopsy usually does not yield enough information, and findings may be misleading.[288] After the biopsy, the tumor should be staged according to the schemes of the Intergroup Rhabdomyosarcoma Study (IRS) and American Joint Commission on Cancer (AJCC).[289,290]

Simplification of the staging system by Shields and coworkers is a practical approach that can be applied to orbital rhabdomyosarcomas. Because most orbital tumors are biopsied without attempt at resection, gross residual disease is inevitable (group III); thus, most tumors will be stage I or group III; a minority will be stage I or group I or II, and rarely a primary orbital RMS will be found to be stage IV.[278]

Current treatment for rhabdomyosarcoma consists of surgery, chemotherapy, and EBRT, based on the recommendations of the IRS.[291,292] Some surgeons limit the therapeutic role of surgery to excisional biopsy only; others, however, perform extensive surgery to remove or debulk the tumor. The surgical approach should be planned according to the clinical and imaging findings. We recommend that tumor excision be pursued if it can be done without damaging the vital structures of the orbit. It has been shown that 4000 cGy in fractionated doses provides satisfactory tumor control.

Children with orbital rhabdomyosarcoma treated on IRS protocols have had an extremely high cure rate. The 5-year survival rate for children with alveolar tumors was 74%; infants diagnosed with an alveolar rhabdomyosarcoma die very young. The 5-year survival rate for children with embryonal tumors, on the other hand, was approximately 95%.[293] Multiple malignant neoplasms in rhabdomyosarcoma survivors has become of increasing concern over the last 2 decades or so. These tumors, which occur in higher numbers after EBRT, may be benign or malignant and usually develop in a different site from that of the primary tumor several years after treatment.[47,294] The ongoing IRS-V study uses actinomycin D and vincristine combined with a decreased dose of EBRT (4500 cGy compared with 5000 cGy) for patients with low-risk rhabdomyosarcoma, including group III orbital disease. Further reduction in radiation complications may result from the use of three-dimensional conformal radiation therapy techniques by minimizing the inclusion of normal tissues in the treated volume.

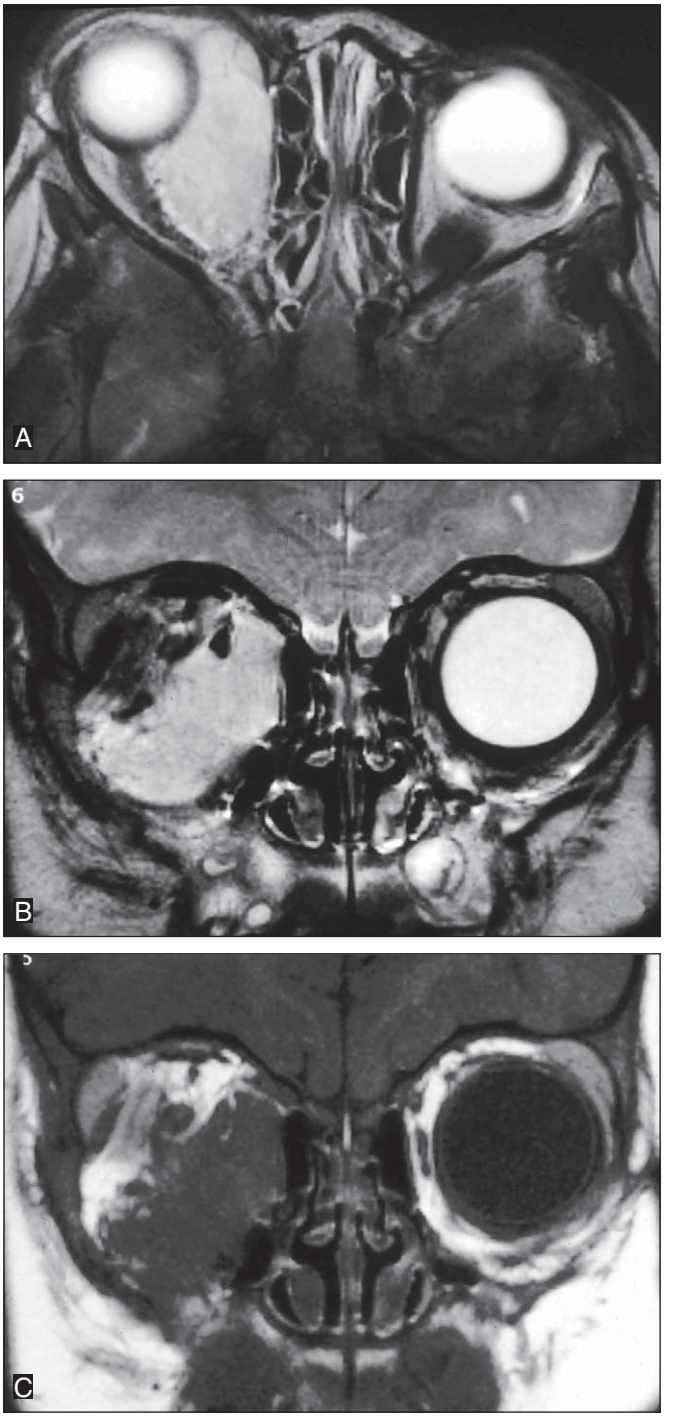


Figure 71-26 • Large inferomedial rhabdomyosarcoma seen on magnetic resonance imaging. **A,** Axial T_2-weighted image; **B** and **C,** coronal T_1- and T_2-weighted images.

Ocular and Orbital Histiocytosis

Histiocytic cell dysfunctions and proliferations are important to the ophthalmic oncologist because these "pseudotumors" are encountered in many ophthalmic disorders of the eye and the orbit.[295]

Pathogenesis

Histiocytes are divided into two major types: macrophages and dendritic cells. Both types are nonlymphoid mononuclear cells

involved in immune and nonimmune inflammatory responses. *Macrophages*, which derive from the bone marrow, are tissue phagocytes that serve both antigen processing and effector functions in T cell-mediated immunity. *Dendritic cells* are nonphagocytic immune accessory cells that also appear to originate from the stem cells of the bone marrow.[296] Dendritic cells are further divided into *Langerhans cells* (LCs) and *non-Langerhans cells* (nLCs). Both cell types express CD1 and CD45 antigens and S-100 protein and contain high levels of adenosine triphosphatase (ATPase). The distinct feature differentiating these two cell types is the presence of an intracytoplasmic organelle called a Birbeck granule in the LC but not in the nLC; Birbeck granules can be demonstrated only with electron microscopic examination.

Clinical Features

LC histiocytoses are class I histiocytoses (histiocytosis X in old terminology), including eosinophilic granuloma, Letterer-Siwe disease, Hand-Schüller-Christian disease, and Hashimoto-Pritzker disease.[297]

Current thinking is that LC histiocytosis is a clonal, "tumor-like" proliferation with variable biologic behavior that occurs most often in children aged 1 to 3 years, with a 2:1 male predominance; LC histiocytosis is rare in adults. An increased incidence of LC histiocytosis has been reported in patients with leukemia and solid tumors. Furthermore, these tumors, particularly acute lymphoblastic leukemia (ALL), commonly are reported in patients who received treatment for LC histiocytosis with chemotherapy and irradiation. Ophthalmic manifestations, which are seen in approximately 10% of cases, occur more often in eosinophilic granuloma and Hand-Schüller-Christian disease. The latter typically manifests with the triad of orbital lesions, diabetes insipidus, and bone lesions. Eosinophilic granuloma is the localized variant of LC histiocytosis, most often involving the orbit in the superior temporal area with lytic or sclerotic bone lesions. Solitary lesions of eosinophilic granuloma manifest only in the cranium. Multifocal LC histiocytosis manifests with multiple bone lesions scattered throughout the skeleton.

Necrobiotic xanthogranuloma is another non-LC disorder that manifests with destructive skin and soft tissue lesions of the periorbital region. In approximately 50% of the patients, other ophthalmic manifestations also develop, including proptosis due to orbital masses, ptosis, lid-apposition abnormalities, scleritis, and uveitis.[298] Necrobiotic xanthogranuloma frequently is associated with immunoglobulin G (IgG) monoclonal gammopathy, hepatosplenomegaly, plasma cell dyscrasias, and, less commonly, cryoglobulinemia and lymphoproliferative tumors.

Juvenile xanthogranuloma is an infantile disease with serious ophthalmologic consequences; it currently is considered to be a neoplasm of the non-LC. This disorder manifests with small papules of the skin in the head and neck region and tends to be self-limiting.[299] When the iris and anterior chamber are involved, which occurs in less than 1% of the cases, the intraocular histiocytic nodules easily break down, leading to hyphema, secondary glaucoma, cataracts, and corneal damage. Juvenile xanthogranuloma may occur on the external eye, on the eyelids, or in the orbit as a localized mass as well.[300]

Another type of non-LC proliferation is adult-onset xanthogranuloma, which occurs as a localized or systemic disease.[301] The localized form usually involves the eyelids and the orbit and consists of dense infiltrates of histiocytes intermingled with occasional multinucleated giant cells (Fig. 71-27). These lesions show CD68 immunoreactivity. In its systemic form, known as Erdheim-Chester disease, the long bones, heart, lung, brain, and other organs may be involved, with histiocytic proliferations leading to serious, sometimes fatal symptoms.[302]

Differential Diagnosis

The differential diagnosis is based on morphologic features. The histologic pattern in LC histiocytosis consists primarily of proliferation of large histiocytes surrounded by neutrophils, eosinophils, lymphocytes, and plasma cells. Specialized cells such as mast cells and multinucleated foreign body giant cells, called Touton cells, also may be seen. Definite characterization of the cell type should be done by identification of Birbeck granules with electron microscopy. Immunohistochemical identification is not dependable because non-LC disorders also may show positivity with markers such as CD-68, HAM-66, and CV1a.[303]



Figure 71-27 • Two patients with bilateral orbital xanthogranuloma. The patient in **A** had diffuse xanthomas (yellow plaque lesions) of the eyelids, which responded well to bilateral external beam irradiation, without any recurrence. The patient in **B** failed to respond to any kind of treatment, including surgical excision, steroid injection, irradiation, and interferon alfa-2B treatment. Orbital, eyelid, and skin lesions recurred.

Management

Because these histiocytic lesions occur in a variety of ocular and adnexal locations, the details of treatment will depend on the anatomic site. In general, however, chemotherapy with adjuvant radiotherapy is the currently preferred modality of treatment.[304] Chemotherapy protocols consisting of systemic steroids, vinca alkaloids, antimetabolites, and antifols produce a variable response and have a high morbidity. The treatment of recurrent eosinophilic granuloma is challenging.[305] Necrobiotic xanthogranuloma does not respond well to medical, surgical, or radiation therapy; topical, regional, or oral corticosteroids are of no benefit. Minimal surgery consisting of gentle débridement is recommended.

Non-LC proliferations are treated with localized or systemic steroids, excisional surgery, radiation, or chemotherapy. Localized lesions respond well to treatment; diffuse or disseminated lesions, however, are difficult to control with any form of treatment.[306,307]

Orbital Meningioma

Orbital meningiomas may develop primarily from the meninges of the optic nerve sheath or extend into the orbit secondarily from the intracranial cavity.[308,309]

Meningiomas usually occur in middle-aged patients, with a female-to-male ratio of 3:1, and and whites are affected more often than blacks.[309] An increased incidence of this tumor is associated with neurofibromatosis types 1 and 2 (NF-1 and NF-2); multiple meningiomas and bilateral optic nerve sheath meningiomas (ONMs) may occur in these patients, particularly those with NF-2.[310]

Meningioma usually is a benign neoplasm; a malignant histologic pattern is very rare but is known to occur with metastatic potential. The most frequent sites of metastasis are the lung and bone. Histologic grading is the most important predictor of malignancy. Some physicians suggest that, in patients with a history of relapsed meningioma, a total-body CT scan should be performed in order to assess for other possible sites of disease.[311,312]

Pathogenesis

Meningioma originates from the meningoendothelial cells of the meninges. Loss of the *NF2* tumor suppressor gene in a biallelic fashion is believed to be central to the pathogenesis of NF-2-associated and sporadic meningiomas. The mechanism includes nonsense or missense mutation in the *NF2* gene and loss of the other *NF2* allele as a part of chromosomal losses on 22q.[313]

Clinical Features

The primary clinical manifestation of a meningioma affecting the anterior visual pathway is painless and gradually progressive loss of visual acuity or visual field. Patients with frontal or olfactory meningiomas may exhibit mental status changes. Ocular motility impairment, with or without diplopia, may occur with extraocular muscle, orbital, or cavernous sinus involvement. Other clinical findings include loss of color perception and ipsilateral afferent pupillary defect. Optic disc edema and optic atrophy may be seen on fundus examination; the disc, however, may look normal in early cases, particularly with posteriorly located lesions. Optociliary collateral ("shunt") vessels may be present on the optic nerve head secondary to increased choroidal and retrobulbar venous pressure.[314]

Imaging of the orbit in general shows typical but not necessarily pathognomonic features of meningioma. MRI usually is superior to CT in the evaluation of patients with meningioma; however, a CT scan may show hyperostosis of adjacent bone or foci of calcification within the lesion, which are consistent with meningioma (Fig. 71-28). MRI typically shows an isointense lesion on T_1-weighted images with homogeneous gadolinium enhancement.[315] ONMs have a more diagnostic radiographic appearance and may display a classic "railroad track" appearance of enhancement of the optic nerve sheath.

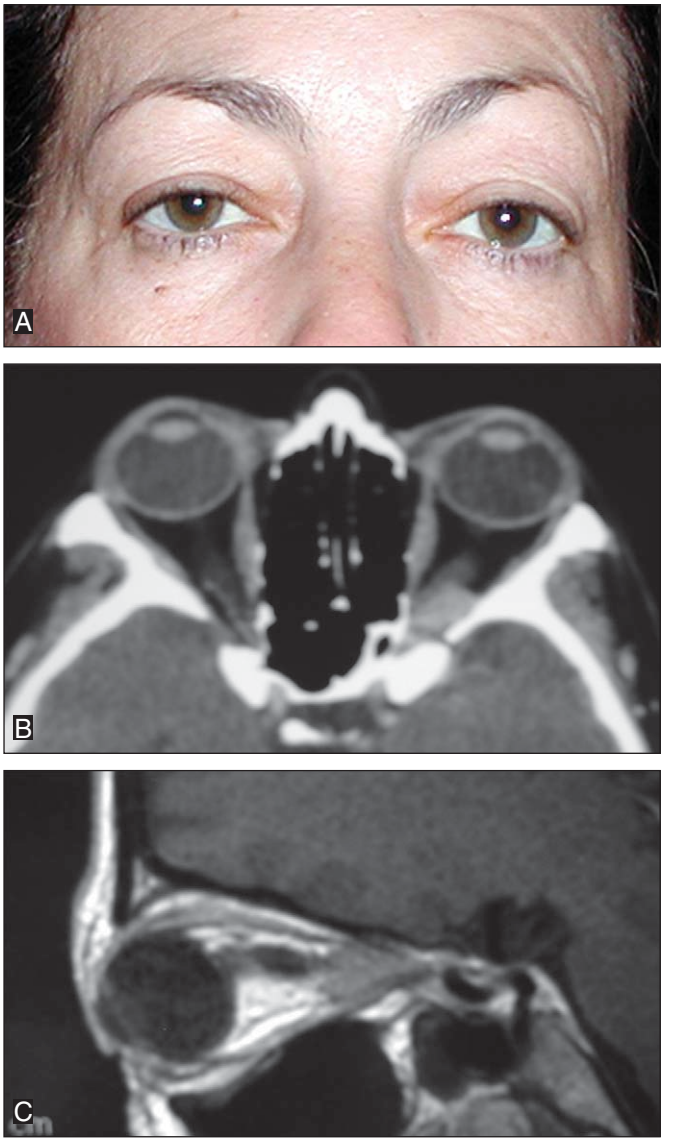


Figure 71-28 • Orbital meningioma. **A,** The patient had minimal proptosis of the left eye with diplopia at extreme left and upper gazes. The vision was severely diminished. **B,** The axial computed tomography reveals the apical location of the tumor with focal calcification. **C,** The sagittal T_1-weighted magnetic resonance image depicts extension of the tumor into the optic canal.

Differential Diagnosis

Metastatic tumors to the optic nerve are exceedingly rare and usually can be differentiated from ONM easily because of their rapid growth. However, occasional metastatic carcinomas are known to mimic ONM owing to their initial radiologic appearance and minimal growth on serial imaging.[316]

Imaging features considered characteristic of ONM, such as the "railroad track" sign or central optic nerve lucency seen on CT, also may be seen with metastases to the optic nerve.[317] Although typically more sensitive than CT, MRI also can be inconclusive because the appearances of these two pathologic conditions on ophthalmic imaging overlap considerably. Other rare lesions that may mimic an ONM include meningoceles and arachnoid cysts.[318,319] Arachnoid cysts are cystic lesions filled with a cerebrospinal fluid-like content within the leptomeninges. Usually they represent congenital malformations.[320]

Management

The management of symptomatic intracranial meningiomas must be individualized. The tumor usually is benign but may compress adjacent vital structures. In general, total surgical resection is attempted if the patient is a good surgical candidate, and if the surgery is technically possible. If the meningioma encases vital structures, such as a cavernous sinus or internal carotid artery, a subtotal excision may be considered. Sequential neuro-ophthalmic evaluations and neuroimaging studies are recommended to detect postoperative recurrence or progression. Postoperative irradiation may be employed for malignant or aggressive pathologic processes or for residual, recurrent, or nonresectable meningiomas.

ONMs usually do not require biopsy for diagnosis if the typical clinical and radiographic features are present; tissue diagnosis may be needed in rapidly growing tumors to rule out an aggressive

histopathologic type. Observation for progression is a reasonable first step in management. Surgical excision of ONM usually produces irreversible visual loss and generally is reserved for eyes without visual potential or cosmetically unacceptable proptosis. In patients with severe disk edema and rapid vision loss, however, surgery may serve an adjuvant role to fractionated stereotactic radiation therapy.[321] Orbital decompression by transnasal endoscopic ethmoidectomy has been reported to delay the visual loss in sphenoid wing meningiomas for some years. Some patients require additional radiotherapy for progressive tumor growth.[322] Rare patients with acute visual deterioration also may benefit from optic nerve sheath fenestration.[323]

If no tumor growth is observed, an ideal monitoring protocol is repeated MRI of the head and orbits with gadolinium and fat suppression every 6 months for 2 years and then yearly. On the other hand, if visual acuity and visual field are lost, even in the absence of tumor enlargement, most physicians would consider radiation therapy to be the treatment of choice.[324,325] Improved techniques for delivery of radiotherapy (e.g., conformal, three-dimensional, or intensity-modulated radiotherapy) may decrease the risks of radiation side effects. Stereotactic radiotherapy currently is the most effective method for treatment of primary ONM. It provides tumor control and visual preservation with low risk of complications.[325,326] In some patients, the visual improvement may take place early, even before completion of a standard course of radiation therapy.[327]

Turbin and coworkers offered a comparison of treatment (observation, surgery only, radiotherapy only, or surgery and radiotherapy) outcomes in 64 patients with ONM after a minimum of 50 months of follow-up. Of 59 patients with vision better than no light perception at diagnosis, 13 patients were observed only, 12 had surgery only (4 biopsies or partial resections, 8 total resections), 18 received irradiation alone, and 16 had surgery and irradiation (14 biopsies or partial resections and irradiation, 2 total resections and irradiation). Irradiated patients received 4000 to 5500 cGy of conventional multiport or conformal external beam therapy, typically fractionated over 6 weeks. Visual acuity measurements at diagnosis were not different among the four groups. Visual acuity fell significantly for the observation-only, surgery-only, and surgery plus irradiation groups. Patients with ONM receiving radiation alone had the best visual outcome during the follow-up period. The investigators recommended that fractionated external beam irradiation (at a dose of 5000 to 5500 cGy) be considered for initial treatment in adults when preservation of visual function is the therapeutic goal.[328] Other workers also reported very promising CyberKnife radiosurgery results, with high rates of tumor control and preservation of visual function in patients with these tumors. In one study in which the radiation was delivered in two to five sessions to an average tumor volume of 7.7 cm^3, with a cumulative average marginal dose of 20.3 Gy, 94% of the patients retained or improved pretreatment vision.[329]

Orbital Glioma

Optic pathway gliomas, which are tumors of childhood, account for approximately 1% of all CNS tumors.[330] No sex predilection has been noted, and although these tumors can manifest at any age, most patients are less than 10 years old. The presentation of this tumor in adulthood may suggest a more malignant behavior.[331,332]

The incidence of optic gliomas in children with NF-1 is as high as 15%, with symptomatic visual loss in approximately 20% of affected patients.[333] Any part of the optic pathway may be occupied with tumor. In approximately 25% of the cases, one or both optic nerves alone are involved; in the remaining 75%, the optic chiasm or tract contains glioma.

Pathogenesis

A majority of optic pathway gliomas are low-grade astrocytomas. The astrocytic nature of the tumor can be confirmed using immunohistochemical techniques with antibodies against glial fibrillary acidic protein (GFAP; molecular weight of 15,000). Although this protein also may be present in some schwannomas, increased GFAP expression is typical for astrocytic tumors.

Clinical Features

Gliomas that develop in the orbit produce painless proptosis, ophthalmoplegia, and progressive visual loss.[332] Visual loss is noted at presentation in approximately 90% of the patients. Optic disc swelling (35%) or atrophy (60%) generally is present, and rarely optociliary shunts may be observed. In children with NF-1 and optic pathway gliomas, the likelihood of visual loss depends on the extent and location of the tumor as determined by MRI.[334]

Hypothalamic symptoms and endocrine abnormalities may occur with chiasmal-hypothalamic tumors.[335]

On CT, the glioma manifests as a fusiform enlarged, uncalcified optic nerve mass with frequent kinking and cystic areas. MRI with gadolinium is superior to CT to display the tumor and monitor intracranial extension. The imaging typically reveals intrinsic enlargement of the optic nerve with variable contrast enhancement. On T_1-weighted images, the lesion usually is isointense to the cerebral gray matter. When the tumor is large, it may show marked enhancement centrally without peripheral enhancement; this appearance is consistent with ectactic or hyperplastic arachnoid around the nerve. On T_2-weighted images, fusiform lesions reveal high signal intensity, whereas large, lobulated tumors tend to have a more heterogeneous signal. A double-intensity "tubular thickening," with kinked and elongated optic nerves, suggests, but does not confirm, a diagnosis of glioma in patients with NF-1 (Fig. 71-29). Enlargement of the chiasm or the optic tracts is a sign of intracranial involvement.[336]

Differential Diagnosis

Considerations in the differential diagnosis for optic nerve glioma include idiopathic optic neuritis, sarcoidosis, demyelinating disease, and other tumors and cysts of the optic nerve and its sheath, including metastatic tumors.[337–339]

Management

A period of observation for progression prior to initiation of therapy is recommended by most authorities, because gliomas often are static or slowly growing lesions.[340] Non-NF-1 patients usually have larger and more rapidly progressive tumors. Rapidly progressive chiasmatic tumors are best treated by radiotherapy and respond well by regression.[341]

EBRT generally is reserved for patients older than 5 years of age with progressive imaging findings or worsening clinical signs and symptoms.[342] The risks of radiation are substantial and include cerebral atrophy, cerebrovascular disease, moya moya disease, subnormal intelligence or learning disabilities, and secondary primary malignancies, cataracts, radiation damage to the retina and optic nerve, endocrinopathy, and hypothalamic dysfunction. These risks generally are higher in younger patients.[343] The usefulness of surgical therapy generally is limited. An optic nerve glioma in a patient with no useful vision or that demonstrates progression may be resected. However, chiasmal, hypothalamic, or optic tract gliomas cannot be completely resected because of unacceptable ocular and CNS morbidity.

Chemotherapy frequently fails in a majority of patients but serves to delay implementation of radiotherapy or surgery until the child has progressed neuropsychologically. In infants or children younger than 3 years of age, however, chemotherapy with carboplatin and vincristine is emerging as a possibly safer alternative to EBRT. Surgical debulking does not appear to enhance chemotherapy effectiveness.[344] The prognosis of optic pathway gliomas is quite variable and is primarily based upon location; the more anterior the location, the better the prognosis. The 10-year overall survival rate is between 85% and 100%. In approximately 80% of patients with gliomas, vision stabilizes after an initial period of visual loss.[345] The natural history of the optic pathway glioma usually is more indolent in patients with

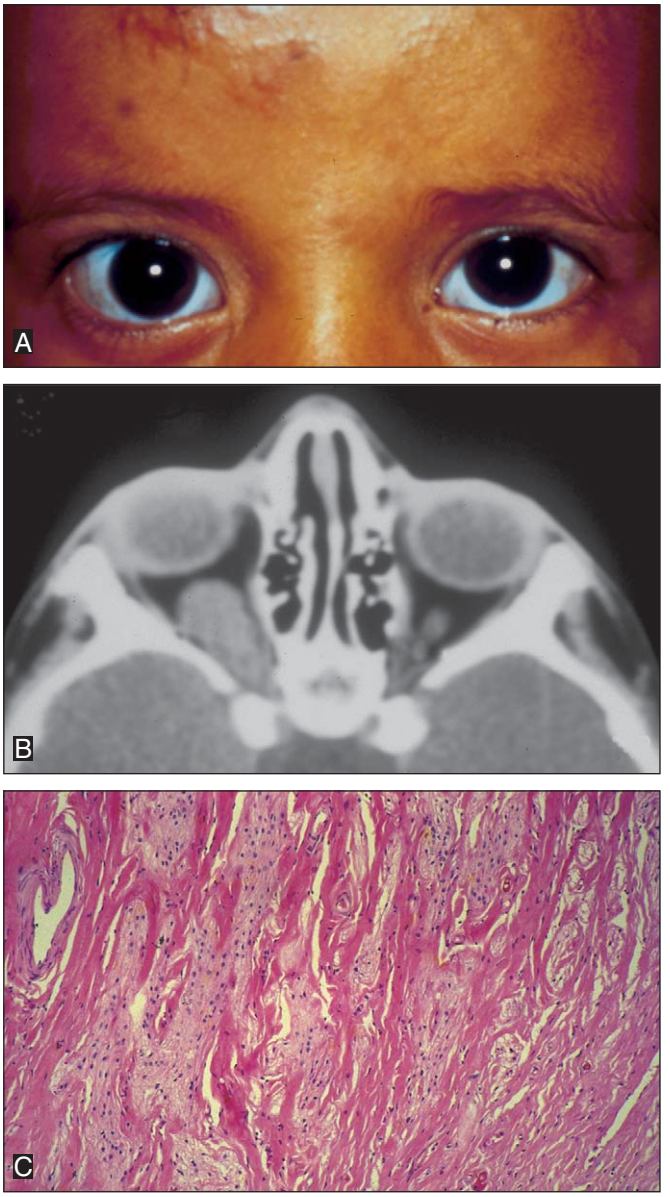


Figure 71-29 • Optic nerve glioma. **A,** Barely noticeable proptosis of the right eye in a child with long-standing optic nerve glioma. Because of the very slow growth of these tumors, proptosis is subtle in a majority of affected children. This patient also has multiple skin neurofibromas of neurofibromatosis type 1. **B,** Optic nerve glioma seen on axial computed tomography (CT) scan. Although the tumor is clearly seen on the CT scan, magnetic resonance imaging is preferred to monitor for extension of tumor into brain. **C,** Histopathologic appearance of a low-grade astrocytoma of the optic nerve.

NF-1 than in the others, and regressions are observed.[346] The prognosis with these tumors also is dependent on the patient's age at presentation. Those tumors that manifest before the age of 6 years have a tendency to grow fast and must be followed closely.[347]

Metastatic and Secondary Tumors

Metastatic Tumors

Systemic malignancies may metastasize to the orbit, with a frequency ranging from 2% to 10% of all orbital tumors.[348] Although almost, any human neoplasm has been reported to metastasize to the orbit, the most frequent primary tumors in adults include *breast*, *lung*, *prostate*, and *gastrointestinal tract carcinomas* and *cutaneous melanoma*.[349] Most orbital metastases appear as solitary nodules, rather than infiltrating tumors, and approximately 10% are bilateral. Bilateral orbital and sino-orbital disease most frequently is seen with metastasis from breast carcinoma. Approximately 50% of orbital metastatic tumors were reported to have concurrent involvement of other metastatic sites, including the eye. Patients with metastatic orbital tumors most frequently present with rapidly developing unilateral motility disturbance, painful proptosis, and occasionally, a palpable mass.[350] Imaging studies with CT and MRI provide information regarding the location of the tumor and the pattern of orbital involvement (Fig. 71-30); however, they rarely offer any clues in terms of the primary site. Fine-needle aspiration biopsy is an effective method for histopathologic confirmation of orbital metastasis.[351] Carcinoid tumors in the orbit may be primary or metastatic; the latter type is reported to be a slowly growing tumor associated with long survival after surgical treatment.[352]

In approximately 10% of metastatic orbital tumors, the site of the primary lesion is unknown; this condition is known as *occult primary malignancy*.[353]

In children, metastatic neoplasms to the orbit are predominantly small, round, blue-cell tumors, including neuroblastoma, Ewing sarcoma, granulocytic sarcoma, and Wilms tumor. Neuroblastoma is the most common malignant tumor in infants, with an approximate incidence of 1 per 1000 live births, and it is the most common metastatic tumor of the orbit in this age group. Neuroblastoma, which originates from primitive neuroectodermal cells, most often is diagnosed during the first year of life. On histopathologic examination it is seen to be made of round or oval, small round cells with hyperchromatic nuclei and minimal cytoplasm containing numerous mitotic figures. Differentiating neuroblasts and ganglion cells, as well as rosette formations (Homer-Wright rosettes), may be seen in primary tumors. Approximately 75% of affected children excrete increased amounts of catacholamine byproducts, including vanillyl-



Figure 71-30 • Multiple orbital and brain metastases from an abdominal neuroblastoma on an axial T_1-weighted image.

mandelic acid (VMA), norepinephrine, homovanillic acid (HVA), and dopamine, in the urine; assays for these substances are very helpful in diagnosis.

Secondary Tumors

Tumors extending into the orbit range from congenital malformations, hamartomatous and teratomatous lesions, and reactive proliferations to most malignant neoplasms such as retinoblastoma. Secondary orbital tumors may originate from the cranial bones and CNS tissues (*meningioma*, *pituitary adenoma*, *craniopharyngioma*), periorbital bones (*osteoma* and *osteogenic sarcoma*, *giant cell-rich reactive lesions*), paranasal sinuses and nasal cavity (*squamous cell carcinoma*), nasolacrimal drainage apparatus (*squamous cell carcinoma*), globe (*uveal melanoma*, *retinoblastoma*) and conjunctivae and the eyelids (*squamous cell carcinoma*, *basal cell carcinoma*, *melanoma*, and *sebaceous gland carcinoma*).

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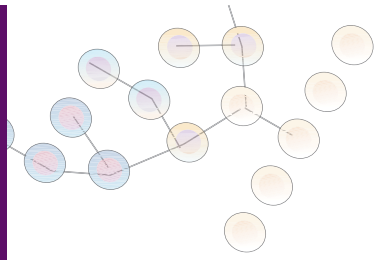
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72 Cancer of the Head and Neck

Harry Quon

SUMMARY OF KEY POINTS

Incidence
- More than 37,000 estimated new cases of head and neck cancer are diagnosed each year in the United States.
- More than 11,000 estimated deaths due to head and neck cancer occur annually in the United States.

Epidemiology and Risk Factors
- The dominant risk factors for the development of head and neck cancers are tobacco and alcohol use.
- Other risk factors may include immunosuppression and viral infection (human papillomaviruses and Epstein-Barr virus [EBV]).

Pathology and Tumor Biology
- A majority of head and neck cancers are squamous cell carcinomas with a well-delineated local-regional spread pattern.

Clinical Findings
- The clinical presentation in head and neck cancer depends on the anatomic site of involvement.
- Common symptoms may include hoarseness of voice, dysphagia, odynophagia, and referred otalgia.

Differential Diagnosis
- Considerations in the differential diagnosis include lymphoma, sarcoma, and other solid malignancies.

Staging
- Clinical evaluation should include endoscopic evaluation of the upper aerodigestive tract.
- Local-regional anatomic imaging is accomplished by computed tomography (CT) or magnetic resonance imaging (MRI).
- Chest radiography also is indicated.
- Ultrasound examination of the neck is indicated in select cases.
- Chest CT, bone scan, or positron emission tomography (PET) may be indicated as well.
- Complete blood count (CBC) also is part of the workup.

Primary Therapy, Salvage Therapy
- *Early-stage definitive therapy*: Subsite-specific with either definitive surgery or radiotherapy. Involvement of sites important for speech or swallowing function or sites in which surgical risks are prohibitive may favor therapy that provides functional organ preservation. This often favors primary radiotherapy.
- *Advanced-stage definitive therapy*: Subsite-specific with either definitive surgery with postoperative radiotherapy as indicated or chemoradiotherapy with concurrent chemoradiotherapy often favored. Involvement of sites important for speech or swallowing function may favor therapy that provides functional organ preservation. This often favors chemoradiotherapy. Altered fractionated radiotherapy may be used in patients not able to receive chemotherapy or as a alternative therapeutic option for nonbulky primary but advanced-stage disease.
- *Advanced-stage palliative therapy*: Treatment options may include radiotherapy. Systemic chemotherapy or treatment on protocol with systemic chemotherapy often is favored owing to a more favorable toxicity profile.
- *Local-regional recurrent salvage therapy*: For resectable disease with no prior irradiation, surgery with postoperative radiotherapy is favored; for resectable disease with prior irradiation, surgery with considerations for re-irradiation with or without brachytherapy implant is favored. For unresectable disease without prior irradiation, chemoradiotherapy is favored; for unresectable disease with prior irradiation, re-irradiation on protocol or systemic chemotherapy is favored.

Complications
- *Surgical* complications may include: nerve injury, hematoma formation, and organ dysfunction.
- *Radiotherapy-related* complications seen acutely may include skin desquamation, mucositis, dysphagia, odynophagia, xerostomia, and taste alterations; late complications include xerostomia, skin–soft tissue–mucosal atrophy, soft tissue fibrosis, permanent swallowing dysfunction, hypothyroidism, transverse myelitis, and blindness.
- *Chemotherapy-related* complications may include bone marrow suppression.

Prognosis
- Prognosis is both subsite-specific and histology-specific. For locally advanced head and neck cancers of the squamous cell type, the long-term disease control rate is less than 40%.

Future Directions
- Further improvements in local-regional management with the integration of novel targeted agents in combination with current chemotherapy and radiotherapy regimens may lead to better outcomes.
- Continued development of novel radiotherapy techniques, including intensity-modulated radiotherapy (IMRT) and proton radiotherapy, is essential.

INTRODUCTION

In the United States for the year 2003, cancers of the head and neck accounted for 2.8% of all new cancer cases and 2% of all cancer deaths.[1] Because these tumors are relatively uncommon, misdiagnosis along with patient neglect not uncommonly contributes to an advanced stage at presentation and limited survival.[2] Despite their relatively low numbers in clinical practice, research and management of head and neck cancers continue to receive significant emphasis owing to the rich anatomic and functional complexity of this body site, which is critical to issues of self-esteem, communication, and social integration. Although squamous cell carcinomas constitute a majority of adult histopathologic patterns (95%)[3] that may be seen in head and neck cancers, the variation in histopathologic types and the differing features of the possible anatomic subsites of involvement result in tremendous discordant variability in the natural course of the diseases for this small anatomic region.

The site begins at the base of the skull and extends only to the clavicles and includes the base of the skull, temporal bone (external auditory canal, middle and inner ear), paranasal sinuses, nasopharynx, oropharynx (soft palate, tonsil structures, base of tongue, oropharyngeal wall), larynx, hypopharynx (pyriform sinuses, postcricoid, posterior pharyngeal wall), oral cavity (lips, buccal mucosa, alveolar ridges, floor of mouth, oral tongue, retromolar trigone), major and minor salivary glands, skin, and the neck.

Accordingly, management of head and neck cancers has evolved to require a multidisciplinary approach with effective integration of various skills and treatment modalities to achieve the desired goals of cure and functional organ preservation. Despite improvements in the diagnosis and local-regional management of head and neck cancer, few significant increases in long-term survival rates over the past 30 years have been realized. The desire for more effective yet organ-preserving therapies with acceptable toxicity is currently being addressed with recent technological advancements in surgical and radiotherapy techniques and the development of novel biologic agents. These agents are particularly attractive because they have been demonstrated in cell model systems to target various aberrant molecular proteins that appear to have dominant roles in mediating biologic aggressiveness or therapeutic resistance. These advances, coupled with tremendous clinical research activity, have resulted in a number of therapeutic options for patients with head and neck cancer.

EPIDEMIOLOGY

An estimated 37,000 new cases of head and neck squamous cell carcinoma (HNSCC) were diagnosed in the United States in 2003, with 68% being diagnosed in males, accounting for approximately 11,000 cancer deaths, with 71% in males.[1] Additionally, cancers of the oral cavity and oropharynx represent 3% of all malignancies in men and 2% in women in the United States.[4] Worldwide, 15% of male cancers, 600,000 cases annually, are HNSCCs. Head and neck cancers affect both sexes and all races, but a preponderance continues to be seen in males, African Americans, and Asians.[4] Oral and pharyngeal cancers have decreased significantly in white males over the past 20 years and in white females younger than 65 years of age.[5] Conversely, the incidence and mortality rates have significantly increased in African-American males but have decreased in black women. The incidence of laryngeal cancer appears to mimic that of lung cancer; a small decline in the incidence in white men younger than 65 has been noted, but the incidence continues to increase in white and black males older than 65 and in women in all age groups.[6]

Limited knowledge exists concerning the epidemiology of in situ head and neck cancers (lip, oral cavity, larynx, and pharynx). Data extrapolated from population-based cancer registries in the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER) program revealed that annual age-adjusted incidence rates for in situ HNSCC rose from 6.33 per 1 million person-years in 1976 to 8.04 per 1 million in 1995 (a 35% change).[7] The predominant anatomic sites of change were the larynx and lip, with this significant rise thought to be attributable to improved surveillance.

Of significant concern are the rising trends of head and neck malignancies in the pediatric population and younger adults. Again, according to data from SEER, the average annual rate in children younger than 15 years of age rose 35% from 1.10 to 1.49 between 1973 to 1975 and 1994 to 1996, respectively.[8] This incidence reflects a greater increase than for childhood cancer in general, which increased 25% during that same period. In a selected population at the M.D. Anderson Cancer Center, the percentage of adults younger than 40 years with oral tongue squamous cell carcinomas rose from 4% to 18% between 1971 and 1993.[9] This finding has been substantiated by SEER data indicating that the incidence of tongue cancer (oral cavity and oropharynx) increased by 60% in adults younger than 40.[10] The prognosis tended to be worse in black than in white males in the same age category. Trends in laryngeal cancers, documented most accurately in the Veterans Affairs (VA) system increased as well between 1983 and 1993 but more notably among those older than 65 years.[11]

Successful therapy for HNSCC may be limited by the recognized risk of second primary malignancies in the aerodigestive tract. Using data from a population-based cancer registry, investigators from the United Kingdom observed 5.5% of males and 3.6% of females to have developed a second primary cancer after an initial diagnosis of head and neck cancer.[12] They also noted a significantly increased risk for a second cancer in most of the upper aerodigestive tract sites commonly associated with tobacco exposure, with a standardized incidence ratio for subsequent oral cancer of 5.56 in men and 15.31 in women. Excluding these tobacco-associated sites resulted in a nonsignificant risk for a second malignancy. Patients with a first detected pharyngeal cancer experienced the highest incidence of a second malignancy. The relative risk for multiple primary cancers was higher in younger patients and among patients who received radiotherapy for their first primary malignancy. These investigators estimated that within 20 years of diagnosis of the first primary HNSCC, subsequent primary malignancies would develop in 30% of males and 20% of females.

ETIOLOGY AND PATHOGENESIS

Tobacco and alcohol continue to remain the two major risk factors for HNSCC in developed countries, with their carcinogenic risks summarized in several working group reports by the International Agency for Research on Cancer (IARC).[13,14] It is estimated that 75% to 90% of all head and neck carcinomas are attributable to tobacco consumption, particularly cigarette smoking.[15,16] The cumulative evidence easily fulfills the criteria for causality between cigarette smoking and the development of HNSCC.[17,18] Supporting a causal relationship has been the demonstration that the risk of developing HNSCC rises with increasing numbers of cigarettes smoked per day and increasing years' duration of the habit.[3,19] Current smokers have an approximate 20-fold higher risk of oropharyngeal and laryngeal cancers than that in lifelong nonsmokers.[19,20] The relative risk of developing head and neck cancer in the heaviest smokers is quoted as 20 to 40 times that of nonsmokers.[19–21] Even light or occasional cigarette smoking leads to an increased risk of cancer.[3,19,21] In addition to the duration of smoking and number of cigarettes, the type of cigarettes and the age, sex, and race of the smoker also influence the relative risk. By contrast, it has been estimated that the relative risk of developing head and neck cancer for heavy consumers of alcohol is two- to sixfold.[22]

Approxiamtely 300 known carcinogens are present in tobacco, with tobacco-specific *N*-nitrosamines (TSNAs) being the most harmful.[23] These substances are metabolites of nicotine, the major

alkaloid responsible for addiction to tobacco.[17] TSNAs are known to bind to DNA and to cause mutations that can activate proto-oncogenes or inactivate tumor suppressor genes.[24] Other harmful mutagenic compounds found in tobacco include polycyclic aromatic hydrocarbons (PAHs), carbon monoxide, and hydrogen cyanide.[23]

Despite limited data, an association between cigar and pipe smoking and an increased risk for HNSCC also is recognized. Cigar consumption in the United States has increased substantially since 1993. Cigars are known to contain even higher concentrations of TSNAs than in cigarettes.[25] With regard to environmental smoke, compared with cigarettes, cigars emit 20 times the carbon monoxide and twice the PAHs, owing in large part to their greater size.[25] The increased risk of HNSCC associated with cigar smoking is between 1.9 and 10.3 times that in nonsmokers.[15,25–28] Smoking more than 4 cigars per day increases the risk more than 20-fold.[29] A recent study analyzed prospectively the rates of cancer deaths among cigar-smoking men. Men who never smoked cigarettes or pipes were excluded. Risk of death from oral cavity or pharynx and larynx cancers was 4.0 (95% confidence interval [CI], 1.5 to 10.3) and 10.3 (95% CI, 2.6 to 41.0), respectively.[26] Although fewer dedicated studies have been performed, pipe smoking has been similarly implicated.[15,30,31]

Active cigarette smoking is not the only form of tobacco exposure that poses a risk. Exposure to secondhand, or environmental, smoke also has been implicated in several publications as a risk factor for the development of head and neck cancer.[32–34] A recent study of more than 300 patients and control subjects found that secondhand smoke increased the risk of HNSCC, with a confirmed dose-response pattern. Persons who were exposed to the highest levels of environmental cigarette smoke were up to four times more susceptible to the development of HNSCC.[34]

Tobacco is consumed in a smokeless form in many cultures around the world. In the West, the most common form of smokeless tobacco is termed snuff, whereas in parts of Asia, it often takes the form of betel quid. Betel quids consist of a betel pepper leaf wrapped around a mixture of areca nut, slaked lime, and tobacco; the slaked lime releases an alkaloid that causes a sense of euphoria in the user. Approximately 200 million persons throughout the western Pacific basin and south Asia regularly chew betel quid.[35] Habitual use of betel quid can lead to a progressive scarlike formation known as oral submucous fibrosis. The data regarding an increased risk of oral cancer in persons who chew betel are incontrovertible, with an estimated odds ratio of 17 for the development of HNSCC.[35–38]In Europe and the Americas, a large variation has been found in the amounts of TSNA among the various brands and forms of smokeless tobacco available.[39] Therefore, a discrepancy exists between estimated cancer risks associated with smokeless tobacco consumption in Europe and in the Americas.[18,39] Recent studies of Swedish moist snuff users showed no increase in cancer incidence over that in control subjects,[18,40] which may be due to the lower concentrations of TSNA in Swedish snuff.[39] The link between other forms of smokeless tobacco and oral cancer is well established, however.[41–43] A recent review of the known literature found relative risks ranging between 0.6 and 13, depending on the type of smokeless tobacco studied.[42]

Alcohol consumption also is a known independent risk factor for HNSCC.[19,44–47] For those individuals that drink heavily but do not smoke, the increased relative risk reportedly ranges from 5.0 to 11.6, increasing in significance with higher numbers of drinks consumed.[45,46] When alcohol and tobacco are consumed together, the risk increases multiplicatively, rather than additively.[15,19,48] Extremely high odds ratios have recently been quoted for heavy consumers of both tobacco and alcohol.[19,44] Franceschi and colleagues reported an odds ratio of 228 for oral cancer in consumers of more than 25 cigarettes per day and more than 11 drinks per day.[44] One other report noted an odds ratio of 177 for laryngeal cancer in heavy tobacco and alcohol users.[19]

The mechanism for alcohol-induced carcinogenesis is not fully understood. Pure ethanol has been shown not to be carcinogenic.[49] Alcohol, however, often is regarded more as a cocarcinogen, facilitating carcinogenesis rather than initiating it.[50] Several mechanisms for this effect have been proposed. It has been suggested that alcohol may increase the penetration of carcinogens across the oral mucosa,[51] as well as causing mucosal atrophy, which may result in an enhanced susceptibility to chemical carcinogens.[52] It also has been suggested that alcohol may have an effect on DNA repair mechanisms.[53] Other suggested mechanisms include nutritional deficiencies associated with heavy drinking, the effects of contaminants and congeners in alcoholic beverages, and the induction of microsomal enzymes that enhance the metabolic activation of tobacco or other carcinogens.[3] These mechanisms also may explain the observation of an increased risk of cancer with heavy alcohol consumption in nonsmokers. Several reports suggest that women may be more susceptible than men to alcohol-induced carcinogenesis in the head and neck.[46,54,55]

Several studies have implicated the lack of vitamin and fresh fruit intake as a risk factor for head and neck cancer.[56–61] It often is difficult, however, to separate malnutrition from other confounding variables, including alcohol consumption and cigarette smoking. Related to malnutrition is the problem of poor oral hygiene, which also has been found to be associated with HNSCC.[62–64]

It has been proposed that patients with HNSCC have increased chromosomal sensitivity to carcinogen exposure that predisposes them to developing cancer.[65–68] In vitro laboratory studies have shown that cells from these patients suffer more chromosome breaks on exposure to a mutagen than are seen in normal control cells.[67,69] In addition, mucosa from young patients with HNSCC who were nonsmokers was particularly mutagen sensitive.[70]

Immunosuppression may predispose individuals to an increased risk of HNSCC. The risk of carcinomas of the lip is particularly increased in renal transplant recipients.[71–73] Cutaneous malignancies including lip cancers appear to be increased in cardiothoracic transplant recipients.[74] Other sites of malignancies may include the oral cavity, although the risk does not appear to be as significantly increased as it is with cutaneous malignancies including the lip in transplant recipients. An increased risk of oral cavity carcinomas has been reported in human-immunodeficiency virus (HIV)-infected patients.[75] These tumors generally are more aggressive, with decreased patient survival[74,76] and a demonstrated association between the degree of medical immunosuppression, most notably involving prednisone, and advanced-stage presentation and an adverse survival.[76]

A potential causal relationship is believed to exist between viral infections and carcinomas of the head and neck. Human papillomaviruses (HPVs) have been associated with a risk for oral cavity[77,78] and oropharyngeal carcinomas.[78,79] Of interest, these carcinomas may carry a better prognosis[80,81] and may respond better to therapy such as radiotherapy.[79] A nested case-control study suggested that the risk may be with the HPV-16 serotype, with 50% and 14% of oropharyngeal and oral tongue carcinomas, respectively, containing HPV-16 DNA. In a large retrospective study, 90% of HPV-positive tumors were of the HPV-16 subtype. Two oncoproteins encoded by HPVs, E6 and E7, are known to inactivate p53 and the tumor suppressor protein for retinoblastoma, presenting potential mechanisms of action.[82,83] The EBV is a human herpesvirus that has been implicated in a number of human malignancies, including nasopharyngeal carcinoma (NPC). A consistent association between EBV and less differentiated types of NPC has been reported.[84–86] Although the extent to which EBV infection may contribute to NPC carcinogenesis has not been completely elucidated, an early role is supported by evidence of clonal EBV infection in preinvasive lesions (carcinoma in situ).[87] The expression of various viral gene products, EBV nuclear antigen (EBNA), and latent membrane proteins (LMP1, LMP2) has been demonstrated to have the capacity to induce transformation in vitro, consistent with a carcinogenic role for EBV infection.

PATHOLOGY

Squamous Cell Carcinoma

Oral Cavity

Squamous cell carcinoma accounts for 95% of all malignant tumors in the oral cavity. Other malignancies involving the oral cavity include malignant salivary gland lesions, mucosal melanoma, lymphoma, and sarcoma. Although squamous cell carcinoma can occur anywhere in the oral cavity, the most common locations include the floor of the mouth, tongue, and hard palate. In the earliest recognizable stage, squamous cell carcinoma appears as firm, pearly plaques or as irregular, roughened, or verrucous areas of mucosal thickening, which can be mistaken for leukoplakia, a premalignant lesion. Larger lesions seldom are mistaken for leukoplakia and form either exophytic masses (Fig. 72-1A) or endophytic lesions, often with associated ulceration and heaped-up edges (see Fig. 72-1B).

Histologic examination frequently reveals an association with in situ lesions, sometimes with surrounding areas of epithelial dysplasia of varying degrees (see Fig. 72-1C). Histologically, these tumors range from well-differentiated keratinizing neoplasms to poorly differentiated squamous cell carcinoma without keratinization to anaplastic and sometimes sarcomatoid growth patterns (see Fig. 72-1D). Less common patterns include verrucous carcinoma.

Larynx

Epithelial changes in the larynx include a spectrum of pathologic changes beginning with hyperplasia and progressing through dysplasia, carcinoma in situ, and invasive carcinoma.[88] As in the oral cavity, these early pathologic lesions appear as white (leukoplakia) or reddened (erythroplakia) thickenings and cannot be reliably distinguished from early invasive carcinoma. The earliest lesions (hyperplasia) have little or no malignant transformation potential, whereas mild dysplasia progresses to carcinoma in 1% to 2% of cases over a 10-year period and rises to 5% to 10% with high-grade dysplasia over a similar time span. In general, the more severe the dysplasia, the greater the risk of progression to carcinoma.

Approximately 95% of laryngeal carcinomas are the typical squamous cell carcinoma. Squamous cell carcinoma may develop on the vocal cords, but it also may develop in a supraglottic or subglottic location. Similar to oral squamous cell carcinomas, these lesions begin as in situ carcinoma and, left untreated, grow into infiltrating, ulcer-

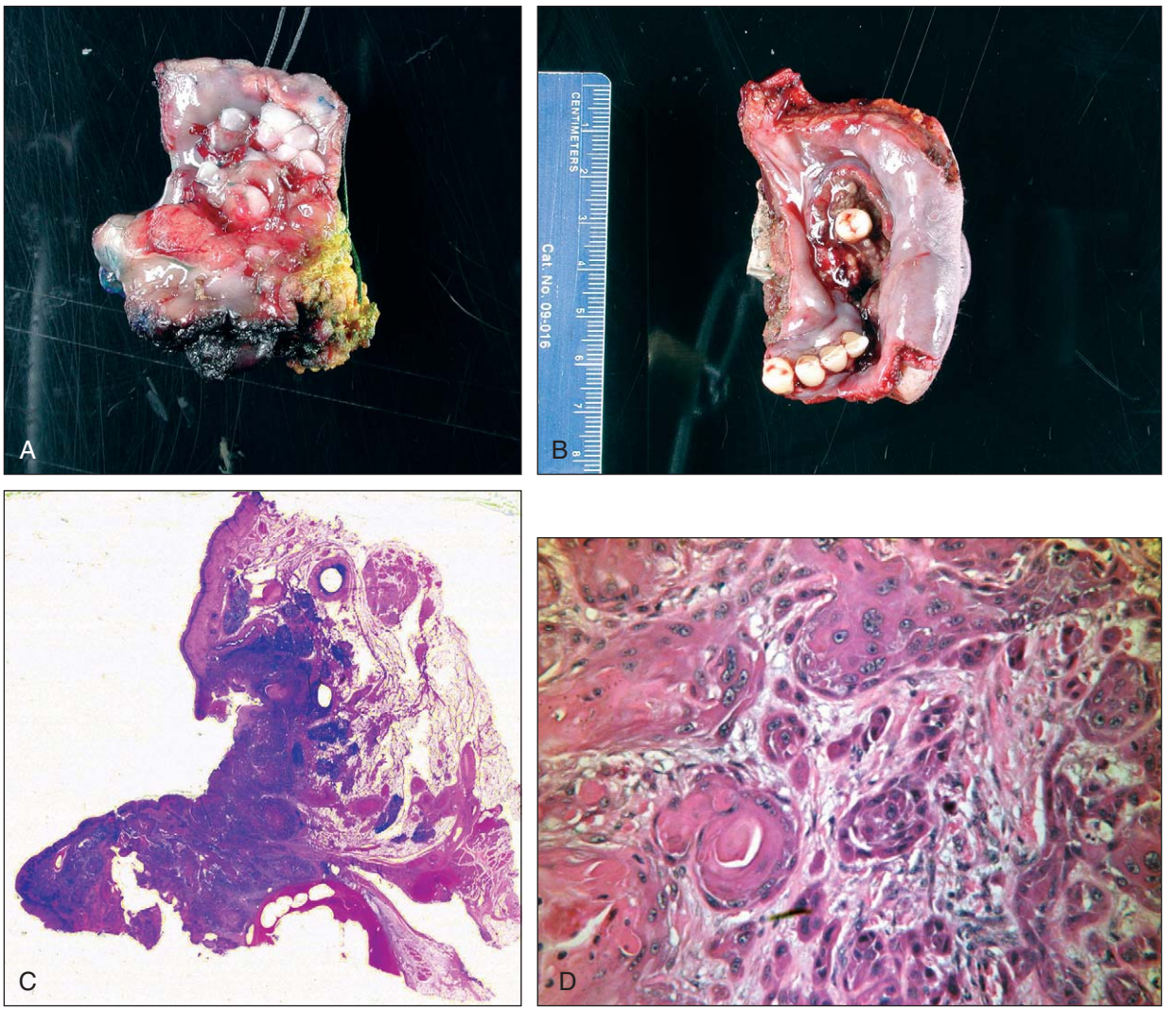


Figure 72-1 • **A,** Squamous cell carcinoma growing as an exophytic lesion in the floor of the mouth. **B,** Squamous cell carcinoma growing as an ulcerated endophytic lesion along the alveolar ridge of the mandible. **C,** Invasive squamous cell carcinoma and adjacent precursor lesion of the tongue. **D,** Squamous cell carcinoma, moderately differentiated, of the tongue.

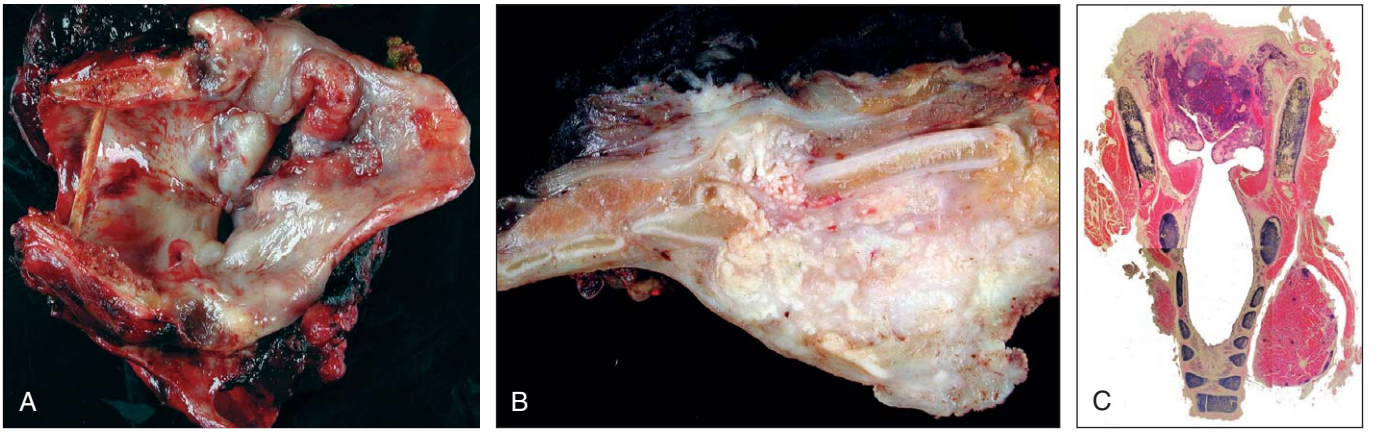


Figure 72-2 • **A,** Squamous cell carcinoma of the larynx, supraglottic opened posteriorly. **B,** Squamous cell carcinoma of the larynx invading between thyroid and cricoid cartilages. **C,** Coronal section of larynx showing a supraglottic squamous cell carcinoma.

ated, and fungating lesions (Fig. 72-2A–C). The degree of differentiation of squamous carcinoma is highly variable and similar to that in tumors of the oral cavity. Rare cases show sarcomatoid differentiation.

Nasal Sinus and Nasopharynx

Epithelial carcinomas in the nasal sinus are grouped under the entity of NPC. Within this clustered entity are three distinct histopathologically recognizable tumor patterns: (1) keratinizing squamous cell carcinoma; (2) nonkeratinizing squamous cell carcinoma; and (3) undifferentiated carcinoma, also referred to as the lymphoepithelial type of NPC. The nonkeratinizing and undifferentiated carcinoma is most closely associated with EBV infection.

Keratinizing and nonkeratinizing squamous cell carcinoma in the nasopharynx is morphologically similar to lesions found in the larynx and oral cavity. The nonkeratinizing forms also may take the appearance of transitional epithelium—hence the designation of some nasal carcinomas as transitional type. The undifferentiated form of NPC, by contrast, shows a unique morphology characterized by the growth of large tumor cells with round to oval nuclei, prominent nucleoli, fine vesicular chromatin, and indistinct cell borders (which produces a syncytial appearance). An abundant lymphoid response is seen within this tumor, sometimes obscuring the malignant epithelial cells. EBV genome frequently is found within the epithelial tumor cells (Fig. 72-3A–C).

A rare and highly aggressive variant of squamous cell carcinoma, the so-called basaloid squamous cell carcinoma, can be found in the upper aerodigestive tract and nasopharynx and less commonly in other sites within the head and neck.[89,90] This tumor is characterized by cells infiltrating in small to large nests with prominent central comedo-type necrosis. At the edges of the nests, the tumor cells form an organized palisade. In addition, variable areas of the tumor show malignant squamous cell morphology with keratinization. Cytologically, the tumor cells show marked nuclear pleomorphism with single cell necrosis and high mitotic rates (see Fig. 72-3D).

A rare and highly aggressive carcinoma found within the nasal sinus is the sinonasal undifferentiated carcinoma (SNUC) believed to originate from the schneiderian mucosa.[91] These lesions may manifest with or without neuroendocrine differentiation but without evidence of squamous or glandular differentiation. SNUCs are distinguished from undifferentiated nasopharyngeal carcinoma by the absence of a surrounding lymphoid reaction. SNUC cells are medium in size and grow in nests. Cytologically, the tumor cells show a fine chromatin pattern, hyperchromasia, and variably sized nucleoli. Mitotic rates are high, and necrosis is common.

Malignant Salivary Gland Neoplasms

Salivary gland tumors constitute a rare and interesting heterogeneous group of tumors. The vast majority of salivary gland tumors are benign and develop in the parotid gland. A subset of salivary gland tumors is malignant, however. Malignant salivary gland tumors are more common in the minor salivary glands (50% to 60%) and sublingual salivary glands (80% to 90%) in contrast to the parotid (20% to 30%) and submandibular (30% to 40%). A brief discussion of the major types of malignant salivary gland tumors follows.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinomas are the most frequent type of malignant salivary gland tumor. Although occurring most often in the parotid gland, they also can be seen with high frequency in the minor salivary glands. These tumors, as their name implies, are composed of a mixture of squamous cells (epidermoid component) and mucus-secreting cells (mucoid component). A third cell type found within these lesions is the intermediate cell.

Mucoepidermoid carcinomas vary in size and lack a well-defined capsule. Microscopically, the tumor shows a pushing or infiltrative border. They vary in appearance from white to gray and frequently contain small to microscopic mucinous cysts (Fig. 72-4A). Microscopically, the tumor is composed of cells arranged in cords, nests, and sheets with varying amounts of squamous, mucous, and intermediate cells. These tumors can vary from well differentiated to highly aggressive, poorly differentiated histopathology. Various grading schemes to account for these differences cluster tumors into low-, intermediate-, and high-grade categories based on the amount of mucinous cells, solid squamous nests, mitotic rate, necrosis, and pleomorphism.[92,93] These tumor grades also correlate with patient outcome. Low-grade tumors (see Fig. 72-4B) rarely metastasize, often are locally infiltrative, and recur in 10% to 15% of cases, and therefore have an excellent 5-year survival rate of greater than 90%. By contrast, high-grade tumors (see Fig. 72-4C) are highly infiltrative, recur in 30% to 40% of cases, and have metastasized in 30% to 40% of cases at presentation, producing 5-year survival rate of only 50%.[94–96] Grading appears to have less prognostic importance when the submandibular glands are involved. Involvement of this site appears to be associated with an increased risk of distant relapse regardless of grade.[96,97]

Adenocarcinoma, Not Otherwise Specified

These tumors are now restricted to lesions that do not show histopathologic patterns of the other salivary gland tumor types. These

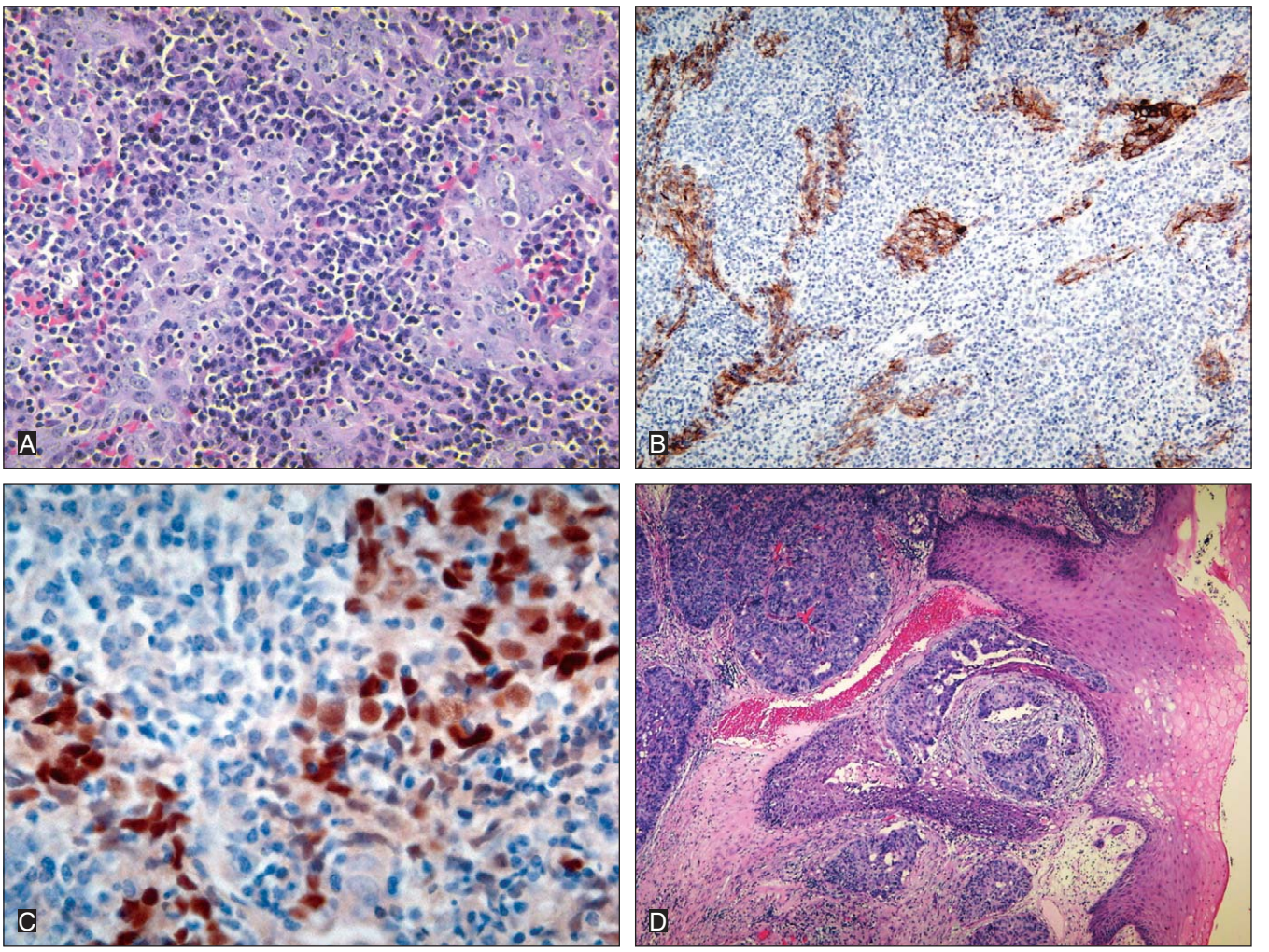


Figure 72-3 • **A,** Nasopharyngeal carcinoma, undifferentiated type, lymphoepithelial type (hematoxylin-eosin stain). **B,** Nasopharyngeal carcinoma, undifferentiated type, lymphoepithelial type (cytokeratin stain). **C,** Nasopharyngeal carcinoma, undifferentiated type, lymphoepithelial type (Epstein-Barr virus in situ hybridization). **D,** Basaloid squamous cell carcinoma of nasopharynx showing in situ squamous cell carcinoma.

tumors can occur in the parotid gland as well as minor salivary glands and typically present in the sixth to eighth decade of life. At presentation, varying histologic patterns including tubular, papillary (with varying degrees of differentiation from well to poorly differentiated), and adenocarcinoma may be observed. Important in the workup for these patients is to exclude an adenocarcinoma from another body site because salivary gland adenocarcinomas can mimic adenocarcinomas from other organ sites.

Adenoid Cystic Carcinoma

Adenoid cystic carcinomas account for some 20% of malignant salivary gland tumors. They are frequently located in the minor salivary glands (40% to 50% of cases) and less often in the parotid gland (20% to 30%). The most common histologic pattern is the classic cribriform type or "Swiss cheese" pattern, characterized by neoplastic cells forming oval or circular spaces or nests. Within these nests is dark, eosinophilic, hyaline-like basement membrane material. The amount of the hyaline material can distort the cell nests and produce a small acinar- or cord-like appearance to the tumor nests (see Fig. 72-4D). Perineural invasion is almost invariably observed in these tumors (see Fig. 72-4E) and a diagnosis of adenoid cystic carcinoma without finding perineural invasion should be carefully reconsidered. Adenoid cystic carcinomas are graded into low-, intermediate- and high-grade tumors based on the amount of solid growth, mitoses, necrosis, and pleomorphism[98]; as with mucoepidermoid carcinoma, the degree of differentiation is correlated with long-term survival.

Acinic Cell Carcinoma

More than 90% of acinic cell carcinomas arise in the parotid gland. These tumors occur between the ages of 50 to 70, with men affected more than women (2:1 male-to-femael ratio). The gross appearance of these tumors varies, but they often are white-tan in color and present as a well-circumscribed but unencapsulated mass. Microscopically, the most common histologic pattern consists of solid sheets of cells with low-grade cytology and granular basophilic cytoplasm similar to the serous acinar cells of a normal salivary gland. Less common variants include a cystic and microcystic pattern, in which the tumor cells are arranged at the edges of the cyst, and cells with granular basophilic cytoplasm are arranged among cells, with a tombstone appearance and capitation-type secretion, as well as cells with a bubbly vacuolated appearance. Rare cases of acinic cell carcinoma have been reported to undergo dedifferentiation into a high-grade aggressive malignancy[99]; most acinic cell carcinomas, however, behave in a more indolent fashion.[100,101]

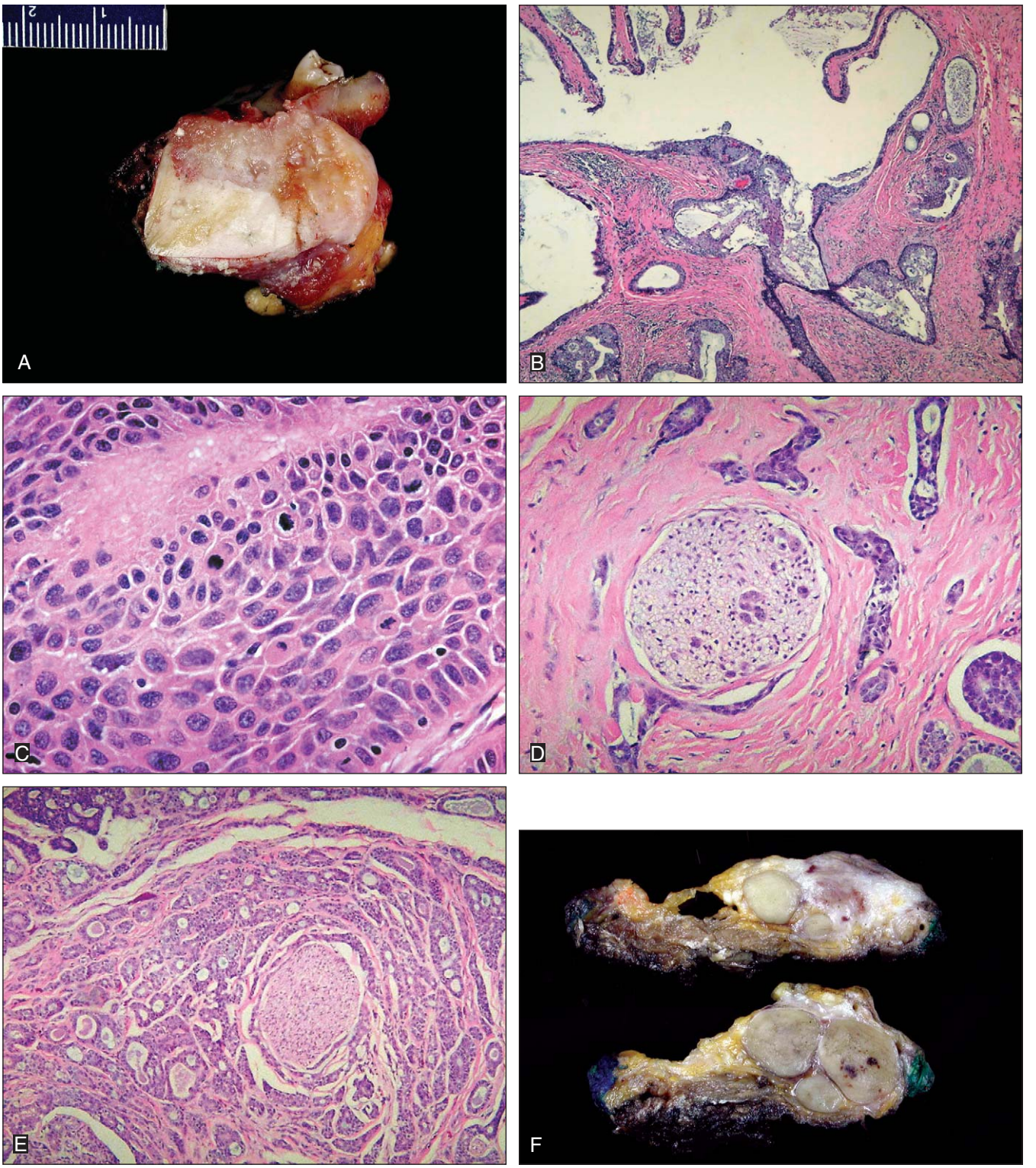


Figure 72-4 • **A,** Mucoepidermoid carcinoma of the minor salivary gland eroding mandibular bone. **B,** Mucoepidermoid carcinoma, low grade of the palate showing microcystic architecture. **C,** Mucoepidermoid carcinoma, high grade showing solid growth and high mitotic rate (other areas of the tumor showed focal mucinous pattern). **D,** Minor salivary gland with adenoid cystic carcinoma growing in a typical cribriform pattern, with many lumina showing eosinophilic basement membrane material. **E,** Parotid gland with adenoid cystic carcinoma growing in cribriform plates and cords with perineural invasion. **F,** Parotid gland with carcinoma ex pleomorphic adenoma.

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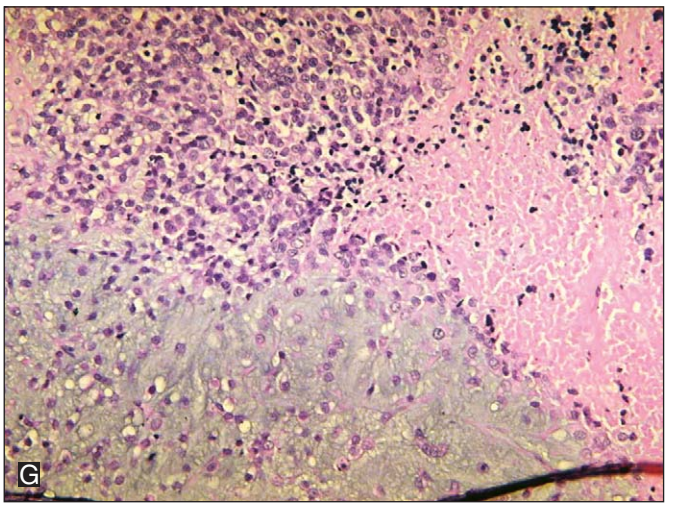


Figure 72-4, cont'd • G, Parotid gland with carcinoma ex pleomorphic adenoma showing adenocarcinoma not otherwise specified, with comedo-type necrosis.

Malignant Mixed Tumor (Carcinoma ex Pleomorphic Adenoma)

Malignant mixed tumors of the salivary gland are predominantly tumors that started as pleomorphic adenomas in which the epithelial tumor component subsequently underwent malignant transformation. This transformation may be confined to the adenoma, resulting in the noninvasive carcinoma ex pleomorphic adenoma.[102] A majority of carcinomas that arise out of pleomorphic adenomas, however, are infiltrative and aggressive lesions (see Fig. 72-4F and G). The transformation to a malignant phenotype is heralded by a change in the behavior of the patient's underlying pleomorphic adenoma characterized by sudden enlargement of an otherwise stable adenoma, or by the onset of pain in a previously asymptomatic adenoma. Morphologically, the malignant transformation can take on any malignant epithelial salivary tumor phenotype, the most common being adenocarcinoma not otherwise specified.[103] Occasionally, multiple recognizable histologic patterns may be present. These tumors are highly aggressive, with 5-year survival rates as low as 25%. Another form of the malignant mixed tumor is the true carcinosarcoma, which again often arises from a pleomorphic adenoma background. These tumors have both malignant epithelial and malignant stromal elements.

Polymorphous Low-Grade Carcinoma

Polymorphous low-grade adenocarcinoma (PLGA) is a rare low-grade carcinoma of minor salivary glands. These tumors grow as infiltrative masses and are composed of uniformly low-grade tumor cells arranged in a variety of histologic patterns, including tubular, solid, papillary, microcystic, cribriform (with true lumina), pseudoadenoid cystic (without true lumina), fascicular, single file, and cordlike.[104] Perineural invasion is common. In contrast with adenoid cystic carcinoma, PLGA stains positively for EMA, which may be relied on to distinguish between these two pathologic lesions. Rare cases of PLGA have metastasized, and these cases have been associated with more than focal areas of papillary growth. Rare cases have dedifferentiated into high-grade aggressive carcinomas.[105]

Salivary Duct Carcinoma

Salivary duct carcinomas are rare tumors with a male predilection. These are rapidly growing tumors that can produce pain and nerve palsies. Morphologically, these tumors resemble comedo-type duct carcinoma of the breast and also may grow in a cribriform or papillary pattern. Cytologically, these tumors tend to be high grade, with nuclear pleomorphism, single-cell necrosis, and high mitotic rate. Clinically, these tumors behave in an aggressive fashion, with poor long-term survival.[106,107]

Lymphoid Tumors of Head and Neck

Extranodal Lymphoma

Extranodal lymphomas of the head and neck can take on the same morphologic spectrum as that seen anywhere in the body. Large cell lymphoma predominates, but any morphologic pattern can be seen. Although many of these lymphomas arise in association with lymphoid tissue within Waldeyer's ring, they are not limited to this location.

Angiocentric Lymphoma

Formerly called by a variety of terms (polymorphic reticulosis, lethal midline granulomatosis), this lymphoid malignancy manifests as an aggressive destructive lesion characterized by ulceration and tissue necrosis. The tumor cells are visible, growing in an angiocentric location. Immunophenotypically, these tumors often are either NK or T cells, with rare B cell phenotype reported.[108–110] It is important to distinguish this entity from nonmalignant sinonasal processes, such as Wegener's granulomatosis, that also can produce an ulcerating and necrotizing lesion.

Plasmacytoma

Extramedullary plasmacytomas occur in the area of Waldeyer's ring of lymphoid tissue. These tumors represent clonal plasma cell tumors. Some 30% of patients with plasmacytomas will eventually develop multiple myeloma if followed for 20 years. Cytologically, the plasma cells can vary from well-differentiated plasma cells to very atypical-appearing plasmablasts. Occasionally, plasmacytomas with increased plasmablasts are misdiagnosed as poorly differentiated carcinoma, unless the pathologist considers plasmacytoma in the differential diagnosis and orders the appropriate immunohistochemical studies.

Olfactory Neuroblastoma

Olfactory neuroblastomas or esthesioneuroblastomas are rare tumors that arise from the olfactory neuroepithelium. This epithelium can be found along the roof of the nasal cavity to the midportion of the nasal septum and onto the superior turbinate. These tumors appear to be morphologically similar to neuroblastomas that arise in the adrenal gland. They are characterized by proliferation of small round blue cells arranged in nests and surrounded by a vascular network in a loose connective tissue stroma. Rosette formations can be seen as well as neurofibrillary material in the center of the rosette and within the connective tissue matrix. These tumors stain for neuroendocrine markers including S100, NSE, chromogranin, and Leu-7, which aids in distinguishing them from poorly differentiated carcinoma.[111,112]

Melanoma

In addition to cutaneous melanomas that can occur anywhere on the head and neck, melanomas may also involve the mucosal surface of the oral cavity or nasal sinus. These tumors often manifest in the fifth or sixth decade of life. Mucosal melanomas often appear histologically similar to their cutaneous counterparts and may display a similar range of architectural and cytologic variability to that exhibited by cutaneous melanomas. One interesting exception is that some mucosal melanomas display a small cell phenotype that on biopsy can easily be mistaken for a nonkeratinizing squamous cell carcinoma (Fig. 72-5A and B).

Sarcomas

Angiosarcoma

Angiosarcomas may occur in the head and neck and most commonly manifest on the face and scalp, usually in the sixth or seventh decade

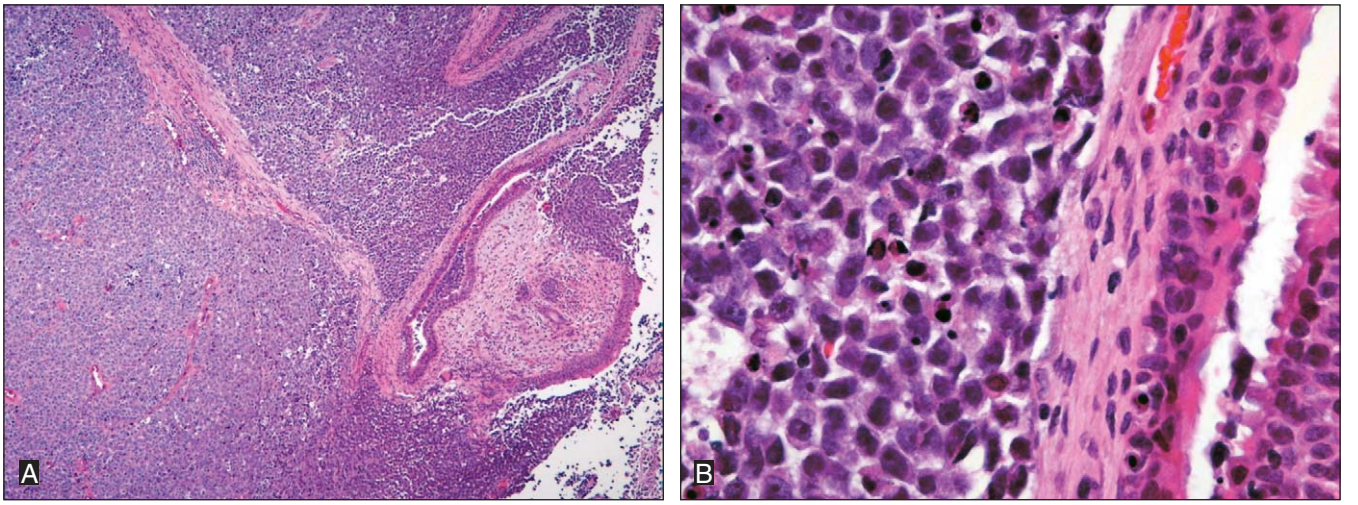


Figure 72-5 • **A,** Sinus with primary mucosal melanoma showing infiltrative destructive growth by large epithelioid cells beneath respiratory mucosa. **B,** Sinus with primary mucosal melanoma showing infiltrative destructive growth by large epithelioid cells beneath respiratory mucosa. Cells exhibit a blastic appearance, with prominent single-cell necrosis and high mitotic rate.

of life. Angiosarcomas of the oral or nasal cavity are exceedingly rare. Morphologically, these tumors show anastomosing vascular channels, with varying degrees of nuclear atypia in the malignant endothelial cells. Those with better differentiation are associated with a better prognosis.

Chondrosarcoma

Chondrosarcomas may arise in any bone within the head and neck as well as within the larynx. They are typically seen in the sixth or later decade of life. As with chondrosarcomas occurring in other areas, malignancy is defined by infiltrative, permeative growth as nuclear crowing and atypia within cartilage lacunae.

Osteosarcoma

Osteosarcomas may occur in any bone of the head and neck. This lesion often is seen in younger patients, with a peak in the third decade of life. In addition, osteosarcomas have been seen after radiation therapy or in association with Paget's disease.[113,114] Morphologically, these tumors are characterized by infiltrative and destructive growth of surrounding bone and soft tissue.

Chordoma

Chordomas are low-grade tumors derived from notochord remnants. The two most common locations for the tumors are at the base of the skull (spheno-occiput) and sacrum. In the head and neck area, these tumors may involve the clivus, sphenoid, upper nasopharynx, occipital bone, maxilla, ethmoid, pterygoids, or cervical vertebrae.[115] These tumors grow as lobulated, infiltrative lesions that destroy adjacent normal structure. Microscopically, a myxoid matrix predominates with epithelioid cells growing singly or in small nests. These epithelioid cells are granular or vacuolated (physalipherous cells) and show staining for both keratin and S100 on immunohistochemistry studies, helping to differentiate them from low-grade chondrosarcomas, which are keratin negative.

TUMOR BIOLOGY

In the simplest terms, cancer formation can be regarded as the escape of cells from the normal regulatory mechanisms of the cell cycle. Consequently, the cells proliferate without regard to their surroundings. Their progeny often become less differentiated, and they become able to invade surrounding tissues and spread to distant sites.

The genetic alterations associated with these changes are myriad. With regard to head and neck squamous cell carcinoma, much of the seminal work has elucidated the potential role of the tumor suppressor gene in the pathogenesis of cancer. These genes are expressed at appropriate levels in normal tissue and have a negative effect on cellular growth. If one or more of these genes is inactivated through mutation, chromosomal deletion, or DNA methylation, however, the loss of negative regulatory control may lead to unregulated growth and subsequently to cancer. The tumor suppressor genes encoding p53, p16, and $p19^{ARF}$ are the major tumor suppressor genes involved in HNSCC pathogenesis. The p53 gene lies on the short arm of chromosome 17 (17p), and p53 is a negative regulator of the cell cycle by means of the cyclin/cyclin-dependent kinase complex. The p53 gene frequently is mutated in HNSCC, with 40% to 70% of tumors harboring mutations.[116,117] The proteins p16 and $p19^{ARF}$ also are cell cycle inhibitors, and these genes also frequently are inactivated in HNSCC.[118] The mechanism of inactivation, however, includes not only gene mutation but also chromosomal deletion and promoter methylation.[119] Approximately 70% to 80% of cancers have allelic loss of the chromosomal region 9p, where p16 resides.[120,121] The loss of these cell cycle inhibitors is thought to contribute to progression from normal mucosa to preneoplastic lesions to invasive cancer.[122]

Certain genes are overexpressed in HNSCC as well. These oncogenes include those encoding cyclin D1, C-myc, and epidermal growth factor (EGF), and their increased expression also can contribute to the pathogenesis of HNSCC.[123–125] More recently, attention has turned to cell adhesion receptors such as integrins and E-cadherin with regard to tumor invasion and recurrence.[126,127] E-cadherin has been shown to be highly underexpressed in oral tongue carcinomas, and weak expression of the molecule was significantly correlated with a higher recurrence rate and worse 5-year survival.[127] Integrin expression is closely tied to the invasiveness of HNSCC cell lines.[126]

Theoretically, many of these genetic alterations should result in the expression of altered proteins that the host immune system would recognize as foreign. The cells would then be identified and targeted for immune-mediated destruction. It is clear, however, that tumor cells are able to escape from the host immune system through a variety of mechanisms.[128] A significant proportion of tumor cells have decreased expression of human leukocyte antigen (HLA) class I, a molecule necessary for the presentation of foreign peptides to the immune system.[129] Furthermore, T lymphocytes that infiltrate the

tumor are not as competent at killing tumor cells, presumably due to factors within the tumor microenvironment.[128]

New technologies will soon enable researchers to analyze further the genetic and immunological changes that occur in HNSCC. Complementary DNA microarrays allow for large-scale analysis of gene expression. Researchers have already identified hundreds of genes that are either overexpressed or underexpressed in HNSCC.[130,131] Future studies will elucidate the relationship of these genes to the pathogenesis of cancer, and novel tumor markers will be identified against which new chemotherapeutic and immunotherapeutic modalities can be targeted.

CLINICAL PRESENTATION AND PATIENT EVALUATION

Patients with head and neck cancers present with certain symptoms according to the location of the tumor. Some signs and symptoms and patient characteristics are common to many of these patients regardless of the site of tumor origin, however. Patients with head and neck cancer are mostly male and in their sixth decade of life or older. Most have a history of tobacco and alcohol use. They often present with cachexia due to dysphagia, tumor burden, or malnutrition. Rapid weight loss is sometimes reported. Hemoptysis also is frequently found. Pain, either primary or referred to the ipsilateral ear, also is often encountered. Many tumors manifest with cervical metastasis as the first sign of disease, and a thorough examination must be performed to identify the primary site.

More specifically, signs and symptoms associated with oral cavity tumors include bleeding, dysphagia, dysarthria, and halitosis. The patient may complain of ill-fitting dentures that previously fit properly. Oropharyngeal tumors cause similar signs and symptoms. In addition, pain often is experienced at the site within the oropharynx or is referred to the ear. A neck mass is often the presenting sign of an oropharyngeal tumor. Supraglottic tumors can manifest with dyspnea, dysphagia, and voice change. Glottic and subglottic tumors are likely to cause hoarseness and dyspnea. Dysphagia and ear pain often is experienced by patients with hypopharyngeal cancer.

Initial Head and Neck Examination

An initial examination of the head and neck should be performed with the patient sitting upright in a chair. A standard and complete head and neck examination should then be conducted. All 12 cranial nerves are assessed. Otoscopy and anterior rhinoscopy also are indicated. Examination of the oral cavity is preferably done using a head light to allow bimanual examination of the lips, buccal mucosa, gingiva, floor of the mouth, and oral tongue. Palpation of the tongue and the base of the tongue often is forgotten but is crucial for a thorough evaluation. The tongue base can be further examined using a mirror and a flexible fiberoptic laryngoscope. The larynx also is visualized using these instruments. While viewing the larynx fiberoptically, the physician should ask the patient to perform several maneuvers: vocalization to allow assessment of vocal cord motion; tongue protrusion to aid in viewing the vallecula; and filling the cheeks with air to help visualize the pyriform sinuses. After the subglottis is evaluated, the laryngoscope can be removed and the examination completed with palpation of the neck for masses. The size, mobility, and consistency of any mass should be carefully noted.

Staging Investigations

Radiography is a necessary component of the evaluation. It is now standard practice to order a CT scan of the head and neck for any patient with suspected cancer. Not only does this examination help to evaluate the size and location of the primary, but also any possible metastasis. An MRI scan can provide useful additional information in certain cases, such as in previously treated patients or in those lesions in which skull base involvement must be ruled out. Routine preoperative laboratory values should be obtained, as well as appropriate medical consultations as indicated.

If accessible in the clinic, biopsy of any suspicious mucosal lesion should be undertaken after local administration of anesthetic. Generally, oral cavity lesions and selected oropharyngeal lesions are easily biopsied in the clinic. For most lesions of the tongue base, larynx, and hypopharynx, direct laryngoscopy with biopsy under anesthesia is required. During this procedure, flexible esophagoscopy should be undertaken to rule out tumor spread into the cervical esophagus. In addition, a tracheostomy or gastrostomy tube should be placed at this time if indicated. If no primary tumor is identified, but a firm node 1 cm or greater is present, the node should be sampled by means of fine-needle aspiration (FNA). An open biopsy of a neck node in an adult suspected of head and neck cancer should be undertaken only after FNA diagnosis is inconclusive and a primary site cannot be identified.

Based on this extensive clinical and radiologic evaluation, the cancer is assigned a stage. Generally, T1, T2, and T3 represent increasing tumor size, whereas T4 is defined by invasion of a surrounding structure (skin, nerve, vessel, cartilage). The node, or N, stage is identical for all head and neck cancer sites and is defined in Table 72-1. The absence or presence of distant metastases is defined as M0 or M1. The T, N, and M stages are combined into overall groupings that are presented in Table 72-1. Because the natural history of head and neck cancer varies somewhat according to specific anatomic location of the primary disease and since stages III and IV include a large number of different T and N stages, it is customary to refer to specific head and neck cancers by their individual T, N, and M stage and the primary site.

Follow-up Program

After completion of initial treatment, patients are seen every 4 to 6 weeks for 2 years in the office; during this period a complete set of

Table 72-1 Overall Group Staging of Head and Neck Cancer: Tumor-Node-Metastasis (TNM) Classification

Stage	Grouping		
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

From American Joint Committee on Cancer: AJCC Cancer Staging Manual, 6th ed. New York, Springer, 2002, p 65.

laboratory data and chest radiographs are obtained every 6 months to look for metastatic disease or second malignancies. It is important to monitor levels of thyroid-stimulating hormone, because many patients who have received therapeutic irradiation to the neck will become hypothyroid and will require thyroid hormone supplementation. A baseline post-treatment CT scan (or MRI after skull base procedures) is obtained approximately 2 months after the end of postoperative radiation therapy as a reference point for comparison in the event that disease recurs.

During the third year, the patient is seen every 3 months, and every 4 months during the fourth year. After 5 years, the patient should be examined once per year.

PROGNOSIS

Prognostic and treatment-predictive factors play a central role in the treatment decision-making process, because the current therapeutic approach uses a risk stratification paradigm. This approach recognizes that currently accepted treatment modalities are associated with significant risk and a spectrum of toxicities. Identification of these factors facilitates this risk assessment and helps to guide decisions on whether to initiate therapy and also may influence what type of therapy to administer. An ideal prognostic factor would provide information about the biologic behavior of a tumor, permitting the prediction of the outcome and response to therapy. The use of such factors has become confusing, however, owing to the spectrum of factors reported, often with conflicting results. This dilemma has led to efforts to systematically classify head and neck prognostic factors based on the level of significance and reliability, including a recent meta-analysis.[132]

This heterogeneity results from several sources, including statistically underpowered studies, absence of statistical modeling for independent prognostic effects, variability in the nature of the therapy applied, the composition of prognostic factors as represented in the study group, and the inherent biologic heterogeneity of cancer. The heterogeneity is compounded further by the heterogeneity associated with the tests and instruments that often are used to measure aspects of the tumor biology. Although it may be said that clinical prognostication often is imprecise, several clinical factors have an established role. In the head and neck, tumor site is a strong prognostic factor for survival, regardless of the treatment modality, and reflects the precision with which it can be identified by the clinician, although exceptions may exist, particularly for large tumors that overlap anatomic subsites.[133–135] Within each subsite, the current American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM > staging criteria have been demonstrated to have prognostic significance and continue to evolve through efforts to stratify further the staging classification based on prognosis.[136] Most problematic are patients who constitute the heterogeneous locally advanced AJCC stage IV group.

The sixth edition of the TNM classification introduces a distinction of the heterogeneous T4 disease group based on the probability of disease control, with T4a disease representing a reasonable probability and T4b disease representing such extensive disease that an adverse outcome is certain. In essence, the watershed between T4a and T4b reflects for most subsites the transition to unresectable disease that has been a recognized prognostic factor. Criteria for T4 subclassification by each anatomic subsite have been developed.[137] Consideration of this subclassification scheme in the context of N and M staging facilitates recognition of three distinct prognostic groups: advanced lower-risk stage IVA (potentially curable); advanced high-risk stage IVB (of dubious curability); and stage IVC with distant metastatic disease (undoubtedly incurable).[137] The critical distinction is the definition of IVB as N3 disease or T4b with any N category (excluding the nasopharynx subsite), for which aggressive local-regional therapy may be undertaken but with a potentially low expectation of success—a philosophical view that has been termed "aggressive palliation." In this subgroup, other patient-based prognostic factors, such as performance status, comorbid conditions, and the patient's ability to tolerate and comply with local-regional aggressive therapy, may have significant effect on the anticipated outcome and hence treatment decisions. Although the committee acknowledges that comparative outcome data do not exist for these new stage IV groupings, these groupings are likely to be surrogate groupings for tumor volume and resectability that have established prognostic effects and form the basis for the current therapeutic paradigm.

Within each subsite, various tumor features, noteworthy for their prognostic impact and not necessarily reflected in the new TNM staging criteria, warrant additional comments. In the oral cavity, tumor thickness or depth of invasion has been well recognized to influence the risk of nodal metastases[138,139] and to reflect biologic aggressive disease with an adverse survival.[138,139] Po and colleagues recently demonstrated that tumor thickness in oral tongue carcinomas was the only significant factor that had significant predictive value for subclinical nodal metastasis, local recurrence, and survival in multivariate analysis. With the use of 3-mm and 9-mm division, tumor of up to 3 in mm thickness is associated with an 8% risk of subclinical nodal metastasis, zero local recurrence, and 100% 5-year actuarial disease-free survival; tumor thickness of more than 3 mm and up to 9 mm carried a risk of 44% subclinical nodal metastasis, 7% local recurrence, and 76% 5-year actuarial disease-free survival; tumor of more than 9 mm carried a 53% risk of subclinical nodal metastasis, 24% local recurrence, and 66% 5-year actuarial disease-free survival.[139] With disease of the nasopharynx, the staging classification reflects the prognostic importance of soft tissue extension beyond the nasopharynx, particularly the presence and the degree of extension into the parapharyngeal space.[140] In this regard, MRI is superior to CT imaging for such prognostication. For well-differentiated thyroid carcinomas, young age (younger than 45 years) is an important favorable prognostic factor such that patients with other favorable prognostic factors including small tumors (1 to 1.5 cm) that are well encapsulated and confined to the thyroid, may be monitored by observation, with no adjuvant therapy recommended.[141] Anaplastic thyroid carcinomas carry an adverse prognosis irrespective of the local disease extension at the time of presentation.

For patients with HNSCC treated with radiotherapy, CT-based tumor volume assessment[142–146] and the presence of anemia[144,147–151] appear to be prognostic for local-regional control and survival. Of interest, in a series of 258 patients with T1 to T4 glottic carcinoma treated with surgery only, anemia and positive surgical margins were independently associated with an adverse 5-year local-regional control rate.[151] Protracted overall treatment duration for a course of radiotherapy is well established as an adverse prognostic factor for local-regional control.[152–156] Limited data suggest that this adverse prognostic factor also may be important in patients receiving concurrent chemoradiotherapy, when the risk of toxicity and treatment interruptions is increased.[157] For early-stage glottic larynx carcinomas treated with radiotherapy, a dose per fraction less than 2 Gy appears to be associated with poor local control rates in various univariate analyses, but this has not been conclusively demonstrated to be independent of other time-dose parameters.[156,158,159] Nevertheless, current consensus recommendations are for dose per fraction of 2 to 2.25 Gy.[160] Tumor response to radiotherapy has been demonstrated in a large prospective series of 228 patients with HNSCC treated uniformly with conventionally fractionated radiotherapy to be associated with local control. Multivariate analysis showed that the probability of local relapse was significantly and independently increased for minor regression at 5 weeks (less than 75%) (relative risk, 2.3), for nonlaryngeal tumors (relative risk, 2.4) and for T3-T4 disease (relative risk, 2.4).[134]

In patients requiring postoperative radiotherapy who demonstrate high-risk adverse prognostic features, the time interval between

surgery and radiotherapy and the overall treatment time from the time of surgery to completion of the radiotherapy appear to be important.[161] Investigators from the M.D. Anderson Cancer Center have previously demonstrated that the most adverse prognostic postoperative risk factor is the presence of extracapsular extension.[162] These investigators have proposed and prospectively validated a risk stratification criterion that identifies patients as high-risk if extracapsular extension is present or two or more pathologic risk factors are present. These include oral cavity primary, mucosal margins close or positive, nerve invasion, more than one positive lymph node, more than one positive nodal group, the largest node greater than 3 cm, and treatment delay longer than 6 weeks.[161,162] Cooper and colleagues noted similar risk factors in a review of the Radiation Therapy Oncology Group (RTOG) database.[163] In the high-risk group of patients, progressively protracted treatment time was associated with worsening local-regional control rates ($P = 0.005$) and overall survival ($P = 0.027$), with the most favorable outcome noted when the overall treatment time was less than 11 weeks.[161] Other retrospective studies have reported similar observations.[164,165]

The heterogeneity and imprecision of clinical prognostic factors have encouraged recent efforts to evaluate the potential prognostic significance of various molecular factors[166] and various quantitative measures describing functional tumor imaging such as magnetic resonance spectroscopy.[167,168] Grandis and colleagues reported a strong independent prognostic value for the epidermal growth factor receptor (EGFR) and its ligand, transforming growth factor-α (TGF-α), in a mature but heterogeneous group of 91 patients with a mixture of stages and sites treated with surgery and adjuvant therapy. Of the 91 patients, 56 (62%) received postoperative external beam radiation therapy (EBRT) and 16 (18%) received adjuvant chemotherapy. Protein expression was quantitated by computer immunohistochemistry image analysis on paraffin-embedded specimens. Increasing levels of overexpression of either EGFR or TGF-α were associated with an increasing adverse disease-free and cause-specific survival. Other investigators using various quantitative assays of this surface receptor also have demonstrated an independent prognostic effect of EGFR overexpression.[169–172] These series are noteworthy for the strong prognostic significance observed in multivariate analysis, possibly owing to the reduced test heterogeneity with such quantitative assays and the biologic significance of EGFR overexpression.

PRIMARY TREATMENT AND TREATMENT COMPLICATIONS

General Principles

Effective management of head and neck cancers requires comprehensive consideration of several often-competing treatment goals. This routinely requires the efficient integration of various treatment modalities and supportive services for appropriate patient care. Accordingly, representation from disciplines including head and neck surgery, reconstructive surgery, radiation oncology, medical oncology, pathology, neuroradiology, dentistry, oral and maxillofacial surgery, nutrition, nursing, rehabilitation medicine, social services, and psycho-oncology is routinely required.

Before the start of any therapy, it is important not only to evaluate issues of histologic diagnosis and the anatomic extent of disease but also to review issues that may have an impact on treatment compliance. This assessment should include a review of the level of social support a patient has, with appropriate referrals to support services as indicated. Similarly, effective attention to nutritional support and pain management can significantly improve patient compliance to any subsequent therapeutic plan. Depending on the treatment modalities that are required, pretreatment evaluation by oral and maxillofacial services may be indicated. If radiotherapy is indicated, prophylactic enteral tube placement for nutritional support may be appropriate, especially if concurrent chemoradiotherapy will be given. Whenever possible, review of a patient's case within the context of a multidisciplinary tumor conference is strongly advocated.

On establishment of a histologic diagnosis of cancer in the head and neck, subsequent treatment decisions follow from a hierarchy of considerations. Because treatment for head and neck cancer is associated with significant risk and spectrum of toxicities, it becomes important to identify patients with a poor prognosis, for whom treatment may be appropriately tailored. Determining a poor prognosis can be complex and imprecise, influenced not only by the anticipated clinical outcome but also by various patient factors including treatment tolerance and toxicity. In large part, the imprecision of prognostication results from the clinical heterogeneity of established prognostic and treatment predictive factors, as already discussed. When a poor prognosis is uncertain, it may be appropriate to adopt a curative intent, but the potentially low expectations of treatment success should be discussed with the patient.

In tailoring treatment to the prognosis, it is the hope that patients with a poor prognosis will only be subjected to treatment toxicities that are appropriate for the goals of any palliative treatment. Hence, palliative (or curative) intent should be clearly distinguished from palliative (or curative) treatment goals. Unfortunately, palliative treatment goals for advanced head and neck carcinomas (HNSCCs) often require achieving some degree of local-regional disease control but with constraints to minimize toxicity. Although various palliative radiotherapy schedules have been reported, in general, it may be more appropriate to consider the role of systemic chemotherapy to minimize the adverse quality of life that results from radiotherapy-induced xerostomia and taste alteration. In appropriate circumstances, surgical intervention including the use of high-dose rate brachytherapy implants may achieve treatment goals with the most favorable therapeutic ratio. When and how best to achieve such palliative treatment goals become issues of judgment that follow from engaging a thoughtful dialogue between various members of the multidisciplinary team and the patient and family members.

In treating patients thought to be appropriate candidates for potentially curative therapy, a higher threshold for unacceptable toxicity on the part of the treating physician and patient is implicitly accepted. As a result, an evidence-based approach in deciding between various treatment options is preferred to justify the increased tolerance of toxicity. This has favored a systematic categorization of the quality of clinical reports reflecting the study methodology employed and the confidence that the results reported are free of biases and random variability. In general, randomized trials with sufficient statistical power provide the greatest unbiased level of evidence and confidence that the results are reproducible. Not uncommonly, treatment effects often are smaller than anticipated, leading to variable results among similar randomized trials, which limits consensus treatment recommendations. For head and neck carcinomas, competing comorbid conditions and the risk of second malignancies contribute to underpowered trials in demonstrating improvements in patient survival. As a result, prospective and retrospective comparative analyses of different treatment options often are relied on to provide significant treatment guidance. These studies are, however, subject to potential biases from patient selection and the generalizability of the reported results may be limited by the nature of the patients selected. Attempts often are made to match groups by stage to ensure their comparability, leaving only the treatment to vary. This strategy may be limited, however, by the effects of stage migration and should be carefully reviewed for this potential influence. For HNSCC, this is particularly important in light of the significance of anatomic tumor extent on treatment prognosis[137] and the recent evolution of various sensitive imaging modalities. Finally, the usefulness of data from institutional series, case series, and reports also may be limited by the size of the sample study population and the absence of comparative analysis of different therapeutic strategies. Such data often

provide insight into the management of rare histologic diagnoses, however. When insufficient evidence-based literature exists, consensus treatment principles have evolved to further guide treatment recommendations. Alternative systematic quantitative tools such as decision tree analysis techniques and cost-effectiveness analysis have not been well studied and remain limited in their impact on the management of head and neck cancers.

For HNSCC, therapeutic principles traditionally have considered competing treatment goals of local-regional control and the level of risk and spectrum of toxicity in defining the concept of a therapeutic ratio. Both quantitative and qualitative issues in toxicity must be considered, because a severe but low-probability toxicity may be important in defining what is an acceptable therapeutic ratio for the patient. This concept of a therapeutic ratio is important, because a dose-response relationship exists for both disease control and toxicity in several treatment modalities, including chemotherapy and radiotherapy, and may even be extended conceptually to surgery. Although treatment toxicity is an important consideration in evaluating treatment options, the emphasis remains on local-regional control as a principal measure of treatment success. This focus underscores the natural history of the disease and the cosmetic and functional impact of cancer in this body site. Accordingly, definitive therapeutic decisions often involve evaluation of surgery- or radiotherapy-based strategies. Although rigorous randomized comparisons of these two treatment approaches are extremely limited, several generalizations may be noted.

When local-regional control rates appear comparable between competing treatment modalities, such as surgery and radiotherapy, the use of a single modality associated with the most favorable therapeutic ratio is preferred. This principle is most applicable to the use of surgery or radiotherapy for early-stage disease (typically T1-2N0-1). For early-stage disease, local-regional control rates reported from surgical and from radiotherapy institutional series appear to be comparable, with the possible notable exception of the oral tongue subsite, for which anecdotal experience suggests that local control rates with EBRT are inferior. (Rather, the incorporation of a brachytherapy implant appears to provide comparable results to surgery.) Surgery is often preferred for disease involving sites that are readily accessible, such as the oral cavity site, to minimize the risk of complications. By contrast, early-stage NPC typically is treated with radiotherapy owing to the risks associated with surgery in this location.

Radiotherapy has traditionally been considered to be more attractive for early-stage tumors involving sites at which surgical resection may compromise organ function, such as involvement of the oropharynx, larynx, and hypopharynx. Again, this consideration is appropriate when local control rates appear comparable. Evolving experience and sophistication with various organ-preserving surgical techniques, however, offer the potential for good function preservation with no apparent compromise in oncologic results. Examples include various innovative larynx preservation techniques, including the supracricoid laryngectomy.[173,174] These techniques are influenced by patient and tumor selection, with some techniques being very operator-dependent and thus not necessarily generalizable. When available, these techniques provide a potential single-treatment modality for patients in the early stage of disease that involves critical sites of organ function, such as the larynx, without the issues of radiotherapy-induced late complications. It also allows radiotherapy to be reserved for the management of relapses and second head and neck malignancies. Currently, the relative efficacy with regard to oncologic results and organ function between these surgical options and radiotherapy remains unexplored.

This single-modality principle for treatment of early-stage disease attempts to minimize toxicity and emphasizes the importance of patient and tumor selection. When postoperative radiotherapy appears likely, definitive radiotherapy may be more appropriate, particularly for small volume disease, as it is unclear that combined-modality therapy is superior to radiotherapy alone. This consideration is particularly relevant when initial definitive en bloc resection may, in combination with postoperative radiotherapy, further complicate treatment toxicity and organ function. Not uncommonly, these issues arise with more extensive early-stage HNSCC or in cases in which the anatomic location limits achieving adequate surgical margins. For these and more advanced lesions, the role of debulking surgery also has been proposed.[175] This has been favored as a strategy for efficient reduction of the number of tumor clonogens without the surgical morbidity of more extensive tissue resection. Altough attractive, the value of this approach remains controversial, because it has not been subjected to critical scientific scrutiny and remains ill defined in the literature.

For more advanced primary lesions (typically defined as T3 and T4 disease), increased treatment-related toxicities generally have been accepted owing to inferior local control rates attained. Accordingly, a combined-modality approach typically has been employed. Traditionally, this approach has included surgery and radiotherapy with either preoperative or postoperative conventionally fractionated radiotherapy. A postoperative protocol typically has been favored because the radiotherapy can be delayed until more accurate delineation of the tumor extent of disease and histopathologic stratification of patients requiring postoperative radiotherapy (PORT).[176] When evaluated in a randomized trial in 277 patients with supraglottic larynx and hypopharynx carcinomas (RTOG 73–03), PORT demonstrated superior mature local-regional control rates although the results were confounded by use of a higher dose delivered in the postoperative setting.[177] Recent randomized trials have permitted optimization of not only selection of patients requiring PORT[161] but the dose required,[162] as well as the identification of prognostic factors adversely influencing the outcome particularly in high-risk patients.[161] Of greater significance, it is now clear that the time from surgery to the start of PORT and the overall treatment time of PORT are important determinants of local-regional control in patients with high-risk features. Because the issue of patients with more extensive disease undergoing higher risk surgical resection may confound these observations, the magnitude of benefit from manipulating these time variables remains to be determined. Nevertheless, it remains prudent to regard these observations, emphasizing the importance for effective coordinated management, which is best achieved in the context of a multidisciplinary team of health care providers. Strategies to improve the results of surgery and PORT have included adjuvant chemotherapy, concurrent postoperative chemoradiotherapy, and altered fractionated radiotherapy schedules such as various accelerated radiotherapy schedules. These strategies remain subjects of ongoing study to further define their role and efficacy in patients with resectable locally advanced HNSCC.

For unresectable advanced disease, conventionally fractionated radiotherapy alone has been traditionally recommended. Results of suboptimal local-regional disease control in the absence of surgical options, however, have favored an acceptance of intensifying treatment with increased treatment toxicities. Of note, however, the increased toxicity associated with this strategy warrants careful patient selection, because the therapeutic ratio is clearly reduced. This has included the use of concurrent chemotherapy with daily-fractionated radiotherapy,[178] altered fractionated radiotherapy alone,[179] and recently developed combinations of concurrent chemotherapy with altered fractionated radiotherapy schedules.[180] In general, modest success has been realized with both daily-fractionated chemoradiotherapy and altered fractionated radiotherapy, and they are regarded as acceptable therapeutic options. For concurrent chemoradiotherapy, determining the optimal agents and schedule remains largely undefined and is the subject of ongoing evaluation. Although a recent updated patient-based meta-analysis has demonstrated a modest survival benefit with concurrent chemoradiotherapy,[181] the generalizability of these results to current popular taxane-based chemoradiotherapy regimens is unclear.[157,182] Randomized data currently also support the use of either a dose-escalated hyperfractionated schedule

or an accelerated schedule reducing the overall treatment time by 1 week with twice daily treatments in the final 2.4 weeks for this group of patients.[179] The relative efficacy and indications for these two treatment strategies also remain largely undefined. Despite the improvements in local-regional control rates observed with the various altered fractionated schedules, the predominant relapse pattern continued to be local-regional (approaching 50%), with distant relapse rates of less than 20%, leading current opinion to favor the use of concurrent chemoradiotherapy for large volume disease manifesting at the primary site or in the neck.[183] The integration of chemotherapy has been particularly favored for bulky neck disease, because the risk of distant relapses is increased with some chemoradiotherapy regimens, demonstrating an impact on this risk.[135]

In recent years, treatment decisions have been progressively influenced by obligations to achieve functional organ preservation for advanced but resectable HNSCC. This treatment goal has been buoyed by the fact that the superiority of altered fractionated radiotherapy schedules[179] and concurrent chemoradiotherapy[178] demonstrated in randomized trials has, in general, been observed in study populations that have been unselected based on the resectability of the disease.[184] This treatment goal has been particularly paramount for disease in the larynx[185,186] and oropharynx subsites[187] and continues to evolve; the optimal definitions, methodology, and instruments for studying functional organ preservation remain to be defined. Because surgical resection for more advanced disease often results in greater normal tissue extirpation and loss of function, radiotherapy-based management strategies typically have been favored. It is noteworthy, however, that the oncologic efficacy of surgical resection, often followed by PORT, relative to these radiotherapy-based strategies has not been rigorously evaluated. In fact, studies have demonstrated that patients will prioritize length of life if compromises in speech or swallowing function are required.[188] Accordingly, surgical resection remains an appropriate treatment consideration, particularly when organ function already has been compromised by tumor. Invasion of bone or cartilaginous structures by advanced HNSCC has been also considered an indication for surgery on the basis of historic experience of poor responsiveness to radiation therapy, although this is debated.[189] Recent results with treatment intensive intra-arterial chemoradiotherapy strategies have challenged this indication.[190]

In general, two therapeutic paradigms involving radiotherapy have been adopted for organ preservation. A nonselective strategy may be adopted whereby the tumor response serves as an in vivo test for radiosensitivity reserving surgery for salvage.[191] This strategy poses increased risks of difficulties and complications with salvage surgery but increases the number of patients achieving organ preservation. It also is limited by the recognition that not all patients who fail at the primary site after radiotherapy are amenable to surgical salvage. Alternatively, selecting tumors and patients who may have a more favorable probability of local control with radiotherapy minimizes the proportion of patients subjected to increased surgical complication rates, but may subject patients with radiosensitive lesions to unnecessary surgery. A hybrid strategy that continues to have proponents is based on treatment response to either chemotherapy[187,192,193] or an intermediate radiotherapy dose, typically between 50 and 55 Gy.[134,135] Responses to chemotherapy have been argued to predict for biologically favorable and responsive disease to subsequent radiotherapy. It also has been argued that significant radiotherapy responses possess sufficient predictive power, allowing for the selection of patients who are destined to require salvage surgery, in turn limiting the subsequent toxicity from cumulative therapy with higher radiotherapy doses. A large prospective radiotherapy series has demonstrated this to have independent prognostic value for local control.[134]

Early experiences of organ preservation with conventionally fractionated radiotherapy were limited to the larynx, and the results were disappointing.[143,194–197] Salvage surgery was possible in 50% to 80% of patients with early-stage disease treated with radiotherapy.[194–196] Inferior local-regional control rates were reported for bulky disease such that a majority of patients required salvage surgery, with a success rate of 50%, and also were associated with increased surgical complication rates.[191,197] This gave rise to the use of various neoadjuvant chemoradiotherapy regimens in attempts to achieve organ preservation. The value of the neoadjuvant chemotherapy in contributing to local disease control was questioned, however. In a recently completed randomized trial, it was subsequently demonstrated to have minimal value and the trial indicated that intensive local-regional therapy was a more appropriate strategy.[198] Recent studies have now demonstrated that the use of an altered fractionation schedule (hyperfractionated and accelerated schedules)[179] or the use of concurrent chemotherapy[135,198] in combination with daily-fractionated radiotherapy offers superior local-regional control rates. This gain in local-regional control rate, however, may still come at the increased risk of surgical complications with salvage surgery. The risk of pharyngocutaneous fistula increased from 15% to 30% in patients randomized to receive radiotherapy alone or concurrent chemoradiotherapy with cisplatin for larynx preservation, respectively.[185] It remains to be demonstrated whether this risk is observed with other treatment-intensive regimens (and for other head and neck disease sites) that aim to improve on local-regional disease control.

Accordingly, patients deciding between initial surgical therapy and organ preservation therapy must balance the issues of immediate organ loss with lower complication rates and a reduced probability of delayed organ extirpation but at an increased risk of surgical complications. To guide these decisions, attention has focused on the probability of organ preservation with radiotherapy-based strategies and the degree of function that will be achieved. To date, radiotherapy predictive factors remain limited to considerations of clinical tumor features such as tumor volume.[142,143,146] Although predictive factors of organ function remain in evolution, it is clear that when nonexisting pretreatment function is observed, successful radiotherapy is unlikely to restore function.

In the evolution of organ preservation as a curative treatment goal, several additional concerns have been raised. Initial concerns focused on the potential risk of an adverse outcome due to the potential risk of ongoing tumor metastasis. Early randomized trials comparing surgery and PORT with neoadjuvant chemoradiotherapy have demonstrated that organ preservation can be achieved without immediate surgical extirpation and with no compromise in overall survival.[192,193] The second trial has centered on treatment toxicity, especially with recent evidence favoring the concurrent integration of chemoradiotherapy for organ preservation.[185,186,198]

With concurrent chemoradiotherapy, increased swallowing dysfunction and secondary risks of aspiration, events contrary to the goal of functional organ preservation have been observed.[187,199] The mechanisms contributing to these events remain to be fully understood but in general may relate to the severity and location of the treatment-induced mucosal edema with subsequent fibrosis and damage to peripheral nerves, all compounded by significant radiotherapy-induced xerostomia. Despite these concerns, preliminary data suggest that patient quality of life may still be improved as a consequence of organ preservation.[200]

Traditionally, the management of the primary tumor site dictated the treatment modality for the neck as a strategy to facilitate efficient management of HNSCC. Treatment decision-making for the neck has adopted a similar therapeutic paradigm of risk stratification to optimize the therapeutic ratio, but the decision-making becomes more complex as a result of the primary treatment considerations. Conceptually, the issue of functional organ preservation also may be extended to the neck, because neck dissection may result in cosmetic changes and compromised neck and shoulder function. Similarly, radiotherapy-induced edema and fibrosis may compromise the goal of functional neck preservation and may be exacerbated by a neck dissection.

Typically, single-modality treatment is favored for early-stage neck disease and combined-modality strategies for advanced neck disease. In the clinically negative neck, when surgical resection has been elected for the primary site management, elective neck dissection may be omitted if preoperative evaluation determines a high risk of requiring PORT and the risk of occult nodal metastasis is sufficiently high to warrant elective management. When radiotherapy has been selected for management of the primary site, neck dissection in the clinically negative neck is not indicated. In fact, preradiotherapy neck dissection may alter the lymphatic flow of the neck, necessitating larger volumes of the neck to be irradiated and requiring surgical wounds to be irradiated to higher doses. It also may contribute to delays in the delivery of radiotherapy, which have been reported to contribute to an adverse overall survival when compared with postradiotherapy neck dissection in a retrospective analysis.[201]

In the clinically positive neck with adverse risk features, combined-modality therapy (surgery and radiotherapy) also has been favored owing to the increased recurrence risk and morbidity associated with regional relapses and the limited salvage options. Postoperative radiotherapy after a neck dissection is indicated in accordance with the presence of adverse pathologic nodal risk factors such as extracapsular extension. Again, delays in the start of PORT may be detrimental, particularly when high-risk nodal factors are present.

When conventionally fractionated radiotherapy alone has been employed for locally advanced HNSCC, suboptimal regional control rates coupled with the morbidity and the limited success of subsequent salvage neck dissection have prompted the incorporation and general acceptance of a planned neck dissection. This approach, generally accepted in the presence of residual adenopathy after radiotherapy, also has been selectively applied to patients with adverse risk factors such as large nodal size (typically 3 cm or greater). This risk stratification follows from radiotherapy series demonstrating an inverse relationship between nodal size and control rate.[202,203] In a study of radiotherapy alone for treatment of HNSCC in 1251 patients, Dubray and colleagues noted 3-year neck control rates, by maximum nodal size, of 0.5 cm, 77%; 2 cm, 67%; 4 cm, 60%; 6 cm, 52%; 8 cm, 37%; and 10 cm, 7%. Multivariate analysis revealed that regional relapses independently increased with increased nodal size ($P = 0.0001$), decreasing radiation dose ($P = 0.0001$), T4 primary disease ($P = 0.0001$), node fixation ($P = 0.02$), bilateral neck disease ($P = 0.03$), and geographic miss ($P = 0.0001$).[203]

Controversy continues, however, regarding the benefit of a planned neck dissection in the setting of a complete clinical response in the neck, particularly in large pretreatment lymph nodes, after completion of radiotherapy.[204] Treatment with conventionally fractionated radiotherapy has demonstrated that the prognosis of large neck nodes with a complete response is associated with a prognosis comparable with that of smaller nodal metastases, and that the risk of relapse is low.[202,205] This suggests that perhaps the subgroup of patients with a complete response in the neck may have more radiosensitive disease and may not require a neck dissection. A neck dissection continues to be favored, particularly for advanced neck disease, however, because the likelihood of achieving a complete response with radiotherapy alone is limited. The efficacy of this approach is further supported by several retrospective series demonstrating improved regional control rates,[205–207] with a possible improvement in survival[208] despite the absence of a randomized trial. Attempts to definitively treat advanced neck disease also increase the risk of subsequent wound complications with any subsequent salvage neck dissection,[209] if that is even possible given that salvage options are almost always limited owing to disease encasing critical structures such as the carotid artery.[210,211]

This issue has been further compounded by the use of concurrent chemoradiotherapy strategies that have reported improved local-regional control rates. One trial of concurrent hyperfractionated chemoradiotherapy versus hyperfractionated radiotherapy suggested a lower frequency of residual disease in the dissected neck specimen in favor of concurrent chemoradiotherapy (21% for chemoradiotherapy versus 37.5% for radiotherapy).[212] No neck relapses occurred in either arm in cases for which a planned neck dissection was performed. McHam and colleagues retrospectively reported on 109 patients who received concurrent chemoradiotherapy with or without a neck dissection for indications of residual neck disease or as a planned procedure.[211] Residual neck disease was observed in 33% of the neck specimens (25% and 39% of neck specimens with complete clinical responses or partial clinical responses, respectively). Neck relapses were observed in 5 out of 76 (6.6%) and 4 out of 33 (12%) patients receiving and not receiving a neck dissection, respectively. The only factor significantly correlating with neck relapses was the presence of residual disease (5 out of 25 versus 0 out of 51). These findings suggest that both chemoradiotherapy and neck dissection are contributing to high neck control rates, with clinical evaluation of the neck not possessing sufficient predictive power to select for a subgroup of patients for whom a planned neck dissection may be held. The role of PET imaging, which carries a risk of false-negative results, remains to be defined.[213,214] Although there is no appreciable increased risk of surgical complications with the addition of concurrent chemotherapy,[215–217] increased neck and mucosal edema, particularly with bilateral neck dissections, may contribute significantly to treatment morbidity.

Management of patients with HNSCC is further complicated by the risk for development of second primary carcinomas and relapses within an aerodigestive tract that may have been extensively exposed to prior treatment. This challenging scenario further emphasizes the single-modality treatment principle when appropriate and favors surgery alone when possible. An irradiated aerodigestive tract not only limits re-irradiation but also may preclude an effective surgical salvage, because concerns of residual microscopic disease often exist in cases that would otherwise warrant consideration of postoperative radiotherapy. In general, repeat surgery is associated with fewer normal tissue toxicity constraints but greater immediate functional consequences than are seen with re-irradiation. Accordingly, when a second primary or relapse occurs within a previously irradiated field, surgical resection should be the primary treatment option.[218] Experiences with various repeat EBRT strategies, including the integration of chemotherapy, have unfortunately demonstrated limited success, often at the risk of significant toxicities.[218] The exception appears to be NPCs that are more radiosensitive. Even then, significant late complications may arise but may be more accepted in view of the limited surgical options.

Institutional series have demonstrated that higher repeat radiation doses are more likely to be successful; this has favored the incorporation of conformal radiotherapy techniques when possible. Such techniques may include stereotactic radiosurgery or radiotherapy, three-dimensional conformal radiotherapy, IMRT, and brachytherapy techniques. The first option has been used as a preferred strategy with nasopharyngeal cancer in which infiltrative disease extends beyond the limits of an intracavitary brachytherapy implant. The last has been particularly favored when the disease is well defined and for its ability to deliver a biologically effective dose to a limited volume. In fact, limited institutional series have reported on the efficacy of a brachytherapy implant for the base of tongue and tonsil for selected well-defined lesions as an alternative to surgery for lesions that also are suitable for surgical resection. In general, a coordinated brachytherapy implant at the time of complete gross surgical resection of either the second primary relapse or in the dissected neck may facilitate successful re-irradiation. When surgical reconstruction and wound closure incorporate unirradiated tissue, the risk of complications from brachytherapy re-irradiation may be reduced. This approach is limited by the ability to define the extent of microscopic disease in the head and neck when normal anatomic barriers and lymphatic drainage patterns have been altered from prior therapies. It thus becomes important to apply a brachytherapy implant appropriately, because these results are not necessarily generalizable.

Treatment Modality Considerations

Surgery

GENERAL. The decision to treat HNSCC with surgical therapy must be undertaken carefully. To assess whether a patient is a surgical candidate, the input of a multidisciplinary team is invaluable. Of the many issues to be considered, among the most important is the medical condition of the patient. Severe cardiac or pulmonary disease, profound malnutrition, and generalized debilitation are relative contraindications to immediate surgical intervention. Therefore, a detailed assessment by an experienced internist or cardiologist is mandatory when a major resection is planned.

The next important consideration is whether the lesion can be removed safely with adequate margins. The resectability of a tumor is assessed via physical examination and radiographic studies. In general, tumor involvement with certain anatomic landmarks, including the base of skull and the prevertebral fascia, renders the lesion unresectable. This is due to the inability to achieve an adequate normal tissue margin in these areas. In addition to tumor location, massive tumor size also can preclude total extirpation. In such cases, tumor-free margins may be impossible to obtain. In addition, adequate reconstruction may be exceedingly difficult, and other forms of therapy should be considered.

Postoperative function also is a primary concern in considering surgical therapy. The ability to speak clearly and swallow effectively is greatly affected by surgery in the head and neck region. Although complete resection of the malignancy is of paramount importance, reconstruction of the surgical defect must be designed so that the patient has an opportunity to regain as much speech and swallowing function as possible. Site-specific considerations are discussed in the following sections.

The cognitive ability of the patient to participate in postoperative rehabilitation should be reviewed as well. Patients who are neurologically or emotionally unable to participate should be identified early in the decision-making process. They may be better served with different forms of therapy. The social situation of the patient also should be considered. Patients who live alone may require admission to a nursing home or skilled nursing facility to ensure adequate postoperative care.

In general, primary surgical therapy is reserved for patients with tumors of the oral cavity, selected early staged larynx cancer, skin cancer, salivary gland tumors, paranasal sinus tumors, and thyroid neoplasms. Patients with very advanced tumors invading bone, destroying cartilage, or extending into the soft tissues of the neck are considered for primary surgical therapy. When patients have severe organ dysfunction as a consequence of cancer infiltration, surgery also should be considered since functional restoration with nonsurgical therapy is unlikely.

NECK DISSECTION. It is important to understand the different types of neck dissections that can be performed (Fig. 72-6). The radical neck dissection is a procedure wherein the lymph nodes from all five levels of the neck, the sternocleidomastoid muscle, the internal jugular vein, and the spinal accessory nerve are all removed. The specimen is removed en bloc, theoretically so that there is no spillage of tumor and so that there is a complete resection of any metastases. This procedure is indicated only in the setting of massive neck metasases involving most of the levels of the neck as well as the nonlymphatic structures.

A modified radical neck dissection removes all of the lymph nodes in the neck but spares one or more of the nonlymphatic structures. Three types of modified radical neck dissection are in general use:

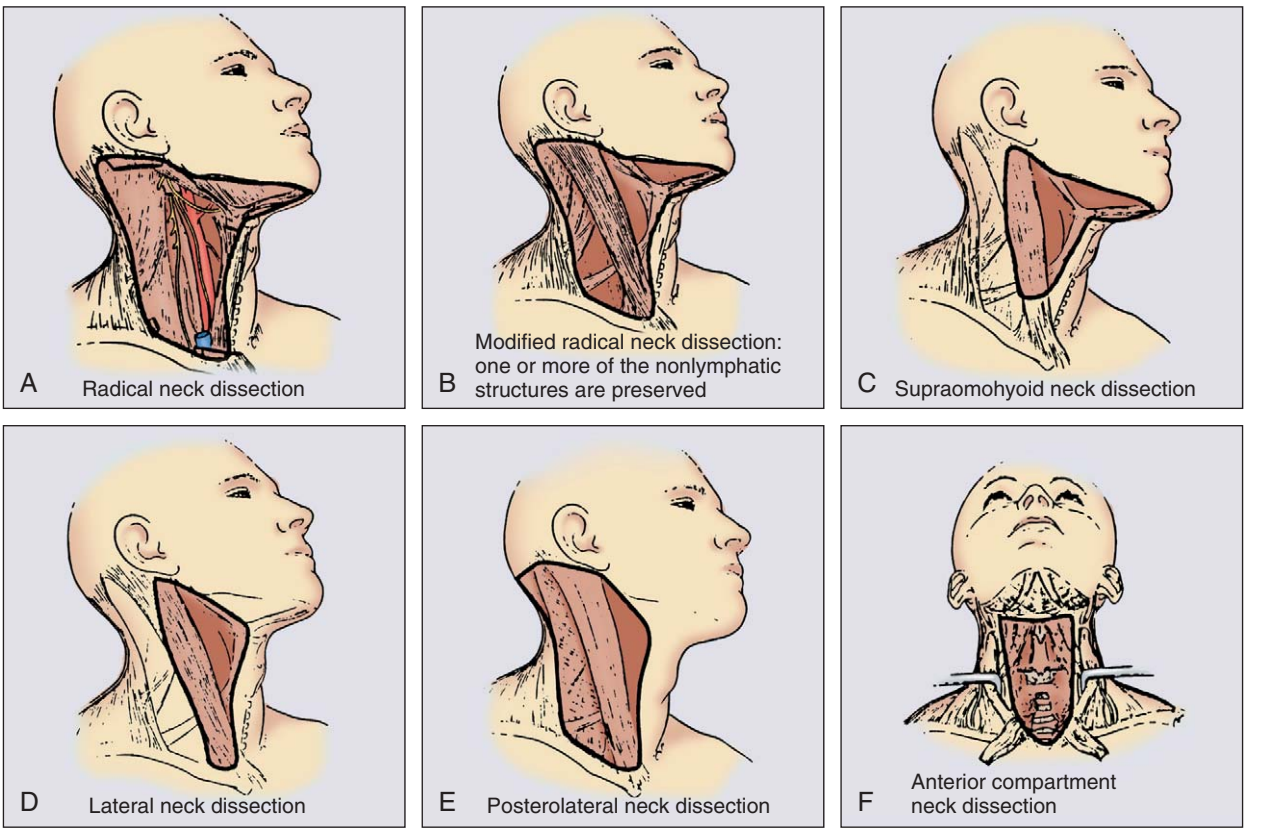


Figure 72-6 • Types of neck dissection. **A,** Radical. **B,** Modified radical: One or more of the nonlymphatic structures are preserved. **C,** Supraomohyoid. **D,** Lateral. **E,** Posterolateral. **F,** Anterior compartment.

Type I spares the spinal accessory nerve, type II spares the nerve and the internal jugular, and type III spares the nerve, vein, and sternocleidomastoid muscle. A type III dissection also is termed a functional or Bocca neck dissection, named after the Italian surgeon who pioneered the surgery.[219]

Selective neck dissections do not involve the resection of all five levels of lymph nodes but usually involve three or more according to the site of the primary cancer. These neck dissections are usually perfomed in the setting of the N0 neck. There is some controversy regarding the use of a selective neck dissection versus a modified radical or radical neck dissection when known metastases are present, although a consensus is forming that a selective neck dissection is appropriate for patients with N1 and selected N2 disease.[220–222]

Radiotherapy

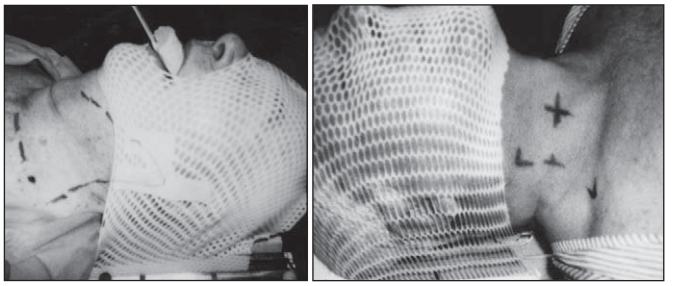
GENERAL. Historical experiences with EBRT have demonstrated that acute treatment-limiting radiotherapy-induced dermatitis may be limited by fractionation and the use of higher energy radiotherapy. which results in less surface dose. Accordingly, current standard radiotherapy practices have evolved to utilize a fractionated radiotherapy prescription using modern linear acceleration (linac)-model radiotherapy machines that can produce a spectrum of beam energies. With fractionation, issues of patient immobilization and treatment setup reproducibility become important considerations. For the head and neck, several critical normal tissue structures such as the spinal cord and optic chiasm often are in close proximity to the irradiated target. For these reasons, a prerequisite treatment simulation whereby patients are immobilized with various devices including a custom-made face mask and frame, with the setup referenced to a laser light coordinate system in the treatment rooms, is required before treatment can be initiated (Figs. 72-7 and 72-8).

Various immobilization devices exist, achieving different degrees of immobilization. Immobilization addresses the issue of the precision of the treatment delivery as a strategy to optimize the therapeutic ratio. The most examples of this are recently described stereotactic radiotherapy and radiosurgery techniques that involve immobilization of the patient in a rigid head frame system that may be removed daily for fractionated treatments in the former case or bolted to the cranium for a single large dose of radiation in the latter case.

More sophisticated treatment planning may involve obtaining axial images, typically with a dedicated CT scanner, of the immobilized referenced patient to facilitate non-coplanar three-dimensional beam arrangements or the use of IMRT techniques. The former utilizes geometric shielding to effect shaping of the radiotherapy beam; the latter utilizes various approaches that result in modulation of the radiotherapy beam fluence to achieve additional degrees of radiotherapy beam conformality. Increasing the conformality provides an additional strategy to optimize the therapeutic ratio, separate from the issue of radiotherapy beam precision. Radiotherapy beam conformality, however, often is dependent on achieving beam precision for it to be successful. This again places emphasis on achieving sufficient reproducible patient immobilization.



Figure 72-7 • Linear accelerator with reference laser lights shown for reproducible patient setup.



A B

Figure 72-8 • Patient in mask in the treatment position. **A,** Supraglottic carcinoma. **B,** Glottic cancer. (From Liebel S, Phillips TL (eds): Clinical Radiation Oncology, p 503.)

Although these new conformal techniques often are advantageous in the sparing of dose to critical head and neck normal structures, it is important to recognize that this benefit comes at the expense of increasing the volume of normal tissue that is exposed to low doses of the entry and exit radiotherapy beams. This issue is particularly emphasized with the IMRT technique, which often may dose many small segments of a radiotherapy beam or exploit the automated delivery process to deliver many more radiotherapy beams to achieve the degree of conformality sought. Concerns have been raised with regard to the potential long-term consequences of exposing larger volumes of normal tissue to low doses of radiation. In particular, a genotoxic and possibly carcinogenic effect has been speculated. These concerns remain to be fully evaluated, but they emphasize the importance of judiciously and appropriately applying these techniques in counseling young patients, particularly those with an anticipated good prognosis.

The success of these techniques is also dependent on the ability to accurately identify anatomic sites that may harbor subclinical disease. Currently, the basis for this determination is derived from surgical and clinical documentation of disease extension that is often unique to each head and neck subsite. Recent functional imaging techniques, such as PET-based studies, remain promising active areas of investigation. As a result, the transition to the use of axial images for radiation treatment planning places a significant emphasis on the knowledge and experience of the radiation oncologist with regard to the natural history of the disease as it pertains to axial anatomy. In particular, the identification of nodal groups that typically are at risk for harboring subclinical nodal metastases may be more problematic. To aid in this regard, several reports have been published delineating axial anatomic structures that may be used to delineate the various nodal groups (Table 72-2).[223] The incidence of nodal metastases has also been summarized and can significantly aid the radiation oncologist (Table 72-3). Of note, however, when prior treatment to the neck has occurred, altered flow of lymphatics is a significant concern. As with the head and neck surgeon, skill and judgment must be exercised with these precise treatment techniques. The alternative may be particularly detrimental.

EXTERNAL BEAM RADIOTHERAPY TIME-DOSE-FRACTIONATION CONSIDERATIONS. Conventional or daily radiotherapy fractionation (typically, daily 1.8- to 2-Gy fractions to

Table 72-2 Recommendation for the Radiologic Boundaries of the Neck Node Levels

	Anatomic Boundary					
Level	**Cranial**	**Caudal**	**Anterior**	**Posterior**	**Lateral**	**Medial**
Ia	Geniohyoid m.	Platysma m.	Symphysis menti; platysma m.	Body of hyoid bone	Medial edge of anterior belly of digastric m.	n.a.*
Ib	Mylohyoid m., cranial edge of submandibular gland or caudal edge of medial pterygoid m.	Platysma m.	Symphysis menti	Body of hyoid bone; posterior edge of submandibular gland	Basilar edge of mandible; platysma m.	Lateral edge of anterior belly of digastric m.
II	Bottom edge of the body of CI	Bottom edge of the body of hyoid bone	Posterior edge of submandibular gland; posterior edge of posterior belly of digastric m.	Posterior border of sternocleidomastoid m.	Medial edge of sternocleidomastoid m.	Internal edge of internal carotid artery, paraspinal (levator scapulae) m.
III	Bottom edge of the body of hyoid bone	Bottom edge of cricoid cartilage	Posterolateral edge of sternohyoid m.	Posterior edge of sternocleidomastoid m.	Medial edge of sternocleidomastoid m.	Internal edge of carotid artery, paraspinal (scalenius) m.
IV	Bottom edge of cricoid cartilage	Cranial border of clavicle	Posterolateral edge of sternohyoid m.	Posterior edge of sternocleidomastoid m.	Medial edge of sternocleidomastoid m.	Internal edge of internal carotid artery, paraspinal (scalenius) m.
V	Skull base	Cranial border of clavicle	Posterior edge of sternocleidomastoid m.	Anterior border of trapezius m; scalenius m.	Platysma m; skin	Paraspinal (levator scapulae, splenius capitis) m.
VI	Bottom edge of the body of hyoid bone	Sternal manubrium	Skin; platysma m.	Posterolateral edge of sternohyoid m.	Medial edge of common carotid artery, skin and anterior-medial edge of sternocleidomastoid m.	n.a.
Retropharyngeal	Base of skull	Cranial edge of the body of hyoid bone	Levator veli palatini m.	Prevertebral m. (longus colli, longus capitis)	Medial edge of internal carotid artery	Midline

*Midline structure lying between the medial borders of the anterior belly of the digastric muscle.

From Grégoire V, Coche E, Cosnard G, et al: Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience. Radiother Oncol 2000;56:135–150.

Table 72-3 Distribution of Clinical Metastatic Neck Nodes from Head and Neck Squamous Cell Carcinomas[3,28,49]

Tumor Size	Patients with N+ (%)	Distribution of Metastatic Lymph Nodes per Level (% of Node-Positive Patients)					
		I	II	III	IV	V	Other*
Oral cavity (*N* = 787)	36	42/3.5†	79/8	18/3	5/1	1/0	1.4/0.3
Oropharynx (*N* = 1479)	64	13/2	81/24	23/5	9/2.5	13/3	2/1
Hypopharynx (*N* = 847)	70	2/0	80/13	51/4	20/3	24/2	3/1
Supraglottic larynx (*N* = 428)	55	2/0	71/21	48/10	18/7	15/4	2/0
Nasopharynx (*N* = 440)	80	9/5	71/56	36/32	22/15	32/26	15/10

*Parotid buccal nodes.
†Ipsilateral/contralateral nodes.
From Grégoire V, Coche E, Cosnard G, et al: Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience. Radiother Oncol 2000;56:135–150.

a total dose of 70 Gy) has permitted the delivery of higher radiotherapy doses that currently are limited by normal tissue tolerances, such as in the mandible. Conceptually, radiotherapy failures may result from insufficient doses of radiotherapy relative to the number of tumor clonogens or may be due to cellular mechanisms of radioresistance. The former has proved to be more amenable to therapeutic manipulation with studies of various altered fractionation schedules, which may be generalized into two groups: hyperfractionation and accelerated fractionation (Fig. 72-9). Various randomized trials have been conducted and have been recently summarized.[183]

A *hyperfractionation* schedule, or the use of lower doses per treatment fraction, has been hypothesized to reduce the risk of late radiotherapy-induced complications associated with an increase in the total radiotherapy dose. Typically, the dose per fraction is reduced to 1.15 to 1.2 Gy and exploits a differential radiosensitivity between normal late-responding tissues and most cancers, including HNSCC. To ensure that the overall treatment time is not adversely protracted, fractions often are delivered twice a day, with an interfraction period of 6 hours.

Several randomized trials support the concept of hyperfractionation as a strategy to increase the biologically effective dose delivered without a significant increase in the risk of late radiotherapy-induced complications[179,224–226] (Table 72-4). In general, improved local-regional control rates were observed, with improved survival rates, in two trials.[225,226] The largest trial (RTOG 90–03) of radiotherapy fractionation schedules randomized over 1000 patients with locally advanced AJCC stage III and IV HNSCC (greater than 60% stage IV) for all subsites except nasopharynx (stage II disease permitted for base of tongue and hypopharynx) to one of four fractionation schedules including hyperfractionation to a dose of 81.6 Gy in 1.2 Gy per fraction twice daily in 68 fractions over 7 weeks, treated every Monday to Friday.[179] The standard control regimen consisted of 70 Gy in 2 Gy per day in 35 fractions over 7 weeks. With a median follow-up period of 23 months, the 2-year local-regional control rate, 2-year disease-free survival rate, and 2-year overall survival rate were 54.4% (versus standard arm of 46%; $P = 0.045$; Fig. 72-10), 37.6% (versus 31.7%; $P = 0.067$) and 54.5% (versus 46.1%; not significant), respectively. The modest but superior local-regional control rates in the hyperfractionated schedule reflected a 2-year local relapse and 2-year regional relapse rates of 37.8% (versus 43.7% in the control arm) and 26.6% (versus 32.1%), respectively. A planned neck dissection was permitted for residual neck abnormalities and for N2 and N3 neck disease regardless of the response. The 2-year distant relapse rate was 16.8% (versus 17.8%).

Increased acute mucositis was the predominant acute toxicity in patients receiving the hyperfractionated protocol in the RTOG 90-03 trial. No increased risks of late toxicities were observed through the follow-up at the time of report, although this report would be regarded as immature for this endpoint. Of note, however, a prior prospective dose-escalation hyperfractionation study (also using 1.2 Gy per fraction twice daily) conducted by the RTOG (83-13) demonstrated that the risk of late toxicities was significantly increased with an interfraction time of less than 4.5 hours.[227] A large retrospective review also observed the importance of interfraction time.[228] Because this strategy can be logistically demanding for the patient, it becomes important to recognize that the current recommended interfraction time of 6 hours should be maintained.

Alternatively, an *accelerated fractionation* radiotherapy schedule attempts to deliver the prescribed total dose over a shorter treatment duration. This strategy is founded on observations of adverse local-regional control rates with protracted treatment durations (with conventional fractionated schedules) such that higher total doses are required to maintain the same probability of tumor control. These results have been interpreted to be consistent with a model whereby tumor clonogens surviving each daily radiotherapy fraction undergo an accelerated rate of repopulation. As a consequence, a larger tumor burden would be expected with increasing duration of treatment interruptions. It has been rationalized that by reducing the overall treatment time, the opportunity and impact of accelerated tumor repopulation would be minimized. As the severity of acute toxicities is increased, some accelerated schedules studied have attempted to

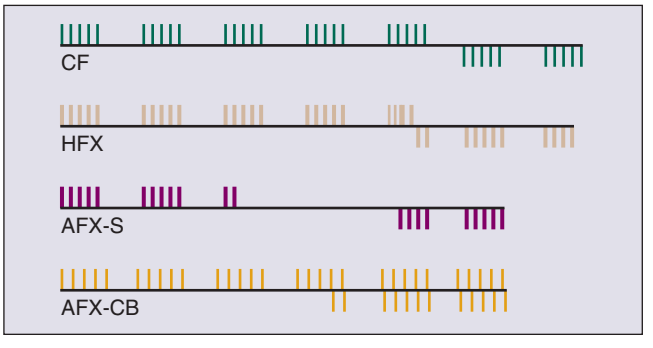


Figure 72-9 • Schematic illustration of the fractionation regimens investigated by the Radiation Therapy Oncology Group. Each bar represents one radiation fraction. Bars above the lines represent large-field irradiation and those below the lines stand for coned-down boost irradiation. CF, conventional fractionation; 70 Gy in 35 fractions over 7 weeks. HFX, hyperfractionation; 81.6 Gy in 68 fractions over 6.8 weeks. AFX-S, accelerated split-course fractionation; 67.2 Gy in 42 fractions over 6 weeks. AFX-CB, accelerated fractionation with concomitant boost strategy; 72 Gy in 42 fractions over 6 weeks. (From Nguyen LN, Ang KK: Radiotherapy for cancer of the head and neck: altered fractionation regimens. Lancet Oncol 2002;3:693–701.)

Table 72-4 Phase III Trials Addressing Hyperfractionation in Patients with Head and Neck Cancer

Study	Tumor Site and Stage	No. of Patients	Dose per Fraction (Gy)	Fractions per Day	Total Dose (Gy)	Overall Treatment Time (weeks)	Tumor Response	Complications
Fu et al, 2000	Various sites, stage III–IV, stage II of tongue base, hypopharynx	1073	1.2	2	81.6	6.0	LRC, higher with HF and CB ($P = 0.045$ and 0.05); DFS, trend in favor of HF and CB ($P = 0.067$ and 0.054); no difference in OS	More acute mucositis with all altered fractionations; no difference in late complication rate
			1.8*	1–2	72.0	7.0		
			1.6	2	67.2	6.0		
			2.0	1	70.0	7.0		
Horiot et al, 1992	Oropharynx, T2–3 N0-1	356	1.15	2	80.5	7.0	5-year LRC, 59% vs 40% ($P = 0.02$); improved local control of T3 tumors	More acute mucositis with HF: no difference in late complication rate
			2.0	1	70.0	7.0		
Pinto et al, 1991	Oropharynx, stage III–IV	98	1.1	2	70.4	6.5	Tumor response, 84% vs 64% ($P = 0.02$) 3–5 year OS, 27% vs 8% ($P = 0.03$)	Earlier onset of acute reactions with HF, late complications, no details
			2.0	1	66.0	6.5		
Cummings et al, 2000	Various sites, T3–4, N0 or any TN	331	1.45	2	58.0	4.0	5-year LRC, 45% vs 37% ($P = 0.01$); 5-year OS, 40% vs 30% ($P = 0.01$)	More acute mucositis with HF; 5-year grade 3–4 late toxic effects, 8% vs 14% ($P = 0.31$)
			2.55	1	51.0	4.0		

CB, constant boost; DFS, disease-free survival; HF, hyperfractionation; LRC, locoregional control; OS, overall survival.
*Boost dose given in 1.5 Gy fractions.
From Nguyen LN, Ang KK: Radiotherapy for cancer of the head and neck: altered fractionation regimens. Lancet Oncol 2002;3:693–701.

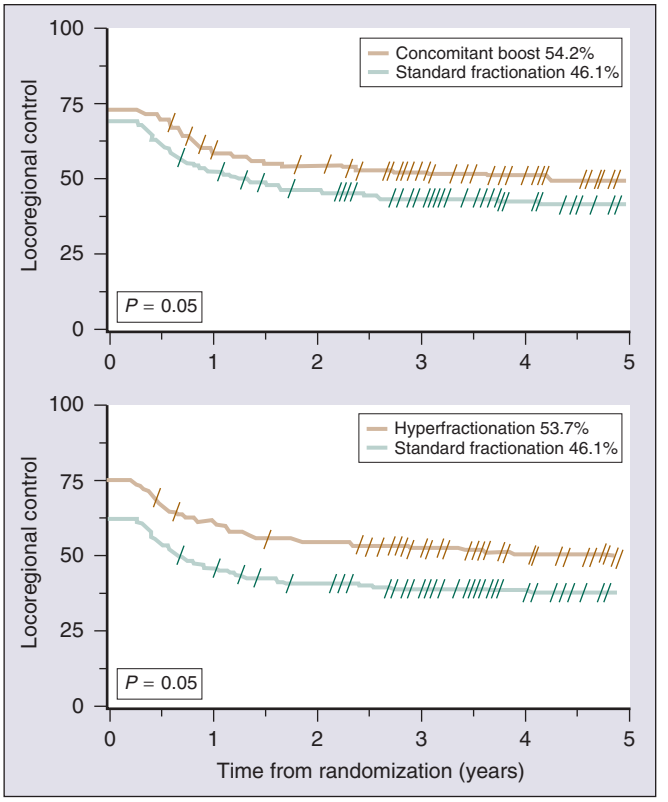


Figure 72-10 • Local-regional control rates for concomitant boost accelerated and hyperfractionation regimens relative to that for conventional fractionation. (From Nguyen LN, Ang KK: Radiotherapy for cancer of the head and neck: altered fractionation regimens. Lancet Oncol 2002;3:695.)

modify the risk of unacceptable acute toxicities by modifying either the dose per fraction or the total dose as a strategy to achieve an acceptable therapeutic ratio. Accelerated radiotherapy schedules may therefore be categorized into two groups: schedules that do not modify the dose per fraction or the total dose (pure accelerated schedules)[229–232] (Table 72-5) and those that do (hybrid accelerated schedules)[179,233–236] (Table 72-6). Examples of the former are two fractions delivered per day on some or all treatment weekdays and daily treatments for 6 to 7 days per week. A variety of hybrid schedules reflecting a spectrum of dose modifications has been studied. Conceptually, the success of these hybrid schedules is dependent on the dose equivalent of the reduction in the overall treatment time being greater than the biologic equivalent dose reduction in the fractionation schedule.

A review of the 4 randomized trials of pure accelerated fractionation demonstrates that the overall treatment time may be reduced by 1 week without unacceptable acute and late toxicities, achieving modest improvements in local-regional control with no evidence of consistent survival gains.[229–231,237] The most aggressive of these schedules was conducted at the BC Cancer Agency, where the experimental treatment protocol consisted of 66 Gy in 33 fractions with twice-daily fractions of 2 Gy, with an interfraction time of 6 hours, resulting in an overall treatment time of 3.4 weeks (versus 6.6 weeks). Patients receiving the accelerated schedule were more likely to experience RTOG grade 3–4 acute toxicity (seen in 27 of 41 versus 8 of 41; $P = 0.00005$). Increased grade 4 late toxicity (seen in 8 of 41 versus 2 of 41) resulted in premature termination of the study, which precluded definitive conclusions regarding the therapeutic efficacy of this schedule. Of the eight cases of late toxicity, four occurred after salvage surgery, two were soft tissue necroses, and two followed from persistent acute toxicity. Investigators at the Sklodowska-Curie Institute observed similar observations of consequential late effects involving the mucosa in their experimental arm of 70 Gy in 35 fractions with daily fractions of 2 Gy 7 days per week with an overall treatment

Table 72-5 Phase III Trials of Pure Accelerated Fractionation in Patients with Head and Neck Cancer

Study	Tumor Site and Stage	No. of Patients	Dose per Fraction (Gy)	Fractions per Day	Total Dose (Gy)	Overall Treatment Time (weeks)	Tumor Response	Complications
Jackson et al, 1997	Various sites, stage III–IV	82	2.0	2 (at least 6 h apart)	66.0	3.4	CR, 35% vs 29%	Grade 3–4 reactions
			2.0	1	66.0	6.8	No difference in 3-year relapse-free survival	Grade 4 late toxicity ($P = 0.10$)
Skladowski et al, 2000	Various sites, T2–4, N0-1	100	1.8–2.0	1	–70.0	5.0	3-year LC, 82% vs 37% ($P < 0.0001$); 3-year OS, 78% vs 32% ($P < 0.0001$)	Severe mucositis, 62% vs 26%; late complications, 10% vs zero
			1.8–2.0	1	–70.0	7.0		
Overgaard et al, 2003	Various sites, all stages	1485	2.0	1	–66.0	6.0	5-year LRC, 66% vs 57% ($P = 0.01$); 5-year DFS, 72% vs 66% ($P = 0.04$); no difference in OS	More acute mucositis with AF; no difference in late complication rate
			2.0	1	–66.0	7.0		
Hliniak et al, 2002	Laryngeal carcinomas, T1–3, N0	396	2.0	1–2 (at least 6 h apart)	66.0	5.5		
			2.0	1	66.0	6.5	LRC, higher with AF ($P = 0.03$)	More acute reactions with AF; no difference in late complications except for telangiectasia

AF, accelerated fractionation; CR, complete response; DFS, disease-free survival; LC, local control; LRC, locoregional control; OS, overall survival.
From Nguyen LN, Ang KK: Radiotherapy for cancer of the head and neck: altered fractionation regimens. Lancet Oncol 2002;3:693–701.

time of 5 weeks. These investigators observed no additional late toxicities when the dose per fraction was reduced to 1.8 Gy per day. Although a significant gain in local-regional control and overall survival was observed, concerns regarding the validity of these observations have been raised owing to the unexpected poor outcome of the control arm, especially when the study did not include patients with N2 or N3 disease.

In contrast, investigators from both the Danish[232] and Polish[238] Cooperative Groups conducted randomized trials accelerating treatment with six treatments per week, either as an additional treatment on the weekend[232,238] or as a single second daily fraction, with no evidence of any increased late toxicities.[232] Acute toxicities were increased, as would be expected. Significant improvements in local-regional control rates were observed, but with no survival gains. Hence, the evidence to date suggests that late toxicities, possibly resulting from severe acute pathologic processes that exceed normal tissue repair capacities, limit the increased biologic effect to only an approximately 1-week reduction in overall treatment time. It may be possible to realize additional therapeutic gains with a modest reduction in the dose per fraction to 1.8 Gy, but this needs to be further validated.

Various hybrid accelerated radiotherapy schedules have been studied as strategies to further achieve increased biologic effects with greater reductions in the overall treatment time (see Table 72-6).[179,233–236] These schedules may be further differentiated depending on whether or not the total dose was reduced (type A versus types B and C). Typically, the total dose has been reduced where more than a 2-week treatment time reduction (from a conventional 7-week course) has been attempted. The most aggressive schedule was the CHART schedule, which reduced the treatment time by 4.5 weeks by delivering 1.5 Gy three times a day with an interfraction time of 6 hours over a total duration of 2 weeks to a total dose of 54 Gy (representing an 18% dose reduction).[233] In a randomized trial of 918 patients with stage II to IV HNSCC involving various sites (a majority had laryngeal carcinomas), no improvement in local-regional control or overall survival was observed. Although this trial did demonstrate increased acute toxicities that occurred earlier, it is noteworthy that fewer late radiotherapy toxicities were observed in the accelerated arm. Poulsen and colleagues performed a randomized trial of 350 patients with stage III or IV HNSCC through the Trans-Tasman Radiation Oncology Group (TROG) studying a schedule with a 3.5-week reduction in the treatment time and a total dose reduction of 10.6 Gy (15%).[234] The experimental arm consisted of twice-daily1.8 Gy (6-hour interfraction time) to a total dose of 59.4 Gy. No improvement in local-regional control rates, disease-free survival, or survival was noted. Again, acute toxicities were more severe and occurred earlier, but no increased late toxicities were observed. Lastly, a French Cooperative Group Study (GORTEC 94–02) reported the preliminary results of a randomized trial of 268 patients with the majority having advanced T4 oropharyngeal carcinomas with the experimental arm receiving a 4-week reduction in treatment time and a modest 10% (7 Gy) reduction in the total dose.[235] The schedule used consisted of 2 Gy twice daily over 3 weeks to 62 Gy versus 70 Gy in 2 Gy per day. With only a median follow-up period of 28 months, a significant improvement in 2-year actuarial local-regional control rate was observed (58% versus 34%; $P < 0.01$) with no difference in overall survival. Increased acute mucosal toxicities were reported with no increased late toxicities noted with the limited follow-up. Hence, the data to date suggest that with only a modest total dose reduction of 10%, reducing the overall treatment time by more than 3 weeks may achieve improvements in local-regional control. With only a modest total dose reduction, however, it remains to be seen if late toxicities are increased.

Two other randomized trials have attempted to accelerate the overall treatment but without reductions in the total dose. The European Organization for Treatment of Cancer (EORTC) Radiotherapy

Table 72-6 Phase III Trials of Hybrid Accelerated Fractionation in Patients with Head and Neck Cancer

Study	Tumor Site and Stage	No. of Patients	Dose per Fraction (Gy)	Fractions per Day	Total Dose (Gy)	Overall Treatment Time (weeks)	Tumor Response	Complications
ACCELERATED FRACTIONATION WITH TOTAL DOSE REDUCTION								
Dische et al, 1997	Various sites, mainly stage II–IV	918	1.5	3 (every 6 h)	54.0	2.0	No difference in LRC, disease-free interval, or ulceration	More acute mucositis, less epidermal telangiectasia, mucosal ulceration, and edema with AF
			2.0	1	66.0	6.5		
Poulsen et al, 2001	Various sites, stage III–IV	350	1.8	2 (at least 6 h apart)	59.4	3.5	5-year LRC, 52% vs 47% ($P = 0.30$); 5-year DFS, 41% vs 35% ($P = 0.32$); 5-year DSS, 46% vs 40% ($P = 0.40$)	More severe acute mucositis ($P = 0.00008$) but lower frequency of grade ≥2 late soft-tissue effects ($P < 0.05$) with AF (except for mucosal late effect)
			2		70.0	7.0		
Bourhis et al, 2000	All sites, 75%; T4, 70%	269	2.0	2	–63.0	3.3	2-year LRC, 68% vs 34% ($P < 0.01$)	Grade 3–4 mucositis, 83% vs 28% ($P < 0.01$); similar late toxic effects
			2.0	1	70.0	7.0	No difference in OS	
ACCELERATED FRACTIONATION WITH SPLIT-COURSE (TYPE B) OR CONCOMITANT BOOST (TYPE C)								
Horiot et al, 1997	Various sites, T2–4 N0-1	500	1.6	3	72.0	5.0	5-year LRC, 59% vs 46% ($P = 0.02$); trend for higher 5-year DFS ($P = 0.08$); no difference in OS ($P = 0.95$)	More severe acute mucositis and higher frequency of severe late morbidity ($P < 0.001$) with AF
			2.0	1	70.0	7.0		
Fu et al, 2000	Various sites, stage III–IV; stage II of tongue base, hypopharynx	1073	1.8*	1–2	72.0	6.0	LRC, higher with CB and HF ($P = 0.06$ and 0.045); DFS, strong trend in favor of CB and HF ($P = 0.054$ and 0.067); no difference in OS	More acute mucositis with all altered fractionations: no difference in late complication rate
			1.2	2	81.6	7.0		
			1.6	2	67.2	6.0		
			2.0	1	70.0	7.0		

AF, accelerated fractionation; CB, conconstant boost; DFS, disease-free survival; DSS, disease-specific survival; HF, hyperfractionation; LRC, locoregional control; OS, overall survival.

*Boost dose given in 1.5-Gy fractions.

From Nguyen LN, Ang KK: Radiotherapy for cancer of the head and neck: altered fractionation regimens. Lancet Oncol 2002;3:693–701.

Cooperative Group randomized 512 patients with T2 to T4 HNSCC of all sites excluding the hypopharynx to conventional arm of 70 Gy in 35 fractions daily over 7 weeks or 72 Gy in 45 fractions over 5 weeks (EORTC 22851).[236] The experimental arm introduced a split in the treatment duration with the first half delivering 28.8 Gy in 18 fractions over 8 days with 1.6 Gy per fraction three times a day. This was followed by a 12- to 14-day treatment interruption, followed by a second course of 43.2 Gy in 27 fractions over 17 days again with 1.6 Gy per fraction three times a day. Although the 5-year local-regional control rate improved by 13% (59% versus 46%; 95% CI 3% to 23%), with a 24% reduction in local failure rate, this treatment regimen was associated with unacceptable toxicities including twice as many grade 3 or 4 acute morbidities, with grade 5 toxicity reported. Significantly more grade 3 fibrosis ($P < 0.001$) and severe neurologic complications, including permanent peripheral neuropathy, occurred in the accelerated arm. In contrast, the RTOG conducted a four-arm randomized trial in 1073 patients with stage III or IV HNSCC (stage II base of tongue and hypopharynx permitted), with one of two accelerated schedules also using a treatment interruption and a 4% total dose reduction (RTOG 90-03).[179] This treatment protocol consisted of 1.6 Gy twice daily (6-hour interfraction time) to a dose of 67.2 Gy in 42 fractions over 6 weeks. No improvement in local-regional control or overall survival was noted, suggesting that the treatment interruption employed also contributed to the absence of treatment benefit that was not sufficiently compensated in the dose intensity of fractionation schedule.

In the RTOG 90-03, a second accelerated schedule consisted of twice-daily fractions in the final 2.4 weeks, with the second fraction delivered with a 6-hour interfraction interval and limited to only the boost volume.[179] A total dose of 72 Gy was delivered, with the morning fraction 1.8 Gy and the afternoon boost fraction 1.6 Gy in the final 2.4 weeks of a 6-week treatment schedule. This limitation in volume was developed as a strategy to minimize the toxicity with the twice-daily fractionation. The timing of the concomitant boost followed from prior work by Ang and colleagues, who demonstrated slightly better local control rates than if the concomitant boost was delivered at the beginning of the radiotherapy schedule.[239] The results of the RTOG 90–03 demonstrated that the local-regional control rate was significantly improved (2-year survival rate of 54.2% versus 46.1%), with a trend to improved disease-free survival (see Fig. 72-10). The modest but superior local-regional control rates with this delayed concomitant boost accelerated schedule reflected a 2-year local relapse rate and 2-year regional relapse rate of 36.9% (versus 43.7% in the control arm) and 33.3% (versus 32.1%), respectively. A planned neck dissection was permitted for residual neck abnormalities and for N2 and N3 neck disease regardless of the response. The 2-year distant relapse rate was 16.6% (versus 17.8%). No improvement in overall survival was observed. Comparable increased

acute toxicities were observed as with the other altered fractionation schedules including the hyperfractionated arm. No significantly increased late toxicities were observed though the incidence of late toxicities was higher in the accelerated schedule. Because the benefits from this fractionation schedule appear to be comparable to the hyperfractionated schedule reported in RTOG 90-03, investigators have concluded that an accelerated schedule with a delayed concomitant boost may be preferred due to the more favorable logistical treatment delivery issues.[183]

Although the use of an altered fractionated radiotherapy schedule offers an improved local-regional control rate of approximately 15%, this comes at the price of increased acute toxicities. Most notable is the increased mucositis, which can occur earlier and be more severe depending on how the various dose and time parameters are manipulated. The results from the Conventional Accelerated Irradiation (CAIR) trial highlight the potential for excessive mucosal toxicities to exceed their normal repair capacity, leading to consequential late effects.[238,240] A similar potential for increased mucosal toxicities with consequential late effects also appears to have emerged with various concurrent chemoradiotherapy schedules including both conventionally fractionated[187,199] and altered fractionated schedules.[241] These results highlight that a limit to local-regional intensive therapy does in fact exist and have led to interest in the development of normal tissue protectants.

TREATMENT TOXICITIES AND NORMAL TISSUE PROTECTANTS. The most developed of these normal tissue protectants is amifostine. This thiol-containing compound and its metabolite, WR-2721, are believed to function as free radical scavengers and appear to have preferential normal tissue uptake, with the highest concentration found in salivary glands and kidneys.[242,243] Amifostine has been shown to reduce cisplatin-induced nephrotoxicity.[244] It has been the subject of tremendous clinical interest, initially for the protection of salivary glands from radiotherapy-induced xerostomia, and most recently as a mucosal normal tissue protectant. To date, clinical trials have reported improvements in the rate and severity of radiation-induced xerostomia[245–248]; reduced hematologic effects, particularly with concurrent chemoradiotherapy[245]; and reduced radiotherapy-induced mucositis with altered fractionated radiotherapy and from concurrent chemoradiotherapy.[246,249] No compromise in treatment outcome has been reported, either by a small randomized trial using definitive chemoradiotherapy[246] or by a larger randomized trial containing a mixture of patients receiving postoperative radiotherapy and definitive therapy.[247] The latter trial led to the current approved indication for amifostine limited to the postoperative setting, owing to concerns of potential tumor protection that may not be adequately detected.

This trial randomized 315 patients undergoing conventionally fractionated radiotherapy to receive an intravenous 3-minute infusion of amifostine (200 mg/m^2) 15 to 30 minutes before each daily fraction.[247] The main toxic effects were nausea (any grade, 44% versus 16%; $P < 0.001$), vomiting (any grade 37% versus 7%; $P < 0.001$), hypotension (any grade, 15% versus 2%; $P < 0.001$), and a hypersensitivity reaction (any grade, 5% versus 0%; $P = 0.003$) with 21% discontinuing the amifostine before completing the scheduled treatment. The mean quantity of unstimulated saliva 1 year after treatment was significantly higher, correlating with a lower frequency of late grade 2 or higher xerostomia in the group receiving amifostine. In this trial, mucositis was not reduced (grade 3 or higher, 35% with amifostine versus 39% no amifostine; $P = 0.48$), in contrast with to the results of other randomized trials.[246,249] It has been postulated that this discrepancy may relate to dose, becuase Buntzel administered 500 mg as a flat dose and only on the days during which daily concurrent carboplatin was administered (days 1 to 5 and days 21 to 26).[246] Ongoing trials are under way to verify these results. It is clear, however, that the toxicities related to amifostine are dose-related, particularly the emetogenic side effects. These concerns along with logistical issues with coordinated daily administration have prompted studies with a subcutaneous schedule of administration.

A French Cooperative Group study (GORTEC) compared intravenous amifostine as a 3-minute infusion of amifostine (200 mg/m^2) 15 to 30 minutes before each daily fraction with a subcutaneous schedule delivering 500 mg 20 to 60 minutes before each daily fraction.[248] Preliminary results have been promising. Early reporting describes reduced incidence of hypotension (6% versus zero, in favor of the subcutaneous route), with nausea and vomiting remaining dominant side effects in both treatment groups. The rates of acute xerostomia appeared to be similar in both treatment groups, offering a potential alternative schedule for administration.

INTENSITY-MODULATED RADIOTHERAPY. In recent years, significant technological advances have enabled the ability to vary the fluence of the radiotherapy beam, permitting an additional degree of dose conformality and some exciting potential therapeutic applications. These may include an improved therapeutic ratio with irradiation near the base of skull, parotid sparing to minimize the risk of xerostomia, and manipulation of the effective radiotherapy dose per fraction that is delivered to the tumor or surgical bed. Coupled with promising advances in functional imaging, there exists the potential to manipulate the dose to critical areas within the tumor that may harbor radioresistant cells. In particular, interest has focused on identifying areas of tumor hypoxia that may be amenable to in vivo hypoxia imaging with various promising compounds including Cu-ATSM[250] and EF-5.[251] Although this technique remains promising, it is important to recognize its evolving nature and the potential for geographic tumor "misses," particularly areas of subclinical tumor extension, which also may be complicated by a lower dose per fraction delivered. In addition, successful sparing of normal tissues requires knowledge of the dose and volume constraints that are associated with acceptable risks for toxicities. This knowledge base remains in evolution. The generalizability of not only the technique but also target delineation is the subject of several ongoing trials through the RTOG. Nevertheless, early reports are promising.

Several prospective reports demonstrated that with IMRT, dose and volume constraints to the parotid glands may be successful in reducing the xerostomia associated with radiotherapy to the head and neck.[252–255] Quality of life instruments have been used and suggest that there may be additional benefits resulting from reduced xerostomia.[256] These investigators noted that the probability of a geographic tumor miss was low,[255,257] with the majority of relapses within field, emphasizing the importance to identify potential radioresistant subvolumes.[254,257] Lee and colleagues reported a promising 4-year local-regional progression free rate of 98% without any increased acute toxicities for 67 patients with stage I to IV NPC, with stage III or IV disease in 70%.[255] Although toxicities to important critical structures may be manipulated, this may come at the expense of increased skin toxicities,[258] as a result of increased radiation dose resulting from multiple complex beam arrangements that expose more normal tissue that would otherwise have been excluded with conventional techniques. It is this observation that has led to concerns regarding potential long-term adverse effects and a call for prudence in the application of IMRT.[259]

POSTOPERATIVE RADIOTHERAPY. The indications for postoperative radiotherapy (PORT) may follow a risk-stratification paradigm that identifies patients as low, intermediate, or high risk for local-regional relapse, based on the absence, presence of one, or presence of two or more risk factors, respectively (Fig. 72-11). These risk factors include: oral cavity primary, mucosal margins close or positive, nerve invasion, more than one positive lymph node, more than one positive nodal group, largest node greater than 3 cm, and treatment delay longer than 6 weeks.[161,162] In addition, the presence of nodal extracapsular extension by itself placed patients in the high-risk group.[162,163] Although no randomized trial exists to demonstrate

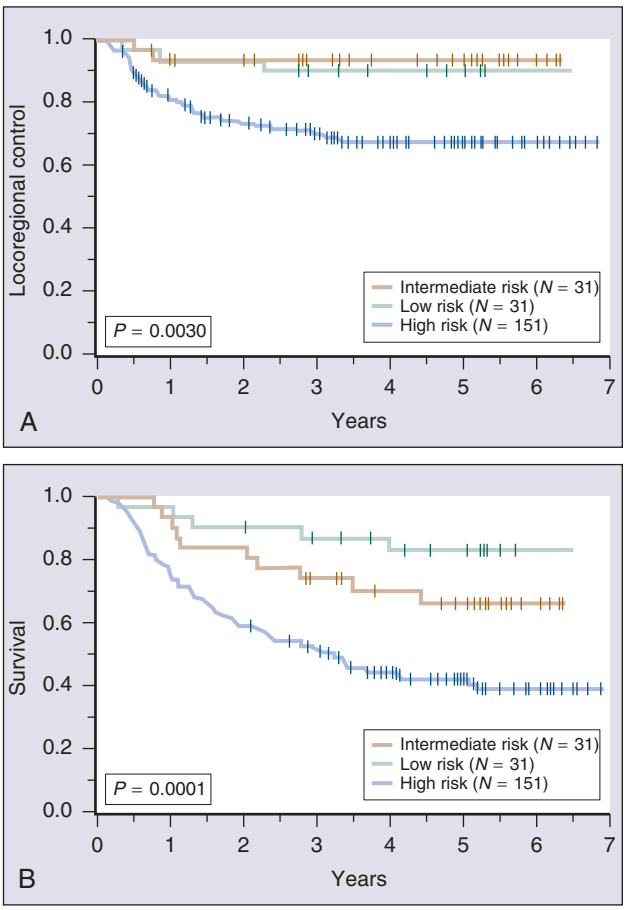


Figure 72-11 • Actuarial local-regional control rates **(A)** and overall survival **(B)** by postoperative risk stratification. (Ang KK, Trotti A, Brown BW, et al: Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571–578.)

the efficacy of postoperative radiotherapy, Ang and colleagues demonstrated in a prospective trial in patients with an intermediate risk of relapse a local-regional control rate (greater than 90%) comparable to that in patients with no adverse risk factors, deemed to be low risk, and not subjected to PORT (see Fig. 72-11).[161] The overall survival for the intermediate group appeared to be inferior to that for the low-risk group; nevertheless, PORT continues to be recommended owing to the importance of local-regional control.

Peters and colleagues previously reported on a dose-finding randomized trial demonstrating that a minimum tumor dose of 57.6 Gy to the whole operative bed should be delivered, with a boost of 63 Gy to sites of increased risk, especially regions of the neck in which extracapsular nodal disease is present.[162] These investigators did not find any benefit with dose escalation above 63 Gy at 1.8 Gy per day and postulated that this might be offset by tumor repopulation. Accordingly, Ang and colleagues recently reported the results of a multi-institution prospectively registered trial of 288 patients with HNSCC deemed to require PORT.[161] Of these 288 patients, 151 patients were stratified as high-risk and subsequently randomized to receive radiation therapy in either a conventionally fractionated schedule or an accelerated schedule using the delayed concomitant boost technique, with a total dose of 63 Gy delivered in each arm. These investigators report in this mature trial a nonsignificant trend for higher local-regional control ($P = 0.11$) and survival ($P = 0.08$) in favor of the accelerated schedule that appeared to result from an underpowered sample size (Fig. 72-12). Acute confluent mucositis (62% versus 36%) was significantly greater in the experimental arm as would be expected. The actuarial probability of a patient sustaining one or more late complications between the two fractionation schedules ($P = 0.94$) did not significantly differ between the two arms. These investigators therefore concluded that the benefits of an accelerated PORT schedule had not been definitively established, but comment that, in practice, an accelerated PORT schedule may be used to keep the overall treatment time to less than 11 weeks in unavoidable situations where there has been protracted time before PORT. The latter follows from the demonstration of a significant adverse impact on both local-regional control and survival rates when analyzed by the overall treatment time (Fig. 72-13). These results must be interpreted with caution, however, as the study design did not stratify by the time interval before starting PORT.

Care should be exercised in the use of an accelerated schedule as concern has also been raised of a possible increased risk of late toxicities in the postoperative setting.[260] Rather, patients anticipated to require postoperative radiotherapy should be appropriately identified with the appropriate arrangements made for the patient so as to prevent unnecessary interruptions to starting PORT. In a prospective comparative trial with a median follow-up period of 6 years Trotti and colleagues demonstrated that patients initiating PORT within 4 weeks had a significantly lower rate of crude in-field relapses (seen in 0 of 10 versus 10 of 32).[260]

It has also been proposed that the integration of chemotherapy with postoperative radiotherapy be favored in light of the increased risk of distant relapses also observed in the high-risk group. Ang and colleagues noted a 5-year actuarial distant relapse rate of 33% (versus

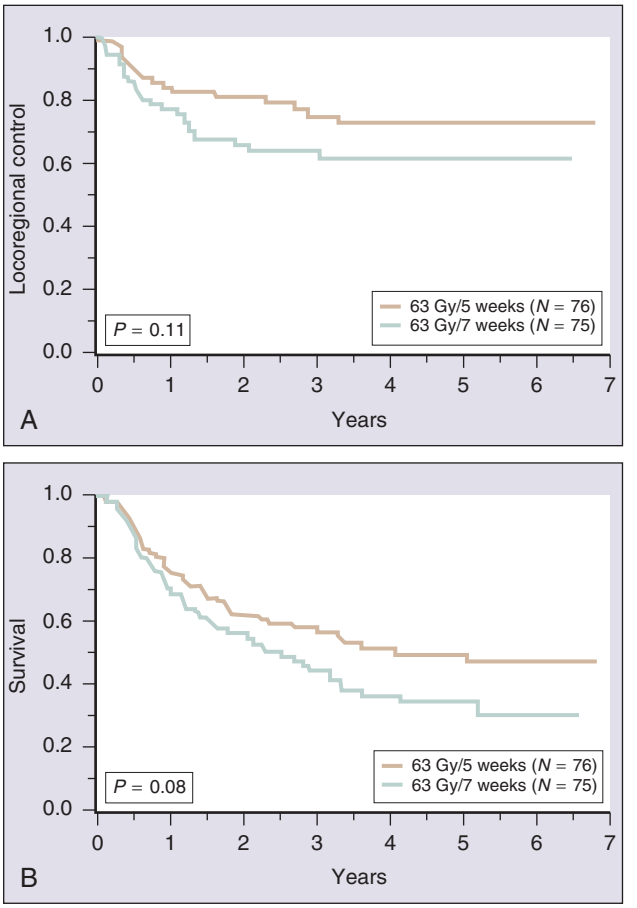


Figure 72-12 • Actuarial local-regional control rates **(A)** and overall survival **(B)** for high-risk patients according to the postoperative radiotherapy fractionation schedule. (Ang KK, Trotti A, Brown BW, et al: Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571–578.)

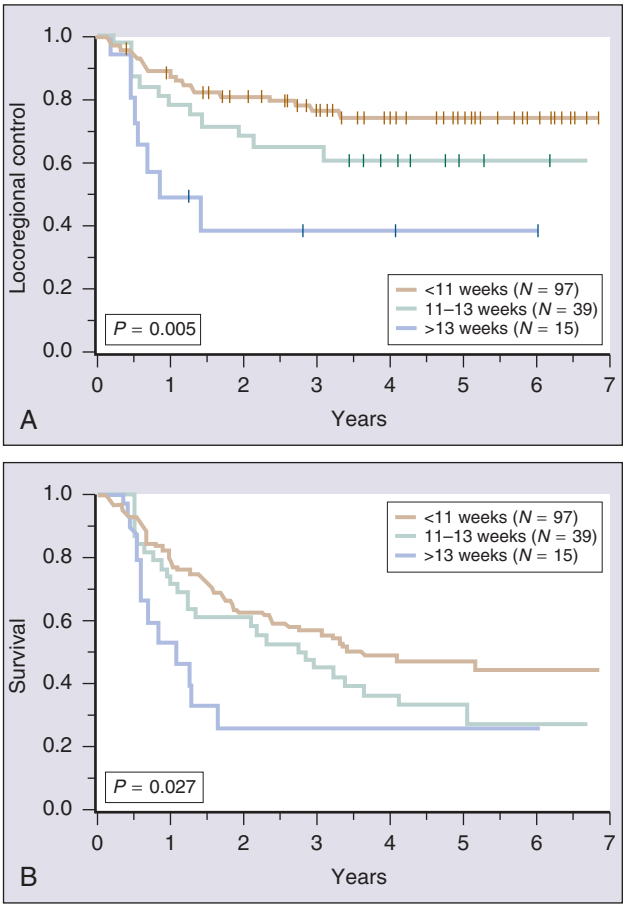


Figure 72-13 • Actuarial local-regional control rates **(A)** and overall survival **(B)** for high-risk patients according to the overall treatment time (from the time of surgery to the completion of radiotherapy). (Ang KK, Trotti A, Brown BW, et al: Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571–578.)

3% in the low-risk group). Although attractive, this remains an active area of investigation with no established chemoradiotherapy regimen. Two randomized trials of postoperative chemoradiotherapy with concurrent cisplatin and daily fractionated radiotherapy have been reported.[261,262] Bachaud and colleagues reported the results of a randomized trial prematurely closed due to poor patient accrual, demonstrating improved local-regional control rate, disease-free survival, and overall survival with weekly concurrent cisplatin. Only 88 patients with stage III or IV disease with the presence of extracapsular extension were were accrued, however, so the authors suggest that these results require validation in a larger study. Recently, the RTOG presented the preliminary results of a randomized trial of 459 patients with high-risk postoperative features including extracapsular extension receiving radiotherapy or radiotherapy and bolus cisplatin on weeks 1, 4, and 7 (RTOG 9501).[262] Modest improvement in local-regional disease control and disease-free survival (54% versus 43%; $P = 0.049$) in favor of the chemoradiotherapy arm, with no difference in overall survival, was reported.

Several institutional retrospective reports have suggested that the addition of a brachytherapy implant to postoperative radiotherapy when surgical margins are positive or close may improve the local control rates for a mixture of tumor sites.[263–267] This strategy may be particularly attractive for management of early oral cavity lesions, for which the risk of nodal metastasis is low, thereby avoiding the morbidity associated with EBRT. Site-specific indications for the floor of the mouth[263] and the oral tongue[264] have been reported. Pernot and colleagues reported a 5-year local control rate of 89% for 97 patients who received either postoperative EBRT followed by an implant or brachytherapy with an implant alone for oral cavity tumors.[265] Self-resolving grade 1 and 2 complications occurred in 19% and 12%, respectively, with only 6% of complications requiring surgical intervention (grade 3). These results are particularly promising in light of the fact that one third of the patients who received this treatment had T3 and T4 lesions. Accordingly, this therapeutic may be considered when the surgical margin of concern can be located and when experience exists for the safe administration of the implant.

BRACHYTHERAPY. Brachytherapy has a significant role in the management of head and neck squamous cell carcinomas[268,269] with various techniques described.[270] Owing to the unique physical properties of this region, treatment morbidity is minimized as a result of reduced irradiation in the surrounding normal tissues. An implant may be used in the definitive setting for several tumor sites including the tonsil and soft palate,[271–276] oral tongue,[277–280] base of tongue,[281–288] and lip.[289,290] The use of an implant in the base of tongue has the advantage of being a functional organ-preserving treatment strategy validated with quality of life instruments,[291,292] with the results suggested to be superior to those achievable with EBRT alone and comparable with those for surgery with PORT.[284] It may be used as an alternative to surgery for selected cancers of the floor of mouth in specific circumstances. In early-stage lesions, for which the risk of nodal metastases is low, brachytherapy may be employed definitively or in an adjuvant fashion after surgery. In more advanced lesions, it often is combined with external irradiation of the head and neck. The ability to provide specific high local irradiation also permits the selective use of brachytherapy in the setting of recurrent[293,294] or second HNSCC occurring within a previously irradiated region.[295]

Appropriate application of a brachytherapy implant begins with patient selection. This process requires assessment of the patient's understanding and ability to comply with the inherent radiation precautions associated with brachytherapy implants, especially for continuous low dose rate (LDR) implants. Patients should be selected for their ability to provide for their baseline self-care needs, in addition to the treatment-related needs such as the care of a tracheostomy, nasogastric feeding tube, and patient-controlled analgesic pump as indicated. Patients subject to periods of confusion and disorientation may not be suitable for this mode of therapy.

Several considerations influence the decision of a permanent or a temporary implant. Permanent implants, emitting radiation over the lifetime of its radioactivity, use sources that provide LDR irradiation. Suboptimal placement of a permanent implant and the potential adverse dosimetric effects of organ swelling and movement pose potential risks for an unfavorable therapeutic ratio. A permanent implant affords the delivery of a very high total dose delivered, however, and may be advantageous when implanting complex and irregular surfaces not amenable to placement of temporary catheter-based implants where chinking of the catheters is a significant risk. The judicious use of permanent sources with low-energy photons, such as iodine 125 (^{125}I), may be advantageous when critical normal structures, such as the spinal cord, are adjacent to the implant.

Temporary implants more commonly are applied in the head and neck because they permit a more deliberate and accurate placement of the implant applicator system without the radiation exposure concerns that occur with a permanent implant. Typically, nylon catheters are placed, approximating the desired position of the radioactive sources, which then may be subsequently afterloaded with LDR radioactive seeds embedded at defined positions within a nylon strand. This technique affords optimization of the implant dosimetry after placement of the implant applicator system. Commonly, this has involved obtaining orthogonal plain x-ray films of the implant with dummy seeds placed within the selected applicator system, with digitization of the relative seed positions into a treatment planning software. Variations in the activity, number of radioactive sources, and loading duration and, for high dose rate (HDR) computer-

guided remote afterloading systems, variations in the dwell time and position allow for dosimetric optimization. Optimization cannot obviate the adverse dosimetry associated with poor implant geometry, however.

Temporary LDR implants also offer several radiobiologic advantages, including a reduced treatment time, the capability to irradiate a potentially less hypoxic tumor bed early in the postoperative period, a reduced adverse influence of hypoxia itself, and exploitation of cell cycle-specific radiosensitization. These implants further exploit the differential repair capacities between tumor and normal tissues, reducing the risk of normal late complications. The risk of radiation exposure to personnel, however, necessitates good source-handling skills and strict radiation precautions. Alternatively, HDR sources with computer-guided remote afterloading significantly reduce the exposure risks and required precautions. Fractionated radiotherapy is delivered with a single iridium 192 (^{192}Ir) source fixed to the end of a cable wire that may be variably stepped along the length of each catheter. HDR implants confer greater flexibility in conforming the implant dosimetry to the target volume, yield a relatively more homogeneous dose distribution to those of LDR implants, and, because the delivery of the radiation occurs over a shorter time period, are less subject to the effects of organ movement. These advantages may yield a lower complication rate as a result of this precise geometric sparing. Concerns remain, however, with regard to the risk of increased late complications from the higher dose rate of radiation.[296] This has prompted ongoing studies to define the optimal fractionation schedules to reduce this risk. Several other promising but investigational techniques include the use of pulsed dose rate (PDR) radiation, which has been studied as a technique to exploit the logistical advantages and reduced radiation exposure of remote afterloading and the LDR biologic advantages that may be expected with this technique.[268,297,298] HDR intraoperative radiation therapy (HDR-IORT) remains a promising investigational technique that has the advantage of accurately delivering radiation to the areas at risk for tumor recurrence potentially at a time when the tumor burden is the lowest.[299]

Chemotherapy

GENERAL. The role of chemotherapy in the primary treatment of locally advanced disease became more prominent in the 1970s due to the poor outcome of stage III and IV disease treated with surgery or radiation, or both. Definitive treatments with chemotherapy emerged in nasopharyngeal cancer and in organ preservation protocols for the larynx,[193] the hypopharynx,[192] and, most recently, the oropharynx.[300] Systemic chemotherapy continues to have a role for palliation in patients with locally advanced-stage disease, locally recurrent disease beyond salvage techniques such as surgery, and metastatic disease.

PROGNOSTIC FACTORS. The decision to treat with chemotherapy remains dependent on various factors that can contribute to response. Those factors include the patient's performance status, nutritional status, the tumor burden and extent, disease stage, degree of tumor differentiation, and primary cancer site.[192,301–303]

NEOADJUVANT AND INDUCTION CHEMOTHERAPY. Over the last 10 to 15 years, approaches to the treatment of patients with stage III and IV disease began to include the use of chemotherapy as induction therapy before planned surgical resection and, more recently, before radiotherapy. The concept of induction chemotherapy arose from several principles. It has been postulated that chemotherapy may promote regression of tumor, enhancing local-regional therapy through sensitization, and also may identify patients who may be candidates for a more conservative surgical approach as the need for improved quality of life through functional preservation has arisen. Thus, organ preservation, rather than extensive, potentially morbid surgical procedures, came into vogue as a philosophical consideration in the management of advanced-stage disease. An additional attractive feature with this approach was the conceptual ability to treat micrometastatic disease in hopes of reducing distant failure rates, which can be 40% or greater with conventional local-regional surgical/radiation approaches. Finally, it was felt that the use of chemotherapy before the tumor and vascular bed are altered by surgery or irradiation may improve the ability to identify responding tumors for which adjuvant chemotherapy may be beneficial.

Nonrandomized phase II trials in the 1970s used single-agent chemotherapy based on strategies used in the recurrent and metastatic setting. These single-agent trials reported 30% to 40% response rates.[304] Induction strategies subsequently involved multiple chemotherapy regimens. The first reported trials by Wittes and colleagues[304] showed a 71% response rate with complete responses noted in 21% of patients using cisplatin and continuous infusion bleomycin in 21 patients. Other studies followed, using cisplatin/bleomycin with other drugs such as hydrea and revealing increased toxicity with no improvement in response rates or survival.[305] Investigators from Wayne State University reported the first trial using neoadjuvant cisplatin with infusional 5-fluorouracil, with an overall response rate of 88% and a complete response rate of 54%.[306] The investigators reported that 120-hour infusional 5-fluorouracil showed improvement over 96-hour infusions and that complete response rates after three total cycles were double those achieved after two.[305–307] More recent studies appear to confirm that complete response rates will increase after three to five cycles; other studies have confirmed the activity of this combination but at varied response rates (38% to 100%) and complete response rates (13% to 54%).[308,309] A 38% complete response rate also was achieved by the RTOG.[310] Numerous other combinations reported have included high-dose cisplatin with fixed-dose 5-fluorouracil, high-dose 5-fluorouracil with fixed-dose cisplatin, intra-arterial cisplatin, and additional drugs, such as bleomycin, cyclophosphamide, mitoguazone, taxanes, and methotrexate, have been given with the cisplatin plus 5-fluorouracil regimen, with significant toxicity and no overall difference in response or survival.[307,310–312] Trials using carboplatin with 5-FU have shown similar response rates of 70% to 80% and complete response rates of 30% to 40%, which are similar to those with cisplatin plus 5-fluorouracil.[313]

Although these experiences with chemotherapy plus irradiation included several randomized trials with neoadjuvant chemotherapy, many were characterized by methodological problems. In 1985, the increasing interest in laryngeal preservation coupled with disappointing experiences with upfront radiotherapy for advanced disease, laid the foundation for the Veterans Affairs Cooperative Studies Program (VACSP) to initiate a multi-institutional randomized trial of neoadjuvant chemotherapy as an organ preservation strategy.[193] Patients with previously untreated, locally advanced but potentially resectable stage III (T2-3N1 or T3N0) or stage IV (T1-3N2-3 or T4N0-1) disease of the supraglottic or glottic larynx were randomized either to receive neoadjuvant chemotherapy or to undergo surgical resection (Fig. 72-14). The chemotherapy regimen was cisplatin (CDDP) with continuous-infusion 5-fluorouracil for 5 days with response after 2 cycles used to stratify patients to either continue with an additional cycle of chemotherapy followed by radiotherapy or, for nonresponders, salvage surgery followed by postoperative radiotherapy. In total, 332 patients were enrolled: 216 patients with T3, 85 with T4, and 240 patients with N0-1 disease. Laryngeal preservation was achieved in 64% of patients enrolled in the chemotherapy arm. The local failure rate was significantly higher in the chemotherapy plus irradiation arm, but the distant failure rate was significantly lower in this arm. The long-term overall survival rate was approximately 30% in each arm. On subset analysis, sequential chemotherapy plus irradiation was less effective in the T4 tumors or those with N2 or greater disease; 50% of these patients required salvage laryngectomies. Although this trial demonstrated that laryngeal conservation was achievable in 64% of

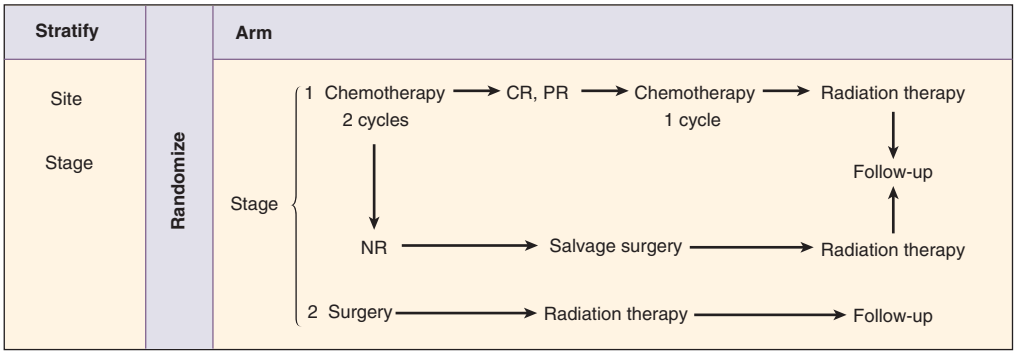


Figure 72-14 • Study schema of Veterans Affairs larynx preservation trial. CR, complete response; NR, no response; PR, partial response. (From Department of Veterans Affairs Laryngeal Cancer Study Group: N Engl J Med 1991;324:1685–1690.)

patients with advanced laryngeal carcinoma, the incremental role neoadjuvant chemotherapy contributed to this is unclear. This laryngeal preservation rate appears to be comparable to the results achieved with radiotherapy alone followed by salvage surgery, which ranged from 50% to 73%.[191,197] The value of neoadjuvant chemotherapy has also been questioned as only a subset of patients with advanced laryngeal cancers had chemoresponsive tumors.

These results subsequently were approximated in a similar randomized trial conducted by the EORTC.[192] The EORTC randomized a smaller population of 194 patients with locally advanced hypopharyngeal cancer (6% with stage II, 57% with stage III, and 37% with stage IV) to receive either cisplatin plus 5-fluorouracil or total laryngectomy, partial pharyngectomy or radical neck dissection with adjuvant radiation therapy. Only patients who achieved a complete response received radiation alone; 54% had a complete response at the primary site, 51% at the nodal site, and 43% achieving a complete response both at the primary and nodal site. Treatment failures at the local, regional, and second primary sites occurred at approximately the same frequencies in the immediate surgery arm (12%, 19%, and 16%, respectively) and in the induction chemotherapy arm (17%, 23%, and 13%, respectively). By contrast, there were fewer failures at distant sites in the induction chemotherapy arm than in the immediate surgery arm (25% versus 36%, respectively; $P = 0.041$). The median duration of survival was 25 months in the immediate surgery arm and was 44 months in the induction chemotherapy arm, which the investigators concluded were equivalent. The 3- and 5-year estimates of retaining a functional larynx in patients in the induction chemotherapy group were 42% (95% CI, 31% to 53%) and 35% (95% CI, 22% to 48%), respectively. It would appear that with a more stringent response to chemotherapy, fewer local relapses may be anticipated, in contrast with the results of the VA study.[193]

Recently, a French Cooperative trial (GETTEC) reported the randomized results using a neoadjuvant chemotherapy approach for organ preservation for the oropharynx site.[300] Patients with a squamous cell carcinoma of the oropharynx for whom curative radiotherapy or surgery was considered feasible were randomized to undergo either three cycles of neoadjuvant chemotherapy, followed by local-regional treatment determined by the treating physician, or the same local-regional treatment without chemotherapy. The local-regional treatment consisted either of surgery plus radiotherapy or of radiotherapy alone. The chemotherapy regimen consisted of cisplatin (100 mg/m^2) on day 1, followed by a 24-hour intravenous infusion of fluorouracil (1,000 mg/m^2 per day) for 5 days delivered every 21 days. A total of 318 patients were enrolled in the study between 1986 and 1992; the study was prematurely closed as a result of a loss of clinical equipoise, because the treating physicians believed that neoadjuvant chemotherapy was efficacious. The investigators note, however, that this decision was independent of any knowledge of the trial results, minimizing the impact of any bias. Overall survival was significantly better ($P = 0.03$) in the neoadjuvant chemotherapy group than in the control group, with a median survival of 5.1 years versus 3.3 years in the no chemotherapy group. The effect of neoadjuvant chemotherapy on event-free survival was less and of borderline significance ($P = 0.11$). In summary, it is clear that systemic chemotherapy can have an impact on the risk of distant relapses, with possible improvements in overall survival.

The preceding studies led to the more recent intergroup trial, RTOG 9111, conducted in patients with stage III or IV resectable disease of the larynx.[198] Patients were randomized to three treatment groups: chemotherapy (cisplatin plus 5-fluorouracil) followed by radiation therapy; concurrent chemoradiation therapy with high-dose cisplatin as the radiosensitizer; or standard fractionated EBRT daily. Patients with T4 lesions were not included in this trial. If a patient initially had N2 or N3 neck disease, a modified neck dissection was performed independent of response. Two-year laryngectomy-free survival was superior in the group of patients receiving concurrent chemoradiotherapy ($P = 0.018$), reducing the number of laryngectomies performed by approximately 50%, with the number of laryngectomies performed identical in the other two treatment arms (43 versus 21 versus 49, respectively). Two-year local-regional control rates were also superior in the concurrent chemoradiotherapy arm (61%, 78%, and 56%, respectively), with the overall survival (approximately 75%) not differing among the treatment arms.

Efforts continue to improve on the clinical efficacy of neoadjuvant chemotherapy in hopes of achieving significant activity to yield consistent survival benefits.[314] Recent strategies have focused on the use of neoadjuvant chemotherapy followed by concurrent chemoradiotherapy. Various phase II studies[187,301,315–318] have been reported. These also include variations of the "gold standard" chemotherapy regimen, cisplatin and 5-fluorouracil, incorporating leucovorin rescue (Platinol-fluorouracil-leucovorin [PFL] regimen), with or without interferon-α, efforts pioneered by Vokes and colleagues in Chicago.[301,317] A recently completed Eastern Cooperative Oncology Group (ECOG) phase II trial of neoadjuvant carboplatin and paclitaxel followed by concurrent weekly paclitaxel and daily-fractionated radiotherapy for oropharynx carcinomas included functional swallowing assessments as a measure of functional preservation. This trial follows from promising preliminary data reported by Machtay and colleagues, who noted a major clinical response rate of 89% after induction chemotherapy, with a 90% complete response rate after concomitant chemotherapy.[187] The 3-year survival and 3-year progression-free survival rates were 68% and 60%, respectively. Local-regional control was 82%, and the 3-year distant failure rate was reported at 18%. Organ preservation was achieved in 77% of all patients. In general, increased toxicities have been observed in these trials with promising activity that will require study in the context of a randomized trial. These strategies offer the promise of not only improved local-regional control rates with organ preservation but also a reduced risk of late distant relapses and more consistent improvements in overall survival. Recent results from a large patient-based meta-analysis, however, have drawn attention to the potential

negative effects of neoadjuvant chemotherapy when used as a larynx preservation strategy, because a nonsignificant hazard ratio of death (1.19; range, 0.97 to 1.46) was noted.[181]

CONCURRENT AND CONCOMITANT CHEMORADIOTHERAPY. A significant body of literature exists, including numerous randomized trials of concurrent chemotherapy that have been systematically summarized by several investigators.[181,319–321] These independent reviews have consistently favored the concurrent integration of chemotherapy. Pignon and colleagues reported the largest and recently updated of these meta-analyses.[181] This patient-based meta-analysis of more than 10,000 patients derived from 63 randomized trials confirmed an absolute survival benefit of 4% at 2 and 5 years, with the greatest benefit of 8% observed in the group receiving concurrent chemotherapy. The group that contributed to this survival benefit was found to be the group of studies that used radiotherapy as the local-regional treatment. The survival benefit was found to be significantly greater with multiagent versus single-agent concurrent chemotherapy. A nonsignificant increase in the risk of death was noted with multiagent chemotherapy regimens containing a platinum agent (Fig. 72-15). When results were analyzed with covariants, a significant decreasing benefit on survival for concurrent chemotherapy was noted with increasing age, which may be partly explained by lower compliance and higher toxicities (Fig. 72-16). These results are consistent with anecdotal clinical experiences and highlight the importance of patient selection for concurrent chemoradiotherapy in light of the small incremental benefit. No survival benefit was observed with either neoadjuvant or adjuvant chemotherapy, leading the study investigators to recommend its use only within the context of a clinical trial.

Although concomitant chemoradiotherapy is probably the most promising and feasible approach in locally advanced patients, there remain several issues including the generalizability of these survival benefits to specific subsites, specific chemoradiotherapy regimens, including recent popular taxane-based regimens, and whether or not, differences exist between resectable and unresectable disease. The latter distinction becomes important, because concurrent chemoradiotherapy has emerged as a popular strategy to achieve functional organ preservation.[198] Because the addition of concurrent chemotherapy increases mucosal toxicity and poses the potential of adversely affecting swallowing function,[187,199] if the survival benefits, particularly with multi-agent regimens, are generalizable to those patients with resectable disease, compromises in organ function may result. Even if survival benefits are not observed, multi-agent regimens may still be preferred, as recently noted by Adelstein and associates.[135] In their mature report of 100 patients with resectable HNSCC at various tumor sites, improved local-regional control rates without surgical salvage (77% versus 45%; $P < 0.001$), although with no survival benefit, were observed with concurrent chemotherapy (both 5-fluorouracil [1000 mg/m^2 per day] and cisplatin [20 mg/m^2 per day] given as a continuous intravenous infusion over 4 days beginning on day 1 and again on day 22). Successful primary salvage surgery was possible in 73% of cases, which contributed to the absence of any demonstrable survival benefit.

Although concurrent chemoradiotherapy has been studied in patients with stage III and IV HNSCC, often without selection for resectability, it becomes important to recognize the narrowed therapeutic ratio in its application.[184] In this regard, the relative efficacy of altered fractionated radiotherapy schedules is an important consideration, because the randomized trials establishing their efficacy have used comparable selection criteria. To date, limited randomized data exist comparing conventionally fractionated radiotherapy with concurrent chemotherapy with altered fractionated radiotherapy. Olmi and colleagues recently reported the results of a three-arm multi-institutional randomized trial of concurrent chemoradiotherapy versus altered fractionated radiotherapy versus conventionally fractionated radiotherapy alone.[322] These investigators randomized 192 patients with previously untreated, stage III and IV oropharyngeal carcinoma (excluding T1N1 and T2N1) to undergo one of three therapy regimens described as arms A, B, and C: for arm A, conventionally fractionated radiotherapy to a dose of 66 to 70 Gy in 33 to 35 fractions, 5 days a week over 6.5 to 7 weeks; for arm B, altered fractionated radiotherapy to a dose of 64 to 67.2 Gy, in two fractions of 1.6 Gy every day, with an interfraction interval of at least 4 hours and preferably 6 hours, 5 days a week with a 2-week split at 38.4 Gy, with radiotherapy resumed at the same fractionation after the split (arm B); or for arm C, chemotherapy in a regimen consisting of carboplatin and 5-fluorouracil (CBDCA 75 mg/m^2, days 1 to 4, plus 5-fluorouracil 1000 mg/m^2 given by intravenous infusion over 96 hours, days 1 to 4, every 28 days [at weeks 1, 5, and 9]), plus radiation therapy using the same daily fractionation schedule as described for the standard arm (arm A). No significant differences were detected in overall survival ($P = 0.129$): 40% of patients in arm A, 37% of those in arm B, and 51% of those in arm C were alive at 24 months.

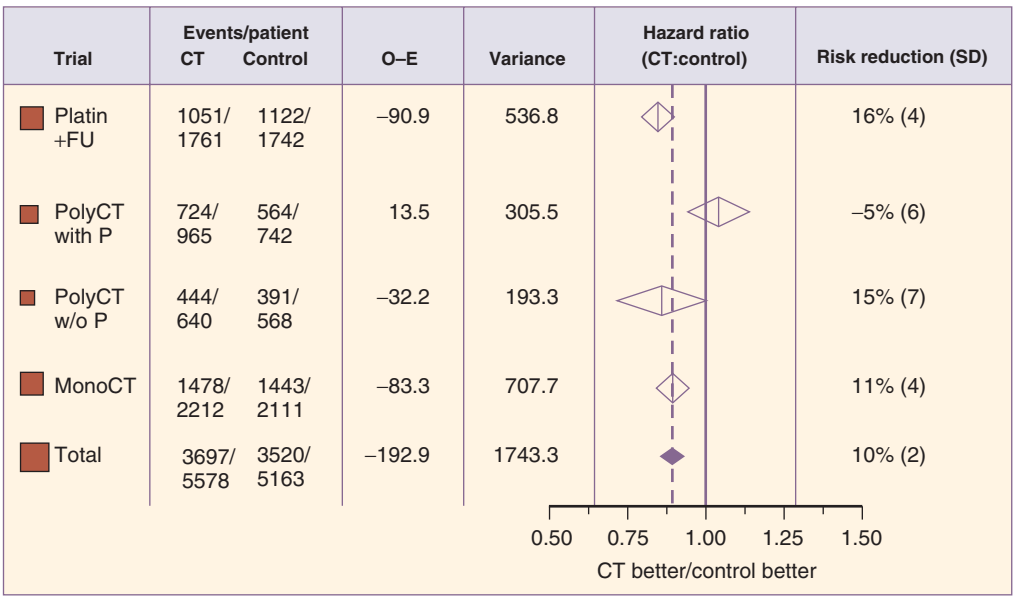


Figure 72-15 • Hazard ratio of death with local-regional treatment plus chemotherapy (CT) with local-regional treatment by chemotherapeutic regimen: Platin (cisplatin or carboplatin) + fluorouracil (FU), combination CT with platin (polyCT + P), combination CT without platin (polyCT w/o P), single-agent CT (monoCT) including platin. Test for heterogeneity between types of chemotherapy ($P = 0.02$). (From Pignon JP, Bourhis J, Domenge C, Designé L: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Lancet 2000;355:949–955.)

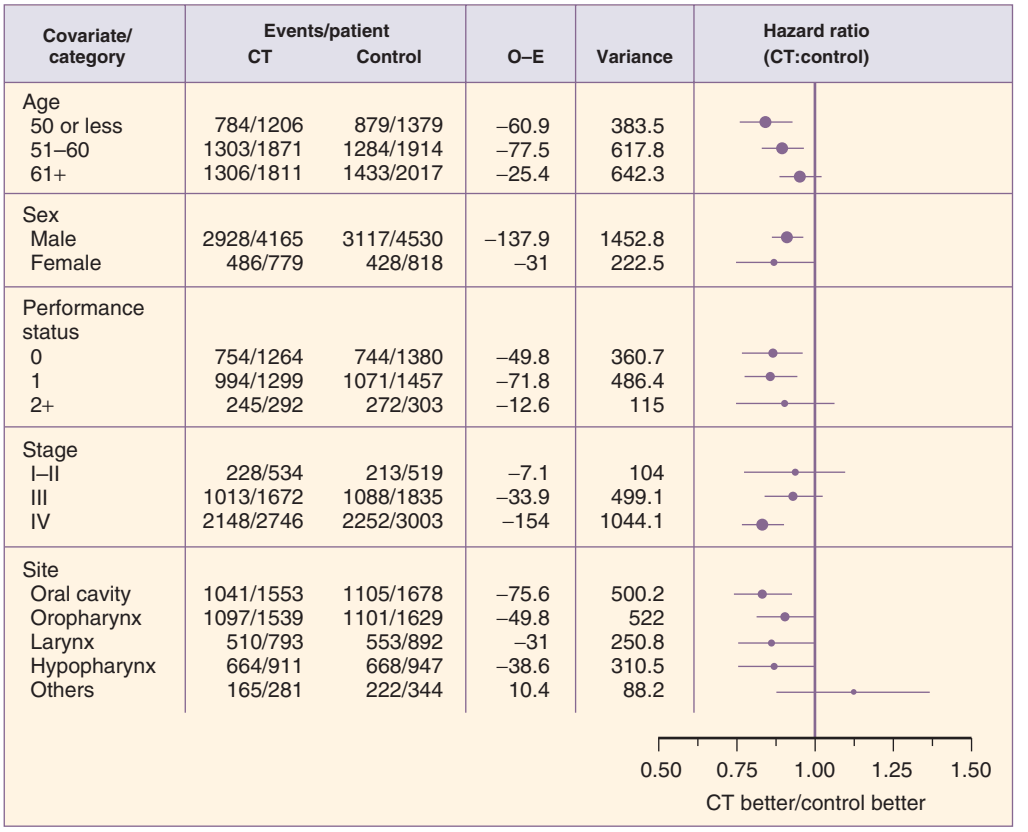


Figure 72-16 • Hazard ratio of death with local-regional treatment with or without chemotherapy (CT) by age, sex, performance status, stage, or tumor site. Test for trend for age was significant ($P = 0.05$). (From Pignon JP, Bourhis J, Domenge C, Designé L: Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Lancet 2000;355: 949–955.)

The 2-year disease-free survival rates, however, were significantly different among the three arms ($P = 0.022$), with the highest rate in the chemoradiotherapy arm. At 24 months, the proportion of patients without relapse was 42% for arm C, 23% for arm A, and 20% for arm B. Increased grade 3 skin and mucosal toxicities were noted in the concurrent chemoradiotherapy arm and the altered fractionated schedule. A suggestion of increased late skin and mucosal toxicities was noted in the chemoradiotherapy arm. Nguyen and Ang also have favored concurrent chemoradiotherapy in patients who are able to tolerate the increased toxicity, particularly in the setting of advanced T3 or T4 primary disease or in patients with advanced N2 or N3 neck disease, stratifying patients with T2 or exophytic T3N1 disease to altered fractionated radiotherapy.[183]

Multi-agent regimens continue to be favored over single-agent regimens owing to concerns of late distant failures that have become more evident with improved local-regional management. A favorable effect for many multiagent regimens on the risk of distant relapses, however, remains to be clearly established.[178,323] A reduced risk of distant relapse has been suggested in several reports[135,324] and may indicate that the local-regional therapy is effective in addressing micrometastases, but control of the local-regional disease is necessary for this benefit to manifest. Accordingly, significant interest has been focused on the incorporation of altered fractionated radiotherapy schedules with concurrent chemotherapy (Table 72-7). In total, six randomized trials have been reported and may be characterized by the type of altered fractionation used.[212,241,323–326] In the trials combining an accelerated schedule, acute mucosal toxicities were significantly increased, with two trials demonstrating unacceptable toxicity,[241,326] one of which included a high rate of chronic swallowing dysfunction.[326] Jeremic and colleagues reported an improved 5-year local-regional control rate (50% versus 36% at 5 years; $P = 0.041$), 5-year overall survival (46% versus 25% at 5 years; $P = 0.0075$), and distant metastasis-free survival (86% vs. 57% at 5 years; $P = 0.0013$) with the concurrent administration of daily cisplatin (6 mg/m^2) with a hyperfractionated schedule delivering 77 Gy as 1.1 Gy twice daily in 70 fractions over 7 weeks compared with this same hyperfractionated schedule alone.[324] No significantly increased acute or late toxicities were reported. This remains a promising aggressive regimen that requires further validation of the concept of daily radiosensitization with an altered fractionation schedule. Finally, both 5-fluorouracil and cisplatin with or without leucovorin have been administered concurrently with a split-course schedule. Wendt and colleagues demonstrated improved local-regional control rates with an accelerated split-course schedule with concurrent bolus schedule of cisplatin, 5-fluorouracil, and leucovorin, but the results were overall disappointing (36% versus 17%; $P = 0.004$).[323] A significant reduction in the total dose was used. Brizel and colleagues administered concurrent cisplatin and 5-fluorouracil with a split-course hyperfractionated schedule of 1.25 Gy twice daily over 47 days with a 7- to 10-day treatment interruption after 40 Gy.[212] Improved local-regional control rates with no difference in overall survival were noted, with increased risk of sepsis and enteral feeding noted in the experimental arm. To date, the generalizability of any of these regimens is limited not only by the increased toxicity, but also by the intensive resources required on the part of the treating team and the patients.

POSTOPERATIVE AND ADJUVANT CHEMOTHERAPY. The use of postoperative adjuvant chemotherapy in patients at high risk for local and regional recurrence from HNSCC remains under evaluation.[181] Patients with two or more positive regional nodes, extracapsular extension of disease, positive resected margin, or perineural or perivascular invasion are considered to be in a high-risk category. Ang and colleagues noted a 5-year actuarial distant relapse rate of 33% (versus 3% in the low-risk group).[161] A comparable level of risk for distant relapses in various chemoradiotherapy series with patients treated nonsurgically has been described ranging from 15%

Table 72-7 Phase III Trials of Concurrent Chemotherapy and Altered Fractionation in Patients with Head and Neck Cancer

Study	Tumor Site and Stage	No. of Patients	Therapy Regimens	Tumor Response	Complications
ACCELERATED FRACTIONATION PLUS CHEMOTHERAPY					
Dobrowsky and Naude, 2000	Various sites, T1-4 N0-3	188	55.3 Gy over 17 days (2.5 Gy on day 1, then 1.65 Gy, twice a day) ± mitomycin; conventional fractionation, 60 Gy over 7 weeks	Combination treatment yielded higher LRC ($P < 0.05$) and survival ($P < 0.03$)	More mucositis than in the combination group but not intensified by mitomycin; late toxic effects not reported
Staar et al, 2001	Various sites, stage III–IV	240	69.9 Gy over 5.5 weeks plus carboplatin (70 mg/m^2 per day) and fluorouracil (600 mg/m^2 per day) for 2 cycles of 5 days; 69.9 Gy over 5.5 weeks (1.8 Gy once daily for 3.5 weeks, then, individual fractions of 1.8 Gy and 1.5 Gy, daily for 2 weeks)	2-year OS, 48% vs 39% ($P = 0.11$); 2-year LC, 51% vs 45% ($P = 0.14$); patients receiving radiochemotherapy had worse LRC	Grade 3–4 mucositis, 68% vs 52% ($P = 0.01$); grade 3–4 vomiting, 8.2% vs 1.6% ($P = 0.02$); late swallowing problems and feeding tube dependency, 51% vs 25% ($P = 0.02$)
Bourhis et al, 2001	Various sites, advanced-inoperable	109	62.64 Gy over 5 weeks plus cisplatin (100 mg/m^2 on days 1, 16, and 32) and fluorouracil (1 g/m^2 on days 1–5 and 31–35); 62–64 Gy over 3 weeks	Not yet reported	Early stopping due to higher number of treatment-related deaths in the combined-treatment group
HYPERFRACTIONATION PLUS CHEMOTHERAPY					
Jeremic et al, 2000	Various sites, stage III–IV	130	77 Gy over 7 weeks plus cisplatin (6 mg/m^2 per day); 77 Gy over 7 weeks (1.1 Gy, twice daily)	5-year LRPFS, 50% vs 35% ($P = 0.04$); 5-year PFS, 46% vs 25% ($P = 0.007$); 5-year DMFS, 86% vs 57% ($P = 0.001$); 5-year OS, 46% vs 25% ($P = 0.008$)	No significant difference in acute morbidity (except for leucopenia, $P = 0.006$) or late toxic effects
SPLIT-COURSE ALTERED FRACTIONATION PLUS CHEMOTHERAPY					
Wendt et al, 1998	Various sites, stage III–IV	270	70.2 Gy over 51 days plus cisplatin, fluorouracil, and leucovorin; 70.2 Gy over 51 days (23.4 Gy in 1.8-Gy fractions, twice daily × 3 cycles with a 10-day break)	3-year LRC, 36% vs 17% ($P < 0.004$); 3-year OS, 48% vs 24% ($P < 0.0003$)	Grade 3–4 acute mucositis, 38% vs 16% ($P < 0.001$); serious late side effects, 10% vs 6.4% (NS)
Brizel et al, 1998	Various sites, T2–4 N0–3	122	70 Gy over 47 days as 1.25 Gy, twice daily (7- to 10-day break after 40 Gy) plus cisplatin and fluorouracil in weeks 1 and 6; 75 Gy over 42 days as 1.25 Gy, twice daily	3-year LRC, 70% vs 44% ($P = 0.01$); 3-year RFS, 61% vs 41% ($P = 0.07$); 3-year OS, 55% vs 34% ($P = 0.07$)	Similar mucositis; increased enteral feeding and sepsis with combination therapy; similar late complications

DMFS, distant metastasis-free survival; LC, local control; LRC, locoregional control; LRPFS, locoregional progression-free survival; NS, not significant; OS, overall survival; PFS, progression-free survival.

From Nguyen LN, Ang KK: Radiotherapy for cancer of the head and neck: altered fractionation regimens. Lancet Oncol 2002;3:698.

to 30%.[135,178,212] Laramore and colleagues reported the results of a randomized trial conducted through the Intergroup (0034), randomizing patients after surgical resection to either three cycles of cisplatin and 5-fluorouracil chemotherapy followed by postoperative radiotherapy (CT/RT) or postoperative radiotherapy alone (RT). Patients were stratified as having either low-risk or high-risk treatment volumes depending on whether the surgical margin was greater than or equal to 5 mm, there was extracapsular nodal extension, and/or there was carcinoma in situ at the surgical margins. Radiation doses of 50 to 54 Gy were given to low-risk volumes and 60 Gy were given to high-risk volumes. A total of 442 patients were analyzable with no difference noted in the overall survival (4-year actuarial survival rate was 44% on the radiotherapy arm and 48% on the chemotherapy plus radiotherapy arm [P = not significant]), 4-year disease-free survival (38% versus 46%, respectively), and 4-year local-regional control rates (29% versus 26%, respectively). The overall incidence of distant metastases, however, was 23% on the radiotherapy arm, compared with 15% on the chemotherapy-radiotherapy arm ($P = 0.03$), again confirming activity as noted in trials employing neoadjuvant chemotherapy, but with no improvement in overall survival as noted in the recently updated meta-analysis reported by Pignon and colleagues.[181] A limited number of other randomized trials have been conducted. These include a small randomized trial of adjuvant chemotherapy for oral cavity lesions reported in abstract only that favored the control arm,[327] and a second trial also limited to the oral cavity that did not demonstrate any improvement in disease-free survival or overall survival.[328]

CHEMOPREVENTION. Retinoids have been increasingly used in the treatment of oral leukoplakia and dysplasia of the head and neck since the 1960s. Studies have been published using retinoids in the treatment of head and neck cancers in conjunction with interferon. 13-*Cis*-retinoic acid also has been looked at in the adjuvant setting. More recently, retinoids have been evaluated in the "preventive" setting after definitive therapy.

A phase I/II study looked at *cis*-retinoic acid, cisplatin, and ifosfamide in patients with advanced or recurrent HNSCC.[329] Patients were given cisplatin at 20 mg/m^2 per day for 5 days every 3 weeks, with *cis*-retinoic acid at 0.5 mg/kg orally for 5 days per week and dose-escalating ifosfamide at 1000 to 1500 mg/m^2. A response rate

of 72% was reported, with median time to progression of 10.4 months and overall survival time of 13 months.

The combination of retinoids and interferons has synergistic effects in modulating proliferation, differentiation, and apoptosis. A German study evaluated 30 patients after treatment for stage IV HNSCC in which adjuvant "chemopreventive" *cis*-retinoic acid and interferon were administered for 6 months.[330] The dose of *cis*-retinoic acid was 0.5 mg/kg per day given orally, and the dose of interferon was 3 million IU per week given subcutaneously. Sixteen patients remained disease free 1 year after definitive treatment. Associated side effects were weight loss, flushing, cachexia, worsening xerostomia, and dysphagia from *cis*-retinoic acid. Interferon side effects were reported as pyrexia and hematologic changes.

Based on the preceding data, a phase II study was conducted in this country using *cis*-retinoic acid, alpha-tocopherol, and interferon as adjuvant therapy in patients receiving definitive treatment for locally advanced HNSCC.[331] Three million units of interferon were given subcutaneously three times weekly with alpha-tocopherol at 1200 IU per day orally and *cis*-retinoic acid at 50 mg/m^2 per day orally for 12 months. Forty-five patients were enrolled; 38 completed the 1-year trial. On follow-up evaluation at a median of 24 months, the local-regional failure rate was 9%, with 5% failing distantly. Median survival at 2 years was reported as 84%. This adjuvant regimen is being tested at the phase III level.

Celecoxib is a novel compound that specifically inhibits the inducible form of the enzyme cyclooxygenase (COX-2) (prostaglandin G/H synthase). Celecoxib is an oral anti-inflammatory agent indicated for the treatment of rheumatoid arthritis and osteoarthritis. Nonsteroidal anti-inflammatory drugs (NSAIDs) and related drugs such as COX-2 inhibitors are attractive candidates for prevention based on recent epidemiologic and case-control studies suggesting that the risk of several malignancies such as colon, esophagus, gastric, and bladder is reduced in chronic NSAID users.[332–336] Many tumors, both human and animal, express elevated levels of COX-2 compared with normal tissue. [337,338] This elevation also is noted in premalignant lesions.[339] In the head and neck area, COX-2 overexpression is seen in oral leukoplakia as well as in squamous cell carcinomas. Increased levels of COX-2 can contribute to carcinogenesis by modulating xenobiotic metabolism, apoptosis, immune surveillance, and angiogenesis. In animal models, selective COX-2 inhibitors suppress the formation of tumors, including tongue cancer. Selective COX-2 inhibitors also can suppress the growth and metastasis of established tumors and enhance the anticancer activity of both radiation and chemotherapy agents. Celecoxib is now being evaluated for efficacy and safety as an adjunct in the prevention of cancer and the prevention of recurrence and metastasis after therapy. Thus, COX-2 inhibition may be a promising strategy to prevent and treat HNSCC.

Targeted Therapy and Novel Approaches

Novel biologic agents have been developed to target multiple specific regions of cancer cells. Protein tyrosine kinases are major components of cell signaling pathways. Various subfamilies of these kinases include receptors for the epidermal growth factor (EGFRs), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor, and hepatocyte growth factor. EGFR is one of four receptors involved in cellular proliferation, differentiation, and survival and is widely expressed in many malignant tissues. EGFR inhibitors such as anti-EGFR monoclonal antibodies, tyrosine kinase inhibitors, ligand conjugates, and antisense oligonucleotides have received significant attention in patients with HNSCC, because the EGFR commonly is overexpressed in 80% to 90% of patients.

EPIDERMAL GROWTH FACTOR RECEPTOR. EGFR–erb-B1 is part of the erb-B family of receptor tyrosine kinases, which includes erb-B2/Her2/neu, erb-B3/Her3, and erb-B4/Her4.[340,341] EGFR is composed of three domains: an extracellular ligand-binding domain, a transmembrane lipophilic region, and an intracellular protein tyrosine kinase domain.[342,343] Endogenous ligands to EGFR include EGF, TGF-α, and heparin-binding EGF. When activated, phosphorylation of the intracellular tyrosine residues results in a cascade of protein phosporylations, resulting in turn in the activation of various downstream signal transduction pathways, including ras/MAP kinase, phosphatidylinositol-3 kinase, and STAT-3. The signal transduction pathway can lead to cell proliferation, tumor growth, and progression of invasion and metastasis signals.[344,345] Based on its overexpression in many cell types (particularly HNSCC cell lines) and the fact that EGFR-based signals can mediate resistance to chemotherapy and radiotherapy, it has been hypothesized that inhibition of EGFR may result in a synergistic antitumor effect.

Numerous EGFR inhibitors have been evaluated, including anti-EGFR monoclonal antibodies, tyrosine kinase inhibitors, ligand conjugates, immunoconjugates, and antisense oligonucleotides. Small molecules such as the tyrosine kinase inhibitors target intracellular tyrosine kinase signaling and inhibit EGFR; antibodies are more directed at the extracellular domain.

IMC-C225 (ImClone Systems, Somerville, New Jersey) is a monoclonal antibody targeting the EGFR and has been studied in several tumor types. In vitro, this antibody appears to enhance the antitumor activity of chemotherapy such as cisplatin (CDDP) and doxorubicin as well as the radiosensitivity of HNSCC cell lines.[346] Similar in vitro data have shown C225 to enhance radiosensitivity.[347,348]

Recent evidence now supports a role for EGFR to mediate a cytoprotective stress response to ionizing radiation. Therapeutically relevant doses of ionizing radiation have been demonstrated to increase expression of EGFR[349] and cytosolic release of TGF-μ from its membrane-bound form,[350] modulate an activated EGFR autophosphorylation profile,[350–353] with increased mitogenic signals involving the MAPK pathway with cellular proliferation,[352,354] and protect from radiation-induced cell death.[350] In a series of experiments with the radioresistant vulva squamous carcinoma cell line A431, inhibition of EGFR with the tyrosine kinase inhibitor tyrphostin AG1478 was associated with reduced MAPK activation and reduced EGFR-mediated tumor cell proliferation.[352] When these findings are taken collectively, it is intriguing to postulate that such a response may serve to mediate the clinical phenomenon of accelerated tumor repopulation during radiotherapy for HNSCC.[152] This hypothesis may be particularly relevant in HNSCC in light of the significant body of clinical data supporting the notion of tumor clonogen repopulation contributing to radiation failure.[179,238]

Early phase I trials of C225 alone and in combination with CDDP were reported. Fifty-two patients were initially treated with dose-escalation of C225 as well as CDDP weekly.[355] C225 was dose escalated to 200 to 400 mg/m^2, but CDDP dosing was found to be optimal only at 60 mg/m^2, owing to toxicity at higher doses. One patient experienced a humoral response. Toxic manifestations included acneiform rashes, gastrointestinal distress, seborrheic dermatitis, flushing, asthenia, and transaminitis. This led to subsequent studies in the metastatic setting.

In a phase I trial, 12 patients with metastatic HNSCC with high levels of EGFR expression were given three doses of C225 with 100 mg/m^2 of CDDP every 3 weeks.[356] Weekly maintenance of C225 was given at 250 mg/m^2. Responses were seen in 67% of the 12 patients enrolled, with minimum toxicity. The specifics for a follow-up study of the use of C225 plus CDDP in patients with recurrent HNSCC were presented at the American Association for Cancer Research (AACR) in 2001. Sixty-three patients were evaluated and given a loading dose of 400 mg/m^2 of C225, followed by weekly maintenance at 250 mg/m^2, plus CDDP at 75 or 100 mg/m^2. The overall response was 24%. Use of C225 by itself has produced response rates of 10%, which is encouraging. ECOG recently compared single-dose CDDP and CDDP plus C225 in a doubleblind randomized trial in patients with previously untreated recurrent or metastatic HNSCC, with 35% to 40% stable disease in both treatment groups.[357]

Anti-EGFR antibodies have radiosensitization properties in cell cultures and preclinical animal studies. A phase I study with C225 and radiation in 16 patients with locally advanced disease (13 with stage IV) was recently reported with an overall clinical response rate of 100% and a complete response rate of 87%.[358] The impressive complete response rate has been interpreted to be consistent with radiosensitization. A multi-institutional phase III trial comparing radiation therapy alone with radiation therapy plus C225 in locally advanced HNSCC has recently closed to accrual with results currently being analyzed.

TYROSINE KINASE INHIBITORS. ZD1839 (Iressa, AstraZeneca Pharmaceuticals LP, Wilmington, Delaware) is a selective EGFR tyrosine kinase inhibitor, recently approved by the U.S. Food and Drug Administration (FDA) as palliative therapy in non-small-cell lung cancer. Preclinically, ZD1839 potentiates the antitumor and apoptotic effects of several cytotoxic agents, including CDDP and taxanes.[359,360] In combination with radiation, ZD1839 shows dose-dependent inhibition of cellular proliferation in human SCC cell lines. ZD1839 also can inhibit tumor angiogenesis in tumor zenograft models in vivo.[348]

Four phase I trials using ZD1839 as monotherapy mostly in patients with prostate, lung, colorectal, ovarian, and head and neck cancer have reported modest toxicity such as diarrhea, nausea and vomiting, transient transaminitis, and rash. Most patients had been heavily pretreated and most were lung cancer patients. The results of the non-small-cell lung cancer monotherapy trial were presented. The overall response rate in 208 patients was 53% and the median progression-free survival rate was 84 days.[361] This study, as well as several other trials, led to recent FDA approval.

The role of ZD1839 as a radiosensitizer is the subject of an ongoing NCI-sponsored multi-institutional trial in combination with a delayed concomitant boost accelerated radiotherapy schedule and with concurrent chemoradiotherapy. The chemoradiotherapy incorporates a weekly cisplatin schedule. The use of oral tyrosine kinase inhibitors may be particularly attractive for its flexible daily dosing schedules. It is hypothesized that this may permit continued arrest of tumor repopulation during any unplanned radiotherapy treatment interruptions. Accordingly, this clinical trial seeks to continue daily dosing of ZD1839 during these unplanned interruptions and during the weekends in light of the provocative positive results with an accelerated schedule that delivered radiotherapy through the weekends.[238]

A phase II trial in recurrent or metastatic squamous cell carcinoma of the head and neck also was recently published.[362] Fifty-two patients who previously received treatment with only one other strategy were allowed to enroll. Patients were given the higher dose of 500 mg per day orally; 250 mg per day is the approved dose based on phase I data in non-small-cell lung cancer. Patients were able to tolerate this drug through feeding tubes. The observed response rate was 10.6%. Median time to progression and overall survival time were 3.4 and 8.1 months, respectively.

OSI-774 (Genetech, San Francisco, California) also is an orally active quinazoline and potent selective inhibitor of EGFR tyrosine kinase. This results in cell cycle arrest at G_1. Phase I studies with OSI-774 were well tolerated, again with toxicities including diarrhea, skin rash, and gastrointestinal upset. OSI-774 in a dose of 150 mg per day has been tested in patients with HNSCC refractory to chemotherapy. In a phase II trial in 114 patients, 13% of patients had a partial response and 29% exhibited disease stabilization.[363] Toxicities were as previously noted and included acneiform rash, diarrhea, nausea, vomiting, headache, and fatigue.

RAS INHIBITORS. It has been suggested that oral cavity cancers have a 27% mutation rate in H-*ras*.[364] Farnesyl transferase inhibitors (FTIs) inhibit a critical enzymatic step in the post-translational modification of ras, allowing the constitutive expression of mutated *ras* genes. Several FTIs are available in the study setting: R115777 (Janssen Pharmaceutica); BMS214662 (Bristol-Meyers Squibb); and SCH66336 (Schering Plough, Kenilworth, New Jersey).

R115777 is a nonpeptidomimetic orally available FTI. Clinically, it can be used alone or in combination with chemotherapy. Toxicity has been minimal. Reversible myelosuppression is the most common dose-limiting toxicity, as well as fatigue, nausea, renal dysfunction, and peripheral neuropathy. A phase I trial using R115777 with irinotecan was reported.[365] Another trial with docetaxel is being conducted, as is a third with gemcitibine.[366,367]

BMS214662 has preferential cytotoxicity against nonproliferating cells. Combination chemotherapy from preclinical human colon cancer cell lines has exhibited synergy with paclitaxel, irinotecan, gemcitabine, and an epothilone analog, BMS247550.[368] Phase I studies are ongoing in advanced solid tumors, including using this drug with CDDP at 75 mg/m^2 every 3 weeks.

p53 TARGETS. As discussed elsewhere in this chapter, p53 mutations occur in 45% to 70% of patients with HNSCC and are associated with continual tobacco and alcohol use.[29,30] p53 is a multifunctional protein that can be induced by DNA damage and plays a significant role in the detection and repair of damaged DNA. P53 can induce apoptosis in severely damaged cells and has been associated with both carcinogenesis and poor prognosis in many cancers, including HNSCC.

ONYX-015 is an E1B-55kD gene-deleted replication-selective adenovirus that replicates and causes cytopathogenicity in certain cancer cell lines.[369,370] Selective intratumoral replication and tumor-selective tissue destruction of ONYX-015 have been demonstrated in phase I and II trials in patients with refractory or recurrent HNSCC.[371,372] Clinical benefit was seen in 15% of patients. A phase II multicenter trial of intratumoral ONYX-015 in combination with CDDP and 5-fluorouracil in patients with recurrent HNSCC was reported.[373] Forty patients received injections, 30 for 5 consecutive days and 10 twice daily for 2 weeks. Responses and stable disease were noted in both groups. Pain was noteworthy in the twice-daily injection group, but otherwise this was well tolerated.

Thus, novel modalities involving molecular targets are actively being investigated. Cytotoxic agents have limited efficacy as demonstrated throughout many sections of this chapter, so targeted therapies may improve treatment in the setting of recurrent and metastatic disease and, eventually, for definitive treatments.

Site-Specific Treatment Considerations

Nasopharynx

The nasopharynx is a cuboidal structure bounded by the sphenoid bone superiorly, the posterior choanae anteriorly, the clivus and the first two cervical vertebrae posteriorly, and the soft palate inferiorly. The eustachian tube enters through the lateral wall, with the posterior portion of the tube being cartilaginous and forming the portion of the lateral nasopharyngeal wall known as the torus tubarus. Just posterior to this is the fossa of Rosenmuller.

The vast majority of malignancies in the nasopharynx are epithelial neoplasms and arise from the lateral wall, particularly from the fossa of Rosenmuller. Local spread may include extension anteriorly through the submucosa including the nasal cavity, laterally and superiorly through the foramen lacerum with cranial nerve involvement, and inferiorly into the oropharynx. Extension into the cavernous sinus commonly results in a sixth cranial nerve palsy. Two cranial nerve syndromes have been characterized. The *petrosphenoidal syndrome* describes involvement of the third, fourth, fifth, and sixth cranial nerves. The *retroparotidian syndrome* describes involvement of cranial nerves IX, X, XI, and XII. Metastatic spread to the adjacent upper cervical lymph nodes and to the retropharyngeal lymph nodes that are located in the retropharyngeal space that lies between the lateral border of the posterior nasopharyngeal wall and medial

to the carotid artery may extend inferiorly to the level of the hyoid bone.

Both the tumor stage and the histologic grade of epithelial malignancies are prognostic. The World Health Organization (WHO) identifies three histopathologic types: type 1, differentiated; type 2, nondifferentiated; and type 3, undifferentiated or lymphoepithelial, which highlights the presence of numerous infiltrating lymphocytes. The presence of keratin is an adverse prognostic feature for local control and overall survival. Other malignancies may include lymphoma, plasmacytomas, melanomas, and, in the pediatric population, juvenile angiofibromas and rhabdomyosarcomas. Approximately 60% to 90% of patients with nasopharyngeal cancer present with palpable adenopathy and up to 50% of patients with involved nodes have bilateral disease.[374–376] Patients with adenopathy at the mastoid tip require exclusion of a malignancy in the nasopharynx due to the characteristic lymphatic drainage pattern from the retropharyngeal space. Staging follows the sixth edition of the AJCC TNM criteria. No modifications have been recommended, including subdivision of the T4 stage that is new to this sixth edition.[137] Both MRI and CT scans are complementary in this tumor site, with the former favored in most cases and the latter beneficial when bone invasion or destruction has occurred.

Because of the anatomic location of the nasopharynx, surgical resection typically has not been recommended owing to the inherent surgical complication rates with surgery in this area, including the inability to achieve tumor-free margins. Accordingly, radiation therapy is the treatment of choice. Fortunately, NPCs are both sensitive and responsive to radiotherapy and chemotherapy, the two principal treatment modalities that are used. For early-stage disease, radiotherapy alone may be used, with excellent results reported, with 3-year overall survival rates ranging from 70% to 100%[374,377–379] and 65% to 100%[374,377–379] for stage I and II disease, respectively, based on the AJCC 1997 staging system. Typical local control rates to current treatments have been summarized by Lee[380]: approximately 80% (72% to 90%) for T1 and approximately 70% (5% to 100%) for T2. Even with locally confined disease (T1), generous initial radiotherapy margins are advised.

Unfortunately, a majority of patients present with locally advanced disease. Local control for T3–4 disease may be expected to be approximately 50% (39% to 72%).[380] For locally advanced-stage III and IV disease, concurrent chemoradiotherapy has emerged as the standard treatment option following from the results of the Intergroup 0099 (IG0099) study reported by al-Sarraf and coworkers.[381] These investigators reported the results for 147 evaluable patients of 193 registered randomized to receive radiotherapy alone or radiotherapy with concomitant cisplatin (100 mg/m^2 given intravenously on days 1, 22, and 43) followed by adjuvant chemotherapy with cisplatin 80 mg/m^2 on day 1 and fluorouracil 1000 mg/m^2 per day on days 1 to 4, administered every 4 weeks for 3 courses. An improvement in the 3-year progression-free survival rate (69% versus 24%; $P < 0.001$) and overall survival (76% versus 46%; $P = 0.001$) was observed on interim analysis, prompting premature study closure. These results are not without debate, however.[380]

Several investigators have questioned whether this positive study may have resulted from inferior outcomes in the control arm rather than a therapeutic effect. Chow and coworkers from the Princess Margaret Hospital recently published the results of a large institutional series using radiotherapy alone administered in a homogeneous manner to 172 patients with advanced-stage disease, demonstrating 5-year disease-free survival and overall survival rates of 48% and 62%, respectively.[382] Although these investigators acknowledge that direct comparisons with the control arm of IG0099 have limited validity, these observations made during a similar time period as the IG0099 provide a context within which the positive results of the IG0099 should be interpreted. In a similar report by Cooper and colleagues, 86 patients with locally advanced disease treated with radiotherapy alone had a 3-year actuarial disease-free survival and overall survival rates of 43% and 61%, respectively.[383] These investigators also observed that in 35 patients undergoing the IG0099 protocol, the projected 3-year disease-free survival and overall survival rates were 63% and 93%, respectively, suggesting benefit. Recently, Cheng and colleagues reported the results for 107 patients with NPC treated with concurrent 5-fluorouracil and cisplatin (weeks 1 and 6) and radiotherapy followed by two cycles of adjuvant 5-fluorouracil and cisplatin. The 5-year overall survival rate, disease-free survival rate, and local-regional control rate were 84.1%, 74.4%, and 89.8%, respectively. The 3-year overall survival rates for stage II, III, and IV were 100%, 92.8%, and 69.4% ($P = 0.0002$), and the 3-year disease-free survival rates were 96.9%, 87.7%, and 51.9% ($P = 0.0001$). Although a confirmatory randomized trial is noted to be under way,[384] the current consensus opinion continues to recommend concurrent chemoradiotherapy. These results further suggest that Asian patients also may benefit from concurrent chemoradiotherapy, which has been questioned owing to geographic differences in the histologic subtype between North America and Asia. A pilot trial of a modified schedule of the IG0099 regimen (reduced cisplatin dose) has been demonstrated to be safe and has given rise to a phase III trial to confirm the generalizability of these results to the Asian population.[384]

With concurrent chemoradiotherapy, toxicities clearly are increased. In addition, the late toxic effects with concurrent chemoradiotherapy have not been well described. Increased acute toxic effects include not only mucosal toxicity, further compounded by the large volume of normal mucosa that is irradiated, but also the asthenia and emetogenic side effects of concurrent high-dose cisplatin. As Cooper describes,[383] the observations by Cheng and colleagues may suggest that other alternative regimens may be equally if not more effective. The impact of these toxicities is important to consider in patient management, because treatment interruptions during radiotherapy also have been demonstrated to result in inferior local-regional control and disease-free survival rates.[385] These investigators estimated that local-regional relapses increased 3.3% per day of treatment interruption. The timing of the interruption, including interruptions early in the course of treatment, appeared to be equally detrimental. Although it is unclear if NPC tumor kinetics may be different with concurrent administration of chemotherapy, close attention to the toxicities of treatment and causes for interruption during a course of radiotherapy may be prudent.

One attractive strategy to minimize toxicities associated with concurrent chemoradiotherapy has been to employ lower but more frequent doses of chemotherapy. Chan and colleagues recently reported the results of a randomized trial of concurrent weekly cisplatin (40 mg/m^2) with daily fractionated radiotherapy in 350 patients.[386] Although no improvement was observed overall for the primary endpoint of progression-free survival, subgroup analysis demonstrated benefit in Ho's T3 stage owing to an improved time to first distant failure. The treatment was well tolerated. The results of a second randomized trial of concurrent 5-fluorouracil and cisplatin, however, showed a significant improvement in progression-free survival.[387]

Despite the improved outcome that appears to have been realized with concurrent chemoradiotherapy for locally advanced NPC, a proportion of patients may continue to have persistent disease that is slow to respond. The therapeutic options recommended have been further irradiation and observation. A limited number of studies have reported on the role of an implant in patients with persistent disease after standard therapy.[388–393] These studies have suggested that further irradiation in early-stage disease that is amenable to intracavitary and interstitial techniques may result in local control rates comparable to those achieved in patients demonstrating a prompt complete response.[389] Hence, dose escalation may be adequate in compensating for tumors demonstrating a low radioresponsiveness. The optimal dose schedule remains to be determined, with both 60-Gy LDR and 22.5- to 25-Gy HDR schedules reported. Stereotactic radiosurgery has been used with preliminary data, suggesting that up to 70% of

patients with organ-confined recurrences may achieve local control for up to 2 years.[394] Late toxicity does not appear to be increased. In light of the poorer local control rates and survival rates in patients managed for local recurrences, a brachytherapy implant or stereotactic radiosurgery may be considered in the management of patients demonstrating persistent disease.

Neck control for NPC is unique for its increased sensitivity to radiotherapy compared with the typical HNSCC.[395] In the clinically negative neck, elective irradiation is recommended owing to the high probability of subclinical nodal metastases, with a risk of 40% neck relapse if untreated, which is associated with a significantly higher incidence of distant failure (21% versus 6%) despite successful nodal salvage.[396,397] With appropriate doses of radiation (50 Gy), the probability of relapse is less than 5%.[398] In the clinically positive neck, doses of 60 Gy or greater are typically recommended; average regional control rates of 90% (range, 86% to 96%) and 75% (range, 71% to 87%) might be expected for neck nodes 3 cm or less and greater than 6 cm, respectively.[380] Accordingly, a planned neck dissection typically is not recommended but may be appropriate. When a residual abnormality remains, a neck dissection typically is recommended. This approach may be complicated, however, by the recognition that in some NPC lesions, gross disease response can be slow at both the primary site and in the neck. As well, the integration of a neck dissection can create conflicts with regard to the prompt initiation of adjuvant chemotherapy. In light of the association between local-regional relapses and the subsequent risk of distant metastases,[397] a neck dissection continues to be a prudent recommendation at this time.

Various strategies have been used in attempts to improve upon the survival rates, particularly for locally advanced disease. The first is to optimize local-regional control, not only because this is a major pattern of relapse in this group of patients but also for the potential impact on the risk of distant metastases. The second is the integration of various chemotherapy agents with definitive radiotherapy. Because a dose-response relationship appears to exist for local control,[399] and the overall treatment time[385] also appears to have an adverse impact on treatment outcome, several institutions have reported their results using altered fractionation for locally advanced NPC with[400] or without concurrent chemotherapy.[401] Jian and colleagues used the same chemotherapy regimen as that described by Cheng and colleagues, with cisplatin and 5-fluorouracil on weeks 1 and 6, with concurrent hyperfractionated radiotherapy to a total dose of 74.4 Gy, in 48 patients. With a median follow-up period of 57 months, 3-year local-regional control rate was 93%, the disease-free survival rate was 71%, and the overall survival rate was 72%. In particular, patients with T4 disease had a 3-year local-regional control rate of 91%, disease-free survival of 62%, and an overall survival of 63%. The major acute toxicity was grade 3 mucositis in 73% and grade 2 weight loss in 31% of patients. These investigators concluded that the treatment was well tolerated, with 88% of patients completing their radiation treatment within 8 weeks.[400] These promising results require further validation of the results and definition of the increased toxicity risks, particularly in light of the unacceptable toxicities observed in other non-nasopharyngeal concurrent chemoradiotherapy series employing altered fractionation.[326]

Various randomized trials incorporating various sequences of chemotherapy and radiotherapy have been reported. To date, a number of randomized trials have failed to demonstrate a benefit with either neoadjuvant[402–406] or adjuvant chemotherapy.[404,407,408] These results are consistent with a recent large patient-based meta-analysis.[181] Accordingly, the use of adjuvant chemotherapy, particularly with definitive chemoradiotherapy, should be judiciously applied.

Because NPCs are radiosensitive, locally recurrent carcinomas may be amenable to re-irradiation. The risk of late complications, including soft tissue and brain necrosis and neuropathies, is highly dose- and volume-dependent with re-irradiation, so the general strategy has been to incorporate conformal radiotherapy techniques for the boost component of the re-irradiation regimen. As with treatment for persistent disease, this may take the form of either brachytherapy or stereotactic radiosurgery boost.[409] In a series of over 891 patients undergoing re-irradiation, the extent of the recurrence was prognostic. Overall, approximately 30% achieved local disease control with local control best seen when a repeat radiation dose of 60 Gy or greater was delivered.[410] The selection of small EBRT fraction size and the use of a brachytherapy implant was associated with a reduced risk of late complications. Several other institutional series have reported sustained local control rates of 20% to 60%, with the variability due to the extent of initial disease presentation and at recurrence and the dose of re-irradiation.[388,390–392] In selected series treating only disease confined to the nasopharynx mucosa amenable to management by either intracavitary or interstitial implant, sustained local control rates of 50 to 60% may be realized. These series also have demonstrated, however, a significant risk of developing late radiation-related complications including soft tissue and bone necrosis, trismus, fistula formation, and neurologic complications such as radiation myelitis and temporal lobe necrosis.

Salvage surgery is now being performed in Taiwan for NPC in selected patients. Large prospective studies are needed to determine efficacy, but small retrospective studies have demonstrated feasibility and success in local control.[411,412] Hsu and colleagues studied 60 patients who underwent salvage surgery, and showed that the results of surgical resection in terms of local control and overall survival were slightly better than those in patients undergoing high-dose re-irradiation for local relapse, with fewer late complications.[412] These investigators favored salvage surgery for rT1–2 and limited rT3 disease, owing to the lower complication rate. This therapeutic option may be considered for selected lesions and in appropriate centers with expertise in this technique, as its relative efficacy to high-dose re-irradiation remains to be defined.

Locally recurrent and metastatic nasopharyngeal cancers generally remain chemosensitive. Many patients have been previously treated with combined modality strategies involving a platinum agent and 5-fluorouracil. Several phase II trials have evaluated carboplatin and paclitaxel in this setting. Carboplatin at an area under the curve (AUC) value of 7 with 3-hour infusional paclitaxel at 200 mg/m^2 revealed an overall response rate of 57% in the metastatic setting.[413] Another phase II study investigated carboplatin at AUC 6 with 135 mg/m^2 paclitaxel infused over over 3 hours, with an overall response rate of 59%.[414] Two other phase II studies, again using similar dosing schedules of carboplatin AUC 6 or 5.5 with 175 mg/m^2 paclitaxel, demonstrated 75% and 25% response rates, with median overall survival rates of 12 and 9.5 months, respectively.[415,416]

Paranasal Sinus and Nose

Malignant tumors of the sinonasal tract are relatively rare, constituting approximately 3% of upper respiratory tract cancers. Accordingly, the scientific literature is limited to multiple small retrospective reports describing the treatment and outcome of these patients. This has limited progress in defining the optimal management for these malignancies. Although squamous cell carcinoma is the most common, several other types of epithelial tumors are less commonly found, including melanoma, adenocarcinoma, adenoid cystic carcinoma, and esthesioneuroblastoma.[417] Nonepithelial malignancies arising in the sinonasal tract include sarcomas and lymphoma.

Among the different subsites within the paranasal sinuses, squamous cell carcinomas occur most commonly in the maxillary sinus.[418] The second most common location is the nasal cavity. The ethmoid sinus is more frequently the site of adenocarcinoma or esthesioneuroblastoma. Cancer arises rarely in the frontal and sphenoid sinuses.[418] The prognosis with these lesions is based on staging classification, as well as on their relationship to Ohngren's line. This theoretical plane extends from the medial canthus of the eye to the angle of the mandible. Tumors anteromedial to this plane are thought to have a considerably better prognosis. Staging follows the sixth-edition AJCC

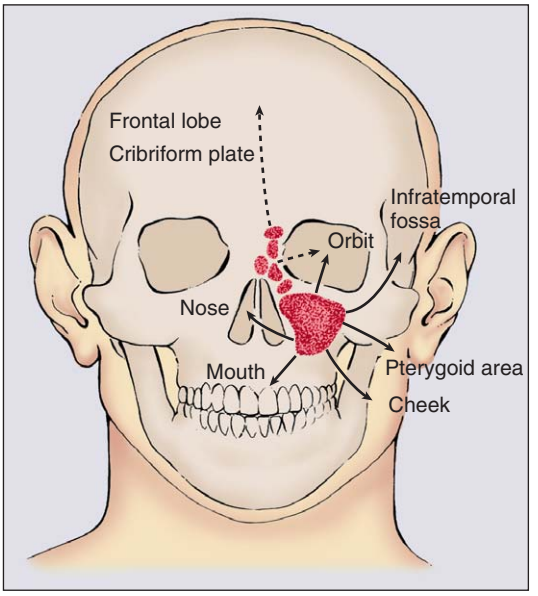


Figure 72-17 • Routes of spread of cancer of the paranasal sinuses. *Solid arrows*, maxillary sinus cancer; *dashed arrows*, ethmoid sinus cancer.

staging criteria. The nasoethmoid complex was added as a tumor site with subdivision of the T4 stage for both maxillary sinus and nasal cavity and ethmoid sinus.[137]

Most malignancies are advanced at presentation and commonly involve one or more adjacent structures (Fig. 72-17). Orbital invasion often occurs early with cancers of the maxilla and of the ethmoid sinuses, whereas it often is a late event for nasal cavity tumors. Malignancies beginning in the anterolateral infrastructure of the maxilla often erode through the inferolateral wall and extend into the oral cavity, with involvement of the maxillary gingival or the adjacent gingivobuccal sulcus. In general, the risk of cervical nodal metastases is low unless the tumor has progressed to involve mucosal surfaces with abundant lymphatics such as the oral cavity.

Management of paranasal sinus malignancies is primarily surgical, with adjunctive irradiation and possibly chemotherapy for advanced lesions.[419,420] For maxillary sinus tumors, a partial or total maxillectomy is required to excise the tumor with disease-free margins, depending on its location. The maxilla can be accessed through a variety of approaches. For smaller, medially based tumors, a medial maxillectomy can be performed using a mid-face degloving approach, in which incisions are made under the lip. For larger lesions, well-placed skin incisions in the nasal crease and upper lip often are required for access. Reconstruction in these cases usually involves a skin graft or acellular dermal graft to reline the mucosal surface, as well as a dental appliance to recreate the hard palate.

Tumors that involve the ethmoid sinuses frequently require a craniofacial resection for surgical access because of the proximity to the skull base. This procedure requires not only an anterior approach to the sphenoethmoid area but also a craniotomy by a skilled neurosurgeon to address the skull base and dura. Orbital exenteration must be considered if the tumor involves the periorbital fat or extraocular muscles. The surgical indications for this vary, however, with an inclination toward eye conservation and an evolving consensus that bone erosion is not an absolute indication. The decision is an intraoperative decision.

When surgical resection is not feasible, either medically or surgically, definitive radiotherapy may be used. It also has been favored as an organ preservation strategy to avoid an orbital exenteration. In this capacity, it may be used definitively, reserving surgery for salvage,[421] or as preoperative radiation as a strategy to downstage the tumor. In view of the proximity of these cancers to many critical normal structures, new radiotherapy techniques including IMRT, stereotactic radiosurgery, or fractionated stereotactic radiotherapy are recommended because they are likely to improve the therapeutic ratio. These techniques are an important consideration in light of evidence suggesting a potential dose-response relationship, with doses greater than 65 Gy recommended.[422] Other technical considerations include the use of computer image fusion software that can permit the use of MRI and the superiority of delineating soft tissue disease during the radiotherapy treatment planning process. Although the current literature does not necessarily support the potential incremental therapeutic efficacy, this is due to the relative rarity of this disease and not to the absence of any effect. As well, the value of concurrent chemotherapy as a radiosensitizer, including early interest in the use of intra-arterial chemotherapy, remains to be established.[423] The value of elective management of the neck remains unclear. Because this often increases the treatment morbidity, it may be omitted. Where considered, most nodal metastases occur in the level I and II regions.

The overall 5-year survival rate for patients with maxillary sinus cancer is 30% to 50%.[422,424,425] Cervical metastases occur in less than 10% of maxillary sinus cancers.[426] Therefore, a prophylactic neck dissection is not indicated in the N0 neck. Cervical metastases are associated with a very poor prognosis, with 5-year survival rates less than 10%.

Oral Cavity

The oral cavity (Fig. 72-18) is composed of the lip, anterior two thirds of the tongue (oral tongue), floor of mouth, buccal mucosa, gingiva, hard palate, and retromolar trigone. The floor of the mouth is bounded by the lower alveolar ridge anteriorly and laterally and the ventral tongue surface and anterior tonsillar pillar posteriorly. The oral tongue lies anterior to the circumvallate papillae. The buccal mucosa overlies the buccinator muscle, is bounded superiorly and inferiorly by the gingiva, and extends posteriorly to the retromolar trigone. The gingiva is the soft tissue overlying the alveolar ridges of the mandible and maxilla. The hard and soft palates form the roof of the mouth. The retromolar trigone mucosa overlies the mandibular ramus and is bounded anteriorly by the buccal mucosa and posteriorly by the anterior tonsillar pillar. As elsewhere in the head and neck, squamous cell cancer is the most common type, except in the hard palate, where most tumors originate in the minor salivary glands. For staging of cancers of the oral cavity, the AJCC classification system is used (Table 72-8). The principle management approach is surgical resection followed by postoperative radiotherapy. Carcinomas of the oral cavity have an adverse prognosis and often require postoperative radiotherapy.[162]

LIP. Surgical management of squamous cell carcinoma of the lip is complex, due to the challenges in reconstruction of this unique part of the body. Although secondary to the complete resection of the lesion, the preservation of speech, oral competence, and cosmesis must be considered. Surgical therapy is considered to be equal in effectiveness to irradiation for the treatment of early, T1, or T2 lesions.[427–430] Small lesions of the lip can be managed surgically by means of wide local excision and primary closure. The morbidity associated with this approach often is less than would be experienced with irradiation. With larger lesions that require resection of more than one half of the lip, local flap reconstruction will be necessary. These flaps involve the mobilization of remaining lip tissue, or even the use of tissue from the opposite lip.

Metatases from lip carcinoma is relatively rare, with the incidence reported at 12% or less.[431,432] In the N0 neck, occult metastases are estimated to occur in 5% to 10% of cases. Therefore, elective neck dissection is not routinely performed in the N0 neck. Neck dissections are generally performed when cervical metastases are clinically or radiographically apparent.

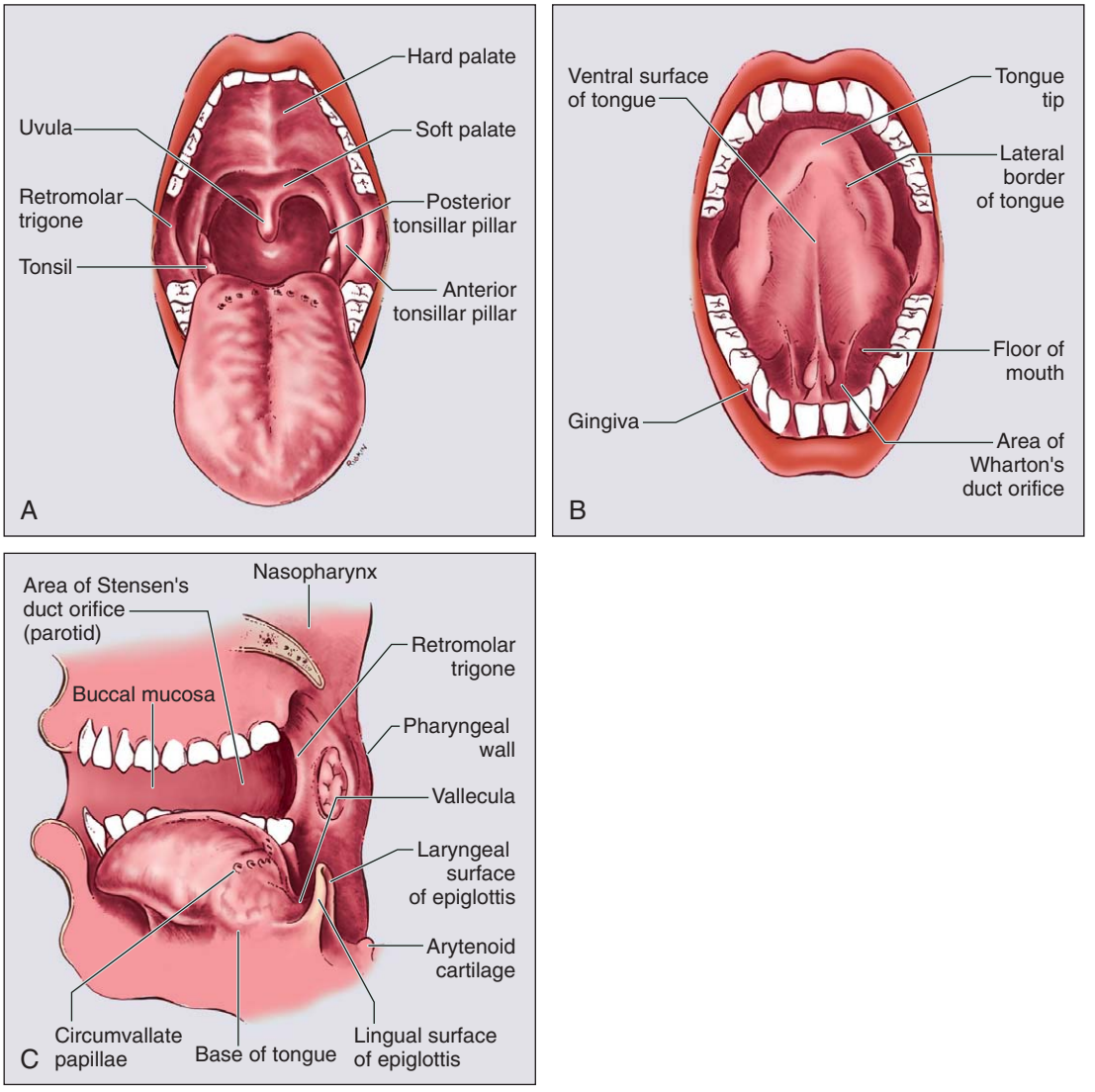


Figure 72-18 • Anatomy of oral cavity and oropharynx. **A,** Open-mouth view. **B,** Tongue elevated, showing floor of mouth. **C,** Sagittal view.

Table 72-8 American Joint Committee on Cancer Tumor Classification System for Staging Cancer of the Oral Cavity

Stage	Characteristics
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
	Tumor more than 4 cm in greatest dimension
T3	Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin)

From the American Joint Committee on Cancer: Manual on Staging of Cancer, 4th ed. Philadelphia, JB Lippincott, 1992, with permission.

Predictably, the results of these procedures depend on the extent of disease. The 5-year survival rate for T1 and T2 cancers of the lip is greater than 90%, whether treated with surgery or irradiation.[428] For larger cancers, especially those that have metastasized, the cure rates are in the range of 40% to 50%.[428,433] Thus, for stage III and IV cancers, a combined approach with surgery and postoperative radiation is indicated. For smaller lesions, surgery and irradiation are equally effective; however, surgery often is recommended because of shorter treatment time and excellent rehabilitation with minimal morbidity.

BUCCAL MUCOSA. Malignant tumors arising from the buccal mucosa are rare, and early lesions are treated primarily with surgery. Although surgical management of T1 buccal mucosa lesions can be managed with transoral wide local excision, larger tumors may require more complex resections. Extension to the mandible or maxilla may lead to a partial mandibulectomy or maxillectomy. Reconstructive options for smaller lesions include primary closure, fat grafting, or a split-thickness skin graft. Larger defects would require local mucosal flaps, myocutaneous rotational flaps, or free flaps, depending on the size and extent of the lesion. Neck dissections are indicated only for

clinically positive cervical metastases. The treatment algorithm for carcinoma of the buccal mucosa is similar to that for other sites in the oral cavity, with surgery indicated for early lesions and combined therapy with surgery and irradiation for advanced lesions.

ORAL TONGUE. Oral tongue carcinomas represent approximately 25% of oral cavity carcinomas. These lesions are characterized by early infiltration into the underlying tongue musculature with an early and high risk for regional metastases. Surgical resection has been favored, because EBRT results alone have been disappointing.[434,435] Although it has been shown that irradiation and surgery are equally effective in treating early lesions,[436] a recent review of 332 patients revealed that disease-free survival was better with surgery alone than irradiation alone.[435] In general, surgery is often the treatment of choice for early lesions because of the ease of surgical access, excellent reconstruction options, and quick treatment time. For stage III and IV lesions, a combined treatment approach is favored. For select lesions, various series describe comparable results with the use of EBRT and a brachytherapy implant as definitive therapy.

Surgical management for squamous cell carcinoma of the oral tongue can take a variety of forms depending on the size and location of the lesion. Small T1 or T2 tumors are treated with a partial glossectomy accomplished through a transoral approach. Larger lesions may require a total or near-total glossectomy, often requiring a mandibulotomy or a cervical pull-through procedure. T4 lesions that involve the mandible require composite resection including either a marginal or segmental mandibular resection.

Reconstruction of the surgical defects also depends on their size and location. After resection of smaller lesions, allowing healing through secondary intention may best preserve function. For larger defects resulting from resection of T2 or T3 defects, healing is facilitated by primary closure, or split-thickness skin graft. For near-total or total glossectomy defects, a pedicled myocutaneous flap or free-tissue transfer is needed for reconstruction. For those patients with mandibular involvement, reconstruction options vary with the location of the defect. Mandibular defects that are large and are located near the mandibular symphysis often require vascularized composite free flaps to restore mandibular continuity with acceptable function and cosmesis.

Surgical or radiation treatment of the neck is indicated in most cases of oral tongue squamous cell carcinoma. The rates of occult cervical metastases exceed 30% for lesions T2 and greater.[277,278,433,437,438] Therefore, for the N0 neck, a selective neck dissection is indicated in T2–T4 lesions, or T1 lesions with depth of invasion greater than 3 to 4 mm.[139,438–440] Patients with clinical or radiographic evidence of cervical metastasis may require more radical procedures depending upon the number and size of nodal involvement.

A significant body of literature exists supporting a role for brachytherapy in the management of selected oral tongue carcinomas that tend to be well defined and thus probably less infiltrative. Brachytherapy has been used alone or in combination with EBRT, demonstrating local control efficacy. The largest experience, comprising more than 600 patients, from the Curie Institute reported local control rates of 86%, 78%, and 71% for T1, T2, and T3 lesions, respectively.[277] Early T1 and T2 lesions were treated with temporary interstitial LDR ^{192}Ir implants alone, delivering 70 Gy in 6 to 9 days. Larger T2 and T3 lesions were treated with EBRT (50 to 55 Gy), followed by an implant (20 to 30 Gy). Other investigators have demonstrated comparable results, demonstrating a high rate of local control.[280,296,441–445] Several series reported local control rates of 90% or greater for very selected lesions often amenable to a single-plane implant alone with a lesion thickness of less than 1 cm.[296,441] Mazeron and colleagues reported their series of 121 patients with T1 or T2N0 tumors treated with 60 to 70 Gy by the Paris system.[442] The crude local control rates for T1, T2a (2.1 to 3 cm), and T2b (3.1 to 4 cm) reported were 86%, 89%, and 74%, respectively. The dose prescribed was found to be significantly associated with the risk of local control, with doses less than 65 Gy associated with a fivefold risk of relapse. Selection by the growth pattern has been shown to influence the 5-year local control rates, with 85%, 79%, and 45% reported for superficial, exophytic, and infiltrative lesions, respectively.[445] Implant of the oral tongue has been associated with a 10% to 20% risk of mild to moderate self-limiting soft tissue ulceration and a low risk (less than 10%) of mandibular osteoradionecrosis in experienced hands. Custom lead-embedded mandibular prostheses and spacers are recommended and have been demonstrated to reduce the risk of bone complications.[441] A predicted 5-year probability of osteoradionecrosis of 38% was reduced to 4% with the use of a spacer. When implant brachytherapy is used in combination with EBRT, the overall treatment time and the proportion of dose delivered with the implant may be important.[446]

Several studies suggest that treating selected early-stage T1 and T2 node negative lesions with HDR brachytherapy alone may facilitate treatment delivery.[296,444,447] One promising schedule comes from a small randomized trial of 29 patients comparing LDR brachytherapy (70 Gy over 4 to 9 days) with an HDR schedule (60 Gy in 10 fractions of 6 Gy per fraction delivered twice daily over 6 days) for a selected group of patients with T1 or T2N0 squamous cell carcinoma of the lateral oral tongue.[444] The lesions had a thickness of 10 mm or less, allowing treatment with a single-plane HDR implant with the dose prescribed at 0.5 cm from the reference plane. The 1-year local control rates were 86% and 100% ($P = 0.157$) in the LDR ($N = 15$) and HDR ($N = 14$) groups, respectively. The 2-year local control rate was identical, although the median follow-up period of 24 months (10 to 32 months) limits this observation. One soft tissue ulceration and one bone exposure complication arose in the HDR arm, although a prosthetic spacer was not used in the latter case. Leung and colleagues have reported preliminary results in 8 patients subjected to the same HDR treatment schedule, showing a 100% local control rate with a median follow-up period of 26 months.[447] Alhough these results are promising, the short follow-up coupled with the significant risk of a false-negative error limits any definitive conclusions regarding the generalized application of HDR brachytherapy in place of standard LDR implants for the oral tongue.

In a subset of patients with a close or positive surgical excision margin and no indication for neck irradiation, treatment with a brachytherapy implant alone (^{192}Ir LDR to 60 Gy) has been used. This obviates the risk of further major surgery or EBRT-related toxicities, including xerostomia. A promising mature local control rate of 89% has been observed in a small retrospective series.[263] Similar results have been reported in other studies.[448,449]

FLOOR OF MOUTH. Most floor of mouth cancers are amenable to surgical treatment. T1 and T2 cancers that do not involve the mandible are often treated with wide local excision with 1 cm margins. In contrast to lip cancers, postoperative loss of speech and swallowing function is not as prevalent with small floor of mouth tumors. Therefore, reconstruction can be performed simply with primary closure, secondary intention, skin graft, or an acellular dermis graft. Although not always necessary, it is recommended that the patient undergo preoperative extraction of any decaying teeth close to the lesion.

For those tumors that approach the mandible, a more complex procedure is indicated. Tumors that involve in periosteum of the mandible require a marginal mandibulectomy, where the top half of the involved bone is removed. The overall continuity of the mandible remains intact. T4 tumors that have invaded the cortex of the mandible require a segmental resection of the involved bone. Reconstruction mandates either composite free-flap reconstruction or no reconstruction if the defect is laterally based.

Surgical management of the neck must take into consideration that occult metastases occur frequently in floor of mouth cancers. The incidence is between 23% and 35% of lesions.[277,278,450,451]

Therefore, most investigators recommend treatment of the node-negative neck in all patienrs with T2 or higher-grade lesions.[450–452] For T1 lesions, tumors greater than 2 to 4 mm in thickness have been found to have a high rate of metastasis, and treatment also is recommended.[453,454] If surgical rather than radiation treatment is pursued, a selective neck dissection that includes the first-echelon nodes (level I and upper level II regions of the neck) should be performed. Unless the lesion is clearly unilateral, a bilateral neck dissection is recommended. Treatment of floor of mouth primaries generally calls for a supraomohyoid neck dissection with resection of levels I, II, and III. Level IV should be included in performing a dissection for cancers of the oral tongue and oropharynx.[455] Levels I and V rarely are involved with laryngeal cancer; therefore, a lateral neck dissection of levels II, III, and IV is the procedure of choice for these lesions.[222]

The cure rates with surgical therapy for floor of mouth cancers have been quoted as 95% for stage I cancers and 86% for stage II cancers.[456] Another study in which the vast majority of patients were treated surgically also demonstrated cure rates of 80% or greater for early lesions.[457] The cure rates for similarly staged cancers treated with irradiation are reported by one study as 88% and 47% for T1 and T2 lesions, respectively.[265] Another study showed, however, that surgery and radiation are equally effective in treating early lesions, and that stage III and stage IV lesions should be treated with combined therapy.[458] In general, the early lesions of the floor of mouth are best managed surgically unless a contraindication exists. Combined therapy is necessary for larger lesions.

HARD PALATE. The type of surgical management indicated for lesions originating in the hard palate depends largely on the presence of bone involvement. With those lesions that do not involve the periosteum, the tumor can be excised without the underlying bone with an adequate mucosal margin. Tumors invading the periosteum, however, require full-thickness resection of the involved bone. Larger tumors may require partial or total maxillectomy. Reconstruction usually involves a skin graft and a dental prosthesis for large palatal defects. Neck metastases are rare and should be managed surgically with a neck dissection. The role of primary irradiation is limited in this disease, but postoperative irradiation is indicated for advanced lesions.

Oropharynx

Although radiation therapy plays a large role in the treatment of squamous cell carcinoma of the oropharynx, surgery often is indicated in combination with radiation for larger T3 and T4 lesions.[459] Although site-specific considerations are recognized, certain principles apply to surgery in the oropharynx whether the lesion is in the tonsil, base of tongue, or soft palate. Selected T1 tumors can be approached transorally. A transoral approach, however, may not provide the access necessary to excise larger lesions completely and safely. In these cases, an anterior or lateral mandibulotomy often is used to gain access. Mandibular involvement by oropharyngeal lesions necessitates marginal or segmental mandibular resection. A neck dissection can be performed in continuity with or separately from the primary tumor.

The goal of reconstruction in this region is to minimize the severe disfigurement and functional compromise that may result from oropharyngeal procedures. Reconstruction options for surgical defects of the oropharynx depend on the size and location of the lesion. Defects from small T1 lesions can be repaired via secondary intention, primary closure, or a split-thickness skin graft. Reconstruction options for larger lesions include a skin graft, a tongue flap, a myocutaneous flap, and free-tissue transfer. Reconstruction after segmental mandibular resection preferably includes osseous free-tissue transfer to replace the excised bone. If a marginal or small segmental resection is performed, however, the bone does not need to be replaced. The complications associated with surgical treatment of oropharyngeal tumors are similar to those encountered with the treatment of oral cavity tumors. Because the tongue base is critical to swallowing function, dysphagia and aspiration are frequent complications after tongue base resection; these problems can be managed with aggressive swallowing rehabilitation. Site-specific surgical and nonsurgical considerations within the oropharynx also are recognized.

TONSIL. Although T1 and T2 tonsil lesions generally are best treated with irradiation, large T2, T3 and T4 lesions are often treated with combined therapy. If the mandible is not involved, the procedure of choice is a radical tonsillectomy that includes the tonsil, the tonsillar pillars, and a portion of the underlying muscle. If the mandible is involved, a composite resection including a segmental mandibulectomy is required.

Some authors argue that early tonsil lesions are best treated with surgery. A recently published small study of 18 patients, cited a 5-year survival rate of 92% for surgically treated patients with T1 or T2 cancers of the tonsil.[460] Similar results are found in patients managed with irradiation alone, with less functional morbidity, however.[461,462] In addition, the use of radiotherapy alone for early tonsil lesions allows the retropharyngeal lymph nodes to be included in the treatment plan, particularly for progressively more posterior lesions and those involving the posterior pillar. Although early lesions are best treated with irradiation, advanced-stage III and IV cancers require combined surgical therapy with radiotherapy for best results.[459,463] The efficacy of this approach relative to an increasing role for concurrent chemoradiotherapy in advanced oropharyngeal carcinomas including tonsil carcinomas is unknown. With increasing involvement of the soft palate and of the pharyngeal wall, however, surgical resection becomes less favored (although often preferred owing to concomitant bulky tumor) because of the functional consequences and increased risk of complications, respectively. For more advanced lesions, with increasing posterior disease extension, the risk of parapharyngeal involvement and retropharyngeal lymph node metastases increases, necessitating radiotherapy as either definitive therapy or in the postoperative setting. When surgical resection is not indicated, concurrent chemoradiotherapy is emerging as a favored definitive strategy on the basis of recent randomized trials and meta-analyses.[181] This treatment approach is limited by the uncertainty with regard to the optimal chemoradiotherapy schedule and the potential for these results not to be generalizable to the tonsil site specifically. It also is recognized that salvage surgery, when chemoradiotherapy is used for potential organ preservation indications, is limited by the proportion of patients with recurrences able to undergo salvage surgery and then the proportion of those in whom salvage surgery can be expected to be successful.

Despite these concerns, several prospective studies have demonstrated high local-regional control rates (80% to 90%) when oropharyngeal and tonsil sites were the predominant tumor sites. It is not clear whether these results are superior to local-regional control rates that have been reported for treatment with radiotherapy alone. Several institutional series have outlined the results that may be expected with fractionated radiotherapy alone. It is recognized, however, that the fractionation schedule may in turn influence the results.

To address these concerns, Withers and colleagues reported the results of a remarkable collaborative retrospective multi-institutional study of carcinoma of the tonsil fossa treated with radiotherapy alone as part of the Patterns of Fractionation Study.[153] A total of 676 patients from 9 participating institutions provided sufficient treatment variability in fractionation schedules resulting from institutional treatment policies to permit study. Several noteworthy observations were made. With the exception of T1 disease, decreased local control rates were observed with the presence of clinically evident nodal disease across each T stage. Cox regression modeling demonstrated that T stage, N stage, total dose, and the overall treatment time were independent significant factors. Although the optimal fractionation schedule could not be identified, a nonsignificant reduction in local relapse was observed with altered fractionated

schedules consistent with the observations of RTOG 90–03.[179] Modeling of the relationship between local tumor control and the overall treatment time suggested that an accelerated growth rate may occur at approximately day 30 but did not significantly improve on the basic model of a constant tumor growth rate throughout the treatment duration. Whether or not these tumor kinetics differ with perturbations from the use of concurrent chemotherapy is unclear but should remain respected.

Hence, when radiotherapy is used as definitive therapy alone, an altered fractionation schedule is preferred, with particular attention paid to minimize any treatment interruptions at any time during treatment. Several reports provide a basis for selection of lesions appropriate for homolateral irradiation.[464–466] The advantages of homolateral irradiation include reduced acute toxicities, less risk of treatment interruptions, reduced dose to the contralateral parotid, and less risk of complete xerostomia. O'Sullivan and colleagues reported the results of a large retrospective analysis of data for 228 patients who received daily fractionated radiotherapy alone, with mature follow-up.[464] Based on an institutional policy of homolateral irradiation for lesions that did not cross midline structures, these investigators were able to demonstrate a spectrum of risk of contralateral neck relapses to guide treatment selection. Patients at low risk (less than 5%) for contralateral neck relapse include those with T1 or T2 lateralized lesions with involvement of even the lateral two thirds of the soft palate or lateral one third of the base of the tongue. With involvement of these structures, however, judicious use of ipsilateral irradiation will be required.

SOFT PALATE. Soft palate lesions that are large may require a partial maxillectomy for complete excision. In general, soft palate tumors are amenable to definitive radiotherapy for cure. The fields should cover the draining lymphatics and the retropharyngeal lymph nodes. With this modality, palatal function usually can be preserved. Reconstruction of this defect may include a skin graft along with a prefabricated prosthesis to maintain swallowing function. Irradiation has been shown to be effective in controlling early lesions, whereas combined-modality therapy is needed for stage III and IV lesions.[467–469]

Cervical metastases should be treated with surgery, or irradiation, or both. Neck dissections can be performed before or after radiation therapy. The decision to perform surgery or irradiation first depends on how the primary is to be treated, and on the size and extent of the neck metastasis. If the metastasis is of sufficient size to require a radical neck dissection, or if it encases the carotid artery, primary treatment with irradiation is preferred to shrink the neck mass to a more resectable size. Bilateral treatment should be considered in large oropharyngeal tumors or those that cross the midline.

Even with a clinically negative neck, treatment by surgery or irradiation is indicated when the primary malignancy originates from the oropharynx. The risk of occult disease is 30% or greater, and these nodes can be found anywhere in levels I to IV of the neck.[470–472] Therefore, if an elective neck dissection is performed rather than radiation therapy, a selective neck dissection exploring these levels is indicated. For midline lesions, bilateral treatment of the neck must be performed.

BASE OF TONGUE. Treatment options for carcinomas of the base of tongue may include surgery or radiotherapy-based strategies. Limited comparative studies have been published to guide the treatment decision-making process. In view of the functional impact of therapy to this site, the feasibility of functional organ preservation has received increasing consideration, because comparable local-regional control and survival rates have been suggested. In this regard, although radiotherapy typically has been preferred, several surgical issues are important to consider.

With regard to the tongue base, additional considerations relate to the size and location of the lesion. If a small tumor lies posteriorly and inferiorly in the base of tongue, a transhyoid approach through the neck can be considered rather than a mandible splitting approach. For small tumors that lie laterally in the tongue base or on the pharyngeal walls, a lateral pharyngotomy can be considered. For larger tumors, resection of a significant portion may result in chronic aspiration because the tongue base is critical to swallowing function. Recurrent pulmonary infections in the elderly or immunocompromised can be life threatening. Thus, a laryngectomy often is considered when more than half of the tongue base is to be removed, especially in high-risk patients. If the larynx is preserved, postoperative functional results can be optimized with swallowing therapy or a laryngeal suspension procedure.[473]

For base of tongue tumors, the data show that early tumors are best treated by radiotherapy or surgery while patients with advanced lesions should receive combined treatment. In one study of 173 patients, early primary tumors treated with surgery or radiotherapy gave a control rate of 83% (5 of 6 tumors) and 89% (40 of 45 tumors), respectively. For advanced primary tumors, definitive radiotherapy produced a local control rate of 55% (42 of 76 tumors), compared with 79% (23 of 29 tumors) for surgery and postoperative radiotherapy.[474] Radiotherapy is preferred for early lesions because of the decreased treatment morbidity compared with base of tongue surgery.

In this regard, data exist to demonstrate that the local control rates for EBRT followed by a brachytherapy implant are superior to those achieved with EBRT alone.[284] One retrospective review demonstrated comparable local control rates between EBRT with an implant and surgery, both of which were superior to EBRT alone.[287] Several independent investigators have consistently demonstrated that a brachytherapy implant boost (20 to 30 Gy) after EBRT (45 to 55 Gy) is associated with effective local control rates. No significant functional deficits with this organ-preserving strategy have been reported when several quality of life domains were studied, even for advanced lesions.[291,292] The most extensive experience has been with temporary interstitial LDR ^{192}Ir implants. Mature local control rates of 85% or greater may be expected for T1 and T2 lesions and 80% to 85% with T3 lesions.[281] Similar results have been reported in other series.[282–288,475,476] In general, selection of the more advanced lesions for treatment has been based on favorable exophytic growth patterns. The experience with a brachytherapy implant in T4 lesions remains limited.[281,283,284,288,475] Concurrent chemoradiotherapy techniques are favored, particularly for the more advanced T3 and T4 lesions. Puthawala and colleagues reported a mature crude local control rate of 67% with more relapses observed in patients with more advanced neck disease[288] and used a higher brachytherapy boost dose of 30 to 40 Gy, compared with 20 to 25 Gy for T1 and T2 lesions. The value of an implant for T4 lesions appears promising, but this approach requires further evaluation, particularly when combined with combination chemoradiotherapy, because late swallowing complications may compromise the benefits of an organ-preserving treatment strategy.

Larynx

From the standpoint of staging and treatment, the larynx is divided into supraglottic, glottic, and subglottic regions (Table 72-9; Fig. 72-19). The supraglottic region is composed of the epiglottis, arytenoid cartilages, aryepiglottic folds, false cords, and laryngeal ventricles. The glottic larynx includes the true vocal cords as well as the anterior and posterior commissures. The subglottic region extends to the inferior edge of the cricoid cartilage. Transglottic tumors involve the glottic level as well as another site within the larynx.

SUPRAGLOTTIC LARYNX. With regard to early lesions, surgical management of supraglottic tumors varies depending on the exact location of the lesion. T1 tumors of the suprahyoid epiglottis are readily managed endoscopically by CO_2 laser excision. Tumors of the infrahyoid epiglottis are not amenable to this type of resection because

Table 72-9 American Joint Committee on Cancer Classification for Staging Primary Laryngeal Cancer

Stage	Characteristics
SUPRAGLOTTIS	
T1	Tumor limited to one subsite of supraglottis, with normal vocal cord mobility
T2	Tumor invades more than one subsite of supraglottis or glottis, with normal vocal cord mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invades postcricoid area, medial wall of pyriform sinus, or pre-epiglottic tissues
T4	Tumor invades thyroid cartilage and/or extends to other tissue beyond the larynx (e.g., to oropharynx, soft tissue of neck)
GLOTTIS	
T1	Tumor limited to vocal cord(s) (may involve anterior or posterior commissures) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis or subglottis, or both, with or without impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation
T4	Tumor invades through thyroid cartilage and/or extends to other tissue beyond the larynx (e.g., oropharynx, soft tissue of neck)
SUBGLOTTIS	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4	Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (e.g., oropharynx, soft tissues of neck)

From the American Joint Committee on Cancer: Manual for Staging of Cancer, 4th ed. Philadelphia, JB Lippincott, 1992, with permission.

of the possibility of pre-epiglottic space invasion.[477] An open procedure is more oncologically sound in these cases.

Surgical treatment of early lesions of the false vocal folds often requires a supraglottic laryngectomy, which spares the true vocal folds. If a supraglottic tumor extends to the true cords, the patient may be a candidate for a supracricoid laryngectomy, which spares at least one arytenoid cartilage but not the true cords. Patients who undergo this procedure generally have excellent functional results with regard to speech and swallowing.[478,479]

Surgical treatment of T4 lesions requires a total laryngectomy in most cases. This procedure involves the resection of the entire larynx, including the epiglottis, the true and false vocal cords, the thyroid cartilage, one lobe of the thyroid gland, and the involved mucosa of the hypopharynx or base of tongue. The remaining pharyngeal mucosa is then closed, either primarily or with additional tissue from a free or rotational flap. The long-term functional swallowing results for this procedure generally are excellent, especially if the pharynx was closed primarily.[480–482] Speech rehabilitation is performed with a number of devices and techniques, including esophageal speech, an electrolarynx, or a tracheoesophageal puncture device.

Owing to the high rate of occult metastasis, bilateral treatment of the neck is recommended in most cases of squamous cell carcinoma of the supraglottis. In the clinically node-negative neck, surgical treatment includes a selective neck dissection including levels II, III, and IV, because these are the most likely locations for occult metastases.[221,483]

The decision to treat T1, T2, and T3 lesions with irradiation or surgery can be difficult. Recent studies in the surgical literature show good 5-year survival rates with either modality.[484–487] Irradiation with surgical salvage may be the best option for patients who have pulmonary disease who are at a high risk for severe complications from aspiration.

Salvage surgery often entails a total laryngectomy. Patients who are surgical candidates for a partial laryngectomy retain glottic function without compromising oncologic outcome.[488] The status of the cervical nodes also must be taken into consideration in deciding on treatment modality. Surgery certainly is indicated when large metastatic nodes are present, because this allows for combined therapy. Surgery or irradiation is sufficient to treat the node-negative neck.

GLOTTIC LARYNX. Early lesions of the true vocal cords that are not treated with irradiation can be treated surgically in a number of ways. Carcinomas in situ may be managed endoscopically with vocal cord stripping or with the CO_2 laser. T1 lesions of the true vocal cords may be treated surgically with cordectomy or CO_2 laser excision. T2 lesions often require open procedures for adequate surgical resection, although radiotherapy is an equally effective option. Operations geared toward organ preservation such as a vertical hemilaryngectomy or a supracricoid laryngectomy should be considered before total laryngectomy for T2 lesions. T3 and T4 lesions of the glottis almost always require a total laryngectomy if surgical management is chosen, although selected patients with T3 cancers are candidates for a supracricoid hemilaryngectomy.[489]

Management of the neck in glottic carcinoma differs from supraglottic carcinoma because the risk of occult metastasis is less, ranging from 3% to 21%.[490–493] Observation is the treatment of choice for the neck in T1 and T2 primary glottic cancers, but some authors recommend treatment of the N0 neck in T3 and T4 cancers.[494] If surgical management is chosen, a selective neck dissection of levels II to IV is the procedure of choice. In the node-positive neck, a selective or modified radical neck dissection may be indicated, depending on the size and location of the metastasis.

The oncologic results with treatment of T1 lesions of the glottis are good. Endoscopic cordectomy is equal in effectiveness to radiotherapy for most lesions, with cure rates greater than 90%.[495,496] Several factors should determine which modality to use. Patient concerns and health are of paramount importance. It must be made clear that although irradiation often can be used for salvage after surgery, the salvage procedure indicated after failed radiation therapy may be a total laryngectomy. Lesions of the anterior commissure, although classified as T1, are not as effectively treated with irradiation and are difficult to excise endoscopically.[497,498] An open partial laryngeal procedure such as a hemilaryngectomy or supracricoid laryngectomy can be considered, depending on the extent of the lesion.

T2 lesions can be managed with radiation or surgery equally well. The 5-year local control rate has been estimated to be greater than 80% after either primary surgical therapy or radiation therapy.[489,496,499–502] It is more likely, however, that an open partial laryngectomy approach rather than a simpler endoscopic approach will be needed for adequate surgical treatment.[489,496,501] Therefore, it becomes very important to choose surgical candidates carefully with regard to pulmonary function, intelligence, motivation, and home situation.

For advanced-stage tumors, it has been shown that survival is similar between patients managed with an organ preservation protocol and those managed with surgery.[503,504] It should be noted that in the landmark Veterans Affairs study, although 66% of patients in the organ preservation arm retained a functional larynx, 39% were tracheostomy-dependent. Patients should be offered chemotherapy and radiation therapy as an alternative to total laryngectomy, however. It recently has been shown that salvage laryngectomy after organ pres-

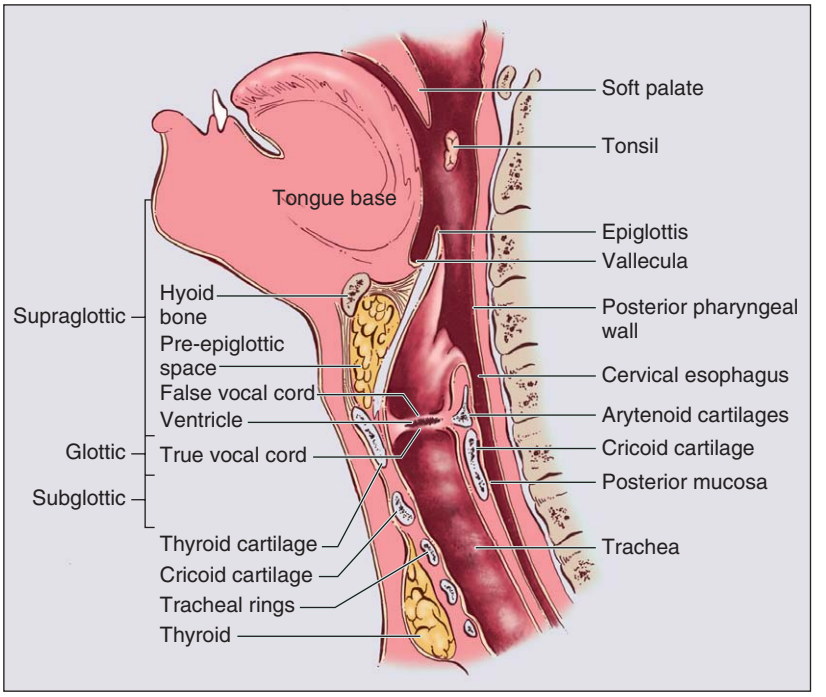


Figure 72-19 • Anatomy of larynx and hypopharynx: Sagittal view. (From Grégoire V, Coche E, Cosnard G, et al: Selection and delineation of lymph node target volumes in head and neck conformal radiotherapy. Proposal for standardizing terminology and procedure based on the surgical experience. Radiother Oncol 2000;56:135–150.)

ervation therapy is associated with acceptable morbidity, and that survival after the surgery was not affected by the initial organ preservation treatment.[185]

SUBGLOTTIC LARYNX. Primary cancers originating in the subglottis are relatively rare.[505] Because conservative endoscopic procedures would fail to clear the tumor, management of these tumors most often requires total laryngectomy. A paratracheal lymph node dissection and ipsilateral thyroidectomy also should be considered. Subglottic extension of T3 or T4 subglottic cancers should be managed similarly. Postoperative radiation therapy should be added to decrease the risk of a stomal recurrence.

HYPOPHARYNX. Surgical management of hypopharyngeal cancers is particularly challenging because the mucosa of the hypopharynx is vital to swallowing function. Thus, surgical extirpation of large tumors often requires complex reconstructions to minimize postoperative dysphagia.

The surgical options vary with the size and precise location of the tumor within the hypopharynx. Selected small tumors of the pyriform sinuses can be managed using conservation procedures that maintain laryngeal function. These procedures include the partial laryngopharyngectomy and supracricoid hemilaryngopharyngectomy.[506,507] To be a candidate for these procedures, a patient must have a small lesion that does not involve surrounding structures or impair vocal cord motion. In addition, the patient must have good pulmonary function and motivation to undergo rigorous swallowing rehabilitation.

For most tumors of the pyriform sinus staged as T2 and larger, a total laryngectomy with partial pharyngectomy is indicated. This procedure can carry significant morbidity, especially when performed as salvage after failed radiation therapy. To reconstruct the pharynx, surgical options include myocutaneous flaps such as the pectoralis flap, fasciocutaneous flaps such as the deltopectoral flap, and free-tissue transfer from the forearm or jejunum. A gastric transposition procedure, facilitated by a general surgeon in the operating room, also is used in cases in which a circumferential pharyngeal defect is present.

Tumors of the posterior pharyngeal wall are more accessible anatomically, making surgical management less complex than for pyriform sinus cancers. Most pharyngeal wall cancers can be resected directly, without laryngectomy, through a suprahyoid or lateral pharyngotomy approach. Reconstruction is often performed using a split-thickness skin graft or acellular dermal graft. Larger tumors may require myocutaneous or free flap reconstruction.

Cancers that involve the postcricoid region of the hypopharynx require an extensive procedure if they are to be managed surgically. A total laryngectomy, partial pharyngectomy, and cervical esophagectomy usually are required. A total esophagectomy may be indicated, depending on the inferior extent of the lesion.

Occult metastases from hypopharyngeal cancers are present in greater than 30% of N0 necks.[490,508] Therefore, selective neck dissection of levels II, III, and IV is indicated, even in patients with tumors staged N0. In addition, if the tumor approaches the midline, bilateral neck dissections should be performed.[508,509]

The outcome for patients with hypopharyngeal cancer is poor, especially if the tumor originates in the pyriform sinus. Marks and colleagues estimated the 5-year survival rate to be 14% for patients with advanced pyriform sinus cancers.[510] In the same retrospective study, it was demonstrated that surgery alone was significantly superior to radiotherapy, with or without chemotherapy, for treatment of the disease. Another retrospective study showed that surgery is superior to combined chemotherapy and radiation therapy, although the difference was not statistically significant.[511] A prospective study showed that organ preservation is superior in terms of survival, but again, the difference was not statistically significant.[192] The treatment of advanced hypopharyngeal cancer must be individualized for each patient.

MAJOR AND MINOR SALIVARY GLANDS. Surgical treatment is the mainstay of management of salivary gland cancer, whether arising from the parotid, submandibular, sublingual, or minor salivary glands. Surgery for parotid gland malignancy is perhaps the most challenging because of the location of the facial nerve coursing between the superficial and deep lobes. Most parotid tumors are located in the superficial lobe of the gland and therefore are treated with a superficial parotidectomy through a transcervical approach, sparing the facial nerve. Those tumors within the deep lobe of the gland require a total parotidectomy. The facial nerve is spared in these

cases if it is not involved with the malignancy. For deep lobe malignancies, additional access via a submandibular or, rarely for massive tumors, a mandible splitting approach.

Submandibular gland tumors usually are contained within the gland, so resection is limited to the submandibular triangle. The marginal mandibular, lingual, and hypoglossal nerves should be spared. If spread to the surrounding tissues has occurred, these structures, as well as surrounding bone, floor of mouth, and skin, may need to be removed surgically. The extent of surgery for malignancies of the sublingual glands and minor salivary glands depends on the size and location of the tumor within the oral cavity.

Combined therapy usually is recommended for high-grade malignancies of the salivary gland such as high-grade mucoepidermoid carcinoma. Postoperative irradiation has been shown to improve local-regional control in several studies.[512,513] Neck dissections are indicated in the event of known cervical metastasis.

Unknown Primary

The treatment for unknown primary squamous carcinoma may include neck dissection followed by postoperative radiotherapy alone or radiotherapy followed by a neck dissection. The relative efficacy of these two strategies has not been evaluated. No established role for the addition of concurrent chemotherapy has been recognized at this time, although this remains an attractive therapeutic strategy. The increased mucosal toxicity, including the potential for long-term swallowing dysfunction, however, must be balanced against unclear benefits including regional control and survival. Currently, irradiation may include the neck alone, or elective mucosal irradiation of potential primary sites may be performed. Weir and colleagues noted no survival benefits with elective mucosal irradiation,[514] although Reddy and colleagues continued to recommend elective mucosal irradiation owing to reduced risk of contralateral nodal and primary relapses.[515] The latter depends on the location of the nodal metastases. For level II nodal metastases, this may require elective irradiation of the oropharynx and laryngeal structures.

Recurrent Head and Neck Squamous Cell Carcinoma and Second Head and Neck Squamous Cell Carcinoma

The optimal management for recurrent non-nasopharyngeal HNSCC and second primary HNSCC remains to be defined and is complicated by retrospective series reporting on outcomes for heterogeneous groups of patients. Re-irradiation of the head and neck is possible, however, with increased but potentially acceptable toxicities. Various investigators have studied combinations of chemotherapy and radiotherapy in hopes of realizing significant radiosensitization such that the total required for re-irradiation is reduced. The results have been summarized by Kao and associates.[218] Unfortunately, only a select few demonstrate benefit with survival prolongation. Higher total doses appear to be important, with a re-irradiation dose of 60 Gy typically recommended.[516] Accordingly, the limited potential for gains must be balanced with an increased risk of complications, including soft tissue necrosis and neurologic damage. Currently, re-irradiation with EBRT and chemotherapy remains limited to clinical trials at centers with ongoing systematic experience with particular protocols. Various conformal radiotherapy techniques may facilitate safer re-irradiation. These include recent techniques such as IMRT. The use of brachytherapy implant for re-irradiation, however, can play an important role in improving the therapeutic ratio, because full-dose irradiation is required for any potential for cure.

Surgery is preferred and offered for resectable lesions in the absence of unacceptable functional and cosmetic sequelae. In this setting, management of microscopic residual disease with radiotherapy often is necessary. A planned introduction of nonirradiated tissue flaps with coordination of the implant placement and of the wound reconstruction can reduce the risk of wound complications. Both pedicled myocutaneous flaps[517] and microvascular free flaps have been described.[518] Nevertheless, complication rates of 20% to 50%, including a risk of carotid rupture during placement of the implant in the neck, have been reported. Factors other than the radiation may be contributing to this increased risk of complications. These considerations are tempered by local control rates of 44% to 80%, suggesting a limited therapeutic ratio.[519–522] Hence, patient selection is particularly important with this indication.

A brachytherapy implant alone may be used for treatment of selected second primary HNSCCs. Peiffert and colleagues reported the results with use of a ^{192}Ir implant alone for 73 patients with tonsil carcinoma treated at the Centre Alexis Vautrin.[295] A majority of the patients presented with early node-negative disease; a median dose of 60 Gy was prescribed according to the Paris dosimetry system. The 5-year actuarial local control rates for T1N0 and T2N0 lesions were 80% and 67%, respectively. Acceptable grade 2 self-resolving complications were observed in 10 cases (13%), with a majority of the complications being soft tissue necrosis due to a dose greater than 60 Gy. This appeared to be increased when compared with the same institution's series when tonsil implants were prescribed in unirradiated tissues.[272] The 5-year actuarial disease-specific survival and overall survival rates were 64% and 30%, respectively. No long-term survivors were observed, reflecting the increased risk of other malignancies and other alcohol- and smoking-related comorbid conditions in this patient population.

Other retrospective series have reported the results of re-irradiation with an implant, but include both patients with a second primary HNSCC and recurrent HNSCC, confounding the overall analyses. Treatment of recurrent HNSCC may be expected to give lower local control rates as a result of the presence of more radioresistant clonogens, an observation consistent with clinical data.[293,294,523] Langlois and colleagues reported the re-irradiation results for a larger and heterogeneous group consisting of 123 patients with T1 to T3 disease treated with a ^{192}Ir implant to a mean dose of 62 Gy at the Centre Alexis Vautrin.[294] A 5-year actuarial local control rate of 59% was observed. Local control correlated with tumor size less than 3 cm, second primary (versus recurrent lesion), dose greater than 60 Gy, and tumor site (oral cavity favorable compared with oropharynx). Only a 5-year actuarial survival rate of 24% was realized, with local control achieved, and a time interval between re-irradiation of more than 2 years associated with a better prognosis. Mucosal necrosis was observed in 28 cases (23%). Stevens and colleagues also noted favorable local control rates with second primary HNSCC, a re-irradiation dose of 60 Gy or greater for second primary HNSCC, a treatment interval longer than 1 year for recurrent lesions, and the use of an implant in addition to EBRT.[523] Mazeron and colleagues reported a 5-year actuarial local control rate of 69% for 70 patients with oropharyngeal carcinomas re-irradiated with a ^{192}Ir implant alone delivering a mean dose of 60 Gy with the Paris system.[524] Similarly, tumor site (glossotonsillar sulcus and base of tongue being unfavorable) and tumor size (larger than 2 cm) adversely influenced the local control rate, although larger lesions occurred more frequently in the base of tongue. Regional nodal irradiation was not intentionally treated, with only 7 of 69 (10%) developing nodal relapses. Soft tissue necrosis was the main complication (seen in 27%), was self-resolving in 13 of 14 patients, and appeared to be increased when a large lesion was implanted.

Levandag reported the results for 73 patients with either second primary HNSCC or recurrent HNSCC comparing EBRT re-irradiation with implant with or without EBRT re-irradiation (18 patients), although significant heterogeneity existed in the treatment applied in each of the patient cohorts, precluding definitive conclusions.[525] Selection bias was minimized because the two cohorts represented sequential treatment periods resulting from an institutional policy change. Crude local control rates of 29% and 50% were reported, respectively, suggesting improved control rates with an implant though this was confounded by the higher mean dose delivered in the implant cohort compared with the EBRT cohort. The

high rate of temporary mucosa ulcerations (in 13 of 18 versus 9 of 55) probably was related to the implant technique used. To reduce the increased risk of mucosal ulceration associated with an implant, Housset and colleagues employed a planned treatment interruption, delivering the intended dose using two separate implants with a source shift.[293] A total of 55 patients with both recurrent and second primary base of tongue squamous cell carcinomas underwent this implant protocol; 31 patients received a single-course implant delivering 60 Gy and 24 patients received a split-course implant delivering 35 Gy and then 30 Gy after a 1-month interruption. A significant reduction in the risk of mucosal necrosis was observed with the introduction of a treatment interruption (16% versus 43%), although a trend toward a lower crude local control rate (37.5% versus 52%) suggests that such a strategy warrants further investigation.

In summary, selective application of a brachytherapy implant for re-irradiation may be appropriate in view of the poor prognosis associated with this patient population. Favorable local control rates may be expected in patients with second primary HNSCC, small tumor sizes, tumor sites other than the base of the tongue, and the delivery of 60 Gy or greater. For recurrent HNSCC, treatment intervals of longer than 1 year appear to select for lesions that are less radioresistant. Soft tissue complications appear to be increased, with a frequency ranging from 20% to 30%; a majority of such complications are self-resolving.

SUMMARY AND FUTURE DIRECTIONS

A paradigm shift has occurred in the management of squamous cell carcinoma of the upper aerodigestive tract over the past 25 years. In the 1970s and 1980s, Fletcher and others demonstrated the ability to preserve function through the use of definitive radiation therapy for patients with cancers of the larynx and oropharynx. In the mid-1980s, Wolf and Hong introduced the concept of laryngeal preservation by combining induction chemotherapy and definitive radiotherapy for patients who demonstrated a significant response to the induction phase of treatment. For the first time, organ preservation was achieved without a deleterious effect on survival. After this favorable report by the Veterans Affairs Cooperative Group, treatment intensification trials were designed to increase the rate of organ preservation and to improve survival rates. Concomitant chemotherapy and radiation therapy were demonstrated to provide a survival benefit over neoadjuvant chemotherapy and irradiation, albeit with increased toxicity. The RTOG implemented a three-arm trial for laryngeal preservation in 1992 to test this concept. Preliminary results from this trial demonstrated a higher rate of organ preservation among patients receiving concomitant chemotherapy than among those receiving induction chemotherapy and radiation therapy or radiation alone. Despite an increased rate of laryngeal preservation, however, treatment intensification did not translate into improved survival.

Current therapeutic approaches have been designed to improve local-regional cancer control and survival through further treatment intensification. Phase III trials are evaluating different chemotherapeutic agents combined with altered fractionated radiation schemes and take advantage of the radiosensitizing effects of chemotherapy when administered concurrently with radiation. Although the outcome from these trials will not be reported for some time, the toxicity associated with aggressive combination therapy is of increasing concern. Anatomic organ preservation through nonsurgical means has been convincingly demonstrated; nevertheless outcome data that demonstrate effective functional preservation of the organ are lacking. Assessment of organ function and quality of life are now integrated into these trials and will provide longitudinal data on pre- and post-treatment organ function and how these relate to the patient's perceived quality of life. In the future, the success of anatomic as well as functional organ preservation will be clarified.

Further treatment intensification is likely to be associated with unacceptable toxicity and will require new approaches to ameliorate the side effects of cytotoxic therapy. Toxicity scoring schemes are being developed and implemented to provide a more quantitative assessment of early and late treatment side effects. Mucosal injury, an early treatment effect, and fibrosis, a late effect, will constrain further attempts to intensify treatment. Mucositis contributes to nutritional deficits and may lead to circumferential scarring and stenosis of the pharynx. Fibrosis contributes to laryngeal and pharyngeal dysfunction through loss of neuromuscular coordination and muscle function. IMRT to limit exposure of normal tissues and agents to mitigate these side effects are being studied in clinical trials. To date, none of the systemic agents intended to lessen toxic side effects has convincingly demonstrated effectiveness.

Although current therapeutic approaches destroy neoplastic cells, collateral damage to normal tissues is responsible for the toxic side effects and long-term functional impairment. Future directions may come from continued technological advancements including organ-preserving surgical techniques and the use of more precise radiotherapy techniques such as IMRT. The greatest potential for gain, however, comes from capitalizing on the molecular mechanisms specific to cancer cells that are responsible for tumor progression. The hope is for more cancer-specific therapy without the increased toxicity. The results from clinical trials conducted with several of these agents alone support the notion that there may be more specific tumor targeting, as the toxicity profiles have to date been very modest. Activity also has been modest, however, which has lead to the use of surrogate measures to determine if in fact these agents are inhibiting the molecular targets in vivo. Although the head and neck site lends itself to tissue biopsies for these assays, the hope is for the continued development of functional imaging to provide these answers. In view of the modest activity with these agents alone, the challenge of the moment is to develop novel strategies for combining these targeted biologic agents with cytotoxic drugs and radiation therapy in a rational manner. This will depend on successful translation of knowledge gained from laboratory investigations, particularly about the molecular mechanisms of treatment resistance. Today's oncologists are at the threshold of realizing a long-sought goal of effective cancer control through the use of targeted therapy that will optimize local-regional control and enhance survival within the context of acceptable toxicity.

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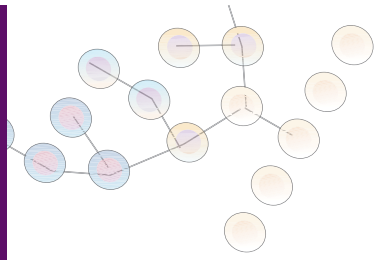
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73 Melanoma

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SUMMARY OF KEY POINTS

Incidence
- The incidence of melanoma has risen dramatically over the past few decades.
- Approximately 59,940 new cases of invasive melanoma are diagnosed each year in the United States, and it is estimated that 1 in 49 men and 1 in 73 women in the United States will be diagnosed with melanoma in their lifetime.

Etiology and Epidemiology
- Risk of melanoma is strongly related to exposure to ultraviolet irradiation, and to a susceptible host phenotype: fair hair and skin, a tendency to burn, and numerous benign or atypical nevi.
- Family and personal history of skin cancers also are important risk factors.

Pathology
- The most important pathologic features of the primary lesion are thickness (in mm), presence or absence of histologic ulceration, and mitotic rate

Clinical Findings
- Many primary melanomas display typical features of border irregularity and variegated pigmentation.
- Some melanomas may be recognized by a patient's report of a change in the size or color of a pigmented lesion or by a report of itching or bleeding from a skin lesion.
- Other primary melanomas may lack these features and, therefore, may be more difficult to recognize.

Differential Diagnosis and Staging
- Any suspicious lesion or questionable new or changing lesion should have a full-thickness biopsy.
- Staging categorization of the primary lesion relies on accurate determination of the thickness of the lesion and determination of whether histologic ulceration is present.
- The current American Joint Committee on Cancer (AJCC) staging system includes the thickness and presence or absence of ulceration of the primary tumor, the number of positive nodes, whether the nodes are microscopically or macroscopically positive, and whether distant disease is present.

Primary Therapy and Salvage Therapy: Surgical
- All primary melanomas need wide local excision for local control.
- Margins of excision are determined by the thickness of the primary lesion.
- For patients presenting with a new primary melanoma ≥1 mm and a clinically negative regional node basin, sentinel node biopsy is used to determine the node status.
- For patients with known metastatic nodes, regional node dissection is performed.

Complications
- Primary surgical therapy usually can be accomplished with preservation of full function and reasonable cosmesis. Node dissection carries a risk of lymphedema.

Primary Therapy and Salvage Therapy: Systemic
- Adjuvant therapy should be offered to patients with high-risk, resected disease (e.g., nodal metastases or a primary tumor ≥4 mm), either with interferon-alfa or as part of a clinical trial.
- Although interferon has been approved by the U.S. Food and Drug Administration (FDA) for high-risk patients, subsequent clinical trials of interferon have shown a consistent disease-free survival (DFS) benefit, but failed to show a clear overall survival benefit; thus its routine use remains controversial.
- For advanced melanoma, dacarbazine (DTIC) and high-dose interleukin-2 (IL-2) are the only FDA-approved agents.
- Durable complete responses with high-dose IL-2 are possible, and this therapy should be considered for all eligible patients.
- A number of promising new molecular and immunologic agents are under active investigation.

Prognosis
- Prognosis is strongly related to the thickness and ulceration status of the tumor at its original presentation and the nodal status.
- Today, most patients are diagnosed early and usually have an excellent prognosis.
- Once disseminated metastatic disease is recognized, median survival is approximately 6 to 9 months.
- With current therapies, the outcome for patients with advanced disease is poor. Further research is needed to identify therapeutic targets and to improve systemic therapies for melanoma patients.

INTRODUCTION

In the early part of the 20th century, melanoma was considered a rare disease, and often was recognized only at an advanced stage. Today, melanoma is one of the most common malignancies, and it usually is recognized at an early stage, when survival rates are high, often with surgery as the only necessary treatment. Melanoma can occur at all ages, and, therefore, can be associated with potential loss of many years of productive life. For early melanoma, improved understanding of the natural history of melanoma and a number of well-run studies of surgical treatment of melanoma have resulted in standard surgical procedures that are much less radical than those

commonly performed just a few decades ago. Advanced melanoma is difficult to treat and presents opportunities for research to improve treatment strategies. Interest in the biology of melanoma continues to increase; ongoing research in the biology of melanoma and its potential application to the medical treatment of melanoma may lead to improved management strategies. This chapter reviews the current treatment of melanoma.

EPIDEMIOLOGY

According to the American Cancer Society, approximately 59,940 new cases of melanoma and 8110 deaths attributable to melanoma were expected to occur in the United States in 2007. It is the sixth most frequently diagnosed malignancy in both men and women, occurring slightly more commonly in men than in women.[1] The incidence of melanoma has risen dramatically over the last several decades, and it is now estimated that the lifetime risk of melanoma in the United States is approximately 1 in 49 for men and 1 in 73 for women.[1] Melanoma can occur in children and teenagers: the Centers for Disease Control and Prevention estimates that in 2002 there were 475 cases of melanoma in persons younger than 20 years of age.[2] The incidence of melanoma in persons under 20 years of age rose 2.9 % per year from 1973 to 2001.[3] Mortality from melanoma is significant. The overall mortality attributable to melanoma has increased because of the great increase in the incidence of the disease; however, case mortality rates have improved, and today 92% of patients are alive 5 years after their diagnosis.[1] Because melanoma often affects young and middle-aged adults, the potential for years of life lost is great. For most of the 20th century, the incidence of melanoma in populations of European origin rose faster than any other cancer except lung cancer. Current reports indicate that the incidence of melanoma is stabilizing or slightly decreasing, particularly among younger adults.[4]

CLINICAL RISK FACTORS

Most known risk factors for melanoma fall into one of two categories: susceptibility of the host and exposure to ultraviolet irradiation. Persons who are most susceptible to melanoma are fair-skinned, with a tendency to sunburn. They may have more than 20 benign moles, atypical moles, or congenital moles. A family history of melanoma also is associated with increased risk.

Skin Type

Fair-skinned persons with a tendency to burn are at higher risk than darker-skinned persons. Red or blond hair and blue or green eyes are associated with increased risk. Freckling is common.[5]

Common and Atypical Nevi

Common benign nevi, if numerous, are associated with increased risk.[6,7] Atypical nevi are flat macules greater than 5 mm, with variable pigmentation, asymmetrical outlines, and indistinct borders. Atypical nevi are found in 2% to 7% of the white population, but in approximately 40% of patients with melanoma. The presence of atypical nevi implies a greatly increased risk of melanoma, particularly when combined with a family history of melanoma. There is a rare, autosomal dominant syndrome of atypical nevi with variable penetrance. These nevi may occur on non–sun-exposed areas. The lifetime risk of melanoma in some affected families is nearly 100%, with many melanomas occurring de novo and apparently not in pre-existing atypical nevi.[8]

Giant Congenital Nevi

Patients with large nevi present at birth or in early childhood are at increased risk for melanoma. Giant congenital melanocytic nevi often are elevated, and usually are large, prominent, irregular, pigmented lesions. They may follow a dermatome distribution and may cover large areas. They occur in fewer than 1 in 20,000 births. Malignant changes may occur in the deeper areas of the dermis and may, therefore, be difficult to detect.[9] Excision early in life when possible with limited morbidity is advised.

Personal History of Melanoma

Patients with a personal history of melanoma have an approximate 5% lifetime risk of a second melanoma. Persons who have had melanoma need lifelong skin screening.

Exposure

Ultraviolet (UV) radiation exposure, to both UVA and UVB, is strongly associated with subsequent development of melanoma. The exposure history most strongly associated with subsequent melanoma development is intermittent intense exposure, particularly a history of blistering sunburns in childhood. Exposure to UV radiation is of particular interest because it is a modifiable risk factor. However, such exposure is not necessary for the development of melanoma—areas with no sun exposure, such as the soles of the feet and the anal area, can be sites of primary melanoma. The development of melanoma is, like many cancers, a result of a complex interaction between patient susceptibility and carcinogen exposure.

Risk Management

Identification of persons with no prior diagnosis of melanoma who are at increased risk of melanoma can be difficult, and the role of routine screening is poorly defined. A case-control study evaluated the relative risk of melanoma in non-Hispanic whites, using data including common risk factors such as complexion, exposure, and number of moles. The authors developed a statistical tool that can be used to estimate an individual's risk of melanoma. This tool may prove useful in counseling at-risk individuals for reduced UV exposure and regular screening.[10] Further research is needed in risk assessment, risk management and in disease prevention.

CLINICAL PRESENTATION AND BIOPSY

The most important clinical feature of a cutaneous melanoma is change in the color, size, perimeter, or contour of a mole or pigmented skin lesion.[11] Sometimes patients report an itching sensation around a mole or an unusual sensation in a mole. Cutaneous melanoma can arise anywhere on the body. The most common site in women is the lower extremity; the most common site in men is the back. Clinical features typical of melanoma include variegated color, irregular borders, or a history of a change in such a skin lesion. A simple mnemonic to remember concerning features of a pigmented lesion is "ABCDE": **A**symmetry, **B**order irregularity, **C**olor change/variegation, **D**iameter change, and **E**volution (change over time) of the lesion.[12] Some melanomas do not have typical features; some are nonpigmented and may resemble other dermatologic entities such as basal cell carcinoma, squamous cell carcinoma, dermatofibroma, or seborrheic keratosis.

Melanoma appears in five clinical growth patterns: superficial spreading melanoma (SSM); nodular melanoma (NM); lentigo maligna melanoma (LMM); acral lentiginous melanoma (ALM); and desmoplastic melanoma (DM). The clinical features, anatomic distribution, ethnic distribution, and etiology are distinctive. SSM, the most common type of cutaneous melanoma among the white population, is largely responsible for the increased incidence of melanoma over the last few decades and may arise from a pre-existing nevus over a period of months to a few years. The average age at diagnosis is 51 years, which is one to two decades earlier than that for LMM or ALM. SSM has a predominant radial growth phase, both clinically and histologically. These lesions are more common on the trunk in

men and on the legs in women, and typically are larger than common benign moles, with asymmetry, notched or irregular borders, and multiple colors (brown, black, pink, and gray).

NM is the second most common type of melanoma. It is similar to SSM in terms of age at diagnosis and anatomic distribution, but does not have a precursor radial growth phase. The lesions usually are shiny, smooth nodules, often with a single color, usually black, dark brown, or bluish. Nodular melanomas usually are thicker and thus are diagnosed at a more advanced stage than SSM. The survival rates and prognosis for SSM and NM are virtually the same when matched for thickness and ulceration. Both SSM and NM appear to be associated with acute exposure to UVB irradiation in fair-skinned persons who tend to sunburn rather than suntan. SSM is more common in individuals living in areas with greater UVB exposure.

LMM occurs on chronically sun-exposed skin, especially the face and neck, in older persons. More than 75% of such patients are older than 60 years of age, and they typically have a history of a slowly growing mole that has been present for a decade or more. Histologically, LMM lesions have a predominant radial growth phase, and there is associated solar elastosis of the surrounding skin as a result of chronic sun damage. These lesions probably are less aggressive in their metastatic behavior compared with other growth patterns, although this is controversial.

ALM is relatively uncommon. In contrast to SSM, NM, and LMM, which occur almost exclusively in fair-skinned persons, ALM can occur in any ethnic group or in persons with any degree of skin pigmentation. Lesions occur on the palms, soles of the feet, and nail beds. They tend to present as more locally advanced lesions. Even when accounting for their greater tumor thickness at presentation, they tend to be more aggressive in their behavior.

DM is uncommon. Lesions often are nondescript papules, plaques, or nodules, and may be nonpigmented; the appearance of DM may be more suggestive of basal cell carcinoma or a verruca. DM often occurs in the head and neck area and can be associated with neurotropism. The biologic behavior of DM is similar to that of a soft tissue sarcoma, in that lesions can invade across fascia and along peripheral nerves. DM has a higher rate of local recurrence than the other common forms of melanoma.

Biopsy Technique

Proper biopsy of a suspicious lesion is critical for accurate staging.[13] When melanoma is in the differential diagnosis, a full-thickness biopsy is done to interpret the maximum tumor thickness and the presence or absence of ulceration accurately. Excisional biopsy with a narrow margin of normal-appearing skin is preferred for small lesions and can be performed on most small lesions. The biopsy scar should be oriented to be compatible with a subsequent wide local excision should the lesion prove to be melanoma. On the extremities a longitudinal or oblique incision is preferred. On the trunk or the head and neck the biopsy should be oriented parallel to the skin lines. Punch biopsy is appropriate for large lesions or those at a vital anatomic site where one would want to know the diagnosis before removing the entire lesion. Punch biopsy should be performed at the most raised area. Final determination of the tumor thickness cannot be made until the entire lesion has been excised and examined. A thin shave biopsy of suspicious lesions should be avoided, because it may compromise histologic interpretation and proper measurement of thickness.

PATHOLOGY

Melanoma Histopathology

The histopathologic diagnosis of melanoma often is straightforward and relies heavily on the presence of specific alterations in growth pattern relative to that of benign nevi. Melanocytes are identified easily and differentiated from keratinocytes by their propensity for "retraction artifact" on well-prepared, routine hematoxylin and eosin (H & E)-stained sections. In normal skin they usually are located in the basal layer of the epidermis, where the ratio of melanocytes to keratinocytes is approximately 1 : 9. Benign nevi are characterized by the presence of nevus cells that are arranged in clusters or nests. Their nuclei are small, without hyperchromasia or mitoses. Nevic melanocytes are arranged uniformly and predominantly as nests and occasional single units at the rete tips of the dermo-epidermal junction and within the dermis. Nevic cells "mature" or diminish in size as they descend into the dermis. Significant alterations in these basic growth patterns are cause for concern, and when they occur, a diagnosis of melanoma must be considered.

In contrast to nevi, and with few exceptions, melanomas are asymmetric and poorly circumscribed. Melanocytes, as nests and single units, may be present at all levels of the epidermis, a pattern known as *Pagetoid spread.* Dermal melanocytes do not mature evenly, and are characterized by enlarged, hyperchromatic nuclei. *In situ melanoma* is defined as an irregular proliferation of atypical melanocytes confined to the epidermis. *Invasive melanoma* is defined as the presence of melanoma cells, at a minimum, within the papillary dermis. The concept of radial and vertical growth phases of melanoma initially was introduced by Wallace Clark and colleagues.[14] *Radial growth phase* refers to the progressive intraepidermal proliferation of melanocytes that occurs in superficially invasive melanoma in the papillary dermis. It precedes the vertical growth phase of melanoma in all subtypes except nodular melanoma, which lacks prominent radial growth. Approximately one third of melanomas arise in association with a pre-existing nevus. Distinguishing between melanoma and a benign process can be challenging, particularly when attempting to distinguish a Spitz nevus from a Spitzoid melanoma or a nevus from a nevoid melanoma.[15] In these instances, the histologic differences may be subtle, and interpretation by an experienced dermatopathologist is necessary.

PROGNOSIS AND MICROSTAGING OF MELANOMA

Multivariate statistical analysis has revealed several features of primary melanoma that have prognostic significance and should be incorporated into pathology reports of invasive melanomas.[16] At a minimum, melanoma pathology reports should include site, Breslow thickness, presence or absence of histologic ulceration, Clark's level, mitotic rate, presence or absence of vascular or neural invasion, presence and degree of regression, degree of lymphocytic infiltrate, presence or absence of a pre-existing nevus, and subtype classification. Greater Breslow thickness, presence of histologic ulceration, elevated mitotic rate, microscopic satellite deposits, and angiolymphatic invasion are associated with a poorer prognosis.[17] Clark level, histologic subtype, and the presence of a coexisting nevus are of limited value in determining prognosis.[16] *Histologic regression* is defined as the absence of melanoma in a focal area that, instead, consists of dermal fibroplasia mixed with blood vessels, lymphocytes, and melanophages; melanoma is present in the immediate adjacent areas. Regression of the radial growth phase of melanoma is associated with poorer prognosis.[18] Regression of the vertical growth phase, which is less rigorously defined as the presence of tumor-infiltrating lymphocytes (TILs), in contrast, is associated with a better prognosis.[19]

Breslow Thickness

Alexander Breslow determined that melanoma thickness correlates with prognosis. A micrometer is used to measure the distance from the top of the granular layer to the deepest level of invasion, excluding adnexal extension. A Breslow thickness of 0.75 mm or less is associated with excellent prognosis. Breslow thickness is the strongest and most reproducible prognostic feature of the primary tumor.[20]

Ulceration

Histologic ulceration is defined as the loss of continuity of the epithelium over the tumor surface and has prognostic significance. Increasing breadth of the ulceration, specifically of 3 mm or greater or defined as involving the majority of the epithelium, has a greater chance of correlating with true ulceration. Ulceration is included in the AJCC staging system.[21]

Histologic Subtypes of Melanoma

Lentigo maligna melanoma (LMM) arises predominantly on sun-exposed areas of the head, neck, and extremities. These lesions may arise de novo or in association with a pre-existing nevus. These melanomas are characterized histologically by the confluence of enlarged hyperchromatic or atypical melanocytes arranged as single units at the dermo-epidermal junction. Prominent adnexal extension of confluent melanocytes often is present. Pagetoid spread is not always evident. Adjacent atypical keratinocytes and prominent dermal elastosis often are present, attesting to the long-standing nature of sun exposure at these sites. Complete excision of LMM sometimes is difficult, because the extent of the pathologic abnormality is not always clinically apparent. The invasive component of LMM may consist of spindled or epithelioid melanocytes.

Superficial Spreading Melanoma

Superficial spreading melanoma (SSM) is characterized by a marked intraepidermal proliferation of atypical melanocytes which are present at all levels of the epidermis. If the tumor is invasive, atypical melanocytes are found in the dermis and are arranged as irregular nests, fascicles or lobules that fail to mature. The melanocytes may appear spindled, epithelioid, or even nevus-like. Melanin pigmentation may be irregular. The dermal component may have an associated lymphohistiocytic infiltrate, with or without prominent melanophages.

Nodular Melanoma

Nodular melanoma, by definition, lacks a radial growth phase and shows extensive dermal invasion. The presence of a pre-existing nevus or an epidermal connection allows for distinction from metastatic melanoma in most cases.

Acral Lentiginous Melanoma

Acral lentiginous melanoma occurs on the hands and feet, including subungual locations. The most common location of this subtype is the sole of the foot. This subtype of melanoma can occur in all races, and is the most common subtype found in darkly pigmented races. The poorer prognosis of this subtype has been attributed to the likelihood of higher stage at diagnosis.

Desmoplastic or Spindle-cell Melanoma

Desmoplastic or spindle-cell melanoma is characterized by a fibroblastic or scar-like proliferation of spindled melanocytes. Desmoplastic melanoma tends to have a surrounding sclerotic stromal response associated with blood vessels and characteristic lymphoid aggregates scattered throughout the dermis. They may occur alone or in association with an overlying lentigo maligna melanoma. This subtype of melanoma ranges from a paucicellular, fibrosing variant, with a prominent stromal response, to a high-grade cellular and spindled or sarcomatous subtype exhibiting only focal desmoplasia. Most desmoplastic melanomas stain strongly and diffusely with S100, but are negative or only focally positive for other melanoma markers such as HMB45. They must be differentiated from other malignant spindle cell tumors of muscle, epithelial, neural, or fibroblastic origin, typically by the use of a panel of immunohistochemical markers, as discussed earlier. In some series, the paucicellular variant of desmoplastic melanoma has been shown to have improved survival relative to other, more common types of melanoma.[22]

PATHOGENESIS

Melanoma arises from transformation of melanocytes, which are of neural crest origin. Most melanocytes reside in the basal layer of the epidermis or within benign common nevi. Melanocytes synthesize melanin using the enzyme tyrosinase, and thus, under normal conditions, help to protect against UV damage. Melanoma induction by UV radiation is a multistep process, involving both UVB and UVA. Melanoma has been conceptualized as growing first in a radial growth phase with little risk of metastatic behavior. This phase is followed by the vertical growth phase with the capacity for metastasis. Different clinical and histologic features are associated with the different phases. Tumor progression likely is the consequence of multiple genetic events.

Melanoma can arise in a pre-existing nevus or de novo. Most melanomas probably do not arise from pre-existing benign nevi. Only about 20% to 30% of melanomas are pathologically associated with melanocytic nevi, and epidemiologic studies strongly suggest that the risk of an individual nevus undergoing malignant transformation is low.[23] Thus, although the presence of large numbers of nevi is associated with increased risk of melanoma, the actual precursor lesion is still in question. It is likely that both the stepwise evolution of melanocytic nevi to melanoma and the de novo onset of melanoma from malignant conversion of epidermal melanocytes are mechanisms of tumorigenesis.

BIOLOGY

Over the last decade, much progress has been made in defining the genetic events that influence melanoma development. Most recently, systematic approaches to identifying cancer-associated genetic defects have been undertaken, abetted, in large part, by the sequencing of the human genome. Such studies have brought new molecular pathways to light in the area of melanoma investigation. Greater knowledge of the molecular events that govern melanoma development is expected to result in the design of targeted therapeutic strategies that may improve patient outcomes.

RAS and RAF and the MAP Kinase Pathway

Although mutations of RAS genes are uncommon in human melanomas, mouse models of melanoma suggest that activation of this pathway in conjunction with inactivation of the p16/INK4a tumor suppressor pathway is important for tumor development.[24] Recent studies have supported the importance of this pathway in melanoma development, because a genome-wide screen of alterations in RAS or its downstream effectors identified activating mutations of the serine/threonine kinase BRAF in 59% of melanoma cell lines and six of nine primary melanomas.[25] Most BRAF mutations identified (80%) were accounted for by a single amino acid substitution (V600E, formerly identified as V599E) that rendered the kinase constitutively active. Subsequent studies showed a similarly high incidence of activating BRAF mutations in benign nevi,[26] suggesting that activation of BRAF kinase may be an initiating event for melanocyte proliferation, but is unlikely to be an important mediator of malignant conversion to melanoma. Additional studies have not identified BRAF kinase germline mutations in large-scale evaluations of patients with familial melanomas,[27–29] but it has been suggested that *BRAF* mutations in nevi may serve as markers of melanoma susceptibility in an individual.[26]

Interestingly, studies of mucosal, uveal, and other noncutaneous melanomas identified considerably fewer activating mutations of BRAF versus intermittently sun-exposed cutaneous melanomas, suggesting that the high-frequency BRAF mutation is targeted specifically to cutaneous melanocytic lesions that are intermittently sun exposed, rather than those that are chronically exposed or unexposed.[30–32]

Although evaluation of primary melanocytic lesions confirmed the high rate of activating BRAF kinase mutations in both benign and malignant lesions,[33,34] it was specifically noted that early, radial-growth-phase melanomas showed the lowest incidence of BRAF mutation (10%),[34] suggesting that BRAF kinase activation may not be necessary for malignant conversion of melanocytes. Because most large radial growth phase melanomas would be of the "lentigo maligna" type, such chronic sun-exposed melanomas could, alternatively, be initiated through non-BRAF-associated genetic events. Indeed, a recent study of genome-wide alterations in DNA copy number and *BRAF* and *N-RAS* mutational status in primary human melanomas demonstrated correlation between genomic changes and unique melanoma subtypes, stratified according to site and UV exposure.[35] Array-based comparative genomic hybridization, DNA sequencing, and immunohistochemical analyses were used to determine DNA copy number and *BRAF*/*N-RAS* mutational status, where primary melanomas were classified into four groups: mucosal, acral, and cutaneous melanomas with and without chronic sun-damaged (CSD) skin (defined by presence of solar elastosis). Most cutaneous melanomas on non-CSD skin (intermittent sun-exposed) possessed mutations in *BRAF* or *N-RAS* (59% and 22%, respectively). Other common findings included alterations in DNA copy numbers of *CDK4, CCND1* (cyclin D1 gene), *CDKN2A (p16INK4a),* and chromosome 10 (site of *PTEN*).[35]

Current data on BRAF kinase mutations in benign and malignant melanocytic lesions suggest that these mutations are not sufficient to induce malignant conversion of melanocytes to melanoma. However, it may be necessary for the mutations of BRAF or other genes within the MAP kinase pathway to be activated for melanoma to develop. Thus, inhibition of BRAF kinase may be a useful therapeutic intervention when used in conjunction with other therapeutic modalities. Because therapeutic targeting of tyrosine kinases has resulted in effective treatment for a variety of malignancies, there has been much excitement over the development of BRAF kinase inhibitors as treatments for melanoma. Sorafenib, originally thought to be a raf kinase inhibitor, but clearly a multitargeted tyrosine kinase inhibitor (TKI), has been investigated in a variety of solid tumors, including melanoma.

Cell-Cycle Regulatory Proteins in the Development of Melanoma

p16/INK4A and the Retinoblastoma Pathway

Cell-cycle regulatory proteins are required for the precise regulation of cell growth and division and, therefore, are critical targets in the malignant conversion of all cells. Frequent deletions in the 9p21 locus were found in familial primary melanomas and melanoma cell lines, and linkage studies eventually led to the identification of the p16/INK4a gene as a candidate tumor-suppressor gene for familial melanoma.[36,37] It later was discovered that this same genetic locus (referred to as CDNK2A) also encodes a second tumor suppressor gene, *p14/p19ARF*. The p16/INK4a gene encodes an inhibitor of the cyclin-dependent kinases, CDK4 and CDK6, and leads to cell-cycle arrest at the G1 phase of the cell cycle. Because CDK4/CDK6 phosphorylates the retinoblastoma protein pRb and inactivates its tumor suppressor function, this was considered a major mechanism of p16/INK4a tumor suppression in melanomas. Inherited mutations of the gene encoding the cell-cycle regulatory protein p16/INK4a or its associated cyclin-dependent kinase, CDK4,[38] predispose patients to melanoma. Defects in the p16/INK4a gene or CDK4 play a role in the development of a relatively small percentage of sporadic melanomas, and only about 20% of familial melanoma cases harbor p16/INK4a mutations, suggesting that most familial melanoma cases are associated with other genetic defects. Expression of p16/INK4a is silenced in sporadic melanomas via epigenetic inactivation through promoter methylation[39]; however, this form of gene silencing seems to be activated in a limited number of primary tumors. Of note, in thin sporadic melanomas, loss of p16 expression is associated with disease progression, despite the low incidence of loss of heterozygosity at the p16/INK4a locus, p16/INK4a intragenic mutations, and p16/INK4a promoter methylation (<10% in lesions thinner than 4 mm).[40,41] This finding suggests that alternative mechanisms exist to allow for decreased expression of p16/INK4a in these early lesions. Other mechanisms of p16/INK4a inactivation in melanoma are under investigation, including transcriptional repression of the p16/INK4a promoter itself.

An area of interest is the potential role of Id helix-loop-helix transcription factors in melanoma initiation. In general, high Id expression levels are found in proliferative, undifferentiated cells, a feature that is characteristic of tumor cells. Id genes have been identified as potential proto-oncogenes because overexpression of Id proteins in primary cells promotes cellular immortalization.[42,43] Id gene expression also is elevated in various tumor cell lines as well as a broad spectrum of primary human tumors.[44] In situ evaluations have shown a correlation between tumor invasiveness, aggressiveness, and progression and Id expression. Recently, Id1 was shown to be a repressor of the familial melanoma gene p16/INK4a,[45,46] and early studies of primary melanocytic lesions showed that Id1 expression correlated with decreased p16/INK4a expression in early melanomas that were confined to a radial growth phase. In addition, later stages of melanoma that did not express Id1 had sustained genetic mutations that inactivated the p16/INK4a gene. The data suggest that Id1 transcriptional repression of p16/Ink4a may represent one of the earliest mechanisms of dysregulation of p16/INK4a expression, resulting in melanoma initiation, and that Id1 expression may be a useful marker for malignant disease in melanocytic lesions of questionable malignant potential.[47] Large-scale studies are underway to determine the utility of Id1 expression in melanocytic lesions as both a marker of malignant disease and an independent predictor of clinical outcome.

p53 and Melanoma

As with the retinoblastoma pathway, the p53 tumor suppressor pathway often is inactivated in cancers; however, alterations of p53 itself rarely are seen in melanomas (0–25%).[48] p53 is a transcription factor that functions to maintain the genome during cellular stress, including the DNA damage induced by UV radiation. Downstream functions of p53 include repair of DNA damage, growth arrest through inhibition of the cell cycle, senescence, and apoptosis.[49]

Given the importance of such functions to the prevention of cancer, it is not surprising that the regulation of p53 functions in the cell is complex. HDM2, a negative regulator of p53, promotes p53 loss through ubiquitin-mediated proteasomal degradation and is overexpressed in early melanomas.[50] As mentioned earlier, the p16/INK4a gene has been shown to reside at a genetic locus that encodes a second tumor suppressor gene, p14/ARF. This gene functions through the p53 tumor suppressor pathway by binding to MDM-2 and decreasing its ubiquitin ligase functions. Melanoma-associated CDKN2A mutations have been documented to occur within p16/INK4a alone, p14/ARF alone, or both genes simultaneously, confirming the independent tumor suppressor functions of each.[51] PAF-1, a downstream effector of p53 involved in induction of apoptosis, has been shown to be inactivated in metastatic melanomas,[52] suggesting that p53 dysfunction in melanoma is related to targeting of p53-associated molecules.

Apoptotic Pathways and the Development of Melanomas

The process of apoptosis, or programmed cell death, is critical to cellular responses to stress and is a major pathway of cell death induced by radiation therapy and traditional chemotherapy. Melanoma cells can be resistant to therapies that have shown efficacy in other tumor types; this is related, in part, to their ability to evade normal apoptotic signals.[53] Over the last decade, the particular signaling cascades regulating apoptotic pathways have been delineated. The

two major apoptotic pathways have been designated the *extrinsic pathway,* which is induced on activation of cell-membrane-associated death receptors by their associated ligands, and the *intrinsic pathway,* which is dependent on mitochondrial membrane permeability in response to cellular stress signals. Both pathways result in activation of caspases that are critical effectors of apoptosis. Melanomas evade both intrinsic and extrinsic apoptotic pathways, critical determinants of tumor response to traditional cytotoxic therapies. The cytochrome c-associated factor Apaf-1 is downregulated in advanced melanomas and influences the death response of melanoma cells to cytotoxic agents.[52] In addition, Fas and TNF-related apoptosis-inducing ligand (TRAIL) death receptors are downregulated by a variety of mechanisms, leading to impaired activation of the extrinsic apoptotic pathway.[53] Therapeutic strategies aimed at circumventing impaired apoptotic pathways in melanoma are likely to require multiple interventions to ensure the continued activation of effective death pathways, given the variety of resistance mechanisms present in melanoma cells.

CLINICAL EVALUATION AND IMAGING

On initial presentation, patients with newly diagnosed thin or intermediate-thickness melanoma rarely show evidence of metastatic disease. Most melanoma metastases cause symptoms or can be discovered on physical examination. Appropriate evaluation of patients with newly diagnosed primary cutaneous melanoma includes a thorough history, a skin examination to search for other primary skin cancers, and examination of the regional node basins. For patients with a primary melanoma 1 mm or thicker, chest x-ray and liver enzymes, including lactate dehydrogenase (LDH) are reasonable screening tools. In patients with findings on history and physical examination that raise concern or abnormal findings on chest x-ray or liver function tests, further imaging studies are warranted.

Liver function tests, including LDH, are commonly used screening tools for patients with newly diagnosed invasive melanoma, although there is no universal agreement about the utility of these tests for screening. Extensive routine radiographic evaluation of asymptomatic patients with American Joint Committee on Cancer (AJCC) stage I, II, or IIIA melanomas with routine computed tomography (CT) or positron emission tomography (PET) rarely shows distant metastases. For most asymptomatic patients, a standard chest x-ray provides adequate basic radiologic screening. Patients who have findings that raise concern on screening history and physical examination or on chest x-ray or liver enzyme tests should undergo further evaluation.

For patients with suspected intra-abdominal or hepatic metastases based on abnormal findings on physical examination or abnormal liver chemistry findings, contrast-enhanced spiral CT scan of the abdomen should be obtained. Magnetic resonance imaging (MRI) also can be used to detect melanoma deposits by a high signal on T1-weighted images. Other than MRI, a bone scan is probably the most sensitive test to detect skeletal metastatic disease, but a careful history and directed radiographs are necessary to ensure that areas of uptake do not represent old trauma or inflammation.

PET and CT scans obtained with 2-[^{18}fluorine]-fluoro-2-deoxy-D-glucose(^{18}FDG) have gained acceptance as a tool for detecting metastatic melanoma and for following the results of systemic or surgical therapy in stage IIIB, IIIC, or IV melanoma.[54–56] PET scanning is based on metabolic changes that could detect early metastatic disease in high-risk patients and has a reported sensitivity of 78% to 100% in detecting metastatic melanoma.[57,58] False-positive findings have been observed in association with inflammatory responses and second primary or metastatic tumors. Wagner and associates[59] reported that the sensitivity of PET with FDG (FDG-PET) for detection of metastatic melanoma in lymph nodes depends on sufficient tumor volume. FDG-PET begins to detect metastatic tumor in lymph nodes reliably at volumes greater than approximately 80 mm^3, but sensitivity decreases rapidly below this point. Fused PET-CT scans also allow correlation of metabolic findings with morphologic findings and have come into frequent use in the evaluation and treatment planning of patients with stage III and IV melanoma.

Prognostic Features

In a multifactorial analysis of 13,581 patients with localized melanoma (either clinically or pathologically), the two most powerful and independent characteristics of the primary melanoma, among all of the prognostic variables analyzed, were tumor thickness and ulceration.[16] No other feature of the melanoma or the patient with localized melanoma had the predictive capability of these two factors. Other factors that were statistically significant prognostic factors were patient age, site of the primary melanoma, level of invasion, and sex. Subsequent studies have demonstrated that mitotic rate is an independent predictor of melanoma survival outcome and risk of sentinel node metastasis.[60–64]

Thickness

In virtually all studies analyzing the prognosis of patients with stages I and II melanoma using a Cox regression analysis, melanoma thickness is the strongest predictor of outcome. Increasing melanoma thickness correlates with increasing risk of local recurrence, regional metastasis, and distant metastasis, and with poorer melanoma-specific survival.[16,64,65] Melanoma thickness is a continuous variable for which there are no naturally occurring breakpoints that delineate different biologic risks for melanoma-specific mortality.

Ulceration

Melanomas with histologic ulceration are more biologically aggressive, and are associated with a substantially increased risk of metastasis. In virtually every Cox regression analysis of prognostic factors that includes ulceration, melanoma ulceration portends a significantly worse prognosis and a higher risk of metastatic disease compared with nonulcerated melanomas of equivalent thickness.[16,66] Melanoma ulceration correlates with increased tumor thickness, mitotic rate and increasing age, further suggesting that this factor is associated with increased risk of metastatic behavior.

Mitotic Rate

Tumor mitotic rate is a reflection of the proliferation rate of the primary melanoma. Although the pathologic definition has not yet been standardized, mitotic rate is an independent factor in predicting both incidence of sentinel node metastases and survival.[60–64,67] Mitotic rate also has been associated with ulceration, further supporting its recognition as an indicator of poor prognosis.[62,63,68]

Site of Primary Melanoma

The anatomic site of the primary melanoma correlates significantly with survival, with trunk and head and neck sites having a poorer prognosis than extremity sites. The biological reasons for this are unclear; nevertheless, several large studies have shown this to be an independent prognostic indicator of survival.[69,70]

Age

Although older patients have thicker melanomas and a higher incidence of ulcerated melanomas, age is an independent adverse prognostic factor, even after multivariate adjustment for other factors.[71] There is a consistent and incremental decline in both 5- and 10-year survival rates with each decade increase in age. Many studies have shown that older patients have a lower survival rate, especially those older than 60 years of age.[66,72]

Anatomic Site

The anatomic site of primary melanoma is directly associated with prognosis, with extremity lesions having a better prognosis than truncal or head and neck lesions.[69,70]

Level of Invasion

The level of dermal invasion has been viewed as a valuable prognostic factor for decades.[73,74] There is less reproducibility in this determination than for thickness, and when all of the prognostic factors are analyzed in a multifactorial fashion, the level becomes much less important than thickness and ulceration for melanomas thicker than 1 mm. However, among patients with thin (≤1 mm) melanoma, the level of invasion was more predictive of survival outcome than was tumor ulceration.[16]

Sex

Men in general have a worse prognosis than do women of similar melanoma presentation and stage, a finding that has been consistent across many studies [69,75]

STAGING CLASSIFICATION

The current staging system went into effect in January 2003.[76] The AJCC Melanoma Database consisted of a total of 30,450 patients with melanoma. Of this group, 17,600 patients (58%) had information available for all of the factors required for the proposed TNM classification and stage grouping. Of the 17,600 patients included in this analysis, 12,837 (73%) had at least 5 years of follow-up information, 8633 (49%) had at least 10 years of follow-up, and 2485 (14%) had at least 20 years of follow-up. The data were merged from prospective databases of patients who did not receive any adjuvant systemic therapy and all of whom had quality control measures in place for data entry, pathology, and surgery. The current melanoma TNM categories are listed in Table 73-1, and the stage groupings are shown in Table 73-2. The 15-year survival curves for patients with stage I to IV melanoma are shown in Figure 73-1.[21] The distinction between clinical and pathologic staging is worth noting.

Clinical Staging

Patients with clinical stage I and II disease have invasive melanoma with no evidence of metastases at either regional or distant sites, based on clinical, radiologic, or laboratory evaluation. Patients with clinical stage III melanoma have clinical or radiologic evidence of regional metastases in the regional lymph nodes or evidence of intralymphatic satellite or in-transit metastases. The clinical or radiologic assessment of the regional lymph nodes is inherently difficult, especially with respect to assessing the presence and number of metastatic nodes. There are, therefore, no subgroup definitions of clinically staged patients with nodal or intralymphatic regional metastases. Patients with clinical stage IV melanoma have metastases at a distant site and are not subgrouped.

Pathologic Staging

In contrast to clinical staging, greater accuracy is possible in defining distinctive prognostic subgroups for appropriate patients for whom pathologic information is available about the regional lymph nodes (after sentinel or complete lymphadenectomy). Pathologic stage I and II melanoma has no evidence of regional or distant metastases, based on absence of nodal metastases after pathologic examination of the regional lymph nodes and absence of distant metastases based on routine clinical and radiologic examination.

Pathologic stage III melanoma has pathologic evidence of regional metastases, either in the regional lymph nodes or in intralymphatic sites. Quantitative classification of pathologic nodal status requires that pathologists perform a careful examination of the surgically resected nodal basin and report on the number of lymph nodes examined and the number of nodes involved with metastases, and that they determine whether the nodes are microscopically or macroscopically involved. Pathologic stage IV melanoma has histologic documentation of metastases at one or more distant sites.

Table 73-1 American Joint Committee on Cancer TNM Definitions

PRIMARY TUMOR (T)

Tx: unable to assess (e.g., shave biopsy or regressed melanoma)

T0: no evidence of primary tumor

Tis: melanoma in situ

T1: 0.1–1.0 mm thick

- T1a: without ulceration and level II/III
- T1b: with ulceration or level IV/V

T2: 1.01–2.0 mm thick

- T2a: without ulceration
- T2b: with ulceration

T3: 2.01–4.0 mm thick

- T3a: without ulceration
- T3b: with ulceration

T4: >4.0 mm thick

- T4a: without ulceration
- T4b: with ulceration

REGIONAL LYMPH NODES (N)

Nx: Cannot be assessed

N0: No regional lymph node metastasis

N1: metastasis in one node

- N1a: micrometastasis (clinically occult)
- N1b: macrometastasis (clinically apparent)

N2: metastasis in two to three nodes or in-transit metastases without nodal metastases

- N2a: micrometastases
- N2b: macrometastases
- N2c: in-transit met(s)/satellite(s) without metastasis in nodes

N3: metastasis in four or more regional nodes, matted notes, or in-transit metastasis or satellite(s) with metastasis in node(s)

DISTANT METASTASES (M)

Mx: cannot be assessed

M0: no distant metastasis

M1: Distant metastasis

- M1a: skin, subcutaneous, distant lymph node metastases
- M1b: lung metastases
- M1c: all other visceral metastases, or distant metastases at any site with elevated serum LDH

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag, 2002.

Clinical versus Pathologic Staging

The ability to stage patients more accurately with sentinel node evaluation has had a profound effect on staging, treatment planning, and the conduct of clinical trials of patients with melanoma.[77,78] The widespread use of sentinel lymphadenectomy has led to considerable stage migration of patients previously staged as "node-negative" when their nodal metastases were undetected.[79] These patients have shown the extraordinary heterogeneity of metastatic risk for stage III melanoma.[16,66] Survival differences between patients with clinically and pathologically staged disease were statistically significant among all T substages, except T4b.

Table 73-2 American Joint Committee on Cancer Pathologic Stage Grouping

Stage 0:	TisN0M0
Stage IA:	T1aN0M0
Stage IB:	T1bN0M0
	T2aN0M0
Stage IIA:	T2bN0M0
	T3aN0M0
Stage IIB:	T3bN0M0
	T4aN0M0
Stage IIC:	T4bN0M0
Stage IIIA:	T1–4aN1aM0
	T1–4aN2aM0
Stage IIIB:	T1–4bN1aM0
	T1–4bN2aM0
	T1–4aN1bM0
	T1–4aN2bM0
	T1–4a/bN2cM0
Stage IIIC:	T1–4bN1bM0
	T1–4bN2bM0
	Any T N3M0
Stage IV:	any T, any N, M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag, 2002.

TNM Criteria

The primary criteria for the T classification are tumor thickness (measured in millimeters) and the presence of histologic ulceration. The T category thresholds of melanoma thickness are defined in even integers (i.e., 1.0, 2.0, and 4.0 mm), because they represent a statistical "best fit" and are most compatible with current thresholds in clinical decision-making.[80,81] A clinically convenient and widely used threshold of 1.0 mm or less is used for T1 melanomas. T2 melanomas are 1.01 to 2.0 mm thick, T3 melanomas are 2.01 to 4.0 mm thick, and T4 melanomas are more than 4.0 mm thick. Melanoma ulceration heralds a high risk for metastases; survival rates for patients with an ulcerated melanoma are remarkably similar to those for patients with nonulcerated melanomas of the next highest T category.[21,73] The level of invasion is an independent prognostic feature of "thin" (T1) melanomas, but not of thicker lesions.[16,73] Therefore, the level of invasion is incorporated into the stage grouping definitions of T1 melanomas only. In the cohort of T1 melanomas, the assignment of T1a is restricted to patients whose lesions meet three criteria: (1) lesion thickness of 1.0 mm or less; (2) absence of ulceration; and (3) depth of invasion limited to level II or III. T1b melanomas are defined as those with a thickness of 1.0 mm or less and with the more aggressive features of level IV or V, or with ulceration. All T2, T3, and T4 melanomas are defined according to the thickness and ulceration criteria as described previously, but not according to the level of invasion.

The definitions used for clinical and pathologic staging of stage III disease are more complicated than those used for the other stages because of the need to accommodate the marked diversity in the natural history of pathologic stage III melanoma. This is demonstrated by fivefold differences in 5-year survival rates for defined substages, ranging from 69% for patients with a nonulcerated melanoma (regardless of thickness) and a single clinically occult nodal metastasis to a low of 13% for patients with an ulcerated melanoma of any thickness and four or more clinically apparent nodal metastases documented by therapeutic lymphadenectomy (Table 73-3).[16]

The stage groupings for pathologic stage III melanoma use four criteria to assign patients with regional metastases to one of three groups, designated as stages IIIA, IIIB, and IIIC (Fig. 73-2). Patients with pathologic stage IIIA disease have three or fewer microscopic (clinically occult) nodal metastases arising from a nonulcerated melanoma (T1–4aN1aM0 and T1–4aN2aM0). Three subgroups of patients with pathologic stage IIIB disease have equivalent survival rates: (1) those with three or fewer microscopic (clinically occult) nodes arising from an ulcerated primary melanoma (T1–4bN1aM0 and T1–4bN2aM0); (2) those with three or fewer gross metastatic nodes and a nonulcerated primary (T1–4aN1bM0 and T1–4aN2bM0); and (3) those with satellite or in-transit metastases, but no evidence of nodal or distant metastases (T1–4 a/bN2cM0). Patients with stage IIIC disease include (1) those with four or more microscopic metastatic nodes and an ulcerated primary melanoma (T1–4bN2aM0); (2) those with three or more grossly involved nodes and a nonulcerated primary lesion (T1–4aN2bM0 and T1–4aN3M0); and (3) those with any combination of satellite or in-transit metastases and nodal metastases[16,21] (see Fig. 73-2).

In patients with distant metastases, the site (or sites) of metastasis and elevated serum levels of LDH are used to classify the M categories into three groups: M1a, M1b, and M1c. The 1-year survival rates range from 40% to 60%.[16,21] The factors that are most predictive of poor survival are the site and number of metastases and elevated serum LDH levels.[82–84] Patients with distant metastases to the skin, subcutaneous tissue, or distant lymph nodes are categorized as M1a. Patients with metastasis to the lung are categorized as M1b, and have

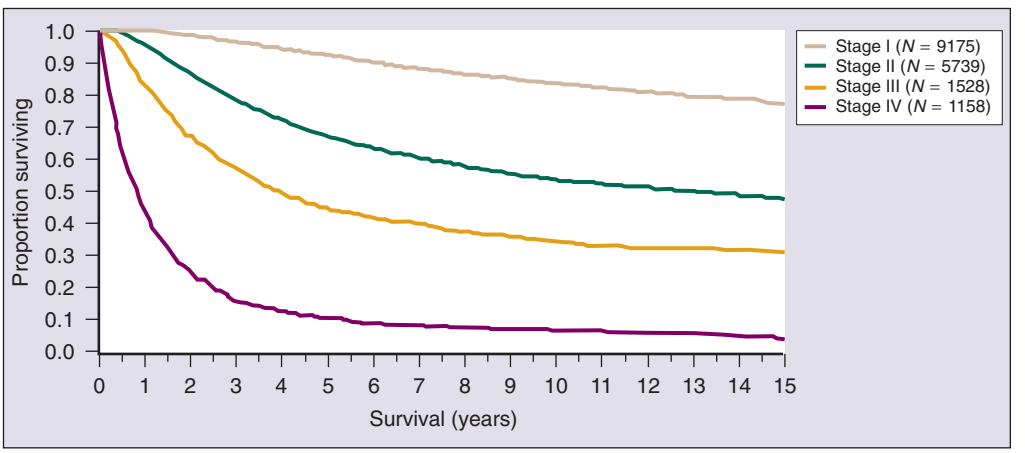


Figure 73-1 • Fifteen-year survival curves for stages I, II, III, and IV melanoma. For each curve, *N* = the number of patients in the AJCC melanoma database used to calculate rates. Curve differences are all highly significant ($P < 0.0001$). (From Balch CM, Buzaid AC, Soong SJ, et al: Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 19:3635, 2001.)

Table 73-3 Five-Year Survival in Node-Positive Melanoma Patients

No. Positive Nodes and Tumor Burden	Nonulcerated Primary Percent ± SE (No.)	Ulcerated Primary Percent ± SE (No.)
Microscopic involvement		
1	69 ± 3.7 (252)	52 ± 4.1 (217)
2–3	63 ± 5.6 (130)	50 ± 5.7 (111)
≥4	27 ± 9.3 (57)	37 ± 8.8 (46)
Macroscopic involvement		
1	59 ± 4.7 (122)	29 ± 5.0 (98)
2–3	46 ± 5.5 (93)	25 ± 4.4 (109)
≥4	27 ± 4.6 (109)	13 ± 3.5 (104)

SE, standard error.

From Balch CM, Soong SJ, Gershenwald JE, et al: Prognostic factors analysis of 17,600 melanoma patients: validation of the American Joint Committee on Cancer melanoma staging system. J Clin Oncol 2001;19:3622.

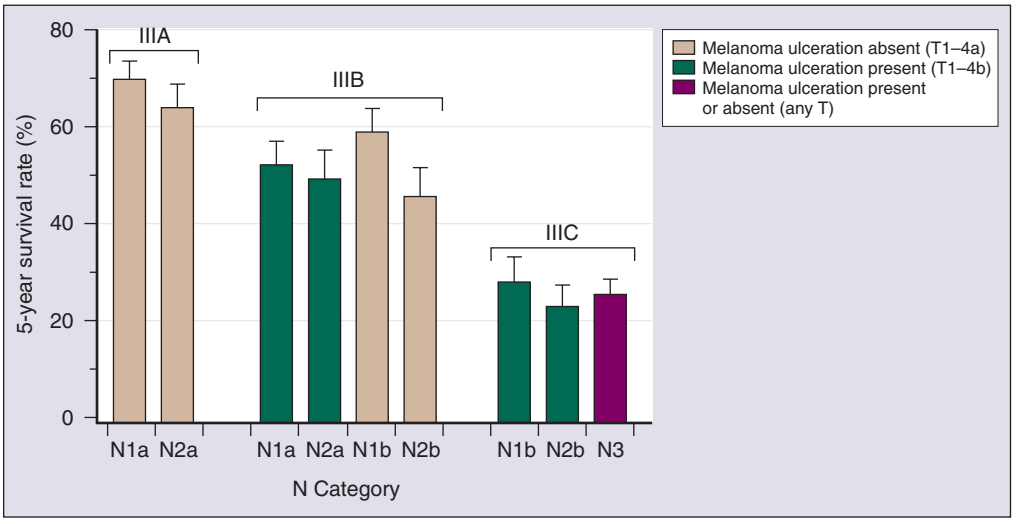


Figure 73-2 • Five-year survival rates in the AJCC melanoma database displaying different stage groupings for stage III melanoma. (From Balch CM, Buzaid AC, Soong SJ, et al: Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 19:3635, 2001.)

an "intermediate" prognosis when comparing 1-year survival rates.[85] Patients with metastases to all other visceral sites have a relatively worse prognosis, and are designated as M1c. When the serum LDH level is elevated above the upper limits of normal at the time of staging, patients are classified as M1c, regardless of the site of distant metastasis.

PROGNOSIS

Patients with Primary Melanoma

In a multifactorial analysis of 13,581 patients with localized melanoma (either clinically or pathologically), the two most powerful and independent characteristics of the primary melanoma were tumor thickness and ulceration. Other statistically significant prognostic factors were patient age, patient sex, site of the primary melanoma, and level of invasion.[16]

Patients with Regional Metastases

There are four major determinants of outcome for patients with pathologic stage III melanoma: (1) the number of metastatic lymph nodes; (2) the tumor burden, either microscopic (clinically occult and detected pathologically by sentinel node biopsy or elective lymphadenectomy) or macroscopic (clinically apparent by physical or radiologic examination and verified pathologically); (3) ulceration of the primary melanoma; and (4) satellite or in-transit metastases.[86,87] Table 73-2 shows the stage groupings for stage III melanoma. Figure 73-2 shows the survival rates for these patients.

Patients with Advanced Disease

The site of metastasis, the number of metastatic sites, and elevated serum LDH levels were the factors that were most predictive of poor survival in all studies analyzing prognosis in patients with distant metastases using a Cox regression analysis.[88,89] Patients with distant metastasis to the skin, subcutaneous tissue, or distant lymph nodes have a relatively better prognosis compared with patients with metastasis to another anatomic site.[88,90] Lung metastases are associated with better prognosis compared with other visceral sites.[16] The number of metastases at distant sites is as an important prognostic factor.[82,83] There is significant variability in the use of diagnostic tests to comprehensively search for distant metastases. Until the indications for testing and the types of tests used are better standardized, the number of metastases cannot be used reliably for staging purposes. Elevated serum LDH is among the independent factors most predictive of decreased survival, even when the site of metastasis and the number of metastases are considered.[88,89]

TREATMENT OF THE PRIMARY

Locoregional Disease

Margins

Every primary melanoma requires wide local excision of the surrounding skin to decrease the risk of local and satellite recurrences. In most cases, wide local excision can be done as an elliptical excision with primary closure. Excision is carried down to a plane between the superficial and the deep (muscular) fascia. Primary closure often can be facilitated by a length-to-width ratio of the ellipse of approximately 3 : 1 and by undermining the flaps to close the defect with an advancement flap, if needed. In areas where the skin edges cannot be approximated primarily, a split-thickness skin graft or a rotational flap can be used to cover the defect. The skin graft donor site preferentially should be chosen outside the area of potential in-transit metastasis. Today, surgical excision margins are less radical than in most of the 20th century; the previously routine margin of 5 cm is no longer used. Primary invasive melanoma should be excised with a 1- to 2-cm minimum radial margin of normal-appearing skin around the biopsy site, with the margin determined by the anatomic site and the thickness of the melanoma.

Five randomized clinical trials have been conducted that address surgical margins around a primary melanoma.[91–95] Three trials involved patients with "early melanomas," those less than 2.0 mm in thickness and with a low risk for local recurrences. The WHO Melanoma Program, the first to conduct a prospective clinical trial of patients treated in Europe and the United States, randomized patients with melanomas smaller than 2 mm to either a 1- or 3-cm margin of excision.[92,96] This seminal clinical trial showed that melanomas less than 2 mm in thickness could be safely excised with a 1-cm margin. The Swedish and European (French) randomized trials were initiated at the same time but were published later.[91,93] These two trials were more conservative; both studies randomized melanomas smaller than 2 mm to either a 5- or a 2-cm radial margin of skin excision. Both studies concluded that the narrower 2-cm margin was safe.

Two clinical trials were conducted for thicker melanomas: the Intergroup Melanoma Trial conducted in the United States on melanomas 1.0 to 4.0 mm in thickness, comparing 2- vs. 4-cm radial margins, and the British study of melanomas larger than 2.0 mm in thickness, comparing 1- vs. 3-cm margins of excision. The Intergroup Melanoma Trial showed that the narrower 2-cm surgical margin was safe with regard to local and regional recurrences, and overall survival.[94] The British study concluded that the 1-cm margin might not be as safe in this cohort of higher-risk patients, since the disease-free survival rates were lower in the narrower excision margin cohort, although there was no difference in overall survival.[95] This study, therefore, leads to some circumspection about adopting a 1-cm surgical margin in all patients, because a narrower margin appeared to be associated with some increased risk for the subsequent development of local and regional metastases.

Difficult Sites

EAR. Primary melanoma of the ear usually can be treated with wedge excision. Primary closure usually is possible, with acceptable cosmetic results. Complete amputation is used only for extensive involvement of the ear or for a local recurrence that is not amenable to wedge excision.

FINGERS AND TOES. Digital melanoma often requires amputation at the midphalanx proximal to the melanoma and follows the same margin recommendations as other sites. The great toe is the most common site of melanoma of the digits and generally requires amputation at the midproximal phalanx. Sufficient skin and soft tissue often can be saved on the plantar surface to allow soft tissue coverage of the stump. As long as the metatarsophalangeal joint is preserved, this amputation causes essentially no functional impairment. Primary melanoma of the distal second through fifth toes usually requires amputation at the midproximal phalanx. Melanoma of the distal finger or nail bed typically requires amputation one phalanx proximal to the melanoma. Melanoma of the proximal finger or web space may be managed with soft tissue excision, with preservation of underlying tendon and bone and coverage with a full-thickness skin graft. For optimal preservation of function, patients with melanoma of the hand should be treated by a hand surgeon.

SOLE OF THE FOOT. Primary melanoma on the sole of the foot requires wide local excision down to the plantar fascia, with either skin graft or soft tissue coverage. When primary melanoma occurs on the instep, a split-thickness skin graft may be sufficient. On weight-bearing surfaces, the tendons should be preserved, and a myocutaneous free flap can be used to provide optimal coverage.

Management of the Clinically Negative Regional Node Basin

Most melanoma experts recommend lymphatic mapping and sentinel lymphadenectomy as a staging procedure for patients with clinical stage I or II melanoma if their primary tumor is at least 1 mm thick, or, if thinner, when the melanoma is ulcerated or is level IV or V (T1bN0M0). The morbidity of the procedure is low and the staging information gained is valuable. Patients found to be node positive are then classified as having pathological stage III melanoma and usually should undergo a therapeutic lymphadenectomy of that nodal basin and should be considered for systemic adjuvant therapy.

Accurate detection of the sentinel node depends on mapping the lymphatic drainage from the skin directly next to the melanoma in a coordinated effort by the surgeon and the nuclear medicine specialist. Preoperative lymphoscintigraphy is vital to the success of sentinel node biopsy. With truncal or head and neck primary lesions, drainage to more than one node basin often occurs, and it is important to retrieve the sentinel node(s) from each node basin in which a sentinel node is identified.[78,97] Preoperative lymphoscintigraphy facilitates the identification of sentinel nodes that lie outside traditional node basins or at unexpected sites. Sentinel nodes occasionally have been identified at popliteal and epitrochlear sites and in the triangular intramuscular space in the back, at the supraclavicular fossa, and at internal mammary and paravertebral sites.

The sentinel node should be placed in formalin for permanent fixation. Frozen section analysis is discouraged; it is preferable to save the lymph node intact for permanent processing only, so that multiple sections can be taken with immunohistochemical stains (e.g., HMB-45, S-100, Melan-A) to look for microscopic evidence of disease. Immunohistochemical staining increases the node-positive rate by 10% to 12% over staining with H & E alone.[98,99] The risk of histologic node positivity is related to the thickness of the primary melanoma[78,100]: In patients with lesions less than 0.76 mm thick, the chance of finding a positive sentinel node is minimal; for melanomas 0.76 to 1 mm thick, the chance of finding a metastatic sentinel node is 5% to 6%; for melanomas 1.1 to 1.5 mm thick, the chance is 7% to 8%; for melanomas 1.5 to 4.0 mm thick, the chance is 18% to 19%; and for melanomas 4 mm or thicker the chance is 29% to 34%.

Sentinel lymphadenectomy, initially described by Morton and colleagues, is a highly accurate, minimally invasive method of identifying those primary melanoma patients who have clinically occult nodal metastases. In a recent report of the results of a randomized prospective study of 1269 patients with intermediate-thickness melanomas (1.2–3.5 mm), Morton and colleagues[101,102] confirmed the prognostic significance of the sentinel node and documented improved disease-free survival among the patients having a sentinel node biopsy. This report conclusively showed that nodal metastases could be detected 16 months earlier (median) than with the nodal observation approach in the 20% of patients who had nodal metastases. In the SLN biopsy arm, SLN status was the most significant predictor of survival in a multifactorial analysis; these results con-

firm other analyses examining the prognostic significance of SLN biopsy.[78,103]

With regard to regional disease control, the nodal observation group had multiple follow-up examinations before nodal metastases became clinically detectable; most of those who suffered a regional recurrence did require a radical lymphadenectomy, as it was usually a solitary site of metastasis. In the group with regional recurrence, there were a larger number of metastatic lymph nodes (3.3 metastatic lymph nodes vs. 1.4 in the SLN group). The implications for this higher number of nodal metastases are important. First, the subsequent regional recurrence rates increase significantly as the number of metastatic nodes in a nodal basin increases, and reaches about a 20% regional failure rate after standard lymphadenectomy in patients with four or more metastatic nodes (compared with <5% in patients with a single metastatic node). In many melanoma centers, patients with multiple, grossly detectable nodal metastases would be considered for adjuvant radiation therapy to the nodal basin, and would be more likely to receive adjuvant high-dose interferon. In contrast, patients with one or two nodal micrometastases would not be considered for adjuvant radiation therapy and would be candidates for other systemic treatments, especially on clinical trials, such as melanoma vaccine trials, in lieu of high-dose interferon.

With regard to survival rates, the two randomized groups overall were comparable; however, among the 16% of patients in each randomized cohort who had nodal metastases, survival rates were higher in the arm with early surgical intervention as directed by the SLN biopsy. The dilutional effect on overall survival rates by the 84% of patients who, in retrospect, never had nodal metastases, will make it difficult ever to demonstrate a survival advantage of the group. It would also be difficult—perhaps even impossible—to design a randomized trial differently to address this issue, because the presence or absence of nodal metastases is known only retroactively, after either the SLN procedure or close clinical examination of the regional nodal basin by palpation or ultrasound.

The use of SLN biopsy has changed the current management of melanoma dramatically, and it offers many significant benefits. First, it provides accurate prognostic information. Second, patients with a positive sentinel node biopsy can undergo a completion lymphadenectomy when the nodal metastatic burden is low. Third, patients with nodal micrometastases can be considered for adjuvant therapy or clinical trials if deemed appropriate. And finally, future trials of systemic therapy can use the results of sentinel node biopsy to assure more homogeneous groups of patients entering trials. The concept of the sentinel node is now well-established and should be used in all melanoma patients where the staging information will be useful for staging and treatment planning.

Management of Regional Nodal Metastases

Complete lymphadenectomy currently is standard treatment for patients with identified regional nodal metastases (Fig. 73-3). The goals of surgery include staging, regional control of disease, and, possibly, improved survival. Most patients who require lymphadenectomy are those who have histologically positive sentinel nodes. In an era when most node-positive patients have micrometastases found by sentinel node biopsy, the value of routine dissection for patients

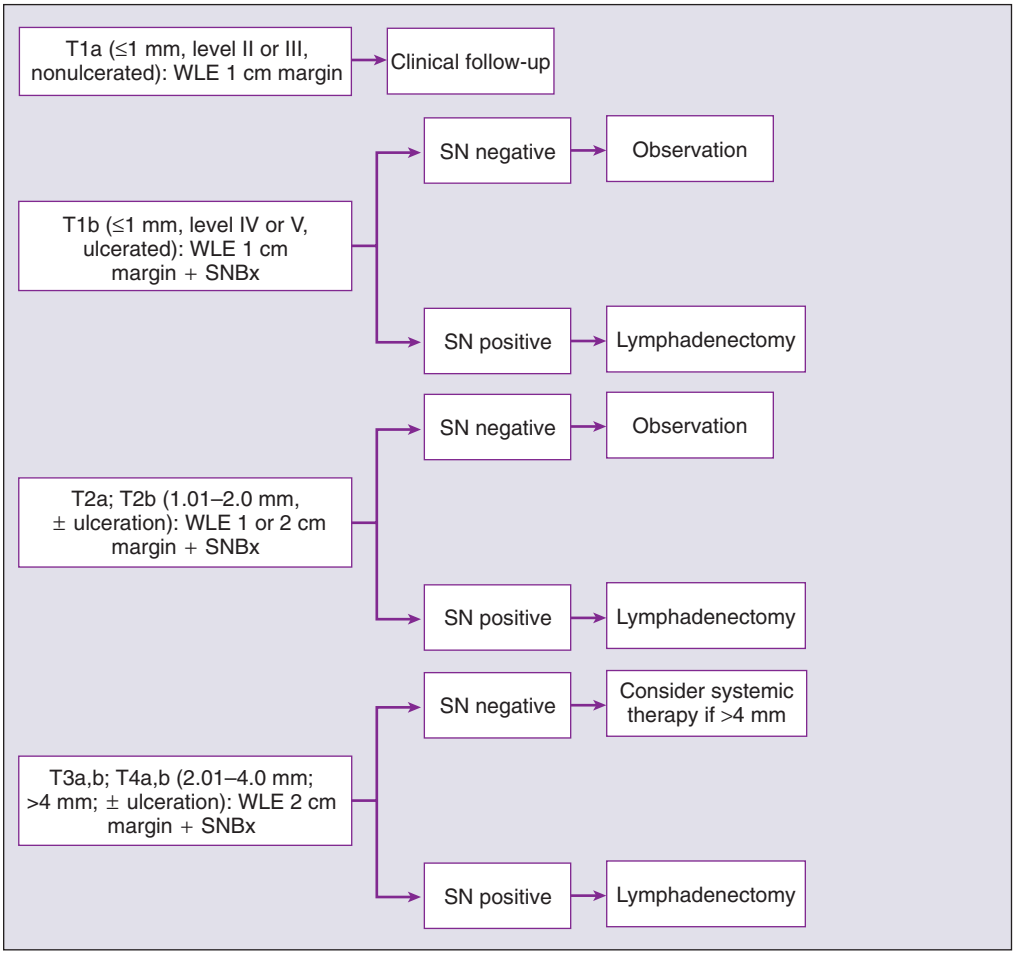


Figure 73-3 • Surgical management of clinical stage I and II melanoma. Sentinel nodes should be evaluated with multiple levels of immunohistochemical staining. All patients with positive nodes or melanoma >4 mm should be strongly considered for interferon or a clinical trial of systemic adjuvant therapy. Some patients with negative nodes and melanoma >1.5 mm may qualify for clinical trials and should be considered for them if interested. SN, sentinel node; SNBx, lymphatic mapping and sentinel node biopsy; WLE, wide local excision.

with microscopically positive nodes has been questioned, and clinical trials are ongoing to determine the magnitude of any benefit in this population.

Patients presenting with clinically suspicious nodes should be evaluated with fine-needle aspiration, if possible, with excisional biopsy done only if the results of fine-needle aspiration are indeterminate. Patients with biopsy-proven bulky nodal disease should be evaluated with baseline spiral CT scans, a complete blood count, and measurement of liver enzymes, including LDH, to rule out identifiable distant disease before proceeding with nodal surgery. As a general principle, lymphadenectomy should be anatomic. The nodal contents are excised in a single block of tissue within their surrounding fatty tissue, preserving motor nerves and muscle whenever possible.

Axillary Dissection

Therapeutic axillary dissection for melanoma should include complete dissection of levels I, II, and III. The long thoracic nerve and the thoracodorsal neurovascular bundle are left intact unless they are directly invaded by tumor. A closed-suction drain is placed. Patients should have no appreciable loss of range of motion or motor function. Complete dissection carries approximately a 10% risk of lymphedema in the upper extremity.

Inguinal and Iliac Dissection

For patients with positive inguinal or femoral nodes, anatomically complete inguinofemoral dissection is performed. The boundaries of the dissection extend superiorly to approximately 6 cm above the inguinal ligament, medially to the pubic tubercle and the midbelly of the adductor longus, laterally to the anterior superior iliac spine and the lateral border of the sartorius, and inferiorly to the apex of the femoral triangle. In patients not known to have iliac nodal metastases in preoperative imaging, the femoral canal is opened and Cloquet's node (the lowest node in the iliac chain) is removed. If Cloquet's node is negative, iliac and obturator dissection usually is not done, and the femoral canal is closed. The sartorius muscle is taken down from its insertion to the anterior superior iliac spine, rotated over the femoral vessels, and tacked in place to the edge of the inguinal ligament and the fascia of the adductor longus. A closed-suction drain is placed in the inguinofemoral area. Inguinal dissection wounds have an infection rate of at least 10% to 15%. The risk of symptomatic lymphedema of the lower extremity is approximately 20%. Routine measures to reduce the risk of lymphedema include a program of wearing a fitted compression garment at 20 to 30 mm Hg during the day for the first 6 months postoperatively and leg elevation when possible.

Absolute indications for iliac and obturator dissection include the finding of a positive Cloquet's node intraoperatively and the finding of enlarged, suspicious iliac or obturator nodes on preoperative imaging. Iliac and obturator dissection may also be considered if four or more lymph nodes positive for disease are found at the inguinofemoral level or if the patient has bulky disease at the inguinofemoral level. The boundaries of the dissection are from the inguinal ligament inferiorly to the bifurcation of the common iliac vessels superiorly and to the obturator vessels medially.

Cervical Dissection

The extent of cervical lymphadenectomy depends on the location of the positive node and the presence of direct invasion into the structures of the neck. When a positive sentinel node is found, a functional neck dissection preserving the internal jugular vein, spinal accessory nerve, and sternocleidomastoid is appropriate. These structures should be sacrificed only if they are directly invaded by tumor.

Radiation Therapy

The risk of regional recurrence sometimes can be lowered by judicious use of radiation therapy after lymphadenectomy in selected patients at particularly high risk, such as those with four or more positive nodes or bulky nodal disease with extracapsular extension. Although there are no prospective randomized studies showing superior outcome with the addition of postoperative radiation, a few retrospective studies strongly suggest that radiation may improve regional control in patients at particularly high risk for treatment failure.[104–107]

Management of Locoregional Recurrence

Local Recurrence

Local recurrence rates after appropriate wide local excision are low. With long-term follow-up of intermediate-thickness lesions in the Intergroup Melanoma Trial, 2.1% to 2.6% of patients overall had a local recurrence.[66] Patients at particularly high risk for local recurrence include those with thick primary lesions (≥4 mm) and those with histologic ulceration, desmoplastic features, or a high mitotic rate. Local recurrence can be a sign that the patient either has or soon will have systemic disease. When local recurrence is detected, the minimal systemic workup that should be done includes careful physical examination, chest x-ray, and measurement of liver enzyme levels, including LDH. If any abnormalities are found by this examination, CT scans, PET scan, or other investigations may be indicated. Local recurrences are treated with wide local excision with 1-cm margins whenever possible (Fig. 73-4). Radiation therapy or systemic IL-2 therapy for unresectable or confluent lesions also is a consideration in selected patients.

In-Transit Disease

In-transit metastases of melanoma appear as identifiable tumor nodules in the subcutaneous or cutaneous tissues between a primary site and its nearest draining node basin. Approximately 2% to 4% of

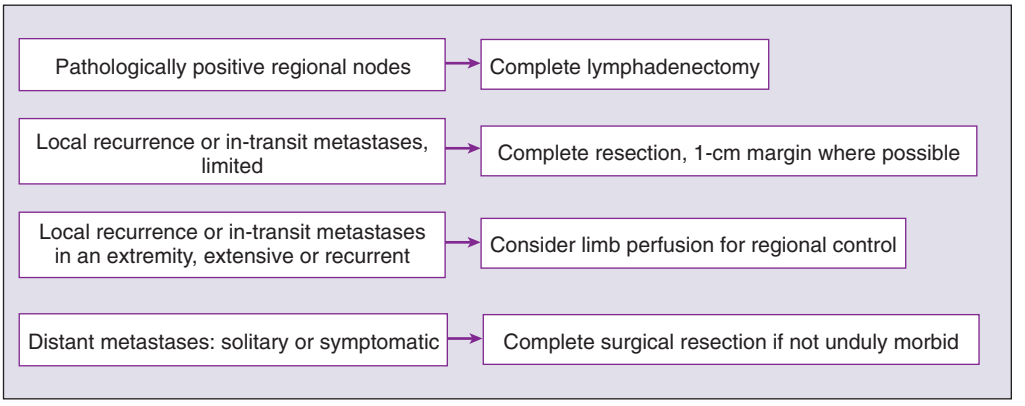


Figure 73-4 • Surgical management of stage III and IV melanoma. All stage III and IV patients should be strongly considered for systemic therapy. Radiation therapy may be considered after lymphadenectomy for patients with ≥4 positive nodes or extranodal extension.

patients with melanoma eventually have in-transit disease after excision is performed for localized primary melanoma.[108] As with local recurrence, in-transit disease can be a harbinger of impending systemic disease; therefore, patients with in-transit disease should undergo a staging evaluation. If limited in-transit lesions are present and they are amenable to excision, wide local excision with negative margins is the treatment of choice.

Nodal Recurrence

Patients with recurrence in a previously undissected node basin should undergo evaluation and complete node dissection, as described previously. Recurrence in a previously dissected basin should be evaluated with a staging workup, including CT scans and measurement of liver enzymes, including LDH, and should undergo surgical excision of the area of recurrence. Adjuvant radiation therapy can be considered as well.

Isolated Limb Perfusion or Infusion

The indications for isolated limb perfusion or infusion are confined to extensive in-transit lesions or local recurrences involving an extremity.[109,110] Limb perfusion with hyperthermia and melphalan has never been shown to be associated with improved survival, but it has a role in securing local and regional control for patients with unresectable local recurrence or a large volume of in-transit disease.[110,111] Still under study is the addition of tumor necrosis factor, which in some studies shows a suggestion of improved disease response, but in others appears to offer no benefit.[112,113] However, the risk of regional toxicity is significant; isolated limb perfusion should be performed only in centers with experience with the technique, preferably in the setting of a clinical trial. A technique of isolated limb infusion using a low-flow infusion of melphalan and actinomycin without oxygenation via percutaneous catheters has been reported that is technically simpler and has reported responses similar to those of melphalan limb perfusion with hyperthermia.[109,114] Overall response rates were reported at 85% (41% complete response) with median response duration of 16 months.[114]

SYSTEMIC THERAPY AND SPECIAL TOPICS

Systemic Adjuvant Therapy

The recently revised AJCC staging system for melanoma allows us to predict an individual's chance of survival more accurately and to identify the patients most likely to benefit from adjuvant therapy, e.g., those with relapse rates of 50% or greater.[76] Trials of adjuvant therapies for high-risk patients have been largely unsuccessful. In 1996, based on a randomized trial showing a survival benefit of 1 year, high-dose interferon alfa-2b was approved by the U.S. Food and Drug Administration (FDA) as adjuvant therapy for patients with resected stage IIB (≥4 mm primary) or stage III (regional lymph node involvement) disease.[115] Subsequent randomized trials of high-dose interferon alfa-2b have shown a consistent disease-free survival benefit, but no significant overall survival benefit.[116] The use of high-dose interferon alfa-2b remains controversial. A variety of therapies, including vaccines, biochemotherapy, and biologic agents, continue to be evaluated in clinical trials for high-risk patients in the adjuvant setting, but to date none have improved overall survival rates.

Early Adjuvant Therapy Trials

A variety of chemotherapeutic agents, including dacarbazine (DTIC)[117] and carmustine (BCNU),[118] showed no benefit in the adjuvant setting. The biologic agents bacillus Calmette-Guérin[119] and interferon-gamma[120] did not improve survival in high-risk postoperative patients. A small, prospective, randomized study showed a survival benefit for patients who took megestrol acetate compared with control subjects.[121] One of four randomized studies of levamisole hydrochloride showed a survival benefit for patients in the treatment arm.[122]

High-Dose Interferon Alfa-2b

Three large published randomized trials conducted under the auspices of the Eastern Cooperative Oncology Group (ECOG) evaluated 1 year of treatment with high-dose interferon alfa-2b in high-risk patients. All defined high-risk patients as those with primary melanomas at least 4 mm thick or with regional lymph node involvement. The high-dose interferon alfa-2b dose schedule was the same in all three studies: 20 million units/m^2 intravenously (IV), Monday through Friday for 4 weeks, followed by 10 million units/m^2 subcutaneously (SC), three times a week for the remaining 11 months. In ECOG protocol 1684, the first trial, 287 patients were randomized to receive high-dose interferon alfa-2b or no treatment postoperatively. In 1996, a statistically significant disease-free survival (DFS) benefit (1.72 years vs. 0.98 years) and an overall survival (OS) benefit (3.82 years vs. 2.78 years) were seen in the interferon alfa-2b arm, at a median follow-up of 6.9 years.[115] The FDA then approved high-dose interferon alfa-2b for high-risk patients, as defined in this study. While at a median follow-up of 12.6 years, the DFS benefit persisted, the OS benefit did not, with both arms now having an equal number of deaths.[123]

The follow-up study, ECOG protocol 1690, involved a three-way randomization with patients receiving high-dose interferon alfa-2b, low-dose interferon alfa-2b (3 million units/day SC three times a week for 2 years), or no therapy. The study enrolled 642 patients; statistical analysis in this study focused on hazard ratios. At a median follow-up of 4.3 years, high-dose interferon alfa-2b led to a reduction in the risk of recurrence compared with no treatment (hazard ratio = 1.28). However, there was no difference in OS at 5 years.[116] The relapse-free survival (RFS) benefit, with no OS benefit, was confirmed at median follow-up of 6.6 years as well.[124] Of note, two confounding issues were that the patients in the observation arm had a surprisingly good survival rate, median survival of 6 years, even after relapse and that some of these patients eventually received high-dose interferon alfa-2b therapy.

In ECOG protocol 1694, high-dose interferon alfa-2b was compared with a GM2-ganglioside vaccine in 880 high-risk patients (high risk as defined previously). The Data Safety Monitoring Committee stopped this study early, at a median follow-up of 16 months, because a statistically significant DFS benefit (hazard ratio = 1.47) and an OS benefit (hazard ratio = 1.52) were noted for the high-dose interferon alfa-2b arm. The estimated DFS rate at 2 years for the patients receiving high-dose interferon alfa-2b was superior (62% vs. 49%), as was OS (78% vs. 73%).[125] Because there was no observation arm, it is impossible to know whether the vaccine was inferior or equivalent to no therapy.

A pooled analysis of ECOG trials upheld the finding of prolonged RFS, but not OS, in patients treated with high-dose interferon alfa-2b vs. observation on two-sided univariate log-rank analysis of E1684 and E1690 pooled data. Multivariate models adjusted for negative prognostic factors also confirmed a significant RFS benefit in pooled populations.[124] A meta-analysis of adjuvant interferon randomized trials also attempted to clarify the varied results.[126] RFS and OS were evaluated, and a subgroup analysis was performed according to interferon alfa-2b dose. Again, a significant RFS improvement was seen in those treated with high-dose interferon alfa-2b (three studies) compared with control (hazard ratio = 0.83, CI: 0.77–0.90). However, the benefit in OS was less clear as the confidence interval crossed 1.0 (hazard ratio = 0.93, CI: 0.85–1.02). Odds reduction in RFS appeared to correlate directly with increasing dose of interferon alfa-2b; namely, the greatest reduction in odds for recurrence was in the high dose groups (hazard ratio = 0.74). Yet again, no consistent benefit in OS was seen.[126]

High-dose interferon alfa-2b is associated with a number of potential toxicities, which necessitate dose reduction in approximately 75% of patients. Side effects include fatigue, anorexia, flu-like

symptoms, depression, liver abnormalities, and cytopenia. Patients require frequent blood draws: weekly for 4 weeks, and then monthly.[115] The treatment is expensive, and some insurers do not reimburse for home SC administration. Many patients are not candidates for high-dose interferon alfa-2b because of age or comorbid conditions.

The results of studies of high-dose interferon alfa-2b continue to inspire much controversy.[123,127] Since the FDA approved high-dose interferon alfa-2b in 1996, the treatment regimen has not been widely embraced by U.S. medical oncologists and has not been accepted at all by European practitioners.[123] There is a consistent DFS benefit in multiple studies that cannot be denied. However, the OS benefit faded in ECOG protocol 1684 and was never seen in ECOG protocol 1690. In ECOG protocol 1694, at a median follow-up of 2 years there was a survival benefit, but no subsequent data have been published. If there is a survival benefit to high-dose interferon alfa-2b therapy, it is likely small.

Other Interferon Alfa-2b Schedules

A number of other interferon alfa-2b schedules have been evaluated in the adjuvant setting. High-dose interferon alfa-2b given for 3 months was ineffective.[128] Low-dose interferon alfa-2b schedules of 3 million units/day SC three times a week for 3 years for patients with stage III disease,[129] or for 18 months for patients with primary melanomas more than1.5 mm thick,[130] did not show an OS benefit compared with observation. The European Organization for Research and Treatment of Cancer (EORTC) studied intermediate-dose schedules of interferon alfa-2b, 10 million units SC five times a week for 4 weeks, then three times a week for 12 or 24 months in a randomized controlled trial of 1388 patients with stage IIB or III melanoma (protocol 18952).[131] The measured endpoints were distant-metastasis-free interval (DMFI), distant metastasis-free survival (DMFS), and OS. After a median follow-up of 4.5 years, neither group evidenced a statistically significant improvement in DMFI or OS. There was a trend toward significance in DMFI and OS in patients treated with 2 years of interferon alfa-2b vs. observation; among those patients, those with stage IIb melanoma showed the greatest effect. These findings were thought to underscore the impact of tumor burden and duration of treatment on treatment effect. Another EORTC protocol (18991) that involves an extended course of pegylated interferon alfa-2b for 5 years versus observation in 1256 stage III melanoma patients reported that subjects with micrometastasis in regional nodes had improved relapse-free survival, but not improved overall survival, when treated with 5 years of pegylated interferon alfa-2b.[131]

Vaccines

Currently, increasing numbers of melanoma vaccines are in preclinical development and in phase I, II, and III clinical trials in the adjuvant setting. Despite the scientific promise of melanoma vaccines, to date none has proven beneficial in the adjuvant setting when tested in a randomized clinical trial. A notable disappointment in the field of melanoma research came in 2005 when the phase III study of CancerVax (CancerVax Corporation) in resected stage III melanoma, as well as the phase III study in resected stage IV melanoma, were stopped early by the respective external data safety monitoring committees. After interim analyses, the likelihood of a survival benefit in the Canvaxin-treated patients was sufficiently low to warrant trial closure. CancerVax was an allogeneic whole-cell vaccine composed of three highly antigenic, irradiated melanoma cell lines. In a phase II trial, CancerVax appeared to improve survival compared with historical controls.[132] M-Vax (AVAX Technologies, Philadelphia, PA), an autologous whole-cell melanoma vaccine modified by the hapten dinitrophenol and then irradiated, also improved survival in patients with stage III disease compared with historical control subjects and demonstrated that development of a delayed type-hypersensitivity response (DTH) correlated with improved DFS and OS.[133,134] A phase III study of M-vax in metastatic melanoma is ongoing.

In addition to the Canvaxin trial just mentioned, a limited number of other phase III adjuvant vaccine trials have been completed. A vaccinia melanoma oncolysate vaccine did not improve outcome in patients with stage III melanoma.[135] In a large randomized trial, a vaccinia viral lysate of melanoma showed no benefit in patients with melanomas more than 4 mm thick or with regional lymph node involvement.[136] Melacine (Corixa Corp., Seattle, WA), a cell-lysate vaccine, was compared with observation by the Southwest Oncology Group (SWOG) in patients with melanomas 1.5 to 4 mm thick without lymph node involvement. No DFS benefit was seen.[137] However, in a retrospective analysis, vaccinated patients who were positive for HLA-A2 or C3 had a DFS rate of 77%, compared with 64% for those who received observation only.[138] Unfortunately, no further studies are planned. In a study by Bystryn and colleagues,[139] polyvalent shed-antigen vaccine showed a survival benefit in a very small phase III trial that involved 38 patients with stage III disease. In ECOG protocol 1694, discussed earlier, the GM2-ganglioside vaccine was inferior to high-dose interferon alfa-2b at a relatively short median follow-up.[125]

Granulocyte-Macrophage Colony-Stimulating Factor

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a colony-stimulating factor approved by the FDA for treatment of bone marrow transplant graft delay or failure and for speeding neutrophil recovery after induction chemotherapy in elderly patients with acute myelogenous leukemia. It also promotes melanoma antigen presentation through activation of macrophages, monocytes, and dendritic cells. GM-CSF was studied in 48 high-risk patients with melanoma (stage III with >4 involved lymph nodes or stage IV) after surgical resection with no evidence of disease. The outcome was much better in the treated patients compared with historical controls, with a median survival of 37.5 months vs. 12.2 months.[140] Based on these results, ECOG designed a double-blinded, randomized, six-arm phase III study of various combinations of a peptide vaccine, GM-CSF, and placebos of both (protocol 4697) in resected high-risk stage III and stage IV patients, which recently closed to accrual.

Adjuvant Biochemotherapy

With the initial success of biochemotherapy in advanced disease,[141] it seemed logical to design a trial for the high-risk adjuvant setting. Intergroup trial S0008 is comparing three cycles of biochemotherapy with 1 year of high-dose interferon alfa-2b administration in very-high-risk patients with stage III disease (i.e., ulcerated primary lesion with regional lymph node involvement, grossly involved or clinically palpable nodes, matted nodes, two or more involved nodes, or satellite lesions). The study continues to accrue patients, although the disappointing recently released data on biochemotherapy in patients with stage IV disease casts doubt on the utility of this intensive, toxic approach in stage III disease.[142]

Neoadjuvant Therapy

A newer strategy involves neoadjuvant therapy for regionally advanced melanoma. A dramatic response recently was reported in patients with stage IIIB-C melanoma who were treated with standard high-dose interferon alfa-2b: IV infusion daily for 4 weeks prior to curative surgical resection, followed by SC injections three times a week for 11 months.[143] Of the 20 enrolled patients, 11 demonstrated an objective clinical response and 3 evidenced a complete pathologic response. Fifty percent of patients were free of recurrent disease at median follow-up of 18.5 months.[143] Biochemotherapy in the neoadjuvant setting also has been evaluated in two phase II studies.[144,145] Both studies showed promising results that urge further evaluation in randomized phase III setting.

MANAGEMENT OF ADVANCED DISEASE

Diagnosis and Evaluation

When metastatic disease is suspected, the diagnosis should be pathologically confirmed whenever possible. Often this can be accomplished with a minimally invasive procedure, such as excisional biopsy, fine-needle aspiration, or core biopsy. Routine staining of the pathology slides plus immunohistochemical staining with S100, HMB-45, and anti-MART-1/Melan-A, should confirm the diagnosis of melanoma and differentiate it from other malignancies. In the rare circumstance in which it is necessary to differentiate clear cell sarcoma from melanoma, the presence of the t(12;22)(13;q13) translocation can be used to exclude the diagnosis of melanoma. Patients should be fully staged with appropriate imaging studies before therapy is initiated. All patients should undergo an MRI scan of the brain, and whole-body imaging with either spiral CT scans of the chest, abdomen, and pelvis or combined PET/CT. Patients with bony symptoms should have a bone scan, plain x-rays, or MRI, depending on the clinical assessment.

Role of Surgery in Advanced Melanoma

Because highly effective chemotherapy is not available, surgery can be an appropriate treatment for isolated metastases. Surgical excision of isolated metastatic melanoma can provide quick and effective palliation and, in some cases, long-term survival.[146,147] Surgical candidates should be selected carefully. Surgery should be used only in cases of accessible lesions and when the risk of perioperative morbidity is acceptable. Isolated visceral metastases, especially to the brain and lung, are amenable to surgical therapy. The same is true for both symptomatic and asymptomatic gastrointestinal metastases, as well as for lesions in the skin, subcutaneous tissues, or distant lymph nodes.

Chemotherapy

DTIC is an alkylating agent that is converted to its active metabolite, 5-(3-methyl-1-triazeno) imidazole-4-carboxamide (MTIC), in the liver. As a single agent, it has been studied extensively in metastatic melanoma. In early studies by the Central Oncology Group, DTIC had an overall response rate of 20%, with 5% of patients achieving complete responses.[148] Most of the patients responding to this treatment had nodal or cutaneous metastases. Subsequent randomized studies showed objective response rates of 5% to 20%.[148,149] With modern antiemetic agents, DTIC is very well tolerated. Although multiple dosage schedules have been studied, 800 to 1000 mg/m^2 IV over 1 hour every 3 to 4 weeks is more convenient and at least as effective as any other schedule.[149] Unfortunately, DTIC has not been proven to provide a survival benefit compared with supportive care or other treatments. Temozolomide, also an alkylating agent, is a pro-drug of MTIC. In contrast to DTIC, temozolomide is orally available and penetrates the blood–brain barrier. It currently is FDA-approved for the treatment of primary brain tumors, but not for melanoma. In a phase II trial, temozolomide at a dose of 150 to 200 mg/m^2 orally on days 1 to 5 in a 28-day cycle had similar activity to DTIC, with a complete response rate of 5% and an overall response rate of 21%, with some responses in the central nervous system (CNS).[150] In a head-to-head comparison, the survival rates were similar—6.4 months for DTIC and 7.7 months for temozolomide.[151] Both agents are well tolerated. The oral administration route for temozolomide is attractive to patients, but without FDA approval, it is not always adequately reimbursed by insurance. Temozolomide also is used on an extended schedule, 75 mg/m^2 orally every day for 6 weeks followed by a 2-week break. This is the preferred dosing when concurrent external beam radiation to the CNS, or elsewhere, is indicated, since temozolomide is radiosensitizing.[152,153] Studies currently are in progress to determine whether one dosing regimen is better than the other. A phase I study showed greater drug exposure with an extended dosing regimen,[154] whereas selective CD4+ lymphopenia is more common with the extended regimen.[155] Consideration should be given to prophylaxis against *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) pneumonia in these patients, especially those who are receiving concomitant radiation.

A long list of chemotherapeutic agents has shown low levels of activity in metastatic melanoma, including the platinum compounds cisplatin[156] and carboplatin,[157] BCNU,[158] vindesine,[159] paclitaxel,[160] docetaxel,[161] and vinorelbine.[162] None has been shown to be superior to DTIC as a single agent, in either efficacy or toxicity profile. Two-drug combinations have not yet yielded superior results to single-agent DTIC. A small, randomized trial comparing DTIC with DTIC plus tamoxifen showed almost a doubling of the response rate with the addition of tamoxifen.[163] This result, however, was not confirmed in a follow-up study.[164] A three-drug combination of cisplatin, vinblastine, and DTIC showed encouraging early results in a phase III trial comparing the combination with single-agent DTIC, but unpublished follow-up data showed no advantage to the combination.

Two combination chemotherapy regimens—bleomycin, vincristine, lomustine, and DTIC (BOLD) and a combination of three alkylating agents (DTIC, BCNU, and cisplatin) with tamoxifen, known as the Dartmouth regimen—showed great promise in the treatment of metastatic disease and became quite popular among clinicians during the 1980s and early 1990s. The BOLD regimen demonstrated an objective response rate of greater than 40% in a phase II trial.[165] However, in a phase III study, the response rate dropped to the single digits and the regimen fell out of favor.[166] In several single-institution studies of the Dartmouth regimen, very high response rates of greater than 50% were consistently reported.[167] In one single-institution study, when tamoxifen was removed from the regimen to minimize the risk of deep vein thrombosis, the response rate dropped precipitously.[168] In a randomized trial performed by the National Cancer Institute of Canada in which the Dartmouth regimen was compared with the Dartmouth regimen minus tamoxifen, no survival advantage was shown to occur with the addition of tamoxifen.[169] However, there were more objective responses in the tamoxifen group, particularly in patients who would now be categorized as stage M1a. In an Intergroup study led by investigators at Memorial Sloan-Kettering Cancer Center, the Dartmouth regimen was compared with single-agent DTIC. In this large randomized study, no survival benefit was seen with the Dartmouth regimen. Of note, again there were more objective responses seen in the combination chemotherapy arm.[149] Further, in a randomized trial comparing the Dartmouth regimen with Melacine (Corixa Corp.), a melanoma cell-lysate vaccine, alone, survival rates were equally poor in both arms, but toxicity was significantly less with the vaccine.[170]

Immunotherapy

Since the early 1980s, two biologic therapy agents, interferon-alfa (2a and 2b) and interleukin-2 (IL-2) have been studied extensively in metastatic melanoma. In multiple studies of single-agent interferon alfa in metastatic disease, the objective response rate was approximately 15%. With single-agent interferon alfa, there are very few complete responses, and a survival benefit has never been demonstrated. Most responses are in patients with soft tissue or lymph node involvement (stage M1a).[171,172] Higher, more toxic doses appear more active, but low, nontoxic doses (1 to 3 million units/m^2 SC) appear inactive in the metastatic setting.[172] There is no randomized clinical study showing a survival benefit when interferon-alfa is added to any single agent, such as DTIC[164] or IL-2,[173] or to any combination therapy regimen, including the BOLD[174] and Dartmouth regimens.[175]

IL-2, originally known as T-cell-derived growth factor, was first reported by Rosenberg and associates[176] to have significant response

rates in metastatic melanoma when given at high doses. While it does activate several types of immune effector cells, including lymphokine-activated killer cells, natural killer cells, B and T lymphocytes, and macrophages, its mechanism of action remains unclear. Its principal anti-melanoma activity is believed to be mediated by the activation of melanoma-specific cytotoxic T cells. High-dose IL-2 has been extensively studied in metastatic melanoma. Two large series have been published using the high-dose schedule of 600,000 to 720,000 units/kg IV every 8 hours for 14 doses originally described by Rosenberg and associates.[176] The National Cancer Institute reported an overall response rate of 18% and a complete response rate of 5%, with some of the responses being quite durable.[177] Similar results were reported by Atkins and associates.[178] The striking finding in both studies was that of a few, very durable responses, some maintained for longer than 120 months.

Adoptive immunotherapy with lymphokine-activated killer cells does not appear to improve the response rate seen with high-dose IL-2 alone.[179] The response rate with tumor-infiltrating lymphocytes and IL-2 was reported to be 40%, but this has not been confirmed in a phase III trial.[180]

High-dose IL-2 can cause substantial toxicity. The patient must be hospitalized for administration of the drug and subsequent close monitoring. Major side effects include fluid retention, renal failure, myocardial ischemia, and neurologic changes. Patients with underlying cardiac, renal, or pulmonary disease are not candidates for high-dose IL-2 therapy.[181] Patients with any risk factors for cardiac disease should have a normal cardiac stress thallium study before receiving high-dose IL-2. Many low-dose, alternative IL-2 regimens have been evaluated, including low-dose bolus administration, continuous infusion, and SC administration. Although these regimens are associated with less toxicity, none has shown a significant objective response rate and none has provided long-term remission. Polyethylene glycol modified-IL-2[182] and liposomal IL-2[183] have not shown any substantial clinical benefit.

Based on the in vitro synergy between IL-2 and interferon alfa-2b in metastatic melanoma, several clinical trials have been conducted combining the two agents. Activity was seen only with doses of IL-2 that required inpatient administration.[173] The hope that combined therapy with relatively nontoxic, low-dose, outpatient IL-2 and interferon would yield significant clinical activity in metastatic melanoma has not been realized.

Biochemotherapy

In the early 1990s, several investigators began to study intensive regimens that included combination chemotherapy and the biologic agents interferon alfa-2b and IL-2. Single-institution studies showed significant objective response rates. Richards and colleagues[184] combined BCNU, cisplatin, and DTIC with high-dose IL-2 and interferon in a sequential fashion and obtained an overall response rate of 55% and a complete response rate of 14%. Legha and colleagues[141] combined the cisplatin, vinblastine, and DTIC (CVD) chemotherapy regimen with continuous-infusion IL-2 and SC interferon alfa-2b, first sequentially and then in a combined regimen, with all of the drugs given over a 5-day period and the cycle repeated every 3 weeks. The combined regimen consisted of cisplatin, 20 mg/m^2 IV on days 1 through 4; vinblastine, 1.5 mg/m^2 IV on days 1 through 4; DTIC, 800 mg/m^2 IV on day 1 only; IL-2, 9 million units/m^2 daily by continuous infusion on days 1 through 4; and interferon alfa-2b, 5 million units/m^2 SC on days 1 through 5, and on days 7, 9, 11, and 13; and was repeated every 21 days. The authors reported an overall response rate of 64% and a complete response rate of 21%. The combined regimen seemed as active as the more protracted sequential regimen.

Two large single-institution randomized phase III studies have been reported comparing combination chemotherapy with biochemotherapy. The National Cancer Institute Surgery Branch compared a regimen of cisplatin, DTIC, and tamoxifen with the same regimen followed immediately by high-dose IL-2 and interferon alfa-2b. The overall response rate was higher in the biochemotherapy arm, but median survival was superior in the chemotherapy arm (15.8 vs. 10.7 months).[185] At M.D. Anderson Cancer Center, CVD was compared with CVD plus IL-2 and interferon alfa-2b given sequentially. The overall response rate and median survival rate were superior in the biochemotherapy arm (48% vs. 25% and 11.8 months vs. 9.5 months, respectively).[186]

The encouraging results reported in these studies led to a large randomized Intergroup study led by ECOG (protocol 3695).[142] This study compared CVD with the combined CVD, IL-2, and interferon alfa-2b regimen of Legha,[141] with several modifications, including reducing the dose of vinblastine by 25%, using prophylactic G-CSF, and limiting the number of chemotherapy cycles to four. This modified Legha biochemotherapy regimen previously was studied in a phase II trial and yielded an objective response rate of 48% and a complete response rate of 20% in 40 patients.[187] In ECOG 3695, 416 patients were enrolled between 1998 and 2002 and no previous chemotherapy or IL-2 was permitted. Sixty percent of the patients had received high-dose interferon alfa-2b prior to the development of metastatic disease. The overall response rate was 17.1% in the biochemotherapy arm vs. 11.4% in the chemotherapy arm, and complete response rates were 3% vs. 1.4%, respectively. OS was equally poor in both arms of the study, 8.7 months for biochemotherapy vs. 8.4 months for chemotherapy.[142] The results of this large, well-done, randomized trial were very disappointing. It may be that the reduced vinblastine dose and the lack of familiarity by physicians and nurses with the complex biochemotherapy regimen contributed to the low response rates in the cooperative group setting. However, the results show that biochemotherapy, as given in this trial, leads to very few durable responses and should not be considered a standard therapy. It is possible that when this study is published with a more detailed analysis, subsets of patients may be identified who are more likely to benefit from biochemotherapy, such as those who have an excellent performance status, low-volume disease, or no previous treatment with interferon alfa-2b. It seems unlikely that any variation of biochemotherapy currently being evaluated will prove superior to the regimen studied in ECOG 3695.

O'Day and colleagues[188] explored the use of maintenance biotherapy (IL-2 and GM-CSF) for patients who achieved stable disease or partial remission with biochemotherapy. One hundred thirty-three patients were enrolled and treated on a 1-year program consisting of IL-2, 1 million units/m^2 SC Monday through Friday; GM-CSF, 125 μg/m^2 SC, 2 weeks on and 2 weeks off; and seven 2-day IV infusions of decrescendo IL-2. The reported 12- and 24-month survival was 57% and 23%, respectively, and 12% of patients were disease-free at a median follow-up of 30 months. Although the results are intriguing, in light of the low response rates to biochemotherapy reported in the ECOG 3695 trial, it seems that only a very small number of patients would benefit from this approach.

New Therapies

New treatment options are under development for patients who have advanced locoregional or widely disseminated melanoma. From a clinical and basic research perspective, melanoma occupies the crossroads of molecular biology and immunology. As an externally visible tumor, it offers a unique opportunity to investigate lesions at the earliest stages of carcinogenesis for molecular events or signatures portending progression, invasion, and dissemination. Knowledge of the genetic basis for aggressive melanoma behavior has led to the design of molecularly targeted therapies. In addition, melanoma is among the most immunogenic of all human cancers, and as such has been the prototype for defining cancer-specific antigens and developing anti-cancer immunotherapies.

IMMUNOTHERAPY

Cancer vaccines are a form of active immunotherapy, the effects of which depend on target-specific activation of the patient's immune system. Vaccines directed against melanoma-associated or melanoma-specific proteins (antigens) have proved capable of enhancing anti-tumor immune responses in patients that can be detected in vitro, and yet have had limited clinical success in the setting of advanced metastatic disease. Most melanoma vaccine trials for advanced melanoma have been nonrandomized phase I/II studies. These have included inoculation with whole melanoma cells or gene-modified cells, heat shock proteins, naked DNA, recombinant viral vectors, recombinant proteins, synthetic peptides, and dendritic cells pulsed with peptides or cell lysates.[189] Peptide vaccines have been studied most intensively, due to ease of manufacturing at relatively low cost, low potential for toxicity, and well-developed laboratory techniques for immunomonitoring. The targeted antigens have included commonly expressed cancer-testis antigens (e.g., MAGE, NY-ESO-1) and melanoma differentiation antigens (e.g., tyrosinase, gp100, MART-1/Melan-A). Clinical trials have explored the best way to administer peptide vaccines, whether as a single peptide, with multiple peptides binding to HLA class I alone or to both class I and class II (eliciting both cytotoxic and helper T cell responses); with amino acid substitutions that augment their immunogenicity; or in combination with other biologic agents. However, the results of melanoma vaccine trials to date, and cancer vaccine trials overall, have been generally disappointing in the setting of advanced disease, with objective response rates of less than 5%.[190] It is possible that melanoma vaccines will be more efficacious in the adjuvant setting, against microscopic disease burdens.

The immunosuppressive in vivo milieu of the tumor microenvironment is now thought to play a critical role in determining the outcome of interactions between the immune system and cancer. Recent studies indicate that immune responses are tightly regulated by positive and negative signals, through receptor-ligand interactions on the cell surface. Specific interactions between costimulatory or coinhibitory receptors on resting and activated T lymphocytes (CD28 family of molecules), and their ligands on tumor cells or professional antigen presenting cells (B7 family), trigger biochemical signals leading to cascades of transcription and expression of downstream genes in the cell nucleus. These are among the earliest events regulating the initiation, differentiation, functional maturation and termination of innate and adaptive immune responses. CTLA-4, an inhibitory member of the CD28 family of molecules which binds to B7.1 and B7.2 on antigen presenting cells, has been recently targeted in phase I and II clinical trials via infusions of blocking antibodies to treat patients with advanced stage III/IV melanoma.[191,192] Objective response rates (complete + partial responses) of 13%, including durable complete responses, have been observed, but a significant rate of serious autoimmune complications (approximately double the response rate) has limited the use of this agent.[193] Current investigations aim to identify molecular markers that might make it possible to select patients most likely to benefit from this therapy and least likely to develop autoimmune responses. However, available clinical data indicate a significant correlation between autoimmunity and tumor regression,[192,193] consistent with the mechanism of action of anti-CTLA-4. Blocking antibodies directed against other CD28 and B7 family members are under clinical development, and based on information from preclinical models they may provide a more favorable therapeutic ratio than anti-CTLA-4. These include antibodies blocking PD-1, a co-inhibitory receptor on T cells, and B7-H1, a ligand for PD-1 that is expressed on most melanomas.[194] Because preliminary data have revealed PD-1 expression on highly activated melanoma-specific T cells stimulated by cancer vaccines and other means, the combination of PD-1:B7-H1 blockade with immunization is envisioned for future clinical trials.

Adoptive immunotherapy, a form of passive immunotherapy involving the transfer of ex vivo-expanded tumor-specific T lymphocytes into immune-replete or depleted patients, has been under study for the past two decades as a treatment for advanced metastatic melanoma.[195] Preclinical models have indicated the potential advantages of removing tumor-specific lymphocytes from the immunosuppressive in vivo milieu, and manipulating them in vitro to express a "favorable" phenotype of rapid proliferation and anti-tumor reactivity (cytokine secretion, cytolysis, highly avid T cell receptors) prior to transfer back into the autologous cancer-bearing host. For patients with at least one surgically resectable metastatic lesion, tumor infiltrating lymphocyte (TIL) therapy seems to offer the highest probability of objective clinical response. Adoptive TIL transfer in the context of lymphodepleting chemotherapy and high-dose IL-2 has yielded an objective response rate of 51%, including heavily pretreated patients who have not responded previously to high-dose IL-2 therapy.[196] As expected, serious toxicities related to chemotherapy-induced cytopenias and IL-2 administration, as well as some significant autoimmune events, were encountered. For patients without resectable tumors, or whose tumors fail to yield reactive TIL, alternative T cell transfer options have been explored in the clinic. These include melanoma peptide-specific T cell clones and cell lines derived from peripheral blood,[197,198] or peripheral blood lymphocytes genetically engineered to express melanoma peptide-specific T cell receptors.[199] These approaches have yielded relatively low objective response rates (0 to 15%), possibly due to the lack of T cell help, failure of transferred T cells to traffic to tumor sites, expression of PD-1 or other coinhibitory receptors on T cells, or emergence of antigen-negative tumor variants. Currently, clinical development of adoptive T cell transfer still is restricted to a limited number of medical centers due to the complex and intensive nature of this treatment.

Anti-Angiogenic Agents

Melanoma is a highly vascular tumor, and because new blood vessel formation is thought to play an important role in its pathobiology, the clinical use of anti-angiogenic agents is being actively investigated in advanced metastatic disease. Thalidomide, which has anti-angiogenic as well as immunomodulatory properties, is ineffective as a single agent against metastatic melanoma.[200] However, recent clinical trials have investigated the activity of thalidomide in combination with extended dosing of temozolomide. In a phase II trial which excluded patients with brain metastases or prior chemotherapy, an objective response rate of 32% was observed among 38 patients with advanced stage IIIC or IV disease.[201] A markedly lower response rate of 12% was observed in a phase II study using the same dosing regimen, which included patients with brain metastases and prior chemotherapy.[202] Of note, a phase II trial of the same combination regimen in patients with brain metastases, with or without extracranial metastases, was discontinued prematurely because of a high rate of serious or lethal adverse events (31%), particularly thromboembolic events, in the absence of objective tumor regressions.[203] Newer anti-angiogenic agents evaluated in early-phase melanoma clinical trials include the thalidomide analog lenalidomide (CC-5013, Revimid)[204]; the anti-avβ3 integrin antibody MEDI-522[205]; and anti-vascular endothelial growth factor (anti-VEGF, bevacizumab, Avastin).[206] Owing to the mechanism of action of this class of antineoplastic agents, it is possible that disease stabilization, rather than objective tumor regression, will prove to be the most appropriate indicator of efficacy.[207]

Targeted Therapies

Recent scientific advances have increased our understanding of the molecular events promoting melanoma carcinogenesis and maintaining the cancer cell phenotype. Most commonly, these involve

aberrations in the mitogen-activated protein kinase (MAPK) pathway supporting cell proliferation, the phosphatidylinositol 3′ kinase (PI3K) pro-survival pathway, and/or the melanocyte-stimulating hormone (MSH)/microphthalmia-associated transcription factor (MITF) melanocyte lineage-specific survival pathway.[35,208] Knowledge of these genetic events has permitted the rational targeting of critical molecules supporting melanoma growth and survival.[209] In the largest randomized trial conducted to date in patients with advanced stage III/IV melanoma, Bcl-2 antisense oligonucleotide (oblimersen, Genasense [Genta Incorporated]) was combined with DTIC in an attempt to enhance the chemosensitivity of melanoma cells by blocking pro-survival mechanisms. Studies have shown variable overexpression of Bcl-2, which inhibits the intrinsic apoptosis pathway, in melanomas. Compared to patients treated with DTIC alone, patients receiving the combination regimen showed small but statistically significant increases in objective response rate, durable response, and progression-free survival. Increased benefits were observed in a subset of patients with normal serum LDH, suggesting that such patients should be selected for future trials with oblimersen.[210]

BRAF is a member of the MAPK signaling pathway, which transduces extracellular signals via cell surface receptor tyrosine kinases to promote cell activation and proliferation. A somatic Val600Glu missense mutation in the kinase domain of BRAF is associated with more than 50% of melanomas, as well as with smaller percentages of some other cancers, and causes constitutive activation of the MAPK pathway contributing to melanoma progression.[25] The multikinase inhibitor sorafenib (Nexavar [Onyx Pharmaceuticals]), which targets mutant and wild-type BRAF as well as c-Kit, VEGFR-2, VEGFR-3, and some other proliferation and angiogenesis receptors, recently was shown to be ineffective against advanced melanoma as a single agent.[211] In addition, in 2006 the corporate drug sponsor announced failure to demonstrate improvement in PFS, the primary endpoint, in its international randomized phase III trial comparing sorafenib to placebo in combination with carboplatin and paclitaxel in chemotherapy-refractory patients with advanced melanoma.[212] An ECOG trial that is of similar design but targets chemotherapy-naïve patients and has OS as its endpoint, is currently in progress.

Several clinical trials exploring the efficacy of imatinib (Gleevec) in advanced melanoma have been conducted, despite varied data regarding the expression of c-Kit tyrosine kinase receptor in melanoma.[213,214] The results of two phase II trials using high-dose imatinib as a single agent have shown no evidence of clinical efficacy.[215,216] However, a recent report has demonstrated the association of genetic abnormalities in c-Kit (mutations, amplifications) with distinct clinical subtypes of melanoma, specifically acral melanoma, mucosal melanoma, and melanomas arising from chronically sun-exposed skin.[32] Kit abnormalities were not observed in melanomas arising from skin without chronic sun damage. Of note, this pattern of genetic abnormality is distinct from that observed in melanomas with mutated NRAS/BRAF, underscoring the fact that clear genetic subtypes of melanoma exist. Thus, rational selection of patients for treatment with imatinib as well as other molecularly targeted agents in future clinical trials will depend on the identification of subsets of melanoma patients harboring the relevant genetic alterations.

Ending Treatment

Patients with a poor performance status, comorbid conditions, multiple brain metastases, or advanced age are unlikely to benefit from intensive systemic therapy. These patients also may experience more side effects than healthier patients from the currently available therapies. Providing comfort measures only may be a reasonable option in some patients with metastatic melanoma. Likewise, if first-line therapy for metastatic melanoma has been unsuccessful, the patient should undergo a thoughtful assessment of his or her overall status before additional anti-tumor therapy is given. In any case, supportive care and comfort measures are essential aspects of oncologic practice.

Special Clinical Situations in Stage IV Disease

Solitary Metastasis

Occasionally, patients have a solitary metastatic lesion. There have been several reports of prolonged survival after surgical resection of solitary brain, lung, and liver metastases, regardless of whether patients also received postoperative adjuvant therapy.[146] A number of clinical trials are underway for patients with stage IV melanoma and no evidence of disease, and patient enrollment should be strongly considered. There is no established role for adjuvant therapy in this setting, including interferon alfa-2b, outside of a clinical trial.

Brain Metastasis

Patients with brain metastases generally do poorly. Standard therapy is whole-brain irradiation, which offers some palliation. Patients with a solitary brain lesion and no disease elsewhere, or responding or slowly growing systemic disease, should be considered strongly for neurosurgical resection, stereotactic radiosurgery, or gamma-knife therapy.[217] For patients with multiple brain metastases and a good performance status, consideration should be given to stereotactic radiosurgery or gamma-knife surgery, after whole-brain radiation. Those patients with measurable brain metastases also should be considered for temozolomide therapy, in addition to local measures, because this is the only systemic treatment that penetrates the blood–brain barrier. In the appropriate setting, these approaches can provide significant local control and palliation.

Unusual Problems

Unknown Primary Site

Patients can present with stage III or IV disease without a history of previously diagnosed melanoma. All of these patients should have a thorough skin examination, including the anal region. An eye examination is appropriate if the metastatic pattern is consistent with ocular melanoma. Unless there are specific intestinal or gynecologic signs or symptoms to suggest a mucosal primary, invasive tests, such as colonoscopy or upper endoscopy, are not recommended. Often a primary site is not found. Sometimes patients provide a history of an unusual skin lesion arising and disappearing without biopsy or treatment, or a history of a skin lesion that was cauterized or frozen. Patients who appear to have only regional lymph node involvement should undergo a potentially curative regional lymph node dissection, like any other patient with regional metastases. These patients should then be considered for systemic adjuvant therapy. Patients with isolated or disseminated metastatic disease should be treated according to the same paradigms as those with known primaries. Periodic follow-up with a dermatologist still is recommended.

Uveal Melanoma

Uveal, or ocular, melanoma is rare. Although it can be morphologically similar to cutaneous melanoma, clinically it behaves differently. Primary ocular melanoma most often is treated with iodine 125 plaque brachytherapy or enucleation.[218] Ocular melanoma metastasizes via a hematogenous route, often spreading primarily to the liver. Sometimes the metastatic process moves relatively slowly, with several years passing before recurrence with metastatic disease. It appears to respond less often to chemotherapy and biologic therapy, although this was not confirmed in a review of the SWOG experience.[219] Some biologic correlates may explain these differences: human leukocyte antigen expression appears downregulated on ocular melanoma cells,[220] the BRAF mutation is not present,[221] and distinct chromosomal abnormalities, such as monosomy 3, are present.[222] Although initial results using the BOLD plus interferon alfa-2b regimen in metastatic ocular melanoma were promising, these results were not

confirmed in a large trial.[223] Some patients with primarily liver metastases appear to benefit from chemoembolization[224] or liver perfusion.[225] Many clinical trials for metastatic melanoma exclude patients with ocular melanoma.

Mucosal Melanoma

Primary mucosal melanoma also is rare. Patients often have advanced disease at the time of initial diagnosis because primary sites in locations such as the gastrointestinal tract or sinuses make early detection difficult. This, too, appears to be a distinct disease, although morphologically similar to cutaneous melanoma.[32,35] Interestingly, a retrospective analysis showed a surprisingly good response rate of 44% for biochemotherapy in 18 patients with metastatic anorectal melanoma.[226] Currently, treatment options for metastatic disease are the same as those for cutaneous metastatic melanoma.[227]

TREATMENT COMPLICATIONS

Serious postsurgical complications are uncommon. The risks of bleeding and infection after most surgeries for melanoma are small. After sentinel node biopsy, some patients have a transient lymphocele at the site of node excision. The risk of lymphocele can be minimized by tying off the lymphatics during the sentinel node resection. If a lymphocele is large or painful, a simple office aspiration should provide adequate management. Small, asymptomatic lymphoceles can be observed and usually resolve on their own. Lymphedema has been reported in patients after sentinel node biopsy of the axilla and the inguinal area, but the incidence is low.[228]

Complete lymphadenectomy for regionally metastatic melanoma carries a risk of seroma, sensory loss, and lymphedema. A few patients have a seroma or prolonged drain output. Lymphedema is the most feared common complication of lymph node dissection and can occur after axillary or inguinal lymphadenectomy. The risk of lymphedema in this population in general is low, and most cases are mild to moderate and controllable with diligent care.

FOLLOW-UP AND SURVEILLANCE PLANS

Most melanoma recurrences are recognized first by the patient him- or herself or on a routine physical examination. A study from the Sydney Melanoma Unit reported that 73% of all first melanoma recurrences were detected by the patients themselves.[229] Mooney and colleagues[230] reported the results of a surveillance program using physical examination, blood tests, and chest x-rays for 1004 patients with stage I or II cutaneous melanoma. Physical examination detected 72% of recurrences, constitutional symptoms indicated 17% of recurrences, and chest x-ray showed 11% of recurrences. Among the 373 patients followed in a surveillance program at the Yale Melanoma Unit, of the 78 patients who had recurrences, 76% were diagnosed by a complete history and physical examination alone.[231] Routine laboratory or radiologic studies have never been shown to be beneficial for follow-up of patients with early stage melanoma.

For patients with stage III or IV disease there is no consensus about utility of, or the optimal frequency of, routine surveillance imaging. Occasionally, false-positive lesion findings on CT scan can lead to anxiety, further diagnostic tests, or even biopsy of lesions that may be unrelated to the melanoma. CT scans are useful for evaluating suspected pulmonary, mediastinal or intra-abdominal metastases, and often are of greatest use in the evaluation of patients with symptoms that raise concern or new findings on physical examination.

In patients with known distant metastases, scans are most useful when the presence of additional metastases would alter the treatment plan or when better definition of lesions is required for treatment planning or patient entry into a research protocol. FDG-PET has a sensitivity of 78% to 100% in detecting metastatic melanoma. False-positive findings may be seen in patients with inflammatory processes, such as sarcoid, and in those with second primary tumors.[57,58,232] PET also can be used to determine the need for further diagnostic procedures, such as radiologically guided needle biopsy of suspicious, accessible lesions.

In a patient with symptoms, an abnormal finding on physical examination or laboratory tests, or an abnormal x-ray, the definitive diagnosis of metastatic melanoma can be made only by a biopsy. Excisional or needle biopsy is relatively easy to perform when the suspected metastasis is easily accessible. However, in the right clinical setting, radiologic studies are sufficient for a clinical diagnosis, especially if the metastases involve more than one site and the abnormality was not present on previous studies.

ISSUES FOR THE FUTURE

Today, most melanomas are found at an early stage and thus are very treatable. In fact, surgery often is the only necessary treatment. However, some melanomas are at an advanced stage when they are detected, and even some early melanomas eventually will recur. There is no routinely reliable and successful way to treat patients with advanced disease. Today the most important ways to improve melanoma-related survival are prevention and early detection.

Although much progress has been made in identifying the molecular defects that are common to malignant melanocytic lesions, few of these discoveries have thus far been translated to effective therapies. It is expected that further research in the molecular genetics and the immunology of melanoma will result in an explosion of information about the events governing melanoma onset and progression. Given the limited pathologic materials available for study, multi-institutional collaboration will be required to substantially improve our understanding of the pathogenesis of melanoma. Ultimately, these discoveries will provide the framework for the design of targeted therapies for future melanoma patients.

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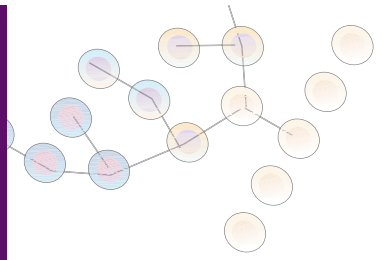
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74 Nonmelanoma Skin Cancers: Basal Cell and Squamous Cell Carcinomas

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SUMMARY OF KEY POINTS

Incidence
- 1 million new cases occur annually including 80% basal cell carcinomas (BCCs) and 20% squamous cell carcinomas (SCCs).
- Incidence is increasing 2% to 3% per year.
- SCC incidence is increased 18- to 36-fold in organ transplant recipients.

Etiology and Epidemiology
- Ultraviolet radiation from sun exposure is a major risk factor and causes mutations in key genes.
- Hedgehog signaling pathway mutations are involved in BCC pathogenesis.
- p53 mutations are involved in both SCC and BCC pathogenesis, as well as in the development of actinic keratoses, which are the precursors of SCCs.

Pathology and Biology
- Several histopathologic subtypes exist.
- The more infiltrative or poorly differentiated variants are more clinically aggressive (e.g., morpheaform BCC and spindle cell SCC).

Clinical Findings
- BCC and SCC are found mainly on sun-exposed skin.
- Classic BCC is a pearly, telangiectatic, variably ulcerated nodule or a pale, sclerotic plaque.
- Classic SCC is a flesh-tone or red, variably keratotic, variably ulcerated nodule.

Differential Diagnosis and Staging
- Amelanotic melanoma, keratoacanthoma, cutaneous metastasis, cutaneous lymphoma, cutaneous lymphoid hyperplasia, adnexal tumor, Merkel cell carcinoma, and sebaceous gland carcinoma are included in the differential diagnosis.
- BCCs that are large, deep, or infiltrative may be locally aggressive and recurrent but metastasize only rarely (<0.05%).
- SCCs have a greater metaststic rate, especially those that are large, deep, have perineural invasion, or are located on the dorsal hands, lips, ears, penis, or sites of chronic infection, ulceration, or radiation.

Primary Therapy and Salvage Therapy
- Primary treatment for both BCCs and SCCs is surgical. Mohs' surgery is preferred for ill-defined or aggressive lesions because it allows microscopic control of tumor margins.
- Alternative therapies include various forms of physical destruction and radiation therapy. Interferons and inducers of interferons (e.g., imiquimod) are proving useful in selected cases.
- Retinoids, COX-2 inhibitors, and difluoromethylornithine are promising chemopreventive agents.
- Combinations of surgery, radiation therapy, and chemotherapy can be used for metastatic disease.

Complications
- Complications are principally related to local factors and include local recurrence, destruction of adjacent structures, scarring, and loss of function.

Prognosis
- Relative to most other forms of cancer, the overall prognosis for BCCs and SCCs is very good. There are only about 2000 deaths annually in the United States as compared with about 1 million new cases diagnosed.
- Local recurrence is a problem for large, deep, or histologically infiltrative variants. SCCs with these features may also metastasize. The 5-year survival for patients with metastatic SCC is <50%.
- The rarer forms of nonmelanoma skin cancer have a significantly more aggressive clinical course as compared with BCC and SCC. These include sebaceous carcinoma, Merkel cell carcinoma, dermatofibrosarcoma protuberans (DFSP), and cutaneous angiosarcoma.

INTRODUCTION

Most nonmelanoma skin cancers (NMSCs) are basal cell carcinomas (BCCs) or squamous cell carcinomas (SCCs). However, several rarer forms of NMSC exist, including four malignant neoplasms discussed in this chapter: sebaceous gland carcinoma, Merkel cell carcinoma, angiosarcoma, and dermatofibrosarcoma protuberans (DFSP). Each of these neoplasms is discussed separately after a summary of genetic alterations in BCC, SCC, and selected genodermatoses. Understanding the genetic basis of skin cancer is an important step in improving prognosis among patients with these neoplasms. Analysis of germline mutations in familial cancer syndromes and somatic mutations in sporadic skin cancers is providing new information that will facilitate the diagnosis of cutaneous malignant diseases and revolutionize their management.

GENETICS OF NONMELANOMA SKIN CANCER

Advances in molecular genetics have allowed for key advances in our understanding of NMSC, the most common cancer in the United

States. Like visceral malignant neoplasms, cancer of the integument is caused by defects in the normal genetic code. These genomic defects are either germline mutations (those caused by inherited mutations) or somatic mutations (those caused by acquired mutations). Actual tumor formation, however, is a complicated process, usually requiring more than a single mutation and sometimes a combination of germline and somatic mutations. In addition, these cancerous cells are frequently altered in ways that help them escape detection by the host's immune system.

Tumor suppressor genes and oncogenes are two basic classes of genes that undergo mutations leading to skin cancer. Examples of tumor suppressor genes include the patched gene involved in development of BCC, p53 involved in development of SCC, and the xeroderma pigmentosum genes involved in development of BCC, SCC, and melanoma.[1–3] These genes can be further divided into tumor suppressor genes that directly participate in growth regulation, such as the patched and p53 genes, and those that participate indirectly and are called caretaker genes, such as the xeroderma pigmentosum genes encoding DNA repair enzymes.

Oncogenes are the other class of genes contributing to skin cancer formation. These are generally growth-signaling molecules that once mutated can perpetually lead normal cells to become malignant cells by altering cellular growth. One example is the *ras* oncogene implicated in several skin cancers, including BCC, SCC, and melanoma.[4,5]

Sonic Hedgehog Pathway

The sonic hedgehog (Shh) pathway has been implicated in both hereditary and sporadic cases of BCC. These tumors are the most common of all skin cancers, with an estimated 1 million new cases per year.[6] In the Shh pathway, the transmembrane protein receptor for Shh, known as patched1 (Ptch1), binds and inhibits another transmembrane protein called smoothened (Smoh).[7] Smoh is responsible for growth promotion, and binding by Ptch1 keeps this growth in check. However, when the soluble lipoprotein Shh binds Ptch1, this regulation is disrupted. Smoh is thus activated, and unregulated growth is promoted through downstream zinc-finger family transcription factors, such as gli1, gli2, and gli3.

The hedgehog pathway was originally elucidated in the fruit fly (*Drosophila melanogaster*), in which mutations in the gene cause segmental patterning defects, hence the name patched.[8] Involvement in human disease was found through analysis of nevoid BCC kindreds (Gorlin's syndrome, basal cell nevus syndrome).[9] Persons with this autosomal dominant disease have odontogenic cysts, skeletal defects, palmar pits, various associated visceral tumors (medulloblastoma, meningioma, fibrosarcoma, cardiac fibroma, and ovarian fibroma), and multiple BCCs by a median age of 20 years. Early analyses mapped the defect to a tumor suppressor gene on chromosome 9q22–q31.[10] This site proved to be the location of the *Ptch1* gene. It was later elucidated that patients with nevoid BCC syndrome inherit one defective chromosome 9q region with loss of heterozygosity in the *Ptch1* locus. Many BCCs from these patients show inactivation of the remaining *Ptch1* gene through acquired somatic mutations, consistent with the view that the BCC phenotype develops once both alleles are nonfunctional. Thus, *Ptch1* acts as a classic tumor suppressor gene in the skin. Mutations in *Ptch1* also are present in many sporadic BCCs, as are mutations in other Shh pathway genes, including *Smoh*, *Ptch2*, and *Shh*.[11]

p53 Mutations

The protein p53 is encoded by the *TP53* gene on chromosome 17p and is an important regulator of cell proliferation, DNA repair, and apoptosis.[12] *TP53* can act classically as a tumor suppressor gene or act in a dominant-negative role whereby abnormal, mutant p53 protein can bind normal p53 molecules and disrupt their function.

Inactivation of the p53 gene seems to play a principal role in the development of both premalignant actinic keratosis and SCC.[13] SCC is the second most common skin cancer, accounting for approximately 200,000 cases per year and 2000 deaths per year.[6] p53 mutations causing SCC are ultraviolet (UV) induced, and many are pyrimidine alterations with CC to TT changes.[14,15] It seems that it is both the loss of the tumor suppressor ability of p53 and the ability of UV irradiation to affect induction of apoptosis by p53 that leads to tumor formation.[13]

Mutations of *TP53* have been implicated in development of sporadic BCC.[15] It seems that UV-induced alterations similar to those in SCC are involved in BCC induction. Many of the mutations are CC to TT or C to T alterations, consistent with UV damage.

Mutations of Caretaker Genes

Tumor suppressor genes involved in maintaining genomic integrity are called caretaker genes.[16] Examples of diseases associated with cutaneous malignant tumors and known defects in caretaker genes include xeroderma pigmentosum, Bloom syndrome, Rothmund-Thomson syndrome, Werner's syndrome, and Muir-Torre syndrome.

The tumor suppressor genes involved in all of these familial syndromes have the common feature of being involved in an enzymatic DNA reparative process following a mutagenic insult. Defects in these genes inhibit the ability to repair genetic damage from naturally occurring events or environmental carcinogens such as UV radiation.

Xeroderma pigmentosum is a collection of autosomal recessive disorders characterized by severe photosensitivity with onset of cutaneous malignant lesions at a very early age. BCC, actinic keratosis, SCC, and melanoma develop during the first decade of life in persons without adequate photoprotection. Mutations in eight genes have been implicated in different xeroderma pigmentosum phenotypes, which vary in severity of cutaneous neoplasia and frequency of neurologic delay.[17] All xeroderma pigmentosum-associated genes encode proteins that are part of a DNA repair process known as nucleotide excision repair, which responds to UV-induced DNA damage.[3] These proteins recognize the damaged DNA, unwind the coiled DNA structure, and repair the damaged strand. Germline mutations in these genes result in defects in the repair process and their genomic caretaker role; however, actual tumor production is still caused by mutagenic inactivation of tumor suppressor genes such as *TP53* and activation of oncogenes such as *ras*.[18,19]

Rothmund-Thomson syndrome, Bloom syndrome, and Werner's syndrome all are rare autosomal recessive disorders that have known defects in helicase genes and affect nucleotide excision repair. Like xeroderma pigmentosum, these defects allow development of malignant skin lesions in affected patients. Rothmund-Thomson and Bloom syndromes both are marked by early onset of SCC; however, patients with Werner's syndrome seem to have only increased risk of melanoma. Other syndromes with helicase gene defects, such as Cockayne's syndrome and photosensitive trichothiodystrophy, have no associated increase in cutaneous malignant tumors. It is becoming clear that development of cutaneous malignant tumors is a complex process in which ability to repair DNA is but one part of an intricate pathway. It seems that other mutations in tumor suppressor genes and oncogenes, whether germline or somatic, are necessary to invoke a tumor phenotype, as seen in xeroderma pigmentosum.

Muir-Torre syndrome (MTS) is an autosomal dominant syndrome characterized by various sebaceous gland tumors and internal malignant lesions. The sebaceous gland tumors range from benign sebaceous adenoma to malignant sebaceous gland carcinoma predominantly on the face. Keratoacanthoma is another cutaneous neoplasm of variable malignant potential that has been reported in as many as 20% of MTS patients.[20]

In initial studies of MTS families, investigators identified germline mutations in the human *MSH2* gene.[21,22] Subsequently, mutations in human *MLH1* have also been identified in patients with MTS.[23] It seems that, like other caretaker genes, human *MSH2* and *MLH1* encode a type of DNA-mismatch repair enzyme involved in repairing errors in DNA replication that occur naturally at a low rate.

In cells that have this defect, the result is varying lengths of repetitive DNA sequences known as microsatellite instability.[23] This microsatellite instability can result in functional gene mutations and has been observed in keratoacanthoma and sebaceous tumors from MTS patients.[24]

ras Oncogene

Mutations in *ras* have been implicated in development of sporadic BCC, premalignant actinic keratosis, and sporadic SCC. They are among the most common mutations in human malignant disease.[25] ras proteins are small G-proteins responsible for transducing intracellular signaling. Activation of *ras* occurs only when guanosine triphosphate (GTP) is bound. The signal is attenuated by hydrolysis of GTP to guanosine diphosphate (GDP). Mutations in *ras* alter the rate of this hydrolysis, resulting in activated protein and promotion of cell growth and hence tumor growth. There is a class of proteins that deactivates ras by increasing GTP hydrolysis to GDP (GTPase-activating proteins).[26] There is evidence that alterations in GTPase-activating proteins are implicated in the development of sporadic BCC.

BASAL CELL CARCINOMA

Epidemiology and Pathogenesis

BCC is the most common malignant tumor in the United States and in other areas with predominantly white populations. Approximately 900,000 cases per year are identified in the United States.[6] Australia has the highest incidence of skin cancer, the incidence of BCC being more than 2% among men and that of SCC being approximately 1% among men.[27] The incidence of BCC has increased over the past decades in a manner similar to the increase in melanoma. It is estimated that the incidence of NMSC is increasing 2% to 3% yearly.[28] One study, conducted in New Hampshire, showed an annual increase in incidence of SCC of approximately 10% and of BCC of approximately 5%.[29] Cumulative UV exposure and, more important, severe sunburn during childhood and adolescence are risk factors for BCC.[30] Other associated risk factors are Fitzpatrick skin types 1 and 2, red hair, freckling in childhood, family history of skin cancer, male sex, and Celtic ancestry.[31] BCC is more common in lighter skinned African Americans than in darker persons.[32] Immunodeficiency secondary to acquired immunodeficiency syndrome or transplantation also is associated with increased risk of BCC. Other uncommon risk factors include exposure to arsenic and ionizing radiation, especially among patients who have received radiation for acne.

Keratin pattern and immunohistochemical results suggest the origin of BCC is the outer root sheath of the hair follicle below the isthmus.[33] The locally invasive characteristic of BCC could be related to the presence of abnormal hemidesmosome-anchoring fibril complex.[34] Genetic abnormalities and mutations are thought to play a major role in development of BCC, especially in inherited syndromes of BCC. Patients with xeroderma pigmentosum cannot repair the UV-induced DNA mutations; therefore, they are at increased risk of cutaneous carcinogenesis. Mutations in the hedgehog signaling pathway genes and *TP53* are important in the pathogenesis of sporadic BCC and those arising in patients with the nevoid BCC syndrome and xeroderma pigmentosum.[11,13, 35–37]

Clinical Manifestations

The most common location for BCC is the head and neck, especially the nose. BCC occurs on hair-bearing skin; mucosal surfaces are not involved. The major types of BCC include nodular, pigmented, superficial, and morpheaform. The typical nodular BCC is a dome-shaped, pearly papule with a telangiectatic surface and translucent rolled borders (Fig. 74-1). The surface might become ulcerated (Fig. 74-2). In darker skinned individuals, especially African Americans, the more darkly pigmented BCCs may be misdiagnosed as seborrheic keratosis or nodular melanoma. Superficial BCC is a well-demarcated erythematous scaly plaque with elevated borders that often occurs on the trunk or extremities. It might be confused with Bowen's disease or nummular eczema. The most difficult BCC to diagnose and manage is the morpheaform or sclerosing variant. This ill-defined, white, indurated plaque can be mistaken for a scar or localized patch of scleroderma and therefore is ignored by patient and physician, with resulting wide subclinical extension.



Figure 74-1 • Typical presentation of basal cell carcinoma on the nose.

Histopathology

In common nodular BCC, nodular masses of basaloid cells extend from the epidermis or outer root sheath into the dermis with surrounding connective tissue stroma (Fig. 74-3). A palisade arrangement of cells is present in the periphery. Sometimes as a result of tumor necrosis and disintegration, cystic spaces form. The

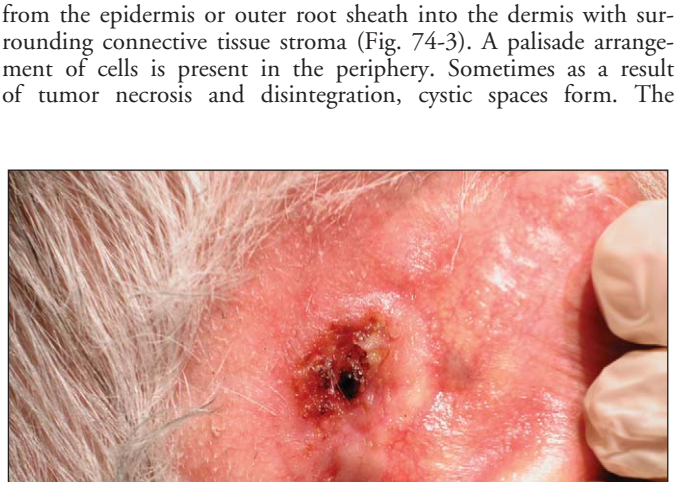


Figure 74-2 • Ulcerated basal cell carcinoma with rolled borders on posterior ear.

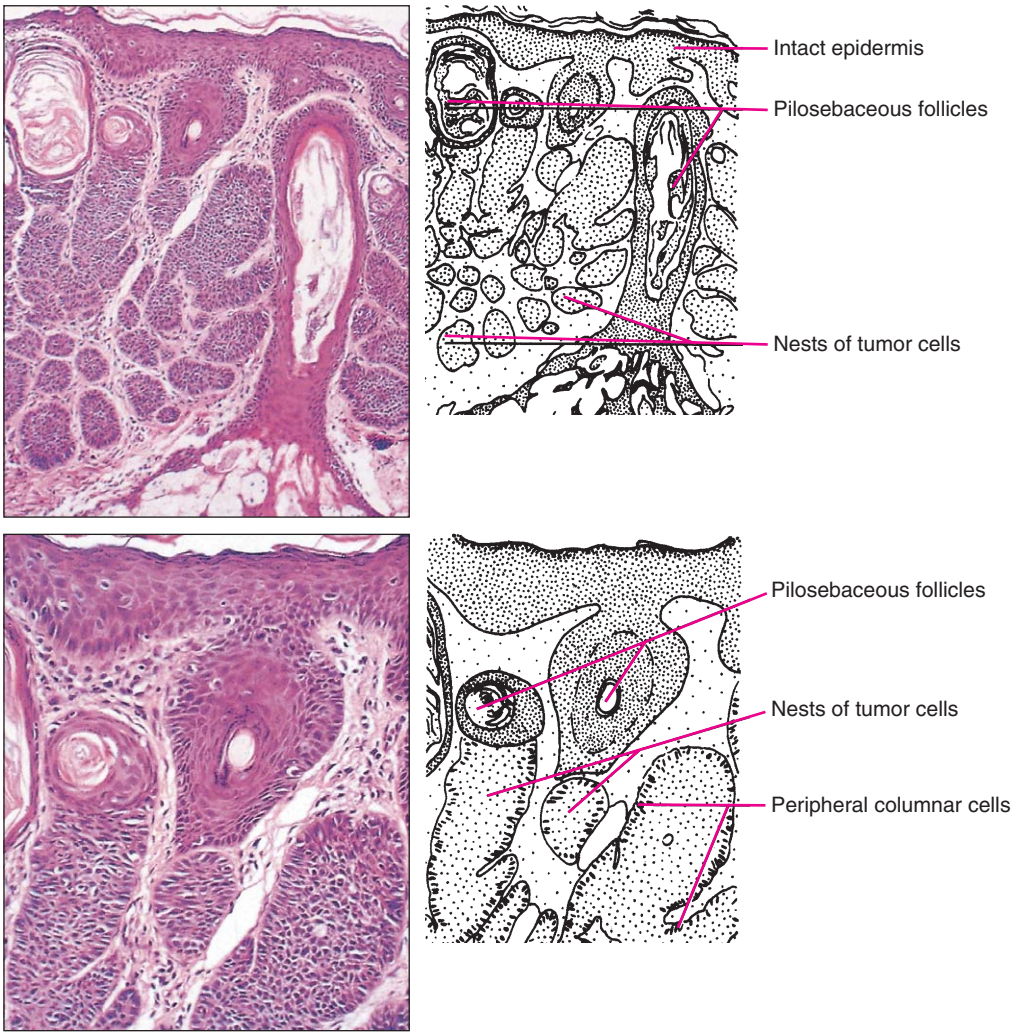


Figure 74-3 • Histopathology of basal cell carcinoma. (From Skarin AK [ed]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 374.)

surrounding stroma may retract from the tumor mass forming the typical lacunae, a sign that aids in diagnosis. In the pigmented type of BCC, large amounts of melanin are produced in the melanocytes that colonize the tumor. The many melanophages in the surrounding stroma also contribute to pigmentation. The superficial type of BCC shows multifocal small nests of basaloid tumor cells budding off the epidermis and adnexa. Morpheaform BCC is different in that strands of tumor cells are embedded in a dense fibrous tissue stroma. These strands often extend in the deeper dermis. Micronodular BCCs contain small nodules of tumor cells that invade surrounding stroma. The morpheaform and micronodular types are generally the most locally invasive variants of BCC. It is common for BCCs to show mixed histologic patterns of these various types. Even the less invasive variants may invade deeply when located in regions of embryonic fusion planes, such as around the nose and ears.

Treatment

BCC is rarely metastatic but can be locally invasive (Fig. 74-4). Therefore, eradicating the primary tumor is the goal of therapy. Several treatment options are available, both surgical and nonsurgical. Selection depends on the tumor type, patient profile, size and location of tumor, recurrence, physician's experience, and patient preference. Surgical modalities include Mohs' micrographic surgery,



Figure 74-4 • Basal cell carcinoma of 10 years' duration invading the scapula.

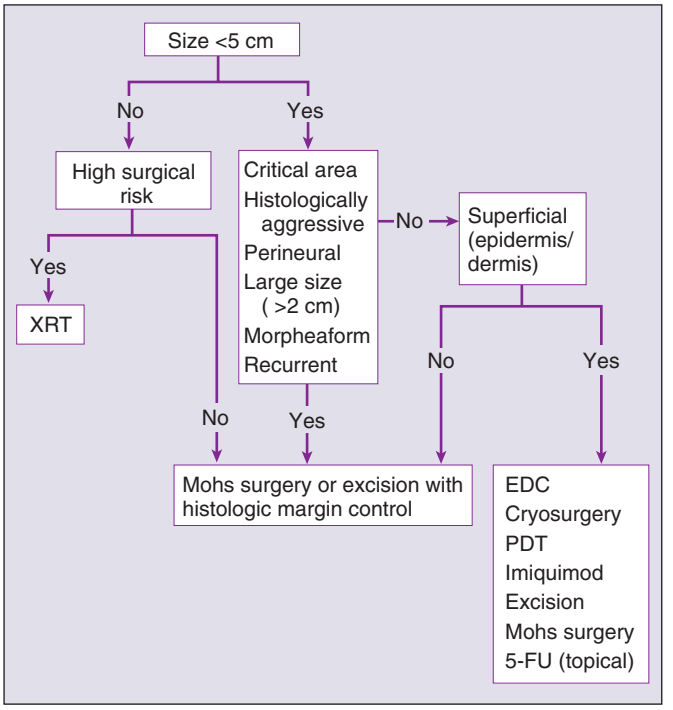


Figure 74-5 • Treatment for basal cell carcinoma. EDC, electrodesiccation and curettage; 5-FU, 5-fluorouracil; PDT, photodynamic therapy; XRT, radiation therapy.

surgical excision, cryosurgery, and electrodessication and curettage (EDC).[32] Nonsurgical options include radiation therapy and photodynamic therapy.[38] Other treatment modalities, such as immunotherapy with intralesional interferon[39] and topical 5% imiquimod (Aldara),[40] chemotherapy with 5-fluorouracil,[41] and retinoids,[42] have been reported with variable success (Fig. 74-5).

A systematic review of studies in which investigators reported recurrence rates of BCC after different treatment modalities showed that the mean 5-year recurrence rates after Mohs' surgery and surgical excision were approximately 1% and 5.3%, respectively.[43] Risk factors for BCC recurrence include greatest dimension larger than 2 cm, location in the midface (H zone) or ear, morpheaform or other aggressive histologic pattern, and long duration.[44] These tumors should be completely resected, preferably by Mohs' technique or excision with margin control. Mohs' surgery should be used in areas where preserving maximum tissue is important, such as eyelids, nose, and lips. It is also indicated for recurrent BCC and tumors with ill-defined clinical margins. If simple excision is used, the margin for excision should be at least 4 mm around tumors of 1 cm or less and 5 to 10 mm for tumors larger than 1 cm.[45] If there are contraindications to surgery, or the tumor is small and located on less critical sites such as the trunk, cryotherapy or EDC can be used with good outcome. Because of the less favorable long-term cosmetic results and possibility of secondary radiation-induced skin cancer, radiation therapy is best avoided in the care of relatively young patients. Very large or poorly controlled BCC may necessitate a coordinated approach of standard surgical excision, Mohs' surgery, radiation therapy, and immunotherapy or chemotherapy.[46]

Prognosis and Follow-up Evaluation

The prognosis of BCC is generally good. Metastasis is rare, and tumor growth is slow. Two thirds of recurrences occur during the fist 3 years after treatment.[47] The risk of development of another BCC is approximately 45% within 5 years.[48] The risk of development of another NMSC is associated with the number of previous NMSCs. In an Australian study of patients with three to nine previous NMSCs, the risk of development of a new cancer was 93%.[49] Patients treated for BCC need to be examined at least once a year for the first few years, preferably for 5 years after the last cancer was diagnosed. For patients with a history of multiple skin cancers, more frequent follow-up examinations are recommended. Photoprotection starting at a young age is advised to reduce the cumulative damage induced by the sun.

SQUAMOUS CELL CARCINOMA AND BOWEN'S DISEASE

Epidemiology and Pathogenesis

SCC is a malignant tumor of keratinocytes of the skin or mucosal surfaces. SCC has greater metastatic potential than BCC and causes the majority of NMSC deaths. SCC can arise de novo or from a precursor like actinic keratosis. Bowen's disease is a SCC in situ arising de novo. If Bowen's disease occurs on the glans penis or rarely vulva it is referred as erythroplasia of Queyrat. Bowen's disease can slowly progress into invasive SCC.

SCC is the second most common skin cancer in the United States, representing about 20% of NMSCs. Interestingly, SCC occurs more than BCC in blacks and Asians.[50] It is more common in men than women.[6] There are many risk factors for SCC, the most important being solar radiation. The incidence of SCC is increasing especially on the head and neck area as a result of exposure to sunlight.[51] SCC is thought to be correlated with recent (in the 10 years preceding diagnosis) chronic sunlight exposure[52] and cumulative sun exposure.[53] Phototherapy with PUVA (psoralen + ultraviolet A) increases the risk of SCC. Other risk factors for SCC include fair skin, red hair, albinism, and Celtic origin. Nonsolar risk factors include exposure to chemicals (insecticides and herbicides),[54] arsenic, organic hydrocarbons, chronic thermal injury and scars, ionizing radiation, and chronic immunosuppresion.[55] SCC is increased 18 to 36 times in organ transplant patients.[56] This increase of risk is correlated with the type of organ transplantation and elapsed time after transplantation. Heart transplant recipients have a higher risk of NMSC than kidney transplant recipients, possibly because of more intense immunosuppression.[57] Tobacco is a risk factor for oral SCC. Viruses, especially human papillomavirus (HPV), have been linked to epithelial malignancies including SCC. This is especially true among patients with epidermodysplasia verruciformis, who have an underlying immunodeficiency and can develop SCCs within HPV-infected warts.[55]

Carcinogens such as ultraviolet radiation (UVR), certain chemicals and viruses play a role in the pathogenesis of SCC by damaging keratinocyte DNA and other cellular contents. It is known that UVR, especially UVB, causes mutations in DNA of keratinocytes.[58] Early repair of these mutations is important for the prevention of SCC. Patients with NMSC are thought to have decreased ability for DNA repair compared with controls, thus making them more susceptible to the effects of UVR.[59] One example is the effect of UVR on DNA alterations in patients with xeroderma pigmentosum who are genetically unable to repair these defects. UVR also causes cutaneous immunosuppression, weakening the host's immune response against tumor cells and promoting tumor growth.[60,61] Studies of SCCs have shown that mutations in the *TP53* tumor suppressor gene are an early event.[2,62] Most of the mutations occur at dipyrimidine sequences, in the form of UV-induced cyclobutane pyrimidine dimers.[63] The development of SCC does not occur by a simple single step, but rather through a multistage process. Conversion of susceptible keratinocytes to premalignant cells and then progression to carcinoma occurs as a result of successive genetic hits.[64] In the initiation stage of carcinogenesis there is clonal expansion of premalignant cells. The next stage is increased proliferation of premalignant cells and

subsequent chromosomal aberrations. The final stage is conversion to SCC. DNA aneuploidy with a single peak was detected by flow cytometry in lesions of Bowen's disease, suggesting a monoclonal proliferation of abnormal keratinocytes and a clonal basis for skin cancer.[65] Aberrant expression of P-cadherin, and changes in expressions of cytokeratins and transforming growth factors all play a role in tumor progression.[66]

Clinical Manifestations

SCC occurs more on the head and neck area in whites, but in blacks there is no predilection for sun-exposed areas of the body.[67] SCC in situ may develop from premalignant lesions such as actinic keratosis or arsenical keratosis. In fact, in whites the majority of SCCs arise from actinic keratoses. These can eventually spread beyond the epidermis and become invasive. Invasive SCC can also arise from normal skin. It starts as a small, firm, dull red nodule, which can undergo central ulceration. Sometimes if SCC arises from solar keratosis an adherent keratotic scale can be seen. If ignored, the lesion grows horizontally and vertically and may become fixed to the underlying tissue. The surface might become ulcerated with bleeding, malodorous exudate or crust. The borders are usually elevated and firm. Occasionally a fungoid lesion without ulceration can be seen. SCC of the lower lip often arises from previously solar-damaged areas (actinic cheilitis). Initially local thickening of the vermilion border occurs that then progresses into a noduloulcerative lesion (Fig. 74-6). Persistent subungual erythema with pain and swelling should alert the physician for SCC of the nail region. This form of SCC may be confused with warts (Fig. 74-7). As mentioned earlier, SCCs can arise from chronic sinuses, scars, and chronic thermal damage.

Verrucous carcinoma is a distinct slow-growing low-grade type of SCC. The most common location is the plantar foot (epithelioma cuniculatum) but it can occur on the buttocks, genitals (giant condyloma of Buschke and Löwenstein), face, oral cavity (oral florid papillomatosis), trunk, nails, and extremities. It grows as an exophytic verrucous mass. Clinically, on the foot it can be mistaken for a plantar wart. It is locally aggressive and may penetrate into deep soft tissue or bone.

Bowen's disease often appears as a well-defined single red plaque with dry surface scaling. Lesions are slow growing and asymptomatic, thus ignored by many patients. The physician might initially treat it as psoriasis or nummular eczema with no response. There is a 3% to 5% chance that Bowen's disease can progress into invasive SCC.[68] Clinically erythroplasia of Queyrat resembles Bowen's disease but lacks the dry superficial scale. Instead the surface is moist and smooth.



Figure 74-6 • Squamous cell carcinoma of the lip of 5 years' duration.



Figure 74-7 • Squamous cell carcinoma of the nail bed. Patient was being treated for a wart.

The risk of metastasis of SCC is variable, depending on the site and tumor characteristics. The deeper and larger the tumor, the higher is the chance of metastasis. Recurrent tumors are at high risk for metastasis. Lesions with perineural involvement have a 35% metastatic rate.[69] Among the different histologic types, desmoplastic SCCs are more likely to metastasize.[70] The risk of metastasis of SCC derived from actinic keratosis is low (0.5% to 3.7%) compared with SCC arising in radiation-induced SCC and chronic osteomyelitis (20% and 31%, respectively).[71,72] High-risk areas for metastasis include tumors arising from the dorsal hands, lips, ears, and penis. For example, SCC of the lower lip has a 15% risk of metastasis.[73] Bowen's disease and erythroplasia of Queyrat also have a low chance of metastasis, but once they become invasive the risk of metastasis increases significantly.

Histopathology

A deep shave or punch biopsy that includes the base of the tumor is needed to distinguish SCC in situ from invasive SCC. Bowen's disease is carcinoma in situ. The stratum corneum is thickened, and epidermis is hyperplastic with disordered maturation of keratinocytes. Mitotic figures, mutinucleated keratinocytes, and dyskeratotic cells with hyperchromatic nuclei and eosinophilic cytoplasm are seen in the epidermis. The histology of SCC shows masses of epidermal cells proliferating into the dermis. Atypical squamous cells and mitotic figures are seen (Fig. 74-8). The cells have abundant eosinophilic cytoplasm and large nuclei. Horn pearls, which are a result of keratinization of squamous cells, are seen. The dermis may show a marked inflammatory reaction. Spindle cell SCC is a rare variant composed of mainly spindle cells, but some squamous differentiation may be seen. Spindle cells have large vesicular nuclei and scant cytoplasm and intermingle with the collagenous stroma. Spindle cell SCC is poorly differentiated with numerous mitoses and deep invasion and requires immunohistochemistry to differentiate it from other spindle cell tumors. Another uncommon histologic variant of SCC is the acantholytic or adenoid SCC, seen more on the face and neck. There are nests of tumor cells with dyskeratotic cells and central acantholysis forming pseudoglandular structures.

Treatment

The treatment options for SCC are similar to BCC treatment, with some differences (Fig. 74-9). The first step is to estimate the peripheral and vertical extension of tumor cells. Tumors at high risk for local or distant spread are those larger than 2 cm or deeper than

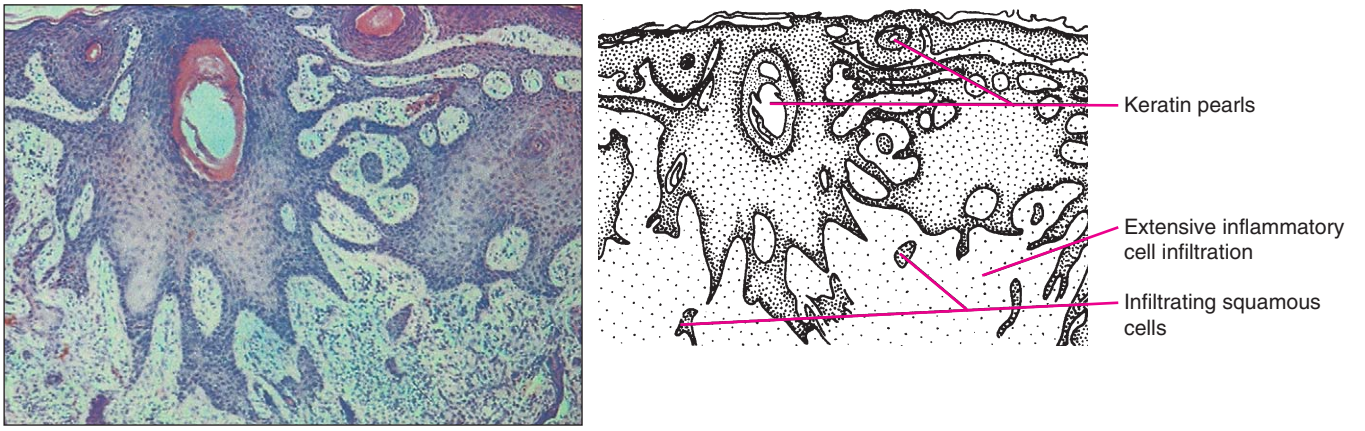


Figure 74-8 • Histopathology of squamous cell carcinoma. (From Skarin AK [ed]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 376.)

6 mm, recurrent tumors, poorly differentiated tumors, and those with perineural invasion or arising in immunocompromised hosts.[74] Second, the patient should be evaluated for metastasis to the lymph nodes and other organs.

Destructive methods or surgical excision can treat Bowen's disease effectively. Small uncomplicated SCCs (<1 cm) in low-risk locations are frequently treated with EDC. Cryotherapy is an alternative treatment. Simple surgical excision with margin control is commonly used for smaller tumors and those on the trunk and extremities. The recommended margin for low-risk SCC is 4 mm and for high-risk tumor is 6 mm.[75] The excision should include the subcutaneous fat. Mohs' micrographic surgery is the treatment of choice for high-risk SCCs or for tissue preservation where tissue sparing is cosmetically or functionally vital.[76] Aggressive or deeply invasive SCCs are treated with deep surgical excision with margin control when practical. Mohs' surgery may be helpful in delineating critical areas in massive tumors or tumors with ill-defined borders. SCC invading surrounding structures such as bone and cartilage must also be excised. Tumors with neural or perineural involvement that are at high risk of recurrence should be completely excised preferably with the Mohs' technique. High-risk tumors may require adjuvant therapy with radiation therapy[77] or chemotherapy.[78,79]

Radiation can also be used as a primary choice of treatment. Usually 4000 cGy of radiation is given in 5 to 16 fractions. This form of treatment might be appropriate in the elderly at high risk for surgical complications or other patients with contraindications to

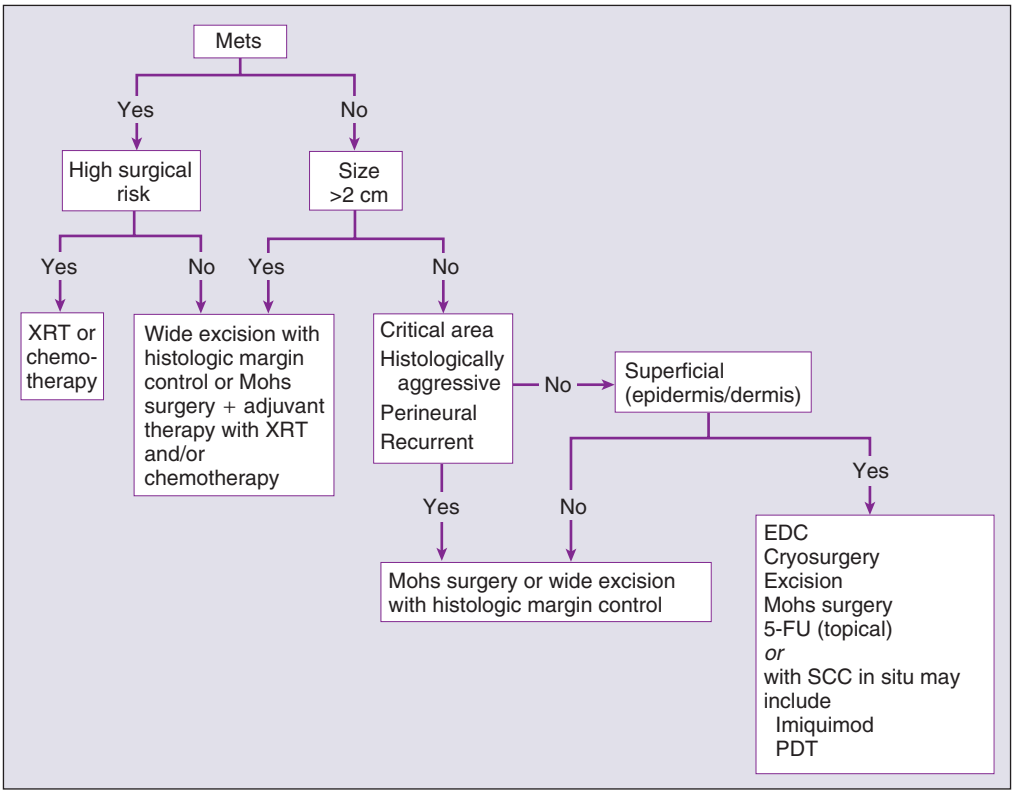


Figure 74-9 • Treatment for squamous cell carcinoma (SCC). EDC, electrodesiccation and curettage; 5-FU, 5-fluorouracil; PDT, photodynamic therapy; XRT, radiation therapy.

anesthesia or surgery. Radiation can be useful to treat tumors on the eyelids, nose, ears, and lips when surgery is not practical. The disadvantages are the cost, blind margin control, and prolonged treatment duration. The cure rate for tumors larger than 2 cm is about 85% to 95%.[80] Radiation therapy is best avoided in treating verrucous carcinomas and younger patients because of poor long-term cosmetic results. SCCs that have arisen from ulcers, scars, and irradiated sites are better removed by margin-controlled surgery than by radiation therapy.

If lymph node metastasis has occurred, treatment is wide surgical resection of tumor with regional lymph node dissection with or without adjunctive radiation. However, elective lymph node dissection is not commonly performed in the absence of evidence for regional spread. Sentinel lymph node biopsy may be considered.[81]

For patients with Bowen's disease or advanced SCC, chemotherapy with isotretinoin alone or in combination with α interferon has been used with success.[82,83] Promising chemopreventive agents for lesions in the actinic keratosis–SCC spectrum include retinoids, COX-2 inhibitors, and difluoromethylornithine.

Prognosis and Follow-Up

SCCs in general have a greater potential for recurrence and metastasis than BCCs; therefore, the follow-up must be more aggressive. The patient should be followed at close intervals (every 3–6 months) for the first several years, depending on the location, size, aggressiveness, and node status of the primary tumor. The exception would be small SCCs arising from actinic keratoses on sun-exposed surfaces, where the rate of metastasis is very small (0.5%). In these patients, routine follow-up every 6 to 12 months is all that is required.

KERATOACANTHOMA

Keratoacanthomas are common cutaneous neoplasms that are thought to derive from the infundibular portion of hair follicles. They most often present as solitary rapidly growing, pink or flesh-colored, dome-shaped, or cratiform nodules. They occur most commonly on sun-exposed areas in fair-skinned elderly individuals. Keratoacanthomas are historically characterized by their spontaneous involution over several months with residual atrophic scarring and local tissue destruction. Histologically, a mature keratoacanthoma has a distinctive architecture characterized by a keratin-filled crater lined by a proliferating squamous epithelium with abundant pale eosinophilic "glassy" cytoplasm, epithelial lipping, and multiple keratin horn pearls with central orthokeratosis. Cytology is often indistinguishable from that of a well-differentiated cystic SCC. At the base of the tumor, islands and strands of atypical cells may invade the dermis. Frequently there is a heavy inflammatory infiltrate at the base of the lesion comprising lymphocytes, plasma cells, neutrophils, and eosinophils. Atypical mitoses as well as perineural and perivascular invasion may also be present, particularly in tumors involving the head and neck. Several cases of highly aggressive and metastatic keratoacanthomas have also been reported; however, some have questioned whether these were truly keratoacanthomas or rather keratoacanthoma-like SCCs.[84]

Although most cases of keratoacanthoma are solitary, subsets of individuals with multiple keratoacanthomas have been described. These include the familial Ferguson Smith type comprising multiple keratoacanthomas at an early age, and the generalized eruption of thousands of small keratoacanthomas as described by Grzybowski (see ref. 84). Keratoacanthomas frequently occur in individuals with the Muir-Torre syndrome, xeroderma pigmentosum, and solid-organ transplantation.[85] They also occur in areas of scarring from prior trauma, thermal burns, and surgical treatment, and in association with many benign conditions such as stasis dermatitis, lichen planus, lichen simplex chronicus, psoriasis, and discoid lupus erythematosus.

Debate exists as to whether keratoacanthomas are a distinct clinical entity or a subtype of well-differentiated SCC. Significant efforts have been made to find practical, reliable criteria to distinguish keratoacanthoma from SCC, but none have yielded reliable criteria for routinely distinguishing these entities. Recent studies with the apoptotic marker $P2X_7$ and with comparative genomic hybridization suggest that keratoacanthoma and SCC possess distinct genetic aberrations that result in separate developmental pathways.[86,87] These findings may provide an avenue in the future for reliable separation of keratoacanthoma and SCC. However, given the potential for local destruction and metastatic disease, it is recommended that keratoacanthomas be treated in the same manner as SCCs. Complete conservative excision is the most common treatment technique for keratoacanthomas. Radiotherapy, EDC, systemic medications, and topical and intralesional modalities have been reported with varying success.

NONMELANOMA SKIN CANCER IN IMMUNOCOMPROMISED HOSTS

The incidence of NMSC is significantly increased in patients who are immunocompromised secondary to human immunodeficiency virus/acquired immunodeficiency syndrome, heritable immunodeficiencies, the effective immunosuppression of chronic lymphocytic leukemia, and immunosuppressive medications. Patients with human immunodeficiency virus infection, congenital immunodeficiency, and lymphoma manifest decreased immunosurveillance due to defects in cell-mediated immunity. An increased susceptibility to infection with oncogenic HPV types may be important in the pathogenesis of Bowen's disease (SCC in situ), SCC, keratoacanthomas, and genital dysplasias in these patients.[88] Epidermodysplasia verruciformis is a rare inherited disorder of unknown etiology that predisposes those affected to widespread infection with HPV types 5 and 8, which is associated with the development of SCC. A history of UV exposure further compounds the risk in these populations.[89]

Iatrogenic immunosuppression, an important treatment modality for autoimmune diseases and for prevention of transplant rejection, is associated with both direct carcinogenic effects and decreased immunosurveillance. Solid-organ transplant recipients (OTRs) require long-term immunosuppression and, therefore, are at increased risk for BCC, melanoma, Kaposi's sarcoma, and especially SCC over their lifetime. The highest incidence is seen in heart transplantation followed by renal and then liver transplantation. The impact on public health is significant, in that more than 25,000 solid-organ transplants are performed in the United States annually, the majority being renal, and survival rates for OTRs are increasing. In OTRs, SCC can be more aggressive and the SCC/BCC ratio is increased.[90]

Factors associated with SCC in OTRs include sun exposure, epidermodysplasia verruciformis-associated HPV types 5 and 8, fair skin, heart transplant, older age at transplant, male sex, and intense immunosuppression. Indeed, intensity and duration of immunosuppression have been associated with development of aggressive SCC.[89] Studies suggest that antirejection therapies using tacrolimus, mycophenolate mofetil, or rapamycin versus cyclosporine, glucocorticoids, or azathioprine may decrease incidence of NMSC in OTRs.[89,91]

The burden of skin cancer, especially SCC, is markedly elevated in OTRs. The magnitude and severity of disease can be devastating.[90] Many are diagnosed with numerous lesions annually, each lesion with an increased potential for aggressive behavior and metastasis relative to occurrences in the general population.[92] Metastatic disease usually involves noncontiguous spread along lymphatic vessels and nerves, and represents a poor prognosis and therapeutic challenge.[93]

Management of NMSC in OTRs consists of the same treatment modalities described for NMSC in the general population. Increased vigilance including frequent follow-up, a high level of suspicion for new or changing skin lesions, and a low threshold for biopsy is

essential to ensure early detection and timely treatment. By stratifying lesions as lower versus higher risk (rapid growth, large size, recurrence, aggressive histology, or location on lip, ear, or scalp), those lesions more likely to recur or metastasize can be prioritized in a treatment regimen in OTRs with an overwhelming burden of disease.[90,93] Whereas topical agents, curettage, and cryotherapy may be appropriate for treatment of lower risk lesions, higher risk lesions usually require a surgical approach (excision or Mohs' micrographic surgery) to ensure clear margins. Radiation therapy can be an important adjunct for metastatic and perineural disease. Although the diagnostic and therapeutic role of sentinel lymph node biopsy in such cases is not established, it may be considered in selected high-risk cases.[89,90]

Data suggest that acitretin may be beneficial as a chemopreventive agent in this population. Moreover, reducing immunosuppressive therapy has been shown to decrease the development of NMSC and metastatic disease, although coordination with the primary transplant physician is essential to avoid allograft rejection.[89,90]

SEBACEOUS CARCINOMA

Epidemiology and Pathogenesis

Sebaceous carcinoma is a rare, potentially devastating tumor derived from the adnexal epithelium of sebaceous glands. Principally, the tumor occurs in two different clinical scenarios: ocular sebaceous carcinoma (OSC) and extraocular sebaceous carcinoma.[94,95] OSC accounts for 0.2% to 0.8% of all eyelid tumors and 1% to 1.5% of all malignant tumors of the eyelid. Approximately 400 cases have been described in the English literature.[96] OSC affects women 1.5 times more frequently than men; however, a slight male preponderance occurs in cases of extraocular sebaceous carcinoma.[97–101] The mean age at diagnosis is 65 years (range, 40–60 years), but OSC has been reported in young children (12 years of age, after radiation therapy for retinoblastoma) and in persons as old as 90 years.[102,103] Sebaceous carcinoma seems to have a higher incidence in the Asian population.[102,104–106] This tumor has been associated with MTS, an autosomal dominant disorder of mismatch repair genes characterized by sebaceous tumors (benign and malignant) as well as other visceral malignant tumors.[20,107] Sebaceous carcinoma with microsatellite instability has been found in several renal organ transplant recipients.[107]

Clinical Manifestations

OSC typically manifests as a painless, slowly growing, yellowish papule (Fig. 74-10). The upper lid is affected two to three times more frequently than the lower lid. The tumor usually originates from the meibomian gland (sebaceous gland in the tarsus) or from a sebaceous gland of the eyelash (glands of Zeis).[101,103] Clinically, the signs can be subtle with only moderate lid thickening, eyelash alopecia, pale corneal changes, conjunctival injection, or thickening along the temporal or inferior temporal limbus.[97,108–110] There have been case reports of ipsilateral upper and lower eyelid involvement and bilateral upper and lower lid involvement.[96,109,111] The diagnosis is often elusive, because OSC is notorious for masquerading as more common ocular disorders, such as chalazion (most common), keratoconjunctivitis, blepharoconjunctivitis, SCC, BCC, granulomatous disorders, and benign neoplasms.[97,109–112] Initial recognition is 50% among ophthalmologists and only 18.6% among general practitioners.[113–115] Often there is a delay in diagnosis of 6 months to a year and in some series up to 2.9 years, contributing to increased morbidity and mortality.[97,113] With regard to the rarer extraocular sebaceous gland carcinoma, initial diagnosis can be elusive because the clinical appearance often is pleomorphic and nonspecific and varies from a banal-appearing nodule to large ulcerating masses.[116–119] This variant of sebaceous gland carcinoma most often occurs on the head and neck region, reflecting the abundance of sebaceous glands there.



Figure 74-10 • Ocular sebaceous carcinoma involving the lower eyelid.

Histopathology

Full-thickness biopsy is required to ensure adequate tissue sampling. Microscopic examination shows that OSC invades surrounding tissue by direct extension into the dermis or the overlying epithelium.[113,120,121] The tumor demonstrates epitheliotropic spread in 37% to 80% of cases. Atypical sebaceous cells have a pagetoid distribution within the conjunctival epithelium.[103,113] As many as 18% of cases of OSC may have multifocal regions of tumor involvement.[96]

There are basically two broad classification schemes with regard to light microscopic findings. Font[122] described three classes of tumor based on degree of differentiation: well differentiated, moderately well differentiated, and poorly differentiated. Others prefer to classify the tumor on the basis of growth pattern: lobular, comedocarcinoma, papillary, and mixed.[100] The intraepithelial neoplasia growth pattern and pagetoid spread are not addressed in this classification scheme. The histologic features are anaplastic cells with varying degrees of differentiation. Squamoid or basaloid features may be present.[97] Lobulated aggregates of basaloid cells usually contain irregular, hyperchromatic nuclei and vacuolated cytoplasm.[96,109,123,124] In cases of intraepithelial neoplasia, the epithelial pagetoid cells lack intercellular bridges and contain large hyperchromatic nuclei, prominent nucleoli, and abundant, pale-staining cytoplasm. Special stains, such as oil red O or Sudan black, often are helpful in delineating the atypical sebocytes; however, poorly differentiated tumors may not stain positively for lipids.[110,113] In addition, undifferentiated sebocytes often lack the foamy cytoplasm of their more differentiated counterparts and may resemble atypical SCC at standard hematoxylin and eosin staining.[97,109,123] Recognition of this particular biphasic nature of OSC is critical to appreciating the biologic behavior of this recalcitrant tumor. Ophthalmologists have known for years about the difficulty of assessing the tumor margins of this epitheliotropic neoplasm. It has been recommended that as many as nine mucosal biopsy specimens be obtained and mapped from the medial and lateral portions of the bulbar and palpebral conjunctiva of the upper and lower lids.[125,126]

Treatment

Evaluation of patients with known or suspected sebaceous gland carcinoma includes complete history with review of systems, family history and consideration of MTS, complete skin examination, and palpation of nodal basins and structures adjacent to the lesion. A chest radiograph, complete blood cell count, liver function tests, and electrolytes are recommended. If MTS is a consideration, colonoscopy is warranted.

Management of sebaceous gland carcinoma is primarily surgical, although there are a few reports of tumors managed primarily with radiation.[127] Given the paucity of cases, no randomized, controlled studies have been conducted to evaluate therapy. Traditionally, wide local excision with a margin of 4 to 6 mm of clinically normal tissue has been used.[97] Exenteration is recommended for extensive bulbar conjunctival involvement or evidence of orbital invasion.[101] In his personal series of 60 consecutive patients with a mean follow-up of 41 months, Shields and colleagues reported a local recurrence rate of 18%, exenteration of 13%, and metastasis of 8%.[113] Some experts consider Mohs' micrographic surgical technique the treatment of choice, because it preserves the maximum amount of healthy tissue. This quality is especially crucial in the treatment of ocular tissue.[109,113,128–131] In addition, it allows for microscopic examination of all margins of the obtained tissue to ensure complete tumor eradication. In 2002, we reported our results of nine cases treated by Mohs' micrographic surgery achieving a 90% success rate with 3-year follow-up.[118] Four of these patients have now gone 5 years without evidence of local recurrence in all patients (unpublished data).

Local recurrence usually is the result of inadequate management of the primary tumor.[97] If the recurrent lesion is small enough, treatment can be repeated with Mohs' micrographic surgery or local excision.[113] More extensive OSC tumor involvement usually necessitates exenteration.[115,124] Ophthalmologists have considered cryotherapy a useful modality in the management of epibulbar disease in a small subset of patients, and this therapy may be an alternative to exenteration.[105,132,133] Regional lymph node metastasis is managed by surgical resection and adjuvant radiation.

Prognosis and Follow-up Evaluation

Both OSC and extraocular sebaceous gland carcinoma are aggressive tumors that recur locally if inadequately managed and readily metastasize. Metastasis may occur through lymphatic vessels, and in the case of OSC, it is postulated to occur through the lacrimal and excretory systems.[97] Risk factors associated with poor prognosis include duration longer than 6 months; vascular or lymphatic involvement; orbital extension; poorly differentiated tumor morphology; multicentricity; pagetoid spread into the conjunctival epithelium, cornea, or skin; upper and lower lid involvement; and history of radiation exposure.[102,103,109,113] In the past, 14% to 25% of patients reportedly had metastasis, most frequently involving regional nodal basins, followed by spread to the liver, lung, brain, and bones.[97,99–102] Because of increased index of suspicion, physician education, and earlier recognition with biopsy, the metastatic rate has decreased to 10% in some series.[113] Among industrialized countries, periocular mortality is reportedly 9% to 15%. Systemic disease is associated with a grave prognosis.

Follow-up care includes examining the individual on a regular basis, probably for the rest of his or her life. Given the complex issues in dealing with this aggressive tumor, individuals are best served by being cared for in a tertiary care setting with a multidisciplinary approach. Physical examination, evaluation of the surgical site, and a low threshold for biopsy of suspicious lesions is a reasonable approach.

MERKEL CELL CARCINOMA

Epidemiology and Pathogenesis

Merkel cell carcinoma (MCC) is a rare aggressive tumor of unknown incidence. Fewer than 700 cases have been reported since the tumor was first described by Toker in 1972.[134–135] Many names have been ascribed to this neoplasm, including primary small cell carcinoma of the skin, trabecular carcinoma, APUDoma, neuroendocrine carcinoma, endocrine carcinoma, and primary undifferentiated tumor of the skin.[135–138] New SEER data indicates that the incidence of MCC is rising with about 470 new cases reported annually.[139]

MCC is a tumor that primarily affects elderly persons. Ninety percent of cases reported occur in patients older than 50 years, and the mean age at diagnosis is 69 years.[135,138,139] There does not appear to be a sex predilection.[140] White persons are more frequently affected than those of other races; however, MCC has been reported among Asian and black persons.[141–145] MCC has been reported in association with BCC, SCC, a history of radiation exposure, certain familial cancer syndromes, and immunosuppressed states[121,142,146–148] such as OTRs.[149]

Clinical Manifestations

MCC often manifests as a painless, indurated, erythematous to violaceous nodule on sun-damaged skin, 50% of tumors arising on the head and neck.[134–139,142,150] Ten percent of these tumors are in the periocular areas (Fig. 74-11).[151] The extremities are the second most affected site, followed by the trunk.[136,141,152,153] MCC also has been reported in areas not normally exposed to sunlight, such as the vulva, endocervix, penis, esophagus, bladder, and calvarium.[154–158] The overlying epidermis usually is unremarkable; however, ulceration may be found.[138,142,159] In addition, there may be overlying or surrounding telangiectasis.[135] The clinical differential diagnosis includes BCC, SCC, amelanotic melanoma, lymphoma, and metastatic disease. The ultimate diagnosis is made on the basis of clinical appearance, histologic findings, and supporting immunohistochemical studies of the tissue subjected to biopsy.

Histopathology

MCC has a histologic appearance similar to that of other small cell neoplasms and must be differentiated from cutaneous metastatic lesions from carcinoid or small cell undifferentiated carcinoma of the lung.[135,137,142,159] The tumor cells are characteristically uniform in size, monomorphic, basophilic, and ovoid, and measure up to 15 mm in diameter. The nuclei have finely dispersed chromatin with minimal surrounding cytoplasm.[137,152,159–161] Pathognomonic features include numerous mitotic figures, vesicular nuclei with essentially inconspicuous nucleoli, and apoptosis, especially when appreciated with certain architectural features.[135,137,162] The tumor involves the dermis, may extend into the subcutaneous fat or deeper, and usually spares the epidermis.[142] There may be a pagetoid pattern of epidermal spreading, which can mimic Bowen's disease, Paget's disease, extramammary Paget's disease, melanoma, and mycosis



Figure 74-11 • Merkel cell carcinoma involving the upper eyelid.

fungoides.[150,162] MCC also may have both squamous and adnexal differentiation.[138,161]

The architectural patterns of MCC have been classified into three separate groups: trabecular, intermediate cell, and small cell.[137] The trabecular pattern is the least common.[134,163,164] The cells are arranged in cords admixed among a fibrovascular background.[134,136,160] This pattern may be associated with pseudoglandular structures.[164,165] The tumor often involves tissue surrounding adnexal structures, such as hair follicles. More often, in the intermediate cell type, MCC displays large sheets or clusters of uniform cells with foci of necrosis.[136] The tumor also can arise near adnexal structures and connect with the epidermis.[164,165] The cells in this pattern are less compact than those in the trabecular type. There often is a surrounding lymphocytic infiltrate.[135,162–166]

Finally, the small cell type of MCC arises in the dermis and appears as sheets of cells interrupted by strands of connective tissue.[164] Glandular or pseudoglandular structures are absent. The cells are round and small and may demonstrate "crush" artifact. It has been proposed that the intermediate cell type and the small cell type behave in a clinically more aggressive manner than the trabecular type.[164,165] Lymphatic invasion is frequently encountered and has negative prognostic implications.[137,142,163,164,166,167]

Immunohistochemical studies aid in the diagnosis of MCC and help to differentiate it from other tumors. A characteristic paranuclear dotlike pattern against cytokeratin 20 is probably the most useful immunohistochemical stain.[135,164,168,169] In addition, MCC stains positively for neuron-specific enolase.[136,160,164,168] However, neuron-specific enolase is not specific for MCC and cannot be relied on for differentiation of MCC from small cell carcinoma of the lung.[135,169] Chromogranin A and synaptophysin are specific for MCC but less sensitive than neuron-specific enolase. MCC also stains positively for epithelial membrane antigen and Ber-EP4.[135,160,169]

Treatment

When MCC is diagnosed, a detailed history should be obtained and a physical examination performed with emphasis on the skin and lymph nodes. Complete blood cell count and hepatic and renal function tests are reasonable. Evaluation of the chest, abdomen, and pelvis with computed tomography may be useful in differentiating MCC from metastatic small cell carcinoma and for initial staging.[150] Individuals with MCC of the head and neck region need imaging for evaluation of draining nodal basins, especially if there is clinically evident lymphadenopathy.[135,150] Tumor staging is performed at clinical presentation.[170] Stage I disease is a primary tumor with no evidence of nodal involvement. Stage II disease equates to regional lymph node involvement. Stage III disease is defined by the presence of systemic metastasis.

Local disease is best managed by surgical excision to lower the tumor burden, and excision is followed by radiation.[139,141,150,166,170] Wide local excision of 2.5- to 3.0-cm margins is especially suitable for MCC of the trunk or extremity, being the historical standard.[135,139,141,150,166,170] The use of Mohs' micrographic surgery for areas in which this goal would not be achievable, such as the face or neck, has been a logical extension of surgical therapy.[150,171] In addition to tissue conservation, the technique allows microscopic examination of all margins.[150,171]

Prophylactic or elective lymph node dissection in all patients has been advocated by some surgeons.[135,136,170,172] Others suggest that sentinel lymph node biopsy for evaluation of draining lymph node basins would be a reasonable approach and avoid the morbidity of elective lymph node dissection.[137–139] Sentinel lymph node biopsy is best performed when the primary surgical site has been subjected to the least amount of manipulation. Thus far no studies have been conducted to compare the two methods. Elective lymph node dissection currently is recommended for large primary tumors, head and neck lesions, small cell subtype, and evidence of vascular or lymphatic invasion.[136,139,141,153]

MCC is considered a radiosensitive tumor. Thus, radiation therapy has been used as adjuvant primary treatment when surgery is not an option and for palliation.[139–142,150,170,172] Use of adjuvant external beam radiation therapy has been advocated by many authorities.[139,141] Current recommendations call for surgical management of the primary MCC followed by radiation to the primary site as well as the regional lymph node draining system.[141,142,150,172–177] Adjuvant chemotherapy has not been studied in a controlled manner. Many cytotoxic regimens have been used, including cyclophosphamide, methotrexate, 5-fluorouracil, cisplatin, etoposide, doxorubicin, procarbazine, dacarbazine, streptozocin, and nitrogen mustard.[138,139,178–180] Review of the literature on adjuvant chemotherapy has not demonstrated clear clinical benefit regarding relapse or survival.[143,146,170,176,177] Chemotherapy has been used for salvage therapy in patients with systemic disease.[147,170,178–180] Most regimens involve two or three drugs, and results are modest at best. No large, randomized studies have been conducted because of the rarity of MCC.

Prognosis and Follow-up Evaluation

MCC has been compared to malignant melanoma because of its similar aggressive behavior.[138,139,174] The local recurrence rate is 26% to 44% after primary treatment. As many as 30% of patients have regional lymph node involvement at the time of diagnosis with a 55% rate of regional lymph node relapse after treatment and a 34% to 49% rate of distant metastasis.[139,142,150,176,177,180] Survival rates reportedly are 68% for women and 36% for men at 3 years.[152,179] Given the relative rarity of the tumor, no large multicenter randomized trials have been conducted to assess stage, treatment modality, recurrence rate, and overall survival. There have been reports of individuals with spontaneous resolution of MCC.[181–183]

Patients should be monitored closely for recurrence of locoregional or distant disease. Lymph node or distant metastatic disease has a uniformly grave prognosis; however, there may be a role for chemotherapy in prolonging survival. Almost all individuals with metastatic disease eventually die of the disease.

DERMATOFIBROSARCOMA PROTUBERANS

Epidemiology and Pathogenesis

DFSP is an uncommon tumor of intermediate malignancy that arises in the dermis. It is a locally aggressive neoplasm with notoriously high recurrence rates even after wide local excision. In 1924, Darier and Ferrand[184] first described DFSP as a distinct clinicopathologic entity; however, it was Hoffman in 1925 who introduced the term dermatofibrosarcoma protuberans.[185]

DFSP constitutes less than 1% of all malignant tumors. The estimated incidence is 0.8 to 5 cases per 1 million persons per year.[186–190] The tumor commonly occurs between 20 and 50 years of age, rare cases occurring in young children.[191] In addition, there have been a few reported cases of congenital DFSP.[191–194] The sexes are affected equally; however, in some series there is a slight male preponderance.[186–188,191,195] Most reported cases of DFSP occur in white persons, but historically race rarely is mentioned.[186–188,196] DFSP also occurs in African Americans and Asians.[191,196,197]

DFSP is not known to have a genetic or familial predisposition.[198,199] The cause of DFSP is unknown. Chromosomal abnormalities consistent with a monoclonal origin have been found in several studies.[200,201] Most frequently, these abnormalities include ring 22 chromosomes, ring chromosomes containing chromosome 17 sequences, abnormal clones, and t(2;7) translocations.[201–204] Approximately 10% to 20% of patients report a history of antecedent trauma.[186,191,199,205,206] There have been reports of DFSP arising in multiple immunization sites, burn scars, and surgical

scars.[196,207,208] DFSP has been associated with pregnancy as well as long-term arsenic exposure, acanthosis nigricans, and acrodermatitis enteropathica.[186,209–211]

Clinical Manifestations

DFSP usually manifests as a flesh-colored, firm, asymptomatic nodule or plaque (Fig. 74-12). The tumor is firm to palpation, and a subcutaneous component often is appreciated. There may be fixation to overlying skin but rarely to deeper structures. Lesions associated with pigment are known as Bednar's tumors.[212] In addition to pigment, there may be red to violaceous erythema. Characteristically, DFSP initially manifests as a solitary nodule; however, there may be multiple primary lesions. The size typically ranges from 1 to 5 cm, but neglected lesions can be as large as 20 cm in diameter.[186,188,196] The lesion slowly enlarges in a relentless manner. Accelerated growth phases can result in nodularity or multiple outcroppings or protuberances. Ulceration occurs when the tumor erupts through the epidermis. Atypical clinical manifestations include sclerotic plaques with a morpheaform appearance.[213]

Approximately 50% to 60% of DFSP lesions occur on the trunk, 25% of those occurring on the chest and shoulders.[187,188,191,196] Twenty percent to 30% arise on the proximal aspects of the extremities.[188–191] Ten percent to 15% occur on the head and neck, the scalp being affected less than 5% of the time.[187,188,191,196] In rare instances acral sites have been reported, mostly in young children and adolescents.[187,191,192,214] Often there is a delay in diagnosis given the indolent and nonspecific features of the tumor. DFSP often is mistaken for lipoma, deep-seated epidermal cyst, scar, hypertrophic scar, keloid, dermatofibroma, nodular fasciitis, and insect bite. The diagnosis is confirmed with biopsy and microscopic examination of the tissue.

Histopathology

The histological features of DFSP often are easily recognized on low-power view. There is densely packed proliferation of monomorphic, bluish, spindle-shaped cells seated in and expanding the dermis. The overlying epidermis usually is normal appearing unless there has been invasion by the tumor. The central or nodular areas of the tumor demonstrate numerous spindle cells arranged in a characteristic "whirling, storiform or herringbone" configuration.[160] The lateral tumor margins have sharply pointed tumor cells and irregular strands dissecting between the native collagen bundles. Inferiorly, the DFSP cells invade downward within the fibrous septa that separate the adipose cells of the panniculus. The peripheral margins may have a deceptively bland appearance resembling normal collagen and making interpretation of tumor margins difficult.[188] Fascia, muscle, and underlying bone may be involved in long-standing lesions.[188,191,196,200] Histological variants include DFSP with entirely myxomatous features (myxoid DFSP) and pigmented DFSP, also known as Bednar's tumor.[212,214–216] This variant tends to occur more often in dark-skinned persons and accounts for approximately 1% to 5% of all cases of DFSP.[212] Bednar's tumor has the characteristic storiform pattern of spindle cells admixed with a variable amount of melanin-laden dendritic cells. Immunohistochemical studies that may be helpful include positive staining for CD34, a human hematopoietic progenitor cell antigen. Unlike dermatofibroma, DFSP stains negatively for factor XIIIa.[160]



Figure 74-12 • Dermatofibrosarcoma protuberans involving the back. Central linear scar from previous partial excision is encircled by ink to highlight clinical margins of the lesion.

Treatment

After the diagnosis of DFSP has been confirmed, a complete history, review of systems, and physical examination with focus on the skin and structures contiguous with the tumor and palpation of lymph node basins are performed. Unless the physician suspects metastatic disease, extensive laboratory studies and radiological investigation are not indicated.

The traditional mainstay of therapy for DFSP has been surgical resection, specifically wide local excision with a margin of 2 to 4 cm of normal-appearing skin.[196,217,218] Unfortunately, the biological and histological features of the tumor coupled with the inability to clinically determine tumor margins account for exceptionally high recurrence rates with standard surgical therapy. Reported local recurrence rates are as high as 60% after standard surgical excision and 23% after wide local excision with margins greater than 4 cm.[217] Approximately 80% of local recurrences occur within 3 years.[186,196,201] Local recurrence after 10 years is rare but has been reported.[188,191] Mohs' micrographic surgery has been receiving greater recognition as a useful method of management of DFSP.[217–226] The capability of microscopic examination of the entire specimen margins allows the surgeon to localize and excise the tumor in a precise manner. This method also allows for maximum conservation of tissue, a crucial factor in certain anatomic areas, such as the face, scalp, distal extremities, and genitalia. Results of several studies have suggested that Mohs' micrographic surgery may be beneficial in the management of DFSP; however, few series have provided complete 5-year follow-up data.[217–226] At the University of Wisconsin, Madison, 36 patients with DSFP were treated with Mohs' micrographic surgery. Of these, 29 participated in follow-up study for 5 or more years (range, 5–20 years). As of this writing, there have been no local recurrences or cases of regional metastasis.[227] Recently, imatinib mesylate (Gleevec), an inhibitor of platelet-derived growth factor receptors, has shown promise for unresectable DFSP.[228]

Prognosis and Follow-up Evaluation

Although it is locally aggressive, DFSP rarely metastasizes. The overall rate of distant metastasis is approximately 5% and of regional metastasis is 1%.[195] In the past the causes of the higher rate of metastasis were probably inclusion of malignant fibrohistiocytoma (MFH) in the database and degeneration of DFSP to a more sarcomatous subtype with its subsequent increased risk of metastasis.[227–229] MFH is now understood to be a totally different entity from DFSP. Its cellular morphological characteristics and architecture have been clarified, and pathologists and dermatopathologists have reached consensus on the diagnostic criteria for MFH. The regional rate of metastasis of MFH is estimated to be greater than 50%.[160,226–228]

Recommendations for patient follow-up care include physical examination every 3 to 6 months postoperatively for 3 years and then annually for life. Particular attention to evaluation of surgical site,

regional lymph node palpation, and a complete review of systems is appropriate.

CUTANEOUS ANGIOSARCOMA

Epidemiology and Pathogenesis

Cutaneous angiosarcoma (CAS) is a rare, highly malignant, potentially lethal tumor originating from the dermal vasculature endothelium. Elderly persons are most commonly affected, and there is a 2 : 1 male predominance.[230–233] White persons are affected most often, but CAS has been reported among other persons as well.[234,235] With the exception of CAS associated with lymphedema, the cause of CAS is uncertain. Cases have been associated with history of trauma, radiation, herpes zoster, fistula of chronic osteomyelitis, vinyl chloride and arsenic oxide exposure, and arteriovenous fistula sites in renal transplant recipients.[230,231,236–245] UV light exposure does not seem to be an inciting factor. Only a minority of patients with CAS have temporally associated skin cancer.[232,233,246]

Clinical Manifestations

Principal clinical patterns include (1) CAS of the scalp and face, (2) CAS associated with chronic lymphedema most commonly following mastectomy (Stewart-Treves syndrome), and (3) radiation-associated angiosarcoma, which is the least common variant.[230,236] CAS of the scalp and face usually manifests as a painless, rapidly proliferating growth of the subcutaneous tissue plane (Fig. 74-13). CAS of this pattern occurs 50% of the time on the scalp and 30% of the time on the face or neck.[230–233,237,240,246] The tumor may be firm or spongy to palpation, the overlying skin surface smoothened because of tumor distention of the underlying structures.[247] An ill-defined area of dusky to violaceous erythema resembling a bruise or healing contusion often is present. The tumor infiltrates the surrounding tissues in a centrifugal and multifocal manner. As a result tumor involvement extends much farther than the clinical appearance of the margins. Multiple lesions may be separated by an isthmus of normal-appearing skin found at initial presentation if the primary tumor is more than 6 cm in diameter. Long-standing CAS may develop superimposed tumors and nodules. Ulceration and bleeding are not characteristic unless the CAS is larger than 10 cm in diameter. Misdiagnosis is common given the subtlety and nonspecific nature of the clinical findings. Initial differential diagnoses include cellulitis, nonspecific inflammatory changes, fungal infection, trauma, and hemangioma.[230,231,247] Reported atypical clinical scenarios include rosacea-like signs and symptoms, chronic edema of the eyelids, xanthelasma-like lesions, and even recurrent angioedema.[235,247,248]



Figure 74-13 • Cutaneous angiosarcoma involving the scalp. Ink highlights clinical margins of the lesion.

Because the prognosis of advanced CAS is poor, every effort should be made for early diagnosis and treatment. Favorable outcomes are more likely when the tumor (1) has been present for less than 6 months, (2) is less than 5 cm in size, and (3) is amenable to combined surgery and radiation therapy (e.g., CAS of the nose).[246]

In 1948, Stewart and Treves described six patients with postmastectomy chronic lymphedema in whom CAS developed in the affected extremity.[249] The estimated risk among postmastectomy patients who survive more than 5 years is approximately 0.5%.[250] The time interval between mastectomy and recognition of angiosarcoma ranges from 1 to 30 years with a mean duration of 10 years.[251] Clinically, the ipsilateral, upper inner aspect of the arm is a frequent site of early involvement. Less frequent are lesions distal to the elbow or on the chest wall that most often resemble a bruise or blotchy erythema. These color changes initially are attributed to trauma; however, rapid growth and induration often lead to ulceration and hemorrhage. Other causes of chronic lymphedema have been associated with development of angiosarcoma, including congenital lymphedema and postsurgical, post-traumatic, and infectious etiological factors.[251–257]

Histopathology

Histologically, CAS has essentially three different cell growth patterns: (1) angiomatous or well differentiated with obvious vasoformative activity, (2) spindle cell with a range of differentiation, and (3) undifferentiated or highly anaplastic.[246,258] A single tumor may have all three growth patterns.[237,246,247,258] The well-differentiated variant (angiomatous) is characterized by recapitulation of atypical endothelial cells lining irregular vascular channels. These atypical vessels are located throughout the dermis, dissect through the collagen, and surround but do not invade the adnexal structures. With time there is infiltration into the subcutaneous fat, muscle, and fascia. This particular variant is often poorly recognized initially with frozen sections. The vessels do not contain red blood cells, because hemolysis of the red blood cells during processing makes microscopic examination difficult. The spindle cell tumor variant forms dense cellular bundles that penetrate the dermis and underlying tissue.[246] Vascular channels are not easily recognized. The more anaplastic or undifferentiated CAS characteristically contains large, basophilic, pleomorphic polyhedral cells arranged in solid sheets or cords.[246,258] The dermis and subcutaneous structures often are occupied by tumor. Immunohistochemical stains for endothelium-related markers such as CD34 antigen, factor VIII–related antigen, or *Ulex europaeus* agglutinin I lectin binding may be helpful. Negative cytokeratin staining is helpful for differentiating CAS from carcinoma. Negative staining results for S-100 help to differentiate the tumor from melanoma.[247,258]

Treatment

Computed tomography and magnetic resonance imaging have not been extremely helpful unless there has been marked bony invasion.[259,260] Soft-tissue invasion of the tumor may be partially visualized, but the exact extent of the margins is poorly delineated because of the diffuse infiltrating nature of the tumor. Radiographic imaging is even more unreliable if the tumor is poorly appreciated microscopically. The peripheral margin of CAS may be partially assessed with random biopsies performed in a gridlike pattern circumferentially around the tumor.[246] Ideally, the biopsies should be full thickness of the skin and include the muscle and fascia if possible for complete assessment of the depth of the margin.

Traditional management of CAS has been wide local excision with a margin of 3 to 6 cm of normal-appearing skin. More recently,

Mohs' micrographic surgery with adjuvant radiation has been shown to produce favorable outcome.[246,261–263] The Mohs' technique combines the benefits of both fresh-tissue and fixed-tissue technique. Well-localized lesions are good candidates for the fresh-tissue technique, because a microscope can be used for identification of the tumor and excision of the entire lesion. After excision, zinc chloride fixative paste may be applied circumferentially around the surgical skin edges to stimulate an immune response around the operative site.[262] The final defect is repaired with a flap or skin graft.

For scalp lesions, orthovoltage or electron beam radiation with a curvilinear delivery system is administered over the entire scalp in a swimming cap distribution.[264] The region from the eyebrows to the occipital nuchal line is included, and both auricular-temporal sulci are encompassed. The curvilinear delivery system distributes the radiation equally to all parts of the scalp simultaneously. Thus are avoided overlapping and undertreatment of radiation sites that would otherwise accompany conventional flat-plate radiation when applied to curved surfaces, such as the scalp and forehead. Attention to these details of radiation treatment is essential, because CAS is resistant to most forms of surgical therapy, and chemotherapy has not been reported effective.

Recurrence of CAS of the scalp usually is the result of inadequate treatment of the primary tumor.[232,246] Localized recurrence can be managed with radiation with a good response.[246,261] Management of regional lymph node metastasis is surgical resection and adjuvant radiation.[232,246] Systemic disease has a grave prognosis. Given the rarity of angiosarcoma, no single institution has enough experience to establish definitive treatment guidelines. Practical strategies include use of Mohs' micrographic surgery combined with radiation, in the manner described earlier, for tumors less than 5 cm in diameter. For tumors larger than 5 cm, peripheral margin assessment (because of the multicentricity of the tumor spread), followed by orthovoltage or electron beam radiation should be considered.[246]

Prognosis and Follow-up Evaluation

The prognosis among patients with any form of angiosarcoma is uniformly poor. CAS of the scalp has an expected 5-year survival rate of less than 12%.[232] Histologic degree of differentiation, mitotic index, age, sex, location of primary lesion, and clinical appearance have no statistical bearing on survival. Tumor size has been found the only statistically significant indicator of prognosis. Lesions smaller than 5 cm correlate with improved survival at 5 years.[230] Another favorable indicator has been the presence of prominent lymphocytic infiltrate associated with the tumor. Local recurrence is common, and metastasis occurs hematogenously and through lymphatic vessels to the cervical lymph nodes, lungs, liver, and soft tissues.[232,234] There have been rare reports of spontaneous regression of CAS of the scalp and face.[265,266] Complete regression in one unreported case at the University of Wisconsin, Madison, was associated with frequent application of hot compresses.

Follow-up recommendations include frequent physical examinations with particular attention to the surgical site, contiguous structures, and palpation of lymph nodes. A complete review of systems, laboratory data, and radiologic studies should be performed as indicated. These individuals are best treated in a tertiary care center with a multidisciplinary approach.

BEST PRACTICES FOR PATIENT SCREENING AND TUMOR PREVENTION

A full-body skin examination is advised as part of an annual physical, especially for older adults or those with a family history of skin cancer. For those with a personal history of skin cancer, examination every 4 to 6 months is advised. For NMSC, special attention is paid to sites of previous skin cancer, changing or new skin lesions, and sun-exposed areas in general. Peripheral lymph nodes are palpated if there is a history of skin cancer with above average metastatic potential, such as SCC of the lip.

Prevention of NMSC mainly involves protection from the sun. Suntans should be avoided because they are a sign of, and response to, UV damage. The skin should be protected with a combination of clothing and SPF 30 sunblock effective against both UV-A and UV-B wavelengths. Hats should have a 360-degree brim to protect the neck and ears as well as the face. Sunglasses that block UV light should be worn to protect the eyes, eyelids, and periorbital skin. Outdoor daylight activities are best restricted to the early morning, late afternoon, and early evening. The peak sunlight hours of 10 AM to 3 PM are best avoided by planning indoor activities during this period. The UV index is a daily rating of local UV intensity on a scale of 1 through 10. Although the scale can be useful in assessment of relative sun exposure risk, the best practice is always to follow the sun protection measures just outlined. Protect children, because sun-induced genetic damage begins in childhood, and most persons receive most of their lifelong sun exposure before adulthood. Retinoids, antioxidants, and COX-2 inhibitors may be beneficial for chemoprevention of NMSC.

WHEN AND HOW TO PERFORM BIOPSY

Unless logistical reasons preclude it, biopsy should be performed on all lesions suspected of being NMSC to establish the correct diagnosis, plan definitive therapy, and obtain prognostic information. The most important subjective symptoms can be summarized under the heading "change". The changes may be appearance of a new growth or a change in the size, shape, color, sensation (itch or pain), crusting, or bleeding of a pre-existing lesion.

For most cases of NMSC, standard shave biopsy performed with a scalpel or razor blade is adequate. Well-differentiated SCC and keratoacanthoma can be difficult to diagnose unless the deepest portions are included in the biopsy specimen, because these often are the areas most likely to yield enough information for a diagnosis. Deep shave, punch, incisional, or excisional biopsy often is preferable to standard shave biopsy in these cases. For large or ill-defined tumors it is frequently helpful to perform multiple mapping biopsies to identify the most biologically aggressive features, define margins, and plan treatment.

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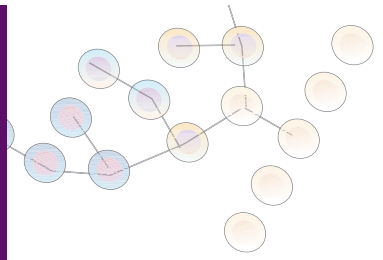
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75 Cancer of the Endocrine System

Geeta Lal, Thomas O'Dorisio, Ross McDougall, and Ronald J. Weigel

SUMMARY OF KEY POINTS

Thyroid Cancer

Incidence
- 33,500 cases per year

Types
- Follicular cell
- Differentiated (papillary follicular variants)
- Undifferentiated (anaplastic)
- Parafollicular cell (medullary)
- Connective tissue (lymphoma, sarcoma)
- Miscellaneous metastases (breast, lung, kidney, melanoma)

Presentation and Diagnosis
- Mass in the neck
- Mass noted on ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) by chance
- Abnormal cervical lymph nodes
- Differentiate primary thyroid cancer, lymphoma, benign nodule, other causes of enlarged lymph nodes
- Tissue diagnosis required, usually by fine-needle aspiration
- Ultrasound identifies cysts likely to be benign.
- Scintiscan distinguishes functioning nodules with a low likelihood of cancer.

Treatment
- Thyroid resection (lobectomy or total thyroidectomy)
- ^{131}I for differentiated tumors
- External beam irradiation—palliative
- Chemotherapy—palliative

Adrenocortical Cancer

Incidence
- Rare (2 cases per 1 million)

Clinical Features
- Abdominal mass, metastases
- Virilization in females
- Cushing's syndrome
- Feminization in males (rare)
- Hyperaldosteronism (rare)

Diagnosis
- Imaging techniques: CT scan and MRI of upper abdomen
- Biochemical: increased urinary steroid excretion (functional tumors)

Treatment
- Radical adrenalectomy for localized tumor
- Antihormonal therapy—palliative
- Chemotherapy—palliative

Malignant Pheochromocytoma

Incidence
- Rare

Diagnosis
- Episodic hypertension
- May be familial
- May be part of MEN-2a or MEN-2b

Biochemical
- Vanillylmandelic acid, metanephrine, and catecholamine in urine
- Serum catecholamine measurements

Imaging
- CT and MRI scans
- Metaiodobenzylguanidine (MIBG) radionuclide scanning

Treatment
- Surgical resection of localized disease with preoperative α-blockade
- Palliative α- and β-adrenergic blockade

Parathyroid Carcinoma

Incidence
- Rare

Diagnosis
- Refractory hypercalcemia
- Mass in neck

Imaging
- Sestamibi
- Imaging may be unnecessary

Treatment
- En bloc resection of cancer and involved structures and ipsilateral lobe of thyroid
- Radiation—palliative only
- Chemotherapy—dacarbazine
- Therapy for hypercalcemia (etidronate, gallium nitrate)—palliative

Carcinoid Tumors

Incidence
- Clinical disease: 7 to 13 cases per 1 million
- Autopsy: 6500 per 1 million

Diagnosis
- Nonfunctional bowel obstruction
- Abdominal pain
- Carcinoid syndrome (diarrhea, flushing, hypotension)

Imaging Techniques
- CT scan of the abdomen
- Contrast radiography study with small bowel follow-through
- Enteroscopy—investigational

Special Diagnostic Techniques
- Urinary 5-hydroxyindoleacetic acid (5-HIAA) measurement
- Radiolabeled sandostatin imaging

Treatment
- Complete surgical resection—curative
- Partial surgical resection—palliative
- Tumor embolization—palliative
- Somatostatin analog
- Antiserotonin agents
- Antihistamines
- Anticholinergics
- Streptozotocin + 5-FU chemotherapy; 30% partial response

Pancreatic Islet Cell Tumors

Incidence
- 1 case per 100,000

Diagnosis
- Pancreatic mass
- Metastatic disease
- Varies with hormone produced

Imaging Techniques
- CT scan of the abdomen
- Ultrasound of abdomen
- Endoscopic ultrasound
- Celiac angiography
- Intraoperative ultrasound

Special Diagnostic Techniques
- Plasma hormone assays
- Selective venous catheterization for hormonal levels

Treatment
- Complete surgical resection—curative
- Partial surgical resection—palliative
- Tumor embolization—palliative
- Antihormonal therapy
- Somatostatin analog (for most hormonal excess syndromes)
- H_2-blockers, Na/K pump inhibitors (for gastrinoma)
- Insulin antagonists (for insulinoma)
- Chemotherapy: doxorubicin/streptozotocin 60% response rate

INTRODUCTION

Cancers of the endocrine glands are uncommon. Endocrine tumors—both benign and malignant—although infrequent, present challenges in diagnosis and treatment. Cancers of the thyroid usually do not alter thyroid function, but abnormal hormone secretion can cause the earliest symptoms or signs in cancers of these others endocrine glands. Abnormal plasma levels of these hormones can be useful in monitoring the effects of therapy, and specific inhibitors of hormone biosynthesis or activity can palliate symptoms significantly without having any effect on tumor growth. Diagnosing and treating endocrine cancers requires oncologists, endocrinologists, surgeons, and other subspecialists to work together. This chapter provides a practical guide to the diagnosis and management of endocrine tumors.

THYROID CANCER

Thyroid cancer is the most common tumor of the endocrine system. The biologic behavior of the different histologic types of thyroid neoplasms varies greatly. Approximately 33,550 new cases of thyroid cancer will be diagnosed in 2007, and about 1530 patients will die from thyroid cancer.[1] Recently published studies indicate that the incidence of this malignancy is increasing, from 3.6 per 100,000 to 8.7 per 100,000 in 2002. However, the mortality rate remains unchanged at 0.5 per 100,000 population. This increase in incidence has been attributed largely to the increased detection of small cancers.[2] In general, thyroid tumors do not exhibit aggressive growth characteristics. Papillary cancer, the most common type in the United States, has an excellent prognosis.

Etiology

External radiation to the cervical region has been found to be a cause of thyroid cancer. This association has been recognized in patients who had thymic irradiation in childhood, in patients who had irradiation for acne in teenage years, and in patients with cancer such as Hodgkin's disease who received neck irradiation.[3–6] The incidence of thyroid cancer is increased in children who received irradiation to the scalp.[7] Reports from Israel of children who received scalp irradiation to treat ringworm have shown an increase in thyroid cancer compared with siblings and age-matched nonirradiated control subjects.[8] Retrospective phantom studies demonstrate that radiation doses as low as 0.09 Gy could be incriminated as the cause of cancer in these children. In addition, children exposed to radioactive fallout from Chernobyl have shown an increase in thyroid cancer.[9,10] The radiation doses that originally were blamed were in the range of 1 to 10 Gy, but based on the evidence in patients with Hodgkin's disease, doses as high as 40 Gy are potentially carcinogenic.[11] In laboratory animals, combining radiation with increased thyroid-stimulating hormone (TSH) increases the potential risk.[12,13] The lag time from radiation exposure to diagnosis of cancer usually is 10 to 20 years; however, periods from 5 to 50 years have been reported. Epidemiologic studies show that between 7% and 9% of patients who received 5 to 10 Gy external radiation develop thyroid cancer.[14] About 20% have a palpable abnormality; therefore, about one third of these nodules are cancers. Patients now are rarely given external radiation to the neck for benign disease, so this association should become uncommon. Patients treated for cancer usually are followed closely, and careful palpation of the neck and measurement of TSH annually is advisable. Radiation to the thyroid from internal sources and diagnostic or therapeutic doses of iodine 131 (^{131}I) have not been associated with an increased incidence of thyroid cancer. However, the recent epidemics of childhood thyroid cancers in Belarus and the Ukraine have a clear connection with the massive release of radionuclides, including radioisotopes of iodine, from the Chernobyl reactor.[15] Almost all of these patients were children at the time of exposure, and there was internal radiation to the thyroid from ^{131}I and other shorter-lived radionuclides of iodine,[16] as well as exposure to external radiation and probably internal radiation from ^{137}Cs. The etiology of these cancers probably is multifactorial, but the data must cause us to reconsider the risks from internal radiation.

There is increasing evidence of genetic alterations in some thyroid cancers, especially in Chernobyl survivors.[17,18] Approximately 70% of cancers in children following radiation from this nuclear disaster carried RET and papillary thyroid cancer (RET/PTC) rearrangements, the most common of which were RET/PTC1 and RET/PTC3. The latter was associated with a distinct solid growth type and appeared to be more aggressive.[19] A family history of thyroid cancer also is a risk factor for development of this tumor, particularly medullary thyroid cancer. This tumor occurs commonly within the spectrum of multiple endocrine neoplasia (MEN) syndromes 2A and 2B, and familial medullary thyroid cancer syndrome, all characterized by inherited mutations in the RET proto-oncogene.[20] Familial nonmedullary thyroid cancer (FNMTC) is now recognized as a true phenomenon, with several families reported in the literature. Several candidate gene loci for FNMTC have been explored. Bignell and colleagues[21] studied a large Canadian family with 18 cases of nontoxic multinodular goiter and 2 cases of papillary thyroid cancer and noted linkage to *MNG1* on 14 q. However, detailed analysis of 37 FNMTC families showed that *MNG1* does not account for most cases of this disorder. Linkage analysis in a French family with multinodular goiter and papillary thyroid cancer with oxiphilia revealed *TCO* on 19p13[22] to be a potential candidate gene in a small number of families. Another group noted linkage to *FPTC/PRN* on 1q21[23] in a large three-generation pedigree with papillary renal neoplasia, thyroid nodules, and papillary thyroid cancer. There is an association of nonmedullary thyroid cancer and Gardner's syndrome, Cowden's syndrome, and Werner's (adult progeroid) syndrome.[24,25] Some studies also indicate that individuals with familial nonmedullary thyroid cancer have a worse overall prognosis.[26,27]

Because of varied incidences of thyroid cancer in different ethnic groups, the role of an environmental factor or factors must be considered. A higher incidence of papillary cancer is found in regions with high dietary iodine intake such as the Pacific rim and Iceland.[28] In contrast, follicular cancer is more prevalent in iodine-deficient countries.

Classification and Prognosis

The most common thyroid cancers are papillary carcinoma and mixed papillary and follicular carcinomas (Table 75-1; Fig. 75-1A and B), the latter of which are also classified as papillary carcinomas.

Table 75-1 Histologic Classification of Thyroid Cancers and Their Incidence

Tumor Histology	Incidence (%)
Differentiated carcinomas	81–87
Papillary	
Follicular variant of papillary	
Follicular and Hürthle cell	
Medullary	6–8
Anaplastic	5
Lymphoma	1–5
Metastatic	<1

Occult cancers, now classified as papillary microcarcinoma, are less than 1 cm in size and have been reported in 10% to 30% of autopsy series. These tumors usually were identified at surgery for benign thyroid disease but are being identified more frequently due to the widespread use of ultrasound. They generally are believed to have a better prognosis than larger tumors; however, other studies indicate that these tumors may be more aggressive than previously appreciated.[29,30]

Death from papillary cancer is rare, and in most reports nodal metastasis does not adversely influence prognosis.[31] Recent series, however, have demonstrated a slightly lower survival rate with locoregional nodal metastases.[32,33] The prognosis in intrathyroidal papillary carcinoma depends on the age of the patient and size of the tumor; when the cancer is less than 5 cm in diameter, the prognosis is excellent.[34,35] Lymph node metastases can occur, but even in patients with nodal metastases only a small percentage of patients die of thyroid cancer.[36] The situation in older patients with larger, more aggressive papillary cancers is different. In patients with local invasion and cancers that cannot be totally resected, the recurrence rate and mortality rate are higher.[34] Death can result from local invasion and extensive metastases; nevertheless, the overall death rate from papillary cancer is low (<10%).[37]

In summary, the prognosis for papillary cancer is better in younger patients and in those with cancers smaller than 2 cm that are intrathyroidal and have no evidence of distant spread. The presence of metastases to lymph nodes has not been a negative prognostic factor in most series, although some series have reported increased recurrence and mortality rates for node-positive patients. Based on simple criteria such as the age of the patient, the size of the primary cancer, and whether local invasion or distant metastases are found, it is possible to determine the prognosis at presentation. Scoring systems such as AGES (age, grade of cancer, extrathyroidal spread, and size) and MACIS (metastases, age, complete excision, invasion, and size) are examples of these approaches.[38] The TNM system also stresses the importance of age at time of presentation. In patients under 45 years of age, those without distant metastases are all stage I, and those with distant metastases are stage II.

Pure follicular carcinoma carries a poorer prognosis.[39,40] Even when the disease appears confined to the thyroid gland, 5% to 15% of patients ultimately die of cancer, although survival is measured in decades. Lymph node metastases are seen less frequently than with papillary cancers of similar size. Approximately 50% of follicular cancers demonstrate intrathyroidal spread.[41] Follicular cancers cannot be distinguished from follicular adenomas based on fine-needle aspiration biopsies, because the diagnosis is based on the identification of vascular or capsular invasion. Prognosis in follicular carcinoma

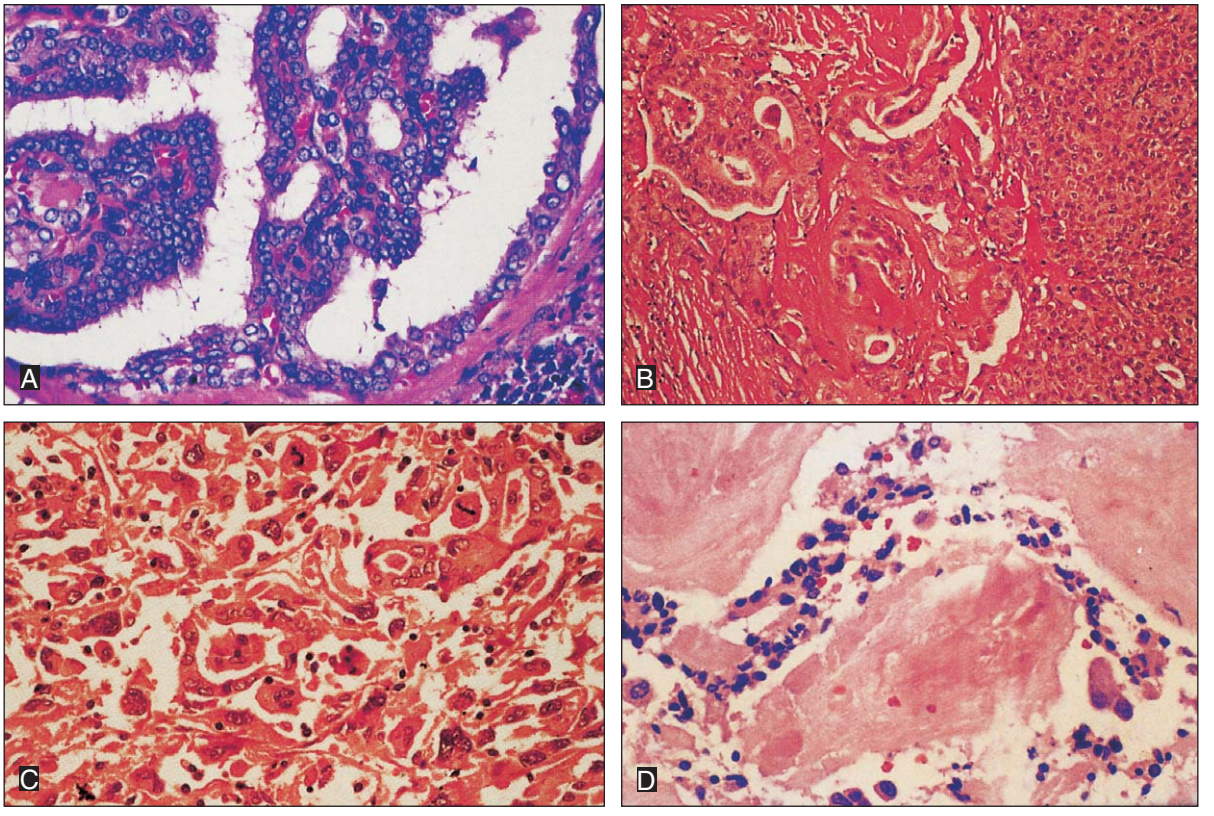


Figure 75-1 • Histologic patterns of thyroid cancer. **A,** Papillary carcinoma. **B,** Pure follicular carcinoma. **C,** Anaplastic carcinoma. **D,** Medullary carcinoma.

depends on the patient's age, the size of the cancer, and the amount of capsular and vascular invasion.[42] Minimally invasive tumors are grossly encapsulated but have evidence of microscopic invasion of the tumor capsule and/or invasion into small or medium-sized vessels in or immediately outside the tumor capsule. In contrast, widely invasive tumors are characterized by large vessel invasion and/or broad capsular invasion. Even though exact definitions are variable among pathologists, widely invasive tumors have a worse prognosis.[43]

The incidence of anaplastic carcinoma appears to be decreasing. and this type now represents less than 3% of thyroid malignancies in the United States[44] (Fig. 75-1C). This apparent decrease may be secondary to improvement in the techniques available to differentiate thyroid lymphoma and medullary carcinoma (Fig. 75-1D) from true anaplastic thyroid cancer. A proportion of patients with anaplastic cancers are immigrants from countries where goiter is common, and the anaplastic cancer probably has arisen from a more differentiated cancer that went undiagnosed for many years. In some cases there is a spectrum from papillary to anaplastic cancer, indicating that anaplastic cancers arise from more differentiated lesions,[45] and earlier diagnosis of the latter also plays a role in the reduced incidence. Anaplastic carcinomas usually occur in persons older than 60 years. These carcinomas are highly malignant and typically cause death within 6 months, either by local invasion or by distant metastases. Cure of anaplastic carcinoma is rare.[46]

Hürthle cell tumors of the thyroid are derived from the follicular cell.[47] Both carcinomas and adenomas of Hürthle cell origin have been described. Hürthle cell cancers often are classified with follicular cancer. As with follicular cancer, the differentiation of Hürthle cell adenoma from carcinoma is based on vascular features, or capsular invasion in the latter. However, Hürthle cell cancers seldom concentrate iodine, and their prognosis is worse, so a separate category is justified. Adenomas have an excellent prognosis with resection, and less than 2.5% are subsequently found to demonstrate malignant behavior.[48,49] Large (>2 cm) malignant tumors have a recurrence rate of 21% to 59% after surgical resection.[50]

Because of differences in the biology and behavior of thyroid cancers, determinging the prognosis of an individual patient may be difficult. Byar and associates[51] examined the impact of several variables on survival. Age, gender, cell type, clinical extent of cancer, lymph node status, and number of metastatic sites had prognostic significance, but not all were independent variables. However, a prognostic index that mirrored actual data was developed. Thus, in the "best" group (i.e., young patients with small localized differentiated tumors), the 5-year survival rate was approximately 95%, whereas in the "worst" group, which contained many patients with anaplastic carcinoma, the 5-year survival rate was less than 5%. These data agree with those from many other large series. To achieve uniformity in assessing the results of therapy, it is important that a single tumor, node, metastasis (TNM)[52] and clinical staging system be used. Tables 75-2 and 75-3 outline the most recent iteration of the TNM staging system for thyroid cancer. This system takes into account not only the effect of histologic type (papillary/follicular, medullary, anaplastic) on staging but also the negative prognostic effect of advancing age on stage and prognosis in differentiated thyroid neoplasms.

Primary lymphoma of the thyroid is not common. It usually occurs in an older woman with untreated Hashimoto's thyroiditis.[53] The condition characteristically presents as a rapidly growing thyroid mass with compressive symptoms and signs and sometimes causes pain. Diagnosis often can be made by fine-needle aspiration and immunophenotyping of the lymphocytic aspirate. Treatment usually consists of chemotherapy in addition to radiation therapy.

Diagnosis

Despite extensive experience with thyroid neoplasms, diagnostic recommendations continue to evolve.[54] In a patient presenting with a thyroid nodule, history and physical examination are important, because a history of radiation exposure to the head and neck or a family history of thyroid cancer should increase the clinician's suspicion of thyroid cancer. In younger patients, a solitary nodule is more likely to be cancerous. The solitary nodule is more likely than a multinodular goiter to be malignant, and a history of recent painless growth is suggestive of cancer. Malignant nodules tend to be harder, and fixation to the underlying structure is suggestive not only of cancer but also of a poorer prognosis. The presence of enlarged cervical nodes also increases the likelihood that a thyroid nodule is malignant. Table 75-4 categorizes the risk factors for a variety of clinical characteristics of thyroid nodules. Patients with nodules demonstrating high-risk characteristics should be referred for surgical resection.

Table 75-2 TNM Classification of Malignant Tumors of the Thyroid Gland

PRIMARY TUMOR (T STAGE)	
Tx	Tumor cannot be assessed
T0	No clinical evidence of tumor
T1	Tumor ≤2 cm limited to the thyroid
T2	Tumor >2 cm and <4 cm limited to the thyroid
T3	Tumor ≥4 cm limited to the thyroid or any tumor with minimal extrathyroid extension
T4a	Tumor of any size extending beyong the thyroid capsule to invade the subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
T4b	Tumor that invades prevertebral fascia or encases carotid artery or mediastinal vessels
Anaplastic carcinomas*	
T4a	Intrathyroidal—surgically resectable
T4b	Extrathyroidal—surgically unresectable
REGIONAL LYMPH NODES (N STAGE)	
Nx	Regional nodes cannot be assessed
N0	No palpable nodes
N1	Regional nodal metastases
N1a	Level VI nodes (pretracheal, paratracheal, prelaryngeal)
N1b	Metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal nodes
DISTANT METASTASES (M STAGE)	
Mx	Metastases cannot be assessed
M0	No evidence of distant metastases
M1	Distant metastases present

*All anaplastic carcinomas are considered T4 tumors.

Adapted from Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Laboratory Tests

Except for measurement of calcitonin in the diagnosis of medullary carcinoma, assessment of plasma levels of thyroid hormones has limited value in the diagnosis of thyroid cancer except in the rare patient who has a suppressed TSH and has a functioning nodule. Serum thyroglobulin (Tg) levels can be elevated in patients with cancer, but this test is not specific, and similar increases are seen in benign thyroid disorders. The American Thyroid Association guidelines do not recommend measurement of Tg preoperatively.[55] However, serum thyroglobulin is an important test in the follow-up of patients who have undergone thyroid resection for differentiated

thyroid cancer. A level greater than 2 ng/mL with a suppressed TSH or 10 ng/mL while off thyroid hormone is a reliable indicator of locally recurrent or metastatic disease[56,57] and could predict the need for ablative doses of ^{131}I; undetectable values (<0.5 ng/mL), especially after TSH stimulation, greatly reduce the need for further imaging studies to detect presumptive metastases.[58]

In patients who are hyperthyroid with a nodule, scanning with ^{123}I is advised; hyperfunctional or "hot" nodules rarely are malignant.[59] There is one exception to this rule: a functioning nodule in a child has a higher risk of being cancerous.[60] In contrast, patients with Graves' disease can have a nonfunctioning nodule, which can be malignant and should be investigated by fine-needle aspiration.[61] In euthyroid patients, fine-needle aspiration is the best first test.[62] Although "hot" nodules rarely are malignant, approximately 10% to 20% of "cold" nodules are malignant. Thyroid radionuclide imaging, therefore, has limited efficacy in distinguishing reliably between benign and malignant abnormalities. Differentiated thyroid cancers will trap iodine but are less efficient at concentrating iodine than the normal thyroid gland. Therefore, iodine uptake in a thyroid cancer typically can be demonstrated only after all normal thyroid tissue has been ablated and the TSH level is allowed to rise. There can be biochemical, quantitative, and intracellular positional alterations in the sodium-iodide symporter (NIS) in thyroid cancer cells.[63] Ultrasonography may be useful in distinguishing among cysts, cystic tumors, and solid tumors of the thyroid.[62] Small cysts are unlikely to be cancerous, but all cysts should be aspirated and the aspirate examined cytologically. Aspiration of a benign cyst often will suffice for both diagnosis and therapy, whereas fluid tends to reaccumulate in a cystic cancer. Because a malignant tumor of the thyroid may present as a solid, cystic, or mixed lesion, ultrasonography alone is not diagnostic.[64]

Needle biopsy, particularly fine-needle aspiration, is the diagnostic procedure of choice for thyroid nodules in euthyroid patients.[62] When the result of fine needle aspiration biopsy is clearly positive or clearly negative, the decision regarding surgery, or no surgery, can be made confidently.[65,66] However, a negative fine-needle biopsy or cutting needle biopsy does not ensure that a thyroid mass is not malignant (false-negative rate, 1% to 5%), and clinical concern and careful follow-up will dictate the decision to proceed to resection. Fine-needle aspiration biopsy appears to be less reliable in patients with a history of radiation exposure to the head and neck or a family history of thyroid cancer, primarily due to the multifocal nature of the tumors present in these scenarios.[67] High-resolution ultrasound guidance to perform fine-needle aspiration accurately is being used routinely. Ultrasound alone can identify features of nodules that increase the a priori risk of malignancy such as fine stippled calcification and enlarged regional nodes, but a tissue diagnosis is strongly recommended prior to thyroidectomy. The common indications for ultrasound-guided fine-needle aspiration are for biopsy of nodules that are nonpalpable or difficult to palpate, for previously failed fine-needle aspiration, and for nodules incidentally identified during neck

Table 75-3 Staging of Thyroid Cancer

Stage	TNM
Patients < age 45 years	
I	Any T, any N, M0
II	Any T, any N, M1
Patients ≥ age 45 years	
I	T1, N0, M0
II	T2, N0, M0
III	T3, N0, M0
	T1–3, N1a, M0
IVA	T4a, N0–1a, M0
	T1–4a, N1b, M0
IVB	T4b, any N, M0
IVC	Any T, any N, M1
MEDULLARY THYROID CANCER	
I	T1, N0, M0
II	T2–3, N0, M0
III	T1–3, N1a, M0
IVA	T4a, N0–1a, M0
	T1–4a, N1b, M0
IVB	T4b, any N, M0
IVC	Any T, any N, M1
ANAPLASTIC CANCER	
IVA	T4a, any N, M0
IVB	T4b, any N, M0
IVC	Any T, any N, M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Table 75-4 Risk Factors for Malignancy in Nodular Thyroid

	LOW RISK ↔ HIGH RISK				
Factor	**1**	**2**	**3**	**4**	**5**
Age					
Elderly				•	
Child				•	
Sex					
Male				•	
Female		•			
Low-dose radiation in childhood					•
Family history		•			
Cystic mass	•				
Solid mass				•	
Multiple masses		•			
Solitary mass			•		
Growing mass					•
Stable mass			•		
Hot scan	•				
Cold scan			•		
Warm scan		•			
Fine-needle aspiration (–)		•			
Fine-needle aspiration (+)					•
Associated cervical adenopathy					•
Complete resolution in response to thyroid suppression	•				
Partial resolution in response to thyroid suppression			•		
No response to suppression				•	

Modified from Sessions RB, Diehi WL: Thyroid cancer and related nodularity. In Myers E, Suen J (eds): Cancer of the Head and Neck, 2nd ed. New York, Churchill Livingstone, 1981, p 766.

imaging for other reasons. Ultrasound-guided fine-needle aspiration has been shown to result in improved cancer diagnosis on significantly smaller nodules compared with fine-needle aspiration performed by palpation.[68]

Treatment

Treatment of thyroid cancer includes surgery, ^{131}I radiation, and suppression with thyroid hormone.[39,69] External-beam therapy also (rarely) has been employed.

Surgery of the Thyroid

Debate continues concerning the optimal surgical treatment of well-differentiated thyroid carcinoma. Preoperatively, the surgeon often cannot be certain whether a thyroid nodule is cancer, and must make a decision concerning the extent of operation based on clinical judgment. Young patients with small, well-encapsulated tumors that appear benign on frozen section, with a normal contralateral lobe, can be treated with lobectomy. A history of neck irradiation, the presence of contralateral disease, and cytologic or histologic findings suggestive of malignancy influence the decision to perform a total or near-total thyroidectomy. The location of the parathyroid glands and recurrent nerve also can influence the extent of lobectomy on the contralateral lobe. When a diagnosis of thyroid carcinoma is clear, a total or near-total thyroidectomy is preferred.[70–72] The rationale for this decision is based on several facts related to the biology of thyroid carcinoma. First, thyroid cancer often can be multicentric, and resection of the contralateral lobe often identifies malignancy. Second, a total thyroidectomy can be performed safely with a low morbidity rate. Patients with thyroid carcinoma will be treated with thyroid replacement postoperatively, regardless of whether an adequate, normal-functioning thyroid is left intact. Resection of the entire gland facilitates both the use of radioiodine postoperatively and the use of thyroglobulin levels as a tumor marker. Because papillary cancer often metastasizes to regional lymph nodes, if enlarged nodes are identified at thyroidectomy, a midneck dissection on the ipsilateral side is performed at resection. Follicular cancer rarely demonstrates lymph node metastases, and a midneck dissection is not routinely justified during thyroidectomy. Modified neck dissection is advocated only in instances of obvious nodal metastases involving the lateral cervical nodes.

Debate continues as to whether recurrence and fatality are influenced by the extent of surgery.[73,74] A study by Van Nguyen and associates[75] showed that for low-risk patients total thyroidectomy gave results identical to those with lobectomy. Shaha and associates[76] reported 1038 patients with thyroid carcinoma, 465 of whom were in the low-risk group. The mean follow-up period was 20 years. Their study did demonstrate significant improvement in local recurrence with lobectomy compared with less extensive operations. However, results for lobectomy compared with those of total thyroidectomy failed to achieve significance, with local recurrence of 4% versus 1% ($P = 0.1$) and overall failure of 13% versus 8% ($P = 0.06$). However, these studies did demonstrate a trend for total thyroidectomy giving superior results when compared to lobectomy. Sanders and Cady[35] did not demonstrate a difference in survival comparing total thyroidectomy and lobectomy in low-risk patients. Of particular interest is the study by Wanebo and associates,[77] who examined extent of operation for low-, intermediate-, and high-risk groups. Their work failed to demonstrate any difference in survival with extent of operation in all risk groups.

Other studies have demonstrated improved outcome with total thyroidectomy. Samaan and associates[78] examined 1599 patients with well-differentiated thyroid carcinoma and reported improvement in recurrence for total thyroidectomy compared to lesser operations. DeGroot and associates[34] demonstrated a decreased recurrence rate for total thyroidectomy compared with lobectomy and a significant improvement in mortality rate. Mazzaferri and Jhiang[33] reported their study of 1355 patients with a mean follow-up of 15.7 years. They reported significant improvements in recurrence rate (26% vs. 40%; $P < 0.002$) and mortality rate (6% vs. 9%; $P = 0.02$) comparing total thyroidectomy with lesser procedures. Loh and associates[79] reported their results in 700 patients with a mean follow-up period of 11.3 years. They demonstrated significant improvement in recurrence and mortality rates with total thyroidectomy or near-total thyroidectomy compared with lesser operations, particularly for advanced tumors. Given these reports, and the fact that accurate risk-stratification of patients preoperatively is not possible, it is recommended that all patients with differentiated thyroid cancers identified preoperatively undergo a near-total or total thyroidectomy, provided the procedure can be accomplished with minimal morbidity.

A thyroidectomy begins with the patient anesthetized in the supine position with the neck in extension (Fig. 75-2). A Kocher collar incision is made, and dissection is carried out through the platysma. Superior and inferior flaps are raised by dissection in the avascular plane deep to the platysma muscle, superiorly to the level of the thyroid cartilage and inferiorly to the suprasternal notch. Strap muscles can be divided in the midline. It rarely is necessary to transect either the strap muscles or the sternocleidomastoid muscle. The thyroid lobe is exposed using blunt dissection. Occasionally, it is necessary to resect en bloc regions of muscle invaded by tumor. The thyroid lobe is reflected medially and the middle thyroid vessels are ligated. The isthmus can be divided between clamps and ligated early in the procedure; this often facilitates dissection, particularly for large goiters. Branches of the superior pole vessels are identified close to the superior pole and ligated individually to avoid injury to the external branch of the superior laryngeal nerve. Once the superior pole is mobilized, the recurrent nerve is identified by careful dissection in the region of the inferior thyroid artery. The parathyroid glands should be sought and left with their blood supply intact. The parathyroid glands usually can be identified within 1 cm of the crossing of the recurrent laryngeal nerve and the inferior thyroid artery. Occasionally, a parathyroid gland is devascularized; after confirmation of identity by frozen section, this gland can be reimplanted into the sternocleidomastoid muscle. The inferior thyroid pole also is mobilized by a combination of blunt dissection and ligation of the inferior thyroid vessels. The thyroid then is dissected off the trachea until the ligament of Berry is reached. This structure often contains small vessels, and the nerve is most vulnerable in this location. Once the ligament is carefully divided, the thyroid can easily be separated off the trachea. The contralateral lobe always should be exposed to examine for gross pathologic processes. A total thyroidectomy is completed by performing the contralateral lobectomy in a fashion identical to that used for the ipsilateral lobe. Occasionally, to preserve the blood supply to the parathyroid glands, it is reasonable to perform a subcapsular dissection of the contralateral lobe, leaving a small area of thyroid in the region of the parathyroid gland. This procedure is referred to as a near-total thyroidectomy.

Radiation Therapy

Metastatic cancer shown to accumulate ^{131}I warrants treatment with 100 to 200 mCi of ^{131}I. Radioiodine treatment is accomplished by discontinuing thyroid hormone replacement and allowing the patient to become hypothyroid, with resultant TSH stimulation of metastases to achieve increased uptake of ^{131}I. A low-iodine diet is advised for 2 weeks prior to testing and treatment. Figure 75-3 shows an example of a radionuclide scan in a patient with pulmonary metastases from papillary thyroid carcinoma. Most authorities obtain a whole-body scan with a diagnostic dose of ^{131}I, or ^{123}I before treatment with ^{131}I. That scan provides information about the quantity of residual thyroid tissue and the presence of local or distant metastases. The information helps in the selection of the appropriate therapeutic dose of ^{131}I. Knowledge of normal and variants of normal distributions of iodine help ensure that interpretation of the scan does

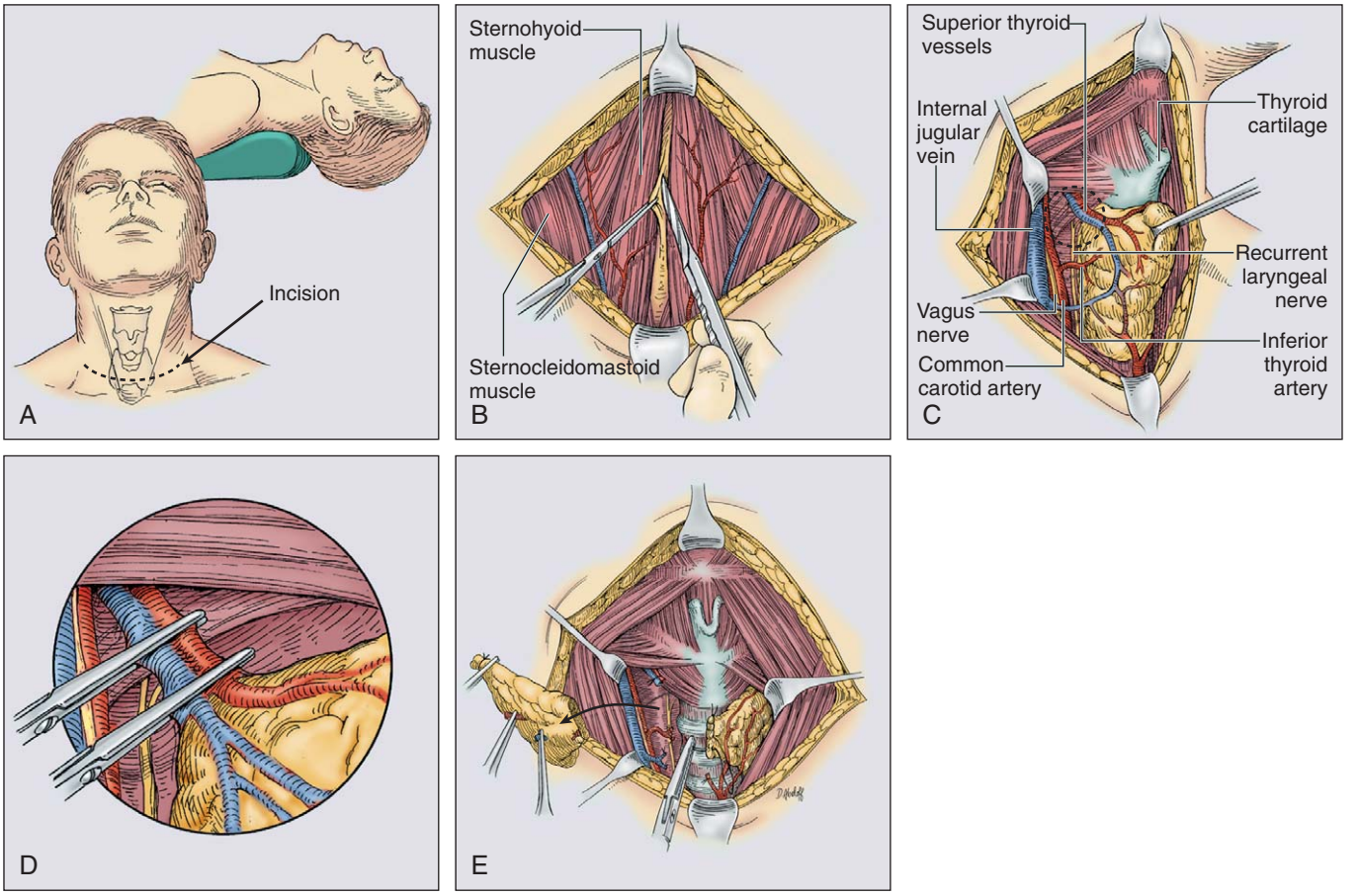


Figure 75-2 • Thyroidectomy. **A,** The patient is placed with the neck in extension. The thyroid is approached through a Kocher collar incision, which is commonly made approximately 2.0 cm superior to the sternal notch. **B,** The strap muscles are divided in the midline to expose the thyroid gland. **C,** The strap muscles are retracted laterally and the thyroid is retracted medially, exposing the structures of the midneck. The recurrent laryngeal nerve can be seen lying within the tracheosophageal groove. **D,** The superior pole vessels are individually clamped and ligated as they enter the thyroid gland. Inferior thyroid vessels, as well as the thyroidea ima vessels, are individually suture-ligated. **E,** The dissection is completed by dissection of the thyroid gland off the trachea. The isthmus is then transected and can be oversewn with a suture for hemostasis.

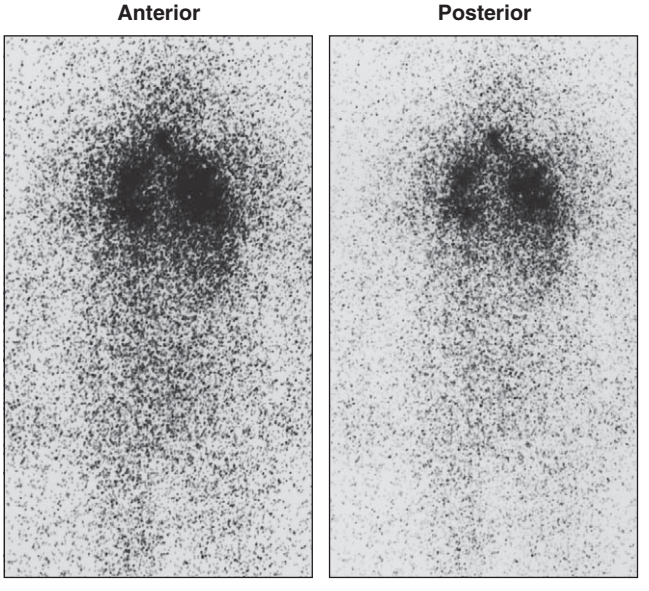


Figure 75-3 • ^{131}I scan in a patient with metastatic papillary thyroid cancer demonstrating diffuse pulmonary metastases from papillary thyroid carcinoma. Anterior and posterior views are shown.

not produce a "false" positive.[69,79] In Figure 75-4 a whole-body scan shows metastases in cervical lymph nodes. In contrast, Figure 75-5 shows uptake in the mediastinum indicating the thymus, not nodal metastasis.[80] Following administration of ^{131}I, thyroid replacement therapy is restarted. This cycle can be repeated at 6- to 12-month intervals. Residual thyroid and locally invasive thyroid cancer can be eliminated, but success is related to extent of thyroidectomy.[81–83] Similarly, functioning metastases in lymph nodes can be eliminated[84–86]; however, when the nodes are palpable it is recommended that they be removed.[87] Small homogeneous pulmonary metastases can be cured, but in bulky distant lesions, especially in the skeleton, cure is uncommon.[88,89] Recent data have failed to demonstrate an improved disease-specific survival or disease-free survival in patients with Stage I thyroid cancer treated with ^{131}I.[36,90]

A number of controversial topics are related to radioiodine therapy:

- Park and associates[91] showed in a small number of patients that large diagnostic doses, especially 5 to 10 mCi, can "stun" the thyroid, and subsequent therapy is not trapped as expected. In a comparison of 300 diagnostic scans made with 2 mCi ^{131}I and subsequent post-therapy whole-body scans, possible stunning was found in only 2%.[92] In two of the four patients, the follow-up scan was negative, so stunning probably had not occurred.
- Is it necessary to conduct a diagnostic whole-body scan? Because of the report of Park and associates, some physicians prescribe ^{131}I

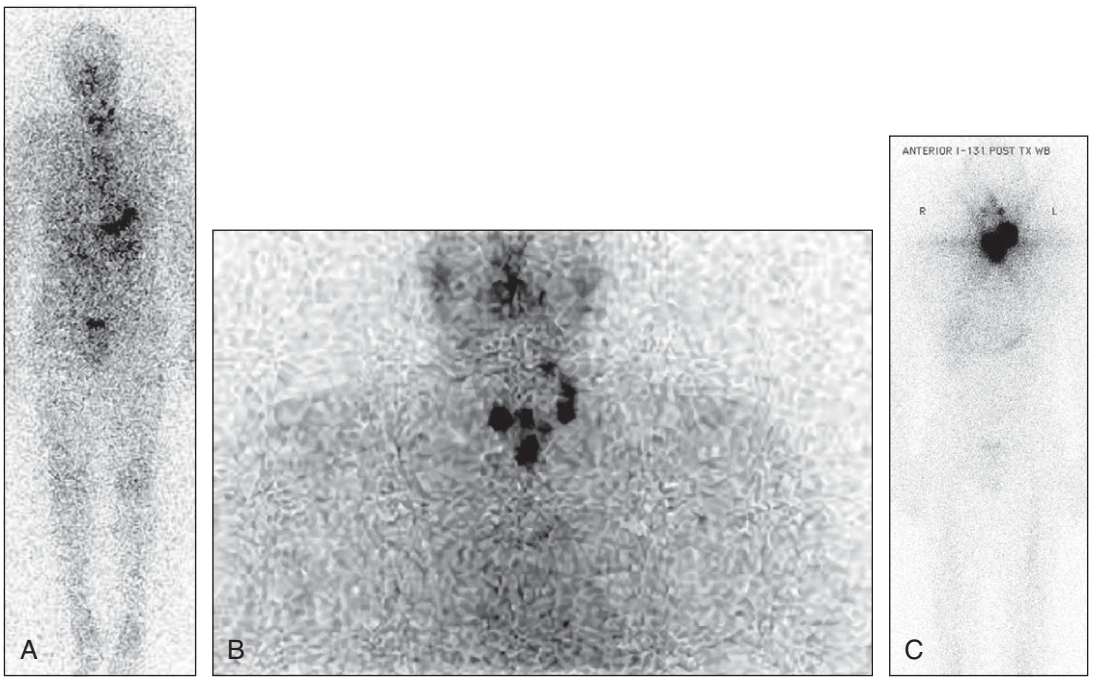


Figure 75-4 • **A,** Whole-body scan acquired 24 hours after administration of 2 mCi ^{123}I. **B,** Spot view of the neck and chest. There are several areas of uptake indicative of residual thyroid and functioning metastases in cervical lymph nodes. **C,** Post-therapy scan made 7 days after administration of 150 mCi ^{131}I. There is intense uptake in the region, but the resolution is not as good as with ^{123}I. There is faint uptake in the liver on the post-treatment scan due to metabolism of radioiodinated thyroid hormones at that site.

therapy without a prior diagnostic scan. This practice could result in treating patients who do not require therapy, and, furthermore, it does not allow tailoring of the dose. For those concerned about stunning, ^{123}I provides superior images and substantially less radiation to the residual thyroid, making stunning extremely unlikely.[93,94]

- How should patients who have a negative diagnostic scan but have elevated thyroglobulin be treated? A small number of patients have been treated with large doses of ^{131}I when the prior diagnostic scan was negative but serum thyroglobulin was elevated.[95] The rationale is that cells producing thyroglobulin can trap enough ^{131}I to expect a therapeutic effect. These patients are then followed by serum Tg measurement and are re-treated when the thyroglobulin remains high. On the other hand, both high-resolution neck ultrasounds and positron emission tomographic (PET) scans, particularly when

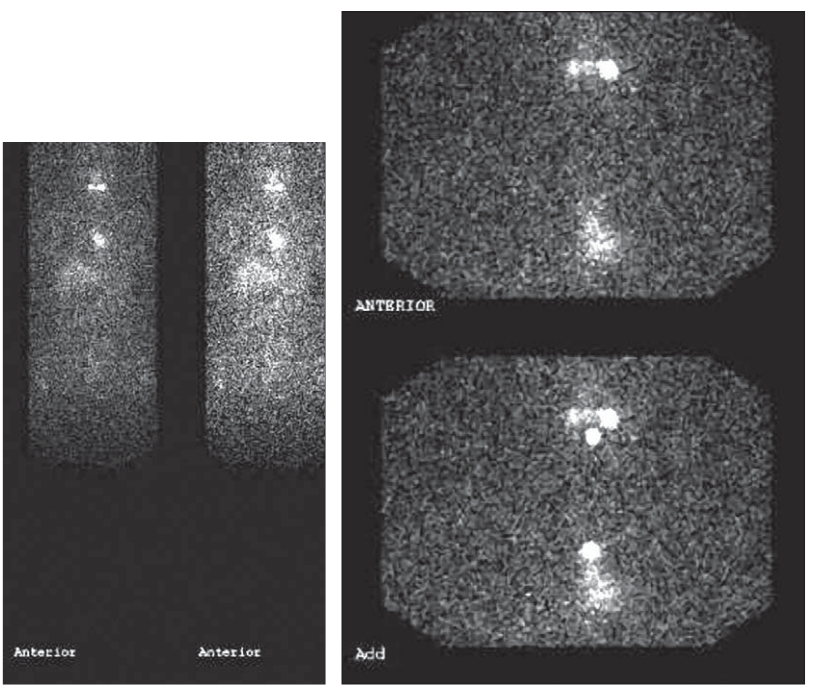


Figure 75-5 • Whole-body scans of a patient who had total thyroidectomy and ^{131}I for thyroid cancer (*left*). Spot views of the neck and chest (*right*). The lower panel has markers at the chin and mid-sternum to help anatomic interpretation. The patient was treated with a second dose of ^{131}I because of an elevated Tg level. This post-treatment scan shows no uptake of ^{131}I in the neck, but there is physiologic uptake in the salivary glands and uptake in the mediastinum. The mediastinal uptake is characteristic of the thymus and is a potential false positive finding.

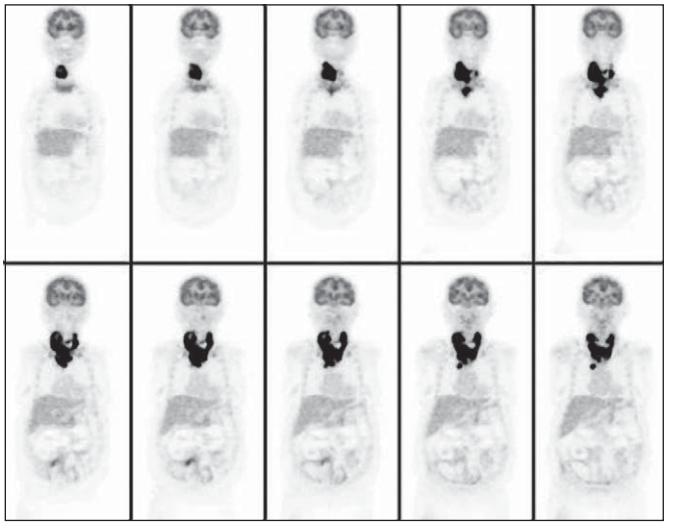


Figure 75-6 • PET scan of a 75-year-old woman with anaplastic cancer of the thyroid. Images were acquired 1 hour after intravenous injection of 15 mCi ^{18}F-fluorodeoxyglucose (FDG). There is intense uptake of FDG in the undifferentiated cancer.

combined with CT scans, have shown utility in identifying sources of increased Tg in patients with biochemical evidence of recurrent or persistent disease but negative ^{131}I scans.[96,97] Figure 75-6 shows a PET scan that was performed to stage the extent of an anaplastic cancer and is presented to demonstrate the superb resolution.

Radioactive iodine treatment generally is well tolerated. Some patients develop swelling of the salivary glands, which can be reduced or prevented by having them suck lemon candy. A dry mouth can be a troubling aftermath. Leukemia has been reported to occur following ^{131}I when given in repeated doses and at shorter intervals than is currently advised.[98] Although there have been reports of pulmonary fibrosis developing when uptake in pulmonary metastases was extensive, the risk of dying from pulmonary metastases is significantly greater. Radiation safety precautions are necessary. The patient should be kept isolated until the body load of ^{131}I is reduced. This approach requires consultation among the patient, the family, and a nuclear medicine physician.

Some studies have examined the use of recombinant human TSH (rhTSH) as an alternative protocol in preparation for ^{131}I treatment. Treatment with rhTSH has been shown to induce increased Tg and improved uptake of iodine in a manner similar to induction of hypothyroidism.[99] However, in a recent study of 127 patients in whom rhTSH and thyroid hormone withdrawal were compared, induction of hypothyroidism was found to be superior to rhTSH.[100] Patients treated under the rhTSH protocol do avoid the symptoms associated with hypothyroidism. We have used rhTSH in more than 160 patients and have found it can replace withdrawal scans provided both the scan and Tg are obtained. The average TSH is well above 100 IU/mL. RhTSH treatment was preferred by the patient over withdrawal of thyroid hormone in all but one patient.[101] In addition, improvement in the treatment protocol with rhTSH may result in improved efficacy.[102] Although ^{131}I is the mainstay of radiation treatment of thyroid carcinoma, external-beam radiation also plays a role in the treatment of this disease.[103,104] Persistent or recurrent thyroid cancer may fail to take up ^{131}I, especially tumors that recur after multiple radioactive iodine treatments. Extremely bulky tumors may fail to be completely controlled with ^{131}I, and the treatment of anaplastic thyroid cancer[105] almost always includes external-beam treatment. Radiation therapy also is useful for bony metastases not amenable to resection.[106] Treatment of the thyroid tumor bed involves both sides of the neck and the upper mediastinum. Minimal residual disease (positive surgical margins or small gross residual in an ^{131}I-negative tumor) can be treated with 60 Gy, whereas larger amounts of disease will require doses of 65 to 70 Gy. Because the target volume wraps around the spinal cord and the tolerance of that structure is only 45 Gy, the dosimetry of thyroid bed irradiation is extraordinarily challenging. Figure 75-7 illustrates the type of complex radiation therapy performed for this disease.

Use of Thyroid Preparations for Suppression of Thyroid-Stimulating Hormone

Differentiated thyroid cancers respond to TSH by growing, producing, and secreting Tg and by trapping more iodine. Conversely, suppression of TSH can slow or reverse growth and lower Tg. Some reports suggest that thyroxine suppression of TSH decreases recurrence after thyroid resection for differentiated carcinomas.[107] When using the strategy of TSH suppression, it is important to follow plasma TSH levels to ensure an adequate thyroxine dose. In patients who have been adequately treated by surgery or radioiodine and who have no clinical evidence of disease, a negative ^{131}I scan, and undetectable Tg, it is debatable whether suppressed TSH adds any benefit,

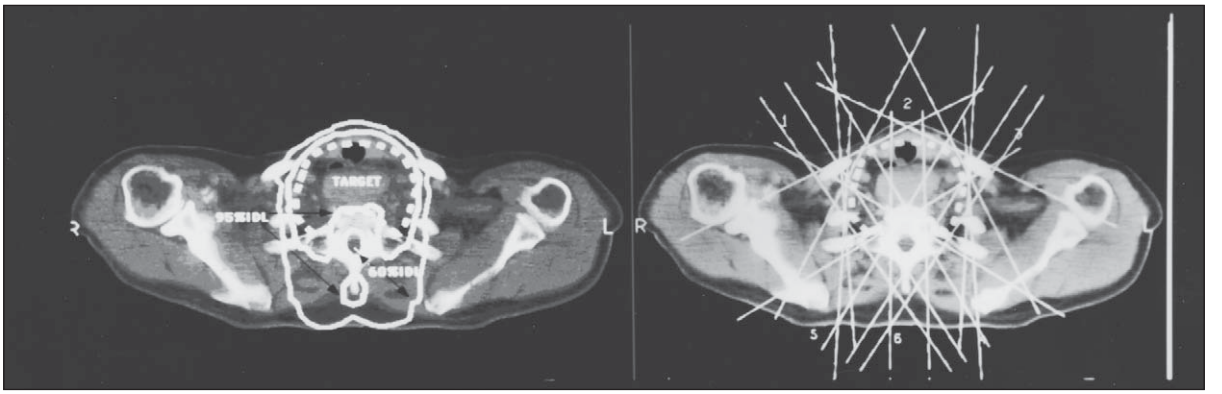


Figure 75-7 • External beam radiation for thyroid carcinoma can be quite complex. On the left, the target for this bulky thyroid carcinoma is marked with a dashed line. The high-dose volume (95% dose line) encompasses this target while avoiding the spinal cord. The radiosensitive spinal cord is in the 60% isodose line, which permits delivery of doses up to 70 Gy with this plan. On the right is a superimposition of the six cross-firing fields that are used to create this dose distribution. The fields either avoid the spinal cord or include a lead block to shadow the spinal cord, protecting it from the high-dose radiation. The treatment planning and dosimetry of thyroid carcinoma treatment is one of the most complex challenges in radiation oncology.

and side effects of long-term TSH suppression such as anxiety, bone loss, and arrhythmias have to be considered, particularly in older patients.

Postirradiation Tumors

The natural history of postirradiation thyroid carcinoma has been reviewed by Roundebush and DeGroot.[108] Patients tend to be younger (mean age, 28 years) and have a higher incidence of multifocal tumors. This study and others[109] have contributed to the development of treatment recommendations for persons known to have been exposed to ionizing radiation. When palpation of the neck is normal, the patient is followed by careful clinical examination at yearly intervals. The value of a thyroid scan has not been proved. When a discrete nodule is noted, fine-needle aspiration is indicated, and if the result is suspicious, the patient is referred to surgery. In the case of small benign nodules, clinical follow-up with or without thyroid hormone is appropriate. Shimaoka[110] noted that exogenous thyroid hormone caused shrinkage of the nodules in about 50% of cases. Some authorities recommend thyroidectomy for patients with a history of radiation exposure and a thyroid nodule, skipping fine-needle biopsy due to the high rate of false-negative biopsy in this setting.[111]

Schneider and associates,[112] reporting on a large surgical experience with postirradiation thyroid carcinoma, found results similar to those noted for spontaneous thyroid cancers. Because many thyroids have multifocal disease, the surgeon usually cannot perform lobectomy for an apparent single nodule, and in general, when there is preoperative suspicion of thyroid cancer, total or near-total thyroidectomy is advised. Schneider and associates[112] found that the likelihood of nodules developing in the remnant following subtotal thyroidectomy was 36%. The risks of total thyroidectomy (i.e., damage to the laryngeal nerve and hypoparathyroidism) must be balanced against the slow growth of papillary carcinoma and the potential for cure.

Chemotherapy

Cytotoxic drug treatment for metastatic thyroid cancer has not been evaluated extensively. The largest experience is with anaplastic carcinomas, which have high growth rates and a very poor prognosis. Doxorubicin is the most active single agent in both medullary and nonmedullary carcinomas of the thyroid.[105,113] In a report from the Southwest Oncology Group, the combination of doxorubicin and cisplatin resulted in an objective response in 27% of 41 patients.[114] A similar trial reported by the Southeastern Cancer Study Group, however, failed to document this level of activity, with only two partial responses out of 22 subjects.[115] Novel therapies currently being investigated for the treatment of thyroid cancers refractory to other treatments include tyrosine kinase inhibitors targeting RET/PTC translocations[116] and angiogenesis inhibitors.[117,118] A small phase II clinical trial has shown that treatment with rosiglitazone, a peroxisome proliferator-activated receptor gamma agonist resulted in increased radioactive iodine uptake in 4 out of 10 patients with persistent thyroid cancer that was radioactive iodine scan negative at study initiation.[119]

MEDULLARY CARCINOMA OF THE THYROID

Medullary thyroid carcinoma (MTC) arises from the parafollicular C cells, which are part of the amine precursor uptake decarboxylation (APUD) system, rather than thyroid epithelial cells (see Fig. 75-1D). Medullary thyroid carcinoma accounts for 6% to 10% of all thyroid cancers. It can occur sporadically or in a familial form, either as part of multiple endocrine neoplasia type 2 (MEN-2) or as a familial MTC without MEN association. The gender distribution is approximately equal. The tumor is unilateral in most sporadic cases and bilateral and multifocal in familial cases.[120–122]

Diagnosis

Any thyroid nodule could be MTC (Fig. 75-8); however, a family history of MTC, pheochromocytoma, hyperparathyroidism, or other manifestations of MEN-2 increases this likelihood. Plain film radiography of the neck may be useful. Keiser and associates[123] reported that tumor calcification was present in 35% of the patients in their series. Lymph nodes often are enlarged clinically and at surgery are involved pathologically in two thirds of patients.[124] Amyloid deposition between the spindle-shaped tumor cells is characteristic of MTC. The presence of calcitonin messenger RNA (mRNA) has been used to diagnose MTC when the histologic type is unclear.[125] The molecular diagnosis of MEN-2 is discussed later in this chapter. The parafollicular C cells secrete calcitonin, a peptide hormone that inhibits bone resorption. Calcitonin secretion is stimulated by calcium infusion. In patients with MTC, the basal calcitonin level is elevated above normal[126] and can be increased further with infusion of calcium and pentagastrin. The few cases of MTC that exhibit normal basal plasma calcitonin levels demonstrate an exaggerated response to calcium and pentagastrin.[126,127] The excessive calcitonin secretion does not appear to exert any metabolic effect. In the familial form, the associated parathyroid hyperplasia is an independent manifestation of the MEN syndrome inasmuch as it may precede MTC. MTC tumors also may contain large quantities of histaminase[128] and dopadecarboxylase,[129] neither of which produces any clinical syndrome. Serum histaminase is increased in many patients with metastatic disease, and its presence suggests metastases.[130] The diarrhea that

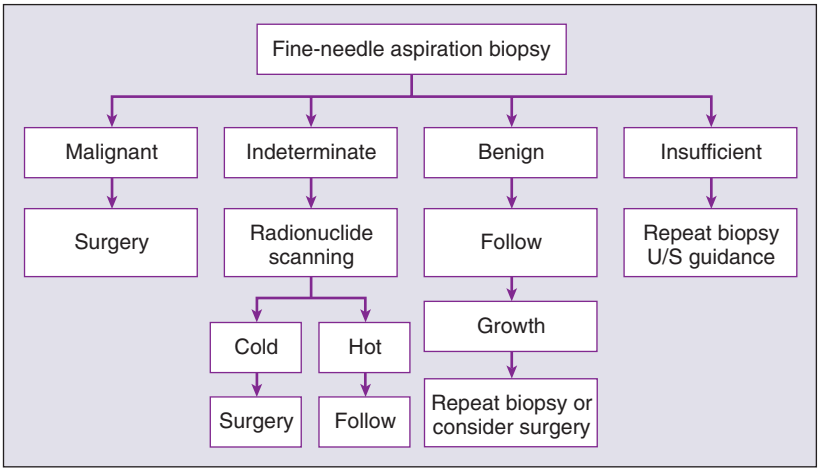


Figure 75-8 • Diagnosis of a thyroid mass.

occasionally accompanies the syndrome has been attributed in some studies to prostaglandin secretion,[131] but other investigators have not found this association.[132] Other compounds secreted by C-cells include carcinoembryonic antigen (CEA), corticotrophin, vasoactive intestinal peptide, and serotonin. MTC is one cancer in which it is possible to recognize the precancerous state. In the familial form, C-cell hyperplasia occurs prior to the development of carcinoma,[133] making it crucial for the physician to measure basal and stimulated calcitonin levels in all family members of a patient with MTC. Stimulation tests performed with calcium or pentagastrin predicted MTC in 12 members of one family, 11 of whom had no clinical evidence of disease.[134,135] Similarly, Jones and Sisson[136] were able to identify eight children, whose disease was diagnosed by appropriate testing, who were members of a family with the MEN-2 syndrome. However, these stimulation tests were associated with unpleasant side effects that could potentially affect compliance with annual provocative testing in members of MTC families. Because mutations in the RET proto-oncogene have now been established in MEN-2, family members can be screened at birth, obviating yearly provocative testing and allowing affected members to be offered early thyroidectomy.[137]

Treatment

Treatment of MTC is surgical excision. Because the cancer often is multifocal, surgery should include total thyroidectomy with complete resection of nodes in the central neck, that is, between the carotid sheaths laterally and from the thyroid cartilage superiorly to the suprasternal notch inferiorly. This includes paratracheal and upper mediastinal lymph nodes as well. If the patient presents with palpable lymph node disease, an ipsilateral modified radical neck dissection is also performed. Since the rate of contralateral lymph node metastases in this setting is high, some authors advise a prophylactic contralateral lymph node dissection, whereas others advise following postoperative calcitonin levels. In the absence of palpable disease, prophylactic modified radical neck dissection is recommended for primary tumors larger than 1.5 cm.[138,139] Deftos and Stein[140] have reported that ^{131}I treatment is occasionally a useful adjunct to surgery when a calcitonin-secreting remnant is identified following total thyroidectomy; however, subsequent studies have failed to show any benefit from ^{131}I.[122] The cancer per se does not trap iodine. Because pheochromocytomas occur in the MEN-2 syndrome, it is necessary to exclude their presence in MTC patients, as thyroid surgery in a case with an undetected pheochromocytoma could be disastrous. An identified pheochromocytoma should be removed first and the patient given time to recover before the MTC is excised.

The clinical course in cases with metastatic MTC is variable. Death due to lung, liver, or bone metastases may occur quite quickly. However, it is not uncommon for patients with MTC to be relatively asymptomatic, even with large tumor burden. Many patients may be debilitated by intractable diarrhea,[132131] which correlates with plasma calcitonin levels of greater than 20 ng/mL and which may be palliated by cytoreductive surgery[141] or the somatostatin analog octreotide.[142] Other therapies that have shown promise in small clinical trials include an anti-CEA antibody (Labetuzumab)[143,144] and tyrosine kinase inhibitors STI571 (Imanitib) and SD6474 (Zactima). STI571 has been used as therapy for gastrointestinal stromal tumors and has shown some efficacy against medullary thyroid cancer cells in vitro, however the doses needed to achieve inhibition indicate that it is less likely to be useful in clinical studies.[145,146] SD6474 is an orally administered tyrosine kinase inhibitor that has shown activity against medullary thyroid cancer in a small phase II study. About 26% of patients had evidence of partial response by CT criteria.[20,147]

ADRENOCORTICAL CANCER

Adrenocortical carcinoma is infrequent, representing less than 0.2% of all cancers,[148] and has an incidence of only 2 per 1 million population.[149] Adrenal cancer may develop at any age but most frequently appears in middle age. Hormonally functional tumors are slightly more common in women, and nonfunctioning tumors are more frequent in men. Although both functioning and nonfunctioning adrenal tumors occur, steroid-producing tumors[148,150] are more common. Secreted hormones include cortisol, androgens, estrogens and aldosterone, with up to 35% of tumors secreting multiple hormones. Nonfunctioning tumors are usually diagnosed after the patient has complained of pain or presents with a large abdominal mass. The combination of retroperitoneal location and inefficient steroid biosynthesis makes it likely that adrenal cancers will attain a large size before symptoms due to the mass or to hormonal secretion are noted. Thus, early detection and cure are unlikely.[148,150]

Clinical Features

Adrenocortical carcinomas may or may not produce steroid hormones. However, the steroid-synthesizing potential of adrenal tumors explains many of their laboratory and clinical features. For example, many women with functional adrenal cancers are virilized. This finding derives from the fact that the biosynthetic pathway to C19 steroids is almost always intact in functioning adrenal cancers, resulting in high urinary 17-ketosteroid (17-KS) excretion. Because adult men cannot be "hypervirilized," excessive androgen synthesis will not be clinically apparent in them unless urinary 17-KS or plasma androgens are measured. However, women are easily virilized, and this detection bias may account to some extent for the apparent predominance of functional tumors in women. Table 75-5 lists the hormonal syndromes produced by adrenal cancer, with estimates of their frequency. Specific diagnostic features of these syndromes are described in the following paragraphs.

Cushing's Syndrome

The characteristic endocrine abnormality of Cushing's syndrome is an increase of plasma 11-deoxycortisol and its urinary metabolite.[150] Cushing's syndrome may be a paraneoplastic syndrome associated with ectopic adrenocorticotropic hormone (ACTH) production by solid tumors. However, in such cases, virilization is rare. Virilization in association with Cushing's syndrome almost always indicates adrenal cancer,[151] because urinary 17-KS secretion ranges from 100 to 1000 mg/day—considerably higher than that produced by ectopic ACTH.

Virilization

Virilization is caused by testosterone, which is synthesized peripherally from adrenal androstenedione and dihydroepiandrosterone. It is the excess urinary 17-KS resulting from metabolism of these steroids that helps distinguish adrenal cancer from other virilizing syndromes. Occasionally, hirsutism is the only presenting feature with virilizing tumors.

Table 75-5 Clinical Syndromes Produced by Adrenocortical Cancer and Their Frequency

Syndrome	Frequency (%)
Virilization and Cushing's syndrome	50
Virilization	25
Cushing's syndrome	20
Feminization	<5
Precocious puberty	<5
Hypokalemia alkalosis	<5
Hypoglycemia	<5

Feminization

Plasma androstenedione may be converted peripherally to estrogen, a phenomenon that results in gynecomastia. Feminization with adrenal cancer is unusual. The relatively few cases in the world literature have been summarized.[152] Rates of aromatization are low; therefore, large quantities of androstenedione are required to produce significant plasma estrone concentrations. The major fraction of androstenedione is metabolized to urinary 17-KS. Thus, measurement of urinary 17-KS will distinguish the feminization caused by adrenal carcinoma from the gynecomastia seen with human chorionic gonadotropin (hCG)-producing tumors of the testis and with hCG-producing cancer. One should also be aware that prepubertal adrenal cancers have been reported to produce hCG in quantities large enough to cause a positive result in pregnancy testing.

Precocious Puberty

In children, precocious puberty or virilization may be an important and presenting clinical finding because androgens are the predominant products of adrenal cancer secretion. Isosexual precocious puberty in boys and virilization in girls are usual. A few cases of feminizing adrenal cancer causing isosexual precocious puberty have been reported in girls.[153]

Sodium Retention and Hypokalemic Alkalosis

Rarely patients with adrenal cancer will present with the picture of primary hyperaldosteronism. Most patients with Conn's syndrome have either idiopathic hyperaldosteronism (IHA) or an aldosterone-producing adenoma (APA). Carcinomas that secrete aldosterone are rare, although a syndrome of mineralocorticoid excess may be caused by secretion of deoxycorticosterone.[151,154,155] In this situation, urinary 17-KS is high, and the tumor is generally much larger than the APA.

Hypoglycemia

As with other large mesenchymal tumors in the abdomen, adrenal cancer may cause hypoglycemia. Measurement of plasma insulin levels will rule out insulin-secreting tumors as a cause of hypoglycemia.

Diagnosis

The diagnosis of adrenal cancer depends on clinical suspicion, urinary and plasma biochemical tests, and diagnostic imaging studies (Fig. 75-9). The size of the adrenal mass is important because in masses larger than 6 cm, the incidence of cancer has been reported to be 35% to 98%.[156] Copeland demonstrated that 92% of 114 examined adrenocortical cancers were >6 cm.[157] The sensitivity, specificity and likelihood ratio of tumor size in predicting malignancy (based on SEER data) was recently reported as 96%, 51% and 2 tumors = 4 cm; and 90%, 78% and 4.1 tumors = 6 cm.[158] The most useful imaging tests are CT scan, ultrasonography, and MRI. The CT scan also defines local extent of cancer, thereby facilitating surgical planning. Evidence of calcification in an abdominal mass on CT scan or plain abdominal film suggests adrenal carcinoma. MRI scanning can define the presence or absence of regional extension and influence the decision in regard to resectability. The characteristics of the adrenal mass on T_2-weighted MRI scanning can be useful in distinguishing adenomas and pheochromocytoma from carcinomas or metastatic cancer to the adrenal gland.[159,160] Iodocholesterol imaging is not useful[161] because steroid synthesis rates are low. More recently, PET scans have been used to identify malignant and metastatic lesions but these results need further validation.

Pathology

Adrenal cancers are frequently large and can weigh more than 100 g. They can be locally invasive into kidney, liver, and large blood vessels, with the inferior vena cava involved in many cases of right adrenal tumors. Grossly, the tumor is yellow to tan, with areas of necrosis and hemorrhage. Cytologically, it may be difficult to distinguish carcinoma from adenoma.[162,163] The tumor cells vary in configuration from spindle-shaped in less differentiated cancers to large polyhedral cells with abundant eosinophilic cytoplasm. Mitoses can be rare; some variation in nuclear morphology may be evident in both adenomas and carcinomas. Capsular invasion or blood vessel invasion is the most reliable sign of cancer. The combination of the following nine criteria was studied by Weiss and associates for usefulness in distinguishing malignant from benign adrenal tumors: nuclear grade III or IV; mitotic rate greater than 5/50 high-power fields; atypical mitoses; clear cells comprising 25% or less of the tumor; a diffuse architecture; microscopic necrosis; and invasion of venous, sinusoidal, and capsular structure. Tumors with four or more of these criteria were likely to metastasize and/or recur.[164,165] The diagnosis of malignancy of a completely resected adrenal tumor, however, may be made only in retrospect by the finding of metastatic disease many years later. Patterns of steroid secretion cannot be predicted by histologic or histochemical characteristics of adrenal neoplasms.

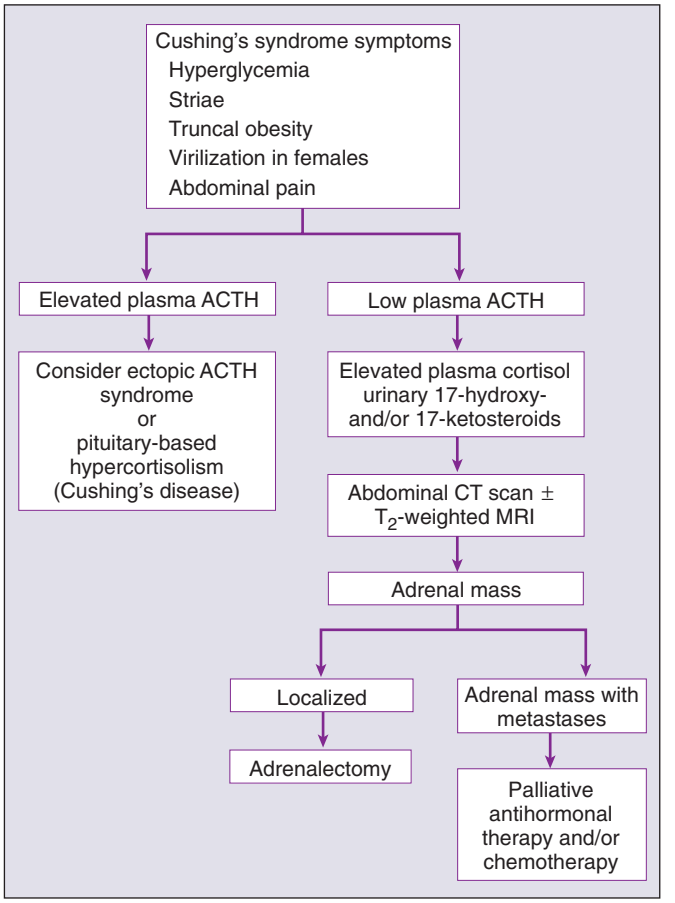


Figure 75-9 • Diagnosis and treatment of adrenal carcinoma. ACTH, adrenocorticotropic hormone.

Primary Treatment and Prognosis

The only curative therapy for adrenal cancer is aggressive en bloc resection of the primary tumor including the ipsilateral kidney.[166] This approach is attempted only in patients who have relatively limited cancers deemed to be potentially resectable.[167] Even with this approach, adrenocortical cancer is highly lethal, with a 5-year survival rate of 20% to 30%.[168] Fifty percent of patients have metastatic

disease at diagnosis. In patients with incurable adrenal carcinoma, suffering from symptoms secondary to tumor bulk or hormone excess, partial resection of tumor may offer significant palliation. In a minority of cases, the course may be indolent, with metastases developing over a period of 5 to 10 years. Metastases occur in lung, liver, and peritoneum, but uncommonly involve brain or bone.

Therapy for Metastatic Disease

Antihormonal Therapy

Some patients suffer more symptoms from hormonal excess than from tumor bulk. In them, antihormonal therapy can be useful. Metyrapone, an inhibitor of the 11β-hydroxylation step in cortisol biosynthesis, has been reported to be useful in the management of individual cases of Cushing's syndrome of adrenal carcinoma. However, it has proved largely ineffective in patients with metastatic disease.[169] Chemical confirmation of its effectiveness requires direct measurement of plasma cortisol. Urinary concentration of 17-OH steroids cannot be used to assess the efficacy of metyrapone, because the drug produces elevation in urinary 11-deoxycortisol, and therefore elevation in 17-hydroxycorticosteroids (17-OHCS), even though it decreases plasma cortisol.

Aminoglutethimide, an anticonvulsant that causes adrenal insufficiency, has been used in the treatment of adrenal carcinoma.[170] It is an effective palliative treatment in Cushing's syndrome secondary to adrenocortical carcinoma, adenoma, and ectopic ACTH production by extra-adrenal carcinoma, with the potential for rapid and sustained suppression of corticosteroid synthesis.[171,172] Because the drug may alter extra-adrenal metabolism of cortisol, measurement of urinary 17-OHCS excretion alone may overestimate the effectiveness of therapy; plasma cortisol concentration is a more reliable index of drug efficacy.[173] The usual clinical dose is within the range of 1 to 2 g/day. Significant adverse effects include anorexia, dermatitis, somnolence, ataxia, and decreased thyroid function.

Ketoconazole is another 11-β-hydroxylase inhibitor and blocks the production of not only cortisol, but also mineralocorticoids and androgens.[174] There are some reports of its efficacy in treating metastatic ACC.

Antineoplastic Therapy

In animals, the drug o,p′-DDD (mitotane) induced adrenocortical necrosis. Studies also demonstrated that mitotane was capable of inhibiting steroidogenesis.[175–177] Mitotane was initially evaluated in the 1960s.[178] In 138 cases of adrenal cancer evaluated, 17-KS and 17-hydroxycorticosteroid excretion was decreased by 50% in 70% of cases. A minimum of 4 weeks of therapy was required to ensure an adequate trial of therapy. Although steroid secretion was frequently improved with mitotane, tumor regression was uncommon, occurring in only 34% of cases with measurable disease. The mean duration of antitumor response was 10 months. Although objective response correlated with increased survival, hormonal response did not. The prognosis in women was better than in men; 52% of women and 38% of men survived for 4 years following diagnosis, with median survival times of 56 and 19 months, respectively.[178] Complete regression of tumors was not achieved.

Other investigators have also reported experience with mitotane. Libitz and associates[179] reported 115 patients with adrenal carcinoma treated with mitotane between 1965 and 1969. The measurable disease response in this series was 61%, with a steroid excretion response of 89%. The improved response rate in this series is attributed to a shorter median time between diagnosis and treatment with mitotane. Nader and associates[180] reported only a 19% remission rate in 77 patients. These results are likely secondary to differences in patient selection. Most patients treated with mitotane have experienced some degree of toxicity when the dosage was increased to the therapeutic range of 8 to 10 g/day. In general, the toxic reactions are mild, consisting of anorexia, nausea, vomiting, or diarrhea. Neuromuscular toxicity develops in 40% to 60% of patients, usually in the form of lethargy and somnolence. Vertigo and dermatologic toxicity are observed in 15%. Leukopenia and liver function abnormalities are rare.[178,179] Plasma mitotane levels may be useful in preventing toxicity.[181] With successful treatment of a functioning tumor, a substantial number of patients will develop signs of adrenal insufficiency. In summary, it is reasonable to expect objective rates of tumor regression following mitotane therapy in approximately 25% of cases.[150,178] The median duration of remission is 1 year, although some remissions have lasted longer than 3 years. Dosage regimens vary. Most clinicians initially administer 10 g/day, reducing the dose gradually to 1 to 2 g/day as regression is obtained. Diminution in size of metastases is rarely apparent before 6 weeks, although laboratory evidence of decreased steroid production may be noted earlier. Prolonged regression has been reported, and an apparent cure was seen with combined use of mitotane and 5-fluorouracil (5-FU).[182] Mitotane treatment is generally not recommended in the adjuvant setting since trials addressing this question have not been able to show a survival benefit.[183]

Very few chemotherapeutic agents other than mitotane have been evaluated in adrenocortical carcinoma in other than anecdotal experiences. Partial responses have been reported with doxorubicin.[184,185] Cisplatin has caused tumor regression in four patients, three of whom had previously received mitotane adjuvant therapy.[186] In two reports of only six patients, the combination of etoposide and cisplatin was reported to produce a response in five or six cases.[187,188] One patient had a complete response lasting 1 year. In general, adrenocortical cancers respond poorly to chemotherapy, likely due to increased expression of the multi-drug resistance (MDR-1) gene product which has been identified as p-glycoprotein. Mitotane has been demonstrated to inhibit p-glycoprotein, leading to increased efficacy of chemotherapeutic agents.[189] There has been recent interest in the use of suramin, a growth factor inhibitor, as therapy for adrenocortical carcinoma. In a Phase I study in 21 heavily pretreated patients, three cases developed partial response to suramin.[190–192] The role of suramin requires further definition, particularly because this drug may be associated with significant neurotoxicity. There was some interest in a new drug, gossypol, a naturally occurring (from the cotton plant *Gossypium* species) insecticide which appeared to inhibit the growth of adrenocortical cancer cell lines and tumors in vivo.[193,194] However, poor response rates combined with high death rates in limited clinical studies have reduced enthusiasm for this agent.

Surgical Approach to the Adrenal Gland

The surgical approach to the adrenal gland is influenced by the type of adrenal tumor. Adrenalectomy may be performed laparoscopically or via the open approach. Both open and laparoscopic adrenalectomy can be performed via the transperitoneal or posterior approach. The choice of approach depends on several factors including size of the lesion, nature of the lesion, and surgeon expertise. Laparoscopic adrenalectomy has been reported by a number of institutions with excellent results and has rapidly become the procedure of choice for benign-appearing lesions smaller than 6 cm in size. Laparoscopic adrenalectomy in the setting of malignancy is a subject of debate.[158] Although the data on the risk of local recurrence and widespread intraperitoneal carcinomatosis following these procedures is conflicting, most authorities agree that open adrenalectomy is indicated for suspected or known adrenocortical cancers and malignant pheochromocytomas.

Adrenocortical Adenomas

Laparoscopic adrenalectomy via the transperitoneal approach can be performed with the patient supine or in the lateral decubitus position. The latter is preferred as it uses gravity to aid retraction of surrounding organs, however, the patient does need to be repositioned for a bilateral procedure. This approach is depicted in Figure 75-10.

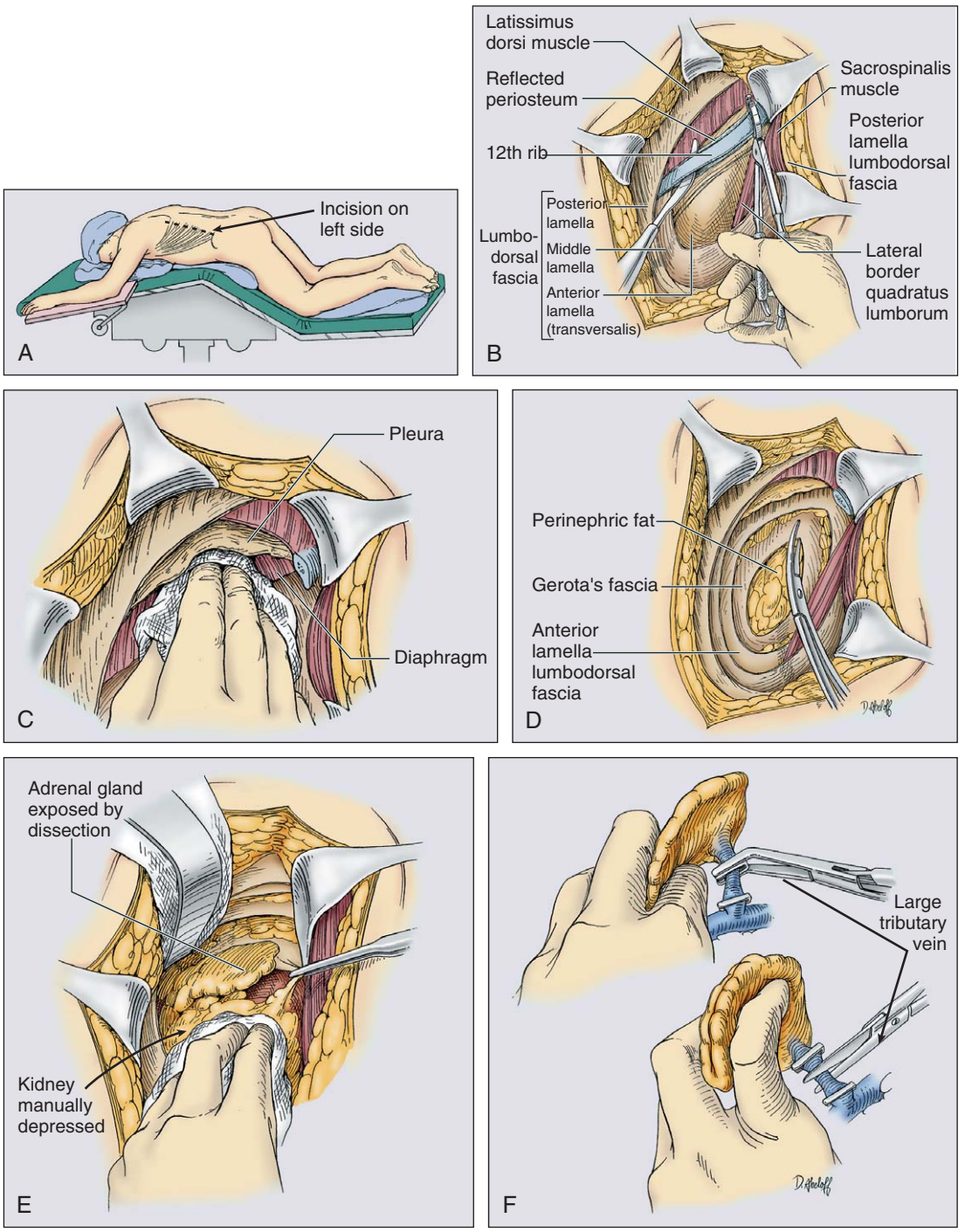


Figure 75-10 • Posterior approach to the adrenal gland: **A,** The patient is placed in a jack-knife, prone position, and a curvilinear incision is made in the flank. **B,** The 12th rib is removed subperiosteally, exposing the lumbodorsal fascia. **C,** The pleura is swept superiorly using a gauze-covered finger. **D,** The diaphragm is transected, exposing Gerota's fascia, which is then opened. **E,** The adrenal gland is exposed. **F,** Vessels of the gland are ligated with hemoclips and then transected. Abdominal approach to the adrenal gland: **G,** The adrenal glands commonly can be approached through a chevron incision. When only unilateral adrenal exploration is required, this incision can be limited to either a right or left subcostal incision. **H,** Basic anatomy of the adrenal glands as shown from an anterior approach. **I,** Positioning and trocar placement for laparoscopic adrenalectomy. The camera is inserted through port # 2, the fan retractor through port # 1; ports 3 and 4 are working ports. **J,** Dissection of the right adrenal. The liver is retracted upward with a fan retractor, and the adrenal is dissected circumferentially with L-hook or harmonic scalpel. **K,** Dissection of the left adrenal. The spleen is retracted upward, and the adrenal is dissected circumferentially. **L,** The right adrenal gland can be exposed by performing a Kocher maneuver and retracting the duodenum to the left. This allows good exposure of the right adrenal gland. **M,** Exposure of the left adrenal gland in the retroperitoneum is accomplished by mobilizing the spleen and retracting the spleen and stomach medially.

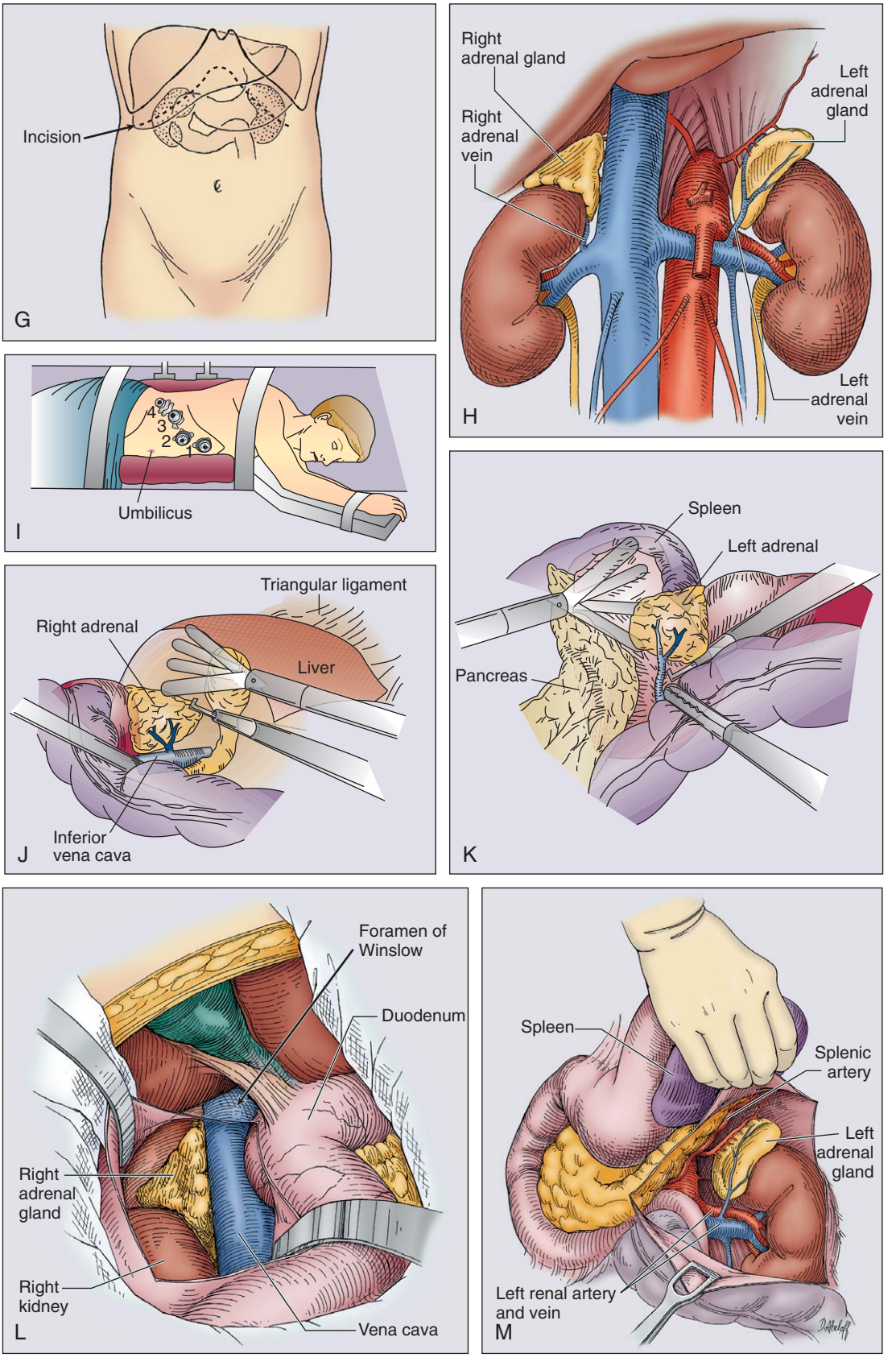


Figure 75-10, cont'd

The patient is placed in the lateral decubitus position with the table flexed at the waist to open the space between the lower rib cage and the iliac crest. After pneumoperitoneum is created, four 10-mm trocars are placed between the mid-clavicular line medially and the anterior axillary line laterally, 1 to 2 fingerbreadths below the costal margin. For a right adrenalectomy, a fan retractor is inserted through the most medial port to retract the liver. The right triangular ligament is divided and the liver is rotated medially. Rarely, the hepatic flexure of the colon may need mobilization during a right adrenalectomy. The right kidney is identified visually and by palpation with an atraumatic grasper. The adrenal gland is identified on the superomedial aspect of the kidney. Gerota's fascia is incised with cautery. Dissection of the adrenal is started superomedially and then proceeds inferiorly, dissecting around the adrenal in a clockwise manner. The periadrenal tissues are grasped or moved with a blunt grasper to facilitate circumferential dissection. The right adrenal vein is identified at its junction with the inferior vena cava, ligated with clips and divided using endoscopic scissors.

For a left adrenalectomy, the fan retractor is used to retract the spleen. The splenic flexure is mobilized early and the lateral attachments to the spleen and the tail of the pancreas are divided using electrocautery. Gravity allows the spleen and the pancreatic tail to fall medially. The remainder of the dissection proceeds similarly to that described for the right adrenal. In addition to the adrenal vein, the inferior phrenic vein, which joins the left adrenal vein medially, also needs to be divided.

Current techniques of adenoma localization permit a unilateral posterior approach to adrenocortical adenomas. This approach has several advantages over an abdominal approach, including a lower complication rate, avoidance of postoperative ileus, and shorter hospital stay. The adrenal gland is approached through a posterior incision, as shown in Figure 75-10A. The gland is approached through the bed of the 12th rib, and the kidney is retracted inferiorly to expose the adrenal gland. These incisions are well tolerated, and much of the postoperative care is dictated by the metabolic consequences of removing the hormonally active adenoma.

Adrenal tumors may also be resected via an open anterior transperitoneal approach and a chevron incision is often used, as shown in Figure 75-10. On the right, a Kocher maneuver mobilizes the duodenum and exposes the adrenal gland. On the left, the spleen is mobilized; Gerota's fascia is then opened to expose the left adrenal gland.

Pheochromocytoma

Surgical treatment of resectable pheochromocytoma requires careful preoperative preparation. α-Adrenergic blocking agents are administered to inhibit the effects of excess norepinephrine secretion. Phenoxybenzamine is a selective α-adrenergic blocking agent, administered in an oral dose of 20 to 40 mg two to four times daily. Titration of the dose is performed by following physiologic parameters. Prazosin also has been used successfully in the preoperative setting. β-Adrenergic blockers (e.g., propranolol) are added to control tachycardia as a sequela of excess epinephrine secretion. After adequate pharmacologic control and correction of fluid and electrolyte imbalance have been achieved, surgical resection is performed. Intraoperative control of blood pressure can be maintained using short-acting intravenous medications such as nitroprusside. Careful physiologic monitoring during the operation is mandatory. Pheochromocytomas may also be resected via a laparoscopic approach.

MALIGNANT PHEOCHROMOCYTOMA

Ten percent of pheochromocytomas are malignant,[195] and malignancies are reported more commonly in tumors arising in extra-adrenal sites (25% to 40%).

Pheochromocytomas are also a component of MEN-2a and MEN-2b.[196] These syndromes are discussed in detail later in this chapter. Pheochromocytomas are also associated with other inherited disorders such as von Hippel-Lindau (VHL) caused by germline mutations of the VHL gene, neurofibromatosis type I caused by germline NF1 mutations and familial paraganglioma and pheochromocytoma syndromes caused by mutations in the succinyl dehydrogenase family of genes (SDHB, SDHC and SDHD). When pheochromocytomas develop in the MEN syndromes, they are frequently bilateral but rarely malignant. In contrast, patients with familial paraganglioma or pheochromocytoma syndrome caused by germline SDHB mutations appear to have a higher propensity for extra-adrenal and malignant tumors.[197] Some studies also suggest that older patient age and large tumors are associated with a higher risk of malignancy. However, malignancy cannot be determined on clinical features alone. Although risk of malignancy increases with size for all pheochromocytomas, size does not seem to reliably predict malignancy in pheochromocytomas with local disease only.[198] The pathologic diagnosis of malignancy can also be difficult, because pleomorphism, nuclear atypia, and abundant mitotic figures are seen in benign tumors.[199] Even capsular invasion can be seen in benign tumors, although invasion of adjacent tissues indicates malignancy. Recent data suggest that flow cytometry and molecular markers such as expression of Ki-67, tissue inhibitor of metalloproteinase (TIMP-4), and cyclooxygenase (COX)-2 can be useful in determining malignancy.[200–203] Malignant pheochromocytomas can be nonfunctional.

Diagnosis

Functioning malignant pheochromocytomas exhibit the same secretory pattern as benign tumors. The diagnosis is made by finding elevated catecholamines or catecholamine metabolites in the urine or plasma, or both (Fig. 75-11). Urinary metanephrines are useful in diagnosing functional pheochromocytomas,[203] but the results may be falsely negative. The single most useful screening test is analysis of a 24-hour urine for vanillylmandelic acid (VMA), metanephrine, and catecholamines. Alternatively, plasma free metanephrines and normetanephrines may be measured. These tests are highly sensitive (99%) but not specific (89%) for pheochromocytoma.[204] Plasma catecholamines can also be elevated.[205] Oral clonidine will not reduce elevated plasma catecholamines to normal levels in patients with pheochromocytoma.[206] The clonidine suppression test is therefore highly useful in distinguishing pheochromocytoma from other causes of hypertension associated with elevated plasma catecholamine levels. Angiography has been largely superseded by CT and MRI scanning for tumor localization. Van Heerden and associates[207] reported that both techniques are highly accurate in localizing tumor at all sites, obviating other more invasive diagnostic procedures such as angiography and selective venous sampling for catecholamine levels.

Another useful technique for localization is radionuclide scanning with ^{131}I-MIBG, which concentrates in adrenergic tissues. The MIBG scan has proved to have a sensitivity of 87%[208] and a specificity of 96%.[209] An MIBG scan in a patient with metastatic pheochromocytoma is shown in Figure 75-12. Other more recently described techniques for localizing pheochromocytomas include PET with 6-[18F] fluorodopamine ([18F]-DA) and 2-[fluorine 18]fluoro-2-deoxy-D-glucose ([18F]-FDG-PET). Preliminary studies show that PET scanning may be superior to MIBG scanning for localizing pheochromocytomas.[210,211]

Course and Treatment

Complete surgical resection[212] after careful preoperative preparation with α- and β-blocking agents is curative in localized pheochromocytoma. If a malignant pheochromocytoma is suspected preoperatively, open rather than laparoscopic adrenalectomy is indicated. Malignant pheochromocytoma metastasizes to lung, brain, and bone. Metastatic disease generally progresses slowly. However, life-

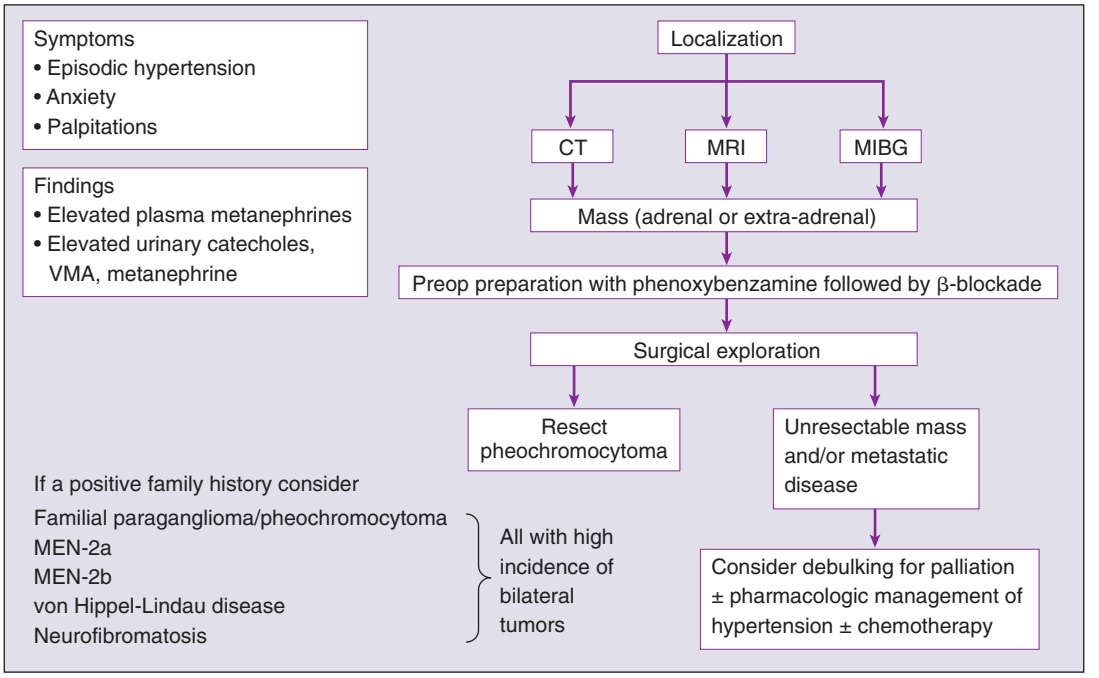


Figure 75-11 • Diagnosis and treatment of pheochromocytoma. MEN, multiple endocrine neoplasia; MIBG, metaiodobenzylguanidine;VMA, vanillylmandelic acid.

threatening complications due to secretory products can develop over a period of many years. Survival for up to 20 years has been noted.[212]

Modern therapy for inoperable metastatic disease uses the same strategies employed in preparing a patient with primary pheochromocytoma for surgery. Blockade of α-adrenergic receptors is accomplished with phenoxybenzamine; a gradual increase in dose can be required as disease advances. β-Adrenergic blockade may be of additional benefit but should always follow establishment of α-adrenergic blockade. Otherwise, the absence of the vasodilating effects of the β-adrenergic receptors can precipitate severe hypertension. Surgery and radiation have palliative roles in treating metastatic disease; surgical reduction of metastatic tumors can decrease catecholamine secretion and result in symptomatic improvement. The results of chemotherapy are mainly anecdotal. However, a series of 14 patients treated with a combination of cyclophosphamide, vincristine, and dacarbazine (DTIC) has been reported.[213] The rates of biochemical response and measurable cancer reduction were 79% and 57%, respectively. Median duration of response was greater than 20

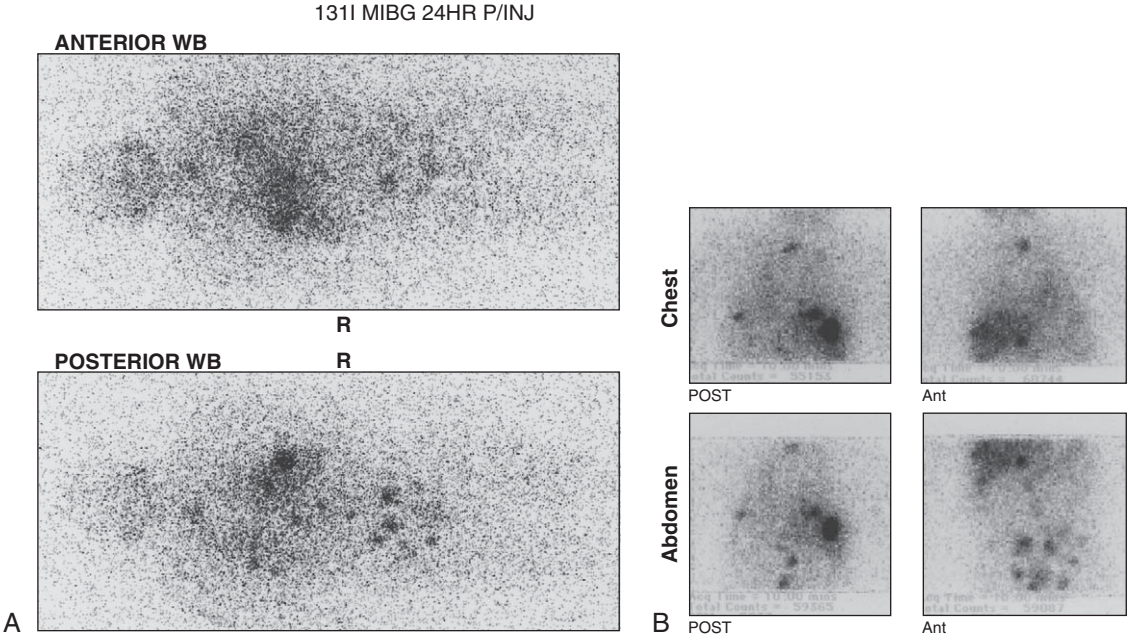


Figure 75-12 • MIBG scan in patient with metastatic pheochromocytoma. **A,** ^{131}I-MIBG scan in a patient with metastatic pheochromocytoma demonstrates hepatic and bony metastasis. **B,** Magnified view of chest and abdomen.

months. Other chemotherapy agents including streptozotocin, doxorubicin, and carmustine (BCNU) have not been effective.[214] Thalidomide, alone or in combination with temozolomide, has shown some promise in treating pheochromoctyomas, but their use may be limited due to severe toxicity.[215] Some studies have suggested a therapeutic value of ^{131}I-MIBG, however complete remissions are rare and disease has been reported to progress after therapy.[216–218]

PARATHYROID CARCINOMA

Parathyroid carcinoma is one of the rarest cancers. Schantz and Castleman[219] reported the largest study of such cases. These investigators described 487 cases of hyperparathyroidism, of which only 70 (14%) were documented to be parathyroid carcinoma. In most series, parathyroid carcinoma accounts for about 1% of cases of hypercalcemia and hyperparathyroidism. The prevalence in Japan is higher.

Data concerning the possible origin of parathyroid carcinoma from pre-existing abnormalities are rare. For example, transition to carcinoma from hyperplasia in patients with MEN-1 and MEN-2 syndromes does not appear to occur. However, parathyroid carcinoma has been reported to have developed in patients with familial hyperparathyroidism,[220] suggesting that transition from hyperplasia to cancer can take place. More recent data show an increased incidence of parathyroid carcinoma in families with the hyperparathyroidism and jaw tumor (HPT-JT) syndrome, which is caused by germline *HRPT2* mutations.[221] Interestingly, somatic and germline *HRPT2* mutations have been detected in cases of apparently sporadic parathyroid carcinoma.[222]

Diagnosis

Almost all cases of parathyroid carcinoma are associated with hypercalcemia, and about 70% have values greater than 14 mg/dL, which is rare in benign hyperparathyroidism. The disease usually is diagnosed at surgery for hyperparathyroidism. No unequivocal diagnostic tests distinguish benign parathyroid neoplasms from carcinomas, although plasma calcium concentration and PTH levels tend to be higher (>10 times normal) in carcinoma than in adenoma or hyperplasia.[223] Evidence of a neck mass,[223] cervical lymphadenopathy, hoarseness, or intraoperative finding of invasion of adjacent structures such as the strap muscles, thyroid, esophagus, or recurrent laryngeal nerve also suggests the presence of cancer.

The histologic pattern of parathyroid cancer shows frequent mitosis, and blood vessel and capsular invasion also may be seen. In one study, these features and a trabecular pattern with thick fibrous bands were considered characteristic of malignancy and helped to distinguish cancer from benign hyperplasia or adenoma.[223] However, as with many endocrine tumors, it is difficult to differentiate benign from malignant tumors by histologic features alone.

Natural History

The 5-year survival rate of patients with parathyroid carcinoma varies between 29% and 44%,[223,224] and the 10-year survival rate averages 20%. A smaller, more recent study has been reported, however, with an 89% (eight of nine cases) survival rate at a median follow-up period of 6 years.[225] Although parathyroid cancer metastasizes to lung, bone, and liver in about 20% of patients, metastatic disease is less commonly a cause of morbidity and death than is the severe hypercalcemia associated with this disease.

Management

When parathyroid carcinoma is recognized at surgery, careful en bloc excision of the cancer and involved structures is indicated.[225] In most cases, this is accomplished by an ipsilateral thyroid lobectomy with segmental resection of involved strap muscles and adjacent fibrolymphatic tissue. This tumor usually does not metastasize via the lymphatics; therefore, radical neck dissection is not warranted. Careful dissection without tumor spill is important, because local recurrence has been demonstrated. Local recurrence occurs in about two thirds of patients, in some due to intraoperative seeding. If hypercalcemia persists or recurs after surgery, an attempt should be made to locate the metastasis using selective venous catheterization and measurement of hormone levels in the event other diagnostic modalities fail. Prolonged remission of hypercalcemia has been reported after resection of metastases.[226] In case of unresectable disease, debulking should be attempted for palliation of hypercalcemia.

Nonsurgical treatment of recurrent or metastatic parathyroid cancer is disappointing. Radiation therapy has not been of significant value in treating primary or recurrent neck disease, although it may have some palliative benefit in controlling pain in bone metastases. Cytotoxic chemotherapy has been tested only infrequently, but it appears that dacarbazine has some activity in this disease.[227,228] Essentially, all patients with incurable parathyroid cancer require control of hypercalcemia. Diphosphonates, mithramycin, and calcitonin have been only marginally effective. It appears that the more recently developed pharmacologic therapies for hypercalcemia—etidronate[229] and gallium nitrate[230]—may be more effective in the palliative management of the severe hypercalcemia associated with parathyroid cancer. A new class of drugs known as calcimimetics can reduce PTH by binding directly to the calcium-sensing receptor cells on the parathyroid gland. Cinacalcet hydrochloride, a calcimimetic, has been shown to be useful in controlling hypercalcemia in patients with refractory parathyroid carcinoma.[231]

MULTIPLE ENDOCRINE NEOPLASIA

MEN syndromes are characterized by the familial occurrence of endocrine neoplasms in various sites. MEN syndromes are inherited as autosomal dominant with high penetrance, variable expressivity, and pleiotropic expression. The neoplasms of the MEN syndromes may be either benign or malignant.[133,232] Manifestations of MEN-1, MEN-2a, and MEN-2b are summarized in Table 75-6. Steiner and associates[233] were the first to characterize MEN-1 and MEN-2.

Table 75-6 Syndromes of Multiple Endocrine Neoplasia

MEN-1	MEN-2
Pituitary tumors	MEN-2a and -2b
Eosinophilic adenoma (acromegaly)	Medullary carcinoma of the thyroid
Prolactinoma	Pheochromocytoma
Nonfunctional tumors	MEN-2a
ACTH-secreting tumors	Hyperparathyroidism
Hyperparathyroidism	MEN-2b
Pancreatic tumors	Mucosal neuromas
Most common	Marfanoid habitus
Gastrinoma	Typical facies
Insulinoma	Bowel abnormalities
Pancreatic polypeptide-secreting tumor	
Glucagonoma	
VIPoma	
GRFoma	

ACTH, adrenocorticotropic hormone; MEN-2a, -2b, multiple endocrine neoplasia types 2a, 2b.

Multiple Endocrine Neoplasia Type 1

MEN-1 syndrome is a disorder of three glands: parathyroid, pancreatic islet cells, and pituitary. Recently, the disease gene for MEN-1, *MENIN*, has been localized to the long arm of chromosome 11.[234] *MENIN* has been reported to encode for a nuclear protein[235] of still undefined function, although recent studies suggest roles in physiologic regulation of cell growth, control of the cell cycle, and genome stability.[236]

Clinical Features

Parathyroid hyperplasia is the most frequently noted abnormality.[237] Adenomas of the pituitary gland are noted in 50% to 80%of patients with MEN-1.[237,238] When pituitary adenomas are functioning, prolactin is the most common hormone produced.[239] Acromegaly caused by growth hormone-secreting adenomas occurs in approximately 25% of adenomas.[238] Cushing's syndrome secondary to pituitary adenoma is uncommon. Approximately 80% of patients with MEN-1 will have functional pancreatic islet cell tumors.[239] Islet cell tumors represent the most common cause of death in patients with MEN-1, with 60% of deaths resulting from ulcer disease or problems caused by islet cell tumors.[238]

A wide spectrum of pancreatic islet cell tumors can occur in MEN-1. In a comprehensive review,[238] pancreatic tumors were present in 100 of 122 patients (82%) with MEN-1 with the following frequency: gastrinoma (64%); insulinoma (24%); glucagonoma (3%); and nonfunctioning tumor (9%). Rare cases of secretion of vasoactive intestinal peptide (VIP) and other peptides were observed. Forty-two percent of the gastrinomas were malignant, and 25% of the insulinomas were malignant. This finding is in contradistinction to sporadic insulinomas, in which only 10% are malignant. Pancreatic polypeptide (commonly), α- and β-hCG (less commonly), and other peptides such as ACTH may be elevated in patients with MEN-1 and may serve as tumor markers. The adrenal cortex may be abnormal in about one third of cases, usually with hyperplasia associated with pituitary adenomas producing ACTH. Rarely, a pancreatic tumor may produce ACTH ectopically.[240] Clinical Cushing's syndrome is uncommon. Bronchial carcinoids may occur in approximately 5% of cases.

Surgery

Management of MEN-1 first requires an awareness of the existence of the syndrome. Because almost all of these patients eventually will manifest hyperparathyroidism, continued surveillance of serum calcium is necessary. Parathyroidectomy usually is curative. In cases in which all four glands are enlarged, complete resection with forearm implantation is the preferred treatment. However, parathyroid hyperplasia can be limited to one or a few glands. In this case, it is preferred to resect the abnormal glands and to obtain a biopsy of the normal-appearing parathyroids. The location of these normal glands should be marked with nonabsorbable suture. If possible, all parathyroid tissue on one side of the neck should be removed to avoid the need for repeat bilateral neck exploration. Detectable pituitary tumors may be treated with bromocriptine or are occasionally removed by transsphenoidal resection. The management of pancreatic islet cell tumors is described elsewhere in this chapter.

Multiple Endocrine Neoplasia Type 2

MEN-2 syndrome first was reported by Sipple[241] in 1961. MEN-2 tumors include MTC, pheochromocytoma, and adenoma or hyperplasia of the parathyroid glands. When mucosal neuromas—with or without marfanoid habitus—are present as part of a distinctive syndrome, the designation is MEN-2b. Parathyroid disease is rare in MEN-2b. Specific MEN-2a[242,243] and MEN-2b[244] gene defects map to different regions of the *RET* proto-oncogene in the centromeric region of chromosome 10. More than 70% of pheochromocytomas occurring with MEN-2 are bilateral. These tumors may be derived from a hyperplastic adrenal medulla, yet still be benign, although carcinomas may occur in the same family. This progression from hyperplasia to tumor is similar to the progression noted in MTC.

RET encodes a receptor tyrosine kinase with an extracellular ligand binding domain, a transmembrane domain, and an intracellular domain with tyrosine kinase activity. Genotype–phenotype correlations have been observed in MEN-2a and MEN-2b, with the type of *RET* gene mutation indicating the aggressiveness of the disease.[245]

Clinical Features

The clinical presentation of patients with MEN-2 can be dictated by any of the three neoplasms seen in the syndrome. However, all patients with MEN-2 have medullary carcinoma of the thyroid. In reviews of MEN-2a, pheochromocytoma was seen in 21% to 41% of patients, and parathyroid hyperplasia or adenoma was present in 17% to 60%.[246] All patients had medullary carcinoma of the thyroid.[123,247] In a series of patients with MEN-2b, all had medullary carcinoma, and 60% developed pheochromocytomas.[248] In general, MEN-2b tends to be a more rapidly progressive clinical entity because the medullary carcinoma of the thyroid that develops in this syndrome has a more aggressive course than that seen in MEN-2a. Patients suspected of having MEN-2 syndrome should be screened for medullary carcinoma of the thyroid, pheochromocytoma, and hyperparathyroidism. The most effective way to screen for medullary carcinoma of the thyroid is to measure plasma calcitonin levels initially. All patients with medullary carcinoma of the thyroid will have either elevated basal plasma calcitonin levels or elevation after pentagastrin and calcium infusion stimulation tests.[126] In patients at risk for inherited medullary thyroid cancer, genetic screening for *RET* mutations has replaced yearly calcitonin measurements, because detection by this method allows treatment prior to the development of cancer.[245] The appropriate screening tests for pheochromocytoma include measuring urinary levels of epinephrine, norepinephrine, VMA, and metanephrines as described previously, or serum metanephrines. When these tests are abnormal, tumor localization studies, including MRI and abdominal CT scanning, should be undertaken. When there is biochemical evidence of pheochromocytoma with a negative CT scan, MIBG scan may be useful. MIBG concentrates in pheochromocytoma cells, permitting tumor detection by scintigraphy.[249] Hyperparathyroidism can be assessed by measurement of calcium and PTH levels.

Surgery

Management of patients with MEN-2 syndromes is primarily surgical. The surgical treatment of medullary carcinoma is total thyroidectomy, because the tumor always is bilateral. Central lymph node dissection also should be performed. In patients with MEN-2a and hyperparathyroidism, only abnormal parathyroid glands should be removed at the time of surgery. Patients with pheochromocytoma should undergo preoperative α-adrenergic blockade with phenoxybenzamine.[248,249] After adequate α-blockade has been obtained, β-blockers may be added if the patient has significant tachycardia, although in many instances β-blockade is not needed.

Postoperatively, patients with resected MTC may be followed with serum calcitonin levels, which are a sensitive marker for recurrence of disease. Likewise, appropriate urinary catecholamine studies will demonstrate recurrence of pheochromocytoma. Because MEN-2 syndromes exhibit autosomal dominance, it is important to evaluate family members of patients with documented MEN-2 for presence of the syndrome. Genetic analysis for inheritance of the allele containing the mutant *RET* gene will identify family members likely to develop MEN. Family members who have not inherited the disease allele require no further evaluation. Genetically affected members can be offered early thyroidectomy, usually by age 5 or 6 years in MEN-2a and prior to 6 months of age in MEN-2b.[245]

CARCINOID TUMORS

Carcinoid is an English translation of a term first used by German pathologists in the early 20th century—"karzinoid"—to describe a carcinoma-like tumor that behaves less aggressively than carcinomas.[250] Although their malignant potential was noted, other unique characteristics of the tumors also were described. These tumors arise from enterochromaffin cells in the gastrointestinal tract and lung.[251] Enterochromaffin cells take up and reduce silver. Silver staining documented the argyrophilic nature of carcinoid tumors, ultimately leading to their being described as neoplasms of the diffuse endocrine or APUD system.[252] Other tumors of the APUD system include medullary carcinoma of the thyroid, pheochromocytoma, and pancreatic endocrine tumors. Newer immunohistochemical techniques including neuron-specific enolase (NSE)[253–255] and chromogranin A[256] hormone assays have allowed further characterization of the synthesis and secretion of neuroendocrine peptides by carcinoid tumor cells. It is important to know that these neoplasms have common characteristics as defined by the APUD concept to be able to understand that the production of polypeptides arises from pancreatic islet cell tumors.

Carcinoid tumors typically have been classified as originating in the foregut (lung and upper gastrointestinal tract and, less often, pancreas), the jejunum and midgut (which includes the ileum and appendix), and the hindgut (colon and rectum). The origin of carcinoid tumors may, in part, explain the ectopic hormone secretion and syndromes related to primary tumor site.[257]

About 85% of carcinoid tumors develop in the gastrointestinal tract, usually the appendix. In one report, 44% of carcinoids were appendiceal, accounting for more than three fourths of all tumors in that organ.[258] In the same series, the intestine (19%), rectum (15%), and lung (10%) also were common sites. A recent National Cancer Database (NCDB) study using Godwin's initial experience[258] was recently published,[259] and a revised classification of neuroendocrine tumors of the lung, pancreas, and gut has more recently been released.[260]

Carcinoids account for one third of tumors in the small intestine. Carcinoids of the appendix commonly are discovered incidentally. Most are smaller than 1.0 cm and are cured by surgical resection.[259] In the Mayo Clinic series, no tumor of 1.0 cm or less recurred after resection.[215] Therefore, appendectomy alone is adequate treatment. With the uncommon large appendiceal carcinoid, a true cancer operation (e.g., right hemicolectomy) can be required. Carcinoids of the rectum are similar to appendiceal carcinoids and typically are small and are best treated with conservative local measures. Carcinoids of the small intestine are the most clinically important tumors because of their frequency of presentation, their more advanced stage at diagnosis, and their association with the carcinoid syndrome. The largest and most carefully followed series of patients with small bowel carcinoid has been reported from the Mayo Clinic, where 183 consecutive cases have been followed for a median period of 15 years.[261] Approximately 40% of the tumors occurred within 2 feet of the ileocecal valve, with very few in the proximal small intestine. Thirty-five percent of patients had more than one lesion, and most primary tumors were 2.0 to 4.0 cm in diameter. More than 80% of patients with resectable primary tumors were free of disease at 20 years' follow-up. The overall survival rate in these patients was similar to that of an age- and sex-matched control group. Of the 72 patients who had resected regional node metastases, one half experienced recurrence by 16 years, with continued evidence of relapse after that time. Patients who had unresectable abdominal metastases and hepatic metastases fared least well, with median survival rates of 5 and 3 years, respectively. These data confirm that, even with advanced disease, carcinoid tumors tend to have a relatively indolent course. Goblet cell or adenoid carcinoid tumors may be more aggressive than typical gastrointestinal carcinoids.

Clinical Pathology

Carcinoid tumors usually are readily identified microscopically. Immunohistochemical staining is performed to identify and classify these tumors. In addition to immunohistochemical staining to reveal specific tumor-produced peptides, other semispecific markers including NSE[255] and chromogranin A[256] aid in diagnosis.

Carcinoid Syndrome

Many patients with metastatic carcinoid tumor manifest the signs and symptoms of abnormal hormone production—the malignant carcinoid syndrome.[262] Serotonin (5-hydroxytryptamine, 5-HT), synthesized by the tumor from tryptophan and metabolized to 5-HIAA, which appears in the urine, is particularly important because urinary 5-HIAA levels are used to monitor the course of carcinoid syndrome. However, the relation of serotonin levels to symptoms of the clinical carcinoid syndrome is uncertain.

Carcinoid tumors also release the enzyme kallikrein, which acts on α_2-globulin to produce bradykinin and its precursor, lysyl-bradykinin, both of which can induce flushing.[263,264] Serotonin may be responsible for intestinal hypermotility and hypersecretion, but it probably does not cause the characteristic flushing that occurs with the carcinoid syndrome.[265] Vasodilation, which causes flushing, can be due to one or more substances released by the tumor cells, including bradykinin, substance P (midgut carcinoids), tachykinins, and prostaglandins. The symptoms of the carcinoid syndrome vary in frequency. Flushing is most frequent, followed by diarrhea, heart disease, and bronchoconstriction.

Flushing

Two types of flushing generally are accepted as accompanying the usual metastatic ileal carcinoid. It is thought that any of the activities that drive plasma catecholamines, which instigate the flushing, maybe mediated, in part, by peptides such as the tachykinin substance P or the amine serotonin. Stressors associated with hypercatecholemia include **e**xercise, **e**xcitement, **e**motion, **e**thanol, and decongestants such as **e**phedrin. One type of flushing is red and diffuse, involving the face and upper body; it is of short duration and can be provoked by alcohol, excitement, emotional stress, and catecholamine release.[266] The other is more prolonged, produces venous dilation and a purplish hue about the face, and can give rise to permanent dilation of facial veins and even telangiectasia. This flush is more commonly precipitated by alcohol ingestion. Because infusion of serotonin does not cause either flush, it has been suggested that the kinins cause this symptom.[267] Brief flushes may be due to catecholamine-induced release of vasoactive substances such as kallikreins; these flushes can be blocked effectively by α-adrenergic blocking agents.[268] Carcinoid of the foregut produces a more intense and erythematous flush (such as seen in a serotonin burst), sometimes associated with itching, conjunctival suffusion, and facial edema suggestive of histamine release. Occasionally, gastric carcinoids cause an urticarial reaction, which may be inhibited by the histamine H_1- and H_2-receptor antagonists diphenhydramine and cimetidine.[269,270]

Diarrhea

The diarrhea of carcinoid syndrome does not necessarily correlate with flushing. Diarrhea appears to be related to increased gut motility, rather than to secretion of fluids. Methysergide, a serotonin antagonist, sometimes is effective in treating or preventing diarrhea, hence the presumption that serotonin is directly responsible for this symptom. Infusion of serotonin produces intestinal dysmotility similar to that seen in the carcinoid syndrome.[270] Diarrhea of the carcinoid syndrome rarely is of high volume and, therefore, typically requires only mild palliative antidiarrheal therapy. Although abdominal cramping can be associated with this diarrhea, other possibilities for abdominal pain must be considered, including intermittent partial

small bowel obstruction secondary to mesenteric fibrosis or bowel obstruction secondary to tumor bulk.

Heart Disease

The cardiac disease associated with the carcinoid syndrome is an endomyocardial fibrosis typically involving the right side of the heart, although left-sided lesions have been described. Fibrotic deformation of the tricuspid and pulmonary valves usually leads to pulmonary stenosis and tricuspid insufficiency.[271,272] When left-side lesions are involved (primarily mitral valve), there is usually a patent foramen ovale. In the Mayo Clinic series, carcinoid heart disease was a late complication, with only 5 of 91 deaths identified as having a primary cardiac cause. In that series, most patients with heart disease had high levels of 5-HIAA as well as a lengthy history of carcinoid cardiac disease averaging more than 5 years.

Other, relatively rarer, signs and symptoms may be associated with carcinoid syndrome. Bronchoconstriction may occur in both pulmonary and extrapulmonary carcinoid and usually is associated with flushing. The classic triad of dermatitis, dementia, and diarrhea seen with pellagra occasionally has been identified. This syndrome is secondary to niacin deficiency as a result of shunting of dietary tryptophan from niacin synthesis to indole synthesis. It is very rare, because of better overall nutrition in the population. It is treated simply with nicotinamide from over-the-counter vitamin supplements.

Diagnosis

The diagnosis of carcinoid tumor is made by finding tumor or symptoms related to tumor bulk, biologically active peptides, or urinary tumor markers (Fig. 75-13). While measurement of 5-HIAA is the most common and reproducible test for the presence of carcinoid syndrome, significantly raised levels of 5-HIAA usually occur only after there is a 20% to 25% liver tumor burden. In most laboratories, the upper limit of normal for 24-hour urinary 5-HIAA excretion is 6 to 10 mg. In one study, 5-HIAA measurements were 100% specific and 73% sensitive for the presence of carcinoid syndrome.[273] Not all patients with carcinoid tumor have the associated syndrome, and the sensitivity of assays for detecting the presence of tumor alone is inadequate. Although markedly elevated 5-HIAA in the urine is remarkably specific for carcinoid tumor, a low-level false-positive increase of 5-HIAA may be seen in patients with noncarcinoid tumor and after intake of certain foods (e.g., bananas, walnuts, and pecans) and serotonin reuptake inhibitors (e.g., Zoloft, Prozac) and medications (e.g., acetaminophen, salicylate, guaifenesin).[273–277] 5-HIAA also may be elevated to low abnormal levels (<30 mg) in patients with diarrhea or malabsorption from any cause. In addition to excellent specificity and high sensitivity, 5-HIAA measurement has a high level of consistency, both in individual patients and among groups. In the Mayo Clinic series, the level of 5-HIAA excretion remained constant in a group of 85 patients in whom paired determinations were done during a 10-day period.[261] Moreover, in any given patient, the level of 5-HIAA secretion is a relatively accurate indicator of tumor bulk. Platelet serotonin levels have been reported to be more sensitive than urinary 5-HIAA levels and may be useful in patients with tumors that produce low levels of serotonin.[278] Recently, serum NSE and chromogranin A levels have been shown to correlate with the presence and natural history of gastrointestinal neuroendocrine tumors.[255,256] For midgut carcinoids, which produce high levels of serotonin, the sensitivity of chromogranin A levels is only slightly better than urinary 5-HIAA levels. However, for foregut and hindgut derived tumors, chromogranin A levels are highly sensitive compared with urinary 5-HIAA levels.[279]

The most commonly used modality for imaging carcinoid tumors is CT scanning, although the technique is more sensitive for detecting metastases, rather than primary tumors.[280] Recently, localization of carcinoid and islet cell tumors has been investigated by nuclear medicine techniques, including octreotide scan (Fig. 75-14).[281] The sensitivity of somatostatin receptor or octreotide scanning is reported to be up to 87%, with a positive predictive value of 100%, making it the most useful imaging study for carcinoid tumors.[282] ^{131}I-MIBG scans also have shown usefulness in evaluating carcinoid tumors.[283] PET scans using 11-C-labeled 5-hydroxytryptophan also have shown promising results when compared to CT scan in small series.[284]

Treatment

Patient management depends not only on traditional methods of dealing with bulky disease and its manifestations, but also on management of associated medical problems typically caused by overproduction of hormonally active peptides. In this regard, treatment of carcinoid is similar to that of other neuroendocrine tumors, such as islet cell tumors. For patients on long-term somatostatin therapy, a long-acting somatostatin analog is effective and may be given monthly.[285]

Surgery

Surgery has an important role throughout the course of carcinoid tumor management. Resection of the primary tumor and of associated resectable nodal metastases is primary therapy.[286] Also, complications secondary to recurrent or residual carcinoid may benefit from surgical intervention. Nearly one half of all carcinoids arise in the appendix, and most are small and cured by appendectomy, although right hemicolectomy is recommended for lesions larger than 2 cm.[261,287] The same is true for small lesions of the rectum, but tumors larger than 2 cm in diameter require standard cancer operations such as a low anterior resection or abdominoperineal resection.[286] In small bowel tumors, small bowel resection with removal of mesenteric nodes is recommended. It follows that the surgical approach to bronchial, gastric, or gonadal carcinoid will depend on the location and stage at presentation.

These tumors often elicit a mesenteric fibrosing reaction, in which the bowel becomes shortened and kinked, frequently causing partial small bowel obstruction. Pain or physiologic abnormalities secondary to partial bowel obstruction may be greatly relieved by palliative surgical resection or bypass, or both. The indolent course of carcinoid tumors mandates a high index of suspicion for such complications and an aggressive approach in considering surgical palliation.

Management of hepatic metastases is important given the frequency of such metastases. In many patients, bulky hepatic metastases constitute most of the tumor burden, so that tumor reduction may, at the least, diminish production of peptides that promote the carcinoid syndrome, as well as extend survival.[288] Principles of surgical management of hepatic metastases are similar to those for islet cell tumors. The indications to proceed with hepatic metastases resection are more liberal in carcinoid tumors than in metastases from other solid tumors. For example, partial resection of hepatic metastases is contraindicated in metastatic colon cancer, as neither effective palliation nor prolongation of survival is achieved. However, the much longer survival in carcinoid tumor makes palliative resection of hepatic metastases appropriate to decrease tumor burden and improve patient well-being. A variety of cancer therapies for hepatic metastases may be attempted, including hepatic irradiation, hepatic embolization, and liver-directed chemotherapeutic agents. These therapies are discussed in the following individual treatment sections.

Radiation Therapy

Radiation therapy seldom is used to treat carcinoid tumor or carcinoid syndrome. Patients with carcinoid syndrome often have extensive hepatic metastases, and the dose-limiting toxicity of hepatic radiation limits its usefulness. Palliative treatment of bone metastases

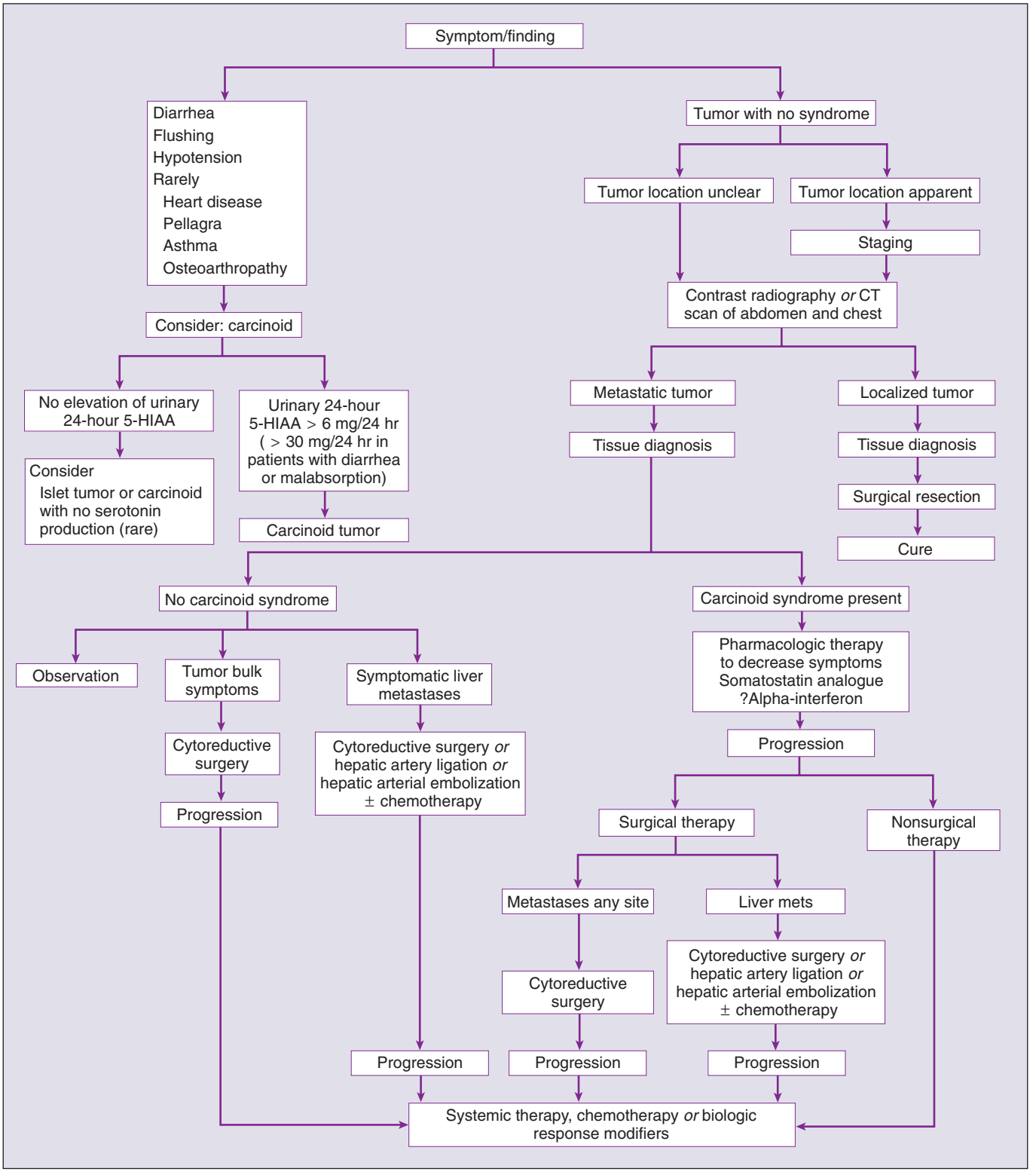


Figure 75-13 • Diagnosis and treatment of carcinoid tumors.

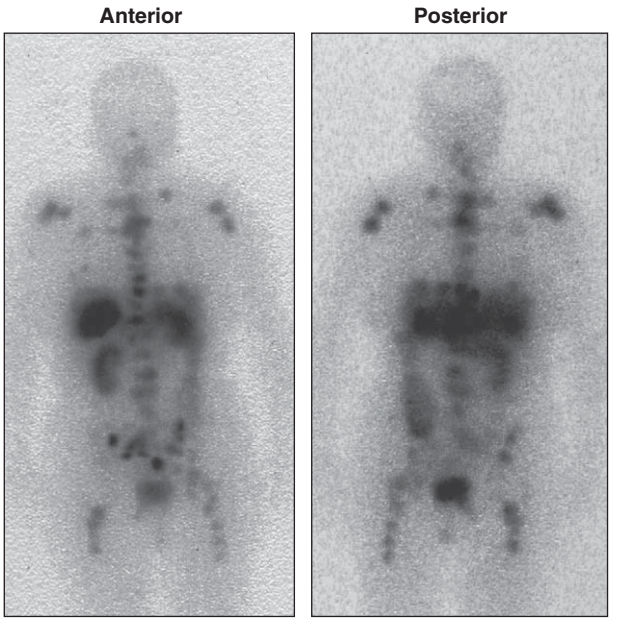


Figure 75-14 • ^{111}In octreotide scan. Patient with metastatic carcinoid with octreotide scan showing bony and visceral metastases with anterior and posterior views.

is an indication for radiation therapy. A trial of whole-abdomen radiation therapy (20–25 Gy)[289] yielded mixed results, with reduction of abdominal pain but less consistent control of the cancer. Radiation therapy should be considered in patients who require local control and palliation.[290]

Antihormonal Therapy

When the symptoms attributed to serotonin are mild, they can be managed successfully over lengthy periods with simple measures, such as administration of opiates and diphenoxylate hydrochloride with atropine. With more severe symptoms, the peripheral serotonin antagonists methysergide and cyproheptadine are effective in controlling diarrhea and, in some cases, malabsorption.[291] Another approach has been the use of agents known to inhibit serotonin synthesis. α-Methyldopa, which partially inhibits the decarboxylation of 5-hydroxytryptophan (5-HTP) to serotonin, has been disappointing, except in patients with the rare 5-HTP-secreting metastatic carcinoid of gastric origin.[292] Parachlorophenylalanine (PCPA) inhibits the enzyme tryptophan 5-hydroxylase, which converts tryptophan to 5-HTP, the immediate precursor of serotonin.[293] Although good to excellent control of diarrhea has been observed, the toxic effects of PCPA, including hypersensitivity reactions and mental aberrations, have limited its clinical value.

Somatostatin inhibits carcinoid flush,[294] but is not practical for therapy because it has a half-life of less than 2 minutes.[295] Synthetic octapeptide analogs of somatostatin, octreotide acetate, lanreotide, and vapreotide have a longer half-lives, and can be given subcutaneously every 4 to 8 hours to maintain the action of somatostatin. As well, the long-acting repetitive, Sandostatin LAR (Novartis), has been shown to be highly effective in control of both carcinoid flushing and diarrhea.[285] Somatostatin influences the inhibition of numerous gastrointestinal hormones, gastric secretion, gastric and small intestinal motility, splanchnic blood flow, pancreatic enzyme secretion, intestinal nutrient absorption, and gallbladder contractility.[296]

Somatostatin analogs have two established uses in carcinoid tumors: chronic treatment of symptoms such as diarrhea and flushing,[297] and treatment of carcinoid crisis.[296] Kvols and associates,[297] in 1986, described the use of the somatostatin analog octreotide in therapy for carcinoid syndrome. Fifty-seven patients with carcinoid tumor and carcinoid syndrome were treated with daily doses of octreotide acetate, ranging from 100 to 1127 μg (mean, 414 μg). Flushing was abolished in most patients, and diarrhea was controlled adequately in approximately 75%. Control of symptoms usually was associated with a decrease in the urinary 5-HIAA level, but reduction in tumor bulk was not seen consistently. The median duration of response to somatostatin analog was 4 months, with some patients escaping control quite early but others continuing for more than 2 years. Increased doses of somatostatin may partially overcome resistance.[298] More recent studies have confirmed that somatostatin improves symptoms but has little effect on tumor regression.[299]

Somatostatin analog usually is well tolerated.[296,297] Minimal irritation at the injection site and alterations in bowel patterns have been observed. Fecal fat excretion may increase, and aberrations in glucose tolerance resulting in hyperglycemia have been observed. Very early studies in the 1980s demonstrated that neostimulated pancreatic enzyme inhibition due to octreotide acetate diminishes after a continued use of octreotide. Clinically significant fat malabsorption is not a widespread problem. We routinely use and recommend pancreatic enzyme supplementation when beginning either subcutaneous octreotide acetate or the long-acting repeatable octreotide.

Long-term therapy may predispose to the formation of gallstones; the drug promotes cholelithiasis by inhibition of cholecystokinin release and a resultant inhibition of gallbladder emptying. Approximately 50% of patients receiving chronic therapy will develop cholelithiasis and should, therefore, undergo elective cholecystectomy at the time of tumor debulking.[300]

Chemotherapy

Because the disease is indolent, little information is available on the role of chemotherapy.[301] Antineoplastic therapy may be called for in patients whose cancers are aggressive, with progressive liver metastases, signs of partial or impending complete intestinal obstruction, or severe symptoms of carcinoid syndrome uncontrollable by other methods. Controlled clinical trials have been difficult to carry out because of the rarity of the tumor, but cooperative study group trials have been useful in assessing tumor responsiveness. In our experience, the less positive the octreoscan and more active the PET scan, the more effective chemotherapy may be.

During the 1970s, systemic therapy with single agents was reported, with 5-FU and streptozotocin shown to be active drugs.[302] The Mayo Clinic experience with more than 200 patients suggests that with single agents the response rates of greater than 10% were seen with only three adequately tested drugs: doxorubicin, 7 of 33 (21%); 5-FU, 5 of 19 (26%); and dacarbazine (DTIC), 2 of 15 (13%).[303] Based on initial observations of patient response to 5-FU and streptozotocin, investigators at the Mayo Clinic studied that regimen and noted an overall response rate of 33% in 43 patients. A larger series of patients was reported in a phase III study by the Eastern Cooperative Oncology Group (ECOG)[304] comparing 5-FU plus streptozotocin to cyclophosphamide plus streptozotocin. Response rates for the two treatment arms were not significantly different (33% vs. 26%, respectively), nor were there significant differences in overall survival. Assuming the 5-FU plus streptozotocin regimen to be standard, the ECOG subsequently reported their trial of this combination, with streptozotocin given less frequently to decrease toxicity, compared with doxorubicin alone.[305] Twenty-three percent of patients in each arm responded, further documenting doxorubicin activity. Most recently, ECOG reported the results of their largest trial of combination chemotherapy.[306] This trial randomly allocated patients with measurable carcinoid tumors to the standard regimen of 5-FU plus streptozotocin (FS) and a new regimen of 5-FU and doxorubicin (FA). Patients who had either renal or heart disease making them ineligible for streptozotocin or doxorubicin-containing therapies were treated with DTIC. Of 208 patients who were eligible and analyzed for response and survival, FA and FS

therapies were associated with response rates of 13% and 16%, respectively, in the randomized group. With DTIC, the response rate was approximately 10%, with no significant differences between previously treated and untreated patients. Although the response rates for FA and FS did not differ, there was a trend toward improved survival in the FS group. The median survival time of the group was 24 months, compared with 16 months for patients receiving FA ($P = 0.11$). This suggestive disparity between response rate and survival time may reflect the fact that reduction in tumor bulk has little correlation with survival in patients with an indolent disease such as carcinoid tumor. Alternatively, it may be true that survival is a better measure of tumor response, with inadequate determination of response by traditional techniques.

Because no highly effective chemotherapy regimen is available, it is clear that patients should be carefully selected for use of cytotoxic chemotherapy in metastatic carcinoid tumor and carcinoid syndrome. Less toxic and more effective palliative therapies for carcinoid syndrome should always be used initially, reserving chemotherapy for those patients who are significantly disabled by unresponsive hormonally related symptoms or those with refractory symptoms due to tumor bulk. Clinical trials of more recently available drugs (taxanes, gemcitabine, camptothecins) need to be carried out. More recent clinical trials suggest potential benefit and possible indications for such anti-agonist compounds such as RAD001 and mTOR inhibitors.[307]

Interferon

Early clinical trials from Sweden suggested a role for low-dose human leukocyte interferon in the treatment of carcinoid tumors.[308] Subsequently, this group reported the results of three consecutive studies using interferon.[301] In the first study, involving 36 patients, an overall response rate of 47% was observed. In the second randomized trial, human leukocyte interferon was compared with FS. No response was observed in the 10 patients treated with chemotherapy, but 5 patients in the interferon-treated group did respond. In the third study, 20 patients were treated with recombinant interferon; an objective response rate of 55% was observed, with the bulk of responses being symptomatic or chemical responses manifested by a decrease in 5-HIAA, rather than by reduction in tumor bulk. The Mayo Clinic subsequently reported the results of their phase II trial of recombinant interferon-α (IFN-α) in 24 patients with malignant carcinoid syndrome.[309] Five patients (20%) with measurable tumor experienced objective tumor regression, and nine patients (37.5%) had a significant reduction in urinary 5-HIAA excretion. Flushing and diarrhea were transiently relieved, with objective responses lasting less than 2 months. The results suggest a limited role for this agent in treating carcinoid tumor. Clinical trials currently are being developed in which chemotherapy and interferons are being combined, although early results do not suggest additional benefit compared to single modalities.[310] Similarly, combinations of octreotide and IFN-α are being investigated to determine whether lower doses of interferon would be effective and whether the tachyphylaxis associated with octreotide could be overcome by the addition of interferon.[311] Patients with carcinoid tumors treated with interferon may develop a wide variety of autoimmune diseases, such as thyroid disease (thyrotoxicosis, hypothyroidism), pernicious anemia, and vasculitis.[312]

Hepatic-Directed Therapy

The results of surgical resection for hepatic metastases and anecdotal reports of hepatic and abdominal radiation in carcinoid tumors have already been described. The Mayo Clinic has investigated the role of hepatic arterial occlusion in metastatic carcinoid and islet cell tumors.[261] Significant improvement in symptoms and reduction in hepatic metastases were noted in 14 patients with carcinoid tumors, but the median length of response was less than 7 months. Mayo Clinic investigators also have examined the role of sequential hepatic arterial occlusion (HAO), followed by systemic chemotherapy with DTIC and doxorubicin alternating with the combination of 5-FU and streptozotocin in carcinoid tumors.[261,313] With 65 carcinoid cases treated, more than two thirds of all patients demonstrated objective regression with either HAO or HAO plus chemotherapy. The median duration of regression was longer in the groups receiving chemotherapy, but this trial was not randomized, and better-risk cases may have been selected for the chemotherapy plus HAO treatment. Other groups are investigating the role of selective hepatic arteriography with sequential hepatic arterial embolization or chemoembolization.[314–316] Significant reduction in the signs and symptoms associated with both carcinoid tumors and islet cell tumors have been reported in the majority of patients so treated. In a study of 15 patients with advanced metastatic carcinoid tumors, hepatic artery chemoembolization improves symptoms and short-term quality of life.[317] Unfortunately, there is a paucity of data on the benefit of either intermittent or prolonged continuous hepatic arterial infusion of chemotherapeutic agents in patients with metastatic carcinoid tumors.

PANCREATIC ISLET CELL TUMORS

The advent of radioimmunoassay (RIA), immunofluorescence, and other techniques for identifying peptide hormones has expanded our knowledge of the prevalence and endocrine effects of islet cell tumors.

The pancreatic islet contains α cells (glucagon), β cells (insulin), and δ cells (somatostatin), as well as enterochromaffin cells (serotonin). These cells are all part of the APUD system, and tumors so derived secrete a wide variety of polypeptides. Some of these peptides share the characteristics and functions of classic hormones: (1) their release follows a physiologic stimulus; (2) they have the ability to effect response in a distant organ; and (3) these effects are mimicked by exogenous infusion of the hormone. By contrast, some abnormal peptides produced by islet cell tumors have no known clinical hormonal effects.[318]

Equally important, these peptide-secreting tumors are, for the most part, nonautonomous. This is thought to be due to tumor cell regulation by somatostatin and its predominant tumor cell receptor somatostatin receptor subtype 2.[319,320] Clinically, in evaluating patients with islet cell tumors, it is important to understand that there appear to be two different types of patients with APUDomas. The first group consists of those patients who experienced their tumors singularly, in the absence of significant personal or family history of endocrine disorders. The second group includes those with clear evidence of an inherited predisposition to multiple neoplasia of the endocrine system in an autosomal dominant pattern. These MEN syndromes have been described earlier.

As with carcinoid tumors, the approach to the patient with an islet cell tumor must be individualized, balancing management of the effects of hormone production with symptoms of tumor bulk. In any individual patient, one or the other management issue may predominate. Treatment should be directed not only by the presence of symptoms, but also by a consideration of the relatively lengthy natural history of islet cell tumors (Fig. 75-15).

Diagnosis

Specific syndromes and diagnostic tests for each of the more common islet cell tumors are discussed separately. However, a few generally applicable principles should be understood. RIA[321] of peptides obtained by selective venous catheterization is most helpful in localizing tumors and may demonstrate the presence of metastatic spread, particularly in patients with gastrinomas (Zollinger-Ellison syndrome). CT scan and arteriography are particularly helpful in tumors greater than 1.0 cm in diameter. However, because many islet cell tumors and their metastases may be small, neither procedure may be adequately sensitive. As with most endocrine neoplasms, islet cell tumors have a rich vascularity, so that "tumor blush" can be seen on

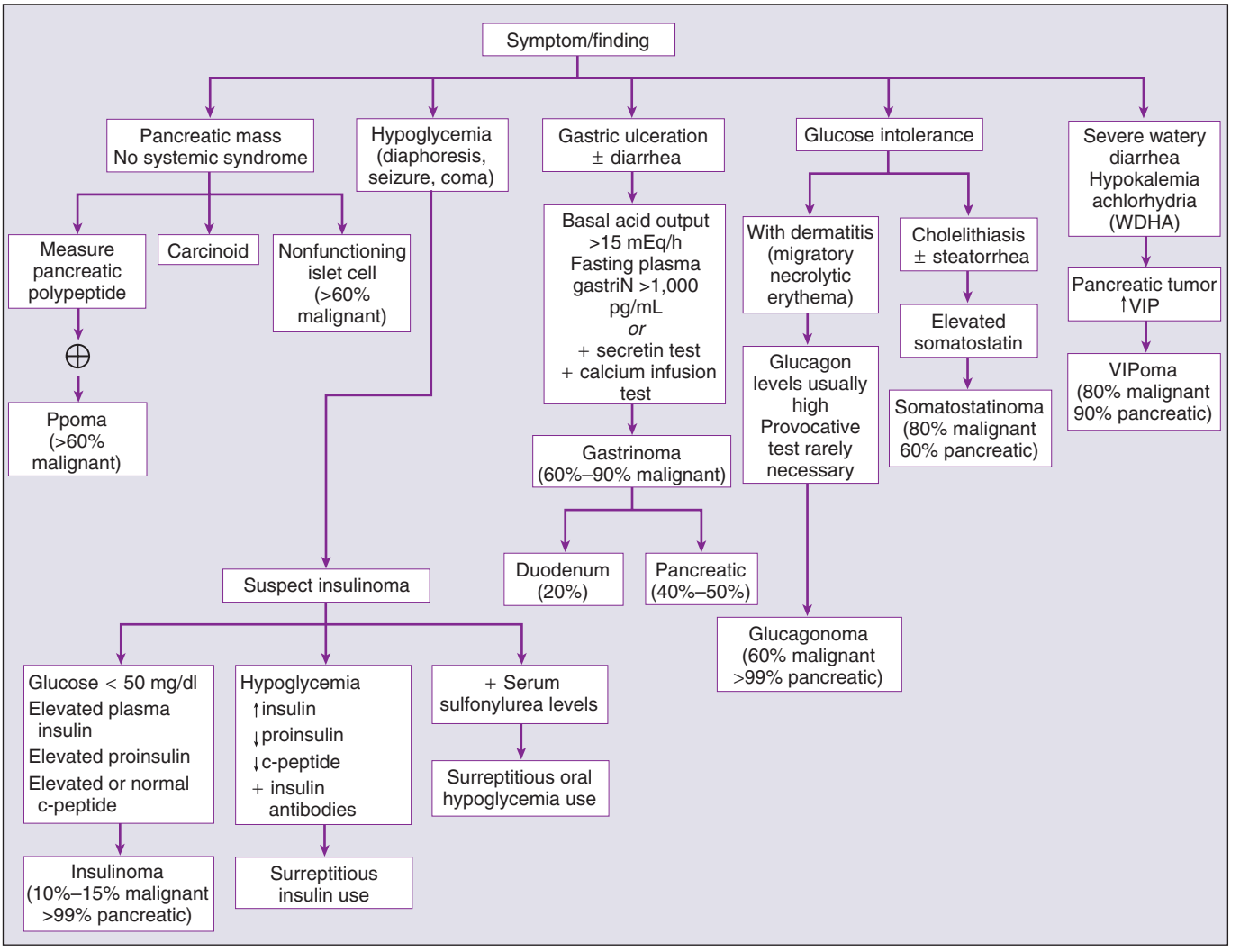


Figure 75-15 • Diagnosis of pancreatic islet cell tumors. Ppoma, pancreatic polypeptide-secreting tumor; VIP, vasoactive intestinal peptide; VIPoma, vasoactive intestinal peptide secreted by a pancreatic islet tumor.

angiography. This sign may be a useful finding in differentiating between endocrine and nonendocrine gastrointestinal tumors. Ultrasonography is of some use in imaging both pancreatic primary tumors and hepatic metastases. Newer imaging techniques are required, therefore, for better diagnosis and staging. For example, MRI has been shown in some studies to be superior to contrast-enhanced CT scans for the identification of all islet cell tumors.[318] The mainstay of diagnosis remains the RIA to detect NSE and chromogranin, which are secreted by these tumors.[255,256]

Insulinoma

The average age of presentation of insulinoma is in the mid-40s, and the sine qua non in diagnosing this syndrome is fasting or inappropriate hypoglycemia accompanied by a relatively high plasma insulin level.[322,323] Other tests have been proposed, including a hypernormal response to tolbutamide, the response of plasma insulin to an infusion of calcium gluconate, and the ratio of proinsulin[323,324] to insulin in the plasma. The key to the diagnosis is a high index of suspicion.

Sporadic insulinomas usually are single and benign; about 10% are malignant.[325] Differentiation of benign from malignant is difficult based on the pathologic features alone, but the presence of metastases defines malignancy. In patients with carcinoma, proinsulin may be increased in plasma[326] or circulating hCG.[327] In both malignant and benign insulinomas, jaundice may occur secondary to biliary tract obstruction from tumors in the head of the pancreas. The typical patient with symptoms of insulinoma has a single small, benign pancreatic nodule. In atypical cases, with multiple primary endocrine tumors, including an insulinoma, MEN-1 syndrome should be suspected.[239]

These tumors usually are imaged with high-resolution, fine-cut CT, MRI, or abdominal ultrasound as the initial study. Although not very sensitive for small, primary tumors, these studies are useful to identify metastatic tumors, if present. If these studies are negative, some authors recommend proceeding with exploration with manual palpation of the pancreas and intraoperative ultrasound, citing success rates greater than 90% at initial exploration.[328] Because insulinomas almost always are confined to the pancreas, selective arteriography and portal venous sampling usually identify the lesion.[325] However, these techniques are technically demanding and not always accurate. Endoscopic ultrasound is being used increasingly to image these tumors. In a prospective series of 37 patients, endoscopic ultrasonography was highly sensitive and specific for pancreatic endocrine tumors, as ultimately confirmed by surgical excision.[329] Endoscopic ultrasound has been reported to be accurate for identifying tumors larger than 5 mm in the pancreatic head.[330] Invasive localization

procedures usually are reserved for patients who present with recurrent or persistent disease.

Surgical resection usually is curative because of the small size and benign nature of insulinomas. As in carcinoid tumor, partial resection may afford palliation in patients whose symptoms are disabling or cannot be controlled with nonsurgical modalities. A patient with unresectable malignant insulinoma and recurrent episodes of hypoglycemia often benefits, during the early stages, from appropriate diet and administration of an insulin antagonist. Frequent feedings between meals and at bedtime are administered with sufficient glucose to control symptoms. Adjustments in the carbohydrate content of the diet may be required, depending on the reactivity of the individual tumor, because the stimulus of a large glucose load may lead to an exaggerated release of insulin.[331] Parenteral glucose supplementation becomes an important adjunct in frequent or sustained hypoglycemic attacks; in emergencies, rapid injection of 50% glucose can be required.

Corticosteroids, human growth hormone (hGH), and glucagon have been useful palliative agents in individual patients.[332,333] However, because of their limited effectiveness, they are best used in combination with other antihormonal measures. Furthermore, glucagon stimulates pancreatic insulin secretion and may cause paradoxic exacerbation of a hypoglycemic episode.

A major advance in the palliation of malignant insulinoma came with the development of diazoxide. Its potent hyperglycemic properties, originally recognized during its use as an antihypertensive agent, have now been extended to the palliation of insulinoma and leucine-sensitive hypoglycemia of infancy.[334,335] Its principal action is to inhibit insulin release directly from the β cell. It also may have an extrapancreatic hyperglycemic effect.[336] Diazoxide is administered orally in divided doses, ranging from 100 to 1000 mg/day. Although the plasma insulin level often can be reduced to a level that causes no symptoms, the tumor will continue to grow and metastasize if malignant, because diazoxide lacks anticancer activity. Diazoxide can cause edema, which can be corrected or prevented with a thiazide diuretic, which also may serve to reinforce the hyperglycemic effects.[323] Octreotide is valuable in the general management of all hormone-producing islet cell tumors and has been found to reduce plasma insulin levels in at least 65% of patients with insulinoma.[337] Octreotide is especially useful when there are insulinoma metastases, because there appears to be upregulation of somatostatin receptor subtype 2 (SST 2) of the metastatic lesions. A caveat remains when using octreotide. Up to 60% of the primary insulin-secreting tumors may not have SST 2 receptors, and hypoglycemia may worsen. Initiation of octreotide acetate requires close monitoring when used in insulinoma therapy.[320]

Chemotherapeutic agents such as streptozocin, 5-fluorouracil, and doxorubicin have been used to treat metastatic insulinomas, but have limited efficacy.[338]

Glucagonoma

Glucagon from pancreatic α cells plays an important role in modulating serum glucose concentrations. Unregulated secretion of glucagon by α-cell tumors[339] produces a distinctive clinical syndrome.[340] A cutaneous rash, described as a necrotizing migratory erythema, is the most characteristic feature.[341] Mild insulin-resistant diabetes and weight loss attributable to the catabolic effects of glucagon also are seen. Glossitis, cheilosis, and venous thromboses can develop. Glucagon inhibits intestinal motility, and the glucagonoma syndrome often includes ileus and constipation. Because symptoms commonly are mild and nonspecific, the tumor often is recognized late, when metastases are present.[340] Most tumors have grown to greater than 4 cm[342] in size at diagnosis, and 50% to 80% are metastatic.[342,343]

The diagnostic test for glucagonoma is the finding of a high plasma glucagon concentration (normal, <60 pg/mL). In patients with glucagonoma, the plasma hormone level typically is markedly elevated and often is greater than 1000 pg/mL.[343] The diagnosis is further suggested by failure of glucose to suppress glucagon, by an abnormal rise in plasma glucagon following infusion of arginine, by the presence of hypoaminoacidemia, and, if tumor is available, immunoperoxidase staining for glucagon. Reviews suggest that the tumor is more common in women and typically presents in the fifth and sixth decades.[344,345] Symptoms persist for many years before the diagnosis is made; survival, even with metastatic disease, may be lengthy. The primary tumor is in the tail or body of the pancreas in 50% of patients and in the head of the pancreas in 8% of patients; the remaining 42% of patients have diffuse involvement. CT scans and MRI are useful in identification of the primary tumor, as is octreoscanning.[346] The tumor is resectable for cure in less than one third of cases,[344] and recurrence after resection, mainly in the liver, is common.

In addition to surgical resection, octreotide produces an improvement of skin rash in up to 90% of patients and complete disappearance of rash in 30%.[347,348] Chemotherapeutic agents may have some activity.

Somatostatinoma

Somatostatin first was identified in pituitary cells, and a role in the regulation of growth hormone secretion was ascribed to it. Subsequently, it was recognized as a hormone of the islet δ cells. Somatostatin may serve as a paracrine regulator of other pancreatic islet cell hormones.[348] Inhibition of secretion of those hormones may account for some of the signs of somatostatinoma. In a review of 20 patients, 11 were noted to present with diabetes, 13 with gallbladder disease, and 7 with diarrhea.[349]

Somatostatinoma occurs most frequently in the head of the pancreas,[350] and as many as 80% of patients have evidence of metastases at diagnosis.[349] Somatostatinomas produce such common symptoms as diabetes (type 2–like diabetes mellitus) and gallbladder disease; therefore, the clinician usually does not consider the diagnosis of somatostatinoma until late in the disease, by which time metastases are likely. Surgical resection usually is not curative.[349,351] Because of the relatively mild hormonally induced symptoms produced by somatostatin, octreotide does not have the same palliative benefit it has in other islet cell tumors. Cytoreductive surgery and chemotherapy may be the most appropriate palliative strategies.

Gastrinoma

Gastrin, the polypeptide hormone normally secreted by the G cell of the gastric antrum, stimulates gastric acid secretion. Tumors of the pancreatic or duodenal wall G cells are responsible for the signs and symptoms of Zollinger-Ellison syndrome, a disorder characterized by hypersecretion of gastrin. First described in 1955,[352] this syndrome is characterized by hypersecretion of gastric acid, severe peptic ulcer disease, and an islet cell tumor of the pancreas. It is estimated that less than 0.1% of patients with peptic ulcer disease have Zollinger-Ellison syndrome.[353]

The hallmark of the gastrinoma syndrome is recurrent peptic ulcer disease in spite of adequate medical or surgical treatment. Intermittent diarrhea, often with steatorrhea, may be present as a result of digestive enzyme inactivation in the small intestine by unbuffered gastric acid. All manifestations of the Zollinger-Ellison syndrome are secondary to hypersecretion of gastric acid.[354] A history of the MEN-1 syndrome has great significance, and gastrinoma may be present in up to 50% of these patients.[355] The combination of high gastric acid secretion and hypergastrinemia is strongly suggestive of gastrinoma, but this combination also can occur in patients with retained gastric antrum following surgery for peptic ulcer (antrectomy and Billroth II gastric resection) and following gastric outlet obstruction. Gastric rugal hypertrophy, multiple ulcers, or ulceration of the small bowel on radiographic studies suggests gastrinoma.[356]

In a review of 60 patients treated surgically for gastrinoma at Ohio State University, Ellison and associates[357] reported that the duration of ulcer symptoms prior to diagnosis averaged slightly more than 4 years. The incidence of MEN was 27%, and a primary tumor was detected in nearly 90% of cases. Gastrinoma can occur not only in the pancreas but also in extrapancreatic locations, including the duodenum, the stomach, and the retroperitoneal lymph nodes. More than one third of patients in the Ohio State series had multiple tumors; metastatic disease in the liver was identified in 20% of patients.[357]

The clinical diagnosis of Zollinger-Ellison syndrome has changed. Although the original case reports stressed the appearance of extensive and multiple gastric ulcers, a heightened index of suspicion and early detection have altered this pattern of disease presentation. The complete diagnosis of Zollinger-Ellison syndrome is based on four steps.[355] The first step is to identify fasting hypergastrinemia in association with a basal acid output greater than 15 mEq/hour. Generally, a gastrin level greater than 1000 pg/mL is pathognomonic. Less convincing elevations in fasting serum gastrin can be further evaluated by the secretin test, in which a peak level of serum gastrin higher than 200 pg/mL over the baseline following administration of secretin is considered diagnostic.[358] The remaining three steps include documentation of peptic ulcer disease, localization of the primary tumor, and assessment of malignancy.[359]

Localization of gastrinomas has been discussed extensively.[360,361] Techniques such as abdominal ultrasonography, CT scan, MRI, selective venous sampling for gastrin, and abdominal arteriography all have a role in the diagnosis and management of this disease. Octreotide scanning is very useful for identifying primary and metastatic lesions,[362] and is valuable as an initial imaging modality. Endoscopic ultrasound also is being used increasingly to identify gastrinomas. Because gastrinomas are so frequently malignant,[363,364] it is necessary to use every diagnostic modality to rule out metastatic disease before planning surgery.

The role of surgery in Zollinger-Ellison syndrome has changed over the past 20 years as a result of the introduction of RIA to diagnose hypergastrinemia and use of histamine H_2-receptor antagonists. The latter therapy has very significantly reduced the need to remove the end organ (the stomach); therefore, few patients will require surgical management to control the signs and symptoms of hypergastrinemia. In addition, gastrinomas are significantly less likely than insulinomas to be isolated, benign, or completely resectable. In a collected series of 457 surgical patients, only 69 patients (15%) were considered to have received surgery with curative intent.[357]

Ellison and associates[357] also analyzed 60 cases from their own institution to determine whether the introduction of the RIA for gastrinoma made earlier diagnosis more likely, with a higher possibility of curative resection. Before the introduction of the assay for serum gastrin levels, 15 of 25 (60%) patients underwent complete excision of all gross tumor. Of the 30 patients who underwent surgical treatment following availability of the assay, 18 (60%) had complete tumor resection. These results indicate no differences in rates of curative resection. However, resectability was associated with prolonged survival, with a 5-year survival rate of 69% in patients with resected tumor, compared with 38% in patients with unresectable disease. The 10-year survival rates were 38% and 9%, respectively. Nearly one half of the deaths were due to the effects of tumor and metastases. These data suggest, but do not prove, that earlier surgical intervention may prevent progression to the complications of bulky malignant tumor in some cases.

Medical management in gastrinoma is directed toward the hypersecretion of gastric acid. Before the introduction of histamine receptor antagonists, the only practical way to treat recurrent duodenal and jejunal ulcers was total gastrectomy. Cimetidine was reported to enhance recovery and make surgery less complicated, and to obviate surgery in some patients.[364] Histamine H_2-receptor antagonists alone or in combination with anticholinergic agents such as propantheline have been successful in producing long-term remissions of peptic ulcer disease complicating gastrinoma.[355] Second- and third-generation histamine H_2-receptor antagonists, such as ranitidine, famotidine, and the ion pump inhibitor omeprazole, have been reported to have progressively superior antisecretory activity, with few failures observed in patients who receive adequate doses.[365] Treatment for symptoms arising from tumor bulk from metastatic gastrinoma are discussed at the conclusion of this section.

Tumors Secreting Vasoactive Intestinal Peptide

In 1958, Verner and Morrison[366] described a syndrome of watery diarrhea, hypokalemia and hypochlorhydria, and metabolic acidosis (the WDHA syndrome), which is due to high circulating levels of vasoactive intestinal peptide secreted by a pancreatic islet tumor (VIPoma). Most studies of VIP infusions in healthy volunteers have supported the concept that the diarrhea in VIPoma patients may be caused directly by elevated circulating levels of vasoactive intestinal polypeptide.[367] Because most patients with this syndrome have metastatic disease at presentation, usually to the liver, management is mainly medical, with chemotherapy or somatostatin analog. Surgical resection is rarely curative. As with carcinoid tumors and other islet cell tumors, however, in patients with locally unresectable disease or those with hepatic metastases, surgical cytoreduction may improve symptom control.

Ghrelin Secreting Tumor

Ghrelin is a 28-amino acid peptide that is secreted in the stomach and stimulates growth hormone release. A recent publication described a patient with hypertension and perspiration and a malignant gastric ghrelinoma with hyperghrelinemia.[368] Although this tumor is exceedingly rare, the expression of ghrelin peptide has now been identified in almost all gastric and intestinal carcinoids, as well as pancreatic neuroendocrine tumors. Its possible role as a tumor marker along with chromogranin A (CGA) in all gastroenteropancreatic neuroendocrine tumors remains to be clarified.

Surgical Management

Pancreatic islet cell tumors present a challenge for the endocrine surgeon. Most are sporadic, but they also can occur as part of the MEN-1 syndrome. Patients with MEN-1 usually develop multicentric tumors that often preclude the ability to perform a curative resection. The commonly occurring islet cell tumors secrete gastrin, insulin, glucagon, pancreatic polypeptide, or somatostatin. These tumors can have profound physiologic effects; even in cases in which complete resection is not possible, tumor debulking may be indicated to alleviate the physiologic effects of hormone secretion.

Gastrinoma

Gastrinomas occur within the pancreas or are found submucosally within the duodenum. Most gastrinomas are located in the "gastrinoma triangle," which is surrounded by the cystic duct superiorly, the second and third portions of the duodenum inferiorly, and the junction of the body and neck of the pancreas medially. Approximately 75% are malignant, with liver metastases a common finding. CT scanning is the best method for evaluating patients for resection. Patients with solitary tumors in the tail of the pancreas can be treated with enucleation or distal pancreatectomy; however, a Whipple procedure may be needed for large or obviously malignant tumors in the head of the pancreas. Duodenal tumors can be resected locally from the wall of the duodenum. It may be necessary to use intraoperative ultrasound, endoscopy with duodenal transillumination, and a longitudinal duodenotomy to identify these tumors. Usually, all enlarged peripancreatic and periduodenal lymph nodes are removed. Occasionally, localized metastases can be resected to control excess gastric

secretion. Patients with unresectable gastrinoma whose acid secretion cannot be controlled medically require a total gastrectomy with esophagojejunostomy.

Insulinoma

Approximately 75% of insulinomas are solitary benign tumors. Preoperative evaluation begins with a double-contrast, fine-cut CT scan. Small tumors that cannot be found by CT scan may be localized preoperatively with transgastric endoscopic ultrasound, which has been reported to have a sensitivity of 83% to 93%.[369] Selective arteriograms with calcium stimulation are used rarely. At laparotomy, the entire pancreas should be exposed by a generous Kocher maneuver. A combination of inspection, palpation, and intraoperative ultrasound will identify most tumors and their relation to the pancreatic duct. Small, benign tumors in any part of the pancreas can be enucleated provided they are not in close proximity to the duct. After enucleation, the pancreatic surface is closed, and the area should be drained because of the possibility of pancreatic fistula.

Larger tumors (≤5 cm) in the head of the pancreas also can be enucleated; however larger tumors in the tail are best treated with a spleen-preserving distal pancreatectomy. Large, potentially malignant, tumors in the head of the pancreas may need a Whipple procedure. Resection of peripancreatic and duodenal nodes also is advised. Some centers now are approaching these tumors laparoscopically. Although feasible, long-term follow up data are needed.[370,371]

Medical Management

Somatostatin Analog

The somatostatin analog octreotide is as useful in the treatment of syndromes associated with ectopic hormone production in islet cell tumors as it is in treatment of carcinoid tumors. In 1985, Santangelo and associates[372] described a single patient with life-threatening pancreatic cholera, successfully controlled by the synthetic somatostatin analog. A later series of patients from the Mayo Clinic significantly supplemented these data; in this series, 24 patients with islet cell tumor were treated.[373] The response to somatostatin analog was prompt and palliated symptoms. However, the median duration of response was only 2.5 months, with only 2 of 24 patients (8%) continuing to benefit beyond 1 year. In another review of 66 cases treated with octreotide, only 8 patients (12%) showed any indication of objective tumor response.[337] The short duration of response and low incidence of objective tumor regression suggest that somatostatin analog in the treatment of metastatic islet cell tumors has a more limited role than in carcinoid tumors. Two recent publications suggest that high-dose octreotide therapy may have additional stabilizing and antiproliferative effects in some patients who suffer malignant, advanced, midgut carcinoid tumors.[374,375] Patients on long-term octreotide therapy should have a cholecystectomy at the time of initial exploration due to the high incidence and morbidity of biliary complications.[300]

Interferon

As somatostatin analogs were being shown to be useful in patients with pancreatic cholera, the first reports of the use of interferon in such patients appeared.[376] In the initial report, two patients with the therapy-resistant pancreatic cholera syndrome were treated successfully with human leukocyte interferon, with reduction in tumor mass in one of the patients. Extending these observations, Swedish investigators reported on 22 patients treated with human leukocyte interferon, with an objective response rate of 77% and a median duration of response of 8.5 months.[301] Most of these responses were documented by decreased hormone production. Only 6 of 22 cases (27%) had objective reduction in tumor bulk. Further evaluation of interferon, with and without chemotherapy, is warranted. The mechanism of action of interferon in islet cell and carcinoid tumors is unknown.

Chemotherapy

As with carcinoid tumors, the use of cytotoxic chemotherapy in a patient with an islet cell tumor is not a first choice for therapy.[377] Chemotherapy usually is attempted in patients with symptoms due to tumor bulk that may not be palliated by cytoreductive surgery or in patients with uncontrolled syndromes of hormone excess. In contrast to carcinoid tumors, islet cell carcinomas generally are more responsive to chemotherapy. The first chemotherapeutic drug to elicit significant attention in the treatment of islet cell tumors was the antitumor antibiotic streptozotocin. This drug has a diabetogenic action in some animals that is correlated with selective uptake of the drug by pancreatic β cells.[377,378] In 1975, Kahn and associates[379] described two patients with pancreatic cholera and islet cell carcinoma successfully treated with intra-arterial streptozotocin. Subsequently, a number of chemotherapeutic drugs were identified as having activity in islet cell tumors. With the identification of 5-FU as a potentially useful drug in these tumors, combination chemotherapy also began to be investigated. In a phase II trial of the combination of 5-FU and streptozotocin, six objective responses were noted in eight patients. In 1980, a larger study from the ECOG was reported, in which streptozotocin alone was compared with streptozotocin plus 5-FU in advanced islet cell carcinomas.[302] The combination was superior to streptozotocin alone in overall rate of response (63% vs. 13%). These responses generally were of long duration and yielded meaningful improvements in performance status and symptoms. The median survival time of patients receiving the combination was 26 months, compared with 16.5 months in the group receiving streptozotocin alone. The combination was associated with a higher degree of nausea and vomiting, myelosuppression, and nephrotoxicity. With the identification of doxorubicin as a potentially useful drug in islet cell tumors,[380] the ECOG also piloted a randomized trial in which doxorubicin plus streptozotocin was compared with the earlier standard of 5-FU plus streptozotocin. Results from this study demonstrate that the doxorubicin plus streptozotocin combination produced objective response in 69% of cases, with a median duration of response in excess of 20 months and a median survival time of 2.2 years.[381] This regimen is superior to the 5-FU plus streptozotocin combination in both tumor response and survival. A study of 12 patients with islet cell carcinomas treated with the combination streptozotocin, doxorubicin, and 5-FU reported a 54% response.[300] However, these were partial responses; no complete responses were found.

A number of other chemotherapy drugs have demonstrated activity in islet cell tumors. Chlorozotocin, an analog of streptozotocin, has been shown to be less nephrotoxic but more myelosuppressive than the parent drug. In phase II trials of chlorozotocin, responses were significant when it was used alone or with 5-FU.[382,383] Unfortunately, chlorozotocin is no longer being produced. DTIC also has activity in islet cell tumors, and this agent is undergoing a prospective clinical trial by the ECOG. Other agents of interest include etoposide and cisplatin, which are active in various neuroectodermally derived tumors. The combination of etoposide and cisplatin has been shown to have activity in small cell lung cancer, and a recent trial demonstrates that more than 60% of anaplastic carcinoid and islet cell tumors respond to this combination, whereas well-differentiated tumors do not respond.[384] A phase II trial with DTIC, 5-FU, and leucovorin reported an overall response rate of 27%; however, 50% of the patients had carcinoid tumors, which, as a subset, demonstrated particularly poor response.[385]

Liver-Directed Therapy

As with carcinoid tumor, islet cell tumors often result in predominantly hepatic metastases, and reduction in tumor bulk in the liver may significantly influence hormone production and quality of life.

For that reason, resection of hepatic metastases is warranted in selected patients. The use of hepatic radiation has been reported only anecdotally. Of two patients treated at the National Cancer Institute, one patient with a VIPoma had significant resolution of watery diarrhea for 25 months; the other, with gastrinoma, had significant diminution in abdominal pain and of gastrin levels.[386] Endocrine and tumor response to hepatic arterial occlusion, with or without chemotherapy, can be impressive. The Mayo Clinic experience documents, in 46 patients with islet cell tumor regression rates of 43% with hepatic artery occlusion alone, versus 78.1% when chemotherapy was included.[261,313] Chemotherapy in addition to hepatic arterial occlusion improved the duration of response, but this was not a randomized comparison. However, both objective tumor responses and hormonal regressions were common, and the increased activity of chemotherapy in these tumors supports the use of systemic therapy with or without HAO techniques. The use of cryosurgery for treatment of hepatic metastases that are resistant to chemotherapy also has been reported.[387] This approach has been reported to be effective in treating symptoms, but effect on survival has not yet been demonstrated.

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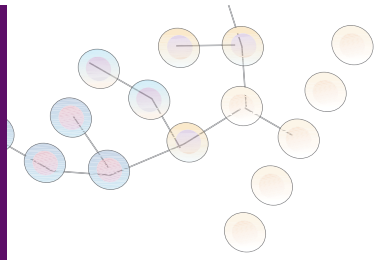
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76 Cancer of the Lung: Non-Small Cell Lung Cancer and Small Cell Lung Cancer

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SUMMARY OF KEY POINTS

Non-Small Cell Lung Cancer

Incidence and Epidemiology

- Non-small cell lung cancer (NSCLC) constitutes 80% to 85% of new cases of lung cancer in North America.
- Its most frequent histologies include adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.
- It is the leading cause of cancer death in the United States for both men and women; it represents one of the most preventable forms of cancer death.
- Tobacco use is considered responsible for 87% of lung cancer deaths use

Screening

- Because it is considered controversial, screening is not recommended by the U.S. Preventive Services Task Force.

Staging Evaluation

- A history and physical examination, and routine hematologic and biochemical testing are done.
- Imaging studies include
  - Computed tomography (CT) scan (with contrast) evaluating lungs, mediastinum, liver, and adrenals
  - Positron emission tomography (PET) useful with clinically early-stage disease
  - If patient has locally advanced or metastatic disease should add magnetic resonance imaging (MRI) of brain
  - If PET not available should add bone scan
- Mediastinal node evaluation includes
  - If disease in early stage (I, II) and PET of mediastinum negative, proceed directly to surgery; if PET positive, proceed to biopsy depending on node location
  - Cervical mediastinoscopy
  - Mediastinotomy
  - Transesophageal endoscopic ultrasound
  - Bronchoscopy
  - If disease is clinically more advanced, use the least invasive biopsy procedure from the foregoing list. At surgery all nodal areas must be sampled at minimum.

Primary Therapy

- Stage I disease
  - Surgery often curative
  - Role of pre- or postoperative therapy unclear
  - Radiation therapy appropriate in selected cases
- Stage II disease
  - Surgery often curative
  - Survival prolonged by postoperative chemotherapy in patients with a good performance status
  - Radiation therapy appropriate in selected cases
- Stage IIIA disease
  - Postoperative chemotherapy useful in resected IIIA if performance status good
  - Role of preoperative chemotherapy with or without radiation therapy for limited-extent stage IIIA unknown except for Pancoast tumors, where it is recommended
- Stage IIIB disease
  - Concurrent chemotherapy combined with irradiation superior to radiation alone; increased toxicity limits this approach in frail patients
  - Malignant pleural effusion treated as stage IV
  - Clinical trials of new approaches deserving of high priority
- Stage IV disease
  - Improvemenet of quality and quantity of life associated with primary chemotherapy with platinum-based doublet
  - No advantage for triplet therapy
  - Non-platinum-based therapy appropriate in selected patients
  - Single-agent therapy reserved for select populations.
  - More clinical trials at this stage clearly needed
- Second- or third-line therapy
  - Further treatment with any of several agents appropriate with progression after chemotherapy if patient sustains a good performance status; docetaxel, pemetrexed, and erlotinib (all approved by US Food and Drug Administration [FDA]).
  - Erlotinib and possibly gefitinib useful in this setting
  - Local recurrence after surgery treatable with combined chemotherapy and radiation after complete restaging

Small Cell Lung Cancer

Incidence and Epidemiology

- Small cell lung cancer (SCLC) accounts for approximately 15% of new cases of lung cancer each year in United States; incidence decreasing
- Subtypes: small cell carcinoma and combined small cell carcinoma (most often combined with squamous cell carcinoma, adenocarcinoma, or large cell carcinoma)

Staging Evaluation

- History and physical examination, routine histologic and biochemical testing
- Imaging
  - CT scan (with contrast) evaluating lungs, mediastinum, liver, and adrenals
  - Brain evaluation (MRI preferred) if neurologically symptomatic
  - Bone scan recommended if signs or symptoms of bone involvement present.
  - PET scan considered investigational
  - Mediastinal node evaluation not required unless as a convenient site for biopsy

- A major task: identifying the presence or absence of M1 disease
- If peripheral smear or hemogram abnormal, bone marrow biopsy may be obtained if no other site of metastatic disease has been confirmed

Therapy

- Limited disease
  - Concurrent etoposide plus cisplatin and radiation to the intrathoracic disease
  - Prophylactic cranial irradiation in complete (or near complete) responders
- Extensive disease
  - Etoposide (or irinotecan) plus cisplatin or carboplatin
  - No evidence a third agent or dose intensification improves outcome
  - Research studies a clear priority given the lack of progress in this arena
- Recurrent disease
  - Second-line therapy useful mainly in individuals who have experienced a longer treatment-free interval and a good performance status
  - Topotecan FDA approved; however, any of several chemotherapy agents offer short-term benefit.
  - Research protocols a preferred choice for individuals with disease recurrence

INTRODUCTION

Although reports of pulmonary malignancies date to antiquity, lung cancer is largely a disease of modern humans. Before 1900 lung cancers were viewed as "matters of medical curiosity not known to be in any degree influenced by medicine and too rare to be of much practical importance".[1] By the mid-twentieth century, however, lung cancer had become epidemic and firmly established as the leading cause of cancer-related death in North America and Europe.[2] It should not be forgotten that lung cancer is potentially one of the most preventable of all of the major malignancies afflicting humanity. Its primary cause is tobacco smoke.[3] King James I was among the first to chronicle the adverse health effects of tobacco smoke,[4] but it was Raymond Pearl's landmark 1938 report that conclusively established the devastating impact smoking has on longevity.[5] It would be another decade before tobacco smoking was firmly established as a causative agent of lung cancer[6,7] and nearly 30 more years before the emergence of the U.S. Surgeon General's initial report of the ill effects of tobacco smoking. Regrettably it would be yet another 3 decades before the tobacco industry publicly acknowledged this obvious truth but only after a long, drawn-out battle of misinformation and deception[8] ironically helped along by the unwitting (perhaps) complicity of physicians.[9] With the belated recognition of the etiologic role of tobacco smoke the incidence of lung cancer started to decline in North America and parts of Europe. For the most part the decline is seen most clearly in men. Only recently has this decline become apparent in women in the United States following a similar decline among men 10 to 15 years ago.[10] In short, the story of lung cancer is replete with controversy,[11] politics,[12] pessimism,[13] and, more recently, guarded optimism.[14] This chapter focuses on our perceptions of current management of lung cancer with an emphasis on advances made over the past 5 years. We refer the reader to previous editions of *Clinical Oncology* for earlier works of historical importance.

EPIDEMIOLOGY

Lung cancer was an uncommon disease in the early part of the twentieth century but then began an epidemic rise to far surpass all other cancers in numbers and rates of death.[15] Indeed, lung cancer is now the second most common cause of death among American men. The increase peaked in the late 1980s among men but did not plateau until around the year 2000 among women. It is estimated that more than 170,000 individuals will be diagnosed with lung cancer in the United States in 2006.[15] Lung cancer is relatively rare in individuals younger than age 40, but rates rise steadily until age 80 and then taper off; the projected lifetime probability of developing lung cancer is estimated to be approximately 8% among males and approximately 6% among females.[16] The incidence of lung cancer varies by racial and ethnic group, with the highest age-adjusted incidence rates among African American men (Fig. 76-1). The excess in age-adjusted rates among blacks occurs only among men, but examinations of recent age-specific rates show that below age 50 mortality from lung cancer is more than 25% higher among black than white women.[16] Incidence and mortality rates among Hispanic, Native, and Asian Americans are only 40% to 50% those of whites. Figure 76-2 shows trends in age-adjusted mortality rates from lung cancers in the United States since 1930.

The trends in overall lung cancer rates mask differences in temporal patterns according to lung cancer cell type. Figure 76-3 shows changes in age-adjusted incidence rates for squamous cell carcinoma and for adenocarcinoma during 1973 to 2003 based on data from nine continuing cancer registries in the National Cancer Institute's (NCI's) SEER program of cancer registration. Among men, squamous cell cancers predominated in the first two thirds of this period. The decline in incidence of lung cancer among men was first apparent for squamous cell tumors, however, with decreases beginning in the early 1980s so that by the mid-1990s rates of squamous cell carcinoma among men had dropped below those for adenocarcinoma, which did not peak until over a decade later. Among women, adenocarcinomas have been more common than squamous cell carcinomas across the 3 decades. The adenocarcinoma excess among women has become more pronounced over time, in that rates of squamous cell cancers increased steadily through the 1980s before

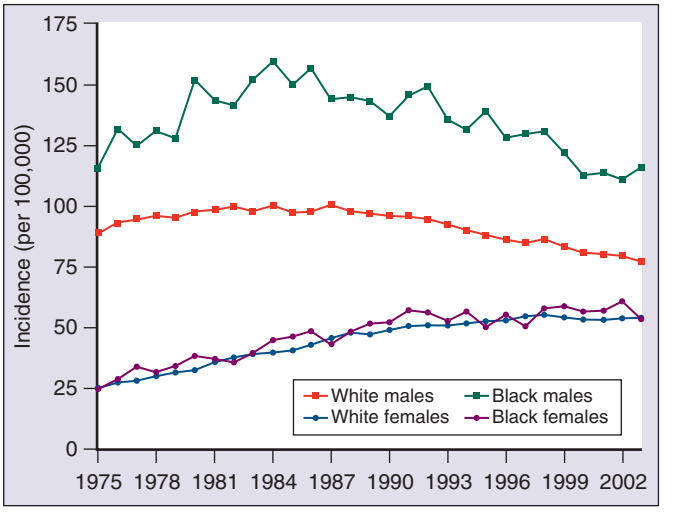


Figure 76-1 • Lung cancer incidence in United States between 1975 and 2003. Age-adjusted to the 2000 U.S. standard population. (Data from National Center for Health Statistics, Centers for Disease Control & Prevention, 2005).

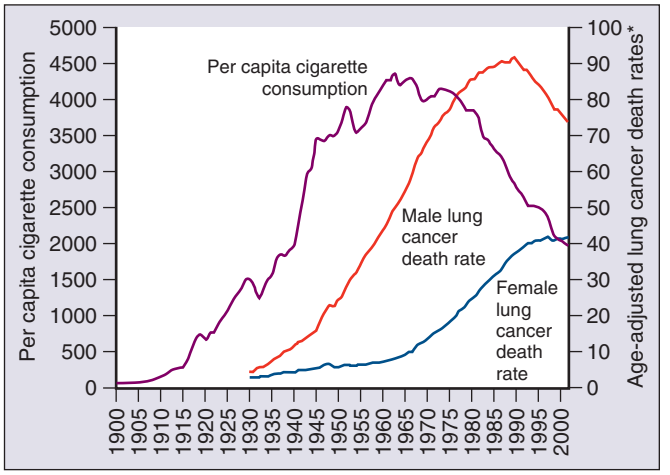


Figure 76-2 • Tobacco use and lung cancer mortality in the United States 1900–2002. *Per 100,000, age-adjusted to the 2000 U.S. standard population.

beginning to decline, whereas adenocarcinoma did not plateau until about a decade later. Although not shown in Figure 76-3, rates of small cell carcinoma, the third most frequent cell type, tended to parallel those for squamous cell cancer among both sexes. Trends for other cell types of lung cancer, including large cell carcinomas and bronchioloalveolar carcinomas, tend to be intermediate between those of squamous cell carcinomas and adenocarcinomas. As discussed later in the chapter, although 5-year relative survival rates for lung cancer have improved over time, the survival rates are low, currently about 15% overall.[16] Some variation exists by sex, race, and cell type, with slightly higher survival among whites than blacks and females than males, but for no group does the overall 5-year relative survival exceed 20%.

Risk Factors

The cause of the large majority (80% to 90%) of lung cancers is cigarette smoking.[17,18] There is a massive compilation of scientific evidence from epidemiologic studies conducted around the world since the 1950s demonstrating the link between smoking and lung cancer. Epidemiologic research has also revealed that several other factors have been implicated as causes of lung cancer, though none to the extent of tobacco.[19,20] Cigarette smokers have been shown to have large increases in the risk of lung cancer. Numerous investigations typically show 10-fold or greater increases in risk of this cancer among smokers as compared with those who have never smoked.[17,18]

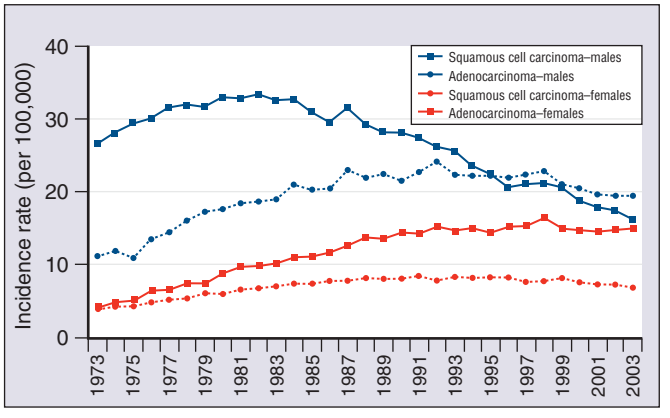


Figure 76-3 • Age-adjusted SEER lung cancer incidence, nine registries.

One of the largest studies is the American Cancer Society's prospective cohort study of over 1 million Americans wherein a greater than 20-fold excess of lung cancer has been observed among men who were current smokers at the start of the follow-up in the early 1980s.[17,18] In contrast, even the most prolonged and intense exposures to asbestos, perhaps the most prominent occupational cause of lung cancer, are associated with no more than about fivefold increases in lung cancer.[21]

Risks of lung cancer are lower among persons who quit smoking than among those who continue smoking.[17,18] The reductions in risk indicate that quitting smoking is beneficial (and conversely that continuing to smoke is harmful). Risk among former smokers on average is less than one half that of those who continue to smoke. In the American Cancer Society cohort study cited discussed earlier, former smokers had a 9-fold increase in lung cancer as compared with men who had never smoked versus the 20-fold excess in those who continued to smoke.[17,18] Such relative reductions have been consistently seen, with the size of the reduction in risk increasing the longer the time period since the person has quit smoking, although generally even long-term former smokers have higher risks of lung cancer than those who never smoked.[17,18]

Cigarette smoking has been shown to increase risk of all the major lung cancer cell types.[17–20] The magnitude of the increase varies by histologic type, however, with highest risks for squamous cell, small cell and large cell carcinomas of the lung. Some early studies tended to show only small increases in risk of adenocarcinoma among smokers, but more recent studies indicate that the excess of lung adenocarcinoma is substantial.[17,18,20]

Cigarette smoke has also been implicated in increasing risk of lung cancer among nonsmokers. A 2006 update of the Surgeon General's report declared that there is sufficient evidence to list passive smoking as an established cause of lung cancer and called for further control of environmental tobacco smoke (ETS) exposures.[22] The risk from ETS is far less than from active smoking, with about a 20% to 30% increase in lung cancer observed among nonsmokers married for many years to smokers, in comparison to the 2000% increase among continuing active smokers. Nevertheless, cancer control activities based on the knowledge that ETS exposure may convey an increased risk of lung cancer have helped reduce exposures in public places and have also provided additional incentive for smokers to quit the habit.

Although cigarette smoking is the dominant cause of lung cancer, several other risk factors for this cancer have been identified.[19,20] These include occupational exposures to asbestos and some other workplace agents, some of which have been evaluated for nearly as long as cigarette smoking. Among the occupational agents considered as known lung carcinogens are arsenic, bischloromethyl ether, hexavalent chromium, mustard gas, nickel (as in certain nickel refining processes), and polycyclic aromatic hydrocarbons.[19,20,23] Several other occupational exposures have been associated with increased rates of lung cancer, but the causal nature of the association is not clear. Epidemiologic studies have attempted to assess the potentially synergistic interrelationship between certain workplace exposures and smoking. Risk of lung cancer among men exposed to asbestos who also smoked was originally thought to be exceptionally high (with early reports of 50-fold or greater excesses compared with unexposed nonsmokers), but recent modeling of larger data pools suggests that asbestos and tobacco combine to enhance lung cancer risk in a less than multiplicative manner.[24] Occupational observations have also provided clues to the mechanisms of lung cancer induction. Risk of lung cancer among asbestos-exposed workers, for example, is increased primarily among those with underlying asbestosis, raising the possibility that the scarring and inflammation produced by this fibrotic nonmalignant lung disease may in many cases (though probably not in all) be the trigger for asbestos-induced lung cancer.[25]

Increased risks of lung cancer have also been associated with other variables. Diet and nutrition are thought to be involved, because numerous investigations have shown somewhat higher risks of this

cancer among those with low fruit and vegetable intake during adulthood.[19,20] The early observational studies led to hypotheses that specific nutrients, in particular retinoids and carotenoids, might have chemopreventative effects for lung cancer. Randomized clinical trials were launched, but hopes were crushed when reports from interventions involving supplementation with β-carotene in trials both in Finland and the United States found increased rather than decreased incidence of lung cancer among those supplemented.[26,27] The current consensus regarding diet and lung cancer remains muddled, with a minor role for nutritional factors probable but difficult to assess epidemiologically. Ionizing radiation has been established as a lung carcinogen, most convincingly demonstrated from studies showing modestly increased rates of this cancer among persons exposed to the atomic bombs of Hiroshima and Nagasaki and large excesses among workers exposed to α-irradiation from radon in underground uranium mining.[19,20] Extrapolations from the high exposures in mines to low-level radon exposures in homes, as well as direct observations from case-control studies assessing measured levels in homes, suggest that prolonged radon exposures above the recommended remedial levels might impart a risk of lung cancer equal or greater than that of ETS.[28] Prior lung diseases such as asbestosis (mentioned previously), chronic bronchitis, emphysema, and tuberculosis also have been linked to increased risks of lung cancer. Although smoking itself is a cause of the chronic obstructive pulmonary diseases (COPDs), the link between chronic bronchitis and emphysema and lung cancer persists after adjustment for smoking, with up to about a doubled smoking-adjusted cancer risk among those with COPD.[19,20,29] Familial clustering of lung cancer has been observed, raising the possibility of inherited traits that may increase risk among some individuals, with risk about doubled in families with prior lung cancer.[19,20] Smoking also clusters within families, so some of the familial aggregation of lung cancer may be smoking-related. Nevertheless, there seem to be multiple genetic factors that help determine the way in which individuals metabolize, detoxify, repair, or otherwise respond to lung carcinogens, including the carcinogens in cigarette smoke, as discussed in more detail later in this chapter.

SMOKING CESSATION

Given the undeniable link between cigarette smoking and lung cancer,[3] it is incumbent upon physicians to promote tobacco abstinence and help their patients who smoke to stop smoking.[30] Smoking cessation, even well into middle age, can minimize an individual's subsequent risk of lung cancer, and stopping before middle age avoids more than 90% of the risk attributable to tobacco.[31,32] By contrast, there is little health benefit realized by simply "cutting back".[33] Among victims of lung cancer, smoking cessation is associated with improved survival,[34–37] fewer side effects from therapy,[38] and an overall improvement in quality of life.[39] It is often forgotten that smoking alters the metabolism of many chemotherapy drugs, potentially adversely altering the toxicities and therapeutic benefits of the agents.[40] Therefore, it is important to promote smoking cessation even *after* the diagnosis of lung cancer is established.[41,42] To do so requires that oncologists be well versed in the treatment of nicotine addiction.[43] Although smoking cessation is extremely difficult, patients with lung cancer tend to be highly motivated and success rates mirror that of other disease states.[44] However, the individual must want to stop smoking and must be willing to work hard to achieve the goal of smoking abstinence. Nicotine replacement therapies, bupropion and varenicline (an $\alpha_4\beta_2$-nicotinic acetylcholine receptor partial agonist), are approved by the U.S. Food and Drug Administration (FDA) as first-line treatments for nicotine dependence.[45] Recently varenicline was demonstrated to be significantly more efficacious than bupropion alone for smoking cessation.[46] Furthermore, prolonged use of varenicline beyond the initial induction phase proved useful in maintaining smoking abstinence.[47] Clonidine and nortriptyline are recommended as second-line treatments.[41] A systematic review of extant smoking cessation studies indicates self-help strategies alone only marginally affect quit rates, whereas individual and combined pharmacotherapies and counseling either alone or in combination can significantly increase rates of cessation.[48]

BIOLOGY OF LUNG CANCER

The specific events that trigger malignant transformation of bronchoepithelial cells are unknown in the vast majority of cases. However, it is clear that exposure to environmental carcinogens, such as those found in tobacco smoke or asbestos fibers, induce or facilitate the transformation (extrinsic component).[49] The contribution of the extrinsic carcinogen on transformation is modulated by variations in genes (intrinsic component) that affect aspects of carcinogen metabolism, such as the conversion of procarcinogens to carcinogens and their subsequent inactivation.[50] These genetic variations occur at relatively high frequency in the population. Their contribution to an individual's lung cancer risk is generally low, but because of their population frequency, their overall impact on lung cancer risk could be high. Epidemiologic studies further suggest that a familial predisposition to lung cancer exists that is independent of tobacco smoke exposure. One study found evidence for an autosomal dominant model linked to 6q23–q25,[51] but other studies have proposed a complex multigene model for inherited risk.[52] A familial clustering of lung cancer cases has been reported with an inherited T790M mutation in the epidermal growth factor receptor (*EGFR*) gene.[53] The identification of individuals at particularly high risk for the development of lung cancer could justify more intense screening regimens, and the identification of the responsible chromosomal loci for lung cancer susceptibility genes could allow the development of specific chemopreventative strategies.

Environmental factors, as modified by inherited modulators, probably affect specific genes by deregulating important pathways to permit the cancer phenotype. Particularly important in lung cancer are acquired abnormalities in the genes encoding ras, Rb, p53, Akt, LKB, and BRAF.[54] However, the single most clinically significant acquired genetic abnormality in lung cancer is the recently described mutation of the *EGFR*.[55–58] These are mutations, primarily in exons 19 (in-frame deletions of four amino acids, LREA) and 20 (L858R point mutants), that result in constitutive signaling and AKT activation,[59] and are associated with very high response rates (60% to 90%) to the specific tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib.[60] Interestingly, almost all of the mutations occur in nonsmokers and adenocarcinomas, and the frequency of mutations is much higher in Asian than Western populations (30% to 70% versus 8%).[61,62] These responses are often dramatic and occur even in heavily pretreated patients, demonstrating that tumors with these mutations are "addicted" to the activation of this pathway. Almost all patients with these impressive responses, however, develop progressive, resistant disease, and about half of these tumors with acquired resistance to TKIs demonstrate a second T790M mutation associated with resistance.[63,64]

Despite the incontrovertable high response rate in patients with *EGFR* mutations, analysis of samples from BR.21, a placebo-controlled randomized clinical trial of erlotinib in second-line non-small cell lung cancer (NSCLC) showed that the presence of an *EGFR* mutation was not associated with prolonged survival,[65] but in univariate analysis amplification of the receptor was associated with improved survival.[66] Interestingly, there was a survival benefit in the entire erlotinib arm compared with placebo, as well as every subset of patients, including smokers and patients with squamous cell cancers,[67] suggesting that variables other than mutation may contribute to clinical benefit, and that this was not necessarily related to objective response rates. Other assays, including serum proteomics, show potential for selecting patients likely to achieve clinical benefit.[68]

It is clear that the vast majority of lung cancers are not driven by single aberrant genes, however, and not all aberrancies are mutations.

Complex networks of genes are finely tuned in normal cells to maintain normal growth, apoptotic responses, and differentiation. These networks can be perturbed at multiple points to deregulate key pathways in lung cancer tumors. A simple example is the mutation of *Rb* and the loss of p16, a regulator of Rb function; NSCLCs disrupt cell cycle control by either mutation of *Rb* or loss of expression of p16, but not both.

Attempts have been made to look at the genome in "comprehensive" ways so as to dissect tumors with common groups of genetic features that might provide biologic or clinical guidance beyond traditional classification by light microscopy. Single-nucleotide polymorphism arrays have been developed that are able to analyze loss or gain of genetic material at very high resolution,[69,70] and cancer genome resequencing efforts are likely to uncover common mutations. Protein expression and therefore function is probably more often modulated by epigenetic alterations than by mutations to cause perturbations in pathway function.[71] Detection of specific promoter methylations may in fact be a useful biomarker of malignancy.[72] These sorts of pathway alterations are more likely to be detected by the analysis of gene expression, protein expression, or post-translational modification-type changes (e.g., phosphorylation) than by gene mutation analysis. High-throughput technologies have been developed for each of these, and they are beginning to be applied to lung cancer. Several studies, for example, have been able to identify prognostically distinct subgroups of lung adenocarcinomas by complementary DNA microarray analysis,[73–75] as well as likelihood of recurrence after surgical resection.[76,77] More important than prognosis, early progress is being made in the analysis of single genes and pathways important for predicting response to targeted therapies, allowing rational individualization of therapy selection. Low expression of the DNA repair gene *ERCC1* has been shown to correlate with poor prognosis in NSCLC but with improved survival after treatment with platinum drugs.[78] For the newer targeted therapies, patterns of gene expression are being developed that may identify those more likely to respond.[79] Even closer to function than gene expression, analysis of protein expression patterns[68,80,81] or even phosphorylation patterns[82] may hold even greater practical promise in the future.

The histologic sequence of events that leads to the various forms of lung cancer is not well understood, and it is clearly different for the various histopathologic entities.[82–85] Current knowledge suggests that squamous cell carcinoma arises in an ordered progression that includes squamous metaplasia and carcinoma-in-situ (CIS). Peripheral adenocarcinomas are thought to arise from atypical adenomatous hyperplastic lesions, but this process is much more obscure largely because this type of lesion is much less accessible by bronchoscopy. Small cell carcinoma might arise from neuroendocrine hyperplasia, but evidence in support of this hypothesis is scarce.

The pathology of premalignancy will be discussed in more detail in the next section, but the molecular biology of premalignancy is of great clinical importance, not only to better understand the process of cancer development, but to provide potential therapeutic targets to intervene in this process and intermediate biomarkers to assess risk and evaluate candidate chemoprevention strategies. Premalignant lesions of the lung have been investigated for molecular alterations in NSCLC, but much less information is available for SCLC.[86] Microdissected specimens derived from normal, hyperplastic, metaplastic, dysplastic, and CIS, as well as invasive neoplastic foci of patients with lung cancer, were studied for gene mutations, promotor hypermethylation, and allele loss. Results obtained thus far suggest that allele loss on chromosome 3p is the earliest event, followed by allele loss/hypermethylation on chromosome 9p and subsequently on chromosome 8p.[85] Loss of heterozygosity at the p53 gene locus (17q13.1) is relatively rare (10%) and occurs predominantly at the dysplasia or CIS stage. Point mutations in the p53 gene[87] and the EGFR gene,[88] however, have been observed in morphologically normal bronchial epithelium obtained from the airways of patients with lung cancer. In contrast, K-ras gene mutations represent a late event, found only in CIS or invasive cancers.[89] In addition to copy number changes and mutations, alterations in the expression of the retinoic acid receptor β (RARβ) have also been used as a molecular marker for premalignancy and as an intermediate biomarker for chemoprevention trials.[90]

The fate of morphologically or molecularly abnormal areas is currently an intense area of research. One study showed that 54% of patients with high-grade dysplastic lesions developed lung cancer within 2 years, but 80% of these arise in a different part of the lung than the CIS.[91] None of the patients with low-grade dysplastic lesions progressed to cancer in this study. Of the low-grade lesions studied, 82% spontaneously regressed, 18% remained unchanged, and none progressed to CIS. Preliminary data also suggest that abnormal regions display reproducible molecular changes on repeat biopsies over time, and that these and additional abnormalities can be observed in tumors arising from these lesions.[92]

Part of the problem with the studies of preneoplasia is that we may be evaluating the microscopic appearance and molecular characteristics of the wrong population of cells. The vast majority of the respiratory epithelium (and most other tissues) is thought to be terminally differentiated and incapable of sustained replication; however, one theory holds that a small subset of the cells have unlimited, but normally tightly regulated, replicative potential. These are the pulmonary "stem cells",[93,94] whose biology is very poorly understood. The stem cell concept may also underlie the failure of standard medical therapies to eradicate lung cancers, even when there is a clinical complete response. The theory is that therapies have been refined to induce measurable reductions in the bulk tumor mass, while true replicative potential exists only in a small subset of "cancer stem cells" that are not effectively targeted by current therapies. Specific isolation of these cells and development of stem cell-targeted therapies may thus not cause rapid tumor regressions but instead result in significantly increased long-term survival.

Understanding of the molecular biology and discovery and validation of reliable biomarkers predictive of relapse, response to therapy, and poor outcome from lung cancer have long been pursued by investigators with the goal of guiding clinicians in selecting treatment for patients. One future approach to improve patient outcome is tailored therapy based on individualized phenotypic or genotypic tumor characteristics. We are now seeing the beginning of this with commercial EGFR mutation screening. Recent technological advances in mutation detection and quantitation of gene expression in minute clinical specimens herald the advent of clinical therapeutic decisions based on the expression of specific therapeutic targets and/or other host and/or tumor characteristics.

PATHOLOGY

The latest World Health Organization (WHO) classification of lung tumors from 2004 is essentially unchanged from the preceding classification from 1999 (Table 76-1).[95,96] The 1999 WHO classification reorganized and introduced several lesions. It defined bronchioloalveolar carcinoma (BAC) as a noninvasive tumor for the first time, and it introduced the concepts of atypical adenomatous hyperplasia and diffuse neuroendocrine hyperplasia as precursors to adenocarcinoma and neuroendocrine tumors, respectively. Since these additions, more studies have focused on evaluation of diagnostic criteria and prognosis of these preneoplastic and in situ lung lesions.

Tissue and Cytologic Diagnosis of Lung Cancer

The diagnosis of lung cancer can be made on tissue specimens such as transbronchial biopsy or resected specimens, or assessment of cytologic specimens such as transbronchial or transthoracic fine-needle aspirates (FNAs), bronchial brushes, bronchial washes, bronchioloalveolar lavage, or sputum cytology. The diagnostic yield depends on several variables including location (accessibility) of the

Table 76-1 2004 World Health Organization Classification of Malignant Epithelial Tumors

Squamous cell carcinoma
Papillary
Clear cell
Small cell
Basaloid
Small cell carcinoma
Combined small cell carcinoma
Adenocarcinoma
Mixed pattern
Acinar
Papillary
Bronchioloalveolar
Mucinous
Nonmucinous
Mixed
Solid with mucin production
Fetal adenocarcinoma
Mucinous (colloid) carcinoma
Mucinous cystadenocarcinoma
Signet ring
Clear cell
Large cell carcinoma
Large cell neuroendocrine carcinoma
Basaloid carcinoma
Lymphoepithelioma-like carcinoma
Clear cell carcinoma
Large cell carcinoma, rhabdoid phenotype
Adenosquamous carcinoma
Sarcomatoid carcinoma
Pleomorphic carcinoma
Spindle cell carcinoma
Giant cell carcinoma
Carcinosarcoma
Pulmonary blastoma
Carcinoid tumor
Typical carcinoid tumor
Atypical carcinoid tumor
Salivary gland tumors
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Epithelial-myoepithelial carcinoma

tumor, tumor size, tumor type, or technical aspects of the diagnostic procedure including the experience level of the bronchoscopist and pathologist.[97] In general, central lesions such as squamous cell carcinomas, small cell carcinoma, or endobronchial lesions such as carcinoid tumors, are more readily diagnosed by bronchoscopic examination, whereas peripheral lesions such as adenocarcinomas and large cell carcinomas are more amenable to transthoracic FNA. Diagnostic accuracy for small cell carcinoma versus non-small cell carcinomas for most specimens is excellent,[98] with lesser accuracy for subtypes of non-small cell carcinoma.[97]

Bronchoscopic specimens include bronchial brush, wash, bronchioloalveolar lavage, and transbronchial FNA. Of these, transbronchial FNA consistently demonstrates the highest sensitivity, surpassed only by the use of a combination of bronchoscopic specimens.[97–101] Overall sensitivity for combined use of bronchoscopic methods is approximately 80%, and together with tissue biopsy, the yield increases to 85% to 90%.[97,98,100] In fact, transbronchial FNA is more often diagnostic that transbronchial biopsy when the lesion of interest is submucosal.[97,102]

Like transbronchial FNA specimens, transthoracic FNA specimens are also very good, yielding diagnostic material in 70% to 95% of cases. Sensitivity is highest for larger lesions and peripheral tumors.[103] In general, FNA specimens, whether transbronchial, transthoracic, or endoscopic ultrasound-guided, are superior to other specimen types.[104] This is primarily because of the higher percentage of lesional tumor cells with fewer confounding conditions such as obscuring inflammation and reactive nonneoplastic cells.

Sputum cytology is inexpensive and noninvasive but has a lower yield than other specimen types due to poor preservation of the cells and more variability in acquiring a good-quality specimen. The yield for sputum cytology is highest for larger and centrally located tumors such as squamous cell carcinoma and small cell carcinoma histology, although occasionally an accurate diagnosis is possible with tumors located more peripherally within the lung.[97] The specificity for sputum cytology averages close to 100%, although sensitivity is generally less than 70%. The accuracy of sputum cytology improves with increased numbers of specimens analyzed; consequently, analysis of at least three sputum specimens is recommended. Sputum cytology also has been extensively studied as a screening tool for early detection of lung cancers with varying success. Sputum cytology is not currently recommended as a routine screening tool, but recent advances in molecular diagnostic techniques may result in a resurgence of this methodology.[105–108]

Precursor Lesions of the Lung

Squamous Dysplasia

The most established carcinoma sequence in lung cancer is that of preinvasive squamous lesions. In response to toxins, normal bronchial epithelium may undergo hyperplasia and squamous metaplasia, then dysplasia (Fig. 76-4), leading to squamous cell carcinoma in situ (Fig. 76-5) and finally to invasive squamous cell carcinoma. Although higher grade lesions such as severe dysplasia or carcinoma in situ are thought to portend a higher risk of development of invasive carcinoma, the progression through these degrees of dysplasia is not necessarily linear, and many preinvasive lesions are reversible or do not progress to invasive carcinoma.[109,110] The 1999 and 2004 WHO classifications of preinvasive lesions detail the microscopic features defined as mild, moderate, and severe dysplasias, and carcinoma in situ. In general, these microscopic features consist of increasing epi-

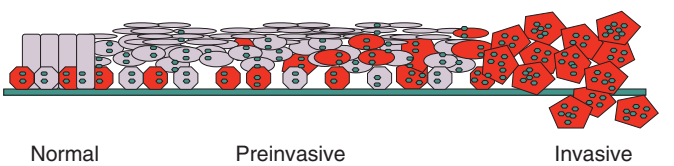


Figure 76-4 • Schematic representation of lung neoplasia showing the transition from normal mucosa to squamous metaplasia, dysplasia, and finally to invasive carcinoma. (Adapted from Massion PP: Genomic alterations in lung cancer. In Pass HI, Carbone DP, Johnson DH [eds]: Lung Cancer Principles and Practice. Philadelphia, Lippincott Williams & Wilkins, 2005, p 89).

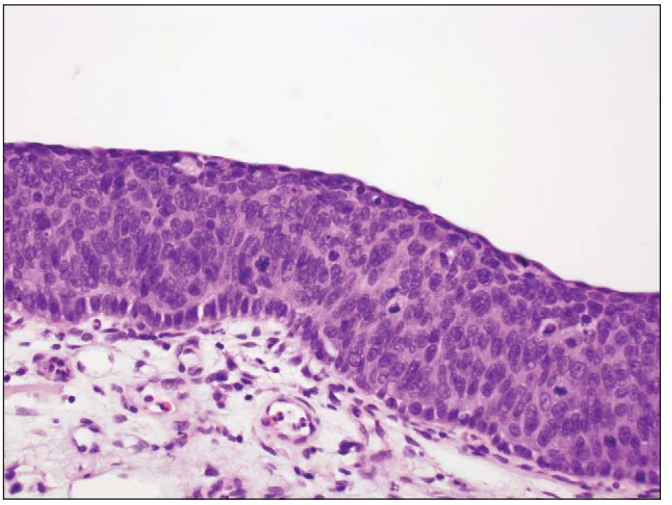


Figure 76-5 • Squamous cell carcinoma in situ. A full-thickness dysplastic squamous epithelium shows disordered cells with high nuclear-to-cytoplasmic ratio and numerous mitotic figures throughout the epithelium.

thelial thickness, cellular crowding and disorganization, and nuclear atypia.[96] Although these changes have been shown to be reproducible among expert lung pathologists, in practice, accurate grading may be hampered by specimen size, quality, and reactive lesions that may mimic dysplasia.[111,112] In general, molecular abnormalities increase with increasing morphologic dysplasia, but some low-grade or even normal epithelium can harbor many molecular abnormalities. In the future a combination of histology and molecular analysis might predict the lesions more likely to progress.[113]

Atypical Adenomatous Hyperplasia

Atypical adenomatous hyperplasia (AAH) is a small noninvasive lesion (usually less than 5 mm) consisting of atypical cells lining the alveoli in the absence of an underlying inflammatory process (Fig. 76-6). These lesions are thought be a precursor lesion to adenocarcinomas of the lung, a theory supported by the detection of molecular abnormalities within AAH similar to those found in adenocarcinomas. AAH is usually an incidental lesion, found either in lung tumor resection specimens or on radiographic imaging.[96] Because these lesions (along with bronchioloalveolar carcinoma) preserve the underlying lung architecture and alveolar spaces, they may appear as "ground-glass opacities" radiographically.[114] Although most often associated with adenocarcinomas of the lung, AAH has also been identified in conjunction with large cell carcinomas, squamous cell carcinomas, and metastatic tumors.[96]

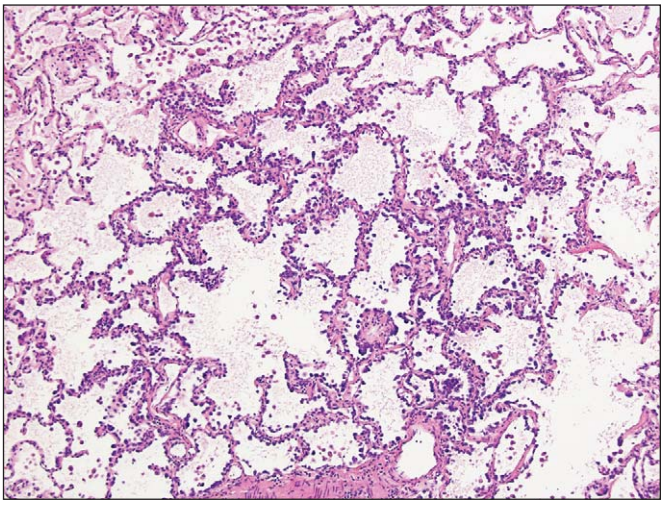


Figure 76-6 • Atypical adenomatous hyperplasia. An area of intact alveolar walls is lined by irregularly spaced enlarged atypical alveolar cells with hyperchromatic nuclei.

AAH differs from BAC in size and in degree of atypia. On a review of tumors identified through spiral CT screening studies performed by the Early Lung Cancer Action Project (ELCAP), a panel of expert lung cancer pathologists identified foci of AAH in roughly 25% of specimens (17 of 65). Six cases originally submitted as AAH (all less than 5 mm) were subsequently determined to be either BAC or invasive carcinoma by the ELCAP review panel based on the degree of atypia or presence of invasion.[115] Thus, it would appear that strict adherence to WHO criteria and additional experience will help to improve consistency in classification of these lesions.

Evaluation of AAH by cytology is difficult, because the atypia is less than that of carcinoma (mimicking many reactive lesions), and is similar to assessment of BAC, in that assessment of the architecture necessary for the diagnosis cannot be performed on a cytologic specimen.

Squamous Cell Carcinoma

Squamous cell carcinoma (Fig. 76-7), which tends to occur centrally and is highly associated with smoking history, is defined as a malignancy showing squamous differentiation. As such, the tumor cells classically contain intercellular bridges and form keratin, although these features may be difficult to identify in poorly differentiated tumors. Histologically, the most common pattern is that of infiltrating nests of malignant squamous cells (Fig. 76-7A), with central necrosis, often resulting in a central cavitation. Several important variants are described, including a papillary pattern (Fig. 76-7C) that can present as an exophytic and endobronchial growth,[116] and a basaloid variant (Fig. 76-7D) that can mimic other basaloid or neuroendocrine tumors histologically.[117] On cytologic evaluation intercellular bridges are not usually identified, but keratin can be clearly seen when present. In addition, the tumor tends to consist of sheets of cells rather than the three-dimensional groups of cells characteristic of adenocarcinomas (Fig. 76-7B).

Squamous cell carcinomas of the lung are morphologically identical to extrapulmonary squamous cell carcinomas; moreover, immunohistochemistry does not clearly distinguish primary from metastatic tumors. Differentiating a primary from metastatic squamous cell carcinoma requires clinical correlation. In rare cases in which the invasive tumor is clearly associated with a squamous cell CIS component or squamous dysplasia, a primary tumor is highly likely. The differential diagnosis of squamous cell carcinoma of the lung includes reactive processes that may result in squamous metaplasia with reactive atypia such as that observed with infection or radiation-induced injury. In these cases, clinical correlation is also essential.

Adenocarcinoma

In North America and Japan, adenocarcinoma is the most common histologic type of lung cancer. As true of other histologies, adenocarcinomas occur predominantly in smokers, although nonsmokers are more likely to develop adenocarcinoma than other lung cancer types. Adenocarcinomas tend to occur more peripherally, but can occur almost anywhere, can be multifocal, or fill an entire lobe. Radiographically they are associated with solid opacities, ground-glass opacities, or mixed patterns, generally correlating with the amount of in situ and invasive components of the tumor.[114,118] On tissue sections the diagnosis is made based on presence of glands (acini), papillary structures, bronchioloalveolar pattern, cellular mucin, or solid pattern if poorly differentiated[96] (Fig. 76-8A–C). A mixture of at least two of these patterns occurs in 80% of adenocarcinomas,[119]

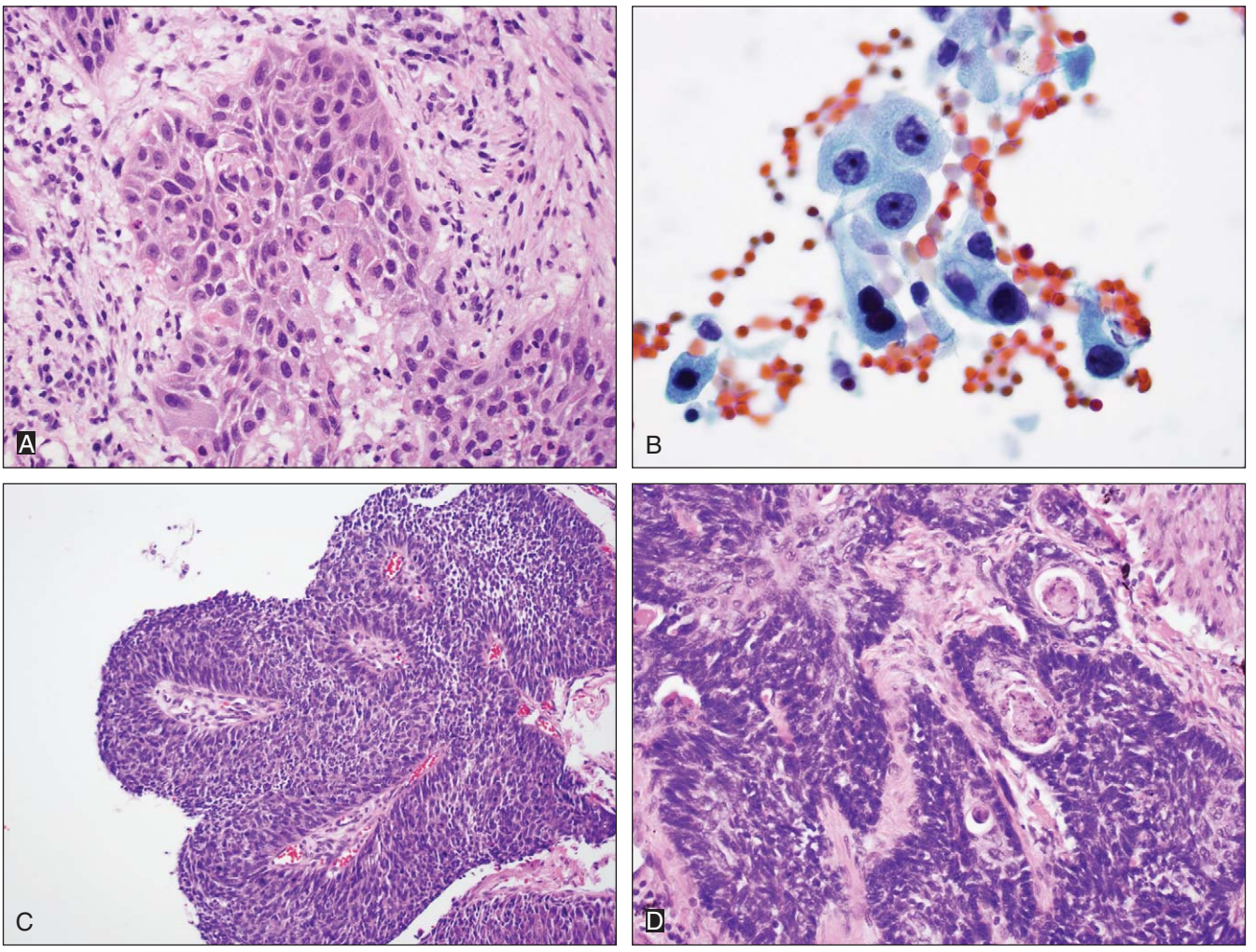


Figure 76-7 • Squamous cell carcinoma. **A,** Histologically, nests of invasive squamous cell carcinoma invade into a fibrous stroma. The tumor cells show an eosinophilic keratinized cytoplasm and intercellular bridges. **B,** Cytologically (Papanicolaou stain), there are malignant squamous cells in clusters with irregular nuclear shape and nuclear chromatin, and abundant "hard" (keratinized) cytoplasm. **C,** The papillary variant of squamous cell carcinoma is an exophytic papillary lesion composed of a malignant squamous epithelium. **D,** The basaloid variant of squamous cell carcinoma consists of invasive nests of basaloid cells demonstrating palisading of tumor nuclei at the periphery and keratinization toward the center of the nests.

and many mixed adenocarcinomas (>20%) show a focal BAC pattern.[115,120] Of these patterns, the solid and micropapillary patterns in adenocarcinomas may predict a worse prognosis.[121–127] On cytologic preparations, three-dimensional groups or glandular and papillary patterns may be identified and are diagnostic of adenocarcinoma (Fig. 76-8D). Variants of adenocarcinomas include signet ring, clear cell, mucinous, and fetal adenocarcinomas. The former three are primarily descriptive, whereas the latter is a distinct but rare tumor occurring in younger smoking patients in the fourth decade and is associated with a better prognosis.[128]

Bronchioloalveolar Carcinoma

Only those adenocarcinomas that show a pure noninvasive bronchioloalveolar pattern are diagnostic of BAC as defined by the WHO[95,96] (Fig. 76-8B). This definition arose out of studies showing that noninvasive tumors less than 3 cm resulted in a 100% 5-year patient survival;[129] in addition, tumors with limited fibrosis, smaller size, and limited invasion have a better prognosis.[129–132] Minimally invasive tumors, though not defined as BAC in the strictest sense, may nonetheless experience an excellent prognosis.[114] BAC is classified as mucinous, nonmucinous (most common), or mixed. Mucinous BACs are more likely to present as multifocal tumors or a lobar consolidation[96] and to show molecular and immunohistochemical features not seen in the nonmucinous type.[133,134]

Cytologically, bronchioloalveolar patterns may be suggested,[135] (Fig. 76-8E), but BAC cannot be definitively diagnosed without evaluation of the tissue architecture necessary to rule out an invasive component. The same is true for small biopsies in which a bronchioloalveolar pattern is seen. Unless the entire lesion can be evaluated for invasion, the diagnosis can only be interpreted as adenocarcinoma with BAC pattern. Because this more strict diagnosis of BAC is fairly recent,[95] pathologists are still refining their interpretation of BAC pattern lesions. Many tumors clinically consistent with BAC may contain areas of microinvasion and subtle papillary patterns that may affect prognosis.[115,136]

The differential diagnosis of adenocarcinoma is broad and includes not only metastatic adenocarcinomas from other sites, but similar-appearing tumors such as mesothelioma. Clinical information including location of the tumor or tumors and history of prior malignancy is the most helpful in differentiating primary from metastatic tumor, but immunohistochemical stains may help narrow the differential

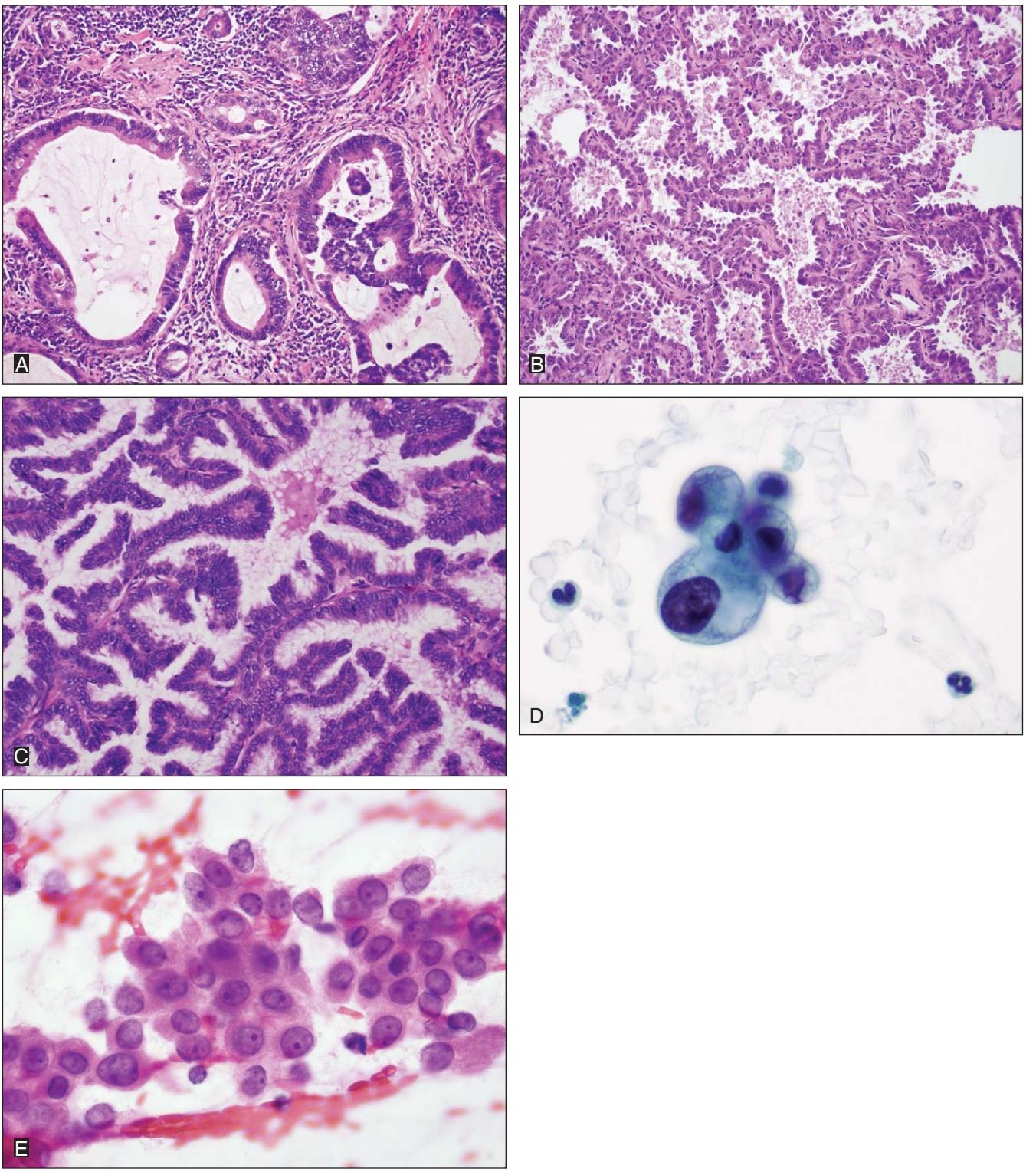


Figure 76-8 • Various patterns of adenocarcinoma. **A,** The acinar (glandular) pattern shows malignant glandular structures invading a fibrous stroma. **B,** The bronchioloalveolar pattern can be pure, as seen in bronchioloalveolar carcinoma (BAC), or mixed with other patterns of adenocarcinoma. It consists of malignant epithelial cells lining alveolar walls without invasion. **C,** Papillary adenocarcinoma shows papillary structures with fibrovascular cores and loss of the underlying alveolar architecture. **D,** Adenocarcinoma by cytology (Papanicolaou stain) shows three-dimensional clusters of malignant cells with vacuolated cytoplasm. **E,** By cytology (H&E stain), the diagnosis of BAC is not definitive but may be suggested by flattened clusters of bland tumor cells with nuclear grooves or inclusions.

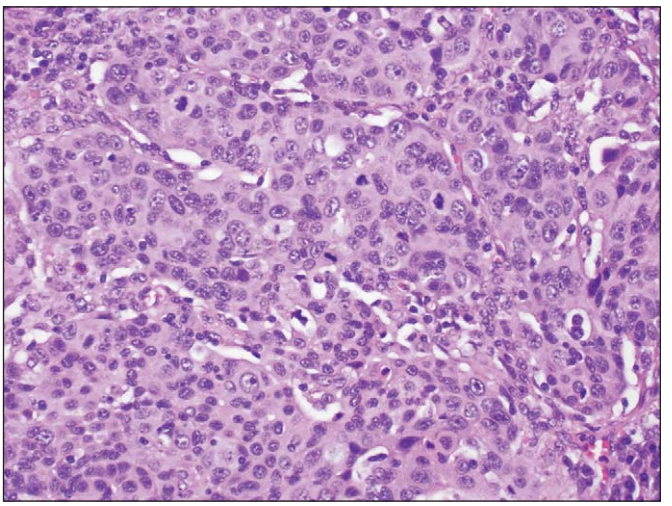


Figure 76-9 • Large cell carcinoma consists of sheets of undifferentiated cells without glandular or squamous differentiation. Prominent nucleoli are seen.

diagnosis when a metastatic lesion is suspected (see the immunohistochemistry discussion that follows).

Large Cell Carcinoma

Large cell carcinomas compose fewer than 10% of lung carcinomas, tend to occur peripherally, and are defined as poorly differentiated carcinomas of the lung composed of larger malignant cells without evidence of squamous, glandular differentiation, or features of small cell carcinoma by light microscopy (Fig. 76-9).[96] These tumors usually consist of sheets of large malignant cells, often with associated necrosis. Cytologically, the tumor is also arranged in syncytial groups and single cells, again without evidence of squamous, glandular, papillary, or features of small cell carcinoma. By electron microscopy, large cell carcinoma may show some evidence of glandular, squamous, or neuroendocrine differentiation, whereas others show none of these.[137] Variants of large cell carcinoma include basaloid carcinoma, which may present as an endobronchial lesion and may resemble a high-grade neuroendocrine tumor, and lymphoepithelioma-like carcinoma, which is similar to the same-named tumor of other sites and is associated with Epstein-Barr virus infection.

Large Cell Neuroendocrine Carcinoma

Large cell neuroendocrine carcinoma (LCNEC) is a subtype of large cell carcinoma that shows neuroendocrine differentiation by light microscopy and accounts for approximately 3% of lung cancers; it is included in the differential diagnosis of neuroendocrine lung tumors (see later discussion). LCNEC is a high-grade carcinoma showing neuroendocrine patterns (formation of rosettes, trabeculae, organoid nests, or perilobular palisading patterns), greater than 10 mitoses per 2 mm^2, and positivity with neuroendocrine markers.[96] LCNEC may be difficult to diagnose cytologically and may be difficult to differentiate from a small cell carcinoma. Cytologic features include evidence of neuroendocrine differentiation (sheets or groups of cells with peripheral palisading or rosette formation, nuclear molding, or immunohistochemical staining with neuroendocrine markers), as seen in other neuroendocrine tumors, but unlike small cell carcinoma, these tumors tend to have larger cells with prominent nucleoli.[96,138–140] LCNEC is an aggressive tumor and shares several molecular abnormalities with small cell carcinoma. The prognosis for these tumors is intermediate between other non-small cell carcinomas and small cell carcinoma.

Small Cell Carcinoma

Small cell carcinoma is a poorly differentiated neuroendocrine tumor that tends to occur centrally and is highly associated with smoking. Incidence rates of small cell carcinoma are higher among men than women,[16] but a higher percentage of lung cancers are of small cell origin among women than men.[141] Small cell carcinoma consists of smaller but obviously malignant cells with little cytoplasm, characteristic finely granular ("salt and pepper") chromatin without prominent nucleoli, and greater than 10 mitoses per 2 mm^2 (Fig. 76-10A).[96] The tumor cells may be arranged in sheets or may show neuroendocrine patterns such as rosettes, trabeculae, or peripheral palisading of cells at the periphery of nests. Often there is necrosis and crushing of tumor cells. The cells are defined as "small," meaning fewer than 21 μm in diameter; however, variation in size is common in these tumors, and the nuclear features are the more characteristic finding,[142] including characteristic "molding" of tumor nuclei.[143,144] The characteristic cytologic features are usually easily identified in well-

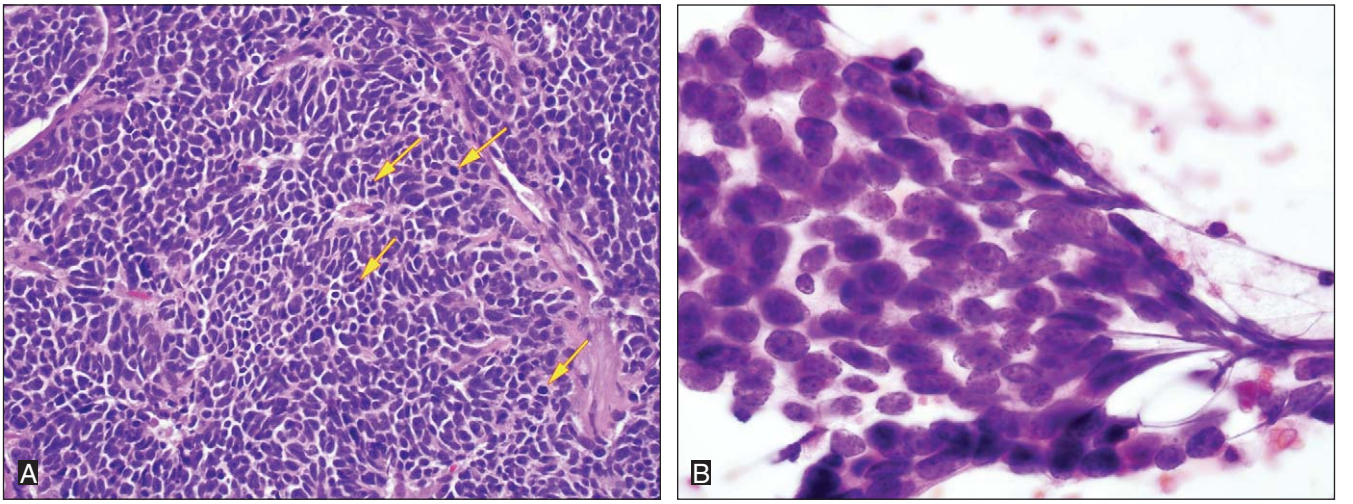


Figure 76-10 • Small cell carcinoma. **A,** A resected small cell carcinoma shows well-preserved tumor cells with little cytoplasm, nuclear molding, and numerous mitotic figures (*arrows*). Note the lack of nucleoli. **B,** By cytology (H&E stain) the nuclear features ("salt and pepper" chromatin pattern), scant cytoplasm, nuclear molding, and crushing of cells in this small cell carcinoma are also evident.

preserved cytologic specimens, but they may be more difficult to differentiate from other round blue cell tumors on ThinPrep cytology[144] or on less well-preserved specimens or small specimens (Fig. 76-10B).[100] As with other histologic types of lung carcinoma, small cell carcinoma may occur alone or combined with other tumors. Combined small cell with LCNEC, large cell carcinoma, adenocarcinoma, and squamous cell carcinoma have all been well documented. The differential diagnosis of small cell carcinoma includes poorly differentiated non-small cell carcinomas and neuroendocrine carcinomas, especially poorly differentiated squamous cell carcinoma and LCNEC, as well as nonepithelial tumors such as lymphoma, small round blue cell tumors, and some sarcomas (e.g., synovial sarcoma).

Typical Carcinoid Tumor

Typical carcinoid tumor is a low-grade neuroendocrine tumor showing tumor cells arranged in organoid nests, trabeculae, or spindled patterns characteristic of neuroendocrine differentiation, but is differentiated from other tumors by its bland uniform cells, lack of necrosis, and no significant mitotic activity (fewer than 2 mitoses per 2 mm^2). Typical carcinoid tumor occurs in nonsmokers, most often as an endobronchial lesion, but can occur more peripherally. Cytologic specimens show uniform low-grade cells with finely stippled ("salt and pepper") chromatin. Although these tumors are known for their excellent prognosis, as many as 10% to 15% can have metastases at diagnosis.[96] A *carcinoid tumorlet* is defined as a carcinoid tumor measuring less than 5 mm. Although tumorlets are usually an incidental finding, tumorlets can be associated with other tumorlets, carcinoid tumors, or neuroendocrine hyperplasia of the bronchial epithelium.[96]

Atypical Carcinoid Tumor

Atypical carcinoid tumor shows neuroendocrine morphology similar to the typical carcinoids, but is a slightly more aggressive tumor, with mitoses in the range of 2 to 10 per 2 mm^2 and higher risk of metastasis (as high as 50% lymph node metastasis at presentation).[96] Cytologically, atypical carcinoids have a similar appearance to typical carcinoids, although tumor cells may show more atypia and nuclear enlargement.[96]

Differential Diagnosis of Neuroendocrine Tumors of the Lung

Neuroendocrine tumors of the lung include a wide variety of lesions from the very bland to the most aggressive pulmonary neoplasms. The four main neuroendocrine tumors of the lung are carcinoid tumor, atypical carcinoid tumor, LCNEC (a type of large cell carcinoma), and small cell carcinoma (Fig. 76-11). In general it is helpful to think of these tumors according to clinical or behavioral characteristics. Carcinoid tumor and atypical carcinoid tumors are less associated with smoking history, tend to occur in younger patients, and are less aggressive, whereas small cell carcinoma and large cell neuroendocrine carcinoma occur in smokers and behave much more aggressively. Differentiating these tumors from one another histologically is usually straightforward based on morphologic features. In some cases, however, there can be overlap in the morphologic features. The WHO classification of these tumors emphasizes mitotic count in differentiating these tumors, and in fact, these criteria are used to define these tumors (Table 76-2). This approach is usually straightforward unless the tissue available is small or in the case of a cytologic specimen. Immunohistochemistry may be performed to support or verify the neuroendocrine nature of the tumor and thus differentiate neuroendocrine tumors from other non-small cell carcinomas.[138]

Immunohistochemistry

The diagnosis of lung cancer most often rests on the morphologic or cytologic features correlated with clinical and radiographic findings. Immunohistochemistry may be used to verify neuroendocrine differentiation within a tumor, or in differentiating primary from metastatic tumor. A summary of commonly used immunohistochemical stains is shown in Table 76-3.[96,117,119,134,138,145–151]

Neuroendocrine markers include neuron-specific enolase, CD56 or neural cell adhesion molecule, synaptophysin, chromogranin, and Leu7. Most often a combination of these stains (e.g., CD56, synaptophysin, and chromogranin) is used to establish a diagnosis.[119] These markers support neuroendocrine differentiation but do not distinguish between specific types of neuroendocrine tumors.

Immunohistochemistry is also helpful in distinguishing primary lung tumors from malignancies metastatic to the lung. This is especially true for distinguishing primary lung adenocarcinomas and metastatic adenocarcinomas. Thyroid transcription factor-1 (TTF-1), identified in tumors of thyroid and pulmonary origin, tests positive in over 70% of pulmonary adenocarcinomas.[151] When present, TTF-1 is a reliable indicator of a primary lung cancer provided a thyroid primary has been excluded. A negative test for TTF-1 does not exclude the possibility of a lung primary, however. Interestingly, TTF-1 also tests positive in neuroendocrine tumors of pulmonary and extrapulmonary origin.[138,146,152,153] Thus, TTF-1 is often used in combination with other immunohistochemical stains to differentiate among various diagnostic possibilities. Individually, TTF-1 and many neuroendocrine markers can show some immunohistochemical positivity in both small cell and non-small cell carcinomas, and have not been shown to be prognostically significant.[154] Cytokeratins 7 and 20, used in combination, also assist in categorizing certain tumors. These stains are not specific for a particular site of origin but can narrow the differential diagnosis.

Although mesothelioma can be easily identified ultrastructurally, it has historically been difficult to differentiate from adenocarcinoma through morphology and immunohistochemical staining. Several markers in the last few years have proven to be more helpful, including CK5/6, calretinin, and Wilms' tumor gene-1,[96] all of which show positivity in mesothelioma.

Molecular Alterations Associated with Lung Cancer Subtypes

The molecular alterations found in lung cancer are varied and not entirely specific to histologic subtype. However, there are molecular abnormalities that are more commonly associated with certain histologies. Examples of a few of the more commonly identified changes are summarized (Table 76-4).[96,148,155–158] Thus far these findings have been of limited value in diagnosis and classification of lung cancer type, but future uses may include lung cancer screening, identifying markers for chemoprevention, and predicting prognosis.[155,157,159] One of the more clinically significant molecular discoveries in the last few years is mutations of the EGFR gene, which were identified in adenocarcinomas of patients showing a response to treatment with TKIs.[55,57] Response to treatment is often associated with the presence of the mutation, and *EGFR* mutations are associated with female gender, nonsmoking status, and adenocarcinoma histology.[57,62] Interestingly, some responders without this mutation have also shown a response.[160] Thus far *EGFR* mutations have been identified in adenocarcinomas of the lung, most often of mixed type with a focal bronchioloalveolar pattern.[161–167] *EGFR* mutations have also been found in AAH but are rare.[167] There is some suggestion that *EGFR* gene amplification by fluorescence in situ hybridization (FISH) or immunohistochemistry may be predictive of response,[168,169] and some agreement between presence of mutation and FISH copy number,[169] and FISH positivity with overexpression by immunohistochemistry.[170,171] However, further study will be needed to determine what

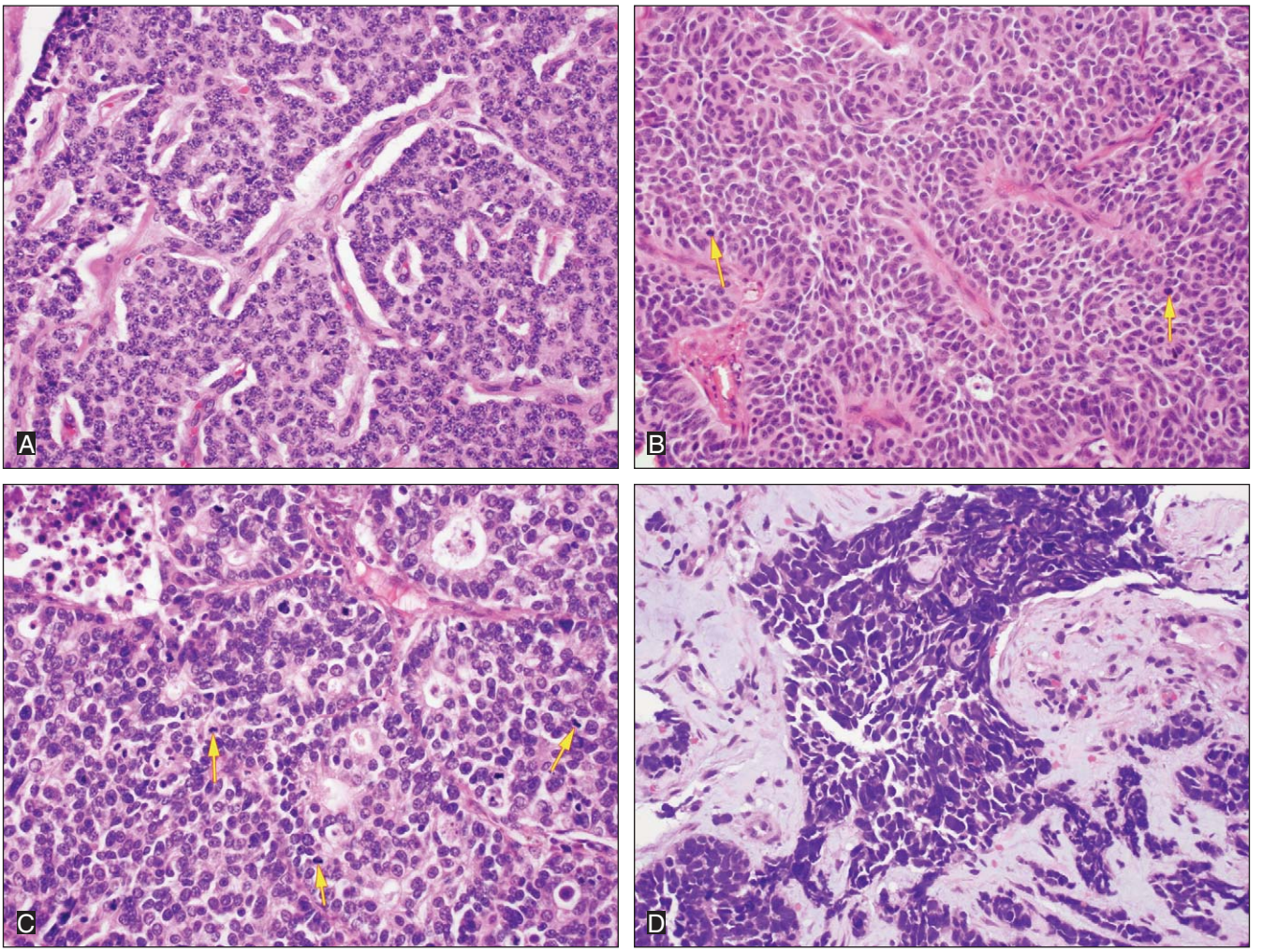


Figure 76-11 • Neuroendocrine tumors of the lung. **A,** A typical carcinoid tumor shows a subtle organoid and trabecular pattern of growth. The tumor cells are uniform with round nuclei showing a neuroendocrine ("salt and pepper") chromatin pattern. No mitoses are identified. **B,** An atypical carcinoid tumor is arranged in sheets with focal palisading of tumor cells, relatively bland neuroendocrine nuclei, and only a few scattered mitoses (*arrows*). **C,** A large cell neuroendocrine carcinoma is arranged in organoid nests and rosettes. Tumor cell nucleoli, necrosis, and abundant mitoses (*arrows*) are readily identified. **D,** A small cell carcinoma shows prominent molding and crushing on a transbronchial biopsy.

Table 76-2 General Histologic Features of Neuroendocrine Tumors

Diagnosis	Morphology	Mitotic Count (per mm^2)
Typical carcinoid tumor	Generally bland neuroendocrine morphology	<2
Atypical carcinoid tumor	Generally bland neuroendocrine morphology with or without focal necrosis	2–10
Large cell neuroendocrine carcinoma	High-grade neuroendocrine carcinoma—larger cells with nucleoli	>10
Small cell carcinoma	High-grade neuroendocrine carcinoma—smaller cells and few nucleoli	>10

Table 76-3 Common Immunohistochemical Markers Used in the Diagnosis of Lung Tumors

Diagnosis	Positive Immunohistochemical Markers
Squamous cell carcinoma	Cytokeratin (CK) cocktail (e.g., AE1/AE3)
	CK5/6
	CK7 rare
Adenocarcinoma including bronchioloalveolar carcinoma, nonmucinous	CK cocktail (e.g. AE1/AE3)
	CK7
	TTF-1
	Neuroendocrine markers rare, e.g., CD56, NSE
Bronchioloalveolar carcinoma, mucinous	CK cocktail (e.g., AE1/AE3)
	CK7
	CK20
	TTF-1 rare
Large cell carcinoma	CK
	TTF-1 rare
	Neuroendocrine markers rare (e.g., CD56, NSE)
Large cell neuroendocrine carcinoma	CK cocktail (e.g., AE1/AE3)
	TTF-1
	CD56
	Chromogranin
	Synaptophysin
Small cell carcinoma	CK cocktail (tends to be patchy)
	TTF-1
	CD56
	Chromogranin
	Synaptophysin
Carcinoid tumor	CK cocktail (e.g., AE1/AE3)
	TTF-1 (weaker than high-grade neuroendocrine tumors)
	CD56
	Chromogranin
	Synaptophysin
Atypical carcinoid tumor	CK cocktail (tends to be patchy)
	TTF-1
	CD56
	Chromogranin
	Synaptophysin
Common differential diagnoses	
Colonic adenocarcinoma	$CK20^+/CK7^-$
Breast, biliary, upper GI adenocarcinoma	$CK7^+/CK20^-$
Urothelial carcinoma	$CK7^+/CK20^+$
Prostatic adenocarcinoma	$CK7^-/CK20^-$
Mesothelioma	Calretinin, WT-1
Malignant melanoma	S-100, HMB-45, Melan-A

GI, gastrointestinal.

Table 76-4 Examples of Common Molecular Alterations in Lung Tumors

Diagnosis	Common Molecular Alterations
Squamous preneoplasia	LOH: 3p, 9p21, 8p21–p23, aneuploidy, methylation
Atypical adenomatous hyperplasia	LOH: 3p, 9p
	Aneuploidy
	K-*ras* codon 12 mutation
Adenocarcinoma	*TP53* mutation
	CDKN2A mutation/inactivation
	K-*ras* (42%) mutation; smokers more common
	EGFR overexpression (40%)
	EGFR mutation
	Her2/neu, COX-2 overexpression
Squamous cell carcinoma	*TP53* mutation
	CDKN2A inactivation
	Allelic loss 3p
	EGFR overexpression (80%)
Large cell carcinoma	K-*ras*, *TP53*, loss *CDKN2A*
Large cell neuroendocrine carcinoma	p53
	BCL-2 overexpression
	Rb mutation
	3p21, FHIT, 3p22–p24, 5q21, 9p21
Small cell carcinoma	Rb mutation (≥80%)
	TP53 mutation (50% to 80%)
	BCL-2 expression
	3p21, FHIT, 3p22–p24, 5q21, 9p21

EGFR, epidermal growth factor receptor; LOH, loss of heterozygosity; Rb, retinoblastoma.

combination of testing will be predictive of response to TKIs or prognosis.[172,173]

EARLY DETECTION AND SCREENING

Early detection is a process that involves screening tests, surveillance, and diagnosis and also implies early treatment,[174] whereas screening is defined as the systematic testing of asymptomatic individuals for preclinical disease.[175] The purpose of screening is to prevent or delay the development of advanced disease in patients with preclinical disease through early detection and treatment. Screening presumes that a test or series of tests will identify asymptomatic persons at risk for a specific disease and that a positive result leads to further testing to establish definitively the presence or absence of disease.[175] The monitoring of these subjects (surveillance) intends to detect the disease early and to treat it early. Under ideal circumstances, early intervention should change the course of the disease once the diagnosis is established, resulting in a decrease in disease-related mortality (the number of disease-specific deaths relative to the total number of persons evaluated). In addition, screening should apply to large populations that would benefit from early detection (therefore with chance of survival greater than 5 years). Finally, screening should cause no harm and be cost effective.[176]

Previous lung cancer screening efforts using periodic chest radiographs coupled with regular assessment of sputum cytology failed to

demonstrate a decrease in lung cancer-related mortality.[177–180] Details of these trials have been extensively reviewed elsewhere.[181] Ironically, more lung cancers were diagnosed in the screening arms of these trials. The lung cancers identified in the screened population were often found at very early stages, allowing more patients in the screened arms to go to definitive surgery. Nonetheless, there was not an improvement in *lung cancer-related mortality*, which is considered a requirement to validate potential screening methods.[181] Several hypotheses have been advanced to explain the findings including flawed trial design, lead-time bias, length time bias, and overdiagnosis bias.[182,183] Briefly, these biases can be defined as follows: *lead-time bias* implies that earlier detection could result in longer survival from the time of diagnosis even if death is not delayed. *Length time bias* occurs when screening examination detects slow-growing cancers. In other words, the slower the growth of the neoplasm, the longer it is present without symptoms and the greater the likelihood of detection. *Overdiagnosis* bias refers to the phenomenon of detecting a lung cancer that would otherwise have remained subclinical before death from other causes. Overdiagnosis is of particular concern in lung cancer screening, because newer screening modalities can identify small nodules of unknown clinical significance. Mayo Clinic investigators found a persistence of excess lung cancer cases in the intervention arm of their original screening after an additional 16 years of follow-up,[183] providing continued support for overdiagnosis in lung cancer screening.

Thus far there is no screening procedure recommended for individuals "at risk" for lung cancer. In 2004 the U.S. Preventive Services Task Force concluded that there is insufficient evidence to recommend screening for lung cancer in asymptomatic individuals at risk for lung cancer (http://www.ahrq.gov/clinic/uspstf/uspslung.htm). Although it is assumed that the higher the risk of cancer the more useful the surveillance program, the field also lacks clear guidelines for the surveillance of "high-risk" individuals. Perhaps the greatest challenge is defining the optimal population to be screened—the population that could best benefit from lung cancer screening.[184] Entry criteria to lung cancer screening trials are still debated and no one has ever shown efficacy of surveillance program for lung cancer. Moreover, the challenges of large population screening programs are considerable and include the potential for diagnostic errors (i.e., false positives) related to pulmonary scarring from smoking or prior infection, areas of inflammation, or other noncancerous conditions as well as the anxiety experienced by the participant, the potential for unnecessary biopsy, surgery or both as well as repeated radiation exposure. Although the amount of radiation exposure engendered by a low-dose spiral CT scan is relatively modest (roughly equal to 10 chest radiographs or one tenth that experienced with a regular chest CT scan), it is not an insignificant issue.[185,186]

High-Risk Population, a Susceptible Subgroup

As noted, a challenging problem in screening for lung cancer is the definition of a "high-risk" population—the population that could best benefit from lung cancer screening.[184] Individuals "at risk" include current and former smokers, those with specific various occupational exposures (e.g., asbestos; see section on Epidemiology), the presence of airflow obstruction, a family history of lung cancer, older individuals, and those with a prior history of a cancer of the aerodigestive tract. Individuals who smoke bathe their entire aerodigestive tract with multiple carcinogens, and it is therefore not surprising that this population experiences a high rate of second primary tumors, estimated to be between 1% and 4% per patient per year.[187–189] However, mere recognition of these features is not sufficient to identify "high-risk" individuals. For example, although smoking is an obvious risk for lung cancer—the cumulative risk of dying from lung cancer for a lifelong smoker is estimated to be approximately 16% in men and approximately 10% in women[31]—the risk of developing lung cancer varies greatly among individual current and former smokers.[190] For example, in the Carotene and Retinol Efficacy Trial, a large, randomized trial of lung cancer prevention, the 10-year cancer risk among current and former smokers ranged from less than 1% to 15%.[190] An example of an individual with a relatively low risk of developing lung cancer would be a 51-year-old woman who smoked one pack per day for 28 years and quit 9 years earlier. By contrast, a 68-year-old man who had smoked two packs per day for 50 years and continued to smoke might have a 15% risk of lung cancer.[190] Both of these individuals would be potentially eligible for screening, and yet the "payoff" would be quite different. This suggests that an accurate risk prediction model may facilitate greatly the admission of subjects in screening (or chemoprevention) trials.[190]

Cytologic atypia in sputum samples reflect the abnormalities that develop in the bronchial epithelium. Moreover, the presence of cytologic atypia has been shown to predict lung cancer risk.[191] The presence of moderate dysplasia or worse cytologic atypia is associated with a increased risk of developing lung cancer in a cohort of heavy smokers with airflow obstruction (adjusted hazards ratio of 2.8).[192] This translates into a cumulative lung cancer incidence of 10% at 3 years and 20% at 6 years. Given the limitations of cytologic evaluation of sputum samples, however, the study of molecular abnormalities in the sputum (e.g., methylation patterns of specific genes involved in lung cancer progression, cytogenetic alterations) may strengthen the assessment of risk for lung cancer in this population.

Molecular epidemiology may be used to identify patients at risk for developing lung cancer through the identification of specific genes, single-nucleotide polymorphisms, or other genetic traits associated with increased susceptibility for lung cancer.[193] Although many genotypes show increased risk (relatively low odds ratios) with lung cancer (e.g., *CYP2A6*, thymidylate synthase, *GSTM1*, *XPA*), their large number and low penetrance make targeted intervention extremely challenging. Assessing genetic susceptibility for lung cancer may allow the identification of susceptible subgroups most likely to represent ideal candidates for early detection. Although autosomal dominant genes have not been found in association with family history of lung cancer, there is epidemiologic evidence demonstrating a 2.5 times increased risk in patients with a family history of lung cancer after controlling for smoking.[194] A recent genomic locus on chromosome 6q23–q25 was identified as a locus of susceptibility with a maximum heterogeneity LOD score of 2.79, 3.47, and 4.26 for families with three, four, or five or more affected individuals.[51] Further complicating the picture is the role of the environment in modifying these specific genes and the interaction of genes between each other and evidence to support a genetic predisposition to smoking addiction.[195,196] If markers of these genetic predispositions can be firmly established, intensive intervention to alter risk factors in these selected populations may alter their clinical outcome.

Imaging Approach

The last decade has witnessed a marked improvement in technology allowing for faster, higher resolution imaging of the chest. The CT scanner first became available in the 1970s but was impractical for screening because of its slow speed and radiation exposure. In the mid-1990s low-dose scanners capable of imaging the chest in less than 15 sec using radiation doses equivalent to 10 radiographs became available, opening the door to their potential use for screening.[197] Moreover, new bronchoscopic methods also demonstrate promise for the detection of preinvasive lesions. Other imaging modalities such as PET scan are able to provide metabolic information on lesions and can be combined with CT scan to give detailed resolution.

Low-Dose Spiral Computed Tomography Scan

In recent years there has been a substantial increase in the use of spiral CT scans to screen for lung cancers in former and current smokers.[174,181] Spiral CT screening allows for a rapid and comprehensive evaluation of the lungs and is attractive because of its potential increased sensitivity, low radiation exposure, and potential cost effec-

Table 76-5 Results of Prevalence and Incidence Screens in Computed Tomography (CT) Screening Trials

Study	Year	No. of Patients Screened	No. of Abnormal CT Scans	Cancers Detected	Stage I Lesions
PREVALENCE CT					
Henschke et al[199]	1999	1,000	233	27 (2.7%)	81%
Sone et al[209]	2001	5,483	676	22 (0.4%)	100%
Swensen et al[210]	2002	1,520	782	22 (1.4%)	59%
Sobue et al[208]	2002	1,611	186	14 (0.9%)	77%
Pastorino et al[200]	2003	1,035	199	11 (1.1%)	55%
Henschke et al[205]	2006	31,567	4186	410 (1.3%)	85%
INCIDENCE CT					
Henschke et al[207]	2001	1,184	63	7 (0.6%)	85%
Sone et al[209]	2001	8,303	518	34 (0.4%)	100%
Swensen et al[210]	2002	1,464	191	3 (0.2%)	0%
Sobue et al[208]	2002	7,891	721	22 (0.3%)	82%
Pastorino et al[200]	2003	996	99	11 (1.1%)	100%
Henschke et al[205]	2006	27,456	1460	74 (0.3%)	86%

tiveness.[174] Many pilot studies using spiral CT scans to screen for lung cancers have shown that this technology can identify a higher percentage of early-stage lung cancer than can conventional imaging studies.[198–200] These results are summarized in Table 76-5 and discussed in detail elsewhere.[174,201,202] Lung cancer prevalence rates range between 0.4% and 2.7%, depending on the population screened. In general, these prevalence rates are significantly higher than that reported using conventional imaging studies. The mean diameter of screened detected cancers ranges between 14 and 21 mm. Incidence rates based on detection of new malignancies at annual repeat screening range from 0.07% to 1.1%.[174,203] Notably, as many as 85% of CT-screened detected lung cancers are clinical stage I lesions. By contrast, only 15% of lung cancers diagnosed through routine clinical care are found to be stage I.[204] Because stage I lung cancer is the most curable form of this disease, a high frequency of detection of stage I tumors is considered a necessary (though not sufficient) indication of a favorable screening outcome.[174] International Early Lung Cancer Action Program (IELCAP) investigators recently reported a 92% 10-year survival rate among screened detected clinical stage I lung cancer patients who underwent surgical resection within 1 month after diagnosis.[205] In a separate report, IELCAP investigators reported that the cancers identified by CT screening met standard criteria for full-fledged aggressive lung cancer.[115] Although these data are intriguing and encouraging, long-term follow-up of these patients will be very important to exclude lead-time bias (simply diagnosing the cancer earlier, but not altering its outcome) as a confounder for an improved survival and a reduced disease-related mortality.

A major challenge confronting advocates of CT screening is the high false-positive rate.[206] On initial screening of at-risk populations, false-positive rates range between 10% and 20% but can be as high as 50%.[207–210] Positive predictive values range from 2.8% to 11.6%.[207–210] False positives can have a substantial impact on patients through the expense and risk of unneeded further evaluation and emotional stress. False-positive rates and positive predictive values are somewhat improved in annual follow-up CT scans, but there is still significant room for improvement. Based on extant data it seems that nodules smaller than 5 mm are unlikely to be cancerous and those 5 to 10 mm in diameter (25% to 40% of noncalcified nodules detected) are of uncertain significance.[211] The management of these patients usually consists of repetitive CT scans over time to see if the nodules grow, attempted FNAs, or surgical resection. PET has limited usefulness in detection of lesions smaller than 1 cm and has proved to be of limited value in adenocarcinoma, particularly of bronchioloalveolar subtype.[212] Each of these is costly, and some have significant morbidity. The impact of waiting to assess nodule growth on patient outcome is also not clear but can only decrease curability. Even for patients with disease that is highly suspicious for lung cancer on clinical grounds, there is a 10% to 20% incidence of "futile thoracotomies" wherein the suspicious lesion is found to be benign, and thus, the patient unnecessarily incurred the morbidity and potential mortality of a thoracotomy.[213–215] Eliminating unnecessary surgery should be one of our priorities, although this may not be feasible without the development of other strategies of early detection.

To address many of these ongoing issues, the NCI initiated the National Lung Cancer Screening Trial (NLST). The NLST is a prospective comparison of spiral CT and standard chest radiograph in 50,000 current or ex-smokers between the ages of 55 and 74 years and is designed to determine the best strategy to reduce lung cancer-related mortality. The NCI estimates that the trial may produce results that could inform policy decisions as early as 2010 (http://www.nci.nih.gov/NLST). A similar study is continuing in Europe comparing CT scanning with standard of care among 20,000 subjects with history of heavy smoking.

Finally, CT scanning has also shown promise in the detection of some preinvasive lesions. High-resolution CT has proven to be sensitive enough to detect ground-glass opacities, some of which may represent inflammatory lesions, BAC, adenocarcinomas, or AAH. AAH is a presumed precursor lesion to adenocarcinoma.[216–219] Because adenocarcinoma is now the most common histologic type of lung cancer in the United States, there is some hope that CT may be able to improve survival for these patients by detecting a precursor lesion before its transformation to invasive carcinoma. Chest CT scanning, however, is not yet sensitive enough to detect preinvasive epithelial lesions of the bronchial tree with squamous differentiation, probable precursors of squamous carcinoma of the lung.

Positron Emission Tomography Scan

Many CT screening protocols now use PET scan as a method of reducing this high false-positive rate. PET scanning attempts to identify malignancy based on glucose metabolism by measuring the

uptake of [^{18}F]fluorodeoxyglucose (FDG). Lung cancers will preferentially take up FDG and appear as a "hot spot". Thus far PET has been used mostly for staging and detection of metastases in lung cancer[220,221] and in the diagnosis of nodules larger than 15 mm in diameter.[200,222] In combination with another imaging modality, PET may provide information about the metabolic state of lung nodules. Combined FDG PET-CT scan has been shown to improve the accuracy of staging in lung cancer compared with visual correlation of PET and CT or either study alone.[223] The added information gained from PET and combined PET-CT may help reduce the high false-positive rates seen in trials using CT alone. A trial of low-dose CT used in combination with PET scan of 1035 patients resulted in only 6 false positives, defined as a surgical biopsy of a benign nodule, out of 27 surgical biopsies of suspicious nodules.[200] There are important limitations to this study, however. First, lung nodules of 5 mm or less in size were followed, with repeat CT in 1 year, and no other intervention. Second, PET scanning was only performed on larger nodules (7 mm or larger). Typically, PET scan has not performed well in the identification of small nodules (<15 mm), so its usefulness in intermediate lesions remains in question, in particular in areas with high prevalence of pulmonary fungal infections.[224] There is no evidence of a survival benefit using PET scan as part of a screening protocol.

Other Imaging Techniques

Fluorescence endoscopy uses differences in the autofluorescence characteristics of normal and neoplastic epithelium to localize lesions. Fluorescence bronchoscopy has been shown to be more sensitive than white-light bronchoscopy in the detection of preneoplastic lesions in many studies, including a randomized trial.[225–228] The randomized trial demonstrated that the use of the laser-induced fluorescence endoscopy procedure resulted in a 46.9% absolute increase in the sensitivity of detecting moderate dysplasia in high-risk patients when compared with white light bronchoscopy, although specificity was worse.[225] Fluorescence bronchoscopy has not been proven as a validated method of early detection of lung cancer, but it is a very important research tool.

New imaging techniques are currently being developed to help improve not only the resolution of current imaging techniques but also to image lesions based on biologic activity. Both magnetic resonance and gamma camera techniques are being tested as molecular imaging tools.[229–231] Near-infrared Raman spectroscopy,[232] optical coherent tomography,[233] and confocal microscopy use optical differences within tissue to allow imaging of individual cell nuclei. This technology is being adapted for use during endoscopic examinations and may be able to provide real-time histologic evaluation of bronchial mucosa.

Blood Biomarkers for Lung Cancer

Although various serum biomarkers have been investigated in lung cancer, none has proved useful in general clinical practice, mainly because of the lack of sufficient sensitivity and specificity. For example, cytokeratin fragment antigen 21.1 (Cyfra-21.1), a marker of cytokeratin,[234–236] carcinoembryonic antigen,[235] and tissue polypeptide antigen[234] were found to have relatively poor sensitivity (31% to 64%) when specificity limits of 95% were set. In addition, most markers reach better sensitivity in advanced-disease stages as compared with stage I lung cancer. Thus, their use for early diagnosis or screening has not had an impact on patient care in the clinic. Blood-derived biomarkers used in combination with other clinical, imaging, or molecular tools might play an important role in early detection, in monitoring response to therapy, in risk assessment of recurrence, and in prognosis.

In conclusion, although no data are available from randomized trials, spiral CT of the chest and autofluorescence bronchoscopy offer excellent sensitivity to detect lung cancer at early stage, even during the preinvasive stage. The high sensitivity of these tests, however, is associated with a low specificity. Better selection of individuals at highest risk of lung cancer, using biomarkers of disease and of genetic susceptibility, may improve their positive predictive values, minimize the false-positive rates and associated unnecessary investigations or treatment, as well as reduce the cost of the early-detection process.

CLINICAL PRESENTATION AND STAGING OF LUNG CANCER

Presenting Signs and Symptoms

Symptoms, signs, and laboratory test abnormalities relating to lung cancer can be classified as those caused directly by the primary lesion, those related to intrathoracic spread or to distant metastasis, and those related to paraneoplastic syndromes.[237–239] The prototypical lung cancer patient is a current or former smoker of either gender, usually in the seventh decade of life, who presents with symptoms attributable to bulky intrathoracic disease (i.e., cough, dyspnea, chest pain, hoarseness, and/or hemoptysis) or distant metastases (e.g., bone pain, central nervous system symptoms, etc).[238,240] Constitutional symptoms may include weakness, anorexia, weight loss, and, rarely, fever.[238,240] Apart from the brevity of symptom duration, these parameters fail to clearly distinguish SCLC from NSCLC or even from neoplasms metastatic to the lungs.[241] Lung cancer arising in a individuals who have never smoked is more common in women and certain ethnic groups and tends to be an adenocarcinoma.[242–245] Such individuals also tend to be slightly younger than their smoking counterparts at the time of diagnosis.[242] However, the clinical presentation of lung cancer in those who have never smoked tends to mirror that of current and former smokers, even though lung cancers arising in lifelong nonsmokers seem to be biologically distinct as suggested by the differing molecular abnormalities found in tumors derived from smokers and nonsmokers.[244] The prognosis of lung cancer in lifelong nonsmokers is generally better compared with cancers in current or former smokers irrespective of stage.[35,242,246] The reason for the improved survival is unclear.

Cough, dyspnea, and chest discomfort are the most common presenting symptoms in lung cancer (Table 76-6).[237] A history of chronic cough with or without hemoptysis in a current or former smoker with COPD aged 40 years or older should prompt a thorough investigation for lung cancer even in the face of a normal chest radiogram.[237] A persistent "pneumonia" without constitutional symptoms and unresponsive to repeated courses of antibiotics also should prompt an evaluation for an underlying cause (e.g., an occult endobronchial lesion), especially if the individual is a current or former smoker. Less frequently individuals present with hemoptysis that rarely is massive and usually described as streaks of fresh or old blood in sputum. The spread of disease within the chest may result in hoarseness secondary to recurrent laryngeal nerve paralysis and less frequently phrenic nerve paralysis. The latter is associated with an elevated hemidiaphragm on standard chest radiogram. Chest wall involvement is commonly accompanied by pain that in turn may serve as a more accurate indicator of chest wall invasion than radiographic studies. Chest wall pain is usually related to either direct invasion of the pleura or chest wall by the primary tumor, or due to a rib metastasis. Tenderness may be elicited at the site of rib involvement and, rarely, a soft-tissue mass can be palpated.[237] The chest pain may have a pleuritic component if there is pleural involvement. The disappearance of pleuritic chest pain may signify the development of a pleural effusion that in turn may cause shortness of breath or worsen existing dyspnea. Venous distension of the neck and chest wall, cyanosis, facial plethora, and upper extremity edema may indicate obstruction of the superior vena cava, which today is most commonly seen with SCLC.[237,247] Although the heart and other mediastinal structures are often involved with tumor at postmortem examination, only rarely does this involvement serve as the source of a presenting symptom.

Approximately one third of patients present with symptoms as a result of distant metastases.[237] The most common sites of distant

Table 76-6 Presenting Sign and Symptoms of Lung Cancer

Symptoms and Signs	Range of Frequency (%)
Cough	8–75
Weight loss	0–68
Dyspnea	3–60
Chest pain	20–49
Hemoptysis	6–35
Bone pain	6–25
Clubbing	0–20
Fever	0–20
Weakness	0–10
Superior vena cava obstruction	0–4
Dysphagia	0–2
Wheezing and stridor	0–2

From Beckles MA, Spiro SG, Colice GL, Rudd RM: Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes. Chest 2003;123:97–104.

metastasis from lung cancer are the bones; liver, adrenal glands, and intra-abdominal lymph nodes; brain and spinal cord; and lymph nodes and skin. Lung cancer can metastasize to virtually any bone, with pain being the primary presenting symptom in as many as 25% of individuals at diagnosis.[237] Similarly, liver metastases are common at initial presentation in both SCLC and NSCLC. However, liver function test results are seldom abnormal until the metastases are numerous and large. Hepatic metastases most commonly produce symptoms of weakness and weight loss. Adrenal lesions, only rarely associated with adrenal insufficiency, and para-aortic lymph node metastases are most commonly seen with SCLC. Intracranial metastases at presentation are most commonly in SCLC and adenocarcinomas of the lung. Presenting symptoms may include headache, nausea and vomiting, focal neurologic symptoms or signs, seizures, confusion, and personality changes.

The stigmata of COPD in smokers may be the only findings on physical examination, or one may detect lymphadenopathy, hepatomegaly, bone tenderness, or abnormal neurologic findings. Digital clubbing and hypertrophic osteoarthropathy may be associated with any histologic subtype of lung cancer but are most frequently associated with squamous cell and adenocarcinoma and least likely to occur in a patient with small cell carcinoma.[237,248] Digital clubbing is more common than hypertrophic osteoarthropathy, which is characterized by painful symmetric arthropathy and periosteal new bone formation of the distal limbs. Its mechanism of development is unknown. In a published series of 111 consecutive lung cancer patients, clubbing was noted in 29% with an incidence of 35% in NSCLC and only 4% in SCLC.[248] As many as 20% of patients present with palpable lymphadenopathy in the supraclavicular fossa during the course of the disease. Subcutaneous metastases while rare may serve as a source of diagnostic material.

Paraneoplastic Disorders

Although many of the symptoms of NSCLC and SCLC are attributable to mass effect and direct impingement upon vital organs, less commonly individuals with lung cancer present with symptoms related to hypercalcemia,[249] hyponatremia,[241,250] Cushing's syndrome,[251] Lambert-Eaton syndrome, and other neurologic disorders.[252–254] These so-called paraneoplastic phenomena can be seen in any histologic type of lung cancer but are most frequently associated with SCLC. In general a majority of these paraneoplastic phenomena fall into endocrine or neurologic categories.[255–257]

Hypercalcemia

Hypercalcemia of malignancy (HCM) is the most common life-threatening metabolic complication of malignancy, affecting approximately 10% to 20% of patients with advanced cancer. Hypercalcemia may be associated with or due to production of a parathyroid hormone-related peptide.[249] The incidence of HCM varies widely by cancer type but occurs most frequently in patients with multiple myeloma and carcinomas of the lung, breast, kidney, and head and neck. With respect to lung cancer, squamous cell carcinoma is the most common histologic subtype. Clinical symptoms of HCM include nausea, vomiting, abdominal pain, constipation, polyuria and thirst, and altered mental status. HCM may lead to renal failure. The early symptoms of nausea, vomiting, and constipation may be easily confused with the initiation of narcotics for pain control. Management of HCM is covered in Chapter 48.

Hyponatremia and the Syndrome of Inappropriate Antidiuretic Hormone

The inappropriate secretion of antidiuretic hormone, or arginine vasopressin (AVP), with its resultant euvolemic, refractory, hypoosmolar hyponatremia, is observed in as many as 15% of individuals with SCLC.[250,258] However, as many as one third of patients with hyponatremia have no evidence of ectopic AVP production.[259] In such cases hyponatremia may be caused by ectopic production of atrial natriuretic peptide (ANP). SCLC is the most common malignant cause of acute or chronic syndrome of inappropriate secretion of antidiuretic hormone (SIADH).[260] The presence of SIADH does not correlate with clinical stage, distribution of metastatic sites, or patient gender, nor does SIADH influence response to chemotherapy or overall survival as an independent variable.[250] As with most paraneoplastic syndromes, the best therapy for SIADH is effective treatment of the underlying SCLC. SIADH typically resolves with 1 to 4 weeks of initiating chemotherapy in the vast majority of cases.[250] While awaiting the effects of chemotherapy, serum sodium can usually be managed and maintained above 128 mEq/L via strict fluid restriction alone.[261] Demeclocycline, which blocks the action of vasopressin at the level of the renal tubule, can be a useful adjunctive measure when fluid restriction alone is insufficient to restore sodium level.[262,263] The starting dose is 150 mg four times a day but may have to be increased to 1200 mg. Tolvaptan, an oral vasopressin V_2-receptor nonpeptide antagonist, also is effective in increasing serum sodium concentrations in patients with euvolemic and hypervolemic hyponatremia.[264] Notably, patients with ectopic ANP secretion do not respond to fluid restriction.[259] In fact, fluid restriction may actually worsen hyponatremia if sodium intake is not concomitantly increased. Accordingly, if hyponatremia fails to improve or worsens after 3 to 4 days of adequate fluid restriction, plasma concentrations of AVP and ANP should be measured to determine whether inappropriate secretion of ADH or ANP is the causative syndrome.[259]

Ectopic Adrenocorticotropic Hormone Production

Cushing's syndrome may be due to ectopic secretion of adrenocorticotropic hormone from a nonpituitary tumor resulting in bilateral adrenocortical hyperplasia and hypercortisolemia.[265] Neuroendocrine lung tumors including SCLC and pulmonary carcinoids account for approximately half of the cases of ectopic tumors producing adrenocorticotropic hormone.[251,266] Although hypercortisolemia has been documented in as many as 50% of SCLC cases, only 2% to 5% of SCLC patients have the characteristic clinical features of Cushing's syndrome.[251] Unlike Cushing's disease, the onset of symptoms in ectopic adrenocorticotropic hormone production is often abrupt because of the characteristic rapid growth of SCLC. Consequently the classical features of Cushing's disease—a buffalo hump, striae, and moon facies—are frequently absent. By contrast, hypokalemic alkalosis, hypertension, hyperglycemia, and, rarely, edema and muscle wasting are common.[251] The effect of Cushing's syndrome on survival is unclear, although some investigators hold that its onset heralds a

more aggressive tumor behavior.[251] Treatment with standard medications, such as metyrapone and ketoconazole, is largely ineffective due to extremely high cortisol levels.[267] Some patients require bilateral adrenalectomy to control symptoms.[265] The most effective strategy for management of the Cushing's syndrome is effective treatment of the underlying SCLC.[251]

Neurologic Paraneoplastic Syndromes

The paraneoplastic neurologic disorders are a diverse group of diseases characterized by the presence of neurologic dysfunction in the setting of a remote cancer.[256,257] They are often the result of production of antibodies that react with both the small cell cancer cells and with normal host tissue. Well-described syndromes include the Lambert-Eaton myasthenic syndrome, paraneoplastic encephalomyelitis and sensorimotor neuronopathy, and paraneoplastic cerebellar degeneration.[254,268] Less frequent abnormalities include subacute sensory neuropathy, autonomic disturbances, myelopathies, progressive encephalopathy, and visual paraneoplastic syndromes.[253,256,269]

Lambert-Eaton myasthenic syndrome is caused by autoantibodies directed against presynaptic voltage-gated P/Q calcium channels.[254,268] The P/Q calcium channel autoantibodies decreases calcium entry into the presynaptic terminal, which prevents binding of vesicles to the presynaptic membrane and acetylcholine release. Individuals with this disorder present with proximal muscle weakness, usually in the lower extremities, occasional autonomic dysfunction, and rarely with cranial nerve symptoms or involvement of the bulbar or respiratory muscles. Depressed deep tendon reflexes are frequently present. As contrasted to individuals with myasthenia gravis, strength improves with serial effort. The diagnosis is confirmed by electrophysiologic testing, which demonstrates small compound muscle action potentials and facilitation with exercise or 20-Hz repetitive stimulation. A serum test for voltage-gated calcium channel antibodies, estimated to occur in 5% of patients with SCLC, is commercially available. Plasma exchange and intravenous immunoglobulin can provide short-term benefit, while 3,4-diaminopyridine, which enhances the release of acetylcholine from presynaptic terminals,[270] prednisone, and azathioprine can provide limited long-term benefit.[271] Some patients who respond to chemotherapy will have resolution of the neurologic abnormalities, and this is the initial treatment of choice.

Paraneoplastic encephalomyelitis and sensory neuronopathies, cerebellar degeneration, limbic encephalitis, and brainstem encephalitis occur in SCLC in association with a variety of antineuronal antibodies such as anti-Hu, anti-CRMP5, and ANNA-3.[253,256,272] These antibodies have been found in as many as 25% of individuals with SCLC though not always in association with a clinically obvious neurologic disorder.[256] These disorders may predate the diagnosis of SCLC.[256] Most paraneoplastic neuropathies are sensorimotor and axonal, symmetric in distribution, and frequently disabling.[256] Limbic encephalitis is characterized by degeneration of neurons in the medial temporal lobe with clinical features that include behavioral changes, hallucinations, short-term memory loss, anosmia, ageusia, and dementia.[273] Symptoms of brainstem encephalitis include vertigo, nystagmus, oscillopsia, ataxia, diplopia, dysarthria, and dysphagia reflecting the predominant involvement of the floor of the fourth ventricle and inferior olives.[274] Some patients develop respiratory insufficiency requiring assisted ventilation. Cerebrospinal fluid studies may show pleocytosis and elevated protein levels. MRI brain scans are typically normal. As with voltage-gated calcium channel antibodies, the presence of anti-Hu antibodies does not correlate with neurologic symptoms nor with an improved prognosis.[272,275]

Paraneoplastic cerebellar degeneration, manifesting with ataxia, dysarthria, and nystagmus, may be associated with anti-Hu, anti-Yo, or P/Q calcium channel autoantibodies.[255,276,277] Patients often present with loss of coordination that usually starts on one side and rapidly progresses over days to weeks to involve both sides equally.[278] Additional presenting symptoms include limb and truncal ataxia, lack of coordination, dysarthria, and nystagmus. More rarely patients experience opsoclonus, myoclonus, memory disturbances, pyramidal signs, sensory disturbances, or hyporeflexia. After progressing for a few weeks, the symptoms stabilize, leaving the person in a severely disabled state. On examination, patients may be unable to stand without assistance because of severe truncal and neck ataxia with markedly ataxic gait. Ocular findings may include horizontal or vertical nystagmus, dysconjugate gaze, ocular dysmetria, and opsoclonus.[277] Speech also can be affected severely, presenting initially as mild dysarthria and progressing to incomprehensible words in severe cases. Mild deterioration of mental status may also be seen, but marked changes in mental status are not compatible with this diagnosis.[277] Treatment may include steroids, plasmapheresis, and chemotherapy.[255,276] However, treatment of the tumor and/or immunomodulation does not alter the course of paraneoplastic cerebellar degeneration but may improve Lambert-Eaton myasthenic syndrome symptoms. Death is frequently due to neurologic complications. Paradoxically, the tumor frequently remains localized to the chest or not detected.[277]

Diagnostic Workup and Staging

Assessment of Intrathoracic Disease

Accurate staging of lung cancer is extremely important, because treatment options and prognosis are dictated by stage.[279] The most significant dividing line is between those individuals who are candidates for surgical resection and those who are inoperable but will benefit from chemotherapy, radiation therapy, or both. Staging with regard to an individual's potential for surgical resection is most applicable to NSCLC. The basis for staging NSCLC is the TNM system (Table 76-7),[280,281] whereas for SCLC a more simplified staging classification is used (described later). Of note, the TNM system is currently undergoing revision.[280] From a practical standpoint, the involvement of disease in the mediastinum, which is reflected in the "N" designator in the system, most often determines the appropriateness of the individual for surgical resection.[279] In other words, individuals with mediastinal node involvement are usually not candidates for surgical resection, although there are selected individuals in whom surgery is appropriate as discussed later in this section. Several noninvasive imaging studies are available to aid in identifying disease both within and outside of the chest. A majority of lung cancers are detected by plain chest radiography (Fig. 76-12). However, the chest radiogram is not sufficiently sensitive to accurately assess the mediastinum. Accordingly, a chest CT scan should be performed in virtually every case of suspected NSCLC. The chest CT scan provides anatomic detail that better identifies the location of the tumor, its proximity to local structures, and whether or not lymph nodes in the mediastinum are enlarged (see Fig. 76-12). Unfortunately, the accuracy of chest CT scanning in differentiating benign from malignant lymph nodes in the mediastinum based on node size is low. The most commonly used size criterion is a short-axis diameter of 1 cm or larger on a transverse CT scan. Whole-body PET scanning provides functional information on tissue activity and is more sensitive and specific than chest CT scanning for staging lung cancer in the mediastinum (Fig. 76-13). In addition, metastatic disease can be detected by PET scan. Still, positive findings of PET scans can occur from nonmalignant etiologies (e.g., infections), so that tissue sampling to confirm the suspected malignancy is strongly recommended.[104,279] MRI can be useful in selected circumstances such as superior sulcus tumors to rule out brachial plexus involvement but in general does not play a major role in NSCLC staging. Of course, abnormalities detected by any of the aforementioned imaging studies are not necessarily cancer. Unless overwhelming evidence of metastatic disease is present on an imaging study, in situations in which it will make a difference in treatment, all abnormal scan findings require tissue confirmation of malignancy so that individuals are not prevented from having potentially curative surgery.[279]

Table 76-7 TNM Staging of Lung Cancer

PRIMARY TUMOR (T)

T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3 cm and not involving the mainstem bronchus
T2	Tumor is: >3 cm, involving mainstem bronchus ≥2 cm from the carina, invading visceral pleura, or associated with lobar atelectasis or obstructive pneumonitis
T3	Direct invasion of chest wall, diaphragm, mediastinal pleura, pericardium, mainstem bronchus <2 cm from carina, or associated with atelectasis or obstructive pneumonitis of entire lung
T4	Direct invasion of mediastinum, heart, great vessels, trachea, esophagus, vertebrae, carina, or associated with malignant effusion or satellite nodules in the same lobe

REGIONAL LYMPH NODES (N)

N0	No regional nodal metastasis
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, or intrapulmonary nodes involved by direct primary tumor extension
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes

DISTANT METASTASIS (M)

M0	No distant metastasis
M1	Distant metastasis present or metastatic nodules in nonprimary tumor lobe(s)

TNM STAGING

IA	T1N0M0
IB	T2N0M0
IIA	T1N1M0
IIB	T2N1M0
	T3N0M0
IIIA	T3N1M0
	T1N2M0
	T2N2M0
	T3N2M0
IIIB	T4N0M0
	T4N1M0
	T4N2M0
	T1N3M0
	T2N3M0
	T3N3M0
	T4N3M0
IV	Any T Any N M1

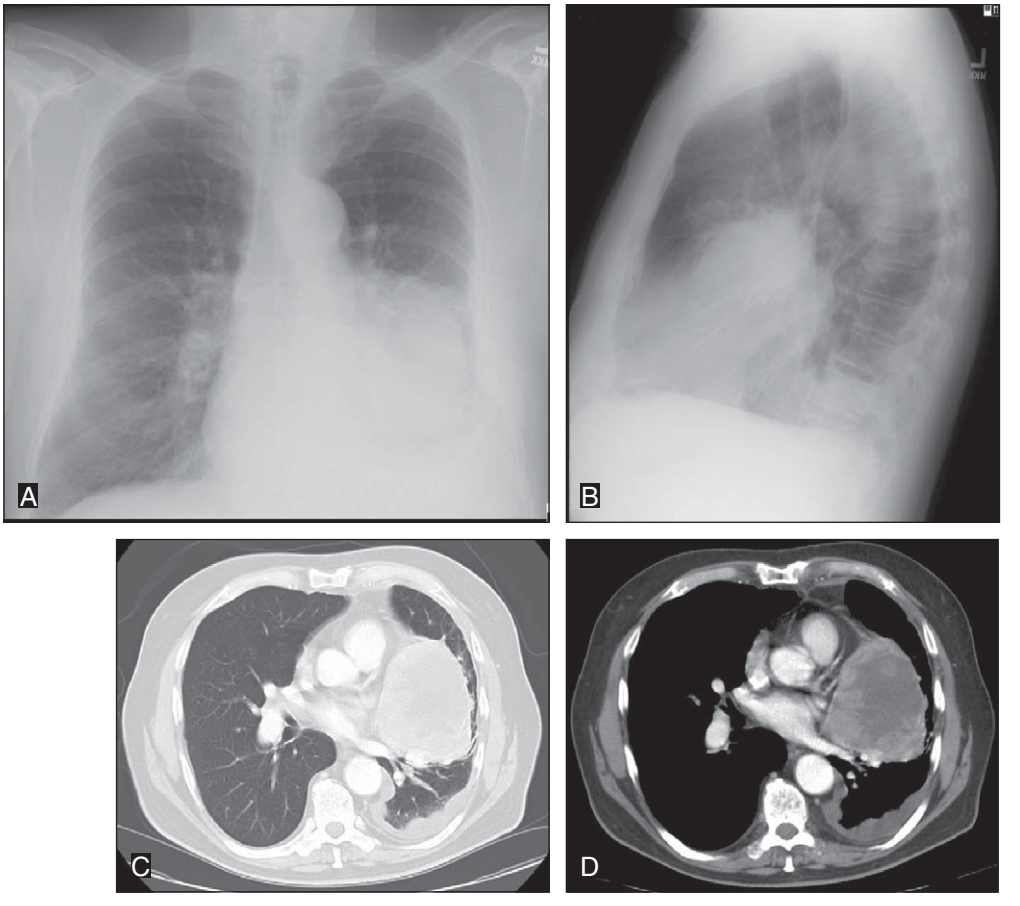


Figure 76-12 • Imaging NSCLC. (**A**) Posteroanterior and (**B**) lateral chest radiogram of patients with locally advanced disease. (**C**) CT imaging using lung and (**D**) mediastinal windows.

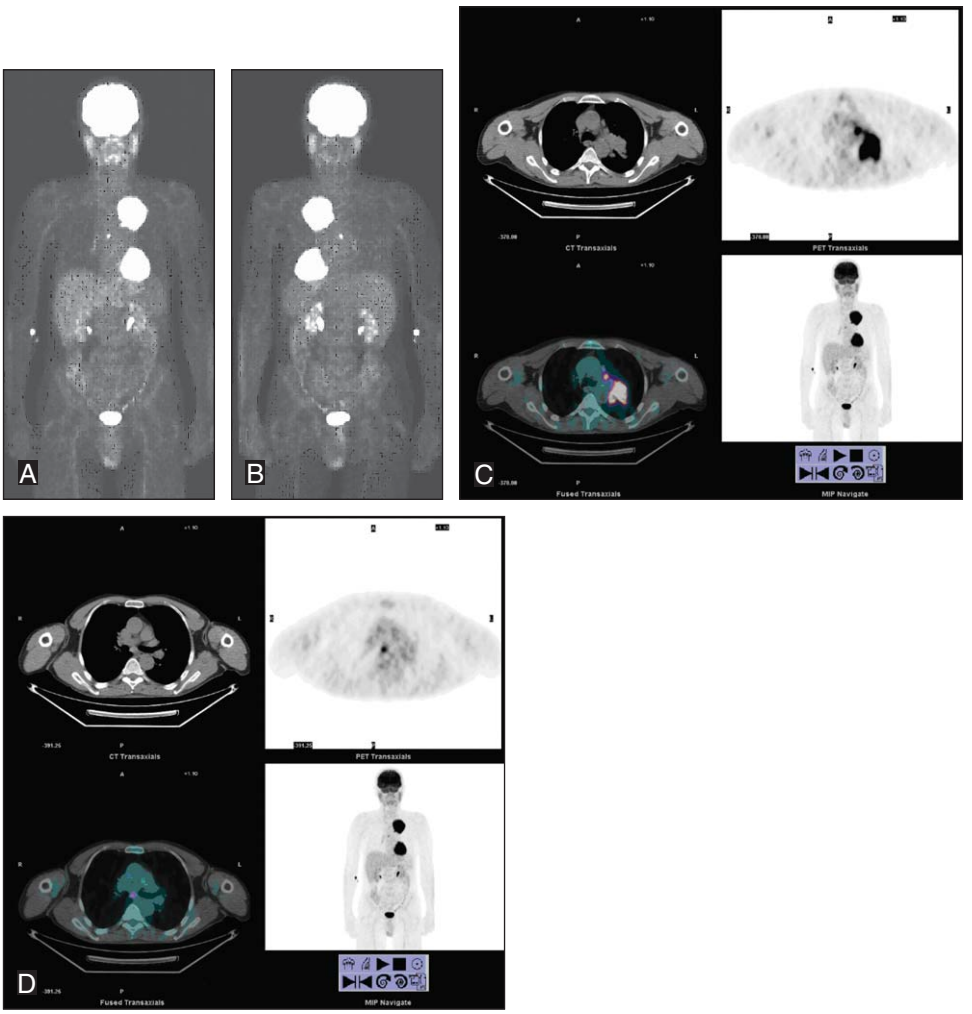


Figure 76-13 • [^{18}F]Fluorodeoxyglucose positron emission tomography with integrated computed tomography. FDG-PET demonstrates (**A**) activity in left upper lobe lesion and (**B**) activity in the subcarinal space. Physiologic uptake is noted in the brain, bones, liver, spleen, kidney, and musculature. Increased activity is also identified at intravenous insertion site, renal collecting system and the bladder. Fused CT/PET images confirm (**C**) lymph node in the anteroposterior window is FDG avid and (**D**) mild FDG uptake in a subcarinal lymph node.

Assessment of Extrathoracic Disease

The best predictor of metastatic disease remains a careful history and physical examination. If signs, symptoms, or findings from the physical examination suggest the presence of malignancy, then sequential imaging, starting with the most appropriate study based on the clues obtained by the clinical evaluation, should be performed. If the findings from the clinical evaluation are negative, then imaging studies such as a CT scan of the head, a bone scan, or an abdominal CT scan are unnecessary, and the search for metastatic disease is complete. Clinical findings suggestive of metastatic disease are listed in Table 76-8.[279] Patients with abnormal clinical evaluations should undergo imaging for extrathoracic metastases. Site-specific symptoms warrant directed evaluation of that site with the most appropriate study (e.g., head CT scan, bone scan, and abdominal CT scan).[279] More controversial is how one should assess individuals with known stage III disease. Because these patients are more likely to have asymptomatic occult metastatic disease, current guidelines recommend a more extensive imaging evaluation to include a head CT scan, an abdominal CT scan, and bone imaging.[279]

Solitary Pulmonary Nodule

The approach to a patient with a pulmonary nodule is based on an estimate of the probability of cancer, determined according to the size of the nodule, the presence or absence of a history of smoking, the patient's age, and characteristics of the nodule's margins on CT imaging.[282] Mayo Clinic investigators reported that clinical charac-

Table 76-8 Clinical Findings Suggesting Metastatic Disease

Symptoms elicited in history	Constitutional: weight loss >10 pounds
	Musculoskeletal: focal skeletal pain
	Neurologic: headaches, syncope, seizures, extremity weakness, recent change in mental status
Signs found on physical examination	Lymphadenopathy (>1 cm)
	Hoarseness, superior vena cava syndrome
	Bone tenderness
	Hepatomegaly (>13-cm span)
	Focal neurologic signs, papilledema
	Soft-tissue mass
Routine laboratory tests	Hematocrit, <40% in men; <35% in women
	Elevated alkaline phosphatase, GGT, SGOT, and calcium levels

GGT, gamma-glutamyltransferase; SGOT, serum glutamic-oxaloacetic transaminase.

From Silvestri GA, Tanoue LT, Margolis ML, et al: The noninvasive staging of non–small cell lung cancer: the guidelines. Chest 2003;123(1 Suppl):147S–156S.

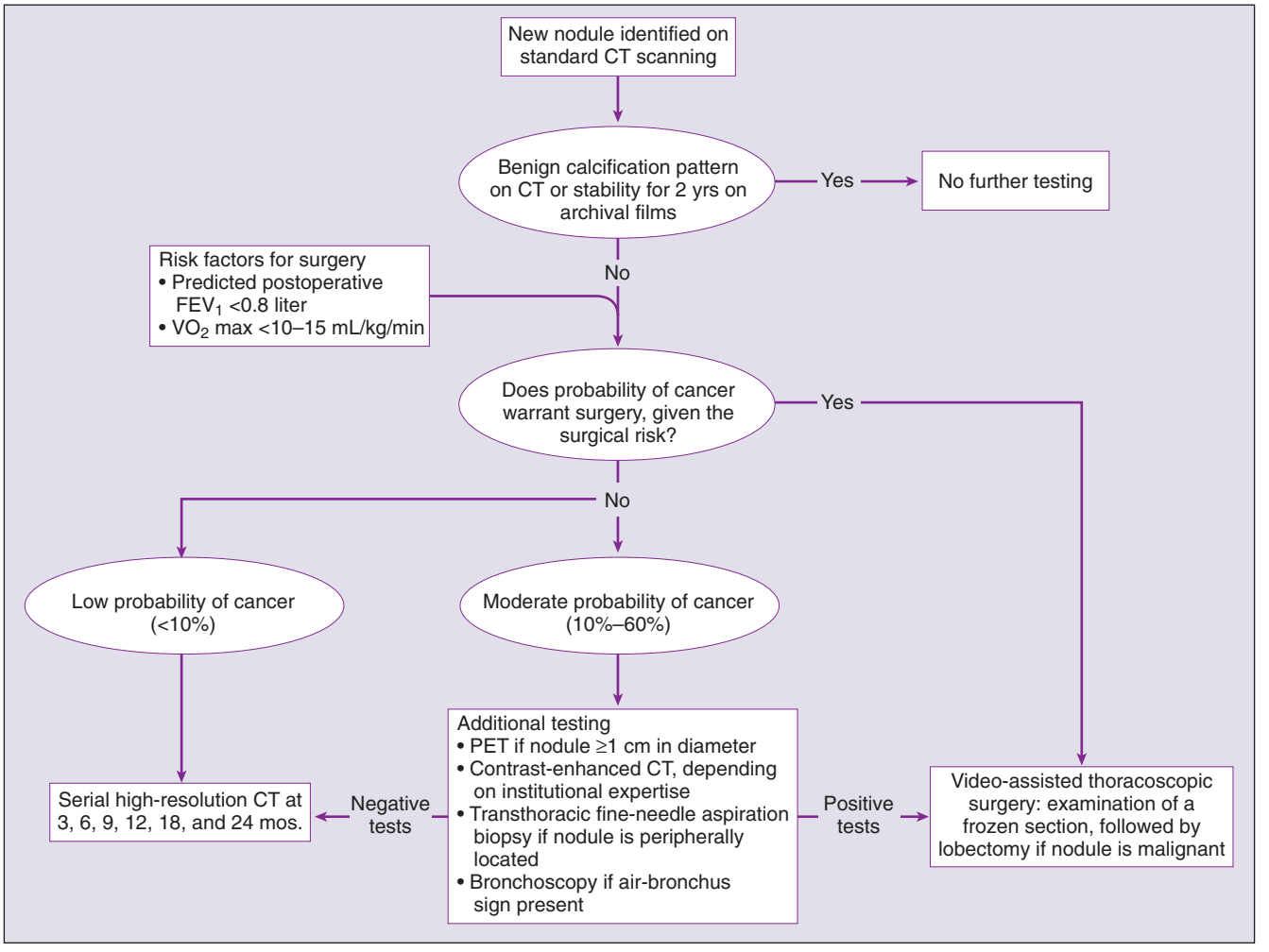


Figure 76-14 • Approach to the management of solitary pulmonary nodules. (Adapted from Ost D, Fein AM, Feinsilver SH: The solitary pulmonary nodule. N Engl J Med 2003;348:2535–2542.)

teristics (age, cigarette smoking status, and prior cancer diagnosis 5 or more years ago) and three radiologic characteristics (diameter, spiculation, and upper lobe location) were independent predictors of malignancy.[283] An efficient algorithm for assessing these lesions is outlined in Figure 76-14.

NON-SMALL CELL LUNG CANCER

The four major histologic types of lung cancer—squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and small cell undifferentiated carcinoma—together account for more than 90% of lung cancer cases in the United States.[15] The first three are traditionally lumped together into the category of NSCLC. The incidence of NSCLC has been decreasing since the mid-1970s to 1980s among men in North America, northwestern Europe, Australia, and New Zealand, but the age-adjusted rate continues to increase among women in these countries, and among both men and women in southern and eastern Europe.[284] These trends followed changes in smoking behavior. Over time there has been a significant shift in the incidence rates of lung cancer by histologic type. Following a steadily increasing occurrence during the period 1973 to 1987, adenocarcinoma supplanted squamous cell carcinoma as the most frequent form of lung cancer.[285] Several hypotheses have been posited as to the underlying cause of this shift, but recent data suggest that changes in smoking behavior and cigarette design are major contributors.[286]

Presurgical Evaluation

Physiologic Evaluation

The physiologic evaluation must be individualized for each patient but generally emphasizes the pulmonary and cardiac function, and follows a stepwise progression. In some cases, history, physical examination, and routine spirometry are all that is required for physiologic assessment. For many patients further physiologic assessment is indicated before pulmonary resection. The assessment of an individual's ability to tolerate lung resection from a cardiopulmonary standpoint is fundamental to patient selection for surgery. Persons with advanced pulmonary disease and severe pulmonary dysfunction may have prohibitive risk in greater than one third of patients with otherwise resectable disease.[287] The most oncologically sound and perfectly executed operation for lung cancer falls far short of success in the event of a major cardiopulmonary complication or severe long-term functional detriment.

Smoking Cessation

Cigarette smoking is associated with an increase of as much as sixfold in the incidence of postoperative pulmonary complications after surgery.[288] Although there are few studies specific to pulmonary resection, there is evidence that preoperative smoking abstinence of 4 to 8 weeks' duration is necessary to reduce the incidence of complications.[288,289] Interestingly, higher rates of complications occur for

patients who cease smoking within fewer weeks of surgery as compared with those who continue to smoke. In evaluating the current smoker with NSCLC for potential resection, the powerful addictive properties of cigarette smoking must be recognized. Individuals should be offered pharmacologic adjuncts (discussed earlier) and should be enrolled in a formal tobacco cessation program before consideration for resection. Wherever possible, smoking should cease a minimum of 4 weeks before surgery. Whether or not to offer resection to individuals with NSCLC who continue to smoke is a subject of controversy among thoracic surgeons. Whatever a particular surgeon's approach to this group, the significant deleterious effect of cigarette smoking on outcome must be recognized. Furthermore, an individual's success in preoperative tobacco cessation may reflect his or her commitment to recovery and compliance with further therapy.

Nutritional Status

Weight loss and malnutrition are very common among individuals with NSCLC. In a recent study[290] more than 40% of patients undergoing resection for NSCLC had a body mass index and skin fold thickness below the twenty-fifth percentile. Poor nutrition in surgical patients correlates with impaired wound healing and a greater propensity to postoperative infection.[291]

Impact of Age

Advanced age is an independent predictor of mortality after resection for NSCLC.[292] With recent advances in patient selection and perioperative care, however, lung resection may be performed with acceptable rates of morbidity and mortality in patients well beyond the age of 70 years. Advanced age does predict a higher incidence of perioperative cardiovascular complications, but age reflects a surrogate marker for additional comorbidities rather than an independent risk factor.[292,293]

Spirometry and Pulmonary Diffusion Capacity

Spirometry is mandatory for patients under consideration of pulmonary resection for NSCLC and provides an objective assessment of pulmonary function. The forced expiratory volume in 1 sec (FEV_1) is the historical standard to determine suitability for resection; a predicted postoperative FEV_1 ($ppoFEV_1$) can be estimated based on the planned extent of resection:

$$ppoFEV_1 = \text{preoperative } FEV_1 \times (\text{no. segments remaining/total segments}).$$

FEV_1 is an independent predictor of mortality from surgery for lung cancer[294] and serves as the primary determinant of the need for further physiologic assessment before surgery for NSCLC. The criteria of ppo FEV_1 of at least 0.8 L has been widely used in decisions for lung cancer resection.[295] However, an absolute value of FEV_1 predicts postresection pulmonary function less accurately than FEV_1 expressed as a percentage of the expected value for age and size.[296] The use of absolute FEV_1 measurements in patient selection may bias against older individuals, those of small stature, and females.[297] Nevertheless, patients with an absolute FEV_1 of greater than 2.0 L are likely to tolerate pneumonectomy, and those with FEV_1 over 1.5 L have adequate pulmonary reserve for lobectomy.[298,299] Patients deemed unable to tolerate lobectomy from a pulmonary functional standpoint may be candidates for more limited resections, such as wedge or anatomic segmental resection, although such procedures are associated with significantly higher rates of local recurrence and a trend toward decreased survival,[300,301] or from minimally invasive techniques and improved postoperative pain management techniques (patient-controlled analgesia, epidural anesthesia, etc.)

Pulmonary diffusing capacity for carbon monoxide (D_LCO) is an adjunctive test to spirometry and lung volume measurements. D_LCO provides a measurement of the lung surface area available for gas exchange and is determined by measuring expired carbon monoxide levels during controlled exhalation. Variability in the D_LCO may be as much as 12% or greater. The D_LCO measures the rate at which test molecules such as carbon monoxide move from the alveolar space to combine with hemoglobin in the red blood cells. The D_LCO is determined by calculating the difference between inspired and expired samples of gas. D_LCO levels below 50% are associated with increased perioperative risk.[302] A low D_LCO reflects the presence of emphysema, fibrosis, or pulmonary vascular disease. Similar to FEV_1, preoperative D_LCO measurement is most useful when expressed as a percentage of predicted value[297,299,302] and may be used to estimate predicted postoperative D_LCO ($ppoD_LCO$).

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing (CPET) can be extremely useful in the evaluation of marginal candidates ($ppoFEV_1$ or $ppoD_LCO$ <40% predicted) or for patients who appear more disabled than expected from simple spirometry measurements.[303,304] Formal CPET includes exercise electrocardiography, heart rate response to exercise, and the measurements of minute ventilation and oxygen uptake per minute. CPET allows a calculation of maximal oxygen consumption (VO_{2max}) and provides insight into overall cardiopulmonary function (the cardiopulmonary axis) that cannot be ascertained from other objective studies. CPET may identify clinically occult cardiac disease and may provide a more accurate assessment of pulmonary function than spirometry and D_LCO, which tend to overestimate functional loss after resection.[303,304] A patient's risk of perioperative morbidity and mortality may be stratified by VO_{2max}. Those with VO_{2max} above 20 mL/kg/min are not at increased risk for complications or death after resection of NSCLC. A level below 15 mL/kg/min is associated with an increased risk, and VO_{2max} less than 10 mL/kg/min indicates very high risk, generally precluding operation.[297,305–307]

Quantitative Perfusion Study

Quantitative radionucleotide perfusion scanning involves the injection of ^{99m}Tc-radiolabeled albumin particles, followed by the visual inspection of planar images. Unlike perfusion scanning in the setting of suspected pulmonary thromboembolism, concomitant ventilation scanning is not routinely performed for preoperative assessment, because studies have demonstrated that both are usually well matched and equally effective in assessing function. Quantitative perfusion provides a measurement of the relative function of each lobe and lung, allowing a prediction of pulmonary function after lung resection:

$$ppoFEV_1 = \text{preoperative } FEV_1 \times (1 - \text{fraction of perfusion to region of planned resection})$$

Quantitative perfusion studies may be useful in selecting patients with marginal pulmonary reserve for resection. Like FEV_1 and D_LCO, quantitative perfusion studies tend to slightly underestimate actual postoperative function, erring on the side of safety in the selection of patients for resection.[308] A recent study compared quantitative perfusion studies to the segment-counting technique and reported no difference in the predictive value for the assessment of postoperative pulmonary function.[296] The study of quantitative perfusion is therefore most useful when there is clinical suspicion that the area of planned resection is not contributing homogeneously to lung function, such as in the setting of heterogeneous emphysema or an obstructive process.

Arterial Blood Gas Analysis

Arterial blood gas analysis is not a mandatory component of preoperative assessment for lung resection. It may be indicated in marginal candidates, or if there is a clinical suspicion of significant hypoxia or carbon dioxide retention.

Informal Exercise Assessment

Observed performance during stair climbing has historically been practiced in the preoperative assessment of patients with lung cancer. Stair-climbing ability has some correlation with values on spirometry[297,309] but perhaps is most correlated with a person's global cardio-

pulmonary status and determination,[309] both of which are fundamental to a successful outcome after surgery. This modality has not been standardized in duration, extent, or technique, and studies thus far represent limited single-institutional experiences. Given the wide availability of more objective and standardized noninvasive tests for cardiopulmonary function, stair-climbing performance should not be used as the sole criterion to determine physiologic suitability for lung cancer resection.

Cardiovascular Status

Cardiovascular evaluation should conform to American College of Cardiology and American Heart Association guidelines for noncardiac surgery.[310] Patients with greater than one major risk factor for coronary artery disease, those with prior cardiac interventions, and those whose functional limitations preclude adequate assessment for angina should be evaluated further. Preoperative electrocardiography should be performed in all patients, and echocardiography is indicated in all patients with a heart murmur, clinical features suggestive of congestive heart failure, or unexplained dyspnea. Echocardiography is also a useful initial evaluation for clinically suspected pulmonary hypertension, which represents a contraindication to lung resection. Pulmonary resection for NSCLC should generally not be undertaken within 6 weeks of an acute myocardial infarction. Patients with a prior history of cerebrovascular events and those with cervical bruits on physical examination should be assessed by carotid Doppler studies and referred for vascular consultation as appropriate.

Effects of Induction Chemotherapy

Patients who have received chemotherapy for NSCLC before surgery typically have more advanced-stage disease and may require greater extent of resection than early-stage disease. There seems to be no significant difference for stage-matched patients who receive induction chemotherapy followed by resection compared to those with resection alone.[311] Malnutrition and current cigarette smoking must be recognized as potentially reversible risk factors for complications after resection and should be modified where possible. It is unclear whether deferral of surgery for any prescribed interval after the completion of chemotherapy may offset some of these deleterious effects. Although induction therapy is not the current standard for NSCLC, many institutions have adopted its use in selected patients with stage IIIA disease. The thoracic surgeon must be aware of the increased attendant perioperative risk, which should be part of the global assessment of a patient's fitness to undergo surgery.

In summary, every person with potentially resectable NSCLC must be carefully assessed by the thoracic surgeon for his or her physiologic fitness to undergo surgery, because patients with severe cardiopulmonary deficiency are at a predictably increased risk for major complications and death after resection. All patients should be assessed for cardiovascular risk using American College of Cardiology and American Heart Association guidelines. Spirometry allows a determination of ppoFEV_1, and D_LCO should be liberally used as an adjunct to spirometry measurements. Patients with a ppoFEV_1 or ppoD_LCO below 40% of expected values should be further evaluated with CPET. At institutions where CPET is not available, supervised stair-climbing assessment may be an acceptable alternative means for assessment. Quantitative perfusion scanning should be considered in patients with marginal ppoFEV_1 or ppoD_LCO, particularly where heterogeneous pulmonary function is clinically suspected. There are several studies reporting acceptable outcomes for lung resection in patients with preoperative measurements well below accepted standards,[312,313] and no single test result should be viewed as an absolute contraindication to surgical resection for NSCLC. Although the physiologic assessment of a patient with normal spirometry and minimal comorbidity is fairly straightforward, patients with marginal preoperative indices must be considered on an individual basis. Surgical decision making in this patient population should incorporate input from the pulmonologist and medical oncologist. The decision whether to pursue lobectomy, limited resection, or primary nonoperative treatment of NSCLC is made best under the guidance of this multidisciplinary team.

Surgical Management of Non-Small Cell Lung Cancer

Since the introduction of the pneumonectomy for extirpation of lung cancer, surgeons and surgical resection have played a pivotal role in the management of early-stage NSCLC.[314] However, in the last 2 decades the management of NSCLC has become a multidisciplinary process involving not only surgeons but also pulmonologists, pathologists, radiologists, radiation oncologists, and medical oncologists. Notably, however, thoracic surgeons retain a key role in the management of all stages of lung cancer from premalignant lesions to the management of selected individuals with advanced stage IV disease.

Surgical management of NSCLC is multifaceted and entails the invasive staging for optimal therapeutic decisions, extirpation of the local disease with mechanical and other physical strategies, alone or in combination with chemotherapy or radiation therapy, and management of the physical sequelae of progressive neoplastic growth with dyspnea from airway compromise, pleural effusion, or other consequences. Fundamentals of surgical management of NSCLC include complete resection of the tumor with negative margins, systematic mediastinal lymph node dissection, and integration of the multidisciplinary team in all but the most early or late stages of disease (i.e., clinical stage IA or metastatic disease, respectively). Ideally NSCLC should be managed by a thoracic surgeon trained in the management of thoracic neoplasms and their sequelae. Both the skill of the surgeon and the volume of procedures performed at a particular facility significantly influence survival following lung cancer surgery.[315,316] Experienced thoracic surgeons working in facilities that perform a high volume of procedures invariably have better outcomes than nonthoracic surgeons and/or thoracic surgeons and nonthoracic surgeons operating in facilities that perform a low volume of lung cancer operations.[315,316] The thoracic surgeon cannot eliminate perioperative risk but can manage it by optimizing patient selection, and various parameters for patient preparation, intraoperative care, and convalescence. Resection of lung cancer can be done with low mortality by experienced thoracic surgeons (i.e., <1.5% mortality rates), as demonstrated in a recently completed multiinstitutional prospective randomized trial of over 1000 patients evaluating mediastinal lymph node dissection versus node sampling.[315]

Although the extant International Staging System is undergoing revision, the current iteration has served surgeons well since its publication in the late 1990s (see Table 76-7).[280] Clear survival differences are demonstrable by stage as determined by differences in tumor size and location, characteristics of hilar, mediastinal, or other nodal groups, and presence or absence of metastatic disease. Patients are selected for a specific treatment on the basis of the clinical stage as determined by the clinician's best and final estimate of the extent of the NSCLC based on all available data before the initiation of definitive therapy. Consequently treatment decisions require accurate and complete staging as an integral component of pulmonary resection for lung cancer. For postoperative treatment decisions, mediastinal lymphadenectomy determines pathologic stage and provides information about potential survival and the need for postresection therapy. The pathologic stage of the tumor most accurately defines the overall and disease-free survival.

Without question, surgical resection of NSCLC provides the best opportunity for cure and offers the greatest potential for prolonged survival.[314] Historically, a pneumonectomy was considered the only procedure that reliably achieved complete resection. However, with the advent of more detailed staging as outlined previously, coupled with more specific survival data, less aggressive surgical resections have been performed for early-stage NSCLC, with improvements in postoperative morbidity and mortality. Currently, patients with stages I, II, and select IIIA (T3N1) NSCLC, as determined by pre-

operative imaging and staging strategies, are candidates for attempting pulmonary resection in the absence of other contraindications to surgery. In some parts of the world individuals with known mediastinal nodal involvement (i.e., N2 disease) also are treated with resection. However, in North America and much of Europe, individuals with known N2 disease are typically treated without primary surgical intervention, although selected patients may undergo surgery as part of a multidisciplinary approach.[314,317] The surgical procedure of choice is a thoracotomy and complete resection to obtain negative surgical margins via lobectomy, sleeve lobectomy, bilobectomy, or pneumonectomy depending on tumor burden and location.[314] Moreover, recent data demonstrate that postoperative chemotherapy is beneficial in selected patients with completely resected stages II and IIIA disease and very possibly in some patents with stage IB disease. The subject of adjuvant and neoadjuvant therapies is covered in greater detail immediately after the following brief overview of the surgical management of some of the more common and not so common presentations of NSCLC.

Occult Lung Cancer

Screening for second aerodigestive malignancies can result in identification of CIS or microinvasive tumor by flexible bronchoscopy. These occult lung cancers (Tx-TisN0M0) occur without symptoms or other radiographic finding and may be treated with endoluminal therapy. However, most patients would be considered for resection with segmentectomy or lobectomy. The choice of anatomic resection must be carefully considered, because field cancerization may exist with many involved areas present. Mucosal ablating techniques include photodynamic therapy, brachytherapy, electrocautery, cryotherapy, and neodymium-yttrium-garnet (Nd-Yag) laser therapy.[318]

Stage I Lung Cancer

Stage I NSCLC includes individuals with a T1 or T2 primary tumor designation and no evidence of hilar or mediastinal nodal disease (N0) or metastatic spread (M0). Medically fit persons with stage I disease should be considered for aggressive local therapy, and curative treatment is possible with 5-year survival rates ranging from 45% to 70% in most series depending in large part on tumor size and whether or not pleural invasion is found.[314,319] Surgical resection is the accepted treatment for individuals with stage I disease.[314,320,321] Only rarely is a pneumonectomy necessary in stage I NSCLC. Lobectomy is usually sufficient to achieve negative surgical margins and is considered the surgical preferred approach, although lesser resections (wedge, segmentectomy, etc.) have advantages in persons with limited pulmonary reserve.[322,323] Compared with a lobectomy, a segmental resection tends to spare pulmonary reserve without significant impairment of survival, although additional local control measures are needed.[324,325] Iodine-125 brachytherapy mesh applied to the suture line may be helpful in decreasing local recurrence.[326,327] Notably, video-assisted thoracic surgery (VATS) techniques have advanced to a common level commensurate with safe anatomic resection of parenchymal neoplasms and lymph node sampling.[328,329] Anatomic resection (open or VATS) is preferred to a wedge resection of NSCLC, because the latter is associated with increased rates of local recurrence.[325] In experienced hands, VATS is associated with low morbidity and mortality, and the risk of intraoperative bleeding or recurrence in an incision is minimal.[328] Moreover, VATS is associated with less postoperative immunosuppression compared with the thoracotomy approach.[330] However, the clinical relevance of better preserved cellular immunity in the early postoperative period is unclear. There are insufficient data to suggest that one method of resection (open thoracotomy, minimally invasive techniques) is superior to another.

Accurate pathologic staging in stage I disease requires adequate segmental, hilar, and mediastinal lymph node dissection.[331,332] The performance of a systematic sampling or full mediastinal lymph node dissection may improve pathologic staging but is unproven therapeutically.[321] Mediastinal lymph node dissection provides for a significantly larger amount of material, which can refine pathologic (nodal) stage determination. On the right side, mediastinal stations 2R, 4R, 7, 8R, and 9R should be dissected; on the left side, stations 5, 6, 7, 8L, and 9L should be dissected. Hilar lymph nodes are typically resected and sent with the specimen, although it is helpful to specifically dissect and label level 10 lymph nodes when possible. On the left side, level 2 and sometimes level 4 lymph nodes are generally obscured by the aorta. Mediastinal lymph node dissection optimizes the accuracy of the pathologic stage and provides information to the clinician as to potential survival and the need for postresection therapy.[331,332] Although the therapeutic benefit of nodal dissection versus nodal sampling remains controversial, in a recent pooled analysis of three trials, 4-year survival was superior in individuals undergoing resection with stage I through IIIA NSCLC who had complete mediastinal lymph node dissection compared with lymph node sampling (hazard ratio [HR] 0.78; 95% confidence interval [CI], 0.65 to 0.93).[333] Moreover, a complete mediastinal lymphadenectomy adds little morbidity to a pulmonary resection for lung cancer.[315] Thus, the recommendation is that patients should have a complete mediastinal node dissection.

Although the cost effectiveness of surveillance is not well established, many surgeons choose to follow patients with resected stage I NSCLC for the development of a second primary tumor.[334,335] About 5% of stage I NSCLC patients will develop a second primary cancer (incidence = 1.99/100 patient-years),[336,337] and surgical intervention in such cases may prove beneficial.[338]

Stage II Lung Cancer

Clinically stage II patients are often misclassified as stage I disease. Stage II NSCLC is a heterogeneous classification covering patients with T1–2N1 or T3N0 tumors. Stage II composes only 5% of all NSCLC based on clinical assessment alone.[339] By definition, patients with tumor invading the chest wall apex, mediastinum, diaphragm, pericardium, phrenic nerve, azygos vein, or right or left pulmonary artery or even the mainstem bronchus have T3 tumors.[339,340] Stage II patients with N1 metastases may require more aggressive surgical strategies to remove all evidence of tumor. For example, one recent retrospective series of 124 patients with T1N1 or T2N1 disease suggested a survival advantage with pneumonectomy compared with a lobectomy in patients with hilar (level 10) lymph node involvement,[341] a finding supported by a lower local recurrence rate in the pneumonectomy patients. The risks of pneumonectomy must be considered for these individuals, because nodal metastasis at level 10 often portends occult distant metastases more so than inadequate local control. The relatively poorer survival as compared with stage I disease had prompted several clinical trials specifically for this subgroup of patients.

Mainstem Bronchus Tumor Less Than 2 Cm from the Carina

Even when the NSCLC lesion is located in the proximal airway a complete resection is feasible in some cases. Although pneumonectomy can be performed, specific techniques that spare noninvolved lung parenchyma are preferred.[314,342] These parenchymal sparing procedures include sleeve resection, bronchoplasty, pulmonary artery sleeve resection, pulmonary arterioplasty, and tracheal resection/reconstruction. Candidates for these procedures must be carefully staged by contrasted CT and bronchoscopy so as to permit surgical airway reconstruction.[314] Bronchial sleeve resection with or without pulmonary artery resection and reconstruction can be accomplished with excellent results and good long-term survival.[343–345] Morbidity, mortality, and functional data suggest that such reconstructions are comparable to lobectomy in terms of pulmonary function. Parenenchymal sparing techniques are infrequently required; however, they may be critical in individuals with marginal pulmonary reserve, and highly desirable in all others. Persons with N2 metastasis should not undergo thoracotomy. Five-year survival with complete resection is approximately 50%.[343–345]

Superior Sulcus Tumors

Superior sulcus tumors are apical masses that often extend to involve the chest wall, upper ribs, vertebral body, brachial plexus, stellate ganglion, or subclavian vascular structures.[346] These tumors account for roughly 3% of all NSCLC and always should be considered for surgery to improve function and relieve pain. Extension of apical tumors into the thoracic inlet may be accompanied by shoulder and/or arm pain, Horner syndrome, and occasionally paresthesias in the ulnar nerve distribution of the hand (fourth and fifth fingers). Patients with all these characteristics may be classified as having Pancoast syndrome.[346,347] Pain arises from involvement of the C8 and T1 nerve roots, whereas Horner syndrome (miosis, ptosis, anhidrosis, and enophthalmos) is caused by sympathetic nerve involvement. Frequently the first, second, and third ribs are involved, requiring resection.[347] Reconstruction of the defect is not required because the scapula and arm protect the defect. CT and MRI are used to assess treatment options. Reportedly, the complete resection (50%) and the 5-year survival (30%) rates for superior sulcus tumors have not changed for over 4 decades.[348] Historically superior sulcus tumors were treated with external beam irradiation (30 Gy) to the primary tumor before resection. However, no prospective trial has proven the benefit of this therapy over surgery alone, and several disadvantages may occur. The usual dose of irradiation is inadequate to completely control most tumors, and accelerated repopulation may occur. If negative surgical margins are not achieved, subsequent attempts to obtain local control via further irradiation can prove problematic. Resection of tumors abutting or invading the brachial plexus after radiation therapy also can be challenging. Finally, definitive postresection radiation therapy can be performed easily. In one retrospective review of 143 superior sulcus tumors, overall 5-year survival was 47% for stage IIB, 14% for stage IIIA, and 16% for stage IIIB superior sulcus tumors. Individuals without gross residual disease after surgical resection who received postoperative radiation therapy with total doses of 55 to 64 Gy had a 5-year survival rate of 82% as compared with the 5-year survival rate of 56% in persons who received 50 to 54 Gy.[349]

Because combined-modality therapy has improved outcome in other subsets of locally advanced NSCLC the North American Intergroup tested the feasibility of induction chemoradiation and surgical resection in superior sulcus tumors with the ultimate aim of improving resectability and survival.[348] Individuals with mediastinoscopy-negative superior sulcus tumors received two cycles of cisplatin and etoposide with concurrent irradiation (45 Gy), followed by resection 3 to 5 weeks later. More than 90% of patients had a complete resection, and postoperative mortality was 2.4%. A complete pathologic response or microscopic residual disease only was noted in 65% of all resected specimens. Two-year survival was 55% for all patients and 70% for patients with an R0 resection. Local failure rates are improved with this strategy. Systemic failure, mostly cerebral metastases, occurs in about 25% of patients. Although this approach has not been compared to surgical intervention with or without postoperative irradiation, it has become the default standard of care for patients meeting the eligibility criteria of this study. Accordingly we believe a multidisciplinary approach is warranted in all cases of superior sulcus tumors with attention to the need for preoperative induction therapy and the use of alternatives to surgery (e.g., definitive chemotherapy and radiation therapy) for medically inoperable patients.

Mediastinal Involvement

Mediastinal involvement is generally identified at the time of operation with tangential involvement of the mediastinal pleura, pericardium, phrenic nerve, or mediastinal fat. Complete resection of the primary tumor en bloc with the mediastinal structure is recommended in an otherwise suitable patient. Unilateral phrenic nerve resection is appropriate if negative margins can be achieved.

Chest Wall Invasion

In the absence of other contraindications to surgery, tumors invading the chest wall should be considered for complete resection. Reconstruction of the chest wall with a muscle flap or patch may also be performed.[350] In the case of pleural invasion and chest wall involvement, en bloc resection is advised over extrapleural resection, because of significantly more favorable survival rates.[350,351] Long-term survival is stage and sex dependent. The best survival is observed in women who have T3N0M0 disease.[351] Persons found to have N2 disease should be managed with multimodality therapy as outlined later in this chapter. Adjuvant irradiation is not recommended for patients with complete resection of T3 chest wall NSCLC but may be considered for local control in patients with positive resection margins.

Stage IIIA Locally Advanced Lung Cancer

Stage IIIA NSCLC constitutes roughly 30% of all NSCLC patients at diagnosis.[317] It is an extraordinary heterogeneous category of patients with metastatic disease to the ipsilateral mediastinal (N2) lymph nodes and also includes T3N1 patients. Approximately one third of stage IIIA patients present with ipsilateral N2 lymph node metastases. Presentations of disease can range from apparently resectable tumors with occult microscopic nodal metastases to unresectable, bulky multistation nodal disease. It is the latter group that constitutes one of the more therapeutically challenging and controversial subsets of NSCLC, with a published 5-year survival of only 23%. Accordingly, the management of IIIA NSCLC patients challenges the surgeon and the multidisciplinary team given the heterogeneity of the local disease and the variable, yet common, occult systemic metastasis.

Clinical staging of stage IIIA typically involves both diagnostic imaging and invasive staging. Invasive staging with pathology examination of lymph node or other tissues further describes the extent of the disease needed to optimally determine treatment decisions. Pathologic staging occurs after resection and typically reveals a spectrum of disease extent. Patients with enlarged mediastinal lymph nodes must undergo mediastinoscopy as node size alone does not predict pathologic findings. Patients with positive N2 nodes determined preoperatively should be referred for definitive chemotherapy and radiation therapy, or entry into a prospective clinical trial (which may or may not evaluate resection as a therapeutic intervention; see later discussion). Resection following chemotherapy and radiation therapy, so-called trimodality therapy, should not routinely take place outside of a clinical trial or without a multidisciplinary plan to include resection established before initiation of therapy.

In each situation a spectrum extends from occult, unrecognized IIIA disease (typically identified after resection such as T3 with N1 nodal involvement, or microscopic N2 disease in the mediastinal lymph node dissection specimen) and single-station N2 disease identified by mediastinoscopy or guided by FDG-PET, to multistation and/or bulky mediastinal N2 disease identified by CT, FDG-PET, or mediastinoscopy. If the surgeon finds involved but resectable mediastinal nodal disease at the time of operation, a complete anatomic resection and mediastinal lymph node dissection is recommended. If the individual has many involved N2 stations, or bulky mediastinal disease, then the decision to proceed with resection must balance risk and benefit (e.g., improved local control). If the patient is at high medical risk for resection (advanced disease with poor predicted survival), then the operation should be aborted and concurrent chemoradiation therapy initiated.

"Incidental" N2 Disease

Despite a careful preoperative staging evaluation, as many as a quarter of patients will be found to have metastases to N2 nodes at the time of thoracotomy.[352–354] Frequently occult N2 disease is identified only at the time of final pathologic examination of the surgical specimen. In other individuals, metastases will be found on intraoperative frozen-section examination of mediastinal nodes. For individuals

with an occult, single-station mediastinal node metastasis recognized at thoracotomy in which a complete resection of the nodes and primary tumor is technically possible, most thoracic surgeons proceed with the planned lung resection and a mediastinal lymphadenectomy. If a complete resection is not possible or there is multistation or bulky nodal disease or extracapsular nodal disease, then the planned lung resection should be aborted. These patients can then be considered for multimodality therapy as described later in this chapter. Although incomplete resection rarely results in long-term survival, collected results indicate that surgery alone in stage IIIA disease (N2 disease) is associated with a 14% to 30% 5-year survival. The best survival is seen in cases with minimal N2 disease and complete resection.[354]

"Clinically Evident" N2 Disease

Individuals with stage IIIA clinically evident N2 disease present more of a problem. Induction chemotherapy (±preoperative radiation therapy) has the theoretical attraction of improving the "resectability" of patients with "bulky" N2 disease stage IIIA (N2) disease based on the premise that improved resection rates would translate into improved overall survival. Both small single-institution studies and multi-institutional trials support this possibility.[355–357] However, such trials are usually inadequately powered to provide definitive proof. Concern vis-à-vis perioperative morbidity has limited this approach to a large extent.[358] More recently data have emerged that suggest induction therapy does not increase the risk of survival complications compared to surgery alone based on a clinical and pathologic stage-specific analysis.[311]

In an important but as yet unpublished North American Intergroup study (INT-0139), individuals with clinical stage IIIA-N2 (T1–3pN2M0) NSCLC, a good performance status (PS) (Eastern Cooperative Oncology Group [ECOG] PS: 0–1) and considered technically resectable at initial evaluation were randomized to induction chemotherapy–radiation therapy followed by surgical resection or chemotherapy–radiation therapy alone.[359] Progression-free survival but not overall survival was improved with resection after induction chemotherapy–radiation therapy. As found in other trials of induction therapy, pN0 status was associated with prolonged survival. Pneumonectomy accounted for 14/15 postoperative deaths and may have compromised overall survival. Thus, the trimodality approach used in this study cannot be considered standard of care for persons with positive N2 disease determined preoperatively. These individuals should be managed with combined chemoradiation therapy as outlined later if they are otherwise physically fit.

A multicenter European trial (EORTC 08941) was designed to determine the optimal local-regional treatment for NSCLC patients with positive N2 involvement.[360] Selected individuals with NSCLC with histologically or cytologically proven stage IIIA (N2) disease were initially treated with three cycles of platinum-based induction chemotherapy. Those individuals who responded to induction chemotherapy were then randomized to a radical resection with lymph node dissection and optional postoperative radiation therapy or thoracic radiation therapy (TRT) alone to a minimal dose of 40 Gy in 2-Gy daily fractions to the mediastinum, with a boost to at least 60 Gy on the involved field. With a median follow-up of 72 months, median (16.4 vs.17.5 months) and 5-year survival rates (16% vs. 13%) were not significantly different between the two arms (HR 0.95, 95% CI 0.75–1.19; $P = 0.6$).

The downstaging of pN2 to pN0 that may occur with induction therapy seems to be important in identifying patients with improved chances for survival. In a phase II trial conducted by the Southwest Oncology Group (SWOG 8805) persons with clinical stages IIIA or IIIB disease received induction chemotherapy–radiation therapy followed by resection. This strategy provided a pathologic complete response in 22% and an overall 3-year survival rate of 27%. Notably, individuals with no residual mediastinal lymph node involvement had a median survival of 30 months compared with 10 months for those with with residual disease ($P = 0.0005$).[361] Whether or not patients without pathologic downstaging of N2 disease should undergo surgery is controversial. In a subset analysis of the aforementioned EORTC study 08941, it was determined that failure to downstage to pN0 after induction chemotherapy portended a worse outcome that may be improved with the application of postoperative radiation therapy. However, surgical resection in this subset of patients was not apparently beneficial.[362] These data warrant prospective validation.

Pulmonary resection after induction chemotherapy–radiation therapy presents several technical challenges. For example, patients who have received in excess of 50 Gy during their neoadjuvant treatment have a higher rate of serious complications such as bronchopleural fistula, prolonged air leak with empyema, and prolonged postoperative ventilation; therefore, the dose should be limited to 45 Gy. The sequelae of chemotherapy–radiation therapy include dense fibrous tissue in the hilum and mediastinum, and tissue planes are often obliterated.

Outside of a clinical trial, individuals with bulky or multistation N2 disease should not be considered for trimodality therapy. These individuals are usually treated with alternatives to resection such as chemoradiation (see later discussion). Trimodality therapy should be used only in rare circumstances. Even if mediastinal nodes are downstaged to pN0 the usefulness of surgical resection remains highly questionable.[363] Moreover, although repeat cervical mediastinoscopy can be performed, the risks of this repeat operation after mediastinal chemoradiation therapy are greater than standard mediastinoscopy. Alternatives to the initial mediastinal staging include esophageal ultrasound and transbronchial ultrasound.[364] Without question, resection should be avoided after induction therapy in persons who have biopsy-proven residual tumor in the mediastinal nodes.

Unresectable N2 Disease

In general, individuals with histologically involved lymph nodes larger than 2 cm in short-axis diameter measured by CT, who have extranodal involvement or multistation disease along with groups of multiple involved smaller lymph nodes, are considered to have bulky, unresectable disease. These individuals are referred for protocols involving chemoradiation as described later in this chapter if they are functionally fit to tolerate the therapy.

Stage IIIB Locally Advanced Lung Cancer

Stage IIIB includes individuals with T4, any N, M0, and any T, N3, M0[365] (e.g., tumor invading into the trachea, carina, esophagus, vertebrae, aorta, vena cava, great vessels, or atrium/cardiac structures; any N3 nodal description; malignant pleural effusion; or more than one nodule in one lobe). Resection with or without neoadjuvant chemotherapy or chemotherapy–radiation therapy is typically reserved for those persons with clinical T4-N0-M0 status in whom the tumor can be removed with negative margins (R0 resection). Survival may approach 25% to 30 % at 5 years for selected patients. Individuals with N3 lymph node involvement are not considered as surgical candidates. For those with unresectable disease, good performance score, and minimal weight loss, treatment with combined chemotherapy and radiation therapy has resulted in better survival than treatment with radiation therapy alone. Multiple daily fractions of radiation therapy have not resulted in improved survival compared to standard fractionation once daily.[365] Concurrent chemotherapy–radiation therapy seems to be associated with improved survival compared with sequential chemotherapy and radiation therapy (see later discussion).[365]

Carinal Resection

Tracheal resection and reconstruction for NSCLC is infrequently performed. More commonly, the extent of the disease requires a nonsurgical approach to include radiation therapy, or chemotherapy and radiation therapy. Palliative techniques include mechanical fulguration, laser ablation, or placement of expandable metal stents. Resection is reserved for localized endobronchial disease of the carina or very distal trachea but is contraindicated in the presence of N2 or N3 disease.[366] Resection of the carina with or without right pneumonectomy is performed with anastomosis between the trachea and the

left mainstem bronchus. Mediastinoscopy is required and reserved until the operation itself is planned so as to avoid any disruption of blood supply and to facilitate mobilization anteriorly. Consistent success requires excellent surgical technique and meticulous attention to detail. Gentle handling of tissue, avoiding disruption of the tracheal blood supply, anastomosis under no tension, and complete resection of the neoplasm with negative margins are necessary.[343,366,367]

Other Mediastinal Structures

Various mediastinal structures may be involved with tumor and may be resected and reconstructed as necessary.[368] The superior vena cava may be resected en bloc with the tumor and reconstructed with primary repair, patch venoplasty, or reconstruction with vascular graft. Limited resection of the left atrium or esophagus for tangential invasion would be appropriate if such resection would provide an R0 resection. The esophageal musculature can be removed, leaving the mucosa intact. Preoperative endoscopy is required for tumors that may abut the esophagus. Resection of the aorta with reconstruction is rarely performed. Individuals with involvement of the vertebral body would require en bloc resection of the tumor and anatomic portion of the lung, with the involved portion of the chest wall and vertebrae.[347] A multispecialty surgical team with thoracic surgery and either neurosurgery or orthopedic surgery, and stabilization of the vertebral column would be needed. Superior sulcus tumors with vertebral invasion can be treated with success.[369] Most patients resected in this small study had received external beam radiation therapy. The absence of perioperative mortality and a 2-year actuarial survival of 54% suggest that benefit can accrue to patients. Tumors that invade the vertebral column can undergo resection with posterior-lateral thoracotomy, lobectomy with en bloc chest wall resection, laminectomy, vertebrectomy, and anterior spinal column reconstruction with methylmethacrylate and spinal instrumentation.[347,369] Additional studies have examined the outcomes of superior sulcus tumors with a T3 or T4 status.[348] Five-year survival was 46% for stage IIB, 0% for stage IIIA, and 13% for stage IIIB.

Other T4 Presentations

Various other clinical presentations are included in stage IIIB NSCLC. These include satellite nodules, and extrathoracic or contralateral nodal metastasis (N3). A satellite nodule is a separate NSCLC of identical histology contained within the same lobe as the primary tumor. These are resectable with good survival. A satellite nodule is a secondary tumor nodule in the same lobe as the primary cancer having histology identical to that of the primary tumor. These are resectable with 5-year survival of 33%.[370] Such individuals should be carefully staged for occult nodal or distant metastasis. Even with treatment, persons with extranodal or contralateral nodal disease typically have poor survival (15% 5-year survival).[371] Although bilateral nodal dissection has been advocated by some Japanese surgeons, the presence of contralateral mediastinal disease or supraclavicular disease suggests a more widely advanced tumor that would be treated with chemotherapy and radiation therapy.[365,372]

Malignant Pleural Effusions

Patients with malignant pleural effusions frequently present with dyspnea, cough, and loss of function.[373] Symptomatic treatment is initially achieved via simple and complete drainage by thoracentesis. Those with a good performance status are subsequently managed like individuals with stage IV disease as described later in this chapter. However, many patients have recurrent effusions in which case treatment options may be much more varied. Treatment for individuals with initial or recurrent malignant pleural effusions should focus on relief of symptoms of dyspnea and restoration of normal activity.[373] The traditional practice of arbitrarily requiring pleural symphysis (obliteration of the pleural space), achieved by in-hospital drainage of the effusion followed by sclerosis with chemical or other agents, may subject the individual to a prolonged hospitalization or other interventions that may significantly reduce quality of life and remaining survival time outside the hospital. Persons with cancer frequently develop recurrent malignant pleural effusions secondary to their disease. In 25% of patients with cancer, malignant cells may not be identified by pathologic examination of the fluid. Median life expectancy in cancer patients with malignant pleural effusion ranges from 3 to 9 months depending upon the histologic subtype of the primary tumor. In one prospective randomized study, the median survival time for all persons with malignant pleural effusions was 90 days.[374]

Treatment options for malignant pleural effusion include thoracentesis or repeat thoracentesis; tube thoracostomy, drainage, and sclerotherapy using talc, bleomycin, or other material; placement of a chronic indwelling pleural catheter[374,375]; and thoracoscopy with drainage and talc insufflation. In the past, successful treatment of malignant pleural effusions required hospitalization for chest tube drainage, sclerosis, and, hopefully, pleural symphysis followed by removal of the drainage catheters. If pleural symphysis could not be achieved during the individual's hospitalization the treatment was considered "failed," and the patient was then treated with the best available means. Pleurodesis was required for discharge. In contrast, today's patient-centered treatment focuses on relief of the patient's symptoms and restoration of normal function. Pleurodesis is not necessarily required to accomplish these goals.[373]

Stage IV Non-Small Cell Lung Cancer

In individuals with metastatic NSCLC, surgery is reserved for palliation of symptoms or resection of metastases with significant local manifestations (e.g., brain metastasis and seizures).[376] Persons with two synchronous nodules of NSCLC with identical histology in different lobes have M1 disease by the current staging system, although it is impossible to exclude synchronous stage I NSCLC by clinical means alone. When doubt exists, the benefit of resection should be considered in selected physiologically fit individuals. Appropriate staging with CT and PET scanning and cervical mediastinoscopy is required. If there is no evidence of nodal or other metastatic disease, and the nodules are completely resectable with an appropriate risk-to-benefit ratio, then resection could be considered.[377,378]

Brain metastases are often seen in individuals with NSCLC, and although they are frequently multiple, a subset of patients with a solitary brain metastasis (with controlled primary tumor) is occasionally encountered in clinical practice. Patients with isolated brain metastases may do well with resection of the symptomatic lesion.[379,380] Although treatment of a solitary brain metastasis is usually surgical whenever possible, the development of new stereotactic techniques of radiation therapy using a linear accelerator or the gamma knife provides new potential treatment options.[381] Before resection all patients should have additional staging to include CT and PET scans. In those considered as candidates for resection, cervical mediastinoscopy should also be performed even if the preoperative CT reveals no enlarged nodes, and the PET demonstrates no FDG-avid lesions. The primary lung tumor is then treated according to T and N stage.[379,380] Survival may range between 20% and 40% at 5 years.

Hematogenous metastases to the adrenal gland and elsewhere, in general, portend a poor survival, and although isolated reports of resection have occurred, this treatment strategy is not uniformly successful.[376,382–384] Resection of metastatic lung cancer with curative intent is not recommended, because adrenal and other extrathoracic metastases represent systemic metastases.[382] The curious survival advantage seen in some patients may be related to overdiagnosis bias in individuals with early primary-stage disease.

Experimental Surgical Techniques

Experimental techniques for treatment of parenchymal NSCLC in medically inoperable individuals include radiofrequency ablation and stereotactic thoracic radiation.[385,386]

Second Primary Tumors or Metastasis

Recurrent tumors may be resected safely and with good survival. Generally, lung cancer that recurs with identical histology within 2

years is considered a metastasis; lung cancer that recurs after 2 years is considered a second primary. Patients with resection of second (metachronous) primary lung cancers can have up to 5-year survival of 40% after resection that is based on the T and N status of the second primary.[336,338,387] A completion pneumonectomy, if required, can be performed safely, with good local control achieved, and as much as a 25% 5-year survival.

In summary, the thoracic surgeon must balance the risks from mechanical extirpation of lung cancer (local disease control, pain relief, improved survival) and the benefits of improvement in survival and quality of life. Typically, when the risks are high, resection is not considered; however, in some high-risk patients risk may be successfully managed with good local control and survival.[314] Resection of NSCLC can be performed safely in most individuals who meet certain minimal physiologic thresholds. Consistency of approach, application of proven intraoperative and perioperative techniques, completeness of resection, and adequacy of mediastinal lymph node dissection all benefit the patient in optimizing local control and subsequent therapeutic decisions. Selection of optimal surgical treatment for individuals with NSCLC requires excellent pretreatment staging and clinical evaluation with discussion of all therapeutic possibilities by the integrated multidisciplinary care team: thoracic surgeon, pathologist, pulmonologist, radiation oncologist, medical oncologist, and allied specialties. Individuals with advanced-stage lung cancer (i.e., stage IIIA or greater, biopsy-proven N2, etc.) inconsistently benefit from resection alone, because the risks of resection frequently do not exceed the benefits.[314] In selected individuals resection of advanced-stage lung cancer may be desirable for local tumor control (alone or as part of a multidisciplinary treatment plan), palliation of symptoms, improved quality of life, and the potential for improved survival. Few prospective multi-institutional clinical trials have specifically addressed surgery compared to other therapies for early-stage disease. Future clinical trials should consider accurate and noninvasive measures of local control and recurrence, specific measures of response, quality-of-life measures, as well as overall and disease-free survival.

Adjuvant Chemotherapy

Until recently convincing evidence supporting the routine use of postoperative adjuvant chemotherapy in resected NSCLC was lacking. Notably, an evaluation of adjuvant studies completed before 31 December 1991 was included in a landmark 1995 meta-analysis of 52 randomized chemotherapy trials in NSCLC.[388] Globally no improvement in overall survival was identified following postoperative chemotherapy. However, when the data were analyzed by composition of the adjuvant chemotherapy regimen, there was a nonsignificant 13% reduction in the risk of death observed with platinum-based regimens that translated into an absolute survival benefit of 5% at 5 years ($P = 0.08$).[388] The magnitude of the survival benefit was similar to that observed with adjuvant chemotherapy in early-stage breast cancer,[389] prompting several groups to initiate a new series of adjuvant trials in NSCLC using a newer and more efficacious generation of platinum-based chemotherapy regimens.[390–396] A few of the recent studies also permitted the use of postoperative radiation therapy. Meta-analyses of these data estimate a relative risk reduction in mortality of 11% to 13% at 5 years.[397–399] Collectively the results of these trials clearly support the use of postoperative therapy in individuals with good performance status with stage II or IIIA NSCLC (Table 76-9).[400–402]

Much less clear and far more controversial is the role adjuvant chemotherapy plays in the management of individuals with resected stage I NSCLC.[401–403] The controversy stems in part from subgroup analyses of recently completed adjuvant trials data that suggest stage I patients do not obtain a meaningful survival improvement following postoperative chemotherapy.[393,394] This is somewhat surprising, in that extrathoracic metastases are the most common site of recurrence in resected individuals with stage I disease,[404] and one would predict a favorable effect with systemic therapy. Nonetheless, the verisimilitude of the subgroup analyses was bolstered by the negative results of a Cancer and Leukemia Group B (CALGB 9633) phase III trial that specifically addressed the utility of adjuvant chemotherapy in stage IB NSCLC.[395,405] Although the initial report of the CALGB

Table 76-9 Results of Recent Postoperative Adjuvant Trials in Non-Small Cell Lung Cancer

Trial	Stage	Treatment	No. of Patients	5-Yr Survival (%)	HR	*P* Value
ALPI[390]	I–III	Surgery	540	45	0.96	0.59
		MVP	548	50		
IALT[391]	I–III	Surgery	935	40.4	0.86	<0.03
		CDDP-based	932	44.5		
ANITA[394]	IB–IIIA	Surgery	433	42.6	0.80	0.017
		CDDP + VNB	407	51.2		
BLT[396]	I–IIIA	Surgery	189	58†	1.02	0.90
		CDDP-based	192	60†		
NCI-C[393]	IB–II	Surgery	240	54	0.60	0.03
		CDDP + VNB	242	69		
CALGB[395]	IB	Surgery	171	57	0.80	0.10
		CBDCA + Pac	173	59		
JLCRG[392]	IA–B*	Surgery	488	85	0.71	0.047
		UFT	491	88		
Roselli et al[406]	IB	Surgery	70	42	NR	0.02
		CDDP + E	70	62		

CDDP + E, cisplatin + etoposide; CDDP + VNB, cisplatin + vinorelbine; CBDCA + Pac, carboplatin + paclitaxel; MVP, mitomycin, vinblastine, cisplatin; UFT, uracil-tegafur.
*Adenocarcinomas only.
†2-year survival.

study indicated that postoperative carboplatin and paclitaxel imparted a significant survival advantage compared with no adjuvant therapy,[405] the survival benefit was no longer apparent upon longer follow-up.[395] Five of the adjuvant chemotherapy trials listed in Table 76-9 were included in a recent meta-analysis[390,391,393,394,396]—the so-called Lung Adjuvant Cisplatin Evaluation (LACE) analysis.[398] Despite the increased statistical power, there was not a survival benefit among individuals with stage I NSCLC. In fact, there was a trend toward detriment with treatment in persons with stage IA disease. The effect of adjuvant chemotherapy in stage IB disease seemed to be neutral.

Three of the post-1995 meta-analysis adjuvant trials specifically addressed the question of postoperative chemotherapy in resected stage I NSCLC,[392,395,406] whereas a fourth study was limited to persons with stages IB and II disease.[393] None of the stage I-only adjuvant trials was included in the LACE meta-analysis.[398] Two of these trials demonstrated a statistically significant improvement in survival in stage I individuals given adjuvant chemotherapy.[392,406] Only the CALGB 9633 proved negative for a survival improvement, although interestingly disease-free survival was statistically significantly improved with chemotherapy.[395] Collectively the data derived from studies confined to stage I NSCLC suggest there may be some patients with stage I disease who benefit from adjuvant chemotherapy. This is not too surprising, because stage I NSCLC is a heterogeneous disease that in some circumstances carries a prognosis that rivals that of stage II or stage IIIA disease (e.g., large primary lesions >5 cm; visceral pleural involvement).[407,408] Adjuvant therapy may be appropriate for such individuals, provided he or she understands the risks of treatment. Our approach to resected stage I NSCLC is outlined in the accompanying algorithm (Fig. 76-15).

There are several promising technologies on the horizon that may soon permit oncologists to prospectively assign persons with NSCLC into "good" or "bad" survival categories and help guide treatment decisions.[76,78,81] However, until these newer technologies are proved to be reliable predictors of treatment response and survival, clinical judgment is still required when making a decision to offer adjuvant chemotherapy to individuals with resected NSCLC. Most experts agree that adjuvant therapy should be limited to those with a good performance status (i.e., ECOG PS = 1), few comorbidities, and a relatively short postoperative recovery period (i.e., <8 weeks).[400–402]

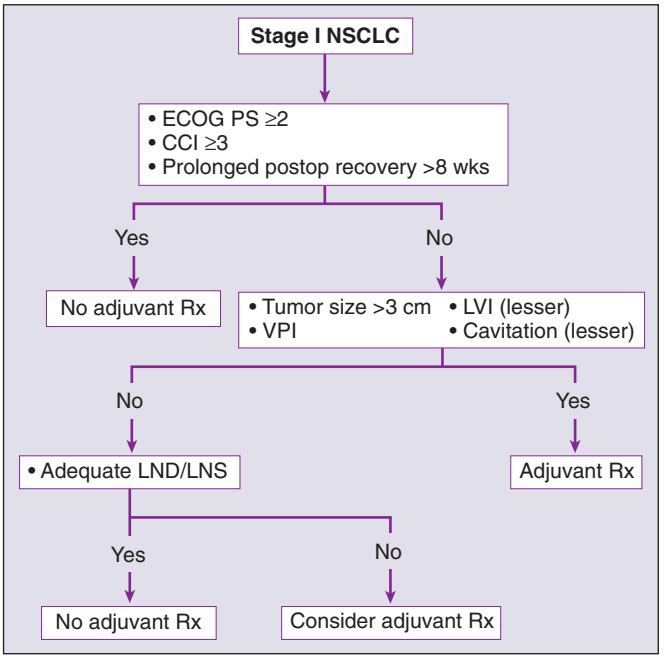


Figure 76-15 • Algorithm for selecting stage I NSCLC patients for postoperative adjuvant chemotherapy. CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; LND, mediastinal lymph node dissection; LNS, systematic mediastinal lymph node sampling; LVI, lymphovascular invasion; PS, performance status; Rx, treatment; VPI, visceral pleural invasion.

Adjuvant Radiation Therapy

Individuals with resected node-negative lung cancer do not benefit from adjuvant radiation therapy.[4,409–411] Likewise, randomized trials studying the efficacy of adjuvant radiation therapy after surgical resection of persons with N2 disease have shown no improvement in survival.[411,412] A recent clinical trial studied overall survival, progression-free survival, and toxicity associated with concurrent paclitaxel plus carboplatin and TRT for patients with completely resected stage II and IIIA NSCLC.[413] Eighty-eight eligible individuals had surgical resection for pathologic stage II or IIIA disease and received postoperative paclitaxel and carboplatin. Concurrent TRT at 50.4 Gy in 28 fractions for 6 weeks was given. A boost of 10.8 Gy in six fractions was given for extracapsular nodal extension or T3 lesions. The median overall survival time was 56.3 months, with 1-, 2-, and 3-year survival rates of 86%, 70%, and 61%, respectively. Local failure was a component of first failure in 15% of these individuals. Our current practice is to consider postoperative radiation therapy when surgical resection is incomplete (positive surgical margins), surgical margins are close (≤1 mm), or when there is extracapsular extension from lymph node metastases.

Neoadjuvant Chemotherapy

Neoadjuvant or induction chemotherapy offers several potential advantages compared with adjuvant chemotherapy, such as improved compliance and drug delivery, early control of micrometastases, and reduction of the primary tumor size before surgery, thus allowing for more conservative and possibly complete resection of the tumor.[414–416] Several phase II clinical trials have shown that induction chemotherapy is safe and feasible, with no significant increase in surgical complications, and results in favorable survival rates in persons with resectable NSCLC (see reviews[414–416]). Improved survival is seemingly greatest in individuals in whom a complete pathologic response is achieved.[417] Randomized neoadjuvant chemotherapy trials, however, have revealed conflicting results.[418,419]

Initial enthusiasm for neoadjuvant chemotherapy originated in part with the publication of two small randomized trials conducted exclusively in persons with N2-positive stage IIIA NSCLC.[356,357] Although these trials closed prematurely as a result of accrual problems, both studies yielded a positive survival advantage with neoadjuvant therapy. Subsequently, two larger phase III trials were undertaken in an attempt to validate these results and extend the observation with earlier stage, resectable NSCLC.[355,420] The first of these was conducted by the French Thoracic Cooperative Group in which individuals with stage I through IIIA NSCLC were randomized to surgery or surgery combined with two cycles of neoadjuvant mitomycin, ifosfamide, and cisplatin.[355] Two cycles of postoperative mitomycin, ifosfamide, and cisplatin were administered to responding individuals. In addition, persons with pathologic T3 or N2 disease or incomplete resection received postoperative radiation therapy. There was a statistically non-significant 3.8% (95% CI, 1.3% to 25.1%) improvement in 1-year survival increasing to 8.6% (95% CI, 2.64% to 24.4%) survival benefit at 4 years in persons treated with preoperative chemotherapy. This benefit, however, was seemingly limited to persons with N0 and N1 disease (relative risk [RR], 0.68, 95% confidence interval [CI], 0.49–0.96, $P = 0.027$).[355] Neoadjuvant chemotherapy was associated with nonsignificant higher perioperative mortality (9% vs. 5%), a problem not reported by others.[311,356,357] Complicating the interpretation of these data were potentially important differences in the patient characteristics and treatment of the two arms. For example, almost twice as many patients in the chemotherapy arm had N2 disease (40% vs. 28%), whereas almost twice as many patients in the surgery-alone arm

received postoperative radiation therapy (48% vs. 28%). These differences may or may not have contributed to the overall outcomes.

A U.S. Intergroup study (S9900) enrolled individuals with clinical stages IB through IIIA NSCLC (T2N0, T1–2N1, and T3N0–1) into a randomized study of surgery alone or surgery preceded by three cycles of paclitaxel and carboplatin.[420] Individuals with superior sulcus tumors were excluded. The study was closed prematurely with the recognition that postoperative adjuvant chemotherapy imparted a survival benefit in this group of individuals with NSCLC (discussed earlier). Neoadjuvant paclitaxel and carboplatin yielded an objective response of 40%. Although progression-free and overall survival tended to favor the neoadjuvant chemotherapy arm, these differences were not statistically significant (median and 2-year survivals were 42 months and 68% with neoadjuvant chemotherapy vs. 37 months and 64% with surgery alone; $P = 0.47$). There were six treatment-related deaths within 30 days of surgery in the neoadjuvant arm compared with three deaths in the surgery-alone arm.

A recent literature-based meta-analysis examined the role of induction chemotherapy in early-stage NSCLC.[419] The analysis involved all randomized studies conducted between 1965 and 2004 published in English or French. The overall hazard ratio was 0.66 (95% CI, 0.48–0.93) in favor of the addition of induction chemotherapy to a standard surgical procedure. Although the trend was in favor of neoadjuvant chemotherapy in stage III disease (HR = 0.65; 95% CI, 0.41–1.04), it was not statistically significant. By contrast, a second meta-analysis evaluating trials published between 1994 and 2004 failed to note a survival advantage for persons with resectable NSCLC who had preoperative chemotherapy.[421]

At the present time the role of induction chemotherapy remains ill-defined. Similar to other solid tumors (e.g., breast cancer), neoadjuvant chemotherapy may ultimately prove useful in rendering a marginally resectable lesion more amenable to definitive resection but without imparting a positive survival benefit. Only prospective trials will answer this question. However, defining the optimal candidate for preoperative versus postoperative chemotherapy comparative trials will prove challenging. Our approach has been to treat individuals with clinical stage I and II disease with surgery and to administer postoperative adjuvant chemotherapy to those who are appropriate candidates as described previously. Individuals with so-called marginally resectable lesions are assessed on a case-by-case basis. We are more inclined to administer neoadjuvant chemotherapy to those with minimal involvement of N2 lymph nodes. Persons with multiple positive N2 disease are not thought to be candidates for surgery and are treated with concurrent chemotherapy–radiation therapy as discussed later.

Neoadjuvant Chemotherapy–Radiation Therapy

The addition of TRT to preoperative chemotherapy further increases the frequency of pathologic clearance of mediastinal lymph nodes, suggesting that trimodality therapy (i.e., neoadjuvant chemotherapy–radiation therapy followed by surgery) might be superior to a bimodality approach.[416] To address this possibility several investigators have conducted trials combining induction chemotherapy with radiation given either sequentially or concurrently before surgery for individuals with stage III NSCLC (see review[416]). A variety of cisplatin-based chemotherapy regimens have been administered in combination with various total doses of TRT (typically 30–45 Gy) given once or twice daily, and some trials even included stage IIIB patients (excluding pleural effusions). For example, SWOG investigators administered concurrent TRT (45 Gy) with two cycles of induction cisplatin plus etoposide to 126 patients with biopsy-proven stage IIIA (N2) or IIIB NSCLC.[361] Persons who experienced an objective response or stable disease were taken to definitive resection. The objective response rate to induction was 59%, and 29% had stable disease. Resectability was 85% for the IIIA group and 80% for the IIIB group. Although 13 treatment-related deaths (10%) were observed, 3-year survival rates were 27% and 24%, respectively, for stage IIIA (N2) and IIIB disease. As noted by others, the strongest predictor of long-term survival after thoracotomy was absence of tumor in the mediastinal nodes at surgery (3-year survival: 44% vs. 18%; $P = 0.0005$).

The phase II trials of preoperative chemoradiation yielded results that were similar to the induction chemotherapy-alone trials in terms of response, resection, and survival rates.[416] The need for surgery also in the treatment of individuals with N2-positive stage IIIA NSCLC has not been fully determined. Intergroup trial 0139 was designed to address this controversy and prospectively compared preoperative concurrent chemotherapy–radiation therapy to concurrent chemotherapy–radiation therapy alone.[359] Eligible patients had a good performance status (0–1) and proven involvement of N2 nodes with no evidence of metastatic disease. All study participants received cisplatin and etoposide with concomitant TRT to 45 Gy starting day 1. The trimodality group went to a resection if there was no evidence of disease progression with induction therapy and then received two additional cycles of etoposide and cisplatin (EP). The bimodality group continued with TRT to a total dose of 61 Gy with EP for two additional cycles. Although progression-free survival was superior following trimodality therapy, this did not translate into an improvement in 5-year survival (27.7% vs. 20.3%; $P = 0.10$). There were 16 treatment-related deaths in the trimodality arm (10 within 30 days of surgery) and 4 treatment-related deaths in the bimodality arm. Postoperative mortality was particularly high in those requiring simple or complex pneumonectomy. Improved long-term survival was observed in persons with downstaging from positive to N2 to N0 disease at surgery (5-year survival: pN0 = 41%; pN1–3 = 24%; no surgery = 8%; $P < 0.0001$). This is similar to several smaller studies that have highlighted the importance of N0 disease at the time of resection following neoadjuvant chemotherapy–radiation therapy.[416,417]

Although these data are intriguing, there remain no data that definitively prove that radiation therapy improves outcome over chemotherapy and surgery, or that surgery adds to the therapeutic efficacy of chemotherapy and radiation therapy.[416] The subsets for which trimodality treatment is preferred include patients with T4N0–1 disease and superior sulcus tumors. Cancers located in the superior sulcus are difficult to resect and frequently have residual disease after resection. For these reasons, neoadjuvant chemotherapy–radiation therapy is indicated before thoracotomy.[348] Our current practice is to only use neoadjuvant chemotherapy and radiation therapy when this therapy is needed to facilitate resection of locally extensive tumors such as superior sulcus tumors. Moreover, a strong statement can be made that patients who will require a pneumonectomy should NOT be considered for a trimodality approach and should be treated with concurrent chemotherapy–radiation therapy.

Treatment of Locally Advanced Unresectable Non-Small Cell Lung Cancer

Locally advanced NSCLC consists of stages IIIA (T3N1M0 or T1–3N2M0) and IIIB (T4NanyM0 or TanyN3M0) and is considered unresectable in all but the most unusual of cases.[317,365,372] Nonetheless, with the exception of the subset of persons with malignant pleural effusion, individuals with stage III lung cancer are treated with curative intent.[317,365] Individuals with malignant pleural effusion preferentially are treated with chemotherapy (see later discussion; metastatic disease). Until the 1980s radiation therapy alone had been the standard of care for locally advanced NSCLC despite dismal survival results.[422–424] Using standard traditional radiation doses and technique, survival rates of 40%, 15%, and 5% were achieved at 1, 2, and 5 years respectively.[422–424] During the early 1990s, however, results of many randomized phase III studies shifted the standard toward concurrent chemoradiation therapy.[424] The key trials that led to the evolution in treatment of locally advanced NSCLC are described later. In addition, recent technologic advances in radiation therapy and novel chemotherapeutic approaches have provided pre-

Table 76-10 Multicenter Phase III Trials Comparing Sequential Chemoradiation versus Radiation Alone

Study	CT-RT Sequence	No. of Patients	RT Dose (Gy)	CT	MST	5 Yr (%)	Acute Grade ≥3 Toxicity (%)
CALGB 8433[425,440]	Daily RT	77	60	N/A	9.6 mo	6	7
	CT → daily RT	78	60	PVbl	13.7 mo	17	3
RTOG 8808[426,427]	Daily RT	152	60	N/A	11.4 mo	5	1
	CT → daily RT	152	60	PVbl	13.8 mo	8	1
	Twice daily RT	154	69.9	N/A	12.3 mo	6	3
CEBI 138[661]	Daily RT	167	65	N/A	10 mo	3	3
	CT → daily RT	165	65	VCPC	12 mo	6	5

CT, chemotherapy; MST, median survival time; P, cisplatin; RT, radiotherapy; Vbl, vinblastine; VCPC, vindesine, cyclophosphamide, cisplatin, and lomustine.

liminary data for further improving clinical outcome while minimizing the morbidity associated with the therapy.[423]

Sequential Chemoradiation versus Radiation Alone

With sequential chemoradiation, full doses of both modalities can be delivered without compromise of either. The rationale behind the sequential combination of chemotherapy and radiation therapy is based on the premise that radiation therapy addresses the local-regional disease whereas chemotherapy acts systemically to eradicate micrometastases. The first large-scale trial to demonstrate a survival benefit with sequential chemoradiation therapy compared to standard radiation therapy alone was conducted by the Cancer and Leukemia Group B (CALGB); (Table 76-10).[425] These investigators administered cisplatin and vinblastine before standard TRT (i.e., 60 Gy over 6 weeks) and observed an improvement in median and long-term survival (23% vs. 11% at 3 years). These findings were later validated by a North American Intergroup trial (Radiation Therapy Oncology Group [RTOG] 88–08) in which persons with unresectable NSCLC were randomized to one of two radiation-alone arms (daily to 60 Gy or twice daily to 69.6 Gy), or to a third arm of induction chemotherapy with cisplatin and vinblastine followed by daily radiation therapy to 60 Gy.[426,427] Similar to the CALGB trial, there was a statistically significant improvement in median survival with sequential chemoradiation therapy, compared with those of the two arms using radiation therapy alone (see Table 76-10). These in addition to other landmark trials consistently demonstrate a significant survival benefit with the addition of induction chemotherapy over conventional or hyperfractionated irradiation alone. Induction chemotherapy seems to reduce the number of distant relapses, which translates into a modest benefit in survival. As a result of these studies, sequential chemoradiation became the basis for comparisons in clinical trials of the 1990s.

Sequential versus Concurrent Chemoradiation Therapy

The mechanism of chemotherapeutic radiosensitization is thought to be direct inhibition of repair of radiation-induced damage; elimination of radioresistant, chemosensitive clones; and/or suppression of interfraction tumor repopulation.[428] Concurrent chemoradiation addresses both distant and local-regional disease simultaneously. The two modalities should act synergistically on tumor clonogens susceptible to both modalities and in a complementary fashion on local-regional clonogens that are susceptible to only one of the modalities. The superiority of concurrent chemotherapy with radiation therapy compared with sequential chemotherapy followed by irradiation was conclusively demonstrated in large multicenter trials.[429–431] In the first of these trials, Japanese investigators randomized individuals with locally advanced NSCLC to receive either concurrent or sequential chemoradiation therapy.[431] Chemotherapy consisted of mitomycin (8 mg/m^2 days 1 and 29), vindesine (3 mg/m^2 days 1, 8, 29, and 36), and cisplatin (80 mg/m^2 days 1 and 29). TRT (56 Gy) was administered as a split course in the concurrent arm but was given continuously in the sequential arm. Overall response rate and survival were statistically significantly improved with concurrent chemotherapy–radiation therapy (Table 76-11). The survival benefit seemed to be due primarily to improved local tumor control based on a marked improvement in local failure-free survival (30 vs. 11 months), whereas

Table 76-11 Multicenter Phase III Trials Comparing Concurrent with Sequential Chemoradiotherapy

Study	Sequence	No. of Patients	RT Dose (Gy)	CT	MST	3 Yr (%)	5 Yr (%)	Gr ≥3 Esophagitis (%)
West Japan Lung Cancer Group[431]	CT → daily RT	158	56	MVP	13.3 mo	15	9	2
	CT + daily RT	156	56*	MVP	16.5 mo	22	16	3
RTOG 9410[429,433]	CT → daily RT	201	60	PVbl	14.6 mo	n.r.	10	4
	CT + daily RT	201	60	PVbl	17 mo	n.r.	16	23
	CT + twice daily RT	193	69.6	PE	15.1 mo	n.r.	13	46
GLOT-GFPC NPC 95-01[430]	CT → daily RT	101	66	PVbl	14.5 mo	19	14†	3
	CT + daily RT → CT	100	66	PE → PVin	16.3 mo	25	21†	32
Czech study[434]	CT → daily RT	50	60	PVbl	12.9 mo	9.5	n.r.	4
	CT + daily RT	52	60	PVbl	16.6 mo	18.6	n.r.	18

CT, chemotherapy; E, etoposide; MST, median survival time; MVP, mitomycin, vindesine, cisplatin; P, cisplatin; RT, radiotherapy; Vbl, vinblastine; Vin, vinorelbine; n.r., not reported.
*Split course RT.
†4-yr survival.

distant failure rates were similar at approximately 50%. These findings recapitulate earlier reports of improved local tumor control without improvement in the rate of distant metastasis when cisplatin is administered with split-course radiation therapy.[432]

The RTOG addressed the question of sequential versus concurrent chemotherapy–radiation therapy in study 9410.[429,433] The trial also included a third arm designed to assess the value of twice-daily irradiation in conjunction with chemotherapy. Chemotherapy consisted of cisplatin and vinblastine. The twice-daily radiation therapy arm demonstrated improved local control without improving survival, whereas the concurrent chemotherapy–radiation therapy arm was superior to the sequential treatment in terms of local control, median survival (17.0 vs. 14.6 months; $P = 0.0038$), and 4-year survival rate (21% vs. 12%; $P = 0.046$; see Table 76-10). Acute grade 3 to 5 toxicities were more frequent in the two concurrent chemotherapy–radiation therapy arms. However, the differences in late effects were not statistically significant.

French investigators also compared sequential and concurrent chemotherapy–radiation therapy in individuals with unresectable stage III NSCLC.[430] Sequential therapy consisted of three cycles of cisplatin (120 mg/m^2) every 3 weeks and weekly vinorelbine (30 mg/m^2 per week) followed by TRT (66 Gy in 33 fractions), whereas the concurrent arm used the same radiation therapy with simultaneous initiation of daily cisplatin (20 mg/m^2 daily) and etoposide (50 mg/m^2 per day) on days 1 to 5 and 29 to 33. The concurrent arm then received two courses of consolidation therapy with cisplatin (80 mg/m^2) and vinorelbine (30 mg/m^2 per week). Treatment-related deaths (10 vs. 3) and WHO grade 3 to 4 esophageal toxicity (32% vs. 3%; $P < 0.0001$) were significantly more frequent in the concurrent arm than in the sequential arm. Median survival (16.3 vs. 14.5 months) and 4-year survival rates (21% vs. 14%) were not statistically significantly different; this result the investigators attributed to insufficient powering of the trial (see Table 76-11). However, an alternative explanation might be the excess of toxic deaths in the concurrent arm, which in turn may be attributable to the dose and scheduling of cisplatin and vinorelbine. Less life-threatening toxicity has been observed with different doses and scheduling of these agents without an apparent compromise in overall efficacy.[424]

These and similar trials[434] consistently demonstrate a survival advantage for the concurrent chemotherapy–radiation therapy as opposed to the sequential use of chemotherapy followed by TRT but always with an increase in host toxicity—most specifically with respect to an increase in treatment-related esophagitis. Of concern is the modest but clinically meaningful increase in treatment-related deaths accompanying concurrent chemotherapy–radiation therapy in some of the aforementioned trials. Nonetheless, the results from these trials established concurrent chemoradiation therapy as the current standard for locally advanced NSCLC in good-performance-status patients with limited comorbidities.

Concurrent Chemoradiation Therapy with Consolidation or Induction Chemotherapy

Building on the survival benefits achieved with concurrent chemotherapy–radiation therapy in locally advanced NSCLC, SWOG investigators conducted a series of sequential phase II trials designed to assess the benefit of consolidation therapies in locally advanced NSCLC (Table 76-12). The first of these trials, S9019, assessed the feasibility and impact on long-term survival of full-dose cisplatin and etoposide given during and after full-dose TRT (61 Gy).[371] The study enrolled only individuals with pathologically confirmed stage IIIB NSCLC and yielded a median survival time of 15 months and 5-year survival of 17%. In a follow-up study (S9504), 83 individuals with pathologic stage IIIB NSCLC were treated with the same regimen of cisplatin and etoposide with concurrent TRT followed by docetaxel.[435,436] With a median follow-up of 71 months, median survival time was 26 months, and the 5-year survival rate was 29%. Long-term survival compared favorably with the data from the SWOG S9019 study. Despite a lack of phase III confirmatory data, this regimen became the reference arm for a third SWOG trial (S0023) in which patients were randomized to gefitinib, an inhibitor of the EGFR tyrosine kinase, or a placebo.[437] Notably, the median survival of patients randomized to gefitinib was dramatically lower than that of patients given a placebo (19 vs. 29 months; $P = 0.09$). This trial was closed early, because gefitinib was deemed unlikely to improve overall survival. At the same time SWOG S0023 was under way, the Hoosier Oncology Group (HOG) undertook a phase III trial (LUN-01–24) designed to confirm the results of SWOG trial S9504 (i.e., to evaluate the role of consolidation docetaxel in individuals with unresectable stage III disease).[438] In the HOG study, persons with stage III NSCLC and no evidence of local disease progression or distant metastases were randomized to receive docetaxel or observation after completing concurrent cisplatin and etoposide with TRT. The HOG trial recently closed on the recommendation of a Data and Safety Monitoring Committee as a consequence of a statistical improbability that the docetaxel arm would yield an increase in overall survival. (Overall median survival = 21.15 months; median survival for those taking docetaxel = 21.6 months vs. 24.2 months for those in the observation arm; $P = 0.94$.)[439]

In contrast to SWOG, CALGB investigators opted to evaluate the role of induction chemotherapy with concurrent chemotherapy–radiation therapy based on their long-standing interest in the use of induction chemotherapy.[440] In CALGB 39801 individuals with unresectable stage III NSCLC were randomized to immediate concurrent

Table 76-12 Phase II Trials Comparing Induction or Consolidation Chemotherapy with Concurrent Chemoradiotherapy

Study	Sequence	No. of Patients	RT Dose (Gy)	CT	MST	3 Yr (%)	Gr ≥3 Esophagitis (%)
SWOG S9019[371]	CT + daily RT → CT	50	61	PE → PE	15 mo	17	20
SWOG S9504[435,436]	CT + daily RT → CT	83	61	PE → D	26 mo	40	n.r.
CALGB 39801[440]	CT → CT + daily RT	184	66	CbT	14 mo	54*	n.r.
	CT + daily RT	182	66	CbT	11.4 mo	48*	n.r.
LAMP[442]	CT → daily RT	91	63	CbT	13 mo	17	3
	CT → CT + daily RT	74	63	CbT → low-dose CbT	12.7 mo	15	19
	CT + daily RT → CT	92	63	low-dose CbT → CbT	16.3 mo	17	28

CbT, carboplatin/paclitaxel; CT, chemotherapy; D, docetaxel; MST, median survival time; PE, cisplatin/etoposide; RT, radiotherapy; n.r., not reported.
*1-year survival.

chemotherapy–radiation therapy (i.e., carboplatin AUC = 2 and paclitaxel 50 mg/m^2 each given weekly during 66 Gy TRT; 182 patients) or two cycles of induction carboplatin (AUC 6) and paclitaxel (200 mg/m^2) followed by concurrent chemotherapy–radiation therapy.[441] There were no differences in survival outcomes (median and 1-year survival of 11.4 and 14.6 months and 48% to 58% respectively; $P = 0.154$), although follow-up is short (see Table 76-12). Curiously, the results of both arms were somewhat inferior to historical controls and the results in the control arms of the studies listed in the preceding section. Nonetheless, the results of this study suggest that induction chemotherapy before concurrent chemoradiation is not beneficial.

The American College of Radiology conducted a randomized phase II study designed to determine the optimal sequencing and integration of chemotherapy with standard daily TRT in individuals with locally advanced unresectable stages IIIA and IIIB NSCLC.[442] This trial, better known as the Locally Advanced Multimodality Protocol (LAMP) study, randomized patients to induction chemotherapy followed by irradiation (arm A), induction chemotherapy followed by concurrent chemoradiation (arm B), or chemoradiation followed by consolidation chemotherapy (arm C; see Table 76-12). Participants received full systemic doses of carboplatin and paclitaxel as induction or consolidation therapy and weekly low doses of carboplatin and paclitaxel during concurrent chemotherapy–radiation therapy. All patients received TRT to 63 Gy. The LAMP trial suffered from poor accrual and was terminated before enrolling the target number of patients. Nonetheless, LAMP is the only large trial directly comparing induction and consolidation chemotherapy in the setting of concurrent chemoradiation. With a median follow-up time of more than 3.5 years, median overall survival was virtually identical in the induction arms (arm A 13.1; arm B 12.7 months) and longest with the concurrent chemotherapy–radiation therapy–consolidation approach (16.3 months). Toxicity, however, was greater in the latter arm. The results of the LAMP trial suggest a benefit of consolidation chemotherapy following concurrent chemotherapy–radiation therapy,[442] although these results can hardly be considered definitive because of inadequacies in the study design and imbalances in prognostic factors among the three arms.[424] Likewise, the role of consolidative docetaxel after full-dose EP and concomitant chemoradiation therapy is not supported by phase III data.[438] Neither docetaxel nor gefitinib is recommended as consolidation therapy following concurrent chemotherapy–radiation therapy for locally advanced NSCLC given the lack of a survival advantage and an increase in toxicity. Further studies are necessary to fully define the optimal administration of concurrent chemotherapy–radiation therapy with or without induction or consolidation chemotherapy.

Optimal Chemotherapy Regimen in Stage III Non-Small Cell Lung Cancer

There is a paucity of data comparing different chemotherapy regimens in the setting of locally advanced NSCLC. For many theoretical reasons a regimen that includes cisplatin may be superior to a non-platinum-containing regimen. However, questions remain as to whether a low-dose platinum regimen is actually equivalent to a full-dose cisplatin-based regimen given concurrently with radiation therapy. One regimen that has consistently stood the test of time consists of that first used in SWOG trial S9019.[371] The SWOG approach consists of two cycles of induction EP administered concurrently with once-daily TRT (45 Gy). In the absence of progressive disease, radiation therapy is continued to a total dose of 61 Gy after which two additional cycles of EP are delivered. An alternative approach is to use the LAMP regimen of concurrent low-dose weekly carboplatin plus paclitaxel with radiation therapy followed by two additional cycles of full-dose consolidation carboplatin plus paclitaxel chemotherapy.[442] The decision to use one particular regimen over others is often made on the basis of secondary factors such as cost, logistical convenience, ease of administration, toxicity profile, patient preference, and physician experience.

Modulation of Concurrent Chemoradiation Therapy Toxicity

Although concurrent chemoradiation provides a significant survival benefit in locally advanced NSCLC, it comes at the cost of increased toxicity.[443–445] Radioprotectors are an attractive way to reduce the morbidity associated with combined-modality therapy and thereby may allow radiation therapy dose escalation to improve local control and survival. Amifostine is a candidate drug and acts primarily by scavenging free radicals released during the interaction of ionizing radiation and water. It theoretically protects normal tissue preferentially, thus increasing the therapeutic window. Thus far four randomized studies have been performed with amifostine in the setting of lung cancer with divergent results.[446–449] The largest of these trials was conducted by RTOG (RTOG 98–01).[449] All patients enrolled in the RTOG study received induction and concurrent carboplatin and paclitaxel with hyperfractionated radiation therapy (69.6 Gy) with or without amifostine. The primary endpoint was the frequency of grade 3 or higher esophagitis, a common toxicity of concurrent chemoradiation administration. However, no difference in the rate of grade 3 or higher esophagitis was detected, and there was a significant increase in the rate of nausea and vomiting, cardiovascular toxicity, and infection and febrile neutropenia with amifostine. Individuals given amifostine reported subjective improvement in swallowing and improved pain control, but quality-of-life measures were not statistically different nor was there an improvement in treatment compliance or survival. These data coupled with negative results achieved in other settings in which concurrent chemoradiation therapy is used[450] suggest that further study of this approach using amifostine is unlikely to be productive. However, some experts believe improved schedules of amifostine administration (such as more frequent dosing closer to the treatment time) could yield improved results.[446,447] The cost-to-benefit ratio of such frequent, strict dosing of this expensive drug in routine clinical practice has not been adequately studied, and thus we believe there is no compelling reason to use amifostine in this setting.

Molecular-Targeted Combined Modality Therapy

Molecular-targeted therapy is a novel strategy evolving from our increasing understanding of the underlying pathways and key molecules involved in tumor growth and progression. Theoretically, the specificity of molecular-targeted therapy should improve the therapeutic window by affecting the tumor cells and sparing normal cells. EGFR is an important mediator of growth factor signaling pathways that affect normal cell proliferation, motility, adhesion, and survival, as well as angiogenesis. EGFR is highly expressed in many solid tumors, and there have been reports correlating overexpression of EGFR with poor prognosis. Gefitinib, an inhibitor of EGFR tyrosine kinase activity, was the first targeted agent to be approved for the treatment of third-line NSCLC. As noted previously, SWOG investigators evaluated the potential benefit of maintenance therapy with gefitinib in locally advanced NSCLC in trial S0023.[437] An interim analysis prompted study closure when it showed that the gefitinib arm had no possibility of improving overall survival or progression-free survival compared with placebo. University of Chicago investigators are conducting a randomized phase II trial evaluating another EGFR-TKI, erlotinib, in a concurrent fashion with chemoradiation therapy consisting of either EP and radiation therapy followed by consolidation docetaxel for three cycles or induction chemotherapy with paclitaxel and carboplatin followed by concurrent chemoradiation consisting of weekly paclitaxel, carboplatin, with daily erlotinib.[451]

Another promising targeted agent is cetuximab, a chimeric antibody to IgG1 subclass with fivefold greater affinity than the murine monoclonal antibody. It works by blocking the binding of ligand to EGFR and suppressing the downstream activity. In individuals with squamous cell carcinoma of head and neck cetuximab combined with

radiation therapy improved overall survival,[452] prompting similar studies in locally advanced NSCLC. In a recently completed RTOG phase II trial (RTOG-0324) cetuximab was combined with carboplatin and paclitaxel and daily fractionated radiation therapy.[453] The study has completed planned accrual and is awaiting maturation.

Metastatic Non-Small Cell Lung Cancer

Before the widespread use of chemotherapy, individuals with metastatic NSCLC experienced a median survival of 4 to 5 months and 1-year survival rates of approximately 10% when managed with supportive care alone.[454,455] Moreover, with rare exception, clinical trials conducted during the 1970s and 1980s comparing chemotherapy to best supportive care failed to provide definitive evidence supporting the use of chemotherapy for individuals with advanced NSCLC. The failure to demonstrate a survival benefit was attributed to a lack of effective treatment and to the intolerable side effects of the agents available. However, the statistical power of these studies was inadequate to detect a modest improvement in survival. To remedy this shortcoming a landmark meta-analysis of the extant data was undertaken.[388] No survival benefit was observed with chemotherapy regimens composed of alkylating drugs or vinca alkaloids. However, the meta-analysis also included eight trials involving nearly 800 patients who received cisplatin-based chemotherapy versus supportive care alone. In these trials the hazard ratio for death was 0.73 in favor of cisplatin-based chemotherapy ($P < 0.0001$), corresponding to a 1.5-month increase in median survival time and a 10% increase in survival at 1 year. For most oncologists these data firmly established the survival benefits of platinum-based chemotherapy. Numerous subsequent studies confirmed this survival advantage and also convincingly demonstrated an improvement in quality of life compared with supportive care alone and the cost effectiveness of chemotherapy as well.[456,457]

Platinum-based chemotherapy assessed in the aforementioned meta-analysis mainly consisted of drug combinations consisting of older or second-generation cytotoxic agents (e.g., etoposide or vinca). These older drugs were associated with significant side effects that may have contributed to a less than optimal outcome. Beginning in the 1990s newer and less toxic chemotherapy drugs such as gemcitabine, vinorelbine, paclitaxel, and docetaxel were shown to possess good single-agent activity against advanced NSCLC and, in some instances, to impart a survival benefit compared with supportive care alone.[458,459] Subsequently these third-generation drugs were compared as single agents to older platinum-based combinations containing second-generation drugs (e.g., etoposide, vindesine, etc.) and platinum-based doublets containing third-generation drugs (see reviews[460,461]). For the most part third-generation agents used alone seemed to perform as well as the older platinum-based doublets in terms of overall survival but proved inferior to platinum-based doublets containing the newer third-generation drugs.[460,461] This observation was later borne out in a meta-analysis of studies conducted between 1994 and 2003 involving third-generation drugs as single agents or in combination with platinum.[462] Platinum-based doublets using third-generation agents produced a twofold higher overall response rate than the new agent alone (OR = 2.32; 1.68–3.20) and a 13% prolongation of survival (HR = 0.87; 0.80–0.94, $P < 0.001$). Despite significant increases in the frequencies of various toxic effects in patients receiving newer platinum-based doublets, no significant difference in treatment-related mortality was observed.

Newer versus Older Platinum-Based Doublet Drug Combinations

As the newer third-generation drug combinations emerged they naturally led to randomized phase III trials aimed at defining an optimal platinum-based doublet therapy regimen in advanced NSCLC. Several of these important trials are listed in Table 76-13. For example, the ECOG conducted a landmark phase III trial in which chemotherapy-naive individuals with advanced NSCLC were randomized to receive cisplatin plus paclitaxel as the reference standard based on earlier work from an earlier ECOG study[463] or to one of three experimental arms: cisplatin plus gemcitabine, cisplatin plus docetaxel, or carboplatin plus paclitaxel.[464] Overall response rates and survival, however, did not differ significantly between the reference regimen of cisplatin plus paclitaxel and the three investigational arms. Similar results have been reported by other groups.[465,466] Although response rates and survival times differ slightly among these trials, the

Table 76-13 Phase III Trials with Third-Generation Drugs in Advanced Non-Small Cell Lung Cancer

				Survival	
Group	**CT**	**No. of Patients**	**RR (%)**	**Median (mo.)**	**1 Yr (%)**
ECOG[464]	Paclitaxel/cisplatin	288	21	7.8	31
	Gemcitabine/cisplatin	288	22	8.1	36
	Docetaxel/cisplatin	289	17	7.4	31
	Paclitaxel/carboplatin	290	17	8.1	34
EORTC[480]	Paclitaxel/cisplatin	159	31	8.1	35
	Gemcitabine/cisplatin	160	36	8.8	31
	Gemcitabine/paclitaxel	161	27	6.9	26
ILCP[662]	Vinorelbine/cisplatin	201	30	9.5	37
	Gemcitabine/cisplatin	205	30	9.8	37
	Paclitaxel/carboplatin	201	32	9.9	43
SWOG[465]	Paclitaxel/carboplatin	206	25	8.0	38
	Vinorelbine/cisplatin	202	28	8.0	36
TAX-326[468]	Cisplatin/vinorelbine	394	25	10.1	41
	Cisplatin/docetaxel	406	32	11.3	46
	Carboplatin/docetaxel	404	24	9.4	38

RR, response rate.

differences are relatively minor and mainly attributable to subtle but important differences in the characteristics of the various study populations.[467] For example, in the TAX-326 study, approximately one third of the participants had stage III disease, compared with fewer than 20% stage III disease in the other large trials.[468] Because individuals with stage III disease tend to live longer, this difference introduces a potential bias and makes it difficult to compare across trials (although within the trials the balance of stages was similar between the randomized arms). Collectively these data indicate platinum-based doublets using third-generation agents represent the standard of care in individuals with advanced NSCLC.[454,469] No clinically significant differences among the common regimens have emerged.

Triplet versus Doublet Platinum-Based Drug Combinations

Given that the third-generation chemotherapy agents often have nonoverlapping toxicity profiles, triplet chemotherapy regimens have considerable theoretical appeal. Several phase II and III trials have demonstrated the tolerability and activity of various triplet combinations.[460] However, although response rates and progression-free survival often improved with the addition of a third agent, overall survival was rarely impacted in a positive manner. Not surprisingly, however, toxicity and cost increased with the addition of a third agent. Two recent meta-analyses revealed a statistically significant improvement in response rate favoring the three-drug regimen.[470,471] However, the improvement in response rate did not translate into an improvement in survival. Moreover, toxicity was greater with triple-drug therapy as compared with doublet therapy.[461,471] Accordingly, triplet-drug chemotherapy is not recommended outside the confines of a clinical trial.

Duration of Therapy

How long one should administer chemotherapy in advanced NSCLC is a subject of ongoing debate.[461] American Society of Clinical Oncology practice guidelines for advanced NSCLC recommend cessation of first-line chemotherapy at four cycles in patients who are not responding to treatment and recommend no more than six cycles in responding patients.[472] These recommendations are based on limited data. A seminal study randomized individuals with advanced NSCLC to three versus six cycles of mitomycin, vinblastine, and cisplatin.[473] The dose of cisplatin was 50 mg/m^2, considered by some experts to be a low and possibly less effective dose of this agent (although this concern is not borne out in prospective trials; see Gandara and colleagues[474] and Klastersky and associates[475]). Median survival (6 vs. 7 months) and 1-year survival rates (22% vs. 25%; $P = 0.2$) were essentially identical in the two arms of the trial, as were the median durations of symptom relief (4.5 months in both arms). Quality-of-life parameters also were the same or improved for patients randomized to only three courses, including a significant decrease in fatigue ($P = 0.03$) and a trend toward decreased nausea and vomiting ($P = 0.06$). A second trial compared four cycles of carboplatin and paclitaxel to continuous treatment with these agents until disease progression in individuals with stages IIIB or IV NSCLC. Among individuals allocated to four cycles, 57% completed the intended course of chemotherapy. The median number of courses delivered in the continuous treatment arm was four, with 42% receiving five or more cycles of carboplatin and paclitaxel. Overall response rates (22% and 24%; $P = 0.80$), median survival (6.6. and 8.5 months), and 1-year survival rates (28% vs. 34%; log-rank $P = 0.63$) were not statistically different. Except for neuropathy, hematologic and non-hematologic toxicity rates were similar between the two arms. There were no differences in quality-of-life parameters. The frequency of patients who received second-line therapy was identical in the two groups as well (42% vs. 47%; $P = 0.42$). Collectively these indicate that treatment beyond three or four cycles of platinum-based therapy is of limited or no benefit in individuals with advanced NSCLC.[461,476]

Cisplatin versus Carboplatin

One of the more enduring controversies surrounding the treatment of persons with metastatic NSCLC is whether cisplatin-based chemotherapy is superior to carboplatin-based chemotherapy.[477] The ongoing controversy is fueled in part by a lack of a direct comparison of these agents. However, two recent randomized trials in advanced NSCLC suggest that carboplatin-containing doublets are inferior to cisplatin-based doublets in terms of overall survival when third-generation drugs are used.[468,478] A meta-analysis of extant data lends further support to this possibility.[477] Among eight trials (involving nearly 3000 patients) that directly compared a cisplatin-based doublet with a carboplatin-based doublet, five investigated drug regimens containing a third-generation agent. Taking into account all eight studies, cisplatin-based chemotherapy produced a statistically significant higher response rate but no survival advantage (HR = 1.050; 0.907–1.216; $P = 0.515$). However, a subgroup analysis of the five trials that used third-generation platinum-based doublets revealed that cisplatin plus a newer agent yields an 11% longer survival than carboplatin plus the same newer agent (HR = 1.106; 1.005–1.218; $P = 0.039$). Cisplatin-based chemotherapy more frequently induced grade 3 or higher nausea and vomiting, whereas grade 3 or higher thrombocytopenia was more frequent during carboplatin-based chemotherapy. There was not a significant difference in treatment-related deaths (3.9% vs. 2.9%, respectively). Given the palliative nature of chemotherapy for advanced disease, however, the modest survival benefit derived from cisplatin-based therapy may be offset by the increase in host toxicity. Accordingly, it is reasonable to consider substituting carboplatin for cisplatin in selected circumstances where the toxicities of cisplatin could be particularly problematic (i.e., pre-existing neuropathy, hearing difficulties, renal dysfunction, etc.). The situation in early-stage disease may be quite different (discussed earlier).

Platinum-Containing versus Non-Platinum-Containing Chemotherapy

Improvement in survival is a crucial factor in choosing chemotherapy, but serious consideration also should always be given to other factors, such as tolerability, quality of life, convenience, and cost.[472] These factors have led to the investigation of non-platinum-containing chemotherapy regimens. Given the activity and tolerability of newer non-platinum drugs (e.g., gemcitabine, vinorelbine, paclitaxel, docetaxel, oxaliplatin),[479] there has been considerable interest in developing non-platinum-based chemotherapy regimens.[469] However, many of these data are from phase II studies and must be interpreted with some degree of caution. This is particularly relevant given that a recent European phase III trial suggested non-platinum-based chemotherapy might be less efficacious than platinum-based chemotherapy.[480] Moreover, a recent meta-analysis analyzed 1-year survival using data obtained from 37 randomized phase II and phase III trials that compared platinum- to non-platinum-based chemotherapy regimens.[481] Collectively these trials enrolled more than 7600 patients. The analysis found that platinum-based chemotherapy was associated with a 62% increase in the odds ratio for response (OR, 1.62; 1.46–1.8; $P < 0.0001$) and a 5% increase in the 1-year survival rate (34% vs. 29%; OR, 1.21; 1.09–1.35; $P = 0.0003$). However, compared to third-generation-based combination regimens there was not a statistically significant increase in 1-year survival with platinum-based therapies (35% vs. 36%, respectively; OR, 1.11; 0.96–1.28; $P = 0.17$) when single-agent trials were excluded. In addition, the toxicity of platinum-based regimens was significantly higher for hematologic toxicity, nephrotoxicity, and nausea and vomiting, but not for neurotoxicity, febrile neutropenia rate, or toxic death rate.

This aforementioned meta-analysis has been criticized for the inclusion of single-agent comparisons as well as phase II trials regarded as too small to provide reliable survival data.[482] The criticism prompted a second meta-analysis restricted to phase III trials that compared

platinum-based doublets to non-platinum-based doublet therapies.[482] The latter analysis involved 14 phase III trials that compared platinum-based to non-platinum-based regimens using survival at 1-year as the endpoint of interest. The analysis included nearly 6000 patients. The results revealed a statistically significant benefit in the reduction of death for the platinum-based regimens at 1 year (OR, 0.88; $P = 0.044$) and a lower risk of being refractory to chemotherapy with platinum-based chemotherapy (OR, 0.87; 0.73–0.99; $P = 0.049$) (an issue of potential greater importance when chemotherapy is used in the adjuvant setting; see earlier discussion). The risks of grades 3 and 4 gastrointestinal and hematologic toxicities were substantially higher with platinum-based chemotherapies, although this was not associated with a significant increase in the risk of febrile neutropenia (OR, 1.23; 0.94–1.60; $P = 0.063$). There was, however, a trend toward an increase in treatment-related deaths on the platinum-based regimens (1.9% vs. 1.3%; $P = 0.08$). Based on these data non-platinum-containing regimens do have activity that is similar to that of platinum-based regimens. Although arguably somewhat less effective than platinum-based therapy, some non-platinum-based chemotherapy regimens seem appropriate for patients in whom platinum-associated toxicities are a major concern.

Chemotherapy for Palliation of Symptoms

The notion that chemotherapy can be used primarily for palliation purposes is an anathema to many nononcologists. However, several investigators have shown that cytotoxic chemotherapy is associated with symptom improvement even in the absence of a classic tumor response.[483] Symptomatic response is usually achieved within the first or second course of chemotherapy in responding patients. Nonetheless, some practitioners shy away from recommending platinum-based palliative chemotherapy because of the toxicities known to accompany platinum agents. Newer agents such as gemcitabine and vinorelbine can be used with beneficial effect. For example, in one study patients given gemcitabine were far less likely to require palliative radiation therapy at 2 months than those treated with supportive care alone (7% vs. 42%).[484] The median time to receiving palliative radiation therapy was 7 months for patients receiving gemcitabine versus 1 month for patients treated with best supportive care alone. Duration of symptom relief achieved varied considerably but resulted in a median relief of 3–5 months for dyspnea, cough, and chest pain and 2–3 months for anorexia and hemoptysis.[485] Symptomatic relief derived from chemotherapy is not limited to first-line therapy. In individuals with recurrent NSCLC second-line docetaxel provided greater improvement in tumor-related symptoms, including asthenia, pain, and pulmonary and neurologic symptoms compared with supportive care as well as a survival benefit.[486]

Elderly Patients

Lung cancer is primarily a disease of older individuals; the median age at diagnosis is 68 years and as many as 40% of patients may be 70 years old at diagnosis.[487] Because older people with NSCLC tend to have substantial comorbidities, many oncologists are often reticent to administer standard chemotherapy regimens fearing excessive toxicity.[487,488] However, when deciding a treatment strategy the biologic rather than the chronologic age should be carefully assessed, and treatment should only be modified or withheld for very good reason.[489] This applies equally to surgery and radiation therapy as well as chemotherapy, in that numerous prospective studies have clearly demonstrated the benefits of chemotherapy in the elderly. Randomized trials have confirmed the superiority of single-agent vinorelbine to supportive care and to combination therapy with vinorelbine and gemcitabine.[490,491] In addition, retrospective analyses of many cooperative-group phase III studies indicate that patients aged 70 years and older experience survival and quality-of-life benefits similar to that of their younger counterparts.[464,466,468,492] Recently a panel of international experts in geriatric oncology was convened to develop guidelines for the treatment of elderly patients with NSCLC.[488] The panel recommended single-agent chemotherapy with a third-generation agent (vinorelbine, gemcitabine, docetaxel, or paclitaxel), as an option for elderly individuals with advanced NSCLC. Several variables must be considered when selecting a particular drug, including the expected toxicity profile of the agent, pharmacokinetics, organ function, and comorbidities as well as the patient's preferences. The expert panel indicated that a platinum-based chemotherapy represented a valid option in older patients with a good performance status and adequate organ function. Appropriate supportive care measures (e.g., growth factors) were encouraged in older patients suffering from comorbidities and disease symptoms. Finally, as is true of lung cancer patients of any age, the expert panel noted that supportive care alone represented an appropriate management plan for patients who are not suitable for active treatments.

Patients with Poor Performance Status

Retrospective reviews of early clinical trials in advanced NSCLC identified poor performance status (i.e., ECOG PS 2) as a strongly negative prognostic variable.[493] The use of chemotherapy in patients with PS 2 is controversial, because the survival benefit derived from cisplatin-based chemotherapy seems to be confined to those with PS 0 to 1.[494] Not surprisingly, what happens in clinical practice is fairly inconsistent.[495] Data derived from pooled studies suggest that patients with PS 2 do experience improved quality of life with chemotherapy even if a survival benefit is not obtained.[496] Monochemotherapy with one of the third-generation cytotoxic agents (e.g., vinorelbine, gemcitabine, or a taxane) or newer formulations of these agents (e.g., paclitaxel, poliglumex) may provide clinical benefit with less toxicity, whereas newer combination regimens seem to improve survival albeit quite modestly.[466] In addition, the oral EGFR inhibitors gefitinib and erlotinib have demonstrated promising activity in persons with advanced NSCLC who have previously received chemotherapy (see later discussion). The favorable toxicity profile of these agents makes them an attractive option for patients with PS 2 as well. A cautionary note is warranted, however. In a randomized phase II trial, patients with PS 2 seemed to fare better with standard doublet chemotherapy than with single-agent erlotinib as initial therapy.[497] Thus, caution is warranted in selecting initial treatment for patients with PS 2 or greater. There remains a critical need for novel therapeutic strategies for all persons with NSCLC and especially for those with a poor PS.

Second-Line Therapy

As first-line chemotherapy regimens improve, a substantial number of patients will maintain a good performance status and a desire for further therapy when they develop recurrent disease. Numerous trials of single-agent and combination therapies have been performed; the results of more than 50 trials have been summarized elsewhere.[498] At present only three drugs are approved by the FDA for second-line therapy of NSCLC in the United States, including docetaxel, pemetrexed, and erlotinib. In general these agents have similar overall response rates of around 5% to 10% (depending on the patient's prior exposure to taxanes and platinum) and yield median survivals of 6 to 8 months (Table 76-14). However, the available drugs have distinct toxicity profiles that can influence their use in the second-line setting.[499] In a prospective comparison of docetaxel and pemetrexed, for example, overall response rates (9.1% vs. 8.8%; $P = 0.105$), median time to progression (3.5 vs. 3.4 months), and median survival times (8.3 vs. 7.9 months) were not significantly different (see Table 76-14).[500] However, patients receiving docetaxel were much more likely to experience grade 3 or 4 neutropenia (40.2% vs. 5.3%; $P < 0.001$), febrile neutropenia (12.7% vs. 1.9%; $P < 0.001$), neutropenia with infections (3.3% vs. 0.0%; $P = 0.004$), hospitalizations for neutropenic fever (13.4% vs. 1.5%; $P < 0.001$), hospitalizations due to other drug-related adverse events (10.5% vs. 6.4%; $P = 0.092$), use of granulocyte colony-stimulating factor support (19.2% vs. 2.6%; $P < 0.001$), and all-grade alopecia (37.7% vs. 6.4%; $P < 0.001$)

Table 76-14 Phase III Trials of Docetaxel and Pemetrexed in Recurrent Non-Small Cell Lung Cancer

	SHEPHERD ET AL[486]				HANNA ET AL[500]	
		DOCETAXEL			DOCETAXEL	PEMETREXED
	BSC	**Overall**	**75 mg/m²**	**100 mg/m²**	**75 mg/m²**	**500 mg/m²**
RR	0%	5.8%	5.5%	6.3%	8.8%	9.1%
TTP	1.6 mo	2.5 mo	2.5 mo	2.5 mo	3.5 mo	3.4 mo
MST	4.6 mo	7.0 mo	7.5 mo	5.9 mo	7.9 mo	8.3 mo
1 Yr	19%	29%	37%	29%	29.7%	29.7%

BSC, best supportive care; MST, median survival time; RR, response rate; TTP, time to progression.

compared with patients receiving pemetrexed. Thus, based on the current available data, the efficacy of these three drugs is similar in a general patient population, but their toxicity profiles differ substantially. Hematologic toxicity is greater for docetaxel compared with pemetrexed and erlotinib, whereas nonhematologic toxicity, namely rash and diarrhea, is greater with erlotinib. For smokers who derived benefit from first-line chemotherapy and maintain a good performance status (i.e., ECOG PS 0–1), a trial of pemetrexed is reasonable. Erlotinib should be strongly considered as second-line treatment in those who have never smoked, including those who failed to benefit from first-line chemotherapy. Most of the survival benefit for any of these agents is realized in those patients who maintain a good performance status.

Epidermal Growth Factor Receptor Inhibitors

EGFR overexpression occurs in a variety of solid tumors including NSCLC and is associated with a poor prognosis in some retrospective reports.[60,501] When stimulated, the transmembrane receptors trigger a cascade of intracellular signaling that affects cellular proliferation and apoptosis. Strategies to target the EGFR include use of TKIs, monoclonal antibodies, antisense oligonucleotides, and ligand-toxins or immunoconjugates.[501] Thus far the EGFR inhibitors used in the treatment of NSCLC fall into two main categories: monoclonal antibodies to the extracellular domain of the EGFR (cetuximab and panitubimab) and small molecules that are inhibitors of the intracellular tyrosine kinase domain by interfering with autophosphorylation by adenosine triphosphate (gefitinib and erlotinib). Gefitinib, erlotinib, and cetuximab have demonstrated modest activity in phase II studies conducted in unselected individuals with recurrent NSCLC.[502–504] However, only erlotinib is approved by the FDA for the treatment of NSCLC based on the results of a randomized placebo-controlled trial in which erlotinib demonstrated a statistically significant survival benefit in persons with recurrent NSCLC.[65]

Table 76-15 Phase III Trials of Erlotinib and Gefitinib in Recurrent Non-Small Cell Lung Cancer

	BR.21[65]		ISEL[505]	
	Erlotinib	**Placebo**	**Gefitinib**	**Placebo**
RR	8.9%	<1%	8%	1%
Stable disease	35%	27%	32%	31%
TTP	2.2 mo	1.8 mo	3.0 mo	2.6 mo
MST*	6.7 mo	4.7 mo	5.6 mo	5.1 mo
1-yr survival	31.2%	21.5%	27%	21%

MST, median survival time; RR, response rate; TTP, time to progression.

Patients enrolled in the erlotinib trial all had received prior platinum-based chemotherapy and/or were considered ill-suited for further chemotherapy. A trial of similar design failed to demonstrate a survival advantage with gefitinib, although the trends in time to progression and overall survival favored the EGFR TKI arm[505] (Table 76-15).

Notably, the start of the aforementioned placebo-controlled phase III trials predates the discovery of somatic mutations in the EGFR gene that seem to associate with clinical responses to EGFR TKIs but not to the monoclonal antibodies cetuximab and panitubimab targeting EGFR and its ligands.[55,57,58,60] The clinical relevance of these *EGFR* mutations, however, remains unclear. For example, many different mutations have been reported. Thus far four of the described mutations associate with tumor response (validated from in vitro studies or from actual tumor responses in human patients) including point mutations in exons 18 (G719A/C) and 21 (L858R and L861Q) and in-frame deletions in exon 19 that eliminate four amino acids (LREA) just downstream of a critical lysine residue at position 745 (Fig. 76-16).[60] Three mutations, an exon 19 point mutation (D761Y), an exon 20 point mutation (T790M), and an exon 20 insertion (D770_N771insNPG) are associated with drug resistance.[60] Notably, mutations in *KRAS* also are associated with a lack of sensitivity to EGFR TKIs.[506] The most common of these four drug-sensitive mutations are exon 19 deletions and the exon 21 L858R substitution that together account for 85% to 90% of *EGFR* mutations in NSCLC.[62] The existing data show an approximate 75% response rate to EGFR TKIs in tumors with drug-sensitive mutations versus a less than 10% response in tumors with wild-type EGFR. However, the presence of mutations failed to correlate with survival benefit in the erlotinib placebo-controlled trial.[66] By contrast, amplification of the EFGR gene as detected by FISH did correlate with survival outcome in the placebo-controlled erlotinib and gefitinib trials.[66,507] In cell lines *EGFR* mutations are often accompanied by gene amplification. Indeed, in most studies, amplification of *EGFR* has been associated with mutations in *EGFR*.[508] It has been suggested that the failure of *EGFR* mutations to correlate with survival outcome in the erlotinib trial is due to inadequacies of technique used to assess for mutations in this pivotal trial.[173,509] Moreover, whereas *EGFR* mutations and increased copy number have been treated as separate molecular events thus far, accumulating data suggest that they are not mutually exclusive.[173]

Individuals with gastrointestinal stromal tumors harboring mutations in *KIT* exon 11 have a significantly longer overall survival when compared with persons with mutations in *KIT* exon 9.[510] Similar observations have been made in NSCLC; individuals with tumors harboring *EGFR* exon 19 deletions have a longer overall survival when compared with persons with *EGFR* L858R (34 vs. 8 months; log-rank, $P = 0.01$).[511] The molecular basis for this observation is not known, although kinetic analyses of EGFR-mutant proteins suggest that the off-rate for erlotinib may be slower for the deletion mutant, compared with the L858R mutant, thereby prolonging the duration of erlotinib binding to the deletion mutant.[512]

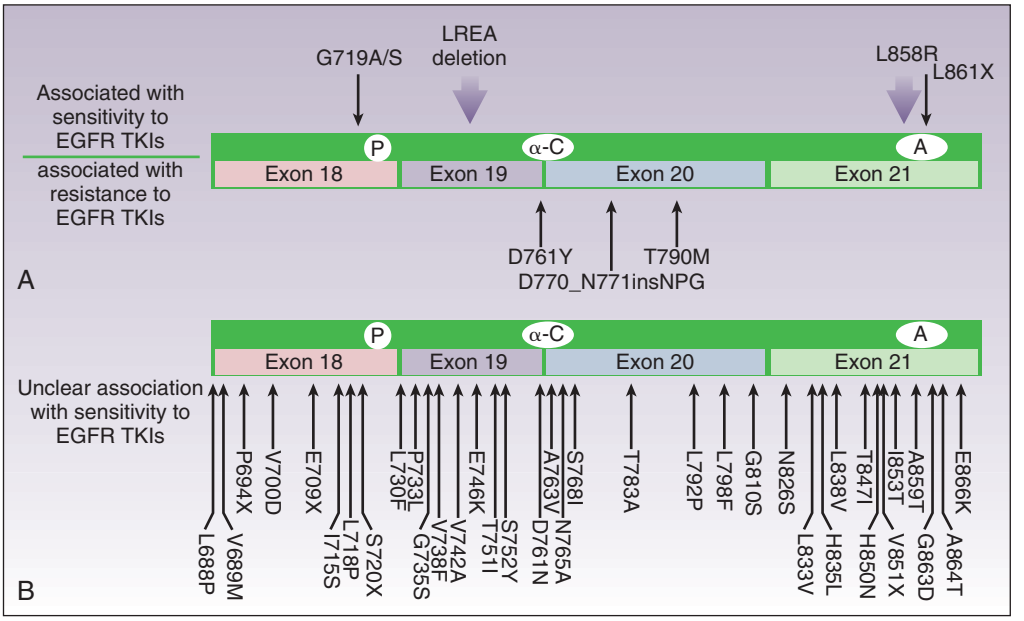


Figure 76-16 • Schematic diagram of reported mutations in *EGFR* in NSCLC tumors. **A,** Mutations associated with sensitivity to gefitinib or erlotinib (*top*). The relative frequencies of mutations are indicated by size of arrows. Mutations associated with resistance to gefitinib or erlotinib (*bottom*). **B,** Mutations isolated from NSCLC tumors with unclear association with response to erlotinib or gefitinib. X, Multiple substitutions have been reported at an amino acid. A, activation domain; C, -C helix domain; P, P-loop. (Reproduced with permission from Riely GJ, Politi KA, Miller VA, Pao W: Update on epidermal growth factor receptor mutations in non–small cell lung cancer. Clin Cancer Res 2006;12: 7232–7241.)

Despite an initial response to EGFR TKIs, individuals with *EGFR* mutations rarely achieve a complete pathologic response, and with continued treatment tumors typically develop resistance to gefitinib or erlotinib.[60] The mechanisms of this acquired resistance are only now being defined. Studies of tumor material taken from individuals with initial responses to EGFR TKIs and subsequent progression have identified additional mutations in *EGFR* in specimens with acquired resistance.[63,64] The major lesion identified thus far is an EGFR T790M mutation reported to occur in approximately half of the published cases.[60,63,64] This T790M substitution in EGFR is predicted to block binding of erlotinib or gefitinib to the kinase adenosine triphosphate-binding pocket.[63,64]

Routine testing for *EGFR* mutations is not recommended, although there are several ongoing trials testing the practicality and value of such an approach.[60] These studies should help determine the importance of mutation testing in selecting therapy for subsets of patients with lung cancer, providing prospective data on response rates, time to progression, and survival with and without mutations treated with either gefitinib or erlotinib. From a practical standpoint, the extant data suggest that there may be a subgroup of persons with NSCLC that preferentially respond to EGFR TKIs, including those with adenocarcinomas (especially adenocarcinomas with bronchioloalveolar features), those who have never smoked, patients of Asian ethnicity, and females.[60,501] Investigators at Memorial Sloan-Kettering Cancer Center developed a response and survival prediction model shown in Table 76-16.[513] Data developed after the development of this model suggest that bronchioloalveolar carcinoma per se is not predictive of responsiveness to EGFR TKIs.[62] Instead, it seems that the more responsive histology is adenocarcinoma with BAC-like features (as described previously). The model also ignores a patient's ethnicity, which seems to play a substantial role in the likelihood of response to these agents.[62] Nonetheless, the prediction model developed by the Memorial investigators provides practical clinical guidance as to a patient's likelihood of deriving benefit from an EGFR TKI like gefitinib or erlotinib. Once an EGFR TKI is administered individuals with responding tumors often experience marked and rapid tumor regression, often within days of starting treatment (Fig. 76-17). Moreover, a growing body of evidence suggests that these clinical features tend to be associated with the presence of *EGFR* somatic mutations.[62] Prospective trials utilizing the clinical parameters to select patients are under way. SWOG investigators completed one such trial using gefitinib in patients with chemonaive or recurrent BAC.[514] The overall response rate was 17% among previously untreated individuals and 9% among pretreated individuals. Median survival was 13 months, with a 23% 3-year survival. Toxicity consisted mainly of rash and diarrhea, but 2% of patients died of presumed interstitial lung disease. Such trials have raised the question of whether patients who fit these specific criteria should be considered for first-line therapy with an EGFR TKI.[60]

Table 76-16 Response and Survival with Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Positive Predictive Factors	RR (%)	MST
Never smoker	56	14+ mo
BAC-like features		
Female		
2 of 3 above	30	12 mo
1 of 3 above	9	5 months
0 of 3 above	3	3 months

From Shah NT, Kris MG, Pao W, et al: Practical management of patients with non–small-cell lung cancer treated with gefitinib. J Clin Oncol 2005;23:165–174.

Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors with Combination Chemotherapy

Thus far, attempts to move EGFR TKIs into front-line therapy of advanced NSCLC have concentrated on combining these agents with standard chemotherapy[515–517] (Table 76-17). Each of the completed studies was designed with the knowledge that gefitinib and erlotinib had demonstrated impressive antitumor activity in individuals with refractory, advanced NSCLC with only modest toxicity, and was based on the premise that these drugs could enhance the cytotoxic effects of standard chemotherapy agents, as shown in preclinical studies.[518,519] Unfortunately none of the studies yielded a survival improvement with EGFR TKIs. There are several potential explanations for the failure of EGFR TKIs to effect survival benefit when combined with chemotherapy. For example, it is certainly possible

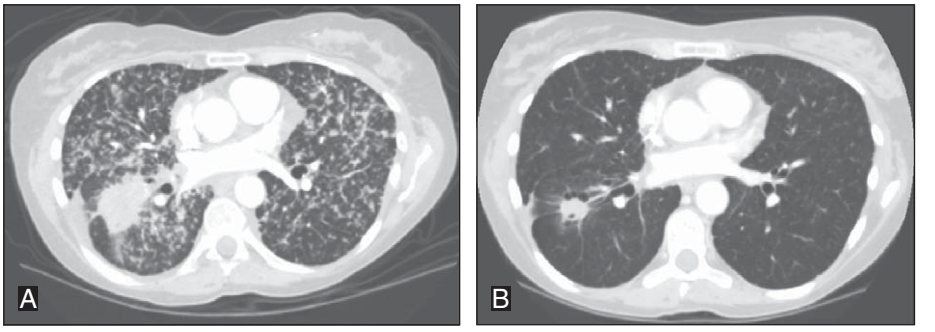


Figure 76-17 • Chest CT scans of a 60-year-old female who had never smoked with adenocarcinoma before (**A**) and after 28 days of erlotinib therapy (an EGFR TKI) (**B**). The patient had a mutation in exon 19 of the *EGFR* gene.

that more careful patient selection might have led to a better outcome (see later discussion). In none of these studies were patients selected based on EGFR expression, somatic mutations, or any other putative marker of efficacy. Some experts also have speculated that EGFR inhibitors act mainly by reducing proliferation in wild-type EGFR tumor cells. Because proliferating tumor cells are those most affected by chemotherapy, an antagonistic effect between EGFR TKIs and chemotherapy may occur.[509] Interestingly, neither *EGFR* mutations nor amplification seemed to identify distinct subsets of NSCLC with an increased response to gefitinib in the phase II/III randomized trials, nor did the combination of gefitinib with chemotherapy improve survival in individuals with these molecular markers.[520] Notably, however, patients who had never smoked who were treated with erlotinib and chemotherapy seemed to experience an improvement in survival in a preplanned subset analysis.[517] Never smoking has been associated with a greater probability of response to EGFR TKIs and may represent a surrogate marker for the presence of *EGFR* mutations.[521] Nonetheless, neither erlotinib nor gefitinib combined with standard chemotherapy regimens confers a survival advantage over chemotherapy alone in unselected patients with previously untreated advanced NSCLC.[517] Consequently, at present, concurrent chemotherapy with an EGFR TKI is not recommended as routine therapy.

Vascular Endothelial Growth Factor Inhibitors

Inhibition of angiogenesis has been a major thrust of new drug development in many solid tumors including lung cancer. Bevacizumab is a recombinant humanized monoclonal antibody to the vascular endothelial growth factor (VEGF) that has shown great promise in the treatment of breast and colon cancer. In a randomized phase II trial, bevacizumab combined with carboplatin and paclitaxel seemed to improve both overall response rates and times to disease progression.[522] However, bevacizumab engendered a high rate of life-threatening pulmonary hemorrhage that was observed primarily in individuals with squamous cell carcinomas. The ensuing ECOG phase III trial was therefore limited to individuals with NSCLC of nonsquamous histology, no history of hemoptysis, and no brain metastases to limit the potential for serious bleeding.[523] Patients assigned to the bevacizumab group experienced an improved response rate (35% vs. 15%; $P < 0.001$), progression-free period (6.2 vs. 4.5 months; HR = 0.66; $P < 0.001$), and overall survival (12.3 vs. 10.3 months; HR = 0.79; $P = 0.003$). However, these benefits came at a cost, including a greater number of treatment-related deaths (15 vs. 5) and a higher rate of clinically significant bleeding (4.4% vs. 0.7%; $P < 0.001$). Nonetheless, the substantial improvement in overall survival indicates that bevacizumab plays a key role in the management of selected patients with NSCLC with metastatic disease.

Lung Cancer Vaccines

There are many diverse approaches to attempting to harness the specificity and generality of the immune system in the fight against cancer, and most of them remain theoretical or relevant only in animal studies. However, despite some remarkable failures,[524] several recent studies suggest that real progress is being made in the development of immunotherapeutic strategies for lung cancer. The most promising approaches can be divided into three main groups: (1) whole-cell vaccines, where either autologous or allogeneic tumor cells are used as the source of a mixture of potential, primarily undefined,

Table 76-17 Results of Phase III Trials Combining Chemotherapy and Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

Study	Treatment	No. of Patients	ORR (%)	TTP (mo.)	MST (mo.)	1 Yr (%)
INTACT-1[515]	PGem	363	47.2	6.0	10.9	44
	PGem + ↓G	365	51.2	5.8	9.9	41
	PGem + ↑G	365	50.3	5.5	9.9	43
INTACT-2[516]	CbPac	345	28.7	5.0	9.9	42
	CbPac + ↓G	345	30.4	5.3	9.8	41
	CbPac + ↑G	347	30.0	4.6	8.7	37
TALENT[663]	PGem	536	29.9	5.7	10.3	42
	PGem + E	533	31.5	5.5	10.0	41
TRIBUTE[517]	CbPac	533	19.3	4.9	10.5	44
	CbPac + E	526	21.5	5.1	10.6	47

Cb, carboplatin; E, erlotinib; G, gefitinib; Gem, gemcitabine; MST, median survival time; ORR, overall response rate; P, cisplatin; Pac, paclitaxel; TTP, time to progression; ↓ 250 mg; ↑ 500 mg.

tumor antigens; (2) defined-antigen vaccines using synthetic protein or peptide antigens; and (3) immunostimulatory preparations without administered tumor antigens.

WHOLE-CELL VACCINES. The clinically apparent diversity of lung cancers suggests that the best source of tumor antigens might be the patient's own tumor, killed and formulated into a vaccine in a manner that allowed the induction of a specific, effective immune response directed at the residual live tumor in the patient. This theoretically attractive but practically difficult approach was tested in a vaccine based on the concept that tumor cells engineered to express large amounts of the cytokine granulocyte-macrophage colony-stimulating factor were very effective at inducing tumor-specific immunity.[525] In this trial patients with resectable tumor deposits had their own tumor cells engineered to overexpress this cytokine formulated into a vaccine and injected intradermally, and durable, complete responses were observed in 3 of 33 patients treated.[526] This approach was dropped for commercial development, however, because of the practical difficulties in harvesting and processing autologous tumor to prepare the vaccine, but despite this was the first trial to show objective responses to vaccine therapy alone in individuals with lung cancer.

A similar study used a mixture of four allogeneic lung cancer tumor cell lines engineered to overexpress antisense transforming growth factor-β2 (TGFβ), a potent immunosuppressive cytokine, to treat individuals with advanced lung cancer.[526] In this randomized phase II testing three different doses of the vaccine, a 15% partial response rate was observed and the survival of the higher dose groups was statistically significantly longer than that of the lowest dose group (52% vs. 20% 2-year survival). Because all patients in this study received the same vaccine, it is much more amenable to commercial-scale manufacture and is currently being tested in a phase III trial.

DEFINED-ANTIGEN VACCINES. Proteins that are somatically mutated in the development of the cancer and thus absolutely specifically expressed in the cancer and not in normal tissues also present an attractive target for immunotherapy, and one trial immunized patients with synthetic peptides custom-made to match the mutated ras or p53 protein products present in each patient's tumor.[527] In this study specific immune responses were observed, and survival was prolonged in the individuals who achieved such a response, but no objective responses were observed. Instead of using a custom-made mutant oncogene peptide, it is possible to target nonmutated p53 peptides based on the overexpression of the protein frequently observed in lung cancer. In fact, an objective response and improved clinical outcomes compared with historical controls were also observed in a trial immunizing persons with SCLC using a vaccine targeting overexpressed wild-type p53.[528]

An approach that is much more practical for commercial development is to find a tumor antigen that is frequently expressed in lung cancer and formulate this antigen into a vaccine. Two such examples in large-scale clinical development now are those based on the MUC and MAGE antigens, both frequently overexpressed in lung cancer. The BLP-25 vaccine is a MUC lipopeptide that was given to persons with advanced NSCLC with responding or stable disease after chemotherapy or chemoradiation therapy.[529] In a subset analysis of stage IIIB patients who received radiation therapy for local-regional disease (no pleural effusion) there was a trend toward an improved survival compared with nonvaccinated patients. In another study a vaccine based on the MAGE antigen was given as adjuvant therapy to individuals with completely resected disease,[530] and a strong trend toward an improved survival was observed in a planned interim analysis.

IMMUNOSTIMULATORY APPROACHES. Because cancers develop and become clinically evident despite an apparently intact immune system in the majority of individuals, there must be mechanisms by which cancers avoid an effective immune response. One of the factors that cancers make to suppress effective responses is TGFβ, as discussed previously, but another is VEGF.[531] With the recent approval of bevacizumab, combinations of anti-VEGF with immunotherapy are being tested in early-phase clinical trials.

It is clear that prokaryotic DNA, specifically unmethylated DNA, is recognized as foreign by a primitive component of the eukaryotic cell involving the TLR-9 receptor. This observation has led to the development of TLR-9 agonists to activate innate and adaptive immune induction. In one randomized phase II trial a TLR-9 agonist, PF-3512676, was given in combination with chemotherapy versus chemotherapy alone in a randomized, placebo-controlled design, and a significant increase in response rate was observed (Pfizer, unpublished data). This is currently being tested in a large phase III trial.

There are therefore suggestions of clinical activity for vaccines in lung cancer, and this has stimulated resurgent interest by pharmaceutical companies and large-scale clinical development in lung cancer. The true extent and potential for lung cancer immunotherapy remains to be elucidated, however.

In summary, for much of the twentieth century advances in the systemic treatment of advanced NSCLC were considered modest at best.[455,532] In fact as recently as 1998 the noted oncologist B.J. Kennedy derisively commented on the "snail's pace" of progress in the management of late-stage NSCLC.[13] Much has changed since Dr. Kennedy's scholarly rebuke. It is now well established that modern chemotherapy can prolong survival of individuals with NSCLC in the late stages of disease as well as improve the symptoms and quality of life in a cost-effective manner.[454,455] It is now well accepted that doublet platinum-based chemotherapy with a third-generation drug is the preferred treatment for physically fit patients with advanced NSCLC. No single regimen stands apart as the optimal program for all patients. Non-platinum therapy is a reasonable alternative approach in selected circumstances where cisplatin or carboplatin is not appropriate. Subtle differences among the extant regimens allow clinicians flexibility to choose among toxicity profiles, convenience, and cost. For a subset of patients, namely those with adenocarcinoma, no brain metastases, and no hemoptysis, the addition of bevacizumab to chemotherapy is warranted based on a significant improvement in overall survival. Whether the addition of bevacizumab to doublets other than carboplatin and paclitaxel is beneficial remains to be determined. The available data indicate that no more than three to six cycles of chemotherapy regimen are required to achieve optimal survival results and minimize host toxicity. Second-line chemotherapy is beneficial in term of survival, quality of life, and cost. Older patients who are physically fit should be treated in a manner that mirrors that of their younger counterparts. Older patients who are not physically fit and patients with a poor initial performance status may be candidates for monotherapy with a third-generation drug or possibly one of the newer so-called targeted agents (e.g., erlotinib). Finally, all therapy in the setting of metastatic disease is ultimately palliative. Consequently treatment decisions must be tempered by this sobering reality.

SMALL CELL LUNG CANCER

The absolute incidence of SCLC increased at an annual rate of 6.5% until 1982, continued to increase at an annual percentage change rate of 1.2% between 1982 and 1989, and since 1990 has decreased at a statistically significant rate of 2.4% per annum[533] (Fig. 76-18). SCLC now constitutes approximately 13% of all newly diagnosed lung cancers in the United States,[533] a marked decline from previous estimates of 20% to 25% noted 2 decades ago.[238] The change in the incidence of SCLC is most evident in men but has recently shown a favorable downward trend among women as well.[286] The declining SCLC incidence is a direct result of reduced smoking among U.S. adults.[286,534] It is estimated that without these reductions in smoking, there would have been virtually no reduction in overall cancer mortality in either men or women since the early 1990s.[535] Nonetheless,

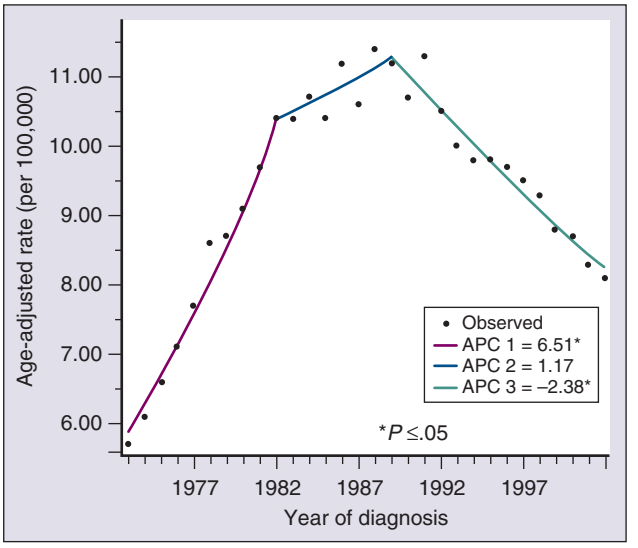


Figure 76-18 • Annual percentage change in the diagnosis of small cell lung cancer in the United States over the last 30 years. (Reproduced with permission from Govindan R, Page N, Morgensztern D, et al: Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006;24:4539–4544.)

the natural history of untreated SCLC remains extremely poor with median survival of only 2 months for metastatic SCLC and less than 3 to 4 months for disease confined to the thorax.[536] Although SCLC was once considered highly curable, in fact, the median survival and the proportion of long-term survivors of patients treated with chemoradiation for limited-stage SCLC and stage III NSCLC or extensive-stage SCLC and metastatic NSCLC are essentially identical.[239] The time required for treatment-resistant clones to cause a fatal outcome is similar for SCLC and NSCLC. Both are virulent epithelial neoplasms that respond somewhat to radiation therapy and chemotherapy.[239]

Small Cell Lung Cancer Staging

The TNM staging system is rarely used to stage SCLC. Instead, SCLC is staged using the Veterans Administration Lung Study Group system mainly because of its simplicity and clinical utility.[537] Approximately one third of individuals with SCLC present with limited-stage disease, defined as tumor confined to one hemithorax that can be encompassed within a single tolerable radiation therapy portal. This definition becomes somewhat problematic, however, when applied to the staging of patients with local-regionally advanced disease manifested as the presence of an ipsilateral pleural effusion, contralateral supraclavicular lymphadenopathy, or contralateral mediastinal lymphadenopathy.[538] Extensive-stage disease is any disease beyond these boundaries. Metastatic disease may involve the liver, adrenals, bone, brain, supraclavicular or retroperitoneal lymph nodes, pleura, contralateral lung, soft tissues, and bone marrow. The diagnosis is usually established via fiberoptic bronchoscopy or via transthoracic needle biopsy.[238] Only rarely is the diagnosis established on the basis of larger biopsy specimens. Histologically small cell carcinoma consists of small round, oval, and spindle-shaped cells with scant cytoplasm, ill-defined borders, finely granular nuclear chromatin, prominent nuclear molding, and a high mitotic rate and absent or inconspicuous nucleoli.[142,539]

In addition to a history and physical examination, individuals with SCLC should undergo routine hematologic and serum chemistry tests and a chest CT study. The chest CT scan is customarily extended caudally to encompass the liver and adrenal glands given the frequency of involvement of these organs. A radionuclide bone scan is indicated in persons with bone pain. Neurologic findings should prompt appropriate imaging studies of the brain or spinal cord (i.e., CT or MRI scans). For a person with an abnormal complete blood count or peripheral blood smear that cannot be otherwise explained, bone marrow biopsy should be considered, particularly if there is no other site of extensive-stage disease. In general, however, a bone marrow assessment is rarely required.[540] Once a patient is found to have unequivocal evidence of metastatic involvement confirming extensive-stage disease, no further workup is necessary unless the patient is being considered for a clinical trial requiring more rigorous staging. This stepwise approach minimizes the cost of the staging assessment without compromising patient care.[541]

The role of PET with FDG in the staging of SCLC is not fully defined.[542,543] In one recent report just 1 of 120 patients was incorrectly staged by FDG-PET, as a result of failure to detect brain metastases.[543] Similarly, in a small prospective trial FDG-PET scans identified metastatic lesions in individuals who were thought to have limited-stage disease by standard staging methods.[542] Thus, it would seem that FDG-PET may reduce the number of tests and invasive procedures required to optimally stage patients and could impact patient management by altering radiation portals in persons with limited-stage disease.[544]

Prognostic Factors

Several pretreatment factors are reported to have prognostic significance in SCLC (Table 76-18).[545–549] The most consistent of these are stage and performance status. The importance of stage has already been mentioned, but it is perhaps worth noting that patients with a single metastatic site will often fare better than the typical extensive-stage patient with many metastatic sites.[550] Patients with poor performance status are less likely to respond favorably to chemotherapy and are more likely to experience major clinical toxicity.[551] Nonetheless, as discussed elsewhere, poor performance status per se does not automatically exclude a patient from consideration to receive combination chemotherapy, in that the occasional patient will experience substantial clinical improvement and survival benefit.[552,553] Female gender has been shown consistently to be a favorable prognostic factor in SCLC.[554] Women enjoy higher overall response rates and longer survivals compared with their male counterparts but do so at the cost of greater treatment-related toxicities. Substantial weight loss (≥10% of body weight) is an independent adverse prognostic factor,[555] as is a high serum lactate dehydrogenase in persons with extensive-stage disease.[545] Hypoalbuminemia, hyponatremia, elevated alkaline phosphatase, and leukocytosis are associated with an adverse outcome in some studies, but these findings are inconsistent from study to study.[546,547,555,556]

Table 76-18 Favorable Prognostic Factors in Small Cell Lung Cancer

Consistently Reported	Inconsistently Reported
Limited-stage	Single metastatic site
Good performance status	Absence of pleural effusion
Female sex	Absence of brain metastasis
Normal lactate dehydrogenase	Absence of liver metastasis
	Age <40 yr
	Normal serum sodium
	Normal liver function

Reproduced with modifications from Jackman DM, Johnson BE: Small-cell lung cancer. Lancet 2005;366:1385–1396.

Small Cell Lung Cancer Treatment

Chemotherapy Overview: The Emergence of Etoposide and Cisplatin

For more than 3 decades combination chemotherapy has served as the foundation of SCLC therapy.[238,239] In the earliest phase of SCLC clinical investigation combination regimens typically included alkylating agents such as cyclophosphamide or anthracyclines such as doxorubicin (Adriamycin). Common drug combinations included cyclophosphamide, doxorubicin, and vincristine (CAV) or its variant CAE in which etoposide is substituted for vincristine.[557] Over the past 2 decades, however, platinum-based chemotherapy has supplanted these older regimens in part because of an increase in overall response rates and greater survival without a perceptible increase in the frequency of toxic death.[558] Specific interest in the combination of etoposide and cisplatin (EP) was stimulated initially by the observation that the regimen could produce tumor regression in persons whose cancers had progressed following initial drug treatment with a cyclophosphamide-based regimen.[559–561] In many subsequent comparative studies and in meta-analyses,[562–565] EP has been found to consistently outperform CAV or similar regimens in terms of survival benefit, reduced host toxicity, or both. The consistent performance of EP over nearly 2 decades of clinical trials coupled with the added benefit of its compatibility with TRT (see later discussion) has rendered this regimen the treatment of choice for most individuals with SCLC irrespective of initial stage.[238,239] EP has been described as "[o]ne of the best bargains for state of the art cancer care".[239]

Although EP is widely regarded as the gold standard for the treatment of SCLC, the optimal dose and scheduling of these agents are not well defined.[239] Etoposide has greater efficacy in SCLC when given over multiple days as compared with a dose administered on a single day[566] and is usually administered cyclically over 3 to 5 days. Cisplatin is not schedule dependent but nonetheless is sometimes administered as a split dose to lessen its gastrointestinal and renal toxicities. Increasing doses of etoposide does effect higher complete response rates but has no impact on overall response rates.[567] By contrast, complete or overall responses are not affected by cisplatin dose per cycle, and there is no correlation between survival and dose per cycle of either agent.[567] These data suggest minor variations in the dosing and scheduling of EP have little impact on survival (at least in persons with extensive-stage SCLC). Individuals with limited-stage SCLC given EP using any of the common regimens listed in Table 76-19 should experience complete-response rates of 80% or higher, a median survival of approximately 18 months, and a 5-year cancer-free survival of up to 25%.[568] In persons with extensive-stage SCLC EP is associated with a complete-response rate of more than 20% and median survivals of 7 to 9 months; in addition, 2% of patients will be alive and without cancer at 5 years.[569] The death rate related to EP therapy should be under 2%.[239]

Extensive-Stage Small Cell Lung Cancer

A multitude of therapeutic strategies have been evaluated as a means of improving response rates and overall survival in extensive-stage SCLC.[238,239,557] For the most part these efforts used older alkylating- or anthracycline-based chemotherapy regimens and were uniformly ineffective as reviewed in detail elsewhere.[238,239,557] Attempts to enhance the therapeutic efficacy of the EP regimen have focused on the addition of a third active agent,[570–574] substitution of a newer active agent for etoposide,[575–577] dose intensification,[578] weekly administration of EP with additional active agents,[579,580] integration of putative alternating non-cross-resistant regimens,[562,564] and use of maintenance or consolidation chemotherapy.[581] Unfortunately, none of these strategies has yielded a consistent or clinically meaningful prolongation of survival, nor has host toxicity been consistently or meaningfully reduced relative to a standard EP regimen.[238,239]

Additional Active Agents with Etoposide and Cisplatin

Combining agents with differing mechanisms of action and nonoverlapping toxicities is a time-honored approach to incremental improvement in cancer therapy and a strategy used by several investigative groups (Table 76-20). One of the earliest attempts to use this approach to improve EP was undertaken by a group of HOG investigators.[570] In a phase III trial the HOG investigators compared EP to EP plus ifosfamide. Although the addition of ifosfamide to EP yielded a statistically significant survival benefit (median survival 7.3 vs. 9.0 months; 2-year survival 5% vs. 13%; $P = 0.045$), most experts have viewed the modest survival gain as insufficient to change clinical practice given the added cost and accompanying increase in host toxicity.[239]

The addition of paclitaxel to EP failed to improve overall survival in extensive-stage SCLC (median survival 9.9 vs. 10.6 months; $P = 0.169$) and was accompanied by an increase in renal toxicity, motor-sensory neuropathy, and hearing loss.[572] There was also a tripling of the toxic death rate (6.5% vs. 2.4%), even with the addition of granulocyte colony-stimulating factor support.[572] Similar uninspiring results were reported in a Greek Lung Cancer Cooperative Group randomized trial of EP plus paclitaxel versus EP that was closed early because of unacceptable toxicity in the three-drug arm.[571]

Using a different approach, ECOG investigators treated individuals with extensive-stage SCLC with four courses of induction EP.[574] Persons with stable or responding disease were then randomized to observation or consolidation therapy using four cycles of single-agent topotecan. Progression-free survival was statistically superior for the topotecan arm (3.6 vs. 2.3 months; $P < 0.001$), but there was no difference in median survival (8.9 vs. 9.3 months; $P = 0.43$), and topotecan added substantial toxicity. It is noteworthy that even when individuals with extensive-stage SCLC were selected for chemoresponsive biology (i.e., only patients without progressive disease were

Table 76-19 Dose and Schedule of Etoposide and Cisplatin Administration in Small Cell Lung Cancer

Group	Etoposide	Schedule	Cisplatin	Schedule
NCIC[664]	100 mg/m^2	Days 1–3 every 3 wks	25 mg/mg^2	Days 1–3 every 3 wks
SECSG[357]	80 mg/m^2	Days 1–5 every 3 wks	20 mg/mg^2	Days 1–5 every 3 wks
NCCTG[665]	100 mg/m^2	Days 1–3 every 3 wks	30 mg/mg^2	Days 1–3 every 3 wks
ECOG[574]	120 mg/m^2	Days 1–3 every 3 wks	60 mg/m^2	Day 1 every 3 wks
GLCCG[571]	120 mg/m^2	Days 1–3 every 3 wks	80 mg/m^2	Day 1 every 3 wks
FFCI[573]	100 mg/m^2	Days 1–3 every 4 wks	100 mg/m^2	Day 1 every 3 wks
JCOG[577]	100 mg/m^2	Days 1–3 every 3 wks	80 mg/m^2	Day 1 every 3 wks
CALGB[572]	80 mg/m^2	Days 1–3 every 3 wks	80 mg/m^2	Day 1 every 3 wks

FFCI, French Federation of Cancer Institutes; GLCCG, Greek Lung Cancer Cooperative Group.

Table 76-20 Multidrug Cisplatin + Etoposide Combinations in Small Cell Lung Cancer

Reference	Regimen	No. of Patients	MST	1-Yr Survival	*P* Value
Loehrer et al[570]	EP	84	7.3 mo	27%	0.045
	EP + ifosfamide	87	9.0 mo	36%	
Niell et al[572]	EP	282	9.9 mo	37%	0.169
	EP + paclitaxel	283	10.6 mo	38%	
Mavroudis et al[571]	EP	62	10.5 mo	38%	0.588
	EP + paclitaxel	71	9.5 mo	37%	
Schiller et al[574]	EP	111	8.9 mo	28%‡	0.43
	EP + topotecan*	112	9.3 mo	25%‡	
Pujol et al[573]	EP	109	9.3 mo	29%	
	EP + epidoxorubicin + cyclophosphamide†	117	10.5 mo	40%	0.0067

EP, cisplatin + etoposide; MST, median survival time.
*Topotecan administered as consolidation therapy in patients with responding or stable disease.
†Toxicity-related death rate = 9%.
‡One-year survival from time of randomization (overall 2-year survival = 35%).

randomized), maintenance treatment beyond four cycles of EP with putatively non-cross-resistant properties failed to improve survival.[239]

Finally, a French group conducted a trial that compared EP to EP plus cyclophosphamide and epirubicin and reported a modest but statistically significant improvement in median survival (10.5 vs. 9.3 months; $P = 0.0067$).[573] The survival benefit, however, was accompanied by a marked increase in overall toxicity that included a trebling of the rate of documented infections and a near doubling of the toxicity-related death rate.

In summary, the addition of a third (or more) active agent to EP has thus far proved ineffective as a means of improving survival and is generally associated with increased toxicity.[571–574] Outside of a clinical trial setting, such an approach is to be discouraged.

Active Agents Substitutions in Etoposide and Cisplatin

The substitution of an active agent for etoposide or cisplatin presumes the newer agent will enhance survival, reduce host toxicity, or both. Japanese investigators took this approach in a trial that prospectively compared EP to a regimen consisting of irinotecan and cisplatin (IP); (Table 76-21).[577] The IP regimen consisted of irinotecan 60 mg/m^2 on days 1, 8, and 15 and cisplatin 60 mg/m^2 on day 1 every 4 weeks, whereas EP was administered as follows: etoposide 100 mg/m^2 days 1 through 3 with cisplatin 80 mg/m^2 on day 1 every 3 weeks. The trial was stopped early when an interim analysis revealed that the IP combination had demonstrated survival superiority (median survival 12.8 vs. 9.4 months, respectively; $P = 0.002$). At 2 years the percentage of patients surviving was 19.5% versus 5.2% in favor of the IP arm. The verisimilitude of these results was bolstered by the view that the survival of EP-treated patients was characteristic of this regimen. Severe or life-threatening myelosuppression was more frequent in the EP group than in the IP group, whereas severe or life-threatening diarrhea was more frequent in the IP group compared with those given EP. The authors concluded that IP "is an attractive option for patients with metastatic small-cell lung cancer who have a good performance status."

More recently an American group undertook a confirmatory trial but used a slightly different schedule and dosing of the IP regimen (irinotecan 65 mg/m^2 plus cisplatin 30 mg/m^2 days 1 and 8 every 3 weeks).[576] In keeping with the Japanese trial, grades 3 or 4 anemia, thrombocytopenia, neutropenia, and febrile neutropenia were less common in IP-treated patients, whereas grades 3 or 4 diarrhea and vomiting were more frequent as compared with EP-treated patients. However, in contrast to the Japanese experience, there was no significant difference in response rates (48% vs. 43.6%), median times to progression (4.1 vs. 4.6 months), or median survival (9.3 vs. 10.2 months; $P = 0.74$; see Table 76-21).[576] These investigators determined that IP and EP are therapeutically equivalent and distinguishable only by modest differences in toxicity profile. They have further suggested that IP might be useful when it is anticipated that hematologic toxicity will be a limiting toxicity or when the toxicity is found to be severe during the early cycles of EP.[576]

Given the divergent survival results of the preceding studies, the SWOG initiated a third phase III study that compares IP with EP (S0124). The SWOG trial uses the same IP regimen and study design used in the Japanese study under the presumption that a change in

Table 76-21 Etoposide Drug Substitution Trials in Small Cell Lung Cancer

Reference	Regimen	No. of Patients	MST	1-Yr Survival	*P* Value
Noda et al[577]	EP	115	9.4 mo	37.7%	0.002
	Irinotecan + P	115	12.8 mo	58.4%	
Hanna et al[576]	EP	110	10.2 mo	35%	0.74
	Irinotecan + P	221	9.3 mo	35%	
Eckhardt et al[575]	EP	395	9.4 mo	31%	0.48
	Topotecan + P	389	9.1 mo	31%	

EP, etoposide + cisplatin; MST, median survival time; P, cisplatin.

the IP dose and scheduling may account for the negative outcome of the North American study. A more likely explanation resides in the ethnic differences between Asians and Caucasians in the enzymes responsible for irinotecan metabolism.[582] This possibility will be addressed in the SWOG trial that includes pharmacogenomic endpoints (e.g., UGT1A1 polymorphisms) and markers of drug resistance (e.g., ERCC-1 and XRCC-1).

A third attempt to incorporate a topoisomerase I poison into frontline therapy was undertaken by a multinational group that randomized individuals with extensive-stage SCLC to EP or oral topotecan and cisplatin.[575] However, like irinotecan, topotecan did not improve response rates, median time to progression, or overall survival (see Table 76-21). Therefore, the combined data from North America and Europe indicate that the substitution of topoisomerase I inhibitors for etoposide in a platinum protocol is unlikely to displace EP as standard therapy for extensive-stage SCLC in patients of European descent.[239] There may be ethnic and pharmacogenetic differences that favor the IP regimen in patients from Japan and perhaps other Far East countries.[582]

Carboplatin is an active agent against SCLC, with less toxicity and better tolerance than cisplatin.[583] It is also well tolerated when combined with etoposide.[584] The Hellenic Co-operative Oncology Group prospectively compared EP to etoposide plus carboplatin and reported comparable response rates and survival.[585] However, the trial was not adequately powered to discern noninferiority.[586] Nonetheless, these data are frequently cited as justification for the substitution of carboplatin for cisplatin.

Other newer agents such as pemetrexed and amrubicin are under active investigation as possible substitutions for etoposide.[587,588] In general the survival data from these preliminary studies do not suggest these newer agents represent a true major breakthrough.

Etoposide and Cisplatin Dose Intensification

Previous efforts to improve outcome in extensive-stage SCLC through dose intensification were conducted primarily using older alkylating agent or anthracycline-based regimens, and all failed.[238,239] So it is with the EP regimen. In a prospective trial conducted at the NCI, standard-dose EP (etoposide 80 mg/m^2 days 1–3 and cisplatin 80 mg/m^2 day 1 every 3 weeks) was compared to high-dose EP (etoposide 80 mg/m^2 days 1–5 and cisplatin 27 mg/m^2 days 1–5 every 3 weeks for two cycles) in persons with extensive-stage SCLC and good performance status.[578] Although patients in the high-dose EP arm received 68% higher doses and a 46% higher dose-rate intensity, complete response rates (23% vs. 22%; $P = 0.99$) and median survival durations (10.7 vs. 11.4 months; $P = 0.68$) were identical. Leukopenia, thrombocytopenia, febrile neutropenia, and weight loss were all significantly more common in patients randomized to receive high-dose compared with standard-dose EP. Notably, grade 4 leukopenia and thrombocytopenia were infrequent (2% of patients) in the standard-dose EP arm. Although trials of high-dose chemotherapy with stem cell support for SCLC are still under way in Europe,[589] the failure of this approach to overcome drug resistance in other epithelial cancers coupled with the substantial added costs in financial and logistic terms limits this line of investigation to a few enthusiasts. The NCI data, in conjunction with additional supporting data,[562,564] strongly suggest that drug regimens with severe hematologic toxicities are simply not necessary to yield optimal therapeutic results. Recent advances in antiemetic therapy and intravenous hydration regimens suitable for the outpatient clinic can ameliorate the nonhematologic toxicities associated with cisplatin and further enhance the therapeutic index of EP.[238,239]

Weekly Administration of Etoposide and Cisplatin with Additional Active Agents

In general weekly chemotherapy programs combined EP with the active agents used in older cyclophosphamide- and anthracycline-based regimens (i.e., CAV or CAE). A popular regimen for a short period of time was the CODE regimen (EP with doxorubicin and vincristine). CODE was unique in that it combined drug diversity with dose intensity.[239] Unfortunately the approach proved excessively toxic, even in a select group of individuals with extensive-stage SCLC and good performance status, and was no more effective than standard dose and scheduling of alternating EP with CAV.[580] Notably, in extensive-stage SCLC, alternating EP with CAV is not more effective than EP alone.[562,564] Likewise, efforts to interdigitate topotecan and paclitaxel with EP have proved unsuccessful, with no survival improvement but substantially increased myelosuppression.[590] In short, weekly chemotherapy administration is not recommended in the care of patients with extensive-stage SCLC.

Maintenance Therapy

Several randomized trials of maintenance therapy have been carried out since 1980.[591,592] With rare exception,[593] no survival advantage was observed in any of the individual published trials.[592] Highly instructive in this regard is a trial conducted more than 2 decades ago in which individuals with SCLC were treated with induction EP chemotherapy and, where appropriate, thoracic and cranial irradiation depending on initial stage.[581] Only the patients responding to induction EP were randomized to either observation or up to 10 cycles of maintenance CAV chemotherapy. Maintenance therapy with CAV yielded no survival advantage, although there was considerable increased host toxicity. A recent meta-analysis of 14 maintenance chemotherapy trials suggested that there may be a modest survival improvement with maintenance therapy.[591] However, the studies included in this analysis go back to the early 1970s in some instances, and individual patient data were not used. Thus, the clinical relevance of this report is questionable.

Marimastat, an orally administered synthetic inhibitor of matrix metalloproteinases, has been evaluated as maintenance therapy in a placebo-controlled trial.[594] Eligible patients first received four or more cycles of an induction chemotherapy regimen, and only those who achieved a complete or partial remission were randomized. The choice of induction therapy and the decision to use radiation as part of the induction regimen were left to the discretion of individual investigators. Median times to progression (4.3 vs. 4.4 months; $P = 0.81$) and median survivals (9.3 vs. 9.7 months; $P = 0.90$) were identical for marimastat and placebo-treated patients. Quality of life, however, was considerably worse on the marimastat arm at both 3 and 6 months because of substantial side effects. Thus, treatment with marimastat after induction therapy for SCLC did not improve survival and imparted a negative effect on quality of life.

Collectively these data suggest that a plateau has been reached in the management of extensive-stage SCLC using classical cytotoxic agents similar to that observed in metastatic NSCLC.[238,239]

Limited-Stage Small Cell Lung Cancer

Median survival of persons with limited-stage SCLC treated on the control arms of NCI-sponsored randomized trials initiated between 1972 and 1981 was just 12.0 months (range, 10–16 months) compared to a median survival of 17.0 months (range, 11–20 months; $P < 0.001$) in trials carried out between 1982 and 1992.[568] Thus, in contrast to the modest survival progress made in extensive-stage SCLC over the past 2 decades, the survival of individuals with limited-stage SCLC has improved substantially.[238,239,568,595] The relative contribution of improved therapeutic options, better supportive care, and/or stage migration to the observed survival prolongation is difficult to assess from the available literature. However, it is noteworthy that among persons with limited-stage SCLC treated within the context of these U.S. cooperative group trials, some modification in radiation therapy accounted for the improved survival noted in all five of the positive studies, suggesting that modifications in the delivery of irradiation played a prominent role in the survival advances.

In none of the NCI-sponsored randomized trials carried out between 1972 and 1992 did a change in chemotherapy alone account for an obvious survival improvement.[568] However, in subsequent trials EP has demonstrated a survival advantage in limited-stage SCLC compared with older chemotherapy regimens.[565] A Norwegian group randomized limited-stage and extensive-stage SCLC patients to receive EP or a regimen of cyclophosphamide, epirubicin, and vincristine (CEV), the European equivalent of CAV.[565] Among the entire study cohort, survival at 2 and 5 years was significantly better in the EP arm (14% vs. 5%) compared with the CEV arm (6% vs. 2%; $P = 0.0004$). Among the patients with limited-stage disease, EP plus TRT conferred a clear survival advantage compared with patients treated with CEV plus TRT (median survival 14.5 vs. 9.7 months), with 2- and 5-year survival rates of 25% and 10% versus 8% and 3% in the EP and CEV arms, respectively ($P = 0.0001$).[565] In light of these results, EP is now considered the preferred chemotherapy regimen for limited-stage SCLC in virtually all parts of the world.

Attempts to improve upon the results achieved with standard EP regimens and TRT in limited-stage SCLC have used drug substitutions or dose intensification.[596,597] Both strategies yielded improved survival compared with standard combined-modality therapy with EP alone, but a closer look at the data reveals median and long-term survival rates in the standard treatment arms that are clearly inferior to what is usually obtained with concurrent EP and TRT.[596,597] The explanation for this disparity is not clear, although both studies delayed TRT until after administration of the modified chemotherapy program. The need to delay TRT in these studies suggests that these therapeutic strategies may be incompatible with optimal delivery of TRT.[239] Although it is possible there were differences in the prognostic factors or staging methods used in these trials that rendered the participants markedly different from the participants in other recently published studies,[239] this does not seem to be the case. Moreover, the changing demographics of individuals with SCLC do not seem to be particularly conducive to wide-scale use of increasingly toxic combined-modality approaches.[598] Accordingly, these data fail to establish a new treatment standard in limited-stage SCLC as outlined following.

Combined-Modality Therapy for Limited-Stage Small Cell Lung Cancer

Meta-analyses of the individual trials comparing chemotherapy alone to chemotherapy plus TRT show a modest improvement in survival rates in patients on combined-modality therapy.[599,600] The overall relative risk of death in the combined-modality group as compared with the chemotherapy group is 0.86 (95% CI, 0.78–0.95; $P = 0.001$), that is, a 14% reduction in the mortality rate.[599] During the initial 12 months individuals irradiated after diagnosis seem to do slightly less well than nonirradiated patients, but by 1 year a survival benefit emerges that persists beyond 5 years.[239] At 3 years 8.9% of the chemotherapy-only group is alive compared with 14.3% of the combined-modality group. At 2 years local failure rate is 23% for irradiated patients and 48% for nonirradiated patients ($P = 0.0001$).[599] Combined therapy is accompanied by a 1% increase in treatment-related deaths.[239] Because a majority of the trials included in these meta-analyses involved non-platinum-based chemotherapy regimens, it is likely the meta-analyses underestimate the absolute benefit of combined-modality therapy in individuals with limited-stage SCLC and good performance status, because platinum-based therapy allows for easier integration of full-dose chemotherapy and radiation therapy.[239,601] Although these data clearly establish combined-modality therapy as the preferred treatment for patients with limited-stage SCLC and a good performance status, there are unanswered questions relating to the optimization of TRT including timing and sequencing of TRT, optimal total dose, fractionation, and volume of irradiation.[239,595] These issues are covered in the following sections.

Timing of Thoracic Radiation Therapy

Two literature-based meta-analyses addressed the question of optimal timing of TRT in limited-stage SCLC.[602,603] These analyses differ in their definition of early versus late TRT. One defined early chest irradiation as starting within 30 days after the start of chemotherapy and identified eligible studies according to the Cochrane Collaboration Guidelines.[602] Altogether seven trials met the inclusion criteria, most of which used platinum-based chemotherapy regimens.[604–610] Overall survival at 2 or 5 years was not significantly different between early or late TRT, nor was there a significant effect on local tumor control comparing early and late radiation therapy.[602] However, the elimination of one trial that used a non-platinum therapy[611] resulted in a significantly higher 5-year survival when TRT was started within 30 days of starting platinum-based chemotherapy.[602] The survival benefit was even more pronounced when the overall treatment time of TRT was less than 30 days (see later discussion). The second meta-analysis included randomized trials addressing timing of TRT published after 1985 and defined early TRT as beginning before 9 weeks after the initiation of chemotherapy and before the third cycle of chemotherapy.[603] Late TRT was defined as beginning 9 weeks or more after the initiation of chemotherapy or after the beginning of the third cycle of chemotherapy. The 2-year overall survival risk ratio of 1.17 (an absolute 5% survival benefit) favored early radiation therapy (Fig. 76-19).[603] Patients treated with platinum-based chemotherapy and early TRT experienced a significant survival benefit at both 2 (RR, 1.30; 95% CI, 1.10–1.53; $P = 0.002$) and 3 years (RR, 1.35; 95% CI, 1.07–1.70; $P = 0.01$), whereas patients treated with non-platinum-based regimens derived no survival benefit from early TRT. There was also a significant survival benefit associated with early TRT among patients treated with hyperfractionated radiation

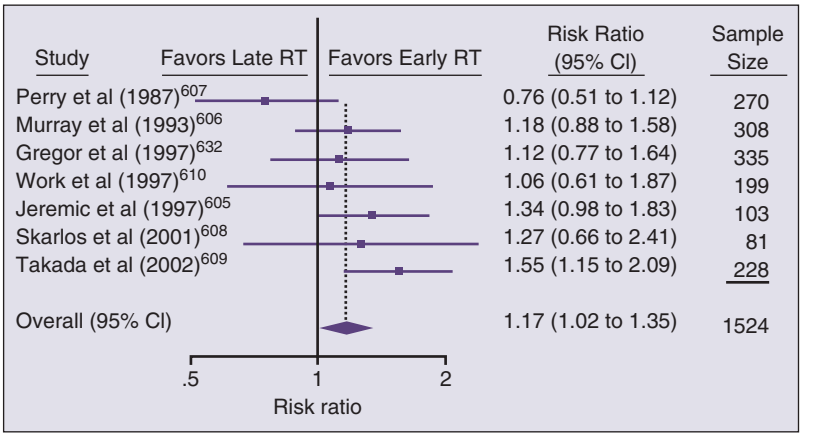


Figure 76-19 • Two-year overall survival risk ratio forest plot for early versus late thoracic radiation therapy. (Reproduced with permission from Fried DB, Morris DE, Poole C, et al: Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 2004;22:4785–4793.)

(RR, 1.44; 95% CI, 1.17–1.83; $P = 0.001$ and RR, 1.39; 95% CI, 1.02–1.90; $P = 0.04$, respectively). Patients treated with once-daily irradiation derived no survival benefit from receiving early TRT.

Collectively these data support a small but significant improvement in 2-year overall survival with early TRT in limited-stage SCLC. The greatest difference occurs with platinum-based chemotherapy and hyperfractionated TRT.[603] Both meta-analyses indicate that early combined-modality therapy extracts a price, however, in that severe esophagitis and leukopenia are more frequent and there is a trend toward a higher incidence of severe pneumonitis.[602,603]

Duration of Combined-Modality Therapy

It has been suggested that repopulation of clonogenic tumor cells triggered by one or two cycles of chemotherapy can inhibit the effectiveness of subsequent TRT and may contribute to treatment failure.[612] In other words, the time interval from the start of any treatment in limited-stage SCLC until the end of radiation therapy (known as SER) may have a major bearing on response and survival rates.[613] In a recent analysis of SER, a shorter SER interval was associated with significantly higher 5-year survival (RR, 0.62; 95% CI, 0.49–0.80; $P = 0.0003$). When the SER was less than 30 days, survival improvement was more than 20%. For each week SER is extended beyond 3 weeks there was a decrement in the 5-year survival rate of approximately 1.8% per week. However, improved survival was gained at the expense of greater toxicity mainly as a higher incidence of severe esophagitis. Curiously the study failed to identify a significant relationship between SER and local failure rates, although this is probably attributable to problems in assessing local failure rates in clinical trials. These data indicate that the total time in which the entire combined-modality treatment is delivered is critical in determining survival outcome in limited-stage SCLC.[612,613] This might be achieved in a variety of ways including delivering TRT early as discussed previously and/or through other means such as hyperfractionation.

Fractionation of Thoracic Radiation Therapy

Conventional radiation therapy fractionation can be modified by hyperfractionation (radiation therapy given more than once a day), acceleration (shortening of the overall treatment time), or both.[595] A potential advantage of accelerated radiation therapy is a shortening of SER and the avoidance of accelerated tumor cell repopulation and the attendant detrimental effects.[602] Repopulation of surviving tumor cells may occur between dose fractions of either radiation therapy or chemotherapy and effectively decreases tumor cell kill.[612] Multiple small fractions of radiation therapy or hyperfractionation may be useful, because the radiation dose-response curves for SCLC cell lines lack a shoulder,[614] meaning that even at relatively low doses per fraction, tumor cells are killed exponentially. By contrast, lower radiation dose fractions spare cell populations that have a shoulder as is true of most normal tissues. For these reasons, multiple small fractions of radiation therapy can kill small cell cancer cells while reducing permanent damage to normal tissues lessening the risks of late effects of radiation.

Two U.S. cooperative groups performed randomized trials comparing hyperfractionated with conventional once-daily fractionated TRT in individuals with limited-stage SCLC.[601,615] The results of these studies are seemingly contradictory (Table 76-22). ECOG investigators compared twice-daily irradiation (45 Gy in 1.5-Gy fractions twice daily) to standard once-daily radiation therapy(45 Gy in 1.8-Gy fractions) starting with the first cycle of EP chemotherapy.[601] With a median follow-up of almost 8 years, the median and 5-year survival rates favored patients treated twice daily. There was a higher rate of severe esophagitis in the twice-daily treated arm but little in the way of increased toxicity otherwise. A North Central Cancer Treatment Group (NCCTG) trial, however, found no survival benefit with twice-daily TRT as compared to conventional once-daily TRT.[615] There are important differences in the design of these two trials that may have impacted outcome. In the NCCTG trial all patients initially received three cycles of EP. Only patients without significant progression were randomized to once- or twice-daily TRT, thereby delaying irradiation until the fourth and fifth cycles of chemotherapy.[615] The lengthy delay in TRT administration may have allowed chemotherapy-resistant clones to develop.[612] Further confounding the interpretation of the NCCTG data, the total duration of TRT was not different in the hyperfractionated scheme, because these investigators included a mid-course interruption in the twice-daily arm. In effect this mid-course interruption negated the planned overall acceleration in the hyperfractionated arm, potentially permitting tumor repopulation to take place.[616]

Dose of Thoracic Radiation Therapy

Another unresolved issue is the optimal dose of TRT in limited-stage SCLC. Historically, relatively lower doses of TRT have been used, mostly because of a perceived greater intrinsic radiosensitivity.[239] However, low-dose schedules are associated with a high rate of local failure, suggesting that dose escalation of radiation therapy to levels employed in NSCLC might be beneficial. There is surprisingly little evidence that higher doses of TRT can improve survival because of a paucity of prospective randomized trials addressing the optimal TRT dose question.[239,595] Retrospective studies do suggest that TRT doses greater than 50 Gy translate into improved progression-free survival.[617,618] Some U.S. cooperative groups have escalated TRT doses to 60 Gy and higher, paralleling the doses used in locally advanced NSCLC,[239,595] with individual investigators increasing radiation therapy doses to as high as 70 Gy in 35 fractions over 7 weeks.[618] However, none of these efforts seems to provide survival results superior to the dose and schedule used in the aforementioned ECOG trial (i.e., 45 Gy delivered over 3 weeks).[601] Moreover, the increased treatment times required by the high-dose treatments administered over 6 to 7 weeks are associated with a longer SER. Longer SER is generally associated with a less favorable outcome as outlined previously. In addition, protracted TRT will necessarily overlap with more chemotherapy cycles that in turn will probably result in more frequent dose reductions and treatment delays, further compromising chemotherapy delivery.[239] Ideally, TRT doses of 60 Gy or more should be evaluated against the twice-daily schedule

Table 76-22 Hyperfractionated Thoracic Radiation Therapy in Small Cell Lung Cancer: Randomized Phase III Trials

Group	No. of Patients	TRT Schema	MST (mo.)	5-Yr Survival (%)
ECOG[601]	211	45 Gy, 1.5 Gy twice daily, wk 1–3	23	26
	206	45 Gy, 1.8 Gy daily, wk 1–5	19	16
NCCTG[615]	130	48 Gy, 1.5 Gy twice daily, wk 13–14; 17–18	20.6	22
	131	50.4 Gy, 1.8 Gy daily, wk 13–18	20.6	21

MST, median survival time; TRT, thoracic radiation therapy.

used by ECOG investigators to clearly define "a dose effect" in the management of limited-stage SCLC.[239,595] Unfortunately no such study is under way or planned.

Target Volume for Thoracic Radiation Therapy

Two issues tend to dominate the debate surrounding optimal target volume: the need to electively irradiate lymph nodes and the decision to treat the pre- or postchemotherapy volume of disease if TRT is to be delayed. With modern planning capabilities many experts feel that the irradiation portal should be confined to clinically palpable nodes in the supraclavicular fossa, disease found by bronchoscopy and lymph nodes that measure ≥1 cm on CT scans.[239] Larger treatment ports increase exposure to the esophagus, lung, and other sensitive normal tissues and increase normal tissue toxicities (e.g., esophagitis and pneumonitis).[239] However, limited-stage SCLC can present as a large mediastinal mass. This presents a challenge for radiation dosimetry planning, because the thoracic spine dose must be held to less than 46 Gy, and the volume of lung receiving 20 Gy (V20) must be less than 30% of the entire lung volume. The volume of the radiation should include areas of bulky lymph nodes along with the primary neoplasm so as to reduce esophagitis and pneumonitis.[239] When initial bulk of tumor is too large to reasonably treat with a radiation port, two cycles of chemotherapy may reduce the volume sufficiently with radiation ports that do not excessively irradiate the lungs.[619] Recent studies have explored the feasibility of using intensity-modulated radiation therapy to treat these large mediastinal masses to higher doses. For example, non-coplanar (parasagittal) fields can be used to minimize the volume of lung treated. Intensity-modulated radiation therapy can be considered if the volume of lung receiving 20 Gy is less than 30% and if patients have FEV_1 exceeding 1 L. Otherwise, anteroposterior/posteroanterior fields should be considered to 39 Gy followed by oblique (off spinal cord) fields.

On the basis of the extant data we believe that concurrent twice-daily TRT (45 Gy in 3 weeks) beginning with the first cycle of EP chemotherapy represents the "gold standard" for combined-modality treatment in patients with limited-stage SCLC and good performance status.[601] Higher dose once-daily fractionated TRT may be equivalent to this approach, but prospective randomized data supporting this supposition are lacking. In circumstances where the early application of TRT would necessitate treating an excessively large volume, delaying TRT until one or two cycles of chemotherapy seems justified.[602] The treatment portal should then be limited to the postchemotherapy tumor volume to minimize toxicity to normal tissues.[619]

Surgery in Small Cell Lung Cancer

The role of surgery for SCLC has come full circle in the past 4 decades. The disease has been thought of as systemic from the outset, and chemotherapeutic treatment has long been standard. In the mid-twentieth century, however, the British Research Medical Council randomized individuals with SCLC to surgery or TRT.[620] The patients on the surgical arm had worse survival, but neither arm did particularly well, with less than 5% of patients alive at 5 years. Subsequently, The VA Surgical Oncology Group entered more than 2000 patients in a study looking at the role of adjuvant chemotherapy after resection of NSCLC.[621] A total of 148 individuals with SCLC were incidentally entered in the study, and those with early-stage disease enjoyed superior survival.

Surgery for early-stage small cell carcinoma, particularly those cancers presenting as small single pulmonary nodules, may be more appropriate, as these tumors may be biologically distinct from more advanced disease.[622–624] For example, in a retrospective study, Roswell Park Cancer Institute investigators identified a small number of individuals with SCLC whose lesions were "isolated". These persons did not receive "prompt" diagnosis or treatment of their cancers. Moreover, extremely slow growth of the tumors was documented ranging from 14 to 40 months, and no lymph node involvement or metastatic disease was found at the time of surgery. Thus, this experience is not characteristic of SCLC in general. Nonetheless, other studies of resection for individuals with T1N0M0 tumors have suggested a 50% to 80% 5-year survival rate, although it is extremely rare for patients to fall into this category.[625] In the early 1990s University of Toronto investigators reviewed a 15-year surgical experience with SCLC at that institution.[625] They reported that resection improved control at the primary site, and a significant proportion of patients with stage I (N0) disease achieved long-term survival and cure with combined-modality therapy including surgery. Moreover, patients with stage II and IIIA SCLC had survival durations similar to patients with stage IIIA NSCLC who were treated surgically.[625]

There may be other circumstances where one might consider performing surgery with or without systemic therapies in selected individuals with SCLC.[623] First, small cell cancer treated with chemotherapy plus radiation therapy still has a high local recurrence rate. Surgery for other thoracic malignancies, particularly esophageal cancer, affords significant improvement in local control, even when added to radiation therapy. Second, surgery immediately puts the patient into a "no clinical evidence of disease" category, and both chemotherapy and radiation therapy work better on small-volume or microscopic disease. Finally, mixed-histology SCLCs contain non-small cell elements that may be less responsive to irradiation or chemotherapy. NSCLC is relatively resistant to chemotherapy, and surgery is the best curative option for this disease.[626] Therefore, an argument could be made for resection of residual disease after chemotherapy, especially if the remaining element represents a non-small cell fraction. There has been one randomized study testing this role for surgery in SCLC.[627] The Lung Cancer Study Group gave individuals with limited-stage SCLC standard chemotherapy for five cycles, followed by prophylactic cranial irradiation (PCI) and TRT; the patients were also randomized to receive or not receive surgery. It is interesting to note that 9% of individuals who did undergo surgery had residual non-small cell elements. Actuarial 2-year survival was identical on the two arms at 20%; thus, no survival benefit was demonstrated for surgery. However, this study excluded persons who would have fallen into the extremely limited T1N0M0 or T2N0M0 non-small cell staging schema—the ones who had shown the most benefit from surgery in earlier studies. Thus, this trial does not definitively exclude a role for postinduction surgery in SCLC, although admittedly such an approach is likely to be exceedingly uncommon in clinical practice.

In summary, the benefits of surgical resection in SCLC are mainly seen in persons with TNM stage I disease with peripheral tumors and no nodal involvement, and who are able to tolerate the procedure. Adjuvant chemotherapy should be offered postoperatively.

Prophylactic Cranial Irradiation

The need for PCI in individuals with limited-stage SCLC had long been an area of controversy.[628,629] This issue is critical in the management of limited-stage disease for two key reasons: the central nervous system has long been considered a sanctuary site from many chemotherapeutic agents, and the brain is a common site of metastasis in this cancer. Limited-stage SCLC successfully treated with induction chemotherapy plus radiation therapy is estimated to have a 50% to 67% chance of relapse in the brain, with one third of these patients having disease solely in the central nervous system.[630] A meta-analysis of seven randomized trials published in 1999 demonstrated a significant benefit to PCI.[631] Patients who received PCI were 5.4% more likely to be alive at 3 years, had a 54% reduction in the risk of brain metastases, and a 25% increase in disease-free survival.[631] Although there has been some concern that PCI can lead to late cognitive impairment, no detectable difference in post-treatment cognitive impairment or quality of life is found at 1 year after treatment.[632] Because the overall benefits seem to outweigh the risks,[628] current guidelines recommend PCI for all patients with a good

performance status who have attained remission after induction chemotherapy plus radiation therapy.[631,632] This includes individuals with extensive-stage disease in complete remission, although the benefit for this subset of patients is not as clear-cut.[631] PCI should be given sequentially, rather than concurrently, to avoid additional toxicity.[633] Typically patients receive 25 to 36 Gy in 10 to 18 fractions.[239]

Elderly Individuals with Small Cell Lung Cancer and Poor Performance Status

The proportion of people 70 years of age and older that has limited-stage SCLC has increased from 32% in 1985 to 45% in 2000.[598] This percentage is likely to increase in the coming decade as members of the post-World War II "baby boomer" generation enter into their sixth and seventh decades of life. Given the lengthy smoking history in the majority of persons with SCLC, many also suffer from the cardiovascular and pulmonary sequelae of smoking, which can negatively impact performance status. In turn, impaired performance status associates with greater treatment-related toxicity, as does the abnormal cardiac, liver, or renal function often observed in the elderly.[634,635] As a result, curative chemotherapy is often not even attempted in the elderly with a wide variety of malignancies.[636] Age alone, however, is not a sufficient reason to deny an elderly patient potentially curative or appropriate palliative therapy. At one point it was assumed that single-agent cytotoxic therapy might afford a measure of palliation in such individuals without engendering the toxicity associated with combination chemotherapy while simultaneously preserving a survival benefit. However, in two randomized trials that compared single-agent oral etoposide with combination-chemotherapy regimens, persons assigned to combination regimens not only lived longer but also had fewer side effects.[552,553] Given these findings, intravenous combination chemotherapy is considered the standard treatment in this setting. Among elderly individuals with limited-stage SCLC and a good performance status, the standard combined-modality approach remains the preferred option.[615,637] When the tolerability of standard-dose EP is deemed to be problematic, options include dose reduction, substitution of carboplatin for cisplatin,[585,638–640] or possibly a combination of low-dose cisplatin, doxorubicin, vincristine, and etoposide.[641] Selected, fit older patients are as able as younger patients to tolerate chemotherapy, although their management may require more attention to supportive care.[642]

Second-Line Chemotherapy in Small Cell Lung Cancer

There is no best salvage regimen or drug for recurrent or resistant SCLC.[643] Topotecan is the only agent approved by the FDA for use as second-line chemotherapy in SCLC.[644,645] It is associated with a modest prolongation of survival and quality-of-life benefit whether given intravenously or orally.[646] Other agents such as paclitaxel,[647,648] oral etoposide,[649] irinotecan,[650] and amrubicin[651] are useful in this setting as well. From a practical standpoint, the most important influences on the decision to administer second-line therapy are the person's current performance status, the level of sensitivity to induction therapy, and the interval from prior therapy. Patients with a good performance status, sensitivity to prior therapy, and a progression-free period of more than 3 months are much more likely to respond to second-line treatment. Retreatment with the induction regimen or one of the agents listed previously is appropriate for individuals meeting these criteria. For all others, second-line therapy tends to be a process of "trial and error" of single agents or combinations.[643] Paclitaxel-containing regimens may be especially useful in individuals without prior response or a very short treatment-free interval after initial first-line treatment, especially if non-platinum therapy is used as induction therapy.[647,648] Radiation therapy can be an effective treatment for palliation of specific symptoms and isolated intrathoracic relapses.[643]

Novel and Targeted Therapy in Small Cell Lung Cancer

In contrast to NSCLC, *EGFR* mutations are virtually never found in SCLC.[62] Notably, however, two independent groups found *EGFR* mutations in females who had never smoked and who were diagnosed with SCLC.[652,653] Both patients were initially diagnosed as having an adenocarcinoma and were treated with an EGFR TKI (gefitinib or erlotinib). Subsequent analyses of tumor material obtained at the time of disease progression or at postmortem revealed SCLC with an *EGFR* mutation. In both cases the mutation involved exon 19. It is unclear whether these women originally had a combination of SCLC and NSCLC or whether the NSCLC transdifferentiated to SCLC after prolonged treatment with erlotinib.[653] Nevertheless, these data suggest that *EGFR* mutations may be important in the rare circumstance where SCLC develops in a person who has never smoked. Although extremely rare in nonsmokers, SCLC is found in nearly 3% of women with lung cancer who had never smoked.[245] Additional novel targeted agents investigated in SCLC include inhibitors of matrix metalloproteinases,[594] c-kit,[654] farnesyl transferase,[655] proteasome inhibitors,[656] and mTOR,[657] conjugated antibodies against CD56,[658] bcl-2 antisense oligonucleotide[659] and anti-idiotype vaccines.[524] Essentially all these efforts have proved negative or inconclusive.[660] Antiangiogenesis agents such a bevacizumab are worthy of additional study given recent successes in NSCLC[523] and other solid tumors.

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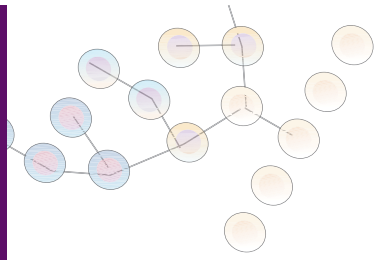
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77 Tumors of the Pleura and Mediastinum

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SUMMARY OF KEY POINTS

Malignant Pleural Mesothelioma

Epidemiology

- Malignant mesothelioma is a rare disease closely associated with asbestos exposure (all fiber types).
- Based on the prior use of asbestos, more than 8 million people are exposed and at risk in the United States.
- More than 3000 cases are estimated to be diagnosed in the United States annually, with the incidence still increasing.
- It is more likely to be seen in men and more likely to occur on the right side.
- Three subtypes exist: epithelial, fibrosarcomatous, and mixed.

Differential Diagnosis

- The epithelial form must be distinguished from metastatic adenocarcinomas.
- To establish the diagnosis, a generous tissue biopsy or cell block is needed so that a battery of tests may be performed, including histochemistry and immunohistochemistry.
- Immunohistochemistry now can be defining.
- Electron microscopy often is helpful; normal adjacent lung for fiber count is helpful.

Staging Evaluation

- Take a medical history and a complete occupational history, and perform a physical examination.
- Obtain computed tomography (CT) scan of chest and abdomen and a positron emission tomography (PET) scan to define the extent of disease and of mediastinal involvement.
- Focus on potential operability: CT scan of chest, bone scan, and pulmonary and cardiac function tests.
- Evaluation can be abbreviated if disease is not operable; CT scan is the best modality for following the disease.
- Use new TNM staging system.

Primary Therapy

- Therapeutic interventions are limited; consider referral to a specialty center.
- Assess symptoms carefully, and discuss risk-benefit ratio for any therapy, especially in patients with compromised performance.
- For operable disease, perform either pleural stripping with postoperative irradiation or extrapleural pneumonectomy. The role of adjuvant therapies is not certain.
- Intrapleural therapies are possible only in early disease.
- Consider radiation therapy to incision sites and needle traces to prevent growth.
- Radiation therapy may be used as a postoperative adjuvant or for symptom control.
- Chemotherapy: pemetrexed plus cisplatin; high-dose methotrexate; gemcitabine plus cisplatin; new agents remain justified.

Metastatic Tumors of the Pleura

Incidence

- Occurrence is related to the incidence of primary tumors.
- Metastases are seen most commonly with lung, breast, lymphoma, gastric, colon, melanoma, ovary, and prostate tumors.

Differential Diagnosis

- Cytology often is able to diagnose malignancy—cell block for immunohistochemistry (adenocarcinoma vs. other). Metastases should be distinguished from primary tumors, especially in high-risk individuals.
- Mucin positivity virtually excludes mesothelioma.
- Primary source identification could help to define treatment for the underlying primary disease.

Staging

- Metastatic disease, by definition (M1).

Primary Therapy

- Drain effusions for symptom control and treat the underlying primary neoplasm.
- For recurrent effusions, drain and sclerose using talc. Antibiotics (minocycline), chemotherapy (bleomycin), or biologics (*Corynebacterium parvum* [interferon {IFN} or IL-2]) have been used.

Secondary Therapies

- For highly selected patients, consider pleurectomy if effusion is resistant and the prognosis is reasonable.

Mediastinal Neoplasms

General

- Tumors are categorized or catalogued by anatomic compartments: anterior, middle, and posterior.
- Anterior compartment tumors are predominantly thymomas, lymphomas, and germ cell tumors.
- Middle compartment tumors are myxomas and malignant tumors and cysts of the heart and pericardium, including angiosarcomas, rhabdomyosarcomas, mesotheliomas, fibrosarcomas, lymphomas, extraskeletal osteosarcomas, neurogenic sarcomas, malignant teratomas, thymomas, leiomyosarcomas, liposarcomas, and synovial sarcomas.
- Posterior compartment tumors are neural crest tumors: peripheral neuroectodermal tumor (PNET), neuroblastoma, ganglioneuroma, pheochromocytoma, schwannoma, and neurofibroma.

Tumors of the Anterior Mediastinum

Epidemiology

- Thymoma
  - Twenty percent of all mediastinal tumors in adults
  - Equal male/female distribution

- Most common in the fifth and sixth decades of life
- More aggressive in children
- A possible association with Epstein-Barr virus (EBV) exists.
- Complications include myasthenia gravis, red cell aplasia, and hypogammaglobulinemia.

- Lymphoma
  - Lymphomas commonly include Hodgkin and non-Hodgkin lymphomas.
- Germ cell tumors
  - Anterior mediastinal tumors form 1% of all germ cell neoplasms and are related to malignant transformation of mediastinal germinal elements.
  - Malignant forms seen are predominantly similar to those of testicular germ cell tumors.

Differential Diagnosis

- Thymoma
  - To establish diagnosis, a generous tissue biopsy is needed for special stains and definition of architecture.
  - Subtypes include lymphocytic, epithelial, thymic carcinoma, and thymic carcinoid.
- Lymphoma
  - To establish diagnosis, sufficient material is needed for flow cytometry for immunophenotyping.
  - Tissue biopsy is helpful for special stains to define nodal architecture and cellular types.
  - Flow and biopsy should be reviewed by a pathologist with experience in lymphomas.
- Germ cell tumors
  - In the presence of appropriate biomarkers, fine-needle biopsy can establish diagnosis.
  - Subtypes (seminomatous and nonseminomatous) could require more generous tissue samples in the absence of biomarkers.

Staging and Evaluation

- Thymoma
  - Take history and perform physical examination, complete blood count, serum protein electrophoresis, and chest CT scan (role of MRI scans is not yet clear).
- Lymphoma
  - Take history and perform physical examination.
  - The remaining steps of staging and evaluation are described in the chapters on Hodgkin's and non-Hodgkin's lymphoma.
- Germ cell tumors
  - Take history and perform physical examination, chest CT scan, α-fetoprotein (AFP), β-human chorionic gonadotropin (HCG), and lactate dehydrogenase (LDH).

Primary Treatment

- Thymoma
  - Perform complete surgical resection.
  - If residual disease exists after surgery, add radiation therapy. The role of chemotherapy is not established; if the tumor is nonresectable, use radiation therapy.
  - The role of neoadjuvant therapies is not well defined.
- Lymphoma
  - Therapeutic approaches are defined in the chapters on lymphoma.
- Germ cell tumors
  - Therapeutic regimens generally follow the approaches outlined for poor-prognosis testicular germ cell tumors, with primary and secondary chemotherapy regimens and autologous bone marrow transplantation.

Tumors of the Middle Mediastinum

Incidence

- These are all very rare tumors.
- More than half are benign atrial myxomas; malignant tumors of the heart are very rare.
- Malignant tumors can originate from or metastasize to the pericardium. Other mediastinal structures can be involved depending on site and histology.
- Too few cases of pericardial mesothelioma exist to draw any inferences about an association with exposure to asbestos.

Differential Diagnosis

- Myxomas are suspected from patterns of congestive failure or embolic disease; excisional biopsy often is based on angiographic studies.
- Malignant tumors sometimes can be biopsied through bronchoscopy or via thoracoscopy. Generous amounts of tissue often are needed to define histology. Pathology experience with soft tissue tumors usually is helpful.

Staging and Evaluation

- A careful history and a physical examination are needed.
- Myxomas are best seen by cardiac catheterization. MRI might also be useful.
- Malignant tumors are best visualized by CT or MRI scan.

Primary Treatment

- Perform surgical excision of myxomas and soft tissue tumors; radiation therapy or chemotherapy have no defined role in the absence of metastases.
- Treat the underlying primary malignancy in the case of metastatic disease.

Posterior Mediastinal Tumors

Incidence

- These are rare tumors mostly originating from the neural crest; others (rarely) include lymphoma and soft tissue tumors.

Differential Diagnosis

- Tumors are in two basic groups: (1) neuronal origin, including the nerve ganglion cells (neuroepithelioma, neuroblastoma, ganglioneuroblastoma, and ganglioneuroma) and neuroendocrine cells (e.g., pheochromocytoma, paraganglioma, and medullary thyroid carcinoma); and (2) neural sheath cells or Schwann cells, including schwannoma and neurofibroma.
- Most tumors are benign.
- Adequate tissue samples are needed to perform special stains, electron microscopy, and possible cytogenetics (peripheral neuroectodermal tumors).

Staging Evaluation

- Perform CT scans; test for metanephrines in the case of labile hypertension.

Primary Treatment

- Perform surgical resection; local recurrence is likely with incomplete resection.
- Roles of radiation therapy and chemotherapy are not well defined.

PRIMARY TUMORS OF THE PLEURA

Benign and malignant primary tumors of the pleura constitute a group of unusual and rare diseases. In contrast, metastases to the pleura are a relatively common manifestation of many cancers. The diagnosis and management of the benign and malignant tumors of the pleura present important but often difficult challenges for clinicians.

Primary tumors of the pleura can originate either from the surface of the mesothelium or from the submesothelium. These various rare

Table 77-1 Classification of Tumors of the Pleura

Localized	Diffuse
MESOTHELIAL (PLEURAL)	
Adenomatoid tumor	Epithelia malignant mesothelioma
Cystic mesothelioma	Tubulopapillary
Benign papillary mesothelioma	Nonglandular (solid)
Mesothelioma of the atrioventricular node	Sarcomatous (fibrous)
	Biphasic (mixed)
	Undifferentiated
SUBMESOTHELIAL (SUBPLEURAL)	
Fibroma (localized mesothelioma)	Angiosarcoma
Fibrosarcoma (localized malignant fibrous mesothelioma)	
Angioma	
Angiosarcoma	

tumors can present as either localized or diffuse (Table 77-1). With the exception of the localized malignant soft tissue tumors, most of the localized tumors tend to behave in a benign manner, whereas the diffuse tumors tend to be more malignant in their behaviors. The usual approach to localized tumors is surgical excision, including the chest wall as needed. The role of adjunctive radiation therapy to augment local control is not well defined. For the localized soft tissue sarcomas, excision still remains the treatment of choice. In one review of 82 malignant localized tumors, 37 (45%) were cured by simple excision.[1] Because of the rarity of these tumors, studies of postoperative therapy are lacking, and there is no convincing evidence for the role of any adjunctive postoperative therapy.

Benign Mesothelioma

Benign (localized) tumors arising from the mesothelium have been described as arising from the pleura, the peritoneum, the tunica vaginalis testis, the atrioventricular (AV) node, the mediastinum, the liver, and the adrenal gland.[2–8] These tumors tend to grow to considerable size and produce symptoms by the effect of their mass, such as compression or blockage of adjacent structures. The most common approach to treatment is surgical excision. Local recurrences are prominent in cases of incomplete resection. These tumors are believed to originate from the mesothelial cells; however, there remains some uncertainty regarding the origin of AV node mesotheliomas, which might arise from submesothelial mesenchymal cells.

Benign fibrous tumors of the pleura are believed to arise from submesothelial fibrous tissue and thus have been called submesothelial fibromas, localized fibrous mesotheliomas, or solitary fibrous tumors of the pleura.[9–11] These tumors are considerably less common than malignant mesotheliomas, with no defined association with asbestos exposure. They can present as very large, pedunculated intrathoracic masses and sometimes are seen with hypertrophic pulmonary osteoarthropathy or serosanguineous effusions. These tumors rarely invade the visceral pleura and, therefore, produce clear margins between the tumor and the compressed lung. Diagnostic imaging with either computed tomography (CT) or magnetic resonance imaging (MRI) scans tends to be highly suggestive of the tumor, and complete surgical resections thus are possible, although chest wall resections could be required. Definitive diagnosis and exclusion of malignant mesothelioma must be based on histologic confirmation and immunohistochemical staining (CD 34+), however.[12] Local recurrences can be seen late and can result in fatality, although curative re-excision often is possible.[11,13]

Malignant Pleural Mesothelioma

Epidemiology

Before 1960, the existence of mesothelioma as a distinct pathological entity was still debated. In 1960, Wagner and colleagues[14] initially reported 33 cases and then added 14 additional cases of mesothelioma diagnosed in a South African asbestos (crocidolite) mining community, where patients were exposed to asbestos. Selikoff and coworkers[15] noted an association between asbestos exposure and mesothelioma among pipe fitters, and these observations were followed by reports of mesotheliomas among asbestos workers in other parts of the world.[16,17] Malignant mesothelioma of the pleura, peritoneum, and tunica vaginalis testis now are well recognized as being associated with asbestos exposure, with other potential causal factors including prior radiation therapy, extravasated Thoratrast, and certain other fibers with physical properties similar to asbestos, such as zeolite and erionite.[18] Current estimates suggest that about 3000 new cases of mesothelioma are seen annually in the United States.[19] The frequency with which malignant mesothelioma can be linked to asbestos exposure varies somewhat according to the geographic location. On the east and west coasts of the United States, the association approaches nearly 80%, whereas in the Midwestern states, the association is seen about 60% of the time.[20] The exact incidence and death rate from malignant mesothelioma remain difficult to estimate, due in part to the continued coding of mesothelioma as lung cancer. Although the incidence of mesothelioma continued to rise throughout the 1980s, reflecting a marked increase in the use of asbestos since World War II, more recent studies suggest a declining incidence in the United States, perhaps a result of governmental regulations instituted in the 1970s.[21–23] However, the incidence worldwide is expected to continue to rise for at least the next 10 to 20 years.[24]

Reflecting the association with asbestos exposure in the workplace, malignant mesothelioma is seen more commonly in men than in women. Furthermore, because of the long latent period in its development, the incidence rises with age, and the median age at presentation is greater than 65 years. Mesothelioma has been reported as a consequence of household exposure among family members of asbestos workers, however, and in young adults as a consequence of household or neighborhood exposure.[24] The risk of mesothelioma thus is not limited to those who are directly involved with the mining, milling, or application of asbestos but also extends to those who are in proximity to the use of the asbestos material or are exposed to it when it is carried home in clothing or hair.

Asbestos is a group of mineral silicate fibers that are found widely throughout the world, with mining activity in Canada, China, Russia, South Africa, and the United States.[25] Because of its superior fire-resistant qualities, it was used extensively in the shipping and construction industries. Two major forms of asbestos exist: a serpentine form (chrysotile) and the thin, rodlike amphiboles (crocidolite, amosite, anthophyllite, tremolite, and actinolyte).[25] The carcinogenic effects of asbestos are believed to be a function of their physical rather than chemical properties, with amphiboles potentially being the more carcinogenic form.[24,26,27] Asbestos fibers separate easily to form numerous minute strands. The small, inhaled fibers, which are not cleared by mucociliary action, migrate distally through the endothelial lining and into the interstitial tissues, where they accumulate in the lower third of the lungs and then penetrate into the visceral pleura. The fibers are ingested by macrophages, which often are damaged in the process, leaking lysosomal enzymes, cytokines, superoxides, and other free radicals. The asbestos fibers thus produce inflammatory and fibrotic reactions.[28] The fibers also can carry absorbed carcinogens, which might contribute further to the carcinogenic process.

The number of asbestos-exposed individuals rose throughout most of the 20th century as a consequence of increased asbestos mining and

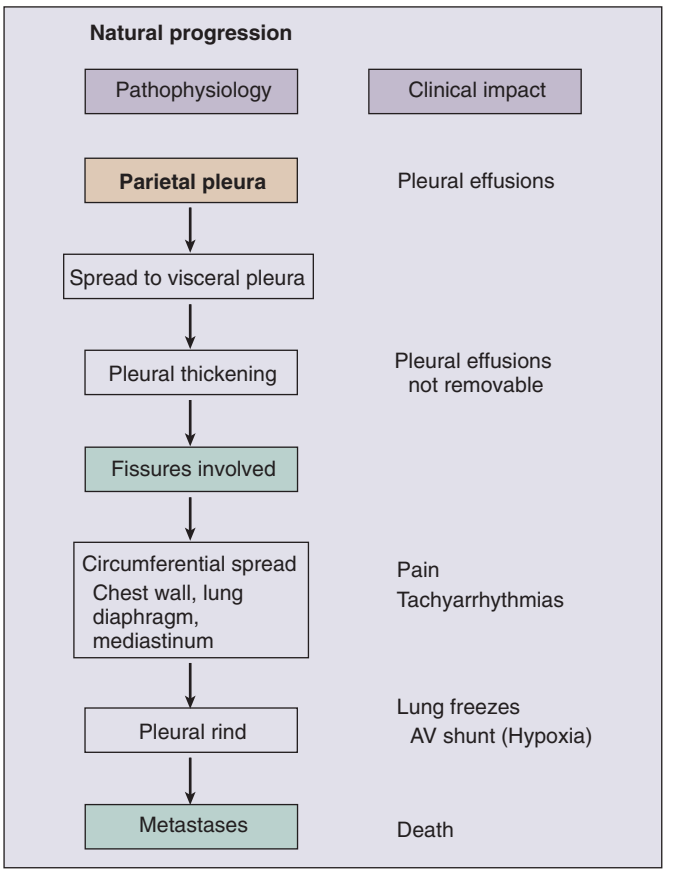


Figure 77-1 • Outline of the progress of the natural history of malignant pleural mesothelioma and the approximate clinical events and findings at various stages of evolution.

use. Despite the large number of exposed individuals, mesothelioma remains a fairly rare cancer, leading some observers to argue that additional factors, such as accumulating genetic alterations or viruses, could contribute to the causation. Advances in molecular technology now allow the identification of various oncogenes, tumor suppressor genes, and signaling pathways, which are perturbed in cases of mesothelioma. One hypothesis suggests that simian virus 40 (SV-40) might play an important etiologic role.[29] Based on experimental findings of SV-40-associated mesotheliomas in hamsters, several investigators performed polymerized chain reaction (PCR) analysis in human mesothelioma specimens and found SV-40 sequences in 40% to 50% of the specimens.[30–34] This hypothesis is of considerable concern, because as many as 32 million adults in the United States were vaccinated with polio vaccine contaminated with infectious SV-40.[35] However, a clear etiologic link remains to be proven.[36,37] Nonetheless, if this hypothesis is correct, malignant mesothelioma could become a far more common cancer, and further study of the molecular mechanisms of pathogenesis are needed urgently.

Clinical Presentation and Diagnosis

Most commonly, signs and symptoms associated with pleural effusion, such as shortness of breath, dyspnea on exertion, or nonpleuritic chest wall pain, bring patients to medical attention. Other common features at presentation include fever of unknown origin, sweats, a declining performance status, and weight loss.[38] Physical examination usually discloses unilateral shifting dullness, and chest roentgenograms show a large pleural effusion, more often involving the right side. Roentgenograms also might show evidence of asbestos exposure, such as pleural plaques or calcifications in the diaphragm, although asbestosis is not a necessary precondition. With the recent emphasis on asbestos-associated illness, increased surveillance occasionally identifies asymptomatic individuals with an incidental effusion on chest x-ray.[39] CT scans of the chest, however, are far more sensitive and are used to assess the extent of disease. Pleural thickening with involvement of the interlobar fissures and atelectasis are evident early on CT scan.[40] Thrombocytosis, disseminated intravascular coagulation, thrombophlebitis, pulmonary emboli, and Coombs-positive hemolytic anemia also have been reported.[38,41–43] The median duration of survival ranges from 4 to 18 months in most reported series. Prognostic factors at presentation that are associated with a better survival include the following[44,45]:

- Younger age
- Good performance status
- Stage
- Epithelial histology
- Lack of chest pain
- Normal platelet count

Figure 77-1 outlines the natural progression and associated clinical findings of malignant pleural mesothelioma. As mesothelioma progresses, the tumor obliterates the pleural space, encasing the lung and invading lung parenchyma as well as adjacent organs, with distant metastases developing only late in the course of the disease (Fig. 77-2). The tumor can grow along thoracentesis, chest tube drainage, or thoracotomy tracts in 10% or more of cases, and direct extension into esophagus, ribs, vertebrae, nerves, and the superior vena cava can cause dysphagia, chest pain, cord compression, plexopathy, Horner's syndrome, or superior vena cava syndrome.[18,46] Direct extension also occurs commonly into the pulmonary parenchyma, the chest wall, into the mediastinum, and through the diaphragm into the abdominal cavity (Figs. 77-2 through 77-4). Mediastinal and cervical lymph nodes also can be involved. As the disease progresses, loss of diaphrag-

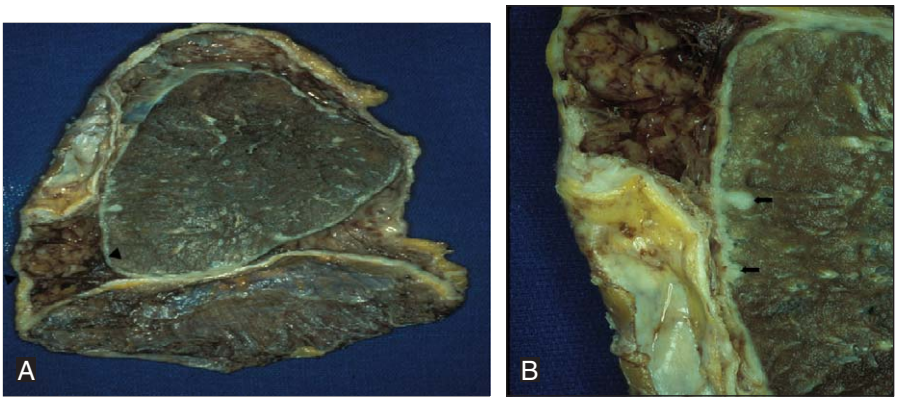


Figure 77-2 • **A,** Resected lung and diaphragm showing thick rind of tumor *(arrowhead)* encasing entire lung and trapping its function. **B,** Extension of the pleural tumor *(arrows)* into adjacent lung from the visceral pleura. Attempts to remove the visceral pleura obviously would leave residual tumor on the pulmonary surface. (Courtesy of S.C. Aisner, MD.)

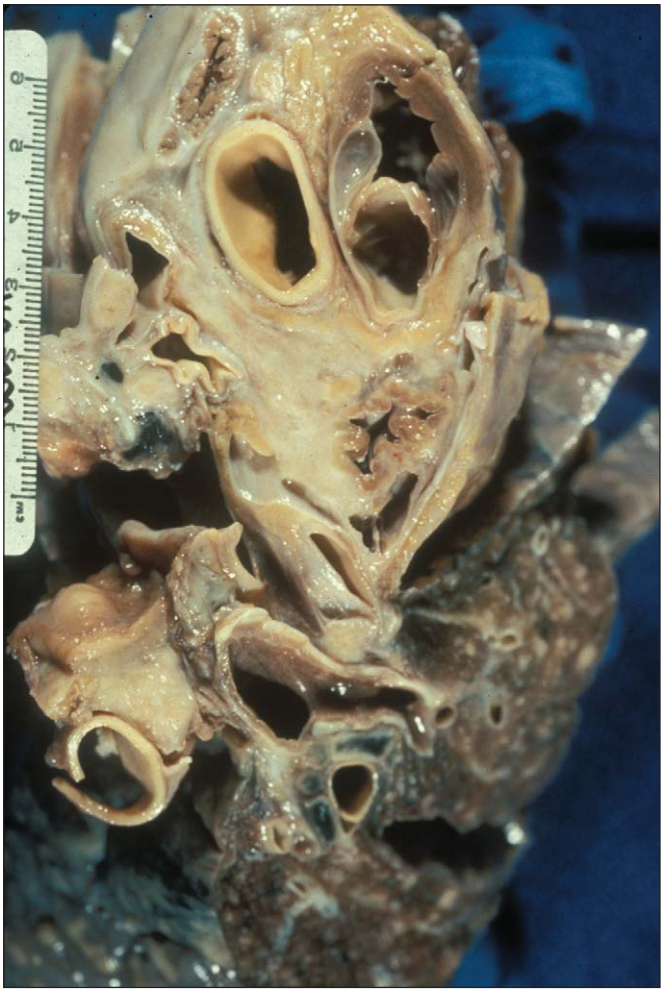


Figure 77-3 • Autopsy specimen showing extension of the mesothelioma into the mediastinum, trapping the heart, great vessels, and airways. (Courtesy of S.C. Aisner, MD.)

matic and intercostal muscle movement, chest contraction, and scoliosis also develop. Symptomatically, as the disease advances, patients complain of fatigue and dyspnea out of proportion to chest x-ray findings due to the shunting of poorly aerated blood in the trapped lung.

Most patients undergo repeated thoracenteses with negative or indeterminate cytology despite active tumor, because pleural effusions often produce atypical mesothelial cells that confound diagnosis. Needle biopsies might disclose tumor; however, pathologic distinction from adenocarcinoma can be difficult on the small specimens obtained. Thoracoscopy and pleuroscopy have been successful in obtaining adequate tissue samples.[47] Boutin and Rey[48] showed that thoracoscopy can be nearly 95% as accurate as diagnostic open thoracotomy. In early disease, discrete nodules and coalescent plaques are seen on the visceral and parietal pleura at the time of surgery. In more advanced disease, the pleural space is obliterated by a thick cake of tumor (see Fig. 77-2). Generous samples usually are taken for diagnosis. In view of the highly litigious nature of the disease, and although it is probably irrelevant, samples of uninvolved lung probably should be obtained as well for counting asbestos fibers.[49]

Pathology

Three histologic subtypes of mesothelioma usually are described: epithelial, sarcomatous, and mixed (epithelial/sarcomatous). Most mesotheliomas occur in the epithelial form, and these can exhibit papillary, solid, tubular, or vacuolated patterns. The sarcomatous form appears similar to a fibrosarcoma, with predominantly spindle-shaped or ovoid cells. The mixed or biphasic form demonstrates both epithelial and sarcomatoid elements. The finding of both elements on histology is usually diagnostic of malignant mesothelioma.

Metastatic adenocarcinoma can be difficult to distinguish grossly and histologically from epithelial mesothelioma. Historically many different modalities have been used to distinguish these entities (Table 77-2). Today, however, the diagnosis often can be made using immunohistochemical analysis (mesotheliomas are calretinin, WT-1, and cytokeratin positive and CEA negative).[24,50,51] Table 77-2 lists some of the differences seen among the various histochemical, immunohistochemical, and electron microscopy studies performed to distinguish mesothelioma from adenocarcinoma. The sarcomatous form should be distinguished from other soft tissue sarcomas.[52] Electron microscopy remains the major reference method for defining the diagnosis of malignant mesothelioma, although it is not used frequently in view of the immunohistochemistry.[53,54]

Staging

Staging systems usually are developed to help define comparable groups for therapy and prognosis, and thus provide a more accurate method for comparing results. To date, there is no uniformly accepted staging system that accomplishes these goals in the staging of mesothelioma. The first staging system proposed by Butchart and colleagues[55] did not uniformly predict survival outcomes, did not provide tumor or organ invasion descriptions, and provided only vague statements about lymph node and chest wall involvement. Based on the large surgical experience at the Brigham and Women's Hospital and Dana Farber Cancer Institute, a clinical, postoperative staging system was proposed (Table 77-3).[56] After several attempts to develop a TNM-based staging system that considered the influence of regional lymph nodes and the extent of local invasion, the International Mesothelioma Interest Group (IMIG) organized a consensus TNM staging system, which forms the basis of the current AJCC Staging system (Table 77-4).[57]

Imaging Studies

Chest x-rays usually are obtained when a patient presents with shortness of breath or chest pain, and most typically demonstrate a pleural effusion. In addition, pleural plaques or calcifications in the diaphragm denote asbestos exposure, although they are found in fewer than 20% of patients with mesothelioma. Abnormal chest x-ray findings are followed by CT scans, the most widely used imaging technique, which can provide details of the extent of disease as it progressively encircles and traps the lung (see Figs. 77-1 and 77-2), extends into the fissures and along the pericardium, and invades the chest wall, diaphragm, and mediastinal structures.[58] The CT scan also can define enlarged mediastinal lymph nodes, a finding that carries an adverse prognosis. Other technologies also have been applied to imaging. MRI theoretically can improve differentiation between tumor and surrounding normal tissue. This could be of particular value in evaluation of penetration into the mediastinal structures, chest wall, and diaphragm. One small study, however, compared the staging information derived from CT and MRI scans and concluded that the two techniques offer approximately equivalent information.[59] Thus, it usually is not necessary to use both techniques. In recent years, PET scanning has offered the ability to identify tumors based on their metabolism of 18-F fluorodeoxyglucose (FDG). Preliminary studies suggest that PET scans may be most useful in the identification of mediastinal and distant mestastases and defining prognosis,[60–62] and further studies may prove that PET scanning is a valuable adjunct to CT or MRI scanning.

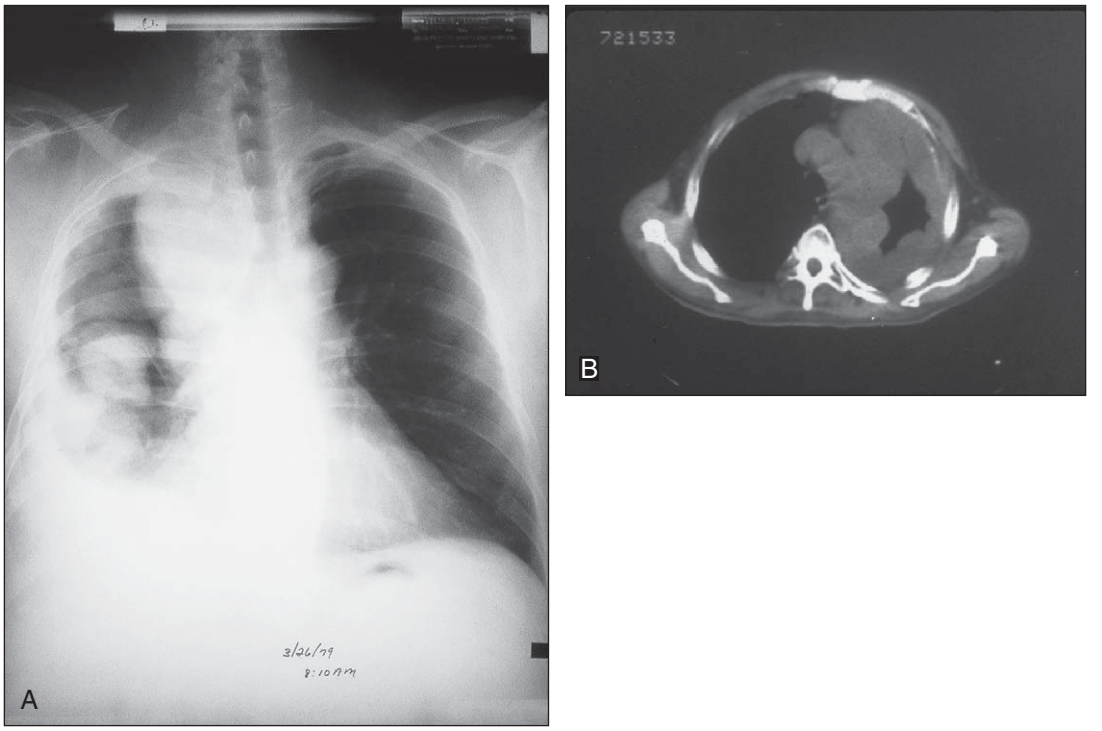


Figure 77-4 • Right-sided mesothelioma. **A,** Conventional chest x-ray demonstrating right-sided pleural thickening, haziness of the lung, and obliteration of the border of the right side of the heart. **B,** CT image of the chest showing right-sided pleural thickening and invasion of lung, mediastinum, and chest wall.

Table 77-2 Histochemistry, Immunohistochemistry, and Electron Microscopy Findings Used to Distinguish Epithelial Malignant Mesothelioma from Adenocarcinoma

Marker	Malignant Mesothelioma	Adenocarcinoma
HISTOCHEMISTRY		
Mucicarmine*	Negative	Positive
PAS-diastase†	Rare	Frequent
Alcian blue with hyaluronidase‡	Digested	Not digested
IMMUNOHISTOCHEMISTRY ANTIGENS	**INVOLVED (%)**	**INVOLVED (%)**
Cytokeratin	100	100
CEA	<10	>95
Calretinin	>95	<10
LeuM1	<10	70–100
EMA	>80	100
CD34	<10	>70
CD15	<10	60–100
B72.3	<15	>80
Vimentin	40	<10
WT-1	>75	<10
ELECTRON MICROSCOPY FINDINGS		
Microvilli	Long, thin, branched, curved, interdigitated	Short, thick, not branched, straight, single
Mucin granules	None	+/–
Myelin figures	None	+/–
Core rootlets	None	+/–
Glycocalyx	None	+/–

CEA, carcinoembryonic antigen; EMA, epithelial membrane antigen; WT-1, Wilms' tumor suppressor gene.
*Mucicarmine stains for mucin production and neutral or weakly acidic mucopolysacharides.
†PAS-diastase: periodic acid-Schiff stain with diastase digestion stains for neutral mucopolysaccharides.
‡Alcian blue stains for hyaluronic acid after pretreatment with hyaluronidase; positive, no stain.

Table 77-3 Brigham and Dana Farber Cancer Institute Revised Postoperative Staging System for Malignant Mesothelioma

Stage	Definition
I	Disease completely resected within the capsule of the parietal pleura without adenopathy. Ipsilateral pleura, lung, pericardium, diaphragm, or chest wall disease limited to previous biopsy sites.
II	All of stage I with positive resection margin and/or intrapleural adenopathy.
III	Local extension into the chest wall or mediastinum; into the heart or through the diaphragm or peritoneum; or with extrapleural lymph node involvement.
IV	Distant metastatic disease.

Brigham, Brigham and Women's Hospital; DFCI, Dana Farber Cancer Institute.

Surgery

The first decision point in the management of mesothelioma is resectability of disease (Fig. 77-5). Because of the rarity of the disease and the highly selected nature of the patients entered into surgical trials, the role of surgery in mesothelioma for any reason other than biopsy remains controversial. Although pleurectomy can reduce the recurrence of effusions in most patients, surgery has little role in the palliative management of mesothelioma, and many clinicians advocate pleurodesis and supportive care.[63] With the recognition of the risk of disease in asbestos-exposed individuals, however, many patients now are found with earlier stages of mesothelioma, and such patients could have longer survival times. Thus, surgical excision could be a reasonable approach among patients whose disease is confined to the pleural space. Before considering aggressive surgery, bronchoscopy should be performed to define the anatomy and eliminate the possibility of endobronchial disease. Endobronchial tumor is likely to be a result of primary lung cancer rather than mesothelioma.[64] Because of the progressive nature of mesothelioma and the extent of surgery needed to eradicate the disease, any patient being considered for radical surgery must be able to withstand possible pneumonectomy and prolonged anesthesia. Careful evaluation of cardiac and pulmonary functions are thus critical.[65] For therapeutic approaches, three surgical techniques have been advocated: pleurodesis, pleurectomy (decortication), and extrapleural pneumonectomy (EPP). There are no comparative studies of these approaches, and patients treated often are highly selected for the various procedures. Thus, the studies of the different approaches often contain patient groups with highly different prognostic factors and so cannot be compared.

Pleurodesis usually is performed for palliation and is accomplished alone or with a partial pleurectomy by means of video-assisted thoracoscopic surgery (VATS) and the insufflation of sclerosing agents, such as talc.[66] This approach can control pleural effusions in about 90% of cases but does not offer any opportunity for cytoreduction of tumor. Advocates of this approach cite the lack of definitive data favoring more aggressive debulking procedures and the relative sparing of postoperative complications. This technique produces median survivals that recapitulate the natural history of the tumor, however, and it further complicates any subsequent attempt to perform a cytoreductive procedure.[66] Nevertheless, this approach could be the most appropriate for those with significant comorbid disease or those with adverse surgical prognostic factors.

Pleurectomy or decortication has been advocated by a number of investigators, with the median survival in these series ranging from 6.7 to 21 months (Table 77-5).[67–78] This approach also has been used to control effusions (including cases of pleurodesis failure) and has achieved control of effusions in more than 80% of cases. With this

Table 77-4 International Mesothelioma Interest Group Staging of Mesothelioma

PRIMARY TUMOR AND EXTENT (T)	
Tx	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
T1	Tumor involves ipsilateral parietal pleura, with or without focal involvement of visceral pleura.
T1a	Tumor involves ispilateral parietal (mediastinal, diaphragmatic) pleura. No visceral pleura involved.
T1b	Tumor involves ipsilateral partietal (mediastinal, diaphragmatic) pleura with focal involvement of visceral pleura.
T2	Tumor involves any of the ipsilateral pleural surfaces and one or more of the following: confluent visceral pleura and fissure, diaphragmatic muscle, ipsilateral lung parenchyma.
T3*	Tumor involves any of the ipsilateral pleural surfaces and one or more of the following: endothoracic fascia, mediastinal fat, solitary ipsilateral chest wall, soft tissues, nontransmural invasion of the pericardium.
T4†	Tumor involves any of the ipsilateral pleural surfaces and one or more of the following: diffuse chest wall invasion, rib involvement, invasion through diaphragm, invasion through pericardium, positive pericardial effusion cytology, involvement of myocardium, involvement of any mediastinal organ, contralateral pleura, invasion of spine, or invasion of brachial plexus.
LYMPH NODES (N)	
Nx	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastases.
N1	Metastases in ipsilateral bronchopulmonary or hilar lymph nodes.
N2	Metastases in subcarinal lymph nodes or in ipsilateral mediastinal or internal mammary lymph nodes.
N3	Metastases in contralateral mediastinal internal mammary, or hilar lymph nodes or any supraclavicular, or scalene lymph nodes.
METASTASES (M)	
Mx	Distant metastases cannot be assesed.
M0	No (known) distant metastases.
M1	Distant metastasis.
STAGE GROUPINGS	
I	T1, N0, M0
IA	T1a, N0, M0
IB	T1b, N0, M0
II	T2, N0, M0
III	T1, T2, N1, M0
	T1, T2, N2, M0
	T3, N0, N1, N2, M0
IV	T4, any N, M0
	Any T, N3, M0
	Any T, Any N, M1

*T3, locally advanced but technically resectable disease.
†T4, locally advanced but technically unresectable disease.

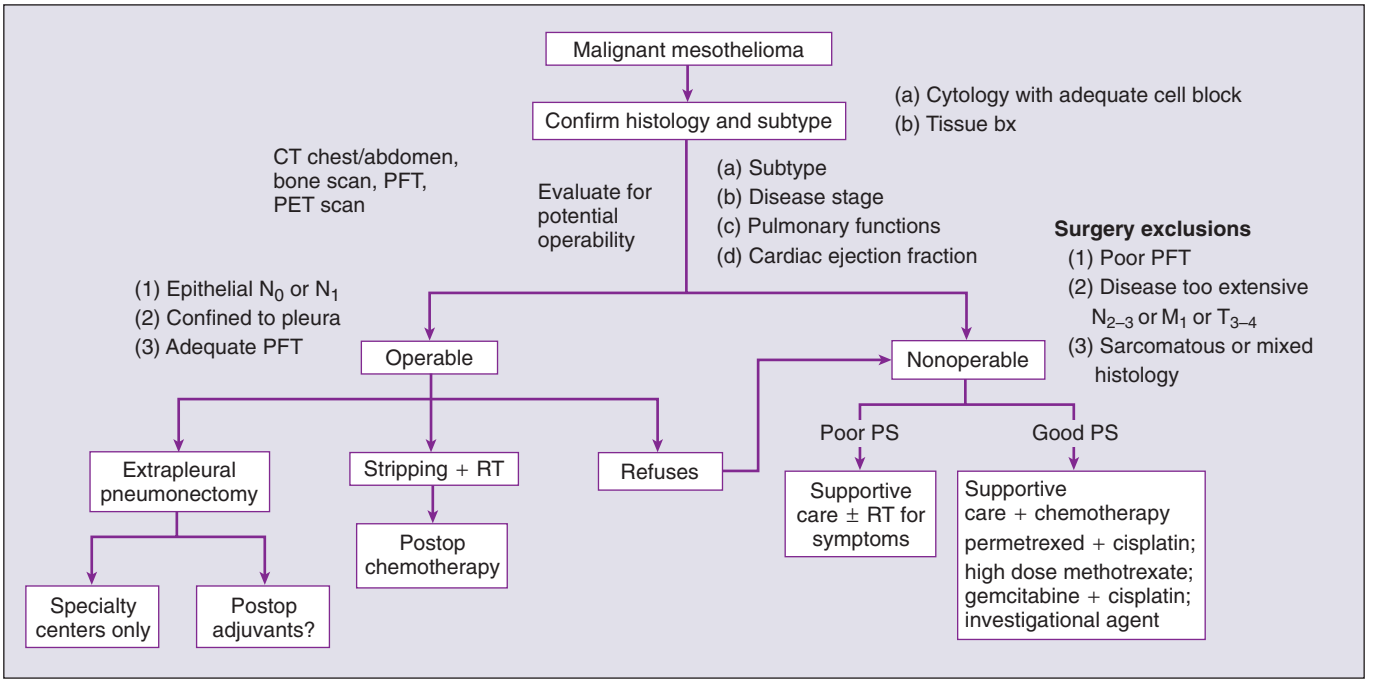


Figure 77-5 • Treatment of malignant mesothelioma.

technique, the pleura are stripped from the apex of the lung to the diaphragm, removing pericardium and parietal pleura in the course of dissection. Clean separation of lung and visceral pleura often is difficult because of the pattern of growth. The diaphragmatic pleura usually cannot be completely resected, which eventually leads to a very high local recurrence rate. Chest tubes are placed to drain blood and to manage any possible bronchopleural fistulae. Operative mortality from pleurectomy usually is quite low (1.5%–5%), but complications include bronchopleural fistulae, hemorrhage, and subcutaneous emphysema. Of considerable interest is the impact of histological subtype on the outcome. In most surgical series in which subtype is specified, the median survival duration for the epithelial subtype is two- to threefold greater than for the sarcomatous form, and the mixed subtype shows an intermediate survival. Investigators at Memorial Sloan-Kettering Cancer Center published some of the largest experiences with this technique when combined with external beam with or without interstitial irradiation, or in combination with postoperative intrapleural therapies and irradiation.[64,69,72] In their experience with 95 patients (see Table 77-5), a select group of 27 patients who had the epithelial subtype and who did not require an implant had a median survival of 22.5 months and a 2-year survival rate of 41%. Wanebo and colleagues[76] also evaluated their surgical pleurectomy series by histologic subtype and found that those patients with the epithelial form had a better survival than those whose tumor showed the fibrosarcomatous form. The relatively poor results (with a median of 6.7 months survival) that were reported by Lewis and coworkers[71] were derived from an older group of patients. DaValle and associates[68] advocated the use of extrapleural pneumonectomy for patients with minimal invasion of the visceral pleura (free pleural space without tissue invasion) as an approach for possible cure, because the survival with pleurectomy was not striking (a median of 11.2 months). Although no studies have directly compared the various surgical approaches, the reported median survival for pleurectomy appears similar to the medians reported for even more aggressive surgical approaches.

Table 77-5 Pleurectomy for Diffuse Pleural Mesothelioma

First Author	No. of Patients	2-Year Survival (%)	Median Survival (mo)
Lewis[71]	4	25	6.7
Hilaris[69]	95*	35	12.6
Law[70]	28	32	20
DaValle[68]	23		11.2
Wanebo[76]	16(F)		11
	1(E)		21
Achatzy[78]	46	11	10
Brancatisano[67]	45		16
Rusch[75]	25		
Rice[73]	5		13†
Soysal[77]	100		

E, epithelial form; F, fibrosarcomatous form.

*41 patients received pleurectomy followed by external beam radiation therapy; 54 patients received pleurectomy followed by implant and external beam radiation therapy.

†Includes patients receiving pleurectomy and extrapleuropneumonectomy.

EPP is a more aggressive, extirpative procedure in which the parietal pleura, lung, pericardium, and diaphragm are resected en bloc. A graft to prevent herniation of the abdominal contents replaces the diaphragmatic defect. To prevent cardiac herniation, the right pericardium also often is reconstructed. A thoracoabdominal approach allows for easier access for the resection of the diaphragm. DaValle and colleagues[68] advocated extrapleural dissection to the hilum, early entry into the pericardium retrosternally to accomplish intrapericardial pneumonectomy, and use of double-lumen anesthesia. With either approach, intercostal chest tubes usually are placed to drain blood and fluid, and to treat possible bronchial air leaks. The trials reporting extrapleural pneumonectomy show median survival ranging from 4 to 20 months (Table 77-6).[55,56,68,73,79–83] Because of the extent

Table 77-6 Extrapleural Pneumonectomy for Diffuse Pleural Mesothelioma

First Author	Year	No. of Patients	Mortality (%)	Median Survival (mo)
Butchart[55]	1978	29	31	4
DaValle[68]	1986	33	9.1	11.2
Vogt-Moykopf[82]	1987	55	5.5	10.2
Faber[79]	1988	33	9	13.5
Geroulanos[80]	1990	18	7	20
Rusch[81]	1991	20	15	10
Rice[73]	1994	10	–10	13*
Sugarbaker[56]	1999	183	3.8	19
Stewart[83]	2004	7.5	16.6	

*Includes patients with pleurectomy and extrapleural pneumonectomy.

of the procedure and the learning curve, the early studies showed postoperative mortality as high as 31%. With increasing experience, more recent studies demonstrate operative and postoperative mortality below 4%. Serious complications have been reported in as many as 25% of patients, including bronchial leaks, empyema, vocal cord paralysis, chylothorax, arrhythmias, and respiratory insufficiency.[84] Recent studies with careful preoperative screening also have reduced these postoperative complications.[85] The evolution of this approach is demonstrated in Table 77-6 by the increasing median survival and decreasing surgical mortality. Rusch and coworkers[81] reported a 2-year survival of 33% with a 10-month median survival in 20 patients, whereas Sugarbaker and associates[56] reported a 38% 2-year survival and 19-month median survival for those patients undergoing EPP. The surgical mortality reported in the two studies was 15% and 3.8%, respectively. These latter two studies probably are representative of modern selection criteria and contemporary surgical management. Both studies also offer the details of treatment failure sites. In contrast to the pleurectomy series, some of the reports of extrapleural pneumonectomy showed a small percentage of 5-year survivors. Although the degree of surgery, the selection criteria, and the possible stage shift biases preclude definitive statements, overview of the sites of treatment failure and long-term outcomes suggest that extrapleural pneumonectomy could alter the natural history of pleural mesothelioma.

Surgical Prognostic Factors

Results from both pleurectomy and EPP series suggest that certain pre- and postoperative factors carry important prognostic information that can help select appropriate surgical candidates. These factors include the following:

- Subhistologies (epithelial vs. other types)
- Preoperative tumor bulk
- Mediastinal lymph node involvement
- Resection margins
- Invasion beyond the pleural envelope.

Among those studies that specify subhistology, nearly all show that patients with the sarcomatous and mixed forms of mesothelioma have a significantly worse disease-free and overall survival than those with the epithelial form.[56,78,86] These data strongly suggest that patients with sarcomatous or mixed subhistology should be offered palliative therapies such as pleurodesis and be spared the operative consequences of aggressive surgical procedures. Similarly, mediastinal lymph node involvement defines an adverse prognosis.[56,86] Because patients with mediastinal lymph node involvement have a significantly decreased survival, preoperative staging probably should assess the mediastinum. Whether this dictates a preoperative mediastinoscopy, or whether imaging techniques such as FDG-PET scanning can provide adequate preoperative assessment, remains to be determined. Other factors that can predict survival include penetration through the diaphragm, extension to other extracapsular sites, and large preoperative tumor volume.[56,86] These surgical prognostic factors suggest that further revision of the staging systems could be required to better define which patients are most likely to benefit from surgical approaches. An alternative, postoperative, functional staging system based on the surgical experience at Brigham Hospital and Dana-Farber Cancer Institute is shown in Table 77-3.

Radiation Therapy

The diffuse nature of the disease and toxicity of tumoricidal doses of irradiation to vital organs, including the lung, heart, and liver, limit the utility of radiation therapy in the treatment of mesothelioma. Radiation therapy alone has not resulted in a survival benefit, though its role in the palliation of localized pain or in combination with other treatment modalities remains promising.[87,88] Seeding along biopsy or chest tube tracts can result in painful chest wall masses. Prophylactic radiation to these tracts or radiation of these masses once they recur may provide temporary pain relief.[89–91] In one report, 21 Gy delivered in three fractions prevented the recurrence of tumor in the wound after thoracoscopy or thoracotomy in 20 patients, whereas 8 of 20 (40%) patients not undergoing radiation developed tumors at the wound site.[90] The addition of radiation therapy to pleurectomy to reduce local recurrences has considerable appeal because of the high local recurrence observed with this surgical technique, and the addition of radiation therapy to EPP also might be better tolerated because the underlying lung has been removed. Alberts and colleagues[92] compiled the treatment outcomes for 262 patients treated between 1965 and 1985 with either chemotherapy, radiation therapy (RT), both chemotherapy and RT, or decortication plus RT and chemotherapy. The median survival of 9.6 months was similar for all groups. Only a small group of patients treated with doxorubicin and irradiation with 10 Gy every 6 weeks for four courses appeared to show prolonged survival, with a median survival of 22.6 months.

Chemotherapy

SINGLE AGENTS. In the past, the role of chemotherapy for malignant pleural mesothelioma was difficult to assess because of the small numbers of patients entered into individual chemotherapy trials, the pessimism regarding treatment, the difficulty in assessing response, and the bias associated with reporting predominantly positive results. Thus, much of the older data regarding single-agent and combination chemotherapy activity was derived from summary overviews of small pilot trials or from chemotherapy trials of soft-tissue sarcomas.[93] Since 1990, however, both the incidence and the accuracy of diagnosis have increased, thus permitting larger disease-specific trials to occur. The advent of CT and MRI has further allowed for assessment of response using rind thickness as a criterion. Table 77-7 shows the activity of various chemotherapy agents, based on trials of adequate size that include 14 or more patients.[94–147] At one time, the anthracyclines were considered the mainstay of chemotherapy for mesothelioma. However, adequately sized trials have proven this class of drugs to have only modest activity, and their use has essentially ceased. Among the alkylating agents, one trial of mitomycin C suggested a response rate of 21%. The platinums (cisplatin and carboplatin) show only modest response rates of 14% and 11%, respectively, but their value could reside in their ability to synergize with other agents. The camptothecins, taxanes, and vinca alkaloids have been disappointing as single agents. In contrast, the antimetabolites, specifically antifolate compounds, are of considerable interest, especially because recent studies have shown enhanced folate expression in human mesotheliomas and potentially unique transport

Table 77-7 Response Rates for Adequately Evaluated* Single Agents in Malignant Mesothelioma

Agent	No. of References Evaluable	Response (%)†
ANTHRACYCLINES		
Doxorubicin[94,95]	66	9
Detorubicin[96]	35	26
Pirarubicin[97]	35	22
Epirubicin[98,99]	59	14
Liposomal doxorubicin[100–102]	72	5
Mitoxantrone[103,104]	62	5
Menogaril[105]	22	3
ALKYLATING AGENTS		
Cyclophosphamide[95]	16	0
Ifosfamide[106–108,110,111]	64	8
Mitomycin C[112]	19	21
PLATINUMS		
Cisplatin[113,114]	295	14
Carboplatin[116–118]	88	11
ANTIMETABOLITES AND ANTIFOLATES		
High-dose methotrexate[119]	60	37
Trimetrexate[120]	51	12
Edatrexate[121]	20	25
Edatrexate + folinic acid[121]	40	15
Pemetrexed[122]	64	14
ANTIMETABOLITES, OTHER		
5-fluorouracil[123]	20	5
Capecitabine[124]	26	4
Di deazafolic acid (CB3717)[125]	18	6
Dihydro 5-azacytidine[126,127]	56	7
Gemcitabine[128–130]	61	12
Camptothecins		
Topotecan[131]	22	0
Irinotecan[132]	28	0
Vincas and Related Compounds		
Vincristine[133]	23	0
Vindesine[134,135]	38	3
Vinblastine[136]	20	0
Etoposide (VP16)[137,138]	111	3
Taxanes		
Paclitaxel[139,140]	60	0
Docetaxel[141,142]	50	8
Miscellaneous		
M AMSA[144]	19	1
AZQ[143]	20	0
Onconase[145]	105	5
Gefitinib[146]	43	2
Imatinib[147]	25	0

*Individual trial with 14 or more entries.
†Complete plus partial response.

mechanisms for pemetrexed.[148,149] Solheim and associates[119] showed that high-dose methotrexate had an appreciable response, with a 37% response rate. Vogelzang and colleagues[120] reported a 12% response rate for trimetrexate, and Kindler and coworkers[121] reported a 25% response with the antifolate agent, edetrexate. Another antifolate agent, pemetrexed, showed modest activity of 14% as a single agent, but provided both improved response and improved survival when added to cisplatin compared to cisplatin alone.[115,122]

COMBINATION CHEMOTHERAPY. The vast majority of combination chemotherapy regimens tested with adequate sample size are either anthracycline- or platinum-based (Table 77-8). Similar to the data on single agents, the early studies of combination chemotherapy suffered from small and often inadequate trials, and the various trials are difficult to compare because of issues concerning disease subgroups, pretreatment characteristics, and prior therapies. These make the survival data difficult to interpret, and for this reason, responses rather than survival are evaluated. More recent studies include more appropriate numbers of patients and modern response criteria, thus allowing for a better assessment of activity. Recently tested combination regimens are listed in Table 77-8.[115,122,150–181]

Most recent trials of combination chemotherapy are platinum based and show a somewhat greater response to therapy than prior combinations. Whether this apparent improvement in response is an artifact of patient selection, earlier treatment, or better agents remains uncertain, but it is illustrated in the recent single-agent data for cisplatin, which was part of a randomized trial and showed a 16.7% response rate.[115] An interesting model of human mesothelioma transplanted onto nude athymic mice suggested that the combination of cisplatin and mitomycin C is highly synergistic.[182] A prospective randomized phase II study by the Cancer and Leukemia Group B (CALGB) showed a response of 26% when the stable disease category was included, but the response rate declined to less than 20% if only objective criteria were considered.[156] Two combination chemotherapy regimens appear to show significant promise, and both focus on an antimetabolite plus cisplatin (see Table 77-8). Several phase II trials have shown reproducible responses for the combination of cisplatin and gemcitabine, with potential schedule-dependent differences. The combination of cisplatin and pemetrexed showed activity in a phase I study and led to the large, randomized trial of this combination vs. cisplatin alone.[183] The response rate for this combination was 41.3%, compared with 16.7% for cisplatin alone, and the combination showed significant superiority in terms of both time to progression and overall survival.[115] This trial led to a new standard of therapy for malignant pleural mesothelioma that will clearly be the basis for comparison for new treatments.[184]

Intrapleural Therapy

Another approach to the treatment of pleural mesothelioma has been the instillation of therapeutic agents into the pleural space. Because mesothelioma develops superficially along pleural and peritoneal cavities, intracavitary instillation of chemotherapy, radioisotopes, or biologics potentially could treat the superficial disease. Anecdotal reports of prolonged survival with certain radioisotopes also has stimulated interest in this approach.[185,186] High intracavitary concentrations of chemotherapeutic agents potentially could capitalize on any dose-response relationships for the agents. This approach is limited, however, by the propensity of the pleural space to become progressively obliterated with advancing disease, and even in early disease the intracavitary chemotherapy penetrates only a very shallow level of the tumor. Thus intrapleural therapies have limited applications, only to either very early disease or post-debulking surgical procedures.

Cisplatin is the agent that has been most extensively studied for intracavitary use.[187–189] Pharmacokinetic studies of its intracavitary use show that exposure and peak levels are much greater than for intravenous administration of cisplatin. This approach has not met

Table 77-8 Chemotherapy Combinations for Malignant Pleural Mesothelioma

Combination	No. of Patients	Response (%)*
ANTHRACYCLINE-BASED		
Doxorubicin + interferon[151]	24	16
Doxorubicin + cyclophosphamide[155]	36	11
Doxorubicin + cyclophosphamide + DTIC[163]	60	17
Doxorubicin + ifosfamide[153,154]	40	23
Doxorubicin + cisplatin[152,156]	59	16
Doxorubicin + cisplatin + cyclophosphamide[158]	23	30
Doxorubicin + 5-azacytidine[150]	36	22
Doxorubicin + cisplatin + mitomycin-C[157]	24	21
Epirubicin + ifosfamide[160]	17	6
Epirubicin + interleukin-2[159]	21	5
PLATINUM-BASED		
Cisplatin + interferon[161,162]	55	32
Cisplatin + vinblastine[164]	20	25
Cisplatin + Dihydro 5-azacytidine[163]	29	17
Cisplatin + irinotecan[165]	15	27
Cisplatin + etoposide[166]	25	24
Cisplatin + mitomycin-C[156]	35	26
Cisplatin + mitomycin + vinblastine[167]	39	20
Cisplatin + mitomycin + interferon[168,169]	62	19
Cisplatin + mitomycin + etoposide + fluoruracil[173]	45	38
Cisplatin + gemcitabine[170–172,174]	133	37
Cisplatin + gemcitabine[175]	50	26
Cisplatin + pemetrexed[115]	226	41
Cisplatin + interferon[176]	14	7
Cisplatin + pemetrexed[178]	27	32
Oxaliplatin + raltitrexed[179]	89	27
Oxaliplatin + vinorelbine[177]	26	23
ANTIFOL-BASED		
High-dose methotrexate + interferon α[180]	24	29
High-dose methotrexate + interferon α + δ[181]	39	21

*Complete plus partial response.

with the same degree of success as has been seen with intraperitoneal administration of cisplatin for peritoneal mesothelioma.[189] The role of other agents, such as doxorubicin, cytosine arabinoside, and mitomycin-C by the intracavitary route, is not well established. Various permutations of this approach currently are under investigation, including hyperthermic perfusion.[190] Given the complexity of such maneuvers, it is unlikely that this approach will become well established unless a significant benefit occurs, which has yet to be demonstrated.

Biologic and Targeted Therapies

Another approach to treating mesothelioma has been the exploration of several biologic response modifiers, including the interferons, other cytokines such as IL-2, gene therapy, and vaccines.[152,161,191–204] Some of the various biological agents tested either systemically or intrapleurally are shown in Table 77-9. In addition, studies of cancer cell biology have identified various molecular targets that control growth and proliferation pathways; these studies have opened new vistas for therapeutic intervention. Tissue and molecular technology even offer the possibility of specifically phenotyping a given tumor for its molecular targets.

The interferons (IFNs) have been tested extensively because preclinical studies showed that malignant mesothelioma cell lines are susceptible to IFN-α alone and that this effect is enhanced in combination with other cytokines (e.g., IFN-γ and tumor necrosis factor [TNF]) and with chemotherapy.[202,203] Additionally, IFNs offer the possibility of improving immune recognition of the tumor. These data have served as the rationale for clinical trials with the IFNs (see Table 77-9), which mostly have been disappointing and have produced considerable systemic toxicities, including fever, nausea, vomiting, chill, myalgias, and anorexia. Intrapleural therapy also has produced some empyema. Intrapleural IFN-γ, however, is worthy of notice. Boutin and colleagues[205] performed pleuroscopy upon recognizing effusion in asbestos-exposed individuals and instilled IFN-γ if tumor was identified. Pleuroscopy was repeated for subsequent evaluation. The overall response rate was 20%, but those patients with stage IA disease had a 45% response, with eight confirmed complete responses and a prolonged disease-free survival. These data served as part of the impetus for the IMIG revision of the staging system.[57] Interleukin 2 (IL-2) also was shown to have an antiproliferative effect on mesothelioma cell lines.[172] Two small studies of intrapleural IL-2 produced responses of 55% and 19%, respectively (see Table 77-9), but showed considerable systemic toxicities.[199,200] Intramuscular administration of TNF plus IFN-γ and intralesional administration of GM-CSF produced disappointing results and considerable toxicity (see Table 77-9).

The biologic agents also were combined with chemotherapy, and most of these trials combined chemotherapy agents with IFN-α (see Table 77-8). Doxorubicin plus IFN-α produced a modest response with unacceptable toxicity.[151] Two different doses of IFN-α plus 60 mg/m^2 cisplatin produced responses of 25% and 30%, respectively.[161,162] The toxicities—which included nausea, vomiting, fever, anorexia, and asthenia—were unacceptable, however. Carboplatin plus IFN-α produced a 7% response, but the carboplatin was dosed by body surface area.[176] A trial of IFN-α plus mitomycin and cisplatin produced a response in 6 of 43 patients (14%), including complete response in 2 patients (5%).[168,169] The combination of high-dose methotrexate and systemic IFN-α and IFN-γ produced a 29% response, similar to that seen for high-dose methotrexate alone.[180] Given the significant systemic toxicities of this combined

Table 77-9 Clinical Trials of Interferons and Other Cytokines in Malignant Mesothelioma

Agent	Route	No. Entered	Response (%)
IFN-α[191,204]	Systemic	38	11
IFN-γ[191]	Intrapleural	89	20
IFN-β[194]	Systemic	14	0
IL-2[195,199,200]	Intrapleural	58	41
IL-2 + LAK cells[196]	Intrapleural	5	0
TNF + IFN-γ[201]	Intramuscular	36	3
GM-CSF[202]	Intralesional	14	7

GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LAK, lymphokine-activated killer cell; TNF, tumor necrosis factor.

approach, further studies await better chemotherapy and biotherapy combinations.

GENE THERAPY. Another approach for biotherapeutics has been the use of gene therapies. Because early tumors are relatively localized, gene therapy via the pleuroscope has been tested by investigators at the University of Pennsylvania.[206] They used replication-defective adenovirus containing HSV-tk (a viral protein sensitive to gancyclovir) to test the concept that insertion of the HSV-tk genome into the tumor cells would make the transfected tumor cells (in contrast to normal mammalian cells) lethally susceptible to gancyclovir. Only a small percentage of screened patients were eligible, and 26 patients were treated intrapleurally with escalating doses of virus. Gene transfer was seen in 17 patients, humoral and cellular immune responses were seen, and two patients achieved either a response or a prolonged disease-free survival. The median survival was 11 months, and further studies are in process, although the issues of generalized inflammatory responses remain of some concern. Other gene therapy approaches, such as inserting cytokines onto viral vectors and tumor vaccines, also are under development.[207]

TARGETED THERAPIES. The identification of specific molecular targets that control tumor cell growth, replication, and metastases has led to the identification of agents that target these molecular abnormalities specifically. Antibodies and specific tyrosine kinase inhibitors (TKIs) have been developed that target the epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). EGFR is overexpressed in many human epithelial tumors, including mesothelioma.[203] Interfering in this signaling pathway could influence growth, angiogenesis, and apoptosis. Inhibition of VEGF also could inhibit angiogenesis. PDGF is believed to be an important autocrine growth factor for growth of mesothelioma.[203] Thus, interfering with this autocrine loop could inhibit growth. The initial trials of some of these agents, however, have shown disappointing results so far. Gefitinib, an EGFR TKI, was tested by the CALGB, and one response (2%) was seen among 43 patients.[146] Imatinib, a PDGF TKI, produced no responses among 25 patients.[147] Multi-target agents that inhibit both vascular endothelial growth factor receptors involved in angiogenesis, as well as PDGF, also have been tested. Two such agents, sorafenib and vatalanib, have only moderate activity (4% and 11% response rates, respectively).[208,209] However the optimal use of these agents most likely depends on finding the correct biological indicators of the responses, and studies are ongoing.

Combined-Modality Therapies

Another approach to the treatment of mesothelioma is to combine or sequence several treatment modalities to reduce both local and distant recurrences. Thus surgery, radiation therapy, chemotherapy, and biologics might be combined in various groupings.

Because of the advanced stage of disease at presentation in the United States, most patients are not candidates for surgical resection. Thus, one possible approach is the use of chemotherapy with radiation therapy. There is, however, only limited experience with this approach, despite the recognized potential of many agents such as cisplatin to act as radiosensitizers. Doxorubicin plus radiation therapy was studied in two small trials.[150,210] A small subgroup of patients from the large series reported from South Africa was treated with doxorubicin and radiation therapy.[92] Compared with most of the patients in the report, this subgroup appeared to show a prolonged survival (median survival of 22.6 months). Drawing a conclusion about outcomes in a small, highly selected subgroup, however, is difficult at best.

Several trials have added either interstitial or external beam irradiation to pleurectomy, as described in the earlier section on radiation therapy. Rusch reviewed the multimodality experience at Memorial Sloan-Kettering Cancer Center.[211] One hundred five patients underwent pleurectomy followed by interstitial and external beam irradiation. The median survival was 12.5 months, and those with early disease and epithelial histology demonstrated better survival. Another approach to postoperative irradiation is the use of photodynamic therapy (PDT) to the interior of the pleural or thoracic cavity. After a debulking procedure such as a pleurectomy or EPP, a diffusing solution is placed in the hemithorax, and a unique wavelength (usually red) light is used to activate the dye. Moskal and colleagues[212] treated 40 patients (24 with advanced disease) using surgical debulking and PDT. Although the median survival was 15 months for those who survived surgery, the patient with Butchard stage I disease survived for 36 months. Pass and coworkers[213] tested PDT as part of a complex, randomized, postoperative chemoimmunotherapy protocol. Sixty-three patients were randomized to receive cisplatin, tamoxifen, and IFN-α with or without PDT after maximal cytoreductive surgery. The two treatment arms were comparable in terms of local failure rate, time to progression, and median survival. Further studies using this approach do not seem likely.

In the United States, most patients, even among the patients in whom surgical resection is attempted, usually have disease beyond the parietal pleura. Thus adjuvant therapies to improve local control and prevent systemic recurrence often are attempted. Rusch and coworkers[214] followed pleurectomy with intracavitary cisplatin and mitomycin-C to assess the pharmacokinetic behavior of these agents. The investigators observed a high intracavitary concentration of drug with adequate plasma levels and systemic chemotherapy toxic effects. Postoperative systemic cisplatin and mitomycin-C chemotherapy also were added subsequently. Thirty-six patients were enrolled; of these, 28 underwent surgical debulking, and 23 went on to postoperative therapy. The median survival was 17 months. Rice and associates[73] used a similar approach for 19 patients, and the median survival was 13 months. A variation of this postoperative intrapleural therapy tested hyperthermic perfusion with cisplatin,[215] cisplatin plus mitomycin,[216] or cisplatin plus doxorubicin.[190] Although these studies showed that this approach is feasible, the clinical complexity and toxicity remain difficult to justify on the basis of the early results.

Sugarbaker and coworkers[56] built a trimodality therapy program using EPP followed first by various chemotherapy regimens (cyclophosphamide plus doxorubicin plus or minus cisplatin or carboplatin plus paclitaxel) and then by subsequent (or concurrent) external beam chest irradiation. One hundred eighty-three patients were entered into the sequential studies, and there were seven postoperative deaths. The median duration of survival (excluding the seven postoperative deaths) was 19 months. Epithelial histology, negative mediastinal lymph nodes, tumor confined to the pleural envelope, and negative resection margins were all highly favorable prognostic factors. This subset analysis led to the Brigham/Farber postoperative staging system (see Table 77-3). The subgroup that satisfied these prognostic factors (Brigham/Farber stage I) had a median duration of survival of 51 months and 2- and 5-year survivals of 68% and 46%, respectively. Whether this represents lead-time bias is unclear, however. Newer chemotherapeutic agents such as gemcitabine plus cisplatin, or pemetrexed plus cisplatin, also are being incorporated into trimodality regimens as neoadjuvant therapy, and studies are ongoing.[217,218] The results of these trials argue that careful staging and preoperative patient selection will be crucial in determining which patients may benefit the most from aggressive therapy.

METASTATIC TUMORS OF THE PLEURA

Metastatic tumors in the pleura are far more common than primary pleural tumors. Clinically, patients with these tumors present in a manner similar to those who have primary tumors in the pleura, with effusions, dyspnea, cough, atelectasis, and (less often) pain and fever. Symptoms related to the primary site of tumor are seen in nearly half

of the patients, and the prognosis with metastatic disease to the pleura is related most to the ability to control the underlying primary tumor. Compromised performance status and weight loss are adverse prognostic features. The pleura can be the site of metastases from many cancers, but the most common origins are tumors of the lung, breast, stomach, colon, ovary, prostate, and thyroid, and melanoma and lymphoma/leukemia, with tumors of the lung and breast most common in men and women, respectively.[219,220] Most often, the primary site of disease becomes clinically evident or is found easily after the history, physical examination, and roentgenographic studies.

Diagnosis

The most effective means to deal with symptomatic pleural disease is to exercise effective treatment of the underlying disease. However, even when metastatic tumors are resistant to therapy, palliation of symptoms is of utmost importance. This includes radiation therapy for localized painful areas, therapeutic thoracentesis, sclerosis, or pleurodesis, and pleural resection in selected cases. The choice of therapeutic options must be based on a realistic appraisal of the patient's disease and prognosis, the potential risks and benefits of each procedure, and a careful assessment of the goals of therapy.

For patients who present with pleural effusion, a diagnostic thoracentesis can provide sufficient material to determine whether it is malignant, and help identify the primary site of disease if not clinically evident. Evaluation of the pleural fluid with cytology, histopathology, and immunohistochemistry can be important in suggesting an area of primary tumor, although up to 35% of initial specimens will be nondiagnostic, thus necessitating repeat thoracentesis.[221] Molecular analysis of pleural fluid for tumor markers or epigenetic changes associated with cancer, such as DNA hypermethylation, may improve diagnostic capabilities and is a promising area of research.[222–224] If histology suggests an adenocarcinoma, then appropriate diagnostic pathology studies should be performed to exclude an epithelial form of malignant mesothelioma, because patients with early mesotheliomas could be candidates for various aggressive therapies. Exclusion of nonmalignant causes of the effusion (e.g., parapneumonic effusions, pulmonary embolism, congestive heart failure), or causes accompanying disease or its treatment (e.g., superior vena cava syndrome, chylothorax from lymphatic obstruction trapped lung) can have important implications for therapy.

If thoracentesis or small-needle biopsies provide inadequate diagnostic material, a complete thoracentesis (i.e., dry tap) may be required to harvest enough freshly shed tumor cells to assist in diagnosis, as well as providing a potential therapeutic maneuver, because some effusions will not recur or will recur only slowly. Caution must be exercised when performing a thoracentesis to near dryness, however, as this approach increases the risk of pneumothorax, and removing a large effusion increases the risk of postexpansion pulmonary edema.[225,226] Draining the effusion to dryness might thus require multiple sequential attempts. If repeated thoracenteses are needed for symptom control, more aggressive procedures (e.g., pleurodesis or pleural resection) may be appropriate.[227,228]

Symptom Management

Pleural Sclerosis and Pleurodesis

One of the standard approaches in the treatment of recurrent symptomatic pleural effusions is obliteration of the pleural space by inciting irritation or inflammation of the pleural surfaces, resulting in fibrosis and adherence. Techniques to accomplish this have included repeated thoracentesis, chronic tube drainage, instillation of various agents, or partial pleurectomy.[229–234] The procedure most commonly used is chemical pleurodesis. Several important issues surround this procedure: drainage of the effusion, choice of sclerosing agent, and management of the side effects of both in these patients, who already are suffering from significant respiratory compromise. Until recently, drainage usually was accomplished through a large-bore (28–32F) chest tube evacuated through a water seal by gravity or suction, a procedure that is associated with significant patient discomfort.[235] Effective drainage (and pleurodesis) can alternatively be achieved via small-bore (10–12F) catheters, which may be better tolerated by the patient.[236–239] Regardless, the use of intravenous pain medication and/or sedatives should be strongly considered as premedication for both placement of the chest tube and instillation of sclerosing agent. Both relief of dyspnea and lung re-expansion should be demonstrated before proceeding to pleurodesis. If thoracentesis fails to re-expand the lung, pleurodesis is unlikely to be successful, and a chronic small-bore indwelling catheter (e.g., Pleurx) may allow symptomatic relief.

Which sclerosing agent is optimal is debatable, because studies in this area are hampered by heterogeneous patient populations, differences in the definition of response to treatment, and the various techniques used. The many and various agents used include talc; antibiotics such as tetracycline, doxycycline, and minocycline; the antiparasitic agent quinacrine; various chemotherapeutic agents; biological substances such as interferon-β, IL-2, and *Corynebacterium parvum*; and radioisotopes.[233,240,241] Thoracoscopic drainage and talc pleurodesis have been studied extensively and have been shown to be highly effective (93%) in achieving control of effusions.[237–239,242–258] Several antibiotics have been tested as sclerotic agents, including tetracycline and doxycycline. In the United States, parenteral forms of tetracycline are no longer available, and some investigators substituted doxycycline. Pain is a fairly significant side effect in the use of the antibiotics, and many clinicians add xylocaine into the pleural cavity before or during the instillation of the antibiotic. Xylocaine, however, is recognized as paralyzing both leukocytes and monocytes, and to the degree that these cells are helpful in the etiology of sclerosis, the effect of instilling the topical anesthetic on the effectiveness of sclerosis has not been studied adequately.[259] Chemotherapeutic agents also have been used as intrapleural therapies with some success, although many were associated with significant side effects, including severe pain (nitrogen mustard, doxorubicin) and myelosuppression (nitrogen mustard, mitomycin-C).[230,233] Ruckdeschel and coworkers performed a randomized study of tetracycline vs. bleomycin and concluded that there appeared to be an advantage for the bleomycin, with less frequent recurrences of effusions.[260] The pain associated with bleomycin was less severe than with tetracycline, although many patients experienced some febrile response. Bleomycin remains the most commonly used chemotherapeutic agent for sclerosis. However in comparison trials, talc appeared to be more effective than bleomycin or tetracycline, and most investigators believe that talc probably is the most effective agent.[233,248,249,258,261] Talc has thus become the dominant approach to pleurodesis.

The use of biologic agents such as *Corynebacterium parvum*,[262–269] OK-432 (lyophilized *Staphylococcus pyogenes*),[270] interferon-α,[271] interferon-β[193], and recombinant IL-2[199,272,273] is limited, given their disappointing efficacy, significant side effects, or the need for multiple instillations. Among the other agents tested, quinacrine was used in the past with some modest success; however, fever, pain, hypotension, hallucinations, and anecdotal reports of sudden death essentially removed this agent from use.[274–276] The use of radioactive isotopes such as P^{32} and Au^{198} in patients is somewhat onerous, and they have been used with only disputable success.[277,278]

A last option for the control of recurrent pleural effusions is thoracotomy and limited pleural stripping or pleurectomy, thereby achieving a mechanical form of pleurodesis. Although this procedure is highly successful in achieving control of pleural effusions, it is of limited potential application because of the high morbidity (23%) and mortality (18%) associated with it, even in experienced hands.[77,279] However more recent studies suggest that the use of VATS can reduce

these complications significantly.[231,234] Nevertheless, pleurectomy should be reserved for the unique ambulatory patient with an otherwise "good" prognosis whose effusion cannot be controlled with less aggressive techniques.

Future Studies

Although the therapy for metastatic effusions is difficult, and the prognosis for patients with these metastases is poor, further studies are of some importance because of the symptoms involved, the cost of care, and the need to maintain quality of life as long as possible. Thus outpatient programs for pleural drainage and research into sclerosing agents with minimal side effects are important areas of development. Another area of further development includes the use of talc insufflation at the time of initial diagnosis, when the thoracoscope is used for intrapleural biopsies.

In some cases a more aggressive surgical procedure such as pleuroscopy may be necessary to obtain a diagnosis. This procedure has a diagnostic accuracy of 90%, and has the added benefit that pleurodesis can be performed at the same time if malignancy is detected.[280,281]

MEDIASTINAL TUMORS

General

The mediastinum is a complex space in the center of the chest, bounded by the thoracic inlet superiorly, the diaphragm inferiorly, the sternum anteriorly, the spine posteriorly, and the mediastinal pleura bordering each lung laterally. A number of tumors, both benign and malignant, are known to occur in this area, which is divided anatomically into anterior, middle, and posterior compartments, each extending from the thoracic inlet to the diaphragm. These tumors often are difficult to differentiate, either clinically or with available imaging techniques. The anterior mediastinum encompasses the space between the sternum anteriorly and the anterior pericardium posteriorly and contains the thymus gland, lymph nodes, and mesenchymal tissues. The middle mediastinum contains the heart and great vessels, the trachea and esophagus, the vagus and phrenic nerves, and most of the mediastinal lymph nodes. Finally, the posterior mediastinum is bounded by the posterior aspect of the pericardium and trachea anteriorly and the vertebral bodies to the costovertebral sulci posteriorly, and it includes the paraspinal tissues along with sympathetic and peripheral nerves. Occasionally, a distinction is made for the superior mediastinum, which is part of the anterior mediastinum residing behind the manubrium sterni, extending from the suprasternal notch to the angle of Lewis.

Tumors of the mediastinum usually are categorized according to their specific histologic subtype and anatomic location (Table 77-10). Only one third of all primary mediastinal masses are malignant, but they include a wide variety of neoplasms. The location and site of the tumor often provide valuable clues toward making a clinical diagnosis. The clinical presentation of these tumors is shown in Table 77-11.

Thymomas, lymphomas, and germ cell tumors account for most of the anterior mediastinal masses. In a series of 41 patients with isolated anterior mediastinal masses, the pathological diagnosis was lymphoma in 13 patients, thymoma in 11, germ cell tumor in 6, carcinoid in 2, bronchogenic carcinoma in 2, and benign process in the remaining 7 patients.[282] The middle mediastinum is the site of lymphoid malignancies in addition to the neoplasms that are related to metastases from visceral organs (e.g., lung cancer). Most neurogenic tumors are located in the posterior mediastinum. These generalizations according to anatomic site, however, are clinically helpful but not uniformly accurate because of the exceptions to these guidelines. A number of rare tumors, such as carcinoids, neoplasms of mesenchymal origin, melanomas, and undifferentiated carcinomas are known to occur in the mediastinum without any regular compartmental localization.

The substernal thyroid extends downward from the thyroid and does not arise in the mediastinum, although it can first present as a mass in the anterosuperior compartment and can result in symptoms due to compression of the structures in the thoracic inlet, such as the

Table 77-10 Classification of Mediastinal Tumors by Location

ANTERIOR MEDIASTINUM
Thymoma
Thymic carinoma
Thymic carcinoid
Mediastinal germ cell tumors
Hodgkin's disease
Non-Hodgkin's lymphoma
MIDDLE MEDIASTINUM
Angiosarcoma of heart
Rhabdomyosarcoma of heart
Fibrosarcoma
Mesothelioma of pericardium
Lymphoma
Malignant teratoma
Extraskeletal osteosarcoma
Thymoma
Liposarcoma
POSTERIOR MEDIASTINUM
PNET (primitive neuro-ectodermal tumor)
Neuroblastoma
Ganglioneuroma
Ganglioneuroblastoma
Pheochromocytoma
Schwannoma
Neurofibroma

Table 77-11 Clinical Presentation of Mediastinal Neoplasms

ASYMPTOMATIC
Approximately 50% discovered incidentally on imaging studies
SYMPTOMATIC
Mass effect: cough, dyspnea, pain, dysphagia, hoarseness and stridor, Horner's syndrome
Superior vena cava syndrome, cardiac tamponade, spinal cord compression
Nonspecific symptoms: fever, night sweats, malaise, weight loss, anorexia
SPECIFIC MANIFESTATIONS
Hypertension with catecholamine-producing neurogenic tumors
Myasthenia gravis with thymomas

Table 77-12 Transthoracic Needle Biopsy for Diagnosis of Anterior Mediastinal Masses

Anterior Mediastinal Mass (Final Diagnosis)	Thoracic Needle Biopsy (%)				
	No. of Patients	Sensitivity	Positive Predictive	Negative Specificity	Predictive
Thymoma	26	42	96	73	87
Lymphoma	28	71	94	77	92
Germ cell tumor	11	91	98	83	99
Metastatic carcinoma	33	70	100	100	90

Adapted from Herman SJ, Holub RV, Weisbrod GI, Chamberlain DW: Anterior mediastinal masses: utility of transthoracic needle biopsy. Radiology 1991;180:167, with permission.

trachea, esophagus, superior vena cava, and other neurovascular structures.[283] Most substernal thyroids are benign, but occasionally carcinoma can be detected in the substernal goiter. Substernal thyroid can be detected by radioactive iodine scanning and usually is excised using a cervical approach, but in certain cases, median sternotomy could be required.

Approach to Obtaining Diagnostic Material

Transthoracic needle biopsy (aspiration biopsy or true-cut needle biopsy) of a mediastinal mass can be used to obtain tissue, and imaging techniques such as CT, MRI, fluoroscopy, or ultrasound have made these procedures safe and effective.[270,284,285] These small-volume biopsies are of value only in certain specific situations, however.[270,285,286] Because of the need to establish a definitive diagnosis, thymoma, lymphoma, and other neoplasms might not be categorized reliably by small tissue samples obtained by transthoracic needle aspiration and/or biopsy. In contrast, metastatic carcinoma and germ cell tumors can be diagnosed with a high degree of specificity and sensitivity (Table 77-12).[287] The pneumothorax rate with transthoracic needle biopsy varies from 11% to 34% in reported studies.[285,286] This procedure should not be performed if the lesion is suspected of being vascular or if the patient has a history of bleeding disorders or previous pneumonectomy.

When needle aspiration or biopsy is not feasible or is unlikely to yield sufficient material, mediastinoscopy or anterior mediastinotomy can provide adequate material for definitive histologic diagnosis, cell-surface marker studies, and flow cytometric and cytogenetic studies.[287] Thoracotomy has given way to VATS thoracoscopsy, which is being used increasingly for diagnosis and staging of mediastinal and intrathoracic masses.[288] Bronchoscopy and esophagoscopy are of limited value for mediastinal masses and should be reserved for patients with apparent involvement of the aerodigestive tract.

TUMORS OF THE ANTERIOR MEDIASTINUM

Imaging modalities for the diagnosis of mediastinal tumors are presented in Box 77-1.

Thymoma

Thymoma is the most common cause of anterior mediastinal masses in adults (Tables 77-10 and 77-13). Thymomas are derived from thymic epithelial cells demonstrating a spectrum of histologic patterns that encompass both epithelial and lymphocytic components in varying proportions.[289] The epithelial cells are embryologically derived from the lower portion of the third pharyngeal pouch and are believed to be responsible for the neoplastic element in thymomas. The lymphocytes associated with both the normal thymus and thymomas are predominantly immature T lymphocytes and demonstrate TdT postivity.[290,291] Immunoglobulin and T-cell receptor gene studies failed to show genotypic evidence supporting the neoplastic nature of the lymphocytic component.[292]

Although thymomas initially were classified according to their proportion of epithelial and lymphocytic components, this classification repeatedly showed a lack of clinical relevance to patient response and survival.[293–295] In the mid-1980s, Marino and Muller-Hermelink[296] revised this traditional classification based on the

Box 77-1. AN APPROACH TO THE DIAGNOSIS OF MEDIASTINAL TUMORS BY IMAGING STUDIES

Chest radiography
- Essential for diagnosis of mediastinal tumors

Computed tomography scan with contrast
- Imaging modality of choice and "gold standard" for noninvasive evaluation
- Differentiates mediastinal masses from vascular and cystic lesions
- Delineates the compartment involved
- Defines the mass in relationship to adjacent tissues
- Valuable in determining the best approach for diagnostic biopsy of the mediastinal mass

Magnetic resonance imaging
- Modality of choice for evaluating posterior and superior mediastinal masses, chest wall abnormalities, and diaphragmatic processes
- Study of choice for detecting masses adjacent to the spinal cord and vertebral bodies
- Defines the characteristics of neurogenic tumors and neural cysts
- Defines intracardiac masses with gating studies
- Unique image reconstruction with coronal and sagittal views
- Avoids use of iodinated contrast and ionizing radiation
- Might help to distinguish residual tumor from fibrosis
- Should be reserved for specific situations described, until spatial resolution limitations are overcome

Intraesophageal ultrasonography
- Eliminates the lungs as a source of interference and thus is useful for imaging cysts

Radionuclide scanning
- I-scanning for thyroid neoplasms or goiter (must be performed before intravenous administration of contrast for CT because the iodine load will interfere with normal thyroid uptake of radioactive iodine)
- I-labeled MIBG scanning for pheochromocytoma

Double isotope (technetium and thallium) subtraction imaging for parathyroid tumors

Gallium scanning for lymphomas and Hodgkin's disease

Positron emission tomography (PET) scanning for Hodgkin's and non-Hodgkin's lymphomas

Table 77-13 Thymic Tumors

Thymoma
Thymic carcinoma
Thymic lymphoma
Thymic Hodgkin's disease
Thymic carcinoid
Thymic germ cell neoplasm
Thymic lipoma
Thymic cyst
Thymic myoid tumor
Thymic histiocytic tumor

Table 77-14 Staging of Thymoma

Stage	Definition
I	Macroscopically, completely encapsulated; microscopically, no capsular invasion
IIa	Macroscopic invasion into surrounding fatty tissues or mediastinal pleura
IIb	Microscopic invasion into the capsule
III	Macroscopic invasion into the neighboring organ (i.e., pericardium, great vessels, or lung)
IVa	Pleural or pericardial dissemination
IVb	Lymphogenous or hematogenous metastases

Modified from Masaoka A, Monden Y, Nakahara K, et al: Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485. © 1981 American Cancer Society, with permission.

subtyping of tumors according to their microscopic resemblance to the normal thymic epithelial cells and thymic cortex. The 1999 WHO classification of thymomas further modified the Muller-Hermelink classification, adding thymic carcinoma to the classification schema, simplifying the terminology, and providing prognostic relevance.[297,298] Typically, thymomas are solid tumors covered by a thick, fibrous capsule (Fig. 77-6). The cut section reveals tan, fleshy lobulations divided by fibrous septae. Cystic degeneration, calcification, and focal hemorrhage may be seen.[289]

Histologically, thymomas are classified according to their cytologic appearance in association with the proportion of lymphocytes present.[289] These tumors typically are bland in appearance and can demonstrate mild to moderate cellular atypia. Thymic carcinomas, on the other hand, appear cytologically malignant with marked nuclear atypia and demonstrate a high correlation between cytologic malignancy and clinical outcome.[297]

The staging system used for thymoma as proposed by Masaoka is outlined in Table 77-14.[299] Tumor staging is considered the most significant prognostic factor in determining patient survival. Thymoma spreads via direct extension through its capsule into adjacent structures such as lung, mediastinal soft tissue, or pleura and can metastasize distantly. The extent of capsule invasion and the involvement of thoracic and extrathoracic structures determine the stage, which is correlated to the risk of recurrence and survival.[299,300] Thus extensive tissue sampling of the resected tumor is essential to define microscopic and macroscopic invasion through the fibrous capsule. Other prognostic factors include the completeness of excision, tumor size, histologic typing, involvement of the great vessels, and performance status.[301–304]

Epidemiology

Thymomas constitute 20% of all mediastinal masses in adults. In general, they occur with about the same frequency in males and females, and there is no predilection for a particular race or geographic distribution. They are most commonly seen in the fifth and sixth decades of life.[305,306] A recent study indicated that in thymomas found to have capsular invasion, there is a predilection for males and persons of Asian or Pacific Island descent.[307] Thymomas are extremely rare in children, but when they occur, they present as highly aggressive tumors with a high mortality rate.[308]

Clinical Manifestations

In 30% to 50% of cases, thymomas present as an asymptomatic anterosuperior mediastinal mass seen on a chest radiograph (Fig. 77-7). When symptomatic, patients usually present with cough, chest pain, dyspnea, dysphagia, fever, weight loss, or anorexia.[306] A number of associated conditions are seen in patients with thymoma, including myasthenia gravis, red cell aplasia, hypogammaglobulinemia, polymyositis, and (rarely) systemic lupus erythematosus, rheumatoid arthritis, thyroiditis, hyperthyroidism, and other cytopenias.[309] When an anterior mediastinal mass is present with myasthenia gravis, red cell aplasia, or hypogammaglobulinemia, the diagnosis of thymoma is essentially established.

Myasthenia gravis is an acquired autoimmune disorder caused by circulating acetylcholine receptor antibodies, resulting in acetylcholine receptor deficiency at the motor end-plate.[310] Two thirds of patients with myasthenia gravis have thymic lymphoid hyperplasia,

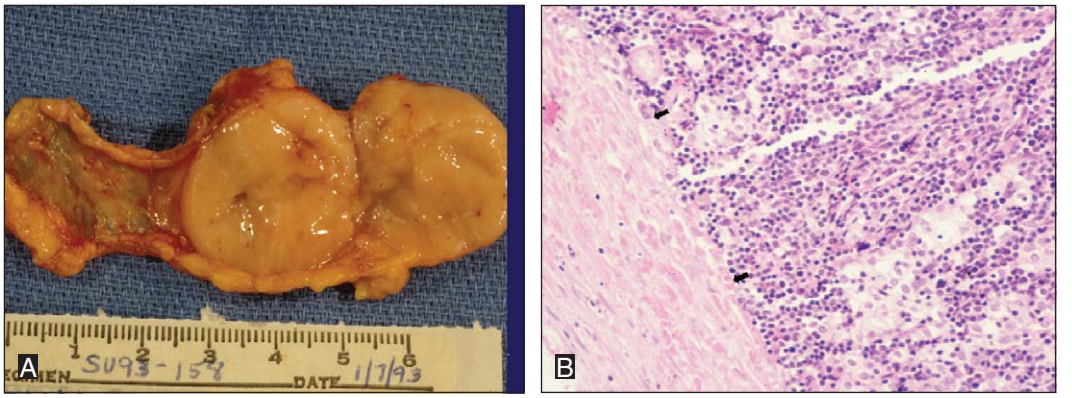


Figure 77-6 • **A,** Gross anatomy of a bisected thymoma demonstrating a complete capsule. **B,** Microscopic demonstration of a thick capsule *(arrows)*. (Courtesy of S.C. Aisner, MD.)

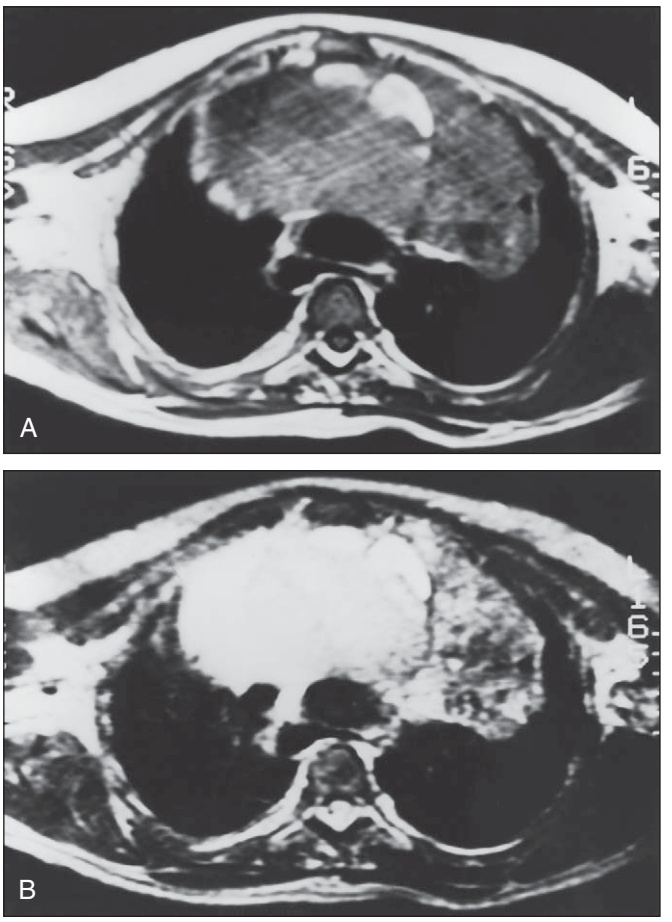


Figure 77-7 • Anterior mediastinal mass that was determined on biopsy to be thymoma. **A,** Axial T_1-weighted MRI through the upper chest showing a large anterior mediastinal mass that extends laterally to both hemithoraces. **B,** Axial T_2-weighted MRI of the same mass, illustrating enhancement compatible with thymoma.

and 8.5% to 15% have thymoma.[299,311] In keeping with this correlation, one third of patients with thymoma have myasthenia gravis.[299,311,312] Thymomas with concurrent myasthenia gravis tend to be less aggressive tumors than those without this associated disorder, and histologically, the tumors tend to have a greater lymphocyte-to-epithelial cell ratio.[313,314] Myasthenia gravis can involve the external ocular muscles selectively, with the patient presenting with diplopia and ptosis. When the other bulbar muscles are involved, the presenting symptoms can include difficulty with deglutition, slurred speech, and loss of facial expression. The general voluntary muscle system can be affected, either alone or with the involvement of the external ocular and bulbar muscles, resulting in fatigability of the limb muscles. The proximal muscles are more severely affected than the distal ones. In advanced cases, the weakness is universal, and the grade of dyspnea depends on the severity of the disease. Progression is most rapid during the first few years, and most deaths caused by myasthenia gravis occur within the first 3 years after diagnosis.[311]

The anticholinesterase test usually is diagnostic for myasthenia gravis. Administration of edrophonium results in rapid (although transient) clinical improvement, with objective response assessed by degree of ptosis, range of ocular movements, and the force of the hand grip. Electromyography performed with supramaximal stimulation of a motor nerve at 2 to 3 Hz results in progressive decrement of the amplitude of the evoked compound muscle action potential from the first to the fifth response. Other diagnostic studies include serologic tests for acetylcholine receptor antibody, C_3 localization of immune complexes at the end-plate in cryostat sections, and electrophysiologic studies of neuromuscular transmission.[315]

The initial current therapy of myasthenia gravis includes anticholinesterases and, alternately, prednisone. Pyridostigmine-bromide is widely used because of its longer duration of action and reduced muscarinic effects compared with neostigmine bromide.[316] The identification of thymoma in patients with myasthenia gravis represents an absolute indication for thymectomy. Although most patients experience some improvement in the thymoma-associated myasthenia gravis symptoms, complete remission of the associated myasthenia gravis symptoms can be expected in only a minority of patients.[317,318] Conversely, more than 75% of all patients with myasthenia gravis without thymoma show some improvement with thymectomy.[319] All thymus tissue, not only the thymoma, should be removed at the time of thymectomy, because residual thymus tissue can lead to persistence of the autoimmune disorder.[320] Other therapies for myasthenia gravis include immunosuppressive agents (e.g., azathioprine and plasmapheresis) in fulminant cases.

Red Cell Aplasia

As many as 5% to 10% of patients with thymoma may have isolated red cell aplasia, which is characterized by an almost total absence of red cell precursors in the bone marrow and reticulocytes in the peripheral blood. One third of these patients also have reduced counts of both leukocytes and platelets. The exact etiology of this disorder is not known, but it has been reported to occur together with myasthenia gravis and thymoma, which suggests an autoimmune mechanism.[321] Thymectomy results in improvement in approximately 30% of these patients.[322]

Hypogammaglobulinemia

Hypogammaglobulinemia is seen in about 5% of patients with thymoma. Both cellular and humoral immunity are decreased in these patients. Only occasional remissions in hypogammaglobulinemia have been seen after thymectomy.[322]

Management of Thymoma

Surgical resection is the principal treatment modality for thymoma. All normal thymic tissue, including the perithymic fat, should be removed, especially if there is an associated autoimmune disease.[320] The usual surgical approach is by median sternotomy, but it can depend on the extent of the disease; more extensive resections might be required, including partial or total pneumonectomy or pericardiectomy.[323,324] Postoperative adjuvant radiation therapy is recommended for those patients found at the time of surgery to have invasive disease or thymic carcinoma, because such therapy leads to definite improvement in long-term survival, as shown by the results of randomized studies.[323] Patients with incompletely resected or unresectable disease also are candidates for radiation therapy. A dose of 30 to 60 Gy has been recommended. Even after whole mediastinal irradiation, recurrences have been seen in the pleural cavity.[305,325] The role of radioisotope implants in areas of unresected tumor is not clear. Occasional responses of myasthenia gravis to radiation therapy have been noted in patients with persistent myasthenia gravis after thymectomy.[326]

Chemotherapy achieves only moderate responses for patients with recurrent or metastatic disease.[327] Agents with some degree of activity include cisplatin, doxorubicin, procarbazine, cyclophosphamide, ifosfamide, and corticosteroids. Only octreotide, cisplatin, and ifosfamide have completed phase II testing.[328–330] Anecdotal reports of responses to corticosteroids exist.[331] Chemotherapy combinations usually produce higher response rates. Cisplatin-based combinations have been tested most extensively.[332–335] Fornasiero and colleagues[333] reported a 92% response rate in 37 patients with cisplatin, doxorubicin, vincristine, and cyclophosphamide. Loehrer and coworkers[330] reported a 50% response among 29 patients using cisplatin,

doxorubricin, and cyclophosphamide. In another report, Park and associates[336] reported a 64% response rate with a similar regimen, with or without prednisone. The European Organization for Research and Treatment of Cancer (EORTC) reported a 56% response rate among 16 patients treated with cisplatin and etoposide; the addition of ifosfamide was not beneficial.[337] A recent trial by Loehrer and colleagues[330] added ifosfamide to this regimen and demonstrated similar response rates. Thymic tumors have demonstrated a high uptake of indium-labeled octreotide (^{111}In-DTPA-D-Phe^{1}), which could be useful for imaging, but which in combination with prednisone has demonstrated complete and partial responses in patients with advanced disease.[330,338] These results indicate that thymoma could, in fact, be a chemosensitive tumor, and thus the role of chemotherapy in the adjuvant and neoadjuvant settings and in advanced disease must be further defined.

Thymic Carcinoma

Thymic carcinomas are epithelial neoplasms of the thymus that are characterized by a high degree of cytologic atypia. These tumors, unlike thymomas, express highly aggressive behavior and thus should be classified separately. Thymic carcinoma includes a heterogeneous group of neoplasms, of which more than half are undifferentiated carcinomas. Other tumor subtypes include squamous cell carcinoma, spindle cell carcinoma, lymphoepithelioma-like carcinoma, mucoepidermoid carcinoma, basaloid carcinoma, clear cell carcinoma, and adenoid cystic tumor.[339,340] Unlike their thymoma counterpart, thymic carcinomas lack immature T lymphocytes and are TdT negative.[341] Additionally, thymic carcinomas express the cytokeratin marker CD5, which is helpful in distinguishing these tumors from nonthymic epithelial malignancies.[342]

These tumors usually present in adult men and are seen only rarely in children. Symptoms include weight loss, shoulder discomfort, cough, and dyspnea. Paraneoplastic syndromes usually are not associated with thymic carcinoma. Well-differentiated thymic carcinoma has been reported in association with myasthenia gravis.[341] The spindle cell variety generally is an aggressive subtype, with mortality rates of up to 50% within 5 years.[340,343,344] There is increasing evidence that Epstein-Barr virus (EBV) might play a role in the development of a lymphoepithelioma-like carcinoma of the thymus gland, as is seen in nasopharyngeal carcinomas. EBV nuclease antigen has been detected in tumorous cells, and Southern blot analysis has demonstrated the EBV viral genome in the cells of thymic lymphoepithelioma-like carcinoma.[345] Although EBV-associated lymphoepitheliomas of the nasopharynx often are treated successfully, the thymic counterpart appears to have a poor prognosis, probably because it usually has become very large by the time it is discovered.[340] Other forms of thymic carcinoma just mentioned are rare. CT scans usually show an anterior mediastinal mass infiltrating along the pleura or mediastinum with necrosis or calcification.[346]

Thymic carcinomas are aggressive and highly lethal tumors. Usually, patients present with advanced-stage disease and are candidates for multimodality treatment, including surgery, radiation therapy, and chemotherapy.[305,347] The combination of cisplatin, vinblastine, and bleomycin as used in the treatment of germ cell tumors has been applied to these neoplasms.[347]

Thymic Carcinoid

Thymic carcinoid (see Chapter 75) arises from the neuroectodermal cells of foregut origin within the thymus and is an amine precursor uptake and decarboxylase (APUD) tumor, usually not associated with the classical carcinoid syndrome seen in carcinoids arising from the midgut.[348] These thymic carcinoids usually are locally invasive but can metastasize to bone, lymph nodes, skin, and liver.[349] In a large review of mediastinal thymic carcinoids, patients with three types of thymic carcinoid were identified.

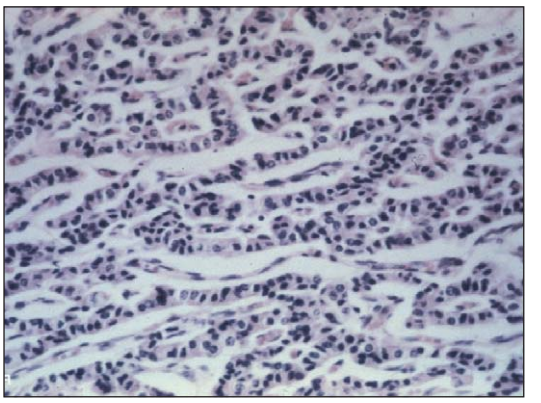


Figure 77-8 • Microscopic view of thymic carcinoid with ribbon pattern of tumor, typical of mediastinal carcinoid. (Courtesy of S.C. Aisner, MD.)

1. Thymic carcinoid associated with Cushing's syndrome or other endocrinopathies (38%; age range 9–48 years).
2. Thymic carcinoid without other endocrinopathies (44.5%; age range 21–87 years).
3. Thymic carcinoid with multiple endocrine neoplasia, type I or II (17.5%; age range 30–46 years).[350]

Cushing's syndrome due to adrenocorticotropic hormone production by tumors is seen most often in children with thymic carcinoid.[351,352] Compared with bronchial carcinoid tumors, thymic carcinoid tumors are a much less common cause of ectopic corticotropin syndrome.[353] Macroscopically, thymic carcinoids resemble thymomas but usually are not encapsulated. On histopathologic examination, thymic carcinoid is characterized by formation of tumor cells arranged into organoid clusters with tumor rosettes and ribbons (Fig. 77-8). The vast majority of cells are positive for neuroendocrine markers such as chromagranin and synaptophysin, which are useful in confirming the diagnosis.[354] Wide excision, when possible, is the mainstay of treatment.[349] The roles of postoperative radiation and chemotherapy are not known, but patients with unresectable or persistent tumors probably should be treated with radiation therapy. Control of hypercortisolism with metyrapone in patients with ectopic corticotropin syndrome is an important part of management.[351]

Mediastinal Germ Cell Tumors

Primary germ cell tumors constitute approximately 10% to 15% of all mediastinal neoplasms.[355] These tumors, although histologically similar to testicular neoplasms, are recognized as distinct entities with separate clinical and biological behaviors (see Chapter 90). They initially were thought to represent metastasis from occult testicular primary lesions, based on the presence of testicular scars representing healed tumors.[356] Malignant transformation of germinal elements in the mediastinum without a primary gonadal tumor has now been well established, however, as isolated mediastinal metastasis from gonadal germ cell tumors rarely occurs. Autopsy series have failed to confirm the presence of either testicular occult primary tumors or fibrous scars in most of the cases with extragonadal germ cell tumors.[357,358] In addition to the mediastinum, other common sites of extragonadal germ cell tumors have been located along the body midline and identified in the pineal gland, sacrococcygeal region, and retroperitoneum.[359] This finding could be due to either abnormal migration of germinal elements to these areas during embryogenesis or their widespread distribution during early development.[360]

Epidemiology

The mediastinum is the most common site of extragonadal germ cell tumors in young adults.[361,362] They can be benign or malignant.

Benign germ cell tumors show no predilection for sex, whereas malignant mediastinal germ cell tumors occur almost exclusively in men.[362] The racial distribution of mediastinal germ cell tumors is unknown, unlike the distribution of gonadal germ cell tumors, which are seen most commonly among whites. There is some evidence that extragonadal germ cell tumors—especially mediastinal tumors—might occur with higher incidence among blacks and Hispanics. The mediastinal nonseminomatous germ cell tumors have been recognized recently in association with Klinefelter's syndrome, with characteristic clinical features and cytogenetic abnormality 47XXY.[363] Whether the chromosomal abnormality seen in Klinefelter's syndrome plays a role in the development of these tumors is not known, but approximately 20% of patients with nonseminomatous germ cell tumors have Klinefelter's syndrome.[364] Systemic mast cell disease with circulating heparin-like anticoagulant has been reported in association with mediastinal germ cell neoplasms.[365] Acute nonlymphocytic leukemia and malignant histiocytosis also are known to occur in association with nonseminomatous mediastinal germ cell tumors; these clearly are not attributable to the therapy but seem to arise from a common progenitor.[366]

All histologic variants of germ cell tumors arise in extragonadal sites such as the mediastinum and are identical to those seen in the testes. This finding is compatible with the embryologic concept that extragonadal germ cell tumors arise from primordial germ cells in the yolk sac or urogenital ridge that have failed to migrate into the scrotum. Benign teratomas are the most common germ cell tumors seen within the mediastinum, in both children and adults.[367,368] These tumors contain elements from all three germ layers: ectoderm, mesoderm, and endoderm. Seminoma is the most common malignant variety of germ cell tumor in the mediastinum, with an incidence of 40%.[369] Other subtypes include embryonal carcinoma, teratocarcinoma, choriocarcinoma, and endodermal sinus tumors, with pure and mixed forms of each type.[370] In a report of 11 cases of primary mediastinal germ cell tumors from a single institution, 4 were seminomas, 3 were mixed germ cell tumors, 2 were embryonal carcinomas, and 2 were teratocarcinomas.[371]

Clinical Presentation

The benign forms often do not give rise to any symptoms and are discovered incidentally on chest radiographs obtained for other reasons. If symptoms do occur, they usually are due to the enlarging mass in the anterior mediastinum (Fig. 77-9).[368] On the other hand, almost all patients with malignant extragonadal germ cell tumors present with chest pain, cough, dyspnea, and constitutional symptoms such as fever, weight loss, and anorexia. Nonseminomatous tumors grow rapidly and metastasize early.[370] Occasionally, these patients develop superior vena cava syndrome or present with symptoms related to the site of metastasis, the most common of which are lungs, liver, bone, and brain.

The anterosuperior mediastinum is the most common site of mediastinal involvement, with rare presentation in the posterior compartment. Useful imaging studies include CT scans of the thorax to gauge the extent and characteristics of mediastinal involvement. Abdominal CT scans can detect the presence of liver metastasis or retroperitoneal disease. A testicular primary tumor should be suspected if significant retroperitoneal disease is found. Elevation of β subunit of human chorionic gonadotropin (hCG) and α-fetoprotein (AFP) suggest the malignant, nonseminomatous nature of these tumors. The incidence of elevated AFP is higher in patients with mediastinal, nonseminomatous germ cell tumors than in those with primary metastatic testicular tumors. Choriocarcinomas can produce both hCG and gynecomastia, which can be seen on initial presentation.[372] Elevation of lactic dehydrogenase is seen in 80% to 90% of patients with either seminomatous or nonseminomatous tumors. Serum markers, when present, are used both to assess response to treatment and to detect early recurrence.[373] Fluorescence in situ hybridization (FISH) has permitted specific recognition of a genetic marker i(12p) for germ cell tumors.[374] The fluorescent signal at the centromere of the i(12p) is larger than that obtained from a normal chromosome 12 centromere using a probe specific for chromosome 12 centromeric DNA.[374] Presence of the i(12p) or excess 12p copy numbers tends to be associated with complete response to chemotherapy and long-term disease-free survival.[375]

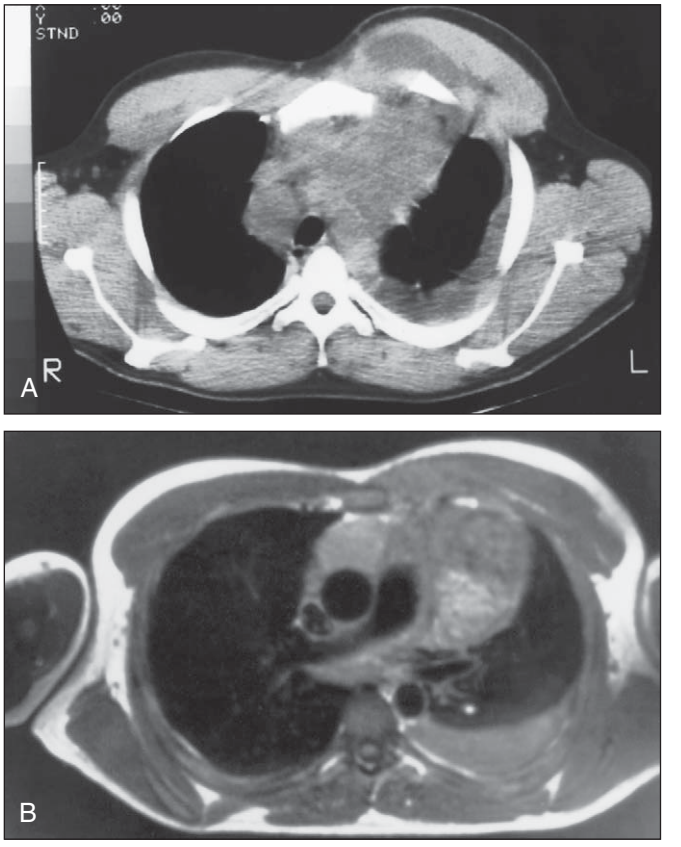


Figure 77-9 • Anterior mediastinal mass-germ cell tumor. **A,** Unenhanced CT image of the chest at the level of the aortic arch showing a large anterior mediastinal mass that extends to the left to or through the chest wall. Note the extension of the pectoralis minor and the bulge of the pectoralis major anteriorly. Paratracheal adenopathy is evident on the right, as is a moderate left pleural effusion. **B,** T_1-weighted MR image at the same level, clearly demonstrating extension of the mass into the chest wall.

Establishment of a definitive histopathologic diagnosis is crucial for the management of these patients. The classic presentation is a young adult with an anterosuperior mediastinal mass and a characteristic marker profile. Percutaneous imaging-guided fine-needle aspiration of the anterior mediastinal mass often establishes the diagnosis of germ cell neoplasms, but definitive tissue diagnosis is best obtained by parasternal mediastinotomy. If considerable risk is involved with surgical intervention for diagnosis because of a patient's poor overall condition, and if there is a high index of suspicion with elevated markers, management can be initiated with chemotherapy without a diagnostic biopsy.[359]

Benign Mediastinal Germ Cell Tumors

Benign mediastinal teratomas are treated exclusively with surgical resection, which results in cure; there is no role for adjuvant therapies after surgical resection.[376] Lewis and coworkers[368] reported a series of 69 patients from the Mayo Clinic with benign mediastinal teratoma, 64 of whom are long-term survivors. The five remaining patients died either from surgical complications or from unknown causes.

Mediastinal Seminoma

Mediastinal seminomas tend to be slow-growing and can reach considerable size with few or no symptoms. Traditionally, the disease was treated with supradiaphragmatic irradiation because of the tumor's radiosensitivity.[377] Large masses might require large fields of irradiation, however, which can cause considerable compromise to surrounding organs. Several trials, therefore, have tested the role of cisplatin-based chemotherapy and have found significant activity and long-term disease control.[359,378,379] Either approach offers the possibility of disease control. Depending on the individual characteristics of the patient and the comorbid diseases, small tumors might be considered for radiation therapy, whereas larger tumors most likely would be best treated with initial cisplatin-based chemotherapy. Surgical excision or management does not appear to play a role in the management of this disease.[359] Whether cisplatin-based chemotherapy or radiation therapy alone followed by chemotherapy at recurrence should be considered as the optimum treatment for mediastinal seminoma is still open to question; both result in comparable long-term survival rates. For patients who have bulky mediastinal disease or extramediastinal involvement, there is substantial evidence that cisplatin-based chemotherapy might be superior.

Mediastinal Nonseminomatous Germ Cell Tumors

Cisplatin-based chemotherapy is the cornerstone of management of mediastinal nonseminomatous germ cell tumors.[380–382] Overall, the prognosis of mediastinal nonseminomatous germ cell tumors is poor compared with that of their testicular counterparts, and they have the worst survival characteristics of all the nonseminomatous germ cell tumors.[383] In an old series from Memorial-Sloan Kettering Cancer Center before the advent of cisplatin, only 5% of patients survived beyond 17 months with surgical resection followed by radiation therapy.[362] A French multicenter retrospective study reported a 53% 2-year projected survival rate and a median survival of 28 months for patients with mediastinal nonseminomatous germ cell tumor using cisplatin-based chemotherapy followed by resection of residual tumor, if present.[379] Complete response rates with cisplatin-based therapy have ranged from 50% to 70% in most series, with a long-term survival of approximately 50%.[380,381] Second-line chemotherapy combinations for patients with resistant or recurrent disease generally have yielded poor results.[384,385] These patients, therefore, either should be entered into clinical trials with investigational agents in an effort to identify new active agents in this disease, or should be treated with high-dose therapy followed by peripheral blood stem cell or autologous bone marrow transplantation.[386] Chemotherapy in general and salvage chemotherapy specifically tend to be less effective for the management of patients with mediastinal germ cell tumors than of patients with their testicular counterparts.[387]

Mediastinal Hodgkin's Disease

Approximately one half of patients with Hodgkin's disease have mediastinal involvement, usually in the anterior compartment, either as a component of widespread disease or presenting solely as a mediastinal mass (see Chapter 111). The most common histologic subtype with mediastinal involvement is nodular sclerosis, which is seen predominantly among young women.[388] The diagnosis usually is made from biopsy of a cervical lymph node and rarely requires biopsy of the mediastinal mass. The extent of mediastinal and pulmonary involvement can be gauged better with CT and MRI scans than with plain chest radiograph (Fig. 77-10).[389] The CT scan also is useful in planning the radiation fields. Approximately 40% of cases also have involvement in the form of hilar adenopathy and lung nodules. Pleural and pericardial effusions, although less common, are known to occur.[390] In cases of bulky mediastinal disease, acute tracheobronchial obstruction can occur during anesthesia.[391] Management of mediastinal Hodgkin's disease is based on the bulk of the tumor and the extent of parenchymal lung involvement.

Pulmonary extension significantly increases the risk of relapse and decreases the overall survival. In a study reported by the Baltimore Cancer Research Center, small-volume mediastinal involvement with early-stage (stage I or II) Hodgkin's disease was treated successfully with upper-mantle radiation therapy alone.[392] For those with large mediastinal masses or pulmonary extension, radiation therapy alone was associated with 38% disease-free survival at 10 years; combined chemotherapy and irradiation resulted in 88% disease-free survival at 10 years.[392] The risk of relapse at the margin of the irradiation field was increased when a "shrinking field technique" was used to decrease the incidence of pulmonary complications in patients with large mediastinal masses treated with radiation therapy alone. Although salvage chemotherapy can be useful in patients who fail to achieve a complete response to radiation therapy alone, the results are inferior when compared with combined-modality treatment. Combined-modality therapy also was superior to chemotherapy alone as reported in various studies for patients with large mediastinal masses due to Hodgkin's disease. Currently, therefore, the standard of care for patients with large mediastinal masses is combined chemotherapy and irradiation.

Gallium scans, and both CT and PET scans, have been used for detection of viable Hodgkin's disease in the mediastinum after chemotherapy or combined-modality therapy.[393–395] According to the results of a recent study, the value of these studies is limited in predicting disease sterilization, although a few patients have benefited from treatment modification due to abnormal activity seen on these scans.[393,395]

Mediastinal Non-Hodgkin's Lymphoma

Mediastinal non-Hodgkin's lymphomas have a wide clinical spectrum, ranging from nodal involvement as a part of generalized disease to bulky anterior mediastinal mass resulting in symptoms of compression of other structures such as the pericardium, heart, lungs, or great vessels (including the superior vena cava; see Chapter 112). The most common symptoms of bulky mediastinal disease include chest pain, dyspnea, sternal tenderness, superior vena caval compression syndrome, and pleural or pericardial effusions.[388,396] Constitutional symptoms such as fever, weight loss, and anorexia occur in 50% of patients and are associated with a poorer prognosis than disease without these symptoms.[397] In isolated mediastinal involvement, thoracotomy or mediastinotomy could be required for obtaining adequate diagnostic material. Complete staging evaluation is required, because extensive involvement of other organs is seen frequently. The two most common subtypes of non-Hodgkin's lymphoma that are seen predominantly in the mediastinum include diffuse large cell lymphoma.

Diffuse large cell lymphoma can present as an anterior mediastinal mass. Mediastinal presentation is more common among young females, with a median age of about 30 years. The disease usually is bulky and extends from the mediastinum into contiguous structures such as pleura, pericardium, and lung. Pleural and pericardial effusions are known to occur in nearly one third of patients. Bone marrow and central nervous system involvement usually are not seen at presentation. These are predominantly B-cell neoplasms, with the dominant phenotype reported to be CD19+, CD22+, CD37+, CD21–, CD30–, CD10–, CD5–, and immunoglobulin negative.[398,399]

Lymphoblastic lymphoma is a distinct entity that presents as an anterior mediastinal mass in older children and young adults. It is seen predominantly in males and is clinically and immunologically similar to acute lymphoblastic leukemia. The cell of origin is the T cell or middle or late thymocyte in most cases, but rarely, it may be of the pre-B cell or null cell types. Immunophenotyping reveals E rosette+, T6+, T4+, T8+, T1+, and T3+. On histopathology exam-

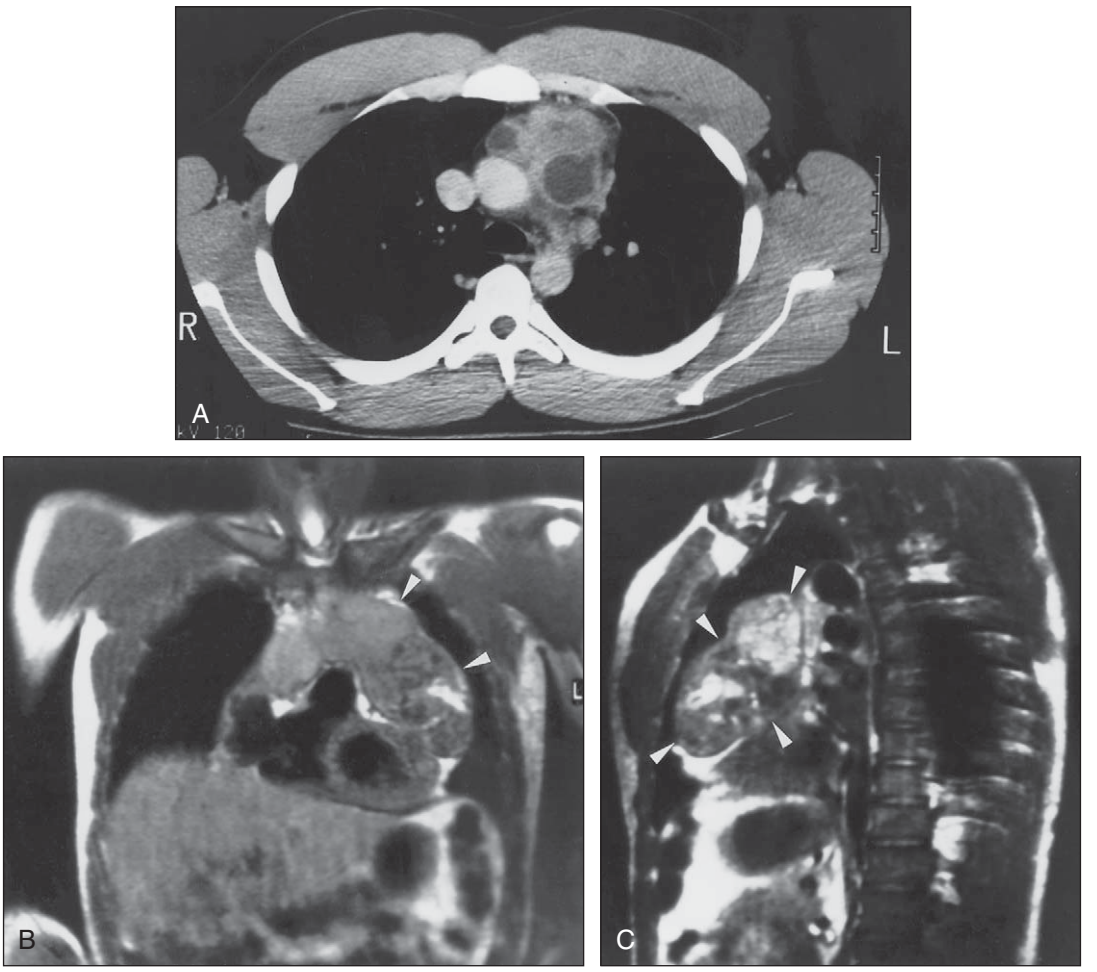


Figure 77-10 • Anterior mediastinal mass that was determined to be Hodgkin's disease. **A,** Enhanced CT image of the chest at the AP window showing a large mixed solid and cystic mass with extension to the left. **B,** Coronal T_1-weighted MR image of the chest showing the large mediastinal mass *(arrowheads)* with extension to the left. **C,** Sagittal T_1-weighted MR image of the chest showing the large mediastinal mass with areas of mixed signal corresponding to the mixed solid and cystic areas.

ination, cells have convoluted or nonconvoluted nuclei with fine chromatin without nucleoli. The histology-stained section gives a "starry sky" appearance. Staining with terminal deoxynucleotidyl transferase (TdT) usually is positive. Clinically, these cases present as a thymic mass with paracortical involvement of the thymus-dependent lymph nodes. There is a high incidence of meningeal spread and involvement of the bone marrow, peripheral blood, and testes. Cells obtained from cerebrospinal fluid should be stained with TdT.[400]

The management of lymphoblastic lymphoma is essentially similar to that of acute lymphoblastic leukemia. The response to chemotherapy usually is rapid.[401,402] Earlier regimens, such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), produced low complete remission rates and substantially fewer survivors.[403] Intrathecal therapy with or without craniospinal irradiation is applied early in the treatment course to prevent central nervous system relapse.[402–404] There is no evidence that radiation therapy in addition to chemotherapy improves survival, but it should be initiated if the patient is in severe distress and objective improvement is not seen quickly with chemotherapy.

TUMORS OF THE MIDDLE MEDIASTINUM

Malignant tumors of the heart and pericardium are rare entities. Approximately 75% of all cardiac tumors are benign, and more than half of these are myxomas (Fig. 77-11). Other malignant tumors and cysts of the heart and pericardium include angiosarcoma, rhabdomyosarcoma, mesothelioma, fibrosarcoma, lymphoma, extraskeletal osteosarcoma, neurogenic sarcoma, malignant teratoma, thymoma, leiomyosarcoma, liposarcoma, and synovial cell sarcoma.[405] In a series recently reported by Chen and coworkers,[406] 79 patients with cardiac tumors were seen at the Shanghai Institute from 1957 to 1988. Of these, 49 patients had benign and 30 had malignant tumors. All except two of the benign tumors were myxomas, and 86% of these were located in the left atrium. Among the 30 malignant tumors, 15 were secondary metastases, 3 were lymphomas, 2 were mesotheliomas, 2 were malignant myxoma, 1 was angiosarcoma, 1 was rhabdomyosarcoma, 1 was leiomyosarcoma, 1 was fibrosarcoma, and 4 were undiagnosed. Metastatic tumors to the heart and pericardium can result from direct extension from the mediastinal lymph nodes or hematogenous dissemination of tumor. Metastatic renal cell carcinoma has been demonstrated to grow into the right atrium from the vena cava without myocardial infiltration, and such tumors occasionally have been surgically resected.[407] The manifestations of cardiac and pericardial tumors are varied and depend on mass effect, local invasion, embolization, and systemic constitutional symptoms.[408] Pericardial involvement can result in severe substernal chest pain due to pericarditis with frequent effusion or tamponade (Fig. 77-12). Other manifestations include congestive heart failure, pulmonary

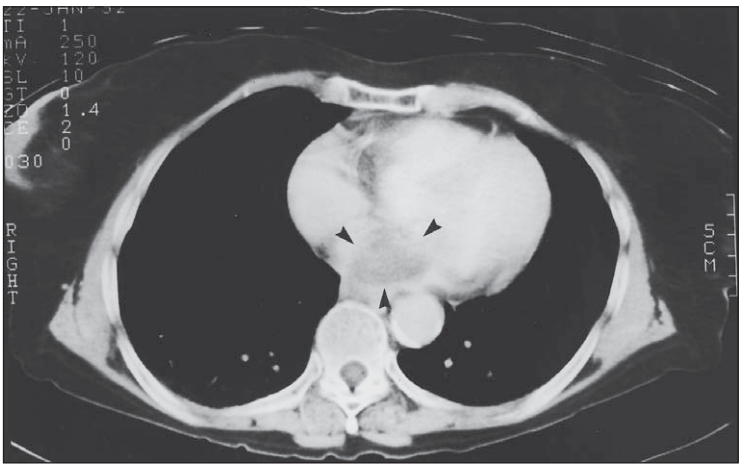


Figure 77-11 • This middle mediastinal mass represents a left atrial myxoma. Enhanced CT image through the heart showing a left atrial defect *(arrowheads)* with lower attenuation than the surrounding contrast-filled atria and ventricles.

hypertension, and dysrhythmias. Diagnostic procedures include echocardiography and CT of the chest in addition to chest radiographs and electrocardiograms.[408] CT with contrast can detect the intracavitary filling defect and its relationship to cardiac chambers and invasion. More recently, MRI has been used to localize intracardiac tumors, to assess their vascularity, and to distinguish them from cardiac metastasis.[409] Cardiac catheterization is able to detect mass effects resulting in compression or deformity of various chambers, intracavitary filling defects, myocardial motion abnormalities, or pericardial effusion. Angiosarcoma and rhabdomyosarcoma are the two most common malignant cardiac tumors.[405,410,411] Microscopically, angiosarcomas contain foci of solid areas and spindle cells forming vascular channels, while rhabdomyosarcomas contain rhabdomyoblasts, but in both types of tumors, there can be high degrees of anaplasia and pleomorphism with necrosis and hemorrhage. Most patients with malignant cardiac tumors survive less than a year from diagnosis. Local excision of intracardiac tumors occasionally is successful, but the patients usually are left with residual disease.[412] Radiation and chemotherapy have been tried but are of limited value in these cases. Cardiac transplantation might result in improved survival in patients with inoperable cardiac tumors, but definitive data are lacking.

Malignant Mesothelioma of the Pericardium

Malignant mesothelioma originating on the pericardium is an exceptionally rare tumor; just over 100 cases (including children) have been reported in the literature.[413] Because of the rarity and age distribution of these tumors, no association has been made with asbestos exposure in most of the reported cases. The clinical presentation can include mediastinal mass, pericardial effusion, congestive heart failure, or tamponade.[413–416] Diffuse involvement of the pericardium with invasion of myocardium and mediastinal structures often is seen. The diagnosis of this tumor is rarely made or suspected before surgery or autopsy.[417–419] Surgical excision is rarely complete, and most cases rapidly become fatal. The role of radiation therapy or chemotherapy is not known.

POSTERIOR MEDIASTINAL TUMORS

Malignant Neural Crest Neoplasms

The overall incidence of tumors arising from the neural crest is low, but they are the most common tumors found within the posterior mediastinum (Fig. 77-13).[420] The neurogenic tumors encompass a

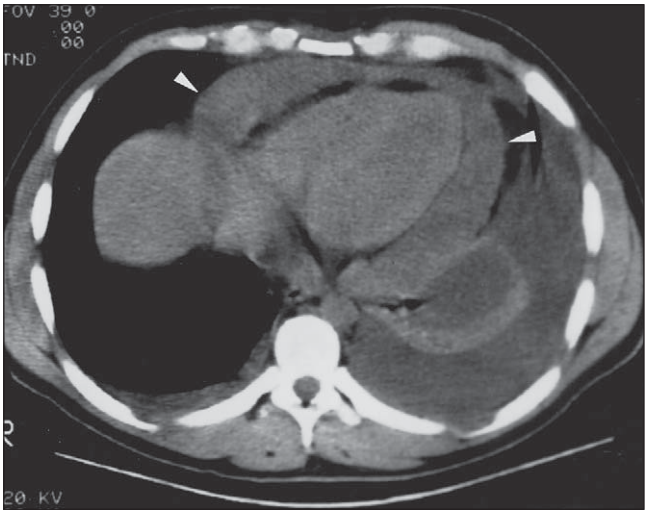


Figure 77-12 • The middle mediastinal mass was found to be malignant pericardial effusion. Enhanced CT image showing a large pericardial effusion *(arrowheads)* and bilateral pleural effusions, greater on the left than on the right. The collapsed left lower lobe is seen extending into the effusion at the left base.

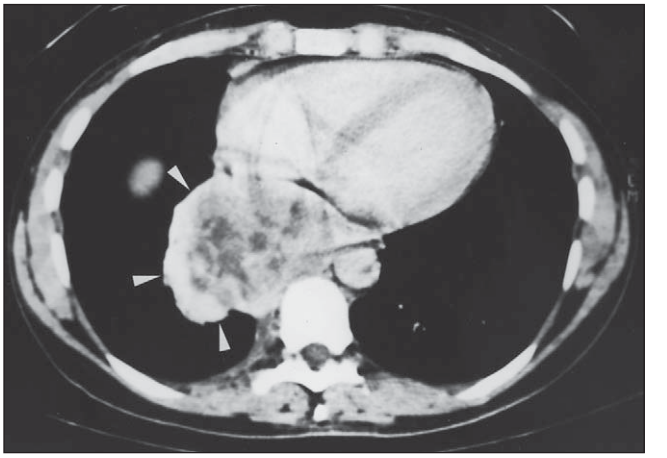


Figure 77-13 • Posterior and middle mediastinal mass that was found to be a neurogenic tumor. Enhanced CT image of the lower chest just above the level of the diaphragm showing a large mass *(arrowheads)* in the posterior mediastinum extending to the middle mediastinum with variable CT attenuation. Comparison with prior unenhanced CT image showed a strong enhancement of the mass.

wide and complex spectrum of neoplasms that occur in both children and adults. These tumors can range in their usual clinical behavior from benign (schwannoma) to highly aggressive (neuroblastoma). They commonly are solitary and asymptomatic but can cause constitutional symptoms such as cough, dyspnea, and pain with tumor enlargement. Children are more likely than adults to present with malignant disease with metastasis. Mediastinal tumors of the neural crest can be divided into two groups. One group of tumors arises from the neuronal cells, which include the nerve ganglion cells (ganglioneuroblastoma and ganglioneuroma) and the neuroendocrine cells (e.g., pheochromocytoma, paraganglioma). The second group arises from the neural sheath cells or the Schwann cells and includes schwannoma and neurofibroma.

Peripheral Primitive Neuroectodermal Tumor

Peripheral primitive neuroectodermal tumor (PNET; peripheral neuroepithelioma, Askin tumor, extraosseous Ewing's sarcoma) of the thorax can present either as a pleural-based mass or as a paraspinal posterior mediastinal mass. The clinical picture varies depending on the presence or absence of pleural effusion, rib destruction, or epidural spinal cord compression.[421] High fevers with other constitutional symptoms are usual accompaniments. These tumors usually occur in children or young adults and occur equally in males and females.[422] Histologically, these tumors are lobulated and have small, blue round cells with occasional rosettes. Electron microscopy reveals dense, neurosecretory granules and neurofilaments. The cells stain strongly for the antibody O13, demonstrating membranous positivity.[423] PNETs also may stain for neuron-specific enolase, synaptophysin, and Leu-7. They demonstrate high levels of choline-acetyl transferase but are devoid of catecholamine enzymes seen in neuroblastomas, such as dopamine decarboxylase and tyrosine hydroxylase.[421,424] Cytogenetically, PNETs demonstrate a consistent pattern of chromosomal translocation: rcp (11;22) (q24;q12).[425] Whether the altered regulation of synthesis of the proteins encoded by the cellular protooncogenes at the site of chromosomal translocations contributes to malignant transformation is not entirely clear.[426] Fluorescence in situ hybridization (FISH) probes directed at the EWS gene rearrangement now can be performed accurately on fixed and paraffin-embedded tissue.[427] In the past, a multimodality approach was used for the management of PNETs, but the median survival was only about 8 months despite the aggressive therapies. Radiation therapy (45–55 Gy) could produce shrinkage, but local recurrence was common. Metastases to the lung, bone, and bone marrow occurred with regularity.[428] Chemotherapy combinations of cyclophosphamide, doxorubicin, and vincristine (CAV) or CAV with actinomycin-D were used with some success, both as neoadjuvant therapy prior to local radiation therapy and wide surgical excision and to treat advanced metastatic disease.[421,429] High-dose chemotherapy with total body irradiation and autologous bone marrow transplantation was also attempted.[430] Recently, the combination of etoposide and cisplatin has shown somewhat better success in the treatment of this tumor, although large masses still are likely to recur and could require radiation therapy as part of combined modality therapy.[431]

Neuroblastoma, Ganglioneuroblastoma, and Ganglioneuroma

Neuroblastoma, ganglioneuroblastoma, and ganglioneuroma occur in children, although there are rare reports of these tumors arising in adults.[432–434] These tumors differ from each other only in terms of their degree of differentiation, with neuroblastoma being a high-grade, undifferentiated neoplasm and ganglioneuroma being a benign tumor possessing mature ganglion cells. Occasionally, these tumors present as masses in the posterior mediastinum rather than in their usual abdominal or widely disseminated presentation. When present in the thorax, these tumors are reported to have a better prognosis, possibly because of early detection due to the occurrence of symptoms.

Neuroblastoma

Neuroblastoma is the most common cause of mediastinal neurogenic mass in children and is a highly aggressive tumor thought to arise from primitive neural crest-derived cells called neuroblasts.[435,436] A thoracic presentation accounts for 15% of all cases of neuroblastoma, although it is seen predominantly in the very young. More than half of patients with mediastinal presentation already have disseminated disease.[437] The most common sites of metastatic involvement include lymph nodes, bone, liver, and subcutaneous tissues. The signs and symptoms depend on the site of dissemination. Mediastinal neuroblastoma usually occurs in the posterior compartment and usually is seen as an incidental finding on a chest radiograph obtained for other reasons. Occasionally, patients can present with cough, dyspnea, malaise, and spinal cord compression. Bone marrow involvement is common. The presence of the opsoclonus polymyoclonus syndrome—characterized by acute cerebellar and truncal ataxia and dancing eyes—could indicate a favorable prognosis. Amplification of n-myc has been seen in neuroblastoma and is associated with early disseminated disease.[438,439] DNA content assessed by flow cytomety also can be clinically useful as a predictor of response in unresectable disease.[438] A number of specific genetic changes, including a deletion in the short arm of chromosome 1 (1p-) and abnormalities in chromosome 17, have marked neuroblastoma as a paradigm for the study of molecular changes and cancer.[440] Therapy usually consists of a multidisciplinary approach, with surgery for localized disease and chemotherapy being the mainstay of treatment for those with disseminated disease.

Pheochromocytoma

Pheochromocytoma, a tumor of the autonomic nervous system, is a form of paraganglioma that both secretes and stores catecholamines. Extra-adrenal presentations are unusual, but the posterior mediastinum is the usual site of occurrence of intrathoracic pheochromocytoma. Pheochromocytomas also have been reported to occur in the middle mediastinum, with involvement of the cardiac atria and arch of the aorta.[19] The vast majority of all mediastinal pheochromocytomas are clinically benign but share histological similarities with their malignant counterparts.[441] Nuclear atypia and pleomorphism are the hallmarks of both benign and malignant tumors. Membrane-bound dense core neurosecretory granules (150–250 nm) are seen routinely with electron microscopy.[442] On immunohistochemical analysis, pheochromocytomas demonstrate neuron-specific enolase, chromagranin, synaptophysin, and corticotropin-like reactivity.[441,443,444] Metastatic disease is the only reliable benchmark for defining malignancy.[445] The malignant forms also can be locally aggressive and can metastasize to bone, lymph nodes, liver, lung, and brain. Clinically, patients with pheochromocytomas present with symptoms of catecholamine excess such as persistent hypertension, palpitations, headache, perspiration, orthostasis, chest pain, and constitutional symptoms.[446] Occasionally, cardiomyopathy can result from catecholamine excess. In addition to the usual diagnostic tests for mediastinal tumors, specific studies include measurement of urine and plasma catecholamines, ^{131}I-MIBG [I-131-meta-iodobenzylguanidine], scintigraphy, and pharmacologic tests using provocative agents such as glucagon, tyramine histamine, or suppressive agents (e.g., phentolamine and clonidine).[447]

Pheochromocytomas are managed with surgical resection, which can result in cure in some cases. Pharmacologic adrenal blockage preoperatively is achieved with phenoxybenzamine and subsequent beta-adrenergic blockade with propranolol, while short-acting phentolamine is reserved for management if hypertension arises. Sometimes a-methyl tyrosine may be used to decrease catecholamine synthesis. The 5-year survival of patients with malignant mediastinal

pheochromocytomas approaches 50%. The role of radiation therapy after surgical resection of malignant forms is not clear, although these tumors are relatively sensitive to radiation.[446] A number of chemotherapeutic agents have been tried for malignant pheochromocytoma with limited success; these include cyclophosphamide, vincristine, doxorubicin, dacarbazine, methotrexate, and streptozotocin.[448–450] Conceptually, ^{131}MIBG with high specific activity could have a therapeutic role in the management of malignant pheochromocytomas.[447,451]

Schwannomas and Neurofibromas

Schwannomas and neurofibromas derive from neural sheath cells (see Chapter 70). Together, they form a group with the highest incidence among all mediastinal tumors in adults and are the most common tumors seen in association with Von Recklinghausen's disease.[452,453]

Schwannoma and Malignant Schwannoma

Schwannoma (neurilemmoma) is a benign, encapsulated nerve sheath tumor that usually is solitary except when seen in association with neurofibromatosis (NF-1).[454] Schwannomas arise from Schwann cells of the cranial, spinal, or peripheral nerves.[453] The lung and heart are other sites of intrathoracic involvement.[455,456] Schwannomas tend to be slow-growing tumors, usually in the right side of the upper posterior mediastinum, and they rarely extend into the intervertebral foramina. Clinically, they usually do not cause any symptoms until, in rare cases, there is involvement of the vagus or phrenic nerve. On histopathologic examination, these tumors demonstrate an alternating pattern of palisading spindle cells (Antoni A) and loose myxoid hypocellular areas with scattered spindle cells (Antoni B). Immunohistochemistry demonstrates strong S-100 positivity.[457] They can be treated with simple surgical resection without sacrificing neural structures.[458]

Malignant schwannomas or malignant peripheral nerve sheath tumors are aggressive spindle cell neoplasms most commonly arising from nerve trunks in the posterior mediastinum or in the vagus or other peripheral nerves. They rarely result from malignant transformation of their benign counterpart but can arise from either degeneration of neurofibroma in neurofibromatosis (NF-1) or within the field of prior radiation therapy.[459,460] On histologic examination, these malignant tumors demonstrate a variably cellular spindle cell and myxoid neoplasm. Mitotic figures are seen easily. Occasionally, mesenchymal elements such as fat, cartilage, bone, and muscle are seen in malignant schwannomas.[461,462] In one study, MRI and pathologic correlation showed that a nonhomogeneous, high-intensity appearance of schwannomas on T_2-weighted images corresponded to alternating Antoni A and Antoni B areas, whereas a central, very-high-intensity region was noted in areas of cystic degeneration.[462] Immunohistochemical studies show S-100 variable positivity.[463] Clinically, in addition to symptoms due to mass effect, patients can present with pain and constitutional symptoms such as fatigue, weight loss, anorexia, and, occasionally, fever. The tumor advances locally, invading nearby structures such as the heart, great vessels, and vertebral bodies, and it can extend into the intervertebral foramina. Lung, liver, bone, skin, and serous surfaces are common sites of metastases. Surgical resection is the primary treatment.[464] The role of adjuvant radiation therapy is not well defined. This family of malignant tumors tends to be very resistant to chemotherapy, although some anecdotal responses have been seen with novantrone plus vinblastine and the combination of cyclophosphamide, ifosphamide, doxorubicin, dacarbazine, and vincristine.[465,466]

Neurofibromas

Neurofibromas also are believed to originate from the Schwann cell and, like schwannomas, they usually are solitary masses except when seen in association with neurofibromatosis (NF-1), tuberous sclerosis, Sturg-Weber syndrome, or von Hippel-Lindau disease.[467,468] They are slow-growing, benign tumors and can arise from any nerve. Clinically, they usually are asymptomatic until there is interspinal extension, resulting in signs of epidural cord compression. On histologic examination, the solitary forms are unencapsulated and consist of elongated wavy spindle cells separated by collagen and mucoid material. The plexiform variety, seen in patients with NF-1, involves expanded nerve trunks in a neurofibromatous background. Malignant transformation has been reported and is a serious complication of this disease.[453,469] On T_2-weighted MRI, high-intensity regions in the periphery of neurofibromas correspond to myxoid degeneration, and curvilinear or nodular areas of low signal intensity correspond to collagenous fibrous tissue. On immunohistochemistry, neurofibromas show S-100 reactivity and demonstrate the presence of cholinesterase. Surgical resection is the treatment of choice.

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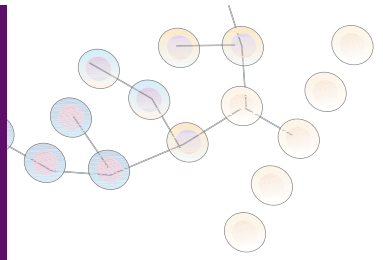
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78 Cancer of the Esophagus

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SUMMARY OF KEY POINTS

Classification

- Esophageal cancer is subdivided into the following four groups: epithelial tumors, metastatic tumors, lymphomas, and sarcomas.
- Cancers of epithelial origin, predominantly squamous cell carcinomas and adenocarcinomas, are the most common; other histologic types are rare.

Incidence

- Within the United States, the incidence of esophageal cancer in people younger than 80 years is 3.2 per 100,000 persons.
- Historically and internationally, squamous cell tumors are the most common histologic type; however, a dramatic increase in the incidence of adenocarcinoma has been documented in the United States, the United Kingdom, and western Europe.

Pathogenesis

- Exact etiology is unknown.
- The data support the hypothesis that epithelial tumors arise as a result of chronic irritation from a wide variety of sources, including gastric contents in chronic reflux and known carcinogens.
- A strong association of Barrett's esophagus and adenocarcinoma is seen, but a benefit to screening endoscopy for those who are at risk for or have known Barrett's esophagus is unknown, as the overall risk of cancer-related mortality is low. Studies with longer-term follow-up are needed to clarify this issue. Other identified risk factors are gastroesophageal reflux disease, obesity, and smoking.
- Squamous cell carcinoma is associated with smoking as well as alcohol use, and the declining incidence has paralleled the decline in smoking.
- Point mutations, increased copy number, and promoter region hypermethylation all appear to be important in the progression to malignancy.

Diagnosis and Staging

- Symptoms and demographics will strongly suggest the diagnosis.
- Endoscopy is the best screening examination, but esophagram may also be utilized.
- Diagnosis is made by endoscopy with cytology and biopsy of tumor.
- Transesophageal ultrasound should be used to assess T and N stage to guide optimal definitive therapy.
- Computed tomography (CT) of the chest and abdomen is useful in screening for metastatic disease.
- Positron emission tomography (PET) scan is useful to detect additional cases of metastatic disease before costly and toxic definitive therapy. PET may be superior to endoscopic ultrasonography in detecting intra-abdominal lymph nodes but not periesophageal nodes adjacent to the primary tumor.
- Additional studies include laparoscopy, thoracoscopy, bone scan, and CT of the brain when indicated by clinical circumstances.

Treatment

- Treatment of premalignant dysplasia is guided by grade of histology. Low-grade dysplasia should be closely followed by endoscopy. High-grade dysplasia is treated with esophagectomy, although close follow-up or endoscopic treatments might be appropriate for selected patients.
- Selection of appropriate treatment for carcinoma depends on tumor stage and patient performance status.
- Surgery is an accepted single-modality therapy for patients with localized disease (T1 to 3 N0 to 1 M01a). The selection of surgical approach depends on location and experience, but no approach has been demonstrated to lead to superior cure rates.
- Combined chemoradiation leads to prolonged median survival and long-term survival compared with radiation alone, at the price of increased toxicity. This represents a potentially curative alternative to surgery for squamous cell cancers and is appropriate for most unresectable T4 N(any) M0 lesions of either histology. As most patients treated on prospective chemoradiation trials had squamous cell carcinomas, the benefits of nonoperative management for adenocarcinoma are not known.
- Randomized trials have not confirmed a survival benefit with surgery added to chemoradiation in squamous cell carcinoma, but there was a significant local control benefit.
- Accumulating evidence, including multiple modestly powered randomized trials and meta-analyses, suggests that combination therapy with preoperative chemoradiation followed by surgery improves local control and may increase survival compared with surgery alone.
- Postoperative adjuvant chemotherapy or chemoradiation is less well studied in esophageal cancer, but trials in gastric cancer, including gastroesophageal junction adenocarcinoma, have demonstrated a benefit.
- Combined modality chemotherapy regimens frequently include 5-fluorouracil and cisplatin agents; other commonly used regimens include taxanes and irinotecan.
- Endoscopic palliative therapy includes laser or electrical fulguration, photodynamic therapy, or stenting. Except for very superficial lesions, these therapies are not alternatives to surgery, as they do not address deeper disease or lymphatic spread.
- Radiation therapy, with or without chemotherapy, may be used to palliate local symptoms.
- Chemotherapy may be used for metastatic disease, but response rates and duration of response are modest for most patients. Clinical trials are recommended.

INTRODUCTION

Carcinoma of the esophagus is a devastating disease associated with poor survival outcome and with adverse affects on swallowing and quality of life. Although esophageal cancer is an aggressive malignancy that usually presents in a locally advanced stage, significant progress has been made in the treatment of this disease, including expanded treatment options, decreased surgical morbidity and mortality, and improvements in identifying patients who are at risk. These advances are resulting in incremental improvements in outcome, but there remains considerable controversy over the optimal management under individual scenarios. The emphasis of this chapter is on selecting the appropriate options in the curative and palliative management of esophageal cancer.

CLASSIFICATION AND LOCATION

Esophageal cancer (Table 78-1) is classified on the basis of histologic appearance and cell of origin, as follows: (1) epithelial tumors, (2) metastatic tumors, (3) lymphomas, and (4) sarcomas. Cancers of epithelial cell origin, predominantly squamous cell carcinoma and adenocarcinoma, are the most common.

Squamous cell cancer usually occurs in the middle third of the esophagus. In a collective review of over 28,000 cases of squamous cell cancers, Postlethwait[1] estimated the ratio of upper, middle, and lower cancers to be 15 : 50 : 35, respectively. Adenocarcinoma, on the other hand, is most common in the lower third of the esophagus. In a collective review of 4783 cases of esophageal adenocarcinoma, Ming[2] noted an upper esophageal location in 4%, middle in 18%, and lower in 67%. Of the rare primary histologic types, 95% of small cell cancers occur in the middle and lower thirds; both malignant melanoma and choriocarcinoma tend to occur in the lower third. Esophageal sarcomas may occur anywhere along the esophagus, as is the case for esophageal lymphomas or metastases from other primary cancers.

INCIDENCE

Tumors of the esophagus other than squamous cell carcinoma and adenocarcinoma are very rare. This chapter therefore focuses on esophageal squamous cell carcinoma and adenocarcinoma. Epidemiologic data show that the incidence of esophageal cancer varies considerably from one country to another and often within a single country. The geographic diversity of esophageal cancer worldwide, of which over 90% are squamous cell cancers, underscores the multifactorial etiologies of this group of diseases. In the United States and other Western industrialized countries,[3–8] however, there has been a slight decline in squamous cell esophageal cancer over the past three decades and a dramatic rise in adenocarcinoma of the distal esophagus and gastroesophageal (GE) junction. This histology has increased in incidence approximately sixfold and, since the mid-1990s, has been the predominant esophageal cancer in Caucasians.[7] The absolute incidence in the United States has increased from 3.8 per million in 1973–1975 to 23.3 per million in 2001, according to the National Cancer Institute's Surveillance, Epidemiology and End Results database.[7] This rate of increase exceeds that of all other cancers, including lung, breast, prostate, and melanoma. Adenocarcinoma is much less common in African Americans but has increased from 0.4 per 100,000 to 0.9 per 100,000, and 0 to 0.2 per 100,000 in females. Obesity and gastroesophageal reflux disease (GERD) appear to contribute to this rise in adenocarcinoma incidence. In contrast, the incidence of squamous cell carcinoma decreased in all of these groups during this period, perhaps owing to a decline in the prevalence of smoking and increased consumption of fresh fruits and vegetables.[9]

Table 78-1 Classification of Esophageal Cancer

EPITHELIAL
Squamous cell carcinoma
Ordinary squamous cell
Verrucous squamous cell
Spindle cell (carcinosarcoma)
Adenocarcinoma
Ordinary
Adenoacanthoma
Mucoepidermoid
Adenoid cystic
Small cell
Melanoma
Choriocarcinoma
METASTATIC DISEASE
Lymphoma
Sarcoma

PATHOGENESIS

Data support the hypothesis that epithelial esophageal tumors arise as a result of chronic irritation and inflammation of the esophagus leading to a sequence of genetic alterations in the damaged epithelium and histologic changes of dysplasia to carcinoma. The geographic and demographic distributions of esophageal cancer vary widely. Whether this variance can be explained solely by environmental factors or whether a genetic component exists as well is conjectural. The most commonly reported irritants include tobacco, alcohol, dietary factors, lye, radiation, and refluxed bile salts and gastric contents. There are important differences between the risk factors, histologic progression, and molecular events that support the concept that squamous cell carcinoma and adenocarcinoma should be considered as separate entities with potential to respond differently to newer treatment approaches. These differences are highlighted in the following sections.

Clinical Risk Factors

Tobacco smoking is a proven etiologic factor in the development of squamous cell esophageal cancer for both men and women according to epidemiologic studies from various countries worldwide. This relationship is dose-dependent, and the risk of esophageal cancer decreases with smoking cessation. Smokeless tobacco products have also been shown to correlate with an increased risk of cancers of the mouth, larynx, throat, and esophagus.[10] There is also a multiplicative interaction of alcohol intake and tobacco use.[11–14] In a study from Taiwan, the strongest risk for squamous esophageal cancer was alcohol consumption, with a 13.9-fold increased risk, while combined exposure with smoking increased the risk to nearly 20-fold.[11]

A prospective study of tobacco, alcohol, and risk of esophageal squamous cell carcinoma and adenocarcinoma in the United States found an increased risk of squamous cell carcinoma among current smokers compared with nonsmokers (hazard ratio (HR): 9.27, 95% confidence interval (CI): 4.04, 21.29) and also an increased risk for adenocarcinoma (HR: 3.70, 95% CI: 2.20, 6.22). For people who drink more than three alcoholic beverages a day compared to one drink, there was increased risk of esophageal squamous cell carcinoma but not adenocarcinoma of the esophagus, GE junction, or cardia.[13] The association of adenocarcinoma with smoking, though much less

striking than that of squamous cell carcinoma, appears to remain elevated for more than 30 years after smoking cessation.[15]

Other factors that are associated with an increased risk of squamous cell esophageal cancer are lye ingestion, radiation therapy (RT), achalasia, Plummer-Vinson syndrome, and previous head and neck squamous cell cancer. The interval between injury and the development of cancer may be considerable in patients who sustain lye ingestion or are irradiated.

Nutritional and dietary factors have been evaluated in an attempt to explain the worldwide variability in the incidence of squamous esophageal cancer. Ghadirian and colleagues[16] reported that the populations with the highest incidence of esophageal cancer shared dietary characteristics, including a rapidly consumed high-starch diet with few or no fruits and vegetables. Many dishes consist of granular foods or foods that are served quite hot, both of which irritate the esophagus.[16] Associations between fruit and vegetable intake and esophageal cancer risk have been found for both squamous cell carcinomas and adenocarcinomas of the esophagus and aerodigestive tract cancers in general,[17,18] some data suggesting that this relationship might vary according to histologic type.[19] For example, risk factors for esophageal, gastric cardia, and noncardia gastric cancers in Linxian, China, which has one of the highest rates of these cancers in the world, were prospectively evaluated in a population-based study of over 25,000 adults performed by the National Cancer Institute.[20] After 15 years of follow-up, improved socioeconomic status seemed to be a common factor for lowering risks for all three sites. Protective factors for esophageal squamous cell cancer included formal education; water piped into the home; and increased consumption of meat, eggs, and fresh fruits. A study in Sweden that controlled for other risk factors assessed the importance of three diets as a risk factor: "healthy diet" (high in vegetables, tomatoes, fruits, fish, and poultry), "Western diet" (high in processed meat, red meat, sweets, high-fat dairy, and high-fat gravy), and "alcohol drinker" (high in intakes of beer, liquor, and French fries). A Western diet was associated with increased risks of gastric cardia adenocarcinoma (high third tertile versus low first quartile, odds ratio [OR]: 1.8, 95% CI: 1.1 to 2.9, *P* for trend: 0.04) and esophageal adenocarcinoma (high third tertile versus low first tertile, OR: 1.6, 95% CI: 0.9 to 3.1, *P* for trend: 0.13), whereas a dietary pattern characterized by high beer and liquor intake (alcohol drinker) significantly increased the risk of squamous cell carcinoma of the esophagus (third tertile versus low first tertile, OR: 3.5, 95% CI: 1.9 to 6.3, *P* for trend: <0.0001).[21]

The increased risk of adenocarcinoma over the past several decades, primarily in Western nations and among white males, is attributable to a combination of factors, including obesity,[22] diets low in vegetables and high in processed and red meat, and a close association with GERD and Barrett's esophagus (BE).[23,24] Obesity, defined as a body mass index of 30 or greater, is a strong risk factor for esophageal adenocarcinoma, as is demonstrated in epidemiologic studies in the United States and Sweden.[14,22] The relative risk of adenocarcinoma was increased 7.6-fold for obese individuals compared to lean individuals (body mass index <22) in a study from Sweden.[14] This has clear implications for the increasing obesity rates in the United States and could in part explain the rising incidence of esophageal adenocarcinoma. The exact mechanism for this association of obesity is not understood but might reflect an increased propensity for GERD.

Further study to identify the individuals who are at highest risk and to understand the molecular progression from BE to dysplasia and invasive malignancy could lead to effective strategies for screening or prevention. Squamous cell carcinoma generally arises in a sequence through normal epithelium to atypia onto malignancy. The initial change is characterized by epithelial proliferation, followed by development of dysplasia, then carcinoma in situ. Esophageal adenocarcinoma frequently arises in BE, a metaplastic columnar epithelium that develops in the esophagus, generally as a result of injury from chronic reflux. As is described in the following sections, there is then progression through low- and high-grade dysplasia to invasive malignancy, which may be within or adjacent to dysplastic columnar epithelium or may replace it.

Adenocarcinoma: Role of Gastroesophogeal Reflux Disease and Barrett's Esophagus

Gastroesophageal reflux disease is a well-established risk factor for esophageal adenocarcinoma.[23,24] A population-based case-control study that was performed in Sweden demonstrated a relative risk of 7.7 for development of esophageal cancer in patients with chronic reflux disease.[23] With longstanding, severe symptoms, the relative risk was 43.5. Similar increases in risk were not observed for esophageal squamous cell carcinoma or adenocarcinoma of the gastric cardia. Interestingly, the increased risk of esophageal carcinoma existed whether or not BE could be identified, leading the authors to speculate that GERD might cause esophageal adenocarcinoma by a mechanism independent of BE. An alternative explanation might be that the area of BE in these patients was overgrown by tumor.[25] It remains controversial whether treating reflux in the setting of BE will significantly reduce or eliminate the risk of adenocarcinoma. The role of screening for BE is unknown.[26] According to the American College of Gastroenterology practice guidelines, a one-time endoscopic examination could be prudent to rule out BE in patients with chronic GERD, especially in the highest-risk population: white males. The value of this approach has been questioned by those who point out that BE is uncommon, progression to malignancy is infrequent, and the effect on overall population mortality appears quite low. These data are summarized following, and screening with endoscopy is further discussed later in this chapter.

There is a clear relationship between BE and dysplasia and neoplasm.[27] BE refers to a condition in which the normal stratified squamous mucosa is replaced by columnar-lined epithelium that extends upward from the esophagogastric junction. Various lengths of esophagus may be involved. The condition is an acquired, metaplastic process that develops in response to an esophageal mucosal injury that heals in the setting of the inflammatory stimulus of continued GE reflux. BE may progress to dysplasia and then malignancy as the dysplastic epithelial cells accumulate genetic alterations.

The incidence of BE is not known, although reports range from 1% to 2% of the general population. Miros and colleagues[28] prospectively followed 81 patients with BE. Three patients developed adenocarcinoma: two with antecedent high-grade dysplasia and one with low-grade dysplasia. No patient without dysplasia developed adenocarcinoma. The length of time for the progression from high-grade dysplasia to adenocarcinoma is unknown. Because the lifetime risk may be as high as 8% to 15% or 0.5% to 1% per 50 patient years, many advocate lifelong endoscopic surveillance for patients with Barrett's mucosa with the goal of treating dysplastic changes and thereby reducing the risk of developing adenocarcinoma. Indeed, tumors that are discovered during surveillance appear to be of an earlier stage and therefore to have a higher chance of cure.[29,30] Still, it is not certain whether surveillance reduces mortality; the overall risk of death from esophageal cancer is relatively low even in this high-risk population.[26,31,32]

Several centers have reported results of endoscopic screening that suggest that progression of BE to esophageal cancer might be less common than was originally thought, at least in the short term. A Veterans Administration study of patients requiring therapy for reflux disease found a 0.4% per patient-year risk in patients with BE and 0.07% per year in those without BE.[33] A study of 60 patients with a new diagnosis of BE followed for a median of 10 years (range: 5 to 15 years) demonstrated that 3% developed esophageal cancer and 15% developed other cancers, with no significant difference in life expectancy compared with the general population.[31] There is uncertainty about the actual risk of esophageal adenocarcinoma in individuals with GERD, estimates ranging from a 30-fold to a 125-fold increase in risk. In the setting of confirmed BE and surveillance,

progression to esophageal adenocarcinoma is estimated as 1 per 250 patient-years, or 0.4% per year. These uncertainties are in part due to the problem of sampling error when biopsies are performed during endoscopy and to a high degree of interobserver variability in dysplasia grading.[34] Thus, the current method for detecting esophageal cancer early in at-risk individuals through endoscopic screening and biopsy has low sensitivity and is controversial.

Approximately two thirds of patients who develop adenocarcinoma have histologic evidence of BE[35–37]; however, an estimated 40% will give no clear-cut history of GERD. Thus, screening endoscopy of individuals with symptomatic GERD will still miss the substantial proportion of individuals who do not report reflux symptoms.[38]

Although there has been much progress in unraveling the relationship between Barrett's mucosa, dysplasia, and esophageal adenocarcinoma, there are still many unanswered questions, such as why Barrett's mucosa is seen in such a specific demographic pattern, and what is the trigger to initiate the progression to dysplasia and carcinoma.

Molecular Progression to Adenocarcinoma

Molecular genetic data support the histologic observation that there is a progression from normal epithelium to BE to dysplasia to adenocarcinoma.[39,40] Although a clearly defined sequence of genetic alterations leading to adenocarcinoma has not been defined, an accumulation of abnormalities has been identified in a wide range of genes that regulate proliferation, apoptosis, invasion, metastasis, angiogenesis, growth, and cell cycle regulation. Tumor suppressor genes such as p53 and p16 have been implicated as early events, as loss of cell cycle checkpoints may be permissive for genetic instability, allowing later transformation in the metaplasia-dysplasia-adenocarcinoma sequence.[39,41,42] Moskaluk and colleagues[43] performed immunohistochemical staining for p53, an important regulatory gene in cell cycle control and apoptosis, and p21/WAF1, a cyclin-dependent kinase inhibitor, in 98 adenocarcinoma esophagectomy specimens. They found similar p53 and p21 WAF1 expression in adenocarcinoma specimens with and without associated Barrett's mucosa, and they concluded that the molecular mechanism of carcinogenesis for these two groups is the same. Wu and colleagues[44] investigated DNA replication errors and allelic losses of chromosomes 17p, 18q, and 5q in esophageal adenocarcinoma (without associated Barrett's mucosa), Barrett's adenocarcinoma, and Barrett's mucosa with dysplasia. More recently, Barrett and colleagues[45] have reported that alteration in p53 and p16 are generally seen throughout an area of Barrett's abnormality, suggesting that these abnormalities were inherent in the original clonal development of BE. Additional mutations involving loss of heterozygosity at 5q, 13q, or 18q occurring in no particular order appeared to be important in the bifurcation into aneuploidy and onto progression into neoplasm.[45] Wong and colleagues[46] focused on the role of p16 inactivation and found that more than 85% of BE clones had inactivation of one or both p16 alleles by loss of heterozygosity (53%), hypermethylation (61%), and point mutation (15%). The loss of cell cycle regulation from these early changes may promote DNA instability, leading to additional changes required for progression to malignancy. Interestingly, in patients with Barrett's mucosa that harbor p16 +/− or p16 −/− alterations, the prevalence of other abnormalities, including 17p (p53) LOH, aneuploidy, or tetraploidy, can be 44% higher than that in patients without any p16 loss in their esophageal mucosae. In addition, the median length of Barrett's mucosa increased from 1.5 in patients without p16 loss to 6.0 to 8.0 cm in those with p16 abnormalities. This again suggests that p16 might be an important step in the field change leading to Barrett's epithelium and invasive cancer.[46]

There appears to be a diversity of molecular abnormalities in esophageal cancer that are caused by actual genetic mutations, epigenetic inactivation, and altered cell regulation. Lagarde and colleagues have reviewed many of the abnormalities of in gene expression in esophageal cancer, which occur in a wide variety of genes, such as cyclin D1, EGFR, Her-2/Neu, APC, TGF-β, Endoglin, CTGF, P53, Bcl-2, NF-kappaB, Cox-2, E-cadherin, beta-catenin, uPA, MMP-1,3,7,9, the TIMP family, T(h)1/T(h)2 balance, CRP, and PTHrP.[41,47] The method of identifying and codifying alterations in these genes into a clinically useful paradigm has not yet proved superior to standard histology for predicting outcome, but more complex analyses using sophisticated molecular techniques such as genomic arrays could be helpful in the future. In the meantime, new molecular abnormalities continue to be identified.[48]

In the last decade, epigenetic modifications have emerged as heritable and fundamental features of most malignancies.[49] The best-studied epigenetic modification of the DNA is promoter region hypermethylation, an epigenetic modification that is associated with gene inactivation. A meaningful understanding of the molecular events that lead to progression to adenocarcinoma will likely require a greater understanding of this phenomenon as it occurs at least as frequently as point mutation. DNA hypermethylation is biologically important in development where it is associated with the inactivation of genes on the X chromosome. In oncogenesis, hypermethylation is often associated with inactivation of tumor suppressor genes, of genes that suppress metastasis and angiogenesis, as well as of genes that repair DNA. Methylation of DNA occurs mostly at CpG sites in the genome and is catalyzed by a family of three active DNA methyltransferases that transfer a methyl group from S-adenosyl-methionine to cytosine to form 5-methylcytosine. Because this reaction can be blocked effectively by a drug, 5-azacytidine, which acts as an irreversible inhibitor of the DNA methyltransferases, the therapeutic potential inherent in reversing DNA hypermethylation is significant.[50]

In esophageal adenocarcinoma, CpG-island methylation at CDKN2A/p16INK4a has been implicated in the progression of BE to malignancy with 38% of premalignant and malignant lesions demonstrating this abnormality. Eads and colleagues[51,52] reported results for 31 normal esophagus specimens and 22 adenocarcinoma specimens. The following genes were observed to be methylated in a substantial portion of esophageal cancer specimens but less often in normal esophagus from the same patients (percent tumor versus percent normal specimens): CDKN2a/p16 (41% versus 0%), ESR1 (86% versus 0%), MYOD1 (45% versus 0%), TIMP3 (86% versus 19%), APC (68% versus 3%), and CALCA (50% versus 13%). Others have found that CDH1 is methylated with substantially greater frequency in adenocarcinoma than in normal esophagus, BE, or dysplasia. In contrast to colon cancer, in which point mutations of CDKN2a/p16 are frequent, such mutations are rarely found in esophageal adenocarcinoma, and methylation predominates. Hypermethylation of various genes is also prevalent in esophageal dysplasia. Of note, APC was found to be methylated in normal stomach in 12 of 12 specimens.[52] MGMT was methylated in 55% of normal esophagus specimens, 73% of adenocarcinoma specimens, and 25% of stomach specimens. Hypermethylation of nel-like 1 gene[53] and DAPK[54] is uncommon in normal esophagus but is found in 40% to 60% of BE, dysplasia, and esophageal adenocarcinoma specimens and is associated with poorer prognosis, whereas MGMT hypermethylation has not been associated with prognosis.[53,55,56]

A study at Johns Hopkins found methylation[57] frequencies of the genes APC (68%), E-cadherin (66%), O6-methylguanine DNA methyltransferase (56%), ER (51%), p16 (39%), DAP-kinase (19%), and TIMP3 (19%).[57] Analysis of DNA methylation of these genes individually showed only trends toward diminished survival, whereas patients whose tumors had more than 50% of their gene profile methylated had both significantly poorer survival ($P = 0.04$) and earlier tumor recurrence ($P = 0.05$) than those without positive methylation. By multivariate analysis, the hazard ratios (HRs) with positive methylation status were more powerful predictors of survival (HR: 2.7 [1.14 to 6.45, 95% CI]) and tumor recurrence (HR: 2.5 [1.11 to 5.6]) than was age (HR: 2.03 and 1.96, respectively) or stage (HR: 1.48 and 1.67, respectively).

Molecular Steps to Squamous Cell Carcinoma

Gene expression profiling studies have delineated some important differences between adenocarcinoma and squamous cell carcinoma. A comparison of adenocarcinoma, squamous cell carcinoma, BE, and normal esophagus suggested that both histologies had upregulation of genes commonly involved in carcinogenesis such as cell cycle regulators, extracellular matrix genes, immune response genes, kallikreins, and serine protease inhibitors with downregulation of genes related to calcium ion binding and gap junctions.[58] Despite these similarities, other aspects of the gene expression profile of squamous cell carcinoma were more closely related to normal esophagus, whereas adenocarcinoma was more closely related to the profile identified in BE.

As with adenocarcinoma, there exists great complexity in the molecular events that are involved in progression to squamous cell carcinoma. Loss of heterozygosity of Rb, p53, and CDKN2A/p16INK4a has been identified as a common event. Methylation, although less well studied in squamous cell cancer than in adenocarcinoma, appears to play an important role.[59] At Johns Hopkins, Guo and colleagues used a panel of methylation markers, including p16, MGMT, MLH1, APC, BRAC1, RAR, CDH1, and DAPK, to suggest that there was a tendency for each of these genes to be methylated at higher frequencies as the grade of the lesion increased through dysplasia to malignancy.[59] The conclusion was that accumulation of DNA methylation changes suggests epigenetic progression and that this progression parallels visible histologic changes that are observed as squamous dysplasia progresses to frank carcinoma. In this study, the most commonly methylated gene was p16 (52%). Interestingly, the rates of methylation for more than one and two genes was 29% and 0%, respectively, for normal esophagus; 56% and 56%, respectively, for high-grade dysplasia; and 91% and 70%, respectively, for carcinoma.[59] Wu has extensively reviewed methylation of individual genes in adenocarcinoma and squamous cell carcinoma, but the limitations of the currently available data do not allow for definitive identification of any differences.[60] Ischii and colleagues[61] have also reported that for a large panel of promoter regions, there was a higher tendency toward methylation of many of the candidate genes in carcinoma and intraepithelial neoplasm than in the adjacent nonepithelial neoplasm. The data from Ishii and colleagues corroborate the findings of Guo and colleagues of an accumulating progression of DNA methylation changes on top of a background of low-level DNA methylation in nonneoplastic esophageal epithelium.[61,62] Interestingly, in the same study, p53 mutations occurred almost exclusively in intraepithelial neoplasm (57%) or carcinoma (63%) and in only 4% of adjacent nonneoplastic mucosa.

The possibility of detecting hypermethylated DNA in circulating plasma and serum has also been investigated in squamous cell cancer. This ultimately could play a role in early detection and/or following response to therapy. For example, in one study, hypermethylation of the APC gene in tissue occurred in 48 of 52 patients (92%) with esophageal adenocarcinoma, in 16 of 32 patients (50%) with esophageal squamous cell carcinoma, and in 17 of 43 patients (39.5%) with Barrett's metaplasia but not in matching normal esophageal tissues.[62] In the plasma of these patients, hypermethylated APC DNA was observed in only 13 of 52 adenocarcinoma patients (25%) and in 2 of 32 squamous cell carcinoma patients (6.3%). High plasma levels of methylated APC DNA were statistically significantly associated with reduced patient survival in this study ($P = 0.016$).[62] In another study, aberrant promoter methylation of the p16 gene was detected in the tumor tissue of 31 of 38 patients (82%) with esophageal squamous cell cancer.[63] In subsequent testing for p16 promoter methylation in the paired serum DNA of 31 patients with a p16 methylated in the primary tumor, only 7 of these 31 patients (23%) had the same methylation changes in the serum DNA.[63] In another analysis, preoperative blood samples were obtained from 44 esophageal squamous cell cancer patients and were subjected to CEA-specific reverse transcriptase polymerase chain reaction assay and methylation-specific polymerase chain reaction (MSP) assay for p16, E-cadherin, and RAR-β gene methylation. Circulating tumor cells were detected in 12 patients (27%), and 14 patients (32%) had aberrant methylation in the promoter region of at least one gene (6, 4, and 4 patients for p16, E-cadherin, and RARbeta, respectively). No abnormality was detected by either assay in control plasmas. Altogether, 23 patients (53%) had a positive result with either molecular assay.[64]

OVERVIEW: THE CHOICE OF THERAPY

The primary goals of therapeutic interventions for esophageal cancer are to relieve symptoms (predominantly dysphagia) and to treat the underlying cancer. An ideal therapy would accomplish both, safely and effectively. Currently, three main treatment strategies exist. The first utilizes endoscopic palliative techniques to control the tumor locally for the purpose of palliation, the second uses single modalities (e.g., surgery, radiation, or chemotherapy), and the third involves intensive combination therapies aimed at cure. There is substantial controversy about the optimal management of curable (localized) esophageal cancer; the treatment options include surgery alone, chemotherapy followed by surgery or adjuvant chemotherapy after resection, chemoradiation followed by surgery, and definitive chemoradiation. Radiation alone as definitive treatment aimed at cure is inferior to combined chemoradiation for locally advanced disease and should be considered only when the other options are not feasible. Similarly, RT used in the adjuvant or neoadjuvant setting has not been shown to improve outcome. These options and the supporting data are summarized in Table 78-2. The survival outcome of patients with localized disease who were enrolled in selected randomized controlled trials is summarized in Table 78-3 according to treatment group. The median survival ranges from 9.0 months for patients in RT-alone control groups to as long as 19 months for those receiving preoperative chemoradiation. A statistically significant 10% to 15% improvement in survival rate with any of these approaches would be of major importance. As Table 78-3 shows, the median survival rates with surgery, definitive chemoradiation, and preoperative chemotherapy or preoperative chemoradiation do not clearly differ, although selection factors might have varied substantially among the trials.

Surgery is a standard treatment option, and there are substantial data, although not a definitive randomized controlled trial, supporting the hypothesis that preoperative chemoradiation (trimodality therapy) improves outcome over that achievable with surgery alone. Preoperative chemotherapy has been evaluated in randomized controlled trials with conflicting results among U.S. and non-U.S. trials. It is not a standard of care or common practice in the United States. On the other hand, definitive chemoradiation is a potentially curative alternative to surgery and is indicated for patients with unresectable primary tumors or inoperable disease due to medical comorbidities.

Given the lack of comparative data to demonstrate the superiority of any of one approach for resectable disease, clinical decision making for optimal management is complex and controversial. Surgery as a single therapeutic modality is the appropriate management for early-stage disease (stages I and IIA); however, for more advanced disease (stages IIB, III, and IVA), combined-modality therapy, specifically preoperative chemoradiation with its associated risks of toxicity but potential for improved long-term survival, is frequently utilized. (See Table 78-4 for stage definitions.) The available data from phase II trials, underpowered phase III trials, and meta-analyses indicate improved local control and suggest a survival benefit on the order of 10%. However, an adequately powered, randomized controlled trial has not been conducted to validate the observations from phase II clinical trials, and it is unlikely that such a trial will be performed in the United States. Commonly used preoperative chemoradiation regimens are associated with substantial toxicity; therefore,

Table 78-2 Options in the Therapy of Esophageal Carcinoma

Treatment	Recommendation
SINGLE MODALITY	
Surgery	• Accepted standard for resectable AC and SCCa
Radiotherapy	• Recommended for high-grade dysplasia and stage I carcinoma
	• Definitive treatment of inoperable patients unsuitable for chemoradiation
	• Palliation of obstructive symptoms
COMBINED MODALITY	
Definitive chemoradiation	• Inoperable SCCa and selected resectable SCCa
Preoperative chemotherapy	• Inoperable AC
Preoperative chemoradiation	• Investigational
	• Preferred approach for resectable SCCa and AC
POSTOPERATIVE ADJUVANT THERAPY	
Following preoperative chemotherapy or chemoradiation	• No demonstrated benefit
Following surgery alone	• R0 resection: no demonstrated benefit for adjuvant radiotherapy, chemotherapy, or chemoradiation for SCCa; potential benefit for AC based on gastric trial data
	• Microscopic or gross residual tumor: consider chemoradiation in good performance status patients or radiation indicated

AC, adenocarcinoma of the distal esophagus and gastroesophageal junction; SCCa, squamous cell carcinoma.

Table 78-3 Results from Treatment Arms from Selected Recent Randomized Trials

Randomized Trial	1-Year Survival Rate (%)	2-Year Survival Rate (%)	3-Year Survival Rate (%)	5-Year Survival Rate (%)	Median Survival (Months)	Local Failure (%)
SURGERY						
U.S. Intergroup[66,174]	60	37	26		16.1	59
MRC[65]		34			13.3*	37
Bosset et al.[179]					18.6	
Walsh et al.[186]	42	26	6		11*	
Urba et al.[176]	58		16		17.6	52*
RADIOTHERAPY						
RTOG[178,208,209]	34	10	0	0	9.3*	68*
ECOG (surgery added in 24/56)[210]	33	12	8	7	9.2*	
CHEMORADIOTHERAPY						
RTOG[178,208,209]	52	36	30	26	14*	46*
RTOG (nonrandomized confirmatory group)[178,208,209]	62	35	26	14	16.7	58
ECOG (surgery added in 21/58)[210]	54	27	13	9	14.8*	
Bedenne et al.[214]		37			17.7	
Stahl et al.[67]		35	24		15	
PREOPERATIVE CHEMOTHERAPY						
U.S. Intergroup[66,174]		35			14.9	58
MRC[65]		43			16.8*	27
PREOPERATIVE CHEMORADIOTHERAPY						
Walsh et al.[186]	52	37	32		16*	
Bosset et al.[179]					18.6	
Urba et al.[176]	72		30		16.9	23*
Bedenne et al.[214]		37			19.3	
Stahl et al.[67]		39	31		16	

*Significant difference between respective arms in these trials.

Table 78-4 TNM Staging for Esophagus

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
CLASSIFICATION OF DISTANT METASTASES	
Tumors of the lower thoracic esophagus	
M1a	Metastasis in celiac lymph nodes
M1b	Other distant metastasis
Tumors of the midthoracic esophagus	
M1a	Not applicable
M1b	Nonregional lymph nodes and/or other distant metastasis
Tumors of the upper thoracic esophagus	
M1a	Metastasis in cervical nodes
M1b	Other distant metastasis

STAGE GROUPING			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
	T3	N0	M0
Stage IIB	T1	N1	M0
	T2	N1	M0
Stage III	T3	N1	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

trimodality therapy should be used cautiously in patients with poor performance status or comorbid conditions that increase the risk of life-threatening toxicity. There are no data to support the notion that chemoradiation is useful to convert an unresectable lesion into a resectable lesion.

Preoperative chemotherapy has less associated toxicity than does preoperative chemoradiation and is the favored combined modality approach in the United Kingdom, stemming from a survival benefit that was demonstrated in a randomized controlled trial conducted in the United Kingdom by the Medical Research Council (MRC).[65] By contrast, a similarly designed U.S. Intergroup trial found no advantage over the surgery control group; hence, this approach is considered experimental in the United States.[66]

Definitive chemoradiation eliminates the risk of surgery but at the cost of inferior local control and disease-free survival compared to trials of trimodality therapy.[67] In evaluating clinical trial results, though, it is important to consider selection factors that might be at work: chemoradiation may be selected for patients with more advanced lesions, unresectable disease, or with significant comorbid disease leading to inoperability, a population that is less likely to achieve long-term survival. Definitive chemoradiation has been studied in patients with esophageal squamous cell carcinoma, a population with a high prevalence of cardiopulmonary and hepatic disease from excessive tobacco and alcohol use, which increases operative risks. In contrast, nonsurgical treatment aimed at cure has not been adequately tested in patients with resectable adenocarcinoma and therefore cannot be recommended for this histology.

The role of adjuvant therapy after complete surgical resection has not been as well studied as preoperative therapies. For patients who are undergoing immediate surgery, data to support adjuvant chemoradiation is extrapolated from gastric trials that included a minority of patients (about 20%) with GE junction primaries. At best, these data showing significant improvement in survival for patients with gastric cancer but not powered to look at site-specific subsets provide a rationale for additional treatment for resected patients with adenocarcinoma of the distal esophagus or GE junction, stages IIB, III, or IVA. Adjuvant RT has been studied and shown not to be beneficial, whereas there are insufficient data on adjuvant chemotherapy to recommend its use. In patients who are undergoing primary surgery with microscopic or gross residual disease, postoperative chemoradiation should be considered if it is tolerable.

When palliation of obstructive symptoms rather than cure is the goal, several options exist. These include RT with or without chemotherapy and the endoscopic therapies of stent placement, laser therapy, and photodynamic therapy (PDT). The choice of palliative treatment is influenced by the severity of symptoms, patient performance status, expected survival time, and physician expertise. When survival expectations exceed a few months, palliation with radiosensitizing chemotherapy and concurrent radiation limited to the tumor bulk may provide more durable symptomatic relief. RT may also be added after endoscopic palliation to increase the durability of local palliation for patients who are likely to survive more than 3 to 6 months.

For metastatic disease, chemotherapy is indicated, with the goal of improving survival and preventing or treating symptoms at all locations. Given the modest response rate and brief duration of response with available regimens, chemotherapy alone has limited ability to effectively palliate obstructive symptoms.

DEFINITIVE TREATMENT OPTIONS

Diagnostic Evaluation

The most common presentation of esophageal carcinoma includes solid food dysphagia and weight loss of several months' duration. Other presentations that occur with esophageal adenocarcinoma in particular include chest pain in the absence of myocardial ischemia and anemia from a chronic gastrointestinal (GI) bleed from the mucosal lesion. These clinical signs and symptoms should prompt endoscopic evaluation and diagnostic imaging. The diagnosis is usually evident by the characteristic narrowing of the esophagus on barium esophagram, but endoscopy and biopsy are essential for histopathologic diagnosis. Endoscopic biopsies and brushings of the lesion will yield the diagnosis in more than 90% of patients. Multiple biopsies might be necessary to obtain the diagnosis of an invasive malignancy that is submucosal or necrotic.[68] A diagnosis of in situ carcinoma in the face of a large lesion seen on radiographic studies should not be accepted, and biopsy should be repeated.

Once the pathologic diagnosis has been established, evaluation to determine the extent of disease should include a computed

tomography (CT) scan of the chest and complete abdomen. The chest CT is useful for evaluating lung parenchyma and mediastinal structures.[69] Lymph nodes that are more than 1 cm in diameter or have necrotic centers suggest metastatic involvement. The chest CT also is helpful for assessing aortic or pericardial invasion of tumor that would preclude esophagectomy. In contrast, the actual length of the esophageal lesion is better assessed on the barium esophagram.

The accuracy of identifying metastases to the liver and celiac axis by abdominal CT depends on the bulk of the disease. Small liver metastases, peritoneal studding, and abdominal nodes will often be undetectable.[69–75] For squamous cell lesions of the upper and mid-thoracic esophagus, a CT scan of the upper abdomen that includes the liver and adrenals is sufficient. For the patient with an adenocarcinoma of the distal esophagus, GE junction or cardia, a complete abdominal-pelvic CT is necessary to visualize potential areas of nodal metastases. Cancers of this histologic type are more likely to metastasize early to periaortic lymph nodes. A complaint of back pain might signal the presence of enlarged retroperitoneal nodes.

Positron emission tomography (PET) scanning enables the identification of metastatic disease in patients who might otherwise inappropriately receive definitive local therapy and therefore is now considered a standard if not mandatory staging test. Prospective studies [76,77] demonstrated that PET will detect unsuspected metastatic disease in approximately 15% of patients after all other staging tests are completed, although it is not as useful as other techniques in identifying involved regional nodes. A prospective study of 79 patients[76] found that the specificity and sensitivity of PET for identifying stage IV disease was 90% and 74% versus 47% and 78% for the combination of CT and endoscopic ultrasonography (EUS), with an overall accuracy of identification of stage IV disease of 82% versus 64% ($P = 0.004$). Furthermore, when PET was added to CT and EUS, 22% of patients had a change in stage that altered their planned treatment (15% upstaged to incurable stage IV disease, and 7% downstaged to a stage at which curative therapy would be appropriate). Other investigators have confirmed that PET scanning will change management from curative to palliative in 10% to 20% of patients while also occasionally demonstrating that suspicious findings on other staging tests did not represent metastatic disease.[78–80] Combined PET and CT imaging allows viewing of both sets of images in register and is optimal for accurate identification of smaller-volume metastatic tumor.[81,82]

A bone scan is recommended for patients with an elevated alkaline phosphatase level or symptomatic painful areas, although this might not be necessary when a PET scan is performed. Bone metastases are infrequent as the initial site of metastases, but they do occur, more commonly in patients with adenocarcinoma. Evaluation for tracheal involvement with bronchoscopy is necessary for all lesions located at or above the carina.

Accurate determination of the extent of disease has a major impact on therapeutic decision making for single-modality versus multimodality treatment or curative versus palliative intent; therefore, it is essential that comprehensive staging be performed. A substantial literature now exists regarding transesophageal ultrasound (EUS), laparoscopy, and thoracoscopy. The largest and earliest experience was with EUS.[83–87] Recent surveys of the literature indicate an accuracy for T stage of approximately 85% and an accuracy of approximately 75% for N stage. The accuracy for N stage is increased to 85% if fine-needle aspiration biopsy is included.[88,89] EUS is not a reliable technique for diagnosing liver and peritoneal metastases because of the limited depth of penetration of ultrasound.[89]

The indications for minimally invasive staging techniques are not yet fully defined. Laparoscopic evaluation of abdominal lymph nodes can be achieved with minimal risks when high-yield staging information is not obtainable with standard imaging studies. The staging accuracy of laparoscopy for nodal involvement exceeds 95%.[72–75,90–92] Unsuspected findings such as liver metastases or peritoneal studding that alter treatment occur in 12% to 17% of patients studied.[72–74,90,93] Laparoscopy appears to be most useful for evaluating intra-abdominal spread of disease in patients with a bulky distal third or GE junction primary and/or celiac adenopathy. Small hepatic metastases and peritoneal carcinomatosis that are below the limit of resolution of CT and PET imaging may be detected. Laparoscopy is commonly performed at the time of jejunostomy tube placement for patients who are planning to receive preoperative chemoradiation. Thoracoscopy also has a high level of accuracy: 95% in detecting regional nodal involvement compared with surgical staging.[71,90,94]

Surgery Alone

Esophagectomy with reconstruction has a clear goal of both achieving local tumor control and restoring swallowing function. Esophageal surgical intraoperative risks, postoperative complications, and length of hospitalization have all decreased over the past decade to acceptable levels that are now compatible with those of other major oncologic resections.[95–100] Whether surgical resection is performed as the sole therapy or as part of a combined approach, the surgical principles and techniques are the same. A combination of concurrent chemotherapy and radiation without surgery is a potentially curative alternative for patients who refuse surgery, who are at high risk for surgery, who have unresectable tumors, or who have upper esophageal lesions for which resection might also require laryngectomy. A so-called palliative esophagectomy to restore swallowing function but with little or no change of long-term survival due to the extent of disease is rarely acceptable treatment and usually should not be contemplated. The standard operation in the United States to resect an esophageal cancer includes resecting the involved portion of esophagus, the proximal stomach, and the regional lymph nodes, as illustrated in Figure 78-1. The surgical resection is therefore properly termed a

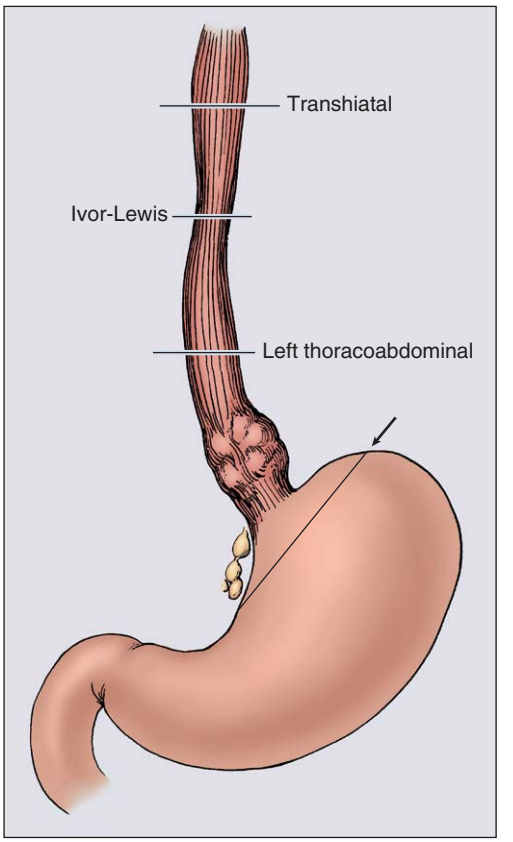


Figure 78-1 • Regardless of the surgical approach used, a partial esophagogastrectomy is performed to resect esophageal tumors. Depending on the approach, different lengths of esophagus are removed.

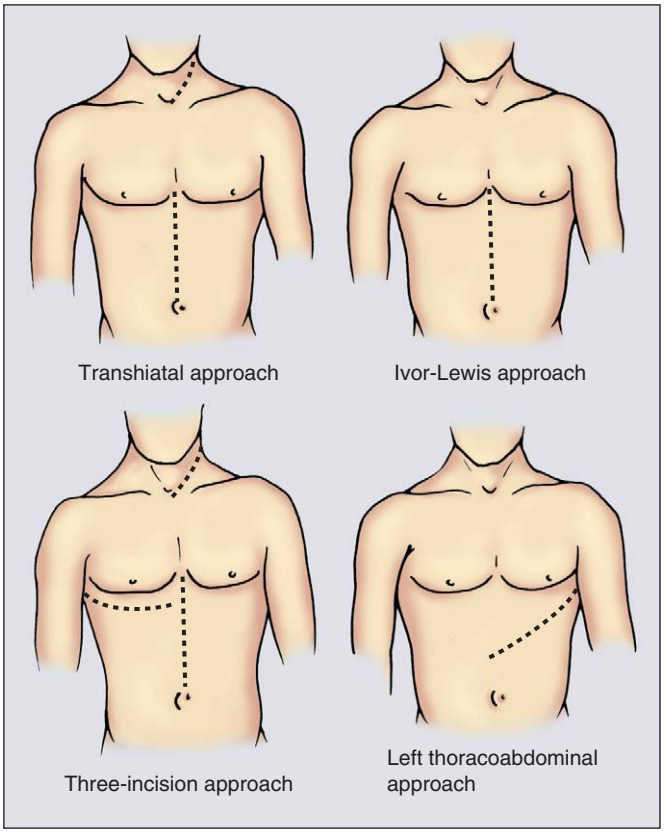


Figure 78-2 • The different incisions used to perform partial esophagogastrectomy are depicted.

partial esophagogastrectomy with regional (or one field) lymphadenectomy. The resected esophagus is replaced with a conduit, usually the stomach or segments of the small or large intestine, which are in turn mobilized as a vascularized pedicle and anastomosed to the remaining proximal esophagus.

A number of incisional approaches are used to perform a partial esophagogastrectomy, including the transhiatal, Ivor-Lewis, left thoracoabdominal, and three-incision techniques (Fig. 78-2). The specific incisional approach that is used generally determines how much esophagus is removed and where the esophageal anastomosis will be located (see Fig. 78-1). In the past, various surgeons have argued in support of their preferred techniques, giving the impression that all of these approaches were uniquely different procedures. It is now appreciated, however, that all of these incisional techniques use partial esophagogastrectomy (except segmental esophagectomy with free jejunal grafting, which is discussed separately), and the patient outcome results that have been reported are similar in terms of surgical morbidity and mortality. Long-term disease-specific survival after esophagectomy is related to pathologic tumor stage. Prospective studies do not demonstrate a survival advantage related to the surgical esophagectomy technique.[101,102] The data continue to demonstrate no difference in morbidity, mortality, or survival between transthoracic and transhiatal esophagectomy approaches.[103] The main variables in performing a partial esophagogastrectomy are which incision(s) to use, the length of esophagus to resect, what to use to replace the esophagus, and which route through the chest this conduit will take.

Transhiatal Approach

The transhiatal esophagectomy (THE) is a frequently used approach, "rediscovered" in 1976 by Dr. Mark Orringer, in which the intrathoracic esophagus is mobilized distally through the esophageal hiatus and proximally through a cervical incision. The increased prevalence of adenocarcinoma of the distal esophagus and GE junction has largely been responsible for the widespread popularity among surgeons of the transhiatal approach. Because of their distal esophageal location, these tumors are invariably near the esophagogastric junction and readily accessible for direct-vision dissection through the hiatus. Moreover, the regional lymph nodes for these distal tumors are in the parahiatal and proximal lesser curvature regions, both accessible via laparotomy. The resected esophagus is then reconstructed by using stomach or long-segment colon, which are passed up into the neck as vascularized grafts to be anastomosed to the proximal cervical esophagus.[99,104–106] Although reports exist on the use of jejunum for long-segment esophageal replacement, small bowel is generally not an option for esophageal replacement because of its mesenteric vascular anatomy unless specialized techniques with vascular augmentation are used.[107] The esophageal replacement conduit is passed through the chest into the neck by one of three routes: subcutaneous, substernal, or posterior mediastinum. The posterior mediastinum is the preferred route when possible. The advantages of the THE include avoiding post-thoracotomy discomfort, wide proximal esophageal margins to ensure complete resection of tumor and Barrett's mucosa, cervical anastomosis in which the consequences of anastomotic leak are minimized, and an esophageal reconstruction that results in an excellent quality of swallowing. It is well documented that the approach is acceptable for both benign and malignant esophageal disease.[108,109] The disadvantages include inability to visualize middle or proximal third tumors, inability to perform extensive intrathoracic regional lymphadenectomy, potential for injury to intrathoracic structures, and the need for long-segment esophageal replacement. The technique is safe, well tolerated, and associated with infrequent major complications in experienced hands.[110] In large series, late functional results have been good or excellent in 73% of surgeries, and mortality rates as low as none to 3% have been reported.[106,110,111] Recently, Orringer and colleagues reported a series of over 2000 patients who underwent a THE with a mortality rate of only 1% in the patients who underwent surgery since 1998, an anastomotic leak rate of 9%, and 2% pulmonary complications.[110]

Ivor-Lewis Approach

Partial esophagogastrectomy with an abdominal and right thoracotomy approach, also known as the Ivor-Lewis approach, was designed to optimize exposure of the intrathoracic esophagus, which passes through the upper two thirds of the chest along the right posterior mediastinum.[111] Once the involved intrathoracic esophagus is mobilized, a partial esophagogastrectomy is performed, and the esophagus is replaced by stomach, colon, or (less frequently) jejunum, which is passed into the chest along the esophageal bed and anastomosed to the proximal esophagus, usually at or above the level of the azygos arch. The advantages of the technique are the excellent exposure of the middle to upper intrathoracic esophagus, and the disadvantages are related to the use of a thoracotomy, with limits on the proximal resection margin and the potential for an intrathoracic esophageal anastomotic leak, which is a more difficult management problem than a cervical anastomotic leak. Reported complications include respiratory problems in 11% to 20%, anastomotic leak in 3% to 7%, and wound infection in 5%. Operative mortality ranges from none to 4%.[95,98,112,113]

Left Thoracoabdominal Approach

The left thoracoabdominal approach uses a single incision extending from the left chest onto the abdomen; it provides excellent exposure of the lower third of the esophagus and left upper quadrant of the abdomen.[114] This technique is ideal for patients with tumors near the GE junction, especially when the extent of gastric invasion is unclear, because it yields superb exposure and maximizes reconstructive options of the lower third of the esophagus. Respiratory

complications are the most common with this approach. At least some degree of atelectasis, usually involving the left lower lung, occurs in most patients. Pneumonia is reported to occur in up to 24% of cases. Anastomotic leaks occur in as many as 12% (mean: 3.7%) of cases. Other complications include atrial fibrillation in 10%, wound infection in 1.5% to 5.2%, and, infrequently, empyema and subphrenic abscess. The reported operative mortality is none to 6.2%.[115,116]

Multiple Incisions

Multiple-incision surgical approaches combine the incisional strategies of the standard techniques. Of these, the three-incision approach using a cervical incision (right or left), right thoracotomy, and midline laparotomy, as described by McKeown,[117] is the most common and is also referred to as the three-incision, three-hole, total esophagectomy or modified McKeown approach. It combines the exposure of the thoracotomy approach for esophageal mobilization or nodal dissection with the advantages of a cervical esophageal anastomosis. Patient outcome results with this technique are similar to those of other approaches, with reported mortality rates of 3% to 4% and esophageal anastomotic leak rates of 5% or less.[118–120]

Radical Resections

The majority of patients with esophageal cancer are first seen with locally advanced (stage II and III) disease. In these patients, survival results are poor with surgery alone. Two approaches attempt to improve survival in these patients. One involves the use of combination therapies, such as preoperative chemoradiation followed by surgery (to be discussed later); the second involves adding an en bloc, wide-field lymphadenectomy to the standard esophagectomy technique. The esophagus has an extensive regional lymphatic drainage. Arbitrarily, the lymphatic drainage has been divided into three zones or fields: cervical, intrathoracic, and abdominal. Standard esophagectomy techniques involve regional, or one-field, lymphadenectomy. Radical approaches advocate two- or three-field lymphadenectomy in conjunction with esophageal resection and replacement. Hagen and colleagues[121] believe that proximal hemigastrectomy should also be included as part of an en bloc approach, using colon to replace the resected esophagus. Radical esophagectomy is more complex surgery than standard techniques. This is reflected in morbidity rates as high as 58%.[122] Nonetheless, 30-day mortality rates as low as 1.6% to 4.3% have been reported.[121–124] Survival data using radical esophagectomy techniques are conflicting; therefore, it is unknown whether there is sufficient benefit to outweigh the increased operative morbidity. Hagen and associates[121] reported an improved survival in early-stage tumors using en bloc esophagectomy compared with a standard transhiatal technique. Although prospective, their trial was not randomized. Also, earlier-stage patients were selected for the en bloc approach and therefore biased the results and conclusions. A more recent update of their results continues to suggest excellent local tumor control and improved survival.[125]

In another nonrandomized series, Altorki and coworkers[124] reported improved survival in patients with stage III disease with radical esophagectomy compared with standard surgical techniques. Nishimaki and colleagues[122] reported an overall 5-year survival rate of 41% with extended radical esophagectomy for thoracic esophageal cancer. Their results are supported by more recent publications.[126,127] In contrast, Bumm and coworkers[123] demonstrated no difference in overall survival between standard transhiatal and radical THE in which two-field lymphadenectomy is added. Despite the wide surgical dissection with radical techniques, Bhansali and colleagues[128] still documented a 21% locoregional cancer recurrence rate. The determination of which cell type and tumor stage, if any, will benefit from radical surgical techniques has yet to be made.

Free Jejunal Interposition

Free jejunal interposition permits proximal segmental esophageal resection and replacement without the need to resect distal esophagus. For technical reasons related to the microvascular anastomosis that is necessary to support the jejunal interposition, this technique has been limited to replacement of the cervical esophagus for either esophageal, laryngeal, or hypopharyngeal cancers or benign strictures (e.g., lye, radiation). Contraindications include factors that would jeopardize the proposed blood supply to the free intestinal segment, such as advanced age, previous carotid surgery, and cervical radiation, or factors that would interfere with the ability to harvest a suitable jejunal segment, such as peritoneal adhesions or inflammatory bowel disease. In resection of the cervical esophageal segment, the branches of the external carotid artery and external jugular veins are preserved as potential host vessels. A segment of jejunum is selected at least 15 to 20 cm distal to the ligament of Treitz. The specific jejunal segment that is chosen should have a mesenteric arcade supplied by an adequate size artery and vein. Approximately 20 to 25 cm of jejunum can be resected, although 10 to 15 cm is usually sufficient. The free jejunal segment is then transferred to the neck, where in an isoperistaltic fashion, the proximal esophageal anastomosis is performed, the arterial and venous microvascular anastomosis is carried out to the selected host vessels, and then the distal anastomosis is completed.

With this technique, the reported graft survival rate is 85% to 95%, and the operative mortality rate is 5%. For patients with successful grafting, 90% are reported to have an adequate swallowing quality. If graft failure occurs, a second attempt will be successful in 50% to 75% of cases.[129–131]

Minimally Invasive Esophagectomy

With the advent of minimally invasive surgical techniques, an interest has been shown in applying thoracoscopic and laparoscopic techniques to esophagectomy.[132] Certainly, the techniques of gastric and esophageal mobilization have been well established for other complex minimally invasive surgeries. Minimally invasive esophagectomy required that these individual techniques be "spliced" together. Approaches that have been used have included laparoscopic transhiatal resection, combined laparoscopic-thoroscopic procedures, and laparoscopic creation of gastric tube with thoracotomy and other combinations. The need to convert to an open surgery has been uncommon. The number of lymph nodes that are removed also appears similar to that achieved with open surgery.[133]

A steep learning curve exists for these surgeries. The total length of hospitalization may be shortened somewhat. However, equipment costs and length of operative procedure can negate cost savings with this approach. Mortality rates of 40% to 70% in experienced hands are extensively reported.[133–135]

Survival with Surgery Alone

Survival after surgical resection is discussed separately from the description of individual techniques to emphasize the fact that postesophagectomy survival is a function of stage and not of surgical approach. Several points concerning postesophagectomy survival have now become quite clear. The first is that regardless of whether a thoracotomy or nonthoracotomy technique is used, cumulative postoperative survival is the same, approximately 20% to 25%. This has been underscored most graphically by Muller and associates,[136] who reviewed the world literature to compare overall postesophagectomy survival by technique and showed no significant difference. Hulscher and coworkers[137] performed a meta-analysis of the English language literature of transthoracic and transhiatal resection of esophageal cancer and found a higher risk of pulmonary morbidity and mortality with the transthoracic procedure but a similar 5-year survival rate of approximately 20%. These investigators also compared limited transhiatal resection with THE with extended en bloc lymphadenectomy in 220 patients with adenocarcinoma of the esophagus.[137] No significant difference was found in survival or operative mortality. More recent large retrospective series suggest a modest improvement in long-term outlook in recent years, probably the result of lower operative mortality.[138–140] Gockel and colleagues found

that for the periods 1985 to 1995 and 1995 to 2005, the 5-year survival rate increased from 15% to 25%, and the 30-day surgical mortality rate improved from 8.3% to 3.1%.[139] In addition, better patient selection could play an important role in improved outcome. For example, Steyerberg and colleagues have proposed a simple scale based on important comorbidities, age, neoadjuvant therapies, and esophagectomy volume at the treating hospital that divides patients into groups with predicted 30-day mortality of under 4% to approximately 20%.[141] It is also expected that more accurate preoperative staging with PET scanning and esophageal ultrasound could improve surgical outcome by removing some patients who have existing gross metastatic disease.

The second fact is that postoperative survival is stage related. Notably, the majority of patients who are considered for surgery are found to have stage III disease, and the survival rate for these patients, even with surgery, is poor (approximately 10% to 15%). Hofstetter and associates[142] reported results for 1097 consecutive patients undergoing resection and compared outcome by stage from 1970 through 1985, 1986 through 1996, and 1997 through 2001. Although median survival increased from 7 to 34 months, the surgical mortality rate decreased from 12% to 6%, and the R0 resection rate increased from 78% to 94%; no difference was found in survival according to stage. Three-year survival rates through this period were 63%, 52%, and 44% for pathologic stage IIA and 10%, 18%, and 6% for pathologic stage III. Multivariate analysis showed that survival was associated with complete resection and thorough preoperative staging and that preoperative chemotherapy used in the later years was associated with increased complete resection. For T1 N0 M0 adenocarcinoma of the esophagus,[143] survival rates at 5 and 10 years may be closer to 77% and 68% after surgical resection.

New methods of pathologic staging could improve our ability to predict surgical outcome. Immunohistochemical staining may detect lymph node micrometastasis. In one study,[144] 62% of patients (adenocarcinoma and squamous cell carcinoma) with pathologic node-negative stage by conventional criteria had nodal disease, detected by using monoclonal antibody Ber-EP4. This monoclonal antibody binds to certain glycoproteins found on epithelial tissues. The identification of micrometastatic nodal disease had a significant impact on survival. A somewhat lower incidence of micrometastatic disease was found by using anticytokeratin antibodies,[145–148] and there is some suggestion that patients who are upstaged from node-negative disease do have inferior long-term survival.[149,150] These novel techniques require validation in prospective trials and could provide valuable prognostic information as well as allowing optimal selection of patients for adjuvant therapy.

The third point is that postsurgical survival is little influenced by whether the patient's esophageal cancer has a squamous cell carcinoma or adenocarcinoma histology. Holscher and coworkers[151] documented a postresection survival advantage only for patients with stage I adenocarcinoma. Salazar and colleagues[152] reported no difference in cumulative postoperative survival for patients with squamous cell carcinoma and adenocarcinoma. Finally, despite advances in surgical techniques and results, postesophagectomy survival has remained remarkably stable over time. Wilkins[153] made this same point almost a decade ago after reviewing postoperative survival figures for the years 1952 and 1986. On the basis of his review, he queried whether surgery had gone as far as it could go and speculated that further improvement in survival statistics would require combination therapy regimens that included systemic chemotherapy. As new systemic agents are developed, a differential response may be seen in adenocarcinoma and squamous cell carcinoma, which suggests that new agents will need to be evaluated separately in each histologic type.

Optimizing Surgical Outcome

Evidence-based surgery uses the treatment outcomes of cost, morbidity, mortality, and quality of life to help physicians, health care administrators, and hospitals determine the most appropriate setting and specific management of patients. Data consistently show that increased provider experience improves patient outcome, lowers complication rates, and reduces cost for complex surgeries. In terms of technical difficulty, length of stay, morbidity, and mortality, esophageal surgery is classified as a complex GI operation. Gordon and associates[154] reported reduced hospital mortality, length of stay, and cost for a wide range of complex GI procedures, including esophagectomy. The institution of standardized patient care pathways, a product of the evidence-based surgery approach, reduced hospital cost for esophagectomies while keeping surgical mortality low (1.3%).[155] Indeed, the use of clinical protocols for postoperative care has the potential to substantially reduce operative mortality resulting from a variety of surgical approaches, perhaps to 1% or less.[140]

Dimick and colleagues[156,157] documented the importance of surgical volume, hospital experience, and intensive care staffing in optimizing outcome after esophagectomy. These studies underscore the fact that even complex surgical procedures, such as esophagectomy, can be both effective therapy and cost-effective.

In an important multi-institutional analysis[158] of outcome in Medicare patients, a substantial difference in operative mortality was found to exist on the basis of the number of esophagectomies per year at the institution. This varied from 23% for centers doing fewer than 2 of these procedures per year to 8.1% for high-volume centers performing more than 19 per year. The operative mortality rates that were reported in this series are higher than those reported in clinical trials, and this might relate not only to particular expertise of the study centers in esophageal cancer treatment but also to patient selection for clinical research. A subsequent analysis suggested that the variation among hospitals was explained, in part, by lower mortality of individual high volume surgeons with adjusted operative mortality among Medicare patients of 18% for surgeons performing fewer than two esophagectomies per year and 9% for those performing more than six.[159] Other studies have since confirmed this finding.[160,161]

Chemotherapy Followed by Surgery

Promising results for survival improvement that were reported from numerous phase II trials of preoperative chemotherapy regimens tested in newly diagnosed patients[162–173] prompted two large randomized trials with differing results.[66,174] These data are summarized following. Although preoperative chemotherapy can be justified on the basis of an advantage that was demonstrated in the MRC trial, it is considered an investigational approach in the United States. The U.S. Intergroup trial was well conducted and adequately powered. It failed to demonstrate either improved local control or improved survival with preoperative chemotherapy compared to surgery alone. By contrast, there are data indicating survival benefit and improved local control when RT is added to chemotherapy in a concurrent fashion prior to surgery. Hence, trimodality therapy is favored in the United States over the preoperative chemotherapy approach that is preferred in the United Kingdom.

The U.S. G-I Intergroup trial included 467 who were patients randomized to receive either three courses of cisplatin 100 mg/m^2 plus infusional 5-fluorouracil (5-FU) 1000 mg/m^2/day from days 1 to 5 before surgery and two courses after surgery (total: five courses) or immediate surgery.[174] No benefit was demonstrated for the addition of chemotherapy in this trial (see Table 78-3), in which 45% of patients had squamous cell carcinoma and 55% had adenocarcinoma. There were no differences in resectability or median 1-, 2-, or 3-year survival rates between treatment groups and between histologic types. The pathologic complete response (pCR) rate was 2.5%. The median survival and 2-year survival rate were 14.9 months and 35%, respectively, with chemotherapy versus 16.1 months and 37%, respectively, without chemotherapy. In both arms, approximately 60% of enrolled patients underwent a gross total resection (R0), and 17% of those patients had a subsequent local recurrence, for an ultimate 57%

failure to control local disease. There were no differences in surgical morbidity and mortality rates (6% for both arms). Most patients did not receive the planned two cycles of postoperative chemotherapy; 52% received one cycle, and 38% received both cycles. A recent update reported a 32% disease-free 5-year survival rate for patients who had complete resection and negative margins (R0), whereas only 5% of those with a lesser resection (R1 or R2) were alive at 5 years.[67]

The MRC[65] conducted a randomized trial involving 802 patients, testing two cycles of cisplatin 80 mg/m^2 and 5-FU 1000 mg/m^2/day continuous infusion for 4 days given prior to resection of squamous cell carcinoma or adenocarcinoma of the esophagus (see Table 78-3). Patients were required to have resectable tumor, although the staging evaluation was not prescribed by the study. Two thirds of patients had adenocarcinoma. Median survival was significantly improved from 13.3 to 16.8 months, with 2-year survival rates improved from 34% to 43%. No information about patterns of failure was reported, but, similar to the results of the U.S. Intergroup trial, 57% had a complete resection with negative margins (R0). There is no immediate explanation for the difference between the results of this trial and the U.S. Intergroup trial, but these conflicting results may relate to the greater power or the less rigorous staging in the British study, to chance, or to unknown differences between the populations in the two studies. Another trial conducted by the MRC, Adjuvant Gastric Cancer Infusional Chemotherapy, demonstrated a survival benefit for three cycles of preoperative epirubicin, cisplatin, and 5-FU (ECF) and three cycles of postoperative ECF compared with surgery alone. This trial enrolled patients with gastric, GE junction, and distal esophageal adenocarcinoma (26% of patients). Although not powered for subsite analysis, there did not appear to be heterogeneity in treatment effect for distal esophageal lesions or gastric lesions.

A meta-analysis[175] was performed of eight trials of preoperative chemotherapy or chemoradiation compared with immediate surgery to explore the value of chemotherapy. With all-cause mortality as an endpoint, there was not a significant benefit to preoperative chemotherapy alone. When analyzed by histologic type, there was no benefit for squamous cell carcinoma, but the hazard ratio for adenocarcinoma was 0.78 (0.64 to 0.95); however, this estimate was based on only the MRC trial described previously, as outcome by histology was not available from other trials. A greater benefit was seen with preoperative chemoradiation, with a 13% versus 7% absolute 2-year survival benefit for chemotherapy alone.

There has been only one trial directly comparing preoperative chemotherapy and preoperative chemoradiation, and the preliminary results were reported in abstract form. This trial, conducted by investigators in Germany, compared preoperative chemoradiation using cisplatin, folinic acid, and 5-FU to the same chemotherapy without radiation followed by surgery. The trial was closed early because of poor accrual after 126 of 394 planned patients were enrolled. The results favored preoperative chemoradiation but did not reach statistical significance; the pCR rate was 17% versus 2.5%, the complete resection (R0) rate was 85% versus 77%, the 3-year survival rate was 43% versus 27%, and median survival was 33 versus 21 months. These results, albeit limited by inadequate accrual and hence an underpowered study, provide additional support for the concept of preoperative chemoradiation over chemotherapy alone.[67]

Concomitant Chemotherapy and Radiation Therapy Followed by Surgery

The rationale for neoadjuvant chemoradiation or trimodality therapy is the high rate of both local and distant failure that is seen with surgery alone, such that intensified local and systemic therapies are needed to improve survival outcome. For example, data from the surgery-alone control arm of the U.S. Intergroup trial (1990 to 1995) showed a 57% failure to control local disease (including 41% failure to resect all local disease) and 50% distant failure rate in patients who did have complete resection.[174] A single-institution randomized trial that was conducted at the University of Michigan[176] demonstrated similar survival, local control, and distant first failure rates with surgery alone. Another single-institution study of adenocarcinoma of the distal esophagus and GE junction examined patterns of failure after surgery alone. Thirty-four percent of patients had distant failure, 19% had local failure, 14% had locoregional nodal failure, and 6% had peritoneal seeding.[177] These studies show that the rate of complete resection with negative margins and ultimate local control is not improved by the addition of chemotherapy alone prior to surgery. Similarly, the local recurrence rate is high (nearly 50%) after definitive chemoradiation.[178] However, the trimodality approach of chemoradiation followed by surgery results in a significant improvement in local control compared to surgery alone in trials of patients with squamous cell carcinoma and adenocarcinoma.[176,179]

A number of randomized controlled trials of chemoradiation compared to surgery alone have been conducted, with conflicting results. Those that either were limited to adenocarcinoma or included both histologies have been criticized for being underpowered or having a worse than expected outcome for the surgery control arm. However, the combined weight of multiple underpowered or otherwise limited trials supports a local control and survival benefit when compared with the outcome of surgery alone. A number of meta-analyses of randomized controlled trials are now in the literature to evaluate the effect of chemotherapy or chemoradiation prior to surgery.[175,180–183] The most comprehensive analysis was recently reported by Gebski and colleagues.[175] A total of 10 trials and 1209 patients from the period 1983–2006 were identified that compared preoperative chemoradiation with immediate surgery; individual patient data were available for two of the trials. The analysis found a benefit for concomitant chemoradiation followed by surgery compared with surgery alone; the hazard ratio for death by any cause was 0.81 (0.70 to 0.93), which corresponded to a 13% reduction in mortality at 2 years. The benefit was similar for both histologies, but no benefit was identified in trials that gave chemotherapy and radiation sequentially rather than concurrently. Another smaller meta-analysis found improved 3-year survival when the analysis was restricted to trials that used concurrent chemotherapy and radiation (OR: 0.45, 95 % CI: 0.26 to 0.79) but no benefit with sequential regimens.[181] Additionally, patients who received preoperative chemoradiotherapy were more likely to undergo complete resection (R0) (OR: 0.53, 95 % CI: 0.33 to 0.84). In this latter analysis, use of a reduced radiation dose was associated with higher mortality, which might be a design weakness of some of the randomized trials described in the following sections.

A series of randomized trials tested chemoradiation with 5-FU/cisplatin followed by surgery compared with surgery alone. Most of these trials were underpowered, and the results were conflicting. The results of these trials are summarized in Table 78-5. Two trials, those of Nygaard and colleagues[184] and Le Prise and colleagues,[185] utilized a sequential chemotherapy and RT design followed by surgery and failed to demonstrate any significant difference in median, disease-free, or overall survival. These trials will not be further discussed. Notably, the studies published by Walsh and colleagues,[186] Urba and colleagues,[176] and Tepper and colleagues[187] included patients with adenocarcinoma. Those of Bosset and colleagues,[179] Burmeister and colleagues,[188] Walsh and colleagues,[186] Urba and colleagues,[176] and Tepper and colleagues[187] compared concomitant cisplatin-based chemotherapy and RT followed by surgery to immediate surgery. Walsh and colleagues[186] and Tepper and colleagues[187] demonstrated a significant survival benefit, while Urba and colleagues reported a significant improvement in local control, but survival differences were not significant. Bosset and colleagues[179] showed an improvement in disease-free survival and fewer deaths from esophageal cancer but not improvement in overall survival. The trial of Burmeister and colleagues did not demonstrate a survival benefit, but the chemotherapy and RT were suboptimal. All trials (see Table 78-3) reported similar

Table 78-5 Preoperative Chemotherapy and Radiotherapy: Randomized Trials

Author	Treatment Arms	Median (mos.)	Survival Rate (%)		
			1-Year	2-Year	3-Year
Nygaard et al.[184]	S			13	9
	Cisplatin/bleomycin + 35 Gy + surgery			23	17
Le Prise et al.[185]	S	10	47		14
	Cisplatin/5-FU + 35 Gy + surgery	10	46		19
Bosset et al.[179]	S	18.6	67	42	34
	Cisplatin + 37 Gy + surgery	18.6	69	48	37
Walsh et al.[186]	S	11	44	26	6
	Cisplatin/5-FU + 40 Gy + surgery	16	52	37	32
		$P = 0.01$			$P = 0.01$
Urba et al.[176]	S	17.5	58	39	16
	Cisplatin/5-FU/VBL + 45 Gy + surgery	16.3	70	42	32
Burmeister et al.[188]	S	19.3			$P = 0.07$
	Cisplatin/5-FU +35 Gy + Surgery	22			
Tepper et al.[187]	S	22			16 (5 year)
	Cisplatin/5-FU + 50.4 Gy + Surgery	48			39 (5 Year)
					$P = 0.02$

5-FU, 5-fluorouracil; S, squamous cell carcinoma; VBL, vinblastine.

3- to 5-year survival rates of 32% to 39% for the investigational combined treatment (trimodality) groups, while the survival rate of patients in the surgery control arms varied from 6% to 16%. This probably reflects differences in the patients who were enrolled in each trial and the rigor of baseline staging. The details of these trials are described following.

The trial reported by Walsh and colleagues[186] was limited to adenocarcinoma of the distal esophagus-GE junction and demonstrated significantly improved survival with concurrent 5-FU 15 mg/kg on days 1 to 5 and days 30 to 35, cisplatin 75 mg/m^2 on days 7 and 37, and RT 40 Gy in 15 fractions on days 1 to 19. The three-year survival rate was 32% versus 6%, and median survival was 16 months versus 11 months ($P = 0.01$). The complete response rate for all patients who were enrolled in the preoperative chemoradiation arm was 22%, and there was evidence of nodal downstaging with 82% node-positive in the surgery arm versus 25% after neoadjuvant therapy ($P < 0.001$). This study has been criticized for the relatively small sample size (it closed when an early stopping rule was met), for unexpectedly poor results in the surgery-alone arm, and for lack of uniform preoperative staging.

The trial reported by Urba and colleagues[176] randomized 100 patients to surgery (transhiatal esophagectomy) with or without preoperative chemoradiation (cisplatin 20 mg/m^2 on days 1 to 5 and days 17 to 21, vinblastine 1 mg/m^2 on days 1 to 4 and days 17 to 20, 5-FU 300 mg/m^2 on days 1 to 21, RT 1.5 Gy twice a day to 45 Gy). Median survival was 17.6 months with neoadjuvant therapy and 16.9 months with surgery alone, and the 3-year survival rate was 30% versus 16%, respectively ($P = 0.18$). Survival of patients in the trimodality arm was consistent with the Walsh study. The gross total resection rate was in excess of 90% in both arms. The pCR rate was 28% and did not differ by histology, but the number of patients was small (75 adenocarcinoma, 25 squamous cell carcinoma). Preoperative therapy reduced the incidence of locoregional failure as the site of first failure from 42% in the surgery control arm to 19% ($P = 0.0002$). Distant failure was not affected; it was approximately 60% in both arms. While the improvement in the overall survival rate from 16% to 30% is in an expected range of 10% to 15%, the study was powered to show a much larger difference on the basis of the results of prior phase II trials from this group.

Bosset and colleagues[179] reported the results of a multicenter trial that was limited to squamous cell carcinoma, stages I and II. These investigators found no difference in overall survival with preoperative therapy, although there was a significant improvement in disease-free survival and local recurrence-free survival. The regimen was cisplatin 80 mg/m^2 given 0 to 2 days prior to each set of RT treatments, and the RT consisted of two 1-week courses of 18.5 Gy in five 3.7-Gy fractions beginning on days 1 and 22. Postoperative mortality was significantly higher, 12% versus 4% in the combined treatment arm. This trial has been criticized because chemotherapy was often not administered on the same day as RT, the chemotherapy was less intensive than that in the other trials, and an unusual hypofractionated and split-course regimen of RT was utilized.

The Trans-Tasman Radiation Oncology Group and the Australasian Gastro-Intestinal Trials Group randomized 256 patients to surgery alone or to one cycle of preoperative cisplatin 80 mg/m^2 on day 1 and 5-FU 800 mg/m^2 on days 1 to 4, with concurrent RT, 35 Gy given in 15 fractions.[188] Sixty-two percent of patients had adenocarcinoma. No survival benefit was identified, but treatment was less intensive with only one cycle of chemotherapy given and a lower radiation dose, although there was a suggestion of benefit for patients with squamous cell carcinoma.

An adequately powered U.S. Intergroup trial was initiated to definitively assess survival outcome with preoperative cisplatin and 5-FU chemotherapy and concurrent radiation in comparison with surgery alone. Unfortunately, this trial was closed early as a result of poor accrual likely because of the existence of a strong bias among physicians about the benefits of preoperative chemoradiation, lack of consensus about an optimal preoperative regimen, and patient resistance to randomization. The long-term outcome for the 56 enrolled patients has been reported in abstract form.[187] The 5-year survival rate was 39% (21%, 57%) versus 16% (5%, 33%; $P = 0.005$). There was no appreciable difference in surgical complications. In that this attempt at a definitive intergroup trial failed to accrue enough patients, it is unlikely that such a trial will be mounted again in the

United States, and treatment guidelines will be formulated on the basis of the aggregated existing data.

On the basis of these data and the results of published series with long-term follow-up (Table 78-6), the use of preoperative chemoradiation is a rational strategy that significantly improves local control and might improve survival. Cisplatin and 5-FU concurrent with standard fractionation RT, total dose 44 to 50 Gy, is most commonly used. Other platinum-based regimens containing paclitaxel, docetaxel, oxaliplatin, or irinotecan have been tested in phase II trials, and pCR rates, preliminary survival outcome, and toxicity do not appear to be improved over those of cisplatin and 5-FU. For example, the Eastern Cooperative Oncology Group conducted trial E1201 to evaluate the potential for improved outcome with two alternative regimens in a randomized phase II design.[189] The pCR rate was the primary endpoint. The regimens that were tested were cisplatin 30 mg/m^2 and irinotecan 50 mg/m^2 on days 1, 8, 22, and 29 of 45 Gy RT/5 weeks and cisplatin 30 mg/m^2 and paclitaxel 50 mg/m^2 1-hour infusion on days 1, 8, 15, 22, and 29 with RT. The trial was limited to patients with resectable adenocarcinoma of the distal esophagus, GE junction, and cardia (stages II, III and IVA); the staging evaluation included esophageal endoscopic ultrasound. Of all eligible randomized patients, 83% (38 of 46) and 70% (31 of 44) had a complete resection with negative margins, and 6 of 46 (15%) (95% CI: 5%, 26%) and 7 of 44 (16%) (95% CI: 7%, 30%) had pCR with preoperative cisplatin, irinotecan CI + RT and cisplatin, paclitaxel + RT, respectively. These pCR rates were lower than those observed with standard 5-FU and cisplatin in other multicenter trials, but survival and pattern of failure are not yet available.

The results of phase II and III preoperative chemoradiation trials demonstrate that pathologic stage based on the resected esophageal specimen and nodes is an important predictor of survival. Patients who are found to have no residual tumor in the resected esophagus and nodes or minimal residual tumor (stage I) have the best prognosis with overall survival rates of 60% to 70% at 5 years. This ability to downstage patients with locally advanced disease and improve survival is a powerful rationale for utilizing preoperative chemoradiation and a reason that it has become common practice. Surgical stage may also be useful in selecting patients for trials of novel adjuvant therapies, given that the rate of distant metastases is high and that they are the predominant cause of death from disease.

Safety of Esophagectomy after Chemoradiation

The question of whether preoperative chemoradiation increases surgical morbidity and mortality is an area of controversy but appears to be less relevant in the modern era. The majority of randomized trials discussed previously reported no significant increase in surgical mortality when trimodality therapy was compared to surgery alone. The results of 120 patients who were treated at Johns Hopkins with preoperative chemoradiation were analyzed for surgical morbidity and mortality to evaluate the overall complication rate.[190] The surgical mortality rate was 1%. The complication rate was 59% for squamous cell carcinoma and 31.6% for adenocarcinoma. The higher complication rate that was observed for squamous cell carcinoma, relative to patients with adenocarcinoma, was attributed to an increased risk of pulmonary complications due to the more proximal location of the primary and potential increased prevalence of chronic lung disease in this population. These results are comparable to the mortality rate (2.2% to 9.0%) and morbidity rate (22% to 74%) that were reported after surgery alone and suggest that with careful technique and attention to postoperative management, preoperative therapy does decrease surgical morbidity. The operative mortality rate when transhiatal esophagectomy was performed was 4% with surgery alone and 2% after preoperative therapy. Similar mortality rates have been reported from recent multicenter trials of patients with adenocarcinoma only or including both histologies.[187,189] A retrospective comparison of squamous cell carcinoma patients who had neoadjuvant chemoradiation or surgery alone demonstrated an operative mortality rate of 6.3% versus 9% and a morbidity rate of 40.3% and 41%, respectively.[191] In contrast, the trial reported by Bosset and colleagues including only patients with squamous cell histology had an operative mortality rate of 12% operative after chemoradiation and 4% after surgery alone.[179]

Assessment of Response to Preoperative Therapy May Predict Outcome

Radiographic and endoscopic assessment of response has not proven accurate enough after chemoradiation to serve as a selection criterion for proceeding to surgery, to guide changing unsuccessful neoadjuvant therapy, or to select patients for more aggressive postoperative therapy. Post-treatment inflammatory changes and thickening are difficult to distinguish from tumor and limit the utility of both CT scanning and endoscopy, even with ultrasound.[190,192,193] The lack of predictability is exemplified by one report[194] of seven patients with no residual tumor in the resected esophagus (pCR) whose staging with endoscopy and EUS immediately prior to resection indicated persistent advanced disease (T4 N1 (one patient), T3 N1 (three patients), T2 N1 (two patients), and T3 N0 (one patient). By contrast, retrospective and prospective[195–197] studies suggest that [^{18}F] FDG-PET imaging that is performed early in treatment may predict outcome and potentially create an opportunity to modify therapy. In a 39-patient prospective study at Memorial Sloan-Kettering Cancer Center,[198] a decrease in the standardized uptake value of more than 60% compared to baseline was associated with a better 2-year disease-free survival rate (67% versus 38%, P = NS). In a 40-patient trial of preoperative chemotherapy,[197] a 35% reduction in standardized uptake value on repeat PET after 2 weeks of neoadjuvant chemotherapy was associated with histologic complete tumor response rate (53% versus 5%, $P < 0.001$), median time to progression (16 months versus 9 months, $P = 0.01$), and overall survival (19 months versus 13 months, $P = 0.04$). An expanded study from these same investigators performing FDG-PET imaging 2 weeks after the start of preoperative chemotherapy found that a more than 35% reduction in metabolic activity was associated with a 70% 3-year survival rate and a 44% pCR rate, while with a lesser reduction in metabolic activity, the median survival was 24 months, and the complete histologic response rate was 5%.[199] Similarly, the preliminary results of a prospective CALGB trial support a possible value of PET imaging.[200] Patients were treated with irinotecan and cisplatin (CI) in weeks 1, 2, 4, 5, and then with concurrent CI in weeks 7, 8, 10, and 11 and RT. Repeat PET imaging was performed after week 5, prior to beginning RT. A decline in standardized uptake value of more than 22% was associated with a median time to progression of 18.5 months versus 5.5 months. It should be emphasized that these prospective studies assessed the prognostic value of repeat PET after chemotherapy alone, in which case the local inflammatory effects from chemoradiation may be substantial and confounding.[201] To date, no prospective study has yet assessed the value of altering therapy on the basis of PET response.

Pathologic stage at the time of surgery is an important predictor of survival outcome that can be used to advise patients and potentially to select high-risk patients for trials of novel adjuvant therapies. In a prospective trial performed at Johns Hopkins and Yale, patients with a pCR had a 67% survival rate at 5 years (median not reached), whereas the remainder of the patients had a 5-year survival rate of 27% (median: 21 months; $P < 0.001$).[202] Patients with pathological stage I tumor at the time of surgery had survival times that were similar to those of patients with a complete response to preoperative therapy. Median survival times for patients with pathologic stage IIA, IIB, III, and IV disease at the time of surgery were 22, 13.5, 18, and 4.9 months, respectively. A review of 276 patients who were assessed after preoperative chemoradiation suggested that the presence of only limited residual nodal disease, even without a complete response of

Table 78-6 Published Series with 5-Year Follow-Up

Author	Patient Number	Percent of Patients with Adenocarcinoma (%)*	Preoperative Chemotherapy	Radiotherapy	Complete Resection with Negative Margins (%)	Pathologic Complete Response (%)	Median Survival (mos.)	5-Year Survival Rate (%)
Forastiere et al. (1993)[†]	43	48	Cisplatin 20 mg/m^2/day, days 1–5, 17–21; vinblastine 1 mg/m^2/day, days 1–4, 17–20; 5-FU 300 mg/m^2/day, days 1–21	5-FU 300 mg/m^2/day, days 1–21	84	24	29	34
Bedenne et al. (1998)[‡]	94	0	Cisplatin 20 mg/m^2/day; 5-FU 800 mg/m^2/day, days 1–5, 22–26	30 Gy/10 fx, split course given, days 1–5, 22–26	82	20	17	23
Urba et al. (2000)[176]	50	26	Cisplatin 20 mg/m^2/day, days 1–5, 17–21; vinblastine 1 mg/m^2/day, days 1–4, 17–20; 5-FU 300 mg/m^2/day, days 1–21	4500/30 fx/BID	90	28	17	22
Posner et al. (2001)[§]	44	75	5-FU, cisplatin, and interferon in varying schedules	4000/20 fx or 4500/30 fx BID	81	24	28	32
Kleinberg et al. (2003)[‖]	92	71	Cisplatin 20 or 26 mg/m^2/day, days 1–5, 26–30; 5-FU 225 or 300 mg/m^2/day, days 1–30	44 Gy/22 fx	87	37	35	40
Tepper et al.[187]	30	75	Cisplatin 100 mg/m^2 and 5-FU 1000 mg/m^2/day × 4 days, weeks 1 and 5	50.4 Gy/25 fx		40	54	39

*Patient either had adenocarcinoma or squamous cell carcinoma.

[†] Forastiere AA, Orringer MB, Perez-Tamayo C, et al: Preoperative chemoradiation followed by transhiatal esophagectomy for carcinoma of the esophagus: final report. J Clin Oncol 1993;11:1118–1123.

[‡] Bedenne L, Seitz JF, Milan C et al: Cisplatin, 5-FU and preoperative radiotherapy in esophageal epidermoid cancer. Multicenter phase II FFCD 8894 study. Gastroenterol Clin Biol 1998;22:273–281.

[§] Posner MC, Gooding WE, Lew JI, et al: Complete 5-year follow-up of a prospective phase II trial of preoperative chemoradiotherapy for esophageal cancer. Surgery 2001;130:620–626.

[‖] Kleinberg L, Knisely JP, Heitmiller et al: Mature survival results with preoperative cisplatin, protracted infusion 5-fluorouracil, and 44-Gy radiotherpay for esophageal cancer. Int J Radiat Oncol Biol Phys 2003;56:328–334.

the primary tumor, could be used as an important prognostic factor. The 3-year survival rate was 70% for T0 to T1 with up to one positive node, 52% for T2 to T4 node negative, for T2 to T4 with one positive node, and 26% for more than two nodes regardless of T stage. Patients with metastatic disease had worse outcomes.[203] These issues may be considered in future modifications of the staging system.

Postoperative Therapy

Several randomized trials have failed to demonstrate a benefit of postoperative RT,[204,205] although postoperative chemotherapy and chemoradiation remain areas of active investigation, with some limited data to support their use under select circumstances. As was discussed in the preceding sections, adjuvant chemotherapy is poorly tolerated following combined modality therapy that includes chemotherapy. Only 54% completed the planned adjuvant chemotherapy after definitive cisplatin and 5-FU and radiation in RTOG 8501,[178] 58% received planned adjuvant taxol/cisplatin chemotherapy[202] after neoadjuvant cisplatin and 5-FU chemoradiation, and 38% received it after neoadjuvant cisplatin and 5-FU chemotherapy.[174] This lack of feasibility limits the usefulness of this strategy in spite of the concern for distant metastases. Several retrospective studies have suggested a benefit for postoperative chemoradiation after surgery alone. The only prospective data to support chemoradiation following surgery are from the randomized GI Intergroup trial for gastric adenocarcinoma or GE junction that compared postoperative 5-FU, leucovorin, and RT with observation.[206] There is a significant survival benefit when 5-FU, leucovorin, and RT are administered after resection of adenocarcinoma of the stomach or GE junction. In that trial, approximately 20% of the patients had tumor of the GE junction, and the remainder had gastric tumors. Therefore, determining the applicability of the finding to patients with tumor primarily involving the GE junction will require further study. Nevertheless, median survival for the entire population in the study was improved from 27 months to 36 months ($P = 0.005$). The 3-year survival rate was 50% versus 41%, and the 3-year relapse-free survival rate was improved from 36% to 47%.

On the basis of these limited data, it is reasonable to consider postoperative chemoradiation for patients after complete resection of stage II or III adenocarcinoma of the GE junction, but the issue is likely to remain controversial until more data that are applicable to this particular subset of patients are obtained. When there is incomplete resection, definitive chemoradiation or palliative single-modality chemotherapy or RT may be considered, depending on the clinical circumstances. Preoperative chemoradiation has been more rigorously studied and has the potential advantages of increasing long-term survival through downstaging and also that most patients are able to complete the neoadjuvant portion of therapy.

Definitive Chemoradiation

Chemoradiation (without surgery) has been demonstrated for squamous cell carcinoma to confer a statistically significant improvement in survival compared with radiation alone. It is the standard of care for locally advanced, unresectable disease and for patients with inoperable disease due to medical comorbidities. Its use as an alternative to operative management for patients with resectable squamous cell carcinoma is controversial, but the curative potential of this approach has been shown in trials that did not require unresectability as an eligibility criterion. Radiation alone should be used only in potentially curable patients who are not candidates for chemotherapy or surgery owing to medical risks. Acute and late toxicities, such as tracheal-esophageal fistula, are increased in comparison to radiation alone, but long-term survival is possible even for patients with extensive, T4 primary disease.[207] To date, there is insufficient information about this approach in the treatment of adenocarcinoma; therefore, it is recommended only for patients of this histology with medically inoperable or unresectable disease.

The landmark trial, RTOG 8501,[178,208] established the role of concurrent chemoradiation in the therapy of locally advanced squamous cell esophageal cancer (see Table 78-3). One hundred and twenty-three patients were randomized to 64 Gy RT alone or 50 Gy RT with 5-FU 1000 mg/m^2 on days 1 to 4 and cisplatin 75 mg/m^2 on day 1 every 4 weeks during RT and for two cycles every 3 weeks after RT. Eligibility criteria included localized (M0) esophageal cancer as documented with CT scan of chest and abdomen, bone scan, and pan-endoscopy. Eighty-eight percent of patients had squamous cell carcinoma. With the addition of chemotherapy, median survival was improved from 9.3 months to 14.1 months, and the 2-year survival rate was 10% versus 36%. Notably, although there were no 3-year survivors with RT alone, the 5-year survival rate with combined modality therapy was 27%. Longer follow-up demonstrated a 10-year survival rate of 20%, establishing combined chemoradiation as an alternative therapy for locally advanced, nonmetastatic squamous cell esophageal cancer. The rate of isolated locoregional persistent or recurrent disease as the site of first failure was reduced from 53% to 38%, whereas the rate of distant failure was 30% versus 16% when chemotherapy was added.[209] Although patients getting combined-modality therapy had the expected increase in acute mucosal and hematologic toxicities, there was no significant increase in late toxicities.

Randomization to chemoradiation or radiation alone on RTOG 8501 was terminated when a significant survival benefit for the chemoradiation group was demonstrated on interim analysis. A confirmatory nonrandomized group of 69 patients was treated with the experimental combined modality arm. The 5-year survival rate for this group was only 14%. The pattern of failure was similar to that of the randomized group. In the randomized and confirmatory portions of the study, there was no difference in outcome for the 15% of patients who had adenocarcinoma and the remainder with squamous cell carcinoma, although the number of patients with adenocarcinoma was too small for meaningful analysis.

The Eastern Cooperative Oncology Group[210] conducted a trial comparing RT (60 Gy) alone with the same total dose of RT and concurrent mitomycin C 10 mg/m^2 on day 2 and 5-FU 1000 mg/m^2/day for 4 days in patients with squamous cell carcinoma of the esophagus (see Table 78-3). The results of this 135-patient study were confounded by the circumstance that patients could undergo resection after 40 Gy of RT was given. Thirty-eight percent of patients were selected to have surgery. Nevertheless, median survival was improved from 9.2 to 14.8 months with the addition of chemotherapy. Two- and 5-year survival rates were 12% versus 27% and 7% versus 9%, respectively. Of note, there were no 3-year survivors who were treated with radiation alone who did not also have surgery.

Long-term follow-up is available from a phase II trial conducted by the National Cancer Institute of Milan.[211] A total of 106 patients with squamous cell carcinoma of the esophagus were treated with cisplatin 100 mg/m^2 on day 1 and 5-FU 1000 mg/m^2 on days 1 to 4 for two cycles with concurrent RT, with a total dose of 30 Gy in 15 fractions. Twenty-four of these patients also had surgery with complete resection. The overall survival rate was 22% at 5 years and 12% at 10 years, which did not differ whether or not surgery was added. These data confirm the curative potential of combined chemoradiation in squamous cell carcinoma.

A successor trial, Intergroup 0122, tested intensification of both chemotherapy and RT by increasing the dose of each drug and the total number of cycles of chemotherapy and escalating the total dose of radiation. Thirty-eight patients, all with squamous histology, were to receive a total of five cycles of infusional 5-FU and cisplatin, three cycles prior to starting radiation and two cycles concomitant with 6480 cGy of RT. This approach was subsequently abandoned, as many patients failed to complete the entire treatment course owing

to toxicity, including a 9% treatment-related death rate, and there was no suggestion of improved efficacy. However, an ongoing trial of the CALGB is now assessing this approach using irinotecan and cisplatin chemotherapy, with investigation of the predictive value of PET response assessed after neoadjuvant chemotherapy but prior to chemoradiation. A similar regimen was shown to be feasible to deliver in a multicenter phase II trial.[212]

A phase III randomized controlled trial, RTOG 94-05 (Intergroup 0123), was then pursued, addressing only intensification of the radiation dose: 64.8 Gy compared to 50.4 Gy, both combined with the identical chemotherapy of two cycles of cisplatin 75 mg/m^2 on day 1 and 5-FU 1000 mg/m^2/day for 4 days during radiation and two adjuvant cycles.[213] Of note, as in the prior two studies, RTOG 94-05 enrolled few patients with adenocarcinoma histology. Surprisingly, not only was there no improvement in median survival (13.0 versus 18.1 months) or in the 2-year survival rate (31% versus 40%) for the comparisons of the high-dose RT regimen versus the standard 50.4-Gy dose, respectively, but there was also no beneficial effect on locoregional control (44% versus 48%). The reason why higher-dose RT did not affect local control is unclear. Thus, the standard of care for definitive chemoradiation remains essentially the treatment program that was published in 1992 from RTOG 85-06: 50 to 50.4 Gy RT by once-daily fractionation (1.8 to 2.0 Gy) with four courses of cisplatin/5-FU.

While randomized trials have clearly demonstrated that chemoradiation is a curative approach for squamous cell carcinoma, this has not been established for adenocarcinoma. Prospective trials evaluating chemoradiation, including RTOG 8501, included few if any patients with adenocarcinoma, such that conclusions about survival benefit for this histology cannot be made, although the data are often extrapolated to justify this approach for unresectable or inoperable adenocarcinoma. For example, only 23 patients with adenocarcinoma were enrolled in RTOG 85-01, with a 5-year survival rate of 13% but a 95% CI of 0% to 27%.[209] The retrospective data related to chemoradiation alone for adenocarcinoma are similarly limited, suggesting poor outcome, and are subject to substantial selection bias.

The Radiation Therapy Oncology Group is planning a phase III U.S. Intergroup trial of nonoperative management that will include paclitaxel, cisplatin, and radiation with randomization to receive or not receive cetuximab. This trial will include stratification for squamous cell carcinoma and adenocarcinoma histology. In addition to determining the benefit of cetuximab in patients who are managed nonoperatively, this trial will provide important prospective information about the use of nonoperative therapy in patients with adenocarcinoma.

It is also important to note that there has not been a definitive randomized comparison of chemoradiation versus surgery alone in squamous cell carcinoma to ascertain the advantages of the two approaches in differing patient populations. Given the potential bias in the selection of patients for treatment with a nonoperative versus a surgical approach, the relative benefits of these two approaches under various clinical scenarios is unknown. However, as is discussed later, surgery might have a substantial local control benefit that can affect quality of life.

Two randomized trials of patients with resectable squamous cell carcinoma have addressed the benefit of surgery added to 5-FU and platinum-based chemoradiation regimens (Table 78-7).[214,215] To date, a survival benefit has not been demonstrated. These particular trials were associated with significant postoperative mortality, which might have diminished the possibility of detecting a therapeutic benefit. However, these trials clearly demonstrate that with the addition of surgical resection, there is substantial improvement in local control and decreased need for stent placement, which could have important quality of life benefits. These trials do not appear to have the statistical power to rule out a small long-term survival benefit, especially as immediate operative mortality is reduced over time. In addition, these trials have not included informative numbers of patients with adenocarcinoma.

A multi-institutional Fondation Française de Cancérologie Digestive trial enrolled 444 patients to receive 5-FU and cisplatin with concurrent continuous course RT 45 Gy in 4.5 weeks or split-course RT 15 Gy on days 1 to 5 and days 22 to 26. Only the 230 responding patients (88% squamous cell carcinoma) were randomized to surgery or three additional cycles of chemotherapy with additional RT, either 20 Gy with conventional fractionation or 15 Gy over 5 days. Each chemotherapy cycle was 5-FU 800 mg/m²/day continuous infusion and cisplatin 15 mg/m² 1-hour infusion on days 1 to 5. Response was assessed by esophagram and clinical improvement. Results for chemoradiation and trimodality therapy were a median survival of 17.7 versus 19.3 months, a 2-year survival rate of 34% versus 40% and a 2-year local control of 66% versus 57%. Interestingly, stents were required in 5% of surgery patients but in 32% of chemoradiation patients even though the population was preselected for positive response. The 3-month mortality rate was 9.3% with surgery versus 0.8% with combined modality therapy. Patients who were judged as nonresponders on the basis of the limited evaluation were excluded, and it is unclear whether such a population would be more likely to benefit from surgical resection of resistant tumor.

The second trial, reported by Stahl, looked at 172 patients with squamous cell carcinoma and had a median follow-up of 6 years. Patients were randomized to either three cycles of induction chemotherapy with bolus 5-FU, leucovorin, and etoposide followed by one additional cycle of chemotherapy with 40 Gy RT followed by surgery or to the same induction chemotherapy followed by chemoradiation with at least 65 Gy of RT. Overall survival was equivalent for surgical and nonsurgical treatment, while the 2-year local progression-free survival rate was significantly improved with surgery: 64% versus 41% ($P = 0.003$). The limitation of this trial was the small sample size. The survival curves began to separate after 3 years, which, along with improved local control, suggests that survival benefit from the addition of surgery might be demonstrable in a larger study. Given the limitations of both trials, chemoradiation followed by surgery remains the standard of care recommendation for patients with good performance status.

Salvage Therapy after Local Failure

The results of surgery for recurrence after definitive chemoradiation for esophageal cancer have been described for small selected groups of patients.[216–218] This intervention is associated with an increase in operative complications and mortality but also may result in long-term survival. Given the risks, only highly selected patients should be considered candidates for this approach.[219,220] Reserving surgery for patients who have clinical evidence of residual disease after chemoradiation requires prospective evaluation. A significant barrier to the success of this approach is the difficulty of assessing response to chemoradiation with noninvasive techniques, as described elsewhere in this chapter. Nevertheless, there is great interest in testing a therapeutic approach in which patients who have an apparent complete response would have close follow-up with surgical salvage if needed rather than immediate surgery.

Similarly, there is only limited information about the results of RT for isolated local failure after surgical resection.[218,221] Because combined chemoradiation is beneficial in gross disease when there is newly diagnosed esophageal cancer, we advocate this approach for the rare patient with isolated locoregional failure after full restaging evaluation. The RT dose may be limited to 45 Gy by the presence of a gastric pull-up in the treatment field.

Radiation Therapy for Management of Tracheoesophageal Fistula

The use of definitive or palliative RT in the setting of a tracheoesophageal fistula has been controversial. Although tracheoesophageal

Table 78-7 Randomized Trials Assessing Benefit of Planned Surgery After Chemoradiation

Author	No. of Patients	Patients with Adenocarcinoma (%)*	Median Survival, CRT and Surgery (mos.)	Median Survival, CRT Alone (mos.)	CRT and Surgery Local Control Rate (2-year)	CRT Alone Local Control Rate (2-year)	Treatment	Additional Findings
Bedenne et al.[214]	444	11	17.7	19.3	66% (2-year) 5% need for stent	57% (2-year) 32% need for stent	Concurrent 5-FU, cisplatin, radiation (either conventional 46 Gy or split-course treatment). If no objective clinical or radiographic response, treatment determined by the investigator. Additional chemotherapy if no surgery.	Only 229 patients responding to chemoradiation were randomized; 3-month mortality rate: 9.3% versus 0.8%.
Stahl et al.[215]	292	0	16.4	14.9	64%	41%	Chemotherapy followed by concurrent chemoradiation then surgery or more intensive chemoradiation without surgery.	Decreased cancer death rate but 12.8% treatment-related mortality in surgery arm versus 3.5%.

*Patient had either adenocarcinoma or squamous cell carcinoma.

fistula has historically been considered a contraindication to RT for fear that RT will worsen the fistula, there are data supporting its use and palliative benefit. In a report from the Mayo Clinic,[222] lysis of tumor by RT could not be shown to be an important cause of tracheoesophageal fistula. In 22 patients who developed fistula after prior RT, recurrent tumor was the cause in all cases. For 10 patients who were irradiated with known tracheoesophageal fistula, the fistula did not worsen in any patient, and 6 of 10 had local disease controlled until the time of death from metastatic esophageal cancer.[223] Combined chemotherapy and RT has also been demonstrated to close fistula in four of five responders in one series.[224,225] Additionally, stent placement with or without subsequent radiation can provide successful palliation.[226]

Cervical Esophageal Cancer

Cervical esophageal cancer is a particular treatment challenge. Surgery is extensive, requiring a total laryngopharyngoesophagectomy, an operation associated with significant dysfunction and morbidity. Frequently, postoperative RT is needed for positive margins or nodal disease, unless the primary tumor is found quite early. This has led to the use of chemoradiation as an alternative.

Extrapolating from the results of RTOG 85-01 using chemoradiation for curative treatment of thoracic esophageal carcinoma and the experience with larynx preservation for head and neck cancer, concurrent chemoradiation is used as an alternative. Definitive RT is fraught with technical difficulty in achieving adequate dose, given the complexity of treating a structure in close proximity to the spinal cord, the varying shape of the thorax and upper neck, and the bilateral lymph nodes at risk. The optimal dose is unknown, with many clinicians advocating the higher dose (70 Gy) used for treatment of head and neck squamous cell carcinomas in or bordering the cervical esophagus. Radiation techniques have included raising the arms next to the head and filling the gap between the arms and neck with tissue-equivalent material to create a simpler box shape and use of complex treatment planning with three-dimensional planning and/or intensity-modulated radiation. Burmeister and colleagues reviewed their experience treating 34 patients with cisplatin and 5-FU chemotherapy and RT 61.2.[227] The local control rate was 88%, and the 5-year estimated survival rate was 55%. Acute toxicity was acceptable, although two patients died from complications of strictures. Investigators at M.D. Anderson Cancer Center used intensity-modulated radiation with concurrent 5-FU/platinum chemotherapy to enable excellent radiation coverage of tumor plus 2 to 5 cm superiorly, 4 to 5 cm inferiorly, and 2 cm radially with coverage of nodal areas when involved. All six evaluable patients had a complete response with doses that were generally higher than those typically used in thoracic cancer: 59.4 to 66 Gy to the primary tumor.[228] Other small series have reported success with similar chemoradiation approaches.[229,230]

Nonsurgical Management of Early-Stage (Tis, IA) Esophageal Cancer

RT alone may be an alternative for some cases of early esophageal cancer. Hishikawa reported 68 patients treated with RT alone, dose 60 to 72 Gy with external beam radiation or 55 to 60 Gy plus a brachytherapy boost.[231] The 5-year cause-specific survival and locoregional control rates were 79% and 82%, respectively. Because the locoregional control rate was only 58% for tumors longer than 5 cm long, it was recommended that those patients be treated with combined chemoradiation. Modern staging with esophageal endoscopic ultrasound (not performed in this series) is essential to assess depth of invasion and stage accurately.

Endoscopic techniques may be useful for lesions that are limited to the mucosa. RT can successfully treat a bulky lesion, but the effectiveness of PDT is limited to a depth of 4 to 6 mm, and the penetration of laser or thermal energy is 6 mm or less. These techniques might be sufficient for the treatment of BE and selected patients with high-grade dysplasia but are not considered curative therapy for invasive disease. Submucosal invasion increases the risk of lymph node involvement, which cannot be addressed by these therapies. In one series, the rate of local recurrence was 29% in patients who were treated for mucosal confined adenocarcinoma at a median follow-up of 36 months.[232] In another, Tis/T1 lesions had a 44% complete response rate to PDT, and T2 lesions had a 28% complete response rate to PDT alone, with control maintained in approximately half of complete responders.[233] Although these techniques can be effective for very superficial lesions, esophagectomy is still considered the standard of care, with RT an accepted alternative for patients who are unable to undergo surgery. Endoscopic procedures for high-grade dysplasia, in situ carcinoma, or T1a (carcinoma limited to mucosa) are experimental.

Radiation Therapy Dose Selection and Outcomes

The RT dose required depends on the clinical circumstances. When RT alone is used as definitive treatment in patients who are not appropriate chemotherapy candidates, a dose of 60 to 64 Gy should generally be used. This dose is limited by esophageal tolerance, as well as the need to limit RT dose to the lung. The incidence of both early and late complications varies with total dose, administration of systemic chemotherapy, and volume of esophagus irradiated. Emami and colleagues[234] estimated the radiation dose (with conventional fractionation) that would lead to a 5% rate of clinical stricture or perforation within 5 years to be 60 Gy when one third of the esophagus is treated, 58 Gy if two thirds are treated, and 55 Gy for all of the esophagus.

Dose escalation, when RT is used as a single modality, has been safely carried out by the addition of brachytherapy, although there has been no clearly demonstrated benefit in survival or local control. Nevertheless, it is reasonable to add brachytherapy in patients treated with RT alone when the entirety of the residual disease can be encompassed in the treated volume. The American Brachytherapy Society Clinical Research Committee has published guidelines suggesting that a good candidate for brachytherapy has tumor that is no longer than 10 cm, confined to the thoracic esophagus, and without regional nodes. When brachytherapy is used, the external beam dose should be limited to 45 to 50 Gy in 1.8- to 2.0-Gy fractions, followed by a high-dose-rate boost with two to three treatments of 5 Gy or followed by one low-dose-rate brachytherapy application of 20 Gy over 24 to 48 hours. The dose is prescribed to 1 cm from the midpoint of the treatment catheter.

Given that local control is still not optimal with existing definitive chemoradiation regimens, there has been interest in intensifying the RT dose (above 50.4 Gy) used in this combined-modality approach. This question was addressed in the previously described Intergroup trial 0123 that randomized patients to a dose of 50.4 or 64.8 Gy with concurrent cisplatin and 5-FU.[213] The high-dose regimen did not improve any outcome when compared to the standard of 50.4 Gy in median survival (13.0 versus 18.1 months), 2-year survival (31% versus 40%), or control of local disease (44% versus 48%). There were 11 deaths during treatment in the high-dose arm but only 2 in the lower-dose arm. However, 7 of the deaths in the high-dose arm occurred before the dose of 50.4 Gy was reached; therefore, the dose escalation was not considered to play a role in this imbalance. Otherwise, there was no significant difference in toxicity. A separate analysis excluding the early deaths did not demonstrate any potential benefit for the higher dose. Use of intensified chemotherapy regimens or new agents that are under investigation might ultimately improve outcome but can also lead to substantially increased toxicity. For these reasons, 50.4 Gy is considered the standard dose when radiation is combined with chemotherapy.

The addition of surgery following chemoradiation can be viewed as another means of intensifying local treatment. When surgery is planned, the radiation dose should not exceed 44 to 50.4 Gy with conventional fractionation followed by a 4- to 6-week interval before

surgery. With trimodality therapy, the isolated local failure rate is low, 0% to 15%; therefore, escalating the dose of RT or further intensifying the local is not indicated or recommended. Doses greater than 50 Gy are associated with increased surgical mortality, while lower doses may be associated with increased local failure. We do not favor preoperative chemotherapy without RT, as the initial isolated local failure rate is higher.

When postoperative RT is given with or without chemotherapy, the dose should be limited to approximately 45 Gy to avoid injury to the gastric pull-up or interposed bowel.

Radiation Therapy Techniques

The treatment fields should extend a minimum of 5 cm above and below the radiographically identifiable lesion to account for microscopic or submucosal tumor extension. If definitive RT is used to doses above 50 Gy, a cone down to a margin of 2 cm above and 2 cm below the tumor should be considered. A radial margin of 1.5 to 2.5 cm to the block edge should be used, but this may be limited posteriorly as needed to keep the spinal cord dose within tolerance. In a series of patients with pathologic specimens that were analyzed after surgery alone, Gao and colleagues[235] reported that for squamous cell carcinoma, the median proximal spread and distal spread beyond gross tumor were 10.5 ± 13.5 mm and 10.6 ± 8.5 mm, respectively, with 94% of patients having all tumor contained within a 30-mm margin. For adenocarcinoma, the figures were 10.3 ± 7.2 mm proximally and 18.3 ± 16.3 mm distally, with a distal margin of 30 mm encompassing all tumor in 27 of 32 cases and a margin of 50 mm required to encompass all tumor in 94% of cases. Lymph nodes, which may be identified on CT scan, in EUS, or in PET scanning may extend beyond these margins.

Defining the extent of the tumor requires integration of data obtained from a variety of radiologic studies and procedures. Modern treatment techniques for planning esophageal RT involve the use of CT scans that depict the radial extension of the primary disease that cannot be visualized on barium studies. In addition, because barium can also underestimate the longitudinal extent of disease, all available data from endoscopy and ultrasound should be integrated into the planning process. The extent of nodal disease should be evaluated by CT scan and endoscopy with ultrasound. When appropriate, pathologic assessment of nodal disease can be obtained by ultrasound-guided needle biopsy and/or laparoscopy. PET imaging can also provide important information. Whether there is a benefit to elective treatment of clinically uninvolved supraclavicular nodes for proximal lesions is unknown. Oral contrast administration at the time of simulation and/or CT simulation enhances visualization of the tumor and adds to the precision of treatment planning. This enhances the ability to deliver an adequate dose to the target while limiting dose to the spinal cord. Consideration should be given to using immobilization devices to aid in ensuring uniform day-to-day patient positioning.

The standard approach of a three-field or four-field beam arrangement using an anterior and two posterior oblique off-cord fields with or without the addition of a fourth posterior field has become relatively standard in the treatment of esophageal cancer and allows high doses to be delivered to the tumor while limiting the radiation dose delivered to the spinal cord and lung. The dose that is delivered by the treatment fields should be weighted such that the maximal possible dose (that which delivers up to 45 Gy to the spinal cord) is delivered by the anterior and/or posterior fields, while only the remainder of the dose is delivered by the off-cord oblique fields to minimize the dose delivered to the lung tissue. However, in distal lesions, the need to limit treatment of the heart might require that more of the dose be given through the oblique fields.

This beam arrangement can also be used for treatment of upper esophageal tumors, as none of the beams enter laterally through the arms and shoulders. All fields can be treated from the first day of treatment, which has the advantage of delivering a lower fractional daily dose to uninvolved structures such as the lung, or treatment can begin with anteroposterior/posteroanterior fields only, which may allow a quicker start to treatment while a formal plan is developed, allow more margin for error in daily patient setup, and decrease daily treatment time. Under the latter circumstance, the multifield plan is generally implemented at a dose of no more than 30 to 36 Gy, as a significant daily dose to spinal cord will continue to be delivered even after the initial anteroposterior/posteroanterior treatment has been completed. When preoperative RT is given to the limited dose of 44 to 45 Gy, we generally use anteroposterior/posteroanterior fields to a total dose of 36 to 40 Gy, the remainder of the dose being given by opposed lateral off-cord fields. With this approach, the spinal cord dose is kept below tolerance levels to allow an additional 16 Gy of RT to be given by off-cord oblique fields postoperatively if there is a positive margin. In all cases, care must be taken through careful dosimetry to keep the spinal cord dose within safe limits and to take account of varying thickness of the chest longitudinally. Wedges and compensators should be used as needed to maintain homogeneity of the RT dose distribution. The spinal cord should be limited to 45 Gy, and the dose to lung tissue should be minimized. Care must also be taken to avoid an excess risk of cardiac toxicity when distal lesions are treated, which could necessitate giving a larger proportion of the radiation dose through oblique or lateral fields rather than through anteroposterior/posteroanterior portals, which generally treat more of the heart.

More recently, advanced radiation techniques such as three-dimensional planning or intensity-modulated RT are frequently used. The greater confidence in dosimetry may allow tighter margins with greater shielding of normal tissues while still ensuring more reliable coverage of the targeted volume. These techniques, while they may decrease normal tissue toxicity, are unlikely to improve outcome substantially, as marginal miss of the tumor has not been implicated as an important cause of treatment failure, dose escalation has not improved outcome, and the esophagus itself, rather than potentially shielded nearby normal structures, is generally the dose-limiting structure. It does, however, remain possible that local control was not improved with higher radiation doses in trial[213] because of an underdose of some tumor-bearing areas that can occur in using the standard radiation techniques.

We suggest that target volumes when advanced planning techniques are utilized include a clinical target volume that is 4 cm proximal and distal to the esophageal gross target volume, with caution utilized not to treat an excessive portion of the stomach. A radial margin of 1 to 1.5 cm is suggested as is a similar margin around all involved lymph nodes. For the planning target volume, an additional 0.5 to 1 cm appears prudent. Imaging to assess motion may prove to be helpful in guiding creation of a planning target volume. Although it is controversial, elective treatment of the celiac nodes may be considered for lesions in the distal third, and supraclavicular nodal treatment may be considered for lesions with significant extension above the carina. As always, patient condition and normal tissues might require limitation of margins.

There is also interest in evaluating the potential role of radiation technique for reducing the risk of postoperative pulmonary complications. Limiting the lung dose may be important, and intensity-modulated radiation therapy can be useful for achieving that goal. Interestingly, there is evidence that the volume of esophagus that is exposed to a low dose of radiation as well as the more limited volume that is exposed to a high dose, the lung effective dose, and absolute volume that is shielded from more than 5 Gy all correlate with outcome. This is possibly because these parameters are not independent and are all correlated with each other.[236] It will be important to explore this issue further, as depending on the optimization algorithm, intensity-modulated RT inverse planning systems may use a large number of beam angles to reduce the high-dose volumes, thereby exposing a higher volume of lung to radiation through these weak beams.[237] Better understanding of lung toxicity from studies of

esophageal cancer and lung cancer will allow optimal integration of this new technology. A rough guideline for lung dose in preoperative therapy based on current knowledge is to limit the total lung receiving 20 Gy or more to 20% to 30% and that receiving 10 Gy or more to 40% to 50%, although these guidelines may be exceeded as needed to achieve other important planning goals.

With improvement in survival time, there might also be a need to reevaluate treatment planning techniques to limit injury to other organs such as the heart. Some series with long-term follow-up have raised concerns about cardiac complication such as myocardial infarction or pericardial effusions. Cominos has suggested attention to techniques, such as the use of a four-field rather than a three-field technique. With a targeted dose of 54 Gy, 65% of the heart received more than 45 Gy with two fields, 57% using three fields, and 26% using four fields. Intensity-modulated RT may be useful in reducing the risk of late cardiac toxicity. Suggested dose limits include limiting the whole heart to 30 Gy and less than two thirds of the heart receiving approximately 45 Gy or more, but as long-term survivorship increases, these guidelines could require modification.

Toxicities of Radiation Therapy

Patients will experience a marked esophagitis during radiation treatment, which clears within several weeks of the conclusion of therapy. Topical anesthetics, narcotics, and H_2 blockers are used to minimize discomfort during eating. Oral nutritional supplements should be used to maintain nutritional state. Feeding tubes can be placed prior to therapy if necessary. Other grade III or greater early effects are uncommon but can include skin reactions, laryngeal toxicity (if in treatment field), and pneumonitis. In RTOG 8501, toxicity with both radiation alone and combined chemoradiation were prospectively collected.[178] Five percent of patients who were treated with 60 Gy RT alone developed grade III or greater esophagitis, whereas 20% of those who were treated with concurrent chemoradiotherapy (50 Gy) developed these symptoms. Late esophageal toxicity was observed in 10 of 53 patients versus 11 of 51 patients. Benign stricture is the most common serious late complication, reported to occur in 12% to 30%[238–240] of curatively treated patients, and can be treated with dilation, although experience shows that most long-term strictures are associated with recurrent tumor rather than with the radiation. Decreased esophageal motility, delayed emptying, and reflux may occur. With increased long-term survival, the issue of radiation-induced cardiac and lung injury may be more important to consider in radiation technique.

The toxicities with brachytherapy have not been well quantified. One series of 148 patients who were treated with external beam RT 60 Gy over 6 weeks followed a week later by 12-Gy high-dose-rate brachytherapy in two fractions reported a 28% rate of ulceration, a 10% rate of stricture, and a 6% rate of fistula. Except for fistula formation, which was generally fatal, the complications were rarely severe.[231] In RTOG 9207,[241] the concept of adding brachytherapy, 5 Gy three high-dose-rate treatments, to chemoradiotherapy (as in RTOG 8501) was tested, but the incidence of fistula was excessive (6 of 35 patients), and this approach is not recommended.

Swallowing Function and Palliative Radiation Therapy

Esophageal obstruction due to malignancy can lead to dysphagia that can be painful, associated weight loss, malnutrition, fatigue, and a loss in the enjoyment of eating. Since these signs and symptoms reduce the quality of life of esophageal cancer patients, the restoration of the ability to swallow is a key objective of both curative and palliative treatments. The management of malignant esophageal obstruction should not compromise or interfere with curative therapy. Placement of a percutaneous gastric or jejunostomy feeding tube and esophageal stents may be useful in temporizing symptoms, improving quality of life, and optimizing the patient's nutritional status while curative therapy is initiated. Other endoluminal treatments such as laser, PDT, or brachytherapy are generally not appropriate in situations in which curative treatment is the goal. For patients who are not candidates for curative therapy, the palliative treatment that is selected often depends on the likelihood of success given the length and location of the lesion, life expectancy, and the expertise of the treating team.

Radiation alone improves dysphagia in approximately 70% of patients, and chemoradiotherapy improves dysphagia in 88%.[242–244] Relief is not immediate but is reasonably rapid, with a median time to maximal improvement of 4 weeks (range: 2 to 21 weeks). High doses of RT are generally required for effective palliation and should be used whenever life expectancy is greater than 3 months and Karnofsky performance status is 60 or greater. The addition of chemotherapy should be considered for appropriate patients because of the potential for enhanced response and local control. Relief of dysphagia for the remaining lifetime occurs in approximately half to two thirds of patients who are treated with such aggressive palliative regimens.

A recent review of 106 patients with malignant esophageal obstruction who were treated palliatively with radiation and 5-FU chemotherapy demonstrated that 49% of patients had complete resolution of dysphagia and 78% had improvement of their dysphagia. Over half maintained their improved swallowing function until death or last follow-up with a median survival of 7 months.[245] In considering this option, it should be noted that the toxicity of therapy may transiently worsen swallowing prior to improvement. Therefore, this option, which provides more durable long-term control, is best utilized in patients who have an estimated survival time that justifies the treatment time, toxicity, and recovery period associated with this approach.

Palliative RT with or without chemotherapy can be used to prevent recurrence of swallowing difficulty after stent placement or laser therapy.

Brachytherapy, a procedure that uses endoscopically delivered radiation, is useful in selected cases for palliative treatment of esophageal cancer and can be used in patients who were previously treated with external beam RT.[246] A catheter with a width of 0.6 to 1 cm is inserted, and the lesion is treated with a 1- to 2-cm margin. The dose is generally prescribed at a distance of 1 cm from the radioactive sources, and dose falloff beyond this range is rapid. Therefore, only patients with symptoms resulting from tumor that is confined primarily to the esophageal wall and lumen itself can be effectively and durably palliated. High-dose-rate brachytherapy uses short applications of several minutes each, which are more convenient for the patient and do not require inpatient care. However, several applications are usually required, as fractionated treatment is thought to be safer. With low-dose-rate RT, in which treatment is given at 0.4 to 1.0 Gy/hr, treatment is given with one or two insertions of the applicator but over 24 to 48 hours. Although this approach does require overnight admission and prolonged esophageal intubation, fewer applications are needed, and the technology is more widely available.

The American Brachytherapy Society Consensus Guidelines panel has recommended several palliative regimens as being appropriate.[246] Palliation occurs in 50% to 90% of cases.[247–251] In previously untreated patients, a limited dose of external beam RT (i.e., 30 Gy) can be followed by high-dose-rate brachytherapy (10 to 14 Gy in one or two fractions) or low-dose-rate brachytherapy (20 to 25 Gy in a single application over 1 to 2 days). Dysphagia was palliated by external beam RT followed by brachytherapy in 90%[252] in one series, but the relative benefits of this approach compared with higher doses of external beam RT alone are unknown.

These brachytherapy regimens are generally considered safe, although the rate of complications, including acute esophagitis, ulceration, and stricture, are not well quantified in patients treated for palliation. Brachytherapy along with chemotherapy or immediately following concurrent conventional chemoradiation can result in an unacceptable rate of fistula formation. Brachytherapy can be safely

given several weeks after laser therapy and may increase the dysphagia-free interval,[253–255] while its role along with PDT is uncertain.

Chemotherapy alone may also be considered for palliation of dysphagia, but there are few data evaluating this endpoint. It has been found that 20% to 30% of patients generally respond to chemotherapy used for palliation, and an equivalent proportion would be expected to experience transient improvement in dysphagia symptoms. Depending on the clinical situation, a trial of chemotherapy could be reasonable before endoscopic therapies are considered.

Endoscopic Palliation

Endoscopic techniques to restore esophageal luminal patency are usually palliative procedures that are reserved for patients who are not candidates for curative therapy. However, endoscopic therapy can also be quite useful to provide symptom improvement prior to curative therapy in patients with total or near total malignant obstruction prior to initiation of curative therapy. This can result in increased patient tolerance of subsequent therapy.

The available endoscopic options for management of malignant dysphagia have shifted from using rigid funnel-shaped tubes to the use of expandable stents, laser fulguration, and PDT. Since there are no studies directly comparing the efficacy of the available endoscopic treatment modalities, the treatment modality that is chosen for each patient depends on the length, location, and angulation of the stricture; the patient's overall health status; the cost of the technique; the experience of the endoscopist; and the presence or absence of an esophagorespiratory fistula.

Owing to the relatively high incidence of complications, rigid funnel tubes have been replaced by self-expanding metallic stents (SEMS) and self-expanding plastic stents (SEPS), which are compressible, are easier to place, and have fewer complications. The first-generation SEMS were uncovered and were associated with rapid tumor ingrowth that resulted in stent obstruction. Up to 78% of patients who survived at least 4 months required repeat endoscopic intervention for palliation from tumor ingrowth. Newer SEMS are covered with polyethylene, polyurethane, or silicone sheaths to delay or prevent in growth of tumor, substantially reducing the need for repeat endoscopic procedures. SEMS require less tumor dilatation for insertion and expand to greater luminal diameter than rigid stents and have thinner walls to minimize erosion and hemorrhage. SEMS may be "stacked" on top of another to manage tumor growth over the top of a previously placed expandable stent. Successful insertion of SEMS is reported to occur in over 90% of patients. Initial complications are less frequent and less morbid than those reported with the use of rigid tubes.

A series of 127 stent placements in 100 patients reported no fatal complications; 1.6% of patients suffered severe pain necessitating removal, 3.1% of patients had inadequate deployment, 0.8% of patients suffered perforation, 7.9% of patients had a food impaction, 11% of patients reported severe reflux, and 8.7% of patients suffered stent migration requiring removal. Two of sixteen patients who underwent subsequent chemotherapy after stent placement suffered stent erosion through the esophageal wall. Studies suggest an increased rate of stent-related complications in patients who have undergone prior chemoradiation.[256] Patients will suffer from severe reflux when the esophageal stent traverses the GE junction, and this could result in life-threatening aspiration. There is a SEMS with an antireflux valve that might reduce risk of reflux; however, its success in clinical practice is limited, and widespread use of the antireflux stent is not practiced. Stents that are placed distally into the gastric lumen may be prone to migration and/or the distal end can cause gastric mucosal ulceration, resulting in hemorrhage. This can often be managed endoscopically. SEMS cannot be placed within 2 cm of the cricopharyngeal muscle, as patients cannot tolerate the SEMS owing to severe pain and the sensation of a foreign body in the upper esophagus. There is no difference in efficacy or complication rates among any of the currently available SEMS. SEPS are also available and are indicated for malignant dysphagia, but there have been no comparative studies between SEPS and SEMS. SEPS can be better tolerated if they are placed near the cricopharyngeal muscle and are removable. However, the migration rate might be increased in comparison to SEMS. Despite these complications, placement of esophageal stents for malignant dysphagia does improve swallowing in 88% to 100% of patients.

A clear indication for placement of a SEMS is the presence of a esophagorespiratory fistula. In comparison to other endoscopic options, placement of a SEMS is often a successful palliative measure. In small series, SEMS were found to be effective in sealing esophagorespiratory fistulas with low complication rates.[257] Consideration should be given to placing a respiratory stent as well. A retrospective comparison of self-expandable stent placement and palliative esophagectomy demonstrated palliation with stents that was as least as good as that of surgery over the limited follow-up period with less risk when compared to esophagectomy.

Other endoscopic options for palliation of malignant dysphagia include neodymium : yttrium- aluminum-garnet laser, electrofulguration with a monopolar or bipolar (BICAP) coagulation, and PDT. Short, circumferential, and nonangulated strictures are ideal for laser or electrocoagulation techniques. The mean number of endoscopic sessions that are required to achieve adequate luminal patency is three to four, and there does exist a risk of perforation. After initial success in achieving adequate palliation, repeat endoscopic treatments are usually required to maintain esophageal luminal patency. Successful improvements in swallowing symptoms have been reported in 64% to 100% of patients.

Endoscopic laser therapy is not recommended in the setting of an esophagorespiratory fistula, which is best managed with placement of a SEMS. Complications include fevers, perforation, aspiration pneumonia, and later stricture formation. The reported procedural mortality rate ranges from 0% to 5%. Siegel and colleagues[258] have reported improved survival in patients with squamous cell esophageal tumors who are treated with endoscopic laser therapy when compared with clinical stage-matched controls. The authors speculate that the survival advantage in the treated group might be due to tumor debulking, improved nutritional status, decrease in aspiration pneumonia, enhanced sense of well-being, and patient motivation. A randomized trial has demonstrated that palliative RT reduces the need for repeat procedures for recurrent obstruction and might be warranted in patients with good performance status and limited disease who are likely survive for a long period,[259] a concept that also might apply when other means of endoscopic palliation are utilized.

Electrofulguration techniques use either a monopolar probe or a BICAP. The monopolar probe directly coagulates the obstructing endoluminal tumor under endoscopic control. The BICAP tumor probe is passed through the narrowed esophageal lumen over a guide wire. The mechanism of action of the BICAP includes dilation of the narrowed lumen, tumor coagulation, hyperthermia, and tissue necrosis with delayed sloughing. Because the BICAP probe coagulates blindly and circumferentially, it is not recommended for noncircumferential lesions, since injury to the normal esophageal mucosa may result in perforation. Comparisons of electrocoagulation (monopolar or bipolar) with neodymium : yttrium-aluminum-garnet laser techniques have shown comparable results in terms of morbidity, mortality, and relief of dysphagia. Electrocoagulation is generally less costly than laser.

PDT is a technology that has generated a great deal of interest in the lay and scientific literature. This technique involves the administration of a chemical sensitizer, usually hematoporphyrin derivative or dihematoporphyrin ethers, that accumulates preferentially in the target tumor. The tumor is then exposed to a specific-wavelength low-power laser light that activates the accumulated sensitizing chemical, resulting in tumor necrosis mediated by production of singlet

oxygen radicals. Tumor cell death results from a photochemical and not a thermal effect as with laser techniques. The clinical feasibility of using PDT to manage early or unresectable esophageal cancer is well documented. PDT can be repeated to maintain tumor control. Since the light penetrates only several millimeters, this therapy is most useful for palliative benefit, as only superficial tumors would be treated in their entirety. One series with long-term follow-up demonstrated that 6 of 7 patients maintained controlled disease with an estimated 5-year survival rate of 62%. In another series with median follow-up of 19 months, superficial adenocarcinoma was ablated in 9 of 12 patients.[260]

For more advanced tumors that are thicker or where lymph nodes are involved, PDT is not a potentially curative therapy and is used for palliation. There are studies that document that PDT is at least as effective as laser therapy in palliation for patients with esophageal cancer and is associated with a lower incidence of perforation.[261,262] In a series of 215 patients undergoing palliative PDT, the mean dysphagia-free interval was 66 days. Complications included perforation (2% of treatment courses), stricture (2%), Candida esophagitis (2%), pleural effusions (4%), and sunburn (6%). The procedure-related mortality rate was 1.8%, and median survival was 4.8 months in this population.[263] Disadvantages of PDT relative to other methods of endoscopic palliation include a prolonged period of photosensitivity that may seriously affect quality of life, the risk of post-treatment esophageal strictures, and significant cost (for both the laser and the chemical agents). The potential role of PDT in the therapy of BE is discussed in the section related to therapy of that condition. Newer agents for PDT may be developed that absorb wavelengths of light that will penetrate more deeply into tissue.

Chemotherapy for Advanced Disease

In general, patients with metastatic or recurrent carcinoma of the esophagus have a large tumor burden, their response to chemotherapy is brief (several months), and systemic therapies have limited impact on survival. Clinical trials of new agents are appropriate for this patient population. Palliation of symptoms and improvement in quality of life should be the major goals, but these endpoints are rarely measured. Many of the published trials of the regimens that are most commonly used consist of small numbers of patients and both histologic types; response rates are quite variable, often influenced by the extent of prior treatment and patient performance status, and the 95% confidence intervals for response are often wide. It is not known whether giving chemotherapy prolongs survival over best supportive care and whether treatment with single-agent chemotherapy confers any benefit over combination chemotherapy. In general, combination chemotherapy regimens have greater efficacy than do single agents on the basis of response rates that vary from approximately 30% to 50%. The evaluation of biologics in esophageal cancer, as single agents or added to standard chemotherapy, is just beginning and consists of very limited preliminary data that have mainly been reported in abstract form. There is a rationale for and interest in targeting the epidermal growth factor receptor and vascular endothelial growth factor receptors, in particular as discussed in recent reviews.[264,265] Trials are in progress, and as yet, no biologics have been approved for treatment of esophageal squamous cell carcinoma or adenocarcinoma.

Single agents with reported activity include bleomycin, 5-FU, mitomycin-C, doxorubicin, methotrexate, cisplatin, venorelbine, paclitaxel, and docetaxel. The major response rate to these single agents is in the range of 15% to 30%. Only a few drugs have been adequately tested in patients with esophageal adenocarcinoma. A 31% response rate was observed in a phase II trial of paclitaxel tested in a total of 51 chemonaive patients with esophageal squamous cell carcinoma or adenocarcinoma that was recurrent or metastatic. The dose of paclitaxel was 250 mg/m^2 infused over 24 hours, repeated every 3 weeks.[266] Thirty-three patients had adenocarcinoma, and 11 patients responded. For all patients, the median duration of response was 17 weeks, and the median survival time was 10.2 months. Two other schedules of paclitaxel have been tested. A weekly 1-hour infusion of 80 mg/m^2 was inactive (5% response rate) in patients with prior chemotherapy; in those without prior chemotherapy, a 16% (8 of 50) response rate was reported for adenocarcinoma and a 13% (2 of 15) response rate for squamous cell carcinoma.[267] In contrast, no responses were observed in a small trial of 14 patients who were treated with a 96-hour infusion schedule of paclitaxel 140 mg/m^2 every 21 days.[268] It is noteworthy that the commonly used dose of 175 to 225 mg/m^2 by 3-hour infusion every 21 days has not been evaluated. Also noteworthy is the lack of efficacy of carboplatin that was observed in three well-conducted phase II trials from the 1980s and 1990s in patients with chemonaive recurrent or metastatic adenocarcinoma. Docetaxel has been studied less in esophageal carcinoma. Two phase II trials have been reported; one tested 75 mg/m^2 every 21 days in a total of 22 patients with recurrent esophageal adenocarcinoma and reported an 18% (95% CI: 2.3 to 52) response rate in chemonaive patients and no responders in those who had previously been treated for recurrence.[269] The second trial evaluated docetaxel 100 mg/m^2 every 3 weeks in patients with adenocarcinoma of the upper GI tract origin and reported a 17% (95% CI: 8 to 30) response rate in 41 patients.[270] Cytotoxics that have not been tested as single agents in esophageal cancer, although frequently used in combination regimens because of their activity in other adenocarcinomas of the GI tract, include irinotecan, oxaliplatin, and gemcitabine.

The combination regimens that are most frequently used in the current management of patients with recurrent or metastatic esophageal cancer are shown in Table 78-8. Response rates vary from series to series, with many trials enrolling small numbers of patients and a mix of patients with esophageal squamous cell carcinoma and adenocarcinoma. Response rates are generally in the range of 30% to 50%, with response duration of 3 to 6 months and median survival time of 6 to 8 months. Studies reporting longer median survival rates may reflect variation in patient characteristics, such as better performance status, fewer comorbidities, and limited prior treatment, rather than reflecting more effective therapy. Cisplatin plus 5-FU has been used in patients with both adenocarcinoma and squamous histologic types with similar response rates, in the 30% range.[271] Irinotecan, paclitaxel, docetaxel, and gemcitabine have been studied in various two-drug combinations, most often paired with cisplatin. Whether these regimens improve on the outcome of standard 5-FU/cisplatin has not been assessed, nor is it clear whether any of these regimens improve survival compared to best supportive care.

The combination of cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 has been evaluated by using a weekly schedule for 4 weeks recycled every 6 weeks or a two-out-of-three-week schedule (days 1 and 8 every 21 days). The results of three trials that included patients with both histologic types demonstrated a major response rate ranging from 36% to 58%.[272–274] Because of toxicity concerns (neutropenia and diarrhea) with the 4-weekly dose regimen, the days 1 and 8 schedule is preferred and appears to be equally effective. A multicenter trial of irinotecan + cisplatin (days 1 and 8 schedule) plus bevacizumab is noteworthy for impressive response rates albeit in a small number of patients with GE junction adenocarcinoma.[275] A 65% (95% CI: 46 to 80%) major response rate was reported in 47 previously untreated patients with either metastatic or unresectable gastric (24 patients) or GE junction (23 patients) adenocarcinoma. The median time to progression was 8.3 months, and median survival was 12.3 months. These encouraging results require confirmation in a larger study limited to adenocarcinoma of the distal esophagus/GE junction.

Paclitaxel has been combined with cisplatin with reported response rates of 41% to 44%. A response rate of 41% was reported in a trial of 32 patients using a biweekly regimen of paclitaxel 90 mg/m^2 infused over 3 hours and cisplatin 50 mg/m^2 repeated every 14

Table 78-8 Activity of Combination Chemotherapy in Recurrent and Metastatic Disease

Chemotherapy	Histology	No. of Trials	Response Rate (%)	Reference
Cisplatin + 5-FU	S	1	34	271
Cisplatin + irinotecan	S + A	3	36–58	272, 273, 274
Paclitaxel + cisplatin	S + A	2	41–44	276, 277
Docetaxel + irinotecan	S + A	2	30–33	278, 279
Docetaxel + venorelbine	S	1	60	280
Gemcitabine + cisplatin	S + A	2	41	281, 282
Gemcitabine + 5-FU + leucovorin	S + A	1	31	285
Oxaliplatin + 5-FU + leucovorin	S + A	1	41	284
Paclitaxel + cisplatin + 5-FU	S + A	1	48	286

days.[276] In an earlier phase II trial, paclitaxel 200 to 250 mg/m^2 as a 24-hour infusion on day 1 followed by cisplatin 75 mg/m^2 on day 2 produced a response rate of 44% (46% for adenocarcinoma and 25% for squamous cell carcinoma) with a median response duration of 3.9 months.[277] However, toxicity was unacceptable with the 24-hour infusion schedule of paclitaxel (grade IV neutropenia occurred in 47% of patients, 50% required hospitalization, and 11% died of therapy-related complications). The most commonly used dosing schedule of this regimen is paclitaxel 175 mg/m^2 infused over 3 hours followed by cisplatin 75 mg/m^2, repeated every 21 days, which, as used in other solid tumor malignancies, is well tolerated. This particular regimen has not been formally tested in recurrent/metastatic esophageal cancer. Docetaxel has also been combined with irinotecan and tested in patients with metastatic disease including both histologies.[278] A 30% response rate was observed in 15 patients treated with irinotecan 160 mg/m^2 followed by docetaxel 60 mg/m^2 every 21 days. However, a 71% incidence of grade IV neutropenia and a 43% incidence of febrile neutropenia was unacceptable, and the regimen was abandoned. By contrast, an alternative low-dose weekly scheduling of these two agents (docetaxel 35 mg/m^2 and irinotecan 50 mg/m^2, days 1 and 8 every 21 days) has been evaluated in esophageal cancer[279] and other GI malignancies with acceptable toxicity. A 33% response rate was reported in previously untreated patients with metastatic adenocarcinoma and squamous cell carcinoma histologies. The combination of docetaxel and venorelbine has activity in recurrent squamous cell esophageal carcinoma according to a small phase II trial in 20 patients that reported a 60% response rate and median overall survival of 10.5 months, although this combination is also associated with substantial myelotoxicity.[280]

Gemcitabine-based doublets have also been studied. The Southwest Oncology Group tested gemcitabine 1000 mg/m^2 on days 1, 8, and 15 and cisplatin 100 mg/m^2 on day 15 repeated every 28 days in patients with recurrent or metastatic esophageal carcinoma.[281] Survival was the primary endpoint of this trial, which enrolled 64 patients and found a median survival of 7.3 months and a 1-year survival rate of 20%. Another group evaluated cisplatin 50 mg/m^2 on days 1 and 8 followed by gemcitabine 800 mg/m^2 on days 2, 9, and 16 in chemonaive patients with unresectable or metastatic squamous cell carcinoma (12 patients) or adenocarcinoma (24 patients) and reported a 41% (14/34) response rate and a median survival of 9.8 months.[282] Cumulative myelosuppression was the major toxicity. The Southwest Oncology Group also evaluated the combination of gemcitabine 1000 mg/m^2 and irinotecan 100 mg/m^2, both drugs given on days 1 and 8 based on preclinical data suggesting dose-dependent synergy.[283] The primary endpoint of this trial, which enrolled 57 patients with recurrent/metastatic squamous cell carcinoma or adenocarcinoma, was 6-month survival. Although the predetermined statistical endpoint was reached with a 56% 6-month survival rate, toxicity was substantial, and the median survival of only 6.3 months was not better than that expected with other doublets.

Two small (35-patient) single-institution phase II studies that included both histologies evaluated the combination of oxaliplatin, 5-FU, and leucovorin[284] and the combination of gemcitabine, 5-FU, and leucovorin.[285] Response rates of 41% and 31.4%, respectively, and median survivals of 7.1 months and 9.8 months, respectively, were reported. Finally, two trials added a taxane to the cisplatin/5-FU base regimen. One tested paclitaxel, cisplatin, and 5-FU in 60 chemonaive patients with unresectable or metastatic esophageal cancer, including both histologic types. A 48% response rate (46% adenocarcinoma, 50% squamous cell carcinoma) and median survival of 10.8 months were reported.[286] The other trial was a phase III multicenter comparison of docetaxel, cisplatin, and 5-FU (DCF) versus cisplatin and 5-FU (CF) as first-line therapy for recurrent or metastatic gastric cancer.[287] A total of 445 patients were enrolled, 22% of whom had a primary tumor in the GE junction. While benefit cannot be determined for GE junction cancers separate from distal gastric adenocarcinoma, nor can it be assumed owing to the differing natural history and pattern of failure for these cancers, the results are noteworthy given the dearth of comparative trial data for esophageal carcinoma of either histologic type. Response, overall survival, and time to progression endpoints were all significantly improved with the three-drug regimen; the median time to progression was 5.6 months for DCF versus 3.7 months for CF (HR: 1.47, 95% CI: 1.19 to 1.82, $P < 0.001$), and the median overall survival was 9.2 months for DCF versus 8.6 months for CF (HR: 1.29, 95% CI: 1.0 to 1.6, $P = 0.02$). These results, however, must be balanced against the significantly increased incidence of severe and life-threatening toxicity (neutropenia, febrile neutropenia, infection, and diarrhea) with DCF compared to CF in this population of untreated patients with good performance status.[288]

In summary, there are now a number of chemotherapy options for treating metastatic or recurrent esophageal squamous cell carcinoma and adenocarcinoma in addition to cisplatin and 5-FU. Whether any one regimen is superior to another in terms of response, survival, or palliation of symptoms is unknown, owing to a lack of comparative trial data. All regimens are associated with substantial toxicity. A recent Cochrane database review attempted to sort out these issues.[289] Randomized controlled trials comparing chemotherapy to best supportive care or comparing two chemotherapy regimens in patients with metastatic squamous cell carcinoma of the esophagus or adenocarcinoma of the esophagus and GE junction were included. Two randomized trials with best supportive care as the control arm were found, but the total number of patients was only 42; five trials compared different regimens (with a total of 1242 patients), but the patient populations and chemotherapy regimens were so varied that a formal pooled analysis could not be performed. The authors rightly

concluded that there is a need for well-designed, adequately powered controlled trials and assessments of quality of life for esophageal cancer patients.

BARRETT'S ESOPHAGUS WITH HIGH-GRADE DYSPLASIA

BE is a premalignant condition for esophageal and GE junction carcinomas and is characterized by intestinal metaplastic changes in the esophageal epithelium as confirmed by biopsy. Because of its premalignant nature, it is recommended that patients with BE undergo regular endoscopic surveillance, primarily to assess for dysplasia. The consensus statement from the American College of Gastroenterology recommends annual surveillance endoscopy for patients with low-grade dysplasia and more aggressive intervention in patients with high-grade dysplasia, since this can be associated with adenocarcinoma. Patients with high-grade dysplasia should undergo a second endoscopic biopsy surveillance procedure to increase the chance of detecting a concomitant early cancer. If no cancer is detected, then patients have several options, including remaining in an endoscopic biopsy surveillance program every 2 to 3 months, esophagectomy, or endoscopic ablative therapy with continued surveillance.[25,290]

The care of patients with high-grade dysplasia is controversial, and treatment should be individualized, taking into account the patient's desires, medical fitness to undergo esophagectomy, and willingness to return for frequent endoscopies. Any patient who will not return at the recommended endoscopic intervals and who has a diagnosis of high-grade dysplasia, confirmed by an expert GI pathologist and a repeat endoscopic biopsy surveillance procedure, should undergo esophagectomy performed by an experienced esophageal surgeon. Esophagectomy is the only treatment option that allows a patient to safely stop periodic endoscopic biopsy surveillance.[24] Even the patient who chooses endoscopic ablative therapy must be willing to undergo endoscopic biopsy surveillance indefinitely. A recent randomized controlled trial of photodynamic therapy of patients who had high-grade dysplasia reported that although numbers of cancers were cut in half compared to numbers in patients who did not have ablation, it did not completely eliminate the risk of malignancy.[291]

Dysplasia in Barrett's mucosa refers to cytologic and histologic epithelial changes that are considered neoplastic. It does not refer to reactive or inflammatory epithelial changes, which are most commonly seen with esophagitis. Historically, it was thought that a minimum of 3 cm of columnar lined epithelium was required for the diagnosis of BE. These shorter lengths of columnar lined epithelium were considered to be normal variants and exempt from the complications of BE. Currently, it is accepted that no length of columnar lined epithelium is normal and that these short segments of BE are susceptible to all of the potential complications of BE, including the development of dysplasia and adenocarcinoma.

On the basis of mucosal architecture, epithelial morphology, and cytologic findings, dysplasia is classified as low, intermediate, and high grade. It is generally accepted that dysplasia in BE precedes the development of invasive adenocarcinoma. Tytgat and Hameeteman[292] illustrated that dysplasia is a prerequisite of adenocarcinoma, that low-grade dysplasia is potentially reversible and that once the threshold of high-grade dysplasia is reached, the patient is at risk for progression to adenocarcinoma. It is unclear which factors influence the time of progression from high-grade dysplasia to adenocarcinoma. As was discussed in the earlier section on pathogenesis of adenocarcinoma, evidence exists that an accumulation of mutations or epigenetically mediated changes in expression of key genes may play an important role.

The diagnosis of Barrett's mucosa with dysplasia is made histologically via endoscopic biopsies. Because of the significance of high-grade dysplasia in terms of patient management, it is important that the diagnosis be confirmed by a pathologist who is experienced in this area, and second opinions obtained as needed.[293–295]

As was noted earlier, three options are available to manage patients with high-grade dysplasia. Heitmiller and colleagues[296] advocated prophylactic esophagectomy for patients with high-grade dysplasia, citing data showing that high-grade dysplasia is a premalignant condition in which no regression has been documented and that occult invasive adenocarcinoma is found in 45% to 50% of patients who undergo esophagectomy with the diagnosis of high-grade dysplasia alone. In their series, operative mortality was 3.3%, occult invasive adenocarcinoma was found in 43% of patients, and the tumor was locally advanced in five of these patients. The authors emphasized that this aggressive surgical therapy is recommended only for patients who are suitable surgical candidates. This is the current standard of care, although it is controversial.

The data to settle the controversy about optimal approach to high-grade dysplasia are not yet available. The existing data suggest a high enough risk that esophagectomy should be strongly considered. Levine and associates[297] reported an endoscopic biopsy protocol that they believe can accurately differentiate high-grade dysplasia from adenocarcinoma. Four-quadrant jumbo forceps biopsies were performed at 2-cm intervals, with additional specimens from any areas of known dysplasia. On the basis of their series of seven patients in whom follow-up surgery confirmed the absence of invasive cancer, the authors advocate endoscopic follow-up for patients with high-grade dysplasia alone. In their series of 22 patients who were followed up in such a fashion for an average of 32 months (range: 4 to 67 months), in none has a known invasive adenocarcinoma developed. However, another group[298] used similar biopsy procedures before esophagectomy, and 10 of 38 were found to have unsuspected invasive adenocarcinoma in the surgical specimen. When high-grade dysplasia is followed up rather than treated, varying risk has been found in several recent large series. This incidence of adenocarcinoma has been reported to be 59% (5-year cumulative),[299] 32% (8-year follow-up),[300] and 16% over a period of 7.3 years.[301] The reason for the varying risks identified is unclear, although in the series with the smallest incidence, no confirmation of diagnosis of high-grade dysplasia was made by a central pathologist. Therefore, although intensive endoscopic surveillance might be a reasonable approach, a substantial portion of patients may have existing adenocarcinoma that was not detected on biopsy, or adenocarcinoma will develop over several years of follow-up. Novel endoscopic imaging techniques and equipment are being developed to improve detection of dysplastic BE.[302–304]

A third option is endoscopic ablative therapy for high-grade dysplasia, although long-term data are only beginning to be assessed. Recent data show resolution of high-grade dysplasia in 78% of patients who were treated with PDT, over a 5-year follow-up.[305] This is an extension of prior data, which showed that patients who were treated with PDT demonstrated 88% resolution of high-grade dysplasia and 78% resolution of low-grade dysplasia.[260] Berenson and coworkers[306] recently reported that endoscopic argon laser photoablation of Barrett's mucosa, in conjunction with antacid therapy with omeprazole, resulted in squamous epithelial reepithelialization. More advanced techniques include endoscopic mucosal resection (which can be combined with PDT) and cryotherapy. Ablation rates are comparable, but long-term data are lacking.[307–309] Such ablative techniques are intriguing; however, further investigation is required to determine whether they reduce the risk of adenocarcinoma.

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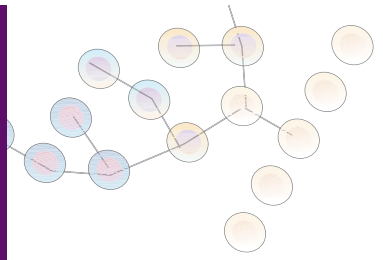
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79 Cancer of the Stomach

Leonard L. Gunderson, John H. Donohue, and Steven R. Alberts

SUMMARY OF KEY POINTS

Epidemiology and Pathology
- For stomach cancer in the United States the expected incidence in 2007 was 21,260 cases and 11,210 deaths.
- These cancers are usually adenocarcinomas.
- In the United States the site of origin is shifting as more proximal lesions are diagnosed.

Biologic Characteristics
- Prognostic factors relate to tumor extent and include nodal involvement and extension beyond the gastric wall.
- Ploidy may be an independent prognostic factor.

Staging Evaluation
- Staging should always include history and physical examination, complete blood cell count, liver chemistries, chest film, endoscopy with biopsy, ultrasonography (determine degree of direct tumor extensions), and computed tomography (CT) of the abdomen (define extragastric disease).
- Additional studies that may help define extragastric extent of disease include upper gastrointestinal imaging, CT of the chest (for gastroesophageal junction lesions), and laparoscopy (rule out peritoneal seeding or early liver metastases).

Primary Therapy
- Surgical resection is the primary therapy of resectable gastric cancers.
- Cure rates of 80% or higher are achieved only with early lesions (nodes negative, confined to mucosa or submucosa), which are uncommon in the United States.
- Role for extended node dissection has not been found in randomized trials.

Adjuvant Therapy
- Adjuvant therapy (chemotherapy, irradiation) is indicated on the basis of patterns of relapse and survival results with surgery alone (high incidence of local-regional relapse and distant metastases).
- Most Western chemotherapy trials are negative for both single and multiple drugs.
- Irradiation alone reduced local-regional relapse and improved overall survival in a Beijing trial of 370 patients testing preoperative irradiation versus surgery alone (5-year survival rate 30% vs. 20%, $P = 0.009$).
- U.S. intergroup phase III trial of 556 patients found a survival benefit for combined-modality postoperative irradiation plus chemotherapy versus surgery alone (3-year relapse-free survival [RFS] 48% vs. 31%, $P = 0.001$; 3-year overall survival [OS] 50% vs. 41%, $P = 0.005$).
- A British phase III trial of 503 patients demonstrated a survival advantage for perioperative ECF chemotherapy (epirubicin, cisplatin, 5-fluorouracil [5-FU]) when compared with surgery alone (5-year OS 36% vs. 23%, $P = 0.009$).

Locally Advanced Disease
- Combined external beam irradiation (EBRT) plus chemotherapy or intraoperative irradiation (IORT) produced long-term survival in 10% to 20% of patients in most randomized and nonrandomized trials.
- Neoadjuvant chemotherapy studies reveal possible increase in resection rates but high incidence of local-regional relapse (consider addition of IORT alone or with EBRT and concurrent chemotherapy to neoadjuvant chemotherapy regimens).

Palliation
- Palliative resection of gastric component of disease may be indicated.
- Multiple-drug chemotherapy regimens have response rates of 30% to 50%, but most regimens do not affect survival. The ECF regimen had improved response rates and survival when compared with FAMTX (5-FU, doxorubicin, high-dose methotrexate) in a British Phase III trial. European phase III trials demonstrate improved quality and duration of life with palliative chemotherapy versus supportive care.

INTRODUCTION

At the time of diagnosis, gastric cancers are localized and surgically resectable in approximately 50% of patients; however, regional nodal metastases or direct invasion of surrounding organs or structures are frequently encountered and preclude cure by surgery alone in many patients. Analyses of patterns of relapse after complete surgical resection demonstrate that subsequent relapse of cancer is common in both the tumor bed and nodal regions as well as systemically.

The standard of care for resectable gastric cancer for patients who can tolerate a surgical procedure is surgical resection. For patients with lower risk lesions (confined to gastric wall, nodes negative; T1–2N0M0 [see Table 79-2]) adjuvant treatment is usually not recommended except in select instances. Because both local and systemic relapses are common after resection of high-risk gastric cancers (beyond wall, nodes positive, or both; T3–4N0, TanyN+), adjuvant treatment is indicated for these patients. The results of phase III trials that demonstrate a survival benefit for preoperative

irradiation, postoperative chemoradiation, or perioperative chemotherapy with epirubicin, cisplatin, and continuous-infusion 5-FU (ECF) versus surgery alone will be summarized and future trial designs will be discussed.

For patients with locally advanced disease that seems unresectable for cure, several treatment options seem to have a favorable impact on disease control and survival. These options include primary external beam irradiation (EBRT) plus concomitant chemotherapy, maximal resection plus intraoperative irradiation (IORT), and preoperative chemotherapy or chemoradiation before resection. Results of these approaches will be summarized and future trial design will be discussed.

In the setting of metastatic disease, many active chemotherapy agents can produce meaningful response alone or in combination with other agents, but the duration of response is often limited. Trials now exist that demonstrate both a survival and quality-of-life benefit for multidrug chemotherapy versus best supportive care for individuals with metastatic cancers.

EPIDEMIOLOGY AND ETIOLOGY

In 2007, cancer of the stomach had an expected incidence in the United States of 21,260 cases and an expected number of 11,210 deaths.[1] Despite these impressive figures, age-adjusted gastric cancer death rates have decreased markedly in the United States since 1930 from approximately 28 to 2.3 in 100,000 females and from 38 to 5.2 in 100,000 males (Fig. 79-1). Of the 45 countries in which age-adjusted death rates for gastric cancer were compared for 2000 (Fig. 79-2), the United States ranked forty-fifth for both males and females.[2] Kyrgyzstan ranked first for both males (47.0 in 100,000) and females (18.9 in 100,000).

The causes of the decline in the U.S. rates are incompletely understood, but environmental factors, chiefly dietary, are suspected. Within the United States the lowest incidence is in whites, Chinese, and Filipinos, with a higher incidence in U.S. Japanese. However, epidemiologists have noted a significant decrease in incidence among migrants from high-incidence countries (such as Japan and Chile) to low-incidence countries. Although there is an overall reduction in gastric cancer incidence, there has been a steady rapid increase in the incidence of gastroesophageal junction and proximal gastric cancers.

Factors that have been associated with a higher incidence of gastric cancer include smoked or salted foods, foods contaminated with aflatoxin, low intake of fruits and vegetables, low socioeconomic status, and possibly a decreased use of refrigeration.[3,4] Possible occupational relationships include coal mining and rubber or asbestos workers. Precursor pathologic conditions include pernicious anemia, achlorhydria atrophic gastritis, gastric ulcers, and adenomatous polyps. Between 5% and 10% of individuals with pernicious anemia subsequently develop malignancy. Prior partial gastrectomy for benign gastric or duodenal ulcer disease produces an increased risk of subsequent malignancy in the gastric remnant with latency periods of 20 years or more.[5,6]

Several studies have shown a three- to sixfold increased risk of gastric cancer in individuals with *Helicobacter pylori* infection versus those with no infection, but the precise role of this bacterium in the etiology of gastric cancer remains unknown.[7–9] A variety of bacterial, patient, and environment factors most likely act in combination to affect the development of gastric carcinoma. The increased association of *H. pylori* with gastric cancer seems to be mainly with distal gastric cancers and intestinal-type malignancy. Only a minority of *H. pylori*-infected individuals develop gastric cancer, and data do not yet exist on the effect of treatment of the *H. pylori* infection on subsequent malignancy.

PREVENTION AND EARLY DETECTION

Early detection would markedly improve the prognosis of gastric cancer in the United States, because surgical resection has a high cure rate with lesions limited to the mucosa or submucosa. However, the incidence of such early gastric cancers is less than 5% in most U.S. series. In Japan the incidence of carcinomas confined to the mucosa or submucosa was only 3.8% in the 1955 to 1956 period. However, by 1966 the incidence of early lesions had increased to 34.5% because of vigorous screening procedures, leading to 5-year survival rates of 90.9% in this cohort of patients.[10] Although mass screening has been useful in Japan to detect early cancers, defined high-risk populations have not existed in the United States in the past to justify the expense of widespread screening endeavors. Whether screening of individuals with *H. pylori* infection would be of value is not yet known. Individual practitioners should use upper gastrointestinal (GI) series or preferably endoscopy to screen patients who have occupational or precursor risk factors or individuals with persistent dyspepsia or gastroesophageal symptoms.

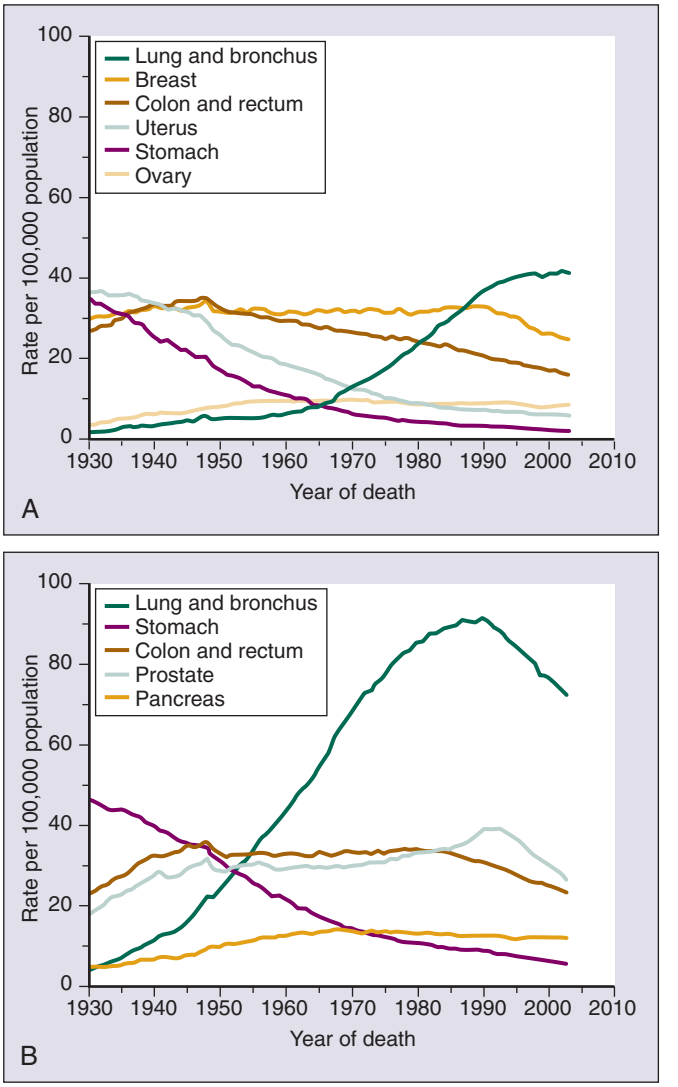


Figure 79-1 • Age-adjusted (to U.S. 1970 standard population) cancer death rates in the United States from 1930 to 2003 in selected sites for females (**A**) and males (**B**). Females have a steady decrease in death rates for stomach, breast, and colorectal cancers. From 1960 to 1998, a continual increase in death rates occurred for lung cancer in females. For males, a similar decrease in death rates occurred with gastric cancer. An increase in death rates for lung cancer existed in males from 1930 to 1990 with a continual decrease during the 1990s. (Data from Jemal A, Siegal R, Ward E, et al: Cancer statistics, 2007. CA Cancer J Clin 2007;57:43–66.)

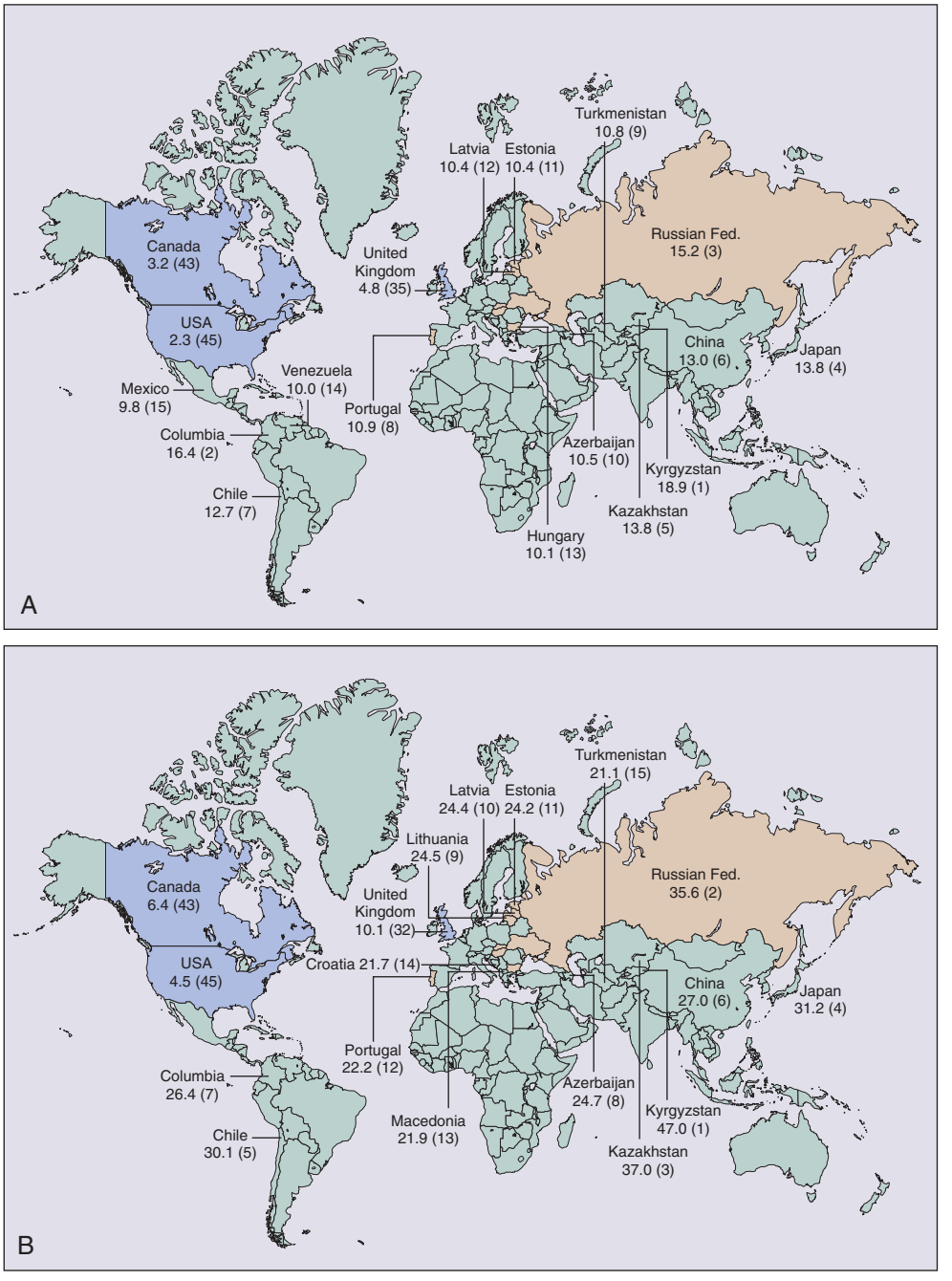


Figure 79-2 • Age-adjusted (to World Health Organization world standard population) death rates for gastric cancer from 2000 in 45 countries for females (**A**) and males (**B**). Rates in the United States, Canada, and United Kingdom are compared with selected countries, including the 15 countries with the highest death rates. (Data from Jemal A, Thomas A, Murray T, et al: Cancer statistics, 2002. CA Cancer J Clin 2002;52:23–47.)

Germline mutations in the *CDH1* gene, which encodes the E-cadherin protein, have recently been recognized in families with hereditary diffuse gastric adenocarcinoma. Carriers of these mutations have a 70% lifetime risk of developing gastric cancer. Several reports of prophylactic gastrectomy[11–13] have demonstrated the routine presence of microscopic intraepithelial carcinomas in patients having regular endoscopic surveillance that includes multiple random biopsies. Early total gastrectomy has been recommended for this small patient population because of the lack of effective early tumor detection by less aggressive techniques. Microscopic evaluation of the proximal and distal resection margins for complete removal of the gastric mucosa is necessary, because residual gastric mucosa can degenerate and result in a gastric cancer.[13]

PATHOLOGY

The terms gastric cancer and stomach cancer usually refer to adenocarcinoma, which accounts for 90% to 95% of all gastric malignancies. Other histologic types include lymphoma (usually intermediate- or high-grade histologic types), leiomyosarcoma, carcinoid, adenoacanthoma, and squamous cell carcinomas. The site of origin within the stomach has changed in frequency in the United States over recent decades, with more proximal lesions now being diagnosed and treated. The largest percentage of gastric cancers still arises within the antrum or distal stomach (around 40%), are least common in the body of the stomach (around 25%), and are of intermediate frequency in the fundus and esophagogastric junction (around 35%).[14]

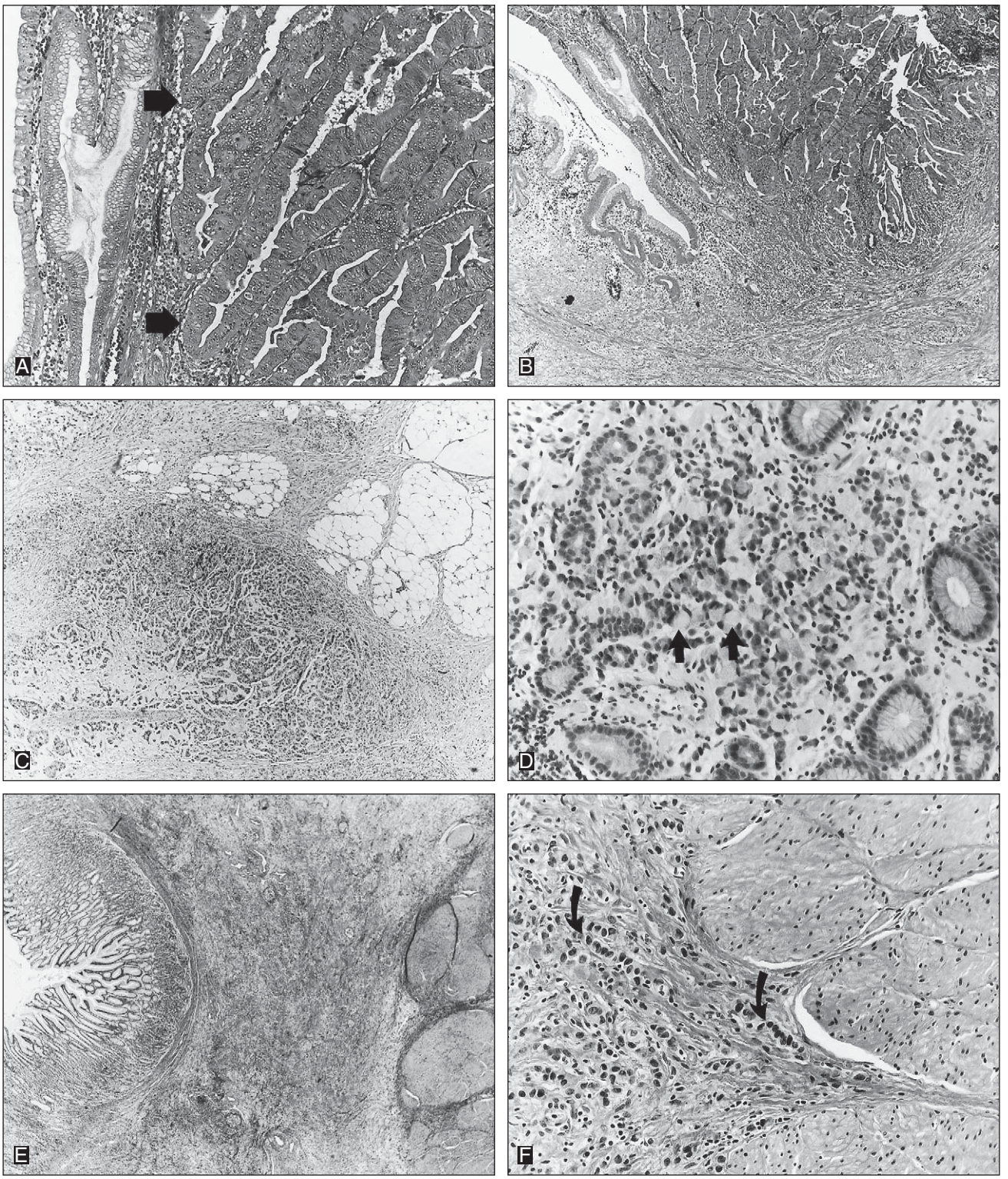


Figure 79-3 • Photomicrographs demonstrating histopathologic features of gastric cancer. **A–C,** Gastric adenocarcinoma, intestinal type. **A,** The neoplasm shows complex gland formation (*arrows*). This type would be regarded as moderately differentiated or grade 2 in a four-grade system. (×125.) **B,** This tumor infiltrates the superficial portion of the submucosa. Typical of intestinal-type adenocarcinoma, the pre-existing gastric epithelium is obliterated. (×42.5.) **C,** This tumor extends into perigastric serosa and, in view of the more irregular gland formation, would be graded with grade 3 of 4. (×42.5.) **D–F,** Diffuse-type gastric adenocarcinoma. **D,** Diffuse-type adenocarcinomas often contain signet cells (*arrows*). (×225.) **E,** Linitis plastica. Note how the underlying mucosa, submucosa, and muscularis propria appear thickened but are otherwise intact, in contrast to intestinal-type adenocarcinomas (**B**). (×22.5.) **F,** Linitis plastica at high power. Neoplastic cells may be very subtle (*arrows*). This tumor extended to the peritoneal surface and had metastasized. (×125.) (Courtesy of K. Batts, MD, Department of Pathology, Mayo Clinic, Rochester, MN.)

Gastric carcinomas have been categorized by using both microscopic (Fig. 79-3) and gross pathologic features. The Lauren classification system includes an intestinal type with improved prognosis that predominates in regions with high prevalence of gastric cancer, as well as a diffuse histologic type, with poor prognosis, which occurs more commonly in countries with low prevalence of stomach cancer.[15] Grossly, gastric cancers can be categorized according to Borrmann's[16] five types: I, polypoid or fungating; II, ulcerating lesions surrounded by elevated borders; III, ulceration with invasion of the gastric wall; IV, diffusely infiltrating (linitis plastica); and V, unclassifiable. The Japanese Research Society for Gastric Cancer has a classification system that divides lesions into protruded (I); superficial (II) with elevated (IIa), flat (IIb), and depressed (IIc) subtypes; and excavated (III) types.[17]

Pathways of Tumor Spread

Direct Extension

The stomach is surrounded by a number of organs and structures that can be involved by direct extension once a lesion has extended beyond the gastric wall. These structures include the omenta, pancreas, diaphragm, transverse colon or mesocolon, duodenum, jejunum, spleen, liver, superior mesenteric and celiac vessels, abdominal wall, left adrenal gland, and kidney. Adherence from inflammatory conditions can mimic direct extension of tumor, but all adhesions between a gastric carcinoma and adjacent structures must be regarded as malignant.

Lymphatics

Abundant lymphatic channels are present within the submucosal and subserosal layers of the gastric wall. Microscopic or subclinical spread well beyond the visible gross lesion (intramural spread) occurs via these lymphatic channels. Accordingly, frozen sections of the gastric resection margins should be obtained intraoperatively to ensure that margins of resection are uninvolved microscopically. The submucosal lymphatic plexus is also prominent in the esophagus and the subserosal plexus in the duodenum, allowing both proximal and distal intramural tumor spread.

Because of the numerous pathways of lymphatic drainage from the stomach, it is difficult to perform a complete nodal dissection (Fig. 79-4). Although initial drainage is usually to lymph nodes along the lesser and greater curvatures (perigastric or N1 nodes using the Japanese Research Society for Gastric Cancer designation), primary node drainage includes nodes along all three branches of the celiac axis (common hepatic, splenic, left gastric) and the celiac artery itself (Japanese N2 nodes).[14] Node groups that are more distal include hepatoduodenal, peripancreatic, root of mesentery (N3), periaortic, and middle colic (N4). When proximal gastric lesions extend into distal esophagus, the paraesophageal nodal system is at risk for involvement.

Hematogenous Spread

For malignancies confined to the stomach, venous drainage is primarily to the liver via the portal system. At initial exploration, liver involvement is found in up to 30% of patients, predominantly as a result of hematogenous metastases but sometimes because of direct tumor extension. For lesions that extend proximally to involve the esophagus or posteriorly, the lung may be at risk for distant metastases.

Peritoneal Involvement

Because the stomach is an intraperitoneal organ, peritoneal dissemination is possible once a lesion extends beyond the gastric wall to a free peritoneal (serosal) surface. Peritoneal spread may initially be a localized process limited by surrounding organs and ligaments (gastrohepatic, gastrosplenic, and gastrocolic).

BIOLOGIC CHARACTERISTICS

Prognostic Factors

The most meaningful prognostic indicators relate to extent of tumor. With either hematogenous metastasis or peritoneal seeding, prognosis is almost uniformly fatal. Recent immunohistochemical analysis of bone marrow aspirates has shown the presence of tumor cells to be an independent predictor of adverse outcome; however, confirmatory studies have yet to be published.[18,19] Survival decreases with progressive direct tumor extension both within and beyond the gastric wall.[20,21] Lymph node involvement, per se, is not as important as the number and location of nodes.[22–24] Minimal lymph node involvement adjacent to the primary lesion results in the most favorable prognosis in node-positive patients, but even micrometastases in regional nodes may adversely impact survival.[25] The solitary finding of either involved lymph nodes or complete penetration of the gastric wall is usually not as ominous as the presence of both[20,23] (Table 79-1).

The tumor grade and the gross and histologic pathologic appearance of the primary malignancy seem to provide some prognostic information, but none of these factors is a prognostic variable independent of the tumor stage. Prognosis is generally worse with higher grade and diffuse-type carcinomas, which usually present with higher pathologic stages of disease (see Fig. 79-3). Borrmann types I and II carcinomas have a relatively favorable 5-year survival rate, but patients with type IV tumors (linitis plastica) fare very poorly.[26,27]

Some investigators have suggested that tumors of the gastric cardia may have epidemiologic factors different from cancers of the distal stomach[28,29] and may exhibit different tumor biology.[30] The prognosis is worse for cardia lesions,[31,32] and flow cytometry reveals a greater incidence of aneuploidy when compared with tumors of the antrum and body.[33]

Flow cytometry provides valuable prognostic information for gastric cancer and may be an independent prognostic factor.[33,34] As noted previously, aneuploidy is associated with unfavorable tumor location such as the cardia[33,35] but is also associated with lymph node metastasis[34,35] and direct tumor extension.[34] Unfavorable DNA flow cytometry characteristics seem to relate closely to an unfavorable prognosis.[33,34] In one series in which multivariate analysis of DNA ploidy was analyzed with other known prognostic factors such as stage, age, and sex, DNA ploidy carried statistically significant independent prognostic information.[34]

The presence of several peptides including estrogen receptor,[36] epidermal growth factor receptor,[37] the e-erb-b2 protein,[38] and plasminogen activator inhibitor type 1[19] seems to affect prognosis adversely. The expression of epidermal growth factor receptor and high levels of epidermal growth factor correlate with a higher incidence of primary tumor infiltration, poor histologic differentiation, and linitis plastica. The pathophysiologic relationship between these peptide receptors and poor patient prognosis is not clear. Gastric cancers with class II major histocompatibility complex antigen expression (human leukocyte antigen [HLA]-DR) have a better prognosis, but the loss of expression is not an independent prognostic factor.[39]

CLINICAL MANIFESTATIONS, PATIENT EVALUATION, STAGING

Neither patient symptoms nor routine physical examination will lead to an early diagnosis of gastric cancer. The most common presenting symptoms and signs are loss of appetite, abdominal discomfort, weight loss, weakness (due to anemia), nausea and vomiting, and melena. The duration of symptoms is less than 3 months in nearly 40% of patients and longer than 1 year in only 20%.

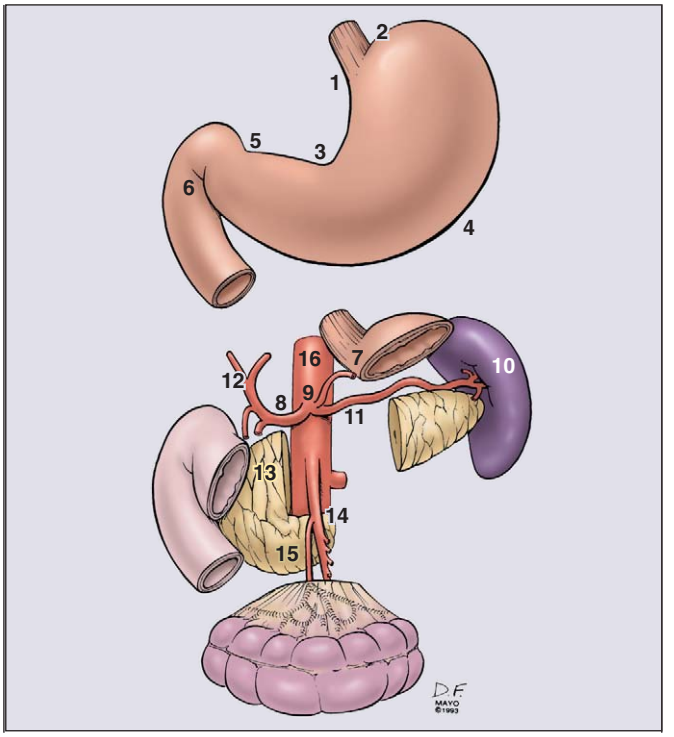


Figure 79-4 • Classification and anatomic location of lymph node groups. Involvement of nodes along the lesser or greater curvature (groups 1–6) constitutes N1 disease, and the celiac axis and its three branches are N2 (7–11), N3 (12–14), and N4 (15, 16). N1: 1, right paracardial; 2, left paracardial; 3, lesser curvature; 4, greater curvature; 5, suprapyloric; 6, infrapyloric. N2: 7, left gastric artery; 8, common hepatic artery; 9, celiac artery; 10, splenic hilus; 11, splenic artery. N3: 12, hepatic pedicle; 13, retropancreatic; 14, mesenteric root. N4: 15, middle colic artery; 16, para-aortic. (Reprinted by permission of the Mayo Foundation.)

Evaluation of the Patient

Positive findings on physical examination are those of advanced disease. Findings may include an abdominal mass (representing the primary tumor, hepatic metastasis, or ovarian metastasis [Krukenberg's tumor]), remote node metastasis (left supraclavicular [Virchow's node]; periumbilical [Sister Mary Joseph node]; or left axillary [Irish's node]), ascites, or a rectal shelf (peritoneal seeding).

The diagnosis of gastric cancer is usually confirmed by upper GI endoscopy, or radiographs. Double-contrast radiographs may reveal small lesions limited to the superficial (inner) layers of the gastric wall. Endoscopy is now the preferred initial diagnostic test, because it allows direct tumor visualization, cytologic testing, and histologic biopsy that yield the diagnosis in 90% or more of patients with exophytic lesions. Ulcerated cancers and linitis plastica lesions may be harder to diagnose endoscopically, but multiple biopsies and washings enhance the probability of accurate diagnosis. Endoscopic ultrasonography (EUS) has a high degree of accuracy in determining depth of tumor invasion (i.e., does the lesion extend beyond the muscularis propria?) but is less accurate in detecting regional nodal metastasis.[40–42] Ultrasound-guided fine-needle aspiration for cytologic test allows the assessment of regional lymph nodes and some distant metastatic sites (e.g., liver), further enhancing the ability of EUS to determine tumor stage and resectability.

The extent of disease at exploration or laparoscopy is usually more extensive than is suggested on upper GI radiography or endoscopy. Abdominal CT scan is valuable in determining the abdominal extent of disease with regard to larger liver metastasis (1 cm or greater), involvement of celiac or periaortic nodes, or extragastric extension (may help determine which lesions extend to surgically unresectable structures). CT scan is of little value, however, in ruling out peritoneal metastases or small hepatic metastasis. Diagnostic laparoscopy allows visualization of small serosal or liver metastases and may give added information with regard to the amount of direct extension of the primary tumor. Distant (hematogenous) metastases should be ruled out with a chest radiograph, serum liver chemistries, and abdominal CT scan, or liver ultrasonography (we prefer CT scan to ultrasonography because of the additional information concerning regional nodal status, extragastric extent of disease, and extension within the distal esophagus). CT scans also provide valuable tumor

Table 79-1 Extent of Initial Disease versus Survival Rates in Stomach Cancer*

Extent of Disease	5-YEAR SR (%) Dockerty[20†]	5-YEAR SR (%) Kennedy[22]	>5-yr DFS University of Minnesota Reoperation Series[21]
LYMPH NODES –			
Mucosa only	100	85	—
>Mucosa but within wall	61	52	—
Through wall	44	47	—
LYMPH NODES +			
Lymph node extent	15	—	19
Regional only	—	17	—
Nonregional	—	5	—
Extent of primary			
Within wall	—	—	40
Through wall	—	—	12

DFS, disease-free survival; SR, survival rate.
*Compilation of data from various series.
†Percentages are only of patients who left the hospital.

Table 79-2 TNM Staging for Carcinoma of the Stomach*

Stage	T	N	M
0	TIS	0	0
IA	1	0	0
IB	1	1	0
	2	0	0
II	1	2	0
	2a/b	1	0
	3	0	0
IIIA	2a/b	2	0
	3	1	0
	4	0	0
IIIB	3	2	0
IV	4	1–3	0
	1–3	3	0
	Any	Any	0

TIS, carcinoma in situ; intraepithelial tumor without invasion of the lamina propria; T1, tumor invades lamina propria or submucosa; T2, tumor invades the muscularis propria (T2a) or the subserosa (T2b); T3, tumor penetrates the serosa (visceral peritoneum) without invasion of adjacent structures; T4, tumor invades adjacent structures; N0, no regional lymph node metastasis; N1, metastasis in 1–6 regional nodes; N2, metastasis in 7–15 regional nodes; N3, metastasis in more than 15 regional nodes; M0, no distant metastasis; M1, distant metastasis.

*Metastases to other intra-abdominal lymph nodes such as hepatoduodenal, retropancreatic, mesenteric, or para-aortic are considered distant metastases within this system but are N3 or N4 in the Japanese Research Society Classification.

localization information should irradiation be indicated. If a proximal gastric tumor extends to involve the esophagus, CT scan of the chest is useful in determining mediastinal node involvement or parenchymal lung metastases.

Staging

With the development of laparoscopic general surgery, diagnostic laparoscopy is commonly used to assess for distant metastasis or unresectable locally advanced abdominal cancers. Several groups[43,44] have reported the use of laparoscopy in stomach cancer patients. Metastatic disease was documented laparoscopically in 35% to 40% of patients.[43–45] The sensitivity for metastases was 85% or greater[44,45] and this technique was particularly sensitive in detecting liver and peritoneal disease. Laparoscopy is more sensitive and accurate in staging patients with regard to intra-abdominal metastases than either ultrasound or CT scan.[45,46] Many surgeons now routinely perform laparoscopy in all gastric cancer patients who do not require palliation, to avoid nontherapeutic laparotomy.

The current TNM (tumor, lymph node, metastasis) staging system is depicted in Table 79-2 and is acknowledged as the standard system for reporting outcomes in stomach cancer.[47] Several comparison studies, including some from Japan,[48,49] have shown better prediction of prognosis using the AJCC TNM system compared with other staging systems, including that of the Japanese Research Society for Gastric Cancer.

PRIMARY THERAPY AND RESULTS

Surgical Method

Surgical excision of the gastric and nodal components of disease remains the primary therapy for all potentially curable gastric carcinomas. Based on pathologic findings, the Japanese Research Society for Gastric Cancer has defined four categories of surgical resection: (1) absolute curative (no peritoneal or hepatic metastases, no serosal involvement, and a level of lymph nodes removed beyond those involved); (2) relative curative (same as 1 but nodal involvement to the level excised); (3) relative noncurative (complete gross tumor excision but curative criteria not met); and (4) absolute noncurative (residual cancer).[17] Most curable tumors can be removed with adequate margins by subtotal gastrectomy; total gastrectomy is used when mandated by proximal cancer location or disease extent. Routine total gastrectomy does not improve survival by providing wider margins and eliminating multicentric disease but may increase the rates of patient morbidity and mortality. A randomized study[50] showed similar survival rates with subtotal and total gastrectomy. Surgical resection alone, including endoscopic mucosal resection in selected patients[51], is an excellent treatment for gastric carcinomas limited to the mucosa or submucosa without nodal involvement (TIS or T1N0M0). These early gastric cancers now occur with an incidence of over 30% in Japan but still less than 5% in the United States and other Western countries. At least one Japanese report showed similar excellent results for T2 cancers if lymph nodes were uninvolved.[52] For the more invasive gastric carcinomas, curative or palliative resection is indicated for 50% to 60% of patients at the time of disease presentation, but only 25% to 40% of these patients will have potentially curative surgical procedures. Increasingly subtotal[53] and total[54] laparoscopic gastrectomies are being performed safely and without apparent compromise of patient outcome.

Only one prospective randomized trial[50] exists with regard to the extent of gastric resection, but extensive experience exists with various different surgical procedures, and appropriate generalizations can be made. The preferred treatment for lesions arising in the body or antrum of the stomach is a radical distal subtotal resection (Fig. 79-5). This removes approximately 80% of the stomach along with the first portion of the duodenum, the gastrohepatic and gastrocolic omenta, and the nodal tissue adjacent to the three branches of the celiac axis. Extensive or proximal cancers will require a total gastrectomy to achieve an adequate proximal gastric margin (Fig. 79-6). Total gastrectomy provides no advantage when subtotal gastrectomy will provide a 5-cm clearance of the gross tumor.[50] The propensity for gastric carcinoma to spread via submucosal and subserosal lymphatics dictates the need for a 5-cm surgical resection margin of normal stomach beyond the visible tumor. It may be necessary to extend the resection to include some (or additional) esophagus or duodenum if frozen-section pathologic evaluation of the surgical margins fails to confirm the adequacy of proximal and distal resection margins. If total gastrectomy is necessary, a splenectomy is sometimes performed, particularly in gastric cancers of the proximal third of the stomach, and tumors of the body near the greater curvature. These cancers are more apt to metastasize to lymph nodes in the splenic hilum that cannot be completely excised without a splenectomy. The value of routine splenectomy has been addressed in a prospective randomized trial. No benefit of splenectomy was apparent in this trial.[55]

Direct spread beyond the gastric wall should be treated with en bloc extended resection to achieve negative margins of resection, if a curative resection is contemplated.[56,57] These extended resections are potentially curative but increase perioperative morbidity and mortality. Common examples of local tumor extension include involvement of the body or tail of the pancreas (treated by distal pancreatectomy and splenectomy), invasion of the transverse mesocolon (often requires transverse colectomy), and involvement of the spleen (splenectomy) or left lobe of the liver (usually requires wedge resection with a 1-cm or wider clearance).

The optimal extent of lymph node dissection for gastric cancer remains controversial. The presence and extent of lymph node metastasis correlate with the depth of primary tumor invasion.[58] Japanese surgeons universally advocate regional lymph node removal for all

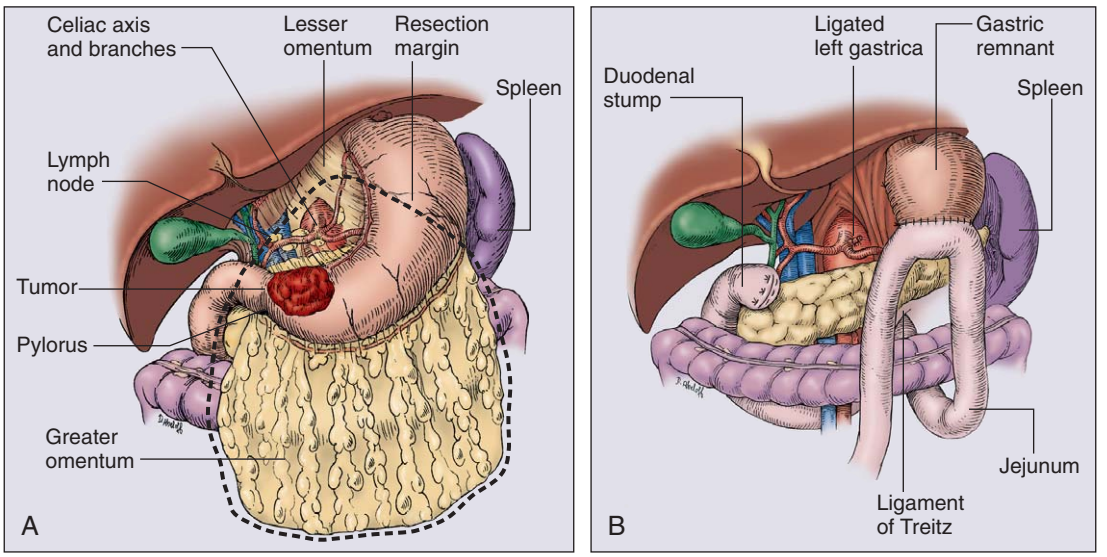


Figure 79-5 • **A,** Radical subtotal gastrectomy. The extent of resection for this tumor of the antrum includes the distal 80% of the stomach, the lesser and greater omenta, the perigastric lymph nodes (Japan N1), and lymph nodes along the left gastric, celiac, and common hepatic arteries (Japan N2). **B,** Radical subtotal gastrectomy reconstruction. After closure of the duodenal stump and lesser curvature of the stomach, the gastric remnant and proximal jejunum are anastomosed end to side in an antecolic position. The spleen and distal pancreas have been left in situ.

but in situ or intestinal mucosal tumors as a means to improve both local control and survival.[59] Because more distal nodes can be involved with metastasis in 11% of patients with negative perigastric nodes, a wider regional nodal dissection is deemed necessary for cure.[58] A recent study of sentinel lymph node biopsies in gastric cancer patients in Japan[60] demonstrated that 37% of tumors drained to N2 nodes, either in combination with N1 sentinel nodes (32%) or as the sole site of lymphatic drainage (5%). When performing a radical subtotal gastrectomy and omentectomy, all N1 and N2 nodes should be removed (D2 dissection; see Fig.79-4) (N1, perigastric nodes; N2, nodes along the left gastric, common hepatic, celiac, and splenic arteries). Some surgeons in Japan routinely remove N3 lymph nodes (D3 dissection, usually portal and retropancreatic). A recently completed prospective trial of D2 versus D3 dissections determined that the more extensive lymphadenectomy did not increase complication rates, but no long-term survival outcomes are available for this study.[61]

Thus far, randomized trials[62,63] have not demonstrated either disease-free or overall survival advantage for extended lymphadenectomy (D2 dissection). A large multicenter phase III study that accrued 711 curable gastric cancer patients in the Netherlands[62] noted significantly higher morbidity and mortality rates with the more exten-

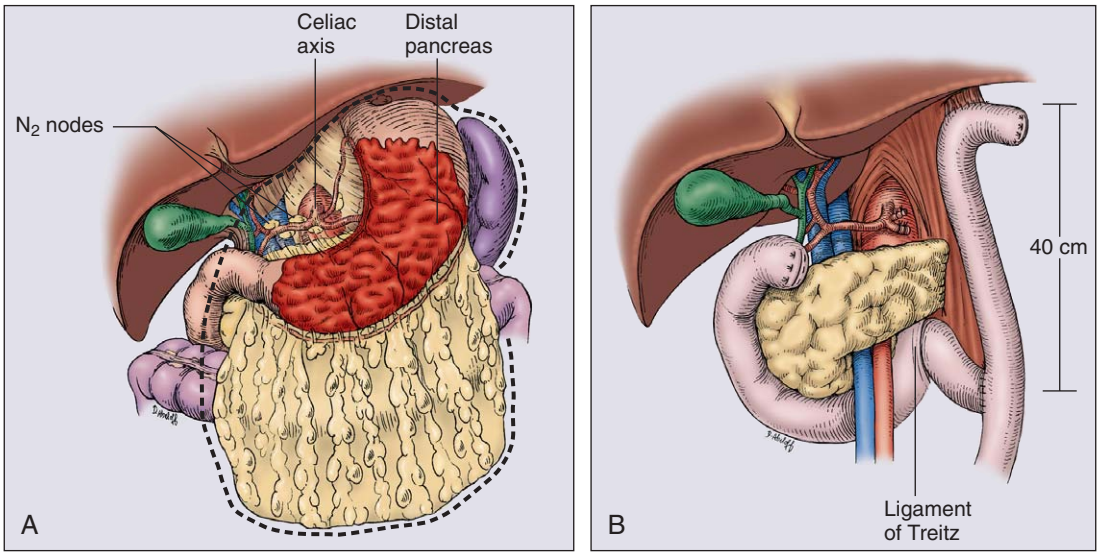


Figure 79-6 • **A,** Radical total gastrectomy. A total gastrectomy is indicated for this extensive tumor of the stomach. Both omenta, the spleen, distal pancreas, and Japan N2 lymph nodes are to be included with the operative specimen. **B,** Radical total gastrectomy reconstruction. Although a variety of anastomoses and jejunal pouches have been described, no benefit seems to accrue from any approach, except to keep the biliary and pancreatic secretions away from the esophageal mucosa. The Cohn end-to-side Roux-en-Y esophagojejunostomy with a 40-cm limb is depicted.

Table 79-3 Extent of Surgery: Randomized Trials of D1 versus D2 Dissection

Series	No. of Patients	5-YR SURVIVAL (%)		OPERATIVE MORTALITY (%)		
		D1	D2	D1	D2	*P* Value
Dutch[62]	711	45	47	4	10	<0.05
MRC[63]*	400	35	33	6.5	13	<0.05

Both trials showed significantly increased morbidity and mortality with more extensive dissections.
*Defined D1 dissection as resection of AJCC nodes (those within 3 cm of primary tumor).

sive nodal dissection (Table 79-3). A randomized study from the United Kingdom that included 400 patients with gastric adenocarcinoma also demonstrated higher morbidity and mortality rates in the extended lymphadenectomy cohort (see Table 79-3).[63] Neither the Dutch[62] nor the British trial[63] demonstrated any improvement in overall or disease-free survival (see Table 79-3). In the Dutch study,[62] patients who did not undergo a splenectomy or distal pancreatectomy had an improvement in relapse-free survival ([RFS] 71% vs. 59% at 5 years, $P = 0.02$). Splenectomy and pancreatectomy had significant adverse impact on survival in both trials.[62,63] Preliminary data from a Japanese trial comparing D2 and D3 resections[61] and an Italian study comparing D1 and D2 resections[64] did not show increased morbidity with extended lymphadenectomy. Results for disease-free and long-term overall survival are not yet available from either study.

Any potential survival benefit seen with the extended node dissection performed in Japan may be due to the phenomenon of a stage migration rather than superior surgical therapy.[65] In Japan and the United States gastric resection specimens are handled quite differently.[66] Japanese pathologists evaluated an average of 62 nodes in subtotal gastrectomy specimens and as many as 100 in total gastrectomy cases, including lymph nodes less than 3 mm in diameter.[67] This number compares with an average of 12 and 13 nodes examined after subtotal and total gastrectomy, respectively, at Memorial Sloan-Kettering.[68] Patient survival after a curative operation significantly improves when more than 15 lymph nodes are pathologically examined.[69,70] Failure to evaluate an adequate number of regional lymph nodes probably results in the understaging of many gastric cancer patients. N2 nodes cannot be defined as positive if they are not resected and examined; involvement of resected N1 nodes cannot be assessed if the specimen is not thoroughly evaluated by the pathologist. Most patients with more than six lymph node metastases or with lymph node metastasis not adjacent to the primary tumor still have a very poor outcome.[24] Extended lymph node dissection seems reasonable for experienced surgeons who can perform this procedure without significantly increased surgical morbidity or mortality, because it improves pathologic staging.[61,64,71]

Endoscopic laser surgery has been used in selected individuals with early gastric cancer.[72] Small lesions (≤3 cm) that are not ulcerated, do not involve the submucosa, and are well differentiated infrequently have lymph node metastasis (<5%). As many as 75% of these select tumors can be completely removed endoscopically. Although early gastric cancer may have a long natural history before progression, standard surgical resection rather than endoscopic removal is still preferable for most Western patients.

Survival after Surgery Alone

Overall survival results with surgery alone remain poor, despite improved perioperative treatment, which has resulted in a substantial decline in postoperative mortality rate (median of 4.6% in the 1980s).[73] A large review from Europe reported excellent 5-year survival rate for early gastric cancer patients (83%) but a marked diminution in survival for more invasive cancers.[74] Excellent survival in excess of 90% has been achieved throughout the world with surgical resection of lesions confined to the mucosa or submucosa[52,75,76] (Table 79-4). In contrast, for gastric cancers with deeper invasion or nodal involvement, survival decreases proportionally to the degree of invasion or involvement (see Table 79-4). When N1 or N2 nodes are involved, Western reports continue to show 5-year survival rates of 10% to 30%,[77] whereas Japanese authors report 5-year surgical cure rates of 25% to 60% (vs. <10% with N3 or N4)[78,79] (see Table 79-4). Although pathologic staging differences, different tumor biology, and more radical surgical extirpation have been proposed as explanations, the cause of the difference in U.S. and Japanese results with N1 or N2 disease remains uncertain. Even in the Orient half of all individuals with more invasive gastric cancer die of their disease, a fact that underlies the need for new nonsurgical therapies.

Relapse Patterns after "Curative Resection"

Local regrowth or failure in the tumor bed and regional lymph nodes, or distant failures via hematogenous or peritoneal routes are all common mechanisms of failure after "curative resection" in clinical,[80,81] reoperative,[21] and autopsy[82–85] series. For lesions of the esophagogastric junction, both the liver and lungs are common sites of hematogenous spread. With gastric lesions that do not extend to the esophagus, the initial site of hematogenous spread is usually the liver, and many relapses could be prevented if an effective "abdominal" therapy could be combined with treatment of the primary tumor and regional lymph nodes.

Local-regional failures occur commonly within the region of the gastric bed and nearby lymph nodes (Table 79-5). Tumor relapse in anastomoses, the gastric remnant, or the duodenal stump is also frequently seen. In a University of Minnesota reoperative analysis,[21] local-regional failure occurred as the only evidence of relapse in 29% of the 86 patients with relapse (23% of the 105 evaluable patients at risk) and as any component of failure in 88%. More extensive

Table 79-4 Comparison of 5-Year Survivals Following Surgery for Gastric Carcinoma

Tumor Classification	Nodal Status	5-YR SURVIVAL (%)	
		United States	Japan
T1	N0	90	90
T2	N0	52	60
T3	N0	47	30
T4	N0	15	5
—	N1	20	53
—	N2	10	26
—	N3	—	10
—	N4	—	3

Modified from Noguchi Y, Imada T, Matsumoto A, et al: Radical surgery for gastric cancer. A review of the Japanese experience. Cancer 1989;64:2053.

Table 79-5 Gastric Cancer: Patterns of Local-Regional Failure in Clinical, Reoperation, and Autopsy Series

	Incidence—Any Component			
	MGH[80] (Clinical) (*N* = 130)	U. Minn.[21] (Reoperation) (*N* = 105)	McNeer et al[83] (Autopsy) (*N* = 92)	Thomson and Robins[84] (Autopsy) (*N* = 28)
Failure Area	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Gastric bed	27 (21)	58 (55)	48 (52)	19 (68)
Anastomosis or stumps	33 (25)	28 (27)	55 (60)	15 (54)
Abdominal or stab wound	—	5 (5)	—	—
Lymph node(s)	11 (8)	45 (43)	48 (52)	—

From MacDonald JS, Steele G, Gunderson LL: Carcinoma of the stomach. In DeVita V, Hellman S, Rosenberg SA (eds): Principles and Practices of Oncology, 2nd ed. Philadelphia, JB Lippincott, 1989, p 675.

operative procedures including routine splenectomy, omentectomy, and radical lymph node dissection neither improved survival[86] nor decreased the incidence of local or regional regrowth[21] in the reoperative analysis. Subsequent relapse within the scope of the initial node dissection occurred in a high percentage of the patients even when radical node dissections were performed (removal of N1, N2, and sometimes N3 nodes; Table 79-6).[87] This indicates the difficulty of obtaining a complete lymph node excision encompassing this anatomic location.

Patterns of failure by stage were analyzed in detail in a series of 130 patients who underwent resection performed with curative intent at the Massachusetts General Hospital (MGH).[80] Local-regional failure occurred as any component of failure in 49 patients (38%) and as the sole failure in 21 (16% of 130 patients at risk and 24% of the 88 patients with disease progression). The incidence of local-regional failure by stage was in excess of 35% for T3N0, T4N0, T3N1–3, and T4N1–3 lesions. The sites at highest risk for local-regional failure included the gastric bed (27 of 130 patients, 21%) and the anastomosis or gastric remnant (33 of 130 patients, 25%). The true incidence of gastric bed, regional lymph node, and peritoneal failures may be higher, because this was neither a reoperative nor an autopsy series (see comparative findings in Tables 79-5 and 79-6). In a more recent clinical analysis of patterns of relapse, D'Angelica and colleagues found that 50% of patients with relapse had a local-regional component.[81] Some additional information on patterns of relapse by stage exist in both the University of Minnesota reoperation analysis[21] and the University of Washington autopsy analysis.[84] Although patterns of failure data are more accurate in such analyses, patient selection is biased.

All these data suggest that the development of an effective therapy for local-regional disease as an adjuvant to surgery could potentially benefit at least 20% of patients. However, effective systemic therapy is also essential to improve the outcome for resected high-risk gastric cancer patients.

ADJUVANT TREATMENT AFTER COMPLETE RESECTION—RESULTS

Adjuvant Systemic Chemotherapy

The results of surgery alone for resectable gastric cancer have already been presented and justify the evaluation of adjuvant chemotherapy with regard to an attempt to reduce systemic risks of relapse and thereby improve survival. Although many active single agents exist and several drug combinations have been associated with response rates of 40% or more, randomized North American and European (Western) trials have generally failed to show positive survival findings for adjuvant chemotherapy. Differences in outcome have been noted between Western and Asian studies.

Initial trials to assess the benefit of adjuvant chemotherapy in the United States were conducted by the Veterans Administration in 1957 testing *single agents*. Survival was not improved with the adju-

Table 79-6 Operative Method versus Patterns of Failure—Reoperation Series*,†

		Local-Regional		Peritoneal Seeding		Distant Metastases	
		Alone	Component	Alone	Component	Alone	Component
Operative Procedures‡	**No. of Failures/ Total at Risk (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Method 1 (pre-1950)	25/36	9 (25)	23 (64)	1 (3)	12 (33)	—	7 (19)
Method 2 (1950–1954)	29/32	6 (19)	24 (75)	1 (9)	17 (53)	3 (9)	9 (28)
Method 3 (1954 on)	26/37	8 (22)	23 (62)	1 (3)	15 (41)	2 (5)	7 (19)
Totals	80/105‡	23 (22)	70 (67)	3 (3)	44 (42)	5 (5)	23 (22)

*186 Patients with failure, 80 evaluable by all parameters.

†Data represent number of patients with failure; data in parentheses represent percentage total group at risk who had complete follow-up.

‡Method 1 (pre-1950), subtotal or total gastrectomy, greater omentectomy, regional node dissection; method 2 (1950–1954), method 1 plus splenectomy, total omentectomy, additional node dissection regarding splenic, suprapancreatic, and central celiac axis; method 3 (1954 on), methods 1 and 2 plus extension of node dissection to porta hepatis and pancreaticoduodenal (intent: total lymph node dissection of all primary node areas equivalent to D2 or D3 dissection).

Modified from MacDonald JS, Steele G, Gunderson LL: Carcinoma of the stomach. In DeVita V, Hellman S, Rosenberg SA (eds): Principles and Practices of Oncology, 2nd ed. Philadelphia, JB Lippincott, 1989, p 765.

vant use of either single-agent 5-fluorodeoxyuridine (FUDR) or triethylenethiophosphoramide (thiotepa) when compared with surgery alone.[88,89]

In subsequent North American and European trials, the potential benefit of *multidrug regimens* that had shown benefit in the metastatic setting were evaluated in the adjuvant setting. These regimens included: (1) a combination of 5-fluorouracil (5-FU) and methyl-CCNU (MeCCNU); (2) FAM, a combination of 5-FU, doxorubicin (adriamycin), and mitomycin C; and (3) FAMTX, a combination of 5-FU, doxorubicin, and methotrexate. Although a trial from the Gastrointestinal Tumor Study Group (GITSG) demonstrated a survival advantage for the 71 patients assigned to combination chemotherapy with 5-FU and MeCCNU when compared with an equal number of control patients assigned to surgery alone ($P < 0.03$)[90], subsequent studies performed by the Eastern Cooperative Oncology Group (ECOG), and the Veterans Administration could not confirm a survival advantage for patients treated with the same adjuvant chemotherapy.[91,92] Phase III trials testing the use of either FAM or FAMTX in an adjuvant setting also failed to demonstrate a survival advantage when compared with a surgery-alone control arm.[91–99]

Mixed results have been seen in trials performed in Asia. Nakajima and colleagues have performed a series of adjuvant studies in individuals with resected gastric cancer.[100–103] In their first study, mitomycin C was given on a twice-a-week schedule for 5 weeks, but no survival benefit was seen for the whole cohort of patients.[100] In a subsequent three-arm adjuvant trial, patients were randomized to surgery alone, mitomycin C alone, or the combination of twice-weekly MFC (mitomycin C, 5-FU, and cytosine arabinoside).[101] Forty-two patients were entered in each arm of the study. At 5 years a survival benefit for MFC-treated patients was seen when compared with surgical control subjects. No significant benefit was seen for the mitomycin C arm. These same investigators studied the regimen of MFC followed by either long-term oral 5-FU or ftorafur compared to surgery alone.[102] A significant survival benefit was seen for individuals with stages I to III disease treated with MFC and oral 5-FU. In a fourth study the role of adjuvant mitomycin C and 5-FU followed by oral uracil and tegafur was evaluated in patients undergoing complete resection for early-stage gastric cancer.[103] When compared to a control group, adjuvant therapy for this group of patients showed no benefit over surgery alone.

Many of the trials reported from North America, Europe, and Asia were underpowered to adequately assess any potential differences between the control and treatment arms in regard to overall survival. Accordingly, a clinically meaningful result may have been missed. In an attempt to better determine the benefit of adjuvant therapy after potentially curative surgery for stomach cancer, several *meta-analyses* have been performed.

The two most recent meta-analyses both showed a significant survival advantage to the use of chemotherapy following surgical resection of gastric cancer.[104,105] In one of the meta-analyses, 21 randomized clinical trials before 2000 were summarized.[104] This analysis included 3658 patients enrolled in trials from Europe and North America. Whereas a variety of individual trials had failed to show benefit to adjuvant therapy, the meta-analysis indicated that adjuvant chemotherapy reduces the risk of death by 18% (hazard ratio [HR] 0.82, 95% CI 0.75–0.89, $P < 0.001$). An expanded meta-analysis that included Asian trials showed similar results.[105]

Six subsequent phase III trials of adjuvant postoperative chemotherapy have been performed with a surgery-alone control arm,[106–111] but only two demonstrated a survival benefit from the adjuvant chemotherapy (Table 79-7). Neri and associates treated surgically resected node-positive patients with the addition of adjuvant epirubicin, 5-FU, and leucovorin (68 patients) and compared them to 69 surgery-alone control patients.[106] A significant improvement in 5-year survival was noted in patients receiving the adjuvant chemotherapy (30% vs. 13%, $P < 0.01$). In the large Japanese trial by Sasako and coworkers, 1059 patients with stomach cancer were randomized to either surgery alone or to surgery followed by 1 year of treatment with the oral fluoropyrimidine S-1.[111] Although this trial has been published only in abstract form, a hazard ratio in favor of decreased deaths at 3-years was noted (HR 0.68, 95% CI 0.52–0.87).

Summary—Adjuvant Systemic Chemotherapy

The role of chemotherapy in the adjuvant postoperative treatment of resected high-risk stomach cancer remains uncertain. Except for the recent Japanese trial with S-1, individual trials have generally not shown clinically meaningful benefit. Future trial design must include adequate statistical power to detect meaningful differences in outcome. Surgery-alone control arms will probably not be feasible in

Table 79-7 Gastric Cancer—Randomized Phase III Trials, Adjuvant Postoperative Chemotherapy versus Surgery Only

			Overall Survival		
Reference	**Regimen**	**No. of Patients**	**Interval**	**Percentage**	***P* Value**
Neri et al[106]	5-FU, epirubicin, LV	69	5 yr	30	<0.01
	Surgery alone	68		13	
Bajetta et al[107]	EAP, 5-FU + LV	137	5 yr	52	0.87
	Surgery alone	137		48	
Nashimoto et al[108]	5-FU, MMC, Ara-C	127	5 yr	91.2	0.13
	Surgery alone	123		86.1	
Chipponi et al[109]	5-FU, cisplatin	101	5 yr	39	NS
	Surgery alone	104		39	
Bouche et al[110]	5-FU, cisplatin	127	5 yr	46.6	0.22
	Surgery alone	133		41.9	
Sasako et al[111]	S-1	529	3 yr	80.5	0.0015
	Surgery alone	530		70.1	

Ara-C, cytosine arabinoside; EAP, epirubicin, doxorubicin, and cisplatin; 5-FU, 5-fluorouracil; LV, leucovorin; MMC, mitomycin C.

future trials in view of survival benefit achieved with either perioperative chemotherapy or adjuvant combined-modality chemotherapy–radiation therapy when compared with a surgery-alone control arm (see subsequent sections).

Intraperitoneal Therapy

The use of postoperative intraperitoneal chemotherapy has been evaluated based on the pharmacokinetic advantage of intraperitoneal chemotherapy and the finding that many patients relapse in the peritoneum after surgical resection. A variety of phase II and III trials have been performed.

Building on early promising results from phase II trials, several phase III studies have evaluated the role of intraoperative or postoperative intraperitoneal therapy in patients undergoing potentially curative surgery. In an early study by Dixon and colleagues patients were randomized to surgery alone or to surgery followed by intraperitoneal thiotepa.[88] No significant difference in survival was seen between the two groups. In a more recent study Sautner and associates examined the use of postoperative intraperitoneal cisplatin compared with surgery alone in a group of 67 patients.[112] Although the primary lesion was resected in each case, 21% of the individuals had localized peritoneal carcinomatosis. No survival benefit was seen for the treated patients.

In a phase III trial from Japan, 113 patients were randomized to surgery alone or intraoperative mitomycin C at the time of surgery.[113] For patients who underwent curative surgery, intraperitoneal therapy led to a significant improvement in 2- and 3-year overall survival. No difference in survival was seen for patients with macroscopic peritoneal carcinomatosis.

In a single-institution phase III trial from Korea, 248 patients with clinical stage II or III gastric cancer were randomized to surgery alone or to receive intraperitoneal mitomycin C on day 1 and intraperitoneal 5-FU on days 2 to 5.[114] Overall, 110 of the 248 patients had either stage I or stage IV disease. When 5-year survival was calculated for the entire group, benefit to adjuvant therapy was seen ($P = 0.0278$). In a subset analysis, however, the benefit was limited to patients with stage III or IV disease.

The use of intraperitoneal therapy in the adjuvant setting remains investigational and requires further evaluation. Until further studies show clear benefit to this approach, the use of intraperitoneal therapy should be restricted to controlled clinical trials.

Adjuvant Irradiation

Postoperative Irradiation

Irradiation has only been minimally evaluated as the sole adjuvant treatment following complete surgical resection in randomized phase III trials (Table 79-8). Adjuvant EBRT reduced local-regional failures when compared with the surgery-alone control arm in a British adjuvant trial, but no survival benefits were found.[115] Although phase III trials from Japan[116] and China[117] suggest some survival benefit for IORT versus a surgery-alone control arm, the advantage was found only in subset analyses. At the National Cancer Institute, Sindelar and coworkers[118] performed a small randomized trial of IORT versus EBRT following complete surgical resection; this trial demonstrated improved local control with IORT but no survival benefit.[118] A surgery-alone control arm did not exist in the National Cancer Institute trial. Phase II studies combining EBRT and IORT have been conducted in Pamplona (Spain) and the United States (by the Radiation Therapy Oncology Group [RTOG]) and are still under way in Lyon (France).

The British Stomach Cancer Group completed a prospectively randomized trial of surgery only versus postoperative FAM or EBRT (45 Gy in 25 fractions ± 5-Gy boost).[115] A total of 436 patients were randomized and followed for a minimum of 12 months; arms were well balanced with regard to prognostic factors. No patient survival differences by treatment arm were seen (median, 15 months). However, local-regional failure was documented in only 15 of 153 (10%) in the EBRT arm versus 39 of 145 (27%) in the surgery-alone arm, and 26 of 138 (19%) in the FAM group. Interpretation of the results is complicated by the inclusion of 93 patients (21%) with resection but gross residual disease (British Stomach Cancer Group stage IVAi) and 78 (18%) with gross total resection but microscopically positive resection margins. Neither group of patients would be candidates for current gastric surgical adjuvant trials in the United States. In addition, nearly one third of patients randomized to receive adjuvant treatment did not receive the assigned therapy. Of 153 patients randomized to the EBRT arm, only 104 (68%) received a dose of 40.5 Gy or more, and 36 (24%) received none. Only 62% of patients received six or more cycles of chemotherapy. The results in this study are similar to results seen in the adjuvant treatment of rectal cancer, in which adjuvant pre- and postoperative irradiation as a single adjuvant modality improve local control but do not increase patient survival in most trials, unless combined with chemotherapy.

Takahashi and Abe[116] reported results from a large Japanese trial in which 211 patients were randomized on the basis of day of hospital admission to receive either surgery only or surgery plus IORT (28–35 Gy). Five-year survival rates for Japanese stages II to IV were improved approximately 15% to 25% in the IORT group versus those treated with surgery alone (stage II, 84% vs. 62%; stage III, 62% vs. 37%; stage IV, 15% vs. 0%). This magnitude of survival improvement correlates nicely with the approximately 20% of patients who fail only local-regionally after complete surgical resection. Although the data are intriguing, this method of randomization is susceptible to bias in treatment selection, and the trial failed to stratify for important prognostic factors.

In an analysis from Beijing, individuals with stage III (serosal involvement or node-positive tumors) or stage IV (unresectable metastasis or adjacent organ involvement) disease were randomized to surgery alone or IORT (single dose, 25–40 Gy).[117] In their most recent report of 200 patients, a survival advantage with IORT was demonstrated for only stage III patients (65% vs. 30% 5-year survival; 52% vs. 22% 8-year survival; $P < 0.01$).

Preoperative Irradiation

Randomized trials testing preoperative irradiation have been performed in both Russia and China. All have reported a positive survival benefit when compared with surgery-alone control arms.

Three prospective randomized Russian trials have evaluated preoperative irradiation in potentially resectable gastric cancer.[119–121] The first trial randomly assigned 293 patients to receive either surgery alone, surgery after preoperative EBRT (20 Gy in four fractions), or surgery after the same EBRT plus daily hyperthermia. The survival rates at 3 and 5 years were improved in both irradiation arms compared with surgery alone, and the improvement with combined EBRT and hyperthermia was statistically significant at both 3 and 5 years.[119] The second trial compared preoperative EBRT (20 Gy) with surgery alone in 279 patients. Both 3- and 5-year survival rates were increased, and no increase in operative morbidity was observed.[120] The third trial compared surgery alone to preoperative EBRT (32 Gy with concomitant inhalation of 8% oxygen) plus surgery. A survival advantage was observed with preoperative treatment, and the resection rate was increased by 17%.[121] There are some methodologic uncertainties with all three of these trials, and their applicability to Western gastric carcinoma is not clear.

A double-blind randomized trial from Beijing, conducted from 1978 to 1989, compared a surgery-alone control arm ($N = 199$) with preoperative EBRT plus surgery ($N = 171$) for individuals with adenocarcinoma of the gastric cardia.[122] Irradiation was given with 8-MV photons or cobalt with anteroposterior-posteroanterior (AP-PA) fields to a dose of 40 Gy in 20 fractions of 2 Gy over 4 weeks. Surgery was performed 2 to 4 weeks after completion of irradiation. Both downstaging of disease and improvements in radical resection

Table 79-8 Surgery ± Adjuvant Therapy for Resected Gastric or Gastroesophaged Junction Cancer

Treatment	No. of Patients	Survival			Local-Regional Relapse			Reference
		Median (mo.)	Long-term (%)*	*P* Value	No.	Percentage	*P* Value	
PHASE III TRIALS								
1. British Stomach Group (3 yr)		15						115
a. Surgery alone	145	—	20	—	39	27	—	
b. Postop chemo	138	—	19	—	26	19	—	
c. Postop EBRT	153	—	12	—	15	10	—	
2. Japan—Surgery ± IOERT†	S/IOERT		S/IOERT					116
		110/101						
a. Stage I	43/24	—	93% vs. 87%	—	—	—	—	
b. Stage II	11/20	—	62% vs. 84%	—	—	—	—	
c. Stage III	38/30	—	37% vs. 62%	—	—	—	—	
d. Stage IV	18/27	—	0 vs. 15%	—	—	—	—	
3. China—Surgery ± IOERT†	100/100							117
a. Stage III (5 yr)	—	—	30% vs. 65%	<0.01		—	—	—
b. Stage III (8 yr)	—	—	22% vs. 52%			—	—	—
4. Mayo Clinic‡								128
a. Surgery alone	23	15	4	—	—	54	—	
b. Postop EBRT + 5-FU	39	24	23	0.05	—	39	—	
5. China-Beijing								122
a. Surgery alone	199	—	20		—	52		
b. Preop EBRT	171	—	30	0.009	—	39	<0.025	
6. U.S. GI Intergroup (INT 0116)			(3-yr)		(3-yr)			129,130
a. Surgery alone	275	27	41		31			
b. Postop EBRT + 5-FU leucovorin	281	36	50	0.005	48	0.001		
7. British MAGIC Trial§			(3-yr)	(5-yr)				172
a. Surgery alone	253	NA	31	23		23		
b. Perioperative ECF Chemo	250	NA	44	36	0.009	38	<0.001	
PHASE II TRIALS								
1. MGH								
a. Surgery alone	110	—	38 (B2, B3)	—	46	42	—	80
					15 (C1–3)			
b. Postop EBRT + Chemo	14	24	43 (4 yr)	—	2	14	—	123
2. TJUH								
a. Total group T3, T4, or N+	120							125
• Surgery alone	70	12	13			17/38	45	
• Postop Chemo, EBRT, both	50	19	17	<0.05	13/36	36	—	
• Postop EBRT + Chemo	20 of 50	19	21		3/16	19	—	
b. T3/T4, N1/N2 (surg ± adjuv)	44, 30	9 vs. 13	4 vs. 22	0.04	—	—	—	
3. South Korea								
a. Surgery alone (D2 resection)	446	62.6	51	21.7				133
b. Postop EBRT + Chemo	544	95.3	57	0.02	14.9	0.005		

Chemo, chemotherapy; EBRT, external beam irradiation; 5-FU, 5-fluorouracil; ECF, epirubicin, cisplatin, 5-FU; IOERT, intraoperative electron irradiation; MGH, Massachusetts General Hospital; postop, postoperative, preop, preoperative; S, surgery; TJUH, Thomas Jefferson University Hospital.

*Long-term survival = 5-year data unless otherwise specified.

†Advantage to IOERT in subset analyses—Japan stages II–IV, China stage III (37% of patients).

‡Survival data based on intent to treat, relapse data on actual treatment.

§Three-year survival estimated from published survival curves.

rates were found with the addition of preoperative EBRT (radical resection rates of 80% vs. 62% with preoperative EBRT vs. surgery alone).

Survival and local-regional disease control were improved in the patients assigned to preoperative EBRT versus surgery alone (see Table 79-8). The 5- and 10-year survival rates were 30% versus 20% and 20% versus 13%, respectively ($P = 0.009$ Kaplan-Meier log rank). The divergence in survival curves began in the first year of follow-up and persisted through 9 years. Local and regional disease control were also improved with combined-modality treatment with local relapse rates of 39% versus 52% ($P < 0.025$) and regional node relapse rates of 39% versus 54% ($P < 0.05$). The rates of distant metastases were the same at 24% versus 25%. The improvements in survival and disease control (local-regional) were accomplished with no increase in treatment-related morbidity or mortality rates (operative mortality 0.6% vs. 2.5% with or without preoperative EBRT; intrathoracic leak rates were 1.8% and 4.2%, respectively).

In view of the survival advantage with or without disease control and radical resection rates demonstrated for preoperative EBRT in four published trials from Russia and China, such approaches need to be evaluated further in U.S. and European study groups. As suggested by the authors from the Beijing trial, factors to be evaluated include radiation dose escalation to 45 to 50 Gy (1.8- to 2.0-Gy fractions) and the addition of chemotherapy (maintenance, concurrent with EBRT).

Adjuvant Irradiation Plus Chemotherapy

Postoperative External-Beam Irradiation Therapy Plus Chemotherapy

Phase II single-institution gastric cancer trials that showed promise for combination postoperative adjuvant therapy were reported from MGH,[123] Israel (Hadassah),[124] Thomas Jefferson University Hospital,[125] the University of Pennsylvania,[126] and the Mayo Clinic.[127] Gunderson and associates,[123] from the MGH, reported a median survival time of 24 months and 4-year survival rate of 43% in 14 patients who had complete resection of tumors with extension beyond the wall, nodal involvement, or both. Patients received postoperative irradiation (45–52 Gy, 1.8 Gy/day) plus concomitant 5-FU-based chemotherapy. Subsequent local-regional relapse was documented in only 2 of the 14 (14%), in contrast to a 42% incidence in similar high-risk patients treated with surgery alone at MGH.[80]

A prospective randomized trial conducted at the Mayo Clinic included 62 patients with poor-prognosis completely resected gastric cancers who were randomized to either surgery alone or surgery followed by irradiation (37.5 Gy in 24 fractions over 4–5 weeks) plus concomitant 5-FU (15 mg/kg, days 1–3 by IV bolus).[128] A nonstratified, prerandomization scheme was used with a 2 : 3 ratio favoring treatment. Informed consent was requested only of the 39 patients randomized to treatment. Of the 39 patients, 10 refused further therapy and were observed. When analyzed by intent to treat, the adjuvant arm had statistically significant improvement in both relapse-free and overall survival (5-year OS 23% vs. 4%; $P < 0.05$; Tables 79-8 and 79-9). When patient outcome was compared by actual treatment received (29 adjuvant treatment, 33 surgery alone), 5-year survival rate still favored the adjuvant group (20% vs. 12%), but the differences were not statistically significant in view of small patient numbers. As seen in Table 79-9, the 10 patients who refused assignment to adjuvant treatment had more favorable prognostic findings than the other two groups of patients. When the two groups with equally poor prognostic factors were compared, the 5-year OS rate was 20% versus 4%, with an advantage to those receiving adjuvant treatment.[128] When analyzed by treatment delivered, local-regional relapse was decreased with adjuvant treatment (54% incidence with surgery alone vs. 39% with irradiation plus 5-FU).

Because of conflicting results in earlier small phase III studies, a confirmatory U.S. GI trial (INT 0116) was initiated to evaluate postoperative combined 5-FU-based chemotherapy and irradiation to the gastric bed and regional nodes versus surgery only in completely resected but high-risk gastric cancer patients.[129] Eligibility included patients with stages IB, II, IIIA, IIIB, and IV nonmetastatic adenocarcinoma of the stomach or gastroesophageal junction (extension beyond muscularis propria [T2–4N0] or involved nodes [T1–2N1–3]). After an en bloc resection, 556 patients were randomized to either surgery alone or postoperative combined-modality therapy

Table 79-9 Randomized Gastric Adjuvant Trial at the Mayo Clinic (Surgery ± Irradiation + 5-FU)

	Adjuvant EBRT + 5-FU (%; *N* = 29)	Surgery Control (%; *N* = 23)	Refused Adjuvant (%; *N* = 10)
PATHOLOGIC CHARACTERISTICS			
Cardia	55	56	30
Ulcerative	72	70	50
Grade 2	7	9	3
Grades 3, 4	93	91	70
	Adjuvant EBRT + 5-FU (%)	**Surgery Control (%)**	***P* Value**
FIVE-YEAR SURVIVAL			
Treatment intent (total patients)	(*N* = 39)	(*N* = 23)	
Overall survival	23%	4%	<0.05
Treatment delivered (total patients)	(*N* = 29)	(*N* = 33)	
Overall survival	20%	12%	
Disease-free survival	17%	9%	
LOCAL FAILURE			
Treatment delivered	39%	54%	

EBRT, external-beam irradiation; 5-FU, 5-fluorouracil.

Modified from Moertel CG, Child DS Jr, O'Fallon JR, et al: Combined 5-fluorouracil and radiation therapy as a surgical adjuvant for poor prognosis gastric carcinoma. J Clin Oncol 1984;2:1249.

consisting of one 5-day cycle of 5-FU plus leucovorin followed by concurrent chemoradiation (45 Gy in 25 fractions plus concurrent 5-FU and leucovorin, 4-day cycle on week 1, 3-day cycle on week 5) and subsequently by two additional 5-day cycles of 5-FU and leucovorin given at 1-month intervals. Nodal metastases were present in 85% of patients. With median follow-up period of 5 years, RFS at 3 years is 48% for adjuvant treatment and 31% for observation ($P = 0.001$); 3-year OS rate is 50% for treatment and 41% for observation ($P = 0.005$; see Table 79-8). The median OS in the surgery-only group was 27 months, as compared with 36 months in the chemoradiation therapy (CRT) group. The median duration of RFS was 30 months in the CRT group and 19 months in the surgery-only group. Patterns of relapse were based on the site of first relapse only and were categorized as local, regional, or distant. Local recurrence occurred in 29% of the patients who relapsed in the surgery-only group and 19% of those who relapsed in the CRT group. Regional relapse—typically abdominal carcinomatosis—was reported in 72% of those who relapsed in the surgery-only group and 65% of those who relapsed in the CRT group. Extra-abdominal distant metastasis was diagnosed in 18% of those who relapsed in the surgery-only patients and 33% of those who relapsed in the CRT group. Treatment was tolerable, with 3 (1%) toxic deaths. Grade 3 and 4 toxicity occurred in 41% and 32% of cases, respectively.

The results of the large randomized phase III U.S. GI trial (INT 0116) demonstrate a clear survival advantage to the use of postoperative CRT in resected high-risk patients.[129] Furthermore, the results strongly support the integration of postoperative CRT into the routine care of individuals with curatively resected high-risk carcinoma of the stomach and gastroesophageal junction. This approach is now viewed by many as the standard of care in the United States.

Quality control of irradiation field design in INT 0116 was conducted during the cycle of chemotherapy given before the start of concurrent CRT.[130] The initial quality control provided the mechanism to correct most of the major or minor deviations (35% incidence) in irradiation field design before the start of treatment, and resulted in only a 6.5% final major deviation rate. Use of initial quality control may have been a key factor in achieving a positive survival advantage for adjuvant CRT.

Postoperative Chemoradiation Plus D2 Resection

Because extended node dissections were not commonly performed as a component of surgery in the U.S. GI trial INT 0116, some have questioned whether postoperative CRT would give added benefit following a D2 nodal resection. Although this is unlikely to be tested in a phase III trial, a recent South Korea analysis evaluated the potential role of postoperative CRT in a series of 990 patients with D2 resection who were at high risk for relapse.[131] Disease and patient characteristics and the method of chemoradiation treatment paralelled the U.S. GI INT 0116 trial. Both disease control and survival were improved in the 544 patients who received postoperative CRT when compared with the 446 patients treated with surgery alone (5-year OS, 57% vs. 51%, $P = 0.02$; 5-year RFS, 54.5% vs. 47.9%, $P = 0.016$; local-regional relapse, 14.9% vs. 21%, $P = 0.005$; Tables 79-8 and 79-10).

Preoperative External Beam Irradiation Therapy Plus Chemotherapy

Randomized trials testing preoperative EBRT plus chemotherapy for gastric cancer alone have not yet been published, but the Walsh and colleagues trial for adenocarcinoma of the esophagus and gastric cardia certainly has relevance.[132] Patients were randomized to either immediate surgery (control arm) versus preoperative EBRT (40 Gy in 15 fractions), 5-FU (15 mg/kg/day continuous infusion [this is approximately equivalent to 600 mg/m^2] for 5 days, weeks 1 and 6), and cisplatin (75 mg/m^2 on the first day of each 5-FU infusion), followed by surgical resection 8 weeks after completion of EBRT plus chemotherapy. A highly significant difference in survival was observed with combined-modality therapy (intent to treat median survival time, 16 vs. 11 months, 3-year survival rate, 32% vs. 6%; $P = 0.01$; actual treatment median survival time, 32 vs. 11 months; $P = 0.001$; 3-year survival rate, 37% vs. 7%; $P = 0.006$). Survival rates for the control group of patients were inferior to other historical data.

A confirmatory intergroup trial was attempted in North America for patients with either esophagus or esophagogastric junction cancers (squamous or adenocarcinoma) but was stopped because of poor accrual. Despite the low accrual, patients randomized to trimodality treatment had a survival benefit when compared with patients randomized to surgery alone (median survival 54 vs. 21.6 months; 5-year OS, 39% vs. 16%, $P = 0.008$.[133]

Summary—Adjuvant Irradiation Alone or Plus Chemotherapy

In summary, both preoperative irradiation[122] and postoperative CRT[129,130] have been demonstrated to be superior to surgery alone for resectable gastric and gastroesophageal cancers in randomized phase III trials. Future preoperative irradiation trials should evaluate the addition of concurrent and maintenance chemotherapy. Postoperative CRT trials are evaluating more aggressive chemotherapy both as concurrent and maintenance components of treatment.

Irradiation Techniques

The irradiation field should include unresected or residual tumor or the tumor bed plus major nodal regions. The pattern of tumor bed and nodal failures in the reoperative series from the University of Minnesota is demonstrated in Figure 79-7A in conjunction with an idealized, shaped AP-PA irradiation portal that incorporates the areas

Table 79-10 Surgery (D2 resection) ± Postoperative Chemoradiation for Gastric Cancer, South Korea Series

	5-Year Overall Survival			5-Year Relapse-Free Survival		
Stage	**Surgery Alone**	**Postop CRT**	***P* Value**	**Surgery Alone**	**Postop CRT**	***P* Value**
II	70.9	78.8	0.04	66.6	76.2	0.03
IIIA	43.9	61.6	0.001	42.3	57.6	0.0015
IIIB	20.5	40.8	0.0045	17.5	39.6	0.006
IV (M0)	12.1	26.4	0.015	11.3	26.3	0.025
Total	51.0	57.1	0.02	47.9	54.5	0.02

Postop CRT, postoperative chemoradiation therapy.

Modified from Kim S, Lim DH, Lee J, et al: An observational study suggesting clinical benefit for adjuvant postoperative chemoradiation in a population of over 500 cases after gastric resection with D2 nodal dissection for adenocarcinoma of the stomach. Int J Radiat Oncol Biol Phys 2005;63:1279.

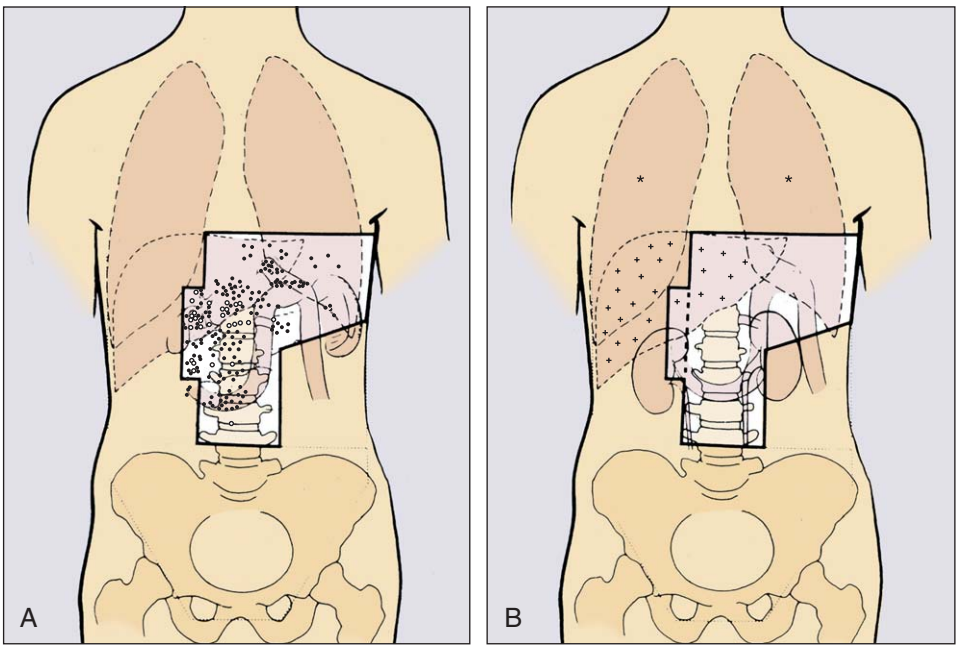


Figure 79-7 • **A** and **B,** Patterns of failure in the University of Minnesota gastric cancer reoperative series with superimposed idealized irradiation fields, and relationship to dose-limiting organs or structures (**A**). •, local failures in surrounding organs or tissues; ○, lymph node failures; *, lung metastases; +, liver metastases.

of local-regional relapse.[21,82] The tumor bed and nodal volumes are reconstructed with the aid of preoperative and postoperative imaging studies and surgical clip placement. In Figure 79-7B the idealized AP-PA field is superimposed on the organs and structures that define irradiation tolerance.

Dose-limiting organs and structures in the upper abdomen are numerous (stomach, small intestine, liver, kidneys, and spinal cord). With properly shaped fields, doses of 45 to 50.4 Gy in 1.8- to 2.0-Gy fractions can be delivered to stomach and small intestine with a 5% or less risk of severe toxicity.[134] In most patients a portion of both kidneys will be within the AP-PA treatment field, but at least two thirds to three fourths of one kidney should be excluded (can include entirety of both kidneys to the level of 20 Gy if necessary). For patients with gastroesophageal junction or proximal to mid-gastric cancers (Figs.79-8 and 79-9), one half to two thirds of the left kidney can often be spared as a result of accurate field definition, which is aided by pre- and postoperative imaging studies and clip placement. The pancreaticoduodenal nodes can be included, if indicated, while sparing 75% to 90% of the right kidney. However, for distal gastric lesions with narrow or positive duodenal resection margins, the duodenal circumference may need to be included as target volume (Fig. 79-10). In such instances 50% or more of the right kidney is within the field, and two thirds to three fourths of the left kidney should be spared. Chronic renal problems are infrequent when these techniques are utilized.[123,135–137]

With preoperative or primary CRT for individuals with gastroesophageal junction or proximal gastric lesions, a 3- to 5-cm margin of distal esophagus should be within the irradiation field (see Fig. 79-9). If the lesion extends beyond the gastric wall with proximal lesions, a major portion of the left hemidiaphragm should be included. In either instance, Cerrobend blocks or multi-leaf collimators should be used to decrease the volume of irradiated heart (see Figs. 79-8 through 79-10) and lung when technically feasible. For patients with gastroesophageal junction cancers, preoperative EBRT fields can usually be much more conservative than postoperative fields with regard to both heart and lung volumes, and are preferred, if preoperative imaging and EUS demonstrate indications for preoperative adjuvant treatment (see Fig. 79-9). Lateral or oblique fields can be used as a component of treatment to decrease the volume of heart within the irradiation field (see Fig. 79-9).

More routine use of multiple field techniques should be considered when preoperative imaging exists to allow accurate reconstruction of target volumes (see Figs. 79-8 through 79-10).[137] Single-institution data suggest that multiple field arrangements may produce less toxicity.[127] When patients are treated preoperatively, paired lateral fields are usually combined with AP-PA fields to achieve improve dose homogeneity (see Fig. 79-9). Dependent on the posterior extent of the gastric fundus, either oblique or more routine lateral portals can be used to deliver a 10- to 20-Gy component of irradiation to spare spinal cord or kidney. When lateral fields are used, liver and kidney tolerance limits the use of lateral fields to 20 Gy or less for patients with gastric cancer; for patients with gastroesophageal junction cancers the contribution from lateral fields would preferably be limited to 10 to 15 Gy because of lung tolerance. With the wide availability of three-dimensional treatment-planning systems, it may be possible to target more accurately the high-risk volume and to use unconventional field arrangements and/or intensity-modulated radiation therapy[138,139] to produce superior dose distributions. To accomplish this without marginal misses it will be necessary to both carefully define and encompass the various target volumes, because use of oblique or noncoplanar beams could exclude target volumes that would be included in AP-PA fields or nonoblique four-field techniques (AP-PA and lateral).

In individual patients the idealized field must be modified depending on the surgical/pathologic extent of disease and site of the primary tumor.[136,137] The relative risk of nodal metastases at a specific nodal location is dependent on both the site of origin of the primary tumor and other factors including width and depth of invasion of the gastric wall. Tumors that originate in the proximal portion of the stomach and the gastroesophageal junction have a higher propensity of spread to nodes in the mediastinum and pericardial region but a lower likelihood of involvement of nodes in the region of the gastric antrum, periduodenal area, and porta hepatis. Tumors that originate in the body of the stomach can spread to all nodal sites, but have the highest likelihood of spreading to nodes along the greater and lesser curvature, near the location of the primary tumor mass. Tumors that originate in the distal stomach have a high likelihood of spread to the periduodenal, peripancreatic, and porta hepatis nodes, but they have a lower likelihood of spread to the nodes near the cardia of the stomach, the periesophageal and mediastinal nodes, or to the splenic hilar nodes (see Fig. 79-10). Any tumor originating in the stomach

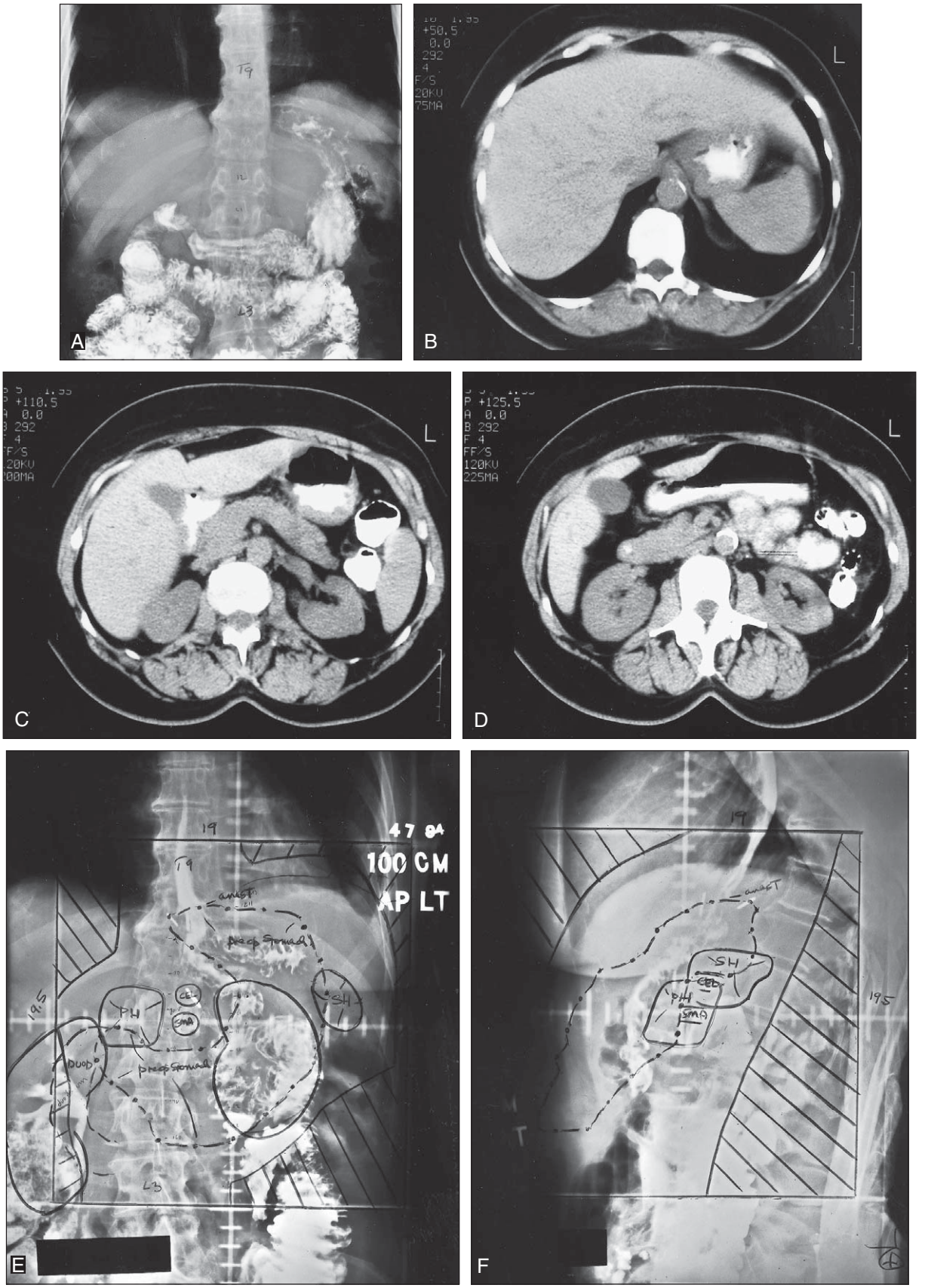


Figure 79-8 • Postoperative irradiation fields based on preoperative radiographs following complete resection of a proximal gastric cancer (T3N2M0); patient was randomized to the irradiation chemotherapy arm on the intergroup gastric adjuvant study. **A–D,** Reconstruction of tumor bed/target volumes with preoperative upper gastrointestinal radiograph (**A**) and CT scans (**B** and **D**). CT cuts demonstrated thickened gastric wall proximally (**B** and **C**) and normal thickness distally (**D**), as well as relationship of the stomach to surrounding organs including liver and spleen (**B**), liver, body and tail of pancreas, and splenic flexure (**C**), and head of pancreas (**D**). **E** and **F,** AP-PA irradiation field (**E**) with cross-hatched blocks encompasses all the left kidney but less than 20% of the right. Nodal groups at risk and preoperative gastric duodenal locations (-•-•) are demonstrated on the AP-PA and lateral (**F**) simulation fields. CEL, celiac; PH, porta hepatis; SH, splenic hilum; SMA, superior mesenteric artery.

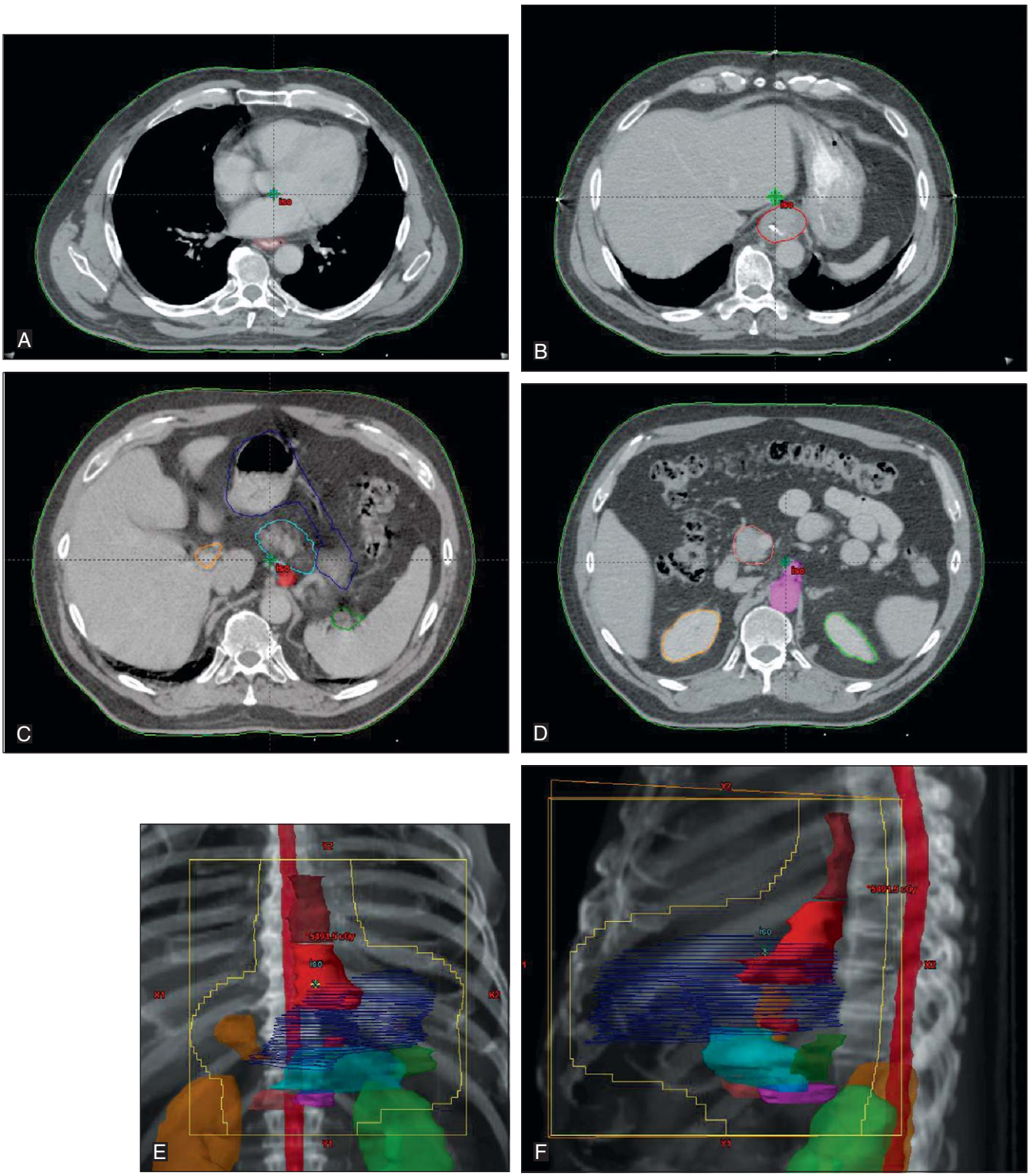


Figure 79-9 • Patient is a 54-year-old male with a T3N1 adenocarcinoma of the distal esophagus extending into the proximal stomach who was treated with preoperative concurrent CRT at Mayo Clinic in Arizona (45 Gy in 25 fractions over 5 weeks to extended field and 50.4 Gy in 28 fractions within boost field). CT simulation was performed with intravenous and oral contrast, and structures of interest were delineated (**A–D**). The normal thickness of the more proximal esophageal wall (**A**) contrasts with the markedly thickened distal esophagus wall seen at the level of the adenocarcinoma (**B**). An enlarged gastrohepatic node (**C**) was biopsy positive for adenocarcinoma at the time of pretreatment EUS. Other delineated organs/structures were celiac artery, body and head of pancreas, porta hepatis, and splenic hilum (**B–D**). Three-dimensional conformal irradiation fields (**E** and **F**) were designed to include the primary tumor (red) with at least 5-cm margins of esophagus proximally and stomach distally (to include potential submucosal tumor spread) plus nodal volumes (periesophageal and celiac, as per Table 79-12; decision was made to also include porta hepatis, suprapancreatic and splenic hilar nodes in view of the documented gastrohepatic nodal disease [also shown in red]). Lateral fields (**F**) were used as a component of treatment for purpose of sparing heart and spinal cord. The patient subsequently had a laparoscopic esophagogastrectomy, mediastinal and celiac node dissection, pyloroplasty, and neck anastamosis (esophagogastrostomy) at Mayo Clinic Hospital in Arizona. Pathologic examination revealed a 3.5 × 2.5 × 1.0 cm ulcerated mass at the esophagogastric junction that microscopically consisted of paucicellular and acellular mucin and rare tumor cells floating in mucin with 0/20 positive nodes.

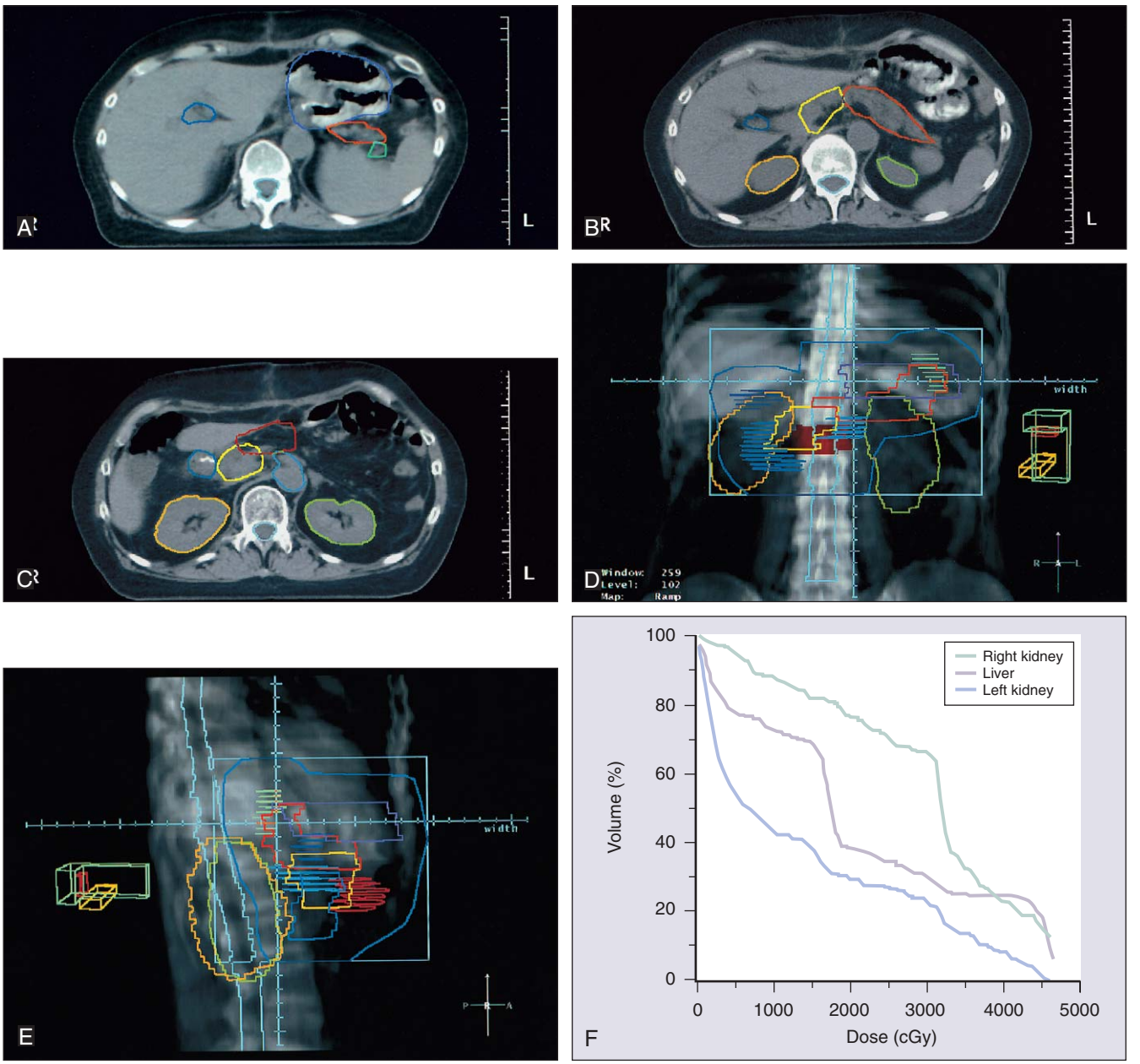


Figure 79-10 • Optimized postoperative irradiation fields for patient with T3N2 antral primary tumor (see Table 79-13). **A–C,** Structures of interest were delineated at time of CT simulation. **D** and **E,** Irradiation fields were designed with the aid of digitally reconstructed radiographs. A dose volume histogram was performed to be certain that appropriate volumes of liver and at least one kidney were excluded beyond certain dose levels. **A,** Gastric remnant (lavender) is demonstrated along with the body/tail of pancreas (red-orange), splenic hilum (light green), and porta hepatis (dark blue). **B,** Head of pancreas (yellow) and kidneys (*left*, yellow green; *right*, yellow orange) are delineated in addition to the body/tail of the pancreas. **C,** The celiac artery (light blue), antral tumor bed (red), and duodenum (medium blue) are shown together with the head of pancreas and kidneys. A four-field technique of AP (**D**), PA, and paired lateral fields (**E**) was designed. The fields included the gastric remnant (lavender), tumor bed (red), head of pancreas (yellow), first and second part of the duodenum (medium blue, cross-hatched), pertinent nodal volumes (perigastric, pancreaticoduodenal, porta hepatis [dark blue cross-hatched], suprapancreatic), and the optional nodal volume of splenic hilum (light green cross-hatched). **D,** AP field (field margins as shown in medium blue exclude approximately two thirds of the left kidney while including approximately 90% of the right kidney). Exclusion of the optional splenic hilar nodes would not have allowed any additional sparing of the left kidney in view of the adjacency of the gastric remnant and the splenic hilum. **E,** Right lateral field demonstrated exclusion of the spinal cord (turquoise) along with substantial portions of both kidneys. **F,** The dose volume histogram, combining dose from all four fields, demonstrated that the dose volume of 20 Gy included about 30% of the left kidney versus approximately 75% of the right kidney. With regard to the liver, about 30% receives a dose of 30 Gy and about 25% receives a dose of 35 Gy and 40 Gy.

Table 79-11 General Guidelines of Impact of T and N Categories on Inclusion of Remaining Stomach, Tumor Bed, Nodal Sites within Irradiation Fields

TN Stage	Remaining Stomach*	Tumor Bed	Nodes
T1–2 (not into subserosa) N0	N	N	N
T2N0–into subserosa†	Variable	Y	N
T3N0	Variable	Y	N
T4N0	Variable	Y	Variable
T1–2N+	Y	N	Y
T3–4N+	Y	Y	Y

*Inclusion of the remaining stomach is preferable in most patients if two thirds of one kidney can be excluded. This is dependent on the extent of surgical resection and uninvolved margins (in cm).

†Posterior wall T2N0 lesions, or those that extend beyond muscularis propria, especially tumors located in the proximal or distal stomach, are at risk for local relapse. In addition, patients with low-stage disease with close or positive surgical margins should be considered for treatment to the tumor bed.

From Tepper JE, Gunderson LL: Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Radiat Oncol 2002;12:187.

has a high propensity of spread to nodes along the greater and lesser curvature, although they are most likely to spread to those sites in close anatomic proximity to the primary tumor mass.

Recently, guidelines for defining the clinical target volume for postoperative radiation fields have been developed based on location and extent of the primary tumor (T category) and location and extent of known nodal involvement (N category).[136,137] Table 79-11 presents general guidelines on the impact of T and N categories on inclusion of the remaining stomach (gastric remnant), tumor bed and nodal sites, and Tables 79-12 and 79-13 present treatment guidelines based on TN stage for two of the four primary sites (esophagogastric junction, proximal, mid-, and distal stomach). In general, for individuals with node-positive disease there should be wide coverage of tumor bed, remaining stomach, resection margins, and nodal drainage regions. For node-negative disease, if there is a good surgical resection with pathologic evaluation of at least 10 to 15 nodes, and there are wide surgical margins on the primary tumor (at least 5 cm), treatment of the nodal beds is optional. Treatment of the remaining stomach should depend on a balance of the probable normal tissue morbidity and the perceived risk of local relapse in the residual stomach.

LOCALLY ADVANCED DISEASE (BORDERLINE RESECTABLE, UNRESECTABLE, AND RESIDUAL)—TREATMENT AND RESULTS

The term locally advanced disease has different interpretations depending on the author and institution. In our institution and for the purposes of this chapter, this term refers to primary cancers that the surgeon would not expect to resect with negative pathologic margins (i.e., locally unresectable for cure as determined at surgical exploration or as defined preoperatively with CT scan, EUS, laparoscopy, or other studies; locally recurrent cancers with no evidence of metastasis). Other authors use the term also to include lesions that are completely resected but have high-risk factors for local recurrence or distant metastasis (nodal involvement, extension beyond gastric wall, or both).

Surgical Aspects

The extent of the surgical procedure must be tempered by the knowledge that cure is at best improbable. Patients with symptomatic obstruction, hemorrhage, and ulceration, and the rare patient with perforation can be successfully relieved of symptoms by even a limited gastric resection. Radical subtotal or total gastrectomy may be indicated in some patients whose cancers cannot be completely resected with negative pathologic margins for symptomatic palliation. Our own results with total gastrectomy in advanced gastric cancer showed good quality of life when this procedure was indicated for bulky or proximal malignancies, but symptom relief was less likely for patients

Table 79-12 Impact of Site of Primary Lesion and TN Category on Irradiation Treatment Volumes for the Gastroesophageal Junction: General Guidelines

Site or Primary and TN Category	Remaining Stomach	Tumor Bed Volumes*	Nodal Volumes	Tolerance Organs or Structures
GE junction	If allows exclusion of 2/3 R kidney	T-category dependent	N-category dependent	Heart, lung, spinal cord, kidneys, liver
T2N0 with invasion of subserosa	Variable dependent on surgical pathologic findings†	Medial left hemidiaphragm; adjacent body of pancreas	None or perigastric, periesophageal‡	
T3N0	Variable dependent on surgical pathologic findings†	Medial left hemidiaphragm; adjacent body of pancreas	None or perigastric, periesophageal, mediastinal, celiac‡	
T4N0	Preferable but dependent on surgical pathologic findings†	As for T3N0 plus site(s) of adherence with 3- to 5-cm margin	Nodes related to site of adherence, ± perigastric, periesophageal, mediastinal, celiac	
T1–2N+	Preferable	Not indicated for T1, as above for T2 into subserosa	Periesophageal, mediastinal, proximal perigastric, celiac	
T3–4N+	Preferable	As for T3, T4N0	As for T1–2N+ and T4N0	

*Use preoperative imaging (CT, barium swallow), surgical clips, and postoperative imaging (CT, barium swallow).

†For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is optional, especially if this would result in substantial increase in normal tissue morbidity.

‡Optional node inclusion for T2–3N0 lesions if adequate surgical node dissection (D2 dissection) and at least 10–15 nodes examined pathologically.

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Table 79-13 Impact of Site of Primary Gastric Lesion and TN Stage on Irradiation Treatment Volumes—Antrum/Pylorus/Distal Third of Stomach: General Guidelines

Site or Primary TN Category	Remaining Stomach	Tumor Bed Volumes*	Nodal Volumes	Tolerance Organs or Structures
Pylorus/distal third stomach	Yes but spare 2/3 of one kidney, usually left	T-category dependent	N-category dependent	Kidneys, liver, spinal cord
T2N0 with invasion of subserosa	Variable dependent on surgical pathologic findings†	Head of pancreas (± body), 1st and 2nd duodenum	None or perigastric; optional pancreaticoduodenal, porta hepatis, celiac, suprapancreatic‡	
T3N0	Variable dependent on surgical pathologic findings†	Head of pancreas (± body), 1st and 2nd duodenum	None or perigastric; optional pancreaticoduodenal, porta hepatis, celiac, suprapancreatic‡	
T4N0	Preferable but dependent on surgical pathologic findings†	As for T3N0 plus site(s) of adherence with 3- to 5-cm margin	Nodes related to site(s) of adherence ± perigastric, pancreaticoduodenal, porta hepatis, celiac, suprapancreatic	
T1–2N+	Preferable	Not indicated for T1	Perigastric, pancreaticoduodenal, porta hepatis, celiac, suprapancreatic; optional, splenic hilum	
T3–4N+	Preferable	As for T3, T4N0	As for T1–2N+ and T4N0	

*Use preoperative imaging (CT, barium swallow), surgical clips, and postoperative imaging (CT, barium swallow).

†For tumors with wide (>5 cm) surgical margins confirmed pathologically, treatment of residual stomach is optional if this would result in substantial increased normal tissue morbidity.

‡Optional node inclusion for T2–3N0 lesions if adequate surgical node dissection (D2 dissection) and at least 10–15 nodes examined pathologically.

Tepper JE, Gunderson LL: Radiation treatment parameters in the adjuvant postoperative therapy of gastric cancer. Semin Radiat Oncol 2002;12:187.

with linitis plastica.[140] Although resection of adjacent organs should be undertaken if all the gross tumor can be removed, it is rarely justified if residual tumor would remain.[56,57] If sites of residual disease or adherence are judiciously marked with clips, postoperative irradiation plus chemotherapy can be delivered with greater accuracy.

Primary Irradiation or Chemoradiation

Although some patients with no resection have long-term survival using irradiation alone or plus chemotherapy, this approach is not a viable alternative to surgical resection plus adjuvant therapy as indicated, because the initial bulk of disease and the limited tolerance of the stomach and surrounding organs prevent a suitable therapeutic ratio between cure and complications. When locally advanced disease is diagnosed before surgical exploration, preoperative radiation would preferably be used in combination with chemotherapy (concomitant and maintenance), followed by restaging and an attempted resection of all gross primary and lymph node disease.

Irradiation Alone

The available literature suggests that adenocarcinoma of the stomach is radiation responsive. Wieland and Hymmen[141] used 60 Gy when feasible (1.5 to 2.0 Gy daily) with 11% (9 of 82) 3-year and 7% (5 of 72) 5-year survival rates. Takahashi[142] compared historical control subjects with patients who were unresectable or who had palliative procedures and received postoperative radiation therapy (unknown if chemotherapy also used). The average survival time for the irradiated group was 9 to 10 months longer, with 74% 1-year (32 of 43) and 27% 2.5-year survival rates (12 of 43). Takahashi and Abe[116] reported 15% 5-year survival rate with a single dose of IORT (28–35 Gy) in a group of 27 patients with stage IV disease. Three of the four long-term survivors had residual disease after resection. In the same study, 18 stage IV patients were randomized to a surgery-alone control arm; the 5-year survival rate was 0%.

Irradiation Plus Chemotherapy

Most early reports of combined irradiation and chemotherapy for gastric cancer involved patients with residual or unresectable primary disease, and most phase III trials in this setting show an advantage for combined-modality treatment over single-modality treatment. In a randomized series from the Mayo Clinic,[143] 5-FU was used during the first 3 days of irradiation in one half of the patients (irradiation, 35–37.5 Gy in 4 to 5 weeks; 5-FU, 15 mg/kg for 3 days, week 1 of irradiation). For the combined-treatment group, mean and overall survival was improved (13 months vs. 5.9 months and 3 of 25 patients or 12% vs. 0 of 23 patients surviving over 5 years; Table 79-14). In a randomized study by the GITSG,[144,145] the combination of irradiation and 5-FU followed by maintenance 5-FU plus MeCCNU resulted in statistically superior long-term survival when compared with 5-FU plus MeCCNU alone (3- and 4-year survival rates of 18% vs. 6% to 7%; $P < 0.05$). GITSG performed a second trial in which combined irradiation plus chemotherapy did not produce a survival advantage when compared with chemotherapy alone.[146] Because 46% of patients on the combined arm either did not receive full-course irradiation or had a major deviation in the delivery of the irradiation, the results are difficult to interpret. In a randomized European Organization for Research and Treatment of Cancer (EORTC) trial of external irradiation with or without 5-FU, residual disease after resection was identified in 22 patients.[147] The three long-term survivors (14%) received both irradiation and 5-FU.

Data from nonrandomized single-institution or group analyses also suggest that the combination of external irradiation and chemotherapy may have an impact on disease control and survival. In published series from the Mayo Clinic[148] and MGH,[123] long-term survival of 10% or more was demonstrated in patients who received external irradiation plus chemotherapy following subtotal surgical resection with residual disease (MGH) or with unresectable lesions. In a University of Pennsylvania analysis[126] of individuals with unresected adenocarcinoma of the esophagogastric junction or esophagus,

Table 79-14 Unresectable or Residual Gastric Cancer: Treatment Results

Group or Institution	Treatment Arms	EBRT Dose/ Schedule (Gy)	Chemotherapy	No. of Patients	Results (Failure Patterns and Survival)
RANDOMIZED					
Mayo Clinic[143]	EBRT ± 5-FU	35–40 Gy; 9–12 Gy/wk	5-FU 15 mg/kg, d 1–3, wk 1 EBRT	48	Increased SR for EBRT + 5-FU with mean SR 13 vs. 5.9 mo and 3/25 (12%) vs. 0/23 5-yr SR
GITSG study 8274[144,145]	Chemo ± EBRT	50 Gy/8 wk/2 wk split after 25 Gy/3 wk	5-FU 500 mg/m^2, d 1–3, wk 1 + 6 EBRT plus 5-FU/ MeCCNU maint vs. 5-FU + MeCCNU	90	Advantage in long-term SR with EBRT + CT at 18% vs. 7% ($P < 0.05$)
Japan[116]	Operation ± IORT*	IORT, 28–40 Gy	None	110 surgery, 101 IORT	Increased 5-yr SR for 27 patients with IORT + resection for stage IV disease vs. 18 patients with surgery alone (15% vs. 0%)
NONRANDOMIZED					
MGH[123]	EBRT ± Chemo	45–55 Gy in 5–6.5 wk	5-FU 500 mg/m^2, 3 d wk 1 EBRT ± maint FAM or 5-FU MeCCNU	32	Median SR res(m) 24 mo, res(g) 15 mo, unresected 14 mo; survival ≥30 mo, unresected 0%, residual after resection ~10%
Mayo Clinic[148]	EBRT ± Chemo ± IOERT	45–54 Gy in 6–6.5 wk; IOERT boost 13 patients	5-FU 500 mg/m^2 3 d wk 1, wk 5 or 5-FU 400 mg/m^2 leucovorin 20 mg/m^2	87	Median SR res(m) 17 mo, res(g) 9 mo, unresectable 12 mo, locally; recurrent 10 mo; 4-year SR ≤9%; res(m) and res(g); 18% unresectable or locally recurrent

Chemo, chemotherapy; EBRT, external-beam radiation therapy; GITSG, Gastrointestinal Tumor Study Group; IORT, intraoperative radiation; maint, maintenance; MGH, Massachusetts General Hospital; res(m), microscopic residual; res(g), gross residual; SR, survival. For other abbreviations, see footnotes to Table 79-7 and 79-8.

*Treatment method based on date of hospitalization.

local control was better with combined- versus single-modality treatment (irradiation, 1 of 23 or 4%; chemotherapy, 0 of 8; irradiation plus chemotherapy, 11 of 21 or 52%). Median survival time with the combined-modality treatment was 10 months compared with 5 months for irradiation alone. In a Mayo Clinic North Central Cancer Treatment Group (NCCTG) dose escalation pilot study, external irradiation was combined with 5-FU plus low-dose leucovorin (400 mg/m^2 and 20 mg/m^2, respectively, for 3–4 days, weeks 1 or 1 plus 5 of irradiation).[149] Two of six patients with locally advanced gastric cancer were alive and free of disease beyond 3 years.

Published analyses from both GITSG and MGH suggest an improvement in survival if partial resection with gross residual disease or gross total resection with microscopic residual can be accomplished. In the GITSG series 3-year survival rate was about 25% as compared with 10% in partially resected versus unresected patients.[144,145] In the MGH analysis, median survival with irradiation plus chemotherapy was 24 months for microscopic residual, 15 months with gross residual, and 14 months in unresected patients.[123] Four-year survival rate was 0% in unresected patients as compared with 10% in those with residual disease after maximal resection.

In the most recent Mayo Clinic analysis of irradiation alone or plus chemotherapy for gastric or esophagogastric cancers, an improvement in median survival was also suggested for patients with gross total resection but microscopic residual disease when compared with higher risk subsets of patients.[150] In this analysis, the results of irradiation or chemoirradiation therapy were evaluated in 87 patients with either locally advanced primary or locally recurrent adenocarcinoma of the stomach or gastroesophageal junction treated from July 1980 through January 1996 at the Mayo Clinic. Of those with primary lesions, 28 had unresectable disease, and 39 had resection but residual disease (microscopic, 28; gross, 10). An additional 21 presented with a local or regional relapse with no evidence of abdominal (liver, peritoneal) or extra-abdominal metastasis (lung, other). Chemotherapy with 5-FU (alone or plus leucovorin) was given during or following EBRT in 75% of the individuals with microscopic residual disease and 92% of the other subgroups (concomitant with EBRT in 84%). An intraoperative electron radiation therapy (IOERT) supplement to EBRT was given in 13 patients. Median survival time in primary cancer patients with microscopic residual was 16.7 months compared with 9.2 months in patients with subtotal resection and gross residual or 12 months in those with unresectable disease. Patients who presented with local or regional relapse had a median survival of 10 months.

Prognostic factor analyses showed that long-term survival seemed slightly poorer in patients who had resection before irradiation or CRT in the latest Mayo Clinic analysis. Actuarial 4-year survival rate was 0% versus 9% in individuals with gross residual disease after partial resection (1 of 11 patients alive with no evidence of disease 2 years after treatment), 9% in those with microscopic residual after gross total resection, and 18% in patients with unresectable primary or locally recurrent cancers. The survival trends may be a reflection of both treatment sequence and higher irradiation dose; 12 of 13 patients with EBRT plus IOERT had unresectable primary or locally recurrent cancers. In the 21 patients with locally or regionally recurrent cancers, irradiation dose greater than 54 Gy had a trend for improved survival (median survival, 25.6 vs. 5.5 months; $P = 0.06$). If patients with microscopic residual disease are excluded, an increase in the number of cycles of chemotherapy seemed to correlate with an improvement in median survival (median survival 5.2 months with less than two cycles, 11.5 months with two or three cycles, and 14.5 months with four or more cycles; $P = 0.014$).

Although problems with excess toxicity from combined CRT were encountered in the GITSG study,[144] such problems were minimal or nonexistent in the MGH series of 46 patients.[123] In the latter series, 43 of 46 patients received both irradiation and chemotherapy, but shaped radiation portals and single-fraction size of 1.8 Gy or less were used.

Neoadjuvant and Perioperative Chemotherapy

The use of adjuvant preoperative (neoadjuvant) chemotherapy has been less well studied than has adjuvant postoperative therapy. Due to the frequent inability of adjuvant postoperative systemic therapy to prolong survival in surgically managed gastric cancer, several investigators have pursued the approach of neoadjuvant (preoperative) chemotherapy in an attempt to increase resectability and improve survival. These studies involve a mix of patients including those determined surgically or clinically unresectable for cure, those with "locally advanced" disease (as defined by the study authors), and those with clinically operable lesions. Some patients were staged clinically by a variety of methods, making it difficult to know which patients were truly resectable before neoadjuvant treatment.

Unresectable Disease

Seven different trials have assessed the potential benefit of preoperative chemotherapy for patients with initially "unresectable" stomach cancer.[151–158] Each of the trials was small in size. The seven trials combined included 155 patients and demonstrated that preoperative chemotherapy in this subset of patients was feasible and resulted in clinical response rates of 30% to 68%. Curative resections were possible in as few as 8% or as many as 73% of patients. This wide range of resectability probably reflects patient selection rather than superiority of any one regimen. Unfortunately, pathologic complete responses (CRs) were uncommon except for the Wilke trial (pathologic CR in 5 of 34 patients or 15%).[151]

Borderline Resectable and Locally Advanced Disease

Three phase II studies have tested the use of preoperative systemic treatment in individuals defined by the study authors as having "locally advanced" stomach cancer.[159–161] Presumably this represents a mix of clinically resectable and unresectable or borderline resectable patients. Resectability rates ranged from 60% to 77%, which seems to be higher than for patients with unresectable cancers. It is likely that more patients in these trials were potentially (borderline) resectable before neoadjuvant chemotherapy.

Kang and associates have presented an updated report of the only phase III trial of neoadjuvant chemotherapy in locally advanced or borderline resectable gastric cancer.[162] In the trial, 107 patients were randomized to receive two to three cycles of etoposide, 5-FU, and cisplatin followed by surgery versus surgery alone. Of the 53 patients randomized to preoperative treatment, 47 (89%) were explored and 37 (70%) were resected for cure. A 7% complete pathologic response rate was noted. In the control group of 54 patients, 100% were explored and 61% curatively resected. Median survival was 43 versus 30 months in favor of neoadjuvant treatment, but this difference did not reach statistical significance ($P = 0.114$).

Resectable Disease

Several investigators have examined the role of neoadjuvant chemotherapy in patients with clinically resectable disease. Ajani and colleagues have performed two phase II studies of preoperative chemotherapy in this setting.[163,164] In their first study, 25 patients were treated with two cycles of etoposide, 5-FU, and cisplatin preoperatively.[163] Three cycles were administered postoperatively if a positive response to neoadjuvant treatment could be detected endoscopically or radiographically. All 25 patients underwent surgery, and 72% were resected for cure. No pathologic complete responses were seen, and the median survival was 15 months overall. Following the report of Wilke and coworkers of pathologic complete response to chemotherapy with epirubicin, doxorubicin, and cisplatin (EAP),[151] Ajani and associates treated 48 potentially curable patients with three cycles of preoperative EAP and two cycles following surgery if a response to preoperative treatment was observed.[164] Of the 85% of patients who underwent exploration, 77% were resectable. Although 12% of patients achieved a complete clinical response, no pathologic complete responders were seen. The overall median survival was 15.5 months. Unfortunately, in this group of resectable patients with potentially smaller tumor burdens, the impressive results obtained with neoadjuvant EAP in Wilke's study could not be reproduced.

One of the few randomized trials to assess the potential benefit of preoperative chemotherapy to surgery alone in potentially resectable patients failed to show any benefit in outcomes.[165,166] In this Dutch trial, 59 patients were randomized to either FAMTX followed by surgery ($N = 29$) or surgery alone (30). Patients with T1 tumors, tumors arising from the gastric cardia, or evidence of distant metastases were excluded from participation. The study was closed early as a result of poor accrual. No benefit was seen with the addition of FAMTX before surgery (Table 79-15).

Preoperative Systemic and Postoperative Intraperitoneal Chemotherapy

Recently, other investigators have examined the usefulness of combining preoperative chemotherapy and postoperative treatment with intraperitoneal chemotherapy in view of the high peritoneal failure rate following resection of gastric cancer. Initial attempts to use intraperitoneal chemotherapy alone in the adjuvant setting did not show benefit.[112,113,167–171]

Kelsen and associates studied 56 patients with high-risk (clinical stage T3–4) gastric cancer as determined by EUS.[169] Patients received

Table 79-15 Recent Randomized Phase III Chemotherapy versus Surgery-Only Trials (Neoadjuvant, Perioperative) for Gastric Cancer

Reference	Regimen	No. of Patients	Overall Survival		*P* Value
			Interval	Percent	
NEOADJUVANT					
Hartgrink et al[166]	FAMTX	29	5 yr	21	0.17
	Surgery alone	30		34	
PERIOPERATIVE					
Cunningham et al[172]	ECF	250	5 yr	36	0.009
	Control	253		23	

5-FU, 5-fluorouracil; FAMTX, 5-FU, doxorubicin, and methotrexate; ECF, epirubicin, cisplatin, and 5-FU.

three cycles of neoadjuvant FAMTX. Following surgery, patients were treated with intraperitoneal 5-FU and cisplatin along with infusional 5-FU for three cycles. Fifty (89%) patients were explored and 34 (61%) resected for cure. When the initial EUS result was compared to the final pathologic staging, 51% of these patients were downstaged. No complete pathologic responses were observed, and the median survival was 15.3 months.

Crookes and colleagues updated their promising results with a somewhat similar trial design.[170] Fifty-nine potentially resectable patients received two cycles of 5-FU, leucovorin, and cisplatin preoperatively, and two cycles of intraperitoneal 5-FUDR and cisplatin were given postoperatively to resected patients. Ninety-five percent of the patients underwent exploration, and 68% had a curative resection. The rate of pathologic CR was only 9%, but the median survival is estimated to be an impressive 52 months.

In a more recent phase II trial, 32 evaluable patients with locally advanced but potentially resectable stomach cancer received two cycles of systemic cisplatin and irinotecan.[171] Twenty-nine patients were able to undergo surgery, and 25 had an R0 resection. Patients with resection subsequently received two cycles of intraperitoneal FUDR and cisplatin. Preoperative chemotherapy led to downstaging in 50% of the patients. With a median follow-up of 28 months, 10 (31%) were alive without relapse, 4 (13%) were alive with relapse, and the remainder had died from either disease (41%) or other causes (16%). Of the 25 patients with an R0 resection, none had a local relapse. A phase III trial of this approach has not yet been reported.

Summary

Preoperative systemic treatment may have certain advantages, such as the potential of reducing tumor bulk and increasing resectability. Micrometastatic disease may also be addressed earlier using this approach. Potential negatives to preoperative treatment include toxicity, delay in definitive therapy, and possibly increased surgical morbidity and mortality rates.

The high response rates achieved with neoadjuvant chemotherapy are of interest, and this form of treatment will undoubtedly be the subject of further investigation as new and more active systemic therapies are developed. Thus far, however, no survival advantage has been demonstrated in phase III trials, and neoadjuvant chemotherapy should be considered investigational. Resectability rates in neoadjuvantly treated patients seem higher than the median rate of 40% from several surgical studies, but the patients in these studies are highly selected. Except for the trials in which some patients were unresectable on the basis of prior exploration, the successful operations in these reports may not have been influenced by neoadjuvant chemotherapy. In general, pathologic CR rates are low (≤15%), and no proof exists that clinically staged patients are made more resectable by such treatment. The impact of preoperative systemic treatment on survival is even less clear. The one randomized trial that has been reported shows a nonsignificant improvement in survival for neoadjuvant treatment in borderline resectable/locally advanced disease.[163] Newer technologies such as EUS may identify patients who will do poorly with standard therapy alone and would be reasonable candidates for future neoadjuvant studies. The reports of combined systemic and intraperitoneal approaches are provocative and may warrant future phase III trials, because only through such studies will any impact on survival be determined.

Perioperative Chemotherapy

The use of perioperative chemotherapy was recently addressed in a phase III trial referred to as the MAGIC (Medical Research Council Adjuvant Gastric Infusional Chemotherapy) trial.[172] A total of 503 patients with resectable adenocarcinoma of the stomach (372 patients), gastroesophageal junction (58 patients), or lower esophagus (73 patients) were randomized to either surgery alone or to perioperative chemotherapy with three cycles of epirubicin, cisplatin, and continuous-infusion 5-FU (ECF) before surgery and three cycles of ECF after surgery. With a median follow-up of 4 years, patients randomized to receive perioperative chemotherapy had significantly improved OS when compared with patients randomized to receive surgery alone (5-year OS 36% vs. 23%; HR for death 0.75; 95% CI 0.60–0.93; $P = 0.009$).

In general the use of ECF was well tolerated in the preoperative setting. The incidence of overall postoperative complications was similar (45.7% vs. 45.3%) as well as 30-day mortality rates (5.6% vs. 5.9%). Of the 237 patients who started chemotherapy, 215 completed the planned three cycles of preoperative therapy. Of the 209 patients who went to surgery, 137 started postoperative chemotherapy. The most common reasons for not starting chemotherapy included disease progression, early death, postoperative complications, and patient choice. Overall 103 patients completed all six cycles of chemotherapy.

Preoperative Chemoradiation

Several series of neoadjuvant chemotherapy for initially unresectable have demonstrated high rates of local-regional relapse in patients who were resected after the neoadjuvant chemotherapy. In the neoadjuvant EAP phase II trial reported by Wilke and associates, 15 of the 34 initially unresectable patients (44%) could subsequently be resected, and 5 of 15 were pathologic complete responders (15% of the original 34).[151] Median survival was 18 months for the entire study group. In an update of these data at an international gastrointestinal cancer symposium in Germany, results were reported in a series of 21 patients who had total resection after EAP chemotherapy for locally unresectable disease.[173] Of 21 patients 14 had relapsed, and 11 of 14 had a local-regional component of disease (79% of relapses, 52% of group at risk). Plukker and coworkers studied 20 patients with unresectable gastric cancer.[153] Seventeen of the patients had undergone laparotomy, and three patients were deemed unresectable on the basis of CT imaging. After receiving up to four courses of sequential 5-FU and high-dose methotrexate, 14 patients (70%) underwent attempted resection. Eight of 20 patients (40%) were found to be resectable for cure, but subsequent local relapse occurred in five of eight.

In view of the high incidence of local-regional relapse in several series of patients resected after neoadjuvant chemotherapy for initially unresectable lesions, irradiation would be logical to incorporate into the study design of trials for patients with borderline or unresectable cancers. As previously noted, the phase III study by Walsh and colleagues compared preoperative 5-FU and cisplatin plus radiation therapy followed by surgery ($N = 58$) versus surgery alone ($N = 55$) in individuals with esophageal and gastric cardia adenocarcinoma.[132] Pathologic CR was found in 13 of 52 patients (25%) who had surgery after preoperative CRT. Both median and long-term survival were improved with the preoperative treatment ($P = 0.01$). Thirty-five percent of the patients had lesions of the gastric cardia; however, there were more of these patients in the control group (42% vs. 28%). The positive esophagus/gastric cardia trial by Walsh and associates and high pathologic CRs in similar pilot studies with gastric cancer[132,174,175] led to a U.S. GI Intergroup confirmatory trial of neoadjuvant combined-modality therapy in carcinoma of the esophagus and gastroesophageal junction. Although this study was stopped because of inadequate accrual, a survival advantage was demonstrated for trimodality treatment versus the surgery-alone control arm ($P = 0.008$).[133]

PALLIATION OF THE INCURABLE PATIENT

This section is limited to discussion of patients with documented hematogenous or peritoneal metastasis. Patients with locally unresected disease are occasionally cured and were discussed in the previous section (5-year survival rate of 5% to 20%).

Surgery

Surgical intervention in the patient with metastatic gastric cancer requires sound judgment. The underlying health and function (performance status) of the patient, the estimated duration of patient survival, and the nature of the symptoms must all be taken into account before deciding to proceed with an operation. Resection for palliation is generally better than bypass or intubation in appropriate selected patients, leading to better symptomatic relief and often longer survival.[176] Laparoscopic procedures, including subtotal and total gastrectomy, are feasible and are becoming increasingly popular. Obstructing lesions may be resected with excellent palliation, but endoluminal stents, endoscopic laser treatments, or gastrostomy tube placement should be considered for poor operative candidates. Although significant hemorrhage from an ulcerating or necrotic polyploid tumor may be temporarily controlled by endoscopic techniques, stabilization and urgent surgical intervention should be undertaken when appropriate. A perforated gastric cancer usually presents as an emergency and may be unrecognized preoperatively. Aggressive treatment with gastric resection should be carried out in the fit patient, but pain control and hydration alone are preferable for the moribund or unfit patient.

Irradiation Alone or Plus Chemotherapy

If palliative resection is not indicated in symptomatic patients with metastases, a shortened course of irradiation alone or plus concurrent 5-FU-based chemotherapy could be used (37.5 Gy in 15 fractions over 3 weeks), to be followed by systemic treatment. Patients who have proximal lesions with esophageal obstruction may be candidates for laser ablation instead of irradiation. If laser is successful in overcoming obstruction, patients could proceed directly to treatment with chemotherapy.

Chemotherapy

Overview

Several clinical trials assessing the benefit of chemotherapy have been performed, including several that compared *chemotherapy* to *best supportive care*. Six trials assessed the potential benefit of early forms of chemotherapy for advanced gastric cancer compared to an untreated control group.[177–182] In the largest of these trials 193 patients were randomized to either 5-FU + MeCCNU or to no treatment.[178] The median survival time was 22 weeks for control subjects and 25 weeks for those who received at least one 6-week course of chemotherapy. Patients who died in the first 2 months were excluded from these figures. Median survival, estimated from survival curves, was in the 8- to 10-week range for all the patients, with no apparent difference between the two groups. It is of interest that a quality-of-life analysis was done in this trial and that it was published in 1978. Pain, well-being, and performance status were assessed at 8 and 16 weeks. Results of this quality-of-life analysis slightly favored the patients treated with chemotherapy, but few patient results were available for the 16-week time point. Subsequent trials with chemotherapy versus best supportive care have in general demonstrated a trend toward improved survival and quality of life with the use of chemotherapy.[179–182]

The initial trials with chemotherapy reported response rates of 10% or higher and included agents such as 5-FU, mitomycin C, doxorubicin, epirubicin, cisplatin, BCNU (carmustine), methotrexate, etoposide, chlorambucil, and hydroxyurea. More recently a variety of new chemotherapy drugs have become available. Some have shown promising response rates in advanced gastric cancer, as discussed in the following sections, including docetaxel, irinotecan, and oxaliplatin. Multiple phase II trials of combination chemotherapy have built upon the promising activity seen with a variety of single agents. Many of the combinations have shown promising activity based on initial results, only to be shown to be less active and more toxic in subsequent phase II and III trials. It has therefore been important to interpret the results of initial phase II trials with caution. With some of the more recent combinations showing promise, using drugs such as docetaxel or oxaliplatin, older regimens such as FAM, FAMTX, and the combination of etoposide, leucovorin, and 5-FU are now less commonly used.

Fluoropyrimidines

A number of trials with 5-FU have been performed over the last several decades culminating in a recent series of phase III trials (Table 79-16).[183–185] In a trial that mixed 254 patients with either adenocarcinoma, squamous cell carcinoma, or undifferentiated carcinoma of the esophagus or stomach, patients were randomized to either protracted-infusion 5-FU or protracted-infusion 5-FU with mitomycin C.[183] The overall response rates were 16% and 19%, respectively, with median survivals of 6.3 and 5.3 months ($P = 1.0$), respectively. In a phase III trial performed in Japan, 280 patients with advanced stomach cancer were randomized to receive one of three protocols: protracted-infusion 5-FU, continuous-infusion 5-FU combined with cisplatin, or the oral fluoropyrimidine UFT combined with mitomycin C.[184] This trial also showed no advantage of the two combinations over the benefits obtained with 5-FU alone. In a third phase III trial the potentially promising combinations of etoposide + leucovorin + 5-FU, infusional 5-FU + cisplatin, and FAMTX were compared.[185] A total of 399 patients with advanced carcinoma of the stomach were randomized. All three regimens showed modest activity with no significant difference in the primary outcome measures.

While these 5-FU-based phase III trials were under way a variety of phase II trials and several additional phase III trials were performed evaluating potentially more promising agents or combinations.

Taxanes

Taxanes have been evaluated in a variety of phase II trials. Two North American trials of single-agent paclitaxel have been reported. Paclitaxel (210 mg/m^2 over 3 hours every 3 weeks) as a single agent in previously untreated patients with metastatic gastric cancer provided a response rate of 11% and a median survival of 5.8 months.[186] In a separate trial, assessing two different infusion schedules (200 mg/m^2 over 3 hours vs. 24 hours every 3 weeks), an overall response rate of 17% was seen with a higher rate occurring in those receiving a 24-hour infusion. The median survival in this trial was 8 months.[187] In several trials performed in Japan, using paclitaxel (210 mg/m^2 over 3 hours every 3 weeks) as a single agent in the treatment of previously untreated patients with advanced gastric cancer, response rates of 23% and 28% were reported with a median survival of 7.7 and 11.2 months.[188–190] Subsequent trials have assessed paclitaxel in combination with other chemotherapy agents. Phase II trials assessing paclitaxel in combination with cisplatin have given response rates of 33% to 46%, with median survivals of 8.9 to 13.8 months.[191,192] The use of low-dose paclitaxel in combination with cisplatin did not seem to alter outcome, with a response rate of 44% and overall survival of 12.1 months in a phase II trial performed in Korea.[193]A response rate of 33% and a median survival of 7.5 months have been reported in a small phase II trial with paclitaxel and carboplatin.[194] Paclitaxel in combination with 5-FU and leucovorin has been assessed in several phase II trials. In two trials using a 24-hour infusion of 5-FU response rates of 46% to 48% and median survivals of 11 months were reported.[195,196]

Docetaxel as a single agent has been evaluated in several phase II trials. In several single-institution trials of docetaxel 100 mg/m^2 every 3 weeks, a response rate of 17% and 24% was reported along with a median survival of 7.8 months in one of the trials.[197,198] Other trials assessed lower doses of docetaxel (60 mg/m^2 or 75 mg/m^2) and have reported similar results with response rates of 18% to 24% and a median survival of 11 months with the 75-mg/m^2 dose.[199–201]

Subsequent trials have evaluated docetaxel in combination with several other chemotherapy agents. The combination of docetaxel,

Table 79-16 Recent Randomized Phase III Trials of Chemotherapy for Advanced or Metastatic Stomach Cancer

Reference	Regimen	No. of Patients	Response (%)	Overall Survival (mo)	*P* Value
Tebbutt et al[183]	PVI 5-FU	123	16.1	6.3	1.0
	PVI 5-FU + MMC	127	19.1	5.3	
Ohtsu et al[184]	5-FU	105	11.4	7.1	0.11
	5-FU + cisplatin	105	34.3	7.3	
	UFTM	70	8.6	6.0	
Vanhoefer et al[185]	ELF	132	9	7.2	0.77
	5-FU + cisplatin	134	20	7.2	
	FAMTX	133	12	6.7	
Van Cutsem et al[216]	DCF	227	37	9.2	0.02
	5-FU + cisplatin	230	25	8.6	
Cocconi et al[232]	PELF	98	39	7.7	0.19
	FAMTX	97	22	6.9	
Cunningham et al[249]	ECF	249	NS	9.9	NS
	EOF	241		9.3	
	ECX	235		9.9	
	EOX	239		11.2	

DCF, docetaxel, cisplatin, and 5-FU; ECF, epirubicin, cisplatin, and 5-FU; ECX, epirubicin, cisplatin, and Capecitabine; ELF, etoposide, leucovorin, and 5-FU; EOF, epirubicin, oxaliplatin, and 5-FU; EOX, epirubicin, oxaliplatin, and capecitabine; FAMTX, 5-FU, doxorubicin, and methotrexate; 5-FU, 5-fluorouracil; MMC, mitomycin C; NS, not stated; PELF, cisplatin, epirubicin, leucovorin, and 5-FU; PVI, protracted venous infusion; UFTM, uracil, tegafur, MMC.

5-FU, and leucovorin has been evaluated in several phase II trials from Europe and Korea. This combination led to a response rate of 26% to 28% and a median survival of 7.7 to 9.7 months.[202–204] In a randomized phase II trial the combination of docetaxel and 5-FU was compared to paclitaxel and 5-FU.[205] Similar response (33% and 42%) and median survival (9.3 and 9.9 months) rates were reported for the two regimens. Several trials have assessed the combination of capecitabine and either weekly or every-3-week docetaxel and reported response rates of 39% to 60% and median survivals of 9.4 to 12 months.[206–208]

The combination of docetaxel and cisplatin has been evaluated in several clinical trials as either the two-drug combination or in combination with other chemotherapy agents. With the two-drug combination in phase II trials the reported response rate was 28% to 46% and median survival of 10.4 to 11.5 months.[209–212] Given the apparent promising activity of this combination, other trials explored the added benefit of 5-FU and reported response rates of 40% to 43% and median survivals of 9.0 to 9.7 months.[213,214] A multicenter randomized phase II trial, involving 158 patients, assessed docetaxel and cisplatin with or without 5-FU as potential support for a phase III trial.[215] In this trial the combination of docetaxel and cisplatin gave a response rate of 26% and a median survival of 10.5 months. The addition of 5-FU increased the response rate to 43%; however, the median survival was only 9.6 months.

In a subsequent phase III trial (see Table 79-16) the combination of docetaxel, cisplatin, and 5-FU was compared to cisplatin and 5-FU.[216] Overall survival was significantly longer with docetaxel, cisplatin, and 5-FU ($P = 0.02$). The response rate was also higher with this combination (69% vs. 59%, $P = 0.01$). However, the combination of docetaxel, cisplatin, and 5-FU was also more toxic, with 69% of patients developing treatment-related grade 3 or 4 adverse events compared with 59% of patients receiving cisplatin and 5-FU. Neutropenia and neutropenic fever were both significantly higher with the three-drug combination.

Platinums

Platinum-containing regimens have been the focus of many different trials. Many of the trials conducted in the past focused on the use of cisplatin, whereas more recent trials have begun to evaluate the potential use of oxaliplatin. The combination of 5-FU and cisplatin has been evaluated in several trials and provided a response rate of 41% to 45% and a median survival of 7 to 11 months.[217–221] Given the apparent activity of this combination, a variety of phase III trials have compared 5-FU and cisplatin to other regimens (see Table 79-16). The response rates in these larger trials were 20% to 51%, whereas the median survival was 7.2 to 8.6 months.[216,222–224]

Building on this two-drug combination a variety of trials have assessed the combination of either 5-FU, cisplatin, and doxorubicin (FAP) or EAP. The FAP combination resulted in response rates of 31% to 50% and median survivals of 9 to 12 months in phase II trials.[225–228] A phase III study, however, could not show an advantage for FAP over 5-FU alone.[229] Less favorable outcomes were noted for the combination of EAP in phase II trials.[230,231] This combination also caused significant toxicity, with a toxic death rate averaging 12%. The combination of cisplatin, epirubicin, leucovorin, and 5-FU (PELF) was compared to FAMTX in a randomized phase III trial. Although both the overall and CR rates with PELF were significantly higher (overall, 39% vs. 22%; CR, 13% vs. 2%), only a nonsignificant improvement in overall survival was seen with PELF (see Table 79-16).[232]

The ECF combination has been recognized as a potentially more promising cisplatin-containing regimen. Based on the results of phase II trials, this regimen showed activity at least comparable to other platinum regimens, but with less toxicity.[233–236] A subsequent phase III trial of patients with previously untreated locally advanced or metastatic gastroesophageal cancer compared ECF to the combination of FAMTX.[237] The overall response rate (45% vs. 21%; $P = 0.0002$) and median survival (8.9 vs. 5.7 months; $P = 0.0009$) were

both significantly higher with ECF. The global quality-of-life scores were also better in patients receiving ECF.

Both carboplatin and oxaliplatin have been evaluated as potential alternatives to cisplatin. Only limited trial data are available for carboplatin. Carboplatin as a single agent has minimal activity.[238,239] However, the combination of carboplatin and paclitaxel has a reported response rate of 33% and median survival of 7.5 months with only moderate toxicity.[194]

Oxaliplatin was initially developed for colorectal cancer but has been evaluated as a potential treatment option for gastric cancer when used in combination with 5-FU and other chemotherapy agents. Although the use of 5-FU and leucovorin alone result in response rates of 5% to 12% with short median survivals,[240,241] the addition of oxaliplatin seems to significantly improve response and overall survival. A variety of schedules using the combination of 5-FU, oxaliplatin, and leucovorin have been evaluated in phase II trials, including FUFOX, FOLFOX, and XELOX. These regimens have generally shown similar results with response rates of 38% to 65% and median overall survivals of 8.6 to 11.5 months.[22,242–247] No phase III trials have yet been reported using one of these combinations.

Given the potentially promising activity of ECF, as described previously, a recent phase III trial for gastroesophageal cancer was conducted to assess the potential benefit of replacing cisplatin with oxaliplatin and infusional 5-FU with capecitabine using a 2 × 2 design (see Table 79-16).[248] This trial enrolled 1002 patients from 61 centers, and the results have been presented in a meeting abstract. Using a noninferiority statistical design for the trial, the combination of epirubicin, oxaliplatin, and capecitabine (EOX) was shown to be the most active of the four regimens evaluated. Compared with ECF, patients receiving EOX had both an improved 1-year survival (46.8% vs. 37.7%) and a statistically improved median survival (11.2 months versus 9.9 months; HR, 0.80, 95% CI, 0.65–0.97).[249]

Oral Fluoropyrimidines

The recent use of oral fluoropyrimidines in gastric cancer has focused on capecitabine and S-1. As a single agent in previously untreated patients capecitabine provided an overall response rate of 23% using a 3-week treatment schedule in a trial performed in Japan.[250] OS was 10 months. Various combinations of capecitabine and other chemotherapy drugs, such as cisplatin or docetaxel, have been evaluated.[206,251–253] The majority of recent trials, including a phase III trial as described previously, have evaluated capecitabine as a potential replacement for 5-FU.

The drug S-1 is an oral fluoropyrimidine in which the 5-FU prodrug tegafur is combined with two 5-FU-modulating substances, 5-chloro-2,4-dihydroxypyridine (gimeracil), and potassium oxonate (oteracil), at a molar ratio of 1 : 0.4 : 1. The dose-limiting side effects of S-1 are primarily nonhematologic and mainly diarrhea, nausea, and vomiting. There is also a difference in metabolism of the tegafur component of S-1 in Asians and whites related to polymorphic differences in the *CYP2A6* gene.[254] This has led to different tolerable doses of S-1 in studies conducted in Asia compared with those conducted in Western populations. A variety of trials using S-1, alone or in combination with other chemotherapy drugs, have been performed in Asia, Europe, and North America. S-1 as a single agent has a reported response rate of 26% to 32%.[255] Based on the early evidence of activity, S-1 has been evaluated in combination with cisplatin in several phase II trials. In these trials a response rate of 49% to 55% and OS of approximately 11 months were reported.[256–258]

Irinotecan

The topoisomerase-I inhibitor irinotecan (CPT-11) has activity in gastric cancer, though limited as a single agent. In a phase II trial it provided a median survival of 6.4 months with a 14% response rate.[259] CPT-11 has been evaluated in combination with other potentially active chemotherapy drugs. In combination with docetaxel a response rate of 46% and OS of 8.2 months has been reported.[260] Similar response rates and OS have been reported for CPT-11 and cisplatin, CPT-11 and capecitabine, CPT-11 and mitomycin C, and CPT-11 and oxaliplatin.[261–264] The addition of the antiangiogenic agent bevacizumab to the combination of CPT-11 and cisplatin in a phase II trial did increase the response rate to 65% and the OS to 12.3 months.[265] The combination of CPT-11 with leucovorin and infusional 5-FU (FOLFIRI) in a randomized phase II trial also showed promising results, with a response rate of 40% and overall survival of 11.3 months.[266] Phase III trials with these combinations have not been reported.

Summary

In summary, it is clear that chemotherapy may result in response rates of up to 50% or more in selected groups of patients with advanced gastric cancer. There is now growing evidence from both recent phase II and III trials indicating that chemotherapy seems to prolong survival over what would be expected with best supportive care. In recent trials median survival times have begun to clearly increase, with subsequent improvement in outcome measures including overall survival for treated patients compared to what had been observed in the prior several decades of clinical trials. However, it is not clear that there yet exists a standard treatment for advanced gastric cancer. Investigation of new agents and combinations must continue, and any "new standards" should be tested in controlled clinical trials looking at survival, quality of life, and cost analysis endpoints.

THE FUTURE

Completely Resected Lesions

Many patients with gross complete resection of their gastric cancer are not cured with surgery alone. The final results of the British and Dutch multicenter trials evaluating the value of extended lymphadenectomy demonstrated that the procedure produced greater morbidity with no impact on survival. Because experienced surgeons have performed extended node dissection without significant increases in surgical morbidity or mortality rates,[61,64] use of the procedure is still reasonable in node-positive patients. Such patients will still be at high risk for local-regional and systemic relapse, however, and should receive postoperative CRT (Table 79-17). This philosophy is supported by the nonrandomized South Korea analysis by Kim and associates, which appeared to demonstrate an advantage in disease control and survival in 544 patients who received postoperative CRT following D2 resection versus the 446 surgery-alone patients (5-year OS, 57% vs. 51%, $P = 0.02$; 5-year RFS, 54.5% vs. 47.9%, $P = 0.016$).[163]

With regard to replacement postoperative CRT trials, the U.S. GI Intergroup replacement phase III randomized trial was designed to build on the positive results of INT 0116[129,130] by testing 5-FU infusion versus bolus 5-FU + leucovorin as the concurrent chemotherapy during EBRT, and ECF chemotherapy versus 5-FU + leucovorin as the maintenance component of chemotherapy. A phase II trial tested the tolerance of the more aggressive infusional 5-FU and ECF regimen in a multicenter trial involving CALGB institutions together with the Mayo Clinic.[267] The irradiation treatment fields in both the phase II and successor phase III trials are based on idealized field design related to site of the primary lesion and TN stage of disease.[136,137]

On the basis of encouraging results with preoperative chemotherapy and CRT for locally advanced or borderline resectable disease and the survival advantage for perioperative ECF chemotherapy versus surgery alone for resectable gastroesophageal cancers in the British phase III MAGIC trial,[173] future phase III studies should evaluate preoperative chemotherapy (alone or followed by postoperative CRT) and preoperative CRT in combination with resection for patients with potentially resectable lesions. Although some inves-

Table 79-17 Treatment Algorithm for Gastric or Gastroesophageal Junction Cancer, Mayo Clinic Cancer Center

TNM Extent*	Surgery	Irradiation (Alone or with Chemo)	Chemotherapy
T1–2N0M0	Radical subtotal gastrectomy and regional nodes	Not routinely recommended, except posterior wall T2N0M0	NR
T1–2N1–3M0; T3N0–3M0	Radical subtotal and regional nodes	Postop EBRT-Chemo, 45–50 Gy; evaluate preop EBRT-Chemo, gastric; prefer preop EBRT-Chemo, GE junction†	5-FU + leucovorin bolus wk 1,5—CCRT and maint; evaluate maint ECF in current U.S. GI Intergroup phase III
T4N0–3M0	Radical subtotal and regional nodes; attempt en bloc resection, involved organ(s)	Preop EBRT-Chemo, 45–50 Gy; attempt resection and IOERT	5-FU + leucovorin, bolus wk 1, 5; evaluate alternate CCRT including infusion; 5-FU; evaluate other maint chemo (ECF, other)
$T_{any}N_{any}M1$	Palliative if feasible	Palliative CCRT if indicated	MACT; ICT phase I, II, or III

CCRT, concurrent chemoradiotherapy; EBRT, external beam irradiation; EBRT-Chemo, external beam irradiation + chemotherapy; eval, evaluate; ICT, investigational chemotherapy clinical trials; IOERT, intraoperative electron irradiation; MACT, multiagent chemotherapy; maint, maintenance; NR, not recommended; postop, postoperative; preop, preoperative;

*For TNM definitions, see Table 79-2.

†We prefer preop CRT for gastroesophageal (GE) junction cancer found to be T1–2N1–3M0 or T3N0–3M0 on endoscopic ultrasonography, because one can usually design safer EBRT fields with preop CRT rather than postop CRT. If transhiatal resection is performed, keeping the reconstructed stomach in the mediastinal midline, postop CRT can be given more safely than if Ivor-Lewis resection is performed.

tigators and institutions may prefer to simply replace postoperative adjuvant CRT with perioperative ECF chemotherapy, it would seem advantageous to attempt to combine the advances in disease control and survival found with both approaches, in that neither approach by itself resulted in optimal outcomes. This philosophy is being tested in part in the current U.S. GI INT trial by the comparison of ECF versus 5-FU + leucovorin as the maintenance component of chemotherapy. A randomized phase II study was conducted by RTOG to evaluate several combinations of preoperative CRT, and results are awaited. Because some of the newer chemotherapy drug combinations have CR rates of about 20%, the hope is that these regimens will lower systemic relapse rates more than previous combinations. This change has not yet been demonstrated in phase III trials.

Locally Advanced Disease (Unresectable for Cure)

For patients with locally advanced disease that appears unresectable for cure, it seems reasonable to build on existing positive segments of treatment data (EBRT plus chemotherapy, IORT, preoperative chemotherapy, preoperative chemoradiation) plus patterns of relapse information. External irradiation plus chemotherapy or IORT alone or added to EBRT has controlled disease and produced long-term survival in 10% to 20% of patients in most single-institution analyses and randomized trials in patients with residual disease after resection. Neoadjuvant chemotherapy for unresectable disease has resulted in subsequent total resection of disease in 20% to 73% of patients in several European trials with EAP, FAMTX, or other regimens. However, the incidence of subsequent local-regional relapse is significant, even after total resection. It would be of interest to merge these components of treatment.

Following preoperative chemotherapy, patients with marginal gross total or subtotal resection with residual disease or resection but high-risk factors for relapse (beyond the gastric wall, nodes positive, or both) should be placed on studies that evaluate IORT, postoperative EBRT, or both in conjunction with concurrent and maintenance chemotherapy. For patients who are unresectable after preoperative (neoadjuvant) chemotherapy but still have localized tumor on the basis of preoperative staging (including laparoscopy) or exploratory laparotomy, EBRT plus concurrent chemotherapy should be given. Decisions regarding attempts at later resection alone or plus IORT could be individualized by institution.

An alternate approach is to initiate treatment with preoperative CRT followed by restaging, resection (alone or plus IORT), and postoperative maintenance chemotherapy. Questions to be addressed with this approach include whether to give several cycles of multiagent chemotherapy before initiating concomitant CRT or whether to start with concomitant CRT, how many cycles of chemotherapy to deliver, and which agents to give both with irradiation and as the systemic component of treatment.

Metastatic Disease

Recent trials with newer chemotherapy agents in combinations such as EOX and docetaxel, cisplatin and 5-FU (DCF) are beginning to show meaningful increases in overall survival.[216,248] However, it is unlikely that significant advances will be made through the addition of other new chemotherapy drugs to those already available. Advances will more likely occur through the use of targeted therapies. Trials with targeted therapy used alone or in combination with chemotherapy are under way. Ultimately the goal must focus on improvements in both overall survival and response rate, while continually focusing on quality of life. Adequately powered trials in both the phase II and phase III settings will be important in providing meaningful answers.

Treatment Algorithm by Tumor, Lymph Node, and Metastasis Disease Extent

The contents of this section are supported by Table 79-17 and Figures 79-11 and 79-12.

T1–2N0M0

Total surgical resection of the adenocarcinoma with a radical subtotal gastrectomy and reconstruction with gastrojejunostomy is recommended as standard treatment. Patients with posterior-wall T2N0M0 lesions should be evaluated for postoperative adjuvant CRT (see next discussion).

T1–2N1–3M0; T3N0–3M0

Postoperative CRT is the preferred standard of treatment in the United States based on demonstrated improvement in survival (disease-free and overall) when compared with a surgery-alone control arm in the phase III U.S GI trial (INT 0116).[180,181]

Our institutions prefer the use of preoperative CRT for patients who have T1–2N1–3M0 or T3N0–3M0 gastroesophageal junction cancers at the time of EUS, because we can usually design safer EBRT fields for preoperative CRT rather than postoperative CRT. If transhiatal resection is performed, keeping the reconstructed stomach in

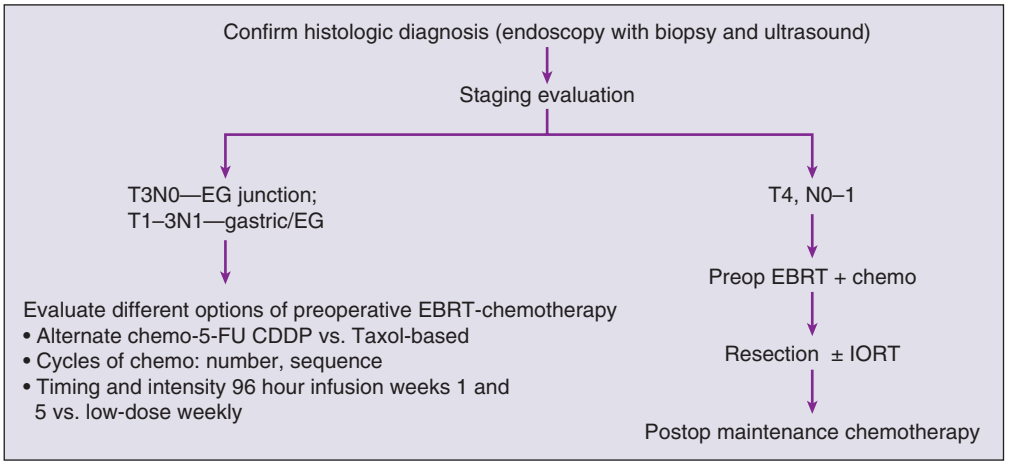


Figure 79-11 • Treatment algorithm: newly diagnosed gastric cancer adjuvant therapy precedes surgery.

the mediastinal midline, postoperative CRT can be given more safely than if Ivor-Lewis resection is performed.

T4N0–3M0

Preoperative CRT followed by restaging, gross total resection (may include en bloc resection of adjacent organs), and IOERT is recommended for potentially resectable T4N0–3 lesions in institutions with IOERT capability. Postoperative CRT has also been used for completely resected lesions.

For patients with locally unresectable T4N0–3M0 gastric cancers, preoperative or primary CRT or multiple-drug chemotherapy can be used, preferably in the setting of controlled prospective clinical trials. For patients with good performance status, the treatment approach would preferably involve preoperative CRT, restaging, and surgical resection with an attempt at marginal gross total resection and IOERT.

TanyNanyM1

Multidrug chemotherapy combinations are the preferred treatment for patients with metastatic cancers. Patients should be placed on controlled trials if available. Palliative irradiation can be used for painful metastatic lesions but is otherwise not indicated. Palliative resection may be indicated for patients with obstruction or bleeding, if total gastrectomy can be avoided.

Nutritional Support during Chemoradiation Therapy

Many patients who receive preoperative CRT (with plans to proceed to surgical resection) or primary CRT may require parenteral or enteral hyperalimentation during treatment. This feeding may also be necessary in subsets of patients with borderline performance status who are candidates for postoperative CRT. Improvement in nutritional status may require stent placement during endoscopy, feeding jejunostomy, or percutaneous endoscopic gastrostomy tube placement. Feeding jejunostomy may be preferable to percutaneous endoscopic gastrostomy tube placement for patients receiving preoperative CRT, so as to preserve later use of the stomach for reconstruction.

CONCLUSIONS

In summary, gastric malignancies present a variety of challenges. Innovative combined-modality approaches will be required to improve survival with acceptable morbidity. This treatment may include combinations of EBRT plus chemotherapy, IORT, and resection for the local component of disease, systemic or intraperitoneal chemotherapy for the abdominal component, and systemic treatment (chemotherapy, other) for the extra-abdominal risks of relapse. For patients with metastatic disease, the availability of growth factors may allow more aggressive multidrug approaches.

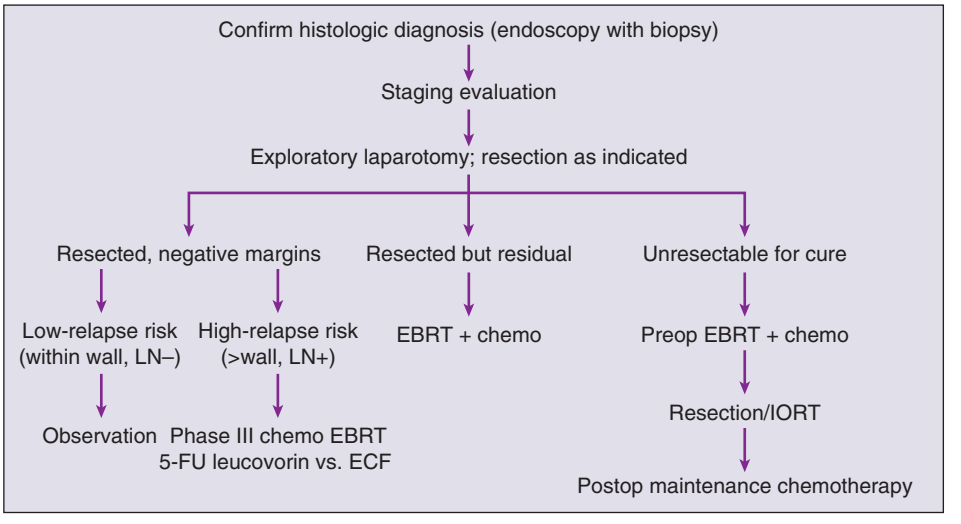


Figure 79-12 • Treatment algorithm: newly diagnosed gastric cancer, surgery precedes adjuvant therapy.

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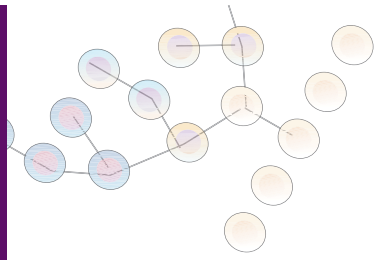
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80 Cancer of the Small Bowel

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SUMMARY OF KEY POINTS

Incidence
- Cancers of the small bowel are rare.
- These cancers account for less than 10% of all gastrointestinal tumors and less than 1% of all malignancies; approximately 5600 new cases are diagnosed each year, with 1100 cancer-related deaths.

Etiology and Epidemiology
- Several factors explain the rarity of these tumors: rapid transit time of carcinogens; carcinogens diluted by gastric, biliary, and pancreatic secretions; small bowel flora being less metabolically active; detoxifying enzymes; immunosurveillance.
- Dietary risk factors for small bowel adenocarcinoma are similar to those for colorectal cancers.
- Increased incidence is seen in Crohn's disease, familial adenomatous polyposis, and hereditary nonpolyposis colorectal cancer, as well as in individuals with a history of irradiation to the abdomen.

Pathology and Biology
- About one third of all small bowel tumors are benign.
- Of the malignant lesions 45% are adenocarcinomas, 30% are carcinoids, 15% are lymphomas, and 10% are sarcomas and gastrointestinal stromal tumors (GISTs).
- The majority of malignant lesions are located in the duodenum (50% to 60%), followed by the jejunum and ileum.
- Molecular markers for adenocarcinomas include: K-ras, p53, c-erbB-2, Ki-67, tenascin, CEA, and CA 19-9.
- KIT immunostaining has greatly facilitated the diagnosis of GIST, because nearly all GISTs are KIT-positive.

Clinical Findings
- Symptoms, when they do occur, tend to be vague and nonspecific and are determined by the tumor's location, growth rate, and size.

Staging
- Small bowel tumors are staged by the tumor-node-metastasis (TNM) staging system published by the American Joint Committee on Cancer (AJCC).
- Small bowel lymphomas are staged by the Ann Arbor system based on lymphatic and extralymphatic involvement on either side of the diaphragm.

Primary Therapy
- The treatment for localized resectable small bowel tumors is surgical excision with negative margins.
- Depending on the location of the tumor, specifically tailored surgical options are available.
- For primary small bowel lymphoma, para-aortic and mesenteric lymph node sampling, liver biopsy, and bone marrow biopsy should be performed upon surgical exploration.

Prognosis
- Factors associated with poor prognosis for small bowel adenocarcinomas are advanced stage, poor tumor differentiation, extramural venous spread, and positive margins.
- Previously, the 5 year survival after resection of a primary GIST was 50% to 75%, and once metastasis occurred patients lived a median of 10 to 20 additional months. Since the introduction of the tyrosine kinase inhibitors imatinib mesylate (Gleevec; Novartis) and sunitinib (Sutent; Pfizer), the median survival in metastatic GIST is now 58 months.

INCIDENCE

Although the small bowel accounts for 75% of the gastrointestinal length and 90% of its absorptive surface, neoplasms of this organ, both benign and malignant, are relatively rare. These tumors represent less than 10% of all gastrointestinal tumors, 1% to 3% of gastrointestinal malignancies, and 0.4% of all malignancies.[1,2] The annual incidence of small bowel cancer is about 5640 cases, with 1090 deaths related to small bowel cancer per year in the United States.[1] Malignant lesions have a slight male predominance[3]; benign tumors occur with roughly equal gender incidence.

Over the last decade, the incidence of two small bowel tumors, lymphomas and GISTs, has increased substantially. In the case of primary small bowel lymphomas, incidence in the United States has nearly doubled in the last 2 decades, as a result of the increased numbers of immunocompromised patients (i.e., those with acquired immunodeficiency syndrome [AIDS] or rheumatoid arthritis, transplant recipients with immune disorders, or individuals with congenital immunodeficiency syndromes) and immigrants from third-world countries.[4] In the case of GISTs, the application of KIT protein (CD117) immunohistochemistry has changed the way spindle cell tumors of the gastrointestinal tract are classified. Previously most intestinal sarcomas were considered to be leiomyosarcomas, but now it is clear that they are in fact GISTs. Because of this increased awareness and recognition, the annual incidence of new cases of GIST in the United States has greatly increased and is estimated to be as high as 4000. The stomach is the most frequent (60%) site of GIST, whereas approximately 30% occur in the small intestine.

EPIDEMIOLOGY

The first reports of duodenal adenocarcinoma and small bowel sarcoma were published in the eighteenth and nineteenth centuries.[5] Since then many reports and reviews have been published based on autopsy data or single-center series. The significance and relevance of these data are limited by the retrospective nature of these studies.

The National Cancer Data Base, a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society, maintains data on as many as 60% of all cancer cases in the United States. It is the main source of epidemiologic data for all cancers, and it represents a particularly useful resource for rare neoplasms, such as small bowel malignancies. Howe and colleagues reviewed the database for nonampullary small bowel cancers and found 4995 cases for the period between 1985 and 1995.[6] The mean age at presentation was 65 years, with equal incidence in both genders. On presentation, 32% had evidence of metastatic disease and 26% were locally advanced.[6]

Epidemiologic studies have identified several predisposing conditions associated with small bowel malignancies. Crohn's disease is associated with a 40- to 100-fold increase in relative risk.[7–14] Patients with familial adenomatous polyposis have a 50- to 300-fold increase in relative risk of developing proximal small bowel malignancy, specifically duodenal adenocarcinomas.[15,16] In a recent series 57% of hereditary nonpolyposis colorectal cancer patients developed small bowel adenocarcinomas as the presenting neoplasm.[17] Other conditions such as blind loop syndrome,[18,19] Peutz-Jeghers syndrome,[20] celiac sprue,[21] neurofibromatosis, and IgA deficiency[18,19] have been associated with an increased risk of small bowel malignancy.

ETIOLOGY AND PATHOGENESIS

The disproportion between the rarity of malignant tumors of the small bowel in comparison with the size of its surface area suggests a significant sparing from or resistance to the development of malignancy. Indeed, several hypotheses, based on experimental animal models,[18,19] have postulated that carcinogens in the enteric content may be in contact with small bowel mucosa over a limited time due to the relatively rapid transit time or may be in a diluted and less carcinogenic form. The preponderance of small bowel adenocarcinomas in the duodenum suggests a role for bile or pancreatic secretions either as primary small bowel carcinogens or even as simple vectors for unknown carcinogens.[22] The fact that biliary diversion decreases the incidence of chemically induced small bowel malignancy in animal models supports a role for bile in small bowel carcinogenesis.[23]

Other specific characteristics of the small bowel microscopic and chemical environment might be responsible for the observed cancer resistance. The limited and metabolically inactive bacterial flora of the small bowel is probably unable to transform procarcinogens into their active metabolites,[24] especially in an alkaline milieu. In addition, the proximal small bowel secretes several enzyme systems (e.g., benzopyrene hydroxylase)[25,26] that detoxify carcinogens.

Finally, the presence of a high concentration of B cells and lymphocytes and high amounts of secretory immunoglobulin A in the distal small bowel might constitute an effective local immunosurveillance system that prevents carcinogenesis and explains the rarity of distal small bowel neoplasms. This theory seems to be supported by the observation that immunocompromised patients (i.e., those with AIDS or rheumatoid arthritis, transplant recipients with immune disorders, or individuals with congenital immunodeficiency syndromes) have an increased incidence of lymphoma and Kaposi's sarcoma of the distal small bowel.

Dietary risk factors that have been involved in colorectal carcinogenesis have been looked at in patients with malignancies of the small bowel. High-caloric dietary intake in general and more specifically consumption of red meat, fat, and salt-cured smoked foods have been shown to increase the incidence of small bowel carcinoma in large population studies.[27–29] This similarity in risk factors explains the relatively high risk of synchronous or metachronous colorectal cancer in patients with a known small bowel malignancy.[30–33]

PATHOLOGY

Approximately one third of primary small bowel neoplasms are benign and two thirds are malignant. The most common benign tumors are leiomyomas and adenomas; less common lesions include inflammatory polyps, hemangiomas, lipomas, hamartomas (Peutz-Jeghers syndrome), and fibromas (Fig. 80-1).[19,20] These tumors can occur throughout the small bowel but tend to increase in frequency from proximal to distal, with the exception of adenomas, which occur with the highest frequency in the duodenum.

Leiomyomas arise from smooth muscle and can grow both intra- and extraluminally. They can often become very large before causing symptoms. On gross inspection it is sometimes difficult to distinguish these lesions from their malignant counterparts. This distinction is made histologically with standard criteria including nuclear pleomorphism, increased mitosis, and the presence of necrosis, although even histologic examination may occasionally fail to unequivocally distinguish between benign and malignant lesions.

Adenomas are the next most common benign tumors of the small intestine. The duodenum is the most common site of involvement, and the lesion most commonly noted is the villous adenoma. These lesions tend to involve the region of the ampulla of Vater. They may present with obstructive jaundice and are easily diagnosed by upper endoscopy and biopsy. Up to 30% of these tumors may have a malignant degeneration. The risk of malignant degeneration in a significant proportion of patients poses challenges to treatment planning.

Malignant tumors tend to increase in frequency from proximal to distal, again with the exception of adenocarcinomas, which are most frequent in the duodenum.[2,6,18,19,34,35] Adenocarcinoma is the most common histologic type (45%), followed by carcinoids (30%), lymphomas (15%), and sarcomas and GISTs (10%).[18,36,37] Pathologic

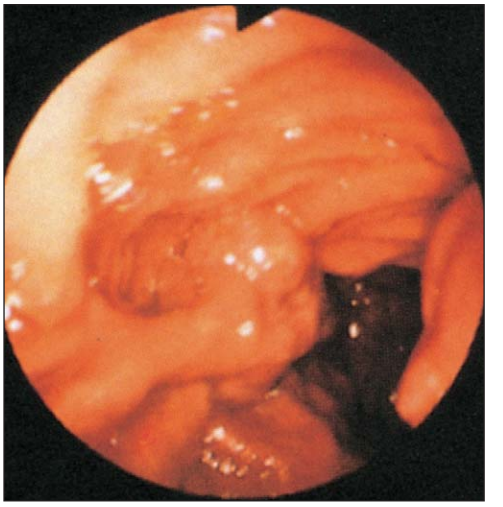


Figure 80-1 • Hamartomatous polyp in Peutz-Jeghers syndrome. Endoscopic view shows a broad-based polyp in the duodenum in a patient with Peutz-Jeghers syndrome. These small intestinal polyps only rarely become malignant. This syndrome is an autosomal dominant condition that is also marked by deposits of melanin on the buccal mucosa, lips, and digits. Ovarian neoplasms arise in almost 5% of women with this syndrome. (Kulke H, Turner J, Skarin A: Cancer of the gastrointestinal tract. In Skarin A [ed]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 113.)

staging is performed according to the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) system.[38]

Most small bowel adenocarcinomas are solitary, sessile lesions, often appearing in association with adenomas. They are usually moderately to well differentiated and almost always positive for acid mucin. Most arise in the duodenum. Within the duodenum 15% of these tumors are located in the first portion, 40% are in the second portion, and 45% are in the distal duodenum.[39,40] Most of these tumors are sporadic, with the exception of the ones originating in the context of familial adenomatous polyposis. Presenting symptoms include epigastric and abdominal pain or discomfort, and possibly jaundice and gastric outlet obstruction, depending on the location of the tumor (Fig. 80-2). These symptoms and the accessibility of the duodenum and proximal small bowel to endoscopic modalities allow a relatively high rate of diagnosis and resectability.[41]

Carcinoid tumors (Fig. 80-3A and B) are the most common endocrine tumors of the gastrointestinal system and the second most common malignancy involving the small bowel.[2,18,19,42,43] In the small bowel itself carcinoids are the most common distal small bowel neoplasm. These neoplasms arise from enterochromaffin cells and are characterized by the ability to secrete many biologically active substances, including serotonin, bradykinin, dopamine, histamine, and 5-hydroxyindoleacetic acid. They tend to be small (<2 cm) and submucosal in location, with a propensity for multicentricity. The most common classification for these tumors is based on embryologic derivation: foregut (stomach and pancreas), midgut (small bowel), and hindgut (colon and rectum). Their presentation depends largely on the hormones elaborated and on the site of origin.[42,43] The majority of these tumors (90% or more) are midgut primary cancers. Up to 40% of small bowel carcinoids are associated with a second gastrointestinal malignancy, and 30% are multicentric. A full evaluation of the small and large intestine is therefore warranted.[42,43]

The gastrointestinal tract is the most frequent site of extranodal lymphoma: within the gastrointestinal tract the stomach is the most common site, followed by the small bowel and the colon, respectively; within the small bowel lymphomas parallel the distribution of lymphoid follicles, resulting in the ileum being the most common site of involvement.[2,18,19,36,44,45] These tumors may be primary or secondary as a manifestation of generalized involvement of systemic lymphoma. For the diagnosis of primary small bowel lymphomas there must be no peripheral or mediastinal lymphadenopathy, with a normal white blood cell count and differential, and the tumor must be predominantly in the gastrointestinal tract. When primary they may be multifocal in as many as 15% of cases. Predisposing conditions include immunodeficiency conditions (i.e., AIDS, rheumatoid arthritis, and immune disorders in transplant recipients), Crohn's disease, and celiac disease.[14,18,19,21]

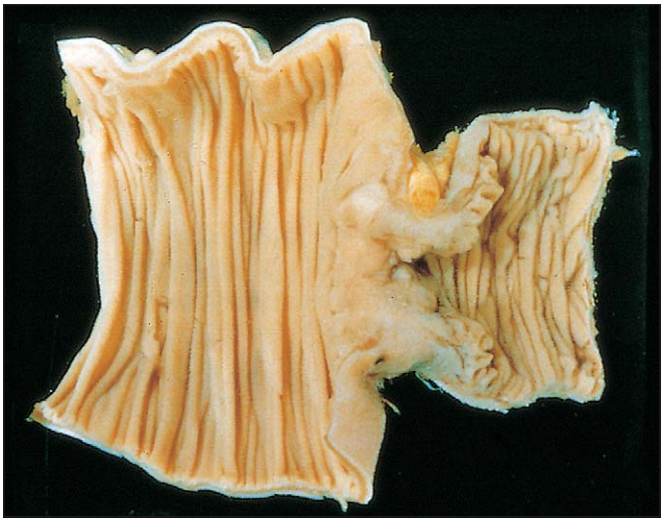


Figure 80-2 • Adenocarcinoma of the jejunum causing annular constriction. (Kulke H, Turner J, Skarin A: Cancer of the gastrointestinal tract. In Skarin A [ed]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 142.)

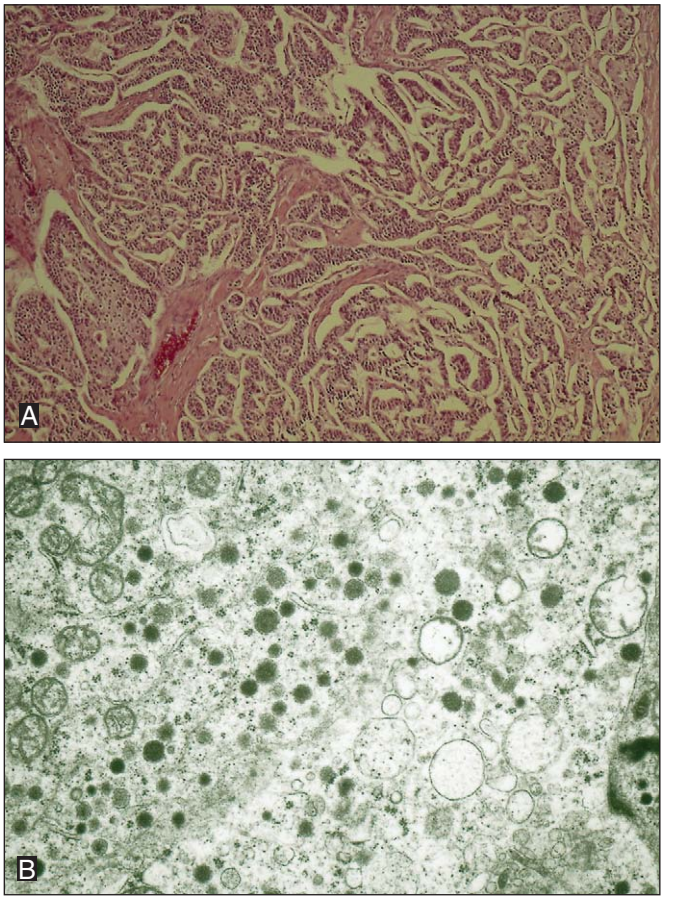


Figure 80-3 • Neuroendocrine tumor of the small intestine (carcinoid tumor). **A,** Small uniform round cells with very infrequent mitoses show a trabecular growth pattern. **B,** An electron microscopic image of the cell cytoplasm reveals the numerous dense core neuroendocrine granules typical of this tumor type.

The five distinct clinical pathologic subtypes of primary small intestinal lymphoma are the adult Western type, the pediatric type, the immunoproliferative or Mediterranean type, enteropathy-associated (celiac sprue) T-cell lymphoma, and Hodgkin's lymphoma.[4] The most common is the adult Western type, occurring in the sixth and seventh decades of life with a male predominance.[45]

Sarcomas make up only 10% of small bowel malignancies.[2,18,19,27,34] Overall, these tumors are located in the jejunum and ileum, are relatively slow growing, and are locally invasive. Their growth pattern is most commonly extramural; therefore, they rarely result in obstruction, but sometimes they present with free intra-abdominal bleeding from central tumor necrosis and peritoneal rupture. As a result of their insidious nature and growth pattern, more than three fourths of these tumors exceed 5 cm in diameter at the time of diagnosis. The most common histologic subtypes (in descending order of frequency) are GISTs (Fig. 80-4), leiomyosarcomas, fibrosarcomas, liposarcomas, and malignant schwannomas and angiosarcomas. Similar to sarcomas from other anatomic regions, small bowel sarcomas rarely metastasize to regional lymph nodes. The initial sites of metastasis include the liver and peritoneum, whereas other sites,

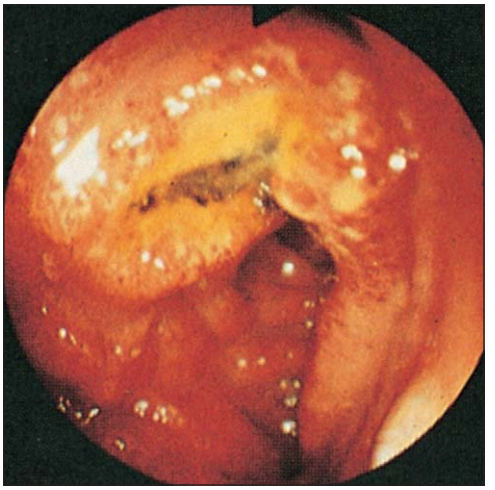


Figure 80-4 • An endoscopic view of a GIST of the duodenum. (Kulke H, Turner J, Skarin A: Cancer of the gastrointestinal tract. In Skarin A [ed]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 142.)

such as lung and bone, might become involved late in the course of disease.

Mazur and Clark introduced the term GIST in 1983 to describe gastrointestinal nonepithelial stromal tumors that lack the immunohistochemical features of Schwann cells and do not have the characteristics of smooth muscle cells.[46] GIST is now considered the most common sarcoma of the gastrointestinal tract and accounts for about 5% of all small bowel malignancies.[47] Clinical, histopathologic, ultrastructural, and molecular biologic findings have clearly shown that GIST is a completely separate entity from leiomyoma and leiomyosarcoma. It is currently thought that GISTs originate from stem cells that differentiate toward the interstitial cells of Cajal (ICCs). ICCs arise from precursor mesenchymal cells and are the pacemaker cells of the gastrointestinal tract.[48] They intercalate between nerve fibers and muscle cells and can be seen in the adult intestine in and around the myenteric plexus.[49] Both ICCs and GISTs express KIT protein, have similar ultrastructural features, and express the embryonic form of the heavy chain of smooth muscle myosin.[50,51] All these features support a common origin, and the term gastrointestinal pacemaker cell tumor has been used to describe these lesions.[51]

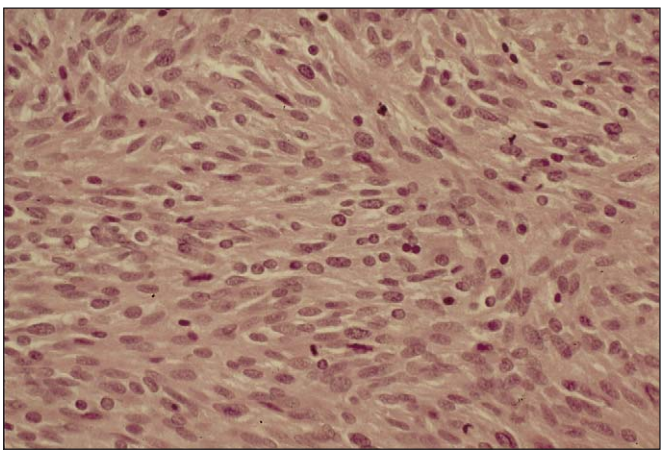


Figure 80-5 • High-grade gastrointestinal stromal tumor. Plump spindle cells with pale eosinophilic cytoplasm with a storiform pattern of growth show a high mitotic rate (20×).

Nearly all GISTs overexpress KIT protein. Consequently, the gold standard for diagnosing GIST has become KIT immunostaining in conjunction with an assessment of tumor morphology on hematoxylin and eosin staining. A small percentage of GISTs lack KIT staining, in which case the diagnosis relies on morphology (Fig. 80-5) and molecular analysis for either a KIT or platelet-derived growth factor receptor-α (PDGFRα) gene mutation.[52] Small intestine GISTs generally contain either a KIT exon 9 or 11 mutation or have no identifiable mutation. In contrast, PDGFRα mutations are basically restricted to gastric GISTs. Approximately 85% of GISTs have a mutation in the KIT proto-oncogene, whereas another 5% contain a PDGFRα gene mutation. Thus, about 10% of GISTs do not have an identifiable mutation, but KIT is nonetheless strongly activated. Such GISTs might contain KIT mutations that are not readily detected by conventional screening methods, or alternately, KIT might be activated by nonmutational mechanisms. Most GISTs have noncomplex cytogenetic profiles, often featuring deletions of chromosomes 14 and 22. Additional chromosomal aberrations are acquired as GISTs progress to higher histologic grade. These cytogenetic aberrations are undoubtedly important in GIST pathogenesis, but currently they do not play a key role as diagnostic adjuncts.[53]

To better characterize GISTs, other markers have been studied: About 60% to 70% show immunopositivity for CD34, 30% to 40% for smooth muscle actin, and around 5% for S-100 protein. None of these antigens are therefore specific for GIST but can help in the differential diagnosis in KIT-negative tumors. Desmin positivity in true KIT-positive GISTs is extremely uncommon (1% to 2% of cases) and is invariably focal, with positivity in only a small number of tumor cells.[52] The immunophenotype of true KIT-positive GISTs varies to some degree by location, with CD34 positivity seen most consistently in colorectal and esophageal lesions and smooth muscle actin positivity seen most often in small bowel tumors.[54]

BIOLOGY

There are similarities in the genetic makeup of small bowel and large bowel adenocarcinomas. K-ras mutations at codon 12 have been noted in duodenal adenocarcinomas, suggesting a possible pathogenetic role similar to that seen in pancreatic and colorectal cancer.[55] As shown in colorectal and other malignancies, overexpression of p53 in de novo small bowel adenocarcinomas has been associated with a worse prognosis.[56] Increased expression of c-erbB-2, Ki-67, and tenascin was associated with poorer survival rate in a small group of patients with duodenal adenocarcinomas.[57] Strong cytoplasmic carcinoembryonic antigen (CEA) staining has been described in small bowel adenocarcinomas.[58] Immunohistochemical staining for CEA, and to a lesser extent CA 19-9, is positive in the majority of ampullary and about half of nonampullary duodenal small bowel adenocarcinomas.[59] However, their independent prognostic value has not been established. The rarity of small bowel adenocarcinomas makes it difficult to carry out meaningful, large, prospective studies to assess the prognostic and clinical significance of these markers.

A recent major advance has been achieved by the recognition of the central role of activating KIT mutations in the pathogenesis of GISTs,[60–62] leading to expression of the KIT protein, a new and reliable phenotypic marker for these neoplasms.[51,63] Constitutive activation of the KIT receptor tyrosine kinase is a central pathogenetic event in most GISTs and generally results from point mutations or deletions, which involve either extracellular or cytoplasmic domains of the receptor. These mutations permit the KIT receptor to phosphorylate various substrate proteins in the absence of the natural ligand to KIT, which is called KIT ligand or stem cell factor. The result is activation of signal transduction cascades, which regulate cell proliferation, apoptosis, chemotaxis, and adhesion. KIT mutations can be broadly assigned to two groups, those that involve the "regulatory" regions responsible for modulating KIT enzymatic activity, and those that involve the enzymatic region itself.[53]



Figure 80-6 • The small bowel is a frequent site for melanoma metastases. This resected jejunum contains multiple pigmented nodules, some with ulceration. (Kulke H, Turner J, Skarin A: Cancer of the gastrointestinal tract. In Skarin A [ed]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 146.)

CLINICAL PRESENTATION

The vast majority of patients with benign small intestine neoplasms are asymptomatic, whereas the vast majority of those with malignancies are symptomatic before diagnosis (Fig. 80-6). The most common presentation of benign tumors is intermittent episodes of acute crampy abdominal pain associated with intussusception, followed by chronic bleeding with iron deficiency anemia in up to 50% of patients.

Malignant lesions are generally associated with weight loss due to delay in the establishment of a diagnosis. Symptoms, when they occur, tend to be vague and nonspecific. In general most symptoms can be attributed to the location of the tumor, its rate of growth, and its size.[2,18,19,34,35] For example, tumors in the duodenum tend to be symptomatic at an earlier stage, presenting with pain, gastric outlet obstruction, or obstructive jaundice, whereas those in the jejunum or ileum may present at a later stage with obstructive symptoms. Obstruction in this setting tends to be progressive, compared with benign lesions, whose obstructive symptoms tend to be intermittent as they relate to episodes of intussusception. Bleeding and perforation (in up to 10%) may also occur, predominantly in lymphomatous lesions, but they can also be features of any malignant tumor because of ulceration or necrosis. GIST may be associated with acute hemorrhage as well.

Carcinoid tumors produce symptoms secondary to hormone production, including hot flashes, bronchospasms, and arrhythmias. This constellation of symptoms, called carcinoid syndrome, occurs when the liver is not able to metabolize the active substances produced by the carcinoid tumor. This problem usually results when tumors are either bulky or metastatic, or when their venous drainage bypasses the liver.

LABORATORY AND IMAGING STUDIES

A high index of suspicion is required because of the nonspecificity of the signs and symptoms of small intestine tumors. A correct preoperative diagnosis is made in only 50% of patients. Biochemical and hematologic studies are often not helpful. Iron deficiency anemia may be detected with chronic blood loss; elevated liver enzymes may be noted with periampullary lesions or hepatic metastases; elevated 24-hour urinary 5-hydroxyindoleacetic acid can be detected in more than 50% of patients with carcinoid tumors.

Radiographic contrast imaging modalities tend to be the most useful in the establishment of the diagnosis (Fig. 80-7). Plain films of the abdomen are generally not helpful and at best may demonstrate nonspecific signs of obstruction or a mass effect. Except for the duodenum and the very proximal jejunum, which can often be evaluated by endoscopy, the diagnosis of small intestinal neoplasms depends on contrast studies such as a small bowel follow-through or preferably enteroclysis. Small bowel follow-through is still the most commonly used method in most institutions in the evaluation of small bowel disease, although enteroclysis may be a superior imaging modality. In a recent study comparing the sensitivity and tumor detection rate of small bowel follow-through and enteroclysis, the sensitivity rates were 61% and 95%, respectively. The actual tumor

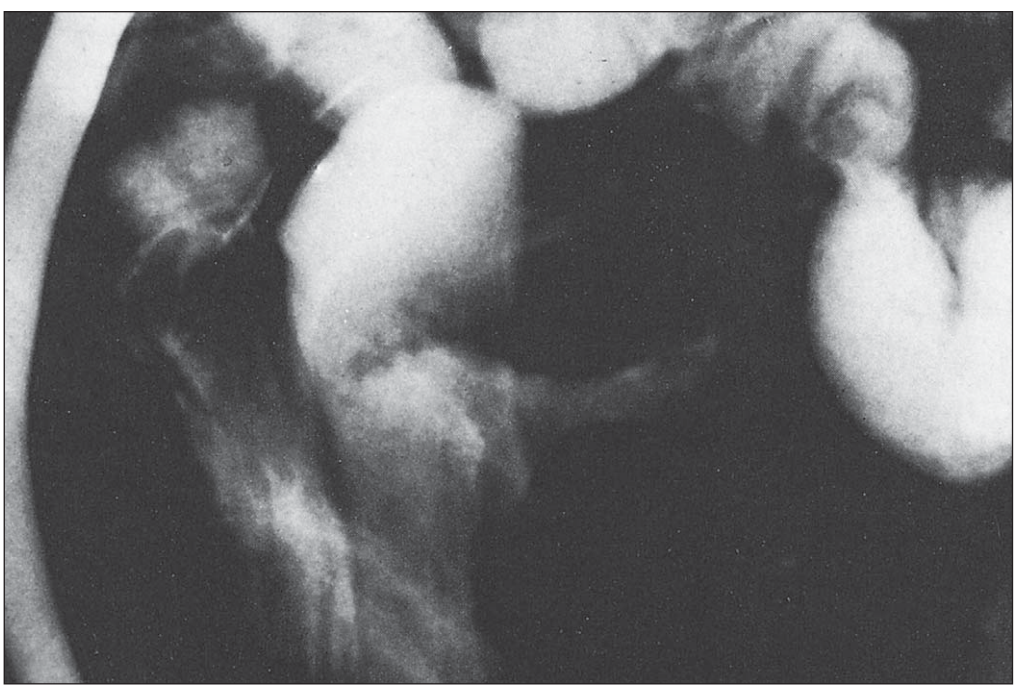


Figure 80-7 • A barium contrast study of the small intestine demonstrating an annular constricting lesion that proved to be an adenocarcinoma of the ileum. (Kulke H, Turner J, Skarin A: Cancer of the gastrointestinal tract. In Skarin A [ed]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 142.)

detection rate was 33% for small bowel follow-through and 90% for enteroclysis.[64]

Computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI) are complementary to barium studies in the detection of small bowel neoplasms. Abdominal CT has a sensitivity of 50% to 80% in detecting the primary small bowel tumors and occasionally plays an important role in differentiating benign from malignant tumors. Additionally, CT is valuable in staging malignant tumors (presence or absence of hepatic metastases) and in providing important information related to local extent (presence or absence of local invasion, mesenteric implants, and metastatic lymph nodes). Contrast-enhanced abdominal CT examination and enteroclysis are truly complementary to each other. Enteroclysis provides optimal wall distension and displays mucosal pattern well; CT demonstrates the extraluminal component of the tumor and aids in the staging process.

Angiography, though helpful in diagnosing and localizing neoplasms of vascular origin, is rarely helpful in establishing or refining a diagnosis of small bowel malignancy. In rare cases angiographic demonstration of tumor neovascularity without contrast agent extravasation may be of diagnostic importance in patients with chronic occult bleeding when other diagnostic studies such as endoscopy and barium contrast have been negative.[65] By contrast, angiography is rarely beneficial in localizing bleeding tumors, because the vast majority of such tumors bleed at a rate considerably below the limit of detection with this technique. Scintigraphy with technetium-labeled red blood cells may identify bleeding sites with blood loss rates as low as 0.1 mL per minute.

Sonde enteroscopy, by now only of historical interest,[66] involved intubation of the small bowel with a thin endoscope equipped with a balloon tip, inserted transnasally, and moved distally by way of peristalsis. Evaluation of the bowel occurred as the scope was withdrawn. This scope did not allow for biopsy or therapeutic intervention, the entire bowel lumen often was not visualized, and the duration of the procedure was on the order of 6 hours. This modality was used in the diagnostic workup of individuals who had had nondiagnostic contrast studies and upper and lower endoscopies.[67]

Enteroscopy is now available in a fiberoptic form, using conventional endoscopes or in a wireless form. Fiberoptic small bowel enteroscopy, or push enteroscopy, initially made use of a pediatric or adult colonoscope that was advanced orally.[68] Specialized scopes that can be used to visualize jejunum 100 cm or farther from the ligament of Treitz are now available. The bowel is evaluated as the endoscope is both advanced and withdrawn, and biopsy or cauterization can be done concomitantly through an accessory channel.

Wireless capsule endoscopy is a new technique that uses a miniature camera that is swallowed by the patient and records images as it progresses down the gastrointestinal tract. It offers the potential to examine the whole small intestine combined with the advantage of being painless. Using a miniature camera and a lens with a short focal length, images are obtained as the capsule progresses though the entire length of the intestine, without requiring air inflation. The capsule endoscope is propelled by peristalsis through the gastrointestinal tract. The video images are transmitted using radiotelemetry and are stored on a small portable recorder carried on a belt and subsequently downloaded for analysis. The system allows more than 7 hours of continuous recording of images of the gastrointestinal tract. The patients are free to continue their daily routine during the examination.[69] Animal studies using this modality have shown that capsule enteroscopy was as effective as enteroscopy in detecting beads in canine small intestine.[70] Recently, several human studies, usually looking at patients with occult gastrointestinal bleeding, have indicated that capsule endoscopy seems to be significantly superior to push enteroscopy in this group of patients,[71–74] and it is invariably preferred by patients undergoing both procedures.[69] A study by Costamagna and associates[75] found wireless capsule endoscopy significantly superior to small bowel follow-through studies, if small bowel disease was suspected.

Fluorodeoxyglucose (labeled with fluorine-18) positron emission tomography (FDG-PET) has been shown to be highly sensitive to assess disease status in patients with GISTs. FDG-PET is sometimes used for preoperative staging, but more important, it can be used to assess response to therapy. Glucose uptake of GIST decreases within a few hours to a few days after the start of treatment with the targeted agent imatinib mesylate, which can be verified by FDG-PET.[76] Furthermore, in case of disease progression, increased areas of FDG uptake are observed by PET.[77] Overall, though, PET is mostly used as a research tool in GIST and contrast CT is the gold standard. It is now understood that a decrease in contrast uptake or decrease in density of a GIST indicates response to treatment. Meanwhile, standard criteria of response based on tumor size are inaccurate, in that GISTs often remain the same size, or even swell, initially during a response.

Limited information is available regarding the efficacy of diagnostic laparoscopy in the diagnosis and workup of small bowel neoplasms. At present its usefulness may reside in obtaining staging information and determining resectability before formal laparotomy in the case of tumors of the duodenum, and in obtaining images and potentially in making tissue diagnoses when other imaging studies have failed to suggest an etiology. It is clear, however, that despite the currently available technology, the diagnosis of these tumors is difficult to establish preoperatively in a significant group of individuals. Laparotomy is often required for definitive diagnosis.

STAGING CLASSIFICATION

Radiologic staging is based mainly on the use of CT and MRI. Intraoperative assessment plays a role in clinical staging, especially when tumor cannot be resected. Metastatic involvement of the liver may be further evaluated by intraoperative ultrasonography. With regard to pathologic staging, the TNM staging system has been recently revised by the AJCC,[38] but no major changes have been implemented for small bowel neoplasms. The primary tumor is staged according to its depth of penetration and the involvement of adjacent structures or distant sites. There is no subdivision within the N category based on the number of nodes involved with tumor. Discontinuous hematogenous metastases or peritoneal metastases are coded as M1. Involvement of the celiac nodes is considered M1 disease (Tables 80-1 and 80-2). Cancers of the small intestine can metastasize to most organs, especially the liver, or to the peritoneal surfaces. For small bowel lymphoma the most commonly used staging system is the Ann Arbor system, based on lymphatic and extralymphatic involvement on either side of the diaphragm (Table 80-3).

PROGNOSIS

Prognosis for small bowel adenocarcinoma is based on similar variables as for colorectal cancer, including stage, perineural and vascular invasion, grade, resectability, and surgical margins.[35,78–80] The majority of tumors have regional spread at time of diagnosis, and up to one fourth of patients have distant organ disease. Overall, the 5-year survival rate is 20% to 30% in most series. For resectable disease of the duodenum the 5-year survival rate approaches 50%.[2,6,35,78–81]

It has been frequently postulated that a small bowel adenocarcinoma carries a worse prognosis in patients with Crohn's disease in comparison with the general population. Recent studies have demonstrated that, in these patients, survival correlates purely with stage of tumor at resection. In our series no patient with regional or distant metastasis survived 5 years, in comparison with an 83% 5-year actuarial survival rate of patients with tumor confined to the intestinal wall. Mean survival time was 6 months for Crohn's disease patients with small bowel cancer in comparison with 65 months for Crohn's

Table 80-1 Definition of TNM Stages

Stage	Definition
PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
TIS	Carcinoma in situ
T1	Tumor invades lamina propria or submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into the subserosa or into the nonperitonealized perimuscular tissue (mesentery or retroperitoneum) with extension 2 cm or less
T4	Tumor perforates the visceral peritoneum or directly invades other organs or structures (includes other loops of small intestine, mesentery, or retroperitoneum more than 2 cm, and abdominal wall by way of serosa; for duodenum only, invasion of pancreas)
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
DISTANT METASTASIS (M)	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 80-2 Stage Grouping

Stage	T	N	M
0	TIS	N0	M0
I	T1	N0	M0
	T2	N0	M0
II	T3	N0	M0
	T4	N0	M0
III	Any T	N1	M0
IV	Any T	Any N	M1

Table 80-3 Ann Arbor Staging System for Small Bowel Lymphoma

Stage	Criteria
I	Involvement of a single nodal group (I) or a single extralymphatic organ or site (IE)
II	Involvement of more than one nodal group on the same side of the diaphragm (II) or a single extralymphatic site with one or more nodal groups on the same side of the diaphragm (IIE)
III	Involvement of nodes on both sides of the diaphragm (III) with or without involvement of extralymphatic sites (IIIE), spleen (IIIS), or both (IIIES)
IV	Diffuse involvement of viscera or bone marrow

disease patients with large bowel cancer, reflecting a tendency toward more advanced lesions in the small bowel.[13]

The prognosis for carcinoid tumors with localized disease is excellent, with 5-year survival rates approaching 100% after resection. More than 90% of the symptomatic patients have metastatic disease at the time of surgical exploration. The likelihood of distant disease correlates closely with both the size of the primary lesion and the depth of invasion. For tumors smaller than 1 cm, the risk of lymph node metastases is on the order of 2%; for 1- to 2-cm lesions, the incidence of lymph node involvement is approximately 50%; and 80% of tumors larger than 2 cm have positive nodes. Survival rates of up to 68% at 5 years have been reported when all gross metastatic disease, including hepatic metastases, is resected. For those unfortunate individuals with extensive unresectable disease, debulking has proved to be of some benefit in terms of symptomatic palliation. It is notable that the 5-year survival rate for unresectable disease is approximately 35% to 40%, reflecting the relatively indolent growth of these tumors.

Prognostic factors for primary small bowel lymphomas include higher grade, greater depth of tumor penetration, lymph node involvement, peritoneal disease, and distant metastases.[35,44,45] Overall 5-year survival rates range from 20% to 40% for all stages. Five-year survival rates of up to 60% have been reported for patients with resected localized low-grade tumors.[18]

Sarcomas tend to have an insidious growth pattern; more than three fourths of these tumors are larger than 5 cm at the time of diagnosis, and up to 50% of them are not resectable for cure when the diagnosis is established. Prognosis correlates most closely with grade, followed by stage.[82] Five-year survival rate after curative resection ranges from 60% to 80% for low-grade tumors and is no more than 20% for high-grade lesions.

Assessment of the risk of recurrence after resection of a primary GIST is difficult. In general, patients with small intestine GIST have a higher chance of developing recurrent disease than those with gastric GIST. Historically, size has been used to assess tumor behavior. All GISTs, except very small (<1 cm) tumors, should be considered as having the potential for metastasis. Although tumors larger than 5 cm carry a higher risk of recurrence, no cutoff diameter predicts subsequent metastasis with certainty.[83]

In addition to size, mitotic rate has been used to predict tumor behavior. Tumors with more than five mitoses per 50 high-power fields (HPFs) have a much higher risk of metastasis, and those with more than 20 to 50 mitoses per 50 HPFs are virtually guaranteed to recur.[49,84] Nevertheless, a low mitotic count does not exclude the possibility of metastasis.[85] Other factors that have shown prognostic value include presence of tumor necrosis, high cellularity, and pronounced pleomorphism; a high S-phase fraction and DNA aneuploidy in flow cytometry or image cytometry; a high Ki-67 score; proliferating cell nuclear antigen expression; presence of telomerase activity[37]; incomplete surgical resection; tumor rupture at surgery[86]; and invasion of adjacent structures.

Whether the presence of a KIT mutation is an independent prognostic factor for individuals with a primary GIST is unclear. Before the era of imatinib, Taniguchi and coworkers[87] suggested that GISTs should be divided into mutation-positive and -negative subtypes, the prognosis being worse in patients with mutation-positive GISTs. More recent data have not substantiated their findings. What is clear is that the response of metastatic GIST to imatinib depends on mutation subtype. Tumors with KIT exon 11 mutation have a greater likelihood of responding than those with KIT exon 9 mutations. Meanwhile, GISTs with no mutation have the least chance of responding to imatinib.

Precise data on long-term survival for patients with GISTs are difficult to provide because of the recent introduction of tyrosine kinase inhibitor therapy (imatinib mesylate and more recently sunitinib) in clinical practice and the recognition of the KIT protein (CD117), which has changed the way spindle cell tumors of the

gastrointestinal tract are classified. Before the introduction of imatinib mesylate, the available chemotherapeutic protocols were not effective against GISTs and the outcome for these patients was bleak.[88] Furthermore, until recently studies on GISTs included tumors that are not presently classified as GISTs. It is nevertheless believed that the overall or disease-specific 5-year survival rate is 28% to 60% among patients with GIST; the median disease-specific survival time is about 5 years for primary disease, and 10 to 20 months in recurrent or metastatic disease.[47,89] Most recurrences take place within 5 years of the primary diagnosis.[85] Remarkably, with the application of the tyrosine kinase inhibitors imatinib and sunitinib, the median survival in metastatic GIST is now 58 months.

The outcome for patients with metastatic malignancies to the small intestine (more commonly ovarian, colon, and lung cancers, renal cell carcinoma, and melanoma) is dismal despite palliative therapeutic intervention.

PRIMARY TREATMENT

Treatment of adenocarcinoma of the small intestine with localized disease is based on oncologic and anatomic principles. For duodenal lesions the availability of endoscopic ultrasound has allowed better preoperative staging,[90,91] and the availability of endoscopic resection techniques[92] has offered additional therapeutic options. Ultrasound-localized and biopsy-proven benign duodenal or ampullary adenomas can be resected endoscopically with excellent results. If these benign lesions are associated with familial polyposis, chemoprevention with sulindac or cyclo-oxygenase-2 inhibitors may be beneficial.[93]

Invasive lesions of the first and second portion of the duodenum without major vessel involvement and distant spread are best treated by a pancreaticoduodenectomy (Whipple procedure). For tumors in the third or fourth portion of the duodenum, segmental resection with regional lymphadenectomy is indicated.[18,19,79–81] Debate persists about the optimal surgical management of early duodenal cancer. Although early reports suggest that an endoscopic approach could be justified in early favorable lesions, long-term follow-up is still lacking,[94] and surgical resection is preferred in the good-risk patients. Palliative options for unresectable or metastatic duodenal carcinoma include gastrojejunostomy or biliary enteric bypass or endoscopic/interventional placement of stents to relieve the intestinal or biliary obstruction.

Adenocarcinoma of the jejunum and ileum is treated by wide excision, including areas of contiguous spread and the associated mesentery, with negative surgical margins. Although only small series have been published, these tumors do not seem to respond to the conventional 5-fluorouracil-based chemotherapy regimens, and there is a radiation dose limitation due to small bowel toxicity. However, for palliation of chronic blood loss in patients with locally advanced unresectable duodenal carcinomas, radiation therapy may provide short-term benefit.

The mainstay of therapy for carcinoid tumors is radical surgical excision. In preparation for surgery a complete assessment of the entire gastrointestinal tract is warranted, because up to 40% of midgut carcinoids are associated with a second gastrointestinal malignancy and 30% may be multicentric.[42,43] In addition, pre-emptive treatment with octreotide is indicated to prevent carcinoid crisis at the time of surgery. At surgery, wide en bloc resection including the draining mesentery is the standard approach,[18,19,42,43] particularly for small bowel carcinoid, because these lesions have the propensity to metastasize even when very small. Large lesions near the ampulla may require a pancreaticoduodenectomy for cure, and smaller lesions may be treated with either local excision or endoscopic resection with close endoscopic follow-up. Likewise, lesions of the terminal ileum or carcinoid tumors of the appendix larger than 2 cm require a formal right hemicolectomy for oncologic clearance of disease.

Treatment for advanced locoregional and distant disease includes both medical and surgical modalities. In one published study, after complete resection of all known disease a 73% actuarial 5-year survival rate was obtained, compared with 29% in patients who were deemed unresectable.[95] Therefore, surgery should be indicated in persons with resectable metastatic disease for potential cure or at least meaningful palliation. Orthotopic liver transplantation has been used in the treatment of metastatic neuroendocrine tumors to the liver.[96–99] In a recent report all patients had complete symptomatic response initially, but tumor recurrence was noted in 6 of 11 cases at a median of 11 months, with a mortality rate of 45%.[98] These discouraging results have limited the use of orthotopic liver transplantation for metastatic carcinoid tumors.

The role of multimodality therapy, including α2b interferon and octreotide, for metastatic carcinoid remains limited.[100–102] Interferon seems to provide symptomatic control in up to 70% of patients with carcinoid syndrome[101] and to increase 5-year survival rates to 71% in patients who continued treatment for 1 year as compared with 37% of those who stopped the treatment.[100] The addition of liver chemoembolization has not been shown to have a significant effect on survival in patients with metastatic disease to the liver[100,101] but may have a role in controlling or decreasing the symptoms associated with carcinoid crisis. Octreotide has been effective in the treatment of individuals with carcinoid syndrome by improving diarrhea in up to 83% of the patients and abolishing flushing and wheezing, but has no effect on survival.[102–104] In consideration of the slow growth rate of many carcinoid tumors, individuals with distant metastatic disease can also undergo resection for debulking and palliation of symptoms.[95,105–107] For those unfortunate individuals with extensive unresectable disease, the indications for surgical intervention are limited to the occurrence of obstruction, perforation, and bleeding. Radiation therapy has not been proved to be effective in either the adjuvant or palliative setting.

Treatment of small bowel lymphoma requires conservative resections with para-aortic and mesenteric lymph node sampling, liver biopsy, and bone marrow biopsy performed for staging. Low-grade localized lesions are treated with resection alone, and for intermediate- and high-grade lesions resection and chemotherapy are recommended. Radiation is used only for palliation in poor-performance patients.[45] This modality is associated with significant side effects, such as bowel necrosis, bleeding, and perforation, and is offered for palliation only to patients unfit for surgery or chemotherapy.

Surgical treatment for small bowel sarcomas consists of an en bloc resection with tumor-free margins. There is no role for extended lymphadenectomy in these tumors.[18,19,82] In the presence of metastatic disease, local excision or palliative bypass procedure might be indicated to prevent or ameliorate bleeding and obstruction. Furthermore, there is no clear benefit from chemoradiation therapy in the adjuvant setting, because radiation doses are limited because of small bowel toxicity. In the presence of recurrent or metastatic disease partial response rates after palliative chemotherapy and radiation therapy have been reported in the 10% to 20% range, with minimal improvement in survival at best.

Despite advances in molecular therapy, the treatment of primary, localized GISTs remains surgical resection. Usually a true tumor capsule does not exist, like in other soft tissue sarcomas, and the tumor should be removed en bloc with its pseudocapsule and margins of normal soft tissue or bowel.[108] In the presence of large lesions involving other organs, where an en bloc resection may be associated with significant morbidity, preoperative neoadjuvant use of imatinib mesylate may be entertained,[37] although at present data to support this practice are still lacking, pending results of the Radiation Therapy Oncology Group/American College of Radiology Imaging Network phase II study of imatinib mesylate in the neoadjuvant setting followed by surgery after 2 months of treatment.

At surgery an effort should be made to obtain tumor-free margins; several studies have shown better overall survival in patients who have undergone margin-negative resections,[82,86,109] and this practice helps

to avoid tumor violation or rupture, which is associated with increased risk of peritoneal implants.[82] Regional lymph node dissection is not recommended unless suspicious nodes are present, because GIST rarely metastasizes to nodes.[108]

A significant breakthrough in the management of small bowel tumors and specifically GISTs has come from understanding the molecular and genetic makeup of these lesions. After the discovery that GISTs characteristically express the KIT protein, a transmembrane tyrosine kinase receptor for a stem cell factor, a specific tyrosine kinase inhibitor, imatinib mesylate, has been introduced in clinical practice with partial response or stable disease occurring in approximately 80% of patients with advanced GIST.[110] Studies are under way examining the potential benefit of giving adjuvant imatinib after resection of primary GIST. The American College of Surgeons Oncology Group is leading two intergroup North American studies. The first is a phase II study for high-risk resected GIST; the second is a phase III study examining GISTs larger than 3 cm and randomizes patients to placebo or imatinib mesylate at 400 mg/day. In each study the treatment is given for 1 year.

The role of surgery for recurrent or metastatic disease has been questioned since the introduction of imatinib mesylate.[111] Currently the standard of care for metastatic GIST is imatinib mesylate at a dose of 400 mg/day. Because few complete responses to imatinib mesylate have been observed and resistance to the drug eventually develops in most patients, investigators at several centers have undertaken removing residual metastatic GIST after initial response to imatinib.[112,113] The idea is to delay or prevent the development of resistance. However, a randomized trial will be necessary to prove the benefit of surgery in metastatic GIST that is stable on tyrosine kinase therapy. Before the advent of imatinib there were data suggesting that resection of metastasis may improve survival in selected patients with well- to moderately differentiated GIST with isolated resectable metastasis and a disease-free interval of more than 12 months.[114,115] Surgery should also be considered in patients with bleeding or obstructive disease and after partial response to imatinib mesylate if the residual disease is deemed to be resectable.

Occasionally patients may appear to develop new metastatic disease, especially in the liver, while receiving imatinib mesylate. However, these lesions often represent occult disease not detected on the initial CT scan that becomes evident as the tumor mass necroses or changes density with decreased perfusion. Obviously, in these cases it is important to continue treatment with imatinib mesylate. On the other hand, acquired clinical resistance to imatinib mesylate has been reported in chronic myeloid leukemia[116] and more recently in GISTs.[77] In chronic myeloid leukemia, resistance to imatinib mesylate treatment is primarily associated with reactivation of BCR-ABL signal transduction.[114,115] This reactivation is caused by several different molecular mechanisms, including BCR-ABL gene amplification and single-amino acid substitution.[114,117] In GIST the median time of resistance to imatinib is 2 years from starting therapy. The mechanism of resistance in half of patients is the development of an additional KIT mutation.[118,119] Once patients become resistant to imatinib, sunitinib is generally used as a second-line agent. Like imatinib, sunitinib inhibits KIT and PDGFRα but also inhibits vascular endothelial growth factor receptor.

Because imatinib mesylate is used more and more often in the treatment of GISTs, it is important to briefly review side effects and complications associated with its use. The recommended starting dose for imatinib is 400 mg/day, and tolerability has been reported for daily doses up to 800 mg or more. Most side effects are mild to moderate and include periorbital and lower extremity edema, nausea, muscle cramps, diarrhea, headache, dermatitis, fatigue, anemia, and neutropenia.[77] Grades 3 and 4 toxic effects occur in less than 30% of patients at a dose of 400 to 600 mg/day.[77,120] Dramatic response to imatinib mesylate may be complicated by intratumoral bleeding in less than 5% of patients, sometimes resulting in free intraperitoneal or intraluminal bleeding requiring surgical exploration. Minor side effects usually resolve after cessation of treatment.[37] Drug interactions with warfarin and paracetamol have been reported, and these combinations should be avoided.

FOLLOW-UP

In general, routine follow-up for small bowel cancers is accomplished with endoscopy and radiologic imaging. In GIST, because highly effective therapies are now available, it seems reasonable, though unproven, to follow patients closely after resection of a primary GIST. Contrast CT scans are recommended every 3 to 6 months for 5 years. For patients with metastatic or unresectable primary GIST who are being treated with a tyrosine kinase inhibitor, CT scans should be performed every 3 to 4 months to survey for the development of drug resistance.

CONCLUSIONS

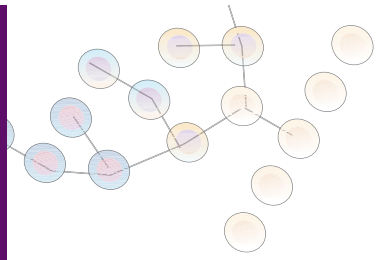
Despite the remarkable advances in the imaging, classification, and treatment of small bowel cancer, much is still to be achieved. Capsule endoscopy, enteroclysis, endoscopic ultrasound, and PET scan have all improved our diagnostic ability, but differentiating diagnostic tools for earlier diagnosis of these rare malignancies are needed. Imatinib mesylate represents an innovative therapy, one of the first successful pharmacologic manipulations of the product of a constitutively activating mutation that drives pathogenesis of a solid tumor. As such, imatinib mesylate has an impact on the actual mechanism of cancer development and progression. However, many questions remain unanswered with this new drug: optimal duration of therapy, its role in the neoadjuvant or adjuvant setting, its role in combination therapy, and the overall long-term results. More important, the mechanisms behind acquired resistance to imatinib mesylate have to be further elucidated. Finally, combination therapy with conventional chemotherapy and other signal transduction inhibitors must be further investigated.

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81 Colon Cancer

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SUMMARY OF KEY POINTS

Epidemiology

- Colorectal cancer (CRC) is the fourth most common cancer in the United States, with about 153,760 new cases expected in 2007. With 52,180 deaths expected in 2007, it is the second leading cause of U.S. cancer mortality.
- Worldwide, with 1,023,152 new cases and 528,978 deaths estimated for 2002, CRC is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related death.
- There is a 5.5% lifetime risk of developing CRC in the United States.
- The overall 5-year survival in the United States improved greatly in past the decades and is now approximately 65%, with variations across racial and ethnic subgroups.
- African Americans have the highest age-adjusted CRC incidence and mortality rates in the United States.
- Ninety percent of U.S. cases occur after 50 years of age.
- U.S. incidence and mortality rates are higher in men than in women.
- Worldwide, there is a 25-fold variation in incidence, developed areas having the highest rates.

Etiology

- Initiation begins as a clonal proliferation within an aberrant crypt focus with progression to adenoma and on to invasive carcinoma.
- The APC tumor suppressor gene is defective in more than 80% of adenomatous polyps and colon cancers.
- Defective DNA mismatch repair is believed to be responsible for 15% to 20% of CRC.
- Inherited genetic variation increases risk in concert with dietary and environmental exposures.
- A high body mass index is associated with a twofold excess risk of CRC, relating to the concept of energy balance.
- Hereditary syndromes account for fewer than 10% of cases.

Screening for Colon Cancer

- Colonoscopy is the mainstay of screening as well as a useful tool in diagnosis.
- Other acceptable screening tools are fetal occult blood tests, flexible sigmoidoscopy, and double-contrast barium enema. Virtual colonography is being developed as a potential screening tool.
- Screening is based on risk categories that take into account age; race; personal history of inflammatory bowel disease, polyps, or cancer; family history of colon cancer; and presence of familial syndromes.

Prevention of Colon Cancer

- Calcium/vitamin D and selenium supplementation might have preventive benefits.
- Chemopreventive drugs such as cyclooxygenase-2 inhibitors may prevent polyps in high-risk patients.
- Hormone replacement therapy reduces the incidence of colon cancer but increases the risk of breast cancer and cardiovascular complications.
- Ursodexycholic acid has been shown to reduce incidence of high grade adenomas.
- There have been mixed results in studies of the effect of statins on colon cancer risk.

Diagnosis and Staging

- Colorectal cancer is often insidious in development, underlying the importance of screening.
- Fatigue, anemia, altered bowel function, and weight loss are frequent symptoms.
- Obstruction is the most common acute surgical problem (about 30% of left-sided lesions present with an obstruction).
- About 5% of people with CRC will have synchronous cancer. About 20% to 40% will have synchronous polyps with cancer primary.
- Imaging used in staging includes computed tomography, magnetic resonance imaging, and positron emission tomography.
- Intraoperative ultrasound is the most sensitive way to evaluate the liver.
- The liver is the most common site for synchronous metastases.
- Tumor size is not as critical as are depth of invasion and nodal status in determining prognosis.
- High histologic grade, lymphatic invasion, venous invasion, and involvement of surgical resection margins are independent adverse prognostic factors

Surgical Treatment

- Treatment may consist of en bloc resection of anatomically defined portions of colon with in-continuity draining nodes to the root of the mesocolon.
- Laparoscopic-assisted surgery is investigational; sentinel node mapping remains to be studied.
- Careful preparation of the bowel prior to surgery minimizes the risk of morbidity and mortality.
- Experienced surgeons and the use of high-volume hospitals improve the chance of good surgical outcome.

Surveillance

- 80% to 90% of recurrence after curative resection occurs within the first 2 or 3 years. Fewer than 5% of recurrences occur after 5 years.
- Recurrent disease is frequently isolated and surgically resectable; 35% of surgically managed metastatic disease results in a cure. A high percentage of first failures occur in the liver and are asymptomatic. Of those patients who

are followed closely for evidence of recurrence, about 20% are candidates for surgery to clear metastases. They have a 5-year disease-free survival rate of 18.6% compared to only a 5.6% 5-year disease-free survival rate when metastatic disease is diagnosed because it has become symptomatic (patients who are not undergoing surveillance).
- Suggested surveillance
  - Physician exam every 3 months for first 2 years and then every 6 months
  - Carcinoembryonic antigen level monitoring every 3 months
  - Colonoscopy 1 year postsurgery and then every 3 to 5 years
  - In patients with nonmetastatic disease, annual CT scan for 3 years in patients who are at high risk of recurrence
  - In patients with metastatic disease, CT scan every 3 to 6 months for 2 years, then every 6 to 12 months in years three to five.

Adjuvant Therapy
- Fifty to sixty percent of patients who undergo successful surgery for colon carcinoma have residual micrometastatic disease.
- Systemic chemotherapy is given in an effort to clear micrometastatic disease and is routine for patients with nodal disease (stage III). Adjuvant therapy is also used for higher-risk stage II patients.
- Recommended therapy is 6 months of oxaliplatin with 5-fluorouracil (5-FU) and leucovorin.
- Adjuvant radiation therapy has no standardized role but may be considered for cases in which resection of T3 and T4 lesions leaves potentially positive circumferential resection margins.

Management of Metastatic Disease
- Patients with metastatic disease, particularly liver metastases, should be evaluated to determine whether curative resection is possible.
- Chemotherapy with infusional 5-FU and leucovorin regimens (or capecitabine) in combination with irinotecan or oxaliplatin and bevacizumab has prolonged median survival to more than 20 months.
- Additional trials have demonstrated advantages for both FOLFOX and IFL-bevacizumab compared with IFL.
- Cetuximab and panitumumab, as well as agents that are still being investigated, provide a variety of available treatments that can be tailored to meet an individual patient's situation.

INTRODUCTION

Adenocarcinoma of the colon and rectum is one of the most common human malignancies. It is a major public health issue in developing and underdeveloped countries. In developed countries, thanks to screening, removal of neoplastic polyps, and advances in surgery, radiation, and chemotherapy, there has been a small but persistent improvement in survival over the past two decades, improvements that have not yet been seen in the rest of the world. This chapter reviews progress in understanding the biology of colon cancer, the epidemiology and prevention of colon cancer, and its diagnosis and treatment. The chapter has been divided into eight sections pertaining to the following topics:

- Epidemiology and etiology of colon cancer
- Screening for colon cancer
- Prevention of colon cancer
- Anatomy and physiology of the colon
- Diagnosis and staging of colon cancer
- Surgical treatment
- Outcomes of surgical treatment and the role of adjuvant therapy
- Medical oncology management of metastatic disease

EPIDEMIOLOGY OF COLORECTAL CANCER

Colorectal Cancer in the United States

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer and second most common cause of cancer-related mortality in the United States, with 153,760 new cases and 52,180 CRC-related deaths anticipated in 2007.[1] These statistics are sobering given that CRC should be one of the most preventable cancers through well-established screening and surgical techniques, if not molecularly-targeted approaches that are increasingly available. Nevertheless, the incidence and mortality of CRC have declined fairly consistently over the last 25 years, with well-documented 20% to 25% reductions in CRC mortality rates from 1990 to 2003 (Fig. 81-1). The lifetime risk of developing CRC is approximately 5.5%. This risk can be effectively reduced by any of several screening techniques, and a few primary prevention approaches seem promising. In addition, new targeted therapeutics are making important contributions to early-stage disease management, but advanced CRC remains largely refractory to available therapeutics. Five-year survival is highly dependent on the stage at diagnosis, with localized, regional, and distant presentations resulting in estimated survival rates of 90%, 68%, and 10%, respectively. Overall 5-year survival rates in the United States have improved significantly over the last 30 years, most recent estimates averaging 65%.

Substantial variations in CRC rates across various sectors of the U.S. population suggest the etiologic importance of aging and

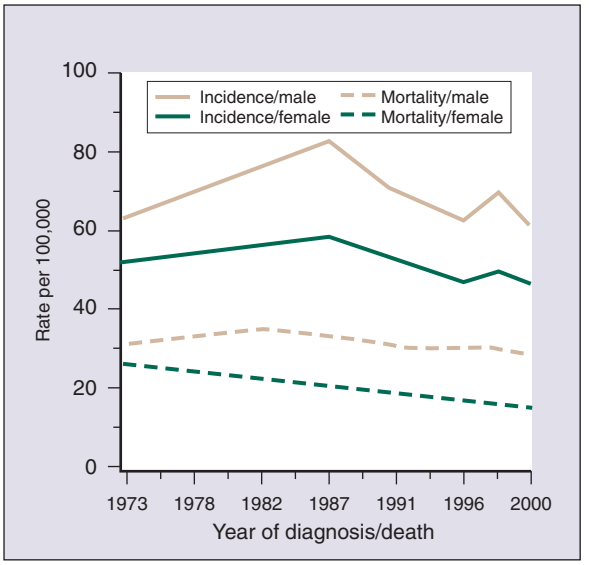


Figure 81-1 • Decline in incidence and mortality of colorectal cancer in the United States from 1973 to 2000. The decline of new cases per year began in the mid-1980s first for women and then for men. The decline occurred in each stage with a recent increase in localized disease. The decline in mortality began for women before 1973 and for men in the mid-1980s.

environmental influences and highlight disparities in CRC screening and care. As with many other cancers, CRC risk rises strongly with age, more than 90% of CRCs occurring in people older than 50 years of age. SEER data from 2000–2003 demonstrate a dramatic fourfold rise in age-specific CRC incidence rates from 52.1 cases per 100,000 in those 50 to 54 years of age, to 415.9 cases per 100,000 in those 85+ years of age.[2] CRC's strong association with aging reinforces the notion of adenomatous polyps as precursor lesions of most sporadic CRC as well, because the age-stratified prevalence of adenomas among residents of developed countries is striking: 30% at 50 years, 40% to 50% at 60 years, and 50% to 65% at 70 years.[3] CRC subsite distributions also vary by age, as is demonstrated by several recent analyses in which proximal cancers appear to be more common in elderly patients.[4] This shift is hypothesized to result from the greater likelihood of prior polypectomy in the distal colorectum.

CRC is a significant health issue for aging Americans of both genders, but there are some differences between CRC rates in men and women. Age-adjusted CRC incidence and mortality rates based on SEER data between 2000 and 2003 were higher for men (61.7 and 24.0 per 100,000, respectively) than for women (45.3 and 16.9 per 100,000, respectively).[2] Five-year survival rates from the same period were more similar at 65.0% for men and 63.2% for women. Finally, incidence trends were falling for both men and women between 1994 and 2003; however, the annual percent change was a bit greater in men (−1.3% per year in men, −0.8% per year in women). Gender differences in CRC rates are largely unexplained but might relate to differences in sex hormones, since estrogens could protect against microsatellite instability-positive cancers in particular.[5]

SEER estimates of age-adjusted CRC incidence, mortality, and survival rates from 2000–2003 differ substantially across racial and ethnic subgroups, based on five subgroups: blacks, whites, Asian/Pacific Islanders, American Indians/Alaskan Natives, and Hispanics. Blacks have the highest age-adjusted rates of CRC incidence (62.8 cases per 100,000) and mortality (27.3 deaths per 100,000), followed by whites at 52.0 cases per 100,000 and 19.3 deaths per 100,000, respectively.[2] Among these groups, Hispanics have the lowest rate of CRC incidence (39.0 cases per 100,000), and the next to the lowest mortality rate (13.8 deaths per 100,000). Five-year survival rates are better for whites than for blacks regardless of the stage of disease at diagnosis, by as much as 17%, but survival has improved for both subgroups between 1975 and 2002, albeit with more dramatic improvements for whites than for blacks.[1,2] One explanation for these disparities lies in the fact that blacks present more often with distant disease (i.e., 24% of CRC in blacks versus 19% of CRC in whites). Other arguments that have been advanced to explain black-white disparities in CRC outcomes include racial dissimilarities in age at diagnosis, anatomic subsite distribution, histopathologic characteristics, screening utilization, medical oncology referral patterns, comorbidities, social support, and medical treatment.

Socioeconomic status has been inconsistently associated with variations in CRC rates, but geographic differences seem robust in both resident and migrant populations. Typically, variations in incidence between countries are much more dramatic than variations within each country, but in high-risk countries, notable differences can still be seen. A study of the geographic distribution of the predicted incidence and observed mortality rates for CRC using 1999 data noted the highest rates in the northeastern and upper Midwest regions of the United States and the lowest rates in the West.[6] In some instances, detailed assessments of geographic variations seem to correlate with lifestyle practices.[7]

Colorectal Cancer in the World

The International Agency for Research on Cancer prepares periodic estimates of the global cancer burden in terms of age-adjusted incidence, mortality, survival, and prevalence, stratified by sex and geographic region. The most recent analysis estimated that there would be 1,023,152 new CRC cases (550,465 in males, 472,687 in females) and 528,978 CRC-related deaths (278,446 in males, 250,532 in females) in 2002, making CRC the third most common malignancy and the fourth most common cause of cancer-related death.[8] There is at least a 25-fold variation in the occurrence of CRC across various regions of the world, developed areas—particularly Australia, Western Europe, Japan (in males), and North America—having the highest incidence rates. Estimated 5-year survival rates also vary widely by region, from 30% in India to 65% in North America. The large differences in incidence are probably due to environmental factors, which are believed to play a very important role in CRC etiology. For more than 30 years, epidemiologists have described strong international correlations between CRC and various dietary constituents, including the consumption of fiber, animal fats, and meat; recent evidence seems to suggest that red meat consumption and physical inactivity are likely to play the largest role.[9] Incidence trends suggest that risks are rising in previously low-risk regions (e.g., Asia) but are either stable or falling in many previously high-risk regions (e.g., North America). The substantial differences in survival probably arise from variations in screening, early diagnosis, and therapeutic services.

The study of migrant populations has provided important insights into CRC development, and highlighted the importance of environmental factors. Overall, migrant groups tend to assume the CRC risks of their adopted country, typically within one or two generations. For example, studies of Japanese and Chinese immigrants to the United States demonstrated clear increases in risk, perhaps owing to changes in dietary habits, available food sources, or physical activity.[10,11] The converse is also true; resettlement from a high-risk region to a low-risk region can reduce a population's CRC risks. For example, Italian immigrants to South America assumed the risks of their adopted homes, with CRC rates falling among those settling in low-risk Sao Paulo but increasing in migrants to high-risk Argentina.[12]

ETIOLOGY OF COLORECTAL CANCER

Molecular Pathogenesis

The development of cancer appears to result from the accumulation of genetic and epigenetic alterations that affect at least six essential cellular and tissue-level functions.[13] An important multistep model outlining key pathogenic changes in oncogenes and tumor suppressor genes was first hypothesized for CRC development by Vogelstein and colleagues in 1988.[14] Since publication of this model, other work has provided consistent support for the Vogelstein model of the adenoma-to-carcinoma sequence (Fig. 81-2), but additional alternative mechanisms have been described as well. Potter recently summarized these data by describing three genetic pathways to CRC.[15]

APC-β-Catenin-Tcf-MYC Pathway

The initial mutation probably occurs at the tumor suppressor gene APC, which is on chromosome 5q. The APC tumor suppressor gene is defective in more than 80% of adenomas and colon cancers. It is the most common defect and the one that appears earliest in the sequence of accumulated genetic alterations. In CRC, the majority of mutations in the APC gene cause a truncation of the APC protein and therefore a loss of its normal function to degrade cytoplasmic β-catenin. This degradation occurs when β-catenin is bound to the APC/AXIN/GSK-3β complex. GSK-3β acts to phosphorylate β-catenin, leading to its conjugation to the ubiquitin protein and degradation. β-Catenin stability is regulated by diacylglycerol-independent protein kinase C-like kinase activity, which is required for β-catenin ubiquitination[16] (Fig. 81-3). The absence of a functioning APC protein leads to the accumulation of β-catenin in the cytoplasm and its translocation to the nucleus. β-Catenin plays an important role in cell-cell adhesion by linking cadherin receptors to the actin

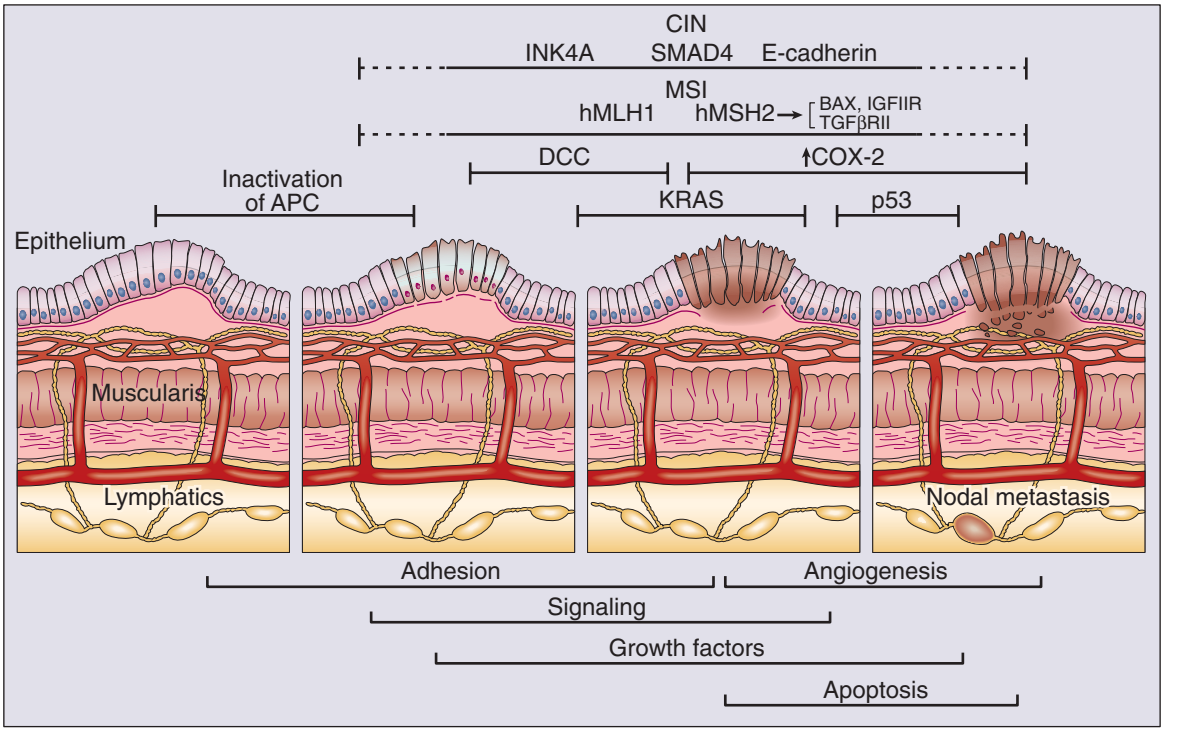


Figure 81-2 • Adenoma-to-carcinoma sequence and the associated molecular alterations involved in colon cancer development.

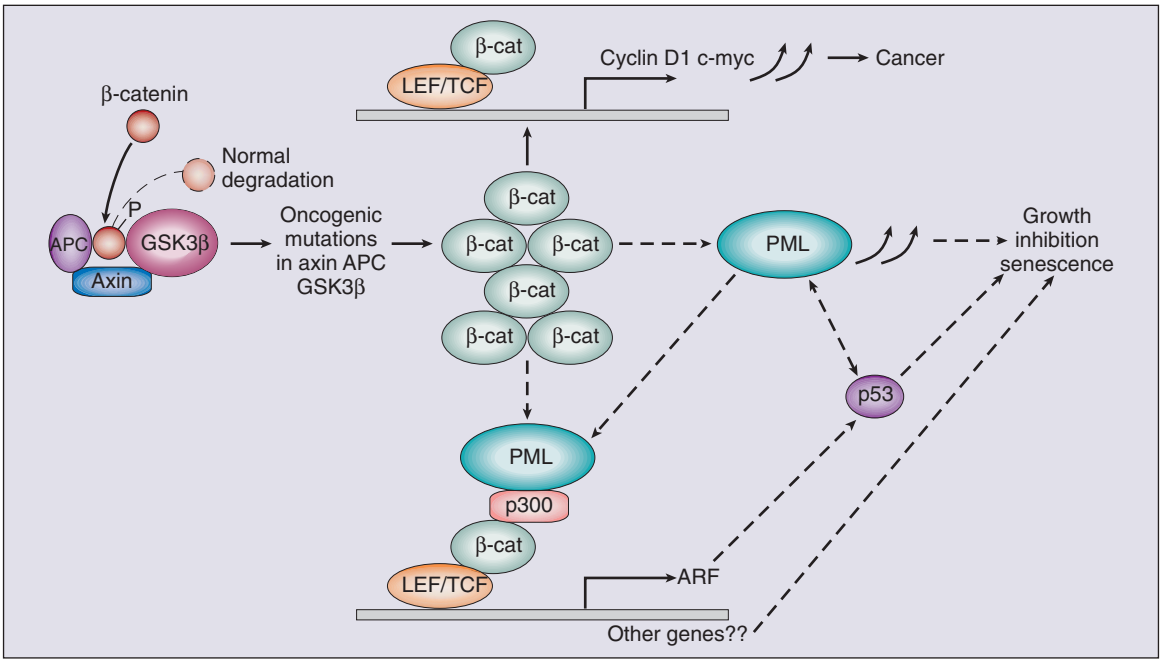


Figure 81-3 • Molecular pathway for the oncogenic and tumor-suppressive effects caused by the activation of β-catenin (overexpression). In the normal colonic epithelial cell, β-catenin is phosphorylated by GSK-β after it is bound to the APC-Axin-GSK-3β complex. This leads to normal degradation of β-catenin. Oncogenic mutation of APC leads to failure to bind, phosphorylate, and degrade β-catenin. The result is increasing cytoplasmic concentrations of β-catenin which translocates to the nucleus and activates the LEF-TCF complex, in turn activating a number of target genes promoting cell proliferation. β-Catenin induces expression of the PML gene and other pathways. (Adapted from Shtutman M, Zlurinsky J, Oren M, et al: PML is a target gene of β-catenin and plakoglobin, and coactivates β-catenin-mediated transcription. Cancer Res 2002;62:5947–5954, fig. 6.)

cytoskeleton. β-Catenin is also related to the Wnt-signaling pathway that determines cell fate, specifically during development. If Wnt signaling is activated and in turn activates the Wnt receptor, phosphorylation and inactivation of GSK-3β occur, which then prevent GSK-3β from phosphorylating β-catenin.[17] The nuclear accumulation of β-catenin causes it to complex with Tcf/LEF (T-cell factor/lymphocyte enhancer factor). The β-catenin LEF protein complex can activate genes with Tcf/LEF promoter recognition sites, including c-Myc, cyclinD1, PPARS, matrilysn, Fra-1, UPAR, c-Jun, PML, and gastrin. These changes, in turn, stimulate cell proliferation and inhibit apoptosis.[18]

In this model of CRC development, progression from adenoma to carcinoma is dependent on the accumulation of other genetic and epigenetic aberrations as well. Another important alteration includes point mutation of the K-ras proto-oncogene. Additionally, hypomethylation of DNA leading to gene activation seems to play a role. Deletions of 18q21 have also been described, and DCC, a tumor suppressor gene, was identified at this chromosomal location.[19] In addition, SMAD2 and SMAD4, two other genes that are involved in CRC, have been identified at 18q21.[20,21] SMAD2 is a receptor-regulated gene and is activated by transforming growth factor-β and activin signaling. Its role in colon cancer appears to be a late event, acting to accelerate progression in the later stages of invasive carcinogenesis.[22] Finally, allelic loss or mutation at chromosome 17p, which has been associated with the p53 tumor suppressor gene, appears to play a late role in CRC by stimulating invasion. It is generally assumed that it is the accumulation of lesions, rather than their precise order, that is critical to progression.

Defective Mismatch Repair Pathway

Some 15% to 20% of CRCs are believed to develop through a different pathway in which there is a defective DNA mismatch repair system. This pathway is characterized by instability of short, repetitive DNA sequences (i.e., DNA microsatellites). Several mismatch repair genes—hMLH1, hMSH2, hPMS1, hPMS2, and hMSH6—are involved in identifying and correcting errors in these sequences.[23] In most sporadic CRCs that are associated with microsatellite instability, hypermethylation of the promoter region of the hMLH1 gene has been found.[24] Most familial cases, identified as hereditary nonpolyposis colorectal cancers (HNPCC), have been associated with mutations in the hMLH1 or hMSH2 genes. Importantly, tumors that develop from defective mismatch repair can also acquire additional somatic frameshift mutations of coding repeats within other important genes. For example, a frameshift mutation of the BAX gene,[25] a gene that promotes apoptosis, and mutations of the transforming growth factor-β type II receptor gene,[26] and a tumor suppressor gene have been described.

Ulcerative Colitis Dysplasia and Carcinoma Pathway

Patients with chonic ulcerative colitis are at an approximately 20-fold increased risk of CRC.[27] The development of CRC in these patients appears to have several unique features that distinguish it from the pathways outlined previously. First, rapid cell turnover and oxidative injury are commonly observed in inflammatory conditions. These conditions lead to accelerated telomere shortening, increased chromosomal fusing, damage, and instability.[28] In addition, p53 mutations appear to occur earlier than in most sporadic CRC.[29]

Other Molecular Pathways and Lesions

Although investigations have focused on identifying the genetic alterations that are present in the adenoma to carcinoma model of CRC, recent work has suggested another alternative, but probably minor, path for CRC development. The term *serrated adenoma* has been used for hyperplastic polyps with serrated morphology that demonstrate dysplasia throughout the lesion. This alternative molecular route evolves from hyperplastic polyps through serrated adenomas and is characterized by mutations in the BRAF kinase gene and hypermethylation of CpG islands.[30] Studies suggest that BRAF mutations are rare in traditional adenomas (i.e., 3% to 10%) but common in serrated adenomas.[31]

What is becoming clear is that CRC is a heterogeneous disease made up of several genetically discrete subsets, each of which evolves through quite separate pathways of genetic alterations.[32] Each of these subsets will require considerable study before a final understanding of CRC as a disease can be reached. This will be essential to the future of designing rational molecularly targeted approaches to prevention and therapy.

Environmental Influences

The importance of environmental factors in CRC is underscored by migrant studies that suggest that changes in lifestyle can affect a population's cancer rates within a single generation and the 25-fold variation in international CRC incidence rates. Determining which environmental risk factors account for these observations and translating them into specific public health recommendations that can be offered to reduce CRC risks remains an active area of research.

Nutrition

Support for the role of dietary factors in CRC development comes from six lines of evidence: geographic observations,[33] chronologic observations,[34] migration studies,[10,11] mechanistic inquiries, animal models, and human trials. Intuitively, the relationship between ingested substances (or their metabolites) and CRC makes sense because they have direct, topical contact with the colorectum, thereby potentiating any inherent procarcinogenic or anticarcinogenic effects.

High fiber intake has been proposed as a CRC protective factor for more than 40 years, since Burkitt originally suggested that high-fiber diets and low rates of CRC in Africa were correlated.[35] Subsequent case-control and cohort studies have examined the relationship between fiber, as well as fruits and vegetables in general, and CRC risk. Taken together, more than 10 case-control studies generally showed a 40% to 50% protective association between vegetable intake and CRC risk.[36,37] However, subsequent cohort studies involving tens of thousands of participants have shown much weaker, if any, protective effects of fiber, fruit, or vegetable intake on CRC risk.[38–40] The situation is made more complex by a recent report from the European Prospective Investigation into Cancer and Nutrition cohort study involving 10 countries and more than 500,000 people that reported a 40% reduction in CRC incidence between those consuming the highest versus lowest levels of fiber.[41] On the basis of observational studies alone, the association between dietary fiber, fruits, and vegetables and lowering CRC risk seems inconsistent and modest at best; however, diets that are high in these components may have many other health benefits, such as reducing the risk of symptomatic colonic diverticuli, coronary artery disease, hypertension, and diabetes.[42]

Dietary fat has been proposed as a CRC risk factor for decades; however, the association has been inconsistent across studies. Although multiple retrospective studies described positive associations between total fat intake and CRC risk,[43] a meta-analysis of 13 case-control studies found that overall dietary fat consumption was not associated with CRC risk.[37] One reason for the inconsistent observations might be that only specific sources or subtypes of fat are linked to CRC; another reason might be that risk is related more to excess energy intake than to fat intake per se. Red meats have been reported to increase the risk of CRC across multiple studies, perhaps owing to their fat content.[38,39,44] Two recent meta-analyses related to processed meats in particular suggested strong risks for CRC.[45,46] The reasons underlying red meats' association with CRC are unclear, but hypotheses related to their total fat content, saturated fat content, or carcinogens derived from their cooking have been advanced. Mutagenic heterocyclic amines can be generated during cooking, and the

CRC risk of meat eaters who prefer heavily browned surfaces or who cook meat at high temperatures is often elevated.[47] Select gene polymorphisms might potentiate the risks of ingesting charred red meats by differentially metabolizing cooking-related carcinogens.[48]

Folate and methionine are dietary methyl donors that support critical cellular functions such as nucleotide synthesis and gene regulation. Therefore, diets that are deficient in these substances might contribute to CRC by altering the capacity for DNA synthesis, repair, or transcriptional control. Observational studies have generally supported the notion of an inverse association between folate and methionine intake and CRC risk,[49–51] risk estimates suggesting reductions on the order of 25% to 50%. A recent pooled analysis based on more than 500,000 participants followed for up to 13 years identified a 21% lower risk of CRC among those with the highest intake of folate, regardless of whether it was received as a part of the diet or through supplements.[52] Once again, polymorphisms in key genes associated with the metabolism of folate to methionine or thymidylate synthesis, involving the methylenetetrahydrofolate reductase enzyme, may play an important role.[53] Given that alcohol is a potent antagonist of folate metabolism, the role of these variants in CRC might be most relevant in alcohol users. Overall, a twofold to fivefold increase in risk has been described in people with high-alcohol, low-folate diets.[50] These risks might be particularly important for individuals with the methylenetetrahydrofolate reductase TT genotype, who are at relatively low risk if they have a good diet but have an elevated risk if they have a diet that is low in folates and high in alcohol.[54,55] More recently, a meta-analysis of 18 studies involving Japanese populations has reported a consistently increased risk associated with alcohol intake, even among those with moderate levels of use.[56]

Calcium intake has been hypothesized to reduce the risk of CRC owing to its ability to bind ionized fatty acids and secondary bile acids to reduce their mucosal toxicity and/or directly reduce intestinal proliferation.[57,58] A meta-analysis of 16 case-control and 8 cohort studies reported a statistically significant 14% risk reduction among subjects in the highest versus lowest categories of intake.[59] More recent large prospective studies have typically reported a modest inverse association but without a clear dose-response relationship.[60] In addition, some studies suggest that the maximum benefit can be achieved with intakes of 700 to 800 mg/day, and effects are most striking for distal, rather than proximal, CRC.[61] Recent randomized controlled trials confirm calcium's protective effects (see later in the chapter). Vitamin D has also been proposed as a potent CRC preventive agent on the basis of its ability to suppress proliferation and to induce differentiation and apoptosis in certain preclinical settings.[62] While the proposal has intuitive appeal, definitive results are lacking, and it remains a topic of intense research.

Several other dietary constituents have been investigated for their possible association with CRC risk. Antioxidant micronutrients, including retinoids, carotenoids, ascorbic acid, α-tocopherol, and selenium, have been considered in both retrospective and prospective studies but without a clear conclusion regarding their role in CRC etiology.[63] Alcohol's role in CRC etiology has been debated for decades; recent analyses suggest a modest but significant increase in CRC risk among those who drink more than two drinks per day.[64] For example, the Pooling Project of Prospective Studies recently reported a 24% increase in CRC risk in those who consume at least 30 grams per day.[65] The mechanisms underlying alcohol's effects on CRC might involve its ability to induce cellular proliferation, block methyl group donation, and inhibit DNA repair. Deleterious effects of alcohol could be particularly important for individuals with marginal dietary intakes of folate and methionine (see the earlier discussion).

Energy Balance

Accurate measurements of energy balance can be difficult in an epidemiologic context because of the inherent complexity of the various factors involved—dietary intake, individual metabolic rates, and physical activity—as well as their variation over time. Therefore, a variety of surrogate measures have been employed to investigate the role of energy balance in CRC etiology. A high body mass index has been reliably associated with at least a twofold excess CRC risk across multiple epidemiologic studies,[66,67] and some studies suggest increased risks with central adiposity even independently of body mass index, particularly in men.[68]

Moderate levels of physical activity have also been consistently associated with a reduced risk of colorectal neoplasia, regardless of gender. Colditz and colleagues summarized 23 case-control and 18 cohort studies and reported a 40% to 50% reduction in CRC risk among subjects reporting high versus low levels of physical activity.[69] The effects may be most striking for distal CRC, but even moderate levels of activity (such as walking 3 to 4 hours per week) may be effective. More recently, the European Prospective Investigation into Cancer and Nutrition study reported a 22% reduction in the hazard ratio for CRC among the most active participants compared with the inactive ones, with a dose-response trend.[70]

Finally, there are strong similarities between risk factors for CRC and non-insulin-dependent diabetes mellitus, which include excess caloric intake, physical inactivity, and central adiposity; suggesting a possible link between these diseases. Although the pathogenic details remain to be elucidated, non-insulin-dependent diabetes mellitus has consistently been associated with a 30% to 40% increased risk of CRC in retrospective and prospective studies.[71,72]

Environmental Exposures

At least three environmental exposures have been evaluated for their roles in CRC etiology. Tobacco use has been consistently associated with a twofold to threefold risk of colorectal adenomas and recently also with an increased risk of CRC.[73] Interestingly tobacco appears to act early in CRC development, so its effects on CRC incidence might take 30 to 40 years to manifest themselves. Tobacco cessation might reduce risks, but it is likely that some level of excess risk persists indefinitely. Sporadic reports suggest that pelvic irradiation for gynecologic malignancies can increase the risk of rectal cancers by twofold to threefold; newer, more focused treatment modalities should minimize these risks.[74] Finally, asbestos has been reported in some studies to increase CRC risks by up to 40%,[75] but this association is considered controversial.[76]

Host Influences

Hereditary Factors

Several genetic susceptibility syndromes have been described that place individuals who harbor characteristic mutations at increased risk for CRC. Although the associated CRC risks are dramatically elevated in these groups, the proportion of CRC that is attributable to these syndromes is small (probably less than 10% in total) because of the rarity of the syndromes.

Familial adenomatous polyposis (FAP) is a rare autosomal dominant disorder that is characterized by the occurrence of hundreds to thousands of colorectal adenomas by 20 to 30 years of age[77] (Fig. 81-4). In general, the disorder is the result of an inherited defect in one allele of the APC gene, which acts as a tumor suppressor gene (see earlier in the chapter); however, up to 20% of cases could represent de novo mutations without an apparent family history. When the second allele is inactivated through mutation early in childhood, the colonic epithelium begins a process of uncontrolled hyperplasia and polyposis. The lifetime risk of CRC is nearly 100% and appears to be correlated with the number of adenomas,[78] but given the rarity of the disorder, it accounts for only 1% to 2% of all incident CRC. In addition to the risk of CRC, other phenotypic manifestations of the disorder can include tumors of the central nervous system (also known as Turcot's syndrome),[79] epidermal cysts, osteomas, dental abnormalities, mesenteric or abdominal wall desmoid tumors (also known as Gardner's syndrome),[80] congenital hypertrophy of the



Figure 81-4 • A segment of a large intestine covered with adenomatous polyps in a patient with familial adenomatous polyposis. The entire colon is covered with hundreds of polyps. (From Skarin AT, Shaffer K, Wieczorek T [eds]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 153.)

retinal pigmented epithelium, and upper gastrointestinal tumors, especially periampullary duodenal carcinoma. Several of these phenotypic features have been correlated with specific mutation sites.[81] The most common genetic abnormality results in a stop codon, leading to the production of a truncated and nonfunctional APC protein. The in vitro production of this abnormal protein now serves as a genetic screening procedure for the disease following appropriate genetic counseling. In the absence of preventive measures, invasive CRC occurs in FAP patients at an average age of 42 years. This provides a compelling rationale for a variety of preventive interventions, including early endoscopic screening, proctocolectomy, colectomy with ileorectal anastomosis, lifelong upper and lower intestinal surveillance, and participation in clinical trials evaluating the potential benefits and risks of chemopreventive options. An attenuated form of FAP has been described in some individuals who harbor mutations at the extreme 3′ or 5′ end of the APC gene. In these individuals, disease onset is typically delayed by 20 years; polyposis is not nearly as dramatic, with 100 or fewer colorectal adenomas; and polyps are more common in the proximal colon. Although the lifetime penetrance of CRC appears to be high in this variant, extracolonic features are less common.[82]

Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant disorder involving one of several genes involved in the mismatch repair system, including hMSH2, hMLH1, hPMS1, PMS2, or hMSH6. Defects in one or more of these proteins result in microsatellite instability and characteristic clinical phenotypic features that include early-onset CRC (often by 50 years of age) typically in the proximal colon; the occurrence of rare, villous, high-grade adenomas; and a variety of extracolonic tumors involving the endometrium, ovary, upper GI tract, pancreas, ureter, or renal pelvis.[83] Penetrance of the disorder has been estimated to be approximately 80% to 85%, and the syndrome is believed to account for 4% to 6% of all incident CRC.

In addition to high-penetrance genes such as those described earlier in the chapter, a variety of low-penetrance, polymorphic genes have been investigated for their potential to influence CRC risks, particularly when considered in the context of concomitant dietary or environmental exposures.[84] Most of these analyses involve genes that play a role in metabolizing various carcinogenic compounds, including heterocyclic amines or polycyclic aromatic hydrocarbons (e.g., N-acetyl transferase, cytochrome P450s, glutathione-S-transferase enzymes), catabolizing alcohol (e.g., aldehyde dehydrogenase), and maintaining methyl donor activity (e.g., methylenetetrahydrofolate reductase) or directly affect carcinogenesis through their activity as oncogenes (e.g., HRAS1) or tumor suppressors (e.g., p53). De Jong and colleagues recently performed a pooled analysis of 30 polymorphisms in 20 genes and identified 7 polymorphic genes that were significantly associated with CRC risk in more than one study.[84] Specifically, polymorphisms associated with an increased risk of CRC included the NAT2 fast phenotype (70% increased risk); the GSTfi1 null genotype (40% increased risk); one or two mutant alleles of ALDH2; any of four rare variants of the proto-oncogene HRAS1; and the a2, a5, and a13 alleles of TNFa. The pooled analysis also revealed reductions in CRC risk for the following polymorphisms: homozygous carriers of the C677T variant allele of methylenetetrahydrofolate reductase (20% to 30% reduced risk) and heterozygous or homozygous carriers of an intron 3 polymorphism of the p53 gene. Not included in De Jong and colleagues' analysis are whole-genome scanning techniques that have also recently identified single-nucleotide polymorphisms at the 8q24 locus as associated with increased risk of CRC.[85,86]

Inflammatory bowel disease (IBD) is described in two clinical forms: ulcerative colitis and Crohn's disease.[87] Both forms of IBD appear to result from a polygenic disorder with a strong familial component. For example, in a patient with IBD, the lifetime risk that a first-degree relative will be affected averages 10%. In addition, monozygotic twins are much more likely than are dizygotic twins to be affected. CRC risk in chronic ulcerative colitis increases with the duration and extent of disease. Estimates of CRC risk rise 0.5% to 1.0%, on average, per year after 10 years of chronic inflammation, making colonoscopic surveillance mandatory, although improvements in medical management seem to be reducing risks in some individuals. IBD-associated CRC has several unique features that distinguish it from sporadic CRC.[88] Specifically in IBD, CRCs occur about 20 to 30 years earlier, are more often mucinous or anaplastic in nature, arise from either flat or dysplasia-associated lesions versus adenomas, and occur in a multiple, synchronous manner in up to 12% of individuals; also, in contrast to sporadic CRC, p53 mutations occur earlier in the disease course, while APC mutations occur much later.

Familial clustering of CRC is common even in those without a definable genetic predisposition. For example, twin studies suggest that heritable factors are important in CRC development, even in the absence of known genetic predispositions.[89] Two recent meta-analyses of observational studies demonstrated an approximate relative risk of 2.25 in individuals with a single first-degree relative affected by CRC and a 4 to 4.25 relative risk in those with more than one affected relative or with a family member who developed CRC before 45 years of age.[90,91] Risks were slightly higher for colon cancer than for rectal cancer. Population lifetime CRC risk estimates for a 50-year-old increased from 1.8% to 3.4% with one affected relative and to 6.9% with two or more affected relatives. Risks were also elevated approximately twofold for individuals with first-degree relatives who harbored colorectal adenomas, lending support to the notion that colorectal adenomas and carcinomas are linked.

Somatic Factors

Nearly all CRCs are believed to arise from prior adenomas, but fewer than 10% of adenomas progress to become CRCs.[92] Nevertheless individuals with a prior history of colorectal neoplasia (either adenomas or carcinomas) are at increased risk for developing metachronous or recurrent CRC. Important features of adenomas that increase the individual's subsequent risk of CRC include their size, villous histopathology, and multiplicity. In a cohort study of more than 800 patients with adenomas, the relative risk estimate for CRC after 13 years of follow-up was 3.6; the relative risk rose to 6.6 among patients with more than one adenoma at baseline.[93] Risks for CRC are similarly elevated among patients with prior resected CRC.

Prior cholecystectomy has been suggested as a risk factor for CRC owing to the resulting continuous excretion of bile acids, which, when metabolized by intestinal bacteria, can be mutagenic.

Two meta-analyses of retrospective studies found modestly increased risks for proximal CRC, but the potential for confounding by other related factors tempers the implications of the association.[94,95] At present, prior cholecystectomy does not affect any of the prominent GI screening or surveillance guidelines.

A variety of other uncommon conditions have been associated with an increase in CRC risk. For example, there are several reports of colon carcinoma occurring years after ureterosigmoidostomy for congenital extrophy of the bladder.[96] Risk estimates suggest that the incidence of CRC in this setting may be as high as 5% to 10% after 20 to 30 years of follow-up. *Streptococcus bovis* bacteremia or endocarditis has also been noted in many case series as a warning sign of latent colorectal neoplasia.[97] Acromegaly is a endocrinologic disorder that is characterized by excessive circulating levels of growth hormone and its tissue mediator, insulin-like growth factor-1, and up to a 13-fold higher prevalence of colorectal neoplasia compared to population controls.[98] More recent studies have found twofold to ninefold increased relative risks for colorectal adenomas and cancer among acromegalics and identified a correlation between serum concentrations of growth hormone and CR neoplasia.[99,100] Serum levels of insulin-like growth factor-1 during childhood and adolescence influence linear growth and correlate with height.[101] Interestingly, observational studies have commonly reported positive associations between height and colon cancer risk as well, although risk estimates have been modest.[102,103]

SCREENING FOR COLON CANCER

Screening the General Population at Low to Average Risk

The American Gastroenterological Association and other groups recommend that "men/women at average risk should be offered options for screening for colorectal cancer and polyps beginning at age 50 years." African Americans are considered to be at above-average risk, according to the American College of Gastroenterology, and will be discussed later in the chapter.[104] Screening options for average-risk patients should be offered, with information about the advantages and disadvantages associated with each approach. If the result of a screening test is abnormal, physicians should recommend a complete structural examination of the colon and rectum by colonoscopy (or flexible sigmoidoscopy and double-contrast barium enema if colonoscopy is not available).[105]

Fecal occult blood testing (FOBT) should be offered annually, using a guaiac-based test with dietary restriction or a fecal immunochemical test (FIT) without dietary restriction. Two samples from each of three consecutive stools should be examined without rehydration. Patients with a positive test on any specimen should be followed up with colonoscopy.[105] The sensitivity of a single FOBT is low, detecting only about 26% to 69% of cancers. A single FIT performs better, with a sensitivity of 66% to 90% and specificity over 90%.[106] In the case of either test, its success as a screening tool is not evaluated on a one-time basis. A program of repeated testing can detect the majority of cancers and result in an 18% to 21% reduction in colon cancer mortality, according to strong evidence from randomized prospective clinical trials.[107–109]

Flexible sigmoidoscopy should be offered every 5 years, on the basis of evidence of reduced mortality from four case-control studies and two randomized controlled trials.[110–115] When combined with FOBT or FIT, the fecal test should be done first; if it is positive, a complete colon exam would be indicated.[116–118] The combination of flexible sigmoidoscopy and FOBT or FIT is preferred to either one alone.[119,120]

Colonoscopy should be offered every 10 years. The interval of 10 years is based on the typical rate of progression from adenoma to cancer.[121] Although there are no studies evaluating whether screening colonoscopy alone reduces the incidence or mortality from colorectal cancer in people who are at average risk, several lines of evidence support the effectiveness of screening colonoscopy.[105] Colonoscopy has not only diagnostic but also therapeutic benefits, as it allows removal of adenomas and reduces the incidence of colorectal cancer, as was demonstrated in two cohort studies of people with adenomatous polyps.[122] Colonoscopy examines more of the colon than sigmoidoscopy, and as expected, it has been proven to detect twice as many significant adenomas and cancers as sigmoidoscopy in two large prospective studies in which half of all patients with advanced proximal neoplasms had no distal colonic findings on sigmoidoscopy that would have prompted referral for a complete colon exam.[123,124]

Both the American Cancer Society[119] and the National Comprehensive Cancer Network (NCCN) list double-contrast barium enema as a screening option to be offered every 5 years.[120] No trials have been done to evaluate the effect of double-contrast barium enema screening on CRC incidence or mortality; however, in studies of patients with known disease, double-contrast barium enema was shown to have a sensitivity level ranging from 80% to 90% for colorectal cancer.[125] Although these numbers cannot be directly applied to general screening, the efficacy of double-contrast barium enema in detecting adenoma and early cancers has made it an attractive screening option.[126]

Virtual colonography (VC), though not listed among any current screening guidelines, is a screening technology that is likely to be adopted in the near future.[126] VC, also referred to as CT colonography, is a noninvasive radiologic study for the detection of colonic polyps and masses (Fig. 81-5). VC was introduced in 1994 and uses two-dimensional and three-dimensional reconstruction of conventional CT data sets to examine the luminal surface of the prepped and insufflated colon. Early reports in polyp-rich patient cohorts were highly encouraging, but these results could not be duplicated in initial studies of low-prevalence cohorts.[127–129] Improved techniques, including stool tagging and the use of a primary three-dimensional approach that mimics the endoluminal display of conventional colonoscopy, have dramatically improved the detection of polyps with diameters of 6 mm and greater.[130,131] Of the three multicenter trials that have been performed to date, only the largest trial (the sole trial to use three-dimensional techniques and stool tagging) showed performance comparable with that of optical colonoscopy for detection of relevant lesions.[130]

Several challenges remain prior to the widespread implementation of screening with VC, despite encouraging results at some centers

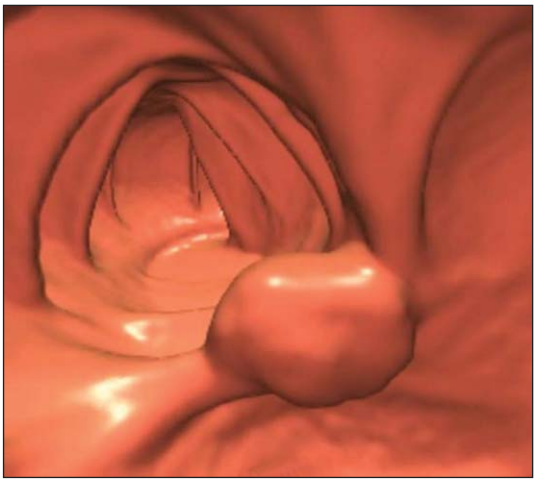


Figure 81-5 • Three-dimensional endoluminal image from screening CT colonography in an asymptomatic average-risk 62-year-old man shows a large 17-mm polyp in the transverse colon, which proved to be a well-differentiated invasive adenocarcinoma after removal at same-day colonoscopy. The patient underwent subsequent extended right hemicolectomy without complication.

and a patient preference for VC versus optical colonoscopy or barium enema.[132] Differences in software, technical parameters, and viewing techniques clearly affect results, and many of the systems and techniques that are in clinical use have not been adequately validated or have fallen short when measured against optical colonoscopy. The lack of widespread reimbursement for the procedure is another limitation, but the single center that has third-party reimbursement has successfully screened over 4000 patients in the 3 years since coverage was secured.[131] The inability to remove polyps at the time of detection is a further limitation that requires the availability of a same-day colonoscopy service if the patient is to avoid a second bowel preparation for polyp removal. Despite these limitations, the use of VC is likely to increase substantially as the results of large state-of-the-art single-center and multicenter trials that are currently in progress become available.

Screening Individuals with Moderately Increased Risk

Surveillance colonoscopy should be performed earlier and at more frequent intervals for patients who are at increased risk because they are African American,[104] have been treated for colorectal cancer, have had an adenomatous polyp diagnosed, have a disease that predisposes them to colorectal cancer (e.g., IBD), or have a family history of colon polyps or cancer.[119] NCCN adds to this list individuals with a history of endometrial or ovarian cancer before age 60.[120]

Individuals with a first-degree relative affected with colon cancer, an adenoma before age 60 years, or two or more first-degree relatives affected by colon cancer at any age should have colonoscopy every five years beginning at age 40 or 10 years younger than the earliest diagnosis in the family, whichever comes first.[119] Those with a personal history of IBD should begin colonoscopy screening with biopsies 8 to 10 years after onset of symptoms. Screening should be repeated every 1 to 2 years.[120] African Americans should begin screening at age 45 rather than 50 and, because of the prevalence of proximal bowel lesions in this population, should undergo colonoscopy.

Screening Individuals with High-Risk Familial Syndromes

Patients with more severe family history or syndromes, including FAP and HNPCC, require more frequent colon exams beginning at younger ages because of the earlier onset and higher frequency of cancers and polyps in individuals with an inherited or germline mutation.

Hereditary Nonpolyposis Colorectal Cancer

Colonoscopy exams for patients with HNPCC and their at-risk relatives has been proven an effective method for reducing the incidence and mortality of colorectal cancer.[133] The incidence of cancer is reduced by more than half, presumably owing to the removal of precursor polyps, when complete colonoscopy is begun at an early age and repeated at regular intervals.[134] Colonoscopy in HNPCC families generally should begin at least 5 to 10 years before the youngest age at cancer diagnosis in an affected family member or no later than age 21 years. No guidelines or authorities recommend intervals longer than 3 years in HNPCC. The American Cancer Society guidelines recommend that colonoscopy for HNPCC screening be repeated every 2 years until age 40 and then annually.[119] Once a polyp or cancer has been detected, more frequent screening should be considered, perhaps every 6 to 12 months.

Familial Adenomatous Polyposis

Screening is a well-established method of cancer prevention in FAP because polyposis can be diagnosed and colectomy completed long before cancer develops.[135] Screening for FAP should be done by videoendoscopic rather than radiologic methods because of the usual small polyp size and because of the requirement of histology to confirm the diagnosis of adenomas. Full colonoscopy should be done in anyone with polyposis that is already well developed at the time of initial diagnosis, because in such cases, larger polyps and malignancy could be present in the proximal colon. Flexible sigmoidoscopy is considered sufficient for scheduled screening of any descendants of a person with FAP, because those with the classic severe phenotype will develop numerous polyps throughout the colon. Annual examinations with flexible sigmoidoscopy or colonoscopy should begin by 10 to 15 years of age in anyone with a known deleterious mutation of the APC gene and in those for whom genetic testing has not been done or is uninformative or not definitively negative. In patients without adequate genetic testing, screening intervals can be increased to every 2 years at age 25, every 3 years at age 35, and every 5 years from age 45 on. Full colonoscopy should be considered to screen patients every 5 years starting at age 20, even in the absence of polyposis, on the chance that the patient has attenuated FAP.[120]

PREVENTION OF COLORECTAL CANCER

The term *prevention* refers to an intentional intervention that is taken or recommended to reduce the development or risk of colorectal neoplasia from its earliest clinical manifestation—typically, a preinvasive neoplastic lesion, such as an adenoma, through its downstream clinicopathologic manifestations (e.g., cancer, cancer-related morbidity or mortality). Drawing on this concept, the most solid recommendations related to CRC prevention are derived from adequately powered, well-controlled trials that focus on reductions in important clinical endpoints. The selection of appropriate endpoints for clinical trials in colorectal cancer prevention is an area of controversy. Clearly, the most compelling endpoint for trials is overall mortality, followed in turn by CRC-associated mortality, CRC incidence, and adenoma incidence. Trials that intend to change current standards of practice (i.e., phase III trials) have typically used the latter two endpoints, but the choice of endpoints is a contentious issue. While all investigators seek to reduce these parameters in a consonant manner and thus improve the clinical status of participants across time, experts disagree about the importance of treatment-related reductions in anything less than CRC-associated mortality, which could take thousands of participants and/or decades of time to demonstrate even with an effective agent, particularly if the control arm includes polypectomy.

In recognition of the infeasibility of this approach for all agents and trials and because adenomas are already a meaningful focus of clinical practice, most contemporary trials of investigational preventive agents use colorectal neoplasia—inclusive of measurable adenomas, "advanced" adenomas, and colorectal cancers—as their primary efficacy endpoint.[63] Biomarker-based trials that focus on earlier or lower-level histopathologic, cellular, or molecular endpoints can provide important supportive and/or mechanistic data but are not reasonably validated to serve as primary measures of efficacy at this time.

CRC prevention trials have typically focused on patient groups that are at greater than average risk owing to germline mutations (e.g., FAP or HNPCC patients) or prior colorectal adenomas or carcinomas.[63] This approach has been taken because these patients are both the most likely to benefit from prevention efforts (at least in the near term) and the most likely to tolerate some degree of toxicity. In addition, this approach is appealing because of its practical implications; that is, trials in these high-risk cohorts can typically be conducted more effectively and more efficiently in terms of the numbers of patients, time, and resources required to demonstrate significant effects.

Agents that were initially considered for clinical testing were identified because of their association with reduced CRC risks based on epidemiologic studies (e.g., low-fat/high-fiber diets, calcium supplements) and/or preclinical/mechanistic studies (e.g., cyclooxygenase-2 inhibitors). As our molecular insights into colorectal carcinogenesis

have grown and the correlation between human cancer and animal models of carcinogenesis has improved, the selection of candidate agents has become more rigorous. Currently, candidates are prioritized by their in vitro activity against mechanistic targets, their efficacy and lack of apparent toxicity in animal models, and (when available) epidemiologic evidence of efficacy and apparent safety.

Surgical Prevention

Surgical prevention by the identification and removal of endoscopic polyps (and, in particular, adenomas) is an effective means of CRC risk reduction with an estimated efficacy of up to 75% based on comparisons of surveillance colonoscopy with polypectomy compared to data from three historical controls.[136] This approach has become the current standard of care; therefore, randomized, controlled trials evaluating polypectomy versus observation are felt to be infeasible in the United States.

Molecular Prevention (Chemoprevention)

Molecular or medical prevention by lifestyle alterations or putative chemopreventive strategies have been investigated for the last 15 to 20 years (Table 81-1). Early trials that focused on dietary modifications (e.g., fiber supplements, fat reductions, increases in fruits and vegetables) or nutritional supplements (e.g., wheat bran fiber, antioxidants) largely failed to identify significant reductions in risk.[63,137–141]

Dietary Modification

Several trials have evaluated the efficacy of dietary modifications—including adjustments in total fat, fiber, and/or fruit and vegetable intake—in reducing colorectal neoplasia. A randomized trial of wheat bran fiber in 1429 subjects with prior adenomas showed no significant reduction in colorectal adenomas associated with high-fiber cereal supplements over a 3-year period.[140] Another phase III trial involving 665 participants found that fiber supplementation increased participants' risk for recurrent adenomas by 67%.[137] By contrast, a large international observational study, the European Prospective Investigation into Cancer and Nutrition study, found a statistically significant 25% reduction in CRC risk between individuals who consumed the highest versus lowest quintiles of dietary fiber.[41] Another trial that assessed the efficacy of a diet that was low in fat (<20% of total calories), and high in fiber (18 g of dietary fiber/1000 kcal) and fruits and vegetables (3.5 servings/1000 kcal) also reported null results with regard to recurrent adenomas over a 3-year period.[141]

Finally, the Women's Health Initiative involving 48,835 postmenopausal women aged 50 to 79 years has contributed information about the effect of diet on CRC risk.[142] In one component of the trial, participants were randomized to a modified diet of 20% total fat intake and increased daily vegetables, fruits, and grains. As a result, the participants on the experimental arm achieved a 10% reduction in fat intake over 8.1 years of follow-up. However, invasive colorectal cancers were not reduced by the modification (hazard ratio: 1.08; 95% CI: 0.90 to 1.29). Similarly, the modified diet did not yield significant reductions in cardiovascular disease, cancer mortality, or overall mortality.[143] These mixed results suggest that trials using different types of fiber or dietary modifications, different schedules (i.e., earlier, later, or in a manner not yet determined), and/or different biologic endpoints (i.e., CRC incidence [in some], overall cancer incidence, and/or cancer-associated mortality) in different cohorts (i.e., younger people or those without prior adenomas) might help to determine whether dietary modifications can protect against colorectal carcinogenesis.[63] At least two ongoing placebo-controlled international trials are evaluating the efficacy of resistant starch and/or aspirin in patients who are at increased risk for CRC due to hereditary mutations associated with FAP or HNPCC.[144,145]

Calcium and Vitamin D Supplementation

Mechanistic, preclinical, and observational data have largely supported the notion that calcium supplementation could reduce colorectal neoplasia, although threshold effects have been suggested.[61] In a randomized, controlled trial of calcium carbonate supplementation at 1200 mg elemental calcium per day in 913 patients with prior adenomas, approximately 20% reductions in recurrent adenomas were reported after 3 years, with initial effects within 1 year.[146] A recent update suggests that these preventive benefits may extend to 5 years.[147] Similarly, a 34% reduction (albeit not statistically significant) in adenoma recurrence was observed in a European trial involving 655 patients who were randomized to 2 grams of elemental calcium versus placebo per day over 36 months.[137] At a minimum, these results suggest that calcium supplementation is well-tolerated and achieves modest reductions in recurrent adenomas.

More recently, the Women's Health Initiative randomizing more than 36,000 postmenopausal women to calcium and vitamin D versus placebo (among other agents) did not identify a reduction in invasive CRC although the short duration of follow-up (approximately 7 years) relative to the endpoint of invasive CRC may account for this.[148] Limited data suggest that vitamin D supplementation alone might be associated with up to a 50% reduction in colorectal cancer risk, but definitive data from ongoing randomized controlled trials are not yet available.[149,150]

Vitamin, Antioxidant, or Selenium Supplementation

Several lines of evidence, observational and experimental, suggest that folic acid might reduce the risk of colorectal neoplasia, although the findings are not entirely consistent, and they do not generally account for the current situation in which the U.S. food supply is already being broadly fortified.[151] Observational studies that have been published after the U.S. government's implementation of folate fortification in 1998 continue to suggest that higher folate levels might reduce the risk of recurrent adenomas, but only in individuals with lower baseline intakes and/or high homocysteine levels.[152] Several ongoing randomized, placebo-controlled trials are evaluating the efficacy of supplemental folate, with or without other chemopreventive agents such as aspirin, in reducing colorectal adenomas.[153]

In theory, antioxidant vitamins (e.g., α-tocopherol, ascorbic acid, β-carotene) could prevent carcinogen formation and blunt genotoxicity, thereby offering an appealing chemopreventive strategy. Epidemiologic associations have been inconsistent and difficult to interpret because of the many strong correlations between antioxidants and other putative chemopreventive components of healthy diets. Therefore, randomized, controlled trials have been helpful in sorting out their effects.[63] Thus far, efficacy with these agents has not been convincing. For example, the Alpha-Tocopherol Beta Carotene Trial randomized 15,538 male smokers to α-tocopherol, β-carotene, both, or neither and reported a statistically significant 66% increase in colorectal adenomas with α-tocopherol but a discordant, nonsignificant 16% reduction in CRC incidence.[154,155] Explanations for these findings include a slightly higher rate of gastrointestinal symptoms among subjects who were on α-tocopherol, which might have led to more endoscopies. Long-term follow-up will be essential to confirm the effects of α-tocopherol on colorectal cancer (if any).

Other prevention trials investigating antioxidants have used vitamin C or vitamin E or both, most often in combination with other micronutrients.[63] Although two trials described protective effects against mucosal hyperproliferation or adenoma recurrence,[156,157] a larger, longer-term trial failed to demonstrate significant protective effects against recurrent adenomas.[138] Finally, a large trial, evaluating the incidence of all cancers in 13,017 people taking a combination of antioxidant agents, did not identify significant reductions in overall cancer incidence, cardiovascular disease, or overall mortality, although secondary analyses suggest possible benefits in

Table 81-1 Randomized, Controlled Colorectal Neoplasia Prevention Trials

Cohort	Sample Size	Intervention	Outcome(s)	Reference
AVERAGE RISK				
U.S. male physicians	22,071	Aspirin 325 mg QOD vs. placebo × 5 years	Primary CRC incidence RR = 1.15 (95% CI = 0.80–1.65) In situ cancer/polyp incidence RR = 0.86 (95% CI = 0.68–1.10)	Gann et al.[167]
Male cigarette smokers 50–69 years old	29,133	α-Tocopherol 50 mg every day vs. β-carotene 20 mg vs. both every day vs. placebo every day × 5–8 years	Primary CRC incidence • α-Tocopherol RR = 0.78 (95% CI = 0.55–1.09) • β-Carotene RR = 1.05 (95% CI = 0.75–1.47) Adenoma incidence (analytic cohort = 13,017) • AT RR = 1.66* (95% CI = 1.19–2.32) • BC RR = 0.98 (95% CI = 0.71–1.35)	Albanes et al.,[155] Malila et al.[154]
Postmenopausal women aged 50–79 years	48,835	Dietary modification targeting reductions in dietary fat and increases in fruits, vegetables, and grains × 8.1 years average follow-up	Primary CRC incidence HR = 1.08 (95% CI = 0.90–1.29)	Beresford et al.[142]
Postmenopausal women aged 50–79 years	36,282	Calcium carbonate 500 mg (elemental) + vitamin D3 200 IU BID vs. placebo × 7.0 years	Primary CRC incidence HR = 1.08 (95% CI = 0.86–1.34)	Wactawski-Wende et al.[148]
Postmenopausal women aged 50–79 years with an intact uterus	16,608	Conjugated equine estrogens 0.625 mg + medroxyprogesterone acetate 2.5 mg every day vs. placebo × 5.6 years average follow-up	CRC incidence HR = 0.56* (95% CI = 0.38–0.81) • Greater number of positive lymph nodes (mean = 3.2 vs. 0.8, $P = 0.002$) • More advanced stage = 76.2% vs. 48.5% $P = 0.004$	Chlebowski et al.[179]
French adults (7876 women aged 35–60 years and 5141 men aged 45–60 years	13,017	Ascorbic acid 120 mg + vitamin E 30 mg + β-carotene 6 mg + selenium 100 mcg + zinc 20 mg every day vs. placebo × 7.5 years	Cancer incidence • RR for men = 0.69* (95% CI = 0.53–0.91) • RR for women = 1.04 (95% CI = 0.85–1.29) All-cause mortality: • RR for men = 0.63* (95% CI = 0.42–0.93) • RR for women = 1.03 (95% CI = 0.64–1.63)	Hercberg et al.[158]
Patients 18–80 years of age with a history of basal or squamous cell skin carcinoma	1.312	Selenium 200 mcg every day vs. placebo × 4.5 years	Primary CRC incidence RR = 0.42 (95% CI = 0.18–0.95)	Clark et al.[160]
MODERATELY ELEVATED RISK				
Recent resected adenoma	864	β-carotene 25 mg every day vs. vitamin C 1 g + vitamin E 400 mg every day vs. both vs. placebo × 4 years	Adenoma recurrence • β-Carotene RR = 1.01 (95% CI = 0.85–1.20); • Vitamin C + vitamin E RR = 1.08 (95% CI = 0.91–1.29)	Greenberg et al.[138]
Prior resected adenoma	255	Vitamin A 30,000 IU + vitamin C 1 g + vitamin E 70 mg every day vs. lactulose 20 g every day vs. no treatment × 18 months	Adenoma recurrence significantly different by Kaplan-Meier log rank comparison ($P < 0.0001$) • Vitamins = 5.7%* • Lactulose = 14.7%* • Untreated = 35.9%	Roncucci et al.[157]
Recent resected adenoma	424	Low dietary fat (25% of calories) vs. wheat bran 25 g every day vs. β-carotene 20 mg every day vs. combinations vs. placebo × 4 years	Adenoma recurrence: No significant effect with any of the interventions; Secondary analysis of large adenoma recurrence: low fat + wheat bran combination reduced recurrence,* $P = 0.03$	MacLennan et al. (1995)†
Recent resected adenoma	1429	Wheat bran fiber 13.5 g every day vs. 2 g every day × 5 yrs	Adenoma recurrence adj. OR = 0.88* (95% CI = 0.70–1.11)	Alberts et al.[140]
Recent resected adenoma	2079	Intensive low fat, high fiber, high fruits and vegetable diet vs. no intervention × 4 years	Adenoma recurrence RR = 1.00 (95% CI = 0.90–1.12)	Schatzkin et al.[141]
Recent resected adenoma	665	Calcium gluconolactate/carbonate 2 g every day vs. ispaghula husk 3.5 g every day vs. placebo × 3 years	Adenoma recurrence • Calcium adj. OR = 0.66 (95% CI = 0.38–1.17) • Fiber adj. OR = 1.67* (95% CI = 1.01–2.76)	Bonithon-Kopp et al.[137]

Continued

Table 81-1 Randomized, Controlled Colorectal Neoplasia Prevention Trials—cont'd

Cohort	Sample Size	Intervention	Outcome(s)	Reference
Recent resected adenoma	913	Calcium carbonate 3 g every day vs. placebo × 4 yrs	Adenoma recurrence adj. RR = 0.85* (95% CI = 0.74–0.98)	Baron et al.,[146] Grau et al.[147]
Recent resected adenoma	1285	Ursodeoxycholic acid 8–10 mg/kg/day vs. placebo × 3 years	Adenoma recurrence RR = 0.88 (95% CI = 0.73–1.05) High-grade dysplastic adenoma recurrence RR = 0.61* (95% CI = 0.39–0.96)	Alberts et al.[185]
Recent resected adenoma	272	Lysine acetylsalicylate 160 or 300 mg every day vs. placebo × 1 year	Adenoma recurrence RR = 0.73 (95% CI = 0.52–1.04) Secondary analysis of large adenomas: 83%* reduction, $P = 0.01$	Benamouzig et al.[170]
Recent resected adenoma	1121	Aspirin 81 mg every day vs. 325 mg every day vs. placebo × 3 years	Adenoma recurrence • 81 mg RR = 0.81* (95% CI = 0.69–0.96) • 325 mg RR = 0.96 (95% CI = 0.81–1.13) Secondary analysis for advanced adenoma: • 81 mg RR = 0.59* (95% CI = 0.38–0.92) • 325 mg RR = 0.83 (95% CI = 0.55–1.23)	Baron et al.[168]
Resected early stage colorectal cancer	635	Aspirin 325 mg every day vs. placebo × 3 years	Recurrent adenoma RR = 0.65* (95% CI = 0.46–0.91); Time to first adenoma prolonged HR = 0.64* (95% CI = 0.43–0.94)	Sandler et al.[169]
Recent resected adenoma	2035	Celecoxib 200 mg BID vs. 400 mg BID vs. placebo BID × 36 months	Adenoma recurrence • 200 mg BID RR = 0.67* (95% CI = 0.59–0.77) • 400 mg BID RR = 0.55* (95% CI = 0.48–0.64) Advanced adenoma recurrence: • 200 mg BID RR = 0.43* (95% CI - 0.31–0.61) • 400 mg BID RR = 0.34* (95% CI = 0.24–0.50)	Bertagnolli et al.[174]
Recent resected adenoma	1561	Celecoxib 400 mg every day vs. placebo × 3 years	Adenoma recurrence: RR = 0.64* (95% CI = 0.56–0.75) Advanced adenoma recurrence: RR = 0.49* (95% CI = 0.33–0.73)	Arber et al.[175]
Recent resected adenoma	2587	Rofecoxib 25 mg every day vs. placebo × 3 years	Adenoma recurrence RR = 0.76* (95% CI = 0.69–0.83) Advanced adenoma recurrence reduced* ($P < 0.01$)	Baron et al.[177]
EXTREMELY ELEVATED RISK				
FAP with prevalent adenomas	10 (crossover design)	Sulindac 300 mg every day vs. placebo × 4 months	Complete or near complete CR adenoma regression Sulindac: 9 vs. placebo 0 (increase in 5, stable disease in 2, relative reduction in 2)*, $P < 0.01$	Labayle (1991)[‡]
FAP with prevalent adenomas	22	Sulindac 150 mg BID vs. placebo × 9 months	CR polyp number: 56%* reduction, $P = 0.014$; CR polyp diameter: 65%* reduction, $P < 0.001$	Giardello et al.[164]
FAP with prevalent adenomas	24	Sulindac vs. placebo × 6 months	CR polyp number: significantly reduced, $P = 0.01$ Duodenal polyp number: trend toward reduction, $P = 0.12$	Nugent (1993)[§]
FAP with prevalent adenomas	77	Celecoxib 100 mg BID vs. 400 mg BID vs. placebo × 6 months	Mean number of adenomas: 28%* reduction, $P = 0.003$ Polyp burden: 30.7%* reduction, $P = 0.001$	Steinbach et al.[173]
Genotype + phenotype: FAP patients 8–25 years old	41	Sulindac 75 or 150 mg BID vs. placebo × 48 months	Adenoma incidence: sulindac = 43% vs. placebo = 55%, $P = 0.54$; mean number or size of adenomas: no significant differences	Giardiello et al.[166]

CRC, colorectal cancer; CI, confidence interval; HR, hazard ratio; OR, overall risk; RR, relative risk.

[†]MacLennan R, Macrae F, Bain C, et al: Randomized trial of intake of fat, fiber, and beta carotene to prevent colorectal adenomas: The Australian Polyp Prevention Project. J Natl Cancer Inst 1995;87:1760–1766.

[‡]Labayle D, Fischer D, Vielh P, et al: Sulindac causes regression of rectal polyps in familial adenomatous polyposis. Gastroenterology 1991;101:635–639.

[§]Nugent KP, Farmer KC, Spigelman AD, et al: Randomized controlled trial of the effect of sulindac on duodenal and rectal polyposis and cell proliferation in patients with familial adenomatous polyposis. Br J Surg 1993;80:1618–1619.

men and in healthy individuals with low antioxidant levels at baseline.[158,159]

Selenium has been reported to reduce CRC incidence by as much as 58% in a phase III trial that enrolled 1312 persons with a history of skin cancer randomized to selenium versus placebo.[160] After an average of 6.4 years follow-up and on the basis of a total of 27 cases, the effect on colorectal cancer was reported, albeit as a secondary endpoint, suggesting only that additional investigation is probably warranted.

Cyclooxygenase Inhibitors (Nonsteroidal Anti-Inflammatory Drugs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been investigated for their chemopreventive effects in animals for more than 25 years on the basis of the promotional effects of prostaglandins on carcinogenesis. More than 40 retrospective and prospective observational studies have consistently shown that NSAID use (especially aspirin, based merely on the frequency of its use in the population) is associated with approximately 50% reductions in colorectal adenoma incidence, CRC incidence, and CRC-associated mortality as compared with nonuse.[161] The mechanisms underlying the efficacy of NSAIDs are probably numerous. Cyclooxygenase (COX) exists as two isoforms, COX-1 and COX-2, which transform arachidonic acid into a variety of bioactive prostanoids. COX-1 plays a housekeeping role in a variety of tissues, but COX-2 is induced in response to a variety of stimuli and is commonly found overexpressed in a wide variety of tumors. In neoplastic tissues, COX-2 activity induces cellular proliferation and neoangiogenesis and blocks apoptosis and immune responses, thus promoting neoplastic progression. By blocking COX activity and possibly by a variety of non-COX effects as well, NSAIDs and COX-2 selective inhibitors inhibit colorectal carcinogenesis. For example, COX-2 is overexpressed in nearly 50% of colorectal adenomas and 80% to 85% of adenocarcinomas, whereas it is rarely expressed in normal colorectal epithelium.[162] COX-2 overexpression appears to be functionally important for neoplastic progression, as suggested by the lower incidence of intestinal polyps in mice lacking a functional COX-2 gene.[163]

In terms of randomized, controlled trials, sulindac treatment resulted in a significant reduction in adenoma prevalence after 6 months of administration in patients with FAP, although long-term efficacy is more limited.[164,165] Initial suppression of adenomas with sulindac in prephenotypic FAP patients has not proven successful.[166]

The only randomized evaluation of NSAIDs against CRC incidence comes from a secondary analysis of the Physicians' Health Study, which randomized 22,071 U.S. male physicians to aspirin 325 mg every other day versus placebo for an average of 5 years.[167] Somewhat surprisingly, aspirin did not reduce CRC or in situ colorectal cancers significantly. This null effect has been attributed variously to the cohort (i.e., average risk male physicians), the lack of uniform colorectal surveillance guidelines, the limited dose and duration of aspirin, and, most important, the limited duration of follow-up relative to the long natural history of colorectal carcinogenesis. Subsequently, the same or higher doses of aspirin were evaluated in three placebo-controlled trials in patients with prior colorectal adenomas or carcinoma, and statistically significant reductions in recurrent adenomas were reported after 1 or more years.[168–170] Sandler and colleagues randomized 635 CRC survivors to aspirin (325 mg/day) versus placebo and reported a significant reduction in patients with incident adenomas and a delay in the time to a first adenoma.[169] Baron and colleagues randomized 1121 patients with prior colorectal adenomas to aspirin (81 or 325 mg/day) versus placebo and reported a 4% to 19% reduction in the number of people with a recurrent adenoma and a 17% to 41% reduction in advanced adenomas.[168] Finally, interim results from Benamouzig and colleagues' trial involving 272 patients with prior adenomas noted a significant reduction in recurrent adenomas as well.[170] Recent data suggest that aspirin might be most effective in individuals with a high body mass index.[171] Although these efficacy results are consistent and compelling, aspirin use is associated with significant risks of gastrointestinal ulceration and hemorrhagic stroke; therefore, the U.S. Preventive Services Task Force does not currently recommend it as a strategy for CRC risk reduction in average-risk individuals.[172]

In an effort to improve the therapeutic index of COX inhibitors for CRC risk reduction, COX-2-selective inhibitors (e.g., celecoxib, rofecoxib) have been evaluated for their efficacy and safety in a variety of clinical settings. Celecoxib administered for 6 months to 83 individuals with FAP produced significant reductions in colorectal adenoma number and size, with a side effect profile comparable to that of placebo.[173] These data prompted the U.S. Food and Drug Administration (FDA) in 2000 to approve celecoxib to complement the standard care (i.e., surveillance and prophylactic surgery) of patients with FAP. In patients with prior sporadic adenomas, celecoxib was associated with an approximate 40% and 66% reduction in recurrent colorectal adenomas and advanced adenomas, respectively, in two recent placebo-controlled trials of 3 years' duration.[174,175] Despite this profound efficacy, celecoxib use was also associated with an elevated risk for serious cardiovascular events in these trials (i.e., twofold to threefold higher rates of CV-associated death, myocardial infarctions, unstable angina, heart failure, or stroke).[176] A placebo-controlled trial of rofecoxib 25 mg/day in 2587 patients with prior colorectal adenomas reported a significant 24% reduction in recurrent adenomas and greater efficacy against advanced adenomas but an increased risk of serious cardiovascular events, leading to its eventual withdrawal from the marketplace.[177] Therefore, additional work to verify these data and to understand the mechanisms underlying the efficacy and safety of COX-2-selective inhibitors are needed before this strategy can be pursued further for average-risk individuals.

Postmenopausal Hormone Replacement

A meta-analysis of 18 observational studies suggested that the use of hormone replacement therapy in postmenopausal women reduced the development of colon cancer by approximately 20%.[178] Subsequently, a large randomized controlled trial of estrogen + progesterone in postmenopausal women participating in the Women's Health Initiative demonstrated a 44% reduction in colorectal cancer incidence[179]; however, incident cancers in those using hormone replacement therapy were more advanced, with more nodal involvement. In addition, women who were treated with estrogen alone did not experience a similar reduction in incidence. Furthermore, the Women's Health Initiative identified several safety concerns associated with estrogen and progesterone therapy, including a 26% increase in invasive breast cancer, a 29% increase in cardiac events, a 41% increase in strokes, and a twofold increase in thromboembolic events.[180]

Ursodeoxycholic Acid

Unconjugated fecal bile acids are mutagenic and cytotoxic to the colorectal epithelium, possibly promoting the transformation of adenomatous lesions to invasive carcinoma.[181] Deoxycholic acid, a secondary bile acid, stimulates colorectal epithelial proliferation in animal models and serum levels correlate with rectal mucosal proliferation in humans.[182] Interestingly, other reports suggest that ursodeoxycholic acid, a noncytotoxic, hydrophilic epimer of chenodeoxycholate, reduces the mucosal concentrations of phospholipase A2 at the messenger RNA and protein levels, and thereby, the concentrations of mucosal prostaglandin E_2 and 6-keto prostaglandin $F_{1\alpha}$, as well as the incidence of aberrant crypt foci in azoxymethane-exposed rats.[183] Thereafter, ursodeoxycholic acid reduced carcinogen-induced colorectal adenomas and carcinomas in a rat model[184] and was subsequently tested in a phase III, placebo-controlled, randomized clinical trial involving 1285 individuals with a past adenoma.[185]

After 3 years of treatment, ursodeoxycholic acid resulted in a statistically insignificant 12% reduction in recurrent adenomas and a statistically significant 39% reduction in adenomas with high-grade dysplasia.

Statins

3-Hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (or statins) have been associated with a significant 50% reduction in colorectal cancer risk in a well-conducted, population-based case-control study,[186] but other studies, including a meta-analysis of placebo-controlled trials evaluating statins for their potential to reduce cardiovascular risks, have not reported any significant effects—positive or negative—of statins on CRC risk.[187]

Future Directions

There are many promising preventive interventions based on preclinical mechanistic screens, animal models of colorectal carcinogenesis, and/or observational studies. Examples include NSAID derivatives (e.g., nitric oxide-donating NSAIDs); selected dietary components such as omega-3 fatty acids, curcumin, and quercetin; peroxisome proliferator-activated receptor agonists; physical activity; and possibly targeted therapeutics with infrequent or minimal toxicities. For instance, in a small, uncontrolled trial involving five FAP patients, a combination of curcumin and quercetin given over 6 months was recently reported to reduce both polyp number and size by 50% to 60%.[188] Ongoing placebo-controlled trials are evaluating the effects of folate, vitamin D, and various NSAID-based combinations. Trials evaluating combinations of chemopreventive agents in particular hold great promise based on the inherent molecular complexity of colorectal carcinogenesis and preclinical data suggesting synergistic efficacy.[189–191] Preliminary clinical studies of complex combinations have recently been reported.[192]

DIAGNOSIS AND STAGING OF COLON CANCER

Colon cancer is usually quite insidious in its development. Asymptomatic patients are suspected of having colon cancer because of anemia or a positive fecal occult blood test that is found during routine physical exam. With increasing awareness of the benefits of screening colonoscopy, cancer could be discovered at the time of this examination. Symptomatic patients might relate episodes of bleeding per rectum (hematochesia) or increased frequency of bowel dysfunction—constipation or diarrhea and/or vague abdominal discomfort. Weight loss is less common unless disease is advanced, but fatigue is frequent. On occasion, the degree of anemia can be severe enough to produce cardiac ischemic symptoms in patients with occult coronary artery disease and syncope, which leads to the finding of anemia and evidence of bleeding from the colon tumor. On occasion, patients present with hypokalemia secondary to diarrhea from large villous tumors producing excess mucous.

Fatigue and anemia are symptoms that are associated with right-sided lesions. Gross bright red blood per rectum, increasing constipation, and cramping abdominal pain are symptoms that suggest a left-sided lesion. Advanced tumors can present with symptoms that are indicative of extension to other organs, such as the bladder (pneumaturia). A perforated colon cancer must always be considered when the patient presents emergently with abdominal free air and diffuse peritonitis. At times, the emergent status presents the surgeon with the difficult task of differentiating between an inflammatory mass secondary to a perforated colon cancer of the sigmoid colon or upper rectum and a perforated diverticulitis. Obstruction, however, is the most common acute problem requiring emergency surgery for colon cancer (with an incidence of approximately 30%). Although obstruction almost always occurs secondary to the tumor that is obstructing the lumen, the tumor can cause intussusception in the adult.

The diagnosis of colon cancer is best established by colonoscopy. Colonoscopy provides direct visualization, a fairly accurate determination of location, and the opportunity to obtain tumor tissue for histologic evaluation. There are two issues to keep in mind during the course of evaluating the patient with suspected colon cancer. The first is the possibility of a second occult primary cancer (approximately 5%); the second is the presence of additional polyps (approximately 20% to 40% probability), which must be cleared or tattooed so that they can be dealt with at the time of surgery. When it is not possible to complete colonoscopy to the ileocecal valve, air-contrast barium enema and virtual colonoscopy are options for completing the evaluation of the colon.

Laboratory Evaluation

The goal in preoperative evaluation of the patient who is newly diagnosed with colon cancer is to determine whether comorbid conditions exist that could affect perioperative morbidity and mortality. The standard laboratory evaluation includes a hemogram, evaluation of clotting capacity, liver injury and renal function tests, fasting blood sugar, electrolytes, a urinalysis, and measurement of carcinoembryonic antigen (CEA) level. Other laboratory studies are determined by a careful history of past medical problems and a thorough system review.

Imaging Modalities for Staging of Colon Cancer

The use of imaging for the staging of colon cancer can be divided into two broad categories: (1) detection and staging of the primary tumor and (2) determination of the extent of metastatic disease. For the detection of the primary cancer and of polyps greater than 1.0 cm in diameter, conventional single- and double-contrast barium enema has been used for many years. With the advent of helical computed tomography (CT) scanning, CT colonography has been used for screening for polyps and other masses (Figs. 81-6 and 81-7), and more recently, some investigators are examining techniques for magnetic resonance imaging (MRI) colonography. For the staging of potential extracolonic metastatic disease, ultrasound, CT, MRI, and positron emission tomography (PET) have been used with varying levels of success.[193,194]

Barium Enema

Until the advent of modern colonoscopy, barium enema was considered the mainstay for detection of large colonic polyps and colon

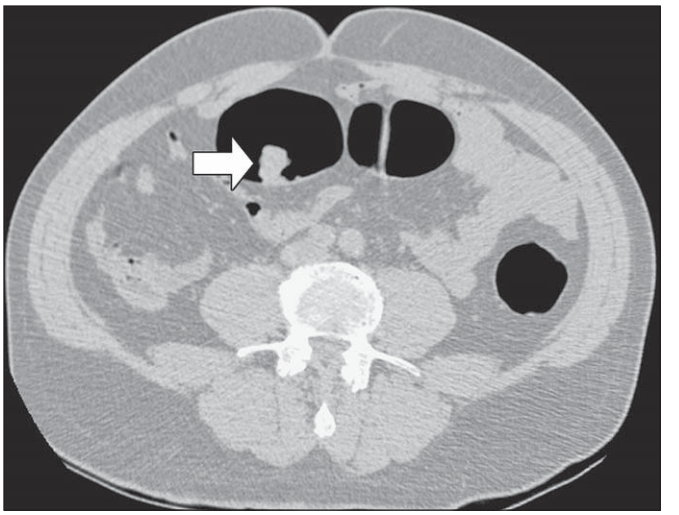


Figure 81-6 • Nonenhanced CT image (source data for a virtual colon examination) demonstrates a large pedunculated polyp in the transverse colon (*arrow*). This was later proven to contain colon carcinoma.

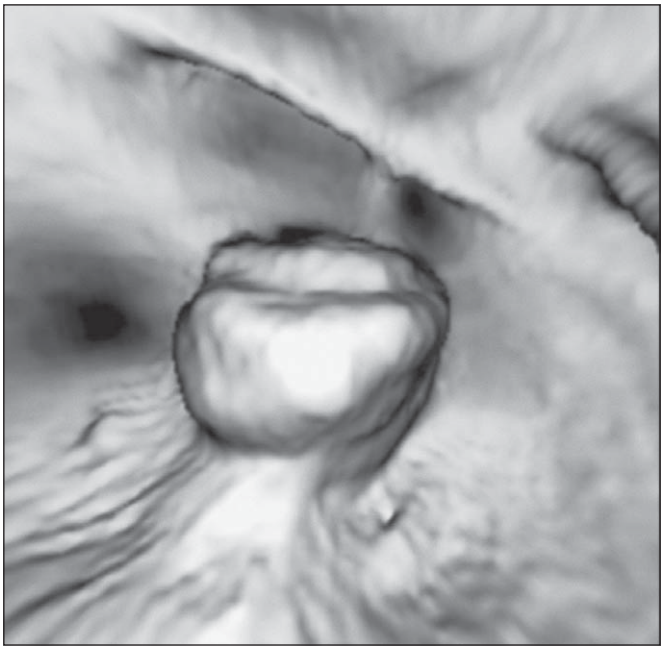


Figure 81-7 • Surface-rendered three-dimensional reconstruction of the polyp seen in Figure 81-6. Primary three-dimensional image interpretation is now available. When combined with an appropriate software platform, "fly-through" examinations that mimic the views obtained by conventional video-assisted colonoscopy are now possible.

cancer (Fig. 81-8). Single-contrast barium enema uses a continuous column of barium injected in a retrograde fashion, and double-contrast barium enema uses a thicker barium mixture that adheres to the colonic mucosa, resulting in a mucosal relief image. For small polyps, double-contrast studies are generally considered to have a higher sensitivity than single-contrast enemas. Regardless of the technique, barium enema is not as sensitive or specific as colonoscopy for colonic pathology and should be chosen as the initial screening test only for patients in whom colonoscopy has failed, who are at high risk for complications from colonoscopy, or for whom colonoscopy is not available.[195] Barium enema has no role in determining the extent of colonic wall invasion by colon cancer, lymph node involvement, or distant disease in patients who are at high risk for metastases.

Ultrasound

Conventional transcutaneous ultrasound plays no role in the detection of primary colonic tumors. Because the liver can be imaged by transcutaneous ultrasound with varying degrees of success, ultrasound has been used to screen the liver for signs of metastatic disease in patients with known colon cancer. In addition, liver metastases often are found incidentally when sonography is used in patients who present with vague gastrointestinal symptoms or for other reasons. In studies performed on North American patients, the sensitivity of hepatic ultrasound is not sufficient for it to be used as a sole modality for screening or as a preoperative evaluation in patients who are to undergo primary tumor resection or hepatic metastasectomy.[196] The sensitivity for detection of liver metastases appears to improve substantially when contrast-enhanced ultrasound techniques are used. In one multicenter study, the sensitivity improved from 71% to 87% with the addition of contrast material.[197] However, ultrasound contrast agents are not available for routine clinical use in the United States, although they are available and widely used in Europe. Ultrasound is the modality of choice for liver biopsy for most hepatic masses (Fig. 81-9) owing to its low cost, real-time imaging, and excellent needle-guidance systems.[198,199]

Intraoperative Ultrasound (Open and Laparoscopic)

Intraoperative ultrasound is considered the most sensitive and specific imaging test for detection of hepatic metastases from colon cancer (Fig. 81-10). It is far more sensitive for the detection of metastatic lesions than are inspection and palpation of the liver by the surgeon, particularly for deep tumors.[200,201] Liver metastases as small as 3.0 mm can be detected routinely by intraoperative ultrasound.[202] Additional advantages of intraoperative ultrasound are its ability to guide biopsies of suspicious hepatic lesions and its use as an aid in both liver resection planning and guiding tumor ablation (e.g., cryoablation or radiofrequency ablation; Fig. 81-11). Intraoperative ultrasound has a very limited role in the evaluation of extrahepatic metastases from colon cancer because of the highly targeted nature of the examination. Occasionally, retroperitoneal lymph nodes and other metastatic deposits can be imaged if specific abnormalities are noted on preoperative imaging or if an abnormality is noted during inspection and palpation of the abdomen.

Laparoscopic ultrasound can be used for the same purposes as open intraoperative ultrasound of the liver. Owing to lack of access to some areas of the liver, the sensitivity of laparoscopic ultrasound appears to be slightly less than that of open intraoperative ultrasound, but laparoscopic ultrasound has the advantage of being a less invasive approach.[203] This is particularly useful in patients who have a high likelihood of unresectable liver disease or peritoneal disease or in patients who are to undergo another minimally invasive treatment for known liver metastases, such as tumor ablation.

Computed Tomography

Contrast-enhanced helical CT is considered the mainstay of preoperative imaging of colon cancer patients. CT combines a high

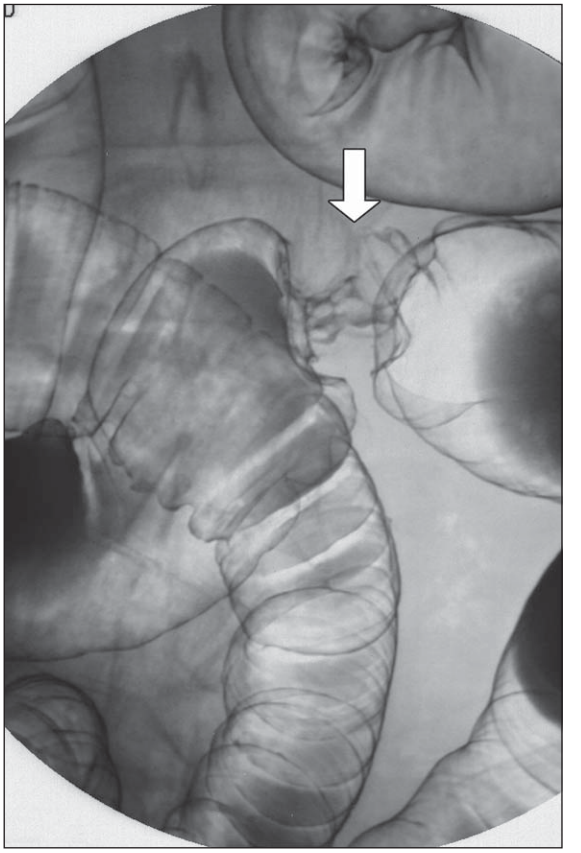


Figure 81-8 • Double-contrast barium enema demonstrates circumferential luminal narrowing with mucosal destruction (*arrow*) due to colon carcinoma, the so-called apple core lesion.

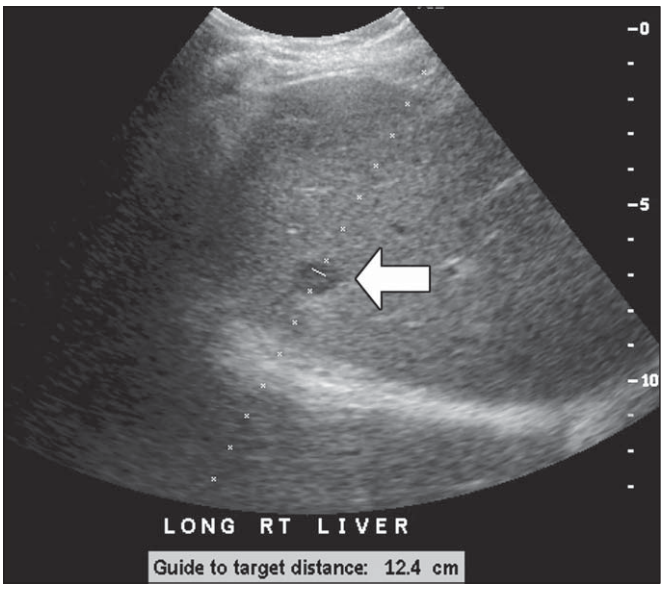


Figure 81-9 • Ultrasound-guided biopsy of the liver lesion with small right lobe metastatic tumor (*arrow*) from a primary colon carcinoma. Note the needle guidance software that predicts the path of the biopsy needle before its deployment through a fixed guide. This procedure can also be performed freehand without the use of a guide. Ultrasound-guided biopsy has been found to be both efficient and cost-effective in comparison with other modalities owing to the real-time capability and low cost of ultrasound.

sensitivity for the detection of lung and liver metastases with availability, safety, and the ability to aid in the detection of peritoneal disease and metastatic lymph nodes. The sensitivity of CT is low, however, for abnormalities that adhere to peritoneal and visceral surfaces, such as peritoneal carcinomatosis. An added advantage of CT as a preoperative imaging modality for hepatic surgery is that CT

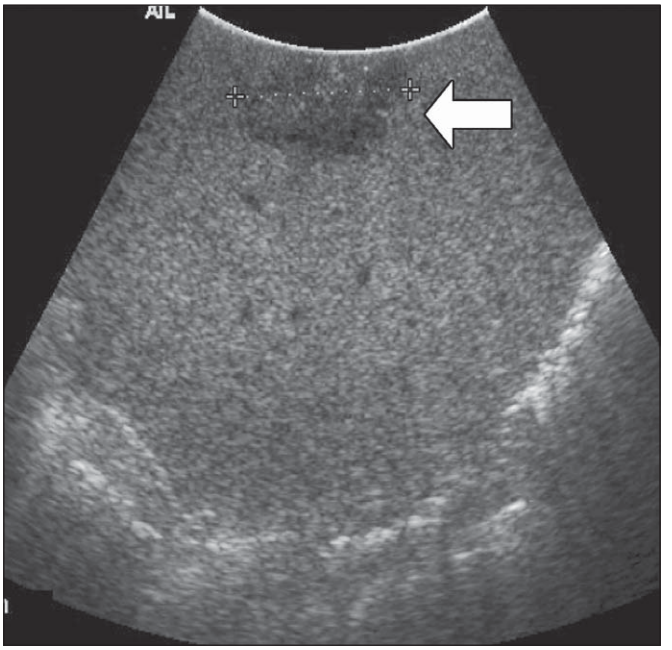


Figure 81-10 • Intraoperative ultrasound of right lobe liver metastasis in a patient with known colon cancer. Note the high-quality ultrasound images that are possible with intraoperative ultrasound (*arrow*). Tumors as small as 3.0 mm are detected routinely with this technique.

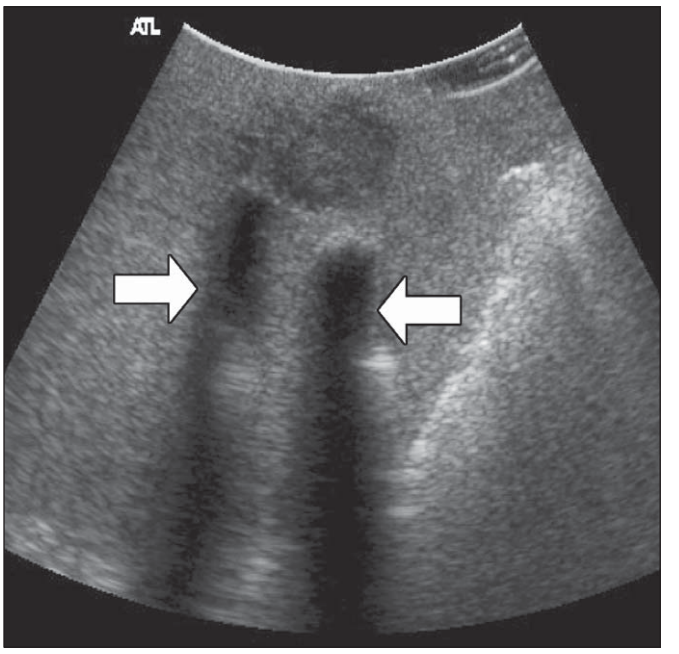


Figure 81-11 • Intraoperative ultrasound of the liver during cryoablation. The right lobe hepatic metastasis in Figure 81-10 has undergone cryoablation with formation of an iceball superimposed over the tumor. Ice does not conduct sound, hence the lack of information from within the iceball and the posterior acoustic shadowing. Two cryoablation probes are also visible (*arrows*) with acoustic shadows.

angiography can be obtained at the same time as a conventional diagnostic CT (Figs. 81-12 through 81-15). This can be important in screening for hepatic arterial and venous anomalies prior to hepatic resection or if the surgeon is considering inserting a hepatic artery infusion pump. CT angiography is an excellent modality for determining the hepatic arterial, portal venous, and hepatic venous anatomy and for assessing variants of these vessels.[204]

CT technology recently has undergone major changes due to the introduction of multidetector row helical CT scanners. Currently, 64-channel scanners are becoming increasingly available. These

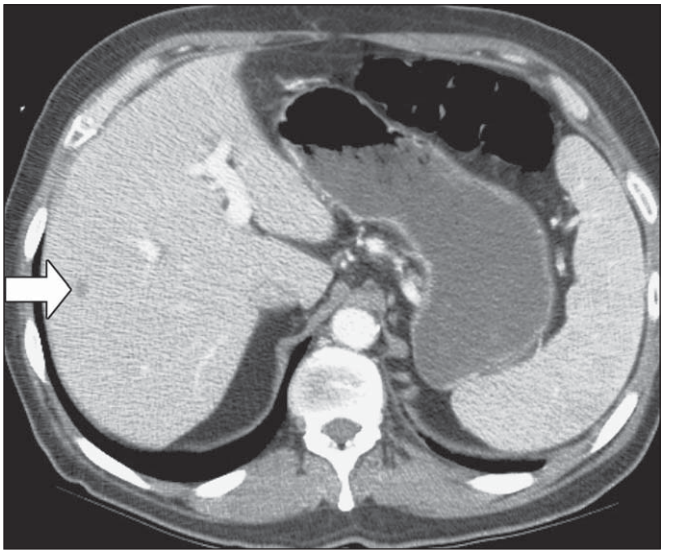


Figure 81-12 • Helical CT image of the liver after intravenous contrast injection demonstrates a liver lesion (*arrow*) in Figure 81-9.

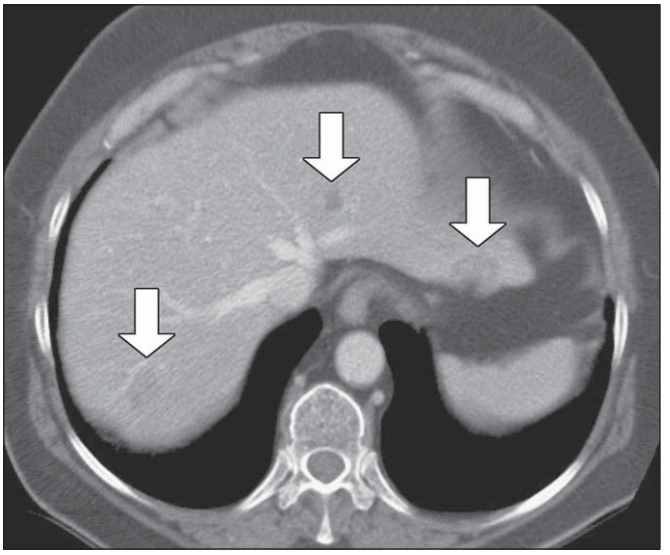


Figure 81-13 • Helical CT image of the liver after intravenous contrast in patient shown in Figure 82-10. Three low-attenuation hepatic metastases are visible (*arrows*).

scanners can reconstruct image data with thicknesses as low as 0.5 mm. Unfortunately, although the thin slices that are possible with multidetector row CT are likely to increase sensitivity for the detection of hepatic metastases, there is a paucity of data comparing single-detector row to multidetector row helical CT or comparing multidetector row scanners that have fewer detector rows (4 to 32) to 64 row scanners. Recent data for detection of colon cancer metastases using single-detector row CT demonstrate sensitivities on the order of 85% and specificities approaching 96%, but this sensitivity greatly decreases for metastases smaller than 1.0 cm.[205,206] A recent meta-analysis of 15 studies using helical CT of various detector row configurations yielded an overall sensitivity of 64.7%.[207]

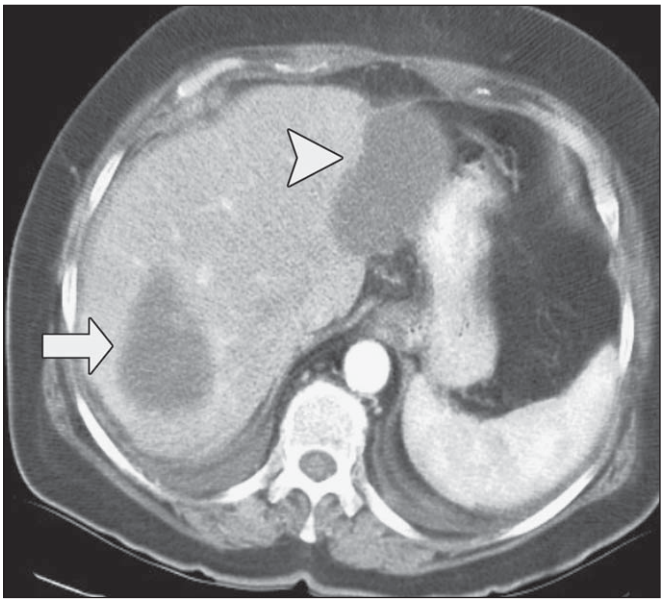


Figure 81-14 • Helical CT image of the liver after intravenous contrast in the same patient shown in Figure 81-10. This postoperative image demonstrates a small hematoma after a left lobe hepatic resection (*arrowhead*) and typical postcryoablation changes of the right hepatic lobe tumor (*arrow*).

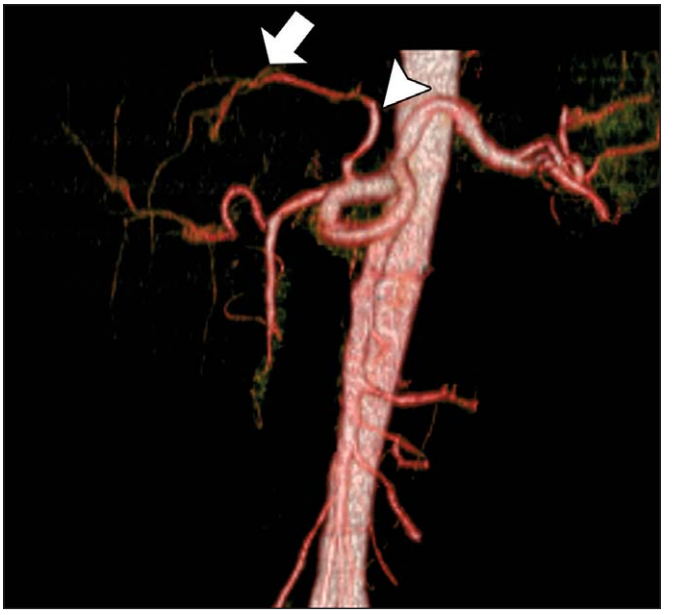


Figure 81-15 • CT angiogram of the abdominal vasculature shows a replaced left hepatic artery (*arrow*) arising from the left gastric artery (*arrowhead*). CT angiogram can be a valuable preoperative screening tool to evaluate hepatic arterial, portal venous, and hepatic venous anatomy.

Magnetic Resonance Imaging

Compared with CT, MRI is probably slightly more sensitive and specific for detection and characterization of colon cancer metastases in the liver.[207–209] On the other hand, the long scan times, the relatively high degree of image artifacts, the lack of availability of MRI scanners and scan time, questions about the ability of MRI to detect bowel abnormalities and other evidence of extraperitoneal disease, and the increased expense of MRI combine to limit the use of MRI for the routine preoperative staging of colon cancer. Indications for preoperative MRI (rather than or in addition to CT) for colon cancer include an inability to tolerate conventional iodinated contrast materials (renal insufficiency or allergies) and further clarification of abnormalities that were detected at CT. Recently, gadolinium-enhanced fat saturation MRI, particularly when combined with delayed imaging, has shown promise in identifying even very thin, "sheetlike" peritoneal tumor involvement.[210] MRI is specifically indicated in evaluating patients with central nervous system symptoms to determine the presence of metastases and in evaluating difficult to image pelvic wall recurrences.

Most colon cancer metastases show high signal intensity on T_2-weighted images compared with background liver (Fig. 81-16) and low signal intensity on T_1-weighted images. Rapid gradient-echo pulse sequences are now available that allow imaging of the entire liver in a single breath-hold. When combined with a bolus injection of gadolinium-based contrast agents, information similar to that derived from contrast-enhanced CT scanning can be obtained, which aids in lesion characterization. New liver-specific contrast materials have recently become available for clinical use. These agents are based on targeting of either hepatocytes (gadobenate dimeglumine, gadoxetic acid, mangafodipir trisodium) or the reticuloendothelial cell system (superparamagnetic iron oxides).[211] Several studies have demonstrated increased sensitivities for the detection of liver metastases for MRI enhanced with these targeted agents, but their increased expense, the complicated delivery methods, and lack of availability of MRI time have hampered the routine use of these compounds.[209,210]

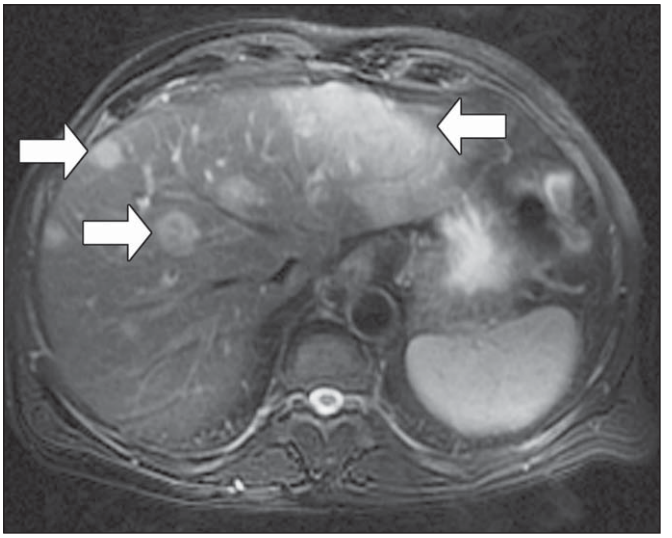


Figure 81-16 • Axial MRI (T_2 with fat suppression) demonstrating rounded high-intensity metastatic lesions (*arrows*) throughout the liver in a patient with known colon cancer primary.

Fluorodeoxyglucose Positron Emission Tomography

The advent of fluorodeoxyglucose positron emission tomography (FDG-PET) imaging has been a huge advance in triaging patients who are potential candidates for surgery. The main value of PET imaging has been in the detection of small-volume, extrahepatic metastatic disease. Compared with CT imaging, PET has a lower sensitivity for the detection of hepatic metastases but a higher sensitivity for extrahepatic metastases.[212] Therefore, many centers now use a combination of CT and PET scanning to stage patients prior to potential hepatic resection. This can be accomplished with dedicated PET/CT machines that decrease misregistration artifacts and allow precise localization of areas of increased glucose metabolism or with CT and PET performed at different settings (Figs. 81-17 and 81-18).[213] The use of a dedicated PET/CT strategy increased the accuracy of staging from 78% to 89% on a patient-by-patient basis.[214] Overall, the sensitivity of PET for detecting recurrent tumor throughout the body is in the range of 92% to 95%.[207,215]

Table 81-2 Sensitivity of Imaging for Detection of Hepatic Metastases

Modality	Detection Rate for Individual Metastases (%)
Transabdominal sonography	40–70
Noncontrast CT	50
Nonspiral contrast-enhanced CT	60–75
Spiral contrast CT (single detector)	90–92
MRI	80–90
CT arterial portography	85–95
Intraoperative ultrasound	90–96

Adapted from Paulson EK: Evaluation of the liver for metastatic disease. Sem Liver Dis 2001;21:225–236.

In detection of extrahepatic disease, the increased sensitivity of PET compared with CT often has changed patient management (29% to 40% of cases).[216,217] Patients who might otherwise be considered candidates for potentially curative resection but who have retroperitoneal metastases identified by FDG-PET may be referred for systemic chemotherapy and spared the complications and risks of surgical procedures that will not be curative. The uptake of FDG in colorectal cancers could also hold prognostic significance. In one study, patients with low FDG uptake in metastases of colorectal cancer (standardized uptake values < 4.26) had longer median survivals (32 months) than did patients with high FDG uptake (19 months).[218] Table 81-2 compares the various methods of imaging and their relative sensitivities with regard to the detection of hepatic metastases.[219]

Staging

The anatomic extent of disease at presentation (stage) is the strongest predictor of survival for patients with colorectal cancer and forms the basis of appropriate patient management. The Tumor, Node, Metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC)[220] and the International Union Against Cancer[221] is considered the international standard for colorectal cancer staging.[222] In contrast to other staging systems for colorectal cancer, the TNM

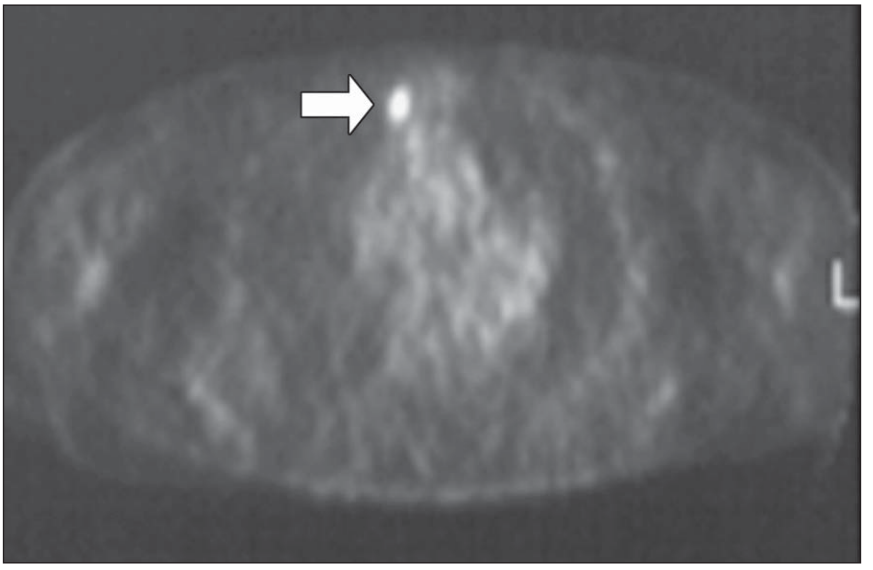


Figure 81-17 • PET image of the chest in a patient with colon carcinoma. The patient was being evaluated for a hepatic resection. PET imaging unexpectedly showed a lesion in the chest wall (*arrow*), which changed management from hepatic metastectomy to systemic chemotherapy.

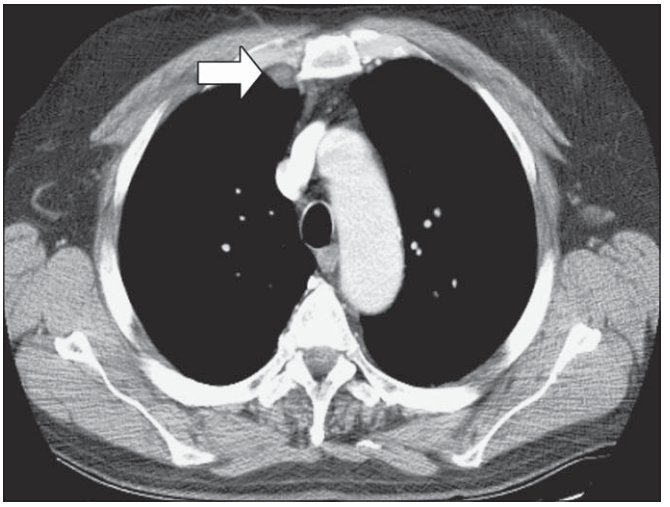


Figure 81-18 • Helical CT image of the chest (same patient as in Fig. 81-17) demonstrates the small chest wall metastasis (*arrow*).

system is continuously updated on the basis of existing data, multidisciplinary in design, allowing for the incorporation of all technologic approaches to staging, and has a comprehensive set of rules of application that ensure uniform use. The predictive accuracy of TNM staging can be increased through incorporation of validated prognostic features, such as lymphatic or venous invasion, into the overall assessment process. (Table 81-3; Fig. 81-19).

In the TNM system, the designation "T" refers to the local extent of the untreated primary tumor, "N" to the status of the regional lymph nodes, and "M" to distant metastatic disease at the time of diagnosis and initial workup. The prefix "p" is used to denote the pathologic determination of a staging parameter (i.e., T, N, or M), as contrasted with the clinical determination, which is designated by "c." By convention, pathologically assigned T and N parameters are considered more accurate than clinically assigned parameters but require a resection of the primary tumor or biopsy that is adequate to evaluate the highest pT category and nodes that are adequate to validate lymph node metastasis, respectively. Assignment of M0, signifying a global determination of the absence of distant metastasis anywhere in the body, is impossible by pathologic means. Therefore, pM0 is not part of the TNM staging system. A pM1 designation, however, is assigned when any distant metastasis is confirmed by tissue or cytologic examination. Clinical classification (cTNM) is based on evidence acquired through a variety of techniques that include but are not limited to physical examination, radiologic imaging, endoscopic examination, biopsy, and surgical exploration. Clinical staging is carried out during initial evaluation of the patient before any cancer-directed therapy is initiated and, once assigned, is not changed in the medical record on the basis of subsequent information, remaining as documentation of the basis for treatment planning. It may be revised only if more accurate clinical information becomes available (e.g., higher-resolution imaging studies) before initiation of treatment or before making the decision not to treat the patient. Stage evaluation continues through the first course of surgery or 4 months following presentation, whichever is longer. Staging ends at the time of diagnostic workup if a decision is made not to treat the patient or if pathologic classification is not possible. When pathologic staging information becomes available following surgical resection, a combined pathologic and clinical stage (typically pT, pN, cM) can be constructed.

The definitions of the individual TNM categories and stage groupings and stage-related survival are shown in Figure 81-19, and comparisons of the TNM system to other historical staging systems are shown in Table 81-3.

All tumors should be verified microscopically as carcinomas to confirm the appropriateness of TNM staging, which applies only to

Table 81-3 Surgical Stage and Survival Rates in Colorectal Cancer

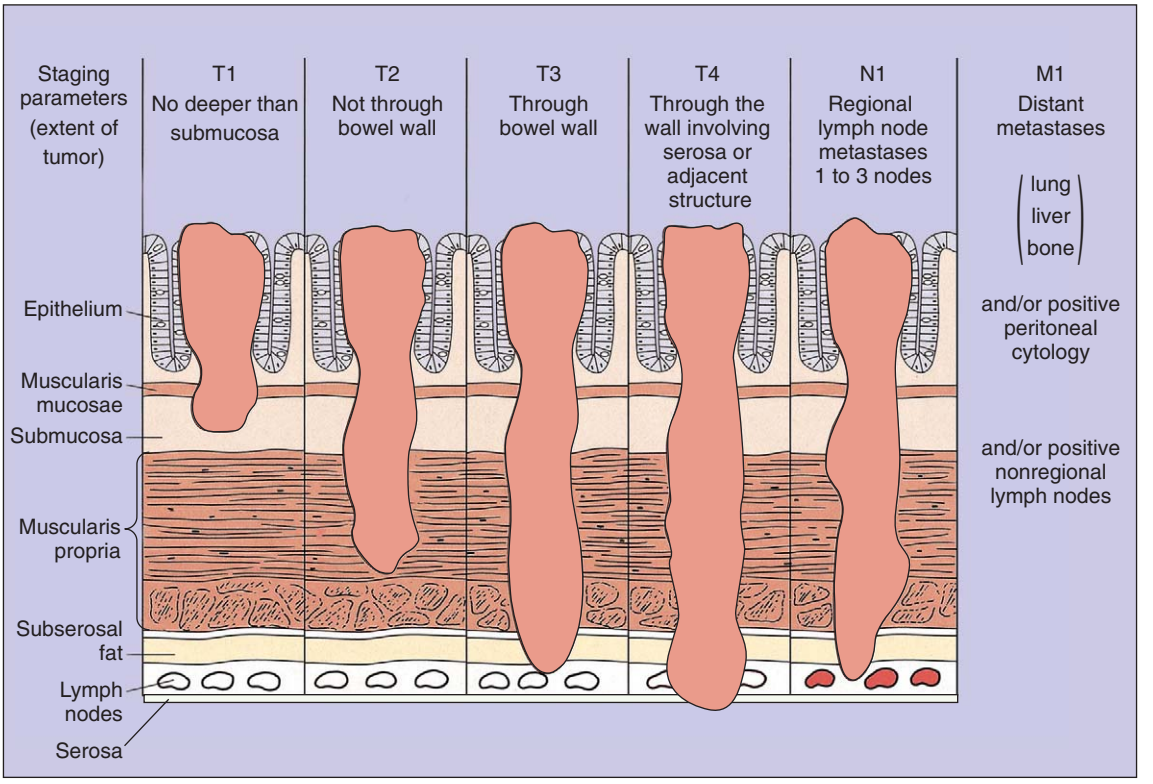
AJCC/UICC CANCER STAGING*							
AJCC/UICC Cancer Stage	**Tumor**	**Regional Lymph Nodes**	**Distant Metastases**	**Comparison to Dukes and MAC Classifications**	**Astler, Coller†**	**Comparison to SEER**	**5-Year Survival Rates (%)‡**
Stage 0	Tis	N0	M0	—	Limited to mucosa	In situ	
Stage I	T1	N0	M0	Dukes A, MAC A	Extending into submucosa	Localized	
	T2	N0	M0	Dukes A, MAC B1	Extending into muscularis propria	Localized	93.2
Stage IIA	T3	N0	M0	Dukes B, MAC B2	Extending through muscularis propria	Regional	84.7
Stage IIB	T4	N0	M0	Dukes B, MAC B3			72.2
Stage IIIA	T1–T2	N1	M0	Dukes C, MAC C1	Limited to bowel wall with involved nodes	Regional	83.4
Stage IIIB	T3–T4	N1	M0	Dukes C, MAC C2-C3	Extension through bowel wall with involved nodes	Regional	64.1
Stage IIIC	Any T	N2	M0	Dukes C, MAC C1-C2-C3		Regional	44.3
Stage IV	Any T	Any N	M1	—, MAC D	Distant metastases	Distant	8.1

MAC, modified Astler-Coller.

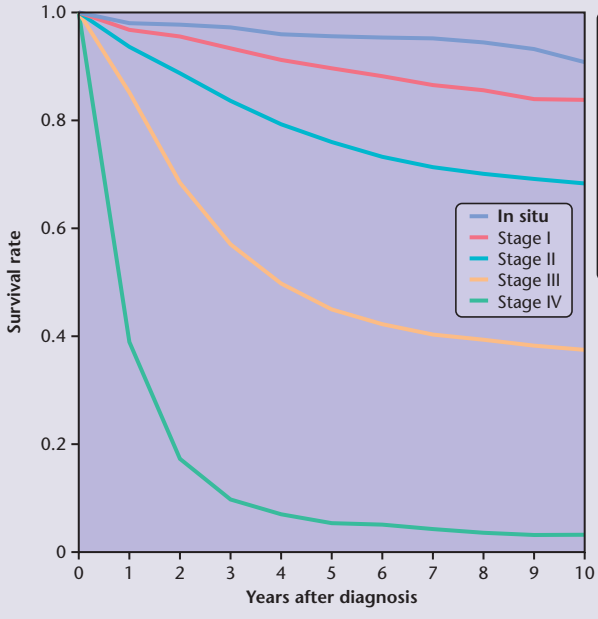
*Greene FL, Page, DL, Fleming ID, et al (eds): Colon and rectum. In American Joint Committee on Cancer: AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002, pp 113–119.

†Astler VB, Coller FA: The prognostic significance of direct extension of carcinoma of the colon and rectum. Ann Surg 1954;139:846.

‡O'Connell JB, Maggard MA, Ko CY: Colon Cancer Survival Rates with the New American Joint Committee on Cancer Sixth Edition Staging. J Natl Cancer Inst 2004;96: 1420–1425.



A



Stage Grouping

AJCC/UICC				Dukes
Stage 0	Tis	N0	M0	—
Stage I	T1	N0	M0	A
	T2	N0	M0	—
Stage II	T3	N0	M0	B
	T4	N0	M0	—
Stage III	Any T	N1	M0	C
	Any T	N2	M0	—
Stage IV	Any T	Any N	M1	—

Definition of TNM
The same classification is used for both clinical and pathologic staging.

Primary Tumor (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues
T4 Tumor directly invades other organs or structures, and/or penetrates visceral peritoneum

Regional Lymph Nodes (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes

Distant Metastasis (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

B

Figure 81-19 • **A,** Modified Duke's staging classification of colon cancer. Stages B3 and C3 (not shown) signify perforation or invasion of contiguous organs or structures (T4; see also Table 81-3). **B,** The TNM classification provides a more accurate staging system. (Adapted from Skarin AT, Shaffer K, Wieczorek T [eds]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, pp 155–156.)

primary colorectal carcinomas, and to plan appropriate treatment. Other tumor types that may resemble colorectal carcinoma clinically include colorectal lymphomas, carcinoid tumors, gastrointestinal stromal tumors, metastatic tumors that exhibit tropism for the gastrointestinal tract (e.g., melanoma), malignancies of adjacent organs that directly invade the colorectum (e.g., cancers of the ovary, endometrium, bladder, or prostate), or appendiceal tumors. Benign lesions that may mimic colorectal cancer include adenomas, hamartomas, solitary rectal ulcers, stercoral ulcers, endometriomas, and Crohn's disease or diverticular disease producing mural strictures.

Because the colorectal mucosa is architecturally unique and lacks stromal lymphatics, tumor invasion of the lamina propria has no associated risk of regional nodal metastasis and is included in the definition of pTis. To be classified as pT1, tumor must invade through the muscularis mucosae into the submucosa. T2 connotes invasion of the muscularis propria, and the T3 category refers to all transmurally invasive tumors that are confined to the perimuscular soft tissue (i.e., that have neither violated the serosal surface nor infiltrated an adjacent structure). Extramural extension of the tumor within lymphatics or veins does not count as local spread of tumor as defined by T3 but is instead denoted as L1 or V1 disease, respectively, in the L or V classification schema of the TNM system. In contrast, discrete smooth-contoured extramural tumor nodules of any size are classified as replaced lymph nodes, and each is counted separately in the N category on the basis of evidence that the number of pericolonic tumor-involved nodes correlates inversely with disease-free survival.[223]

The highest category of local extent is pT4, which includes either extension into adjacent organs or structures or penetration of the parietal peritoneum with or without gross perforation of the wall or involvement of an adjacent structure. Among the features that define T4 tumors, serosal penetration is the direst.[224] It is also possible to classify a tumor as pT4 on the basis of positive cytologic specimens of touch preparations from the serosa overlying the primary tumor. Direct invasion of adjacent organs or structures or other segments of the colorectum by way of the serosa or mesocolon (e.g., invasion of the sigmoid colon by carcinoma of the cecum) all should be classified as pT4. In contrast, intramural (longitudinal) extension of tumor from one subsite (segment) of the large intestine into an adjacent subsite or into the ileum (e.g., for a cecal carcinoma) or anal canal (e.g., for a rectal carcinoma) does not affect the pT classification.

Stage-related outcome data are based on pN assignment by conventional histologic staining of lymph nodes that are identified on routine macroscopic examination. Because many nodal metastases in colorectal cancer are found in small lymph nodes (<5 mm in diameter),[225] diligent search for lymph nodes in resection specimens is essential. The number of lymph nodes that are recovered from resection specimens varies widely and depends on several factors: patient factors such as age and anatomic variation; surgical resection technique; and diligence of the pathologist in harvesting all existing nodes. It has been shown that a minimum of 12 to 18 lymph nodes must be examined to accurately predict regional node negativity in colorectal cancer.[226] For this reason, it has been suggested that 12 lymph nodes be considered the minimum acceptable harvest from a careful specimen dissection. If fewer than 12 nodes are found after careful gross examination, additional techniques (i.e., visual enhancement techniques such as fat clearing) may be considered. It has been further recommended that all grossly negative or equivocal lymph nodes be submitted entirely for microscopic examination and that involvement of grossly positive lymph nodes be confirmed by either complete or partial microscopic examination.

To be included in the N category, a lymph node must be within the regional lymphatic drainage area of the primary tumor. Metastasis in other lymph nodes is classified as M1. Occasionally, however, a colorectal cancer may involve more than one site or subsite by continuous longitudinal extension. For example, a cecal carcinoma might extend across the ileocecal valve into the ileum. In these cases, the regional lymph nodes are defined as those of all involved sites and subsites. In rare cases, the regional nodes of the primary tumor site are free of malignancy but the nodes in the drainage area of an organ directly invaded by the primary tumor contain metastases. In this circumstance, the lymph nodes of the invaded site are considered as those of the primary site and are classified in the N category.

Increasingly, attention is being focused on alternative methods of detection of very small amounts of metastatic tumor in draining lymph nodes, but the impact on outcome of single or minute clusters of tumor cells in such nodes has not yet been definitively demonstrated. To ensure uniform pathologic assessment and data collection on this issue, small numbers of tumor cells that are detected only by special techniques or that are seen histologically but measure 0.2 mm or less in diameter are defined as "isolated tumor cells" (ITCs). According to current American Joint Committee on Cancer/International Union Against Cancer recommendations, ITCs are classified as N0 or M0, as appropriate. In contrast, small amounts of metastatic tumor that measure greater than 0.2 mm but less than 2.0 mm are defined as "micrometastases" and classified as N1 or M1. The number of lymph nodes that are involved by micrometastases or ITCs should be stated in the pathology report. To date, the data on the prognostic impact of ITCs in colorectal cancer are conflicting.[227–229] Therefore, changes in routine methodologies for lymph node evaluation currently are not recommended. Pending definitive demonstration of the biologic impact of ITCs and the clinical utility of more sensitive methods of lymph node analysis, neither routine examination of multiple tissue levels of paraffin blocks nor use of special or ancillary techniques such as immunohistochemistry or polymerase chain reaction techniques to enhance tumor cell detection are considered standard of care.

Positive peritoneal fluid cytology or tumor that is present (only) in lymphatic vessels of a distant site is considered pM1 disease. Excluded from pM1 designation are ITCs that are found in the bone marrow and tumor foci in the mucosa or submucosa of adjacent bowel, also known as satellite lesions or skip metastases. However, the latter must be distinguished from synchronous primary tumors.

For tumors that are treated prior to staging, stage-related prognosis is altered in comparison to tumors that are staged prior to treatment. This is especially relevant to rectal cancers that are treated with neoadjuvant radiation. However, the rules of application of TNM allow for description of the extent of post-treatment disease using the same TNM parameters modified by the prefix "y." The classification of residual disease also may be a strong predictor of post-treatment outcome, and the ypTNM classification provides a standardized framework for the collection of data that are needed to accurately evaluate new therapies.

Stage-related prognosis is also modified by the presence of residual tumor in the patient after primary surgical resection. Stage-related prognosis in disease with no (or limited hepatic) distant metastasis at presentation is predicated on complete eradication of all detectable tumor with cancer-directed surgery. The postoperative residual disease status of the patient, reflecting the efficacy of primary treatment, is categorized by a system known as the R classification, as follows:[220]

RX Presence of residual tumor cannot be assessed
R0 No residual tumor
R1 Microscopic residual tumor
R2 Macroscopic residual tumor

The R classification has stage-independent prognostic significance in that R1 and R2 are adverse prognostic factors compared to R0 status at any stage of disease. The relevance of the R classification to the pathologist is primarily related to resection margin evaluation. By convention, tumor that is present microscopically or macroscopically at a resection margin corresponds to R1 or R2, respectively. However, R0 status cannot necessarily be assigned to a case with negative resection margins because R0 refers to absence of residual tumor anywhere in the patient, including distant metastatic sites.

The pertinent margins of a colorectal cancer resection specimen include the proximal and distal transverse margins, the mesenteric margin, and, when appropriate, the circumferential (radial) margin. The circumferential resection margin (CRM) represents the retroperitoneal or perineal adventitial soft tissue margin of the excised bowel. For all segments of the large intestine that are either incompletely encased (ascending colon, descending colon, upper rectum) or not encased (lower rectum) by peritoneum, the CRM is created

by surgical dissection of the retroperitoneal or subperitoneal aspect, respectively, at operation.

When the distance between the tumor and the nearest transverse margin is 5 cm or more, anastomotic recurrences are very rare. Therefore, histologic examination of the proximal and/or distal margin might not be necessary if these margins are 5 cm or more from the tumor. By extension, the donuts from stapling devices, which are the true margins of resection, need not be examined histologically if the tumor is greater than 3 cm from the cut end of the main specimen.[230] In low anterior rectal resection specimens of rectal cancers, however, wide distal cuffs of normal mucosa can be hard to achieve, owing to anatomic constraints. In this circumstance, a margin of 2 cm is accepted as adequate, and in many cases, distal margins of 1 cm or less also prove sufficient, especially for T1 and T2 tumors.

In rectal carcinoma, the CRM has been demonstrated to be the margin of greatest importance in predicting risk of local recurrence, which is itself a strong predictor of survival.[231,232] In fact, multivariate analyses have suggested that tumor involvement of the CRM is the single most critical factor in predicting local recurrence in rectal cancer.[231] Emerging data on CRM involvement in the ascending or descending colon suggest a similar relationship to risk of local recurrence.[233] Therefore, routine assessment of the CRM is recommended in all applicable colorectal cancers, and measurement of the distance from the tumor to the nearest CRM, representing the "surgical clearance" around the tumor, is suggested.[232] On the basis of published data from clinical trials, the risk of local recurrence is strongly increased if tumor is present 1 mm or less from the nonperitonealized surface of the specimen.[234] By convention, therefore, the AJCC and VICC now define a positive CRM as one that is 1 mm or less from the closest approach of tumor. Some data have suggested that the risk of local recurrence also is significantly increased with clearances of 2 mm or less.[235] In contrast, the risk of recurrence is very low with clearance of more than 2 mm and can be considered "negative."

For segments of the colon that are completely encased by a peritonealized (serosal) surface (e.g., cecum, transverse, and sigmoid colon), the mesenteric resection margin may be a relevant "radial" margin, since tumors may extend to this margin with (pT4) or without (pT3) penetrating the serosal surface. It should be examined when the point of deepest penetration of the tumor is on the mesenteric aspect of the colon, especially when the mesentery has been trimmed close to the colonic wall. For tumors that are limited to an antimesenteric peritonealized aspect of the bowel, the mesenteric margin usually is not relevant.

Histopathology

The internationally accepted histologic classification of colorectal carcinomas proposed by the World Health Organization (Table 81-4) is recommended by the College of American Pathologists (CAP). According to this classification, the majority of colorectal cancers are adenocarcinomas of no special type. Aside from a few notable exceptions, histologic type has no stage-independent prognostic significance. The exceptions include the non-gland-forming tumor types such as signet-ring cell carcinoma, small cell carcinoma, and undifferentiated carcinoma, which are prognostically unfavorable, and medullary carcinoma, which is relatively favorable compared to other non-gland-forming tumor types. By convention, histopathologic types that do not form glands are always considered to be high-grade, except for medullary carcinoma, which is not graded. High tumor grade is itself an adverse prognostic factor (see later in the chapter). Medullary carcinoma was added to the revised World Health Organization classification in 2000.[236] It has a distinctive morphology composed of large polygonal tumor cells and abundant tumor-infiltrating lymphocytes (Fig. 81-20). The importance of this rare and unique histologic type is its strong association with defective DNA replication fidelity and high microsatellite instability, molecular features that are, in turn, associated with a more favorable stage distribution and prognosis compared to microsatellite stable tumors.[237] Most tumors of this type occur in the proximal colon in association with the hereditary nonpolyposis colon cancer syndrome.

Table 81-4 World Health Organization Classification of Colorectal Carcinoma*

Adenocarcinoma
Mucinous (colloid) adenocarcinoma (>50% mucinous)
Signet-ring cell carcinoma (>50% signet-ring cells)
Squamous cell (epidermoid) carcinoma
Adenosquamous carcinoma
Small cell (oat cell) carcinoma
Medullary carcinoma
Undifferentiated carcinoma
Other (e.g., papillary carcinoma)

*The term *carcinoma, NOS* (not otherwise specified) is not part of the WHO classification.

The grading of colorectal carcinoma, overall, is based on both architectural features and cytologic features (e.g., pleomorphism, hyperchromatism, and mucin production), but the degree of gland formation is widely regarded as the most important feature in grading. For adenocarcinoma, however, the estimation of grade is largely subjective. The lack of uniformity in histopathologic grading is further complicated by the existence in the literature of a number of different grading schemas without widespread acceptance and uniform use of any single system by practicing pathologists. Furthermore, the published systems have varied markedly as to the number, type, and relative importance of the specific features used to distinguish different grades. Irrespective of the type or complexity of the criteria, however, most systems stratify tumors into three or four grades as follows:

Grade 1: Well differentiated
Grade 2: Moderately differentiated
Grade 3: Poorly differentiated
(Grade 4: Undifferentiated)

Despite the lack of standardization and the existent interobserver variation in assessment, histologic grade repeatedly has been shown by multivariate analyses to be a stage-independent prognostic factor.[238–240] More specifically, high tumor grade has been shown to

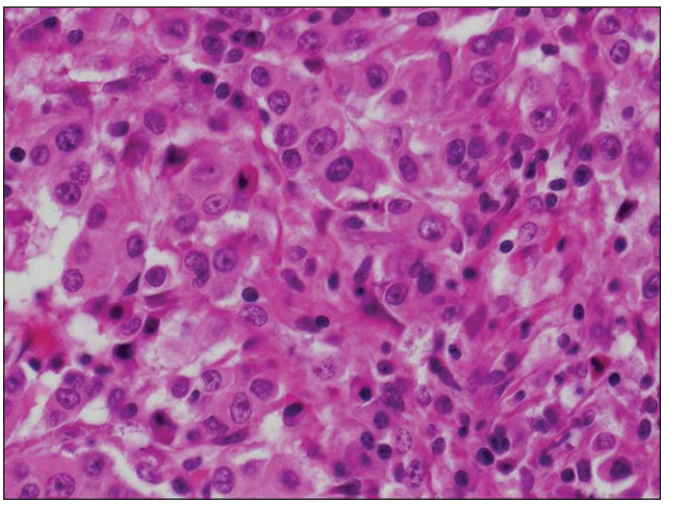


Figure 81-20 • Medullary carcinoma of the colon.

be an adverse prognostic factor. In almost all studies documenting the prognostic power of tumor grade, three- or four-tiered grading schemas have been collapsed for data analysis as follows:

Low-grade = grades 1 and 2
High-grade = grades 3 and 4

On the basis of these data, a two-tiered grading system for colorectal carcinoma (i.e., low-grade and high-grade) has been recommended by a multidisciplinary colorectal working group of a consensus conference sponsored by the CAP.[241]

There are no special histopathologic studies, such as histochemical or immunohistochemical assays, that are performed routinely for colon cancer. In some cases, immunostaining may be electively performed for MLH1 and MSH2, the two DNA repair genes that are most often found to be silenced in sporadic microsatellite unstable colon cancer. Immunostaining for cytokeratin also may be performed in special circumstances. For example, colon adenocarcinoma is characteristically positive for keratin 20 and negative for keratin 7, and although it is not pathognomonic, this feature can be helpful in distinguishing a metastatic lesion in the lung from a primary lung adenocarcinoma. Another example of the elective use of cytokeratin immunohistochemical staining is the examination of the advancing edge of the tumor for a phenomenon known as budding or dedifferentiation. This phenomenon is an adverse prognostic factor and is associated with a high risk of recurrence after curative surgery. It is characterized by small clusters or single infiltrating carcinoma cells (<5) at the invasive edge. The finding correlates with loss of adhesion molecules expression and increased metalloprotease expression[242] corresponding to a more aggressive tumor phenotype on a molecular level.[243] Because these cells may be quite small and neither form glands nor make mucin, they may require immunostains for identification, especially when accompanied by an inflammatory reaction that obscures their presence on routine histologic stains. The survival rate for stage II patients with tumor budding might not be significantly different from the survival rate for all stage III patients.[244–246]

ANATOMY AND PHYSIOLOGY OF THE COLON

For the purposes of this chapter on colon cancer, a discussion of the anatomy of the colon and its physiology will address aspects that are important to the spread of colon cancer and its surgical management. Anatomically, the colon is divided into the ascending or right colon, the transverse colon, the left or descending colon, and the sigmoid colon. The right colon is derived embryologically from the midgut, whereas the left colon is derived from the hindgut. Colon length varies not only according to body size but also among normal individuals of the same size and is estimated to range from 91 to 125 cm. The luminal diameter varies from its greatest width at the cecum (approximately 8.5 cm) to its narrowest at the distal sigmoid (approximately 2.5 cm). This change in diameter and the consistency of formed fecal content in the descending and sigmoid colon account for the frequent presentation of obstructive symptoms among patients with annular cancers in these colonic segments. The merging of the three taenia coli (from the Latin word for "tape") or longitudinal muscle bands into a continuous (encompassing) longitudinal muscle layer for the rectum at the pelvic peritoneal reflection marks the junction between the sigmoid colon and rectum.

Three segments of the colon—the cecum, transverse colon, and sigmoid colon—are intraperitoneal. The ascending colon, hepatic flexure, splenic flexure, and descending colon and the beginning and end of the sigmoid colon are retroperitoneal structures. As a result, the surgical resection and the patterns of recurrence are greatly influenced by the location of the tumor within the colon and, for the segments that are retroperitoneal, by its position within the bowel at the primary site (e.g., primarily posterior in location versus on the anterior wall of the colon). Although the beginning of the colon (cecum) and its appendix are largely intraperitoneal, the ascending colon and its mesocolon are fused to the posterior abdominal wall in a retroperitoneal position. It should be noted that the ileocecal valve at the junction of the ileum to the colon is actually formed by two reflected folds of the mucosal wall of the cecum. These folds unite and project further around the cecum as the frenulum. The opening of the appendix into the cecum is near the ileocecal valve.

Examination of the inner surface of the colon reveals the semilunar folds, the sacculations that are termed *haustrae*, and the longitudinal muscle bands, or taenia. Lymphoid follicles are also visible on the luminal surface. As was noted previously, the taenia start at the base of the appendix and continue throughout the colon.

The hepatic flexure lies just below the right lobe of the liver and the gallbladder and overlies the lower pole of the right kidney. The transverse colon extends across the abdomen and can be of variable length. It is intraperitoneal and is attached to the transverse mesocolon along the taenia mesocolica. The greater omentum attaches to the transverse colon along the taenia omentalis. The taenia libera is free of any attachments. Along the intraperitoneal transverse colon and sigmoid colon, one sees numerous fatty appendages hanging from the serosa. These are called *appendices epiploicae*. They are small, saclike structures containing fat and have no known function.

The splenic flexure lies, as its name suggests, in close proximity to the hilum of the spleen and the tail of the pancreas. This is an important relationship when the transverse or descending colon is being surgically mobilized. Attachments between the splenic flexure and the lower pole of the spleen must be divided carefully to avoid injury to the spleen. The descending colon, like the ascending colon, is fused to the posterior abdominal wall and lies in the retroperitoneum. The sigmoid colon begins the intraperitoneal distal portion of the colon and is of variable length. Its lumen is the narrowest diameter of the entire colon. The sigmoid colon terminates at the upper rectum in the general area of the sacral prominence (Fig. 81-21).

Vascular Supply to the Colon

The superior mesenteric vessels supply the cecum, the ascending colon, and a good portion of the transverse colon. The major branches of the superior mesenteric artery (SMA) are the ileocolic artery supplying the ileocecal region, the right colic artery in support of the ascending colon, and the middle colic branch to the hepatic flexure and transverse colon. These vessels have extensive branching near the colon and contribute to the formation of the important marginal artery (marginal artery of Drummond). The veins that accompany these arteries drain back to the superior mesenteric vein and thence to the portal vein. It is this unique venous drainage to the liver that is believed to account for the high incidence (approximately 80%) of first-site metastatic failure in the liver for colon and upper/middle third rectal cancers.

The inferior mesenteric artery (IMA) arises from the aorta and supplies the descending colon via the left colic artery. The marginal artery acts as a collateral vessel to link the branches of the superior mesenteric artery to the right colon with the arterial flow from the inferior mesenteric artery and its left colic artery (see Fig. 81-21A). Distally, the inferior mesenteric artery gives rise to several sigmoid arteries and the superior rectal artery. Veins draining the left side accompany these arteries and drain via the inferior mesenteric vein to the splenic vein and thence to the portal vein. A patent, healthy marginal artery provides a measure of safety in performing resections of the colon by providing collateral arterial flow. These arteries and veins lie within the "leaves" of the mesocolon.

Lymphatics of the Colon

Lymphatics and nerves to the colon also lie within the mesocolon and follow the course of the arteries. The lymphatic channels originate in the lower lamina propria and muscularis mucosae at the base of the colonic mucosa. These channels drain into the extramural lymphatics. Cancer that is growing superficial to the level of the

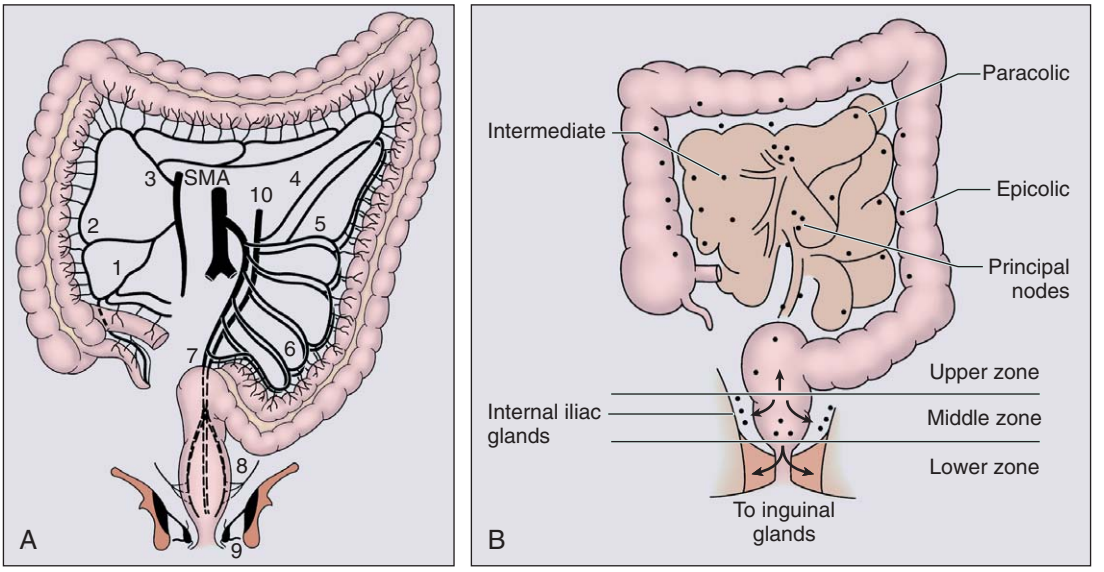


Figure 81-21 • **A,** Arterial and venous supply of the colon. Branches of the superior mesenteric artery: (1) ileocolic, (2) right colic, (3) middle colic. Branches of the inferior mesenteric artery: (4) ascending left colic, (5) left colic, (6) sigmoid branches, (7) superior rectal artery, (8) middle rectal artery, (9) inferior rectal artery, (10) inferior mesenteric vein. **B,** Principal nodal drainage sites of the colon.

muscularis mucosae has not been shown to have access to the lymphatic channels and therefore has not been found to have metastatic potential. The lymph nodes lie roughly along the vessels and are grouped as epicolic; paracolic (located along the marginal artery); intermediate (located along mesenteric vessels); and principal or central nodes at the junction with the superior mesenteric artery or, in the case of the inferior mesenteric artery, with the aorta (see Fig. 81-21B).

All collecting lymph channels from the abdominal viscera, the abdominal wall, and the lower extremities converge in an elongated sac (approximately 5 cm) known as the cisterna chyli. The cisterna chyli lies along the aorta, and a large afferent lymph channel proceeds from the cisterna superiorly through the aortic opening in the diaphragm along the right diaphragmatic crus. There are numerous communicating lymphatics between the larger channels, which could account for the observed "skipping" of metastases and multiple "sentinel" nodes for a given tumor site. Malignant cells might also pass through initial nodes before being trapped in more distant nodes. Lymph nodes also have an arterial supply and a venous drainage feature, which could play a role in metastatic spread to nodes as hematogenous metastases and account for unusual sites of node involvement that appear completely unrelated to direct drainage of lymph fluid from the original tumor.

Autonomic Innervation

The autonomic nervous system mediates control of colonic motor and secretory function and primary visceral sensation. The autonomic innervation includes both sympathetic and parasympathetic components. The preganglionic parasympathetic nerve fibers are quite long, extending from the brain stem to the colon wall, where they terminate within the mesenteric and submucosal plexuses. In contrast, the first synapse of the sympathetic fibers can occur within the paravertebral ganglia, but most pass through the ganglion without synapsing. The sympathetic fibers are gathered into bundles know as the greater (fourth to tenth thoracic), the lesser (ninth to eleventh thoracic), the least (eleventh thoracic to the first lumbar), and the lumbar (second and third lumbar) splanchnic nerves. The splanchnic nerves (preganglonic fibers) pass to the preaortic ganglia, so named for the adjacent arterial trunks such as celiac and superior mesenteric ganglia and plexus. These preganglonic sympathetic fibers synapse within the preaortic ganglia. The postganglionic adrenergic fibers follow arteries to their effector organs in the wall of the colon.

An extensive network of fibers and ganglia cells lies within the submucosa and muscular walls of the colon. The intact mucosa of the colon is insensitive to direct stimuli. Sensory receptors in the colon wall react to stretching (as with gas) and to muscular spasm. The mesentery is sensitive to tugging or stretching. Impulses arising from these stimuli are sent over the autonomic (mainly sympathetic) afferent fibers.

Visceral pain derived from distension of the bowel or traction on the mesentery of the cecum, the ascending colon, and the majority of the transverse colon (structures of midgut origin) initially presents as periumbilical pain. If there is inflammation, ischemia, or direct tumor infiltration of the abdominal wall, the pain is somatic and located at the site of involvement. Referred pain is rare. Pathology of the distal transverse colon, splenic flexure, and descending and sigmoid colon (structures of hindgut origin) produces visceral pain, initially along the midline below the umbilicus. Somatic pain from the left colon may occur with tumors, causing inflammation or invasion into the abdominal wall.

The pain that is associated with an obstructing colon tumor is initially experienced as cramping waves of pain located below the umbilicus. In the beginning, these spasms last for minutes, but they gradually increase in intensity and duration. Over 24 to 48 hours of obstruction, the pain becomes constant and more diffuse throughout the abdomen.

Embryology

By the 6-week embryo stage, the midgut has formed and exists as a long intestinal loop in an elongated celomic cavity within the umbilical cord. At the beginning of the third month, the intestinal loop residing in the umbilical cord begins to rotate counterclockwise around the axis of the superior mesenteric artery. In doing so, the distal limb of the intestinal loop, consisting of the future cecum, terminal ileum, and ascending colon, passes over and to the right of the future jejunum and ileum. With this twist, the superior mesenteric artery comes to cross in front of the duodenum. As the intestinal loop withdraws from the umbilical cord, the proximal limb leads

the way and, as a result, pushes the distal colon to the left side of the abdomen. The cecum and terminal ileum migrate downward and to the right lower quadrant of the abdomen.

From this brief discussion, it is obvious that any interruption of this rotation can alter the position of certain segments of the colon. The most common is a high position of the cecum beneath the liver in the right upper abdomen. Earlier interruptions of rotation could find the colon remaining on the left side.

When the rotation process proceeds normally, the entire mesentery to the cecum and ascending colon becomes fused to the right posterior abdominal wall as a triangle with the apex at the base of the mesentery just above the emergence of the superior mesenteric artery. The upper section of this mesenteric triangle covers the second and third segments of the duodenum, which sweeps from right to left behind the superior mesenteric artery.

The mesentery of the transverse colon is retained, and the transverse colon develops an attachment horizontally with the greater omentum. Similar to the ascending colon, when the descending colon becomes fixed to the left posterior abdominal wall, its mesentery becomes part of the posterior wall. The sigmoid colon retains its redundancy and therefore a mesentery.

A thorough knowledge of the embryonic development of the colon is important to the surgeon and to the safe mobilization and resection of various colonic segments.

Microscopic Anatomy of the Normal Colon

A single layer of columnar epithelium covers the colonic mucosa, overlying the internal surface and lining the crypts along the lamina propria (Fig. 81-22). The single layer of colonic epithelium consists of columnar or cuboidal cells and serves as a protective barrier against the luminal content. At the level of bases of the glands, there is a thin, continuous muscle layer termed the *muscularis mucosae* that separates the lamina propria from the submucosa.

The epithelial layer has two additional functions. One is to facilitate the process of water absorption, and specific cells are responsible for colonic ion and water transport. These cells do not contain mucin and have an eosinophilic cytoplasm. The second function of the epithelium is to synthesize, store, and secrete mucous granules; this is accomplished by goblet cells in the colonic epithelial layer. The colonic epithelium is supported by a thin basement membrane that anchors the epithelial cells. The basement membrane consists of collagen and other proteins and is permeable to absorbed or secreted ions, water, and proteins. One of the unique characteristics of the colon mucosa is the presence of straight-sided crypts, which have a somewhat heterogeneous population of epithelial cells. At the base of each crypt are undifferentiated stem or precursor cells. These cells are continually dividing (see Fig. 81-22). Daughter cells migrate toward the surface epithelial layer to renew the surface epithelium, which is constantly being shed into the lumen or undergoing apoptotic death. As the daughter cells move from the base of the crypt toward the lumen of the colon, they lose their ability to divide but continue to differentiate to become functionally mature. The upper 25% of the crypt represents such mature cells. Neuroendocrine cells and Paneth cells are found in the bases of the crypts, but Paneth cells are found only in the mucosa of the cecum and proximal right colon.

The lamina propria extends from the basement membrane to the muscularis mucosae. It is composed of loose strands of collagen, and B lymphoid cells are abundant and may occur in small aggregates between crypts. These B cells produce immunoglobulins, mostly of IgA class. T lymphocytes and macrophages are also found in the lamina propria, as are fibroblasts.

The muscularis mucosae is a thin layer of muscle that separates the superficial layers of epithelium and lamina propria from the deeper submucosa. Between the muscularis mucosae and the submucosa are found the neural plexus of Meissner and the deep submucosal neural plexus of Henle. The muscular layers of the colon include a circular inner layer of smooth muscle fibers and an outer longitudinal layer. Auerbach's neural plexus lies between the circular and longitudinal muscle layers. These muscle layers are covered by a thin layer of connective tissue (the subserosa) and a layer of mesothelial cells (the serosa or visceral peritoneum), except at the points of attachment of the ascending and descending colon to the abdominal sidewall where the visceral peritoneum is discontinuous.



Figure 81-22 • Normal colonic basal crypt epithelium. Among the absorptive cells and goblet cells are a mitotic figure and endocrine cells with basally oriented secretory granules (red stained). (From Sternberg SS: Histology for Pathologists. New York, Raven Press, 1992.)

Physiology of the Colon

The colon functions to prepare the normal waste products left after digestion and absorption of nutrient food products for elimination in a controlled manner. Water is withdrawn through the colonic mucosa from the fluid stool entering the cecum and ascending colon. Both water and salt are absorbed as the right colon acts to reduce the daily liter of ileal liquid chyme to approximately 200 g of formed fecal matter. The left colon is responsible for storage and eventual expulsion. The movement of fecal matter through the colon is regulated hormonally and neurally.

The mucosal lining of the colon keeps its surface coated with mucous to protect the epithelial cells from injury and to act as a lubricant. Mucus is produced by the tubular glands, which contain many goblet cells, and mucous production is controlled primarily by parasympathetic nerve fibers.

The colon has abundant bacterial flora, including *Escherichia coli*, *Aerobacter aerogenes*, *Clostridium welchii*, various lactobacilli, cocci, and yeast organisms. The flora is somewhat influenced by diet, being more gram-negative when the diet is primarily protein in nature and more gram-positive if the diet is mainly carbohydrates and green vegetables. Some of the colonic organisms synthesize vitamins of the B complex and vitamin K.

Carbohydrate-consuming bacteria within the lumen work on undigested carbohydrates and dietary fiber, producing short-chain fatty acids, flatus, and water. These short-chain fatty acids can be absorbed by colonic mucosal epithelial cells and can be a source of dietary calories. Although these various bacteria reside in relative balance, the normal equilibrium of bacteria can be altered significantly by antibiotics, giving rise to an overgrowth of harmful bacteria such as *Clostridium difficile*.

Antibiotic-associated diarrhea occurs in an estimated 1% to 15% of individuals who are given broad-spectrum antimicrobic therapy. It is caused by an overgrowth of *C. difficile* when the normal bacterial flora of the colonic mucosa is suppressed. *C. difficile* colonic infection generally causes cramping and mild diarrhea, but it can result in a more life-threatening pseudomembranous colitis. Patients with colon cancer or those who are receiving treatment for recurrent disease are frequently at risk for developing antibiotic-associated diarrhea. In such cases, the antibiotic should be stopped and the patient should be given vancomycin (250 mg every 6 hours orally for 7 days) or metronidazole (500 mg every 8 hours for 7 days). Treatment should be started when the diagnosis is suspected, before the results of a stool assay for *C. difficile* toxins are available.

SURGICAL TREATMENT

Radical resection of the tumor-bearing segment of colon, with wide margins and removal of the lymphatic drainage of the tumor, is the standard for curative therapy. The extent of resection is determined by tumor size, location, histologic grade, and tumor extension into the colon wall and into adjacent tissue or organs. Historically, resections of the colon for cancer have been quite radical with respect to the removal of the mesocolon-bearing draining lymphatics at risk for tumor spread. Studies, however, indicate that there is no major survival advantage by extended lymph node dissection. Even so, limited segmental resections are indicated primarily when the surgery is deemed palliative.

Preoperative preparation of the colon to clear the colon of fecal matter and to reduce the quantity of bacteria within the colon is important to ensure a safe operation with minimal morbidity (Box 81-1 summarizes this preparation). For elective surgery, patients are placed on a liquid diet starting 3 days before scheduled surgery. For the last 24 hours of diet preparation, they are urged to take only clear liquids. The night prior to surgery, patients have an active mechanical bowel preparation to ensure optimal cleansing of the colon. Before surgery, they are given parenteral antibiotics. Patients should be given intravenous hydration before surgery, preferably during the night of their mechanical bowel preparation. It might be necessary to modify the preparation of the colon if the tumor is large enough to cause partial obstruction.

It is important to use a suitable regimen to minimize the risk of deep venous thrombosis and thereby to reduce the likelihood of pulmonary embolism. Routine use of low-molecular-weight heparin and intermittent compression leggings during the perioperative period may be appropriate. Early ambulation is an important adjunct to heparin and compression.

The choice of placement of the incision is dependent on the location of the tumor and the surgeon's preference. A midline or Para median incision is favorable for two reasons. First, it allows better access to the liver in case unexpected synchronous liver metastases are discovered; second, it is not uncommon to reoperate such patients for recurrent tumor. A midline approach, in contrast to a transverse approach (incision), allows the surgeon to move up or down within the abdomen for future surgical therapy.

Once the abdomen has been entered, the surgeon performs a thorough exploration of the abdomen to assess the extent of the tumor and to search for metastatic disease. The liver deserves special attention because it is most commonly the site of first failure, and approximately 10% to 15% of patients will have synchronous metastatic involvement of the liver. Intraoperative evaluation of the liver is generally accomplished by visual inspection and palpation. If there is any suspicion of liver metastasis based on preoperative CT scan, intraoperative ultrasound of the liver is performed and increases the frequency of detecting occult metastases.[200–202,247,248] Particular attention should be paid to nodes in the porta hepatis, and if unusually large or suspicious nodes are found, they should be sampled.

The four classic resections for colon cancer are depicted in Figs. 81-23 through 81-26. A right hemicolectomy (see Fig. 81-23) is the standard approach for tumors involving the cecum and right colon. The mesocolon and its vascular structures are transected at the base of the mesocolon along the superior mesenteric artery. The ileocolic and right colic arteries are the branches of the superior mesenteric artery that are ligated, along with branches of the middle colic artery. The middle colic artery is usually preserved unless the tumor is located in the hepatic flexure of the colon. In this situation, the resection is extended to include the middle colic artery. For a right

Box 81-1. PREPARATION OF BOWEL FOR ELECTIVE RESECTION

- Begin diet restriction to full liquids 3 days before scheduled surgery.
- Limit diet to clear liquids for 24 hours preceding surgery.
- Admit patient to hospital 1 day before surgery for intravenous hydration.
- Administer metoclopramide, 10 mg intramuscularly or orally, 30 minutes before beginning mechanical bowel preparation.
- Administer D5/0.5 saline solution with 40 mg KCl intravenously at 100 mL/hr beginning at 11:00 P.M. on the evening before surgery.
- Administer 1.5 L GI lavage solution four times hourly by mouth until stool is clear. Begin lavage at approximately 4:00 P.M. on the afternoon before surgery.
- Administer neomycin base orally 1 and 2 hours after completion of GI lavage (approximately 10:00 P.M.)
- Administer erythromycin base orally 1 and 2 hours after completion of GI lavage.
- Check serum potassium 2 hours after completion of GI lavage and at 6:00 A.M. preoperatively.
- Ensure that intravenous Cefotetan is available on call to the operating room.

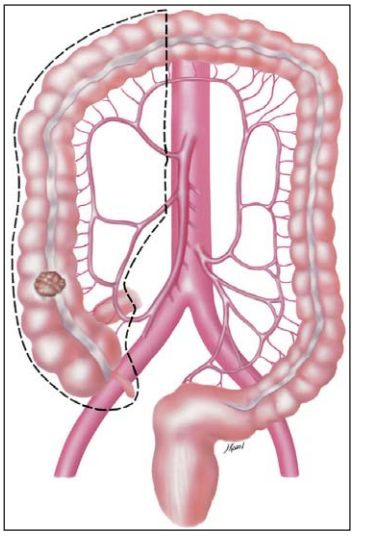


Figure 81-23 • Right hemicolectomy resection margins for right colon carcinoma.

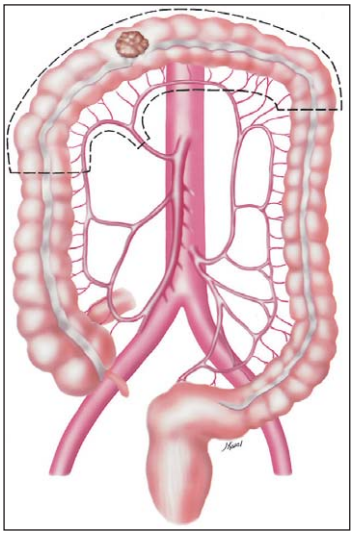


Figure 81-24 • Transverse colon resection margins for transverse colon carcinoma.

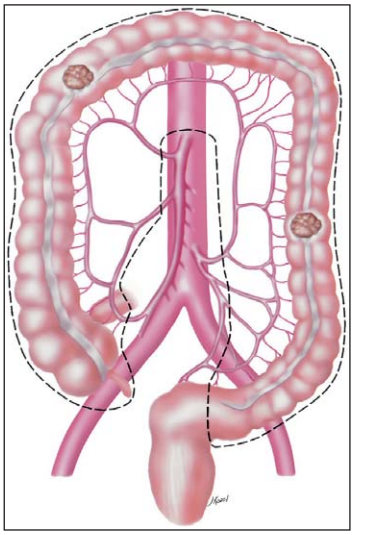


Figure 81-26 • Resection margins for synchronous right colon and left colon carcinomas with reconstruction via ileorectostomy.

hemicolectomy, the ileum is divided approximately 10 cm from the ileocecal valve. Continuity of the bowel is reestablished by anastomosis of the terminal ileum to the transverse colon. Although the greater omentum is often removed in part or completely to facilitate resections of the right and transverse colon, there is no evidence that this measure improves survival.

Cancer involving the transverse colon requires mobilization of both the hepatic and splenic flexures. The middle colic artery is transected at the superior mesenteric artery (see Fig. 81-24). When the tumor is located in the splenic flexure region, the surgeon must be more concerned about adequate collateral blood supply through the marginal artery. This concern is increased in elderly patients who have a history of significant vascular disease.

Tumors that are located in the left colon are managed by a left hemicolectomy. The inferior mesenteric artery is ligated near its origin on the aorta. The more distal the location of the cancer, the more mobilization of the upper rectum will be needed. It is almost always necessary to mobilize the splenic flexure. Cancers that involve the sigmoid portion of the colon are resected by what is commonly termed an anterior sigmoid colon resection or a low anterior sigmoid resection. The more distal sigmoid tumors require resection of the upper rectum to achieve an adequate distal margin. It is always more difficult, in cases of left colon and sigmoid colon cancers, to determine an appropriate amount of colon and mesentery for resection. It is helpful to map the vascular structures draining the area of the tumor visually. There is increasing evidence that aggressive radical resections of the left colon provide no additional survival benefit.

As has been noted, in colon surgery it is the arterial blood supply that usually dictates the extent of resection. The rule is to provide a minimum of a 5- to 6-cm margin of colon in the resection. Evidence suggests, however, that it is rare to find colon cancer spread beyond 1.2 cm from the gross margin of the tumor. Figure 81-26 illustrates a subtotal colectomy and ileorectostomy. A subtotal colectomy might be required in patients who harbor synchronous cancer in the right and left colon and patients presenting with colon cancer at a young age. Other indications for subtotal colectomy could include obstructing cancer, extensive diverticular disease, and a right colon lesion with extension into the sigmoid colon or, similarly, a cancer of a redundant sigmoid colon that invades into the right colon.

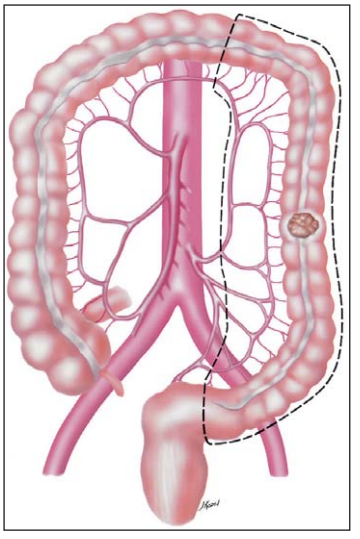


Figure 81-25 • Left colon resection margins for left colon carcinoma.

Restoring Continuity

The restoration of bowel continuity is an important step in the procedure. Use of appropriate techniques for accomplishing the anastomosis minimizes the risks of abscess, sepsis, and the significant morbidity associated with a leak postoperatively. The anastomosis is performed either hand-sewn or by using a stapling technique. There is little if any evidence that one technique is superior to the other. It is important to use surgical packs to isolate the anastomosis procedure from the rest of the abdomen until it has been completed.

Using a separate set of instruments once the bowel is opened and discarding these when the closure of the anastomosis is completed is considered prudent. Schwab and colleagues[249] reported the results of an in vitro study comparing initial bursting strength for three different anastomosis techniques. These authors performed 10 hand-sutured anastomoses, 10 biofragmentable ring anastomosis, and 10 stapled anastomoses of fresh human colon that was harvested at time of colon cancer surgery. They measured the pressure that was required to burst the anastomosis and found no significant difference. They concluded that because there were no differences, hand-sutured anastomoses were certainly the least expensive and should remain the standard.

In prior years, some surgeons advocated a "no-touch technique" in removing colon cancer. This was based on the concern that manipulation of the tumor-bearing tissue before high ligation of the draining veins and lymphatics might increase the risk of metastasis. A study by Sales and coworkers[250] failed to show a survival benefit for rigorous application of the "no-touch" high ligation of vessel technique.

Occasionally, surgeons either use povidone-iodine to irrigate a segment of colon during preparation for anastomosis or inflate the distal rectum and sigmoid colon to kill shed tumor cells within the lumen. Concern had existed regarding mucosal injury and absorption of iodine. Studies have shown that the elevated serum iodine levels that can occur with irrigation do not cause thyroid or bowel injury, and such irrigations can be performed with negligible risk.[251]

Surgical Management of Lymph Nodes in Colon Cancer

Lymph node metastasis is the most important prognostic factor in locoregional colon cancer. As was described previously in this chapter, colon resection has classically involved taking the mesocolon of the resected bowel at the origin of the vessels supplying the segment of colon to be removed. This ensures removal of the first level of lymph nodes (often called the epicolic and pericolic nodes) and the intermediate or second level of nodes in the resection when the vascular branches supplying the segment are taken at the SMA and IMA. The rationale for these more or less standard resections is based on the assumption that lymphatic tumor dissemination follows an orderly, sequential route of first-order nodes, second-order nodes, and so forth.

It is known, however, that metastases can be found in distant node groups—para-aortic, celiac, and porta hepatis—even when regional nodes appear to be normal. Supporting this observation is a report of administering 25-mci ^{99m}Tc-tagged fab-fragment-antibody to carcino-embryonic antigen (CEA) before the patients underwent colon resection. Intraoperatively, a hand-held scintillation probe was used, and surgeons removed all nodes that were identified as suspicious. Seven of 20 patients were upstaged, and metastatic spread was found at distant sites of retroperitoneum and renal hilum.[252]

The accuracy of regional node analysis and its prognostic value are directly proportional to the thoroughness of the surgical technique in removing all regional nodes and the pathologic examination of the resection specimen in identifying and harvesting all regional lymph nodes for microscopic assessment (see section on staging). The AJCC and the CAP have recommended examination of at least 12 lymph nodes to assign stage II.[253] It has been shown that a minimum of 12 to 18 lymph nodes must be examined to accurately predict regional node negativity in colorectal cancer.[223,225,254–260] For this reason, it has been suggested that 12 lymph nodes be considered the minimal acceptable harvest from a careful specimen dissection, and the National Quality Forum has accepted this recommendation as a quality indicator.[261]

Increasingly, however, the evidence indicates that the greater the number of nodes that are examined, the greater is the likelihood that metastasis will be found. In one study of T3 tumors, for example, nodal metastases were found in 22% of cases if fewer than 15 lymph nodes were harvested from the specimen, whereas 85% of cases with 15 or greater recovered nodes showed metastasis.[254] In a study of more than 2400 pT3 colorectal cancers that were resected at a single institution over 45 years, Goldstein and colleagues showed by mathematical analysis that the predictive probability of identifying a single positive node increased in a continuous manner as the number of recovered lymph nodes increased, suggesting that there is no minimum number of nodes that accurately or reliably stages all patients.[254]

More important, it has been shown that clinical outcome is linked to the lymph node harvest. Numerous studies have shown that conventional pathologic examination of increased numbers of lymph nodes is itself associated with an increased survival advantage in stage II disease,[255–259,262,263] indicting a positive effect of optimal mesenteric resection by the surgeon, optimal lymph node harvest from the resection specimen by the pathologist, or both. Similarly, a large study based on Intergroup Trial INT-0089, which included 3759 patients with stage III or high-risk stage II disease, showed that overall survival and cause-specific survival both increased as more lymph nodes were examined, suggesting that the number of lymph nodes that are analyzed is itself an independent prognostic variable in colorectal cancer.[255] In contrast, survival is significantly worse for patients with stage II colon cancer, roughly equivalent to stage III disease, in cases with fewer than 7 to 9 lymph nodes harvested from the resection specimen, suggesting clinically significant understaging when too few nodes are sampled.[264–266]

Despite the strength of the data demonstrating the critical nature of adequate lymph node assessment in colorectal cancer, significant variation in lymph node recovery from resection specimens exists within and among medical centers.[267–270] In addition, the average number of lymph nodes examined per specimen is often found to be lower than the minimal recommended number, suggesting that a large number of patients with colorectal cancer are staged inadequately.[271] The number of lymph nodes that are recovered from resection specimens is dependent on several factors. Surgical technique, surgery volume, and patient factors such as age and anatomic variation alter the actual number of nodes in a resection specimen, but the diligence and skill level of the pathology examination in identifying and harvesting lymph nodes in the resection specimen also are major factors.[270] Since it has been shown that many nodal metastases in colorectal cancer are found in small lymph nodes (<5 mm in diameter),[225] diligent search for lymph nodes is required on gross examination of resection specimens.

Lymphatic mapping and sentinel lymph node (SLN) identification can help surgeons and pathologists to identify lymphatic drainage routes and apply ultrastaging techniques to the first draining lymph nodes. While some studies have suggested that this is a useful procedure for micrometastasis detection,[272–276] other studies have highlighted the lack of established techniques and high false-negative rates.[277] The overall usefulness of SLN analysis in colorectal cancer is questionable, since fewer than 20% of cases are SLN-only positive.[278] The high rate of non-SLN metastases, with or without SLN metastases, may be attributed to the rich anastomotic relationship of lymphatics in colonic mesentery. For micrometastasis/ITC detection, greater accuracy is achieved by applying the special techniques to all lymph node blocks. Overall, the data are still insufficient to support routine use of specialized techniques for lymph node mapping or SLN analysis. As was discussed earlier in the chapter (in the section on Staging), the prognostic significance of the finding of ITCs remains to be definitively demonstrated, so the value of ultrastaging techniques might be moot.

Surgical Management of Obstructing Colon Cancer

In a large population of 4583 patients in the United Kingdom, obstruction was noted in 16%.[279,280] The obstructing tumor, as expected, occurred more frequently on the left side, the splenic flexure being the most common site (49%). Twenty-three percent of obstructions occurred in the descending colon, and 23% occurred in the right colon. Serpell and associates[281] reported a similar incidence of 16%, with 30% demonstrating symptoms and evidence of partial obstruction.

Malignant obstruction can present as a progression of symptoms associated with colon function, such as increasing frequency and severity of episodes of cramping abdominal pain or decreasing frequency of bowel evacuation leading to constipation and abdominal distention. It is not uncommon to have the patient present in the emergency room with the acute onset of symptoms. Diagnosis is confirmed by abdominal x-rays and CT scan. Carefully conducted

colonoscopy to avoid dangerous distention of colon by air insufflation and barium contrast study could prove useful in localizing the tumor and clearing the colon of other polyps or synchronous cancer.[282]

There are several options for managing obstructing tumors, depending on their location. These include the following:

- Resection with proximal temporary colostomy and Hartmann's procedure (closed distal stump)
- Intraoperative lavage of colon, systemic antibiotics, and primary anastomosis
- Subtotal colectomy with primary anastomosis

A temporary colostomy and Hartmann's procedure require a second operation for colostomy takedown and restoration of bowel continuity. Although this is a safe approach, with approximately 10% morbidity, subsequent colostomy closure might not be feasible or advisable in the poor-risk patient and itself carries an additional risk of complications of 40%.[280]

The second approach, intraoperative colon lavage, is accomplished by placing a Foley catheter through the appendiceal stump and irrigating the preserved colon until it is mechanically clean. Although this procedure is time consuming, the overall morbidity is approximately 10%, and the rate of anastomotic leak is quite low.[283]

The third approach, subtotal colectomy, has become more acceptable. It can be accomplished quickly, does not require a temporary colostomy, and has the advantage of removing any proximal synchronous lesions.[284–286] Wong and colleagues,[285] in an analysis of 35 patients undergoing subtotal colectomy for an obstructing cancer, found a significant incidence of proximal synchronous tumors in 32% of patients. Thus, patients with complete obstruction of their colon and dilated proximal colon might best be served by undergoing a subtotal colectomy. In general, fewer than 50% of obstructing lesions can be resected for cure, and a review of 12 reports by Sugarbaker and coworkers[286] found a 5-year survival rate of only 40% for those patients who were resected for cure.

Surgical Management with Involvement of Adjacent Organs

When a cancer of the colon is adherent to the peritoneal surface of the abdominal wall, the area of contact should not be divided, even if it is suspected to be an adhesion. In more than 50% of patients, what appears to be an adhesion will involve direct invasion of the tumor into the peritoneum.[287] Surgically disrupting these sites of adherence could result in a spill of cancer cells within the peritoneal cavity, leading to an increase in intra-abdominal recurrence and a decrease in survival. Adjacent organs are usually partially resected or totally resected in continuity with the colon tumor. When the tumor involves the abdominal wall, a portion of the peritoneum and underlying muscle are resected by developing a 2- to 3-cm margin around the site of adherence. Such carefully performed resections can lead to a good outcome in 20% to 50% of patients.[287] The redundant nature of the sigmoid colon frequently is responsible for involvement of the bladder by a sigmoid tumor. Fujisawa and colleagues[288] reported an analysis of 35 patients requiring some aspect of urologic surgery to accomplish a removal of their cancers. This group included 19 sigmoid cancers that involved 15 patients undergoing bladder-sparing partial cystectomy. An ileal conduit and ileal neobladder were needed in two patients.

Surgical Management of Perforated Colon Cancer

The frequency of colon cancer presenting as isolated acute perforation with peritonitis is low. But perforation combined with fistulation into an adjacent organ or into the retroperitoneum with the development of an abscess is estimated to occur in 6% to 8% of patients with colon cancer.[289] When the presentation is acute, with free air and diffuse peritonitis, an emergent surgery is required, and prognosis for long-term survival is poor. Sugarbaker and coworkers[286] found a 5-year survival rate of 7.3% for free perforation and 41% for contained perforations. The risk of peritoneal seeding and the future development of carcinomatosis is reported to be approximately 20% for patients with perforation.[290]

Surgical Management of the Malignant Colon Polyp

"Malignant polyps" are adenomas that contain any amount of invasive carcinoma, which is defined as tumor that penetrates through the muscularis mucosae into the submucosa. They also include polypoid carcinomas, in which the entire polyp head is replaced by carcinoma. By definition, malignant polyps exclude adenomas that contain intraepithelial carcinoma or intramucosal carcinoma because these polyps possess no biologic potential for metastasis. Polyps that contain invasive carcinoma represent about 5% of all endoscopically resected adenomas.[291] Malignant polyps often constitute a form of early carcinoma (pT1) that may be cured by endoscopic polypectomy alone. However, the incidence of an unfavorable outcome (i.e., lymph node metastasis or local recurrence from residual malignancy) for malignant polyps that are treated by polypectomy alone varies from about 10% to 20%.[292] Pathologic features that are associated with a significantly increased risk of residual or recurrent disease include (1) high tumor grade, (2) tumor at or less than 1 mm from the polyp resection margin, and lymphatic vessel involvement.[293] One or more of these features increases the risk of regional nodal metastasis or local recurrence following polypectomy by about 10% to 25%.[294] Therefore, if one or more of these high-risk features are found on pathologic examination, further therapy is usually indicated.

Sessile polyps containing cancer are more problematic. They have a higher incidence of lymph node involvement: approximately 10% to 25%, compared with 3% for pedunculated polyps.[295] Unless there are significant comorbid conditions that preclude resection, it is safest to resect the segment of the colon in which a cancerous sessile polyp has been found.[295] Extension of cancer to "Haggitt" level 3 in a pedunculated polyp is a good indicator for performing colon resection (Fig. 81-27).[296]

In dealing with malignant polyps, it is best to err on the side of overtreatment. Any polyp for which there is a question of adequate margin or angiolymphalic invasion should have a resection of the involved colon if the histology is grade 3. Identifying the correct segment to resect can be difficult at the time of surgery. Identification of the polyp site is facilitated by the endoscopist tattooing the site or by placing small metal chips at the polypectomy site. The histology of benign and malignant polyps is illustrated in Figure 81-28.

A reasonable approach is a limited segmental resection measuring 6 to 10 cm in either direction and including enough mesentery to provide assessment of the first level of draining lymph nodes. Often, this type of segmental resection can be accomplished by laparoscopic or laparoscopic assisted approaches.

Surgical Management of Synchronous Metastatic Disease

Synchronous metastatic disease is present in 10% to 15% of patients with a newly diagnosed colon cancer. The vast majority of such patients present with synchronous involvement of the liver. It is rare for patients to present with extensive peritoneal metastases or visceral metastases other than in the liver. When the latter, more extensive disease is found, the surgeon is faced with determining whether surgery is indicated. Organs other than the liver that are most commonly involved are kidney, duodenum, pancreas, and pelvic organs such as the bladder.

As a rule, patients with synchronous metastases should be managed aggressively. Surgical resection of the primary tumor and of those

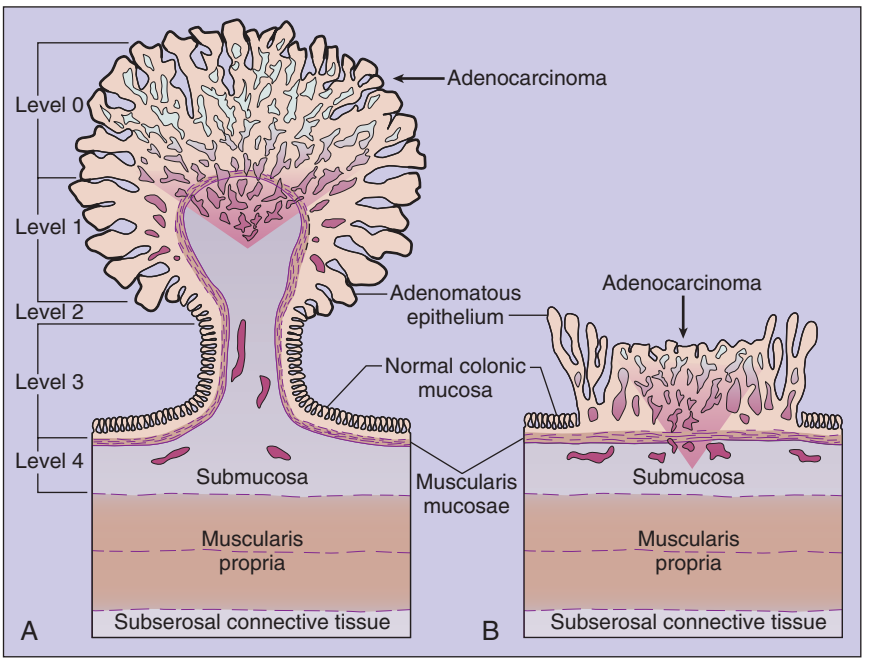
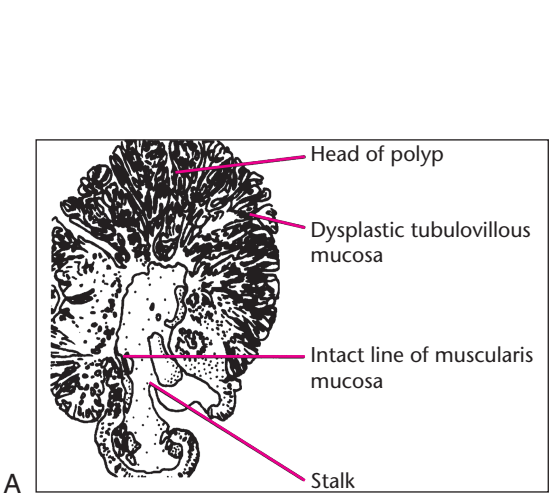


Figure 81-27 • **A,** Pedunculated polyp showing the layers through which the invasion in a pedunculated polyp would need to travel in the stalk before reaching the submucosa of the bowel wall. **B,** Sessile polyp; contrasted with pedunculated polyp. (From Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD: Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology 1985;82:328–336.)





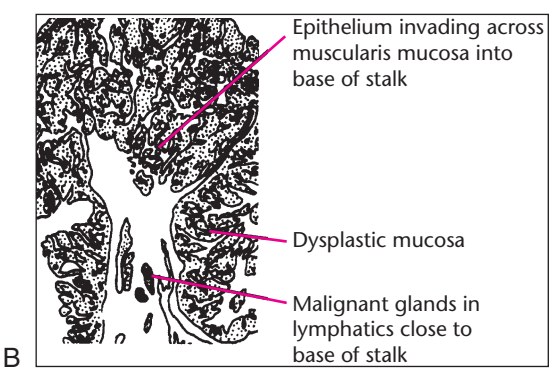




Figure 81-28 • Adenomatous lesions of colon. **A,** In the premalignant neoplastic lesion, the muscularis mucosa is intact. **B,** In the malignant lesion, the muscularis is obviously invaded by malignant epithelium. Malignant glands in the lymphatics are seen close to the base of the stalk. (From Skarin AT, Shaffer K, Wieczorek T [eds]: Atlas of Diagnostic Oncology, 3rd ed. St. Louis, Mosby, 2003, p 149.)

metastases that are appropriately resectable is the accepted approach for surgical management. As was stated previously, the synchronous disease usually involves the liver. Surgical resection combined with either cryogenic or radiofrequency ablation of liver metastases has greatly extended the operative management of such patients.

Patients who present with a metastatic burden that is clearly unresectable could require a palliative operation. For example, a patient with extensive peritoneal involvement could require palliative resection of the primary colon cancer to control bleeding (chronic anemia), obstructive symptoms, or perforation. Quality of life could be improved in an obstructed patient by ileostomy, colostomy, or intestinal bypass procedures. When patients are deemed to be truly advanced and asymptomatic with regard to their primary tumors, they can be safely treated nonoperatively. In one study, only 8.7% required subsequent surgery, and none of these was for perforation or bleeding.[297] Endoscopic fulguration using electrocautery or laser is occasionally used for rectal lesions but is generally too risky for colonic tumors because of the danger of perforation.

Patients who have resectable, synchronous liver metastases generally received adjuvant therapy. Therapy with five-times-daily 5-fluorouracil (5-FU) and LV after liver resection had improved 5-year disease-free survival (DFS) rates (33.5% versus 26.7%, $P = 0.028$), with a trend toward improved overall survival (OS) (51.1% versus 41.1%, $P = 0.13$).[298] The European Organisation for Research and Treatment of Cancer has completed accrual (364 patients) of a trial comparing 12 weeks of preoperative and 12 weeks of postoperative FOLFOX 4 and surgery only for patients with up to four potentially resectable liver metastases; 3-year progression-free survival (PFS) results were presented at the meeting of the American Society of Clinical Oncology (ASCO) in 2007.[299] Only 303 patients, evenly balanced between the two arms, actually underwent resection, and 115 of 151 in the chemotherapy arm received postoperative chemotherapy. The 3-year PFS rate was 28.1% in the surgery-only arm versus 35.4% for the patients who were randomized to combined therapy ($P = 0.058$ for ITT analysis). Excluding the 6% ineligible patients, the PFS rate was 28.1% versus 36.2%, and for those who actually underwent resection, the 3-year PFS rate was 33.2% versus 42.4%. Although the usual adverse events related to FOLFOX chemotherapy occurred, there was also an increased rate of postoperative complications (25.3% versus 15.9%), including biliary fistula, liver failure, intra-abdominal infection, and repeat surgery.

Patients who present with synchronous, unresectable metastatic disease should be evaluated by a multidisciplinary team to establish the need for surgery, radiation, and/or chemotherapy; to ensure that a curative approach is not feasible; and to select appropriate palliative therapy. Patients who present with metastatic disease and who do not require resection of the primary colon cancer to address acute or subacute problems such as significant bleeding, impending obstruction, or perforation and abscess may receive chemotherapy as their initial treatment. A review of 82 patients who were treated without prior resection compared with 280 concurrent patients who did undergo resection showed no increased incidence of peritonitis, fistula formation, or intestinal hemorrhage, occurring in 2.4%, 3.7%, and 3.7% of unresected patients, respectively. Nor was there an increased incidence of obstruction, which occurred in 13.4% of the unresected patients and 13.2% of the resected patients.[300]

Endoscopically placed self-expanding stents have been shown to have a palliative role for the obstructed patient who is not a candidate for surgery, as well as a role in acting as a bridge to surgery. In a systematic review of 598 patients,[301] the stents were successfully placed and deployed in 92% of cases. In the 336 patients for whom the stents were palliative, 90% achieved colonic decompression within 96 hours without reintervention, complications, or reobstruction. In the 262 patients for whom the stents were a bridge to surgery, 80% were associated with a one-stage colonic resection.

Surgical Management of the Ovaries

The ovaries have been known as a site of both synchronous metastases and metachronous involvement. As a result, prophylactic oophorectomy at the time of initial colon resection has been advocated in the past to improve survival. The synchronous involvement of the ovaries as the sole site of disease, however, occurs in fewer than 5% of newly diagnosed colon cancer patients, and about the same percentage of patients will develop isolated ovarian metastases at a later time.

Sielezneff and colleagues[302] studied prophylactic oophorectomy in postmenopausal women and found an incidence of only 2.4% having ovarian metastases, with no difference in 5-year survival.

The Mayo Clinic found no gross or microscopic ovarian involvement in 77 women who were randomized to prophylactic oophorectomy. There was no evidence of a survival benefit in the oophorectomy arm.[303] As a result, there is no evidence to support prophylactic oophorectomy, even in the postmenopausal patient.

Occasionally, the surgeon and pathologist will be confronted with a Krukenberg's tumor of the ovary that presents the dilemma of whether the cancer is primary ovarian with direct extension or metastasis to the colon or a colonic cancer extending to the ovary. Because very different chemotherapy regimens are used to treat these two primary cancers, it is important to diagnose them accurately. Serum markers CEA and CA125 are not very helpful in this situation, and careful histologic examination, including immunohistochemistry by an experienced pathologist, is essential.

Minimally Invasive Laparoscopic Colon Cancer Resection

Laparoscopically assisted colon resection was first described in 1991. Its advantages, as with any minimally invasive procedure, are reduced pain, reduced impact on pulmonary function, more rapid return of bowel function, and less fatigue.[304]

The surgical approach is either completely laparoscopic or laparoscopically assisted colon resection with intraperitoneal gas insufflation or mechanical abdominal wall lift. The anastomosis can be performed intraperitoneally by using a double-staple technique or extraperitoneally through a small (7- to 8-cm) incision to permit stapling or hand sewing the anastomosis.

The learning curve for laparoscopic colorectal surgery has been estimated to range from 20 to 70 cases. This presents a significant hurdle for the average general surgeon in this country, who performs only six to seven open colorectal resections annually.[305,306]

One of the concerns that hampered widespread acceptance of laparoscopic surgery for cancer was the reported incidence of port site recurrences. However, a meta-analysis[307] of four randomized control trials with follow-up to 4.4 years showed an incidence of only 0.5% port site recurrence in laparoscopic surgery as compared with 0.2% wound recurrence in open procedures. The incidence of port site recurrence appears to be related to operator experience. Schneider and associates[308] reported a study of port site recurrences using a porcine model. The authors created a pneumoperitoneum and injected 107 human HeLa cells, creating a xenogeneic tumor. The pigs were subjected to a laparoscopic sigmoid colon resection in which four trocars were used. Schneider and associates tested preventive measures in nine animals, including trocar fixation, prevention of gas leaks, rinsing of instruments with povidone-iodine, rinsing of trocars before removal, peritoneal closure, and irrigation of port wounds with povidone-iodine. Tumor was found in 23 of 36 port sites in control animals and in only 5 of 36 port sites of animals in the prevention group. These results strongly supported the importance of high-quality technique in minimizing the risk of port site recurrence.

Advantages of Laparoscopically Assisted Colon Resection

Short Term

- Earlier return of bowel function (2 days versus 4.5 to 5.0 days)
- Shorter hospital stay (an estimated 40% reduction in length of stay)
- Fewer days of parenteral and oral analgesics
- Earlier recovery
- Fewer infections and wound complications

Long Term

- None yet apparent

Several prospective randomized trials have been designed and implemented to test the hypothesis that DFS and OS are equivalent for laparoscopic-assisted colectomy and standard open colectomy. A meta-analysis of 1536 patients[309] (796 patients in the laparoscopic arm and 740 patients in the open surgery arm) enrolled in four of these trials: Barcelona, Clinical Outcomes of Surgical Therapy (COST), Colon Cancer Laparoscopic or Open Resection (COLOR), and Conventional versus Laparoscopic-Assisted Surgery in Patients with Colorectal Cancer (CLASSIC) with endpoints measuring 3-year DFS and OS has shown no difference in the two approaches. While laparoscopic surgery in colon cancer is concluded to be oncologically safe, it appears that the principal advantage of the minimally invasive procedure is in the short term. Further enhancement of laparoscopic surgery through the use of surgical robots has been attempted in one study[310]; however, only short-term outcomes (estimated blood loss, length of operation, length of hospital stay, and complications) and cost variables were evaluated. There are no current data that clinical outcome, measured by survival, mortality, and recurrence, favors robotic colectomy over traditional laparoscopic surgery much less open colectomy in colon cancer. The cost-benefit analysis of laparoscopic versus open surgery favors the latter.[311] Though the greater expense of laparoscopic surgery can be nearly offset by shorter hospital stays, it has been suggested that the use of enhanced protocols during postoperative recovery would eliminate differences in recovery time between the two types of surgery.[307]

Age as a Factor in Surgery of Colon Cancer

Although colon cancer is a major cause of morbidity and mortality in elderly people, it does occur in patients younger than 40 years of age. Although younger patients present with the same symptoms (abdominal pain, rectal bleeding, weight loss, changes in bowel habits), they are more likely to experience a delay in diagnosis and to present with stage III or IV disease. Survival by stage is comparable for the younger patients and those older than 40 years.[312] Some reports suggest that the younger population is less responsive to chemotherapy.[313]

Older patients are more likely to present with right-sided cancers and to have disease detected when it is less invasive than the younger than 40 years age group.[314] Elderly patients, as expected, are more likely to have comorbid conditions that increase their risk for surgery. Simmonds and coworkers[315] reported the results of a systematic review of published and aggregated data examining the outcomes of colorectal surgery in elderly patients. They grouped patients aged 65 to 74 years, 75 to 84 years, and older than 85 years and compared these groups to those younger than 65 years. They analyzed 28 studies that included 34,194 patients. Their review found that elderly patients had an increased risk of comorbid diseases, presented with later-stage disease, had a higher incidence of emergent surgery, and were at greater risk for having noncurative surgery when compared with the age group younger than 65 years.

As expected, postoperative morbidity and mortality increase with advancing age. Differences in cancer-specific survival, however, are much less dependent on increasing age. Thus, careful preoperative evaluation to diagnose comorbid conditions, so that these can be appropriately managed during surgery and the period of postoperative recovery, is important to providing a successful outcome. Elderly patients (older than 85 years of age) can anticipate a good survival and should be managed similarly to younger people when at all possible.

Managing Complications of Colon Cancer Surgery

The most common postoperative morbidity associated with colon cancer surgery is prolonged ileus. With open resection of the colon, the majority of patients have return of bowel function as manifested by the presence of bowel sounds on abdominal auscultation and the passage of flatus by $4^1/_2$ to 5 days following surgery. For the majority of patients, postresection nasogastric decompression is not required. An exception is the patient who presents with significant obstruction or perforation. If the delay in return of function exceeds 7 to 10 days, there must be concern for an underlying cause. The surgeon must look for electrolyte imbalance, evaluate the level of narcotic use (ruling out excessive use), and search for evidence of intra-abdominal abscess or mechanical obstruction. Instituting nasogastric decompression is often generally indicated.

Anastomotic leaks are reported to be between 4% and 18%, but subclinical leaks could occur much more frequently.[316] More severe leaks with abscess can be managed by percutaneous drainage using CT or ultrasound guidance to place the drain tube. Larger leaks with anastomotic dehiscence and peritonitis require operative intervention, with closure of the anastomosis or resection of the anastomosis and proximal diverting colostomy or ileostomy. A long-term complication of anastomotic leaks that do not require emergency surgery may be stricture formation.

Wound infections are dependent on preoperative preparation of the bowel for surgery, decreasing skin bacteria, and operative technique, all of which measures are designed to minimize bacterial contamination of the wound. The risk of wound infection after colon surgery is 3% to 16% for all presentations. For elective colon cancer resection performed under ideal circumstances and optimal bowel preparation (which accounts for the majority of cases), the risk of wound infection is less than 5%. When an infection occurs, the portion of the wound involved is opened to allow irrigation and twice-daily packing. Wound dehiscence is uncommon and should raise suspicion of anastomotic leak and peritonitis. As might be expected, such dehiscence is significantly increased for patients who are undergoing emergency surgery for colon cancer.[317]

As with other major cancer operations, there has been interest in whether a surgeon's training, experience, and operative volume are important to patient outcome in patients undergoing colon resection for cancer. One such report involved a retrospective analysis of 15,427 admissions in northern Illinois undergoing segmental colon resection between 1994 and 1997. These surgeries were performed at 76 nonfederal hospitals and involved 514 surgeons. The authors determined inpatient mortality, complications of surgery, and hospital length of stay. They found that American Board of Surgery certification and increasing years of experience were associated with reduced mortality. Added colorectal certification and site of training did not factor significantly into the outcomes.[318] Other studies suggest that high-volume colonic surgery performance by the surgeon and having the procedure at a high-volume hospital are important predictors of in-hospital outcome.[319]

Managing Uncommon Tumors of the Colon

More than 98% of the tumors of the large intestine are adenocarcinomas. The remaining 2% of colon tumors are lymphomas, leiomyosarcomas (including gastrointestinal stromal tumors), carcinoids, and (rarely) nonpulmonary small cell cancer. Gastrointestinal stromal

tumors are tumors that arise from the "pacemaker" cells located in the muscularis propria. These tumors tend to present as large masses within the colon but can extend to other organs.[320,321]

The peak incidence of stromal tumors of colon is in the fifth decade, slightly more males than females being diagnosed. Pain is the most frequent presenting symptom.[322]

Gastrointestinal stromal tumors are managed by resection, and recurrences may be found in the peritoneal cavity and liver. The introduction of imatinib mesylate (STI-571, Gleevec), an inhibitor of tyrosine kinase activity of the c-kit proto-oncogene, has provided the first significant opportunity to treat this malignancy by means other than surgery.

Carcinoid tumors (well-differentiated endocrine neoplasms) of the colon account for an estimated 6% of all gastrointestinal carcinoids, more than half originating in the cecum. They almost never present as classic carcinoid syndrome but tend to be advanced, with abdominal pain and weight loss in most patients, nodal involvement in 60%, and liver metastases in 40% of patients. Carcinoid tumors tend to be indolent in their course, and although patients generally live more than 5 years (often with known disease), the OS rate is probably only 25% to 35% with standard treatment.[323]

Lymphomas are known to arise in the gastrointestinal tract, and the colon is the site of origin for approximately 15% of gastrointestinal lymphoma cases. They are extremely rare, accounting for fewer than 1% of colon malignancies. For the colon to be accepted as the primary site, there must be no clinically detected peripheral adenopathy and no imaging evidence of disease in the chest, the peripheral blood smear and bone marrow analysis must be negative, and there must be no evidence of liver or spleen involvement. Malignant lymphoma of the colon has been found as a complication of ulcerative colitis. Both Hodgkin's and non-Hodgkin's lymphoma have been diagnosed.[324] The majority of colon lymphomas are B-cell type and of intermediate- to high-grade histology. Treatment is often surgical resection, but systemic chemotherapy is the mainstay of long-term survival, and surgery might be better used for chemotherapy failures. The overall 5-year survival rate is usually cited to be approximately 50%. There have been a few case reports of multiple mucosal lymphomatous polyps affecting various lengths of colon that appear to be similar to the mucosa-associated lymphoid tissue lymphoma that is seen in the stomach; treatment is 3 months of combination chemotherapy.[325] There are rare reports of mast cell sarcoma and clear cell sarcoma arising in the colon.[326,327]

Surgical Management of Tumors of the Appendix

An estimated 1% (0.9% to 1.4%) of all appendectomy specimens contain a neoplasm. The majority of appendiceal tumors are carcinoids, while the remaining 10% to 20% are mucinous cyst adenocarcinoma, adenocarcinoma, lymphosarcoma, paraganglioma, and granular cell tumors.[328] As expected, most present as acute appendicitis, and in some 40% of cases, the diagnosis is made after appendectomy.

If a mass in the appendix is encountered incidentally during the course of abdominal surgery, an appendectomy is performed with frozen-section analysis of the mass. Most masses prove to be benign mucoceles or very small carcinoids. When carcinoid tumors of the appendix are small (<1 cm in diameter), they may be treated adequately by standard appendectomy. If they are greater than 2 cm in diameter, the patient should have a right hemicolectomy.

Treatment of appendiceal adenocarcinoma is a right hemicolectomy. Mucinous cystadenocarcinoma can be very difficult to manage. Treatment should be a right hemicolectomy and debulking of peritoneal implants.

Currently, the best results in treating mucinous cystadenocarcinoma appear to be obtained with an aggressive combination of cytoreductive surgery, perioperative intraperitoneal chemohyperthermia, and early postoperative intraperitoneal chemotherapy.[329] These measures could provide 5-year and 10-year survival rates as high as 80% and 60%, respectively. If debulking is incomplete, the survival rates are markedly reduced to only 20% and 0%, respectively, and long-term survival cannot be achieved. This tumor can be indolent in its course, and patients commonly have multiple debulking surgeries before ultimately succumbing to their disease.

Managing Colon Cancer in the Pregnant Patient

The incidence of diagnosing a cancer of the colon during pregnancy is estimated to be less than 0.1%. It is interesting that pregnant women have a much higher incidence of rectal cancer (83%), compared with colon sites (17%). This is in contrast to nonpregnant women younger than 40 years of age, among whom the site distribution is 68% colon and 32% rectum.[330]

Certainly, any pregnant patient who reports rectal bleeding or has hemoccult positive stool on examination deserves careful evaluation to rule out cancer.

OUTCOMES OF SURGICAL TREATMENT AND ROLE OF ADJUVANT THERAPY

Optimal Surveillance after Curative Resection

The natural history of colon cancer has several aspects that influence the approach to follow-up. For example, it is well recognized that 80% to 90% of recurrences after curative resection are discovered within the first 2 to 3 years.[331] Fewer than 5% of all recurrences occur after 5 years. Furthermore, these recurrences are often isolated, and when resected completely, they provide about 35% of patients with a cure of their disease.[332,333] This is somewhat distinctive to colon cancer and clearly influences the frequency and method of postsurgical evaluation. It is also recognized that a high percentage of first failures occur in the liver and lung, which could therefore be asymptomatic at the time when they are detected by imaging.

In theory, early detection of recurrent disease can alter the long-term prognosis for an individual patient if the disease that is found is resectable (e.g., isolated liver or lung metastases) or if prompt treatment can alter the long-term prognosis. Patients who can undergo salvage surgery—approximately 20% of patients who are followed closely for recurrence—have an 18.6% 5-year DFS compared with only 5.6% of patients whose recurrences are identified by new symptoms.[334]

Surveillance strategies and inadequately powered trials of surveillance have been reviewed recently.[335] NCCN practice guidelines recommendations for follow-up, using evidence-based medicine approaches, suggest the following measures:

- Physician visits every 3 to 6 months for the first 2 years, then at 6-month intervals until 5 years
- CEA testing at 3- to 6-month intervals for 2 years, then every 6 months until 5 years for T2 or greater lesions
- Consider chest/abdominal/pelvic CT for 3 years in high-risk nonmetastatic disease, that is, with lymphatic or venous invasion or poorly differentiated tumors
- CT scan every 3 to 6 months for 2 years, then every 6 to 12 months in years three to five in patients with metastatic disease
- Colonoscopy 1 year postoperatively, another 3 years later and then every 5 years[336]

Current recommendations are available at www.nccn.org.

For these reasons, patients are initially seen every 3 to 4 months for examination and review of symptoms. In addition, liver injury tests and serum CEA are obtained. Patients with suspicious symptoms, whether focal or constitutional, should undergo evaluation at the time they present. Constitutional symptoms include fatigue, decreased appetite, night sweats, and fever. Suspicious focal

symptoms include early satiety, right-upper-quadrant or right shoulder pain, and crampy abdominal pain.

If complete colonoscopy was not achieved at the time of diagnosis, the first postoperative colonoscopy for the detection of synchronous disease and elimination of any additional polyps should be performed 6 months after surgery to permit complete healing of the anastomosis. Otherwise, colonoscopy is usually performed at yearly intervals for the first 2 years, then every third year, unless additional adenomatous polyps are identified or the patient is in a group that is genetically at high risk for rapid development of invasive malignancy (as discussed previously).

There is a school of thought that the expense of CT imaging as well as the low prevalence of colon cancer recurrences amenable to surgical intervention argues against its routine use as a postoperative surveillance tool.[337–340] However, a number of analyses of prospective randomized trials have offered different conclusions.[334] A review of 1247 patients with resected stage II or III colon carcinoma who were followed in cooperative group trials identified recurrences in 548 patients,[334] of whom 109 underwent a second surgical procedure with curative intent. Of the patients who went to surgery, 77 recurrences were identified by CEA or CT scan. The 5-year DFS rate for all patients undergoing surgery with curative intent was 23%. A second review from the University of Barcelona looked at the outcomes for 199 patients who were followed at 3-month intervals.[338] Of the 140 patients who underwent regular surveillance, 18 of the 56 patients with recurrence were operable, compared with only 3 of 28 patients with symptomatic recurrence. This difference also resulted in differences in long-term cancer-related deaths, 51% of the nonscreened patients dying of cancer within 5 years of their original surgery, compared with 31% of the patients who underwent close follow-up. Obrand and Gordon[339] reported that 24% of their 146 patients with recurrence underwent attempts at reresection, with a 47% 80-month survival rate (i.e., 17 of 146 patients with recurrence were reresectable with long-term survival).

Finally, the evaluation of a multicenter prospective randomized study comparing efficacy of two adjuvant therapy regimens in 530 patients with colorectal cancer that included follow-up surveillance by clinic visit, CEA measurement and thoracic, abdominal, and pelvic CT has shown value in the use of CT scans.[340] The median time to recurrence was 20.6 months in patients whose symptoms led to discovery of new lesion, 14.5 months for CEA, and 13.2 months for CT. Eligible patients underwent reresection. Although there was no significant difference in overall survival from time of randomization among the groups, 5-year survival rates from time of relapse were 0%, 18.6%, and 25.9%, respectively, for symptomatic, CEA, and CT groups. Lead time (7.4 months) bias alone could not explain the difference, as there was a 13.8-month median survival advantage between the symptomatic and CT groups.

For patients with hereditary colon cancer syndromes who develop cancer, postoperative recommendations do not differ from those already described for screening these patients. For all other patients, recommendations for follow-up are described in the NCCN practice guidelines and in the 2000 update of guidelines agreed to by the ASCO.[336,341]

Carcinoembryonic Antigen in the Management of Patients with Colorectal Cancer

CEA is an oncofetal antigen that was first described by Gold and Freedman[342] in 1965. Although CEA is the most commonly used serum marker for malignancies of the gastrointestinal tract, it has never proved useful as a screening test for early cancers. Primary colorectal cancers are commonly CEA negative, even though 90% of tumors can be shown to produce CEA.[343] An explanation for this can be found in the fact that CEA that is produced by colorectal cancer (except for the very low rectal cancers) enters the portal venous circulation and is extracted on the first pass through the liver. As a result, CEA is hypothetically a useful marker of systemic recurrence, even for patients who initially at time of diagnosis presented with normal levels (<5 μg/mL for normal individuals), because the venous drainage from the recurrence is into the systemic circulation. CEA can be modestly elevated in about 19% of smokers who do not have cancer and in 3% of the normal population.[344] These false elevations, however, are almost always less than 10 ng/mL and remain stable during serial testing, in contrast to CEA that is produced by recurrent tumor, for which increasing values are evident over a period of months.[344,345]

When CEA levels are elevated preoperatively for the primary colorectal cancer, they predict a worse prognosis. The sensitivity of CEA as a monitoring test varies from 43% to 89%, with a specificity of 70% to 90%. Elevation of CEA in primary tumors correlates with stage (45% of stage III and 25% of stage II). Even though CEA predicts a worse prognosis, studies have not proved it to be useful in determining the need for adjuvant therapy.[346]

Persistent elevation of CEA 1 month postoperatively suggests the presence of occult metastatic disease and predicts for early development of measurable recurrence. For patients with a normal preoperative CEA and patients whose CEA returns to normal within 4 to 6 weeks of the resection of their primary tumor, a CEA increase is often the first warning of metastatic disease. A significant and progressively increasing CEA is associated with 75% of patients with metastatic colorectal cancer.[347] Monitoring of CEA at intervals of 3 to 6 months is the single most effective method of detecting early failures. The benefit of monitoring, however, decreases after 2 years. Opponents of regular CEA monitoring argue that the gain in lives saved or significantly prolonged is quite small, perhaps only in the 1% to 3% range.[334,339] Patients whose disease is detected by CEA and who have proved to have isolated recurrence (e.g., solitary hepatic metastasis) do achieve significant benefit, however (having an approximately 50% 2-year survival rate).[339,340]

CEA measurements during therapy of metastatic disease are quite helpful. A decrease to normal levels after metastasectomy is a positive finding that predicts a more favorable course. Similarly, during chemotherapy, a substantial fall in CEA occurs in patients who have image-based responses. It is not, however, a substitute for appropriate tumor imaging. The ASCO Tumor Marker Panel recommends monitoring CEA every 2 to 3 months during chemotherapy treatment of metastatic disease if CEA is elevated initially.[341] If CEA increases in two consecutive occasions above baseline or lowest level during therapy, this usually indicates progression of disease; however, patients can develop modest elevations of CEA during adjuvant therapy in association with fatty infiltration of the liver. Intercurrent acute events such as pneumonia, hepatitis, and severe gastroenteritis can also produce modest, reversible elevations of CEA as high as 20 ng/mL.

Metastatic disease patterns for colon cancer include a 15% incidence of local recurrence as the first site of recurrence. Patients have a 36% chance of having liver metastasis as their first site of failure. Reviews of patients in large randomized trials (randomized to the surgery-only arm) confirm these patterns of recurrence.[347] The majority of patients who do recur develop recurrence within the first 3 years, providing a logical basis for less frequent screening visits after that period. Patients with nodal involvement have earlier recurrence than those without nodal involvement.

Evaluation of a Patient with Symptoms

Patients with recurrent cancer can present with very nonspecific symptoms, such as weight loss, malaise, fatigue, or night sweats. They can have focal pain complaints, right upper quadrant or right shoulder pain from liver metastases, or diffuse crampy abdominal pain and abdominal distension from peritoneal carcinomatosis, or pelvic or low back pain from pelvic recurrence. They can develop unilateral pedal edema or pleuritic chest pain from Trousseau's syndrome, with

Box 81-2. SURVEILLANCE GUIDELINES

- Serum CEA performed every 3 months (64% of recurrences are detected first by CEA*)
- Liver injury tests
- Colonoscopy following resection of primary 6 to 12 months after surgery and repeated every 3 years if no polyps are found.
- CT every 3 to 4 months for 2 years, then every 6 months through 5 years. This is controversial absent elevation in CEA (CT scan is first positive test in 11% of patients)

*Castells A, Bessa X, Daniels M, et al: Value of postoperative surveillance after radical surgery for colorectal cancer. Dis Colon Rectum 1998;41:714–724.

deep venous thrombosis or pulmonary emboli. Cough or dyspnea on exertion could indicate pulmonary metastases. Morning headache or focal neurologic complaints (from central nervous system metastases) or focal musculoskeletal pain (from bony metastases), although they are rarely the first signs of metastatic disease in patients with colorectal cancer, could suggest recurrence. New subcutaneous nodules, particularly at pre-existing scar sites, can also be the first presentation of metastatic disease and are a more common physical finding than is new lymphadenopathy in otherwise asymptomatic patients.

Patients with symptoms that are suggestive of recurrent disease should be assessed both with focal radiologic techniques (e.g., CT of the chest, abdomen, and pelvis), clinical chemistries, and serum CEA. The peritoneal surface is notoriously difficult to evaluate, however, and some patients with extensive, symptomatic peritoneal carcinomatosis can have false-negative CT scans because of the difficulty in evaluating this area. For patients with abdominal symptoms, CT scanning, newer MRI techniques, or FDG-PET scanning as discussed earlier for primary staging can suggest the diagnosis and direct further treatment. See Box 81-2 for a summary of surveillance guidelines.

Evaluation of a Patient with Findings on Screening Evaluations

In patients with CEA elevations at the time of initial resection, many clinicians obtain serial CEA measurements to aid in the early detection of potentially resectable recurrence. To trigger further evaluation, CEA not only should be above the normal limit but also should have doubled in value twice. For the majority of patients, history, physical examination, and CT will identify the source of CEA elevation. Up to 10% of patients may have lesions identified that appear to be amenable to curative reresection. When conventional evaluations do not reveal the source of CEA elevation, patients become, understandably, even more distressed than they were when informed that they could have recurrent disease.

Single photon emission computed tomography (SPECT) with radiotagged antibodies has been evaluated for its utility in identifying potentially resectable sites of recurrence. To date, immunoscintigraphy has not been shown to alter clinical outcomes, and its cost effectiveness is unproven.[348] Murine and humanized antibodies directed against tumor-associated antigens have been evaluated for their utility in identifying the site of disease recurrence in these patients.[349] 111In-CYT-103, a murine monoclonal antibody targeting TAG-72, has been shown to be comparable to CT in sensitivity, although it did identify lesions in six patients with negative CT scans.[350] Immunoscintigraphy with ^{99m}Tc anti-CEA showed 20% greater sensitivity for pelvic and retroperitoneal disease.[351] In 173 patients with at least one tumor site that had been identified by CT scan, a totally monoclonal antibody, 88BV59, technetium scan was able to identify only 87% of the lesions (sensitivity 87%) but had a better specificity, with 57% of the lesions identified by SPECT actually representing malignancy at exploration.[352] In 29 patients with rising CEA and no apparent disease, 15 patients (68%) had true positive SPECT findings. Of all 43 lesions that were identified, only 10 were in the liver (where resection of limited disease may be curative), and the number of patients who had disease that was actually resectable for possible cure was not stated. The authors point out, however, that use of CT alone results in an underestimate of disease extent in 41% of patients, compared with 27% underestimation for patients who undergo both procedures.[352] Given the limitations of SPECT scanning, despite the approval of two different preparations for this purpose, its utility at present is limited to identifying disease that is unlikely to be resectable (e.g., inapparent retroperitoneal adenopathy) to avoid futile attempts at surgical ablation of apparently limited metastatic disease.

In patients who have a rising CEA and no apparent disease shown via CT, FDG-PET, or enhanced MRI, surgical exploration failed to find the source of the CEA elevation in 7 of 29 patients (25%) who proceeded to laparotomy.[353] In a series of patients undergoing resection for recurrent disease, however, more than half will actually have resectable disease at exploration.[338]

Patients with Potentially Resectable Recurrent Disease

When a suspicious lesion is identified by CT scan of an asymptomatic patient, further evaluation is directed at ascertaining the feasibility of curative resection. Thus, a solitary lesion in the liver or lung will precipitate spiral CT scan of the remainder of the thorax, abdomen, and pelvis and FDG-PET scan to identify any additional lesions that might preclude resection. In the absence of symptoms or signs of metastatic disease to the bone or brain, these sites are so rarely involved that radiologic evaluation is not undertaken. However, in patients in whom the suspicion of additional metastatic sites is high (i.e., liver metastasis within 1 year of the primary surgery in patient with multiple positive nodes), scanning with radioimmunoglobulin or PET scanning may suggest sites of additional disease that would mandate against an attempt at surgical resection.

In patients who have potentially resectable abnormalities identified by CT and PET scans, 5% to 6% will have benign findings at laparoscopy.[353] PET scanning with FDG could identify the site(s) of disease for 80% to 90% of these patients. Before PET scanning became available, surgical exploration for potentially resectable disease was undertaken in selected patients. At present, if no disease sites are identifiable in an asymptomatic patient, regular reevaluation at 3- to 6-month intervals is appropriate.

Additional imaging could be valuable for patients who appear to have potentially resectable liver metastases to identify the 5% to 10% of patients who have extrahepatic disease and spare them the morbidity and expense of surgery (see Chapter 59). A second group that might benefit from more accurate assessment of the extent of disease consists of patients who will undergo reresection of recurrent rectal carcinoma, identifying those who might have a chance of benefiting from radical surgical resection.

Experienced cancer surgeons regularly evaluate patients with recurrence for their potential resectability. Patients with isolated, solitary metastasis in the liver or lung, in the absence of other life-limiting illnesses, are widely considered to be candidates for resection.

INDICATIONS FOR ADJUVANT THERAPY

Surgical stage remains the most accurate predictor of survival, including the depth of invasion (T1/2 versus T3 versus T4), nodal status, and grade. Table 81-3 shows the 5-year survival rates associated with stage after surgical resection for cure. Patients with five or more positive nodes continue to have a poor prognosis, although they receive comparable benefits from adjuvant therapy. Greene and colleagues reviewed the course of 50,000 patients in the early

1990s, documenting a 5-year survival rate of 22% for surgery alone compared to 33% for adjuvant therapy.[354] Similarly, in a review of 3300 patients in National Surgical Adjuvant Breast and Bowel Project (NSABP) trials, patients with more than five nodes and low grade had 5-year survival rate of 11% to 39% (T4 to T1/2) after surgery, increasing to 27% to 57% with 5-FU-based adjuvant therapy.[355] Another recent study of adjuvant therapy estimated 5-year survival at 82% for N0, 74% for N1, and 54% for N2–3 patients.[356]

Molecular Risk Factors

At present, all molecular risk factors remain in the IIB category, according to the CAP.[241] Unfortunately, despite some studies analyzing data from larger patient populations, markers or combinations of markers that might identify patients who are more (or less) likely to benefit with current adjuvant therapy have not been identified. Many small series have explored additional prognostic factors for patients with colorectal carcinoma, including angiogenic factors such as vascular endothelial grown factor (VEGF) and nitric oxide,[357,358] tumor aggression factors such as microsatel-lite instability or loss of heterozygosity of chromosome 18, proliferation measures such as Ki-67, survival measures such as p53, and factors related to chemotherapy effects such as thymidylate synthase (TS).[359–365]

Mutations in p53, frequently leading to overexpression of nonfunctional protein, have been associated in the laboratory with decreased sensitivity to several classes of chemotherapy, including DNA-damaging agents such as irinotecan and oxaliplatin.[363,364,366] There have been serious limitations in the assessment of p53 status from clinical samples, so direct sequencing is rarely used, and immunohistochemistry results correlate with sequencing results only in the 60% to 80% range.[362] The association of p53 overexpression with poor outcome has not been demonstrated consistently in clinical trials.[359,361]

Several studies have reported that patients with cancer who overexpress TS have a lower response rate to treatment with 5-FU.[360,361,364,365,367,368] Ichikawa and colleagues[369] evaluated both dihydropyrimidine dehydrogenase expression (lower activity would result in decreased catabolism of 5-FU and greater exposure to active drug) and TS, finding that patients with low dihydropyrimidine dehydrogenase and low TS had a median survival time of 16.3 months, compared with 8.4 months for patients with high dihydropyrimidine dehydrogenase and high TS. Johnston and colleagues[370] found that the expression of TS as measured in primary tumors using TS106 antibody did not correlate with 5-FU activity in metastatic sites. Overexpression of TS, however, predicts a poorer survival, regardless of whether patients received adjuvant therapy, and formal tests for interaction with chemotherapy suggest that patients with differing levels of TS expression maintained benefit from adjuvant chemotherapy.[361]

Kidd and coworkers[371] obtained samples for pharmacogenomic analysis from 524 of 795 patients treated for metastatic colorectal carcinoma with IFL, FOLFOX, or IROX (see chemotherapy regimens discussed later in this chapter). They looked at panels relevant to 5-FU metabolism and variations in its targets of thymidylate synthase and methylenetetrahydrofolate reductase, panels relevant to oxaliplatin metabolism, excision repair (ERCC2 and XRCC1), and irinotecan metabolism (14 potential variants in all). Only ERCC2 K751Q (14% frequency) was correlated with response to treatment ($P = 0.0052$), and UGT1A1 7/7 was associated with neutropenia from irinotecan (7% frequency, $P = 0.007$). The only other statistically relevant association with response and time to progression was the thymidylate synthase variant 1494del, with a 47% frequency ($P = 0.02$). The TRAIL receptor, DR5, has been shown to be important for response to 5-FU in xenograft models.[372] High expression of the DR4 receptor for TRAIL has also been identified as a negative prognostic factor for patients receiving adjuvant therapy, with a relative risk of recurrence of 2.19 for the 82% of patients who were high expressors.[373]

Other proposed prognostic markers include the CpG island methylator phenotype (CIMP), a phenotype that has been observed in 20% to 40% of patients with colon cancers, which presumably is associated with transcriptional silencing of tumor suppressor genes.[374] Although CIMP-positive patients have poorer survival if treated with surgery alone, there was a trend for improved survival of CIMP-positive patients who received adjuvant chemotherapy. Van Rijnsoever and colleagues hypothesize that the hypermethylated DNA status in CIMP-positive tumors could be a marker for aberrations in cellular folate and methyl group metabolism, rendering CIMP-positive cancers more sensitive to 5-FU. This proposal needs to be evaluated prospectively in a larger patient population.

History of Development of Adjuvant Treatment and Established Adjuvant Regimens

As many as 50% to 60% of patients who undergo "successful" surgery for colon carcinoma have residual micrometastatic disease, and clinically evident cancer will develop, either locally or at distant sites, within 5 years of surgery. Systemic treatment, known as adjuvant therapy and intended to reduce the risk of recurrence, is now widely recommended for patients with lymph node involvement (stage III), as well as higher-risk patients with T3N0, although the absolute percentage benefit for stage II is quite small. There has been considerable variability regionally in both the United States and elsewhere in the use of adjuvant therapy after curative surgery. In Japan, adjuvant chemotherapy has been used for all patients except those in stage A; in the United States, on the other hand, adjuvant therapy is used for patients with stage B2 rectal carcinoma (see Chapter 82), and is used selectively for patients with higher-risk B2 colon cancer. Adjuvant therapy is generally recommended for patients with lymph node involvement without other significant comorbidities. In Europe, in contrast, even patients with stage C (nodal involvement) did not receive routine adjuvant therapy until 1995.

The original trials of systemic chemotherapy after surgery for colorectal cancer were undertaken more than 40 years ago. Although some clinicians favored adjuvant therapy on the basis of these early experiences, the studies were underpowered to identify the realistic benefits of such treatment. Larger trials with more aggressive drug administration schedules were initiated in the 1970s and showed small but statistically significant benefits for adjuvant therapy. A small positive trial of levamisole, an antihelminthic agent with immunostimulatory properties, led to a series of large confirmatory trials. In contrast to the initial trial, these studies showed no benefit for levamisole as a single agent.[375] Selected recent randomized trials of 5-FU adjuvant regimens versus surgery alone are listed in Table 81-5. Compared with 5-FU modified with folinic acid (leucovorin), however, 5-FU with levamisole was inferior, and it is no longer used in this setting. Subsequently, the addition of oxaliplatin to 5-FU/LV (MOSAIC trial) has set the current standard of care. Additional trials have addressed the duration of therapy (6 months versus 12 months), the use of 5-FU with leucovorin (LV) or oral capecitabine on a variety of schedules and durations, and the addition of irinotecan. Ongoing trials are exploring the use of bevacizumab and cetuximab in the adjuvant setting.

Adjuvant Treatment of Patients with Full-Thickness Bowel Wall Invasion and Negative Lymph Nodes (Stage II, T3 N0 M0, Dukes B2)

The role of adjuvant therapy for node-negative patients with disease extending through the bowel wall has not been established unequivocally, as many underpowered clinical trials have been published. Many current trials accrue these patients to trials of adjuvant therapy but in numbers that are inadequate to establish the expected small

Table 81-5 Selected Early Randomized Trials of Adjuvant 5-FU-Based Chemotherapy versus Observation Following Surgical Resection in Colon Cancer

Study, Time Period, and Country	*N*	Stage	Treatment Regimens	5-Year DFS (%)	*P*-Value	5-Year OS (%)	*P*-Value	Comments	Reference
INT 0035, 1984–1987, United States	929	Stage III	1. Observation 2. Levamisole 3. 5-FU/LEV	47 (3-year) NR 63 (3-year)	<0.0001 (1 vs. 3)	55 (3-year) NR 71 (3-year)	0.007 (1 vs. 3)	5-FU + LEV reduced recurrence rate by 40% and the death rate by 33%. No survival benefit was associated with LEV alone.	Moertel et al.[375,379]
INT 0085, 1988–1989, United States	309	Stage II (high- risk) and stage III	1. Observation 2. 5-FU/LV	58 74	0.004	63 74	0.01	5-FU + LV for 6 months demonstrated a survival advantage over observation alone in patients with high-risk colon cancer.	O'Connell et al.[392]
NSABP C-01, 1977–1983, United States	1166	Stages II and III	1. Observation 2. 5-FU/semustine/ vincristine (MOF) 3. Bacille Calmette-Guérin	51 58 56	0.02 (1 vs. 2) 0.09 (1 vs. 3)	59 67 67	0.05 (1 vs 2) 0.03 (1 vs. 3)	Survival advantage demonstrated for adjuvant chemotherapy for Dukes B and C (stages II and III) colon cancer	Wolmark et al.[393,394]
IMPACT-1, 1982–1993, Meta-analysis of trials from Italy, France, Canada*	1526	Stages II and III	1. Observation 2. 5FU/LV	62 (3-year) 71 (3-year)	<0.0001	68 (3-year) 74 (3-year)	0.018	Long-term follow-up demonstrated a survival benefit for 5-FU/LV for patients with stage III cancer.	International Multicentre Pooled Analysis of Colon Cancer Trials (IMPACT) Investigators,[390] Marsoni[395]

DFS, disease-free survival; 5-FU, 5-fluorouracil; LEV, levamisole; LV, leucovorin; NR, not reported; OS, overall survival.

*The three trials (GMO, NCIC-CTG, FFCD) included in this meta-analysis were those that were stopped prematurely when surgery-alone control arms were no longer thought to be the standard of care in Dukes' C (stage III) disease.

Adapted from Chau I, Cunningham D: Chemotherapy in colorectal cancer: new options and new challenges. Br Med Bull 2002;64:159–180.

fractional benefit definitively. Because surgery alone results in 5-year DFS rates of 75% to 80% for patients with stage II colon carcinoma, 3572 patients must be randomized to show a 4% improvement to 84% with 80% power.[376] The QUASAR study was nearly this size, as 92% of the 3239 patients had stage 2 and were randomized between observation or 5-FU/LV regimens. With a median follow-up of 5.5 years, the 5-year recurrence-free rates were 84% for chemotherapy and 80% for observation, and 5-year survival rates were 85% versus 82%, respectively.[377]

Clinicians and groups vary in their recommendations to patients, most reserving adjuvant therapy for patients who have some adverse prognostic indicator, such as T4 lesions, inadequate node sampling (<13), bowel perforation, or poorly differentiated histology.[378]

The same schedule of 5-FU and levamisole that was used for patients with lymph node involvement (see later discussion) was evaluated in patients with stage II colon cancer.[379] Although the recurrence rate was reduced by 31% in these patients (71% DFS rate for the observation arm versus 79% for patients receiving 5-FU/levamisole), there was no difference in OS rate (72% at 5 years). The lack of survival advantage was attributed in part to the unexplained occurrence of twice the number of noncancer-related deaths in the patients who received adjuvant chemotherapy. It should be noted that these deaths also were not directly associated with treatment. In addition, six of seven patients who had surgically curable recurrences were in the surgery-only group.[379] This result was confirmed in a European study that showed a similar improvement in survival rate from 70% to 78%.[380] An Italian study comparing surgery alone with postoperative 5-FU and LV (370 mg/m^2 plus 200 mg/m^2 daily for 5 days for the first week of each 4-week cycle) for 6 months (six cycles of chemotherapy) showed a 21% reduction in mortality rate (23% to 20%). There was an 8% absolute difference in the DFS rate at 5 years (76% versus 68% alive without recurrence). It should be noted that the 5-year DFS rate in this study was somewhat inferior to that in other trials that were conducted during the same period.[381]

A single trial of autologous tumor cell vaccine augmented with bacille Calmette-Guérin has also shown some DFS benefit for patients with stage II disease, although trials attempting to evoke immune responses to eradicate micrometastatic disease have not yet shown improvement in overall survival (see the following discussion).[382] There is an ongoing Japanese trial evaluating the uracil-tegafur combination, UFT, with krestin, a polysaccharide immune modulator, although it is likely underpowered (340 patients).

A discussion of approaches to meta-analysis of the many inadequately powered trials has been undertaken.[383] Meta-analysis from four large trials conducted by the National Surgical Adjuvant Breast and Bowel Project has assessed the improvements in OS and DFS rates to be comparable for patients with stage II tumors: from 82% to 88% ($P = 0.08$).[384] Another group, however, found a smaller (and also statistically nonsignificant) possible benefit in their meta-analysis, with 5-year OS rates of 80% for untreated patients and 82% for treated patients.[385] The results for the 318 stage II patients in the Intergroup trial of 5-FU plus levamisole versus postoperative observation also favored adjuvant therapy, but again the trial was too small to demonstrate a probability of false positive of less than 5%.[379]

Adjuvant Treatment of Patients with Lymph Node Involvement (Stage III, Dukes C)

Chemotherapy with 6 months of 5-FU and LV after primary surgery was the first established beneficial adjuvant based on trials conducted in the 1980s. Adjuvant therapy is currently recommended for patients with colon carcinoma and nodal involvement to reduce the rate of cancer recurrence and prolong survival; however, the original 5-FU regimens have been supplanted by the combination of fluoropyrimidines with oxaliplatin.[386–388] Although adjuvant therapy does not necessarily alter the recurrence rate for each patient and therefore is not universally useful to patients, an additional 10% to 20% of patients with nodal involvement are cured by postoperative adjuvant chemotherapy, and others have prolongation of disease-free survival, although they eventually relapse. Recently published trials have addressed replacing intravenous 5-FU/LV with capecitabine, the duration of treatment and reduction of adverse events, as well as the use of newer chemotherapy agents such as oxaliplatin and irinotecan and the use of agents with novel targets such as bevacizumab, cetuximab, and panitumumab.

The NSABP C-03 was the first trial to demonstrate the value of 5-FU and LV in the adjuvant setting.[389] Those results were subsequently confirmed in additional large trials.[390–397] Table 81-6 summarizes selected randomized trials comparing various 5-FU-based adjuvant regimens. Early adjuvant trials were not sized adequately to detect survival differences as small as 10% to 15%, and chemotherapy was not widely prescribed postoperatively until 15 years ago. Most of the early trials enrolled only 100 to 200 patients, a sample size that can detect only survival differences greater than 30%. The initial trials of 5-FU and levamisole, using a 5-day bolus "loading dose" followed 1 month later by weekly 5-FU, showed absolute differences of 8%. A large confirmatory trial randomizing 929 patients reduced the recurrence rate by 40% and the death rate by 33%, resulting in 5-year DFS rates of 47% compared with 35% in patients who underwent surgery alone or with levamisole.[375]

Because of the advances that were observed in patients with metastatic disease who were treated with fluorouracil modulated by LV, this regimen has been evaluated widely in the adjuvant setting. The NSABP trial found similar improvements in DFS and OS rates for 1 year of treatment with 5-FU (500 mg/m^2 weekly for 6 out of 8 weeks) and LV (500 mg/m^2).[384,391] Subsequent studies have evaluated the role of LV and the duration of treatment in this setting. Patients undergoing 6 months of treatment with 5-FU (425 mg/m^2 daily for 5 days every fourth week) plus LV (20 mg/m^2 daily for 5 days every fourth week) experienced a 16% absolute difference in 5-year DFS rate compared with patients undergoing surgery only (74% versus 58% DFS at 5 years).[392] The overall 5-year survival rate difference was 11%, improving from 63% to 74% for the patients who received 5-FU plus LV. Six months of treatment with 5-FU and LV produced 5-year survival rates comparable to 12 months of either 5-FU plus LV or 5-FU plus levamisole. Six months of treatment with 5-FU plus levamisole yields results inferior to those of the other regimens.[398]

A three-armed trial of 5-FU plus LV (weekly intravenous bolus) versus 5-FU plus levamisole versus all three agents enrolled 2151 patients with Dukes B or C colon carcinoma. 5-FU with LV, used for 6 months, resulted in a modest increase in the DFS rate at 5 years (65% versus 60%, $P = 0.04$) and in the OS rate (74% versus 70%, $P = 0.07$); levamisole added toxicity and resulted in lower (statistically insignificant) DFS and OS rates.[399]

Adjuvant infusional regimens of 5-FU have been evaluated in European studies and have been demonstrated to have efficacy similar to 5-day intravenous bolus regimens given monthly but with reduced adverse effects.[400,401] An FULV2 regimen (LV 200 mg/m^2 over 2 hours, 5-FU intravenous bolus 400 mg/m^2 followed by 5-FU 600 mg/m^2 over 22 hours on days 1 and 2) was compared with five-times-daily treatment in the first of 4 weeks (LV 200 mg/m^2 intravenous bolus plus 5-FU 400 mg/m^2 intravenous bolus for 5 days in the first week of a 4-week cycle), prescribed for either 24 or 36 weeks in a 2 × 2 factorial design. In this study, 905 patients were followed for a median of 40 months.[400] The 48-hour infusional regimen was less toxic, and no difference in DFS or OS was found between the arms, although the cohort size precludes demonstrating small advantages for one arm. Protracted venous infusion of 5-FU at 300 mg/m^2/day for 12 weeks has been compared with 6 months of 5-FU/LV (5-FU 425 mg/m^2 plus LV 20 mg/m^2 as intravenous bolus on days 1 through 5 repeated every 28 days) in a cohort of 716 patients with stage II or III colon cancer. Although overall survival at 3 years did not differ statistically between the study arms (83.2% versus 87.9%), patients receiving 6 months of bolus therapy had a worse relapse-free survival

Table 81-6 Selected Randomized Trials of Adjuvant Chemotherapy Comparing 5-FU-based Regimens in Colon Cancer

Study, Time Period, Country	Stage	*N*	Regimen	5-Year DFS (%)	5-Year OS (%)	Comment (*P*-values)
NSABP C-03, 1987–1988, United States[389]	Stages II and III	1080	1. 5-FU-HDLV (1 year)	66	76	Both a DFS benefit ($P = 0.0004$) and OS benefit ($P = 0.003$) were noted for 5-FU-LV over the MOF regimen
			2. 5-FU/semustine/vincristine (MOF)	54	66	
INT 0089, 1988, United States[397]	Stage II (high-risk Dukes B2) and stage III	3759	1. 5-FU-LEV (1 year)	56	63	5-FU-LDLV + LEV had improved DFS ($P = 0.014$) and OS ($P = 0.007$) compared to 5-FU-LEV. All other did not demonstrate any differences. 6 months of 5-FU-LV became the standard for adjuvant therapy.
			2. 5-FU-LDLV (6 months)	59	66	
			3. 5-FU-HDLV (6 months)	60	65	
			4. 5-FU-LDLV + LEV (6 months)	60	67	
NSABP C-04, 1989–1990, United States[399]	Stages II and III	2151	1. 5-FU-HDLV (1 year)	65	74	5-FU-HDLV was superior to 5-FU-LEV in DFS ($P = 0.04$) and not significantly better for OS ($P = 0.07$). The addition of LEV to 5-FU-HDLV was not beneficial.
			2. 5-FU-LEV (1 year)	60	70	
			3. 5-FU-HDLV + LEV (1 year)	64	73	
NCCTG 894651 [NCCTG-NCIC], 1996, United States, Canada[398]	Stage II (Dukes B2) and stage III	890	1. 5-FU-LEV (6 months)	57	60	5-FU-LDLV + LEV for 6 months was superior to 5-FU + LEV for 6 months ($P < 0.01$); however, there were no significant difference between 6 and 12 months of treatment with the same regimen
			2. 5-FU-LEV (1 year)	63	68	
			3. 5-FU-LDLV + LEV (6 months)	63	70	
			4. 5-FU-LDLV + LEV (1 year)	57	63	
QUASAR, 1994–1997, United Kingdom*	Stages II and III (2×2 factorial design)	4927	1. 5-FU-LDLV + LEV (6 months)	64 (3-year) HDLV arms	70 (3-year) HDLV arms	No significant difference in DFS and OS between high-dose or low-dose LV and no difference between LEV and placebo
			2. 5-FU-LDLV + placebo (6 months)	64 (3-year) LDLV arms	71 (3-year) LDLV arms	
			3. 5-FU-HDLV + LEV (6 months)	63 (3-year) LEV arms	69 (3-year) LEV arms	
			4. 5-FU-HDLV + placebo (6 months)	65 (3-year) placebo arms	72 (3-year) placebo arms	
French National Study, 1996–1999, France[400]	Stages II and III (2×2 factorial design)	905	1. Infusional LV5FU2 (semimonthly) (24 weeks)	73 (3-year) LV5FU2 arms	86 (3-year) LV5FU2 arms	No significant difference in DFS and CS between treatment arms but small trial size precluded demonstration of small advantages for one arm and LV5FU2 was less toxic
			2. Bolus 5FU/LV (monthly) (24 weeks)	72 (3-year) 5FU/LV arms	88 (3-year) 5-FU/LV arms	
			3. Infusional LV5FU2 (semimonthly) (36 weeks)	73 (3-year) 24-week arms	87 (3-year) 24-week arms	
			4. Bolus 5FU/LV (monthly) (24 weeks)	72 (3-year) 36-week arms	83 (3-year) 36-week arms	
MOSAIC, 1998–2001, Europe[386]	Stages II and III	2246	1. LV5FU2 (de Gramont regimen) (6 months)	73 (3-year)	Results not yet available	3-year DFS benefit ($P < 0.01$)
			2. FOLFOX4 (6 months)	78 (3-year)		
NSABP C-07, 2000–2002[387]	Stage II/III	2407	1. Weekly FU/LV	71.8 (3-year)	Pending	
			2. FLOX (wkly FU/LV with biweekly oxaliplatin)	76.1 (3-year)		
X-ACT, 1998–2001, global[402]	Stage III	1987	1. Capecitabine	64.2 (3-year)	81.3 (3-year)	$P = 0.12$ NS
			2. 5-FU/LV d × 5	60.6	77.6 (3-year)	$P = 0.005$

DFS, disease-free survival; 5-FU, 5-fluorouracil; FOLFOX4, oxaliplatin with infusional 5-fluorouracil (de Gramont regimen); HDLV, high-dose leucovorin; LDLV, low-dose leucovorin; LEV, levamisole; LV5FU2, de Gramont regimen of infusional 5-fluorouracil with leucovorin; OS, overall survival.

*QUASAR Collaborative Group: Comparison of flourouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. Lancet 2000;355:1588–1596.

Adapted from Chau I, Cunningham D: Chemotherapy in colorectal cancer: new options and new challenges. Br Med Bull 2002;64:159–180.

rate (68.6% versus 80%) and greater toxicity, including increased neutropenia, diarrhea, and stomatitis.[401]

Capecitabine, an oral agent that delivers fluorouracil in tumor tissue (see later in the chapter), has been evaluated in a large (1987 patients) randomized adjuvant trial, demonstrating equivalent DFS compared with 5-FU/LV given five times daily every 4 weeks for 24 weeks, with fewer adverse events. The 3-year rates of disease free survival were 64.2% (capecitabine) versus 60.6% ($P = 0.12$) , with 3-year OS rates of 81.3% versus 77.6%.[402] Another large adjuvant trial comparing capecitabine and oxaliplatin (CAPEOX or XELOX) with bolus 5-FU/LV has accrued 1886 patients; safety results from this trial have been reported, confirming the expected increase in emesis, hand-foot syndrome, and neurosensory adverse events; the expected decrease in diarrhea; and a 0.6% treatment related mortality, which is comparable to perioperative mortality. Final results from this study are expected in 2008.[388]

Adjuvant Oxaliplatin Combinations

The value of adding oxaliplatin to fluoropyrimidine regimens in the adjuvant setting was established in 2004 in the first of three large multicenter trials. Andre and colleagues compared patients with stage 2 and 3 colon carcinoma receiving infusional 5-FU and LV (LV5FU2) with or without oxaliplatin for 12 2-week cycles. 1123 patients were assigned to each arm, with a 3-year DFS of 78.2% versus 72.9% ($P = 0.002$) for all eligible patients. The 3-year DFS rate for patients with stage III disease was 72.2 versus 65.3%, and for patients with stage II disease, it was 87.0 versus 84.3 %; stage II patients represented 40% of the study population.[386]

Two phase III trials have compared bolus 5-FU/LV with or without oxaliplatin in the adjuvant setting. NSABP confirmed the benefit of adding oxaliplatin to a weekly bolus 5-FU/LV regimen.[387] In this study, randomizing 2407 patients (29% stage II) to either weekly bolus FU/LV for 6 out of 8 weeks for 6 months with or without oxaliplatin 85 mg/m^2, every other week, the 3-year DFS rates were 76.1% versus 71.8%. Safety data from a third adjuvant trial evaluating adjuvant capecitabine with oxaliplatin versus bolus 5-FU/LV on the five-times-daily (Mayo) regimen was just reviewed.[388]

In contrast to the consistent improvement in DFS for trials of oxaliplatin with 5-FU/LV, the addition of irinotecan to either infusional or bolus regimens did not improve DFS in three separate trials that were presented at ASCO meetings in 2004 and 2005 (but have not yet been published in final form); each trial differed in design from the successful oxaliplatin combination trials in specific ways: The PETACC trial included second noncolorectal carcinomas as an endpoint; T staging was not included as a stratification factor in the ACCORD study, which was also powered to establish an absolute 15% difference in 3-year DFS and therefore was underpowered. However, these unsuccessful trials illustrate the critical importance both of trial design and of not extrapolating activity in patients with advanced disease to the adjuvant setting.

Adjuvant therapy regimens for colon carcinoma are generally well tolerated after individual dose adjustment. Treatment-related mortality has been found to be less than 1% for 5-FU/LV, and only 18 deaths while on chemotherapy occurred among the 2151 patients who were treated in NSABP C-04.[389,399] On regimens using 5-FU at 425 mg/m^2 for 5 days, one third of patients will experience severe (grade III or IV) stomatitis, and one quarter will have severe diarrhea. Grade III leukopenia occurs in 10% to 15% of patients and severe nausea in only 5% to 7%. On a weekly bolus schedule, hematologic toxicity occurs in fewer than 2% of patients, ataxia in 1%, and grade III or IV diarrhea occurs in at least one course for 35% of patients, resulting in dose reductions.[399] About half of patients treated require dose reduction, with a reduction to 75% of baseline as the median adjustment. The percentage of the total prescribed dose that is actually given averages 70%, with 77% of patients completing all courses of therapy (excluding patients who die or have disease recurrence).[389] Dose reduction (either 4 days of treatment or reduced daily doses) usually abrogates the intensity of these side effects in subsequent cycles. When starting at a lower dose (375 mg/m^2), only 5% of patients experience grade III to IV mucositis, while 4.5% experience severe diarrhea and 2.5% experience severe emesis. Transient grade IV neutropenia occurs in 14%. If lower doses are used initially, however, physicians should consider dose escalations for patients who have no side effects in the first cycle of treatment, as dose intensity of 5-FU has been correlated with activity against disease.

The National Cancer Institute-sponsored CALGB trial, which randomized 1263 stage III patients between irinotecan, 5-FU, and LV (IFL) for 30 weeks versus 5-FU/LV weekly, was closed in April 2001 because of concerns about the 60-day all-cause mortality rate of 2.5% in the IFL arm versus 0.7% (see the discussion later in the chapter in the section on Irinotecan).[403] This trial has subsequently not shown an advantage for the addition of irinotecan in the adjuvant setting. Attention to dose-adjustment recommendations and supportive care can minimize the adverse effects of 5-FU/LV on patient well-being. In particular, close nursing observation is critical for the safety of these regimens and ensures that treatment breaks are initiated when patients experience mucositis or diarrhea. Patients who develop oral pain or diarrhea before receiving their fifth of five daily doses should not receive the final scheduled dose(s). It is important to assess any changes in the patient's bowel habits prior to administering weekly doses of 5-FU/LV. Persisting in the administration of a cell cycle-specific antimetabolite after diarrhea or mucositis has developed exposes proliferating crypt cells that have been recruited into S phase to a drug that is specific for cells in S phase and can result in more severe diarrhea and mucositis symptoms that could require hospitalization for management. Symptomatic measures could be helpful; for example, mucositis can be reduced by using oral ice chips for 30 minutes when 5-FU is administered by intravenous bolus.[404] Patients who experience moderate to severe diarrhea usually benefit symptomatically from loperamide administration but still require a treatment break even if their symptoms are subsiding with supportive care. Comparison of FOLFOX and LV5FU2 regimens[386] had the expected differences in adverse event profiles, with a higher frequency of grade III/IV neutropenia (41% versus 5%), neutropenic fever (1.8% versus 0.2%), grade III/IV diarrhea (10.8% versus 6.6%), grade III/IV emesis (5.8% versus 1.6%), allergic reaction (2.9% versus 0.2%), and peripheral neuropathy (92% versus 15%), although only 12.4% had grade III neuropathy, and only 1.1% had persistent grade III neuropathy at 12 months. There was a 0.5% 60-day (treatment-related) mortality rate for each arm and a 1.2% (FOLFOX) versus 1.8% (LV5FU2) rate of thromboembolic events. Toxicity was somewhat more intense with oxaliplatin combined with bolus FU-based regimens[387,388]; The 60-day mortality rate was slightly higher (1% and 1.2%), as was the incidence of grade III/IV diarrhea (38% and 32%), but the rate of grade III neurotoxicity was slightly lower (8.2%). The NSABP investigators carefully described chemotherapy-induced enteropathy, with diarrhea and bowel wall thickening, which occurred in 9.1% of the FLOX arm and 3.9% of the FULV arm.[387] Adjuvant trials that have recently completed accrual or are still in progress for patients with stage III colon cancer are listed in Table 81-7.

Adjuvant Therapy in the Elderly

Older patients who otherwise meet eligibility requirements have been included in recent large randomized trials, albeit at rates that are substantially lower than the incidence of disease (16% of trial patients versus approximately 50% of all patients with colon carcinoma). In older patients without comorbidities that are likely to result in limited survival, the effectiveness of adjuvant regimens is comparable to its utility in younger patients. In a review of the safety of FOLFOX regimens (adjuvant and therapeutic) involving patients older than 70

Table 81-7 Selected Randomized Trials of Adjuvant Chemotherapy in Colon Cancer That Have Closed Recently or Are Still in Progress*

Study, Country	Stage	*N*	Regimens	Status
ECOG 5202, United States	II	3610	FOLFOX ± bevacizumab; stratification by IIa vs IIb, MSI	Open 2005; potential accrual through 2010
NSABP C-08, United States	II/III	2632	FOLFOX ± bevacizumab	closed to accrual
AVANT, Europe	II/III	3450	FOLFOX ± bevacizumab and xelox/bevacizumab (3 arms)	Open Dec 2004
ECOG/INT 0147, United States	III	2300	FOLFOX ± cetuximab	Open 2004; irino arms closed 2005; may complete accrual 2008
PETACC-8, France	III	2000	FOLFOX ± cetuximab	Open 2005

*As of August 2007.

years of age (614 of 3742 total patients), only neutropenia (43% versus 49% incidence of grade > III) and thrombocytopenia (2% versus 5%) were somewhat more frequent in the older patients, and there was a nonsignificant trend to an increased 60-day mortality rate (1.1% versus 2.3%, $P = 0.2$). However, only 15 of the reviewed patients in these four trials were 80 years or older.[405] Sanoff and colleagues have recently reviewed the issues of managing older patients with colorectal carcinoma.[406]

Radiation Therapy

While prospective randomized trials have largely defined the role of adjuvant chemotherapy in patients with high-risk colon cancer, the role of adjuvant radiation therapy remains poorly defined. Adjuvant radiation therapy has not attained common practice, primarily because failure patterns after attempted curative resection tend to favor abdominal rather than local recurrence. However, although the overall incidence of local failure is 20% or less, local failure risk can be significantly higher in certain subsets of patients, implying that a selective application of postoperative radiation therapy could provide benefit. Such subsets might be identifiable from various reports on patterns of failure.[407–410] Analysis of failure patterns in patients undergoing reoperation or autopsy indicates that patients with tumor adherence (T4) and/or lymph node involvement have increased local recurrence risk.[407] Gunderson and colleagues[407] found a 67% incidence of local regional failure in 24 patients with adherence to or invasion of surrounding structures, while Russell and coworkers[409] found a 69% incidence in a similar group of patients and a 30% incidence of local failure in patients with both regional nodal involvement and bowel wall penetration.

In addition to these pathologic factors, anatomic location has also been proposed to influence risk of local recurrence, presumably by compromising radial margins, although there is less consensus over this issue. Gunderson and colleagues[407] have suggested that lesions located in immobile areas such as the ascending and descending colon, particularly when posteriorly located, could have compromised margins of resection, a situation that is not likely to occur in mobile, intraperitoneal structures such as the sigmoid and transverse colon. But whereas Willett and associates[410] also found differences in local recurrence rates by location, the observed patterns differed from the observations that had been made in the previous study. In addition, Minsky and associates[408] found no difference in failure rates between regions of colon that were considered to be mobile or immobile, further calling into question the degree to which location and bowel mobility are predictive of local recurrence risk.

Overall, then, pathology rather than location appears to be the clearest predictor of local recurrence risk, with tumor adherence to abdominal structures and with bowel penetration in combination with nodal involvement predicting local recurrence risks that can be substantial.

Role of Adjuvant Radiation Therapy

Although several randomized clinical trials for rectal cancer have shown postoperative chemoradiotherapy to decrease pelvic recurrence and increases survival in T3 or higher T stage and/or N-positive rectal cancer, there is only a single, underpowered, negative randomized trial for colon cancer.[411] There are, however, several single-institution studies suggesting that postoperative irradiation reduces local failure.[410,412,413]

Willett and colleagues[410] have reported on the largest single-institution experience. In this retrospective trial, 203 patients received postoperative radiation therapy (45 Gy plus a reduced-field boost to 50.4 to 54 Gy) with and without concurrent 5-FU chemotherapy after resection of T3, T4, and T3/4, N-positive colon tumors. Of the 203 patients, 30 (15%) had residual local tumor after resection. The 173 remaining patients treated with adjuvant radiation therapy were compared with a historical control group of 395 patients undergoing surgery only. Improved local control and recurrence-free survival rates were seen for patients with T4 N0 and T4 N+ colon carcinoma treated with postoperative radiation therapy, compared with a similarly staged group of patients undergoing surgery only. In addition, irradiated patients whose tumors had an associated abscess or fistula formation had improved local control and recurrence-free survival rates compared with a similar group of patients undergoing surgery only. Finally, patients with residual local disease after subtotal resection still had a 37% 5-year DFS rate, indicating that a certain proportion of patients with residual disease can be salvaged. Treatment toxicity rates were significant but acceptable, with 4.5% of patients developing bowel conditions requiring surgery. A 10-year update of this series again found increased control for adjuvantly treated T4 N0 and T4 N+ patients.[414] In this study, the nonrandomized addition of 5-FU chemotherapy to radiotherapy did not alter local control, the rate of distant metastasis, or disease-free survival.

Another retrospective study, from the University of Florida,[412] carried out in patients with locally advanced but completely resected colon cancer, found a local control rate of 88% after adjuvant radiotherapy. A dose response was also found, with local control rate of 96% versus only 76% for patients receiving greater than or less than 50 Gy, respectively. An additional retrospective study carried out in 103 patients with locally advanced colon cancer who received postoperative radiation therapy found 5-year actuarial local failure rates of 10%, 54%, and 79% in patients with no residual disease, microscopic disease, or gross residual disease after surgery, respectively.[413] In the 35 patients with gross residual disease, the addition of intraoperative radiotherapy to external beam radiation reduced the local failure rate from 82% to 11%. In a prospective phase II trial, Palermo

and colleagues treated 45 patients between 1984 and 1989 with combined intraperitoneal 5-FU and local plus para-aortic nodal radiation therapy.[415] Six cycles (five times daily) of intraperitoneal 5-FU were given, separated from each other by 4 weeks, with two courses of radiotherapy (22.5 Gy each delivered in 1.5-Gy fractions) given after the first and third chemotherapy cycles. Potential advantages of intraperitoneal 5-FU delivery could include a higher drug concentration for at-risk peritoneal surfaces as well as delivery of 5-FU by the portal circulation to the liver. Only four patients experienced local recurrence, and tolerance was acceptable with four patients experiencing grade III peritonitis. In spite of a lower than expected rate of locoregional recurrences, however, survival rates were similar to those reported by others using systemic chemotherapy and radiation. With a 112-month median follow-up, actuarial DFS and OS rates of 49% ± 8% and 53% ± 7%, respectively, were found.

These retrospective studies, in spite of their inherent limitations, suggest that selected groups of patients with more locally advanced colon carcinoma might benefit from postoperative irradiation. Therefore, it became important to validate these retrospective findings in a prospective randomized trial. Given the proven benefit of adjuvant chemotherapy in node-positive colon cancer and its enhancement of radiation efficacy in rectal cancer, an Intergroup trial (INT 0130) was designed to compare adjuvant chemotherapy alone to chemotherapy plus radiation in a randomized fashion.[411] Patients with tumor adherence or invasion of surrounding structures or T3N1-2 tumors were randomized to 1 year of 5-FU plus levamisole with or without 45 to 50.4 Gy in 25 to 28 fractions. A total of 222 out of an original accrual goal of 700 patients were randomized, and of these, 187 were eligible for analysis.

Five-year DFS and OS rates were 52% and 62% for chemotherapy patients, respectively, and 51% and 58% for chemoradiotherapy patients, respectively (both with $P > 0.50$). Grade III or higher toxicity occurred in 42% of chemotherapy patients and 54% of chemoradiotherapy patients ($P = 0$ .04) with the excess in toxicity in the radiotherapy arm being primarily hematologic in nature. Extent of nodal involvement influenced outcome in both arms while extent of invasion (T4 versus T3) did not. Thus, patients in this trial who received chemotherapy or chemoradiotherapy had similar OS and DFS rates, while toxicity was higher among chemoradiotherapy patients.

As was mentioned, this intergroup study is the only published, randomized trial of adjuvant radiation therapy in colon cancer. As was discussed by the investigators, the low accrual, frequent lack of preoperative imaging, frequent failure to place radiopaque clips to guide treatment fields, and inconsistent pathology detail could have limited the ability of the study to detect a meaningful benefit from adjuvant radiotherapy. Furthermore, the study was somewhat diluted by the approximately 19% of its patients who had T3 tumors and might therefore not have had the highest risk for local failure.

In conclusion, several retrospective trials suggest that a subset of patients with high-risk, resected colon cancer derive benefit from the addition of adjuvant radiation therapy to the resected tumor bed. The one randomized trial that tested adjuvant radiation therapy did not confirm a benefit, but several problems might have limited the study's power. At present, therefore, definitive evidence is lacking to support the universal application of adjuvant radiotherapy in locally advanced colon cancer, whereas adjuvant therapy in selected highest-risk patients may offer benefit. There arguably are clinical situations in which its use is reasonable, including when the risk of local recurrence is high because of known or likely microscopic or gross residual disease, as in patients with positive margins or T4 tumors with invasion of or adherence to unresectable abdominal or pelvic structures. Such a selective application of adjuvant radiotherapy is consistent with current NCCN guidelines.[416] Given the efficacy of concurrent, adjuvant chemotherapy and radiotherapy for rectal cancer, adjuvant radiation therapy, when given for colon cancer, should be combined with systemic chemotherapy. Other options include intraoperative radiotherapy, which allows a more localized delivery of a higher dose and may play a role as well, particularly in subtotally resected tumors. Also, newer chemotherapy agents or targeted agents such as cetuximab or bevacizumab, having proven useful in metastatic and adjuvant settings, might be beneficially combined with radiotherapy.

Hepatic and Whole-Abdominal Irradiation

High rates of hepatic metastasis and peritoneal failure have led to several investigations of adjuvant hepatic or whole-abdominal radiotherapy. A phase III trial exploring the role of adjuvant hepatic irradiation was performed by the Gastrointestinal Tumor Study Group.[417] A total of 300 patients with resected T3, T4, or node-positive colon cancer were randomized to either observation or 21 Gy of hepatic radiation in 1.5-Gy fractions with concomitant 5-FU chemotherapy. Results of the study, however, indicated no therapeutic benefit for either survival or recurrence endpoints, with the liver recurrence rate remaining unchanged by hepatic therapy.

Several small, nonrandomized studies of whole-abdominal irradiation have also been reported.[418–420] The study by Wong and colleagues[420] treated 30 patients who had undergone a complete resection with whole-abdominal irradiation and reported a 5-year actuarial survival rate of 55%. An additional 25 patients who had either gross total residual disease after surgery or peritoneal metastases had very poor outcomes after whole-abdominal irradiation. The largest of these studies, a Southwestern Oncology Group phase I/II trial (SWOG 8572), reported on 41 patients who received 30 Gy whole-abdominal irradiation in 1-Gy fractions (20 Gy maximum to the liver) with an additional 16-Gy tumor bed boost, along with concurrent, continuous infusional 5-FU.[419,421] Five-year DFS and OS estimates were 58% and 67%, respectively, for all T3N1–2 patients. Seventeen percent of patients had severe toxicity, and 7% had life-threatening toxicity of any kind. Although conclusions are difficult in the absence of randomized trials, patients in SWOG 8572 who received whole-abdominal irradiation plus tumor bed irradiation with infusional 5-FU did demonstrate reduced tumor bed, liver, and peritoneal relapse rates when compared with patients who were treated in other studies with either surgery alone or surgery plus chemotherapy. However, on the basis of all studies to date, there is no compelling evidence that whole-abdominal irradiation is superior to locoregional irradiation, particularly when the higher toxicities of whole-abdominal irradiation are accounted for.

In conclusion, adjuvant radiation therapy to the tumor bed can decrease the risk of local recurrence after resection of locally advanced colon cancer and may be useful in patients who are at very high risk for recurrence. Intraoperative radiation therapy to achieve higher, more directed doses could further improve tumor control in patients with incompletely resected disease. In addition, hepatic irradiation and whole-abdominal irradiation have not improved survival and remain highly investigational.

MEDICAL ONCOLOGY MANAGEMENT OF METASTATIC DISEASE

As was noted previously, 45% of the 153,000 patients who are diagnosed with colorectal cancer in the United States each year will either present with or eventually develop disease recurrence.[1] Similar risks apply to the more than 1,023,000 patients who will be diagnosed worldwide, as 529,000 deaths were estimated in 2001.[422] At the time of diagnosis of metastatic disease, the median survival was estimated to be 6 months without additional therapy. Chemotherapy regimens have increased that survival to more than 20 months.[423–432]

Several randomized trials have now reported median survivals over 20 months from the time of diagnosis, including fluoropyrimidine-based regimens combined with chemotherapy (oxaliplatin or irinotecan) and antiangiogenic agents (bevacizumab) particularly when followed by second-line alternate regimens.[428–432]

Assessment of the effect of treatment is a tenet of all medical care. For cancer, this assessment is still made for an individual patient by measuring the diameter of lesions and establishing that no new lesions have developed since treatment was initiated. It is important that the baseline measurements be obtained within a short period before initiation of treatment (i.e., within 1 week and certainly within 1 month), as growth of disease before chemotherapy is initiated could otherwise be misinterpreted as progression. Clinical trials frequently reevaluate for response at 8-week intervals. Response can be assessed by radiologic measurements (e.g., chest x-ray of lung lesions or CT of liver metastases). Other markers have also been used and generally correlate with cell kill and extended survival—50% decline in CEA, for example (see the discussion on carcinoembryonic antigen earlier in this chapter). Improvement in patient well-being can also be an indication that treatment is containing the neoplastic process, although the placebo effect has been implicated in some improvements, particularly in pain assessment. Nonetheless, patients whose performance status improves and who gain weight on treatment in the absence of a change in measurable disease may be clinically benefiting from the treatment. In randomized clinical trials in colorectal carcinoma, measures of population benefit such as PFS or OS are critical to the establishment of evidence-based therapeutics producing clinical benefit.

In evaluating a patient with colon cancer prior to therapy, CT of the chest, abdomen, and pelvis usually suffices to establish measurable disease. Because metastases to the brain and bone are rare (<10%) and tend to occur late in disease progression, only patients with symptoms such as headache and skeletal pain are evaluated with imaging of the brain or bone scan. Assessing hematopoietic function (with blood counts), liver injury, and renal function are included in all protocols before start of treatment.

Historically, alterations in overall survival were difficult to detect owing to study size and the modest effect of single-agent 5-FU therapy. If only 33% of patients have substantial decrease in disease (partial or complete regression) and the responding patients have a true median survival of 18 months compared with 12 months for patients receiving only supportive care, and if the remaining 66% of patients receiving chemotherapy have no change in their 12-month survival, a randomized trial with 100 patients treated and 100 observed would show a 2-month difference in survival, with a *P* value of 0.1. With more effective regimens for patients with metastatic colorectal carcinoma, differences in overall survival produced by initial therapy can be obscured by additional poststudy therapies; this has led to the use of progression-free survival as a primary trial endpoint for first- and second-line therapies.

The quandary of patients who have definite tumor regression (partial regression assessed as greater than 50% decline in the area of lesions) but also a decline in functional status due to treatment-related morbidity is commonly faced in general oncology and has recently become an issue for patients with colon cancer with the addition of more effective but more toxic agents such as irinotecan and oxaliplatin to 5-FU. Patients with specific toxicities, such as oxaliplatin-induced peripheral neuropathy or who have failure to thrive while receiving chemotherapy need to be reassessed carefully regarding the goals of treatment. Patients who are receiving potentially curative adjuvant therapy in a high-risk setting are balancing short-term toxicity against the possibility of a normal life span. In the setting of metastatic disease, in which cure is generally not feasible, both quality and quantity of life—usually assessed as adjusted quality-of-life years—have to be balanced. For many patients with symptomatic disease, even a minimal regression can be associated with improved quality of life (resolution of jaundice, return of appetite, increased performance status, diminished pain, absence of tumor fever, weight gain) at the cost of inconvenience and intermittent mild fatigue, nausea, and loose stools. Patients who are asymptomatic fall somewhere between two opposite ends of a spectrum in their approach to treatment. Some, possibly with unrealistic expectations of cure, want the most aggressive (i.e., toxic and expensive) approach available, hoping to maximize their survival and possibly be one of the few long-term survivors with unresectable metastatic disease. Others are, understandably, reluctant to impair their currently excellent quality of life for the small chance that they might have a modestly longer survival if chemotherapy is initiated at the first evidence of recurrence.

As a tumor marker CEA, though neither sensitive enough nor specific enough to be useful for screening, is helpful in monitoring the course of disease during and after treatment, particularly in patients with metastases that are not easily evaluated by current imaging technology, such as peritoneal carcinomatosis. Evidence of regression in patients with colon carcinoma is generally not rapidly apparent, even in the few patients who eventually have complete regression of measurable disease. Thus, reevaluation after 8 weeks of treatment, in the absence of signs or symptoms that suggest progression in the interval, is generally appropriate. Measurement of CEA earlier than this can result in false impressions of progression, as CEA can be released from dying tumor cells, and with its slow systemic clearance, it could initially be elevated before eventually declining.

For the approximately 50% of patients who have measurable regressions with current chemotherapy regimens, response is durable for the majority, with the median time to progression after first-line therapy at 7 to 11 months (see the later discussion). Even patients with less than 50% regression could have meaningful improvement in duration of survival with minimal symptoms.

Fluorinated Pyrimidines in the Treatment of Metastatic Colorectal Carcinoma

For the past 30 years, 5-FU has been used to treat patients with metastatic colorectal cancer, but improved understanding of its pharmacology has led to steady improvements in the usefulness of treatment. Bolus intravenous administration of 5-FU was the standard of care until 1990. Compared with best supportive care, intravenously administered 5-FU might result in small improvements in survival duration.[433]

Our understanding of the role of inhibition of thymidylate synthase and the cofactor, folinic acid, by the active metabolite of 5-FU, 5-FdUMP, reflects 5-FU's status both as the first "molecularly targeted agent" and as an outstanding example of the potential benefits of careful biochemical pharmacology research. Improved understanding of the biochemistry of 5-FU and its congeners has permitted the development of more effective agents and regimens. To enhance the duration of thymidylate synthase inhibition, 5-FU can be given by 48-hour or continuous infusion and/or in conjunction with LV (also called folinic acid) to improve the response rate.[434–437]

Infusion regimens permit the administration of higher doses of 5-FU while minimizing hematologic toxicity and reducing diarrhea. Meta-analysis of trials that compared infusional regimens (with or without LV) also confirm the increase in response rate (22% versus 14%) and modest increase in survival (12.1 versus 11.3 months) that this approach provides.[438]

The intensity of treatment with fluorouracil has been well correlated with its activity in patients with advanced disease. Patients with a lower 5-FU exposure (measured as the area under the concentration-versus-time curve) were more likely to have disease progression even when treated with the same regimen.[439] In a multivariate analysis in patients with head and neck cancer, the exposure to 5-FU correlated with both response and with survival.[439] A meta-analysis of randomized trials comparing 5-FU alone with 5-FU and LV has confirmed the improved response rates (23%) and median survival (10.5 months) provided by modulating 5-FU with LV.[440]

It is possible to use 5-FU without any side effects, but only at the cost of compromising its activity. On the other hand, patients with intolerable toxicity generally are receiving the highest drug exposures, and their doses can be reduced to produce acceptable quality of life

Table 81-8 Commonly Used 5-FU and LV Regimens

Regimen	Reference
LV 20 mg/m^2 days 1–5, 5-FU 425 mg/m^2, days 1–5, q4–5 weeks (Mayo 5-FU/LV regimen)	Poon et al.[423]
LV infusion 500 mg/m^2 over 2 hours 5-FU IV bolus 600 mg/m^2 weekly × 6, then 2 weeks rest (Roswell-Park regimen)	Petrelli et al.[424]
LV 200 mg/m^2 over 2 hours followed by 5-FU IV bolus 400 mg/m^2 plus 5-FU 600 mg/m^2 over 22 hours, days 1 and 2, every 2 weeks (DeGramont regimen)	de Gramont et al.[435]
LV 500 mg/m^2 over 2 hours followed by 5-FU 2600 mg/m^2 over 24 hours weekly × 6 then 2 weeks rest (AIO regimen)	Kohne et al.[426]
5-FU 3000 mg/m^2 over 48 hours	Diaz-Rubio et al.[425]
5-FU 250–300 mg/m^2/day continuous IV infusion for 6 weeks, then 2 weeks rest (Lokich regimen)	Lokich et al.[434]
Capecitabine 1250 mg/m^2 bid days 1–14/21	Twelves et al.[402]

while still providing enough drug to produce a predictable likelihood of benefit. This information is important to reassure patients who worry that dose reductions mandated by severe toxicity will compromise their chances of cure in the adjuvant setting. The corollary, however, is that patients who have minimal or no side effects when receiving 5-FU could have their doses increased as tolerated in subsequent courses.

Although few of these regimens have been compared directly in randomized trials, regimens that produce similar rates of moderate to severe toxicity produce similar response rates. The various regimens do differ in their dose-limiting toxicities and with respect to the time, cost, and technical demands for their delivery, although all can be provided in the outpatient setting. Regimens that deliver 5 days of treatment every 3 to 4 weeks result in dose-limiting mucositis, diarrhea, and neutropenia. Weekly 5-FU/LV regimens are generally limited by diarrhea. Continuous-infusion regimens are limited by hand-foot syndrome or mucositis and rarely result in severe diarrhea or neutropenia, but they do require placement of vascular access catheters. High-dose regimens delivered over 24 to 48 hours of continuous infusion also can cause altered mental status or angina-like chest pain that is rarely seen in the other regimens, but the de Gramont 48-hour bolus and infusion regimens (Table 81-8) are generally well tolerated, with diarrhea and hand-foot syndrome generally dose limiting. Oral capecitabine (see the section on Orally Available Fluoropyrimidines later in the chapter) requires better patient adherence than do regimens that are delivered in a clinic and has a substantial incidence of hand-foot syndrome and diarrhea.

Randomized Trials of 5-FU Regimens

In patients without prior therapy, 5-FU administered continuously intravenously as 750 mg/m^2/day for 7 out of 21 days was compared to administration of 500 mg/m^2/day via intravenous bolus for 5 days every 28 days (without LV), with response rates of 26% versus 13%, respectively. Diarrhea and stomatitis were more common in the infusion group and would have been less prominent at lower daily doses without interruption.[436] In another four-arm randomized trial (477 patients) comparing a conventional loading dose followed by weekly 5-FU (500 mg/m^2/day for 5 days followed by a 1-week break, then 600 mg/m^2 once a week, compared with infusional 5-FU at 300 mg/m^2/day), responses were seen in 18% of 153 patients versus in 28% of 159 infusion patients.[313] Median time to progression overall was 5.1 months for the group receiving intravenous bolus administration versus 6.2 months for the group receiving continuous intravenous infusion.[313] Survival was 10.4 months for the intravenous bolus group and 13 months for the continuous intravenous infusion group; 6% of the patients were still alive at 3 years. These extended infusion regimens are much less likely to cause neutropenia (24% grade 4 for the intravenous bolus group versus 1% for the continuous intravenous infusion group). Hand-foot syndrome is seen in only 20% of patients, and infusion site infections are seen in 14% of patients; 2% of patients have bacteremia.[435–438]

The de Gramont (LV5FU2) regimen of bolus followed by 48-hour infusions, for total FU doses of 2000 mg/m^2 every 2 weeks, has been evaluated with several modifications. The basic regimen is LV 200 mg/m^2 over 2 hours at 0 and 24 hours, with bolus 5-FU 400 mg/m^2 after the 2 hours, at 2 and 26 hours, and then 600 mg/m^2 over the ensuing 22 hours on both the first and second days. The first phase II trials reported a 38% response rate (2.5% complete remissions) with an overall median survival of 10.3 months and 17 months median survival in patients with a response.[435] More than 60% of patients treated at this dose had either no toxicity or minor side effects, and only 8% experienced grade III or IV toxicity.[435] In a randomized trial that compared this dose with 5-FU 425 mg/m^2 plus LV 20 mg/m^2 daily for 5 days out of 4 weeks (Mayo regimen), response rates were 14.4% (somewhat low for the Mayo regimen) versus 32.6% (GERCOD), with a 5-week improvement in median survival (56.8 weeks versus 62 weeks). The Mayo arm produced grade III to IV toxicities in 24% versus GERCOD reporting 11%, primarily neutropenia, diarrhea, and mucositis (7% grade 4 versus 2% to 3% for de Gramont).[435] Further dose escalation of the GERCOD regimen to 500 mg of LV and 1500 to 2000 mg/m^2/day 5-FU resulted in toxicity equal to that of the Mayo regimen (grade III to IV in 15%, 2% with grade IV neutropenia, 5% with grade III to IV diarrhea, 1% encephalopathy) and produced a similar response rate (34%, 101 patients) but with five complete responses and a median survival of 18 months. The median time to progression was 8 months.[435,441]

Orally Available Fluoropyrimidines

Because extended exposure to short-lived, cell-cycle-specific agents such as 5-FU is desirable, many attempts to provide 5-FU orally have been undertaken to eliminate extended infusion regimens and their requirements for indwelling lines and pump hardware. Efforts to develop oral cytotoxic agents are complicated by patient adherence to oral regimens, an issue that most cancer treatment protocols do not directly address.

Several approaches to overcoming the inconsistent and minimal absorption of oral 5-FU have been undertaken in the past decade, including agents that would inactivate the principal catabolic enzyme, dihydropyrimidine dehydrogenase, such as eniluracil/5-FU or UFT[442–445] and prodrugs such as capecitabine (Xeloda, Roche), tegafur, and S-1.[446–448]

Capecitabine is a fluoropyrimidine carbamate that is adequately absorbed after oral dosing. It is metabolized by carboxyl esterase in the liver to 5′-deoxy-5-fluorocytidine, deaminated via cytidine deaminase in both liver and tumor tissue to 5′-deoxy-5-fluorouridine (5-dFUR), and then further transformed by thymidine phosphorylase in tumors to 5-FU.[449,450] The final steps of anabolism to 5′FdUMP and binding in a ternary complex to TS in the presence of folinic acid are then identical to those of parenterally administered 5-FU. The relative concentration of 5-FU that is generated in tumors is eightfold to 14-fold higher than the plasma concentrations.[449,450] These differentials, though substantial, are not as large as those in murine studies, which reported intracellular levels of 5-FU 16- to

35-fold higher than those produced by administration of 5-FU, with tissue levels 100- to 200-fold higher in tumors than in plasma or muscle, where the final conversion of 5′-dFUrd to 5-FUra does not occur.[450] Two phase III trials of capecitabine (1250 mg/m^2 twice daily for 2 weeks out of 3) in 1207 patients with previously untreated metastatic colon cancer compared the oral regimen to the Mayo regimen (5 days of bolus 5-FU/LV every 28 days).[451–454] The overall response rate was 26% for capecitabine and 17% for 5-FU/LV ($P < 0.002$); the median time to progression was 4.3 to 5.2 months versus 4.3 to 4.7 months; and the OS was 13.2 to 12.5 months versus 12.1 to 13.3 months (combined, 12.9 months versus 12.8 months).[455–457] Neither trial showed a statistically significant difference in any activity parameter except response rate. Adverse effects for capecitabine on this schedule are comparable to those for high-dose, 48-hour infusional 5-FU, with hand-foot syndrome prominent and occurring in 53% of patients (17% grade III) and diarrhea occurring in 48%. Bilirubin elevations to grade III to IV were reported in 28% of patients for capecitabine versus in 6% for 5-FU/LV, but less stomatitis (2% grade III to IV) and neutropenia (2.2% grade III to IV) were seen with capecitabine.[458] Because the Mayo five-times-daily regimen is also more toxic than is continuous infusion or de Gramont 48-hour infusion (LV5FU2), the significance of these toxicity differences is unclear.

Capecitabine adverse effects are comparable to those for infusional 5-FU regimens, although capecitabine is more likely than protracted continuous infusions to produce diarrhea and hand-foot syndrome. Dose-limiting toxicity is gastrointestinal, involving diarrhea, nausea, and vomiting. When capecitabine is used without any break, hand-foot syndrome, fatigue, and dizziness also occur. A variety of small (150 to 160 patients) phase II trials of combinations of capecitabine with oxaliplatin or irinotecan have been completed, with the expected differences in frequencies of adverse events such as diarrhea (greater with irinotecan) or peripheral neuropathy (greater with oxaliplatin).[459,460]

In combinations with oxaliplatin, neurosensory toxicity occurs in 78% (11% grade III/IV), nausea in 66%, diarrhea in 60%, fatigue in 35%, hand-foot syndrome in 29%, and neutropenia in 27% to 50% of patients (9% grade III/IV), and grade 3/4 thrombocytopenia occurs in approximately 5%.[388]

Current Combinations of Fluoropyrimidines with Other Chemotherapy: Oxaliplatin and Irinotecan Combinations

Although LV modulation and infusion of 5-FU have resulted in improved response rates, for decades, colon carcinoma was not treated with combination chemotherapy. Clinical trials showed no advantage for combining either nitrosoureas (principally methyl-CCNU) mitomycin, cisplatin, or interferon with 5-FU. Over the past decade, two new classes of chemotherapy have been introduced into clinical use: the topoisomerase I inhibitor irinotecan (CPT-11, irinotecan, Camptosar-Pfizer) and the platinating agent oxaliplatin (Eloxatin, Sanofi-Synthelabo).

Oxaliplatin

Although prior studies suggested that cisplatin in conjunction with 5-FU would enhance response rate and duration of response by altering DNA repair, clinical trials comparing the addition of cisplatin to 5-FU by continuous intravenous infusion showed insignificant improvement in response at the cost of substantial additional toxicity.[313] Oxaliplatin (trans-l-1,2 diaminocyclohexane oxaloplatinum), a diaminocyclohexane platinum complex, has greater in vitro activity in colon lines than do other platinum analogs.[461,462] Oxaliplatin has not only demonstrated synergistic cytotoxicity in vitro,[461,463–465] it also has clearly improved both progression-free and overall survival compared to IFL427 and was approved by the U.S. FDA in 2002 for patients with colon cancer. Like cisplatin and carboplatin, this compound platinates DNA and forms DNA interstrand links and adducts that block DNA transcription and replication.[464,465]

The single-agent response rate for oxaliplatin is 10% in previously treated patients with colorectal cancer.[466,467] In patients without prior therapy, oxaliplatin as a single agent produces an 18% to 24% partial response rate, with a median time to progression of 6 months and a median survival of 13 to 14 months.[468,469]

Oxaliplatin's role in combination with a fluorinated pyrimidine in patients with disease that is refractory to 5-FU/LV was demonstrated by partial responses in 20 of 97 patients with documented progression on infusional 5-FU/LV who received the same initial regimen with oxaliplatin 85 mg/m^2, a response rate that is approximately double that for oxaliplatin as a single agent in second-line therapy. The median duration of response was 7.5 months.[470] The combination of continuous intravenous infusion 5-FU with oxaliplatin was shown to improve response rates compared with high-dose infusional 5-FU alone in several small trials, with response rates between 29% and 58%.[455,456,471]

Initial treatment for 420 patients with intravenously administered LV5FU2 (de Gramont-5-FU bolus 400 mg/m^2/day for 2 days, followed by 22-hour infusion of 600 mg/m^2/day for 2 days administered every 2 weeks) with oxaliplatin 85 mg/m^2 on day 1 [FOLFOX]) was shown to be superior to LV5FU2 without oxaliplatin, producing an improvement in progression-free survival from 6.2 months to 9 months, and improving the response rate from 22.3% to 50.7%. The study cohort was too small, however, to show an improvement in OS (16.2 months versus 14.7 months, $P = 0.12$).[457]

The combination results in a 42% rate of grade III to IV neutropenia, 12% grade III/IV diarrhea, and 18% grade III neurotoxicity, which is the most common reason for discontinuing therapy.[457] When compared with a 5-day chronomodulated 5-FU infusion (700 mg/m^2/day given for 5 days, with peak dose delivered at 4:00 A.M.) with oxaliplatin, 125 mg/m^2 versus the same 5-FU/LV regimen, there was a difference in response rate (53% for the oxaliplatin/FU/LV versus 16% for the 5-FU/LV) and a trend for progression-free survival (8.7 months versus 6.1 months, $P = 0.48$).[472] This regimen also resulted in a 43% rate of grade III to IV diarrhea, 13% moderate neuropathy, and less than 2% grade IV neutropenia.[472]

The survival benefit that FOLFOX provided was definitively demonstrated in N9741, a National Cancer Institute-sponsored cooperative group trial led by the North Central Cancer Treatment Group, which incorporated six different treatment arms. Time to progression for FOLFOX compared with IFL was 8.7 months versus 6.9 months ($P = 0.0014$), response rates were 45% versus 31% , and the overall survival was 19.5 months versus 15.0 months ($P = 0.0001$), unequivocally demonstrating that FOLFOX can prolong survival as first-line therapy for metastatic colon cancer.[427] A three-arm trial for second-line use of FOLFOX after disease progression on IFL found no response to infusional 5-FU (LV5FU2), a 1.3% response rate for oxaliplatin alone, and a 9% response rate for FOLFOX.[473] Two subsequent trials comparing infusional 5-FU regimens combined with either oxaliplatin or irinotecan (FOLFIRI versus FOLFOX) in first-line metastatic colorectal carcinoma did not demonstrate differences in either progression-free or overall survival.[429,474]

A series of combinations of oxaliplatin on the background of de Gramont bolus and infusions of 5-FU/LV (LV5FU2) have been published, referred to collectively as FOLFOX 1 to 7. Table 81-9 lists selected combination regimens. The FOLFOX 4 regimen is inconvenient for patients and caregivers, requiring a second intravenous 2-hour infusion of LV and 5-FU on the second day. FOLFOX 6 has yielded similar results as second-line therapy, with a response rate of 27% and a median survival of 10.9 months, and it is now commonly used in clinical trials.[475]

Oxaliplatin has also been combined with capecitabine for patients with metastatic disease. Oxaliplatin and capecitabine were given to 43 patients, with a response rate of 44%. Diarrhea was dose limiting, occurring in 28% of the patients.[476] The median OS was 20 months

Table 81-9 Commonly Used 5-FU/LV Chemotherapy Combination Regimens

Regimen	Doses/Schedule	Reference
IFL	Irinotecan 125 mg/m^2 over 90 minutes day 1: LV 20 mg/m^2 IV bolus; 5-FU 500 mg/m^2 IV bolus weekly for 4 weeks followed by 2-week rest in a 6-week cycle	Saltz et al.[492]
FOLFIRI	Irinotecan 180 mg/m^2 in 90-minute infusion day 1; leucovorin 200 mg/m^2 IV over 2 hours after irinotecan administration or concurrently with irinotecan in separate infusion line day 1; 5-FU bolus 400 mg/m^2, followed by 5-FU 22-hour continuous infusion 600 mg/m^2 day 1 and day 2, every 2 weeks	Douillard et al.[493]
FOLFOX 4*	Oxaliplatin 85 mg/m^2 over 120 minutes day 1; LV 200 mg/m^2 2-hour infusion day 1 and day 2; 5-FU 400 mg/m^2 IV bolus plus 5-FU 600 mg/m^2 IV over 22 hours day 1 and day 2, every 2 weeks	Andre et al.[470]
FOLFOX 6	Oxaliplatin 100 mg/m^2 over 120 minutes day 1; LV 400 mg/m^2 2-hour infusion day 1; 5-FU bolus 400 mg/m^2 plus 2400 (to 3000) mg/m^2 46-hour (–48-hour) infusion day 1, every 2 weeks	Maindrault-Goebel et al.[475]
mFOLFOX 6	Oxaliplatin 85 mg/m^2 over 120 minutes day 1; 1-LV 175 mg/m^2—2-hour infusion day 1; 5-FU bolus 400 mg/m^2 plus 2400 (to 2800) mg/m^2 46 hour–48-hour infusion day 1, every 2 weeks	Braun et al.,[480] Cheeseman et al.,[†]
FOLFOX 7	Oxaliplatin 130 mg/m^2 over 120 minutes day 1; LV 400 mg/m^2 2-hour infusion day 1; 5-FU bolus 400 mg/m^2 plus 2400 mg/m^2 46-hour infusion day 1, every 2 weeks	Maindrault-Goebel et al.[481]
FLOX	LV 500 mg/m^2 IV over 2 hours; 5-FU 500 mg/m^2 IV bolus 1 hour after the infusion has begun weekly (days 1, 8, 15, 22, 29, 35) for 6 weeks followed by a rest period; Oxaliplatin 85 mg/m^2 IV over 120 minutes before the 5-FU and LV (days 1, 15, 29). Repeat treatment begins 21 days after last dose previous cycle (1 cycle = 8 weeks) for a total of 3 cycles	Kuebler and de Gramont[482]
CAPOX	Oxaliplatin 120–130 mg/m^2 over 120 minutes day 1; capecitabine 1000–1250 mg/m^2 po bid days 1–14, every 3 weeks	Zeuli et al.,[476] Scheithauer et al.,[477] Sumpter et al.,[478] Borner et al.[479]
IROX	Oxaliplatin 85 mg/m^2 IV over 120 minutes day 1; irinotecan 200 mg/m^2 IV over 30 minutes day 1, every 3 weeks	Goldberg et al.[427]

*The doses of leucovorin used in the FOLFOX4 regimen may vary; some refer to D,L-leucovorin and some to pure L-leucovorin.

[†]Cheeseman SL, Joel SP, Chester JD, et al: A modified de Gramont regimen of fluourouracil alone and with oxaliplatin, for advanced colorectal cancer. Br J Cancer 2002;87:393–399.

in this phase II study. Additional studies have been published, including both formal trials and institutional experiences.[477–479] Oxaliplatin (130 mg/m^2 on day 1) and capecitabine (1250 mg/m^2 twice daily on days 1 to 14 every 3 weeks) produced a partial response rate of 49% in 42 patients without prior therapy and in 15% of 26 patients with prior 5-FU.[479] Borner and colleagues[479] recommend a reduced dose of capecitabine (to 1000 mg/m^2 twice daily) for patients with prior therapy. Two- and three-week courses were also explored in a randomized trial of either

- Oxaliplatin, 130 mg/m^2 on day 1 with capecitabine, 1000 mg/m^2 twice daily for 14 days of a 21-day cycle

or

- Oxaliplatin, 85 mg/m^2 on day 1 with capecitabine, 1750 mg/m^2 twice daily for the first 7 days of a 14-day cycle in 89 patients. The biweekly regimen had a higher response rate (54.5% versus 42.2%) and a longer progression-free survival (10.5 months versus 6 months, $P = 0.013$). Overall survival was not reported because the median had not been reached.[477]

Cumulative delayed neuropathy frequently limits the total dose of oxaliplatin that can be delivered; the median time to development of grade 3 neuropathy is 22 weeks,[430] with approximately 70% of patients stopping treatment without evidence of disease progression. In an effort to delay the onset of cumulative neurotoxicity that would result in discontinuation of treatment, a modified FOLFOX 6 (mFOLFOX 6) regimen appears to maintain efficacy in phase II studies and is being used in several trials.[480–482] An additional approach to circumvent this limitation is the use of interrupted schedules of oxaliplatin (OPTIMOX regimens).[483] The initial study evaluated the use of six 2-week cycles of FOLFOX 7 (with 130 mg/m^2 oxaliplatin), followed by 12 weeks of weekly infusions of 5-FU and LV, followed by a second six 2-week cycles of FOLFOX 7 compared in a randomized trial to FOLFOX 4. Patients receiving FOLFOX 4 (the control arm) had a median time on treatment of 12 cycles (24 weeks), median PFS of 9 months, and OS of 19.3 months with a response rate of 58.5%; patients receiving 6 cycles of FOLFOX 7 followed by maintenance weekly LV5FU2 (the investigational arm) had a median time on treatment of 15 cycles (30 weeks, with the 6 cycles of FOLFOX 7 being the median received), median PFS of 8.7 months and OS of 21.2 months with a response rate of 59.2%. As anticipated, 17.9% of patients receiving FOLFOX 4 had grade III neuropathy; despite the higher biweekly doses of oxaliplatin in patients receiving OPTIMOX the incidence was 13.3% ($P = 0.12$); no patients in either arm had grade IV neuropathy, suggesting that physician and patient decisions to discontinue oxaliplatin (which occurred at a median of 12 cycles in patient receiving FOLFOX 4) might have minimally reduced the number of patients with moderate neuropathy compared to automatically stopping at 6 cycles of FOLFOX 7.

Delayed peripheral neuropathy and acute oral-pharyngeal dysesthesia occur in many patients who are receiving oxaliplatin and are particularly exacerbated by cold exposure.[427,468,484] The acute dysesthesia can be quite disconcerting for patients if they have not been warned in advance. Patients can experience a "TMJ-like syndrome"

when chewing; a sharp pain can occur with the first few bites and then abate quickly as the meal continues. Patients can also experience an acute dysesthesia during or shortly after drug infusion, which produces a sensation that they are not breathing, although their tidal volume and oxygenation remain normal. The sensation subsides quickly and is well addressed by forewarning the patient and providing reassurance. Grade III delayed neurotoxicity can present as a fine movement disturbance, as tingling or numbness in a peripheral sensory neuropathy, or as ataxia at an oxaliplatin median cumulative dose of 900 mg/m^2 (about 10 doses/20 weeks). The incidence increases from 10% of patients at 790 mg/m^2 to 50% at 1170 mg/m^2 to 75% of patients receiving 1560 mg/m^2. The likelihood that neurologic symptoms will regress after treatment is discontinued is inversely related to cumulative dose and severity of the neuropathy. Within 4 to 6 months, grade I to II neuropathy will have improved in 82% of patients and will have resolved entirely in 41% of patients by 6 to 8 months. The neurotoxicity of oxaliplatin has been reviewed recently.[485] Grade III or worse neutropenia occurs in 50% of patients receiving FOLFOX.[427] Other toxicities that are commonly reported are nausea and vomiting (which usually are well controlled with 5-HT3 antagonists), anemia, and infrequent diarrhea.

Irinotecan

Irinotecan is a prodrug that is catabolized to its much more potent, active form, SN-38, which interacts to stabilize topoisomerase I bound to DNA, resulting in DNA strand breaks. It was approved by the U.S. FDA in 1997 for the treatment of patients with refractory colorectal cancer. The response rate for single-agent irinotecan is 32% in patients without prior therapy and 13% in patients with prior 5-FU therapy, with a median duration of response of 9 months.[486–488] The U.S. phase III trials used a schedule of 125 mg/m^2 weekly for 4 out of 6 weeks, and the European trials used 300 mg/m^2 once every 3 weeks. A randomized trial comparing these two schedules for patients with progression on 5-FU/LV confirmed that there was no difference in response rate, survival, or time to progression.[489] The type of serious toxicity differed between the two schedules: Grade III to IV diarrhea was reported in 36% of patients treated weekly and in 19% of patients receiving the therapy every 3 weeks, while grade III to IV neutropenia occurred in 29% of weekly and 34% of triweekly patients. Treatment-related mortality was high in both regimens: 5.3% and 1.3%, respectively. Acute cholinergic symptoms and nausea were more common with the triweekly schedule.[489] Irinotecan alone is somewhat more toxic than 5-FU/LV regimens, producing severe or life-threatening neutropenia and diarrhea in one fourth to one third of patients. Despite the combination of neutropenia and diarrhea, neutropenic fever was unusual (4 of 121 patients, or 3.3%).[486,487] Patients with prior radiation therapy are more likely to develop severe leucopenia. Diarrhea can generally be well controlled with the aggressive use of loperamide. During the infusion, irinotecan can produce nausea, vomiting, and cholinergic symptoms (sweating, cramping, nasal stuffiness, and acute diarrhea). Rougier and Bugat have reviewed clinical experience with irinotecan.[487]

Second-line single agent irinotecan was initially shown to improve survival in patients with disease progression on 5-FU/LV when compared with either best supportive care or infusional 5-FU.[490,491] Rougier and colleagues[490] reported a randomized trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer, and Cunningham and coworkers[491] reported a randomized trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. The trial comparing infusional therapy and irinotecan (300–350 mg/m^2) given every 3 weeks permitted sites to use their infusional regimen of choice—either the de Gramont bolus/46-hour infusion every 2 weeks, the Lokich continuous infusion, or the AIO 24-hour infusion weekly (see Table 81-8)—and demonstrated better response rates, progression-free survival (5.2 months versus 2.9 months), and 1-year survival rates (54% versus 32%) for the combination with irinotecan. For patients with disease progression after initial 5-FU/LV treatment, median survival was 10.1 months, compared with 8.5 months for patients receiving infusion 5-FU.[490,491]

The overlapping dose-limiting toxicity—diarrhea—initially precluded delivering both 5-FU and irinotecan at full doses at maximal dose intensity.

Two combination regimens have been in widespread use: IFL (and modified IFL) and FOLFIRI.[492] It has also been feasible to combine irinotecan and oxaliplatin with 5-FU in one regimen.[432] IFL in comparison with 5-FU/LV bolus daily for 5 days resulted in significantly longer progression-free survival (median: 7.0 versus 4.3 months; $P = 0.004$), higher response rate (39% versus 21%, $P < 0.001$), and longer OS (median: 14.8 months versus 12.6 months; $P = 0.04$).[492] Combining irinotecan with 48-hour infusional schedules (FOLFIRI) also improved time to progression (median: 6.7 months versus 4.4 months; $P < 0.001$), response rate (35% versus 22%, $P < 0.005$) and OS (median: 17.4 months versus 14.1 months, $P = 0.031$).[493]

A direct comparison of FOLFIRI, modified IFL, and CapeIri has been undertaken in a trial of 430 patients, demonstrating a trend for improved efficacy for FOLFIRI compared with either modified IFL or CapeIri (overall response rate: 47% versus 43% versus 39%, P = NS), improved PFS (7.6 versus 5.9 versus 5.8 months, $P = 0.004$) and OS (23.1 versus 17.6 versus 18.9 months, $P = 0.087$).[494]

Careful screening of patients to ensure that they can tolerate IFL's potential for diarrhea and neutropenia, close monitoring during the first month of therapy, aggressive treatment of diarrhea, attention to symptoms and mandated dose adjustments, and institution of aggressive inpatient support (including antibiotics for patients who have neutropenia, diarrhea, and fever) are critical to minimizing mortality associated with this regimen. The life-threatening toxicity of IFL became evident in randomized trials for patients with both metastatic disease and in the adjuvant setting.[430,493] Early deaths on those trials were threefold higher in comparison with the other arms in the trials (2.5% versus 0.8% and 3.5% versus 1.1%). Although these values appeared higher than the treatment-related death rate in the phase III IFL studies (0.2% to 1.3%), it is consistent with the 60-day "all cause" mortality reported in Saltz's original publication.[440,492,493] The subsequent cohort in N9741 received reduced-dose IFL but still had a 3.3% 60-day mortality rate compared to 2% for patients receiving FOLFOX 4.[430]

For patients without prior therapy for metastatic disease (first-line regimens), direct comparison of IFL with FOLFOX (see earlier in the chapter) in a National Cancer Institute-sponsored randomized trial conducted by the North Central Oncology Group with six initial arms found FOLFOX to produce superior response rates (38% versus 29%, $P = 0.03$), time to progression (8.6 months versus 6.9 months, $P = 0.0009$), OS (18.1 months versus 14.4 months, $P = 0.004$), and adverse event profile.[427]

At the cost of manageable increases in neutropenia and neuropathy, it has been feasible to combine infusional 5-FU with oxaliplatin (85 mg/m^2) and irinotecan (165 mg/m^2) with 5-FU (3200 mg/m^2 over 48 hours) every 14 days.[432] In a first-line randomized trial in 244 patients comparing FOLFIRI with FOLFOXIRI, the PFS was 6.9 months versus 9.8 months ($P = 0.0006$), and the OS was 16.7 months versus 22.6 months ($P = 0.032$). The majority of patients (75% to 75%) in both arms received subsequent chemotherapy, again supporting the importance of delivering oxaliplatin in first-line regimens in relationship to increasing survival. A similar-sized trial (283 patients) that used a bolus dose of 5-FU (400 mg/m^2, followed by 600 mg/m^2/24 hours for 2 days) and lower doses of oxaliplatin (65 mg/m^2) and irinotecan (150 mg/m^2) had the same survival trends, without statistical significance: 21.5 months versus 19.5 months ($P = 0.34$), with a time to progression of 8.4 months versus 6.9 months ($P = 0.17$).[495] Falcone and colleagues[432] recommend that FOLFOXIRI be offered, as they did for entry

into that trial, only for older patients with performance status 0 to 1 and younger patients with performance status 0 to 2. The 60-day mortality rates in the HORG trial's arms were 2.7% and 2.9%, while in the GONO trial, there was no treatment-associated mortality.

Antiangiogenic Approaches

Considerable evidence has been developed regarding the importance of angiogenesis in tumor growth and progression.[496] VEGF is a central regulator of normal and neoplastic angiogenesis. Increased expression of VEGF in patients with colorectal carcinoma has been associated with recurrence and poor prognosis.[497]

Bevacizumab

Bevacizumab (anti-VEGF, Avastin, Genentech) is a human monoclonal antibody directed at VEGF as an antiangiogenic strategy and is now approved for use with 5-FU-containing regimens for patients with metastatic colorectal carcinoma. Several large randomized phase III studies in colon cancer have been published. Bevacizumab (5 mg/kg daily every other week with IFL, which was the "standard" U.S. first-line regimen at the time the study was initiated) was compared with IFL alone in 925 patients receiving initial treatment for metastatic colorectal carcinoma. Median survival was 20.3 versus 15.6 months, the PFS was 10.6 months versus 6.2 months, and the response rate was 45% versus 35%, respectively.[428] In 2004, the U.S. FDA approved bevacizumab in combination with 5-FU-based chemotherapy for first-line treatment. The role of bevacizumab has been evaluated in patients who previously had been given IFL, randomizing 829 patients to second-line treatment FOLFOX plus bevacizumab versus FOLFOX versus bevacizumab alone.[431] The PFS was 7.3 months for the triplet compared with 4.7 months for second-line FOLFOX 4 (hazard ratio: 0.61, $P = 0.0001$) and 2.7 months for bevacizumab as a single agent. Survival was also improved in those receiving the triplet: 12.9 months versus 10.8 months versus 10.2 months (with many patients receiving additional treatment postprotocol).

An intergroup phase III trial led by SWOG compared mFOLFOX 6 to CAPOX with or without bevacizumab in a 2×2 factorial design for patients with metastatic disease who had not previously received chemotherapy, but results are not yet available. A phase II study of two doses of bevacizumab (5 or 10 mg/kg every 2 weeks) with 5-FU and folinic acid (weekly) in patients without prior chemotherapy produced response rates of 40% in the low-dose arm, 24% in the high-dose arm, and 17% in the chemotherapy-alone arm; longer time to progression (9 months versus 7.2 months versus 5.2 months, respectively), and improved survival (21.5 months versus 16.1 months versus 13.8 months, P = NS) were also noted. Only 2 of 22 patients who were treated with bevacizumab as second-line therapy after failure of chemotherapy alone had partial responses, and median time to progression for these patients was only 2 months.[498] The current National Cancer Institute-sponsored first-line trial compares the administration of either FOLFOX or FOLFIRI with cetuximab and/or bevacizumab.[499]

In common with most targeted therapies and in contrast to the unrealistic expectation that such treatments will be as benign as low-dose aspirin, bevacizumab treatment is associated with adverse events, including hypertension (generally responsive to medical management but severe on rare occasions), thrombotic events and bleeding (venous and arterial), bowel perforation, and delayed wound healing. An increased incidence of hypertension was observed on the bevacizumab arm of the IFL bevacizumab study (11% versus 2.3%), as was an increase in bowel perforation, but there was no statistically significant increase in grade III or IV bleeding (2.5% versus 3.1%) or thromboembolic events (16.1% versus 19.3%). If major surgery is required during treatment, wound complications increased from 1 of 29 control patients to 10 of 75 patients receiving bevacizumab.[500,501] In patients with lung cancer, lethal hemoptysis has been reported; an increased rate of perforation and gastrointestinal bleeding can occur in patients with colon cancer; and other serious and life-threatening hemorrhages have been reported. Less serious events include epistaxis (grade I or II), proteinuria with rare nephrotic syndrome, fever, headache, and rash.

Many additional antiangiogenic approaches are currently in clinical development for patients with colon carcinoma, including other agents directed at VEGF itself (VEGF-TRAP) and additional small molecules directed at the VEGF, such as sunitinib, sorafinib, vandetinib, and cediranib. Other elements of angiogenesis have been shown to be upregulated in colorectal carcinoma, such as CXCL1.[502]

New Molecularly Targeted Agent: Epidermal Growth Factor Receptor

Four related receptor tyrosine kinases (ErbB1, ErbB2, ErbB3, ErbB4) are involved as heterodimers in proliferative signaling as both autocrine and paracrine mediators of the RAS/RAF/MAPK and PI3K/AKT pathways, among others. Each protein has extracellular, transmembrane, and intracellular ATP-binding sites that present potential therapeutic targets. Monoclonal antibodies to the extracellular domain are presumed to act by preventing ligand binding and dimerization. Agents that mimic the intracellular ATP-binding site interfere with the tyrosine kinase phosphorylation and downstream activation of proliferative networks. These interactions can produce cell cycle arrest, potentiate apoptosis, and reduce angiogenesis, invasion, and metastases in the laboratory.[503,504]

ErbB1 (EGFR) is overexpressed in 25% to 77%[505] and expressed in 80% to 90% of screened patients[506] with colorectal cancers. Overexpression is associated with poor prognosis.[507] However, there is no evidence that overexpression is required for activity of EGFR-directed therapy. Overexpression of erbB2 (Her-2/neu), the target of trastuzumab (herceptin), is infrequent in colorectal carcinoma, resulting in very limited accrual of patients to a clinical trial of trastuzumab.

Two EGFR-directed antibodies have been approved for the treatment of patients with advanced colorectal carcinoma: cetuximab, a chimeric antibody, and panitumumab, a fully human antibody. Cetuximab (C-225, IMC-C225, Erbitux, Imclone) is a partially humanized (chimeric) IgG1 antibody directed at EGFR. Binding of both natural ligands (EGF and transforming growth factor-α) is blocked, and ligand-induced activation of the tyrosine kinase is inhibited. When used as a single agent in 346 patients with advanced disease that is refractory to irinotecan, oxaliplatin, and fluorinated pyrimidines, the response rate was 11.6%, with a PFS of 1.4 months and an OS of 6.6 months.[506,508]

A randomized phase III trial was performed in Europe, in which a total of 329 patients with metastatic colorectal cancer whose disease had progressed on a previous irinotecan-based therapy were randomized in a 2 : 1 manner to either cetuximab plus irinotecan or cetuximab alone. The response rate (primary endpoint of the study) in patients who received the combination was 23% compared with 11% in those who received cetuximab alone. The median time to progression was 4.1 months in the combination arm compared with 1.5 months in the single-agent arm. There was no difference in OS between the two arms; however, patients were allowed to cross over from the single-agent arm to the combination arm at progression.[508] In 2004, the U.S. FDA approved cetuximab for use in second-line treatment.

Preliminary results of a randomized trial for 1217 patients with metastatic disease treated initially with either FOLFIRI plus cetuximab versus FOLFIRI demonstrated an increase in overall response rate (46.9% versus 38.7%, $P = 0.005$) and median PFS (8.9 months versus 8 months, $P = 0.036$).[509] In a randomized trial in 572 EGFR-expressing patients who had received two prior combination regimens, single-agent cetuximab had a documented benefit in median OS of 6.1 months versus 4.6 months for best supportive care.[510]

Adverse events related to cetuximab include the mechanism-associated acneiform skin rash, which occurs in 75% of patients

but is grade III or IV in only 15%, and allergic infusion reactions, which are reported in 21% of patients, although only 1% to 5% have severe reactions.[505,506,508,510] Patients also can have fatigue, nausea, emesis, and diarrhea; one third of patients have these symptoms, with fewer than 10% at an intensity of grade III or IV.[511] CALBG attempted to compare first-line chemotherapy (FOLFOX or FOLFIRI) with or without cetuximab, but the trial was prematurely terminated with only 238 patients accrued. The response rate was higher for each combination with cetuximab: FOLFIRI: 36%, FOLFIRI plus cetuximab: 44%, FOLFOX: 40%, FOLFOX + cetuximab: 60%, but PFS data might lack statistical significance when available.[512]

Panitumumab is a fully human IgG2 antibody. It was approved by the FDA on the basis of a randomized trial of 6 mg/kg every other week with best supportive care versus best supportive care in 463 third-line patients with EGFR expression out of 1040 screened patients.[505] The partial response rate, 10%, was consistent with prior phase II trials presented at AACR and ASCO meetings. PFS was 49% at 8 weeks for patients receiving panitumumab versus 30% for patients receiving best supportive care alone. The mean PFS was 13.8 versus 8.5 weeks. However, the large randomized phase III trial adding panitumumab to FOLFOX/bevacizumab and FOLFIRI/bevacizumab has not demonstrated benefit in multiagent first-line therapy.[513] Like other antibodies, panitumumab has a long half-life (7 days) and can be administered at doses of 2.5 mg/kg weekly or 6 mg/kg every other week. The EGFR-mediated skin rash occurs in 90% of treated patients, but only 14% have grade III or IV cutaneous toxicity. As a fully human antibody, panitumumab has a slightly lower rate of allergic reactions compared to chimeric antibodies (e.g., 1% for panitumumab and 3% to 5% for cetuximab).[514] Several additional anti-EGFR monoclonal antibody or related compounds (EMD 72000) are also in early clinical development.

Gefinitib (ZD1839, Iressa), erlotinib (OSI-774, Tarceva), PKI-166, and GW2016 are small molecule inhibitors of the phosphorylation of EGFR. These agents are dose limited by both the mechanism-specific acneiform rash and diarrhea. As single agents, they have not produced responses in phase II trials in patients with refractory colorectal carcinoma, although there was evidence that gefitinib inhibited EGFR activity and decreased proliferation in patients.[515,516] The reasons for the difference in activity of the antibodies and small molecules in colon cancer is being explored actively, and combinations of novel agents are being evaluated. For example, a phase III trial of FOLFOX/bevacizumab or CAPEOX/bevacizumab ± erlotinib is accruing 640 patients in Europe, CALGB 80405 was discussed earlier (in the section on Bevacizumab), and SWOG 0600 will accrue 1260 second-line patients to a three-arm trial comparing an irinotecan regimen (either irinotecan or FOLFIRI) with either (1) cetuximab, (2) cetuximab and bevacizumab, or (3) cetixumab and higher-dose bevacizumab.

Immunologic Approaches to the Treatment of Colon Cancer

Attempts to activate lymphocytes and/or antibodies that would eliminate colon cancer have been undertaken for decades. Tumor-associated antigens present targets for these effector arms (which might be activated by enhancing the immunogenicity of the tumor-associated antigens) and by increasing the activity of the immune response. In the third in a series of adjuvant trials in patients with stage II and III disease, comparing vaccination with autologous tumor cells mixed with bacille Calmette-Guérin for three weekly doses postoperatively in 412 patients, no improvement in DFS or OS was evident.[517] In a phase II trial, the autologous tumor cell plus bacille Calmette-Guérin approach was combined with 5-FU/LV to assess alterations in immunity; delayed-type hypersensitivity measured by induration decreased only from 20.3 mm to 18.4 mm.[518] Addition of a fourth vaccination at 6 months, when immunity was waning, was evaluated in a randomized trial involving 254 patients. This study was felt to have better quality control for the vaccine production (one facility was used, and 98% of all vaccines met quality control specifications); 97% of all patients receiving vaccine developed induration greater than 5 mm by the third vaccination, compared with only 88% of the vaccines prepared and only 85% of the patients developing induration in the ECOG trial. Only 101 of 128 vaccination patients received all four vaccinations, however. The four-year DFS rate was 70% versus 59% for those who were observed, but there was no difference in OS.[382]

Another strategy for breaking tolerance to tumor antigens is to use anti-idiotype antibodies that mimic the tumor-associated antigen and permit the immune system to generate anti-anti-idiotype antibodies that also recognize the tumor antigen. CeaVac (3H1 IgG) is an anti-idiotype murine monoclonal antibody to a murine antibody against CEA, and TriAb (11D10 IgG) is a murine anti-idiotype antibody to a murine antibody against HMFG (another tumor-associated antigen).[519] These are being evaluated in patients who have had resection of liver metastases as adjuvant therapy.

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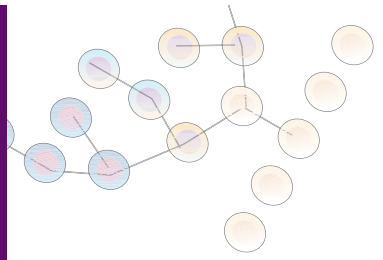
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82 Cancer of the Rectum

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SUMMARY OF KEY POINTS

Incidence

- The incidence of rectal cancer in the United States is 44 cases per 100,000 population for a total number of new cases of approximately 34,000 annually.
- Since 1985, the incidence rate has been decreasing by 1.6% per year.
- The peak incidence of rectal cancer is during the fifth decade of life.
- Blacks have a 7% to 10% higher mortality rate from rectal cancer than whites.

Clinical Presentation

Numerous clinical features suggest the presence of rectal cancer:

- Located approximately 12 cm from the anal verge
- Rectal bleeding, often bright red and on the surface of the stool
- Subtle changes in bowel habits
- Decreased caliber of stool; mucus in stool
- Sensation of fullness and tenesmus
- Increased straining during defecation
- Synchronous colon cancer (in 2% to 9% of patients with rectal cancer)

Staging and Assessment

- Careful rectal examination yields 67% to 84% accuracy in staging (superficial, mobile, tethered, fixed) and should include pelvic examination for women and prostate examination in men.
- Rigid proctosigmoidoscopy provides the most accurate assessment of distance, size, and position as well as tethering to surrounding structures.
- Colonoscopy or double-contrast barium enema is used to assess for synchronous colon tumors.
- Endorectal ultrasound can assess the depth of invasion and nodal status. (Nodal assessment is less reliable.)
- Magnetic resonance imaging (MRI) with endorectal coil is equivalent to ultrasound, and both are more sensitive and accurate than computed tomography alone. MRI is used to assess locally advanced or recurrent local disease. Computed tomography should be performed on all patients to assess intra-abdominal spread. CT or chest x-ray is required to rule out synchronous lung metastases.
- The liver is the most frequent site of distant spread, followed by lung, retroperitoneum, ovary, and peritoneal cavity.
- Baseline carcinoembryonic antigen levels and prostate-specific antigen are assessed in men.

Differential Diagnosis

Differential diagnosis includes the following:

- Kaposi's sarcoma
- Inflammatory mass
- Developmental cysts
- Embryonic tumors (teratomas, chondromas, meningoceles)
- Sacral and presacral tumors (neurogenic tumors, liposarcomas, neurofibromatosis)
- Carcinoid tumors
- Gastrointestinal stromal tumors

Treatment

- Goals of treatment are cure, local control, and quality of life.
- All retrorectal tumors should be resected, and preoperative biopsy must be avoided.
- Full-thickness local excision is feasible for highly selected patients with T1 mucosal, submucosal, and early invasive cancer, particularly in patients with high-risk comorbidities.
- For T1–T3 rectal adenocarcinomas, surgical procedures are low anterior resection, low colorectal or coloanal anastomosis with J-pouch, and abdominoperineal resection, leaving at least 2 cm distal margin and clear lateral margins. With surgery, mortality rates are 1% to 7%, and morbidity rates are 13% to 46%. The survival rate at 5 years is 74% to 87%.
- The optimal therapy for T3 tumors is sharp mesorectal excision combined with total mesorectal excision.
- The majority of N0 patients are cured by surgery and, for some selected patients, adjuvant multimodal therapy. Combined therapy cures 50% of N1 patients; 25% of tethered or fixed rectal cancers treated by neoadjuvant chemoradiotherapy are subsequently resected and cured.
- Of patients who die of rectal cancer, 25% fail with pelvic disease only.

INTRODUCTION

Although the incidence of distal (rectal and lower sigmoid) cancers has declined, with a concurrent increase in more proximal colon cancers, approximately one quarter of colorectal cancers are located in the rectum. For many years, almost all patients with rectal cancer underwent abdominoperineal resection with a permanent colostomy. Today, this approach is rarely required. The successful treatment of patients with rectal cancer involves optimal surgical technique and frequently adjuvant chemoradiotherapy. This combined modality approach will maximize cure, minimize the risk of a subsequent symptomatic local or pelvic recurrence, and maintain quality of life. Such multimodality approaches are applicable to patients with rectal cancers at or below the peritoneal reflection. This designation

generally represents cancers below 12 cm from the anal verge. Tumors in the upper rectum or rectosigmoid are treated by surgical resection, and adjuvant therapy is based on the colon cancer paradigm.

EPIDEMIOLOGY

The incidence of rectal cancer in the United States is 44 cases per 100,000 population for a total number of new cases annually of approximately 34,000.[1] Since 1985, the incidence rate decreased by 1.6% per year through 1997. A decrease in colon and rectal cancer incidence rates has been observed in males and females and in all racial and ethnic groups. The incidence rate rises dramatically during the fifth decade of life. A study of 75,000 Medicare enrollees[2] observed that proximal colon cancers appear to be disproportionately high among elderly patients. Blacks have a higher mortality rate than whites for colorectal cancer, which holds true for both rectal and colon cancers. In a 25-year period,[1] 1974 to 1999, the gap between the survival rates of blacks and whites increased from a difference of 5% to 11% for colon cancer and from 7% to 10% for rectal cancer.

The anatomic subsites of colorectal cancer also changed in the same 25-year period. The cancer incidence by anatomic subtype has shown that the incidence of rectal cancer has decreased from 9.6 cases per 100,000 population to 7.6 cases per 100,000 population.[3] This same finding has been reported in Japan[4] in a report that shows an increasing percentage of right-sided colon cancers and a continuous decline in percentage of rectal cancers in both sexes and at all ages. Sharpe and colleagues[5] reported an observational study that showed a positive association between cigar smoking and cancer of the rectum. They also noted a weak positive association between cigarette smoking and cancer of the proximal colon. Several large cohort studies have shown that cigarette smoking is an independent risk factor for colorectal cancer.[6–11]

In a large cohort study of more than 22,000 healthy male physicians aged 40 to 84 years who were followed for more than 12 years, cigarette smoking was an independent risk factor for colorectal cancer incidence, the strongest risk being observed in current smokers of 20 cigarettes or more per day (relative risk: 2.14), Cumulative lifetime exposure and exposure during various periods of life also increased the risk of colorectal cancer.[12]

A recent study showed that the increased risk of colorectal cancer associated with cigarette smoking is dependent on the molecular characteristics of the tumor as defined by *APC* mutation and *hMLH1* expression status. The association between frequency of cigarette smoking (for a five-cigarette/day increment) and colorectal cancer was most apparent and stronger in tumors without a truncating APC mutation, while duration of smoking was associated with increased risk in *hMLH1*-deficient tumors.[13]

CLINICAL PRESENTATION, EVALUATION, AND STAGING

Patients with rectal cancer can have a broad range of clinical presentations. Early symptoms that suggest rectal carcinoma include rectal bleeding and subtle changes in bowel habits. Rectal bleeding is often mixed with stools or may coat the surface of the stool. It can be bright red and separate from the stools and therefore is often mistakenly attributed to hemorrhoids. Bright red blood only on the tissue paper may be evaluated in a young person with proctosigmoidoscopy. All other types of bleeding, including the presence of occult blood in the stools during a routine physical examination or presence of iron deficiency anemia, warrant a more complete endoscopic evaluation. Increased frequency of defecation, decreased caliber of the stools, mucus with stools, or mucous diarrhea (particularly associated with large villous adenomas) is quite common. Advanced tumors induce a permanent sense of fullness and tenesmus and increased straining during defecation. Sacral or deep pelvic pain, sometimes radiating down the perineum and thighs, occurs when the tumor invades the sacrum and the sacral plexus of nerves. Anal pain, initially on defecation and later continuous, may occur when low rectal cancer invades the anal canal. Incontinence supervenes when the anal sphincter is involved.

The importance of a detailed history and a thorough physical examination cannot be overstressed. Comorbid conditions and the patient's physical habitus may preclude major surgery and influence the decision of adjuvant therapy. Physical examination should always include a digital rectal examination to feel for a mass, assess its location and mobility, and feel for enlarged extrarectal lymph nodes (50% accuracy). Depth of invasion and whether the tumor is tethered or fixed can also be assessed during rectal examination with 67% to 84% accuracy.[14,15] A careful pelvic examination in women and a prostate assessment in men are essential. A rigid proctosigmoidoscopic examination of the rectum and the anus should follow. The distance of the tumor from the anal verge, anterior/posterior/lateral position, size, morphologic configuration, and extent of circumferential involvement are determined. Tumor mobility and tethering to surrounding structures are ascertained. If not obstructed, patients with rectal cancer should have a preoperative double-contrast barium enema or preferably a colonoscopy to assess for synchronous colon cancer (2% to 9%). Subjective and objective assessment of the patient's anal sphincter function is desirable. A weak or incompetent sphincter may favor a colostomy.

Endorectal ultrasound provides valuable preoperative staging (Fig. 82-1), including depth of tumor invasion into the rectal wall (89% to 92% accuracy,[16,17] 96% sensitivity, 90% specificity, 96% negative predictive value[18]) and nodal enlargement (79% sensitivity, 74% positive predictive value, 84% negative predictive value[19]), but confirmation of nodal metastasis with ultrasound-guided needle biopsy is less reliable (77% accuracy, 71% sensitivity, 89% specificity, 92% positive predictive value, and 62% negative predictive value[20]). Malignant nodes are differentiated from reactive nodes by being hypoechoic, hypervascular, and irregular.[21,22] Endorectal ultrasonography and magnetic resonance imaging (MRI) with endorectal coil exhibited similar accuracy and were superior to conventional computed tomographic (CT) scans in preoperative assessment of depth of invasion and adjacent organ invasion.[23] This improved diagnostic staging information is essential in considering local treatment for rectal cancer, deciding selective use of preoperative chemoradiotherapy in locally advanced tumors, and choosing between an abdominoperineal and low anterior resection.

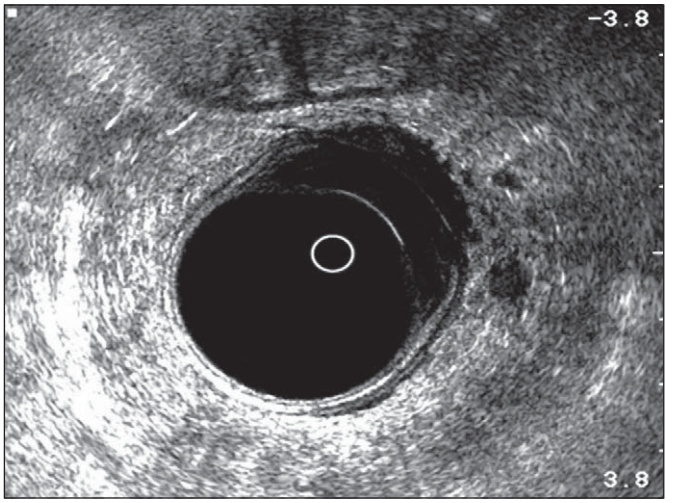


Figure 82-1 • Endorectal ultrasound of T3N1 rectal cancer. (Courtesy of Dr. W.D. Wong, Memorial Sloan-Kettering Cancer Center.)

The liver is the most frequent site of metastasis, followed by the lung, retroperitoneum, ovary, peritoneal cavity, and rarely the adrenal glands. Contrast-enhanced CT scan of the abdomen and the pelvis is recommended in all patients with rectal cancer, excluding the very elderly and those with very early cancer, such as cancer within a polyp or T1 rectal cancer. MRI is reserved for patients with locally advanced and recurrent rectal cancer requiring an exenterative procedure. A plain chest radiograph is useful and economical for screening for lung metastasis. Laboratory studies should be ordered as indicated by the patient's medical condition and anesthetic requirements. Measurement of the carcinoembryonic antigen (CEA) level in combination with imaging can refine the accuracy of preoperative assessment and overall prognosis and is useful if postoperative CEA monitoring is planned. Up to 95% of patients with advanced hepatic metastasis will have a CEA level above 20 ng/mL.[24] Normal preoperative CEA levels will identify patients who will not benefit from following CEA levels postoperatively. In men, a prostate-specific antigen level should be checked, particularly if the prostate gland is enlarged.

DIFFERENTIAL DIAGNOSIS

Kaposi's sarcoma of the rectum should be suspected in patients with acquired immunodeficiency syndrome who present with an unusual or atypical anorectal lesion. It is often associated with proctalgia (62%), hematochezia (50%), and diarrhea (50%).[25] Rectal carcinoids are often found incidentally during a screening colonoscopy or typically present with symptoms of bleeding, rectal pain, or constipation. They tend to be more indolent and less aggressive than colonic carcinoids, but as with most gastrointestinal carcinoids, tumor size correlates with the risk of metastasis and survival rates. Endoscopic resection is often adequate. Gastrointestinal stromal tumors of the rectum (Fig. 82-2) are uncommon and often present as source of lower gastrointestinal bleeding, rectal pain, or constipation. Because of their malignant potential and recent advances in the management of gastrointestinal stromal tumors with imatinib mesylate (Gleevec), it is imperative that these tumors be correctly diagnosed. Positive immunohistochemical staining with CD34 and CD117 confirms the diagnosis. For large or low-lying rectal gastrointestinal stromal tumors, neoadjuvant therapy with Gleevac can facilitate local and sphincter-preserving excision. Except for inflammatory masses, developmental cysts (such as dermoid, epidermoid, duplication, and tailgut cysts) and embryonic tumors (such as teratomas, chondromas, and meningoceles) are the most common retrorectal tumors. Other sacral and presacral tumors include neurogenic tumors, liposarcoma, and neurofibromatosis. Sacral pain and the sensation of fullness in the perirectal area are the most common symptoms of retrorectal lesions.[26] Digital rectal examination is the most important diagnostic maneuver. Posteroanterior and lateral radiographs of the sacrum and CT scanning are the preferred methods for characterization and differential diagnosis of retrorectal masses. MRI may also aid in planning the operative approach. Barium enema evaluation will confirm the presence of mass effect. Proctoscopy, although indicated, is usually normal. Most retrorectal lesions should be resected when diagnosed, even if they are asymptomatic and seem benign. Preoperative biopsy is generally not recommended, as it will not change the surgical need for resection and may contaminate the surgical field or lead to abscess formation. Biopsy is reserved for unresectable large retrorectal tumors.

SURGICAL TREATMENT OF RESECTABLE RECTAL CANCER

For most patients with early rectal cancer (T1 to T3), surgical resection is the primary treatment modality. Sound surgical techniques and adjuvant therapy can improve outcomes and maximize local and overall cure rates. Tumors in the upper third of the rectum have their lowermost edge 12 cm from the anal verge. Anterior resection or low anterior resection is the primary surgical procedure. Middle and lower third rectal cancers can be treated with restorative proctectomy with colorectal or coloanal anastomosis or abdominosacral resection with results similar to those that are achieved with abdominoperineal resection and permanent colostomy.[27] Overall surgical success depends on the ability to obtain a 2-cm distal margin; surgical expertise in obtaining clear lateral margins; the patient's body habitus, pelvic width, and prostate size; adequate collateral blood flow through the marginal artery; and whether or not there is associated colonic disease such as diverticulosis. Local approaches may be appropriate for patients with early rectal cancer within 8 cm from the anal verge or in patients with major medical contraindications to radical surgery.

Local Treatment

Selection Factors

Selection factors for full-thickness local excision are the same as or similar to those that are used for endocavitary radiation therapy (RT). This decision is therefore based largely on findings of digital rectal examination with increasing integration of use of transrectal ultrasound or MRI with endorectal coil.[20,23,28] Patients with T1 tumors without adverse pathologic features have a low incidence of local failure (5% to 10%) or lymph node involvement (<10%). With unfavorable pathologic features (lymphovascular invasion, high grade, deep submucosal invasion, signet ring cell, or colloid histology)[29–32] or evidence of tumor invasion into or through the muscularis propria,[30,33,34] the local recurrence rate is at least 17%, and the risk of regional lymph node involvement is at least 10% to 15%.[29] In an analysis by the Massachusetts General Hospital (MGH) of 40 patients who underwent local excision only, patients were categorized according to unfavorable clinical or pathologic features.[30] Among patients with T1 or T2 cancers following local excision, Blumberg and associates reported positive lymph nodes in 10% of T1 cancers and 17% of T2 cancers.[35] In addition, among the total group of 159 patients,

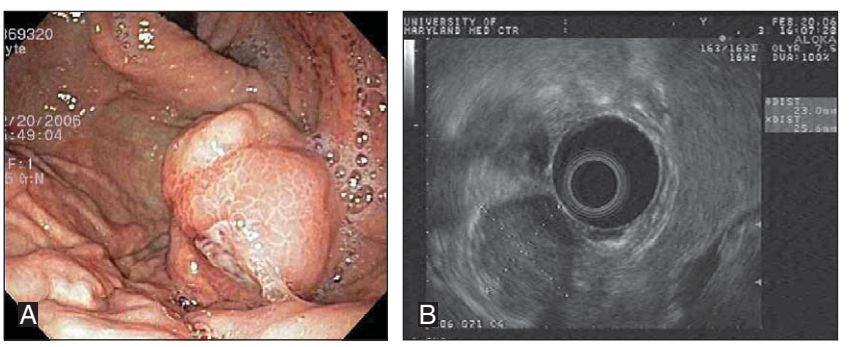


Figure 82-2 • Endoscopic (**A**) and TRUS (**B**) images of rectal gastrointestinal stromal tumors. (Courtesy of Dr. Nader Hanna, University of Maryland Medical Center.)

the incidence increased with the presence of lymphatic and vascular invasion (14% without versus 33% with). Even among the 42 patients with the most favorable features (negative lymphatic and vascular space involvement, well- or moderately differentiated T1 cancers), 7% were found to have lymph node involvement. The overall 5-year survival rate for the whole group was 65% with a locoregional recurrence rate of 27%. Hager and associates reported on a series of 20 patients with T2 rectal cancer for which local excision was performed and who were otherwise thought to be "low risk" (well to moderately differentiated, nonmucinous, no lymphovascular invasion, and negative margins), despite which the incidence of locoregional failure was still 17%.[33] Others have reported locoregional failure rates as high as 43% following either local or transanal excision in patients with T2 cancers.[36] There have been no randomized trials that compared transanal full-thickness local excision alone for T1/T2 with or without adjuvant chemoradiation to low anterior resection or abdominoperineal resection. Recent published results of local excision of T1/T2 rectal lesions without adjuvant therapy show local recurrence rates of 3.4% to 18% for T1 lesions and 27% to 67% for T2 lesions; these results are summarized in Table 82-1.

Local Approaches

Local approaches for treatment of early rectal cancer include transanal local excision, suprasphincteric posterior proctectomy (the Kraske procedure), transsphincteric posterior approaches (Bevan or York-Mason procedure), transanal endoscopic microsurgery (TEM), transanal fulguration, or local/contact radiation therapy (Papillon approach). TEM is a minimally invasive surgical technique that was introduced in 1984 by Buess. It incorporates a high-quality binocular operating system and pressure-regulated insufflation with continuous suction. Compared with conventional transanal resection, TEM provides superior intraoperative visualization and the ability to perform full-thickness excision of the tumor with clear margins, together with perirectal fat and adjacent lymph nodes[37,38] of tumors higher up in the rectum (4 to 18 cm from the anal verge). The technique is not yet generally established because of the high cost, the necessary special instrumentation and tools, and the unusual technical aspects of the approach.[38–46]

Treatment of cT2 rectal tumors with TEM combined with preoperative high-dose radiotherapy in 35 patients achieved survival rates similar to those of conventional open surgery.[47] Only minor postoperative complications occurred in five (14.3%) patients and included suture line dehiscence in three patients and stool incontinence in two patients. At a median follow-up period of 38 months, one patient presented with a local recurrence (2.85%) at 30 months of follow-up, and four patients developed systemic metastasis (11.4%). The survival and local recurrence rates that were reported in that study led to a prospective multicenter randomized trial (the so-called Urbino trial) to evaluate the efficacy of local excision in T2 tumors that were preoperatively treated by chemotherapy and high-dose radiotherapy versus standard open treatment (low anterior resection or abdominoperineal resection). At a median follow-up period of 56 months (range, 44 to 67 months), the local failure rate (5%) and distant metastasis rate (5%) were equal in the two groups.[48]

A recent review of the United Kingdom national TEM database from 21 centers since 1993 showed that of 454 rectal cancer patients, 69% underwent TEM with curative intent. The overall morbidity and mortality of TEM were 17.2% and 1.5%, respectively. Pathologic staging was as follows: pT0 (1.8%), pT1 (52.9%), pT2 (32.8%), pT3 (9.9%), and pTx (3.1%). Neoadjuvant therapy and adjuvant radiotherapy were administered in 8% and 18% of cases, respectively. Margin positivity (<1 mm) occurred in 20% of cases and was stage dependent. The 5-year disease-free survival rate was 77% for pT1, 74% for pT2, and 35% for pT3 with local recurrence rates of 20%, 25%, and 59%, respectively.[49]

Radical Resections

Sharp, total mesorectal excision (TME) with autonomic nerve preservation is the radical surgical technique of choice in conjunction with low anterior resection or abdominoperineal resection (APR). The mortality rate is 1% to 7%, and the morbidity rate (including genitourinary dysfunction, fecal incontinence, and permanent colostomy) is 13% to 46%. Locoregional recurrent disease is observed in 4% to 20% of cases, and the 5-year survival rate is 74% to 87%.[50–54]

Table 82-1 Local Excision of T1, T2 Lesions Without Adjuvant Therapy in Selected Series with More Than 50 Patients

Reference	No. of Patients (Per Stage)	Follow-up Time	LR	Survival Rate	Salvage Surgery for Isolated LR
Paty et al.*[223]	125 (T1 = 74, T2 = 51)	6.7 yr	T1 = 17% T2 = 26%	10-year OS: T1 = 74%, T2 = 72%	14/17
Mellgren et al.[224]	108 (T1 = 69, T2 = 39)	4.4 yr	T1 = 21% T2 = 47%	5-year OS: T1 = 72%, T2 = 65%	24/27
Garcia-Aguilar et al.[225]	83 (T1 = 55, T2 = 27)	54 mo	T1 = 18% T2 = 37%	5-year: T1 = 98%, T2 = 89%	17/20
Chakravarti et al.[176]	52 (T1 = 44, T2 = 8)	52 mo	28%	5-year DFS: 66	NS
Steele et al.[177]	59 (T1 = 59)	48 mo	T1 = 5%	6-year survival: 85	2/2
Kim and Madoff[226]	69 (T1 = 44, T2 = 25)	NS	T1 = 9% T2 = 28%	Cancer-specific 5-year survival: 88%	NS
Hager et al.[33]	59 (T1 = 39, T2 = 20)	33–40.5 mo	T1 = 8% T2 = 17%	5-year survival: T1 = 90%, T2 = 78%	NS

DFS, disease-free survival; LR, local recurrences; NS, not specified; OS, overall survival.

*In this series, 16 patients received postoperative radiotherapy and 15 additional patients received postoperative 5-FU and radiotherapy; however, local and overall recurrence rates were similar in both groups.

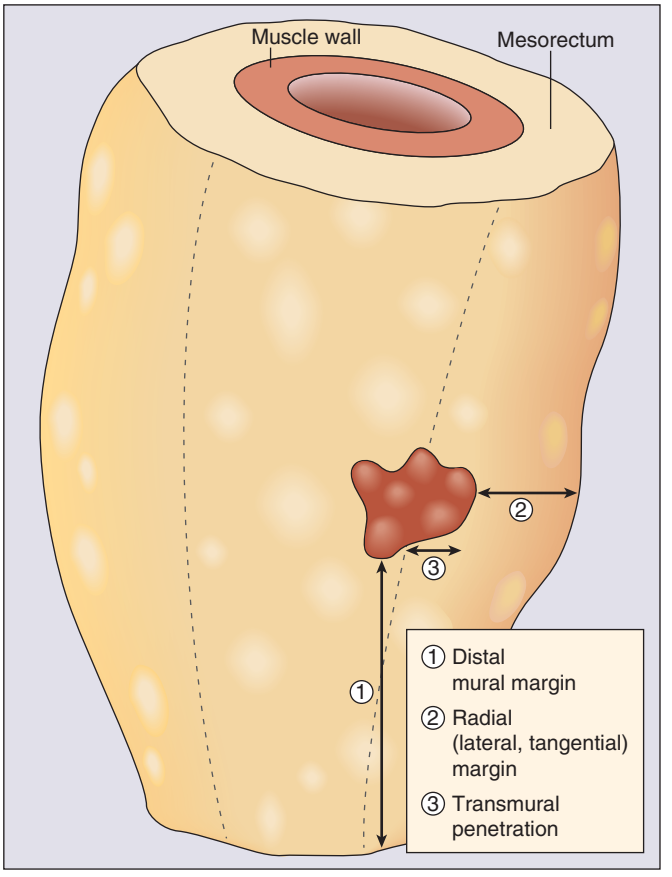


Figure 82-3 • Rectal cancer primary tumor margins.

Surgical Issues in Radical Resections

LATERAL CIRCUMFERENTIAL MARGINS AND TOTAL MESORECTAL EXCISION. The ability to obtain a negative lateral circumferential margin is associated with a decreased risk of local recurrence.[55–58] In a multivariate analysis, circumferential margin involvement was the most powerful predictor of local recurrence (hazard ratio: 12.2) and of overall cancer mortality (hazard ratio: 3.2; Fig. 82-3). Heald and colleagues have advocated TME in conjunction with low anterior resection or APR as the optimal surgical treatment for rectal cancer.[50] This technique involves removal of the entire rectal mesentery, including that distal to the tumor, as an intact unit. Complete distal TME is essential for clearance of any tumor deposits, which occur in 50% of T3 tumors with a maximal distal spread of 4 to 5 cm,[59] and is associated with increased frequency of local recurrence and decreased overall survival.[60,61]

Sharp mesorectal excision combined with TME provides the optimal surgical strategy. In contrast to conventional blunt dissection techniques, sharp mesorectal excision facilitates nerve preservation, enables complete hemostasis, and emphasizes gentle handling to avoid tearing or disruption of the smooth outer surface of the mesorectum. Sharp TME has been shown to achieve a negative circumferential margin in 93% of resected specimens. Although no randomized trial of TME has been performed, TME has been evaluated prospectively in Sweden, where it has been introduced via a formal preceptorship-based training program. A 5-year prospective audit reveals a local recurrence rate of 7% following the addition of TME compared to a historical control rate of 23%.

DISTAL MUCOSAL MARGIN. The ability to perform sphincter-preserving surgery is dictated by the requirements of a 2-cm distal margin rather than the traditional 5-cm margin.[62–66] Only 2.5% of patients (usually with poorly differentiated and node-positive rapidly disseminating disease) had disease spread greater than 2 cm.[27] There is no correlation between risk of local recurrence and the extent of distal margin in excess of 2 cm.[67–72]

PROXIMAL EXTENT OF LYMPH NODE DISSECTION. Proximal lymph node dissection should extend just distal to the origin of the left colic artery. No evidence indicates a relationship between local recurrence and survival and dissection of deep iliac lymph nodes[73] or high ligation of inferior mesenteric pedicle.[74,75] Patients with pathologically positive nodes along the inferior mesenteric artery have very low 5-year survival rates.[76,77]

Laparoscopic Surgery

Laparoscopic surgery for curable rectal cancer is controversial and still considered investigational. Laparoscopic anterior resection with curative intent generates considerably more reservations than does laparoscopic APR, which is technically much easier to perform. Data on the extent of lymphadenectomy, margins of resection, actuarial survival, and local recurrence rates have not been determined, and the current randomized trials of laparoscopic resection for colorectal cancer specifically exclude rectal cancer. The technique of laparoscopic TME is well described by Pikarsky and associates.[65] Reports suggest short-term gains of reduced pain, shortened hospital stay, accelerated activity, possible cost reduction, and improved cosmesis.[66] Hand-assisted laparoscopic surgery is a new technique that has the potential to overcome many of the existing limitations of pure laparoscopy.[78] A recent prospective nonrandomized single institution trial comparing open versus laparoscopic resection in 191 consecutive patients with low and midrectal cancer demonstrated a conversion rate of 18.4%. In the laparoscopic group, the mean time for complete patient mobilization was shorter (1.7 versus 3.3 days; $P < 0.001$), and patients were earlier in passing flatus (2.6 versus 3.9 days; $P < 0.001$) and stools (3.8 versus 4.7 days; $P < 0.01$) and in resuming oral intake (3.4 versus 4.8 days; $P < 0.001$). The mean hospital stay and overall morbidity and mortality rates were similar with no statistically significant differences. Laparoscopic patients had a higher rate of anastomotic fistulas (13.5% versus 5.1%) and reoperations (6.1% versus 3.2%), but the difference was statistically nonsignificant. Laparoscopic resection presented a significantly lower local recurrence rate (3.2% versus 12.6%; $P < 0.05$). Although the cumulative survival and disease-free rates at 5 years were nonsignificant between both groups (80% and 65.4% after laparoscopic surgery and 68.9% and 58.9% after open surgery), stage-by-stage comparison showed prolonged cumulative survival for stages III and IV cancer in the laparoscopic group (82.5% versus 40.5%; $P = 0.006$ and 15.8% versus 0%; $P = 0.013$, respectively) and a reduced rate of cancer-related death for stage III in the laparoscopic group (11.4% versus 51.9%; $P = 0.001$).[79]

The U.K. Medical Research Council (MRC) prospective multicenter, randomized, controlled trial of conventional versus laparoscopic-assisted surgery in colorectal cancer, included 128 rectal cancer patients in the open group and 253 patients with rectal cancer in the laparoscopy assisted group with intent to treat. (The actual treatment groups included 132 open and 160 laparoscopy-assisted surgeries). About 10% more patients underwent total mesorectal excision in the laparoscopy-assisted group than in the open surgery group. The rate of abdominoperineal resection was similar (27% in the open surgery group and 25% in the laparoscopic group). Lymph node yield was equally high in the two groups. The intraoperative conversion rate from laparoscopic to open was 34%. In the intent-to-treat population, there was no significant difference in the open versus laparoscopy-assisted group in regard to positive circumferential margin (14% versus 16%), overall intraoperative complications (14% versus 18%), overall morbidity (50% versus 59%), and mortality (5% versus 4%).While laparoscopic rectal resection did not adversely affect

Table 82-2 Patterns of Locoregional Recurrence and Overall Failure Following Standard/Conventional Surgery Alone for Rectal Cancer

Multi-Institutional Series	N*	MAC Stage	LR (%)	OF (%)
GITSC[83]	58	B/C	24	44
EORTC[84]	166	A–C	32	41
NSABP[85]	191	B/C	33	58

	Stage I			Stage II			Stage III		
Single Institution Series	**N***	**LR (%)**	**OF (%)**	**N**	**LR (%)**	**OF (%)**	**N**	**LR (%)**	**OF (%)**
MDAH[86]	39	8	18	59	31	47	44	50	70
UT[87]	28	21	28	37	29	45	43	51	74
MSKCC[88]	47	14	—	69	44	—	52	61	—

		MAC	
Single Institution and Predominantly Single Operator Series	**N***	**Stage**	**LR (%)**
Patel et al[89]	435	A–C	24
Enker et al[90]	412	A–C	27

EORTC, European Organization for Research and Treatment of Cancer; GITSC, Gastrointestinal Tumor Study Group; LR, locoregional recurrence; MDAH, M.D. Anderson Hospital; MSKCC, Memorial Sloan-Kettering Cancer Center; NSABP, National Surgical Adjuvant Breast and Bowel Project; OF, overall failure; UT, University of Texas.
*Number of patients.

bladder function, there was a trend toward worse male sexual function, which might be explained by the higher rate of TME in the laparoscopic rectal resection group.[80,81]

In a systematic review by the Cochrane group, it was noted that most reported laparoscopic surgery studies for rectal cancer are individual cohort studies, individual case-control studies, or case series with only one reported randomized controlled trial. Collectively, in 48 studies representing 4224 rectal cancer patients, there appear to be no significant differences in terms of disease-free survival rate, local recurrence rate, mortality, morbidity, anastomotic leakage, resection margins, or number of lymph nodes harvested. Laparoscopic approaches are generally associated with less blood loss, quicker return to normal diet, less pain, and less narcotic use but are also associated with longer operative time and higher costs, and no results of quality of life were reported.[82]

Patterns of Failure

Following potentially curative standard or conventional surgical resection for adenocarcinoma of the rectum, the incidence of locoregional or distant treatment failure is related to the extent of transmural disease and associated involvement of regional lymph nodes by metastases.[83–90] The incidence of locoregional failure is 8% to 21% in AJCC stage I disease (MAC stage A/B1), 29% to 44% in AJCC stage II disease (MAC stage B2/B3), and 50% to 61% in AJCC stage III disease (MAC stage C). The incidence of distant failure (as a component of failure) is up to 28% in AJCC stage I disease, 47% in AJCC stage II, and up to 74% in AJCC stage III disease. It has been claimed that when one compares these patterns of failures between multi-institutional trial settings versus single-institutional and predominantly single-operator (surgeon) series, great differences in results can be seen. These patterns of failures according to multi-institutional versus single-institutional/single-operator series are summarized in Table 82-2.[83–90] Although distant metastasis is most likely to be attributed as the cause of death in rectal cancer patients, the potential influence of locoregional failure as an antecedent event to the development of distant metastases is clinically important. Hence, decreasing locoregional failure is an important endpoint of treatment in rectal cancer. These data and rationale serve as the basis for consideration of adjuvant chemoradiotherapy in the management of rectal cancer and, in particular, as a standard for AJCC stage II (MAC stage B2/B3) and stage III disease (MAC stage C). It is important to note that limited retrospective data identify subsets of patients with stage I disease who may be considered for adjuvant therapy as well as subsets of patients with T3N0 disease who may not require adjuvant therapy.[91,92] Willett and associates identified a subset of patients with stage I disease who have an increased incidence of locoregional failure following an APR.[92] In an additional review of 117 patients with T3N0 disease, Marks and associates identified a favorable group of patients with moderately or well-differentiated cancers invading less than 2 mm into perirectal fat who had a 10-year actuarial locoregional failure rate of only 5% following surgery alone, compared to 29% in T3N0 patients without these favorable features.[93]

ADJUVANT THERAPY

Treatment Sequencing Issues

Preoperative versus Postoperative Therapy: Potential Advantages and Disadvantages

Table 82-3 summarizes the advantages and disadvantages of preoperative (typically chemoradiotherapy) versus postoperative adjuvant therapy. The major advantages of preoperative therapy are tumor

Table 82-3 Advantages of Preoperative versus Postoperative Adjuvant Therapy*

Advantage	Preoperative Therapy	Postoperative Therapy
Tumor downstaging	+	–
Increased tumor resectability	+	–
Increased sphincter preservation	+	–
Treatment based on operative/pathologic findings	–	+
Decreased locoregional recurrence	++	+
Increased survival	+	–

* Typically chemoradiation therapy.

downstaging with increased resectability and sphincter preservation as well as a reduced incidence of acute and chronic toxicity. Adequate doses of radiation (>4000 Gy) can sterilize peripheral margins of disease.[90] Marginally resectable and unresectable tumors can undergo tumor shrinkage, making them amenable to curative surgical resection, particularly within the confines of the ridged, funnel-shaped bony pelvis, which often limits the potential for adequate circumferential margins of resection.[55,58] Preoperative therapy also allows tumors to be resected with limited longitudinal surgical margins, thereby extending the level to which sphincter-sparing procedures can be performed safely in the distal rectum.[93] These advantages in turn are associated with the potential for a significant reduction in a source of tumor spillage associated with locoregional recurrence of disease as well as a reduction of the dissemination during surgery of viable tumor cells increasing the risk for developing distant metastatic foci. The potential therapeutic advantage of preoperative therapy (particularly radiation) with enhanced oxygenation prior to surgical disruption of tumor blood supply is well established.[94,95]

Preoperative therapy also has the potential advantage of reducing the risk of treatment of both chemotherapy- and radiation-related morbidity compared to that seen with postoperative therapy.[96–99] Following surgical resection, adhesions often develop and cause loops of bowel to be fixed within the pelvis. These fixed bowel loops often show enhanced tissue reaction with associated bacterial invasion, increasing the risk of severe treatment-related complications. In the preoperative therapy setting, the small bowel is less likely to be fixed within the treatment field and thereby is less prone to both acute and chronic treatment-related injury.

The major advantage of postoperative therapy is the ability to select patients who are at high risk for locoregional or distant disease recurrence based on pathologic staging of disease and operative findings. This also minimizes the potential of overtreating patients with either early disease (pathologic stage I) or radiographically occult metastatic disease found at time of surgery. Other potential advantages include the avoidance of possible wound-healing problems associated with preoperative therapy. Otherwise, studies have failed to demonstrate any increased potential for the development of disseminated disease during preoperative therapy and the subsequent waiting period prior to surgery.

Optimal Timing of Surgery Following Preoperative Therapy

Until the publication of the Lyon R90-01 randomized trial,[99] the optimal timing of surgery following preoperative therapy in rectal cancer was based on hypothesis or retrospective data. This study randomized 201 patients with stage T2/T3, NX, M0 into two treatment groups: (1) the short-interval group, in whom surgery was performed within 2 weeks of completion of preoperative radiation therapy (39 Gy and 13 fractions) versus (2) the long-interval group, in whom surgery was performed within 6 to 8 weeks after completion of preoperative radiation therapy. At a median follow-up time of 33 months, there was no difference in morbidity, local recurrence, or short-term survival between the two groups. These findings along with the previously demonstrated findings that rectal cancers undergo slow tumor shrinkage over several months after radiation[100] lend further support to the rationale that a longer delay before surgery, particularly in locally advanced tumors, might be desirable to allow for maximal tumor regression prior to surgery. Current randomized trials are systematically investigating the optimal timing of surgery out to as long as 12 weeks following completion of neoadjuvant therapy. In the most extreme example of delayed surgical intervention, Habr-Gama and colleagues have reported their continuing series of patients in whom they have delayed surgical intervention indefinitely following a clinical complete response (CR) that was assessed 8 weeks following neoadjuvant chemoradiation by clinical, endoscopic, and radiographic studies.[101,102] This approach is considered highly investigational; however, it is thought-provoking in terms of a treatment paradigm mirroring that for patients with cancers of the anal canal, in whom surgery is reserved for salvage of chemoradiation failures in patients who achieve a clinical CR to initial treatment.

Optimal Timing of Adjuvant Radiation Following Surgery

Lee and associates reported the results of a phase III study of postoperative adjuvant therapy in stage II and III rectal cancer that was designed to define the optimal sequencing of chemotherapy and RT.[103] In this study, 308 patients were randomized to early RT versus late RT. Patients received 45 Gy in 25 fractions of RT with eight monthly cycles of 5-fluorouracil (5-FU)/leucovorin chemotherapy. RT began with the start of chemotherapy in the early RT group versus with the start of the third cycle of chemotherapy in the late RT group. With a median active follow-up of 37 months, the disease-free survival rate was significantly improved in the early RT group compared to the late RT group (81% versus 71% at 4 years; $P = 0.043$). This finding was associated with an increase in both distant and locoregional disease recurrence in the late RT group and with an overall recurrence rate of 17% in the early RT group versus 27% in the late RT group ($P = 0.047$). Although overall survival was not significantly different between the treatment arms, these results suggest that the timing of adjuvant postoperative RT can have a significant impact on the outcome of patients with rectal cancer.

Radiation Treatment Planning

Preoperative Planning

Preoperative chemoradiation is the most common approach employed in the treatment of locally advanced rectal cancer treatment. The target tissues include the tumor, the perirectal lymphatics, the internal iliac lymph nodes (and the external iliac lymph nodes in T4 tumors or those with external iliac nodal involvement), and the presacral lymph nodes. Plans typically consist of three or four fields (left lateral, right lateral, posteroanterior, and/or anteroposterior). Every effort is made to exclude the small bowel from the field of treatment; therefore, small bowel contrast is utilized in the CT simulation of these patients so that the small bowel can be visualized well on the CT scan acquired for treatment planning. Typically, this consists of 100 mL of diluted barium by mouth at least 1 hour prior to the CT acquisition. In addition, it is preferable to position the patient prone on a modified "belly board" to allow for displacement of the small bowel up and out of the pelvis (Fig. 82-4). This displacement can be further maximized by giving patients explicit instructions to increase fluid intake to allow maximal distension of the bladder to further push the small bowel out of the pelvis during actual treatment. All patients should be simulated in a body mold for reproducible setup from day to day during treatment. It is also recommended that an anal verge marker be used as a reference point for CT-based planning. Typical preoperative treatment in the United States consists of 45 Gy in 1.8-Gy daily fractions to the pelvis followed by a 5.4- to 9-Gy boost.

Postoperative Planning

Treatment planning in the postoperative setting targets the postoperative bed and the draining lymphatics as described previously (and consideration can be given to including the inguinal lymphatics in patients with a rectal cancer that involves the anal canal). The risk of small bowel complications is higher in the postoperative treatment setting because the small bowel "falls" down into the virtual space in the pelvis that is consequent to the patient's surgical resection. It is of critical importance to delineate the small bowel on CT scans and pay careful attention to the dose that is delivered. As with the preoperative patients, a belly board should be utilized when possible to minimize small bowel dose.

For patients who have undergone an APR, the perineal scar should be marked and included within the radiation treatment fields with consideration of the addition of bolus depending on treatment distribution. For cancers arising in the mid- to proximal portion of the rectum, only the posterior half of the pelvis/presacral space needs to

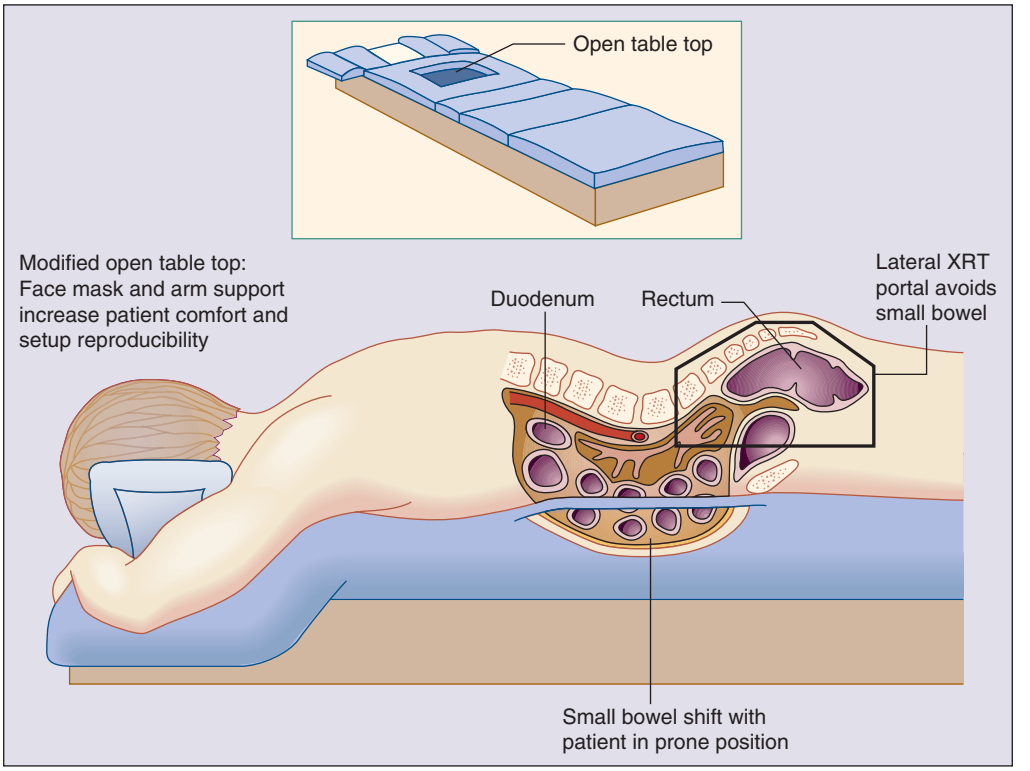


Figure 82-4 • The belly board or open tabletop device allows for maximal displacement of the small bowel (with bladder distension) during radiation treatment. An example of a lateral treatment portal is shown. The pubic bone is positioned just inferior to the edge of the opening. (From Mak AC, Marijnen CAM, Nagtegaal ID, et al: Late complications of postoperative radiation therapy for cancer of the rectum and rectosigmoid. Int J Rad Oncol Biol Phys 1994;28:597–603.)

be included within the treatment field with the anterior border posterior to the symphysis. However, for patients with very low-lying or distal rectal cancers, particularly those involving surrounding adjacent organs such as the prostate, bladder, uterus, and vagina, the anterior border should be placed anterior to the symphysis, in association with shaped alloyed blocks to maximize small bowel exclusion. Such technical considerations have been previously published in detail.[104–107] Typical postoperative treatment in the United States consists of 45 Gy in 1.8-Gy daily fractions to the pelvis followed by a 5.4- to 9-Gy boost in patients with negative surgical margins.

TREATMENT RELATED TOXICITY

Acute Toxicity

The acute complications generally include diarrhea with or without abdominal cramping, acute proctitis with or without tenesmus, bloody or mucous discharge, dysuria/cystitis, leukopenia, and thrombocytopenia. Although the addition of concurrent chemotherapy with radiation is associated with improved patient outcome, it also clearly increases the occurrences of these toxicities. Fortunately, these acute events are usually transient and resolve within a few weeks following the completion of therapy. The management of bowel-related toxicity usually involves the use of loperamide or diphenoxylate/atropine. Radiation proctitis can be treated with hydrocortisone foam or suppositories. Controlling bowel frequency will also help to control the symptoms of proctitis. The bowel mucosa typically recovers within 1 to 3 months following completion of therapy.

Cystitis is due to the effects of radiation on the transitional cells lining the bladder. Symptoms include dysuria, frequency, urgency, and nocturia. An infectious process must be ruled out, particularly if symptoms occur early in the course of therapy or if bladder catheterization was performed for treatment planning. Infection should be treated with an antibiotic based on urine culture and antibiotic sensitivity. Urinary analgesics, such as pyridium, are helpful for dysuria. Bladder spasms may require antispasmodics such as flavoxate.

Perineal dermatitis is more common in patients who are being treated postoperatively after APR in which the inferior border of the radiation fields is extended to cover the perineal scar and in patients with low-lying rectal tumors who are being treated preoperatively. Concurrent chemotherapy and bolus over the scar can often exacerbate the reaction. Treatment should be aimed at controlling the frequency of bowel movements, which tend to further exacerbate and irritate the perineal skin and reaction. Mild dermatitis can be treated with sitz baths and aloe wipes. More severe cases can be treated with nonmetallic skin creams.

Chronic Toxicity

Long-term complications include diarrhea, proctitis, small bowel obstruction, perforation or fistula, perineal and scrotal tenderness, urinary incontinence, and bladder atrophy/bleeding. In the MGH experience of 165 patients receiving 45 Gy postoperatively to the pelvis with a boost to the tumor bed to 50.4 Gy total, the incidence of long-term mild to moderate complications was 8% (4% transient and 4% persistent).[108] Persistent long-term complications were limited to proctitis (2%), delayed perineal wound healing (1%), and urinary incontinence (1%). The incidence of small bowel obstruction requiring surgery was essentially equal in the patients who received radiation (6%) and a historical control group of patients who were treated with surgery alone (5%).

Modern Radiation Therapy Techniques Toward Reducing Toxicity

When radiation is given concurrently with chemotherapy, the risk of radiation-related side effects increases owing to the radiosensitization

of tissues by the chemotherapy. Additionally, chemotherapy has its own side effects, some of which overlap with those associated with radiation therapy to the pelvis. Randomized trials have demonstrated that the grade 3 or 4 side effects of chemoradiation are less frequent when given preoperatively versus postoperatively.[98,109]

In the modern landscape of clinical trials in rectal cancer, many trials employ a second chemotherapy that is given concurrently with radiation therapy and 5-FU (or capecitabine). The most common dose-limiting toxicity associated with these novel approaches is gastrointestinal toxicity. In an effort to reduce the degree of gastrointestinal toxicity conveyed by the delivery of radiation therapy, newer radiation delivery techniques are being explored.[110–112] One of the most promising modern highly conformal radiation delivery techniques, intensity-modulated radiation therapy, may result in less gastrointestinal toxicity owing to reductions in small bowel dose. This technique will be the subject of an upcoming cooperative group trial (Radiation Therapy Oncology Group [RTOG] 0628). This trial will employ intensity-modulated radiation therapy planning and treatment in the neoadjuvant setting of locally advanced rectal cancer patients who are receiving concurrent capecitabine and oxaliplatin prior to a planned TME resection and adjuvant chemotherapy. The results will be compared with the identical arm of the RTOG 0247 trial, which employed conventional three-dimensional radiation planning.

Toxicity: Preoperative versus Postoperative Therapy

Despite the survival advantage in select patients receiving adjuvant postoperative chemoradiotherapy, such treatment is associated with substantial toxicity. In the previously discussed Gastrointestinal Tumor Study Group (GITSG) trial, the incidences of greater than grade 3 toxicity in patients who received adjuvant postoperative chemoradiotherapy was 35% for nonhematologic effects and 26% for hematologic effects.[83] In the North Central Cancer Treatment Group (NCCTG) trial, greater than grade 3 toxicity among patients receiving postoperative adjuvant radiation therapy alone was limited to a 5% rate of diarrhea.[113] In comparison, in the treatment group receiving combined adjuvant postoperative chemoradiotherapy, greater than grade 3 toxicity included a 41% rate of diarrhea and 33% rate of leukopenia. In both the GITSG and NCCTG trials, 35% of patients were unable to complete all planned cycles of chemotherapy owing to toxicity. Also, in the NCCTG trial, an additional 25% refused to complete their therapy.

As was discussed previously, preoperative treatment has the potential advantage of reducing the risk of treatment-related morbidity as compared to that seen with postoperative therapy.[96,97] In addition, it would appear that higher doses of chemotherapy can be delivered within the preoperative setting than in the postoperative setting. This is particularly evidenced in review of serial phase I studies of combined chemoradiotherapy performed at the Memorial Sloan-Kettering Cancer Center in both the postoperative and preoperative setting with similar design.[114,115] With the doses of leucovorin and radiation remaining constant, the maximally tolerated dose of 5-FU was higher for the preoperative radiation therapy regimen. Results from the German preoperative versus postoperative chemoradiotherapy study have reinforced that toxicity is greater when treating in the postoperative setting and treatment compliance is lower in the postoperative setting.[98] Grade 3 and 4 acute and chronic toxicity were 40% and 24% for the postoperative group versus 27% and 14% for the preoperative group. The Eastern Cooperative Oncology Group (ECOG) study recently reported by Bossett and colleagues lends further evidence to reduced chemotherapy compliance in the postoperative setting of patients receiving multimodality therapy.[116]

Use of preoperative radiation, particularly high-dose (>40 Gy) radiation, has raised some concerns about technical difficulty in surgical resection and delayed healing of abdominal and perineal wounds. As was previously discussed, in both the Swedish and MRC trials, the postoperative mortality rate was not increased with the use of preoperative radiation; and with use of the more conventionally fractionated preoperative MRC regimen (40 Gy at 2 Gy per fraction), there was no increase in postoperative or late complications.[117,118] Delay in wound healing has been implicated to be more likely associated with patients undergoing immediate surgical resection following preoperative radiation as compared to patients whose surgery was delayed 6 to 8 weeks. However, in the previously discussed Lyon R90-01 randomized trial of short-interval (2 weeks after completion of radiation therapy) versus long-interval (6 to 8 weeks after radiation therapy) time to resection, there did not appear to be a significant difference in perioperative morbidity and mortality rates.[99] It would appear that an increase in perioperative morbidity or a delay of wound healing is more likely associated with the use of a higher dose per fraction, similar to the intensive short course of 25 Gy given in five fractions.[119,120]

Sphincter and Bowel Function

Radiation therapy can affect sphincter function; however, systematic, prospective data inclusive of uniformly treated patients with pretreatment baseline sphincter assessment are lacking. Two such studies reporting on the impact of postoperative therapy on long-term sphincter function utilized nonrandomized, nonblinded, and retrospective telephone survey methods. The report from the Mayo Clinic evaluated the impact of postoperative chemoradiotherapy utilizing conventional doses and techniques of pelvic radiation combined with 5-FU-based chemotherapy in comparison to a matched group of patients undergoing surgery alone.[121] In comparison to the 59 patients who underwent surgery alone, the 41 patients who received chemoradiotherapy had a significant increase in bowel movements, incontinence, urgency, and the need to wear pads. Paty and associates reported on sphincter function in a series of 81 patients following coloanal anastomosis. The 40 patients who received preoperative or postoperative radiation therapy (with or without chemotherapy) following coloanal anastomosis had increased stool frequency and difficulty with evacuation compared with 41 patients who underwent surgery alone.[122]

In contrast to the preceding series, Birnbaum and colleagues have reported on the prospective evaluation of both the short-term and long-term impact of preoperative radiation on sphincter function.[123,124] All the patients were treated with conventional radiation techniques and doses and were assessed objectively with anal manometry with or without transrectal ultrasound. Radiation therapy had minimal effect on sphincter function in the 20 patients who were assessed for short-term results and the 10 patients who were assessed for long-term results.

POSTOPERATIVE THERAPY: RESULTS OF RANDOMIZED TRIALS

As was previously discussed, the major advantage of postoperative therapy in rectal cancer is to base treatment on operative/pathologic staging (Table 82-4). Early studies that were instrumental in defining the role of postoperative adjuvant therapy for rectal cancer included the GITSG and NCCTG studies.[83,107]

The GITSG study randomized 202 patients who had undergone "curative" surgical resection for adenocarcinoma of rectum to one of four treatment arms: (1) surgery alone, (2) surgery plus postoperative radiation (40 to 48 Gy over 4.5 to 5.5 weeks), (3) postoperative chemotherapy (5-FU plus methyl-CCNU), or (4) postoperative combined chemoradiotherapy.[83] At a median follow-up time of 94 months for all survivors, this study found a significant improvement in the long-term survival of patients receiving adjuvant postoperative chemoradiotherapy compared to surgery alone (59% versus 44%, $P = 0.005$).[107] This improvement was associated with a significant reduction of locoregional recurrence from 24% with surgery alone to 11% with postoperative adjuvant chemoradiotherapy. However, this was also associated with the increase in overall "severe or worse" toxicity associated with adjuvant postoperative chemoradiotherapy.

Table 82-4 Results of GITSG, NCCTG, and NSABP Studies Evaluating Postoperative Adjuvant Therapy for Rectal Cancer

	GITSG[83]		NCCTG[107]		NSABP R-02[127]	
Type of Therapy	**LR (%)**	**5-Year Survival (%)**	**LR (%)**	**5-Year Survival (%)**	**LR (%)**	**5-Year Survival (%)**
Surgery alone	24	44	—	—	—	—
Radiation therapy	20	50	25	48	—	—
Chemotherapy	27	50	—	—	13	~65
Chemoradiotherapy	11	59	13	57	8	~65

GITSG, Gastrointestinal Tumor Study Group; LR, locoregional recurrence; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Subsequent to the GITSG study, the NCCTG study randomized 204 patients with pathologic high-risk rectal carcinoma to surgery and postoperative radiation (45 to 50.4 Gy in 5 to 5.5 weeks) versus surgery plus postoperative chemoradiotherapy utilizing 5-FU plus methyl-CCNU, which both preceded and followed combined chemoradiotherapy.[113] At a median follow-up time of over 7 years, there was a significant benefit in the adjuvant postoperative chemoradiotherapy group versus the postoperative radiation-alone group. This benefit was characterized by a significant reduction in locoregional recurrence rate, 25% versus 13% ($P = 0.036$); reduction in distant metastases, 46% versus 29% ($P = 0.011$); and improvement in overall 5-year survival rate, 57% versus 48% ($P = 0.0016$). These trials led to the 1990 NIH Consensus that recommended adjuvant therapy as the standard of care in the United States.[125]

An additional intergroup study evaluated the addition of biologic response modifiers, leucovorin and levamisole, as means of improving patient outcome; 1695 patients were entered on this three-arm phase III randomized trial, and at a median follow-up period of over 7 years, there was no advantage to leucovorin or levamisole regimens over bolus 5-FU in the postoperative adjuvant chemoradiotherapy treatment of high-risk rectal cancer.[126] Meanwhile, the NSABP R-02 trial was in part designed to evaluate the effect of radiation on overall survival in the postoperative adjuvant setting. It also evaluated the potential modulation of 5-FU by leucovorin. The study randomized 694 patients to receive either postoperative adjuvant chemotherapy alone ($N = 348$) or postoperative chemoradiotherapy ($N = 346$). In addition, all female patients received 5-FU plus leucovorin chemotherapy; male patients received either methyl-CCNU, vincristine, and 5-FU or 5-FU plus leucovorin. This latter aspect of the study design was related to the enigmatic findings of the prior NSABP postoperative rectal adjuvant trial showing differences in outcome related to gender.[85] With surviving patients on the R-02 study being followed on average over 7 years, adjuvant postoperative radiation resulted in no beneficial effect on overall survival ($P = 0.89$). The cumulative incidence of locoregional relapse among patients being treated with chemotherapy alone was 13% compared to 8% among those receiving postoperative adjuvant chemotherapy at 5 years ($P = 0.02$).[127] The results of the trials comparing preoperative chemoradiation versus postoperative chemoradiation are discussed in a separate section.

PREOPERATIVE RADIATION THERAPY: RESULTS OF CLINICAL TRIALS

Preoperative Radiation Plus Surgery versus Surgery Alone

In the early 1970s and 1980s, a number of studies evaluated preoperative radiation therapy (no chemotherapy) for rectal cancer that primarily utilized relatively low doses (<35 Gy; Table 82-5).[128–132] The interpretation of these trials within the context of contemporary management requires some consideration. Eligibility criteria in these studies generally allowed all patients to be entered, including those patients without imaging (e.g., CT scan or ultrasound) to rule out distant liver disease or those without transrectal ultrasound or MRI with endorectal coil to confirm extent of local transmural disease. In addition, there is great variance in the fraction size that was used. Nevertheless, although there appears to be some benefit in local control, there was no improvement in survival.

In Europe, the European Organization for Research and Treatment of Cancer (EORTC) completed a study of moderate-dose preoperative radiation, 34.5 Gy in 19 days at 230 cGy per fraction followed by immediate surgical resection compared to surgery alone.[84] The results of this study showed a significant improvement in locoregional control of disease with preoperative radiation (15% versus 35%; $P = 0.003$).

In a follow-up trial to their preoperative versus postoperative radiation trial, the Swedish group reported the results of a study evaluating 25 Gy in 5 days preoperatively (no adjuvant chemotherapy) versus surgery alone for resectable rectal cancer.[133] This trial is remarkable for being the first to demonstrate a survival benefit. After 5 years of follow-up and randomly assigning 1168 patients, the overall 5-year survival rate was 58% in the preoperative radiation plus surgery group versus 48% in the surgery-alone group ($P = 0.004$). This was associated with a local recurrence rate of 11% in the preoperative radiation group versus 27% in the surgery-alone group ($P < 0.001$). In addition, this benefit was seen for all stages of disease compared with surgery alone, suggesting that the initial clinical stage of rectal cancer may not be as important as previously considered.

The MRC rectal cancer working party staged a randomized trial of 40 Gy in 4 weeks preoperatively (no chemotherapy) versus surgery alone in only 279 patients with "potentially operable" locally advanced

Table 82-5 Rectal Cancer: Results of Low-Dose Preoperative Radiation Therapy

Randomized Studies	Dose (Gy)	RT (%)*	Surgery (%)*
Rider[128]	0.5	39	35
MRC[129]	0.5	42	38
	2.0	40	38
MSKCC[130]	2.0	52	59
VASOG I[131]	2.5	40	32
VASOG II[132]	3.15	35	35

MRC, Medical Research Council; MSKCC, Memorial Sloan-Kettering Cancer Center; RT, radiation therapy; VASOG, Veterans Administration Surgical Oncology Group.
*Five-year survival rates.

Table 82-6 Rectal Cancer: Results of High-Dose Preoperative Radiation Therapy

Study	No. of Patients	Dose (Gy)	Local Recurrence Rates		5-Year Survival Rates	
			RT (%)	Surgery (%)	RT (%)	Surgery (%)
Mendenhall et al[135]	71	3–4.5	8	—	71	41
Fortier et al[136]	60	4.5	16	40	52	48
Stevens et al[137]	57	5.6	0	—	53	38
Kondner et al[138]	112	4.5	2	—	86	—
Mohiuddin et al[143]	220	4.5–7	15	—	72	—

RT, radiation therapy.

rectal cancer.[134] The results indicated a reduction in local recurrence ($P = 0.04$) and benefit in disease-free survival ($P = 0.02$) with use of preoperative radiation without a significant increase in overall survival ($P = 0.10$).

In the United States, several single-institution studies have examined the use of high-dose preoperative radiation (>40 Gy) and have reported lower recurrence rates with improved resectability and 5-year overall survival rates; some of these experiences are summarized in Table 82-6.[135–139] These results appear to be better than published results following surgery and postoperative adjuvant therapy. This benefit of preoperative radiation has been further substantiated by the results of a meta-analysis published by Camma and associates[133] (Fig. 82-5). This analysis involves 14 randomized controlled clinical trials of preoperative radiation (alone) followed by surgery versus surgery alone for "resectable" rectal cancers. It included a total of 6426 patients, 3081 of whom were treated with surgery alone. The meta-analysis found that the addition of preoperative radiation compared to surgery alone significantly reduced the 5-year overall mortality rate (odds ratio [OR]: 0.84; 95% confidence interval [CI]: 0.72 to 0.98; $P = 0.03$) and cancer-related mortality rate (OR: 0.71; 95% CI: 0.61 to 0.82; $P < 0.001$). This reduction was associated with a significant reduction in local recurrence rate (OR: 0.49; 95% CI: 0.38 to 0.62; $P < 0.001$) without a significant reduction in the observed occurrence of distant metastases.

Preoperative Radiation plus Total Mesorectal Excision versus Total Mesorectal Excision Alone

Between 1996 and 1999, the Dutch Colorectal Cancer Group randomly assigned 1861 patients with "resectable" rectal cancer to preoperative radiation (5 Gy for 5 days) prior to TME versus TME alone.[140] The trial used rigid quality control measures, training, and standardization as a requirement for selected surgeons, as well as pathologists, who met such requirements for study participation. At a median follow-up period of approximately 2 years for surviving patients, the overall 2-year survival rates for the two treatment groups were essentially identical at approximately 82%. However, with this relatively early follow-up, preoperative radiation was associated with a significant reduction in the relative risk at 2 years of local recurrence compared to TME alone: 2.4% in the preoperative radiation group

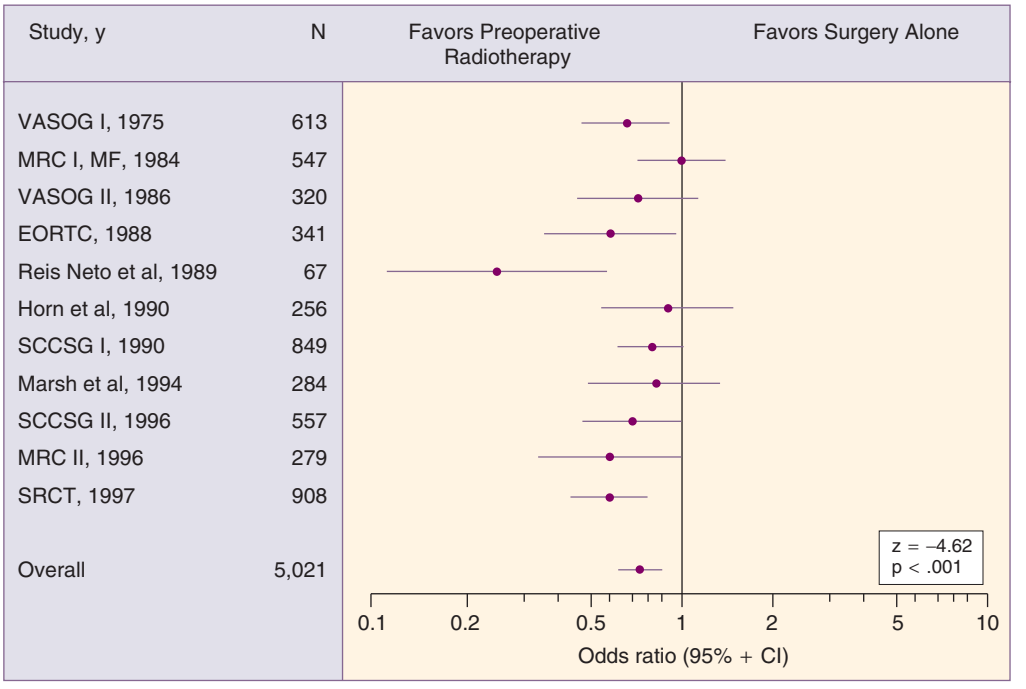


Figure 82-5 • Results of meta-analysis of 11 randomized trials of preoperative radiation versus surgery alone for "resectable" rectal cancer. The odds ratio and 95% confidence interval (CI) for treatment effect on 5-year cancer-related mortality rate are shown on a logarithmic scale. (From Camma C, Giunta M, Fiorica F, et al: Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. JAMA 2000;284:1008–1015.)

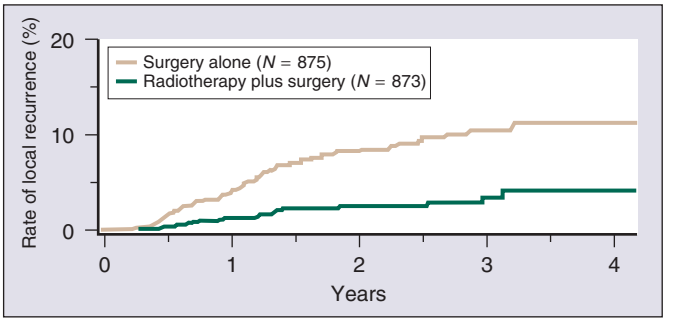


Figure 82-6 • Local recurrence rates from the Dutch Colorectal Cancer Group randomized trial of total mesorectal excision (TME; surgery alone) versus preoperative radiation plus TME. (From Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al: Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638–646.)

versus 8.2% in the TME-alone group ($P < 0.001$); actuarial curves are shown in Figure 82-6. Actuarial analyses from the Dutch and Swedish groups utilizing TME without adjuvant therapy suggest that local failure rates in node-positive patients will likely remain in the 15% to 20% range at 5 years.

Whether the preoperative combined modality therapy as is currently used in this country with 5-FU-based chemotherapy is more effective than preoperative radiotherapy alone is unknown. This question is being addressed within an ongoing randomized EORTC trial. In the meantime, consideration of the use of pathologic response as a "surrogate" measure that would be predictive of long-term outcome in rectal cancer patients has been suggested by a number of series.[134,141–143] Such a surrogate marker for survival or outcome could expedite evaluation of rapidly evolving novel preoperative combined modality/chemoradiotherapy combinations. This strategy is being utilized nationally by the RTOG in a randomized phase II trial evaluating preoperative 5-FU and hyperfractionated radiation versus preoperative 5-FU and CPT-II with once-daily radiation in T3 and T4 rectal cancer patients and will be reviewed later. However, routine use of pathologic response following preoperative adjuvant therapy as a surrogate marker for outcome awaits further confirmation and long-term evaluation.[144]

Technical considerations in the preoperative setting are similar to those for postoperative radiation therapy. There is one major exception, however: the ability to dose escalate above 50 Gy (with its potential benefits),[145,146] particularly in the locally advanced setting, by way of once- or twice-daily hyperfractionated radiation.[146–148] Dose escalation is more feasible within the preoperative setting without an associated exponential increase in complication rates, as would be likely with similar attempts within the postoperative setting.[146–148]

Preoperative Radiation versus Postoperative Radiation

The evaluation of the advantages or disadvantage of preoperative versus postoperative radiation therapy alone in the setting of a randomized trial has been limited, including a failed attempt of such a study in the United States that was closed early owing to poor patient accrual (Intergroup Study R1023). In a Swedish multicenter trial[95] comparing preoperative versus postoperative radiation in rectal and rectosigmoid carcinoma, 471 patients were randomized to 25 Gy in 5 to 7 days preoperatively versus 60 Gy in 8 weeks after surgery. The local recurrence rate was statistically lower after preoperative radiation (12%) than after postoperative radiation (21%; $P = 0.02$). This improvement was observed despite the relatively modest dose of preoperative radiation (25 Gy) compared to the postoperative radiation dose (60 Gy). There was no difference in survival between the two groups (43% versus 40%), with a minimum follow-up period of 3 years and a mean follow-up period of 6 years.

Table 82-7 Rectal Cancer: Clinical Staging

Stage	Description	Location*
I	Mobile	A: >6 cm
	Free movement in all directions	
II	Partially fixed (tethered)	B: 3–6 cm
	Movable in at least one direction (cephalocaudad or lateral)	
III	Fixed	C: 0–3 cm
	Immovable in any direction due to fixation (not size) or perforated, obstructed, deeply ulcerated	
IV	Frozen pelvis	D: <0 cm (i.e., into anal canal)
	Invasion of pelvic sidewalls and/or sacrum—unresectable	

*Location as measured from the anorectal junction.

Preoperative or Postoperative Adjuvant Therapy Based on Clinical Staging

Parameters include tumor fixation, distance from the anorectal junction, and the consideration/feasibility of sphincter preservation. Such parameters, along with modern imaging techniques (e.g., CT scan, transrectal ultrasound, or MRI with endorectal coil), can be integrated into the use of a clinical staging system such as that previously published by Mohiuddin and Marks (Table 82-7).[149] Clinical staging systems have been proposed by others.[150] Such a staging system can then be used to determine an optimal treatment strategy (utilizing preoperative or postoperative therapy) for patients with rectal cancer.

PREOPERATIVE CHEMORADIATION: INCORPORATION OF NOVEL AGENTS

There are now seven drugs that the FDA has approved for the treatment of advanced metastatic disease in colorectal cancer: 5-FU, capecitabine,[151,152] oxaliplatin,[153] CPTII,[154] cetuximab,[155] bevacizumab,[156,157] and panitumumab.[158] The complete plus partial response rates varied from 35% to 50% in chemotherapy-naive patients when used in combination. Consequent to the use of these novel agents, the median survival of stage IV patients is approaching 2 years, and an increased median survival of 3 years is not out of reach.[159] A number of these agents are now being investigated in clinical trials in the treatment of nonmetastatic patients toward improved outcomes (Tables 82-8 through 82-10).

5-FU Plus Oxaliplatin Plus Radiation

The Lyon R04 trial is a prime example of the addition of one of these new chemotherapeutic agents.[160] The study had 40 patients T3/T4 N × M0 who received oxaliplatin at 130 mg/m^2 on day 1 followed by a 5-day continuous infusion of 5-FU 330 to 350 mg/m^2 and leucovorin 100 mg/m^2 given in two cycles with external beam radiation of 45 Gy in daily fractions of 1.8 Gy. Total mesorectal surgery was planned 5 weeks postradiation. The addition of oxaliplatin produced a complete plus partial response in 30 patients (75%).

Table 82-8 NSABP R-04 Trial

Stratify, according to
- Gender
- Clinical staging
  - T3N0 or T4N0
  - TanyN1 or TanyN2
- Type of surgery
  - Sphincter-saving
  - Non–sphincter-saving

Randomize into two treatment arms

Arm 1
- RT + chemotherapy*
- 4500 cGY (25 fractions)†
- 5-FU 225 mg/m^2/day CVI
- 7 days/week beginning the day of the start of RT and ending the evening of the last dose of RT

Arm 2
- RT + chemotherapy*
- 4500 cGY (25 fractions)†
- Capecitabine 825 mg/m^2 PO bid throughout course of RT
- 7 days/week beginning the day of the start of RT and ending with the last dose of RT

*Epoetin-alfa 40,000 IU/SQ q wk (begin 7–10 days prior to starting RT/chemotherapy).
†+540 cGy boost for nonfixed tumors (3 fractions); 1080 cGy boost for fixed tumors 6 fractions.

Pathologic examination noted 6 (15%) patients with no residual tumor pT0N0. Sphincter-sparing surgery was performed in 26 patients. The minimal added toxicity of the oxaliplatin did not adversely affect any of the patients.

Complete sterilization of an operative specimen has been reported in other series to be between 5% and 32%[161–163] depending on tumor size, low stage, preoperative chemotherapy, and high-dose radiation therapy. Minsky[164] described 12 studies using oxaliplatin in varying doses with either 5 FU or capcitabiene. The CR rates in these phase I studies ranged from 14% to 58% and the maximum tolerated dose for oxaliplatin when given concurrently with 5-FU and radiation therapy has been established at 80 mg/m^2.

Chau, using an MRI criteria for poor-risk patients, studied the addition of oxaliplatin 130 mg/m^2 every 3 weeks to capecitabine 2 g/m^2 in divided doses times for 14 days with 7 days rest with radiation therapy and surgery.[165] The regimen was repeated four times. The radiation was delivered to a total of 45 Gy in 25 fractions of 1.8 Gy with a boost of 5.4 Gy to include the entire pelvis and pelvic lymph nodes. Capecitabine was given continuously without interruption with the radiation. All patients had a total mesorectal excision. Following surgery, capecitabine was given at 2.5 g/m^2 for 14 days with 7 days rest for 12 weeks. Seventy-seven patients were eligible for study; 67 underwent a total mesorectal excision. An R0 resection was noted in all but one patient. After undergoing neoadjuvant therapy, 88% of the patients were radiologic responders as defined as stable or better. After the chemoradiation therapy arm, 97% of the patients were noted to have stable disease or better following surgery. The CR rate of 24% was augmented by an additional 48% of the patients with only microscopic disease. MRI evaluation demonstrated a 76% downstaging of the primary tumor. Of the 26 patients in the pathologic T3 group, 16 were noted to have only microscopic disease. Thirteen patients were also noted to have downstaging. At the end of 1 year, the OS was 95%, and the 1-year disease-free survival rate was 87%. No comment could be made on the use of capecitabine in the postoperative adjuvant setting. It is one of the most important studies because of its neoadjuvant/adjuvant nature. It should set the bar for numerous protocols to come, as modern trials typically incorporate neoadjuvant chemoradiation therapy followed by surgery and further adjuvant chemotherapy.

Table 82-9 Intergroup Rectal Adjuvant Trial E 3201

Stratify
- Group I: Preoperative chemotherapy plus radiation therapy
- Group II: Postoperative chemotherapy plus radiation therapy

Randomize

5-FU/RT → Surgery → CPT-II/LV/5-FU*
OXAL/LV/5-FU*
LV/5-FU

Surgery →

Arm A
CPT-II/LV/5-FU→5-FU/RT→CPT-II/LV/5-FU

Arm B
OXAL/LV/5-FU→5-FU/RT→OXAL/LV/5-FU

Arm C
LV/5-FU→5-FU/RT→LV/5-FU

5-FU, 5-fluorouracil; LV, lencovarin; OXAL, oxaliplatin.
*Infusion.

Table 82-10 RTOG R-0012 Trial

Stratify, based on clinical staging
- Group 1: T3
- Group 2: T4

Randomize into two treatment arms

Arm 1: CVI 5-FU (*225 mg/m^2/day, 7 days, 7 days/week, until completion of RT*)
+ Pelvic RT 45.6 Gy (*1.2 Gy bid, 6-h interval*)
+ Boost to tumor (*9.6 Gy for T3 and 14.4 Gy for fixed T4*)*
+ Surgery+ 4–10 weeks after completion of RT

Arm 2: CVI 5-FU (*225 mg/m^2 day, M-F, 120 hr/week, until completion of RT*) plus CTP-II (*50 mg/m^2, once weekly × 4 weeks*)
+ Pelvic RT 45 Gy (*1.8 Gy/day*)
+ Boost to tumor (*5.4 Gy for T3 and 9 Gy for fixed T4*)*
+ Surgery† 4–10 weeks after completion of RT

Maintenance chemotherapy is recommended for all patients after irradiation.
*Boost radiation may be delivered using conformal 3D techniques.
†IORT (optional) may be delivered to areas of tumor fixation at time of surgery.

5-FU Plus Irinotecan Plus Radiation

A phase I trial performed at Thomas Jefferson University Hospital defined the maximum tolerated dose of weekly CPT-II when combine with 5-FU and concomitant RT in rectal cancer.[166] Escalating doses of CPT-II (30 to 60 mg/m^2 over 90 minutes) on days 1, 8, 15, and 22 were combined with 5-FU during perioperative radiation treatments (45 Gy in 1.8-Gy daily fractions plus 5.4-Gy boost). All

patients went to a planned surgery and received adjuvant chemotherapy (5-FU and leucovorin). The maximum tolerated dose of CPT-II was established at 50 mg/m^2, and the dose-limiting toxicity was gastrointestinal. This study demonstrated a 24% pathologic CR rate.

Investigators at Stanford University performed a phase II trial incorporating CPT-II (50 mg/m^2 on days 1, 8, 15, and 22) with 5-FU (200 mg/m^2/day) and preoperative radiation (50.4 Gy) in patients with T3 rectal cancers.[167] This study demonstrated a 37.5% pathologic CR rate in the 37 patients who were enrolled. The major toxicity was gastrointestinal (28% grade 3 diarrhea).

A randomized cooperative group (RTOG 0012) phase II preoperative chemoradiation trial incorporating irinotecan for distal rectal tumors was reported by Mohiuddin and colleagues.[168] In this study, 106 patients were randomized to receive continuous infusion 5-FU (225 mg/m^2/day, 7 days per week until completion of RT) or the same 5-FU regimen plus CPT-II (50 mg/m^2 weekly for 4 weeks) during radiation. All patients went on to a planned surgery and adjuvant chemotherapy. The CR rate was similar in both arms (29% versus 31%). Tumor downstaging was equal in both arms, with an overall downstaging of 80%.

Capecitabine/Irinotecan/Radiation versus Capecitabine/Oxaliplatin/Radiation

Both irinotecan and oxaliplatin have shown promise in the preoperative setting when combined with standard 5-FU or capecitabine-based chemoradiation. Whether one is better than the other with respect to improving response rates and downstaging is the subject of an ongoing randomized phase II clinical trial being conducted by the RTOG (RTOG #0247), which accrued to completion in 2007. This study will provide a platform for future phase III preoperative chemoradiation studies.

PREOPERATIVE VERSUS POSTOPERATIVE CHEMORADIATION: RESULTS OF RANDOMIZED TRIALS

In patients with resectable locally advanced disease, adjuvant chemoradiotherapy has been demonstrated to significantly improve local control and overall survival when compared with surgery alone or surgery plus radiation.[169,170] After the results of the Krook trial were reported,[170] the 1990 NIH Consensus Conference established that standard postoperative treatment for locally advanced patients (T3/T4 or N+) in the United States was adjuvant chemoradiation.[171] Since that time, international debate has ensued as to whether neoadjuvant chemoradiation would offer advantages over adjuvant chemoradiation. Three prospective randomized trials have been conducted to assess the potential benefits of neoadjuvant chemoradiation over adjuvant chemoradiation in patients with resectable, locally advanced rectal cancers. The two U.S. trials (RTOG 94-01 and NSABP R-03) suffered from poor accrual and ultimately were closed prematurely and provided only preliminary information.[109] The third study, conducted by the German Rectal Cancer Study Group, was completed to full accrual, and the results were published in 2004.[98]

The landmark German study randomized 823 locally advanced patients (T3, T4, or N+) to either preoperative or postoperative chemoradiation. Chemoradiation consisted of 50.4 Gy of radiation in 1.8 Gy daily fractions concurrent with infusional 5-FU (1000 mg/m^2 daily during weeks 1 and 5 of radiotherapy). Radiotherapy was targeted at the tumor (or tumor bed) and draining pelvic lymphatics. Surgery consisted of a TME, and all patients received adjuvant chemotherapy consisting of four cycles of 5-FU (500 mg/m^2) given on days 1 through 5 of a 28-day cycle. The 5-year disease-free survival rate (68% versus 65%) and overall survival rate (76% versus 74%) were not statistically different for patients receiving preoperative versus postoperative therapy. Local control was statistically superior, with preoperative treatment (94%) versus postoperative treatment (87%). Additionally, there were threefold more protocol violations in the postoperative arm, indicating that compliance was higher when treating in the preoperative setting.

Considering the 194 patients in this study with "low-lying" tumors (those that were thought to require an APR on evaluation prior to randomization), patients in the preoperative chemoradiation arm were twice as likely to have a sphincter-sparing surgery (39% versus 19%) and threefold less likely to have an anastamotic stenosis (4% versus 12%) when compared with patients in the postoperative chemoradiation arm. In addition, grade 3 or 4 toxicities were significantly higher in the postoperative chemoradiation group than in the preoperative chemoradiation group (40% versus 27% for acute, 24% versus 14% for chronic). The results of this trial have helped to establish preoperative chemoradiation as the current preferred approach, particularly for patients with low-lying tumors.

ADJUVANT CHEMOTHERAPY FOLLOWING COMPLETION OF CHEMORADIATION AND SURGERY

The German trial established that preoperative chemoradiation was superior to postoperative chemoradiation, particularly for patients with low-lying tumors.[98] However, the trial did not address the potential added benefits of further adjuvant chemotherapy. The EORTC attempted to answer the question of the optimal timing of chemotherapy in relation to radiation therapy in clinically advanced T3 and T4 resectable rectal cancers[172] and sought to determine the potential additive value of adjuvant chemotherapy following preoperative treatment and surgery. The EORTC 22921 trial was a four-arm randomized study in which 1011 patients underwent randomization to either (1) preoperative radiation followed by surgery, (2) preoperative chemoradiation followed by surgery, (3) preoperative radiation followed by surgery and adjuvant chemotherapy, or (4) preoperative chemoradiation followed by surgery followed by adjuvant chemoradiation. The radiotherapy consisted of 45 Gy delivered to the posterior pelvic wall in 25 fractions of 1.8 Gy over a period of 5 weeks. The chemotherapy was similar in preoperative and postoperative treatment groups. There were two 5-day courses of 5-FU 350 mg/m^2 given IV bolus with 20 mg of leucovorin given in the first and fifth weeks of radiation therapy. Four 3-week cycles of postoperative chemotherapy were given. With a median follow-up of 5.4 years, there was no significant difference in overall survival between the groups that received chemotherapy preoperatively and those that received it postoperatively. The 5-year incidence rates for local recurrence were 8.7%, 9.6%, and 7.6% in the groups that received chemotherapy preoperatively, postoperatively, or both, respectively. The local recurrence rate in the group that did not receive chemotherapy was significantly higher at 17.1% ($P = 0.002$). As with the German trial, there was a higher degree of compliance with preoperative chemotherapy (82%) versus postoperative chemotherapy (42.9%). Preoperative chemoradiotherapy resulted in downsizing and downstaging of tumors, which were associated with an increase in local control but not overall survival.[116]

If we look specifically at the additive benefit of adjuvant chemotherapy, the 5-year overall survival was 63% in the groups that did not receive adjuvant chemotherapy and 67% in the groups that did receive adjuvant therapy. This 4% difference is similar to the 6.8% disease-free survival benefit of FOLFOX 4 seen for patients with stage III colon cancer as demonstrated in the MOSAIC trial.[173] The MOSAIC trial was designed to evaluate the efficacy of FOLFOX 4 compared with LV5FU2 in patients with stage II and III colon cancer. At 4 years, FOLFOX 4 significantly improved the disease-free survival rate when compared with LV5FU2 (75.9% versus 69.1%) in stage III patients but was not significant in the stage II patients. Wolmark and colleagues presented data from phase III of the C-07 trial, which randomized patients to either a FLOX or weekly 5-FU/high-dose leucovorin adjuvant regimen.[174] With a median follow-up of 24 months, preliminary results have been reported, and demon-

strate a 3-year disease-free survival benefit to FLOX (76.5% versus 71.6%), which is very similar in magnitude to the benefit seen in the MOSAIC trial.

ECOG trial E5204[175] is a recently initiated randomized phase III adjuvant study comparing oxaliplatin/5-FU/leucovorin with oxaliplatin/5-FU/leucovorin and bevacizumab in stage II and III patients who have received preoperative chemoradiation. This study was modified to incorporate patients who were put on the NSABP R-04 trial. The treatment schema is as follows: All patients will have received a minimum radiation dose of 40 Gy and not more than 54 Gy external beam radiation therapy (XRT) at 1.8 Gy per fraction per day for 28 fractions over a total of 5 1/2 weeks. Pelvic fields will receive 45 Gy in 25 fractions, followed by a boost of 5.4 Gy in 3 fractions. Intraoperative radiation therapy and/or brachytherapy are strictly prohibited. NSABP R-04 patients are exempt from meeting the minimum/maximum radiation therapy guidelines. Patients will have received concurrent radiation and chemotherapy, consisting of one of the following regimens. The radiation/capecitabine ± oxaliplatin regimens are open only to the patients who are enrolled on NSABP R-04. Physicians will report the chosen chemotherapy regimen at the same time of randomization. The allowed regimens are as follows:

- XRT + continuous infusion 5-FU
  5-FU 225 mg/m^2 over 24 hours 7 days per week during XRT
- XRT + 5-FU/leucovorin
  5-FU 400 mg/m^2 + leucovorin 20 mg/m^2 for 4 days during weeks 1 and 5 of XRT
- XRT + capecitabine ± oxaliplatin (allowed only for patients treated on NASBP Protocol R04)
  Capecitabine 825 mg/m^2 PO twice daily concurrently throughout course of XRT (beginning 2 hours before start of XRT and ending with the last dose of XRT 5 days per week)
  Oxaliplatin 50 mg/m^2 IV weekly for 5 weeks
- XRT + continuous infusion 5-FU ± oxaliplatin (allowed only for patients treated on NASBP Protocol R04)
  5-FU 225 mg/m^2/day by continuous IV infusion 5 days per week on days of planned RT (concurrent with XRT)
  Oxaliplatin 50 mg/m^2 IV (concurrent with XRT) weekly for 5 weeks

Surgery schedule: Surgical resection should occur 28 to 56 days (4 to 8 weeks) after the patient completes concurrent chemo/radiation therapy.

ECOG E5204 is a true adjuvant study aimed at defining the value of the biologic bevacizumab when added to FOLFOX chemotherapy in patients who have completed neoadjuvant chemoradiation and surgery. The NSABP R-04 study is significant in that it tries to answer the question "Is capecitabine as good as continuous infusion 5-FU and does oxaliplatin increase response rates when added to 5-FU or capecitabine?" The combined results of NSABP R-04 and ECOG E5204 will help to define optimal preoperative chemoradiation (5-FU versus capecitabine ± oxaliplatin) and adjuvant chemotherapy (FOLFOX ± bevacizumab).

ADJUVANT THERAPY FOLLOWING LOCAL EXCISION

Standard therapy for resectable rectal cancer has been radical or conventional surgical resection (inclusive of the possibility of TME) with increasing integration of preoperative or postoperative adjuvant therapy. In highly select patients, this approach has often been challenged by the use of more conservative local measures (see Table 82-1).

Table 82-11 summarizes the results of local excision with and without postoperative therapy.[176–181] It is important to note that most series are retrospective, single-institution studies, with varying degrees of integration of chemotherapy (typically 5-FU-based) and relatively limited follow-up.[177–181] Although these factors limit the degree with which results from these selective series can be reproduced within general practice and in the community, they at least suggest survival data that are comparable to those seen with radical or more conventional surgery alone for T1/T2, N0 rectal cancer.

Such results can now perhaps be considered to be reproducible in the general community setting with a greater degree of confidence given the results of the CALGB trial 8984. This trial was an intergroup trial and is the only multi-institutional prospective phase II trial evaluating the outcome of local excision in patients with T1/T2 rectal cancers.[177] Study entry criteria included T1/T2 adenocarcinomas that were more than 4 cm in diameter, encompassing less than 40% of the bowel wall circumference, being less than 10 cm from the dentate line, and having negative excisional margins. A total of 110 eligible patients were entered into the study. Of these patients, 59 had T1 adenocarcinoma and received no further therapy; 51 had T2 carcinomas and received external beam irradiation (54 Gy in 30 fractions at 5 days per week) and 5-FU (500 mg/m^2 IV days 1 to 3 and days 29 to 31) after full-thickness local excision. It is interesting that 51 additional patients were also entered into the study but were later (postsurgery) found to be ineligible, most commonly owing to (1) unclear/involved or uninterpretable surgical margins (49%; $N = 25$), (2) tumor stage above T2 (25%; $N = 13$), and (3) tumor diameter greater than 4 cm (24%; $N = 13$). Those who had excisions that were not thought to be "full thickness" were also considered ineligible (10%; $N = 5$). With a median follow-up period of 48 months, the local failure rate was 3%, the 6-year failure-free survival rate was 85%, and the overall survival rate was 87% among the T1 patients; among the T2 patients, the local failure rate was 14%, the 6-year failure-free survival rate was 71%, and the overall survival rate was 85%. Overall, five of the nine local-only recurrences were able to be surgically salvaged (by APR) without evidence of distant disease. However, local failure seen beyond 5 years of treatment has been reported and is not uncommon.[176] Careful follow-up and review of long-term results of this treatment strategy are clearly required.

Table 82-11 Local Excision for T1–T3 Rectal Cancer Plus Postoperative Adjuvant Therapy

Series	No. of Patients	5-FU (%)	T3 (%)	Follow-up Time	Survival Rates	Initial Local Control (Salvaged with APR/ Local Failures)
U. Florida[163]	45	4	2	2 yr (minimum)	88% 5-yr disease specific	89% (1/5)
Memorial Sloan-Kettering[164]	39	51	21	41 mo (median)	70% 5-yr actuarial	79% (5/8)
M.D. Anderson[27]	46	17	33	36 mo (median)	93% 3-yr overall	87% (–/4)
N.E. Deaconess[166]	48	54	10	41 mo (mean)	94% overall	92% (3/4)
CALGB[166]	51*	100	0	48 mo (median)	85% 6-yr actuarial	86% (4/7)
MGH[160]	47	55	0	51 mo (median)	74% 5-yr disease free	90% (5/9)

*Analysis is limited to the 51 of 110 patients with T2 disease who underwent a full-thickness local excision and received postoperative chemoradiotherapy.

SPECIFIC RECTAL CANCER MANAGEMENT ISSUES

Management of Medically Inoperable Patients: Results of Radiation and Chemoradiation

Outcomes of inoperable patients following treatment with radiation alone or radiation in combination with radiosensitizing chemotherapy are limited to phase I and II trials and retrospective institutional experiences. No phase III trials or randomized studies have been conducted in this population. Princess Margaret Hospital is credited with the largest retrospective series of medically inoperable patients treated with primary radical external beam radiation therapy. They have continued to add to this experience over recent decades.[182–184] In the most recent update, they report the long-term outcome of 271 patients who underwent primary radical external beam radiotherapy without prior or concurrent chemotherapy.[184] All patients received radiation doses of at least 40 Gy. On multivariate analysis, only tumor fixation was a significant predictor of CR. They reported outcome based on fixation. For patients with mobile, partially fixed, and completely fixed tumors, the overall 5-year survival rates were 48%, 26%, and 6% respectively. CR rates also varied with degree of fixation and were 49%, 22%, and 9% respectively. Acute and late grade 3 or higher toxicity was less than 2%, leading the authors to conclude that radical external beam radiotherapy represents a tolerable and potentially curative treatment option for rectal carcinoma patients without complete tumor fixation who are not surgical candidates or refuse surgery.

Local relapse following a CR to radical radiotherapy alone is high. In the previously cited Prince Margaret Hospital series, 78% of patients relapsed after initial CR, including 100% of patients with fixed tumors. Therefore, to improve local control (particularly for fixed tumors), dose escalation of radiation therapy and/or the addition of radiosensitizing chemotherapy is warranted. Overgaard and colleagues demonstrated a dose-response relationship between duration of CR and radiation dose in patients with inoperable rectal cancers.[185] Concurrent chemoradiotherapy should be strongly considered in patients whose performance status makes them able to tolerate a more aggressive regimen, particularly those with partially or completely fixed tumors.

Experiences of definitive chemoradiation in rectal cancer are limited. It has been demonstrated in randomized adjuvant studies that chemotherapy combined with radiation is superior to radiation alone. No such studies exist for medically inoperable patients. However, as was mentioned earlier in this chapter with respect to optimal timing of surgery after chemoradiation, there is a Brazilian experience that continues to be updated in which potentially operable patients who achieve a clinical CR to preoperative chemoradiation are not taken to surgery and rather are observed.[101,102] These data can be extrapolated to some degree to the medically inoperable patients with respect to expected outcomes with chemoradiation. In the 2006 update of this series, 122 patients had been included as having achieved a clinical CR at first assessment following completion of chemoradiation.[102] Reevaluation at 12 months revealed that 99 of the 122 patients (81%) who had achieved a clinical CR to chemoradiotherapy (consisting of 5-FU, LV, and RT to a total dose of 50.4 Gy) had sustained a complete clinical response. With a median follow-up of 5 years, overall and disease-free survival rates for these patients were an impressive 93% and 85%, respectively. The management of the medically inoperable patient or the patient who refuses surgery is always tailored to the patient's performance status and degree to which they can tolerate therapy. Aggressive management with dose-escalated chemoradiation is the preferred approach when feasible.

Management of Locally Advanced Rectal Cancer

Locally advanced rectal cancer is characterized by invasion through the muscle wall adherent to or invading surrounding structures yet confined to the pelvis. The accurate incidence of locally advanced rectal cancer is unknown and estimated at 5%.[186,187] Surgical resection within the context of a multimodality approach is essential for successful treatment outcome and control of symptoms. Surgery often involves TME with en bloc resection of contiguously involved structures to obtain negative margins of resection, which is essential to minimize risk of recurrence. At the time of surgery, thorough exploration to rule out metastatic disease is essential. The operative goal is complete resection with negative margins. Gross residual disease or microscopic margins have a negative impact on prognosis.[188] Adherent structures must be resected. Clinical distinction between benign adherence and malignant invasion is impossible, particularly if the patient received preoperative radiation. Approximately half of clinical attachments are inflammatory, not from tumor invasion. The most commonly resected organs are ovaries, uterus, vagina, and bladder, in that order.[189] Bladder preservation can be achieved with partial cystectomy with 2-cm margin. If the trigone is involved, total cystectomy with urinary diversion with ileal conduit or continent reservoir is required. The presence of positive bladder margins will adversely affect survival.[190]

Multimodality Approaches

Locally advanced patients are best managed with trimodality therapy, which typically includes neoadjuvant chemoradiation followed by surgical intervention and further adjuvant chemotherapy as suggested by the results of the recently reported trials by the EORTC and German Rectal Cancer Study Group.[98,191] Consideration can be given to more aggressive treatment during concomitant chemoradiation through either increased external beam boost dose or the use of intraoperative radiation therapy (IORT) as a boost strategy.

M.D. Anderson Hospital[192] has reported on its study of locally advanced tumors. Forty-five patients were evaluated. 5-FU was given at 300 mg/m^2 daily as a continuous infusion 5 days per week with radiation therapy. Radiation therapy was given as a concomitant boost using a three-field belly board technique. The boosts were given during the last week of therapy with a 6-hour intrafraction dose to the tumor plus 2- to 3-cm margin. The boost dose equaled 7.5 Gy per five fractions for a total dose of 52.5 Gy for 5 weeks to the primary tumor. Sphincter preservation was noted in 79% of the patients, and 31% of the patients achieved a pathologic CR rate. Tumor downstaging was pathologically confirmed in 86% of the patients.

The University of Kentucky reported in 1999 that preoperative chemoradiotherapy was effective in the control of fixed distal rectal cancers.[148] Two chemotherapy regimens were studied (5-FU at 1000 mg/m^2 on the first and fifth weeks of radiation days 1 to 4 and 28 to 32, and the continuous infusion 5-FU was 225 mg/m^2 for the duration of radiation). Two radiation arms were studied: 45 to 50 Gy and 55 Gy. Pathologic CRs were noted more often in a continuous infusion and in radiation therapy when given in doses above 55 Gy. The analysis showed that 10% of the patients who were given bolus 5-FU achieved a CR, while 67% achieved a CR with continuous infusion. With higher-dose radiation therapy, 67% achieved a CR with continuous infusion chemotherapy and none with the bolus 5-FU. Similar results were reported by Minsky and colleagues[193] in 1991 and by Rich and colleagues[194] in 1995. Rich and colleagues at that time had the largest number of patients studied: 77 to be treated with continuous infusion 5-FU, with a CR rate being reported at 29% and a local recurrence for T3 lesions at 9%.

SEER data review of surgically treated patients with locally advanced rectal cancer from January 1, 1988, through December 31, 2002, showed that younger age at diagnosis (<65 years) and female sex were positively and statistically significantly associated with multivisceral resection, whereas receipt of neoadjuvant radiation was inversely and statistically significantly associated with multivisceral resection. Compared with standard resection, multivisceral resection was associated with improved overall survival for patients with rectal

cancer (HR: 0.81, 95% CI: 0.70 to 0.94) with no associated increase in early mortality.[195]

A European trial randomly assigned 762 patients with locally advanced (T3/T4) rectal cancer within reach of DRE to radiotherapy alone (45 Gy over 5 weeks) or with concomitant bolus 5-FU (350 mg/m^2 per day) and leucovorin (20 mg/m^2 per day), each daily for 5 days during weeks 1 and 5. At a median 69-month follow-up, the combined modality group had a higher pathologic CR rate (11.7% versus 3.7%) and a significantly lower local failure rate (8% versus 16.5%), but the rate of sphincter-preserving surgery (52% versus 53%) and 5-year overall survival rates (67% versus 68%) were similar.[196]

In the randomized, controlled German rectal cancer study, 823 patients with clinically staged T3/T4 or node-positive rectal cancer were randomized to the same chemoradiotherapy regimen (50.4 Gy in 28 daily fractions to the tumor and pelvic lymph nodes concurrent with infusional 5-FU (1000 mg/m^2 daily for 5 days during the first and fifth weeks of RT) administered either preoperatively or postoperatively, with all patients having TME, and four additional cycles of adjuvant single agent 5-FU (500 mg/m^2 daily for 5 days every 4 weeks). The 5-year overall survival and disease-free survival rates were not significantly different between the neoadjuvant and adjuvant groups (76% versus 74%% and 68% versus 67%, respectively), However, the local recurrence rate was significantly less in the neoadjuvant treatment group (6% versus 13%, $P = 0.006$). Prognosis was related to final tumor stage in the surgical specimen (5-year disease-free rates of 86%, 95%, 81%, 65%, and 42% for T0, T1, T2, T3, and T4 tumors, respectively) and the presence of involved lymph nodes in the surgical specimen (5-year disease-free rates of 85%, 65%, and 18% for those with N0, N1, and N2 disease, respectively). The rate for sphincter preservation surgery was 39% in the neoadjuvant group and 19% in the adjuvant group.

A recent study compared 2-week versus 4- to 6-week intervals between radiation therapy and surgery. Significantly higher numbers of complete remissions (12% versus 0%) and tumor downstaging (55% versus 26%) and fewer lymph node metastases (22% versus 44%) were found in the group with the longer interval. No significant differences were found regarding operative data, short-term morbidity, local control, or long-term survival after a median follow-up of 34 months.[197]

Preoperative chemoradiation (5-FU infusional) with a hyperfractionated radiation boost to 61.8 Gy was evaluated in locally advanced rectal cancer with surgery performed 4 to 6 weeks later. All patients had either T4 or T3 and greater than 4 cm or 40% of the bowel circumference. RT consisted of 45 Gy to the pelvis (1.8 Gy per fraction) followed by 1.2 Gy twice daily (to the gross tumor volume) to a total RT dose of 61.8 Gy. Of the 20 patients who were evaluable for response, 10 (50%) had evidence of clinical downstaging, and 5 (25%) had more than 90% fibrosis in the resected specimen. With a median follow-up of 40 months, the 4-year actuarial rate for all patients ($N = 22$) of overall survival was 64%, that of disease-free survival was 62%, and that of local control was 84%. Three of 21 patients (14%) had positive margins; all of these patients developed a local failure ($P < 0.001$).[198]

Data from the MGH, the Mayo Clinic, and the Memorial Sloan-Kettering Cancer Center have suggested the beneficial effect of IORT (primarily, reducing the local recurrence rate to 10%) when combined with high-dose external beam radiation therapy and surgical resection in locally advanced primary rectal cancer. IORT is given in a single dose ranging from 10 to 20 Gy in patients who received preoperative external beam radiation therapy and 20 to 40 Gy when given alone. The 5-year actuarial local control and disease-specific survival rates in patients receiving IORT correlate with extent of residual cancer (Table 82-12).[199] In a retrospective analysis by Sadahiro and associates,[200] survival, disease-free survival, and local recurrence-free survival rates in the intraoperative radiotherapy group were significantly more favorable than those in the non-IORT group ($P = 0.01$, $P = 0.04$, and $P = 0.02$, respectively). Differences in survival were observed in stage II patients but not in stage I or stage III patients. There was no difference in the distant metastasis rate between the two groups. The results are less satisfactory for patients with recurrent rectal cancer, regardless of the extent of resection.[201]

Table 82-12 5-Year Actuarial Local Control and Disease-Specific Survival Rates*

Treatment	Local Control Rate (%)	Disease-Specific Survival Rate (%)
Complete resection	89	63
Microscopic residual disease	68	40
Macroscopic residual disease	57	14

*For patients with locally advanced primary rectal cancer, receiving adjuvant and intraoperative radiation therapy.

Pelvic exenteration and sacral resection for locally advanced primary rectal cancer have survival benefit if curative resection is possible. However, they are associated with high rates of morbidity. In a recent report by Yamada and coworkers,[202] the morbidity, reoperation, and mortality rates were 50%, 4.5%, and 0%, respectively. The overall 5-year survival rate for this group of patients was 74.1% for Dukes' B and 47.4% for Dukes' C (difference not statistically significant).

MANAGEMENT OF ISOLATED LOCAL AND PELVIC FAILURE

Typically, 55% to 80% of local recurrences present during the first 2 years after surgery. Several large reviews of outcome have identified an overall recurrence rate higher than 40% in rectal cancer, with pelvic recurrence the most common first site of relapse.[203] Among patients who relapse locally, half have isolated pelvic failure.[204,205] Two studies of patterns of recurrence in rectal cancer have demonstrated that local failure, without clinical evidence of distant metastases, accounts for about half of cancer-related deaths at 5 years. In a large series, reported by McDermott and associates,[206] 27% of rectal cancer deaths were attributable to isolated local relapse, and another 24% had combined local and systemic failure. In an autopsy series reported by Welch and Donaldson,[207] 25% of patients had only local disease at the time of death, 50% had both local and systemic disease, and only 25% died of systemic metastases alone. On average, two thirds of patients with pelvic relapse after simple local excision of their tumor are able to undergo curative reexcision, whereas for more radical primary surgery, complete reexcision is usually possible in only 30% of patients.[208]

Low anterior resection also appears to result in a small number of central, anastomotic recurrences that are easy to detect and treat. Unfortunately, these relatively favorable lesions account for only 25% of locoregional relapses after anterior resection.[208] Most appear to arise in the residual mesorectum and encroach on the lumen only secondarily, at a more advanced stage of their growth. APR, the most extensive of the standard operations for rectal cancer, is apt to relapse, with diffuse pelvic tumor or laterally situated masses invading the pelvic sidewall. Therefore, recurrence after APR has, in general, a poorer prognosis.[208,209]

PET scan can differentiate between recurrent tumors in the pelvis and scar. Bone scan to rule out osseous metastasis is indicated in the presence of musculoskeletal pain or if deep bony invasion in the pelvis is suspected. A positive bone scan, indicating that the tumor has penetrated the cortex of bone to invade the marrow, eliminates the possibility of curative resection. Pelvic MRI can be quite helpful to evaluate local encroachment of the tumor on adjacent vascular structures as well as pelvic bony destruction. Other clinical and radiologic criteria of unresectability include unilateral or bilateral hydronephrosis,[210] sciatic nerve pain,[211] frozen pelvis, and unilateral leg edema.[212]

Surgical Salvage of Pelvic Failures

Treatment of clinically apparent local recurrence is palliative rather than curative for most patients. Although systemic chemotherapy and radiation offer effective palliation, surgery, when possible, remains the treatment of choice. Radical surgical treatment of recurrent rectal cancer offers excellent pain relief, improved quality of life, and, in some cases, significant prolongation of life.[213]

In patients with posterior pelvic recurrence near or adherent to the sacrum, even more radical surgery is required. APR with in-continuity sacrectomy or pelvic exenteration with in-continuity sacrectomy (composite or sacropelvic exenteration) may help highly selected younger patients. The technical aspects of the procedure with the expected outcomes and potential complications should be thoroughly discussed with the patient. The impact of sacropelvic resection on all facets of a patient's life is tremendous. Sexual function is severely affected, the bladder is usually replaced by an ileal conduit, and a colostomy is required. Wanebo and colleagues have now reported on over 50 patients who underwent curative abdominosacral resection, with seemingly good palliation with excellent pain control and long-term survival in 31% of the patients.[214] These operative procedures have a formidable morbidity rate and a high mortality rate from hemorrhage or infection. Pearlman and associates[215] resected 21 patients with recurrent rectal cancer, 18 of whom had had prior radiation. Twelve patients had complete abdominosacral exenteration. Of the 16 patients who had potentially curative surgery, 8 were free of recurrence at 6 to 48 months after the procedure. If tumor is adherent only to the distal sacrum, then rather than full-thickness sacrectomy, the anterior cortex can be removed. This procedure is quite simple from S4 down. The use of argon beam coagulation provides additional tumor destruction along the periosteum without the need for sacrectomy. Finally, intraoperative radiation therapy may replace or add to the bone resections for posterior pelvic recurrence.

Multimodality Salvage of Patients Not Previously Irradiated

Patients with no history of prior radiation treatment can be considered for external beam radiation as a part of their salvage therapy, typically preoperatively in combination with chemotherapy. In addition, IORT has been utilized at select institutions in this setting. The Mayo Clinic has previously reported one of the largest IORT experiences in the literature: 123 patients (including 80 rectal cancer patients) who were treated with a combination of pelvic fractionated external beam radiation (45 Gy + 5.4 Gy) with or without 5-FU-based chemotherapy.[216] Maximal surgical resection was performed before or after radiation, and all patients received IORT with electrons to a dose of between 10 and 20 Gy. The 5-year local control and overall survival rates for the entire group were 63% and 20%, respectively. Patients who were able to undergo gross total resections had improved 5-year survival rates compared with those who were not (24% versus 18%). Single institutional analyses of the potential benefits of IORT in the setting of microscopically positive surgical salvage margins have demonstrated that IORT cannot compensate for incomplete resection. In a series of 41 patients with locally recurrent rectal cancer at MGH treated with external beam radiation, surgery, and IORT, the 5-year survival was 21% for those undergoing complete surgical resection versus 7 percent for those who were able to get only a partial resection.[217] Poorer outcomes in patients who were unable to get complete surgical resections (despite IORT) have held true across other institutional series of IORT use in this setting.[218,219] The relative paucity of institutions that are capable of delivering IORT and the lack of randomized data validating its potential benefits over conventional multimodality approaches continue to limit the utility of IORT in the recurrent setting.

Multimodality Salvage of Previously Irradiated Patients

Patients with local recurrences in previously radiated fields have traditionally not been considered for multimodality salvage approaches owing to concern over the late normal tissue complications that are anticipated; in most cases, these patients are relegated to palliative chemotherapy only. However, there is a growing experience demonstrating that reirradiation is a tolerable and potentially curative approach in these patients, including a recently reported phase II multicenter trial.[220–222] Mohiuddin and colleagues from the University of Kentucky reported a series of 103 patients treated with reirradiation to a median total dose of 85.8 Gy, with approximately one third of the patients going on to planned surgical salvage.[221] The 5-year survival rate was 22% for patients who were treated with reirradiation plus surgery versus 15% for those who received reirradiation alone. Grade 3 and 4 late toxicity occurred in approximately one fourth of the patients.

Valentini and colleagues reported the results of a phase II Italian multicenter trial of preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients who had previously been irradiated to the pelvis at a dose of ≤55 Gy.[222] Fifty-nine patients were treated with hyperfractionated radiation therapy (1.2 Gy twice daily) in a two-staged cone-down plan to a total of 40.8 Gy while receiving infusional 5-FU (225 mg/m^2). Thirty-nine patients were able to undergo surgery following chemotherapy and radiation. All patients received adjuvant chemotherapy with raltitrexed.

ISSUES FOR THE FUTURE

Optimal surgery combined with selected neoadjuvant therapy will continue to enhance the end results. Improved chemoradiotherapy regimens may lead to such high clinical response rates that the anal cancer paradigm could be adopted. At present, most patients with clinical CRs have microscopic residual tumor at resection. The biologic significance of these nests remains unclear. Because it is unlikely that patients will accept randomization between resection and observation, we should continue to capture data on a cohort of patients who decline radical surgery after neoadjuvant therapy. Correlative molecular markers and improved imaging (such as FDG-PET) may provide additional insight into which patients are likely to respond to neoadjuvant therapy or, if a complete clinical response is observed, which patients can be followed and could avoid radical surgery. Integration of targeted therapies, newer cytotoxic agents, and a more selective approach to the use of postoperative chemo-targeted therapy strategies will be defined.

Expanding the high-quality surgical initiatives into the community setting, combined with pathologic assessment of surgical quality indicators, remains a major challenge. It might be most appropriate to develop a rectal cancer treatment paradigm that encourages patients to seek treatment at specialty centers.

SUMMARY

The goals in the treatment of rectal cancer are cure, local control, and maintenance of quality of life. A small subset of patients with mucosal, submucosal, or early invasive cancer can be treated by local excision. Adjuvant chemoradiotherapy can improve the outcomes (particularly local control) in such patients. The majority of patients with invasive resectable rectal cancer require radical surgery. Optimal surgery for mid and low rectal cancer involves autonomic nerve-preserving sharp pelvic dissection, total mesorectal excision, and colorectal reconstruction. For many patients, restorative J-pouch colorectal or coloanal reconstruction will maximize the restorative reconstruction. Adjuvant chemoradiotherapy improves the local control and increases the overall cure, even with optimal surgery. For most patients who will be candidates for adjuvant chemoradiation therapy, the preoperative neoadjuvant strategy followed by surgery and then systemic chemotherapy will maximize local control and overall cure. Current clinical trials are exploring combinations of cytotoxic chemotherapy and targeted therapies concurrent with radiation and for an additional 4 to 6 months of treatment after operative resection.

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83 Cancer of the Anal Canal

Uzma Malik and Mohammed Mohiuddin

SUMMARY OF KEY POINTS

- Cancer of the anal canal is an uncommon malignancy accounting for approximately 1.5% to 2% of all cancers of the lower alimentary tract in the United States. However, the risk has increased over the past 3 decades as a result of its association with human papillomavirus (HPV) and human immunodeficiency virus (HIV).
- The annual incidence of anal canal cancer in the United States is 1.3 per 100,000 in white men and 1.8 per 100,000 in white women.
- Anal cancer is considered one of the more curable cancers.
- Anal cancer is predominantly a locoregional disease with possible direct extension to surrounding tissues and lymphatic dissemination to inguinal and pelvic nodes. Hematogenous distant metastasis is relatively rare.
- The most common presenting manifestation is rectal bleeding, occurring in about 50% of patients.
- The treatment of anal canal cancer has changed from radical surgery to organ-sparing chemotherapy and radiotherapy and constitutes one of the success stories in recent oncologic management.

INTRODUCTION

Cancer of the anal canal is an uncommon malignancy, accounting for approximately 1.5% to 2% of all cancers of the lower alimentary tract in the United States.[1] The risk of anal canal cancer has increased over the past 30 years with its association with HPV and HIV, and although well over 4000 new cases per year are expected, it is still considered one of the more curable cancers. Significant advances have been made in the pathophysiology and treatment of anal cancer.[2] In the 1960s, anal canal cancer was routinely treated by abdominoperineal resection requiring a permanent colostomy.[3] Over the years, however, as a result of carefully designed studies, it is now possible to cure anal canal cancer in a majority of patients, with preservation of the anal sphincter.

ANATOMY

The anal canal is a 4-cm-long structure that passes downward and backward from the rectal ampulla (level of pelvic floor) to the anus (anal verge). The proximal border of the anal canal clinically corresponds to the anal sphincter at the level of the puborectalis muscle (palpable as the anorectal ring on digital rectal examination). This is where the rectum enters the puborectalis sling, made by fibers from both sides. The distal end of the anal canal is at the level of the anal verge, where the groove between the internal sphincter and the subcutaneous part of the external sphincter is palpable. This also is the level of the squamous-mucocutaneous junction and the perianal skin. At the dentate or pectinate line, which is a line that corresponds to the anal valves and anal sinuses, a zone of transitional mucosa is often present. This is defined as the zone interposed between uninterrupted colorectal-type mucosa above and uninterrupted squamous epithelium below.[4] Distal to the dentate line, the anal canal is lined by nonkeratinizing squamous epithelium, which merges with perianal skin (true epidermis). This junction has historically been called *anal verge* or *anal margin*. It follows that two distinct categories of tumors arise in the anal region. Tumors that develop from mucosa (columnar, transitional, or squamous) are true *anal canal cancers*, whereas tumors that arise from skin at or distal to the squamous-mucocutaneous junction are termed *anal margin tumors* (Fig. 83-1).

Lymphatic drainage of anal cancers depends on the location of the primary tumor. Tumors below the dentate line drain to superficial inguinal nodes, with some communication to femoral nodes and to the external iliac nodes. Tumors that originate above the dentate line drain to internal pudendal, hypogastric, and obturator nodes of the internal iliac system. The most proximal portion of the canal drains to perirectal and superior hemorrhoidal lymph nodes of the inferior mesenteric system.[5]

EPIDEMIOLOGY

The annual incidence of anal canal cancer in the United States is 1.3 per 100,000 in white men and 1.8 per 100,000 in white women.[6] More than 85% of cases diagnosed are in non-Hispanic whites. Approximately 4650 new cases of anal canal cancer are predicted this year.[7] Overall, the risk of anal cancer is increasing.[8] The median age at diagnosis is 62 years, although more cases are being seen in younger HIV-positive patients. Women more commonly have lesions above the dentate line, whereas distal anal canal cancers tend to be somewhat more common in men. Marked predominance is noted in females, and the preferential location is the posterior wall of the anal canal.[9] Anal canal incidence is higher in urban than in rural populations.[10]

ETIOLOGY AND RISK FACTORS

The incidence of anal cancer and its precursor lesions (such as anal intraepithelial neoplasia) is increasing in HIV-positive patients.[11] The absolute risk in persons with acquired immunodeficiency syndrome (AIDS) is 1 per 1000. Increased risk is found in young homosexual men, irrespective of HIV status. This suggests anal sexual activity as

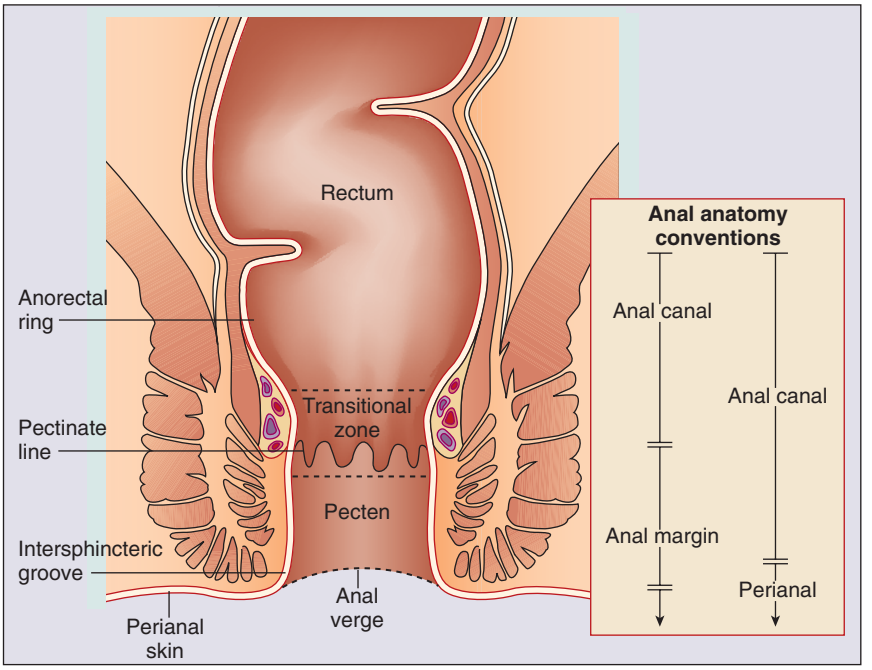


Figure 83-1 • Anatomy of the anal region.

an etiologic factor.[12] Association with HIV positivity may be the consequence of chronic immunosuppression, which in itself also has been associated with an increased risk of anal canal cancer and has been demonstrated also with vulvar cancer in renal transplant recipients.[13] HPV is a sexually transmitted agent that also has been implicated; among all of the known subtypes, HPV-16, -18, -31, -33, and -35 have been associated with malignancy or high-grade dysplasia.[14] The premalignant condition of cervical intraepithelial neoplasia (CIN) associated with HPV infection also occurs with HPV infections involving the anus (termed *anal squamous intraepithelial lesions* [ASILs]). As in CIN, ASILs can be morphologically low grade (LSILs) or high grade (HISLs).

HPV-6 and HPV-11 have been associated with benign genital condylomata. An association of other infectious agents with anal cancer has been suggested, such as syphilis and gonorrhea in men[15] and chlamydial infection and herpes simplex type 2 in both men and women.[16] It appears that cancers of the genital tract and anal cancer share some common etiologic factors.[17] An association between anal cancer and a higher number of sexual partners has been shown in women,[16] and anal cancer patients are more likely to have a prior diagnosis of CIN.[17]

Smoking and anal cancer have been associated in some studies, with a positive correlation with the number of cigarettes smoked per day and the duration for which a patient had been a smoker.[18] The possibility that the presence of benign conditions may lead to the development of anal cancer also has been suggested.[19] An association with anal fistulae, perianal abscesses, fissures, and hemorrhoids has been reported, which may be a result of the chronic inflammation and irritation associated with these conditions. This may not be a clear-cut association, however, because some evidence indicates that the risk of anal canal cancer is the highest during the first year after diagnosis of the benign condition, and this decreases after 5 years with an almost 10-fold reduction, suggesting that patients with benign conditions may actually have had undiagnosed anal malignancy as a cause of their symptoms.[20] Further studies showed little to no evidence that presence of these benign conditions leads to the development of anal cancer.[21,22] Molecular alterations also may play an important role in anal canal cancer causation. Alterations in the expression of wild-type p53 protein have been demonstrated.[23] As mentioned previously, cancers of the anus and cervix appear to have similar etiology, and approximately 80% of squamous cell cancers of the cervix contain a subtype of HPV, whereas most anal canal squamous cell cancers that lack HPV have a p53 mutation. Patients who have cervix cancer that contains HPV DNA tend to have a better prognosis,[23] perhaps because tumor DNA damaged by ionizing radiation is left unrepaired because of the absence of wild-type p53. Therefore, it is possible that anal cancers also are more susceptible to radiation if functional p53 protein is absent. This was shown in results from the Radiation Therapy Oncology Group (RTOG) 8704 study, which suggested that tumors with overexpression of p53 had a worse outcome than that for tumors with normal or absent expression. Overexpression of the c-*myc* oncogene also has been implicated in the pathogenesis of squamous cell cancers of the anal region.[24]

SCREENING, EARLY DETECTION, AND PREVENTION

Screening efforts in high-risk patients include physical examination, anal Papanicolaou (Pap) smear, and anoscopy if the Pap smear shows abnormalities. HSILs may be a precursor to invasive anal cancer, which may be detected by cytologic smears or anoscopy and biopsy, because the specificity of anal cytologic studies for the detection of HSIL is low.[25] This screening should not undermine efforts at prevention, which should include educating the general population about the risks associated with sexually transmitted infections, especially HPV infection, and anogenital cancers. Prevention efforts also may include development of a prophylactic vaccine, treatment of HPV infection with development of antiviral agents, delayed onset of sexual intercourse, and cessation of smoking. These are recommendations by the National Institutes of Health Consensus Panel of 1996.[26]

NATURAL HISTORY

Anal cancer is predominantly a locoregional disease, with possible direct extension to surrounding tissues and lymphatic dissemination to inguinal and pelvic nodes; hematogenous distant metastasis is a relatively rarer occurrence. Anal canal cancers constitute 75% of all

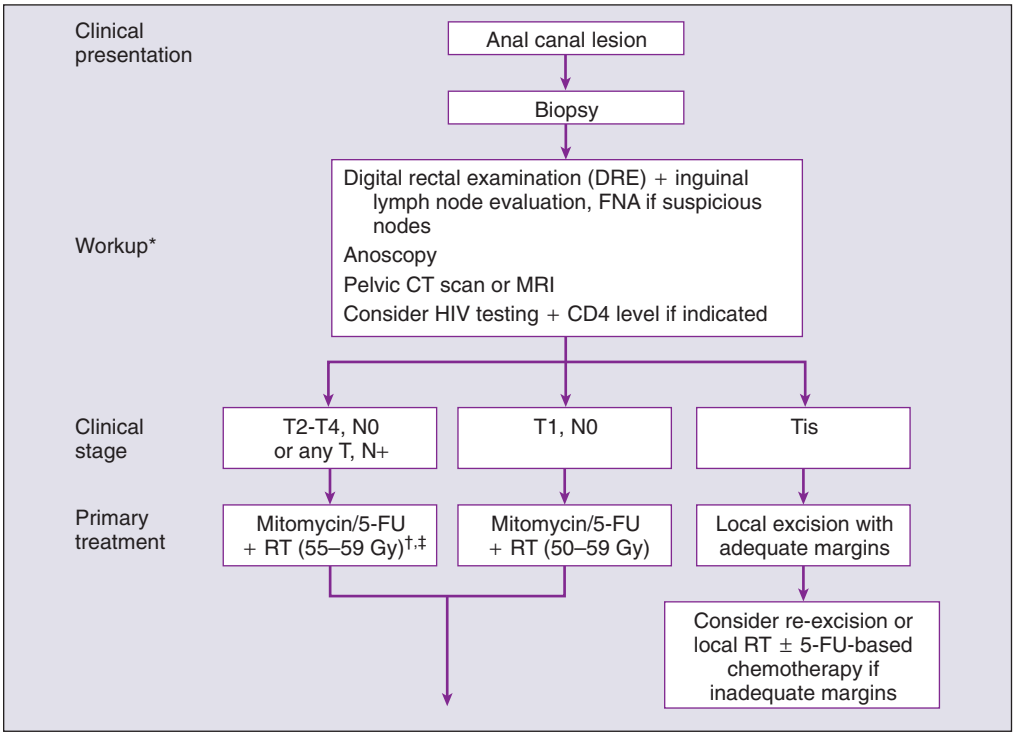


Figure 83-2 • Diagnostic algorithm for evaluating lesions of the anal canal and margin. CT, computed tomography; FNA, fine needle aspiration; 5-FU, 5-fluorouracil; MRI, magnetic resonance imaging; RT, radiotherapy. *Human papillomavirus (HPV) testing does not contribute to management. †Include bilateral inguinal/low pelvic nodal regions based on estimated risk of inguinal involvement. ‡Patients with anal cancer as the first manifestation of HIV/AIDS may be treated with the same regimen as non-HIV patients. Patients with active HIV/AIDS-related complications or a history of complications (e.g., malignancies, opportunistic infections) may not tolerate full-dose therapy and require dosage adjustment.

lesions, and only 25% are anal margin tumors. Local spread may be present in approximately 50% of cancers at diagnosis with involvement of the anal sphincter or surrounding soft tissues.[27] Extension to the rectum and perianal skin also may occur. Invasion of the vaginal septum is more common than invasion of the prostate gland because of the presence of Denonvillier's fascia in men, which acts as a barrier.[28]

Lymphatic drainage is dependent on the anatomic location of the primary tumor. Tumors that arise distal to the dentate line drain to inguinal lymph nodes (superficial and deep), and those above the dentate line spread primarily to the internal iliac system, and with more proximal lesions, spread occurs to the inferior mesenteric group. The regional nodes are considered to be inguinal (superficial and deep femoral), internal iliac, and perirectal (anorectal, perirectal, and lateral sacral). All other nodal groups represent sites of distant disease. The incidence of involvement of inguinal nodes is directly proportional to the size and extent of the primary tumor. Overall, this risk may be approximately 10% at diagnosis but may increase to 20% for tumors larger than 4 cm, and with T4 disease, this may be as high as 60%.[29] One report suggested that the risk of lymph node metastasis is not directly related to tumor size.[30] Distant metastasis may occur to any organ, but the liver and lungs are most frequently involved. Overall, distant metastases are relatively rare, because anal canal cancer tends to be a locoregional process. At diagnosis, only 5% to 10% of patients will be found to have distant disease. After curative treatment, the risk of distant disease varies, ranging between 10% and 30%, and depends on the initial tumor (T) stage.[31] The risk of distant metastasis also increases with the number of regional nodes involved.[27]

CLINICAL PRESENTATION AND DIAGNOSIS

Most patients with anal cancer are first seen with rectal bleeding. This occurs in approximately 50% of patients; 30% experience pain or the sensation of a rectal mass.[32] A common concern with most anal neoplasms is the frequent delay in diagnosis resulting from confusion with more common, benign conditions. Thus, the clinician must maintain a high index of suspicion when evaluating lesions of the anal canal and margin.[33]

An interval of 4 to 6 months may ensue between onset of symptoms and diagnosis in up to 50% of patients. A thorough evaluation of any patient with a lesion in the anal canal is therefore recommended (Figs. 83-2 and 83-3). This evaluation includes a digital rectal examination, palpation of inguinal nodes, and an anoscopic visual examination with biopsy of suggestive lesions, including enlarged lymph nodes, which may be caused by tumor or reactive hyperplasia in as many as 50% of palpable nodes (Box 83-1). The anal cancer need not be excised at the time of biopsy. Computed tomography (CT) scan or magnetic resonance imaging (MRI) is done to assess pelvic and suspicious inguinofemoral nodes. Rectal ultrasound examination is an accurate means of determining the depth of penetration of the tumor into the anal wall. It also serves to visualize local lymph nodes. CT scan of the abdomen and pelvis and chest radiography are recommended to assess locoregional and distant disease. Positron emission tomography (PET) scan also is recommended for staging. HIV testing also is suggested in patients with risk factors such as sexual history and drug abuse history. Carcinoembryonic antigen (CEA) level may be elevated in 20% of cases, but this study is rarely requested because no clinical benefit in patient management derives from obtaining this information.[34]

STAGING

Staging for anal canal cancers in based on the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) staging system. The TNM classification for tumors is based on clinical or histopathologic findings, or both, as well as results of radiographic studies. The latter assesses local and locoregional extension. Surgical excision is infrequently done, so few tumors are staged histopathologically (Table 83-1). At initial presentation, approximately 50% to 60% of patients have T1 or T2 lesions, and 12% to 20% are node positive.

HISTOPATHOLOGIC CLASSIFICATION

The staging system applies to all carcinomas arising in the anal canal, including carcinomas that arise within anorectal fistulae. Melanomas,

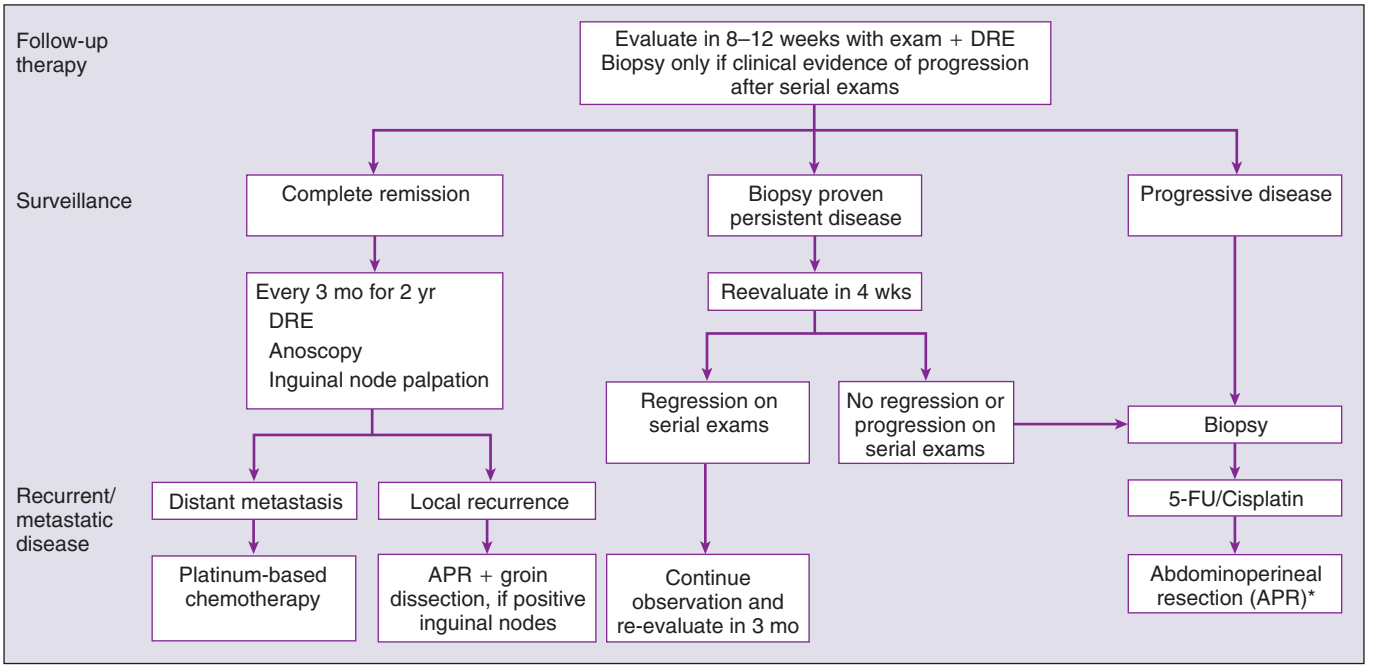


Figure 83-3 • Algorithm for treatment of anal cancer. APR, abdominoperineal resection; DRE, digital rectal examination; 5-FU, 5-fluorouracil. *Consider muscle flap reconstruction.

carcinoid tumors, and sarcomas are excluded from this staging system. Most carcinomas of the anal canal are squamous cell carcinomas. The World Health Organization (WHO) classification of the types and subtypes of carcinomas of the anal canal is presented in Box 83-2. The terms "transitional cell carcinoma"and "cloacogenic carcinoma" have been abandoned because these tumors are now recognized as nonkeratinizing types of squamous cell carcinoma.[35]

Box 83-1. DIAGNOSTIC WORKUP FOR CANCER OF THE ANAL CANAL

Essential Components of Evaluation

History
Physical examination
- Regional lymph nodes
- Adjacent organs for direct invasion
- Anogenital areas for concurrent malignancies

Proctoscopy
Biopsy of primary tumor
Fine-needle aspiration biopsy or simple excision of enlarged inguinal nodes
Chest radiograph
CT of abdomen and pelvis
Liver and renal chemistry
Complete blood cell count
HIV antibody assay, if risk factors are present

Useful Studies

Colonoscopy or air-contrast barium enema (to exclude other sources of lower gastrointestinal tract bleeding)
Bipedal lymphangiography

CT, computed tomography; HIV, human immunodeficiency virus.

TREATMENT

Carcinoma of the anal canal is a chemoradiotherapy-sensitive tumor and therefore is often a curable cancer, with anal sphincter preservation in 65% to 75% of patients. Significant advances have occurred over the past 30 years in its treatment. The treatment of anal canal cancer has changed from radical surgery to a combined approach of organ-sparing chemotherapy and radiotherapy and constitutes one of the success stories in recent oncologic management (Box 83-3). This principle also has served as a model for treatment of other types of malignancy.

Surgery

Surgical treatment was the primary therapy 20 to 35 years ago, but it has been replaced by sphincter-sparing therapy with combination chemoradiotherapy. Surgical therapy is now used most often as a method of salvage. Surgical treatment, when it was used as a primary therapy, required an abdominoperineal resection (APR). This con-

Box 83-2. WORLD HEALTH ORGANIZATION CLASSIFICATION OF CARCINOMA OF THE ANAL CANAL*

Squamous cell carcinoma
Adenocarcinoma
- Rectal type
- Of anal glands
- Within anorectal fistula

Mucinous adenocarcinoma
Small cell carcinoma
Undifferentiated carcinoma

*The term *carcinoma NOS* (not otherwise specified) is not part of the World Health Organization (WHO) classification.

Table 83-1 Tumor-Node-Metastasis Staging System

PRIMARY TUMOR (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but ≤5 cm in greatest dimension
T3	Tumor >5 cm in greatest dimension
T4	Tumor of any size invades adjacent organ(s) (e.g., vagina, urethra, bladder)*

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

DISTANT METASTASIS (M)

Stage	GROUPING		
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	Any T	N1	M0
	Any T	N2	M0
Stage IV	Any T	Any N	M1

MX, distant metastasis cannot be assessed; M0, no distant metastasis; M1, distant metastasis.

*Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.

sisted of wide local excision of the anus, to include the levator ani muscles and contents of the ischiorectal fossa. The operation results in a permanent colostomy, as well as loss of sexual function, in most patients. Overall, 5-year survival rates were approximately 50% after curative APR for anal canal cancer, with slightly better results of 55%

Box 83-3. COMBINED-MODALITY TREATMENT FOR SQUAMOUS CELL CANCER OF THE ANAL CANAL

Chemotherapy

5-Fluorouracil, 1000 mg/m^2 per 24 hours by continuous intravenous infusion for 96 hours, starting on days 1 and 28

Mitomycin C, 10 mg/m^2 by intravenous bolus on days 1 and 28

Radiation Therapy

45 Gy delivered in 25 fractions to pelvis ± boost to residual disease, to total dose of 54 to 59.6 Gy

to 71% in more recent series.[36–40] Despite reasonable survival rates, local recurrence continues to remain a significant cause of treatment failure. A review of 118 cases treated at the Mayo Clinic showed an overall survival rate of 70% and local recurrence rate of 40% (including patients with inguinal node recurrence). Local recurrence was a component of failure in more than 80% of patients who relapsed.[27] Frost and colleagues[37] reported an overall survival of 62%, with a 45% rate of failure in the pelvic and inguinal lymph nodes. Because of the high morbidity associated with inguinal lymph node dissection and the fact that the risks associated with the procedure outweigh its benefits, prophylactic groin dissection is not recommended. Surgery alone should be considered only for lesions of the anal margin in which the sphincter can be spared. The results of several major surgical series are summarized in Table 83-2. Tumor size, depth of invasion, and presence of inguinal or pelvic lymph nodes have been shown to have prognostic significance in terms of higher risk of local recurrence and worse survival.[27,36–39] A large series from the Memorial Sloan-Kettering Cancer Center demonstrated survivals of 63%, 55%, and 40% for T1, T2, and T3 lesions, respectively. The corresponding local recurrence rates were 16%, 35%, and 56%. Furthermore, patients with superficial invasion of the anal sphincter had a 79% survival rate, compared with 52% for those with deep muscle invasion.[38] Another review by Pintor and associates[39] demonstrated 60% survival for patients with T1 and T2 lesions, compared with 54% for patients with T3 and T4 disease. In a series from the Mayo Clinic, tumors confined to the anal epithelium and subepithelial connective tissues did not recur, whereas those invading the anal sphincter recurred in approximately one fourth of the cases, and those invading adjacent pelvic tissues recurred in almost half of the cases. Survival was affected by inguinal node metastases, with a 5-year survival rate of only 18%.[38]

APR is rarely used as initial therapy. It remains a useful procedure, however, for salvage after sphincter-preserving therapy and for management of complications related to conservative therapy.[40]

Radiotherapy

Radiotherapy has been used for treatment of anal cancers since the early 1900s, especially in Europe, whereas surgery was the treatment

Table 83-2 Results of Abdominoperineal Resection for Anal Cancer

Study	Years	No. of Patients	Local Recurrence (%)	Survival (%)
Dillard et al.[36]	1940–1957	40	—	45
Boman et al.[27]	1950–1976	118	40	70
Frost et al.[37]	1954–1979	132	27 (pelvic) 18 (inguinal)	62
Greenall et al.[38]	1950–1978	103	—	55
Pintor et al.[39]	1948–1984	118	—	62

Table 83-3 Results of Radiation Therapy Alone for Anal Cancer

Study	Irradiation Schema	No. of Patients	Tumor Stage/Size	Local Recurrence (%)	Survival (%)	Anal Sphincter Preserved (%)
Cummings et al.[44]	45–50 Gy, 2.5 Gy/day	51	0	43	59	77
Salmon et al.[41]	60–65 Gy	158	<4 cm	—	70	76
			4–6 cm	—	57	57
			>6 cm	—	33	—
Eschwege et al.[42]	60–65 Gy over 6–12 wk	64	T1 and T2	9	72	91
			T3 and T4	30	35	50
Papillon and Montbarbon[47]	30–42 Gy in 10 fractions; rest 2 mo, 15–20 Gy/implant	159	<4 cm	11	76	82
			>4 cm	27	58	70
Schlienger et al.[43]	40–45 Gy over 4–5 wk, rest 4–6 wk	29	T1 and T2	85	55	
		26	T3a	75	55	
	15–20 Gy/perineal boost	39	T3b	65	55	
		43	T4	59	55	
Martenson and Gunderson[45]	47–67 Gy over 5–5.7 wk	18	T1, T2 (17 pts)	10	86	
			T3 (1 pts)			
Dobrowsky[46]	45–70 Gy over 4–7 wk	23	Unknown	18	65	
Doggett et al.[48]	45–76 Gy over 4.5–8 wk	35	1.3–4.5 cm	23	92	

of choice in the United States. Most series have demonstrated survival rates on the order of 45% to 65%. As with surgery, better outcomes have been seen with smaller tumors and in patients with disease-negative inguinal lymph nodes.[41–43] In a series from the Institut Curie between 1968 and 1979, the 5-year overall survival rate was 59% (70% for tumors less than 4 cm in diameter, 57% for those between 4 and 6 cm, and 33% for those greater than 6 cm). Correspondingly, anal-sphincter function was retained in 76% and 57% of cases, respectively, for tumors smaller than 4 cm and those from 4 to 6 cm in diameter. Likelihood of survival and local recurrence also depended on the extent of the tumor's circumferential involvement of the anal canal. For tumors with a circumferential involvement of 25% and 50%, survival rates of 71% and 61%, respectively, were demonstrated. Survival decreased to 19%, however, with 75% or more circumferential involvement. Local recurrence rates were 16%, 28%, and 100%, respectively.[41] Local control and survival rates from retrospective series of radiation alone are summarized in Table 83-3.

Complications of radiotherapy may result in the need for colostomy in 2% to 10% of patients.[41–47] Overall, results with a definitive course of radiotherapy are similar to if not better than results with surgery, especially for tumors smaller than 4 cm in diameter.[48] Radiotherapy allows sphincter preservation, thus making it a more preferred option compared with surgery. Excellent results also have been obtained with use of external beam and interstitial irradiation in combination. In their series of 222 patients with anal cancer, Papillon and Montbaron[47] used a treatment regimen consisting of external beam irradiation at a dose of 30 to 42 Gy, followed 2 months later with an interstitial implant using iridium (Ir) 192 to deliver 15 to 20 Gy. The 5-year survival rate was 65%. Patients with tumors smaller than 4 cm had a 76% survival rate, compared with 58% for patients with larger lesions. Sphincter preservation was achieved in 82% and 70%, respectively.[47]

Combined-Modality Treatment

Combined-modality therapy was described initially by Nigro and coworkers.[49] This was a preoperative regimen inspired by reports that 5-fluorouracil (5-FU) potentiated the effects of radiotherapy on gastrointestinal tumors.[50] This regimen consisted of delivering 30 Gy in 15 fractions to the primary tumor and pelvic lymph nodes with concurrent 5-FU (1000 mg/m^2 as a 4-day continuous infusion) and mitomycin C (MTC) (15 mg/m^2 bolus injection) chemotherapy, and APR 6 weeks after completion of the protocol.[52,53] Promising early results, however, suggested that surgery may not be necessary. The series of Nigro and colleagues[51] included 31 patients who underwent surgery and 73 who received chemoradiotherapy alone. Twenty-two of the 31 surgical specimens had no evidence of disease (NED) on histopathologic examination, and on long-term follow-up evaluation, an NED rate of 79% was found for the surgical patients, compared with 82% NED for patients receiving combined-modality treatment. Overall death rates were 6% in patients with tumors smaller than 4 cm and 26% for those larger than 4 cm.

Subsequent to the Wayne State protocol of Nigro and associates, Cummings and coworkers[53] performed a series of sequential prospective nonrandomized studies at Princess Margaret Hospital in Canada, evaluating radiation alone, radiation with 5-FU, and radiation with 5-FU and MTC. The best results were observed with both 5-FU and MTC along with radiation therapy. These investigators compared 30 patients treated with chemoradiation with 25 patients treated previously with similar doses and techniques of radiotherapy alone. The local control rate was 93% in the combined group, with no difference found between continuous and split-course regimens, and 60% in the radiotherapy-alone group. The overall survival rate was 70% in both groups. The RTOG confirmed these results in a phase II trial with the same chemotherapy regimen and a total radiation dose of 40.8 Gy at 1.8 Gy per fraction. Patients with smaller tumors (less than 3 cm in diameter) had a 2-year disease-free survival rate of 77%, compared with 53% for large tumors. Local control rate also was tumor size dependent: 84% for smaller lesions and 66% for larger tumors. Other investigators have suggested higher radiation doses for larger tumors.[54–57]

The rate of sphincter preservation also appears to be higher in patients who receive combined-modality therapy; rates of 85% to 100% were reported by several studies.[44,55,57,59] No definite evidence was found of a survival benefit with the combined-modality approach, but local control and colostomy-free survival are definitely improved

Table 83-4 Results of Combined-Modality Therapy for Anal Cancer

Study	Treatment Regimen	No. of Patients	Tumor Stage/Size	Local Recurrence (%)	Survival (%)
Cummings et al.[44,53]	RT, 50–60 Gy in 20–30 fractions	69	—	14	—
	5-FU, days 1–4, repeat at beginning of each RT course; MTC, day 1				
Nigro et al.[51,52]	RT, 30 Gy in15 fractions	104	—	—	82
	5-FU, days 2–6; MTC, day 1				
Leichman et al.[54]	RT, 30 Gy in15 fractions	45	—	16	76
	5-FU, MTC				
Sischy[55]	RT-60 Gy in 33 fractions	29	—	10	—
	5-FU days 2–5; MTC, day 2				
Flam et al.[56]	RT, 41–50 Gy in 1.8 Gy fractions	30	—	3	90
	5-FU, MTC				
Sischy et al.[57]	RT, 40 Gy in 24 fractions	79	<3 cm	16	85
	5-FU days 2–5, days 28–31; MTC, day 2		>3 cm	38	68
Tveit et al.[58]	RT, 50 Gy in 25 Gy fractions	24	—	17	58
	5-FU, MTC				
Zucali et al.[59]	RT, 54 Gy in 30 fractions	38	—	32	84
	5-FU, days 1–5; MTC, day 1				

5-FU, 5-fluorouracil; MTC, mitomycin C; RT, radiation therapy.

with the combination of chemotherapy and radiotherapy. The need for chemotherapy in addition to radiation has been established by two well-conducted randomized trials. Table 83-4 summarizes a number of series consisting of treatment with radiation therapy and chemotherapy, the latter using 5-FU and MTC, as initially described by Nigro and colleagues. Most of the series show good survival and local control rates in the range of 60% to 90%.

Following up a trial from Princess Margaret Hospital,[53] the EORTC (European Organization for Research and Treatment of Cancer) and the UKCCR (United Kingdom Coordinating Committee for Cancer Research) have done two randomized studies comparing radiation alone with combined radiation therapy and 5-FU–MTC chemotherapy.[60,61] Results of these two trials on follow-up evaluation at a median of 42 months are outlined in Table 83-5. In the EORTC trial, a locally advanced primary tumor (T3 or T4) or regional lymph node involvement was required for eligibility. Any stage of disease was eligible for the UKCCR trial. Initial radiotherapy consisted of 45 Gy to the pelvis in both trials but the boost was different. In the EORTC trial, a 20-Gy boost was delivered to partial responders 6 weeks after completion of therapy and complete responders received 15 Gy. In the UKCCR trial, a 15- to 25-Gy boost was given to patients who had a more than 50% response, and those who had a less than 50% response underwent surgery. The chemotherapy regimen consisted of 5-FU, 750 mg/m^2 per 24 hours on days 1 to 5 and 29 to 33, with a single 15-mg/m^2 dose of MTC on day 1, in the EORTC trial. In the UKCCR trial, 5-FU was given at a dosage of 1000 mg/m^2 per 24 hours on days 1 to 4 and on days 29 to 32 or 750 mg/m^2 per 24 hours on days 1 to 5 and 29 to 33, with a single

Table 83-5 Results of EORTC and UKCCR Trials Comparing Radiation Alone with Radiation and Chemotherapy

Treatment Regimen	No. of Patients	Complete Response (%)	3-Year Local Control (%)	3-Year Overall Survival (%)
EORTC, 1987–1994[61]	103			
RT	52	54	55	64
RT plus 5-FU, MTC	51	80	69	69
P value	—	0.02	0.02	0.17
UKCCR, 1987–1995[61]	577			
RT	285	30	39	58
RT plus 5-FU, MTC	292	39	61	65
P value	—	0.08	<0.0001	0.25

EORTC, European Organization for Research and Treatment of Cancer; 5-FU, 5-fluorouracil; MTC, mitomycin C; RT, radiation therapy; UKCCR, United Kingdom Coordination Committee and Cancer Research.

Table 83-6 Results of RTOG-ECOG Trial: Radiation Therapy and 5-Fluorouracil ± Mitomycin C

Treatment Regimen	No. of Patients	Total RT Dose (Gy)	Negative Biopsy Result* (%)	4-Year Findings (%)					Grade 4/5 Toxicity (%)
				Local Control	Colostomy Rate	Colostomy-Free Survival	Disease-Free Survival	Overall Survival	
RT plus 5-FU	145	45–50.4	85	66	22	59	51	67	8
RT plus 5-FU, MTC	146	45–50.4	92	84	9	71	73	76	26
P value	—	—	0.135	0.0008	0.002	0.014	0.003	0.31	≤0.001

ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil; MTC, mitomycin C; RTOG, Radiation Therapy Oncology Group; RT, radiation therapy.
*Performed 4 to 6 weeks after completion of therapy.

12-mg/m^2 dose of MTC. Complete response rates at 6 weeks after boost radiotherapy were 80% and 54%, respectively, favoring the combined-modality regimen in the EORTC trial. A trend toward a higher complete response rate also was reported in the UKCCR trial. This was measured 6 weeks after induction therapy, however, as opposed to 6 weeks after completion of all therapy, as was done in the EORTC trial. Although the local control rate was low in the UKCCR study at 39% at 3 years, it should be noted that the definition of failure in this study was less than 50% tumor reduction at 6 weeks after delivery of 45 Gy to the pelvis.

Local control was significantly better in both trials with the combination regimens, but no impact was seen on survival.[60,61] The need for MTC in combined-modality therapy of anal cancers was evaluated in a randomized U.S. RTOG–ECOG trial (RTOG 87–04/ECOG 1289). This was the first study comparing two methods of chemoradiotherapy in patients with anal cancer. One study arm used 5-FU alone with radiotherapy, and the other arm used 5-FU and MTC with radiotherapy.[62] (Results of this study are summarized in Table 83-6.). The addition of MTC was associated with fewer colostomies and higher rates of local control and disease-free survival, but with a significantly greater risk of grade 4 or 5 toxicity, seen in 26% of patients, compared with 7%. Survival was slightly higher with the MTC-containing regimen, but the difference was not statistically significant. The disease-free survival rate was 73% versus 51%, favoring the MTC-containing regimen. 5-FU was administered at 1000 mg/m^2 per day as a continuous infusion for 4 days beginning on days 1 and 28 of radiotherapy. MTC was administered at 10 mg/m^2 by intravenous bolus on day 1 of each 5-FU course. Two of the four treatment-related deaths in the MTC regimen group were believed to be due to failure to follow protocol dosage-reduction guidelines for the second MTC dose. The investigators concluded that despite the greater toxicity, the use of MTC in a definitive complete response regimen for anal cancer was justified.

Future Directions in Treatment

Chemotherapy regimens incorporating 5-FU and cisplatin have resulted in significant antitumor activity in patients with metastatic anal carcinoma.[63,64] Use of this combination has generated great interest, with a number of reports demonstrating response rates ranging from 55% to 82%. Table 83-7 summarizes the findings in some of these series. The RTOG study 98–11, which investigated use of such regimens for the management of metastatic disease, compared external beam radiotherapy (EBRT) with 5-FU plus MTC, given during weeks 1 and 5, and two courses of induction 5-FU and cisplatin, followed by concurrent EBRT plus 5-FU and cisplatin, with radiotherapy beginning on day 57. The study hypothesis was that induction chemotherapy may reduce tumor bulk before combined chemoradiation therapy and thereby provide better local control and colostomy-free survival; an additional two cycles of chemotherapy may positively affect the distant metastatic rate.[65] The trial enrolled 682 non–HIV-infected patients with squamous cell cancer of the anal canal. A preliminary report found no significant difference in rates of 5-year disease-free survival (48% and 56% for the experimental and control arms, respectively) or overall survival (69% in both groups), but the colostomy rate was significantly higher in the cisplatin treatment group (hazard ratio, 1.63).[65] Although hematologic toxicity was worse in the MTC group, nonhematologic toxicity and late radiotherapy-related toxicity rates were similar in the two groups. The investigators concluded that a 5-FU–cisplatin combination was not superior to the standard regimen of 5-FU plus MTC. Thus, 5-FU plus MTC remains the standard regimen for concur-rent chemoradiotherapy at most treatment centers and is included in published guidelines of the National Comprehensive Cancer Network.[66]

Radiotherapy Techniques

Photon energy of 6 MV or greater is indicated for irradiation of pelvic fields. In the past, large anteroposterior (AP) and posteroanterior (PA) fields were used for comprehensive coverage of the area of primary disease and inguinal nodes. Although this still is an appropriate technique, alternate-field arrangements also have been used. One such technique suggests that supplementary inguinal node radiation be given, preferably with electrons. In this alternate technique, initial pelvic fields include AP and PA fields to include the pelvis, anus, perineum, and inguinal lymph nodes. The lateral inguinal nodes should be irradiated using the AP field, but not the PA field, to minimize radiation dose to the femoral head and neck. The PA field should extend 2 cm lateral to the sciatic notch and should be designed to include the primary tumor and pelvic nodes. Electron fields are

Table 83-7 Response Rates with Cisplatin-Based Chemotherapy

Study	No. of Patients	Chemotherapy Regimen	Response Rates			Description of Disease
			CR	PR	Overall	
Mahjoubi et al.[86]	20	CDDP, 5-FU	2	9	11 (55%)	Locally recurrent and/or metastatic
Brunet et al.[85]	22	CDDP, 5-FU	6	13	18 (82%)	Primary tumors: neoadjuvant therapy

CDDP, *cis*-diaminedichloro-platinum; CR, complete response; 5-FU, 5-fluorouracil; PR, partial response.

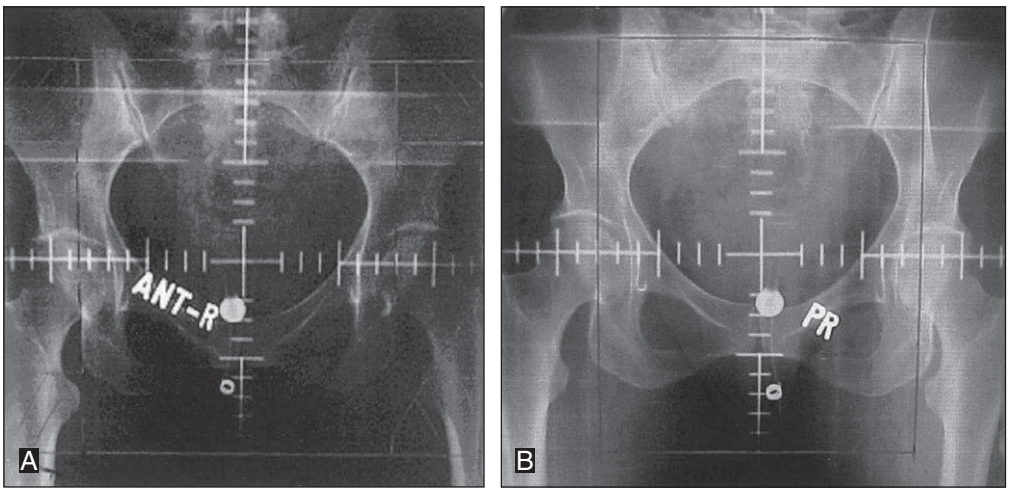


Figure 83-4 • A, Initial anterior photon fields *(solid line)* and supplementary electron fields to boost dose to lateral inguinal nodes *(dotted line)*. **B,** Initial pelvic posterior photon field.

designed to incorporate the lateral inguinal nodes not included in the posterior field (Fig. 83-4). The superior border of the initial pelvic fields starts at L_5-S_1 and is dropped to the level of the inferior border of the sacroiliac joints at 36 Gy (Fig. 83-5). The inferior border includes the anus, with at least a 2.5-cm margin. The initial dose is 36 Gy given at 1.8 Gy per fraction. This is calculated to midplane from the anterior and posterior pelvic fields. Dose to inguinal nodes is calculated, because these do not receive a contribution from the initial posterior pelvic field, which is not as wide as the anterior photon field. The remaining dose is supplemented with electrons to make up to 180 cGy per day (typically, inguinal nodes are situated at 3 cm). Another method of treatment uses a three-field technique as for rectal cancer, with one posterior and two lateral fields. The PA field is large enough to include the lateral inguinal nodes. The dose to the inguinal nodes is calculated and typically is approximately one third of the contribution from the PA field. The remaining dose is supplemented with inguinal electron fields.

Intensification of Radiation Dose

It is not yet known whether escalating radiation doses to more than 45 to 50 Gy in combined-modality therapy will result in greater benefit. Analysis of data from the Massachusetts General Hospital, the University of Kansas, the University of Maryland, and M.D. Anderson Cancer Center suggests a benefit in local control with higher radiation doses of 54 to 66 Gy.[67–71] A benefit with higher radiation dose also was suggested in the RTOG 8704–ECOG 1289 trial.[62] This issue was investigated recently in the RTOG 9811 study. After delivery of 45 Gy, use of an additional boost of 10 to 14 Gy was an option for residual disease.[65] A phase II RTOG study, RTOG 9208, unfortunately demonstrated a high incidence of colostomies of 23% with use of a radiation dose of 59.4 Gy with 5-FU and MTC.[72] This complication rate was thought to be related to absence of planned treatment break, and the investigators concluded that for higher doses to improve local control, radiation therapy may have been given in a continuous fashion, thereby increasing toxicity. A subsequent RTOG pilot trial, however, showed only an 11% colostomy rate with no treatment break.[73]

Side Effects and Radiation Complications

Anal sphincter function is maintained in 65% to 80% of patients after combined-modality treatment.[65] Late complications may result in loss of anal function, and colostomies may be needed in 2% to 10% of patients.[67] APR usually is done for disease recurrence. Acute toxicity may be significant with radiation and chemotherapy. The severity of toxicity may be influenced by fraction size and the type of chemotherapy. Fraction size was found to be a contributing factor by Cummings and associates[53] at Princess Margaret Hospital. The incidence of toxicity was decreased by approximately 50% when

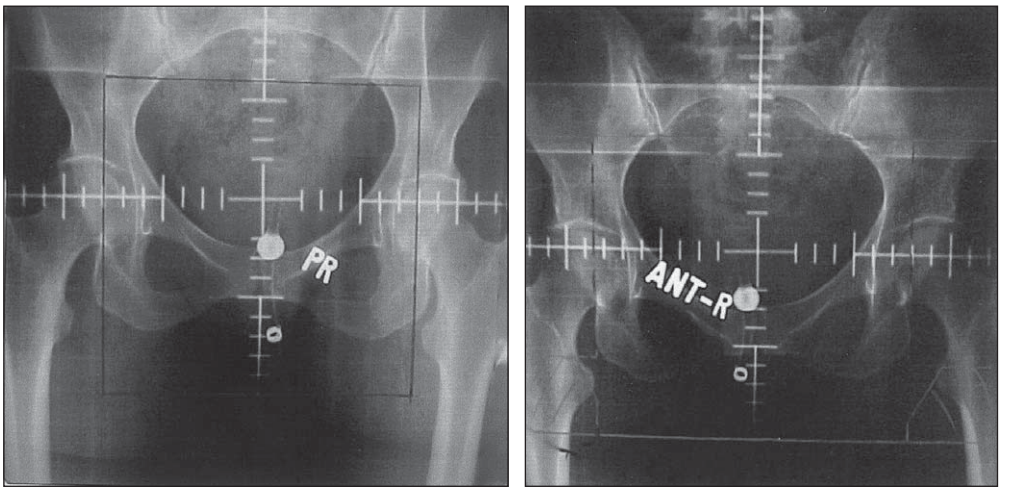


Figure 83-5 • A, Posterior pelvic field with its superior border at the level of the inferior sacroiliac joints. **B,** Anterior pelvic field reduction when the superior border is brought down to the inferior border of the sacroiliac joints.

fraction size was decreased from 250 cGy to 200 cGy, or when a planned treatment break was given. The type of chemotherapy in the RTOG-ECOG trial also determined the severity of toxicity. With 5-FU plus MTC, 26% of patients experienced grade 4 or 5 toxicity, compared with only 7% in the 5-FU-alone arm.[53] In the short term, most patients experience significant perineal skin reactions, often with confluent moist desquamation, such that a treatment break is necessary during most treatment courses. Other reactions may include fatigue, nausea, vomiting, diarrhea, dysuria, rectal and vaginal irritation, and possible bleeding secondary to proctitis, cystitis, and vaginitis.

Late complications may consist of perineal fibrosis, telangiectasia, and intermittent bleeding from the anorectal region or the bladder or vagina. Other late complications may include hyper- or hypopigmentation of the skin, pruritus, and atrophy of the skin. Edema of the genitals or lower extremities also may occur. A possibility exists for long-term alteration of bowel function, fecal incontinence, and fistula formation necessitating colostomy. Other rare complications may include painful nonhealing ulcers of the skin or anal mucosa, strictures of the anus or vagina, and osteoradionecrosis of the femoral head or neck. In patients with comorbid conditions that would compromise tolerance to combined therapy or specifically chemotherapy, treatment with radiation alone may be best. This strategy may be appropriate both in patients who may not be able tolerate chemotherapy and in HIV-positive patients with $CD4^+$ counts less than $200/cm^3$. In our experience, the usual combined-modality approach can be used effectively, without an increased risk of toxicity or complications, in patients with $CD4^+$ counts higher than $200/cm^3$ without any alteration in dose or chemotherapeutic agents.

Assessing Response to Primary Chemoradiotherapy and Persistent Disease

Prognosis is directly dependent on the size of the primary tumor and the likelihood of lymphatic spread of the cancer. Tumors 2 cm in diameter or smaller are cured in 80% of cases, whereas those 5 cm across or larger are cured in less than 50% of cases. Tumor regression after radiotherapy may be slow and may take up to 36 weeks, with a median time to tumor regression of 12 weeks from start of therapy. A majority of recurrences occur within 2 years of treatment.[53] Routine biopsy of regressing or clinically absent tumor is not recommended. Further radiation dose supplementation may be beneficial, but this is controversial, as illustrated in an RTOG trial at a planned biopsy 6 weeks after completion of therapy. Twenty-five of 310 patients were found to have residual disease after 45 days and two courses of 5-FU and MTC. Salvage therapy using irradiation at a dose of 9 Gy and cisplatin plus 5-FU resulted in a complete response in 55% of these patients 6 weeks later.[62] The supposed benefit of extra radiation dose as salvage therapy may be the result of continued slow tumor regression and may not necessarily be related to the increased radiation. This point is still not absolutely clear, however, and continues to be investigated. Biopsy may be considered after 12 weeks if evidence of progressive disease is found. Additional chemotherapy with 5-FU and cisplatin and APR may be considered for tumor persistence or recurrence.

Treatment of Metastatic Disease

The development of distant metastases is infrequent in patients with squamous cell carcinoma of the anal canal. In the UKCCR and EORTC trials, for example, distant metastases developed after combined-modality therapy in 10% and 17% of patients, respectively.[60,61] The liver is the most frequent site of distant metastases.[74–75] The only widely published active regimen for treatment for metastatic disease is cisplatin plus 5-FU[64,76–79]; single case reports describe activity for single-agent carboplatin,[80] doxirubicin,[81] and irinotecan.[82] No experience with newer agents, such as the taxanes and gemcitabine, in this setting has been reported.

SUMMARY

In summary, squamous cell carcinoma of the anal canal is a disease best managed by a multidisciplinary approach. Optimal treatment is combined chemotherapy and radiotherapy. The recommended chemotherapeutic agents are 5-FU, delivered at a dose of 1000 mg/m^2 per 24 hours by continuous intravenous infusion for 96 hours, starting on days 1 and 28, and MTC, at a dose of 10 mg/m^2 given intravenously on days 1 and 28. It should be kept in mind that MTC can cause delayed thrombocytopenia, and platelet levels should be monitored before the second dose. Radiation therapy consists of 45 Gy delivered in 25 fractions to the pelvis over a 5-week period. The upper border of the field is reduced at a dose of 36 Gy. The issue of boost radiation for residual disease at the completion of the larger pelvic field is controversial. Some data suggest that local control is better with the addition of a boost. An increased risk of complications with a higher colostomy rate also has been reported, however. This issue currently is under investigation in the RTOG 9811 protocol, which is a phase III randomized study of 5-FU, MTC, and EBRT versus 5-FU, cisplatin, and radiotherapy.

This protocol permits a 10- to 14-Gy boost, at a dose of 2 Gy per fraction, to a reduced field after irradiation of the larger pelvic fields at 45 Gy in 25 fractions for T3 and T4 or node-positive lesions, as well as for T2 lesions with residual disease after 45 Gy. Clear evidence exists in the literature of poor local control with T3 and higher stage lesions of only 50%; accordingly, it is reasonable to prescribe a higher dose to lesions that are T3 or higher. Our recommendation as well as current practice is to treat more extensive disease with a dose of 59.6 Gy to a field 2.5 cm around the area of the anal canal malignancy. This field reduction is done after delivery of 45 Gy to the pelvis. Cisplatin currently is not a standard chemotherapeutic agent for the treatment of anal canal cancer. In the future, however, it may play a larger role. Cisplatin and 5-FU chemotherapy regimens have been used by a number of investigators. In their series of 21 patients, Rich and coworkers[71] used a treatment regimen consisting of 5-FU at a dose of 250 mg/m^2 per day and cisplatin 4 mg/m^2 per day. Both agents were delivered by intravenous infusion 5 days a week, along with radiotherapy at a dose of 54 to 55 Gy. Local control rate was 89%. In patients who received 5-FU alone, along with similar radiation dose, a local control rate of only 73% was achieved.[71]

Doci and colleagues[83] also reported the results of a phase II trial in 35 patients. Local recurrence rate with cisplatin treatment was 6%, versus 24% with the MTC-containing regimen. After investigation of its role in the management of anal cancer, however, cisplatin now is not recommended for treatment. It is, however, often considered for management of metastatic disease, for which further 5-FU and MTC or cisplatin may be used.[86] It also may be considered for patients whose medical conditions preclude the safe use of MTC. Patients with AIDS, for whom standard chemoradiotherapy doses may be too toxic, may tolerate 5-FU plus cisplatin as a safer alternative.[86,87] Patients who do not respond to chemoradiotherapy usually are offered an APR. Further chemotherapy consisting of 5-FU and cisplatin often is considered. Zelnick and colleagues[88] reported on 30 patients who underwent APR after chemoradiotherapy for recurrent or persistent anal canal cancer. Seventy-seven percent of tumors that were smaller than 5 cm with negative nodes were disease free 37 months after APR. However, none of the lesions larger than 5 cm was free of disease.[88]

Tumors of the anal margin or perianal region are treated much as for skin cancers.[89] Our treatment recommendation is local excision. If the tumor is large enough such that it requires an APR, we recommend treatment as for an anal canal cancer with combination chemoradiotherapy. Most of the lesions in this area, however, are small enough that a simple excision constitutes sufficient therapy. Adenocarcinoma of the anal canal also can occur, arising from anal ducts. This is a fairly uncommon entity. In general, such tumors are treated with preoperative chemoradiotherapy, followed by an APR.

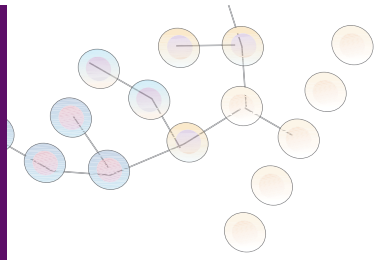
The chemotherapy used in these instances is 5-FU, in a regimen appropriate for adenocarcinoma, with radiotherapy fields appropriate for anal canal cancer. Treatment is governed mainly by the cell type.

Anal canal cancer is a rare entity. Interest in tumors in this area has increased in the recent past because of increased incidence. It is a curable disease with combined chemoradiotherapy, in which significant advances recently have occurred in its management. The selection of therapy for each patient requires the cooperative effort of many physicians, including radiation oncologists, medical oncologists, surgeons, and gastroenterologists.

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84 Liver and Bile Duct Cancer

Sharon Weber, William Jarnagin, Austin Duffy, Eileen M. O'Reilly, Ghassan K. Abou-Alfa, and Leslie Blumgart

SUMMARY OF KEY POINTS

Incidence
- Hepatocellular carcinoma (HCC) is one of the most common solid organ malignancies worldwide, with up to 1 million cases diagnosed per year.
- This high incidence relates to its common association with cirrhosis from either alcohol or hepatitis B or C.
- Cholangiocarcinoma and gallbladder cancer are less common hepatobiliary malignancies.

Etiology and Epidemiology
- The primary risk factor for hepatocellular cancer is underlying cirrhosis.
- Both the incidence of and the mortality rate for HCC and intrahepatic cholangiocarcinoma are increasing, primarily because of chronic infection with the hepatitis B and C viruses (HBV and HCV).
- Although several associated risk factors for gallbladder cancer and cholangiocarcinoma are recognized, most tumors arise as sporadic cancers.

Pathology and Tumor Biology
- These tumors are primarily adenocarcinomas.
- Because a majority of patients present with advanced disease, only a small proportion of these tumors are amenable to curative resection.
- Hilar cholangiocarcinoma has a propensity for local invasion, which makes definitive treatment challenging.

Clinical Findings
- Although patients with cholangiocarcinoma or gallbladder cancer may present with jaundice, a majority of patients with liver neoplasms are asymptomatic.
- Patients with cirrhosis often are incidentally discovered to have hepatocellular cancer because of an elevated serum alpha-fetoprotein (AFP) level or a liver mass found on routine screening.

Differential Diagnosis
- Considerations in the differential diagnosis include secondary hepatic malignancies and benign neoplasms such as focal nodular hyperplasia, hemangioma, or adenoma.

Primary Therapy and Salvage Therapy
- Primary treatment for liver and bile duct neoplasms consists of complete surgical resection.
- For patients with unresectable disease, few effective alternative treatments are available.
- Patients with nonresectable disease are candidates for experimental therapy, liver function and performance status permitting.

Prognosis
- The overall survival rate for all patients with these tumors is less than 5%.
- The 5-year survival rate for patients with *resectable* disease is approximately 30% to 50%.
- Unfortunately, even after complete resection, recurrence is seen in a majority of cases. Clearly, more effective adjuvant treatment is needed.

HEPATOCELLULAR CANCER

INTRODUCTION

HCC is a major worldwide public health problem. In the developing world, HCC has long been considered a priority oncologic problem, and in certain parts of the world, it is the most common solid organ tumor. In recent times, awareness of HCC also has increased in the developed world as a result of markedly rising incidence rates. A greater investigational energy has been focused on optimal management of this disease, and better systemic therapies are emerging. Nevertheless, the main therapeutic modality that can be considered curative is surgical resection.

Surgical resection is reliant on the remarkable regenerative powers of normal liver tissue. For Prometheus, strapped to a rock on the Caucasus mountains, a giant eagle returning daily to tear at his newly regenerated liver, this cycle of recovery was a cursed and unending punishment for giving the gift of fire to mortal beings. For modern patients and their physicians, the power of the liver to absorb, regenerate, grow, and function as a critical organ through the range of surgical and radiologic techniques, chemotherapy regimens, and emerging novel therapies, means that the myth of Prometheus has happier connotations as these strategies are integrated to better affect outcome.

EPIDEMIOLOGY

HCC is the fifth most common malignancy in the world.[1] Approximately half a million cases are diagnosed annually.[2,3] Wide geographic

and temporal variability has been recognized with regard to incidence rates, reflecting the different patterns of exposure to underlying risk factors for the development of the disease. Approximately 80% of cases worldwide arise in the developing world, where the major etiologic factor is exposure to HBV.[4] The highest-risk areas include eastern and southeastern Asia (median age-adjusted incidence rates [AAIRs] 35.5 and 18.3 per 100,000, respectively), middle Africa (median AAIR 24.2 per 100,000), eastern Africa (median AAIR 14.4 per 100,000), and parts of western Africa.[5] Even within these geographic areas, wide variations exist. Intermediate-risk areas include eastern and western Europe (median AAIR 5.8 per 100,000), northern Africa (AAIR 4.9 per 100,000), and South America (AAIR 4.8 per 100,000). The areas at lowest risk are northern Europe, Australia, New Zealand, and North America (AAIR 2.1 to 4.1 per 100,000). Temporal variations exist in the development of HCC, reflecting different patterns of exposure to etiologic factors. In high-risk areas, the age-specific incidence rates begin to increase after the age of 20 years, reflecting the importance of vertical transmission of HBV or acquisition of HBV infection in early childhood, and stabilizes at age 50 and above.[5] In low-risk areas, the incidence rate steadily increases with age, reflecting the later acquisition of viral infection or the impact of other factors such as alcohol-related cirrhosis. It also has been observed that in high-risk areas that have undergone development, the pattern of age-specific incidence rates resembles that in low-risk areas. In all populations, males are affected at a higher frequency than that for females.[6] The male-to-female ratio is further increased in high-risk areas.[5] The risk for migrants from high-risk areas remains high when compared with that for the host population into which they settle.[7] For instance, a 1.3- to 10.9-fold excess mortality from primary liver cancer (predominantly HCC) is reported among Asian migrants to North Ameica, Australia, or Europe.[7–9] Some studies have observed a diminution in risk in the descendants of migrants and in migrants living for a long time in the host country.[5,10] North America, although still categorized as a low-incidence region, has seen a dramatic increase in the incidence of HCC, owing primarily to an increasing incidence of HCV infection. El-Serag and coworkers reviewed records of 1605 patients diagnosed with HCC between 1993 and 1998 in 171 Veterans Affairs (VA) hospitals.[11] These workers noted a threefold increase in the age-adjusted rates for HCC associated with HCV, from 2.3 per 100,000 between 1993 and 1995 to 7.0 per 100,000 between 1996 and 1998.

ETIOLOGY AND PATHOGENESIS

An estimated 60% to 80% of patients present with HCC in the context of cirrhosis from liver parenchymal disease.[1] The risk factors for the development of HCC are therefore synonymous with those for the development of cirrhosis. The pattern of exposure to risk factors is age- and region-dependent. In broad terms, HCC occurring in developing countries generally is related to HBV infection in a younger population.[12] The impact of cofactors such as alcohol or tobacco use is less important than in the developed world, with the exception of aflatoxin contamination of food. The scale of the hepatitis B problem in the developing world is immense.[13] It is estimated that 360 million persons have chronic HBV infection.[14] Spread is predominantly by vertical transmission at the time of birth or by horizontal transmission in early childhood.[15] The probability of acquiring HCC increases with severity of liver disease. The annual risk of HCC is 0.5% for asymptomatic hepatitis B surface antigen carriers, whereas it rises 1000-fold in patients with HBV-associated cirrhosis.[16,17] In developed countries, the major etiologic factors consist of alcohol-induced cirrhosis and hepatitis C.[18] The annual incidence of HCC in the context of HCV-associated cirrhosis is 3% to 8%.[13,19] Nonalcoholic fatty liver disease (NAFLD) has emerged in recent times as an important cause of liver disease including HCC. This condition is associated with obesity, insulin resistance, and hyperlipidemia and commonly manfests with an asymptomatic elevation of liver enzymes. In a follow-up study of 129 patients with biopsy-proven NAFLD, HCC developed in 2.3% over a mean follow-up period of 13.7 years.[20] Other causes of HCC include hereditary hemachromatosis, Wilson's disease, and exposure to chemicals such as arsenic. An association between diabetes mellitus and HCC has been reported.[21] The relationship between tobacco use and HCC is unclear at present.

PATHOLOGY

HCC is an adenocarcinoma that may appear grossly as unifocal, multifocal, or diffusely infiltrative. With all patterns of HCC, a strong propensity for invasion of vascular channels is typical. Histologically, HCCs range from well-differentiated lesions that reproduce hepatocytes arranged in cords or small nests to poorly differentiated lesions. A distinctive clinicopathologic variant of HCC is fibrolamellar carcinoma, which occurs in young adults and has no association with cirrhosis or other risk factors.[22]

TUMOR BIOLOGY

HCC can metastasize to lung and bone late in its course, but for many patients, the tumor manifests as local-regional disease. Commonly, even after a complete and potentially curative resection, tumor recurs in the liver, owing to the common inciting event of chronic damage to the hepatocytes from hepatitis or cirrhosis.

CLINICAL PRESENTATION AND PATIENT EVALUATION

A majority of patients present with locoregional disease; however, in the later stages of HCC, metastases can develop. Recurrences after surgery are either intrahepatic or extrahepatic, with the most common sites of extrahepatic metastasis being lung, retroperitoneal lymph nodes, and bone. Most patients with HCC have few symptoms until late in the disease, when tumors are at an advanced stage. Clinical manifestations may include malaise, anorexia, abdominal pain, abdominal fullness due to ascites or mass effect, or weight loss. Because a majority of cases of HCC occur in patients with underlying cirrhosis, any worsening of hepatic function in a patient with previously diagnosed cirrhosis must prompt an evaluation for occult HCC. After a liver lesion is discovered, the patient should be asked about a history of hepatitis and risk factors for the acquisition of hepatitis (such as blood transfusion), ethanol abuse, or family history of metabolic diseases such as hemochromatosis or α_1-antitrypsin deficiency, all of which are risk factors for the development of HCC.

LABORATORY AND IMAGING STUDIES

Screening Tests

Measurement of serum AFP is the most widely employed screening test for HCC in an at-risk population. This test is recommended by the European Association for the Study of the Liver.[23] Unfortunately, its reported sensitivity ranges from only 25% to 65%,[24] prompting some authors to sound the death knell for serum AFP determination as a screening tool.[25] In a study of 1158 patients with HCC, it was found that serum AFP assay had a 54% sensitivity for a cut-off value of 20 ng/ml.[26] Only 18% of the patients had a serum AFP level in the diagnostic range (greater than 400 ng/ml). This study, however, in common with other AFP studies, had several methodologic flaws,[27] and properly conducted prospective studies are needed to address the issue of its utility in more definitive fashion.

One prospective study in an HBV carrier population randomized 5581 males to undergo either AFP testing every 6 months or no screening.[28] Although more HCCs (257 versus 117) and more early-stage cancers (28% versus 6%) were diagnosed in the screened population, overall survival was not different between the screened and unscreened populations.

The reported specificity in the literature ranges from 79% to 95%.[24] Elevated serum AFP does correlate with advanced tumor-node-metastasis (TNM) stage and other factors such as portal vein thrombosis and is associated with a poor outcome.[26,29] The role of other serologic tests such as assays for des-γ-carboxy prothrombin (DCP), *Lens culinaris* agglutinin-reactive fraction (AFP-L3), and insulin growth factor-1 (IGF-1) is unclear at present.[30]

Adjunctive screening with ultrasonography on an every 6-month basis also is recommended by published guidelines.[23] Of note, however, randomized controlled trials demonstrating a mortality reduction for this approach are lacking. The sensitivity and specificity of screening ultrasound in high-risk patients are 71% and 93%, respectively.[31] In one study in Taiwan with a high endemic hepatitis B infection rate, screening ultrasound examination in a selected at-risk population was found to decrease HCC-related mortality,[32] Ultrasound examination is cheap and safe but has low sensitivity for detection of small nodules, and its usefulness in this regard is particularly operator-dependent. Newer techniques such as helical computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI) have a sensitivity exceeding 80%; however, their impact on mortality rates in at-risk populations needs to be evaluated prospectively before they are applied widely.

One randomized controlled trial has been performed using combined AFP testing and ultrasound examination ever 6 months in a defined "at risk" population. Nearly 19,000 people with HBV infection or a history of chronic hepatitis were randomized to undergo screening with ultrasound examination and AFP testing every 6 months or no screening. The study showed that screening reduced the HCC-related mortality rate by 37%.[33] Screening has not been proved to effect a mortality reduction in a Western population; however, it is unlikely that such proof in the form of a randomized controlled trial will be forthcoming, in view of the questionable ethics of randomizing at-risk persons to a control group.

In evaluating a potential screening test, it is vital to examine the effect on mortality rate, because any screening test has the potential to increase apparent median survival times by virtue of a lead-time bias. In addition, because of the global nature of this problem, any screening test should be cheap, relatively easy to perform, and reproducible.

Diagnostic Studies

All patients with suspected HCC also should undergo hepatitis serologic studies, including testing for hepatitis B surface antigen and hepatitis C polymerase chain reaction (PCR) assay. Depending on the degree of underlying liver damage from fibrosis, results on liver function testing and the prothrombin time may be abnormal. An assessment of liver function should be performed; the most commonly used assessment with the most widespread availability is the Child-Pugh score (Table 84-1). In cases in which an elevated AFP level and liver imaging findings suggest HCC, biopsy is unnecessary if the lesion is treatable with curative intent. In uncertain cases (normal AFP level or equivocal imaging findings, or both), biopsy may be indicated.

Table 84-1 Modified Child-Pugh Classification for Assessing Degree of Liver Impairment

Criterion	1 Point	2 Points	3 Points
Bilirubin	≤2	2–3	>3
Albumin	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.2	>2.2
Ascites	None	Mild	Moderate
Encephalopathy	None	Mild	Moderate

INR, international normalized ratio.

Adding the points for each patient's factors determines the Child-Pugh "class" as follows: A = 5–6 points, B = 7–9 points, C = 10–15 points.

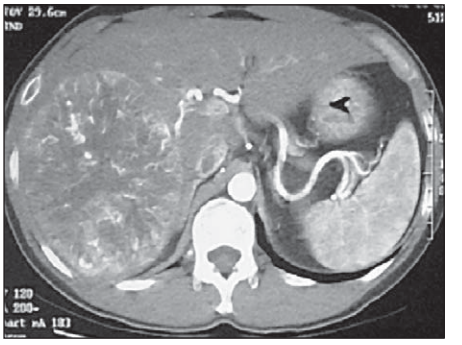


Figure 84-1 • Dynamic computed tomographic scan of a hypervascular right lobe hepatocellular cancer. (Courtesy of Spiros Hiotis, MD, New York University School of Medicine.)

Radiologic assessment in suspected HCC is extremely important in making the diagnosis and deciding which treatment modality is appropriate. Although ultrasound examination is widely available and therefore is often the first imaging study used to examine the liver in a patient suspected to have HCC, ultrasonography in fact is a poor test for characterizing liver lesions in patients with cirrhosis, in whom regenerating nodules often can be mistaken for tumor. On ultrasound scans, HCC typically will have a thin halo, lateral shadows, and posterior echo enhancement.

A more useful imaging test is dynamic CT. In the early phase, the tumor is seen as hyperdense because of its increased vascularity (Fig. 84-1). In the later phase, the tumor is seen as hypodense, as a result of washout of contrast from the more "porous" lesion. Magnetic resonance imaging (MRI) is becoming more frequently used as an imaging modality for evaluation of HCC. On MRI, HCC appears to be of low signal intensity on T_1-weighted images and of intermediate signal intensity on T_2-weighted images. MRI also can be useful in distinguishing HCC from benign lesions such as hemangiomas and regenerating nodules. Because of the propensity of this tumor type for extension into and along major vessels, contrast-enhanced CT or MRI is particularly useful for imaging the portal and hepatic veins. In addition, contrast-enhanced images provide critical information about multifocality, resectability, and presence of extrahepatic disease.

On imaging with CT or MRI, a common feature of HCC is its ability to invade vascular structures, such as the inferior vena cava (Fig. 84-2) or portal vein (Fig. 84-3). The tumor thrombus, which actually is an extension of the tumor itself into the vasculature, can be well seen on contrast-enhanced CT or MRI. The classic appearance is that of a mass within the vasculature, which fills and expands the lumen.

The angiographic appearance of HCC can be even more diagnostic because these tumors characteristically are hypervascular. Because angiography is invasive, it is difficult to recommend routine use of this study for diagnostic purposes. Angiography often is used, however, for therapeutic applications, such as tumor embolization with thrombotic agents with or without chemotherapy, and often detects small tumors not seen on other imaging modalities.

Although positron emission tomography (PET) using fluorine 18-labeled fluorodeoxyglucose (^{18}FDG) has been found to be useful to image a variety of tumors, its use in HCC has yielded disappointing results, with significantly lower standardized uptake value (SUV) for HCC compared with metastatic tumor or other primary liver tumors,[34] and an accuracy of 20% to 50%.[35–37] This is at least partly due to the marked difference in biologic behavior of these tumors, with high-grade tumors demonstrating increased SUV compared with lower-grade tumors.[37] Some investigators have found the SUV to be of prognostic value in those patients undergoing transplanta-

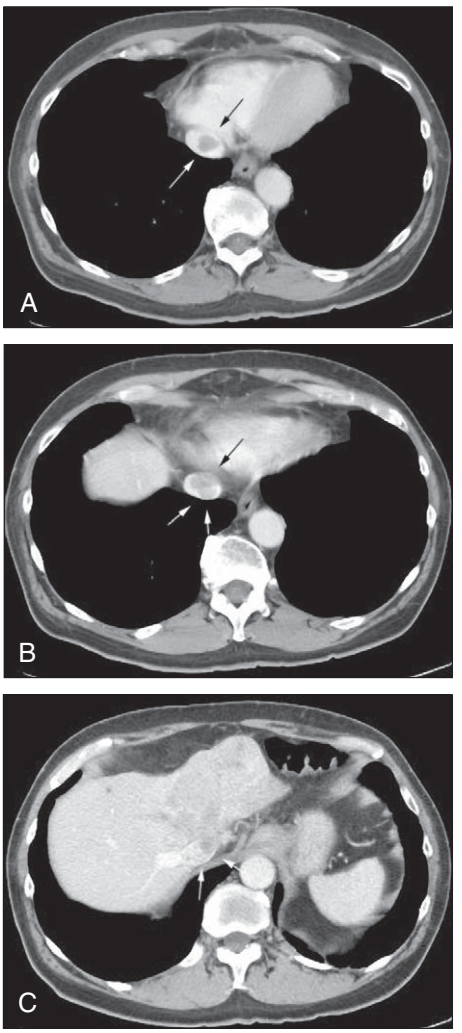


Figure 84-2 • **A–C**, Left lobe hepatocellular cancer with tumor invasion into the inferior vena cava *(arrows)*.

tion, although the practical significance of this variable is unclear.[37,38] The areas of greatest potential impact for FDG-PET appear to be in detecting extrahepatic disease before transplantation or resection and, in particular, in assessing response to therapy.[39,40] This latter role may be especially relevant in the era of novel therapeutics, which may result in metabolic changes in the tumor, rather than conventional response evaluation criteria in solid tumors (RECIST)-type dimensional changes.

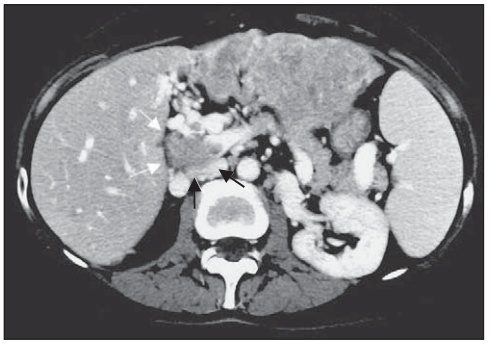


Figure 84-3 • Large left lobe hepatocellular carcinoma with vascular invasion into the portal vein, demonstrated by the classic finding of tumor thrombus filling and expanding the main portal vein *(arrows)*, with cavernous transformation of the portal vein.

STAGING CLASSIFICATION

The sixth edition of the American Joint Committee on Cancer (AJCC) staging classification uses size, presence of vascular invasion, lymph node status, and metastatic disease as prognosticators of outcome (Table 84-2). The main features of this revised system include the following: (1) all solitary tumors without vascular invasion, regardless of size, are classified as T1 because of similar prognosis; (2) all solitary tumors with vascular invasion, again independent of size, are combined with multiple tumors 5 cm or less in diameter and classified as T2 because of a similar prognosis; (3) multiple tumors larger than 5 cm and tumors with evidence of major vascular invasion are combined and classified as T3 because of a similarly poor prognosis; and (4) stage IV refers to metastatic disease only. The subcategories IVA and IVB have been eliminated.

The sixth edition classification has been validated by several investigators. Lei and colleagues applied the classification schemes from current and previous editions to a cohort of 440 patients who underwent curative resection for HCC and found that the current staging system accurately stratified patients into defined prognostic groups.[41]

Table 84-2 American Joint Commission on Cancer Staging System* for Hepatocellular Carcinoma Including Intra-Hepatic Bile Ducts: Tumor-Node-Metastasis (TNM) Classification

Stage	Grouping		
I	T1	N0	M0
II	T2	N0	M0
III-A	T3	N0	M0
III-B	T4	N0	M0
III-C	Any T	N1	M0
IV	Any T	Any N	M1

DEFINITIONS

Primary tumor (T)

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
T1	Solitary tumor without vascular invasion.
T2	Solitary tumor with vascular invasion; or multiple tumors, none more than 5 cm.
T3	Multiple tumors >5 cm, or tumor involving a major branch of the portal or hepatic vein(s)
T4	Tumor(s) with direct invasion of adjacent organs other than the gallbladder or with perforation of the visceral peritoneum.

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

*As published by the American Joint Commission on Cancer: AJCC Cancer Staging Manual, 6th ed. New York, Springer, 2002.

Table 84-3 Results of Hepatic Resection for Hepatocellular Carcinoma in Noncirrhotic versus Cirrhotic Patients

Study	No. of Patients	Operative Mortality (%)	Survival (%)		
			1-Year	3-Year	5-Year
NONCIRRHOTICS					
Iwatsuki et al, 1991[73]	59	12 (90 d)	81	60	44
Nagasue et al, 1993[60]	52	6	87	66	55
Fong et al, 1999[50]	54	4	83	58	42
Belghiti et al, 2002[58]	58	3	95	78	50
CIRRHOTICS					
Tsuzuki et al, 1990*	80	9	82	60	45
Nagasue et al, 1993[60]	177	12	77	43	21
Fong et al, 1999[50]	100	5	77	47	37
Belghiti et al, 2002[58]	168	10	78	55	34

*Tsuzuki T, Sugioka A, Ueda M, et al: Hepatic resection for hepatocellular carcinoma. Surgery 1990;107:511–520.

PROGNOSIS

HCC is unique among other gastrointestinal cancers in that it frequently occurs in the setting of an already diseased organ. The prognosis therefore depends not only on an anatomic assessment of the tumor, as reflected by the TNM system, but also on the extent of underlying liver damage. Scoring systems that evaluate only tumor characteristics (e.g., TNM) or only liver function (e.g., Child-Pugh) are deficient. A number of prognostic scoring systems have attempted to incorporate non-tumor-related factors to better define prognosis. The Barcelona Clinic Liver Cancer (BCLC) staging classification divides cases into four categories of differing severity.[42] The Cancer of the Liver Italian Program (CLIP) looks at Child-Pugh class, tumor morphology (number of nodules and volume), AFP level, and presence of portal vein thrombosis.[43] This scoring system has been externally validated by a number of studies[43,44] and has been recommended by the American Hepato-Pancreatic-Biliary Association/American Joint Commission on Cancer Consensus Conference on Staging of Hepatocellular Carcinoma.[45] Because of differing prognoses for patients with HCC stemming from ethnic diversity and variation in viral etiology (e.g., either HBV- or HCV-related), it is unlikely that one scoring system will suffice for all populations. For example, the Chinese University Prognostic Index (CUPI) was developed in a cohort of patients with predominantly HBV-related HCC and may be more applicable to that population.[46]

Outcome

Overall survival after liver resection or transplantation has been reported from numerous investigators (Tables 84-3 to 84-5). In patients with unresectable disease, the survival rate is dismal, with a median survival time shorter than 12 months even with chemotherapy.[47,48]

Patterns of Recurrence

At 5 years after resection of HCC, the recurrence rate has been reported to be between 30% and 60%.[49–51] Cirrhotic patients experience recurrence at a much greater rate than that observed for noncirrhotic patients. The liver is the first site of recurrence in up to 90% of these patients.[49,52,53] Other common sites of recurrence include lung, peritoneum, bone, and brain.[54,55] It is uncommon for patients to present with isolated extrahepatic recurrences.[54] The median time to

Table 84-4 Results of Total Hepatectomy with Orthotopic Hepatic Transplantation for Hepatocellular Carcinoma

Study	No. of Patients	Follow-up (mo)	Operative Mortality (%)	Recurrence Rate (%)	Survival (%)		
					1-Year	3-Year	5-Year
Bismuth et al, 1993[66]	60	Not stated	5		75	47	
Schwartz et al, 1995[70]	57	Not stated	19 (90 d)	5	75	65	NR
Pichlmayr et al, 1997*	124	36			83	77	76
Llovet et al, 1998[71]	58	31	14 (90 d)		84	74	74
Bruix and Llovet, 2002[69]; Iwatsuki et al, 1991[73]	344	Not stated	14 (90 d)	24	73	59	49
Jonas et al, 2001†	120	49	2	17	90		71
Zavaglia et al, 2005‡	155	49			84	75	72

*Pichlmayr R, Weimann A, Tusch G, et al: Indications and role of liver transplantation for malignant tumors. Oncologist 1997;2:164–170.

†Jonas S, Bechstein WO, Steinmuller T, et al: Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. Hepatology 2001;33:1080–1086.

‡Zavaglia C, De CL, Alberti AB, et al: Predictors of long-term survival after liver transplantation for hepatocellular carcinoma. Am J Gastroenterol 2005;100:2708–2716.

Table 84-5 Results after Resection for Early Hepatocellular Carcinoma

Study	No. of Patients	5-Year Survival (%)	Median Survival (mo)	Disease-Free Survival (%)
Llovet et al, 1999*[67]	77	51	65	25
Poon et al, 2001†	135	70	—	36
Cha et al, 2003‡[68]	36	69	71	48

*Early HCC defined as single tumor <5 cm in size.

†Early HCC defined as those that fit the Milan criteria (single tumor <5 cm in size or ≤3 tumors <3 cm in size). Poon RT, Fan ST, Lo CM, et al: Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. Ann Surg 2002;235:373–382.

‡Early HCC defined as those that fit the Milan criteria (single tumor <5 cm in size or ≤3 tumors <3 cm in size).

recurrence is approximately 24 months, although the range is highly variable.[55]

The most well-accepted risk factors for recurrence include tumor size, multifocal disease, vascular invasion, and high preoperative AFP level.[50,53,56–59] Other risk factors include tumor differentiation,[58] tumor rupture,[57] and cirrhosis,[53,57,60] particularly when tumors are stratified according to size.[50] Of interest, multifocal HCC has been found to be a risk factor for recurrence in few studies.[61,62] Some evidence also suggests that outcome after resection is improved in patients with HCC associated with hepatitis B compared with that in patients with hepatitis C-associated HCC.[63]

PRIMARY TREATMENT

Resection

Partial Hepatectomy

Surgical excision by partial or total hepatectomy represents the only potentially curative therapy for HCC. Resectability for any hepatic tumor, including HCC, is dependent on the patient's ability to withstand a major surgical intervention, absence of extrahepatic disease, and favorable anatomic criteria. The results of surgical resection are influenced greatly by the preoperative liver functional status. Cirrhosis adversely influences surgical outcome in many ways and often is the only determinant that results in an unresectable status. Because the liver parenchyma in cirrhotic patients is fibrotic and firm, retraction and isolation of intraparenchymal vessels are hazardous surgical maneuvers that are associated with increased risk of hemorrhage during resection of HCC. Patients with cirrhosis also are likely to have thrombocytopenia related to portal hypertension, further exacerbating the potential for hemorrhage. Indeed, portal hypertension, even in the face of relatively well preserved hepatic synthetic function, is an ominous finding and generally excludes resection as a treatment option. Finally, cirrhosis is associated with decreased regenerative capacity, increasing the risk of liver failure after partial resections. For these reasons, hepatic resection in patients with cirrhosis carries a significantly higher operative risk than that associated with resection in noncirrhotic patients, and patients with cirrhosis and HCC typically are better served with transplantation if indications regarding tumor size and number are present.

Outcome after resection in noncirrhotic patients is excellent; partial hepatic resection can be performed with a less than 5% operative mortality rate and is associated with a 5-year survival rate in excess of 30% (see Table 84-3). For noncirrhotic patients with resectable tumors, therefore, surgical resection represents the treatment of choice. The adverse influence of cirrhosis on surgical outcome, however, is well documented by clinical data: The operative mortality rate is greater than 10% even at large-volume centers (see Table 84-3). Nevertheless, cirrhotic patients who survive the operation have a 5-year survival rate of approximately 30% (see Table 84-3).

Thus, patient selection for surgery depends primarily on hepatic function. Over the years, many complex methods of evaluating liver function have been tested to assist in patient selection. Assessment by Child-Pugh classification (see Table 84-1) remains the most useful and most widely used in western series, although the indocyanine green (ICG) retention rate commonly is used in Asia. Few surgeons are willing to perform hepatic resection for patients with Child-Pugh C liver status, and the operative mortality rate may be as high as 30% for patients with Child-Pugh B cirrhosis. These patients clearly are better served with transplantation if they meet accepted criteria. Therefore, most surgeons will consider resection only for patients with Child A, or in some cases, Child B, liver function. In patients with cirrhosis but with preserved liver function, no difference in long-term survival has been observed even when a larger tumor size required extended hepatectomy, rather than more limited resection.[64,65]

HCC has a great propensity for vascular extension, and the presence of tumor thrombus within the main portal vein or vena cava (see Figs. 84-2 and 84-3) is an ominous sign that should be regarded as a contraindication to resection. Liver resections accompanied by portal venous tumor thrombectomies are unlikely to yield long-term survival. Multiple lesions do not preclude surgical resection or ablation (or both),[50,60,66] because, in the highly selected patients whose tumor is amenable to complete resection or ablation, 5-year survival rates can still be expected to be between 20% and 30%.[50,60]

Total Hepatectomy and Transplantation

Total hepatectomy and liver transplantation is an attractive option for the patient with cirrhosis and cancer, because it may potentially cure both the underlying liver disease and the tumor. Generally well-accepted indications for liver transplantation (Milan criteria) include Child-Pugh B or C status in patients with a single HCC less than 5 cm in size, or fewer than three tumors all less than 3 cm in diameter. Using these criteria, the most recent series have found a 5-year survival rate of approximately 70%, with a 15% chance for recurrence (see Table 84-4). In comparing the results of transplantation with those of resection, it is important to recognize the inherent selection bias of choosing not only those patients with small HCC, associated with a better prognosis, but additionally the bias of performing transplantation only in those patients whose disease has not progressed while they are waiting for an organ. Thus, the patients who receive liver transplants are those whose tumors have a less aggressive natural history. This point is demonstrated by a recent intention-to-treat analysis that found "drop-out from waiting list" to be the sole survival predictor.[41] This study noted that the 2-year survival rate of patients evaluated for transplantation was reduced from 84% to 54% during two separate time periods in which the waiting time increased markedly, so that more patients were excluded from transplantation as a result of progression of disease. Survival was significantly worse for patients on the transplant list than for patients who were the best candidates for resection.[67]

In addition, two recent papers have evaluated the outcomes in patients undergoing liver resection with tumors that fit the Milan criteria (see Table 84-5). In this select group of patients, the overall survival rate at 5 years was 70%, similar in outcome to that for liver transplantation.[59,68] As expected, the risk of intrahepatic recurrence in patients undergoing resection was higher than after liver transplantation. To address this problem, the authors suggested a strategy of salvage transplantation for those patients whose tumor recurs after hepatectomy.

In practice, many obstacles exist to limit the applicability of transplantation to a large number of patients worldwide. The greatest obstacle is the lack of available organs for transplantation. Some U.S. centers report long waiting times, with nearly equal numbers of patients being excluded from transplantation while on the waiting

list due to progression of disease and of those who receive transplants.[69] In Asian countries, where the need for donor organs is greater, and social and cultural obstacles to organ donation are the norm, livers are in even greater shortage than in the United States. In addition, because of organ scarcity, it is vital that a thorough cost-effectiveness analysis be performed to compare results after liver transplantation for benign versus malignant disease.

The cost associated with the transplantation procedure is also a major obstacle. Although perioperative morbidity and mortality rates are declining, in most centers, the mortality rate is still substantial. Table 84-4 summarizes some of the published data to date, including only relatively recent trials with more than 50 patients. It is clear that operative mortality rates can be as high as 10% to 20%,[70,71] and recurrence rates, as high as 50%,[72] in these series.[61] Nevertheless, for patients with liver dysfunction, total hepatectomy with liver transplantation represents the only potentially curative option, because few of these patients can tolerate major hepatectomy. To demonstrate this point, in noncirrhotic HCC, survival is similar after hepatectomy or transplantation, whereas in patients with cirrhotic HCC, survival was significantly improved after transplantation compared with hepatectomy at each TNM stage.[73]

Long term results of HCC treated by transplantation also are related to extent of original liver involvement, with the best results reported in patients with small HCCs discovered incidentally during transplantation performed for cirrhosis.[74] Clearly, large tumor size and the presence of vascular invasion are associated with a higher risk for recurrence after transplantation.[61,75,76]

Recently, several authors have reported the results of living related donor liver transplantation (LDLT) for HCC. Because this procedure requires a right hepatectomy in a healthy donor, concerns have arisen about the safety and ethical implications of this procedure. In addition, sporadic reports of deaths in donors from the United States and elsewhere have intensified these concerns. In one of the largest series reporting the results of LDLT in 71 patients, with approximately 40% due to HCC, the mean waiting time to transplantation was markedly reduced from 414 (for cadaveric organ transplants) to 83 days (for living related donor transplants), with a recurrence rate of 15%.[77]

To summarize, patients with HCC without liver dysfunction should be considered for resection, whereas patients with HCC arising in the setting of Child-Pugh B or C cirrhosis, and with disease extent meeting the Milan criteria, should be referred for transplantation.

Cryosurgery

Cryoablation is becoming an increasingly popular method for treating HCC. In this modality, probes that are cooled by liquid nitrogen or argon are introduced into tumors, followed by freezing under ultrasound guidance until an adequate volume of tumor plus a 1-cm margin has been treated (Fig. 84-4). Cryosurgery has great theoretical advantage in the treatment of tumors in cirrhotic patients in that very little nonmalignant parenchyma is damaged; thus, patients with cirrhosis often are still candidates for the procedure. In addition, this technique is useful for treating bilobar tumors, whether with cryosurgery alone or with cryosurgery plus resection.[78]

The major disadvantage is the need for general anesthesia and laparotomy, because this technique generally is not performed percutaneously. In addition, some tumors are not treatable with cryosurgery, primarily owing to size, because it is clear that complications increase as more tumor volume is destroyed. A number of series have been published clearly demonstrating safety of such an ablative approach in experienced hands.[78,79]

Radiofrequency Ablation

Radiofrequency ablation (RFA) is an excellent alternative to cryosurgery and offers the advantage of percutaneous as well as intraoperative application (Fig. 84-5). Some authors have suggested that both the complication rate and the recurrence rate after RFA is lower than after cryosurgery.[79] No true prospective comparative trials, however, have been conducted. The disadvantage of RFA is that it is difficult to monitor under real-time ultrasound guidance, unlike in cryosurgical ablation, because no distinct demarcation between viable tissue and RF-ablated tissue can be seen. In a comparison of ethanol injection and percutaneous RFA, data from a randomized trial showed improved 4-year survival after RFA (74%, versus 57% after ethanol injection).[80]

In the largest study on the use of RFA in patients with cirrhosis and HCC, 194 patients underwent RFA of their tumor.[81] The complication rate was 12%, with local recurrence in only 5% after a median follow-up period of 35 months, although recurrent disease developed at other sites within the liver in a large number of patients. Of note, one of the additional advantages of RFA is that it is useful for treatment of recurrent disease.[82]

Microwave Ablation

Ablation of liver tumors using percutaneous microwave coagulation is a relatively new technique that will require further prospective trials before the technique can be widely adapted to treatment for HCC. The advantages of this technique are the higher temperatures it can achieve in a shorter time and the capability for use of multiple probes. In a preliminary study, survival rates for patients with primary disease and recurrent HCC were 47% (5-year) and 50% (4-year), respectively.[83]

Ethanol Injection

Percutaneous ethanol injection is a highly effective treatment for small HCC, with a 3-year survival rate of 60%[84] and a 5-year survival rate of 45%.[85] In this technique, absolute alcohol is injected into liver tumors percutaneously under CT or ultrasound guidance, which results in tissue necrosis[86] (Fig. 84-6). Tumors that are amenable to ethanol injection include those less than 4 cm in diameter, and usually fewer than 4 in number. This method may be curative for small lesions, but trials comparing this technique with other methods of ablation are needed.

In one of the only studies comparing ethanol injection with RFA for patients with small HCC, effective tumor necrosis occurred using either technique, but RFA required fewer treatments to achieve this effect (1.2 sessions for RFA versus 4.8 sessions for ethanol). More complications, however, occurred in the patients undergoing RFA.[87] Thus, treatment decisions for these patients should be individualized.

Hepatic Artery Embolization

Because a large majority of patients present with liver-only disease, which is technically unresectable owing to the presence of multiple, bilateral tumors or underlying hepatic dysfunction, other forms of therapy are acutely needed for HCC. These tumors are intensely vascular and are fed primarily by the hepatic artery; accordingly, embolization of the feeding arterial vessels has been shown to be one possible treatment option for these patients. A recent randomized controlled trial (RCT) compared patients with Child A or B cirrhosis with unresectable HCC who were randomized to receive treatment by chemoembolization or embolization or conservative treatment. The trial was stopped early because of the finding of a survival advantage for chemoembolization, with a 2-year survival rate of 63%, compared with 27% for control and 50% for embolization.[88] In addition, in a prior RCT performed by the same investigators, no difference was noted in survival for embolization compared with conservative treatment.[89] Lee and colleagues assessed the benefits of transcatheter arterial chemoembolization compared with standard hepatic resection in an Asian population of 182 patients. Both groups received initial chemoembolization performed using lipiodol CT. Ninety-one patients who subsequently underwent surgery and 91 who refused surgery were allocated to receive serial chemoembolizations. These investigators observed that chemoembolization appeared to be as effective as resection in the population of patients with locally

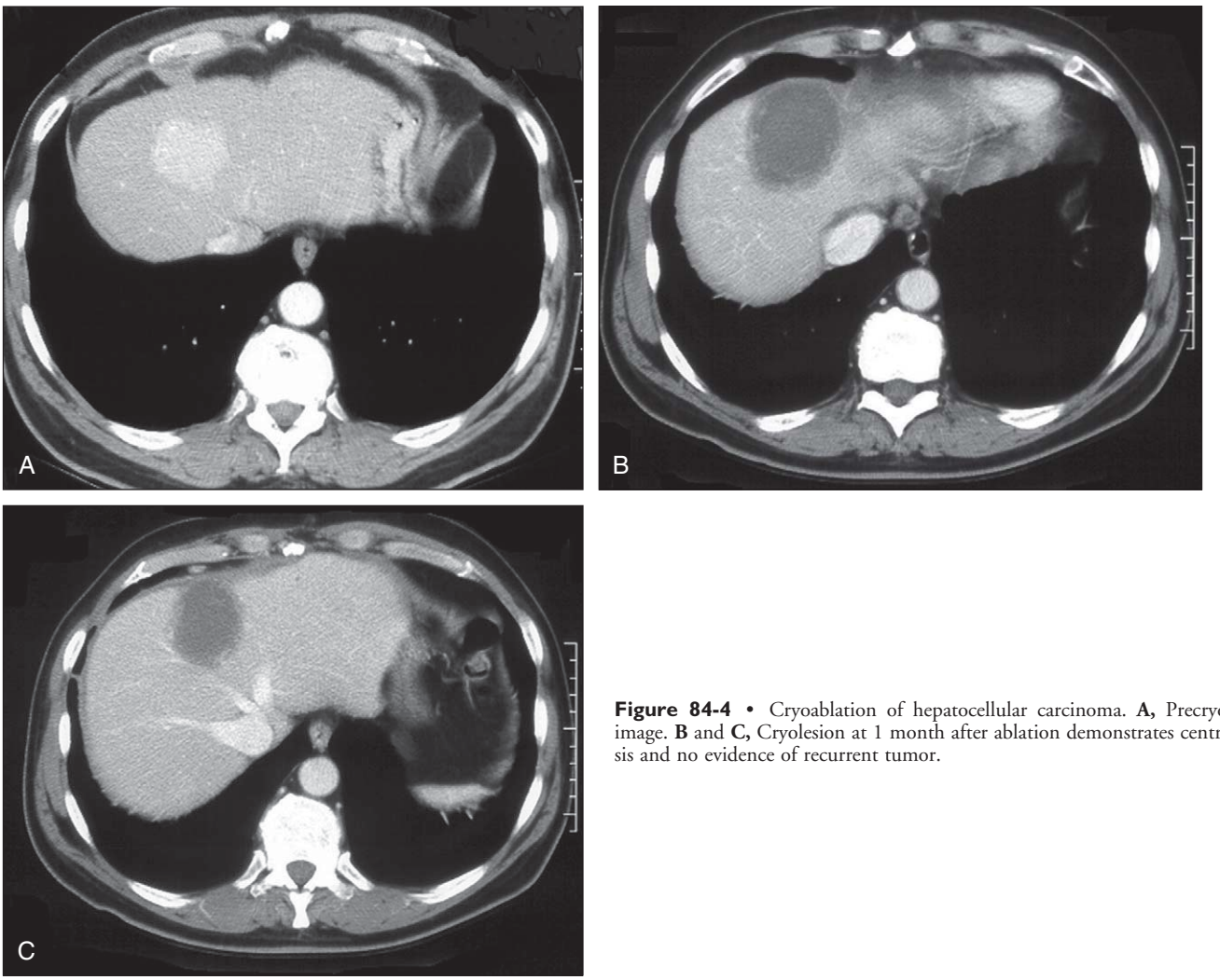


Figure 84-4 • Cryoablation of hepatocellular carcinoma. **A,** Precryoablation image. **B** and **C,** Cryolesion at 1 month after ablation demonstrates central necrosis and no evidence of recurrent tumor.

advanced liver tumors with adequate liver function. Thus, chemoembolization appears to be a potentially viable treatment option for patients with either unresectable or resectable disease, and additionally, it may have an advantage over conservative treatment.

Chemotherapy

It is a fair summation of more than 20 years of investigational work that systemic chemotherapy has had a disappointingly low level of impact on this disease.[90] This limitation is related mainly to the inherent insensitivity of HCC to chemotherapeutics.[91] HCCs express the multidrug-resistant gene *MDR1*,[92] and the underlying hepatic dysfunction that often accompanies HCC precludes or limits aggressive systemic therapies. The most well-studied agent has been doxorubicin.[90] In two recent phase III studies in which doxorubicin therapy served as the control treatment, response rates of 4% and 10.5% were observed for single-agent doxorubicin, with median survival times of 31 weeks and 6.8 months respectively.[93,94] A range of other chemotherapeutic agents, including cisplatin, gemcitabine, capecitabine, paclitaxel, irinotecan, etoposide, and fludarabine, have been investigated and found to have minimal activity.[95–101]

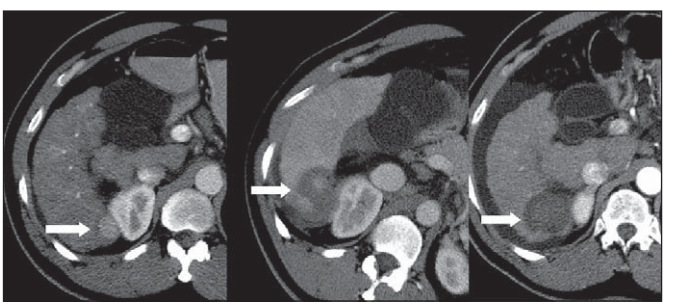


Figure 84-5 • Percutaneous radiofrequency ablation of hepatocellular carcinoma *(arrow)* in a high-risk patient with advanced cirrhosis. *Left panel*, Preablation image; *middle and right panels*, postablation images.

Combination chemotherapy is associated with modestly improved response rates at the expense of greater toxicity. No clear standard has emerged. One of the more promising but toxic combinations is a regimen of cisplatin (Platinol), interferon-α-2b, doxorubicin (Adriamycin), and 5-fluorouracil (5-FU) (PIAF), initially published by Leung and coworkers.[102] The initial phase II report was provocative, noting a high partial response rate of 26%, and of the patients with a baseline elevation of AFP level, 42% demonstrated a greater than 50% decline in AFP level with treatment. Additionally, nine patients were able to undergo surgery, and in four, no evidence of viable tumor was noted at the time of surgery. Of concern was the high rate of myelosuppression and mucositis, and two treatment-related deaths occurred in the context of neutropenic infection. Poor prognostic factors predictably included high Okuda stage, presence of cirrhosis, and vascular involvement.

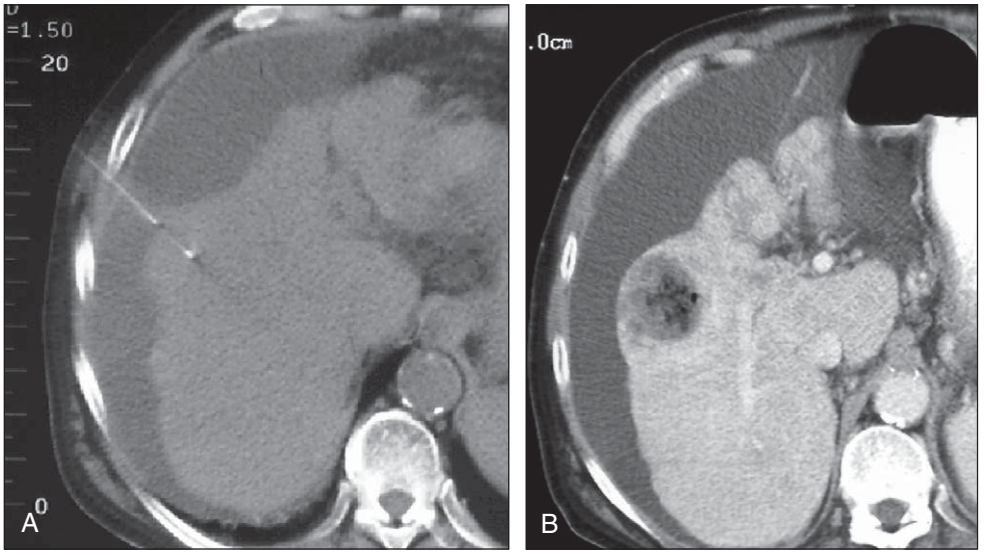


Figure 84-6 • **A,** Percutaneous needle placement under noncontrast computed tomography (CT) guidance for alcohol ablation of small hepatocellular carcinoma in a cirrhotic patient with ascites. **B,** Post-ablation contrast-enhanced CT scan.

Subsequently, Yeo and associates reported a randomized phase III study of 188 patients comparing PIAF with doxorubicin as a single agent.[94] No statistically significant difference in median survival times was found. The combination of gemcitabine and oxaliplatin has been investigated by Taieb and colleagues in a small trial (comprising 21 patients) using two different schedules.[103] Overall response rate was 19%, with disease stabilization in 48% and a median survival time of 12 months.

Novel Therapies

The poor efficacy of chemotherapy in this tumor type probably means that merely combining cytotoxics in different regimens is a strategy unlikely to result in dramatic advances in the way this disease is treated. It is likely that the combination of chemotherapy with so-called biologic therapies—that is to say, therapies that are targeted to a particular known aspect of tumor biology—offer the best hope for more effective therapies in the intermediate-term future.

HCC is a vascular tumor. As in other diseases, high levels of circulating vascular endothelial growth factor (VEGF) have correlated with a poor prognosis.[104,105] The proof of the therapeutic principle of anti-VEGF therapy has been demonstrated in colorectal, breast, and lung cancer with bevacizumab,[106] a humanized monoclonal antibody that targets VEGF. Sorafenib is an oral multikinase inhibitor that targets VEGF receptor (VEGFR) (−2/−3), in addition to RAF kinase and PDGFR-β tyrosine kinases.[107] Abou-Alfa and colleagues performed a large phase II study examining the use of single-agent oral sorafenib in 137 patients with inoperable HCC and Child-Pugh A or B status, with no prior systemic treatment.[108] Median time to disease progression was 4.2 months, and median overall survival time was 9.2 months. Although objective partial response rate was 2.2%, 33.6% achieved stable disease. At the ASCO 2007 annual meeting, data were presented from a large phase III placebo-controlled trial of sorafenib for the first-line treatment of HCC.[109] In this important study, 602 patients with well-preserved liver function (Child-Pugh A status in greater than 95%) were randomized to receive either placebo or sorafenib 400 mg twice daily. Median overall survival, the primary endpoint of the study, was significantly better for the sorafenib arm (10.7 vs. 7.9 months; hazard ratio, 0.69; 95% CI, 0.55 to 0.87; $P = 0.0006$), and the study was closed early because of the improved efficacy based on a preplanned stopping rule. This is the first study to demonstrate a statistically improved survival for any agent in patients with advanced HCC.

With regard to other antiangiogenic agents, bevacizumab has demonstrated only modest single-agent activity[110] in HCC phase I studies. This finding mirrors the experience in other diseases, in which the best results were obtained in combination with chemotherapy. Zhu and associates performed a phase II trial of bevacizumab with a gemcitabine-oxaliplatin combination,[111] obtaining a relative risk of 20%, with stable disease in 27%, median progression-free survival time of 5.3 months, and median overall survival time of 9.6 months. Ligand binding of epidermal growth factor receptor (EGFR) can lead to activation of the Ras/Raf/Erk/MAPK cascade, which is believed to be of major importance in HCC carcinogenesis.[112] EGFR can be inhibited extracellularly by antibody binding or intracellularly through inhibition of its tyrosine kinase. Cetuximab is a chimeric monoclonal IgG1 antibody directed against the EGFR. It has been shown to arrest cell growth in HCC cell lines.[113] A phase II study however showed no activity in 30 patients with advanced HCC.[114] Erlotinib is an oral EGFR tyrosine kinase inhibitor. Two phase II studies have demonstrated modest efficacy in HCC.[115,116] The relative tolerability of erlotinib and its oral formulation makes it an attractive consideration for investigation in chemoprevention and in the adjuvant setting. The combination of erlotinib and bevacizumab also has been explored, with early evidence of activity for this combination in a phase II single-arm study that showed a 22% response rate and 55% progression-free survival at 16 weeks.[117]

Intra-arterial Chemotherapy

The regional administration of chemotherapy using the hepatic artery has the attraction of achieving high concentrations of drug in the liver and minimizing systemic exposure, particularly if drugs are used that undergo a high degree of first-pass metabolism. The usual coexistence of cirrhosis complicates the local delivery of drugs however, and possible arteriovenous shunting may result in unwanted systemic exposure.[118] Numerous small phase II studies have examined various combinations, the most common components being floxuridine (FUDR), mitomycin, doxorubicin, and cisplatin.[118–121] The optimal drug combination to be administered intra-arterially is not known. In a study of 116 patients with HCC and portal venous invasion (an adverse prognostic sign), Obi and colleagues administered thrice-weekly intramuscular interferon with alternate-week intra-arterial 5-FU. Nineteen patients (16%) achieved a complete response, and 42 patients (36%) had a partial response.[122]

ADJUVANT THERAPY

A compelling rationale exists for use of adjuvant therapy for HCC based on the high rate of intrahepatic and extrahepatic recurrence

after potentially curative resections, as well as the development of second primary tumors within the diseased liver. Unfortunately, no adjuvant strategy has been shown to be effective in prospective controlled studies.

In a prospective randomized controlled trial, 64 patients who underwent orthopic liver transplantation for HCC were randomized to receive doxorubicin or no adjuvant treatment.[123] No difference was observed in outcomes for the two arms. Schwartz and associates conducted a larger meta-analysis of 13 randomized trials, 3 involving systemic adjuvant therapy, 4 assessing the role of HA chemoembolization, and 6 assessing a variety of other therapeutic agents.[124] The overall conclusion was similar in that neither systemic or intra-arterial-based chemotherapy nor chemoembolization has been shown to improve overall or disease-free survival after resection, in comparison with that observed with no treatment. Reservations with regard to the quality of the data included small size of trials in patients with heterogeneous underlying liver function and a lack of documented effect for many of the agents tested in a setting of more advanced disease.

One provocative study from Hong Kong assessed a single-dose treatment of intra-arterial iodine 131-labeled lipiodol as adjuvant therapy compared with observation for patients with hepatitis B-related HCC.[125] The study was terminated early after 43 patients were enrolled when an interim analysis demonstrated a marked difference in survival for patients in the treatment group: 57.2 versus 13.6 months. The 3-year survival rates were 86.4% for the treatment group and 46.3% for the control group. Additional larger, randomized trials of this agent are needed in broader patient groups with HCC to investigate its utility.

Early invasion of tumor into the portal venous system is believed to be an important factor underlying postresectional tumor recurrence.[126] This potential mechanism for recurrence forms the basis for considering direct intraportal chemotherapy as an adjuvant strategy. In a small study, Chau and colleagues demonstrated that this approach using a combination of 5-FU, cisplatin, and doxorubicin was safe and feasible. When compared with case-matched control subjects, patients with early-stage disease who received this regimen demonstrated an improvement in disease-free and overall survival[127] (Box 84-1; Fig. 84-7).

OUTCOME AFTER TREATMENT OF RECURRENCE

Because recurrent HCC may be amenable to potentially curative resection, early detection of such recurrences is extremely important. Multiple series have shown that 5-year survival rates between 20% and 82% are possible in patients with recurrent HCC that is resectable.[52,128–131] In addition, repeated liver resection in this group is safe, as demonstrated by one study that found no difference in blood loss, operative time, and incidence of complications when comparing repeated liver resections with first-time resections.[128] Therefore, in patients found to be medically fit for surgery, with adequate liver reserve and technically resectable tumors, repeat hepatic resection is the therapy of choice. In patients who are not candidates for repeat resection but have isolated liver recurrence, liver transplantation may be possible. In patients who are not candidates for any surgical intervention, percutaneous RFA, microwave ablation, and ethanol injection are effective methods to treat recurrent liver disease.[82,83,85] In addition, transcatheter arterial embolization often is an option to treat recurrent HCC. One final option for treating unresectable disease is intra-arterial administration of yttrium 90 particles, although efficacy data are limited.[132]

TREATMENT COMPLICATIONS

After resection, postoperative morbidity occurs in approximately 40% of patients, consisting primarily of transient hepatic insufficiency, intra-abdominal abscess or biloma, gastrointestinal bleeding, and cardiopulmonary complications.[50] Postoperative mortality rates range from 3% to 12% in most series (see Tables 84-3 and 84-4). After transplantation, the 90-day mortality rate is approximately 15% (see Table 84-5).

Box 84-1. TREATMENT OF HEPATOCELLULAR CARCINOMA

Patients with tumors suspicious for HCC based on known risk factors (hepatitis or alcohol) and/or preoperative contrast-enhanced imaging undergo serologic testing for AFP. In patients with elevated AFP and surgically resectable lesions, definitive treatment is then performed (see Fig. 84-7). In patients with known risk factors and a new liver lesion found on axial imaging, we pursue definitive treatment without biopsy. Only in patients in which both the diagnostic imaging is not classic for HCC and the AFP is normal would we consider biopsy of these lesions. This is for two main reasons: (1) suspicious lesions must be dealt with surgically regardless of biopsy results, and (2) the small but real risk of needle-tract seeding.[1,2]

Evaluation of liver functional reserve uses the Child-Pugh classification. Preoperative staging evaluation is performed using abdomen and pelvis contrast-enhanced biphasic CT with thin sections (5 mm) of the liver. Patients with disease limited to the liver undergo treatment according to the following algorithm shown in Figure 84-7.

Patients are not considered surgical candidates if they have high medical risk that precludes surgery. Select patients with bilobar tumors may be treated either with multiple segmental resections or a combination of resection and ablation; however, recurrence in this setting is extremely high, and ablative modalities are probably more appropriate. Select patients with isolated portal vein involvement may be considered candidates for hepatectomy with concomitant portal vein resection.

Patients with unresectable disease not amenable to alcohol injection or percutaneous RFA are first considered for embolization. In patients who are not candidates for embolization, we attempt to place these patients on a clinical trial, particularly since the response to traditional systemic chemotherapy is so poor.

FOLLOW-UP PROGRAM

After surgical treatment of HCC, scheduled follow-up evaluations are extremely important to look for recurrent disease, which can occur in up to two thirds of patients after potentially curative resection. Many patients with recurrent disease actually have metachronous second primaries, which develop in the setting of cirrhosis owing to the fact that the entire liver is diseased and therefore susceptible. These recurrent or new hepatomas can be treated effectively only if discovered early.

Associated Medical Conditions

The follow-up program also must aim to prevent and treat complications of associated parenchymal disease, which is common in this patient population. Patients may need treatment for alcoholism, and patients with hemochromatosis should be treated for iron overload. Of greatest importance is adequate treatment to prevent the complications of portal hypertension, because it is estimated that up to one quarter of patients who die after diagnosis of liver cancer succumb to gastrointestinal bleeding from portal hypertension.[133]

Recommended Follow-up Program

Routine follow-up evaluation after resection of HCC should include an office visit 2 to 3 weeks after hospital discharge. Liver transaminases, as well as tumor markers, are assessed. For classic HCC, the tumor marker is AFP[134]; for the fibrolamellar variant of HCC, levels of neurotensin or other markers[135,136] may be elevated in the serum

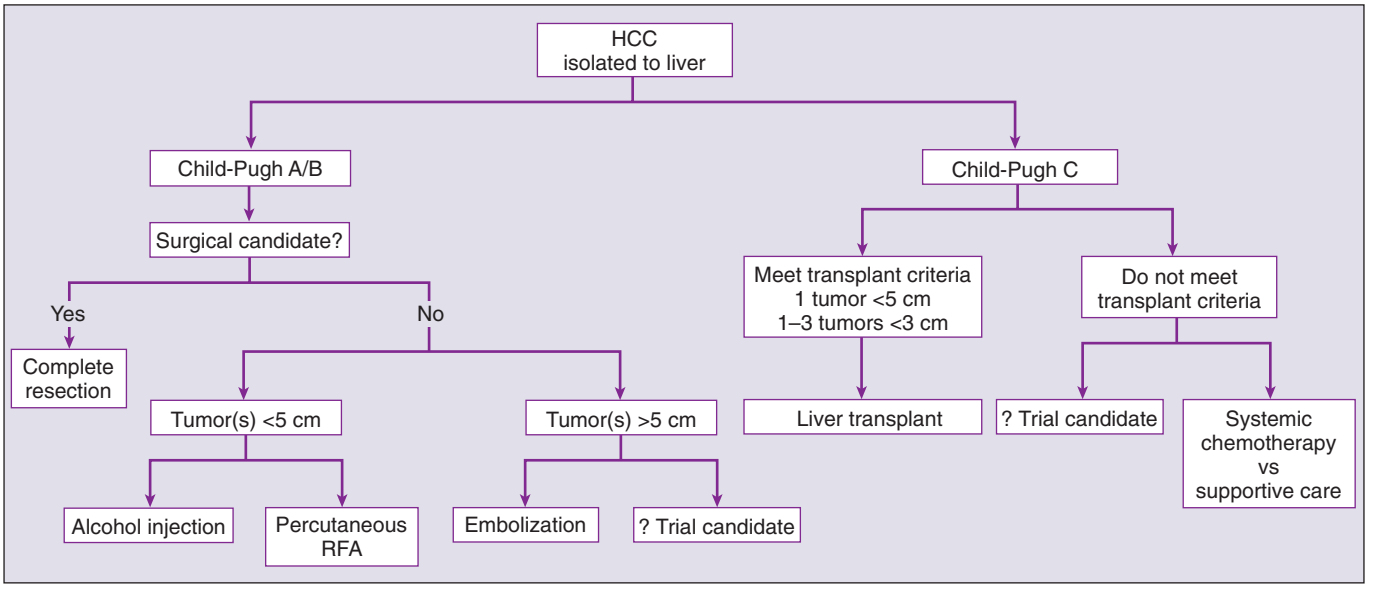


Figure 84-7 • Treatment algorithm for hepatocellular carcinoma (HCC). RFA, radiofrequency ablation.

before resection. A return of tumor markers to normal levels postoperatively should dictate a routine follow-up approach.

The routine follow-up program generally consists of office visits every 3 to 6 months with history and physical examination and measurement of liver function tests and tumor markers. Patients should be asked about symptoms of worsening portal hypertension or liver failure and symptoms of biliary obstruction, including itching or changes in stool or urine color, primarily because a significant proportion of patients die from liver failure, not HCC.[137] New-onset right upper quadrant pain or bone pain should prompt investigation by appropriate radiologic examinations. Physical examination should evaluate for new masses, worsening ascites, and jaundice. The follow-up program also should include contrast-enhanced abdominal CT every 6 months, with a chest radiograph obtained yearly. Five years after resection, office visits should be reduced to every 6 months.

ISSUES FOR THE FUTURE

Because the incidence of hepatocellular cancer is rising, it is imperative to develop improved screening tests that increase the sensitivity and specificity for detecting HCC. Some authors have suggested that a more sensitive means to detect recurrence may be evaluating the serum for the presence of AFP messenger RNA (mRNA) by reverse transcription polymerase chain reaction (PCR) assay. In this study, the postoperative presence of AFP mRNA was an independent prognostic factor for HCC.[138] Molecular studies to assess for genes associated with a high risk of recurrence have shown promise in preliminary studies but require further evaluation.[139–141] Clearly, it would be helpful if the molecular characterization of specific genes associated with an increased risk for developing HCC also could help with either early detection or prevention of the disease.[142]

GALLBLADDER CANCER

INTRODUCTION

Because tumors arising in the gallbladder often are asymptomatic until late in the course of the disease, they frequently manifest at an advanced, often unresectable, stage. Gallbladder cancer is a rare malignancy with a dismal outlook owing to its insidious onset, propensity for local invasion, and rapid disease progression. Gallbladder cancer also frequently manifests as an incidental finding during laparoscopic surgery for ostensibly benign disease. The argument for further definitive therapy in this context has been convincingly made for surgery and less so for systemic therapy and radiotherapy, but in all cases the rarity of the disease has resulted in a dearth of prospective randomized phase III studies to guide therapy at critical decision points. The available data are from small, single-institution and often retrospective studies. Although surgery remains the only curative option, most series report a less than 5% overall 5-year survival rate, probably owing to the fact that 40% of patients present with advanced disease.[143]

EPIDEMIOLOGY

Only 6000 to 7000 new cases of gallbladder cancer are diagnosed in the United States each year.[144] Gallbladder cancer is more common in women than in men in all populations, and in some geographic areas the rates are three times higher for women. Incidence increases with age in all populations.[143,145] Certain geographic areas are characterized by a high incidence of gallbladder cancer, including South America and India. A high incidence also has been documented in North American Native Americans and Mexican Americans, but the highest incidence of gallbladder cancer is in women from La Paz, Bolivia (15.5 cases per 100,000 population).[145] The geographic variability clearly correlates with populations that have a higher rate of gallstone formation.[145] To further strengthen this association, the mortality rate from gallbladder cancer has been inversely correlated with cholecystectomy rates in Chile, a high incidence region.[146]

ETIOLOGY AND PATHOGENESIS

Although an increased risk of gallbladder cancer with cholelithiasis is recognized, gallbladder cancer subsequently develops in less than 0.5% of patients with gallstones.[147] Nevertheless, up to 85% of patients with gallbladder cancer are found to have gallstones.[148,149] The association of gallstones with carcinoma probably is related to chronic inflammation. Larger stones, greater than 3 cm in greatest dimension, are associated with a 10-fold increased risk of cancer.[150]

Besides gallstones, the other main associated risk factors include chronic infections of the gallbladder and environmental exposure to specific chemicals such as Thorotrast, a preparation of colloidal thorium dioxide. Thorotrast is a radiologic contrast medium that emits alpha particles, thus causing chronic exposure to internal alpha-particle radiation when administered systemically. A study conducted in Sweden found that the incidence rates for cancer at all sites was increased 3 times over that in the general population, with the largest increase in primary liver and gallbladder cancers.[151] Because of this increased risk, Thorotrast is no longer used.

Patients with choledochal cysts have an increased risk for the development of carcinoma anywhere in the biliary tree. The incidence is higher in the gallbladder (12%), however, than in the biliary tree (5%).[152] The risk of carcinogenesis increases with age; accordingly, complete surgical resection is recommended for all patients with choledochal cysts at the time of diagnosis. In addition, anomalous pancreaticobiliary junction has been found to be associated with gallbladder cancer, occurring in up to 65% of cases.[153,154]

Because of the strong association of gallbladder cancer with gallstone disease, the question has been raised as to whether all patients with gallstones should undergo elective cholecystectomy. Several arguments have been made against elective cholecystectomy as a means to prevent gallbladder cancer. First, the historical practice of performing cholecystectomy only in symptomatic patients, thus leaving the gallbladder in place in patients with asymptomatic gallstones, has not led to an increase in the prevalence of gallbladder cancer over time. Second, epidemiologic studies have found the 20-year risk of developing cancer in patients with gallstones is less than 0.5% for the overall population and 1.5% for high-risk groups.[147] Thus, routine cholecystectomy for asymptomatic gallstones due to concern for future increased risk of gallbladder cancer does not appear to be warranted.

One higher-risk subset of patients with gallbladder disease is the population with "porcelain gallbladder," a calcified gallbladder wall. Historically, it was thought that the incidence of gallbladder cancer in patients with porcelain gallbladder was as high as 25% to 60% (Fig. 84-8). Because of this, it was standard surgical practice that all patients with calcification of the gallbladder wall should undergo open cholecystectomy, even if asymptomatic. More recently, however, this association has been challenged by the finding that less than 20% of patients with diffuse calcified gallbladder wall are found to have cancer.[149] Of interest, Stephen and Berger recently reported a retrospective analysis of over 25,000 gallbladder specimens and subdivided those patients with calcified gallbladders into two types: those with complete intramural calcification and those with selective mucosal calcification. Although a significant increase was observed in the incidence of gallbladder cancer in patients with focal mucosal wall calcification (7%; odds ratio, 13.89), no patients with diffuse intramural calcification were found to have cancer.[155] Finally, another recent retrospective review found 15 porcelain gallbladders among over 10,000 specimens examined, and none of the patients had gallbladder cancer.[156] The results of these studies indicate that the risk of gallbladder cancer in patients with porcelain gallbladder appears to have been greatly overestimated; therefore, cholecystectomy should be performed only in patients with either selective calcification of the gallbladder wall or other findings on preoperative studies suggestive of carcinoma.

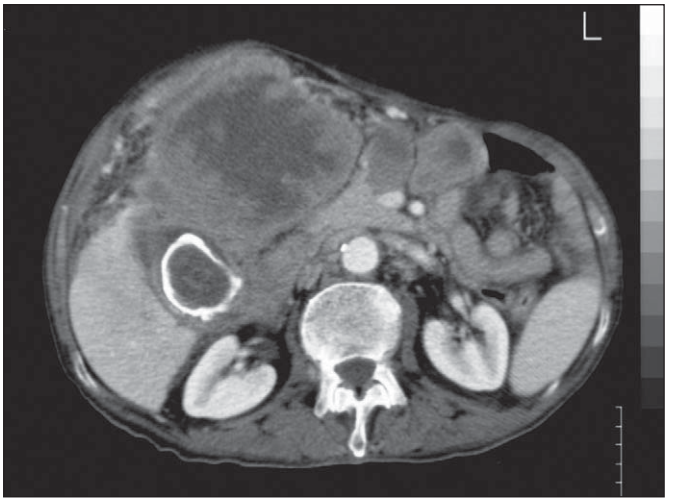


Figure 84-8 • Porcelain gallbladder demonstrated on computed tomographic scan with concentric calcification of the gallbladder wall. A large gallbladder cancer also is present.

PATHOLOGY

More than 80% of gallbladder cancers are adenocarcinomas; several histologic subtypes, including papillary, nodular, and tubular, are recognized. Papillary tumors, which grow predominantly into the gallbladder lumen, have an improved prognosis compared with the other subtypes.[143] Poor prognostic signs in gallbladder cancer include grade[143,157] and vascular invasion.[143] The most important prognostic sign is lymph node involvement,[158] although 5-year survivors with nodal involvement have been documented.[159] Less than 5% of cases are squamous cell carcinomas, with the remaining 10% being anaplastic lesions including small cell carcinoma, which has a particularly virulent course but may be responsive to cisplatin-based chemotherapy.

Limited information exists regarding the genetic changes in gallbladder cancer. The most widely reported gene abnormalities associated with gallbladder cancer include p53,[160] K-ras,[160,161] and CDKN2 (9p21) mutations.[161,162] The finding of a greater frequency of K-ras mutations in patients with an anomalous pancreaticobiliary junction has led investigators to believe that reflux of pancreatic enzymes into the biliary tree may contribute to the development of cancer.[161] Because of current limited knowledge of the sequence of molecular changes, no detectors of early disease or of risk assessment have been identified. Clearly, this is an aspect of investigation that needs improvement, particularly in endemic areas.

TUMOR BIOLOGY

Gallbladder cancer spreads by means of the lymphatic and venous drainage system. Due to drainage of the cholecystic veins directly into the adjacent liver, these tumors often involve hepatic parenchyma, most often portions of segments IV and V that directly abut the gallbladder fossa. The rapid spread of gallbladder cancer has been thought to be due partly to its thin wall and discontinuous muscle layer. In addition, the portion of the gallbladder that is in direct contact with the liver has no serosa; thus, direct liver invasion is common. Lymphatic spread is first to the cystic duct (Calot's) node, then to pericholedochal and hilar nodes, and finally to peripancreatic, duodenal, periportal, celiac, and superior mesenteric artery nodes. Nodal disease in the porta hepatis can cause common bile duct obstruction with resultant jaundice, which is the first clinical symptom in 30% of patients. Jaundice also may be caused by tumors arising in the gallbladder infundibulum, which may spread directly to the cystic duct and common hepatic duct. Although peritoneal metastases are frequent, distant extraperitoneal metastases are not.

CLINICAL PRESENTATION AND PATIENT EVALUATION

In patients with signs or symptoms, abdominal pain, sometimes consistent with biliary colic or acute cholecystitis, is the most common symptom, followed by jaundice.[163] A majority of patients are found

to have gallbladder cancer during evaluation for possible cholelithiasis or choledocholithiasis. Patients also may present with weight loss, anorexia, or an increase in abdominal girth secondary to ascites. Physical findings include right upper quadrant tenderness or a palpable mass, hepatomegaly, and ascites. Owing to its nonspecific presentation, gallbladder cancer is not diagnosed preoperatively in more than half of the cases. Of patients presenting with jaundice in the setting of gallbladder cancer, a majority will have advanced disease.[164]

LABORATORY AND IMAGING STUDIES

Results of laboratory tests usually are normal except in patients with jaundice who have elevated liver enzymes, consistent with biliary obstruction. No reliable screening tests are available to evaluate patients at increased risk for gallbladder cancer.

Imaging evaluation often reveals an asymmetrically thickened gallbladder wall (Fig. 84-9) or a mass within or replacing the gallbladder on ultrasound examination. Because polyps and carcinoma can have an echogenicity similar to that of the gallbladder wall, these lesions often are difficult to distinguish. The diagnostic difficulty increases when inflammation is present from gallstones. At times, ultrasound examination can visualize invasion of the liver, adjacent adenopathy, and a dilated biliary tree. The capability of ultrasound examination to differentiate benign from neoplastic disease is enhanced with use of endoscopic ultrasound techniques, and this modality may be more specific than CT or MRI.[165–167]

A dynamic contrast-enhanced CT scan may identify a gallbladder mass or invasion into the liver parenchyma or adjacent organs. The classic finding in a patient with gallbladder cancer is asymmetrical thickening of the gallbladder wall (see Fig. 84-9). The sensitivity and specificity of contrast-enhanced CT in diagnosing neoplastic lesions are close to 90%.[168] Staging of gallbladder carcinoma using CT, however, is limited by poor sensitivity in identifying nodal spread.[169]

In patients who are jaundiced, direct cholangiography may be useful to delineate extent of biliary involvement, as well as to relieve symptoms of biliary obstruction. A mid-bile duct obstruction not due to gallstones represents gallbladder cancer until proven otherwise. More recently, with the improvements in MRI technology, magnetic resonance cholangiopancreatography (MRCP) has evolved into a single noninvasive imaging modality that allows complete assessment of biliary, vascular, hepatic parenchymal, and nodal involvement, as well as involvement of adjacent organs; thus, this modality may be helpful in select cases.[170–172]

STAGING CLASSIFICATION

The American Joint Committee on Cancer's (AJCC) TNM staging system (Table 84-6) reflects prognostic characteristics of tumor depth, regional nodal disease, or distant spread. Gallbladder cancers frequently spread to the liver, which is involved in 70% of patients at the time of surgical evaluation. The gallbladder differs histologically from the rest of the gastrointestinal tract in that it lacks a muscularis mucosa and submucosa. Thus the gallbladder wall is composed of (1) a single layer of columnar cells, the mucosa, and lamina propria, (2) a fibromuscular layer, (3) a perimuscular, subserosal layer containing lymphatics and neurovascular structures, and (4) a serosal surface, except where the gallbladder is embedded in the liver.[173] Because lymphatics are present in the subserosal layer only, tumors invading less than the full thickness of the muscular layer have minimal risk of nodal spread.

Several changes have recently been incorporated into the AJCC staging system (i.e., the sixth edition of the staging manual, published in 2002)—specifically, the T and N classifications have been simplified in an attempt to separate locally invasiv e tumors into potentially resectable (T3) and unresectable (T4) lesions. The distinction between T3 and T4 based on depth has been abolished. Lymph node metastasis is now classified as stage IIB, and stage IIA refers to resectable tumors with no lymph node involvement. In line with other pancreaticobiliary malignancies, the stage III grouping refers to

Table 84-6 American Joint Commission on Cancer Staging System for Gallbladder Carcinoma: Tumor-Node-Metastasis (TNM) Classification

Stage	Grouping		
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

DEFINITIONS

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades the lamina propria or muscle layer
T1a	Tumor invades the lamina propria
T1b	Tumor invades the muscle layer
T2	Tumor invades the perimuscular connective tissue; no extension beyond the serosa or into the liver
T3	Tumor perforates the serosa (visceral peritoneum) and/ or directly invades the liver and/or one other adjacent organ or structure, e.g., stomach, duodenum, colon, pancreas, omentum or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades multiple extrahepatic organs or structures

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis



Figure 84-9 • Computed tomographic scan demonstrating asymmetrical thickening of the gallbladder wall, a classic finding in gallbladder carcinoma.

locally advanced, unresectable disease, and stage IV indicates metastatic disease. Stage I includes tumors invading into but not through the muscular layer of the gallbladder. Stage II disease is characterized by invasion into the perimuscular, subserosal layer, without spread to the liver and without nodal disease. Stage III and stage IV disease are as previously defined.

PROGNOSIS

The 5-year survival rate for all patients with gallbladder cancer is less than 5% in most series, with a median survival time of 6 months.[174,175] This dismal outlook results primarily from the fact that most patients present with unresectable disease. For those patients undergoing resection, survival is dependent on depth of penetration and nodal status. In large series, the overall 5-year survival rate after resection is 40%.[174] Nearly 100% survival is reported after simple cholecystectomy for T1 disease; patients with T2 and T3 tumors without nodal disease have a 5-year survival rate greater than 50%.[158,159,176–179] Node positivity and presentation with jaundice are ominous findings, with few 5-year survivors among patients with these features.[159,180]



Figure 84-10 • Intraoperative photograph during staging laparoscopy demonstrating occult peritoneal metastases on the inferior surface of the right diaphragm.

PRIMARY TREATMENT

The only curative option in patients with gallbladder cancer is complete surgical resection. In a study of 5836 patients with gallbladder cancer, the 5-year survival rate for patients who had surgery with curative intent was 17% but less than 1% for those with unresectable disease.[147] In a review of data for 10,301 patients with gallbladder cancer from the SEER database, those who underwent surgery had a significantly longer median survival than those who did not.[181] Recognizing the inherent bias of these retrospective analyses, and also the fact that patients who undergo surgery are selected by virtue of a number of factors, including good performance staus, lack of precluding medical comorbid conditions, less advanced stage of disease, and possibly more favorable disease biology, these data nevertheless support the role of surgery as the primary therapeutic modality. Unfortunately, however, resection is possible in only 25% of patients at presentation because of the advanced nature of the disease.[147]

It is essential for optimal patient care that patients with gallbladder cancer be identified before laparoscopic cholecystectomy is performed, owing to the risk of port site seeding and bile spillage with potential tumor spill.[163,179]

Role of Staging Laparoscopy

Because a large percentage of patients have been found to have occult unresectable disease at the time of exploration, several investigators have studied the use of initial staging laparoscopy for this disease.[175,182–184] Gallbladder cancer has a marked propensity to spread intra-abdominally, so patients with this tumor are ideal candidates for detection of intra-abdominal metastases with laparoscopy. Support for this application of staging laparoscopy comes from the fact that up to 50% of patients are found to have unresectable disease at the time of laparoscopy[175] (Fig. 84-10). Patients who are detected to have unresectable disease at laparoscopy can begin other forms of therapy earlier and may undergo the procedure on an outpatient basis. Particularly because patients with unresectable disease have a median survival of only 6 months, the importance of quality of life and time out of the hospital cannot be overemphasized.

Cholecystectomy with or Without Partial Hepatectomy

Gallbladder cancer results in rapid local progression and death unless it can be curatively resected. In a collected review of 5836 patients with gallbladder cancer, the overall mean survival time was between 2 and 5 months, with a 5-year survival rate of 4%.[174] The 5-year survival rate for patients undergoing resection with curative intent was 17%. Of the 2115 patients with unresectable tumors, only a single 5-year survivor was described.[147] Although surgical resection represents the treatment of choice and the only potentially curative therapy available, resection is possible in only 25% of patients at presentation owing to the advanced nature of the disease.[147]

The operation of choice must be tailored to the depth of penetration of the tumor. For tumors limited to the muscular layer of the gallbladder (T1), simple cholecystectomy is adequate.[159,185–187] T1 tumors have not yet invaded the subserosal layer, which contains lymphatics, so lymphadenectomy is not required. Attesting to the fact that early gallbladder carcinoma is completely curable, simple cholecystectomy has resulted in nearly 100% survival when early cancer is an incidental finding after elective cholecystectomy.[188]

Difficulty can arise at the time of surgery in identifying polypoid lesions of the gallbladder as either benign or early gallbladder cancer. Although it appears that frozen section diagnosis is fairly reliable in determining whether lesions are malignant or benign (95% accurate), the accuracy in correctly assessing depth of invasion is only 70%.[189] Thus, it may be difficult at the time of surgery to determine the extent of resection. Accordingly, pursuing a more aggressive resection if the depth of invasion is in doubt is important for adequate clearance of disease.[190]

The extent of surgical resection for T2 or greater tumors has been controversial, with recommendations ranging from simple cholecystectomy to radical excision including hepatectomy. Although it is clear that major hepatic resection can be performed safely, with a mortality rate of less than 5%[158,159,174,186,187] (Table 84-7), the ability to achieve a complete resection of cancer must be balanced with the morbidity of the procedure. Because the gallbladder is not surrounded by serosa at its attachment to the liver in the gallbladder fossa, even T2 tumors (full-thickness invasion of the muscular layer into the perimuscular connective tissue, but not into the serosa) may invade the normal plane of dissection in the gallbladder fossa during simple cholecystectomy. Therefore, T2 tumors cannot be completely removed with cholecystectomy alone, and a radical cholecystectomy, with resection of a 1- to 2-cm rim of normal liver around the gallbladder fossa, is the minimum resection that is required. Many investigators, however, have found that resection of segments 4b and 5 of the liver, which abut the gallbladder fossa, results in a more anatomically controlled dissection with less blood loss.[191] An additional component of the definitive surgical treatment is regional lymphadenectomy, because approximately half of the patients with T2 tumors are found to have nodal spread after resection.[158] Dissection of lymph nodes should include all tissue from the bifurcation of the hepatic ducts to the distal common bile duct. Proponents of this approach advocate liver resection on the basis that it is the only way to obtain

Table 84-7 Results after Radical Resection for Gallbladder Cancer

Study	No. of Patients Undergoing Resection	Perioperative Mortality (%)	5-Year Survival (%)	Median Survival (mo)
Ogura et al, 1991[187]	982	5	50	—
Donohue et al, 1990[186]; Taner et al, 2004*	131	2	21	—
Fong et al, 2000[174]	102	4	38	26
Dixon et al, 2005†	51	2	35	17

*Taner CB, Nagorney DM, Donohue JH: Surgical treatment of gallbladder cancer. J Gastrointest Surg 2004;8:83–89.
†Dixon E, Vollmer CM Jr, Sahajpal A, et al: An aggressive surgical approach leads to improved survival in patients with gallbladder cancer: a 12-year study at a North American Center. Ann Surg 2005;241:385–394.

an adequate margin on the hepatic side of the gallbladder, and that resection of the regional nodes allows the best chance for complete tumor clearance. For all of these reasons, simple cholecystectomy is inadequate for T2 or greater tumors. When segment 4b-5 resections have been performed in patients with T2 tumors, the 5-year survival has increased from a range of 25% to 40% after simple cholecystectomy to 70% to 100% after radical resection.[158,159,177,185,186,188]

For T3 and T4 lesions, a high likelihood exists for intraperitoneal and hematogenous spread and significant morbidity associated with the radical procedures that often are necessary for excision of local disease. In patients with disease limited to the gallbladder, however, recent series support an aggressive approach to resection (see Table 84-7). For large tumors with liver invasion, segment 4b-5 resection or extended right hepatectomy is warranted to completely clear the hepatic bed of tumor.

Surgical exploration should be performed in all patients with no medical contraindications. If a T1 tumor is suspected, a cholecystectomy and biopsy of regional nodes should be performed after thorough examination of the abdominal cavity for any signs of tumor dissemination. The pathology and depth of penetration should be confirmed by frozen section, and the procedure terminated if a T1 tumor with disease-negative margins is confirmed. For T2 lesions, either a radical cholecystectomy (wedge resection of the hepatic bed) or a segment 4b-5 resection with lymphadenectomy should be performed.[158] For T3 or T4 lesions, a segment 4b-5 resection or extended right hepatectomy is performed as needed for complete tumor clearance.

Location of the tumor is important in determining the extent of resection. If the tumor arises in the gallbladder infundibulum, the common bile duct is often involved with tumor, either by direct extension or external invasion of the hepatoduodenal ligament. In this case, an extended liver resection and excision of the common bile duct should be performed. In addition, all patients who present with jaundice will require resection of the common bile duct to clear the tumor. Reconstruction is then performed by Roux-en-Y hepaticojejunostomy. Tumor arising in the fundus of the gallbladder, however, can be treated with limited hepatic resection without excision of the common bile duct. In order to clear the lymph nodes in the porta hepatis, complete lymphadenectomy should be performed skeletonizing the common bile duct, hepatic artery, and portal vein.

Incidentally and Laparoscopically Discovered Gallbladder Cancer

Gallbladder cancer often is discovered during histopathologic examination after cholecystectomy for presumed benign gallstone disease. As a result of the popularization of laparoscopic cholecystectomy in the past decade, an increasing number of patients with gallbladder cancer are found incidentally. Particularly in patients with bile spillage at the time of surgery, laparoscopic resection in patients with unknown gallbladder cancer may convert potentially curable early gallbladder cancer into incurable disease.[179] Because radical resection remains the only possibility for cure, however, patients with T2 or greater tumors without signs of distant disease should be offered a second resection to eradicate all disease. At the time of surgery, excision of laparoscopic port sites also should be performed owing to the well-documented possibility of port site seeding even if they appear grossly normal.[163,188,192,193]

At reoperation, patients presenting with incidentally discovered gallbladder cancer during laparoscopic cholecystectomy present multiple technical challenges. A common finding is postoperative inflammation in the right upper quadrant, which hinders distinction of tumor from normal tissue. Determination of gross ductal or nodal involvement by tumor is always difficult at the time of reoperation. In addition, postoperative fibrosis often encases the right hepatic artery, which crosses behind the bile duct in most patients. For all of these reasons, a second operation for incidentally discovered gallbladder cancer often requires an extended right hepatectomy along with excision of the extrahepatic biliary tree and periductal lymphatic tissues. This resection allows adequate excision of the lymphatic tissues at the confluence of the bile ducts, with a greater likelihood of achieving disease-negative margin on the bile duct, and limits the need for biliary reconstruction to only one side of the liver. The disadvantage is that a large portion of normal liver parenchyma is sacrificed, and consequently, transient postoperative liver dysfunction is common. Although curative resection of incidentally discovered gallbladder cancer may be more difficult to perform, no difference in overall survival has been found between patients who initially undergo noncurative resection and are then re-explored for definitive resection and those patients undergoing initial curative resection.[174]

When a patient presents with T1 gallbladder cancer discovered after simple cholecystectomy, the pathologic findings must be reviewed to determine if the entire gallbladder has been removed and if the cystic duct margin is clear of tumor. If the cystic duct margin is positive for disease, the patient requires local bile duct excision at a minimum. If all margins are disease-negative, no further therapy is warranted. If the tumor is proved to be T2 or greater, however, the patient should undergo a radical resection if evidence of extrahepatic disease is absent. Patients with a known or suspected early gallbladder carcinoma should not undergo laparoscopic cholecystectomy. Rather, open exploration and cholecystectomy should be performed.

ADJUVANT THERAPY AND TREATMENT OF ADVANCED GALLBLADDER CANCER

Adjuvant Therapy

Adjuvant therapy for biliary tract malignancies (gallbladder and cholangiocarcinoma) remains a controversial and largely unproven consideration. Very few randomized trials have been conducted, and those that have are notable for (1) small patient numbers and (2) inclusion of patients with several malignancies (e.g., gallbladder and cholangiocarcinoma, ampullary, and sometimes pancreatic malignancies), thus limiting the statistical power and validity of the conclu-

sions. In view of the relative rarity of these malignancies in the United States, large-scale randomized trials are feasible only in the context of a multi-institutional or cooperative group setting.

One prospective randomized phase III trial by Takada and associates of adjuvant chemotherapy with 5-fluorouracil and mitomycin versus surgery alone for resected patients with pancreaticobiliary malignancies offers some interesting results.[194] A total of 508 patients were accrued from 31 centers over a 6-year period, including 140 with gallbladder cancer. In 112 evaluable gallbladder cancer patients, the 5-year survival rate of 26% for the adjuvant treatment group was significantly better than that for the control group at 14% (P = 0.0367). Similarly, the 5-year disease-free survival rate favored the adjuvant treatment group at 20.3%, versus 11.6% (P = 0.021). Significantly improved body weight also was observed in the adjuvant treatment group. For the other malignancies assessed in this trial, pancreas, bile duct, and ampulla of Vater cancers, no benefits with regard to disease-free and overall survival were observed.[195] This trial suggests that adjuvant chemotherapy may offer benefit for patients with resected gallbladder cancer; however, replication in a larger-scale setting is required before definitive conclusions can be drawn.

A majority of gallbladder cancers recur with both local and systemic disease, so a logical approach is to consider combined chemoradiation therapy in the adjuvant setting. Kresl and coworkers[196] recently reported on the Mayo Clinic retrospective experience with adjuvant 5-FU chemotherapy and external beam irradiation in patients with resected gallbladder cancer. Patients with completely resected gallbladder cancer (i.e., with disease-negative margins) who received adjuvant chemoradiotherapy had a 5-year survival rate of 64%, suggesting a favorable outcome compared with historical data for complete resection without additional treatment (approximately 33%). Again, large-scale prospective trials of postoperative adjuvant chemoradiation therapy are needed to determine the true merits of such an approach. Investigational issues with regard to adjuvant therapy include incorporating drugs with greater systemic activity than that of the fluoropyrimidines (e.g., gemcitabine) into an upfront adjuvant setting, as well as trying to delineate the role of local radiation modalities (e.g., brachytherapy) in the adjuvant context.

Metastatic Disease

A majority of studies assessing the role of chemotherapy in gallbladder cancer also have included patients with cholangiocarcinoma. Many phase II studies have demonstrated feasibility and some degree of efficacy, but the impact of chemotherapy in terms of overall survival and quality of life is unclear. With use of older drugs such as 5-FU, a single-agent response rate of approximately 10% has been reported.[197] Capecitabine, an oral tumor-activated fluoropyrimidine, has shown activity on its own and in combination with platinum agents.[96,198,199] Gemcitabine is a nucleoside analog prodrug that is activated by intracellular phosphorylation. It is a U.S. Food and Drug Administration (FDA)-approved agent for treatment of locally advanced and metastatic pancreatic adenocarcinoma. Many studies have evaluated gemcitabine both as a single agent and in combination with other agents, and it probably has become a first-line drug of choice for a majority of oncologists.[200–205]

Novel Therapies

It is clear that currently available medical therapies for biliary tract malignancies are woefully inadequate. The key to identifying new agents for treatment of this disease lies in developing a greater understanding of the genetics and molecular pathogenesis of gallbladder cancer. Such an approach may lead to the identification of novel targets, as well as paving the way for a more sophisticated approach to identifying persons at risk for developing this cancer and ultimately to screening and early detection, which is likely to represent one of the few strategies that may affect the long-term outcome with this cancer. Along the signal transduction pathway, therapeutic targets are abundant, but their potential has not been verified. Epidermal growth factor receptor (EGFR) and c-Erb-B2 expression has been observed in gallbladder carcinoma.[206] Erlotinib, an EGFR oral tyrosine kinase inhibitor, has some activity. In one study of 42 patients with advanced biliary cancer, a majority of whom had received prior chemotherapy, partial responses occurred in 3 patients, and 7 additional patients remained free of disease progession at 6 months.[207] Cyclooxygenase-2 (COX-2) appears to play an important role in VEGF-mediated angiogenesis, pointing to the potential use of COX-2 inhibitors in conjunction with chemotherapy or as a chemopreventive strategy.[208]

TREATMENT COMPLICATIONS

Larger series of patients with gallbladder carcinoma treated with definitive surgical resection have shown complication rates from 28% and mortality rates of zero to 4%.[163,174,176] The most common postoperative complications include intra-abdominal abscess or biloma and other infectious complications such as pneumonia or wound complications.[163]

FOLLOW-UP EVALUATION AFTER RESECTION FOR GALLBLADDER CANCER

The most common forms of recurrence after resection of gallbladder cancer include carcinomatosis, intrahepatic metastases, and nodal recurrence in the retroperitoneum. Jaundice is a common sign, but patients with recurrence also may present with ascites due to carcinomatosis. For most tumors, local recurrence is found synchronously with diffuse intra-abdominal spread. Therefore, surgical treatment of recurrence has little potential for cure. If recurrent disease is found after resection, prognosis is exceedingly poor, with death occurring secondary to biliary sepsis or liver failure within months of diagnosis.

The main goal of the follow-up program after resection of gallbladder cancer is to provide palliation for symptomatic recurrences. The main symptoms and signs associated with recurrence requiring palliation are pruritus or cholangitis associated with jaundice and bowel obstruction associated with carcinomatosis. Additional goals of the follow-up program are to detect benign complications of surgical treatment such as biliary stricture. When jaundice or cholangitis is the presenting symptom of possible recurrence, a nonsurgical palliative approach using percutaneous transhepatic cholangiography (PTC) and stenting usually is favored unless a benign postsurgical stricture is suspected. Because of the rapid growth of tumor in patients with recurrence, the hospitalization and recovery time from a surgical bypass usually are not justified for recurrences resulting in biliary obstruction.

Routine follow-up evaluation of a patient after resection of gallbladder cancer includes office visits every 3 months with physical examination and measurement. Although CA19-9 may be elevated in patients with gallbladder cancer, the sensitivity and specificity are poor,[209] so this marker should not be used for screening patients for recurrence. Because only limited treatment options are available for patients with asymptomatic recurrence of gallbladder cancer, overaggressive use of imaging studies is not warranted. Therefore, the use of imaging studies should be individualized.

ISSUES FOR THE FUTURE

Clearly, improving the ability to recognize early gallbladder cancer in high-risk geographic areas would have an important impact on outcome in these patients. Such advances probably will require elucidation of the sequential molecular changes associated with gallbladder cancer. Other improvements in screening programs in high-risk areas, potentially resulting in prophylactic cholecystectomy, are likely to be beneficial.[145]

BILE DUCT CARCINOMA

INTRODUCTION

One of the most technically difficult surgical resections is in patients with bile duct tumors arising in the hepatic hilus, named Klatskin tumors, or hilar cholangiocarcinoma. Bile duct cancers can arise at other sites, including within the liver (intrahepatic cholangiocarcinoma) and below the biliary bifurcation but above the pancreas (mid-bile duct cholangiocarcinoma). Distal cholangiocarcinoma involves that portion of the bile duct within the pancreas, which requires pancreaticoduodenectomy and is discussed in Chapter 85. The location of the tumor affects prognosis, as well as the potential for curative resection.

Resection of biliary neoplasms, particularly hilar cholangiocarcinoma, often requires radical resections and complex biliary reconstructions that have only recently become safe in routine practice. Surgery also may offer effective palliation for these cancers by providing biliary bypass for jaundiced patients with unresectable tumors. Because patients often are diagnosed late in the disease course and because complex operative techniques are required for potentially curative resection, these tumors represent one of the greatest challenges for definitive treatment. Adding to this challenge is the lack of proven effective options for adjuvant treatment.

EPIDEMIOLOGY AND PATHOGENESIS

The overall incidence of hilar cholangiocarcinoma in the United States is 1.0 per 100,000 per year, although other geographic regions such as Israel and Japan have higher rates.[210] The incidence of intrahepatic cholangiocarcinoma in the United States is approximately 0.7 per 100,000, with a similar mortality rate. During the last 30 years, it appears that both incidence and mortality in the United States are increasing.[211]

Cholangiocarcinoma is a rare cancer that arises from the biliary epithelium and is diagnosed in fewer than 4500 patients in the United States each year.[212] Cholangiocarcinomas arise slightly more often in males,[213] with a male-to-female ratio of 1.3:1, with a predisposition to affect those between 50 and 70 years of age. Risk factors for this disease include primary sclerosing cholangitis, ulcerative colitis, choledochal cysts, and biliary tract infection, either with *Clonorchis* or in chronic typhoid carriers.[214] Management of patients with cholangiocarcinoma arising from one of these underlying conditions is challenging.[215] Some industrial chemicals such as nitrosamines, dioxin, asbestos, and polychlorinated biphenyls also have been implicated in the pathogenesis of cholangiocarcinoma.[210] Although some evidence suggests an increased risk of cholangiocarcinoma after transduodenal sphincteroplasty,[216] it is difficult to distinguish whether the tumor was secondary to the surgical intervention or whether the underlying disease led to sphincteroplasty.

PATHOLOGY

Similar to gallbladder cancer, hilar cholangiocarcinoma tends to invade locally. More than 95% of these tumors are adenocarcinomas. They are morphologically described as nodular (which is the most common), scirrhous, diffusely infiltrating, or papillary. Histologic subtypes include acinar, ductular, trabecular, alveolar, and papillary. Perineural invasion clearly is a poor prognostic sign.[217] Papillary tumors (Fig. 84-11) appear to be associated with a more favorable outcome[218] and to be similar to intraductal papillary mucinous neoplasms of the pancreas.[219] Much less frequent bile duct tumors include cystadenocarcinomas, hemangioendotheliomas, and mucoepidermoid carcinomas.

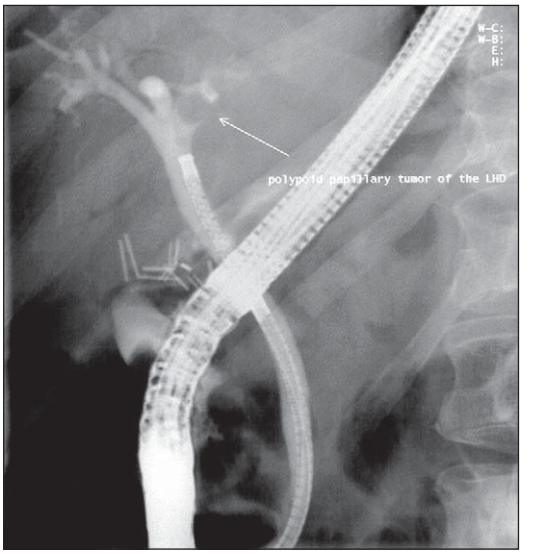


Figure 84-11 • Endoscopic retrograde cholangiopancreatography. The filling defect in the left bile duct proved at biopsy and subsequent examination to be papillary cholangiocarcinoma.

In patients with intrahepatic cholangiocarcinoma, negative prognostic signs include vascular invasion, multiple tumors, disease-positive tumor margins, large size, and lymph node metastases.[220] These tumors can be either sclerotic, mass-like lesions (Fig. 84-12) or cystic lesions[221–223] (Fig. 84-13).

Historically, cholangiocarcinomas have been classified according to their location in the upper (60%), middle (15% to 20%), or lower third (15% to 20%) of the bile duct. Middle third lesions arise between the cystic duct and the superior border of the duodenum. Lower third lesions are found below the superior border of the duodenum but above the ampulla. The problem with this classification is that the anatomic landmarks are somewhat arbitary and not clinically useful. In addition, many mid-bile duct obstructions due to malignancy are from gallbladder cancer, and even when the obstruction is truly secondary to a mid-bile duct cholangiocarcinoma, very few of these tumors are amenable to treatment by local excision of the bile duct. A more useful classification may be to divide these lesions into upper-half and lower-half tumors, based on the location of the cystic duct as it enters the common duct in the case of normal anatomy. The usefulness of this classification scheme is that it allows

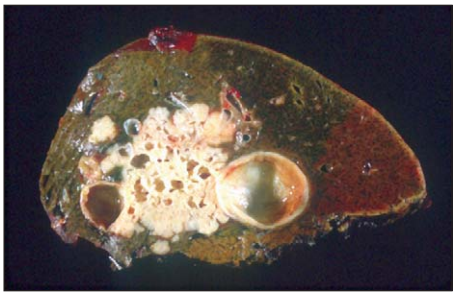


Figure 84-12 • Gross image of resected intrahepatic cholangicarcinoma reveals solid and cystic components of the tumor.



Figure 84-13 • Gross image of resected intrahepatic cholangicarcinoma reveals a sclerotic, solid mass.

the surgeon to determine whether a hepatic or pancreatic resection will be required for clearance of tumor.

TUMOR BIOLOGY

Because hilar cholangiocarcinomas arise in the bile duct, which is in close approximation to the portal vein, the tumor often causes portal vein occlusion as it enlarges. This results in lobar atrophy on the ipsilateral side. In addition to local invasion, nodal metastases occur frequently. Intrahepatic cholangiocarcinoma, unless arising in a location near the hilum, less commonly results in local invasion.

CLINICAL PRESENTATION AND PATIENT EVALUATION

The vast majority of patients with hilar cholangiocarcinoma present with painless jaundice, although mild right upper quadrant pain, pruritus, anorexia, malaise and weight loss also may be reported. Cholangitis is the presenting symptom in 10% to 30% of patients. Some patients have their cancer discovered on evaluation for otherwise asymptomatic elevations of alkaline phosphatase and gamma-glutamyl transferase.

Patients with intrahepatic cholangiocarcinoma usually are asymptomatic. Many patients are found incidentally to have a liver tumor present on cross-sectional imaging performed for other reasons. Many of these patients present to a surgeon with biopsy evidence of adenocarcinoma without a known primary. The standard evaluation in these patients should include assays for tumor markers to rule out an elevated CA19-9, carcinoembryonic antigen (CEA), or AFP; upper and lower endoscopy to evaluate for a primary gastrointestinal source; CT scan to assess for a primary tumor in the gastrointestinal tract or pancreas and to rule out other metastases; and, in women, a mammogram. If no site of primary disease is found, the diagnosis in a majority of patients will be intrahepatic cholangiocarcinoma.

LABORATORY AND IMAGING STUDIES

Laboratory evaluation usually reveals elevated bilirubin or alkaline phosphatase and gamma-glutamyl transferase consistent with biliary obstruction in patients with hilar cholangiocarcinoma or a mid-bile duct lesion. Results of other laboratory tests typically are normal. In patients with intrahepatic cholangiocarcinoma, findings on laboratory evaluation usually are normal.

A variety of imaging tests are available to assess patients with hilar cholangiocarcinoma. Abdominal ultrasound examination is noninvasive, easily available, and inexpensive and thus is commonly used as a first imaging modality. The advantage of ultrasonography is that it can quickly establish the level of biliary obstruction. Cross-sectional imaging with intravenous contrast-enhanced CT scan probably is the most readily accessible technology and provides the moststaging information. CT scans frequently reveal dilated intrahepatic biliary ducts with a normal, collapsed gallbladder and, depending on the level of the tumor, a nondilated or partially dilated extrahepatic biliary tree. In addition, the presence of hilar adenopathy can be assessed. Portal vein patency can be determined with ultrasound examination or helical CT. In addition, signs of hepatic lobar atrophy should be sought (Fig. 84-14), because this fnding is associated with a high incidence of ipsilateral portal vein involvement by tumor. Magnetic resonance cholangiopancreatography (MRCP) offers the potential for evaluating parenchymal, vascular, biliary, and nodal involvement with a single noninvasive examination.[170–172] Frequently, it is possible to visualize the tumor itself with MRI .

In many centers, direct cholangiography is used to evaluate the extent of biliary involvement and provide palliation for jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) has little role to play in high biliary obstruction because opacification, absolutely essential for assessing resectability, is difficult to accomplish in the proximal biliary tree. ERCP can be effectively used to image more distal lesions, however. At the time cholangiography is performed,

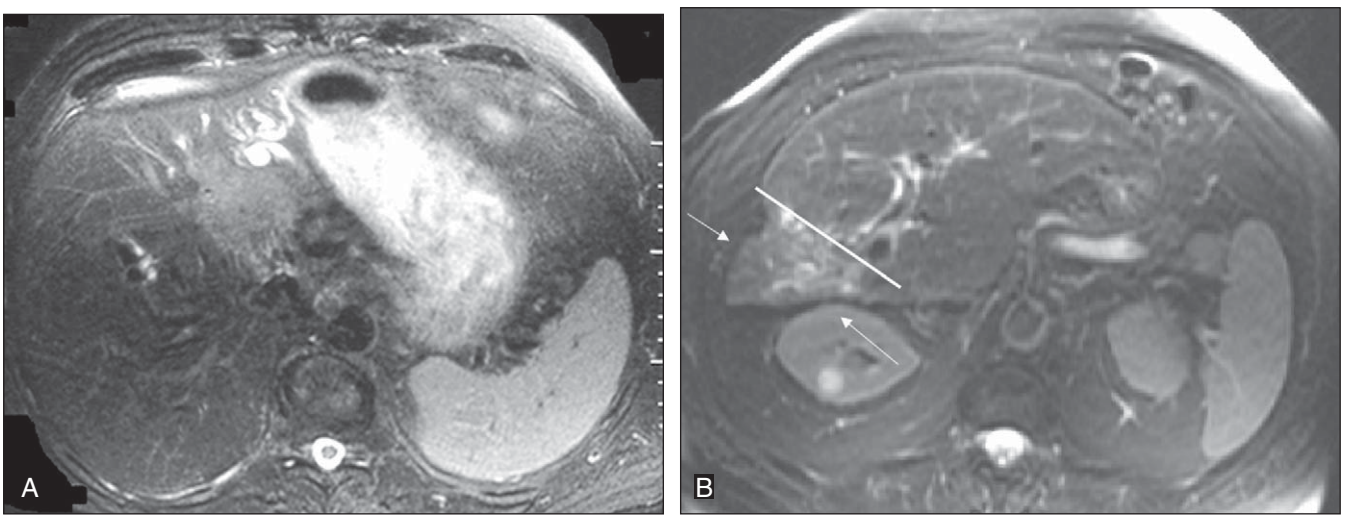


Figure 84-14 • Lobar atrophy in the liver due to portal venous invasion by cholangiocarcinoma. Magnetic resonance image demonstrates left lobar atrophy (**A**) and right lobe atrophy (**B,** *arrows*; *line* marks delineation between right and left lobes).

some authors advocate the routine preoperative placement of biliary drainage catheters to aid in intraoperative identification of the bile ducts.[224,225] Others have found a higher incidence of infectious complications[226] and greater mortality[227] and a longer hospital stay[228] after preoperative placement of biliary drainage catheters. The difficulty in making the decision regarding preoperative stenting is that many patients are severely symptomatic as a result of jaundice and pruritus and thus require palliation. Accordingly, a delay in operative intervention may necessitate biliary stent placement.

In many cases, it is difficult to obtain histopathologic confirmation of cholangiocarcinoma except in very advanced cases, even with the use of biliary brushings and cytologic specimens obtained at the time of direct cholangiography. In a majority of cases, patients are offered surgical therapy based on clinical suspicion and radiographic appearance.

In patients with intrahepatic cholangiocarcinoma, cross-sectional imaging with CT scan usually is sufficient. Tumors may be mass-like or may demonstrate cystic areas (see Figs. 84-12 and 84-13).

STAGING CLASSIFICATION

The AJCC TNM staging system for bile duct cancers is described in Table 84-8. In the 2002 AJCC TNM staging classification for extrahepatic bile duct cancer, several changes have been incorporated. The T and N classifications have been simplified. T1 is now classified as invasion of the subepithelial fibromuscular connective tissue. T2 is defined as invasion beyond the wall of the bile duct. Involvement of branches of the portal vein, hepatic artery, or liver is termed T3. Invasion of the main portal vein, common hepatic artery, or regional organs is now termed T4. In line with other hepatobiliary tract malignancies, stage III now signifies locally advanced, unresectable disease, and stage IV denotes metastatic disease.

In order to attempt to incorporate clinically important indicators of resectability, preoperative staging systems have been advocated that incorporate imaging features consistent with advanced disease, such as hepatic lobe atrophy or portal vein involvement[229] (Table 84-9). Of greatest importance, with the increasing acceptance of major hepatic resection for these tumors, these systems attempt to define whether ipsilateral involvement alone is present, because tumors with bilateral extension, to either the secondary biliary radicles or the portal vein, are not resectable.

Table 84-8 American Joint Commission on Cancer Staging System for Extrahepatic Bile Duct Carcinoma: Tumor-Node-Metastasis (TNM) Classification

Stage	Grouping		
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1

DEFINITIONS

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to bile duct histologically
T2	Tumor invades beyond the wall of the bile duct
T3	Tumor invades the liver, gallbladder, pancreas, and/ or unilateral branches of the portal vein or hepatic artery
T4	Tumor invades any of the following: main portal vein or branches, common hepatic artery, or other adjacent structures, e.g., colon, stomach, duodenum, abdominal wall.

Regional lymph nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Table 84-9 Revised Preoperative Tumor Staging System for Patients with Hilar Cholangiocarcinoma*

Tumor Stage	Description
1	Tumor involving *biliary confluence ± unilateral extension to second-order biliary radicles*
	No liver atrophy or portal vein involvement
2	Tumor involving biliary confluence ± unilateral extension to second-order biliary radicles *with ipsilateral portal vein involvement ± ipsilateral hepatic lobar atrophy*
	No main portal vein involvement
3	Tumor involving biliary confluence plus *bilateral extension to second-order biliary radicles*;
	OR unilateral extension to second-order biliary radicles with *contralateral portal vein involvement*;
	OR unilateral extension to second-order biliary radicles with *contralateral hepatic lobar atrophy*;
	OR *main or bilateral portal venous involvement*

From Jarnagin WR, Fong Y, DeMatteo RP, et al: Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg 2001;234:507–517.

PROGNOSIS

Prognosis after Resection for Hilar Cholangiocarcinoma

Unfortunately, the prognosis with hilar cholangiocarcinoma is limited by the fact that as many as 90% of patients have unresectable disease at the time of presentation.[213] In addition, of those patients in whom surgery with curative intent is undertaken, up to 50% are found to have unresectable disease at the time of surgery.[230,231] In patients who present with unresectable disease, the median survival time is 10 months.[230] The immediate cause of death in these patients is hepatic failure or cholangitis related to tumor growth and inadequate drainage of the biliary tree.[232] In patients amenable to curative resection, the median survival is 35 months with 5-year survival rates of 10% to 30%.[224,230,233–238] The results of major studies on resection of hilar cholangiocarcinoma are summarized in Table 84-10. Surgical resection provides not only improved survival but also improved quality of life.[239] The primary risk factors for recurrence include the presence of positive margins[230,239,240] and node-positive tumors.[241,242]

Table 84-10 Results after Resection for Hilar Cholangiocarcinoma

Study	No. of Patients	Resection Rate (%)	Postoperative Mortality (%)	5-Year Survival (%)	Median Survival (mo)
Jarnagin et al, 2001[230]	160	50	10	—	35
Rea et al, 2004*	46	—	9	26	28
Hemming et al, 2005†	53	46	9	35	40
Liu et al, 2006‡	60	45	3	41	29
Dinant et al, 2006§	99	—	15	27	27

*Rea DJ, Munoz-Juarez M, Farnell MB, et al: Major hepatic resection for hilar cholangiocarcinoma: analysis of 46 patients. Arch Surg 2004;139:514–523.
†Hemming AW, Reed AI, Fujita S, et al: Surgical management of hilar cholangiocarcinoma. Ann Surg 2005;241:693–699.
‡Liu CL, Fan ST, Lo CM, et al: Improved operative and survival outcomes of surgical treatment for hilar cholangiocarcinoma. Br J Surg 2006;93:1488–1494.
§Dinant S, Gerhards MF, Rauws EA, et al: Improved outcome of resection of hilar cholangiocarcinoma (Klatskin tumor). Ann Surg Oncol 2006;13:872–880.

Prognosis after Resection for Intrahepatic Cholangiocarcinoma

In patients with intrahepatic cholangiocarcinoma, expected 3-year survival rates as high as 60% have been reported,[175,243] with 5-year survival rates of 30% to 45%.[231] Patients with unresectable disease have a median survival of 12 months.[222,244] Thus, the prognosis for completely resected intrahepatic cholangiocarcinoma appears to be improved prognosis over that for proximal (hilar) cholangiocarcinoma.

PRIMARY TREATMENT

Proximal (Hilar) Cholangiocarcinoma

Patients with unresectable bile duct cancers die within a year of diagnosis.[228] Surgical excision in those select patients with resectable disease is clearly the treatment of choice, because no other therapies have the potential for cure. The objectives of surgical management for patients with cholangiocarcinoma include both complete removal of tumor and adequate biliary drainage. It has become clear over the past 3 decades that curative treatment of tumors involving the upper half of the bile duct depends on aggressive excision, which often necessitates a major liver resection.[230,238] Until as recently as a decade ago, treatment of hilar cholangiocarcinoma was associated with mortality rates as high as 30%.[233,245–247] Fortunately, major improvements in the safety of these operations have been demonstrated by multiple investigators, and resection of hilar tumors now results in death in less than 10% of the patients, even when major liver resections are required.[233,240,245,247]

Assessment of Resectability and Surgical Procedure

Surgical exploration often is the only means of assessing resectability. Because of the potential morbidity of a laparotomy with no therapeutic benefit, staging laparoscopy has been advocated in order to save patients from unnecessary laparotomy. Of patients with hilar cholangiocarcinoma, up to 25% will benefit from staging laparoscopy because it may lead to detection of occult extrahepatic disease.[175] Laparoscopy is a very sensitive means to detect peritoneal metastases or additional intrahepatic disease through the use of laparoscopic ultrasound examination but is less sensitive in detecting nodal metastases.[175]

Hilar cholangiocarcinoma is considered unresectable owing to both local factors and metastatic spread. Clearly, disease outside the liver is not amenable to curative resection. Local factors that make these tumors unresectable include invasion of the main portal vein or both the right and left portal veins or hepatic arteries and tumor extension into second-order biliary radicals of both right and left hepatic lobes. By contrast, tumors extending into second- or third-order biliary radicles on one side of the liver or the ipsilateral portal vein can be resected with curative outcome.

The goals of surgical management for cholangiocarcinomas are both eradication of tumor and establishment of adequate biliary drainage. Tumors of the biliary confluence are particularly difficult to treat because symptoms often appear late in the disease course, when the lesion has already involved adjacent structures, such as the portal vein and adjacent hepatic parenchyma. Accordingly, complete resection requires biliary and hepatic resection and often major vascular reconstruction. Therefore, it is not surprising that historically, the surgical therapy for proximal biliary malignancies consisted mainly of biliary-enteric bypass as palliation for jaundice and cholangitis. The therapeutic approach to hilar cholangiocarcinoma was largely nihilistic, as a result of difficulty in delineating the extent of disease and the technical challenge of complete resection for such lesions.

Over the past decade, surgical approaches have become more aggressive, as demonstrated by the increasing number of hepatic resections which have been performed for bile duct cancers[230,233,234,245–247] (see Table 84-10). Recent improvements in ultrasonography, CT, and MRI have greatly facilitated preoperative evaluation and staging of cholangiocarcinoma. Such information has allowed improved patient selection and more realistic surgical planning.

The location and local extent of tumor dictate the extent of resection, with most lesions requiring an extended right or left hepatectomy for complete excision. Caudate resection often is required as a result of direct extension into caudate biliary radicles or parenchyma.[229,230,234,247] Common bile duct excision and portal lymphadenectomy also are essential for tumor clearance and accurate staging.

Surgical Treatment of Unresectable Hilar Cholangiocarcinoma

TRANSPLANTATION. Patients with unresectable disease due to bilateral extension into the liver may be candidates for neoadjuvant chemoradiation therapy followed by liver transplantation.[248,249] These patients are highly selected for better prognosis because they all undergo laparotomy and lymph node sampling to exclude patients with nodal involvement from transplantation.[250] In these good-risk patients with locally advanced disease but no evidence of metastatic or regional disease, disease-free survival rates may be as high as 60% after transplantation.[251]

PALLIATIVE PROCEDURES. For patients with unresectable hilar cholangiocarcinomas, significant improvement in quality of life can be obtained with percutaneous or open surgical bypass, because most patients are symptomatic with pruritus due to jaundice. Nonoperative palliative biliary decompression can be accomplished with percutaneous or endoscopic stenting, depending on the level of obstruction. Proximal lesions usually are approached percutaneously with placement of expandable stents or drainage catheters. Use of internal stents results in fewer electrolyte abnormalities and improvement in patient comfort, although morbidity or death has been reported in up to 30% of patients, and stent occlusion is common.[252–254]

Also reported is a significant risk of cholangitis with external and internal drainage, occurring in more than 90% of patients with metallic expandable internal stents in one series.[253] Bleeding and bile leaks also are frequent complications. More recent techniques such as photodynamic therapy have been used for relief of biliary obstruction and may hold some promise for the future.[255] Palliative surgical bypass can be performed by decompressing the biliary tree using the segment III bile duct, approached through the round ligament.

Because patients with unresectable disease have a short median survival, those with incontrovertible preoperative imaging evidence of unresectability should be managed with percutaneous internal or external drainage. In patients in whom surgical exploration reveals unresectable disease, surgical bypass offers the advantage of fewer episodes of cholangitis and stent obstruction, with an improved quality of life.[256] In some series, surgical bypass for unresectable disease is the only biliary drainage procedure ever required by the patient.

Intrahepatic Cholangiocarcinoma

Patients with intrahepatic cholangiocarcinoma typically present with single liver lesions. Standard treatment with anatomically based hepatic resection is the procedure of choice. Because these tumors frequently are asymptomatic, fewer issues with palliative management need to be addressed.

Adjuvant Therapy

Chemotherapy

No standard adjuvant chemotherapy option for cholangiocarcinoma has been established. In the most important study by Takada and colleagues, 508 patients with pancreaticobiliary malignancies (including 139 with bile duct cancers) were randomized to receive adjuvant chemotherapy or no adjuvant therapy after definitive resection of the tumor.[194] The chemotherapy regimen comprised mitomycin and 5U, and although a trend toward reduced recurrence and mortality was observed in the chemotherapy arm, the difference from treatment arm data was not statistically significant. Other reports of the use of adjuvant chemotherapy have been from small or retrospective series.[257,258]

Radiation Therapy or Chemoradiation Therapy

The tendency for cholangiocarcinoma to recur locally provides a rationale for additional local therapy after definitive surgery. This is in contrast with pancreas cancer, for instance, in which concern is focused predominantly on the potential for systemic relapse and has led to a relative diminution of the role of radiotherapy in recent years. This rationale, however, is not underpinned by hard prospective data, and the available evidence is mixed. Small retrospective studies have inferred a benefit.[259,260] Other reports have not shown a benefit.[261]

Chemoradiation therapy has a theoretical advantage stemming from the radiosensitization phenomenon associated with use of 5U. Again, the data do not address this issue satisfactorily. Although several phase II and retrospective series[262,263] suggest a benefit, phase III data on this aspect of treatment are extremely limited.

TREATMENT OF ADVANCED BILE DUCT CANCERS

Chemotherapy

To date, no chemotherapeutic regimen has consistently shown activity against cholangiocarcinoma. Many of the issues that pertain to chemotherapy trials in gallbladder cancer are directly relevant to the interpretation of data from trials for cholangiocarcinomas. Studies performed to date typically have been small, single-institution phase II trials, including patients with both gallbladder and bile duct cancers.[264]

Single-agent 5-FU-based chemotherapy has been shown to give a response rate of approximately 10%.[152] In recent years, gemcitabine has become the most widely used drug in biliary tract malignancies, primarily as a result of its established primacy for treatment of pancreas cancer. Use of gemcitabine as a single agent has resulted in response rates of 16% and 26% in two phase II studies.[265,266] The focus at present is on combining gemcitabine with other agents, and multiple phase II studies of gemcitabine doublets have been performed employing taxanes, platinum agents, fluoropyrimidines, and topoisomerase inhibitors.[202,267–270] The optimal chemotherapeutic regimen for advanced cholangiocarcinoma is unknown.

Intra-arterial Chemotherapy

Chemotherapy delivered by intra-arterial administration for unresectable hepatobiliary malignancies is an attractive concept because of the predilection of cholangiocarcinoma for locoregional relapse and the relative lack of systemic toxicity with this therapeutic approach. The major disadvantage is the need for a port, which requires a laparotomy for placement, as well as the availability of trained skilled surgeons, which limits widespread clinical application. Several small trials have demonstrated promising response rates, with acceptable toxicity, in selected patient populations.[271,272] Additional trials are under way to delineate the role of intra-arterial chemotherapy in cholangiocarcinoma and other biliary tree malignancies.

Radiotherapy in Bile Duct Cancers

In cases of unresectable but nonmetastatic cholangiocarcinoma, the use of external beam radiation therapy may improve pain control and biliary decompression.[273] Anecdotal reports of long-term survivors after external beam radiation therapy show that some patients may benefit from such treatment, but no controlled studies have proved such a benefit, and the potential for complications such as duodenal or bile duct stenosis and duodenitis must be a consideration. Newer techniques such as intraoperative radiotherapy, intraluminal brachytherapy, and intensity-modulated radiation therapy represent a technical advance in terms of dosage delivery and minimization of toxicity; however, their impact on survival is unclear at the present time.[274]

NOVEL THERAPEUTICS IN CHOLANGIOCARCINOMAS

As noted earlier, cholangiocarcinoma cell growth is strongly dependent on EGFR signaling,[275] so the EGFR is a rational therapeutic target. The success of this approach has been documented in mouse models.[276] The response to EGFR inhibition may be dependent on the presence of mutations in the *EGFR* gene,[277] as is the case in non-small-cell lung cancer. Case reports have inferred a benefit, and this approach needs further development.[278,279] COX-2 also is important in cholangiocarcinogenesis, and significant interplay between COX-2 and other growth-regulatory pathways is likely.[280] COX-2 inhibition may have a synergistic role with other strategies or as a chemopreventive agent.

TREATMENT COMPLICATIONS

Attesting to the difficult management of patients with hilar cholangiocarcinoma, the postoperative complication rate is as high as 50% to 60%.[230,281] A majority of these complications are infectious. In many series, treatment of hilar cholangiocarcinoma with aggressive resection results in a perioperative mortality rate of approximately 5% to 10%.[230]

Fewer postoperative complications are expected from surgical procedures for patients with intrahepatic cholangiocarcinoma, because these operations are usually more straightforward and do not usually require bile duct resection. The overall complication rate is approximately 20% to30%, with a mortality rate of less than 3%.[222,223,238,240,281]

FOLLOW-UP PROGRAM

After resection of a hilar cholangiocarcinoma, locoregional recurrence occurs most frequently,[282] followed by distant sites including the liver. For patients with intrahepatic cholangiocarcinoma, the most common site of recurrence is within the liver or regional nodes.[222,283] Therapy for recurrence is palliative, because curative surgical re-excision usually is impossible owing to the challenging anatomic location and the radical procedures that resection of the primary tumor would require. Therefore, the goal of follow-up evaluation is diagnosis of symptomatic recurrences in order to direct palliative therapy and diagnosis of benign complications of surgical treatment such as biliary strictures. The main symptoms of recurrence that demand palliation are pruritus and cholangitis associated with jaundice. For biliary drainage to relieve jaundice or cholangitis, either surgical drainage[253] or drainage by percutaneous transhepatic cholangiography (PTC) can be effective.[284] Endoscopic drainage has little role in the relief of jaundice in patients who have had Roux-en-Y biliary reconstruction. For limited recurrences, intraluminal brachytherapy or external beam radiotherapy[285] may improve palliation and, potentially, survival.

Routine follow-up evaluation consists of office visits every 3 months with physical examination and measurement of liver enzymes. Although a rising alkaline phosphatase level is a good indicator of evolving biliary obstruction, patients recovering from liver resection and biliary obstruction may have persistent elevations of alkaline phosphatase. In up to 10% of patients with biliary surgical reconstruction, however, a benign anastomotic stricture may develop. Most patients with recurrence or a benign stricture will present with jaundice or cholangitis.

ISSUES FOR THE FUTURE

The only known curative therapy for intrahepatic and extrahepatic bile duct cancers is surgical resection. No proven role has been established for adjuvant chemotherapy alone or adjuvant combined chemoradiation, although further studies are needed to fully define the role of these therapies. Continued assessment of new drugs, novel radiosensitizers, and biologic agents is warranted. A better understanding of the molecular pathogenesis and genetics of bile duct cancers may lead to new therapeutic and ultimately preventive strategies for high-risk populations.

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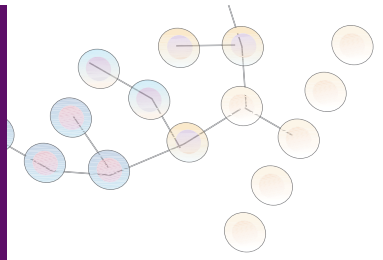
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85 Carcinoma of the Pancreas

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SUMMARY OF KEY POINTS

Incidence
- Approximately 37,000 new pancreatic cancer cases accrued in the United States in 2007.
- Approximately 33,000 deaths from pancreatic cancer occurred in the United States in 2007.
- Pancreatic cancer remains the fourth leading cause of cancer-related death for both men and women.

Pathology
- Adenocarcinomas account for 90% of pancreatic cancers.
- Less than 5% are endocrine tumors.
- Less than 5% are cystic tumors.
- Less than 5% are lymphomas or sarcomas.

Clinical Presentation
- Two thirds of pancreatic tumors are located in the head of the pancreas; clinical features include vague pain, weight loss, fatigue, and jaundice.
- One third of pancreatic tumors are in the body or tail; clinical features include epigastric or back pain, weight loss, fatigue, and evidence of metastatic disease.

Staging Evaluation
- Triple-phase helical computed tomography (CT) scanning is performed in all patients.
- Cholangiography is used for severe jaundice if the patient is not scheduled for immediate surgical exploration or as the result of equivocal findings on the CT scan.
- Endoscopic ultrasound examination with biopsy is used for atypical lesions.
- Fine needle aspiration biopsy is performed before institution of palliative treatment if the lesion is unresectable.
- Magnetic resonance imaging (MRI), angiography, and positron emission tomography (PET) scans are used in selected cases.
- Preoperative tissue diagnosis is unnecessary with resectable lesions.
- Laparoscopic staging may avoid unnecessary laparotomy for unresectable lesions.

Therapy
- Surgical resection of the tumor (10% to 15% of all tumors are resectable; 70% to 80% of tumors staged preoperatively as resectable are resected) is performed.
- Adjuvant therapy (chemoradiation therapy or chemotherapy alone) is given.
- Neoadjuvant therapy may be of use in resectable disease and in rendering borderline-unresectable disease resectable.

Palliation
- Endoscopic or percutaneous transhepatic biliary stents are used.
- Operative gastric or biliary bypass is performed in selected patients.
- Alcohol celiac plexus block is used.
- Chemoradiation therapy is used for locally advanced unresectable lesions.
- Chemotherapy is used for metastatic disease.

Survival
- "Curative" surgical resection gives a median survival of 18 months and a 5-year survival rate of approximately 20%. New adjuvant approaches may substantially improve these results.
- Survival of patients with unresectable lesions is 4 to 8 months, with less than 20% surviving for 1 year.

INTRODUCTION

Pancreatic adenocarcinoma is one of the most lethal malignancies, with an overall 5-year disease-free survival rate on the order of 1% to 2%. Most pancreatic cancers are not diagnosed until they are locally advanced or until regionally disseminated disease has developed that is not amenable to curative surgical resection. Chemotherapy and radiation therapy are of only modest benefit in this disease, and typical survival is on the order of 6 months. Of those patients with apparently resectable disease who undergo surgical exploration, between 20% and 40% are found to have unresectable lesions. Even those patients in whom a margin-negative resection has been achieved have a 5-year disease-free survival rate of less than 30%, and in approximately half of the patients surviving 5 years, the cancer will recur between years 6 and 10. Thus, the treatment of pancreatic cancer remains a challenge to the surgical, radiation, and medical oncologist.

In recent years, a number of positive developments have occurred in the management of pancreatic cancer. Improvements in the preoperative staging of pancreatic cancer have reduced the number of patients undergoing laparotomy for what proves to be unresectable disease. Advances in surgical technique and perioperative management allow pancreatic cancer resections to be performed with very low mortality and tolerable morbidity. In patients who undergo resection, even when not cured, survival appears to be substantially longer than in patients managed with other modalities; thus, at a minimum, resection achieves substantial palliation and extension of survival. Furthermore, evolving approaches to adjuvant chemotherapy and chemoradiation therapy may substantially improve long-term survival after an attempted curative resection.

For patients who are first seen with unresectable disease, an appropriate focus has been placed on optimizing quality of life. Nonoperative methods of relieving obstructive jaundice avoid the need for laparotomy in most patients. Appreciation of the importance of palliating pain is of great benefit to those patients whose cancer is not potentially curable. Furthermore, new approaches to chemotherapy offer the hope of extending both quality and quantity of life in many patients. This chapter reviews current approaches to the management of patients with pancreatic cancer.

INCIDENCE

Pancreatic carcinoma is a relatively uncommon malignancy. Approximately 37,000 new cases were diagnosed in the United States in 2007, accounting for 2.6% of all cancer diagnoses. Because the annual death rate from pancreatic cancer approximates its incidence, pancreatic cancer is a fairly common cause of cancer mortality in the United States. Carcinoma of the pancreas ranks fourth behind carcinomas of the lung, colorectum, and breast as a cause of cancer deaths.[1–3] Because of the relative rarity of breast cancer in men and the nonexistence of prostate cancer in women, pancreatic cancer is the fourth most common cause of cancer-related death in both men and women, accounting for approximately 6% of cancer deaths overall.

The incidence of pancreatic carcinoma has increased three- to fourfold in the 20th century, but appears to have leveled off in recent decades. This probably reflects both improvements in the accuracy of diagnostic techniques such as CT scanning and a genuine increase in incidence. The risk of developing pancreatic cancer increases with age[1,4]; it has been estimated that this risk increases two- to threefold for each decade of life after age 40 years. Although patients typically are first seen in their 60s and 70s, diagnosis of pancreatic cancer in patients in their 40s and 50s is not uncommon; pancreatic cancer is rarely seen in patients younger than 30 years.

EPIDEMIOLOGY

Adenocarcinoma of the pancreas traditionally has been viewed as occurring more commonly in men than in women (relative risk, 1.5 : 1), although recent data suggest that relative risk in women is approaching that seen in men,[1,3] perhaps because of increased tobacco use by women in the latter half of the 20th century. In the United States, pancreatic cancer occurs more frequently in blacks than in whites (relative risk, 2 : 1) and may be somewhat less common in persons of Asian ancestry than in whites (relative risk, 0.7 : 1). Worldwide, incidence rates are highest in industrialized countries and lowest in African and Asian countries,[1,5] suggesting that environmental factors linked to a "Western lifestyle" substantially increase the risk of pancreatic cancer. The high incidence rates observed in African Americans, in contrast with the low rates observed in African countries, also argue strongly for the role of environmental as opposed to hereditary factors in the etiology of most pancreatic cancers.

Environmental Risk Factors

Studies of environmental factors linked to the development of pancreatic carcinoma have identified a number of agents that may play a role in pancreatic carcinogenesis, as summarized in Table 85-1.[1,6–25] Cigarette smoking significantly increases the risk of this form of cancer, as it does for a variety of other tumors. Certain industrial solvents, particularly those used in metal refining, have been linked to the development of pancreatic cancer. Dietary factors also play a role. High dietary fat intake and obesity clearly increase the risk of developing pancreatic cancer, whereas generous vitamin C intake and consumption of fruits and vegetables may decrease the risk of pancreatic cancer. Although alcohol consumption does not appear to be a risk factor for the development of pancreatic cancer, chronic pancreatitis almost certainly is.[8] Consumption of coffee and other caffeinated beverages, which had been suggested to be a risk factor on the basis of early studies, appears to be unrelated to the development of pancreatic cancer.

Table 85-1 Risk Factors for Pancreatic Cancer

Risk Factor	Relative Increase in Risk
Proven risk factors	
Cigarette smoking	2- to 3-fold
Industrial chemical exposure	3- to 5-fold
Chronic pancreatitis	2- to 10-fold
Diabetes mellitus	2- to 3-fold
Obesity	2- to 3-fold
Unproven or disproven risk factors	
Coffee consumption	
Alcohol consumption	

Perhaps the most controversial risk factor is diabetes. Approximately 15% of patients with pancreatic cancer become diabetic in the 6 months preceding the diagnosis of their cancer. This probably reflects local alterations in pancreatic function resulting from an occult tumor, rather than rapid development of cancer after the onset of diabetes. When patients in whom diabetes develops within 2 years of their diagnosis of pancreatic cancer are excluded, however, an approximately twofold increased risk for the development of pancreatic cancer is found among patients with long-standing diabetes.[9]

PATHOLOGY AND TUMOR BIOLOGY

If stromal tissue, nerves, and lymphatics are excluded, three principal cell types are seen in the pancreas: ductal cells, acinar cells, and endocrine cells (Fig. 85-1). Adenocarcinomas are malignancies derived from neoplastic transformation of the pancreatic ducts and comprise the vast majority (greater than 90%) of pancreatic neoplasms. These tumors display a glandular morphology, although occasionally squamous differentiation may be present. In such cases, the term *adenosquamous carcinoma* is used. The stage of pancreatic adenocarcinomas is related to survival, with adenosquamous carcino-

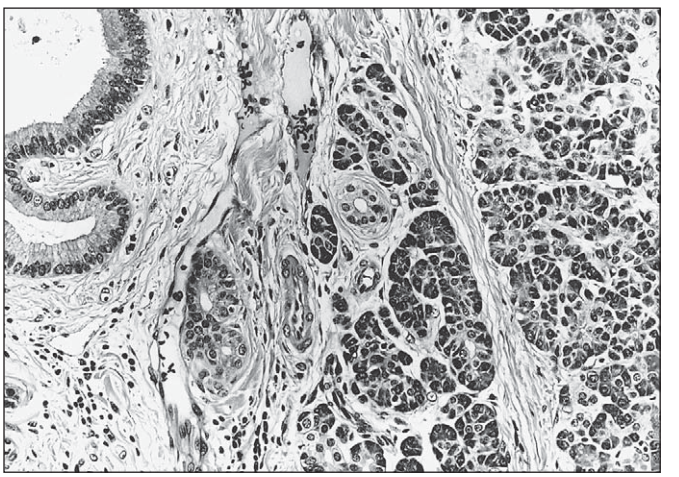


Figure 85-1 • Section of normal pancreas showing exocrine glands on the *right* and a portion of the wall of the large duct on the *left*. Note the regularity of the ductal lining epithelium. (Hematoxylin and eosin, ×200.)

mas representing a particularly lethal subset, with few 1-year survivors.[26] Although ductal adenocarcinoma is the most common pancreatic tumor, a variety of other benign and malignant pancreatic tumors have been described, as shown in Table 85-2. Most other malignant pancreatic lesions, such as pancreatic endocrine tumors, acinar cell carcinomas, and cystadenocarcinomas, appear to be less biologically aggressive than pancreatic adenocarcinomas and have a somewhat better prognosis.

Pancreatic adenocarcinomas arise most commonly in the head of the pancreas; the other lesions are distributed evenly in the body and tail of the gland. An important point is that nonpancreatic tumors of the distal bile duct, duodenum, and ampulla of Vater, although much less common than pancreatic adenocarcinoma, comprise almost one third of resectable tumors in the region of the pancreatic head. Furthermore, these tumors tend to be biologically less aggressive than pancreatic carcinomas, with 5-year disease-free survival rates after resection ranging from 30% to 50%.[27–29] It can be difficult, if not impossible, to distinguish these tumor types from routine adenocarcinoma of the pancreas on the basis of endoscopic, radiologic, or needle cytology criteria. Only histologic sectioning of a resected tumor mass can accurately classify the specific tumor type in some circumstances. Another possibility to be considered is a metastasis to the pancreas, which may mimic a primary tumor. For example, clear cell renal carcinomas that have metastasized to the ampullary region may be confused on imaging studies with a pancreatic carcinoma.

Pancreatic adenocarcinomas tend to be aggressive tumors that disseminate early and tend to follow similar patterns of metastatic spread in most patients. Local invasion into adjacent structures frequently is seen, with encasement of the superior mesenteric or portal vein and the superior mesenteric artery representing a common event that may preclude resection. Spread to regional lymphatics is common, as is metastasis to the liver by way of the portal vein. Spread to peritoneal surfaces (carcinomatosis) frequently is seen in advanced disease, as are lung metastases.

The pathologic staging of pancreatic cancer is based on the extent of tumor involvement of local and distant structures, as shown in Table 85-3. Stage I tumors are limited to the pancreas. Stage II tumors are regionally invasive, without involvement of the celiac or superior mesenteric artery, but may involve regional lymph nodes.

Table 85-2 Histologic Classification of Pancreatic Tumors

BENIGN TUMORS
Serous cystadenoma
Mature cystic teratoma
TUMORS OF INDETERMINATE MALIGNANCY
Mucinous tumors of the pancreas
Intraductal tumors
Solid and papillary tumors
Neuroendocrine tumors
MALIGNANT TUMORS OF PANCREATIC ORIGIN
Ductal adenocarcinoma
Acinar cell carcinoma
Adenosquamous carcinoma
Anaplastic carcinoma
Cystadenocarcinoma
Pancreaticoblastoma
Small cell carcinoma

Table 85-3 Staging for Pancreatic Cancer

PRIMARY TUMOR (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor <2 cm
T2	Tumor >2 cm, confined to the pancreas
T3	Tumor extends locally beyond the pancreas
T4	Tumor involves celiac or superior mesenteric arteries
LYMPH NODES (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
DISTANT METASTASES (M)	
MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
STAGE GROUPING	
IA	T1, N0, M0
IB	T2, N0, M0
IIA	T3, N0, M0
IIB	T1–3, N1, M0
III	T4, N0–1, M0
IV	T1–4, N0–1, M1

Stage I and II tumors are considered potentially amenable to resection with curative intent. Stage III lesions are defined by direct involvement of the celiac or superior mesenteric arteries, and stage IV lesions are defined by the presence of distant metastases. Patients with stage III and IV disease generally are not considered candidates for potentially curative resection, although this view recently has been challenged for selected patients with isolated liver metastases.[30,31]

Cystic Neoplasms

Cystic neoplasms of the pancreas are distinguished from an inflammatory fluid collection (pseudocyst) by the presence of an epithelial lining. Cystic neoplasms of the pancreas can be divided into benign tumors and malignant tumors (cystadenocarcinomas).[26] The presence of invasion defines the cystic lesion as a carcinoma. Benign cystic tumors can be further divided, on the basis of radiologic factors and by analysis of cyst fluid, into lesions with little predilection to become malignant, termed *serous cystadenomas*, and those with a significant risk of malignant degeneration, termed *mucinous cystic neoplasms*. Although the mucinous tumors previously were subclassified as either benign mucinous cystadenomas or malignant cystadenocarcinomas, the preferred designation is *neoplasm*, because of the malignant potential of all mucinous cystic tumors, as evidenced by the frequent identification of cystadenocarcinoma in patients suspected of harboring a mucinous cystadenoma. The epithelial lining of a mucinous cystic neoplasm may range in cytoarchitecture from bland cells to cells with high-grade dysplasia. The biologic behavior of the lesion, however, is driven by the presence or absence of invasion. In order to evaluate for the presence of invasion, complete resection and histologic evaluation of the entire lesion may be needed. Mucinous cystic tumors occur primarily in women and may have ovarian-type stroma surrounding the neoplastic lining.

Although large lesions (greater than 3 cm in diameter) generally should be resected, the management of smaller asymptomatic lesions is controversial. Several centers are observing small asymptomatic cystic neoplasms.[32,33] The evolution of changes on surveillance imaging that led to resection was 8% within 2 years of study entry in one series of patients managed nonoperatively from Memorial Sloan-Kettering Cancer Center.[32] The lifetime risk of evolving malignant changes is the critical factor in determining whether resection should be carried out, and at present this is uncertain. With longer term follow-up in these sizable patient series, a better understanding of the risk of malignant progression should evolve.

Cystadenocarcinomas of the pancreas are less biologically aggressive than pancreatic adenocarcinomas, with a higher cure rate after complete resection. Because even serous cystadenomas can be locally invasive,[3] an aggressive approach to the removal of most serous cystadenomas as well as of all mucinous tumors of the pancreas is justified. In contrast with traditional pancreatic adenocarcinomas, mucinous tumors of the pancreas with an invasive component are less predictable in their biologic behavior, with some malignant tumors remaining indolent for months to years. They may be locally or regionally invasive without forming metastases. When mucinous tumors of the pancreas do disseminate, they tend to form peritoneal implants but rarely give rise to liver or lung metastases, much akin to mucinous malignancies of the appendix.

A related but distinct lesion is the intraductal papillary mucinous neoplasm (IPMN).[26,34] Unlike other cystic tumors, which do not communicate with the main pancreatic duct, IPMNs arise as a result of abnormalities of the pancreatic duct in which all or part of the pancreatic duct epithelium becomes dysplastic, and subsequently may degenerate to overt malignancy. IPMNs may arise from the main pancreatic duct or from side branch ducts; the risk of harboring invasive malignancy at diagnosis is greater for main duct lesions.[35] In some cases the entire pancreatic duct is ectatic and mucus-filled, giving a characteristic appearance on evaluation by endoscopic retrograde cholangiopancreatography (ERCP). Because of their predilection to harbor carcinoma in situ and even areas of invasive carcinoma, surgical resection of IPMNs may require total pancreatectomy in some patients, although margin-negative resections can be achieved with partial pancreatectomy in many patients. No consensus now exists on an appropriate follow-up strategy for patients who have undergone partial pancreatectomy for IPMNs, but the potential for recurrence or the development of new lesions mandates some form of surveillance. Our policy is to perform MRI with magnetic resonance cholangiopancreatography (MRCP) at 6-month intervals.

GENETICS

Molecular Genetics

Research performed over the last several decades has demonstrated that the development of malignancy is a multistep process in which distinct oncogenes are activated and tumor-suppressor genes inactivated in a clonal population of cells. This process ultimately gives rise to a cell population resistant to molecular mechanisms that normally regulate cell proliferation and programmed cell death.[36] Molecular events underlying the development of pancreatic cancer have been studied extensively, and a number of alterations in oncogenes and tumor suppressor genes that are thought to play a role in the development of this disease have been identified.[37–42] Common abnormalities include activating mutations in the K-ras oncogene (which occur in more than 90% of pancreatic cancers), overexpression of the HER2-neu oncogene (seen in 50% to 70% of pancreatic cancers), and loss of expression of the CDKN2, p53, and DPC4 tumor suppressor genes (seen in 100%, 70%, and 50% of pancreatic cancers, respectively).

The identification and characterization of histologically distinct premalignant precursor lesions that give rise to pancreatic adenocarcinomas, termed *pancreatic intraepithelial neoplasms* (PanINs), suggest that the activation of oncogenes and loss of tumor suppressor genes occur in a stepwise fashion. Activation of the K-ras oncogene is seen in very early preneoplastic lesions (PanIN1s) and even in secretions of patients with chronic pancreatitis and no known pancreatic cancer.[26,36] Similarly, HER2-neu overexpression frequently is seen in early intraepithelial neoplasms. By contrast, loss of the CDKN2, p53, and DPC4 tumor suppressor genes appears to be a relatively late event in tumorigenesis, seen in more advanced preneoplastic (PanIN2 and PanIN3) and frankly neoplastic lesions.

An intriguing animal model developed by Tuveson and colleagues in which activated K-ras is expressed in the pancreas of transgenic mice recapitulates the cellular and molecular events observed in human pancreatic cancer quite precisely.[43] In these animals, PanIn lesions develop that are indistinguishable from those seen in human patients, which progress to invasive carcinomas as a result of additional stochastic events. Additional studies have demonstrated that deleting the p53 gene in the pancreata of such mice results in the high-frequency development of invasive pancreatic carcinomas with metastases to regional lymphatics and the liver.[44] Such animal models may be of particular use in the development of novel approaches to treatment and chemoprevention.

Familial Pancreatic Cancer

Although a majority of pancreatic cancers appear to be sporadic in origin, approximately 5% of pancreatic malignancies are seen in patients with a familial history of pancreatic cancer.[45] Among patients with two first-degree relatives with pancreatic cancer, the relative risk of developing pancreatic cancer is increased 18-fold. In patients with three or more affected relatives, the increased risk is 57-fold. Such data strongly support the notion that familial pancreatic cancer is a real entity.

An additional unknown percentage of pancreatic cancers may reflect the presence of an overall cancer family syndrome that is less strikingly specific for the pancreas. For example, it has been shown that a subset of kindreds with the familial atypical mole–malignant melanoma syndrome (FAMM) have approximately a 20-fold increased risk for the development of pancreatic cancer,[42] although the relative risks for other forms of cancer are not substantially increased. Molecular analysis has demonstrated that this subset of FAMM patients has a germ-line alteration in the CDKN2 tumor suppressor gene.[42] Similarly, patients at risk for breast cancer as a result of inherited *BRCA2* gene abnormalities also have a risk of pancreatic cancer at least 10-fold that of the general population.[36,46] Other familial syndromes associated with an increased risk of pancreatic cancer include the hereditary nonpolyposis colon cancer syndrome, familial adenomatous polyposis, and ataxia-telangiectasia. Furthermore, the hereditary pancreatitis syndrome, caused by a mutation in the trypsinogen gene, is associated with a 40% to 70% risk of pancreatic cancer. Thus, genetic factors, although of variable penetrance, clearly play a role in the predisposition to pancreatic cancer development in many patients.

DIAGNOSIS

Signs and Symptoms

Patients with pancreatic cancer often describe feeling vaguely unwell for a number of months before the development of overt clinical manifestations that lead to the diagnosis of their illness. Common signs and symptoms of pancreatic cancer are summarized in Table 85-4. Although the development of "painless jaundice" often is thought of as a typical presenting feature of pancreatic cancer, most patients have mild to moderate abdominal pain. The presence of back pain is a particularly ominous symptom that may reflect retroperitoneal nerve invasion by tumor.

Table 85-4 Signs and Symptoms of Pancreatic Cancer

COMMON SIGNS AND SYMPTOMS
Jaundice
Anorexia
Weight loss
Abdominal pain
LESS COMMON SIGNS AND SYMPTOMS
Vomiting
Palpable mass
Palpable gallbladder (Courvoisier's sign)
Back pain
Splenomegaly
Constipation
Thrombophlebitis (Trousseau's sign)

The development of obstructive jaundice is related to the anatomic location of the primary tumor. It is almost universal in tumors of the pancreatic head and is quite rare in patients with primary tumors of the pancreatic tail. Liver function tests should be performed to distinguish obstructive jaundice from a primary hepatocellular process such as hepatitis. Patients with severe obstructive jaundice may have some degree of associated coagulopathy from hepatic dysfunction. Coagulation parameters should be tested in all jaundiced patients, and those with coagulation abnormalities should receive preoperative vitamin K or perioperative fresh-frozen plasma, or both.

Weight loss is relatively common in patients with pancreatic cancer. This finding may reflect duodenal obstruction by tumor, an as-yet poorly understood inhibitory effect of pancreatic cancer on gastric motility, or effects of tumor-related cytokines on host metabolism. Except in extremely malnourished patients, aggressive preoperative or perioperative nutritional support, or both, has not been shown to be of benefit.[3]

Findings on physical examination often are nonspecific.[3] Jaundice is common, as noted earlier, but not specific for the presence of a malignancy. The presence of a palpable pancreatic mass or gallbladder (Courvoisier's sign) is uncommon and usually is observed only in thin patients. Hepatomegaly due to liver congestion or the presence of metastatic disease is similarly seen in a minority of patients at the time of initial diagnosis.

Radiologic Evaluation

Patients suspected of having a pancreatic malignancy generally are evaluated by thin-cut, contrast-enhanced CT scanning. This modality is of use in identifying the tumor mass, as well as in assessing the liver for metastasis. Vascular involvement of superior mesenteric vein, portal vein, and celiac and superior mesenteric arteries also can be determined by CT scanning (Fig. 85-2). Ultrasonography is useful in identifying the primary tumor mass (Fig. 85-3), particularly in the pancreatic head, but is less sensitive than CT and provides less information regarding local and regional dissemination. MRI has not proved superior to CT scanning for assessment of the primary tumor, metastatic disease, or vascular encasement. Occasional patients with CT findings suggestive but not diagnostic of vascular encasement may benefit from preoperative visceral angiography, although improvements in CT methods, particularly the use of dynamic contrast infusion and helical (spiral) techniques, have largely supplanted angiography.

PET using [^{18}F]fluoro-2-deoxyglucose (FDG-PET) has not proved to be of general use in the diagnosis or staging of pancreatic cancer. Initial hopes that FDG-PET would distinguish chronic pancreatitis from pancreatic neoplasia have not been supported in clinical studies.[47] Furthermore, FDG-PET misses a substantial number of lymph node metastases and peritoneal metastases.[48] Although the addition of FDG-PET to CT-based diagnostic algorithms appears rarely to alter subsequent diagnostic or therapeutic maneuvers, it may be of use in determining tumor response to therapy.[49] Whether PET technology using agents that detect cell proliferation rather than cell metabolism will improve these results is currently under evaluation.

Patients with a pancreatic mass on CT and no evidence of metastatic disease or vascular encasement require no further testing and can be taken to the operating room for surgical resection. At the time of definitive surgery, a laparoscopic evaluation of resectability may be performed, as discussed later. It is not necessary to obtain a preoperative tissue diagnosis. Indeed, because of the frequent presence of a dense reactive stroma surrounding small islands of cancer cells, cytologic assessment of pancreatic malignancies is notoriously inaccurate, rendering absence of malignant cells on percutaneous or endoscopic biopsy of little value in the management of patients with a resectable pancreatic mass. An additional concern with percutaneous techniques is the possibility of tumor dissemination as a result of the biopsy process, as has been suggested in some studies.[50]

Endoscopic Retrograde Cholangiopancreatography

Patients with jaundice but no mass on CT scans generally are evaluated with ERCP. This study may reveal an irregular or tapering biliary stricture characteristic of an obstructing periampullary tumor (Fig. 85-4). Sometimes the biliary stricture is seen in conjunction with a pancreatic duct stricture—the "double duct" sign—which is highly suggestive of the presence of a malignancy. Irregular strictures of the pancreatic duct also may be seen in patients with pancreatic carcinoma. Such endoscopic findings, even in the absence of a pancreatic mass on CT scanning, justify proceeding to surgical resection. Examination of endoscopic brushings and biopsy specimens may confirm the presence of a pancreatic neoplasm but carries a relatively high false-negative rate, as discussed earlier. An aggressive surgical approach to the management of suggestive biliary strictures, particularly in patients without a history of gallstone disease, often will result in removal of tumors at a relatively early stage.

The risks and benefits of decompressing the biliary tree before resecting a pancreatic cancer remain controversial.[51–54] Although the rationale for relieving obstructive jaundice and normalizing liver function before surgery is clear, several randomized prospective trials have failed to show a benefit of preoperative biliary stenting by ERCP or percutaneous techniques. Furthermore, an increased incidence of complications is found in patients who undergo stenting before resection; the presence of an endoscopically placed stent appears to increase the risk of postoperative morbidity, particularly the development of infectious complications, in patients undergoing pancreaticoduodenectomy.[54]

Probably the critical factor in deciding whether to perform preoperative decompression in a jaundiced patient who will definitely be taken for surgical exploration is the interval to surgery. If the patient can be operated on in a few days and is not symptomatic from jaundice, it may be best to proceed directly to surgery. If a delay in scheduling surgery is expected or if the patient is extremely symptomatic from jaundice, it may be best to stent the patient, both for comfort and to minimize the risk of cholangitis.

Endoscopic Ultrasonography

Another important endoscopic technique that has begun to play a major role in the diagnosis and staging of patients with pancreatic malignancies is endoscopic ultrasonography (EUS).[55] EUS can assess tumor size, portal and mesenteric vein involvement, and regional

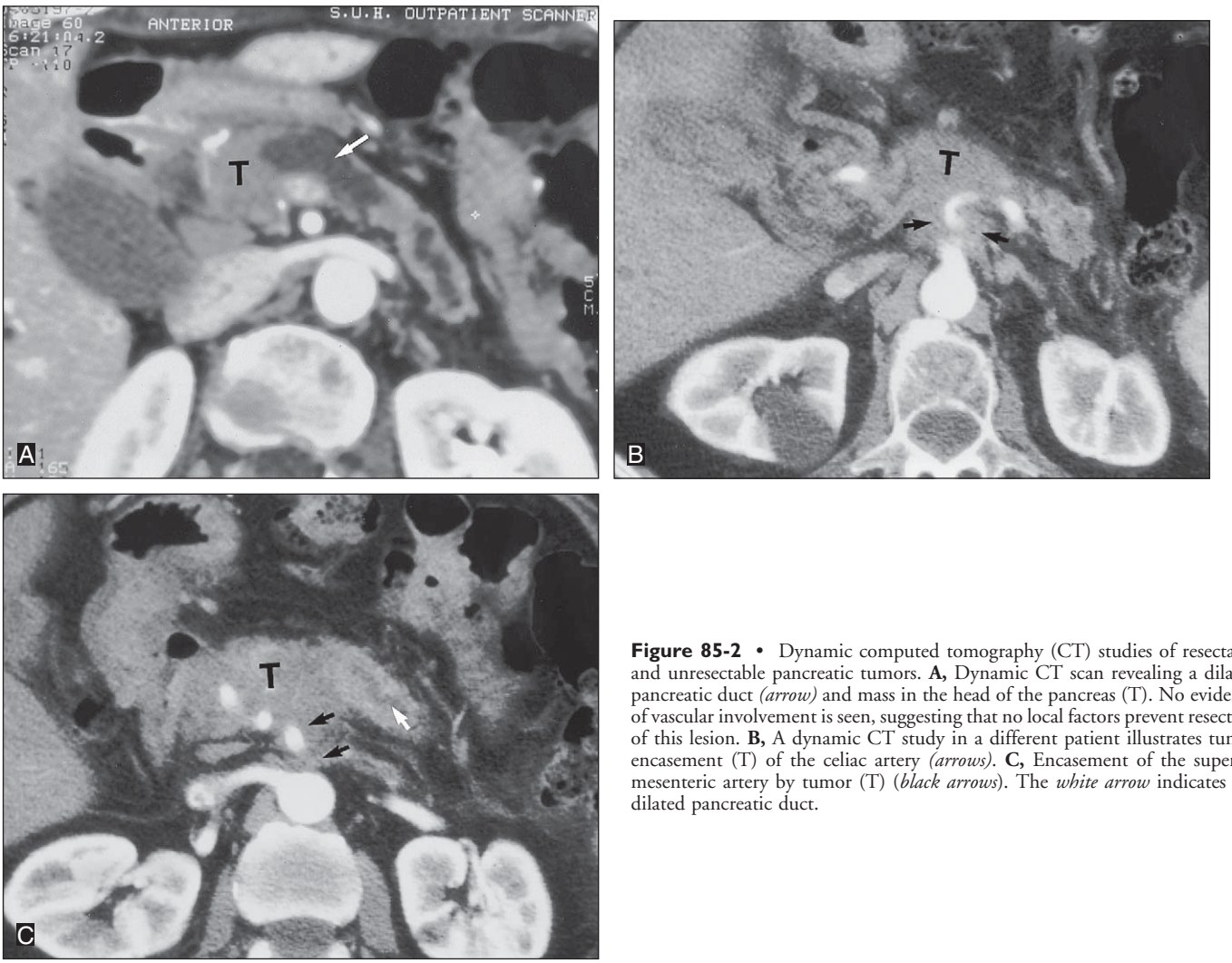


Figure 85-2 • Dynamic computed tomography (CT) studies of resectable and unresectable pancreatic tumors. **A,** Dynamic CT scan revealing a dilated pancreatic duct *(arrow)* and mass in the head of the pancreas (T). No evidence of vascular involvement is seen, suggesting that no local factors prevent resection of this lesion. **B,** A dynamic CT study in a different patient illustrates tumor encasement (T) of the celiac artery *(arrows)*. **C,** Encasement of the superior mesenteric artery by tumor (T) (*black arrows*). The *white arrow* indicates the dilated pancreatic duct.

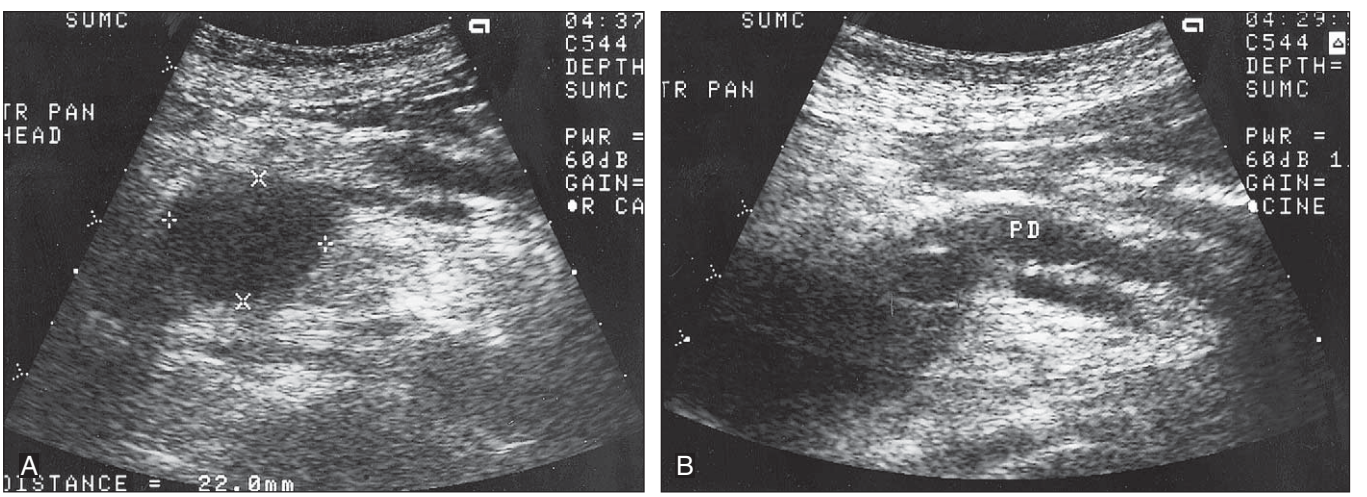


Figure 85-3 • **A,** Ultrasonographic examination of a mass in the head of the pancreas. The pancreatic mass is hypoechoic compared with normal parenchyma and is easily discernible from the surrounding normal pancreatic tissue. **B,** Tranverse ultrasonographic image of the body of the pancreas in the same patient shows marked pancreatic duct (PD) dilatation.

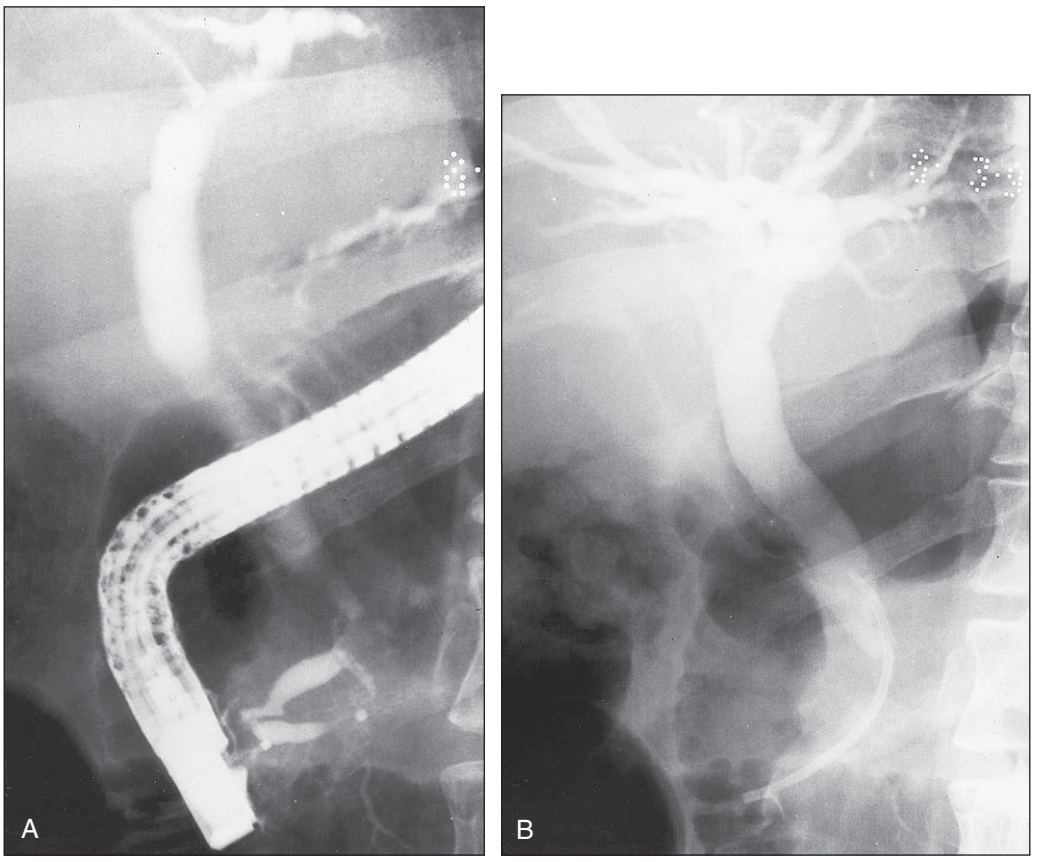


Figure 85-4 • **A,** Fluoroscopic image obtained at endoscopic retrograde cholangiopancreatography shows distal common bile duct obstruction of the "knee" of the distal bile duct. Also evident is occlusion of the main pancreatic duct. **B,** In the same patient, a biliary stent has been placed endoscopically for palliation of jaundice.

nodal involvement. EUS also can allow obtaining tissue samples for histologic analysis from virtually all pancreatic lesions and from suggestive lymph nodes located close to the stomach and duodenum. It has the advantage of not requiring a general anesthetic and can be performed outside an operating suite using only mild sedation. As in all sonographic procedures, the quality of clinical information achieved with EUS is highly operator dependent. Furthermore, EUS cannot evaluate lesions, such as peritoneal metastases, that are located at sites distant from the lumen of the gastrointestinal tract.

Tumor Markers

A number of tumor-associated antigens detectable in the serum of patients with pancreatic carcinoma have been described, the most useful being CA19-9.[56] CA19-9 is a mucin-associated carbohydrate antigen produced by normal pancreatic cells, as well as by pancreatic carcinoma cells. It is biochemically related to the Lewis blood group antigen, and Lewis antigen-negative patients cannot make CA19-9.[57] CA19-9 can be detected in serum and pancreatic juice. As with other tumor markers, the use of CA19-9 in the management of patients with pancreatic cancer is plagued by problems related to sensitivity and specificity. Small tumors often fail to produce enough CA19-9 to be detectable above the accepted serum threshold of 37 units/mL. Non-neoplastic disorders of the pancreas and biliary tract, particularly pancreatitis, are associated with elevations of CA19-9, which may reach several hundred units per milliliter. Patients with CA19-9 levels in the thousands almost definitely have pancreatic cancer but generally are quite asymptomatic from their tumors, which often are unresectable. Thus, little use is found for CA19-9 in screening asymptomatic populations. CA19-9 may be a predictor of pancreas cancer aggressiveness independent of tumor stage[58] and when elevated at diagnosis may be useful in following the response to therapy.

Analysis of tumor markers in pancreatic cyst aspirates may be of use in distinguishing pseudocysts from cystic neoplasms and in separating serous cystadenomas from mucinous neoplasms if radiologic criteria alone are inadequate. Of interest, CA19-9 levels in cyst aspirates are of little use in separating these different lesions. Nevertheless, analyzing the combination of amylase, carcinoembryonic antigen, and CA-125 allows fairly accurate but not perfect separation among the different cystic lesions of the pancreas.[59,60] These studies are particularly useful in the elderly or medically frail patient in whom resection of a cystic lesion of the pancreas poses an unusually high risk. When cyst fluid analysis suggests a low likelihood of malignancy, such high-risk patients can be managed without surgery.

Laparoscopic Staging

The development of laparoscopic staging procedures represents a significant advance in the preoperative staging of patients with pancreatic cancer and other periampullary tumors.[50,61–64] Among patients who appear to have a resectable pancreatic cancer as indicated by helical (spiral) CT scanning, a 20% to 30% incidence is seen of either locally advanced disease or small hepatic or peritoneal implants, undetected by radiologic imaging, which preclude curative resection. With advances in nonoperative palliation of advanced disease, particularly improvements in biliary stenting, as discussed later, no need may be found for formal laparotomy in patients with disease not amenable to curative resection. Avoiding unnecessary laparotomy is an important goal of palliation for patients with advanced disease, which may be facilitated by laparoscopic evaluation.

Simple laparoscopy with biopsy allows the evaluation of visceral and peritoneal surfaces and may reveal disease undetectable by other techniques. Patients may then avoid unnecessary open surgical procedures if adequate palliation of jaundice can be achieved with percutaneous or transhepatic biliary stent placement. Staging laparoscopy, with frozen-section evaluation of biopsy specimens if necessary, can be carried out in 15 to 20 minutes and can be followed by formal laparotomy and tumor resection with the patient under the same anesthetic. Available data suggest that this technique alone can reduce the incidence of unresectable disease at laparotomy by more than 50%.[62,64]

Several more complex techniques may further enhance the utility of laparoscopic staging. Laparoscopic ultrasonography can reveal abnormalities beneath the visceral surfaces and, with the use of flow Doppler techniques, may identify vascular encasement or occlusion.[61,62] Conlon and colleagues described more thorough laparoscopic staging of periampullary tumors, which includes pathologic evaluation of celiac, periportal, and peripancreatic lymph nodes.[63] Finally, the assessment of occult disease by cytologic assessment of peritoneal washings obtained at laparoscopy may further define patients with tumor dissemination who are unlikely to benefit from extensive surgical resection.[50] Of note, however, all of these techniques extend operative time, and several days may be required to obtain a definitive diagnosis in the case of lymph node biopsy or peritoneal fluid cytologic analysis. Surgeons favoring these approaches often perform laparoscopic staging procedures and definitive resections in separate anesthetic procedures, with a corresponding increase in cost and patient morbidity.

THERAPY

Surgical Resection

For patients with potentially resectable pancreatic malignancies, defined as those that have not yet metastasized to distant sites, encased the portal or superior mesenteric vein, or invaded the roots of the celiac or superior mesenteric artery, surgical resection remains the best hope for achieving prolonged disease-free survival. Most resectable tumors occur in the head of the pancreas and are resected by pancreaticoduodenectomy (Whipple procedure). This procedure initially was described as a two-stage operation,[65] although it fairly rapidly evolved into a one-stage procedure.[66] Although individual surgeons perform this procedure differently, in all cases, the head of the pancreas, distal bile duct, and most of the duodenum and proximal jejunum are resected en bloc. In many cases, the entire duodenum, as well as the gastric antrum, is included with the resection specimen. Reconstruction involves the performance of pancreatic, biliary, and gastric or duodenal anastomoses to the remaining jejunum. A schematic drawing of a pylorus preserving pancreaticoduodenectomy and reconstruction is shown in Figure 85-5.

Pancreaticoduodenectomy is a demanding technical operation, requiring meticulous dissection around portal and mesenteric blood vessels and three distinct anastomoses; the morbidity and mortality associated with the Whipple procedure can be significant. Indeed, in the mid-1970s, it was seriously considered whether patients with resectable pancreatic malignancies might be better managed with palliative bypass procedures.[67–69] Over the past several decades, however, a steady improvement has occurred in the results reported after pancreaticoduodenectomy with regard to morbidity and mortality, with a corresponding improvement in long-term survival of patients with resected tumors.

Perioperative Mortality

A steep decline in the perioperative mortality rate of patients undergoing pancreaticoduodenectomy has been noted in recent years.[70] During the past 30 years, postoperative mortality rates have declined from 20% to less than 5% in many institutions around the world. Near-zero mortality rates, which we define as 2% or less, are being reported with increasing frequency in case series numbering more than 100 patients. These mortality rates are so low that many hundreds of cases would be required to determine precise mortality rates. Nonetheless, it is safe to make the general statement that extremely low mortality rates are now the norm for pancreaticoduodenectomies performed in specialized centers.

The reason(s) for the precipitous decline in perioperative mortality rates is not completely understood. It appears, in part, to reflect concentration of pancreaticoduodenectomy procedures at high-volume centers[71–74]; low-volume centers still have perioperative mortality rates of 15% to 20% in national surveys.[73,74] The observed decrease in perioperative mortality in high-volume centers is no doubt multifactorial and parallels a general decline in operative mortality seen for other surgical procedures. Other contributing factors are improvements in intensive care, diagnostic and interventional radiology, and nutritional support. Prophylaxis and management of infection, venous thromboembolism, and gastrointestinal hemorrhage also have improved greatly during this period. As a result, postoperative cardiopulmonary complications and gastrointestinal hemorrhage, which used to be fairly common, have been sharply reduced. Other complications, such as disruption of the pancreaticojejunal anastomosis, which often were fatal 30-some years ago, now lead to death infrequently.[75]

Morbidity

Although mortality rates have decreased significantly, pancreaticoduodenectomy remains a procedure in which major morbidity is common. Complication rates are difficult to evaluate because no uniformly adopted method exists of reporting or even defining complications. Additionally, some series provide numbers of complications, whereas others report the number of patients with complications. Despite these limitations, it is apparent that some complications, such as pulmonary embolism, gastrointestinal bleeding, pneumonia, and myocardial infarction, are less common today than in the past.

Improvements in surgical technique have reduced the incidence of leakage at biliary-enteric anastomoses (biliary fistula) to less than 5% in many series.[70] By contrast, leakage at the pancreaticoenteric anastomosis (pancreatic fistula) is still a major complication of pancreaticoduodenectomy, occurring in 10% to 20% of patients in most series.[70] In reported case series, not much improvement in the incidence of this complication has been achieved over the years. For most surgeons, the pancreaticoenteric anastomosis continues to be the weak point of the operation, leakage being most common when the pancreatic duct is small and the gland very soft. Recent technical advances, however, may lower the incidence postoperative pancreatic fistulae, as described later on, and in the current era, leakage at the pancreaticojejunostomy generally leads to an increased length of hospital stay but rarely to reoperation or death.[75]

Probably the most common postoperative complication seen in patients undergoing pancreaticoduodenectomy is delayed gastric emptying. Although this effect is not well understood, disruption of enterogastric signaling after duodenectomy is thought to be responsible for the gastric motility problems so frequently seen. Although it once was thought to be more common in patients undergoing pyloric preservation,[76] randomized studies have demonstrated that delayed emptying is equally common in patients undergoing classic Whipple resection with hemigastrectomy.[77] Delayed gastric emptying is seen in more than 20% of patients and may range in severity from mild nausea and inability to eat to persistent vomiting requiring nasogastric suction for days to weeks after surgery. Problems with gastric emptying rarely are life-threatening but can significantly prolong postoperative hospitalization. A randomized prospective trial of erythromycin demonstrated modest but statistically significant benefits in improving gastric emptying after pancreaticoduodenec-

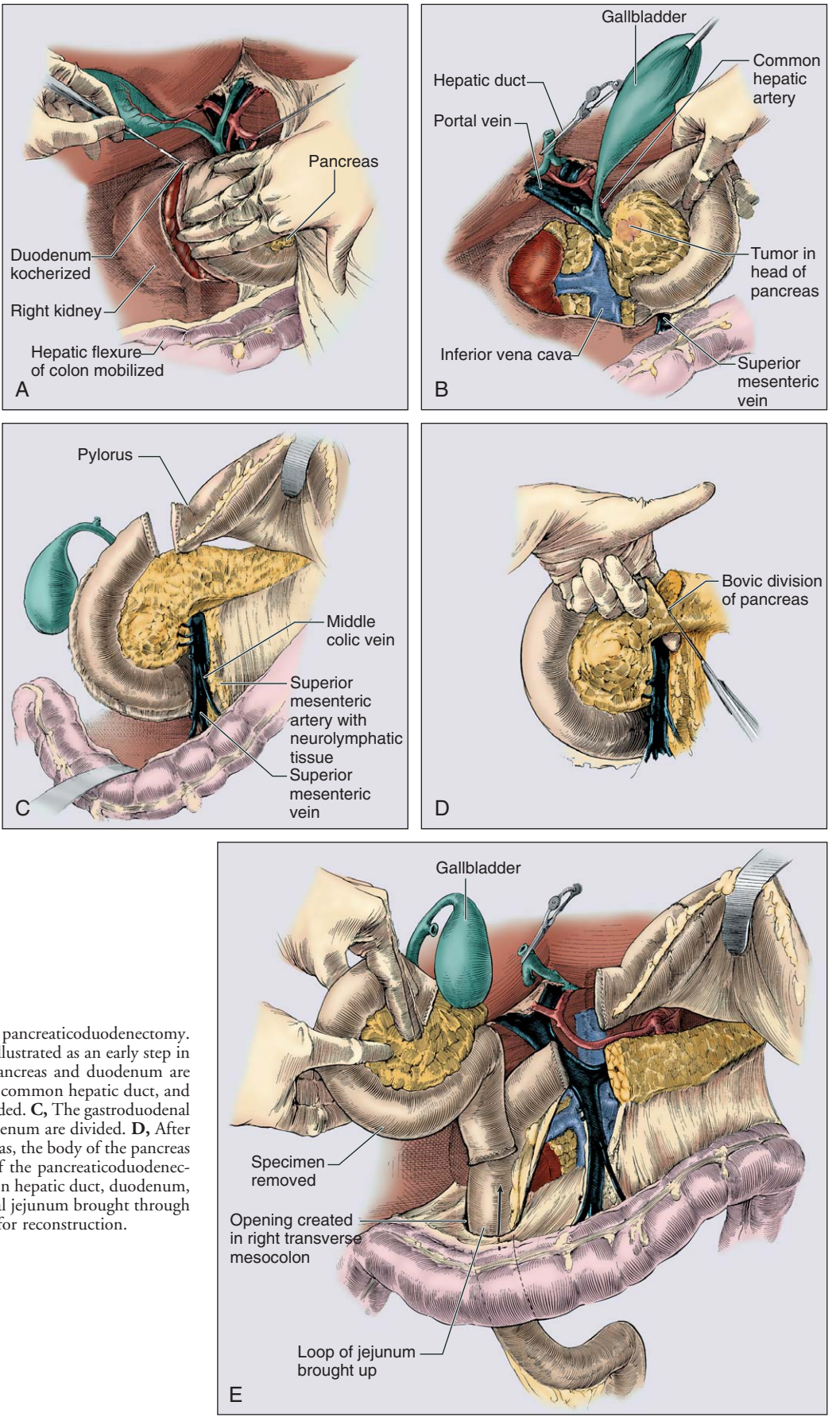


Figure 85-5 • Pylorus preserving pancreaticoduodenectomy. **A,** Kocherization of the duodenum is illustrated as an early step in this procedure. **B,** The head of the pancreas and duodenum are free from the retroperitoneum and the common hepatic duct, and the gastroduodenal artery has been divided. **C,** The gastroduodenal artery and the first portion of the duodenum are divided. **D,** After dissection under the neck of the pancreas, the body of the pancreas is divided as illustrated. **E,** Removal of the pancreaticoduodenectomy specimen, illustrating the common hepatic duct, duodenum, and the residual pancreas. The proximal jejunum brought through the transverse mesocolon will be used for reconstruction.

tomy, presumably through the effects of erythromycin on motilin receptors.[78]

Long-Term Survival after Surgical Resection

With decreased perioperative morbidity and mortality, some improvement in 5-year survival rates has been noted for patients undergoing pancreaticoduodenectomy for pancreatic cancer. Five-year survival rates after Whipple resection for ampullary, bile duct, and duodenal malignancies have always been reasonable, ranging from 30% to 50% in most series, and resection of a mucinous tumor of the pancreas results in 5-year survival rates of more than 75%. By contrast, the long-term survival of patients with pancreatic adenocarcinoma generally has been extremely poor. A review of the world literature dating back over 50 years suggests that the overall 5-year survival rate after attempted curative resection for adenocarcinoma of the pancreas is on the order of 4%.[79] Furthermore, some patients experienced recurrence beyond 5 years, suggesting that they had not been cured by resection of their tumors.

Several large case series from high-volume centers suggest that better long-term results are now being obtained, with greater than 20% of patients with documented pancreatic adenocarcinoma surviving 5 years after resection.[80–82] In patients with disease-free resection margins, small tumors, and no evidence of lymph node metastases, the results may be even better, with more than 40% of such patients expected to survive 5 years. An important point, however, is that not all recent series have noted such results. Researchers who believe that results have improved point to improvements in diagnosis, surgical technique, and the use of adjuvant chemotherapy and radiation therapy as possible contributing factors.

Technical Aspects of Pancreaticoduodenectomy

Variations in pancreaticoduodenectomy technique between experienced surgeons are the rule, and multiple approaches can be reviewed in surgical atlases and texts. Certain strategic aspects to the successful performance of this operation are worth emphasizing here. Probably first and foremost is that this is not an operation that should be carried out by surgeons who do pancreatic surgery on an infrequent basis. Studies from multiple centers have demonstrated a strong relation between surgical volume and outcome in patients undergoing pancreaticoduodenectomy.[71–74] The statewide mortality rates in Maryland and New York and the national Medicare database show remarkably similar findings, with mortality rates three- to fivefold higher in patients undergoing surgery at low-volume centers, defined as those handling fewer than five cases per year, compared with centers treating 20 or more cases per year. The experience of the operating surgeon also is a factor correlated with low postoperative mortality after pancreatic resection.[74] A significant fraction of pancreaticoduodenectomies are still performed by relatively inexperienced surgeons in low-volume centers,[73,74,82] which may account for the higher mortality rates reported in national surveys than in high-volume centers. Other specific technical issues are discussed later in the chapter.

Total Pancreatectomy

One of the oldest controversies regarding resection of pancreatic tumors in the periampullary region was between a classic Whipple-type pancreaticoduodenectomy with preservation of the pancreatic body and tail and a total pancreatectomy. Advocates of total pancreatectomy claimed that the more extensive resection offered the opportunity to resect extensive or multifocal disease and more thoroughly removed potentially involved peripancreatic nodes.[83,84] In addition, complete removal of the pancreas obviated performing a pancreaticoenteric anastomosis, thereby eliminating the risk of a postoperative pancreatic fistula.

Unfortunately, in patients undergoing total pancreatectomy, the development of diabetes, which frequently was quite brittle and difficult to control, was universal. Furthermore, it was shown that pancreatic carcinomas rarely are multifocal[85] and that a total pancreatectomy per se does not remove a significantly greater number of the lymph nodes to which periampullary tumors are likely to metastasize.[86] Improvement in the surgeon's ability to prevent or manage pancreatic anastomotic leaks has changed this once-dreaded complication into one that is rarely a cause of death.[75,87] Finally, analysis of a number of studies of partial and total pancreatectomy for periampullary tumors failed to show a benefit for total pancreatectomy and suggested an equivalent or inferior outcome compared with that for Whipple-type pancreaticoduodenectomy. Thus, total pancreatectomy has been largely discredited as an operation for pancreatic tumors, except for those relatively rare cases in which direct tumor extension into the body and tail of the pancreas, or the presence of an extensive intraductal papillary mucinous neoplasm involving the entire pancreatic duct, makes a total pancreatectomy the only way to excise the primary neoplasm completely.

Regional Pancreatectomy

After careful study of the patterns of local and lymphatic metastases in pancreatic carcinoma, Fortner's group at the Memorial Sloan-Kettering Cancer Center championed a more extensive operation for cancers arising in the pancreatic head, which they termed *regional pancreatectomy*.[88] This operation removed not only the pancreatic mass (with either a total or subtotal pancreatectomy) but also included resection and reconstruction of the superior mesenteric vein–portal vein confluence and an extensive en bloc regional lymph node dissection.[89] In some patients, resection and reconstruction of the superior mesenteric artery or hepatic artery were performed as well.

Fortner has summarized his experience with this procedure in 56 patients,[89] which demonstrated a near-universal occurrence of major morbidity and a 30-day surgical mortality rate greater than 5%. In addition, it appears that several other patients survived more than 30 days but succumbed to surgical complications after a continuous postoperative hospitalization in excess of 30 days. Long-term survival in patients undergoing this procedure was closely related to tumor size, with an estimated 33% 5-year survival rate in patients with tumors smaller than 2.5 cm in diameter and a 12% survival rate in patients with tumors ranging from 2.5 to 5.0 cm; no patients with larger tumors survived 5 years. The survival figures obtained with regional pancreatectomy are not significantly better than those reported with the standard Whipple-type pancreaticoduodenectomy,[60] whereas the morbidity and mortality are clearly greater.

Sindelar and colleagues at the National Cancer Institute also found the regional pancreatectomy to be associated with a significantly greater morbidity and mortality than is standard in pancreaticoduodenectomy.[90] Furthermore, they analyzed the sites of tumor recurrence in patients undergoing regional pancreatectomy and noted both locoregional recurrence and development of evidence of distant metastases in a majority of patients.[91] Thus, the more radical operation was not successful in providing better local control or survival when compared with pancreaticoduodenectomy.

Although few surgeons now perform the regional pancreatectomy as originally conceived by Fortner, two of its principles—portal vein resection and extensive regional lymph node resection—are being carried out elsewhere and may have a role in selected patients. These principles are discussed individually next.

Portal Vein Resection

Among the many factors complicating resection of cancers arising in the head of the pancreas is the close proximity of major vessels in the porta hepatis, particularly the portal vein. In a number of studies, tumor involvement of the portal vein has been associated with a poor outcome.[92,93] This may reflect a difference in the biology of such tumors, with tumors that are more aggressive and invariably associated with a poor outcome being more likely to invade the portal vein. By contrast, portal vein invasion also may be simply a consequence of where the tumor anatomically arises, so that if it can be adequately resected with negative margins, such patients may do as well as

patients undergoing resection who do not have portal vein involvement. Although somewhat controversial, the current data favor the latter conclusion.

The first reports of superior mesenteric vein–portal vein resection for periampullary tumors date to the 1950s. Only recently, however, have large series of patients undergoing portal vein resection been reported.[94,95] Results from both the M.D. Anderson Cancer Center and the Memorial Sloan-Kettering Cancer Center suggest that patients undergoing en bloc resection of the portal vein expereince morbidity and mortality comparable to those in patients undergoing a standard pancreaticoduodenectomy. Analysis of resected specimens from patients whose tumors had invaded the portal vein suggest that these tumors are no more likely to be associated with cancer-positive lymph nodes or to be aneuploid than are tumors that did not invade the portal vein.[94] Thus, vein invasion does not appear to reflect a difference in tumor biology and is most likely to be the unfortunate result of tumor anatomy.

Although the recent data are not completely mature with regard to survival in patients undergoing portal vein resection, preliminary analysis suggests that patients undergoing portal vein resection and reconstruction in whom tumor-negative surgical margins are achieved do no worse than patients in whom the portal vein is uninvolved.[93–95] It seems reasonable to conclude that in patients with tumors involving the portal vein that are otherwise resectable with tumor-negative margins, en bloc resection of the portal vein is warranted.

From a technical standpoint, resection of the portal (or superior mesenteric) vein can be relatively simple or quite complex. Involvement of a small segment of the side wall of the vein can be locally resected, followed by primary venorrhaphy. Longer or more circumferential involvement generally requires segmental vein resection. Reconstruction often can be carried out with primary anastomosis if the resected segment is shorter than 2 to 3 cm and the approximation can be achieved without undue tension. Resection of longer segments generally requires interposition grafting using autologous vein. Either the saphenous vein, the femoral vein, or the internal jugular vein can be used in reconstruction of the portal or superior mesenteric vein and generally can be harvested unilaterally without significant morbidity.

An important consideration is that portal or superior mesenteric vein involvement may be an indication of unresectability. Circumferential involvement (encasement) of the portal or superior mesenteric vein, and particularly occlusion of the portal vein with resulting mesenteric venous hypertension, render resection exceedingly difficult, if not impossible, in most circumstances. Tumors that encase the portal vein often invade or encase the superior mesenteric artery as well. We do not perform pancreaticoduodenectomy in patients in whom preoperative staging demonstrates encasement of the portal or superior mesenteric vein, a position taken at other high-volume centers as well.[94,95]

Extended Lymphadenectomy

Periampullary malignancies may metastasize to lymph nodes beyond the limits of a standard pancreaticoduodenectomy.[86] In an effort to eradicate regional nodal disease before the development of distant metastases, a number of groups of investigators have championed the performance of an extended lymphadenectomy in addition to the standard pancreaticoduodenectomy.[96,97] This procedure involves the wide resection of lymphatic tissue from the celiac axis to the iliac bifurcation, including resection of nodal tissues between the portal vein and the superior mesenteric artery; resection of the portal vein–superior mesenteric vein confluence often is included and renders this portion of the case simpler from a technical point of view.

The Japanese have aggressively adopted this technique, and a number of series demonstrate favorable results compared with historical controls or concurrent patient populations in which a standard pancreaticoduodenectomy was performed.[98,99] Other series, however, have not shown such a difference.[100] In an analysis of the results of multiple series of patients undergoing pancreaticoduodenectomy with extended lymph node dissection, it was concluded that the perioperative morbidity and mortality, as well as 5-year survival results, were not different from results with the standard Whipple-type pancreaticoduodenectomy.[97,101] A more formal meta-analysis reached the same conclusion,[102] and a prospective randomized trial of extended lymphadenectomy in patients undergoing pancreatic cancer resections at the Johns Hopkins Hospital also did not show a significant oncologic advantage.[97] These findings no doubt reflect the fact that, as in other malignancies, lymph node metastases reflect a more advanced stage of disease, in which systemic spread beyond the boundaries of possible resection has occurred. Thus, extensive lymphadenectomy generally is not performed.

Pylorus Preservation

Traverso and Longmire introduced the pylorus-preserving pancreaticoduodenectomy in an effort to minimize complications of the procedure related to the hemigastrectomy—specifically, dumping, marginal ulceration, and bile reflux gastritis.[103] This pylorus-preserving variant of the Whipple procedure preserves the entire stomach and pylorus, as well as the proximal 3 to 6 cm of duodenum, which is anastomosed to the jejunum to restore gastrointestinal continuity. Although this portion of duodenum occasionally is invaded by tumor, in many cases it can be preserved without apparent compromise of the tumor margin. Studies have confirmed preservation of pyloric function, with resulting decreases in dumping and enterogastric reflux.[104]

Surgeons critical of pylorus preservation raise a number of arguments, however. The incidence of marginal ulceration is quite low in the era of histamine H_2 receptor blockers and proton pump inhibitors. Furthermore, delayed gastric emptying, which can occur after either pylorus-preserving or classic Whipple resection, is thought by some investigators to be more common after pylorus preservation,[76] although this view is not supported by randomized studies.[77] Finally, the adequacy of pylorus preservation as a cancer operation has never been formally demonstrated in a randomized study. Of note, however, available data from case series do not suggest a markedly different 5-year survival among patients with pancreatic tumors undergoing either type of pancreaticoduodenectomy.[3]

Improvements in Pancreaticoenteric Anastomosis

As mentioned earlier, leakage at the pancreaticoenteric anastomosis remains a significant source of morbidity. Furthermore, this complication was reported in one large series to double the average postoperative hospital stay from 2 to 4 weeks.[87] Different types of pancreaticojejunostomies have been performed in an effort to minimize leakage from this anastomosis; most are variations on one of two very different techniques. The first approach, the so-called intussuscepting or "dunking" anastomosis, is performed by mobilizing the body of the pancreas 3 to 4 cm off the underlying splenic vein and then invaginating the cut end of the pancreas into the open end of the jejunal limb, which is sutured around the pancreas. This anastomosis is not dependent on the size of the pancreatic duct, although it may be technically difficult in certain circumstances, particularly when the pancreas is quite thick. A variation of this technique is to intussuscept the pancreas into the stomach.[87]

The alternative approach, the duct-to-mucosa anastomosis, is performed by anastomosing the cut edges of the pancreatic duct to the intestinal mucosa through a small opening made in the jejunum, using fine absorbable sutures. A reinforcing layer of sutures between the pancreatic capsule and the jejunal serosa commonly is placed to take tension off the anastomosis. This anastomosis is satisfying from a physiologic viewpoint but may be technically quite difficult in the presence of a nondilated pancreatic duct or a soft pancreas. Pancreatic fistula formation rates in series using either the duct-to-mucosa technique or the intussuscepting technique appear to be equivalent, and both are widely performed. A number of factors undoubtedly play a role in the success of pancreaticoenteric anastomoses.

Recently a number of reports suggesting that the incidence of pancreatic fistula development could be reduced to less than 5% have appeared in the surgical literature.[105–107] Although a number of distinct operative approaches have been used to achieve these remarkable results, several of the studies have championed the performance of a meticulous duct-to-mucosa anastomosis with fine absorbable suture material under loupe magnification. Although it may be impossible to prevent completely the development of pancreatic fistulae after pancreaticoduodenectomy, the incidence of this complication evidently can be substantially reduced. A number of studies have looked at the usefulness of somatostatin analogs such as octreotide in preventing the development of pancreatic fistulae. Although somatostatin analogs have proved effective in some European studies in patients undergoing a range of pancreatic surgical procedures,[108,109] these studies did not show a significant benefit in the subset of patients undergoing pancreaticoduodenectomy. Furthermore, several randomized trials of octreotide in patients undergoing Whipple resections in the United States have failed to demonstrate any benefit from the prophylactic use of this agent to prevent pancreatic fistula formation.[110,111] Octreotide also is expensive and, when administered subcutaneously, uncomfortable for patients. Its use to prevent pancreatic fistula development in the postoperative period cannot be recommended.

Distal Pancreatectomy

Patients with adenocarcinoma of the pancreas involving the body or tail of the pancreas generally do not become symptomatic until their tumors have reached an advanced stage and thus rarely are candidates for resection at the time of diagnosis. Furthermore, the long-term outcome after attempted surgical resection of more distal pancreatic adenocarcinomas is poor.[112,113] Probably the patients most likely to benefit from distal pancreatectomy are those with neuroendocrine or mucinous tumors of the pancreas. These tumors have a high cure rate after surgical resection and therefore warrant aggressive surgical measures regardless of their size or anatomic location.

Distal pancreatectomy is a less daunting technical undertaking than pancreaticoduodenectomy. This procedure involves en bloc resection of the spleen and pancreatic tail. As with the Whipple procedure, it is critical to achieve an adequate resection margin, in this case, the proximal pancreatic margin and the retroperitoneal margin; peripancreatic tissue should be widely mobilized from the retroperitoneum to ensure removal of adjacent lymphatic tissue. Distal pancreatectomy generally is performed by mobilizing the pancreatic tail (along with the spleen in most cases) and proceeding medially (retrograde) toward the pancreatic neck. Recently, the performance of this procedure from the pancreatic neck outward (antegrade) has been proposed as an approach to optimizing the retroperitoneal margin.[114] Whether this difference in technique will improve long-term outcomes is uncertain.

Adjuvant and Neoadjuvant Therapy

The modest success of surgical resection in producing long-term survival of patients with pancreatic tumors has led to a number of studies using chemotherapy and radiation therapy in an effort to diminish local and systemic recurrence after surgery. The classic study of adjuvant therapy for pancreatic carcinoma was performed by the Gastrointestinal Tumor Study Group (GITSG). This study prospectively randomized patients undergoing resection with curative intent to either no additional therapy or combined-bolus 5-fluorouracil (5-FU) and external-beam radiation therapy. Despite small numbers of patients in each arm of the study, a significant difference in outcome was observed between the two groups, with treated patients who received the adjuvant treatment surviving 20 months, versus 11 months for patients in the resection-only control group.[115] The GITSG subsequently completed a small confirmatory trial.[116]

Subsequent studies have yielded conflicting results. Although the initial report of European Organization for Research and Treatment of Cancer (EORTC) trial did not show a statistically significant benefit of adjuvant postoperative chemoradiation therapy, a recent re-analysis demonstrated a positive result, with a 14% improvement in overall survival at 2 years (37% versus 23%) favoring adjuvant chemoradiotherapy in patients with pancreatic head cancers that reached statistical significance ($P = 0.049$).[117] A distinct multi-institutional study also conducted in Europe, ESPAC-1 (European Study Group for Pancreatic Cancer-One), suggested a significant survival benefit of adjuvant chemotherapy with 5-FU but not of adjuvant chemoradiotherapy.[118] Although this study has been criticized for methodologic shortcomings, it has led to significant controversy about the role of adjuvant radiation therapy in pancreas cancer patients.

As another approach to determining whether adjuvant radiation improves overall survival in patients with resected pancreatic cancer, a population-based study of the Surveillance, Epidemiology, and End Results (SEER) registry with 2636 patients records from 1973 to 2003 (1123 received adjuvant radiation therapy and 1513 did not) was conducted.[119] With a mean follow-up period of 19 months, median overall survival for the patients receiving radiation therapy was 18 months, compared with 11 months for the group of patients who did not ($P < 0.01$)—results virtually identical to those seen in the small GITSG trials that initially addressed the role of adjuvant chemoradiation. Cox regression analysis demonstrated that patients who received adjuvant radiation therapy had a statistically significant increase in overall survival when compared with patients who received no such therapy (hazard ratio, 0.57; 95% confidence interval, 0.52 to 0.63; $P < 0.01$), suggesting that adjuvant radiation therapy is of benefit.[119]

A recent European phase III trial has demonstrated a benefit of single-agent gemcitabine chemotherapy in the adjuvant setting.[120] The median disease-free survival time was 13.4 months in the gemcitabine group and 6.9 months in the control group ($P < 0.001$). The estimated disease-free survival rates at 3 and 5 years were 23.5% and 16.5% in the gemcitabine group and 7.5% and 5.5% in the control group, respectively. Although overall survival was not significantly different, a nonsignificant trend favoring the gemcitabine group was observed that may reach significance as the data mature.

A single-institution phase II chemoradiation adjuvant therapy study by Picozzi and colleagues in Seattle, using a combination of 5-FU, cis-platinum, and interferon-α as radiation sensitizers, demonstrated a remarkable improvement in median survival time and 5-year survival rate (longer than 36 months and approximately 50%, respectively) in a cohort of patients after surgical resection.[121] Although only 53 patients received this treatment, these results have led to confirmatory trials at single institutions, as well as a multi-institutional phase II trial conducted by the American College of Surgeons Oncology Group. Results of these trials should be available in the near future. If the improvement in postoperative survival described by the Seattle investigators is verified by these studies, this adjuvant regimen will prove to be one of the most striking advances in the treatment of pancreatic cancer.

Neoadjuvant Chemotherapy and Radiation Therapy

Recently several groups of investigators reported results from studies of preoperative neoadjuvant therapy in patients with periampullary tumors.[122,123] Such therapy is theoretically attractive from several perspectives. Shrinkage of the primary tumor mass may make technical aspects of surgical resection easier. Data from animal experiments suggest that such therapy may reduce the incidence of tumor dissemination at the time of surgery. Furthermore, some otherwise eligible patients may fail to receive postoperative adjuvant therapy in a timely fashion because of the development of postoperative complications.

Although the feasibility and safety of neoadjuvant chemoradiation therapy have been demonstrated clinically, and efficacy is considered encouraging as indicated by the data from recent phase II studies,[124,125]

such treatment should be considered experimental at present and is not recommended outside of a clinical trials setting. In view of the ongoing controversies regarding the roles of radiation therapy, preoperative versus postoperative adjuvant treatment, and newer agents in the adjuvant setting, enrollment in clinical trials should be encouraged. In practice, postoperative adjuvant chemotherapy or chemoradiation therapy should be considered in patients who have undergone curative-intent surgery if no clinical studies are available.

MANAGEMENT OF PATIENTS WITH LOCALLY ADVANCED OR METASTATIC DISEASE

Downstaging

A substantial proportion of pancreatic cancer patients are first seen with locally advanced disease—either encasement of the superior mesenteric or portal veins or involvement of the celiac or superior mesenteric arteries—which precludes curative resection. This recognition has led to a number of studies attempting to use chemoradiation therapy to "downstage" the patient's tumor and permit a margin-negative surgical resection.[126,127] Unfortunately, the results of these studies generally have been poor, with zero to 15% of patients achieving sufficient tumor shrinkage to permit surgical resection; survival after resection for down-staging may be more limited than that usually seen after pancreaticoduodenectomy for resectable disease.[128]

Radiation Therapy

Pancreatic cancer is a challenging target for radiation therapy for a number of reasons. It is difficult to deliver adequate doses of radiation therapy owing to the location of the tumor and regional lymph nodes. Surrounding normal tissues such as the kidneys, liver, bowel, and spinal cord all have limited tolerance to radiation therapy that is below the dose required for sterilization of the pancreatic cancer. Strategies to overcome this issue have included intraoperative radiation therapy, brachytherapy, intensity-modulated radiation therapy (IMRT), and radiosensitizing chemotherapy.[129–134] To date, none of these strategies have had an overwhelming impact on the disease. Many pancreatic cancer patients also are nutritionally depleted, have experienced significant weight loss, and have poor performance status, further limiting the ability to provide aggressive therapy. Use of radiosensitizing drugs has been limited by the concurrent sensitization of surrounding normal tissues.

Currently, the standard of care remains concurrent chemotherapy and radiation therapy for the treatment of locally advanced, unresectable pancreatic cancer. This standard was first established by randomized trials by the Mayo Clinic in the late 1960s and later confirmed by the GITSG. These trials showed a significant benefit with 5-FU plus irradiation over that with radiation therapy alone, with a doubling of the median survival time of about 6 months for radiation therapy alone, to almost 12 months for 5-FU plus irradiation.[135] The GITSG also compared chemotherapy alone with chemoradiation therapy and demonstrated a significant survival advantage for the chemoradiation therapy treatment group, with a 1-year rates of 41% versus 19%.[129] Attempts to substitute other radiosensitizing chemotherapy such as gemcitabine are ongoing. The trend in most of these studies, however, has been to reduce the systemic dose of gemcitabine or to decrease the radiation field size because of toxicity of this combination. Resultant effects may therefore be similar to those seen with 5-FU and full-dose radiation.[134]

Proton therapy, which is now expanding in clinical centers, may offer a better approach for the combination of chemotherapy and radiation therapy in the setting of locally advanced disease. Because of the physical characteristics of the proton beam, the dose of radiation can be conformed to the tumor, with a significant reduction in dose or amount of radiation delivered to normal tissues.[136]

The use of radiation in this disease requires diligence in field design and aggressive nutritional and hydration support of the patient. Radiation technique and field design are critical in the treatment of pancreatic cancer. Treatment typically involves use of 15-MV or higher-energy beams. Conventional fields include the tumor volume with appropriate margins for setup and microscopic extension. Regional lymph nodes for cancer of the pancreatic head include the peripancreatic, celiac, superior mesenteric artery, and porta hepatis lymph node regions. For tumors of the pancreatic tail, the splenic hilum should be included in the radiation fields. Care should be taken to allow for adequate margins for organ motion, particularly with treatment of the portal nodes, because motion with diaphragm movement can be significant.

Radiation therapy can play a role in the adjuvant treatment of patients after resection, as described earlier, and can modestly extend survival in patients with advanced disease.[137] Irradiation thus remains an important palliative treatment in pancreatic cancer; it also can substantially ameliorate pain in some patients with disseminated disease.[138]

Chemotherapy for Advanced Disease

Chemotherapy for pancreatic cancer has had a modest positive impact on the survival of patients with advanced disease.[139] For many years, 5-FU-based therapy, with 5-FU used either as a single agent or in combination with other drugs, was the principal treatment strategy in patients with advanced pancreatic cancer. Although a number of studies suggested that such therapy resulted in a measurable survival advantage over that in patients receiving supportive care alone, the gains were quite modest.

The development and approval of gemcitabine for the treatment of advanced pancreatic cancer represent an advance in both the therapeutic armamentarium and the approach to identifying agents of benefit to patients with this disease. In a prospective randomized study, it was demonstrated that gemcitabine resulted in substantial clinical benefit (including better pain control and improved nutritional status) in approximately 25% of patients, compared with fewer than 5% of patients who received 5-FU.[139] This study also demonstrated a modest but statistically significant extension of median survival in patients receiving gemcitabine (5.4 versus 4.3 months; $P < 0.05$). Furthermore, the fraction of patients surviving more than 1 year was higher in the gemcitabine group (18% versus 2%). Of note, the fraction of patients achieving a partial radiologic response in this study was less than 5% and was not significantly different in the two treatment groups. Thus, this study not only identified an agent that improves the quality and the quantity of life for patients with advanced pancreatic cancer but also demonstrated the limitations of traditional radiologic measures of tumor response and the importance of alternative criteria in testing novel agents for the treatment of pancreatic cancer.

The identification of gemcitabine as an active agent in pancreatic cancer has led to the study of additional regimens using single-agent gemcitabine on different dosing schedules[140] or gemcitabine-based combinations.[138] Unfortunately, gemcitabine-based combinations generally have failed to show activity significantly better than that for gemcitabine alone and, in some cases, have been more toxic.[138,141,142] A notable exception was a randomized phase III study conducted by the National Cancer Institute of Canada, which compared the combination of gemcitabine and erlotinib, a tyrosine kinase inhibitor, with gemcitabine alone in advanced pancreatic cancer patients.[143] A modest difference in overall survival was observed (5.9 versus 6.4 months; $P = 0.025$) that favored the combination arm (hazard ratio, 0.81; 95% confidence interval, 0.67 to 0.97). The corresponding 1-year survival rates were 24% and 17%, respectively, for the two regimens. Additional studies of other targeted therapeutics, both alone and in combination with gemcitabine, are ongoing in patients with advanced pancreas cancer. It is hoped that one or more of these combinations will have substantially greater activity in patients with

pancreatic cancer and will thus represent a real advance in the management of patients with this disease.

Palliative Management of Patients with Advanced Disease

Modern approaches to surgical management of pancreatic carcinoma and the use of adjuvant therapy have made pancreatic resection safer and more effective. Such therapy has resulted in significant extension of survival for many patients. Long-term eradication of disease, however, is still the exception among patients with pancreatic carcinoma who undergo attempted curative resection. Furthermore, only 10% to 20% of patients with pancreatic carcinoma are first seen at an early-enough stage to be eligible for resection. Thus, in the vast majority of patients with pancreatic cancer, either advanced disease already is present or it develops in the setting of tumor recurrence. For physicians involved in the palliative management of patients with advanced pancreatic cancer, a number of important issues must be addressed: palliation of pain, palliation of jaundice, and palliation of gastric outlet obstruction.

Palliation of Pain

Advanced pancreatic cancer can be extremely painful, and most patients experience moderate or severe pain in the course of their illness. Pancreatic malignancies commonly invade neural and perineural tissues. Invasion of neural structures in the retroperitoneum by the growing pancreatic tumor mass is associated with a steady, unrelenting pain, which can be psychologically devastating. In the management of such patients, important aspects include the use of long-acting analgesics in appropriate doses and consideration for celiac plexus ablation. Whereas the use of long-acting oral or topical narcotic preparations should be well understood by all physicians that care for patients with advanced cancer, the use of celiac plexus blockade is less often appreciated.

Probably the best study of celiac plexus ablation was performed by Lillemoe and colleagues.[144] They randomized patients with unresectable disease, who were undergoing laparotomy for palliative biliary and gastric bypass, to receive injections of either 50% alcohol or saline into the celiac ganglia bilaterally. The study was carried out in a double-blind, prospective fashion, and outcomes of interest included pain, narcotic use, and survival among treated patients. This study convincingly demonstrated that patients undergoing chemical splanchnicectomy had significant relief of pain and required less narcotic use than did patients receiving saline. The benefit of such therapy appeared to last for 4 to 6 months. In the subset of patients with moderate to severe pain at the time of treatment, a statistically significant survival advantage was seen among those treated with alcohol injection. Celiac plexus block can be easily and safely performed at the time of a palliative surgical bypass procedure, and it also can be performed percutaneously, with or without CT guidance, in patients who have no other indication for laparotomy.

Palliation of Jaundice

Most patients with tumors of the periampullary region have jaundice when first seen. Although pancreaticoduodenectomy is an effective method of relieving jaundice, most patients have disease too extensive for attempted curative surgical resection. Multiple approaches are available for the management of jaundice in such patients, including endoscopic and percutaneous biliary stent placement and surgical biliary bypass. Several trials compared surgical with nonsurgical approaches for the management of biliary tract obstruction.[145] In general, these trials demonstrated a lower initial morbidity among patients undergoing nonoperative stenting. The stent occlusion rates, however, were significantly higher than the failure rates of surgical biliary bypass, resulting in more frequent bouts of cholangitis and the need for multiple procedures over time in patients managed nonoperatively.

The greater long-term morbidity among stented patients was thought to be approximately equivalent to the greater short-term morbidity among patients undergoing surgical bypass, leading to the conclusion that the treatments were approximately equivalent. It has been suggested that patients with a relatively short life expectancy due to extensive disease, and those with increased operative risk due to other medical problems, may best be managed with biliary stenting. By contrast, patients thought to have less extensive disease and to be reasonable operative candidates may benefit more from surgical biliary bypass.[146]

The development of expandable wall stents has changed this treatment algorithm. Wall stents can be placed endoscopically or percutaneously, and time to stent failure is significantly longer with wall stents than with older stent technology. In one study, it was demonstrated that the stent occlusion rate among patients receiving wall stents was less than 30% at 10 months.[146] Because the median survival of patients with advanced pancreatic cancer ranges from 4 to 8 months, with survival rarely exceeding 1 year, a wall stent will be provide adequate palliation for life in most patients. The rare patient who outlives the functional life of a wall stent generally can be restented using endoscopic or percutaneous techniques. Our practice, therefore, is to spare patients with unresectable pancreatic tumors the morbidity and mortality of surgical biliary bypass in favor of wall stent placement.

Of note, surgical biliary bypass will be preferable in some instances. The most common scenario in which this procedure is indicated is that in which a patient undergoing laparotomy for attempted curative resection is found to have unresectable disease. In such cases, it is our practice to perform surgical gastric and biliary bypass as well as an intraoperative chemical splanchnicectomy. Another group of patients who benefit from surgical biliary bypass are those with duodenal obstruction at the time of diagnosis. Such patients generally require laparotomy for creation of a gastrojejunostomy and should undergo surgical biliary bypass under the same anesthetic procedure. The precise type of biliary bypass created is largely a choice of the operating surgeon. Choledochojejunostomy to a defunctionalized jejunal loop is the preferred approach to surgical biliary bypass, but cholecystojejunostomy may be an acceptable alternative, except in cases in which the tumor is encroaching on the cystic duct.

Palliation of Gastric Outlet Obstruction

Approximately 15% of patients with periampullary tumors experience symptoms of gastric outlet obstruction at the time of diagnosis, and in another 20% to 30% of patients, symptomatic duodenal obstruction will develop in the course of their disease. Surgical gastrojejunostomy is the preferred approach to palliation in such patients. When carcinomatosis involving the small bowel also is present, it is our practice to place a gastrostomy tube along with performing surgical bypass of the gastric or intestinal obstruction. In patients with carcinomatosis, almost invariably, a reobstruction forms in a matter of weeks, and the presence of a gastrostomy tube can greatly facilitate terminal care by avoiding the need for nasogastric suction in most patients.

SUMMARY

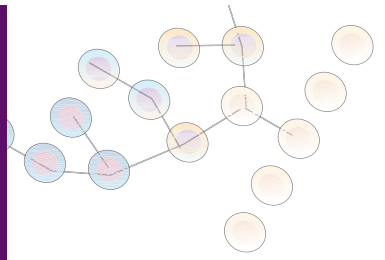
Pancreatic cancer is a particularly virulent neoplasm. Most patients are first seen with disease that is too advanced to permit an attempt at curative resection, and in most patients who undergo resection, tumor will eventually recur. Radiation therapy and chemotherapy are of only modest benefit in extending survival in patients with unresectable tumors. However, a number of advances have been made, including enhanced understanding of the molecular mechanisms leading to pancreatic carcinogenesis, improvements in staging, optimization of surgical techniques, improvements in adjuvant therapy for patients with resectable disease, and a focus on effective palliation for patients with more advanced disease.

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86 Cancer of the Kidney

Roberto Pili and Ronald Rodriguez

SUMMARY OF KEY POINTS

- Renal cell carcinoma (RCC) accounts for 3% of malignancies in adults.
- Cigarette smoking (in more than 20% of cases) and obesity (in more than 30%) are established causal factors for RCC.
- Clear cell RCC is the most common histologic subtype, representing 70% of all RCCs among adults.
- Different subtypes of RCC are characterized by distinct genetic abnormalities and molecular signatures.
- The von Hippel-Lindau tumor suppressor gene is mutated in more than 50% of sporadic cases of clear cell RCC.
- 4% of cases of RCC arise from hereditary syndromes.
- Prognosis for RCC is dependent primarily on tumor stage.
- Radical nephrectomy is the gold standard of care for treatment of RCC; however due to increasing sensitivity of imaging studies, nephron-sparing surgery also has become an effective option.
- Follow-up guidelines for resected RCC include history, physical examination, periodic metabolic panels, and abdominal and chest computed tomography (CT) studies 4 to 6 months after surgery.
- High-dose bolus interleukin-2 (IL-2) is approved by the U.S. Food and Drug Administration (FDA) for the treatment of selected stage IV RCC patients; however, this agent is toxic and limited in efficacy. Better identification of the potentially responsive patient population is needed.
- Antiangiogenesis drugs recently have been approved in the treatment of RCC, although success of single agents is limited. Investigation into rational combination strategies may promise greater success of this strategy.
- Conventional cytotoxic therapy offers little benefit to patients with RCC.

INTRODUCTION

RCC accounts for approximately 3% of adult malignancies. Tumors that arise in the kidney exhibit a variety of histologic patterns that may be benign or malignant. Tumors of benign histology include oncocytomas, angiomyolipomas, fibromas, lipomas, lymphangiomas, and hemangiomas. Historically, RCC was widely known as *hypernephroma*. This term, coined originally by Grawitz in 1883 in the belief that these tumors arise from the adrenal gland, has been replaced by *renal cell adenocarcinoma*. RCC exists in sporadic and hereditary forms. The sporadic form of the disease usually is first seen in the fifth decade or later in life. The clinical presentation of RCC has been described with the classic triad of symptoms of hematuria, flank pain, and fever. With the increased general use of imaging techniques, however, a majority of kidney tumors are being detected incidentally. Improved surgical techniques for treatment of localized disease and recently developed novel systemic therapies for metastatic RCC have changed the management of this condition.

INCIDENCE AND RISK FACTORS FOR SPORADIC RENAL CELL ADENOCARCINOMA

The estimated new cases of kidney and renal pelvis tumors for 2007 are 51,190.[1] A predominance of cases in male patients has been reported, with an estimated 31,590 men developing disease in 2007, compared with 19,600 women. The estimated number of deaths each year is 12,890 for both sexes (8080 in men and 4810 in women). The increasing incidence of RCC observed in the past had been attributed to increased detection due to the widespread use of imaging modalities such as computed tomography (CT), ultrasonography, and magnetic resonance imaging (MRI).[2,3] Although a decrease in the size of diagnosed renal cell tumors over time has been noted, an increasing incidence of large and late-stage RCC also has been observed and accounts in part for the overall increase in incidence.[3] In the United States, increases in incidence have been more rapid among women than men and among African Americans than Caucasians, leading to a shift in excess from among Caucasians to among African Americans.[4] A slight decline in the death rate, however, occurred in 2003 from that for 1991 (−1.5% in men and −7.5% in women), as reflected also by a decline in the general cancer death rate.[1]

Cigarette smoking and obesity are the most consistently established causal risk factors, accounting for more than 20% and 30% of renal cell cancers, respectively.[4,5] Hypertension, rather than antihypertensive drugs, appears to influence renal cell cancer development, although the mechanism is unknown.[4,5] This was the conclusion of a large study of 363,992 Swedish men who received at least one physical examination between 1971 and 1992 and who were followed up until death or until the end of 1995.[5] During the follow-up period, 759 cases of RCC and 136 cases of renal pelvis cancer were diagnosed. The relative risk for RCC was 1.3 for former smokers and 1.6 for current smokers. The relative risk for renal pelvis cancer was even higher at 1.6 for former smokers and 3.5 for current smokers. With regard to obesity, patients with a body mass index in the highest one-eighth of the cohort had a relative risk of 1.9 when compared with patients in the leanest subgroup. Hypertension was confirmed as a third risk factor for RCC. A recent study has tested whether smoking is associated with mutations in the von Hippel-Lindau tumor supressor gene (*VHL*) in 337 cases of sporadic RCC among

120,852 people over a mean follow-up period of 11.3 years; the findings suggest that smoking causes RCC independently of *VHL* mutations.[6]

Patients with end-stage renal disease (ESRD) have an increased incidence of RCC when compared with the general population. Patients receiving prolonged dialysis tend to develop acquired renal cystic disease (ARCD), possibly as a result of disordered proliferation within the native kidney. In these patients, the tumors often are bilateral and multifocal, with a papillary histology.[7] Accordingly, these patients should be monitored regularly with renal ultrasound examinations. Analgesics have not been convincingly linked with renal cell cancer risk. In general, a protective effect has been observed for fruit and vegetable consumption, although no particular component of diet has been clearly implicated. Sporadic and inconsistent reports have noted an association of specific occupations or occupational exposures with this cancer. Additional epidemiologic studies are needed.

PATHOLOGY

Kidney tumors usually are unilateral but may be bilateral in 2% to 4% of cases.[8] These tumors tend to grow into the renal vein and may form a tumor thrombus that extends into the vena cava and even the right atrium. Vascular involvement is present in 4% to 10% of patients at the time of presentation.[9]

RCC is a clinically and pathologically heterogeneous disease.[10] The 2004 World Health Organization (WHO) classification for renal neoplasms recognizes several distinct histologic subtypes of RCC (Table 86-1). These subtypes include clear cell RCC, papillary RCC, chromophobe RCC, hereditary cancer syndromes, multilocular cystic RCC, collecting duct carcinoma, medullary carcinoma, mucinous tubular and spindle cell carcinoma, neuroblastoma-associated RCC, Xp11.2 translocation–*TFE3* carcinoma, and unclassified lesions.[11,12] Clear cell RCC is the most common adult RCC, representing 70% of all RCCs. Papillary type I and type II RCC accounts for 10% to 15%, chromophobe RCC for 4% to 6%, collecting duct carcinoma for less than 1%, and unclassified lesions for 4% to 5% of RCCs. Tumors may be composed of mixed histologic subtypes, and each subtype may feature high-grade sarcomatoid characteristics. Histologic differentiation of most subtypes of RCC can be accomplished with hematoxylin-eosin staining techniques. The conventional histologic pattern is the most common, characterized by large clear cells with abundant cytoplasm. The chromophobe pattern is granular with abundant mitochondria. The papillary or tubulopapillary variant may represent a different type of tumor, because they tend to be smaller with fewer anaplastic features. The most widely used grading system for RCC is the nuclear grading system developed by Fuhrman and colleagues.[13] This system assigns a grade from I to IV, based on nuclear size, roundness, and other morphologic features such as the prominence of nucleoli and the presence or absence of clumped chromatin. Patients with tumors of high Fuhrman grade tend to have poorer clinical outcomes.

GENETICS

Until recently, RCC was thought to represent a monomorphic disease arising from a probable common precursor cell but with different histologic and clinical manifestations. Genetic characterization based

Table 86-1 Histologic Classification of Renal Cell Carcinoma

SPORADIC RCC 2004 WHO CLASSIFICATION

Histologic Tumor Type	Prevalence (%)	Cytogenetic Findings
Clear cell RCC	70	3p deletions, von Hippel-Lindau gene mutations
Papillary RCC	10	3p25-26
Chromophobe RCC	5	Trisomy of chromosomes 7 and 17, loss of Y chromosome, 7q34 chromosomal abnormality
Hereditary cancer syndromes	5	Loss of multiple chromosomes: 1, 2, 6, 10, 13, 17, 21
Multilocular cystic RCC	<1	Loss of multiple chromosomes: 1, 6, 14, 15, 22; gain of chromosome 3
Collecting duct carcinoma	<1	Extracellular matrix gene loss
Medullary carcinoma	<1	Loss of multiple chromosomes: 1, 4, 6, 8, 13, 14
Mucinous tubular and spindle cell carcinoma	<1	
Neuroblastoma-associated RCC	<1	
Xp11.2 translocation–*TFE3* carcinoma	<1	Multiple gene loss (most often 20q13)
Unclassified lesions	4	Translocations involving Xp11.2

HEREDITARY RCC: SYNDROMES AND HISTOLOGIC TUMOR TYPES

Hereditary Syndrome	Chromosome Abnormality	Histologic Type of Renal Tumor	Systemic Manifestations
von Hippel–Lindau	3p26	Clear cell RCC	Retinal angiomas, central nervous system hemangioblastomas, pheochromocytoma
Hereditary papillary RCC	7q34	Type 1 papillary RCC	None
Hereditary leiomyoma–RCC	1q42-43	Type 2 papillary RCC	Cutaneous and uterine leiomyomas
Birt-Hogg-Dube syndrome	17p11.2	Chromophobe RCC, oncocytoma, hybrid tumors	Skin lesions, lung cysts
Medullary carcinoma	11p	Medullary carcinoma	Sickle cell trait

RCC, renal cell carcinoma; WHO, World Health Organization.

Adapted from Prasad SR, Humphrey PA, Catena JR, et al: Common and uncommon histologic subtypes of renal cell carcinoma: imaging spectrum with pathologic correlation. Radiographics 2006;26:1795–1806.

on cytogenetics and molecular biology has established that different subtypes of RCCs are characterized by distinct genetic abnormalities and molecular signatures reflecting the differences in the cell type, biology, and underlying molecular mechanisms.[14] Additional tumor metabolic pathways may explain the biologic diversity of RCC.

Sporadic Renal Cell Carcinoma

A molecular signature of a majority of sporadic cases of RCC is the inactivation of a critical gene on the short arm of chromosome 3. The von Hippel-Lindau tumor suppressor gene (*VHL*), which resides on chromosome 3p25, is mutated or silenced in greater than 50% of sporadic clear cell renal cell carcinomas.[15,16] Germline *VHL* mutations give rise to von Hippel-Lindau disease, which is characterized by an increased risk of blood vessel tumors (hemangioblastomas) and renal cell carcinomas. In this setting, *VHL* inactivation gives rise to premalignant renal cysts. Additional genetic alterations are presumably required for conversion of these cysts to renal cell carcinomas. The *VHL* gene product, pVHL, is the substrate recognition module of an E3 ubiquitin ligase that targets the hypoxia-inducible factor (HIF) for destruction in the presence of oxygen. Hypoxic cells, or cells lacking pVHL, accumulate high levels of HIF, which activates the transcription of a variety of genes, including vascular endothelial growth factor, platelet-derived growth factor B, and transforming growth factor alpha. Restoration of pVHL function in *VHL*–/– mutant renal carcinoma cells suppresses their ability to form tumors experimentally by reducing HIF-1α levels. Inhibition of HIF is necessary and sufficient for tumor suppression by pVHL in renal cell carcinoma nude mouse xenograft assays. This provides a rationale for treating *VHL*–/– renal cell carcinoma with inhibitors of HIF or its downstream targets. The pVHL protein also has other targets in addition to HIF. Elucidating these targets will lead to further knowledge of how pVHL suppresses tumor growth.

Analysis of mutations in exon 3 of the *VHL* gene may be useful in refining the diagnostic criteria for conventional RCC versus chromophobe RCC with clear cells.[17] Single-strand conformational polymorphism (SSCP) has been used to identify mutations in the *VHL* gene in RCCs of various histologic subtypes. The cohort ($N = 67$) included cases of conventional or clear cell ($N = 24$), chromophobe ($N = 14$), and papillary ($N = 14$) RCC and renal oncocytomas ($N = 15$). Thirteen of the 14 *VHL* gene mutations identified were novel. Of interest, no mutations were found in the papillary and oncocytoma subtypes. Mutations in exon 3 appeared to confer a more aggressive phenotype on conventional RCC. Expression profiling of renal epithelial neoplasms with complementary DNA (cDNA) microarrays also may be used to identify novel molecular markers with potential diagnostic utility. A comparison of the expression profiles of 7075 genes has been reported for four conventional RCCs and one chromophobe RCC, as well as two oncocytomas.[14] Conventional RCCs were found to underexpress mitochondrial and distal nephron genes and were distinguished from chromophobe RCC and oncocytomas by overexpression of vimentin and class II major histocompatibility complex-associated molecules. Vimentin was found to be a sensitive and specific marker for conventional RCC. Gene-profiling experiments such as these should lead to improvements in the basic understanding of renal tumor pathogenesis.

The genetic studies in familial RCC have led to the identification of specific molecular signatures in non-clear cell histotypes as well, such as c-Met overexpression in papillary type I, fumarate hydratase in papillary type II, and c-Kit in chromophobe RCC (see later). Preliminary results from ongoing genetic studies have shown the possibility of clustering different histotypes based, for example, on kinase expression[18] (Fig. 86-1).

Familial Renal Cell Carcinoma

In a small percentage (4%) of cases, RCC is a feature of one of several hereditary syndromes.[14,19] Such syndromes are associated with different subtypes of RCC, and tumor presentation can range from a solitary lesion to multifocal.[14,19] Management is dependent on preservation of renal function. Close surveillance and minimization of surgical procedures constitute the mainstay of treatment.

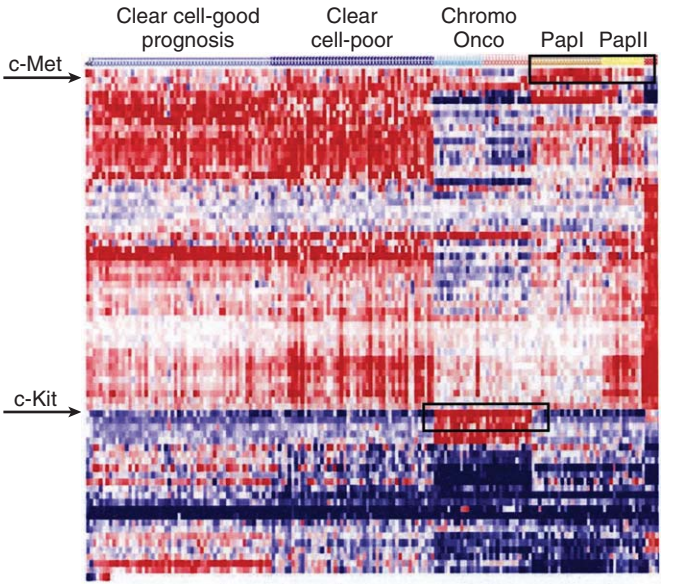


Figure 86-1 • Kinase expression in RCC: Genetic signatures. Determining the genetic signature in renal tumors not only has advanced the tumor classification but also will contribute to patient selection. These data show the gene expression of approximately 80 kinases (of 518) that have differential expression across the subtypes, with *red* meaning strong expression. Recognition of c-Met and c-Kit expression allows clustering the samples in specific subtypes. These types of data will guide the selection of patients undergoing treatment with kinase inhibitors. Chromo, chromophobe; onco, oncocytoma; PapI, papillary type I, PapII, papillary type II. (Adapted from Teh B: Kinome in renal cell carcinoma: mutation analysis of 518 kinases and expression in 400 tumors. J Clin Oncol 2007 ASCO Annual Meeting Proceedings 2007;25[18S]:5013.)

von Hippel-Lindau disease is a disorder of autosomal dominant inheritance that occurs in 1 in 40,000 births. The mean age at onset is in the fourth decade of life. The *VHL* gene is a tumor suppressor gene located on chromosomal band 3p25-26.[14,19,20] The product of this gene is expressed in multiple tissue types including the central nervous system (CNS). Manifestations include retinal or CNS angiomas and hemangioblastomas. The endocrine system is affected by adrenal pheochromocytomas and by pancreatic lesions, leading to pancreatic insufficiency, diabetes mellitus, biliary obstruction, and islet cell tumors. Benign papillary cystadenomas of the epididymis or broad ligament also may develop. Bilateral cystadenomas are pathognomonic for von Hippel-Lindau disease. Endolymphatic sac tumors of the inner ear also may be seen. Renal manifestations include renal cysts and RCC. Clear cell RCC, which tends to be bilateral and multifocal, develops in 70% of patients with von Hippel-Lindau disease.[14,19,20]

Birt-Hogg-Dubé syndrome is a disorder of autosomal dominant inheritance. The *BHD* gene, which codes for the protein folliculin, is located on chromosomal band 17p11.2.[14,19–22] Folliculin has an unknown function. Signs and symptoms usually manifest in the fifth decade of life. This syndrome is characterized by benign skin tumors, which include fibrofolliculomas, trichodiscomas of hair follicles, and skin tags. Other manifestations include medullary carcinoma of the thyroid; multifocal pulmonary cysts, which can lead to spontaneous pneumothorax; and renal epithelial neoplasms. The renal neoplasms are multifocal and bilateral tumors that consist of oncocytomas and clear cell, chromophobe, and papillary types. Tumor size increases with malignant potential. The *BHD* gene appears to have the characteristics of a loss-of-function tumor suppressor gene.[23] Although

studies are under way to determine how damage to this gene leads to chromophobe renal carcinoma, sporadic chromophobe renal carcinoma has been shown to overexpress c-Kit.[24]

Tuberous sclerosis is a syndrome of autosomal dominant inheritance, with two genes identified, *TSC1*, located on 9q34, and *TSC2*, located on 16p13.3. It affects 1 in 6000 people and is usually diagnosed at birth.[14,19,20] This syndrome encompasses multiple organ systems, including dermatologic, cardiac, pulmonary, and renal. Skins lesions include facial angiofibromas, periungual fibroma, shagreen patches, and hypopigmented macules. Patients also develop cardiac rhabdomyomas, pulmonary lymphangioleomyomatosis, retinal hamartomas, subependymal nodules, and giant cell astrocytomas. The renal manifestations include bilateral and multifocal angiomyolipomas (AMLs), clear cell renal carcinoma, and oncocytomas. In contrast with spontaneous AML, AML in this setting can be associated with a low risk of occult RCC.

Hereditary papillary renal cell carcinoma (HPRCC), inherited as an autosomal dominant trait, is caused by mutations in c-*met* protooncogene on chromosomal band 7q31-34.[14,20,25] It is characterized by bilateral, multifocal papillary RCCs. These tumors are not aggressive and rarely metastasize. Age of onset is around the fifth decade. It is associated with tumors of the pancreas, lung, skin, and stomach. Malchoff and colleagues have described a three-generation family with five cases of papillary thyroid carcinoma and two cases with papillary renal neoplasia.[25] With the use of linkage analysis, these investigators demonstrated that the fPTC/PRN phenotype was linked to 1q21.[25] They characterized a distinct inherited tumor syndrome that may establish a link between papillary RCC and familial papillary thyroid carcinoma.[25]

Familial clear cell renal cell carcinoma (FCCRCC) is defined as RCC in persons with a family history of clear cell renal carcinoma in two or more first-degree relatives.[19,20] The genetic defect has not yet been identified. Age at onset is variable, and the tumor tends to be solitary and confined to the kidney.

Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is a disease of autosomal dominant inheritance. The gene for this disorder has been localized to chromosomal band 1q42.3-43.[14,19,20] Age at onset is between the third and fourth decades of life. The syndrome consists of cutaneous leiomyomas, uterine fibroids, and papillary RCC. Affected patients also have a predisposition to uterine leiomyosarcoma. Thirty percent of patients have solitary and unilateral renal tumors, which are aggressive.[19,20] HLRCC is a hereditary cancer syndrome in which affected persons are at risk for the development of cutaneous and uterine leiomyoma and an aggressive form of type 2 papillary renal carcinoma. The gene for HLRCC has been found to be that encoding the Krebs cycle enzyme fumarate hydratase (*FH*).[26] Mutations of *FH* are found in the germline of affected persons in HLRCC kindreds.[27] *FH* appears to function as a tumor suppressor gene; loss of the second allele has been detected in kidney tumors from patients with HLRCC. The type 2 papillary kidney cancer found in these patients is a particularly aggressive form of renal carcinoma; it can metastasize early and often is fatal.

Familial oncocytoma is characterized by multiple and bilateral oncocytomas and cystic lesions.[28] Renal oncocytomas account for 5% of all renal tumors. Teh and colleagues described a patient with bilateral multifocal renal oncocytomas and cysts with a constitutional reciprocal translocation (8;9)(q24.1;q34.3).[28]

DIAGNOSIS OF RENAL CELL CARCINOMA

As the use of imaging methods has become more widespread, the frequency of incidental detection of RCC has increased. Patients with RCC typically present with a mass involving the kidney that is suggestive of the diagnosis. Nephrectomy is the most effective therapy for RCC that is confined to the kidney and should be used both diagnostically and therapeutically in most patients who are suitable surgical candidates. In certain clinical settings, percutaneous biopsy of a renal mass should be considered. In a retrospective study of 115 consecutive percutaneous biopsies performed on renal masses in 113 patients, investigators found percutaneous biopsy to be of high sensitivity in three clinical groups: patients with a known malignancy ($N = 55$), patients with no known malignancy and suspected unresectable tumor ($N = 36$), and nonsurgical patients with a mass suspected to be a resectable RCC ($N = 8$).[29] Percutaneous biopsy of renal masses appears to be safe, carrying only a minimal risk of tumor spread. Urologists should consider increasing the indications for renal biopsy of small renal masses that appear to be RCC, especially in elderly and surgically unfit patients. With more experience and follow-up preoperative biopsy, this strategy has the potential to decrease unnecessary treatment, because up to a third of small renal masses are now reported to be benign at surgery. Percutaneous biopsy also may allow better selection of renal tumors for active surveillance and minimally invasive ablative therapies. Finally, initial therapy for metastatic RCC may potentially be stratified by histologic subtype and, in the future, molecular characteristics.

STAGING SYSTEMS FOR RENAL CELL CARCINOMA

The tumor-node-metastasis (TNM) system is a dynamic staging method that continually changes on the basis of new evidence from clinical studies (Table 86-2).[30] This staging system is a method of stratifying patients with cancer and is based on data from large multicenter studies with large numbers of patients and a good level of evidence. Despite continual revisions to the methodology to incorporate new clinical evidence, however, the optimal RCC patient stratification using the TNM staging system remains controversial, and further revisions probably will be needed. Revision of the TNM staging system for RCC is likely to result in the simultaneous update of the integrated prognostic systems currently used with this traditional method of staging.

The first TNM staging system for RCC was developed in 1978.[31] In the TNM system, tumors are characterized on the basis of the degree of local extension of the tumor at the primary site (T), the involvement of regional lymph nodes (N), and the presence or absence of distant metastases (M). The addition of numbers to each of the TNM components allows one more precisely to categorize the extent of malignant disease at the primary, lymph node, and metastatic sites, respectively. The classification may be clinical (cTNM) or histopathologic (pTNM). In the case of RCC, the regional lymph nodes are defined as the hilar, abdominal para-aortic, and paracaval nodes. Laterality does not affect N categories. A retrospective study ($N = 252$) conducted to validate this system found that survival was most dependent on the local extent of the primary tumor, with 5-year overall survival rates of 100% for pT1, 91% for pT2, 58% for pT3, and 25% for pT4.[32] The system also resulted in poor stratification of patients, with few patients in the pT1 ($N = 7$) and pT4 ($N = 9$) categories.

In the 1987 revision of the TNM system, a value of 2.5 cm was chosen to distinguish pT1 from pT2 tumors, and an entirely new set of criteria was introduced to evaluate lymph node status. Perhaps most important, comprehensive stage groupings were introduced to define more precisely the impact of TNM characteristics on survival. Again, however, very few patients were stratified to stage I, with only 11 of 872 patients classified in this category in one study.[32,33] Furthermore, a study of 337 RCC tumors confined to the kidney found no survival difference between stage I and stage II tumors at the 2.5-cm breakpoint, although a significant difference was identified at the 7.5-cm breakpoint.[34] In 1997, the American Joint Committee on Cancer (AJCC)[35] and the International Union Against Cancer (UICC)[36] published an updated version of the TNM system. The result of this international collaboration was a more uniform categorization of RCC based on improved clinical evaluation and management. In this version, the breakpoint between pT1 and pT2 was

Table 86-2 Tumor-Node-Metastasis (TNM) Staging System for Renal Cell Carcinoma

Staging	Classification	1987	1997	2002
Tumor	T1	Tumor ≤2.5 cm, limited to kidney	Tumor ≤7 cm, limited to kidney	NA
	T1a	NA	NA	Tumor ≤4 cm, limited to kidney
	T1b	NA	NA	Tumor >4 cm and ≤7 cm, limited to kidney
	T2	Tumor >2.5 cm, limited to kidney	Tumor >7 cm, limited to kidney	Tumor >7 cm, limited to kidney
	T3	Tumor extends into major veins or invades adrenal or perinephric tissues, but not beyond Gerota's fascia	Tumor extends into major veins or invades adrenal or perinephric tissues, but not beyond Gerota's fascia	Tumor extends into major veins or invades adrenal or perinephric tissues, but not beyond Gerota's fascia
	T3a	Perinephric or adrenal extension	Perinephric or adrenal extension	Perinephric or sinus fat or adrenal extension
	T3b	Renal vein involvement	Renal vein or vena cava involvement below diaphragm	Renal vein or vena cava involvement below diaphragm
	T3c	Vena cava involvement below diaphragm	Vena cava involvement above diaphragm	Vena cava involvement above diaphragm
	T4	Outside Gerota's fascia	Outside Gerota's fascia	Outside Gerota's fascia
	T4a	Vena cava involvement above diaphragm	NA	NA
	T4b	NA	NA	NA
Node	Nx	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis	No regional lymph node metastasis	No regional lymph node metastasis
	N1	Metastases in one lymph node ≤2 cm in greatest dimension	Metastases in one regional lymph node	Metastases in one regional lymph node
	N2	Metastases in one lymph node >2 cm, but not >5 cm in greatest dimension	Metastases in more than one regional lymph node	Metastases in more than one regional lymph node
	N3	Metastases in one lymph node >5 cm in greatest dimension	NA	NA
Metastasis	Mx	Distant metastasis cannot be assessed	Distant metastasis cannot be assessed	Distant metastasis cannot be assessed
	M0	No distant metastases	No distant metastases	No distant metastases
	M1	Distant metastases	Distant metastases	Distant metastases

From Ficarra V, Galfano A, Mancini M, et al: TNM staging system for renal-cell carcinoma: current status and future perspectives. Lancet Oncol 2007;8:554–558.

increased from 2.5 cm to 7.0 cm. In addition, the requirement for the T3a classification was more precisely defined as invasion of the adrenal gland by direct extension of the tumor or invasion of perinephric fat. The subcategories of venous tumor extension (pT3) were revised so that venous tumor extension above the diaphragm was classified as T3c, whereas venous tumor extension limited to the vena cava below the diaphragm was classified as T3b.This reflected the decreased adverse prognostic significance of venous tumor extension alone. The classification of lymph node metastasis also was simplified to include involvement of a single lymph node (N1) or multiple lymph nodes (N2), with the stipulation that four to eight nodes should be analyzed before assigning the pN0 classification.[37]

In 2002, the AJCC published the sixth edition of the *AJCC Cancer Staging Handbook*.[38] The manual was developed in close collaboration with the UICC to refine further the uniform staging system to bring worldwide consistency to cancer staging. In the case of RCC, the key change was to subdivide T1 lesions into T1a and T1b. The rationale was based on evidence from studies of patients undergoing partial nephrectomy, a procedure commonly used for tumors that are 4 cm or smaller. It has been reported that patients who undergo partial nephrectomy for RCC tumors smaller than 4 cm have equivalent survival to those undergoing radical nephrectomy.[39] In a separate study of 485 patients undergoing nephron-sparing surgery for RCC with a mean follow-up period of 47 months, patients were divided into four groups based on the size of the primary.[40] Patients in group 1 (tumors less than 2.5 cm in diameter) and those in group 2 (tumors 2.5 to 4.0 cm) had equivalent survival, although survival was significantly greater for groups 1 and 2 than for group 3 (tumors 4 to 7 cm) and group 4 (tumors greater than 7 cm). These findings were similar to those previously published in a separate series of 394 patients.[41]

Since the last revision of the system in 2002, data from several studies have provided issues for discussion in the next revision of the system.[30] New data are available from large multicenter studies that recruited adequate numbers of patients with level 2 or 3 evidence.[42–44] Prognostic systems include not only anatomical features but also other clinical and pathological variables, but will also eventually provide more accurate information for patient counseling, follow-up planning, patient selection for clinical trials, and adequate assessment of the results.[30] Integrated systems are less widely used than the TNM

system, because they are difficult to apply and contain several inadequately defined clinical and histopathologic variables. The TNM system will become a more refined and advanced instrument used by all clinicians and researchers involved in the management of RCC.

PROGNOSTIC FACTORS FOR RENAL CELL CARCINOMA

Although TNM stage, Fuhrman grade, and Eastern Cooperative Oncology Group (ECOG) performance status are the most widely recognized prognostic factors in RCC, research continues to determine strong and easily available prognostic parameters that may help to classify patients in groups with different risks for death from renal cancer. The prognosis for patients with RCC is dependent primarily on disease stage. Patients with histopathologic stage pT1 or pT2 (organ confined) disease have the best prognosis, with 5-year cancer-specific survival rates after nephrectomy ranging from 71% to 97%.[45] For patients with locally advanced tumors, 5-year cancer-specific survival rates after nephrectomy decrease by 20% to 53%, and once RCC has metastasized, the 5-year survival rate is less than 10%.

Numerous models exist to predict disease recurrence after nephrectomy for all histologic types and specifically for clear cell RCC.[46] The natural history and risk group stratification have also been evaluated in those with newly diagnosed metastatic RCC and in patients with previously treated metastatic disease. Currently, RCC histologic subtypes are classified according to the UICC and AJCC recommendations.[47] These recommendations are based on the Heidelberg classification system,[48] which categorizes RCCs as clear cell, papillary, chromophobe, collecting duct, and unclassified RCC subtypes. Recent studies have suggested that stratification by histologic subtype could lend prognostic value.[49,50]

To assess the role of different histologic types in outcome, four thousand sixty-three patients from eight international centers were included in a retrospective study.[46] Histologic subtype (1997 UICC criteria of tumor response), age, sex, TNM stage, Fuhrman grade, tumor size, ECOG performance status, and overall survival were determined in all cases. The prognostic value of clear cell, papillary, and chromophobe histologic patterns was assessed by univariate and multivariate analysis using the Kaplan-Meier method and Cox model, respectively. Clear cell, papillary, and chromophobe carcinomas accounted for 3564 (87.7%), 396 (9.7%), and 103 (2.5%) cases, respectively. In univariate analysis, a trend toward a better survival was observed when clear cell, papillary, and chromophobe histologic patterns were considered prognostic categories. In multivariate analysis, however, TNM stage, Fuhrman grade, and ECOG performance status, but not histology, were retained as independent prognostic variables. The stratification in three main RCC histologic subtypes as defined by the 1997 UICC–AJCC consensus probably should not be considered a major prognostic variable comparable with TNM stage, Fuhrman grade, and ECOG performance status. The prognostic issue is not the only reason that it is important to recognize different histologic subtypes in RCC. Different subtypes have different predilections for stage, as well as different metastatic profiles. Further understanding of the molecular basis of histologic subtyping will provide greater insight into the various tumorigenic pathways of kidney carcinogenesis.

The University of California at Los Angeles (UCLA) Integrated Staging System (UISS) was developed for the purpose of improving the prognostic accuracy of the 1997 TNM staging system by incorporating clinical variables.[51] The study was based on the analysis of data for patients with RCC treated at a single institution between 1989 and 1999 ($N = 661$). All patients underwent radical or partial nephrectomy, and most patients with metastatic disease received recombinant IL-2-based immunotherapy within the context of 11 clinical trials. The median follow-up period was 37 months. Patients with papillary tumors ($N = 42$) showed a trend toward improved prognosis that did not achieve statistical significance, whereas patients with sarcomatoid ($N = 45$) and collecting duct tumors ($N = 3$) had worse prognosis. Survival rates for patients with clear cell and chromophobe histologic patterns were similar. The UISS uses five stratification groups (I through V) that incorporate variables commonly used in clinical practice, including 1997 TNM stage, ECOG performance status, and Fuhrman grade. The projected 5-year survival rates published by the UISS group weres as follows: 94% for group I, 67% for group II, 39% for group III, 23% for group IV, and 0% for group V. The original UCLA integrated staging system has since been modified so that patients are grouped into two general categories: those with nonmetastatic disease at the time of diagnosis and those with metastatic disease.[52] Each category is then divided into high-, intermediate-, and low-risk subcategories, based on the 1997 TNM staging system, the Fuhrman grade, and the ECOG performance status.

To confirm the ability of the UISS to stratify patients with localized and metastatic RCC into risk groups, an international multicenter study was conducted.[46] A total of 4202 patients from eight academic centers were classified according to the UISS. The UISS stratified both localized and metastatic RCC cases into three different risk groups. For localized RCC, the 5-year survival rates were 92%, 67%, and 44% for low-, intermediate-, and high-risk groups, respectively. A trend toward a higher risk of death was observed in all centers for increasing UISS risk category. For metastatic RCC, the 3-year survival rates were 37%, 23%, and 12% for low-, intermediate-, and high-risk groups, respectively. In six of eight centers, a trend toward a higher risk of death was observed for increasing UISS risk category. A greater variability in survival rates among centers was observed for high-risk patients. These results suggest that the UISS is an accurate predictor of survival for patients with localized RCC, applicable to external databases. Although the UISS may be useful for patients with metastatic RCC, it may be less accurate in this subset of patients because of the heterogeneity of patients and treatments.

A retrospective, single-institution review of 24 consecutive clinical trials conducted at Memorial Sloan-Kettering Cancer Center using cytokines or chemotherapy for the treatment of advanced RCC ($N = 670$) identified a small subgroup of patients ($N = 30$) who were long-term survivors after nephrectomy and treatment with interferon-α, IL-2, or surgical resection of metastasis.[53] The five most prominent negative prognostic factors that were identified by multivariate analysis included low Karnofsky performance status (less than 80%), elevated lactate dehydrogenase (greater than 1.5 times the upper limit of normal), low serum hemoglobin (below the lower limit of normal), high corrected serum calcium (greater than 10 mg/dL), and absence of nephrectomy. Patients with zero risk factors were assigned a favorable-risk status; those with one or two risk factors, an intermediate-risk status; and those with three or more risk factors, a poor-risk status. All long-term survivors in this study were in either good- or intermediate-risk groups.

In an additional study from the Memorial Sloan-Kettering Cancer Center, the relationship between pretreatment clinical features and survival was assessed in 251 patients with advanced RCC treated during 29 consecutive clinical trials between 1975 and 2002.[54] Clinical features were first examined in univariate analyses, and then a stepwise modeling approach based on Cox regression was used to form a multivariate model. The median survival time for the 251 patients was 10.2 months and differed according to year of treatment, with patients whose tumor was treated after 1990 showing longer survival. In this group, the median overall survival time was 12.7 months. Because the purpose of this analysis was to establish prognostic factors for present-day clinical trial design, prognostic factor analysis was performed on data for these patients. Pretreatment features associated with a shorter survival in the multivariate analysis were low Karnofsky performance status, low hemoglobin level, and high corrected serum calcium. These features were used as risk factors to categorize patients into three different groups. The median time to death in patients with zero risk factors was 22 months. The median

survival time in patients with one of these prognostic factors was 11.9 months. Patients with two or three risk factors had a median survival time of 5.4 months. These results suggest that the Memorial Sloan-Kettering Cancer Center risk categories (proposed by Motzer and coworkers[54]) can be used in clinical trial design and interpretation.

The natural history and risk group stratification also have been evaluated in patients with newly diagnosed metastatic RCC. For patients diagnosed with disease recurrence, no specific risk stratification tools have been available at the time of recurrence. A recent retrospective study sought to evaluate the utility of the prognostic score suggested by Motzer and coworkers.[54] From January 1989 to July 2005, patients with localized RCC treated by nephrectomy in whom recurrent disease subsequently developed were identified. Each patient was given a total risk score of 0 to 5, with 1 point for each of five prognostic variables (recurrence at less than 12 months after nephrectomy, serum calcium concentration greater than 10 mg/dL, hemoglobin concentration less than the lower limit of normal, lactate dehydrogenase level greater than 1.5 times the upper limit of normal, and Karnofsky performance status less than 80%). Patients were categorized into low- (score = 0), intermediate- (score = 1 to 2), and high-risk subgroups (score = 3 to 5). The final cohort included 118 patients, with a median survival time of 21 months from the time of recurrence. Median duration of follow-up for survivors was 27 months. Overall survival was associated with risk group category. Low-risk, intermediate-risk, and high-risk criteria were fulfilled in 34%, 50%, and 16% of patients, respectively. Median survival times for low-risk, intermediate-risk, and high-risk patients were 76, 25, and 6 months, respectively. Two-year overall survival rates for low-risk, intermediate-risk, and high-risk patients were 88%, 51%, and 11%, respectively. These additional data support the use of a scoring system based on objective clinical and laboratory data to achieve meaningful risk stratification for both patient counseling and clinical trial entry.

The Memorial Sloan-Kettering Cancer Center and UCLA prognostic systems are similar in several ways. First, both systems are based on a series of consecutive clinical trials for RCC conducted at single institutions. Second, good performance status was found to correlate with lower risk in both systems. Third, cytoreductive nephrectomy for metastatic disease before immunotherapy was found to confer a more favorable prognosis (Memorial Sloan-Kettering Cancer Center) or was used as standard therapy (UCLA) in both systems. More recently, Karakiewicz and associates have proposed a nomogram for prediction of RCC-specific survival in nonmetastatic and metastatic disease, using a development cohort of 2530 patients and an external validation cohort of 1422 patients.[56] The nomogram differs from the UISS with respect to one predictor. The symptom classification replaces the ECOG performance system within the nomogram. Moreover, the nomogram provides individual estimation of RCC-specific survival, instead of grouping patients within discrete strata. Direct comparison of the nomogram with the UISS strata, within an external validation cohort, demonstrated higher accuracy for the nomogram, with 89% and 87%, respectively, at 2 and 5 years, compared with 86% and 82% for UISS.

SURGICAL APPROACH FOR LOCALIZED DISEASE

The surgical approach for localized disease depends in large part on the extent of disease, tumor location, and the training and experience of the surgeon. For lesions that appear to be locally extensive with potential involvement of neighboring organs, open surgery is still preferred. This is particularly true if a colectomy, splenectomy, or distal pancreatectomy is anticipated. In addition, local adenopathy or invasion by tumor thrombus into the renal vein and vena cava also may be a relative indication for consideration of open surgery as opposed to laparoscopy. Even with extension of tumor thrombus into the vena cava, however, laparoscopic resection may be possible, provided that the thrombus just enters the cava and can be manipulated back into the renal vein with certain maneuvers. Large tumors often are best approached in open fashion. In some instances, however, even large tumors can be approached laparoscopically if the local anatomy is favorable.

When open surgery is required, the choice of surgical approach also is dictated by the surgeon's training and experience and by the location and extent of disease. Resection of tumors with thrombus extending into the inferior vena cava above the level of the hepatic veins usually is performed through a midline incision to allow extension to a sternotomy, if required. Tumors with thrombus extending into the inferior vena cava but below the hepatic veins often can be accessed by a thoracoabdominal approach if the primary lesion is on the right side. For other, less extensive tumors, laparoscopy is the preferred approach when nephrectomy is deemed necessary.

Laparoscopy has gained widespread popularity because it carries less morbidity than open surgery and results in a faster convalescence. Although most laparoscopic surgeons prefer a transperitoneal (transabdominal) approach for this operation, many surgeons prefer the retroperitoneal approach. The difference in approach seems to matter relatively little to the patient but rather is a technical issue for the surgeon. The transabdominal approach allows complete visualization of the viscera with multiple landmarks and visual cues for orientation, but does require more anterior and anteromedial dissection. Surgery through the retroperitoneal approach can be faster in the hands of an experienced laparoscopic surgeon, but many visual cues and landmarks to ensure dissection in the proper planes are lacking with this procedure. Regardless of approach, however, current surgical practice in the United States is to perform nephrectomy laparoscopically (with or without hand assistance), except when an excessively large tumor, locally advanced disease, local adenopathy, or tumor thrombus is present. Even in these situations, it often is beneficial to start a case laparoscopically and then complete it in a controlled open fashion. Such a strategy can result in a smaller incision often in the midline, with less pain and morbidity, than is typical if the entire case is performed in open fashion.

Morcellation

There has been controversy with radical laparoscopic nephrectomy, whether to morcellate the specimen or remove the kidney as a whole. An intact extraction has the benefit of maintaining kidney and tumor integrity for more precise histopathologic evaluation, decreases chance of tumor seeding of the port sites or renal fossa, and requires shorter surgery time.[57] Pautler and colleagues compared the histopathologic diagnosis of their operative needle biopsy before morcellation with the morcellated specimen.[58] They found adequate histopathologic material for diagnosis.[58] They were able to stage only 3 of 15 morcellated specimens. Owing to the increased sensitivity of CT scanning today and other imaging modalities, it has been argued that lack of staging information from surgical specimen does not affect management of the patient. Barrett and associates found precise pathologic staging did not change subsequent tumor management in their patients.[59] Enclosing the kidney in an impermeable sac before morcellation prevents seeding. No difference has been found in length of hospital stay, recovery time or postoperative treatment.[59] While there was initially great enthusiasm among the laparoscopic surgeons to remove the kidneys and tumors through morcellation, this practice has been waning—in part because now most urologic oncologists are performing laparoscopic nephrectomies and prefer intact extraction of the kidney and mass for accurate histopathologic staging purposes.

A retrospective Japanese study of 100 patients with tumors smaller than 5 cm in diameter revealed a longer mean operative time (5.2 versus 3.3 hours), less mean blood loss, and a shorter time to completion of convalescence for patients managed with laparoscopic radical nephrectomy ($N = 60$) rather than open radical nephrectomy ($N = 40$). No significant difference was found in 5-year disease-free

survival rate for patients who had laparoscopy (95.5%) and those who underwent open nephrectomy (97.5%).[60] Cytoreductive radical nephrectomy commonly is performed in patients with metastatic RCC before administration of systemic IL-2. In this setting, laparoscopic techniques that use tumor morcellation reduce surgical trauma and allow resection of larger tumors. In patients with metastatic disease, the precise delineation of local invasiveness and the possibility of surgically mediated tumor dissemination are not primary concerns. Laparoscopic techniques offer the possibility of lower morbidity and faster recovery, to minimize the delay in starting treatment with high-dose IL-2.

Nephron-Sparing Surgery

With increasing sensitivity of imaging studies, nephron-sparing surgery has become an effective surgical option for RCC. Although the classic radical nephrectomy still remains the standard of care for treatment of RCC, nephron-sparing surgery has proved to be a very effective curative therapy for patients with localized disease. Leibovich and associates compared outcomes in 91 patients managed with nephron-sparing surgery and 841 patients who underwent radical nephrectomy for 4- to 7-cm tumors.[61] These investigators found no statistical difference in cancer-specific survival and distant metastases between the two groups. Nephron-sparing surgery can be done with low morbidity, mortality and good surgical outcomes.

Traditionally, indications for nephron-sparing surgery for the treatment of RCC have included conditions such as unilateral renal agenesis, horseshoe kidney, or bilateral RCC in which radical nephrectomy would leave the patient anephric, resulting in the need for immediate dialysis. Additional indications have included unilateral RCC with a diseased contralateral kidney that is at risk for severe compromised function. Examples of such conditions are diabetes, hypertensive nephrosclerosis, renal artery stenosis, renal calculi, and chronic pyelonephritis. Other indications include tumor diameter of 4 cm or less, anatomic position of the tumor, and localized disease.[61,62] With respect to tumor size, an experienced urologist may use this approach to remove larger tumors with curative intent. The indications for nephron-sparing surgery are partly dependent on the skill of the surgeon and the availability of the equipment.

Laparoscopy has become the mainstay of management of RCC. Today the choice between open partial nephrectomy and laparoscopic partial nephrectomy depends on anatomic location of the tumor, body habitus, and ability to tolerate pneumoperitoneum. With increasing usage of minimally invasive therapies the indications for laparoscopy are expanding. Steinberg and coworkers retrospectively reviewed outcomes for 13 patients who had minimally invasive surgery on two or more ipsilateral tumors.[63] Using either LPN (in 7 of the patients) or cryotherapy (in 6 patients), these investigators reported no intraoperative complications, negative surgical margins, and good renal function in the remnant kidney. An experienced surgeon can perform technically challenging laparoscopy with good surgical and oncologic outcomes.

With the standardization of staging and earlier diagnosis of the disease, a more tumor-specific surgical management has proved to be advantageous to maximizing the preservation of functional renal tissue. With increased evidence of the need for long-term dialysis in patients undergoing total nephrectomy, maintenance of renal function in both kidneys represents the strongest argument for nephron-sparing surgery in patients with RCC who have the best chance for cure.

Cryosurgery for Renal Cell Carcinoma

Urologists pioneered minimally invasive surgery and have been constantly searching for less invasive techniques. With the advent of energy-based ablative alternatives to open and laparoscopic surgeries in selected patients, it is now possible to achieve cancer-specific survival with decreased surgical morbidity. Renal cryosurgery is a technique that is being developed for resection of small renal tumors as an alternative to nephron-sparing surgery, with the goal of reducing the morbidity associated with open partial nephrectomy. Use of standard cryoprobes of 3 to 8 mm can cause rupture of the renal capsule and parenchyma, resulting in significant bleeding. The use of multiple 1.5-mm cryoprobes under intraoperative real-time ultrasound guidance may decrease the risk of bleeding and make this technique a more feasible approach.[64]

Increasing evidence suggests that cryoablation is an acceptable surgical alternative to traditional open and laparoscopic nephrectomy.[65–69] In addition to shorter hospital stay and less morbidity, cryoablation has been shown to be a very effective nephron-sparing cancer therapy.[69] Patients selected for this option tend to have peripheral lesions 5 cm or less in diameter.[65,69] Owing to the increased use of CT scan, the number of incidentally found renal lesions has increased; 20% to 40% of these lesions usually are benign or slow-growing tumors.[65,69] Many such lesions tend to enhance on CT and require some treatment modalities. Minimally invasive therapy without the sequelae of open or laparoscopic surgery may be reasonable in these situations, particularly in patients not eligible for surgery. Cryoablation surgery has been described in the literature with open, laparoscopic, and, more recently, imaging-guided percutaneous approaches.[70,71]

Multiple theories have been proposed for the mechanism of action of cryoablative surgery. The most accepted theory postulates direct cellular injury leading to coagulative necrosis.[67,68] Injury to the cancer cells occurs as a result of intracellular ice crystal formation during the freezing phase of the treatment.[67,68] The decreased temperature causes damage to cellular structures, leading to cell death.[67] The freezing process causes protein damage, which injures the cell membrane and essential enzymatic processes.[67] Ice crystals that form within the cell disrupt intracellular organelles and membranes. Additionally, indirect ischemic injury due to occlusion of the microvasculature during the thaw phase creates stasis within blood vessels, leading to end-tissue infarction. These ensuing insults to renal tissue lead to liquefactive necrosis.[67]

In most cases, the cryoprobes used are 2.4 mm in diameter. The usual procedure is percutaneous CT guidance cryotherapy, in which each lesion is treated with a double freeze-thaw cycle, with active freeze at 100% efficiency for a minimum of 10 minutes and a passive thaw of 8 minutes.[65] These cycle times consistently deliver the lethal freeze of −4° C within 1 cm of the iceball edge.[65] The critical threshold for necrosis has been reported as between −19.4° and −40° C.[65] The number of probes used is specific to the size and shape of the lesion, with freeze margins of 0.5 to 1 cm of the lesion.

Some advantages to CT-guided cryotherapy include general availability and its excellent capability to differentiate among the visceral organs. It also provides visualization of the entire ice ball while differentiating between frozen and unfrozen tissue. In addition, it provides real-time guidance in the CT fluoroscopy mode. One major disadvantage with CT guidance is the constant radiation exposure to the patient and the surgeon. This can be corrected by using adequate and appropriate protection from radiation.

No current long-term follow-up study of cryotherapy has been performed. Gill and colleagues described a 98% cancer survival rate at 3 years after surgery.[65] These investigators also found a significant decrease in tumor size 3 to 6 months after surgery. These are promising results, but longer-term data are needed. Because the renal tumor is not excised, with documentation of histopathologic margins, whether the entire tumor has been extirpated remains uncertain.[65] This challenge forces frequent CT and MRI follow-up studies on patients who receive this therapy.

Surveillance after Complete Resection: Sporadic Renal Cell Carcinoma

A need has been recognized for standardization of surveillance protocols after nephrectomy for sporadic RCC. Multiple surveillance

protocols have been proposed.[44,72–74] An important consideration in determining the appropriate frequency of surveillance imaging after surgery is the ability to provide curative or palliative salvage therapy. Because improved survival can be achieved for certain subsets of patients with recurrent disease, an active approach to surveillance is warranted. For instance, patients with solitary metachronous metastases treated aggressively with surgical resection have a 5-year survival rate of 20% to 44%.[75–78] Extended survival (21 to 136 months) also can be achieved in as many as 33% of patients who undergo resection of an isolated local recurrence in the retroperitoneum.[79,80] Follow-up imaging after curative therapy has been challenged on the basis of survival benefit and cost-effectiveness.[81]

No current randomized trials exist, so little evidence on the appropriate follow-up after surgery available. Too much surveillance places a financial and psychological burden on the patient, whereas too little surveillance may increase morbidity and mortality. Patients are risk stratified, and a follow-up schedule is determined on the basis of stage and grade of the disease. Most recurrence occurs within 3 to 5 years after nephrectomy.[82] Ljungberg and colleagues prospectively reviewed data for 187 patients with pT1 to pT3 disease who underwent radical nephrectomy at their center.[74] These investigators found that 80% of metastatic cancers were diagnosed within 3 years after surgery.[74] It has been documented that Furman nuclear grade, TNM stage, ECOG status, and DNA ploidy are good predictors of tumor progression and tumor recurrence.[82] T1 tumors recur between 38 and 45 months; T3 tumors recur between 17 and 28 months.[82] Furman grade 1 through 4 tumors are associated with risk of metastasis of 9%, 61%, 79%, and 87%, respectively. Diploid tumors carry a decreased risk of recurrence compared with aneuploid tumors.[74]

Imaging for surveillance is based largely on risk of of metastasis by anatomic site. The major metastatic sites in order frequency include lung (3% to 16%), bone (2% to 8%), regional lymph nodes, liver (1% to 7%), ipsilateral adrenal, contralateral kidney, and brain (2% to 4%). Currently, a history and physical examination (H&P), serum studies (calcium level, alkaline phosphatase level, and liver transaminases), and imaging studies (chest plain radiographs or chest CT scan and abdominal CT scan) done at time points when disease recurrence is likely are used for surveillance.[83] The lung has the greatest incidence of metastasis, so early diagnosis is pertinent.[83] Chest radiography has been shown to detect up to 90% of lung metastases.[82] Although chest CT is more sensitive than chest radiography, it yields more false positives, and its role in surveillance is still unknown.[82] In the case of bone metastasis however, only palliative therapies are available, therefore screening bone scintigraphy and radiographs are not warranted.[83] Abdominal CT and liver transaminase determination are an integral part of surveillance because of treatment options available for local recurrence or liver recurrence.[83]

Levy and coworkers have suggested a surveillance protocol based on TNM staging.[73] For T1 disease, a 6-month H&P and serum studies are performed annually for 3 years. For T2 disease, 3-month H&P and semiannual chest radiographs and serum studies are performed; at 24 and 60 months an abdominal CT is recommended. For T3 disease, 3-month follow-up visits that include serum studies and chest x-ray are suggested. Then at 24 and 60 months, a CT scan of the abdomen is recommended. Close follow-up is suggested for T4 disease, including H&P, CT of the abdomen, chest radiographs, and serum studies every 3 months for 2 years and every 4 months for the third and fourth years. Complete follow-up is indicated semiannually in year 5 and then annually.

Zisman and coworkers, in an attempt to standardize RCC staging and management protocol, developed the UISS, described earlier.[84] This system incorporates histologic grade, ECOG status, and TMN stage to improve prognostication for RCC.[84] With this system, they created a surveillance protocol for patients grouped according to recurrence risk. For the low-risk group, these investigators recommend H&P, serum laboratory studies, and chest CT scan annually. At 2 and 4 years after surgery, the patient should have an abdominal CT scan. The intermediate-risk group is recommended to have H&P, serum laboratory studies, and chest CT scan semiannually for 3 years and then annually for 10 years. They should also have an abdominal CT annually for 2 years and then every 2 years up to 10 years post surgery. The high-risk group should have H&P, serum studies, and chest CT semiannually for 3 years and then annually for 10 years. These patients also should have an abdominal CT scan semiannually for 2 years and then annually for 5 years and then every 2 years up until 10 years. Throughout the protocol after 3 years of surveillance the chest CT can alternate with chest radiography.

According to the National Comprehensive Cancer Network (NCCN) guidelines, follow-up evaluation for patients with completely resected disease includes abdominal and chest CT scans obtained approximately 4 to 6 months after the surgery to serve as baseline and then as clinically indicated. Patients are seen periodically, and each visit should include a history, physical examination, and comprehensive metabolic panel (i.e., determination of blood urea nitrogen, serum creatinine, calcium levels, lactate dehydrogenase, and liver enzymes).

Lifelong surveillance is necessary for patients with RCC. Late recurrence is arbitrarily defined as a recurrence more than 10 to 20 years after nephrectomy. In sporadic RCC, recurrences has been documented as long as 45 years after initial surgical resection.[85] The appropriate intensity of follow-up after 5 years remains to be established. Approximately 85% of recurrences, however, will be detected in the first 3 years after resection of the primary.[86]

von Hippel-Lindau Disease and Other Familial Renal Cell Carcinomas

Patients with von Hippel-Lindau RCC or other familial forms of RCC are at high risk for local recurrence after nephron-sparing surgery and require close lifelong surveillance. Greater than 80% of patients with von Hippel-Lindau disease treated with nephron-sparing surgical resection will have a recurrence in the ipsilateral kidney within 10 years, and lesions will develop in the contralateral kidney if they have not done so already.[87] This is because multiple microscopic lesions are present throughout the kidneys despite the grossly normal appearance of the parenchyma.[88] A diagnosis of von Hippel-Lindau disease should be considered in any patient with early-onset or multifocal RCC or RCC in conjunction with the following: a history of visual or neurologic symptoms; a family history of blindness, central nervous system (CNS) tumors, or RCC; or coexisting pancreatic cysts, epididymal lesions, or inner ear tumors.[89,90] Standard recommendations for surveillance in patients with von Hippel-Lindau disease include (1) CT of the abdomen and pelvis every 6 months, (2) annual physical and ophthalmologic evaluations, (3) estimation of urinary catecholamines every 1 to 2 years, (4) MRI of the CNS every 2 years, and (5) periodic auditory examinations. Molecular genetic and clinical screening should be offered to appropriate family members based on an autosomal dominant pattern of inheritance.[87,90,91]

ADJUVANT THERAPY AFTER NEPHRECTOMY

A role for adjuvant therapy after nephrectomy remains to be established, and to date observation remains the standard of care outside a clinical trial. Clinical studies with immunotherapies have failed to demonstrate a clinical benefit. One randomized, multicenter prospective study has reported on the efficacy of adjuvant interferon alfa-2b given after nephrectomy to patients with Robson stages II and III RCC.[92] Patients randomized to receive interferon alfa-2b were given a dose of 6 million IU intramuscularly three times per week for 6 months, starting within 1 month of surgery. Patients in the observation-only group who relapsed were given interferon alfa-2b,

10 million IU intramuscularly, three times per week, or the best available treatment at the time of relapse. Treatment groups were well matched at baseline for patient and tumor characteristics. No significant differences were observed in overall or event-free survival for patients randomized to management by observation ($N = 124$) and patients receiving interferon alfa-2b ($N = 123$). This study did not support the use of adjuvant interferon alfa-2b after nephrectomy. A recently analyzed and reported phase III study of interferon-α as adjuvant treatment for resectable RCC by the ECOG/Intergroup showed that adjuvant treatment with interferon did not contribute to better overall survival or relapse-free survival.[93]

As new drugs have become available for the treatment of metastatic disease, a rationale has arisen for testing these agents in micrometastatic disease. A large, randomized, double-blind phase III study conducted by the ECOG (E2805) is currently accruing patients who have undergone nephrectomy for kidney cancer. Patients with lesions staged as above T1c or Fuhrman grade of 3 or higher (or both) are randomly assigned to a placebo group or to either a sorafenib or sunitinib treatment group. Treatment is to continue for 1 year with close monitoring. The primary clinical endpoint will be time to tumor progression among the three groups. The goal of this important study is to identify a possible role for vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) in the adjuvant setting; confirmation of a positive effect will establish a new standard of care after nephrectomy for patients with risk for recurrence.

CYTOREDUCTIVE NEPHRECTOMY FOR PATIENTS WITH METASTATIC RENAL CELL CARCINOMA

Approximately one third of patients diagnosed with RCC present with metastatic disease and around 50% of patients will develop metastasis after initial diagnosis.[94] The role of nephrectomy in patients with metastatic disease at the time of diagnosis has long been the subject of debate. A general consensus exists that noncurative nephrectomy is appropriate when symptoms produced by the primary tumor require palliation, when the metastatic tumor burden is less than that of the primary tumor, and when the patient wishes to receive treatment with high-dose IL-2. With the approval of newer drugs (i.e., sunitinib, sorafenib, and temsirolimus), palliative nephrectomy also is now considered the standard of care in patients who will receive small molecule inhibitors for RCC.

Cytoreductive surgery with systemic therapy has been shown to induce clinical benefit.[94] The Southwest Oncology Group (SWOG) conducted a randomized study in which patients who were acceptable candidates for nephrectomy either underwent radical nephrectomy followed by therapy with interferon alfa-2b ($N = 120$) or received interferon alfa-2b alone ($N = 121$). The primary endpoint was survival, with objective response (OR) as the secondary endpoint. The patients were stratified by SWOG performance status (0 or 1), the presence or absence of lung metastases only, and the presence or absence of at least one measurable metastatic lesion in the region not to be resected. After randomization, patients either underwent immediate radical nephrectomy followed by interferon alfa-2b or were immediately given interferon alfa-2b without surgery. Interferon alfa-2b was then continued until disease progression. The median survival time was 11.1 months for patients who received nephrectomy plus interferon alfa-2b and 8.1 months for patients who received interferon alfa-2b alone ($P = 0.05$), Nonetheless, interpretation of these data is difficult in light of the poor median survival seen in both arms of this study.[95]

The patients benefiting the most from cytoreductive surgery appear to be those who have a good ECOG performance status (0 or 1) and preferably with metastasis limited to the lungs.[96] Risk and benefits, however, need to be weighed in the decision to perform cytoreductive surgery. Patients with poor performance status and a large metastatic disease burden (greater than the tumor in the kidney) are less likely to derive benefit from surgery. Frequently, patients with metastatic disease can undergo resection laparoscopically. This is always preferred when technically feasible, because it allows a shorter recovery interval until starting systemic therapy.

Mickisch and colleagues, in the European Organization for Research and Treatment of Cancer (EORTC) randomized trial, compared radical nephrectomy plus immunotherapy with immunotherapy alone.[97] These investigators found that nephrectomy plus immunotherapy delayed time to progression of the disease and improved survival. Bromwich and associates found a mean survival benefit of 4 to 10 months.[98] Of the 268 patients selected for the study, only 20 (7%) were selected for cytoreductive nephrectomy. Owing to the associated risks of the surgery, recovery time, and adverse reactions of the immunotherapy, they concluded after careful patient selection that cytoreductive surgery may only be beneficial to a small segment of renal cell patients.

Rabets and coworkers compared outcomes data for laparoscopic and for open cytoreductive nephrectomy.[99] The selection criteria for laparoscopic surgery were presence of lesions 15 cm or less in diameter and confined to the kidney. These investigators found no statistically significant survival benefits between the surgical modalities. Laparoscopic nephrectomy was found to have fewer morbidities, including less operative blood loss and shorter hospital stay. They concluded that even with advanced disease, laparoscopic nephrectomy is a safe alternative to open nephrectomy in metastatic disease. With proper patient selection patients with metastatic RCC may still benefit from laparoscopic surgery.[94,96,99,100]

RESECTION OF METASTASES IN RENAL CELL CARCINOMA

Resection of solitary metastases from RCC is associated with improved survival, although the selection criteria have been poorly defined. This issue was addressed in a retrospective, single-institution analysis of patients with recurrent RCC ($N = 278$) at the Memorial Sloan-Kettering Cancer Center.[101] Recurrent disease was defined as solitary if it recurred within the resected renal bed or if one organ system or site was involved. Multiple unilateral lesions in the lung were considered to represent a solitary site of metastasis. Bilateral lung involvement or recurrence in two or more sites was considered to constitute multiple sites. Surgery for metastatic disease was considered curative if metastases were curatively resected and noncurative if gross tumor was left behind. Of the 278 patients who underwent initial curative nephrectomy, recurrence was solitary in 155 patients and multiple in 123 patients, with a median time to first recurrence of 25 months. The overall 5-year survival rate of patients who underwent curative resection for the first recurrence was 44% ($N = 141$), 14% for those who received noncurative resection ($N = 70$), and 11% for those who were treated nonsurgically ($N = 67$). Favorable predictors of survival by multivariate analysis included a single site of first recurrence, curative resection of the first metastasis, a disease-free interval of more than 12 months, and a metachronous presentation with recurrence. Curative resection of isolated metastases to glandular tissue (thyroid, salivary gland, pancreas, adrenal, ovary) was associated with the best 5-year overall survival rate (63%), followed by resection of isolated lung metastases (54%). In this study, resection of solitary brain metastases, however, was associated with poor outcome, with an 18% 5-year overall rate. The 5-year overall survival rates of 46% and 44%, respectively, for patients who underwent second ($N = 62$) or third curative resection ($N = 22$) of subsequent metastases after initial curative metastectomy were not significantly different from those for patients who received only initial curative metastasectomy (44%; $N = 141$). Thus patients who undergo complete resection of metastatic disease in a solitary site after a disease-free interval of longer than 12 months may experience long-term survival. As with previous reports, complete resection is the important factor, rather than the number

of sites resected, even in patients who have undergone prior metastectomy.[102,103]

Brain metastases from RCC raise specific therapeutic problems because they are relatively unresponsive to whole-brain radiation therapy and tend to bleed. Recently, stereotactically guided high-precision irradiation (radiosurgery) has shown promising results in selected patients with brain metastases from RCC.[104] Radiosurgery appears attractive owing to its low risk of toxicity and minimal invasiveness. Multiple lesions can be treated at the same time, and retreatment can be performed for local or distant recurrences.

Lymphadenectomy in Locally Advanced Disease

The role of lymphadenectomy in RCC remains controversial. Nodal disease has been found to be a predictor of poor prognosis even with M0 disease, although, there is very little evidence to support the value of lymph node dissection.[105–107] The decision for LND should be based on multiple factors. The need for accurate staging, decreased local recurrence rates, and improved survival should be weighed against risk of morbidity and mortality.[105,108] One argument against lymph node dissection is that the kidney is drained hematologically and lymphatically through multiple pathways.[105] Owing to the unpredictable pathways of spread accurate staging may not be possible. From 58% to 95% of patients with lymph node disease also have synchronous metastasis[109]; consequently, the likelihood of finding patients with localized disease is low at 2% to 9%. Canfield and associates did a retrospective study supporting the need for aggressive nodal resection in the presence of positive lymph nodes without evidence of metastasis.[109] Blom and coworkers of the EORTC Genitourinary Group conducted a large randomized trial comparing radical nephrectomy with lymph node dissection and radical nephrectomy alone.[107] At 5-year follow-up evaluation, these workers found no significant difference in morbidity and mortality between the two groups after surgery. They also found no significant difference in survival. A small subset of patients may benefit from lymph node dissection. Pantuck and asociates have shown improved survival in patients found to have disease-positive lymph nodes who undergo cytoreductive nephrectomy and postoperative immunotherapy.[108] The literature is variable on the benefits of lymph node dissection in patients with renal neoplasms. Overall, lymphadenectomy provides little staging information and confers no clear benefit in decreasing risk of recurrence or in survival.

CYTOKINE THERAPIES FOR ADVANCED DISEASE

Inpatient high-dose bolus IL-2 received FDA approval for treatment for patients with stage IV RCC in 1992 based on data presented on 255 patients who were entered into seven phase II clinical trials.[110,111] In these studies, patients received 600,000 to 720,000 IU/kg of recombinant human IL-2 by 15-minute infusion every 8 hours during two 5-day courses (maximum, 14 doses per course) separated by 5 to 9 days of rest. Stable or responding patients received two to five courses of therapy at 8- to 12-week intervals and then were observed while not receiving any additional therapy. Objective responses were seen in 37 (15%) of the 255 patients, including 17 complete responses (CRs; 7%) and 20 partial responses (PRs; 8%). The median duration of response was 54 months for all of the responders and 20 months for partial responders; the median has not yet been reached for complete responders. The median survival was 16 months for all 255 patients. Most patients who achieved a CR that lasted longer than 30 months and those with PRs after resection resulting in "no evidence of disease" after a response to high-dose IL-2 were unlikely to experience disease progression and may actually be cured.

Although the inpatient high-dose bolus IL-2 regimen produces favorable outcomes in a handful of patients, it also is associated with significant toxic effects and cost and is not universally available. Low-dose IL-2 regimens (with or without interferon-α) have produced similar response rates and survival in nonrandomized phase II trials, but responses appeared to be less durable than those seen with high-dose IL-2.[112–115]

In an effort to determine the value of outpatient subcutaneous IL-2 and interferon-α relative to high-dose intravenous IL-2, the Cytokine Working Group did a phase III trial in which patients were randomized to receive either outpatient IL-2 and interferon-α every 6 weeks or standard high-dose inpatient IL-2 every 12 weeks.[116] One hundred ninety-three patients were enrolled, and 192 were evaluable for toxicity and tumor response. The response rate for high-dose IL-2 was 23%, versus 10% for IL-2 and interferon-α. Eight patients achieved a CR while taking high-dose IL-2, versus only three patients taking low-dose IL-2 and interferon-α. The median response durations were 24 months for high-dose IL-2 and 15 months for IL-2 and interferon-α. Median overall survival times were 17.5 and 13 months, favoring high-dose IL-2. Ten patients (nine major responders) who received high-dose IL-2 were progression free at 3 years, versus three patients (two major responders) who received IL-2 and interferon-α. Of note, responses to high-dose IL-2 were seen with equal frequency across the stratification criteria, whereas low-dose IL-2 and interferon-α seemed to produce fewer responses in patients with liver or bone metastases and in those who had not undergone prior nephrectomy to remove the primary tumor. For patients with bone or liver metastases, or with unresected primary tumor, survival was superior with high-dose IL-2 compared with IL-2 and interferon-α, whereas no significant survival differences between the two treatments were noted for patients who had undergone prior nephrectomy or who were without bone or liver metastases.

Taken together, these studies suggest that high-dose intravenous bolus IL-2 is superior in terms of response rate and possibly response quality to regimens that involve either low-dose IL-2 and interferon-α, intermediate- or low-dose IL-2 alone, or interferon-α alone.[117] The superiority of high-dose IL-2 is particularly apparent in patients with tumor metastases in immune-sequestered sites, such as liver or bone, or whose primary tumor has not been resected, or who fall into the intermediate-risk or poor-risk group defined by the French Immunotherapy Group. Consequently, although low-dose cytokine therapy has a limited role in metastatic RCC, it must be concluded that high-dose intravenous IL-2 should remain the preferred therapy for appropriately selected patients with access to such therapy. In view of the toxicity and limited efficacy of high-dose intravenous IL-2 therapy, however, additional efforts should be directed at better defining the patient population for whom this therapy is appropriate.[118]

Use of interferon-α as a single agent has resulted in only a modest survival benefit in the randomized setting, although combination of this agent with low-dose IL-2 (and perhaps with fluorouracil) may lead to an improved response rate, but evidence of survival benefit in a prospective randomized trial is lacking.[119–121] Although interferon-α has been the outpatient treatment of choice in most of Europe and the United States until recently, benefit again appears to be restricted to patients with good prognostic risk.[122]

Predictors of Response to Cytokine Therapy

Responses to immunotherapy most frequently are seen in patients with RCC of clear cell histology.[123–126] This observation was detailed in a retrospective analysis of pathology specimens obtained from 231 patients (163 primary and 68 metastatic tumor specimens) who had received IL-2 therapy on Cytokine Working Group clinical trials.[126] For patients with primary tumor specimens available for review, the response rate to IL-2 was 21% (30 of 146) for patients with clear cell histology primary tumors, compared with 6% for patients with non-clear cell histology (1 responder in 17 patients). Among the patients with clear cell carcinoma, response to IL-2 was also associated with

the presence of alveolar features and the absence of papillary or granular features. The response rate in patients whose primary tumors had "good" predictive features (e.g., greater than 50% alveolar and no granular or papillary features) was 39% (14 of 36). Patients with tumors that contained "poor" predictive features (e.g., greater than 50% granular or any papillary features) had a response rate of 3% (1 of 33). When this model was then applied to the 68 patients with specimens from metastatic sites, those patients who were treated without resection of their primary tumors, five tumor responses were seen in the 20 patients with "good" predictive features, whereas no tumor responses were seen in the 16 patients in the "poor" predictive group, thus supporting the validity of the model developed from the primary kidney tumor specimens. As a result of these data, it may be appropriate for patients whose primary tumor is of non-clear cell histologic type, or of clear cell histologic type but with "poor" predictive features, to forgo IL-2-based treatment altogether. Even in the most favorable predictive group, however, more than 50% of patients failed to respond to IL-2 therapy, so additional investigations to identify tumor-associated predictors of responsiveness to IL-2 are still necessary.[123]

Some investigators have begun to examine tumor tissue to identify immunohistochemical markers that may predict the outcomes for patients with RCC. Carbonic anhydrase IX (CAIX) has been identified as one potential marker. Bui and colleagues used a monoclonal antibody designed to detect CAIX expression to perform an immunohistochemical analysis of paraffin-embedded RCC specimens. These investigators showed that greater than 90% of RCCs express CAIX, and that its expression decreases with advancing stage.[127] In their analysis, high CAIX expression in primary tumors was seen in 79% of patients and was associated with improved survival and possibly improved response to IL-2-based therapy. Building on this work, Atkins and coworkers performed a nested case-control study within the larger cohort of patients for whom the histopathologic findings were analyzed.[128] CAIX expression levels were correlated with response to IL-2, pathologic risk categorization, and survival. Median survival times were 3 years and 1 year for high and low CAIX expressors, respectively. Although tumor response was seen in six patients with low CAIX staining, survival beyond 5 years was seen only in the patients with high-CAIX-expressing tumors. High CAIX staining was associated with better histopathologic features but remained an independent predictor of response. Although this model with its associated assumptions require prospective validation, it highlights the potential for using pathologic and molecular features of the tumor to identify optimal patients to receive IL-2 therapy. Additional studies to explain these preliminary observations and correlate results with previously described clinical features are necessary.[123]

Recently, the Cytokine Working Group launched the high-dose IL-2 "Select" Trial. The primary objective of this study is to determine, in a prospective fashion, if the predictive model proposed by Atkins and associates can identify a group of patients with advanced RCC who are significantly more likely to respond to high-dose IL-2-based therapy ("good" risk) than a historical, unselected patient population.[128] New factors (including baseline immune function, immunohistochemical markers, and gene expression patterns) that might be associated with response to high-dose IL-2 therapy will also be explored in an attempt to more narrowly limit the application of IL-2 to those patients most likely to benefit.[123]

ANGIOGENESIS INHIBITORS FOR ADVANCED RENAL CELL CARCINOMA

Inhibiting the development of new blood vessels (antiangiogenesis) has been demonstrated as a valid approach to cancer therapy—particularly for RCC. The discovery of the *VHL* gene–HIF-1α connection in kidney cancers has further intensified interest in drug development for approaches aimed at the disruption of angiogenesis in the treatment of RCC.

Vascular endothelial growth factor (VEGF) thus far is the best-characterized proangiogenic factor. It is virtually ubiquitous in human tumors, and higher levels have been correlated with more aggressive disease in kidney cancer. VEGF-A is a potent stimulator of angiogenesis because its binding to VEGFRs has been shown to promote endothelial cell migration and proliferation, two vital features required for the development of new tumor-induced blood vessels. In addition, VEGF-A increases vascular permeability, which also may contribute to angiogenesis and tumor growth. HIF-1α regulates the activation of *VEGF* gene expression. Several approaches are being taken to block the HIF-1/VEGF axis (Fig. 86-2). Clinical efficacy of antiangiogenic therapy in RCC has led to the recent approval of three antiangiogenesis drugs by the FDA for the treatment of advanced kidney cancer (Fig. 86-3).

Sorafenib

Sorafenib (BAY 43-9006) is an oral kinase inhibitor targeting both tumor cells and the tumor vasculature. It originally was developed as an inhibitor of Raf-1, a member of the Raf/MEK/ERK signaling pathway.[129,130] Sorafenib was subsequently found to have activity against B-Raf, VEGF receptor-2 (VEGFR-2), platelet-derived growth factor receptor (PDGFR), Fms-like tyrosine kinase-3 (Flt-3), and stem cell growth factor (c-Kit).[131] In phase I studies investigating various oral dosing schedules, sorafenib generally was well tolerated; the recommended dose for future trials was 400 mg twice daily continuously. Dose-limiting toxic effects seen at continuous doses higher than 400 mg twice daily were diarrhea, fatigue, and skin toxicity.[132,133] A multicenter placebo-controlled randomized discontinuation trial was performed to determine whether sorafenib inhibits tumor growth in patients with metastatic solid tumors who maintain stable disease after a 12-week run-in period.[134] Patients initially received oral sorafenib 400 mg twice daily during the initial period. After 12 weeks, patients with changes in bidimensional tumor measurements that were less than 25% from baseline were randomly assigned to receive sorafenib or placebo for an additional 12 weeks; patients with 25% or greater tumor shrinkage continued open-label sorafenib treatment; patients with 25% or greater tumor growth discontinued treatment. The primary endpoint was the percentage of randomly assigned patients remaining progression free at 24 weeks after the initiation of sorafenib. Of 202 patients who received treatment during the run-in period, 73 patients had tumor shrinkage of 25% or greater. Sixty-five patients with stable disease at 12 weeks were randomly assigned to receive sorafenib ($N = 32$) or placebo ($N = 33$). At 24 weeks, 50% of the patients in the sorafenib treatment group were progression free, versus 18% of those in the placebo group. Median progression-free survival from randomization was significantly longer with sorafenib (24 weeks) than with placebo (6 weeks). Median overall progression-free survival was 29 weeks for the entire population of patients with RCC ($N = 202$). Sorafenib was readministered in 28 patients whose disease progressed during placebo treatment; these patients continued on sorafenib until further progression, for a median period of 24 weeks. Common adverse events were skin rash or desquamation, hand-foot skin reaction, and fatigue; 9% of patients discontinued therapy, and no patients died from toxicity. These data supported the conclusion that sorafenib has significant disease-stabilizing activity in metastatic RCC carcinoma and is tolerable with chronic daily therapy.

The positive results from the phase II study led to a phase III randomized, double-blind, placebo-controlled trial of sorafenib in patients with advanced clear cell RCC.[135] From November 2003 to March 2005, 903 patients with RCC that was resistant to cytokine therapy were randomly assigned to receive either continuous treatment with oral sorafenib (at a dose of 400 mg twice daily) or placebo. A total of 451 patients received sorafenib; 452 received placebo. The primary endpoint was overall survival. A single planned analysis of progression-free survival in January 2005 showed a statistically sig-

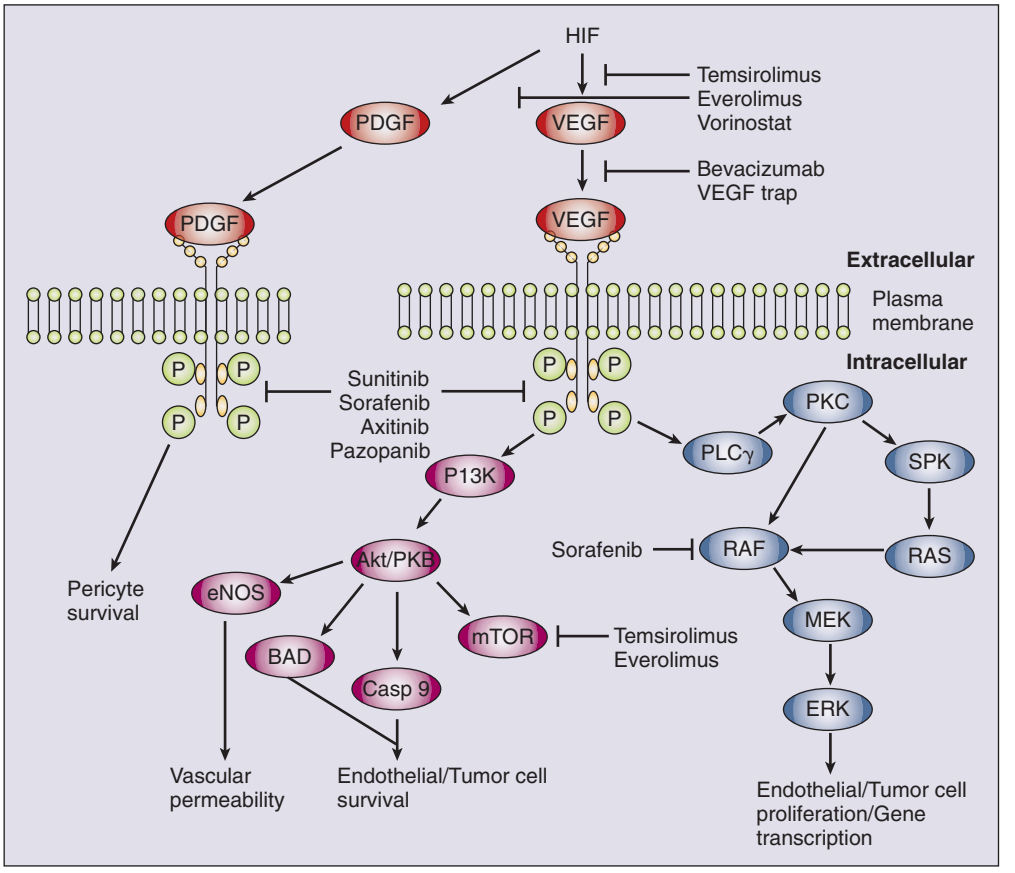


Figure 86-2 • Molecular targets for clear RCC. Several steps in the process of tumor angiogenesis are being targeted for therapeutic purposes.

nificant benefit of sorafenib over placebo. Consequently, crossover was permitted from placebo to sorafenib, beginning in May 2005. At the January 2005 cutoff, the median progression-free survival time was 5.5 months in the sorafenib group and 2.8 months in the placebo group (hazard ratio for disease progression in the sorafenib group, 0.44). The first interim analysis of overall survival in May 2005 showed that sorafenib reduced the risk of death, as compared with placebo (hazard ratio, 0.72), although this benefit was not statistically significant according to the O'Brien-Fleming threshold. Partial responses were reported as the best response in 10% of patients receiving sorafenib and in 2% of those receiving placebo. Diarrhea, rash, fatigue, and hand-foot skin reactions were the most common adverse events associated with sorafenib. Hypertension and cardiac ischemia were rare serious adverse events that were more common in patients receiving sorafenib than in those receiving placebo. As compared with placebo, treatment with sorafenib prolonged progression-free survival in patients with advanced clear cell RCC in whom previous therapy has failed. On the basis of these data, the FDA approved sorafenib in December 2005 for the treatment of advanced kidney cancer.

Sunitinib

Sunitinib (SU11248) is a multitargeted receptor TKI of VEGFRs and PDGFRs. Patients with metastatic RCC who demonstrated progression on first-line cytokine therapy were enrolled into a multicenter phase II trial.[136] SU11248 monotherapy was administered in repeated 6-week cycles of daily oral therapy for 4 weeks, followed by 2 weeks off. Overall response rate was the primary endpoint, and time to progression and safety were secondary endpoints. Twenty-five (40%) of 63 patients who received SU11248 achieved PRs; 17 additional patients (27%) demonstrated stable disease with duration of 3 months or longer. Median time to progression in the 63 patients was 8.7 months. Dosing generally was tolerated well, with manageable toxicities. SU11248 demonstrated antitumor activity in metastatic RCC as second-line therapeutic agent. Based on the phase II study results, the FDA approved sunitinib for the treatment of advanced kidney cancer in early 2006.

Because sunitinib has shown activity in two uncontrolled studies in patients with metastatic RCC, a comparison of the drug with interferon-α in a phase III trial was warranted. A total of 750 patients with previously untreated, metastatic RCC were enrolled in a multicenter, randomized phase III trial to receive either repeated 6-week cycles of sunitinib (at a dose of 50 mg given orally once daily for 4 weeks, followed by 2 weeks without treatment) or interferon-α at a dose of 9 MU given subcutaneously three times weekly.[137] The primary endpoint was progression-free survival. Secondary endpoints included the OR rate, overall survival, patient-reported outcomes, and safety. The median progression-free survival was significantly longer in the sunitinib group (11 months) than in the interferon-α group (5 months), corresponding to a hazard ratio of 0.42. Sunitinib was also associated with a higher OR rate than was interferon-α. The proportion of patients with grade 3 or 4 treatment-related fatigue was significantly higher in the interferon-α treatment group, whereas diarrhea was more frequent in the sunitinib group. Patients in the sunitinib group reported a significantly better quality of life than did patients in the interferon-α treatment group. Progression-free survival was longer and response rates were higher in patients with metastatic renal cell cancer who received sunitinib than in those receiving interferon-α.

Temsirolimus

Temsirolimus (CCI-779) is a novel mammalian target of rapamycin (mTOR) kinase inhibitor. It has been shown to bind with high

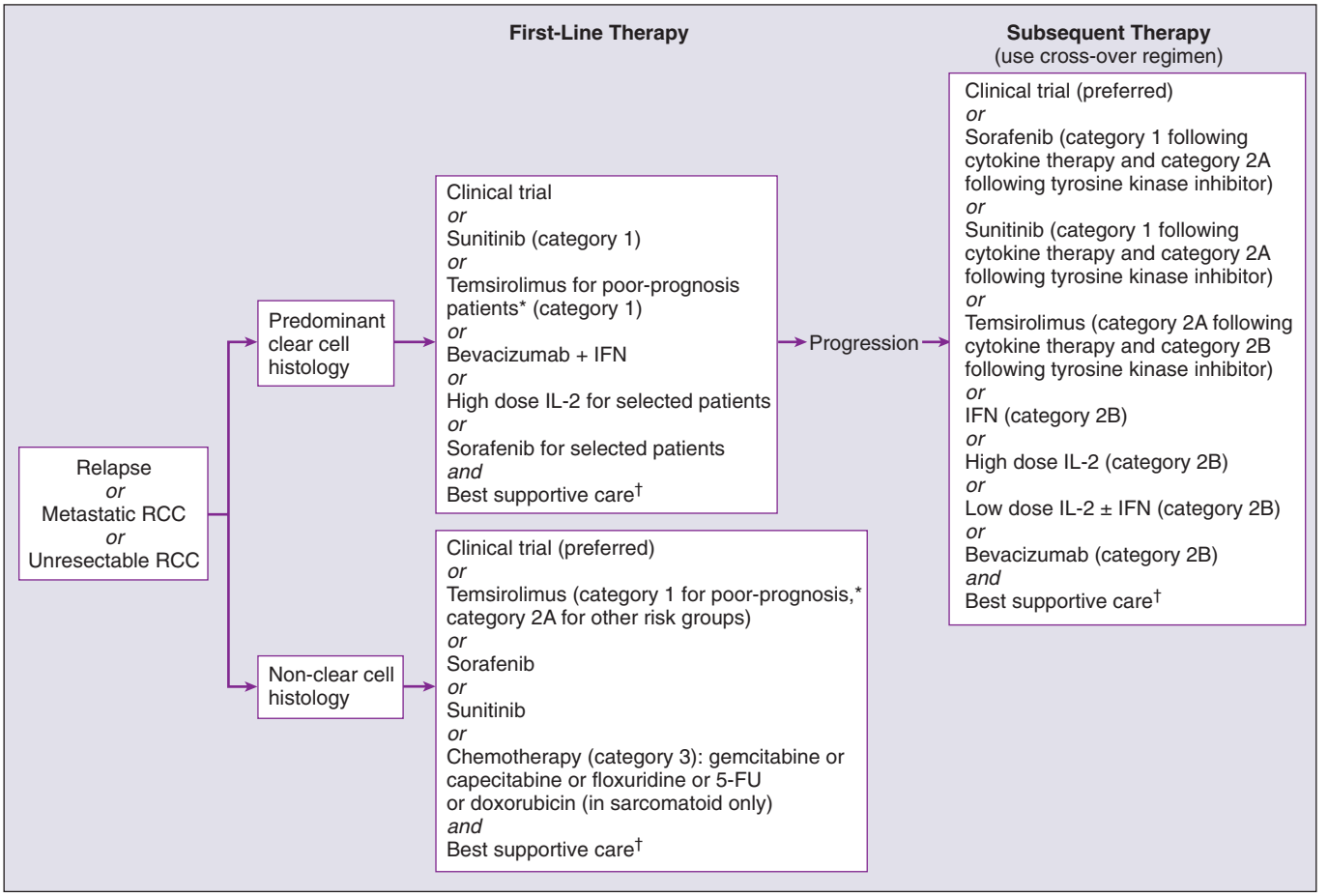


Figure 86-3 • National Comprehensive Cancer Network (NCCN) 2008 guidelines for the treatment of metastatic renal cell carcinoma (RCC). Recent NCCN treatment guidelines show the incorporation of newly approved antiangiogenic agents into standard treatment regimens. 5-FU, 5-fluorouracil; IFN, interferon; IL-2, interleukin-2. *Temsirolimus indicated for poor-prognosis patients, defined as those with 3 or more predictors of short survival. †Best supportive care can include palliative radiation therapy, metastasectomy, or bisphosphonates for bone metastases. (Adapted from The NCCN Kidney Cancer Guideline. Clinical Practice Guidelines in Oncology [Version 1.2008]. © 2007 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed November 30, 2007. To view the most recent and complete version of the guideline, go online to www.nccn.org.)

affinity to the immunophilin FKBP, and this complex inhibits mTOR kinase activity as evidenced by inhibition of phosphorylation of the eukaryotic translation initiation factor 4E-binding protein-1 and the 40S ribosomal protein p70 S6 kinase, the primary downstream effectors of mTOR.[138–140] The upstream activator of mTOR is the serine-threonine kinase Akt. Akt activity is in turn regulated by phosphoinositol-3 (PI3)-kinase and the *PTEN* tumor suppressor gene. Although mutations in *PTEN* have not been detected in RCC, *PTEN* gene expression often is downmodulated.[141,142] In addition, the mTOR pathway appears to be involved in the development of a hereditary form of RCC seen in patients with tuberous sclerosis.

Activation of mTOR increases HIF-1α gene expression at the levels of both messenger RNA (mRNA) translation and protein stabilization.[143] Thus, inhibition of mTOR by CCI-779 also could prevent the enhanced angiogenesis associated with sporadic RCC and loss of *VHL* function.

In a phase II study, 111 patients were randomly assigned to receive 25, 75, or 250 mg of CCI-779 weekly as a 30-minute intravenous infusion.[144] Patients were evaluated for tumor response, time to tumor progression, survival, and adverse events or effects. Blood samples were collected to determine CCI-779 pharmacokinetics. CCI-779 produced an OR rate of 7% (one CR and seven PRs) and minor responses in 26% of these patients with advanced RCC. Median time to tumor progression was 5.8 months, and the median survival time was 15.0 months. The most frequently occurring CCI-779-related adverse effects of all grades were maculopapular rash (76%), mucositis (70%), asthenia (50%), and nausea (43%). The most frequently occurring grade 3 or 4 adverse effects were hyperglycemia (17%), hypophosphatemia (13%), anemia (9%), and hypertriglyceridemia (6%). Neither toxicity nor efficacy was significantly influenced by CCI-779 dose level. Patients were retrospectively classified into good-, intermediate-, or poor-risk groups on the basis of criteria used by Motzer and colleagues for a first-line study population with metastatic RCC treated with interferon-α. Within each risk group, the median survival rates of patients at each dose level were similar. In patients with advanced RCC, CCI-779 showed antitumor activity, encouraging survival, and generally was well tolerated over the three dose levels tested.

The promising data from the phase II study led to a multicenter phase III trial in which 626 patients with previously untreated, poor-prognosis metastatic renal cell carcinoma were randomly assigned to receive 25 mg of intravenous temsirolimus weekly, 3 million U of interferon-α (with an increase to 18 million U) subcutaneously three times weekly, or combination therapy with 15 mg of temsirolimus weekly plus 6 million U of interferon-α three times weekly.[145] The primary endpoint was overall survival in comparisons of the temsirolimus group and the combination-therapy group with the interferon group. Patients who received temsirolimus alone had longer

overall survival (hazard ratio for death, 0.73) and progression-free survival than did patients who received interferon-α alone. Overall survival in the combination-therapy group did not differ significantly from that in the interferon group (hazard ratio, 0.96). Median overall survival times in the interferon group, the temsirolimus group, and the combination-therapy group were 7.3, 10.9, and 8.4 months, respectively. Rash, peripheral edema, hyperglycemia, and hyperlipidemia were more common in the temsirolimus group, whereas asthenia was more common in the interferon-α group. There were fewer patients with serious adverse events in the temsirolimus group than in the interferon-α treatment group. Compared with interferon-α, temsirolimus improved overall survival among patients with metastatic RCC and a poor prognosis. The addition of temsirolimus to interferon-α did not improve survival. These recent data led the FDA to approve temsirolimus for the treatment of advanced kidney cancer in July 2007.

Bevacizumab

Because of the mechanistic link between VEGF overexpression and *VHL* inactivation in clear cell RCC, a randomized, placebo-controlled, double-blind study of bevacizumab in patients with measurable metastatic clear cell RCC was conducted.[146,147] The two bevacizumab doses selected were 3 mg/kg (predicted by pharmacokinetics to produce a serum level equal to the optimally effective level in nude mice bearing human tumor xenografts) and 10 mg/kg (the maximum dose in the phase 1 trial, although limiting toxicity was not reached). Beginning 1 week after a loading dose of 150% of the assigned dose, treatment was given by intravenous infusion every 2 weeks. The primary endpoints were time to tumor progression (by WHO criteria) and response rate. Survival was a secondary endpoint, because crossover from placebo to 3 mg/kg of bevacizumab was allowed for patients with disease progression on placebo. Minimal toxic effects were seen, with hypertension and asymptomatic proteinuria predominating. The trial was stopped after the interim analysis met the criteria for early stopping. With 116 patients randomly assigned to treatment groups (40 to placebo, 37 to low-dose antibody, and 39 to high-dose antibody), a significant prolongation of the time to progression of disease was found for the high-dose antibody group, compared with the placebo group (hazard ratio, 2.55). A small difference, of borderline significance, was observed between the time to progression of disease in the low-dose antibody group and that in the placebo group (hazard ratio, 1.26). The probability of being progression-free for patients given high-dose antibody, low-dose antibody, and placebo was 64%, 39%, and 20%, respectively, at 4 months and 30%, 14%, and 5% at 8 months. In this trial, four partial responses occurred for a 10% response rate, and time to tumor progression was substantially prolonged in patients receiving the higher dose of bevacizumab. No major responses to the 3 mg/kg dose were noted, and the effect on time to progression was minimal and of borderline statistical significance. No difference in survival was shown. A substantial number of patients taking bevacizumab showed evidence of mixed tumor responses. Because sensitive criteria for tumor progression were used (a 25% increase in the product of perpendicular diameters of any lesion; even a single lesion increasing in diameter by 12% could meet this criterion), protocol therapy was truncated in some patients who may have been experiencing a net benefit from bevacizumab. No significant differences in overall survival between groups were found.

In view of the positive results from the phase II study, a phase III trial was conducted to evaluate the efficacy and safety of bevacizumab in combination with interferon-α as first-line treatment in metastatic RCC.[148] Nephrectomized patients with clear cell RCC, KPS of 70%, no CNS metastases and adequate organ function received interferon-α (given three times weekly at a recommended dose of 9 MIU for up to 1 year) plus bevacizumab (10 mg/kg every 2 weeks) or placebo until disease progression. Tumor assessments were performed every 8 weeks until week 32 and then every 12 weeks thereafter. Patients were stratified according to Motzer score. Between June 2004 and October 2006, 649 patients were randomized (641 for treatment) at 101 centers in 18 countries. At data cutoff, 505 progression events had occurred, 111 patients remained on treatment, 287 had discontinued (rates of discontinuation due to adverse events were 12% with interferon and 28% with interferon-α plus bevacizumab), and 251 died. Bevacizumab-related side effects generally were mild and consistent with previous observations. The addition of bevacizumab to interferon-α significantly increased progression-free survival (10.2 versus 5.4 months) (hazard ratio, 0.63) and objective tumor response rate (30.6% versus 12.4%). A trend toward improved overall survival was observed with the addition of bevacizumab to interferon-α. These data suggest that bevacizumab improves progression-free survival when combined with interferon-α in RCC. No unexpected safety events were observed. These results were presented at the American Society of Clinical Oncology (ASCO) plenary session in 2007, and FDA approval of bevacizumab is expected soon.

Other Angiogenesis Inhibitors

A critical survival step for proliferating endothelial cells is the ligation of fibronectin in the extracellular matrix to integrin $\alpha_5\beta_1$. Voloxicimab, a chimeric monoclonal antibody, blocks fibronectin binding to $\alpha_5\beta_1$ and induces apoptosis of proliferating endothelial cells. Voloxicimab activity is independent of growth factor stimulus, suggesting that $\alpha_5\beta_1$ signaling occurs downstream of growth factor signaling, and is possibly a final common pathway for the development of neovasculature. A multicenter, open-label phase II study of volociximab for RCC was recently conducted.[149] Patients received intravenous volociximab 10 mg/kg every 2 weeks until disease progression was noted. Patients were evaluated for efficacy of this agent every 8 weeks using response evaluation criteria in solid tumors (RECIST). A total of 40 patients were enrolled. Median time since first diagnosis was 2.5 years. Nineteen patients (47.5%) had received up to 2 prior therapies. The most frequent side effects were fatigue in 27 patients (67.5%), nausea in 14 (35%), dyspnea in 8 (20%) and arthralgia in 7 (17.5%), of which none were grade 3 or 4. Seven (17.5%) patients experienced serious adverse effects. Stable disease was observed in 32 (80%) patients, including 1 confirmed PR. Duration of disease stability ranged from 2 to 22 months. Median time to progression was 4 months. Median overall survival has not been reached after 22 months. Overall survival rates at 6 months were 79% and 68%, respectively, at 22 months. Six (15%) patients died in the study, 5 (12.5%) from progressive disease and 1 with arrhythmia (unrelated to volociximab). Volociximab was demonstrated to be well tolerated at a dose of 10 mg/kg every 2 weeks. Stable disease was noted in 80% of patients. Based on clinical activity, a randomized controlled trial is planned.

AG13637 (axitinib) is a potent inhibitor of VEGFRs 1, 2, and 3 and showed substantial efficacy in a phase II study in patients with cytokine-refractory RCC.[150] The activity of AG13637 in metastatic RCC patients refractory to prior TKI therapy was recently evaluated.[151] Patients with sorafenib-refractory RCC were enrolled in this multicenter, open-label phase II study. All patients received a starting dose of AG13637 5 mg orally twice daily, titrated according to tolerance. The primary endpoint was RECIST-defined OR, with a null hypothesis of OR = 8%, versus OR = 20% under the alternative hypothesis. Partial response was observed in 6 of 42 evaluable patients (14%), stable disease was noted in 15 patients (36%), 12 patients (29%) experienced progressive disease, and 9 patients (21%) withdrew because of adverse effects. Overall, 57% of patients experienced some degree of tumor regression. With a median follow-up period of 5.3 months, the median progression-free survival was not reached. Preliminary analysis indicates an overall median progression-free survival longer than 7.1 months. No ORs have yet been observed in patients who received prior sunitinib treatment, although

tumor regression was demonstrated in 55% of patients with median progression-free survival longer than 6.1 months. Treatment-related grade 3 or 4 adverse events included hypertension (16%), fatigue (14%), and hand-foot syndrome (14%).

Pazopanib is a potent and selective multitargeted receptor TKI (of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β, and c-Kit) that blocks tumor growth and inhibits angiogenesis. In a phase II randomized discontinuation trial, the effects of pazopanib on tumor growth in patients with RCC was assessed after 12 weeks of treatment.[152] Patients with cytokine-naive and -refractory (as indicated by failure to respond to 1 previous cycle of a cytokine- or bevacizumab-containing regimen) RCC ECOG stages 1 and 2 were enrolled. Pazopanib 800 mg was given orally once daily. In the first 60 patients, response at week 12 by independent review showed PR in 24 (40%); stable disease in 25 (42%); disease progression in 5 (8%); unknown response in 2 (3%); and withdrawal before week 12 in 4 (7%). On the basis of findings on investigator review at week 12, 27 (45%) patients were randomized for treatment. Total disease control rate was 82% (PR plus stable disease). Approximately 67% of patients were treatment naive, and the remaining 33% had failed to respond to one previous treatment regimen. Most common adverse effects or laboratory abnormalities in all patients were alanine and aspartate aminotransferase elevations, diarrhea, fatigue, nausea, hair depigmentation, and hypertension. Grade 3 or 4 adverse effects occurred in 26% of patients; most common were hypertension (8%) and increase in alanine transaminase (8%). Interim analysis of findings in this phase II study demonstrated that pazopanib treatment resulted in a PR rate at week 12 of 40% among patients with RCC and an acceptable toxicity profile.

RAD001 (everolimus) is an oral mammalian target of rapamycin (mTOR) inhibitor. A phase II study was recently conducted.[153] Forty-one patients have been enrolled, and 37 patients were evaluable for response and toxicity. Twelve patients had PRs; 19 patients were stable for longer than 3 months. Median duration of therapy is greater than 8 months (range, 1 to 20 months). Treatment-related adverse effects included mucositis, skin rash, pneumonitis, hypophosphatemia, hyperglycemia, hypertriglyceridemia, hypercholesterolemia, thrombocytopenia, anemia, and elevated liver enzymes. PET scans have demonstrated decreased metabolic activity in responding or stable patients. Median overall survival was 11.5 months (range, 1 to 20 or longer). RAD001 has promising antitumor activity in patients with MRCC demonstrated by partial response rate. Antitumor activity is further suggested by a prolonged time to progression of 3 months. A phase III randomized trial of RAD001 versus supportive care in patients with metastatic RCC recently has been completed, and the results are pending.

Future Directions for Antiangiogenesis Therapies

Although sorafenib, sunitinib, temsirolimus, and bevacizumab have added greatly to the therapeutic armamentarium for patients with advanced renal cancer, as single agents, these drugs produce PRs rather than CRs in a minority of patients, require long-term administration for continued disease control, and have side effects. Treatment resistance typically develops within 6 to 12 months, and tumors often progress quickly once treatment is stopped. Reasons for these results can be multifold: (1) optimal dosing has not been achieved; (2) the signaling pathway is not sufficiently understood; or (3) tumor heterogeneity may be responsible for different dependence from the targeted pathway among patients. Combination therapy has been proposed as a way of potentially producing more durable benefit. Although critically important, testing of combination regimens must proceed cautiously because of the potential for synergistic toxicity or countervailing activity inherent with use of these multitargeted agents.[154] Approaches to combination therapy currently being investigated include "vertical" combinations, in which the HIF/VEGF pathway is blocked at several steps, and "horizontal" combinations, in which multiple separate signaling pathways are blocked simultaneously[155] (Fig. 86-4).

The term *targeted* with respect to therapies in kidney cancer raises several questions: (1) Can the selected target be effectively inhibited? (2) Is the target the same in each patient? (3) Is the therapy endothelial cell or tumor cell specific? New clinical tools to determine whether a patient is going to respond to a certain targeting agent or whether the inhibition of an alternative target will lead to a greater clinical benefit are urgently needed. The vast majority of patients eventually progress through anti-VEGF therapies. Different hypotheses for the resistance mechanisms have been proposed. A recent report suggests that in a transgenic mouse model of pancreatic cancer, an early phase of response to anti-VEGF therapy leads to decrease in blood vessel formation and consequent hypoxia with induction of HIF-1α with downstream overexpression of proangiogenesis growth factors.[156] It is conceivable that overexpression of HIF-1α is responsible for increased levels of VEGF that cannot be counteracted by VEGF TKI, or that such overexpression induces alternative growth factors such as placental growth factor and basic fibroblast growth factor. Clinical evidence also indicates that circulating VEGF levels are increased in patients receiving TKIs. Taken together, these observations suggest that the anti-VEGF therapy "escape" may be neutralized with a therapeutic strategy aimed to achieve a "vertical" inhibition of the VEGF pathway. For example, inhibition of tumor cell adaptation to hypoxia induced by TKIs may be achieved with HDAC or mTOR inhibitors that block the HIF pathway. These hypotheses can be tested in rationally designed clinical trials. An upcoming ECOG study (E4805) will test the strategy of sequential inhibition of angiogenesis by means of treatment with VEGF-trap, a neutralizing decoy consisting of VEGFRs 1 and 2, after TKI failure (Fig. 86-5A). A second upcoming ECOG trial (E2804) will randomize patients to receive duplets of agents including sorafenib, CCI-779, or bevacizumab to test concomitant inhibition (see Fig. 86-5B). Our institution has recently opened a trial combining bevacizumab with suberoylanilide hydroxamic acid (SAHA), a small-molecule inhibitor

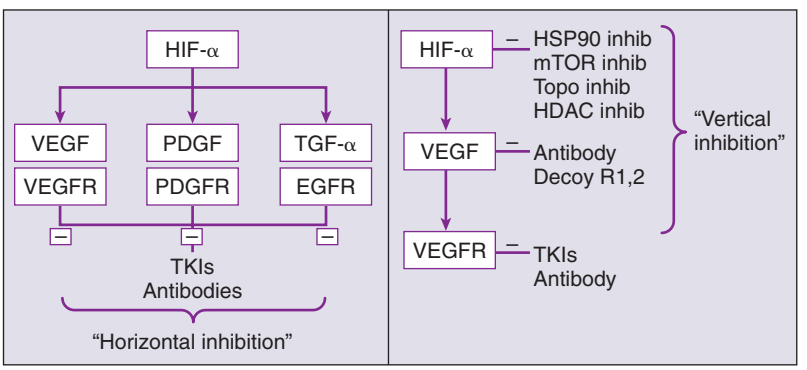


Figure 86-4 • Strategies targeting the HIF-1α pathway. Dysregulation of the HIF pathway is likely to contribute to the development of renal cell carcinoma. Therefore, drugs that inhibit HIF or its downstream targets warrant testing for treatment of this disease. EGFR, epithelial growth factor receptor; HIF, hypoxia-inducible factor; PDGF, placenta-derived growth factor; PDGFR, platelet-derived growth factor receptor; TGF-α, transforming growth factor-α; TKIs, receptor tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; VEGFR, VEFG receptor. (Adapted from Kaelin WG Jr: The von Hippel-Lindau tumor suppressor protein and kidney cancer. Clin Cancer Res 2004;10:6290S–6295S.)

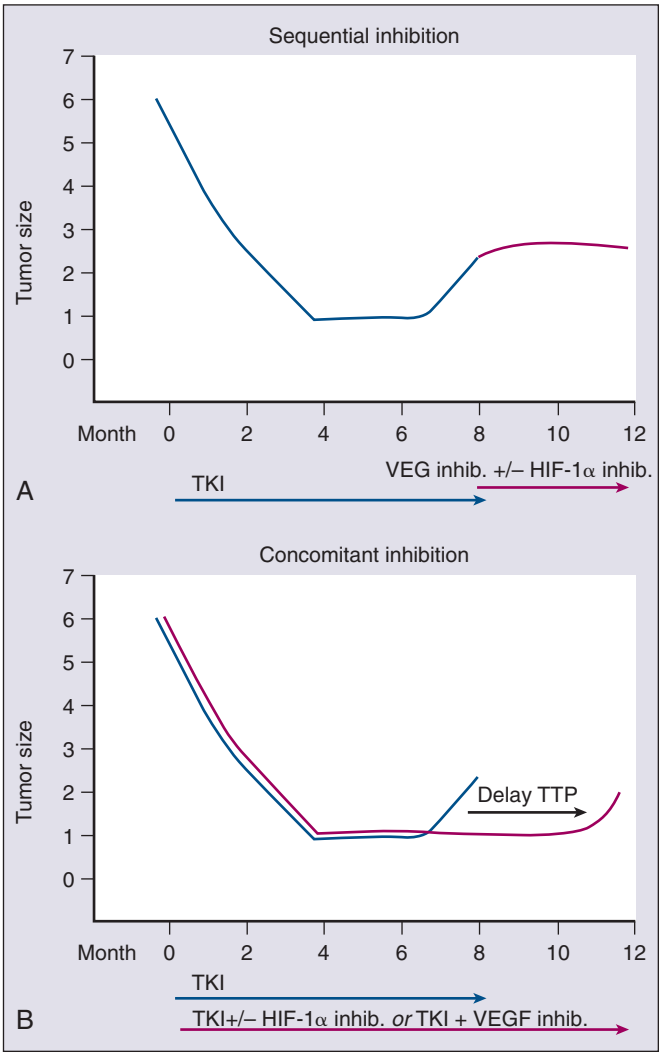


Figure 86-5 • Combination strategies to inhibit angiogenesis: sequential (**A**) versus concomitant (**B**) schedule. The diagram shows a potential lesion that responds initially to a tyrosine kinase inhibitor (TKI) but eventually progresses. A rational intervention at the time of progression would be to treat the patient with an antibody that neutralizes elevated levels of vascular endothelial growth factor (VEGF) (**A**). Another therapeutic strategy to delay the occurrence of anti-VEGF therapy escape is to add a hypoxia-inducible factor-1α (HIF-1α) inhibitor or an anti-VEGF ligand antibody at the time of starting the TKI and delaying the time of tumor progression (TTP) (**B**).

of histone deacetylase (HDAC), in patients with metastatic RCC. SAHA is a potent inhibitor of HDAC, and can be administered orally with good bioavailability.[157] HDAC inhibitors have been shown to reduce HIF-1α protein expression both in tumor and endothelial cells.[158,159] The combination of HDAC inhibitors with VEGF inhibitors has an additive antiangiogenic and antitumor activity in animal models, and may achieve a "vertical" inhibition of the VEGF pathway.[158]

Combination of anti-VEGF therapies with immunotherapies also has shown promising results in phase I/II setting. In particular, the combination of the TKI sorafenib and interferon-α has been reported to have clinical activity that seems greater than historical single-agent activity.[160] Preclinical studies have suggested an immunomodulatory effect of anti-VEGF treatment by effecting dendritic cell maturation.[161]

NONMYELOABLATIVE ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION

Allogeneic hematopoietic stem cell transplantation (HSCT)has been used successfully for decades to treat lethal hematologic malignancies. Nonmyeloblative allogeneic peripheral blood stem cell transplantation also has been tested as a therapeutic approach in metastatic RCC. Evidence supporting the existence of graft-versus-tumor effects against metastatic RCC has been reported recently by a number of transplant centers using a variety of different nonmyeloablative transplantation approaches.[162–167] At the National Heart, Lung, and Blood Institute, 10 of the first 19 patients (54%) to undergo this treatment demonstrated tumor regression, including 7 PRs and 3 CRs.[162] The first patient in this series remains without evidence of disease more than 6 years after transplantation. Responses occurred most commonly in patients with a clear cell histologic subtype that was limited to the lungs, although regression of tumor lesions in multiple sites, including the bones, liver, and lymph nodes, occasionally was observed. Although significant and occasionally complete regression of metastatic disease has been observed, a number of factors currently limit the application of allogeneic immunotherapy for RCC. Unfortunately, most responses have been partial, with CRs occurring in a small subset of patients. Although toxicity appears less compared with conventional myeloablative approaches, regimen-related mortality rates of 10% to 15% persist, largely as a consequence of severe grade III to IV acute graft-versus-host disease (GVHD).

The experience with allogeneic HSCT for RCC in 124 patients from 21 European centers has been recently reported.[168] The cumulative incidence of moderate to severe, grades II to IV acute GVHD was 40%; for chronic GVHD, it was 33%. The transplantation-related mortality rate was 16% at 1 year. Complete ($N = 4$) or partial ($N = 24$) responses, median 150 (range, 42 to 600) days after transplantation, were associated with time from diagnosis to HSCT, mismatched donor, and acute GVHD II to IV. Factors associated with survival included chronic GVHD, donor lymphocyte infusion, fewer than 3 metastatic sites, and a KPS score greater than 7. Patients ($N = 17$) with chronic GVHD and given donor lymphocte infusion had a 2-year survival rate of 70%.

Second-generation allogeneic HSCT trials that incorporate methods to enhance the donor immune system against the tumor through the use of adoptively infused tumor-reactive donor T cells and NK cells, as well as post-transplantation tumor vaccination strategies are being considered for further investigation.[169]

VACCINE STRATEGIES FOR RENAL CELL CARCINOMA

Many cancer vaccines are in various stages of preclinical and clinical development. These vaccines are based on the hypotheses that tumor-associated antigens (TAAs) are inherently weakly immunogenic or functionally nonimmunogenic and that effective vaccines will enhance the efficacy of presentation of TAAs to the immune system, resulting in dramatically increased activation of host T cells. To "break tolerance" against TAAs is the common purpose of antigen presentation by vaccination. Strategies for the development of cancer vaccines include (1) identifying novel TAAs for RCC reactive cytotoxic T lymphocytes, (2) improving modes of antigen delivery and antigen presentation by using dendritic cells, (3) enhancing antigen immunogenicity (e.g., alternating vaccine prime and boost, enhancing T-cell costimulation, and engineering amino acid sequences in peptide TAAs); (4) improving systemic T-cell dissemination, (5) enhancing destruction of tumor cells (effector phase), (6) improving T-cell memory, and (7) enhancing the adaptive response to tumor variants (e.g., use of cytokines as vaccine adjuvants). Thus, multiple hurdles must be overcome before the promise of cancer vaccines as adjuvant therapy becomes a reality for patients with RCC.

To date therapeutic cancer vaccines have little proven effect in the area of RCC. Vaccine approaches have included isolated tumor cell suspensions either alone or mixed with heat-shock protein, gene-modified tumor cells, and dendritic cells that express RCC-associated antigens. These cancer vaccines have reported response rates ranging from 1.9% to 9.5%.[170]

Recent insights into the tumor-derived factors that inhibit the immune system have provided new opportunities to enhance vaccine-mediated antitumor immunity and thereby potentially increase vaccine efficacy. Future vaccine investigations probably will incorporate concomitant modulation of proinflammatory and immune inhibitory pathways that have hindered generation of tumor-specific immunity. Promising approaches include the combination of vaccines with antibodies to B7 molecules or agents that deplete $CD25^+$ T-regulatory cells or block the generation of arginase-expressing tumor-associated myeloid cells. In addition, combinations of dendritic cell vaccines with cytokines, such as IL-2, interferon, or granulocyte macrophage colony stimulating factor, may produce more clinical benefit in patients with RCC.[171]

CHEMOTHERAPY FOR ADVANCED RENAL CELL CARCINOMA

Conventional cytotoxic agents generally offer little benefit to patients with RCC. The response rates for a wide variety of chemotherapeutic agents in phase II trials generally have been in the range of 6% to 20%. Although these responses are durable on occasion, no improvement in median survival has been reported.[172] In a review of 83 trials of a variety of chemotherapeutic regimens published from 1983 to 1993, Yagoda and colleagues reported a 6% overall response rate for 4093 patients with advanced RCC.[173] Data from a multi-institutional phase II trial of gemcitabine and 5-FU suggested that this regimen could be active for patients with advanced RCC.[174] Another multi-institutional study with gemcitabine and capecitabine, however, showed only modest activity in patients with metastatic renal cancer, and the degree of clinical benefit and its associated toxicity did not support further evaluation in a phase III trial in unselected patients.[175] More focused investigations to identify patients most likely to benefit from chemotherapy or to enhance activity with additional agents such as anti-VEGF drugs would be worthwhile.

TREATMENT OF KIDNEY CANCERS WITH NONCONVENTIONAL HISTOLOGIC FEATURES

The incidence of non-clear cell carcinoma of the kidney has been reported as approximately 20% to 30%. These percentages, however, reflect data from surgical series of patients undergoing primary nephrectomy. Because primary non-clear cell carcinomas tend to have a better prognosis than clear cell carcinomas, the percentage of metastatic non-clear cell carcinomas is much lower.[176,177] Recent reviews suggest that only 5% to 8% of patients who receive treatment in clinical trials have non-clear cell histologic characteristics.[178–180] The data on response rates for non-clear cell RCC also are relatively limited. This is not only because of the rarity of these variants in the metastatic setting, but also because in the past, studies have not typically reported on response by subtype. More recently, the Cytokine Working Group has reported that only 1 of 17 patients with non-clear cell tumors responded to high-dose IL-2,[179] and in the Memorial Sloan-Kettering Cancer Center series, only 1 of 37 responded to interferon-based therapy,[178] suggesting that immunotherapy should not be offered to patients with non-clear cell RCC.

Sarcomatoid differentiation in RCC indicates an aggressive subtype of renal parenchymal tumors, and is associated with a poor prognosis.[181,182] Some evidence suggests that metastatic RCC with sarcomatoid differentiation do not respond to immunotherapy and should be treated with combination chemotherapy.[183] Based on the antitumor activity of doxorubicin and gemcitabine in collecting duct carcinoma of the kidney, Nanus and coworkers have tested this combination for treatment in selected patients with sarcomatoid or rapidly progressing RCC.[184] Eighteen patients with RCC (56% sarcomatoid; 44% other) were treated at two institutions. Seven patients had received previous treatment with interferon or IL-2. Sites of metastases included the lung, soft tissue, bone, liver, and brain, with 88% of patients prersenting with three or more sites of disease. Treatment consisted of doxorubicin (50 mg/m^2) and gemcitabine (1500 or 2000 mg/m^2) every 2 to 3 weeks with granulocyte colony stimulating factor support. A median of 5 courses was administered (range, 2 to 12 cycles). Therapy was well tolerated with no grade 4 toxicity. Two patients had a CR, five had a PR, three had a mixed response, and one had stable disease. The median duration of response was 5 months (range, 2 to 21 months or longer). These data suggested that the combination of doxorubicin and gemcitabine has antitumor activity in patients with sarcomatoid RCC or with rapidly progressing RCC. An ongoing ECOG study is testing this combination in patients with sarcomatoid RCC.

Collecting duct RCC is a rare and aggressive neoplasm of the distal collecting duct system for which no effective therapy has been established. In a case report, a 37-year-old woman with metastatic collecting duct RCC demonstrated 80% reduction in her tumor burden, including complete regression of lymph node metastases and significant shrinkage of the primary, after treatment with paclitaxel and carboplatin. The patient was subsequently rendered free of disease by nephrectomy without evidence of recurrence on follow-up evaluation at 20 months.[185] A number of case reports have described responses of collecting duct carcinoma to gemcitabine- or taxane-based therapies similar to those used in transitional cell carcinoma.[186,187] This finding is consistent with expression data suggesting that these tumors are closely related to transitional cell cancers.[188]

The activity of sunitinib and sorafenib in non-clear cell histologic tumor types has been recently evaluated.[189] Clinical features at study entry and treatment outcomes were evaluated in all patients with metastatic papillary and chromophobe RCC who received either sunitinib or sorafenib as their initial TKI treatment at one of five different cancer centers in France and USA between 2002 and 2006. Overall response rate, progression-free survival, and overall survival for the entire cohort were 10%, 8.9, and 12.2 months, respectively. Twenty (38%) and 33 (62%) patients received sunitinib and sorafenib, respectively. Three of 12 patients (25%) with chromophobe histology had an OR, versus two of forty-one (4.8%) with papillary histology. Progression-free survival for patients with chromophobe histology was 9.3 months, compared with 6.6 months for those with papillary histology. Overall survival was not different across histologic types and types of TKI received. Patients who received sunitinib had an overall response rate of 15% and progression-free survival of 11.9 months, compared with 6% and 5.5 months, respectively, for patients who received sorafenib. Other factors found to be associated with shorter progression-free survival include ECOG performance status greater than 0 and subnormal hemoglobin concentration. These preliminary results suggest that TKI may have activity in metastatic chromophobe RCC, similar to what is seen with tumors of clear cell histology. Minimal activity, however, was noted in papillary RCC, justifying continued investigations of novel agents for treatment of this histologic tumor type.

SUMMARY

Recent advances in molecular classification of RCC with techniques such as DNA microarray analysis with laser capture of single malignant cells and comparative genomic hybridization will lead in the near future to novel targeted therapies to be developed for specific histologic subtypes. Surgical resection remains the principal therapeutic modality when RCC is confined to the kidney. Surgical tech-

niques continue to be refined through the growing use of laparoscopic procedures and nephron-sparing resections that resulted in less morbidity, preservation of renal function, and comparable therapeutic outcomes. Patients at high risk for recurrence after nephrectomy include those with positive lymph nodes, high Fuhrman grade, extension beyond Gerota's fascia, or extension into the renal vein or vena cava. Overall survival is influenced by stage, performance status, Fuhrman grade, and histologic subtype (sarcomatoid or collecting duct). No adjuvant therapy for resected disease has been established, but a large adjuvant trial with TKIs is ongoing. Cytoreductive nephrectomy for patients with metastatic disease may enhance responsiveness to high-dose IL-2 and also remains the standard treatment modality for patients receiving the new antiangiogenesis drugs. Metastasectomy is considered acceptable if all disease can be resected, and in some instances, this may be curative.

Recent years have witnessed an explosion of new potential systemic therapeutic options for metastatic RCC. Accordingly, many standards of initial care are in place for management of this disease. High-dose IL-2 remains the only approach to produce durable CRs and can thus be considered in appropriately selected patients with excellent performance status, normal pulmonary and cardiac functions, and limited disease burden. As indicated by currently available data on antiangiogenic and molecularly targeted therapies, sunitinib is recommended for first-line treatment for patients in low- and intermediate-prognosis groups, and temsirolimus is recommended for patients with multiple adverse prognostic features.

Great progress in treatment for patients with advanced renal cancer has been made. Three potentially distinct therapeutic approaches (targets) have been identified: VEGF+/− platelet-derived growth factor (PDGF), mTOR, and immunotherapy. Considerable room for additional improvement remains, however. Any of these approaches alone is not sufficiently active to achieve durable clinical benefit in a majority of patients. Continued exploration of molecular pathways and investigations to identify prognostic and predictive markers in this disease will be critical. Physician encouragement of patient participation in clinical trials will dictate the pace of progress in the development of rationally designed and effective combination strategies.

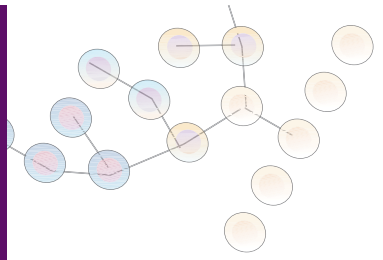
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87 Carcinoma of the Bladder

David C. Smith, James Montie, and Howard Sandler

SUMMARY OF KEY POINTS

Incidence
- Bladder cancer accounts for 5% of all cancers in the United States, with an estimated 67,160 cases and 13,750 deaths in 2007. The male-to-female ratio is 3:1.

Epidemiology and Risk Factors
- Risk increases with advancing age, with 70% of male bladder cancers and 75% of female bladder cancers occurring in individuals over the age of 65 years.
- Cigarette smoking is an established cause of bladder cancer, accounting for half of male and one third of female bladder cancers in Western populations. Smokers have twice the risk of bladder cancer as nonsmokers.
- Occupational chemical exposure associated with bladder cancer includes arylamines and derivatives (also found in cigarette smoke), O-toluidine, and benzidine-based dyes; those at risk include workers in the dye, rubber and leather industries, painters, truck drivers, and drill press operators.
- Long-term cyclophosphamide therapy increases bladder cancer risk, probably by as much as 30-fold.
- Schistosomiasis and spinal cord injury are associated with increased risk for squamous cell carcinoma of the bladder.

Clinical Presentation
- The primary symptom of bladder cancer is hematuria; 20% to 30% of patients will have symptoms of frequency, urgency, and dysuria.

Diagnosis
- Cystoscopy with transurethral resection (TUR) is the mainstay of diagnosis.
- Upper tract imaging is necessary to detect additional urothelial tumors and obstruction.

Pathology and Staging
- Almost all bladder cancers are urothelial (transitional cell) in origin. Most present with a papillary growth pattern: flat carcinoma in situ (CIS) and solid nodular tumor are other forms.
- At diagnosis, approximately one third of cases are noninvasive (Ta/TIS), one third are minimally invasive (T1), and another third are more deeply invasive (T2 and higher).
- Grade and stage are strong prognostic factors and primary determinants of therapy.

Therapy
- Most bladder cancers recur in the bladder, but can be managed with a combination of TUR and intravesical chemotherapy or immunotherapy.
- Few low-grade cancers progress (invade the bladder wall), but high-grade cancers have significant risk.
- Bacillus Calmette-Guérin (BCG) vaccine is the most effective agent for treating high-grade superficial lesions, resulting in decreased progression and potentially increased survival.
- Most muscle-invasive cancers are not cured by TUR alone.
- Radical cystectomy with urinary diversion is the most effective means to eliminate the cancer.
- Orthotopic diversion with a neobladder provides improved rehabilitation by allowing volitional voiding.
- Pelvic recurrence rates, as well as distant metastases, in patients with locally advanced cancer remain disappointingly high.
- Radiation therapy combined with an aggressive TUR and a chemotherapeutic radiation sensitizer, such as cisplatin, may allow bladder preservation.
- Preoperative radiation has not been demonstrated to be consistently effective.
- Traditional systemic chemotherapy for urothelial cancers such as MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin), have not produced durable results, and toxicity is high.
- New agents, such as paclitaxel and gemcitabine, are active, and combinations of these agents with platinum-based compounds have comparable response rates with substantially less toxicity.
- Neoadjuvant chemotherapy prior to cystectomy is supported by increasing evidence, particularly in patients with locally advanced (T3b) tumors.
- Fewer data are available on the degree of benefit for adjuvant chemotherapy. Treatments must be individualized based on risk, benefits, and patient preference.

BACKGROUND AND INCIDENCE

Bladder cancer poses a wide spectrum of risk to the patient. Well-differentiated, papillary tumors rarely present a threat of death or loss of the bladder. High-grade cancers commonly are lethal, and treatment may greatly alter urinary and sexual function. The physician and patient often face difficult decisions about under- and overtreatment. The initiation of therapy at every stage depends heavily on clinical judgment, because this cancer typically occurs in an older population with significant comorbidities. Even experienced clinicians often find it difficult to separate patients who are appropriate candidates for cystectomy from those in whom it may be unnecessary at one extreme or futile at the other. The integration of effective and less toxic systemic chemotherapy as well as radiation therapy remains

a challenge. Substantial progress in the delivery of bladder cancer care is clearly evident in the last two decades, but fundamental uncertainties in management decisions persist.

EPIDEMIOLOGY AND RISK FACTORS

Bladder cancer represents approximately 7% in men (fourth most common neoplasm) and 2.5% in women (eleventh most common neoplasm) of new cases of cancer in the United States.[1] In 2007, there were an estimated 67,160 cases. The age-adjusted incidence in the United States is 32 per 100,000 men and 8 per 100,000 women. The historic male-female ratio of 3 : 1 remains essentially stable despite the changing pattern of smoking in women. Overall there were an estimated 13,750 deaths from bladder cancer in 2007. Bladder cancer incidence and mortality rates increase strongly with age and will be an increasing problem as the population ages. Based on 2007 data, the probability of being diagnosed with invasive bladder cancer is increases 3.5-fold in both men and women over the age of 70 when compared with those 60 to 69 years of age. Bladder cancer mortality rates continue to decrease, although the rate of decrease has slowed. Death rates decreased 0.2% per year in the period from 1987 to 2003 after decreasing 2.1% per year from 1977 to 1987.

Most bladder cancers are noninvasive or minimally invasive at the time of diagnosis. Based on Surveillance, Epidemiology, and End Results (SEER) data, 74% were localized in the pelvis at diagnosis.[1] Women are slightly more likely to be diagnosed with advanced stages than men. African-Americans are more likely to be diagnosed with regional or distant disease than whites. Women, particularly African-American women, appear to have a shorter survival when diagnosed with bladder cancer.[2] Marriage has a positive influence on survival in patients with bladder cancer independent of other known factors.[3] The incidence of familial transitional cell carcinoma is uncertain, although some data support a familial form.[4]

Defined risk factors account for an estimated 80% of all bladder cancer cases.[5,6] In Western populations, cigarette smoking may account for 50% of cases of bladder cancer. Zeegers and associates[7] performed a meta-analysis of 43 epidemiologic studies on smoking characteristics for bladder cancer risk and concluded that current cigarette smokers have an approximately threefold higher risk of urinary tract cancers than nonsmokers. The carcinogenic effect of cigarette smoking is related to dose as well as the type of tobacco used. Black (air-cured) tobacco carries a higher risk than blond (flue-cured) tobacco, most likely because of higher concentrations of the known carcinogens arylamines. Quitting smoking is associated with a drop in the risk of bladder cancer, regardless of type of tobacco.[8] The age at which one begins smoking also carries an associated risk; those starting at a younger age have an increased risk for bladder cancer, even 10 to 15 years after quitting. Cigarette filters do not provide protection. The increased risk is likely due to exposure to the carcinogens 4-aminobiphenyl and 2-naphthylamine in cigarette smoke, possibly with modulation based on metabolic phenotype which governs noninducible enzymes in the liver under autosomal dominant control. The carcinogens are metabolized in the liver by N-acetylation; "slow" acetylators are homozygous for the slow acetylator gene and at higher risk for bladder cancer.[9]

Data from the U.S. National Bladder Cancer Study on Occupation and Bladder Cancer suggest that population-attributable risks for occupation in Caucasian men range from 21% to 25%.[6] Occupational bladder cancer remains a public health issue around the world. Leather and rubber workers are at increased risk, but this risk is decreasing as workplace exposure diminishes. New higher-risk occupations—for example, painters, truck drivers, primary aluminum workers, and metal machinery workers—are being recognized. There is a positive trend for increased risk associated with increasing duration of employment in such jobs, particularly longer than 10 years. Recent studies have shown an increased risk in several occupations not traditionally associated with chemical exposure. These include physicians, clerical workers, male and female sales workers, and female health service personnel.[10–12]

Several medications increase bladder cancer risk as use and exposure increase. Chronic phenacetin use increases risk of transitional cell carcinoma (TCC) of the bladder and the renal pelvis. Long-term oral cyclophosphamide use increases the risk for bladder cancer by as much as 30-fold.[13] In a cohort of 1065 patients treated with cyclophosphamide for Wegener's granulomatosis, the risk of bladder cancer was both dose and duration dependent, with an absolute risk of 10% at 16 years. The presence of an upper tract TCC is highly associated with bladder cancer. Forty percent of patients with this lesion will have a bladder cancer at some point in the course of their disease; thus, surveillance cystoscopy is appropriate and necessary. Chronic irritation of the bladder also is associated with bladder cancer, typically squamous cell carcinoma (SCC) rather than TCC. Schistosomiasis also is highly associated with development of SCC of the bladder and remains a major public health problem in endemic areas, even though a true causal link has not been established.[14] Patients with spinal cord injury who have chronic or recurrent urinary tract infections, particularly with indwelling catheters, are at increased risk for bladder cancer by as much as 25 times that of the general population.[15] Periodic cystoscopy is advocated in patients with spinal cord injury after more than 10 years following the injury.

CLINICAL PRESENTATION

The classic symptom of bladder cancer is hematuria, usually gross and painless, but occasionally only microscopic. Some patients (20% to 30%) may have primarily "irritable" bladder symptoms of frequency, urgency, and dysuria, particularly those patients with carcinoma in situ of the bladder. It is remarkably common for patients to present to a urologist with a substantial delay in diagnosis, which may be either patient- or physician-driven, because of attributing the hematuria to an infection or a stone without proper investigation. Gross hematuria requires a urologic evaluation. One study suggests that microscopic hematuria may be present years before the detection of the bladder cancer, and thus may be a predictor of bladder cancer.[16]

More advanced local disease causes pelvic pain, bladder outlet obstruction, or flank pain secondary to an obstructed upper tract. Extensive pelvic disease can cause rectal obstruction, lymphedema of the extremities, and deep venous thrombosis from compression of iliac veins.

DIAGNOSIS AND NATURAL HISTORY

No current accepted screening methods for bladder cancer are available. The prevalence of bladder cancer, particularly if male current or previous smokers were targeted, could justify a screening program. Bladder cancer rarely is diagnosed at autopsy, and so overdiagnosis is not a concern. Messing and colleagues[17] performed two pilot studies between 1987 and 1992 on 1575 men, and the long-term outcome was recently updated. Using home hematuria dipsticks, men tested their urine for 14 consecutive days; 16.4% were determined to have at least one unexplained abnormal test and thus underwent further testing. Of these, 9.7% were found to have urinary tract cancer, including 21 bladder cancers. These cases were compared with a matched cohort of men for the State of Wisconsin Tumor Registry. The noteworthy finding of this pilot study was confirmation that repetitive home hematuria screening could detect high-grade bladder cancers at a noninvasive stage and thus a prospective, randomized screening could be supported.

The mainstay of detection of bladder cancer is cystoscopy.[18] Most diagnostic cystoscopies are now done in an outpatient setting using a 16F flexible cystoscope (approximately the caliber of a small Foley catheter) and local intraurethral lidocaine for topical anesthesia. A flexible instrument with excellent optics substantially decreases

discomfort associated with the procedure, particularly in men. Most bladder cancers appear grossly as a papillary, exophytic tumor, and low-grade tumors have a reliable, characteristic appearance. A higher-grade, invasive cancer may appear as erythema and edema of the mucosa with distortion of the bladder wall. If an abnormality is visualized in the bladder, an outpatient transurethral resection (TUR) or biopsy is done with anesthesia. This TUR is diagnostic, important for staging, and often therapeutic, in cases when it is the only treatment needed. In many cases, an examination under anesthesia to identify a pelvic mass or induration of the bladder is necessary. Occasionally, patients require a brief hospital admission after the procedure for hematuria, urinary retention, or bladder perforation.

During the evaluation of hematuria or after the diagnosis of bladder cancer is established, imaging of the upper urinary tract collecting system is essential. An intravenous pyelogram (IVP), retrograde pyelogram, or computed tomographic (CT) or magnetic resonance (MR) urogram identifies additional urothelial tumors and obstruction of the upper tract due to bladder cancer.[19] With typical papillary tumors, 2% to 4% of patients have or will develop an upper tract tumor. Patients with carcinoma in situ may have a substantially greater risk for upper tract cancers. Imaging of the bladder with an IVP, CT scan, or ultrasonography can demonstrate a bladder cancer as a "filling defect" displacing contrast material or urine.

The natural history of bladder cancer is such that recurrences in the bladder are the rule, with documented recurrence in 50% to 75% of patients.[20] This propensity for recurrences requires surveillance of the bladder at defined intervals. The mainstay of surveillance is cystoscopy, which is easily performed as an outpatient procedure with local anesthesia. If the cystoscopy is likely to be positive and require biopsy or resection, general or regional anesthesia is necessary. The classical follow-up protocol for patients without recurrence entails cystoscopy at 3-month intervals for 1 year, 4-month intervals during the second year, 6-month intervals for years 3 and 4, and then annually. This regimen is excessive in many patients at low risk for recurrence and very low risk for progression and can be altered by lengthening the intervals between cystoscopies more quickly. The results of the first cystoscopy 3 months after the initial diagnostic resection often set a precedent for the future recurrence pattern.[21]

Bladder cancer requires lifelong follow-up consisting of cystoscopy and periodic imaging of the upper tracts, because recurrences may occur late, even after prolonged disease-free intervals.[22] Supplemental diagnostic aids in addition to or in place of an "invasive" cystoscopy are attractive. A test performed on a voided urine sample would be ideal. Unfortunately, no currently available test in the urine can replace cystoscopy for either detection or follow-up.[23] Research is expanding on urinary markers for detection, but performance remains disappointing.[24]

Urinary cytologic examination plays an important role in detection and monitoring of bladder cancer and has stood the test of time. Cytologic testing is particularly effective in patients with carcinoma in situ manifested by irritable symptoms and nonspecific inflammatory changes on visual cystoscopic examination. In these cases, cytologic examination may be the most important test to alert the physician to the presence of the cancer. Unfortunately, cytologic examination has substantial limitations in detection of bladder cancer; the sensitivity is approximately 60% and specificity is 70% to 80%.[24,25] Urine cytologic assessment is subjective, has considerable interobserver variability, and depends on an adequate number of cells in the specimen; interpretation can also be influenced by collection method and cellular preservation techniques. Cytologic testing is extremely valuable for detection and follow-up of high-grade lesions populated by cells with substantial abnormal morphologic characteristics, but less definitive in low-grade cancers in which the cells often closely resemble normal bladder epithelial cells. Methods to improve cytologic assessment using immunostaining, either with Lewis-X antigen or cytokeratin 20, also are under exploration.[26]

Several urinary tests are now approved by the U.S. Food and Drug Administration (FDA) as aids for the detection or monitoring of bladder cancer. However, their clinical utility remains uncertain.[25] The ideal test fulfills at least one of two requirements: (1) it is highly sensitive so that a cystoscopy could be avoided, or (2) it identifies patients with occult mucosal disease not visualized at cystoscopy, allowing a better assessment of treatment response or identification of a recurrence earlier. No test currently available consistently performs these functions well enough.

More than 300 proteins shed into the urine of bladder cancer patients have been detected.[27] The first urine assay available for bladder cancer detection, the BTA test, detected basement membrane complexes and was attractive as a point-of-service urine test that gave immediate results.[28] Initial trials demonstrated superiority over urinary cytologic testing, but cytologic accuracy in these trials was less than the degree commonly accepted. Several nuclear matrix proteins are present in bladder cancer but not in normal urothelium.[29] Urinary nuclear matrix protein (NMP-22) is approved by the FDA for detection of occult or rapidly recurring disease after a TUR and may perform better than cytologic examination as a diagnostic tool.[30] Higher NMP-22 levels correlated with cancer with a favorable receiver operating characteristic curve, but experience is limited. Antigens associated with bladder cancer, such as M344 and DD23, are potential detection targets.[31] Measurements of the urinary level of hyaluronic acid and hyaluronidase have shown promising results.[24] Telomerase is an enzyme responsible for maintenance of the chromosome-end telomere, which commonly is active in cancer. A polymerase chain reaction-based telomeric repeat amplification protocol assay on urine yielded a high sensitivity, but special collection techniques may be required.[32] Other molecular studies, such as fluorescent in situ hybridization (FISH) of centromere probes for abnormalities of chromosomes 3, 7, 17, and band 9p21 (Urovysion) recently have been shown to predict recurrent disease.[26,33]

A study of three bladder tumor markers in urine (NMP22, BTA stat test, and urinary bladder cancer antigen test for fragments of cytokeratin 8 and 18) and bladder wash cytologic test by Boman and colleagues demonstrated that no combination of the studies could reliably replace surveillance cystoscopy, primarily because most recurrences are small.[34] Similarly, "virtual cystoscopy" with multiplanar CT did not provide comparable sensitivity to cystoscopy, even when a catheter was inserted into the bladder to improve visualization.[35] Bladder "washing" to obtain a larger cellular yield improve sensitivity of cytology and is used commonly in the follow-up of bladder cancer patients.

In summary, cystoscopy remains a requirement for the diagnosis of bladder cancer. Cytology is widely available and particularly valuable in high-grade cancers. Newer urinary diagnostic tests are fascinating, but not, as yet, practically helpful.

PATHOLOGY AND NATURAL HISTORY

An appreciation of the growth pattern and histology of bladder cancer is essential for appropriate treatment decisions. Most bladder cancers are epithelial in origin, and 95% of epithelial tumors demonstrate transitional cell histology.[36] Grade and depth of invasion (stage) are both independent prognostic variables. A complete review of bladder cancer pathology is beyond the scope of this discussion, but certain aspects are crucial. A superb review by Grignon is available.[37]

An important consensus on the terminology of urothelial tumors by members of the International Society of Urological Pathology is available (Table 87-1).[38] These recommendations have been incorporated into the description of bladder cancers, and clinicians must be cognizant of the changes. A consensus statement was necessary because of considerable confusion regarding the definition of a papilloma and poor reproducibility of grading, with a preponderance of cases falling into the intermediate grade category. Nevertheless, the acceptance and use of the new classification is an ongoing process.[39]

Table 87-1 International Society of Urological Pathology Consensus Classification

NORMAL
Normal urothelium*
HYPERPLASIA
Flat urothelial hyperplasia
Papillary urothelial hyperplasia
FLAT UROTHELIAL LESIONS WITH ATYPIA
Reactive (inflammatory) atypia
Atypia of unknown clinical significance
Dysplasia (low-grade intraurothelial neoplasia)
Carcinoma in situ (high-grade intraurothelial neoplasia)†
PAPILLARY UROTHELIAL NEOPLASMS
Urothelial papilloma
Inverted urothelial papilloma
Papillary urothelial neoplasm of low malignant potential
Papillary urothelial carcinoma, low grade
Papillary urothelial carcinoma, high grade
INVASIVE UROTHELIAL NEOPLASMS
Urothelial carcinoma with lamina propria invasion
Urothelial carcinoma with muscularis propria (detrusor muscle) invasion

*May include cases formerly diagnosed as "mild dysplasia."
†Includes cases with "severe dysplasia."
Rasmussen HH, Orntoft TF, Wolf H, Celis JE: Towards a comprehensive database of proteins from the urine of patients with bladder cancer. J Urol 1996;155:2113–2119.

A basic aspect of terminology is preference for the more precise term *urothelial* to describe the epithelium as opposed to *transitional*. The term *superficial* also is imprecise and is discouraged.[39] A *papilloma*, defined as an exophytic papillary growth lined by urothelium of normal thickness and cytologic appearance, is a rare, benign condition. A *papillary urothelial neoplasm of low malignant potential* has minimal cytologic and architectural abnormalities but is an important entity because of a propensity for recurrent lesions, occasionally of higher grade. *Papillary urothelial carcinoma, low grade* is composed of overtly neoplastic cells and may invade in a small percentage of cases. *Papillary urothelial carcinoma, high grade* is disorganized by both cytologic and architectural abnormalities. High-grade papillary lesions that originally are noninvasive may progress in 15% to 40% of cases.

Carcinoma in situ (CIS), a high-grade intraurothelial neoplasia, is worthy of special attention. CIS is defined as high-grade (anaplastic) carcinoma confined to the epithelium growing in a flat, disordered, nonpapillary configuration, and is likely underdiagnosed.[39] CIS can be focal, multifocal, or diffuse. Diffuse CIS often is characterized by irritable voiding symptoms of frequency, urgency, and dysuria, but smaller-volume disease may be asymptomatic. The gross appearance of CIS is a slightly raised, reddened, velvety mucosa, occasionally with associated edema. Smaller areas of CIS not associated with underlying bladder inflammation may not be so apparent cystoscopically, and it is common for a urologist to underestimate the extent of mucosal disease. The mechanism of mucosal spread of CIS is poorly understood, but a substantial portion of cases have involvement of the prostatic urethra, prostatic ducts, seminal vesicles, or distal ureters resulting in frequent failure of intravesical treatments.[40] Extension into von Brunn's nests is not uncommon and must be distinguished from invasion.

Most bladder cancers are composed of urothelial cells. Mixed histology tumors with areas of squamous or adenocarcinoma differentiation are not uncommon and are well recognized. Less common variants such as nested, micropapillary, or small cell carcinoma are seen with increasing frequency either de novo or after intravesical treatments and are critically important to recognize because of a required change in therapy from what would be based on stage only. The nested variant, which has a deceptively bland-appearing pattern, and the micropapillary variant, which may be a form of glandular differentiation, usually metastasize early, and prompt cystectomy usually is warranted.[41,42] A small cell component usually requires initial treatment with chemotherapy followed by consolidation with either surgery or radiation therapy.[43]

STAGING

An experienced urologist recognizes the gross differences between well and poorly differentiated cancers. Also, whether or not the lesion is grossly invasive often is easily apparent. Nevertheless, confirmation of depth of invasion relies on the pathologic examination of the resected tissue. Adequate tissue must be provided to the pathologist for proper interpretation of depth of invasion. Cold-cup biopsies of the tumor have the advantage of avoiding cautery artifact and are useful for sampling mucosa, but a TUR is the common method to remove the cancer as completely as possible and provide tissue to the pathologist. In general, sampling of the muscle beneath the papillary tumor is necessary to exclude muscle invasion (with the possible exception of an extremely well-differentiated, grossly noninvasive lesion). Carcinoma in situ has a propensity for the mucosa to become denuded, leaving only the appearance of "chronic cystitis" in the underlying stroma. When CIS is suspected, special care is needed to minimize mucosal trauma during the biopsy process. Cytologic examination of the urine is particularly helpful in this setting.

The staging of bladder cancer greatly influences treatment decisions. The American Joint Committee on Cancer (AJCC) 2002 TNM staging classification is recommended (Table 87-2).[44] The 2002 system retains the modifications initially described in 1997 by (1) placing all tumors invading muscularis propria into the T2 category (T2a superficial muscle, T2b deep muscle) and (2) segregating tumors outside the bladder into microscopic (T3a) and macroscopic (T3b). In practice, the clinical differentiation between T2a and T2b based on a TUR only is difficult and arbitrary and is barely reliable on a cystectomy specimen.[37] In addition, the segregation of prognosis becomes most evident when comparing organ-confined (≤T2) versus extravesical (≥T3a) disease. CIS in the prostatic urethra or ducts does not decrease survival, but prostatic stromal invasion does, thus justifying classification as T4a. Based on large data sets from

Table 87-2 Primary Tumor Staging of Bladder Cancer

Ta:	Noninvasive papillary carcinoma
T1:	Tumor invades lamina propria
T2:	Tumor invades muscle
T2a:	Invades superficial muscularis propria
T2b:	Invades deep muscularis propria
T3:	Tumor invades perivesical tissue
T3a:	Microscopic perivesical fat invasion
T3b:	Macroscopic perivesical fat invasion (extravesical mass)
T4a:	Invades adjacent organs (uterus, ovaries, prostate stoma)
T4b:	Invades pelvic wall, abdominal wall

hospitals in the United States and Germany, the stage at diagnosis typically is Ta or TIS in 30% to 35% of cases, T1 in 25% to 30%, and T2 and higher in 30% to 35% of cases.[36,45] However, the microscopic assessment of depth of invasion is subject to interobserver variability, exemplified by an alteration in stage observed in 18% of cases when reviewed at a single referral center.[46]

The staging of bladder cancer, along with the grade, provides the basis for most treatment decisions. Noninvasive cancers (Ta and TIS) represent a biologically different tumor from those demonstrating invasion (T1 and greater). T1 cancers often are lumped together with Ta as "superficial" cancers, but these tumors often behave differently in terms of recurrence rates, risk for later invasion into the muscle, and response to intravesical therapy.[21,47] Use of the imprecise term *superficial tumor* should be discouraged.[37,38] Ta and grade 1 and 2 (low-grade) tumors have a propensity for recurrence but a low risk for progression to muscle invasion. The later recurrence risk depends on several factors. The presence of three or more tumors and larger cancers (>2 cm) are predictive of more recurrences.[21,48] A recurrence at the time of first cystoscopy heralds a pattern of more recurrences.[22] Progression to muscle invasion is seen in only 5% to 10% of patients.[48] Thus, the primary goal of therapy is to decrease or eliminate recurrences. Intravesical therapy should be reserved for patients demonstrating a need for treatment based either on the initial characteristics or, more commonly, on the recurrence pattern evident.

Disease invading the lamina propria represents a more dangerous disease (low or high grade, T1). Such disease has a higher recurrence rate and a substantial progression rate of 30% to 50% in spite of therapy.[46,48] Incomplete resection may lead to understaging, and a repeat TUR 6 to 8 weeks after the initial resection may identify such patients earlier.[48–50] The risk of understaging is as high as 60% in patients in whom no muscle demonstrating invasion of lamina propria is present in the specimen.[50] The risk for death due to progression is as high as 30% of patients with long follow-up.[47,48] Thus, the goal of therapy for such patients with high-grade cancers must be complete elimination of the cancer; simply reducing the recurrence rate will be insufficient in the long term. Increasing evidence (although not all of the evidence is consistent) indicates that the depth of penetration into the lamina propria is important. The muscularis mucosa (MM) is a discontinuous band of muscle fibers in the lamina propria. Invasion deep to the MM causes a higher risk for later muscularis propria invasion.[49] Orientation of the specimen often makes precise interpretation of the depth of invasion difficult.

Imaging studies of the bladder contribute minimally to the staging of bladder cancer. However, imaging of the upper tracts with an IVP, retrograde pyelogram, or CT scan at the time of diagnosis is essential. The practical information obtained from pelvic imaging is limited.[51] CT is the study applied most commonly, but understandably cannot differentiate noninvasive disease from small volume muscle-invading cancers. Also, the depth of muscle invasion cannot be reliably differentiated (Fig. 87-1). Bulkier tumors with gross invasion of perivesical fat are reliably visualized on CT, but the incremental increase in information gained over that provided by a cystoscopy and examination under anesthesia is poorly quantified. In addition, CT imaging commonly occurs after the diagnostic/therapeutic TUR, which distorts the bladder wall and surrounding tissue. Stage divergence between clinical and pathologic staging is common, with downstaging and upstaging occurring in 27% and 49% of patients, respectively, in one institutional study.[51] The limitation may be that scans may be obtained 4 to 8 weeks prior to the actual cystectomy, allowing for disease progression in the interval. Nevertheless, the appearance of a mass in the bladder wall and the presence of perivesical fat generally predict a large-volume tumor with a worse prognosis. The presence of a palpable mass on examination under anesthesia portends a poor response to external radiation therapy, and the presence of T3 disease at cystectomy corresponds to a diminished survival. CT scan identifies large, probably malignant, lymph nodes, but not all abnormal nodes harbor cancer, especially if the scan is done soon after a TUR. Percutaneous biopsy of an abnormal lymph node to confirm cancer is necessary prior to major treatment decisions.

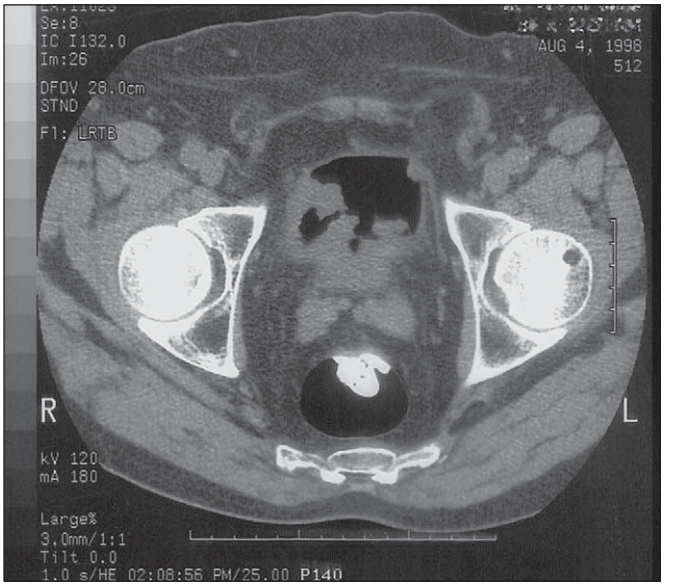


Figure 87-1 • Pelvic computed tomographic (CT) scan demonstrating multiple exophytic bladder cancers with thickening of the bladder wall on the right. Muscle invasion is suspected, but the depth of invasion is uncertain.

MRI provides some advantages over CT scanning with multiplanar projections.[52] However, this somewhat better demonstration of the tumor is offset by greater expense and inconvenience to the patient. Evolving refinements in CT data manipulation allow image display in different planes as well, further diminishing any incremental benefit of MRI over CT scan. Positron emission tomography (PET) theoretically is attractive in evaluating bladder cancer, but use of the radiotracer 2-FDG is significantly limited by urinary excretion of the radiotracer, and 11C-choline may provide better imaging.[53,54] Studies to search for metastases in patients with invasive bladder cancer are not standardized. Common sites of metastases from bladder cancer are regional lymph nodes, lungs, liver, and bone. A chest x-ray and abdominal/pelvic CT scan are in essence part of standard practice, although the clinical utility of such studies is poorly quantified. Bone scans are not obtained routinely unless a clinical suspicion has arisen because of bone pain or an elevated alkaline phosphatase level.

MOLECULAR BIOLOGY

Stage and grade provide the most important prognostic information for bladder cancer. However, mounting evidence points to molecular biologic characteristics of malignant lesions as an important aid in treatment decisions. Currently, no molecular characteristics are sufficiently reliable to dictate a conservative or aggressive deviation from traditional therapy. A large number of genetic alterations occur in bladder cancers, and some may correlate with clinical behavior.[55] Noninvasive Ta tumors have fewer genetic alterations than invasive cancers, but changes commonly occur at 9q, 9p, 1p, and the Y chromosome.[56] Over the last decade, alterations in two distinct molecular pathways have been identified.[57] The receptor tyrosine kinase-Ras pathway often is activated in low-grade papillary lesions. Mutations in the fibroblast growth factor receptor 3 (FGFR3) and HRAS genes result in activation of this pathway in up to 70% of these lesions, suggesting a significant role in tumorigenesis.[58]

Invasive cancers, T1 and higher, have many more genetic abnormalities, and the challenge is to both categorize the gene abnormalities and correlate with functional alterations in the cell. The pathway altered in these cancers involves the fundamental regulation of the cell cycle.[57] Regulatory proteins p53 and RB appear to be particularly important in urothelial cancer. The p53 tumor suppressor protein is a critical molecule in control of the cell cycle, and an increased accumulation of p53 protein as a result of mutation is a signal event in the development of many cancers.[59] In urothelial cancer, accumulation of p53 protein correlates with progression and is prognostic for poor outcomes in patients with muscle invasive disease. Downstream of p53, the p21 protein plays a modulating effect. Encoded by the p21(WAF1/CIP1) gene, this protein is a cyclin-dependent kinase inhibitor (CDKI). Loss of this protein predicts for progression independent of alterations in p53, while retained expression modulates the effect of p53 mutation.[60] Loss of expression of the retinoblastoma (RB) protein has been documented in both low-grade noninvasive cancers and high-grade invasive lesions.[61] The interaction among p53, p21, and Rb is complex, and abnormalities in these proteins may have an additive prognostic effect.[62] The relationships between these cell cycle regulators, growth factors (including the epidermal growth factor family), and tumor angiogenesis further complicates the picture. Molecular alterations in all of these pathways have been implicated in tumorigenesis and progression of urothelial cancers.

THERAPY

The common papillary, noninvasive growth pattern of most bladder cancers makes them amenable to TUR. TUR as primary therapy has low rates of immediate complications and long-term morbidity. However, the multifocal and recurrent nature of bladder cancer emphasizes the limitations of TUR as an isolated modality. Because TUR is the mainstay of bladder cancer therapy, all urologists are assumed to be proficient with TUR, but the procedure is more difficult than commonly appreciated (Fig. 87-2). Data from the European Organization for the Research and Treatment of Cancer (EORTC) suggest that the quality of a TUR may influence recurrence rates.[63] Tumors may range from a few millimeters to many centimeters. Cancer location at the dome or anterior wall makes the resection considerably more difficult and increases the risk for incomplete resection or perforation of the bladder. Tumors in obese patients also are more difficult to resect. Tumors on the floor or trigone of the bladder may involve a ureteral orifice, causing obstruction and hydronephrosis. Tumors at the bladder neck may extend into the prostatic urethra or prostatic stroma. The fundamental value of an adequate TUR to diagnose, stage, and potentially cure the cancer cannot be overemphasized. Inappropriate treatment decisions often are grounded in an inadequate initial TUR. For most cancers, the TUR should include sampling of the muscularis propria of the bladder at the base of the bladder.

For noninvasive (Ta) or minimally invasive (T1) cancers, a TUR often is sufficient to eradicate individual lesions. If there are multiple tumors, a large tumor (>5 cm), recurrent tumors, or adjacent carcinoma in situ, TUR alone is less likely to provide durable cancer elimination. Another important prognostic factor for recurrence is the findings of the first cystoscopy 2 to 3 months after the initial resection.[22] If additional tumors are present, then the probability of continuing recurrences is as high as 80%. At the time of the TUR, the urologist commonly can estimate if the cancer is high or low grade and if gross muscle invasion is present (see Fig. 87-1).[19] The presence of an invasive, palpable mass at the time of the TUR is an important indicator of gross extravesical (T3b) disease and is an adverse prognostic factor. A long-term consequence of repeated TUR may be fibrosis of the bladder wall, causing a small-capacity bladder. This process can take 5, 10, or more years to become evident and can be accelerated by intravesical treatments or radiation therapy. Symptoms of a small-capacity bladder are frequency, urgency, and nocturia; bilateral hydronephrosis may occur due to increased intravesical pressure.

Intravesical Treatments

A TUR of a noninvasive or minimally invasive tumor (Ta, TIS, T1) often is supplemented with intravesical therapy to either decrease recurrences or lower the risk of progression to a more invasive cancer. Introduced in the 1950s, intravesical treatments are based on either the cytotoxic effects of the agent or an immunologic response.[64]

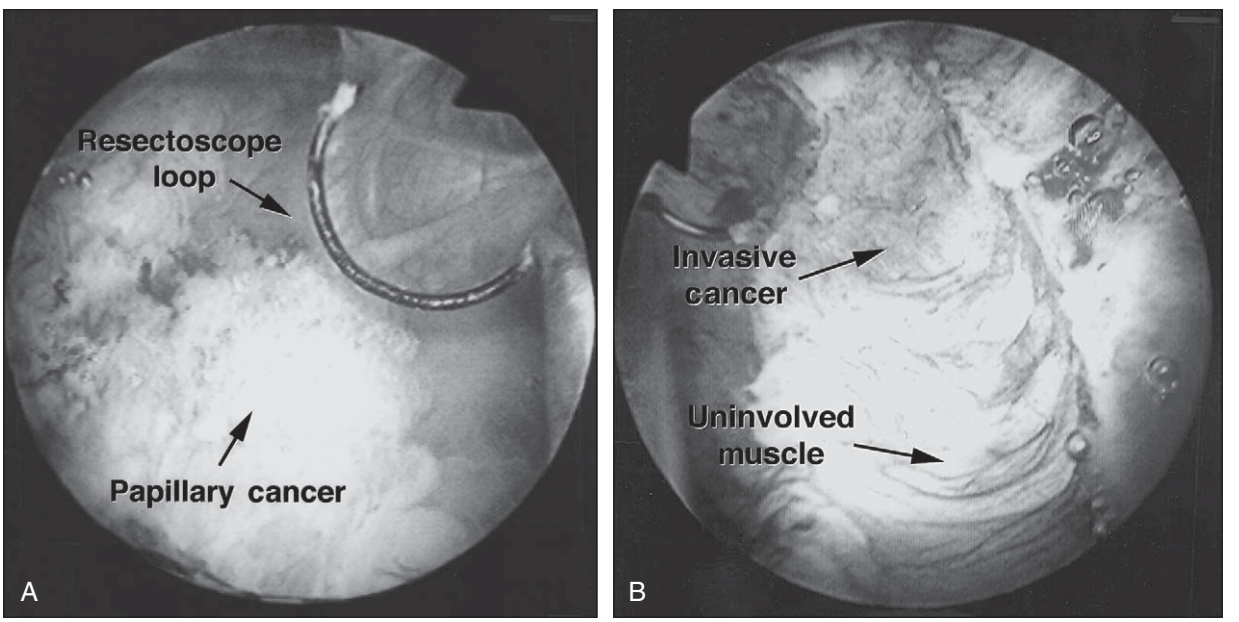


Figure 87-2 • **A,** Papillary bladder cancer with resection loop poised to begin transurethral resection. **B,** Demonstration of grossly uninvolved muscularis propria *(bottom)* and cancer grossly invading the bladder wall *(top)*.

Treatments commonly are administered on a weekly or monthly schedule by inserting a catheter into the bladder, emptying the bladder of urine, instilling the medication, and then emptying the bladder after 2 hours by either voluntary voiding or catheterization. Much of the literature on the results of extravesical treatments is flawed owing to poorly designed studies with small numbers of patients, heterogenous patient populations with varying risk for relapse, and poorly defined outcomes.[65] Data suggest intravesical chemotherapy with mitomycin C, doxorubicin, ethoglucid, epirubicin, or thiotepa may reduce recurrence rate (the number of positive cystoscopies), but has no impact on progression (i.e., development of muscle-invading disease) rate.[64–68] The most commonly used chemotherapeutic intravesical agent in the United States is mitomycin, which has few systemic or local side effects because of its high molecular weight and minimal systemic absorption. Recent animal and human studies have aimed at enhancing mitomycin efficacy by increasing the concentration, decreasing urine volume during treatment, and causing urine alkalinization to stabilize the drug.[69] Thiotepa is used less commonly now than previously because of marginal efficacy, although it causes relatively few local symptoms; life-threatening hematologic toxicity from bone marrow suppression is possible with chronic use. Noteworthy but as yet unexplained is the observation that most agents selected for topical therapy are ineffective systemically, and, likewise, effective systemic agents, such as cisplatin, methotrexate, or vinblastine, are ineffective intravesical treatments. However, in recent small trials of intravesical gemcitabine in bacillus Calmette-Guérin (BCG)-refractory patients, up to 50% of patients had an apparent complete response.[70]

Urologists historically have overused intravesical treatments, treating some patients at very low risk for recurrence or prolonging treatment when it was minimally beneficial.[65] In general, patients chosen for such treatment should have either a high-grade Ta, TIS, or T1 cancer or frequently recurring low-grade cancers. Several mechanisms may produce recurrence of bladder cancers, including incomplete resection, implantation of tumor cells to spatially separate sites, or mucosal migration of carcinoma in situ. Immediate intravesical therapy consisting of a single dose of a chemotherapeutic agent instilled in the bladder within 24 hours of the resection is designed to interfere with the implantation process. Randomized studies using either mitomycin C or thiotepa support such a strategy, and use is increasing.[68]

The most efficacious, although somewhat more toxic, intravesical therapy available is BCG, an attenuated strain of live tuberculosis organisms.[47,64,71] Surprisingly, of all the strategies employing BCG treatment for a wide variety of cancers, intravesical BCG has stood the test of time and has been proved to increase patient survival by diminishing the rate of progression to invasive cancers. The mechanism of BCG's effect is unknown, but contact between live BCG organisms and the tumor plus an intact host immune response is necessary. The dose and schedule are empirically derived; the most common protocol uses 120 mg intravesically weekly for 6 weeks. A reinduction with another 6 weeks of therapy may benefit partial responders. Approximately 70% to 80% of patients with carcinoma in situ alone or carcinoma in situ associated with a resected papillary tumor will have a complete response to BCG.[72,73] In a landmark randomized trial, Herr and colleagues[72] demonstrated a significant decrease in the need for a cystectomy and decreased death rate from bladder cancer when BCG plus TUR was compared with TUR alone. BCG also is more effective than mitomycin C (20 mg/dose) and doxorubicin.[71,73,74] Finally, maintenance BCG for complete responders, using a schedule of one weekly dose for 3 weeks administered every 6 months for approximately 2 to 3 years, is superior to a 6-week induction cycle only.[73] Monthly maintenance BCG is not effective, particularly due to a high dropout rate from bladder toxicity.[74] Nevertheless, the ideal amount of BCG required to obtain the highest and most durable response is variable; some patients respond to half the originally recommended dose, some patients obtain a complete response with only the 6-week induction course, and others cannot tolerate intravesical BCG because of local bladder or systemic symptoms.

The drawbacks of BCG are common local bladder symptoms and rare, but potentially serious, systemic complications.[75] Dysuria, frequency, a flulike syndrome with fever, and some degree of hematuria are seen for approximately 24 hours in most patients treated with BCG. Such symptoms are self-limiting, and persistence beyond 48 hours causes concern for active *Mycobacterium* infection. Prophylactic isoniazid does not appear to decrease the frequency of side effects, but may be of value for persistent but non-life-threatening symptoms.[76,77] Deaths have occurred secondary to overwhelming BCG sepsis, and aggressive antibacterial therapy, possibly with corticosteroids, is necessary.[76] Severe systemic symptoms are more likely if treatment is initiated too soon after a large TUR or if there is a traumatic catheterization at the time of instillation of the BCG.

Although BCG is highly effective initially, its durability raises some concerns. Witjes has decribed a useful catagorization of BCG "failures": *intolerant* means the patient cannot continue the treatments due to side effects; *recurring* implies later tumors after a period of complete response; and tumors are *refractory* when a complete response cannot be attained.[78] Early failure at 6 months is ominous, and more aggressive treatment usually is needed.[79] Later relapse after many years of a disease-free state can occur in the bladder, upper tracts, or prostate in 20% to 40% of patients.[47,78,80,81] Continued surveillance of patients with previous CIS requires cystoscopy, upper tract imaging, and cytologic testing.

Many other agents are available or under testing as intravesical treatments for bladder cancer, but none are comparable to BCG. Interferon-α has been studied extensively, but its role is still uncertain.[82] More promising but yet unconfirmed results have been suggested with a combination of interferon and low-dose BCG.[82,83] The mainstays of follow-up after intravesical therapies remain cystoscopy and urine cytology. However, there is increasing confidence that the urine FISH test (Urovysion) may identify recurrences of high-grade tumor in patients with only an atypical abnormal cytology and negative cystoscopy.[26,33]

Treatment of Invasive Cancers

Historically, bladder cancers were segregated into "superficial" and "invasive" cancers. The inclusion of T1 cancers into the "superficial" category is not necessarily inaccurate, but is biologically unsound because T1 cancers have already demonstrated invasion by penetration of the basement membrane and thus may access angiolymphatic spaces and the deeper muscle, and potentially metastasize.[38,84] T1 cancers represent the early part of the spectrum of invasive cancers and thus have a somewhat better prognosis than more deeply invading cancers. The classical paradigm of treatment of T1 cancers was endoscopic management, with or without intravesical therapy, until muscle invasion was found, and then a cystectomy was recommended. Such a strategy has not proven wise, however, because when muscle invasion was discovered and the patient subjected to a cystectomy, the chance of survival was no better than that for an individual presenting with a muscle-invasive cancer, implying some decrement in survival for those progressing to muscle invasion while under observation.[85,86] Thus the last decade has witnessed an increased respect for the danger posed by such tumors, prompting some to favor early cystectomy as opposed to more conservative approaches, such as TUR and intravesical therapy.[87] T1 cancers have a molecular phenotype more typical of lethal cancers, and the urologist's biggest worry is underestimation of the extent of the disease, thereby leaving cancer remaining in the lamina propria (or muscle) that will be undertreated.[84,85] Early re-resection by TUR of the site of a T1 lesion shows a rate of up to 25% to 50% of persisting cancer and thus is worthwhile to assure accurate staging and complete excision.[88,89] Once the tumor is completely resected, intravesical agents, such as

BCG, may treat the rest of the mucosa, which likely harbors incipient cancers.

Transurethral Resection Alone

Historically, TUR was used as long as possible to treat muscle-invading cancers because of the severe morbidity of cystectomy. As cystectomy became safer, TUR alone was employed more selectively but with admirably good results. An oft-quoted figure of approximately 50% 5-year survival rate is not substantially different from cystectomy results in large series. However, the patients treated with TUR alone often were selected by a second TUR at a referral institution that did not demonstrate any residual disease, indicating the initial TUR removed the cancer entirely.[90] The comparison of survival of such selected patients with smaller cancers to the entire group of patients undergoing a cystectomy is inappropriate; indeed, the good survival rate of these TUR-only patients might have been even better had they had an immediate cystectomy.[87,91] Circumstantial evidence to support such an expectation exists in the survival data of patients with small-volume muscle-invading disease at cystectomy in which the 5-year survival rate is in the range of 60% to 80%.[91] Nevertheless, some patients are cured by a TUR alone, based on the survival data, absence of recurrence in bladder, and a p0 (no residual cancer) in a cystectomy specimen. Selection of patients cured with TUR alone or who may have only a small volume of residual disease, making cure possible with the addition of radiation with or without chemotherapy, is the perplexing dilemma. One can hope that molecular markers predicting responsiveness to either radiation therapy or chemotherapy would be particularly helpful in such a setting. Because of the inherent uncertainty of the completeness of the TUR, it rarely is used alone for muscle-invading cancers if the patient is medically fit for aggressive treatments.

Partial Cystectomy

Removal of a portion of the bladder wall may cure a patient in whom the cancer is confined to the segment removed. A 50% 5-year survival rate is reported for partial cystectomy, similar to that for cystectomy and TUR alone.[92] However, selection criteria are critical, and may be best summarized as the patient has a "single tumor in space and time." Additional criteria include no or minimal carcinoma in situ, a site amenable to a partial cystectomy, and no history of previous multifocal bladder cancers. In general, only about 5% of patients with muscle-invading cancers meet such criteria. A recent review of a 21-year experience at M.D. Anderson Cancer Center found that only 2.8% of patients with muscle invasive bladder cancer were deemed suitable for a partial cystectomy.[92,93] Partial cystectomy is best accomplished by removal of the overlying peritoneum along with the involved bladder wall; high posterior and anterior wall locations of the cancer are better suited for partial cystectomy than other sites.[92] If too much of the bladder is excised, the patient can be left with a small-capacity bladder with poor function. A bilateral pelvic lymphadenectomy should be performed at the time of a partial cystectomy. The impetus for partial cystectomy is diminishing in view of better functional results of total cystectomy followed by orthotopic neobladder formation, as discussed later.

Total Cystectomy

The current most effective local therapy for potentially lethal bladder cancer is total cystectomy. The term *radical cystectomy* implies removal of the bladder plus the prostate in men, and the uterus and anterior vaginal wall in women, as well as a pelvic lymphadenectomy. The rationale for removal of the prostate in men is the historical observation of a 40% to 50% pelvic recurrence rate in cystectomy series from 40 to 50 years ago when the prostate was left in situ, but also the more relevant and recent identification of carcinoma in situ in the prostatic urethra or ducts in 30% to 40% of men undergoing cystectomy.[94] Such disease would be left behind if the prostate was not removed entirely. However, the concept of preservation of the prostate in selected patients has been proposed.[95] Removal of the uterus and anterior vaginal wall in women provides a greater soft tissue margin of normal tissue, but may be necessary only for larger, posterior wall or trigonal cancers. Currently, cystectomy in men almost always includes resection of the prostate, whereas in women the extent of removal of adjacent organs is based more on the local extent of the tumor.[96]

If cystectomy is the most efficacious treatment to control bladder cancer, why is it not used exclusively as the sole treatment? The reason is the undeniable morbidity from cystectomy imposed by the risk of the operation and the long-term impact on urinary and sexual function. Cystectomy historically has been the most dangerous operation performed by a urologist. Mortality rates after cystectomy in the 1940s were in the 40% to 50% range. In the last 50 years, steady progress is evident, such that the mortality rate has now been reduced to 1% to 3%.[97] Previously in the United States and still in some segments of the world, cystectomy was reserved only for the young and healthy, with older patients (>70 years of age) being relegated to less effective therapies. It is now clear that cystectomy can be done safely in patients of all ages when attention to perioperative care of comorbid disease is emphasized.[91,97] A higher operative mortality rate in older patients (>80 years of age) of 3% to 5% is evident, but defensible when the potential ineffectiveness of alternative therapies in this population is considered and when the risk imposed by the cancer is greatest in the short term. For a relatively healthy 80-year-old, the greater risk in the ensuing 3 to 4 years is the invasive bladder cancer rather than general cardiovascular concerns. Thus there is a growing appreciation that an expedient cystectomy in the relatively healthy elderly person offers the greatest potential for tumor control and successful rehabilitation when compared with external radiation therapy or chemotherapy, in which optimal intensity of the treatment may not be deliverable.

The therapeutic results of cystectomy can be evaluated by two parameters: pelvic recurrence rate and survival, a reflection of local recurrences and systemic disease. Pelvic recurrence rates after cystectomy are approximately 10% to 20% and clearly depend on clinical stage.[91] Large cancers, clinical T3b, may have a pelvic recurrence rate as high as 25%, and thus additional strategies may be necessary to specifically address this failure site in such patients. Preoperative radiation therapy is not beneficial to the entire group of patients undergoing cystectomy, but some data suggest a possible role for preoperative radiation in the subset of patients with stage T3b disease, who are at higher risk for local recurrence.[98] Neoadjuvant or adjuvant chemotherapy needs additional investigation in this patient subset and is discussed later.

Survival after cystectomy depends largely on pathologic stage.[91,99] Grade is an important overall prognostic factor; most patients coming to cystectomy have grade III or poorly differentiated cancers, so the discriminatory value is lost. However, pathologic stage is clearly relevant. The overall 5-year survival rate after cystectomy is 50%. However, it is more evident now that an apparent cut point of organ-confined (≤T2b, muscle-invading) disease has a substantially better prognosis than extravesical disease (≥T3a) as reflected in the newer staging system.[44]

Lymphatic metastases are a strong predictor of relapse, but again a spectrum of risk is evident, and some patients are cured by surgery alone in the face of positive lymph nodes.[91,100–102] Both the extent of the nodal metastases and the pathologic stages of bladder cancer are important variables; a single positive microscopic lymph node involvement associated with organ-confined disease (≤T2b) has a 5-year survival rate of up to 50%. Greater volume of nodal metastases and more extensive local disease progressively increase the risk of later metastases, such that involvement of multiple pelvic lymph nodes associated with a T3b cancer may have only a 10% 5-year survival rate with surgery alone. Increasing evidence supports the therapeutic value of a pelvic lymphadenectomy, particularly in patients with lower stage local disease in whom micrometastases may

be present, but cure is still possible and particularly when a sufficiently complete pelvic node dissection was accomplished. The traditional pelvic lymphadenectomy has a superior limit bounded by the bifurcation of the common iliac artery; however, some advocate a more extensive dissection up to the aortic bifurcation.[102] Standardization of the limits of a pelvic node dissection is needed, and data suggest a sufficient number of nodes must be removed for the therapeutic benefit to be realized.[101]

Improvements in perioperative care have fueled the decrease in operative mortality rate evident in the last few decades.[91,97,103,104] Of note, recent data suggest that comorbidity also may negatively affect cancer control and survival after cystectomy. In a study of 2538 cystectomies captured in the National Surgical Quality Improvement Program, the 30- and 90-day mortality rates were 2.9% and 6.8%, respectively.[105] Preoperative factors associated with death and prolonged length of stay were older patient age (OR 1.2–1.4), American Society of Anesthesiologists class 3 or greater (OR 1.5–3–3), dependent functional status (OR 1.7–2.0), and low serum albumin (OR 2.1–12.0). A major etiologic factor for bladder cancer, cigarette smoking, also contributes to greater risk for cardiovascular and pulmonary disease, with attendant increased risk for postoperative complications. Optimization of pulmonary and cardiac function preoperatively, as well as aggressive perioperative monitoring, are valuable adjuncts. The overall complication rate in 6577 patients undergoing cystectomy in the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project from 1998 to 2002 was 28.4%, and the mortality rate was 2.6%.[106] Surgical complications greatly increase the cost of cystectomy and prevention of a complication, and recognition of a complication early in its evolution (e.g., congestive heart failure before an arrhythmia or myocardial infarction or deep venous thrombosis before a pulmonary embolism) reduces morbidity and potentially can decrease length of stay and costs.[104,105] A perioperative "care pathway" in which anticipated milestones for care are articulated and incorporated into the care delivery is beneficial for the resident staff, nursing caregivers, outpatient support personnel, and the patient. Not only are costs diminished, but deviations from the anticipated quality of care become quickly evident and are opportunities for improvement. The potential role of laparoscopic or robot-assisted cystectomy remains uncertain, although experience is gradually increasing.[107,108]

Urinary Diversion

After cystectomy, the urinary system must be reconstructed to preserve renal function and to keep the patient dry. The mainstay of urinary diversion since 1951 has been the ileal conduit, in which a 15- to 20-cm isolated segment of small bowel drains urine from the ureters to the skin; urine flows directly from the stoma of the bowel into a collecting pouch that adheres to the skin around the stoma Although considerable adjustment is necessary, ultimate return to usual activities is anticipated, including walking, exercising (including swimming), and social events. Improved quality of appliances and stomal care by enterostomal therapists lessens the risk for urinary leakage or "accidents" and improves confident rehabilitation. Nevertheless, the presence of a stoma and the need for an external collecting device have a negative impact on body image, possibly disabling some patients.[109] In the early 1980s, continent cutaneous reservoirs became available, with the advantage of not needing an external collecting pouch, but the disadvantage remained of requiring an abdominal stoma that was catheterized every 4 to 6 hours by the patient to empty an internal reservoir configured from the bowel. Such reservoirs initially were plagued with a reoperation rate of 20% to 50% to obtain continence, easy catheterization, and adequate reservoir function. Ultimately, the ileal colic reservoir termed the *Indiana pouch* became the most popular surgical procedure, with a reoperation rate of less than 10%. Nevertheless, the higher complication rate and continued need for intermittent catheterization offset the marginal benefit of avoiding a collecting device for many patients and surgeons.

Later in the 1980s, experience increased with an internal, orthotopic urinary reservoir termed a *neobladder*. Most urologists and patients believe the neobladder to be a substantial improvement in rehabilitation of urinary function by allowing volitional urination with continence and excellent preservation of renal function in both men and women. Refinements in the operation providing an adequate size and detubularized bowel segment reconfigured into a spherical shape now allow reliable reservoir formation with minimal increase in operative time and no increase in postoperative complications, even in patients with more comorbid medical conditions[110] (Fig. 87-3). Patient satisfaction appears to be better, although the quality-of-life studies are difficult to interpret because of unavoidable selection biases inherent in the choice of urinary diversion.[109]

Selection of patients for neobladder urinary diversion depends on characteristics of both the cancer and the patient. Because the bowel reservoir is anastomosed to the urethra, patient selection should identify those patients with a low risk for a urethral recurrence. No or minimal involvement of the prostatic urethra in men and absence of involvement of the bladder neck in women is needed, both with a negative margin at the time of surgery.[111,112] Such practices select patients with a risk of urethral recurrence of only 2% to 3%. Even with ideal selection, the remnant urothelium remains at some risk for further urothelial cancer and consequently must be monitored.[113] Advanced local disease is not necessarily a contraindication to orthotopic diversion because adjuvant treatments, such as radiation or chemotherapy, also can be administered as necessary. From a patient's perspective, both motivation to endure some initial frustration with the function of the reservoir until it enlarges and tolerance for potential nocturnal incontinence are necessary. For many elderly patients who are frail and sedentary, the ileal conduit remains the best choice because of the quickest and easiest rehabilitation.[114] Adequate renal function of a serum creatinine level less than 2.5 to 3 mg/mL to prevent postoperative electrolyte abnormalities, as well as normal preoperative bowel function, are necessary for orthotopic diversion. Lifelong follow-up is necessary to monitor upper tracts and the metabolic and functional consequences of the diversion.[113,114]

The functional benefits of neobladder formation in both men and women have potentially lessened the pressure to delay cystectomy until absolutely necessary, and some authors have suggested that such a strategy will improve overall survival results.[115] Also, bladder preservation strategies using combinations of TUR, chemotherapy, and external radiation therapy provide a smaller incremental gain in the functional preservation that must be measured against the risk of incomplete elimination of the cancer.[116] However, it must be stressed that the neobladder does not reproduce entirely normal bladder function, with some persisting annoyance for many patients, including nocturnal enuresis and stress incontinence in a few.[116] Maturation of the neobladder takes several months following surgery, and patient expectations must accommodate such an adjustment period. Despite increased experience with this procedure, there are still disparities in the use of continent diversion, particularly in women, African-Americans, and less educated patients.[117]

Interference with sexual function in men after cystectomy and urinary diversion remains problematic. A "nerve-sparing" dissection, which preserves the neurovascular bundles containing microscopic nerves that innervate the corpora cavernosa, is feasible.[91,110] Even in highly selected patients, return of even adequate erectile function is seen in only 20% to 40% of men. Continued refinement in techniques is necessary. Measures to assist erections, such as alprostadil or Viagra (Pfizer), will help in some, but experience is currently limited. The emotional adjustment after a very large operation, changes in body image, and concern about cancer recurrence all contribute to alterations in health-related quality-of-life (HR QOL) concerns.[109] No widely accepted, validated measurement tool for HR QOL is yet available for postcystectomy patients.

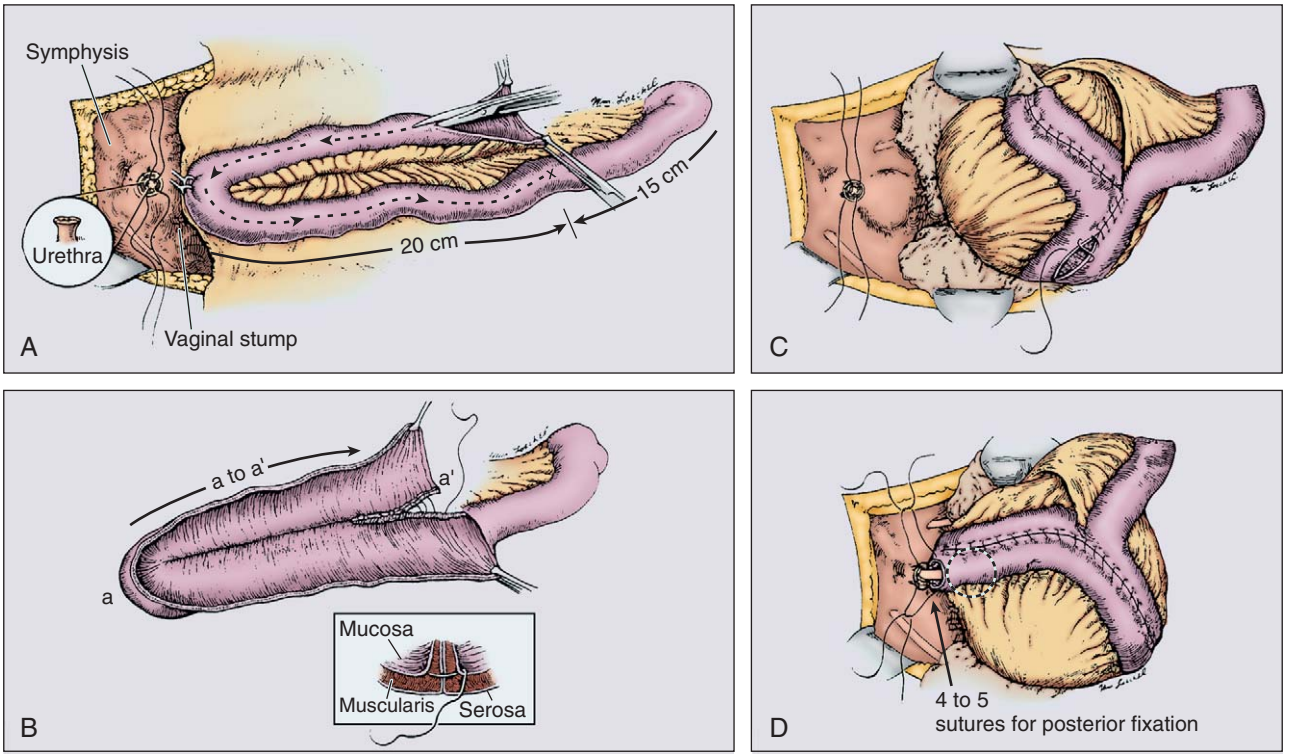


Figure 87-3 • Studer reservoir neobladder construction in a woman. **A,** The urethral stump is shown at the left of the drawing. A segment of ileum is isolated from continuity and opened on the antimesenteric border for approximately 45 cm. **B,** Posterior walls of adjacent limbs are anastomosed to form the "back" wall of the reservoir. **C,** Anterior wall of the reservoir is closed to detubularize the segment and give a spherical shape. **D,** After construction of the neobladder is complete, the dependent portion on the left is anastomosed to the urethra. The ureters are anastomosed to the afferent limb, which protrudes superiorly. (From Montie JE: Orthotopic bladder replacement in women. In Webster GD [ed]: Urinary Diversion: Scientific Foundation and Clinical Practice. Oxford, Blackwell Scientific Publications, 1995.)

Radiation Therapy

Preoperative Radiotherapy

Preoperative radiotherapy (RT) has a long history of use in bladder cancer treatment, although it currently is not employed frequently. The purported benefit has been a decreased risk of local failure following the combination of RT and radical cystectomy compared with radical cystectomy alone.[118,119] The available data are difficult to interpret but generally confirm that preoperative RT results in significant downstaging. This downstaging occurs when doses of 40 to 50 Gy are used preoperatively rather than short courses of RT followed within a few days by radical cystectomy. Older data, primarily using RT without concurrent chemotherapy, have been summarized and seem to suggest that a survival benefit exits,[118] but a more recent systemic review[120] concludes that a survival benefit cannot be confirmed with the available literature. Nevertheless, a modern experience[121] shows that for a series of patients most of whom had stage cT3 disease, a well-tolerated schedule consisting of two courses of cisplatin concurrently with 40 Gy of RT followed one month later by cystectomy led to a pT0 rate of 36%, which compares with the rate of 38% with preoperative methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) in a series more heavily weighted toward patients with cT2 disease.[122]

Given the problems with comparing retrospective reviews and the methodologic problems with the available prospective clinical trials, it seems clear that published data are insufficient to either confirm or refute the hypothesis that preoperative RT results in a survival advantage compared with radical cystectomy alone. However, assuming that a decrease in local recurrences, and the potential morbidity which local failures bring, is beneficial, there may be a role for preoperative RT in some patients with bladder cancer, especially those with locally advanced disease who are at higher risk for pelvic recurrences. Although local failure estimates for pathologically staged cases are low,[123] other reports suggest that the failure rate for cT3b disease is relatively high. A study compared patients receiving preoperative RT treated between 1960 and 1983 to the more modern patients treated with radical cystectomy only, many of whom received adjuvant chemotherapy.[124] In this review, the 5-year actuarial pelvic failure rate for clinical T3b disease was substantially reduced, from 28% without preoperative RT to 9% with preoperative RT. No significant difference in pelvic failure was observed for patients with T2 and T3a disease. The 28% failure rate with surgery alone for T3b patients is similar to that reported earlier by Greven for clinically staged T3 patients (39%).[125] Thus, for locally advanced disease, surgery alone has a substantial pelvic failure rate and, despite the high rate of distant failure, an argument can be made in favor of preoperative RT. This issue may be worthy of further study in future clinical trials.

Palliative Therapy

Radiation therapy often is used to palliate locally advanced bladder cancer, particularly when gross hematuria, not amenable to local surgical procedures, is causing clinical problems. Usually, this situation is treated with a shorter course (hypofractionation) of RT than is used for the definitive treatment of potentially curative disease. In bladder cancer, like many other malignancies that have bleeding as a symptomatic manifestation, hematuria usually is well controlled. Control of other local urinary symptoms is not as good, with control of dysuria and urinary frequency of approximately 25%. It is expected that some acute RT effects will occur during a course of therapy, but

they usually are mild, if multiple treatment fields and customized blocks are created to spare normal tissues.

Jose and coworkers[126] from the Royal Marsden Hospital performed a phase II study evaluation of a palliative, hypofractionation regimen consisting of either 5 or 6 weekly fractions of 6 Gy each for a total dose of 30 to 36 Gy; 65 poor-performance status patients with median age of 81 years were enrolled. Median survival time was just 35 weeks, but 23 of 37 patients who were evaluated cystoscopically at 3 months had a complete response. In addition, although nocturia rarely was improved, most patients had symptomatic control of hematuria, frequency, and dysuria. Duchesne and associates[127] reported the results of an international, multicenter, randomized trial of two palliative radiotherapy regimens for bladder cancer; 500 patients were entered and were randomized to receive either 35 Gy in 10 fractions over 2 weeks or 21 Gy in 7 Gy fractions over 1 week on alternating weekdays. To be eligible, patients were either medically unable to tolerate cystectomy (64%) or had advanced disease (T4b, N1, or M1) (36%). Median age was 80 years. The median survival time was 7.5 months. Of 272 patients available for assessment at 3 months, 68% had improvement in at least one bladder cancer symptom by at least one grade without worsening of any other symptoms. There were no differences between the two regimens for either survival or symptom control. Recent trials thus confirm older data indicating that radiation therapy can play an important role in ameliorating local symptoms from inoperable or unresectable bladder cancer.

Bladder Preservation Using Radiotherapy with or without Chemotherapy

Organ preservation approaches, using RT as one of the treatment modalities, have been applied to several malignant diseases. Given the potential disruption in lifestyle associated with radical bladder surgery, there has been strong motivation for exploring bladder-conserving techniques and decades of experience to draw on. Early attempts using RT for preservation focused on RT as the sole modality of treatment with surgery reserved for salvage treatment; more recent studies have used concurrent chemotherapy agents to increase the efficacy of RT.

Bladder preservation using RT as the only treatment modality, with surgery reserved for salvage of local, nonmetastatic recurrences has been compared to radical cystectomy in randomized trials. Although differences in 5-year survival rates have been detected in these studies, which favor early cystectomy, the differences are small and usually do not reach statistical significance. For example, Bloom and colleagues reported for the Institute of Urology, London, the 5-year results of a randomized trial of preoperative pelvic RT (40 Gy) and radical cystectomy versus RT only (60 Gy) for patients with T3 bladder cancer.[128] Nearly 200 patients were randomized. The 5-year survival rate was 38% for the immediate cystectomy arm and 29% for the RT alone arm ($P = 0.2$). Although salvage cystectomy was not part of the planned protocol therapy, 18 patients underwent this salvage treatment with 60% 5-year survival rate for this subset. This study completed patient accrual in 1975, and it is unclear how relevant it is to today's patients, given changes in staging evaluation and improvements in surgical and radiotherapeutic techniques over the past 25 years. Nevertheless, it remains interesting that the survival rate differences are small enough to be due to chance alone, despite the higher risk of local recurrence in the RT-alone group. Tumors that recur locally after RT may serve as markers for lesions that tend to recur distantly. Thus local recurrence may not adversely affect the overall survival rate. In a more recent study, Sell and colleagues performed a randomized trial with treatment arms similar to the Bloom study (preoperative RT and radical cystectomy versus RT with surgical salvage), and which randomized patients between 1983 and 1986. The results are remarkably similar to the Bloom report: 5-year survival rate is 29% for immediate surgery versus 23% for RT alone (P = NS). In this study, 28% of the patients receiving RT underwent salvage surgery.[129]

Thus RT, as a sole modality, has an appreciable 5-year survival rate in the treatment of invasive bladder cancer, although the local control rate is only approximately 25% to 50% at 5 years. Favorable prognostic factors for patients who are treated with RT alone include papillary morphology, extensive TUR, lack of ureteral obstruction, and higher pretreatment hemoglobin level.[130,131]

As discussed fully elsewhere in this chapter, chemotherapy has become a highly useful treatment for bladder cancer, and approaches combining active agents with RT to improve bladder conservation have proliferated. Strategies have included the use of concurrent RT and 5-FU; concurrent RT and intra-arterial cisplatin; concurrent 5-FU, cisplatin, and large dose per fraction RT; and, more recently, concurrent paclitaxel.[132–136] However, most interest has been in the use of RT with concurrent intravenous cisplatin, with or without the use of neoadjuvant chemotherapy to address the issue of systemic disease.[137–141] Most of these strategies employ an aggressive TUR prior to conservative therapy, and this procedure is considered to be an important component of therapy.

A recent update of results from Massachusetts General Hospital (MGH) and the Radiation Therapy Oncology Group (RTOG) summarizing the results of sequential clinical trials employing transurethral resection of the bladder tumor (TURBT), chemotherapy, and radiotherapy for bladder preservation illustrates the outcome with this approach.[142] Most commonly, the studies led by Shipley and colleagues have used neoadjuvant chemotherapy with methotrexate, cisplatin, and vinblastine (MCV) up front for two cycles followed by RT. However, as discussed later in this chapter, the use of neoadjuvant therapy in this setting is debatable. Regardless of the use of neoadjuvant chemotherapy, concurrent chemotherapy and RT is used, and a dose of 39.6 Gy with two courses of concurrent cisplatin (70 mg/m^2 or 100 mg/m^2) was the most common regimen. Frequently at this point in the treatment regimen—two thirds through the radiotherapy—treatment is paused, and patients are restaged. Those with tumors sensitive to treatment, as demonstrated by a complete response (i.e., negative biopsies and negative urinary cytology) continue with additional concurrent cisplatin and RT to a total dose of 64.8 Gy. Patients with less than a CR go on to radical cystectomy. Other clinicians who perform bladder-sparing treatment forgo the intra-RT tumor assessment and perform a restaging shortly after the completion of the full dose of radiation therapy, with salvage surgery performed on incomplete responders.[137]

Results of treatment for 190 patients with the MGH approach reveal a 5-year survival rate of 54% and a 10-year survival rate of 36%.[143] Of the surviving patients, 73% (46% of the total) have an intact bladder at 5 years. Bladder function after TURBT, chemotherapy, and RT is reported to be good as quality of life data emerges. For example, in a large German series of 282 consecutive patients treated with RT alone ($N = 98$) or RT and concurrent cisplatin or carboplatin ($N = 184$), only three patients underwent a cystectomy for poor bladder function or radiation cystitis.[144] Of note, approximately 25% of patients who achieve a complete response when treated with bladder-sparing approaches subsequently develop noninvasive recurrences, and the long-term outcome of these patients remains of some concern. Zietman and coworkers[145] have examined the results of 32 patients who developed noninvasive recurrences. These cancers usually were carcinoma in situ and usually occurred at the site of the original tumor. Of the 32 patients, 27 were treated conservatively, and the irradiated bladder tolerated this therapy well; ten patients ultimately required salvage cystectomy. In general, the noninvasive recurrences that occur after RT-containing, bladder-sparing approaches can be managed with conventional intravesical therapies.

A recent review article discussed the status of quality of life after bladder-sparing and noted that a main objective of bladder preservation is improvement in quality of life by preserving a functional

bladder and avoiding the need for a urinary diversion.[146] Shipley and associates[147] have reported a less than 1% rate of salvage cystectomy for radiation cystitis or bladder contracture. A series by Henningsohn and coworkers[148] reported the results from 71 patients in Stockholm treated between 1977 and 1995 with doses ranging from 58 to 63 Gy. Anonymous questionnaires were used to compare irradiated patients with 460 age-matched controls and 250 patients who underwent cystectomy. Of note, 74% of irradiated patients reported little or no distress from urinary symptoms, and 68% denied moderate or severe gastrointestinal symptoms. More irradiated patients retained sexual function compared with patients who had had cystectomy. Of surveyed patients, 38% of irradiated patients had intercourse in the previous month compared with 13% of cystectomy patients. For surviving patients, 75% retained an intact urinary bladder after radiation therapy; this was similar to other multimodality series. Zietman and colleagues[149] reported the experience from Massachusetts General Hospital using both QOL questionnaires and formal urodynamic studies. QOL questionnaires revealed no significant urinary symptoms in more than 80% of patients. On urodynamic evaluation, 80% of patients (19/26) had normal bladder function. Bowel dysfunction was low, and 55% of men reported sufficient erection for intercourse within the month prior to the survey. A French study assessed 53 patients treated with concurrent chemotherapy and radiation therapy between 1999 and 2001.[150] With a median follow-up of 2 years, 82% of patients had preserved bladders. Of the patients with a preserved bladder, 67% reported satisfactory urinary function at 2 years.

As mentioned earlier, the role of neoadjuvant chemotherapy as a part of bladder preservation has come into question. This component of treatment was added to provide additional downstaging and also to address the potential for subclinical metastatic disease. However, this chemotherapy also added to the acute morbidity of treatment. The RTOG recently reported on a randomized study that compared the approach described previously, with two cycles of MCV prior to concurrent cisplatin/RT, to a treatment arm that had no pre-RT MCV.[147] With a median follow-up of 5 years, no significant difference in survival was detected. Thus, although systemic relapse is an important component of treatment failure, it is not clear yet how to decrease the probability of this event in patients undergoing a modern bladder preservation approach.

A phase I trial of twice-weekly gemcitabine with concurrent radiation for patients with muscle-invasive bladder cancer was undertaken at the University of Michigan.[151] Gemcitabine has known radiosensitizing properties at doses that are below cytotoxic levels. Dose levels of 10 mg/m^2 and 20 mg/m^2 were well tolerated when given twice weekly with radiation, with a maximum tolerated dose (MTD) of 27 mg/m^2. Radiation therapy was delivered with a three-dimensional conformal technique to the bladder and extravesical tumor to a dose of 60 Gy in 2-Gy fractions. Prophylactic nodal irradiation was not given due to concerns about gemcitabine toxicity with a large field, as well as to limit the dose should salvage surgery with neobladder formation be needed. Complete response was noted in 21 of 23 patients (91%). Formal quality-of-life data were collected as well.[152] No statistical difference was seen in the quality-of-life (QOL) scores for the concurrent radiation therapy and gemcitabine patients before, during, or after treatment. However, those patients who received higher gemcitabine doses with dose-limiting toxicities reported lower bladder-specific QOL.

The RTOG continues to evaluate and refine bladder preservation strategies. An active RTOG study (RTOG 0233) is assessing the tolerability and efficacy of two regimens in a randomized phase II trial. Patients receive radiosensitization with cisplatin and either 5-FU or paclitaxel. Adjuvant systemic therapy is then delivered with gemcitabine, cisplatin, and paclitaxel. One additional subset of patients is under evaluation in RTOG. These are patients who are not surgical candidates, usually because there are medical comorbidities that do not allow either reasonably safe cystectomy or delivery of cisplatin. A recently activated RTOG trial (RTOG 05–24) evaluates therapy for these patients and also examines the role of targeted therapy. Based on examination of specimens from RTOG's bladder cancer tissue repository, it was noted that overexpression of Her-2 was significantly associated with a decreased complete response rate.[153] Thus, an approach to target the Her-2 pathway was initiated. This trial (05–24) enrolls patients with T2-T4a urothelial bladder cancer. Patients will have tissue examined at a central laboratory for Her-2 expression. Patients with 2+ or greater immunohistochemical staining will be treated with radiation therapy for 7 weeks along with 7 weekly treatments of paclitaxel and trastuzumab. Patients with less than 2+ staining will receive RT and weekly paclitaxel but not trastuzumab. The sample size is 88 patients and the primary endpoint is tolerability, but secondary efficacy endpoints will be obtained.

Future studies will examine the role of newer chemotherapy agents, such as docetaxel and gemcitabine as radiosensitizers in bladder preservation approaches, and at present, bladder preservation using TURBT, chemotherapy, and RT should be considered a method that is still being enhanced. However, it is clear that for selected patients, this conservative approach is a feasible technique to achieve both tumor eradication and organ preservation.

Chemotherapy

Adjuvant and Neoadjuvant Chemotherapy

Advances in surgery and radiation therapy have markedly improved the treatment of invasive transitional cell carcinoma, providing improved local control while decreasing the morbidity and mortality associated with therapy. Despite these advances, a large proportion of patients with muscle-invasive disease will develop metastases, accounting for much of the morbidity and almost all the deaths associated with this disease. These metastatic lesions presumably are due to the presence of disseminated disease at the time of local therapy. The development of chemotherapeutic agents and regimens with activity in the setting of metastatic transitional cell carcinoma, along with the demonstrated efficacy of both neoadjuvant and adjuvant chemotherapy in other diseases, has prompted considerable interest in these strategies for the treatment of transitional cell carcinoma.

Both approaches aim to improve the overall mortality rate associated with bladder cancer by treating in the setting of minimal metastatic disease. The hope is that the disease will be more susceptible to therapy and that the patients will be more tolerant of associated side effects. Adjuvant therapy is given following definitive local therapy, and neoadjuvant chemotherapy is given prior to local treatment. The decision to proceed with adjuvant therapy can be based on the pathologic stage as dictated by the findings at cystectomy. Criteria can be defined for patient eligibility, and the population enrolled on trials can be fairly uniform. The disadvantage, however, is that definitive local therapy may render some patients either unable or unwilling to undergo adjuvant therapy due to complications associated with the procedure. Patients may develop overt metastatic disease while recovering from their definitive local therapy, which may render the advantage of adjuvant therapy moot.

Neoadjuvant chemotherapy, by contrast, delivers treatment at the earliest possible time. It allows assessment of the chemotherapeutic responsiveness of the primary tumor, which has been shown to be a prognostic indicator for response.[25] In addition, tumors that initially may be judged unresectable may be rendered resectable by neoadjuvant therapy. Neoadjuvant therapy also allows maximal delivery of chemotherapy, because vascular beds have not been disrupted by either surgery or radiation. The disadvantages of neoadjuvant therapy are that it must be based on clinical staging criteria, which often overstate the extent of disease when compared to pathologic review, and that a significant proportion of patients will receive treatment when they do not need chemotherapy.

Although both neoadjuvant and adjuvant therapy are attractive in concept, major problems have arisen in the study of these approaches.

To date there is suggestive, but no definitive, evidence that either approach improves overall survival of patients with bladder cancer.

Adjuvant Chemotherapy

Adjuvant chemotherapy of transitional cell carcinoma has been the subject of several single-institution randomized trials. Unfortunately, no multicenter randomized study has ever been conducted. The single center studies which have been reported have been flawed by being either retrospective or limited in their enrollment.[154–158] Although these studies demonstrate a clear improvement in time to progression for adjuvant therapy, they have never shown a definitive benefit in terms of overall survival, primarily because they are too small to show a difference.

The results of these studies are summarized in Table 87-3. Despite the widespread use of adjuvant chemotherapy for invasive transitional cell carcinoma, we still do not have definitive evidence of benefit in terms of overall survival. This is primarily due to the limited number of patients entered on the randomized studies reported to date, resulting in too few patients being treated and followed to detect a difference in overall survival. Only 75 patients have actually received chemotherapy on the three randomized trials reported to date; the conclusions that can be drawn from such small studies are extremely limited. The improved disease-free survival in patients treated with adjuvant chemotherapy on the trials provides a tantalizing hint that this approach may result in a higher cure rate for this disease. Proof of the benefit of adjuvant chemotherapy will require a multicenter randomized trial with appropriate sample size, and clinical trials designed to address this question should be the first priority for these patients. In the absence of such a trial, adjuvant chemotherapy remains of uncertain benefit.

These hints of activity led investigators at M.D. Anderson Cancer Center to address the question in a different way.[159] They randomized 140 patients with high-risk resectable bladder cancer to receive either two cycles of neoadjuvant MVAC followed by surgery and three additional cycles of adjuvant therapy, or surgery followed by five cycles of MVAC. Only 65% of the patients received at least four cycles of chemotherapy because of a variety of reasons, but chiefly because of toxicity. There was no difference in overall survival in the two groups, suggesting that the timing of chemotherapy is not a major factor in determining its impact. The design of this study does not allow evaluation of the overall efficacy of chemotherapy in either setting, but two observations emerged confirming prior findings that have potential impact on future trials. First, a high rate of clinical understaging in terms of nodal involvement was documented and lymphatic or vascular invasion on the initial resection specimen is correlated with this finding. Second, tumor downstaging by neoadjuvant therapy is associated with a high rate of long-term survival. Both factors are critically important in the design of future neoadjuvant trials.

Neoadjuvant Chemotherapy

Despite the theoretic advantages cited for neoadjuvant chemotherapy, its use remains limited. The primary reason is that large multicenter trials with the potential to provide definitive evidence of benefit have only recently been completed, and the results have not been fully incorporated into the standard armamentarium. Neoadjuvant chemotherapy has been used in multiple single-agent trials. Chemotherapy has been used alone, concurrently with radiation therapy, sequentially, or alternating with radiotherapy. Most of these trials used cisplatin either singly or in combination, with pathologic complete response rates reported from 0% to 96%. The wide range of response rates points to the major problems in interpreting this data. Case selection is based entirely on clinical criteria, and biologic markers of invasive metastatic potential were unknown at the time these studies were designed and conducted. Most of the studies enrolled patients who had undergone TUR in their bladder tumor and may, therefore, have been in complete response at the time they were treated. At least a fraction of these patients may actually have been cured by their local therapy. Finally, the initial workup of patients enrolled on these studies varied widely, with some of the studies being conducted prior to the incorporation of modern diagnostic techniques into the eligibility criteria. Some of the early studies may well have included patients with early metastatic disease, resulting in a significant impact on the survival data. Drawing any conclusion from these nonrandomized studies is extremely difficult.

Seven randomized studies have been completed. Most of these studies have been relatively small and failed to show a definitive benefit for neoadjuvant chemotherapy. A total of 845 patients were enrolled on five phase III trials completed in the late 1980s using primarily cisplatin alone as the chemotherapy regimen. These trials were the subject of a meta-analysis, published in 1995, that used individual patient data from 479 of the patients.[160] Two of these trials tended to favor chemotherapy, while two showed no benefit. The fifth and largest trial, which provided no individual patient data for the meta-analysis, enrolled 325 patients and used a combination of cisplatin and doxorubicin. This trial favored chemotherapy.[161] The overall survival curves for the meta-analysis showed no statistically significant benefit to chemotherapy ($P = 0.33$).

Two large modern studies have reported their results. The largest randomized trial of neoadjuvant therapy was conducted in Europe

Table 87-3 Adjuvant Combination Chemotherapy Trials

First Author Reference	Arms	Total No. of Patients (No. Receiving Chemotherapy)	Results
Logothetis[155]	Nonrandomized trial	339 (71)	Improved survival in chemotherapy group
Skinner[156]	PAC	44 (33)	Improved disease-free survival in chemotherapy group; survival advantage for single-node-positive group
	Observation	46	
Stockle[157]	MVAC or MVEC	26 (18)	Halted early with improved disease-free survival in chemotherapy group
	Observation	23	
Freiha[154]	CMV	25 (24)	Improved disease-free survival in chemotherapy group
	Observation	25	

CMV, cisplatin, methothexate, vinblastine; MVAC, methothexate, vinblastine, doxorubicin, cisplatin; MVEC, methothexate, vinblastine, epirubicin, cisplatin; PAC, cyclophosphamide, doxorubicin, cisplatin.

by the Medical Research Council (MRC) and the EORTC.[162] The study was designed to detect a difference in 3-year survival of 10% or greater with the use of chemotherapy. A total of 975 patients were enrolled, with patients randomized to receive CMV every 3 weeks for three cycles, or no chemotherapy prior to a previously selected definitive local therapy. The definitive local therapy was either radical cystectomy, full-dose external beam radiotherapy, or preoperative radiotherapy followed by cystectomy. Four hundred eighty-nine patients were randomized to receive chemotherapy, and 486 received local therapy alone. A total of 484 underwent cystectomy, 414 received radiotherapy, and 77 were treated with combined radiotherapy and surgery. There was a 21% improvement in the pathologic complete response rate at cystectomy in the patients receiving chemotherapy. At 3 years the overall survival rate was 55.5% for the chemotherapy arm and 50% in the no chemotherapy arm ($P = 0.075$). The chemotherapy therefore failed to demonstrate the anticipated 10% improvement in overall survival at this time. However, subsequent follow-up has shown that the survival curves clearly diverge with an advantage for the arm receiving chemotherapy.[163]

In the United States, results of an Intergroup randomized trial compared MVAC plus cystectomy versus cystectomy alone.[122] This trial randomized 317 patients enrolled over 11 years. By intention to treat analysis, the median survival of the combination arm of therapy was 77 months compared to 46 months in the cystectomy alone arm. At 5 years 43% of the subjects in the cystectomy alone arm were still alive while 57% of those who received combined modality therapy survived ($P = 0.06$). Improved survival was associated with pathologic complete response in the cystectomy specimen. There were significantly more patients with no residual disease at operation in the combination therapy arm (38% versus 15%, $P < 0.001$). These data have been the subject of considerable debate.[164,165] The results of both the Intergroup and EORTC/MRC trials strongly suggest that there may be a benefit to neoadjuvant chemotherapy.

One limitation to the use of neoadjuvant chemotherapy is the toxicity associated with cisplatin-based regimens. A multicenter phase II trial recently explored the use of paclitaxel, carboplatin, and gemcitabine in the neoadjuvant setting. This combination demonstrated an unexpectedly high rate of toxicity in this setting, but the pathologic complete response rate was comparable to that reported for MVAC on the Intergroup trial.[166] A similar phase II trial of this regimen with a variation on the drug schedule has recently been completed by the Southwest Oncology Group.

Chemotherapy for Metastatic Disease

Urothelial carcinoma has long been known to be a chemotherapy-sensitive malignancy. Single-agent phase II trials conducted in the 1970s identified cisplatin and methotrexate as the most active agents, with response rates of approximately 30%.[167] Doxorubicin, 5-fluorouracil, vinblastine, vincristine, and mitomycin C were all shown to have single-agent response rates of approximately 15%. These phase II trials provided the basis for the development of combination regimens such as CMV (cisplatin, methotrexate, and vinblastine), CISCA (cisplatin, cyclophosphamide, and doxorubicin), and MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin). The initial trial of MVAC, with 121 evaluable patients, showed an overall response rate of 72%, with a complete clinical response rate to chemotherapy alone of 18%.[168] An additional 11 patients were rendered disease-free by surgery following chemotherapy. The median survival time for the entire group was 13.3 months, and only 20% of the patients were long-term disease-free survivors. MVAC subsequently was compared to CISCA in a phase III randomized trial.[169] The combined complete and partial response rate was significantly better for patients treated with MVAC (65% versus 46%), as was the overall survival time (median 11 months versus 10 months). Based on these studies MVAC has emerged as the standard therapy for metastatic transitional cell carcinoma, although it has never been compared head-to-head with CMV.

Despite the encouraging early results, MVAC has not proved to be curative therapy for transitional cell carcinoma, nor has the high response rate been replicated in the cooperative group or community setting. A randomized trial comparing MVAC to single-agent cisplatin showed an overall response rate to MVAC of 39%, with only 13% complete responses.[170] Median survival time for patients receiving MVAC was 12.5 months, similar to prior studies, but an update showed that only 4% of patients were alive at 5 years.[171]

Several attempts have been made to improve both the toxicity profile and response rate of MVAC. Even at standard doses, MVAC is a highly toxic regimen, and most patients are unable to receive the full prescribed dose over sequential cycles. Use of colony-stimulating factors has yielded mixed results in terms of allowing patients to receive standard therapy.[172–174] Subsequent efforts to improve the efficacy of the regimen have focused primarily on the use of dose-escalated MVAC, which demonstrated responses in up to 40% in initial trials with patients with disease refractory to prior systemic chemotherapy including standard dose MVAC. A randomized trial conducted by the EORTC demonstrated that high-dose MVAC given on an every-2-weeks schedule with granulocyte colony-stimulating factor (GCSF) had markedly increased complete and overall response rates when compared to standard MVAC.[175] Median time to progression and 2-year progression-free survival times favored the high-dose arm, but the trial did not demonstrate the 50% improvement in median overall survival it was designed to detect. Toxicities were roughly equivalent in the two arms of the study, slightly favoring the high-dose arm, presumably due to the use of the GCSF. To date dose escalation of MVAC has not demonstrated a significant benefit to patients.

The toxicity and relatively limited efficacy of MVAC have prompted a search for new agents and combinations. The two most promising agents to emerge are paclitaxel and gemcitabine. Both show significant activity as single agents. Single-agent trials of gemcitabine showed response in approximately 25% of patients treated.[176–178] These trials reported relatively minimal toxicity and serve as a basis for the incorporation of gemcitabine into combination chemotherapy regimens. Three phase II trials combined gemcitabine with cisplatin (GC) and demonstrated response rates comparable to MVAC.[179–181] Based on these results, this regimen was compared to MVAC in a randomized multicenter trial conducted in Europe and North America,[182] in which 405 patients were randomized between the two therapies. Overall survival times (median: GC 13.8 months, MVAC 14.8 months) and response rates (GC 49.4%, MVAC 45.7%) were similar in the two arms of the study, but patients receiving GC had much less severe toxicity despite receiving much more therapy. Although this study was not designed to demonstrate that GC was equivalent to MVAC, it does appear that efficacy is roughly similar with markedly less toxicity.

The next major questions under investigation are whether taxanes can add to the efficacy of therapy for advanced disease, and what the role of targeted therapy is in metastatic urothelial cancer. A phase II trial of paclitaxel was conducted by the Eastern Cooperative Oncology Group in patients who had received no prior chemotherapy or radiotherapy.[183] Using a 24-hour continuous infusion of 250 mg/m^2 every 3 weeks along with GCSF, 11 patients out of 26 (42%) showed evidence of response, with 7 patients (27%) achieving a complete response. Paclitaxel was then combined with carboplatin in a phase I–II trial.[184] With a target area under the curve (AUC) for carboplatin of 6 mg/mL/min and paclitaxel at 225 mg/m^2, the overall objective response rate was 50%. A nearly identical response rate of 52% was documented in a phase II trial of paclitaxel at 200 mg/m^2 over 3 hours, followed by carboplatin at a target AUC of 5 mg/mL/min every 3 weeks.[185] These results prompted further investigation in the cooperative group setting. The Southwest Oncology Group used this regimen in previously untreated patients, demonstrating an overall response rate of only 21%.[186] The Eastern Cooperative Oncology Group evaluated the combination in patients with renal insufficiency

and demonstrated an overall response rate of 24%.[187] Although the combination was well tolerated in both trials, this low response rate has discouraged further development.

Subsequent studies added gemcitabine to the paclitaxel–carboplatin doublet. In a multicenter phase II trial, this triplet showed an overall response rate of 68%, with 32% of patients showing complete response.[188] Investigators in Spain added paclitaxel to the gemcitabine–cisplatin doublet, demonstrating a 77% response rate in a phase I/II trial.[189] These trials served as the basis for several new studies including an ongoing phase III trial comparing GC to GC plus paclitaxel and a recent trial adding trastuzumab to the paclitaxel/carboplatin/gemcitabine triplet in patients with tumors overexpressing Her2.[188]

These new regimens hold significant promise in terms of both efficacy and increased tolerability. In assessing a patient with metastatic transitional cell carcinoma for chemotherapy, toxicity is a major consideration. In general, patients with bladder cancer are older and may have significant comorbidity. Currently therapy is not curative, and toxicity has a significant impact on quality of life. This situation is particularly true with MVAC, although the newer regimens also can be associated with significant toxicity in patients with poorer performance status.

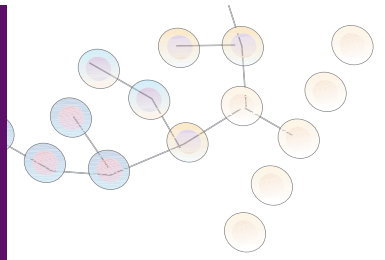
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88 Prostate Cancer

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SUMMARY OF KEY POINTS

Incidence

- Prostate cancer is the most commonly diagnosed life-threatening cancer in men (218,890 cases and 27,050 deaths in 2007).
- Small prostate cancers are present in 29% of men between age 30 and 40 and 64% of men between age 60 and 70.
- The lifetime risk of a prostate cancer diagnosis is 1 in 6, and the risk of dying from prostate cancer is 1 in 35.
- Age, family history, diet and lifestyle, and ethnicity are risk factors for prostate cancer development.

Molecular Pathogenesis

- Germline mutations in *RNASEL* and *MSR1*, encoding proteins that function in host responses to infection, appear responsible for some cases of hereditary prostate cancer.
- An inflammatory lesion, proliferative inflammatory atrophy (PIA), may be an early precursor to prostate cancer.
- Somatic inactivation of *GSTP1*, encoding a carcinogen-detoxification enzyme, may initiate prostatic carcinogenesis by increasing the vulnerability of prostate cells to damage mediated by oxidant and electrophilic carcinogens.
- Gene fusions, involving TMPRSS2 and ETS family transcription factor genes, may contribute to the androgen dependence of prostate cancers.
- Defects in the functions of NKX3.1, PTEN, and CDKN1B are common in prostate cancer cells.

Prevention

- The type 2 5α-reductase inhibitor finasteride reduced the overall number of prostate cancers, but may have increased the number or the detection of high-grade cancers, in a randomized clinical trial.
- The antioxidants selenium and vitamin E are under scrutiny in a large randomized clinical trial for prevention of prostate cancer.

Screening and Diagnosis

- Prostate cancer screening using serum prostate-specific antigen (PSA) and digital rectal examination detects prostate cancers early, when the disease is clinically localized to the prostate gland.
- Transrectal ultrasound (TRUS)-guided core needle biopsies are used to diagnose prostate cancer.
- Stage, histological grade (Gleason score), and serum PSA levels are prognostic factors.

Treatment of Localized Disease

- Treatment options include watchful waiting, anatomic radical retropubic prostatectomy, external beam radiation therapy, and brachytherapy.
- Adjuvant androgen suppression can improve survival for some men with prostate cancer treated with external beam radiation therapy.
- A progressive rise in the serum PSA after treatment indicates prostate cancer recurrence.
- Depending on the approach used, side effects associated with treatment of localized prostate cancer can include erectile dysfunction, irritative voiding symptoms or difficulties with urinary control, and rectal irritation.
- Radiation therapy can be used to treat local prostate cancer recurrences following radical prostatectomy.

Treatment of Advanced Disease

- Androgen suppression, most often accomplished via the use of luteinizing hormone-releasing hormone (LHRH) agonists, with or without anti-androgens, is the most commonly used treatment.
- Side effects can include loss of libido, hot flashes, gynecomastia, loss of lean muscle mass and bone density, and the development of metabolic syndrome.
- Docetaxel chemotherapy improves the survival of men with progressive androgen-independent prostate cancer.
- Bisphosphonates antagonize loss of bone density accompanying androgen deprivation, and reduce skeletal complications associated with metastatic prostate cancer progression.
- Other agents, including various immunotherapies, are under development in clinical trials.

INTRODUCTION

In 2007, an estimated 218,890 prostate cancer diagnoses will be made in the United States, accompanied by an estimated 27,050 prostate cancer deaths.[1] Since about 1994 to 1996, with widespread use of serum prostate-specific antigen (PSA) testing and digital rectal examination for prostate cancer screening, and with increased treatment of clinically localized prostate cancer with surgery or radiation therapy, age-adjusted prostate cancer death rates have fallen steadily. Although this trend might indicate a beneficial impact of prostate cancer screening and/or early prostate cancer treatment on prostate cancer mortality, mass screening of the general population for prostate cancer remains controversial.[2,3] One challenge for prostate cancer screening is the prevalence of the disease in the U.S.: autopsy series have revealed small prostate cancers in as many as 29% of men between age 30 and 40 and 64% of men between age 60 and 70.[4] Obviously, not all of these men are at risk for symptomatic or life-threatening prostate cancer progression. In fact, many such men, if diagnosed with prostate cancer, may be at greater risk for treatment-associated morbidity.

Currently, for U.S. men, the lifetime risk of a diagnosis of prostate cancer is about 1 in 6, while the lifetime risk of death from prostate cancer is on the order of 1 in 35.[1] Over the past two decades, treatment approaches for men with prostate cancer have changed dramatically, with improvement in established prostate cancer treatments and the introduction of new prostate cancer treatment approaches. Now, men diagnosed with prostate cancer often face a bewildering array of treatment choices. Physicians must weigh the risks of prostate cancer progression against the potential for side effects from treatment, in the context of other health risks and life choices, to use the current collection of treatments for the greatest benefit.

This chapter provides an overview of prostate cancer etiology, biology, screening, detection, diagnosis, prevention, and treatment.

PROSTATE ANATOMY AND FUNCTION

The prostate is a male sex accessory gland that surrounds the urethra and contributes secretions to the ejaculate (Fig. 88-1). Located in the pelvis, the prostate sits adjacent to the bladder and rectum, is surrounded incompletely by a thin capsule composed of collagen, elastin, and smooth muscle, and at the apex of the gland, forms part of the urethral sphincter apparatus.[5] Nerves to the corpora cavernosa of the penis, needed for penile erection, travel through fascia along the posterolateral surface of the prostate. These nerves can be recognized as a neurovascular bundle by urologists and preserved during radical prostatectomy to minimize sexual dysfunction postoperatively.[6,7] The prostate parenchyma has been divided into three zones that can be seen by transrectal ultrasonography, and recognized readily by surgical pathologists examining radical prostatectomy specimens: a central zone, surrounding the ejaculatory ducts and accounting for some 25% of the prostate; a transition zone, near the prostatic urethra with 10% of prostate tissue normally; and a peripheral zone, with the bulk of prostate tissue encompassing posterolateral region of the prostate (Fig. 88-2).[8,9]

In addition to prostate cancer, the prostate also frequently manifests benign enlargement (benign prostatic hyperplasia [BPH]) and chronic or recurrent inflammation (prostatitis). Like prostate cancer, each of these conditions can elevate the serum prostate-specific antigen (PSA), confounding the use of serum PSA testing for prostate cancer screening. When present, BPH usually is located near the prostatic urethra (in the transition zone), while prostate cancer, as well as the prostate cancer precursor lesion prostatic intraepithelial neoplasia (PIN), usually arises in the periphery (the peripheral zone). Prostatic inflammation, although often prominent in the peripheral zone, can be seen throughout the prostate. Although prostate cancer, BPH, and prostatitis all commonly afflict U.S. men, and can be simultaneously present in a single prostate gland, mechanistic associations of the three diseases have been difficult to demonstrate.

The prostate requires androgenic hormones and an intact androgen receptor for normal growth and development. In the prostate, the major circulating androgenic hormone, testosterone, produced by Leydig cells in the testes upon stimulation by luteinizing hormone (LH), is converted by 5α-reductase (nicotinamide-adenine dinucleotide phosphate-dependent Δ(4)-3-ketosteroid 5α-oxidoreductase) to 5α-dihydrotestosterone (DHT).[10] DHT, a more potent androgen than testosterone, binds to intracellular androgen receptors, alters androgen receptor conformation to promote dissociation from chaperone proteins, triggers androgen receptor dimerization and transport into the cell nucleus, and activates the expression of selected target genes.[11,12] Stereotypically, androgen receptor target genes are characterized by the presence of androgen response element (ARE) DNA sequences within the transcriptional regulatory region, permitting direct binding and *trans*-activation by the androgen receptor.[13] For genes like *PSA*, which are activated by the androgen receptor selectively in prostate cells, and not in cells of other tissues, the transcriptional regulatory region also contains additional DNA sequences (prostate-specific enhancer [PSE]) conferring prostate-specific expression.[14]

The normal prostate epithelium is composed of (1) basal epithelial cells, characterized by the expression of cytokeratins K5 and K14, and p63; (2) columnar secretory epithelial cells, which express the androgen receptor, PSA, cytokeratins K8 and K18, prostate-specific membrane antigen (PSMA), and prostate-specific acid phosphatase (PAP); and (3) rare neuroendocrine cells, which secrete chromogranin A, neuron-specific enolase, and synaptophysin (Fig. 88-3).[15,16] The basal epithelial cell compartment likely contains pleuripotent prostatic stem cells, capable of self-renewal proliferation and of differentiation. In contrast, columnary secretory cells, specialized to produce secretions for the ejaculate, are terminally differentiated, particularly under the influence of androgenic hormones. The

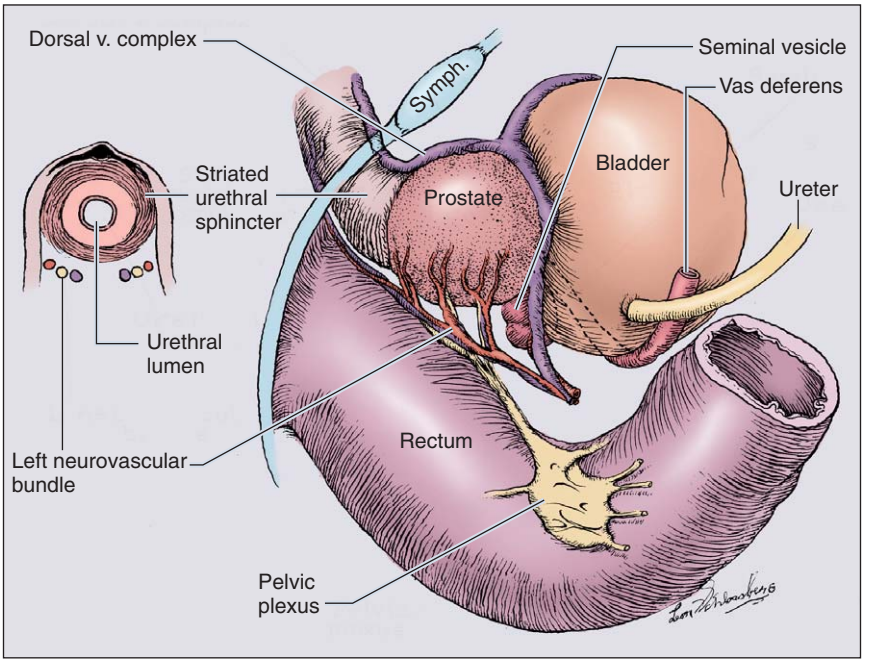


Figure 88-1 • The anatomy of the prostate: rectum, bladder, dorsal vein complex, striated urethral sphincter, pelvic plexus, and neurovascular bundle.

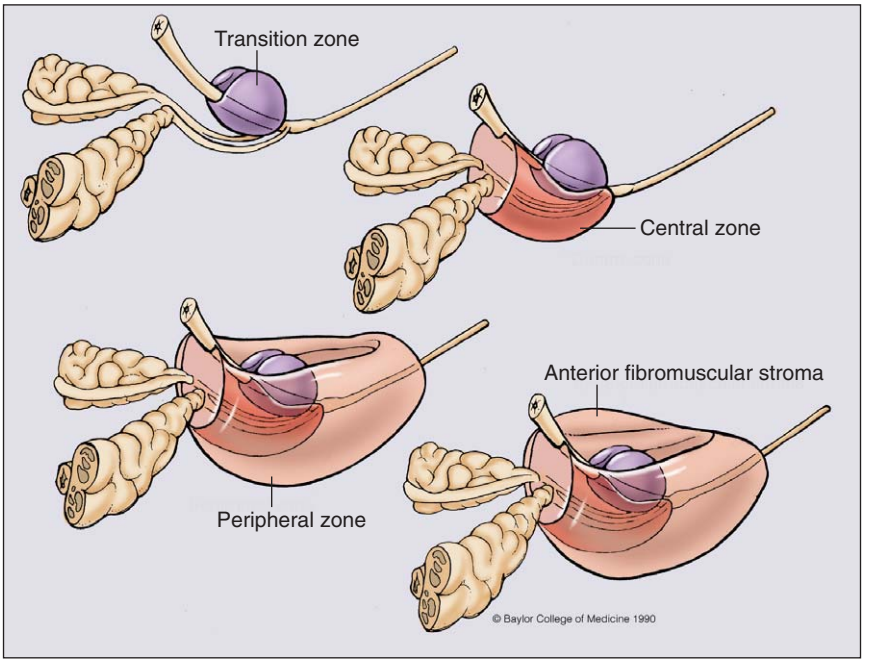


Figure 88-2 • Zones of the prostate. The peripheral zone, accounting for 70% of the prostate gland, is the site of origin of ≥70% of prostate cancers; the central zone, approximately 25% of the prostate gland, gives rise to only 1% to 5% of prostate cancers; and the transition zone, ~5% to 10% of the prostate gland, gives rise to 20% of prostate cancers and is the site of origin of benign prostatic hyperplasia (BPH). (From Green DR, Shabsign R, Scardino PT: Urological ultrasonography. In: Walsh PC, Rettic AB, Stamey CA, Vaughan ED Jr [eds]: Campbells's Textbook of Urology, 6th ed. Philadelphia, WB Saunders, 1992.)

prostate epithelium is supported, in turn, by a stroma containing fibroblasts, smooth muscle cells, nerves, and blood vessels. Stromal cells, which also express the androgen receptor, secrete polypeptide growth factors, such as keratinocyte growth factor (KGF), that contribute to the regulation of epithelial homeostasis via a paracrine signaling mechanism.[17,18] Abnormal stromal–epithelial interactions, with disordered regulation of epithelial cell proliferation and differentiation, may contribute to the pathogenesis of both prostate cancer and BPH.[19]

Prostate cancer cells and PIN cells arise from the prostatic epithelium. Even though transformed, such cells typically retain many of the phenotypic attributes characteristic of differentiated columnar secretory cells, including the expression of androgen receptor, PSA, PSMA, and PAP. Prostate cancers reminiscent of basal epithelial cells are exceptionally rare; prostate cancers with features of neuroendocrine cells are somewhat more common.[20] However, unlike normal columnar epithelial cells, neoplastic prostate epithelial cells are capable of proliferation. This feature has led to the concept that the target cell for neoplastic transformation in the prostate may be an "intermediate" cell, in transit from a basal epithelial stem cell to a differentiated columnar secretory epithelial cell, with properties of both stem cells and differentiated cells.[15,16] Another feature of neoplastic prostate epithelial cells, as compared to normal basal or columnar secretory cells, is that the neoplastic cells appear to use androgen receptor signaling not only for differentiation, but also for proliferation, as most prostate cancer cells tend, at least initially, to display

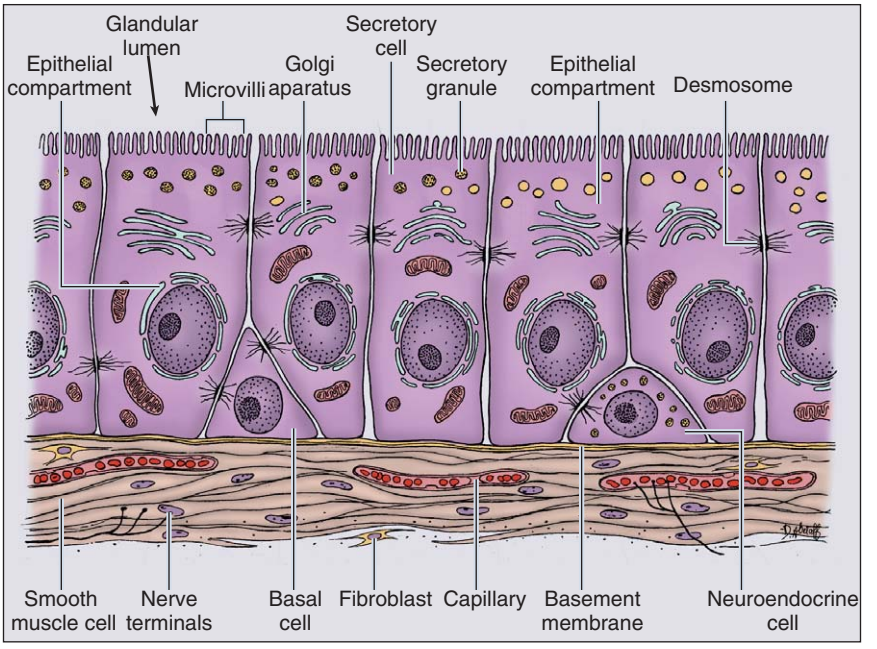


Figure 88-3 • The prostate epithelium.

some dependence on androgens for maintenance of growth and survival.[21] Somatic fusions between an androgen-regulated gene, *TMPRSS2*, at chromosome 21q22, and genes encoding members of the ETS family of transcription factors, commonly found in prostate cancers, may provide a mechanistic explanation by which androgen signaling can promote prostate cancer cell growth.[22] Ultimately, in life-threatening prostate cancer, prostate cancer cells escape from the prostate gland, proliferate to lymph nodes, in bones, and in other organs, and become less and less dependent on androgenic hormones.

ETIOLOGY OF PROSTATE CANCER

Genetic Predisposition to Prostate Cancer

Familial clusters of prostate cancer have been recognized since at least 1956, when Morganti and colleagues[23] reported that men with prostate cancer were more likely to have relatives with prostate cancer than men without a prostate cancer diagnosis. In a study conducted more than 3 decades later, when detailed family histories were collected from men with prostate cancer and their spouses, the men with prostate cancer were more likely to have a brother or father with prostate cancer.[24] Furthermore, the presence of one, two, or three affected family members appeared to increase the risk of prostate cancer to first-degree relatives by two-, five-, and eleven-fold, respectively, while the risk to more distant relatives was only marginally increased.[24] Similar findings have been reported in a number of additional studies. Twin studies, comparing the tendency for concordant prostate cancer development between monozygotic twins, sharing all of their genes, and dizygotic twins, sharing half of their genes, also have hinted at a significant contribution of hereditary to prostate cancer. In one study of 44,788 pairs of twins in Sweden, Denmark, and Finland,[25] 42% of the prostate cancer cases (with a 95% confidence interval of 29% to 50%) were attributed to heredity.

In principle, familial clustering of prostate cancer cases could be a result of inherited susceptibility genes, shared exposure to carcinogenic stresses, or to some sort of detection or diagnosis bias (e.g., the brother of a man diagnosed with prostate cancer may be more likely to pursue screening for prostate cancer). To discriminate these possibilities, several complex segregation analyses have been undertaken testing the mode of prostate cancer inheritance in familial prostate cancer clusters. In one study, rare autosomal dominant prostate cancer genes were predicted to account for as many as 43% of prostate cancer cases before age 55 and some 9% of all prostate cancer cases.[26] In another study, an additional X-linked gene also appeared to be responsible for inherited prostate cancer in certain families.[27] Mendelian inheritance of prostate cancer risk has been further supported by a number of genome-wide screens of polymorphic DNA markers; when data from more than 1233 hereditary prostate cancer families have been combined, several regions of linkage have been identified.[28]

Genetic mapping studies have identified *RNASEL* and *MSR1* as potential prostate cancer susceptibility genes.[29,30] *RNASEL*, a candidate *HPC1*, encodes a latent endoribonuclease component of an interferon-inducible 2′,5′-oligoadenylate-dependent RNA decay pathway that functions to degrade viral and cellular RNA upon viral infection.[31] The evidence that *RNASEL* mutations might predispose to hereditary prostate cancer development included the finding that four brothers with prostate cancer were found to carry *RNASEL* alleles with a base substitution $795^{G\rightarrow T}$, predicted to result in the conversion of a glutamic acid codon to a termination codon at amino acid position 265 ($aa256^{glu\rightarrow X}$), and that four of six brothers with prostate cancer in another family were found to carry *RNASEL* alleles with a base substitution $3^{G\rightarrow A}$, affecting the initiator methionine codon ($aa1^{met\rightarrow ile}$).[29] In addition, in a case-control study, a common polymorphic variant *RNASEL* allele with a base substitution $1385^{G\rightarrow A}$, encoding a less active enzyme (with an amino acid change $aa462^{arg\rightarrow glu}$), was correlated with increased prostate cancer risk ($P = 0.011$).[32] In this study, the polymorphic *RNASEL* allele accounted for as many as 13% of all prostate cancer cases. Provocatively, a new retrovirus, XMRV, has been detected in prostate tissues from men with *RNASEL* defects.[33,34] Whether this virus may lead, directly or indirectly, to prostate cancer in these men has not been determined. *MSR1* encodes subunits of a trimeric class A macrophage scavenger receptor capable of binding bacterial lipopoylsaccharide and lipoteichoic acid, and oxidized high- and low-density serum lipoproteins (oxidized HDL and LDL).[35] For *MSR1*, mutations not only have been linked to prostate cancer susceptibility in some prostate cancer families, but one mutant allele, encoding a receptor subunit polypeptide with an $aa293^{arg\rightarrow X}$ expected to have "dominant negative" function, has been detected in ~3% of non-hereditary prostate cancer (HPC) cases but only 0.4% of unaffected men ($P < 0.05$).[30,36]

The identification of *RNASEL* and *MSR1* as candidate prostate cancer susceptibility genes has intensified interest in the possibility that infection and/or inflammation might contribute to the pathogenesis of human prostate cancer. In mice, targeted disruption of *RnaseL* leads to increased diminished interferon-α activity and increased susceptibility to viral infection,[37] while targeted disruption of *Msr-A* leads to increased vulnerability to infection with *Listeria monocytogenes*, *Staphylococcus aureus*, *Escherichia coli*, and herpes simplex virus type 1.[35,38–40] Further genetic support for this etiologic mechanism has come from analyses of common variants of other genes encoding participants in host inflammatory responses, including *TLR4,* and other members of toll-like receptor signaling pathways, *MIC-1*, *IL1-RN*, and *COX-2*, also have been associated with prostate cancer risk.[41–45]

Androgenic hormones are necessary for prostate growth and development. Thus, it is not surprising that polymorphic variants of genes involved in androgen action, such as *AR*, *CYP17*, and *SRD5A2*, may affect prostate cancer risk. Polymorphic polyglutamine (CAG) repeats, varying in length from 11 to 31 amino acids,[46] and polymorphic polyglycine (GGC) repeats, varying in length from 10 to 22 amino acids, have been described for *AR*. For the polyglutamine repeats, androgen receptors with shorter repeats may possess increased transcriptional *trans*-activation activity.[47] African-Americans, who have higher prostate cancer risks than Asians, also have shorter androgen receptor polyglutamine repeats. Furthermore, genetic epidemiology analyses have correlated high prostate cancer risk with short androgen receptor polyglutamine repeats.[48–51] Variations in androgen receptor polyglycine repeats also may affect prostate cancer risk.[48,50–52]

SRD5A2, encoding the type 2 5α-reductase, the enzyme that generates DHT from testosterone in the prostate, has several polymorphic variants.[53,54] Some variant alleles encoding enzymes with increased activity have been associated with increased prostate cancer risk, and with poor prostate cancer prognosis.[53,55] 5α-reductase variants also may respond differently to inhibition by finasteride, used to treat BPH and under scrutiny as a prostate cancer prevention drug.[56,57] *CYP17*, encoding cytochrome P450c17α, an enzyme that functions to synthesize sex steroids, also has polymorphic variants. One variant allele, with a T→C transition in the transcriptional regulatory region of the gene that creates an Sp1 transcription factor recognition site, has been subjected to both population and genetic linkage analyses for association with prostate cancer, with inconsistent results.[58]

Prostate Cancer Epidemiology

Accumulated epidemiologic evidence implicates the environment as the major contributor to the development of most prostate cancers. Prostate cancer incidence and mortality display wide geographic variation, with high rates of prostate cancer incidence and mortality in the United States and Western Europe, and low prostate cancer risks more characteristic of Asia.[59] African-Americans in the United

States have very high prostate cancer risks.[60] The geographic variation in prostate cancer incidence and mortality can best be explained by lifestyle influences, as Asian immigrants to North America typically adopt higher prostate cancer risks.[61–63]

The key aspect of lifestyle in the United States most likely responsible for high prostate cancer incidence and mortality is the diet, generally rich in animal fats and meats and poor in fruits and vegetables. In the Health Professions Follow-up Study, a prospective cohort study involving 51,529 men, total fat intake, animal fat intake, and consumption of red meats were associated with increased risks of prostate cancer development.[64] Red meat consumption was similarly correlated with prostate cancer risks in the Physicians' Health Study[65] and in a large cohort study in Hawaii.[66] The cooking of red meats at high temperatures, or on charcoal grills, is known to lead to the formation of both heterocyclic aromatic amine and polycyclic aromatic hydrocarbon carcinogens.[67,68] Ingestion of 2-amino-1-methyl-6-phenylimidazopyridine (PhIP), one of the heterocyclic amine carcinogens that appear in "well-done" red meats, leads to prostate cancer in rats.[69] Consumption of dairy products also appears to increase prostate cancer risks, an effect that may be more attributable to calcium intake than to dietary fat or protein.[70]

Consumption of vegetables and antioxidant micronutrients reduces prostate cancer risks. High intake of tomatoes, which contain lycopene, and of cruciferous vegetables, which contain sulforaphane, may protect against prostate cancer development.[71,72] Lycopene likely prevents prostate cancer development by acting as an antioxidant. As part of a recent clinical trial, men were provided tomato sauce-based pasta dishes for three weeks before radical prostatectomy for prostate cancer.[73] For these men, tomato consumption was associated with increased lycopene levels in the blood and in the prostate, with decreased oxidative genome damage in leukocytes and in prostate cells, and with a reduction in serum PSA.[73] Sulforaphane, a compound that can prevent cancer in animals by triggering induction of carcinogen-detoxification enzymes, also can act as an antioxidant.[74–76] In addition to lycopene and sulforaphane, other antioxidants, such as the micronutrients vitamin E and selenium, also may reduce prostate cancer risks.[77–79] A clinical trial of supplementation with vitamin E and selenium to prevent prostate cancer (the SELECT Trial), involving a planned 32,400 men, has just been initiated.[80] The consistent finding of a protective effect of various antioxidants against prostate cancer development suggests that oxidative stresses might contribute to prostatic carcinogenesis. Oxidants can be generated by metabolic processes, by a number of different exposures, and by inflammation.[81,82] Androgens, necessary for normal prostate development and function, have been reported to increase oxidant production in prostate cancer cells.[83,84]

Prostate Inflammation, Proliferative Inflammatory Atrophy, and Prostate Cancer

Chronic or recurrent inflammation is known to play a causative role in the development of many human cancers, including cancers of the liver, esophagus, stomach, large intestine, and bladder. Inflammatory changes have been recognized in prostate tissues for many years, leading to speculation that inflammation might contribute in some way to prostate cancer development.[85] However, over the past few years, evidence has accumulated in support of a more critical role for prostatic inflammation in the pathogenesis of prostate cancer. Inflammatory changes are present in almost all radical prostatectomy specimens from men with prostate cancer. Because inflammation in the prostate usually is not associated with symptoms, the prevalence of prostate inflammation is not known, and the association with prostate cancer has been difficult to test.[86,87] A syndrome of irritative voiding symptoms and pelvic pain, perhaps attributable to inflammation near the prostatic urethra, is reported by about 9% or more of men between 40 and 79 years of age, with as many as 50% of such men suffering more than one episode by age 80 years.[88] Most episodes of symptomatic prostatitis are not clearly attributable to specific infectious agents. Even so, sexually transmitted infections do appear to increase prostate cancer risks.[89,90] Nonetheless, if prostate infection and inflammation lead to prostate cancer, the mechanism does not appear likely to involve direct transformation of prostate epithelial cells by microbial DNA. Instead, the production of microbicidal oxidants by inflammatory cells, such as superoxide, nitric oxide, and peroxynitrite, may promote prostate cancer development by triggering cell and genome damage.[91,92] Increased production of oxidants by inflammatory cells in the prostate may be why decreased prostate cancer risk has been associated with intake of a variety of antioxidants or of nonsteroidal anti-inflammatory drugs, and why *RNASEL* and *MSR1*, the two prostate cancer susceptibility genes identified thus far, encode proteins that function in host responses to infections.

Despite these provocative hints, the contribution of prostate inflammation to prostatic carcinogenesis has been difficult to assess. However, in 1999, De Marzo and associates[93] provided the most compelling linkage of prostate inflammation to prostate cancer by proposing that a prostate lesion might be a precursor to PIN and to prostate cancer (Fig. 88-4). Areas of the prostate containing epithelial cells that do not fully differentiate into columnar secretory cells have long been recognized as focal atrophy lesions by prostate pathologists.[85,94] The term *proliferative inflammatory atrophy (PIA)* has been used to describe those focal atrophy lesions that contain proliferating epithelial cells, are associated with chronic inflammation, and often

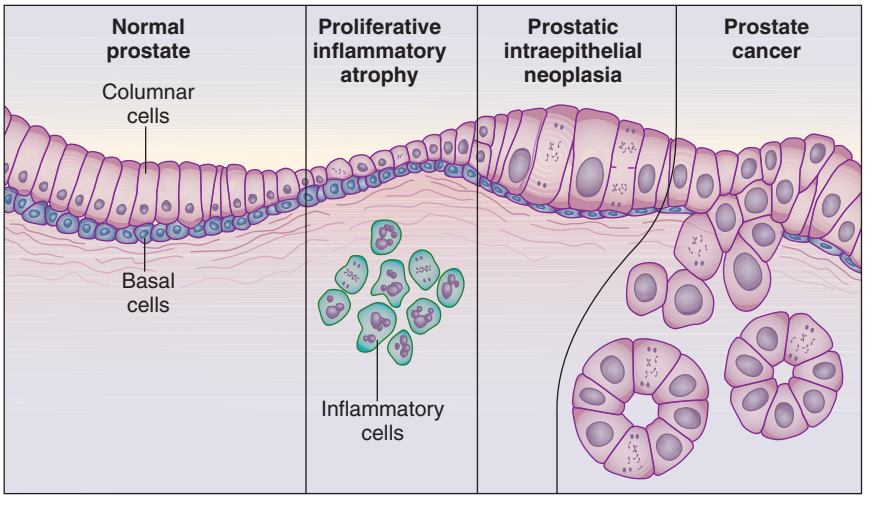


Figure 88-4 • Proliferative inflammatory atrophy (PIA) as a precursor to prostatic intraepithelial neoplasia (PIN) and prostate cancer. (Adapted from Nelson WG, DeMarzo AM, Isaacs WB: Prostate cancer. N Engl J Med 2003;349:366–381.)

Box 88-1. PROSTATE INFLAMMATION AND PROSTATE CANCER

Several lines of evidence have stimulated a renewed interest in the notion that prostate infection and/or inflammation may contribute to the development of prostate cancer. First, two of the inherited susceptibility genes so far identified for prostate cancer, *RNASEL* and *MSR1*, encode proteins that function in host responses to infection. Second, a new candidate prostate cancer precursor lesion, proliferative inflammatory atrophy (PIA), appears to arise as a consequence of prostate inflammation. Third, prostate cancer cells typically acquire defects in genes, like *GSTP1*, that encode enzymes that defend against cell and genome damage inflicted by oxidants, such as those elaborated by inflammatory cells. Finally, epidemiology and early clinical trial data suggest that consumption of a variety of different antioxidants, including selenium, vitamin E, and lycopene, may protect against prostate cancer development.

are located adjacent to PIN lesions and/or prostate cancers.[95] The epithelial cells in PIA lesions typically express high levels of stress-response polypeptides such as GSTP1, GSTA1, and cyclo-oxygenase 2 (COX-2). Loss of GSTP1 expression in rare PIA lesions, attributable to de novo *GSTP1* CpG island hypermethylation, may be what leads to the development of PIN and prostate cancer.[96]

The hypothesis that inflammation might promote prostate cancer development offers new challenges to prostate cancer epidemiology, to the search for prostate cancer susceptibility genes, and to the molecular pathogenesis of prostate cancer (Box 88-1). Although prostatic inflammation is common in regions of the world with high prostate cancer risks, whether regions of the world with low prostate cancer risks have less prostatic inflammation has not been determined. New strategies for assessing the presence and extent of PIA and of prostate inflammation may be needed. Perhaps new biomarkers of prostate inflammation, assayable in blood, urine, or prostate fluid, can be developed for use in epidemiology studies. In addition, it probably will be necessary to evaluate polymorphic genes encoding regulators of immune responses systematically for prostate cancer risk associations. As for prostate cancer pathogenesis, PIA lesions, appearing to arise in response to prostatic inflammation or some other noxious stimulus, may be precursors to PIN and/or prostate cancer.[97] However, whether prostatic inflammation is initiated in response to a prostatic infection or to some other provocation has not been ascertained. Finally, whether prostate cancer risks can be reduced by therapeutically attenuating prostate inflammation must be tested in clinical trials.

MOLECULAR PATHOGENESIS OF PROSTATE CANCER

Somatic Genome Alterations in Prostate Cancer Cells

Prostate cancer cells typically contain a plethora of somatic genome alterations, including gene mutations, gene deletions, gene amplifications, chromosomal rearrangements, and changes in DNA methylation (Fig. 88-5). In the United States, prostate cancer diagnoses typically are made in men 60 to 70 years of age, while small prostate cancers have been detected at autopsy in nearly 30% of men between 30 and 40 years of age.[4] Thus, the somatic genome changes present in prostate cancers often have accumulated over many decades. The acquisition of somatic genome changes in the prostate may be influenced by lifestyle as well: although small prostate cancers have been detected at autopsy in men from geographic regions with low prostate cancer mortality, these small prostate cancers usually are present only in much older men.[98–100] In the United States, prostates removed at radical prostatectomy for prostate cancer usually contain more than one prostate cancer lesion. Several techniques, including karyotyping, fluorescence in situ hybridization (FISH), comparative genome hybridization, and loss of heterozygosity analyses, have been used to catalog somatic genome changes in prostate cancers. Often, these analyses reveal different chromosomal abnormalities in different cancer cases, in different cancer lesions in the same cancer case, and in different areas within the same cancer lesion (Fig. 88-6). Chromosomal abnormalities, including gains and losses, tend to be distributed throughout the genome.[101] The propensity to develop such a heterogeneous collection of somatic genome lesions over so many years, and in a manner so sensitive to environment and lifestyle, suggests strongly that prostate cancers likely arise as a consequence of either chronic or recurrent exposure to genome-damaging stresses, defective protection against genome damage, or some combination of both processes. The resultant genomic instability may be the

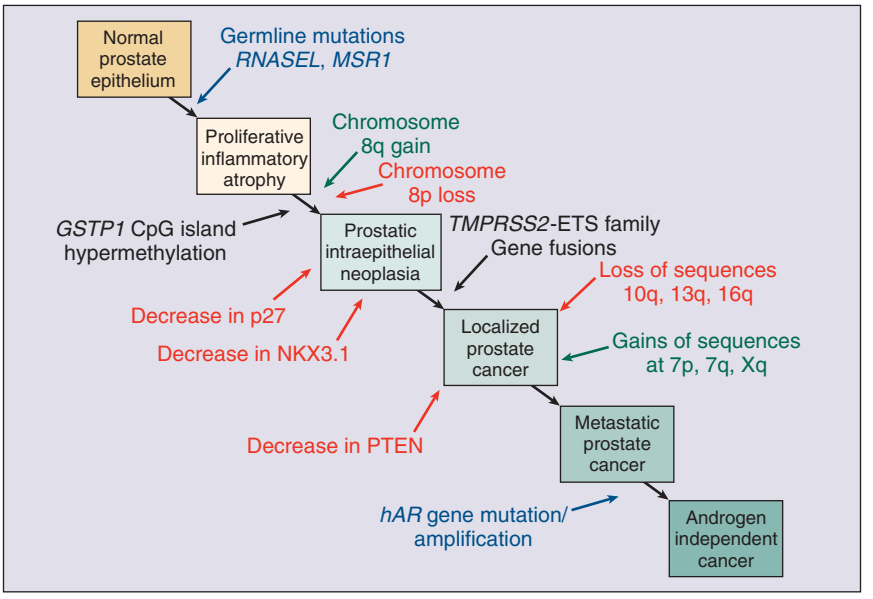


Figure 88-5 • The molecular pathogenesis of prostate cancer.

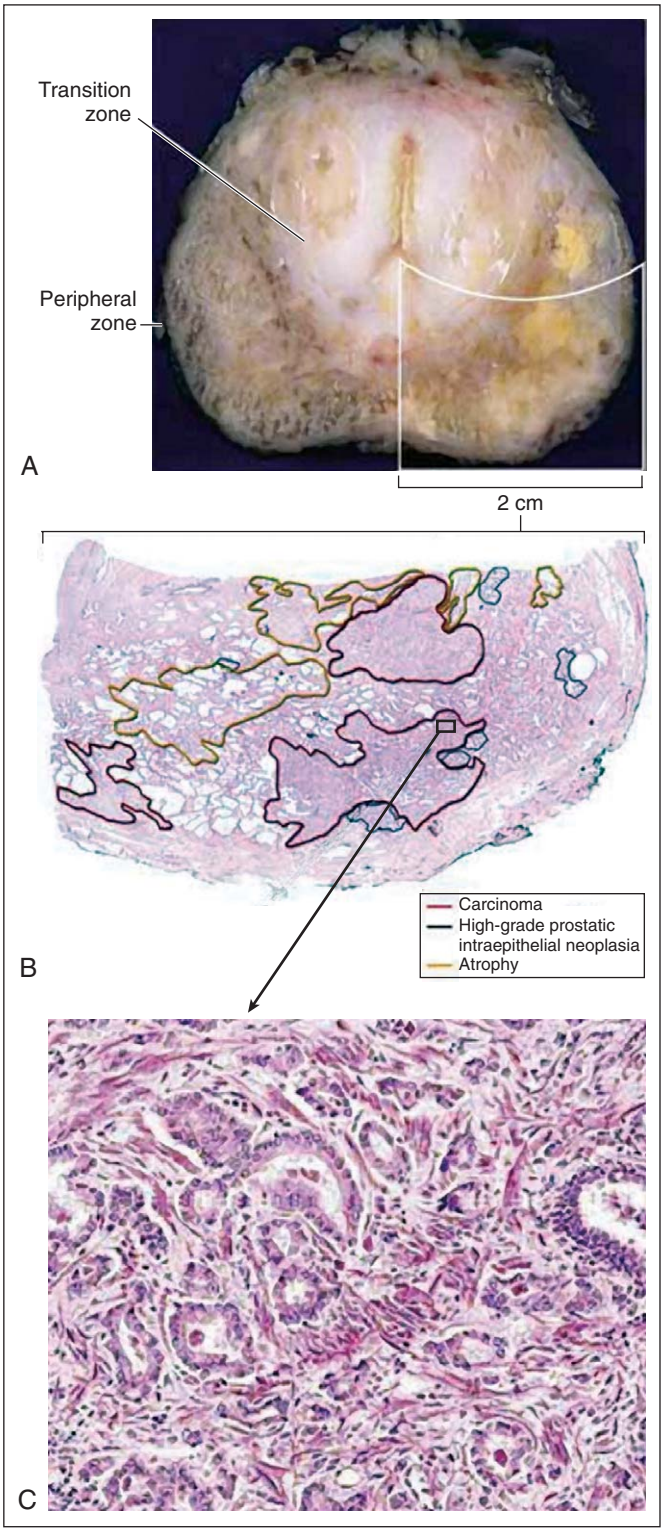


Figure 88-6 • Multiple foci of prostate cancer, and of prostate cancer precursor lesions, in the peripheral zone of the prostate. (From Nelson WG, DeMarzo AM, Isaacs WB, et al: Prostate cancer. N Engl J Med 2003;349:366–381, with permission.)

reason some prostate cancers progress to become life-threatening. Although most prostate cancers initially respond well to therapeutic reductions in circulating androgens, the cancers ultimately become androgen-independent, a process likely resulting from selection of pre-existing variant androgen-independent cancer cell clones, spontaneously generated via the acquisition of critical somatic genome changes.[102,103]

One newly described somatic genome alteration drives the production of fusion transcripts between an androgen-regulated gene, *TMPRSS2*, at chromosome 21q22, and members of the ETS family of transcription factors (Fig. 88-7).[22] Fusion partners for *TMPRSS2* include *ERG* (also at chromosome 21q22), *ETV1* (at chromosome 7p21), and *ETV4* (at chromosome 17q21).[22,104,105] The occurrence of these fusion transcripts provides a plausible mechanism for the dependence of prostate cancer cells on androgenic hormones for growth and survival, as the expression of ETS family transcription factors can be stimulated by androgen action. *TMPRSS2-ERG* fusions have been detected in about 60% of prostate cancers and in more than 20% of PIN lesions.[106] *ERG* is highly expressed by many prostate cancers, although whether *ERG* expression or the presence of *ERG* fusion transcripts has an impact on the prognosis of prostate cancer has not been determined.[106–109]

Hypermethylation of CpG island sequences encompassing the regulatory region of *GSTP1*, encoding the π-class glutathione *S*-transferase (GST) is the most common somatic genome change yet reported for prostate cancer.[110,111] GSTs catalyze the detoxification of carcinogens, and of other reactive chemical species, via conjugation with the intracellular scavenger glutathione. In mice, targeted disruption of π-class GST genes leads to increased skin tumors after treatment with the carcinogen 7,12 dimethylbenz anthracene (DMBA).[113] Similarly, human prostate cancer cells devoid of GSTP1 appear especially vulnerable to genome damage mediated by exposure to *N*-OH-PhIP, the charred meat carcinogen that causes prostate cancer when fed to rats, and by exposure to oxidant stresses.[114] In the normal prostate epithelium, GSTP1 is present in basal cells, but in lower amounts than in columnar secretory cells, although the enzyme can be induced in columnar epithelial cells subjected to genome-damaging stresses. In contrast, the enzyme is almost never

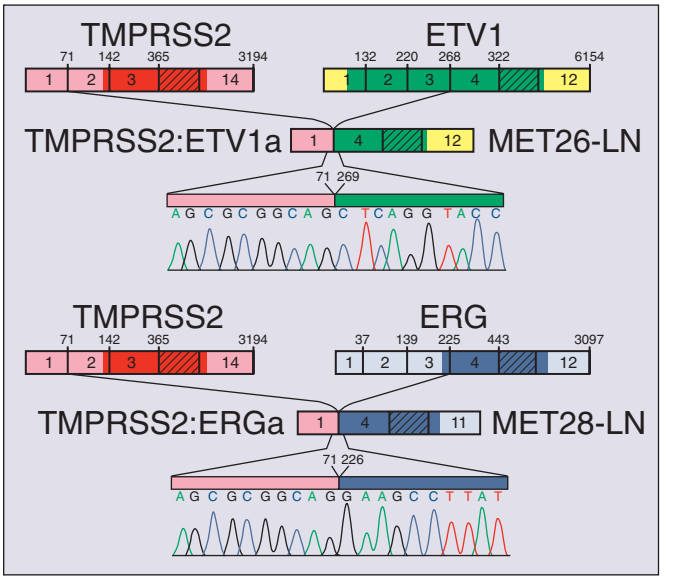


Figure 88-7 • Fusion of transcripts from the androgen-regulated *TMPRSS2* gene and ETS family genes *ETV1* and *ERG* in prostate cancers. (Adapted from Tomlins SA, Rhodes DR, Perner S, et al: Recurrent fusion of TMPRSS2 and ETS transcription factor genes in prostate cancer. Science 2005;310:644–648).

present in prostate cancer cells. For more than 90% of prostate cancer cases, this absence of GSTP1 expression in prostate cancer cells can be attributed to hypermethylation of *GSTP1* CpG island sequences, a somatic genome change that prevents *GSTP1* transcription. Absence of GSTP1 expression and *GSTP1* CpG island hypermethylation also may be characteristic of cells comprising PIN lesions, thought to be precursors to prostate cancer.[115] The mechanism by which hypermethylated *GSTP1* CpG island alleles arise during prostatic carcinogenesis remains to be elucidated. Nonetheless, prostate cells carrying inactivated *GSTP1* genes appear to enjoy some sort of selective growth advantage early during the development of prostate cancer.

NKX3.1 encodes a prostate-specific homeobox gene essential for normal prostate development that may be a target for somatic loss on chromosome 8p21.[116] NKX3.1 has been shown to bind DNA and to repress *PSA* expression via interactions with ETS transcription factors.[117,118] Mice carrying one or two disrupted *Nkx3.1* alleles manifest prostatic epithelial hyperplasia and dysplasia.[119,120] In men, loss of 8p21 DNA sequences occurs early during prostatic carcinogenesis, with 63% of PIN lesions and more than 90% of prostate cancers showing loss of heterozygosity at polymorphic 8p21 marker sequences in one report.[121] However, although mapping studies have indicated that *NKX3.1* lies within a common region of deletion, encompassing two megabases at 8p21, molecular pathology analyses have not yet established *NKX3.1* as a somatic target for inactivation during prostatic carcinogenesis because somatic *NKX3.1* mutations have not been identified. Nonetheless, loss of NKX3.1 expression does appear to accompany prostate cancer progression.

PTEN, a tumor suppressor gene encoding a phosphatase active against both proteins and lipid substrates, appears to be a common target for somatic alteration during prostate cancer progression.[122–129] PTEN is an inhibitor of the phosphatidylinositol 3′-kinase/protein kinase B (PI3K/Akt) signaling pathway needed for cell cycle progression and cell survival. Although PTEN is expressed by normal prostate epithelial cells, and by cells present in PIN lesions, the expression of PTEN is often diminished in prostate cancers, with many prostate cancers containing collections of neoplastic cells with no PTEN.[130] *PTEN* defects have been found in a wide variety of cancers and cancer cell lines.[124] For prostate cancer, a number of somatic *PTEN* alterations have been reported, including homozygous deletions, loss of heterozygosity, mutations, and probable CpG island hypermethylation. However, despite common losses of 10q sequences near *PTEN* in prostate cancers, somatic mutations at the remaining *PTEN* alleles are not as frequent. In a study of prostate cancer metastases recovered at autopsy, somatic *PTEN* alterations were even more common than in primary prostate cancers, and a significant heterogeneity in *PTEN* defects in different metastatic deposits from the same patient was also evident.[129] Haploinsufficiency for *PTEN* may contribute to the phenotype of transformed cells in the prostate. *Pten*$^{+/-}$ mice display prostatic hyperplasia and dysplasia, and crosses of *Pten*$^{+/-}$ mice with *Nkx3.1*$^{+/-}$ mice have revealed that *Pten*$^{+/-}$*kx3.1*$^{+/-}$ mice and *Pten*$^{+/-}$ *kx3.1*$^{-/-}$ mice develop lesions reminiscent of human PIN.[131–133]

Defective regulation of p27, a cyclin-dependent kinase inhibitor encoded by *CDKN1B*, also may accompany prostatic carcinogenesis.[134,135] In PIN cells and prostate cancer cells, p27 levels almost always are diminished, although the mechanism(s) for the reduction in p27 levels appear complex: somatic loss of DNA *CDKN1B* sequences at 12p12–13 has been reported for only 23% of localized prostate cancers, 30% of prostate cancer lymph node metastases, and 47% of distant prostate cancer metastases.[136] In place of *CDKN1B* gene alterations, p27 polypeptide levels may be lowered indirectly by inadequate PTEN repression of the PI3K/Akt signaling pathway.[137–139] In this way, low p27 levels may be as much a result of loss of PTEN function as of *CDKN1B* alterations. The critical contribution of PTEN to epithelial growth regulation in the prostate is evident in mice, where disruption of *Cdkn1b* alleles leads to prostatic hyperplasia, and *Pten*$^{+/-}$*dkn1b*$^{-/-}$ mice develop prostate cancer by 3 months of age.[134,140]

Metastatic prostate cancer almost always is treated with androgen deprivation, anti-androgens, or a combination of androgen deprivation and anti-androgens.[141,142] However, despite such treatment, androgen-independent prostate cancer cells eventually emerge and progress to threaten life. Curiously, in these cells, androgen receptor expression and androgen receptor signaling remain intact despite the absence of androgens.[21,143] Somatic alterations of *AR* have been reported for many prostate cancers, especially for androgen-independent prostate cancers. *AR* amplification, accompanied by high-level expression of androgen receptors, may promote the growth of androgen-independent prostate cancer cells by increasing the sensitivity of the cells to low androgen levels.[144] *AR* mutations encoding androgen receptors with altered ligand specificity also have been detected; for some of the mutant androgen receptors, even anti-androgens can act as agonist ligands.[145–147] When 44 mutant androgen receptors from prostate cancers were evaluated for transcriptional regulatory capabilities, 16% of the receptors had lost transcriptional activation activity, 45% of the receptors had gained some transcriptional regulatory ability, 32% of the receptors maintained some partial transcriptional modulatory activity, and the remaining 7% behaved like wild-type receptors.[148] In addition to somatic *AR* gene changes, androgen-independent prostate cancer cells with wild-type androgen receptors may activate androgen receptor signaling even in the absence of androgens, via post-translational modifications of the androgen receptor and/or androgen receptor co-activators in response to other growth factor signaling pathways.[21,149–152]

Changes in Gene Expression in Prostate Cancers

Alterations in gene expression in prostate cancers have been catalogued using cDNA microarray technologies.[153–164] Among the many genes exhibiting over- or underexpression in prostate cancers, the products of at least two genes appear consistently increased, and the product of a third gene appears to become elevated during androgen-independent progression. Hepsin, located at 19q11–13.2, encodes a transmembrane serine protease, expressed at high levels in many normal tissues.[165] Hepsin may contribute to prostate cancer progression: forced overexpression of hepsin in mouse prostates leads to disorganization of the epithelial basement membrane and increased metastasis.[166] α-Methylacyl-CoA racemase (AMACR), a mitochondrial and peroxisomal enzyme that acts on pristanoyl-CoA and C27-bile acyl-CoA substrates to catalyze the conversion of *R*- to *S*-stereoisomers in order to permit metabolism by β-oxidation, has been reported to be overexpressed in almost all prostate cancers.[167,168] Germline *AMACR* mutations lead to adult-onset neuropathy.[169] Immunohistochemistry studies, which have revealed that AMACR occasionally is present in normal prostate cells, increased in PIN cells, and further elevated in prostate cancer cells, have prompted the use of antibodies against AMACR as tools for prostate cancer diagnosis by surgical pathologists.[168,170] The polycomb protein enhancer of zeste homolog 2 (EZH2), a transcriptional regulatory protein, is elevated in metastatic androgen-independent prostate cancer.[171] The mechanism by which EZH2 contributes to prostate cancer progression has not been established. However, elevated EZH2 expression in primary prostate cancers portends a poor prognosis.[171]

Telomere Shortening During Prostatic Carcinogenesis

Telomeres, containing repeat DNA sequences at the termini of chromosomes, protect against loss of chromosome sequences during genome replication. DNA ends tend to shorten each generation as a consequence of bidirectional DNA synthesis (the "end-replication" problem); the telomere repeat sequences serve as templates for the enzyme telomerase, which can extend the chromosome termini and maintain chromosome integrity through cell division.[172] Growth dysregulation accompanying the development of most human cancers

tends to lead to cell proliferation in the absence of telomerase, and to shortened chromosome telomeres.[173] Critically shortened telomere sequences may promote genome instability by increasing illegitimate DNA recombination.[174,175] Mice carrying disrupted genes needed for a functioning telomerase show increased numbers of cancers, especially when crossed to mice with defective *p53* genes.[176] In the prostate, short telomere repeat sequences appear characteristic of cells in both PIN lesions and prostate cancer.[177–179] At some point, most cancer cells activate the expression of telomerase, providing some maintenance of chromosome termini. Telomerase expression has been detected in prostate cancers, but not at high levels in normal prostate tissues or in BPH.[177]

PREVENTION OF PROSTATE CANCER

The high lifetime risks of prostate cancer development, the morbidities associated with treatment of established prostate cancer, and the inability to eradicate life-threatening metastatic prostate cancer offer compelling reasons for prostate cancer prevention. In addition, epidemiology data, indicating a dominant role for lifestyle factors in prostate cancer development, suggest that prostate cancer risk modification may be feasible, if only through lifestyle modification. Also, because prostatic carcinogenesis takes many decades, there may be a broad window of opportunity to make lifestyle changes in an effort to retard prostate cancer development. Clearly, although the specific lifestyle factors fostering prostate cancer development have not been conclusively identified, it is likely that consumption of a diet rich in fruits, vegetables, and antioxidant micronutrients, and poor in saturated fats and "well-done" red meats, may significantly reduce risks of prostate cancer development, and of the development of other diseases characteristic of life in the developed world. Nonetheless, as the etiology of prostate cancer is better understood, new opportunities for prostate cancer prevention will arise. For example, if prostate inflammation contributes to prostate cancer development, anti-inflammatory drugs might be considered candidate prostate cancer prevention drugs. For drugs to be developed and tested for prostate cancer prevention, randomized clinical trials, capable of assessing both drug safety and drug efficacy, will be required.[180] Ideally, such trials can be targeted at men with a high risk for prostate cancer development, analogous to women thought to be at high risk for breast cancer development identified by the Gail model.[181] Thus far, two classes of agents, 5α-reductase inhibitors and antioxidant micronutrients, have been subjected to large randomized clinical trials.

Prostate Cancer Prevention Trial

In the Prostate Cancer Prevention Trial (PCPT), the propensity for the type 2 5α-reductase inhibitor finasteride to reduce the prevalence of prostate cancer in healthy men age 55 years and older when given for 7 years was tested.[57] Finasteride, which has been marketed both for BPH and for alopecia, was known to have few worrisome side effects and to lower the serum PSA in some men with prostate cancer.[182,183] Also, 5α-reductase inhibitors had shown promising activity in preventing prostate cancer development and/or prostate cancer progression in animal models.[184–186] However, the effects of finasteride on prostate cancer development in various clinical trials have not been as encouraging. In one randomized placebo-controlled trial, in which finasteride was used to treat BPH ($N = 3040$), 4.7% of men treated with finasteride and 5.1% of men treated with placebo ultimately were diagnosed with prostate cancer ($P = 0.7$).[187] In another randomized trial ($N = 52$), 30% of men with an elevated serum PSA but no cancer on an initial prostate biopsy who were given finasteride for 12 months had cancer on a subsequent prostate biopsy versus 4% of men who did not receive finasteride.[188] In this small trial, finasteride also had little beneficial activity in men with PIN.[188] For PCPT, 18,882 men with a PSA of 3.0 ng/mL or less and a normal digital rectal examination were randomized to treatment with finasteride (5 mg/day) or to placebo.[57] While on-study, men with a PSA elevation or an abnormal rectal examination were subjected to prostate biopsy; in addition, at the end of the treatment period, a prostate biopsy was planned for all of the men in the trial. The Data and Safety Monitoring Committee for PCPT closed the study 15 months before the anticipated completion, with some 9060 men evaluable for the presence of prostate cancer.[57] Prostate cancer was detected in 18.4% of the men treated with finasteride versus 24.4% of men receiving placebo ($P < 0.001$).[57] Of concern, however, high-grade prostate cancers appeared more commonly associated with finasteride treatment than with placebo (6.4% versus 5.1%).[57] This may mean that finasteride prevents or treats low-grade cancers better than high-grade cancers. Also, some 37% of men treated with finasteride, versus 29% of men receiving placebo ($P < 0.001$), discontinued treatment, usually citing side effects of reduced ejaculate volume, erectile dysfunction, loss of libido, and gynecomastia.[57] These mixed results—a reduction in overall prostate cancer prevalence, but an increase in high-grade prostate cancers—associated with finasteride treatment make recommendations for healthy men who want to reduce their prostate cancer risks very difficult. A large clinical trial testing the effects of dutasteride, an inhibitor of both type 1 and type 2 5α-reductases used to treat BPH, on prostate cancer development is ongoing.[189]

Selenium and Vitamin E Cancer Prevention Trial

Epidemiologic studies have provided compelling evidence that intake of selenium and of vitamin E might diminish prostate cancer risks.[190–196] In addition, two clinical trials have provided further evidence for protection against prostate cancer through consumption of these antioxidant micronutrients.[77–79,112,197] In one of the studies, men and women ($N = 1312$) with a history of nonmelanoma skin cancer received 200 μg selenized brewer's yeast or a placebo daily to ascertain whether selenium consumption might decrease the risk of a second skin cancer.[78] Although selenium supplementation failed to prevent new skin cancers, a reduced risk of prostate cancer was noted for men receiving selenium supplements, particularly men with low baseline selenium levels.[77,78,197] In the other study, α-tocopherol, β-carotene, the combination of α-tocopherol and β-carotene, or placebo was administered to male smokers ($N = 29,133$) in Finland for lung cancer prevention.[112] Again, although neither of the supplements appeared to prevent lung cancer, a reduced risk of prostate cancer was evident for men receiving α-tocopherol.[79,112]

A prospective, randomized, placebo-controlled clinical trial of selenium and vitamin E, the Selenium and Vitamin E Cancer Prevention Trial (SELECT; $N > 32,400$) was initiated in 2001 to test the ability of the antioxidant micronutrients to prevent prostate cancer.[198] Selenium (200 μg selenomethionine), α-tocopherol (400 mg), the combination of selenium and α-tocopherol, or neither, will be given to men randomized to four different treatment groups, using a 2×2 factorial design, for 7 to 12 years.[198] The trial subjects will be men, age 55 years or older (50 years or older for African Americans), with an unremarkable digital rectal examination and a serum PSA of 4 ng/mL or less.[198] Until the SELECT results are available, it will be difficult to make definitive recommendations about micronutrient supplementation to prevent prostate cancer. Nonetheless, the limited data available from epidemiology studies and early clinical trials suggest that men with low blood levels of the micronutrients tend to be at the highest risk for prostate cancer development, and that micronutrient supplementation might be most effective at preventing prostate cancer if given to such men.[191,192,196,197] For this reason, perhaps a supplementation strategy designed to correct antioxidant micronutrient deficiencies might ultimately prove generally safe and effective. The risks and benefits of high doses of antioxidant micronutrients, or other supplements, are not known.

PROSTATE CANCER SCREENING, DIAGNOSIS, AND STAGING

Clinical Evaluation

The staging system for prostate cancer includes the results of histopathology analysis and of imaging studies in the stage assignment (Table 88-1).

Prostate cancer rarely causes symptoms early in the course of the disease, because most of the adenocarcinomas arise in the periphery of the gland (the peripheral zone) distant from the urethra. The presence of symptoms attributable to prostate cancer suggests locally advanced or metastatic disease. With progressive growth of prostate cancer into the urethra, or into the bladder neck, lower urinary symptoms of obstruction (e.g., urinary hesitancy, decreased force of urine stream, intermittency) and irritation (e.g., urinary frequency, nocturia, urgency, urge incontinence) can occur. Local progression of prostate cancer and obstruction of the ejaculatory ducts can result in hematospermia and a decrease in the ejaculate volume. Extension of prostate cancer outside the prostate capsule can damage the branches of the pelvic plexus (neurovascular bundle) responsible for innervation of the corpora cavernosa and cause erectile dysfunction.

Metastatic cancer involving the axial or appendicular skeleton can lead to bone pain, or, via replacement of the bone marrow, can cause pancytopenia. Lower extremity edema can result from cancerous involvement of the pelvic lymph nodes and compression of the iliac veins. Less common consequences of metastatic disease include malignant retroperitoneal fibrosis from dissemination of cancer cells along the periureteral lymphatics, paraneoplastic syndromes from ectopic hormone production by small cell variants of adenocarcinoma, and disseminated intravascular coagulation (DIC).

Although men with prostate cancer can present with voiding symptoms suggesting locally advanced cancer, or with signs and symptoms suggesting metastatic cancer, currently more than 90% of men diagnosed with prostate cancer are initially detected as a result of digital rectal examination (DRE) abnormalities or of serum PSA elevations.

Digital Rectal Examination

In men with early-stage prostate cancers, physical findings, if present, usually are limited to an abnormal DRE, used for both diagnosis and staging. Palpable areas of induration, or asymmetric firmness of the gland, suggest the presence of prostate cancer, but these findings can also be caused by prostate inflammation (especially granulomatous prostatitis), by BPH, and by prostatic stones. DRE has only fair reproducibility in the hands of experienced examiners.[199] When used alone for detection of prostate cancer, DRE misses 23% to 45% of the cancers that are subsequently detected by prostate biopsies done for serum PSA elevations or for transrectal ultrasound (TRUS) abnormalities.[200–202] In addition, prostate cancers detected by DRE are at an advanced pathological stage in more than 50% of men.[203,204]

The positive predictive value of DRE (the fraction of men who have prostate cancer if the DRE is abnormal) depends on age, race, and PSA level.[205,206] African-American race, older age, and higher PSA levels are associated with a higher positive predictive value for DRE.[206] The positive predictive value of a suspicious DRE was 5%, 14%, and 29% in white men, and 8%, 37%, and 50% in black men with PSA levels of 0 to 1.0, 1.1 to 2.5, and 2.6 to 4.0 ng/mL, respectively (Table 88-2). The positive predictive value of a suspicious DRE ranged from 33% to 83% in men with PSA levels of 3.0 to 9.9 ng/mL or more.[200–202,207–211] A prostate biopsy usually is recommended for men with an abnormality on DRE that is suspicious for prostate cancer, regardless of the PSA level.

Serum Prostate-Specific Antigen

PSA is a member of the human kallikrein gene family of serine proteases encoded by genes located on chromosome 19.[212] A component

Table 88-1 TNM and AUA Staging Systems for Prostate Cancer

TNM STAGING SYSTEM

PRIMARY TUMOR (T)

- TX Primary tumor cannot be assessed.
- T0 No evidence of primary tumor
- T1 Clinically inapparent tumor neither palpable nor visible by imaging
  - T1a Tumor incidental histologic findings in ≤5% of tissue resected
  - T1b Tumor incidental histologic finding in >5% of tissue resected
  - T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)
- T2 Tumor is confined within prostate.*
  - T2a Tumor involves one half of a lobe or less
  - T2b Tumor involves more than one half of lobe, but not both lobes
  - T2c Tumor involves both lobes†
- T3 Tumor extends through the prostate capsule.
  - T3a Unilateral extracapsular extension
  - T3b Bilateral extracapsular extension
  - T3c Tumor invades seminal vesicle(s)
- T4 Tumor is fixed or invades adjacent structures other than seminal vesicles.
  - T4a Tumor invades bladder neck, external sphincter, or rectum.
  - T4b Tumor invades levator muscles or is fixed to pelvic wall, or both.

NODE (N)

- NX Regional lymph nodes cannot be assessed.
- N0 No regional node metastasis
- N1 Metastasis in single lymph node, ≤2 cm
- N2 Metastasis in a single node, >2 cm but ≤5 cm
- N3 Metastasis in a node >5 cm

METASTASIS (M)

- MX Presence of metastasis cannot be assessed.
- M0 No distant metastasis
- M1 Distant metastasis
  - M1a Nonregional lymph node(s)
  - M1b Metastasis in bone(s)
  - M1c Metastasis in other site(s)

AUA STAGING SYSTEM

STAGE A: CLINICALLY UNSUSPECTED DISEASE

- A1 Focal carcinoma, well differentiated
- A2 Diffuse carcinoma, usually poorly differentiated

STAGE B: TUMOR CONFINED TO PROSTATE GLAND

- B1 Small, discrete nodule of one lobe of gland
- B2 Large or multiple nodules or areas of involvement

STAGE C: TUMOR LOCALIZED TO PERIPROSTATIC AREA

- C1 Tumor outside prostate capsule, estimated weight ≤70 g, seminal vesicles uninvolved
- C2 Tumor outside prostate capsule, estimated weight >70 g, seminal vesicles involved

STAGE D: METASTATIC PROSTATE CANCER

- D1 Pelvic lymph node metastases or ureteral obstruction causing hydronephrosis, or both
- D2 Bone, soft tissue, organ, or distant lymph node metastases

AUA, American Urological Association; PSA, prostate-specific antigen; TNM, tumor-node-metastasis.

*Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified as T2, not as T3.

†Tumor found in one or both lobes by needle biopsy but not palpable or visible by imaging is classified as T1c.

Table 88-2 Positive Predictive Value of DRE and PSA in a Multicenter Screening Trial

DRE	PSA	PPV (%)
Abnormal	Any	21.4
Any	PSA >4	31.5
	4–10	26.1
	>10	52.9
Normal	PSA >4	24.4
Abnormal	PSA <4	10.0
	4–10	40.8
	>10	69.1

DRE, digital rectal examination; PPV, positive predictive value; PSA, prostate-specific antigen.

Data from Catalona WJ, Richie JP, Ahmann FR, et al: Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicenter clinical trial of 6,630 men. J Urol 1994;151:1283.

of the ejaculate, PSA is produced by columnar secretory cells in the prostate. PSA expression is regulated by androgens, becoming detectable in serum at puberty accompanying increases in luteinizing hormone and testosterone. In the absence of prostate cancer, serum PSA levels increase with age and prostate volume and usually are higher in African-American men. Cross-sectional population data suggest that the serum PSA increases 4% per mL of prostate volume, and that 30% and 5% of the variance in PSA can be accounted for by prostate volume and age, respectively.[213]

Serum PSA elevations likely occur as a result of disruption of the normal prostate architecture, permitting PSA to diffuse into the prostate parenchyma and gain access to the circulation. This can occur in the setting of both benign and malignant prostate diseases (prostatitis, BPH, and prostate cancer) and as a result of prostate manipulation (prostate massage and prostate biopsy).[214] Although the presence of some type of prostate disease is the most important determinant driving elevation of the serum PSA, an increased serum PSA *is not specific for prostate cancer*. Furthermore, not all men with prostate disease have elevated serum PSA levels.

Treatments targeting the prostate gland (for BPH or for prostate cancer) can lower serum PSA by decreasing the number of prostatic epithelial cells capable of producing PSA, and by decreasing the amount of PSA produced by each cell. Modulation of sex steroid hormone levels for treatment of BPH or prostate cancer, radiation therapy for prostate cancer, and surgical ablation of prostate tissue for BPH or prostate cancer can all lead to decreases in serum PSA. 5α-reductase inhibitor such as finasteride and dutasteride lower PSA levels by 50% after 12 months of treatment.[215] Thus, for men treated with these agents for 12 months or more, the serum PSA level should be doubled to estimate the "true" PSA value. Interpretation of serum PSA values should always take into account the presence of prostate disease, previous diagnostic procedures, and prostate-targeted treatments.

Numerous studies have documented the validity of serum PSA testing as a strategy for assessing the risk that prostate cancer is present. Routine use of serum PSA testing increases the detection of prostate cancer over that of DRE, improves the predictive value of the DRE for cancer, and leads to detection of prostate cancers at an early stage. The lead time (time by which a cancer diagnosis is advanced) with PSA screening has been estimated to be, on average, ~10 years.[216,217] As a result of the lead time associated with PSA screening, most men today are diagnosed with early-stage disease that is considered appropriate for curative intervention with radiation or surgery. The extent to which PSA screening has contributed to the decline in prostate cancer mortality that began in the early 1990s, and whether early detection of prostate cancer does more harm than good, are being debated.[218]

The serum PSA value is correlated directly with prostate cancer risk.[201] Gann and coworkers first showed that the risk of a cancer diagnosis increases incrementally and directly with PSA over the decade after a baseline measurement, even at low PSA levels (below 4.0 ng/mL), a finding that has now been confirmed by many others, including recent data from the PCPT.[219,220] These observations emphasize that the serum PSA should be used not as a dichotomous test, but rather as a test that represents a continuum of prostate cancer risk. The probability that prostate cancer is present varies according to PSA and DRE results (see Table 88-2).

The most effective method for early detection of prostate cancer is the combined use of DRE and serum PSA testing. When DRE and the serum PSA are used as screening tests for prostate cancer, detection rates are higher with serum PSA determinations than with DRE alone, and highest with a combination of both tests. Because DRE and serum PSA determinations are not always simultaneously abnormal in the presence of prostate cancer, the tests are complementary when used for prostate cancer detection. Experts disagree on the use of DRE for screening when PSA levels are very low, because in that setting, the DRE has a relatively poor positive predictive value.

The widespread use of PSA for early detection of prostate cancer has stimulated efforts to improve the sensitivity (i.e., the percentage of men correctly identified as having prostate cancer among those with the disease) and specificity (i.e., the percentage of men correctly identified as free of prostate cancer among those without the disease) of the test. Altering the serum PSA threshold value used to trigger prostate biopsy, adjusting the PSA level for the prostate volume (the PSA "density"),[221–228] monitoring the rate of change in serum PSA values over time (the PSA "velocity"),[229–231] and the selective assay of various molecular forms of PSA in the serum[232,233] have all been evaluated as methods of distinguishing prostate cancer from BPH and other prostate diseases.

Prostate-Specific Antigen Threshold for Prostate Biopsy

The choice of a serum PSA threshold value or "cut-point," above which further evaluation to rule out prostate cancer (by prostate biopsy) should be recommended historically has been a controversial issue. However, it is now widely recognized that there is virtually no serum PSA value below which prostate cancer, even an aggressive-appearing prostate cancer, can be excluded as a diagnosis.[234] Thus, there has been a greater emphasis on using serum PSA testing as part of a risk assessment algorithm that might include age, race, PSA velocity, etc.[235,236] Physicians should discuss the likelihood of a prostate cancer diagnosis, given the serum PSA level and these other factors, with those men who have chosen to undergo serum PSA testing before recommending further evaluation.

Prostate-Specific Antigen "Density"

The major source of serum PSA in men without prostate cancer is the transition zone (TZ) epithelium, not the epithelium of the peripheral zone.[237] Since BPH represents an enlargement of the transition zone, and since serum PSA levels are largely a reflection of transition zone volume in men with BPH, adjusting the serum PSA for either prostate volume (PSA density) or more specifically, the transition zone volume (PSA-TZ), has been shown to improve the detection of prostate cancer (Table 88-3). Volume adjustment of the serum PSA value is used most often to determine the need for a repeat biopsy in men with a prior negative biopsy, a clinical setting in which a missed cancer is suspected because of a persistently elevated serum PSA.[238]

Prostate-Specific Antigen "Velocity"

Carter and colleagues,[229] using frozen serum samples from an aging study cohort, demonstrated that PSA "velocity" (PSAV; the rate of

Table 88-3 Age-Specific Reference Ranges for Serum PSA and PSA Density

Age Range (yr)	Serum PSA (ng/mL)	PSA Density (ng/mL)
40–49	0.0–2.5	0.0–0.10
50–59	0.0–3.5	0.0–0.12
60–69	0.0–4.5	0.0–0.14
70–79	0.0–6.5	0.0–0.16

PSA, prostate-specific antigen.

Data from Osterling J, Jacobsen S, Klee G, et al: Free, complexed, and total serum prostate specific antigen: the establishment of appropriate reference ranges for their concentrations and ratios using newly developed immunofluorometric assays (IFMA). J Urol 1995;154:1090, with permission.

change of serum PSA in ng/mL per year on repeated testing) was higher among men destined to be diagnosed with prostate cancer, even at a time when serum PSA levels could not distinguish between men with and without the disease (Fig. 88-8). For men with serum PSA levels between 4.0 and 10.0 ng/mL at 5 years before prostate cancer diagnosis, a PSAV of 0.75 ng/mL per year or greater had a specificity of 90% percent for distinguishing men with prostate cancer in the setting of BPH, and a specificity of 100% for distinguishing men with prostate cancer and no BPH. Not only has PSAV been shown to be higher among men with prostate cancer when compared to men without prostate cancer, but PSAV also has been found to be higher in men with high-grade and high-stage prostate cancer as compared with men with lower-grade and lower-stage disease.[239,240] Furthermore, men with a PSAV above 2.0 ng/mL per year in the year before a diagnosis of prostate cancer were at an increased risk of prostate cancer death after surgical intervention when compared with men with a PSAV of 2.0 ng/mL per year or less.[241] Even when PSAV was measured 10 to 15 years before prostate cancer diagnosis (when most men had PSA levels below 4.0 ng/mL), a PSAV less than 0.35 ng/mL per year was associated with a prostate cancer-specific survival 25 years later of 92% (with a 95% confidence interval of 84% to 96%), while a PSAV greater than 0.35 ng/mL per year was associated with a prostate cancer-specific survival of 54% (with a 95% confidence interval of 15% to 82%, $P < 0.001$). All of these data suggest that PSAV is a marker of life-threatening prostate cancer and may be useful as part of the algorithm for determining the need for a prostate biopsy, rather than using absolute serum PSA levels alone.

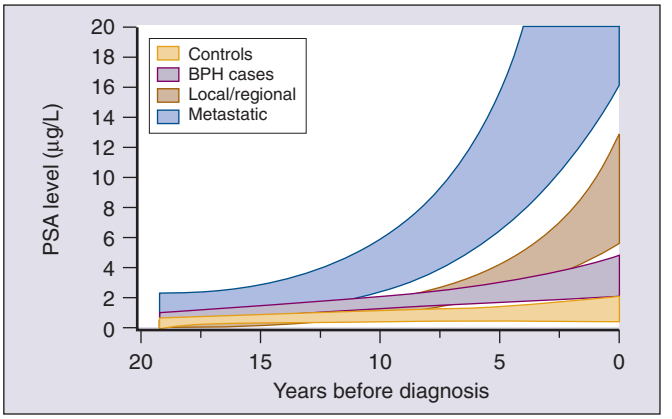


Figure 88-8 • Longitudinal increases in serum prostate-specific antigen (PSA) levels in men with and without prostate cancer. BPH, benign prostatic hypertension. (From Fromter HB, Pearson JD, Metter EJ, et al: Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA 1992;267:2215.)

Molecular Forms of Prostate-Specific Antigen

PSA in the bloodstream circulates in both bound and unbound forms. Most of the detectable PSA in the serum (65%–90%) is bound to α_1-anti-chymotrypsin, while the rest (10%–35%) remains unbound or "free."[212] The assays primarily used for prostate cancer detection and monitoring detect both "free" and "complexed" PSA, providing a determination of the "total" serum PSA. Newer assays that can distinguish "free" and "complexed" serum PSA have more recently been developed and approved by the U.S. Food and Drug Administration (FDA) for use in the early detection of prostate cancer.

In general, men with prostate cancer have a greater fraction of serum "total" PSA that is bound to α_1-anti-chymotrypsin, and a commensurately lower fraction of "total" PSA that is "free," than men without prostate cancer. This difference is thought to be due to the differential expression of PSA isoforms by cells in the transition zone (the zone of origin for BPH) tissue as compared with peripheral zone (the zone where most prostate cancers arise) tissue.

The percentage of "free" serum PSA appears most useful in distinguishing between men with and without prostate cancer in the setting of "total" serum PSA levels between 2 and 10 ng/mL (Table 88-4). Most urologists use "free" serum PSA determinations to help make decisions about the need for a repeat biopsy in a man with a persistently elevated serum PSA and previous negative prostate biopsies, where the possibility of a missed prostate cancer may be a concern. Measurement of "complexed" serum PSA, using a single assay, has been promoted by some investigators as a better method for assessing prostate cancer risk, in place of the two assays ("total" serum PSA and "free" serum PSA) needed for determination of percent "free" serum PSA.

Transrectal Ultrasound-Guided Prostate Biopsy

Transrectal ultrasound (TRUS) is not an accurate method for localizing early prostate cancer and is not recommended for use in prostate cancer screening. The primary role of TRUS in prostate cancer detection and diagnosis is to ensure accurate sampling of prostate tissue by prostate biopsies in men suspected of harboring cancer based on serum PSA levels and DRE.[242] This is best accomplished by targeting peripheral zone lesions that appear hypoechoic by TRUS for biopsy, along with performing systematic sampling biopsies of areas without hypoechoic lesions in the prostate periphery.

TRUS-guided prostate biopsies are performed routinely with an 18-gauge needle fired from a spring-loaded gun through a port mounted on the TRUS probe. Most commonly, in preparation for a biopsy procedure, men are administered a fluoroquinolone antibiotic and given a cleansing enema. Most urologists inject a local

Table 88-4 Probability of Cancer Based on PSA and Percent of FPSA Results

PSA (ng/mL)	Probability of Cancer (%)	FPSA (%)	Probability of Cancer (%)
0–2	1	0–10	56
2–4	15	10–15	28
4–10	25	15–20	20
>10	>50	20–25	16
		>25	8

FPSA, free prostate-specific antigen; PSA, prostate-specific antigen.

Men with nonsuspicious digital rectal examination results, any age: % FPSA can stratify risk for men with PSA of 4–10 ng/mL.

Data from Catalona WJ, Partin AW, Slawin KM, et al: Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA 1998;279:1542.

anesthetic around the periphery of the prostate to reduce discomfort associated with prostate biopsy. Major complications, such as bleeding and/or infection requiring hospitalization, are rare, although hematuria and hematospermia are common sequelae of the procedure.

The optimal biopsy technique, including the number and placement of biopsies for tissue procurement that will minimize the chance of missing a relevant cancer, remains controversial. Nonetheless, the best evidence available suggests that biopsies placed more laterally within the peripheral zone of the prostate may be important to exclude prostate cancer in men with elevated serum PSA values and a nonsuspicious DRE.

Screening for Prostate Cancer

There are legitimate concerns about population screening of asymptomatic men using PSA and DRE, despite the 30% decline in prostate cancer mortality between 1993 and 2003 (*http://seer.cancer.gov/faststats/*) that has been attributed in part to PSA testing.[218]

First, the lifetime risk (from age 0 to 90 years) of death from prostate cancer is 3%, and the lifetime risk of a diagnosis of prostate cancer is 17%. Thus, in the absence of markers that accurately identify those men who have life-threatening cancers, screening will result in the overdiagnosis (i.e., detection of a cancer through screening that would have otherwise remained clinically silent) and over-treatment of some men. In a recent observational study of men over age 65 years who were detected with low to intermediate risk prostate cancer in the PSA testing era, the findings suggested that 200 men would need to be treated over 12 years to prevent 1 prostate cancer death.[243] Remarkably, even though competing causes of death reduce the benefits of screening and treatment among older men, rates of screening in the elderly are higher than the rates of screening among younger men.[244] Second, screening for prostate cancer in asymptomatic men results in false-positive results prompting unnecessary prostate biopsies, and treatment of prostate cancer, by any means, can result in unwanted side effects—a poor tradeoff if the treatment results in no benefit in terms of years of life saved. Third, the costs of screening may not be justified if the societal harm of diagnosis and treatment are far greater than any health benefits obtained. All of these as yet incompletely addressed issues are considerations of any screening program and not unique to prostate cancer screening.

The PLCO (Prostate, Lung, Colon, Ovary) Trial of the National Cancer Institute and the ERSPC (European Randomized Study of Screening for Prostate Cancer) are ongoing randomized trials designed to address whether or not prostate cancer screening reduces prostate cancer mortality. At this time, no organization endorses universal or mass screening for prostate cancer (Box 88-2). The U.S. Preventive Services Task Force concluded that the evidence is insufficient to recommend for or against routine screening for prostate cancer using PSA testing or DRE.[245] This conclusion was based on good evidence that PSA testing can lead to the detection of prostate cancer at an early stage, but inconclusive evidence that early detection improves health outcomes. Specialty organizations such as the American Cancer Society (http://www.cancer.org/docroot/home/index.asp) and the American Urological Association recommend that prostate cancer screening with PSA and DRE be offered to all men over age 50 years and that the risks and benefits of screening be discussed with the patient. Although the value of PSA screening remains controversial, men who present for periodic health examinations should be made aware of the availability of the PSA test, so that they can make an informed decision about the need for routine screening. The general enthusiasm for screening in the United States suggests that most men will elect to be tested.[246]

Histopathology of Prostate Cancer

Microscopic analysis of prostate tissue by a surgical pathologist is needed for the diagnosis of prostate cancer, for determining prostate cancer stage after prostatectomy, and for histological grading, via the assignment of a Gleason score, to predict the behavior of prostate cancer (Table 88-5). Most prostate cancers are adenocarcinomas, although other types of cancers can appear. Most often, the diagnosis of prostate cancer is made using core needle biopsy specimens, which sample small amounts of prostate tissue. In many cases, needle biopsies contain only small numbers of prostate cancer cells among more plentiful noncancerous cells. Also, several prostate conditions, including acute, chronic, or granulomatous prostate inflammation, epithelial atrophy, and PIN, exhibit histological features that mimic some of those present in prostate cancers.[247] Thus, prostate cancers can be difficult to recognize in needle biopsy specimens, and difficult to distinguish from other prostate abnormalities. Most experienced prostate pathologists use a combination of architectural, cytological, and ancillary findings to make a diagnosis of prostate cancer on needle biopsy.[247–249] In addition, because normal prostate glands, but not glands present in prostate cancers, contain basal epithelial cells, immunohistochemical staining for basal epithelial cell markers, such as cytokeratins K5 and K14, can be used to help distinguish benign from malignant glands in prostate tissue samples. Also, immunohistochemical staining for AMACR, a prostate cancer biomarker discovered through cDNA microarray transcriptome profiling, can aid in prostate cancer diagnosis.[168,170,250] Neither of these immunohistochemistry reagents perfectly distinguishes prostate cancer: the absence of basal epithelial cell markers is not always diagnostic of prostate cancer, and AMACR expression is absent in some prostate cancers and present in PIN.[247] For all of these

Box 88-2. POPULATION SCREENING FOR PROSTATE CANCER

There is no proof yet that prostate-specific antigen (PSA) screening in asymptomatic men prevents prostate cancer deaths. Nonetheless, the use of serum PSA testing, along with digital rectal examination (DRE), to screen men for prostate cancer has been proven to detect prostate cancer at earlier stages. As a result, prostate cancers discovered by screening are more likely to be treated with curative intent via surgery or radiation therapy. The major concern about prostate cancer screening is the potential for overdiagnosis of prostate cancers that would be unlikely to pose a threat for morbidity or mortality. For these reasons, screening approaches for prostate cancer are still evolving, with the optimal screening test (serum PSA vs. other molecular forms of PSA), the optimal screening population (younger vs. older men), and the optimal screening interval yet to be determined.

Table 88-5 Cancer-Specific Mortality Rates*

	AGE (YR)			
Gleason Score	**50–59**	**60–64**	**65–69**	**70–74**
2–4	4%	5%	6%	7%
5	6%	8%	10%	11%
6	18%	23%	27%	30%
7	70%	62%	53%	42%
8–10	87%	81%	72%	60%

*Probability of dying of prostate cancer within 15 years of diagnosis in men with clinical stage prostate cancer treated conservatively.

Data from Albertsen PC, Hanley JA, Gleason DF, et al: Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively from clinically localized prostate cancer. JAMA 1998;280:975.

reasons, second opinion interpretations of prostate biopsy findings, especially when foci of atypical glands suspicious for cancer are identified, are often helpful.

High-grade PIN, a lesion characterized by the proliferation of malignant-appearing prostate epithelial cells within the confines of otherwise normal glandular structures, is identified in about 5% of men subjected to prostate biopsies.[251,252] The evidence that high-grade PIN is a likely precursor to prostate cancer includes the findings that (1) high-grade PIN is more commonly present in prostates that also contain prostate cancer; (2) high-grade PIN and prostate cancer both tend to arise in the peripheral zone of the prostate and often are directly contiguous; and (3) high-grade PIN and prostate cancer express similar biomarkers and share many somatic genome abnormalities.[253,254] The notion that high-grade PIN lesions might be prostate cancer precursors has stimulated interest in possibly treating men with high-grade PIN to prevent prostate cancer.[254] Unfortunately, the natural history of individual high-grade PIN lesions is not known. Furthermore, high-grade PIN lesions, which can be recognized only by sampling prostate biopsies, are not easily monitored. These limitations have hindered the use of high-grade PIN as a response surrogate for cancer prevention drug development. Because high-grade PIN is not currently treated, the major significance of the finding of high-grade PIN, in the apparent absence of prostate cancer, by prostate biopsy is that prostate cancer may have been missed by the prostate sampling strategy used for the biopsy procedure. As serum PSA screening was first introduced, men with an elevated serum PSA and high-grade PIN by prostate biopsy seemed to have as high as a 50% chance of having prostate cancer when subjected to repeat prostate biopsies. With more widespread adoption of serum PSA screening strategies, for men with an elevated serum PSA, the chance that a second set of prostate biopsies will detect prostate cancer after an initial diagnosis of high-grade PIN on a first set of prostate biopsies has fallen to 23% to 35%, only slightly greater than the 20% chance that repeat prostate biopsies will detect prostate cancer even in the absence of an initial diagnosis of high-grade PIN.[255–257] Of interest, unlike prostate cancer, prostate inflammation, or BPH, PIN lesions are not thought to perturb prostate architecture enough to elevate the serum PSA. Recently, increasing attention has been afforded the notion that PIA lesions might be precursors to PIN and/or prostate cancer. Like PIN, PIA lesions tend to arise in the peripheral zone of the prostate, where prostate cancers arise, and some PIA cells acquire somatic genome alterations reminiscent of prostate cancer cells.[93,258] Currently, men with PIA lesions are not subjected to any kind of treatment, and the presence of PIA on an initial prostate biopsy is not thought to predict the detection of prostate cancer on repeat biopsy. The major significance of PIA in regard to the diagnosis of prostate cancer by prostate biopsy may be the propensity for such lesions occasionally to exhibit features that mimic prostate cancer.[247]

The most commonly used approach to histological grading of prostate cancer is Gleason scoring.[259] The Gleason grade refers to architectural prostate cancer patterns, numbered 1 (well-differentiated) to 5 (poorly differentiated). Because prostate cancers often are heterogeneous, Gleason scoring (sometimes referred to as the "combined" Gleason grade) is accomplished by adding the Gleason grade of the most abundant pattern to the Gleason grade of the second most abundant pattern (e.g., a Gleason score of 4 + 3 = 7). The Gleason score, when applied by an expert pathologist, is one of the best tools available for predicting the outcomes of men treated with radical prostatectomy or with radiation therapy; prostate cancers with Gleason scores of 8 to 10 are much more likely to recur after primary treatment than prostate cancers with Gleason scores of 2 to 6.[260,261] Furthermore, for prostate cancers with a Gleason score of 7, Gleason 4 + 3 = 7 appears more correlated with prostate cancer recurrence than Gleason 3 + 4 = 7. One challenge presented by Gleason grading is the variability in Gleason scores assigned to the same prostate cancers by different pathologists.[262,263] To address this challenge, Internet educational tools have been developed by expert pathologists to improve the fidelity of Gleason scoring by community pathologists.[264] Of note, since Gleason scoring applies pattern grades to the architecture of cancer within the prostate, metastatic prostate cancers detected by biopsies of metastatic deposits are not assigned a Gleason score.

Evaluation of the Extent of Prostate Cancer

The extent of prostate cancer is correlated with tumor stage, Gleason score (the sum of two Gleason grades), and serum PSA level.[265] Nomograms, incorporating clinical stage, estimated using DRE findings, the serum PSA level, and the Gleason score, have been shown to be capable of predicting both prostate cancer extent (when compared to the pathological stage evident at the time of prostate surgery) and the long-term outcome following primary tumor treatment.[266–268] D'Amico and associates[268] have suggested that men with prostate cancer can be stratified into low-risk (stages T1c to 2a, serum PSA <10 ng/mL, and Gleason score of ≤6), intermediate-risk (stage T2b, or serum PSA of 10–20 ng/mL, or Gleason score of 7), and high-risk (stage T2c, or serum PSA >20 ng/mL, or Gleason score of ≥8) groups, reporting that the fraction of men free of prostate cancer 10 years after radical prostatectomy is significantly different for the risk categories: 83% of men with low-risk prostate cancer, 46% of men with intermediate-risk prostate cancer, and 29% of men with high-risk prostate cancer. When undertaken before initiating prostate cancer treatment, risk stratification of men with prostate cancer aids in counseling such men about the expected outcome of aggressive local prostate cancer treatment, providing estimates of the chance that local treatments might be curative.

Radiographic Imaging

Although CT scanning is used routinely by radiation oncologists for prostate cancer treatment planning, no imaging technique available today has been proven to add additional useful information when used to evaluate the extent of prostate cancer in men with low and intermediate risk disease.[269] TRUS and MRI give the most accurate definition of prostatic architecture and anatomy, but current imaging technologies do not provide very precise assessments of cancer extent within the prostate or the presence of microscopic foci of prostate cancer that have escaped the confines of the prostate gland. Radionuclide bone scans detect metastatic prostate cancer in less than 1% of men with a serum PSA value less than or equal to 20 ng/mL and are not recommended for the initial evaluation of men with low or intermediate risk prostate cancer.[270] Positron emission tomography (PET) has not yet been found to be useful in the evaluation of men with prostate cancer and has no place in the prostate cancer staging.[271] New imaging technologies, including three-dimensional color Doppler, contrast-enhanced color Doppler, magnetic resonance spectroscopy, and high resolution MRI with magnetic nanoparticles, have great potential for improving the assessment of local and distant prostate cancer extent.[269,272] Cross-sectional imaging of the pelvis, by CT scan or MRI, for the purpose of detecting lymph node metastases, and radionuclide bone scans for the detection of bony metastases, should be reserved for men with high-risk prostate cancer.

^{111}In-capromab penditide, a radioimmunoconjugate featuring a monoclonal antibody to an intracellular domain of prostate-specific membrane antigen (PSMA; ProstaScint, Cytogen Corporation) has been approved by the FDA for use in the evaluation of men for treatment of clinically localized prostate cancer. There is some evidence that when ^{111}In-capromab pendetide immunoscintigraphy is used in combination with other pretreatment prostate cancer staging tools, the predictive value for presence of lymph node metastases increases.[273] However, this scan is not being used routinely today for assessment of prostate cancer extent, in large part because of frequent difficulties in scan interpretation, and because of the lack of scan sensitivity, even among men with fairly high-risk prostate cancer.

Serum Biomarker Assays and "Molecular" Staging

Increases in serum PSA and in serum prostatic acid phosphatase (PAP)[274] correlate directly with the extent (stage) of prostate cancer disease. As described earlier, the serum PSA is a useful tool for the preoperative assessment of prostate cancer extent, especially when considered along with other pretreatment parameters. Radioimmunoassays for PAP appear more sensitive, but less specific, than enzymatic assays, when used to detect serum PAP as a marker of advanced prostate cancer. Several studies have documented a correlation between the presence of advanced prostate cancer and elevations of serum PAP.[275–277] Elevated serum PAP values, and serum PAP levels in the upper half of the normal range, portend a high likelihood (>80%) of extra-prostatic cancer.[276,277] However, normal serum PAP levels are not very predictive of the absence of extra-prostatic disease. For men thought to have clinically localized prostate cancer based on the results of serum PSA, DRE, and Gleason score, serum PAP testing rarely adds additional information. The use of serum PAP testing for prostate cancer staging has declined substantially, giving way to the use of serum PSA testing.

"Molecular" staging for prostate cancer refers to the detection of circulating prostate cancer cells and/or cell fragments, either indirectly, by identifying mRNA species, such as those encoding PSA or PSMA, characteristically expressed by epithelial cells from the prostate,[278] or directly, by recovering prostate cancer cells using centrifugation/immunostaining methods.[279,280] To detect prostate lineage mRNAs or prostate cancer DNAs, polymerase chain reaction (PCR) approaches, capable of astonishing sensitivity, typically are used.

Reverse transcriptate-PCR (RT-PCR) for *PSA* mRNA in the blood has been reported to be more predictive of pathologic prostate cancer stage when compared to other pretreatment predictors such as serum PSA and Gleason score,[281] and to be an independent predictor of disease-free survival after treatment.[282] However, as many as one in four men with localized prostate cancer who underwent radical prostatectomy for cancer confined to the prostate had "positive" RT-PCR assays for *PSA* mRNA in blood specimens in one study.[281] These men would be denied aggressive treatment if the presence of circulating prostate cells indicated the presence of distant blood-borne prostate cancer metastases. In another study, 7% of men without prostate cancer exhibited "positive" RT-PCR assays for *PSA* mRNA in blood.[283] The relation between circulating prostate cancer cells, regardless of how they are detected, and the development of metastatic prostate cancer is not well understood, but is likely that the formation of metastatic prostate cancer deposits in bone and at other sites may be a relatively inefficient process, and that dissemination of prostate cancer cells into the bloodstream may be necessary, but not sufficient, for metastasis.[278,284] Until the predictive value of a "positive" RT-PCR assay for *PSA* mRNA in the blood has been established for a cohort of men with long-term follow-up after treatment for clinically localized prostate cancer, the assay will remain a investigational test.

TREATMENT OF LOCALIZED PROSTATE CANCER

Selection of Treatment Approach

Men thought to have localized prostate cancer face a number of treatment choices, including watchful waiting, radical prostatectomy, interstitial brachytherapy, and external beam radiation therapy (Box 88-3). Not all of these treatment approaches are appropriate for every man with prostate cancer. The different treatment approaches tend to be associated with different potential side effects. Also, men diagnosed with prostate cancer may have other medical conditions that can increase the chance or severity of such side effects. Prognostic factors, including prostate cancer stage, Gleason score, and serum PSA, are used to stratify men into low-, intermediate-, and high-risk groups for prostate cancer recurrence after treatment, providing some guidance as to likely treatment efficacy. Age, comorbidity, and life expectancy also should be considered in treatment selection (Table 88-6). Some prostate cancers exhibit a very indolent natural history, progressing slowly to threaten symptoms or survival. Many older men likely die *with* such cancers rather than *because* of them. The increased use of serum PSA for prostate cancer screening and early detection, particularly if applied to older men, may tend to overdiagnose such cancers. In contrast, young, healthy men with more aggressive prostate cancers may benefit from early prostate cancer detection and definitive treatment.

Since the mid-1980s, both surgery and radiation therapy for prostate cancer have improved dramatically, providing effective local control of cancer in the prostate while reducing the threat of side effects. At this point, the optimal treatment approach for men with localized prostate cancer who are appropriate candidates for surgery and radiation therapy has not been fully resolved. Comparisons between the treatment approaches remain difficult because there have been no randomized clinical trials testing differences in treatment

Box 88-3. TREATMENT OF MEN WITH CLINICALLY LOCALIZED PROSTATE CANCER

Men with localized prostate cancer have several treatment options, including watchful waiting, radical prostatectomy, interstitial brachytherapy, and external beam radiation therapy. Age, life expectancy, and medical history, as well as prostate cancer prognostic factors, such as stage, Gleason score, and serum prostate-specific antigen (PSA), typically are used to guide treatment recommendations. For example, men with a life expectancy of less than 5 years and low-risk prostate cancer (defined as stage T1 or T2, a Gleason score of 2–6, and a serum PSA value of 10 ng/mL or less) often are counseled to consider watchful waiting or radiation therapy, while men with a life expectancy of more than 20 years and low-risk prostate cancer might be offered radical prostatectomy or radiation therapy. Men with a life expectancy of more than 5 years and intermediate-risk prostate cancer (stage T2b to T2c, Gleason score of 7, or serum PSA of 10–20 ng/mL) usually are referred for radical prostatectomy or radiation therapy. Men with a life expectancy of more than 5 years and high-risk cancer (stage T3a to T3b, Gleason score 8–10, or serum PSA higher than 20 ng/mL) tend to be candidates for radiation therapy, administered along with adjuvant androgen deprivation therapy.

Table 88-6 Life Expectancy of Men (All Races) in the United States of America, by Age

	LIFE EXPECTANCY (YR)	
Age (yr)	**1989**	**2000**
50	26.4	27.9
55	22.3	23.8
60	18.5	19.9
65	15.1	16.3
70	12.1	13.0
75	9.4	10.1
80	7.1	7.6
85	5.3	5.6

Data from Arias E: United States life tables, 2000. Natl Vital Statistics Rep 2002;51:1–42.

outcomes. Furthermore, historical data offer only limited assistance in choosing between surgery and radiation therapy because each approach has improved in the time since most men were treated in case series with long-term follow-up data, and because most men treated in the past with radiation therapy tended to be older, have more substantial comorbidities, and have more aggressive (i.e., higher stage and grade) prostate cancers.

The 2007 National Comprehensive Cancer Network (http://www.nccn.org) guidelines for the management of clinically localized prostate cancer reflect the need for consideration of both life expectancy and the risk for prostate cancer recurrence in making treatment recommendations. In these guidelines, men with a life expectancy of less than 5 years and low-risk prostate cancer (defined as stage T1 or T2, a Gleason score of 2 to 6, and a serum PSA value of 10 ng/mL or less) are recommended for watchful waiting or for radiation therapy, while men with a life expectancy of more than 10 years and low-risk prostate cancer would be recommended for radical prostatectomy or for radiation therapy. Men with a life expectancy of more than 5 years and intermediate-risk prostate cancer (stage T2b to T2c, Gleason score of 7, or serum PSA of 10 to 20 ng/mL) also are recommended for radical prostatectomy or radiation therapy. Men with a life expectancy of more than 5 years and high-risk cancer (stage T3a to T3b, Gleason score 8 to 10, or serum PSA greater than 20 ng/mL) are recommended for radiation therapy and some sort of adjuvant androgen deprivation therapy, or, in certain specific cases, for radical prostatectomy. No adjuvant chemotherapy has yet been shown to benefit men with clinically localized prostate cancer.

Watchful Waiting (Conservative or Expectant Management)

Even when detected before widespread use of serum PSA for prostate cancer screening, the natural history of localized prostate cancer treated conservatively was characterized by slow progression of the disease, with few deaths within 10 years but a substantial risk of death at 15 years, especially for men with Gleason combined scores of 6 or greater.[285,286] Thus, most men with life expectancies beyond 10 years are thought to be candidates for curative therapy. No long-term studies of conservatively managed patients with prostate cancers detected by serum PSA screening are available. However, several observations suggest that conservative management may be a very reasonable option for selected men with prostate cancers diagnosed after serum PSA screening. First, the lead-time for prostate cancer diagnosis using serum PSA screening has been estimated to be 6 to 12 years.[216,287] Second, among men with palpable (stage T2) disease that was not detected using serum PSA screening, 8 years of follow-up were required to demonstrate an absolute difference of 7% in prostate cancer-specific survival in a randomized trial of surgery versus conservative management that showed an advantage for surgical treatment.[288] Thus, only a small minority of men with palpable prostate cancer benefit from surgery at 8 years. For men diagnosed with nonpalpable prostate cancer via serum PSA screening, with a lead-time of 6 to 12 years, it seems unlikely that most men age 70 years and older will derive much benefit from aggressive treatment. Such men should be offered watchful waiting as an alternative to surgery or radiation therapy. In addition, some younger men who are thought to have small-volume prostate cancer also may not benefit from aggressive treatment.

With the adoption of serum PSA screening, an estimated 20% to 30% of men detected to have nonpalpable prostate cancer (stage T1c) appear to have small-volume cancers (0.5 mL or less) that are not poorly differentiated.[204,289] Given the long natural history of prostate cancer, and the high rates of prostate cancer overdiagnosis (i.e., detection of cancer that would not have been detected without PSA testing) with serum PSA screening, especially for older men, watchful waiting should be considered in selected men with nonpalpable, serum PSA-detected, non-poorly differentiated (Gleason score of 6 or less) prostate cancers.

Most watchful waiting approaches have involved periodic general follow-up with initiation of palliative treatment as needed for symptomatic prostate cancer progression or for the appearance of cancer metastases. However, the ability to use serum PSA as a biomarker for prostate cancer activity has led to newer approaches where older men who are thought to harbor small-volume prostate cancers are followed more closely, with initiation of aggressive treatment with curative intent if and when it becomes appropriate. The challenges for these approaches are to identify men with small-volume disease who may be candidates for such an approach, and to identify which triggers can be used to change the management strategy from conservative to curative.

Epstein and coworkers[204] have presented criteria for identifying men with small-volume cancers. In their analyses, if the serum PSA "density" was less than 0.15 and there were no adverse pathologic findings detected by prostate needle biopsy (Gleason score 6 or less, less than 3 biopsy cores containing prostate cancer, and no more than 50% involvement of any biopsy core with prostate cancer), at the time of radical prostatectomy, 79% of such men had tumors of 0.5 mL or less that were organ-confined and were not high grade.[204] In contrast, if the PSA density was 0.15 or greater, or if any adverse needle biopsy findings were present (Gleason score 7 or higher, more than 2 biopsy cores containing prostate cancer, or more than 50% involvement of any biopsy core with prostate cancer), 83% of men had prostate cancers that were larger than 0.5 mL, cancers that were not confined to the prostate, or cancers that were high grade at radical prostatectomy. The predictive value of these criteria subsequently was confirmed in a prospective study.[290] When the criteria were used to identify a cohort of men (median age 67 years) with small-volume prostate cancer for a watchful waiting program, featuring serial serum PSA determinations and DREs as well as yearly surveillance prostate biopsies, some 30% of the men followed for more than 1 year were found to have adverse findings on surveillance biopsies that prompted a recommendation for curative treatment.[290] Nevertheless, 90% of the men found to have adverse prostate biopsy findings in this cohort still were thought to have curable prostate cancer when treatment was recommended.[290] The absence of prostate cancer on subsequent surveillance biopsies was strongly correlated with an absence of adverse pathology findings on future surveillance biopsies, but serum PSA determinations (including "free" PSA and PSA "velocity") were not helpful in predicting the future appearance of adverse pathology.[290] Thus, watchful waiting, conducted with curative intent, may be a reasonable approach for selected men above age 65 years with a high likelihood of harboring small-volume prostate cancer based on serum PSA and prostate biopsy criteria.

Radical Prostatectomy

Radical prostatectomy is used to treat men with clinically localized prostate cancer who have a life expectancy of at least 5 years. Although there are not specific or universally accepted age limits for radical prostatectomy, the life expectancy of men above 70 to 75 years of age is low enough that few men in this age range undergo radical prostatectomy.[291] Clearly, men with uncontrolled or acute medical conditions are not candidates for surgery. Previous pelvic surgery or radiation therapy, which can lead to increased complications, are relative contraindications to radical prostatectomy. Preoperative assessment of men for radical prostatectomy typically includes a history and physical examination, hematology studies, serum electrolyte studies (with a serum creatinine determination), a urinalysis, coagulation studies, and an electrocardiogram. Surgery for prostate cancer is usually delayed for 6–8 weeks after prostate needle biopsy to permit resolution of hematomata caused by the biopsy procedure. In anticipation of surgery, men avoid aspirin, nonsteroidal anti-inflammatory agents, or high doses of vitamin E that might promote

excess bleeding. Some men bank blood for possible transfusion if necessary. Anesthesia for radical prostate surgery has been provided using general, spinal, and epidural approaches; however most surgeons today prefer regional anesthesia, which has been reported to be associated with less blood loss and a lower risk for pulmonary emboli.[292,293]

The most common radical prostatectomy performed today uses a retropubic approach that has been perfected to better remove all cancer in the prostate and to better preserve anatomic structures essential for erectile function and urinary control.[6,7,294] Other surgical procedures for removal of the prostate gland include radical perineal prostatectomy and laparoscopic approaches to radical prostatectomy.[295–297] The radical retropubic prostatectomy proceeds via performance of a staging pelvic lymphadenectomy, division of puboprostatic ligaments, identification, ligation, and division of the dorsal vein complex to control blood loss, division of the urethra, identification and preservation of the neurovascular bundles needed for penile erection (unless wide excision of a neurovascular bundle is necessary for cancer control), division of the bladder neck and resection of the seminal vesicles, and construction of a urethrovesical anastomosis to best provide urinary continence.[298] The most common intraoperative complication is hemorrhage, although blood loss greater than 1000 mL is uncommon for most procedures.[298] Much less frequently, the obturator nerve can be injured during the pelvic lymphadenectomy, a ureter can be injured near the bladder, or the rectum can be injured during the dissection of the apex of the prostate gland. In the immediate postoperative period, complications include deep venous thrombosis and pulmonary emboli.[299] The operative mortality (death within 30 days) for radical prostatectomy is around 0.2%.[298]

Urinary Continence after Radical Prostatectomy

Urinary incontinence rates after radical prostatectomy vary greatly in different reports, with incontinence rates as high as 31% for men in the general population who underwent radical prostatectomy and as low as 10% or less for men who underwent radical prostatectomy at centers of excellence.[300–303] Some of the variation in reported incontinence rates may be attributable to differences in definitions of incontinence (stress incontinence versus more severe difficulties with urinary control), differences in the time after surgery when urinary continence was assessed (urinary control can continue to improve for as long as a year following surgery), and differences in whether incontinence was reported by treating surgeons in case series or by patients in survey questionnaires. However, surgical technique likely has significant consequences for urinary control following radical prostatectomy. Both the striated urinary sphincter musculature and smooth muscle surrounding the urethra can be injured during surgery.[298] Postoperative strictures at the site of the vesicourethral anastomosis also can affect control of urination.[304] Such strictures can be dilated, if necessary, to improve urination. Avoidance of such injuries, accompanied by modifications of the urethrovesical anastomosis, has led to improved urinary control rates by expert surgeons.[305,306] In the best case series, as many as 95% of men are completely dry 2 years after radical prostatectomy, and as many as 98% of men report no significant urinary problems.[303,307] Men with persistent or severe urinary incontinence after radical prostatectomy can be treated with periurethral collagen injections or with placement of an artificial urinary sphincter.[308,309]

Erectile Function after Radical Prostatectomy

Before 1982, most men subjected to radical prostatectomy were rendered impotent by the procedure. At that time, Walsh and Donker[6] meticulously assessed the anatomy of the nerves traversing the lateral surface of the prostate en route to the corpora cavernosa of the penis, discerning the close proximity of the nerves to vascular structures (the neurovascular bundles) visible at the time of radical prostatectomy. This revelation led Walsh and colleagues[7] to propose a modification of the radical prostatectomy procedure to preserve the neurovascular bundles in an effort to maintain erectile function postoperatively. Wide adoption of this modification has led to improvements in sexual potency rates following radical prostatectomy. As many as 91% of young men (<50 years of age) with good preoperative erectile function and low-stage prostate cancers who undergo an anatomic radical prostatectomy with preservation of both neurovascular bundles can expect recovery of potency after surgery.[310] Improvement in sexual function following surgery tends to occur gradually over at least 24 months or more.[303,311] Poor recovery of erectile function after surgery is correlated with increasing age (75% of men 50–60 years of age, 58% of men 60–70 years of age, and 25% of men 70 years of age or older were potent after radical prostatectomy in one series), poor potency before surgery, advanced prostate cancer stage (with capsular penetration or seminal vesicle invasion), and excision of neurovascular bundles.[310,312] Population studies have confirmed these predictors of erectile dysfunction after radical prostatectomy, with as many as 60% of men reporting impotence following surgery and some 42% reporting that poor sexual function was a significant problem.[301] In the best case series, 86% of men were able to have erections sufficient for sexual intercourse by 18 months.[303] Interposition grafts, from the sural nerve, have been used in attempts to repair nerves severed when wide excision of neurovascular bundles was required during radical prostatectomy, but the effectiveness of this procedure has been questioned.[313,314] Many men use seldenafil citrate (Viagra, Pfizer, Inc.) to improve sexual function following radical prostatectomy.[315]

Control of Prostate Cancer by Radical Prostatectomy

Radical prostatectomy is an effective means of treating localized prostate cancer. In a randomized trial ($N = 695$ men) comparing radical prostatectomy with watchful waiting, the odds ratio for death due to prostate cancer for men treated with surgery was 0.50 (with a 95% confidence interval of 0.27 to 0.91, $P = 0.02$)[288] (Fig. 88-9). Following surgery, serum PSA levels should fall to undetectable levels. A persistently detectable serum PSA after radical prostatectomy most often reflects the presence of disseminated cancer, occasionally indicating an incomplete resection of prostate tissues. After the serum PSA has declined to an undetectable level following radical prostatectomy, subsequent detection of PSA in the serum always indicates prostate cancer recurrence, preceding clinically significant prostate cancer progression by as many as 6 years or more.[316] Most modern case series examining outcomes of men with prostate cancer treated by radical prostatectomy feature the serum PSA as a surrogate biomarker for recurrence of prostate cancer. In such series, some 80% of men remain free of prostate cancer recurrence by 5 years following surgery.[317–321] In multivariate statistical analyses, the risk of serum PSA recurrence after radical prostatectomy has been correlated with clinical stage, Gleason score in prostate biopsies, and serum PSA values, determined preoperatively, and with pathological stage and Gleason score in the resected prostate specimen, determined postoperatively.[266,267]

Radiation Therapy

Radiation therapy has been used in the management of prostate cancer for nearly a century. Following Roentgen's discovery of the x-ray in 1895,[322] and the isolation of radium by Pierre and Marie Curie in 1898,[323] several pioneering physicians began treating prostate disorders, including prostate cancer, with radiation. In 1910, Paschkis and Tittinger inserted radium into the prostatic urethra with a cystoscope in what may be the first use of radiation for prostate cancer. Not long after, Hugh Hampton Young from Johns Hopkins

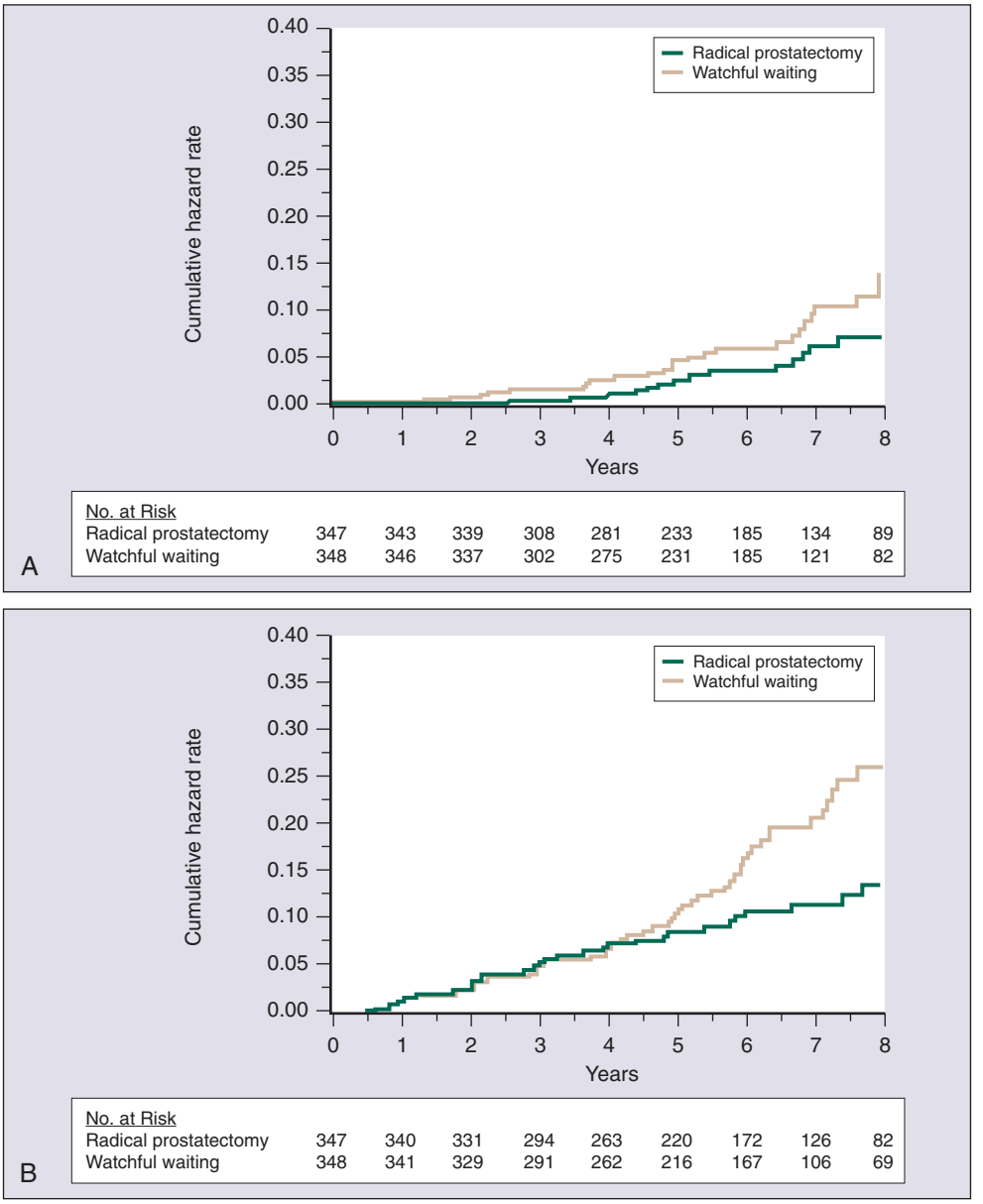


Figure 88-9 • Results of a randomized clinical trial of radical prostatectomy versus watchful waiting. **A,** Cumulative hazard rates of prostate cancer death. **B,** Cumulative hazard rates of prostate cancer metastasis. (Data from Holmberg L, Bill-Axelson A, Helgesen F, et al: A randomized trial comparing radical prostatectomy with watchful waiting in early prostate cancer. N Engl J Med 2002;347:781–789, with permission.)

reported the relatively large experience of treating prostate cancer patients with urethral and rectal radium "applicators."[324] These and other early studies revealed that even when radiation was applied in this crude manner, it could improve symptoms and kill prostate cancer. However, treatment was technically difficult for the physician and uncomfortable for the patient. In 1928, the first report on the use of externally delivered low-energy kilovoltage radiation for prostate cancer was offered by Barringer.[325] The associated dosimetry was not well worked out and, thus, men were treated until their skin turned red. These types of low-energy radiation machines were used until cobalt machines became available and provided the first opportunity to treat tumors more deeply seated in the body. The first reported series of prostate cancer patients treated with ^{60}Co0 therapy was by George and associates in 1965 and featured men with unresectable disease.[326] It was also during this time (beginning in the late 1950s) that the megavoltage linear accelerator was being developed at Stanford University.[327] The pioneering work of Bagshaw, Kaplan, Del Regato, and others, ushered in the modern era of radiation therapy for prostate cancer.[328,329]

Now men with prostate cancer have several different radiotherapeutic options, each of which can be employed with very high precision and with great effectiveness. The integration of computer-based technology for the design of three-dimensional conformal treatment plans, and use of high-energy accelerators with sophisticated dynamic shielding, allows men with prostate cancer to be treated with high doses of radiation while at the same time sparing surrounding normal tissues. In addition, the development of permanently implantable radioactive sources, along with the use of real-time imaging and treatment planning, also has provided the opportunity for sophisticated prostate brachytherapy techniques resulting in safe and efficacious treatment of men with prostate cancer.

Traditionally, men with prostate cancer referred for radiation therapy tended to be older, to be in poorer health, and to have higher-risk, more advanced tumors than those patients treated surgically. Consequently, results using less sophisticated radiation therapy techniques were less than optimal, raising concerns that radiation therapy might not be as effective as radical prostatectomy. However, with long-term results obtained across a broad range of patients, it is now

clear that radiation therapy for prostate cancer provides excellent disease-free survival, comparable to radical prostatectomy for men at similar risk of prostate cancer recurrence.

The following section provides a brief description of how men are evaluated and risk-stratified for radiation therapy, followed by a description of treatment techniques, and a review of treatment outcomes for men with low-, intermediate-, and high-risk prostate cancer. The use of radiation therapy to treat local prostate cancer recurrences after radical prostatectomy is also reviewed.

Conventional External Beam Radiation Therapy for Localized Prostate Cancer

For over three decades, external beam radiation therapy and radical prostatectomy have been widely used for the definitive management of clinically localized prostate cancer. Although there have been no large randomized trials in North America or Europe that have directly compared the two treatment modalities, retrospective comparisons are plentiful, but limited by the tendency of older men with higher prostate cancer to have been treated with suboptimal radiation doses and techniques. In general, the conventional techniques used standard radiation fields, based on bony pelvic landmarks, to define the region of clinical interest for a dose range of 65 to 70 Gy delivered to the prostate. Commonly, a four-field pelvic box with custom Cerrobend (Cerro Metal Products Company, Bellefonte, PA) blocking was used to treat the prostate, seminal vesicles, and proximal lymphatic drainage. These fields were treated to a dose of 45 to 50 Gy in 1.8- to 2.0-Gy fractions. The prostate, and sometimes the seminal vesicles plus a safety margin, were then boosted to 65 to 70 Gy. Cerrobend blocking was used to shield, if possible, the posterior wall of the rectum, anal canal, and any small bowel. In spite of its limitations, this version of external beam radiation therapy was fairly effective: although overall survival numbers generally were higher for men treated with radical prostatectomy (often younger and healthier men), cause-specific survival rates were not significantly different.[330] In an analysis of pathologically staged men with stage A2-B prostate cancer treated as part of Radiation Therapy Oncology Group (RTOG) Trial 77–06, 5- and 10-year survival rates, 87% and 63%, respectively, were comparable to age-matched controls without prostate cancer.[331] The prostate cancer-specific survival was 86%, which was similar the to outcomes of some surgical series.[332,333]

With the ready availability of serum PSA testing, current outcome comparisons focus on PSA as a marker of prostate cancer recurrence following primary treatment ("PSA relapse"-free survival). A rising serum PSA after radiation therapy for prostate cancer is correlated with the appearance of progressive or metastatic prostate cancer on further follow-up.[334] Furthermore, the rate of serum PSA rise may help distinguish between a local or distant treatment failure. Men with slow rates of serum PSA increases are more likely to have local prostate cancer recurrences, whereas men with a rapid serum PSA rise appear more likely to have distant prostate cancer metastates.[335] In 1997, the American Society for Therapeutic Radiology and Oncology (ASTRO) issued a consensus statement establishing the definition of recurrence of prostate cancer following radiation therapy as three consecutive rises in serum PSA levels ("biochemical" treatment failure) with determination made at least 3 months apart.[336] Before these criteria were formulated, treatment outcomes in different studies and case series were difficult to compare because of the lack of uniformity in defining treatment failure.

Pretreatment serum PSA levels are particularly predictive of radiation treatment outcome. In a case series of men ($N = 461$) with stage T1-T2 prostate cancer treated at M.D. Anderson Cancer Center, 5-year PSA relapse-free survival rates for men with pretreatment PSA levels of less than 4 ng/mL, 4 to 10 ng/mL, 10 to 20 ng/mL, and more than 20 ng/mL were 91%, 69%, 62%, and 38%, respectively.[337] In another study, Zietman and coworkers[338] reported 4-year PSA relapse-free survival of 65% for pretreatment PSA level below 15 ng/mL and 6% for patients with levels above15 ng/mL. The routine monitoring of serum PSA to detect cancer recurrence following primary treatment spurred interest in escalating radiation doses to improve cancer control.

Toxicity of Conventional External Beam Radiation Therapy

Dose escalation with conventional external beam radiation therapy has been limited by the toxicity of treatment (Table 88-7). Most men experience dysuria and/or diarrhea during the course of prostate cancer therapy, but these symptoms generally resolve weeks after completion of treatment. Long-term sequelae of conventional external beam radiation therapy (i.e., delivered without the use of conformal techniques) were reviewed in an analysis of 1020 patients treated in RTOG trials 75–06 and 77–06.[339] The incidence of late grade 3 or 4 urinary complications, such as hematuria, cystitis, bladder contracture, or urethral stricture, was 7.7%, with surgical intervention needed for 0.5%. Grade 3 or 4 rectal complications, such as bleeding, ulceration, proctitis, rectal/anal stricture, or chronic diarrhea, were seen in 3.3%, with surgery for bowel obstruction or perforation needed in 0.6%. Notably, the risk of complications was significantly higher when doses greater than 70 Gy were administered by these nonconformal techniques.

Data on the incidence of erectile dysfunction after external beam radiation therapy have been widely variable. Sexual function has many facets that are difficult to evaluate or quantify. A commonly used qualitative definition of sexual potency is the ability to achieve spontaneous erections sufficient for intercourse. While potency rates after radical prostatectomy have increased with use of nerve-sparing techniques, the mechanism of radiation-related erectile dysfunction appears unrelated to the neurovascular bundles. Zelefsky and colleagues[340] specifically addressed this topic by performing duplex ultrasound studies before and after prostaglandin injection to stimulate erections in men with radiation-related erectile dysfunction. A diminished peak penile blood flow rate (<25 mL/min) was evident in 63% of such men, with abnormal distensibility of the corpora cavernosa in 32%. Thus, the primary mechanism of radiation therapy-associated impotence may be vascular damage rather than nerve damage. Fisch and associates[341] demonstrated a correlation between incidence of erectile dysfunction post-radiation therapy and radiation dose to the vascular penile bulb. Men receiving more than 70 Gy to more than 70% of the bulb of the penis are at greatest risk of experiencing radiation therapy-associated erectile dysfunction. A steady decline in potency rates over time is characteristic for men treated with external beam radiation therapy. In a large series ($N = 434$) of men treated with radiation therapy at Stanford University, 86% of the men remained potent at 15 months after treatment, but

Table 88-7 Radiation Therapy Oncology Group Criteria for Late Morbidity after Radiation Therapy

Grade	Criteria
1	Minor symptoms requiring no treatment
2	Symptoms responding to simple outpatient management, lifestyle not affected
3	Distressing symptoms altering patient's lifestyle Hospitalization for diagnosis or minor surgical intervention (such as urethral dilatation) may be required.
4	Major surgical intervention (such as laparotomy, colostomy, cystectomy) or prolonged hospitalization
5	Fatal complication

only 50% were potent 6 years later, and only 30% maintained erectile function for the remainder of their lives.[342] Sildenafil administration resulted in improvement of erectile function in 74% of men with radiation therapy-associated erectile dysfunction in a study at Memorial Sloan-Kettering Cancer Center.[343] Men who do not respond to sildenafil may respond to intracavernosal prostaglandin injections.

Second malignancy after definitive radiation therapy for prostate cancer is uncommon. Using data from the Surveillance, Epidemiology, and End Results (SEER) program cancer registry, Brenner and coworkers[344] compared second malignancy risks for men ($N = 51,584$) who received radiation therapy for prostate cancer from 1973 to 1993 versus the risks for men ($N = 70,539$) who underwent radical surgery during the same time period, finding a small but significant increase in second malignancy attributable to radiation treatment. The most common radiation-induced tumors were carcinomas of the bladder and rectum, and sarcoma. The absolute risk of second malignancy for men who were treated with radiation therapy was 1 in 290. For survivors more than 10 years after treatment, the risk increased to 1 in 70.

Three-Dimensional Conformal Radiation Therapy

The advent of CT-based simulation and treatment planning and the innovation of multileaf collimators in modern linear accelerators have allowed for increased precision and accuracy in radiation therapy. Three-dimensional reconstructions of acquired CT images are generated, and target volumes (e.g., prostate and seminal vesicles) are delineated. Critical structures (e.g., bladder and rectum) to be avoided also are contoured. Computerized treatment planning software allows the iterative process of designing beam arrangements that will deliver a prescribed dose to the regions of interest and minimize dose to a given volume of a critical organ. Target volumes and normal organs are visualized in three dimensions (permitting the so-called "beam's-eye view," a portrayal of the target area as if looking straight down the path of the radiation beam). Computerized multileaf collimators shape each individual beam to conform to the shape of the target in the beam's-eye view. The treatment planning system generates a dose-volume histogram for a selected treatment plan, a graphic description of the relationship between dose administered and volume of an organ that is receiving a given dose (Fig. 88-10), which allows an objective assessment of the anticipated performance of a proposed radiation treatment plan. Since these technologies became clinically available in the 1990s, they have been used in dose escalation studies in prostate cancer.

The profound effect of radiation dose escalation on treatment outcomes for prostate cancer has been demonstrated through work from several institutions.[345–348] Men with intermediate-risk prostate cancer (serum PSA values of 10–20 ng/mL) may benefit most from dose-escalation. However, in a large cohort of men ($N = 1100$) treated with three-dimensional conformal radiation therapy (3D-CRT) at Memorial Sloan-Kettering Cancer Center, a significant benefit of dose escalation was evident regardless of the pretreatment PSA.[347] Initially, men with prostate cancer were treated with conventional radiation dose levels of 64.8 to 70.2 Gy using 3D-CRT techniques, and then the radiation dose was increased to as high as 86.4 Gy. At a median follow-up of 60 months, PSA relapse-free survivals for men with low-risk prostate cancer treated to radiation doses of 64.8 to 70.2 Gy versus 81 Gy, were 77% and 98%, respectively.[347] Men with intermediate- and high-risk prostate cancers also showed significant improvement.

Will improved treatment outcomes from 3D-CRT, evidenced by reduced numbers of men with prostate cancer relapses detected as a rising serum PSA, result in improvements in disease-free survival, freedom-from-distant metastasis, or overall survival? A randomized dose escalation trial detected a substantial improvement in prostate cancer control rates for men with prostate cancer, especially men with a pretreatment PSA higher than 10 ng/mL (Fig. 88-11).[345,349] This study involved the stratification of men ($N = 305$) with stage T1-T3 prostate cancer to undergo treatment to a total dose of either 70 Gy using conventional radiotherapeutic techniques, or to 78 Gy utilizing a six-field 3D-CRT boost after the delivery of an initial 46 Gy. Results revealed a freedom-from-PSA relapse of 64% and 70% at 6 years for the 70 Gy and 78 Gy groups, respectively ($P = 0.03$). Men who had a pretreatment PSA higher than 10 ng/mL were found to have the most significant benefit from radiation dose escalation, with freedom-from-PSA relapse rates of 62% for the 78 Gy arm and 43% for the 70 Gy arm ($P = 0.01$), a benefit not seen for men with a pretreatment PSA below 10 ng/mL. Overall survival was not significantly different between the two radiation doses, but a trend toward an improved freedom-from-distant metastasis was evident in men treated on the 78-Gy arm, 98% versus 88% at 6 years ($P = 0.056$).

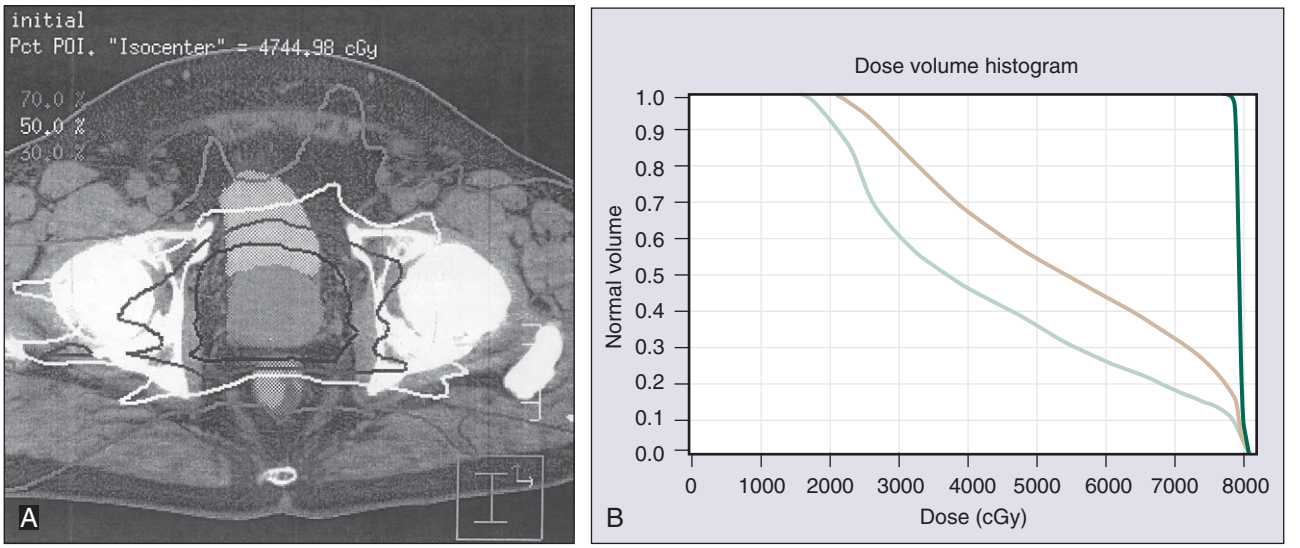


Figure 88-10 • Intensity-modulated radiation therapy (IMRT). **A,** A representative axial CT slice from a man with low-risk prostate cancer treated by using a seven-field IMRT plan. The isodose distribution is displayed. *Dark inner line,* prescription isodose curve. **B,** The IMRT treatment plan shown as a dose/volume histogram: the curves from left to right represent bladder, rectum, and prostate.

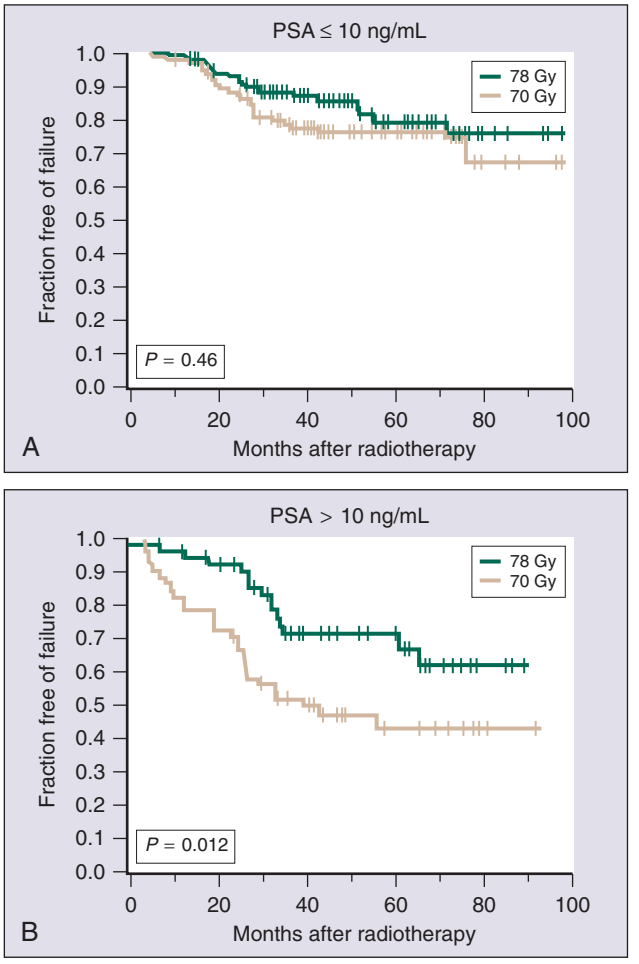


Figure 88-11 • Kaplan-Meier actuarial probability of relapse-free survival after radiation therapy for prostate cancer, stratified by radiation dose (78 Gy vs. 70 Gy). **A,** Men with favorable-prognosis prostate cancer (serum prostate-specific antigen [PSA] ≤10 ng/mL). **B,** Men with poorer-prognosis prostate cancer (serum PSA, 10 ng/mL). (From Pollack A, Zagars GK, Starkschall G, et al: Prostate cancer radiation dose response: results of the M.D. Anderson phase III randomized trial. Int J Radiat Oncol Biol Phys 2002;53:1097–1105.)

Toxicity of Three-Dimensional Conformal Radiation Therapy

While the use of 3D-CRT was intended to minimize the effects of high-dose radiation on normal tissues, increased late toxicities have been noted with escalating radiation doses used in 3D-CRT.[348,350] In the Fox Chase case series, the 5-year incidence of grade 3 or 4 rectal toxicity at a dose of 75 to 76 Gy was 8%. However, after the anterior rectal wall was shielded to keep the dose to this region under 72 Gy, grade 3 or 4 rectal toxicity was evident in only 2% of patients. From the M.D. Anderson Cancer Center dose escalation case series, men who received more than 70 Gy to 30% or more of the defined rectal volume had a significantly higher risk of rectal toxicity.[351] Zelefsky and colleagues[350] reported a 1.2% actuarial risk of grade 3 or higher rectal toxicity by 5 years with 3D-CRT. Grade 2 rectal bleeding was seen in 17% of men who received 75.6 Gy or more as compared to 6% for men receiving 64.8 to 70.2 Gy. Furthermore, even if the rectum was completely shielded in each field above a dose of 72 Gy, grade 2 rectal bleeding was seen in 15% of men. As for urinary toxicity with 3D-CRT, urethral strictures have been observed in 1.5% of treated men, with a 4% incidence of stricture in men with a history of previous transurethral resection of the prostate (TURP). Grade 3 hematuria appears in as many as 0.5% of men, with grade 2 hematuria in 13% of men treated to a dose of 75.6 Gy or higher and 4% of men treated to lower total doses. Urinary incontinence is rare following treatment with 3D-CRT (<0.2% with 2% in the setting of a prior TURP).[352]

Intensity-Modulated Radiation Therapy

Intensity-modulated radiation therapy (IMRT) equipment and treatment planning software have become increasingly available, with the technology attracting interest from both academic and community cancer centers for the treatment of a variety of malignancies. The largest experience with IMRT to date has been in the treatment of prostate cancer. Via inverse planning, IMRT allows identification of the region to be treated along with surrounding critical normal organs so that radiation dose and volume goals can be prescribed for each target and structure. The treatment planning software then derives an optimized dose distribution by modifying the number, orientation, and intensity of the beams across the designated volume. This is in contrast to 3D-CRT, where beam arrangement and field shapes must be designed manually to accomplish radiation dose-volume goals, a task that typically requires multiple time-consuming iterations.

In a case series ($N = 772$) of men with clinically localized prostate cancer treated with IMRT at Memorial Sloan-Kettering Cancer Center, a reduction in late rectal toxicity was seen in comparison to 3D-CRT.[353] Most of the men (698 of the 772) were treated to a total dose of 81 Gy while the remainder received 86.4 Gy. With a median follow-up of 24 months, actuarial rate of grade 2 or higher rectal bleeding at 3 years was 4%, and only 0.5% of men experienced any grade 3 rectal toxicity (no grade 4 rectal toxicity was seen). However, despite the increased conformality of incident radiation and the decreased bladder volumes receiving high radiation doses, there was no improvement in late urinary toxicity with IMRT versus 3D-CRT, with 15% of men suffering late grade 2 urinary toxicity. Because this may be the result of high-dose radiation to the urethra, decreasing urethral doses for men with prostate cancer limited to the peripheral zone of the prostate may be a means of reducing late urinary toxicity with IMRT, but better diagnostic imaging is necessary to identify men with such cancers.

One concern with IMRT techniques, in general, is the potential for inadequate treatment at the margins of radiation fields with increasingly conformal radiation dose delivery. However, preliminary treatment outcome data obtained thus far with IMRT appear similar to those with 3D-CRT, with 3-year actuarial PSA relapse-free survival rates, using American Society for Therapeutic Radiology and Oncology (ASTRO) consensus criteria, for men with low-, intermediate-, and high-risk prostate cancer of 92%, 86%, and 81%, respectively.[353] It should be noted that planning target volume (PTV) definitions for IMRT often are the same as those used with 3D-CRT. If tighter PTV definitions are to be used, better prostate immobilization and localization techniques are likely needed. This strategy currently is being investigated in several centers with the use of electronic portal imaging (EPI), a real-time treatment set-up verification system, and of B-mode acquisition and targeting (BAT), an ultrasound-based real-time localization system.[354]

Brachytherapy

Prostate brachytherapy refers to the implantation of radioactive sources into the prostate under transrectal ultrasound (TRUS) guidance. In principle, brachytherapy offers an attractive means for radiation dose escalation and conformality in the treatment of clinically localized prostate cancer. Modern prostate brachytherapy techniques that use ultrasound or CT-based targeting, a perineal template for precise seed implantation, and computerized treatment planning

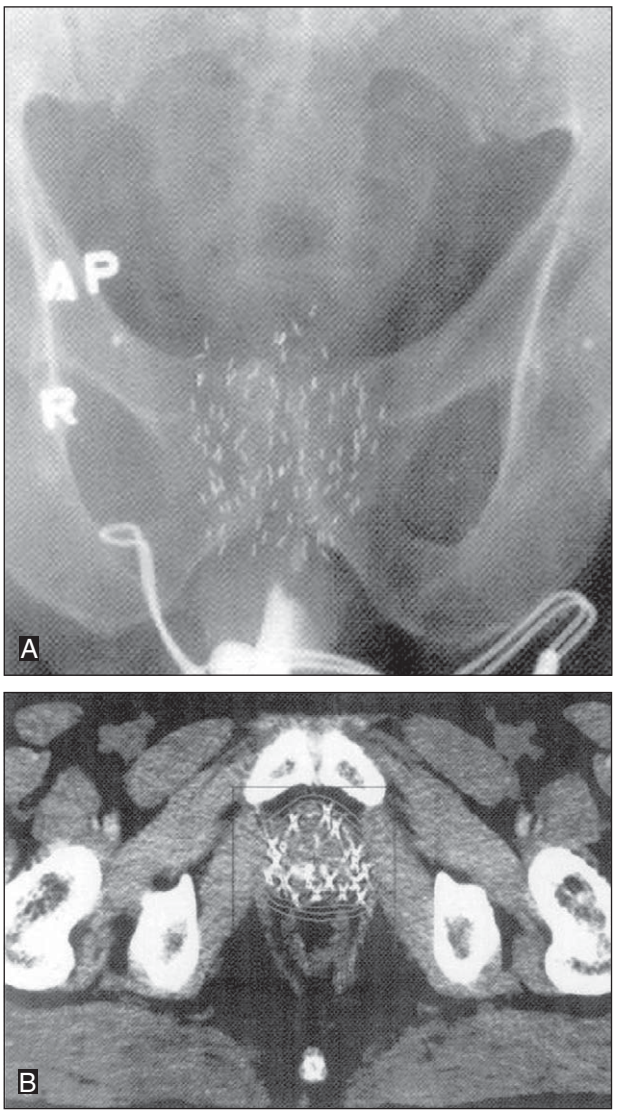


Figure 88-12 • Interstitial brachytherapy for prostate cancer. **A,** Radiograph obtained after implantation of radioactive seeds. **B,** CT image showing radioactive seed location within prostate. (From Speight JL, Roach M III: Imaging and radiotherapy of the prostate. Radiol Clin North Am 2000;38:159–177.)

have gained in popularity over the past 15 years (Fig. 88-12). For the patient with prostate cancer, this option may be most convenient, allowing a rapid return to normal lifestyle and activity. A typical brachytherapy procedure is performed in 2 hours, often under spinal anesthesia, and does not require an overnight hospital stay. Before the procedure, an ultrasound or CT-based volume study is performed and a preplan is formulated, specifying three-dimensional seed distribution to deliver a prescribed dose to the prostate and a periprostatic margin. Typically, peripherally biased seed distributions provide a relatively lower dose to the urethra. In the operating room, using spinal or general anesthesia and with Foley catheter in place, the patient is placed in the dorsal lithotomy position, a TRUS of the prostate volume is registered to approximate the prostate volume obtained from a preprocedure study (some centers use real-time intraoperative treatment planning systems to make adjustments to optimize the dose distribution because the prostate volume may be slightly different from that of the preplan), hollow needles are guided into the prostate through the perineum using a template, and radioactive sources are deposited in the prostate according to the plan as the needles are withdrawn (through use of the Mick applicator or with seeds strewn on ribbons with equal spacing). Post-treatment CT scans are then routinely done to evaluate the quality of the implant procedure.[355]

Thus far, every use of permanent brachytherapy for prostate cancer reported has been a retrospective analysis of a case series from a single institution. Comparisons among these series, or to results from external beam radiation therapy or radical prostatectomy, are fraught with difficulty due to the lack of uniformity in reporting of patient selection and treatment outcome criteria. Additionally, implantation techniques, isotopes, dosimetry, and operator experience vary widely from one prostate cancer brachytherapy series to the next. Many practitioners have recommended brachytherapy for men with low-risk prostate cancer, but have added supplementary external beam radiation therapy to brachytherapy for men with prostate cancer at higher risk for extraprostatic extension. Combinations of brachytherapy and external beam radiation therapy also have been advocated for use in all men with clinically localized prostate cancer.[356] In 1999, the American Brachytherapy Society recommended that brachytherapy using radioactive iodine or palladium might be appropriate for men with prostate cancer of clinical stage T1-T2a, with a serum PSA of 10 ng/mL or less, and a Gleason score 6 or less, and that supplemental external beam radiation therapy should be added for men with higher risk disease.[357] This recommendation was based in part on inferior outcomes reported for men with high-risk prostate cancer treated with brachytherapy.[358] It is possible that favorable outcomes may be achieved even in some men with prostate cancer and some high-risk features through the use of generous periprostatic treatment margins at the time of implant and/or the use of supplemental external beam therapy.[359–361]

In the absence of a prospective randomized trial, the routine use of prostate brachytherapy in the treatment of clinically localized prostate cancer has been based on retrospective studies with varying follow-up time. Recently, treatment outcomes for more than 2500 men with prostate cancer, treated at 11 different institutions with permanent interstitial brachytherapy, were reported.[362] The median follow-up for this group of men with stage T1 or T2 prostate cancer was 63 months, and all were treated with either ^{125}I or ^{103}Pd without use of hormonal therapy. Men with low-, intermediate-, and high-risk prostate cancer had 8-year actuarial PSA relapse-free survivals of 82%, 70%, and 48%, respectively, using ASTRO criteria. As in previous studies, the dosimetric quality of the implant was critical to outcome: for men in whom 90% of the prostate (D_{90}) received 130 Gy or more, the 8-year PSA relapse-free survival was 93%, while for men in whom the prostate D_{90} was less than 130 Gy, the 8-year PSA relapse-free survival was 76%. Three other series have reported long-term results with brachytherapy.[363–365] Ragde and associates[365] reported 12-year treatment results from a group of men ($N = 229$) with T1-T3 prostate cancer who underwent ^{125}I or ^{103}Pd implantation. Men with low-risk prostate cancer ($N = 147$) in this case series were treated with brachytherapy alone, whereas men with high-risk prostate cancer ($N = 82$) received external beam radiation therapy followed by implant. The PSA relapse-free survival was 66% for men with low-risk prostate cancer and 79% for men with high-risk prostate cancer. In light of subsequent superior results in men with low-risk prostate cancer treated with brachytherapy alone, a possible explanation for the poor performance of brachytherapy alone in this case series is that there has been significant refinement of technique and treatment planning since many of these men were treated. In another case series, men with low-risk prostate cancer treated in 1986–1987 exhibited a significantly worse progression-free survival than men treated in 1988–1990.[364]

The addition of supplemental external beam radiation therapy to brachytherapy remains somewhat controversial. Davis and coworkers examined the radial distance of extra-prostatic extension of prostate

cancer and found it to be almost always 5 mm or less, which would be within a typical brachytherapy dose distribution.[366] Thus, generous periprostatic margins in brachytherapy planning may obviate the need for supplemental external beam radiation therapy. Proponents of combination therapy point to the advantage of higher biologic doses and the ability to smooth out cold spots inherent with brachytherapy, the so-called "spackle effect." Sylvester and colleagues[367] recently reported a retrospective review of 232 men with clinically localized prostate cancer treated with either ^{125}I or ^{103}Pd brachytherapy and external beam radiation therapy administered before placement of the implant. At a median follow-up of 9.4 years, the biochemical relapse-free survival for the entire study group was 74%, with biochemical relapse-free survival for low-risk prostate cancer of 85.8%, for intermediate-risk disease of 80.3%, and for the high-risk group of 67.8%. These results compare favorably with all other surgical and/or radiation series with respect to long-term durable prostate cancer control. The RTOG is studying a similar combination therapy approach using brachytherapy and external beam radiation therapy; the results of this study will help to determine the incremental benefit of supplemental external beam radiation therapy in each risk group, as the addition of this therapy nearly doubles the cost of treatment.[368]

Relative contraindications to the use of prostate brachytherapy are large prostate size, preimplant obstructive urinary symptoms, history of prior TURP, and the presence of perineural prostate cancer invasion on prostate biopsy. Large prostate size has been perceived to be associated with a higher risk of urinary morbidity postimplant and with unsuitability for implant due to pubic arch interference. Men with a prostate volume of greater than 50 mL have been either counseled against brachytherapy or placed on androgen deprivation therapy in an attempt to reduce gland size. Nonetheless, the implantation of large prostates with radioactive seeds has been described with acceptable morbidity.[369,370] In one case series, postimplant dosimetry quality was found to be independent of prostate size or use of androgen deprivation therapy.[370] The use of the extended dorsal lithotomy position and steering of needles around the pubic arch increases the fraction of men that can be implanted with radioactive seeds by experienced radiation oncologists.[371] The correlation of preimplantation obstructive urinary symptoms and postimplantation urinary obstruction is not yet resolved. Terk and associates[372] reported that a high International Prostate Symptom Score (I-PSS), a measure of obstructive urinary symptoms, predicted postimplant urinary retention. With the use of α-blockers before and after implant procedures, others have noted no association between preimplant I-PSS and urinary obstruction.[373] A prospective study examining preimplant urinary flow rate and postvoid residual, in addition to I-PSS, showed no association of obstructive urinary symptoms with postimplant urinary retention or long-term urinary function.[374] TURP is thought to be a relative contraindication to prostate brachytherapy, because it has been associated with unacceptably high rates of urinary incontinence. This may be attributable to seed loading approaches that result in a high central dose to the TURP defect. However, by using a peripheral source loading approach to limit dose to the TURP defect to 110% of the prescription dose, the incidence of urinary incontinence may be reduced.[375] Finally, because prostate cancers exhibiting perineural invasion have been shown to be associated with inferior outcome in radical prostatectomy series, this adverse prognostic finding will likely also be associated with inferior outcome from brachytherapy.[376] Curiously, in one case series no difference in brachytherapy treatment outcome attributable to the presence of perineural invasion was evident.[377]

A phenomenon peculiar to prostate brachytherapy that deserves mention is the so-called "PSA spike." With a time of onset between 12 and 30 months postimplantation, approximately one third of men with prostate cancer treated with brachytherapy will experience a transient increase in serum PSA.[378] This spike may be due to radiation-associated prostatitis that compromises prostate architecture, permitting more PSA to appear in the serum. Such PSA spikes portend no worse long-term outcome.

Table 88-8 Physical Differences Between ^{125}I and ^{103}Pd Radioactive Seeds

	^{125}I	^{103}Pd
Year introduced	1965	1986
Photon energy (keV)	28	21
Half-life (days)	59.4	17
Initial dose rate (for monotherapy)	7 cGy/hr	18–20 cGy/hr
RBE	1.4	1.9

RBE, relative biologic effectiveness.

Another controversy for prostate brachytherapy concerns the choice of isotope and use of androgen deprivation therapy. The most common sources in use today are ^{125}I and ^{103}Pd (Table 88-8). Thus far, there have been no compelling data to support the superiority of one isotope or the other. It has been hypothesized that the higher initial dose rate of ^{103}Pd might be advantageous for the treatment of cancers with a relatively low α/β ratio (more radioresistant) such as prostate cancer; however, retrospective data for prostate cancer have been inconclusive.[379] A prospective randomized trial directly comparing ^{125}I to ^{103}Pd for prostate cancer brachytherapy is ongoing. Most of the experience with prostate brachytherapy has been with permanent low dose-rate (LDR) implants. Several centers have collected experience with temporary high dose-rate (HDR) implants for prostate cancer brachytherapy.[380–382] Although this treatment approach is not widely used, the available results appear comparable to those of permanent brachytherapy for clinically localized prostate cancer. HDR approaches have a theoretical advantage over LDR brachytherapy for the treatment of cancers with a low α/β ratio that approximates that of normal tissue. That is, a higher biologically equivalent radiation dose (BED) with HDR implants could be delivered with similar rates of morbidity as compared to LDR implants. Therefore, HDR implants would seem to be ideal for prostate cancer. Further study is needed to validate this theory.

Androgen deprivation therapy has been used with prostate cancer brachytherapy both to reduce the size of the prostate gland and to improve outcomes. Most prostate glands exhibit some decrease in volume after 3 months of androgen deprivation therapy, with an average 30% to 40% reduction and little further volume decreases.[383] About 10% of prostate glands will show no volume reduction at all in response to androgen deprivation. Decreasing the size of the prostate may reduce pubic arch interference in selected men. Blank and coworkers[384] reported that men treated with androgen deprivation therapy tended to have smaller prostates that required fewer seed implants. However, at this point there are no data to suggest that smaller prostate volumes correlate with reduced acute or late morbidity from brachytherapy. Furthermore, although prospective randomized trials have demonstrated improved survival in those men with locally advanced prostate cancer treated with external beam radiation therapy and androgen deprivation therapy, it is not clear that these results can be extrapolated to men treated with brachytherapy. A retrospective matched-pair analysis of men ($N = 60$) with prostate cancer treated at Memorial Sloan-Kettering Cancer Center showed no benefit for the addition of androgen deprivation therapy to brachytherapy for men with low-, intermediate-, or high-risk prostate cancers.[385]

Toxicity of Brachytherapy

The short- and long-term sequelae of brachytherapy for prostate cancer differ from those of external beam radiation therapy and

radical prostatectomy. Kleinberg and colleagues[386] described the morbidity outcomes of the early Memorial Sloan-Kettering Cancer Center experience with permanent transperineal brachytherapy, reporting that the most common side effects were nocturia and dysuria (80% and 48%, respectively, 2 months after implantation). By 12 months following implantation, these figures had declined (to 45% and 20%, respectively). Urinary retention is seen in 3% to 14% of men and usually lasts 1 week or less. The most bothersome late complications of prostate cancer brachytherapy are urethral stricture and urinary incontinence. Ragde and associates[387] reported a 5.1% incidence of urinary incontinence in men treated with prostate cancer brachytherapy and followed for 7 years; each of the men with incontinence had a history of TURP. Urethral stricture developed in 14.4% of the men. Others also have seen an increased incidence of urinary incontinence in the setting of a history of TURP.[388] In a cohort study of Medicare beneficiaries ($N = 2124$) who were treated with brachytherapy, urinary incontinence was noted in 6.6%, and bladder outlet obstruction requiring intervention was found in 8.3%.[389] In a more recent report from the RTOG multi-institution prospective trial (RTOG 98–05) of definitive brachytherapy alone, 23% of the men experienced urinary toxicity of a grade greater than 2.[390]

Rectal morbidity after brachytherapy includes change in bowel habits, rectal bleeding or ulceration, and fistula. Kleinberg and coworkers[386] reported that 25% of men treated with prostate cancer brachytherapy had a change in bowel habits within 2 months of implant. By 12 months postimplant, no patient had grade 2 or higher rectal symptoms. The 3-year actuarial incidence of rectal bleeding was 31% and the incidence of ulceration was 16%. With more operator experience, rates of rectal complications subsequently fell: an update of the Memorial Sloan-Kettering Cancer Center experience revealed only a 9% incidence of rectal bleeding.[391] Among Medicare beneficiaries, rectal injury not requiring colostomy was reported in 5.1% of men treated with prostate cancer brachytherapy, while colostomy was required in 0.3%.[389] Radiation proctitis was reported in 2.2%, fistula in 1.8%, and ulceration in 1.1%.[389] Generally, late rectal complications have their onset within 3 years of implant. Conservative measures usually generally result in spontaneous resolution of bleeding. In the recent RTOG trial of brachytherapy for prostate cancer (RTOG 98–05), 5% of men suffered grade 2 bowel toxicity, and no man experienced long-term grade 3 or 4 bowel toxicity.[390]

As the popularity of prostate brachytherapy for clinically localized prostate cancer grew in the 1990s, a commonly cited advantage of the treatment modality was a lower incidence of treatment-associated erectile dysfunction compared with external beam radiation therapy or radical prostatectomy. Undoubtedly, this selling point tipped the scales in favor of brachytherapy for many men faced with selecting a treatment for early-stage prostate cancer. For instance, Stock and colleagues[392] reported a 2 year potency rate of 94% after implant, while Wallner and associates[393] reported a 3-year potency rate of 86%. Studies with longer follow-up, however, have shown a continued decrease in sexual potency over time. With more long-term follow-up in other case series, only 57% of men retained potency at 5 years.[391] Even Stock and coworkers[394] subsequently reported a 6-year potency rate of 59% in their case series. Notably, their study found that 70% of men with normal erectile function before implant retained potency at 6 years, whereas men with "erectile function sufficient for intercourse" but suboptimal erections had only a 34% 6-year potency rate. Using postimplant dosimetry studies, Merrick and colleagues[395] demonstrated that dose to the penile bulb correlated with postimplant erectile dysfunction. In most men who retained potency, the dose delivered to 50% of the penile bulb was less than 50 Gy. This knowledge potentially may result in improved morbidity outcomes with technical attention to this dose threshold. Erectile dysfunction is not the sole complication of prostate brachytherapy with the potential to affect sexual quality of life, however; there have been reports of hematospermia in 28%, orgasmalgia in 15%, and alteration in the intensity of orgasm in 38% of patients.[396] These side effects tend to be transient in most men.

Recently, health-related quality-of-life instruments have become available to evaluate morbidity outcomes for prostate cancer treatments. A prospective study of health-related quality-of-life outcomes in men treated with brachytherapy, external beam radiation therapy, or radical prostatectomy was recently reported.[397] Men treated with external beam radiation therapy did not show significant changes in health-related quality of life following completion of treatment, whereas men treated with brachytherapy and radical prostatectomy had significant decreases in health-related quality of life within the first month following treatment. By 12 months after treatment, health-related quality of life had returned to baseline in each of the three treatment groups.

Proton Beam Radiation Therapy

Although proton beam radiation therapy is available only at a few centers worldwide, there has been interest in its use for prostate cancer. The unique physical properties of protons make them ideal for the treatment of disease in close proximity to critical structures. Specifically, protons deposit the majority of their energy at the very end of their linear tracks, a phenomenon termed the *Bragg peak*. The dose falls off very rapidly at depths beyond the Bragg peak, a feature that is particularly useful in the treatment of prostate cancer, to minimize rectal and bladder dose. Investigators from Loma Linda University reported their experience treating men ($N = 1255$) with T1-T3 prostate cancer.[398] Men were treated with protons alone to 74 cobalt Gray equivalents (CGE) or with photons to 45 Gy followed by proton boost to 75 CGE. The median follow-up was 62 months, and the 8-year actuarial biochemical disease-free survival rate was 73%. In a recent prospective, randomized trial of 70.2 GyE versus 79.2 GyE (combination of photons plus protons) for men ($N = 393$) with stage T1b-T2b prostate cancer and a serum PSA below 15 ng/mL, at a median follow-up of 5.5 years, 61.4% of the men treated with 70.2 GyE versus 80.4% of men treated with 79.2 GyE were free of biochemical treatment failure, supporting the concept that higher doses of radiation result in a statistically significant reduction in the risk of recurrence of localized prostate cancer.[399]

Adjuvant Endocrine Therapy and Radiation Therapy for Low-Risk Localized Prostate Cancer

Androgen deprivation therapy has been found to improve survival in randomized trials of men with high-risk prostate cancer treated with external beam radiation therapy (Fig. 88-13).[400–402] The role of androgen deprivation therapy in men with low-risk prostate cancer is unknown. D'Amico and associates reported results of a large retrospective study ($N = 1586$) of men treated with 3D-CRT plus or minus androgen deprivation therapy for low-risk, intermediate-risk, and high-risk prostate cancer.[403] In this study, the median radiation dose was 70.2 Gy and androgen deprivation therapy was used for 276 of the men for two months before radiation therapy, during treatment, and for two months after treatment was completed. With a median follow-up of 51 months, the 5-year PSA relapse-free survival for men with low-risk prostate cancer was 92% with the addition of androgen deprivation therapy versus 84% without ($P = 0.09$). Men with intermediate- and high-risk prostate cancer also faired significantly better when given androgen deprivation therapy. RTOG Trial 94–08, which completed accrual in 2001, has been designed to ascertain whether men with stage T1b-T2 prostate cancer and a serum PSA of 20 ng/mL or less benefit from the addition of "complete androgen blockade" given for four months before and concomitantly with external beam radiation therapy.

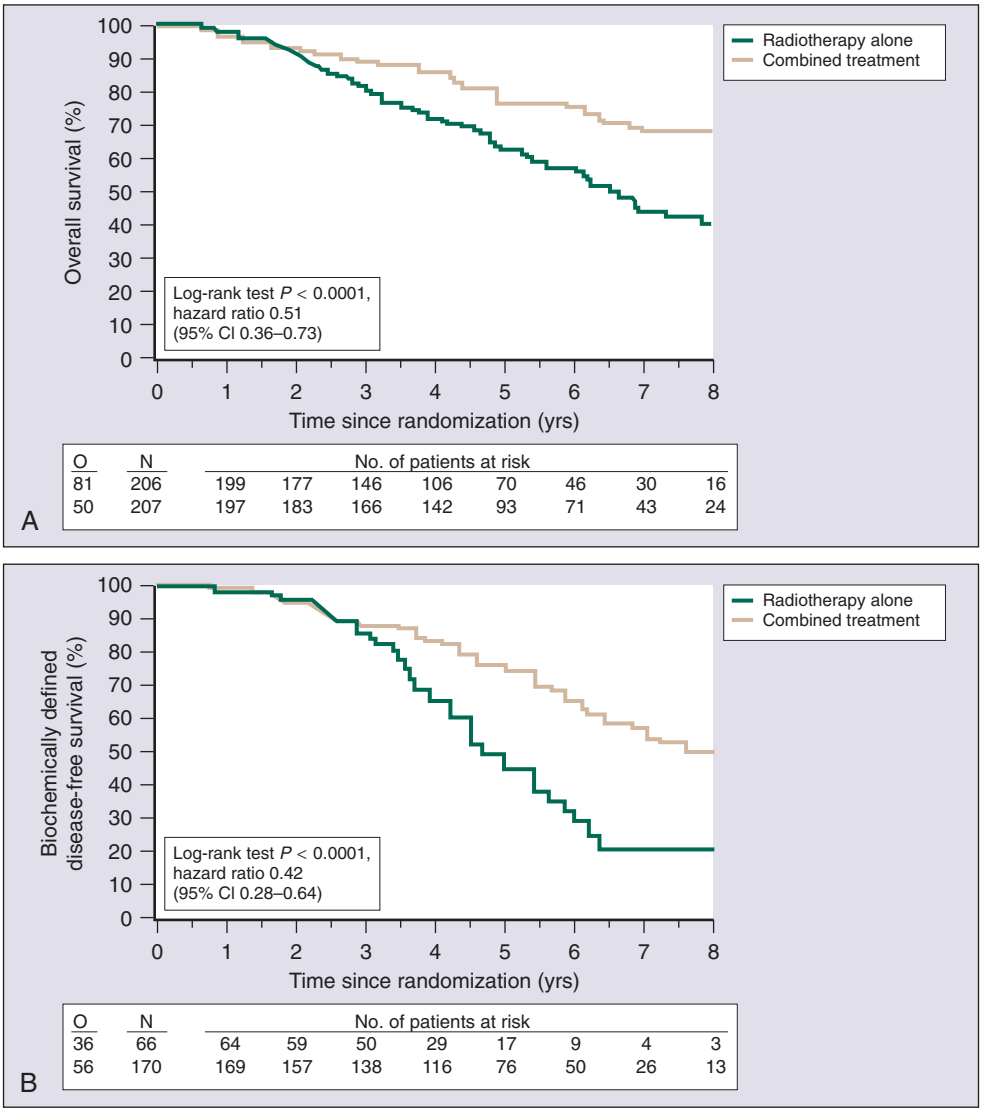


Figure 88-13 • Kaplan-Meier estimates of survival for men with prostate cancer from a prospective randomized clinical trial comparing a combination of androgen-deprivation therapy (goserelin acetate for a total of 3 years with cyproterone acetate for 1 month) and radiation therapy versus radiation therapy alone. **A,** Overall survival. **B,** Relapse-free. O, number of deaths; N, number of subjects. (From Bolla M, Collette L, Blank L et al: Long-term result with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer [an EORTC study]: a phase II randomized trial. Lancet 2002;360:103–106.)

Adjuvant Endocrine Therapy and Radiation Therapy for Intermediate- and High-Risk Localized Prostate Cancer

Men with intermediate-risk prostate cancer (clinical stage T2b, Gleason score of 7, or PSA of 10–20 ng/mL) fall at the break-point of defined prognostic subgroups in many case series reporting treatment outcomes, making treatment recommendations difficult. Although dedicated phase III trials evaluating the role and technique of radiation therapy with this group of men have not been performed, intermediate-risk men often are included in studies of radiation treatment for both men with low-risk prostate cancer and those with more advanced disease. Radiotherapeutic options for men with intermediate-risk prostate cancer include external beam radiation therapy, prostate brachytherapy, or a combination of both modalities. The need for adjuvant androgen deprivation therapy in this subset of men is debatable, but a potential benefit can be inferred from phase III clinical trials and single institution case series. One recent trial of a limited course of androgen deprivation combined with radiation (N = 206) for clinically localized prostate cancer (Gleason score > 7 or a serum PSA > 10 ng/mL or evidence of extraprostatic disease) randomized men to receive radiation therapy to a dose of 70 Gy alone or 70 Gy radiation plus 6 months of androgen deprivation therapy. At a median follow-up of 4.52 years, men treated with the combination of radiation plus androgen deprivation had a significantly higher overall survival than men treated with radiation alone (actuarial 5 year survival = 88% vs. 78% respectively).[404]

High-risk prostate cancer (clinical stage T2c-T4, Gleason score of 8–10, or serum PSA > 20 ng/mL) usually is treated with androgen deprivation therapy in conjunction with radiation therapy. The optimal duration and sequencing of androgen deprivation therapy, however, remains to be determined. Brachytherapy, usually in conjunction with both androgen deprivation therapy and external beam radiation therapy, also has been used to treat men with high-risk prostate cancer.

Adjuvant Endocrine Therapy and Radiation Therapy for Locally Advanced Prostate Cancer

Combined modality treatment using androgen deprivation therapy in conjunction with external beam radiation therapy takes advantage of separate and noncompeting modes of cell death such that cells that can survive the insult of one modality cannot survive the other or the additive/synergistic properties of the two.[405] Androgen deprivation

therapy has been used along with radiation therapy for many years in an attempt to modify the outcome of men with stage C (T3) prostate cancer.[406] Historically, the rationale for this treatment approach was that these men had an inferior outcome compared with men with earlier-stage prostate cancer treated with radiation therapy. In addition, the tumors often were quite bulky, and it was thought that a course of cytoreductive therapy might provide a more favorable geometry for external irradiation. However, the use of androgen deprivation therapy in combination with radiation was not universally accepted throughout the 1970s and 1980s. Radiation therapy techniques were improving, and the results from early case series exploring the benefit of androgen deprivation therapy before and/or during radiation therapy often were negative.[407,408]

In the early 1980s, two case series reported encouraging results with the use of androgen deprivation therapy and external beam radiation therapy to treat men with locally advanced prostate cancer.[409,410] Pilepich and coworkers[411] also found that men with histologically unfavorable prostate cancers who had been treated with androgen deprivation therapy and external beam radiation therapy as part of RTOG trial 75–06 exhibited similar disease-free survival and overall survival rates to those of men with more favorable prostate cancers who did not receive androgen deprivation therapy along with radiation therapy. More recently, phase III clinical trials have established the local control and survival benefits of androgen deprivation therapy given along with external beam radiation therapy for locally advanced prostate cancer. The advantage of androgen deprivation therapy before irradiation, as opposed to starting androgen deprivation therapy and external beam radiation therapy together, has never been established by a direct comparison.

RTOG 86–10 was a randomized phase III clinical trial of external beam radiation therapy alone (standard treatment arm) versus neoadjuvant and concomitant total androgen suppression and external beam radiation therapy (experimental treatment arm).[412] Eligible men had bulky (>25 cm^2), locally advanced prostate cancer (stage T2b-T4, N0-N1, M0). Men randomized to receive total androgen suppression were treated with goserelin acetate, 3.6 mg, every 28 days and flutamide, 250 mg, three times daily for 2 months before the start of, and during, radiation therapy. Standard radiation techniques were utilized, with 45 Gy delivered to the pelvis followed by a 20- to 25-Gy boost to the prostate. Extended fields were used to treat the lymph nodes when they were involved. A total of 471 men were enrolled and randomized to one of the two treatment arms. Analysis of the trial results revealed that men treated with total androgen suppression and radiation had a significant improvement in local control at 5 years compared with those men treated with radiation only ($P < 0.001$). A recent update of this trial, with a median follow-up over 6 years, continues to report a statistically significant difference in the 5-year probability of local treatment failure (22% vs. 35%, $P = 0.004$) as well as an increase in both disease-free survival (33% vs. 21%, $P = 0.004$) and cause-specific mortality (23% vs. 31%, $P = 0.05$), when considering the entire group, in favor of combined treatment. In subset analyses, there also was an improvement in overall survival for those men with Gleason score 2 to 6 prostate cancer (70% vs. 52%, $P = 0.015$), in favor of combined treatment. This improvement in overall survival was not seen when evaluating all men in the study. There are several possible explanations. It is possible that there may not be an overall survival benefit for men when total androgen suppression is added in this fashion and/or in this patient population as a whole. However, it is important to note that this study was limited in that it did not routinely obtain serum PSA levels from all men before entry, a parameter now recognized to be an extremely important prognostic factor and indicator of disease extension. Therefore, it is likely that there were a large number of men with elevated serum PSA levels in the range commonly associated with a high risk for micrometastatic prostate cancer. The study also included men with node-positive disease, also recognized to be a poor risk factor, for which the value of any treatment modality to overall survival can be debated. Nonetheless, this was an important study, performed in rigorous fashion, and revealing important and measurable benefits attributable to the addition of androgen deprivation therapy to external beam radiation therapy for these men with prostate cancer.

The RTOG 85–31 trial also targeted men with locoregionally advanced prostate cancer, including men who had undergone radical prostatectomy and were identified at pathologic examination as being at high risk.[402,413] The aim of this phase III trial was to evaluate the role of long-term adjuvant androgen suppression in men with high-risk prostate cancer. Men enrolled on the trial who underwent definitive radiation were those with clinical stage T3 (>25 cm^2), or T1-T2 disease and radiographic or histologic lymph node involvement. Men were eligible after prostatectomy if prostate cancer with capsular penetration and positive surgical margins or with seminal vesicle involvement was found. A total of 945 evaluable men were enrolled and followed for a median of 4.5 years. Conventional radiation therapy techniques were used to deliver a total dose of 44 to 46 Gy to the whole pelvis with a 20- to 25-Gy boost to the prostate or postoperative prostatic fossa, for a total dose of 65 to 70 Gy. Androgen deprivation therapy was accomplished using goserelin acetate, 3.6 mg, monthly, beginning the last week of radiation therapy. Actuarial projections at 5 years revealed 84% of men receiving adjuvant androgen deprivation versus the 71% of men on the observation arm who remained without evidence of local recurrence ($P < 0.0001$). The corresponding figures for freedom-from-distant metastases and disease-free survival were 83% versus 70% ($P < 0.001$) and 60% and 44% ($P < 0.0001$). The 5-year survival rate for the entire population was 75% on the adjuvant androgen deprivation arm versus 71% on the observation arm ($P = 0.52$). However, in men with prostate cancers with a Gleason score of 8 to 10, a statistically significant difference in actuarial 5-year survival of 66% versus 55% favoring the adjuvant androgen deprivation arm was evident ($P = 0.03$). The most recent update of this trial with a median follow-up of 5.6 years confirmed the statistically significant improvement in both absolute and cause-specific survival for adjuvant androgen deprivation given with external beam radiation therapy.[413]

Bolla and colleagues[400,401] published results of the European Organization for Research and Treatment of Cancer (EORTC) 22863 trial. This phase III trial enrolled 415 men with stage T3-T4 prostate cancer of any grade or stage T1-T2 World Health Organization (WHO) grade 3 prostate cancer with no evidence of nodal or metastatic disease. Men were randomized to receive external beam radiation therapy alone (control arm) or androgen deprivation therapy plus external beam radiation therapy (experimental arm). Androgen deprivation consisted of oral cyproterone acetate, 50 mg, three times daily for 4 weeks before radiation and goserelin acetate, 3.6 mg, started on the first day of radiation and continued every month for 3 years. Radiation therapy was delivered as 50 Gy to prostate and regional lymph nodes, followed by a 20-Gy boost to the prostate, for a total prostate dose of 70 Gy. A total of 401 men were studied, with a median follow-up of 45 months. Overall survival at 5 years was 79% in the androgen deprivation therapy plus external beam radiation therapy arm and 62% in the external beam radiation therapy alone arm ($P = 0.001$). The local recurrence-free survival was 97% for men treated with androgen deprivation therapy plus external beam radiation therapy versus 77% for men treated with external beam radiation therapy alone ($P < 0.001$). The relapse-free survival was reported to be 85% for combined treatment and 48% for radiation alone ($P < 0.001$). The most recent update of this trial, at a median follow-up of 66 months, confirmed the durability of these initial results with 5-year overall survival of 78% versus 62%, favoring the androgen deprivation therapy plus external beam radiation therapy arm ($P = 0.0002$).[401] Five year relapse-free survival also continued to favor the combination treatment (74% versus 40%).

The RTOG 92–02 Trial, which completed accrual in 2000, is a phase III prospective randomized trial of androgen deprivation

therapy plus external beam radiation therapy for men with locally advanced prostate cancer.[414] This study compared the efficacy of short-term androgen deprivation, as was administered in RTOG 86–10, with that of long-term androgen deprivation, similar to that used in the EORTC 22863 trial. A total of 1554 men with locally advanced prostate cancer stage T2c-T4 with serum PSA below 150 ng/mL were enrolled in the trial and followed for a median of 4.8 years. All men received 4 months of goserelin acetate and flutamide, 2 months before and during radiation therapy. Men were then randomized to receive either no further therapy (short-term androgen deprivation) or to be treated with goserelin acetate for an additional 24 months (long-term androgen deprivation). The radiation dose was 65 to 70 Gy to the prostate and 44 to 50 Gy to the pelvic nodes. At 5 years, the long-term androgen deprivation group showed significant improvement in disease-free survival of 54% versus 34% ($P = 0.0001$), in clinical local progression of 6.2% versus 13% ($P = 0.0001$), and in freedom-from-distant metastasis of 11% versus 17% ($P = 0.001$). Five-year overall survival was not significantly different between the two treatment arms (78% versus 79%). Subset analyses were performed for direct comparison of this trial to both the EORTC 22863 study and RTOG 85–31. The first subset included men with high-risk prostate cancer defined by clinical stage T3-T4 or stage T2 with a Gleason score of 8 to 10 for comparison to the results reported by Bolla and associates.[400,401] There was no overall survival difference (77% versus 80%) at 5 years but a significant advantage in disease-free survival for long-term androgen deprivation of 90% versus 86% ($P = 0.03$). A second subset included all men with Gleason score 8 to 10 prostate cancer for comparison with results from RTOG 85–31.[415] Five-year overall survival (80% versus 69%, $P = 0.02$) and disease-free survival (90% versus 78%, $P = 0.007$) were significantly better with long-term androgen deprivation.

The results of RTOG 92–02 have helped to establish the superiority of more protracted courses of androgen deprivation therapy for men with high-risk or locally advanced disease. The optimal sequencing of androgen deprivation therapy and radiation, however, has come into question. Currently it is not known whether the effects of androgen deprivation therapy on prostate cancer control were merely additive to the tumoricidal effects of radiation or were synergistic, providing an enhancement of tumor killing. Of interest in this regard, RTOG 94–13 Trial compared whole-pelvic radiation to prostate-only radiation and neoadjuvant and concomitant androgen deprivation therapy, given 2 months prior and 2 months during radiation therapy, to adjuvant androgen deprivation therapy, given after completion of radiation treatment for 4 months.[416] A total of 1295 men with prostate cancer and an estimated risk of lymph node involvement of more than 15% (based on the equation "+ lymph node = ($^2/_3$) serum PSA + (Gleason score − 6) × 10)" were randomized to one of the four treatment arms. There was no difference in outcome for neoadjuvant versus adjuvant androgen deprivation therapy; however, this may be confounded by a lead-time bias because the follow-up time for men on the neoadjuvant arm is 2 months longer than on the adjuvant arm. When comparing all four treatment arms, there was a progression-free survival advantage for whole-pelvis radiation therapy plus neoadjuvant and concomitant androgen deprivation therapy arm versus the other three arms (61% versus 45%, 49% and 47% respectively; $P = 0.005$). So far, the follow-up (median 59.5 months) is too short to adequately detect a difference in overall survival.

Risk of Pelvic Lymph Node Involvement and Determination of Radiation Field Size

Considerable effort has been directed toward defining the optimal radiation treatment volumes for men with prostate cancer. Men with high-risk prostate cancer are of particular interest in this regard because there is no universally accepted standard of care for this group of men with a defined risk of pelvic lymph node involvement. The rationale for prophylactic irradiation of pelvic lymph nodes is based on well-established surgical data that predict a rate of lymph node positivity, ranging from 5% to 50% for men with prostate cancer and one or more high-risk features.[417] Since the advent of 3D-CRT and its progressive refinement into more accurate dose delivery techniques, the debate of whether or not to treat pelvic nodes has intensified. Because a potentially higher risk of complications may be associated with whole-pelvis irradiation, it would be considered desirable not to treat such a large radiation portal if it were not beneficial. The RTOG 77–06 Trial found no advantage to pelvic radiation for men with T1/T2 prostate cancer.[418] However, this study included men estimated to be at low risk for lymph node involvement, including some proven to be pathologically lymph node-negative. RTOG 76–05, which randomized T3/T4 men to pelvis-only versus pelvic and para-aortic radiation therapy, also failed to detect an advantage for the extended radiation treatment field.[419] Of note, this trial often has been misinterpreted as suggesting that there is no role for radiation of pelvic nodes in men with prostate cancer, although it really only examined the efficacy of para-aortic radiation.

More recently, results of the phase III randomized RTOG 94–13 trial have provided further insight into the use of larger radiation fields,[416] as described previously. In brief, the study featured a 2 × 2 factorial design comparing whole-pelvic radiation to prostate-only radiation (and neoadjuvant and concomitant androgen deprivation therapy to adjuvant androgen deprivation therapy). Whole-pelvis radiation therapy consisted of a conventional four-field technique with a minimum field size of 16 × 16 cm treated to a maximum dose of 50.4 Gy. An additional 19.8 Gy was then delivered to the prostate using a conedown boost technique. Prostate-only radiation therapy was limited to the prostate and seminal vesicles, with a maximum field size of 11 × 11 cm, to a total dose of 70.2 Gy. Four-year progression-free survival (PFS) was 56% for whole pelvic radiation therapy compared with 46% for prostate-only radiation therapy ($P = 0.014$), with no difference in overall survival. There also was no significant difference in acute or late gastrointestinal or genitourinary toxicities between the two treatment approaches.

Postprostatectomy Adjuvant Radiation Therapy

Pathologic features that portend a higher risk of local recurrence are common after radical prostatectomy. A positive surgical margin is associated with a risk of approximately 50% of prostate cancer recurrence.[338,420–423] Other features associated with recurrence are extracapsular extension, seminal vesicle invasion, and Gleason score of 7 or greater. Several retrospective series have demonstrated improved PSA relapse-free survival with the addition of adjuvant radiation therapy following radical prostatectomy for men with these risk factors.[424–426] In one study of men ($N = 149$) with pathologic stage T3N0 prostate cancer and an undetectable postoperative serum PSA, adjuvant radiation therapy was given to a median dose of 64.8 Gy to some men ($N = 52$), while the remainder ($N = 97$) underwent no further treatment.[424] In a matched-pair analysis, the 5-year freedom-from-PSA relapse rate was 89% in the adjuvant radiation therapy group versus 55% for treatment with surgery alone ($P < 0.01$).

Three prospective randomized trials have been completed that tested the benefits of adjuvant radiation therapy versus observation following radical prostatectomy in men with prostate cancer and poor pathologic features. The EORTC has published clinical trial results revealing an improvement in biochemical relapse-free survival and locoregional progression-free survival for the men with pT3 tumors or pT2/T3 prostate cancer and positive surgical margins treated with adjuvant radiation therapy.[401] In a second study targeting the same patient population conducted by the Southwest Oncology Group (SWOG), men with prostate cancer who received adjuvant radiation not only enjoyed better biochemical and local control, but also appeared likely to have better metastasis-free survival and overall survival, although these improvements were not yet statistically

significant even at a median follow-up of 10 years.[427] Nonetheless, men treated with adjuvant radiation therapy were less likely to need hormonal therapy at 5 years (10% vs. 21%, $P < 0.001$). Avoidance of androgen deprivation therapy is likely of significant clinical benefit, reducing or delaying significant morbidity, including hot flashes, diminished bone density, sexual dysfunction, cognitive dysfunction, and overall reduced quality of life. Finally, a third randomized trial comparing adjuvant radiation and observation after prostatectomy, which enrolled only men with pT3 disease regardless of surgical margin status, was reported by the German Cancer Study Group.[428] As with the other two studies, men treated with adjuvant radiation experienced a superior biochemical relapse-free survival with median follow up of only 3.3 years. Thus, overall, data available today provide a convincing case for adjuvant radiation treatment after prostatectomy. However, it is clear that not all men benefit from such treatment. A more precise way to stratify men for adjuvant radiation therapy is needed: one such group may be men with positive surgical margins after radical prostatectomy.

Salvage Radiation Therapy after Radical Prostatectomy

Salvage radiation therapy refers to the use of radiation therapy postprostatectomy in the setting of recognized prostate cancer recurrence. As many as 27% to 53% of men who undergo radical prostatectomy for prostate cancer will have a detectable PSA within 10 years of surgery.[316] Subsequently, approximately 25% of men who undergo radical prostatectomy will be treated with salvage radiation therapy for recurrent prostate cancer.[429] In the setting of persistent or rising serum PSA following radical prostatectomy, it is important to rule out distant metastatic prostate cancer with bone scan, chest radiography, and CT scan of the abdomen and pelvis, prior to the initiation of salvage radiation therapy. Partin and coworkers[430] correlated the rate of serum PSA rise with likelihood of local versus distant relapse after surgery. A serum PSA rise of 0.75 ng/mL/yr was associated with local recurrence. In 1999, an ASTRO consensus panel concluded that treatment of men with local prostate cancer recurrence after radical prostatectomy and a preradiation therapy serum PSA below 1.5 ng/mL was more likely to be successful.[431] In addition, doses above 64 Gy were recommended in the salvage setting. Several studies have demonstrated a Gleason score greater than 7 to be associated with a low likelihood of successful salvage after prostate cancer recurrence postprostatectomy.[432,433] Cadeddu and colleagues[433] reported no men free of PSA relapse treated with salvage radiation therapy after prostatectomy for prostate cancers with Gleason scores of 8 or above. Similarly, Song and associates[432] found only 2 of 14 men with Gleason score of 8 or above to be prostate cancer-free at the time of analysis. These results indicate that men with recurrent prostate cancer and a Gleason score of 8 or greater are unlikely to benefit from salvage radiation therapy due to the likelihood of microscopic systemic prostate cancer metastases.

However, the largest multi-institution retrospective series to date ($N = 501$ men) has provided a clearer view of the likelihood of benefit for various subgroups of men with local prostate cancer recurrence after prostatectomy.[434] In this study, predictors of a poor response to salvage radiation included Gleason score of 8 to 10, preradiation PSA level higher than 2 ng/mL, PSA doubling time after prostatectomy of 10 months or less, negative surgical margins, and seminal vesicle invasion. Nonetheless, a significant fraction of men with one or more of these negative prognostic features still experienced a durable response to salvage radiation, particularly if the radiation was given prior to a PSA level of 2 ng/mL. Even for the group of men with the worst combination of prognostic features, a Gleason score of 8 to 10 and a preradiation PSA of 2 ng/mL or higher, salvage radiation produced a progression-free survival of 12% at 4 years. While these results hint at marked benefit to salvage radiation therapy after prostatectomy, the study itself was retrospective and may have been confounded by selection bias. Prospective studies are needed to determine definitively whether patients with one or more poor prognostic features derive benefit from salvage radiation. However, given the available data and considering the limited morbidity of this treatment, especially with IMRT, it is reasonable to consider salvage radiation for postprostatectomy patients with PSA recurrence regardless of prognostic factors.

The role of androgen deprivation therapy concomitant with radiation therapy given as an adjuvant to surgery as salvage for prostate cancer recurrence following surgery has not been established. In the RTOG 85–31 Trial, a subgroup of men with pathologic T3N0 prostate cancer who underwent radical prostatectomy received adjuvant radiation therapy to a dose of 60 to 65 Gy and then were randomized to immediate androgen deprivation or androgen deprivation initiated at the time of PSA relapse.[435] At 5 years, 65% of men treated with immediate androgen deprivation versus 42% of men treated with delayed androgen deprivation were free of PSA relapse. There are no prospective trials examining the addition of androgen deprivation therapy to salvage radiation therapy for local prostate cancer recurrence after prostatectomy. Taylor and coworkers[436] reported a benefit to the addition of androgen deprivation therapy to salvage radiation therapy in a retrospective case series. In this series, adjuvant androgen deprivation therapy was given to men who received salvage radiation therapy for a median duration of 24 months. At 5 years, 81% of men receiving androgen deprivation therapy (versus 54% not treated with androgen deprivation) were free of PSA relapse. In contrast, Song and colleagues[432] reported identical median disease-free survivals of 26 months for men treated with or without concurrent androgen deprivation therapy along with salvage radiation therapy for prostate cancer recurrence. The 1999 ASTRO Consensus Panel concluded that there was insufficient evidence to support routine use of androgen deprivation therapy with postprostatectomy radiation therapy.[431]

Toxicity of Postprostatectomy Radiation Therapy

In general, men receiving radiation therapy postprostatectomy experience little in the way of additional morbidity. The incidence of urinary incontinence does not seem to be increased, and erectile function does not seem to be worsened in men treated with adjuvant radiation therapy after prostectomy.[437,438] Bastasch and associates[439] reported that 100% of men who were potent after nerve-sparing radical prostatectomy remained potent after adjuvant IMRT. Despite these promising reports, side effects remain possible. Katz and coworkers[440] noted that 19% of men experienced grade 2 or 3 genitourinary toxicity (hematuria or urethral stricture), and 12% of men experienced grade 2 bowel toxicity (with no grade 3 or higher toxicity noted), following salvage radiation with 3D conformal techniques.

SYSTEMIC TREATMENT OF METASTATIC CANCER

Natural History of Metastatic Prostate Cancer

Over the past decade, widespread and routine clinical use of serum PSA testing has changed not only screening and diagnosis of prostate cancer, but virtually all aspects of prostate cancer management.[441,442] Current estimates of prostate cancer incidence by stage illustrate a major prostate cancer stage migration with a categorical shift toward less advanced cancer at the time of diagnosis. Similarly, outcome data from large cohorts and from contemporary large-scale prospective randomized clinical trials reveal that time-to-progression and survival from prostate cancer have changed substantially over the past decade. Previously collected outcome data must be scrutinized and considered in the context of more contemporary findings before making treatment recommendations or designing new clinical trials. For example, for men with newly diagnosed metastatic prostate cancer who have not received androgen suppression therapy (stage D2

disease; sometimes referred to as "hormone-naïve"), randomized prospective trials conducted before the serum PSA testing era consistently have shown a median time-to-progression ranging from 12 to 18 months, and a median survival ranging from 24 to 30 months. Men with limited metastatic prostate cancer (appendicular skeleton and/or nonvisceral soft tissue metastases) tended to have a median survival of 52 months, whereas men with extensive bony metastases and/or visceral disease had a median survival of 24 months. Also, the distribution of men with prostate cancer according to extent of disease in the earlier studies typically included as many as 80% with extensive metastatic disease, while more contemporary studies often have less than 50% of men in this category. In a case series, the median metastasis-free survival of men with recurrent prostate cancer after radical prostatectomy at the Johns Hopkins Hospital who underwent routine yearly follow-ups, with serial serum PSA determinations and bone scans, from the time of biochemical relapse following surgery, was more than 6 years.[316] One explanation for the relatively long survival of these men may be that the overwhelming majority who developed distant metastasis had limited metastatic disease, most likely due to an increased lead-time in diagnosis of metastatic prostate cancer resulting from intensive follow-up featuring serum PSA assays.

This lead-time effect also is apparent in men who suffer prostate cancer progression following initial androgen deprivation therapy. The survival of men with androgen-independent (sometimes called *hormone-refractory*) prostate cancer in chemotherapy trials conducted over a decade ago ranged between 6 and 12 months, whereas in more contemporary studies, median survival has ranged between 15 and 20 months. Furthermore, a large and increasing proportion of men with metastatic prostate cancer who progress after initial androgen deprivation therapy are first identified because of rising serum PSA values without other evidence of prostate cancer progression. Not unexpectedly, survival for men with serum PSA increases as the only manifestation of prostate cancer progression is significantly longer than for men with evidence of radiologic and/or clinical progression (i.e., new findings on physical examination and/or cancer-related symptoms) in addition to rising serum PSA levels (Table 88-9).

Table 88-9 Prognostic Factors for Men with Androgen-Independent Prostate Cancer Treated with Chemotherapy

Prognostic Factor	Significance
Performance status	Definite: seen in virtually all studies
Baseline hemoglobin	Possible: seen in some studies (associations detected using multivariate analysis of uncontrolled clinical trials; not shown to be correlated with survival in randomized trials)
Liver metastases (metastasis to other visceral sites)	
Baseline serum acid phosphatase, alkaline phosphatase, lactate dehydrogenase	
Time from initiation of androgen-deprivation therapy to initiation of chemotherapy	
Response to chemotherapy (reduction in measurable cancer deposits and/or ≥50% decline in serum PSA for ≥4 wk)	
Baseline serum PSA	
Extent of disease (on bone scan)	Equivocal: more data needed
Continuation of androgen-deprivation therapy	

PSA, prostate-specific antigen.

Endocrine Approaches to Prostate Cancer Treatment

The dependence of prostate cancer cells on androgens for growth and differentiation has been well recognized for at least five decades[443] (Fig. 88-14). Testosterone, produced by Leydig cells in the testes upon stimulation by LH, is converted to DHT by the action of 5α-reductase.[10] DHT, a more potent androgen than testosterone, binds to intracellular androgen receptors to activate the expression of target genes.[11,12] Androgen deprivation therapy for prostate cancer involves maneuvers that reduce circulating testosterone to levels around or below levels present in castrated men (<50 ng/mL). Forced reduction of testosterone levels by castration, or via gonadal suppression, triggers a wave of apoptosis in both normal and neoplastic prostate cells, with little or no acute effect on nonandrogen target tissues, providing one of the most effective systemic palliative treatments known for solid organ cancers. Unfortunately, despite the magnitude of the initial beneficial treatment response, prostate cancer inexorably evolves to androgen-independence.[21] As of yet, no therapeutic maneuver has been shown to prevent this sequence of progression.

Strategies for Androgen Deprivation

Currently, the general consensus is that a reduction in testosterone produced by the testes represents the best standard approach to androgen deprivation therapy for prostate cancer (Box 88-4). This can be accomplished by surgical removal of the testis (bilateral orchiectomy), by inhibition of the synthesis and release of pituitary gonadotropins by gonadotropin-hormone-releasing hormone analogues (GnRH or LHRH analogues and LHRH antagonists), or by the administration of pharmacologic doses of estrogens.

Bilateral orchiectomy results in a rapid decline of testosterone to 5% to 10% of normal values and remains the treatment of choice for severely symptomatic patients. Although the suppression of testosterone production associated with LHRH analogues is comparable to bilateral orchiectomy, the nadir of serum testosterone levels is not reached until after 3 to 4 weeks of treatment. The LHRH analogues, highly potent LHRH agonists, initially stimulate LH release by the pituitary, but on chronic administration subsequently suppress LH and testosterone production.[444,445] Thus, LHRH analog treatment also is associated with an initial rise in LH and in serum testosterone in virtually all patients. This brief elevation of testosterone levels has been reported to be associated with a flare of the prostate cancer, manifested by an increase in pain in symptomatic patients, or by more worrisome consequences of prostate cancer progression, including epidural cord compression and urinary obstruction.[446] Longer-acting depot preparations of LHRH analogues (administered monthly, every 3 or 4 months, or yearly) are available for clinical use. Clinical trials comparing bilateral orchiectomy to a variety of LHRH analogues have revealed comparable short- and long-term efficacy in patients with metastatic prostate cancer. Because of convenience, and the ability to avoid surgery, LHRH analogues have become the most widely used method for reducing serum testosterone.

New LHRH antagonists have been introduced to achieve a reduction in serum testosterone without the brief flare associated with initial stimulation of pituitary gonadotropin secretion and testicular androgen production associated with LHRH analogues. These agents appear to be generally as effective as LHRH analogues, achieving a faster suppression of gonadal androgen production to the castrate range with comparable long-term sustained reductions of serum testosterone and no evidence of flare reactions.[447] The efficacy of LHRH antagonists as treatments for prostate cancer, in comparison to bilateral orchiectomy or to LHRH analogues, has not been fully evaluated. Nonetheless, because LHRH agonists can lower the serum testosterone rapidly, like bilateral orchiectomy, these agents may well offer an attractive alternative to the LHRH analogs for the treatment of men with symptomatic prostate cancer for whom a flare reaction might threaten significant morbidity.

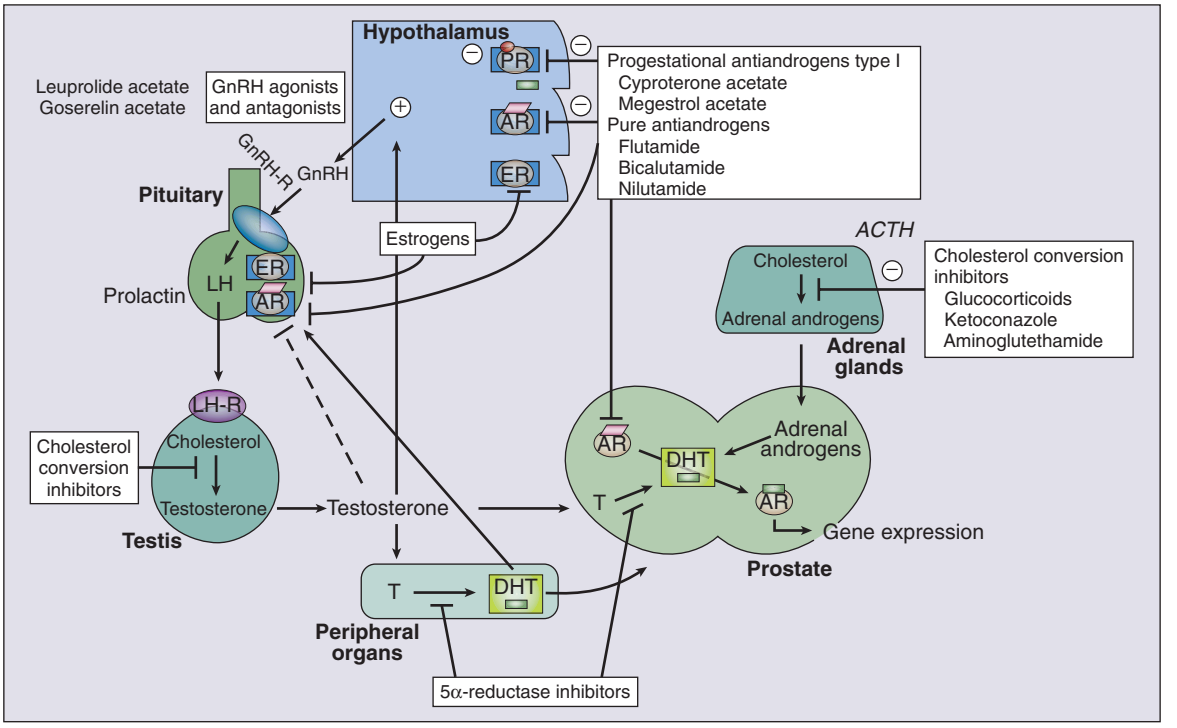


Figure 88-14 • Sites of action of different treatments that affect androgen action. ACTH, adrenocorticotropic hormone; AR, androgen receptor; DHT, 5α-dihydrotestosterone; ER, estrogen receptor; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PR, progesterone receptor; T, testosterone.

The administration of pharmacologic doses of synthetic estrogens represented the earliest strategy for drug treatment of prostate cancer.[448] Initial studies using diethylstilbestrol (DES) revealed a dose-dependent suppression of serum testosterone to the castrate range. When used for prostate cancer progression, DES provided clinical benefits comparable to those achieved with bilateral orchiectomy. In a clinical trial conducted by the Veterans Administration Cooperative Urological Research Group (VACURG Study 1), men with prostate cancer treated with DES had a prostate cancer-specific survival comparable to men treated by bilateral orchiectomy.[448,449] However, men in this study treated with DES (at a dose of 5 mg daily) suffered a high incidence of cardiovascular deaths.[450] A subsequent clinical trial (VACURG Study 2) evaluated different daily doses of DES (0.2 mg, 1.0 mg, and 5.0 mg) versus placebo.[448,449] Results suggested that the 1.0 mg daily DES dose was as effective as the 5.0 mg daily dose in terms of prostate cancer deaths, but was associated with a lower incidence of fatal cardiovascular complications. Subsequent analyses of men treated with DES at a daily dose of 1 mg revealed that testosterone often was not adequately suppressed, especially in younger patients with initially normal gonadal function.[448,449,451] All of these findings led to the recommendation that DES, at a 3-mg daily dose (known to result in effective long-term suppression of testosterone comparable to bilateral orchiectomy), constituted an effective prostate cancer treatment despite the fact that the safety and efficacy of this DES dose, relative to lower or higher doses, remain untested in prospective randomized clinical trials. With the ready availability of LHRH analogues, synthetic estrogens are not currently used for prostate cancer treatment.

Accumulated data from prospective randomized clinical trials in men with metastatic prostate cancer have revealed comparable efficacy of the various forms of androgen deprivation therapy, regardless of the outcome measure used, including rates of subjective and/or objective improvement, time-to-cancer-progression, or survival. However, in 1984, after leuprolide acetate, the first commercially available LHRH analog in the United States, was shown to be comparable to DES in treatment efficacy but associated with fewer serious complications, particularly congestive heart failure and thromboembolic events, DES was virtually abandoned in favor of LHRH analogues for the initial treatment of metastatic prostate cancer. Goserelin acetate, another commercially available LHRH analogue,

Box 88-4. SYSTEMIC TREATMENT OF MEN WITH METASTATIC PROSTATE CANCER

Androgen deprivation therapy, usually accomplished via the administration of luteinizing hormone-releasing hormone (LHRH) agonists, remains the standard treatment approach for men with symptomatic metastatic prostate cancer. In certain cases, antiandrogens are used to prevent the flare reaction associated with initiating LHRH agonist treatment.

With the widespread use of serum prostate-specific antigen (PSA) testing as a monitoring tool for prostate cancer relapse after surgery or radiation therapy, a major new challenge has confronted physicians who treat prostate cancer: many men with recurrent prostate cancer have no symptoms attributable to the disease and no evident metastatic cancer deposits that can be detected by radiographic imaging. Which of these men should be considered for treatment, and when should treatment be initiated? Although these issues have not been fully resolved, available data indicate that the time between surgery or radiation therapy and PSA relapse, the Gleason score at the time of primary treatment, and the PSA doubling time are predictive of the risk and timing of overt metastatic prostate cancer. Men at high risk for progressive metastatic prostate cancer are likely the best candidates for systemic treatment.

also has been found to be comparable to bilateral orchiectomy in men with metastatic prostate cancer.

Anti-Androgens and 5α-Reductase Inhibitors

Anti-androgens compete with androgenic hormones for binding to the androgen receptor, blocking transcriptional activation of androgen target genes.[21] Anti-androgens have been used as adjuncts to androgen deprivation therapy (so-called "complete" or "maximal" androgen blockage) and as single agents, in an attempt to preserve sexual function. However, anti-androgen monotherapy is not without side effects: approximately 50% of men treated with bicalutamide at a 150-mg daily dose develop gynecomastia, and although libido often can be maintained, fewer men remain potent.[452] Bicalutamide monotherapy has been reported to provide similar survival outcomes to bilateral orchiectomy in men with nonmetastatic advanced prostate cancer (stage T3 and T4).[452] Nonetheless, anti-androgens used alone appear inferior to androgen deprivation therapy in prospective randomized clinical trials in men with metastatic prostate cancer.[452] The efficacy of anti-androgens used earlier in the natural history of prostate cancer (as adjuvant therapy for men with high-risk prostate cancer treated with radical prostatectomy or as treatment for men with a rising serum PSA after failure of cancer control with primary therapy) remains to be established. Flutamide, bicalutamide, and nilutamide are the nonsteroidal anti-androgens available currently in the United States.

Although DHT is a more potent androgen than testosterone, 5α-reductase inhibitors have not been found to be particularly effective in the treatment of metastatic prostate cancer when used alone.[183] A combination of the type 2 5α-reductase inhibitor finasteride and the nonsteroidal anti-androgen flutamide has been explored in clinical trials; the results obtained thus far do not suggest any striking advantage for combination treatment.[453] Dutasteride, an inhibitor of both type 1 and type 2 5α-reductases, has not been fully tested against prostate cancer.

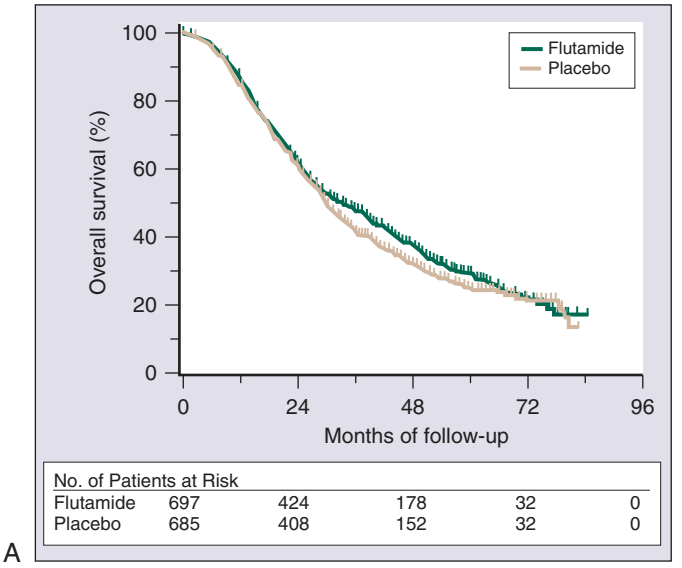
"Complete" Androgen Blockade

A substantial amount of basic research has been devoted to enhancing the understanding of critical mechanisms involved in the hormonal control of prostate cancer growth, and the emergence of androgen-independent prostate cancer.[21] Prostate cancers contain populations of cancer cells that are heterogeneous with regard to androgen dependency and sensitivity. In the 1980s, Labrie and colleagues[454,455] hypothesized that prostate cancer cells could adapt to the low levels of androgens present after androgen deprivation therapy, some produced by the adrenals, and support prostate cancer growth. To neutralize the effects of adrenal androgens, a combination of bilateral orchiectomy (or LHRH analogues) and a nonsteroidal anti-androgen was promoted as "complete" androgen blockade. The initial reports of the efficacy of this treatment combination prompted the conduct of a unprecedented number of clinical trials to assess the possible advantages of "complete" androgen blockade for men with metastatic prostate cancer: 7987 men with metastatic prostate cancer were entered onto 27 prospective randomized clinical trials comparing the efficacy of bilateral orchiectomy (or LHRH analogues) alone (monotherapy) to almost every possible combination of bilateral orchiectomy (or LHRH analogues) and anti-androgens.[456] A comprehensive review of all studies reported thus far has revealed that 24 of the 27 studies reported no significant differences in survival, while only 3 demonstrated modest, statistically significant, improvements in favor of "complete" androgen blockade.[456] Even for the occasional trial showing an apparent benefit for "complete" androgen blockade, there was a lack of consistency when considered in the context of other trials. For example, flutamide resulted in a survival advantage in one trial in combination with an LHRH analogue, whereas nilutamide did not; and nilutamide resulted in a survival advantage in one trial in combination with bilateral orchiectomy, whereas flutamide did not. For each of the trials hinting at a benefit for "complete" androgen blockade, at least one, and as many as five, similarly designed trials found no evidence for the benefit. Taken together, the large collection of clinical trial data testing the efficacy of "complete" androgen blockade suggest that any potential benefit of "complete" androgen blockage is likely minimal and of negligible clinical significance.

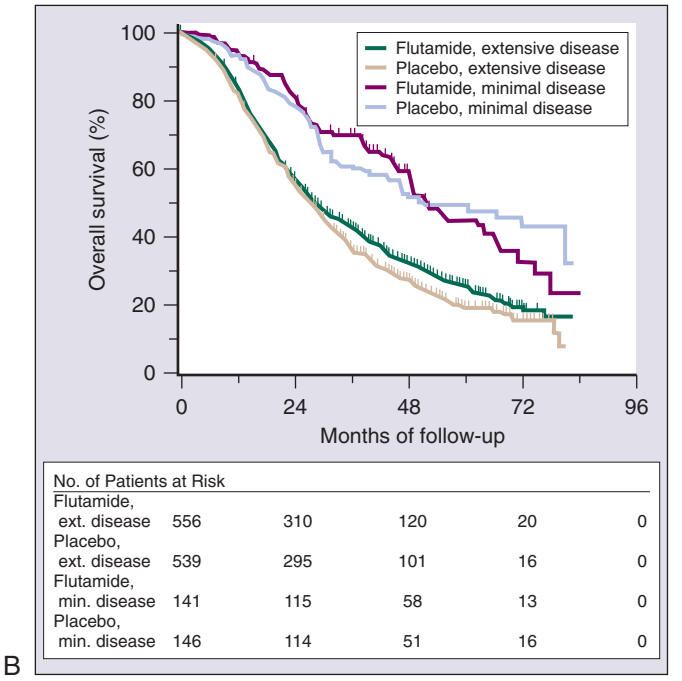
The first published large-scale prospectively randomized clinical trial of "complete" androgen blockade was the National Cancer Institute (NCI)-sponsored trial INT-0036.[142] Men ($N = 603$) with stage D2 prostate cancer were randomly assigned to receive daily subcutaneous injections (1 mg/day) of leuprolide acetate and the nonsteroidal anti-androgen flutamide versus leuprolide acetate and placebo. The median overall survival with "complete" androgen blockade was 36 months, while the median survival with monotherapy was 28 months ($P = 0.035$). While the NCI INT-0036 trial clearly showed a benefit to the treatment combination, several explanations other than the "complete" androgen blockage hypothesis have been proffered to account for the trial results. One argument was that the difference in favor of combination treatment could have been an attenuation of the LHRH analogue flare reaction by the anti-androgen.[457] In support of this contention, men randomized to receive combination treatment exhibited a trend toward more favorable pain control, improvement in performance status, and reduction in PAP, as compared to men treated with monotherapy, that was evident during the first 12 weeks of treatment.[142] However, this notion is not supported by the results of another study that discerned no difference in survival between men randomized to receive leuprolide acetate with 2 weeks of flutamide treatment versus leuprolide acetate alone.[458] A second argument for the superiority of combination treatment in the NCI INT-0036 trial was that noncompliance with the daily leuprolide acetate injection regimen might result in inadequate gonadal suppression, providing the opportunity for an advantage for the combination of daily leuprolide and flutamide. Because routine evaluations of serum testosterone were not included on the study, this argument could not be effectively excluded. To address these issues, a confirmatory trial, using bilateral orchiectomy rather than leuprolide acetate for androgen deprivation, was conducted (the NCI INT-0105 trial).

Bilateral orchiectomy represents the optimal method of reducing testosterone for testing the "complete" androgen blockade hypothesis because it is not associated with a flare reaction and/or compliance difficulties. The NCI INT-0105 clinical trial prospectively randomized men ($N = 1387$) with stage D2 prostate cancer to treatment with bilateral orchiectomy with flutamide versus bilateral orchiectomy with a placebo[141] (Fig. 88-15). The trial was designed to have sufficient power to detect a 25% or better advantage in survival attributable to combination treatment. However, at a median follow-up time of ~50 months, and with 70% deaths occurring by the date of final analysis, the trial failed to detect a survival advantage to "complete" androgen blockade, finding a median survival of 33 months for men treated with combination therapy versus 30 months for men treated with orchiectomy alone (hazard ratio = 0.91 for combination treatment, with a 90% confidence interval of 0.81–1.01, $P = 0.14$). Although a slightly greater fraction of men in the bilateral orchiectomy ± flutamide trial (20%) than in the leuprolide ± flutamide trial (13%) had minimal metastatic prostate cancer, men in the two trials otherwise had very similar characteristics with regard to age and other demographic features.[141,142]

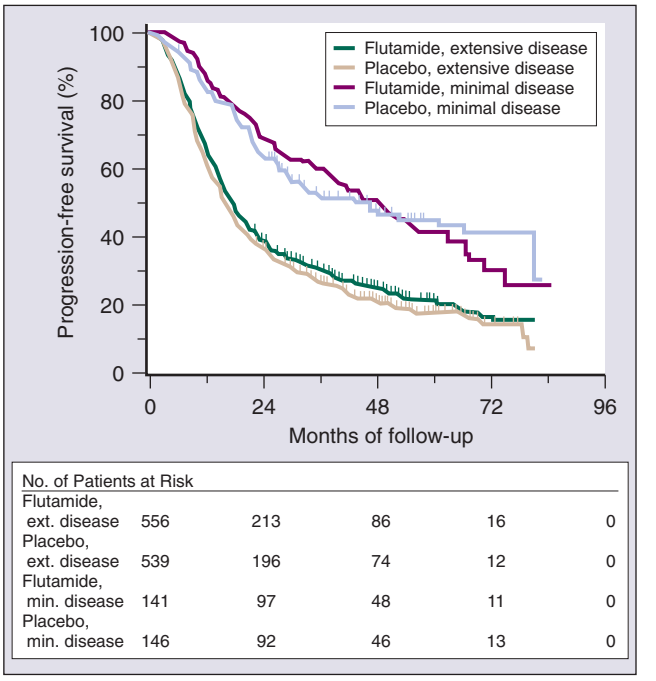
The EORTC conducted a clinical trial ($N = 327$) comparing goserelin acetate plus flutamide to bilateral orchiectomy in men most of whom had stage D2 prostate cancer.[459–462] Although an initial analysis of trial results, at a median follow-up time of 30 months, had disclosed no significant survival differences, a later analysis showed a 7-month improvement in median survival ($P = 0.04$) in favor of combination treatment. The Danish Prostatic Cancer Group



A



B



C

Figure 88-15 • Results of a randomized clinical trial of orchiectomy plus flutamide versus orchiectomy plus placebo for men with metastatic prostate cancer. **A,** Overall survival. **B,** Overall survival, stratified by extent of disease. **C,** Progression-free survival stratified by extent of disease. (Data from Eisenberger MA, Blumenstein BA, Crawford ED, et al: Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998;339:10036–10042.)

(DAPROCA) conducted a virtually identical study, with the same treatment arms and approximately the same number of patients.[463] This trial, which was completed at about the same time as the EORTC trial, revealed a longer overall survival with bilateral orchiectomy, although the difference was not statistically significant.[463] The reason for the discordant results is not clear: both studies recruited similar patient populations. A combined analysis of both studies, undertaken to enhance statistical power, failed to detect significant differences between "complete" androgen blockade and bilateral orchiectomy.[464]

Several studies have examined the use of cyproterone acetate, a steroid anti-androgen, in combination with androgen deprivation therapy, and none reported significant survival benefits attributable to combination treatment.[465–469] In fact, in a meta-analysis, there appeared to be a trend toward decreased survival for men treated with cyproterone acetate as part of a "complete" androgen blockade regimen.[470] The use of cyproterone acetate for "complete" androgen blockade is not recommended.

In 1995, the Prostate Cancer Trialists' Collaborative Group (PCTCG) reported the results of a meta-analysis from 22 randomized trials comparing "complete" androgen blockade to androgen deprivation alone for a total of 5710 men with prostate cancer[471] (Fig. 88-16). To accomplish an intention-to-treat analysis, complete data for each man treated were requested from the investigators for each trial. Hazard ratios were calculated separately for every trial, based on the raw data, and then combined for all of the trials using log-rank statistics. This analysis revealed a 2.1% difference in survival in favor of "complete" androgen blockade (a 6.4% reduction in annual risk

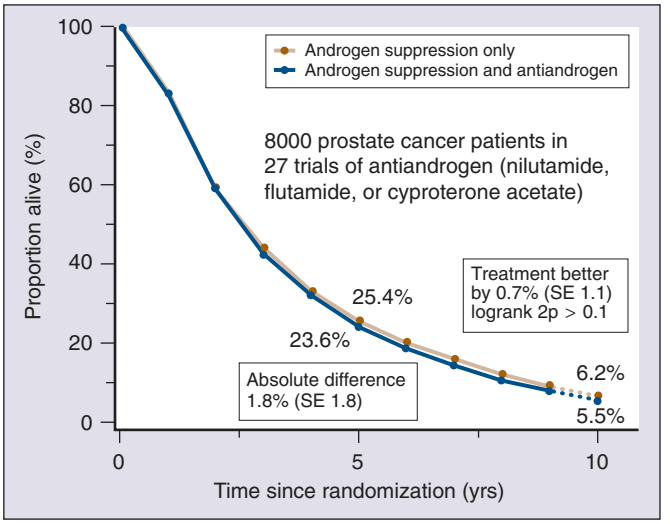


Figure 88-16 • A meta-analysis of survival from metastatic prostate cancer with maximal androgen blockade versus androgen deprivation alone. (From Prostate Cancer Trialists Cooperative Group: Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trial. Lancet 2000;355:1491–1498.)

of death) that was not statistically significant. The results were independent of the androgen deprivation strategy used or the anti-androgen selected for the combination. The Agency for Health Care Policy and Research (AHCPR; results published on the Web (http://www.ahcpr.gov/clinic/index.html#evidence; AHCPR report No.99-E012) also conducted a meta-analysis based on all published "complete" androgen blockade clinical trials. This meta-analysis found no difference in 2-year survival rates (hazard ratio = 0.970 with a 95% confidence interval of 0.866–1.087). Only 10 of the 27 trials reported 5-year survival data, in addition to the 2-year survival figures, and the combined results of these ten trials suggested a minimal 5-year survival difference in favor of "complete" androgen blockade of uncertain clinical significance (hazard ratio = 0.871 with a 95% confidence interval of 0.805–0.9887).

Androgen deprivation therapy and anti-androgens are associated with a number of side effects, whether given alone or in combination, including hot flashes, loss of libido, loss of bone and muscle mass, fatigue, anemia, gynecomastia, and other symptoms. When the impact of such side effects were prospectively evaluated and compared to the beneficial impact of treatment, using a quality-of-life questionnaire, men treated as part of the NCI INT-0105 trial reported an improvement in quality of life attributable to treatment.[472] However, the improvement was more pronounced for men treated with bilateral orchiectomy than for men treated with "complete" androgen blockade, with men receiving "complete" androgen blockade reporting a higher frequency of diarrhea and worsening emotional functioning.[472] The quality-of-life benefit resulting from bilateral orchiectomy for treatment of metastatic prostate cancer appeared to be offset by the addition of anti-androgen treatment, primarily because of an increased incidence of side effects.

A key feature of the "complete" androgen blockade hypothesis was that adrenal androgens might contribute to prostate cancer growth in the absence of gonadal androgens. In fact, Labrie and associates[473,474] suggested that suppression of gonadal androgen production might be associated with an increased expression of enzymes, like 17β-hydroxysteroid dehydrogenase and 5α-reductase, in the prostate and elsewhere, capable of converting weak adrenal androgens (androstenedione and dehydroepiandrosterone) into testosterone and DHT, attributing as much as 30% to 50% of the intracellular pool of androgens to adrenal origin. At this point the role of adrenal androgens in the progression of metastatic prostate cancer is not established. On the other hand, new insights into the diverse molecular mechanisms associated with prostate cancer progression in the face of androgen deprivation therapy, with myriad alterations in androgen receptor function, activation of cell proliferation, loss of apoptosis, increase in tumor angiogenesis, modulation of tumor invasion and metastasis by the extracellular matrix, and maintenance of immune tolerance, have suggested that there is likely considerable heterogeneity in the androgen-independent prostate cancer phenotype.[21] With all of these mechanisms possibly contributing to androgen-independent prostate cancer progression, it is not entirely surprising that the "complete" androgen blockade treatment approach proposed by Labrie and coworkers was not associated with a clinically significant survival benefit.[454]

Optimal Timing for Initiation of Androgen Deprivation Therapy

Although there is a general belief that immediate initiation of androgen deprivation therapy for men with metastatic prostate cancer may improve quality of life, there is no compelling evidence of a reduction in survival resulting from deferring treatment until symptomatic progression has occurred. Effects of the timing of androgen deprivation therapy on the survival of men with metastatic prostate cancer has become a more critical issue recently since an increasing number of men are recognized very early to have recurrent or metastatic prostate cancer because of increases in the serum PSA. The VACURG Study 1, testing the benefits of androgen deprivation therapy achieved by administration of DES, even though conducted decades ago, provides valuable insights into the effect of timing of androgen deprivation therapy on survival from metastatic prostate cancer. In the trial, men with advanced prostate cancer were randomized to initial treatment with bilateral orchiectomy plus a 5-mg daily dose of DES, bilateral orchiectomy plus a placebo, 5 mg DES per day alone, or placebo alone, with results indicating no significant differences in survival among the different treatment groups.[448,449] However, men on the placebo arm who subsequently were crossed over to another treatment arm at the time of progression had a comparable survival to men initially treated on one of the other treatment arms, suggesting that immediate initiation of androgen deprivation therapy was without marked benefit.

The Medical Research Council also evaluated immediate versus deferred androgen deprivation therapy for advanced prostate cancer.[475] In their study, men with prostate cancer ($N = 934$ men; 434 men with and 500 men without prostate cancer metastasis) were randomized to either early androgen deprivation or to androgen deprivation initiated for symptomatic prostate cancer progression. Follow-up procedures were not strictly defined in the trial, relying on the discretion of the treating physicians, and 5% of the men who died of prostate cancer never received androgen deprivation therapy, while 10% or the men were not treated until they suffered a pathologic bone fracture or spinal cord compression. Using death from prostate cancer as a study endpoint for the men who had metastatic prostate cancer, no significant difference was detected between the early (65% prostate cancer deaths) versus late (69% prostate cancer deaths) treatment groups. In an initial report of trial results, the group of men with nonmetastatic prostate cancer appeared to have fewer deaths (32%) when treated with early androgen deprivation therapy than when treatment was delayed (49%). However, of the men in this group who died in the delayed treatment arm, 54% never received endocrine therapy. In a more recent report, reflecting greater follow-up time, no statistically significant differences were evident for men with prostate cancer treated with early versus delayed androgen deprivation therapy.

The Eastern Cooperative Oncology Group carried out a randomized prospective trial of immediate androgen deprivation therapy versus observation in men ($N = 98$) who underwent radical

prostatectomy and were found to have lymph node metastases.[476] After a median of 7.1 years of follow-up, a significant difference in survival, favoring immediate androgen deprivation therapy, was detected. This finding was surprising because a fairly large difference in survival was evident within a relatively short period of observation. In the trial, prostate cancer-specific survival in the observation group was 78% at 5 years. This is quite low compared to rates seen in men with prostate cancer and microscopic lymph node metastasis treated with radical prostatectomy alone. Furthermore, in a nonrandomized case series ($N = 790$) from the Mayo Clinic, representing the largest retrospective collection of data on men with lymph node-positive prostate cancer treated by radical prostatectomy, with almost three decades of follow-up, a survival advantage in favor of immediate androgen deprivation was seen only for men with prostate cancers that were diploid, and this survival advantage did not become apparent until 10 years after surgery.[477] In that case series, men with aneuploid prostate cancers and lymph node metastases subjected to radical prostatectomy did not appear to benefit from immediate adjuvant androgen deprivation therapy. When men with diploid prostate cancers ($N = 57$) were treated similarly and followed for 10 years, there was also no improvement in survival attributable to adjuvant androgen deprivation therapy, but at 15 years of follow-up 14 men with diploid prostate cancers were alive, 12 who had received early androgen deprivation therapy and 2 who had not ($83.2 \pm 4.1\%$ vs. $48.5 \pm 13\%$). Thus, the finding of a benefit to early androgen deprivation therapy was based on the experience with 14 men of 790 men with lymph node-positive prostate cancer who underwent radical prostatectomy.

Why are the ECOG study results, indicating a benefit for early androgen deprivation therapy, different from other data suggesting only a marginal benefit to immediate initiation of treatment? In an editorial that accompanied publication of the ECOG study findings, one concern raised was that this study never realized its projected accrual goal of 240 patients.[478] This fact may be critically important, because the outcome of patients with prostate cancer nodal metastasis is extremely variable and difficult to predict. This problem could have been minimized if a sufficient number of men with prostate cancer were randomized to the different treatment arms. Unfortunately, the ECOG trial was relatively small and might have been affected by imbalances of factors that were not identified at the time the study began. In support of this concern, the fact that 50% of the men in the observation arm had progressed by 5 years, with 22% deaths, suggested that this control group most likely represented a collection of men with poor-risk and/or high-grade prostate cancers.[476]

Intermittent Androgen Deprivation Therapy

Intermittent androgen deprivation therapy has the promise of reducing the impact of treatment-associated side effects while still maintaining some benefits from treatment. Additionally, findings from one group of animal model studies has suggested that intermittent reductions in testosterone levels, versus continuous androgen deprivation, might actually delay prostate cancer progression to androgen-independence.[479] In these preclinical experiments, androgen-dependent cancer carried subcutaneously in mice was treated by bilateral orchiectomy once the tumors grew to 3 g. After the tumors had regressed 30%, they were transplanted into intact mice and then treated again by bilateral orchiectomy once the tumors had again grown to 3 g. This treatment cycle was continued until the cancer became androgen-independent. For comparison, mice carrying 3-g cancers were treated with a single cycle of androgen deprivation. Remarkably, androgen-independent cancer progression occurred 51 days after one-time bilateral orchiectomy versus 147 days for mice cycled through intermittent androgen deprivation. The mechanism for this difference, attributed to a superiority of intermittent androgen deprivation as cancer treatment, has not been fully elucidated. However, other preclinical animal model studies have yielded conflicting results. When rats carrying a transplantable androgen-dependent prostate cancer were treated with immediate bilateral orchiectomy, with continuous high- or low-dose DES, or with intermittent high- or low-dose DES, rats treated with continuous androgen deprivation survived 38%to 50% longer than rats treated with intermittent androgen deprivation.[480] These uncertainties from preclinical studies suggest the clinical use of intermittent deprivation therapy must be carefully evaluated in well-designed clinical trials before routine use in clinical practice. The efficacy and safety of intermittent versus continuous androgen deprivation is currently under scrutiny in clinical trials.

"Second-Line" Endocrine Treatment

During the past several years it has become evident that men suffering with prostate cancer progression after initial androgen deprivation therapy represent a heterogeneous group with varying degrees of residual sensitivity to hormonal manipulations. Kelly and colleagues described the "flutamide-withdrawal" syndrome, later found also to be associated with other anti-androgens, characterized by an improvement seen in 20% to 25% of men on discontinuation of anti-androgen treatment.[481–483] This phenomenon occurred both for men who initially were treated with "complete" androgen blockade and for men who had received anti-androgens at some other time. The clinical observation of an "anti-androgen withdrawal" syndrome prompted a renewed interest in the biology of the androgen receptor in prostate cancer cells. A variety of AR alterations have been described in prostate cancers progressing after initial hormone manipulations, and *AR* mutations, encoding androgen receptors with altered ligand specificity, also have been detected for which anti-androgens can act as agonists.[145,146,148]

Among the agents reported to cause beneficial treatment responses (a drop in the serum PSA or other response) after adequate androgen deprivation treatment are bicalutamide (20%–24%), megestrol acetate (8%–13%), DES (26%–66%), ketoconazole with hydrocortisone (27%–63%), and glucocorticoids alone (18%–22%).[484] PC-SPES, a multi-component herbal mixture with estrogenic properties, was reported to produce treatment responses in men with androgen-independent prostate cancer.[485] However, many PC-SPES lots were contaminated with prescription drugs, including DES, coumadin, and indomethacin, and as a result, PC-SPES is no longer available.[486] Responses to second-line hormonal manipulations usually are brief, with median durations of benefit ranging from 3 to 4 months.

Clinical Approach to Men with Androgen-Independent Prostate Cancer

Most men with androgen-independent prostate cancer demonstrate a rising PSA as the first manifestation of prostate cancer progression following androgen deprivation. In a prospective evaluation of men ($N = 282$) who had received first-line androgen deprivation therapy and suffered cancer progression, an increase in serum PSA levels occurred approximately 6 months before any other clinical (radiologic or bone scan) evidence of worsening cancer.[487] However, for men initially treated with androgen deprivation based only on a rising serum PSA (and no clinical evidence of prostate cancer metastases), the time interval between subsequent serum PSA increases, indicating androgen-independent prostate cancer progression, and the appearance of clinically significant metastases is not known, although the serum PSA level at initial presentation, the rate of serum PSA rise, the Gleason score at the time of prostate biopsy or surgery, the clinical stage at presentation, and the response to androgen deprivation treatment are likely of prognostic significance.[488] When the appearance of androgen-independent prostate cancer is suspected for men treated with androgen deprivation therapy, a determination of the serum testosterone (to ensure that androgen deprivation has been adequately accomplished), serum PSA, PAP, and alkaline

phosphatase, hematology and serum chemistry studies, radiographic imaging (including a bone scan), and a history and physical examination often are undertaken.

For years it has been suggested that discontinuation of androgen deprivation in men who have not undergone bilateral orchiectomy may adversely affect prostate cancer progression and survival.[436] The administration of exogenous testosterone and its derivatives is known to produce a significant prostate cancer flare with severe pain and neurologic, urologic, and coagulation complications in a small proportion of men.[489–491] In a retrospective analysis of men ($N = 205$) with androgen-independent prostate cancer who were treated with chemotherapy, there appeared to be no difference with respect to prostate cancer progression and survival in men with prior bilateral orchiectomy as compared with men treated with gonadal androgen suppression that was discontinued at least 4 weeks before chemotherapy.[492] Of course, many of the men treated with gonadal suppression likely never achieved normal serum androgen levels. Until the issue of whether discontinuation of gonadal suppression might compromise survival from androgen-independent prostate cancer has been resolved, maintenance of gonadal androgen suppression is recommended. Also, because stopping anti-androgen treatment at the time of prostate cancer progression can result in decreases in serum PSA levels, and in occasional symptomatic benefits or objective improvements in soft tissue and bone metastasis, men taking anti-androgens along with androgen deprivation therapy should be encouraged to discontinue these agents for at least 4 to 8 weeks before considering other treatment maneuvers.[493]

Bisphosphonates

Bone metastases, accompanied by destruction of bone architecture and accompanying pain, fracture, and spinal cord compression, arise commonly as part of prostate cancer progression. Furthermore, androgen deprivation therapy causes osteopenia/osteoporosis, with some 19.4% of men treated with androgen deprivation for at least 5 years reported to suffer pathologic bone fracture.[494] Such skeletal complications, whether arising as a result of prostate cancer itself or of prostate cancer treatment, may accelerate life-threatening prostate cancer progression.[495]

Bisphosphonates promote bone ossification and have established benefits for the treatment of osteoporosis, hypercalcemia of malignancy, and cancer bone metastasis.[496–499] For men with prostate cancer, almost any of the available bisphosphonates can treat osteoporosis associated with androgen deprivation. In one trial, men ($N = 47$) with prostate cancer and no bone metastases who required treatment with leuprolide were randomized to receive hormonal therapy alone or with pamidronate (60 mg every 12 weeks) and monitored for bone mineral density via dual-energy x-ray absorptiometry (DEXA) of the lumbar spine and proximal femur, and trabecular bone density via quantitative computed tomography of the lumbar spine.[500] Results indicated that while androgen deprivation therapy decreased bone mineral density at all sites, the addition of pamidronate to hormone treatment prevented this complication. However, in the setting of established prostate cancer bone metastases, only zoledronic acid (4 mg every 3 weeks) has demonstrated benefit sufficient for regulatory agency approval. In a placebo-controlled trial for men with progressive prostate cancer and bone metastasis ($N = 643$), zoledronic acid therapy reduced skeletal complications by 22% (38% with zoledronic acid vs. 49% with placebo), with improvements in time-to-first skeletal complication and pain.[501,502] The superiority of zoledronic acid over the other bisphosphonates for this indication may be a consequence of drug effects on both osteoblasts and osteoclasts.[503] Preclinical models have hinted that bisphosphonate treatment of early-stage prostate cancer might reduce or delay the appearance of bone metastases, and clinical trials of bisphosphonates for the prevention of bone metastasis have been initiated.[504] In addition to the efficacy of zoledronic acid in preventing skeletal complications of metastatic prostate cancer, a single infusion of the drug prevented osteoporosis associated with a year of androgen deprivation therapy in a randomized controlled trial.[505] Bisposphonate treatment has been associated with occasional but significant side effects, including renal dysfunction and osteonecrosis of the jaw.[506]

Bone-Targeted Radionuclides

The contribution of osteoblast action to the pathogenesis of prostate cancer bone metastases has stimulated interest in radioemitting calcium mimetics as treatments for progressive prostate cancer with skeletal involvement. ^{89}Sr, given as ^{89}SrCl, provides some pain palliation, without survival prolongation, for men with prostate cancer and symptomatic bone metastases.[507] A β-emitter with a $t_{1/2}$ of 50.5 days, ^{89}Sr accumulates in metastatic bone lesions. The most clinically significant toxicity of ^{89}Sr is myelosuppression, with nadir blood counts 4 to 6 weeks after administration. This limits ^{89}Sr therapy to men with adequate blood counts, precluding retreatment until after at least 6 months or so, and all but eliminating opportunities for other concurrent treatments. Nonetheless, in a provocative randomized clinical trial, men ($N = 72$) with androgen-independent prostate cancer and bone metastases who had responded to an induction chemotherapy regimen and received ^{89}Sr in addition to doxorubicin enjoyed an improvement in survival when compared to men treated with doxorubicin alone.[508] Newer bone-targeted radiopharmaceuticals, including ^{188}Re-hydroxyethyldidene diphosphonate (^{188}Re-HEDP), which emits both β and γ particles and has a $t_{1/2}$ of 16.9 hours, and ^{153}Sm-ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP), which emits both β and γ particles and has a $t_{1/2}$ of 46.3 hours, may palliate painful bone metastases with less myelosuppression than ^{89}SrCl.[509,510]

Treatment of Androgen-Independent Prostate Cancer

The tendency for prostate cancer to progress after androgen deprivation therapy poses the greatest threat of morbidity and mortality. For men with symptomatic metastatic prostate cancer despite adequate androgen deprivation therapy, randomized clinical trials have demonstrated that systemic treatment with mitoxantrone and corticosteroids tends to reduce bone pain and improve quality of life, but not to prolong survival.[511–513] However, in 2004, two randomized clinical trials showed that docetaxel, alone or in combination with estramustine, improved the survival of men with metastatic androgen-independent prostate cancer in comparison to mitoxantrone and corticosteroids.[514,515] As a consequence of these two clinical studies, the role of systemic chemotherapy in prostate cancer treatment is now well established, and vigorous clinical research is now ongoing to improve the outcomes achievable with taxane chemotherapy.[516] In addition, new avenues of treatment, including prostate cancer immunotherapy, have progressed to advanced phases of clinical assessment (Box 88-5).

Docetaxel

Both paclitaxel, from the bark of the Pacific yew tree (*Taxus brevifolia*), and docetaxel, from the leaves of the European yew tree, disrupt microtubule function, required for chromosome segregation at mitosis in eukaryotic cells, and promote apoptosis.[517,518] Nonetheless, the mechanism(s) by which these drugs act against prostate cancer cells is not clear. Prostate cancers tend to have very low growth fractions, as compared to many normal cells and most other cancers, yet prostate cancer cells remain sensitive to taxane drugs. One possibility is that microtubule function may be needed for other critical cell processes, such as for nuclear-cytoplasmic shuttling of critical regulatory proteins, essential for prostate cancer cell viability.[519]

Although both paclitaxel and docetaxel have shown promising activity against prostate cancer in early clinical trials, only docetaxel

Box 88-5. CHEMOTHERAPY FOR MEN WITH ANDROGEN-INDEPENDENT METASTATIC PROSTATE CANCER

Despite adequate androgen deprivation therapy, prostate cancer tends to progress to threaten morbidity and mortality. For men with metastatic androgen-independent prostate cancer, docetaxel chemotherapy, with or without estramustine, has been proven to prolong survival. Because the addition of estramustine to docetaxel produces an increase in cardiovascular side effects, without a clear benefit in prostate cancer survival, docetaxel, given every 3 weeks at a dose of 75 mg/m^2, along with a corticosteroid, has become the standard systemic treatment for metastatic prostate cancer progressing after androgen deprivation therapy. New docetaxel combinations, with a variety of agents, are under active development in clinical trials.

has been subjected to large-scale trials testing effects on survival for metastatic androgen-independent prostate cancer. Docetaxel, given every 3 weeks (75 mg/m^2) to men with prostate cancer in a small trial ($N = 35$), was associated with a 46% serum PSA response rate.[520] In a series of clinical trials featuring weekly docetaxel (35–40 mg/m^2), serum PSA response rates ranged from 41% to 64%.[521–525] The addition of estramustine to docetaxel appeared also to produce significant benefits in early studies, both for serum PSA responses (45%–74%) and for measurable disease responses (11%–57%).[526–530]

One of the two large randomized trials featuring docetaxel (TAX-327) assigned men with androgen-independent prostate cancer ($N = 1006$) to one of three treatment arms, directly comparing two different schedules of docetaxel (30 mg/m^2 given weekly or 75 mg/m^2 given every 3 weeks) and prednisone against mitoxantrone and prednisone[514] (Fig. 88-17). In the trial, the median survival was 18.9 months for men treated with docetaxel (75 mg/m^2 every 3 weeks) and prednisone, and only 16.5 months for men treated with mitoxantrone and prednisone, a difference that was statistically significant ($P = 0.009$). Weekly docetaxel treatment, with a median survival of 17.4 months, did not provide as compelling a benefit. Along with the survival improvement, docetaxel given every 3 weeks also resulted in a better serum PSA response rate (45% versus 32%) and better pain control (35% versus 22%) than mitoxantrone and prednisone ($P < 0.01$). The other randomized trial (SWOG 99–16) targeted a similar group of men ($N = 770$) and compared treatment with docetaxel and estramustine to treatment with mitoxantrone and prednisone.[515] Again, an improvement in median overall survival was evident for the docetaxel and estramustine regimen (17.5 months versus 15.6 months, $P = 0.02$). In both of the trials, docetaxel chemotherapy was associated with more side effects, including edema, gastrointestinal symptoms, neuropathy, and nail changes, than mitoxantrone treatment, and the combination of docetaxel and estramustine was also associated with a higher incidence of cardiovascular events. The additional complications, and uncertain benefit, accompanying the addition of estramustine to docetaxel has led to the establishment of docetaxel chemotherapy, given every 3 weeks, along with prednisone, as the standard-of-care for men with metastatic androgen-independent prostate cancer. To build on the success of docetaxel against metastatic androgen-independent prostate cancer, several docetaxel combinations—with calcitriol, bevacizumab, and a number of other agents—are being tested in phase 3 trials.[516] In addition, docetaxel itself is being tested in the adjuvant therapy setting. In one phase 2 study, men ($N = 77$) at high risk for serum PSA recurrence following radical prostatectomy were treated with 6 cycles of docetaxel (35 mg/m^2, days 1, 8, 15 every 28 days).[531] With a median follow-up of more than 29 months, the median time-to-PSA recurrence was 15.7 months.

Immunotherapy

The mechanistic basis for prostate cancer immunotherapy is that prostate cancer cells contain antigens that can be recognized by immune cells allowing for selective prostate cancer cell killing.[532,533] T-cells respond to small peptides derived from intracellular proteins that are presented on specialized molecules at the surface of cancer cells. Prostate cancer cells can be recognized by virtue of containing new proteins, formed as a result of somatic gene mutations and translocations, or of expressing lineage proteins, representing prostate cell differentiation. Several such prostate lineage antigens, including PSA, prostate-specific acid phosphatase (PAP), prostate-specific membrane antigen (PSMA), NKX3.1, and others, have become attractive targets for vaccine immunotherapy.[534,535] Unfortunately, prostate cancer cells, and most other cancer cells, tend to evade destruction by immune cells by promoting antigen-specific tolerance, a state in which T cells that could kill cancer cells are inactive and respond poorly to stimuli, including vaccination.[536] The major

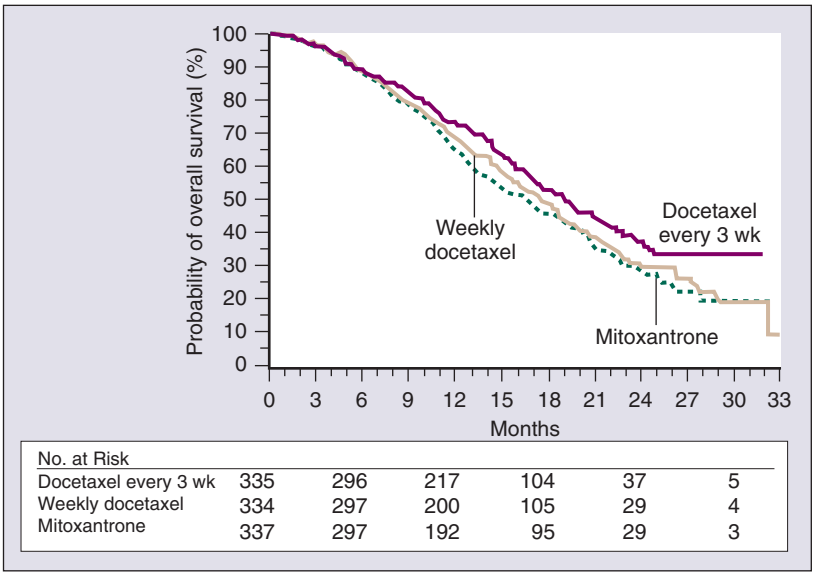


Figure 88-17 • Results of a randomized clinical trial of docetaxel, given at two different dosing schedules, and prednisone versus mitoxantrone and prednisone for men with androgen-independent metastatic prostate cancer. (Data from Tannock IF, de Wit R, Berry WR, et al: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–1512.)

vaccine strategies explored clinically have featured the delivery of prostate cancer antigens to antigen-presenting cells (APCs), such as dendritic cells (DCs) in the skin, which have the capability of stimulating specific T cells to attack prostate cancer cells. However, the clinical experience to date with prostate cancer vaccine immunotherapy has suggested that T-cell tolerance may constitute a significant barrier to treatment success: although measurable immune responses can be elicited by vaccination using a variety of vaccine strategies, these responses only occasionally are accompanied by disease responses.[535] New immunotherapy approaches, featuring strategies to undermine T-cell tolerance, may increase the efficacy of vaccine approaches for prostate cancer.[536,537]

Two immunotherapy approaches have reached phase 3 clinical trials and merit attention. In one strategy, DC vaccines have been created using immature DC precursors recovered from blood mononuclear cells via leukapheresis and loaded with PA-2024, a recombinant protein consisting of PAP fused to GM-CSF.[538,539] In phase 1 and 2 clinical trials of this immunotherapy approach, men with androgen-independent prostate cancer tolerated DC treatment well, exhibited immune responses to PA-2024 after vaccination, and showed a median survival of 29 weeks, with serum PSA responses in 3 men. Phase 3 trials of APC-8015, targeting men with asymptomatic metastatic androgen-independent prostate cancer, with a primary endpoint of objective time-to-progression, have been completed and submitted for regulatory agency approval. A second strategy has featured the use of vaccines created from prostate cancer cells, genetically modified to increase immunogenicity by secretion of GM-CSF.[540] The first clinical application of this strategy for prostate cancer involved genetic modification of autologous prostate cancer cells recovered at radical prostatectomy with *GM-CSF* cDNA.[541] In a phase 1 trial ($N = 8$ men) of irradiated GM-CSF-secreting autologous prostate cancer cell vaccines, 7 of the vaccinated men exhibited delayed-type hypersensitivity (DTH) reactions against unnmodified autologous tumor cells and serum antibody responses to several proteins from prostate cancer cells. To overcome technical problems with generating sufficient numbers of vaccine cells from prostate cancer cells recovered at the time of surgery, prostate cancer vaccine cells have been created by genetic modification of the prostate cancer cell lines LNCaP and PC-3 to permit high level secretion of GM-CSF.[542] In phase 2 studies of this vaccine approach, men with androgen-independent metastatic prostate cancer have been treated with various doses and dose-schedules of GM-CSF-secreting LNCaP/PC-3 vaccines. After a median of 15 months of follow-up, the median survival had not been reached. Also, some 43% of the men had stable or improved bone scans. A phase 3 trial of this vaccine approach, randomized against treatment with docetaxel, for men with androgen-independent metastatic prostate cancer, has been started.

SUMMARY

Although mortality from prostate cancer has declined over the past few years, demographic trends, such as the general aging of the population, suggest that prostate cancer will remain one of the most common health threats for men in the developed world. Widespread implementation of prostate cancer screening using serum PSA has resulted in a changing character of prostate cancer at its initial presentation, with younger men being diagnosed at earlier stages than ever before. The use of serum PSA testing for disease activity monitoring has changed the character of prostate cancer throughout the rest of its natural history, with healthier men having less prostate cancer at later stages of the disease. These changes have put new demands on improving prostate cancer treatment, whether minimizing the morbidity of local prostate cancer treatment or increasing the efficacy of systemic prostate cancer treatment. In the very near future, large clinical studies of prostate cancer prevention, of the benefits of prostate cancer screening, of systemic adjuvant therapies given along with primary local prostate cancer treatment, of systemic chemotherapy for androgen-independent prostate cancer, and of a variety of new agents, will provide new insights of critical importance to prostate cancer care. Ultimately, new biomarkers, new imaging strategies, and new prevention and treatment approaches may hold the secret to eradicating prostate cancer morbidity and mortality.

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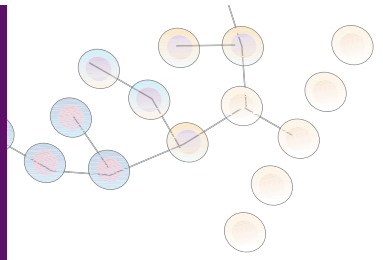
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89 Cancer of the Penis

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SUMMARY OF KEY POINTS

- Penile carcinoma is a rare disease in North America and Europe.
- Penile carcinoma is more common in Africa and South America.
- Greater than 95% of malignant lesions are squamous cell carcinoma (SCC).
- Treatment for SCC is surgical with partial or radical penectomy.
- Treatment often must include inguinal and/or pelvic lymphadenectomy.
- Advanced disease is treated with surgery, chemotherapy, and radiation therapy.
- Five-year survival rates for node-negative disease are favorable.

INTRODUCTION

Penile carcinoma comprises less than 1% of all male malignancies in North America. It is most commonly diagnosed in the sixth decade of life, and as many as 30% of new cases demonstrate advanced disease at the time of initial presentation. SEER (statisitics, epidemiology, and end result) data reveal that more than 95% of the lesions are squamous cell carcinoma (SCC). Generally, lesions start as superficial neoplasms of the prepuce or glans penis and then progress to local invasion of the corpora cavernosa with subsequent development of metastases to the inguinal lymph nodes. The most important prognostic factor for survival remains stage of disease at presentation. Age greater than 65, presence of node-positive disease, and African-American ethnicity have been found to be independent predictors of decreased survival.[1] Early detection and treatment are essential for improved oncologic outcomes and quality of life for patients.

EPIDEMIOLOGY

Geographic Variation

Penile cancer is exceedingly rare in North America and Scandinavia and is far more prevalent in South America, Asia, and Africa. The incidence of SCC of the penis is estimated at 1/100,000 in Western countries.[2,3] In contrast, the incidence has been estimated as high as 17% in Brazil and between 10% and 20% in Africa and Asia.[4,5] Despite geographic differences, the overall incidence has been decreasing worldwide.[3,6,7]

ETIOLOGY

Various factors including an intact prepuce, poor hygiene, presence of sexually transmitted disease, radiation exposure, and cigarette smoking have been linked to the development of penile cancer.

Circumcision

The association of phimosis and penile carcinoma is well established.[8,9] Neonatal circumcision seems to protect against penile carcinoma, because the incidence is essentially zero among this male cohort.[10] In Israel the rate of neonatal circumcision is nearly 100% and the incidence of penile carcinoma is closer to 1/1,000,000 than 1/100,000.[11] The risk of penile cancer in uncircumcised men and in men who undergo postperinatal circumcision are equal and approach three times that of men circumcised in the neonatal period.[12] However, presence of the foreskin alone is not the only risk factor for development of penile cancer. Circumcision rates in Finland and Denmark are much lower than seen in North America, although the incidence of penile cancer is similar.[7,13,14] Furthermore, recent studies show the incidence of penile intraepithelial neoplasia to be quite high in neonatally circumcised men.[15] Ultimately, associated factors such as hygiene, history of sexually transmitted disease, and sexual promiscuity may play an equal or greater role than the presence of the foreskin in the etiology of penile cancer.

Infection

The carcinogenic effect of smegma and the bacteria *Mycobacterium smegmatis* are probably less relevant than once believed in the etiology of penile carcinoma.[16–18] Current investigations implicate the human papilloma virus (HPV), specifically HPV types 16 and 18, in the development of some cases of penile carcinoma.[1] Several studies have demonstrated the presence of HPV DNA from penile cancer specimens in as many as 71% of patients.[19–21] However, other studies have shown much lower detection rates of HPV DNA.[12,22–25]

Warty carcinoma is a subtype of penile SCC that is morphologically distinct.[26] Warty carcinoma seems to be more strongly associated with HPV infection and tends to display a less aggressive clinical phenotype than standard penile SCC.[22,26,27]

Bezerra and colleagues found HPV DNA in 30% of penile carcinoma specimens from 82 patients but demonstrated no significant difference in lymph node metastasis and 10-year survival between HPV^+ and HPV^- groups.[26] These findings suggest that different etiologic pathways may be relevant depending on the type of penile carcinoma diagnosed. The association between penile carcinoma and other sexually transmitted diseases has not been established, nor has any substantive correlation been made between this disease and alcohol consumption or illicit drug usage.[12]

Radiation and Cigarette Smoking

Other factors that seem to play a role in the development of penile carcinoma are ultraviolet (UV) radiation and cigarette smoking. The

former is supported by the increased incidence of cases in men treated with UV light—a phototherapy for psoriasis.[28] Several recent population-based studies have found an increased incidence of penile carcinoma in smokers.[29]

Hygiene

The very low incidence of penile carcinoma in countries such as Denmark and Finland where perinatal circumcision is uncommon supports the notion that proper hygiene and early education in these matters provides equal protection against this disease process.[7] In situations in which hygiene may become an issue because of behavioral or neurologic disorders that limit self-care, circumcision may still be warranted.

PATHOLOGY

Penile carcinoma is one of many pathologic processes that have visible dermatologic signs identified on the genitals. Vigilance on the part of health care providers is essential to early diagnosis because of the myriad benign and premalignant lesions that may imitate or precede penile carcinoma.

Leukoplakia

Leukoplakia presents in diabetic men as perimeatal, blanched plaques or scaled areas that can extend into the urethral meatus. The microscopic appearance is consistent with acanthosis, parakeratosis, and hyperkeratosis and is often seen in close proximity to malignant lesions. This lesion may arise in response to recurrent inflammation or irritation. Treatment of leukoplakia includes excision and biopsy with careful follow-up for the development of possible malignancy. Successful therapy with bleomycin for extensive lesions has been reported in the literature.[30]

Balanitis Xerotica Obliterans (Lichen Sclerosis)

Balanitis xerotica obliterans (BXO) is lichen sclerosis et atrophicus of the penis. First diagnosed in 1928, this disorder can affect the glans, prepuce, and urethra. BXO is associated with SCC of the penis in 2.3% to 5.8% of cases.[31,32] The natural history of BXO is highly variable. Some patients will have an indolent chronic affliction that produces few early symptoms. Others may present with diffuse disease only weeks after onset. The patient often presents with areas of ivory-colored, sclerotic plaque on the glans or inner prepuce and may complain of pruritus. Other symptoms may include phimosis, dysuria, painful erections, or a burning sensation with erection. If untreated, these lesions will spread and coalesce, becoming less pliable and more fibrotic. Sexual intercourse will often result in fissures, blisters, and bleeding. Continued progression of disease can result in contraction of the frenulum and fibrotic phimosis. Topical steroids or circumcision for advanced disease are recommended treatments for BXO. Routine follow-up is important secondary to the rare, but potential malignant transformation of these lesions.[31,33,34]

Carcinoma in Situ

Carcinoma in situ (CIS) of the genitals has different names depending on the location of the lesion. A sharply demarcated, shiny, raised erythematous plaque of the glans or mucosal surface of the prepuce is called erythroplasia of Queyrat (EQ). Bowen's disease (BD) describes the same histologic entity but presents as red, scaling patches on the keratinized genital surfaces such as the penile shaft, scrotum, or perineum.[35,36] These lesions are definitely considered premalignant or malignant because of a progression rate to SCC of 10% to 30%.[37–39] EQ and BD tend to occur in older men, with the most common diagnosis in the fifth decade. BD typically involves the epithelial cell layers of hair follicles with a very similar histologic appearance to EQ. When found on the penis, this lesion often appears as a scaling plaque without notable erythema and signifies the presence of CIS. Only about 1 lesion in 10 will progress to invasive carcinoma, a rate that is comparable to EQ.

Histologically, these lesions demonstrate diffuse changes throughout the squamous epithelial cell layers including keratinocyte hyperplasia, nuclear atypia with many mitoses, proliferation of enlarged hyperchromatic cells, multinucleated cells, and loss of polarity within most cells. Presence of inflammatory cell infiltration and increased density of microvasculature is common. Similar to invasive penile carcinoma, links to HPV infection have been investigated and have revealed a correlation with many of the same viral strains.[40] A small study of EQ identified DNA from HPV type 8 in every sample of penile CIS, whereas this viral DNA was not identified in any samples of BD lesions.[41] In addition, HPV type 16 was found in more than 80% of these samples.[41]

Bowenoid Papulosis

Bowenoid papulosis (BP) is markedly different from EQ and BD in presentation, demographics, and clinical course. Men who have BP are much younger than their EQ counterparts with a mean age of almost 30 years of age.[42] These lesions are groups of scaling, erythematous papules typically seen on the keratinized skin of the penile shaft. Histologically the cellular morphology mimics CIS, but the keratinocytes tend to be slightly more differentiated than those seen in CIS. In addition, histologic sections of Bowenoid papules demonstrate that the more atypical-appearing cells tend to be found among the top epithelial cell layers and in the upper portion of the sweat glands. A physician must combine the clinical presentation and the histologic findings to arrive confidently at the diagnosis (Box 89-1).[42]

Buschke-Lowenstein Tumor (Verrucous Carcinoma)

Commonly known as verrucous carcinoma or giant condyloma acuminatum, Buschke-Lowenstein (B-L) tumors are very similar in appearance to benign condyloma venereatum. Unlike their benign counterparts, B-L tumors tend to invade tissue and cause significant damage. This can be seen histologically. The rete pegs of these lesions are often seen penetrating deeply into surrounding tissue. This aggressive behavior is in contrast to the very well-differentiated cells that compose B-L tumors; cellular anaplasia is very atypical in these specimens. A viral etiology seems to play a role in the development of B-L tumors. Investigators have found associations with HPV

Box 89-1. BOWENOID PAPULOSIS: A DIAGNOSTIC DILEMMA

Bowenoid papulosis resembles carcinoma in situ. The physician needs to be aware of the differences in clinical presentation for these two lesions. The physician will need tissue biopsies to distinguish these lesions histologically.

The etiology of BP is still unclear. Investigations into the viral etiology of BP have provided increasing evidence to support a link to HPV subtypes.[6,14,18,39,165–172] Progression of BP to squamous cell carcinoma has been reported in lesions with high-risk HPV strains.[29,45,173] There have been other reports of malignant conversion as well.[174] Spontaneous regression has also been reported.[175,176]

Recently, treatment for BP has consisted primarily of topical therapy including 5-FU, imiqimod cream, and cidofovir in immunocompromised patients.[177–179] Historically these lesions have been surgically excised, and results with laser and other forms of ablative therapy have been mixed.[43,180] Often topical and extirpative therapy can be used in combination with good results.

strains 6 and 11.[43] Despite the local tissue destruction commonly found with these tumors, metastatic progression of the tumor does not occur. Therefore, local control is the primary objective. Thus, control may require partial or total penectomy.[44] To date, no large-scale trials of topical or radiation therapies have shown efficacy, and most data can be derived from isolated case reports of various treatment modalities.[45,46] A report of B-L tumor regression after treatment with intralesional injections of interferon-α suggests that local nonexcisional therapies directed at viral etiology may hold promise for future therapies.[47] Use of systemic chemotherapy with bleomycin, methotrexate, and cisplatin has been reported to achieve regression of B-L lesions. However, given the known toxicities of these agents, this approach is rarely indicated for this disease.[48] Currently, CO_2 laser ablation is the method of choice for local control of this lesion.[49,50]

Nonsquamous Malignancies

Nonsquamous cell carcinoma of the penis is rare and the tumors compose less than 5% of penile tumors. The most common malignancy is sarcoma. Other histologic penile tumors that have been reported are melanoma, basal cell carcinoma, and lymphoma. With the increasing prevalence of human immunodeficiency virus and acquired immunodeficiency syndrome (AIDS), the incidence of Kaposi's sarcoma is rising, and genital lesions can be found in nearly 20% of patients with AIDS-related Kaposi's sarcoma. Only a very small percentage of these patients will present with a penile lesion. The gross appearance is of erythematous nodules with sharp margins found most often on the glans penis.[51] Standard therapy involves conservative measures such as local excision, laser ablation, or palliative irradiation.[52]

Basal cell carcinoma of the penis most often can be found on the penile shaft, with only a fraction of cases reported on the prepuce or glans.[53] Appearance of this tumor on the scrotum or perineum is even less common.[54,55] The typical appearance of basal cell carcinoma of the penis is a well-circumscribed lesion with clear borders and central pitting. Given the slow rate of growth and lack of metastasis, local excision is often curative.[53,55,56]

In contrast, melanoma of the penis carries a very poor prognosis. Almost 40% of patients present with regional lymph node metastasis.[57] Two of every three lesions are found on the glans. Wide, local excision with a 3- to 5-cm margin is the treatment of choice for lesions less than 1.5 mm Breslow depth.[58] Bilateral inguinal lymph node dissection has been the standard of care for lesions thicker than 1.5 mm.[57]

Tumors that are far more unusual have been reported in the literature as case reports. These tumors include penile schwannoma, plexiform neurofibroma, vascular hemangioendothelioma, leiomyosarcoma, rhabdomyosarcoma, epitheloid sarcoma, Ewing's sarcoma, mucoepidermoid carcinoma, and synovial sarcoma.[59–66] Generally, the prognosis of these tumors is similar to the reported outcomes of these malignancies when they are identified in more typical anatomic locations.

Extramammary Paget's disease is a very rare penoscrotal neoplasm, and distinguishing this lesion from EQ or BD is clinically impossible. Histologically, it is diagnosed by the presence of large, clear-staining cells with hypochromatic nuclei within the epidermis called Paget's cells. This disease is seen in older men and appears as a well-demarcated, erythematous, eczematous lesion. Metastasis to regional lymph nodes occurs very rarely. It is considered the etiology of adenocarcinoma in situ of the epidermis. This entity arises from pluripotent intraepidermal cells undergoing malignant transformation during apocrine differentiation.[67] Clinical suspicion for underlying genitourinary malignancies should be very high, in that 16% to 33% of patients with penoscrotal Paget's disease have concurrent internal genitourinary carcinoma.[67–69] Historically, patients with extramammary Paget's disease were evaluated extensively for occult pulmonary and gastrointestinal malignancy. However, retrospective analysis of patients with penoscrotal Paget's disease reveals that 92% of those with associated malignancy have genitourinary pathology.[67] Treatment generally consists of wide local excision that typically requires coverage of the defect with skin grafting or tissue flaps.[67] Mohs' micrographic surgery has been recommended as the therapy of choice because of the very high incidence of positive margins using standard surgical techniques.[70] Nonexcisional treatments have been described, but these isolated reports do not provide enough data to evaluate for efficacy.[69] Recurrence in these patients is very common, and close follow-up is mandatory.

Metastatic Tumors

Secondary tumors of the penis from metastatic nongenital primary malignancies are rare with only 460 cases reported in the literature.[71] Metastatic tumors to the penis are most often found in the presence of advanced systemic carcinoma. The index of suspicion for penile metastasis should be high in patients who have a known malignancy and subsequently suffer from priapism or complain of a new penile lesion. The common presentation of penile metastases is multiple nodules along the penile skin with occasional ulcerations that have a similar appearance to a syphilitic chancre. These lesions typically are not painful. Almost 50% of patients will have extensive involvement of the corpora cavernosa, which accounts for the common presentation of priapism.[72] The primary tumors that most frequently metastasize to the penis are prostate, bladder, urothelial, renal cell, testis, and rectal carcinomas.[71,72] The prognosis is dismal, with less than 6-month survival for these patients. Treatment should be systemic chemotherapy or local radiation therapy, with surgical treatment reserved for palliation. Partial and total penectomy with negative margins have been reported to render effective palliation.[73]

INVASIVE SQUAMOUS CELL CARCINOMA

Pathology and Natural History

Over 95% of primary penile tumors are SCC. Unfortunately, fewer than half of patients will have superficial disease at the time of diagnosis.[74] This malignancy can arise in any location on the penis, but the lesions of the glans account for nearly half of squamous cell penile carcinomas. Tumors of the prepuce account for more than 20% of penile SCC, and almost 10% of patients will have lesions on both the glans and the foreskin.[74]

Metastasis of penile carcinoma occurs first in the superficial inguinal lymph nodes, and the risk of metastatic disease is related to tumor size. Small tumors found only on the glans or prepuce are rarely metastatic at diagnosis.[75] Large tumors that involve more than 75% of the penile shaft have a very high risk of nodal spread.[76,77]

SCCs of the penis are graded using the Broder scale to quantify the degree of tumor cell differentiation (Table 89-1). Half of all lesions are either grade I or II at initial diagnosis. Histologically these tumors have a hyperkeratotic dermis with cords of carcinoma cells extending into deeper tissue layers, with intercellular bridges, keratin, and keratin pearls prominent throughout the specimen. More than 50% of tumors that first arise on the penile shaft tend to be high-grade carcinoma. By contrast, only 10% of preputial SCC demonstrates poorly differentiated histology.[76]

Other grading systems have been developed to improve the reproducibility of the Broder classification. Factors that influence grading in these systems are the number of mitotic cells per high-power field, degree of keratinization and cellular atypia, and the infiltration of inflammatory cells into the tumor (Fig. 89-1). Each parameter is assigned a score, and these are then summed to give a grade. Application of this system revealed 80% survival among patients with low-grade tumors.[6] Another technique for correlating histology and survival classifies tumors based upon superficial spread, vertical

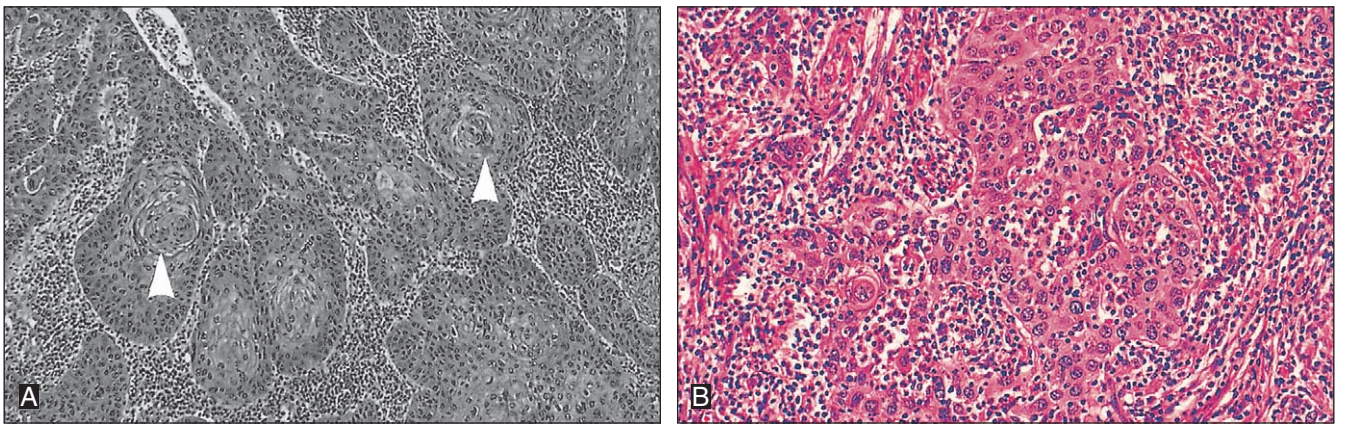


Figure 89-1 • Squamous cell carcinoma. **A,** Irregular nests of neoplastic cells invade the underlying tissue. Note the foci of keratinization (*arrowheads*). **B,** At the point of the deepest invasions, the squamous carcinoma cells are nonkeratinizing and exhibit considerable pleomorphism with large vascular nuclei. Note the associated intense inflammation often seen in invasive carcinoma.

growth, verrucous features, and multicentricity. These categories revealed metastatic disease in 42% with superficial disease and 82% with vertical tumor growth.[78] Other features studied for prognostic significance include ulcerative versus exophytic appearance. Exophytic tumors have a high degree of keratinization on histologic examination with cells that appear fairly well differentiated. Conversely, ulcerative penile malignancy more often has a poorly differentiated appearance and has a higher incidence of lymph node involvement.[4,78]

The natural history of this disease includes invasion and destruction of local tissues with eventual invasion of the corpora and urethra (Fig. 89-2). Metastatic spread occurs as the tumor invades into the lymphatic network of the prepuce and penile skin. These empty to the base of the penis and then to both inguinal node beds. This anatomy has complicated efforts to develop reliable sentinel node biopsy techniques. Once lymph has entered either superficial inguinal nodal chain, it drains into the deep inguinal nodes found below the fascia lata and medial to the femoral vein. The lymphatic system for the glans, urethra, and corpus spongiosum has a variable drainage to either the superficial or deep inguinal nodes. Lymphatic drainage from these structures very rarely goes to the external iliac lymph node complex. Metastatic disease in distant sites such as the liver, lungs, and bones are late signs of advanced disease and carry a poor prognosis.[79] Fortunately, fewer than 5% of patients have evidence of distant metastases at diagnosis.[80,81]

Table 89-1 Broder Classification for Grading of Squamous Cell Carcinoma

Grade	Histologic Features
I	Cells well differentiated with keratinization
	Prominent intercellular bridges
	Keratin pearls
II–III	Increased mitotic activity
	Fewer keratin pearls
IV	Marked nuclear pleomorphism
	Many mitoses
	Necrosis
	Lymphatic and perineural invasion
	Absence of keratin pearls
	Deeply invasive

Clinical Manifestations

Generally, penile carcinoma is a disease of older men in their sixth and seventh decades. Clinical suspicion in younger patients is warranted, because such cases have been reported in the literature.[29,45,77] These lesions may vary in presentation from the innocuous-appearing induration (Fig. 89-3) with slight erythema to the obviously malignant fungating penile tumor that leads to autoamputation (Fig. 89-4). Pruritus of the prepuce or a burning sensation may be an early symptom of this tumor, and careful inspection may reveal a lesion on the prepuce or glans. This lesion may then progress to a papule or mass, which can be found in nearly half of cases. Phimosis may make early identification of these lesions difficult, if not impossible, and patients often delay evaluation by a physician for an average of 1 year as a result.[82] By this time, a chronic malodorous discharge will often drain from under the prepuce. Further delay leads to bleeding from invasion of the deeper penile structures, as well as urethrocutaneous fistula and distortion of basic phallic morphology.[83]

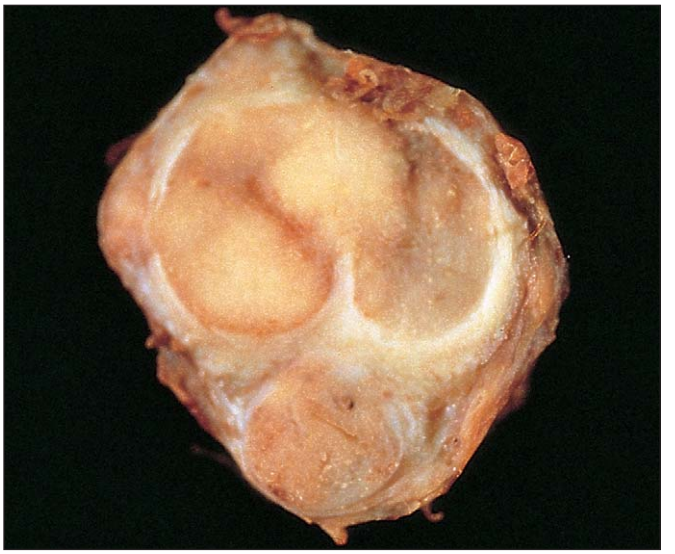


Figure 89-2 • Squamous cell carcinoma. A cross section of the penile shaft illustrating replacement of the corpus cavernosum by tumor.



Figure 89-3 • Carcinoma in situ. This lesion presents clinically as a well-demarcated, slightly elevated erythematous plaque. (Courtesy of K.R. Greer, MD, Charlottesville, VA.)

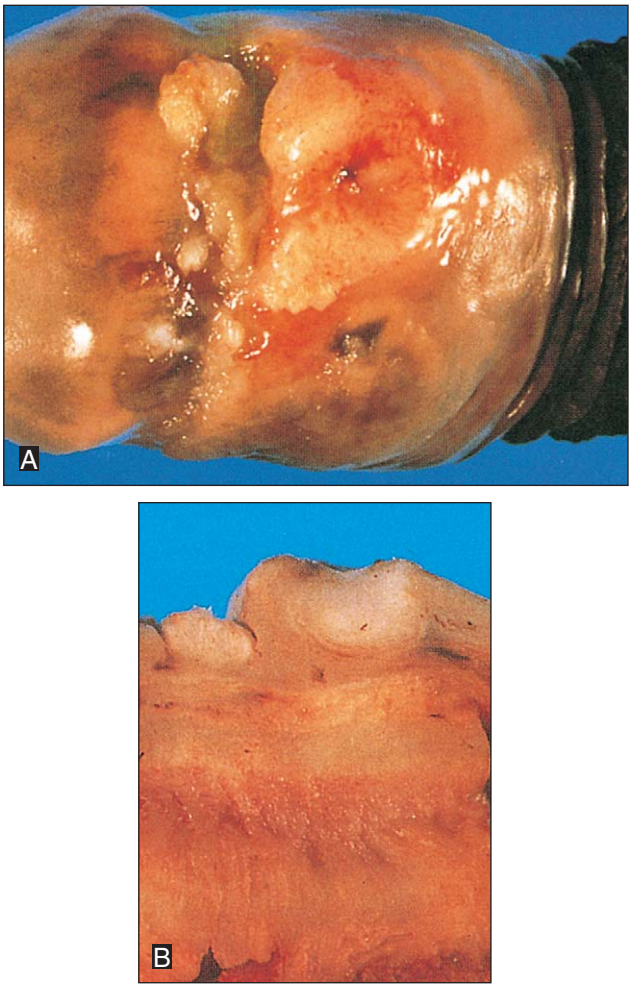


Figure 89-4 • Squamous cell carcinoma. **A,** This resection specimen shows a small lesion arising in the coronal sulcus. **B,** Cut sections from the specimen demonstrated two small nodules of invasive tumor.

Inguinal lymphadenopathy is a common finding at diagnosis, with nearly 60% of patients having palpable inguinal lymph nodes. Many of these patients have concomitant infections that are responsible for the inflammation of the inguinal nodes, and this adenopathy will subside with appropriate treatment. More ominously, one in five patients with clinically negative inguinal lymph nodes will have microscopic evidence of metastatic disease.[79]

Staging and Prognosis

Although many historical staging systems have been used, current staging of penile carcinoma follows the American Joint Committee on Cancer system, which incorporates tumor invasion, local node involvement, and the presence of distant metastases (TNM) to stratify patients based upon prognosis (Table 89-2).[84]

Unlike renal cell carcinoma or prostate cancer in the era of prostate-specific antigen, the importance of physical examination in the setting of a suspected penile malignancy cannot be overstated. A thorough evaluation will provide valuable information regarding the size and location of the tumor as well as the possibility of corporal involvement. Inguinal lymphadenopathy must be noted at the time of diagnosis, because this immediately affects the ensuing treatment algorithm. Inflammation is a confounding variable on physical examination, because it is a probable cause for a worrisome inguinal examination. Consequently, the overall sensitivity and specificity of a careful physical examination of the inguinal region is poor.[85,86] Inflammatory changes also decrease the accuracy of assessing tumor invasion of the corpora. As a result, some investigators are using magnetic resonance imaging (MRI) to improve detection of corporal involvement, but this modality has not become standard of care.[87]

Table 89-2 American Joint Committee Staging System for Penile Carcinoma (TNM Classification)

Classification	Description
TUMOR	
Tx	Primary tumor cannot be assessed.
T0	No primary tumor is present.
Tis	Carcinoma in situ is present.
Ta	Noninvasive verrucous carcinoma is present.
T1	Tumor invades subepithelial connective tissue.
T2	Tumor invades corpus cavernosum or spongiosum.
T3	Tumor invades urethra or prostate.
T4	Tumor invades other adjacent structures.
NODE	
Nx	Regional nodes cannot be assessed.
N0	No regional lymph node metastases are present.
N1	Metastasis exists in a single superficial inguinal node.
N2	Metastasis exists in multiple or bilateral superficial inguinal nodes.
N3	Metastasis exists in deep inguinal or pelvic lymph nodes; unilateral or bilateral.
METASTASIS	
Mx	Distant metastases cannot be assessed.
M0	No distant metastases are present.
M1	Distant metastases are present.

Clinical suspicion of penile malignancy and information gleaned from physical examination must be confirmed by pathologic diagnosis. These tests usually include tissue cultures and special stains so as to exclude infectious etiologies. Small lesions confined to the glans or foreskin can be sampled via circumcision or excisional biopsy. Large lesions are often subjected to biopsy at the time of definitive treatment, and initial diagnosis is made via frozen-section histology.

The management of inguinal lymphadenopathy has been a troublesome issue, because a significant percentage of these patients do not have metastatic disease. It is undesirable to subject patients without metastatic disease to the morbidity of bilateral superficial lymphadenectomy. Consequently some investigators have proposed cytologic aspiration or computed tomography-guided biopsy of suspicious nodes to aid in the decision to excise lymph nodes. Others use ultrasound guidance for needle aspiration of lymph nodes, citing the ability of good ultrasonographers to reliably show changes in nodal architecture such as hypoechogenicity or heterogeneity that suggest the presence of malignancy.[86] The considerable false-negative rate with aspiration cytology limits the clinical utility of this procedure.[88,89] As noted previously, the lack of predictable lymph drainage patterns has also limited the clinical application of sentinel lymph node biopsy for penile malignancy.[90] Also, because this is an uncommon malignancy, sufficient numbers are rarely available to assess the marker characteristics of these tests.

Conservative approaches for the management of inguinal nodes have unacceptably high risks. Only 5% of patients with proven nodal metastases who are treated with expectant management are still alive after 3 years.[91] By contrast, patients with node-negative disease have a 77% survival rate at 5 years.[91,92] The most important prognostic factor predicting nodal involvement is the depth of invasion of the primary tumor. Superficial disease or T1 lesions have a very low rate of metastases to the inguinal region. This is not true for penile carcinoma that has invaded Buck's fascia and involves the corpora. Nearly half of patients with T2 disease will have histologically positive lymph nodes, and the percentage increases with increasing stage, so that more than two thirds of patients with T4 disease have nodal metastasis.[93]

Extent of nodal involvement also has prognostic significance. Five-year survival decreases in conjunction with increasing number of involved lymph nodes. Patients without nodal involvement have an excellent 5-year survival rate of 95%, but only 81% of those with up to three positive nodes will be alive during the same period. Patients with more than three malignant lymph nodes have a 50% mortality, and no patients with pelvic disease are alive at 5 years.[94] A meta-analysis of several series confirms these findings, with a 93% 5-year and 84% 10-year survival for node-negative patients, but only 62% to 65% survival for N1 and N2 patients over the same time span.[95]

Undoubtedly the most reliable method for determining regional node status is the ilioinguinal lymphadenectomy. As noted previously, this invasive procedure is not without significant morbidity.[94,96,97] Consequently, efforts are being made to identify other methods of determining who will benefit most from the procedure so as to limit unnecessary morbidity. Some investigators have suggested that combining the tumor grade with the TNM staging provides better estimation of those at risk for nodal metastases.[93,98]

TREATMENT AND RESULTS

Historically, the foundation of therapy for penile carcinoma has been surgical excision of both the primary tumor and regional lymph nodes. These patients must be counseled preoperatively to minimize negative emotional and psychologic reaction postoperatively.[99] Furthermore, if medically feasible, attempts to incorporate organ-preserving techniques such as Mohs' micrographic surgery or laser ablation into treatment protocols should be considered. Ongoing research to develop less disfiguring treatments are being investigated to maintain or improve outcomes while minimizing the need for complete penile reconstruction.

Treatment of the Penile Tumor

Circumcision is an excellent form of therapy for small Tis or T1 lesions limited to the prepuce. Intraoperative use of frozen-section pathology to determine negative surgical margins is critical to ensure an optimal result. When the malignancy is located on the glans or penile shaft, nonextirpative therapies should be explored in an effort to provide excellent opportunity for a cure without severe disfigurement. 5-Fluorouracil (5-FU) has been applied as a topical chemotherapy in the treatment of CIS of the penis with acceptable results.[100] Limitations include patient compliance due to the long course of therapy (3–7 weeks) and local skin irritation. The gold standard for these lesions is partial penectomy. The recurrence rate for this procedure is from 0 to 8% with negative margins.[101,102] Other surgical techniques include limited local excision and Mohs' micrographic surgery. Lont and colleagues describe penile preservation surgery for T1 and small T2 lesions. The lesion was excised, and the bed was coagulated using laser. The local recurrence rate was 22% at 5 years for microscopically tumor-free margins.[103]

Mohs' micrographic surgery requires microscopic inspection of surgical margins to permit complete excision of the lesion, and initial studies report an 80% cure rate at 5 years. This technique has been used in conjunction with other therapies with good results.[104] The complication rate is very low.[105] Mohs' surgery, however, typically requires multiple procedures and specially trained surgical staff.[106,107] In certain cases, wide local excision of the tumor with skin grafting or skin advancement for coverage can provide a normal appearance without jeopardizing cancer control.[108]

Surgical Therapy in Advanced Penile Cancer

If the primary tumor is large enough to have infiltrated 75% of the penile shaft, it is unlikely that the required 2-cm margin will be achieved while leaving adequate penile length to urinate with sufficient hygiene. In such cases, a total penectomy or complete corporal body resection with a perineal urethrostomy is indicated. More aggressive tumors that appear to invade the surrounding bony structures mandate local bone resection in addition to penectomy and perineal urethrostomy.

The typical patient with advanced penile malignancy will often have associated infections that require treatment and lymph node beds that will require staging. Evaluation of the nodal involvement allows for more accurate stratification of those patients who are likely to have recurrence with conventional therapy. Biopsies of bulky pelvic nodes can be performed with computed tomography or ultrasound guidance, or by open incisional techniques. The literature does not support any suggestion that pelvic lymphadenectomy is curative, but the pathologic information from the dissection allows precise staging and identifies those patients who may benefit from adjuvant treatments. Given the poor long-term survival for patients with known pelvic nodal metastases, experimental protocols that include combinations of chemotherapy and irradiation are advisable in this high-risk cohort. The problem once again is that these patients are a subset of a rare malignancy, and meaningful numbers in these research studies are difficult to attain.

Superficial Inguinal Lymphadenectomy

The presence of metastatic lymph node disease has been shown to be an important predictor of survival. Patients with T2–4 disease and clinically negative or minimally palpable inguinal nodes should undergo a modified superficial inguinal lymphadenectomy (ILND). Frozen-section pathology is a critical intraoperative tool to identify patients who need more extensive nodal excision. Several retrospective reviews have shown that the incidence of noncontiguous or "skip" metastases is almost negligible when fewer than two involved nodes are found in the superficial lymph node bed.[99–113] Consequently, if more than two lymph nodes are found to be involved with

metastatic disease on frozen section, the lymph node dissection must be expanded to include the deeper lymph node chains as well. In addition, patients with T1 penile malignancy but poorly differentiated histology should be offered superficial ILND given the higher incidence of nodal metastasis among this group. Controversy exists regarding the timing of ILND, but some data suggest benefit to early intervention.[82]

Technical considerations for superficial ILND include preservation of the areolar adipose layer superficial to Scarpa's fascia. This decreases the likelihood of flap necrosis and epidermolysis by leaving most of the saphenous vein lymphatic drainage intact. Anatomic boundaries of dissection are confined anteriorly by Scarpa's fascia and posteriorly by the fascia lata; the superior-inferior limits are from 2 cm cephalad to 10 cm caudad to the inguinal ligament. Careful adherence to proper surgical guidelines for superficial ILND is important, because many current series have demonstrated that this procedure when performed properly is effective treatment of limited node involvement.[114–117] Furthermore, the modified superficial ILND seems to have refined the inguinal lymph node dissection with resultant decrease in morbidity.[118] Postoperative sequelae of superficial ILND are lymphedema, deep venous thrombosis, and wound complications. The estimated morbidity of this procedure including all complications is less than 15%.[101]

Sentinel Lymph Node Biopsy

Complications from morbidity associated with inguinal lymph node dissection can be significant when they occur. There appears to be a survival advantage in immediate lymphadenectomy for those patients with tumor-positive nodes.[119,120] However, only about half of patients with *clinically* positive nodes will have nodes positive for cancer after dissection. This can lead to overtreatment of patients without metastases and place these patients at unnecessary risk for significant morbidity.[119] Sentinel lymph node biopsy was introduced to combat this problem (Box 89-2); however, reproducibility of the technique was found to be poor because of difficulty identifying the position of the sentinel node. In addition, the false-negative rate was unacceptably high.[119] Horenblas and colleagues introduced a promising new technique called dynamic sentinel lymph node biopsy.[121] The technique comprises lymphoscintigraphy the day before surgery for lymph node mapping. During surgery a γ-ray detection probe and blue dye are used to identify the sentinel nodes. If the nodes are found to be positive for tumor, further lymph node dissection is carried out. If the nodes are histologically negative, no further dissection is necessary. Morbidity from this procedure is low.[121,122] In a recent series Horenblas and colleagues report that size of metastasis in the sentinel lymph node is important. They found that 80% of patients with micrometastatic disease in the sentinel lymph node had no further lymph node involvement.[121] The dynamic sentinel lymph node biopsy technique continues to be refined. If it is confirmed to be reliable with further studies, it will be a valuable tool in identifying those patients that require minimal or no lymph node dissection.

Along similar lines of research, McDougal and coworkers report on an imaging procedure using lymphotrophic nanoparticle-enhanced MRI with ferumoxtran-10 for staging of lymph nodes in patients with penile cancer.[123] This technique has been used successfully to detect metastatic nodal disease in other primary cancers. Seven patients with penile SCC and planned ILND were enrolled in the study. The patients were imaged with MRI before and 24 hours after infusion of ferumoxtran-10. They then underwent ILND, and the pathology results were compared to the imaging results. This imaging technique was found to accurately diagnose benign and malignant nodes. The sensitivity was 100%, the specificity was 97%, the positive predictive value was 81.2%, and the negative predictive value was 100%.[123] The negative predictive value was significant, because this showed that all patients with positive nodes were identified, and there were no false negatives.[123] Although the series is small, these preliminary data exceed the accuracy of other current modalities.[123] If these findings are confirmed with larger studies, lymphotrophic nanoparticle-enhanced MRI will be a valuable tool for staging penile cancer patients in the future.

Box 89-2. SENTINEL LYMPH NODE BIOPSY

Sentinel lymph node biopsy for penile carcinoma is controversial. There is ongoing research on techniques to best achieve reproducible results. Some techniques seem promising. However, larger studies will be necessary before a consensus can be reached.

Radical Inguinal Lymph Node Dissection

This procedure is currently performed essentially as it was originally described by Daseler and associates in 1948.[124] The limits of the dissection are from the sartorius muscle to the adductor longus in a lateral to medial direction, and from the inguinal ligament inferior to the apex of the femoral triangle. The initial incision is through the tensor fascia lata over the adductor longus, with ligation of the greater saphenous vein, and then carried medially to the border of the sartorius muscle. A requirement for the deep nodal dissection includes incision of the femoral vascular sheath so as to excise the extensive lymphatic networks that completely encase these vessels.

Reconstructive options to cover the exposed femoral vessels include rotation of a sartorius muscle flap as mentioned earlier. This procedure involves dissecting the sartorius tendon from the anterior superior iliac spine and suturing it to the inguinal ligament over the femoral vessels. Ulcerated and matted nodes often result in wide excision of the overlying skin with at least a 3-cm margin. Rotated myocutaneous gracilis, rectus abdominis, or tensor fascia lata flaps can be used to augment coverage and assist healing. Local control of these advanced lymph nodes is critical, because progression of the disease can lead to vascular erosion and hemorrhage. Surgical treatment often requires careful dissection and control of the femoral vessels. Advanced and erosive disease may mandate resection of part or all of the femoral vein wall as well as venous thrombectomy.

As would be expected, complications of the deeper nodal excision are more frequent and severe than those encountered with the superficial and modified procedures. The relative incidence of flap necrosis and large lymphoceles requiring percutaneous drainage is 2% to 5%.[125] The incidence of wound infections, lower extremity and scrotal edema, lymphocele, seroma, and thrombophlebitis ranges from 2% to 13%.[89,103,116,125–129] Improvements in surgical techniques and postoperative care have decreased the severity and incidence of complications, but postoperative morbidity after deep ILND continues to be a significant clinical problem.[118,125,130]

Pelvic Lymphadenectomy

Pelvic lymphadenectomy may be done simultaneously with a superficial ILND or as a staged procedure. The dissection can be performed open or laparoscopically.[131] This procedure excises the nodal chains from the common iliac vessels down to the internal and external perivascular iliac nodes, and from the lateral pelvic sidewall to the bladder medially. The posterior limit of dissection is the obturator nerve. To date, pelvic lymphadenectomy has value only as a staging procedure. The survival of patients who undergo this excision is less than 5% after 5 years.[132,133]

Chemotherapy for Advanced Penile Carcinoma

Single-Agent Therapy

Historically, chemotherapeutic agents have been applied in the treatment of penile carcinoma in combination with surgical or radiation therapies. The most commonly used agents that have proven

Table 89-3 Selected Reports of Single-Agent Chemotherapy for Penile Cancer

Drug and Regimen	No. of Patients	Response (%)*
Bleomycin		
3–20 mg/m^2/day continuous infusion *or* 10–30 mg/m^2 every day or weekly boluses	14	21 (4)
Methotrexate		
Various treatment schedules	8	38 (3)
or 250 mg/m^2 every 2–4 wk *or* 30–40 mg/m^2 weekly	13	61 (8)
Cisplatin		
70 or 120 mg/m^2 every 21 days	14	21 (3)
or 50 mg/m^2 on days 1 and 8 for 28 days	26	15 (4)

*Number of patients responding is given in parentheses.

cytotoxic effects in penile carcinoma are bleomycin, methotrexate, and cisplatin. These drugs have been reported in several combinations in small series with variable doses and medication schedules. As single-agent chemotherapy, these medications have produced only modest results in patients with advanced disease (Table 89-3).[134–137] The vast majority of patients who showed any regression of disease had a partial response; and, in the report on methotrexate activity by Sklaroff and Yagoda, the median duration of remission in partial responders was 3 months.[135] However, two patients did have responses that lasted more than 12 months. Investigation into cisplatin yielded similar results, with the duration of partial response 1 to 3 months and a median survival of only 5 months.[137]

Dose-dependent side effects of bleomycin were pneumonitis and pulmonary fibrosis, with elevated risk when dosing was greater than 400 units.[135] Patients undergoing treatment with methotrexate most frequently had mucositis as the primary adverse reaction. Infrequent side effects of methotrexate were pneumonitis, hepatic insufficiency, myelosuppression, renal insufficiency, skin rashes, and sepsis.[135] The most debilitating effect of cisplatin single-agent treatment was nausea and vomiting.[137] Other significant toxicities of cisplatin therapy were nephrotoxicity that led to cessation of treatment in 8% of patients, as well as ototoxicity, myelosuppression, and neuropathy.[137]

Combination Chemotherapy

The intent of combination chemotherapeutic regimens is to optimize cytotoxicity while increasing the range of activity of treatment and reducing the probability of inducing tumor drug resistance. In a small series, an 80% response rate with 40% complete response was achieved in five patients treated with cisplatin and 5-FU before lymphadenectomy.[138] Another small series had similar success, with one complete response and five partial responses in six patients who subsequently underwent surgical or radiation treatments.[139] In this series all six patients eventually had progression of their disease, but median time to progression was 1 year and median survival was 16 months. However, another small study reported on a similar regimen with 5-FU and cisplatin that resulted in only a 25% response rate in eight patients.[140] The variability in outcomes may be a result of chance given the small sample sizes in each study, or may be related to different modes of delivery of chemotherapeutic medicines or patient selection. Nevertheless, these results suggest that this combination has significant activity in the treatment of penile SCC despite the lack of a durable response.

Another trial of combination chemotherapy used cisplatin, bleomycin, and methotrexate that resulted in a 72% response rate in 10 of 14 patients, with the vast majority having a partial response.[141] The patients underwent leucovorin rescue after treatment with methotrexate. The average duration of response was nearly 6 months, and one patient continued to be disease-free at 2 years. In this study a small percentage of patients received the bleomycin and cisplatin through local-regional infusion into pelvic arteries. In addition, Huang and coworkers reported three of three responders with exclusively intra-arterial administration of all three agents.[142] Reported toxicities were similar to those seen with single-agent treatment with these agents.

These results led to a larger multi-institutional prospective study of methotrexate, bleomycin, cisplatin combination therapy in 45 patients by the Southwest Oncology Group.[143] These investigators were able to achieve a 32.5% response rate, with 5 of 13 responders showing a complete response. However this regimen resulted in 11% treatment-related mortality primarily due to pulmonary complications, with an additional 17% of patients experiencing life-threatening toxicity. The unacceptable level of toxicity prevented further clinical trials of this regimen.

The combination of vincristine, bleomycin, and methotrexate was investigated in patients with advanced penile malignancy, and a 53.8% response rate was reported.[144] In 13 patients with bulky inguinal metastases that were deemed unresectable before chemotherapy, 5 had sufficient response to undergo postchemotherapy radical excision. Two of the five enjoyed long-term disease-free survival longer than 5 years. Toxicities were less severe than other regimens, with fever, cutaneous hyperpigmentation, and pulmonary fibrosis reported.

The activity of chemotherapeutic agents in treatment of advanced penile carcinoma indicates that combination chemotherapy should contribute to multimodality approaches in the management of penile carcinoma. As with chemotherapeutic investigations of other malignancies, identification of active combinations while minimizing toxicity remains the objective. More intensive efforts should be directed toward refining combination chemotherapies for penile SCC. This could be accomplished through multi-institutional, collaborative, international studies.

Chemotherapy with Surgery

No large studies of preoperative chemotherapy in penile cancer patients exist, but reports of patients who have received chemotherapy before surgical treatment can be gleaned from the published literature on chemotherapy for advanced disease. By combining the published series on cisplatin-based chemotherapy, 35 patients with fixed inguinal nodes can be identified who received chemotherapy and then subsequently underwent excisional surgery.[139–141,144,145] Nearly 70% of patients from these series showed some response to chemotherapy, with 23% demonstrating a durable response, and the treatment allowed complete resection of tumor in 15. Of these patients, 8 had long-term survival in excess of 12 months and as long as 10 years. Another study in 27 patients with T1 lesions resulted in 85% penile preservation after treatment with vinblastine, bleomycin, and methotrexate followed by surgical excision or ablation with CO_2 laser. Furthermore, 44% of those treated had no pathologic evidence of disease, and an additional 34% had partial response to this combination therapy.

In another small series, Pizzocaro and Piva treated 12 patients with a postoperative adjuvant chemotherapy regimen consisting of vinblastine, methotrexate, and bleomycin.[146] Only 1 of these 12 patients relapsed during a median follow-up of 42 months. In addition, 5 patients with unresectable bulky inguinal disease were treated with this chemotherapeutic regimen. Subsequently, 3 patients who exhibited a partial response underwent radical lymphadenectomy and continued to be disease-free at 20 to 72 months after surgery. Two minimal responders could not have radical surgery, and they died of the disease within 1 year.[146] Encouraged by these findings, the same group then reported on 26 patients who had fixed inguinal nodes. Ten of these patients were treated with radiation therapy, with or without chemotherapy, and 16 received neoadjuvant chemotherapy.

Radiation therapy made it possible for only one patient to later have lymphadenectomy, and all of these patients died of their disease within 3 years. In dramatic contrast, 10 (56%) of those who were treated with neoadjuvant chemotherapy responded sufficiently to have subsequent node excision, and 5 (31%) were found to be disease-free on 5-years follow-up.[147]

Since then, Roth and colleagues designed a more extensive adjuvant chemotherapeutic regimen including 5-FU, cisplatin, mitomycin, bleomycin, and methotrexate. Eight patients with penile carcinoma received eight intra-arterial infusions over 48 hours.[148] All but one patient had previous resection of disease with pathologic confirmation of nodal involvement, or were found to have recurrence in the inguinal region on follow-up. Three patients had a complete response; three had a partial response, with one demonstrating stable disease. Two of three patients with complete response had long-term disease-free survival for more than 5 years.

Clearly, the use of chemotherapeutic regimens to permit patients with bulky nodal disease to undergo surgical resection, or as an adjuvant after lymphadenectomy, has been shown effective in some patients. Yet these data tend to be hidden within other reports, because no large-scale prospective trials have been designed to assess optimal timing and regimens for the adjuvant chemotherapeutic treatment of penile SCC in conjunction with surgical excision. Again, given the rarity of this disease in many countries, compiling enough cases to perform such a study is certainly a daunting task that emphasizes the need for multi-institutional and international collaboration to determine the optimal therapy for advanced disease.

Radiation Therapy in Penile Cancer

An alternative to topical or extirpative therapy for penile cancer is radiation therapy via interstitial brachytherapy or external-beam radiation. Radiation therapy has been reported in many series as a single-agent treatment for both primary penile tumors and metastatic lymph node disease.[80,94,127,149–154] Crook and associates reported the use of interstitial brachytherapy for penile carcinoma and reported a 93% disease-free rate for patients with T1 and T2 lesions and a 100% cure rate for patients with well-differentiated tumors.[155] This treatment has been the therapy of choice for small, clinically localized penile cancer in France, with a 74% penile conservation rate and only 11% local failure for tumors smaller than 2 cm.[156] The success rates from other reports have varied from 65% to 80% for superficial lesions.[117,120,152,153,157,158]

In more advanced penile malignancy, treatment with radiation therapy has an unacceptably high rate of tumor recurrence that is between 20% and 40%.[152,157,159] Furthermore, radiation therapy for tumors larger than 4 cm often results in a nonfunctional penis or significant active residual disease. Both outcomes defeat the purpose of organ-preserving therapy, which is to adequately treat the disease while maintaining function.[153,158] In choosing radiation treatment rather than surgical extirpation of the primary lesion, the patient must realize that the tumor may progress to lymph nodes or distant metastases despite treatment, thus precluding the opportunity for cure. The complete response rate for external-beam radiation therapy has been reported as 56% with local failure rate of 40%.[94,149] Fortunately, in some cases excision of local recurrence after irradiation can provide local control.

Complications from radiation treatment for penile malignancy can vary from relatively benign telangiectasias and catarrhal reactions seen in more than 90% of patients, to more troublesome urethral strictures in 20% to 35%, and meatal stenosis in 15% to 30%.[80,150,154] In addition, tissue changes in response to radiation treatment often lead to necrosis that is clinically similar to the appearance of residual tumor and results in severe impairment of organ function. Nevertheless, given the undeniable activity of radiation therapy in penile carcinoma, particularly in early-stage disease, this modality will continue to be an integral part of integrated organ-sparing therapy for penile cancer.

Chemotherapy with Radiation

Several small series of combination chemotherapy and radiation regimens demonstrate response rates superior to those reported for radiation therapy alone.[160–162] Modig and coworkers found similar survival rates between 19 patients treated with bleomycin and radiation and a similar cohort of patients who underwent surgery.[160] Most efforts in organ-preserving therapy have involved bleomycin and irradiation, because bleomycin is a known radiosensitizer and most treated patients have had relatively low-stage tumors. A series of 47 patients with penile carcinoma ranging from T1 to T3 disease were treated with bleomycin and 45 or 58 Gy of radiation for a period of 5 to 6 weeks with little overall toxicity. Results from the two arms of this study demonstrated that 2 of 7 (18%) treated with 45 Gy required further tumor excision, whereas 4 of 40 (10%) patients who received 58 Gy subsequently underwent surgical salvage.[163] However, smaller studies do not support these findings; treatment of 10 patients with a similar dose of bleomycin and 60 Gy external-beam radiation administered in three equal doses resulted in one treatment-related death with moderate to severe toxicity in 8 patients. Worse, only 4 patients ultimately achieved organ preservation.[164]

Unquestionably, the published literature supports the notion that penile SCC is sensitive to chemotherapy. Currently no conclusive data exist to suggest that one chemotherapeutic regimen is superior to the myriad combinations that have been investigated. Yet, many other agents other than bleomycin, 5-FU, methotrexate, and cisplatin have not been evaluated for activity in treatment of penile malignancy. In addition, the significant toxicity of the commonly used therapy of bleomycin, methotrexate, and cisplatin, and the heretofore unknown side effect profiles of other chemotherapeutic combinations demand further investigation into other regimens that ultimately have superior outcomes in terms of morbidity as well as response rate and overall mortality.

The gold standard of therapy for penile carcinoma remains early detection with local tumor control if feasible. Treatment guidelines based upon pathologic stage are shown in Table 89-4. Patients at high risk for relapse should strongly consider neoadjuvant therapy. Currently the small numbers in the reported series and the different combinations and administrations investigated limit the ability to draw firm conclusions about multimodality therapy for penile carcinoma. However, the data do suggest that preoperative administration of chemotherapy that includes cisplatin will allow 40% of patients with local-regional dissemination of malignancy to proceed with surgical resection with good probability of negative margins, and will result in long-term disease-free survival in as many as 20%. Other combinations such as vinblastine, bleomycin, and methotrexate do not seem to achieve comparable response rates. Combinations of bleomycin and radiation therapy seem to hold promise for organ-preserving treatment in carefully selected subjects.

Table 89-4 Stage-Based Guidelines for Treatment of Penile Carcinoma

Penile Cancer Stage	Guidelines for Treatment
pT1, pT2	Partial penectomy, superficial ILND, frozen-section confirmation; deep ILND if frozen-section evaluation of superficial nodes is positive
pT3	Total penectomy, superficial and deep ILND
T4	Initial treatment with neoadjuvant chemotherapy followed by salvage lymphadenectomy if possible
N2–N3	Enroll in postoperative neoadjuvant chemotherapy or radiation treatments

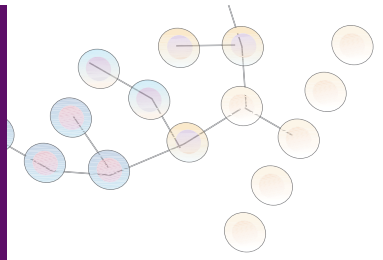
ILND, inguinal lymphadenectomy.

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90 Testicular Cancer

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SUMMARY OF KEY POINTS

Incidence
- One percent of all male malignancies, accounting for 6000 to 8000 new cases a year in the United States
- Most common malignancy among men aged 15 to 35
- Seminoma: 40% of all germ cell tumors
- Nonseminoma: 60% of all germ cell tumors, with embryonal elements most frequent

Differential Diagnosis
- Testicular torsion, hydrocele, varicocele, spermatocele, epididymitis (can coexist with germ cell tumors)
- Other malignancies: lymphoma, metastases from prostate cancer, lung cancer, or melanoma (generally in older age group)

Diagnosis and Staging Evaluation
- Complete history and physical examination
- Bilateral testicular ultrasonography
- Tumor serum markers (lactate dehydrogenase [LDH], β-human chorionic gonadotropin [β-HCG], and α-fetoprotein [AFP])
- Hemogram, chemistry studies including renal function
- Computed tomography (CT) of chest, abdomen, and pelvis
- Additional imaging studies as appropriate (e.g., imaging of brain in patient with pure choriocarcinoma)
- Radical (inguinal) orchiectomy (transscrotal biopsy or orchiectomy should be avoided)

Primary Therapy

Seminoma
- Localized disease is curable with orchiectomy and low-dose adjuvant radiotherapy or single-dose carboplatin to lymph nodes in 98% of patients.
- Locally advanced disease (stage II) is curable with orchiectomy and radiation therapy to involved areas in 85% to 95% of patients with minimal to moderately bulky disease.
- Metastatic disease (stage III) or bulky locally advanced disease is curable in 90% with combination chemotherapy.
- Postchemotherapy retroperitoneal lymphadenectomy can prevent subsequent relapse in selected patients.

Nonseminoma
- Clinically localized disease is curable with orchiectomy alone in 60% to 80%.
- Risk of relapse is decreased with retroperitoneal lymphadenectomy, although in selected patients surveillance without surgery is a possible option.
- Adjuvant combination chemotherapy after lymphadenectomy may further decrease risk of relapse but does not impact on survival.
- Nonbulky locally advanced (stage II) disease is cured with surgery alone in 40% to 60% of cases.
- Moderate to bulky nodal disease requires combination chemotherapy.
- Metastatic disease (stage III), or bulky locally advanced disease is curable in 80% of cases with combination chemotherapy.
- Postchemotherapy retroperitoneal lymphadenectomy can prevent subsequent relapse in selected patients.

Effective Second- and Third-Line Therapies
- Chemotherapy salvage rates are about 80% for patients who have failed surgical or radiation therapeutic treatments.
- Second-line chemotherapy for patients who have failed prior chemotherapy are curative in 20%–75%.
- High-dose therapy with autologous bone marrow transplant/peripheral stem cell transplant (PSCT) possibly curative in 15% to 20% of those in whom second-line therapy has failed

INTRODUCTION

Although testicular cancer accounts for only 1% of all male malignancies, the understanding and study of this disease are important for a variety of reasons. The evolution of therapy for germ cell tumors (GCTs) has been deliberate and thoughtful, and has resulted in cures of 85%. GCT therapy serves as a model for the treatment of curable cancers and is particularly notable because GCT occurs in young men who are entering their most productive years. Nonetheless, challenges in the management of GCTs remain. Because of their young age, patients who have been cured are at risk of delayed, treatment-induced toxicity. Furthermore, an 85% cure rate also implies that 15% of patients with GCTs will not be cured and will ultimately succumb to their disease. An understanding of staging and risk assessment is crucial if (1) patients with good-risk features are not to be overtreated and exposed to undue toxic risks, and (2) patients with poor-risk features are to receive adequate (curative) therapy.

EPIDEMIOLOGY

Incidence

GCTs account for 1% of all male malignancies and it is estimated that 7500 new cases were diagnosed in the United States in the year 2007.[1] Approximately 400 men in the United States died in the year 2002 as a consequence of germ cell tumors, despite their overall curability. Although GCT is an uncommon malignancy, it is the most common malignancy among men aged 15 to 35. Seminoma accounts

for 40% of all GCTs, whereas nonseminoma germ cell tumors (NSGCTs) account for 60%. Although occasionally GCTs occur in children (generally yolk sac tumors) and in men over 70 (generally spermatocytic seminoma), by and large it is a malignancy of early adulthood, with the incidence of seminoma peaking in the 25- to 45-year-old group; the highest incidence of nonseminoma occurs in a slightly younger group of men (15- to 30-year-old group).[2] Although the incidence of germ cell neoplasms in African American men is one fourth that of white men, African Americans have a higher disease stage at diagnosis than white men.[3] Bilateral tumors occur in 2% to 4% of patients.[4]

Etiology

Although risk factors for the development of this disease are largely unknown, a history of cryptorchidism seems to be related to the development of GCT. The risk of developing GCT is 10- to 40-fold higher in cryptorchid testes, and it is anticipated that 12% of all GCTs arise in cryptorchid testes. Conversely, from 1% to 5% of boys with a history of an undescended testicle will go on to develop GCT. The risk is highest (at approximately 5%) when a cryptorchid testis is retained intra-abdominally, falls to 1% if retained in the inguinal canal, and seems to fall further if the undescended testis is surgically placed in the scrotum (orchiopexy) before 6 years of age. However, one fourth of GCTs arising in patients with a history of cryptorchidism occur in the normal, descended testicle, suggesting that systemic sequelae of cryptorchidism (i.e., testicular atrophy) is of greater etiologic importance than local or anatomic abnormalities.[5,6] Further, males exposed to tobacco smoke in utero have a higher incidence of cryptorchidism,[7] although a direct link between tobacco smoke and testis cancer has not been observed.

In patients with testicular feminization syndrome and intra-abdominally retained gonads, a 40-fold increase of GCT is seen. In phenotypically female but genotypically male patients, this syndrome may be mistaken for ovarian cancer.[8]

Although the association between cryptorchidism and the development of GCT is indisputable, it is prudent to recall that a history of cryptorchidism is absent in nearly 90% of men with GCT. The contribution of orchitis, testicular trauma, or irradiation to the genesis of GCT is unknown, but it has been postulated that the final pathway common to all of these associations is testicular atrophy with increased follicle-stimulating hormone (FSH) drive. There is growing support for the concept of transplacental damage to the fetal gonad by maternal estrogen levels as a contributing causative agent of germ cell cancer.[9]

Extragonadal GCTs seem to arise as a consequence of the malignant transformation of residual midline germinal elements, usually in the mediastinum or retroperitoneum, but occasionally in other locations such as the sacrococcygeal region and the pineal gland.[10] Whether these residual germinal elements are a consequence of abnormal germ cell migration is not known, and other factors that may contribute to the development of extragonadal GCT have not been identified.

Molecular Biology

The cytogenetic and molecular biology of GCT has only recently begun to be understood. Most interest has focused on changes involving chromosome 12. The isochromosome of the short arm of chromosome 12, i(12p), has been reported in up to 90% of GCT patients,[11,12] and in cases in which the isochromosome is not seen, excess genetic material is typically found on the p arm of chromosome 12.[13] Although it is occasionally found in gastric cancer, i(12p) is nearly a pathognomonic feature of GCT of all histologic types, whether of gonadal or extragonadal origin. This cytogenetic abnormality has been reported in carcinoma in situ tissue, suggesting it is an early marker, if not a cause, of germ cell tumorigenesis.[14] In patients with mediastinal GCT, in whom there is an increased incidence of hematologic malignancies, often acute myeloid leukemia, i(12p) can be found in both the mediastinal GCT tissue and in the leukemic cells,[15] suggesting a common clonal origin for both. Similarly, i(12p) is found in malignant tissue of diverse histologies that has developed from the malignant transformation of teratoma, which is a component of nonseminomatous germ cell cancers.[16] The presence of i(12p) has been utilized diagnostically in patients with midline carcinomas of unknown origin,[17] allowing, in one series, a definitive diagnosis of GCT in 28% of patients, and also serving as a marker of chemotherapy sensitivity (within the group of patients with midline malignancies of uncertain histogenesis).[18] The presence of three or more copies of i(12p) has been correlated with poor prognosis GCT.[19] Other changes in chromosome 12 are seen in GCT. Deletions of the terminal portion of 12q have been observed in up to 44% of patients with GCT, as well as in several GCT cell lines, suggesting the possibility of a tumor suppressor gene in this area.[20]

The gene or genes on i(12p) that may be involved in carcinogenesis have not been identified, although the oncogene c-Ki-ras-2, which is located on i(12p), has been implicated in GCT cell lines.[21] The cyclin D2 gene has received much attention in normal testicular development as well as in the pathogenesis of GCT. It has an important role in cellular proliferation, and its expression is tightly regulated throughout the cell cycle. It facilitates passage of cells though the G1 cell-cycle checkpoint. The gene is located on the short arm of chromosome 12, and it is overexpressed in nearly all GCTs. Cyclin D2 is therefore a candidate GCT oncogene.[20] Activated mutations in the proto-oncogene c-kit have also been isolated from seminoma specimens.[22] c-kit encodes a transmembrane receptor tyrosine kinase that seems to have a role in normal spermatogenesis, and it is expressed in early fetal germ cells up to 12 weeks of gestation, but not beyond. In addition, it has also been detected in carcinoma in situ (CIS) and seminoma cells, reflecting a possible role in GCT oncogenesis.[22,23] Epidermal growth factor receptor has also been found to be overexpressed in approximately 25% of the β-HCG-expressing component of mixed GCTs.[24] Epidermal growth factor receptor is a plasma glycoprotein that after binding to its ligand activates protein tyrosine kinase activity. This leads to activation of a cascade of biochemical and physiologic responses that are involved in the mitogenic signal transduction of normal as well as malignant cells.

HISTOLOGY AND NATURAL HISTORY

Overview of Histology

Most primary testicular cancers are of germinal origin and are felt by some to be the malignant counterparts of normal embryonic development. In this model, the normal embryonic development counterpart of seminoma is the spermatocyte, whereas pluripotential early cleavage stage tissues are the counterpart of embryonal cell carcinoma. More differentiated malignancies find their normal tissue counterparts in tissues derived from the developing embryo, such as the embryo itself (teratoma), the yolk sac (yolk sac tumors), and the placenta (choriocarcinoma.)

A commonly used histologic classification of testicular neoplasms is derived from the Armed Forces Institute of Pathology classification schema of Dixon and Moore,[25] which recognizes pure seminoma, as well as four other categories, each of which may occur with or without seminoma elements: (1) embryonal carcinoma, (2) teratoma, (3) teratoma with foci of embryonal carcinoma and choriocarcinoma (also termed teratocarcinoma), and (4) choriocarcinoma with and without embryonal elements.

The World Health Organization international classification divides tumors into those of single histologic type (seminoma, spermatocytic seminoma, embryonal carcinoma, choriocarcinoma, teratoma, and yolk sac tumors) and those of more than one type, in which the listing and estimation of relative proportion of each type

Table 90-1 Comparison of Two Classifications of Germ Cell Tumors

WHO*	British Tumor Board†
Seminoma	Seminoma
Typical (classic)	
Anaplastic	
Embryonal carcinoma	Malignant teratoma, undifferentiated
Teratoma	Malignant teratoma, differentiated
Mature	
Immature	
With malignant differentiation	
Choriocarcinoma	Malignant teratoma, trophoblastic
Yolk sac tumor	Yolk sac tumor
Mixed germ cell tumors (specify components)	Malignant teratoma, intermediate

WHO, World Health Organization.

*Data from Mostofi FK, Sesterhenn IA· Reivised international classification of testicular tumors. In Jones WG, Harnden P, Appleyard I (eds): Germ Cell Tumors III. Oxford: Pergamon, 1994, p 153.

†Pugh RCB: Pathology of the Testis. Oxford: Blackwell, 1976.

From Bosl GJ, Bajorin DF, Sheinfeld J, et al: Cancer of the testes. In Devita VT (ed): Principles and Practice of Oncology, 7th ed. Philadelphia, Lippincott Williams & Wilkins, 2005.

Table 90-2 Frequency and Age Distribution of Germ Cell Tumors

	All GCTs (%)	Peak Age
HISTOLOGIC SUBTYPE		
Seminoma	40	25–45
Classic and anaplastic	35	25–45
Spermatocytic	5	Average 65
Nonseminoma	60	15–35
Embryonal ± seminoma	24	20–30
Teratoma ± seminoma	5	
Teratoma + embryonal, choriocarcinoma, or both	25	
Choriocarcinoma (pure)	<1	
Yolk sac tumor (pure)	<1	
SITE OF ORIGIN		
Gonadal	95–99	As above
Extragonadal	1–5	20–35

GCT, germ cell tumor.

is required.[26] The major important differences between these two schemas is the recognition by the World Health Organization schema of yolk sac tumors (endodermal sinus tumors) and spermatocytic seminoma as distinct categories (Table 90-1). Representative photomicrographs of various GCTs can be seen in Figure 90-1.

Testicular cancers that are of nongerminal origin include specialized gonadal stromal neoplasms as well as sarcomas. These, in addition to adenocarcinoma (of the rete testis), and secondary (nonprimary) malignancies such as acute leukemia, lymphoma, carcinoma, and melanoma make up less than 5% of testicular neoplasms. The frequency and natural history of specific histologic subtypes are discussed in the following sections and summarized in Table 90-2.

Overview of Natural History

The natural history of GCT is largely defined by lymphatic spread to the retroperitoneal lymph nodes early in the disease, with hematogenous dissemination developing later. Thus, virtually all GCTs with pulmonary or visceral metastases will have concomitant retroperitoneal lymph node involvement. Pure choriocarcinoma is an exception, characterized by early hematogenous dissemination to lungs, brain, and viscera. The more aggressive biology of nonseminomatous GCT is evidenced by the approximately 60% to 70% of individuals with nonseminomatous GCT who will have nodal or other metastatic involvement at presentation, compared with 25% in individuals with pure seminoma. These figures are somewhat biased, because people with clinical stage I seminoma (confined to testis) do not routinely undergo pathologic staging with a retroperitoneal lymph node dissection (RPLND), whereas pathologic staging is often undertaken in similar nonseminomatous patients.

Seminoma usually spreads to first-station para-aortic nodes, although (as with nonseminomatous GCT) pelvic nodes may be involved if the scrotal sac has been violated, either by the primary tumor or in the case of trans-scrotal exploration by inguinal surgery. Whereas nodal involvement is less common in seminoma than in NSGCT, ureteral obstruction seems to occur more commonly than in nonseminomas, because of either bulky disease or more diffuse sheetlike spreading. It is extremely unusual for seminomas to present with hepatic or pulmonary metastases; when they do, it is virtually always in the setting of retroperitoneal nodal involvement. The presence of nonpulmonary visceral metastasis (e.g., bone or liver) portends an adverse prognosis.

The distribution of retroperitoneal lymph node metastases in nonseminomatous GCT has been described by Ray and colleagues[27] and Donohue and associates[28] and provides the basis for the specific surgical and therapeutic approaches described in the following section. Figure 90-2 diagrams the anatomy and distribution of retroperitoneal lymph node involvement in GCT. A right-sided testicular primary is most frequently found to have interaortocaval nodal metastases, followed (in order of decreasing frequency) by the precaval and preaortic nodes. Contralateral nodal involvement occurs in 15% of patients, but in virtually every case with contralateral involvement, ipsilateral nodes were also involved. Left testis tumors most frequently have nodal spread to the left para-aortic, preaortic, and interaortocaval nodes, in that order. Suprahilar nodal involvement does not occur in patients with microscopic or low burden infrahilar disease (stage B1), whereas 25% of patients with gross infrahilar disease have been found to have positive suprahilar nodes.[27] Other nodal metastases are rare, but can occur in the external iliac and obturator nodes if the primary tumor invades the epididymis or extends up the spermatic cord, or in inguinal lymph nodes if the tumor extends through the tunica vaginalis to involve the scrotum, or if trans-scrotal exploration has been used.[29]

Seminoma

Seminomas account for 40% of all GCTs. The three distinct histologic patterns that have historically been described are classic seminoma, anaplastic seminoma, and spermatocytic seminoma. However, a clinical distinction can only be made between classic seminoma and spermatocytic seminoma, and the histologic definition of anaplastic seminoma (more than five mitotic figures per high-power field, cellular anaplasia, and tissue disruption) is of historic interest only, in that neither response to therapy nor survival are adversely affected by the presence of anaplastic features.[30]

Classic seminoma usually presents in the fourth or fifth decade. It is localized to the testes (stage I) in approximately 70% of patients and is metastatic to lymph nodes (generally stage II) in 25%.[31] Metastases to lymph nodes occurs in an orderly sequential fashion along

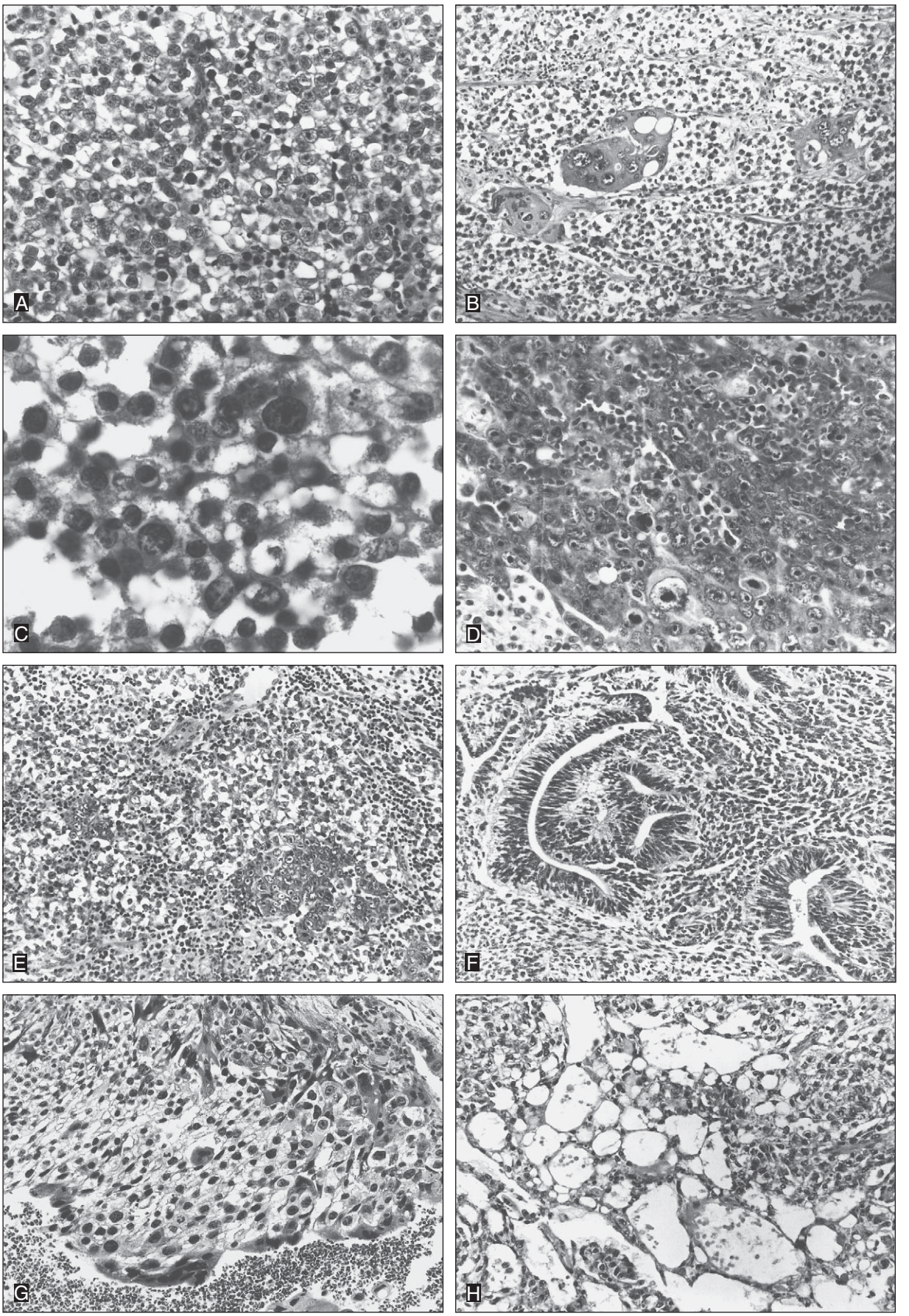

A
B
C
D
E
F
G
H

Figure 90-1 • Representative histology of germ cell neoplasms. **A,** Classic seminoma. Note uniform cells, with central, well-delineated nuclei. Occasional clear spaces represent areas of glycogen deposition (H&E, ×50). **B,** Seminoma with giant syncytiotrophoblast cells. This histologic pattern may be seen in HCG-positive seminomas. Fibrovascular septae with a lymphoid infiltrate are a typical feature of seminoma (H&E, ×25). **C,** Spermatocytic seminoma. Distinguished histologically from classic seminoma by relative lack of fibrovascular septae and lymphoid infiltrate, as well as by marked variation of cell size, but not shape (H&E, ×100). **D,** Embryonal carcinoma. Compared with seminoma (**A**), note cellular and nuclear pleomorphism and syncytial pattern (loss of cellular borders) (H&E, ×50.) **E,** Mixed germ cell tumor, with seminoma and embryonal carcinoma elements. Note fibrovascular septae with lymphoid infiltrate characteristic of seminoma and islands of embryonal carcinoma (H&E, ×25). **F,** Immature teratoma. Note primitive neural differentiation (H&E, ×25). **G,** Choriocarcinoma. The two cell types required for diagnosis are present. Syncytiotrophoblastic cells (giant cells with hyperchromatic nuclei and abundant eosinophilic cytoplasm) are seen in the upper right quadrant. Cytotrophoblasts (sheets of cells with single nuclei and abundant clear cytoplasm) compose the midportion of this photomicrograph. Hemorrhagic infiltrate at the bottom of the photomicrograph is common in choriocarcinoma (H&E, ×25). **H,** Yolk sac tumor, microcystic pattern (H&E, ×25). (Courtesy of Dr. Noel Weidner, Department of Pathology, University of California, San Francisco.)

draining lymph node chains. Visceral metastases are present at presentation in less than 5% of patients, and in general occur late in the course of the disease. Seminomas tend to appear homogeneous, with little necrosis or hemorrhage on gross inspection. Microscopically, they consist of sheets of uniform cells with large central hyperchromatic nuclei and clear or granular cytoplasm, which are divided by thin fibrous septations. Although lymphocytic infiltration and occasional giant cells may be seen, neoplasms in which any teratomatous or embryonal elements are seen are by definition not considered to be pure seminomas.[25] Spermatocytic seminoma represents approximately 5% of all seminomas and warrants special consideration. It generally occurs in the sixth decade. Although it is more likely to be bilateral than typical seminoma (6% vs. 2%), it is nonetheless a fairly indolent malignancy in which metastatic events are distinctly uncommon.[32] Spermatocytic seminoma can be histologically distinguished from classic seminoma by the relative lack of compartmentalization of sheets of cells by fibrous septae, by the marked variation in cell size, and by the absence of lymphocytic infiltration.

Embryonal Carcinoma

Pure embryonal carcinomas account for over 60% of NSGCTs, although foci of embryonal elements may be found in a large majority of NSGCTs. Embryonal carcinoma occurs in 20- to 30-year-olds and is a highly malignant tumor characterized by rapid and bulky growth. In addition to lymphatic spread, these tumors are characterized by hematogenous spread of cancer cells, particularly to lung and liver. Over 60% of patients with embryonal carcinoma have metastases at presentation, and the likelihood of occult nodal metastases in clinical stage I (confined to testis) tumors is a function of the proportion of the tumor that is composed of embryonal carcinoma.[33] Furthermore, embryonal carcinoma has been reported to have the highest rate of venous invasion, lymphatic invasion, and tunica (capsular) invasion in both stage I and II tumors.[30] Embryonal carcinomas exhibit focal necrosis and hemorrhage, and microscopically are quite variable. Cellular features of embryonal carcinoma correlate with its more aggressive behavior and include anaplastic cells with embryoid features. Large pleomorphic nuclei, mitotic figures, and multinucleation are common as well. Stroma varies from loose to thick and fibrous.[25]

Teratoma and Teratocarcinoma

Mature teratoma has elements of one or more of the three germinal layers that are fully differentiated. Pure teratoma is uncommon and makes up less than 5% of GCTs in adults. Over 75% of nonseminomas have been reported to have variable amounts of teratomatous elements, so that "pure" teratomas must be sampled carefully to exclude undifferentiated foci. The term teratocarcinoma refers to teratomas in combination with other elements, although some pathologists reserve the term for the combination of teratoma and embryonal carcinoma. When a teratoma has cellular and active stroma with mitotic figures, it is referred to as immature teratoma. Teratomas and teratocarcinomas are composed of solid and cystic spaces on cut surface, with areas of hemorrhage and necrosis. A histologic mix of fully differentiated cartilage, muscle, or epithelial tissue and malignant embryonal elements is seen. Predominant teratomatous features account for one third of teratocarcinomas, whereas approximately two thirds are mostly composed of nonteratomatous elements.[25] Mature teratoma is the least aggressive of the nonseminoma GCTs, although up to 30% of adult patients with clinical stage I teratoma treated with orchiectomy alone will subsequently relapse, suggesting that pure teratomas should not be exempted from the usual clinical and pathologic staging of GCT or from the usual subsequent therapeutic interventions.[34] The natural history of teratocarcinomas lies somewhere between that of mature teratoma and embryonal carcinoma, but for practical (diagnostic and therapeutic) purposes, teratocarcinomas can be grouped with embryonal cell carcinomas. The likelihood that residual or recurrent masses after treatment are composed of mature teratoma is increased in patients with more extensive teratomatous elements at presentation later in the chapter.

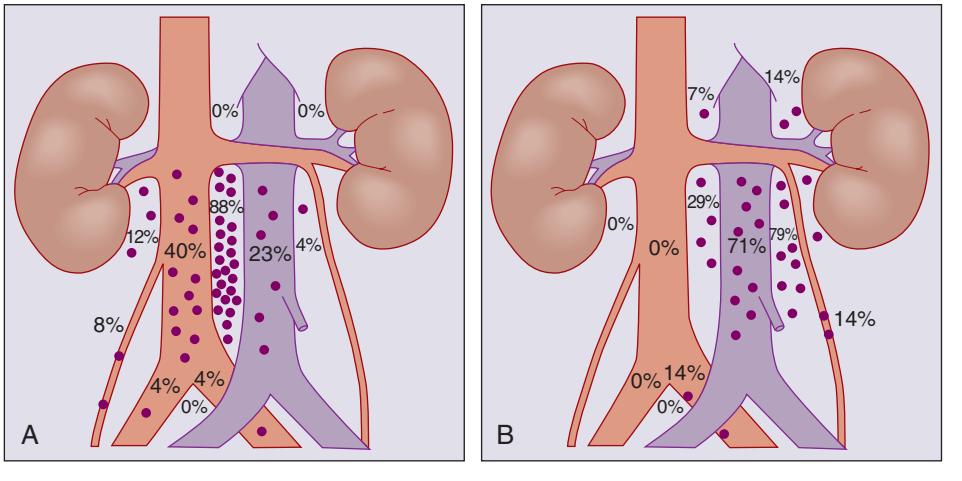


Figure 90-2 • Distribution of retroperitoneal nodal metastases in early-stage nonseminoma germ cell tumor. **A,** Right. **B,** Left. (From Donohue JP, Sachary FM, Maynard BR: Distribution of modal metastases in nonseminomatous testic cancer. J Urol 1982;128:315, with permission.)

Choriocarcinoma

Choriocarcinoma is the most aggressive of the nonseminoma GCTs, with early hematogenous dissemination to lungs, liver, brain, and other visceral sites. Pure choriocarcinoma is exceedingly rare, accounting for less than 0.5% of all testicular malignancies, but focal areas of choriocarcinoma are seen in approximately 12% of embryonal and teratocarcinomas.[35] Because advanced-stage disease at diagnosis is common, pure choriocarcinoma has a particularly poor prognosis. If pure choriocarcinomas are excluded, the specific histologic subtype of NSGCT does not have an influence on survival. The microscopic diagnosis of choriocarcinoma requires the presence of two cell types: syncytiotrophoblastic cells (giant cells with multiple hyperchromatic nuclei and abundant eosinophilic cytoplasm) and cytotrophoblasts (sheets of cells with single nuclei, abundant clear cytoplasm, and well-defined borders) arranged in papillary or pseudovillous patterns.[25]

Yolk Sac Tumors

Also known as endodermal sinus tumors, pure yolk sac tumors occur rarely, accounting for 1% of GCTs in adults. More commonly, yolk sac tumors in adults are found in combination with other tumor types, occurring in up to 70% of GCTs. In one series of 459 patients with stage I and II testicular cancer, the most common histology observed was a mixed one consisting of embryonal carcinoma plus yolk sac tumor and teratoma. Furthermore, the presence of teratoma and yolk sac tumor seemed to be associated with a large primary tumor size.[35] While pure yolk sac tumors are conventionally considered to be more aggressive with early hematogenous distribution,[30] recent histologic reviews have suggested that patients in whom yolk sac tumor elements are present are at lower risk of relapse than patients in whom they are absent. However, the relatively high frequency with which yolk sac tumors and embryonal carcinoma are found together (50% of all tumors in some series) and the extremely rare occurrence of pure yolk sac tumors (1%) make this a difficult conclusion to substantiate.[36] Yolk sac tumors occur more commonly in children, in whom they seem to be a less aggressive histologic subtype.[37] The histology of yolk sac tumors, though characteristic, may be observed in several common patterns. These include a papillary pattern in which Schiller-Duval bodies (a fibrovascular core with a circle of cells around it, vaguely reminiscent of a glomerulus) can be seen, as well as microcystic, glanduloalveolar, and solid patterns.

Stromal Cell Tumors

Derived from the stromal and supporting cells surrounding germ cells, stromal cell tumors consist of Leydig cell tumors, Sertoli cell tumors, and granulosa cell tumors. As a group they account for 3% to 4% of primary testicular tumors but constitute nearly 20% of childhood testicular tumors. Although by and large they are benign, up to 10% may metastasize.[38] Histologic features seem to be useful in predicting the risk of disseminated disease, and management generally consists of orchiectomy and clinical staging with CT scan, without use of RPLND. These tumors may be estradiol-secreting; gynecomastia occurs in 30% of Sertoli cell tumors and 15% of Leydig cell tumors.

Secondary (Metastatic) Neoplasms

Although the large majority of testicular neoplasms in young men are GCTs, in men over 60 years of age only 25% of malignancies will be of germinal origin. Testicular malignancies in this age group are predominantly composed of lymphomas,[39] although metastases to the testicles, primarily from prostatic adenocarcinoma, lung carcinoma, and melanoma primary tumors must also be considered.

CLINICAL MANIFESTATIONS

The most common presentation of testicular cancer is testicular swelling (73% in one series of 450 patients).[35] A commonly held misconception is that testicular cancers are by and large painless and that painful testicular masses need not be evaluated for malignancy. In fact, testicular pain is a presenting feature of 18% to 46% of patients with GCT.[35] Acute pain may be associated with torsion of the neoplasm, infarction or bleeding in the tumor, as well as with epididymitis. Signs and symptoms indistinguishable from acute epididymitis have been observed in up to one fourth of patients with testicular neoplasms. Less commonly presenting symptoms will include gynecomastia in HCG-producing tumors such as choriocarcinoma (10%), back or flank pain from metastatic disease (10%), and infertility in less than 5% of tumors. Approximately 25% of patients with advanced disease have symptoms referable to their metastases, such as back pain.[40] This is frequently the presenting symptom in patients with primary retroperitoneal GCT. Pulmonary symptoms including shortness of breath, chest pain, and hemoptysis are rare but can occur in patients with advanced pulmonary disease or primary mediastinal GCT.

The physical examination of the testicles is performed by fully palpating all areas of the testicle between thumb and fingers. Testicular masses are firm to hard, and generally the scrotal sac is normal in appearance unless there is a large mass causing distension. The man with a testicular mass must of course have a careful and complete physical examination, including examination for lymphadenopathy, intra-abdominal masses, hepatomegaly, bone tenderness, and pulmonary abnormalities.

The constellation of elicited symptoms and physical examination findings can offer a clue to the histology of a testicular mass. For example, it has been reported that pain more commonly occurred in patients who had embryonal carcinoma elements in their tumors than in those without that histologic feature (56% vs. 37%; $P < 0.02$). The same study reported a significantly higher incidence of testicular swelling when the primary tumors contained teratoma or yolk sac tumor elements.[35] Primary tumors from patients with seminoma tend to be larger and more homogeneous, with diffuse involvement of the testicle, whereas embryonal and teratomatous elements tend to form smaller, discrete masses. Rapidly growing tumors, particularly those with extranodal dissemination, should raise the possibility of choriocarcinoma. These observations are of course no substitute for the appropriate clinical staging and histopathologic evaluation.

In addition to malignancy, the differential diagnosis of a testicular mass includes testicular torsion, hydrocele, varicocele, spermatocele, and epididymitis. Benign hydroceles tend to extend along the spermatic cord and can be transilluminated. However, it is prudent to recall that a small percentage of testicular cancers are associated with hydroceles. Varicoceles occur in the venous pampiniform plexus of the spermatic cord and result in what has been classically described as a "bag of worms" on palpation. Spermatoceles are found in the posterior, superior portion of the scrotum and also transilluminate. As noted previously, testicular cancer is perhaps most often mistaken for epididymitis, which is marked by a swollen, extremely tender testicle with occasional fever and pyuria. Delays in treatment of testicular cancer of up to 9 months have been observed as individuals are treated for presumed epididymitis. Thus, the clinical diagnosis of epididymitis should prompt a careful physical examination as well as ultrasonographic examination of the scrotum, particularly in those patients who fail to respond to a 10-day course of antibiotics.

EVALUATION OF THE PATIENT: DIAGNOSIS, CLINICAL STAGING, AND RISK ASSESSMENT

Diagnosis: Testicular Ultrasonography

The initial evaluation of a testicular mass is ultrasonographic evaluation (Fig. 90-3). Testicular ultrasonography is a sensitive and specific

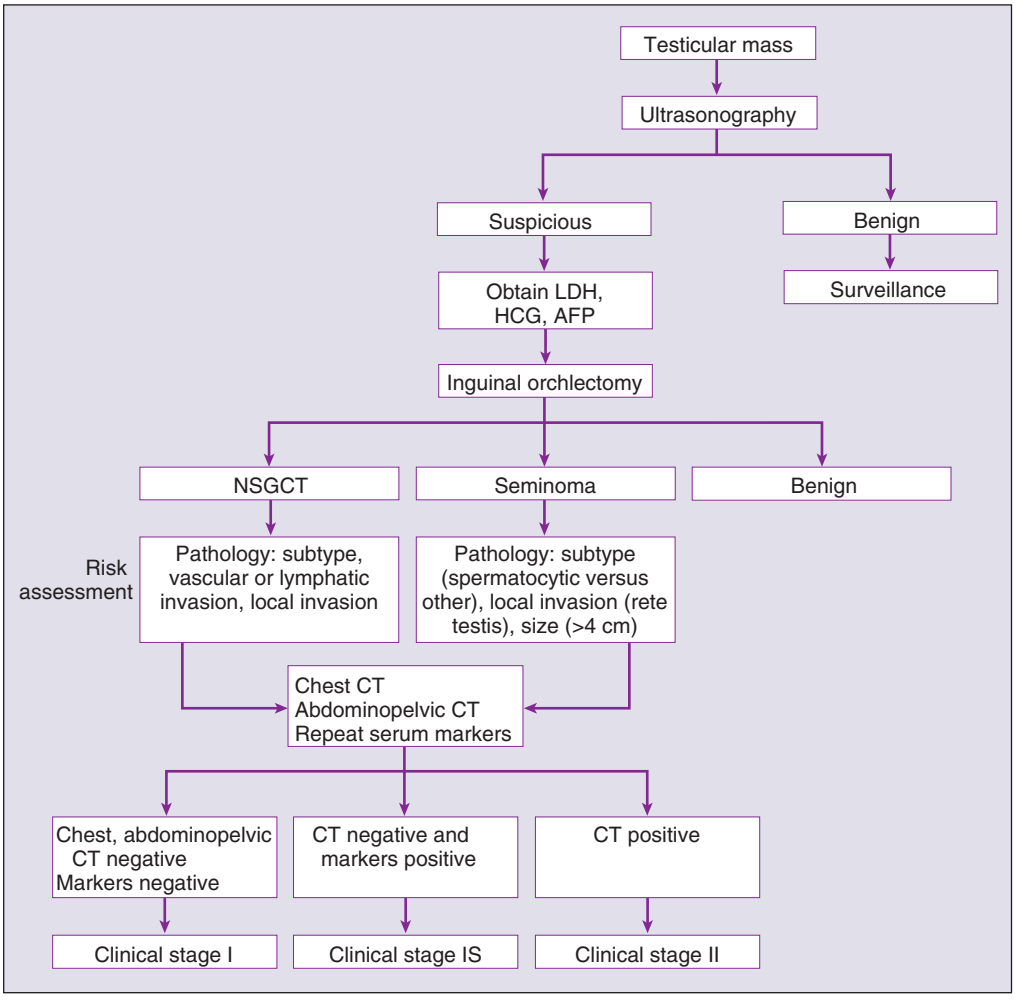


Figure 90-3 • Diagnosis of patients with testicular germ cell tumor.

test that can discriminate between a testicular neoplasm and nonmalignant processes included in the differential diagnosis such as testicular torsion, hydrocele, varicocele, spermatocele, and epididymitis. Thus, the demonstration of hypoechoic or heterogeneous masses on ultrasonographic examination should prompt a thorough subsequent evaluation as described later. Similarly, a negative ultrasonogram fairly reliably establishes the absence of intrascrotal GCT.[41] Both testes should be examined carefully, in that 2% to 4% of patients will harbor bilateral lesions.[28] Extragonadal GCTs are a distinct clinical entity constituting from 1% to 5% of all GCTs; in these patients scrotal ultrasonography will be negative.

Diagnosis: Orchiectomy

Any patient with a testicular mass or abnormal ultrasonography, or both, should have testicular carcinoma ruled out by a unilateral radical transinguinal orchiectomy. Orchiectomy is the definitive procedure for both pathologic diagnosis and local control of the primary tumor and in some cases may be a curative procedure. Furthermore, important predictive factors can be identified with routine histologic techniques that are crucial to risk assessment strategies used in the clinical management of these patients.[31,34,35,42–44] The removal of suspicious testicles by inguinal orchiectomy should be undertaken even in patients in whom a diagnosis of disseminated GCT has been made by biopsy of a metastatic site, because the testes seem to be chemotherapy sanctuaries for cancer cells.[45]

Orchiectomy delay for up to two cycles of chemotherapy is occasionally indicated, when control of metastatic disease must be obtained urgently. There seems to be a blood-testis barrier, so that viable GCTs can persist in the testis despite complete eradication of cancer from metastatic deposits by chemotherapy. Orchiectomy should therefore always be performed once control of metastatic disease is achieved.[46,47] Patients with a diagnosis of extragonadal GCT with normal testicular examinations and ultrasonograms need not undergo orchiectomy. Trans-scrotal orchiectomies or needle biopsies are absolutely contraindicated, in that they have been associated with up to 24% incidence of local recurrence or spread to inguinal lymph nodes.[29]

CLINICAL STAGING AND RISK ASSESSMENT

The first step after the histologic confirmation of a GCT is to determine the extent of the disease (staging) so that appropriate therapy can be undertaken. An assessment of risk of metastases (in the case of local disease) or response to systemic therapy (in the case of advanced disease), utilizing the results of histopathologic, biochemical, and radiographic evaluations, should be an integral element of the staging process; such assessment is discussed in detail for each stage.

Tumor Markers

Tumor markers have become a fundamental component of the laboratory evaluation of individuals with suspected testicular neoplasms, offering diagnostic, staging, and prognostic information, as well as measuring disease progression and response to therapy. Thus, along

with the usual laboratory studies obtained on persons with suspected GCT, preorchiectomy levels of β-HCG, AFP, and LDH are mandatory.

HCG is a glycoprotein of 45,000 MW. It consists of two covalently linked subunits, an α-subunit shared by luteinizing hormone (LH), FSH, and thyroid-stimulating hormone, and a unique β-subunit (β-HCG), which can be readily measured in serum. Whereas it is normally produced at high levels by the placenta, low levels are detectable in normal nonpregnant adults, including some men. HCG elevations are seen in neoplasms other than GCTs, including prostate, bladder, ureteral, and renal cancers.[48] Spurious elevations have been noted in persons using marijuana.[49] Some patients who have undergone systemic therapy develop *cis*-platinum (cisplatin)-induced testicular atrophy in the remaining testis, resulting in lower levels of testosterone, with a compensatory hypersecretion of LH to stimulate Leydig cell secretion of testosterone. Although HCG and LH are not immunologically cross-reactive, very high levels of LH may spuriously elevate measured HCG levels. When necessary, measurement of HCG levels 2 weeks after the administration of depotestosterone should rule out this possibility. The biologic half-life of serum HCG is approximately 24 hours. In GCTs, HCG is produced by syncytiotrophoblastic cells in embryonal carcinoma, choriocarcinoma, and seminoma. Extremely high levels of HCG are generally associated with choriocarcinoma. Although seminomas are generally felt to be marker-negative, the incidence of HCG-positive seminoma varies from 5% to 40%. In general, these HCG elevations do not exceed a level of 100 mIU/mL, and probably do not connote a worse prognosis.[50–54]

AFP is a glycoprotein that is the major serum protein of the fetus. It is also an oncofetal protein, found not only in patients with nonseminomatous GCT, but in pregnant women (fetal hepatic production), in patients with hepatocellular carcinoma, and occasionally, at somewhat lower levels, in patients with cirrhotic livers demonstrating nodular regeneration or in patients with hepatitis. Its biologic half-life is 4 to 6 days. AFP elevations are most commonly seen in embryonal carcinoma and yolk sac tumors, with reports of up to 89% of tumors with yolk sac elements demonstrating elevated AFP.[35] Pure seminomas and pure choriocarcinomas do not produce AFP. Thus, in the absence of hepatitis or other causes of AFP, by definition the presence of an elevated AFP in a histologically pure seminoma identifies the presence of nonseminomatous elements and mandates that the management proceeds accordingly.

LDH is a nonspecific marker that seems to be related to tumor burden and that can serve as both an indicator of response to treatment and a predictor of prognosis. Interestingly, the gene that encodes LDH isoenzyme 1 maps to chromosome 12, and the serum level of LDH isoenzyme 1 has been shown to correlate with the number of copies of i(12p) in the tumor, a fairly specific genetic marker of germ cell malignancies. Furthermore, the presence of three or more copies of i(12p) has been correlated with a worse prognosis.[19]

Overall, approximately 85% of nonseminomas will have an elevation of either AFP or β-HCG.[48,55,56] Approximately 15% are marker-negative. AFP elevation alone is elevated in 40% of nonseminomatous GCTs, and β-HCG elevation alone is seen in 50% to 60%. It is important to note that up to 30% of patients with early-stage nonseminomatous GCT will have normal serum markers, so the absence of marker elevation should not influence the decision to perform an orchiectomy. The incidence of serum marker elevation as a function of tumor histology is shown in Table 90-3.

Even though most seminomas and as many as 30% of nonseminomatous GCTs are marker-negative, AFP, LDH, and β-HCG levels should always be checked before and after orchiectomy. The correct interpretation of serum marker levels requires that the biologic half-life of AFP and HCG be taken into account. Thus, the persistence of elevated AFP or β-HCG levels higher than predicted by the half-lives of these glycoproteins after orchiectomy implies residual (occult) disease. The converse, however, is not true: normalization of markers after orchiectomy does not ensure the absence of occult disease. In fact, as many as 60% of patients with nonseminomatous GCT believed on clinical grounds to be confined to the testis (stage I) with normalization of markers after orchiectomy will have involvement of retroperitoneal lymph nodes with tumor.[34,42–44] The management of clinical stage I cancers reflects this fact and is discussed later in the chapter.

In patients with advanced disease, serum markers can also be used as a measure of response to therapy. Patients with retroperitoneal adenopathy who have been treated by lymphadenectomy should normalize their markers; failure to do so implies residual or recurrent disease. The response of advanced GCT to chemotherapy can also be monitored by a fall in serum markers. However, in this situation, unlike the postorchiectomy or post-RPLND setting, tumor debulking is not instantaneous. Thus, the use of known half-lives to calculate the expected decay of levels of serum tumor markers is more difficult. A 10-fold decrease in the HCG level over a 3-week period has been empirically observed to be consistent with disease eradication. Other investigators have shown that a durable complete response to chemotherapy could be predicted with a high degree of accuracy by the ratio of the HCG level measured on day 22 (after one cycle of chemotherapy) to the day 1 HCG level. In this schema, if the HCG level failed to normalize after one cycle of chemotherapy (day 22), and if the ratio between day 22 and day 1 was greater than 1 : 200 (0.005), an incomplete response could be predicted in 94% of patients. Conversely, if the day 22 HCG value was within normal range, or if the ratio between day 22 and day 1 was less than 1 : 200, a durable complete response could be predicted in 91% of patients.[57] Other reports have noted that observed half-life decays of greater than 7 days for AFP, and greater than 4 days for HCG after treatment with chemotherapy, are associated with poor outcome and probably correlate with the emergence of drug-resistant disease. Likewise, reappearance of serum marker elevation after therapy is an invaluable method of detecting early relapse, often predating any radiologic evidence of relapse or recurrence. On occasion, tumor lysis with chemotherapy will result in transient "flares" or rises in serum markers followed by a subsequent

Table 90-3 Germ Cell Tumors and Serum Markers

Histology	Marker Negative (%)	Elevated HCG Alone (%)	Elevated AFP Alone (%)
Seminoma	90	10 (usually <100 IU/mL)	0 (if +, by definition, NSGCT)
All NSGCT	15	50–60	40
Embryonal		0	10–40
Yolk sac tumors		Rare	80–90 (alone or with elevated HCG)
Choriocarcinoma (or syncytiotrophoblast elements		>90 (level can be very high)	0

AFP, α-fetoprotein; HCG, human chorionic gonadotropin; NSGCT, nonseminoma germ cell tumor.

decline. The prognostic implications of such a flare are not well understood.

Measurements of AFP and β-HCG offer an excellent tool for monitoring disease progression and response to therapy, so that the subset of nonseminomatous GCT patients who are marker-negative requires particularly careful clinical scrutiny. Although the vast majority of seminomas are marker-negative, in general their phenotype is less malignant and their responsiveness to therapy is extremely high, making the usual absence of biochemical markers of disease less troublesome.

Radiologic Evaluation

The goal of routine postorchiectomy radiographic studies is to detect evidence of spread to the retroperitoneum and lungs. Accordingly, all individuals with GCT should undergo CT of the chest, abdomen, and pelvis. Although some investigators have reported a 10% higher detection of metastatic disease by chest CT (compared with chest radiography), the value of the increased sensitivity of tomography has been disputed. In one series of 120 patients staged with both chest radiograph and whole-lung tomograms, tomography led to a change in therapy in only one patient (0.8%). Nonetheless, although interval changes in the size of pulmonary nodules as a response to therapy can be monitored with a chest radiograph, many investigators recommend that the radiographic evaluation of pulmonary nodules for the purpose of initial staging, final documentation of response to therapy, and subsequent follow-up, should consist of a chest CT. Caution is warranted in the interpretation of chest CT scans of persons who have received bleomycin, because subclinical pulmonary fibrosis may have the appearance of metastatic nodules. A comparison of chest CT scans before and after chemotherapy is usually all that is required for the distinction of progression of pulmonary nodules from bleomycin effects, obviating the need for biopsy.

The standard method of staging retroperitoneal disease in a person with testicular cancer consists of abdominal and pelvic CT scanning. In those with nonseminomatous GCT, abdominopelvic CT understaging (e.g., false negatives) occurs in as many as 50% of patients, whereas overstaging (e.g., false positives) occur in approximately 10% of patients.[42–44] The sensitivity and specificity of abdominal CT for detecting lymph node metastases in patients with clinical stage I disease (testis-only disease) has been recently evaluated.[58] Using a cutoff of 10 mm or larger, a sensitivity of 37% and a specificity of 100% were observed, whereas using a 4-mm cutoff enhances sensitivity to 93% but decreases specificity to 58%.

The exact incidence of occult retroperitoneal lymph node metastases in patients with seminoma who have normal CT is not known, because these patients are typically treated with radiation therapy, and do not undergo surgical exploration. Nonetheless, an estimated incidence of occult nodal metastases of 10% to 25% is generally accepted.[31,59]

More recently, ^{18}Fluor-labeled deoxycglucose–positron emission tomography (FDG-PET) has been used to identify viable cancer in residual postchemotherapy masses. Sensitivity and specificity of 88% and 95%, respectively, have been reported, along with high positive and negative predictive values (90% and 96%) in two multicenter trials.[59] By contrast, the utility of FDG-PET in the initial staging of GCT patients is less clear. Several reports comprising more than 110 patients evaluated the accuracy of FDG-PET compared to CT scan staging in patients with stage I and II GCTs. Sensitivity and specificity were reported as 73% to 94% and 40% to 78%, respectively. Moreover, FDG-PET was unable to detect mature teratomas as well as lesions smaller than 5 mm in diameter.[60,61] Hence, FDG-PET is not routinely used or recommended as initial staging for stage I–II GCTs.

In summary, the major limitation of CT imaging is that although gross nodal disease can usually be detected, this is not the case for microscopic metastases. For this reason an assessment of the risk of occult retroperitoneal nodal involvement based on histopathologic features is of importance.

Other imaging modalities such as head CT and bone scan are not routinely undertaken except as warranted by symptoms. One exception to this rule is for choriocarcinoma, in which an increased incidence of brain metastases mandates a CT of the head before proceeding with chemotherapy.[62]

Similarly, in persons with serum marker-positive GCT who have relapsed by serum markers, but have a negative physical examination and a negative imaging evaluation consisting of an ultrasonogram of the contralateral testicle and abdominopelvic and chest CT, it is not unreasonable to complete the evaluation with a head CT and a bone scan.

Staging

Several schemas are incorporated in the current staging of GCT. Because lymphadenectomy is almost never undertaken as a primary therapeutic modality in seminoma it is staged clinically and radiographically. Until recently, the standard treatment of nonseminomatous tumors has included a RPLND, so that most patients with nonseminomatous GCT were pathologically staged. Because as many as 80% of patients with carefully staged clinical stage I nonseminomatous GCT tumors have been found to be free of retroperitoneal disease, many patients with clinical stage I nonseminomatous GCT are offered observation in lieu of lymphadenectomy. A clear distinction must be made in these—and in all patients with nonseminomatous GCT—between clinical stage and pathologic stage. The development of an international consensus GCT risk classification schema (see section on advanced disease) has allowed the use of prognostic groupings as the basis of a revised staging classification. This revised (1997) TNM American Joint Committee on Cancer/Union Internationale Contre le Cancer (AJCC/UICC) classification (Table 90-4) continues to rely on anatomic disease extent, allows for the pathologic classification of lymph nodes, but for the first time also takes into account serum tumor markers. Patients who have only serologic marker evidence of disease after orchiectomy are now classified as stage I-S.

In general, stage I (or A) refers to tumors confined to the testis, with no evidence of nodal or pulmonary parenchymal involvement. Stage II (or B) denotes tumors with retroperitoneal lymph node metastases. Stage II patients are further subdivided by the relative tumor burden. In seminoma patients this is clinically defined by the size of nodal involvement detected by imaging studies, whereas in nonseminomatous GCT this is usually but not always a pathologic diagnosis. Stage IIA (or B1) implies minimal but definite nodal involvement, generally of a microscopic nature; IIB (or B2) refers to macroscopic disease, or a larger number of microscopic metastases, whereas IIC (or B3) indicates bulky retroperitoneal nodal disease. Stage III (or C) refers to disease that has spread beyond the retroperitoneum, usually to supradiaphragmatic lymph nodes, pulmonary parenchyma, or other sites including liver, bone, or brain. Some staging schemas, particularly those for seminoma, distinguish between stage III (supradiaphragmatic lymph nodes) and stage IV (any extranodal metastases, including pulmonary parenchyma, bone, and brain) (Table 90-5). The distinction of hepatic, central nervous system, and osseous metastases is not without merit, because patients with metastases to these regions clearly have a worse prognosis.

MANAGEMENT OF LOW-STAGE DISEASE

The management of clinical stage I GCT is in part dependent on an assessment of the risk of occult nodal metastases. This assessment is in turn based on clinicopathologic features of the primary tumor, including serum marker elevation, size and extent of disease, and histologic features. Pure seminoma and NSGCT are considered separately.

Table 90-4 TNM Classification of Testis Tumors

PRIMARY TUMOR (pT)

The extent of primary tumor is classified after radical orchiectomy.

pT	Primary tumor cannot be assessed (if no radical orchiectomy has been performed TX is used).
pT0	No evidence of primary tumor (e.g., histologic scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma in situ)
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion Tumor may invade into tunica albuginea but not tunica vaginalis.
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through tunica albuginea with involvement of tunica vaginalis.
pT3	Tumor invades spermatic cord with or without vascular/lymphatic invasion.
pT4	Tumor invades scrotum with or without vascular/lymphatic invasion.

REGIONAL LYMPH NODES (N)

Clinical

NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm or less than 5 cm in greatest dimension; or multiple lymph nodes, any one mass more than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

PATHOLOGIC CLASSIFICATION OF REGIONAL LYMPH NODES (pN)

pNX	Regional lymph nodes cannot be assessed.
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and 5 or fewer positive nodes, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass, more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence of extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

DISTANT METASTASIS (M)

MX	Distant metastasis cannot be assessed.
M0	No distant metastasis
M1	Distant metastasis
M1a	Nonregional lymph node or pulmonary metastasis
M1b	Nonpulmonary visceral metastasis

SERUM TUMOR MARKERS (S)

SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH < 1.5 × normal and HCG (mIU/mL) < 5000 and AFP (ng/mL) < 1000
S2	LDH 1.5–10 × normal or HCG (mIU/mL) 5000–50,000 or AFP (ng/mL) 1000–10,000
S3	LDH > 10 × normal or HCG (mIU/mL) > 50,000 or AFP (ng/mL) > 10,000

N indicates the upper limit of normal for the LDH assay

STAGING GROUPING

Stage 0	pTis	N0	M0	S0, SX
Stage I	pT1–4	N0	M0	SX
Stage IA	pT1	N0	M0	S0
Stage IB	pT2	N0	M0	S0
	pT3	N0	M0	S0
	pT4	N0	M0	S0
Stage IS	Any pT/Tx	N0	M0	S1–3
Stage II	Any pT/Tx	N1–3	M0	SX
Stage IIA	Any pT/Tx	N1	M0	S0
	Any pT/Tx	N1	M0	S1
Stage IIB	Any pT/Tx	N2	M0	S0
	Any pT/Tx	N2	M0	S1
Stage IIC	Any pT/Tx	N3	M0	S0
	Any pT/Tx	N3	M0	S1
Stage III	Any pT/Tx	Any N	M1, M1a	SX
Stage IIIA	Any pT/Tx	Any N	M1, M1a	S0
	Any pT/Tx	Any N	M1, M1a	S1
Stage IIIB	Any pT/Tx	N1–3	M0	S2
	Any pT/Tx	Any N	M1, M1a	S2
Stage IIIC	Any pT/Tx	N1–3	M0	S3
	Any pT/Tx	Any N	M1, M1a	S3
	Any pT/Tx	Any N	M1b	Any S

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Clinical Stage I Seminoma

Risk Assessment

A histologic diagnosis of pure seminoma implies an excellent prognosis. Pure seminoma is exquisitely sensitive to radiation therapy and can be readily sterilized by relatively low doses (20 to 35 Gy) of external-beam irradiation.[63] Consequently, prognostic factors are difficult to analyze in patients with early-stage seminoma because treatment failures are uncommon.

Prognostic factors that have been postulated as predictors of outcome include DNA ploidy status, mitotic rate, DNA S phase percentage, presence of syncytiotrophoblasts, degree of lymphocytic infiltration of the primary tumor, and the expression of β-HCG and low-molecular-weight keratin on immunohistochemical analyses. However, none of these factors has been confirmed in prospective trials.[30,64,65] The utility of serum markers in seminoma patients is limited to the identification of nonseminomatous elements by an elevated AFP, even in the face of a histologic diagnosis of pure

Table 90-5 Royal Marsden Clinical Staging Schema for Seminoma

Stage	Definition
I	Confined to testis
IIA	Abdominal nodal disease: <2 cm
IIB	Abdominal nodal disease: 2–5 cm
IIC	Abdominal nodal disease: >5 cm
III	Supradiaphragmatic nodal disease
IV	Extranodal disease

From American Joint Committee on Cancer: Manual for Staging of Cancer, 5th ed. Philadelphia, JB Lippincott, 1997.

seminoma. Ten percent of pure seminoma patients will have an elevated β-HCG. Preorchiectomy elevations of β-HCG do not connote a worse prognosis in stage I seminoma patients.[51–54,65]

Approximately 20% of unselected patients with seminoma who are managed with surveillance will relapse. A pooled analysis of data from four surveillance series identified size of primary tumor (>4 cm) and rete testis invasion as independent predictors of relapse. Other data sets suggest that the risk of relapse in patients who lack the adverse prognostic features of older age (>34 years), size of tumors 6 cm or larger, and small vessel invasion have a relapse rate of approximately 6%.[66] Although previous studies suggested that patients younger than 30 years old were at higher risk of relapse, this was not observed in this pooled analysis. An increased incidence of pelvic nodal involvement is also seen in patients who have had previous inguinal surgery, or in whom the primary tumor has invaded scrotal skin. Scrotal skin involvement also predisposes to relapse in the hemiscrotum.[67,68] Finally, tumor invasion of the spermatic cord increases the risk of relapse in the inguinal orchiectomy scar.[69]

Treatment

Cancer confined to the testis is the most common presentation of seminoma, accounting for nearly 70% of all patients with this diagnosis. For the last half century, the traditional management of these patients after an orchiectomy has consisted of radiation therapy to the para-aortic and pelvic (retroperitoneal) lymph nodes. Recent surveillance studies (see later discussion) suggest that approximately 15% to 20% of clinical stage I seminoma patients will in fact have occult retroperitoneal disease, indicating that the common practice of nodal irradiation is not unreasonable.

Conventional radiation fields for clinical stage I seminoma treat the para-aortic nodes from the diaphragm at the level of the T10 vertebral body down to the lower border of the L4 vertebral body, including the ipsilateral common iliac and external iliac nodes. If pelvic nodes may be involved, the field is extended to include the ipsilateral inguinofemoral lymph nodes. Spermatic cord involvement necessitates a radiation field that covers the entire inguinal orchiectomy scar, whereas scrotal skin involvement mandates radiation to the hemiscrotum.[69]

The results of adjuvant radiation therapy in clinical stage I seminoma patients have been reviewed. Most centers treat patients with 25 to 35 Gy to the retroperitoneal nodes in 15 to 20 fractions over 3 to 4 weeks. In more than 2000 patients reported, the cause-specific 5-year survival is 97%. Most relapses occur within 2 years, and almost always within 5 years of treatment. Failures within the radiated fields are extraordinarily uncommon; most relapses occur in the mediastinum, supraclavicular and cervical lymph nodes, or lung. Isolated recurrences may respond well to radiation therapy, although most radiation failures can be salvaged with systemic chemotherapy since the advent of cisplatin-based chemotherapy. Prophylactic mediastinal and supraclavicular irradiation has been used as a means of reducing relapses in these regions but has not been shown to confer a survival advantage.

The side effects of the low doses of radiation therapy required for the treatment of stage I seminoma are mild and include mild nausea, possibly peptic ulcer disease, transient oligospermia, and a modest but measurable increase in the risk of subsequent (secondary) malignancies. The possibility of reducing both early and late radiation-associated toxicity, coupled with the availability of salvage therapy with excellent results, is the impetus behind the evaluation of lower doses of radiation as well as surveillance as a therapeutic option in clinical stage I seminoma. For example, the use of 26 Gy to the para-aortic region with the omission of iliac irradiation results in a relapse rate of 3.7% with only 0.8% isolated ipsilateral iliac responses, and has been advocated by some to be appropriate therapy.

A trial conducted by the Medical Research Council (MRC) in Great Britain in conjunction with the European Organization for Research and Treatment of Cancer (EORTC) randomized 625 patients with stage I seminoma to therapy with 20 Gy in 10 fractions over 2 weeks or 30 Gy in 15 fractions during 3 weeks after orchiectomy. Interim results suggest that short-term morbidity (lethargy and decreased work capacity) is slightly higher in the patients receiving 30 Gy, although all differences resolve by 12 weeks. At 61 months of follow-up there was no difference in relapse rates.[70] These data suggest that 20 Gy may be reasonable in this setting.

Several large studies have evaluated the role of surveillance in persons with stage I seminoma, with similar results.[71–75] The cumulative risk of relapse within the first year is 5% to 10%, 10% to 15% in the second year, and 15% to 20% by the third year. As noted previously, two adverse prognostic factors can identify patients at high risk of relapse: tumor larger than 4 cm and rete testis involvement. In a pooled analysis, the 5-year relapse-free survival for patients with no or one risk factor was 83% to 88%, whereas patients with two adverse factors had a 5-year relapse-free survival of 69%.[76] These data have allowed an estimation of the frequency of occult nodal metastases in clinical stage I seminoma. The most common site of relapse has been the para-aortic lymph nodes. At relapse, salvage therapy with either radiation or systemic therapy is extremely successful, resulting in a cause-specific survival identical to historical experience with conventional radiotherapy (95% to 100%).[71–75] There is no consensus regarding the optimal follow-up protocol for seminoma patients undergoing surveillance. In general, patients are seen at 3- to 4-month intervals for 3 to 4 years, every 6 months for another 2 to 3 years, and then annually. At each visit, a clinical assessment, chest radiography or chest CT, serum markers, and CT of the abdomen and pelvis are obtained, although ongoing studies seek to determine if a lower frequency of scans may be equivalently effective.[74]

Two major studies have been conducted to determine the efficacy of single-agent carboplatin administered as an adjuvant therapy for stage I seminoma. The MRC of Great Britain conducted a comparative trial in which 1477 patients with stage I seminoma (excluding those with T4 primary tumors) were randomized to therapy with radiation ($N = 904$) administered in a dog-leg or para-aortic field at a dose of 20 to 30 Gy versus a single dose of carboplatin ($N = 573$) administered at an area under the curve of 7. After 3 years of follow-up, the relapse-free rates were similar in both groups—95.9% vs. 94.8% for those receiving radiation therapy versus carboplatin, respectively. Furthermore, quality-of-life parameters such as lethargy and work absence were more significant in the radiation therapy arm.[77] Criticisms of this study include a lack of stratification by risk factors among patients as well as the lack of an arm that included observation, the inclusion of which would have given insight into the margin of benefit for any adjuvant therapy versus none. In the second study, a "risk-adapted" approach was used in which carboplatin (area under the curve of 7 for two cycles) was administered to patients with either rete testis invasion (11%), a primary tumor size of 4 cm or

greater (42%), or both (16%). Patients without these risk factors underwent surveillance. A total of 314 patients were enrolled, and 214 (36%) received carboplatin. Of the 100 patients undergoing surveillance, 6 (6%) relapsed compared to 7 (3.3%) of those who received carboplatin. Interestingly, 9% of the patients with rete testis invasion relapsed compared with 0.8% of those with tumor size of 4 cm or larger. All patients who relapsed were salvaged with standard etoposide plus cisplatin chemotherapy.[78]

Taken together, these trials suggest that in certain settings (large tumors, rete testis invasion) single-agent carboplatin may be an effective alternative to radiation therapy and that chemotherapy is associated with low toxicity and certain benefits compared with irradiation. A definitive trial in which surveillance, carboplatin, and radiation therapy are compared in patients stratified by tumor stage is unlikely to be performed because of sample size limitations.

Clinical Stage I Nonseminoma

Risk Assessment

Controversy over the optimal management of clinical stage I nonseminomatous GCT has prompted a search for prognostic factors that can be used to predict the risk of occult nodal involvement. Histologic subtype, local tumor extension, and vascular or lymphatic invasion have all been shown to correlate with occult nodal metastases (pathologic stage IIA) or a high risk of relapse (summarized in Table 90-6).

Several studies have identified histologic evidence of vascular or lymphatic invasion in the primary tumor as a predictor of either relapse or occult nodal involvement in clinical stage I patients who were followed after orchiectomy with surveillance, or treated with RPLND. In patients with clinical stage I NSGCT, the Testicular Cancer Intergroup Study observed venous or lymphatic invasion in 23.6% and 9.2% of specimens, respectively, compared with 55% and 45%, respectively, of specimens from patients with clinical stage II disease. Not only was vascular invasion more common in node-positive patients than in node-negative patients, but in node-negative patients treated with orchiectomy and RPLND alone, relapse was noted in 10 of 168 (6%) patients who demonstrated no vascular invasion, compared with 12 of 62 (19.4%) if vascular invasion were present.[48] Other studies[36,47,49,62,63,65] have confirmed the significance of vascular or lymphatic invasion as a predictor of occult nodal metastases or relapse, either alone or in combination with other variables. A British study of 259 clinical stage I nonseminomatous GCT patients identified invasion of veins or lymphatics, along with two histologic features (presence of embryonal carcinoma and absence of yolk sac tumor) as four factors most predictive of relapse. If three or four features were present, the likelihood of relapse or occult nodal involvement was 58%; patients with two positive risk factors had a 24% chance of relapse, whereas patients with zero or one risk factor relapsed only 9% of the time.[47] A Swedish/Norwegian study identified vascular invasion, absence of AFP before orchiectomy, or high T stage as predictive factors that identified high-risk clinical stage I nonseminomatous GCT patients.[79] In a Danish study, patients with vascular invasion had a risk of relapse of 36%, compared with patients with no vascular invasion, whose relapse rate was 13%.[63]

Table 90-6 Clinical Features Associated with High Risk of Occult Nodal Involvement in Clinical Stage I Nonseminomatous Germ Cell Tumors*

Vascular/lymphatic invasion
Embryonal carcinoma elements (>30%)
Absence of yolk sac elements
Absence of AFP preorchiectomy
Less than 50% teratoma
Local extension into paratesticular structures

*See text for findings of individual studies.

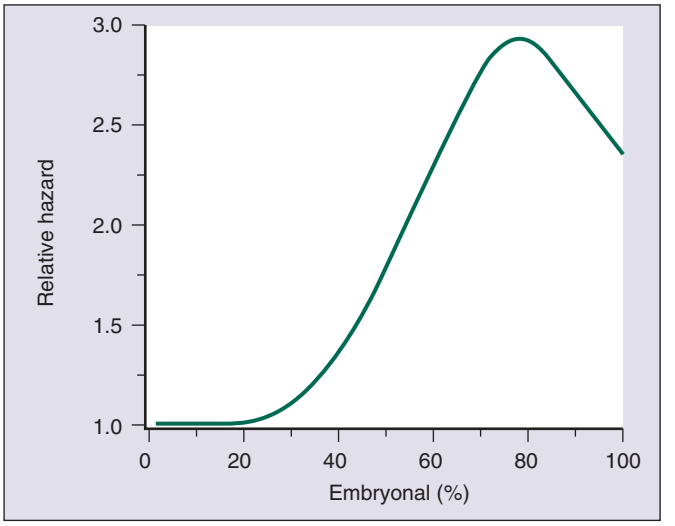


Figure 90-4 • Relationship between percentage of embryonal carcinoma in the primary orchiectomy specimen and relative risk of recurrence. (Data from Sesterhenn IA, Weiss RB, Mostofi FK, et al: Prognosis and other clinical correlates of pathologic review in stage I and II testicular carcinoma: a report from the testicular cancer intergroup study. J Clin Oncol 1992;10:69.)

Several series have demonstrated an association between the presence of embryonal carcinoma in the primary tumor and an increased risk of lymph node metastasis. In 321 patients with either stage I or II nonseminomatous GCT who were treated with orchiectomy and lymphadenectomy, the Testicular Cancer Intergroup Study demonstrated that the risk of relapse remained low until the percentage of embryonal carcinoma exceeded 30% to 40% (Fig. 90-4). However, in this series the percentage of embryonal carcinoma was not found to be a significant prognostic factor after adjustment for either vascular invasion or nodal stage.[48] Another large series of 292 patients with clinical stage I NSGCT from Indiana University suggested that embryonal carcinoma-predominant tumors were both more likely to have occult positive lymph nodes (32% vs. 15.6%) and also considerably more likely to relapse after RPLND (21% vs. 3%).[33]

The absence of yolk sac elements is believed to be a marker of poor prognosis in patients with stage I NSGCT. The confirmation by the Testicular Cancer Intergroup Study that AFP production is linked to yolk sac histology[48] suggests that the identification of AFP negativity as a marker of poor prognosis in stage I NSGCT[62] is a reflection of the fact that yolk sac tumor histology seems to confer some benefit to these patients.[47] Fung and colleagues[41] have confirmed in their series of 60 nonseminomatous GCTs the importance of vascular invasion as a negative prognostic marker but have also identified tumors with less than 50% teratoma as having a higher likelihood of relapse.

Local extension of tumor into paratesticular structures also seems to be predictive of higher relapse rates. Although some studies have noted higher relapse rates in patients with invasion of any structures outside the testis (rete testis, tunica albuginea, epididymis, or spermatic cord), others have noted that tumor involvement of only certain paratesticular structures carried an increased risk of relapse.[80] Thus, Sesterhenn and associates[35] reported a 42% versus 16% relapse rate after RPLND in stage I and II patients with and without tunica

albuginea involvement. Other studies have suggested that involvement of the rete and epididymis, but not the tunica albuginea or spermatic cord, were associated with a higher risk of relapse. Recent studies suggest that negative immunohistochemical staining with an antibody against the Ki-67 receptor, a marker of tumor proliferation, identifies a good-risk population with a negative predictive value for occult nodal involvement of 88%, although this has not been confirmed by others.[81]

Many other factors have been shown to have no prognostic value. Interestingly, increased levels of preorchiectomy β-HCG and AFP, the size of the primary tumor (in contrast to seminoma), and the side of the primary (right vs. left) are not generally predictive of the risk of relapse after orchiectomy.[80]

Treatment

Clinical stage I NSGCTs account for approximately 50% of all NSGCTs. Pathologic staging reduces this number to approximately 40%. The evolution of improved surgical technique, the increased capacity for judicious surveillance, and the advent of highly successful systemic chemotherapy have all served to make the management of clinical stage I NSGCT a controversial one.

RETROPERITONEAL LYMPH NODE DISSECTION. Before the advent of cisplatin-based chemotherapy, it was recognized that radical RPLND offered the potential of cure, even to NSGCT patients with nodal metastases. This dissection is a full, bilateral procedure in which all lymphatic, neural, and connective tissue is removed from a field demarcated by the crus of the diaphragm superiorly, to the bifurcation of the common iliacs inferiorly, and bordered laterally by the ureters.

After RPLND, clinical stage I NSGCT patients are restaged as either pathologic stage I or pathologic stage IIA (microscopic nodal involvement). In the era before cisplastin, survival rates were 93% for pathologic stage I and 75% for pathologic stage IIA patients. Since the advent of cisplatin-based chemotherapy, which is used in this setting as either salvage or adjunctive therapy, the long-term survival rate approaches 100% for patients with pathologic stage I tumors, and 96% for patients with pathologic stage IIA tumors.[82]

A large prospective trial by the Testicular Cancer Intergroup Study enrolled 195 pathologic stage II NSGCT patients (including 64 patients with pathologic stage IIA) who were randomized after RPLND to observation or immediate adjuvant chemotherapy.[82] For patients with pathologic stage I NSGCT, at a median follow-up of 45 months, 28 patients (10.5%) had recurrent disease and six had died, two of drug- resistant cancer. At the time of report, 98% of patients were alive and disease-free.

Patients with pathologic stage IIA disease who are treated with orchiectomy and RPLND only will have a relapse rate as high as 30% to 40%,[82] although some investigators have reported relapse rates in the 10% range in carefully selected pathologic stage IIA patients. Regardless of surgical cure rate, in the cisplatin era, the overall survival of patients with pathologic stage IIA NSGCT treated initially with orchiectomy and RPLND is in the 96% to 99% range.[83–85] The integration of chemotherapy into treatment schemas for stage II NSGCT is discussed later.

In experienced hands, a full RPLND is associated with low morbidity and mortality, but loss of ejaculatory function occurs in 65% to 100% of patients.[28,83,86] It has been stressed that disruption of these fibers results in retrograde ejaculation but not in loss of potency, libido, or ability to have an orgasm.[83] The high incidence of ejaculatory dysfunction after full RPLND, coupled with an understanding of the pattern of nodal involvement in patients with low-volume disease, has led investigators to modify the traditional full RPLND. Extensive experience with full RPLND has allowed accurate mapping of nodal involvement in patients with low- and moderate-volume disease.[36–38] As described previously, this work has shown that (1) suprahilar metastases are exceedingly rare in patients with low-volume retroperitoneal disease, and (2) patients with minimal volume retroperitoneal disease almost always have unilateral retroperitoneal disease. Patients with left-sided primaries characteristically have nodal metastases to the upper left periaortic zone, while patients with right-sided primaries have involvement of the interaortocaval and precaval regions. These observations led to modifications of the traditional full RPLND in patients with low-volume retroperitoneal disease, whereby a suprahilar dissection was eliminated, and a limited dissection template was utilized, depending on the side of the primary. For right-sided lesions dissection is limited on the left by the lateral margin of the aorta to the bifurcation, and for left-sided tumors the right margin is the right renal hilum and the vena cava to the bifurcation.[83] The templates for right and left modified RPLND are illustrated in Figure 90-5. The benefits of a modified RPLND in this group of patients were shorter operative time, shorter postoperative ileus, and a significant reduction in ejaculatory dysfunction (30% to 40% dysfunction after a right modified RPLND, and 60% to 70% dysfunction after left modified RPLND). Furthermore, modification of the traditional full RPLND in patients with minimal retroperitoneal disease does not have an adverse effect on outcome, yielding surgical cure rates of approximately 90% in pathologic stage I patients, 70% in pathologic stage IIA patients, and an overall long-term survival rate approaching 100%.[83]

The most recent modification in technique for RPLND in patients with low-stage NSGCT is the nerve-sparing dissection described by Donohue and associates.[86,87] In this procedure, postganglionic sympathetic fibers from lumbar ganglia are prospectively identified and preserved before lymphadenectomy, with the intent to stage and treat in a standard fashion, while preserving normal ejaculatory function. One hundred percent of 73 patients with clinical stage I disease who underwent a nerve-sparing lymphadenectomy at Indiana University had normal postoperative ejaculation. The distribution of pathologic stages and relapse pattern was no different from what has been described with full or modified RPLND. Of 73 clinical stage I patients, 14 (20%) were found to have occult nodal metastases. The relapse rate was 7% in the 61 pathologic stage I patients, and 28% in the 14 pathologic stage IIA patients. All patients who suffered a relapse were salvaged with platinum-based chemotherapy.[83,86] (The characteristic relapse pattern after RPLND is discussed later and contrasted with the relapse pattern in similar patients who are not treated with an RPLND.) Thus, the nerve-sparing RPLND seems to be diagnostically and therapeutically as efficacious as more morbid full and modified retroperitoneal lymphadenectomies. Overall, approximately 30% of clinical stage I NSGCTs are found to have occult nodal involvement at RPLND and are classified as pathologic stage IIA. The use of adjuvant chemotherapy in these patients is discussed in the section on the treatment of stage II nonseminoma.

Alternatives to Retroperitoneal Lymph Node Dissection

ADJUVANT RADIATION THERAPY. Some investigators have suggested that clinical stage I NSGCT patients believed to be at high risk of relapse could potentially be treated with adjuvant chemotherapy or radiation therapy rather than RPLND.[29,65] Although NSGCT is less radiosensitive than seminoma and requires considerably higher radiation doses (45–55 Gy), radiation therapy nonetheless may occasionally be required under unusual circumstances. The results of radiation therapy alone in clinical stage I NSGCT have been reviewed.[28] Although overall survival rates from 70% to 90% have been reported, the advent of highly effective chemotherapy has largely obviated the role of radiation therapy in the treatment of clinical stage I NSGCT.

ADJUVANT CHEMOTHERAPY. As many as 50% of patients with high-risk clinical stage I NSGCT are subsequently found to have nodal involvement. As discussed later, some of these patients will go on to receive chemotherapy after RPLND or in the salvage setting. It has therefore been suggested that chemotherapy might serve as

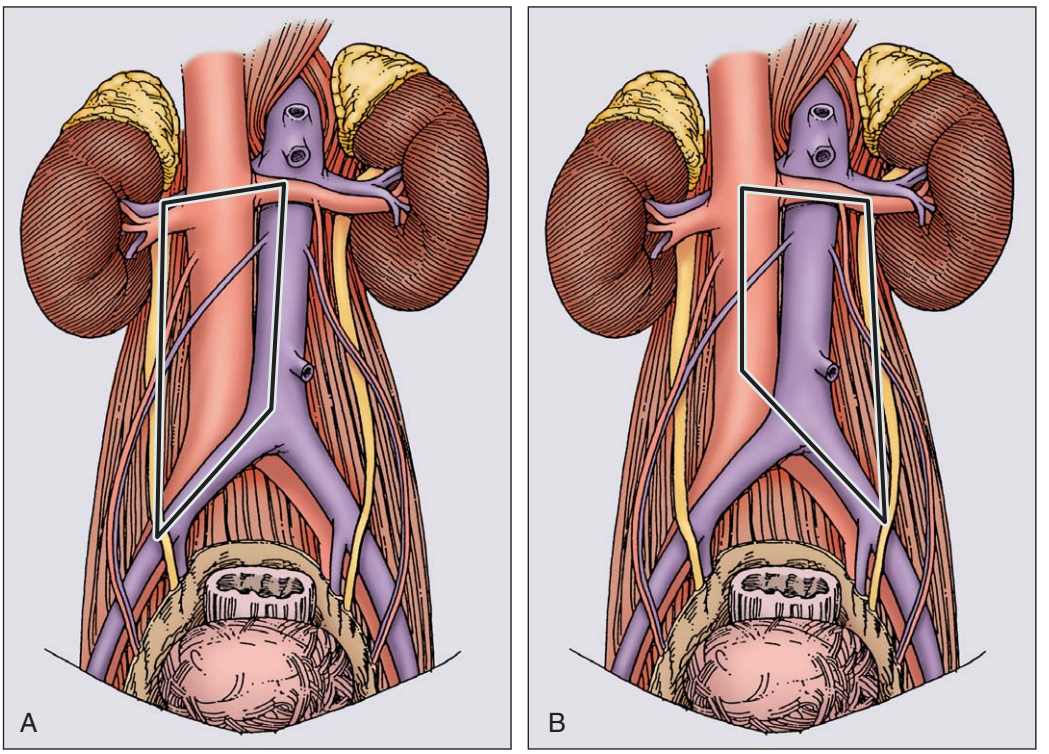


Figure 90-5 • Templates for modified retroperitoneal lymphadenectomy. **A,** Right modified RPLND; **B,** left modified RPLND. (Adapted from Foster RS, Donohue JP: Surgical treatment of clinical stage A nonseminomatous testis cancer. Semin Oncol 1992;19:166, with permission.)

effective primary adjunctive therapy after orchiectomy, thereby sparing patients an RPLND. Several investigators have used two cycles of cisplatin, etoposide, and bleomycin (PEB) in lieu of an RPLND, and have reported very low relapse rates (generally <5%) in patients with median follow-ups as long as 4 to 6 years.[88–90] More recent studies have used a risk-adapted approach, thus sparing patients with very good prognoses the potential toxicity of chemotherapy. One study administered two cycles of carboplatin, etoposide, and bleomycin (CEB) to stage I patients with either vascular invasion in the primary tumor, more than 80% embryonal component, or a preorchiectomy AFP of higher than 80. In this cohort of 76 patients there were no GCT relapses after treatment with CEB, with only one patient requiring resection of a growing teratoma.[91] These results must be balanced with the concern that the use of primary chemotherapy may expose as many as 50% of patients to unnecessary chemotherapy. Although adjuvant chemotherapy for stage I NSGCT in lieu of an RPLND may be used with increasing frequency on the basis of these data, it is not considered a standard of care in the United States.

SURVEILLANCE. The development of extraordinarily effective chemotherapy for disseminated NSGCT has also resulted in an effort to minimize "up-front" treatment for clinical stage I NSGCT. The strategy of surveillance after orchiectomy, followed by systemic therapy at the first sign of relapse, is based on the observation that only 20% to 40% of clinical stage I patients have occult nodal involvement, the belief that the majority of these patients can thus be spared the morbidity associated with RPLND, and confidence in chemotherapy as a curative "salvage" modality for those patients who do relapse.

Surveillance programs for patients with a negative initial staging evaluation have been evaluated primarily in nonrandomized studies.[92,93] A summary of published results from nearly 600 patients who underwent surveillance after orchiectomy revealed a relapse rate of approximately 30%, but an overall disease-free survival rate of more than 95%.[94] The MRC (UK) has reported on a prospective evaluation of surveillance in 373 clinical stage I NSGCT patients. Whereas the 5-year relapse-free rate was 73%, salvage surgical and chemotherapeutic interventions yielded an overall 5-year survival of 98%.[95] These data have been interpreted to suggest that the strategy of surveillance yields equivalent results to RPLND in carefully selected clinical stage I NSGCT patients.[84]

Successful surveillance requires strict adherence to selection criteria and surveillance methodologies. Most centers rely on serum markers, physical examinations, and chest radiographs obtained every 1 to 2 months, as well as CT scan of the abdomen and pelvis every 3 or 4 months the first year, every 6 months the second year, and yearly thereafter. Eligibility criteria must include a compliant and motivated patient, in whom rigorous clinical staging (negative exam, serum markers, chest radiograph or CT, and abdominal/pelvic CT) has been undertaken. Most studies have excluded patients with locally advanced tumors (e.g., spermatic cord, scrotal sac involvement), and it has been suggested that patients at high risk for nodal metastases based on the risk assessment schemas outlined previously should not undergo surveillance alone. Patient compliance with intensive surveillance programs remains a recognized problem, and successful surveillance mandates rigorous patient selection.[93]

The use of adjuvant chemotherapy in patients with stage I disease has become an area of some controversy. In one large Spanish study, a risk-adapted approach was applied to the selection of patients for chemotherapy following orchiectomy.[78] Patients with vascular invasion or invasion of local structures received two cycles of BEP, whereas those without these risks underwent surveillance. A relapse proportion of less than 1% in the first 2 years, compared with a relapse rate of 19% (71 of 358) in the patients undergoing surveillance again suggests that the use of chemotherapy in this setting prevents relapse, but does not address specifically the question of the proportion of patients who were unnecessarily exposed to the risks of chemotherapy.

Characteristically, relapses after RPLND for clinical stage I (pathologic stage I or IIA) NSGCT are either serologic or occur in the chest, although some series have reported from 4% to 6% of relapses occurring in the retroperitoneum.[93,96] Isolated retroperitoneal

nodal relapses in the absence of elevated markers or other sites of relapse are exceedingly rare. Furthermore, relapses more than 2 years after RPLND are extraordinarily uncommon.[82] By contrast, most relapses in clinical stage I patients who have selected orchiectomy alone followed with surveillance are identified by tumor markers and by and large occur in the retroperitoneum. Although some investigators have made the observation that the majority of these retroperitoneal relapses occur with bulky disease,[93] there is no evidence to suggest that overall survival is affected. Additionally, surveillance patients seem to be at risk for relapse for a longer period than patients treated with RPLND. Even though most relapses occur within the first year of instituting surveillance (median, 3–4 months), late relapses in the third to fifth year do occur.[72] These patterns of relapse, along with consideration of the morbidity involved with each therapeutic alternative, have formed the basis of debate regarding the relative merits of surveillance versus immediate RPLND in clinical stage I NSGCT patients.

As long as staging, treatment, and surveillance guidelines are strictly observed, nearly 100% of clinical stage I NSGCT patients can be cured, whether surveillance or RPLND with or without adjuvant chemotherapy are used. Each patient with clinical stage I NSGCT must be informed of these alternatives and allowed to choose the methods of management most suited to his wishes and needs (Fig. 90-6).

Stage II Seminoma: Treatment and Results

The Royal Marsden Hospital clinical staging system (see Table 90-5) divides stage II (abdominal) seminoma patients into subgroups on the basis of tumor bulk, as follows: IIA, smaller than 2 cm; IIB, from 2 to 5 cm; and IIC, larger than 5 cm. Historically, radiation therapy has been used for all stages of seminoma, allowing a retrospective analysis of failure rates and survival rates as a function of tumor mass. More recent series generally report better outcomes, perhaps because the era of CT scanning has allowed more precise definition of nodal margins and tumor volume.[97] Reviews of recent collected series have found recurrence rates generally less than 5% in patients with masses less than 5 cm in size (stages IIA and IIB); 80% to 90% will be cured with standard abdominal radiation therapy alone. The use of salvage chemotherapy or radiation therapy (or both) in patients with masses smaller than 5 cm who relapse after initial radiotherapy results in a cause-specific survival of 95% to 100%.[31] Radiation therapy is therefore recommended for small-volume (<5 cm) retroperitoneal disease. The radiation field is generally limited to the infradiaphragmatic lymph nodes as in stage I disease. Relapses, when they occur, have largely been reported to occur outside the radiation field,[98] although relapse in the mediastinum or supraclavicular nodes is a distinctly unusual event,[99] and when it occurs, salvage with radiation therapy or chemotherapy is successful.[76] Thus, supradiaphragmatic radiation therapy is not warranted in these patients.

By contrast, failure rates of around 10% are reported in patients with masses between 5 and 10 cm, although some series have reported relapse rates as high as 40%.[100] The relapse rate after radiation therapy alone in patients with masses greater than 10 cm is unacceptably high, at approximately 35%.[31] Cure rates with radiation therapy alone for patients with stage IIC seminoma range from 30% to 60%, although an overall cause-specific survival of up to 90% can be expected with salvage chemotherapy.[100] Two major problems are

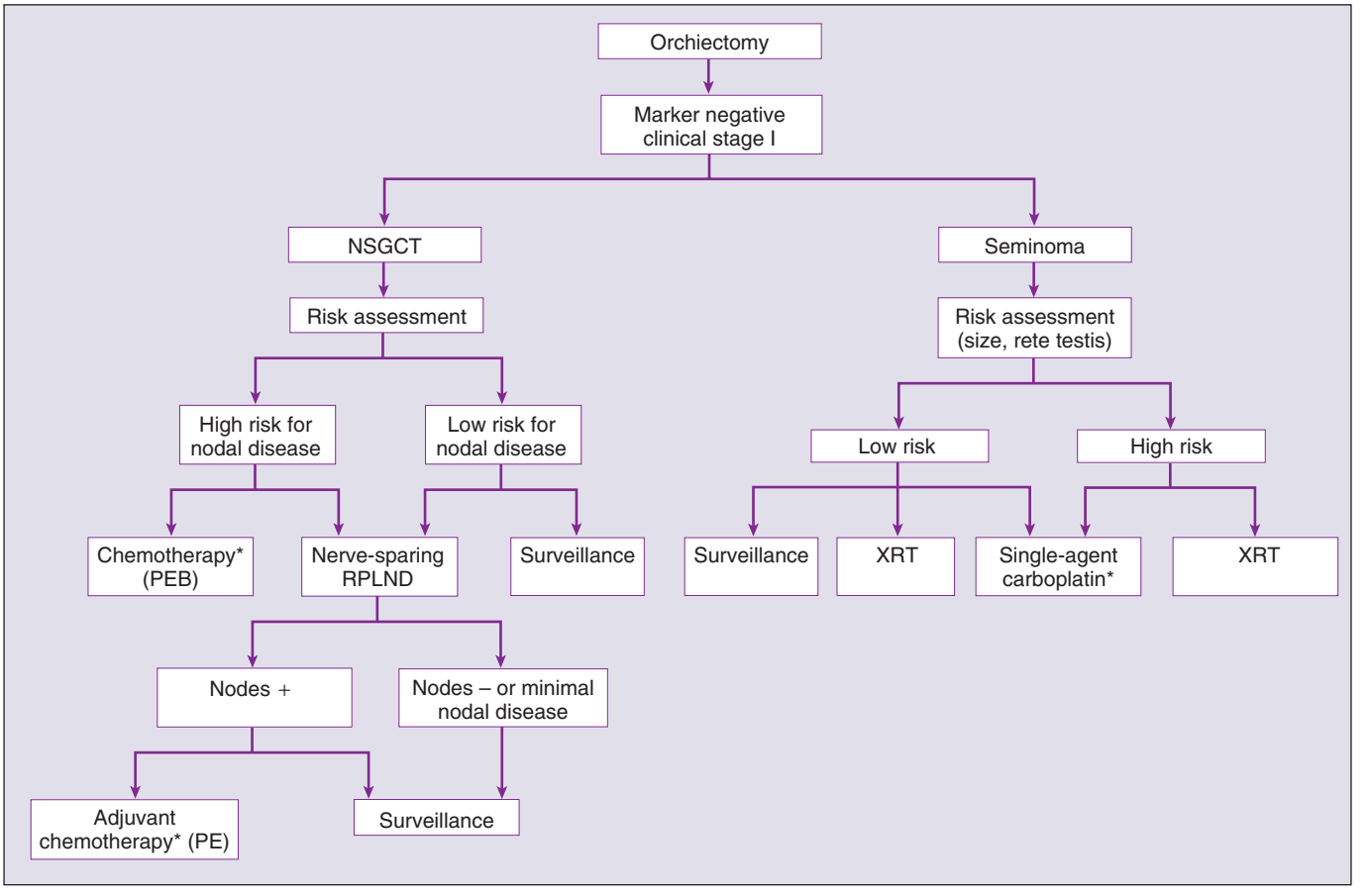


Figure 90-6 • Therapeutic options for patients with clinical stage I germ cell tumors. NSGCT, nonseminoma germ cell tumor; PE, platinum, etoposide; PEB, platinum, etoposide, bleomycin; RPLND, retroperitoneal lymph node dissection. *Investigational.

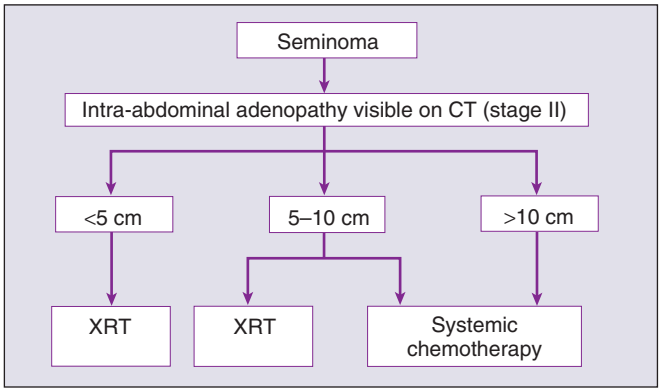


Figure 90-7 • Therapeutic options for patients with clinical stage II germ cell tumors, seminoma. XRT, radiation therapy.

associated with the use of radiotherapy alone for stage IIC seminoma. The first is a risk of mediastinal or supraclavicular relapse in as many as 20% of patients.[99] In general, the degree of marrow compromise in patients receiving infra- and supradiaphragmatic irradiation makes supradiaphragmatic radiation therapy an impractical solution to the problem. Second, it has been suggested that the radiation fields required for treating large masses, even if shrinking-field techniques are used, make renal toxicity difficult to avoid.[101] As a consequence, it is generally recommended that stage IIC seminoma patients (masses >5 cm), and especially patients with masses larger than 10 cm be initially treated with chemotherapy (Fig. 90-7). This approach is discussed in the following section; results in cure rates are from 85% to 95%.[100,101]

STAGE II Nonseminoma

Risk Assessment

The identification of factors uniformly associated with a higher risk of relapse in node-positive NSGCT patients after RPLND has not been possible. The Testicular Cancer Intergroup Study randomized 195 patients with completely resected retroperitoneal disease to observation or two cycles of adjuvant-based chemotherapy. Among the patients randomized to observation, approximately 50% subsequently relapsed.[102] Recurrence rates were higher among patients with advanced nodal stage: 40% for patients with microscopically positive nodes, 53% for nodes less than 2 cm, and 60% for nodes larger than 2 cm. Although these differences were not statistically significant, this study was probably underpowered to detect clinically significant differences. Other series have supported an association between greater nodal involvement and higher relapse rates. Patients with substantial retroperitoneal nodal involvement or extracapsular extension treated with RPLND but no adjuvant chemotherapy have a greater than 50% risk of relapse.[80] By contrast, some series report significantly lower relapse rates (from 0 to 20%) than reported in the Williams trial, for patients with minimal nodal involvement who received no adjuvant therapy.[103–105] The impact of histologic type on risk of relapse after RPLND in stage II NSGCT was confirmed by the Testicular Cancer Intergroup Study pooled data from stage I and II patients, which demonstrated that the presence of embryonal carcinoma clearly increased the risk of recurrence, although histology was not retained as a significant predictor of relapse after correction for vascular invasion or nodal involvement.[82] Although earlier reports from the same group had suggested that vascular invasion was not a predictor of relapse in stage II NSGCT, a later study[35] reported that in node-positive patients, 24% of patients without vascular invasion relapsed, compared with a 63.5% relapse rate among patients with documented vascular invasion.

Treatment of Clinical Stage II Patients

RETROPERITONEAL LYMPH NODE DISSECTION FOLLOWED BY ADJUVANT CHEMOTHERAPY. Stage IIA and IIB NSGCT patients have minimal or moderate retroperitoneal lymphadenopathy. This category includes patients with clinical stage I NSGCT who are found to harbor occult nodal involvement at RPLND (pathologic stage IIA). The standard primary treatment for clinical stage IIA and B patients is RPLND (Fig. 90-8).

Before the advent of cisplatin-based therapy, the observed high rate of relapse after RPLND in patients who were lymph node-positive was the basis of the use of adjuvant chemotherapy. Before the late 1970s this treatment included drugs such as bleomycin, vinblastine, and dactinomycin.[106] Although it was acknowledged that over 50% of patients would be treated unnecessarily, the poor prognosis at relapse mandated this approach. Improvements in chemotherapy for systemic disease led to the use of platinum-based therapy in the adjuvant setting.[107] An international study by Williams and coworkers[106] was published in 1987, in which 195 patients with completely resected retroperitoneal disease (108 patients with pathologic stage II NSGCT) were randomized to either immediate adjuvant chemotherapy consisting of two cycles of cisplatin, vinblastine, and bleomycin (PVB) or vinblastine, dactinomycin, bleomycin, cisplatin, and cyclophosphamide (VAB-6) or no adjuvant therapy followed by chemotherapy at the time of relapse. With a median follow-up of 4 years, 49% of the patients in the observation arm relapsed, compared with 6% in the adjuvant therapy arm. Patients in the observation arm who relapsed were treated with salvage chemotherapy. Because of effective salvage therapy, the overall survival (97%) was the same in both arms. Two conclusions arose from this study: (1) that the deferral of adjuvant treatment was appropriate and (2) that a brief course of cisplatin-based therapy can prevent relapse. Although this report included patients with a mixed group of stage II tumors, ranging from microscopic nodal involvement (N1) to grossly involved lymph nodes greater than 2 cm (N2b) and nodes with capsular penetration (N3b), no subgroup was identified in which adjuvant chemotherapy was mandatory, or with so favorable an outcome that adjuvant therapy was not necessary. Nevertheless, as noted, and despite the results of this study, nodal stage is believed

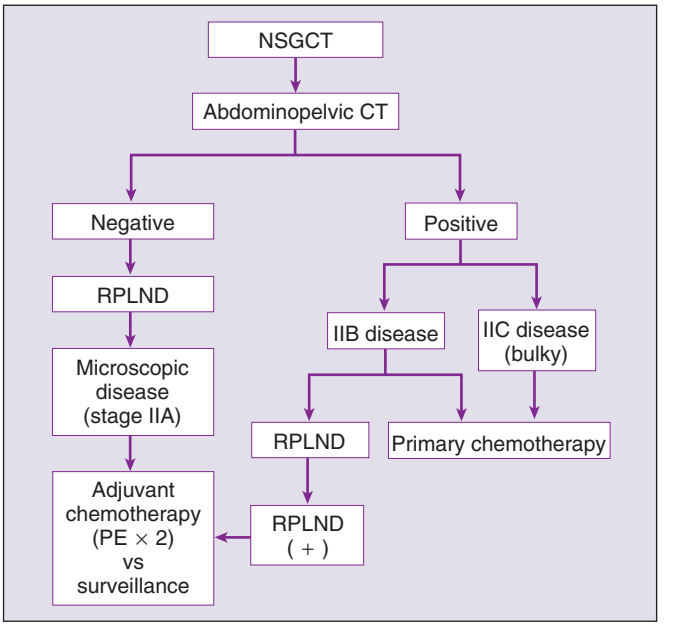


Figure 90-8 • Therapeutic options for patients with clinical stage II germ cell tumors, nonseminoma (NSGCT). PE, platinum, etoposide; RPLND, retroperitoneal lymph node dissection.

by some to have value in predicting relapse.[105,107] For this reason, most centers recommend adjuvant chemotherapy over surveillance in patients with moderate retroperitoneal lymph node involvement (i.e., stage IIB disease), but an option for patients with minimal microscopic disease is surveillance after RPLND, in that true pathologic stage IIA patients are at a very low risk of relapse (0 to 10%). Other reports support these data.[96] A recent series reported 11 relapses (22%) in 50 NSGCT patients with low-volume nodal metastases who were managed expectantly after RPLND. Most relapses consisted of marker elevation. Five of the patients who suffered relapse had elevated markers before RPLND. The relative risk (RR) of relapse in patients with persistent marker elevation before RPLND (8.0) suggests that chemotherapy, and not RPLND, should be the treatment of choice in such patients.[101] These data support earlier observations of a high relapse rate of patients with rising markers following orchiectomy (Stage IS disease).[108]

Nonrandomized series have confirmed the high overall disease-free survival rate (98% to 100%) observed with adjuvant chemotherapy administered after RPLND. Earlier studies used either PVB or one of the VAB regimens. However, studies in the late 1980s demonstrated that the substitution of etoposide for vinblastine produced equivalent survival, with substantially less toxicity when used for patients with advanced disease.[109] Consequently, several centers have tested the substitution of etoposide for vinblastine in the adjuvant setting as well. Bleomycin was omitted in two of these studies.[110–112] Survival in all these series was 99% to 100%, with follow-up ranging from 30 to 72 months.

Taken together, these data demonstrate that excellent long-term survival can be achieved with RPLND followed by either observation (with salvage chemotherapy at relapse) or adjuvant chemotherapy. The disadvantage of adjuvant therapy is that it unnecessarily subjects approximately 50% of the patients (those who would have been cured with RPLND alone) to chemotherapy. Surveillance after RPLND avoids this problem, but it requires half the patients to endure the psychologic trauma of recurrent disease and further requires that patients adhere to a frequent follow-up schedule, which is often difficult in this population of patients. (In the Williams and coworkers' study,[106] for example, 25% of the patients made six or fewer follow-up visits.) Finally, patients who do not receive adjuvant therapy will probably require more extensive chemotherapy for relapsed disease than had they been treated in the adjuvant setting. The excellent results of Motzer and coworkers[112] suggest that two cycles of etoposide and cisplatin may be adequate in the adjuvant setting, yet a chemotherapy-naive relapsed patient would probably receive either four cycles of etoposide and cisplatin or three cycles of PEB.

PRIMARY CHEMOTHERAPY. Patients who have clinical stage IIC NSGCT have traditionally been grouped with those who have stage III disease when therapeutic options are being considered, and they are usually treated with systemic chemotherapy. The rationale for this approach includes the excellent results of chemotherapy in "good-risk" disseminated disease, which includes individuals with clinical stage IIC NSGCT, as well as the increased morbidity associated with RPLND for patients with bulky disease.[113]

The excellent response of advanced disease to systemic therapy on the one hand, and the possibility of cure without an RPLND in selected clinical stage I patients on the other, are the basis for the experimental use of systemic chemotherapy without an RPLND in persons with clinical stage II NSGCT.[114] Two centers, the M.D. Anderson Cancer Center (MDA) and the Royal Marsden Hospital (RMH), have reported on the use of primary chemotherapy in clinical stage II NSGCT patients.[114,115] Postchemotherapy RPLND was required in only 22% to 30% of these patients. Analysis of the clinical and histologic features of the 50 MDA patients suggested that patients with tumors larger than 5 cm had the highest frequency of postchemotherapy RPLND (33%), although this number did not reach statistical significance. At the RMH, 17% of 58 stage IIA patients (nodes <2 cm) required RPLND, compared with 39% of 64 stage IIB patients. In the MDA series the most important predictor of the need for postchemotherapy RPLND was the presence of teratomatous elements in the primary tumor (36% incidence of need for RPLND in these patients, compared with only 8% of patients with embryonal tumors with or without seminoma; $P = 0.014$). A 96% complete response rate with primary chemotherapy followed selectively by an RPLND was reported by MDA, whereas the 5-year actuarial survival probability for the RMH patients was 95%, with a median follow-up of 5.5 years. These series suggest that primary chemotherapy may be a therapeutic option for stage II NSGCT, obviating the need for surgery in 70% to 80% of patients. Patients particularly suited for this approach seem to be those with masses smaller than 2 cm, and with no teratomatous elements in their primary orchiectomy specimens. The risks of persistent disease or progression of residual teratoma for as long as 10 years after apparent clinical eradication of stage II GCT (or both) have been cited as reasons for using this approach with caution.[116,117] The degree of retroperitoneal lymphadenopathy at which patients are directed toward primary chemotherapy rather than primary RPLND varies among institutions and is, in part, based on the experience of the treating surgeon. The approach at the University of California, San Francisco (UCSF) is to perform primary RPLND in all patients with clinical stage IIA and in most patients with stage IIB disease. For some stage IIB patients with more extensive and/or bilateral retroperitoneal disease, which would not be amenable to a modified or nerve-sparing RPLND (generally masses >3 to 5 cm in size), primary chemotherapy is offered with a "good-risk" regimen such as PEB for three cycles or PE for four cycles. The role of adjunctive surgery after chemotherapy in disseminated disease is discussed later in this chapter.

MANAGEMENT OF ADVANCED DISEASE

The functional definition of advanced GCT includes those stages of tumor in which locally directed therapy (radiation therapy for seminoma, RPLND for NSGCT) offers unacceptably poor results. Thus, for NSGCT and for most investigators, lymph nodes larger than 2 cm define advanced disease, whereas in seminoma, bulky IIC disease (generally masses >5 cm) is considered advanced disease. Stages III and IV are considered advanced by definition.

The greatly improved prognosis for disseminated GCT patients is largely attributable to a dramatic improvement in chemotherapy. The introduction of cisplatin into combination chemotherapy regimens in the 1970s and 1980s resulted in markedly superior response rates, as well as long-term survival, as compared with the previous gold standard of bleomycin and vinblastine. Einhorn and colleagues, and the Southeastern Cancer Study Group (SECSG), demonstrated the utility of PVB and further refined their regimen by showing in randomized trials that lower dosage of vinblastine and the elimination of maintenance therapy did not affect response rates or long-term survival.[118,119] Simultaneously, investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) built upon the combination of vinblastine and bleomycin in their series of VAB protocols, by first adding dactinomycin, and then cisplatin.[120] Most recently, the discovery of etoposide as an active agent in advanced GCT led to the substitution of etoposide for vinblastine in the PVB regimen. A randomized trial comparing the etoposide-containing regimen (PEB) to PVB found that use of PEB resulted in an overall identical response rate, complete response rate, and 2-year survival rate, while significantly reducing the toxicity (primarily neuromuscular) associated with PVB,[106]essentially making PVB obsolete (Table 90-7).

Chemotherapy with PVB, PEB, or VAB-6 will result in a complete response in approximately 80% of patients with advanced GCT and long-term cures in 70%. By the same token, however, 20% to 30% of patients will relapse and may ultimately die from their disease, stressing the importance of improving outcomes for high-risk patients as well as developing effective salvage strategies. Studies of pretreat-

Table 90-7 Induction and Salvage Chemotherapy Regimens for Advanced Germ Cell Tumor

PEB (every 21 days) × 3–4
Indiana University
CDDP 20 mg/m^2/day, days 1–5
VP-16 100 mg/m^2/day, days 1–5
Bleomycin 30 units, days 2, 9, and 16
Stanford University/Europe
CDDP 100 mg/m^2/day, day 1
VP-16 150 mg/m^2/day, days 1–3 (In Europe days 1, 3, and 5)
Bleomycin 15 units/m^2, days 1, 8, and 15
PE (every 21 days)
CDDP 20 mg/m^2/day, days 1–5
VP-16 100 mg/m^2/day, days 1–5 (in Europe 150 mg/m^2/day, days 1, 3, and 5)
TIP (every 21 days)
Paclitaxel 250 mg/m^2, 24-hour continuous infusion on day 1
Ifosfamide 1500 mg/m^2, days 2 to 5 *and* cisplatin 25 mg, days 2 to 5
Mesna 500 mg/m^2, before ifosfamide and 4 and 8 hours after ifosfamide daily
VIP (salvage; every 21 days)
Vinblastine 0.11 mg/kg, days 1 and 2 or VP-16 75 mg/m^2/day, days 1–5
Ifosfamide 1.2 g/m^2/day, days 1–5 (with mesna)
CDDP 20 mg/m^2/day, days 1–5
TIP (salvage; every 21 days)
Paclitaxel 175 mg/m^2 continuous infusion over 3 hours on day 1
Ifosfamide 1.2 g/m^2/day, days 2–6 (with mesna)
CDDP 20 mg/m^2/day, days 2–6

CDDP, cis-platinum; VP-16, etoposide. For other abbreviations, see text discussion.

ment clinical characteristics have sought to identify prognostic features that can be prospectively used to segregate this diverse group of advanced GCT patients into poor and good prognostic subsets. Proper identification of the subset of patients who are destined to relapse or fail to achieve a complete response to standard therapy is critical, so as to offer these "poor-risk" patients more aggressive investigational therapies aimed at improving response and cure rates. By contrast, "good-risk" patients are largely adequately treated with conventional therapy. Although the toxicities of these regimens are by and large manageable, they may account for considerable morbidity and on occasion even mortality. Thus, studies of pretreatment prognostic features have also sought to identify the "good-risk patient" cohort, for whom the investigation of less toxic but equally efficacious treatment is appropriate.

Risk Assessment

Several classification systems have been proposed as a means of distinguishing between "good-risk" and "poor-risk" advanced GCT patients. In general, prognostic factors are first identified by a retrospective statistical analysis of the relationship of the risk feature to outcome (generally complete response or survival). Although the specific clinical parameters used to define prognosis vary somewhat in these classification schemas, the pretreatment tumor burden has consistently been identified as an important predictive factor. Different researchers have defined tumor mass by size, number, and location of metastases. Other proposed pretreatment clinical features influencing prognosis in advanced GCT include histology (i.e., seminoma vs. nonseminoma), primary site, serum markers, and site of metastases.[121]

When these schemas were tested prospectively on independent data sets, they seemed to classify good-risk patients equally well but yielded markedly different complete-response rates in the poor-prognosis groups.[71,72] To address this issue a common classification system was developed by the International Germ Cell Cancer Collaborative Group (IGCCCG).[73] The IGCCCG database included 5202 patients with NSGCT and 660 patients with seminoma, and was divided into a test set and a validation set. Prognostic factors for progression-free survival and survival were examined, and prognostic groups for seminoma and NSGCT were developed. The major independent prognostic factors for progression-free survival and overall survival were identified and used to establish prognostic groupings. For NSGCT the independent high-risk factors identified were presence of mediastinal nonseminomatous primary tumor, presence of nonpulmonary visceral metastases (e.g., liver, bone, brain), and increased levels of tumor markers including β-HCG, AFP, and LDH (Table 90-8). For seminoma patients, generally a group considered to carry a more favorable prognosis, the only significant prognostic factor was the presence of nonpulmonary visceral metastases.

This risk assessment schema has been validated both on the IGCCCG validation set and on an independent data set.[74] In this system, good- and intermediate-prognosis patients have a testis or retroperitoneal primary, no nonpulmonary visceral metastases, and low serum tumor markers. Intermediate-prognosis patients are the same as good-prognosis patients except that they have intermediate serum tumor markers. Poor-prognosis patients have a mediastinal primary or nonpulmonary visceral metastases or high levels of serum tumor markers. Five-year overall survival for the good-, intermediate-, and poor-prognosis categories with current regimens is 92%, 80%, and 48%, respectively (see Table 90-8). By definition, seminomas are never poor prognosis. Seminomas are segregated into only good and "intermediate" prognosis cases (any primary site, but with the presence of nonpulmonary visceral metastases), with a 72% 5-year survival.[73]

Several studies have confirmed the post-therapy rate of decline in marker concentration as a predictive marker of outcome in GCT patients. A recent study re-examined this issue in the context of the IGCCCG risk classification system. After adjusting for risk status, satisfactory marker decline (which was defined as a calculated half-life of ≤7 days for AFP and ≤3.5 days for HCG) predicted an improved complete-response proportion, 2-year event-free, and 2-year overall survival.[75]

Treatment of Good-Risk Advanced Germ Cell Tumors

All risk assessment schemas that were used before the development of the IGCCCG classification system were equally able to accurately identify a subgroup of good-prognosis testis cancer patients who had a high likelihood of obtaining a sustained complete response when treated with platinum-based therapy. In general, this group was made up of patients with marker elevation only, or small-volume infradiaphragmatic and/or supradiaphragmatic disease, and without visceral involvement.[72] Because it is not likely that the extraordinarily high cure rate for this group of patients can be improved upon, most efforts have been aimed at optimizing treatment with less toxic regimens that will have equal efficacy.

Trials evaluating (1) the elimination of bleomycin, (2) a reduction in the number of chemotherapy cycles administered, or (3) the substitution of carboplatin for cisplatin have been undertaken. In evaluating the results of these trials, several caveats hold. First, most of these trials have not used the new IGCCCG prognostic classification but instead have relied on different risk assessment schemas, making

Table 90-8 International Consensus Advanced Germ Cell Tumor Prognostic Classification Schema

Nonseminoma	Seminoma
GOOD PROGNOSIS	
56% of nonseminomas	90% of seminomas
5-year PFS, 89%	5-year PFS, 82%
5-year survival, 92%	5-year survival, 86%
Testis or retroperitoneal primary	Any primary site
and	*and*
No nonpulmonary visceral metastases	No nonpulmonary visceral metastases
and	*and*
Good markers (all of the following):	Normal AFP, any HCG, any LDH
AFP < 1000 ng/mL	
HCG < 5000 IU/L (1000 ng/mL)	
LDH < 1.5 ∞ upper limit of normal	
INTERMEDIATE PROGNOSIS	
28% of nonseminomas	10% of seminomas
5-year PFS, 75%	5-year PFS, 67%
5-year survival, 80%	5-year survival, 72%
Testis or retroperitoneal primary	Any primary site
and	*and*
No nonpulmonary visceral metastases	Nonpulmonary visceral metastases
and	*and*
Intermediate markers (any of the following):	Normal AFP, any HCG, any LDH
AFP ≥ 1000 and ≤10,000 ng/mL	
HCG ≥ 5000 IU/L and ≤50,000 IU/L	
LDH ≥ 1.5 × N and ≤10 × N	
POOR PROGNOSIS	
16% of nonseminomas	No seminoma patients classified as poor prognosis
5-year PFS, 41%	
5-year survival, 48%	
Mediastinal primary	
or	
5 Nonpulmonary visceral metastases	
or	
Poor markers (any of the following)	
AFP > 10,000 ng/mL	
HCG > 50,000 IU/L (10,000 ng/mL)	
LDH > 10 × upper limit of normal	

AFP, α-fetoprotein; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; N, normal; PSF, progression-free survival.

Adapted from International Germ Cell Cancer Collaborative Group: International Germ Cell Consensus Classification: a prognostic factor-based staging system for metastatic germ cell cancers. J Clin Oncol 1997;15:594, with permission.

comparison between trials problematic. Second, most etoposide-containing regimens used in the United States (PEB, PE) administer a total of 500 mg/m^2 of etoposide (100 mg/m^2, days 1–5), whereas one European counterpart of these regimens administers 120 mg/m^2 on days 1 to 3, for a total of 360 mg/m^2.

Finally, the inclusion (or exclusion) of patients with advanced seminoma from good-risk trials has been inconsistent. IGCCCG data suggest that although seminoma is clearly a good-risk tumor, it should be evaluated in separate trials. In those series wherein individuals with advanced-stage seminoma were considered separately from NSGCT, platinum-containing regimens, including VIP (ifosfamide, cisplatin, and etoposide), PEB, EP, and VAB-6, result in roughly comparable survival rates of around 90%.[73]

Results of Clinical Trials in Patients with Good Prognosis

As discussed previously, etoposide may be substituted for vinblastine in the PVB regimen, resulting in an improvement in the toxicity profile, without loss of effectiveness. Using the Indiana University staging system the SECSG reported on a randomized trial of four cycles of PVB versus four cycles of PEB, with complete-response rates of 97% and 96%, respectively.[122] (Interestingly, the same study demonstrated PEB to be superior to PVB in the treatment of poor-prognosis advanced GCT patients.) A subsequent randomized trial by the SECSG demonstrated that in good-prognosis patients, three cycles of PEB are as efficacious as four cycles, with complete-response rates of 97% and continuous complete remission rates of 92% in either regimen.[123] The EORTC conducted a prospective randomized 2 × 2 factorial trial in IGCCC good-prognosis patients, which compared three versus four cycles of therapy as well as PEB administered over 5 days (cisplatin 100 mg/m^2 daily × 5 and etoposide 100 mg/m^2 daily × 5) or over 3 days, but with the same total dose (cisplatin 50 mg/m^2 on days 1 and 2, etoposide 165 mg/m^2 on days 1–3).[124] Three cycles of PEB were equivalent to four, and no difference was detected in outcome between the 3- and 5-day schedules. By contrast, a multicenter phase III trial randomized patients to the "Indiana regimen" (cisplatin 20 mg/m^2 days 1–5, etoposide 100 mg/m^2 days 1–5, and bleomycin 30 units days 1, 8, and 15 of each 21-day cycle) administered three times, versus four cycles of a regimen used by the MRC/EOTRC (cisplatin 100 mg/m^2 on day 1, etoposide 120 mg/m^2 days 1–3, and bleomycin 30 units on day 1 of each 21-day cycle). Although there was no statistically significant difference in response proportion between the two groups, overall survival was significantly better for those patients receiving the higher dose etoposide (Indiana) regimen, prompting the early termination of the study.[124] These studies have established three cycles of PEB using 100 mg/m^2 cisplatin and 500 mg/m^2 etoposide as the standard of care and as a benchmark for other good-risk GCT trials.

The relatively high incidence of clinically apparent pulmonary toxicity from bleomycin,[124] observed in as many as 20% of patients, and a small but real bleomycin-related death rate of 2% to 4% (albeit data are largely from the era before routine monitoring of respiratory function) has been the impetus behind the evaluation of regimens for good-risk GCTs that delete bleomycin.

A randomized study conducted at MSKCC compared standard therapy for GCT (three cycles of VAB-6) to four cycles of a two-drug regimen of etoposide and cisplatin (EP) in 170 good-risk patients as defined by the MSKCC risk criteria. Complete-response rates of 92% and 95% (not statistically significant) were observed in the EP and VAB-6 arms, respectively. Whereas patients treated with EP had significantly less emesis, magnesium wasting, neutropenia, and thrombocytopenia, relapse-free and overall survival were similar in both arms.

Although most investigators agree that three rather than four cycles of PEB are adequate in good-risk patients, the role of bleomycin continues to be debated, in part as a result of the heterogeneity of the risk assessment schemas and regimens used. Nevertheless, several published trials now support the inclusion of bleomycin in good-risk chemotherapy regimens. One study conducted by the

Eastern Cooperative Oncology Group (ECOG) compared three cycles of (U.S.) PE to the "benchmark" three cycles of (U.S.) PEB.[125] An interim analysis revealed an increased number of relapses, progressive disease, and likelihood of death for the two-drug combination (durable complete-response rate was 86% for PEB vs. 70% for PE), resulting in early termination of the study. Further, an EORTC study randomized 450 patients to four cycles of (European) PE or four cycles of (European) PEB, and found a significantly higher complete-response rate (95% vs. 87%) in the three-drug combination.[126] In aggregate, these data suggest that the deletion of bleomycin results in inferior outcomes in a three-cycle, good-risk regimen. Whether four cycles of (U.S.) PE is adequate therapy, however, is unknown—of the two previously noted trials using four cycles of PE as a comparator, the EORTC trial used European PE, containing less etoposide,[126] and the MSKCC trial compared PE to a nonbenchmark regimen, VAB-6.[127] In general, the current consensus is that three cycles of PEB or four cycles of EP (with 500 mg/m^2 of etoposide per cycle) are equivalent in terms of efficacy. The decision to eliminate bleomycin in lieu of treatment with a fourth cycle must be weighed against the potential for greater hematologic toxicity and time required to deliver the fourth cycle.

Carboplatin, a cisplatin analogue with less nephrotoxicity and neurotoxicity than cisplatin, has also been evaluated in good-risk GCTs. By contrast, the substitution of carboplatin for cisplatin in the two-drug regimen EP is inferior, as suggested by the results of a randomized trial of four cycles of EP given every 3 weeks versus four cycles of EC (etoposide plus carboplatin) given every 4 weeks, in good-risk patients (MSKCC criteria). Although the complete-response rates were similar (88% to 90%), unfavorable events (incomplete response or relapse) were more common in the EC arm (24% vs. 13%; $P = 0.04$), and EP patients had a superior event-free and relapse-free survival (87% vs. 76%).[81] Whether or not this difference was due to the difference in frequency of administration of each regimen (every 3 weeks for EP vs. every 4 weeks for EC) was addressed by an MRC/EORTC study, which randomized patients to receive either four cycles of European PEB (in which bleomycin was given on day 1 of each cycle only, as opposed to the usual three times per cycle) given every 3 weeks, or the same regimen, also given every 3 weeks, with the substitution of carboplatin for cisplatin. The carboplatin regimen was inferior with respect to the complete-response rate (87.3% vs. 94.4%) and with respect to 3-year survival (90% vs. 97%).[128] This combination of studies, therefore, has definitively demonstrated that carboplatin results in inferior outcomes for good-risk GCT patients.

In summary, although there has been a difference in the classification schemas used to identity good- versus poor-prognosis advanced GCT patients, all are able to identify a good-prognosis subset of patients, in whom the likelihood of a complete response to chemotherapy is in the 90% to 95% range and in whom long-term survival can be expected in 85% to 90% of patients. Three cycles of PEB or four cycles of PE are currently deemed acceptable approaches in this group of patients. There is no role for substituting carboplatin for cisplatin.

Poor-Risk Advanced Germ Cell Tumors

The outlook for poor-risk patients is grim, with only 38% to 62% of patients achieving a complete response and more than 25% of patients dying of the disease within 2 years of diagnosis.[129] Thus, whereas the major concern in good-risk patients has been the reduction of toxicity, the major objective of clinical investigation in poor-risk patients continues to be an improvement in efficacy, with less concern for reducing toxicity. An equally important goal has been the accurate pretreatment identification of poor-risk patients, so that patients are not incorrectly classified as poor risk, and thereby exposed unnecessarily to the toxicity of these regimens. The use of post-treatment variables, in particular the rate of decline of the serum markers AFP and HCG, may also serve to identify the patient for whom standard induction chemotherapy is destined to fail.[83]

Results of Clinical Trials in Patients with Poor Prognosis

The results of clinical trials conducted in patients with poor-risk GCTs have been summarized.[84] Until recently, most trials have included only small numbers of patients in single-armed phase II trials, rendering generalized interpretation difficult. The extraordinarily wide range of reported complete-remission rates (38% to 92%) is probably more a reflection of the diversity of the risk assessment schemas used than of actual differences in efficacy of the regimens themselves.

Clinical trials in poor-prognosis patients have by and large relied on either or both of two approaches. The first has been to exploit agents that have been demonstrated to be efficacious in the salvage setting, such as etoposide, paclitaxel, and ifosfamide, whereas the second has evaluated the role of dose escalation.

The earliest study which specifically identified therapy outcomes in a poor-risk patient population was the SECSG study that randomized GCT patients to receive four cycles of either PVB or PEB. A subset analysis of poor-risk patients demonstrated that PEB resulted in a higher complete-response proportion than PVB (68% and 38%, respectively, using the Indiana risk criteria).[106] This study established four cycles of PEB as a benchmark against which other high-risk GCT trials could be compared.

The appreciation of the activity of etoposide in the treatment of GCT (as in the PEB regimen) led to several trials where etoposide was used in an induction regimen. The Southwest Oncology Group (SWOG) undertook a randomized comparison of standard PVB to a PVB regimen in which etoposide was substituted for bleomycin (termed VPV) in high-risk patients. This study demonstrated that the inclusion of etoposide did not improve the frequency of disease-free status (disease-free survival; 64.5% with PEV vs. 73% with PVB).[13] Furthermore, some investigators have challenged the validity of the risk criteria used, given the high disease-free survival rate obtained with PVB.[128] The observation that the combination of VIP could salvage some patients for whom induction therapy with PVB or PEB had failed led to the use of the VIP regimen as primary induction therapy for poor-risk GCT patients.[85] A randomized trial comparing standard induction therapy (PEB) with the VIP regimen normally used in the salvage setting (see Table 90-8) found no statistically significant difference in patients rendered disease-free (51% vs. 57%), in relapse rate (17% vs. 14%), or in overall survival or progression-free survival (53% vs. 56%).[86] Furthermore, the VIP regimen was associated with increased (primarily hematologic) toxicity, and thus cannot be routinely recommended as initial therapy for high-risk patients.

The apparent dose-response relationship for cisplatin in the 75- to 120-mg/m^2 range in GCT patients[87] prompted several trials that tested the hypothesis that further dose escalation would result in improved efficacy in the high-risk subset. A randomized comparison of a high-dose regimen (consisting of etoposide added to PVB with twice the standard dose of cisplatin) to standard PVB therapy for the therapy of high-risk GCT patients was undertaken by the National Cancer Institute.[131] Although this trial demonstrated an apparent improvement in outcome (albeit with significant ototoxicity), a subsequent randomized trial conducted by the SECSG and the SWOG comparing PEB to cisplatin dose-intense PEB in high-risk patients failed to demonstrate increased efficacy.[86]

Another approach tested in poor-risk GCT patients has been the use of alternating non-cross-resistant therapy. The EORTC compared four cycles of PEB to four cycles of alternating cycles of PEB and PVB, and could show no advantage to the alternating regimen.[132] A similar approach developed by the MRC/EORTC consisted of initial treatment with bleomycin, vincristine, and cisplatin (BOP) followed by a VIP-like regimen. Preliminary results from a randomized trial comparing PEB to BOP-VIP suggested no difference in

outcome (complete-response rate, 59% and 58%; durable complete response, 50% and 52%).[133] Several other alternating regimens have been studied, including POMB-ACE, which alternates cisplatin, vincristine, methotrexate, and bleomycin (POMB) with actinomycin, cyclophosphamide, and etoposide (ACE). This regimen has been reported to yield a survival higher than expected in IGCCCG-defined poor-risk patients (75% at 3 years, vs. 50% expected), and in patients with primary mediastinal disease (73% 5-year survival vs. 40% expected),[134,135] A second regimen, BOP-CISCA-POMB-ACE, which alternates bleomycin, vincristine, and cisplatin (BOP); cisplatin, cyclophosphamide, and doxorubicin (CISCA); cisplatin, vincristine, methotrexate, and bleomycin (POMB); etoposide, dactinomycin, and cyclophosphamide (ACE) has been reported to result in a 3-year progression-free survival greater than expected in the IGCCCG-defined poor-risk patients (67% vs. 50%). A recent European study evaluated a multidrug combination known as C-BOP/PEB (cisplatin, vincristine, bleomycin, and carboplatin, followed by one cycle of vincristine and bleomycin and three cycles of PEB in both intermediate- and poor-risk patients. In a study of 66 patients, 29 of whom were poor risk, the complete-response rate was 68.2% and the 1-year progression-free survival was 82% (95% confidence interval 72.5% to 91.1%).[136] These encouraging results merit prospective evaluation versus PEB × 4 in appropriately matched patients.

The demonstration of the efficacy of high-dose chemotherapy (HDCT) with autologous hematopoietic stem cell support in the salvage treatment of relapsed or cisplatin-insensitive GCT formed the basis for treatment of selected high-risk GCT patients with HDCT earlier in their course, as part of their induction therapy, rather than reserving it as salvage. During the same time period, carboplatin had been shown effective in the treatment of GCT, first as single-agent salvage therapy[137] and then in combination with etoposide and bleomycin as induction therapy for poor-risk NSGCT.[138] These observations, along with the potential for dose escalation with carboplatin, led to its use in dose-intensity trials for high-risk tumors as well. In these trials, patients generally received one to two cycles of standard induction therapy followed by HDCT. Reasonable complete-response rates of 56% to 70%, and durable complete-response rates of 46% to 64% have been described.[139] Several phase II trials and a retrospective analysis comparing poor-risk patients to historical controls suggested that first-line HDCT is well tolerated and initially suggested that this approach may confer a potential survival advantage in poor-risk patients when compared with historical controls treated with standard therapy.[140–143]

To address this question an intergroup study comparing two cycles of PEB followed by HDCT with tandem SCT with four cycles of PEB alone as first-line therapy for patients with poor-prognosis GCT was conducted. Seventy-nine percent of the 219 patients enrolled had IGCCCG poor-risk disease, whereas 21% had intermediate-risk disease. Overall 2-year survival was 68% in the poor-risk cohort and 84% in the intermediate-risk cohort. No difference in overall survival was detected comparing the PEB × 4 group versus the PEB × 2 plus HDCT. Subset analysis of the kinetics of tumor markers revealed a relationship between the degree of change of tumor markers to overall outcome. Kinetics of marker change were defined as "satisfactory" (a decline in elevated markers to normal by the start of cycle 3 or a decrease with a half-life ≤7 days for AFP and ≤3.5 days for β-HCG) versus "unsatisfactory" (half-life of >7 days for AFP or >3.5 days for β-HCG). In this analysis, time to treatment and overall survival were greater in the "satisfactory" arm (63% 1-year durable complete responses vs. 49% [unadjusted *P* value 0.02]). Further, although overall survival at 2 years was superior in the "satisfactory" decline group (83% vs. 68%; $P = 0.03$), there was no difference in this outcome comparing standard therapy with PEB × 4 with the high-dose approach.[128] The results of this trial suggest that there is no benefit to the use of HDCT with stem cell transplantation as induction therapy in high- or intermediate-risk patients, although its use in the salvage setting continues to be defined.

To summarize, a review of available data suggests that there is currently no evidence that any approach other than PEB × 4 is appropriate for poor-risk patients (Fig. 90-9). Every effort should be made to enroll and treat patients with poor-prognosis GCT on clinical trials.

Unique High-Risk Germ Cell Tumors: Brain Metastases and Extragonadal Disease

A mediastinal primary or the presence of nonpulmonary visceral metastasis in patients with NSGCT defines high-risk patients in the IGCCCG Consensus Risk Classification. This is corroborated by a review of nearly 800 patients by the MRC, which has reported 3-year survivals for 86 patients with liver, bone, or brain metastases of 52%, compared with a 3-year survival of 89% in 709 patients without metastases at one of these sites.[42] Two clinical scenarios that warrant special consideration are those involving extragonadal primary tumors and GCT brain metastases.

Extragonadal Germ Cell Tumors

As discussed previously, it is generally accepted that extragonadal GCTs are a consequence of malignant transformation of residual midline germinal elements, generally found in the retroperitoneum or mediastinum. From 1% to 5% of GCTs are of extragonadal origin, and most but not all occur in men. As previously noted, all patients with extragonadal GCT should undergo the standard evaluation for GCT patients, including bilateral testicular ultrasonography to rule out an unsuspected testicular primary.

Extragonadal GCT of nonseminomatous histology appears to be associated with Klinefelter's syndrome. In one series of 22 consecutive patients with nonseminomatous extragonadal GCT, 18% were found to have karyotypically defined Klinefelter's syndrome. Hematologic malignancies have been observed to develop in approximately 10% of persons with the disease, usually within 2 years.[144] A common origin of the two malignancies is postulated based on a shared karyotypic abnormality (i12p).[145]

Seminomas account for approximately 30% to 40% of all these tumors. They seem to be somewhat slower growing than their nonseminomatous counterparts, and approximately 60% to 70% of patients with mediastinal seminoma will have metastases at the time of diagnosis (compared with 85% to 90% in nonseminomatous extragonadal GCT).[10] Although the lungs and intrathoracic structures are the most common site of metastases, these tumors not uncommonly will demonstrate osseous metastases. Extragonadal seminoma, like its counterpart of gonadal origin, is exquisitely radiosensitive, and approximately 60% of patients can be cured with radiation therapy. Cisplatin-based chemotherapy, however, is generally considered to be the superior modality, with complete-response rates of 67% to 89% reported.[10]

Nonseminomatous extragonadal GCTs make up 60% to 70% of all extragonadal GCTs. In contrast to extragonadal seminoma, local treatment with radiation therapy has been unsuccessful and chemotherapy is far less efficacious. A compilation of 158 cases of nonseminomatous extragonadal GCT noted an overall response to cisplatin-based therapy of 54% (range, 38% to 68%), and a long-term disease-free survival rate of 42% (range, 22% to 58%).[33] The optimal chemotherapy regimen is undefined; certainly these patients are in the poor-prognosis category, and when possible should be enrolled on appropriate clinical trials. Mediastinal NSGCTs frequently demonstrate resistance not only to primary but also to salvage therapy. A multivariate analysis of prognostic features in 283 heavily pretreated GCT patients subsequently treated with HDCT as salvage therapy demonstrated that a mediastinal site of origin clearly imparted an adverse prognosis.[146] Surgical resection of mediastinal tumors either before or after chemotherapy can lead to beneficial outcomes and should be attempted whenever possible.[147]

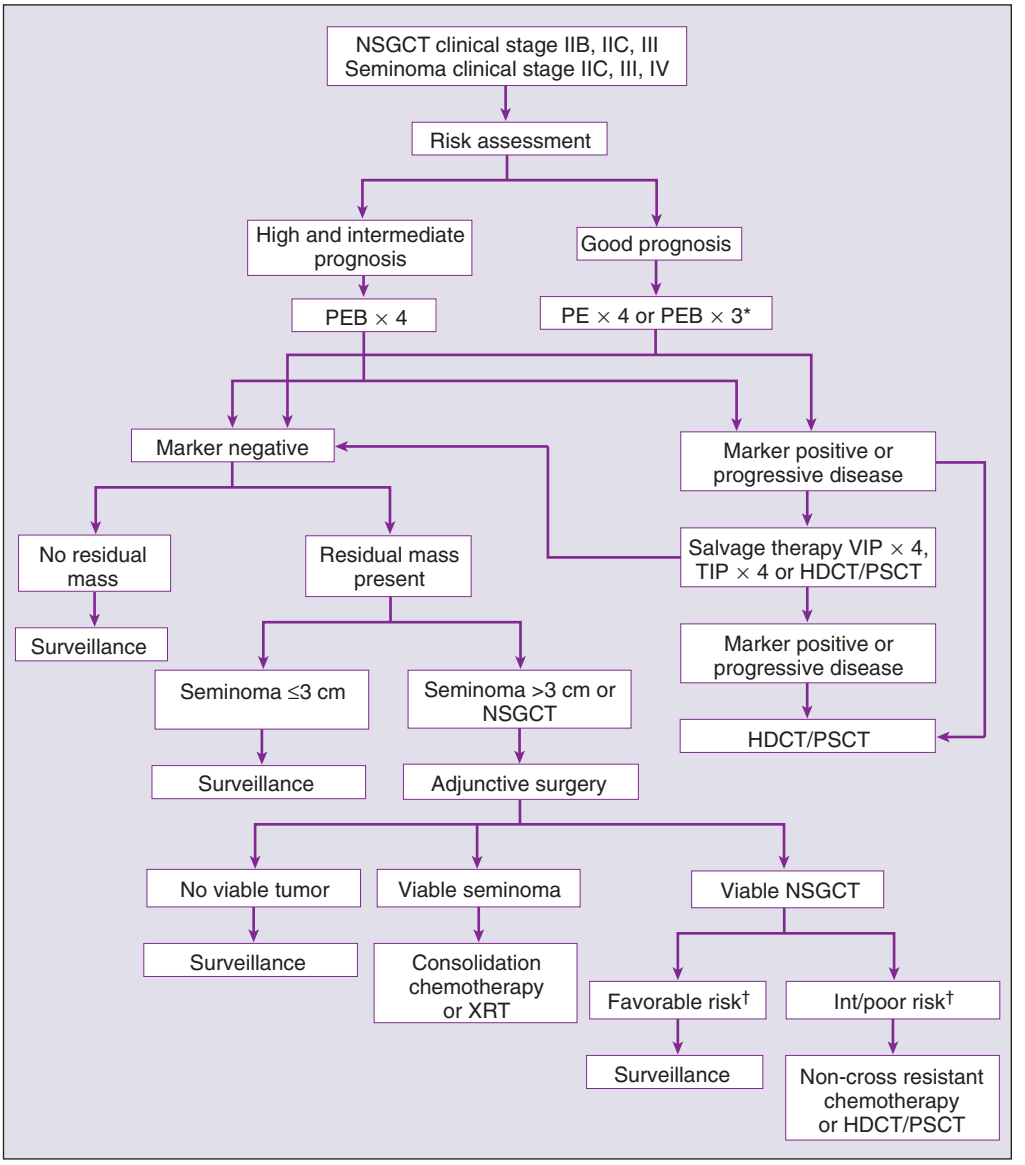


Figure 90-9 • Treatment algorithm for patients with advanced germ cell tumor. HDCT/PSCT, high-dose chemotherapy/peripheral stem cell support. *At UCSF, three cycles PEB unless pulmonary toxicity. †Adverse factors: >10% residual viable cells, incomplete resection, IGCCCC risk group per Table 90-8. Favorable risk, 0 adverse factors; intermediate risk, 1 adverse factor. Poor risk, ≥2 adverse factors.

Brain Metastases

Brain metastases occur in fewer than 5% of patients with GCTs, most frequently in patients with choriocarcinoma or yolk sac elements. The presence of brain metastases is a marker of a particularly poor prognosis. An MRC series of 795 patients included 16 patients with central nervous system involvement, in whom the 3-year survival was 37%.[42] Before the advent of etoposide-based therapy, the early data published by the Indiana University group reported an overall survival of only 31.8% for patients with brain metastases and suggested that the brain was a sanctuary from PVB and that a subset of patients could be cured if aggressive multimodality therapy using surgery, radiation therapy, and chemotherapy was used.[148] Patients with brain metastases as part of their initial presentation have a better prognosis than those who develop brain metastases.[149] Other centers have advocated combined chemotherapy and radiotherapy, with long-term disease-free intervals,[150] or high-dose intravenous methotrexate, along with intrathecal methotrexate, although these approaches have not superceded the de facto standard of care of the combination of radiation therapy and chemotherapy.[151] Taken together, these data make it reasonable to conclude that unlike most malignancies, the presence of GCT central nervous system metastases should not preclude therapy with curative intent.

RISK ASSESSMENT OF RESIDUAL MASSES AFTER CHEMOTHERAPY: THE NEED FOR ADJUNCTIVE SURGERY

The advent of platinum-based chemotherapy has resulted in complete responses in a large percentage of patients with advanced GCT. Furthermore, a number of patients with partial responses can be converted surgically into complete responders. However, surgery is unnecessary in some of these patients, because their postchemotherapy residual masses may not reveal any malignant cells on histologic review. Thus, the identification of patients likely to have residual malignancy is of importance.

Residual Masses in Seminoma

Residual masses after systemic therapy for advanced seminoma are observed in 60% to 85% of patients, whereas 15% to 45% of patients will have normal radiographic evaluations after systemic therapy.

Residual masses after chemotherapy for advanced seminoma most typically result in obliteration of radiographic planes identified on CT. These findings usually represent a dense scirrhous response that merges with the great vessels and other retroperitoneal structures.[152] These "masses" are in fact usually not discrete or well defined, generally are not easily resected, and occur in 40% tp 60% of patients. Only 20% to 30% of patients will have discrete residual masses, which are usually larger than 3 cm and in fact resectable.[152,153] The morbidity associated with attempted resections of these masses, in particular the scirrhous, ill-defined type, has prompted an evaluation of features predictive of residual active seminoma.

Motzer and colleagues[152] made the observation that nearly half (42%) of patients with residual abnormalities larger than 3 cm were found to have viable malignancy, whereas no patient with a normal imaging study or residual mass smaller than 3 cm who then underwent exploratory surgery was found to have viable tumor. The authors concluded that seminoma patients with residual abnormalities smaller than 3 cm should not undergo surgical exploration, whereas attempts to excise masses larger than 3 cm should be undertaken. Other groups have maintained a more conservative posture, performing serial CT scans and performing surgery only at the point of progressive disease.[153] More recently, FDG-PET has been shown to be a useful predictor of viable tumor in postchemotherapy masses in patients with pure seminoma, correctly predicting 96% of residual masses ≤3 cm, and 100% of masses >3 cm. This study demonstrated a superior positive predictive value (100% vs. 50%) and negative predictive value (97% vs. 91%) compared with assessment of residual mass size (≤3 cm or >3 cm).[59]

A prospective study of 56 FDG-PET scans of 51 patients who were followed for clinical recurrence or who underwent surgical resection demonstrated that in all 19 cases with residual lesions >3 cm and confirmed active disease, the PET scan was positive in all 7 patients with residual disease and was negative in all 12 patients without. Further, no false positives or false negatives were reported in tumors this size. Other groups suggest caution in the use of PET scan in these settings based on a positive predictive value for PET scans of only 67%, whereas PET scans that were positive corresponded to patients whose surgical specimens demonstrated only fibrosis, necrosis, or inflammation.[154]

Residual Masses in Nonseminoma

As many as 60% to 70% of patients with advanced-stage NSGCT will be rendered clinically free of disease with platinum-based therapy, and an additional 10% to 20% of patients observed to have residual masses after systemic therapy can be subsequently rendered free of disease surgically. Most investigators agree that, except in rare circumstances, adjunctive surgery is not indicated in the presence of persistently elevated serum tumor markers. (The role of surgery in marker-positive patients is reviewed in the section on salvage therapy.) By contrast, the recommendations for adjunctive surgery in postchemotherapy NSGCT patients in whom serum markers have normalized vary considerably.

Viable malignant GCT cells are found in the surgical specimens of approximately 15% of patients with residual masses after chemotherapy, although some series have reported residual malignancy in as few as 3% of patients.[122] Teratoma or fibrosis and necrosis are found in approximately 50% and 35% of patients with residual masses, respectively.[155,156] It is fairly clear that the histology of resected postchemotherapy masses carries significant prognostic implications. Patients with residual carcinoma in their specimens have an overall long-term survival of approximately 60% to 70%, whereas survival for patients with necrosis/fibrosis is in the 85% to 90% range.[157–159] The presence of viable GCT cells in completely resected specimens has been termed a "surgical complete response." A recent retrospective report from an international study group of 238 patients with viable GCT cells in resected postchemotherapy masses indicated 5-year progression-free survival and 5-year overall survival rates of 64% and 73%, respectively. Three factors were reportedly associated with improved progression-free and overall survival: complete resection of residual masses, fewer than 10% malignant cells in the resected specimen, and initial IGCCC good-risk group classification. These data suggest that complete and aggressive resection of residual masses is warranted. Interestingly, for patients with residual cancer in their resected specimens, in this nonrandomized retrospective analysis, an improved 5-year progression-free survival (69% vs. 52%) was seen in patients who underwent postoperative chemotherapy compared with postoperative surveillance alone. Overall survival was not statistically different, perhaps because those patients who underwent surveillance received adequate salvage therapy at the time of relapse.[160] Whereas teratoma in the residual mass may be histologically benign, the rationale for aggressive and complete early debulking of teratomas includes (1) the risk of local complications as well as growth into unresectable lesions, (2) the risk of late recurrence, and (3) the risk of malignant transformation into non-germ-cell malignancies such as sarcomas and carcinomas.[16] The association of teratoma and late relapse is discussed in the section on late consequences of therapy. Because the diagnosis of residual teratoma is usually made by excisional biopsy, it has not been possible to compare the outcome of patients with known teratoma that has not been resected with that of patients in whom the teratoma was excised. Nonetheless, most series have reported an overall survival of 85% or higher in those patients who were found to have teratoma in their postchemotherapy resected specimen.[155]

Preoperative variables have been evaluated for their usefulness in predicting postoperative histologic diagnosis (and potentially as a means of deriving guidelines for patients in whom chemotherapy after resection could be avoided).[155,156,161] Several series have identified the size of the residual retroperitoneal mass, size of prechemotherapy mass, and/or the extent of shrinkage as predictive factors able to identify a group of patients at lower risk for postchemotherapy teratoma or malignancy. Some[156] but not all[155,161] studies have demonstrated that the presence of teratomatous elements in the prechemotherapy biopsy specimens is predictive of teratoma or malignancy in the postchemotherapy specimen. Prechemotherapy serum markers (high LDH, low AFP) were also identified by logistic regression as predictors of an increased likelihood of finding only necrotic debris.[155] Despite the predictive value of some of these variables, no single variable or group of variables seems to be consistently sufficiently predictive to allow the identification of patients in whom resection can be avoided. Thus, two separate studies have reported the risk of a false-negative prediction (the likelihood of finding residual carcinoma or teratoma in patients predicted to have only necrosis/fibrosis) to be approximately 20%.[155,162] The identification of patients in whom postchemotherapy resection can be avoided remains controversial.[163] When postchemotherapy lymphadenectomy is undertaken, bilateral (non-nerve-sparing) RPLND is recommended.

Most investigators have recommended the resection of residual pulmonary nodules. From 10% to 30% of specimens have been reported as malignant, teratoma has been observed in 26% to 60%, and the fraction of specimens containing only necrosis and fibrosis has ranged from 14% to 64%.[163,164] In some series, as many as one fifth of patients undergoing resection of pulmonary nodules required bilateral thoracotomies. In a series of 39 patients undergoing 47 procedures, the pathology at resection could not be correlated with prechemotherapy size of the nodule, with size of residual nodule, or with extent of shrinkage.[155] Similarly, in the same report the pathology of residual mediastinal masses in 17 patients was not associated with prechemotherapy size or with percentage of shrinkage, although the size of the residual mass seemed to be more strongly correlated with histology.[155] Furthermore, in patients who undergo resection of more than one tumor site, several studies have suggested that histology from the earlier procedure (e.g., RPLND) will be predictive of the histology from the later procedure (e.g., thoracotomy) only 53% to 65% of the time.[164–166] Thus, although as few as 10% of residual

pulmonary nodules may harbor malignancy, the 25% to 60% incidence of teratoma, and the inability to predict which nodules will contain only fibrosis and necrosis, mandates strong consideration of surgical removal of all postchemotherapy residual masses.

SALVAGE THERAPY

Whereas 80% of patients with NSGCT can currently be cured with platinum-based therapy, 20% will ultimately die of their disease because of either failure to achieve a complete response with induction therapy or relapse after becoming disease-free with primary therapy. Before the initiation of salvage therapy, the diagnosis of relapsed or primarily refractory GCT must be clearly established. In particular, false-positive serologic data and the detection of falsely positive radiographic studies of the chest, as described previously, must be ruled out. Persistent or slowly growing masses, particularly in the absence of serologic progression, may represent benign teratoma.

Chemotherapy

Etoposide and ifosfamide are single agents with demonstrated activity in the salvage therapy of GCT, with response rates of 20% to 50% in patients previously treated with cisplatin, although currently they are rarely used as monotherapy. Particularly intriguing is a report that oral etoposide has a response rate of 28% in patients with refractory GCT whose prior combination chemotherapy treatment included etoposide.[167]

Salvage combination chemotherapy regimens have generally included etoposide, ifosfamide, or both. Before the acceptance of etoposide as a standard agent in primary induction therapy, etoposide and platinum-containing regimens resulted in long-term disease-free survival of approximately 20%.[168] Ifosfamide-containing salvage regimens for patients previously exposed to etoposide have either substituted vinblastine for etoposide (VeIP), with approximately 30% to 40% of patients achieving a complete response, but continued to utilize etoposide if the patient had been previously treated with vinblastine,[169] or simply continued to use etoposide (VIP), regardless of prior etoposide treatment (see Table 90-7). The use of etoposide combined with ifosfamide (as in the VIP regimen; see Table 90-7) resulted in a complete-response rate of 33% (including surgical resection of residual masses) in patients previously treated with PVB.[130,170]

Indiana University also reported on the results of salvage VeIP in 84 patients with refractory GCT, 77 of whom had been previously treated with etoposide-containing regimens. The overall complete response rate was 52%, and the authors reported a 33% long-term disease-free survival with a median follow-up of 17 months.[170] The MSKCC experience with salvage therapy consisting of the VAB-6 regimen, EP, or other cisplatin-based regimens suggested roughly equal complete-response rates of 25% to 36%, regardless of regimen used, with an overall durable complete-response rate of 23%.[171] In this setting, VeIP results in an 83% complete-response rate, and 54% of patients remain alive and continuously disease-free. For patients with relapsed or recurrent seminoma this is clearly the most appropiate initial salvage therapy.[172] More recently, a salvage regimen using paclitaxel, ifosfamide, and cisplatin has demonstrated significant activity, resulting in complete responses in 70% of patients who had experienced a relapse after a prior complete response to standard regimens.[173] In this series 50% of patients with a late relapse (>2 years) GCT achieved a complete response.[174] The combination of gemcitabine and oxaliplatin has demonstrated significant activity in patients with platinum-refractory disease, with a partial response rate of better than 40%.[175] Another new regimen consisting of epirubicin plus cisplatin resulted in complete responses in 30% of GCT patients who had received at least one prior cisplatin-containing regimen.[176]

Taken together these studies suggest that salvage chemotherapy has moderate to good activity in patients with a relapse after treatment with curative intent. The optimal salvage regimen is not established, and direct comparison of regimens is precluded by the diverse patient selection criteria of prior studies.

High-Dose Chemotherapy

The use of HDCT with autologous bone marrow transplant or autologous peripheral stem cell transplant (PSCT) as salvage therapy for relapsed or refractory GCT has been extensively explored.[177] The rationale for this approach includes the fact that GCTs are extremely chemosensitive and therefore potentially may demonstrate a dose-response relationship; that GCT patients are generally young and otherwise healthy, and can withstand the rigors of HDCT; and that bone marrow involvement with metastatic GCT is distinctly uncommon. Initial trials with HDCT used cyclophosphamide, etoposide, or thiotepa. Cisplatin, though certainly the most active single agent in the treatment of GCT, is poorly suited for dose intensification because of neurotoxicity, ototoxicity, and nephrotoxicity. Carboplatin, by contrast, is better suited for use in HDCT regimens, because (1) its major toxicity is hematopoietic and (2) it is an active agent in the treatment of germ cell neoplasms. A high-dose carboplatinum and VP-16 regimen pioneered by Indiana University and Vanderbilt University resulted in an overall disease-free survival rate of 60% and has become a skeleton that other investigators have modified, often by the addition of an alkylating agent such as cyclophosphamide or ifosfamide.[178] These results compare favorably with those observed after standard-dose salvage chemotherapy with VeIP and suggested that early HDCT may be beneficial in patients with relapsed GCTs.

Several novel HDCT salvage regimens have been reported, including induction with paclitaxel, ifosfamide, and cisplatin therapy followed by high-dose carboplatin, etoposide, and thiotepa,[179] as well as sequential dose intensive paclitaxel, ifosfamide, carboplatin, and etoposide.[180] From 25% to 50% of patients seem to achieve durable remissions, so that the curative potential of HDCT as salvage (and frequently third-line) therapy is fairly well established. However, preliminary reports from a randomized trial of four cycles of salvage VIP/VeIP compared to three cycles of VIP/VeIP followed by a single treatment of HDCT indicated no difference in response rates. Whether this trial will translate into survival differences, or if more conventional double ("tandem") treatments with HDCT/PSCT are required, remains to be determined.[181] Treatment-related mortality of HDCT/PSCT has declined over the years to levels usually less than 5% to 10%. Nevertheless, HDCT in this setting remains imperfect.

Surgery

In general, resection of residual masses after chemotherapy in NSGCT patients should be reserved for patients in whom serum tumor markers have normalized. Nonetheless, this approach has recently come under question. Several centers have reported on the results of surgical resection of solitary residual masses in highly selected patients with persistently elevated serum markers who were believed to be refractory to platinum (after either primary or salvage therapy). In one series of 15 patients, nearly half (7) obtained lasting complete remissions. The clinical features associated with a likelihood of successful outcome included a retroperitoneal site and/or an elevated AFP only (all 5 patients with elevated preoperative HCG levels subsequently relapsed).[182] A second report indicated a 37% "cure" rate in patients undergoing resection of residual masses in the setting of elevated serum markers.[183] High concentrations of tumor markers within residual tumors, and not systemic disease, may account for such findings.[184] Absolute conclusions regarding the role of salvage surgery cannot be drawn from such a small number of patients, and it must be borne in mind that this is a highly select group of patients. For example, the patients reported in one series accounted for only 4% of all patients who failed to achieve a complete response to

induction therapy at that institution over a 10-year period.[182] Nonetheless, these data suggest that in very carefully selected chemorefractory patients, surgical resection of residual masses, despite the presence of positive serum markers, may be appropriate.

RISK ASSESSMENT IN PATIENTS WITH RELAPSED OR REFRACTORY GERM CELL TUMOR

An analysis of the clinical features of responding versus nonresponding patients may serve to identify the subset of patients likely to benefit from each one of the salvage modalities discussed previously, as well as to identify those patients suited for novel therapeutic approaches.

Most clinical trials utilizing standard-dose salvage chemotherapy have observed that survival or response (or both) are considerably lower in primarily refractory patients, compared with patients who have had a prior response to chemotherapy.[169] MSKCC reported on 124 patients who were treated with salvage therapy. Patients who had relapsed after a prior complete response had a 2-year survival rate of 36%, compared with a 9% survival rate in patients with prior incomplete response to induction chemotherapy.[171] Similarly, the median survival for relapsed GCT patients treated with VIP at Indiana University was 10.7 months if the previous best response to chemotherapy was either an incomplete response or a complete response of less than 2 months' duration, compared with 26 months in patients who had experienced previous complete responses lasting more than 2 months.[169] Other features observed to be predictive of improved survival or response (or both) in some[169,171] but not all series[185] include lower tumor burden. Patients with extragonadal primary sites do poorly.[171] In a review of 203 patients treated with VIP or VeIP at three institutions, four independent prognostic factors have recently been identified: (1) incomplete response at induction, (2) extragonadal origin, (3) presence of lung metastases, and (4) elevated serum marker level (HCG > 1000 IU/L, AFP > 1000 ng/mL). Patients with either marker elevation or extragonadal origin and at least one other poor prognostic feature had a complete response rate of 4%, with no long-term cures, whereas patients with testicular tumors and nonelevated markers were observed to have a complete-response rate of 62% and a 3-year survival of 43%.[186]

HDCT seems to be able to overcome primary cisplatin resistance in some patients, although patients with refractory mediastinal GCTs do not seem to benefit from this approach. In the series of 40 patients with recurrent or refractory germ cell cancer treated with HDCT and autologous bone marrow transplant at Indiana University, 3 of 6 patients who obtained prolonged remissions were primarily refractory to cisplatin, whereas none of the 11 patients with extragonadal GCT obtained a complete remission.[170] Other centers have reported a complete-response rate of approximately 15% in platinum-refractory patients.[187] A multivariate analysis of risk factors in 310 patients treated with HDCT as salvage therapy at four centers in the United States and Europe reported that mediastinal NSGCT, primary platinum resistance, progressive disease before HDCT, and high HCG levels before HDCT (>1000 IU/L) had independent (adverse) prognostic significance.[146] This risk assessment schema has held true in subsequent HDCT trials. In general, patients with more than two adverse features have a poor outcome, with virtually no patient achieving a continuous remission, with median survival limited to less than 1 year.[179,181]

Patients who experience disease progression after HDCT or other second-line therapy do poorly. They often receive further chemotherapy and/or surgery. No single-agent or combination has yet demonstrated significant activity in this subset of patients. Several studies have shown response rates of 11% to 26% for single-agent paclitaxel.[188] Other agents such as gemcitabine and oral etoposide have also been reported to produce responses of 7% to 19%.[189] Chronic oral etoposide has also been used as maintenance treatment for patients at high risk of relapse or progression after salvage chemotherapy and as a palliative regimen for those patients with cisplatin-refractory disease.[190] The ECOG evaluated the combination of paclitaxel-gemcitabine in patients whose disease had progressed after conventional salvage second-line therapy or during initial cisplatin-based therapy. A response rate of 21% was reported. Despite response proportions of 10% to 20%, in general, complete responses are rare in these settings, and long-term survival is uncommon.[190] Regardless of regimen, integration of surgery as a component of post-HDCT seems to be important.[191]

LATE CONSEQUENCES

Testicular cancer is a unique malignancy in its curability. Long-term follow-up of patients treated with chemotherapy suggests that the long-term relapse-free survival for complete responders is in the range of 80% to 90%.[192] Nonetheless, once a complete remission is obtained, patients remain at risk for two types of adverse late consequences: relapse, including contralateral primary testicular neoplasms, and toxicity from therapy.

Germ Cell Tumor Relapse

After obtaining complete remission, 8% to 15% of GCT patients will relapse, usually within the first 2 years after treatment.[192] The timing of a relapse does not seem to be dependent on histology, extent of disease, or induction regimen used.[193]

Late recurrences, defined as relapses occurring more than 24 months after diagnosis, have been reported in 1.5% to 4% of patients achieving a complete response.[193,194] The majority of late relapses occur longer than 5 years from diagnosis. Nearly 50% of relapses were retroperitoneal and 35% intrathoracic (including the mediastinum). Proposed mechanisms for late relapses include the development of second primary lesions, growth of an occult contralateral testicle tumor that is not affected by chemotherapy because of the blood-testicular barrier, the "reactivation" of quiescent carcinoma, or malignant degeneration of mature teratoma. The latter argument is the most favored, in that teratomatous elements are observed in either the orchiectomy or relapse specimens in most patients. Teratomatous elements were present in the orchiectomy specimens of 66% of 21 NSGCT patients with a late relapse reported in three series.[193–195] Nonetheless, this theory does not account for the 33% of late-relapse NSGCT patients who did not have teratoma described in their orchiectomy specimen (perhaps a microscopic focus was missed), or the seven pure seminoma patients in these series who experienced a late relapse.

A late relapse should be treated aggressively as a de novo malignancy. Outcomes in this setting are a reflection of the underlying histology at the time of relapse. Patients with teratoma who are treated surgically have excellent long-term outcomes, whereas the complete-response rates to chemotherapy alone for those who relapse with viable GCT are approximately 50%,[196] and the median survival in this setting is approximately 24 months according to one recent series.[174] Approximately 70% of seminoma patients can be rendered free of disease with chemotherapy, radiation, or both.

Contralateral Testicular Cancer

Contralateral testicular cancer (CLTC), including synchronous neoplasms, has been reported to occur in 2% to 4% of patients. A Dutch tumor registry study of 1909 men with testicular cancer, with a median follow-up of 7.7 years, reported a 15-year actuarial risk of a CLTC of 2.4%.[197] The overall excess risk compared with the general population was 40-fold. This study also demonstrated that testicular cancer patients treated with chemotherapy (primarily PVB) had a significantly reduced risk of a contralateral tumor, compared with

those patients treated with radiation therapy or surgery alone, and that this risk reduction lasted for a period of at least 5 years. Supporting data come from the MRC trial of adjuvant carboplatin versus radiation therapy in patients with stage I seminoma, in which two CLTCs (4%) occurred among the 573 carboplatin-treated patients, compared with 10 cases (11%) among the 904 (11%) patients treated with radiation therapy.[77] Nevertheless, preorchiectomy chemotherapy in clinical stage II patients fails to completely eradicate all of the intratesticular cancer[45] and fails to completely prevent the recurrence of a CLTC.[198] Thus, despite the potential for the reduction of risk of a CLTC by the use of chemotherapy, it must be assumed that all men with testicular cancer are at a small but real risk of a CLTC.

Early Detection of Recurrent Germ Cell Tumor

The optimal schedule for follow-up of patients with GCTs in complete remission varies from center to center but in general consists of intensive follow-up during the first 12 months after completion of therapy (physical examinations, determination of serum marker levels, and chest radiograph every 4 to 6 weeks, with CT scans every 2–3 months), and a slightly diminished intensity of follow-up with scans every 4 months during the second year after therapy. During the third through fifth years, this evaluation is generally undertaken every 6 months. After 5 years guidelines are less well established, although most authors agree that the incidence of late recurrence mandates lifetime follow-up with at least an annual history and physical evaluation as well as tumor markers and chest radiography. In the United States the National Comprehensive Cancer Networks (NCCN) has published consensus guidelines on the timing and type of testing required for surveillance.

Toxicity

Although the acute toxicities of the various therapeutic modalities used in the treatment of GCT are fairly self-apparent and well understood, only recently have the chronic toxic costs of treatment begun to be appreciated. Just as it was only in the 1990s that we learned of the toxic consequences of therapies used in the 1970s and 1980s, an understanding of the potential late consequences of today's therapeutic maneuvers must enter into risk assessment strategies, and accentuate the need for defining low-risk populations in whom less treatment is appropriate. The acute and chronic toxicities associated with surgery, radiation therapy, and chemotherapy have been reviewed and are summarized next.

Acute Toxicities

The acute surgical morbidity of orchiectomy is minimal, similar to that seen with simple inguinal hernia repair. The surgical complications specific to retroperitoneal lymphadenectomy (apart from the usual general complications of major intra-abdominal surgery), which include retrograde ejaculation, have been described earlier in this chapter. It is generally appreciated that RPLND after radiation therapy or combination therapy is more technically demanding, and probably more morbid, because these patients have not only been debilitated by chemotherapy or radiation therapy but are also patients with bulkier tumors, greater invasion of normal tissue, and greater likelihood of fibrosis and/or necrosis of both residual malignant and surrounding nonmalignant tissue.[199]

The acute toxicities from radiation therapy are largely dose-dependent and are less of an issue in seminoma patients who usually are treated with 25 to 30 Gy. Nonetheless, acute gastrointestinal toxicity consisting of nausea, vomiting, and diarrhea has been described in as many as 50% to 100% of patients.[200] Changes in total dosage, equipment used, and treatment planning have largely relegated radiation nephritis, pneumonitis, and bone marrow suppression to historical archives.

The acute toxicities associated with chemotherapy for GCT have been extensively discussed and largely represent the toxicities anticipated from the individual chemotherapeutic agents composing these regimens. Advances in antiemetic agent development, the use of growth factors, and improvement of supportive measures have mitigated some of these toxicities. Nonetheless, specific acute toxicities that bear mention in context of the chemotherapy used for the treatment of GCT include myelosuppression, renal toxicity, pulmonary toxicity, and neuromuscular toxicity.

Myelosuppression is mild to moderate in PVB-, PEB-, or EP-treated patients and somewhat more severe with VAB-6. Considerably more myelosuppression occurs with VIP than with PEB.[85] The importance of timely administration of chemotherapy on outomes for patients with metastatic disease, even in the face of myelosuppression, has been demonstrated.[201] The frequency of myelosuppression that occurs with this therapy, coupled with the necessity of on-time chemotherapy have led the NCCN to issue guidelines that recommend the prophylactic use of growth factors during chemotherapy for GCT.

Nephrotoxicity associated with platinum-containing regimens is perhaps less severe in this group of young, generally otherwise healthy men, than in an older group of oncologic patients. Nonetheless, the potential for chronic renal insufficiency (as well as for peripheral neurotoxicity and/or ototoxicity), the occasional incidence of urinary obstruction by tumor masses, and the need for platinum-containing salvage regimens (VIP or high-dose carboplatin) in as many as 20% of patients mandates careful monitoring of renal function. In general, as noted previously, carboplatin should not be substituted for cisplatin[129,140] unless mandated by impaired renal function.

A recent review of the literature suggests that the incidence of thromboembolic events in GCT patients undergoing chemotherapy can be as high as 8%, the vast majority of which (83%) are venous and 17% arterial. Liver metastases and the administration of high dose of dexamethasone as antiemetic therapy were identified as risk factors for the development of thromboembolic complications.[202] Despite this, prophylactic anticoagulation is not routinely administered to GCT patients receiving chemotherapy, given the relatively low overall incidence of thromboembolic events.

The acute pulmonary toxicity of bleomycin is manifested as noninfectious pneumonitis. As many as 20% of GCT patients treated with bleomycin-containing regimens will develop clinically apparent pneumonitis, and some published series report mortality rates due to pneumonitis of 3% to 4%. This is a dose-related complication, with a markedly increased incidence at cumulative doses greater than 400 units, although toxicity may occur at lower doses. Although the single-breath-diffusing capacity for carbon monoxide (DLCO) is the most common test used to monitor for pulmonary toxicity of bleomycin, its utility remains controversial.[203,204] Despite this controversy, it seems reasonable to assess each patient's pulmonary function clinically before each bleomycin dose and with a DLCO before commencing each new cycle. Measured DLCO may be expressed as a percentage of the predicted DLCO. Bleomycin-stopping rules using a greater than 10-point drop in this percentage have been recommended.

Neuromuscular toxicity associated with PVB has been attributed to cisplatin (peripheral sensory neuropathy, ototoxicity) and vinblastine (peripheral neuropathy, paralytic ileus, myalgias).[124] Peripheral sensory neuropathy and possibly autonomic dysfunction after cisplatin administration have been well described and will not be further addressed. A randomized comparison of PVB to PEB reported that 8% of patients receiving vinblastine, as opposed to 2% receiving etoposide, had severe abdominal cramping, and 14% of PVB-treated patients developed severe myalgias. Four percent of patients treated with PEB (as opposed to 11% of PVB-treated patients) developed severe paresthesias.[155] These data have resulted in the substitution of PEB for PVB as front-line therapy for advanced GCT. Nonetheless, because GCT patients continue to receive cisplatin-based therapy, and vinblastine is used in the salvage VeIP regimen, the potential for neuromuscular toxicity must be appreciated.

Chronic Toxicities of Radiation Therapy

The chronic toxicities associated with modern radiation therapy techniques for GCT are not known. Much of the available information regarding chronic toxicities is derived from late follow-up reports of patients treated on orthovoltage equipment, or using dated techniques, or both. Further, field size has direct implications on the nature of long-term toxicities observed. For example, the relative risk of myocardial infarction was increased 3.7-fold for patients who received mediastinal irradiation, whereas irradiation confined to the infradiaphragmatic areas was not associated with an increased risk of myocardial infarction.[205] Nonetheless, it must be assumed that the potential for some of these toxicities persists even with modern techniques. Although only minimal late nephrotoxicity and peripheral neurotoxicity have been described with radiation therapy,[206] more common late toxicities include chronic peptic ulceration in 5% to 10% of patients,[124] and of greatest concern, the development of delayed non-germ cell malignancies, which are discussed later. Several studies have suggested that testis cancer patients may be at an increased risk of developing a second, non-germ cell malignancy with long-term follow-up, although the relative impact of chemotherapy (vs. radiotherapy) is unknown.[197,207]

Chronic Toxicities of Chemotherapy

Renal, vascular, cardiac, neurologic, and reproductive toxicities as well as the risk of secondary malignancies compose the major long-term toxicities of chemotherapy. The chronic renal toxicity associated with cisplatin administration has been reviewed.[208] Most studies suggest that the acute deterioration of renal function observed after cisplatin may be irreversible and may persist beyond 12 months, although overt renal failure is generally not observed. Presumed renovascular hypertension has been observed in as many as 24% of men after cisplatin-based therapy, although it is not known if this is a consequence of chemotherapy or of increased surveillance.

Chronic vascular toxicities associated with chemotherapy include Raynaud's phenomenon, vascular occlusive events, and potential alterations in cholesterol metabolism. The most common vascular toxicity in GCT patients treated with chemotherapy is Raynaud's phenomenon, occurring in 23% to 49% of patients, usually within a year of treatment.[208] Although the exact cause in this setting is unknown, it seems to occur after treatment with bleomycin alone, and in combination with vinblastine, but the addition of cisplatin may double the incidence. Symptoms of Raynaud's phenomenon abate in approximately 50% of patients. The possibility of a relationship between platinum-based therapy and the less than 5% incidence of fatal major vascular occlusive events involving coronary, cerebral, or peripheral arterial circulation has been raised.[208]

The cardiovascular toxicities associated with chemotherapy agents are a cause of increased concern. Although previous follow-up studies of survivors of metastatic GCT have reported a low prevalence of major cardiac events, ranging from 0% to 3%, recent studies with longer median follow-up times have observed higher prevalence of major cardiac events of up to 6%, including myocardial infarction, angina pectoris, and myocardial ischema. In part this may be explained by the presence of an unfavorable cardiac risk profile (hypertension, obesity, and an elevated serum level of total cholesterol with a decrease of high-density lipoprotein cholesterol level), which has been observed in patients who have received chemotherapy.[209,210] The mechanism behind this increased cardiovascular risk profile is unknown. Although the use of PEB chemotherapy increases the risk of cardiovascular disease in general by approximately 1.5-fold, it does not seem to increase the risk of myocardial infarction. In contrast, PVB chemotherapy increases the risk of both cardiovascular disease and myocardial infarction.[205]

The chronic reproductive toxicities associated with chemotherapeutic treatment of GCT include oligo- and azoospermia and Leydig cell dysfunction.[208,211] The exact role of chemotherapy in this process is often unclear in the individual patient, because many men are hypofertile at the time of diagnosis of GCT, and as many as 80% will be oligospermic following orchiectomy.[208,212] Many men also demonstrate Leydig cell dysfunction after orchiectomy, indicated by elevated LH and FSH levels in the face of normal testosterone levels. In one series only 11% of men treated with orchiectomy alone or orchiectomy plus radiation therapy had residual oligospermia or Leydig cell dysfunction.[211] By contrast, combination chemotherapy seems to have a profound impact on spermatogenesis and Leydig cell function. The same study reported azoospermia in 27% and Leydig cell dysfunction in 86% of patients after treatment with chemotherapy. Sperm counts generally increase in the second and third year after therapy, and return to normal in about 50% of men. Approximately 25% of men are permanently azoospermic, and it seems that Leydig cell dysfunction may persist at 3 to 9 years after therapy.[213] These deleterious effects of chemotherapy on gonadal function seem to be similar for all regimens evaluated thus far. The only exception may be short-course (two cycles) PEB, wherein the gonadotoxic effects may be reversible in nearly all patients. Nonetheless, oligospermic and even azoospermic patients have been able to father children, and approximately one third of men treated with chemotherapy are able to father healthy children.[208]

Secondary Malignancies

In a Danish tumor registry group of more than 6000 patients, in which it is likely that most were treated with radiation therapy, the relative risk of second solid malignancies is approximately 2, with a latency period of 10 or more years.[214] A Dutch tumor registry study of 1909 patients with testis cancer confirmed these results, reporting a lifetime relative risk of a secondary malignancy of 1.6 and of all gastrointestinal malignancies (the most common site of origin of secondary solid malignancies) of 2.9, with the greatest risk (RR 6.5) occurring more than 9 years after therapy. The 15-year actuarial risk of developing a second cancer was 9.8%.[197] Although it has been suggested that the risk of leukemia in patients treated with modern radiation therapy techniques does not seem to be elevated,[185] the Dutch series suggests that the relative risk of leukemia after radiation therapy, though not as high as seen after chemotherapy, remains elevated at 5.2.[197] The latency period was shorter than with solid tumors, with the highest risk occurring at around 5 years. The combination of radiation therapy and chemotherapy resulted, in this study, in significantly higher risks of solid malignancies (RR 9.5) and leukemia (RR 66.7) than if either modality was used alone.[197] Kaldor and colleagues summarized the incidence of second malignancies in 17,730 testis cancer patients identified from 11 population-based tumor registries.[215] These authors found that survivors of testis cancer experienced 30% more tumors than expected for the general population, with a statistically significant increase in the likelihood of developing sarcoma (RR 3.0), melanoma (RR 1.8), non-Hodgkin's lymphoma (RR 2.7), and leukemia (RR 1.7). No information regarding the type of treatment delivered for the initial testis tumor was available in the study. Wanderas and colleagues examined the risk of subsequent non-germ cell tumors in 2006 Norwegian testis cancer survivors who were followed for an average of 12.5 years after diagnosis of testis cancer.[216] The relative risk for developing a second non-germ cell malignancy in this population was 1.65 when compared with the general population, and the cumulative risk of developing such a tumor was 7.8% after 15 years of follow-up. There was an increased risk of colorectal, gastric, hepatobiliary, lung, and bladder cancers, as well as melanoma and sarcoma. The highest relative risk for developing a second non-germ cell tumor was seen in patients treated with either irradiation alone or with irradiation plus chemotherapy. Bokemeyer and Schmoll reported a cumulative incidence of 1.38% for the development of a secondary tumor in 1025 patients followed for an average of 61 months after treatment for testis cancer.[217]

Travis and colleagues reported the results of a regression analysis of the relative risks of second solid malignancies in testicular cancer

survivors collected from 14 population-based tumor registries in North America and Europe encompassing the outcomes of over 40,000 testicular cancer survivors. In this analysis it was determined that the risk of developing any second solid tumor over a 40-year time period (e.g., by age 75 for a patient diagnosed at the age of 35) was 36% and 31% for survivors of seminomas and nonseminomas, respectively, compared with 23% for the general population.[218]

The risk of secondary leukemias after chemotherapy for the treatment of GCT is small but real. Alkylator-associated leukemias have occurred when these agents were used in the treatment of GCT.[124] More recent series suggest that acute leukemias are unlikely to occur after treatment with standard doses of PVB.[197] Though uncommon, etoposide-associated acute leukemias have been described, occurring in approximately 0.5% of patients. From a combined total of 881 GCT patients treated on protocol at Indiana University and MSKCC, a total of four patients developed acute myeloid leukemia. All occurred in patients treated with high cumulative doses of etoposide (2 g/m^2 in all patients but one, who received 1.3 g/m^2) and were diagnosed from 2 to 4 years after treatment.[219,220] Two other centers have reported a total of six leukemias out of a total of 322 patients treated with etoposide (and none in a group of 318 men receiving platinum-based therapy without etoposide), with a somewhat higher cumulative risk (3.5% to 4.7%) of developing leukemia at 5 years.[207] Bearing in mind that even the "easiest" adjuvant regimen consisting of two cycles of etoposide and cisplatin contain 1 g/m^2 of etoposide, careful and considered use of etoposide-containing regimens is warranted as further information accumulates.

Taken together, these data suggest that secondary malignancies are an expected late occurrence in patients with treated testicular cancer, with a relative risk of between 1.38 and 2.0. Treatment regimens including radiation therapy may have a higher association with secondary solid tumors, whereas chemotherapy may be more likely to result in secondary leukemias. These risks, though quite small compared with the impact of not undergoing therapy, must nevertheless be considered in the therapeutic decision-making process, and be discussed with each GCT patient.

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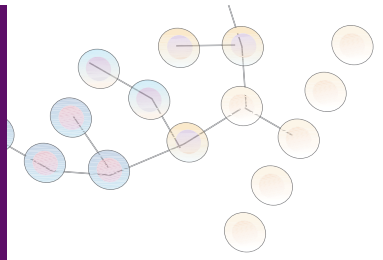
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91 Cancers of the Cervix, Vulva, and Vagina

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CANCER OF THE CERVIX

SUMMARY OF KEY POINTS

Incidence
- An estimated 11,150 new cases of invasive cervical cancer are anticipated in 2007 in the United States, with 3670 deaths projected.
- From 75% to 80% are squamous cell carcinomas.
- Since the advent of cytologic screening in the 1940s, the incidence of cervical cancer has been decreasing; however, a steady increase in the incidence of preinvasive disease of the cervix has occurred.

Etiology
- Associated risk factors include race, early age at first coitus, multiple sexual partners, multiparity, lower socioeconomic standing, cigarette smoking, history of sexually transmitted diseases, immunosuppression, and oral contraceptive use.
- Strong association with human papillomavirus (HPV)
- HPV serotypes 16, 18, 31, 33, 45, and 56 account for more than 80% of all invasive cervical cancers.

Evaluation and Staging
- Screening for cervical cancer historically has been done with the Papanicolaou (Pap) smear and pelvic examination.
- Testing for DNA of high-risk oncogenic HPV may be used to triage atypical smears and to reduce the frequency of cytologic screening.
- Biopsies should be performed of gross lesions.
- Patients without gross lesions but with abnormal cytology should undergo colposcopy with directed biopsies and endocervical curettage (ECC) or brushing.
- Once a diagnosis of cancer is made, the patient requires a complete history and physical examination, including bimanual and rectovaginal examination, as well as supraclavicular and groin lymph node examination.
- Cervical cancer is staged clinically, not surgically.
- Assignment of stage of disease may be influenced by findings from chest and skeletal radiography, excretory urography (intravenous pyelogram [IVP]), barium enema, cystoscopy, and proctoscopy.
- Results of computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), or other imaging modalities do not influence assignment of International Federation of Obstetrics and Gynecology (FIGO) stage, but may be important in directing therapy.

Primary Therapy
- High-grade dysplasia or carcinoma in situ may be treated with excisional cone biopsy (i.e., cervical conization performed with loop electrosurgical excision procedure [LEEP], or cold-knife).
- Stage Ia1 (microinvasive cervical cancer with depth of invasion 3 mm or less and 7 mm in width or less) without lymph-vascular invasion is managed with conservative surgery (i.e., excisional conization or extrafascial hysterectomy).
- Stage Ia2 lesions (invasion of more than 3 mm depth, and lesion up to 7 mm wide) or Ia1 lesions with lymph-vascular invasion are managed with modified radical hysterectomy.
- Stage Ib lesions and stage IIa lesions may be managed with radical hysterectomy or radiation therapy with equivalent probability of cure but different morbidities. Selected surgical patients with adverse risk factors may benefit from adjuvant postoperative radiation or chemoradiation.
- Patients with stage IIb to IVa generally are treated with radiation therapy with concurrent chemotherapy.

Therapy for Recurrent Disease
- Disease that recurs centrally in the pelvis after radiation may be treated with radical exenterative surgery.
- Locally recurrent disease after surgery is generally treated with radiation therapy or chemoradiation.

INTRODUCTION

Cancers of the cervix, vulva, and vagina represent the major malignancies of the lower female genital tract. With the exception of the endocervix, this portion of the genital tract is available for physical examination, including direct visual inspection and palpation. Currently, cytologic screening and surveillance by Papanicolaou (Pap) smear, testing for the presence of oncogenic strains of the human papillomavirus (HPV), colposcopy, and a variety of confirmatory biopsy techniques are capable of diagnosing preinvasive disease or very early-stage invasive disease that can be treated with a high probability of cure.

Improvements in diagnostic imaging and assessment of disease extent before therapeutic intervention and more routine use of integrated, multimodality therapy together offer the opportunity for better outcomes for women with invasive local or regional disease.

Squamous cell carcinomas are the dominant histologic type in all three sites, with many tumors associated with oncogenic strains of

HPV. In the last decade, improved understanding of HPV biology, the epidemiology and natural history of HPV infection, and early studies on HPV-directed vaccines offer hope that the incidence of invasive disease could decrease in the decades ahead. In the future, anticipated use of HPV-targeted vaccines in the pediatric population offers the potential to reduce dramatically worldwide morbidity and mortality associated with this group of diseases.

EPIDEMIOLOGY

For 2007, the American Cancer Society estimates that 11,150 cases of invasive cervical carcinoma and approximately 3670 cervical cancer deaths will occur in the United States, representing only 1.5% of the projected 270,600 annual cancer deaths in American women. A much larger population of American women (approximately four-fold) will be diagnosed with cervical dysplasia that will never develop into invasive neoplasia.

Although cervical cancer is the third most common gynecologic malignancy in the United States, it ranks as the most common gynecologic malignancy worldwide and is the second most common cancer in women in the world, with an estimated 500,000 cases in 2003. Marked disparity in incidence exists between countries where routine gynecologic care and Pap smear screening are available, and countries in Latin America, the Caribbean, and Africa, where cervical cancer is the most common cause of cancer-related death in women.[1]

It has long been appreciated that the incidence of invasive cervical carcinoma is related to sexual activity. Early age at first intercourse, multiple sexual partners, a history of venereal infection, and other parameters of sexual activity have long been recognized as factors associated with the development of invasive cervical cancer. Women from lower socioeconomic strata, and black and Hispanic populations have an increased frequency of disease. Incidence rates in the United States are estimated at 8.1 new cases per 100,000 white women each year as compared with 11 per 100,000 in African-American women and 14.4 per 100,000 in Hispanics.

Molecular epidemiologic studies have demonstrated that correlation of sexual activity with cervical carcinoma is related to transmission of the epithelial trophic and oncogenic HPV.[2–4] Most HPV infections are transient, resulting in no changes or low-grade intraepithelial lesions (cervical intraepithelial neoplasia; CIN 1) that will be spontaneously cleared in most young women.[5,6] Development of high-grade intraepithelial lesions will occur in a small minority of women, usually within 24 months.[7] High-grade lesions (CIN 2/3) may progress to invasive cervical cancer if not treated.[8,9]

Cases of CIN 2/3 that progress to invasive cancer will do so over a period of 8 to 12 years, which has been referred to as the *detectable preclinical phase*.[10–13] Thus the opportunities for early detection and intervention are abundant. However, an estimated one half of the invasive cervical cancers diagnosed in the United States are found in women who have never been screened, and an additional 10% are diagnosed in women who have not been screened within the preceding 5 years.[14]

Based on a comprehensive review of available evidence, the American Cancer Society convened an expert panel in 2001 through 2002 to formulate detailed guidelines for the initiation of screening, screening intervals, discontinuation of screening, screening in the context of prior hysterectomy, and use of various screening tests.[15] A synopsis of their recommendations is found in Table 91-1.

HUMAN PAPILLOMAVIRUS BIOLOGY

HPV is a double-stranded DNA virus in the Papovaviridae family (Fig. 91-1). This virus, constituted of approximately 8000 nucleotides, encodes seven early genes and two late genes, as well as having a small, untranslated region. Approximately 100 different serotypes with limited DNA homology have been identified. Although the identification of high-risk subtypes of HPV has been important in defining potential therapeutic targets for the prevention of cervical carcinoma, HPV infection has not adequately explained all of the biologic features of preinvasive disease and progression to invasive disease. Studies in sexually active college women demonstrated that infection with HPV is extremely common, occurring in up to 50% of women who become sexually active between the ages of 16 and 21 years, with the first abnormal Pap smear appearing in only a subset of women 1 year after infection. These infections typically are associated with low-grade dysplastic lesions and usually are transient. Persistent infection with associated high-grade dysplastic lesions is seen in only a small proportion of infected women (perhaps 1% or 2%). Biologic and/or immunologic cofactors that allow the persistence of HPV infection in a small subset of women remain unclear. Epidemiologic studies suggest that co-infection with herpes simplex virus type II (HSV), long-term oral contraceptive use, cigarette smoking, and high parity may increase the risk of persistent infection, carcinoma in situ (CIS), and invasive disease.[16,17] Whereas long-term epidemiologic studies undertaken since appreciation of the role of

Table 91-1 American Cancer Society Guideline for Screening by Cytology for the Early Detection of Cervical Neoplasia and Cancer

- Cervical cancer screening should begin ~3 yr after the onset of vaginal intercourse and no later than age 21 yr*
- Women who are age 70 or older with an intact cervix and who have had 3 or more documented, consecutive, technically satisfactory normal/negative cervical cytology tests and no abnormal/positive cytology tests within the 10-yr period before age 70 may elect to cease cervical cancer screening†
- Screening with vaginal cytology tests after total hysterectomy (with removal of the cervix) for benign gynecologic disease is not indicated. The presence of CIN 2/3 is not considered benign. Women with a history of CIN 2/3 or without documentation of the absence of CIN 2/3 should be screened until three documented, consecutive, technically satisfactory normal/negative cervical cytology tests and no abnormal/positive cytology tests with a 10-year period are achieved†
- After initiation of screening, cervical screening should be performed annually with conventional cervical cytology smears or every 2 years using liquid-based cytology; at or after age 30, women who have had three consecutive, technically satisfactory normal/negative cytology results may be screened every 2–3 years‡

*Age 21 to initiate screening is a guideline for circumstances in which sexual history is not available because providers do not ask, or because patients are unable or unwilling to provide a history regarding consensual or nonconsensual intercourse. It also is intended to protect victims of sexual abuse.

†Women who have a history of cervical cancer or in utero diethylstilbestrol exposure, or are immunocompromised (including human immunodeficiency virus positive [HIV$^+$]) should continue screening unless severe comorbid or life-threatening illnesses are present.

‡More frequent screening may be advisable in women with in utero DES exposure, and women who are HIV$^+$ or are immunocompromised by organ transplantation, chemotherapy, or prolonged corticosteroid treatment.

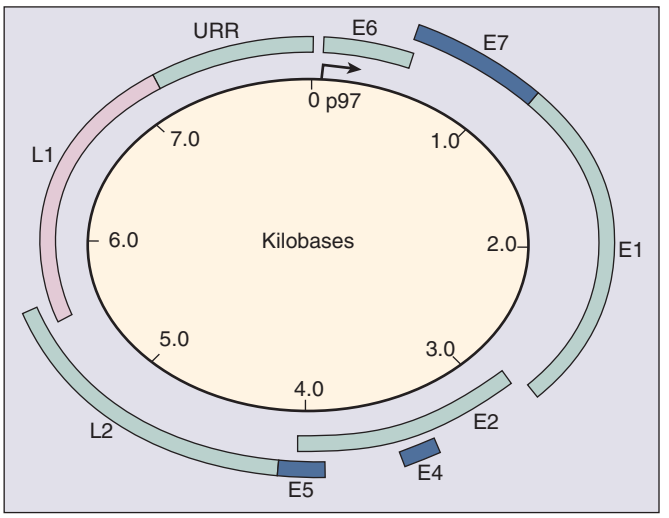


Figure 91-1 • Human papillomavirus (HPV) genome. The HPV virus is a double-stranded DNA virus in the Papovaviridae family. This virus, constituted of approximately 8000 nucleotides, encodes seven early genes and two late genes, as well as having a small, untranslated region. Approximately 100 different serotypes with limited DNA homology have been identified. (From Parker MF, Sausville EA, Birrer MJ: Basic biology and biochemistry of gynecologic cancer. In Hoskins WJ, Perez CA, Young RC [eds]: Principles and Practice of Gynecologic Oncology, 2nd ed. Philadelphia, Lippincott-Raven, 1997, Fig. 3.6.)

HPV remain incomplete, it is known that in the large majority of women, the period between HPV infection, dysplasia, and then invasive carcinoma typically is years to decades, offering the potential for screening and early intervention to change the natural history and morbidity associated with this disease.[18–22]

Molecular epidemiologic studies have divided HPV serotypes into high-, intermediate-, and low-risk subtypes for the development of cervical neoplasia.[23] Low-risk subtypes have been associated with venereal warts (condylomata acuminata), whereas intermediate- and high-risk subtypes have been associated with cervical dysplasia and invasive carcinoma. Recent worldwide review of HPV typing demonstrated that 87% of squamous cell carcinomas had an identifiable HPV genome associated with the tumor as compared with 76.4% of adenocarcinomas. HPV-16 was the predominant type, associated with between 46% and 63% of the squamous carcinomas, whereas HPV-18 was associated with 10% to 14% of squamous cell carcinomas. Sixteen other HPV types were associated with the remaining 25% of cases, including HPV-45, -31, and -33. Most epidemiologic studies have demonstrated a higher incidence of HPV-18 (37% to 41%), followed by HPV-16 (26% to 36%) in women with adenocarcinoma of the cervix. Several authors have shown a positive association between the presence of certain HPV subtypes and prognosis. Barnes and colleagues[24] showed that, among invasive carcinomas, HPV-18 is associated with poorly differentiated histology and higher incidence of nodal metastases. Similarly, Walker[25] reported that HPV-18-associated cancers were more likely to recur than were HPV-16-associated cancers. By contrast, HPV-16 was associated with large cell keratinizing tumors, and these tumors were less likely to recur.[26] Lombard[27] demonstrated HPV-18-associated tumors to have a relative risk of death 2.4 times greater than that observed for patients with HPV-16-associated tumors and 4.4 times greater than that for patients with a tumor associated with another HPV type.

The mechanism by which these epithelial trophic viruses cause neoplasia has been defined through an elaborate collection of experiments that have focused on the role of the E6 and E7 early genes. Virally encoded E6 binds to the p53 protein, leading to targeting of this cellular checkpoint protein for proteosomal destruction. The E6 protein product also enters the nucleus and interacts with the other important nuclear proteins. The second virally encoded protein, E7, sequesters the retinoblastoma gene product (Rb) releasing the RB-associated E2F transcription factor, which results in the initiation of a number of nuclear events important in driving the cell through the cell cycle. Recent studies also have suggested that p21 is sequestered and inactivated by the E7 protein. Elimination of the p53 and Rb checkpoint results in dysregulated cell growth and dysplasia. In addition, the E7/E6 proteins both independently lead to mitotic instability, with abnormality in chromosomal segregation during mitosis and increased chromosome instability. This may explain, in part, the long latency period between HPV infection and carcinoma. Loss-of-heterozygosity studies and other molecular events have defined chromosomal changes and changes in other oncogenic proteins that are neither primary nor secondary effects of HPV infection, but are due instead to co-infection or other non-HPV factors. Although data suggest that HPV infection may be critical in initiating the neoplastic transformation, it is not clear that therapy that targets the HPV genome or HPV-related protein products will be useful in reversing the fully transformed phenotype.

The observation that, in a large portion of HPV-infected women, invasive carcinoma never develops suggests that the preinvasive neoplastic cells can be cleared by the immune system. Recent studies identified T cells that specifically identify peptide epitopes of the E6 and E7 proteins. Certain human leukocyte antigen (HLA) DR2 and TAP genes have been associated with invasive cervical carcinoma. Understanding the biology of cervical cancer initiation and propagation requires an understanding of HPV biology and its interaction with its epithelial cell target, as well as an understanding of cervical immunity. The HPV virus is epithelial trophic. Unlike that in other oncogenic viruses (such as the hepatitis viruses), systemic exposure to the virus is not required for infection of the target organ. Analysis has demonstrated that E6-specific T cells in the majority of healthy women are responsible (at least in part) for eradication of infection. Tetramer analysis in patients with cervical CIS or invasive cervical cancer have in general demonstrated few HPV-16 E7-reactive T cells, typically representing less than 0.1% of the $CD8^+$ T cells in the systemic circulation. Recent attempts to generate productive and/or long-term HPV-16 infection have been accomplished by using an HPV-16 virus-like particle vaccine. In a recent randomized, placebo-controlled study, the delivery of three vaccinations at day 0, month 2, and month 6 reduced the risk of persistent new HPV-16 infection from 3.8 cases per 100 women-years at risk to 0 per 100 woman-years in the group that were vaccinated, for a 100% efficacy rate. In this study, involving 2392 young women between the ages of 16 and 23 years, nine cases of HPV-16-related CIN were noted, all in the placebo recipients.[28] Further study with this and other vaccines is ongoing.

Maiman, Fruchter, and associates[29–32] investigated the disease characteristics, recurrence risks, and survival rates of HIV-seropositive patients with CIN and invasive cervical cancer. HIV-infected women had significantly higher rates of recurrence of CIN after standard therapies than did seronegative women. HIV-infected women with cervical cancer had significantly more advanced disease than did those who were not infected. Only 3 (19%) of 16 HIV-seropositive patients were first seen with an early-stage disease (defined as stage Ia or nonbulky Ib) compared with 35 (52%) of 68 in the HIV-seronegative group. When upstaged based on surgicopathologic findings, only 1 (6%) HIV-infected patient had early-stage disease compared with 40% of uninfected patients. The response to therapy and prognosis were poorer among HIV-seropositive women, with higher recurrence and death rates. The majority of seropositive women had lymph node metastases and high-grade tumors. They generally were asymptomatic with respect to their HIV disease, but died of cervical cancer. The significant impact of immune status on disease progression was made evident by prolonged disease-free follow-up in seropositive patients with CD4 counts greater than

500/mm^3, in contrast to those with CD4 counts less than 500/mm^3. The observed marked increased risk of invasive cervical carcinoma in women infected with the HIV virus and the demonstration that highly effective antiretroviral therapy (HEART) is capable of doubling the CIN regression rates in women infected with HIV, as compared with those women not receiving HEART, provides suggestive, indirect clinical evidence supporting the critical importance of the intact immune system in limiting the progression of HPV infection to invasive cancer in healthier populations.

PATHOLOGY

The epithelium of the cervix is composed of squamous epithelium that covers the exocervix and glands and columnar epithelial cells that line the endocervix. The border between the squamous and columnar epithelium is called the *squamocolumnar junction*, the site of ongoing squamous metaplasia believed to be most vulnerable to viral neoplastic transformation. With increasing age, the squamocolumnar junction migrates from the exocervix into the distal endocervical canal (Fig. 91-2), with the region between the original and subsequent locations termed the *transformation zone*. The transformation zone is the most common location for detection of early cervical cancers (Fig. 91-3) Tumors arising on the ectocervix typically are squamous cell carcinomas, whereas adenocarcinomas are more likely to have their epicenter in the endocervix.

A continuum appears to exist from CIN to frankly invasive squamous cell carcinoma (Fig. 91-4). The mean age of women with CIN is 15.6 years younger than that of women with invasive cancer, suggesting slow progression of CIN to invasive carcinoma.[18] The natural history of HPV infection and CIN in part reflects the host immune system response to the virus. Seventy-five percent of CIN 1 lesions will spontaneously regress or persist as CIN 1, without progression to invasive carcinoma.[18–21]

Miller[22] reported, in a 13-year observational study, that only 14% of CIN 3 lesions had progressed, whereas 61% persisted, and the remainder disappeared. Patients taking corticosteroids or other immunosuppressive drugs and patients with HIV infection are at higher risk of progressing to invasive cancer and may have a shorter transit time for this progression.

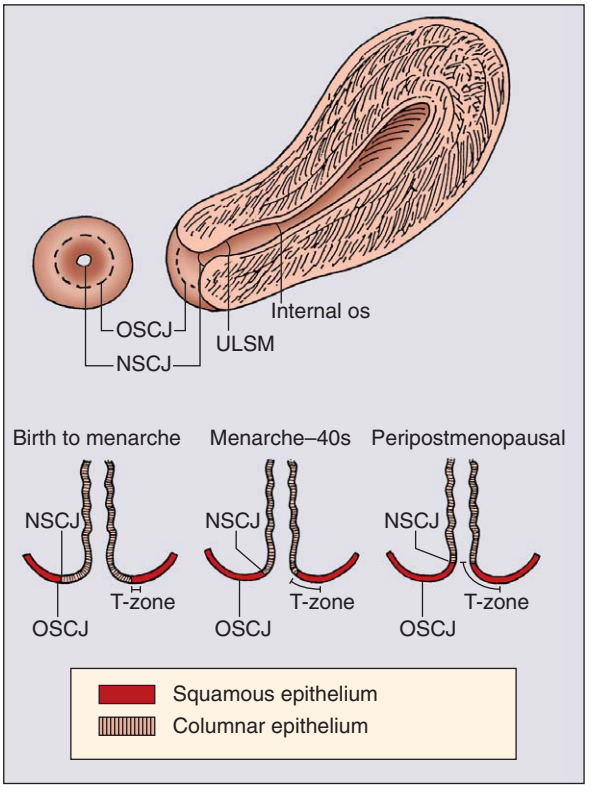


Figure 91-2 • The transformation zone and squamocolumnar junction. NSJC, new squamocolumnar junction; OSJC, original squamocolumnar junction; T-zone, region between original and new squamocolumnar junctions. (From Wright TC Jr, Richart RM: Pathogenesis and diagnosis of preinvasive lesions of the lower genital tract. In Hoskins WJ, Perez CA, Young RC [eds]: Principles and Practice of Gynecologic Oncology, 2nd ed. Philadelphia, Lippincott, 1997, p 678 and Berek JS, Hacker NF: Practical Gynecologic Oncology, 2nd ed. Baltimore, Williams & Wilkins, 1994.)



Figure 91-3 • Invasive squamous cell carcinoma. A mass is present on the external os. (Clement PB, Young RH: Atlas of Gynecologic Surgical Pathology. Philadelphia, WB Saunders, 2000, p 103.)

Squamous Cell Carcinomas of the Cervix

Approximately 75% of invasive cervical carcinomas are squamous cell carcinomas. Tumor histology differs between well, moderately, or poorly differentiated tumors. Squamous carcinomas (Fig. 91-5) may be keratinizing (sometimes containing characteristic keratin pearls) or nonkeratinizing. Large cell and small cell variants exist. True verrucous cancers of the cervix are rare.

Cervical Adenocarcinomas

Adenocarcinomas account for 15% to 25% of invasive cervical carcinomas. Typically arising in the endocervix, adenocarcinomas can be more difficult to detect on visual inspection of the cervix. These tumors may infiltrate deeply into the stroma of the cervix, sometimes with parametrial extension and nodal metastases without gross destruction of the exocervix. In addition to the classic endocervical type, histologic variants of adenocarcinoma include endometrioid carcinoma, villoglandular, mesonephric, serous, intestinal-type, and signet-ring morphologies.

Clinically important subtypes also include clear cell adenocarcinomas of the cervix associated with in utero diethylstilbestrol (DES) exposure, which tend to be diagnosed at a younger age than most other adenocarcinomas, and so-called "adeno malignum" or minimal deviation adenocarcinoma (Fig. 91-6), an entity associated with deceptively bland or benign-appearing cells, which may be cause for undertreatment of a true malignancy, with a significant likelihood of recurrence even when diagnosed at an early stage.[33,34]

Adenosquamous Carcinomas

Adenosquamous carcinomas consist of a malignant glandular component and a malignant squamous component and make up approximately one third of cervical carcinomas with glandular differentiation. Opinions vary regarding the prognosis of adenosquamous carcinoma compared with pure adenocarcinoma or pure squamous carcinoma when prognosis is adjusted for clinical stage at diagnosis. A clinically important variant of adenosquamous carcinoma is the so-called "glassy cell" carcinoma, thought to represent a very poorly differentiated adenosquamous carcinoma, the name of which derives from the ground-glass or granular appearance of the cytoplasm seen in many cases. Additional features may include an intense stromal inflammatory infiltrate composed predominantly of eosinophils and plasma

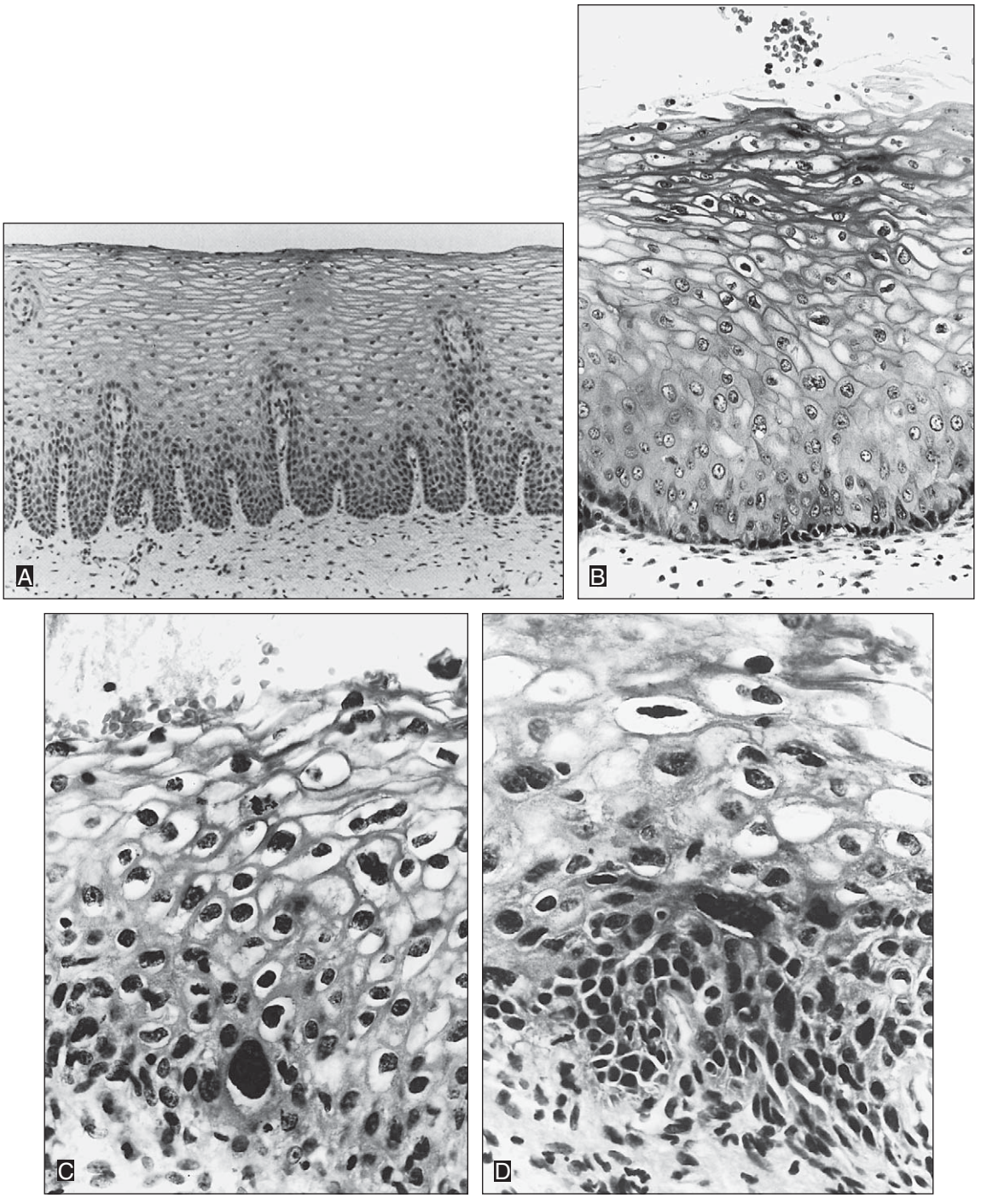


Figure 91-4 • A–F, Histologic portraits of normal stratified squamous epithelium of the cervix and cervical intraepithelial neoplasia. (From Hoskins WJ, Perez CA, Young RC [eds]: Principles and Practice of Gynecologic Oncology, 2nd ed. Philadelphia, JB Lippincott, 1997, p 678, and Crum CP: Papillomavirus-related changes and premalignant and malignant squamous lesions of the uterine cervix. In Clement PB, Young RH [eds]: Tumors and Tumorlike Lesions of the Uterine Corpus and Cervix. Contemporary Issues in Surgical Pathology, Vol 22. New York, Churchill Livingstone, 1993, p 91, with permission.)

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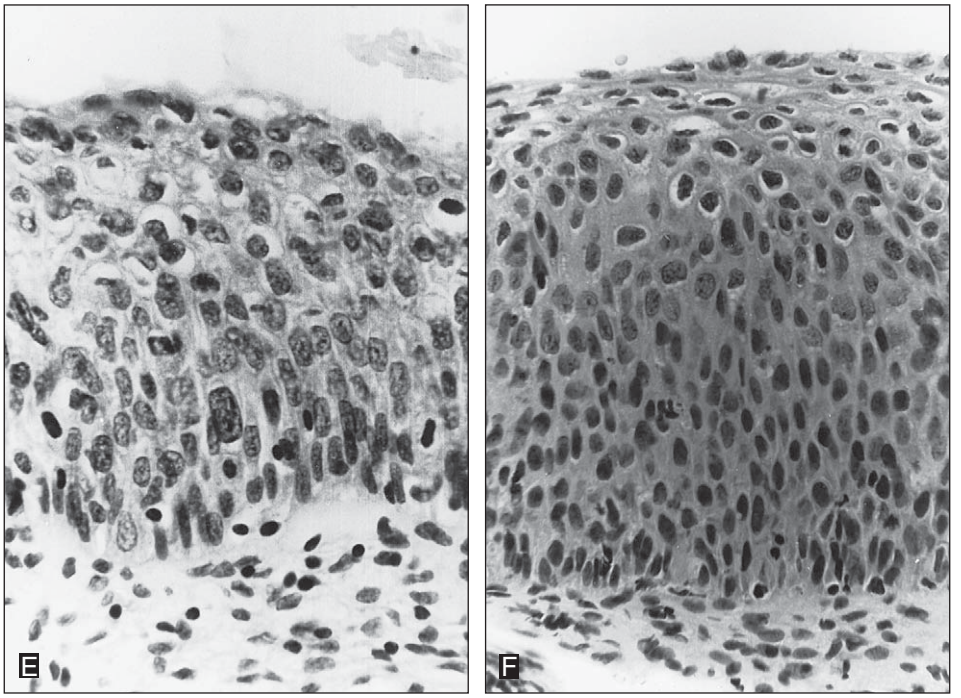


Figure 91-4, cont'd

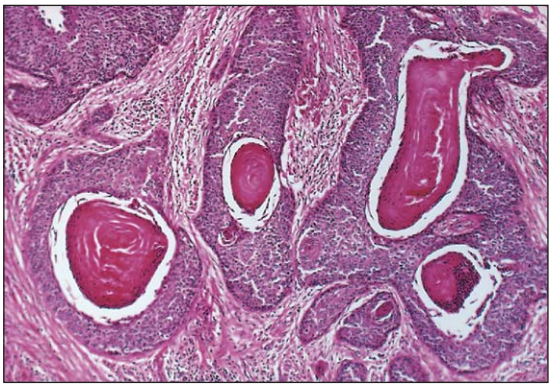


Figure 91-5 • Invasive squamous cell carcinoma of the keratinizing type. (Clement PB, Young RH: Atlas of Gynecologic Surgical Pathology. Philadelphia, WB Saunders, 2000, p 103.)

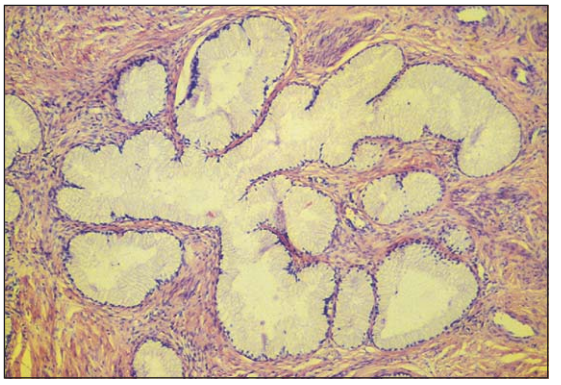


Figure 91-6 • Adenoma malignum. A gland with a bizarre shape is lined by benign-appearing tumor cells. (Clement PB, Young RH: Atlas of Gynecologic Surgical Pathology. Philadelphia, WB Saunders, 2000, p 118.)

cells. Some patients may have accompanying eosinophilia in their circulating blood, with elevated absolute eosinophil counts. This histologic type is associated with a rapid clinical rate of growth, proclivity for early regional dissemination, and increased risk of recurrence after surgical therapy or radiation therapy, even in the absence of other recognized adverse prognostic factors.[35–38]

NEUROENDOCRINE TUMORS OF THE CERVIX

Neuroendocrine tumors arising in the cervix include typical and atypical carcinoid tumors, and large cell, small cell neuroendocrine carcinomas, and undifferentiated small cell carcinoma. Both large cell and small cell neuroendocrine tumors resemble similar carcinomas arising in the lung and other aerodigestive sites.[39,40] Undifferentiated small cell carcinoma is a very poorly differentiated carcinoma with neuroendocrine features, histologically similar to anaplastic small cell carcinoma of the lung.[41] Neuroendocrine carcinomas tend to behave very aggressively, with frequent widespread metastasis to multiple sites, including bone, liver, skin, and other sites. Brain metastases may occur when disease is advanced but usually are preceded by lung metastases.[43] Efforts to treat these tumors by using approaches typically used for small cell carcinomas of the lung have had mixed results.[42]

Clinical Presentation

Preinvasive neoplastic disorders of the cervix usually are asymptomatic, hence the need for regular screening by cytologic evaluation of cells collected from the exocervix and endocervix. Early invasive cancers also may be asymptomatic, although some women will notice postcoital, intermenstrual, or postmenopausal spotting. Other symptoms may include malodorous vaginal discharge, dyspareunia, or cramping pelvic pain from uterine contractions caused by the accumulation of blood and uterine deciduas in menstruating patients with occlusion of the endocervical canal. Chronic blood loss may result in symptomatic anemia in some patients. Major hemorrhage is unusual

except in locally advanced disease. Pelvic pain, lower extremity swelling (from occlusion of pelvic lymphatics or thrombosis of the external iliac vein), or problems with micturition or defecation indicate advanced regional disease and portend an ominous prognosis. Metastatic disease involving supraclavicular nodes, bones, or lungs can be the cause of presenting symptoms, but rarely in the absence of pelvic symptoms. Constitutional symptoms, including anorexia, dysgeusia, and weight loss, are seen most often in patients with very advanced disease.

Screening

Screening for cervical cancer and its precursors with the Pap smear and pelvic examination has resulted in dramatic reductions in cervical cancer mortality in every country where this has been widely used, and is arguably the most effective screening program in effect for any neoplastic disease, in either gender. Current screening guidelines of the American Cancer Society are outlined in Table 91-1. The false-negative rate of the Pap smear is about 10% to 15% in women with invasive cancer, but the sensitivity, as defined by the detection of biopsy-proven CIN, is 51%.[43–45] The sensitivity of the test may be improved by ensuring adequate sampling of the squamocolumnar junction and the endocervical canal. Smears without endocervical or metaplastic cells may be inadequate and possibly should be repeated.[46]

Factors contributing to abnormal cytologic smears include the presence of hemorrhage, necrosis, and intense inflammation. Thus gross symptomatic lesions should be sampled with biopsy rather than assessed with exfoliative cytology.

In the 1980s, cytology laboratories began reporting an increasing number of smears with changes of "squamous atypia" in response to concerns from clinicians over an unacceptably high false-negative cytology rate and increased recognition by cytopathologists of the cytologic changes associated with HPV infection. The use of multiple classification systems with inconsistently defined numeric grading conventions added further imprecision. In an attempt to eliminate confusion among clinicians and cytopathologists, a uniform system for reporting epithelial cell abnormalities was established in 1988 at a National Cancer Institute (NCI) workshop for reporting cervical and vaginal cytologic diagnoses.[47]

The Bethesda System has since been revised, in 1991 and again in 2001 (Table 91-2),[48] to reflect laboratory and clinical experience gained since the original implementation, as well as the increased utilization of new technologies and results from interval research studies. An important contribution of the Bethesda System was the creation of a standardized format and nomenclature for cytology laboratory reports that includes both a descriptive diagnosis and an evaluation of specimen adequacy.

With the formulation of Bethesda 2001, a specimen is designated "satisfactory for evaluation" or "unsatisfactory for evaluation." The category "satisfactory but limited by . . ." has been eliminated as confusing. Minimal cellularity requirements for a specimen to qualify as satisfactory depend on specimen type, with an estimated 8000 to 12,000 well-visualized squamous cells for conventional smears and 5000 squamous cells for liquid-based preparations. Comments on partially obscuring inflammation or blood may be added to the "satisfactory" designation, with a specimen considered "partially obscured" when 50% to 75% of the epithelial cells cannot be visualized. When more than 75% of epithelial cells are obscured, a specimen is designated "unsatisfactory." A notation is made regarding the presence or absence of an endocervical/transformation zone component for specimens with adequate squamous cellularity, with the numeric criterion being at least 10 well-preserved endocervical or squamous metaplastic cells. Cell clusters are not required.

Squamous atypia is a mild cellular abnormality characterized by slight nuclear enlargement and minimal changes of the nuclear chromatin. Cellular changes that show morphologic features of papillomavirus infection or mild CIN (grade 1) are termed low-grade

Table 91-2 2001 Bethesda System

SPECIMEN ADEQUACY

Satisfactory for evaluation (note presence of endocervial/transformation zone component)

Unsatisfactory for evaluation (specify reason)

Specimen rejected/not processed (specify reason)

Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

GENERAL CATEGORIZATION (OPTIONAL)

Negative for intraepithelial lesion or malignancy

Epithelial cell abnormality

Other

INTERPRETATION/RESULT

Negative for intraepithelial lesion or malignancy

- Organisms
  - *Trichomonas vaginalis*
  - Fungal organisms consistent with *Candida* sp.
  - Shift in flora suggestive of bacterial vaginosis
  - Bacteria morphologically consistent with *Actinomyces* sp.
  - Cellular changes consistent with herpes simplex virus

Other nonneoplastic findings (Optional. List not comprehensive)

- Reactive cellular changes associated with inflammation (includes typical repair)
  - Radiation
  - Intrauterine contraceptive device
- Glandular cells after hysterectomy
- Atrophy

Epithelial cell abnormalities

- Squamous cell
  - Atypical squamous cells (ASC) of undetermined significance (ASC-US), cannot exclude high-grade squamous intraepithelial lesion (HSIL [ASC-H])
  - Low-grade squamous intraepithelial lesion (LSIL) encompassing human papillomavirus, mild dysplasia, cervical intraepithelial neoplasia (CIN) 1
  - HSIL encompassing moderate and severe dysplasia, carcinoma in situ; CIN 2 and CIN 3
  - Squamous cell carcinoma
- Glandular cell
  - Atypical glandular cells (AGCs) (specify endocervical, endometrial, or not otherwise specified)
  - Atypical glandular cells, favor neoplastic (specify endocervical or not otherwise specified)
  - Endocervical adenocarcinoma in situ (AIS)
  - Adenocarcinoma
- Other (list not comprehensive)
  - Endometrial cells in a woman 40 yr or older

AUTOMATED REVIEW AND ANCILLARY TESTING

(Include as appropriate)

EDUCATIONAL NOTES AND SUGGESTIONS

(Optional)

Adapted from Soloman D, Davey D, Kurman R, et al: The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002;287:2114.

squamous intraepithelial lesions or LSILs. Cellular changes consistent with moderate (CIN 2) or severe (CIN 3) dysplasia are termed high-grade squamous intraepithelial lesions or HSILs. The division of SILs into high- and low-grade strata reflects accumulating evidence that LSIL generally is indicative of transient infection with HPV, particularly in young women, and does not routinely require colposcopy or treatment, whereas HSIL cytology detects precursor lesions that require further evaluation and treatment. Important refinements in the 2001 Bethesda System relate to the reporting of equivocal results. Atypical squamous cells (ASCs) are now further qualified as "of undetermined significance" (ASC-US) or "cannot exclude HSIL" (ASC-H). The qualifier "undetermined significance" was retained, as some cases of ASC-US are associated with underlying CIN 2 or CIN 3. All ASCs are considered to be suggestive of SILs, and thus the category "ASC-US favor reactive" has been eliminated, with a portion of cases previously so designated being downgraded to "negative for intraepithelial lesion or malignancy." The new term ASC-H includes true HSIL and its mimics and is thought to have a positive predictive value for CIN 2 or CIN 3 intermediate between ASC-US and HSIL. The term *atypical glandular cells of undetermined significance* (*AGUS*) has been eliminated to avoid confusion with ASC-US. Glandular cell abnormalities now are classified as atypical endocervical, endometrial, or glandular cells. The term *atypical epithelial cells* may be used when a squamous versus glandular origin cannot be ascertained.

DIAGNOSIS

Management of the patient with an abnormal Pap smear with respect to further diagnostic assessments, therapeutic intervention, and subsequent surveillance follow-up is a complex arena in which guidelines continue to evolve. The American Society for Colposcopy and Cervical Pathology (ASCCP) has developed contemporary guidelines for management of cervical cytologic abnormalities and CIN based on current reporting terminology (Bethesda 2001).[49,50] Techniques for further evaluation can include colposcopy, endocervical curettage or brushing, and cervical conization by cold knife or loop electrodiathermy excision procedure (LEEP).

Testing for high-risk, oncogenic HPV DNA[51–57] synchronously, or subsequent to cytologic screening, is proving to be a useful complementary tool in triage of patients with ASC-US smears and in determining the need for colposcopy and the intervals for repeated screening. It may be helpful in the follow-up of younger patients with LSIL smears, and a useful tool in identifying older women who can safely be screened at 3-year intervals instead of annually.

HPV triage of patients with an ASC-US smear is at least as sensitive as immediate colposcopy for ultimately detecting CIN 3 and results in referral of about half as many women to colposcopy. A follow-up strategy that uses repeated cytology is sensitive at an ASCUS referral threshold, but requires two follow-up visits and ultimately more colposcopic examinations than does HPV triage.[58]

Cytologic and HPV screening in women older than 30 years (after which most sexually active women have been exposed to HPV and have, or have not, spontaneously cleared the infection) may be a mechanism through which low-risk HPV-negative and cytologically negative patients can be identified for whom screening at 3-year intervals is prudent and appropriate.

Colposcopy

Patients with a gross lesion of the cervix should undergo cervical biopsy. For patients with an abnormal cytologic evaluation, without a gross lesion, a colposcopic examination with directed punch biopsies is required. Colposcopy allows the clinician to identify areas suggestive of dysplasia. A 3% acetic acid solution is applied to the cervix for 30 to 90 seconds, which causes a transient reaction with the envelope proteins of the papillomavirus, in addition to producing an osmotic dehydration of the dysplastic cells, thereby accentuating the optically dense chromatin to produce a whitish area. The skilled colposcopist can further distinguish between grades of dysplasia based on aceto-whitening and types of vascular patterns (Fig. 91-7). An additional technique to help visualize abnormal areas is the application of quarter-strength Lugol's iodine after the initial inspection for aceto-whitening. High-grade lesions turn mustard yellow.

Endocervical Curettage or Endocervical Brush

Study of the endocervical canal is required when no abnormalities are found on colposcopic examination, when the entire squamocolumnar junction cannot be visualized, or when atypical endocervical cells are present on Pap smear. Some experts advocate the use of endocervical curettage (ECC) as part of every colposcopic examination to safeguard against missing occult cancer within the endocervical canal. Others reserve ECC for patients with recurrent cytologic atypia after therapy. A sleeved endocervical brush is an alternative to ECC that is less uncomfortable for many patients. Recent, prospective comparison of ECC specimens with sleeved endocervical brush specimens (both obtained from the same patient sequentially after randomization with respect to the order of obtaining specimens) before cervical conization or hysterectomy revealed a higher rate of inadequate specimens from ECC, comparability of the two techniques with respect to sensitivity and specificity in unmatched analysis, and superior sensitivity of the sleeved endocervical brush in matched analysis. As the sleeved endocervical brush is at least isoeffective and possibly better than ECC but more comfortable for the patient, many clinicians prefer this maneuver, which may serve to increase patient compliance with subsequent surveillance follow-up and repeated assessment.[59]

Excisional Biopsy

Diagnostic cervical conization (cone biopsy) leads to an accurate diagnosis and decreases the incidence of inappropriate therapy in the following situations: (1) the squamocolumnar junction is not visualized on colposcopy; (2) dysplastic epithelium extends into the endocervical canal; (3) cytology is suggestive of high-grade dysplasia or worse; (4) microinvasive carcinoma is found on directed biopsy; (5) sampling of the endocervical canal shows high-grade intraepithelial neoplasia; and (6) cytology is suggestive of adenocarcinoma in situ.

Loop Electrodiathermy Excision Procedure

LEEP uses wire-loop electrodes in conjunction with a radiofrequency alternating current to excise the entire transformation zone and distal canal under local anesthesia (Fig. 91-8). Compared with ablative procedures, LEEP has the major advantage of obtaining tissue for histologic evaluation. At many centers, LEEP has become the preferred treatment for CIN that can be assessed adequately with colposcopy.[60–72]

Complications include bleeding, with a reported incidence of 1% to 8%,[73,74] cervical stenosis (1%), and, rarely, pelvic cellulitis or adnexal abscess. In some cases, LEEP may not be an adequate alternative to formal excisional conization, such as in those patients in whom microinvasive or invasive cancer is suspected, or in those with adenocarcinoma in situ, as it may treat disease within the cervical canal inadequately and complicate pathologic interpretation of the specimen. Appropriate application of this technique will yield tissue suitable for pathologic study and reliable diagnosis. Excess heat may result in thermal artifact that can compromise interpretation of margins and the therapeutic adequacy of the LEEP procedure.

Diagnostic or Therapeutic Excisional Conization (Cone Biopsy)

Diagnostic or therapeutic excisional conization (cone biopsy) must be performed under general or regional anesthesia. Complications,

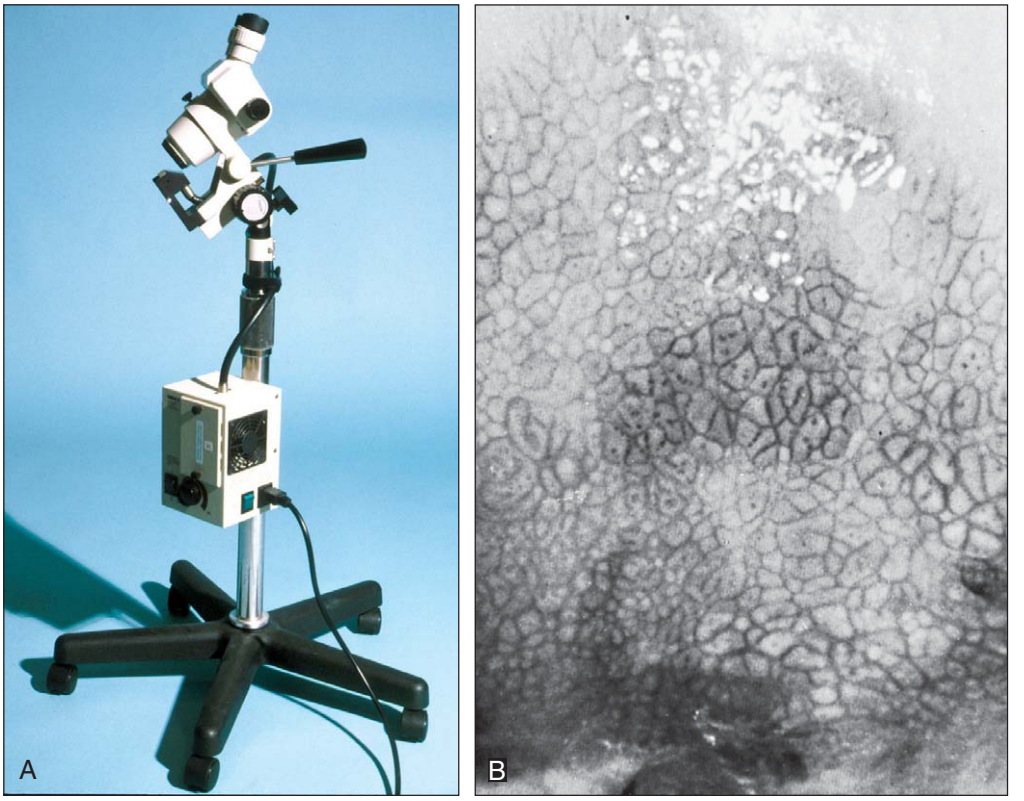


Figure 91-7 • A, Colposcope. **B,** Colposcopic discovery of high-grade cervical dysplasia. (**A** From Apgar B, Brotzman G, Spitzer M [eds]: Colposcopy: Principles and Practice, 2nd ed. Philadelphia, Elsevier, in press. **B,** From Morrow CP, Curtin JP: Synopsis of Gynecologic Oncology, 5th ed. San Francisco, Churchill Livingstone, 1998, p 107.)

which include hemorrhage, sepsis, infertility, stenosis, and cervical incompetence, occur in 2% to 12% of patients, depending on depth and geometry of excision.[73–75] Width and depth of the cone should be tailored to the topography of the lesion, to produce the least amount of injury while providing clear surgical margins. Conization may be performed with a cold knife or with the carbon dioxide laser.

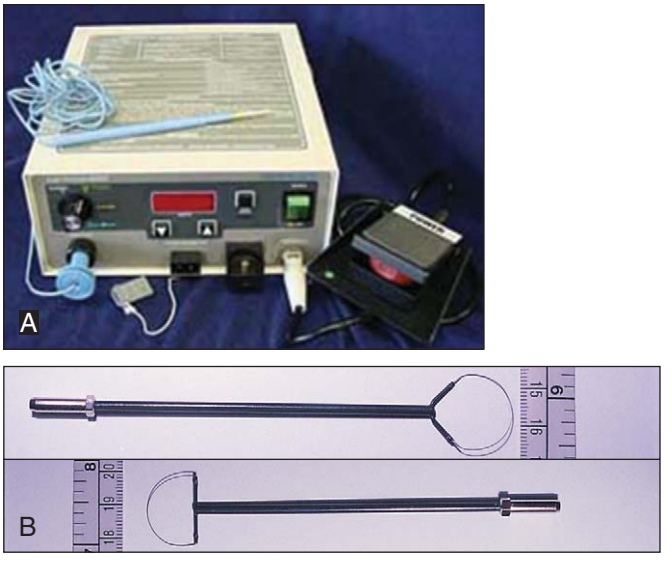


Figure 91-8 • Equipment used for loop electrosurgical excision procedures (LEEP). **A,** LEEP system 6000 (Cooper Surgical). **B,** Large loop electrodes used for LEEP. (**B,** From Baggish MS: Colposcopy of the Cervix, Vagina, and Vulva: A Comprehensive Textbook. Philadelphia, Mosby, 2003, p 96.)

Patient Evaluation in Patients with Invasive Disease

A thorough history should be obtained before diagnostic assessments are initiated, because skilled questioning will elicit information that will serve to guide subsequent evaluation. A sexual history should be obtained from all patients, which may alert the physician to screen for HIV and other sexually transmitted diseases. This also will serve to establish a baseline for sexual function and expectations that may be helpful in the post-treatment counseling and sexual rehabilitation of patients after completion of therapy. A complete history and systems review also should assess comorbid conditions (e.g., neurologic, cardiovascular, pulmonary, gastrointestinal, endocrine) that may affect the selection and implementation of treatment strategy.

A social assessment should be routinely obtained and will assist in determining supportive interventions that may be necessary to facilitate patient compliance with complex diagnostic programs and multimodality treatment programs. In the United States, patients with advanced cervical cancer may be uninsured or underinsured, often will have cultural or language barriers to obtaining and complying with care, may have limited educational attainment and medical sophistication, and will have variable degrees of familial or other social support.

A general physical examination should be carried out, with attention to accessible lymph node groups, including the supraclavicular nodes and the inguinal nodes. Physical examination also should assess the heart, lungs, and large vasculature (i.e., the carotid, dorsalis pedis, posterior tibial, and femoral arteries; the aorta; and the veins of the lower extremities). Pelvic examination must include meticulous inspection of all potentially visible sites and palpation of the perineum, the vulva, the full length of the vaginal barrel, and the anorectum. Some patients will manifest areas of preinvasive disease at multiple separate sites along the lower reproductive tract or synchronous invasive primary cancers of the lower reproductive tract and the anus, representing "field cancerization" consequent to exposure to a common etiologic agent. Typically tumors arising from the ectocervix

or transformation zone are easily visualized and sampled with biopsy. Occasionally tumors arising in the uterine corpus or lower uterine segment can invade the uterine cervix or protrude through the cervical os, causing confusion in the diagnosis. Often this can be sorted out by histopathology and by diagnostic imaging, with magnetic resonance imaging (MRI) being most useful in this context. Once the diagnosis of cervical carcinoma is established, staging includes careful clinical evaluation of the vagina, cervix, uterus, and parametria. The adenexal areas should be palpated as well, because some patients will harbor adenexal pathology (tubo-ovarian abscesses or, less commonly, adenexal metastases) that optimally are diagnosed and addressed before initiation of cancer treatment.

Conventionally, pelvic examinations in the setting of invasive cancer are performed under general or regional anesthesia (EUA) to assist in the most accurate possible physical evaluation of disease extent. Relaxation of the muscles of the pelvic floor and the opportunity to conduct vigorous and prolonged examination without inflicting discomfort or pain may identify disease extension that may be missed in an outpatient clinic examination. For example, EUA may be critical in very anxious, young, nulliparous women, as well as in elderly patients who may not be regularly sexually active and in whom the vagina may be stenotic. EUA also affords the opportunity to perform cystoscopy and proctosigmoidoscopy when indicated. However, in an era of cost containment and constrained health care resources, EUA may be omitted when a cooperative patient is amenable to satisfactory examination in the clinic or in rare circumstances in patients with locally extensive disease requiring rapid initiation of treatment.

Staging

The revised 1995 staging criteria (Table 91-3) of the International Federation of Obstetrics and Gynaecology (FIGO) are a mixture of histopathologic, clinical, and radiographic assessments that reflect the fact that invasive cervical cancer is most prevalent in less-developed portions of the globe where sophisticated and expensive imaging modalities may not be widely available. Cervical cancer is clinically staged, and staging is based primarily on inspection and palpation of the cervix, vagina, parametrium, and pelvic sidewalls. Only the subclassification of stage I (Ia1, Ia2) requires pathologic assessment. The FIGO staging system permits assessment through biopsy, physical examination, cystoscopy, proctoscopy, excretory urography (intravenous pyelography or IVP), and plain film radiography of the chest and skeletal system. Results of lymphangiography (LAG), computed tomography (CT), MRI, and positron emission tomography (PET) may be of great value in planning treatment, but do not influence assignment of clinical stage in the FIGO formalism. When findings are equivocal, by convention, a patient is assigned to a lower stage. Once clinical stage has been assigned, it cannot be altered by subsequent events or findings. Findings from surgical evaluation (by laparoscopy or by surgical assessment of retroperitoneal lymph nodes via extraperitoneal or transperitoneal node dissection) will not alter assignment of clinical stage. However, these findings may profoundly influence subsequent treatment. Similarly, evidence of nodal or other spread discerned at the time of hysterectomy does not alter clinical stage.

A staging system based largely on findings from clinical pelvic examination is inherently imprecise and somewhat subjective, with over- and understaging of the parametria being the most problematic issue and the one most likely to alter management. However, FIGO stage does correlate with prognosis and does permit cautious interinstitutional and intrainstitutional comparisons of treatment outcomes.

Diagnostic Imaging Evaluation of Cervical Cancer

The goals of clinical staging in patients with invasive disease include determining the appropriateness and extent of initial surgical treatment, as opposed to initial treatment with combined radiation therapy and synchronous chemotherapy. Although not formally part of clinical staging, modern sophisticated diagnostic imaging can enhance clinical assessment of disease volume and extent in women with cervical carcinoma, thus refining both selection of treatment and technical implementation of treatment modalities.

The FIGO staging system is based predominantly on clinical EUA, ultrasonography, intravenous urography, cystoscopy, proctoscopy, and chest radiography. Significant inaccuracies occur in this staging because of possible errors in gynecologic examination (24% to 39%).[76] The various imaging modalities have a complementary role in the accurate staging and complete evaluation of the cancer that have important therapeutic implications.

Today, clinicians most often obtain a contrast-enhanced CT scan of the abdomen and pelvis for patients with disease of stage Ib2 or greater (Fig. 91-9).[77] Lymph nodes larger than 1.0 to 1.5 cm in diameter are suspicious for tumor involvement and should be biopsied. Unfortunately, microscopic metastases are not readily detected with CT, and the inflammation commonly associated with advanced disease may cause enlargement of nodes that do not contain metastases. The sensitivity of MRI in the detection of regional metastases is similar to that of CT. However, MRI provides better anatomic delineation and accurate estimation of the tumor size, volume, and local extent within the pelvis, which can influence the choice of therapy (Fig. 91-10). Involvement of the vagina, parametrium, pelvic wall muscles, ureter, bladder, and rectum can be better assessed for accurate staging (Fig. 91-11).[76] MRI before and after vaginal opacification with contrast medium can be used if imaging evaluation of the vaginal wall or fornices is required.[78] T_2-weighted images obtained by using phased-array coil, fast-spin-echo or conventional spin-echo techniques are accurate in local staging and lymph nodal assessment; the former technique is faster with increased resolution.[79] Dynamic contrast-enhanced T_1-weighted images are helpful in identifying smaller tumors, fistulous tracts, and invasion into bladder and rectum.[74] Dynamic contrast-enhanced imaging is useful in differentiating areas composed predominantly of tumor cells (well-enhanced areas) from those of fibrous tissue with scattered cancer cells (poorly enhanced areas). This information can be helpful, as radiation therapy is more effective in well-enhancing tumors.[80]

MRI is very useful in the evaluation of tumor volume and enlarged lymph nodes, inherently important prognostic factors as well as determinants of the design of radiation treatment ports and selection of radiation dose. However, MRI cannot identify micrometastases to lymph nodes and differentiate malignant from nonmalignant enlargement. MRI with newer contrast agents like ultrasmall

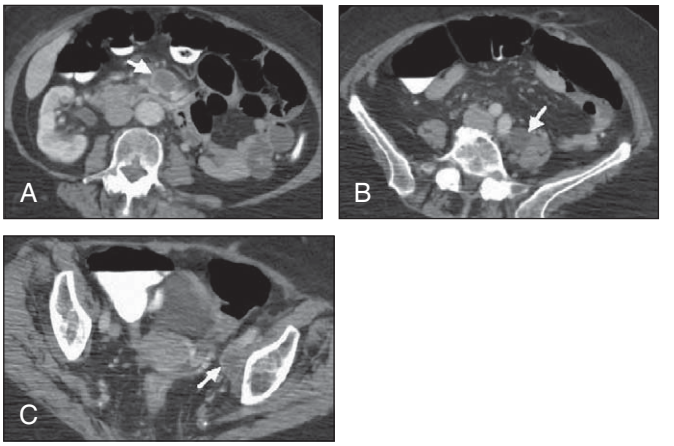


Figure 91-9 • Pattern of nodal metastases *(arrows)* on CT. Necrosis is a common feature of squamous cell carcinoma. **A,** Para-aortic node. **B,** Retroperitoneal node. **C,** External iliac node.

Table 91-3 American Joint Committee on Cancer and International Federation of Gynecology and Obstetrics Staging Systems for Cancer of the Uterine Cervix

AJCC TNM Categories	FIGO Stages	
TX	—	Primary tumor cannot be assessed
T0	—	No evidence of primary tumor
Tis	0	Carcinoma in situ
T1	1	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a	Ia	Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions—even with superficial invasion—are T1b/Ib. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm. Vascular space invasion, venous or lymphatic, does not affect classification
T1a1	Ia1	Measured stromal invasion ≤3.0 mm in depth and ≤7.0 mm in horizontal spread
T1a2	Ia2	Measured stromal invasion >3.0 mm and ≤5.0 mm with a horizontal spread ≤7.0 mm
T1b	Ib	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/Ia2
T1b1	Ib1	Clinically visible lesion ≤4.0 cm in greatest dimension
TIb2	Ib2	Clinically visible lesions >4.0 cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to the lower third of vagina
T2a	IIa	Tumor without parametrial invasion
T2b	IIb	Tumor with parametrial invasion
T3	III	Tumor extends to the pelvic wall, and/or involves the lower third of the vagina, and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIa	Tumor involves lower third of the vagina, no extension to pelvic wall
T3b	IIIb	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4	IVa	Tumor invades mucosa of the bladder or rectum, and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
M1	IVb	Distant metastasis

REGIONAL LYMPH NODES (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

DISTANT METASTASIS (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage Ia1	T1a1	N0	M0
Stage Ia2	T1a2	N0	M0
Stage Ib1	T1b1	N0	M0
Stage Ib2	T1b2	N0	M0
Stage IIa	T2a	N0	M0
Stage IIb	T2b	N0	M0
Stage IIIa	T3a	N0	M0
Stage IIIb	T1	N1	M0
	T2	N1	M0
	T3a	N1	M0
	T3b	Any N	M0
Stage IVa	T4	Any N	M0
Stage IVb	Any T	Any N	M1

Continued

Table 91-3 American Joint Committee on Cancer and International Federation of Gynecology and Obstetrics Staging Systems for Cancer of the Uterine Cervix—cont'd

NOTES ABOUT THE STAGING SYSTEM

Stage 0 cases have full-thickness involvement of the epithelium with atypical cells but with no signs of invasion into the stroma. (Case of stage 0 disease should not be included in any therapeutic statistics for invasive carcinoma.)

As a rule, it is impossible to estimate clinically whether a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded.

A growth fixed to the pelvic wall by a short and indurated but not nodular parametrium should be assigned stage IIb. It is impossible at clinical examination to decide whether a smooth and indurated parametrium is truly cancerous or only inflammatory, and thus such cases should be classified as stage III only if the parametrium is nodular to the pelvic wall or if the growth itself extends to the pelvic wall.

The presence of hydronephrosis or nonfunctioning kidney caused by stenosis of the ureter by cancer permits a case to be classified as stage III even if, according to the other findings, the case should be classified as stage I or stage II.

The presence of bullous edema, as such, should not permit a case to be classified as stage IV. Ridges and furrows into the bladder wall should be interpreted as signs of submucous involvement of the bladder if they remain fixed to the growth at palposcopy (i.e., examination from the vagina or the rectum during cystoscopy). A finding of malignant cells in cytologic washings from the urinary bladder requires further examination and biopsy from the wall of the bladder.

RULES FOR CLINICAL STAGING

Staging should be based on careful clinical examination and should be performed before any definitive therapy. Ideally, the examination should be performed under anesthesia by an experienced examiner.

The clinical stage must under no circumstances be changed on the basis of subsequent findings.

When doubt exists as to the assignment of stage, the case must be classified as the earlier stage. For staging purposes, the following examination methods are permitted: palpation, inspection, colposcopy, endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, intravenous urography, and X-ray examination of the lungs and skeleton. Suspected bladder or rectal involvement should be confirmed by biopsy and histologic evidence.

Findings on examinations such as lymphangiography, arteriography, venography, laparoscopy, and so forth are valuable for planning therapy, but because such studies are not yet generally available and because interpretation of the results is variable, the findings of such studies should not be the basis for changing the clinical staging.

Infrequently, hysterectomy is performed in the presence of unsuspected extensive invasive cervical carcinoma. Such cases cannot be clinically staged or included in therapeutic statistics, but they should be reported separately.

Only strict observance of the rules for clinical staging will allow meaningful comparison of results between clinics and modes of therapy.

From Fleming I, Cooper JS, Henson DE, et al. (eds): AJCC Cancer Staging Manual, 5th ed. Philadelphia, Lippincott Williams & Wilkins, 1997, pp 189–194.

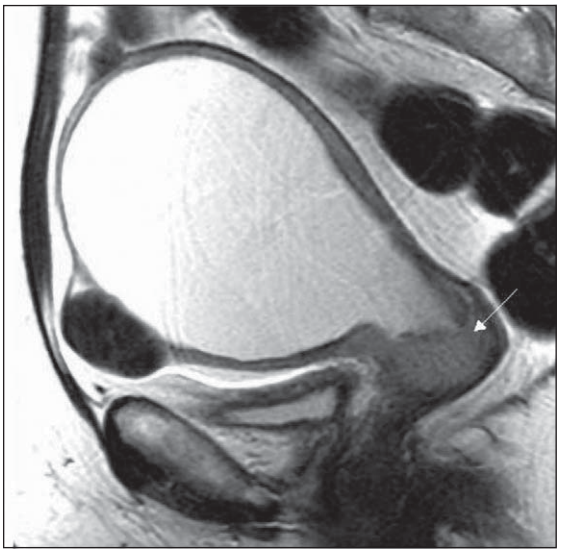


Figure 91-10 • Cervical cancer on MRI. T2-weighted sagittal image shows a cervical mass *(arrow)* causing stenosis and fluid accumulation in uterus.

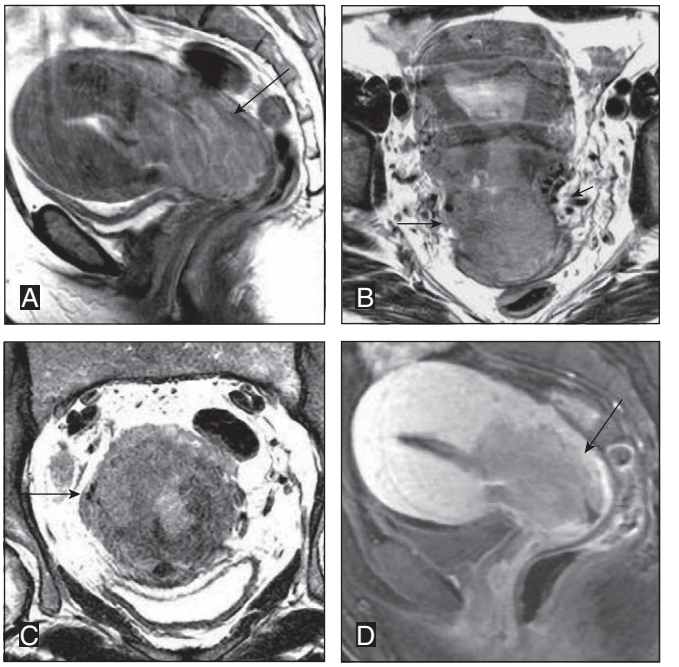


Figure 91-11 • Cervical cancer on MRI. **A,** Sagittal T2-weighted image showing a heterogeneous isointense mass in the cervix extending into the posterior wall of the uterine body *(arrow)*. **B,** T2-weighted image sliced coronally through the cervix showing a mass protruding into the uterine cavity (*arrow*). **C,** T2-weighted image sliced axially across the cervix showing a bulky, eccentric cervical mass on the right side with spread beyond the T2 hypointense ring of the cervical stroma into the parametrium (*arrow*). **D,** T1-weighted gadolinium-enhanced image revealing clear delineation of the mass relative to the adjacent uterus *(arrow)*.

superparamagnetic iron oxide has been useful in distinguishing benign from malignant nodes.[81] The shape, volume, and direction of the growth of the tumor can be well assessed, and these are crucial for planning brachytherapy and external-beam radiotherapy.[74] MRI also is useful in the follow-up evaluation of the tumor, its response to treatment, and identification of recurrences. However, benign conditions like edema or inflammation sometimes cannot be differentiated from tumor. Dynamic contrast-enhanced MRI is useful in differentiating malignant lesions that usually have shorter and stronger enhancement than benign conditions in patients who have abnormalities after treatment for cervical cancer.[82]

Recent studies have suggested that [(18)] fluorodeoxyglucose positron emission tomography (FDG-PET) is more sensitive and specific than more standard radiographic studies in the detection of lymph node involvement by cervical cancer.[83–85] Grigsby and colleagues[86] have reported a strong correlation between abnormal post-therapy FDG uptake and tumor recurrence. Inconsistent reimbursement for the study continues to be a barrier to widespread use in U. S. patients with cervical cancer, and the cost of the study currently prevents its widespread international use in this generally medically underserved group of patients.

Laboratory Evaluation

Routine laboratory assessment should include complete blood counts with differential counts and red cell indices. Many patients with advanced disease will be anemic at the time of diagnosis, often reflecting chronic blood loss and iron deficiency. Anemic patients treated with radiation or chemoradiation have poorer outcomes than do patients with near-normal hemoglobin levels.[87–90] Anemia at diagnosis (before treatment) correlates significantly with reduced pelvic control and survival with univariate analysis, but not always when data are subjected to multivariate analysis. In contrast, multivariate analysis reveals that hemoglobin level during the course of radiation therapy or chemoradiation is a robust predictor of local outcome and survival.[87–90] Transfusion for anemic patients with maintenance of average weekly nadir hemoglobin levels at or above 11 to 12 g/dL through radiation therapy is associated with improvement in prognosis to that associated with patients with near-normal or normal hemoglobin levels at diagnosis.[87,89] This effect may be partially mediated through better tumor oxygenation and oxygen-enhanced radiation lethality to clonogenic cells as well as reduced angiogenesis in better-oxygenated tumors. With pelvic or extended-field radiation that will encompass a substantial percentage of adult bone marrow, hemoglobin may decline slowly, even when adequate iron stores are present and patients are supported with hematinics. Concurrent administration of cisplatin further aggravates this problem, and can result in clinically significant reduction in hemoglobin levels over the course of a 6- to 8-week program of chemoradiation, even in patients with normal hemoglobin levels at the time of diagnosis. Frequent monitoring of hemoglobin levels as well as white cell counts and platelets should be performed throughout a course of chemoradiation, and hemoglobin level should be supported, either by transfusion or through the use of recombinant erythropoietin. The minimal hemoglobin level required is uncertain, but it seems prudent to target a minimum of 10 g/dL.

Neutropenia may indicate supportive treatment with granulocyte-colony-stimulating factor (G-CSF) to avoid prolonged treatment interruptions that are known to adversely affect local tumor control in patients treated with radiation.[91,92] Absolute neutrophil counts should be monitored at least weekly in patients undergoing chemoradiation.

An elevated platelet count has been associated with advanced malignancy and is considered a consequence of increased platelet production.[93] Hernandez and associates[94] identified this effect in advanced cervical cancer, and Rodriguez and coworkers[95] identified the preoperative platelet count as an adverse prognostic factor, even for patients with stage Ib cervical carcinoma. The cumulative 5-year survival of women with a platelet count greater than 300,000 (85 women) was 65%, compared with 84% for the group with a normal value (134 women). At issue was the question of whether the value could have been elevated simply because of bleeding from the primary tumor, but no association was found with the preoperative hematocrit. This study of surgically treated patients with early disease also demonstrated that the effect was not a consequence of metastatic disease and did correlate with tumor volume, with nearly half of the patients with platelet counts in excess of 300,000 having "large" lesion size, in contrast to only 28% (32 of 114) patients with normal counts.[96] In a multivariate analysis, adjusting for age, race, tumor size, and presence of lymph node metastases, high platelet count was still associated with an adverse prognosis.

Additional laboratory tests should include a complete chemistry panel with serum electrolytes and measurements of renal and hepatic function. Electrolytes and renal function should be monitored repeatedly through a course of chemoradiation. Creatinine may be elevated secondary to hydroureter/hydronephrosis that may require ureteral stent placement or nephrostomies before radiation therapy, particularly if cisplatin chemotherapy is anticipated. Serum sodium and potassium may become abnormal during the course of chemoradiation, particularly in elderly patients, consequent to diarrhea with potassium loss, inadequate oral replenishment, and inadequate or inappropriate fluid intake.

PROGNOSTIC FACTORS

Prognostic factors fall into two groups, tumor-related factors and patient-related factors. Probably the most important tumor-related factor is tumor size, and this is true both for patients treated with hysterectomy[96,97] and for patients treated with radiation therapy.[98–100] In fact, FIGO, in 1995, divided stage Ib into two groups according to size; other stage categories act, in part, as surrogates for tumor size. For patients treated with surgery, histologic evidence of extracervical spread is associated with a poorer prognosis. Parametrial extension is associated with a higher rate of lymph node involvement, local recurrence and death from cancer.[101,102] Uterine body involvement is associated with an increased rate of distant metastases in patients treated with radiation therapy or surgery.[103,104]

Lymph node involvement is another important tumor-related factor. After radical hysterectomy, reported-year survival rates usually are about 35% to 40% lower when the pelvic lymph nodes are involved.[105,106] However, recent studies suggest that postoperative chemoradiation improves these results.[107] Several reports suggest that survival decreases with increasing size of the largest involved nodes,[108,109] increasing number of nodes involved,[106,110] and the increasing level of regional involvement and with extent of central disease in the cervix. Overall, the survival rates for patients with positive para-aortic nodes are about half those of patients who have similar stages of disease without para-aortic lymph node involvment.[111–113] LVSI also is correlated with an increased risk of recurrence. This reflects, in part, the strong correlation between LVSI and lymph node involvement; however, in a large number of postoperative studies, LVSI is an independent predictor of prognosis.[106,114–116]

Investigators have compared the outcome of patients with adenocarcinomas with squamous carcinomas and have reached varying conclusions about the relative prognoses of the two histologic types of cervical cancer.[117–119] In a review of 1767 patients with stage Ib disease (229 with adenocarcinoma), Eifel and colleagues[120] found that patients with adenocarcinoma had a significantly higher risk of recurrence and death from disease, independent of age, tumor size, or tumor morphology. The rate of distant metastasis for patients with bulky (>4 cm) adenocarcinomas was almost twice that for patients with squamous carcinoma (37% vs. 21%, $P < 0.01$). Several investigators have reported high recurrence rates after radical hysterectomy

for adenocarcinomas. In a recent subset analysis of a randomized Gynecologic Oncology Group study, Rotman and associates[121] reported a high recurrence rate (11 of 25 patients [44%]) after treatment with radical hysterectomy alone for adeno-adenosquamous carcinomas of the cervix; in contrast, only 3 of 31 patients (10%) who received postoperative radiation therapy had recurrences. However, it is important to remember that all of these comparisons are compromised by the relatively small number of patients treated with cervical adenocarcinomas.

Other tumor factors include correlation between the serum concentration of squamous cell carcinoma antigen and the extent of squamous carcinoma of the cervix.[122–124] Increased tumor vascularity has been associated with a relatively poor prognosis,[125,126] and a strong inflammatory response in the cervical stroma tends to predict a good outcome.[125] Some authors have reported a correlation between HPV subtype and prognosis.[27] Several investigators have reported a higher recurrence rate in patients with histologically negative lymph nodes when a polymerase chain reaction assay of the lymph nodes was strongly positive for HPV DNA.[127,128] Other authors have correlated poor prognosis with the presence of HPV mRNS[128] or HPV-related proteins[129] in the peripheral blood of cervical cancer patients.

Patient-related factors have been discussed in different sections of this chapter and include age, hemoglobin, platelet counts, race, and smoking.[130] Several studies have demonstrated that in the United States, women of color with invasive cervical cancer present with higher-stage disease[131–133] and lower hemoglobin levels[134,135] than white women. Differences in socioeconomic status may influence minority patients' access to care and ability to comply with treatment recommendations.[135] In a study of 1304 women treated with radiation for cervical cancer, Kucera and colleagues[130] reported that smokers with cervical cancer had a poorer 5-year survival rate than nonsmokers. This difference was statistically significant for patients with stage III disease (5-year survival 20.3% vs. 33.9%, $P < 0.01$). However, in their analysis, the authors did not analyze the possible influence of smoking-related deaths from causes other than cervical cancer.

TREATMENT OVERVIEW

The treatment of patients with cervical cancer is determined primarily by the stage and extent of disease. As a general rule, CIS and microinvasive cervical cancer with no more than 3 mm of stromal invasion and no more than 7 mm breadth (FIGO stage Ia1) are managed with conservative surgery (excisional conization or extrafascial/simple hysterectomy). Microinvasive cervical cancer with 3 to 5 mm of stromal invasion and no more than 7 mm breadth (FIGO stage Ia2) may be managed with modified radical hysterectomy. Stages Ib1 and small-volume IIa may be managed with either radical surgery (generally radical hysterectomy or modified radical hysterectomy), radiation alone, or chemoradiation. Controversies surround the optimal management of patients with bulky stage Ib2 (>4 cm) cancer, who may be treated with triple-modality therapy in selected instances (surgery, radiation, chemotherapy in a variety of possible sequences).

After initial radical surgical therapy, patients with adverse histopathologic factors may be advised to undergo adjuvant pelvic radiation or adjuvant chemoradiation. Risk factors for recurrence include metastatic disease in regional nodes, positive surgical margins, parametrial extension, deep cervical stromal invasion, lymphovascular space invasion, and large tumor size.

Patients with large FIGO stage IIa or with stages IIb through IVa usually are managed with chemoradiation. Some patients with an incomplete response to chemoradiation may benefit from a combined approach using adjunctive hysterectomy to clear persistent central disease after chemoradiation. Patients with bulky Ib2 or IIa disease and rare patients with bulky central stage IIb lesions with minimal, medial parametrial invasion may be considered for this approach. For patients in whom disease recurs centrally in the pelvis after maximal chemoradiation, radical exenterative surgery can be performed, provided that no distant disease is present. Optimal candidates have mobile central disease without lymph node involvement.[136–138] Intraoperative radiation therapy (IORT) may be part of salvage surgery when lateral or posterior surgical margins will be predictably inadequate.[139,140] Recurrent disease after initial radical surgery historically has been treated with salvage radiation, but currently should be treated with chemoradiation.[141]

Superficial Ablative Therapy

A major deficiency of all ablative therapies is the absence of full histopathologic assessment of the lesion treated, and the hazard of undertreatment of an occult invasive lesion. For this reason, use of ablative techniques is declining appropriately. Three superficial ablative techniques used historically are electrocoagulation diathermy, cryosurgery, and CO_2 laser therapy.

Hysterectomy

Hysterectomy involves the removal of the uterus and varying amounts of surrounding tissue (Fig. 91-12). Because the risk of ovarian metastases is low (0.5%), ovarian preservation usually is recommended in premenopausal women, obviating the need for hormone replacement therapy.[142] An important exception is when nodal metastases from a primary cervical adenocarcinoma are detected intraoperatively, when the risk of ovarian metastasis escalates steeply, perhaps to as high as 25%.[143] Five types of hysterectomy have been described.[144]

Extrafascial or Simple Hysterectomy (Type I)

Extrafascial or *simple hysterectomy* involves the removal of the cervix, adjacent tissues, and a small cuff of the upper vagina in a plane outside the pubocervical fascia; it is appropriate treatment for stage Ia1 disease. Minimal disturbance occurs to the bladder and ureters, which decreases the risk of urinary complications.

Modified Radical Hysterectomy (Type II)

Modified radical or *Wertheim's hysterectomy*, less extensive than the radical hysterectomy, removes the cervix and proximal 1 to 2 cm of vagina, including the paracervical and parametrial tissues. The ureters are dissected to the point of entry to the bladder to allow safe removal of parametrial and paracervical tissue. The medial half of the cardinal ligaments and the uterosacral ligaments also are removed.

Radical Hysterectomy (Type III)

A *radical* (*Meigs'*) *hysterectomy* includes removal of the uterus, cervix, and paracervical, parametrial, and paravaginal tissues to the pelvic sidewalls bilaterally in continuity, with as much of the uterosacral ligaments as possible. The uterine vessels are ligated at their origin, and the proximal one fourth to one third of the vagina and paracolpos is resected. This operation usually is performed in conjunction with bilateral therapeutic pelvic lymphadenectomies. Acute complications include blood loss (average, 800 mL), ureterovaginal fistula (1% to 2%), vesicovaginal fistula (<1%), pulmonary embolus (1% to 2%), small bowel obstruction (1%), and febrile morbidity (25% to 50%). Subacute complications include transient bladder dysfunction lasting 1 to 7 weeks (30%) and lymphocyst formation (<5%). Chronic complications include bladder hypotonia and atonia in about 3% of patients and, uncommonly, ureteral strictures. Rare patients may have transient or permanent lower extremity lymphedema.

Extended Radical Hysterectomy (Type IV)

In addition to the tissue removed in the type III, *extended radical hysterectomy* removes the periureteral tissue, the superior vesicle artery, and up to three fourths of the vagina. This procedure is rarely done, because patients with the anatomic extent of disease that would warrant such treatment generally should be treated with chemoradiation.

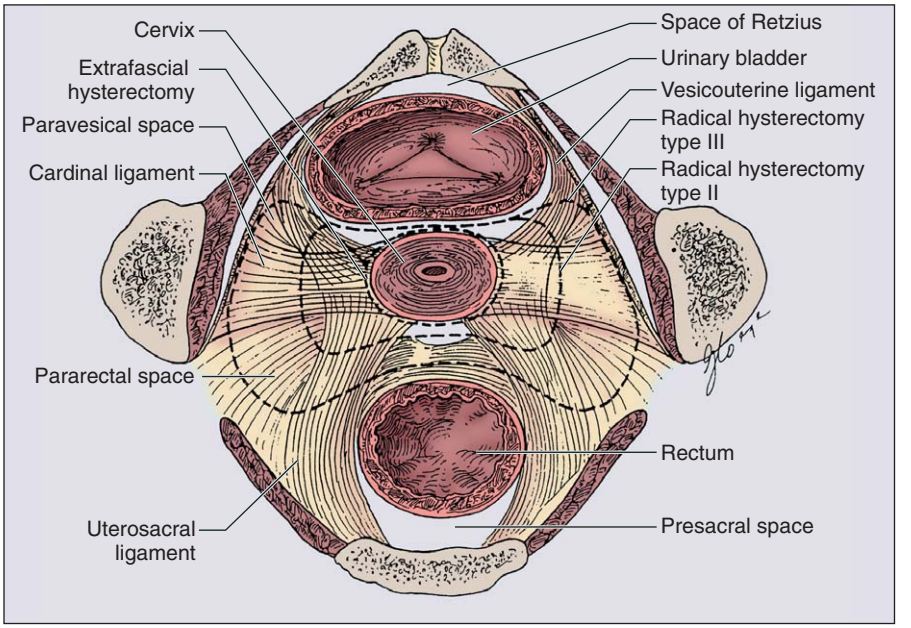


Figure 91-12 • Diagram of pelvic anatomy and types of hysterectomy. (From Berek JS, Hacker NF: Practical Gynecologic Oncology, 2nd ed. Baltimore, Williams & Wilkins, 1994.)

Partial Exenteration (Type V)

Partial exenteration is rarely performed, because radiation therapy should be used for patients with the extent of disease that would require surgery of this extent for gross anatomic clearance. Parts of the distal ureters and bladder are resected in this procedure. This may be appropriate initial surgery for patients with FIGO stage IVa cancer with large vesicovaginal fistulae and incontinence. However, vesicovaginal fistulae may scar closed in some patients after high-dose radiation therapy if the upper vagina is permitted to fuse shut, thus restoring urinary continence.

Surgical Alternatives to Conventional Radical Abdominal Hysterectomy

The late 1980s and the 1990s witnessed a proliferation of surgical techniques consequent to the availability of the sophisticated instruments and optical equipment required for laparoscopic surgery, a resurgence of interest in vaginal hysterectomy, and concerns about preserving reproductive potential in young women with early cervical cancer.

Radical vaginal hysterectomy carried out by the methods of Schauta-Stoeckel (less radical) or Schauta-Amreich (more radical) is a surgical alternative to radical or modified radical abdominal hysterectomy (types II and III) that may be associated with shorter hospital stays and more rapid recuperation. Laparoscopic radical hysterectomy performs an operation comparable to a radical hysterectomy (type III hysterectomy) entirely through the laparoscope, including the vaginal closure.

Laparoscopy has been coordinated with vaginal hysterectomy, with varying amounts of surgery being carried out via the laparoscopic approach, ranging from pelvic and para-aortic lymphadenectomy to lymphadenectomy plus important components of the radical hysterectomy.[145–147]

Radical cervicectomy is an operation suitable for selected patients with small, generally exophytic squamous tumors (usually <2 cm, although some patients with larger tumors have been treated in this fashion) involving primarily the exocervix who desire conservation of reproductive capacity. In this surgery, the main trunk of the uterine artery is preserved, although branches to the cervix and vaginal fornices are sacrificed before amputation of the cervix at a point approximately 5 mm caudal to the uterine isthmus. The uterus is suspended from the lateral stumps of the transected paracervical ligaments. Isthmic cerclage is performed in a fashion similar to that used as prophylaxis against miscarriage, and an anastomosis between the vaginal mucosa and the isthmic mucosa is performed. Variations on this surgery can be performed vaginally with laparoscopy, or abdominally. The margin between the superior extent of the tumor and the uterine isthmus must be a minimum of 1.5 cm, but 2 cm is preferable. MRI can be used preoperatively to assist in patient selection for this procedure. Intraoperative assessment by inspection of the trachelectomy specimen and frozen-section pathologic study are done to ensure an adequate surgical margin, and patients must be prepared for hysterectomy in the eventuality that a satisfactory margin cannot be obtained. Numerous successful pregnancies have been reported after such surgery, although the risk of miscarriage is increased. In carefully selected patients, the risk of cancer recurrence is very small.[148–150]

Damage to the pelvic autonomic nerves during radical hysterectomy is responsible for much of the late morbidity after surgical treatment of FIGO stages Ia2 to IIa cervical cancer, including problems with bladder function, defecation, and sexual dysfunction. Nerve-sparing radical abdominal hysterectomy[151] endeavors to spare important components of the autonomic innervation of the true pelvis by identification and preservation of the hypogastric nerves, which carry sympathetic fibers; the inferior hypogastric plexus formed from the fusion of the hypogastric nerves with fibers of the pelvic splanchnic nerves derived from sacral roots S2 to S4, which carry parasympathetic fibers; and the most distal part of the hypogastric plexus, which extends to the lateral vaginal wall and the base of the bladder. In aggregate, these structures are important in controlling bladder compliance, urinary continence, vaginal lubrication and genital engorgement during sexual arousal, small muscle contractions with orgasm, and some rectal functions. This recent surgical innovation is intended not to compromise the efficacy of the cancer surgery, while preserving important components of quality of life in cancer survivors. Precise criteria for patient selection have not been defined.

Radiation Therapy

Radiation therapy for cervical cancer usually consists of a combination of external radiation (teletherapy) and intracavitary or interstitial radioisotope therapy (brachytherapy). Roentgen discovered r-rays in 1895. Radium was discovered by the Curies in 1898. Biologic effects of so-called "Roentgen rays" on skin soon were appreciated after

prolonged exposures had occurred. Serendipitous discovery of the acute biologic effect of exposure to radium came when the discoverer of radioactivity, Becquerel, carried a 200-mg sample in his vest pocket for 6 hours and experienced an ulcerating burn as a result.

Roentgen rays were first applied to the cervix in 1901 using a transvaginal cone. Intracavitary brachytherapy for cervical cancer with radium first was described around 1902. Interstitial brachytherapy with radium was first proposed by Alexander Graham Bell in 1903. In the past 100 years, the discipline of radiation oncology has evolved as a medical specialty because of continuous refinements in medical radiation dosimetry, increasing sophistication of equipment, and progress in understanding the biologic consequences of radiation exposure in both cancer and normal tissues and cell lines (radiobiology).

Patients with very-small-volume cervical tumors of stages Ia1 to Ib1 (Ib1, <1 cm in diameter) can be treated successfully with intracavitary brachytherapy alone, with results that parallel the efficacy of surgery.[152] Brachytherapy alone, particularly if conducted on an outpatient basis with high-dose-rate (HDR) technology, may serve as suitable alternative therapy for medically compromised patients for whom operative intervention implies more than minimal risk of intraoperative or perioperative morbidity. At the other end of the spectrum of invasive disease, patients with very extensive stage III or IVa cervical cancer may not have geometry compatible with brachytherapy, and cure sometimes may be accomplished with teletherapy administered alone (or, more commonly, in combination with chemotherapy) by using progressively smaller teletherapy treatment volumes carried to progressively higher cumulative radiation dose ("shrinking fields technique"). However, radiation-based therapy with curative intent is accomplished for most patients with a combination of external beam (teletherapy) and intracavitary or interstitial isotope therapy (brachytherapy).

Conventional teletherapy is given in a fractionated course by using daily doses of 1.8 to 2 Gy per fraction, five fractions weekly. Selected patients may benefit from twice-daily fractionation by using a "field within a field" concurrent boost to limited volumes of nodal or parametrial disease. Altered fractionation may serve to keep the overall duration of treatment as short as possible, which has been correlated with improved local control and survival. It should be emphasized that target volumes and teletherapy dose distributions are not standardized and should be based on pretreatment imaging studies that define disease extent rather than on FIGO stage. Depending on the presence or absence of nodal metastases and the anatomic level of nodal disease, teletherapy ports may encompass only nodes caudal to the bifurcations of the common iliac arteries (approximately at the interspace between the fifth lumbar vertebra and the first sacral segment), nodes to the level of the aortic bifurcation (approximately at the level of the third lumbar vertebra), or to a volume extending to encompass para-aortic nodes to the level of the cisterna chyli (approximately at the level of the 12th thoracic vertebra). Treatment of such widely differing volumes, particularly when done with synchronous chemotherapy, implies substantial variability in acute symptomatic tolerance, hematologic tolerance, and potential delayed sequelae of treatment. Routine treatment of standard volumes is not a substitute for appropriate diagnostic assessment of disease extent and treatment tailored in consideration of both tumor and patient factors.

The brachytherapy dose conventionally has been calculated and prescribed at points A and B (Fig. 91-13). Doses to the bladder neck and anterior rectal wall (dose-limiting normal structures) usually are specified as well (Fig. 91-14).[153] Brachytherapy usually is accomplished by using one or two intracavitary or interstitial inpatient applications LDR (40 to 60 cGy/hr) technologies. Most applicators for intracavitary brachytherapy resemble the apparatus in Figure 91-15, and consist of intrauterine tandem and paired colpostats or ovoids, which are placed in the lateral vaginal fornices, resulting in a classic pear-shaped isodose distribution. The customary strategy is intracavitary brachytherapy supplemented by tailored teletherapy

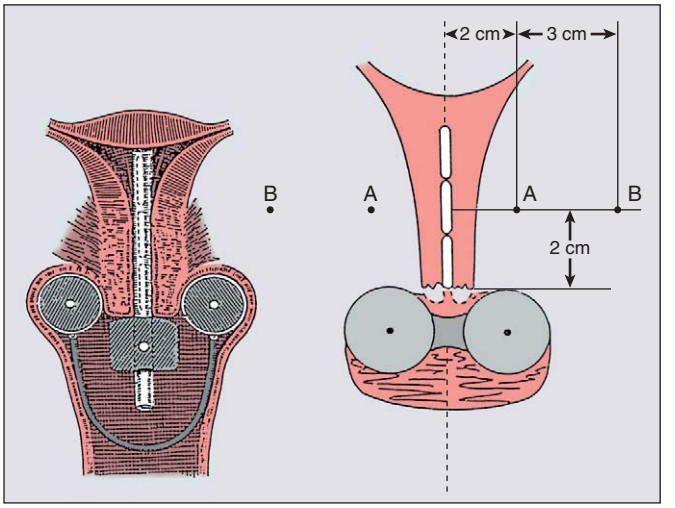


Figure 91-13 • Points A and B for cervical radiation therapy. (From Hoskins WJ, Perez CA, Young RC [eds]: Principles and Practice of Gynecologic Oncology, 2nd ed. Philadelphia, Lippincott, 1997, p 678.)

treatment to boost volumes, generally lateral and posterior to the cervix and medial parametria. In patients whose vaginal anatomy does not accommodate tandem and colpostat devices (a so-called "conical vagina" with flush or ablated fornices and a narrowed upper vagina) or patients with extensive, lateral parametrial invasion, interstitial implantation may provide more satisfactory dose distribution when gross tumor extends beyond the traditional pear-shaped dose envelope provided by intracavitary brachytherapy (Fig. 91-16). Interstitial templates have been used to treat cervical cancer for many years; however, reported series have been small, and patient follow-up rarely has been sufficient to permit calculation of long-term survival rates.[154–156] One of the largest series is from University of California—Irvine, where they described 5-year survival rates of 21% and 29%, respectively, for patients with stage IIB and IIIB disease with high complication rates.[157] (Therefore, at present, there is no definite evidence to indicate that interstitial therapy improves the outcome of patients with advanced intact cervical lesions.)

LDR brachytherapy procedures require insertion under anesthesia and hospitalization for radiation safety and patient immobilization. Alternatively, multiple outpatient intracavitary insertions may be per-

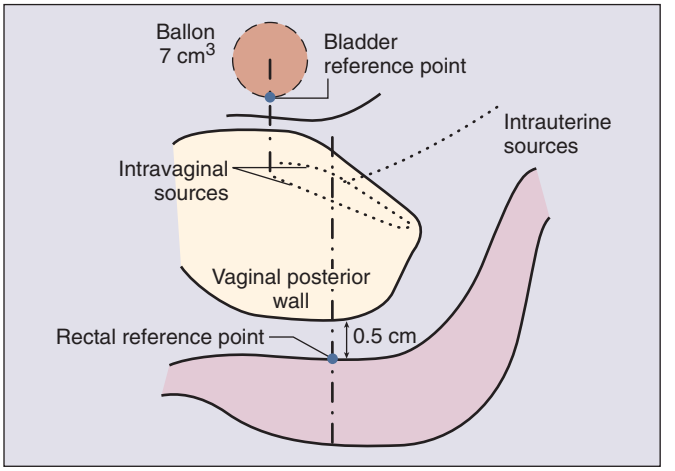


Figure 91-14 • Rectal and bladder reference points according to the International Commission on Radiation Units and Measurements Report 38. (From Cox JD [ed]: Radiation Oncology, 8th ed. St. Louis, Mosby, 2003, Fig. 28-16.)

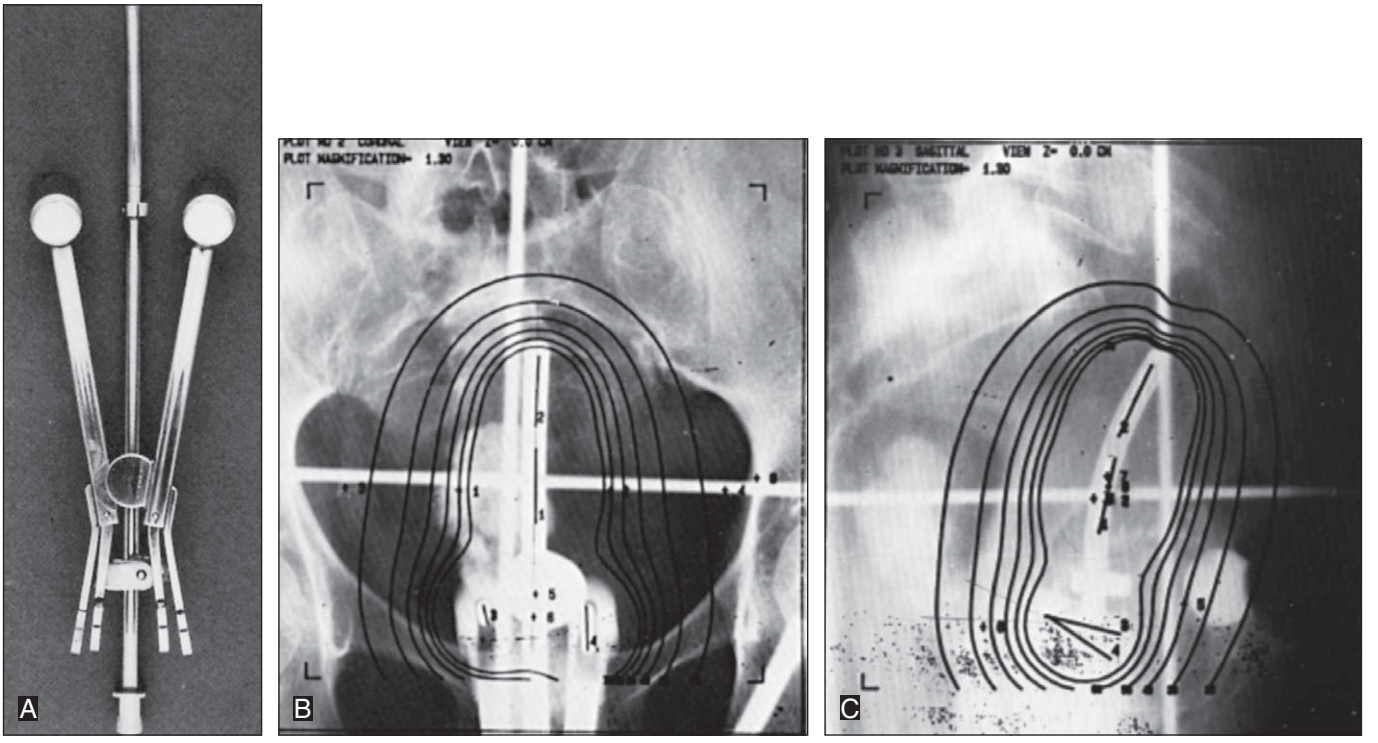


Figure 91-15 • **A,** Intracavitary device for brachytherapy. **B** and **C,** Treatment plan for cervical carcinoma showing a radiograph of the intracavitary irradiation in situ with its isodose distribution in cGy/hr. (**B** and **C,** From Shingleton SM, Kim RY: Treatment of cancer of the cervix. In Gusberg SB, Shingleton HM, Neppe G [eds]: Female Genital Cancer. New York, Churchill Livingstone, 1988, p 297.)

formed by using HDR (100 cGy/min) remote afterloading technology. Most commonly, five intracavitary insertions are performed when HDR technology is used. Because of miniaturization of the high-activity source and the hardware used for treatment, these insertions may be accomplished under conscious sedation when cooperative patients with favorable vaginal anatomy are selected. Because of inherent biologic disadvantages associated with HDR brachytherapy, substitution of this technology for conventional LDR systems has been controversial. More tailored dose distributions often can be designed with the inherently more flexible HDR systems than with historically used LDR equipment employing multiple sources with fixed physical dimensions and a limited spectrum of source strengths. The comparative data that exist suggest that HDR and LDR technologies are approximately isoeffective for tumor control and roughly equivalent with respect to complications when appropriate dose-rate corrections have been applied.[158,159]

It seems increasingly clear that either approach (LDR or HDR) in the hands of seasoned physicians with substantial brachytherapy experience is likely to be superior to the other approach in the hands of the clinician who is inexperienced or treats only a limited number of patients. Brachytherapy often has been defined as an art and not a science. The American Brachytherapy Society is attempting to place brachytherapy on a more rational, scientific basis by developing guidelines grounded in established practice and data driven to replace what has often been based on subjective criteria and intuition coupled with the hard lessons of experience.[160,161] Improvements in diagnostic

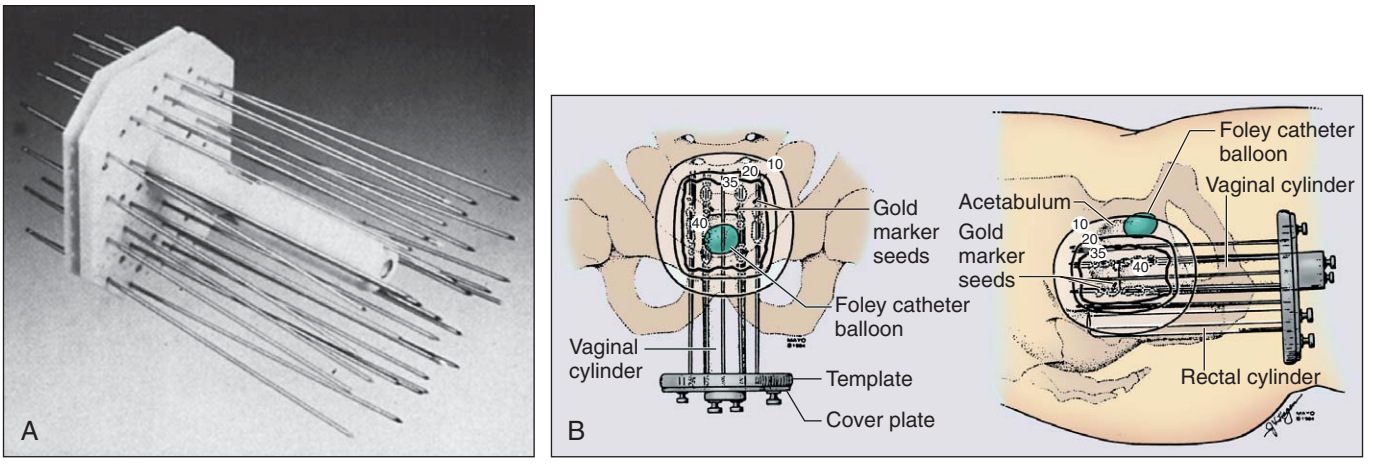


Figure 91-16 • **A,** Device for interstitial brachytherapy. **B,** Diagrams of the same device in coronal and sagittal planes. (From Hoskins WJ, Perez CA, Young RC [eds]: Principles and Practice of Gynecologic Oncology, 2nd ed. Philadelphia, Lippincott, 1997, p 678.)

imaging (MRI, CT, PET, and combination, hybrid, or fusion studies) are anticipated to facilitate these efforts by providing improved understanding of the spatial relations of brachytherapy sources and both cancer and dose-limiting normal tissues. This effort, however, remains a work in progress.

In its definition as partially art rather than pure science, brachytherapy is similar to surgery. Skills atrophy unless used regularly. Understanding that fact should stimulate consideration of referral of patients requiring brachytherapy to centers of excellence where the annual volume provides greater assurance that the requisite skills and experience will be available.

The side effects of radiation therapy include both immediate and late effects. Acute reactions of radiation are seen in tissues with the most rapid cell turnover rates such as skin, intestinal mucosa, urothelium, vaginal mucosa, and bone marrow. Acute side effects of pelvic irradiation include diarrhea, abdominal cramps, tenesmus, urinary frequency, urgency, and dysuria. Some women experience vaginal bacterial overgrowth consequent to alterations in the integrity of the vaginal mucosa, causing symptoms of discharge and pruritus. Occasionally small-volume bleeding from the bladder or rectum may occur. Aggravation of hemorrhoidal disease is common. Older patients with extensive diverticular disease are vulnerable to development of diverticulitis under the influence of pelvic radiotherapy, which may result in pain, bleeding, perforation, and significant delay in completion of treatment. Rare patients experience bacterial overgrowth with *Clostridium difficile*, even in the absence of antecedent antibiotic exposure. Severe, prolonged diarrhea poorly responsive to standard medications and dietary modification should arouse the clinician's suspicion. Not uncommonly, pelvic radiation will provoke a recrudescence of herpes simplex virus type II, usually manifest as focal, discrete, well-marginated ulcerations on the labia caudal to the irradiated volume, although lesions may affect the urethra, bladder, and vagina. It is important for the radiation oncologist to recognize the labial lesions, the pattern of which tends to be discrete ulcerations, usually quite different from the more confluent, irregularly bordered, moist desquamative reaction seen with acute radiation dermatitis, because treatment for these conditions is quite different.

Late complications (onset months to years after radiation therapy) can be due to intimal proliferation in small arteries/arterioles with decreased blood supply and subsequent fibrosis or focal infarction. The larger the dose per treatment fraction, the greater the risk of late complications in normal tissues unavoidably included within the treatment volume. Most late complications of radiation therapy involve the rectum, bladder or small bowel. Although most serious gastrointestinal complications occur with the first 3 years, serious side effects also may occur several decades after treatment. The average time to onset of major urinary tract complications tends to be somewhat longer than that of intestinal complications. Late effects of pelvic irradiation may include chronic radiation cystitis with urothelial atrophy, irritative symptoms, and bleeding. In rare patients, vesicovaginal fistulae may develop, usually at the level of the bladder neck, where the brachytherapy dose often is highest. Vaginal stenosis with dyspareunia and compromised ability to perform surveillance follow-up is a somewhat avoidable consequence of radiation therapy if informed and compliant patients are provided with vaginal dilators and instructed in their use, as well as provided with vaginal estrogen cream. Chronic radiation proctitis or sigmoiditis with pain and small-volume bleeding can occur in some patients, with focal injury to the anterior rectal wall consequent to brachytherapy being the most common site for this late complication. Major hemorrhage is unlikely, except in patients with portal hypertension or therapeutic anticoagulation for medical comorbidities. Distressing bleeding often can be controlled through conservative, judicious laser ablation of bleeding telangiectatic vessels. Symptomatic large bowel stricture is uncommon, but may require fecal diversion in severe instances. Rectovaginal fistulae may be the consequence of severe injury to the rectovaginal septum and anterior rectal wall. This complication usually requires permanent fecal diversion, but occasional patients can have segmental resection with re-establishment of intestinal continuity. Most intestinal injury is to small intestine, commonly manifested by obstructive symptoms. The usual site is in the terminal ileum, but focal jejunal injury may be seen, particularly in patients undergoing extended-field treatment to encompass para-aortic lymph nodes. If the ovaries are in the treatment field, ablation of both endocrine and reproductive function will be the inevitable consequence of pelvic radiation therapy administered in cancerocidal dose to premenopausal women. Symptoms of estrogen deprivation may take several months to develop after pelvic radiation, depending on the age of the patient and endogenous body stores of estrogen. Usually the endometrium is ablated consequent to high mucosal dose from intracavitary brachytherapy. Occasional patients will have remnants of functioning endometrium. With the almost inevitable occlusion of the endocervical canal after brachytherapy, painful hematometra may develop in such patients if unopposed estrogen replacement therapy or cyclical hormone replacement is instituted. Generally, combined hormone replacement therapy will avoid this complication, which may necessitate hysterectomy in severe cases.

Chemoradiation

Synchronous administration of radiation and cytotoxic chemotherapy will enhance acute radiation reactions within all tissues included in the treatment volume, resulting in more severe acute symptoms. Impact on chronic radiation injuries is less predictable. Anxiety regarding normal tissue tolerance, both immediate and late, has delayed extrapolation of successful chemoradiation strategies for anal cancer to the larger volumes of vulnerable tissues routinely irradiated in the treatment of cervical cancer.

Multiple clinical trials have investigated the sequential use of neoadjuvant chemotherapy followed by conventional radical radiation therapy for patients.[162–165] In several of these studies, patients treated with neoadjuvant chemotherapy followed by radiation had worse survival probability than did patients treated with radiation alone. This has been attributed to selection of cross-resistant tumor clonogens as well as delay in initiation of the potentially curative therapy.

In dramatic contrast to the manifest failure of sequential chemotherapy and radiation, the large majority of recent prospective, randomized controlled trials investigating radiation and synchronous chemotherapy have demonstrated improvements in both local control and survival. Data from five phase III randomized clinical trials sponsored by the National Cancer Institute have shown that the addition of concurrent cisplatin-containing chemotherapy to radiation results in a reduction in risk of recurrence by 21%.[102,166–169] Four of these trials pertained to women with locally advanced cervical cancer, stages Ib2 to IVa. The fifth studied high-risk postoperative patients stages Ib to IIa with cancer extension to parametrium, surgical margins, or regional lymph nodes.

The optimal drug regimen is uncertain. Four of these trials had an experimental arm containing 5-fluorouracil (5-FU); however, the Gynecologic Oncology Group (GOG) prospectively compared weekly cisplatin with continuous-infusion 5-FU at 225 mg/m^2 for 5 days weekly (a lower daily dose than the 1000 mg/m^2/24 hr for 96 hours used in the previous positive studies) and terminated the study (GOG protocol 165) when it became clear that no possibility existed that the 5-FU arm might ultimately prove superior. Weekly cisplatin at a dose of 40 mg/m^2 for six doses has become the most commonly used regimen for concurrent chemotherapy with radiation for advanced cervical cancer.

However, the National Cancer Institute of Canada (NCIC) prospectively compared radiation alone with radiation plus weekly cisplatin in 259 patients with squamous cancers with bulky (≥5 cm) stage Ib2 to IIa, or smaller tumors with positive nodes, and patients with stages IIb to IVa cancers. The study was designed to have an 80% probability of detecting a 15% survival difference at 5 years.

Although patients receiving the cisplatin regimen did marginally better, the study failed to find a statistically significant difference.[170]

The Radiation Therapy Oncology Group (RTOG) prospectively compared radiation alone administered to extended volumes (pelvis plus para-aortic nodes) with pelvic radiation with three synchronous cycles of 5-FU and cisplatin, with one cycle administered synchronously with intracavitary brachytherapy. 5-FU was administered at 1000 mg/m^2/24 hr for 96 hours with each cycle, and cisplatin at 75 mg/m^2. The population of 403 patients composing the study population were identified and selected with entry criteria similar to those of the NCIC study (except that nonsquamous cancers were included). The relative risk of recurrence was 0.48 (90% confidence interval) in the chemoradiation arm compared with radiation alone.[171]

Further complicating this issue are the three additional prospective, randomized studies that have found relapse-free survival benefit from the synchronous administration of epirubicin with radiation,[171] mitomycin-C with radiation,[172] or 5-FU plus mitomycin-C with radiation,[173] and a fourth prospective randomized trial that failed to detect benefit from synchronous administration of cisplatin, vincristine, and bleomycin with radiation compared with radiation alone.[174]

Most studies have demonstrated that the use of combined chemotherapy and radiation therapy has been associated with statistically significant increase in gastrointestinal and hematologic toxicity that, although significant, has been tolerable. Data suggest that synchronous administration of chemotherapy potentiates radiation effect in cycling, immediately responding cell systems, in both cancer and normal tissue. Thus both immediate normal tissue reactions and side effects are potentiated. Importantly, an increase in catastrophic late complications such as bowel obstruction, fistula formation, or second malignancies, has not been seen. Given the preponderance of evidence, which now suggests that synchronous radiation with radiopotentiating chemotherapy favorably affects probability of cancer-free survival, clinical research into the optimal drugs and schedule of administration is likely to play a central role in clinical investigation for the foreseeable future.

TREATMENT OF LOCOREGIONAL DISEASE BY STAGE

Stage Ia1 and Ia2 (Microinvasion)

The purpose of defining microinvasion is to identify a group of patients who are not at risk for lymph node involvement and therefore are treatable with conservative therapy. In the current staging classification, stage Ia1 is defined as a tumor with stromal invasion no greater than 3 mm in depth beneath the basement membrane and no wider than 7 mm. Stage Ia2 is defined as a tumor with stromal invasion greater than 3 mm, no greater than 5 mm in depth, and no wider than 7 mm. Patients at highest risk for metastases or recurrence in this group appear to be those with evidence of tumor in the lymphovascular spaces.[106,175]

Patients with stage Ia1 disease can be adequately treated with therapeutic conization if conservation of reproductive capacity is desired, or extrafascial hysterectomy. The risk of pelvic lymph node metastases with 1 to 3 mm of stromal invasion is less than 1%.[176,177] For patients opting for therapeutic conization, the following histopathologic criteria should be met: (1) depth of stromal invasion 3 mm or less, (2) diameter of lesions less than 7 mm, (3) no lymphovascular invasion, and (4) clear margins. Patients treated with conization should be followed up closely with cytologic, colposcopic, and endocervical curettage evaluation every 3 months for the first year.[178] A vaginal or a type I abdominal hysterectomy (extrafascial) is appropriate treatment if future childbearing is not desired.

Microinvasive carcinoma with stromal invasion 3.1 to 5 mm is associated with a 5% risk of nodal metastases.[179] The preferred treatment for stage Ia2 is a modified radical (type II) hysterectomy with bilateral pelvic lymphadenectomy. Treatment with radiation also will have a high probability of success and may be preferable therapy in patients who are compromised surgical candidates based on age and comorbidities.

Stage Ib1, Ib2, and IIa

Stage Ib is defined as a clinically evident lesion confined to the cervix or preclinical lesions greater than those of Ia2. Patients with IIa disease have extension to the upper vagina without parametrial involvement. The incidence of pelvic nodal metastases is approximately 15% to 25% for patients with stage Ib disease.[179] Treatment must be directed toward the lymph nodes, cervix, parametrial tissue, paravaginal tissue, and upper vagina; therefore, a radical (type III) hysterectomy with bilateral pelvic lymphadenectomy and para-aortic lymph node evaluation has historically been the treatment of choice. Radiation therapy is as effective as surgery based on a prospective, randomized comparison conducted in Italy.[180] In that study, 337 analyzed patients (FIGO Ib1, Ib2, and IIa) were randomly assigned treatment with initial type III hysterectomy or with radiation therapy using a radiation dose (cumulative teletherapy and brachytherapy dose of 76 Gy at point A) that is substantially lower than the 85 to 90 Gy used in leading centers in the United States. Postoperative pelvic radiation therapy was administered to patients with positive nodes, positive margins, positive parametria, or less than 3 mm surgical margin. Forty-six of 55 patients (84%) with tumors larger than 4 cm in diameter received postoperative radiation therapy. Chemotherapy was not used. Five-year survival and disease-free survival were identical in both groups (83% and 74%, respectively). Serious complications occurred in 28% of the group treated initially with surgery, and 12% of the radiation therapy group. Theoretically, results with chemoradiation might well be superior to those with surgery, but the benefit for synchronous administration of chemotherapy has been documented only in patients with tumors larger than 4 cm (Ib2) or more advanced stages of disease.

Given that surgery and radiation therapy are approximately isoeffective with respect to cancer control, treatment generally is selected on the basis of physician and patient preference and differences in treatment-related morbidity. Surgery provides important prognostic information and offers premenopausal women the option of ovarian conservation, because the risk of ovarian metastases is only 0.5%.[142] Considerable debate concerns whether sexual function is more feasible or better after surgical treatment or radiation therapy. Both forms of treatment carry some risk of urologic injury or bowel injury. However, the nature of those complications, the ability to remedy those complications, and the impact of chronic complications on quality of life are both challenging to quantitate and vulnerable to quite subjective interpretation. Radiation carries a small but not trivial risk of late induction of second malignancies.

For patients with stage Ib1 who are young and free of major comorbid conditions, surgery tends to be the preferred option. In patients who are poor surgical risks or elderly, radiation therapy is more sensible. Radiation therapy usually is a combination of teletherapy intended to encompass the primary, microscopic regional extensions, and regional lymph nodes, supplemented by intracavitary brachytherapy intended selectively to take the gross disease in the uterus and cervix to a much higher dose while sparing normal tissues including bladder and rectum. When disease is very small (<1 cm in diameter), the risk of nodal metastases is low, and the treatment approach may be modified to intracavitary brachytherapy therapy alone with excellent results.[152]

The treatment of patients with stage Ib2 disease remains a source of continued controversy. With either surgery or radiation therapy, progressive decrements in survival probability are found as tumor size increases. In some centers, patients with stage Ib2 disease continue to undergo initial surgery, recognizing that most will have indications for postoperative radiation therapy, but that surgery will clear gross central disease, which is the most likely site of pelvic failure in

patients treated with radiation. Because the morbidity of combined therapy is greater, some surgeons limit the radicality of surgical extirpation in anticipation of postoperative radiation therapy in a sensible effort to limit morbidity.[181] Neoadjuvant chemotherapy with cisplatin, vincristine, and bleomycin for three cycles at 10-day intervals before attempted radical hysterectomy has been used with encouraging results in Ib2 cancers reported by Sardi and colleagues in Argentina.[182] Pathologic downstaging was observed in patients operated on after neoadjuvant chemotherapy compared with patients undergoing initial surgery. These results have not been reproduced in the context of a multi-institutional trial, when tested by the GOG.

Alternatively, radiation has been used as initial therapy supplemented by type I adjuvant hysterectomy to clear central disease. The GOG compared radical radiation therapy with attenuated preoperative radiation therapy supplemented by extrafascial hysterectomy.[183] A lower cumulative incidence of local relapse was noted in the radiation therapy plus hysterectomy group (at 5 years, 27% vs. 14%). No statistical differences were observed in outcomes between regimens, except for the adjusted comparison of progression-free survival, although all indicated a slightly lower risk in the adjuvant hysterectomy regimen (unadjusted relative risk [URR] of progression, 0.77; $P = 0.07$; URR of death, $P = 0.26$; both one-tailed). Because preliminary analysis of this trial suggested benefit from surgery in improved local control, the GOG carried out a successor trial in which all patients had attenuated preoperative radiation therapy, followed by extrafascial hysterectomy. Half of the patients were randomized to receive weekly cisplatin at 40 mg/m^2 during teletherapy. The rates of both progression-free survival ($P < 0.001$) and overall survival ($P = 0.008$) were significantly higher in the combined-therapy (chemoradiation) group at 4 years.[166]

Although interpretations of the outcomes of these studies vary, it has become less common to carry out adjunctive hysterectomy routinely in patients undergoing chemoradiation for Ib2 or bulky IIa disease. However, selected patients may benefit who have poor response to teletherapy and chemotherapy assessed at the time of intracavitary insertion, or who have poor vaginal anatomy, limiting the dose of brachytherapy that can be prudently prescribed.

Patients undergoing primary surgery for stage Ib and IIa cancer who are found to have adverse clinicopathologic prognostic factors may be advised to undergo adjuvant postoperative pelvic radiation therapy or adjuvant chemoradiation. Much effort has been expended in attempting to define clinicopathologic factors that reliably identify patients at high risk for failure after initial surgical therapy. Primary tumor size, depth of cervical invasion, and lymph-vascular space invasion (LVSI) are thought to be independent prognostic factors in node-negative patients with surgically treated Ib squamous carcinoma of the cervix.[106] Parametrial extension[184] and parametrial node metastasis,[185] independent of retroperitoneal lymph node status,[102] predict an increased risk of recurrence in surgically treated patients. Positive or insecure margins including vaginal margins,[186] extension of cancer to the lower uterine segment,[187,188] and adverse histopathology[37] are additional parameters that may correlate with a more ominous outlook. Controversies persist concerning the relative importance of some of these factors in multivariant analysis. However, with consensus approaching unanimity, metastasis to pelvic lymph nodes is recognized as a dominant prognostic indicator.[189]

Two cooperative NCI-sponsored intergroup studies have been carried out prospectively evaluating adjuvant therapy for patients with adverse histopathologic features after radical hysterectomy. Sedlis[190] reported on 277 "intermediate risk" node-negative patients who were identified based on combinations of tumor size, depth of cervical stromal invasion, and lymphatic space invasion. Based on historic outcomes, these patients were estimated to have an approximate 25% to 27% probability of recurrence after surgery, with the pelvis being the most probable site of relapse. Patients were randomized to observation versus adjuvant pelvic teletherapy. In recent update of this series by Rotman[121] there was a 46% reduction in the risk of recurrence ($P = 0.007$) and a significant improvement in recurrence or death (HR = 0.58) when postoperative pelvic irradiation was given. Although there was a 30% reduction in the risk of death for patients who received radiation therapy, this difference was not statistically significant ($P = 0.07$).

Peters[107] reported on 243 analyzable "high-risk" patients who had positive nodes, parametrial extension, or positive surgical margins. After radical hysterectomy, these patients were randomized to receive adjuvant pelvic radiation therapy, or the same adjuvant radiation regimen with two cycles of synchronous 5-FU and cisplatin followed by two further cycles of sequential 5-FU and cisplatin. Cisplatin was administered at 70 mg/m^2, and 5-FU was administered at 1000 mg/m^2/24 hr for 96 hours with each cycle. The projected progression-free survival at 4 years was 80% for the patients in the radiation-plus-chemotherapy arm compared with 63% in patients receiving adjuvant radiation alone. Analysis of pattern of treatment failure at the time of initial recurrence reveals that 11 of 127 patients receiving chemoradiation had a component of pelvic recurrence compared with 25 of 116 patients receiving radiation, suggesting that the addition of chemotherapy resulted in a 60% reduction in the rate of pelvic failure. A component of distant metastatic spread was seen in 13 of 127 patients in the chemoradiation group and 18 of 116 patients in the radiation group, suggesting that the addition of chemotherapy resulted in a 34% reduction in distant spread. Paradoxically, the effect of the chemotherapy appears to have been greater on local disease than on distant dissemination, suggesting that the primary benefit may have been as a potentiator of local radiation effect.

In a small, randomized trial, Tattersall[191] reported that the addition of three cycles of cisplatin, vinblastine, and bleomycin before adjuvant pelvic radiation produced no benefit compared with immediate postoperative radiation therapy in patients with Ib to IIa disease with pelvic node metastases. In a complementary, randomized trial in which all patients received adjuvant postoperative chemotherapy, Curtin[192] reported that the addition of delayed adjuvant radiation produced no benefit in either pelvic control or survival.

Stages IIb and III

In the United States, patients with advanced disease are treated with chemoradiation. Teletherapy with synchronous chemotherapy is supplemented with intracavitary brachytherapy whenever feasible. The Syed-Neblett or Martinez interstitial templates are alternative brachytherapy approaches that have the theoretic advantage of extending the brachytherapy isodoses laterally to treat pelvic side walls and parametrium.[193,194] However, it is unclear that this provides any advantage compared with conventional intracavitary brachytherapy supplemented by teletherapy boost treatments to limited volumes.

It is important to remember that even patients with very large tumors (even tumors measuring 7 cm or more in diameter) have a chance of being cured with radiation therapy alone, particularly if the patient is not found to have extensive regional metastases. Prior to the use of concurrent chemoradiation, 5-year survival rates for patients with stage IIb disease usually were reported to be between 50% and 75%.[100,195,196] The broad range probably reflects differences in staging, patient selection, and treatment technique between reporting institutions. For patients with stage IIIb disease, reported survival rates after treatment with radiation therapy alone ranged between 30% and 50%.[99,196–198] However, in recent years, prospective trials with concurrent chemotherapy and radiation have improved survival even more[167,168] and have become the standard of care in this group of patients.

Although the preliminary finding of RTOG 90-01, first published in 1999, demonstrated a highly significant overall survival benefit from chemotherapy among patients with stage Ib to IIb (79% vs. 55% at 5 years, $P < 0.0001$), no significant difference was found in survival among patients with stages III to IVa disease; at the time, follow-up was incomplete and the total number of patients with the more advanced stage[114] was small, contributing to large confidence intervals on the results.[168] Nevertheless, an update in 2004[199] did show a significant difference in disease free-survival (54% vs 37%,

$P = 0.05$) and a trend toward improved overall survival (59% vs 45%, $P = 0.07$). A recent update of GOG 120, in which a greater percentage of patients enrolled had III-IV disease, found a significant improvement in PFS and OS in patients receiving concurrent cisplatin-based chemotherapy with radiation therapy compared with patients receiving hydroxyurea and radiation, and the results were analogous in patients with Stage IIb and III (each $P < 0.025$).[200]

Stage IVa

Fewer than 5% of cases of invasive cervical cancer are truly stage IVa. Most of these are classified as IVa because of bladder involvement; rectal involvement very rarely is seen at initial diagnosis. The management of stage IVa disease is challenging because the tumors usually are large, often fixed to pelvic structures, and usually regionally metastatic. Brachytherapy often is compromised or impossible to perform because vesicovaginal fistulae develop before diagnosis or during treatment. However, at least 10% to 20% of stage IVa tumors are curable with radiation therapy alone.

Regional Disease

Most patients treated with radical hysterectomy who are found to have lymph node metastases require postoperative radiation therapy. On the basis of the findings of Peters and colleagues,[107] concurrent chemotherapy also is recommended if no medical contraindications are present.

Patients with para-aortic node involvement can be treated effectively with extended-field irradiation. Five-year survival rates range between 25% and 50%. Some investigators have advocated prophylactic irradiation of the aortic nodes for patients with an increased risk of metastases to this region. The value of prophylactic extended-field irradiation was tested in two randomized trials. In RTOG 79–20[201] patients with stage Ib2 to IIb disease were randomly assigned to receive brachytherapy plus external-beam radiation therapy to the pelvis or to the pelvis and para-aortic nodes. The absolute 5-year survival rate was significantly better for those who had para-aortic treatment, but no difference was found in disease-free survival. A European trial[202] done at the same time had a similar randomization but included patients with more advanced disease (e.g., with pelvic lymph node metastases or bulky stage IIb or IIIb disease). No significant difference was found in the 4-year disease-free survival rates between the two arms, but the rate of para-aortic node recurrence was significantly higher for patients in whom that area was not treated.

In several phase II studies, concurrent chemotherapy has been given with extended field irradiation.[203,204] Although side effects are more significant when treatment fields are enlarged, combined therapy may be tolerable if careful consideration is given to the chemotherapy regimen, the volume of tissue irradiated, and other factors that might increase the risk of serious toxicity. However, new imaging techniques such as PET and safer methods of surgical evaluation of lymph nodes (e.g., retroperitoneal or laparoscopic lymphadenectomy), may increase the precision with which the extent of regional disease can be estimated, decreasing the margin for improvement to be gained by treating large volumes prophylactically. However, it is important to remember that there is no evidence that chemotherapy given concurrently with radiation can prevent recurrence in nonirradiated nodal sites (the rate of aortic recurrence in patients treated on RTOG 90–01 with pelvic chemoradiation was 9%).[199]

Some bulky nodal metastases can be difficult to control with external beam radiation therapy alone. Some investigators have suggested resections of nodes larger than 2.0 cm prior to radiation therapy. Several investigators have reported high local control rates in patients treated with excision of bulky nodes and radiation; however, the numbers of patients in these series are small.[205,206] With standard radiation therapy, it is difficult to deliver a high enough dose to the node without exceeding normal tissue tolerance limits; however, with modern conformal or intensity-modulated radiation therapy (IMRT) techniques, this may be possible.

TREATMENT OF METASTATIC DISEASE AND SALVAGE CHEMOTHERAPY

Cervical cancer is not considered curable with chemotherapy. Chemotherapy traditionally has been reserved for patients with extrapelvic metastatic disease or recurrent disease who are not candidates for radiation therapy or exenterative surgery. In an important GOG study, Thigpen and colleagues[207] found that cisplatin has the greatest antitumor activity in advanced squamous carcinoma of the cervix, with a response rate of 20% to 25%. Unfortunately, in most series, responses to cisplatin are short-lived (3 to 6 months). The median duration of response for complete responders is 6 months, and the median survival is only 9 months.[208,209] Other agents reported to achieve partial responses (15% to 25%) include carboplatin, iphosphamide, 5-FU, doxorubicin, methotrexate, hexamethylmelamine, mitomycin-C, vinblastine, bleomycin, paclitaxel, topotecan, vinorelbine, and irinotecan. Little objective evidence suggests that combination chemotherapy is superior to single-agent cisplatin.

A small portion of patients are first seen with advanced disease that is not amenable to radiation therapy with curative intent. In women in whom recurrent or persistent disease develops in the central pelvis after radical hysterectomy, a cure may be achieved on occasion with radical salvage radiation or chemoradiation. A second small subset of patients with central pelvic recurrence after radiation therapy can be salvaged with aggressive surgical therapy, which often involves removal of the bladder or rectum, or both. For patients with distant disease, the principle goal of therapy is palliation with the aim of reducing pain and suffering associated with metastatic lesions. No convincing data indicate that the delivery of systemic therapy in this clinical setting improves overall survival.

Numerous platinum combination-based regimens incorporating drugs such as doxorubicin, iphosphamide, bleomycin, and, most recently, paclitaxel, have demonstrated higher response rates (typically in the 20% to 40% range) with the combinations with greater toxicity. A limited number of reasonably well powered randomized trials comparing these doublets with either triplet regimens or singlet regimens have demonstrated that combination therapy leads to a slightly higher response rate and a longer progression-free survival that does not appear to affect overall survival.[210,211] Recently the GOG compared paclitaxel and cisplatinum with single-agent cisplatinum. In this study of 241 eligible women, the response rate to single-agent cisplatin was 19%. The response rate to the doublet was 36%. The median time to progression was prolonged from 2.8 months with cisplatin alone to 4.8 months for the doublet. Overall survival for the two arms was equivalent, with an 8.8-month median for cisplatin and a 9.7-month median for the doublet.[212]

The potential role of drugs such as epidermal growth factor-receptor inhibitors, angiogenesis inhibitors, and other molecularly targeted therapies, remains largely unexplored in this disease. Preliminary evaluation of geftinib demonstrates only minimal activity in cervical cancer.

When interpreting clinical trials evaluating the efficacy of chemotherapy in cervical cancer, it is important to recall the patient population under study. Chemotherapy- and radiation therapy-naïve women receiving neoadjuvant therapy for bulky cervical tumors typically demonstrate response rates in excess of 50%. As discussed earlier, this response rate has not reproducibly translated into improved survival or cure. Response rates for recurrent disease outside of the radiation ports (such as pulmonary metastases or high para-aortic nodal recurrences) typically range between 10% and 20% for single-agent therapy and 20% and 45% for multiagent therapy. Finally, response rates for measurable tumors in the previously irradiated pelvis tend to be much lower, with complete responses rare, and response rates generally no higher than 10% to 15%. Evaluation is complicated in the irradiated pelvis, with either physical examination or radiologic studies, both of which are, at times, unable to distinguish postsurgical and postradiation changes from tumor recurrences, which often are infiltrating distorted tissue planes in the post-treatment pelvis.

VULVAR CANCER

SUMMARY OF KEY POINTS

Epidemiology
- The American Cancer Society estimates that there were 3490 new cases of invasive vulvar cancer diagnosed in the United States in 2007, with 880 deaths.
- Vulvar cancers account for 4% of malignancies of the female genital tract.
- Squamous cell carcinoma and its variants are the most prevalent histologies, accounting for 90% of invasive lesions.
- Vulvar melanoma, basal cell cancer, and rare sarcomas constitute most of the remaining tumors.
- Adenocarcinoma and adenoid cystic carcinoma of the vestibular glands (Bartholin's gland) are less common than the squamous cancers arising from these structures.
- Age-adjusted incidence increases steeply after age 70.

Etiology
- An association is found with human papillomavirus (HPV) in approximately one third of cases, primarily in younger patients.
- Vulvar cancer in older patients commonly arises in association with lichen sclerosus or squamous hyperplasia (hyperplastic dystrophy or lichen simplex chronicus), although these conditions are not clearly premalignant.
- Chronic immunosuppression has been implicated in some cases.

Differential Diagnosis
- Paget's disease of the vulva and vulvar intraepithelial neoplasia (VIN) are in the differential diagnosis of a vulvar lesion.
- Giant condylomata may mimic vulvar neoplasia, and vulvar neoplasia may coexist with condyloma accuminata.

Evaluation
- Complete history and physical examination including a thorough pelvic examination and careful palpation of groin lymph nodes.
- Diagnosis must be confirmed by vulvar biopsy.

Treatment of Squamous Cell Carcinoma of the Vulva
- Treatment should be individualized on the basis of disease volume and anatomic extent, histology, age, comorbidities, and patient preference.
- Stage I lesions may be treated with radical local excision alone, or combined with inguinofemoral lymphadenectomy if depth of invasion exceeds 1 mm.
- Surgery for stage II vulvar cancer usually consists of modified radical vulvectomy and inguinofemoral lymphadenectomy.
- Locally extensive (T3,4) vulvar cancers, or cancers invading or encroaching on functionally important midline structures can be managed with synchronous preoperative chemotherapy and radiation (chemoradiation) followed by conservative excision of residual disease, or by radical chemoradiation alone.
- Management of inguinofemoral nodes may consist of surgical dissection alone, or surgery coordinated with preoperative or postoperative radiation if nodes harbor metastatic deposits.
- Surgery of the primary and the groin nodes may be conducted through separate incisions (triple incisions) to reduce both acute and late surgical morbidity.
- Elective radiation or chemoradiation may be an alternative to surgical treatment of inguinofemoral nodes in selected patients with clinically and radiographically negative groin nodes.
- Sentinel lymph node biopsy may be a useful discriminator to guide the selection and sequencing of modalities used to treat the groin nodes.

EPIDEMIOLOGY

Vulvar cancer is predominantly a disease of postmenopausal women, most commonly observed in the seventh and eighth decades, and with a mean age at diagnosis of 65 years. Age-specific incidence rates in the United States increase steeply at age 70 and continue to increase beyond age 80 years.[213] The coexistence of vulvar intraepithelial neoplasia (VIN) or invasive squamous carcinoma of the vulva with in situ or invasive epidermoid carcinoma of the cervix has long been known, and synchronous or sequential (usually antecedent) cervical lesions may be present in as many as 20% of women with primary vulvar lesions. This observation suggests a common etiology in at least some patients.[214–220]

VIN, a precursor lesion, often is multifocal. After conservative local excision of invasive vulvar cancer with preservation of clinically normal vulva, cancer may develop at anatomically distinct structures within conserved vulvar tissues. Rather than recurrence, this phenomenon may be a manifestation of the so-called "field change" model of oncogenesis, representing metachronous appearance of independent primaries.[221]

ETIOLOGY

Risk factors for the development of invasive vulvar cancer include a history of condyloma acuminatum, VIN, smoking, and chronic vulvar dystrophies including lichen sclerosus and squamous hyperplasia (hyperplastic dystrophy).[222–225]

Vulvar carcinoma often coexists with vulvar dystrophy, particularly in older women, with dystrophic changes in adjacent skin in up to 50% of patients with invasive vulvar cancer.[226,227]

However, it is unknown whether lesions such as lichen sclerosus or squamous hyperplasia are true precursor lesions. Detection of human papillomavirus (HPV) in VIN or invasive disease is most common in young patients and less frequent in older patients.[228,229] These observations have led to the hypothesis that patients with vulvar cancer may be segregated into two broad groups: an older population with cancer arising in association with vulvar dystrophy and unassociated with HPV, and a younger population with HPV-associated tumors often adjacent to areas of VIN.[225,230]

An increasing incidence of VIN and reports of invasive vulvar cancer in young patients may be consequences of the sexual revolu-

Table 91-4 Classification of Epithelial Disorders of the Vulva

NON-NEOPLASTIC EPITHELIAL DISORDERS OF THE SKIN AND MUSCOSA	
Lichen sclerosus (lichen sclerosus et atrophicus)	
Squamous cell hyperplasia (formerly hyperplastic dystrophy)	
Other dermatoses	
CLASSIFICATION OF VULVAR INTRAEPITHELIAL NEOPLASIA	
VIN 1	Mild dysplasia (formerly mild atypia)
VIN 2	Moderate dysplasia (formerly moderate atypia)
VIN 3	Severe dysplasia (formerly severe atypia)
CIS	Carcinoma in situ

From Ridley CM, Frankman O, Jones ISC, et al: New nomenclature for vulvar disease; report of the Committee on Terminology of the International Society for the Study of Vulvar Disease. J Reprod Med 1990;35:483.

tion and transmission of HPV. Invasive vulvar cancer has been reported in young patients with both naturally occurring and iatrogenic immune compromise.[231–236] Patients infected with the human immunodeficiency virus-1 (HIV-1) are much more likely to have HPV infection than are women who are not infected with HIV and may be more vulnerable to development of VIN than are HIV-negative controls. VIN may be more difficult to clear in HIV-infected women and may progress to invasive disease with greater rapidity.[237,238]

Detection of HIV in very young patients with vulvar cancer raises the specter of increasing rates of vulvar as well as cervical cancer as the acquired immunodeficiency syndrome (AIDS) epidemic unfolds.[239]

NATURAL HISTORY

Vulvar Dystrophy

A patient with any degree of cellular atypia associated with vulvar dystrophy is at risk of invasive vulvar cancer. Patients with cellular atypia compose approximately 10% of those patients with histopathology-proven vulvar dystrophy, and vulvar cancer will develop in fewer than 5% of these patients.[240] The International Society for the Study of Vulvar Disease (ISSVD) established a classification for vulvar dystrophies and atypias based on histopathology[241] (Table 91-4). The ISSVD now advises that "dystrophy" is no longer an acceptable term and recommends use of specific terminology (e.g., lichen sclerosus, lichen planus, lichen simplex chronicus, psoriasis), although these recommendations have not been adopted uniformly.[242–244]

Paget's Disease

Vulvar Paget's disease was first reported in 1901 by Dubreuilh.[245] The disease is seen predominantly in postmenopausal women, with common presenting symptoms of vulvar pruritus and soreness, sometimes accompanied by persistent oozing. Grossly, Paget's disease may have an eczematoid appearance. With extensive disease, it may appear raised and velvety. Under the light microscope, the presence of large, pale Paget's cells that are rich in mucopolysaccharide and that are periodic acid-Schiff (PAS)-positive and diastase resistant are pathognomonic of this disorder (Fig. 91-17). Paget's cells stain for carcinoembryonic antigen (CEA), cytokeratin 7 (CK-7), and gross-cystic-disease fluid protein.[246,247] Paget's cells rarely express CA-125, and testing for estrogen receptors usually is generally negative.[248,249] Many cases express c-erB2 (HER-2/neu), which is not believed to influence the risk of metastatic spread.[250,251] Nondiploid tumors are more likely to recur. Electron microscopic studies have demonstrated that Paget's cells are derived from the stratum germinativum of the epidermis.[252] Squamous keratinocytes, sweat gland cells, and hair follicles also are derived from this epidermal layer, possibly explaining the characteristic finding of more Paget's cells in juxtaposition to the basal layer of cells in the epidermis, as opposed to within higher strata.

In approximately one sixth of cases, Paget's disease involving the vulva has been associated with an underlying adenocarcinoma of the vulva, often arising in apocrine glands or within Bartholin's glands. Paget's disease also has been associated with a synchronous primary invasive cancer in another female genital tract site in approximately one fourth of patients.[253–255]

Wide local excision is recommended as treatment, with verification of surgical margins by frozen section.[256,257] Repeated excision sometimes is required for marginal recurrence.[258]

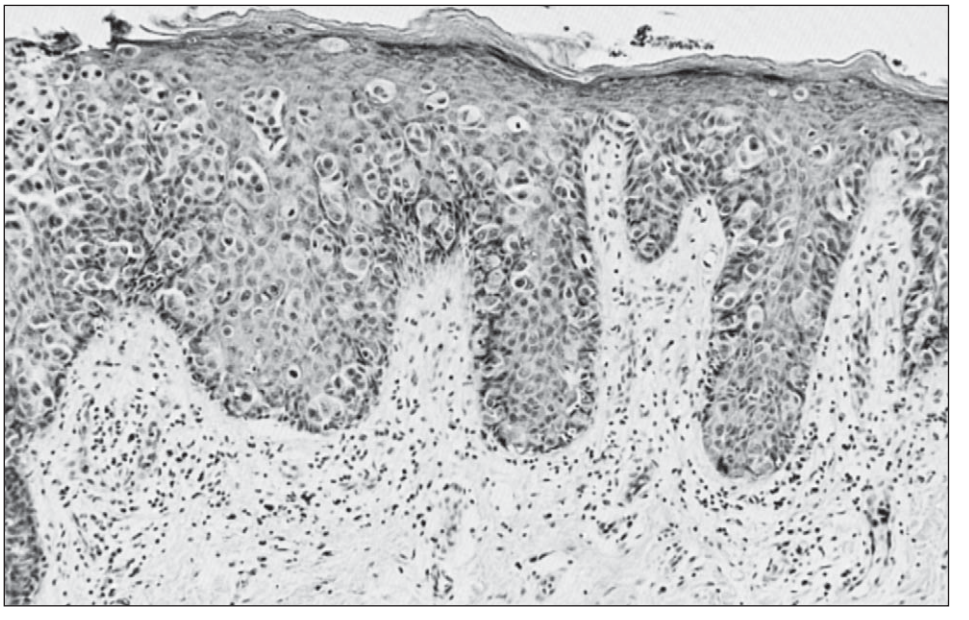


Figure 91-17 • Histologic portrait of Paget's disease of the vulva. (From Wilkinson EJ, Hassanein AM: The vulva and vagina. In Silverberg SG [ed]: Silverberg's Principles and Practice of Surgical Pathology and Cytopathology, 4th ed. New York, Churchill Livingstone, 2006.)

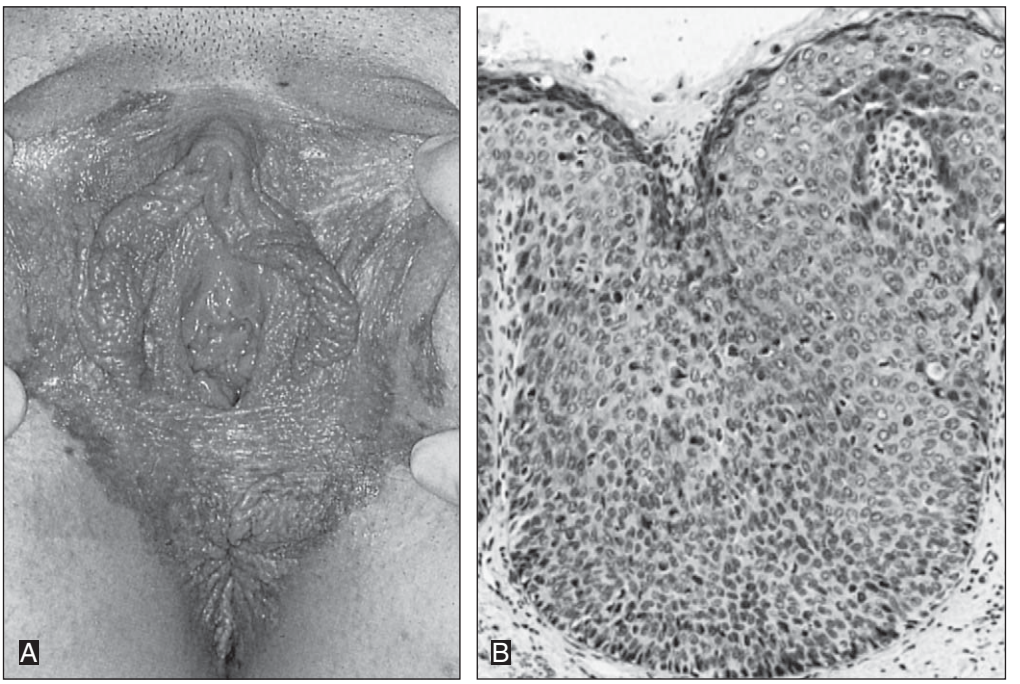


Figure 91-18 • Characteristic gross **(A)** and histologic **(B)** features of vulvar intraepithelial neoplasia. (**A,** From Hoskins WJ, Perez CA, Young RC [eds]: Principles and Practice of Gynecologic Oncology, 2nd ed. Philadelphia, Lippincott, 1997, p 678. **B,** From Deppe G, Lawrence WD: Vulvar dysplasia and neoplasia. In Gusberg SB, Shingleton HM, Neppe G [eds]: Female Genital Cancer. New York, Churchill Livingstone, 1988, p 223.)

Intraepithelial Squamous Cell Neoplasia of the Vulva

The term *VIN* now replaces such terms as Bowen's disease, erythoplasia of Queyrat, carcinoma simplex, bowenoid papulosis, bowenoid dysplasia, hyperplastic dystrophy with atypia, and condylomatous dysplasia. The ISSVD recognizes squamous cell carcinoma in situ. VIN is appearing with increasing frequency in women under the age of 40 years and seems to be associated with high-risk strands of the HPV virus. Histopathologically, these lesions are characterized by varying degrees of cytoplasmic and nuclear maturation, giant cells with abnormal nuclei, and disruption of the normal epithelial architecture (Fig. 91-18). On rare occasions, pearl formation at the base of the rete pegs can be seen, without significant abnormality in the overlying epithelium. Buscema and colleagues[259] reported that invasive vulvar cancer developed in approximately 4% of patients with VIN. Fu and colleagues[260] observed that all intraepithelial lesions analyzed had an aneuploid DNA pattern when associated with HPV. The term *bowenoid papulosis* historically has been used as a synonym for multifocal intraepithelial neoplasia of the vulva. This lesion also is associated with HPV infection. The invasive potential of this entity appears to be very low. Therapy for VIN usually consists of surgical excision. Laser vaporization may be useful as an alternative when large areas would require excision or functionally important areas are involved, but carries a small risk of failure to detect areas of true invasion. The risk of occult invasion may be as high as 20% in patients with VIN 3.[261] Cavitational ultrasonic surgical aspiration (CUSA) provides another conservative surgical modality to treat VIN with minimal loss of functionally important tissue and provision of tissue for histologic study.[262] Laser excision, by providing tissue for histologic evaluation, is less likely to miss a clinically occult area of invasion.[263]

Invasive Squamous Cell Carcinoma of the Vulva

Clinical Features

Histologically, squamous cell carcinoma accounts for more than 90% of cases of malignancy involving the vulva. Common presenting symptoms include chronic vulvar pruritus; a mass, lump, or sore; and small-volume bleeding. About two thirds of the lesions involve the labia majora, whereas lesions originating on the labia minora and the clitoris occur less commonly. Lesions arising in the vestibular (Bartholin's) glands are first seen as a swelling or mass, sometimes without invasion of overlying skin. Tumors arising in the Bartholin's glands tend to be adenocarcinomas. In 10% of cases, the lesion will be too extensive to determine the site of origin, and in 5% of cases, the lesions are multifocal.[264] From the site of origin, carcinomas of the vulva can extend to invade the vagina, urethra, or anus; advanced vulvar carcinoma can invade adjacent pelvic bones, particularly the pubis.

Routes of Spread

Direct extension occurs to adjacent structures including the vagina, perineum, clitoris, and anus. The vulva is richly supplied with lymphatic vessels that often cross the midline. As a result, the risk of regional spread is significant for any vulvar carcinoma that has invaded to a depth of more than 1 mm. The lymphatics of the vulva consist of a network that covers the entire labia minora, fourchette, prepuce, and distal vagina below the hymenal membrane. These coalesce anteriorly, forming larger trunks, which run laterally to the clitoris to the mons veneris, acquiring tributaries from the lymphatics of the labia majora, which run in a parallel fashion anteriorly from the perineal body. The vulvar lymphatics run through the vulva and do not cross the labiocrural fold. The lymphatics of the perineum, however, course lateral to the labiocrural fold through the superficial tissues of the upper medial thigh. In the treatment of patients with advanced vulvar cancer that extends beyond the vulva to the perineal skin, these more lateral channels must be taken into consideration. Similarly, direct proximal extension of an advanced vulvovaginal cancer along the vaginal cylinder may spread through vaginal lymphatics directly to pelvic nodes. At the mons veneris, the vulvar lymphatic trunks diverge laterally to the primary regional nodes, the ipsilateral or contralateral inguinal nodes. Study of the localization of dye or radiolabeled tracer in regional lymph nodes after focal injection of discrete sites in the vulva and on the perineum reveals that the lymphatic drainage of the perineum, clitoris, and anterior labia minora is bilateral, whereas the lymph flow from well-lateralized sites in the vulva is, predominantly, to the ipsilateral groin.[265,266] Discrete (≤2 cm diameter), well-lateralized primary cancers limited to the vulva and not approaching midline structures rarely manifest spread to contralateral groin nodes in the absence of spread to ipsilateral nodes.[267–272]

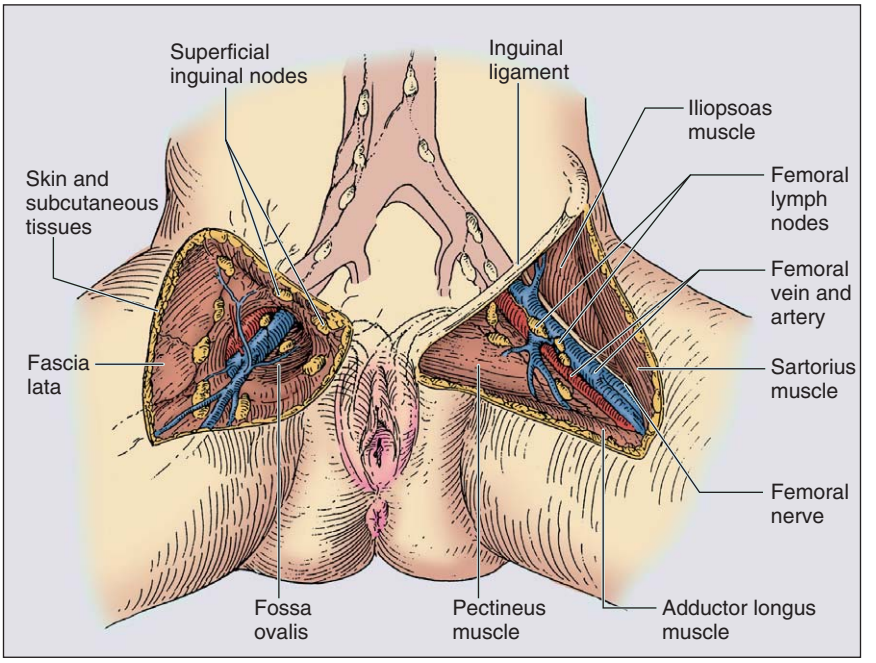


Figure 91-19 • Regional lymph nodes in vulvar carcinoma: inguinal and femoral. (From Berek JS, Hacker NF: Practical Gynecologic Oncology, 2nd ed. Baltimore, Williams & Wilkins, 1994.)

From the superficial inguinal nodes, secondary lymphatic drainage is through the cribriform fascia to the femoral nodes (Fig. 91-19), with subsequent tertiary flow under the inguinal ligaments to the external iliac nodes. However, metastases have been reported to the femoral lymph nodes without involvement of the superficial inguinal lymph nodes, especially from carcinomas of the clitoris and Bartholin's gland.[273,274] A recent GOG study also found an unexpectedly high incidence of ipsilateral groin recurrences secondary to presumed involvement of lymph nodes deep to the cribriform fascia, despite having negative superficial nodes.[275] Levenback and colleagues[276] further supported these data by lymphatic mapping studies.

The frequency of lymph node metastases to the inguinofemoral nodes is related to the lesion size and depth of stromal invasion.[268,277] For lesions smaller than 1 cm in diameter, the incidence is approximately 5%. For lesions exceeding 4 cm, the rate of inguinofemoral lymph node metastases is 30% to 50%.[269,278] The overall incidence of metastases to the pelvic lymph nodes is 5% and is rare in the absence of three or more positive inguinofemoral lymph nodes. Hematogenous spread is rare in the absence of inguinofemoral lymph node involvement and usually occurs late in the course of the disease. However, in patients with three or more positive lymph nodes, the ultimate risk of hematogenous spread is 66%. By contrast, patients with fewer than three positive lymph nodes have only a 4% risk of hematogenous spread.[279,280] Sites of hematogenous spread include lung and bone.

Staging

Staging of invasive vulvar cancer is based on clinicopathologic measurement and assessment of anatomic extent of the primary lesion; the presence, laterality, and extent of regional lymph node metastases; and the presence or absence of distant metastases including pelvic lymph nodes. Historically, staging evaluation of the inguinal lymph nodes was based on palpation and clinical impression. Because the clinical assessment of inguinal lymph nodes is associated with false-positive and false-negative rates of approximately 20%[281–286] (Table 91-5), a surgical staging system for vulvar cancer initially was adopted by FIGO in 1988 and has been revised several times since[287] (Table 91-6). However, many locally advanced vulvar lesions are being treated with initial radiation or chemoradiation; consequently, the absence of a complete surgical specimen may interfere with accurate staging, particularly of the inguinal lymph nodes.

Diagnosis

Diagnosis of vulvar lesions requires a biopsy, which should include some surrounding skin and underlying dermis and connective tissue so that the pathologist can assess the depth and nature of stromal invasion. This procedure usually can be performed under local anesthesia. For lesions of 1 cm or less in diameter, excisional biopsy is preferable. All patients with invasive disease should be evaluated with a careful physical examination, including a detailed pelvic examination, chest radiography, a complete blood count, and a biochemical profile. Computed tomography (CT) or magnetic resonance imaging (MRI) scans should be done to evaluate deep and pelvic lymph nodes.

Treatment

Treatment of Preinvasive Disease

Small VIN lesions are treated with local excision. More extensive VIN can be treated with carbon dioxide (CO_2) laser vaporization. However, careful inspection and biopsies to rule out invasive disease should be done before laser treatment. Extensive disease may require wide local excision or excision of the superficial skin of the vulva (skinning vulvectomy). Although the morbidity of excision may be greater than that of laser vaporization, the ability to examine the surgical specimen is a relative advantage of surgical excision. VIN

Table 91-5 Clinical Assessment of Inguinofemoral Nodes by Palpation

	Histologically (–)	Histologically (+)
Clinically (–) ($N = 451$ patients)	363 (80.5%)	88 (19.5%)
Clinically (+) ($N = 243$ patients)	53 (21.8%)	190 (78.2%)

Pooled data, six institutions.[281–286]

Table 91-6 FIGO/AJCC/UICC 1997 TNM Classification and Stage Grouping

TNM CLASSIFICATION	
T	Primary tumor
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (preinvasive carcinoma)
T1	Tumor confined to the vulva and perineum* ≤2 cm in greatest dimension
T1a	Tumor confined to the vulva or vulva and perineum, ≤2 cm in greatest dimension, and with stromal invasion ≤1 mm
T1b	Tumor confined to the vulva or vulva and perineum, ≤2 cm in greatest dimension, with stromal invasion >1 mm
T2	Tumor confined to the vulva and perineum >2 cm in greatest dimension
T3	Tumor of any size with adjacent spread to the lower urethra and/or vagina and/or anus
T4	Tumor of any size invading any of the following: the upper urethral mucosa, the bladder mucosa, the rectal mucosa, or tumor fixed to the bone
N	Regional lymph nodes†
N0	No nodal metastases
N1	Unilateral regional lymph node metastasis
N2	Bilateral regional lymph node metastasis
M	Distant metastasis
M0	No evidence of distant metastasis
M1	Any distant metastasis including pelvic lymph nodes
STAGE GROUPING	
0	TisN0M0
I	T1N0M0
II	T2N0M0
III	T3N0M0
	T1,2,3N1M0
IVa	T1,2,3N2M0
	T4NxM0
IVb	TxNxM1
(x denotes any T or N category)	

AJCC, American Joint Commission on Cancer; FIGO, Federation Internationale de Gynecologie et d'Obstetrique; UICC, Union Internationale Contre le Cancer.

*The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papilla to the deepest point of invasion.

†Note that assessment of inguinofemoral nodes is histologic.

often is a multicentric disease, and local recurrences often occur even after extensive surgical resection.

Surgical Treatment of Invasive Carcinoma

The operative approach to the treatment of vulvar carcinoma, consisting of a radical en bloc resection of the vulva, was developed at the beginning of the 20th century in response to the combination of patients first seen with regionally advanced disease and the poor results (approximately 20% to 25% 5-year survival) achieved with limited surgical excision.[288]

Basset[289] first reported an en bloc operative removal of the vulva along with the regional lymph nodes, resulting in considerable improvement in 5-year survival (60% to 70%). Three decades later, Taussig[290] of the United States and Way[281,291] of the United Kingdom popularized this radical en bloc dissection, which remained the standard of surgical care for vulvar cancer until the early 1980s. At that time, Hacker and others[292,293] introduced the concept of individualized and conservative surgery, proposing the use of separate groin incisions for women with stage I disease and demonstrating no difference in the incidence of recurrence between those women undergoing a radical vulvectomy compared with those undergoing a radical local excision (modified radical vulvectomy). The trend over the past 20 years has been toward less radical surgery for early-stage vulvar cancer in an attempt to decrease the significant physical and psychological morbidity associated with en bloc dissection (Fig. 91-20). Historically, exenterative procedures were undertaken to clear central disease in patients first seen with locally advanced disease.[294] Increasingly, treatment has evolved to include combinations of preoperative radiation or preoperative chemoradiation to reduce tumor volume sufficiently to permit clearance of central disease without sacrifice of functionally important midline structures.[292–296]

Surgical Techniques

RADICAL LOCAL EXCISION. Radical local excision involves a wide and deep excision of the lesion with the goal of clearing the lesion by 2 cm at all margins, except for posteriorly with perineal lesions in which the distance to the anus is limited. The incision should be carried down to the inferior fascia of the urogenital diaphragm, which is in a parallel plane to the fascia lata and the fascia over the symphysis pubis. The surgical defect is closed in two layers. Limitations to this conservative approach are encountered when cancer is in close proximity to functionally important midline structures (e.g., clitoris, urethra, anus). A histopathologic margin of 8 millimeters or greater (approximately equivalent to 1-cm clinical margin in tissue before fixation) serves as a useful discriminating boundary between patients who are likely to have excellent prospects for local control with surgery alone, as opposed to patients who have a substantial risk of local recurrence and who might require more extensive surgery initially or postoperative adjuvant radiation therapy[297–299] (Table 91-7).

RADICAL VULVECTOMY. The radical vulvectomy may be performed through an incision separate from the groin dissection or in an en bloc fashion. The en bloc technique was based on the concern that leaving tissue between the primary tumor and the regional lymph nodes might leave microscopic foci tumor in the draining lymphatics. However, squamous carcinoma most often spreads by embolization and not by permeation. Although rare instances of recurrence within the skin bridge have been reported, the experience with separate groin incisions has shown that very little chance of recurrence exists in the skin bridge without clinically suggestive groin nodes.[292] Wound seroma, the most common acute complication, occurs in approximately 15% of cases.[292,293] Other acute complications include urinary tract infection, wound cellulitis, temporary anterior thigh anesthesia from femoral nerve injury, thrombophlebitis, and, rarely, pulmonary embolus. The most common chronic complication now is leg edema, and with the use of separate groin incisions, its incidence has decreased from 31% to 14%.[292,293] Other chronic complications include genital prolapse, urinary stress incontinence (10%), temporary weakness of the quadriceps muscle, and introital stenosis. Rare late complications include pubic osteomyelitis, femoral hernia, and rectoperineal fistula. Farias-Eisner and associates[300] and Hacker and colleagues[268] observed a further reduction in acute and chronic morbidity when radical local excision of the primary lesion is used instead of radical vulvectomy.

Groin Lymph Node Dissection

The appropriate application of groin dissection is the single most important factor in decreasing the mortality of early vulvar cancer. The technique for groin dissection involves the removal of an ellipse

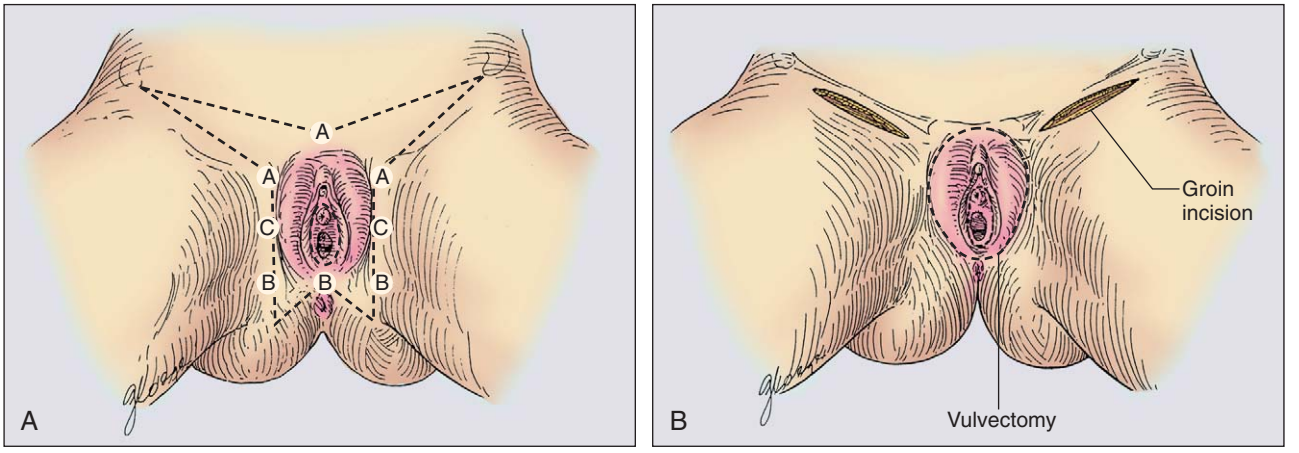


Figure 91-20 • Comparison of incisions used for the en bloc vulvectomy and groin dissection **(A)** versus the modified radical vulvectomy with separate incisions for the groin dissection **(B)**. (From Berek JS, Hacker NF: Practical Gynecologic Oncology, 2nd ed. Baltimore, Williams & Wilkins, 1994.)

Table 91-7 Width of Surgical Margin and Risk of Local Recurrence

First Author	Margin <8 mm	Margin ≥8 mm
Heaps[297]	21/44 (48%)	0/91
Faul[298]	18/31 (58%)	NA
De Hullu[299]*	9/40 (23%)	0/39

NA, not applicable.
*Surgical margin ≤8 mm vs. >8 mm.

Table 91-8 Incidence of Groin Node Metastasis Correlated with Depth of Invasion for Primary Tumors ≤2 cm

Depth of Invasion (mm)	No. of Patients	No. of Positive Nodes	Percentage
≤1	120	0	0
1–2	121	8	6.6
1–3	97	8	8.2
1–4	50	11	22
1–5	40	10	25
>5	32	12	37.5

Pooled data, six series.[268,270,271,277,301,302]

Table 91-9 Primary Tumor Size and Risk of Groin Node Metastasis

Primary Size (cm)	No. of Patients	No. of Positive Nodes	Percentage
≤2	75	5	6.7
2–4	78	19	24.4
>4	79	26	32.9

Pooled data, two series.[303,304]

of skin 1 cm below and parallel to the groin crease. The incision is carried down, with incising and dissecting, to the fascia lata and 2 cm above the inguinal ligament to remove the inguinal nodes. The saphenous vein is tied off, the fascia lata is then split, and the femoral nodes are dissected. Some surgeons conserve the saphenous vein in an effort to decrease both acute and chronic morbidity. A suction drain is placed, and the wound closed in two layers.

Surgical specimens from patients with primary tumors 2 cm or smaller in diameter (T1) clearly show escalating risk of node metastasis with progressive depth of invasion (Table 91-8).[268,270,271,277,301,302] The probability of finding groin node metastasis is related to the size of the primary tumor (Table 91-9).[303,304] An infiltrative pattern of growth correlates with nodal spread,[305,306] and the presence of vascular or lymphatic space invasion substantially escalates the probability of finding metastases in dissected nodes.[303] Metastatic spread to contralateral groin nodes in the absence of disease in ipsilateral nodes occurs in 15% or fewer of all patients with metastases to groin nodes,[307] generally in patients with larger lesions. The risk of contralateral nodal spread in the absence of ipsilateral metastasis is less than 1%,[219,278,282,283,307–312] although it has been described in two patients with lateralized T1 lesions.[166] When metastatic disease is present in multiple groin nodes, pelvic lymphadenectomy will detect disease in 15% to 25% of patients, but rarely when only one groin node is microscopically contaminated.[313,314]

A thoughtful appraisal of the risk of nodal spread and the anatomic level of potential contamination is an essential part of planning surgical therapy and determining target volume, dose, and technique for a course of radiation therapy. Diagnostic imaging may be helpful in the assessment of regional nodes in patients with vulvar cancer and tailoring the extent of surgery or radiation accordingly. MRI is highly specific for the detection of inguinal nodal involvement (97% to 100%). CT scanning also is useful in detecting nodal involvement (Fig. 91-21) that may be deeper in tissue than can be readily detected on physical examination. Fluorodeoxyglucose-positron emission tomography (FDG-PET) has a sensitivity of 67% to 80% in predicting lymph node metastasis. It also is more specific (90% to 95%) and is useful in planning radiation therapy and as an adjunct to lymphatic mapping and sentinel lymph node dissection.[315] Lymphoscintigraphy with technetium-99 m (Tc-99 m) sulfur colloid may be useful in the identification of sentinel nodes.[316]

Given the results of the Gynecologic Oncology Group (GOG) prospective randomized trial demonstrating better efficacy for adjuvant node radiation compared with pelvic node dissection, the

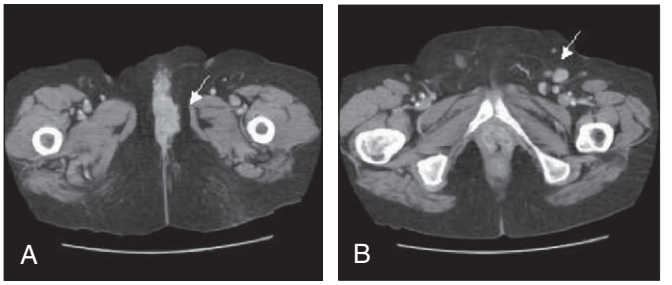


Figure 91-21 • CT of vulvar cancer. **A,** Irregular thickening and growth involving the left vulva with distortion of contour *(arrow)*. **B,** Enlarged left inguinal node *(arrow)*.

indications for extending surgery proximal to the inguinal ligament are diminishing.[310]

RADIATION THERAPY

Radiation therapy is increasingly used in the curative management of vulvar cancer,[317–322] often in conjunction with synchronous administration of radiation potentiating chemotherapy (chemoradiation).[296,323–334]

Radiation salvages some patients with locoregional recurrence after radical vulvectomy and regional node dissection.[334] Postoperative radiation directed to the groins and pelvic nodes improves disease-free survival in patients with metastatic spread to two or more inguinofemoral nodes[310] and may further improve results if residual vulva and perineum (operative bed) are included within the irradiated volume.[335]

Preoperative radiation and chemoradiation have reduced the indications for exenterative surgery and may permit a substantial decrease in the volume of normal tissue that must be removed in patients with tumors invading or intimately approximating the anus, clitoris, urethra, and distal vagina.[317,321,329,334]

Postsurgical, central, limited-volume, local recurrence in the residual vulva, at the introital margin, or on the perineum often is salvaged with secondary surgery, radiation, or combined-modality therapy.[336] A disease-free interval of 2 or more years and lack of involvement of regional nodes portend a favorable outcome with salvage therapy, although most disease recurs within 2 years of initial surgery.[337,338] Under circumstances in which the anticipated surgical margin is less than that of the original surgery, when recurrence approaches or involves critical structures, or when the pattern of recurrence is multifocal, it is prudent to plan for delivery of radiation as at least a component of the salvage strategy. Regional relapse in the groin or in pelvic nodes is much less likely to be salvaged, regardless of the combination of modalities used.[336,338–340] Salvage radiation alone, in doses ranging from 63 Gy to 72 Gy with progressive volume reductions or partial treatment with brachytherapy, often controls small-volume recurrence. Preoperative radiation ranging in dose from 45 Gy to 54 Gy followed by local excision may be less injurious in terms of delayed normal tissue effects than a high radiation dose to a large perineal volume in the absence of surgery.[336]

Adjuvant Postoperative Radiation Therapy

Postoperative radiation therapy usually is indicated in the following situations: more than one positive inguinal node, one grossly positive inguinal node or extracapsular extension of nodal disease, small tumors in patients with medical problems that prohibit radical inguinofemoral lymph node dissection, and a vulvar resection margin of less than 8 to 10 mm.

The GOG conducted a randomized trial comparing pelvic lymphadenectomy with radiation therapy directed to the bilateral groins and pelvic nodes (but not the tumor bed or perineum) in patients who were found to have groin node metastasis. A total of 114 eligible patients were randomized, of whom 40 had only one positive groin node. In 15 (28.3%) patients of 53 undergoing pelvic lymphadenectomy, disease had spread to pelvic nodes; 9 (60%) of these patients died of cancer within 1 year of study entry. The overall survival advantage for radiation at 2 years (68% for radiation, 54% for pelvic node dissection) was limited to patients with two or more involved groin nodes (63% for radiation, 37% for pelvic node dissection) and was attributable to a decrease in recurrence in the groin among the irradiated patients (5.1%) compared with those patients treated with surgery alone (23.6%). Lymphedema was reported in 19% of irradiated patients compared with 11% of patients treated with surgery alone. Of the 44 patients who had recurrence, only 11 patients failed with a component of "distant" disease (including three patients with relapse in the thigh, periaortic nodes, and abdominal skin), whereas 75% of relapsing patients failed with locoregional disease alone (vulvar area, groins, or pelvis). Eleven (25%) patients experienced recurrence in the unirradiated vulvar area; 10 of these had no other apparent sites of failure. As a consequence of this study, pelvic lymphadenectomy is less likely to be performed, and regional adjuvant radiation has become the standard of additional care for patients with metastasis to two or more regional nodes.[310] Katz and coworkers[341] recently found a higher rate of inguinal recurrence when patients started radiation therapy more than 50 days after their operation, and therefore concluded that postoperative radiation therapy should begin whenever possible within 4 to 6 weeks of surgery.

Areas of controversy in the postoperative adjuvant therapy of resected, node-positive vulvar cancer include whether patients with only one node contaminated should receive adjuvant therapy, whether patients with only unilateral groin node metastasis should have radiation delivered to the contralateral groin and pelvis, and whether synchronous administration of chemotherapy might further improve outcomes. Retrospective outcomes analysis of node-positive patients undergoing adjuvant groin and pelvic radiation suggests the wisdom of including the operative bed of the primary lesion within the treatment volume.[335]

Preoperative Chemoradiation

Under circumstances in which the extent of the primary disease suggests that postoperative radiation will be indicated, it is reasonable to consider preoperative radiation if it has the potential to reduce the scope of surgery and to conserve normal tissue structure and function or to convert the patient's status from unresectable to operable.[296,317–321,329] An anticipated margin of 1 cm or less from structures that will not be surgically removed is a useful guide for selecting patients for preoperative radiation.[297–299] Tumors that encroach on the anal sphincter, abut the pubic arch, or involve more than the distal urethra should be considered for preoperative radiation therapy. Patients with tumors that approach the clitoris or extend more than minimally past the vaginal introitus also should be considered for preoperative irradiation if conservation of sexual function is desired. Moderate-dose radiation (36 Gy to 54 Gy) has been given, followed by excision of residual palpable abnormalities that revealed no evidence of persistent cancer in 50% of cases (Table 91-10).

External-beam radiation is used most commonly, but interstitial or intracavitary brachytherapy may apply a higher dose to a discrete tissue volume where a surgical margin is anticipated to be inadequate.[317]

The GOG studied 73 patients with stage III to IV squamous cancers of the vulva who were judged not amenable to resection because of local disease extent beyond the conventional boundaries of radical vulvectomy. Preoperative chemoradiation, consisting of 47.6 Gy delivered in fractions of 1.7 Gy coordinated with two cycles of synchronous cisplatin and 5-fluorouracil (5-FU), converted 69 of 71 patients medically fit for surgery to having lesions considered

Table 91-10 Histologic Tumor Clearance by Preoperative Radiation

First Author	No. of Patients	Dose (Gy)	Negative Specimen	Percentage
Hacker[318]	8*	44–54	4	50
Acosta[319]	14	36–55	5	36
Jafari[320]	4	30–42	4	100
Total	26	30–55	13	50

*Includes one patient who received additional 24 Gy by intravaginal mould.

amenable to resection. Ultimately, urinary and fecal continence was conserved in all but 3 patients. With the use of this approach, local tumor control has been excellent, with conservation of normal tissue integrity in many patients who otherwise would have required exenterative surgery for tumor clearance.[296] By using the identical regimen (Fig. 91-22) in 46 patients with extensive (matted, fixed, or ulcerated) and unresectable groin metastases, physicians of the GOG were ultimately able to resect groin nodes in 37 patients, of whom 15 had histologically negative groin specimens.[342] The observation of complete histologic clearance of malignancy after moderate-dose preoperative radiation (alone or coordinated with synchronous chemotherapy) serves to encourage efforts to control vulvar cancer with radiation-based therapy under circumstances in which surgery is either technically unfeasible or medically contraindicated.

Cycle #1	
Day	Mon. – Fri. 1 2 3 4 5 6 7 8 9 10 11 12 Mon. – Fri.
Radiation 1.7 Gy/Fx	R R R R R 0 0 R R R R R R R R R
5-FU 1000 mg/M^2/24 hrs	F F F F
Cisplatin 50 mg/M^2	P
	1 1/2—2 1/2 week planned rest
Cycle #2	
Day	Mon. – Fri. 1 2 3 4 5 6 7 8 9 10 11 12 Mon. – Fri.
Radiation 1.7 Gy/Fx	R R R R R 0 0 R R R R R R R R R
5-FU 1000 mg/M^2/24 hrs	F F F F
Cisplatin 50 mg/M^2	P

Figure 91-22 • Time/dose/fractionation schedule: Phase II evaluation of preoperative chemoradiation for advanced vulvar cancer. Patients who are judged to be unresectable following completion of 47.6 Gy preoperative chemoradiation receive additional 20 Gy in fractions of 1.7–2 Gy with reduced treatment volume encompassing gross residual disease, or may receive additional radiation dose via brachytherapy. A third cyle of chemotherapy is recommended if teletherapy is employed. The authors would suggest restricting the cumulative dose to 59.5 Gy/35 Fx in the interest of avoiding severe late skin effects. 0, a day without radiation treatment; F, 5-fluorouracil by continuous intravenous infusion; P, bolus cisplatin administration; R, a fraction of external radiation—a 4-hour minimum intertreatment interval is mandatory, but 6 or more hours are suggested when practical. GOG Protocol 101.[296]

Radical Radiation and Chemoradiation

Definitive radiation has been used to treat medically inoperable or technically unresectable patients. Historically, results have been poor, in terms of both tumor control and normal tissue sequelae, although the tumor-control probability for patients with disease of limited volume has approached that of surgery.[321,343,344] Results with radiation alone in recent years have improved with better technique and dosimetry.[322]

The favorable experience with chemotherapy and reduced-dose radiation in the treatment of cancers of the anal canal has prompted increasing utilization of this approach in the treatment of advanced vulvar cancer. Most published experiences have used 5-FU, with or without cisplatin or mitomycin.[325–327,331,333,345–348] Retrospective comparison[348] suggests the superiority of chemoradiation compared with radiation alone, but prospective randomized data do not exist to validate the clinical impression of better results. Unquestionably, the administration of concurrent chemotherapy augments the acute reaction in normal tissues. Moist desquamation of the vulva necessitates treatment interruption in most patients. Hybrid dose/fractionation regimens have been developed to preserve dose intensity and to maximize potential synergistic effects. Twice-daily fractionation has become a popular strategy to exploit the radiation/drug interaction while minimizing the theoretical disadvantages of split-course radiation that is made mandatory by the enhanced effects in normal tissue.[296,332,333] Because of potential enhancement of late normal tissue effects, and because full radiation dose must be administered to some skin when treating what is fundamentally a skin cancer, it is advisable that total dose not exceed approximately 54 Gy in 30 fractions, 59.5 Gy in 35 fractions, or 64 Gy in 40 fractions to gross disease when chemoradiation is used, and that the volume receiving the full dose be as small as possible, while including all areas of initial measurable clinical involvement.

Elective Groin Radiation

A contributing factor to perioperative complications and chronic morbidity is the dissection of the inguinofemoral nodes.[349] In selected patients with limited primary tumors (T1a with ≤1 mm of invasion), omission of the node dissection is prudent. In others, limiting the groin dissection to superficial inguinal nodes (if histopathologically negative) has been an effective strategy for reducing acute and chronic morbidity. Preoperative identification of sentinel nodes may further enhance the safety of this approach. Elective irradiation of the clinically and radiographically negative groin nodes is an alternative strategy that has the theoretical advantage of treating all of the regional nodes rather than leaving some portion untreated. This approach also is applicable in patients with locally advanced primary tumors, in whom less than radical (superficial and deep) bilateral groin dissection would constitute less than adequate surgical treatment. Several series[350–353] have reported favorable results with elective or prophylactic groin irradiation (Table 91-11), but frequently in the setting in which groin nodes would be expected to be histologically uninvolved if treated surgically (T1 or T2 primary tumors of limited extent; Table 91-12).[354]

The GOG conducted a randomized trial comparing groin irradiation with groin dissection in otherwise operable patients with resectable vulvar primaries.[355] The study was terminated early because of an unacceptable rate of groin relapse (5 of 27 patients [18.5%]) and subsequent death from cancer (all 5 patients) in the group of women randomized to radiation. Technical inadequacies in the radiation treatment that may have led to inadvertent underdosage of the nodes could have contributed to this outcome.[356]

Table 91-11 Results of Elective Groin Radiation or Chemoradiation in Patients with Vulvar Cancer and Clinically Negative Inguinofemoral Lymph Nodes*

First Author	No. of Patients	Groin Failure	Percentage
RADIATION ALONE			
Frankendal[350]	12	0	0
Simonsen[351]	65	11	16.9
Boronow[295]	13	0	0
Perez[322]	39	2	5.1
Lee[352]	16	3	18.8
Petereit[353]	23	2	8.7
Stehman[355]	27	5	18.5
Total	195	23	11.8
CHEMORADIATION			
Leiserowitz[357]	19	0	0
Wahlen[358]	17	0	0
Total	36	0	0

*Patients with FIGO 1969 N0,1 negative groin nodes by clinical evaluation.

At the Radiation Oncology Centers of Sacramento[357] and at Loma Linda University,[358] patients have undergone prophylactic chemoradiation to the groin nodes, generally as a component of preoperative or definitive chemoradiation for locally advanced primary cancers. Among 37 such patients treated, no groin relapses occurred (see Table 91-11). It remains unclear whether the better results reflect better radiation technique or the radiopotentiating effect of synchronous chemotherapy.

Radiation Techniques, Volumes, and Doses

No standard approach is found to the treatment of vulvar cancer with radiation. The circumstance of radiation (postoperative, preoperative, or as definitive treatment) will influence the designation of target volume, fractionation, and dose. Clinical and histopathologic characteristics of the primary and regional nodes may independently affect the selection of treatment parameters, which depends further on the scope of any coordinated surgery and whether chemotherapy is to be administered with radiation. Comorbidities in elderly patients may constrain the volume and intensity of treatment. Conservation of ovarian function and possible reproductive integrity in younger patients also may affect the technique of treatment.[359] No substitute can be found for comprehensive assessment of disease extent followed by tailored, individualized therapy that takes into account the intent of treatment (i.e., preoperative, definitive, adjuvant postoperative), patient comorbidities, and patient preference. A guideline for radiation doses and fractionation is found in Table 91-13.

CHEMOTHERAPY

Chemotherapy to potentiate the effectiveness of locoregional radiation is rapidly becoming the standard of care for patients receiving radiation as all or part of treatment for the vulvar primary and regional nodes. Prospective randomized data for chemoradiation versus radiation alone do not exist. However, it is the clinical impression of experienced clinicians that tumor control within the irradiated volume appears to be better than that historically achieved with radiation alone. Additionally, late radiation sequelae in normal tissues may be milder consequent to the use of lower total dose and lower dose per treatment fraction. Most chemoradiation has been done with 5-FU alone or in combination with cisplatin or mitomycin-C. Representative results of treatment are depicted in Table 91-14. Experience with radiation and concurrent bleomycin has been disappointing as both preoperative treatment[360] and as treatment for extensive, inoperable disease,[361] with most patients treated for locoregionally advanced disease manifesting persistent or recurrent disease within the irradiated volume.

Chemotherapy for Recurrent, Persistent, or Metastatic Vulvar Carcinoma

Recurrent or persistent vulvar carcinoma after surgical therapy typically is treated with surgical resection or radiation-based therapy or

Table 91-12 Probability of Clinically Occult Metastasis to Inguinofemoral Lymph Nodes Correlated with Primary Tumor Category and Size

T Stage (1997 FIGO)	N0* (1969 FIG0)—No. (%)	N1* (1969 FIGO)—No. (%)	Total—No. (%)
T1	13/84 (15.5)	3/21 (14.3)	16/105 (15.2)
T2	17/56 (30.4)	4/14 (28.5)	21/70 (30)
T3	11/38 (28.9)	1/11 (9.1)	12/49 (24.4)
T4	0/1	0/0	0/1
Total	41/179 (22.9)	8/46 (17.4)	49/225 (21.7)
Clinical Tumor Size (CM)			
0–1.0	3/39 (7.7)	0/4	3/43 (7)
1.1–2.0	11/46 (23.9)	3/17 (17.6)	14/63 (22.2)
2.1–3.0	13/42 (31)	1/10 (10)	14/52 (26.9)
3.1–5.0	12/33 (36.4)	2/8 (25)	14/41 (34.1)
>5.0	1/10 (10)	2/5 (40)	3/15 (20)
Total†	40/170 (23.5)	8/44 (18.2)	48/214 (22.4)

*N0 denotes no palpable inguinal nodes; N1 denotes nodes palpable, nonsuggestive.
†Clinical tumor measurements not available for all patients.
Data from Gonzalez-Bosquet J, Kinney WK, Russell AH, et al: Risk of occult inguinofemoral lymph node metastasis from squamous carcinoma of the vulva. Int J Radiat Oncol Biol Phys 2003;57:419–424.

Table 91-13 Dose Guidelines

	CANCER VOLUME			
	RADIATION ALONE		CHEMORADIATION	
Treatment Intent	**Microscopic**	**Gross**	**Microscopic**	**Gross**
Preoperative	45–56	45–56	36–48	36–48
Postoperative	45–56	54–64 (+ margin)	36–48	45–56 (+ margin)
Radical	45–56	63–72	36–48	45–64

All doses expressed in Gy. Dose guidelines assume that treatment will be administered in fractions of 1.6 Gy to 1.8 Gy and that multiple daily fractions may be used for all or a part of the treatment. Higher total doses imply fraction size of 1.6 Gy, and lower total doses imply fraction size of 1.8 Gy. Dose guidelines should be interpreted in the contexts of tumor bulk, health of normal tissues unavoidably included within the treatment volume, tolerance, and response to treatment. Use of doses in the lower end of the range for gross disease is predicated on a biopsy at the completion of treatment confirming histologic clearance. Doses for gross disease should be applied with progressively shrinking volumes that confine high dose to not more, and possibly less, than the original volume of measurable disease.

both. Vulvar carcinoma that recurs in a local or regional area of prior radiation often is considered for surgical resection. Tumors that are not controlled or amenable to surgical or radiotherapeutic approaches are difficult to manage because of a lack of active systemic agents; these tumors often are first seen in elderly patients with major comorbidities, and sometimes in individuals with altered immunity due to chronic immunosuppression. Because recurrent tumors are rare, no randomized phase III trials have evaluated systemic therapy. Very few phase II studies have been reported to guide clinicians in selecting treatment. The effectiveness of chemotherapy also is limited by the fact that many treatment failures are local, or locoregional,[268,337–339,362,364] and typically within a prior radiation field (Table 91-15). These radiation-resistant tumors typically are also resistant to chemotherapy. Responses to treatment may be difficult to evaluate because of extensive anatomic abnormalities associated with prior surgery and radiation. Only six agents have been evaluated as single agents, with trials including only 4 to 22 patients, with most of these trials done in the early 1980s. Doxorubicin (Adriamycin) and bleomycin have demonstrated some single-agent activity.[365–367] An anecdotal response has been reported with liposomal doxorubicin.[368] Unfortunately, the

Table 91-14 Results of Radical Chemoradiation for Locoregional Advanced or Recurrent Cancers of the Vulva in Previously Untreated Patients

First Author	No. of Patients, Stages	Drugs	Radiation Dose (Gy)	Complete Response No. (%)	Subsequent Local Failure No. (%)	NED: F/U (mo)
Thomas[330]	9	F, M	40–64	6 (67%)	3 (50%)	NA
	"Advanced"					
Berek[331]	12					
	III (8)	F, P	44–54	8 (67%)	0	7–60
	IV (4)					
Russell[332]	18+					
	II (1)	F, P	46.8–56	16 (89%)	2 (13%)	2–52
	III (10)	M				
	IV (6)					
Koh[333]	14+					
	III (4)	F, P	34–63.1	8 (57%)	1 (17%)	5–75
	IV (10)	M				
Eifel[345]	12					
	II (1)	F, P	40–50	6 (50%)	1 (16%)	17–37
	III, IV (11)					
Cunningham[346]	14					
	III (9)	F, P	50–65	9 (64%)	1 (11%)	7–81
	IV (5)					
Akl[347]	12					
	I (3)	F, M	30–36	12 (100%)	1 (8%)	8–125
	II (5)					
	III (4)					
Total	91			65 (71%)	9 (14%)	

F, 5-FU; F/U, follow-up; M, mitomycin-C; NED, no evidence of disease; P, cisplatinum.

Table 91-15 Pattern of Recurrence* in 267 Patients for Whom Regional Therapy† Failed for Carcinoma of the Vulva

Vulva/Perineum No. (%)	Groin No. (%)	Pelvis No. (%)	Distant No. (%)
162 (60.7)	62 (23.2)	42 (15.7)	51 (19.1)

*Because some patients manifested recurrence at more than one site, the total recurrences exceed 267, and the total of the percentages exceeds 100.

†The majority of patients underwent radical surgery. Adjunctive radiation was administered in some, and a small number were treated with radiation alone.

Pooled data, seven series.[268,337–339,362–364]

duration of response in most instances is disappointing and is measured in months.

Combination chemotherapy regimens that have been evaluated have included bleomycin together with a variety of agents (Table 91-16).[369–373] The largest experience is with the regimen of bleomycin, methotrexate, and N-(2-chloroethyl)-N′-cyclohexyl-N-nitrosourea (CCNU).[369,370] Activity has been seen in two separate phase II studies that included 53 patients and demonstrated 5 complete responses and 27 partial responses, for an overall response rate of 60%, in a group of patients with locally advanced squamous cell carcinoma of the vulva.

In vitro studies with squamous cell cancer lines of the vulva demonstrate high expression of the epidermal growth factor receptor and efficacy of ZD1839 in vitro, either alone or in combination with chemotherapy.[374,375] The role of this targeted agent in the clinic awaits formal testing.

Other Histologic Types

Adenosquamous Carcinoma

The pathogenesis of adenosquamous carcinoma of the vulva remains controversial, as it has been since it was first described by Lever 45 years ago.[376] Initially, it was thought to arise from solar keratoses. However, this theory later was discounted, as cases were described in which vulvar sun exposure was not a factor.[376,377] A currently accepted theory is that the involved glandular elements produce mucin and have their origin from mucin-producing cells of the skin appendages.[378]

Adenosquamous cell carcinoma of the vulva appears to be a biologically distinct tumor. These lesions involving the vulva are highly aggressive, are first seen at a more advanced stage, and are associated with a higher incidence of lymph node metastases than are their corresponding squamous cell counterparts. Five-year survival rates reflect this trend, at 5% and 62% for adenosquamous and squamous cell carcinomas, respectively.[379]

Melanoma

Malignant melanoma of the vulva is the second most common cancer of the vulva, accounting for approximately 10% of primary vulvar neoplasms and representing 0.05% to 0.5% of all malignancies of the female genital tract. Even large, tertiary cancer referral centers see only one or two patients annually.[380–383]

Malignant melanoma occurs predominantly in postmenopausal white women, with a peak incidence between the 6th and 7th decades. These lesions may arise de novo or from pre-existing junctional or compound nevi. Three basic histologic types exist: (1) superficial spreading melanoma, the most common type, which tends to remain superficial in its early course; (2) lentigo malignant melanoma, a "flat freckle" that has a tendency to remain superficial; and (3) nodular melanoma, which is the most aggressive variety, carries the worst prognosis, and tends to invade deeply early.[381]

Amelanotic varieties of these lesions are very rare. These lesions tend to be asymptomatic and insidious. Any pigmented lesions on the vulva should be sampled with biopsy. Melanomas typically contain melanoma antigen and S-100 antigen and lack carcinoembryonic antigen (CEA). These immunohistochemical tests may be required to differentiate superficial spreading melanoma from Paget's disease.[384]

STAGING. The prognosis for vulvar melanoma appears to correlate most closely with the level of skin involvement. Chung and colleagues[381] (Table 91-17) proposed a modified leveling system, retaining Clark's definitions[385] for levels I and V. Levels II, III, and IV are arbitrarily defined by using measurements in millimeters. Breslow's[386] measurements also may be used, but in the vestibule and perineum, because no keratin or granular layers exist, the system must be modified.

Table 91-16 Combination Chemotherapy in Squamous Cell Carcinoma of the Vulva

Regimen	Dose and Schedule	No. of Patients	Complete Responses	Partial Responses	References
Bleomycin, vincristine, mitomycin-C, cisplatin	15 mg/m^2 cont IV days 1–3 1.4 mg/m^2 IV day 3 10 mg/m^2 IV day 3 60 mg/m^2 IV day 3	23	3	4	377, 378
Bleomycin, methotrexate, CCNU	5 mg IM day 1–5 15 mg PO days 1 and 4 40 mg PO days 5–7	28	3	15	373
Bleomycin, methotrexate, CCNU	5 mg IM days 1–5, 8, 15, 22, 29, 36 15 mg PO days 1 and 4, 8, 15, 22, 29, 36 40 mg PO days 5–7	25	2	12	374
Bleomycin, methotrexate, cisplatin	15 mg IV days 1 and 8 300 mg/m^2 day 8 with rescue 100 mg/m^2 day 1	21	0	14	379

CCNU, N-(2-chloroethy1)-N-cyclohexyl-N-nitrosource; cont, continuous; IM, intramuscularly; IV, intravenously; PO, orally.

Table 91-17 Stages of Melanoma of the Vulva According to Three Different Systems of Criteria

Stage	Clark's Levels	Chung	Breslow
I	Intraepithelial	Intraepithelial	<0.76 mm
II	Into papillary dermis	≤1 mm from granular layer	0.76–1.50 mm
III	Filling dermal papillae	1.1–2 mm from granular layer	1.51–2.25 mm
IV	Into reticular dermis	>2 mm from granular layer	2.26–3.0 mm
V	Into subcutaneous fat	Into subcutaneous fat	>3 mm

From Berek JS, Hacker NF: Practical Gynecologic Oncology, 2nd ed. Baltimore, Williams & Wilkins, 1994.

TREATMENT. For level I or II lesions (superficial), the risk of nodal spread is low, and wide local excision is adequate therapy. For deeper lesions, radical vulvectomy with en bloc bilateral inguinofemoral lymphadenectomy should be performed if the inguinofemoral nodes are positive. Estrogen receptors have been demonstrated in human melanomas, and a response to tamoxifen has been reported.[387] PET and sentinel-node groin biopsies may be tools to aid in selecting the extent of regional surgery. Systemic adjuvant therapies for vulvar melanoma parallel adjuvant strategies for cutaneous melanomas arising at other primary sites.

PROGNOSIS. Melanomas of the vulva tend to spread earlier than squamous cell carcinoma and carry a worse prognosis overall. Chung and colleagues[386] reported corrected 5-year survival rates of 100%, 40%, and 20% for patients with level II, III or IV, and V lesions, respectively. The overall 5-year survival rate with negative and positive nodes is 38% and 13%, respectively.[388]

Basal Cell Carcinoma

Basal cell carcinomas represent approximately 2% of vulvar cancers. They usually affect postmenopausal white women and are locally aggressive, although nonmetastasizing. They are commonly seen on sun-exposed skin, but also can be seen rarely on the vulva. Their common appearance is a "rodent" ulcer with rolled edges and central ulceration. Wide local excision is the treatment of choice. Not unlike CIS and Paget's disease of the vulva, basal cell carcinomas are associated with a high incidence of antecedent or concomitant malignancy elsewhere in the body; a thorough search for other primary malignancies is always warranted.

Bartholin's Gland Carcinoma

Bartholin's gland is situated inferior to the bulbocavernosus muscle and superior to the deep perineal muscles. The gland is composed of columnar epithelium, and ducts are lined by stratified squamous epithelium and transitional cell epithelium. Therefore, adenocarcinomas, squamous cell carcinomas, and, rarely, transitional cell carcinomas may arise from Bartholin's gland. Most primary adenocarcinomas of the vulva arise within these glands. The median age at diagnosis is 57 years. In 10% of patients, a history of preceding inflammation of Bartholin's gland is obtained. Malignancy arising from Bartholin's gland constitutes approximately 4% to 7% of vulvar malignancy.

The criteria established by the Armed Forces Institute of Pathology for the diagnosis of Bartholin's gland carcinoma enjoy the broadest contemporary acceptance.[389] A primary Bartholin's cancer should show areas of apparent transition from normal elements to neoplastic elements on histologic study, should be histologically compatible with origin from Bartholin's gland, and should exist without evidence of primary cancer elsewhere. The Bartholin's complex consists of a duct that is lined by squamous epithelium as it enters the distal vagina. The more proximal portions of the ductal system are lined by transitional epithelium and may be lined by columnar epithelium before arborization into secretory glandular elements. Squamous carcinoma constitutes approximately 35% to 50% of cases, with adenocarcinoma only slightly less common.[389–393] Adenosquamous carcinomas and transitional cell carcinomas make up a small minority of cases. Adenoid cystic carcinoma represents a distinct subset thought to be less likely to spread to regional nodes and associated with a long natural history and late recurrences, which may be either local or hematogenous.[394] Bartholin's gland carcinomas have been reported in younger women and in association with pregnancy,[389,390] although an etiologic relation is not apparent. Often first seen with a mass deep in the labia with intact overlying skin, Bartholin's gland carcinomas may be confused with a Bartholin's cyst or abscess, particularly if the patient is young. No persuasive evidence exists that squamous carcinomas of Bartholin's gland behave differently or should be managed differently from squamous cancers arising from other vulvar structures. However, it may be more difficult to accomplish conservative excision with adequate surgical margins in patients with Bartholin's gland cancers, and most patients for whom surgical therapy fails have a component of locoregional recurrence.[392,393] The use of adjuvant postoperative radiation is common.[395,396] A retrospective review of 36 nonrandomized patients at M.D. Anderson Cancer Center revealed that in 6 (27%) of 22 patients treated with surgery alone local recurrence developed, whereas only 1 (7%) of 14 higher-risk patients selected to receive adjuvant radiation manifested local failure.[393]

Sarcoma

Vulvar sarcomas constitute 1% to 2% of vulvar malignancies and include leiomyosarcomas, rhabdomyosarcomas, angiosarcomas, neurofibrosarcomas, and epithelioid sarcomas. The prognosis appears to depend on three main determinants: lesion size, tumor contour, and mitotic activity. Lesions greater than 5 cm in diameter, with infiltrating margins, and demonstrating more than five mitotic figures per 10 high-power fields (HPFs) are most likely to recur. Wide local excision is the usual treatment.

Verrucous Carcinoma

Verrucous carcinoma of the vulva represents a variant of squamous cell carcinoma. These lesions originally were described as occurring in the oral cavity but also have been described involving the vagina, cervix, and vulva. The lesion grossly appears cauliflower-like. Microscopically, the papillary fronds lack the connective tissue core that characterizes condyloma acuminata. These features are very similar to those of the giant condylomata Buschke-Loewenstein, possibly representing successive stages of the same pathologic process. Clinically, these tumors are very slow growing and carry a favorable prognosis. As metastasis to regional lymph nodes is rare, radical local excision is the standard treatment.[397–400] If suggestive groin nodes are present, fine-needle aspiration (FNA) or excisional biopsy should be carried out. Enlarged nodes usually are caused by inflammatory hypertrophy, but if they do contain metastases, radical vulvectomy and bilateral groin lymph node dissections are indicated. Verrucous carcinoma has the reputation of being radioresistant, and reports of favorable outcomes after radiation are uncommon. Surgery remains the treatment of choice whenever feasible.

CANCER OF THE VAGINA

SUMMARY OF KEY POINTS

Epidemiology
- For 2007, 2140 new cases of invasive vaginal cancer in the United States are estimated, with 790 deaths
- Primary vaginal cancer constitutes only 1% to 2% of malignancies of the female genital tract and 0.1% to 0.2% of all cancers.
- The majority of vaginal malignancies (≤90%) are metastatic.
- Squamous cell carcinomas compose approximately 80% of primary vaginal malignancies, with adenocarcinomas, melanomas, sarcomas, and lymphomas accounting for most of the remainder.

Etiology
- The role of human papillomavirus (HPV) in vaginal carcinoma has been the subject of much speculation, but no conclusive etiologic link has been identified. Low socioeconomic status, a history of genital warts, a prior abnormal Papanicolaou (Pap) smear, early hysterectomy, and prior vaginal trauma may be associated risk factors.
- The frequency with which vaginal intraepithelial neoplasia (VAIN) progresses to invasive malignancy is unknown, but the percentage is thought to be small.

Evaluation
- Up to 20% of patients are asymptomatic, with disease being diagnosed on routine pelvic examination and Pap smear.
- Most patients initially have postcoital or postmenopausal painless bleeding or discharge.
- Patients also may have symptoms related to the location of the tumor, such as urinary frequency or dysuria from anterior tumors, or constipation or tenesmus from posterior tumors.
- Vaginal carcinoma may be identified by colposcopy in the setting of an abnormal Pap smear.
- Diagnosis is established by tissue biopsy of a gross or colposcopically detected lesion.
- Vaginal cancer is staged clinically based on findings of physical examination, cystoscopy, proctoscopy, and chest radiography. Additional diagnostic assessments will not alter staging, but may be important in the design of a treatment program.

Treatment
- Depending on the location of cancer within the vagina, tumor size, and extent of invasion, surgery may be effective primary therapy in selected circumstances Patients with stage I disease that can be excised with negative surgical margins without compromising the function of the urinary bladder or rectum are appropriate candidates, as are patients with stage IVa disease in whom urinary or fecal continence has already been destroyed by direct invasion of the cancer through the wall of adjacent viscera.
- Radiation therapy is the treatment of choice for most other patients. Combined chemoradiation, similar to the approach used in anal, vulvar, and cervical cancers, has been reported in a limited number of patients, but has not been established as superior to radiation alone.
- Patients with central recurrence after radiation may be candidates for surgical salvage, which usually entails pelvic exenteration.

EPIDEMIOLOGY

Primary vaginal cancers are rare, accounting for only 1% to 2% of malignant neoplasms involving the female genital tract. By convention, with International Federation of Gynecology and Obstetrics (FIGO) criteria for classification and staging, any tumor that has extended to the cervix and has reached the external os should be classified as a cervical carcinoma. Similarly, any tumor extending to involve the vagina and vulva simultaneously is classified as vulvar carcinoma. In addition, if a patient has been previously treated for a cervical cancer, a subsequent vaginal cancer within 5 years (or 10 years, depending on the author) is considered a recurrence of the cervical cancer rather than a new primary cancer. Thus, some tumors with their epicenters in the vagina will be classified as cervical or vulvar neoplasms by using the FIGO formalism, and other patients, who may have second primary vaginal malignancy as part of a "field cancerization" of the lower genital tract, will be classified as patients with recurrence of prior malignancy. These factors account for some of the rarity of primary vaginal cancer. Over 60% of primary apical vaginal tumors are diagnosed in women who have undergone hysterectomy. Speculation occurs that the lack of a transformation zone and glandular tissue in the vagina (compared with the cervix) makes the vagina less likely to develop neoplasia.

Most cancers involving the vagina are metastatic. Vaginal involvement may occur by direct extension or by lymphatic or hematogenous spread. Primary tumors that most commonly are the source of metastases involving the vagina include cancers of the endometrium, cervix, vulva, ovary, breast, colon and rectum, and kidney.[401–404]

Only 10% of vaginal cancers are primary in the vagina, and most of these are of squamous histology. The nonsquamous primary vaginal malignancies account for a heterogeneous group of histologies (Table 91-18).[405–414] Metastatic tumors are treated according to their primary site of origin, and not as vaginal cancers.

Most women with vaginal squamous cancer are postmenopausal, and more than 75% of patients are older than 50 years at diagnosis. Most single-institution series report average age in the fifth through seventh decades, with ages ranging from the 20s to the 90s. No correlation is found between age and stage of disease or survival. Squamous tumors may be nodular, ulcerative, indurative, or exophytic plaques of any size. Histologically, they are similar to squamous tumors from other sites. Approximately one third of these tumors are keratinizing, and more than one half are nonkeratinizing, moderately differentiated lesions. The degree of histologic differentiation of these tumors has not been shown to correlate with survival.[407,415–418]

Verrucous carcinoma is an uncommon variant of squamous cell carcinoma, morphologically similar in the vagina to verrucous lesions of the vulva (Fig. 91-23). Grossly, it appears as a warty fungating mass. Histologically, it is composed of large papillary fronds covered by dense keratin. Its deep margin creates a pushing border of well-oriented rete ridges. This tumor rarely metastasizes but can infiltrate

Table 91-18 Primary Vaginal Cancer: Reported Incidence of Histologic Types

Histology	No.	Percentage
Squamous	627	83.4
Adencarcinoma	70	9.3
Sarcoma	20	2.6
Melanoma	20	2.6
Undifferentiated	8	1.0
Small cell	5	0.7
Lymphoma	2	0.3
Carcinoid	1	0.1
Total	753	100.0

Modified from Berek JS, Hacker NF: Practical Gynecologic Oncology, 3rd ed. Philadelphia, Lippincott Williams & Wilkins, 2000, p 598.

extensively into surrounding tissues, including the rectum and coccyx. This histologic variant of squamous cancer has the reputation of being resistant to control by conventional doses of radiation. Thus surgery is favored as a treatment modality when clinically feasible.

Adenocarcinomas occurring in the vagina include papillary, mucinous, adenosquamous, small cell, and clear cell variants. The variants that have been best described are the clear cell malignancies, primarily because of their reported occurrence in young women who had been exposed to diethylstilbestrol (DES) in utero.[419,420] Clear cell carcinomas of the vagina usually are polypoid masses. Histologically, well-described patterns are noted: tubulocystic, solid, or papillary. They usually are diagnosed at an earlier clinical stage than is seen with squamous cell carcinomas; 74% of Registry patients were stage I, and 26% were stage II.

ETIOLOGY

The association of vaginal, vulvar, and cervical intraepithelial neoplasia (CIN) and human papillomavirus (HPV) has caused speculation as to the role of HPV in multifocal carcinoma of the lower female genital tract. Ikenberg and coworkers[421] were able to demonstrate the presence of HPV DNA in tumor tissue in 10 of 18 patients (56%) with vaginal cancer, suggesting a possible etiologic role for HPV in the development of vaginal neoplasia. Many women are first seen with multifocal disease of the genital tract, including dysplasias of vulva, vagina, and cervix. Unlike the cervix, where disease usually is present in the transformation zone, vaginal dysplasia can occur anywhere in the vaginal mucosa and often is multifocal. The natural history of vaginal intraepithelial neoplasia (VAIN) is not well understood, and the potential of VAIN to progress to invasive squamous malignancy is not known with precision. Aho and colleagues[422] identified 23 patients with VAIN followed up for at least 3 years without treatment. The mean age was 41 years. Half of the VAIN lesions were multifocal, and half were associated with either cervical intraepithelial neoplasia (CIN) or vulvar dysplasia. The spontaneous regression rate of VAIN was high (78%), including four of five VAIN 3 patients, but two cases (9%) progressed to invasive cancer. Studies by Benedet and Saunders[423] and by Lenehan and associates[424] have shown that only 3% to 5% of patients with VAIN treated with various methods actually progressed to having invasive vaginal carcinoma. Invasive vaginal carcinoma has also been associated with chronic irritant vaginitis, particularly that type caused by chronic use of a vaginal pessary.

The clear cell variant of vaginal adenocarcinoma has been clearly linked to in utero exposure to DES. The Registry for Research on Hormonal Transplacental Carcinogenesis had accessioned more than 580 cases of clear cell carcinoma of the vagina and cervix. In utero exposure to synthetic estrogens accounted for only two thirds of reported cases. Work by Herbst and coworkers[425–427] suggests that the age distribution for clear cell adenocarcinoma of the vagina has two separate peaks. The first peak included women with a mean age of 26 years, and the second peak contained women with a mean age of 71 years. The first peak contained all DES daughters, and the second peak contained women born before 1950 and thus not exposed to DES. However, even when the DES daughters were excluded, a bimodal pattern still was observed. The authors suggested that this pattern might imply a genetic predisposition. The age range of DES-related clear cell adenocarcinoma is 7 to 42 years. The actual risk of clear cell adenocarcinoma developing in DES-exposed women is estimated at only 1 in 1000, with the highest risk in those women exposed before 12 weeks' gestation.[419] Although the risk of clear cell carcinoma of the vagina is small in DES-exposed women, 45% of these patients will have areas of vaginal adenosis, and 25% will have structural abnormalities of the uterus, cervix, or vagina. Thus it is recommended that women exposed to DES in utero be examined initially at menarche (approximately age 14 years) and that a careful examination of the cervix and the vagina be performed in addition to cytologic examinations. Colposcopy is unnecessary if the clinical and cytologic examinations are normal.



Figure 91-23 • Locally recurrent verrucous cancer following radical vulvectomy. Warty, exophytic, cauliflower morphology is characteristic. This patient had persistent local disease, despite salvage chemoradiation consisting of 54 Gy in 30 fractions with twice-daily fractionation over 7 weeks with three cycles of synchronous 5-fluorouracil and cisplatin. (Reproduced with permission from Russell AH: Vulva. In Leibel SA, Phillips TL [eds]: Textbook of Radiation Oncology. Philadelphia, WB Saunders, 1998, pp 907–925.)

PATTERNS OF SPREAD

Vaginal cancer may spread by several routes:

- Direct extension to adjacent soft tissue structures such as the paracolpos/parametria, bladder, urethra, and rectum, with eventual involvement of the bony structures of the pelvis.
- Lymphatic dissemination, the pattern of which will depend on the location of the primary tumor. The lymphatics of the upper vagina communicate with those of the cervix and drain into the pelvic nodes and then to the para-aortic nodes. The posterior vaginal wall drains into lymphatics that anastomose with the inferior gluteal, sacral, and deep pelvic nodes. The anterior wall is drained by lymphatics that drain to the lateral pelvic walls. The lymphatics of the distal one third of the vagina drain into the inguinofemoral nodes and then secondarily to the pelvic nodes.

- Hematogenous dissemination to other organs, including the lungs, liver, and bone, usually is a late manifestation in the natural history of this disease.

SIGNS AND SYMPTOMS

Presenting symptoms commonly associated with vaginal cancer include painless spontaneous or postcoital vaginal bleeding or vaginal discharge. Because of the close proximity of the urethra to the vagina, anterior vaginal tumors may cause symptoms of urinary frequency or dysuria or both. Similarly, advanced posterior vaginal tumors may cause symptoms of tenesmus or constipation. Pelvic pain may be present when disease has extended beyond the vagina. Up to 20% of patients are asymptomatic, with disease detected on routine examination or Papanicolaou (Pap) smear. In a review of the literature by Plentl and Friedman[428] and colleagues in 1971, 51% of vaginal carcinomas arose in the upper vagina, 19% from the middle third, and 30% from the distal third. Fifty-seven percent of the tumors originated from the posterior wall, 27% from the anterior wall, and 16% from the lateral wall.[406] The most common site of occurrence of vaginal carcinoma is along the posterior wall in the upper one third of the vagina. Because the posterior blade of the speculum often obscures this area, the speculum must be rotated to view the vaginal tube in its entirety.

DIAGNOSIS

The diagnosis of carcinoma of the vagina may be missed on initial examination, especially if the tumor is located anteriorly or posteriorly where the blades of a duckbill speculum may obscure a lesion. Thus the speculum must be rotated as it is withdrawn to allow circumferential visualization of all areas of the vaginal mucosa, and the speculum may require multiple insertions and withdrawals to accomplish this goal. If no lesion is detected in the setting of an abnormal Pap smear, use of Lugol's iodine to stain the vaginal mucosa and colposcopy may be helpful to direct biopsies. Diagnosis requires biopsy confirmation of a suspected lesion, as benign lesions such as vaginal warts (condyloma) may mimic the gross appearance of malignancy. An examination under anesthesia with directed biopsies may be necessary if the patient is elderly or has significant vaginal stenosis precluding a satisfactory office examination, or if cystoscopy or proctoscopy is indicated to evaluate the patient adequately because of the location and extent of the vaginal lesion.

STAGING

Vaginal cancers are staged according to criteria set forth by FIGO or by the American Joint Committee on Cancer (Table 91-19). The staging of vaginal cancers is primarily clinical and is based on findings on physical and pelvic examination, cystoscopy, proctoscopy, chest radiography, and skeletal radiography (if indicated for bone pain). Assignment of FIGO stage is necessary, but alone may be insufficient to direct therapy optimally. Rubin and colleagues[408] studied patients with vaginal cancer spanning the years 1958 through 1980. In this study, 18% of patients had stage I tumors, and 46% had stage II tumors. Stock and colleagues[429] reviewed patients spanning the years 1962 through 1992. In this study, 23% of patients had stage I disease, and 58% had stage II disease; the remaining patients had more advanced disease.

In addition to the standard staging investigation, an abdominopelvic computed tomography (CT) scan or pelvic magnetic resonance imaging (MRI) or both may be helpful to evaluate the extent of the primary tumor, confirm patency of the ureters, and screen for the possible presence of metastases to deep femoral, pelvic, and paraaortic lymph nodes.[430] Precise delineation of local disease extent may be helpful in planning intracavitary or interstitial brachytherapy. Positron emission tomography (PET) may be a clinically useful tool to assess for regional (lymphatic) and remote (hematogenous) dissemination, but its value has not been prospectively evaluated in this context (Fig. 91-24).

Table 91-19 Vaginal Cancer: Staging Systems

Type	TNM	FIGO	Definition
Primary tumor	TX		Primary tumor cannot be assessed
	T0		No evidence of primary tumor
	Tis	0	Carcinoma in situ
	T1	I	Tumor confined to the vagina
	T2	II	Tumor invades paravaginal tissues but not to the pelvic wall
	T3	III	Tumor extends to the pelvic wall
	T4	IVa	Tumor invades mucosa* of the bladder or rectum and/or extends beyond the true pelvis
		IVb	Distant metastasis
Regional lymph nodes	NX		Regional lymph nodes cannot be assessed
	N0		No regional lymph node metastasis
Upper $^2/_3$ vagina	N1		Pelvic node metastasis
Lower $^1/_3$ vagina	N1		Unilateral inguinal node metastasis
	N2		Bilateral inguinal node metastases
Distant metastasis	MX		Presence of distant metastasis cannot be assessed
	M0		No distant metastasis
	M1		Distant metastasis

FIGO, International Federation of Gynecology and Obstetrics; TNM, tumor-node-metastasis.

*Presence of bullous edema is not sufficient evidence to classify as T4 or FIGO IVa.

A refinement of the AJCC/FIGO staging system that has been proposed by Perez and colleagues[431] is commonly used by radiation oncologists, both in selection of radiation technique and in the reporting of outcomes after treatment. Patients with stage IIa have paravaginal extension only, whereas patients with stage IIb have extension to parametria. This distinction has both prognostic significance and a potential impact on the volume and technique of teletherapy and brachytherapy (intracavitary vs. interstitial).

TREATMENT

Therapy for vaginal carcinoma must be highly individualized based on tumor location, size, extent, and the functional status of both the vagina and adjacent organs. The close proximity of the bladder, urethra, and rectum limits the doses of radiation that can be given and restricts the surgical margins that can be obtained without performing an exenterative procedure. Up to 50% of patients with primary vaginal cancer may have had prior hysterectomy for malignant or benign indications.[429,432,433] In such patients, the presence of adhesions with fixed loops of small bowel or sigmoid colon above the vaginal apex also may affect selection of treatment modalities and techniques.

Additionally, psychosexual issues and the attempt to maintain a patent and functional vagina in patients desirous of preserving the option of vaginal intercourse should be an important part of treatment planning.

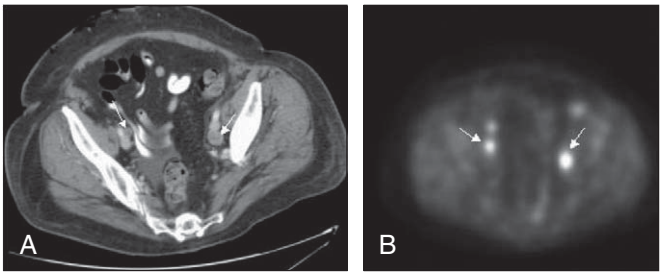


Figure 91-24 • Vaginal cancer with lymphadenopathy. **A,** CT of pelvis showing mildly enlarged bilateral external iliac nodes suggestive of metastases *(arrows)*. **B,** Axial FDG-PET scan showing hypermetabolic nodes as hyperintense spots confirming metastases *(arrows)*.

Surgery

Surgery in vaginal cancer is limited by the propensity of this cancer to spread to adjacent organs because of the lack of anatomic boundaries around the vagina.[406,434] The use of surgery as a primary modality is limited to those cases in which negative margins can be achieved without significant loss of function of bladder and rectum. Surgery also can be used to salvage central pelvic recurrence after radiation.

In the past, many authors have considered radiation to be the primary treatment modality for vaginal cancer. Contributing to this recommendation has been the age of most patients with vaginal cancer and the complicating presence of multiple medical comorbidities. With improved anesthetic techniques and better postoperative care, surgery may be an option available to more women with vaginal cancer.

Surgery for vaginal cancer can be primary therapy or can be used as an adjunct to radiation therapy. Stage I vaginal cancer involving the upper vagina in a young woman can be treated with radical hysterectomy and radical upper vaginectomy with pelvic lymph node dissection. This approach in most cases allows preservation of both vaginal and ovarian function, particularly if no risk factors are found during surgery that would require postoperative radiation therapy.

Traditionally, later-stage vaginal cancers, particularly those in elderly women, have been treated primarily with radiation therapy. However, several recent series have suggested that judicious use of surgery may increase disease-free survival in carefully selected patients.

Tjama and associates[435] reported their experience treating 84 patients with primary invasive vaginal cancers in the Northern Gynecological Oncology Centre, where the policy tended toward operative management. In this series, the treatment was individualized based on patient age, medical status, size of tumor, location of lesion, and stage. Large lesions that did not permit negative margins were treated primarily with radiation, and adjuvant radiation was used postoperatively to treat patients who had positive retroperitoneal nodes or incomplete excision. Forty patients in this series were treated with surgery alone. Fifty-eight patients underwent exploratory laparotomy for either treatment or staging. Primary surgical treatment included radical vaginectomy, partial vaginectomy, wide local excision, and exenteration. This study demonstrated a significantly increased disease-free survival in patients who had surgery as part of their therapy or as their only therapy compared with patients who were treated with radiation alone. When stratified by stage, this difference was significant in those patients with stage II disease. In a multivariate analysis, surgical treatment and FIGO stage were the only significant predictors of improved disease-free survival. Unknown selection biases may have contributed substantially to these results, influencing treatment modality choice and, therefore, outcomes.

The National Cancer Data Base study[436] reported that surgery was used to treat 49% of patients with stage I disease, 28% of patients with stage II disease, and 25% of patients with advanced stage disease. Women with stage I disease treated with surgery only had a 5-year survival of 90%, compared with 63% for women with stage I disease treated with radiation therapy only. Although this difference was statistically significant, differences among these patients with respect to age and medical comorbidities could not be assessed. Similar findings were demonstrated in stage II disease, in which surgery alone gave a 5-year survival rate of 70% compared with 57% for patients treated with radiation therapy alone. Nine women with advanced-stage disease had surgery, radiation therapy, and chemotherapy; remarkably, the 5-year survival for this group was 71%. These findings suggest that in selected cases, surgery may play a role in improving 5-year survival in all stages of disease.

Radiation Therapy

Radiation therapy using various combinations of teletherapy as well as interstitial and intracavitary therapy generally is considered the treatment of choice for most patients with more than small-volume stage I and II cancers of limited extent. The exact combinations of treatment again depend on the tumor location, volume and thickness, and depth of invasion beyond the vagina. Almost all patients with stage I lesions that are larger than 2 cm, and all patients with stage II to IV disease, require initial treatment with external-beam radiation therapy of approximately 45 to 50.4 Gy, both to shrink the primary tumor and to address potential sites of microscopic or clinically occult dissemination. Inclusion of pelvic or inguinofemoral lymph nodes, or both, in the field depends on the tumor location. Tumors extending to involve the distal third of the vagina should have inclusion of the inguinofemoral nodes as well as the pelvic nodes. Extended-field treatment to include the para-aortic lymph nodes is appropriate if these nodes have been found to contain metastatic disease by surgical excision or image-guided fine-needle aspiration. External-beam therapy usually is followed by interstitial or intracavitary brachytherapy to a total tumor dose of approximately 75 to 85 Gy. For tumors involving the upper third of the vagina with intact uterus, intrauterine tandem and vaginal ovoids/colpostats may be used to obtain proper dose distributions encompassing the vaginal wall, paravaginal tissues, and parametria. For a patient in this category whose uterus previously has been surgically removed, a vaginal cylinder or colpostats may be used. The use of intracavitary vaginal brachytherapy generally is restricted to patients with tumor thickness of 5 mm or less because of the rapid fall-off of dose with distance from intracavitary isotope sources. For carcinomas with more than 5 mm thickness after teletherapy, the use of interstitial technique in addition to a vaginal cylinder will increase the depth of the radiation-dose distribution without delivering an excessive dose of radiation to the vaginal mucosa.[442] The treatment of small, superficial, stage I lesions may be satisfactory with brachytherapy alone, involving intracavitary cylinders with or without single-plane interstitial implants.[437,438]

The concomitant use of chemotherapeutic agents such as cisplatin and 5-fluorouracil (5-FU) as radiosensitizers for vaginal cancer has not been extensively studied. As the combination of radiation with synchronous chemotherapy (chemoradiation) has increasingly become the mainstay of therapy for locally advanced cervical cancer, anal cancer, and advanced vulvar cancer, extrapolation to squamous carcinoma of the vagina seems logical. The shared etiology suspected in many patients with primary squamous cancers of the anogenital area supports the notion that a successful treatment strategy used for one disease site also could be expected to be effective at adjacent disease sites. However, because of the rarity of vaginal cancer, the use of chemoradiation in this context has not been prospectively evaluated in randomized cooperative group studies comparable to protocols that have been feasible in patients with cervical and anal cancers.

Intervention by Stage

Stage I Disease

For disease involving the proximal vagina, if the uterus is still in situ, a radical hysterectomy, partial vaginectomy, and bilateral pelvic lymphadenectomy can be performed. In a patient with a prior hysterectomy, a radical upper vaginectomy and bilateral lymphadenectomies can be performed. For disease in proximity to the bladder neck or urethra in the anterior vagina, radiation generally is preferable. Posterior tumors may be more amenable to a surgical approach. Lateral tumors in the middle or distal vagina with minimal invasion may be considered for wide local excision. Radiation therapy with brachytherapy alone may be considered for very small tumors less than 2 cm in largest diameter. Radiation usually consists of a combination of teletherapy and brachytherapy. In a recent review of the M.D. Anderson Cancer Center experience, Frank and associates[439] reported that of the nine patients who received brachytherapy alone, three recurred within the pelvis, resulting in a pelvic control rate of only 67%. Therefore, the authors concluded that patients with invasive disease, no matter what size, should be treated with a combination of external beam radiation and brachytherapy; however, it is not necessary to treat the whole pelvis in all patients. They found that there were no pelvic recurrences in 11 patients who received local external beam irradiation (to the lower pelvis only) combined with brachytherapy.

Stage II or III Disease

Before radiation, exploratory laparotomy may allow precise detailing of the areas of involvement, resection of bulky metastatic adenopathy, and ovarian transposition in premenopausal patients. Radiation therapy will consist of both teletherapy and brachytherapy in most patients, with treatment volume and techniques contingent on the location and extent of the primary, the presence and level of metastatic involvement of regional lymph nodes, and patient comorbidities. Although brachytherapy is an important tool in the treatment of vaginal cancer, it should be used only if the entire tumor can be encompassed with adequate margin. Even very small tumors probably will recur if a portion of the tumor receives less than 60 to 70 Gy. Some patients may be treated successfully with progressively shrinking teletherapy treatment volumes designed to deliver a tumor dose of 60 to 66 Gy as an alternative to large-volume interstitial brachytherapy treatment. Three-dimensional conformal therapy or IMRT may improve the ability to deliver high doses to the tumor with external-beam therapy alone. At the M.D. Anderson Cancer Center, we found IMRT to be particularly helpful for tumors that extensively involve the periurethral space, infiltrate the entire vagina, or involve the rectovaginal septum. However, great care must be taken to consider the influence of internal organ motion and the complex regional lymphatic drainage of the vagina in designing target volumes. With IMRT, careful immobilization, attention to organ motion, and set-up verification, the gross target volume sometimes can be taken to an effective total dose of 70 Gy.

Stage IVa Disease

For patients with a rectovaginal or vesicovaginal fistula or extensive bladder or rectal involvement who are in otherwise good medical condition, a pelvic exenterative procedure with vaginal reconstruction using a gracilis myocutaneous flap or rectus abdominis myocutaneous flap may be the procedure of choice.[440,441] Rarely, in patients with fistulae who are not sexually active, the vagina may be allowed to fuse/scar shut after high-dose radiation therapy, thus effectively sealing the fistula and restoring continence. Treatment for most patients involves radiation therapy, either as primary therapy or as adjuvant treatment after surgical clearance of central disease.

Patients with a Central Recurrence after Previous Surgery or Radiation Therapy

Radiation treatment usually is the most appropriate intervention in patients previously treated with surgery. Surgery for local failure after radiation therapy usually requires anterior, posterior, or total pelvic exenteration. Repeated irradiation rarely is feasible.

Complications of Therapy

Complications from the use of radiation or surgery occur in 10% to 15% of patients. Frank and colleagues[439] reported major complication rates of 4%, 9%, and 21% at 5 years for patients treated definitively with radiation for stage I, II, or III-IVA disease, respectively. The close proximity of other organs to the vagina predisposes them to injury. These complications include rectovaginal or vesicovaginal fistulae, radiation cystitis, radiation proctitis, rectal and vaginal strictures, and vaginal necrosis. To decrease the degree of vaginal stenosis after radiation therapy, patients should use a vaginal dilator, preferably on a daily basis. After radiation therapy, the vaginal mucosa may become thin and atrophic. Topical application of estrogen cream stimulates thickening of the vaginal mucosa after radiation and decreases symptoms of vaginal mucosal atrophy, which can include pruritus, discharge, and dyspareunia.[442,443]

PROGNOSIS

Because of the rarity of vaginal cancer, even large referral centers have only limited experience treating vaginal cancers, and thus data with respect to treatment and survival are scarce and based on retrospective series that may span multiple decades, during which both diagnostic assessments of treatment extent and treatment techniques have changed and evolved. Additionally, some published series have pooled patients with squamous cancers together with patients with other histologic types. Others have included patients with noninvasive disease. Thus precision in assignment of prognosis remains elusive. Although the natural history and biologic behavior of vaginal squamous cancer mimics squamous cancer of the cervix,[349] the cure rates of vaginal neoplasms remain lower, and the morbidity associated with treatment may be higher because of the close proximity of functionally important organs, which limit the intensity of treatment and account for most of the late morbidity consequent to therapy.

The most important variable affecting prognosis is the clinical stage at presentation, which reflects the size and depth of tumor penetration.[438,444] Five-year survival estimates for all patients with this malignancy range from 42% to 56%. Rates of survival according to stage are as follows: stage I, 75% to 95%; stage II, 50% to 80%; stage III, 30% to 60%; and stage IV, 15% to 50%.[439]

Adenocarcinoma

Fewer than 15% of primary vaginal neoplasms are adenocarcinomas. Adenocarcinomas occurring in the vagina include papillary, mucinous, adenosquamous, small cell, and clear cell variants. As glandular tissue is not normally present in the vagina, patients with adenocarcinoma must be carefully evaluated to exclude the probability that adenocarcinoma found in the vagina represents metastatic spread from another primary site. Potential primary sites are most likely to include endometrium, cervix, vulva (Bartholin's gland), ovary, breast, colon and rectum, and kidney.[401,404] The treatment for vaginal adenocarcinoma is similar to that for squamous cell carcinoma of the vagina. Because most women afflicted with clear cell cancer of the vagina are young, efforts should be made to preserve vaginal and ovarian function. Surgical treatment of stage I and II disease has consisted of radical hysterectomy; vaginectomy, with formation of a split thickness of skin graft neovagina; and lymphadenectomy or local surgical excision followed by local irradiation to the tumor bed.[445] With use of local irradiation to a stage I lesion, consideration should

be given to performing a pelvic lymphadenectomy, because 17% of stage I lesions have pelvic nodal metastases.[446] If treatment of larger or more advanced lesions with whole pelvic irradiation is to be undertaken, ovarian transposition before radiation should be considered. Prognosis with clear cell vaginal cancers, if correlated with DES, is favorable. The overall actuarial 10-year survival rate is 79%, improving to 90% for patients with stage I vaginal tumors. However, if not associated with DES, the prognosis of primary adenocarcinoma of the vagina is poorer than squamous carcinomas; at 5 years, Frank and coworkers[447] reported an overall survival rate of only 34% for 26 patients treated with radiation for non-DES-related adenocarcinomas of the vagina.

Sarcomas

Vaginal sarcomas make up 3% of primary vaginal carcinomas. Of the 68 cases of vaginal sarcoma reported by Peters and colleagues,[448] leiomyosarcomas accounted for 46 (68%) of the reported cases. Other reported sarcomas include endometrial stromal sarcoma, malignant mixed müllerian tumor, and rhabdomyosarcoma, among others.[449] Surgical resection is the treatment of choice. The benefit of chemotherapy or radiation therapy is unclear in the treatment of adult vaginal sarcomas. Embryonal rhabdomyosarcoma (sarcoma botryoides) is a highly malignant sarcoma that occurs in children aged 6 years or younger (mean age, 1.8 years). This sarcoma generally appears as soft nodules that fill and protrude from the vagina or as abnormal bleeding. The prognosis for patients with this malignancy has improved with the use of multimodality therapy including surgery, polyagent chemotherapy, and radiation.[450]

Endodermal Sinus Tumors

Endodermal sinus tumors are rare germ cell malignancies that occur primarily in the ovary but have been reported to occur at extragonadal sites, including the vagina. This vaginal malignancy, which occurs in children younger than 2 years, appears as abnormal bleeding or discharge in addition to the presence of a vaginal mass. As in its ovarian counterpart, α-fetoprotein can be detected in this malignancy and can be used as a serum tumor marker. Treatment consists of chemotherapy (vincristine, actinomycin D, and cyclophosphamide), as well as surgical excision, and, occasionally, radiation therapy.

Melanoma

Vaginal melanomas are rare but account for 2.7% of vaginal malignancies.[451–453] Three percent of malignant melanomas involve the female genital tract, with the vulva the most common site of occurrence. Melanomas arising in the vagina are thought to originate from in situ melanocytes in areas of melanosis or atypical melanocytic hyperplasia. These malignancies occur at a mean age of 55 years, with an age range of 22 to 83 years. Patients typically are first seen with abnormal vaginal bleeding, discharge, or a mass. These tumors most commonly occur in the lower one third of the vagina on the anterior wall and appear as a blue-black or black-brown mass or plaque. They have a poor prognosis, with 5-year survival rates of 15% to 20%.[451–453] Management is surgical and, depending on the position of the lesion, may require exenterative procedures to obtain adequate margins. No established curative role is found for radiation, which generally is reserved for circumstances in which surgery either is not feasible or is refused. Local radiation may provide palliation and growth restraint in patients with proven metastatic deposits for whom exenterative surgery may not be appropriate. Adjuvant systemic therapy and treatment for disseminated melanoma parallels the treatment of melanoma arising at other sites.

CHEMOTHERAPY FOR PERSISTENT, RECURRENT, OR METASTATIC VAGINAL CANCER

Most cases of recurrent or persistent vaginal carcinoma occur in the vaginal vault, or pelvic, inguinal, and supraclavicular nodes.[454] Dermal metastasis and lung and bone metastases also have been reported.[455,456] Very limited data exist on the treatment of vaginal cancer, with only few phase II studies describing single-agent experiences with squamous cell carcinoma of the vagina. Even fewer data are available for therapies for clear cell or adenocarcinomas of the vagina. Responses to single-agent cisplatin and doxorubicin have been reported, and a single case reports a complete response to the combination of bleomycin, methotrexate, and cisplatin.[457–460]

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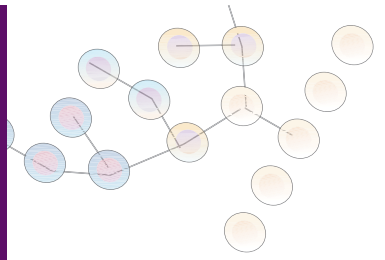
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92 Cancer of the Endometrium

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SUMMARY OF KEY POINTS

Incidence
- There are 39,080 estimated new cases of endometrial cancer in the United States, and 7400 deaths each year.
- Endometrial adenocarcinomas account for 95% of cases, and 5% are uterine sarcomas.

Etiology and Epidemiology
- The median age for endometrial cancer is 63 years; the majority of these cancers occur after menopause.
- Hormonally dependent subtypes arise in hypertrophic endometrium.
- Lifetime estrogen exposure contributes to risk.
- Hormonally independent types occur at an older age and arise in atrophic endometrium.
- Other risk factors include family history, certain systemic diseases, and tamoxifen use.

Pathology and Biology
- Atypical hyperplasia confers a 25% risk of invasive cancer.
- Aggressive subtypes include uterine serous, clear cell, and sarcomas.
- Estrogen and progesterone receptor expression influence biologic behavior.
- Uterine serous pathogenesis is p53-mediated.

Clinical Findings
- Abnormal uterine bleeding and discharge are present in 90% of cases.
- Endometrial biopsy or dilation and curettage is generally required for diagnosis.

Differential Diagnosis and Staging
- Other causes of uterine bleeding include atrophy, infection, medications, coagulopathy, polyps and fibroids, cervical cancer, and nongynecologic malignancies.
- Staging is surgical and is based on whether disease is confined to the uterus.
- Clinical staging is used for inoperable patients.

Primary Therapy
- Surgery, including hysterectomy, bilateral salpingo-oophorectomy, lymph node sampling, and pelvic washings, is performed in all operable patients. Lymph node sampling may be omitted in patients with grade II tumors that are limited to the endometrium or grade I tumors with less than 50% invasion.
- Adjuvant radiation to the pelvis is indicated for high-risk factors, including high grade, deep myometrial invasion, and lymph node spread.
- Systemic doxorubicin, cisplatin, ifosfamide, carboplatin, paclitaxel, and cyclophosphamide are used for metastatic disease.
- Radiation alone is used for inoperable patients and for palliation.

Salvage Therapy
- Failure after surgery alone is treated with radiation therapy.
- Salvage after surgery and radiation is seldom successful, although systemic therapy may be used.

Complications
- Surgical and radiation complications include bladder or bowel dysfunction.

Prognosis
- Survival is strongly correlated with stage and extent of disease as defined by depth of invasion, lymph node metastases, adnexal spread, and peritoneal cytology.
- Survival is worse when the tumor is higher grade or has aggressive histology.

INTRODUCTION

Endometrial cancer is a malignancy that arises from the endometrium, the lining of the uterus. It may also be referred to as uterine cancer. Endometrial cancer is the fourth most common malignancy among women, ranking after breast, lung, and colon cancer, and is the most common gynecologic cancer in the United States. Women have an approximately one in forty lifetime risk of being diagnosed with uterine cancer.[1] The majority of endometrial cancers are stage I (confined to the uterus) at diagnosis as most women present with postmenopausal bleeding. Ninety-five percent of uterine carcinomas arise from endometrial glands and are referred to as carcinomas, the remaining 5% of cases are uterine sarcomas.

ANATOMY

Anatomically, the uterus is contiguous with the cervix, and the two structures are separated at a narrowing called the isthmus, at which point the epithelium begins to transition from endometrial glands to mucus-secreting columnar epithelium.[2] The body, or corpus, of the uterus is typically 7 to 8 cm in length, 5 to 7 cm wide, and 2 to 3 cm in thickness. The corpus is located superior to the bladder, from which it separated by the vesicouterine pouch, and normally projects anteriorly, but in some women, it may be retroverted. Posteriorly, it is separated from the sigmoid colon by peritoneum and from the rectum by the rectouterine pouch (pouch of Douglas). The fallopian tubes extend laterally from the cornu of the fundus, the superiormost

portion of the corpus, and open into the peritoneal cavity adjacent to the ovaries. The corpus and adnexae are enclosed in the broad ligaments, which are folds of the peritoneum that hold the uterus in position, although it is mobile enough to move with the filling and emptying of the adjacent bladder. The round and uterosacral ligaments also extend from the uterine wall to the pelvic wall through the broad ligaments. The round ligaments course toward the deep inguinal ring, and the uterosacral ligaments course posteriorly toward the sacrum.

The main blood supply to the uterus is via the uterine arteries, which are branches of the internal iliac arteries. They enter the broad ligaments near the lateral vaginal fornices and cross the ureters superiorly adjacent to the uterine cervix. The uterine fundus is also supplied by the ovarian arteries, which are branches of the aorta. These vessels form a vascular plexus and anastomose with each other. The uterine venous plexus drains to the uterine veins. The lymphatics follow the vascular structures. The lymphatics that supply the fundus drain to the aortic lymph nodes, and those that supply the lower portions of the uterus drain to the internal and external iliac nodes. Lymphatics may also run along the round ligaments toward the superficial inguinal nodes. The uterus is innervated by the inferior hypogastric plexus.

EPIDEMIOLOGY

According to Cancer Statistics for 2007, there were 39,080 estimated new cases of endometrial cancer in the United States and 7400 deaths attributable to this disease.[3] The median age of diagnosis for endometrial cancer is 63 years and most patients are postmenopausal.[3] Table 92-1 shows the distribution of endometrial cancer by age as reported by the Surveillance, Epidemiology, and End Results program.

The Surveillance, Epidemiology, and End Results Program of the National Cancer Institute, reported stage distribution from 1996 to 2003 that showed that 70% of patients are diagnosed with localized disease, regional spread represented 17%, distant disease only 9%, with 4% unstaged.[1] In this survey, the 5-year overall survival rate for all stages of endometrial cancer from 1996 to 2003 was 82.9%. The 5-year relative survival rates were 95.3% for localized, 67.4% for regional, 23.1% for distant, and 55.8% for unstaged.[1]

Table 92-1 Incidence by Age, 2000–2004

Age	Incidence per 100,000 Females
20–24	0.3
25–29	1.3
30–34	3.4
35–39	6.8
40–44	12.8
45–49	23.1
50–54	42.5
55–59	66.9
60–64	81.8
65–69	89.1
70–74	86.5
75–79	86.6
80–84	81.8
85+	61.4

Surveillance Epidemiology, and End Results Program Incidence Data, Cancer Statistic Review, 1975–2004.

RISK FACTORS

Hormones

For the cancers that arise in hypertrophic or active endometrium, the risk factors are related to the lifetime estrogen exposure, known as the unopposed estrogen effect. According to this hypothesis, exposure to unopposed estrogens leads to increased proliferative activity of the endometrial cells, resulting in increased DNA replication errors and somatic mutations. Table 92-2 lists some of the known risk factors for endometrial adenocarcinomas. Higher endogenous estrogen exposure associated with nulliparity, lower gravidity, early menarche, late menopause, estrogen-producing ovarian tumors, and obesity are all associated with an increased risk of endometrial cancer.[4–6] High circulating blood levels of androstenedione, estrone, and estradiol are associated with a threefold to fourfold increased risk.[7] Exogenous estrogen sources such as hormone replacement therapy without progestins also increase the risk. Taking unopposed estrogens for 3 or more years is associated with a fivefold increased risk of invasive endometrial cancer.[8] Pathologic comparison between cancers that occur in women who did or did not use estrogen replacement has shown that in the nonusers, the cancers are more likely to be of lower grade, while those in users were more likely to be clear cell or adenosquamous.[9] The use of progesterones in a hormone replacement regimen may actually decrease the risk of cancer through downregulation of hormone receptors.[10] Cancers that occur in women who used combined estrogen and progestin hormone replacement tend to be tumors of low stage and grade.[11] A study of endometrial sarcomas and reproductive factors notes that leiomyosarcomas (LMS) are associated with early menarche, induced abortions, and breast-feeding, and both LMS and endometrial stromal sarcomas (ESS) are associated with later menopause.[12]

A potential causal link between the treatment of breast cancer with the selective estrogen receptor modulator drug tamoxifen and the development of endometrial cancer was first suggested in 1985.[13] This link was later confirmed by the results of large series from the Netherlands Cancer Institute and the National Surgical Adjuvant Breast Project (NSABP). The Netherlands Cancer Institute identified 98 patients who developed endometrial cancer after treatment for breast cancer and performed a matched case-control study among women who did not develop endometrial cancer.[14] Among patients with endometrial cancer, 24% had taken tamoxifen, compared to 20% of the controls, and for a longer median duration. The risk of developing endometrial cancer increased with the duration of tamox-

Table 92-2 Risk Factors for Endometrial Adenocarcinoma

Risk Factor	Relative Risk
Nulliparity[5]	1.4
Endogenous estrogen levels[34]	2.0–3.8
Estrogen use[8]	5
Obesity[31]	
High body mass index	3.2
Substantial weight gain	3.5
Diabetes[35]	4.1
Obesity + diabetes[36,37]	3.0–8.0
Hypertension[35]	1.6
Tamoxifen[15]	2.2
Oral contraceptives[19]	0.5

ifen use. Those who were treated for 5 years or more had a 3.0 risk of endometrial cancer compared to controls. The NSABP analyzed data from their B-14 study in which 2834 women with node-negative, estrogen receptor-positive breast cancers were randomized to placebo or tamoxifen (20 mg/day).[15] Twenty-three of 24 cases of endometrial cancers that occurred in women entering this trial occurred in the tamoxifen arm. These were mostly favorable cancers: 88% were stage I at diagnosis, and 78% were of low or intermediate grade. The authors calculated the annual hazard rate of endometrial cancer development to be 1.6 per 1000 patient-years in women taking tamoxifen and 0.2 per 1000 patient-years in the placebo group. However, the use of tamoxifen results in a 38% improvement in disease-free survival for breast cancer, which far outweighed the risk of endometrial cancer, from which there were only four deaths. Another study by the NSABP analyzed data from their P-1 study for patients receiving tamoxifen for chemoprevention of breast cancer and found that patients receiving tamoxifen had a 2.53 times greater risk of developing an invasive endometrial cancer compared to placebo.[16] This risk was predominantly in women 50 years of age or older, with an incidence of about 2 per 1000 women, and regular gynecologic follow-up in women who receive the drug was recommended.

Genetics

Endometrial cancer is uncommon in young women (younger than 50 years at age of diagnosis).[17] A family history of endometrial cancer in a first-degree relative or of hereditary nonpolyposis colorectal cancer syndrome (HNPCC) is associated with a relative risk of 1.5 for development of endometrial cancer in the premenopausal years, although only about 1% of endometrial cancers are attributable to genetic factors.[18] Endometrial cancer is part of the spectrum of cancer predisposition in families with HNPCC syndrome, which results from mutations in DNA mismatch repair genes. Carriers of the HNPCC mutation have a 50% to 60% lifetime risk of developing endometrial cancer, with a median age of less than 50 years.[19] Other risk factors for younger women include use of unopposed estrogen replacement therapy, nulliparity, and other reproductive factors similar to those seen in older women.[20] Compared with older women, young women have a similar stage distribution at diagnosis, the majority of cancers presenting as stage I. Younger women are actually more likely to have lower-grade, less deeply invasive cancers and have an overall survival similar to that of older women.[21,22]

In contrast, elderly patients (older than 75 years) have a higher incidence of poorly differentiated cancers, aggressive histologies, and lack of steroid receptor expression, consistent with nonendometrioid patterns of tumorigenesis.[23] When outcomes are examined by race, African-American women have a somewhat lower incidence of endometrial cancer but a worse overall survival compared to Caucasian women.[24] African-American women are diagnosed more often with aggressive histologies, with higher-grade tumors, and at later stages.

For the uterine serous subtype, women are at increased risk for also developing a concurrent or subsequent breast cancer.[25] In women with uterine serous carcinoma, breast cancers are diagnosed in 25%, compared to 3% of those with endometrioid carcinoma, implicating a genetic or biologic link.

Previous Irradiation

The etiology of uterine sarcomas is not well understood. One factor is prior exposure to pelvic irradiation. Secondary uterine sarcomas and carcinomas have been reported after irradiation for cervix and rectal cancers,[26,27] with a median latency of 17 years and an absolute risk range of 0.03% to 0.8%.[28] Radiation-associated uterine cancers tend to be of higher grade and stage and to have a more unfavorable histology.[29]

Other Comorbidities

Other systemic diseases and lifestyle factors influence the risk of endometrial cancer. Obesity, diabetes and hypertension all increase the risk. Hypertension and diabetes may be associated with an increased risk, though mainly in women who are also obese. Overall nearly 40% of endometrial cancer risk can be attributed to obesity.[30] Obesity from an early age, substantial weight gains over time, and marked obesity all confer higher risks than moderate obesity.[31] When examined by degree of obesity as measured by body mass index (BMI) in comparison to lean women, women who are overweight (BMI: 28 to 29.9) have a relative risk of 1.5 compared to women with a lower BMI, women who are obese (BMI: 30 to 33.9) have a 2.9 relative risk, and women who are markedly obese (BMI: ≥34) have a relative risk of 6.3.[32] Some studies show an association between endometrial cancer and dietary intake of fat, suggesting that healthier diets and reduction of dietary fat could reduce the risk.[33,34] Diabetes confers a relative risk of around 4.0,[35] and the risk is highest for women who are obese and diabetic.[36,37] There may be a link between ovarian hyperandrogenism leading to progesterone deficiency, lifetime weight gain, and chronic hyperinsulinism, which all interact to increase the endometrial cancer risk.

Protective Factors

Known protective factors against endometrial cancer include full-term pregnancy, multiparity or incomplete pregnancies, older age of menarche, older age at first birth, and oral contraceptive use. Use of oral contraceptives for 1 to 5 years is associated with a relative risk of 0.2, and use for at least 1 year reduces endometrial cancer risk by about 45%.[19] Increasing physical activity decreases the risk of endometrial cancer independently of weight and parity.[38] Interestingly, cigarette smoking decreases the risk of endometrial cancer, but this effect might be limited to postmenopausal women or those taking hormone-replacement therapy.[39] It has been postulated that components of cigarette smoke might suppress endogenous estrogens or be associated with lower body weight as a potential mechanism for the protective effect. Clearly, the adverse risks of smoking greatly outweigh any potential benefit with respect to endometrial cancer.

PATHOGENESIS

The most common pathologic subtype is endometrioid adenocarcinoma, which arises from the endometrium and accounts for about 80% of malignant endometrial neoplasms. There are aggressive variants of adenocarcinomas, including uterine serous and clear cell histologies, which have a much poorer prognosis. Less common are the uterine sarcomas, which arise from the myometrium or other mesenchymal elements of the uterine wall, comprising only 2% to 5% of all uterine malignancies.[40] Of the uterine sarcomas, carcinosarcoma (or mixed malignant müllerian tumors) is the most common (8.2 per million women per year), followed by LMS (6.4 per million), both of which are somewhat more common in African-American women than Caucasian women. The incidence of carcinosarcomas rises in incidence with age, while the incidence of LMS peaks in middle age and then declines. Next most common is ESS (1.8 per million). The final group is known as unclassified (0.7 per million); it includes rhabdomyosarcoma, angiosarcoma, fibrosarcoma, chondrosarcoma, and liposarcoma.

Endometrial adenocarcinomas appear to have two distinct mechanisms of pathogenesis.[41] Most adenocarcinomas (type I) arise in normal, functioning endometrium; are associated with hyperplasia; tend to be well differentiated and express steroid hormone receptors; and are hormonally responsive. Others (type II) arise in atrophic endometrium, are associated with endometrial intraepithelial carcinoma without high levels of steroid receptor expression, and do not appear to be related to hormonal exposures. Type I tumors have a better prognosis overall than do type II tumors.

Pathology

Hyperplasia

Proliferative diseases of the endometrium represent a broad continuum of morphologic and cellular changes ranging from simple hyperplasia to invasive carcinoma. Hyperplasia is an abnormal proliferation of the endometrial glands and in some cases precedes endometrial cancer as a premalignant phase. According to the World Health Organization and International Federation of Gynecologic Oncologists (FIGO), hyperplasia is classified as simple or complex with or without atypia.

Simple hyperplasia is the most common type and is a benign change that causes diffuse thickening of the endometrium, with dilation and increased number of endometrial glands but minimal crowding or glandular complexity. Such changes are rarely associated with malignant progression. Complex hyperplasia is characterized by increased endometrial thickness due to increased numbers and crowding of the endometrial glands. The glands have irregular contours and markedly diminished stromal spaces. Epithelial pseudostratification in two to four layers can occur with a variable amount of mitotic activity. These lesions are associated with a 3% rate of malignant progression.[42] The majority of both types of lesions without atypia will regress.

Atypical hyperplasia is characterized by an increased number of cells with cellular atypia, whether the glandular morphology appears simple or complex (although usually complex), including loss of the normal orientation of the epithelial cells, nuclear enlargement, increased nucleus-to-cytoplasmic ratio, nuclear hyperchromatism, and prominent nucleoli. If atypia is present in an endometrial biopsy or curettage, the reported risk of finding adenocarcinoma after hysterectomy ranges from 14% to 57%, with an average risk of about 25%.[43] Among such cancers, myometrial invasion is common, and up to 20% of them will be grade II or III. While Pap smear is not a reliable screening test for endometrial cancer, findings on Pap smears known as atypical glandular cells of undetermined significance may be of endometrial origin. Among patients undergoing biopsy for atypical glandular cells of undetermined significance, 13% have endometrial cancers, 11% have endometrial hyperplasia, and 7% have squamous lesions, so one-third of women with this finding on Pap smear will have a significant endometrial lesion.[44] Table 92-3 lists the risk of progression to malignancy based on the type of hyperplasia.

Endometrioid Adenocarcinoma

Adenocarcinomas arising from hypertrophic endometrium or associated with atypical hyperplasia are typically endometrioid type (Fig. 92-1). For this histologic subtype, the median age of diagnosis is around 65 years. Table 92-4 lists the various types of endometrial carcinomas classified by the International Society of Gynecologic Pathologists. Endometrioid adenocarcinomas are the most common type arising from the endometrium, representing about 75% of cases and are usually designated NOS (not otherwise specified).[45] In addition to NOS, there are four other variants: villoglandular, secretory,

Table 92-3 Progression in Endometrial Hyperplasia

Type of Hyperplasia	Progression to Cancer (%)[42]
Simple with no atypia	1
Complex with no atypia	3
Simple with atypia	8
Complex with atypia	29

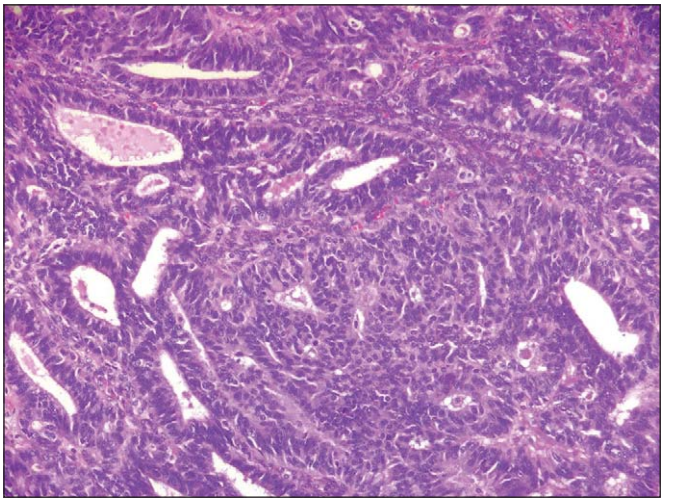


Figure 92-1 • Endometrioid carcinoma. Grade 1 endometrial endometrioid adenocarcinoma. The tumor is composed of back-to-back tubular glands with mild cytologic atypia. More than 95% of the tumor shows gland formation without significant solid growth pattern.

Table 92-4 Classifications of Endometrial Carcinomas and Sarcomas

INTERNATIONAL SOCIETY OF GYNECOLOGIC PATHOLOGISTS CLASSIFICATION OF ENDOMETRIAL CARCINOMAS

- Endometrioid adenocarcinoma
  - Villoglandular
  - Secretory
  - Ciliated cell
  - Adenocarcinoma with squamous differentiation
- Mucinous carcinoma
- Serous carcinoma
- Clear cell carcinoma
- Squamous carcinoma
- Undifferentiated carcinoma
- Mixed type
- Miscellaneous carcinoma
- Metastatic carcinoma

GYNECOLOGIC ONCOLOGY GROUP CLASSIFICATION FOR UTERINE SARCOMAS

- Mesenchymal
  - Leiomyosarcoma
  - Endometrial stromal sarcoma
    - Low grade (endolymphatic stromal myosis)
    - High grade (undifferentiated sarcoma)
- Mixed differentiated sarcomas
- Other
- Mixed epithelial-stromal
  - Adenosarcoma
  - Carcinosarcoma (mixed malignant müllerian tumor)
    - Without heterologous elements
    - With heterologous elements

ciliated cell, and adenocarcinoma with squamous differentiation. The villoglandular variant of endometrioid adenocarcinomas makes up about 7% of all adenocarcinomas. They are low grade and lack the anaplasia that is associated with uterine serous carcinomas. They otherwise have a similar median age, depth of invasion, and frequency of nodal spread compared to the usual endometrioid type.[46] Secretory carcinomas are found in only 2% of cases and tend to be low grade and well-differentiated with a favorable outcome. Progesterone administration may cause a secretory appearance of atypical hyperplasia or low-grade adenocarcinoma. Ciliated cell carcinomas are composed primarily of ciliated cells, which are typically confined to benign endometrial lesions but rarely form cancers that invade the myometrium.[47] Approximately 25% of endometrial adenocarcinomas display focal squamous differentiation. In the late 1960s, distinction was made between tumors in which the squamous component appeared bland and well differentiated (adenoacanthoma) and those in which it appeared frankly malignant and often poorly differentiated (adenosquamous carcinoma). Numerous studies have confirmed the significantly better prognosis that is associated with adenoacanthoma than with adenosquamous carcinoma. However, in large studies in which the glandular and squamous component were graded separately, differentiation of the squamous component was shown to closely parallel that of the endometrial component. Thus, the prognosis can be predicted by the grade of the glandular component alone. Accordingly, the International Society of Gynecologic Pathologists and the World Health Organization recommends the use of the term *adenocarcinoma with squamous differentiation* for these tumors, and grading is based solely on the glandular component.

Adenocarcinomas are further characterized by grade and depth of invasion. Grade 1 or low-grade lesions are well differentiated; grade II lesions are moderately differentiated; and grade III lesions are poorly differentiated. Histologic grading according to FIGO uses a combination of architectural patterns and nuclear features. Grade I tumors are composed of cells and glands that closely resemble those of normal endometrium and show well-preserved glandular growth patterns with 5% or less solid growth pattern; grade II contains 6% to 50% solid growth pattern; grade III tumors are composed of more than 50% nonsquamous solid growth pattern.[48] Although this system relies predominantly on the architectural pattern of the glands, FIGO recommends that in cases in which there is severe nuclear atypia, inappropriate for the architectural grade, the overall grade of the tumor should be raised by one grade. In addition, in cases of serous and clear cell carcinomas, nuclear grading takes precedence. In the nuclear grading system, grade I has uniform oval nuclei with evenly distributed chromatin; grade III has large pleomorphic nuclei with prominent nucleoli and clumped chromatin; grade II is intermediate between these features.[49] Higher grade is associated with myometrial invasion, lymph node metastases, and a poorer overall prognosis. The Gynecological Oncology Group (GOG) found that high-grade tumors made up 42% of those with deep myometrial invasion, compared to 7% of tumors with no myometrial invasion.[50] Depth of invasion is determined by measuring the extension of cancer into the myometrium divided by the total width of the myometrium. Depth of myometrial invasion has been categorized by both thirds and halves. For staging purposes, FIGO classifies depth of invasion as limited to the endometrium, less than one half of the myometrium, or greater than one half of the myometrium. Deeper invasion has a higher risk of nodal metastases.

Uterine Serous Carcinoma

Uterine serous carcinoma (USC) represents 5% to 10% of endometrial carcinomas (Fig. 92-2). The median age of diagnosis is 63 years.[51] This subtype arises in atrophic endometrium from a putative precursor lesion that is designated endometrial intraepithelial carcinoma (Fig. 92-3), and is not hormonally mediated. These cancers are considered high grade; however, depth of invasion might not always be deep. Morphologic features include a papillary or solid growth pattern with slitlike spaces, marked nuclear pleomorphism, multinucleated cells, hobnail cells, psammoma bodies, uneven gland borders, and inflammation.[52] Most have lymphovascular invasion, and lymph node metastases are present in 36% of women with no myometrial invasion, in 50% with inner one half invasion, and in 40% with outer one half invasion.[53] These cancers have a high rate of spread to peritoneal surfaces and to omentum and distant metastases.[54] Because of these features, uterine serous cancers are upstaged postoperatively from clinical stage I to II to clinical stage III to IV in nearly 50% of patients. Survival rates are only 30% to 50% even when disease is confined to the uterus, and median survival is significantly shorter than that for endometrioid carcinoma.

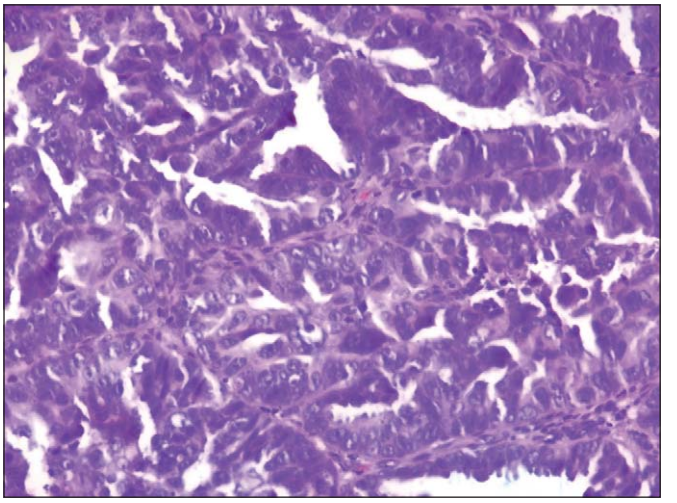


Figure 92-2 • Serous carcinoma. Uterine serous carcinoma composed of highly atypical tumor cells forming irregular, slitlike glandular spaces and solid sheets of cells.

Clear Cell Carcinoma

Carcinomas with clear cell features arise in the uterus, ovary, vagina, and cervix, all of which have been associated with in utero exposure to the synthetic estrogen diethylstilbestrol (DES). DES was prescribed to women during pregnancy between 1940 and 1971 for certain complications. The overall risk to a woman who received DES

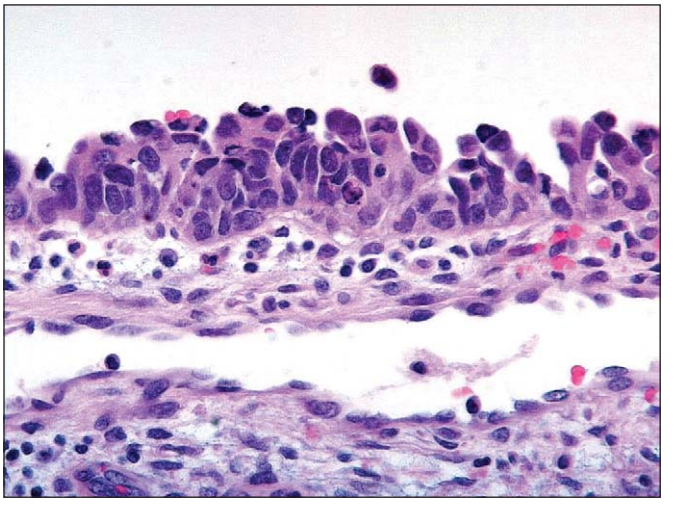


Figure 92-3 • Endometrial intraepithelial carcinoma. Highly atypical tumor cells characteristic of serous carcinoma are present at the surface of the endometrium without evidence of stromal invasion.

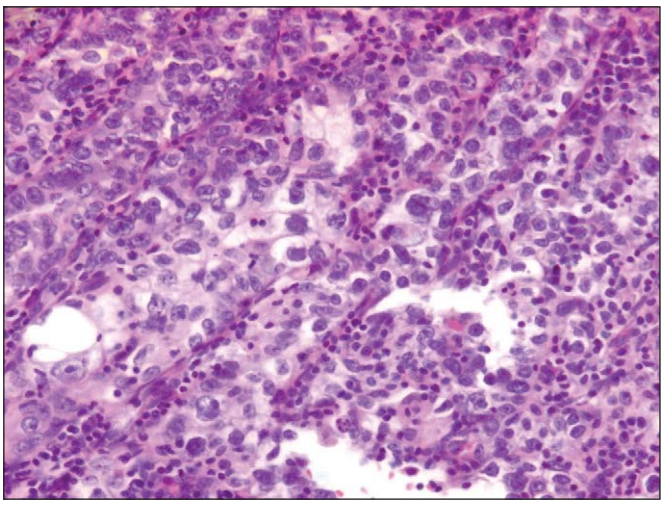


Figure 92-4 • Clear cell carcinoma. Endometrial clear cell carcinoma showing a solid growth pattern. The tumor cells have moderate amounts of clear cytoplasm and show moderate to severe nuclear pleomorphism.

in utero of developing clear cell carcinoma (CCC) of the gynecologic tract is estimated at 0.1%.[55] Clear cell endometrial cancers make up about 5% of adenocarcinomas (Fig. 92-4). The median age at diagnosis is 66 years.[56] Cells form cystic solid or tubular cellular patterns whose cytoplasm appears clear or light pink on hematoxylin-eosin staining. Papillary formations, when present, often have a characteristic hyalinized core, and hobnail cells are frequently seen. This cytoplasmic material is glycogen positive. Nucleic size varies, but high mitotic count is often present, and the cells are generally considered high grade. Although pelvic failures occur in about one third of patients postoperatively without adjuvant radiation, unlike serous carcinoma, this subtype has only a 15% rate of intra-abdominal failure. Relapse in the lung, liver, and bone occurs in 25% of patients. The 5-year disease-free survival rate is about 40%.[57] For stage I, the survival rate is 72%, and for stage II, the survival rate is 60%, which is more favorable than that for serous cancers.[58]

Other Carcinomas (Mucinous, Squamous, Undifferentiated, Mixed, Metastatic)

There are a variety of other relatively rare subtypes of endometrial cancer. Mucinous cancers contain more than 50% cells with periodic acid-Schiff-positive diastase-resistant mucin.[59] These cells have abundant cytoplasmic mucin, and the tumors produce large amounts of mucopolysaccharides. Morphologically similar tumors may occur in other abdominal organs such as the gastrointestinal tract or ovary, so metastasis should be ruled out. For primary cases, the prognosis appears to be similar to that of endometrioid carcinoma. Primary squamous cell cancer of the endometrium is exceedingly rare, reported in only about 100 cases. The median age at diagnosis is 67 years.[60] Chronic pyometria may be a predisposing factor, and these are associated with nulliparity. If the cervix is involved, the tumor should be considered a primary cervical cancer; thus, no stage II squamous carcinomas of the endometrium can be reported. Survival appears to be similar to adenocarcinoma (80% for stage I at 3 years). Undifferentiated carcinomas demonstrate no clear glandular or squamous differentiation, and some may be small cell neuroendocrine carcinomas. They may stain for epithelial or neurosecretory antigens. Mixed cell carcinomas comprise at least 30% each of two or more pure cell types. If serous or undifferentiated components are present, the prognosis is worse than that for pure high-grade endometrioid cancers.[61] Other extragenital cancers may metastasize to the endometrium or myometrium. One study found that primary tumors originated in the breast (43%), colon (18%), stomach (11%), pancreas (11%), gallbladder (5%), lung (5%), cutaneous melanoma (3%), urinary bladder (3%), and thyroid (2%).[62] Among those, the metastatic disease in the uterus was the first indicator of the primary cancer in 25%.

Uterine Sarcomas

Uterine sarcomas arise primarily from the mesenchymal or muscle elements of the uterus. They may be composed of pure mesenchymal elements or of mixed mesenchymal and epithelial elements. The classification that has been proposed by the GOG is shown in Table 92-4. The most common types are carcinosarcoma or mixed malignant müllerian tumors, LMS, and ESS. All of the subtypes combined occur rarely, uterine sarcomas making up only 5% of all malignant uterine neoplasms.

Carcinosarcoma (Malignant Mixed Müllerian Tumor)

Carcinosarcoma represents about 50% of all uterine sarcomas, or 3% of all uterine neoplasms. They occur at a median age of 66 years.[63] These tumors contain mixed epithelial and mesenchymal elements (Fig. 92-5). Adenosarcoma is a tumor with malignant mesenchymal stroma and benign epithelial elements. Carcinosarcomas contain both malignant mesenchymal and epithelial elements, typically adenocarcinoma. The stromal component is usually high grade. The mesenchymal component is classified as either homologous (composed of cell types that are normally found in the uterus, such as endometrial stromal sarcoma, fibrosarcoma, leiomyosarcoma, and undifferentiated sarcoma) or heterologous (composed of cell types that are not normally found in the uterus), each making up about half of carcinosarcomas. The heterologous elements are found in association with overt sarcoma and may comprise rhabdomyosarcoma, chondrosarcoma, liposarcoma, and osteosarcoma, in order of decreasing frequency. Although these tumors are heterogeneous, in general depth of invasion and stage correlate with prognosis. Other prognostic factors may include extensive tumor involvement of the uterus, lymphovascular invasion, extrauterine disease, and heterologous elements.[64] Nodal metastases are seen in about 35% of cases and tend to arise from the epithelial component. However, recurrences are often secondary to the sarcomatous elements. The overall 5-year survival rate is 40% to 50%.[65]

Leiomyosarcomas

LMS makes up about 25% of uterine sarcomas, or 1% of malignant uterine neoplasms (Fig. 92-6). The median age at diagnosis is 52

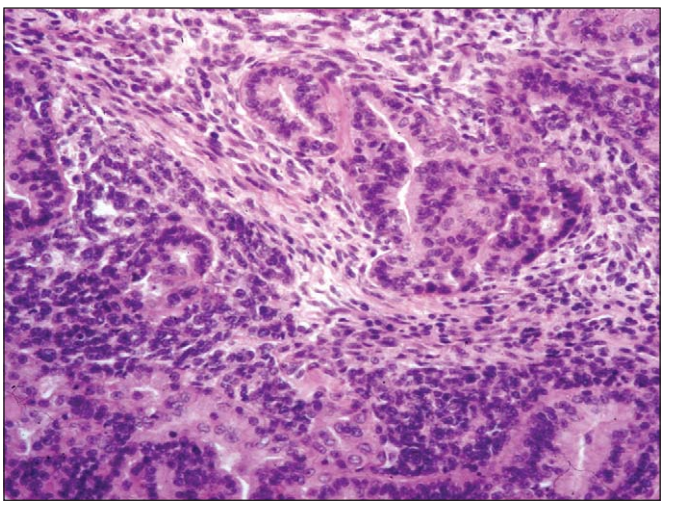


Figure 92-5 • Carcinosarcoma. Mixed malignant müllerian tumor (carcinosarcoma) composed of an admixture of glandular carcinomatous and sarcomatous elements.

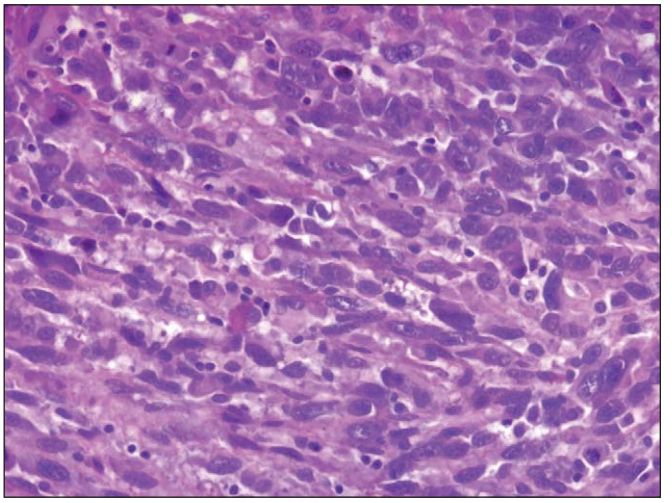


Figure 92-6 • Leiomyosarcoma. Uterine leiomyosarcoma composed of malignant spindled cells with prominent eosinophilic cytoplasm, moderate to marked cytologic atypia, and mitotic activity.

years. Benign leiomyomas occur commonly in the uterus with rare malignant transformation; LMSs are thought to arise independently. LMSs are typically solitary and irregularly permeate the adjacent myometrium and may show areas of hemorrhage and necrosis. The tumor arises from the myometrium and thus may be located deep in the uterine wall. Histologically, the tumors are more densely cellular and are composed of bundles of spindle cells. The degree of smooth muscle differentiation is variable. Nuclear and cellular pleomorphism, nuclear hyperchromasia, and multinucleate giant cells are common. To differentiate leiomyosarcoma from benign leiomyoma, the following factors should be considered: age of the patient; size, gross appearance, and invasiveness of tumor margins; vascular invasion; cytologic atypia; coagulative tumor cell necrosis; and mitotic activity. About 27% of LMSs metastasize to lymph nodes, and 50% recur, the lung being the most common site of metastasis.[66]

Endometrial Stromal Sarcoma

Endometrial stromal tumors are usually defined as neoplasms composed of stromal cells similar to those of normal proliferative phase endometrium. Classically, endometrial stromal tumors have been divided into two categories: benign stromal nodule if the margins are smooth, and ESS if the margins are infiltrating or lymphovascular permeation is present (Fig. 92-7). Sarcomas were further subdivided into those with fewer than 10 mitoses per 10 high-power fields (low grade) and those with 10 or more mitoses per 10 high-power fields (high grade).[67] The tumors that were formerly regarded as high-grade stromal sarcomas, however, are a heterogeneous group, composed partly of tumors made up of endometrial stromal cells but also of anaplastic tumors composed of tumor cells that show marked cytologic atypia. The latter tumors occur at an older age and are associated with a much worse prognosis. Histologically, they more closely resemble the sarcomatous components of a carcinosarcoma than an endometrial stromal tumor. On the basis of these features, endometrial stromal tumors have recently been reclassified as endometrial stromal nodule, endometrial stromal sarcoma, and undifferentiated uterine sarcoma.[68,69]

Endometrial stromal sarcomas are malignant tumors with infiltrative margins that are composed of cells similar to those of endometrial stroma. Histologically, the tumor cells are uniform with scant cytoplasm. A striking feature of many endometrial stromal sarcomas and the origin of their older name of "endolymphatic stromal myosis" are serpentine processes of the tumor that infiltrate between muscle fibers and into lymphatic spaces. Nuclear atypia is typically mild, and mitotic activity is usually less than 10 per 10 high-power fields; mitotic count is not a criterion for diagnosis, however. These tumors generally express estrogen and progesterone receptors and are responsive to progesterone therapy.[70] The clinical course is indolent, characterized by long disease-free intervals, although 36% of patients even with stage I will relapse and 10% will die of disease.

Undifferentiated Uterine Sarcoma

Undifferentiated uterine sarcoma is a rare malignant tumor composed of pleomorphic mesenchymal cells with a high mitotic index that do not resemble cells of endometrial stroma. These tumors are found in older women (median age: 58 to 61 years).[71] These tumors behave aggressively; 55% of patients who have disease that is confined to the uterus develop recurrent disease at a median of 5 months, in both the pelvis and abdomen.[72]

Molecular Pathology and Biology

Endometrioid Adenocarcinoma

About 57% of endometrial adenocarcinomas express estrogen receptors (ER) and progesterone receptors (PR), while 24% are negative for either receptor.[73] Expression correlates with tumor differentiation and stage. Both ER and PR are expressed in about 80% of grade I cancers and 60% to 70% of grade II cancers; for grade III cancers, ER is expressed in 46%, and PR is expressed in 59%.[74] Expression also differs among histologic types, with much lower levels in higher-grade histologies such as uterine serous carcinomas than in endometrioid carcinomas. In patients whose tumors are ER-positive/PR-positive or ER-negative/PR-positive, survivals are significantly better than for patients with either ER-negative/PR-negative or ER-positive/PR-negative tumors.[75] Some studies have also found ER status to be prognostic.[76,77] When tumors metastasize, loss of PR expression is more common than is loss of ER expression.[78] In vitro studies have shown that the PR isoform PRB is downregulated in more poorly differentiated cancers that do not respond to progesterone therapy.[79] For ER isoforms, a higher ratio of ER-β expression correlates significantly with deeper myometrial invasion and more advanced disease.[80] Genetic analysis of DNA from human endometrial cancers has shown that certain polymorphisms on the ER-α gene are present at different frequencies, suggesting that inherited alterations in the ER gene could either predispose or protect against the development of endometrial cancer.[81] More information about the

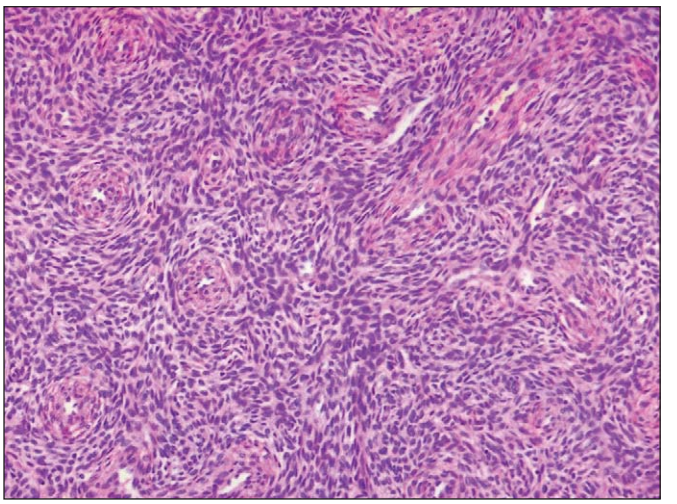


Figure 92-7 • Endometrial stromal sarcoma: Low-grade endometrial stromal sarcoma. The tumor is cellular and shows a solid growth pattern of uniform, bland endometrial stromal-type cells. The tumor cells focally show a whirled arrangement around prominent arterioles.

role of specific steroid receptor isoforms in uterine tissues and how they are expressed in different stages of disease may lead to the development of selective receptor modulators, thereby potentially improving treatment outcomes.

The endometrial hormonal pathways interact with other molecular pathways, further explicating potential mechanisms for tumorigenesis and progression. The proto-oncogene transmembrane receptor Her2/neu (c-erbB2) is a member of the epidermal growth factor family of receptor tyrosine kinases and is overexpressed in about one third of breast cancers. A monoclonal antibody therapy that targets the gene expression has been developed. Her2 is overexpressed in about 10% to 20% of endometrial cancers, correlating with higher grade, advanced disease, and loss of ER expression.[82–85] Her2 overexpression is seen in 27% of patients with metastatic disease compared to only 4% with early-stage disease. One study has shown that Her2 overexpression correlates with poorer overall survival and that the use of radiation therapy or chemotherapy in these patients is associated with improved survival.[86] Overexpression of the oncogene p53, found in about 15% of endometrial cancers, may also correlate with worse prognosis and might predict for recurrence.[87] P53 is almost never overexpressed in endometrial hyperplasia, suggesting that this particular mutation occurs late in the course of tumorigenesis.[88]

Serous and Clear Cell Carcinoma

USC and CCC have often been studied together, both for clinical outcomes and for biologic parameters. Unlike endometrioid, both subtypes are associated with lack of hormonal dependence and arise in atrophic endometrium. Immunohistochemical profiles comparing endometrioid and USC subtypes for ER, PR, and the expression of p53 and HER-2/neu reveal that USC cancers are generally negative for ER and PR, while 80% overexpress p53, and 45% overexpress Her2/neu.[85,89] Another study has found that 80% of USC cancers highly express Her2 and that USC cancer cell lines express Her2 at higher levels than either breast or ovarian cells do.[90] These cell lines are resistant to chemotherapy, but exposure to Herceptin, the monoclonal antibody that targets Her2, is cytotoxic, suggesting that Herceptin might be a useful therapy for USC cancers.

Overexpression of the p53 oncogene appears to play an important role in the biology of USC cancers, which demonstrate a significantly higher p53 expression than endometrioid subtypes (75% to 85%).[91,92] Unlike endometrioid carcinomas, p53 mutations occur early in USC tumorigenesis. USC cancers and their putative precursor, endometrial intraepithelial carcinoma, both commonly have abnormal p53 overexpression.[93] P53 mutation is associated with loss of ER and PR expression confers a poorer overall survival even among USC cancers.[94]

Clear cell carcinoma has a distinctive molecular profile. While demonstrating low expression of ER and PR similarly to USC, CCC has immunoreactivity for p53 significantly less frequently compared to USC.[95] CCC without any serous features is associated with hyperplastic endometrium in 40% of cases. Such findings suggest that CCC is a biologic subtype that is distinct from both USC and endometrioid cancers.

Other molecular markers have been investigated for both endometrioid and USC/CCC types. Overexpression of the epidermal growth factor receptor, which occurs in 50% of endometrial cancers, strongly correlates with squamous differentiation,[96] nonendometrial subtypes, and metastasis (76%) and predicted for a poorer survival in patients with endometrioid subtypes.[97] DNA aneuploidy is associated with higher pathologic stage, higher grade, and more frequent lymph node involvement and is found in the majority of USC and CCC.[98] Metallothioneins are small molecular weight proteins associated with metastatic potential that are expressed in endometrial carcinomas. They are associated with higher grade, higher stage, and uterine serous subtypes.[99] High levels of the cathepsin D protease, another metastatic marker, correlate with high-grade tumors, uterine serous carcinoma subtype, positive nodal status, and deep myometrial invasion.[100] Microsatellite instability has been found in about one third of endometrioid carcinoma, but does not correlate well with other prognostic factors.[101] Early use of gene microarrays has identified 24 transcripts that distinguish USC from endometrioid cancers, promising to expand the knowledge base regarding molecular differences that could lead to targeted therapies.[102] The prognostic or therapeutic usefulness of these markers remains to be determined.

Sarcoma

Little is known about the biology of uterine mesenchymal tumors, owing to their rarity and heterogeneity. Most studies have combined the different types of sarcomas. Histologic grade is a prognostic factor. Mitotic count also predicts for outcome in some sarcomas.[103] Sarcomas express ER and PR less frequently than carcinomas do, with an overall ER positivity of 48% and PR positivity of 30%[104]; however, most sarcomas do not respond to hormonal therapy. Aneuploidy, found in about half of sarcomas, and high S-phase fraction occur more often in sarcomas that are higher-stage, more poorly differentiated tumors and with a higher mitotic index.[105] Histology does not clearly correlate with outcome, as survival rates are similar among the three main subtypes: LMS, carcinosarcoma, and ESS.

CLINICAL PRESENTATION AND PATIENT EVALUATION

The majority (80%) of patients with either uterine carcinomas or sarcomas present with abnormal postmenopausal uterine bleeding. Endometrial cancer may also present as menorrhagia or other abnormal bleeding patterns in premenopausal women. Profuse serous or serosanguinous discharge is a presenting symptom in 10% of cases. Sarcomas may present as a rapidly enlarging uterine mass or be associated with symptomatic fibroids. The differential diagnosis of bleeding symptoms includes other types of gynecologic cancers, such as cervical or vaginal cancers or gastrointestinal or bladder cancers.[106] Nonmalignant causes of bleeding or discharge include atrophy, infection or pyometria, traumatic lesions or foreign bodies, polyps or fibroids (leiomyomas), adenomyosis, and endometriosis. Iatrogenic causes include use of hormonal medications, hypothalamic depressants, digitalis, phenytoin, and anticoagulants. Systemic diseases that may cause abnormal bleeding include liver disease and coagulation disorders.

Less commonly, patients present with more advanced disease in the absence of uterine bleeding in which symptoms are related to a large tumor mass, such as pelvic pain, hematuria or hematochezia, rectal obstruction, renal failure secondary to hydronephrosis, or abdominal discomfort and distension. Advanced cases will present with a pelvic mass on examination. Metastatic disease commonly occurs in the lungs, and there may be associated pulmonary symptoms.

Symptoms should be routinely evaluated with pelvic examination and endometrial biopsy or dilation and curettage. Although Pap smear is not an effective screening or diagnostic test for endometrial cancer, it should be performed to assess cervical pathology. Biopsies are subject to sampling error. If biopsy is negative for cancer but symptoms persist, a fractional dilation and curettage should be performed. A biopsy finding of atypical hyperplasia also needs further sampling, since 15% to 25% of patient with this finding on biopsy will have carcinoma.[107] Samples should be taken separately from the cervix and the uterus so that an endocervical lesion may be differentiated from a lesion in the lower uterine segment. Any suspicious masses that are visible in the uterine cavity at the time of the procedure should be biopsied as well. Sarcomas, leiomyosarcoma in particular, may be located submucosally.

After pathologic diagnosis, a thorough history and physical examination should be obtained to document any signs of local or metastatic disease and to determine risk factors for cancer as well as

comorbidities, which could affect the patient's ability to tolerate surgery and other cancer therapy. An examination under anesthesia might be indicated for patients who have apparent locally advanced disease, during which time cystoscopy and proctoscopy may be performed to document any invasion of the bladder or rectosigmoid colon.

Endometrial cancer screening should be considered in special populations. Women who take tamoxifen for treatment for breast cancer have twice the risk of developing endometrial cancer as the general population. Analysis of the NSABP data shows that the average annual hazard rate of endometrial cancer within 5 years of follow-up is 1.2 per 1000 patient-years, with a cumulative hazard rate of 6.3 per 1000 patient-years.[15]

In a randomized study of ultrasonography or office hysteroscopy for endometrial assessment in asymptomatic women who are using tamoxifen, the sensitivity and specificity of transvaginal ultrasonography for cancer detection were 85% and 100%, respectively, and those for office hysteroscopy were 77% and 92%, respectively.[108] Transvaginal ultrasound detects a high percentage of cases of endometrial thickening. Women who are on tamoxifen have a significantly thicker endometrium than do those who are not, and this correlates with duration of exposure.[109] However, nearly half of women who have undergone follow-up hysteroscopy and sampling have benign or atrophic endometrium, resulting in a high false-positive rate even with up to 10 mm of endometrial thickening.[110] Despite concerns regarding cost effectiveness, it is reasonable to perform an annual pelvic examination and transvaginal ultrasound in women who are taking tamoxifen, as the benefit of early cancer detection is significant. Hysteroscopy and biopsy may be performed as indicated on the basis of the findings of these examinations.

Women with HNPCC have a 50% lifetime risk of developing endometrial cancer, which is the most common noncolonic cancer occurring in these families. While optimal screening protocols in this population have not been established, routine annual screening with pelvic examination and transvaginal ultrasound is recommended.[111] A recent study suggests that prophylactic hysterectomy might be an effective strategy in preventing endometrial cancer in women with HNPCC.[112]

LABORATORY AND IMAGING STUDIES

Routine tests including complete blood count, liver function tests, electrolytes and renal function are obtained for presurgical clearance. The tumor marker CA-125 is elevated preoperatively in the serum of about 20% of patients with endometrial carcinomas and is correlated with stage.[113] Elevated CA-125 levels predict for occult extrauterine or metastatic disease.[114]

Since the lung is a common site of metastasis, a chest x-ray is part of the initial evaluation. Abnormalities on chest x-ray should be further evaluated by computed tomography (CT) scan of the chest with contrast. A mammogram should be performed if a screening study has not been performed in the past year. Imaging of the brain is performed only if indicated by history or examination. Patients who are undergoing surgery also need cardiac evaluation, including an EKG and further studies as indicated for surgical clearance. Further evaluation of the gastrointestinal tract, including colonoscopy and upper endoscopy, is indicated for mucinous tumors, which may be of gastrointestinal origin, or those with symptoms related to the upper bowel.

To assist with preoperative staging and management decisions, imaging of the urogenital tract may include intravenous pyleogram or CT scan of the abdomen and pelvis with contrast. Since endometrial cancer is a surgically staged disease, routine preoperative CT scan is often omitted. In cancers of grade II to III or high-risk histology on biopsy, surgical staging including nodal sampling is performed; therefore, CT scan is not needed to assess lymph nodes. However, for patients who are medically inoperable or in whom more advanced or metastatic disease is suspected, a CT scan may be useful to evaluate the extent of abdominopelvic and nodal disease. Magnetic resonance imaging scans improve on the evaluation of myometrial and cervical invasion and may be warranted in medically inoperable patients or other specific situations.[115] Transvaginal ultrasound is also useful for assessing myometrial invasion and tumor size. Accurate prediction of myometrial invasion by ultrasound compared to pathologic assessment ranges from 70% to 100%.[116,117] The role of positron emission tomography (PET) and CT in uterine cancer has not been clearly defined. A recent report suggests that PET might be useful in determining depth of invasion.[118] PET has been utilized in the early detection of recurrence of uterine sarcomas[119] and endometrial cancers.[120]

STAGING

The system that is used to stage most cancers is the TNM system developed by the American Joint Committee on Cancer[121]; however, the main staging system that is used for endometrial cancer is the FIGO system. The T category from TNM staging corresponds to the FIGO stage. In the TNM system, lymph nodes are designated NX if nodes cannot be assessed, N0 if there is no regional lymph node metastasis, or N1 if there is metastasis to pelvic and/or para-aortic nodes. Distant metastases are categorized as MX if distant metastasis cannot be assessed, M0 for no evidence of metastasis, and M1 if there is any distant metastasis.

In 1988, FIGO instituted a surgical staging system for endometrial cancer. Prior to this system, FIGO utilized a clinical staging system based upon the extent of disease within the uterus that could be assessed primarily by physical exam (Table 92-5). The surgical

Table 92-5 International Federation of Gynecology and Obstetrics Staging Systems for Endometrial Cancer

Stage	Description
1988 STAGING FOR CARCINOMA OF THE CORPUS UTERI	
Stage IA G123	Tumor limited to the endometrium
Stage IB G123	Invasion to less than one half of the myometrium
Stage IC G123	Invasion to more than one half of the myometrium
Stage IIA G123	Endocervical glandular involvement only
Stage IIB G123	Cervical stromal invasion
Stage IIIA G123	Tumor invades serosa and/or adnexa and/or positive peritoneal cytology
Stage IIIB G123	Vaginal metastases
Stage IIIC G123	Metastases of pelvic and/or para-aortic lymph nodes
Stage IVA G123	Tumor invasion of bladder and/or bowel mucosa
Stage IVB	Distant metastases including intra-abdominal and/or inguinal lymph nodes
1971 STAGING OF CORPUS CANCER	
I	Confined to the corpus
Ia	Length of uterine cavity ≤8 cm
Ib	Length of uterine cavity >8 cm
II	Carcinoma involves corpus and cervix
III	Carcinoma extends outside the corpus but not outside the true pelvis (may involve vaginal wall or parametrium but not bladder or rectum)
IV	Carcinoma involves bladder or rectum or extends outside the true pelvis

staging system should be used for all patients who undergo hysterectomy for treatment of their endometrial cancer. Because this system requires specific assessment of the adnexae, lymph nodes, and peritoneal cytology, appropriate surgery for endometrial cancer includes a total abdominal hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node sampling, and pelvic washings. Biopsies of any suspicious nodules in the abdomen or pelvis should be obtained. However, for superficial grade I or noninvasive grade II cancers, the risk of lymph node involvement is sufficiently low that the nodal sampling is sometimes omitted. Surgery may be significantly modified in patients with known metastatic disease when surgery is used for debulking or palliation of symptomatic disease, in which case thorough staging is not indicated. Generally, the pelvic and para-aortic nodes should be sampled whether they appear grossly suspicious or not. Adequate nodal sampling of the obturator, external iliac, and para-aortic regions suffices. Pathologic assessments included in the staging system are grade, depth of myometrial invasion, peritoneal cytology, cervix invasion, serosal or adnexal involvement, vaginal invasion, and lymph node metastases. The FIGO 1971 clinical staging system is used for any patients who are not surgical candidates. Whether the staging is based on surgical or clinical staging systems should be clearly documented. These staging systems may also be used for uterine sarcoma, for which there is no specific system.

The use of surgical staging has become the standard after a GOG study by Creasman and colleagues, who reviewed the patterns of spread in surgically staged patients.[50] Of patients with clinical stage I (disease confined to the uterus), 9% were found to have pelvic node metastasis, and 6% were found to have para-aortic node metastasis. Three factors that predict the risk of nodal metastasis, which can be assessed at the time of surgery, are grade ($P = 0.03$), depth ($P = 0.0001$), and the presence of intraperitoneal metastasis ($P = 0.001$).[50] The risk of pelvic nodal metastases in clinical stage I patients is less than 10% in all tumors with superficial invasion or invasion of up to two thirds of the myometrium only, regardless of grade (range 0% to 9%). Tumors that invade more than two thirds of the myometrial depth have a higher risk of pelvic node metastases, depending on the grade: grade I = 11%, grade II = 19%, and grade III = 34%. Furthermore, grade and depth of invasion are strongly correlated; 58% of grade III tumors demonstrate deep invasion. Para-aortic nodal metastases are present in 14% of grade II deeply invasive tumors and in 23% of grade III deeply invasive tumors. Approximately 20% of patients with clinical stage I disease will have occult extrauterine disease in the nodes or washings. Downstaging in clinical stage I is uncommon.

PROGNOSIS

The most important prognostic factors in endometrial carcinoma are stage or extent of disease, grade, depth of invasion, and histologic subtype. The prognosis for uterine confined, stage I disease is excellent, so survival is highly correlated with the presence of extrauterine disease. These factors influence the risk of extrauterine spread and recurrence and therefore influence survival.

Stage

The stage at the time of diagnosis is an important prognostic indicator; patients with more advanced stage have less favorable outcomes. Overall survival rates are approximately 90% for stage I to II, 60% for stage III, and 25% for stage IV. Surgical staging more accurately predicts for survival than does clinical staging. In one study, survival rates for clinical stages I, II, and IV were 83%, 64%, and 8%, respectively; survival rates for surgical stages I, II, III, and IV were 89%, 100%, 58%, and 24%, respectively.[122]

Histologic Subtype

The most common histology, and one of the most favorable, is endometrioid adenocarcinoma. Other adenocarcinomas, including USC and CCC, have a much higher propensity for both nodal and extrauterine spread; therefore, their prognosis is much poorer. Squamous carcinomas and undifferentiated subtypes also behave aggressively. The overall survival rate among patients with endometrioid adenocarcinoma is over 90%, compared to only 33% for all unfavorable histologies combined.[123] High-grade sarcomas also have a poorer prognosis than does endometrioid adenocarcinoma.

Depth of Invasion

Depth of invasion of the myometrium is the most influential pathologic feature with respect to lymph node metastases. Pelvic node metastases are found in 1% of superficial tumors, in 5% of tumors with invasion of the inner one third of the myometrium, in 6% of tumors with middle one third invasion, and in 25% of tumors with deep outer one third invasion.[50] Para-aortic nodal metastases are seen in 1%, 3%, 1%, and 17% of tumors, respectively. Depth of invasion correlates with the grade, and over half of cancers that are grade III have deep invasion.

Grade

Histologic grade is one of the primary predictors for extrauterine spread. Higher grade is associated with both deeper myometrial invasion and lymph node metastases. Grade I cancers have a 3% risk of pelvic lymph node spread, compared to 9% for grade II and 18% for grade III.[50] Para-aortic nodes are involved in 2% of grade I, 5% of grade II and 11% of grade III tumors. The presence of both high grade and deep myometrial invasion conveys the highest risk of nodal spread: 34% to pelvic nodes and 23% to para-aortic nodes. The correlation is not absolute, however, and 10% of grade I tumors will demonstrate deep invasion, while 7% of grade III are endometrium only.

Adnexal Involvement

Only 5% to 6% of surgically staged patients with clinical stage I disease have isolated adnexal involvement.[50] This pathologic finding is associated with a 32% risk of pelvic lymph node metastases, and 23% have para-aortic lymph node spread, compared to only 8% and 5% risk of pelvic or para-aortic nodal spread, respectively, without adnexal involvement.

Positive Peritoneal Cytology

Positive peritoneal washings are often a marker for other extrauterine spread. Over half of patients with positive pelvic washings will have adnexal or other areas of pelvic spread of disease. About 10% of patients with FIGO stage I endometrial cancer have positive peritoneal washings. This finding is associated with depth of invasion, high grade, and positive nodes, appearing to place these patients at higher risk for recurrence.[124] In a series of 270 patients with stage I disease, 5% demonstrated positive washings, which correlates with tumor grade and depth of invasion.[125] Peritoneal cytology was found to predict for survival; however, peritoneal cytology can fail to identify any additional patients whose prognosis is not apparent from grade and depth of invasion.

Lymphovascular Invasion

Lymphovascular invasion is present in 15% of endometrial cancers, conferring a 27% risk of pelvic nodal spread and a 19% risk of para-aortic nodal spread, compared to 7% and 9%, respectively, if the feature is absent.[50] Lymphovascular invasion correlates with poorer disease-free survival.[126]

Table 92-6 Results of Postoperative External Beam Radiation Therapy for Stage I Endometrial Cancer

Study	No. of Patients	Stages	Radiation Technique	Five-Year Local Control Rate (%)	Five-Year Overall Survival Rate (%)
Aalders et al.[164]	263	I	ICRT ± EBRT	98	89
Creutzberg et al.[165]	354	I	EBRT	96	81
Keys et al.[166]	190	IB, IC, II	EBRT	97	92
de la Cuesta et al.[167]	28	IB	EBRT or ICRT	97	NR
Grigsby et al.[168]	142	I	EBRT, ICRT, or EBRT + ICRT	IA: 92 IB: 86	NR
Irwin et al.[169]	322	I	EBRT, ICRT, or EBRT + ICRT	77 (DFS)	81
Podczaski et al.[170]	148	I/II (occult)	EBRT	95	NR
Weiss et al.[171]	61	IC	EBRT	100	98
Stryker et al.[199]	79	I	EBRT ± ICRT	98	NR
Algan et al.[200]	75	I	EBRT + ICRT	89	83

DFS, disease-free survival; EBRT, external beam radiation therapy; ICRT, intracavitary radiation therapy; NR, not reported.

Age

Older age is associated with a worse prognosis.[127] Age is also associated with a higher risk of presenting with high-risk histologies such as uterine serous, higher grade, deep invasion, and higher stage, possibly reflecting a more aggressive biologic behavior of hormone-independent cancers that occur at a higher median age. However, when endometrial cancers with similar pathologic features are compared, survivals are not significantly different by age (less than 60 years: 74%, 60 to 69 years: 70%, ≥70 years: 60%).[128]

TREATMENT OF EARLY-STAGE ENDOMETRIAL CANCER

FIGO stage I and II endometrial carcinomas consists of tumors that are confined to the uterus or that extend to the uterine cervix only. Five-year overall survival rates of 76% to 100% and 46% to 85% for stage I and II patients, respectively, have been reported (Tables 92-6 and 92-7). Treatment mainly consists of surgical resection with adjuvant radiation therapy reserved for patients who have risk factors for pelvic recurrence (Box 92-1). If recurrences do occur after early-stage endometrial carcinoma, they are predominantly local in nature, and the addition of radiation therapy to the management of early-stage endometrial carcinoma, has been shown to decrease the rate of local recurrence. Definitive radiation is largely reserved for patients who are medically inoperable or who refuse surgical resection.

Surgery

Surgical Technique

Surgery should be performed by utilizing an incision that allows for adequate examination of the abdomen and pelvis as well as retroperitoneal lymph node sampling if indicated. Upon entry into the abdominal cavity, pelvic washings should be obtained for cytologic analysis. Next, a thorough inspection of all peritoneal surfaces should be performed, with biopsy of any suspicious lesions. Prior to removal of the uterus, the fallopian tubes should be clamped or occluded with clips to prevent retrograde spillage of tumor. Extrafascial hysterectomy with bilateral salpingo-oophorectomy may then be completed. The specimen should be bivalved and examined for depth of myometrial invasion and other features that are indicative of high-risk disease in the pathology laboratory as part of intraoperative consultation and frozen section evaluation. (Specimens should never be opened or cut into in the operating room because that compromises pathologic evaluation.) In cases of deep myometrial invasion, grade II or III disease, nonendometrioid histologic type, or obvious extrauterine tumor, pelvic and para-aortic lymph nodes should be sampled.

For selected patients who are at high risk for perioperative complications whose tumors appear clinically confined to the uterus, vaginal hysterectomy may be an alternative.[129] Although this approach might offer reduced surgical morbidity, it has several disadvantages. A vaginal approach can render removal of the ovaries difficult. In

Table 92-7 Results of Postoperative External Beam Radiation Therapy for Stage II Endometrial Cancer

Study	No. of Patients	Stages	Radiation Techniques	Five-Year Local Control Rate (%)	Five-Year Overall Survival Rate (%)
Greven et al.[126]	26	II	EBRT ± ICRT	88	72
Lanciano et al.[175]	70	II	EBRT ± ICRT	87	70
Eltabbakh and Moore[176]	48	II	EBRT ± ICRT	94	92
Sartori et al.[177]	133	II	EBRT	89	80
Onsrud et al.[245]	40	II	EBRT + ICRT	82	85
Grigsby et al.[168]	90	II	ICRT ± EBRT	91	78
Greven and Olds[174]	24	II	EBRT	94	NR

DFS, disease-free survival; EBRT, external beam radiation therapy; ICRT, intracavitary radiation therapy; NR, not reported.

Box 92-1. ADJUVANT RADIATION THERAPY FOR EARLY-STAGE ENDOMETRIAL CANCER

One of the most controversial aspects of clinical management in endometrial cancer involves the use of adjuvant postoperative radiation therapy for stage I disease, including determining who benefits from it and who may safely avoid it. The recommendations for adjuvant radiation are influenced by the risk of nodal metastases and the rate of vaginal recurrence. According to a GOG pathologic study, patients with deep myometrial invasion and grade II or III tumors have a 19% to 34% risk of pelvic lymph node metastases.[50] The risk is also increased by positive peritoneal cytology, location in the lower uterine segment or cervix, adnexal involvement, and capillary space invasion. The risk of vaginal recurrence after surgery alone is greater with grade II or III histology, deep myometrial invasion, lymphovascular space invasion, large tumor size, location in the lower uterine segment or cervix, and close or positive margins. Adjuvant radiation is extremely effective at preventing pelvic and vaginal recurrence but is associated with an increased risk of late side effects. It can also be argued that radiation therapy for isolated vaginal recurrence is relatively effective salvage treatment and therefore may be reserved for those that do recur.

Although three randomized trials have addressed the question of postoperative radiation in early-stage disease, all have been criticized. All three trials entered patients who were predominantly at low or intermediate risk for recurrence. The PORTEC study excluded high-risk patients from eligibility, including those with high-grade or deeply invasive tumors.[50] In the Norwegian Radium Hospital (NRH) trial, 50% of the patients entered had stage IB grade I or II adenocarcinomas, and only 18% had stage IC grade 3 tumors.[164] In GOG Protocol 99, only 18% of patients entered had grade III disease, and only 20% had deep myometrial invasion (outer one third).[166] Two trials (NRH and PORTEC) did not include surgical lymph node staging. Although GOG Protocol 99 did require surgical staging, the median number of lymph nodes that were recovered was relatively low. The therapeutic benefit of nodal sampling and its role in reducing pelvic recurrence are controversial. Therefore, all three randomized trials addressing the role of adjuvant radiation in early-stage endometrial cancer included a preponderance of intermediate-risk patients, diluting the ability to detect a benefit in the patients who are at highest risk for pelvic recurrence: those with high-grade and deep myometrial invasion. In addition, none of these trials has adequately assessed the benefit of adjuvant radiation after comprehensive surgical staging. Not surprisingly, no overall survival benefit for adjuvant radiation has been reported in these trials. GOG Protocol 99 showed an estimated hazard of recurrence that was 58% less in the irradiated arm ($P = 0.007$) and a 4-year overall survival rate of 92% in the radiation arm versus 86% in the observation arm ($P = 0.09$).

What is not controversial is that adjuvant radiation has been consistently shown to significantly reduce the pelvic and vaginal recurrence rates in stage I endometrial cancer patients. In the NRH trial (in which all patients received vaginal brachytherapy and were randomized to pelvic radiation or no further treatment), the vaginal and pelvic recurrence rate in the observation arm was 6.9% compared to 1.9% in the radiation arm ($P = 0.01$). The PORTEC trial reported locoregional recurrences rates of 14% in the observation arm compared to 4% in the radiation arm ($P < 0.001$). GOG Protocol 99 reported a crude vaginal and pelvic recurrence rate of 8.9% in the observation arm and 1.6% in the radiation arm (three patients, two of whom refused radiation after randomization). When risk factors for recurrence were examined in the NRH trials, it was noted that the greatest benefit of adjuvant radiation was for patients with high-grade and deeply invasive tumors.

Complications are increased by the use of both surgery and pelvic radiation. The NRH reported a crude grade III or IV complication rate of 0.7% after postoperative vaginal brachytherapy alone (one fistula and one urethral stricture) and 0.7% after postoperative pelvic radiation and brachytherapy (including one death due to postoperative infection after a bowel obstruction, and one bladder necrosis). The PORTEC trial included no vaginal brachytherapy and reported treatment-related complications (grades I to IV) of 25% in the radiation arm compared to 6% in the observation arm, of which 68% overall were grade I toxicities. Grade III toxicity occurred in seven patients (0.09%), six of whom received radiation therapy. Grade IV toxicity occurred in one patient from the radiation arm who had Crohn's disease and therefore should not have been offered adjuvant irradiation.

On the basis of the patterns of nodal metastases and patterns of recurrence, a management algorithm has been developed for the use of postoperative radiation therapy stage I and II endometrial cancer patients. A multidisciplinary approach is recommended, involving gynecologic oncologists and radiation oncologists in the patients' care. Low-risk patients have a sufficiently small risk of nodal or vaginal recurrence that they require no adjuvant therapy, including stage IA grade I to II and stage IB grade I. The recurrence pattern in intermediate-risk patients is predominantly vaginal. These patients may be offered observation versus vaginal brachytherapy alone after a discussion of the risks and benefits of both approaches and the salvage rates after recurrence. This category includes stage IA grade III, stage IB grade II or III and stage IC grade I or II. The recurrence pattern for high-risk patients includes both vaginal and pelvic relapses; therefore, they should be offered pelvic radiation with or without vaginal brachytherapy. This category includes stage IC grade III and stage II. Vaginal brachytherapy in addition to pelvic radiation is considered for stage II patients (those with extension to the cervix) unless they have undergone a radical hysterectomy and margins are widely negative and for some stage IC grade III patients, including those with large tumors (>4 cm) in the lower uterine segment or extensive lymphovascular invasion. The fraction size for vaginal brachytherapy when given in combination with external beam pelvic irradiation should not exceed 500 cGy. Any patient with very close or positive margins postoperatively should be offered vaginal brachytherapy at a minimum. Patients who have not undergone an adequate pelvic lymph node sampling (several nodes from each side of the pelvis) should be offered pelvic irradiation, even if they have only intermediate-risk features.

addition, peritoneal cytology, thorough abdominal exploration, and lymphadenectomy are not feasible. To overcome these obstacles, some clinicians have advocated use of laparoscopic-assisted vaginal hysterectomy combined with laparoscopic lymphadenectomy.[130] The laparoscopic surgery consists of initial laparoscopic examination of the abdominal cavity followed by sampling of the para-aortic and pelvic lymph nodes through the same incisions. The hysterectomy may be performed vaginally with laparoscopic assistance to ensure ovarian removal (Box 92-2). The procedure is converted to an open laparotomy if the laparoscopy proves to be too difficult or inadequate or if excessive blood loss occurs. Although laparoscopy has been shown to increase the total time of the operation, the length of post-surgical hospital stay is shorter.[131] While rates of complications, lymph node counts, and recurrence and survival rates are reportedly equivalent to those of traditional total abdominal hysterectomy, the technique has yet to be validated over the long term.[132–135] There have been reports of increased need for blood transfusion and increased operative times for the laparoscopic approach, as well as a small

Box 92-2. LAPAROSCOPIC SURGERY FOR ENDOMETRIAL CANCER

Total abdominal hysterectomy and bilateral salpingo-oophorectomy, with lymph node sampling in selected patients, is the standard surgical approach for management of early endometrial cancer. Although vaginal hysterectomy has been utilized in women who are at high risk for perioperative morbidity, the technique does not allow for adequate peritoneal exploration or for lymphadenectomy. However, laparoscopic-assisted vaginal hysterectomy may be combined with laparoscopic lymph node sampling to provide a means of adequate staging as well as to potentially decrease the length of patients' postoperative stay. The Gynecologic Oncology Group (GOG) has completed a phase III randomized study comparing laparoscopy with laparotomy.[137] Laparoscopic surgical staging could be performed in 76.3% of cases. No difference in stage, positive cytology, or lymphatic metastasis could be attributed to the laparoscopic approach. Quality of life and physical functioning improved 6 weeks postoperatively following laparoscopy, but these differences were not significant by 6 months.[137] The role of robotics in minimally invasive surgery for uterine cancer is under investigation. While laparoscopic staging could be a technically feasible option for surgical management, long-term data regarding recurrence and survival have yet to be characterized.

number of deaths directly related to complications associated with laparoscopy. Vaginal cuff recurrence associated with laparoscopic-assisted vaginal hysterectomy has also been reported.[136]

For patients with disease spread outside of the uterus, more aggressive surgical options exist. Radical hysterectomy with removal of the uterus, cervix, parametria, and upper vagina may be an option for those with disease involving the cervix.[138] Fewer than 10% of patients will present with stage IV disease.[139] While the overall survival rate for these patients is less than 10%, aggressive surgical cytoreduction may improve survival.[140–142]

Surgical removal of the uterus not only provides a therapeutic benefit, but is also important for accurately staging the patient. Surgical staging can result in upstaging 12% of patients with clinical stage I disease and 27% with clinical stage II disease as well as downstaging 59% of patients with clinical stage II disease.[143] In addition, surgical staging allows for full evaluation of histologic grade. Histologic grade from the biopsy specimen differs from the histologic grade from the surgical specimen after hysterectomy in over 20% of cases, mainly owing to tumor heterogeneity.[144,145] Surgical staging is also vital for assessing the depth of myometrial invasion and presence of lymph-vascular invasion, all of which are critical in guiding adjuvant therapy.

Surgical Staging of the Lymph Nodes

Surgical staging, including sampling of the pelvic and para-aortic lymph nodes, may be performed at the time of the surgery. When the tumor is limited to the uterine corpus, occult metastases to the lymph nodes most frequently occur to the external iliac and obturator lymph node chains.[146] Spread to the common iliac lymph nodes is more frequent when there is cervical extension of the primary disease. Isolated involvement of the para-aortic lymph nodes can occur, although it is uncommon in the absence of associated pelvic lymph node spread. The presence of lymph node metastases can significantly alter the treatment plan, and removal of the lymph nodes has a strong role in improving staging.[147] However, lymphadenectomy has not been shown to improve survival, other than in small retrospective studies[146,148,149] A review of over 9000 women with endometrial cancer who were registered into the National Cancer Institute's Surveillance, Epidemiology and End Results database revealed that the 5-year relative survival of 2831 women with stage I endometrial cancer who underwent sampling of their pelvic lymph nodes was nearly identical to that of 6363 women with stage I disease who did not undergo lymph node sampling.[150]

Risk factors for metastases to clinically uninvolved lymph nodes include myometrial invasion to the outer one third of the myometrium, lymph-vascular space involvement, cervical involvement, and high-grade histology. Stage I carcinomas without any of these adverse risk factors have histologically involved lymph nodes less than 10% of the time, and lymph node sampling may be omitted in these cases.[151,152] In a nonrandomized, prospective trial of 332 patients with endometrial carcinoma who did not have significant risk factors for lymph node metastases, treatment with hysterectomy and adjuvant postoperative vaginal brachytherapy alone without lymphadenectomy resulted in a 30-year disease-free-survival rate of 96.7%.[153] Involvement of any of these risk factors can increase the risk of pelvic or para-aortic lymph node involvement to 14% to 31%; therefore, sampling of the pelvic and para-aortic lymph nodes to allow for complete pathologic staging is indicated.[152,154] To identify the patients who are at high risk for lymph node involvement, frozen section of the uterine specimen may be performed at the time of surgery to determine the grade, depth of invasion, and presence of lymph-vascular invasion. Such algorithms must be used with caution. Currently, there are no proven methods to definitively predict which patients are at low risk for lymph node metastases.[155,156] Therefore, some surgeons will perform retroperitoneal lymph node staging on all patients with endometrial cancer.

Surgery as a Single Modality

Several series, listed in Table 92-8, have examined the outcomes of patients with stage I/II endometrial cancer who have undergone hysterectomy without adjuvant treatment. Berchuck and colleagues reviewed a series of 354 patients with stage I/II endometrial adenocarcinoma from Duke University who underwent postsurgical surveillance.[157] Twelve percent of patients developed recurrent disease. Of the patients with recurrence, 27% had isolated vaginal recurrences, 27% had pelvic recurrences with vaginal or abdominal involvement, 29% had pelvic recurrences with other distant sites, 10% had isolated lung recurrences, and 7% had recurrences at other distant sites. Another study from the University of Alabama–Birmingham reviewed 613 patients with stage I endometrial carcinoma who underwent primary surgery.[158] The 5-year overall survival rate was 98%, and the 5-year disease-free survival rate was 93%. For stage IB patients, 99% did not receive adjuvant treatment, and only 5% of those patients experienced recurrent disease. All patients who recurred within the pelvis or vagina were successfully salvaged with radiation therapy. For stage IC patients, 69% did not receive adjuvant therapy. Recurrence was seen in only 8% of those patients. A small, prospective series of 33 patients with stage I endometrial carcinoma who had poor prognostic features, including deep myometrial invasion and/or histologic grade III tumors, utilized surgery alone as primary treatment for their endometrial cancer.[159] All 18 patients who presented with disease that was confined to the uterus were without evidence of disease at their latest follow-up. However, 73.3% (11 of 15) of patients with spread beyond the uterus had recurrences. Larson and colleagues reviewed 207 women with uterine-confined endometrial carcinoma who underwent surgery without adjuvant radiation therapy.[160] Forty-five percent were considered to be in a low-risk group with grade I tumors and invasion through less than 50% of the myometrium. The 5-year recurrence-free survival rate was 95% in these patients. Forty-seven percent of patients with additional risk factors, but who had histologically confirmed negative nodes, had a 5-year recurrence-free survival rate of 89%.

A factor that favors the use of surgery only in some patients is the high rate of salvage for recurrences. Patients who experience recur-

Table 92-8 Results of Surgery Alone for Early-Stage Endometrial Carcinoma

Study	No. of Patients	Stages	Five-Year Local Control Rate (%)	Five-Year Overall Survival Rate (%)
Kilgore et al.[149]	74	IA–IC	NR	98
Berchuck et al.[157]	354	I/II	93	NR
Straughn et al.[158]	374	IB/IC	93	98
Chen[159]	18	I	100	100
Larson et al.[160]	199	I–II	97	92
Orr et al.[294]	61	IA	100	100
Keys et al.[166]	190	IB, IC, II	97	92
Creutzberg et al.[165]	361	I	86 (DFS)	85
de la Cuesta et al.[167]	58	IB	95	NR
Irwin et al.[169]	228	I	93	90
Podczaski et al.[170]	152	I/II	93	NR
Sartori et al.[177]	70	II	81	76

DFS, disease-free survival; NR, not reported.

rence after surgery alone can often be successfully salvaged with external beam radiation therapy (EBRT) to the pelvis, vaginal brachytherapy, or, most commonly, a combination of both. The 5-year disease-free survival rate after salvage radiation therapy ranges from 62% to 92% for these patients.[161,162] The long-term grade II or III complication rate from salvage radiation therapy is 10% to 15%.[163]

External Beam Radiation Therapy for Early-Stage Endometrial Cancer

Endometrial carcinoma is a radiosensitive tumor, and the addition of radiation can result in very high rates of locoregional control. The presence of adverse risk factors such as extension beyond the corpus to the uterine cervix, deep myometrial invasion, or high-grade histology significantly increases the risk of locoregional recurrence following surgery alone. In these patients, adjuvant radiation therapy has been used successfully to significantly reduce the risk of local recurrence. In addition, radiation has been used with some success as the primary treatment of patients who are poor surgical candidates, who are medically inoperable, or who refuse surgical removal of the uterus.

Postoperative External Beam Radiation Therapy for Stage I

Several randomized studies, reviewed in Table 92-6, have explored the benefit of adjuvant EBRT. A study by Aalders and colleagues randomized 540 patients with clinical stage I endometrial adenocarcinoma who underwent hysterectomy and received 60 Gy of postoperative radiation delivered via intravaginal radium implants to either no further treatment or an additional 40 Gy to the pelvis via EBRT.[164] The results showed a significant reduction in the 5-year local recurrence rate in the group that received pelvic radiation (1.9% versus 6.9%, $P < 0.01$); however, no overall survival advantage was seen, owing to an increase in the rate of distant metastases in the group receiving additional radiation. On subgroup analysis, the patients who experienced the greatest reduction in local recurrence were those patients with grade III tumors as well as those with more than 50% myometrial invasion.

Another prospective, randomized trial supporting the use of adjuvant radiation for early-stage endometrial cancer was conducted by the Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC) Study Group in the Netherlands.[165] Only patients with intermediate-risk, stage I endometrial carcinoma were enrolled. Eligibility included grade I tumors with 50% or more myometrial invasion, grade II tumors with any depth of invasion, or grade III tumors with less than 50% myometrial invasion. Treatment consisted of a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO) with or without EBRT (46 Gy, 2 Gy/day) delivered to the whole pelvis following surgery. Overall, 715 patients were randomized to postoperative radiation therapy versus no further treatment. Patients were followed for a median of 52 months. The 5-year local and regional recurrence rate was 4% in the group that received postoperative radiation therapy compared to 14% in the group that underwent no further treatment ($P < 0.001$). The overall incidence of distant metastases was similar in both groups (8% versus 7% for the radiation and observation arms, respectively). Despite this improvement in locoregional control, there was no difference in overall survival, largely owing to the high rate of salvage for patients who experienced a recurrence. The 5-year overall survival was 81% in the radiotherapy group compared to 85% in the observation group ($P = 0.31$). Deaths from endometrial cancer were also similar between the two groups (9% versus 6% for the radiotherapy group and the observation group, respectively, $P = 0.37$). On multivariate analysis, the only factors predicting for locoregional recurrence were patient age and the use of postoperative radiation therapy. The histologic grade and depth of myometrial invasion both showed a trend toward predicting recurrence; however, neither reached statistical significance. In terms of patterns of failure, 75% of patients who experienced a local recurrence recurred within the vaginal vault. An increase in late toxicity was associated with the radiation therapy. Twenty-five percent of patients receiving radiation therapy experienced grade I to IV late toxicity compared to 6% of the observation group ($P < 0.001$). However, only seven patients experienced any grade III toxicity, and one patient who had Crohn's disease experienced grade IV GI toxicity.

The study GOG Protocol 99 is the first postoperative radiation trial that required comprehensive surgical staging. They randomized 392 patients with surgical stage IB, IC, or occult IIA or IIB endometrial cancer to treatment with surgery alone versus surgery with 50.4 Gy of postoperative EBRT.[166] The majority of patients had stage IB (60%) disease, and most had grade I or II disease (80%), representing a group without high-risk factors overall. The median follow-up was 69 months. The results estimated that the hazard of recurrence was 58% less in patients who were randomized to the irradiated arm compared to those who were randomized to the observation arm ($P = 0.007$). Importantly, all patients in this study were required to undergo surgical lymph node staging, and this benefit in progression-

free survival was seen even in patients who were found to have pathologically uninvolved lymph nodes. In addition, while 18 patients failed in the pelvis or vagina in the observation arm, only three patients in the radiation arm experienced a locoregional failure; and two of those three patients did not actually receive radiation treatment. At 48 months, the overall survival rate was higher in the radiation arm than in the observation arm (92% versus 86%), though this difference was not statistically significant ($P = 0.09$); however, this trial was not adequately powered to reliably detect overall survival differences. Subgroup analysis identified a high-intermediate-risk group that showed a trend toward a lower overall death rate in the radiation arm, suggesting a possible benefit of adjuvant radiation in patients that have a combination of advanced age, moderate to poorly differentiated rumors, presence of lymphovascular invasion, or outer third myometrial invasion.

A number of retrospective series have examined the efficacy of postoperative radiation therapy in stage I endometrial cancer. In one series, 124 patients with stage IB endometrial carcinoma were reviewed at Massachusetts General Hospital.[167] All patients underwent hysterectomy, and 62 patients did not receive any adjuvant therapy. Only 3% (4 of 124) of the patients developed a recurrence. One of the four patients who relapsed had received adjuvant therapy, and that patient had a grade III tumor. In another retrospective series from Washington University, 858 patients with clinical stage I endometrial cancer were treated with TAH-BSO and radiation therapy.[168] The study included a wide variety of radiation techniques, including EBRT and intracavitary brachytherapy as well as both preoperative and postoperative radiation, and included patients who were treated over a long time period. The 5-year progression-free survival rate was 92% for patients with stage IA disease and 86% for patients with stage IB disease.

A series from Princess Margaret Hospital compared 228 patients who underwent surgery alone for stage I endometrial carcinoma to 217 patients who received adjuvant EBRT with intracavitary boost and 97 patients who received adjuvant EBRT only.[169] Overall, the local control rate was the same among the three groups (93% to 95%); however, the patients who received radiation were more likely to have more than 50% myometrial invasion and grade III tumors. Another series reviewed 300 patients with endometrial cancer confined to the uterus who had undergone hysterectomy.[170] Patients with high-risk features for local recurrence received adjuvant radiation therapy. Treatment with radiation resulted in a pelvic control rate of 95%, and recurrences were more likely to be distant than local in this population. The use of radiation therapy was found to correlate with patient prognosis. A smaller series from the University of Chicago reviewed the outcomes of women with stage IC endometrial carcinoma who were treated with EBRT to the whole pelvis without the addition of intracavitary brachytherapy.[171] No patient developed local recurrence, and the 5-year disease-free and overall survival rates were 87% and 98%, respectively.

A multi-institution review by Straughn and colleagues examined 220 patients with surgical stage IC and compared patients who were managed with and without adjuvant radiation. Forty-five percent of patients were treated with adjuvant radiation on the basis of physician preference. Six percent of patients recurred in the radiation arm, and 12% of patients recurred in the observation arm. Though there were fewer recurrences in the radiation arm, the results were not statistically significant ($P = 0.20$). The 5-year disease-free survival rate was significantly improved in the adjuvant radiation group (93% versus 75%, $P = 0.013$). Overall survival was similar in both groups. The overall salvage rate was 64%.[172]

For patients who are good candidates for postoperative radiation, the time interval between completion of surgery and the initiation of radiation appears to significantly affect local control. In a retrospective study by Ahmad and colleagues, patients with endometrial cancer who were treated with postoperative radiation were found to have significantly decreased 5-year disease-specific survival rates, from 89% to 81% ($P < 0.005$ on multivariate analysis), when the interval between surgery and radiation was greater than 6 weeks.[173] In addition, an increased surgery-to-radiation interval showed a trend to worsened local control (88% for interval less than 6 weeks versus 84% for interval greater than 6 weeks, $P = 0.06$ on multivariate analysis).

Postoperative Radiation Therapy for Stage II

The presence of cervical invasion in endometrial cancer results in an increased risk of local recurrence, particularly at the vaginal cuff. In the setting of known cervical extension, a wider resection, such as a radical hysterectomy, is often performed at the time of surgery. Often, occult cervical involvement is seen only on pathologic examination of the surgical specimen. In either case, postoperative radiation therapy is usually indicated to reduce the risk of local recurrence.

Aside from the inclusion of patients with occult stage IIA or IIB in the GOG Protocol 99 trial, there are no randomized trials that specifically address the role of adjuvant radiation therapy with stage II endometrial carcinoma. Nevertheless, several retrospective series support its use in these patients (see Table 92-7). Greven and Olds reported a 5-year overall survival rate of 86% for patients with stage II disease treated with surgery and adjuvant radiation.[174] Lanciano and colleagues reviewed 184 patients with stage II carcinoma of the endometrium who received a variety of treatments, including TAH-BSO with preoperative RT, postoperative RT, or both, or who received RT alone or radical hysterectomy alone.[175] The overall 5-year disease-free survival and overall survival rates were 79% and 70%, respectively. The only predictors of recurrence on multivariate analysis were histologic subtype and grade. There was no difference in disease-free survival on subgroup analysis with respect to the timing of radiation to surgery. In a series at the University of Vermont, 48 women with stage II endometrial carcinoma were treated with TAH followed by pelvic EBRT and/or vaginal cuff radiation or with radical hysterectomy alone.[176] The 5-year overall survival rate was 92%, and the 5-year disease-free survival rate was 90%. None of the 31 patients who were treated with both EBRT and vaginal cuff boost or with radical hysterectomy recurred. Seventeen percent of patients who received total abdominal hysterectomy with only pelvic radiation or vaginal cuff radiation experienced local recurrence. The authors concluded that use of both pelvic EBRT and vaginal cuff radiation was warranted in this group of patients. Sartori and colleagues reviewed 203 patients with stage IIA and stage IIB endometrial carcinoma among whom 66% underwent simple hysterectomy while 34% underwent radical hysterectomy.[177] Adjuvant radiation was delivered to 59% of stage IIA patients and to 73% of stage IIB patients. Overall survival was better in patients who underwent radical hysterectomy (10-year overall survival rate: 74% versus 94%, $P < 0.05$) compared to simple hysterectomy. Overall survival did not differ between the two treatment groups (10-year overall survival rate: 73% for irradiated patients versus 75% for observation patients). However, the overall recurrence rate was lower in the patients who received adjuvant radiation (11.3% versus 18.6%).

Preoperative Radiation for Early-Stage Endometrial Carcinoma

An alternative approach to postoperative radiation therapy for early-stage carcinoma is the administration of radiation therapy prior to surgical resection of the uterus, either via EBRT, brachytherapy, or a combination of both. Preoperative radiation has the potential advantages of sterilizing the tumor prior to surgery and increasing the ease of resection by decreasing tumor bulk, particularly in patients with extensive involvement of uterine cervix. There are no randomized studies comparing the relative efficacy of preoperative radiation

therapy to postoperative radiation; however, several retrospective studies indicate that preoperative radiation is a reasonable option for patients with early-stage endometrial cancer (Table 92-9). One retrospective study of patients with stage I endometrial carcinoma compared treatment with hysterectomy alone to hysterectomy with preoperative radiation with cesium implants.[178] The 5-year disease-free survival rate was similar for the two groups (94% versus 91%); however, the treatment groups were unbalanced. Patients who received preoperative radiation were more likely to have adverse prognostic features that placed them at higher risk for local recurrence. A study from the Mallinkrodt Institute of Radiology reviewed the results of 90 stage II patients with endometrial cancer, most of whom were treated with a combination of preoperative EBRT and intracavitary low-dose-rate brachytherapy.[179] The 5- and 10-year disease-free survival rates for these patients was 78% and 75%, respectively. Bruckman and colleagues reported the results of 40 patients with stage II endometrial cancer treated with 40 Gy of EBRT with an additional 40 mgh Ra Eq of radiation delivered via intracavitary brachytherapy followed by surgery.[180] In these patients, the 5-year relapse-free survival rate was 78% and the 5-year overall survival rate was 80%. Overall, for stage I or II disease, the addition of preoperative radiation has resulted in a reported 5-year disease-free survival rate of 80% to 88% and a 5-year overall survival rate of 82% to 95%.[181–183]

Grigsby and colleagues[168] reported a decrease in progression-free survival with doses less than 3500 mgh Ra Eq delivered via intracavitary cesium implants. This decrease was greatest for high-grade tumors, though doses greater than 3500 mgh Ra Eq resulted in equivalent results (a 5-year progression-free survival rate of 87%) for all grades. The results of these retrospective series for preoperative radiation are similar to historical results for early-stage endometrial cancer treated with hysterectomy followed by adjuvant radiation. Preoperative radiation remains a viable option for the treatment of stage I/II patients; however, care must be taken to deliver adequate doses, particular in patients with risk factors for recurrence such as high-grade disease or deep myometrial invasion.

Postoperative Radiation Therapy for Early-Stage High-Risk Histology

Several histologic subtypes of endometrial carcinoma have a significantly higher risk of extrauterine spread and propensity for local recurrence, most notably uterine serous and clear cell variants. These histologic subtypes have shown a propensity for distant spread and, when compared to other stage-matched endometrial carcinomas, have significantly worse outcomes. The propensity of uterine serous tumors to spread can be seen even in the absence of definitive evidence of local invasion. Lymph node metastases can be seen in more than 35% of patients with uterine serous tumors who do not have any evidence of myometrial invasion on pathologic examination. Patients with stage I/II uterine serous carcinoma have a recurrence rate of 38% compared to 22% for CCC and 20% for grade III adenocarcinoma.[183] Survival is also worse for these variant histologies with an estimated 5-year overall survival rate of 32% to 44% for patients with uterine serous histology and a 5-year overall survival rate of 59% to 72% for those with clear cell histology.[184]

Owing to the probability of intraperitoneal spread with uterine serous and clear cell histologies, the use of whole-abdominal irradiation has been explored in several studies. At Stanford University, eight patients with stage I or II uterine serous or clear cell histology endometrial cancers were treated with adjuvant whole-abdominopelvic irradiation.[185] The 3-year disease-free and overall survival rates were both 87% for these patients. Another study reviewed the results of 78 patients with stage I to IIIA (positive washings only) endometrial cancer who had tumors with uterine serious histology.[186] Fifty-eight patients received whole-abdominal radiotherapy and had a significantly better 5-year disease-specific survival rate than did those who received either less extensive radiation therapy or no adjuvant therapy (75% versus 41%). These studies indicate that the use of whole-abdominal radiation therapy can improve disease control in patients with these aggressive histologies and should be considered as part of treatment for all patients with these variant histologies, even when they present with early-stage disease. Alternative approaches to the treatment of these high-risk histologies include the use of chemotherapy.

Brachytherapy for Early-Stage Endometrial Cancer

Intravaginal brachytherapy has been used both alone as the primary means of radiation treatment or in conjunction with EBRT. For early-stage disease, brachytherapy offers the advantage of delivering a high dose of radiation locally while minimizing the volume of surrounding normal structures that receives a high dose of radiation. Previously, brachytherapy consisted mainly of low-dose rate (LDR) intracavitary insertions; however, this requires in-patient hospitalizations and lengthy insertion times that increase the risk of exposure to medical personnel. Increasingly, high-dose rate (HDR) techniques with remote afterloading of the radiation source have been used, forgoing the need for hospitalization and minimizing exposure to medical personnel. In appropriately selected patients, brachytherapy offers results similar to those of EBRT, and it appears that HDR brachytherapy offers rates of control similar to those of LDR techniques.[187] The PORTEC-2 trial is currently under way, which randomizes patients to EBRT versus vaginal brachytherapy to compare rates of vaginal relapse and overall survival.

Low-Dose-Rate Brachytherapy

In addition to the preoperative use of LDR brachytherapy with or without EBRT that was described previously, LDR brachytherapy

Table 92-9 Results of Preoperative Radiation Therapy for Early-Stage Endometrial Cancer

Study	No. of Patients	Stages	Radiation Techniques	Five-Year Disease-Free Survival Rate (%)	Five-Year Overall Survival Rate (%)
Grigsby et al.[168]	685	I	ICRT ± postoperative EBRT	96	88
Sause et al.[178]	112	I	ICRT	94	NR
Bruckman et al.[180]	40	II	ICRT ± EBRT	100 (LC)	80
Ritcher et al.[319]	161	I	EBRT	NR	95
Reisinger et al.[320]	30	II	EBRT ± ICRT	97 (LC)	69
Higgins et al.[181]	74	II	EBRT ± ICRT	88	NR
Baram et al.[182]	109	IB	EBRT	91	72

EBRT, external beam radiation therapy; ICRT, intracavitary radiation therapy; LC, local control; NR, not reported.

Table 92-10 Results of Postoperative Low-Dose-Rate Brachytherapy after Hysterectomy

Study	No. of Patients	Stages	Radiation Technique	Five-Year Local Control Rate (%)	Five-Year Survival Rate (%)
Aalders et al.[164]	277	I	ICRT ± EBRT	98	89
Marchetti et al.[188]	68	I	ICRT	100	97
Irwin et al.[189]	217	I	ICRT + EBRT	95	82
Greven et al.[190]	41	I/II	ICRT + EBRT	93	NR
Randall et al.[191]	102	I	ICRT + EBRT	94	NR

EBRT, external beam radiation therapy; ICRT, intracavitary radiation therapy; NR, not reported.

has been used in the postoperative setting to decrease the risk of local recurrence at the vaginal cuff (Table 92-10). In the randomized trial by Aalders and colleagues, all patients were treated postoperatively with 60 Gy of intracavitary radium and then were randomized to either an additional 40 Gy of EBRT to the pelvis or no further therapy.[164] Although the addition of EBRT resulted in improved vaginal and pelvic control, the patients who benefited the most from pelvic irradiation were those with high-grade lesions and deep myometrial invasion. Patients without these features who were treated with brachytherapy only had excellent rates of local control without the addition of external beam radiation. For patients who had less that 50% myometrial invasion and received only intracavitary radiation, the vaginal and pelvic recurrence rate was 4.3%. In addition, patients receiving brachytherapy only who had grade I tumors had a vaginal and pelvic recurrence rate of 3.6%, whereas those with grade II tumors had a local recurrence rate of 3.2%. High rates of local control with postoperative LDR brachytherapy alone in appropriately selected patients have also been seen retrospectively. In one study, 68 patients with grade I or II tumors and less than 50% myometrial invasion were treated with postoperative intracavitary radium only. At a median follow-up of 4.8 years, none of the patients experienced a vaginal recurrence.[188] For patients without significant risk factors for nodal dissemination, postoperative LDR brachytherapy alone provides excellent local control.

The role of adding a brachytherapy boost to EBRT in patients who are at risk for nodal dissemination but at low risk for local recurrence is less clear. A retrospective study from Princess Margaret Hospital described 550 patients with stage I endometrial carcinoma who were treated with surgery alone, surgery followed by EBRT, or surgery with external beam and intracavitary brachytherapy.[189] Local control rates were similar among all three groups (93% versus 94% versus 95%). Grade III or IV toxicity was higher in the patients who received both EBRT and intracavitary brachytherapy. The rate of grade III or IV bowel toxicity was 9.7% when patients received both compared to 5% when they received EBRT as their only postoperative adjuvant therapy. Vaginal stenosis was also worse for patients who received EBRT and brachytherapy (21%, grade III or worse) compared to those who received postoperative EBRT only (3%). Although the authors concluded that neither the addition of EBRT nor the addition of brachytherapy improved local control, patients who received EBRT were more likely to have greater than 50% myometrial invasion than were patients who underwent surgery alone. In addition, the majority of patients who received brachytherapy had lower uterine segment involvement, increasing their risk of local recurrence. Greven and colleagues retrospectively reviewed the outcomes of 270 patients with stage I or II endometrial carcinoma who received either EBRT alone or EBRT with the addition of a brachytherapy boost.[190] Of the 97 patients who received a brachytherapy boost, LDR was used in 41 patients. Five-year pelvic control rates were similar for those who received a brachytherapy boost and those who did not (96% versus 94%). Pelvic control rates remained similar when patients were analyzed separately by stage. In addition, a nonstatistically significant increase in grade III and IV small bowel complications was seen in the group that received brachytherapy. Other retrospective studies have also failed to demonstrate improved local control but show increased complication rates from adding intracavitary radiation to external beam radiation for patients with low risk of nodal spread.[191] Currently, it appears that for patients who are at risk for nodal spread, EBRT alone provides adequate regional and local control. For patients who are at low risk for nodal spread but have risk factors for vaginal recurrence, such as lower uterine segment involvement, the addition of postoperative brachytherapy alone provides excellent local control.

High-Dose-Rate Brachytherapy

Although there are no prospective, randomized data utilizing HDR brachytherapy, a number of retrospective and institutional studies indicate that HDR brachytherapy is an effective means of providing local control for selected patients with an acceptable level of toxicity (Table 92-11). A series from Memorial Sloan-Kettering Cancer Center examined 233 patients with stage IB grades I or II endometrial carcinoma who were treated with simple hysterectomy followed by postoperative HDR intravaginal brachytherapy consisting of 21 Gy in 7-Gy fractions at 2-week intervals.[192] The 5-year vaginal/pelvic control rate was 96%, and the 5-year overall survival rate was 94%. The actuarial rate of grade III or higher complications at 5 years was 2%. Another series from Memorial Sloan-Kettering Cancer Center examined 382 patients with stage IB to IIB endometrial carcinoma who were treated with simple hysterectomy followed by postoperative HDR intravaginal brachytherapy with a median dose of 21 Gy given in three fractions at 2-week intervals. The 5-year vaginal/pelvic control rate was 95%, and the 5-year overall survival rate was 93%. The 5-year actuarial rate of complications was 1%.[193] Noyes and colleagues performed a phase II trial on 63 patients with stage IA grade III or stage IB grade I to II disease, all of whom received HDR brachytherapy alone postoperatively.[194] Most received a total of dose of 32.4 Gy in two fractions delivered to the surface of vaginal ovoids. With a median follow-up of 1.6 years, no patient had developed a vaginal cuff recurrence. Solhjem and colleagues reviewed 100 surgically staged patients with stage I endometrial carcinoma (94% were stage IB or IC) treated with HDR brachytherapy with 21 Gy in three fractions of 7 Gy following hysterectomy.[195] At a median follow-up of 23 months, there were no pelvic or vaginal recurrences. The 3-year estimated disease-free survival rate was 93.3%. On subgroup analysis, grouping patients according to comprehensive surgical staging and stage/grade subgroups provided better predictors of pelvic control than did the GOG-99 high-risk features. For patients with stage IB grade III to IIB disease and no comprehensive surgical staging, the 5-year pelvic control rate was 86% compared to 97% in those who had undergone comprehensive surgical staging; for patients with stage IB grades I to II, the 5-year pelvic control rate was 97% without comprehensive surgical staging and 100% with comprehensive surgical staging ($P = 0.027$).[195] Anderson and colleagues reviewed 102 patients with stage IB and IC endome-

Table 92-11 Results of Postoperative High-Dose-Rate Brachytherapy Alone after Hysterectomy

Study	No. of Patients	Stages	Five-Year Local Control Rate (%)	Five-Year Overall Survival Rate (%)
Noyes et al.[194]	63	I, IIA	98	NR
Alektiar et al.[192]	233	IB2–3	96	94
MacLeod et al.[321]	141	I–II	99	91
Fanning et al.[45]	66	IG3, IC, II	100	84
Horowitz et al.[322]	164	IB, IC, II	98	87
Petereit et al.[201]	191	I	100	95
Anderson et al.[196]	102	IB, IC	97	84
Mandell et al.[197]	330	I/II	97	I: 92 II: 82
Nori et al.[198]	173	I/II	96	91
Solhjem et al.[195]	100	I	100 (23 months)	97.9 (3-year estimate)

NR, not reported.

trial carcinoma who were treated postoperatively with a relatively lower dose of HDR brachytherapy, using 15 Gy in three fractions of 5 Gy per fraction following hysterectomy.[196] Five-year locoregional control was 97% with only one patient experiencing a failure at the vaginal cuff, comparable to that found with higher doses. A number of other institutional series have demonstrated similar excellent local control with postoperative HDR brachytherapy only for appropriately selected patients. These results are similar to historical results that have been seen with LDR brachytherapy.[196]

The use of HDR brachytherapy following EBRT has been described in a number of nonrandomized series. Several studies have included both patients who received postoperative external beam radiation alone and those who received postoperative external beam with an HDR intracavitary brachytherapy boost. However, direct comparisons between these two groups is difficult in these retrospective studies, as patients receiving both modes of radiation therapy frequently have independent risk factors for local recurrence. Mandell and colleagues reviewed 330 endometrial cancer patients with either high-risk stage I or stage II endometrial carcinoma who were treated with a combination of 40 Gy EBRT and a vaginal vault boost of 21 Gy.[197] The overall pelvic and vaginal recurrence rate was 3.7%. Nori and colleagues reviewed 300 patients with stage I or II endometrial carcinoma who were treated with hysterectomy and HDR brachytherapy.[198] EBRT was given to patients with high-risk features. With a median follow-up of 12 years, the actuarial progression-free survival rate was 96.6%. Importantly, on long-term follow-up, no grade III or IV toxicities were seen in any patient. Another retrospective study examined the results of 86 stage I and occult stage II endometrial cancer patients who were treated with surgery followed by EBRT in one of three different fractionation schedules with or without intracavitary brachytherapy.[199] No difference was seen in rates of local recurrence, and on multivariate analysis, the addition of brachytherapy did not affect survival. A retrospective series from Fox Chase Cancer Center looked at 98 patients with pathologic stage I/II endometrial cancer.[200] Most patients received postoperative EBRT with an HDR brachytherapy boost; however, 17 patients received postoperative brachytherapy only. The 5-year freedom from pelvic recurrence rate for the entire population was 89%.

As with LDR brachytherapy, it remains unclear whether the addition of HDR brachytherapy to EBRT adds any benefit to local control. In addition, intravaginal brachytherapy might lead to an increased incidence of complications such as vaginal stenosis, particularly when combined with EBRT. The long-term incidence of this may be decreased with physical adhesiolysis either via use of a dilator, by stent, or through sexual intercourse. These patients require close, appropriate follow-up. Overall, these series indicate that the addition of HDR brachytherapy alone after hysterectomy results in high rates of local control in patients who are at low risk for nodal spread. There is some indication that rates of acute toxicity might be somewhat higher with the use of HDR brachytherapy.[201] The dose that is received by the surrounding normal tissue is critically dependent on positioning of the applicator and in one study was found to result to in a change in the distance from the rectal wall to the applicator of a median of 10.5 mm between two consecutive placements of the applicator.[202] It is critical that the treatment be appropriately planned and that the position of the applicator for each treatment be verified to minimize radiation dose to the surrounding normal tissues.

Radiation Therapy in the Medically Inoperable

Patients who are medically inoperable or who refuse surgery may be treated with primary radiation therapy alone. EBRT with or without vaginal brachytherapy is often used; however, in patients who are at low risk for spread beyond the uterus, vaginal brachytherapy alone may be used. Table 92-12 reviews results for radiation alone. In the work of Patanaphan and colleagues, 5-year overall survival was 46% for all patients receiving radiation alone, and the 5-year overall survival for stage I, grade I patients was only 75%.[203] Langren and colleagues retrospectively reviewed 124 stage I and II endometrial cancer patients who were treated with radiation alone.[204] Although 5-year overall survival was low, owing to the medical comorbidities of this patient population (77% for stage I, 65% for stage II), radiation alone was able to achieve acceptable rates of local control. The 5-year freedom from pelvic recurrence rate was 78% for stage I patients and 82% for stage II patients. Several institutional series have demonstrated the effectiveness of radiation alone for stage I and II endometrial carcinoma. Kupelian and colleagues reviewed 152 patients who were treated with radiotherapy alone.[205] The majority of patients (116 out of 152) were treated with brachytherapy alone. For patients with stage I and stage II disease, the 5-year disease-specific survival rate was 87% and 88%, respectively. Intrauterine recurrence was seen in 14% of patients with stage I or II disease, and extrauterine recurrence was seen in 3%. Chao and colleagues reviewed 101 patients who were treated with primary radiation therapy at Washington University.[206] All patients were either stage IA (18 patients) or stage IB (83 patients). The majority of patients were treated with both whole-pelvic irradiation and intracavitary boost, although a wide range of techniques was used. Pelvic control was achieved in 100% of stage IA patients and in 88% of stage IB patients. The 5-year disease-free survival rate was 80% for stage IA patients and 84% for stage IB.

Table 92-12 Results of Treatment with Radiation Only

Study	No. of Patients	Stages	5-Year Local Control Rate (%)	Five-Year Survival Rate (%)
Patanaphan et al.[203]	54	I	NR	75 (OS)
Langren et al.[204]	124	I, II	I: 78	I: 77 (OS)
			II: 82	II: 65 (OS)
Kupelian et al.[205]	137	I, II	86	I: 87 (DSS)
				II: 88 (DSS)
Chao et al.[206]	101	I	IA: 100	IA: 80 (DFS)
			IB: 88	IB: 84 (DFS)
Fishman et al.[207]	54	I, II	NR	I: 80 (CSS)
				II: 85 (CSS)

CSS, cancer-specific survival; DFS, disease-free survival; DSS, disease-specific survival; NR, not reported; OS, overall survival.

In another series from Yale University, 54 patients with medically inoperable stage I or II endometrial adenocarcinoma were treated with radiation alone.[207] These patients were matched 2:1 by age, stage, and grade with patients who underwent surgical treatment for their endometrial cancer. The cancer-specific survival rate was somewhat worse for patients who underwent primary radiation treatment. For stage I patients, the 5-year actuarial cancer-specific survival rate was 80% for patients who were treated with radiation alone compared to a 5-year cancer-specific survival rate of 98% for those who underwent surgery. For stage II patients, the 5-year actuarial cancer-specific survival rate was 85% and 100% for inoperable and operable patients, respectively. A significant difference in the 5-year overall survival rate was seen between inoperable and operable patients (30% and 24%, respectively, for stage I and stage II inoperable patients versus 88% and 85%, respectively, for stage I and stage II operable patients). However, for patients receiving radiation only who did not die of intercurrent illness, there was no significant difference in medial survival between inoperable and operable patients.

For patients who are not good candidates for surgical removal of the uterus owing to coexisting medical conditions and who are at low risk for nodal spread, brachytherapy alone may be used as the primary treatment for their endometrial cancer. Although LDR brachytherapy may require anesthesia, it can also be performed with an epidural anesthesia in some patients. It is less invasive than hysterectomy and is generally well tolerated with a low procedural complication rate.[208] Grigsby and colleagues reviewed the outcomes of 26 stage II patients who were treated with LDR intracavitary brachytherapy alone.[179] The 5-year disease-free survival rate was found to be 53% in this group with a high major complication rate of 19%. In another retrospective study, the 5-year disease-free survival rates for stage IA, IB, and II disease treated with HDR brachytherapy alone were reported to be 85%, 73%, and 69%, respectively.[209] Another study reported a 3-year disease-free survival rate of 85% in stage I medically inoperable endometrial cancer patients who were treated with HDR brachytherapy alone; however, complication rates were again high at 21%.[210] Overall survival is low in these patients, owing to their medical comorbidities and complication rates higher than those in medically operable patients. The results of brachytherapy alone are worse than those of treatment that includes surgical resection, even for very early-stage disease; however, it does offer a reasonable option for treatment in patients who are poor surgical candidates.

No studies have been conducted in a randomized fashion that directly compare radiation alone and surgery alone for early-stage endometrial cancer. Surgery remains the treatment of choice for patients who are medically fit; however, for patients who are medically inoperable, radiation therapy alone offers a viable alternative for treatment and provides adequate rates of local control.

TREATMENT OF ADVANCED ENDOMETRIAL CANCER

Although the majority of patients who are diagnosed with endometrial cancer present with early-stage disease, 10% to 15% have advanced disease at presentation. This includes patients with positive pelvic and para-aortic lymph nodes, local invasion into other pelvic organs, pelvic recurrence at the vaginal cuff or in pelvic lymph nodes, and distant metastases. Patients may be categorized as having pathologic stage or clinical stage III and IV disease. Hysterectomy remains the primary treatment for any operable advanced-stage cancers. Radiation therapy is often used postoperatively to reduce the risk of local recurrence, to treat areas of residual disease or to palliate symptoms related to recurrent cancer. It may also be used preoperatively in technically inoperable patients or even as the primary therapy in patients with medically inoperable disease. While radiation therapy has not been shown to improve overall survival in these situations, it is very effective therapy for both locoregional control and palliation. Adjuvant radiation has a particularly important role in endometrial cancer, given relatively low response rates to chemotherapeutic agents.

The GOG has conducted a phase III randomized trial for advanced endometrial cancer patients. GOG Protocol 122 randomized 422 patients with stage III or IV endometrial carcinoma with maximal postoperative residual disease of 2 cm to whole-abdominal irradiation versus cisplatin and doxorubicin systemic chemotherapy every 3 weeks for eight cycles.[211] The radiation arm was treated to 30 Gy and included a pelvic boost (15 Gy) to the true pelvis or to an extended field encompassing pelvic and para-aortic lymph nodes. An extended field boost was used in the case of positive para-aortic nodes or in patients whose para-aortic lymph nodes were not sampled. The median dose was 45 Gy for whole-abdominal irradiation plus the boost. Approximately 84% of patients completed radiation therapy, and 63% completed the eight cycles of chemotherapy. Fifty-four percent of patients in the radiation arm and 50% in the chemotherapy arm had a documented tumor recurrence. The hazard ratio for progression adjusted for stage was 0.71 favoring the chemotherapy arm ($P < 0.01$). At 60 months, 50% of patients who received chemotherapy were predicted to be alive and disease free compared with 38% of patients who received radiation, when adjusted for stage. The most common acute toxicities were grade III to IV toxicities—hematologic followed by gastrointestinal—and were significantly more common in the chemotherapy arm. There were eight treatment-related deaths in the chemotherapy arm and five deaths in the radiation arm. The GOG Protocol 184, which has completed accrual but for which results are pending, included a similar patient cohort, all of whom received pelvic radiation with or without para-aortic

fields and then were randomized to cisplatin and doxorubicin with or without paclitaxel.

Treatment of Advanced Endometrial Cancer by Stage

Pathologic Stage III Endometrial Cancer

Results of therapy for stage III disease depend on whether patients have pathologic stage III diagnosed after surgical staging or present with clinical stage III disease. Surgically staged III disease includes those with stage IIIA due to positive washings alone or microscopic extension to the serosa or adnexae, IIIB due to vaginal metastasis, or IIIC due to microscopic lymph node involvement. Clinical stage III disease involves gross extrauterine extension, pelvic adenopathy that is detectable on preoperative scans, or clinically evident vaginal extension. Thus, clinical stage III disease comprises bulkier tumors by definition and often includes patients who require radical surgery, such as an exenteration, or those who are technically inoperable. Inevitably, outcomes are poorer for these patients. For surgically treated pathologic stage III patients overall who are treated with hysterectomy and postoperative radiation, a 5-year disease-free survival rate of 64% and a pelvic recurrence rate of 21% have been reported.[212] Predictors of survival include grade, depth of invasion, number of extrauterine sites of disease, and uterine serous or clear cell histology. Grade is the strongest predictor of pelvic recurrence; histology and number of extrauterine sites predict for abdominal recurrence.

Pathologic Stage IIIA

Surgical stage IIIA represents a heterogeneous group of disease. The most favorable subgroup of stage IIIA patients are those with positive peritoneal washings as their sole criterion of advanced disease, which occurs in about 5% of patients. Such patients have a favorable outcome, with or without adjuvant therapy.[213] The selection of adjuvant treatment of these patients is controversial, and the prognostic significance of this finding remains uncertain. About 10% of patients with FIGO stage I endometrial cancer have positive peritoneal washings. Over half of all patients with positive pelvic washings will also have adnexal or other areas of pelvic spread of disease. This finding is associated with depth of invasion, high-grade and positive nodes, and positive cytology and is predictive of survival.[214,215] Table 92-13 shows the results from series examining the impact of positive cytology, with recurrence rates ranging from 0% to 46% and disease-free survival rates of 17% to 100%, highlighting the difficulty in interpreting positive cytology as a prognostic marker. Overall, peritoneal cytology often fails to identify any additional patients who are candidates for postoperative therapy that are not identified by grade and depth of invasion.

Despite data suggesting a poorer prognosis for these patients, only a few series have reported exclusively on outcomes in pathologic stage IIIA patients. In a series by Creasman and colleagues, 26 patients with stage I disease and positive peritoneal washings had a 34% recurrence rate compared to 9% among women with negative washings.[216] Of thirteen patients with no extrauterine disease and positive cytology, 46% died of disseminated intraperitoneal recurrence. Thus the investigators subsequently treated 23 patients with malignant washings with intra-abdominal P-32 colloid postoperatively. They concluded that P-32 therapy was efficacious, as none of these patients had any pelvic or abdominal recurrence, although three developed distant disease. In a report by Soper and colleagues, 65 women with clinical stage I to III endometrial cancer with malignant cytology were treated with intraperitoneal radioactive P-32 suspension demonstrated an 8% intraperitoneal recurrence rate, most with simultaneous extraperitoneal metastases.[217] Chronic bowel problems were not seen in patients who received P-32 alone but occurred in 29% of women who also received external irradiation to the pelvis, including two deaths. Potish has described 5-year relapse free survival rate

Table 92-13 Results for Stage IIIA with Positive Peritoneal Washings Only

Study	No. of Patients	Adjuvant Treatment	Recurrence Rate (%)	Disease-Free Survival Rate (%)
Turner et al.[323]	28	None	32	84 (5-year OS)
Yazigi et al.[324]	10	None	10	87 (5-year OS)
Zuna and Behrens[325]	8	None	—	17
Morrow et al.[151]	14	None	7	76 (5-year RFI)
	18	Pelvic RT	28	(all patients)
Creasman et al.[216]	13	None	46	—
	23	IP P-32	13	—
Soper et al.[217]	43	IP P-32 (all)	8	89
		Pelvic RT-3; ICRT		
Lurain et al.[326]	30	Pelvic RT; ICRT; CT or hormones	17	—
Konski et al.[98]	11	Pelvic RT	9	100
	8	WART	25	75
Martinez et al.[327]	18	WART	11	73
Mazurka et al.[220]	16	Hormones or CT ($N = 13$)	25	—
Piver[221]	25	Progestins	0	100
Kennedy et al.[124]	14	Various (CT, P-32, hormone)	—	67
Harouny et al.[328]	41	Various (preoperative RT, pelvic RT, CT, hormone)	29	71

CT, chemotherapy; ICRT, intracavitary radiation therapy; IP, intraperitoneal; OS, overall survival; RFI, recurrence-free interval; RT, radiation therapy; WART, whole-abdominal radiation therapy.

of 77% of women with microscopic peritoneal spread treated with whole-abdominal radiation and an overall 4% rate of bowel obstructions.[218] The use of adjuvant radiation in patients with positive cytology as the only evidence of extrauterine spread remains controversial, although it is frequently offered. Whether to offer pelvic or whole-abdominal radiation remains unclear.

Hormonal therapy with progestins or systemic chemotherapy has also been used as an adjuvant treatment in small groups of patients with isolated positive washings. These small series report relapse rates of 0% to 25% and a disease-free survival rate of 67%, compared to 85%.[219,220] Piver conducted a pilot study of 25 patients with surgical stage I disease and malignant pelvic washings who were treated with progesterone.[221] Twenty-two patients underwent a second-look laparoscopy, and 95% had no evidence of disease with negative washings. One patient with persistent positive washings was treated with an additional year of progestins and remained free of disease. Although these data are intriguing, too few patients have been treated exclusively with hormonal therapy to assess the efficacy of this therapy compared to adjuvant radiation, although either treatment appears superior to no adjuvant therapy. Most patients will have other risk factors for pelvic or distant recurrence that guide treatment decisions, including grade, depth of invasion, and lymphovascular space invasion.

Patients with pathologic stage IIIA disease due to isolated adnexal involvement also make up a more favorable subset among stage III patients. Invasion may occur by direct transtubal invasion or may be due to lymphatic spread. Some of these patients might have concurrent early-stage ovarian cancers as well; therefore, careful pathologic assessment is warranted. The GOG reported that 5% of surgically staged patients with clinical stage I disease had adnexal involvement.[50] This pathologic finding is associated with a 32% risk of pelvic lymph node metastases, and 23% of patients have para-aortic lymph node spread. In the largest reported subgroup of 42 patients with isolated adnexal involvement, Greven and colleagues noted a 5-year survival rate of 60%, compared to 54% for the entire group of pathologic stage III patients.[212] The grade and depth of myometrial invasion further defined the prognosis for these patients, in whom high grade reduced the survival rate to 40% and invasion through greater than one third of the myometrium resulted in a 47% survival rate. Most patients had received postoperative pelvic irradiation with or without a boost. Isolated abdominal failure in this series was uncommon, at 7%. Nori and colleagues analyzed a group of patients who were treated with surgery and either preoperative or postoperative pelvic irradiation with an intravaginal boost, which included 21 patients with microscopic involvement of the adnexae and 12 patients with gross adnexal involvement.[222] The 5-year survival rate was better for those with microscopic invasion (80%) than for those with gross invasion of the adnexae (40%), even though this was the only extrauterine disease. Several other smaller series that analyzed this subset of patients have reported 5-year relapse free survival rates from 60% to 90% in patients who were treated postoperatively with either pelvic[223,224] or whole-abdominopelvic radiation.[225,226] Overall, the small patient numbers in these reports preclude any conclusion as to the relative efficacy of pelvic versus whole-abdominal radiation in this subset. Adjuvant pelvic therapy is generally offered to patients who do not have significant comorbidities.

Pathologic Stage IIIB

Stage IIIB is a very uncommon presentation. It is generally treated with a combination of EBRT and intracavitary or interstitial brachytherapy.

Pathologic Stage IIIC

The patients who are at highest risk for recurrence are those with positive pelvic or para-aortic lymph nodes. The GOG examined pathologic factors in clinical stage I to II endometrial cancer patients.[50] In their series of 1180 women, 13% (3% grossly positive) overall had positive pelvic nodes, and about one third of patients with positive pelvic nodes were also documented to have para-aortic nodal metastases. Lymph nodes were involved in 51% of women with extrauterine disease, 32% with adnexal invasion, and 25% with deep myometrial invasion. Patients with positive pelvic nodes who were treated with postoperative pelvic irradiation had a 5-year disease-free survival rate of 72%. The presence of positive pelvic lymph nodes only was more favorable than was involvement of the para-aortic nodes as well. There was a recurrence rate of 28% for those with positive pelvic nodes compared to 40% for those with positive aortic nodes. Of patients with positive para-aortic nodes, 77% received postoperative radiation with a 5-year disease-free survival rate of 36%. A small study of 17 patients with nodal spread confined to the pelvic nodes, all of whom received postoperative radiation, reported a 5-year overall survival rate of 72%.[227] Better survivals have been reported for patients who present with microscopically positive lymph nodes versus grossly involved nodes. One series reported a mean survival greater than 60 months if nodes were microscopically involved compared to 35 months for macroscopically involved nodes.[228]

Outcomes with adjuvant radiation (with or without systemic therapy) have been retrospectively reviewed, although treatment techniques have varied significantly. Table 92-14 reviews the results of various series. In a recent study of 47 patients with stage IIIC disease, 36% had whole-abdominal radiation, 19% had extended pelvic and para-aortic nodal irradiation, and 17% had pelvic irradiation alone.[229] In addition, 17% were treated with chemotherapy and 11% with progestins. The 5-year overall survival rate was 65%, with distant metastases seen in 21% and pelvic recurrence in 9%. Predictors of failure included depth of invasion and positive cytology or adnexal involvement. The role of the various adjuvant treatments used, however, could not be clearly defined. Patients in whom nodal disease is confined to the pelvic lymph nodes and whose para-aortic lymph node sampling is negative are still at risk for para-aortic recurrence. Mundt and colleagues reported on 30 stage IIIC patients, all with positive pelvic nodes, and 54% with positive para-aortic lymph nodes, all treated with TAH-BSO followed by pelvic or extended field radiation.[230] They noted a 5-year disease-free survival rate of 34%, with 23% of patients experiencing pelvic failure (including four vaginal failures), 13% experiencing abdominal failures, and 13% experiencing para-aortic failures; 40% developed distant metastases. No patient who was treated with extended field irradiation developed a para-aortic nodal recurrence, although 8 of 10 had positive para-aortic nodes at the time of surgery. Treatment was well tolerated, with only two late sequelae (one chronic enteritis and one bowel obstruction).

For patients with positive para-aortic nodes and no other abdominal disease, the optimal radiation field arrangement remains uncertain. Potish and colleagues reported on 48 women who were treated with extended para-aortic fields, half of whom had abnormal lymphangiograms and half of whom had pathologically documented nodal metastases. They found that 88% of recurrences were outside the radiation fields, including 44% of first failures in the abdomen.[231] In this series, the survival rate was better in clinically staged patients than in surgically staged patients (57% versus 47%), suggesting an uncertainty in clinical staging of nodal disease. Corn and colleagues examined outcomes in 50 women, 26 with pathologically staged para-aortic nodal involvement and 24 who had been diagnosed with lymphangiography, who were treated preoperatively and postoperatively or primarily with extended field radiation.[232] Para-aortic lymph node dissection significantly decreased the para-aortic failures, and the authors noted only three abdominal failures. Two other series looked at the impact of extended field irradiation in patients all with pathologically documented para-aortic nodal spread. In one group of 26 patients, 17 received extended field radiation treatment, most with adjuvant megestrol acetate (Megace), and the remaining 9 patients received megestrol acetate or chemotherapy alone.[233] The overall

Table 92-14 Results for Stage IIIC Patients with Positive Pelvic or Para-aortic Lymph Nodes

Author	No. of Patients	Treatment	Relapse Rate (%)	Five-Year Survival Rate (%)
Nelson et al.[227]	17 (+ pelvic LNs only)	PRT or WART	PA LNs: 12 DM: 12	72
McMeekin et al.[229]	47	WART; EFRT; PRT; ± CT or progestins	Pelvic: 9 DM: 21	65
Martinez et al.[327]	8	WART, PA + pelvic boost	NS	70 (RFS)
Mundt et al.[230]	30	PRT or EFRT	Pelvic: 23 DM: 40 PA LNs: 13 Abdomen: 13	34 (DFS)
Rose et al.[233]	17	EFRT + Megace	DM: 29	53
Onda et al.[234]	20	CT + EFRT	NS	75 (+ PA LNs) 100 (+ pelvic LNs only)

DFS, disease-free survival; DM, distant metastases; EFRT, extended field radiation therapy; NS, not stated; PA LNs, para-aortic lymph nodes; PRT, pelvic radiation therapy; RFS, relapse-free survival; WART, whole abdominal radiation therapy.

survival rate was significantly improved in the irradiated group (53% versus 22%). In the second series, 20 patients with para-aortic metastases received three cycles of postoperative chemotherapy followed by extended field irradiation.[234] The 5-year survival rate was 75% for positive para-aortic nodes, compared to 100% if only the pelvic nodes were positive. Reported series of patients treated with whole-abdominal radiation have represented heterogeneous stage and histologic groups and generally included small numbers of patients with para-aortic metastases as the primary reason for whole-abdominal radiation fields. Adjuvant therapy with combination chemotherapy combined with involved field radiation has been reported in advanced endometrial cancer.[235–237] These protocols were well tolerated. Additional trials are required to determine long-term survival.

Clinical Stage III and IV Disease

The FIGO staging system from 1971 is based on findings on clinical examination.[238] In that era, fewer patients were treated with surgery, and primary irradiation was often used. Clinical stage III endometrial cancer was defined as carcinoma extending outside the uterus but not outside of the true pelvis. Stage IV disease included invasion of the bladder or rectum or disease beyond the true pelvis.

Clinical Stage III

Treatment for clinical stage III endometrial cancer has included radiation alone or surgery and radiation. Grigsby and colleagues reported on a series including 27 patients with clinical stage III disease who were treated with total hysterectomy and salpingo-oophorectomy combined with preoperative or postoperative irradiation.[239] The 5-year disease-free survival rate was 33%, with a distant metastatic rate of 48% and pelvic recurrences in 33% of patients. Aalders and colleagues compared outcomes in 108 clinical stage III patients with outcomes of 67 patients with pathologic stage III disease.[240] Radical surgery was possible in 70% of pathologic stage III patents compared to only 13% of those with clinical stage III; thus, 66 patients were treated with radiation alone. Surgical debulking was an important prognostic factor. The 5-year overall survival rate was 16% versus 40% for clinical and pathologic stage III, respectively. In the series by Greven and colleagues, 52 patients had clinical stage III disease, and 20 of these patients had radiation alone after biopsy.[212] The overall survival rate for this stage was 36%, with a median survival of 9 months for patients who were treated with radiation alone compared to 60 months for patients treated with surgery and radiation. The radiation-only group also demonstrated very poor pelvic control, with 89% pelvic failures. In the combined treatment group, the 5-year survival rate was 48%, with 40% pelvic failures. Isolated abdominal failure was much less common at 6%, but 38% of patients overall had a component of abdominal failure, and 16% developed distant metastases alone. Thus, while a combined treatment approach of surgery and adjuvant irradiation results in outcomes that are superior to those of radiation alone for clinical stage III patients, they still experience a high rate of pelvic and abdominal failures.

In some patients with locally advanced disease, surgery might be able to achieve only debulking. Bulky residual disease has been defined as more than 2 cm of residual tumor after primary surgery. This may include pelvic implants, residual nodal disease, or intraperitoneal deposits. There appears to be a benefit with respect to recurrence and survival if tumor is optimally debulked. Surgery is then followed by adjuvant irradiation to the pelvis, para-aortic nodes, or whole abdomen, as indicated by the location of residual disease.

Whole-abdominal radiation for bulky residual disease appears to be inadequate, and patients with greater than 2 cm of residual disease are seldom controlled.[226] This may be related to the lower radiation doses that are achievable in whole-abdominal treatment, owing to limitations of dose tolerance for the small bowel, liver, and kidneys. Limited field boosts to areas of bulky residual disease should be considered, particularly for para-aortic nodes, which can be treated to higher doses without exposing the liver or kidneys to excessive radiation. For patients with bulky disease confined to the pelvis, preoperative radiation may be considered to improve the likelihood of optimal surgical resection.

Clinical Stage IV

Patients with stage IVA disease, presenting with invasion of the bladder or rectum, with or without lymph node metastases, should be treated similarly to patients with stage III disease: with combined surgery and radiation with or without systemic therapy. Preoperative radiation may be considered in patients who are marginally operable or inoperable but with disease confined to the pelvis. Although little data exist for this approach in endometrial cancer, it has been used successfully in a variety of other pelvic malignancies. Patients who present with stage IVB disease are rare and are most often treated palliatively. Residual or progressive pelvic disease can be a major source of symptomatology for these patients. The 5-year survival rate is approximately 0% to 10%.[241,242] Surgical debulking may be of benefit or may be considered for palliation of symptoms. In a study

of surgical cytoreduction in 65 stage IVB patients, optimal debulking to less than 1 cm residual was accomplished in 55%.[243] Those patients had a significantly improved median survival of 34 months versus 11 months for those with bulkier residual disease. Among those with optimal cytoreduction, adjuvant chemotherapy or radiation was associated with improved survival. In another series of patients with stage IV disease, including 24 patients who had optimal debulking to less than 2 cm of residual disease and 31 patients with bulkier residual or unresectable peritoneal carcinomatosis, median survivals were 31, 12, and 3 months, respectively.[244]

For inoperable patients with advanced disease, palliative radiation therapy should be considered. Stage IV patients are also candidates for systemic chemotherapy or hormonal therapy. Bulky disease requires high-dose irradiation even for palliation. Unfortunately, owing to poor tolerance of the bowel to high-dose fractions of radiation, palliative treatment can require several weeks of daily therapy. Conventional doses of 45 to 55 Gy of external irradiation may be followed by LDR or HDR brachytherapy depending on the location and extent of disease. Palliation of bleeding may also be accomplished with brachytherapy alone, which is useful for debilitated patients. In one group of 27 patients with endometrial cancer who were not thought to be surgical candidates, usually because of age or comorbidities, one to three doses of 10-Gy fractions to the pelvis were delivered.[245] Bleeding resolved in 90%, malodorous discharge was reduced in 38%, and 22% had a complete tumor response, with a median survival of 9 months. Only three patients had significant bowel effects. The Radiation Therapy Oncology Group reported a phase II trial in patients with advanced pelvic malignancies who were treated with accelerated split-course irradiation consisting of three courses over 6 days in 12 fractions with 2- or 4-week breaks between courses.[246] Patients who completed all three courses had a 42% response rate, and therapy was well tolerated.

For patients who present with distant metastases or with distant relapses after primary therapy, chemotherapy or hormonal therapy is the mainstay of initial treatment. The most common sites of distant metastases are lung (35%), liver (29%), omentum or peritoneum (25%), gastrointestinal tract (21%), and bone (15%), with rare instances of adrenal (10%) or brain (6%) involvement.[247] Radiation is rarely used for visceral disease; however, palliative irradiation is indicated for specific situations, including painful bony metastases, symptomatic brain metastases, spinal cord compression, and airway obstruction. Short courses of hypofractionated radiation are most commonly employed over 1 to 2 weeks. Therapy is delivered to the whole brain or to the painful portion of involved bone.

SYSTEMIC THERAPY FOR ENDOMETRIAL CANCER

Chemotherapy

The role of chemotherapy in early-stage endometrial cancer is limited. The primary pattern of failure in these patients is locoregional; therefore, the benefit of adding systemic therapy is reserved mainly for patients with more advanced disease. However, for certain high-risk, early-stage tumors, particularly those with clear cell or uterine serous histology, systemic dissemination remains a substantial risk. The use of chemotherapy has been examined in these patients. At M.D. Anderson Cancer Center, 62 patients with high-risk stage I or clinically occult stage II endometrial cancer including grade III tumors, deep myometrial invasion, or high-risk histology (clear cell or uterine serous) were prospectively treated with postoperative cisplatin, doxorubicin, and cyclophosphamide chemotherapy.[248] The addition of chemotherapy did not appear to decrease the rate of distant failure in women who presented with extrauterine disease; however, for patients who presented with uterine-confined disease, the recurrence rate was 24%, with an observed progression-free interval of greater than 36 months. A small prospective study from Sweden treated 31 patients with stage I, grade III or uterine serous histology endometrial cancer patients with hysterectomy, postoperative radiation, and chemotherapy consisting of cisplatin and epirubicin.[249] With a median follow-up of 32 months, none of the patients were found to have recurrent disease. Two recent retrospective studies evaluated the efficacy of chemotherapy in surgical stage I uterine papillary serous cancer.[250,251] In particular, Kelly and colleagues showed improved disease-free and overall survival in stage I patients who received platinum-based chemotherapy.[251] Vaginal brachytherapy should be considered to improve local control.

The GOG attempted to address the issue of chemotherapy following surgery and postoperative radiation therapy in high-risk, early-stage endometrial cancer patients. However, the study included patients with nodal metastases as well as adnexal metastases. There were also a high number of protocol violations and patients who were lost to follow-up, making a more definitive analysis of outcome difficult. Although the results of these small trials are promising, chemotherapy is rarely used in early-stage patients, owing to the risk of increased toxicity with chemotherapy and the lack of definitive data documenting a benefit. As a general practice, chemotherapy remains reserved for patients with more advanced or metastatic endometrial cancer.

Adjuvant chemotherapy for women with recurrent or advanced endometrial cancer has not been shown to prolong survival in comparison to more traditional treatment with radiation. Only one large randomized trial has studied the effect of adjuvant chemotherapy. In 1990, Morrow and colleagues treated 181 patients who had poor prognostic factors with postoperative radiation therapy.[252] Patients were then randomized to either observation or treatment with intravenous doxorubicin to a total dose of 500 mg/m^2. No significant difference in recurrence rates was noted between the two groups.

A variety of different single-agents have been studied in phase II trials for the treatment of metastatic or recurrent disease. Drugs with a reported response rate of over 20% include 5-fluorouracil, cyclophosphamide, ifosfamide, doxorubicin, platinum, and paclitaxel. In particular, paclitaxel has been reported to elicit a response rate of 27% to 38% when used in the first- and second-line setting.[253–255]

Several multiagent combinations have also been tested. The GOG randomized patients to receive doxorubicin or cisplatin plus doxorubicin.[256] A significant improvement was noted in both response rate (45% versus 27%) and progression-free survival (13 months versus 8 months) for the combination. GOG 107 randomized 281 patients to receive doxorubicin or doxorubicin plus cisplatin.[257] The addition of cisplatin improved the overall response rate, with 19% complete responses and 23% partial responses compared to 8% and 17%, respectively, for single-agent doxorubicin. The overall response rate was statistically significant ($P = 0.004$). The progression-free survival rate was also improved, with a median of 5.7% versus 3.8%. However, overall survival was similar in both groups, with increased toxicity seen in the combination group. A smaller study conducted by the EORTC Gynecological Cancer Group showed similar results, though no significant difference in overall survival was noted.[258] The combination of paclitaxel and carboplatin has also been investigated, with reported response rates ranging from 47% to 87%.[259–262] The GOG has completed two additional trials of combination therapy for patients with advanced or recurrent endometrial cancer. A phase III randomized study demonstrated that 24-hour paclitaxel/doxorubicin/granulocyte-colony stimulating factor (G-CSF) was not superior to the combination cisplatin/doxorubicin in response or survival.[263] A second phase III randomized study compared 3-hour paclitaxel/doxorubicin/cisplatin/G-CSF with doxorubicin/paclitaxel.[264] The combination of paclitaxel/doxorubicin/cisplatin/G-CSF significantly improved the response rate, the progression-free survival rate, and overall survival. The GOG is currently evaluating paclitaxel/doxorubicin/cisplatin/G-CSF compared to carboplatin and paclitaxel in advanced or recurrent endometrial cancer.

Hormonal Therapy for Endometrial Cancer

The mainstay of hormonal therapy for endometrial cancer consists of treatment with progestins, either megestrol acetate or medroxyprogesterone acetate. These agents yield overall response rates ranging from 15% to 25%. Dose does not appear to be related to response. Thigpen and colleagues randomized 299 women with advanced or recurrent endometrial cancer to receive either 200 mg or 1000 mg of medroxyprogesterone acetate daily.[265] The overall response rate was 25% in the women on the low-dose regimen, compared to 15% for those on the high-dose regimen. Median progression-free survival for both groups was approximately 2 to 3 months. Lentz and colleagues administered high-dose megestrol acetate at 800 mg daily to women with advanced or recurrent endometrial cancer and noted a 24% overall response rate, similar to lower-dose regimens.[266]

Tamoxifen is the most widely studied nonprogestational hormonal agent for the treatment of endometrial cancer. In a review of eight studies, Moore and colleagues reported a pooled response rate of 22%.[267] Other agents such as goserelin acetate, danazol, and anastrozole have demonstrated very limited activity.[268–270] In phase I and II trials, arzoxifene demonstrated clinical response rates of 25% to 31% in recurrent endometrial cancer.[271,272]

For the highly selected patient, there is a role for conservative primary hormonal therapy.[273] Women with grade I adenocarcinomas who have not completed childbearing and for whom hysterectomy is unacceptable may be managed with progestational agents. The optimal regimen has yet to be determined. These patients must be carefully counseled regarding the risks of this conservative approach.

Systemic Therapy for Uterine Sarcoma

Uterine sarcomas display a high rate of recurrence, even in the setting of stage I disease, and tend to recur at distant sites, making the need for effective systemic chemotherapy a pressing issue. There is currently no proven role for chemotherapy in the adjuvant treatment of completely resected stage I disease. Omura and colleagues randomized 156 patients with stage I and II uterine sarcomas to either observation or adjuvant doxorubicin.[274] No statistical difference was detected in recurrence rate, progression-free interval, or overall survival. For single-agent treatment of patients with advanced or recurrent carcinosarcoma, ifosfamide (30% response rate for chemotherapy-naive patients[275]) and cisplatin (18% to 19% response[276,277]) have demonstrated the most activity. A recent study of paclitaxel has also exhibited moderate activity, with an 18% response rate.[278] Combination therapy with cisplatin and ifosfamide may offer a small improvement over single-agent therapy in progression-free interval, though no improvement in overall survival has been noted.[279] The combination of ifosfamide and paclitaxel was investigated in patients with advanced or recurrent uterine carcinosarcoma. The regimen was tolerable, with a crude overall response rate of 45%.[280] Currently, the GOG is evaluating the combination therapies docetaxel/gemcitibine and paclitaxel/carboplatin in patients with carcinosarcoma.

For patients with leiomyosarcoma, doxorubicin has shown to be the most effective single-agent (25% response rate), though ifosfamide has also demonstrated some antitumor activity.[280,281] The combination of gemcitabine and docetaxel has been shown to be tolerable, with a 53% overall response rate.[283] For leiomyosarcoma, resection of retroperitoneal lymph nodes will rarely provide useful information, given the lower incidence of nodal involvement.[284]

Owing to its rarity, ESS has not been well studied in clinical trials. Low-grade ESS are slow-growing tumors with an indolent course that respond well to hormonal therapy. High-grade ESS behaves more aggressively. The GOG demonstrated a 33% response rate among 22 patients with recurrent or metastatic high-grade ESS who were treated with ifosphamide.[285]

COMPLICATIONS OF TREATMENT

Overall, surgery, including staging of lymph nodes, is well tolerated; however, the addition of lymphadenectomy to TAH-BSO does increase the risk of vascular injuries, hematomas, and lymphocysts.[286] In addition, around 10% to 20% of patients who undergo lymphadenectomy develop lower-extremity lymphedema.[287] The addition of adjuvant radiation to lymphadenectomy has also been show to increase postoperative hospitalization rates and result in a higher rate of severe complications.[288,289] The risk of complications from lymphadenectomy has been shown to be related to the number of lymph nodes that are removed at the time of surgery.[290] Despite these increased risks, the importance of accurate lymph node staging cannot be overstated, and surgical staging of lymph nodes should be performed in appropriately selected patients.

Although pelvic radiation is generally well tolerated, the acute and long-term effects of this treatment have been well documented. Long-term follow-up from the PORTEC trial revealed that the 5-year actuarial rate of late complications of grade I to IV was 26% in the patients who received radiation compared to 4% in those who did not ($P < 0.0001$).[165] Although 63% of the patients experienced some degree of acute toxicity, the majority of these patients had symptoms that resolved without further complications, and only 2% of patients discontinued their treatment because of their symptoms. However, the most important predictor of long-term toxicity was found to be the presence of acute symptoms. These rates of complications are similar to those in other series in which whole-pelvic irradiation has been delivered, either preoperatively or postoperatively.[291] In an attempt to decrease the radiation dose that is received by the surrounding normal tissues, several recent studies have examined the dosimetric advantages of using intensity-modulated radiation therapy in the treatment of endometrial carcinoma. The results of these studies suggest that the volume of normal tissue, namely, the bladder, rectum, and small bowel, that receives high doses of radiation can be significantly reduced while still delivering adequate coverage of the postoperative planning target volume.[292,293] The potential advantages of intensity-modulated radiation therapy in decreasing normal tissue toxicity must be weighed against the potential risk of decreased margin on the target volume and an increased volume of normal tissue receiving low doses of radiation. This increases the need for proper patient positioning and adequate immobilization in order to minimize treatment-to-treatment variations in patient position. Because of its potential to deliver a highly conformal radiation dose, intensity-modulated radiation therapy holds promise in improving the toxicity profile of pelvic irradiation. However, further studies are needed to assess the long-term outcome in patients who are treated with intensity-modulated radiation therapy.

When extended field or whole-abdominal irradiation is given, the treatment technique must minimize the exposure to normal tissues, in particular to the small bowel, liver, and kidneys. The most common acute effects of large abdominopelvic radiation fields are acute gastrointestinal symptoms, including nausea, vomiting, diarrhea, and cramping. Loss of fluid and electrolytes through vomiting and diarrhea can lead to acute dehydration, so antiemetics and antidiarrheals should be prescribed early in therapy, and patients should be monitored closely. Myelosuppression through exposure of the bone marrow may also occur; therefore, blood counts should be monitored, and supportive therapy should be given accordingly. Four field pelvic arrangements including anterior, posterior, and lateral fields often allow for blocking of anterior segments of the small bowel. When the para-aortic nodes or whole abdomen is treated, larger volumes of small bowel are inevitably included, leading to a greater likelihood of acute enteritis. Typically, the whole-abdomen dose is limited to a range of 25 to 30 Gy, keeping the exposure of the kidneys to less than 20 Gy and exposure to the whole liver less than 22 to 25 Gy. Doses beyond 45 to 50 Gy to large volumes of small bowel will significantly increase the risk of late complications. Series using these dose parameters and techniques report late bowel complications, primarily small bowel obstruction, in 3% to 12% of patients for extended field irradiation[230,234] and in 0% to 9% of patients for whole-abdominal irradiation.[218,294–296]

TREATMENT OF RECURRENT DISEASE

Incidence of Pelvic Recurrence

Recurrence in the pelvis after hysterectomy is a common site of relapse in patients with endometrial cancer. Most locoregional recurrences are diagnosed in the first 2 to 3 years after initial treatment. For patients who present with pathologic stage I to II disease, the main risk factors for pelvic recurrence are high-grade histology and myometrial invasion greater than one third to one half of the myometrial width. With no postoperative adjuvant therapy, the pelvic recurrence risk for these patients has been reported to be 10% to 40%. This is reduced to less than 5% with adjuvant pelvic irradiation, with or without a vaginal brachytherapy boost.[164,297,298] The distant metastatic rate and overall survival rate are not altered by the addition of adjuvant pelvic irradiation. Most series have reported failures as total pelvic recurrences, including the vaginal cuff, pelvic lymph nodes, or other limited pelvic sites. High-risk stage I patients, such as those with high-grade or deep invasion, appear to have a 15% risk of vaginal recurrence at 10 years when treated with initial surgery alone.[299] The GOG conducted a randomized study comparing surgery alone to surgery and postoperative pelvic irradiation for "intermediate-risk" patients, including stage IB, stage IC, and occult stage II (GOG Protocol 99).[166] Whole-pelvic radiation reduced the risk of recurrence by 58%. When patterns of recurrence were examined, there were 13 vaginal recurrences among 202 women who were randomized to surgery alone (6%), compared to 2 vaginal recurrences in 190 (1%) women who were randomized to adjuvant irradiation. For vaginal and pelvic recurrences combined, there were 18 in the surgery-alone arm compared with 3 in the adjuvant radiation arm. Patients with extrauterine disease have a higher risk of pelvic recurrence, which depends on the type and number of extrauterine sites.

A group of Dutch institutions conducted the PORTEC randomized trial of surgery alone (without lymphadenectomy) versus surgery and postoperative pelvic radiation for selected patients with stage I disease (grade I and >50% myometrial invasion, grade II and any invasion, grade III and <50% invasion).[165] Cancer-related deaths at 5 years were seen in 6% in the surgery-only arm and in 9% in the adjuvant radiation arm. However, locoregional recurrences were significantly reduced in the adjuvant radiation arm. Locoregional relapses were seen in 14% of patients after surgery alone and in 4% of patients after adjuvant radiation at 5 years, 73% of which were confined to the vagina. At 8-year follow-up, the locoregional relapse rates were similar; however, most of the recurrences in the surgery group were in the vagina, while most of the relapses in the radiation group occurred at distant sites. At 8 years, the rates of death were similar between the two groups: 19.7% in the radiation group versus 15.6% in the control group ($P = 0.35$).[300] Adjuvant pelvic radiation reduced both vaginal vault and pelvic recurrences compared to surgery alone. Vaginal relapse was diagnosed in 39 patients, 35 of whom were candidates for curative intent. A complete remission was obtained in 31 of the 35 patients who had curative treatment. At a median follow-up of 44 months, 77% of the 31 patients who had reached a complete remission after salvage therapy were still disease free. The 3-year actuarial survival rates after vaginal, pelvic, and distant relapse were 73%, 8%, and 14%, respectively. This salvage rate was better in the surgery arm, presumably because high-dose radiation could more readily be delivered for salvage therapy when none was given postoperatively.

Treatment of Pelvic Recurrence

Exenteration

Surgical treatment for pelvic relapse often requires partial or total exenteration. Barakat and colleagues reported on 44 patients who were treated with exenteration for recurrent endometrial cancer in the pelvis (location not otherwise described), 77% of whom had received prior irradiation.[301] The median interval to recurrence in this series was 28 months, and half the patients required a total exenteration. The median survival after salvage surgery was 10 months, with nine patients (20%) alive at more than 5 years. However, 80% had major postoperative complications.

Radical Radiation

Radical irradiation is usually the treatment of choice for patients who are initially treated with surgery alone. High-dose pelvic radiation with intravaginal brachytherapy is effective salvage therapy. Isolated vaginal recurrences are more successfully treated than are pelvic side wall or pelvic lymph node recurrences, but the latter might still require high-dose palliation. Factors that are associated with treatment outcome for recurrence include tumor size, grade, location in the vagina (distal versus apical), and disease-free interval.[302]

Outcomes for Pelvic Recurrence

Prognostic factors and outcomes in patients who experience pelvic recurrences have been examined. Methods of salvage therapy have varied depending on the presentation and extent of recurrent disease and the type of prior therapy. A series of 42 women with recurrent endometrial cancer after surgery alone were treated at Princess Margaret Hospital, all with combined EBRT and intracavitary therapy to a median total dose of 81.5 Gy.[303] The median time to recurrence postoperatively was 1.3 years. The 5-year and 10-year survival rates after salvage treatment were 53% and 41%, respectively. The local control rate was 65%, influenced by vaginal stage and size of the recurrence. The authors also noted that local control rates differed by vaginal location (66% for apex and 100% for distal) compared to central pelvic sites (44%). While the local control rate was better with a total dose greater than 80 Gy (72% versus 54% for <80 Gy), this was not statistically significant. Sears and colleagues reported on 45 patients who had not received postoperative pelvic radiotherapy who then developed vaginal (85%) or pelvic (15%) recurrence of endometrial cancer. Recurrences were analyzed by the corresponding vaginal cancer stage.[304] The median time to recurrence was 12 months, and long-term median follow-up had elapsed. Salvage treatment consisted of EBRT alone in 40%, EBRT and brachytherapy in 56%, and brachytherapy alone in 4%, with a median dose of 50 Gy. The 5-year disease-specific survival rate was 51%, the overall survival rate was 44%, and the locoregional control rate was 54%. Factors that were associated with local control were vaginal stage of recurrent disease, tumor size, radiation boost technique, time to recurrence, and age. The disease-specific survival rate was influenced by local control (74% for local control versus 23% without local control).

An Austrian series of 56 patients with pelvic relapse after hysterectomy included 41% who had received adjuvant irradiation, and 71% of recurrences were vaginal.[305] A reirradiation dose of approximately two thirds of the initial dose was used in previously irradiated patients (30 to 40 Gy) and was increased as the interval from prior radiation increased. Almost half the patients were treated with pelvic radiation and brachytherapy, 25% with brachytherapy alone, and 16% with external irradiation only, while 12% had no radiotherapy. Better 3-year survival rates were seen in patients who had no prior irradiation (59% versus 25%), low-grade disease (48% versus 22%), a relapse-free interval exceeding 2 years (55% versus 35%), and recurrence only in the vagina (54% versus 19%). A series of 26 patients who were treated with external radiotherapy and/or brachytherapy for locoregional recurrence of endometrial cancer reported a 5-year overall survival rate of 44%.[306] These authors also noted that the size of recurrent disease affected the success of salvage therapy. Locoregional control was 100% in patients with recurrent tumors less than 2 cm, 83% in those with tumors 2 to 4 cm, and 67% in those with tumors exceeding 4 cm. Also, the use of combined external irradiation and brachytherapy resulted in 100% locoregional control, while use of either treatment mode alone resulted in second relapse in 4 out of 10 patients.

Other series have had less promising results, possibly related to the extent of pelvic recurrence. Kuten and colleagues reviewed a group of patients with recurrent disease, only 33% of whom had isolated vaginal recurrence, while another third had pelvic and distant recurrence simultaneously.[307] For the entire group, locoregional control was only 35%, and the 5-year survival rate was 18%. The overall vaginal control rate was 82%, and patients with isolated vaginal recurrence had a 5-year progression-free survival rate of 40%. No patients with pelvic recurrence were alive beyond 1.5 years. In a study of 73 women undergoing salvage radiotherapy for pelvic recurrence after surgery alone, 60% received combined external and brachytherapy, 23% received brachytherapy alone, and 17% received external radiation alone, to a mean physical dose of 76 Gy.[308] The majority of patients in this study had vaginal stage II (60%) or stage III (34%) disease. The 5-year survival rate was 25%, and the response rate was 73%, with 67% experiencing progressive disease, just over half of whom had local progression.

Isolated Vaginal Recurrence

Salvage therapy for isolated vaginal recurrence may include treatment with external beam irradiation plus a vaginal brachytherapy boost or intravaginal brachytherapy alone. Several series have examined the prognosis and outcomes for this selected group of patients; these studies are summarized in Table 92-15. Overall survival rates after salvage therapy for vaginal recurrence range from 25% to 75%. In the largest retrospective series from M.D. Anderson, 91 patients with isolated vaginal recurrence received pelvic radiation alone (31%), brachytherapy alone (12%), or a combination of the two modalities (57%).[309] At a median follow-up of 58 months, the 5-year local control rate was 75%, and the overall survival rate was 43%. Predictors of better local control included combined modality irradiation and dose greater than 80 Gy. A multi-institution study by Huh and colleagues identified 69 patients who were initially diagnosed with stage I adenocarcinoma treated with surgery alone, with isolated vaginal recurrences. Of those patients, 62 patients (90%) were treated with a combination of whole-pelvic radiation and brachytherapy, and the remaining 2 were treated with brachytherapy alone. The mean time to initial recurrence was 24 months, and the mean follow-up was 63 months. The authors reported an 81% salvage rate with radiation with a 5-year overall survival rate of 75%.[310] Curran and colleagues reported 55 women with isolated vaginal recurrence posthysterectomy.[311] Nearly half received pelvic radiation and vaginal brachytherapy, 30% had external radiation alone, and 7% had brachytherapy alone, to a median dose of 60 Gy. The 5-year survival rate was 31%, and the 5-year pelvic control rate was 42%. The outcome was highly dependent on the radiation dose, with a 68% pelvic control rate at 5 years if 60 Gy or more was delivered, compared to 10% for those who received less than 60 Gy (including some patients who received no radiation). The 5-year survival rate was also worse for patients who were being reirradiated: 16% at 5 years versus 48% for those who were receiving a first course of radiotherapy. Using the vaginal carcinoma staging criteria as descriptors of the extent of disease, this study found that survival rates diminished as the "stage" of recurrent disease increased. In addition, better pelvic control rates were seen in recurrences that were located in the vaginal

Table 92-15 Results for Treatment of Isolated Vaginal Recurrence

Author	No. of Patients	Treatment	Pelvic Control Rate (%)	Five-Year Survival Rate (%)
Curran et al.[311]	55	Pelvic RT and/or brachytherapy (various)	Stage* I: 100	85
			Stage IIA: 53	59
			Stage IIB: 35	26
Wylie et al.[303]	46	Pelvic RT ± ICRT	Stage I: 94	71
			Stage IIA: 65	61
			Stage IIB: 45	27
Sears et al.[304]	39	Pelvic RT and/or brachytherapy (various)	Stage I: 77	44
			Stage II: 51 (entire group)	
Greven and Olds[312]	18	Pelvic RT and ICRT	44	33
Kuten et al.[307]	17	Pelvic RT and/or brachytherapy (various)	82 (vaginal control)	40 (PFS)
Colombo et al.[314]	35	ICRT (LDR)	86	57
Morgan et al.[313]	34	Pelvic RT and/or brachytherapy (various)	85	68
Tewari et al.[316]	30	Interstitial (LDR) ± pelvic RT	83	65
Charra et al.[318]	37	Interstitial (LDR) ± pelvic RT	70	56
Nag et al.[163]	10	Interstitial (LDR)	64	42
	5	Pelvic RT + interstitial (LDR)	100	
Pai et al.[315]	20	IC RT (HDR) ± pelvic RT	74 (10 year)	71 (CSS)
Jhingran et al.[309]	91	Pelvic RT and/or brachytherapy (various) (LDR)	75	43
Huh et al.[310]	69	Pelvic RT and/or brachytherapy (various)	Stage I: 81	75

CSS, cause-specific survival; ICRT, intracavitary radiation therapy; HDR, high dose rate; LDR, low dose rate; PFS, progression-free survival; RT, radiation therapy.
*Stage refers to extent of recurrent vaginal disease.

apex than in recurrences that were located in the suburethral area (56% versus 20%). Greven and Olds treated 18 patients with isolated vaginal recurrence with a combination of external pelvis radiation and intravaginal ovoids.[312] They achieved a 44% 3-year local control rate and an overall survival rate of 33% at a follow-up range of 3 to 10 years. Morgan and colleagues used pelvic fields and either intracavitary or interstitial brachytherapy in 34 patients with isolated vaginal recurrence, resulting in an 85% pelvic control rate, a 5-year survival rate of 68%, and a 60% disease-free survival rate.[313] Better control rates were seen in patients with less than 2 cm of disease and in those who were treated with radiation doses greater than 60 Gy. A group of patients from the University of Milan who presented with isolated vaginal recurrence after surgery alone were treated with LDR intravaginal ovoids or cylinders to a dose of 60 to 70 Gy at the vaginal surface.[314] The median time to relapse was 14 months. Vaginal recurrences were located in the upper third of the vagina in 69% of patients, the middle third in 9%, lower third in 11%, and diffusely in 11%. All patients exhibited a complete response to therapy, and 12% subsequently failed, for an overall local control rate of 86%.

LDR brachytherapy, as described in the previous studies, is thought to provide tumor control rates equivalent to those of HDR. Both methods have been widely used in the adjuvant postoperative setting to deliver a vaginal cuff boost, with or without external pelvic irradiation. Pai and colleagues have reported on the use of HDR intracavitary brachytherapy for isolated vaginal recurrence.[315] Thirteen of 20 patients received external pelvic radiation (44 Gy) and an HDR vaginal boost (24 Gy), while the others were treated with HDR intracavitary therapy alone (35 Gy). Complete response was noted in 90% of patients, with second local relapses in 22% within 30 months, for a 10-year local control rate of 74%. The 10-year disease-free survival rate was 46%, and the complication rate was 15% with no grade III or IV late complications. This study suggests that HDR intravaginal therapy is also an effective treatment for vaginal recurrence and is well tolerated.

Interstitial brachytherapy has also been used for treatment of vaginal wall recurrences. Tewari and colleagues reported on 30 patients who presented with isolated vaginal relapse after initial surgery alone (18 patients), who were treated with external irradiation followed by an interstitial implant, or implant alone for previously irradiated patients (12 patients).[316] The method that was used was the Syed-Neblett vaginal template, placed transperineally for a cumulative dose of 86 Gy in the postoperative relapses and 98.5 Gy in the reirradiation group. All of the recurrent tumors were more than 2 cm in size, with a median time to relapse of 29 months from initial diagnosis. Complete clinical responses were noted in 93% of patients, with 18% second local relapses at a median interval of 16 months. The median survival after recurrence was 60 months, with a 5-year survival of 65%. Only five patients experienced major morbidity, including fistula ($N = 2$), stricture ($N = 1$), and proctitis ($N = 2$). Nag and colleagues also used a perineal interstitial template for vaginal recurrences, combining EBRT with a 30-Gy boost for postoperative relapses and 50 to 55 Gy interstitial therapy alone for previously irradiated patients.[317] These authors report an overall local control rate of 66% and a 5-year survival rate of 42%. A French group utilized an intravaginal template with imbedded needles to treat vaginal vault recurrences and achieved a 70% local control rate and an overall survival rate of 56%.[318] Thus, interstitial brachytherapy provides a reasonable chance of local control and may be used to treat more extensive tumors that are not amenable to simple intravaginal brachytherapy.

FUTURE ISSUES

Endometrial cancer largely presents in the early stage, when surgery is possible and often curative. However, a number of high-risk features require select patients to undergo adjuvant radiation therapy postoperatively. Current screening methods are relatively insensitive, and new imaging modalities such as magnetic resonance imaging and ultrasound may be combined with molecular markers to identify patients in even earlier stages. One of the biggest areas of controversy in early-stage endometrial cancer involves which patients benefit from adjuvant therapy and whether this should include pelvic irradiation with or without a vaginal brachytherapy boost. Because bimodality therapy is associated with an increased risk of both acute and long-term sequelae, better criteria for adjuvant therapy in the various subsets of stage I disease might allow fewer patients to be exposed to the risks of combined surgery and radiation. In addition, the use of less invasive and less extensive laparoscopic surgical approaches for both primary surgery and staging procedures may further reduce the risk of side effects. In patients who are destined to be long-term survivors, the focus must now turn to reduction of treatment sequelae and quality of life issues. The outcomes for high-risk histologies remain poor, necessitating the investigation of more effective systemic agents.

In advanced endometrial cancer, both local control and distant metastases are important challenges. Unfortunately, active systemic chemotherapy or hormonal regimens have not been well defined in this disease. Therefore, trials looking at new systemic agents are warranted. The participation of willing patients in collaborative group trials should be strongly encouraged so that these questions and others can be answered.

The GOG is currently evaluating the molecular and surgical-pathologic staging of endometrial cancer. The purpose is to obtain a better understanding of the biology of endometrial cancer, including metastasis and response to therapy. The goal will be to determine specific molecular targets by evaluating genomic, proteomic, and immunoassay data. In the future, such information could be used to individualize the treatment and prevention of uterine cancer by utilizing novel biologic agents.

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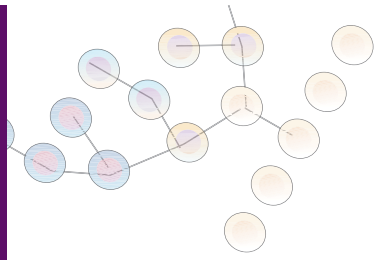
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93 Ovaries and Fallopian Tubes

Deborah Armstrong

SUMMARY OF KEY POINTS

Celomic Epithelial Carcinoma

Basic Characteristics

- Ninety percent of the 23,300 new cases and 13,900 deaths annually in the United States
- Derived from celomic epithelium lining the peritoneal cavity, most commonly from that which invests the ovary
- Most common route of spread: dissemination throughout peritoneal cavity
- Significant prognostic factors: age, histologic type and grade, extent of disease at diagnosis

Screening and Prophylaxis

- High-risk individuals: those with one or more first-order relatives with ovarian carcinoma
- No proven effective screening tests available, although transvaginal sonography and serial CA-125 and proteomic serum patterns under evaluation
- Prophylactic oophorectomy still of no proven value

Initial Evaluation and Management

- Emphasis in initial evaluation placed on the peritoneal cavity, an emphasis requiring exploratory laparotomy in those not clearly stage IV
- Minimum requirements for appropriate laparotomy: surgery through an incision adequate to inspect the entire peritoneal surface, multiple peritoneal biopsies in the absence of gross extrapelvic disease, and a maximal attempt at surgical cytoreduction, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy

Management of Advanced (Stage III–IV) Disease

- After surgery, systemic therapy to include at least a platinum compound
- Combination chemotherapy favored by the weight of evidence, preferred combination being paclitaxel-carboplatin: paclitaxel (175 mg/m^2 intravenously over 3 hours) followed by carboplatin (area under the curve, 6 to 7.5 intravenously) repeated every 3 weeks for six cycles
- Controversial issues: the roles of new agents, the role of dose-intense therapy supported by marrow reconstitution, the role of intraperitoneal therapy, and the role of maintenance paclitaxel

Management of Limited (Stage I–II) Disease

- After careful exploratory laparotomy, patients divided into low-risk and high-risk groups on the basis of the presence of one or more high-risk features: poorly differentiated neoplasm, extracystic tumor, positive peritoneal washings, ascites, or extraovarian disease
- Those who are at low risk of recurrence (no high-risk features): total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy followed by observation
- Those who are at high risk of recurrence (one or more high-risk features): the same surgery as in those who are at low risk followed by adjuvant platinum-based chemotherapy (paclitaxel/carboplatin for three cycles)

Salvage Therapy for Recurrent Disease

- Patients divided into platinum-sensitive and platinum-resistant groups
- Platinum-sensitive patients (responded to initial platinum-based therapy and experienced at least a 6-month platinum-free interval before relapse): retreatment with taxane/platinum combination
- Platinum-resistant patients (progressed on platinum-based therapy, best response to platinum-based therapy stable disease, or relapsed during or within 6 months of platinum-based therapy): treatment with drugs that produce responses (weekly paclitaxel, docetaxel, pegylated liposomal doxorubicin, oral etoposide, topotecan, tamoxifen, gemcitabine, navelbine, ifosfamide)
- Offering no proven advantage over intravenous therapy at standard doses to these patients: intraperitoneal therapy, high-dose therapy with marrow reconstitution, radiation therapy, and biologic agents

Germ Cell Cancers

Basic Characteristics

- Germ cell cancers make up 5% of all cancers of the ovary in the United States
- Histologies: dysgerminomas and nondysgerminomas (endodermal sinus tumors, mixed cell tumors, immature teratomas, embryonal carcinomas, and choriocarcinomas)
- Tumor markers are an important means of detecting early recurrence and monitoring the progress of therapy: α-fetoprotein and human chorionic gonadotropin
- For management purposes, two major groups of patients: (1) stages I to III completely resected and (2) incompletely resected stage III to IV disease

Stages I to III Completely Resected

- Initial management: complete resection of disease
- Adjuvant therapy: combination chemotherapy (either bleomycin/etoposide/cisplatin or vincristine/actinomycin/cyclophosphamide)

Stages III to IV Incompletely Resected

- Systemic therapy: bleomycin/etoposide/cisplatin

All
- Close follow-up after chemotherapy, including monthly assessments of tumor markers, physical examination, and chest radiography

Rare Malignant Ovarian Tumors
- Fewer than 5% of ovarian cancer: granulosa cell tumors, thecoma-fibroma tumors, Sertoli-Leydig cell tumors, gynandroblastomas, and steroid cell tumors
- Treatment of choice: surgical resection with little known about the use of radiation or systemic therapy as either adjuvant treatment or management for advanced or recurrent disease

Cancer of the Fallopian Tube
- Rare (300 cases annually in the United States), with more than 90% of all cases papillary serous adenocarcinomas
- Pattern of spread similar to that of celomic epithelial carcinoma of the ovary
- Surgical resection the mainstay for most patients with disease confined to the fallopian tube
- Radiation or chemotherapy reserved for cases with penetration to or beyond the serosa, with evidence favoring management similar to that used for advanced ovarian carcinoma

INTRODUCTION

Cancers of the ovary and fallopian tube together account for most deaths resulting from cancer of the female genital tract. This statistic relates primarily to the fact that, unlike other common malignant gynecologic neoplasms (cancers of the endometrium and cervix), cancers of the ovary and fallopian tube are first seen at relatively advanced stages of disease because of the lack of an effective early diagnostic test. Ovarian cancers are far more common than tubal malignancies and provide most of the data on which the management of both malignancies is based. This chapter first addresses cancers of the ovary extensively, followed by a discussion of cancers of the fallopian tube.

CANCER OF THE OVARY

Cancer of the ovary will be newly diagnosed in more than 23,300 women in the United States each year and will cause the death of more than 13,900 American women annually.[1] The lifetime likelihood that ovarian cancer will develop in a woman is estimated to be between 1 in 60 and 1 in 70, with a higher frequency associated with certain familial syndromes.[2–5] This group of cancers includes three major types: celomic epithelial carcinoma of the ovary, germ cell neoplasms, and stromal tumors. Each of these groups is discussed separately.

Celomic Epithelial Carcinoma

Almost 90% of cancers of the ovary are celomic epithelial carcinoma, which is one of the three most common gynecologic cancers. Management of these lesions evolves from an understanding of certain basic aspects of the disease process.

Basic Characteristics

CLINICALLY RELEVANT DISEASE FEATURES. Celomic epithelial carcinomas may arise in any part of the peritoneal cavity, although most appear to arise from the celomic epithelium that invests the ovary during embryonic development. The reasons for the preference for ovarian celomic epithelium are not entirely clear. It has been speculated that repeated rupture and repair of this portion of the celomic epithelium with the process of ovulation afford a greater opportunity for mutations that lead to malignancy. Such speculation is supported by observations that associate multiple pregnancies and the use of birth control pills, which suppress ovulation, with a decreased risk for ovarian carcinoma.[6]

Furthermore, most of these lesions arise in invaginated epithelium in areas of repair after ovulation, developing as though within a cyst. The process eventually penetrates the capsule of the ovary, forms tumor excrescences on the surface of the ovary, and then disseminates primarily by direct spread throughout the peritoneal cavity. Subsequent spread via lymphatic and hematogenous dissemination also occurs. This pattern of evolution of the disease is reflected in the International Federation of Gynecology and Obstetrics (FIGO) staging system[7] (Table 93-1), in which the most common stage at presentation is stage III, characterized by spread outside the pelvis to involve the peritoneal cavity. Because the process is an intra-abdominal disease that produces few symptoms before intraperitoneal dissemination and is not amenable to early diagnosis by currently available screening techniques, essentially 70% to 75% of patients are first seen with advanced (stage III or IV) rather than limited (stage I or II) disease.

Several characteristics of celomic epithelial carcinomas distinguish their clinical management from that of the other two common gynecologic cancers: endometrial cancer and cervical cancer. First, the primary route of spread, dissemination throughout the peritoneal cavity, opens the possibility for therapy directed toward the peritoneal cavity. Second, unlike the other two common gynecologic cancers, these lesions usually are first seen at a relatively advanced stage (stage III or IV), which necessitates a larger role for systemic

Table 93-1 International Federation of Gynecology and Obstetrics Staging System for Ovarian Carcinoma

Stage	Description
I	Growth limited to the ovaries
IA	One ovary; no ascites; capsule intact; no tumor on external surface
IB	Two ovaries; no ascites; capsule intact; no tumor on external surface
IC	One or both ovaries with either surface tumor; ruptured capsule; or ascites or peritoneal washings with malignant cells
II	Pelvic extension
IIA	Involvement of uterus and/or tubes
IIB	Involvement of other pelvic tissues
IIC	Stage IIA or IIB with factors as in stage IC
III	Peritoneal implants outside pelvis and/or positive retroperitoneal or inguinal nodes
IIIA	Grossly limited to true pelvis; negative nodes; microscopic seeding of abdominal peritoneum
IIIB	Implants of abdominal peritoneum ≤2 cm; nodes negative
IIIC	Abdominal implants >2 cm and/or positive retroperitoneal or inguinal nodes
IV	Distant metastases

Data from the New FIGO stage grouping.[7]

Table 93-2 Impact of Volume of Residual Disease on Pathologic Complete Response to Combination Chemotherapy in Patients with Advanced Ovarian Carcinoma

Regimen	Minimal	Bulky
PAC (GOG)[8,9]	45/137 (33%)	13/107 (12%)
PAC (Ehrlich et al.)[10]	5/17 (30%)	5/39 (13%)
HCAP (Greco et al.)[11]	18/21 (86%)	3/29 (10%)
CHEX-UP (Young et al.)[12]	5/14 (36%)	5/37 (14%)

CHEX-UP, cyclophosphamide + hexamethylmelamine + 5-fluoruracil + cisplatin; HCAP, hexamethylmelamine + cyclophosphamide + doxorubicin + cisplatin; PAC, cisplatin + doxorubicin + cyclophosphamide.

Table 93-4 Prognostic Factors in Ovarian Carcinoma

Factor	Description
Age	Older patients have poorer survival.
Grade	Poorly differentiated lesions are associated with poorer survival.
Histologic type	Clear cell and mucinous histologies are associated with poorer survival. Tumors of low malignant potential imply a much better survival.
Stage	More extensive disease, as reflected in the FIGO staging system, produces poorer survival.
Volume of disease	In patients with stage III disease, larger volume of residual disease leads to poorer survival.

therapy in the management of these cases. Finally, the volume of residual disease at initiation of systemic therapy influences the subsequent response to chemotherapy and survival. The smaller the largest residual nodule, the more likely it is that the disease will regress with drug therapy[8–11] (Table 93-2) and the more likely it is that the patient will live longer[12–14] (Table 93-3).

Other disease characteristics have been observed to influence outcome (Table 93-4). Shortened survival is associated with older age[15] and more poorly differentiated disease. These factors do not, however, affect therapeutic decisions except for the role of histologic grade in limited disease, a role that is discussed later in the chapter. Histologic subtype also affects survival: Patients who have clear cell or mucinous carcinomas have shorter survival, whereas those with tumors of low malignant potential ("borderline carcinomas") have a markedly better survival. These subtypes constitute fewer than 10% of all celomic epithelial tumors. Because no alternative therapeutic choice offers greater benefit for mucinous or clear cell carcinomas, these histologic types do not currently influence therapeutic decisions. Conversely, tumors of low malignant potential do influence therapeutic choices, as will be discussed.

TUMORS OF LOW MALIGNANT POTENTIAL. Celomic epithelial tumors of low malignant potential account for approximately 15% of ovarian carcinomas.[16] Patients with these lesions tend to be younger than those with invasive ovarian carcinoma (average age at onset: 49 years).[17] The sine qua non of the diagnosis is the absence of invasion of the stroma.[18] The vast majority of cases display serous or mucinous histology with bilaterality in roughly one third of serous tumors.

Recognition of these tumors is important because both prognosis and management differ greatly, in comparison to standard management of invasive ovarian carcinomas.[19–21] In general, management should begin with an exploratory laparotomy and resection of as much disease as possible. Pathology should be reviewed carefully to ensure that no areas of invasive carcinoma are present.[22] After surgery, patients should be observed until such time as the disease begins to behave in a more aggressive fashion. At that point, chemotherapy may be used, although its efficacy in this setting is not clear.

Table 93-3 Impact of Volume of Residual Disease on Survival in Patients with Advanced Ovarian Carcinoma

Regimen	Minimal (months)	Bulky (months)
PAC (GOG)[8,9]	42	19
L-PAM (GOG)[13,14]	33	13

L-PAM, melphalan; PAC, cisplatin + doxorubicin + cyclophosphamide.

EXTRAOVARIAN PERITONEAL SEROUS PAPILLARY CARCINOMA. It has long been recognized that celomic epithelial carcinomas can arise in portions of the peritoneal cavity other than the surface of the ovaries. The Gynecologic Oncology Group (GOG) undertook a study of these extraovarian peritoneal papillary serous carcinomas to determine whether they responded in a fashion similar to that of standard treatment for celomic epithelial carcinomas of the ovary.[23] The study of 47 women with these extraovarian celomic epithelial carcinomas showed that when the data are compared with results of treatment of ovarian carcinomas with the same chemotherapy, similar response rates, surgical complete response rates, and survivals are observed. This is the basis on which these lesions are now included in trials of chemotherapy for ovarian carcinoma.

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS STAGE. The factor that most influences management is the extent of disease at diagnosis (stage). This discussion is organized accordingly: A general approach to initial evaluation and surgical management is followed by a discussion of the role of chemotherapy both in previously untreated patients with advanced disease and in patients with recurrent or persistent disease. The management of patients with limited lesions is then considered.

Initial Evaluation and Management

Patients with celomic epithelial carcinomas generally are first seen with complaints of a full or heavy sensation in the pelvis or with increasing abdominal girth. Unfortunately, these symptoms usually reflect the presence of advanced disease. Efforts directed to earlier diagnosis have largely been unsuccessful, with the possible exception of the application of certain tools to patient populations that are at high risk for the development of ovarian carcinoma.

HIGH-RISK PATIENTS, SCREENING, AND GENETIC TESTING. Within the past decade, interest in using family history to identify patients who are at high risk of developing ovarian carcinoma has escalated.[2,24–26] Data now suggest that women with one first-order relative with ovarian carcinoma have a 3.6-fold higher risk than that of the general population. For those who have two or more relatives with ovarian carcinoma, at least one of whom is a first-order relative, risk is considerably higher, with estimates as great as 50% or better reported but not necessarily substantiated.

Certain hereditary syndromes have been described.[3,25] These include hereditary breast and ovarian cancer syndromes associated with changes at chromosome 17q (BRCA1) and at chromosome 13q (BRCA2) and hereditary nonpolyposis colon cancer syndromes

(Lynch syndrome II with an association with colon and endometrial cancers as well), which exhibit hMLH1, hMSH2, and hPMS2 mutations. These familial ovarian cancers typically appear at a younger age than does sporadic ovarian carcinoma and, despite pathologic factors that should portend a poor survival, predict a significantly better survival than that associated with sporadic ovarian cancer of the same stage.[4,5,25–29] Both hereditary breast/ovarian syndrome and hereditary nonpolyposis colon cancer syndromes appear to be vertically transmitted by an autosomal dominant mode, with incomplete penetrance. Familial ovarian cancer registries have now identified a number of women who either fit one of these syndromes or have at least one first-order relative with ovarian cancer.

These observations raise at least four significant questions with regard to management. First, should prophylactic oophorectomy be recommended to women who are at high risk? The largest experience with prophylactic oophorectomy comes from the Gilda Radner Familial Ovarian Cancer Registry. To date, 324 women with at least one first-order relative with ovarian cancer have undergone prophylactic oophorectomy. The relatively short follow-up evaluation of most of these women shows that in six, celomic epithelial carcinomas of the peritoneal cavity have developed, for an overall rate of 1.8%.[30] Although this rate is low, it exceeds the rate of ovarian carcinoma in the general population. Other reports have documented the occurrence of primary peritoneal neoplasms in women who have previously undergone oophorectomy.[31] This finding raises questions about the value of prophylactic oophorectomy in preventing the development of celomic epithelial carcinomas. No prospective trials have been conducted to examine this question. The weight of evidence suggests that the procedure should not be routinely recommended until further follow-up is available to determine whether a further significant increase in the incidence of peritoneal malignancies will occur. The exception to this might be women who have a true hereditary syndrome with a very high risk of developing ovarian carcinoma, although no clinical trial documents the value of prophylactic oophorectomy even in this population.[32,33]

Second, how should patients who are at high risk be monitored? More simply put, do we have valid screening tests? Family history clearly identifies a high-risk population. Logic dictates that screening leading to early diagnosis would result in a higher cure rate. The problem is the lack of evidence that any monitoring technique yields early diagnosis at a reasonable rate. Both CA-125 and transvaginal sonography have been recommended for screening. Evidence is lacking that CA-125 leads to early diagnosis.[4] By contrast, transvaginal sonography has proved capable of identifying ovarian carcinoma at a limited stage in two series.[5,30] The drawback of the technique is that 15 to 40 laparotomies have to be done to diagnose one case of limited ovarian carcinoma. At least for the present, neither approach can be recommended for routine screening, although selected high-risk patients, with a clear understanding of the attendant difficulties, can be screened with transvaginal sonography.[34,35]

More recently, new technology has offered some hope of an effective approach to screening for ovarian carcinoma. Investigators at the U.S. National Cancer Institute reported the use of proteomic patterns in serum to identify patients with ovarian cancer.[36] In a population of 50 patients with ovarian cancer and 66 patients with nonmalignant disease, the test reportedly had a sensitivity of 100%, a specificity of 95%, and a positive predictive value of 94% for correctly identifying those with or without ovarian cancer. Unfortunately, the calculation of the positive predictive value did not take into account the prevalence of the disease in the target population. When this deficiency is corrected, the true positive predictive value is 1%, not 94%. This is less than the positive predictive value that has been reported for the use of CA-125 alone.[37] Before proteomic patterns can be recommended to screen for ovarian carcinoma, further retrospective and prospective studies are required.

Third, should patients with positive family histories be offered genetic testing? Approximately 10% of ovarian carcinoma is associated with inheritance of an autosomal dominant genetic mutation and a resultant strong family history of ovarian carcinoma and certain other associated cancers, such as breast cancer.[38] These cases fall into two broad categories. The first is commonly called the breast and ovarian cancer syndrome and is associated with mutations at two loci: BRCA1 on chromosome 17q21 (75% to 90% of breast and ovarian cancer syndrome) and BRCA2 on chromosome 13q12 (10% to 25% of breast and ovarian cancer syndrome). In published series, these mutations account for approximately 7% of ovarian carcinoma. The second is commonly called the hereditary nonpolyposis colorectal carcinoma (HNPCC) syndrome and is associated with mutations that include three known genes: hMSH1 (45% to 50% of cases of HNPCC syndrome), hMLH1 (45% to 50% of cases of HNPCC syndrome), and hPMS2 (fewer than 5% of cases of HNPCC syndrome). These lesions account for approximately 3% of ovarian carcinoma.

Although the risk of inheriting a mutation from a parent carrier is 50%, the actual risk of developing a cancer varies from as high as 80% to 85% to as low as 16% for different mutations.[38] This variability of risk and the previously discussed controversy about the efficacy of prophylactic oophorectomy raise questions about the role of genetic testing in individuals with family histories of ovarian carcinoma. The American Society of Clinical Oncology recently issued an updated policy statement about genetic testing and cited three criteria for determining when genetic testing should be offered (Table 93-5).[39] Such testing should be done only if counseling before and after the test is available to discuss such issues as the risks and benefits of genetic testing as well as the efficacy, or lack thereof, of interventions that are prompted by the tests.

Fourth, might interventions other than prophylactic oophorectomy be efficacious in high-risk women? Oral contraceptives have been reported to reduce the risk of ovarian carcinoma by as much as 50% after prolonged (>10 years) use.[40–42] At least some reports suggest that the effects of such oral contraceptive use on cancer incidence differ between women with positive family histories and those with a true hereditary syndrome associated with BRCA1 or BRCA2,[43,44] with an actual increase in breast cancer risk among those BRCA1 or BRCA2 women who take tamoxifen for chemoprevention.[45] Although this implies a need for caution, at least one study reports that prolonged oral contraceptive use reduces the risk of ovarian cancer in women with pathogenic mutations in the BRCA1 or BRCA2 gene,[46] whereas another study shows no impact, negative or positive, of oral contraceptives on ovarian cancer risk.[47] In the absence of clear-cut evidence for a benefit, the role of oral contraceptives to prevent ovarian cancer is not established; hence, they should not be used for such a purpose at present.

Use of other hormones also has been evaluated. At least some reports show a direct correlation between postmenopausal estrogen-replacement therapy and risk for development of ovarian carcinoma with a relative risk ranging from 1.59 to 2.81.[48–50] This correlation

Table 93-5 Criteria for Offering Genetic Testing*

- Individual has personal or family history features suggestive of a genetic cancer susceptibility condition.
- Test can be adequately interpreted.
- Results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer.

*Genetic testing must include pretest and post-test counseling, including a discussion of the risks and benefits of testing and the interventions prompted by the testing.

Data from ASCO Working Group on Genetic Testing for Cancer Susceptibility: American Society of Clinical Oncology policy statement update: genetic testing for cancer susceptibility. J Clin Oncol 2003;21:2397–2406.

appears to hold only for patients who take estrogen only and not for those who take a combined estrogen/progesterone regimen. Other studies have failed to find such a correlation.[51] In women who are survivors of ovarian cancer, no evidence has been found that estrogen use increases the likelihood of relapse or shortens survival.[52]

Finally, one report assessed the relationship between raloxifene and risk for ovarian carcinoma.[53] This study was actually a meta-analysis of seven randomized placebo-controlled trials of raloxifene involving a total of 9837 women. The relative risk associated with the use of raloxifene was 0.50. This suggests that there is no adverse effect, but it does not prove a beneficial effect.

In summary, no scientifically proven screening approach exists for ovarian carcinoma. In addition, no clear role is seen for the use of interventions in the high-risk patient, although the ovarian consensus statement recommends the use of screening with transvaginal sonography and prophylactic oophorectomy in women with true hereditary syndromes. The basis for this recommendation is expert opinion and not appropriate definitive trials.

INITIAL EVALUATION. The initial evaluation of patients with suspected ovarian carcinoma, after the usual history, physical examination, laboratory testing, and CA-125, should be directed toward a detailed assessment of the abdominal cavity. Although a variety of imaging techniques for the abdominal cavity are now available, including sonography, computed tomography (CT), magnetic resonance imaging (MRI), and special isotopic scanning techniques, none provides the level of detailed study necessary for accurate staging of ovarian carcinoma. At the very least, CT scanning of the abdominal cavity, chest radiography, and bone scanning should be done.

Unless this evaluation demonstrates evidence of disease outside the abdominal cavity, exploratory laparotomy is an essential part of the initial evaluation of the patient. The laparotomy should be done through an incision that is adequate to evaluate the entire peritoneal surface, including the undersurface of the diaphragm and the right paracolic gutter, as well as the para-aortic lymph nodes. If no evidence of gross disease is found outside the pelvis, multiple biopsies of the peritoneal surface should be obtained. Many patients in whom the disease is apparently confined to the pelvis will have evidence of microscopic seeding of the abdominal peritoneum in one or more biopsies. At the conclusion of this procedure, accurate staging of the disease will have been accomplished and will serve to direct further management.

Therapeutic Role of Surgery

The volume of residual disease is related both to response to chemotherapy and to survival. As a result, the standard of care of patients with ovarian carcinoma with disease that is confined to the abdominal cavity is to resect as much disease as possible at initial laparotomy. This approach applies to patients with limited disease that can be completely removed as well as to patients with advanced disease that can be only partially resected. Data on which this approach has been based are retrospective analyses showing that patients who initiate chemotherapy with small-volume disease (no nodule larger than 2 cm in diameter remaining in the abdominal cavity) have both a higher frequency of pathologic complete response and a superior survival with chemotherapy[8,10–14,54] (see Tables 93-2 and 93-3).

Several major questions have been raised about the value of cytoreductive surgery in patients with advanced disease that is not amenable to a "curative" resection. First and foremost, detractors have pointed out that approximately one half of the population of patients with small-volume disease consists of patients with stage IIIA or IIIB disease—patients who already have small-volume disease at the time the abdomen was opened without any surgical cytoreduction. According to this line of reasoning, the improved results in small-volume disease relate entirely to this portion of the patients who presumably have biologically less aggressive disease. A retrospective analysis of a GOG database of patients with small-volume disease provided some support for this view.[14] Operative notes on the population in the database were reviewed to separate the patients into two groups: those who had stage IIIA or IIIB disease and those who had stage IIIC disease that was successfully surgically cytoreduced to small-volume residual disease. Patients who required surgical cytoreduction had an inferior survival in comparison with those who already had small-volume disease at the time the abdomen was opened. Although this investigation shows a difference between these two patient groups, it does not prove that surgical cytoreduction has no value, in the absence of a population for comparison in which chemotherapy was started with large-volume disease.

The only way to address the question of the value of cytoreductive surgery is to conduct a randomized trial in which all patients are randomized to surgical cytoreduction or no surgical cytoreduction and are then analyzed by intent to treat. No such study assessing initial surgical cytoreduction has been successfully completed. However, two prospective randomized phase III trials have evaluated the role of interval cytoreduction[55,56] (Table 93-6).

In a European trial by the European Organization for Research and Treatment of Cancer,[55] patients with advanced disease received three courses of cisplatin plus cyclophosphamide and were then randomized to receive either three more courses of the same chemotherapy or interval cytoreductive surgery, followed by three more cycles of cisplatin plus cyclophosphamide. The group that received interval cytoreductive surgery demonstrated a statistically significantly superior progression-free and overall survival.

A GOG study[56] took patients with stage IIIC disease who had undergone an aggressive attempt at initial surgical cytoreduction and still had large-volume disease remaining and randomized them to either six cycles of paclitaxel plus cisplatin or three cycles of paclitaxel plus cisplatin followed by interval surgical cytoreduction and then three more cycles of paclitaxel plus cisplatin. This trial showed no difference between the two study arms.

The most rational interpretation of these two studies rests on an understanding of the differences in study execution. In the European trial, initial surgery was performed by surgeons with varied training backgrounds and, in many instances, probably did not represent true aggressive attempts at surgical cytoreduction. In the GOG study, conversely, virtually every patient underwent an initial attempt at aggressive surgical cytoreduction by a trained gynecologic oncologist. What the two trials show is that patients with a less than optimal initial attempt at surgical cytoreduction benefit from interval bulk reduction, whereas those who undergo an aggressive initial surgery

Table 93-6 Results of Two Studies of Interval Surgical Cytoreduction

Parameter	All	IDS	No IDS
EORTC STUDY[55]			
Patients	408	150	149
Response after three cycles			
Complete response rate	17%		
Partial response rate	55%		
Progression-free survival		15 months	12.5 months
Survival		27 months	19 months
GOG STUDY[56]			
Patients	425	216	209
Progression-free survival		10.5 months	10.8 months
Survival		32 months	33 months

IDS, interval debulking surgery.

and still have large-volume disease do not benefit from interval surgery.

On the basis of the weight of current evidence, patients, except for those with obvious stage IV disease, should undergo an initial laparotomy with intent to carry out maximal surgical cytoreduction. This should improve response to chemotherapy as well as survival. Those who have a less aggressive initial operation should be considered for interval surgical cytoreduction.

Management of Advanced Disease

Patients with stage III or IV disease, on completion of initial surgery, should receive systemic therapy for control of disease. Fortunately, celomic epithelial carcinoma is a chemosensitive disease—hence the significant therapeutic options for patients with advanced disease.

ACTIVE AGENTS. A number of cytotoxic agents as well as biologic and hormonal agents have activity against celomic epithelial neoplasms[6–8,10–15,24–26,54] (Table 93-7). Response rates that have been reported for each of the active agents vary as a result of several factors: (1) volume of residual disease in the patient population at the initiation of therapy, (2) dose and schedule of the agent under study, and (3) whether the patient population has received prior cytotoxic therapy to which the neoplasm has become clinically resistant, as evidenced by clinical progression during therapy. With the reservation that these factors cannot be sorted out in many of the single-agent studies that have been reported, it is possible to point to certain active cytotoxic drugs of major interest: the platinum compounds, the taxanes, the mustard-type alkylating agents, the anthracyclines (including pegylated liposomal encapsulated doxorubicin), the topoisomerase I inhibitors, oral etoposide, gemcitabine, vinorelbine, and hexamethylmelamine. In addition, among hormonal and biologic agents, interferon-α, interferon-γ, and tamoxifen display activity. Among these, the platinum compounds and paclitaxel deserve specific comment because of their current major relevance to front-line therapy for newly diagnosed disease.

Table 93-7 Active Single Agents in Celomic Epithelial Carcinoma of the Ovary*

Drug	Patients	
	N	Percent†
Alkylating agents[57]	1371	33
Ifosfamide[57,213–215]	98	15
Cisplatin[57–59]	190	32
Carboplatin[57,60,61]	82	24
Oxaliplatin[243]	45	16
Paclitaxel[63–66]	157	35
Docetaxel[67–71]	423	29
Doxorubicin[57]	102	33
5-Fluorouracil[57]	126	29
Methotrexate[57]	34	18
Mitomycin[57]	49	16
Hexamethylmelamine[175–182]	296	23
Topotecan[121,122,183–185]	352	17
Irinotecan[186]	29	17
Pegylated liposomal doxorubicin[119,120,187–190]	557	18
Oral etoposide[118,191–194]	193	28
Gemcitabine[123–125]	109	16
Vinorelbine[195–199]	156	22
Dihydroxybusulfan[57]	26	27
Galactitol[57]	39	15
5-Fluorouracil/leucovorin[200]	44	14
Mitoxantrone[201]	33	15
Treosulfan[202]	80	19
Oral trofosfamide[203]	31	16
Progestins[57]	176	12
Tamoxifen[204–206]	141	14
Prednimustine[57]	36	28
Mifepristone[207]	34	26
Interferon-α[57]	21	19
Interferon-γ[57]	14	29
Trastuzumab[127]	41	7

*Response rate >15%.
†Response rate percentage.
Data from references 48–71, 120–125, 175–200, 213–215, and 243.

Platinum Analogs. The platinum analogs are the most systematically evaluated and active cytotoxic drugs. Cisplatin demonstrates clear-cut activity in patients with no prior chemotherapy, as well as in those who are refractory to prior alkylating agents.[57–61] Carboplatin produces less neurotoxicity and nephrotoxicity than does cisplatin, in exchange for thrombocytopenia as the dose-limiting adverse effect, and exhibits activity similar to that seen with cisplatin.[61]

Taxanes. Paclitaxel, a diterpenoid extracted from the bark of *Taxus brevifolia* (the Western yew tree), acts to enhance tubulin polymerization and microtubule stability and hence to produce microtubule bundling throughout the cell.[62] This stability leads to inhibition of the dynamic reorganization of the microtubular structure of the cell before cell division. This unique mechanism of action accounts for the apparent lack of cross-resistance between this drug and the platinum analogs.

Paclitaxel demonstrated significant activity in four phase II trials in patients who had received prior platinum-based combination chemotherapy[63–66] (Table 93-8). In two of the four trials, responses were documented in both platinum-sensitive and platinum-resistant patients. Adverse effects, including myelosuppression, hypersensitivity reactions, and significant arrhythmias requiring continuous cardiac monitoring during therapy, were frequent and severe but manageable and resulted in no deaths attributable to toxicity. The occurrence of significant anaphylactic episodes in the initial experience with the drug led to the use of premedication with steroids and H_1 and H_2 blockers in the phase II trials, with the resultant virtual elimination of significant hypersensitivity reactions. The dose-limiting toxicity is myelosuppression, which, with 24-hour infusions, is severe but brief.

The other taxane, docetaxel, has been less extensively evaluated.[67–71] Activity appears to be similar to that of paclitaxel. Whether toxicity differs significantly awaits publication of randomized trials that have evaluated this, but on the basis of data available to date, docetaxel could be less neurotoxic but more myelosuppressive.

In summary, a variety of drugs have activity against ovarian carcinoma. The most important of these are the platinum compounds and the taxanes. Other agents of particular interest exhibit the ability to obtain responses in patients who have progressed on paclitaxel-platinum front-line therapy and include oral etoposide, topotecan, tamoxifen, gemcitabine, navelbine, ifosfamide, and possibly doxil.

COMBINATION CHEMOTHERAPY. An extensive series of questions had to be addressed to evolve effective regimens for the treatment of advanced ovarian carcinoma after surgical cytoreduc-

Table 93-8 Phase II Trials of Taxol as Salvage Therapy in Patients with Ovarian Carcinoma

Investigators	No. of Patients	Response Rate (%)
McGuire et al.[65]	40	30
Sensitive	15	40
Resistant	25	24
GOG (Thigpen et al.)[63]	43	35
Sensitive	16	44
Resistant	27	30
Einzig et al.[64]	30	20
Kohn et al.[66]	44	48

tion. Over the last two decades, the major themes that have keyed the development of current therapy include the evolution of platinum-based combination chemotherapy, assessment of the value of dose intensity, the defining of the role of paclitaxel, the determination of which platinum compound to use, and the ascertainment of the role, if any, of maintenance or consolidation therapy for those who respond to front-line therapy. Each of these issues is discussed, and a brief look at other significant issues follows.

Evolution of Platinum-based Combination Chemotherapy. A multitude of trials have made a firm case for the value of combination chemotherapy compared with treatment with single agents. The most significant of these studies were three large, randomized trials.[8,9,54] The conclusions from these three GOG studies, supported by other trials of systemic therapy, formed the basis for practice at the end of the 1980s.[72]

The first two GOG trials were successive studies in patients with bulky advanced disease[8,54] (Table 93-9). The first of these (GOG Protocol 22) compared melphalan alone with either melphalan plus hexamethylmelamine or doxorubicin plus cyclophosphamide.[54] The only statistically significant difference that was observed was a greater clinical complete response rate in the patients who were treated with doxorubicin plus cyclophosphamide, as compared with those who received melphalan alone. This was the basis for selection of the two-drug combination as the control arm of the second trial (GOG Protocol 47), which compared doxorubicin plus cyclophosphamide with the same two drugs plus cisplatin.[8] Results showed a statistically significant improvement in clinical complete response rate, overall response rate, progression-free interval, and survival in the patients who were treated with the three-drug cisplatin-based combination.

Table 93-9 Results of Two GOG Studies of Combination Chemotherapy in Large-Volume Advanced Ovarian Carcinoma

	GOG Protocol 22		GOG Protocol 47	
Parameter	**L-PAM**	**AC**	**AC**	**PAC**
Patients	64	72	120	107
CRR	20%	32%	26%	51%
Total response (CRR + PRR)	37%	49%	48%	76%
CRR			4/23	13/39
PCR/total			3%	12%
Duration	8 months	10 months	9 months	15 months
Median survival	12 months	14 months	16 months	20 months

AC, doxorubicin (50 mg/m^2) plus cyclophosphamide (500 mg/m^2), both intravenous, every 3 weeks, for eight courses; CRR, complete response rate; L-PAM, melphalan (0.2 mg/kg/day orally), for 5 days every 4 to 6 weeks, for 10 courses or 18 months; PAC, cisplatin (50 mg/m^2) plus doxorubicin and cyclophosphamide as in AC, all intravenous, every 3 weeks, for eight courses; PCRR, pathologic complete response rate; PRR, partial response rate.

Data from references 8 and 54.

The third critical study (GOG Protocol 52), in patients with minimal residual disease (defined as patients with stage III disease and no nodules larger than 1 cm in diameter), compared the three-drug combination with cisplatin plus cyclophosphamide[9] (Table 93-10). The pathologic complete response rates, as documented at second-look laparotomy, were not significantly different, nor were any differences noted in progression-free interval or survival.

By the late 1980s, these three trials made a strong case for the combination of cisplatin plus cyclophosphamide as the standard chemotherapy for advanced or recurrent ovarian carcinoma. Four other studies focusing on the substitution of carboplatin for cisplatin expanded somewhat the meaning of standard chemotherapy.[73–76] These studies compared the relative efficacy of cisplatin-based versus carboplatin-based regimens (Table 93-11). The trial of the Southwest Oncology Group compared cyclophosphamide (600 mg/m^2) plus either cisplatin (100 mg/m^2) or carboplatin (300 mg/m^2) in patients with bulky stage III or IV disease.[73] The study showed no significant differences between the two regimens with regard to response rate, progression-free interval, or survival. The toxicities of the two regimens was different, the cisplatin regimen producing greater adverse effects. The National Cancer Institute of Canada trial compared essentially the same regimens, except for a slightly lower cisplatin dose of 75 mg/m^2, with similar results.[75]

The study conducted by the Gynaecological Cancer Cooperative Group for the European Organization for Research and Treatment of Cancer compared two four-drug combinations consisting of cyclophosphamide, doxorubicin, and hexamethylmelamine with either cisplatin or carboplatin.[74] No significant differences were noted with regard to response rate, progression-free interval, or survival.

The trial that was conducted by investigators at the Mayo Clinic is flawed by a major design problem.[76] The dose intensity of carboplatin is well below that of cisplatin in the other arm, making it difficult to determine whether the differences in progression-free interval and survival favoring the cisplatin regimen were related to a different platinum compound or to a lower dose intensity of the carboplatin. This study has two other features that distinguish it from the other three trials. The number of patients in the trial is considerably smaller and included 65% with small-volume disease.

Table 93-10 Results of a GOG Study of Minimal Residual Stage III Ovarian Carcinoma

Parameter	PAC	PC
Patients	173	176
Early recurrence	19	30
Refused second look	36	37
Residual disease	73	67
Pathologic complete response (%)	45 (26%)	42 (24%)

PAC, cisplatin (50 mg/m^2) plus doxorubicin (50 mg/m^2) plus cyclophosphamide (500 mg/m^2), all intravenous every 3 weeks, for eight cycles; PC, cisplatin (50 mg/m^2) plus cyclophosphamide (1000 mg/m^2), both intravenous, every 3 weeks, for eight cycles.

Data from reference 9.

Table 93-11 Randomized Trials Comparing Cisplatin-based with Carboplatin-based Combination Chemotherapy in Advanced, Predominantly Large-Volume Ovarian Carcinoma

Study and Regimen	Response Rate (%)	Survival
ALBERTS ET AL[73] (342 PATIENTS)		
Carboplatin (300 mg/m^2), every 4 weeks	CCR, 34	20 months
Cyclophosphamide (600 mg/m^2), every 4 weeks	PCR, 12	
Cisplatin (100 mg/m^2), every 4 weeks	CCR, 27	17 months
Cyclophosphamide (600 mg/m^2), every 4 weeks	PCR, 7	
TEN BOKKEL HUININK ET AL[74] (339 PATIENTS)		
Cyclophosphamide (100 mg/m^2 PO), days 14–28	CCR, 24	107 weeks
Hexamethylmelamine (150 mg/m^2 PO), days 14–28		
Doxorubicin (35 mg/m^2 IV), day 1		
Carboplatin 350 mg/m^2 IV), day 1		
Cyclophosphamide (100 mg/m^2 PO), days 14–28	CCR, 23	108 weeks
Hexamethylmelamine (150 mg/m^2 PO), days 14–28		
Doxorubicin (35 mg/m^2 IV), day 1		
Cisplatin (20 mg/m^2 IV), days 1–5		
PATER ET AL[75] (447 PATIENTS)		
Carboplatin (300 mg/m^2), every 4 weeks	PCR, 13	24 months
Cyclophosphamide (600 mg/m^2), every 4 weeks		
Cisplatin (75 mg/m^2), every 4 weeks	PCR, 18	23 months
Cyclophosphamide (600 mg/m^2), every 4 weeks		
EDMONDSON ET AL[76] (103 PATIENTS)		
Carboplatin (150 mg/m^2), every 4 weeks		20 months
Cyclophosphamide (1000 mg/m^2), every 4 weeks		
Cisplatin (60 mg/m^2), every 4 weeks		27 months
Cyclophosphamide (1000 mg/m^2), every 4 weeks		

CCR, clinical complete response; PCR, pathologic complete response.

In summary, these seven randomized trials[8,9,54,73–76] defined four major concepts about standard chemotherapy for advanced ovarian carcinoma as of 1990. First, combination chemotherapy is superior to single-agent therapy. Second, platinum-based combination chemotherapy offers significant advantages over non-platinum-based regimens. Third, carboplatin offers certain advantages over cisplatin in terms of altered and more tolerable toxicity with no diminution in efficacy. Finally, two-drug combinations of a platinum compound and an alkylating agent offer benefits that are equivalent to those that are achieved with more complex regimens. Three major themes dominated clinical research in the 1990s in attempts to improve further on systemic therapy for advanced disease: dose intensity, the development of combinations of a platinum compound and paclitaxel, and the choice of platinum compound.

Dose Intensity. Although debated to some extent, the concept of the importance of dose intensity to the success of chemotherapy in the management of celomic epithelial carcinomas of the ovary has been generally well accepted among oncologists. In vitro data support the efficacy of increasing drug levels in enhancing cell kill in cultures of ovarian cancer cells.[77] In patients who have experienced recurrence after prior platinum-based chemotherapy for ovarian carcinoma, responses to higher doses of the same platinum compound[78] or to greater exposure as a result of intraperitoneal administration[79] have been cited as evidence that enhanced dose can result in response when lower doses have failed. The use of hypertonic saline to permit escalation of cisplatin dose to 200 mg/m^2 per course in combination with cyclophosphamide has been reported to yield high response rates that are superior to those achieved with lower-dose regimens.[80] Finally, meta-analyses have been reported to show a correlation between dose intensity of platinum and response.[81,82] These kinds of evidence have provided strong support for the value of dose intensity in the treatment of ovarian carcinoma.

At first glance, the case for dose intensity would appear to be very solid. However, several significant questions remain. First, with regard to reported responses of "refractory" ovarian carcinoma to higher doses of drug, it is becoming increasingly apparent that such responses occur not in patients whose disease progresses with the lower-dose therapy but rather in patients in whom recurrent disease develops some time after they have completed prior therapy. For example, Ozols and colleagues[83] reported a series of 30 patients with "refractory" ovarian carcinoma who were treated with high-dose carboplatin (800 mg/m^2 per 35 day cycle). Although eight responses were observed, Ozols and colleagues also noted that "no responses were observed from high-dose carboplatin in [9] patients who had progressive disease during prior therapy with a cisplatin-based regimen." Similar observations emerge from second-line phase II studies of intraperitoneal chemotherapy. In other words, patients whose tumors are clinically resistant to platinum-based chemotherapy do not benefit from treatment with higher doses of the same or similar drugs.

Second, the reported improvement in response rate that was seen with high-dose cisplatin regimens has been reappraised in light of the significant neurotoxicity that emerged from these studies.[80] Although this is not a randomized comparison, it is instructive to compare the results of GOG studies with regimens using 50 mg/m^2 of cisplatin in the combination regimen with results of using high-dose cisplatin. In patients with minimal residual stage III disease (no nodule >2 cm remaining), the high-dose regimen (cisplatin 200 mg/m^2 plus cyclophosphamide 1000 mg/m^2 repeated every 4 weeks) yielded a pathologic complete response rate of 38%,[80] whereas the GOG regimen (cisplatin 50 mg/m^2 plus cyclophosphamide 1000 mg/m^2 every 3 weeks) yielded a pathologic complete response rate of 30%.[9] In patients with bulky stage III or stage IV disease, the high-dose regimen (the same as was noted earlier) yielded a pathologic complete response rate of 12%,[80] whereas the GOG regimen (cisplatin 50 mg/m^2 plus doxorubicin 50 mg/m^2 plus cyclophosphamide 500 mg/m^2 repeated every 3 weeks) yielded a pathologic complete response rate of 11%.[8] Thus, no evidence exists that the high-dose cisplatin regimen yielded a superior result, even though the dose intensity of the platinum compound as a function of dose and time was 3 times as high.

Third, although a dose-intensity meta-analysis conducted by Levin and Hryniuk[81] indeed documented a dose-response relation for cisplatin, this relation held only over the range of 0.4 to 0.8. For purposes of this meta-analysis, the "standard" regimen used a cisplatin dose equivalent to 15 mg/m^2 per week. The dose-response relation for cisplatin thus held over a range of 6 mg/m^2 per week to 12 mg/m^2 per week. This equates to a highest dose of 36 mg/m^2 every 3 weeks. This meta-analysis thus supplied no support for the use of

doses higher than those used by the GOG in their relatively low-dose cisplatin regimens.

An extended meta-analysis by the same investigators[82] included more studies in the higher dose range. This study demonstrated the superiority of combination chemotherapy over single agents and also noted a correlation between response and cisplatin dose up to a level of 25 mg/m^2/week (or 75 mg/m^2 every 3 weeks). In this analysis, the investigators also suggested that total dose delivered might be as important as dose intensity. Neither meta-analysis, however, offered any evidence supporting the importance of total dose nor of a correlation between response and dose intensity for any drug other than cisplatin; nor was either meta-analysis able to support the importance of cisplatin dose intensity beyond 25 mg/m^2/week.

These considerations raise serious questions about the value of dose-intense regimens in the treatment of ovarian carcinoma. Addressing these issues appropriately requires randomized prospective trials. Eight such studies have been reported (Table 93-12).[84–91]

Studies Showing No Advantage from Dose Intensity. GOG Protocol 97[84] randomized patients with large-volume disease defined as having nodules larger than 1 cm or stage IV disease to receive either eight cycles of cisplatin (50 mg/m^2) plus cyclophosphamide (500 mg/m^2) every 3 weeks or four cycles of cisplatin (100 mg/m^2) plus cyclophosphamide (1000 mg/m^2) every 3 weeks. A total of 458 eligible patients was randomized, of whom 130 had measurable disease. Prognostic features were evenly distributed between the two treatment arms. If the prescribed low dose is assigned a dose intensity of 1.0, the actual received dose intensity for the low-dose regimen was 0.95, and that for the high-dose regimen was 1.90. A twofold difference in dose intensity was thus achieved. No difference in total dose received was noted between the two arms as planned.

With regard to response, of 60 patients assigned to the high-dose arm, 19 (32%) achieved a clinical complete response, 16 (27%) achieved a partial response, 18 (30%) had stable disease, and 7 (12%) experienced increasing disease. The overall response rate for the high-dose arm was thus 59%. Of 70 patients assigned to the low-dose arm, 27 (39%) achieved a clinical complete response, 18 (26%) achieved a partial response, 24 (34%) had stable disease, and 1 (1%) experienced increasing disease. The overall response rate for the low-dose arm was thus 65%. No statistically significant differences were noted between the two arms with regard to response.

With regard to progression-free interval and survival, all 458 patients were included in the analysis. Median progression-free intervals for the low-dose and high-dose regimens were 12 and 13 months, respectively, whereas median survivals were 24 and 21 months, respectively. No significant differences were observed in either parameter.

The high-dose regimen was associated with more severe or life-threatening (grade III or IV) toxicity, which included more leukopenia (82% versus 40%), more thrombocytopenia (22% versus 1%), more anemia (9% versus 2%), more nausea and vomiting (16% versus 3%), and more nephrotoxicity (5% versus 1%). Very few cases of grade III or IV neurotoxicity were seen.

This GOG study was designed as a pure dose-intensity study only in patients with large-volume disease. No evidence exists that a twofold increase in dose intensity yields any greater patient benefit over the range of doses used in this trial for patients with large-volume disease, but it is clear that the higher-dose regimen was more toxic.

A Gruppo Interregionale Collaborativo in Ginecologia Oncologica trial[86] randomized 306 patients with advanced disease to either cisplatin 75 mg/m^2 every 3 weeks for six cycles or cisplatin 50 mg/m^2 weekly for 9 weeks. The actual received dose intensity of the high-dose regimen was twice that of the low-dose regimen, and no differences existed in the total dose delivered in either arm of the trial. In contrast to the GOG study, 45% of the patients in this study had small-volume advanced disease. No significant differences were observed between the arms with regard to pathologic complete response (24% high-dose versus 28% low-dose), progression-free interval (21 versus 18 months), and survival (36 versus 33 months). Like the GOG study, this was a trial of pure dose intensity, because each regimen delivered the same total dose of drug. Also like the GOG trial, this study provides no support for the importance of dose intensity over the range of cisplatin dose intensity from 25 mg/m^2/week to 50 mg/m^2/week.

A North-West Oncology Group trial[87] randomized 145 patients with large-volume advanced disease to receive cyclophosphamide 600 mg/m^2 plus epirubicin 60 mg/m^2 plus either cisplatin 50 mg/m^2 or cisplatin 100 mg/m^2 every 4 weeks for six cycles. In contrast to the GOG and Gruppo Interregionale Collaborativo in Ginecologia Oncologica trials, this study called for the delivery of twice as much total dose of cisplatin in the high-dose regimen. Actual received dose intensity achieved a 2:1 ratio between the high-dose and low-dose regimens and evaluated the range of cisplatin dose intensity from 12.5 mg/m^2/week to 25 mg/m^2/week. No significant differences were noted with regard to clinical response (57.5% high-dose versus 61.1% low-dose), pathologic complete response (9.6% high-dose versus

Table 93-12 Eight Randomized Trials of Platinum Dose Intensity in Advanced Ovarian Carcinoma

Trial	Platinum DI	Response Rate (%)	Survival
SHOWING NO DIFFERENCE			
GOG[84]	Cisplatin, 16.7 mg/m^2/week	65	21 months
	Cisplatin, 33.3 mg/m^2/week	59	24 months
GICOG[86]	Cisplatin, 25 mg/m^2/week	61	33 months
	Cisplatin, 50 mg/m^2/week	66	36 months
GONO[87]	Cisplatin, 12.5 mg/m^2/week	61	24 months
	Cisplatin, 25 mg/m^2/week	58	29 months
London[88]	Carboplatin, AUC 6	57	HR: 0.91
	Carboplatin, AUC 12	63	
Danish[89]	Carboplatin, AUC 8		33% 3 years
	Carboplatin, AUC 4		30% 3 years
Austrian[90]	Cisplatin, 25 mg/m^2/week	42	38 months
	Cis, 25 mg/m^2 + Carbo 75 mg/m^2/week	39	42 months
SHOWING A DIFFERENCE			
Scottish[85]	Cisplatin, 16.7 mg/m^2/week	34	27% 4 years
	Cisplatin, 33.3 mg/m^2/week	61	32% 4 years
Hong Kong[91]	Cisplatin, 15–20 mg/m^2/week	30	30% 3 years
	Cisplatin, 30–40 mg/m^2/week	55	60% 3 years

DI, dose intensity; HR, hazard ratio.
Data from references 84–91.

18.1% low-dose), progression-free interval (18 months high-dose versus 13 months low-dose), and survival (29 months high-dose versus 24 months low-dose). The high-dose regimen was clearly more toxic. The trial provides no support for the importance of either dose intensity or total dose over the range of cisplatin dose intensity that was tested (12.5 mg/m^2/week to 25 mg/m^2/week).

A London GOG trial[88] randomized 241 patients with either small-volume or large-volume advanced disease to single-agent carboplatin dosed to an area under the curve (AUC) of either 6 for six courses or 12 for four courses at 4-week intervals. In the high-dose arm, dose intensity was doubled, and total dose increased by 22%. No significant differences were noted with respect to response (63% high-dose versus 57% low-dose), progression-free interval (hazard ratio, 0.98), and survival (hazard ratio: 0.91). This trial also provides no support for the importance of dose intensity or total dose over the range that was tested.

In a Danish Ovarian Cancer Group trial,[89] Danish investigators randomized 222 patients with advanced ovarian carcinoma to carboplatin dosed to an AUC of either 4 or 8 every 4 weeks for six cycles. No differences were observed with respect to pathologic complete response or survival.

An Austrian trial[90] approached the problem of platinum dose intensity by combining cisplatin and carboplatin. A total of 253 patients with stages IC to IV disease were randomized either to cisplatin 100 mg/m^2 plus carboplatin 300 mg/m^2 or to cisplatin 100 mg/m^2 plus cyclophosphamide 600 mg/m^2 monthly for six cycles. Actual received dose intensity for platinum was 1.6-fold greater with the cisplatin/carboplatin regimen. The platinum-intensified regimen produced more myelosuppression, ototoxicity, and gastrointestinal toxicity. The cisplatin/carboplatin regimen produced a response rate of 39%, a complete response rate of 26%, a progression-free median survival of 22 months, and an overall median survival of 42 months. These results were not significantly different from those that were seen with the cisplatin/cyclophosphamide regimen: 42% response rate, 26% complete response rate, 25-month median progression-free survival, and 38-month median overall survival. This trial thus failed to confirm an advantage for a 1.6-fold increase in platinum dose intensity.

These observations contradict the dogma that higher-dose schedules yield better results. Several possible explanations may be found. First, total dose instead of dose intensity could be important. At least four of the six studies, however, used differences in both dose intensity and total dose and showed no advantage. Second, dose intensity may be relatively ineffective in large-volume disease and still yield better results in patients with small-volume disease. All but the GOG trial, however, included patients with small-volume disease, with no advantage noted in the small-volume subset. Third, a twofold increase in dose intensity may be too small to permit observation of differences. Finally, and perhaps most devastatingly, once a certain threshold has been reached, further escalation in dose intensity may yield no further benefit.

Studies Showing an Advantage for Dose Intensity. A study from the Scottish Gynaecology Cancer Trials Group[85] randomized 159 patients with stages IC to IV disease to cyclophosphamide 750 mg/m^2 plus either cisplatin 50 mg/m^2 or cisplatin 100 mg/m^2 every 3 weeks. Actual received dose intensity for the higher-dose regimen versus the lower-dose regimen was 1.8 to 1. The lower-dose regimen produced significantly less neurotoxicity. At 4 years of follow-up, 32% of those receiving the higher-dose regimen were alive compared to 27% of those on the lower-dose regimen. The ratio of deaths among those receiving the higher-dose regimen versus that of those receiving the lower-dose regimen was 0.52 at 2 years and 0.68 at 4.75 years. These results suggest that in contrast to results in the previous five studies, an advantage that diminished with time occurred for the higher-dose regimen. The investigators' conclusion was that the optimal dose of cisplatin would be 75 mg/m^2 every 3 weeks.

This trial has major problems. First, 49 (31%) of the 159 patients had stage IC or II disease. The heterogeneous patient population resulting from the inclusion of these limited-disease patients makes interpretation of results very difficult, especially when one considers the relatively small total number of patients in the study. Second, the actual difference in 4-year survival of less than 6% is not impressive; and the relative death rate of the higher-dose regimen versus the lower-dose regimen after the first 2 years is 1.30. The overall advantage for the higher-dose regimen is significant only at $P = 0.061$. Finally, the choice of 75 mg/m^2 every 3 weeks as the optimal dose of cisplatin does not follow from the results of the study, which did not deal with the recommended dose.

A Hong Kong trial[91] is the smallest of the randomized studies, with only 50 patients entered. The patient population is not well characterized. Cisplatin doses on the two regimens were 60 mg/m^2 and 120 mg/m^2, respectively. The higher-dose regimen yielded a response rate of 55% and a 3-year survival rate of 60% as compared with lower-dose results of a response rate of 30% and a 3-year survival rate of 30%. Even though these results suggest that the higher-dose regimen offered an advantage, the size of the trial and the poor characterization of the patient population make the conclusions less convincing.

Conclusions Regarding Dose Intensity. In conclusion, the case for the use of regimens with greater dose intensity, especially greater dose intensity of the platinum compound, is unclear at best. To understand the apparent contradiction between in vitro data and clinical results, one must look to certain basic principles on which the concept of the value of dose intensity is based. By using a somatic mutation theory for drug resistance, Coldman and Goldie[92] postulated that the failure to cure a patient of malignancy results from either the failure to eradicate all drug-sensitive cells because of insufficient drug dose intensity or the emergence of cells that were resistant to the drug regimen. Enhanced dose intensity functions in two ways to improve the likelihood of cure: (1) eradicating all sensitive cells and (2) eliminating cells that are likely to mutate to resistance before such mutations take place. No evidence exists that drug resistance can be overcome in vivo by enhancement of dose intensity over the range that can be clinically achieved.

If these considerations are translated into simple terms, increasing dose intensity yields increasing clinical response rates up to the point at which all sensitive cells have been eradicated. Further increase in dose intensity cannot be expected to yield further improvement in results over the currently achievable range. The only basis on which an increased cure rate can be expected from dose escalation is that the drugs are started before the emergence of resistant cells, an unlikely circumstance in patients with advanced disease.

Role of Paclitaxel

Paclitaxel, a new agent with a unique mechanism of action, has significant activity in ovarian carcinoma as second-line therapy with a response rate in excess of 20% in patients, regardless of prior response to platinum-based chemotherapy. These results marked paclitaxel as probably non-cross-resistant with the platinum compounds and alkylating agents and suggested a major role for the drug in first-line treatment of ovarian carcinoma. These data prompted four major randomized trials testing paclitaxel in front-line combination chemotherapy.

GOG Protocol 111[93] randomized 386 newly diagnosed patients with large-volume advanced ovarian carcinoma to six cycles of cisplatin 75 mg/m^2 plus either cyclophosphamide 750 mg/m^2 or paclitaxel 135 mg/m^2 over a 24-hour period preceding the cisplatin. The paclitaxel-based regimen proved superior in regard to overall response rate (73% versus 60%, $P = 0.01$), clinical complete response rate (51% versus 31%, $P = 0.01$), percentage grossly disease free at second-look laparotomy (40% versus 24%, $P = 0.001$), progression-free survival (median, 18 versus 13 months, $P < 0.001$), and overall

Table 93-13 Results of GOG Protocol 111 and EORTC/NCIC OV 10: Cisplatin plus Either Cyclophosphamide or Taxol

	GOG 111*		OV 10†	
	TP	**CP**	**TP**	**CP**
Clinical response rate	73%	60%	59%	45%
Clinical complete response rate	51%	31%	41%	27%
Grossly disease-free second look	40%	24%	—	—
Pathologic complete response	26%	20%	—	—
Progression-free survival	18 months	13 months	15.5 months	11.5 months
Overall survival	38 months	24 months	35.6 months	25.8 months

*TP, paclitaxel 135 mg/m^2/24 hours plus cisplatin 75 mg/m^2 every 3 weeks; CP, cyclophosphamide 750 mg/m^2 plus cisplatin 75 mg/m^2 every 3 weeks. Each regimen given for six cycles; all differences statistically significant except pathologic complete response, for which $P = 0.08$.

†TP, paclitaxel 175 mg/m^2/3 hours plus cisplatin 75 mg/m^2 every 3 weeks; CP, cyclophosphamide 750 mg/m^2 plus cisplatin 75 mg/m^2 every 3 weeks. Each regimen given for up to nine cycles; all differences statistically significant.

Data from references 93 and 94.

survival (median, 38 versus 24 months; $P < 0.001$; Table 93-13). Analysis of comparative risk demonstrated a 33% reduction in morbidity and mortality with the addition of paclitaxel to first-line chemotherapy. Although increased myelosuppression, cardiac problems, and alopecia were found with the paclitaxel-based regimen, no major clinical consequences occurred. In particular, the frequency of grade III or IV neurotoxicity was the same with the two regimens. The conclusion of the GOG is that paclitaxel plus cisplatin is the new standard of care for ovarian carcinoma.

In OV-10,[94] a Canadian/European consortium randomized patients with advanced disease to either cyclophosphamide 750 mg/m^2 plus cisplatin 75 mg/m^2 every 3 weeks for six to nine cycles or paclitaxel 175 mg/m^2 over a 3-hour period followed by cisplatin 75 mg/m^2 every 3 weeks for six to nine cycles. This trial shows superiority for the paclitaxel/cisplatin regimen with regard to response rate (59% versus 45%), clinical complete response rate (41% versus 27%), progression-free survival (15.5 months versus 11.5 months), and overall survival (35.6 months versus 25.8 months). This study confirms GOG 111 and conclusively establishes paclitaxel plus a platinum compound as the standard of care.

GOG Protocol 132[95] was completed before availability of the final analysis of GOG Protocol 111. This trial randomized 613 newly diagnosed patients with large-volume advanced disease to six cycles of either cisplatin 100 mg/m^2 every 3 weeks, paclitaxel 200 mg/m^2 over a 24-hour period every 3 weeks, or paclitaxel plus cisplatin, as in GOG Protocol 111 (Table 93-14). No differences were observed among the three arms with respect to survival. The paclitaxel regimen arm was inferior with respect to response and progression-free survival. It is important to note, however, that this trial did not serve as a confirmatory trial for GOG Protocol 111 for a very important reason. At the time of accrual to GOG Protocol 111, paclitaxel was not commercially available in the United States, whereas it was commercially available at the time of accrual to GOG Protocol 132. Very few of the patients on the nonpaclitaxel regimen in GOG Protocol 111 received paclitaxel at the time of first relapse. Conversely, vast majority of patients on the single-agent regimens of GOG Protocol 132 received the other drug before progression of disease. This pattern of second-line therapy blunts differences among the three regimens.

International Collaborative Ovarian Neoplasm (ICON3)[96] (Table 93-15) is the most recently completed of the four trials and the largest (2074 patients). Several features of this trial distinguish it from the other three and dictate how this study should be evaluated. First, the study included patients with all stages of disease, I to IV. Patients with stage I to II disease represent 20% of the patients; hence, the patient population is very heterogeneous. Second, the regimens are not as well defined as those in the other three trials. A choice was made between two regimens for the control arm, and the arms that involved carboplatin allowed a range of AUC doses as long as a minimum was met. That a choice of control regimens was made is perhaps not such a problem as it might have been, because the results of a randomized trial comparing the two has since been reported as showing no differences.[97] Third, the randomization was 2:1 favoring

Table 93-14 Results of GOG Protocol 132: Comparison of Cisplatin versus Paclitaxel versus Cisplatin plus Paclitaxel

	P	**T**	**TP**
Clinical response rate	67%	42%	66%
Clinical complete response rate	42%	21%	43%
Progression-free survival	16.4 months	10.8 months	14.1 months
Overall survival	30.2 months	25.9 months	26.3 months

P, cisplatin 100 mg/m^2 every 3 weeks; T, paclitaxel 200 mg/m^2/24 hours every 3 weeks; TP, paclitaxel 135 mg/m^2/24 hours plus cisplatin 75 mg/m^2 every 3 weeks. Each regimen given for six cycles. Only statistically significant differences are in failure rates: Paclitaxel alone is inferior to the other two.

Data from reference 95.

Table 93-15 Results of ICON3: Comparison of Carboplatin or CAP versus Paclitaxel versus Carboplatin plus Paclitaxel

	Control*	**TP†**
Progression-free survival	16.1 months	17.3 months
Overall survival	36.1 months	35.4 months

*Control regimens included carboplatin or CAP every 3 weeks: carboplatin AUC minimum 5; CAP, cyclophosphamide 500 mg/m^2, doxorubicin 50 mg/m^2, cisplatin 50 mg/m^2.

†TP, paclitaxel 175 mg/m^2/3 hours, carboplatin AUC minimum 5 every 3 weeks. Each regimen given for six cycles.

Data from reference 96.

the control arm, so twice as many patients were assigned to the control regimens as to paclitaxel plus carboplatin. Fourth, quality control was not as tight as in the other three trials. No pathology review is planned. Surgical requirements were nonexistent. No audit of data is planned. These factors detract from the credibility of this trial in comparison with the other three.

The trial shows no significant differences between the control regimens and the experimental regimen in terms of progression-free and overall survival. This contradicts the results of GOG 111 and OV 10. The deficiencies of the study, however, are such that this trial should not detract from the results of the earlier studies.

Conclusions from these four studies should be based not only on the study results, but also on the quality of the study design and execution. Two trials (GOG 111 and OV 10) show a clear advantage for a taxane/platinum combination. One trial (GOG 132) shows no difference, but crossover before progression in all likelihood means that the study actually evaluated concurrent versus sequential use of the two agents. Even in this setting, the concurrent arm was judged to be the treatment of choice because the overall toxicity was less with the concurrent regimen. The last trial (ICON3) has a number of design problems and lack of data audits; hence, its contrary result should be regarded circumspectly. On the basis of these considerations, the current standard of care should be a combination of paclitaxel plus a platinum compound.

Choice of Platinum Compound

Initial studies of paclitaxel in front-line therapy involved regimens with cisplatin. Interest in substitution of carboplatin for cisplatin results from the ease of administration and decreased nonhematologic toxicity associated with carboplatin. Concerns about the use of carboplatin with paclitaxel focused on an interaction between the two agents.[98] This interaction decreases the amount of thrombocytopenia that was observed with carboplatin such that suppression is less severe, and recovery is usually complete by 3 weeks instead of 4, as is seen with carboplatin alone. The mechanism for this interaction is not yet clear; hence, it is not clear whether the same mechanism might also result in tumor protection. This correlation would result in less efficacy than is observed with paclitaxel/cisplatin. This concern led to three phase III trials comparing paclitaxel plus cisplatin with paclitaxel plus carboplatin.[99–101]

The Dutch trial[99] randomized 208 advanced-disease patients to paclitaxel 175 mg/m^2/3 hours plus either cisplatin 75 mg/m^2 or carboplatin AUC 5 every 3 weeks for at least six cycles. No differences in efficacy were observed, and the carboplatin-based regimen had a better toxicity profile. However, the study was too small to permit definite conclusions to be drawn about therapeutic equivalence between the two regimens.

The AGO trial[100] randomized 798 advanced-disease patients to paclitaxel 185 mg/m^2/3 hours plus either cisplatin 75 mg/m^2 or carboplatin AUC 6 every 3 weeks for six cycles. No differences were observed between the two regimens with regard to progression-free or overall survival, though small trends favored the cisplatin regimen. The cisplatin-based regimen was more toxic and produced a significantly inferior quality of life.

GOG Protocol 158[101] randomized 798 patients with small-volume residual advanced disease to either paclitaxel 135 mg/m^2/24 hours plus cisplatin 75 mg/m^2 or paclitaxel 175 mg/m^2/3 hours plus carboplatin AUC 7.5. This study differs from the other two in several important ways. First, the use of the 24-hour infusion of paclitaxel with cisplatin served to decrease the amount of neurotoxicity that was seen with the cisplatin-based regimen. Second, as a result of the 24-hour infusion, the dose of paclitaxel was different in the two regimens. Third, and most important, the dose of carboplatin was substantially higher in this trial. The study showed no difference in progression-free and overall survival between the two regimens, but a strong trend favored the carboplatin-based regimen, with a hazard ratio for survival of 0.86. As a result of the escalated dose of carboplatin, the toxicity of the carboplatin-based regimen was substantially greater than that reported in the other two trials and did not differ greatly from that seen with the cisplatin-based regimen.

Conclusions from these three trials point to no major differences in efficacy between paclitaxel/cisplatin and paclitaxel/carboplatin. The observed trends, however, raise serious questions about the optimal dose of carboplatin in combination with paclitaxel. At the very least, in combining carboplatin with paclitaxel, an AUC of 6 of carboplatin should be used, and serious consideration should be given to the higher AUC of 7.5.

Consolidation or Maintenance Therapy

For patients with advanced ovarian carcinoma, response rates now approach 90%, clinical complete response rates reach 75%, and median survivals range from 26 months for patients with bulky residual disease to more than 60 months for patients with small-volume residual disease. Despite these excellent results, almost 75% of those who achieve a clinical complete response will relapse eventually and die of their disease.

In addition to the continuing effort to improve further the clinical complete response rate, investigators have conducted studies of ways to consolidate or maintain these responses. Over the last 20 years, none of these studies had produced a positive result.[102] The most recent reports focused on consolidation after six initial cycles of paclitaxel plus carboplatin with four cycles of topotecan.[103,104] Neither study showed any advantage for the consolidation therapy. No evidence now supports a role for consolidation therapy.

The one exception to the plethora of negative studies is a recent phase III randomized trial of extended duration paclitaxel as maintenance therapy.[105] This study differs from prior trials in two significant respects. First, only patients who responded to front-line therapy with a clinical complete response were eligible. Second, evidence suggests that extension of the duration of paclitaxel therapy could be beneficial. This includes anecdotal reports of responses to paclitaxel that did not develop until as late as the twelfth cycle of therapy and preclinical observations of an antiangiogenic effect of paclitaxel over a prolonged period of treatment.[106]

Originally designed to accrue 450 patients with clinical complete responses to paclitaxel/platinum and to randomize these patient to either 3 or 12 additional monthly cycles of paclitaxel 175 mg/m^2/3 hours, the study was closed early because of extreme differences in progression-free survival favoring the 12 additional cycles (Table 93-16). Because of patient choice to cross over to the 12-cycle regimen after study closure, survival is not assessable. Toxicity was obviously greater in the 12-cycle regimen, but only 13 patients in the entire study dropped out because of toxicity. Although one study requires confirmation, the trial should certainly prompt discussion of this issue with each patient, and the evidence poses a convincing case for using 12 additional cycles of paclitaxel monthly as maintenance therapy. Whether 12 cycles is enough could be questioned because

Table 93-16 Results of SWOG and GOG Intergroup Study of Maintenance Therapy*

	3 Cycles	12 Cycles
Patients	107	115
Recurrences	34	20
Progression-free survival†	28 months	21 months

*Comparison of 3 versus 12 cycles of monthly paclitaxel in those with clinical complete response to front-line paclitaxel plus cisplatin.[105]

†The difference in progression-free survival was statistically significant ($P = 0.0023$).

of the observation of an increase in recurrence rate after cessation of the paclitaxel on each arm.

Current Standard of Care

On the basis of the series of studies cited over the last two decades, a solid case points to the combination of paclitaxel 175 mg/m^2/3 hours plus carboplatin AUC 6 to 7.5 every 3 weeks for six cycles as the current standard of care. With this approach, an overall response rate of 95%, a clinical complete response rate of 75%, a pathologic complete response rate of 50%, a progression-free survival of 15 to 24 months, and an overall survival of 26 to more than 60 months should result. These results will vary according to the volume of residual disease; patients with small-volume residual disease (no nodule left >2 cm diameter) experienced better outcome.

After this, the issue of maintenance therapy with 12 cycles of paclitaxel should be discussed with the patient. Patient preference will play a large role in determining whether an individual patient will receive maintenance therapy.

Controversies and Issues

Studies of patients with advanced disease address a number of additional issues: optimal paclitaxel schedule, intraperitoneal chemotherapy, high-dose chemotherapy with stem cell support, integration of new agents (both cytotoxic and biologic) into front-line therapy, the role of second-look laparotomy, and the role of CA-125 in assessing response and progression.

Paclitaxel was initially studied in a number of different schedules, from weekly to every-3-week schedules and from 1-hour to 120-hour infusion durations. By 1990, investigators were exclusively using a 24-hour infusion given every 3 weeks because of the higher incidence of hypersensitivity reactions with shorter infusions. Since then, shorter and longer infusions as well as weekly schedules have been studied.

A great deal of interest focused on the potential for shorter infusions because of the inconvenience of 24-hour infusions. A landmark phase III trial of 3-hour versus 24-hour infusions of paclitaxel as a single agent in relapsed ovarian cancer established the feasibility of short infusions preceded by premedication to prevent hypersensitivity reactions.[107] The study dispelled the myth that the 24-hour infusion had superior efficacy by showing no difference in response rate, progression-free survival, and overall survival. In terms of toxicity, the 3-hour infusion produced significantly less myelosuppression in exchange for increased neurotoxicity and other nonhematologic toxicities.

The theoretical advantages of even longer infusions also have been examined. Two studies of 96-hour infusions, prompted by suggestions in breast cancer that this length of infusion produced responses in some patients for whom shorter infusions had failed, defined no role for this approach. Markman and colleagues[108] treated 30 patients, for whom either a 3-hour or a 24-hour infusion had failed, with a 96-hour infusion of a total dose of 140 mg/m^2, to be repeated every 3 weeks. No objective responses were observed, although the regimen was well tolerated. Subsequently the GOG randomized patients with newly diagnosed advanced ovarian carcinoma to either paclitaxel 135 mg/m^2/24 hr plus cisplatin 75 mg/m^2 every 3 weeks for six cycles or paclitaxel 120 mg/m^2/96 hours plus cisplatin 75 mg/m^2 every 3 weeks for six cycles.[109] No differences in efficacy were observed. Therefore, no reason exists to use a 96-hour infusion in the treatment of ovarian carcinoma.

Of potentially greater interest is a weekly schedule of paclitaxel. An initial phase I study of 40 to 100 mg/m^2/1 hour of paclitaxel weekly demonstrated that this approach was feasible and also suggested potential activity (four responses among 13 patients).[110] This study also suggested that these weekly infusions produced fewer adverse effects. Subsequently, a phase II trial treated 53 patients with paclitaxel 80 mg/m^2/1 hour weekly and reported 13 (25%) responses.[111] A randomized phase III trial of weekly versus every-3-week paclitaxel (67 mg/m^2/3 hours weekly versus 200 mg/m^2/3 hours every 3 weeks), however, showed no difference in efficacy and a small advantage for the weekly regimen in terms of toxicity.[112] It should be pointed out that the dose of the every-3-week schedule is higher than is generally used in ovarian carcinoma, and this might account for the greater toxicity seen with that schedule.

In summary, these data on schedule taken together provide the following points that should be considered in the application of paclitaxel to the treatment of ovarian carcinoma. First, efficacy does not appear to be affected by schedule. Second, toxicity does vary with schedule. Longer infusions produce more myelosuppression, whereas shorter infusions produce more nonhematologic toxicity, such as neurotoxicity. With appropriate premedication, hypersensitivity does not appear to be a major problem regardless of infusion duration. Finally, although the weekly schedule is certainly efficacious and feasible, it appears to offer insufficient advantage in general to justify the greater inconvenience of weekly treatments.

Intraperitoneal Chemotherapy

In an effort directed at achieving ever greater dose intensity, three randomized trials involving intraperitoneal therapy have been reported. The first of these studies, an Intergroup study of the Southwest Oncology Group and the GOG, randomized 654 patients with small-volume residual disease to cyclophosphamide 600 mg/m^2 intravenously plus cisplatin 100 mg/m^2 either intravenously or intraperitoneally.[113] Results show a statistically significant small survival advantage and less tinnitus, clinical hearing loss, and neurotoxicity for patients on the intraperitoneal regimen. The study has a flaw in execution (extension of the accrual goal to increase the size of a subset and then an analysis using all patients, an approach that introduces statistical bias) but does suggest an advantage for intraperitoneal chemotherapy. Somewhat counterintuitively, the study shows that the treatment advantage exists only in patients with somewhat larger nodules (0.5 to 2.0 cm) rather than in the expected 0- to 0.5-cm subgroup.

GOG Protocol 114,[114] a second Intergroup trial involving intraperitoneal therapy, randomized small-volume patients to either paclitaxel plus cisplatin as given in GOG Protocol 111 or two cycles of carboplatin dosed to an AUC of 9 at 4-week intervals followed by six cycles of paclitaxel 135 mg/m^2 intravenously over 24 hours followed by intraperitoneal cisplatin 100 mg/m^2 every 3 weeks. The 523 patients with no nodule larger than 1-cm diameter were randomized to study. The intraperitoneal regimen was superior with regard to progression-free survival (median: 27.6 versus 22.5 months, $P = 0.02$), but only a marginal difference in overall survival was observed (median: 52.9 versus 47.6 months, $P = 0.056$).[114] The gain in efficacy, similar to that seen in the prior intraperitoneal study,[113] came at the expense of significantly more toxicity of all types on the intraperitoneal regimen.

The third intraperitoneal study, GOG Protocol 172,[115] randomized 417 small-volume (<1.0-cm nodules) patients to either paclitaxel plus cisplatin, as given in GOG Protocol 111, or six cycles of paclitaxel 135 mg/m^2 intravenously over 24 hours on day 1, intraperitoneal cisplatin 100 mg/m^2 on day 2, and intraperitoneal paclitaxel 60 mg/m^2 on day 8, with the regimen repeated every 3 weeks. Toxicity was dramatically greater on the intraperitoneal regimen, to such an extent that a substantial portion of the patients were unable to complete six cycles of therapy. Analysis of survival awaits sufficient deaths. Progression-free survival, however, is superior on the intraperitoneal regimen, with a hazard ratio of 0.73.

These three trials make the case that intraperitoneal chemotherapy yields a superior survival compared with standard intravenous chemotherapy in patients with small-volume residual advanced ovarian carcinoma. This benefit is bought at the expense of significantly more toxicity, to such an extent that a substantial portion of the patients cannot complete six cycles of therapy. At least at present, the toxicity of the intraperitoneal regimens tested precludes their routine clinical

use. Current efforts are directed at the development of less toxic intraperitoneal regimens that preserve the apparent survival benefit of the approach.

STEM CELL-SUPPORTED HIGH-DOSE CHEMOTHERAPY. The alternative to intraperitoneal chemotherapy for the achievement of higher dose intensity is the use of stem cell-supported high-dose chemotherapy. As with the use of this approach in other cancers, most studies are small and uncontrolled and show high response rates but short response durations and short survivals.[116] The largest study to date reports on the use of stem cell-supported high-dose chemotherapy in 421 patients for whom prior chemotherapy failed.[117] The population had an average age of 48 years, and 59% were platinum sensitive. The reported response rate was 70% (47% complete response and 23% partial response). The 2-year progression-free survival rate was 12%, and the 2-year overall survival rate was 35%. Although these numbers appear promising, patients with similar demographic and disease features fare considerably better with either intraperitoneal chemotherapy or standard intravenous chemotherapy.

To settle the issue of the role of high-dose chemotherapy with stem cell support, a randomized phase III trial should be conducted. Two attempts, one in Europe and one in the United States, have failed to accrue sufficient patients. Until such a trial demonstrates the value of this approach, high-dose therapy should be reserved for clinical trials, preferably phase III clinical trials.

INTEGRATION OF NEW CYTOTOXIC AND BIOLOGIC AGENTS INTO FRONT-LINE THERAPY. The last 10 years saw a veritable explosion of discovery of new agents, both cytotoxic and biologic, with activity in ovarian carcinoma. Many of these agents are active in patients with disease that is still platinum sensitive, but activity in platinum-resistant disease is minimal or nonexistent. Of particular interest for incorporation into front-line therapy are those agents that have activity in patients who have progressed on or shortly after completion of a paclitaxel/platinum front-line regimen. Such agents may be considered at least partially clinically non-cross-resistant with the taxanes and platinum compounds and thus may add additional benefit to front-line regimens.

At least four cytotoxic agents have activity in patients with "paclitaxel/platinum-resistant" disease: oral etoposide,[118] pegylated liposomal doxorubicin,[119,120] topotecan,[121,122] and gemcitabine.[123–125] These four agents have been the focus of efforts by an international consortium to integrate one or more into front-line therapy. Oral etoposide was dropped from further efforts because of the occurrence of three cases of acute myeloid leukemia among 52 patients in the study of paclitaxel plus carboplatin plus escalating duration of prolonged oral etoposide.[126] The other three agents are being evaluated in an ongoing GOG/Gynecologic Cancer Intergroup trial (Table 93-17) that assesses the impact of a third agent added either as a component of a triplet or as part of a sequential doublet.

Biologic agents that are of interest as part of front-line therapy now include tyrosine kinase inhibitors (Iressa); monoclonal antibodies that target either epidermal growth factor receptor (C-225), HER2-neu (trastuzumab), or vascular endothelial growth factor (bevacizumab); agents that reverse resistance (cyclosporine and valspodar); and interferon-γ. Of these, data are available on trastuzumab, cyclosporine, valspodar, and interferon-γ.

The GOG studied trastuzumab in a population of patients with recurrent or refractory ovarian carcinoma.[127] Of a total of 837 patients who were screened, 95 overexpressed HER2-neu ($2^+/3^+$ by immunohistochemistry). Of these 95 patients, 41 were eligible and assessable and agreed to participate in the trial. Among the 41 patients who were treated with trastuzumab, one complete and two partial responses resulted. Investigators concluded that HER2-neu overexpression occurred less frequently than had previously been reported (12% instead of 25%) and that treatment with trastuzumab had at best modest activity (7%).

Table 93-17 Schema for GOG Protocol 182: An International Trial of the Addition of a Third Agent to Front-Line Therapy

Regimen I:	Paclitaxel plus carboplatin × 8 cycles
Regimen II:	Paclitaxel plus carboplatin plus gemcitabine × 8 cycles
Regimen III:	Paclitaxel plus carboplatin plus PLD × 8 cycles (PLD given every other cycle)
Regimen IV:	Gemcitabine plus carboplatin × 4 cycles followed by paclitaxel plus carboplatin × 4 cycles
Regimen V:	Topotecan plus carboplatin × 4 cycles followed by paclitaxel plus carboplatin × 4 cycles

PLD, pegylated liposomal doxorubicin.
Accrual goal: 4000 patients.

The GOG also evaluated cyclosporine (cyclosporin A) for potential ability to reverse resistance to cisplatin.[128] Preclinical data had suggested that cyclosporin A could inhibit P-glycoprotein and reverse MDR-mediated resistance to cisplatin. Among 26 patients with platinum-resistant disease, only three responses to cisplatin plus cyclosporin A occurred. These data were considered insufficient justification for further study. A related compound (cyclosporine D analog), valspodar, subsequently underwent a phase II and a phase III study of its ability to reverse MDR-mediated resistance to paclitaxel. The GOG phase II study[129] administered the combination to 58 patients with clinical resistance to paclitaxel. Five responses resulted and prompted the performance of a phase III trial by an international consortium.[130] This phase III study in patients with newly diagnosed ovarian carcinoma sought to determine whether the concurrent administration of valspodar with paclitaxel/carboplatin produced results that are superior to that of chemotherapy alone. The study report showed no significant differences in efficacy or toxicity. All trends in both efficacy and toxicity favored the chemotherapy-alone regimen. These three trials suggest that these two compounds have no significant role in the management of ovarian carcinoma.

Studies of interferon-γ report significant activity against ovarian carcinoma by either intraperitoneal or intravenous routes.[131] These results prompted a phase III trial of cyclophosphamide/cisplatin with or without interferon-γ administered by the subcutaneous route.[132] Although this study had to be stopped prematurely because of the emergence of paclitaxel/carboplatin as the new standard of care, the trial did show a statistically significant difference in progression-free survival favoring the interferon-γ regimen. As a result, interferon-γ is being evaluated in an ongoing phase III trial of paclitaxel/carboplatin with or without interferon-γ.

Among other biologic agents, agents that are directed against vascular endothelial growth factor attract the greatest interest because of studies suggesting that high levels of vascular endothelial growth factor in tumor specimens are associated with a poorer prognosis.[133] At this point, however, no data define a clear role for any biologic agent.

ROLE OF CA-125. CA-125, a mucin-like glycoprotein, increases in response to disturbances of the celomic epithelium. The marker is most closely associated with the assessment of patients with ovarian carcinoma. As was discussed earlier, the marker has no defined role in the early detection of ovarian carcinoma. The major clinical role is the assessment of disease status in patients receiving treatment for advanced disease.[134] Because of the difficulty in accurately assessing tumor response in a neoplasm often confined to the peritoneal cavity, interest has developed in defining ways to use CA-125 levels to

determine response.[135] Current proposals focus on definitions based on a 50% or 75% decrease of CA-125 levels during the course of therapy and are currently under review by a committee of the Gynecologic Cancer Intergroup.[136]

Until standard definitions are developed, the marker should be confined to allowing a rough idea of whether disease is responding and should not be used as a response criterion. Decreasing CA-125 levels suggest a favorable response of tumor to therapy, whereas increasing levels suggest progression of disease. Certain principles should guide such a use. First, no single CA-125 value should dictate management decisions; a series of increasing or decreasing values (usually three or more) should be required. Second, changes in the CA-125 level should not result in action until the changes are corroborated by other objective evidence.

SECOND-LOOK LAPAROTOMY. Second-look laparotomy is an exploratory laparotomy that is performed at the conclusion of front-line chemotherapy. The purpose of the procedure is to determine disease status accurately so that decisions regarding further management can be made.[137] Patients who are selected as candidates for second-look laparotomy are usually in one of two categories: those with a clinical complete response to front-line therapy and those who are potential candidates for secondary surgical cytoreduction. Among patients who undergo second-look laparotomy, 40% will have no pathologic evidence of disease, yet half of those with a pathologic complete response will relapse.[138,139]

After widespread use in the 1980s, second-look laparotomies are now performed less frequently. Reasons that are cited for decrease in use of the procedure usually focus on the failure of studies to show that patients who undergo second-look laparotomy have improved survival as a result. The most recent and largest study evaluating second-look laparotomy[101,140] came from data that were collected in a study of paclitaxel/carboplatin versus paclitaxel/cisplatin in patients with small-volume residual stage III ovarian carcinoma (GOG Protocol 158). Institutions were required to specify whether women with clinical complete responses on the study would undergo second-look laparotomy at the conclusion of the protocol-assigned therapy. Roughly half of the patients who were entered in the study did undergo the procedure. GOG investigators compared the outcome for patients who did or did not have a second look. No differences were observed; hence, the investigators concluded that second-look laparotomy was of no value.

The problem with the study is the same flaw that has been seen in other reported studies. The potential value of second-look laparotomy lies in the information gleaned from the procedure. What determines whether that value is realized is the value of the management decision that is made on the basis of the information. The proper study should specify the management choice to be made for each finding at second look so that the study evaluates the package of second-look plus a specified management versus no second look. In conclusion, second-look laparotomy is currently not recommended for routine clinical use (Box 93-1).

Summary of Management of Advanced Disease

Patients with advanced ovarian carcinoma should undergo an initial attempt at surgical cytoreduction followed by chemotherapy. The best evidence shows that paclitaxel combined with carboplatin is the regimen of choice. On completion of initial chemotherapy, the use of an additional 12 cycles of paclitaxel monthly as maintenance therapy should be discussed with the patient. Dose-intense regimens, intraperitoneal therapy, and the addition of a third agent to front-line therapy offer no established advantage and hence should be reserved for clinical trials.

Management of Limited Disease

Patients with stage I or II disease compose approximately 25% of all patients with celomic epithelial carcinoma of the ovary. Only a small proportion of these are ever entered into clinical trials, however; hence until recently, it was difficult to provide definitive guidelines for the management of these patients. Recent randomized trials form the basis of current management principles.

Box 93-1. THERAPEUTIC DECISIONS IN NEWLY DIAGNOSED CELOMIC EPITHELIAL CARCINOMA

Newly diagnosed patients with celomic epithelial carcinoma of the ovary must be carefully staged so that appropriate treatment decisions can be made. This necessitates an exploratory laparotomy in all patients but those who have obvious stage IV disease. At laparotomy, as much disease as possible should be resected. Decisions are then governed by the surgical stage of the disease.

For patients with stage I or II disease, total abdominal hysterectomy and bilateral salpingo-oophorectomy should be done. This should be followed by adjuvant therapy if any of the following are present: poorly differentiated disease (grade III), tumor excrescences on the surface of the ovary, ascites, positive peritoneal cytology, or extraovarian disease. The adjuvant therapy of choice at our institution is platinum-based chemotherapy: carboplatin (AUC 7.5 intravenously) after paclitaxel (175 mg/m^2/3 hours intravenously) every 3 weeks for three cycles. At the conclusion of treatment, close observation will suffice.

For patients with stage III or IV disease, an aggressive attempt at surgical cytoreduction should be followed by platinum-based combination chemotherapy for six cycles. The optimal regimen is the combination of paclitaxel 175 mg/m^2 over a 3-hour period plus carboplatin AUC 6 to 7.5 every 3 weeks for six cycles. At the conclusion of initial chemotherapy, the physician should discuss the issue of maintenance paclitaxel 175 mg/m^2 over a 3-hour period monthly for 12 cycles.

GENERAL CONSIDERATIONS. Certain characteristics of the primary lesion are important in determining the prognosis of the patient with limited disease: histologic grade, location of the primary tumor, ascites, peritoneal cytology, and, to a lesser extent, histologic type. These characteristics permit separation of the patient population into those who are at low risk of recurrence and those who are at high risk[141] (Table 93-18). Patients who are at low risk of recurrence exhibit all the following characteristics: one or both ovaries involved, grade I or II (well or moderately differentiated), intracystic (no tumor on the external surface of the ovary), no ascites, negative peritoneal cytology, and no extraovarian disease. Patients who are at high risk have any one of the following characteristics: grade III (poorly differentiated), extracystic (tumor on the surface of the ovary), ascites, positive peritoneal cytology, or extraovarian (stage II) disease. Patients who are at low risk of recurrence have a 5-year survival rate that exceeds 90%, whereas those who are at high risk have a substantially lower survival rate.[142]

The assignment of a patient to a risk category should be based on a careful exploratory laparotomy performed through an incision that permits the exploration of the entire abdominal contents. Ascites should be noted, and samples for cytology should be taken. In the absence of ascites, peritoneal washings for cytology should be obtained. The capsule of the tumor should be inspected for excrescences, dense adherence, or rupture. The peritoneal surface should be carefully examined for implants of tumor. Areas that require particular attention include the undersurface of the diaphragm, the paracolic gutters, and the omentum. Biopsies should be obtained of any suggestive lesion and, in the absence of suggestive areas, of multiple sites. The para-aortic nodes should be examined and sampled. Finally, after inspection of the entire peritoneal surface, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy should be carried out.

Table 93-18 Risk Groups for Limited Ovarian Carcinoma

Group	Characteristics
Low risk	Grade I or II disease
	Intact capsule
	No tumor on external surface
	Negative peritoneal cytology
	No ascites
	Growth confined to ovaries
High risk*	Grade III disease
	Ruptured capsule
	Tumor on external surface
	Positive peritoneal cytology
	Ascites
	Growth outside ovaries

*If any high-risk factors are present, the patient is considered high risk.

Data from Young RC, Walton L, Ellenberg SS, et al: Adjuvant therapy in stage I and stage II epithelial ovarian cancer: results of two prospective randomized trials. N Engl J Med 1990;322:1021–1027.

Because selection of therapy will be based on risk category, a detailed staging procedure is mandatory. In a series of 100 patients who were referred after initial laparotomy-based diagnosis of stage I or II ovarian carcinoma and then reexplored, 31 patients were found to have more advanced disease than was noted at initial laparotomy. Such upstaging can have a significant impact on choice of therapy.

MANAGEMENT. The initial approach to patients with limited disease should be surgical resection of disease. This should be combined with a careful staging laparotomy that defines in detail the anatomic extent of disease. However, controversy characterizes recommendations for the use of adjuvant therapy after surgical resection. At least three different approaches have been used in uncontrolled trials: abdominopelvic radiation therapy, intraperitoneal radioactive chromic phosphate (^{32}P), and chemotherapy.

Radiation Therapy. The use of radiation therapy in the management of ovarian carcinoma fell into disfavor because of two flawed approaches to its use: pelvic radiation therapy as an adjuvant to surgical resection of stage I disease[143,144] and abdominopelvic radiation therapy in patients with gross disease. The first approach failed because a significant proportion of the patients who were treated with pelvic fields already had at least microscopic disease outside the pelvis. The second approach attempted the eradication of disease that was too bulky to handle with the doses that were achievable to a whole-abdominal field. Results with abdominopelvic radiation therapy as an adjuvant treatment in patients with stage I through III disease and no gross residual suggest that the potential role of radiation therapy should be reconsidered.

Investigators at the Princess Margaret Hospital in Toronto, Ontario, Canada, randomized patients with stage I, stage II, and minimal residual stage III disease to either abdominopelvic radiation to a total of 22.5 cGy by a moving-strip technique or pelvic radiation with or without chlorambucil. Patients with stage III disease were not randomized to pelvic radiation alone. The study demonstrated clear superiority for abdominopelvic radiation.[145] A follow-up trial that compared abdominopelvic radiation by a moving-strip and open field technique showed no difference.[146]

A subsequent analysis of patients who received abdominopelvic radiation in these two studies looked at the results in patients who were at intermediate or high risk of recurrence on the basis of histologic type, grade, and stage.[147] Of 211 patients who were at intermediate risk, only 60 were assigned to stage I; the 5-year survival rate was 75%. Of 88 patients who were at high risk of recurrence, there were 72 stage III patients and 16 stage II patients; the 5-year survival rate was 32%. Two groups of patients did not benefit from abdominopelvic radiation: those with stage I grade I disease and those with large-volume disease (nodules >2 cm).

An important problem with these studies is the lack of careful surgical staging, as evidenced by the large number (155 of 325) of patients who were assigned to stage II, an uncommon stage in appropriately evaluated patients. This is a major inconsistency in a patient population that purports to serve as the basis for determining prognostic features that can identify low-risk, intermediate-risk, and high-risk patient subsets.

Despite the questionable nature of the surgical staging, the Princess Margaret Hospital experience makes a strong case for a role for abdominopelvic radiation in the management of patients with limited disease who are at significant risk for recurrence. The comparisons with pelvic radiation with or without chlorambucil do not permit conclusions as to the relative merits of abdominopelvic radiation versus chemotherapy because the chemotherapy that was used consisted of suboptimal doses of a single alkylating agent.

Supporting these observations are a number of uncontrolled reports in the literature.[148,149] These experiences confirm that patients with gross disease, particularly those with nodules greater than 2 cm in diameter, do not benefit significantly from radiation.

In contrast to these experiences is one earlier M.D. Anderson Hospital trial of 149 patients with stage I, II, or minimal residual stage III disease who were randomized to either abdominopelvic radiation by the moving-strip technique or oral melphalan. A 10-year follow-up evaluation showed no difference in survival.[150] The study has been criticized for imbalances in prognostic factors favoring the chemotherapy regimen and for problems with the radiation technique used.

On the basis of current evidence, abdominopelvic radiation cannot be recommended as adjuvant therapy in limited disease. Studies suggesting efficacy have critical flaws. However, further study is indicated on the basis of the Princess Margaret Hospital experience.

Radioactive Isotopes. The intraperitoneal administration of radioactive isotopes to treat limited-stage ovarian cancer after surgical resection has been proposed as a promising approach.[151–157] Early studies were characterized by small numbers of patients accrued over many years, lack of control groups, and inadequate surgical staging. Despite these limitations, reported survival rates were sufficiently high to include this modality as one treatment regimen in three major randomized trials described.[142,158,159]

This approach is based on the facts that ovarian carcinoma spreads initially primarily by intraperitoneal seeding and that ^{32}P is an emitter of beta-radiation, which has a maximum tissue penetration of 3 to 4 mm, with an effective penetration of probably no more than 2 mm. Whereas ^{32}P could not be expected to be effective in patients with visible disease, it might well be an effective agent in patients with microscopic or no documentable residual disease after surgical resection. Uncontrolled trials in limited disease as well as reports of efficacy in patients who have achieved a pathologic complete response of more advanced disease with initial chemotherapy supported the possible efficacy of this approach.[149] A subsequent randomized trial (GOG Protocol 95) comparing intraperitoneal ^{32}P with cyclophosphamide/cisplatin showed a superior progression-free survival with chemotherapy and also highlighted distribution problems and bowel toxicities associated with ^{32}P. The GOG investigators concluded that chemotherapy was the preferred treatment for high-risk limited ovarian carcinoma and essentially laid to rest any role for ^{32}P.[160]

SINGLE ALKYLATING AGENTS. Single alkylating agents, most commonly melphalan, appear to offer benefit in uncontrolled trials.[150,160] One series compared melphalan with abdominopelvic radiation and showed similar survival between the two regimens and an advantage for melphalan because of less toxicity.[150] The other study retrospectively evaluated 50 patients with limited disease accrued over a 13-year period and treated with single-agent melphalan.[160] The survival rate at 2 years was 98%, and that at 4 years was 94%. Consistency of surgical staging techniques was not documented in the report. To draw definite conclusions about the efficacy of melphalan from these reports is impossible, but survival figures suggest that melphalan could be an effective adjuvant therapy.

RANDOMIZED TRIALS. Superseding the previously described uncontrolled trials are nine major randomized trials comparing modalities as adjuvant therapy in patients with limited disease: GOG Protocol 1, a National Cancer Institute of Canada Clinical Trials Group study, two critically important trials from the combined efforts of the Ovarian Cancer Study Group and the GOG, two European trials, two additional studies of the GOG, and the combined analysis of two European trials (ICON1/ACTION).

GOG PROTOCOL 1. GOG Protocol 1, conducted during 1970 to 1976, was a phase III trial of patients with stage I ovarian carcinoma.[144] Although all patients underwent exploratory laparotomy, routine exploration of the diaphragm, lymph node sampling, peritoneal cytology, and omentectomy were not required because the importance of these procedures as a part of careful staging was not fully understood. After surgical resection of disease, patients were randomized to either no further therapy, pelvic radiation to 50 cGy, or chemotherapy consisting of melphalan (0.2 mg/kg/day orally) for 5 days every 4 weeks. Of the 168 patients who were entered into the study, only 86 were both eligible and evaluable, a major problem.

An analysis of prognostic factors showed an even distribution of prognostic factors, except that the control arm contained a greater percentage of favorable histology and stage IA. Among 29 patients who were randomized to no further therapy, five (17%) recurrences were found; among 23 patients who were given pelvic radiation, seven (30%) had a recurrence; and among 34 patients who received melphalan, only two (6%) had recurrence. The difference between melphalan and pelvic radiation was significant ($P < 0.05$).

This trial suggests that patients with limited disease benefit from the use of adjuvant melphalan, but flaws in study execution and the relatively small number of evaluable patients prevent definitive conclusions. The results do indict pelvic radiation as an inadequate approach. The analysis of prognostic factors also points to the importance of grade, histologic type, and extracystic tumor in determining patient outcome.

NATIONAL CANCER INSTITUTE OF CANADA CLINICAL TRIALS GROUP STUDY. This investigation of patients with stage I or IIA high-risk (defined by rupture of a malignant ovarian cyst, poorly differentiated disease, extracystic excrescences of tumor, or positive peritoneal cytology), stage IIB, or stage III with disease confined to the pelvis[158] randomized subjects to pelvic radiation to 45 cGy plus either abdominal radiation to 22.5 cGy, radioactive chromic phosphate 15 mCi intraperitoneally, or melphalan (8 mg/m^2/day orally) for 4 days every 4 weeks for 18 months. Of 257 eligible and evaluable patients, 107 were randomized to abdominopelvic radiation, 106 to pelvic radiation plus melphalan, and 44 to pelvic radiation plus intraperitoneal ^{32}P. The arm including intraperitoneal chromic phosphate was closed early because of an unacceptably high incidence of delayed toxicity. No differences in disease-free or overall survival or in recurrence rate were noted among the three arms. The investigators concluded that the survival results of all three arms point to the need for further improvement in adjuvant therapy.

Table 93-19 Results of OCSG and GOG Protocol 7601*

	Observation	Melphalan
Patients	38	43
Recurrences	4	1
Deaths	4	2
Disease-free 5-year survival rate	91%	98%
Overall 5-year survival rate	94%	98%

*Randomized trial of patients who were at low risk of recurrence.

Data from Young RC, Walton L, Ellenberg SS, et al: Adjuvant therapy in stage I and stage II epithelial ovarian cancer: results of two prospective randomized trials. N Engl J Med 1990;322:1021–1027.

OVARIAN CANCER STUDY GROUP AND GOG STUDIES. These studies were conducted from 1976 to 1986.[142] The first study, OCSG/GOG Protocol 7601, randomized 81 patients with stage I disease at low risk of recurrence (defined as those patients with well- or moderately well-differentiated intracystic lesions associated with no extraovarian neoplasm, no ascites, and negative peritoneal cytology after a careful and detailed exploratory laparotomy) to either no further therapy (38 patients) or melphalan 0.2 mg/kg/day orally for 5 days every 4 weeks for up to 12 cycles (43 patients). At a median follow-up in excess of 6 years, only six deaths had been observed: four in the control arm and two in the melphalan arm. Five recurrences have been observed: four in the control arm and one in the melphalan arm. No significant differences in recurrence rate, disease-free survival, and survival were noted between the two arms (Table 93-19).

The second trial, OCSG/GOG Protocol 7602, involving 141 patients with stage I high-risk disease (defined as having one or more high-risk feature—that is, poorly differentiated disease, extracystic tumor, ascites, positive peritoneal cytology, or extraovarian lesions—or stage II disease completely resected) randomized subjects to either intraperitoneal radioactive chromic phosphate 15 mCi (73 patients) or melphalan (0.2 mg/kg/day orally) for 5 days every 4 weeks for up to 12 cycles (68 patients). At a median follow-up of more than 6 years, 34 (24%) recurrences were seen, 16 (22%) of 73 in the ^{32}P arm and 18 (26%) of 68 in the melphalan arm. Over the same period, 31 (22%) deaths occurred, 16 (22%) of 73 in the ^{32}P arm and 15 (22%) of 68 in the melphalan arm. The 5-year disease-free survival rate for both arms is 80%. No significant differences between arms are present in regard to recurrence rate, disease-free survival, or overall survival (Table 93-20).

Table 93-20 Results of OCSG and GOG Protocol 7602*

	Intraperitoneal ^{32}P	Melphalan
Patients	73	68
Recurrences	14	13
Deaths	16	15
Disease-free 5-year survival rate	80%	80%
Overall 5-year survival rate	78%	81%

*Randomized trial of patients at high risk of recurrence.

Data from Young RC, Walton L, Ellenberg SS, et al: Adjuvant therapy in stage I and stage II epithelial ovarian cancer: results of two prospective randomized trials. N Engl J Med 1990;322:1021–1027.

Italian Trial. An Italian trial,[161] reported in 1992, grouped patients with limited disease into three categories: a low-risk group including stage IA G1 and stage IB G1 with no extracystic involvement (93 patients), an intermediate-risk group including stage IAG2–3 and stage IBG2–3 with no extracystic involvement (91 patients), and a high-risk group including stage I patients with extracystic involvement (185 patients; Table 93-21). Patients in the low-risk group were followed up on no active treatment after surgical resection and demonstrated a 5-year disease-free survival rate of 90% with five relapses and three disease-related deaths.

Patients in the intermediate-risk group were randomized to either cisplatin 50 mg/m^2 every 4 weeks for six cycles, or no further treatment after surgical resection. The 5-year disease-free survival rate was 76% in the cisplatin arm and 58% in the control arm. Eighteen relapses and nine disease-related deaths were observed. The difference in disease-free survival was significant ($P < 0.05$) in favor of the cisplatin arm.

Patients in the high-risk group were randomized to either cisplatin (50 mg/m^2) every 4 weeks for six cycles or chromic phosphate (15 mCi intraperitoneally). The 5-year disease-free survival rate in the cisplatin arm was 84% versus 61% in the ^{32}P arm, a difference that was statistically significant ($P < 0.01$) in favor of the cisplatin arm. Forty relapses and 25 disease-specific deaths were observed.

Norwegian Study. A Norwegian study[162] that was reported in 1992 randomized 265 patients with stage I limited disease to either cisplatin or intraperitoneal ^{32}P, as in the Italian trial. The trial is difficult to interpret on the basis of the only report to date because of the inclusion of patients with borderline lesions (low malignant potential) and because of a failure to separate patients into low-risk and high-risk groups.

GOG Protocol 95. The GOG randomized 205 patients with high-risk limited disease after complete surgical resection to adjuvant therapy consisting of either intraperitoneal ^{32}P or three cycles of cyclophosphamide 1000 mg/m^2 plus cisplatin 100 mg/m^2.[163] The recurrence-free rate at 5 years was 77% on the chemotherapy regimen versus 66% with ^{32}P. The estimated relative risk is 0.693, favoring the chemotherapy regimen ($P = 0.075$). The 5-year survival rate was 84% for the chemotherapy and 76% for the ^{32}P group. Patients receiving the intraperitoneal ^{32}P experienced problems with distribution of the compound in the abdominal cavity and also with bowel toxicities. The GOG concluded from these data that chemotherapy represented the preferred treatment (Table 93-22).

Table 93-21 Results of a Randomized Trial Involving 369 Patients with Stage I Ovarian Carcinoma

Treatment	Relapses	Deaths	5-Year Disease-Free Survival Rate (%)
Group A: IAiG1 and IBiG1 ($N = 93$)	5	3	
No further therapy			90
Group B: IAiG2–3 and IBiG2–3 ($N = 91$)*	18	9	
No further therapy			58
Cisplatin			76
Group C: IAii, IBii, and IC ($N = 185$)†	40	25	
^{32}P			61
Cisplatin			84

i, no extracystic tumor; ii, extracystic tumor.

*In group B, the disease-free survival rate is significantly different ($P < 0.05$) in favor of cisplatin.

†In group C, the disease-free survival rate is significantly different ($P < 0.01$) in favor of cisplatin.

Data from Bolis G, Colombo N, Favalli G, et al: Randomized multicenter clinical trials in stage I epithelial ovarian cancer [abstract]. Proc ASCO 1992;11:225.

Table 93-22 Results of GOG Protocol 95*

	Intraperitoneal ^{32}P	CP†	Relative Risk
Patients	98	107	
Recurrence free at 5 years	66%	77%	0.693‡
Alive at 5 years	76%	84%	

*Randomized trial of patients at high risk of recurrence.[163]

†Cyclophosphamide 1000 mg/m^2 plus cisplatin 100 mg/m^2. Repeat every 3 weeks times 3.

‡$P = 0.075$.

ICON1/Action. The combined efforts of the ICON and the European Organization for Research and Treatment of Cancer produced a combined analysis of two randomized studies of adjuvant chemotherapy in patients with limited disease.[164] Both groups required that patients have stage I to IIA disease and that patients be randomized after surgical resection to either no further therapy or adjuvant chemotherapy containing a platinum compound. Of 925 patients who were randomized to the two studies, at a median follow-up of 4 years, 245 patients had either died or experienced recurrence of disease. The recurrence-free survival rate at 5 years was 76% in the chemotherapy arm and 65% in the observation arm (relative risk: 0.64, $P = 0.001$). The overall 5-year survival rate was 82% in the chemotherapy arm and 74% in the observation arm (relative risk: 0.67, $P = 0.008$). This study marks the first report of improved overall survival with chemotherapy and establishes chemotherapy as the standard of care after surgery in patients with high-risk limited disease (Table 93-23).

GOG Protocol 157. The GOG randomized 457 patients with high-risk limited ovarian carcinoma after complete surgical resection to paclitaxel 175 mg/m^2/3 hours plus carboplatin AUC 7.5 every 3 weeks for either three or six cycles.[165] The basis for this trial included the prior studies that showed an advantage for chemotherapy in high-risk limited disease[163,164] and the randomized trials that established paclitaxel/carboplatin as the standard of care for advanced

Table 93-23 Results of ICON and ACTION*

	Observation	Chemotherapy	Relative Risk
Patients	460	465	
Recurrence free at 5 years	65%	76%	0.64†
Alive at 5 years	74%	82%	0.67‡

*Randomized trial of patients at high risk of recurrence.

†$P = 0.001$.

‡$P = 0.008$.

Data from Vergote I, Trimbos B, Guthrie D, et al: Results of a randomized trial in 923 patients with high-risk early ovarian cancer, comparing adjuvant chemotherapy with no further treatment following surgery [abstract]. Proc ASCO 2001;20:201a.

disease.[93,94,100,101] The chemotherapy regimen that was adopted was the one used in GOG Protocol 158.[101] A large proportion of the patients failed to meet the surgical requirements of the trial (107 of 457, or 23%), so the study was analyzed both with and without these patients. Both analyses showed a reduction in recurrence rate that did not reach statistical significance (relative risk: 0.69 without the surgical exclusions and 0.77 with the exclusions, neither of which was statistically significant). Both also showed no significant difference in survival at 5 years (79% compared to 84% in group without exclusions; Table 93-24).

CONCLUSIONS. The results of the nine randomized trials provide guidelines for the management of patients with limited disease. First, the trials demonstrate the importance of careful surgical staging to establish the patient's risk of recurrence. Second, patients who are at low risk of recurrence have a 5-year survival rate exceeding 90% with or without adjuvant therapy. Additional treatment after surgical resection does not appear to be indicated. Third, patients who are at high risk of recurrence appear to benefit from adjuvant therapy. The weight of evidence supports the use of cisplatin-based chemotherapy as the adjuvant therapy of choice. Although definitive statements about regimen and duration are difficult, it would seem reasonable to use paclitaxel/carboplatin, as in GOG Protocol 157, for at least three cycles of therapy (Box 93-2).

Management of Recurrent, Persistent, or Progressive Disease

Although debate continues about the optimal choice of drugs, dose schedule, and route of administration, platinum-based combination chemotherapy yields the following results in patients with advanced disease:[93,94,100,101] an overall response rate of 95%, a clinical complete response rate of 75%, a pathologic complete response rate of 40% to 50%, a 10-year survival rate of 15% to 40%, and a recurrence rate after clinical complete response of 75% and after pathologic complete response of 40% to 60%. Patients who initiate front-line therapy with small-volume residual disease will fare better than those who start chemotherapy with large-volume residual disease. The fact remains, however, that a majority (60% to 75%) of patients with ovarian carcinoma will require further therapy for recurrent, persistent, or progressive disease. The factors that affect the choice of that therapy and the specific options available are now considered.

RECURRENT DISEASE POPULATION. Long-term follow-up evaluation of 726 women who were treated for ovarian carcinoma on GOG protocols[166,167] identified a number of characteristics associated with increased likelihood of recurrence: clear cell or mucinous histology, non-platinum-based treatment, poor performance status, older age, higher stage, clinically measurable disease, larger residual tumor volume, and ascites. In addition, an analysis of those factors that predict recurrence after pathologic complete response[168] shows that histologic grade is an important determinant of relapse rate, with grade I having a relapse rate of 22%; grade II, 39%; and grade III, 56%.

None of these factors provides guidance in the selection of appropriate subsequent therapy. However, an additional factor that does appear to provide a basis for choosing salvage therapy is the result of immediately preceding therapy. Patients who respond to previous platinum-based therapy and who demonstrate a significant treatment-free interval have a high probability of responding again to platinum-based treatment.[169–174] Patients who progressed during or shortly after completion of platinum-based therapy are unlikely to respond to further treatment with a platinum compound and should be considered for therapy with non-cross-resistant agents.[63–71,118–125,127,175–207] Discussion of salvage therapy is based on this division of patients into "sensitive" and "resistant" populations based on responsiveness to initial platinum-based treatment (Table 93-25).

Table 92-24 Results of GOG Protocol 157*

	TP 3 3 Cycles*	TP 3 6 Cycles†	Relative Risk
Patients	213	216	
Recurrence free at 5 years	75%	81%	0.77‡
Alive at 5 years	79%	84%	

*Randomized trial of patients at high risk of recurrence.
†Paclitaxel 175 mg/m²/3 hours plus carboplatin AUC 7.5. Repeat every 3 weeks.
‡$P = 0.109$.
Data from Bell J, Brady M, Lage J, et al: A randomized phase III trial of three versus six cycles of carboplatin and paclitaxel as adjuvant treatment in early stage ovarian epithelial carcinoma: a Gynecologic Oncology Group study [abstract]. Gynecol Oncol 2003;88:156.

Box 93-2. THERAPEUTIC CHOICES IN RECURRENT, PERSISTENT, OR PROGRESSIVE CELOMIC EPITHELIAL CARCINOMA

Choices of therapy for progressive, persistent, or recurrent celomic epithelial carcinoma of the ovary hinge on the patient's response to front-line therapy. Patients who respond to initial chemotherapy, who become disease free, and who experience a treatment-free interval of 6 months or longer are highly likely, at recurrence, to be responsive to platinum-based salvage therapy. These platinum-sensitive patients should be retreated with a platinum-based combination regimen. The currently preferred regimen is carboplatin AUC 6 to 7.5 intravenously after paclitaxel 175 mg/m²/3 hours intravenously every 3 weeks. Patients who fail to respond should be deemed platinum resistant and treated accordingly. Those who respond and become disease free with a treatment-free interval of at least 6 months should once again receive platinum-based therapy.

Patients whose disease progresses while they are receiving initial therapy, who have persistent disease at the conclusion of initial treatment, or whose tumor recurs within 6 months of initial therapy should be regarded as platinum resistant. These patients should be treated with regimens that induce responses in platinum-resistant disease. Repeated platinum-based therapy is not indicated. Single agents that achieve responses in resistant patients include weekly paclitaxel, docetaxel, pegylated liposomal doxorubicin, oral etoposide, topotecan, tamoxifen, gemcitabine, navelbine, and ifosfamide. No evidence supports the use of combinations in resistant patients. Therapy should be continued until disease progression or achievement of complete response.

Approaches that should be reserved for clinical trials only include high-dose therapy with autologous bone marrow transplantation or peripheral stem cell support, intraperitoneal therapy, and biologic agents.

MANAGEMENT OF PLATINUM-SENSITIVE PATIENTS

IMPORTANCE OF TREATMENT-FREE INTERVAL. Until recently, most studies of patients who have recurrent, persistent, or progressive disease after initial chemotherapy focused on identification of the activity of new drugs or approaches as a basis for the subsequent testing of these active regimens in phase III studies of front-line therapy. As a result, determination of optimal therapy for this setting was extrapolated from data that had been collected for other purposes. These efforts have led to the conclusion that the most important determinant of the likelihood of a response in the setting of progressive, persistent, or recurrent disease is the treatment-free interval.

Succinctly stated, the duration of the interval from the conclusion of preceding therapy to the need for further therapy influences the likelihood of the patient's responding to the chosen further therapy.

Table 93-25 Definitions of Platinum-Sensitive and Platinum-Resistant Patients for Decision Making in Salvage Treatment

Group	Description
Platinum sensitive	Initial response to platinum
	Platinum-free interval: >6 months
Platinum resistant	Progression on platinum
	Best response stable to prior platinum
	Relapse <6 months after prior platinum

The longer the interval, the greater is the likelihood of a response.[173] To illustrate this principle, four among many studies are examined.

In the first example, intravenous cisplatin-based therapy as salvage treatment was evaluated retrospectively in 72 patients with measurable disease who had received at least two cisplatin- or carboplatin-based regimens and had demonstrated a platinum-free interval of at least 4 months between the completion of the first regimen and initiation of the second.[173] The overall response rate was 43% (31 of 72 with 10 pathologic complete responses). The response rate increased as the platinum-free interval increased. In patients with an interval of 5 to 12 months, the response rate was 27% (5% pathologic complete responses); in those with an interval of 13 to 24 months, it was 33% (11% pathologic complete responses); and in those with an interval of more than 24 months, it was 59% (pathologic complete responses, 22%).

In the second example, a salvage regimen of weekly cisplatin combined with either epirubicin or etoposide[174] yielded a 60% response rate (25% complete response) with a median duration of response of 7 months and a median survival of 13.5 months in 40 patients who had responded to initial platinum-based therapy. The longer the disease-free interval before relapse, the greater was the likelihood of response.

In the third example, the combination of carboplatin (300 mg/m^2) on day 8 preceded by cyclophosphamide (100 mg/m^2/day) on days 1 to 7 in 28 patients produced nine objective responses (five complete and four partial).[171] Six of these responses (46%) occurred among 13 patients who were initial responders and hence platinum sensitive. Only three responses (20%) were observed among the 15 platinum-resistant patients. The relatively high response rate among the platinum-resistant group may be accounted for by the response definitions, because the platinum-resistant group included patients with platinum-free intervals of up to 12 months' duration.

The fourth example evaluated the platinum analog iproplatin at an initial dose of 270 mg/m^2 in patients with recurrent disease after prior cisplatin or carboplatin treatment.[172] Among 78 resistant patients, nine responses (three complete and six partial, 12%) were observed. Among the 19 sensitive patients, five responses (two complete and three partial, 26%) were observed.

These four examples demonstrate that patients who respond to platinum-based therapy initially and relapse after a significant platinum-free interval have a high likelihood of responding again to intravenous platinum-based treatment. The correct definition of a significant platinum-free interval is unclear, although the data suggest that the longer the interval, the more likely is the response. Most studies use the interval of 6 months as the point that defines platinum sensitivity.

Choice of Regimen. The principle of the treatment-free interval appears to apply regardless of the drug or regimen that is chosen.[120] Virtually all active drugs tested to date appear to fare better in the platinum-sensitive group than in the platinum-resistant group. The frequency of response, however, does appear to depend on the drug chosen. For any given point along the plot of treatment-free interval, the frequency of response to platinum-based therapy is 1.5 to 2.0 times greater than that reported with nonplatinum agents or regimens.[122,171–174,185,187] In addition, the duration of response and survival is better with platinum-based regimens than with alternative, nonplatinum-containing regimens.[208]

Debate has focused on whether a platinum compound as a single agent offered a less toxic and equally efficacious alternative to combination chemotherapy in the setting of platinum-sensitive disease. A phase III trial has directly addressed this question. ICON4 randomized patients with platinum-sensitive disease, defined as a treatment-free interval from prior therapy of at least 6 months, to a platinum-containing regimen with or without a taxane.[209] The vast majority of patients received either single-agent carboplatin or a combination of paclitaxel/carboplatin. The analysis showed that the patients receiving the taxane/platinum regimen had a superior response rate (66% versus 54%, $P = 0.06$), a superior progression-free survival (50% progression-free versus 40% at 1 year, hazard ratio = 0.76; $P < 0.001$), and a superior overall survival (57% alive versus 50% at 2 years, hazard ratio = 0.82; $P = 0.023$; Table 93-26). This is the first study in the second-line setting to show a survival advantage for combination chemotherapy over a single agent and establishes a taxane/platinum combination as the preferred treatment for patients with platinum-sensitive disease. (A confirmatory trial will be required to make this the standard of care.)

Dose-Intense Second-Line Chemotherapy. Studies of dose-intense approaches to salvage chemotherapy for ovarian carcinoma[117,210–212] purport to show an advantage for such approaches based on the observation of responses in the recurrent-disease situation. The problem with the interpretation of many of these reports is the lack of information on prior response to platinum-based treatment. Without such data, one cannot determine whether the observed responses occurred only in platinum-sensitive patients at a rate that is expected with standard IV platinum therapy or whether platinum-resistant patients are responding to the higher-dose schedules.

Two reports[169,170] do provide this critical information. The first of these is a study of high-dose carboplatin (800 mg/m^2 intravenously) every 5 weeks in 30 patients who had previously been treated with cisplatin.[169] Eight objective responses (27%) were observed, none in patients with progressive disease during platinum-based therapy.

The second report examined retrospectively two phase II trials of salvage cisplatin-based intraperitoneal therapy.[170] Among 89 patients, 52 were considered platinum sensitive, and 37 were considered platinum resistant. Among the sensitive patients, 29 (56%) developed an objective response; 17 were pathologic complete responses. Among the resistant patients only four responded (11%), all partially.

These two reports suggest that the increase in dose intensity that is achievable by dose escalation or intraperitoneal administration of drug

Table 93-26 Results of ICON and OVAR 2.2*

	Platinum	Taxane/ Platinum	Relative Risk
Patients	410	392	
Response	54%	66%	
Progression free at 1 year	40%	50%	0.76†
Alive at 2 years	50%	57%	0.82‡

*Randomized trial of patients with platinum-sensitive recurrent disease.
†$P < 0.001$.
‡$P = 0.023$.
Data from Schwartz P, Keating G, MacLusky N, et al: Tamoxifen therapy for advanced ovarian cancer. Obstet Gynecol 1982;59:583–588.

cannot overcome true clinical resistance. Although this does not rule out the ability of an even greater dose intensity to overcome resistance, the fact that intraperitoneal drug administration with a fairly significant enhancement of drug exposure to cells did not yield a significant response rate in resistant patients certainly argues against the likelihood that other dose-intense programs will succeed. Conversely, the activity of these approaches in sensitive patients is on the same order as that reported with standard intravenous doses of platinum-based regimens.[116] There is little evidence so far to support the routine clinical use of such dose-intense approaches in the salvage setting.

Conclusions. Evidence supports the use of platinum-based therapy to treat patients with recurrent disease who responded to prior platinum-based therapy and experienced at least a 6-month treatment-free interval before recurrence. In such a setting, platinum-based therapy is far more likely to produce a response than is any alternative. Furthermore, recent evidence supports the use of a taxane/platinum-based combination regimen. The goal of therapy in this setting should be both improvement in survival and palliation. Dose-intense approaches do not appear to offer any advantage over standard intravenous doses.

MANAGEMENT OF PLATINUM-RESISTANT PATIENTS. Successful management of platinum-resistant patients (less than 6-month treatment-free interval after a preceding platinum-based regimen) depends on the identification of agents that are non-cross-resistant with the platinum compounds. Until 1989, essentially no such agents had been identified. Now a number of agents have been shown to produce objective responses in patients who have failed to respond to platinum-based initial therapy. Among these are paclitaxel,[57,63–66] docetaxel,[67–71] pegylated liposomal doxorubicin,[119,120,187–190] oral etoposide,[118,191–194] topotecan,[121,122,183–185] tamoxifen,[204–206] gemcitabine,[123–125] vinorelbine,[195–199] and ifosfamide.[57,213–215] Although each of these agents appears to be more active in platinum-sensitive patients, major interest has been generated primarily by their activity in resistant patients.

In platinum-resistant patients, paclitaxel achieves responses in 24% to 30% of patients in phase II trials.[63–66] This agent is clearly the treatment of choice in patients whose disease has failed to achieve an objective response to initial platinum-based regimens. Because paclitaxel is now a part of standard front-line therapy, current focus is on agents that have activity in patients who have disease that is resistant to both the platinum compounds and paclitaxel. Six agents have demonstrated such activity: docetaxel, weekly paclitaxel, pegylated liposomal doxorubicin, topotecan, oral etoposide, and gemcitabine.

To date, no evidence suggests an advantage for combination chemotherapy over single-agent therapy in the platinum-resistant setting; hence, platinum-resistant patients should be treated with single-agent therapy consisting of one of the six agents that have demonstrated activity against resistant disease. The goal in this setting is palliative because no evidence indicates that therapy in this setting prolongs survival.

Other potential options for treatment of resistant ovarian carcinoma include more dose-intense therapy, biologic agents, and hormones. The lack of evidence supporting the value of more dose-intense approaches has been described. Insufficient data are available to establish the value of biologic agents in resistant disease.

CONCLUSIONS REGARDING SALVAGE THERAPY. The current management of patients with ovarian carcinoma who have recurred after initial platinum-based chemotherapy rests on consideration of the results of the initial chemotherapy. Patients who respond to the initial platinum-based therapy and relapse after a platinum-free interval should be considered clinically sensitive to further platinum-based treatment. Recent evidence suggests that combination chemotherapy with a taxane/platinum combination produces a superior response rate and better progression-free and overall survival. Such therapy will yield response rates as high as 60%, with up to 25% of patients achieving a complete response and also median survivals that exceed 2 years. No evidence indicates that more dose-intense approaches yield better results in these patients than results with standard intravenous schedules.

Patients who fail to respond to initial platinum-based therapy or who relapse shortly after completion of initial therapy should be regarded as clinically resistant to further platinum-based treatment. These patients should be treated with drugs that have been shown to have activity against resistant disease: weekly paclitaxel, docetaxel, pegylated liposomal doxorubicin, oral etoposide, topotecan, tamoxifen, gemcitabine, navelbine, and ifosfamide. No evidence exists that combinations of these drugs are more effective than single-agent therapy.

CONTROVERSIAL ISSUES. Two specific situations in the management of patients with recurrent, persistent, or progressive disease deserve further comment: patients who have a rising CA-125 level as the only evidence of recurrence or progression and potential candidates for secondary surgical cytoreduction.

Patients with Increasing CA-125 Only. With the advent of the widespread use of CA-125 to monitor patients with ovarian carcinoma, an increasingly common situation to confront the physician is that of the patient who develops an increasing CA-125 level but is otherwise free of any evidence, objective or otherwise, of recurrence and is asymptomatic. Because of the high level of awareness of CA-125, patients naturally obsess about their CA-125 values and often demand that the physician intervene with therapy in such a situation. Unanswered as yet is the question as to what is the best choice for these patients: treatment or observation until the development of other objective evidence of disease or of symptoms.

Until recently, all treatment in the second-line setting was regarded as purely palliative. In such circumstances, the rationale for waiting until the patient developed either symptoms or other objective evidence of recurrence, which was almost always followed shortly thereafter by symptoms, was obvious. Except for patients who demanded treatment, the general recommendation was that treatment should await the onset of symptoms or the appearance of other objective evidence of disease.

With the report of the results of ICON4/OVAR 2.2[209] and the demonstration that survival could be improved by treatment in the platinum-sensitive setting, the question of immediate treatment should be revisited. As of this writing, no such study is under way; hence, treatment decisions must be made in the absence of definitive evidence. The best recommendation is to discuss the issue with the patient. In the absence of a preference on the patient's part, a policy of watchful waiting until the development of symptoms would seem to be most prudent.

Potential Candidates for Secondary Surgical Cytoreduction. Secondary surgical cytoreduction is debulking that is performed in the patient with recurrent, persistent, or progressive disease before the use of second-line chemotherapy.[216] Mixed results have been reported with secondary debulking.[217,218] The benefit appears to depend on careful selection of candidates for the procedure. Patients whose disease can be surgically cytoreduced to the point at which no gross disease remains appear to be the patients who benefit from the procedure.[219] The procedure should therefore probably be reserved for those patients in whom the surgeon feels that complete resection of all gross disease can be achieved. To some extent, the benefit that is observed also depends on the availability of chemotherapy that will follow the procedure and to which the patient is likely to be sensitive.

Special Situations

The natural history and spread patterns of celomic epithelial carcinomas of the ovary create at least two special circumstances with

which the clinician must deal: intestinal obstruction and malignant effusions.

INTESTINAL OBSTRUCTION. Up to one half of patients with ovarian carcinoma develop symptoms of gastrointestinal obstruction (nausea, vomiting, abdominal pain, and obstipation), most commonly related to progressive cancer rather than to adhesions.[220,221] Small bowel and, to a lesser extent, colonic and gastric outlet obstruction can occur. Nonoperative management with intravenous hydration, intestinal intubation, and parenteral hyperalimentation is acceptable initial management, but only 10% to 30% of cases of true obstruction will be relieved by such an approach; the majority of patients who are so relieved develop recurrent obstruction within 1 month.[222,223]

Surgical management of intestinal obstruction is the remaining option if no relief is obtained with noninvasive measures. If surgery is used indiscriminantly, median survival after such an approach is uniformly less than 8 months and not dramatically different from that seen in patients who are managed without surgery. The selection of patients to be considered for surgery will depend on several features: performance status, contraindications to general anesthesia, and availability of effective postoperative chemotherapy. Particularly in patients who are still potentially sensitive to chemotherapy, surgical relief of the obstruction is warranted.[224]

MALIGNANT EFFUSIONS. Although malignant effusions associated with ovarian carcinoma can involve any one of three cavities (peritoneal, pleural, or pericardial), only the first two are sufficiently common to warrant detailed consideration. With regard to the first of these, ascites is by far the most common of the effusions. At initial diagnosis, ascites is frequent but seldom severe enough to require specific intervention and usually responds to systemic chemotherapy with resolution after one to two cycles of treatment.[225] For cases that are resistant to systemic chemotherapy and productive of significant problems, paracentesis provides symptomatic relief. Intraperitoneal bleomycin[226,227] and peritoneovenous shunts[228,229] have been used in particularly troublesome cases, but success is temporary and most often related to concomitant chemotherapy the patient received.

Pleural effusions occur in 25% to 30% of patients and are cytologically positive for malignant cells in 75% of cases.[230] When symptomatic, these effusions should be approached with thoracentesis. For patients who are receiving first-line chemotherapy, the pleural effusion usually responds and does not become a recurring problem, whereas patients with recurrent disease and associated pleural effusion, particularly those with platinum-resistant disease, can experience major problems with rapid reaccumulation of fluid after thoracentesis. In such cases, drainage of the fluid with a thoracostomy tube can provide complete resolution of the problem in 36% to 55% of patients.[231,232] Instillation of sclerosing agents such as tetracycline, talc, or bleomycin can significantly improve the rate at which complete resolution is observed.[233] Patients with persistent problems after all these measures can be considered for pleurectomy or thoracopic pleurodesis.[234,235]

Germ Cell Cancers

Approximately 5% of ovarian cancer consists of germ cell carcinomas, which are classified into two broad groups: dysgerminomas and nondysgerminomas[236] (Table 93-27). The same staging system as that used for celomic epithelial carcinomas is used for these tumors. Management begins with exploratory laparotomy to determine extent of disease and to permit surgical resection if possible. Subsequent treatment depends on histology and findings at laparotomy that place patients into one of two groups: those with stage I to III disease that has been completely resected and those with incompletely resected stage III and IV disease. Therapeutic decisions, however, are based on comparisons with historic controls, because these lesions are sufficiently uncommon that randomized trials are not feasible.

Table 93-27 Classification of Ovarian Germ Cell Carcinomas

Dysgerminoma
Nondysgerminoma
Teratoma
Immature
Mature
Monodermal or specialized
Endodermal sinus tumor
Embryonal carcinoma
Choriocarcinoma
Polyembryoma
Mixed cell tumors

Data from Gershenson DM, Malone JM Jr: Chemotherapy for malignant germ cell tumors of the ovary. In Deppe G (ed): Chemotherapy of Gynecologic Cancer, 2nd ed. New York, Wiley-Liss, 1990, pp 217–239.

Tumor Markers

Ovarian germ cell tumors produce markers in most cases. α-Fetoprotein elevations have been noted in patients with endodermal sinus tumors, immature teratomas, mixed germ cell tumors, embryonal carcinomas, and polyembryomas. Elevations of human chorionic gonadotropin have been observed with choriocarcinomas, embryonal carcinomas, polyembryomas, mixed cell tumors, and, less commonly, dysgerminomas. These markers are useful in assessing response to chemotherapy and in monitoring patients who are in complete remission for evidence of recurrence.

Stage I to III Completely Resected

In patients with completely resected stage I, II, or III endodermal sinus tumors, mixed cell tumors, embryonal carcinomas, choriocarcinomas, and immature teratoma, the recurrence rate is high enough to warrant adjuvant therapy. The largest experience with adjuvant chemotherapy is that of the GOG in studies evaluating adjuvant VAC (vincristine, actinomycin D, and cyclophosphamide) and adjuvant BEP (bleomycin, etoposide, and cisplatin).[237–239]

The relative value of these regimens is best established by comparison with historic data on no adjuvant therapy (Table 93-28), which shows a steady increase in the percentage of patients remaining disease free at 16 months of follow-up, as treatment progresses from no adjuvant through VAC to BEP. On the basis of these data, adjuvant BEP is the treatment of choice for patients with completely resected stage I to III disease and specific histologies: immature teratoma grade II and III, endodermal sinus tumor, mixed cell tumor, embryonal carcinoma, and choriocarcinoma. For other histologic types, data are insufficient to permit definitive conclusions (Box 93-3).

Stage III Incompletely Resected and Stage IV Disease

At least two chemotherapy regimens are active in patients with advanced or recurrent disease: VAC and PVB (cisplatin, vinblastine, and bleomycin)[239] (Table 93-29). The cisplatin-based combination yields higher response rates and a greater percentage of patients who remain disease free for extended periods. The current study of the GOG evaluates a combination of bleomycin, etoposide, and cisplatin.

Rare Malignant Ovarian Tumors

Accounting for fewer than 5% of all malignant ovarian tumors are a variety of rare ovarian neoplasms, including granulosa cell tumors,

Table 93-28 GOG Trials of Adjuvant Chemotherapy for Ovarian Germ Cell Carcinoma

Therapy	Endometrial Sinus Tumor and Mixed Cell Tumor	Immature Teratoma
No adjuvant	34/165 (21%)*	36/56 (64%)
VAC†	53/82 (65%)	59/70 (84%)
BEP‡	30/31 (97%)	18/19 (95%)

*Percentage of patients remaining disease free at a median follow-up of 16 months after completion of therapy.

†VAC, vincristine (1.5 mg/m^2 intravenously, maximum 2 mg), every 2 weeks, × 12, actinomycin D (350 µg/m^2/day intravenously) × 5 days every 4 weeks × 6, and cyclophosphamide (150 mg/m^2/day intravenously) × 5 days every 4 weeks × 6.

‡BEP, bleomycin (20 U/m^2 intravenously, maximum 30 units) per week × 9, etoposide (100 mg/m^2/day intravenously) × 5 every 3 weeks × 3, and cisplatin (20 mg/m^2/day intravenously) × 5 every 3 weeks × 3.

Data from Slayton RE, Park RC, Silverberg SG, et al: Vincristine, dactinomycin and cyclophosphamide in the treatment of malignant germ cell tumors of the ovary: a Gynecologic Oncology Group study: a final report. Cancer 1985;56:243–248; Williams S, Blessing J, Liao S, et al: Adjuvant therapy of ovarian germ cell tumors with cisplatin, etoposide, and bleomycin: a trial of the Gynecologic Oncology Group. J Clin Oncol 1994;12:701.

thecoma-fibroma tumors, Sertoli-Leydig cell tumors, gynandroblastomas, and steroid cell tumors. Such lesions are best treated with surgical resection if only limited disease is present. Appropriate management of more advanced disease is unclear. Although both radiation therapy and chemotherapy have been used in the management of advanced disease and as adjuvant therapy for limited disease, evidence is largely anecdotal. It is therefore not possible to make definitive recommendations for the management of more advanced cases.

Box 93-3. THERAPEUTIC DECISION IN NEWLY DIAGNOSED GERM CELL CARCINOMAS

Patients with germ cell carcinomas should be divided into two groups: those with stage I to III disease that has been completely resected and those with incompletely resected stage III and IV disease. After complete resection, patients with endodermal sinus tumor, mixed cell tumor, embryonal carcinoma, choriocarcinoma, or immature teratomas, grade II or III, should receive adjuvant therapy consisting of VP-16 100 mg/m^2/day intravenously plus cisplatin 20 mg/m^2/day intravenously for 5 days every 3 weeks for three cycles and bleomycin 30 units intravenously weekly for the 9 weeks of the three cycles. Second-look laparotomy at the conclusion of therapy is unnecessary if all clinical evidence of disease has disappeared and if both α-fetoprotein and human chorionic gonadotropin levels are normal.

Patients with incompletely resected stage III and IV disease, regardless of histologic type, should be treated with four cycles of the combination described earlier. Those with complete remission, including normalization of α-fetoprotein and human chorionic gonadotropin, can be followed with no further treatment. Those with persistent disease will require further therapy with other active agents, but the precise nature of this therapy has not been defined. Other active drugs include actinomycin D, ifosfamide, and other alkylating agents, anthracyclines, methotrexate, and the vinca alkaloids.

Because most tumors produce either α-fetoprotein or human chorionic gonadotropin or both, therapy should be monitored with the appropriate markers. Subsequent follow-up management of complete responders also should include the marker(s) that were positive.

Table 93-29 GOG Trials of Two Three-Drug Combinations in Incompletely Resected Stage III and IV Germ Cell Carcinomas of the Ovary

Histology and Therapy	Complete Response	Partial Response	Disease Free
Immature teratoma			
VAC*	—	—	4/8 (50%)
PVB†	2/9 (22%)	2/9 (22%)	12/24 (50%)
Endodermal Sinus Tumor and Mixed Cell Tumor			
VAC	—	—	3/14 (21%)
PVB	13/24 (54%)	8/24 (33%)	31/58 (53%)
Dysgerminoma			
PVB	3/4 (75%)	1/4 (25%)	7/8 (88%)
Choriocarcinoma			
PVB	2/3 (67%)	1/3 (33%)	2/3 (67%)

*VAC, vincristine (1.5 mg/m^2 intravenously, maximum 2 mg), every 2 weeks × 12, actinomycin D (350 µg/m^2/day intravenously), × 5 days every 4 weeks × 6, and cyclophosphamide (150 mg/m^2/day intravenously), × 5 days every 4 weeks × 6.

†PVB, vinblastine (12 mg/m^2 intravenously) every 3 weeks × 4, bleomycin (20 U/m^2 intravenously, maximum 30 units) per week, and 12 cisplatin (20 mg/m^2/day intravenously), × 5 every 3 weeks × 3–4.

Data from Williams SD, Blessing JA, Moore DH, et al: Cisplatin, vinblastine, and bleomycin in recurrent ovarian germ cell tumors: a trial of the Gynecologic Oncology Group. Ann Intern Med 1989;3:22–27.

CANCER OF THE FALLOPIAN TUBE

The fallopian tube is the least common site of origin in the female genital tract for cancer. The most common histologic type of cancer, accounting for 90% of all malignancies of the tube, is papillary serous adenocarcinoma, but even this type is rare, with only 300 cases reported annually in the United States. The pattern of spread is similar to that seen with celomic epithelial lesions of the ovary, dissemination throughout the peritoneal cavity being perhaps the most important route of spread; hence, it is often difficult to distinguish between ovarian and fallopian tube primary tumors. Criteria have been set for lesions that are designated to be of fallopian tube origin:[240,241] The main tumor arises from the endosalpinx and is in the tube; the histologic pattern shows a papillary pattern; a transition zone between benign and malignant epithelium must be demonstrable if the wall is involved; and the ovaries and endometrium must be either normal or less involved than the tube.

As a reflection of the propensity of tubal cancer to spread by intraperitoneal dissemination, 5-year survival rates correlate well with the degree to which the primary lesion penetrates the wall of the tube: 91% for intramucosal lesions, 53% for those with mucosal wall invasion, and 25% or less for lesions that penetrate the tubal serosa.[242] The actual staging system that is used, however, is a modification of the FIGO staging system for ovarian cancer (see Table 93-1).

In contradistinction to ovarian cancer, fallopian tube cancers tend to be first seen at an earlier stage of development: roughly 33% as stage I, 33% as stage II, and 33% as more advanced disease. The mainstay of therapy for patients with limited disease is surgical resection. Whether postoperative radiation therapy is of value as an adjuvant treatment in patients whose tumors have been completely resected is unclear in the absence of a randomized trial. If radiation therapy does have a role, it would seem to be in patients who have no gross disease. Studies of chemotherapy in fallopian tube carcinoma are anecdotal. Agents that have been noted to produce responses are the same that have been noted to be active in celomic epithelial

Box 93-4. THERAPEUTIC DECISIONS IN FALLOPIAN TUBE CARCINOMAS

Firm recommendations on the management of fallopian tube carcinomas are difficult because of the lack of extensive clinical studies. With the best evidence available, four basic groups of patients are found.

Intramucosal Lesions Only
For patients with intramucosal lesions only, cure is excellent with surgical resection. Patients should undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy and should be monitored closely with no further therapy.

Mucosal Wall Invasion
For patients with mucosal wall invasion, the recurrence rate is approximately 50%. These patients are candidates for adjuvant therapy, but no data support the use of such treatment. If adjuvant therapy is to be used, choices similar to those for high-risk ovarian carcinoma seem reasonable. If radiation therapy is to be used, it would seem appropriate to treat the entire abdominal cavity. A preferable approach would be the use of platinum-based chemotherapy, on the assumption that this disease responds similarly to the response of celomic epithelial carcinoma.

Penetration of the Serosa
For patients with penetration of the serosa but no gross spread, the recurrence rate exceeds 75%. An even stronger case for the use of adjuvant therapy can be made. The choices are similar to those noted earlier.

Metastatic Disease
For patients with obvious spread of disease to locoregional and distant sites, platinum-based chemotherapy is a reasonable choice.
The overall strategy should be similar to that used for patients with advanced or recurrent celomic epithelial carcinoma of the ovary.

carcinoma of the ovary. It would seem reasonable to base the choice of systemic therapy in advanced or recurrent disease on extrapolation from data in ovarian carcinoma (Box 93-4).

FUTURE DIRECTIONS

The development of additional information about the nature and management of germ cell cancers and rarer malignant tumors of the ovary as well as fallopian tube cancer will continue to be restricted by the low frequency of these lesions. With regard to celomic epithelial carcinomas of the ovary, however, progress should continue to be rapid. Current and future investigational efforts focus on several distinct areas: biology of ovarian carcinoma, screening and early detection, the proper role of surgery, new agents and their role in systemic therapy, and the role of dose-intense approaches.

First, with regard to the biology of ovarian carcinoma, specific studies are seeking (1) to characterize factors associated with ovarian carcinoma and its outcome, such as specific genetic defects associated with hereditary ovarian carcinoma, various oncogenes, and DNA ploidy; (2) to identify features that are predictive of the likelihood of developing ovarian carcinoma; and (3) to ascertain the biologic reasons for the observation that more aggressive disease is associated with older patients. As these and other investigations expand the understanding of the basic nature of ovarian carcinoma, the development of better and more specific methods for early detection and treatment of the disease should become possible. Where this line of work will ultimately lead is speculative but exciting.

Second, the evolution of effective techniques for screening for and early detection of ovarian carcinoma has a high priority in ovarian carcinoma, the only one of the major gynecologic cancers for which early detection is not the rule. Most interest centers on the potential for transvaginal sonography, especially when enhanced by color-flow Doppler, to permit earlier detection of disease. The recent report of potential value for proteomic patterns in the serum for early detection of ovarian carcinoma has focused on the biologic front as well. Confirmation of the value of such approaches must await larger trials.

Third, although the efficacy of initial surgical cytoreduction in patients with stage III disease has been accepted on the basis of retrospective analyses, prospective trials are needed to address several important questions. Two trials of interval surgical cytoreduction at the midpoint of a series of chemotherapy courses suggest a role for this procedure in patients with a less than optimal initial surgical effort. Prospective randomized trials of initial or secondary surgical cytoreduction have not been performed. Investigations of the relative merits of each of these approaches versus no surgery are needed, as well as trials evaluating which of these points in the therapy represents the optimal time to introduce surgical resection into the management of advanced disease. Such studies are difficult to conduct because of the widespread acceptance of the role of surgical cytoreduction in ovarian carcinoma.

Fourth, efforts continue to investigate the role of new agents in the management of ovarian carcinoma. Current interest continues to center on further delineation of the role of a number of promising new cytotoxic and biologic agents. The plethora of new agents with activity in patients who are clinically resistant to the platinum compounds and paclitaxel opens the possibility for the addition of clinically non-cross-resistant drugs to front-line paclitaxel/platinum therapy. Defining the role of these new agents is of paramount importance.

Finally, dose intensity continues to command significant interest. Three basic ways to enhance the dose intensity have been proffered: escalation of dose within the range that can be achieved without marrow reconstitution, high-dose chemotherapy with support of autologous bone marrow transplant or peripheral stem cell transfusion, and, in the case of ovarian carcinoma, intraperitoneal administration of drug. Eight randomized trials of dose escalation over a standard range of doses have been completed. Six show no advantage to a doubling of dose intensity, and the other two have major design problems. Further exploration of this approach seems unwarranted.

Although uncontrolled studies and anecdotal reports of high-dose chemotherapy with marrow reconstitution appear promising, the highly selected nature of the patients and the expense of the procedures mandate that randomized, comparative trials demonstrate the superiority of this approach over standard therapy before it can be considered a valid part of the therapeutic armamentarium.

Intraperitoneal administration of drug, although it has been under study for more than a decade, still has no defined role in management. In the salvage setting, it appears to have no advantage over intravenous therapy. In the setting of first-line treatment, three large randomized trials in patients with small-volume disease show small advantages at the expense of markedly enhanced toxicity. The final determination of the role, if any, for intraperitoneal therapy awaits the development of less toxic regimens. If a role for intraperitoneal therapy exists, data show that it will be in only those patients with extremely small-volume disease or perhaps no residual disease; hence, its role will be a very narrow one.

In conclusion, the future holds the promise of continuing advances in the management of patients with celomic epithelial carcinoma of the ovary. Although the explosion of knowledge of the basic nature of the disease holds the greatest potential for improvement, the identification of an effective screening technique, the clarification of the role of surgery in advanced disease, and the introduction of exciting new biologic and cytotoxic agents offer the promise of better treatment in the immediate future. The great promise of dose-intense regimens, which are still worthy of further investigation, suffers from a growing body of evidence that no advantage is obtained at least over the clinically achievable range of doses unsupported by marrow reconstitution.

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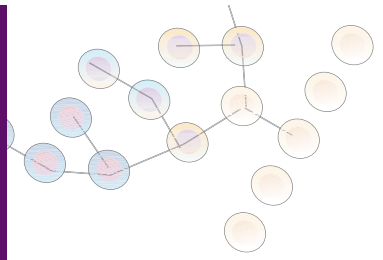
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94 Gestational Trophoblastic Disease

Donald Peter Goldstein and Ross Stuart Berkowitz

SUMMARY OF KEY POINTS

Incidence and Epidemiology
- The incidence of complete hydatidiform mole is approximately 1 in 1500 pregnancies in the United States.
- The incidence of partial hydatidiform mole is approximately 1 in 750 pregnancies.
- Repeat moles occur in 1 in 100 pregnancies, and third moles occur in 1 in 25 pregnancies.
- Complete hydatidiform mole is usually due to an androgenetic diploid conception, in which a haploid sperm fertilizes an egg that lacks female chromosomes.
- A partial hydatidiform mole develops when dispermy occurs, and the resulting conceptus is triploidy.

Pathology
- Earlier diagnosis of complete hydatidiform mole due to improved ultrasound and human chorionic gonadotropin (hGC) assays has made the pathologic diagnosis of complete hydatidiform mole more difficult because of its resemblance to partial hydatidiform mole and nonmolar abortions.
- Hydatidiform mole is characterized by hydropic villi with trophoblastic hyperplasia.
- Invasive mole is characterized by invasion of myometrium by hydropic villi surrounded by hyperplastic trophoblasts.
- Choriocarcinoma is characterized by sheets of neoplastic cytotrophoblasts and syncytiotrophoblasts invading tissue and is associated with necrosis and hemorrhage. Hematogenous spread occurs early.
- Placental site trophoblastic tumor is a rare form of choriocarcinoma made up of mononuclear cells from the implantation site that invade myometrium. Placental site trophoblastic tumor metastasizes late and is relatively resistant to chemotherapy.

Clinical Features
- Hydatidiform mole presents in the first trimester with vaginal bleeding.
- Complete hydatidiform mole is usually diagnosed by ultrasound because of the abnormal appearance of the placenta and the absence of a fetus.
- Partial hydatidiform mole can be difficult to diagnose by ultrasound and is usually confirmed pathologically.
- Persistent gestational trophoblastic disease after molar pregnancy is usually nonmetastatic and is characterized by a rising hCG level and persistent bleeding due to residual molar tissue.
- Metastatic gestational trophoblastic neoplasms after hydatidiform mole usually involves the lungs and, rarely, the brain, liver, and other sites.
- The diagnosis of gestational trophoblastic neoplasis after a miscarriage or term pregnancy can be delayed and can present with significant disease.

Staging and Classification
- The 2002 International Federation of Gynecologists and Obstetricians Staging System combines an anatomic description of the disease (i.e., stages I, II, III, and IV) with a prognostic scoring system.

Primary Therapy
- Single-agent therapy is usually curative in patients with stage I, II, and III disease who have low prognostic scores (<7).
- Patients with stage II, III, and IV disease who have high risk scores (≥7) require combination chemotherapy for optimal outcome.
- Survival rates of 100% in patients with stage I, II, and III disease and 80% in patients with stage IV disease should be achieved with proper staging and the use of well-accepted therapy.
- Response to therapy and remission are determined by hCG levels, which should be tested weekly during chemotherapy.
- Patients with high-risk disease should be treated with three or four consolidation courses after the hCG titer normalizes.

Complications
- Toxicity from the chemotherapeutic agents is the most common early complication.
- Other complications relate to the extent of disease and are usually due to internal bleeding.

Prognosis
- Most women survive their disease and are able to achieve subsequent pregnancy.
- The vast majority of patients are cured and are able to return to normal activity soon after attaining a normal hCG titer.

INTRODUCTION

Terminology

Gestational trophoblastic disease (GTD) is a heterogeneous group of interrelated lesions that is biologically unique for several reasons:

- It elaborates a tumor marker, human chorionic gonadotropin (hCG).
- It is exquisitely sensitive to chemotherapy.
- It has a unique immunobiologic relationship with its host, since it arises from fetal rather than maternal tissue.

Several histologically distinct entities make up GTD:

- Hydatidiform mole (partial and complete)
- Persistent or invasive gestational trophoblastic neoplasia
- Choriocarcinoma
- Placental site trophoblastic tumors

Complete and partial moles are abnormal pregnancies and are considered benign. The last three entities are called gestational trophoblastic neoplasms (GTNs) and are considered malignant because of their potential for local invasion and metastases. GTN is one of the rare human malignancies that can be cured even in the presence of widespread metastases. The term GTN is used instead of the more specific morphologic entity because treatment is frequently undertaken without knowledge of the precise histology.

When GTN develops after evacuation of an hydatidiform mole, the resulting tumor morphologically is either an invasive mole, a choriocarcinoma, or, on rare occasion, a placental site trophoblastic tumor. The tumor that develops after a term pregnancy or miscarriage histologically is choriocarcinoma or placental site trophoblastic tumor, as there is no molar disease in these gestations. When GTN develops after an ectopic pregnancy, the tumor morphology can be molar, choriocarcinoma, or placental site trophoblastic tumor.

Relevant Historical Issues

GTD has an ancient and interesting history going back to Hippocrates, who in 400 B.C. described the passage of hydropic villi from the uterus as "uterine dropsy." The first recorded description of molar pregnancy appeared in *Uterus Hydropii* by Aetius of Amida (c. 483–565 A.D.), who observed that "when the menses have been suppressed for some time and the patient has not become pregnant, the uterus becomes filled with tumor and small bladder-like objects are developed in the fluid." In 1565, Von Grafenburg first described the clinical condition of what we now call a "classical mole." In 1827, Velpeau and Boivin correctly observed that hydatids represented cystic dilatation of chorionic villi. In 1895, Marchand reasoned that choriocarcinoma is an epithelial tumor from the trophoblast.

An important milestone in the history of GTD occurred in 1928, when Ascheim and Zondek first described a reliable pregnancy test, which became the basis for the early measurements of hCG. In 1963, MacVicor and Donald first used ultrasound in the diagnosis of molar pregnancy. In 1977, Kajii and Ohama[1] elucidated the androgenetic origin of hydatidiform moles. Finally, in 1978, Szulman and Surti[2] described the genetic basis for partial mole as a triploid gestation.

Prior to the introduction of chemotherapy, survival with GTN remained limited and precarious, as the only form of treatment consisted of hysterectomy or local excision of metastatic sites where possible. In 1959, Brewer[3] reviewed survival with choriocarcinoma at the Albert Mathieu Chorioepithelioma Registry at Northwestern University. Only 6 of 103 patients with metastatic choriocarcinoma (CCA) were free of disease at 5 years after their diagnosis. Brewer's group also analyzed the 5-year survival rates in patients with nonmetastatic CCA treated by hysterectomy. Only 29 of 70 patients (41%) with presumably localized tumor survived, despite prompt hysterectomy. The remaining patients developed metastases after the operative procedure and died from widely disseminated disease.

A new era in the management of GTN was inaugurated in 1956, when Li and colleagues[4] reported the complete regression of metastatic CCA in three women who were treated with methotrexate. In 1961, Hertz and coworkers[5] reported the initial 5-year experience with chemotherapy for metastatic GTN from the National Cancer Institute. Complete remission was achieved with methotrexate in 28 of 63 patients (47%) who had metastatic disease. After obtaining dramatic results with chemotherapy in disseminated disease, Hertz and associates[6] successfully employed chemotherapy for nonmetastatic tumors. During the 1960s, it became apparent that certain patients with metastatic GTN were relatively resistant to single-agent chemotherapy and experienced a high mortality rate. In 1965, Ross and colleagues[7] reported that patients with prolonged delay in diagnosis, high hCG levels, and liver and/or brain metastases were resistant to treatment with single-agent therapy. The use of intensive combination chemotherapy for so-called high-risk metastatic disease has resulted in substantial improvement in survival.

During the past three decades, the management of GTN has been guided by the results from various regional centers. Virtually all patients with nonmetastatic and low-risk metastatic GTN can now expect to achieve cure with chemotherapy, with preservation of reproductive function in the vast majority of cases. Patients with widespread disease also can anticipate an 80% survival rate. Treatment of GTN represents one of the most dramatic successes of chemotherapy in the treatment of human malignancy.

INCIDENCE AND EPIDEMIOLOGY

The reported incidence of GTD varies significantly in different regions of the world. For example, the frequency of molar pregnancy in Asian countries historically has been seven to ten times greater than the reported incidence in Europe or North America.[8] Japan has a reported incidence of 2 in 1000 pregnancies, which is twofold to threefold higher than the incidence in Europe or North America. The incidence of hydatidiform mole in Taiwan is reported to be one in 125 pregnancies. In Ireland, the incidence of complete and partial moles has been determined to 1 in 1945 and 1 in 695 pregnancies, respectively.[9] In the United States, hydatidiform moles are encountered in 1 in 600 therapeutic abortions and in 1 in 1000 pregnancies.

Although much of the geographic variation in the incidence of molar disease could be due to differences in reporting rather than to true differences in incidence, the high incidence of molar pregnancy in some populations has been attributed to nutritional and socioeconomic factors. Acosta-Sisson and Espaniola[10] carefully studied cases of molar pregnancy that were managed at the Philippine General Hospital. Hydatidiform mole was detected infrequently among wealthy Filipino patients. Although molar pregnancy was diagnosed in 1 in 200 pregnancies in indigent patients, molar gestation occurred in only 1 in 2000 pregnancies in the affluent population. In Korea, the incidence of molar pregnancy has shown a considerable and continuing decrease over the past four decades, presumably owing in part to changing social conditions, including completion of childbearing at an earlier age and improved nutrition.[11] Marked differences in the incidence of molar pregnancy and GTN also occur among various socioeconomic groups in this country. The risk of molar pregnancy or GTN has been reported to two to three times greater in American Indians than in Caucasians, but the incidence in American Indians is declining.[12,13]

Low levels of carotene (vitamin A precursor) and animal fat intake might explain some of the global differences in the incidence of complete mole. We have observed in a case-controlled study that the risk of complete molar pregnancy is associated with low levels of consumption of these nutrients.[14] Parazzini and colleagues[15] also reported from Italy that low carotene consumption was associated with molar pregnancy. Geographic areas with a high incidence of vitamin A deficiency correspond to regions with a high incidence of molar pregnancy.

The risk of having a complete molar pregnancy also increases with increasing maternal age.[8] Women older than age 40 have a 5- to 10-fold greater risk of having a complete molar gestation. Ova from older women could be more susceptible to faulty fertilization and abnormal embryonic development. There does not appear to be any significant association with gravidity or the age of the male consort. The risk for both complete and partial molar pregnancy is increased in women with histories of prior spontaneous abortion and infertility.[16] Women with a history of one molar pregnancy have an approximately 1% chance of a repeat mole in subsequent pregnancies. The risk after two molar pregnancies increases to 16% to 28%.[17]

Certain epidemiologic features of complete and partial mole differ markedly. Parazzini and coworkers[16] reported that the risk for partial mole was not associated with maternal age. Additionally, the risk for partial mole has been reported to be associated with the use of oral contraceptives and a history of irregular menstruation but not with dietary factors.[18] Therefore, the risk of partial mole appears to be associated with reproductive history rather than dietary factors.

The overall incidence of invasive mole has been estimated at 1 in 15,000 pregnancies. Approximately 15% to 29% of hydatidiform moles will result in invasive mole. Choriocarcinoma is reported to occur in 1 in 40,000 pregnancies. Approximately 3% to 5% of hydatidiform moles progress to CCA, which accounts for almost 50% of cases. Twenty-five percent of CCA cases follow abortion or tubal pregnancy (1 : 15,000), and 25% are associated with term pregnancies (1 : 150,000).

ETIOLOGY AND PATHOGENESIS

Our perspectives on the etiology and pathogenesis of hydatidiform mole and GTN have become focused significantly over the past few years. The etiology of hydatidiform mole appears to be due to abnormal gametogenesis and fertilization. Recent studies have defined two different forms of hydatidiform mole: partial and complete. They are distinct cytogenetic processes with characteristic clinical and histopathologic findings and do not represent a transition from normal to molar gestation.

Partial hydatidiform moles (PHMs) usually have a triploid karyotype (69 chromosomes) derived from two paternal and one maternal haploid sets of chromosomes. Most have a 69,XXX or 69,XXY genotype derived from a haploid ovum with dispermic fertilization. Lawler and coworkers[19] and Lage and associates[20] reported that 93% and 90%, respectively, of partial moles were triploid. More recent data from our institution present convincing evidence that all partial moles are triploid. Genest and colleagues[21] reviewed 19 presumed nontriploid partial moles using standardized histologic diagnostic criteria and repeat flow cytometry; on reevaluation, none of these cases was convincingly a nontriploid partial mole. This finding suggests that nontriploid partial moles might not exist. When a fetus is present in conjunction with a partial mole, it generally exhibits the stigmata of triploidy, including growth retardation and multiple congenital anomalies such as syndactyly, hydrocephaly, omphalocele, and hare lip.

Complete hydatidiform moles (CHMs), in contrast, usually have a chromosomal complement that is totally derived from the paternal genome, while the maternal chromosomes are either inactivated or absent. The 46,XX genotype is most common, representing in most cases reduplication of the haploid genome of one sperm. A smaller portion of complete moles have 46,XY karyotype, consistent with dispermic fertilization. It appears that molar disease, both partial and complete, is associated with excess male genetic composition due to an abnormality of the egg, which is either devoid of maternal chromosomal material or allows for dispermy.

Several growth factors and oncogenes have been studied in molar tissues and CCA.[22] Increased expression of p53 and c-fms has been observed in CHM, and increased ras and c-myc RNAS have been measured in CCA.[23,24] Fulop and associates[25] have investigated the expression of various growth factors and oncogenes in normal placenta, complete and partial mole, and CCA. CHM and CCA were characterized by overexpression of c-myc, c-erbB-2, and bcl-2, and these oncoproteins could be important in the pathogenesis of GTN. Expression of c-fms protein did not differ between normal placenta and GTN. CHM and CCA were also characterized by increased expression of p53, p21, Rb, and MdM2. The p53 gene was studied to detect any mutation in 22 complete moles and 11 CCAs that had increased expression of p53. Because only one nonsense mutation in p53 was detected by polymerase chain reaction analysis, it is likely that the overexpressed p53 protein was the wild type. Although studies have identified increased expression of several growth factors in GTN, the precise molecular pathogenesis has not been determined. It was observed that the level of expression of epidermal growth factor receptor (EGFR) in CCA and the syncytiotrophoblast and cytotrophoblast of complete mole was significantly greater than the expression of EGFR in syncytiotrophoblast and cytotrophoblast of placenta and partial mole.[26] This observation was consistent in both immunohistochemical and in situ hybridization studies. In complete mole, strong expression of EGFR and c-erbB-3 in the extravillous trophoblasts was significantly associated with the development of postmolar tumor. The EGFR-related family of oncogenes might be important in the pathogenesis of GTN.

Extracellular proteinases such as matrix metalloproteinases (MMPs) are thought to be important in modulating both cell-matrix interactions and the degradation of the basement membrane necessary for invasion and metastases. CCA exhibits significantly stronger expression of MMP-1 and MMP-2 and decreased expression of tissue inhibitor of MMP-1 (TIMP-1) than are seen in the syncytiotrophoblast of complete and partial mole and normal placenta.[27] The increased expression of MMP-1 and MMP-2 and decreased expression of TIMP-1 in CCA could contribute to the invasiveness of CCA cells.

Certain genes are expressed normally on either the maternal or paternal allele, and this occurrence is described as parental imprinting. Modification of parental imprinting has been associated with tumor formation; both complete moles and CCA have relaxation of parental imprinting.[28] Relaxation of parental imprinting could be important in the pathogenesis of GTN.

PATHOLOGY

Hydatidiform moles can be categorized as either complete or partial on the basis of gross morphology, histopathology, and karyotype (Table 94-1).

Complete Hydatidiform Mole

CHM is a pregnancy that is characterized by vesicular swelling of placental villi and the absence of an intact fetus. Microscopically, there is proliferation of the trophoblast (both cytotrophoblast and syncytiotrophoblast) with varying degrees of hyperplasia and dysplasia (Fig. 94-1). The chorionic villi are fluid-filled and distended, and blood vessels are absent or scant. Complete mole undergoes early and total hydatidiform enlargement of the villi in the absence of a fetus or embryo, and the trophoblastic cells are hyperplastic.

The pathologic features of complete molar pregnancy have changed significantly over the past two decades owing to earlier diagnosis and uterine evacuation.[29] Whereas cavitation and circumferential trophoblastic proliferation were present in three quarters of complete moles in the past, these findings are now present in fewer than half the cases. Mosher and coworkers[30] compared pathologic findings of 23 current complete moles (1994–1997; mean gestational

Table 94-1 Features of Complete and Partial Hydatidiform Moles

Feature	Complete Mole	Partial Mole
Fetal or embryonic tissue	Absent	Present
Hydropic villi	Diffuse	Focal
Trophoblast hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Trophoblastic stromal inclusions	Absent	Present
Karyotype	46,XX; 46,XY	69,XXY; 69,XYY

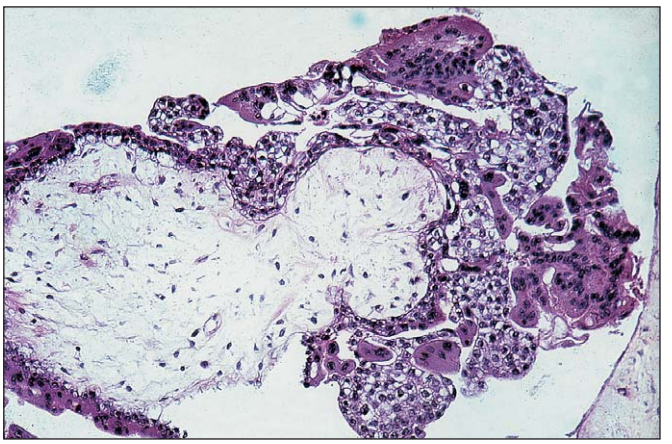


Figure 94-1 • Photomicrograph of complete hydatidiform mole showing diffusely hydropic chorionic villi and diffuse trophoblastic hyperplasia. Embryonic tissue is not present.

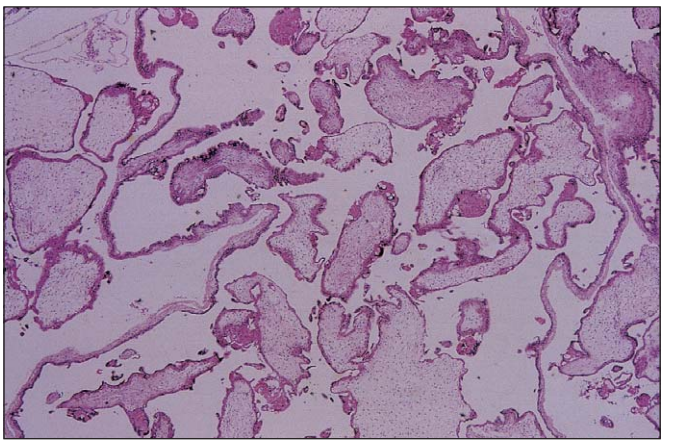


Figure 94-2 • Photomicrograph of partial hydatidiform mole showing varying-sized chorionic villi with focal trophoblastic hyperplasia, stromal trophoblastic inclusions, and villous scalloping. Fetal tissue is present.

age: 8.5 weeks) with 20 past complete moles (1969–1975; mean gestational age: 17 weeks). Histologically, complete moles that are now encountered have smaller mean maximal villous diameter (5.7 mm versus 8.2 mm), less circumferential trophoblastic hyperplasia (39% versus 75%), more primitive villous stroma (70% versus 10%), and less global necrosis (22% versus 54%). Keep and coworkers[31] observed that early complete moles were characterized by focal trophoblastic hyperplasia, minimal villous cavitation, and hypercellular primitive stroma. Complete moles are now often characterized by subtle morphologic alterations that could result in their misclassification as partial moles or nonmolar hydropic abortions. DNA ploidy studies or karyotyping are useful adjuncts in these circumstances.[21] Immunohistochemical tests for maternally expressed genes can also differentiate complete mole from partial mole and hydropic abortion.[32,33]

Partial Hydatidiform Mole

PHM is characterized by the following pathologic features:

- Varying-sized chorionic villi with focal swelling and focal trophoblastic hyperplasia.
- Focal, mild atypia of implantation-site trophoblast
- Marked villous scalloping and prominent stromal trophoblastic inclusions
- Identifiable fetal or embryonic tissues (Fig. 94-2)

Invasive Mole

Invasive mole is a tumor arising from a hydatidiform mole that invades the myometrium by direct extension or by venous channels. It also metastasizes to distant sites in about 15% of cases, most commonly to the lungs and vagina. The tumor is characterized by swollen placental villi and accompanying hyperplastic trophoblast, which is usually dysplastic when located in sites outside the uterine cavity (Fig. 94-3).

Choriocarcinoma

CCA is a highly malignant tumor that is characterized by abnormal trophoblastic hyperplasia and anaplasia, absence of chorionic villi, hemorrhage, and necrosis (Fig. 94-4). It can invade the uterine wall directly or metastasize by vascular channels to the myometrium and distant sites, most commonly to the lungs, vagina, brain, liver, spleen, kidneys, and intestines. The tumor is composed of both cytotrophoblasts and syncytiotrophoblasts.

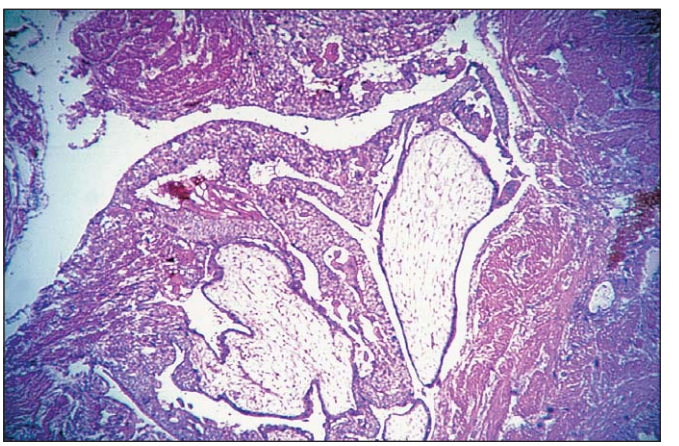


Figure 94-3 • Invasive mole with hydropic villous and hyperplastic trophoblast invading myometrium.

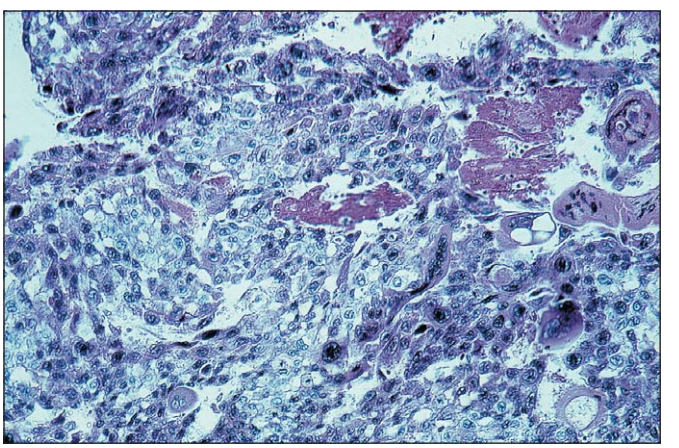


Figure 94-4 • Photomicrograph of choriocarcinoma showing sheets of anaplastic cytotrophoblasts and syncytiotrophoblasts.

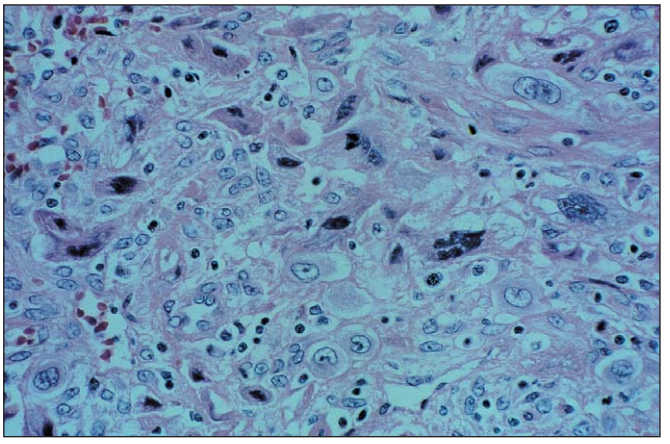


Figure 94-5 • Photomicrograph of placental site trophoblastic tumor composed almost entirely of mononuclear cells of the intermediate trophoblast.

Placental Site Trophoblastic Tumor

Placental site trophoblastic tumor (PSTT) is an extremely rare tumor that arises from the placental implantation site and, in contrast to CCA, is monocellular. Tumor cells infiltrate the myometrium and grow between smooth muscle cells with vascular invasion (Fig. 94-5). PSTT differs from CCA primarily in the absence of an alternating pattern of cytotrophoblast and syncytiotrophoblast, in that the cells are morphologically of one population (intermediate trophoblast) and hemorrhage and necrosis are less evident. There are no placental villi. Human placental lactogen is present in the tumor cells, whereas immunoperoxidase staining for hCG is positive in only scattered cells. Serum hCG levels are relatively low in comparison with those seen in CCA. A relatively high level of free beta subunit of hCG is detectable in patients with PSTT as compared to other forms of GTN.[34] There appears to be a direct correlation between the mitotic activity of the tumor and the prognosis.[35]

IMMUNOBIOLOGY

The remarkable curability of GTN might be attributable partly to a host immunologic response to paternal antigens expressed on trophoblastic cells.[36] The prognosis of patients with gestational CCA has been related to the intensity of lymphocytic and monocytic infiltration at the tumor-host interface.[37] Because the lymphocytes and macrophages that infiltrate gestational CCA are probably exposed to paternal antigens and oncoproteins, the immune cells could become activated. Immunologically active cells might promote the regression of GTN through their release of cytokines. Cytokines have been reported to inhibit the proliferation of CCA cells in vitro and to increase the HLA expression of CCA cells in vitro, thereby increasing immunogenicity.[38]

It has been theorized that the development and progression of GTN could be favored by histocompatibility between the patient and her partner. If the patient and her partner are histocompatible, the trophoblastic tumor that bears paternal antigens might not be immunogenic in the maternal host. The intensity of the host's immunologic response might depend on the immunogenicity of the trophoblastic tumor. On the other hand, histocompatibility between the patient and her partner does not appear to be a prerequisite for the development of persistent GTN.[39] HLA systems could, however, influence the clinical course of rapidly progressive and fatal GTN. Tomoda and colleagues[40] reported that drug-resistant CCA was associated with increased histocompatibility between the patient and her partner. Similarly, Morgenson and coworkers[41] observed that histocompatibility between patients and partners was associated with a greater risk of metastatic disease. Because all chromosomes in a CHM are paternal in origin, a CHM is a complete allograft and could stimulate a vigorous immune response by the maternal host. There is evidence for both a cellular and a humoral response to CHM. When compared with normal placentas, molar implantation sites have fivefold increased infiltration by helper T cells.[40] Circulating immune complexes have also been measured in patients with CHM and have been noted to increase as the patient entered remission.[42,43]

Circulating immune complexes in patients with CHM have been demonstrated to contain paternal HLA antigens.[44] The maternal host with a CHM is therefore sensitized to paternal HLA antigens. The distribution of HLA antigens in molar chorionic villi has been determined by immunofluorescent assays.[45] HLA A, B, and C antigens were detected on the stromal cells of molar chorionic villi but not on the villous trophoblast; however, the molar villous fluid that bathes the stromal cells does not contain soluble HLA antigen.[38] The maternal host could therefore be sensitized to paternal HLA antigen when the villous trophoblastic layer is disrupted and HLA-positive villous stromal cells are released into the circulation.

CLINICAL PRESENTATION

Complete Molar Pregnancy

The clinical presentation of CHM has changed dramatically over the past two decades in the wake of the widespread use of ultrasound and the availability of improved methods for hCG testing. Whereas CHM was usually diagnosed in the second trimester prior to 1980, the diagnosis of CHM is now usually made in the first trimester, before the classic clinical signs and symptoms appear.[29] Table 94-2 summarizes the signs and symptoms of classical CHM and PHM. When patients with CHM present with these classical signs and symptoms, they are at high risk for developing GTN. Soto-Wright and associates compared the clinical presentation and outcome of patients with CHM at the New England Trophoblastic Disease Center (NETDC) between 1988 and 1993 with those of patients between 1965 and 1975. Soto-Wright noted that despite the change in presentation, there was no change in the incidence of GTN disease requiring treatment. Patients now less frequently present with excessive size, anemia, theca lutein cysts, and hyperemesis.

Partial Molar Pregnancy

Patients with partial molar pregnancy typically present with symptoms that are indistinguishable from those of a threatened or

Table 94-2 Presenting Signs and Symptoms of Classical Complete and Partial Hydatidiform Moles

Sign or Symptom	Complete Mole (%) (*N* = 306)	Partial Mole (%) (*N* = 81)
Vaginal bleeding	97	73
Excessive uterine size	51	4
Theca lutein cysts >6 cm	50	0
Preeclampsia	27	3
Hyperemesis	26	0
Hyperthyroidism	7	0
Trophoblastic emboli	2	0

spontaneous miscarriage (rather than with the classical symptoms of CHM) unless diagnosis is delayed until the second trimester. Eighty-one patients with PHM were studied at the NETDC between 1979 and 1984. The diagnosis of PHM is usually suggested by ultrasonography and confirmed by pathologic review of curettage material. The hCG levels in patients with PHM are usually not as elevated as in patients with CHM. When PHM progresses into the second trimester, the ultrasound diagnosis becomes more accurate because of the obvious fetal malformations associated with triploidy and the extent of vesicular change of the placenta. Patients with PHM whose diagnosis is delayed until the second trimester will, in many instances, recapitulate the classical signs and symptoms associated with CHM with regard to the incidence of preeclampsia, hyperthyroidism, trophoblastic embolization, and other complications.[46–48] While patients with complete mole are now diagnosed earlier and their clinical presentation has changed, patients with partial mole have not been diagnosed substantially earlier and their clinical symptoms have not changed.[17]

Gestational Trophoblastic Neoplasia

Gestational trophoblastic neoplasia (GTN) is the term that is used when there is clinical, radiologic, pathologic, and/or hormonal evidence of persistent GTD, which can follow any type of antecedent pregnancy. Rarely, the antecedent pregnancy cannot be determined. GTN that follows a molar pregnancy is diagnosed by a plateau in the level of hCG over more than 3 consecutive weeks, a 10% or greater rise in hCG for three or more values over at least 2 weeks, persistence of hCG 6 months after molar evacuation, or histologic evidence of invasive mole, CCA, or PSTT. GTN comprises two distinct disease entities—nonmetastatic or metastatic—based on whether there is evidence of disease beyond the uterus.

Nonmetastatic Gestational Trophoblastic Neoplasia

Nonmetastatic or locally invasive GTN develops in about 15% of patients after evacuation of a complete mole and infrequently following other pregnancies. Locally invasive GTN occurs after partial mole in 1% to 6% of patients.[17,49] These patients usually present with irregular vaginal bleeding, theca lutein cystic changes in the ovaries (depending on the level of hCG), uterine subinvolution or asymmetrical enlargement, and elevated hCG levels. The invasive tumor can erode through the uterine vessels, causing vaginal bleeding, or can perforate through the myometrium, leading to intraperitoneal hemorrhage. The presence of bulky necrotic tumor, characteristic of CCA, can serve as a nidus for sepsis, particularly *Clostridium welchii*. The presence of deep myometrial invasion can be confirmed by curettage, laparoscopy, or imaging studies, including ultrasound, magnetic resonance imaging (MRI), or angiography.

Metastatic Gestational Trophoblastic Neoplasia

Metastatic GTN occurs in approximately 5% of patients after molar evacuation and infrequently after other gestations. Although invasive mole can metastasize to distant sites, most metastatic GTN is generally associated with CCA, which has the propensity for early vascular invasion and widespread dissemination. Because trophoblastic tumors are highly vascular, metastatic lesions often present with signs and symptoms of spontaneous bleeding. The most common metastatic sites are the lung (80%), vagina (30%), brain (10%), and liver (10%). As a general rule, cerebral and hepatic metastases are uncommon unless there is concurrent involvement of the lungs and/or vagina.

PULMONARY METASTASIS. The pulmonary parenchyma is the most common site of metastasis. Eighty percent of patients with metastatic disease have lung involvement. Patients with pulmonary involvement can present with cough, chest pain, hemoptysis, and/or dyspnea or an asymptomatic lesion on chest x-ray. Respiratory symptoms can have an acute onset or be chronic. Pulmonary involvement produces four principle radiologic patterns:

1. Discrete rounded densities
2. "Snowstorm" or alveolar pattern
3. Embolic pattern resulting from pulmonary artery occlusion
4. Pleural effusion

Patients can develop pulmonary hypertension in the absence of substantial parenchymal involvement. Because the respiratory symptoms and radiographic findings can be striking, the patients might be thought to have a primary pulmonary disease. Unfortunately, the diagnosis of GTN might be made only after thoracotomy is performed. Therefore, it is important to obtain an hCG level in all women of reproductive age who have unexplained respiratory symptoms or a lesion on chest x-ray. Gynecologic symptoms could be minimal or absent in patients with extensive pulmonary involvement. In fact, the reproductive organs could be free of trophoblastic tumor in patients with widespread metastases. Early respiratory failure requiring mechanical ventilation can develop in patients with extensive pulmonary involvement and can cause death before effective chemotherapy can be started.[50–52] Risk factors for early respiratory failure within 1 month of presentation include greater than 50% lung opacification, dyspnea, anemia, cyanosis, and pulmonary hypertension. With chemotherapy, patients could develop bleeding into metastatic sites and potentially worsen pulmonary symptoms and radiologic findings. Kelly and associates[50] observed that reducing the initial dose of chemotherapy did not protect against early respiratory failure and recommended administering intensive chemotherapy at the outset.

VAGINAL METASTASES. Thirty percent of patients with metastatic disease have vaginal involvement. Vaginal metastases occur most commonly suburethrally or in the fornices and cause purulent discharge or irregular bleeding (Fig. 94-6). Vaginal lesions are highly vascular and can bleed vigorously if biopsied. Surgical excision of a vaginal metastasis should be avoided except in unusual circumstances, owing to the risk of hemorrhage that could be difficult to control. We have observed that after instituting chemotherapy when some tumor shrinkage has occurred, the vaginal lesion can be excised with less risk.

HEPATIC METASTASES. Choriocarcinoma involves the liver in 10% of patients who develop disseminated disease. Hepatic metastases are encountered almost exclusively in patients who have extensive tumor burdens and prolonged delays in diagnosis. Hepatic lesions can cause liver rupture with exsanguinating intraperitoneal hemor-

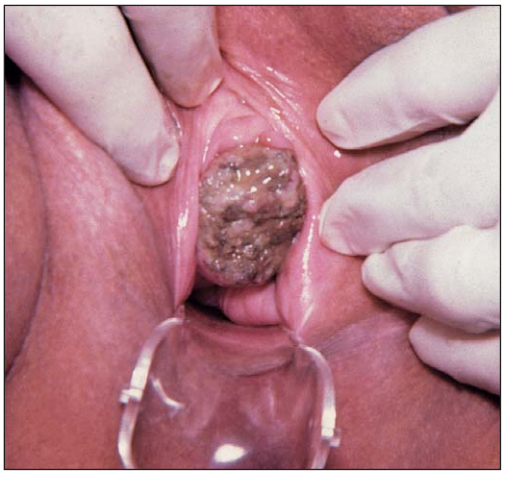


Figure 94-6 • Vaginal metastasis of choriocarcinoma.

rhage; however, patients with liver metastases usually do not present with symptoms that are related to hepatic involvement.[53]

BRAIN METASTASES. Cerebral lesions also occur in approximately 10% of patients with metastatic GTN. Cerebral involvement is usually seen in patients with advanced disease and histologically is almost always related to CCA. The main presenting symptoms of brain metastases are headache, vomiting, seizures, and focal neurologic signs such as slurred speech, hemiparesis, or visual disturbances. Neurologic symptoms usually result from increased intracranial pressure or intracerebral bleeding.[54–56]

Cerebral lesions are associated with elevated levels of hCG in the cerebrospinal fluid (CSF). Bagshawe and Harland[57] reported that the plasma-to-CSF hCG ratio was less than 60 in patients with cerebral involvement. However, a single plasma-to-CSF hCG ratio can be misleading because rapid changes in the hCG levels in the serum might not be reflected promptly in the CSF.[58] With earlier diagnosis of GTN and the advent of improved imaging techniques (particularly MRI), occult brain metastases are now frequently being detected before patients present with neurologic symptoms.

OTHER METASTATIC SITES. Gastrointestinal, renal, and splenic metastases are seen only in patients with advanced disease, most commonly in patients with post-term CCA, where there has been a delay in diagnosis. Abdominal computed tomography (CT) scanning is useful for the early detection of metastases to these sites. Testing for hematochezia should also be part of the workup in any patient who presents with metastatic GTN.

PLACENTAL SITE TROPHOBLASTIC TUMORS. PSTTs are rare tumors that are derived from intermediate cytotrophoblast cells. They can arise from any antecedent pregnancy but most commonly arise from a term pregnancy or miscarriage. They generally present months to years after the antecedent pregnancy with irregular vaginal bleeding or amenorrhea, enlarged uterus, and, rarely, nephrotic syndrome. The serum hCG level is relatively low in relation to tumor volume in comparison to other types of GTNs. Over 30% of patients already have metastases at diagnosis.[59]

LABORATORY AND IMAGING STUDIES

The optimal management of GTN requires a thorough evaluation of the extent of the disease prior to treatment. All patients with persistent disease should undergo a thorough pretreatment evaluation, including a complete history and physical examination; baseline levels of peripheral blood and platelet counts; hCG titer; hepatic, thyroid, and renal function tests; and stool guiac tests. A pelvic sonogram is helpful in detecting adnexal involvement, the presence of residual tissue in the uterine cavity, or the presence of deep myometrial invasion. A baseline chest x-ray should be performed in all patients at the time of molar evacuation to identify pre-existing pulmonary disease that might be misinterpreted if the patient were to develop postmolar GTN. Patients with persistent GTN should undergo CT scans of the chest and abdomen and MRI scanning of the brain as part of the staging workup.

Human Chorionic Gonadotropin Measurement

A reliable assay for total hCG is central to the management of patients with trophoblastic disease. The assay must measure all portions of the hCG molecule, particularly free beta subunit, nicked hCG, and hyperglycosylated hCG.[60] Several commercial assays do not measure free beta subunit or nicked hCG and do not differentially recognize hyperglycosylated hCG. Practically speaking, however, the available clinical assays for β-hCG are adequate in the vast majority of patients for diagnosis, monitoring therapy, and follow-up to ensure that the patient remains in complete gonadotropin remission. Physicians treating patients with GTN, however, must recognize the limitations of the assay they are using and base clinical decisions on the clinical, morphologic, and radiologic findings as well as on hormonal results.

Patients with CHM commonly have markedly elevated pre-evacuation hCG levels. Genest and coworkers[61] noted that 46% of 153 patients with CHM who were managed at the NETDC between 1980 and 1990 had pre-evacuation hCG levels above 100,000 mIU/mL. Patients with PHM less commonly present with markedly elevated hCG values. Czernobilsky and associates reported that only 1 of 17 patients with PHM presented with urinary hCG levels above 300,000 mIU/mL. Review of our own data at the NETDC noted that only 2 of 30 patients with PHM presented with levels greater than 100,000 mIU/mL.[48] Complete and partial moles also differ in their levels of free beta and alpha subunits of hCG. Whereas complete moles have higher percentages of free β-hCG, partial moles have higher levels of free α-hCG.[62]

False-Positive Human Chorionic Gonadotropin Tests

False-positive hCG test results can occur because of a substance in the blood that interferes with the hCG assay. Although this is a rare occurrence (estimated at 1 in 10,000 to 1 in 100,000 tests), false-positive tests can be confusing to clinicians when they are attempting to diagnose disorders of pregnancy, including GTN. The misinterpretation of a false-positive test has led to inappropriate treatment with extirpative surgery and chemotherapy based only on persistently elevated serum β-hCG levels. False-positive hCG tests should be suspected if the clinical picture and the laboratory results are discordant, if there is no identifiable antecedent pregnancy, or if patients under treatment with low levels of hCG do not respond to treatment appropriately. Heterophile antibodies are thought to be responsible for this problem by interfering in the immunoassay systems utilized. These patients are also at risk of other false-positive test results. To avoid the pitfalls of a false-positive hCG test, it is important for the clinician to remember that the patient's clinical presentation should correlate with the laboratory results. If there is a discrepancy, then a repeat hCG assay using a different immunoassay and a sensitive urine hCG test should be performed.[63]

Quiescent Gestational Trophoblastic Neoplasia

Quiescent GTN is another rare entity that is associated with persistent low levels of hCG, which can lead to inappropriate treatment. This entity is thought to be due to the presence of highly differentiated, noninvasive syncytiotrophoblastic cells. Characteristically, foci of disease are not otherwise demonstrable clinically, nor do hCG levels fall with therapy, presumably because the growth cycle of these cells is long and comparable to that of normal cells. Close observation of these patients is indicated because 6% to 10% will eventually develop overt GTN requiring therapy. The hCG of patients with quiescent GTN is not hyperglycosylated, which is useful in correctly identifying these patients.[64,65]

Ultrasonography

Sonographic examination of the first-trimester uterus, particularly when combined with transvaginal color Doppler flow, has made possible the detection of abnormalities of early pregnancy. The diagnosis of molar pregnancy is nearly always made by sonography except in very early pregnancy. The indications for ultrasound in pregnant patients when molar disease or GTN is suspected include the following:

- First-trimester bleeding
- The appearance of signs and symptoms of molar pregnancy
- Unusually high hCG levels

The ultrasonographic appearance of CHM does not vary considerably between the first and second trimesters. At either stage,

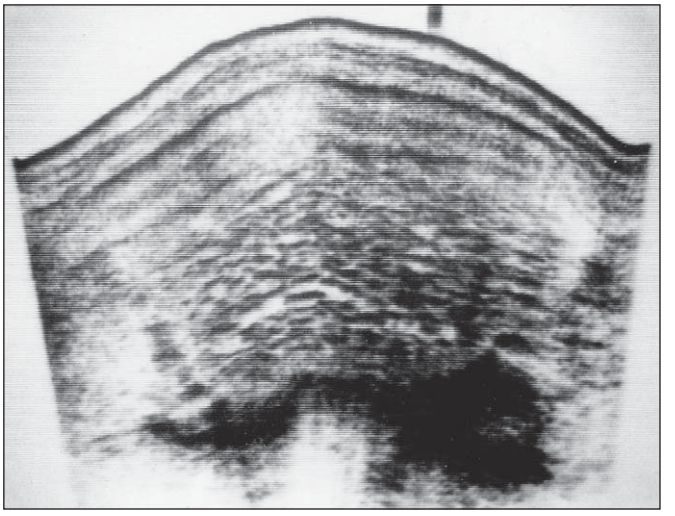


Figure 94-7 • Ultrasound of complete hydatidiform mole characterized by absence of fetus and amniotic sac and the presence of a "Swiss cheese" pattern representing hydropic villi surrounded by blood and hyperplastic trophoblast.

complex, echogenic masses with multiple small cystic spaces are visible within the uterus, and no fetus is identifiable (Fig. 94-7).

Two sonographic features have been described that are significantly associated with PHM: focal cystic changes in the placenta and a ratio of the transverse-to-anteroposterior dimension of the gestational sac greater than 1.5.[66] Changes in the shape of the gestational sac could be part of the embryopathy of triploidy. On rare occasions, particularly when PHM has progressed into the late first or early second trimester, the sonogram will show the presence of a fetus with multiple congenital abnormalities associated with a focally hydropic placenta, oligohydramnios, and abnormal placental Doppler flow pattern. These changes might not be visible in the first trimester.

Ultrasound is also useful after molar evacuation when there is abnormal bleeding or a rising hCG level to determine whether there is sufficient residual tissue in the uterine cavity to justify another evacuation or whether there is evidence of invasive disease or adnexal involvement. Ultrasonography can help the clinician to select patients who will benefit from hysterectomy because it can detect accurately the presence of extensive uterine trophoblastic tumor. Ultrasonography is also useful in monitoring the progress of theca lutein cyst regression and aids in decompression when the cysts cause symptoms such as pain and difficult respiration.

Computed Tomography and Magnetic Resonance Imaging

When a patient develops persistent GTN, the current standard of care is to obtain a CT scan of the chest rather than a plain radiographic film to look for metastatic lesions, particularly for patients who are thought to have nonmetastatic disease and who are likely candidates for primary surgical treatment. The findings of occult metastatic disease on chest CT scan would mandate that chemotherapy be included in the treatment protocol. Because it is unusual for metastatic sites other than the vagina or pelvis to be involved in the absence of pulmonary metastases, a full metastatic workup is usually not indicated unless lung involvement is observed. When a chest CT is positive, metastatic workup should consist of an abdominal CT scan to detect liver, renal, splenic, and gastrointestinal involvement and an MRI scan of the head. These new radiologic techniques for brain imaging have greatly enhanced our ability to diagnose asymptomatic cerebral lesions, which allows for earlier intervention before irreversible neurologic changes occur. However, an initial positive chest CT in the nonmetastatic patient does not affect clinical management, since most of these patients are low risk and do well with single-agent protocols.[67]

Positron Emission Tomography

Positron emission tomography (PET) with [^{18}F]fluorodeoxyglucose (FDG-PET) scanning can aid in identifying residual disease sites in women who relapse from previously treated GTN. Dhillon and colleagues have reported that PET scanning appropriately identified the presence of pulmonary lesions that were successfully resected, when they were equivocal on CT scanning. It is important to realize that a false-positive PET scan can occur in nonmalignant conditions such as sarcoid. Therefore, careful evaluation in combination with other imaging modalities is required to reduce the risk of false-positive results.[68,69]

STAGING AND PROGNOSTIC SCORING SYSTEM

The staging/prognostic scoring system was developed to provide a basis for comparison of treatment outcomes among multiple treatment centers and as a guide for clinicians to estimate prognosis and select optimal therapy.

National Institutes of Health Clinical Classification

The National Institutes of Health Clinical Classification (Table 94-3) separates patients with nonmetastatic disease from those with metastases because virtually all patients with nonmetastatic disease can be cured with single-agent chemotherapy or hysterectomy.[70] Patients with metastatic disease are further subdivided into low-risk and high-risk disease categories based on five risk factors. "Risk" in this context refers to the likelihood that the patient will develop drug resistance and ultimately die of her disease. Patients are classified as being at high risk on the basis of the presence of one or more of the following:

- Pretreatment serum hCG level in excess of 40,000 mIU/mL
- Duration of disease longer than 4 months from the antecedent pregnancy event or from onset of symptoms to treatment if the antecedent pregnancy is not known
- Metastases to sites other than the lungs or vagina
- Antecedent term pregnancy
- Prior unsuccessful chemotherapy

International Federation of Gynecologists and Obstetricians Staging

An anatomic staging system for GTN, adopted by the Cancer Committee of the International Federation of Gynecologists and Obstetricians (FIGO) in 1982 and modified in 1992, was based on material presented by Dr. H. C. Sung at a meeting of the International Society for the Study of Trophoblastic Disease in Beijing in 1979. The FIGO system delineates stages as follows:

- Stage I includes all patients with persistently elevated hCG levels and tumor confined to the uterus.
- Stage II includes all patients with disease outside the uterus but localized to the vagina and/or pelvic structures.
- Stage III encompasses all patients with pulmonary metastases with or without uterine, vaginal, or pelvic lesions. Precise histologic diagnosis is not easily obtained in this group of patients without biopsy or available tissue from another source. Nonetheless, we do not advocate performing thoracotomy or other invasive procedures merely to obtain information about the histologic pattern of the metastatic site, as treatment is based on staging rather than pathology.

Table 94-3 National Institutes of Health Clinical Classification of Gestational Trophoblastic Neoplasm

NONMETASTATIC
METASTATIC
Good prognosis
Duration of disease <4 months from antecedent pregnancy or onset of symptoms
Pretreatment serum hCG level <40,000 mIU/mL
No prior chemotherapy
No evidence of brain and/or liver metastases
Antecedent pregnancy not term
Poor prognosis
Duration of disease >4 months from antecedent pregnancy or onset of symptoms
Pretreatment serum hCG level >40,000 mIU/mL
Prior chemotherapeutic failure
Evidence of brain and/or liver metastases
Antecedent pregnancy term

- Stage IV comprises patients with far advanced disease with involvement of one or more of the following organs: brain, liver, kidney, spleen, and gastrointestinal tract. Patients with stage IV disease are more likely to become drug resistant and are therefore in the highest risk category. Patients with stage IV disease invariably have histologic evidence of CCA, which is more likely to follow a nonmolar pregnancy.

World Health Organization Prognostic Score

In addition to anatomic staging, other variables are needed to predict the likelihood that a patient will develop drug resistance and to serve as a guide to the selection of an appropriate chemotherapy regimen. In 1983, the World Health Organization (WHO) adopted a modification of the Bagshawe prognostic scoring system, which was based on a number of clinical, radiologic, hormonal, and demographic factors, each of which was considered an independent variable and assumed to be additive.[71] Patients with prognostic scores of 7 or lower are considered to be at low risk of developing drug resistance and are ideal candidates for single-agent chemotherapy. When the prognostic score is greater than 7, the patient is considered to be at high risk for developing drug resistance and requires combination therapy to obtain optimal treatment outcomes. In general, patients with stage I tumors have low risk scores, and patients with stage IV tumors have high risk scores. Therefore, the prognostic scoring system is most useful when it applies to stages II and III in that it helps to identify patients who require more intensive therapy for best results.

The variables that are included in the prognostic score include tumor volume (hCG measurement, size, and number of metastases), site of involvement, prior chemotherapy exposure, and duration of disease.

CCA after term pregnancy has been noted to be a poor prognostic factor and to have distinctive clinical features. We reviewed the experience with post-term CCA at the NETDC from 1964 to 1996.[72] Seven of 44 patients (16%) presented with clinical evidence of maternal-fetal bleeding that resulted in severe fetal anemia and nonimmune hydrops or third trimester bleeding. Although none of the infants had evidence of metastatic CCA, rare cases of fetal involvement by CCA have been reported and are usually associated with either fetal or neonatal death. The time interval from delivery to diagnosis, sites of metastases, and pretreatment hCG level were all significant risk factors in predicting outcome. All 31 of our patients with a WHO score less than or equal to 8 survived, whereas 6 of 13 patients (46%) with a WHO score greater than 8 succumbed to their disease.

During the past 5 years, the International Society for the Study of Trophoblastic Disease, the International Gynecologic Cancer Society, and FIGO have moved to modify the staging systems for trophoblastic disease by combining the basic FIGO stages with the WHO Prognostic Score (Table 94-4). Therefore, a patient's stage and total risk score are described by Roman and Arabic numerals, respectively, separated by a colon (e.g., III:8).

TREATMENT

Molar Pregnancy

The primary management of molar pregnancy is surgical evacuation. Before proceeding with surgery, however, the patient should be thoroughly evaluated to identify the presence of medical complications, such as preeclampsia, electrolyte imbalance due to hyperemesis, hyperthyroidism, and anemia, which might complicate the surgical procedure. After evacuation, the clinician must be committed to conscientious hCG follow-up screening for persistent GTN and to counseling regarding the management of future pregnancies.

Surgical Management

Once the patient's medical condition has stabilized, a decision must be made regarding the most appropriate surgical treatment. If the patient no longer desires to preserve fertility, hysterectomy should be considered. At the time of hysterectomy, prominent theca lutein cysts can be decompressed. The advantage of removing the uterus is that it eliminates the possibility that the patient will develop nonmetastatic disease. Although hysterectomy eliminates the risk of local invasion, however, it does not obviate the need for chemotherapy if metastases pre-exist or subsequently appear.

Suction curettage is the preferred method of evacuation, regardless of uterine size, in patients who desire to preserve fertility. At the time of evacuation, if the uterus is larger than 12 weeks' size, it is advisable to administer oxytocin at the onset of cervical dilatation to facilitate uterine involution. In larger uteri, as the cervix is being dilated, the surgeon might encounter brisk bleeding due to the release of retained blood. Shortly after commencement of suction evacuation, uterine bleeding is generally well controlled, and the uterus involutes rapidly. If the uterus is larger than 14 weeks' size, it is helpful for the surgeon to massage the uterine fundus to stimulate uterine contraction. When suction evacuation is thought to be complete, a gentle sharp curettage should be performed to remove any residual chorionic tissue. It is important to avoid too vigorous curettement because of the risk of inducing uterine synechiae (Asherman's syndrome). Patients who are Rh negative should receive Rh immune globulin at the time of evacuation because Rh D factor is expressed on trophoblast.

Some authors have proposed using cervical ripening agents to facilitate cervical dilatation and prevent trauma. In general, we have not found this to be necessary. The size of the curette to be used is determined by the uterine size. Generally, a 10-mm or 12-mm suction curette suffices, and greater dilatation of the cervix is not necessary. Patients with large-for-dates uteri and high hCG levels should be observed for signs and symptoms of acute respiratory insufficiency postoperatively, which could indicate that massive trophoblastic embolization has occurred, as well as for thyroid storm.

Role of Prophylactic Chemotherapy

Patients with complete mole with high pre-evacuation hCG levels (>100,000 mIU/mL) and signs of marked trophoblastic growth (excessive uterine size) are at increased risk (40%) of developing persistent GTN (Table 94-5).[73] In these patients, the use of

Table 94-4 Combined FIGO Staging and WHO Prognostic Scoring System for Gestational Trophoblastic Neoplasm

FIGO STAGES

Stage I	Disease confined to the uterus
Stage II	Disease extends outside the uterus but limited to the genital tract
Stage III	Disease extends to the lungs, with or without genital tract involvement
Stage IV	All other metastatic sites

MODIFIED WHO PROGNOSTIC SCORING SYSTEM

Scores	0	1	2	4
Age	<40 years	>40 years	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval months from index pregnancy	<4	4–7	7–13	>13
Pretreatment serum	<1000 hCG (mIU/mL)	<10,000 hCG (mIU/mL)	<100,000 hCG (mIU/mL)	<100,000 hCG (mIU/mL)
Largest tumor size	—	3–5 cm	>5 cm	—
Site of metastases	Lung	Spleen/kidney	GI	Liver/brain
Number of metastases	—	1–4	5–8	>8
Previous failed chemotherapy	—	—	Single drug	Combination

FORMAT FOR DETERMINING FIGO STAGE AND WHO PROGNOSTIC SCORE

To stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, or IV. This is then separated by a colon for the sum of all the actual risk factor scores expressed in Arabic numerals (e.g., stage II:4, stage IV:9).

chemotherapy prophylactically at the time of evacuation has been shown to reduce the incidence of persistent GTN.[74,75] The administration of methotrexate or actinomycin D reduced the incidence of postmolar tumor from 47% to 14% and from 50% to 14%, respectively. None of the patients in either series developed metastatic disease. Prophylaxis should also be considered in situations in which hCG follow-up is either unavailable or unreliable.

Persistent Gestational Trophoblastic Neoplasia

Persistent GTN can occur after any antecedent pregnancy. The clinical presentation is more important in determining prognosis than is the precise histologic diagnosis, which might not be available. Infrequently, the diagnosis is made solely on the basis of a rising or plateaued hCG level in the absence of a documented pregnancy or of any clinical, radiologic, or pathologic evidence of trophoblastic tissue.

Table 94-5 Sequelae of Low- and High-Risk Complete Hydatidiform Mole*

	Number of Patients (%)	
Outcome	**Low-Risk**	**High-Risk**
Normal involution	486/506 (96)	212/352 (60)
Persistent GTN		
Nonmetastatic	17/506 (3.4)	109/352 (31)
Metastatic	3/506 (0.6)	31/352 (8.8)
Totals	506/858 (59)	352/858 (41)

*All patients were managed by evacuation without prophylactic chemotherapy.

When this occurs, it is important to make certain that the hCG that is being measured by the assay is true rather than a false-positive test (the so-called phantom hCG).[76] Postmolar GTN is diagnosed on the basis of a rising (increase of 10%) or plateauing (<10% for at least 3 weeks) level. Abnormal vaginal bleeding, subinvolution of the uterus, and cystic ovaries can be present. Women with GTN after nonmolar pregnancies can present with subtle signs and symptoms, making diagnosis difficult. Abnormal bleeding after any pregnancy should be evaluated promptly with an hCG test. Because metastases from CCA have been reported in virtually every anatomic site, a diagnosis of persistent GTN should be considered in any woman of reproductive age who presents with metastatic disease from an unknown primary site.

Chemotherapy

SINGLE-AGENT CHEMOTHERAPY. Single-agent chemotherapy with either methotrexate or actinomycin D has induced comparable and excellent remission rates in both nonmetastatic and metastatic GTN.[77] An optimal regimen should maximize the cure rate while minimizing toxicity. Table 94-6 summarizes the various protocols that are in use for the primary treatment of both nonmetastatic and low-risk metastatic GTN. Several regimens of methotrexate and actinomycin D have induced complete remission in 70% to 100% of patients with nonmetastatic GTN and in 50% to 70% of patients with low-risk metastatic GTN. Fortunately, if a patient develops resistance to the single agent that is utilized initially, she usually can achieve remission with the alternative drug.

Methotrexate with Folinic Acid Rescue. Bagshawe and Wilde[78] in 1964 described administering methotrexate with folinic acid to reduce chemotherapeutic toxicity. Methotrexate plus folinic acid has remained the primary treatment of nonmetastatic and low-

Table 94-6 Single-Agent Regimens for Low-Risk Gestational Trophoblastic Neoplasm

Methotrexate Regimens	Remissions (%)
METHOTREXATE	
Methotrexate 0.5 mg/kg IV or IM daily for 5 days	93.0
Pulse methotrexate	81.0
Methotrexate 50 mg/m^2 IM weekly	
METHOTREXATE/FOLINIC ACID	90.2
Methotrexate 1 mg/kg IM or IV on days 1, 3, 5, 7	
Folinic acid 0.1 mg/kg PO on days 2, 4, 6, 8	
HIGH-DOSE METHOTREXATE/ FOLINIC ACID	61
Methotrexate 100 mg/m^2 IV bolus	
Methotrexate 200 mg/m^2 12-hour infusion	
Folinic acid 15 mg every 12 hours × 4 doses IM or PO beginning 24 hours after starting methotrexate	
Actinomycin D Regimens	
5-day actinomycin D	94.0
Actinomycin D 12 µg/kg IV push daily for 5 days	
Pulse actinomycin D	94.0
Actinomycin D 1.25 mg/m^2 IV push every 2 weeks	

risk metastatic GTN at the Charing Cross Hospital. Although methotrexate plus folinic acid is highly effective, a 20% rate of resistance and 6% incidence of toxicity were observed. Methotrexate plus folinic acid has also been the preferred single-agent regimen at the NETDC for the treatment of GTN since 1974.[79] Complete gonadotropin remission was achieved in 147 of 163 patients (90%) with stage I GTN and in 15 of 22 patients (68%) with low-risk stage II and III GTN. Among the 23 patients who were resistant to methotrexate/folinic acid, 14 (61%) subsequently achieved remission with actinomycin D, and 9 required combination chemotherapy. Thrombocytopenia, granulocytopenia, and hepatotoxicity occurred in only 11 (6%), 3 (2%), and 26 (14%) patients, respectively. One patient required platelet transfusion and developed sepsis due to myelosuppression. No patient developed alopecia. The effectiveness of this methotrexate/folinic acid protocol could be due partly to the prolonged exposure to methotrexate. When methotrexate is administered at a higher dose (300 mg/m^2 over 12 hours and 30 minutes), the remission rate declines to 69% in patients with nonmetastatic GTN.[80]

5-Fluorouracil. Although methotrexate and actinomycin D are the two most commonly used single agents in GTN in the United States and Europe, 5-fluorouracil has been the preferred single-agent chemotherapy in China. Sung and associates[81] reported that 5-fluorouracil induced complete remission in 93% of patients with stage I GTN and in 86% of patients with stage II disease.

Dactinomycin. Single-agent dactinomycin is as effective as methotrexate when used for initial therapy in patients with low-risk GTN. Two protocols have been extensively used: the 5-day and biweekly pulsed regimens. Over time, the 5-day regimen has evolved to the pulsed regimen, which is associated with less toxicity and greater ease of administration. The main side effects, regardless of the regimen that is used, are nausea and vomiting, skin rash, mucositis, and alopecia. The 5-day regimen administered at a dose of 10 to 12 µg/kg/day is associated with a 94% response rate in nonmetastatic disease. A similar complete remission rate has been achieved with a biweekly dose of 1.25 mg/m^2. When actinomycin is used for the treatment of methotrexate-resistant nonmetastatic GTN, the 5-day regimen should be used because the biweekly pulse regimen is associated with significantly lower remission rates.

Etoposide. Etoposide administered orally has also been shown to be highly effective in the treatment of nonmetastatic and metastatic GTN by the Hong Kong group, who reported complete sustained remission in 56 of 60 patients (93%).[82] Etoposide can also be used as salvage therapy when resistance to methotrexate is encountered in place of actinomycin.

COMBINATION THERAPY. The use of combination therapy is indicated as primary therapy in patients with high risk scores or as salvage therapy in women who experience single-agent treatment failures.

MAC. Triple chemotherapy with methotrexate/folinic acid, actinomycin D, and cyclophosphamide (MAC) had been the preferred combination drug regimen at the NETDC in patients with high-risk GTN (Table 94-7). This regimen, however, has been shown to be associated with a low success rate in patients with high risk scores and therefore is used almost exclusively as salvage therapy in patients with low-risk disease who are resistant to single-agent therapy.

EMACO. Bagshawe[83] reported an 83% remission rate in patients with metastatic GTN and high risk scores using a regimen that included etoposide, methotrexate/folinic acid, actinomycin D, cyclophosphamide, and vincristine (EMACO). Similarly, Lurain and colleagues reported that 67% of patients with high-risk metastatic GTN achieved remission with EMACO.[84] This has become the preferred treatment for patients with metastatic GTN, particularly those who have high risk scores (Table 94-8). If patients prove resistant to EMACO, remission can still be achieved by treating with a modification of this

Table 94-7 Protocol for MAC Regimen

Day	Drug	Dose
1	Methotrexate	1.0 mg/kg IM or IV
	Actinomycin D	12 µg/kg IV push
	Cyclophosphamide	3 mg/kg IV bolus
2	Folinic acid	0.1 mg/kg IM or PO
	Actinomycin D	12 µg/kg IV push
	Cyclophosphamide	3 mg/kg IV bolus
3	Methotrexate	1.0 mg/kg IM or IV
	Actinomycin D	12 µg/kg IV push
	Cyclophosphamide	3 mg/kg IV bolus
4	Folinic acid	0.1 mg/kg IM or PO
	Actinomycin D	12 µg/kg IV push
	Cyclophosphamide	3 mg/kg IV bolus
5	Methotrexate	1.0 mg/kg IM or IV
	Actinomycin D	12 µg/kg IV push
	Cyclophosphamide	3 mg/kg IV bolus
6	Folinic acid	0.1 mg/kg IM or PO
7	Methotrexate	1.0 mg/kg IM or IV
8	Folinic acid	0.1 mg/kg IM or IV

Table 94-8 Protocol for EMACO Regimen

Day	Drug	Dose
1	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 minutes
	Actinomycin D	0.5 mg IV push
	Methotrexate	100 mg/m^2 IV push
		200 mg/m^2 by infusion over 12 hours
2	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 minutes
	Actinomycin D	0.5 mg IV push
	Folinic acid	15 mg every12 hours ∞ 4 doses IM or PO beginning 24 hours after starting methotrexate
8	Cyclophosphamide	600 mg/m^2 by infusion in saline over 30 minutes
	Oncovin (vincristine)	1.0 mg/m^2 IV push

regimen by substituting etoposide and cisplatin on day 8 (EMACE; Table 94-9). Bower and colleagues[85] reported that EMACE induced remission either alone or in conjunction with surgery in 16 of 21 patients (76%) who were resistant to EMACO. Unfortunately, the use of etoposide in GTN has been reported to increase the risk of later secondary tumors, including myeloid leukemia, melanoma, colon cancer, and breast cancer.[86] The increased risk for breast cancer did not become apparent until after 25 years. Among all patients who were treated with etoposide, 1.5% subsequently developed leukemia. Therefore, toposide should be used only in patients who require it to achieve remission, most commonly patients with metastatic disease and high risk scores. When patients with nonmetastatic and low-risk metastatic disease prove resistant to single-agent therapy, we now administer triple therapy (MAC) at our center before using regimens that contain etoposide.[87]

VBP. Second-line therapy with cisplatin, vinblastine, and bleomycin (VBP) could also be effective in patients with drug-resistant GTN. This regimen has been shown to induce complete remission in 18%, 57%, and 63% of patients with drug-resistant GTN.[87]

5-Fluorouracil and Floxuridine. Matsui and colleagues employed 5-fluorouracil and actinomycin D in 11 patients with drug-resistant high-risk GTN, and 9 patients (81.8%) achieved remission.[88] Two of these patients later relapsed but attained remission with other combination chemotherapy. Similarly, Wan and colleagues administered an FUDR-containing regimen to13 patients with drug-resistant GTN, and all achieved complete remission.[89]

Table 94-9 Protocol for EMACE Regimen

Day	Drug	Dose
1	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 minutes
	Actinomycin D	0.5 mg IV push
	Methotrexate	100 mg/m^2 IV push
		1000 mg/m^2 by infusion over 12 hours
2	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 minutes
	Antinomycin D	0.5 mg IV push
8	Cisplatin	60 mg/m^2 with prehydration
	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 minutes

OTHER MODALITIES. The role of autologous bone marrow transplantation or stem cell rescue in GTN has yet to be defined. Individual cases have been reported in which high-dose chemotherapy with autologous bone marrow techniques have been successful in inducing remission in patients who were refractory to the usual regimens. Efforts continue to identify new agents that are effective in treating patients with GTN. Although ifosfamide and taxol are both active, further studies are needed to better define their roles as primary and second-line therapy in the treatment of this disease.

METHOD OF ADMINISTRATION. At the NETDC, β-hCG levels are measured weekly after each course of chemotherapy and serve as the primary basis for determining the need for additional treatment in patients with stage I GTN. After the first treatment, further chemotherapy is withheld as long as the hCG level falls progressively. A second course of the same agent is administered under the following conditions:

- β-hCG level plateaus for more than 2 consecutive weeks or re-elevates, or
- β-hCG levels do not decline by one log (tenfold) within 18 days after completing the first treatment.

If a second course of methotrexate/folinic acid is necessary, the dosage of methotrexate remains unaltered if the patient's response to the first treatment has been adequate. An adequate response is defined as a fall in the β-hCG level by one log (tenfold) after a course of chemotherapy. When the response to the first treatment is inadequate, the dose of methotrexate is increased by 50%. If the response to two consecutive courses of methotrexate/folinic acid is inadequate, the patient is considered to be resistant to methotrexate, and actinomycin D is instituted promptly. If a patient fails to respond to sequential methotrexate/actinomycin D, then combination chemotherapy using MAC is administered at 3-week intervals or as frequently as toxicity permits until the patient's β-hCG level becomes undetectable. Patients who require combination chemotherapy should be treated intensively to attain remission. To prevent relapse, at least two additional courses of chemotherapy should be administered after the patient achieves undetectable hCG levels.

Patients who require combination chemotherapy must be treated intensively to attain remission. We administer combination chemotherapy as frequently as toxicity permits (usually at 2- to 3-week intervals) until the patient attains three consecutive undetectable hCG values. After the patient achieves normal β-hCG levels, three or four additional courses of chemotherapy are administered to reduce the risk of relapse. Relapse can be attributed to the fact that residual disease is present, producing hCG below the threshold of assay systems that are currently in use.

Stage I (Nonmetastatic Disease)

The protocols for the management of stage I disease at the NETDC are shown in Table 94-10. The treatment of stage I GTN is either surgical or medical, depending on the patient's desire to preserve fertility. Hysterectomy is advisable as initial treatment in patients with stage I nonmetastatic GTN who no longer wish to preserve fertility. The use of hysterectomy to treat nonmetastatic disease results in a reduced number of courses of chemotherapy and a shorter duration and lower dose of chemotherapy required to achieve remission.[90] Adjuvant chemotherapy administered at the time of surgery is indicated to eradicate any occult metastases and to reduce the likelihood of tumor dissemination at the time of surgery. Adjuvant chemotherapy administrated at the time of surgery has not been associated with increased postoperative morbidity. Nonmetastatic PSTT should be treated with hysterectomy because of this tumor's poor response to chemotherapy. Once PSTT metastasizes, the sur-

Table 94-10 Treatment Protocol for Stage I Gestational Trophoblastic Neoplasm

INITIAL

Sequential methotrexate/actinomycin D

Hysterectomy with adjuvant chemotherapy

RESISTANT TO BOTH SINGLE AGENTS

MAC

Hysterectomy with adjuvant chemotherapy

Local uterine resection

FOLLOW-UP HCG

Weekly until normal for 3 weeks, then monthly until normal for 1 year

CONTRACEPTION

12 consecutive months of normal hCG tests

Table 94-12 Treatment Protocol for Stages II and III Gestational Trophoblastic Neoplasms

LOW RISK	
Initial	Sequential methotrexate/actinomycin D
Resistant to both single agents	MAC or EMACO; Local resection with adjunctive CT
HIGH RISK	
Initial	EMACO
Resistant	EMAEC; VBP Local resection with adjunctive CT
Follow-up hCG	Weekly until normal for 3 weeks, then monthly until normal for 12 months
Contraception	12 consecutive months of normal hCG tests

vival rate is lower than that of other GTNs despite multimodal therapy.[91] Thirty-one patients who were treated by primary hysterectomy and adjuvant chemotherapy all achieved complete remission with no additional therapy.

Between July 1965 and June 2006, 543 patients with stage I disease were treated at the NETDC (Table 94-11). Complete sustained remission was achieved in 460 patients (92%) with single-agent therapy. The remaining 83 patients who were resistant to single-agent chemotherapy subsequently attained remission with either further chemotherapy or surgical intervention. If a patient no longer wishes to preserve fertility, hysterectomy with adjuvant single-agent chemotherapy may be performed as the primary treatment.

Stages II and III

The protocol for the management of stage II and stage III GTN is reviewed in Table 94-12. Tables 94-13 and 94-14 summarize the results of treatment of stages II and III, respectively. Between July 1965 and June 2006, all 29 patients with stage II disease achieved remission. Single-agent chemotherapy induced complete remission in 16 of 20 (80%) low-risk patients. In contrast, only 2 of 9 high-risk patients achieved remission with single-agent treatment. Between July 1965 and June 2006, 160 of 161 patients (99%) with stage III GTN attained complete remission. Single-agent chemotherapy induced complete remission in 85 of 104 patients (82%) with low-risk disease and in 13 of 49 patients (27%) with high-risk disease. All patients who were resistant to single-agent treatment later achieved remission with combination chemotherapy. Although low-risk patients (prognostic score ≤7) are treated with primary single-agent chemotherapy with methotrexate or actinomycin, patients with high-risk scores (prognostic score >7) require primary combination chemotherapy to achieve optimal outcomes. Patients who are resistant to single-agent chemotherapy receive salvage therapy with combination chemotherapy, either MAC or EMACO. Patients who are resistant to MAC should then receive EMACO, and those who are resistant to EMACO may be treated with a modification of that regimen by substituting cisplatin and etoposide on day 8 and escalating the dose of methotrexate infusion to 1 g/m^2 (EMACE).

MANAGEMENT OF VAGINAL AND ADNEXAL METASTASES. Because trophoblastic tissue is highly vascular, vaginal metastases can bleed profusely. When bleeding is a problem, it could be necessary to pack the lesion or to perform a wide local excision. The administration of one or two courses of chemotherapy could result in the development of avascular planes around the vaginal tumor, making excision less bloody. Angiographic embolization of the hypogastric artery or of the specific vessels feeding the tumor could be required to control hemorrhage from a vaginal metastasis. Extension of tumor to the adnexa should be monitored by ultrasound when asymptomatic. These tumor deposits usually resolve once chemotherapy is administered; however, surgical intervention could be required if signs of intra-abdominal bleeding appear.

MANAGEMENT OF LUNG METASTASES. Thoracotomy has a limited role in the management of stage III GTN. Thoracotomy should be performed initially if there is the possibility that the lesion

Table 94-11 Results of Treatment in Stage I Gestational Trophoblastic Neoplasm (1965–2006)

Remission Therapy	Total No. of Patients (%)
Initial	460 (85)
Resistant	83 (15)
Total	543 (100)

Table 94-13 Results of Treatment in Stage II Gestational Trophoblastic Neoplasm (1965–2006)

Remission Therapy	Total No. of Patients (%)
Low risk	20/20 (69)
High risk	9/9 (31)

Table 94-14 Results of Treatment in Stage III Gestational Trophoblastic Neoplasm (1965–2006)

Remission Therapy	Total No. of Patients
Low risk	110/110
High risk	50/51*

*One patient died of disease.

is an hCG-producing primary lung tumor. Pulmonary resection is also indicated if a patient has a persistent viable nodule despite intensive chemotherapy. Before undertaking thoracotomy, however, a metastatic workup should be carried out to exclude the presence of other metastatic sites. Excision of persistent nodules in the face of complete gonadotropin remission is not indicated, because treated pulmonary nodules can undergo fibrosis and remain indefinitely on chest x-ray. If there is any question regarding the viability of a pulmonary lesion, a scan with radioisotope-labeled antibody to hCG or a PET scan could be helpful. These scans might also be useful in identifying occult sites of viable tumor.

Tomoda and colleagues[92] reviewed their experience with pulmonary resection in 19 patients with chemotherapy-resistant GTN and proposed the following criteria for successful resection:

- Good surgical candidate
- Primary malignancy is controlled
- No evidence of other metastatic sites
- Pulmonary metastasis localized to one lung
- hCG level below 1000 mIU/mL

In Tomoda's series, complete remission was achieved in 14 of 15 patients who met all five criteria but in none of the 4 patients who had one or more unfavorable clinical features. Similarly, Lurain and coworkers[93] reported that four of five carefully selected patients with drug-resistant pulmonary GTN attained complete remission after lung resection. Several investigators have reported that the achievement of nondetectable hCG levels within 1 to 2 weeks after resection of a solitary pulmonary nodule is highly predictive of a favorable outcome. Survival after salvage surgery is also influenced by other factors, such as the number of preoperative chemotherapy regimens, the number of disease sites, and the patient's WHO score.

Stage IV

The protocol for the management of patients with stage IV GTN at the NETDC is summarized in Table 94-15. All patients are managed with primary combination chemotherapy with EMA-CO. In the presence of cerebral metastases, the methotrexate dosage in the infusion is increased to 1 g/m^2 (in divided doses). Whole-head or focused irradiation is administered immediately. Patients with disease that is resistant to EMACO may then be treated with EMACE. Brain irradiation is both hemostatic and tumoricidal. The concurrent use of combination chemotherapy and brain irradiation appears to reduce the risk of spontaneous bleeding in cerebral metastases. Yordan and associates[94] reported that deaths due to central nervous system involvement occurred in 11 of 25 patients (44%) who were treated with chemotherapy alone but in none of 18 patients who were treated with both brain irradiation and chemotherapy. Evans and colleagues, on the other hand, have reported excellent remission rates in patients with cerebral metastases who were treated with chemotherapy alone.[95] Thirty of 35 patients (86%) with cerebral lesions achieved sustained remission with intensive combination chemotherapy that included high-dose intravenous and intrathecal methotrexate.

Table 94-15 Treatment Protocol for Stage IV Gestational Trophoblastic Neoplasm

INITIAL
EMACO
With brain metastases: Radiation, craniotomy as indicated
With liver metastases: Embolization, resection to manage complications
RESISTANT
Salvage chemotherapy (EMA-EC, VBP)
Local resection as indicated
Hepatic artery infusion as indicated
FOLLOW-UP HCG
Weekly until normal for 3 weeks, then monthly for 24 consecutive months
CONTRACEPTION
24 consecutive months of normal hCG values

SURGICAL MANAGEMENT OF CEREBRAL METASTASES. Craniotomy should be reserved for patients who develop progressive neurologic deterioration, indicating the need for acute decompression or for control of bleeding. In rare instances, cerebral metastases that are resistant to chemotherapy could be amenable to local resection, particularly if they are localized in the periphery. Evans and coworkers[95] reported complete remission in three of four patients who underwent craniotomy to relieve intracranial pressure and in two of three patients undergoing craniotomy for resection of chemotherapy-resistant tumor. Most patients with cerebral metastases who achieve remission have little or no residual neurologic deficits unless there has been an acute hemorrhagic episode.

MANAGEMENT OF HEPATIC METASTASES. The management of liver metastases is particularly difficult and problematic. If a patient is resistant to chemotherapy, hepatic arterial infusion might induce remission in selected cases. Hepatic resection might also be necessary to control acute hepatic bleeding or to remove localized areas of resistant tumor. Grumbine and associates[96] reported the use of selective occlusion of the hepatic arteries and concurrent combination chemotherapy in a patient with bleeding liver metastases who ultimately attained remission. Wong and colleagues[97] also noted that nine out of ten patients with hepatic involvement achieved complete remission with primary intensive combination chemotherapy without hepatic irradiation. Bakri and colleagues[53] similarly reported that five of eight patients (63%) with liver metastases who were treated with combination chemotherapy alone attained remission.

RESULTS OF TREATMENT. Table 94-16 summarizes the results obtained at the NETDC since 1965. Prior to 1975, only 6 of 20 patients (30%) with stage IV disease achieved remission. After 1975, 16 (84%) of 19 patients attained remission. This dramatic improvement in survival resulted both from the introduction of multimodal therapy early in the course of treatment and from the availability of supportive treatments that help to control life-threatening drug-induced toxicity.

Management of Primary Treatment Failure

When a patient becomes resistant to or relapses after treatment with primary and secondary chemotherapy as manifested either by a plateau in or a reelevation of the β-hCG level, it is necessary to reevaluate her status, looking for occult metastases that might be protected from the effects of drug therapy. Mutch and colleagues[98] reported recurrences after initial remission in 2% of patients with nonmetastatic GTN, in 4% of patients with good-prognosis metastatic disease, and in 13% of patients with poor-prognosis disease. Relapses developed within 3 and 18 months in 50% and 85% of patients, respectively. We have observed relapses after initial remis-

Table 94-16 Results of Treatment of Stage IV Gestational Trophoblastic Neoplasm: Number of Remissions

Time Period	Total No. of Patients (%)
1965–1975	6/20 (30)
After 1975	16/19 (84)

sion in 3% of patients with stage I, 8% with stage II, 4% with stage III, and 9% with stage IV disease.[99] The mean time to recurrence from the last undetectable hCG level was 6 months, and this rate did not differ among the four FIGO stages. All patients with stage I, II, and III GTN who relapsed were subsequently cured, whereas both of the stage IV patients with recurrent disease succumbed. Patients with uncomplicated molar pregnancy who spontaneously resolve their β-hCG levels rarely recur after 3 weeks of undetectable tests.

ROLE OF SURGERY. In contrast to its limited role in primary therapy, surgery can play an important role in the treatment of patients who prove resistant to first- and second-line therapy. Surgical removal of resistant disease of the uterus, lung, brain, liver, spleen, and gastrointestinal tract should be undertaken to reduce tumor burden and prevent bleeding when it is apparent that these metastatic sites no longer respond to either primary or salvage therapy.

SALVAGE CHEMOTHERAPY. Resistance to primary and secondary chemotherapy regimens requires the use of salvage regimens in addition to surgery and radiation therapy. A number of well-recognized protocols have been used with some success in this situation, including VBP and EMACE.

FOLLOW-UP

After Evacuation of a Molar Pregnancy

After evacuation, patients with either a complete or partial mole should be followed with weekly quantitative β-hCG tests until the β-hCG levels are undetectable for 3 consecutive weeks. Until recently, the standard follow-up after three successive weekly undetectable hCG titers has been monthly testing for 6 to 12 months before pregnancy is advised. Recent studies at our center have shown that the risk of relapse after achievement of undetectable hCG levels is negligible.[100,101] We have therefore modified our follow-up protocols and now discontinue testing and allow for pregnancy after 3 consecutive weeks and 3 months of undetectable hCG tests.

Patients should be counseled to use effective contraception during the entire interval of β-hCG follow-up. We do not encourage the insertion of intrauterine devices until the patient achieves undetectable β-hCG levels because of the risk of infection or perforation if residual tumor is present. If the patient does not desire surgical sterilization, her options are therefore either hormonal or barrier methods. The incidence of postmolar tumor has been reported to be increased in patients who start oral contraceptives before the β-hCG level becomes undetectable.[102] Data from the NETDC, the Gynecologic Oncology Group, and the Brewer Center, however, indicate that oral contraceptives do not appear to increase the risk of postmolar GTN.[103,104]

After completion of the prescribed follow-up period, pregnancy may be undertaken. Patients should be counseled that they are at increased risk of another molar pregnancy in any subsequent gestation. For that reason, we highly recommend that a pelvic ultrasound be performed at 10 weeks of gestation. There is also evidence that patients who have been treated for GTN have a higher incidence of another trophoblastic event after any subsequent pregnancy. Therefore, all patients with a history of molar pregnancy or GTN should undergo β-hCG testing at the 6-week postpartum or postabortal visit.

After Treatment for Gestational Trophoblastic Neoplasia

Stages I–III

All patients with stage I, II, or III GTN should be followed with weekly β-hCG tests until the level is undetectable for 3 consecutive weeks. Testing should then continue monthly for 12 months. During the entire period of hCG monitoring, patients must be encouraged to use effective contraception. When patients have completed the prescribed period of follow-up, they are free to try for pregnancy. As can be seen in the subsequent pregnancy data, which is summarized in the following sections, patients can be reassured that subsequent pregnancies are not associated with an increase in the risk of congenital malformations, prematurity, or other obstetric problems.

Stage IV

Patients with stage IV disease should be followed with weekly β-hCG tests until the level is undetectable for 3 consecutive weeks. They should then be followed monthly for 24 months. A more prolonged follow-up is required for patients with stage IV disease because of the increased risk of late recurrence.

Subsequent Pregnancy

Pregnancy after Complete Hydatidiform Mole

Patients with molar pregnancies can anticipate normal reproduction in the future. Patients with CHM who were treated at the NETDC had 1278 later pregnancies between June 1965 and November 2001 (Table 94-17). These pregnancies resulted in 877 (69%) normal, full-term live births; 95 (7%) premature deliveries; 11 ectopic pregnancies; and 7 stillbirths. First-trimester spontaneous abortions occurred in 221 pregnancies (17%). Major and minor congenital malformations were detected in only 40 infants. The primary cesarean section rate of 19% was consistent with that of the normal population.

Pregnancy after Partial Hydatidiform Mole

Between June 1965 and November 2001, patients with PHM at the NETDC had 251 subsequent gestations, which resulted in 189 (75%) full-term live births, 1 stillbirth, 1 ectopic pregnancy, and 4 premature deliveries (Table 94-18). First-trimester spontaneous abortions occurred in 39 (15%) pregnancies, and major and minor congenital anomalies were detected in only 3 infants.

After a patient has had a molar pregnancy, she has an increased risk of developing another molar pregnancy at a later conception.[105] Thirty-four (1 in 150) of our patients had at least two molar gestations between June 1965 and November 2001. Patients can have an initial CHM or PHM and then, in a later pregnancy, can develop the other type of molar disease. Following two molar pregnancies, 34 patients had 35 later conceptions resulting in 20 (57%) full-term normal deliveries, 7 (20%) molar pregnancies (6 complete, 1 partial), 3 spontaneous abortions, 1 ectopic pregnancy, 1 intrauterine death, and 3 therapeutic abortions. Bagshawe and colleagues also reported that the risk of a third molar disease after two episodes of molar pregnancy was 15%. In six of our cases, we have documented that

Table 94-17 Subsequent Pregnancy Outcome in Complete Molar Pregnancy (1965–2001)

Outcome	Number (%)
Total pregnancies	1278
Total deliveries	979
Term live	877 (68.6)
Preterm	95 (7.4)
Stillbirth	7 (0.5)
Congenital anomalies	40/979 (4.1)
C/S (1979–2001)	70/373 (18.8)
Spontaneous abortions	229 (17.9)
Therapeutic abortions	41 (3.2)
Ectopic pregnancy	11 (0.9)
Repeat molar pregnancy	18 (1.4)

Table 94-18 Subsequent Pregnancy Outcome in Partial Molar Pregnancy (1975–2001)

Outcome	Number (%)
Total pregnancies	251
Total deliveries	194
Term live	189 (75.3)
Preterm	4 (1.6)
Stillbirth	1 (0.4)
Congenital anomalies	3/194 (1.5)
C/S (1979–2000)	23/194 (14.9)
Spontaneous abortions	39 (15.5)
Therapeutic abortions	11 (4.4)
Ectopic pregnancy	1 (0.4)
Repeat molar pregnancy	6 (2.4)

Table 94-19 Subsequent Pregnancy Outcome in Patients Treated for Gestational Trophoblastic Neoplasms

Outcome	Number (%)
Total pregnancies	581
Total deliveries	437
Term live	393 (67.6)
Preterm	35 (6.0)
Stillbirth	9 (1.5)
Congenital anomalies	10/437 (2.3)
C/S (1979–2000)	68/335 (20.3)
Spontaneous abortions	99 (17)
Therapeutic abortions	28 (4.8)
Ectopic pregnancy	7 (1.2)
Repeat molar pregnancy	8 (1.4)

the patient had different partners at the time of conception of different molar pregnancies.

Pregnancy after Gestational Trophoblastic Neoplasia

Patients who are treated successfully with chemotherapy can also generally experience normal reproductive function. Table 94-19 summarizes the experience at the NETDC in 581 pregnancies that occurred between June 1965 and November 2001. These later pregnancies resulted in 393 (68%) full-term live births, 35 premature deliveries, 7 ectopic pregnancies, and 9 stillbirths. First-trimester spontaneous abortions occurred in 17% of patients, and major and minor abnormalities were detected in only 10 infants. It is reassuring that the frequency of congenital anomalies is not increased despite the use of chemotherapeutic agents, which are both teratogenic and mutagenic.

Our experience is in general agreement with that of other centers regarding the pregnancy outcome after chemotherapy for GTN. A total of 2657 subsequent pregnancies have been reported, which resulted in 77% full-term live births, 5% premature deliveries, 1% stillbirths, and 14% spontaneous miscarriages.[106] Although the frequency of still births appears somewhat increased, congenital anomalies were noted in only 1.8% of patients, which is consistent with the general population. Woolas and associates[107] noted that there were no differences in either conception rate or pregnancy outcome between women treated with single agents and those treated with combination chemotherapy. Furthermore, only 7% of women who wished to become pregnant after GTN failed to conceive.

Psychosocial Consequences of Gestational Trophoblastic Neoplasia

Women who develop GTN can experience significant mood disturbance, marital and sexual problems, and concerns over future fertility.[108] Because GTN is a consequence of pregnancy, patients and their partners must confront the loss of a pregnancy at the same time that they face concerns regarding malignancy. Patients can experience clinically significant levels of anxiety, fatigue, anger, confusion, sexual problems, and concern for future pregnancy that last for protracted periods of time. Patients with metastatic disease and active disease are particularly at risk of serious psychological disturbances.

Psychosocial assessments and interventions should be provided to patients with GTN and their partners; these assessments should be targeted particularly to patients in the metastatic and active disease groups. The psychological and social stresses related to persistent GTN can last for many years beyond achieving remission.

ISSUES FOR THE FUTURE

Survival in GTN has improved dramatically over the past three decades because of the introduction of sensitive and specific hCG assays for diagnosis, treatment, and follow-up and because of the introduction of effective chemotherapy regimens based on patients' risk profiles. Further advances in the treatment of GTN can be achieved through earlier detection and intervention and through the introduction of effective chemotherapeutic protocols for resistant disease.

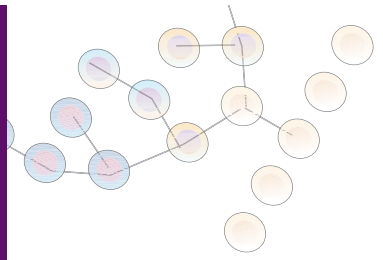
It is well recognized that the treatment of patients, particularly those with high-risk GTN, by physicians who are experienced in the management of this disease achieves optimal results. Therefore, prompt referral to or consultation with treatment centers is always in the best interest of the patient.

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95 Cancer of the Breast

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SUMMARY OF KEY POINTS

Incidence and Epidemiology

- Breast cancer is the most frequently diagnosed cancer in women in the United States, accounting for an estimated 274,900 new cases (212,920 invasive cancers and 61,980 in situ carcinomas) and 40,970 deaths in 2006.
- In the United States, the age-specific incidence of breast cancer increases with age, to a lifetime risk of breast cancer of 1 in 8 (to 110 years of age); by age 40, approximately 1 in 250 women will have been diagnosed with breast cancer annually; at 60 years of age, the figure is 1 in 35 women.
- Incidence rates rose 21% from 1973 to 1990, but then began to decline; mortality rates have stayed relatively constant until recently, when annual decreases have been seen.
- A sharp decline in the incidence of breast cancer in the early 2000s followed a decrease in the use of postmenopausal hormone replacement therapy.
- Age, family history, and both endogenous and exogenous ovarian hormone exposure have an important effect on risk and have been incorporated into models that predict individual risk of breast cancer; diet, alcohol use, and other factors play a smaller role.
- Inherited mutations in BRCA1, BRCA2, and CHEK2 play a role in the development of breast cancer and can be directly tested in individuals.

Biology and Estimation of Risk

- The expression of nuclear estrogen and progesterone receptors plays an important role in the differentiation and growth of normal breast epithelium and the response of breast cancer cells to hormonal therapeutics.
- ERBB2 (HER2) is a growth-signaling molecule on the surface of normal breast cells that is overexpressed in approximately 20% of breast cancer tumors, contributing to growth autonomy and genomic instability.
- TP53 is a tumor-suppressor gene that is mutated in 30% to 50% of breast cancers; loss of normal TP53 function is associated with a poor prognosis and reduced likelihood of treatment response, possibly because of decreased response to apoptotic signaling, increased genome instability, and angiogenesis.
- DNA microarray studies identified an "intrinsic gene list" of 534 genes that defines five biological subtypes of breast cancer including the basal type (HER2-positive, cytokeratins 5 and 17 positive), the "triple negative" type (HER2-, ER-, and PR-negative), two luminal types (so-called luminal-A and luminal-B), and the normal breast-like type.
- BRCA1 and BRCA2 are tumor-suppressor genes that play a critical role in the cellular response to DNA damage; inherited mutations in these genes are associated with an increased risk of breast cancer.
- Regardless of the criteria used by an individual physician and patient to define high risk, four possible actions may be taken, some of which can be used simultaneously: (1) enhanced surveillance, (2) behavioral modification, (3) chemopreventive strategies, and (4) prophylactic mastectomy or oophorectomy.

Screening and Diagnosis

- Despite recent challenges to the benefits of mammographic screening, the United States Preventive Service Task Force and many other organizations recommend screening mammography, with or without clinical breast examination, every 1 to 2 years for women 40 years of age and older.
- Microcalcification and soft tissue density are the major indications for biopsy in mammographic screening; the mammographic abnormality with the highest rate of malignancy is a mass density with associated calcification.
- Computer-assisted digitized mammographic imaging, magnetic resonance imaging, positron emission tomography, and radionuclide scanning are under intense investigation as emerging techniques for breast imaging.
- For patients with breast symptoms or palpable abnormalities, mammography characterizes the suspicious area, evaluates the remainder of the breast for occult lesions, and assesses the contralateral breast.
- Malignant breast masses classically are nontender and firm, with irregular borders.
- Diagnostic methods include fine-needle aspiration cytology, needle core biopsy with ultrasound or stereotactic guidance, and excisional biopsy, with or without wire or tack localization.

Management of Noninvasive Disease

- Lobular carcinoma in situ (LCIS) is a nonpalpable lesion that usually is discovered with another indicator for biopsy; it is more common in premenopausal women and accounts for 30% to 50% of cases of carcinoma in situ.
- LCIS has a propensity for multicentricity and bilaterality; it is an indicator of risk of subsequent invasive breast cancer.
- Management of LCIS had shifted toward observation after biopsy rather than mastectomy; increasing evidence shows that tamoxifen should be considered as a preventive approach.
- The multifocal nature of LCIS makes margin clearance an unrealistic and unnecessary goal.
- Unlike LCIS, ductal carcinoma in situ (DCIS), almost always is first identified by mammography; the peak incidence is

between 51 and 59 years of age, and it accounts for most of the increasing number of carcinoma in situ lesions diagnosed.
- DCIS is more likely to be localized to one area of the breast; thus, most patients are candidates for breast conservation; tamoxifen should also be considered following lumpectomy and radiation to reduce the risk of another ipsilateral or a new contralateral event, invasive or noninvasive.

Management of Early Stage Breast Cancer

- Patients should undergo a complete history and physical examination.
- Hemogram and renal and hepatic function tests as well as serum alkaline phosphatase evaluation should be performed in all patients.
- Bilateral mammography is indicated for all patients, and other breast imaging (ultrasound and MRI) should be used as needed for each individual patient; other imaging studies are recommended only to evaluate specific signs or symptoms or in patients with locally advanced disease.
- Prognostic factors include pathologic tumor size, hormone receptors, axillary nodal status, histologic subtype, tumor grade, and perhaps age.
- HER2 is a strong predictive marker, and accurate determination of HER2 status identifies patients with T1cN0 tumors and above who should be considered candidates for adjuvant therapy with a trastuzumab-based regimen.
- Promising results have been shown with microarray-based expression profiling as a potential means of gauging prognosis or predicting response to therapy.
- Specific gene expression profiling assays also have prognostic value, and two of them are undergoing prospective testing as a predictive marker for therapy selection.
- The revised American Joint Committee on Cancer TNM staging system takes into account the increasing use of novel imaging and pathology techniques, such as sentinel node biopsy and immunochemistry; it also considers the number of involved nodes a strong prognostic factor.
- Axillary dissection of level I and II nodes remains a valuable staging procedure; however, sentinel lymph node mapping is becoming the standard of care for accuracy and less morbidity.
- For patients with stage I and II disease, breast conservation and modified radical mastectomy are the therapeutic options; for most patients, breast conservation is an acceptable approach.
- Factors that affect local control in breast conservation include pathologic margin evaluation, extensive intraductal component, age, and the presence of multiple tumors.
- Adjuvant therapy with cytotoxic drugs or endocrine treatment, or both, is recommended for patients with node-positive disease.
- Pathologic tumor size, hormone-receptor status, histologic subtype, and nuclear grade are used to select patients with node-negative disease for adjuvant therapy.
- The results of the meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) show that the survival benefits of adjuvant chemotherapy and endocrine therapy persist after 15 years of follow-up.
- Challenges that require resolution include identification of biologic parameters that more precisely predict the natural history of disease and the response to systemic therapy; more effective treatments are clearly needed.

Management of Locally Advanced Disease

- Patients with locally advanced disease are a heterogeneous group, including those with T3N1, T0–3N2–3, and T4N0–3 disease.
- Multimodality therapy is recommended for virtually all patients with locally advanced disease; the sequence of chemotherapy, surgery, and radiation depends largely on the operability of the primary disease.
- For women with inoperable or inflammatory breast cancer (or both), preoperative. chemotherapy is recommended, followed by surgery, radiation, and endocrine therapy, if appropriate. Preoperative endocrine therapy for patients with receptor-positive disease is also a reasonable option.

Management of Locally Recurrent Disease

- Local recurrence is an indicator of systemic relapse in most cases; an exception may be local relapse in a breast that has undergone conservation therapy.
- Selection of the treatment modality depends largely on the extent of local and regional failure and the presence of distant metastases.
- Surgical removal alone may be sufficient in some cases, but it often is combined with locoregional radiation and/or systemic therapy.

Management of Metastatic Disease

- Although a small percentage of patients with metastatic breast cancer achieve long-term disease-free survival, this stage of disease essentially is not curable, and therapy is largely palliative.
- A wide range of systemic, local, and supportive therapies are available for the palliation of metastatic breast cancer.
- The selection of endocrine, cytotoxic, or biologic therapy usually is based on disease-free interval, receptor status, HER2 status, site of metastasis, performance status, age, and previous exposure to systemic therapy.
- Trastuzumab has changed the natural history of patients with HER2-positive metastatic breast cancer. Bevacizumab has been shown to improve progression-free survival, but not overall survival, when added to paclitaxel as first-line therapy for metastatic disease. Adjuvant trials began in late 2007.

EPIDEMIOLOGY

Incidence

Worldwide, breast cancer is the most common type of cancer and the most common cause of cancer-related mortality among women.[1] In the United States, approximately 212,920 new cases of invasive breast cancer, 61,980 in situ cases, and 40,970 deaths were expected to have occurred in 2006.[2] In women, breast cancer accounts for 26% of new cases of cancer and 15% of cancer deaths, second only to lung cancer as a cause of cancer-specific death.[3] Approximately 1% of breast cancers occur in males and 90% are estrogen receptor (ER)-positive.[4] Incidence rates continued to increase until 2002, likely reflecting increase use of mamographic screening, but recently have

Table 95-1 Risk of Breast Cancer in U.S. Women

Age Range (yr)	Breast Cancer Risk
30–40	1:252
40–50	1:68
50–60	1:35
60–70	1:27
Lifetime (to age 110 yr)	1:8

Data from www.cancer.gov/cancertopics/factsheet/Detection/probability-breast-cancer. Accessed 2/11/2008.

been reported to be declining. Part of that decline may be due to a decrease in the use of postmenopausal hormone replacement therapy.[5] Although incidence rates (all races combined) are substantially higher for women age 50 and older (375.0 per 100,000) compared with women younger than 50 years (42.5 per 100,000), approximately 23% of breast cancers are diagnosed in women younger than 50 years, because those women represent 73% of the female population (Table 95-1).

Although breast cancer is a major disease for women in the United States, survival analysis performed by the Surveillance Epidemiology and End Results (SEER) program shows that, for women diagnosed between 1988 and 2001, survival rates are better than those observed for many other tumors.[6] Around the world, there are large variations in incidence, mortality, and survival, and these may be due to several underlying complex factors including age, ethnicity, diet, and lifestyles.[1] Most of our knowledge regarding specific risk factors has been derived from large observational studies in developed countries, such as the Nurses' Health Studies (NHS)[7] in the United States and the "Million Women Study" in the UK (www.millionwomenstudy.org). Some of these risk factors are briefly summarized in the following sections.

Diet

Alcohol consumption is the best-established dietary factor associated with increased risk for breast cancer, and folate intake is inversely related to breast cancer, especially among women who consume alcohol.[8] Initial studies correlated fat intake with an increased risk of developing breast cancer, but more recent prospective studies have failed to confirm those observations.[9–11] However, there appears to be an association between body mass index (BMI) and breast cancer, which may be accounted for by increased estrogen levels in women with a higher BMI.[12,13] Dietary phytoestrogens such as those found in soybeans have a chemical structure that is similar to that of 17β-estradiol and can bind to the estrogen receptor to compete with estrogen[14]; their consumption may have a weak protective effect against breast cancer.[15] Interestingly, a recent study of French women correlated consumption of phytoestrogens derived from lignans with a reduced risk[16]; whether these association are causal remains to be proven in prospective intervention studies.

Ionizing Radiation

The accumulated knowledge about radiation-related breast cancer risk in women derives mainly from epidemiologic studies of patients exposed to diagnostic or therapeutic radiation and of the Japanese atomic bomb survivors. Low-dose radiation exposure to the breast is carcinogenic, and risk increases as a linear function of increasing dose. The risk is particularly high in the developing breast (i.e., before the age of 20), and is minimal for women exposed after menopause.[17] Given that germline mutations in DNA repair genes are rare, their influence on radiation-associated risk of breast cancer has been difficult to study. One group that theoretically could be at increased risk are flight attendants exposed to cosmic radiation, although it has been difficult to determine whether such an association exists. The excess estimated lifetime risk of dying from radiation-associated cancers (of all histologies) is about 1% following an exposure of 100 mSievert, which is 10 to more than 100 times the estimated annual exposure of flight attendants.[18]

Exogenous Hormones

The NHS originally was set up to determine whether oral contraceptive usage was associated with an increase in breast cancer. An analysis of data from that study and over 50 additional studies has confirmed that current users of exogenous hormones have a slightly increased risk of developing breast cancer.[19] However, the mortality associated with this risk appears to be offset by a decreased risk of developing colon and ovarian cancer, such that there is no increase in overall cancer mortality associated with their use.[7] Estrogen-only hormone replacement therapy (HRT) for postmenopausal women is associated with a small but significant risk of all types of invasive breast cancer (RR of ~1.6). This relative risk is even higher for estrogen-progestagen combinations (RR of ~2.5); however, the risk drops back to baseline by 5 years after cessation of therapy.[11] Recently, age-adjusted incidences of invasive breast cancer decreased in the United States between 2002 and 2003 by 7%, reflecting an absolute decrease of ~14,000 breast cancer cases (Fig. 95-1). This decrease was limited to women 50 years of age or older, occurred primarily in ER-positive tumors, and coincided closely with a dramatic decrease in the use of HRT following the publication of the Women's Health Initiative results that correlated HRT with an elevated risk of coronary heart disease.[5]

Reproductive Factors and Endogenous Hormones

Breast cancer risk consistently has been correlated with an earlier age of menarche, later age of menopause, nulliparity, and late age of first birth, all of which determine the cumulative number of ovarian cycles. This finding is consistent with the correlation between estrogen levels and breast cancer risk.[13] In addition to sex hormones, insulin-like growth factor 1 (IGF1) is a mitogenic growth factor that had been implicated by in vitro and animal data in breast cancer carcinogenesis, as discussed later in this chapter. IGF-1 plasma levels consistently have been correlated with an increased risk of developing breast cancer in premenopausal women.[20] Finally, prolactin levels also have been associated with an elevated risk in both pre- and postmenopausal women.[21]

Familial History and Predictive Models of Breast Cancer Risk

Breast cancer is approximately twice as common among first-degree relatives of breast cancer patients as in those women with no family history of the disease. The two most important breast cancer susceptibility genes, BRCA1 and BRCA2, were identified by linkage analyses in the mid-1990s.[22] Since then, rare germline mutations in several other genes, such as TP53, PTEN, and ATM, have been shown to confer an increased risk of breast cancer. BRCA1 and BRCA2 account for less than 20% of familial clustering of breast cancer. Given that linkage analyses have failed to yield additional susceptibility loci, it is likely that most of the genetic susceptibility is a result of multiple low-penetrance alleles that co-exist in highly penetrant combinations in a polygenic model.[23]

An increasing understanding of relevant risk factors has led to integrated efforts at evaluating a women's individual risk,[24] and several individualized risk-assessment tools are available, such as the Gail and Claus models.[25] One such tool is available on the NCI website at http://www.cancer.gov/bcrisktool/. These tools are being used for clinical counseling for both breast cancer patients and healthy women perceived to be at risk. Given that for women living in the Western hemisphere the lifetime risk of breast cancer is approximately 11%, even a small relative risk reduction will translate into many thousands of lives saved.

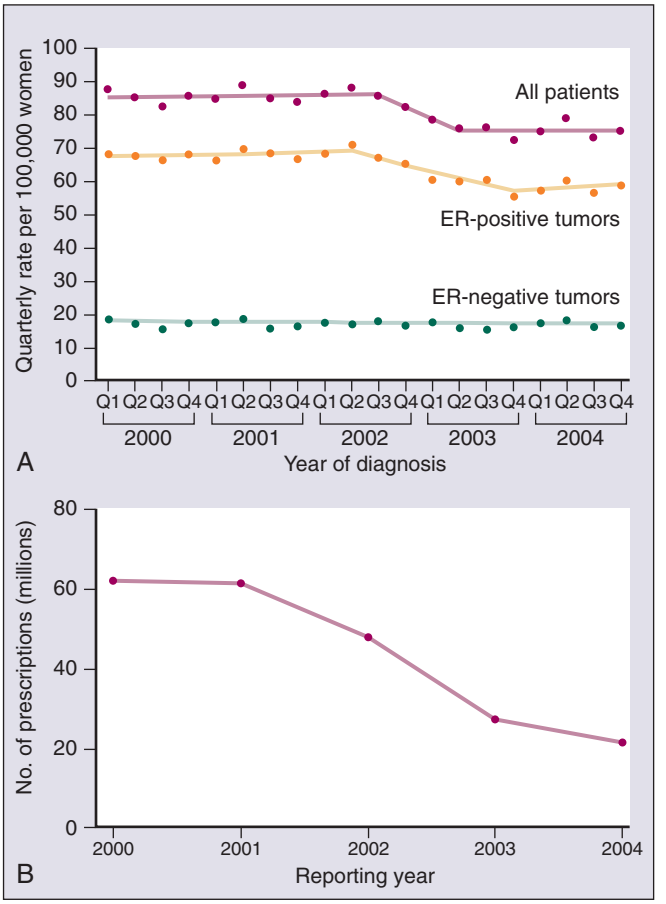


Figure 95-1 • Quarterly incidence of breast cancer in women between the ages of 50 and 69 years, according to estrogen-receptor (ER) status, and the number of prescriptions for hormone-replacement therapy, 2000–2004. **A,** Data are from nine of the NCI's SEER registries, with trends modeled with regression-analysis statistical software (Joinpoint). Trends were age-adjusted to the standard population in the year 2000 and were adjusted for reporting delays. **B,** The number of prescriptions reported in the United States for the combined estrogen-progestin preparation Prempro and the conjugated equine estrogen Premarin, according to year. (Reproduced with permission from Ravdin P, Cronin KA, Howlader N, et al: The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 2007;356:1670–1674.)

BIOLOGY

Modern diagnosis, prevention, and therapy of breast cancer has benefited from a conceptual understanding of cancer as a genetic disease and an ongoing elucidation of molecular lesions that underlie breast cancer. Traditional anti-mitotic chemotherapy has been used empirically in the treatment of breast cancer as in other epithelial cancers; more recently the discovery of breast cancer-specific therapeutic targets such as ER and ERBB2 (human epidermal growth factor receptor 2 [HER2]) has led to the successful development of therapies that are effective only in patients whose tumors harbor these targets. This paradigm, which has been remarkably successful in other cancers where the underlying genetic aberration can be targeted (e.g., imatinib mesylate in CML and GIST, gefitinib in lung cancer with EGFR mutations), has provided the impetus for large-scale sequencing efforts of cancer genomes to identify additional targets. In addition, microarray technologies that enable the simultaneous quantitation of all RNA species and genome-wide DNA copy number changes have begun to provide diagnostic classifications that may be superior to traditional histologic critera for determining prognosis and therapy. Finally, the recent identification of both normal mammary gland and breast cancer stem cells will allow novel therapeutic approaches that may revolutionize therapy for metastatic disease. These advances and their implications for therapy are summarized in the following sections.

Estrogen and Progesterone Receptors

Estrogen plays a key role in the development of both normal breast epithelium and breast cancer, and the modulation of estrogen levels is a key therapeutic modality for breast cancer. Estrogens interact with mammary epithelial cells via specific estrogen receptors that function as nuclear transcription factors.[26] The two known receptors, ERα and ERβ, are encoded by different genes and share an overall sequence homology of about 30%, although the homology is higher in the DNA- and hormone-binding regions. ERα was the first estrogen receptor to be isolated and is the one most closely associated with breast cancer; it is expressed mainly in the breast, uterus, ovary, and endometrium. ERβ is more widely expressed and its relationship to breast cancer is less clear.[27] Most of the literature referring to ER (e.g., the staining of breast cancer cells as "ER-positive") refers to ERα unless otherwise specified. The major ligand-dependent transcriptional activation activity (so called "AF-2") function of ER dislodges from a complex with heat-shock proteins upon binding specific ligands, undergoes a conformational change, and homodimerizes. This homodimer then binds to the estrogen responsive elements (ERE) of the target genes, and recruits various co-activators (or co-repressors) that further influence transcription.[28] The participation in a multimeric signaling process likely contributes to the differential biologic effects that estrogen and estrogen-related compounds (e.g., tamoxifen) can have in different target organs. ER also has a minor ligand-independent transcriptional activating function, which is modified by phosphorylation and can facilitate "cross-talk" between ER activity and receptor tyrosine kinase signal transduction pathways. Approximately 70% of breast cancers express ER (i.e., they are ER-positive); these tumors tend to grow more slowly and appear better differentiated that ER-negative tumors. Moreover, anti-estrogen therapy is effective both in preventing recurrence in the adjuvant setting and in prolonging survival once metastases have developed. However, the relation between the ER expression and cancer initiation is not clear, because ER-positive cells are nonproliferating in the normal breast epithelium that is found adjacent to proliferating cells, suggesting a paracrine effect. The paracrine effect hypothesis is further supported by evidence that even in most ER-positive tumors only a minority of cells express ER by IHC, and breast cancer stem cells do not express ER.

The progesterone receptor (PR), itself an estrogen-regulated gene, gives rise to two distinct isoforms, PRA and PRB, by alternative splicing. PRB appears to be more specific to breast cancer, whereas PRA is more widely expressed. Interestingly, a polymorphism in the PR promoter (+331 G/A) that increases transcription of PRB has been associated with an elevated risk of endometrial and breast cancer.[29] PR is variably expressed in ER-positive tumors, and this variability has prognostic relevance. ER-positive/PR-negative tumors occur more commonly in women over 50, tend to be more aneuploid, and present as larger tumors with more frequent nodal involvement than ER/PR-positive tumors. Furthermore, ER/PR-positive tumors are more likely to respond to anti-estrogen therapy than ER-positive/PR-negative tumors.[30] Historically, ER-positive/PR-negative tumors were thought to have a nonfunctional ER pathway (as PR is downstream of ER). However, recent preclinical and clinical data suggest that these tumors may have a different biology, in that receptor tyrosine kinase pathways are more active and may directly down-regulate PR.[31] This is consistent with the finding that HER2 amplification is inversely correlated to PR expression.[32] While the aromatase inhibitor anastrozole is more active than tamoxifen in all ER-positive patients and the relative activity at first appeared greatest

in patients whose tumors are PR-negative,[33] this theory subsequently was not confirmed.[34] Regardless, the clinical combination of an aromatase inhibitor (e.g., letrozole) with HER2 blockade by trastuzamab may be synergistic.[35]

BRCA1, BRCA2, and Hereditary Susceptibility to Breast Cancer

It is estimated that 5% to 10% of all breast and ovarian cancer cases occur in the setting of inherited susceptibility due to a high-penetrance gene mutation, and the breast cancer susceptibility genes *BRCA1* and *BRCA2* have been identified as responsible for most these cases.[36] Women who carry a germline mutation in *BRCA1* have a cumulative lifetime incidence of 50% to 85% of developing breast cancer and 40% to 60% of developing ovarian cancer.[22] BRCA1 function is implicated in a variety of cellular processes including DNA damage repair, cell-cycle regulation, transcriptional regulation, and chromatin remodeling, whereas BRCA2 is involved primarily in DNA recombination and repair,[37] although it also may be involved in cytokinesis.[38] Tumors that arise in heterozygote carriers of germline mutations usually have an inactivated wild-type allele and do not express a functional protein. Cells that lack BRCA1 or BRCA2 protein have a specific deficiency in the repair of DNA double-strand breaks by the conservative and relatively error-free mechanism of homologous recombination by gene conversion.[38,39] Evidence for this defect is further supported by the finding that BRCA2 functions as part of the Fanconi anemia complex and actually is the long-sought-after FANCD1. Fanconi anemia complementation group FA-N results from biallelic mutations in *PALB2* ("partner and localizer of BRCA2"),[40,41] whereas monoallelic mutations in the same gene are associated with an increase susceptibility to familial breast cancer.[42] Moreover, several additional genes function in the same DNA repair pathway where germline mutations carriers are at increased risk of developing breast cancer—*CHEK2, ATM, NBS1, RAD50,* and *BRIP1*.[43] Why these genes predispose primarily to breast and ovarian cancers remains unknown, and somatic mutations in them are not commonly found in sporadic breast or ovarian cancers.[44] BRCA1-associated tumors usually are of the basal type (so-called "triple negative": HER2-, ER-, and PR-negative). Conversely, sporadic triple-negative breast cancers may share phenotypic similarities with cancers arising in BRCA carriers.[45] The identification of these genes and their function has important implications for prevention, diagnosis, and therapy of breast cancer in carriers.

Clinical management of carriers with *BRCA1* or *BRCA2* mutations is geared primarily toward preventing both ovarian and breast cancer.[46] Prophylactic mastectomy, albeit an invasive procedure with cosmetic consequences, is the most effective strategy available; it is associated with a 90% reduction in the risk of breast cancer. Oopherctomy, in addition to reducing ovarian cancer risk by 95%, reduces the risk of breast cancer by 50%. Finally, chemoprevention with tamoxifen has been associated with a 50% risk reduction in the contralateral breast in patients wth breast cancer, with a concomitant improvement in survival. Additionally, tamoxifen has been shown to reduce the risk of contralateral breast cancer by about 50% in both *BRCA1* and *BRCA2* carriers.

Once cancer is diagnosed, therapy remains dictated by standard prognostic features, with no specific regimens indicated on the basis of genetic predisposition. The involvement of BRCA proteins in DNA repair by homologous recombination suggests that these tumors would be particularly sensitive to chemotherapies that induce DNA inter-strand cross-links such as platinum salts. This hypothesis is supported by in vitro observations in both *BRCA*-null and FA cell lines. An ongoing clinical trial is testing this hypothesis.[47] In addition, *BRCA1*-related breast cancers commonly express EGFR (as is true of sporadic triple-negative cancers).[48] EGFR inhibitors, both antibodies and small-molecule tyrosine kinase inhibitors (TKI), are commercially available, but their specific efficacy in *BRCA*-related tumors remains to be defined. Similarly, it has been shown recently that a tyrosine kinase inhibitor of SRC, dasatinib, is particularly effective against triple-negative breast cancer cells, suggesting utility in *BRCA*-null tumors.[49] Finally, poly (ADP-ribose) polymerase 1 (PARP1) is critical for the base excision repair pathway; when this repair pathway is inhibited, double-strand breaks form at replication forks, and these are lethal to cells that cannot repair those breaks. Accordingly, BRCA-null cells are exquisitely sensitive to PARP inhibitors.[50,51] PARP inhibitors are still in early-phase clinical development, but the near future should enable more efficacious treatment to be tailored to tumors that lack functional BRCA proteins.

TP53

TP53 (*p53*), also termed the "guardian of the genome," is the most frequently mutated gene in human cancer. It plays a central role in sensing genotoxic and nongenotoxic stresses and transducing an antiproliferative effect (cell cycle arrest or apoptosis) in response. It is activated and regulated by post-translational modifications to the N-terminal region, (e.g., phosphorylation and ubiquitination) and, binding as a tetramer to specific DNA sequences via a central DNA-binding core region, exerts its primary biologic function by modulating the transcription of dozens of genes.[52] In transgenic mice, loss of *p53* is associated with multiple spontaneous tumors, although not of the mammary glands.[53] However, *p53* loss accelerates the appearance of mammary tumors in murine mammary tissue that also overexpresses MYC, HER2, IGF1, and/or WNT1. These genetic studies are consistent with a role for *p53* loss late in tumor development.[54] Indeed, the transgenic restoration of *p53* function leads to tumor regressions.[55]

Inheritance of a *p53* mutant allele causes the rare familial Li-Fraumeni syndrome, characterized by multiple early-onset cancers, including breast cancer in women who survive childhood cancers. Germline mutations in *ATM* and *CHEK2*, which are involved in *p53* activation, also cause an increased susceptibility to breast cancer.[56] Thirty to 50% of sporadic cases of breast cancers harbor somatic mutations in *p53* based primarily on sequencing of exons 5 through 8 (the DNA-binding core), where approximately 90% of mutations are found.[57] Currently, 2274 mutations that have been observed in breast cancers are listed in the *p53* database maintained by the International Agency for Research on Cancer (IARC; version R11, October 2006).[58]

p53, when mutated, accumulates in the nucleus of neoplastic cells. Thus, initial studies that described only a weak association between aberrant *p53* and adverse prognosis in breast cancer relied on IHC detection; more recent analyses based on mutation detection have confirmed a strong association.[59] More recently, *p53* mutations from 1794 European patients with at least 10 years of follow-up have been analyzed. Mutations in exons 5 through 8 were more common in ductal and medullary tumors, tumors with an aggressive phenotype (high grade, large size, node-positive cases, and low hormone receptor content), and in women less than 60 years old. Furthermore, the presences of a mutation conferred an overall 2.27-fold increased relative risk of breast cancer-specific mortality, independently of other known prognostic markers (e.g., tumor size, node status, and estrogen and progesterone receptor expression).[60] Finally, although not all mutations confer the same biologic properties (e.g., missense vs. nonmissense), all had similar prognostic utility.

Initial attempts at correlating p53 expression (by IHC) with resistance to chemotherapy have been supplanted with studies directly evaluating mutations. Some of these studies have shown breast cancers with *p53* mutations to be associated with less benefit from both anti-estrogens[61,62] and anthracylines,[63–65] although conflicting results also have been reported.[66] An overall analysis is complicated by different p53 assay methods, different disease settings (adjuvant, preoperative, and metastatic), and different combinations of drugs. In contrast, it appears that no clear relation between aberrant p53 and sensitivity to paclitaxel exists.[67–69]

p53 is an obvious target for cancer therapy, despite the apparent intractability of a loss-of-function genotype. Two approaches are being taken to overcome this limitation—small molecules to restore *p53* function[70] or inhibit its interaction with *MDM2*,[71] or adenoviral-mediated gene delivery. While the latter approach is approved for therapy of head and neck tumors in China, no clear activity in breast cancer has been demonstrated to date.[72]

ERBB2 (HER2)

The proto-oncogene *ERBB2* (*HER2*) encodes a transmembrane tyrosine kinase receptor, one member of a family of related growth factor receptors that include *EGFR* (*ERBB1*), *ERBB3* (*HER3*), and *ERBB4* (*HER4*). The ligands for these receptors, termed *heregulins,* are a family of growth factors known to bind to ERBB3 and ERBB4, inducing heterodimerization with ERBB2 and subsequent transduction of downstream signals. As HER2 does not bind ligand directly,[73] the ability to heterodimerize with other family members that do bind ligand is crucial for its activity. Of these, HER3 appears to be the most important heterodimerization partner.[74]

The amplification and/or protein overexpression of *HER2* is found in 20% of newly diagnosed breast cancers, and is associated with a more aggressive clinical course and decreased survival time compared to tumors with normal levels of HER2.[75] Amplification leads to very high levels of protein expression and constitutive activation of the receptor tyrosine kinase signal transduction pathway, namely RAS-MEK and AKT,[76] although the downstream effects may be more plietrophic than originally believed.[77] In contrast to EGFR, where amplifications in lung cancers frequently harbor activating mutations in the kinase domain, such mutations have not been found in breast cancer (see the Sanger Centre's COSMIC database, http://www.sanger.ac.uk/genetics/CGP/cosmic/). The identification of *HER2* as an oncogene in breast cancer facilitated the development of therapies directed against it. Trastuzumab, a humanized monoclonal antibody that binds to the extracellular domain of HER2, induces clinical responses as a single agent, prolongs survival in combination with chemotherapy, and decreases recurrence rates by about 50% in the adjuvant setting when given to women whose cancers overexpress HER2.[78,79] More recently, lapatinib, an oral small molecule tyrosine kinase receptor inhibitor active against HER2, also has been shown to be of benefit in metastatic, HER2-positive breast cancer. However, not all women with HER2-positive breast cancer respond to trastuzamab or lapatinib, and studies aimed at elucidating mechanisms of resistance are providing further insight into the pathophysiology of HER2-positive breast cancer. For example, increased levels of IGF1R may bypass HER2 blockade by trastuzamab and allow growth factor activation of AKT,[80] and a similar outcome may result from PTEN loss, as discussed earlier. In addition, a truncated form of HER2 that lacks the extracellular domain but retains the kinase activity has been described to correlate with trastuzumab resistance.[81]

The amplicon containing *HER2* frequently contains additional genes that influence therapeutic efficacy. Although initially it was thought that HER2-positive disease is more sensitive to anthracylines, recent data suggest that this sensitivity is conferred by the topoisomerase II gene (*TOP2A*) when it is present in the amplicon.[82] Modern genome-wide analysis methods currently are being applied both to panels of cell lines[83] as well as tissues from patients treated with anti-HER2 agents[84] to better understand mechanisms of resistance. The insights gained, in turn, are being exploited for further drug discovery: both antibody and small molecule inhibitors of IGF1R as well as PI3K and AKT kinase inhibitors currently are in clinical development for breast cancer, and synergy with anti-HER2 therapy has been demonstrated in vitro.[85]

PI3K and PTEN

Phosphatidylinositol-3,4,5-triphosphate (PIP_3) is a lipid second messenger formed by PIP_3 kinase (PI3K) in response to receptor tyrosine kinase signaling. PIP_3 activates AKT and other related pathways to induce proliferation and inhibit apoptosis. Approximately 25% of human breast cancers harbor oncogenic activating mutations in the p110 α catalytic subunits of PI3K (*PIK3CA*).[86] This signal is inactivated by the opposing phosphatase action of the tumor suppressor gene *PTEN*.

Germline *PTEN* mutations cause a hereditary cancer predisposition syndrome known as Cowden's syndrome, characterized by a high incidence of breast, uterine, thyroid, and skin neoplasms.[87] PTEN is inactivated in a wide variety of human tumors as a result of either mutation or, more commonly, epigenetic silencing through methylation, including in breast cancer.[88] PTEN loss is associated with genetic instability, and primary breast tumors that lack PTEN have increased aneuploidy.[89] In addition, PTEN loss has been associated with a decreased likelihood of response to the anti-HER2 therapy with trastuzumab.[90] Recent data elucidating the relationship between presence of *PIK3CA* mutations and PTEN status show that they are inversely correlated. Furthermore, PIK3CA mutations are twice as common in HER2-positive or ER-positive tumors, suggesting that more than one aberration upstream of AKT may be necessary to overcome the effect of an intact PTEN.[91] The relevance of *PIK3CA* mutations to the clinical activity of anti-HER2 directed therapy by trastuzumab and lapatinib is under active investigation.[92]

Breast Cancer Genome

The elucidation of genetic aberrations in cancer genomes (mutations, deletions, and amplifications) has led to a better understanding of cancer pathophysiology and is providing targets for rational drug development. With the determination of the DNA sequence of the normal human genome, efforts have shifted toward a more comprehensive analysis of cancer genomes. This effort began with a focus on tyrosine kinases but recently has been extended to an analysis of whole genomes. Recently, the first report of a comprehensive sequence analysis of 21,000 of the best studied and annotated human genes was published, including data from 11 breast and 11 colon cancer samples.[93] This screen rediscovered cancer genes known to be associated with breast cancer (e.g., *p53* and *BRCA1*) as well as genes not previously characterized as associated with cancer. This impressive effort suggests that an individual breast cancer harbors an average of about 90 mutant genes, of which a small minority (~12) are expected to contribute to the neoplastic process. Unfortunately for ease of therapeutic development, the functionally important mutations often differ among tumors (i.e., no tumor had more than six mutated cancer genes in common with any other tumor). However, when the genes were analyzed by functional groups, mutations in signal transduction pathway and transcription factor genes were found in nearly all breast tumor samples. These preliminary results have begun to allow a more complete genetic characterization of tumors, which will undoubtedly yield novel biologic and therapeutic insights in the near future.

Molecular Profiling in Breast Cancer

Simultaneous genome-wide determination of the relative abundance of RNA species (i.e., *transcriptional profiling*) combined with novel bioinformatic approaches has led to the development of molecular classifications based on continuous expression ranges of thousands of genes (as opposed to a binary determination of discrete factors, i.e., ER/PR and HER2). Tumors can be classified either according to transcripts that tend to segregate together according to underlying biologic differences (*unsupervised clustering*) or sorted by a given endpoint such as prognosis or response to therapy (*supervised clustering*). The first of these studies identified an "intrinsic gene list" of 534 genes that defined five biologic subtypes of breast cancer including the basal type (HER2-positive, cytokeratins 5 and 17 positive), the "triple negative" type (HER2-, ER-, and PR-negative), two luminal types (so-called luminal-A and luminal-B), and the normal-like type (Fig. 95-2).[94] Studies by others have confirmed large-scale gene

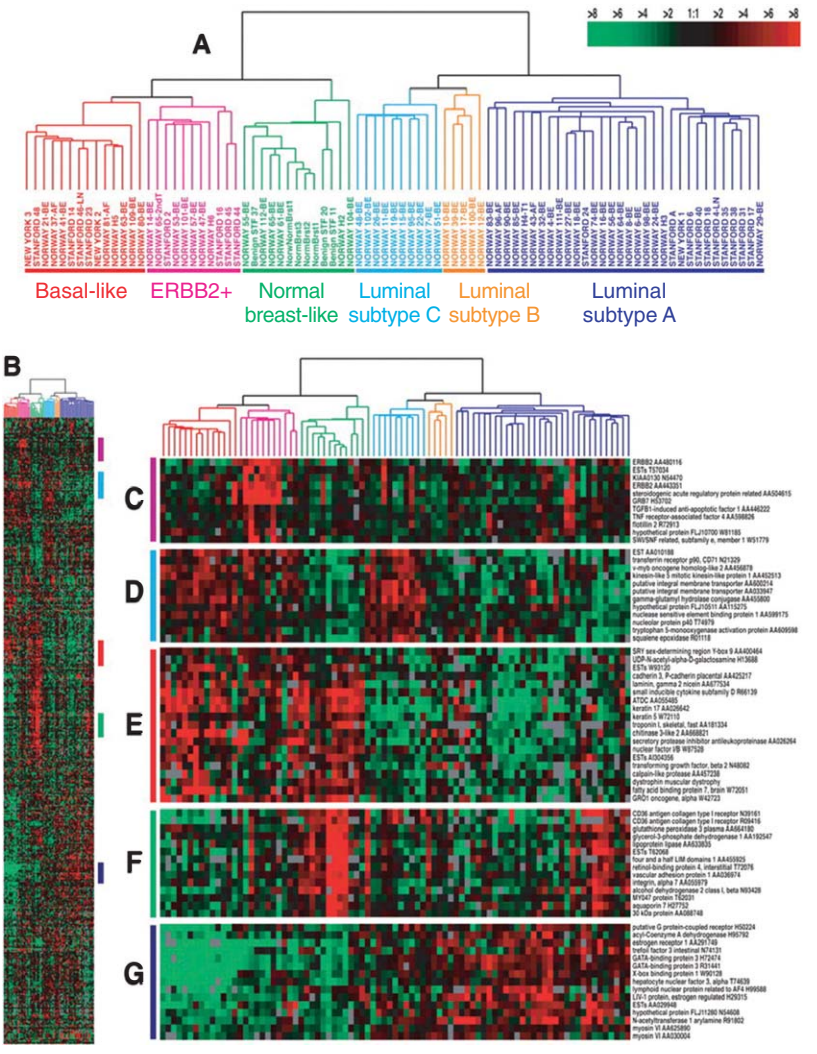


Figure 95-2 • Hierarchical clustering of 115 tumor tissues and 7 nonmalignant tissues using the "intrinsic" gene set. **A,** Scaled-down representation of the entire cluster of 534 genes and 122 tissue samples based on similarities in gene expression. **B,** Experimental dendrogram showing the clustering of the tumors into five subgroups. Branches corresponding to tumors with low correlation to any subtype are shown in gray. **C,** Gene cluster showing the ERBB2 oncogene and other coexpressed genes. **D,** Gene cluster associated with luminal subtype B. **E,** Gene cluster associated with the basal subtype. **F,** A gene cluster relevant for the normal breast-like group. **G,** Cluster of genes including the estrogen receptor (ESR1) highly expressed in luminal subtype A tumors. Scale bar represents fold change for any given gene relative to the median level of expression across all samples. (From Sorlie TR, Tibshirani R, Parker J, et al: Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 2003;100: 8418–8423.)

expression differences between ER-positive and ER-negative tumors and have shown additional molecular subsets within these categories.[95] This molecular classification of breast cancer is robust in that it is observed regardless of microarray platform type, and the various subtypes correlate with overall prognosis. Luminal-type cancers have the most favorable long-term survival, whereas HER2-positive and basal-like cancers may be more sensitive to chemotherapy but have the worst overall prognosis.[96,97] Thus, breast cancer is not a single disease with heterogeneous ER and HER2 expression but appears to be comprised of three to five molecularly and clinically distinct subtypes.

A similar approach can be taken by assaying DNA amplifications and deletions across the genome.[98] Such data recently have been mapped against both the "intrinsic gene set" and clinical outcome data, and have the potential to identify high-level DNA amplification that, similar to HER2, may be useful as therapeutic targets.[99] However, it should be noted that while these classifications are robust across a population, there is no standardized assay of measurement for assigning a molecular class to a new individual case. Furthermore, much of the molecular heterogeneity overlaps with conventional histopathology and is captured by determination of ER, PR, HER2 status, and tumor grade.[95]

In addition, while the intrinsic gene set and its derivations correlate with prognosis, this correlation does not easily translate into the specificity and sensitivity required for clinical decision making. One of the greatest clinical challenges has been determining the value of adjuvant chemotherapy for individual women with early-stage breast cancer, where many patients are treated but only a few benefit directly.

Several multigene prediction scores that correlate with outcome and provide more accuracy than traditional histopathologic markers have been retrospectively derived from microarray data, and, in some cases, prospectively validated on additional datasets. The best known examples are a 70-gene predictor set (Fig. 95-3)[100,101] and a 21-gene predictor set.[102,103] Both of these assays measure RNA levels by qPCR technology (which provides a less expensive and more robust method than microarrays as well as a larger dynamic range) and both have been submitted to the U.S. Food and Drug Administration (FDA) for approval. The 21-gene test is commercially available (Oncotype Dx, Genomic Health). It consists of only 16 target transcripts (and 5 reference transcripts), three of which are ER, PR, and HER2. However, there is an additional "proliferation" group of 5 genes (which includes Ki67 and cyclin B1) and a carefully constructed weighted formula to determine the overall "recurrence score."[102] Although this recurrence score provides a continuous risk variable, for clinical use it is pared down to three categories of low, intermediate, and high (of note, given the weighting schema, it is unlikely that a HER2-positive tumor would be classified as "low risk"). It is interesting that these two gene sets as well as the "intrinsic gene set" described earlier and yet another "wound healing" signature all seem to perform similarly when tested against the same clinical data set, even though they share few to none of the same genes.[104] The ability

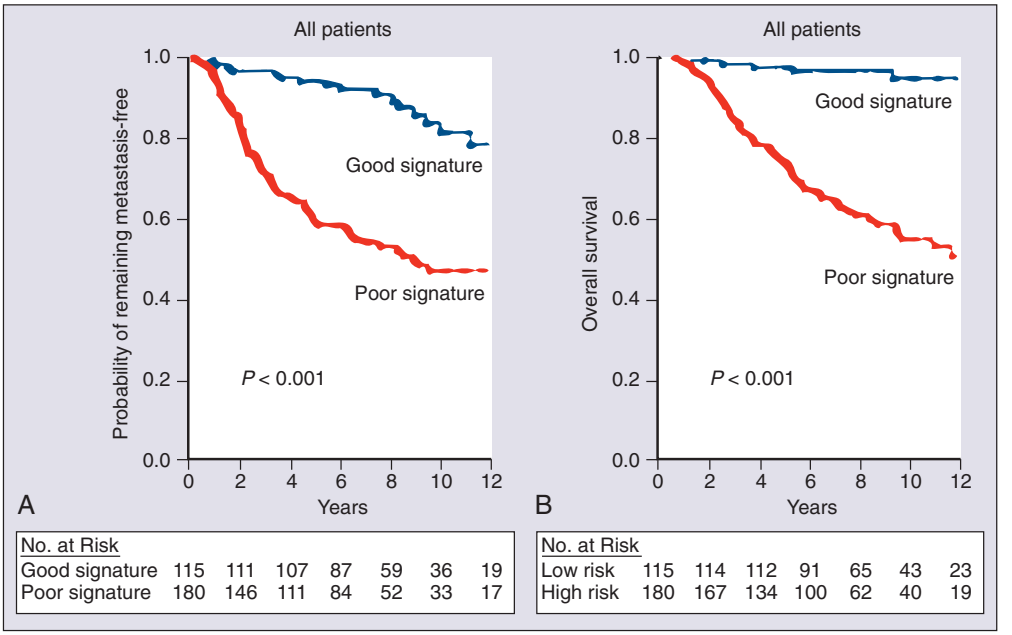


Figure 95-3 • Performance of a microarray-derived 70-gene multigene signature. Kaplan-Meier analysis of the probability that patients would remain free of distant metastases (**A**) and the probability of overall survival among all patients (**B**) according to whether they had a good-prognosis or a poor-prognosis signature. The performance of the signature also was determined separately for patients with lymph node-negative and lymph node-positive disease. The *P* values were calculated with use of the log-rank test. (Reproduced with permission from van de Vijver MJ, He YD, van't Veer LJ, et al: A gene expression signature as a predictor of survival in breast cancer. N Engl J Med 2002;347: 1999–2009.)

of the 70-gene assay to determine which ER-positive node-negative patients are most likely to benefit from adjuvant therapy will be prospectively tested in the Microarray in Node-Negative Disease May Avoid Chemotherapy (MINDACT) trial. Similarly, the Trial Assigning Individualized Options for Treatment (Rx) (TAILORx) study will prospectively test the utility of adjuvant chemotherapy in patients who have an "intermediate risk" according to the test; low-risk patients will not receive therapy, whereas all high-risk patients will be treated. These assays have the potential to revolutionize the way therapy is individualized in the adjuvant setting. However, by providing a continuous variable risk assessment (as in the case of the Oncotype recurrence score) they add complexity to the clinical decision-making process, which hitherto was binary in nature (i.e., ER positivity determines anti-estrogen therapy, HER2 positivity determines anti-HER2 therapy).

Disseminated and Circulating Tumor Cells

From 20% to 45% of patients with primary operable breast cancer and 70% of patients with metastatic disease have disseminated tumor cells (DTCs) that can be detected in bone marrow[105] or in lymph nodes.[106] Historically, DTCs usually have been evaluated by IHC staining for various cytokeratin markers. While their existence has been associated with a worse prognosis,[105] the need for a relatively invasive procedure (a bone marrow biopsy) and the lack of sufficient specificity and sensitivity as well as method standardization has prevented the routing use of such information in clinical decision making.[107] However, it is now possible to measure circulating tumor cells (CTCs) accurately using an automated immunobead enrichment followed by pan-cytokeratin staining. Using this approach, patients with metastatic breast cancer and five or more CTCs per 7.5 mL of blood are predicted to have a significantly worse disease-free survival (2.1 vs. 7 months) and overall survival (8.2 vs. 18 months) than patients with fewer CTCs.[108] This measurement may enable routine minimally invasive assessment of disease progression and response to therapy. Furthermore, the ability to isolate CTCs allows the study of molecular markers such has HER2 amplification and their relationship to the primary tumor[109] in real time. This approach has the potential not just to monitor patients but also to select specific therapy based on a molecular diagnosis obtained at the time of therapy (as opposed to relying on the original diagnostic biopsy.[110] The clinical utility of CTCs is now being prospectively tested in a trial randomizing patients with 5 or more CTCs per 7.5 mL after 1 month of therapy to continue the same course or change systemic therapy.

Breast Cancer Stem Cells

Cancer cells have two somewhat contradictory traits. Although they originate from a single clone, they often display marked genetic, biologic, and morphologic heterogeneity. Historically, the prevailing hypothesis was that genomic instability contributed to continuing evolution and emergence of different and ultimately more virulent subclones. This theory has been invoked to explain both progression (in terms of metastatic spread) and emerging resistance to therapy. Recently, an alternative explanation was provided by ground-breaking work elucidating the "cancer stem cell" model[111] (Fig. 95-4). Initially demonstrated in hematologic reconstitution and malignancies, cancer stem cells, while constituting a small minority of the cancer cell mass, retain the capacity for asymmetric division where they both self-renew and give rise to more differentiated daughter cells. The latter, while forming the bulk of the tumor, are themselves incapable of endless replication. Given that stem cells are long-lived and slow to replicate, this would explain both the accumulation of genetic lesions over time as well as resistance to therapy targeting dividing cells. It would also explain the frequently observed concordance between primary and metastatic cells. For a long time this model for epithelial cancers has been theoretical, as it was technically difficult to identify these cells. However, recently such cells have been isolated from both normal mammary glands and breast cancers, based on the presence and absence of specific surface markers. Thus, in mice, a single $^{Lin+D29}$(hi)CD24^{-} cell can reconstitute a complete functional mammary gland in vivo, contributing to both luminal and myoepithelial lineages.[112] Similarly, the ability to reconstitute human breast cancers in immunocompromised mice seems to reside within a minority CD44^{+}, CD24(−/low) subclone. Notably, tumors formed by these cells gave rise to mixed populations of epithelial cells, recapitulating the morphology of the parent tumor.[113] These findings have several important implications for breast cancer therapy. As a first step, the molecular and biochemical pathways that control CSC division (such as Wnt and Notch pathways) provide novel targets for therapy.[114]

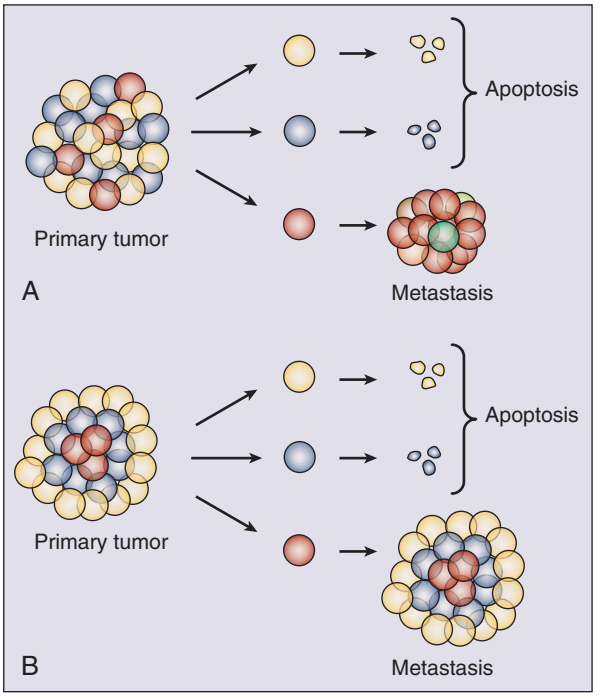


Figure 95-4 • Impact of the cancer stem cell (CSC) model on the origin and biology of metastases. **A,** According to standard cancer models, tumors are composed of heterogeneous mixtures of independent subclones, originated by divergent genetic mutations; different subclones are endowed with different functional properties, and only selected clones (*orange cells*) can migrate and form metastases. The metastasis is predicted to be a homogeneous monoclonal expansion of an individual subclone, which in turn can accumulate further mutations (*blue and yellow cells*) and diverge even further from the primary tumor. Overall, the model predicts that primary tumors and corresponding metastases are substantially different. **B,** The CSC model assumes that intratumor heterogeneity is caused mainly by cell differentiation, and that only CSCs (*orange cells*) can migrate and form overt metastases, while differentiated cells (*yellow cells*) undergo apoptosis. In the CSC model, metastatic cancer tissues undergo differentiation programs that closely resemble those observed in the corresponding primary tissues. Recent experimental evidence based on gene-expression microarrays tends to support the CSC model for human epithelial tumors, such as breast and colon cancer. The two hypotheses are not mutually exclusive, and elements of both are probably true. (Reproduced with permission from Dalerba P, Cho RW, Clarke MF: Cancer stem cells: models and concepts. Annu Rev Med 2007;58:267–284.)

MANAGEMENT OF PATIENTS AT HIGH RISK FOR BREAST CANCER

Once an individual patient's risk has been estimated, it is a matter of personal opinion as to what constitutes high risk. For many women, a relative risk of 1, with a lifetime probability of 1 in 8 of being diagnosed with breast cancer, is already high. For others, a relative risk of 2 or more would be considered high risk. Whatever criteria an individual physician and patient use to define high risk, four possible actions may be taken, some of which can be used simultaneously: (1) enhanced surveillance; (2) behavioral modification; (3) chemopreventive strategies; and (4) prophylactic mastectomy or oophorectomy.

Increased Surveillance

As discussed in the section on mammographic screening, the United States Preventive Task Force recommends screening mammography, with or without clinical breast examination, every 1 to 2 years for women 40 years of age and older. Although this task force recommended mammographic screening only as a category B intervention on the grounds that the quality of evidence was fair and the net gain moderate, and although controversy remains about the utility of routine screening before 50 years of age, ample evidence supports increased surveillance in women at high risk for breast cancer. A number of prediction models for breast cancer risk are available, and surveillance strategies are developing rapidly, particularly for women who are BRCA1 and BRCA2 mutation carriers.[115]

There is general agreement that women at high risk for breast cancer are candidates for mammographic surveillance in their 40s, and in some cases, earlier initiation of mammographic screening may be appropriate. Shorter screening intervals may be necessary because of the accumulating evidence of unacceptably high rates of interval breast cancers, even with annual screening, in BRCA1 and BRCA2 mutation carriers. Additionally, other imaging modalities, such as magnetic resonance imaging (MRI), must be considered in these high-risk groups. Finally, although controversy remains about the role of breast self-examination in the general population, experts in the surveillance of high-risk women still recommend monthly breast self-examination for women with BRCA1 and BRCA2 mutations.[116]

Behavior Modification

Multidisciplinary centers that provide counseling for women who are at substantial risk for breast cancer are well established throughout the United States. These multidisciplinary consultations provide recommendations for a range of surveillance and interventional approaches. In addition to the available surgical and medical preventive strategies, modification of lifestyle factors, such as obesity, high-fat diet, alcohol consumption, and lack of exercise, should be discussed. It probably will be many years before it is possible to say conclusively whether lifestyle modification changes a woman's risk. In the meantime, patients and their physicians must choose whether and how to modify lifestyle factors.

Chemoprevention

Tamoxifen was studied as a chemopreventive agent for breast cancer in four randomized prospective clinical trials. A significant reduction in breast cancer risk with tamoxifen was seen in the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 study[117] and the International Breast Cancer Intervention Study (IBIS-I).[118] Futher analysis of the patients in the NSABP P-1 study showed that tamoxifen reduced the incidence of breast cancer among BRCA2 carriers by 62%, but not among BRCA1 carriers.[119] However, two European chemoprevention studies performed at the Royal Marsden Hospital[120] and by the Italian Tamoxifen Prevention Study Group, respectively, did not show a decrease in the incidence of breast cancer in women using tamoxifen.

Based in large part on compelling evidence from the NSABP study, which showed a 49% reduction in overall risk of invasive breast cancer with the use of tamoxifen, a number of review groups, including the American Society of Clinical Oncology Technology Assessment Working Group, recommended that tamoxifen should at least be considered to reduce the risk of breast cancer in women with a defined 5-year projected risk of 1.66 or greater. However, this group of studies had considerable methodologic differences, and further studies are needed to better define the role of chemoprevention in high-risk women. Furthermore, the NSABP study was not designed to show a difference in death rate from breast cancer as a primary endpoint.

Two selective estrogen-receptor modulators (SERMs), tamoxifen and raloxifene, were compared in the NSABP STAR trial and showed similar outcomes regarding invasive but not in situ disease.[121] The International Breast Cancer Intervention Study (IBIS-II) is randomizing high-risk postmenopausal women to receive the aromatase inhibitor anastrozole or placebo. It is not known whether SERMs

reduce the incidence of breast cancer by preventing the formation of cancer or by a treatment effect on small, clinically occult cancers. The use of these agents outside of a clinical trial requires an in-depth assessment of the risks and benefits of using the specific drug in an individual patient.

Prophylactic Mastectomy or Oophorectomy

Prophylactic mastectomy and oophorectomy are controversial preventive approaches to breast cancer. In recent years, considerable new data have been obtained on the use of these prophylactic surgical procedures in patients with hereditary breast or ovarian cancer syndrome. Current data show that prophylactic mastectomy is effective in preventing breast cancer in patients with either a strong family history of breast and/or ovarian cancer[122] or a genetic predisposition to breast cancer.[123] Additional data show that prophylactic contralateral mastectomy can reduce the risk of breast cancer in patients with a previous diagnosis of unilateral disease.[124] A high prevalence of premalignant lesions is seen in prophylactically removed breasts from women who are at hereditary risk for breast cancer.[125]

The total and incremental life expectancy with prophylactic mastectomy is difficult to demonstrate. Statistical analysis has shown that depending on the assumed penetrance of the BRCA mutation, compared with surveillance alone, 30-year-old patients with early-stage breast cancer who have BRCA mutations may gain 2.9 to 5.3 years from prophylactic bilateral mastectomy and 0.6 to 2.1 years from prophylactic contralateral mastectomy.[126] Still controversial is the gain in quality of life in these high-risk women who chose to have prophylactic mastectomy.[127]

Oophorectomy was first performed as a therapeutic procedure for advanced breast cancer over 110 years ago and as hormonal adjuvant treatment of primary breast cancer over 50 years ago. Uncertainty remains about the appropriate use of oophorectomy in adjuvant treatment, so it is not surprising that preventive oophorectomy in high-risk women remains controversial. Again, the identification of women with BRCA1 or BRCA2 mutations has provided an opportunity to study this prophylactic procedure. Initial results show that bilateral prophylactic oophorectomy reduces the risk of breast cancer and epithelial ovarian cancer in this population.[128]

DETECTION OF BREAST CANCER

Despite a lifetime probability currently estimated as 1 in 8 (in women who live to be 110 years of age) for breast cancer, only 30% of all women have one or more identifiable risk factors. Although these risk factors affect the parameters for breast cancer screening, current screening and education programs must include all women. The goal of breast cancer screening is early detection that will lead to a reduction in mortality. For breast cancer, the ideal screening program is sensitive enough to detect occult cancer with a minimum of false-positive findings. In addition, a screening program for breast cancer should be safe, relatively easy to provide to the public, acceptable to both patients and physicians, and cost-effective. A lower stage at diagnosis is associated with improved 5-year survival (Tables 95-2 and 95-3).[6]

During the last 40 years, an intense effort has been mounted to evaluate the efficacy of mammography, clinical breast examination, and patient self-examination as tools for breast cancer screening. These efforts have included a number of case-control and cohort clinical trials as well as eight major randomized, prospectively controlled studies. More than 650,000 women have participated in the randomized trials alone.[129]

Film screen mammography was the "gold standard" for many years. However, a randomized comparison with the new generation of digital mammography images concluded that both provide an equivalent level of detection overall, although digital images were superior in pre- and perimenopausal women with dense breasts and women under the age of 50.[130] Digital imaging offers a lower average dose of radiation, improvement in storage and retrieval, and easier access to images and computer-assisted diagnosis, which must be weighed against the higher cost of digital imaging equipment.

Computer-aided diagnosis enables a digital reading of the mammogram to identify areas that meet a computer pattern of discrimination. Newer applications "learn" from the radiologist's over-read of their identification points and are being evaluated.[131,132] The goal for optimizing breast cancer screening must be a higher rate of false-positive findings so that the risk of false-negative findings may be virtually eliminated. In breast cancer screening, the discovery of smaller tumors has the added benefit of increasing the number of patients who can be treated by breast-conserving approaches. Although mammography is the best screening tool, it detects only 85% to 90% of biopsy-proven cancers. Mammography is not a substitute for tissue sampling and histologic evaluation of any palpable abnormality, nor is it a substitute for careful physical examination. Other imaging tools are also under evaluation for early detection of breast cancers in young women with dense breasts. These are discussed in the following section.

Screening

The efficacy of screening for occult cancer depends heavily on the following factors: (1) tumor growth rate; (2) the sensitivity of the test related to tumor volume; and (3) the interval between screens. Growth rates of breast cancer vary, and some younger women have more rapidly growing tumors. In determining the efficacy of screening, four biases must be considered: lead-time bias, length bias, selection bias, and overdiagnosis bias. Lead-time bias is the interval that the diagnosis has been advanced by screening. Length bias concerns the timing of detection. When screening is infrequent, fast-growing tumors are not detected as early in their natural history as more slowly growing tumors. Thus, the outcome of cancers detected by screening is better than that for interval cancers. Selection bias is an obvious factor. For example, women who participate in breast cancer screening may have been shown to be more health conscious; they also are more likely to obtain Pap smears, use seat belts, and not smoke.[133] Thus it is likely that their outcomes would be better, even in the absence of screening. Overdiagnosis has always been a concern in screening for cancer. Detection of breast lesions of questionable malignancy affects mortality data, because these lesions would not be diagnosed without screening. It is not known how many of these very early in situ cancers would progress to become invasive malignancies.

These biases complicate the design and evaluation of screening trials. In evaluating the results of screening trials, several points must be remembered. First, the survival and case fatality rates of patients with breast cancer are not adequate endpoints for determining results. Second, the closest endpoint for studying the mortality rate in a population is an observed reduction in the incidence of advanced disease. Finally, if screening detected an excessive number of cancers that were not destined to be lethal, then the death rate among the screened women would not be altered and no benefit would be observed.

Before 1977, no formal guidelines existed for screening women for occult breast cancer. The publication of the Health Insurance Plan (HIP) of Greater New York Screening Project, conducted in the 1960s, led the NCI and the American Cancer Society to support a nationwide breast cancer screening project to evaluate further the efficacy of screening by mammography and physical examination. The Breast Cancer Detection Demonstration Project (BCDDP) took place in 29 centers, and 280,222 women were screened over a period of 5 years.[134]

Although the study is well documented, it is important to review the design and findings of the HIP landmark clinical trial. The HIP study invited women 40 to 69 years of age who were enrolled in the

Table 95-2 Cancer of the Female Breast: Number of Cases and 5-Year Relative Survival Rates (%) by Age (20+) and American Joint Committee on Cancer Stage

	AJCC Stage											
	Total		I		II		III		IV		Unknown	
Histology*	**Cases**	**5-Year RSR (%)**	**Cases**	**5-Year RSR (%)**	**Cases**	**5-Year RSR (%)**	**Cases**	**5-Year RSR (%)**	**Cases**	**5-Year RSR (%)**	**Cases**	**5-Year RSR (%)**
Total	257,730	87.1	108,346	100.0	91,989	86.2	16,928	57.2	11,222	19.9	29,245	83.4
Adeno, NOS	5,559	62.2	1,137	99.0	1,341	81.4	453	49.4	1,460	15.3	1,168	64.9
Tubular adeno	3,771	100.0	2,939	100.0	286	95.8	13	†	8	†	525	99.7
Infilltrating ductal	183,122	87.5	79,900	100.0	68,437	85.1	10,597	57.5	6,493	20.3	17,695	83.6
Scirrhous adeno	456	81.7	172	94.3	188	83.9	16	†	30	13.5	50	71.7
Mucinous adeno	6,476	98.3	3,643	100.0	1,665	94.8	176	75.0	120	33.8	872	95.7
Comedo	5,020	89.9	2,218	99.3	1,653	82.7	223	51.3	82	19.4	844	96.0
Lobular	20,140	91.6	7,640	100.0	7,594	93.0	1,600	72.6	921	30.5	2,385	87.9
Infilltrating duct and lobular	16,060	92.9	6,801	100.0	6,564	91.4	1,013	69.8	375	29.0	1,307	89.5
Inflammatory carcinoma	2,668	34.1	<5	†	25	49.5	2,003	40.9	570	11.2	67	21.6
Paget	1,937	82.6	498	95.8	524	77.7	193	46.3	66	14.3	656	93.0
Papillary adeno	1,646	94.5	741	100.0	463	92.3	67	85.7	43	34.2	332	92.6
Adenoid cystic/cribriform	712	100.0	409	100.0	177	95.3	14	†	6	†	106	96.3
Other adeno	4,261	89.1	1,494	98.7	2,077	88.8	208	57.7	96	21.2	386	84.6
Medullary	3,122	89.5	1,037	98.2	1,703	88.8	131	63.2	33	29.6	218	75.1
Other non-adeno	5,785	64.8	699	99.2	945	80.1	348	42.4	952	13.8	2,841	70.1

Adeno, adenocarcinoma; AJCC, American Joint Committee on Cancer; NOS, not otherwise specified; RSR, relative survival rate.
*Excludes 45, 033 stage 0 cases.
†Statistics not displayed due to fewer than 25 cases.
From http://www.seer.cancer.gov/publications/survival/surv_breast.pdf, p 104.

Table 95-3 Cancer of the Female Breast: Number of Cases and 5-year Relative Survival Rates (%) by Tumor Size and Regional Lymph Nodes Involved, Ages 20+

	Nodes Involved									
	Total		0 Nodes		1–3 Nodes		4+ Nodes		Unknown Number	
Tumor Size (mm)	Cases	5-Year RSR (%)	Cases	5-Year RSR (%)	Cases	5-Year RSR (%)	Cases	5-Year RSR (%)	Cases	5-Year RSR (%)
Total	302,763	89.3	148,192	98.8	43,418	86.8	26,923	65.5	84,230	81.2
1–4	21,530	100.0	9,721	100.0	563	89.9	197	76.6	11,049	100.0
5–9	37,075	100.0	23,816	100.0	2,261	98.1	541	81.1	10,457	100.0
10–19	93,875	97.2	58,654	100.0	14,035	94.5	4,475	80.1	16,711	91.8
20–29	54,610	88.0	27,139	95.4	12,194	87.9	6,440	72.7	8,837	75.7
30–39	23,880	78.1	9,497	91.0	5,704	79.0	4,412	63.8	4,267	61.3
40–49	11,786	72.1	3,866	88.2	2,692	76.0	2,753	60.2	2,475	54.2
50–99	17,015	63.2	4,120	88.8	3,135	72.5	5,054	52.7	4,706	45.7
100+	2,580	46.8	382	83.0	290	59.6	670	46.6	1,238	32.6
Diffuse	3,734	35.1	218	84.0	350	51.1	907	39.6	2,259	27.0
Unknown*	36,678	84.9	10,779	100.0	2,194	81.8	1,474	63.1	22,231	78.4

RSR, relative survival rate.
*Unknown size category includes Paget disease of the nipple with no demonstrable tumor.
From http://www.seer.cancer.gov/publications/survival/surv_breast.pdf], p 109.

HIP of Greater New York to be screened for breast cancer. The HIP project was the first randomized controlled trial and included annual clinical examinations and mammography for 4 years. Using pairwise allocation, 62,000 women were randomized to the study group or the control group. Of the total population, 45% were 40 to 49 years of age at study entry. Of the 31,000 women in the study group, 65% attended one or more screening sessions. Because it was not possible to identify within the control group women who would decline screening, the outcome of the control group was evaluated in relation to the total study group.

A surprising aspect of the initial evaluation of the results was the striking difference in the effectiveness of screening at different ages. At 5 years, the HIP study found a 50% decrease in mortality rate in women older than 50 years of age, but only a 5% decrease in mortality rate in women younger than 50 years of age. However, after further follow-up, this difference in effectiveness began to change. With follow-up, the mortality rate in women younger than 50 years of age showed a 23.5% decrease, and it became statistically significant at year 18 of follow-up. In women older than 50 years of age, the reduction in mortality became evident at approximately the fourth year of follow-up. Significantly, a reduction in mortality rate in younger women took longer than a decade to manifest. Women who refused screening or who had interval cancers had no reduction in mortality rate.

For the first time, the results of the HIP study provided strong evidence that early detection of breast cancer increased the duration of survival. Since the HIP trial was published, seven additional randomized trials of mammography and two of breast self-examination have been reported. The results of these trials have been included in a meta-analysis commissioned by the The United States Preventive Service Task Force (USPSTF)[129] (Table 95-4). Between the ages of 39 and 74 years, the summary relative risk for death from breast cancer was 0.84% for the use of screening mammography. Much like the findings of some of the individual studies included in this analysis, greater reduction in risk was seen in women over the age of 50 years. The summary relative risk for women 40 to 49 years old was 0.85, compared to 0.78 for those 50 years of age and older. Of interest, this same meta-analysis noted "direct evidence of effectiveness among older women, limited to two trials that included women over 65 years of age."

The controversy about the efficacy of screening for women 40 to 49 years of age is ongoing because breast cancer is less frequent in this age group, and there is a greater likelihood that mammographic abnormalities will prove benign on biopsy. To further address this controversy, the Cancer Screening Evaluation Unit in Sutton, in the United Kingdom, conducted a trial called Age, directed at women ages 39 to 41, comparing annual screening mammogram with routine medical care. In selecting this age group, the trial targeted women who would still be younger than 50 years through 10 years of follow-up screening. This trial did demonstrate "a reduction in breast cancer mortality in the intervention group, in relative and absolute terms, which did not reach statistical significance.[135] Table 95-5 lists the screening guidelines for mammography for the American College of Radiology (ACR), the National Comprehensive Cancer Network (NCCN), and the NCI.

Patient Compliance

Over the last decade, aggressive public education programs conducted by the American Cancer Society, the NCI, and public interest groups have led to a dramatic increase in mammographic screening in the United States. A particular concern was its marked underuse by minority women, although the use of mammography has increased dramatically and the racial gap has virtually disappeared. A recent study concluded that ethnicity was "not associated with seeking and obtaining a screening mammogram, once socioeconomic factors are considered."[133] Interventions associated with an increased use of screening included providing women with information, especially if by a health care provider urging compliance, and vouchers for free mammography. Media intervention has little effect on compliance and limited long-range benefit, but educational interventions targeting primary care physicians should become a priority.

Sensitivity of Mammography

Mammography is more effective in detecting occult malignancy as patients begin to age and breast tissue is replaced with fat. Breast

Table 95-4 Results of Randomized, Controlled Trials of Mammography among Women 39 to 74 Years of Age

Study	Age (yr)	Median Follow-up (yr)	Breast Cancer Deaths/ Total Women		Breast Cancer Death Rate per 1000 Women		Relative Risk for Death from Breast Cancer (95% CI)	Absolute Risk Reduction per 1000 Women	No. Needed to Invite to Screening*
			Screened Group	Control Group	Screened Group	Control Group			
			n/n						
Mammography alone									
Stockholm[†]	40–64	13.8	82/39 139	50/20 978	2.10	2.38	0.91 (0.65–1.27)	0.288	3468
Gothenburg[†]	39–59	12.8	62/20 724	113/29 200	2.99	3.87	0.76 (0.56–1.04)	0.878	1139
Malmö[†]	45–70	17.1	161/21 088	198/21 195	7.63	9.35	0.82 (0.67–1.00)	1.712	584
Swedish Two-County Trial[‡]	40–74	17	319/77 080	333/55 985	4.14	5.95	0.68 (0.59–0.80)	1.809	553
Mammography plus CBE									
CNBSS-1[§]	40–49	13	105/25 214	108/25 216	4.16	4.28	0.97 (0.74–1.27)	0.12	—
CNBSS-2[¶]	50–59	13	107/19 711	105/19 694	5.43	5.33	1.02 (0.78–1.33)	–0.097	—
HIP[‖]	40–64	16	232/30 239	281/30 256	5.46	6.89	0.79	1.438	883
Edinburgh[#]	45–64	13	156/22 926	167/21 342	6.80	7.82	0.79 (0.60–1.02)	1.020	980

CBE, clinical breast examination; CNBSS, Canadian National Breast Screening Study; HIP, Health Insurance Plan of Greater New York.

*Number needed to invite to screening to prevent one death from breast cancer 13–20 years after randomization.

[†]Nyström L, Andersson I, Bjurstam N, et al: Long-term effects of mammography screening: updated overview of the Swedish randomized trials. Lancet 2002;359:909–919.

[‡]Tabár L, Vitak B, Chen HIH, et al: The Swedish Two-Country Trial twenty years later. Updated mortality results and new insights from long-term follow-up. Radiol Clin North Am 2000;38:625–651.

[§]Miller AB, To T, Baines CJ, Wall C: The Canadian National Breast Cancer Screening Study-1: breast cancer mortality after 11 to 16 years of follow-up. A randomized screening trial of mammography in women age 40 to 49 years. Ann Intern Med 2002;137: 305–312.

[¶]Miller AB, To T, Baines CJ, Wall C: Canadian National Breast Screening Study-2: 13-year results of a randomized trial in women aged 50–59 years. J Natl Cancer Inst 2000;92:1490–1499.

[‖]Shapiro S, Venet W, Strax P, Venet L: Current results of the breast cancer screening randomized trial: the health insurance plan (HIP) of greater New York study. In Day NE, Miller AB (ed): Screening for Breast Cancer. Toronto, Hans Huber, 1988; pp 3–15.

[#]Alexander FE, Anderson TJ, Brown HK, et al: 14 years of follow-up from the Edinburgh randomized trial of breast-cancer screening. Lancet 1999;353:1903–1908.

Data from Humphrey LL, Helfand M, Chan BK, et al: Breast cancer screening: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2002; 137:347–360.

Table 95-5 National Organizations' Screening Guidelines for Mammography

ACS

For women for normal risk, yearly mammograms are recommended starting at age 40. CBE suggested about every three years for women in the (?) 30's and every year for women age 40 and above. BSE is suggested for women starting in their 20s.

NCCN

Women at normal risk are recommended to have CBE every 1–3 years; periodic SBE is encouraged. Beginning at age 40, annual CBE and mammograms are recommended, and periodic SBE is encouraged.

NCI

Women who are age 40 and above should be screened with mammograms every 1–2 years.

ACS, American Cancer Society; BSE, breast self-examination; CBE, clinical breast examination; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute; SBE, self breast examination.

density most directly affects the risk of false-negative and false-positive interpretations; it is affected by several factors. Age is the most significant factor, because premenopausal women are more likely to have breasts that are more glandular and thus more dense. Mammographic sensitivity may be increased by scheduling evaluation during the first 2 weeks of the menstrual cycle, corresponding with the follicular phase. HRT in postmenopausal women may increase breast density.

The sensitivity, or accuracy, of mammography also is affected by the experience of the radiologist. Features with the highest positive predictive value for carcinoma were spiculated margins, irregular shape, linear calcification, and segmented or linear calcification distribution. In general, the positive predictive value of a Breast Imaging Reporting and Data System (BI-RADS) category 5 lesion is over 80%, while that of a category 4 lesion aproaches 30% to 40%. The last decade has seen the development of full-field digital mammography. A recent multicentric trial comparing conventional to digital mammography showed an improvement over conventional film mammography in the detection of breast cancer in young, premenopausal, and perimenopausal women, and in women who have dense breasts. However, there was no significant difference in diagnostic accuracy between digital and film mammography in the population as a whole or in the other predefined subgroups.[130]

Other Methods of Screening

To overcome some of the variables that affect the predictive value of mammography, a number of new technologies are being explored. Emerging techniques for breast screening, such as MRI, scintimammography, and ultrasound are under study in selected women who present difficulties in screening with mammography. Data increasingly suggest that women with very dense breasts and those with BRCA1 and BRCA2 mutations are more likely to have clinically occult carcinomas detected by other screening than by mammograms.[136] Women who meet the criteria for hereditary breast cancer, as defined by a careful, three-generation family history, should be considered for additional screening as well. Options include the following: (1) initiation of screening 10 years before the onset of a first-degree relative's breast cancer, or at 30 years of age; (2) the addition of MRI screening; (3) shorter screening intervals (e.g., every 6 months); and (4) the addition of ultrasound screening. A woman with BRCA1 or BRCA2 mutations may have a risk as high as 20% with certain mutations by 40 years of age, and MRI appears to be the most sensitive technique for screening these very young women.[137,138] The role of clinical examination and breast self-examination in high-risk women seems particularly limited.[116,139] Shorter screening intervals have been based on modeling data, and no prospective data have validated this recommendation. Although MRI shows improved sensitivity, it has lower specificity than mammography and may lead to additional fine-needle aspiration (FNA) or core biopsy in these young women at high risk.

Ductal lavage is promoted as a screening technique in asymptomatic women who are considered at increased risk. The goal of this technique was to stratify women at increased risk in terms of intervention (e.g., tamoxifen). Although numerous research studies are underway, no data recommend the use of ductal lavage, alone or in combination with other screening techniques, and the technique remains investigational. The sensitivity of ductal lavage to detect breast cancer in women with a known diagnosis treated with mastectomy has been shown to be low,[140] although molecular techniques may improve its yield.[141] The role of FDG-PET scanning for screening of the breast and axilla is limited.[142]

Screening in the Elderly Patient

The life expectancy for women (all races) in the United States increased from 77.4 years in 1980 to 80.4 years in 2002 (see http://www.cdc.gov/nchs/fastats/lifexpec.htm). Biologic parameters suggest a higher prevalence of higher-risk tumors in younger women, with lower-risk tumors (better differentiated and hormone receptor-rich) occurring in older women. Tabar and colleagues[143] showed that for a given tumor size, the likelihood of nodal involvement is lower in older women than in younger women, and these data in aggregate have led some to suggest that it may be appropriate to increase the screening interval to 2 years in older women. However, there are insufficient data to suggest an age when routine screening can be abandoned. At 75 years of age, the average additional life expectancy for a white or a black woman in the United States is 12 years or more. Even so, fewer elderly women are being screened annually, even those with a history of breast cancer. While the benefits from screening appear to be seen in all age groups, and even in patients with comorbid disease, the magnitude of the benefit appears to diminish with age and with the severity of comorbid illnesses. In fact, data from the U.S. National Health Interview Survey show an overall drop in the overall rate of mammography screening, from 70% in 2000 to 66% in 2005.[144]

MAMMOGRAPHIC ABNORMALITIES

The value of mammography relies heavily on the technical expertise available in obtaining the study as well as on the experience of the radiologist interpreting the study. Vigorous compression is essential to even out the breast tissue over the film to provide more uniform exposure. Compression decreases the possibility that glandular areas will obscure masses or calcification. It also avoids motion, which causes loss of fine resolution. Additional views may be required to image all of the breast tissue, especially tissue adjacent to the chest wall. Magnification films are valuable for evaluating areas of architectural distortion and fine calcification. Evidence supports the importance of significant experience in administering mammograms (radiographs) and interpreting the results. Distinct advantages for the patient occur when mammography is provided by a dedicated mammography unit with a full-time technical team and an experienced radiologist. When more than one radiologist specializing in breast radiology reviews films, the accuracy of interpretation is further increased, and evidence also suggests that that having mammography technologists review screening mammograms in addition to radiologist review may increase the rate of breast cancer detection.[145]

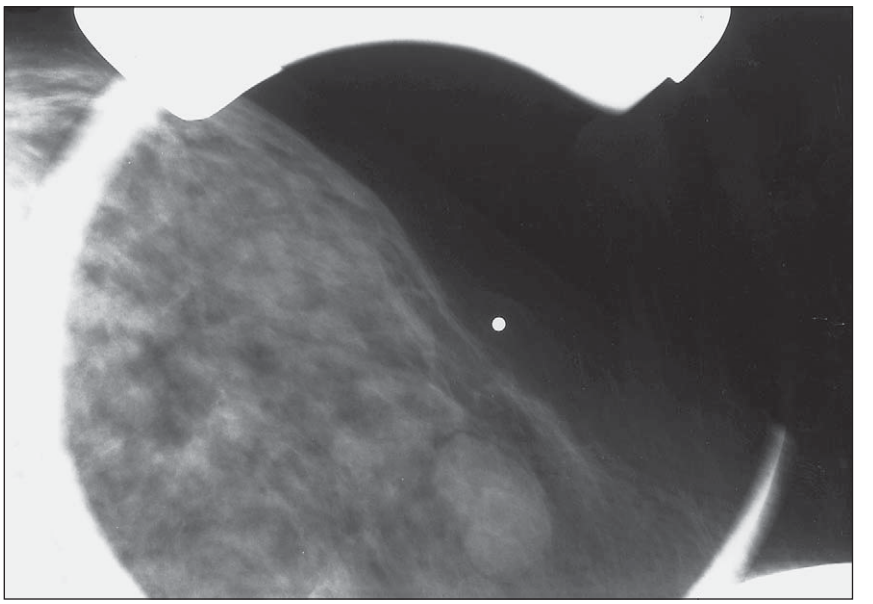


Figure 95-5 • Magnified view showing that a palpable lump is uniform in density, lacks microcalcifications, and has sharp, clear borders. Biopsy established the lump to be fibroadenoma.

Masses

Benign masses typically are well defined, with sharp margins, and have little effect on the surrounding breast architecture. Fibroadenomas, papillomas, intramammary lymph nodes, and cysts are the most common causes of benign mammographic density (Fig. 95-5). Malignant breast densities classically have irregular borders that blend into the surrounding tissue and often appear to infiltrate the breast background tissue with a stellate appearance. Usually, there is some distortion of adjacent breast stroma. The mammographic abnormality that has the highest rate of malignancy is a mass density with associated calcification (Figs. 95-6 through 96-8). Examples of questions that should be asked include the following:

- Is this really a mass? (it must be identified in more than one view, and special views may be required)
- Where is it located?
- Are there associated calcifications?
- Is the mass solid or cystic? (this usually requires ultrasonography)
- Is the mass new?

Calcifications

Malignant calcifications typically are linear, or small (<1 mm) in diameter, nonuniform in size, and clustered. Between 20% and 25% of clustered microcalcifications are positive for cancer on biopsy. Benign calcifications usually are larger and coarser, and are often round, with smooth margins. Table 95-6 lists various types and distributions of calcifications. Benign causes of microcalcification include involuting fibroadenoma, arteriosclerosis, sclerosing adenosis, fat necrosis, and previous mastitis with ductal calcium deposits.

Ultrasonography

Ultrasound is of greatest use when the mammographic findings are equivocal and when examination shows multiple areas of abnormal-

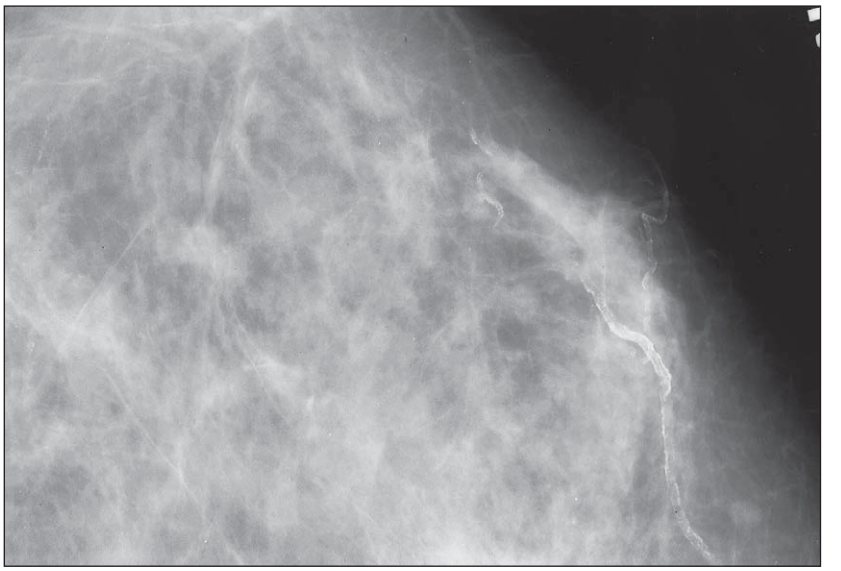


Figure 95-6 • Mammogram showing arterial calcifications in an otherwise normal examination.

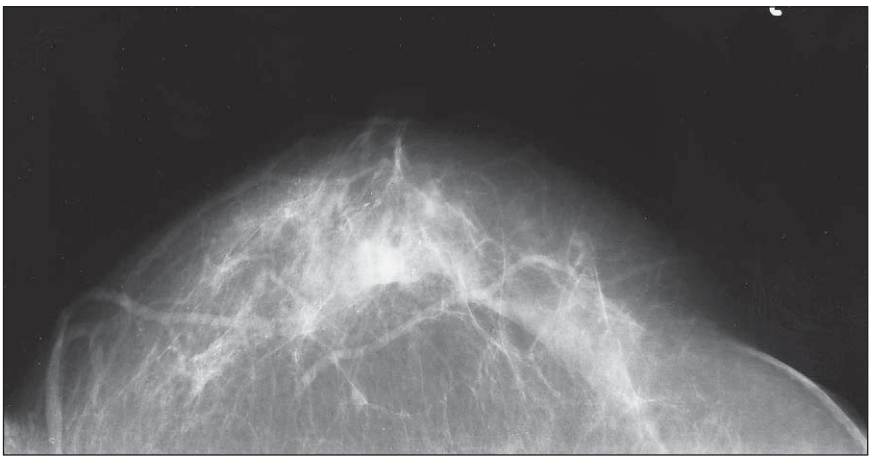


Figure 95-7 • Pleomorphic calcifications in an area of extensive ductal carcinoma in situ.

ity (Fig. 95-9). Ultrasonography is very accurate (>95%) in diagnosing breast cysts. Cysts have well-demarcated, smooth margins and an echo-free center (Fig. 95-10) and usually are rounded and thin-walled and produce distal shadowing. Clear cysts require no further evaluation. Complex cysts that contain evidence of tissue or debris may be aspirated to clarify whether they are simply cysts or represent cystic degeneration of a tumor.

Ultrasonic image texture analysis is an effective way to distinguish benign from malignant breast lesions. This technique is a simple way to reduce the number of biopsies performed on benign lesions without missing additional cancers. Doppler flow analysis may provide additional information about solid lesions. Malignant tumors show increased blood flow compared with benign tumors, resulting in a characteristic blood flow signal.

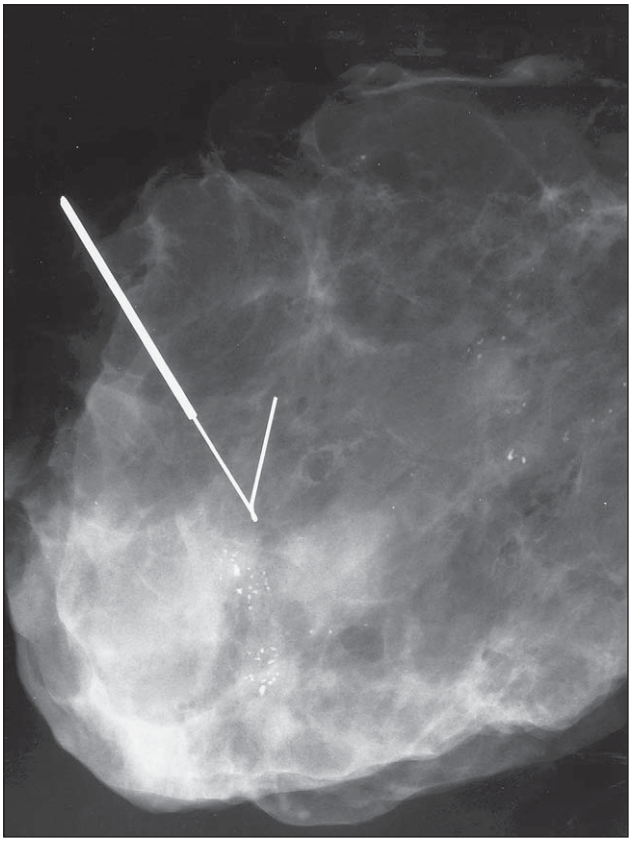


Figure 95-8 • Specimen radiograph confirming removal of the clustered microcalcifications. Histopathologic examination showed ductal carcinoma in situ.

APPROACH TO THE PATIENT

Management of the Palpable Mass

Finding a breast mass by accident or regular self-examination is not uncommon. One study found that 57% of all women presenting to an urban breast clinic in the year 1999 complained of a mass.[146] The determination of whether a palpable abnormality is malignant can be difficult, especially in premenopausal women. In general, if a palpable mass is determined to be solid, histologic diagnosis is required. An area of abnormal thickening in the breast that is not dominant and discrete (asymmetrical thickening compared with the same area in the opposite breast) usually suggests a benign change. Such areas of thickening may be safely observed for one or two menstrual cycles.

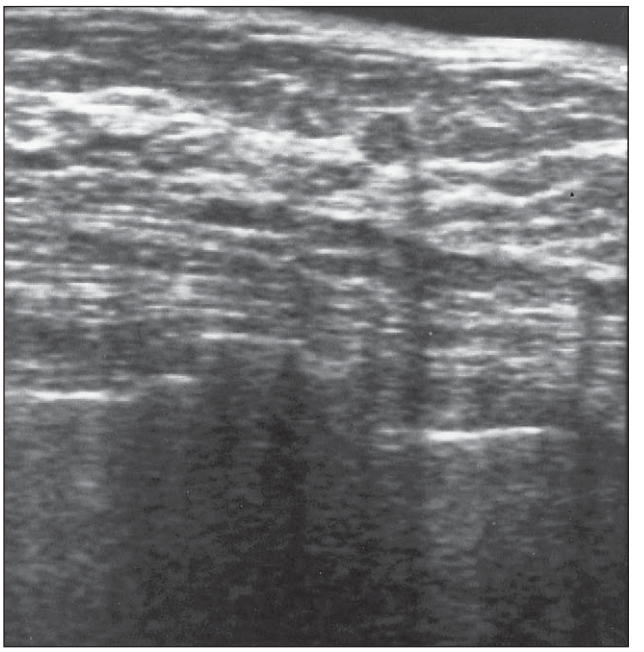


Figure 95-9 • Ultrasonography confirms the presence of a solid mass.

Table 95-6 Types and Distributions of Calcifications

Type of Calcification	Description
TYPICAL BENIGN	
Skin (dermal)	Typical lucent-centered deposits that are pathognomonic. Atypical forms may be confirmed by tangential views to be in the skin.
Vascular	Paralled track or linear tubular calcifications that are clearly associated with blood vessels.
Coarse or popcorn-like	The classic calcifications produced by an involuting fibroadenoma
Large rod-like	Benign calcifications forming continuous rods that occasionally may be branching. They usually are >1 mm in diameter, and may have lucent centers, if calcium surrounds rather than fills an ectatic duct. These are the kinds of calcifications found in secretory disease, "plasma cell mastitis," and duct ectasia.
Round	When multiple, they may vary in size. They usually are considered benign, and when small (<1 mm), they often are formed in the acini of lobules. When <0.5 mm, the term "punctate" can be used.
Lucent-centered	Benign calcifications ranging from <1 mm to ≥1 cm. These deposits have a smooth surface, are round or oval, and have a lucent center. The "wall" that is created is thicker than the "rim" or "eggshell" type of calcifications. Included are areas of fat necrosis, calcified debris in ducts, and occasional fibroadenomas.
Eggshell or rim	Very thin, benign calcifications that appear as calcium deposited on the surface of a sphere. These deposits usually are <1 mm thick when viewed on edge. Although fat necrosis can produce these thin deposits, calcifications in the walls of cysts are the most common "rim" calcifications.
Milk of calcium	Consistent with sedimented calcifications in cysts. On the craniocaudal image, they often are less evident and appear as fuzzy, round, amorphous deposits; on the 90-degree lateral view, they are sharply defined, similunar, crescent-shaped, curvilinear, or linear, defining the dependent portions of cysts.
Suture	Calcium deposited on suture material. They are relatively common in the postirradiated breast. They typically are linear or tubular in appearance, and knots often are visible.
Dystrophic	Calcifications that usually form in the irradiated breast or in the breast after trauma. Although irregular in shape, they usually are >0.5 mm in size. They often have lucent centers.
Punctate	Round or oval, >0.5 mm, with well-defined margins.
INTERMEDIATE CONCERN	
Amophous or indistinct	Often round or flake-shaped calcifications that are so small or hazy that a more specific morphologic classification cannot be determined
HIGHER PROBABILITY OF MALIGNANCY	
Pleomorphic or heterogeneous (granular)	Usually more conspicuous than the amorphic forms. They are neither typically benign nor typically malignant irregular calcifications. They vary in size and shape and are usually <0.5 mm in diameter.
Fine linear, or fine linear branching (casting)	Thin, irregular calcifications that appear linear, but are discontinuous and <0.5 mm wide. Their appearance suggests filling of the lumen of a duct involved irregularly by breast cancer.
DISTRIBUTION MODIFIERS	Used as modifiers of the basic morphologic description. These terms describe the arrangement of the calcification. Multiple similar groups may be indicated when there is more than one group of calcifications that are similar in morphology and distribution.
Grouped or clustered	Although historically the term "clustered" has connoted suspicion, the term is now used as a neutral distribution modifier and may reflect benign or malignant processes. It is used when multiple calcifications occupy a small volume (<2 mL) of tissue.
Linear	Calcifications are arrayed in a line that may have branch points.
Segmental	Worrisome in that their distribution suggests deposits in a duct and its branches, raising the possibility of multifocal breast cancer in a lobe or segment of the breast. Although benign causes of segmental calcifications exist (e.g., secretory disease), this distribution is of greater concern when the morphology of the calcifications is not specifically benign.
Regional	Calcifications scattered in a large volume of breast tissue and not necessarily conforming to a duct distribution. They are likely benign, but are not everywhere in the breast, and do not fit the other, more suspicious categories.
Diffuse/scattered	Calcifications that are distributed randomly throughout the breast.

Adapted from Breast Imaging Reporting and Data System: American College of Radiology, 1998, p 27.

Patients with a palpable mass or a new breast symptom should have mammography and often an ultrasound as well (Fig. 95-11). The goals of diagnostic mammography for patients with breast symptoms or positive findings on examination are different from the goals of screening. For the patient with a breast lump, the goals are to characterize the area of palpable abnormality, to evaluate the remaining breast for signs of additional occult lesions, and to evaluate the contralateral breast.

Whether a mammogram is obtained in women younger than 35 years of age depends on the character of the palpable abnormality (e.g., the level of concern about potential malignancy on examination). Ultrasonography is simple to perform and may distinguish a

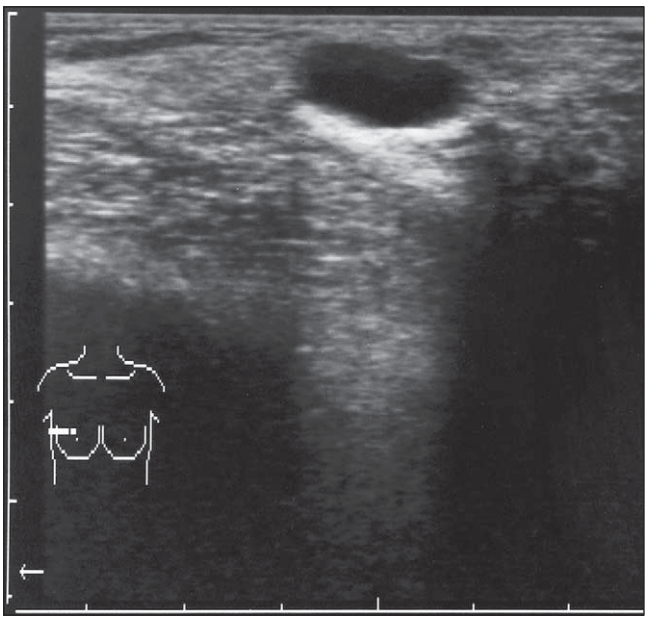


Figure 95-10 • Ultrasonography of the breast showing the palpable lump to be cystic. Cystic lesions have a characteristic hypoechoic pattern, with prominent acoustic shadowing.

solid from a cystic mass; a cyst usually can be aspirated. Cytologic examination of aspirated fluid is not indicated, because cysts rarely are positive for carcinoma. Follow-up of these patients in 3 to 4 months usually is indicated, and most breast surgeons excise a chronically recurring cyst or a cyst with bloody fluid.

A solid mass, as confirmed by mammography, ultrasonography, or needle aspiration, requires histologic confirmation of its character. If the cytologic findings indicate cancer, then definitive therapy is planned. If they do not, then cytologic or core biopsy diagnosis must be consistent with the findings that led to the biopsy. If the lesion is highly suspicious, negative findings on FNA or core biopsy will not completely remove suspicion unless they show a histologic explanation of the findings. When cytologic findings are nondiagnostic, excision of the lesion offers both patient and surgeon peace of mind. The finding of proliferative epithelium, or atypia, affects the risk of subsequent breast cancer. Atypical hyperplasia is found in 4% to 10% of benign biopsy specimens. Associated risk relates strongly to family history. Table 95-7 shows the relative associated risks for patients with benign histologic findings.

Core biopsy has some advantages with respect to FNA in evaluating a solid breast mass. The overall predictive value of a core biopsy is higher than FNA. The tissue sampling optained with core biopsy can diagnose the invasive component of the cancer, allowing final surgery with sentinel lymph node biopsy (SLNB) or axillary dissection to be scheduled. Both false-negative and false-positive rates of FNA and core biopsy depend on the expertise of the operator and

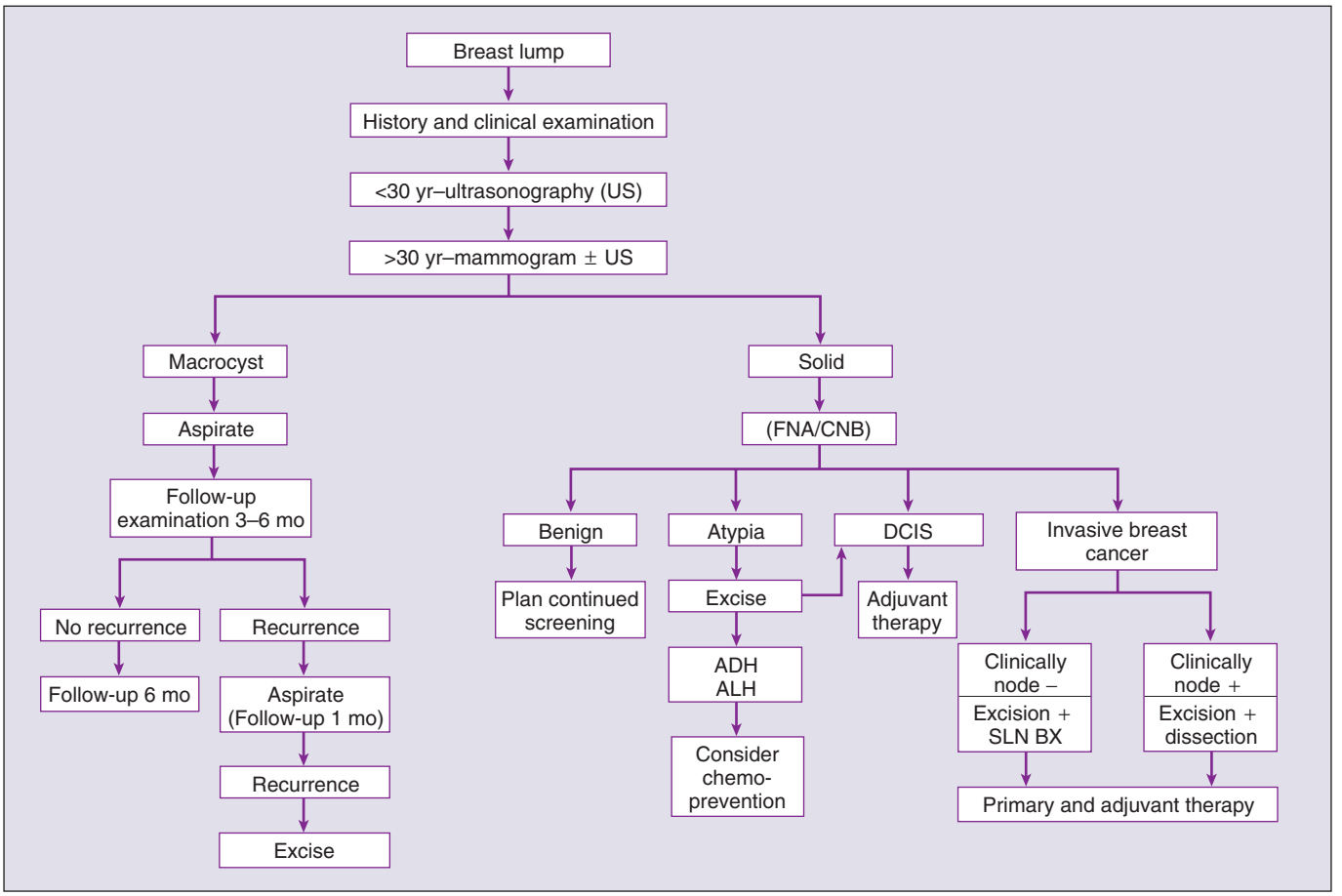


Figure 95-11 • Algorithm for breast lump management. ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; CNB, core needle biopsy; DCIS, ductal carcinoma in situ; FNA, fine needle aspiration.

Table 95-7 American Board of Pathology Histologic Classification of Benign Disease

Histopathology	Approximate Relative Risk
Nonproliferative	No added risk
Cysts	
Duct ectasia	
Calcification	
Fibroadenoma	
Milk ductal epithelial hyperplasia	
Sclerosing adenosis	No added risk
Papillomatosis	Slight added risk
Radial scars	
Complex sclerosing lesions	?
Moderate florid hyperplasia	1.5:1 to 2:1
Atypical hyperplasia (ductal and lobular)	4:1
Extensive ductal involvement of atypical hyperplasia	7:1
Lobular carcinoma in situ	10:1
Ductal carcinoma in situ	10:1

pathologist. If physical examination and mammograms both suggest a benign lesion and FNA cytology or core biopsy findings are consistent, the likelihood of a missed breast cancer is extremely low. If the findings of any of the three tests are suspicious, a more aggressive biopsy to prevent progression of breast cancer is strongly recommended.

Management of the Nonpalpable Mammogram Abnormality

The health care provider often is faced with a patient who is asymptomatic and has a normal breast examination, but has an abnormal mammogram. The mammographic criteria for biopsy are fairly well accepted and include the following:

- A localized soft tissue density that was not previously seen on mammography
- A localized soft tissue density that has changed on successive studies
- A localized soft tissue density with ill-defined borders or stellate distortion of the stroma (or both)
- A focus of suspicious microcalcification, with or without soft tissue density (see Table 95-6)

If these findings are seen on screening mammograms, diagnostic mammograms—including magnification views—are required to confirm the abnormality. Often mammographic changes are not as clear as those listed in Table 95-6. The mammography report may state "cannot exclude an early breast cancer," or "clinical correlation is recommended." In these situations, all previous mammograms must be obtained for comparison. If the mammographic abnormality is believed to warrant histologic evaluation, several options exist: needle core biopsy (NCB) under ultrasound guidance if the abnormality is easily visualized by ultrasound; NCB using a dedicated stereotactic mammography unit; and wire localization and guided excisional biopsy with specimen radiography. Clearly, the expense of tissue sampling is considerably less if stereotactic NCB is used and proves reliable. Candidates for NCB include patients with highly suspicious mammographic findings, those with multiple suspicious lesions in the same breast, and those with lesions of low suspicion.

The procedure requires the patient to lie prone and to remain immobile for 30 to 45 minutes. NCB is not suitable for lesions that are close to the skin or for patients with very small or thin breasts (compressed to < 3 cm). NCB is not optimal in the evaluation of radial scars or areas of diffuse microcalcification. Studies evaluating the efficacy of NCB indicate that a biopsy needle larger than 14 gauge is preferred, because it significantly increases the rate of concordance with surgical biopsy. Approximately half to two thirds of patients diagnosed by stereotactic cores as having DCIS ultimately may be found to have invasive cancer. Similarly, when core biopsy shows atypical ductal hyperplasia, open surgical biopsy shows DCIS in 30% to 50% of cases. Thus, excisional biopsy is indicated in the following situations: (1) for a nondiagnostic core biopsy, (2) when atypical ductal hyperplasia is found, (3) when DCIS is present, (4) when the patient has a radial scar, and (5) when calcifications cannot be sampled. All patients with benign histologic features should have a 6-month follow-up two-view mammogram, and a system should be in place to ensure compliance.

When LCIS is found in a NCB, in situ or invasive cancer can be found in about 25% of cases at surgery.[147] On biopsy, approximately two benign tumors are found for each cancer that is discovered, but some authors argue that biopsy should be performed when the chance of finding cancer reaches 10%. Driving the rate of positive biopsy findings even lower, with the goal of decreasing the incidence of interval cancers, would significantly increase the overall cost of screening. The refinement in technology for the use of NCB suggests that this may be a way to reduce cost and provide an alternative to short-interval follow-up mammography. As with wire-localized biopsy, however, careful evaluation of the criteria for the use of NCB is required. Performing NCB biopsy on all patients would clearly defeat the goal of reducing cost. It is estimated that about 10% of women who undergo screening require either diagnostic biopsy or short-interval (4- to 6-month) follow-up. False-negative rates for NCB are reported to be as low as 2%, a rate similar to that for wire-localized guided excisional biopsies. No cost savings will occur if every negative stereotactically guided NCB is followed by excisional biopsy.

The techniques used for wire-localized excisional biopsy are shown in Figures 95-12 through 95–15. Wire-localized excisional breast biopsy is highly accurate and results in good to excellent cosmetic outcome. The key to success is the accuracy of the needle or wire placement, which should go directly into the area to be removed. Other techniques of preoperative localization using radioisotopes, radioactive seeds, and cryo-assistance, have been described with possible surgical advantages in obtaining more of the lesion in the surgical specimen and higher rate of negative margins.[148] The surgical specimen is sent to the radiology department, where it is filmed and compared with the mammogram to ensure that the suspicious lesion or microcalcifications are contained within the specimen. For patients with a benign biopsy finding, repeat mammogram is obtained 4 to 6 months later to re-establish a baseline and confirm clearing of the suspicious abnormality.

Management of the Magnetic Resonance Imaging Abnormality

With the increasing use of MRI in high-risk women for breast cancer, radiologists and breast surgeons often are faced with an MRI lesion not visible with mammography and ultrasound. A focal ultrasound in an MRI suspicious lesion fails to reveal a sonographic correlate in up to 77% of cases,[149] and MRI-guided percutaneous, vacuum-assisted biopsy should be performed. MRI percutaneous biopsy is not easily available, is expensive, and requires expertise.[150] Open surgical biopsy with MRI needle localization is the other option to diagnose a suspicious MRI lesion. Because the nonmagnetic wire used for the

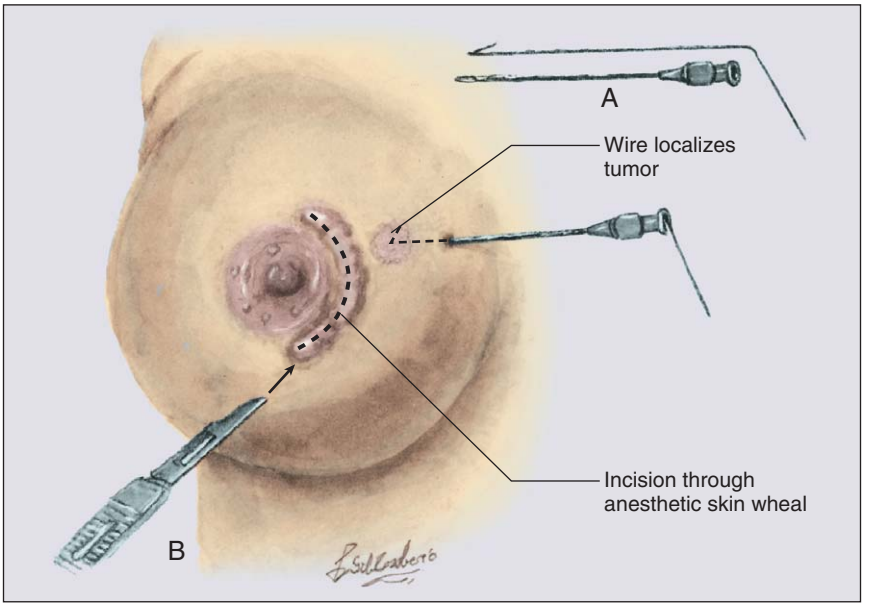


Figure 95-12 • Excision of nonpalpable mammographic abnormalities. **A,** Kopans hook wire and localizing needle. **B,** The incision is placed near or directly over the spot where the tip of the wire and the radiographic lesion are located. In this case, a circumareolar incision was ideal. The skin welt that is seen is the result of infiltration with local anesthetic (1% lidocaine with 1:200,000 epinephrine). (From Baker RR, Niederhuber J: The Operative Management of Breast Disease. Philadelphia, WB Saunders, 1994.)

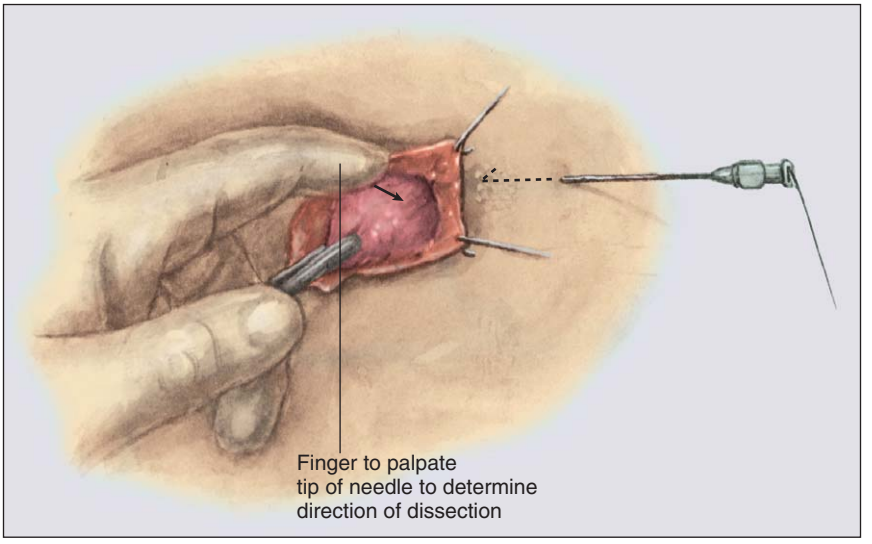


Figure 95-13 • Skin hooks are retracted as the surgeon raises a flap toward the point of entrance of the localizing needle. An Allis clamp is used to grasp the breast tissue as the area surrounding the end of the hook wire is dissected. (From Baker RR, Niederhuber J: The Operative Management of Breast Disease. Philadelphia, WB Saunders, 1994.)

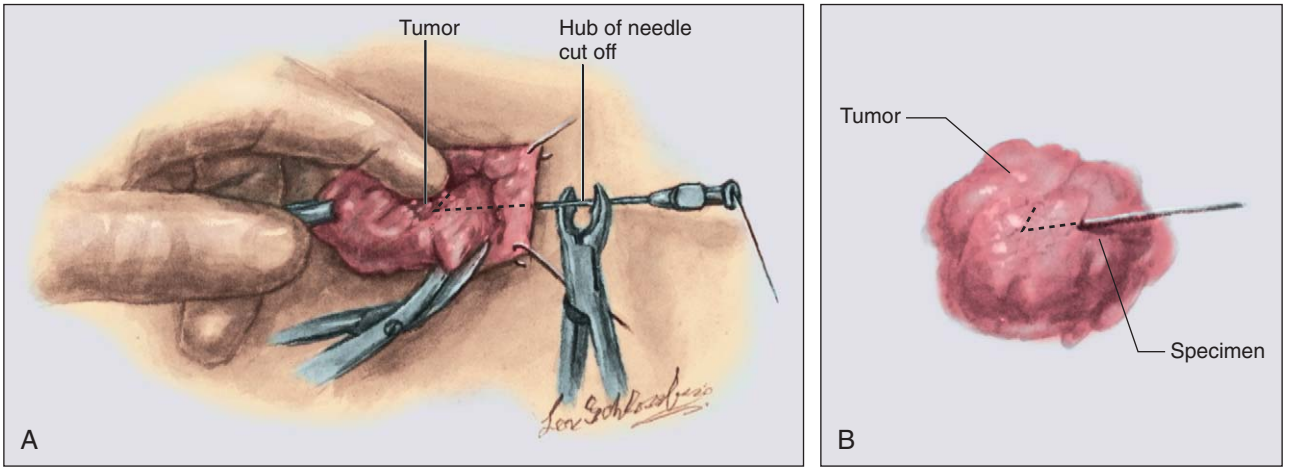


Figure 95-14 • **A,** The hub of the needle is cut off with a wire cutter, allowing the needle and wire to be passed through the skin flap. The surgeon can sharply excise the breast tissue that surrounds the tip of the hook wire, including the mammographic abnormality. **B,** After a specimen radiograph is taken to confirm the radiographic abnormality, the specimen containing the hook wire is oriented and marked for histopathologic assessment. (From Baker RR, Neiderhuber J: The Operative Management of Breast Disease. Philadelphia, WB Saunders, 1994.)

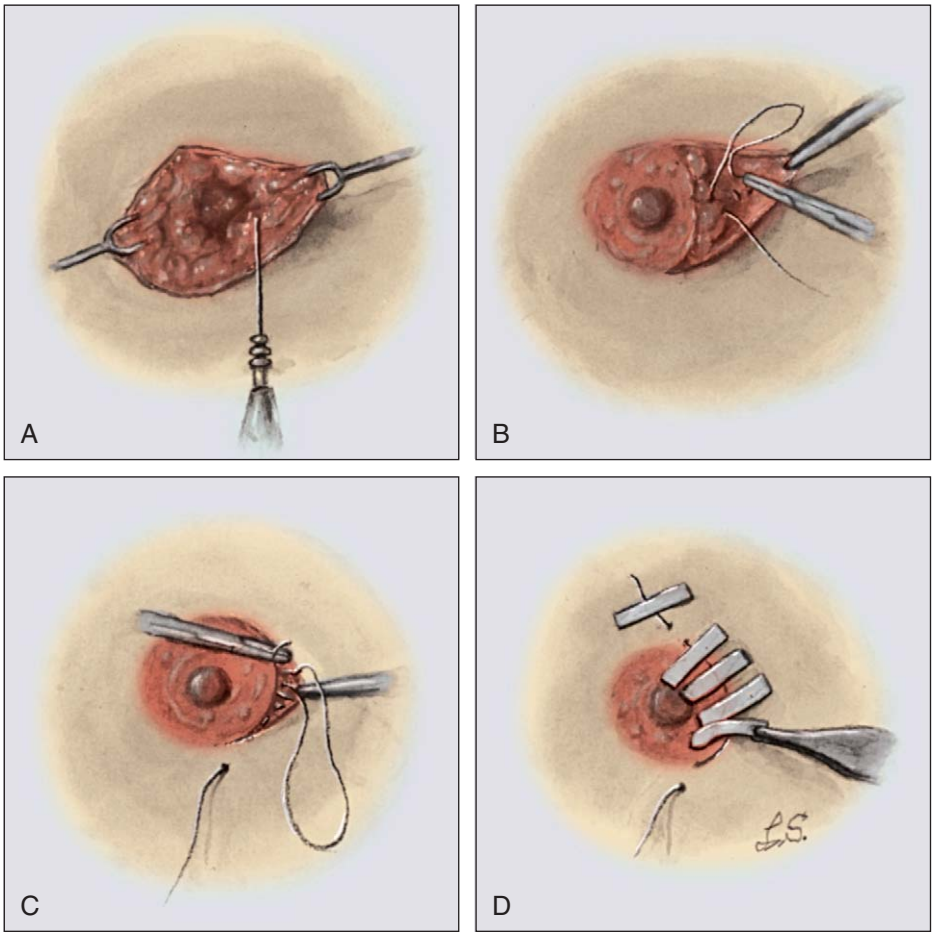


Figure 95-15 • A, After the specimen is removed, careful hemostasis is obtained with electrocautery. **B,** The deep tissues are never reapproximated, to avoid distortion of the breast and poor cosmetic result if subsequent irradiation is required. **C,** The deep dermis is closed with 3–0 absorbable sutures. The skin is closed with a subcuticular pull-out suture of 5–0 Prolene. **D,** Steristrips and dressings are applied. (From Baker RR, Neiderhuber J: The Operative Management of Breast Disease. Philadelphia, WB Saunders, 1994.)

MRI localization is thinner then the wire used for ultrasound or stereotactic localizations, possible transection of the wire during surgery may make removal of the area more challenging. Because the presence of the lesion in the specimen cannot be confirmed by x-ray, postexcisional MRI should be performed 1 month after the procedure to confirm removal of the lesion.

STAGING AND PROGNOSTIC EVALUATION

Once the pathologic diagnosis of breast cancer is established, the clinician should promptly obtain the staging information necessary to make therapeutic recommendations and decisions, which are important for medical, psychological, and economic reasons. The primary goal of staging evaluation is to assess whether the patient is has operable disease and is potentially curable by one or more therapy modalities, which most frequently include surgery plus radiation therapy (if breast conservation and if higher risk factors) plus systemic therapy (before or after surgery and according to predictive and prognostic factors).

2003 Update of the TNM Staging System

In January 2003, the American Joint Committee on Cancer released the sixth edition of the Cancer Staging Manual with a revision of the TNM staging system for breast cancer (Table 95-8).[151–153] This revision considers the increasing use of novel imaging and pathology techniques, such as SLNB and immunohistochemistry. It also considers the number of involved lymph nodes (a strong prognostic factor) in staging allocation. The main changes in the TNM staging system include the following: (1) the distinction between micrometastases and isolated tumor cells on the basis of size and histologic evidence of malignant activity; (2) identifiers to indicate the use of SLNB and immunohistochemical or molecular pathology techniques; (3) indication of the number of malignant lymph nodes as shown by routine hematoxylin and eosin (H&E) staining (preferred method) or by immunohistochemistry staining (i.e., pN1 for 1 to 3 involved lymph nodes, pN2 for 4 to 9 involved lymph nodes, and pN3 for 10 or more lymph nodes); (4) reassignment of metastasis to the infraclavicular nodes as N3 disease and downstaging of ipsilateral supraclavicular node involvement from M1 to N3; and (5) staging of internal mammary lymph nodes based on detection by SLNB (N1 disease), radiologic or clinical examination (N2 disease), or concomitant axillary nodal involvement (N3 disease).

Undoubtedly, the TNM staging system for breast cancer has become more complex, although the allocation of specific TNM combinations to different stage groupings remains the same. A major exception is the creation of a new stage IIIc to include patients with exclusively TanyN3M0 disease. This revised staging system acknowledges the limitations of the previous TNM system, and will help facilitate the collection of uniform data from international databases and allow researchers to better assess the long-term outcome of specific patient subgroups and the effect of novel imaging and pathologic techniques. However, the TNM staging system does not yet account for the biologic diversity of breast cancer and its various phenotypes, and the seventh edition of the AJCC manual is scheduled for release in 2009.

Table 95-8 American Joint Committee on Cancer TNM Staging System for Breast Cancer

TNM STAGING

Primary tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by the physical examination, the examiner uses the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1-cm increment.

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Tis (DCIS)	Ductal carcinoma in situ
Tis (LCIS)	Lobular carcinoma in situ
Tis (Paget's)	Paget's disease of the nipple with no tumor

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

T1	Tumor 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumor more than 1 cm but not more 2 cm in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Regional lymph nodes (N)

Clinical

NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
N2a	Metastases in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically apparent ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
N3	Metastasis in ipsilateral infraclavicular lymph node(s), with or without axillary lymph node involvement, or in clinically apparent ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s), with or without axillary or internal mammary lymph node involvement
N3a	Metastasis in ipsilateral infraclavicular lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

Pathologic (pN)†

PNX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
PN0	No regional lymph node metastasis histologically and no additional examination for isolated tumor cells (ITCs)

Note: ITCs are defined as single tumor cells or small cell clusters not greater than 0.2 mm that usually are detected only by immunohistochemical (IHC) or molecular methods, but may be verified on hematoxylin and eosin stains. ITCs do not usually show evidence of malignant activity (e.g., proliferation or stromal reaction).

pN0(i–)	No regional lymph node metastasis histologically, negative IHC
pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
pN0(mol–)	No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
pN0(mol+)	No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)

Table 95-8 American Joint Committee on Cancer TNM Staging System for Breast Cancer—cont'd

pN1	Metastasis in 1 to 3 axillary lymph nodes, or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent‡
pN1mi	Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent
	(If associated with greater than 3 positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden)
pN2	Metastasis in 4 to 9 axillary lymph nodes or in clinically apparent internal mammary lymph nodes in the absence of of axillary lymph node metastasis
pN2a	Metastasis in 4 to 9 axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b	Metastasis in clinically apparent internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, in infraclavicular lymph nodes, or in clinically apparent ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent ipsilateral internal mammary lymph nodes in the presence of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection, but not clinically apparent
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

Distant metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I	T1§	N0	M0
Stage IIA	T0	N1	M0
	T1§	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1§	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Note: Stage designation may be changed if postsurgical imaging studies show distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

HISTOPATHOLOGIC TYPE

The histopathologic types are the following

In situ carcinomas

NOS (not otherwise specified)

Intraductal

Paget's disease and intraductal

Continued

Table 95-8 American Joint Committee on Cancer TNM Staging System for Breast Cancer—cont'd

Invasive carcinomas

NOS

Ductal

Inflammatory

Medullary, NOS

Medullary with lymphoid stroma

Mucinous

Papillary (predominantly micropapillary pattern)

Tubular

Lobular

Paget's disease and infiltrating

Undifferentiated

Squamous cell

Adenoid cystic

Secretory

HISTOPATHOLOGIC GRADE (G)

All invasive breast carcinomas except medullary carcinoma should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of the Scarff-Bloom-Richardson grading system) is recommended.[1,2] The tumor grade is determined by assessing the morphologic features (tubule formation, nuclear pleomorphism, and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) to each feature, and adding the scores for the three categories. A combined score of 3 to 5 points is grade 1, a combined score of 6 to 7 points is grade 2, and a combined score of 8 to 9 points is grade 3.

1. Elston CW, Ellis IO: Pathological prognostic factors in breast cancer. I. The value of histologic grade in breast cancer experience from a large study with long-term follow-up. Histopathology 1991;19:403–410.

2. Fitzgibbons PL, Page DL, Weaver D, et al: Prognostic factors in breast cancer. College of American Pathologists consensus statement 1999. Arch Pathol Lab Med 2000;124:966–978.

Histologic grade (Nottingham combined histologic grade is recommended)

GX Grade cannot be assessed

G1 Low combined histologic grade (favorable)

G2 Intermediate combined histologic grade (moderately favorable)

G3 High combined histologic grade (unfavorable)

NOS, not otherwise specified; RT-PCR, reverse transcriptase polymerase chain reaction.

*Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

†Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary node dissection is designated (sn) for "sentinel node" (e.g., pN0[i+] [sn]).

‡Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

§TI includes TImic.

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Pathologic Factors for Invasive Carcinoma

For many decades, the most important prognostic characteristic of a breast cancer was the number of axillary lymph nodes involved with the disease (Table 95-9). In addition, increasing pathologic size of the primary tumor is inversely related to disease-free survival and overall survival rates (see Table 95-3). Especially in women with lymph node-negative disease, tumor size is a powerful predictor of recurrence. However, the role that these traditional pathologic characteristics play in assessing the prognosis of the patient is rapidly changing. Specific existing markers, such as ER, PR and HER2, gene expression signatures, and newer predictive and prognostic tests under development not only will aid traditional pathologic assessment but in many cases will serve as the sole determinant of therapy selection. The clinical utility of predictive and prognostic markers is discussed later in this chapter.

Histologic status of the axillary lymph nodes remains the single most important prognostic factor for operable breast cancer as of press time for this book. Axillary staging is an essential procedure because of the strength of axillary lymph node status as a prognostic factor, and SLNB in experienced hands now is accepted as the preferred staging procedure for early-stage tumors.[154] Many pathologic factors of the primary tumor, including histologic subtype, nuclear and histologic grade, and lymphatic or vascular invasion, have been evaluated as additional prognosticators of clinical course. Although each of these parameters can be useful in expert hands, histologic subclassification has the greatest applicability. Most invasive breast cancers are epithelial neoplasms. The rarer sarcomas, lymphomas,

Table 95-9 Axillary Node Status and Outcome in Operable Breast Cancer

	SURVIVAL (%) RELATED TO NODES					
	NEGATIVE NODES		1–3 POSITIVE NODES		4 POSITIVE NODES	
Authors	**5 Yr**	**10 Yr**	**5 Yr**	**10 Yr**	**5 Yr**	**10 Yr**
Milan	89 [91]	—	68 [53]	—	48 [31]	—
Royal Marsden	66 [69]	—	70 [51]	—	42 [32]	—
M.D. Anderson	—	—	91 [69]	—	53 [43]	—
Carter et al.	92	—	81	—	57	—
Valagussa et al.	88 [79]	83 [74]	69 [46]	54 [33]	42 [26]	26 [15]
Ariel	81	63	66	53	48	23
Fisher et al.	78	65	62	38	32	13

Adapted from Yeh I, Fowble B, Viglione MJ, et al: Pathologic assessment and pathologic prognostic factors in operable breast cancer. In Fowble B, Goodman RI, Glick JH, Rosato EF (eds): Breast Cancer Treatment: A Comprehensive Guide to Treatment. St. Louis, Mosby-Year Book, 1991, p 171.

and nonepithelial tumors are discussed elsewhere. Infiltrating breast cancers are histologically heterogeneous, but most of them are adenocarcinomas arising from the terminal ducts. Invasive ductal carcinoma, which accounts for approximately 85% of breast cancers, has no specific histologic features (Fig. 95-16), and it often is accompanied by ductal carsinoma in situ (see the Radiation Treatment section for additional discussion regarding the presence of extensive intraductal component [EIC]). Invasive lobular carcinoma accounts for 5% to 15% of breast cancers. Its overall prognosis is thought to be similar to that of the invasive ductal subtype. One recent report suggests that women with invasive lobular cancers have better long-term outcomes, as compared with those with invasive ductal histology, when treated with neoadjuvant chemotherapy.[155] Microscopically, lobular carcinoma is characterized by single-filing ("Indian file") of small, regular epithelial cells that tend to grow around ducts and lobules (Fig. 95-17).

Many special types of breast carcinoma are less common than the invasive ductal and lobular variants and usually have a more favorable prognosis. These include mucinous, papillary, tubular, and adenoid cystic carcinoma. The better prognoses associated with these special histologic subtypes have been most clearly defined in node-negative patients, and patients with lymph node-negative disease with special tumor types up to 3 cm in diameter have, on average, a prognosis equivalent to that of patients with infiltrating ductal or lobular carcinoma up to 1 cm. The clinical and biologic features of 444 patients with tubular carcinoma and 1221 patients with mucinous carcinoma were compared with those of 43,587 patients with infiltrating ductal carcinoma, not otherwise specified.[156] The actual need and benefit offered by adjuvant systemic therapy in these subsets have not been adequately studied, but it is accepted that therapy is not required in most cases. Mucinous (colloid) carcinoma is characterized microscopically by abundant accumulation of extracellular mucin around tumor cells (Fig. 95-18). A frond-forming growth pattern characterizes papillary carcinoma (Fig. 95-19). Tubular carcinoma is distinguished by the proliferation of small glands that resemble normal mammary ducts (Fig. 95-20).

The histopathologic features that define medullary carcinoma include a well-circumscribed border, intense reaction with lymphocytes and plasma cells, poorly differentiated nuclei, a syncytial growth pattern, and little or no intraductal carcinoma (Fig. 95-21). The more favorable prognosis requires the presence of all of these characteristics. Thus, atypical medullary tumors do not have the same excellent outcome. Furthermore, the risk of incorrectly labeling an aggressive, poorly differentiated carcinoma as medullary carcinoma led some to exclude the latter from the special types of breast cancer with favorable prognoses.

Studies of the prognostic value of other pathologic factors, such as histologic and nuclear grade, vascular-lymphatic invasion,

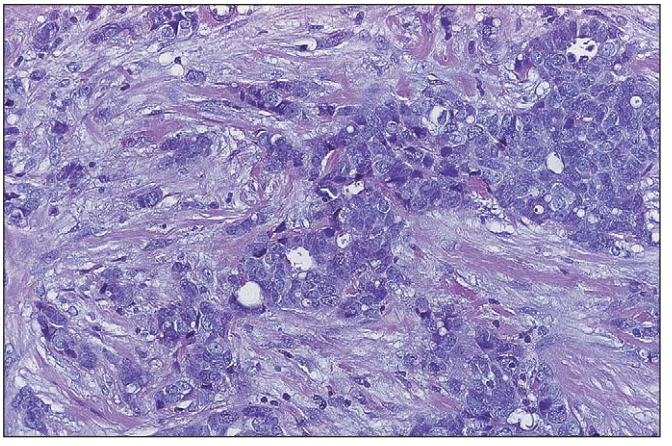


Figure 95-16 • Typical infiltrating ductal carcinoma. Irregularly dispersed glands and cords of tumor cells are set in a desmoplastic stroma.

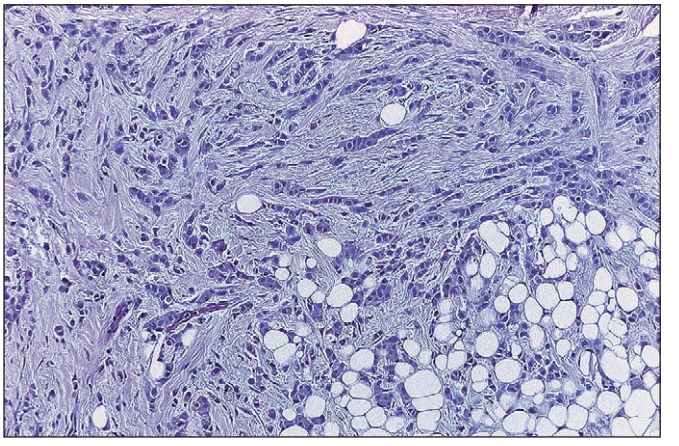


Figure 95-17 • Invasive lobular carcinoma. The tumor cells are small, and form linear, single files.

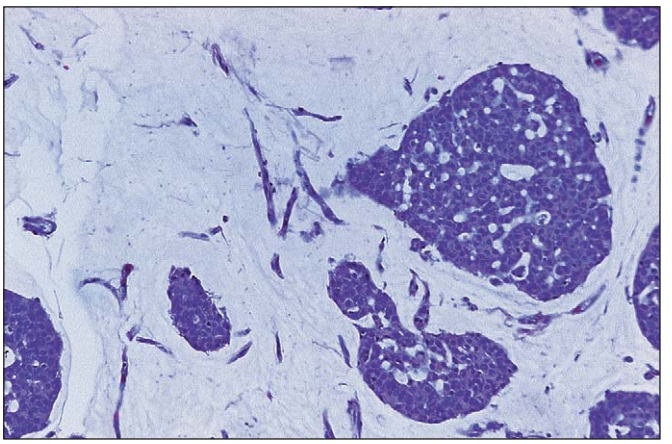


Figure 95-18 • Invasive mucinous (colloid) carcinoma. Bland nests of tumor cells float in abundant extracellular mucin.

inflammatory response, and tumor necrosis, have shown considerable variation. The major criticism of nuclear grade is the lack of observer consistency in making this subjective classification. Various prognostic indices incorporating several parameters have been intensively studied. The Nottingham Prognostic Index,[157] derived from tumor size, nodal status, and tumor grade, was validated by the German Breast Cancer Study Group[158] in a series of 600 patients with node-negative breast cancer.

MANAGEMENT OF NONINVASIVE BREAST CANCER

Much evidence supports the view that the development of malignancy is a multistep process and that invasive breast cancer has a preinvasive phase. During the carcinoma in situ (CIS) phase, normal epithelial cells undergo enough genetic alterations to result in malignant transformation. Transformed epithelial cells proliferate and pile up within lobules or ducts, but lack the additional required genetic alteration that enables cells to penetrate the investing basement membrane. Because of the increasing acceptance of breast cancer screening in the United States, CIS accounts for an increasing proportion of all new breast cancers. Between 1975 and 1978, surveys suggested an incidence of pure in situ lesions of 1.4% to 5.1%. By 2001, nearly 20% of all new breast cancers in the United States were DCIS, and this denominator does not include cases of lobular carcinoma in situ (Fig. 95-22).[159] An important research question attempts to address which CIS is preinvasive cancer, which indicates an unstable epithelium that represents an increased risk of subsequent invasive cancer, and how to intervene optimally (surgery or other preventive measures). Until better predictive markers are identified, traditional methods of estimating risk are still in use.

Lobular Carcinoma in Situ

Although breast CIS was first reported in 1932 by Broders, Foote and Steward in 1941 first described a noninvasive malignancy confined to the lobules and terminal ducts, and referred to this entity as LCIS. Foote and Steward described this lesion as rare and reported it as the sole finding in 2 of the 300 mastectomy specimens reviewed.

Anatomy and Pathology

The original description of LCIS characterized the lesion as a lobular unit with a cluster of ductules or acini-filled, distorted, and distended by proliferating epithelial cells (Fig. 95-23). LCIS cells have a fairly uniform pattern of clear cytoplasm containing rounded, bland nuclei. Intercellular spaces are preserved, and clear vacuoles within the cytoplasm may displace the nucleus. This often is referred to as *classic LCIS*, and while lesser forms of lobular unit involvement are known as lobular hyperplasia, a consensus definition of these two pathologic entities has not been reached. Some investigators argue that the word *carcinoma* should not be included in the term and that it is better to refer to atypical lobular hyperplasia and LCIS as *lobular neoplasia.* However, LCIS is a well-established entity and should be retained as the descriptive label, because it is recognized as a risk factor for the development of invasive breast cancer. Recently, a more pleomorphic type of LCIS has been described, and there is indirect evidence to suggest that this pleomorphic variant may progress to invasive cancer.[160] LCIS is a microscopic diagnosis, usually not associated with a mammographic abnormality. When LCIS is found after needle-localization biopsy of suspicious microcalcifications, the calcifications usually are outside the LCIS. The only exception is the rare fibroadenoma that contains a focus of LCIS within the mass.

Incidence, Multicentricity, Bilaterality, and Invasive Disease

LCIS had been thought of as a disease of younger women. However, SEER data from 1980 through 2001 show an increase in LCIS rates

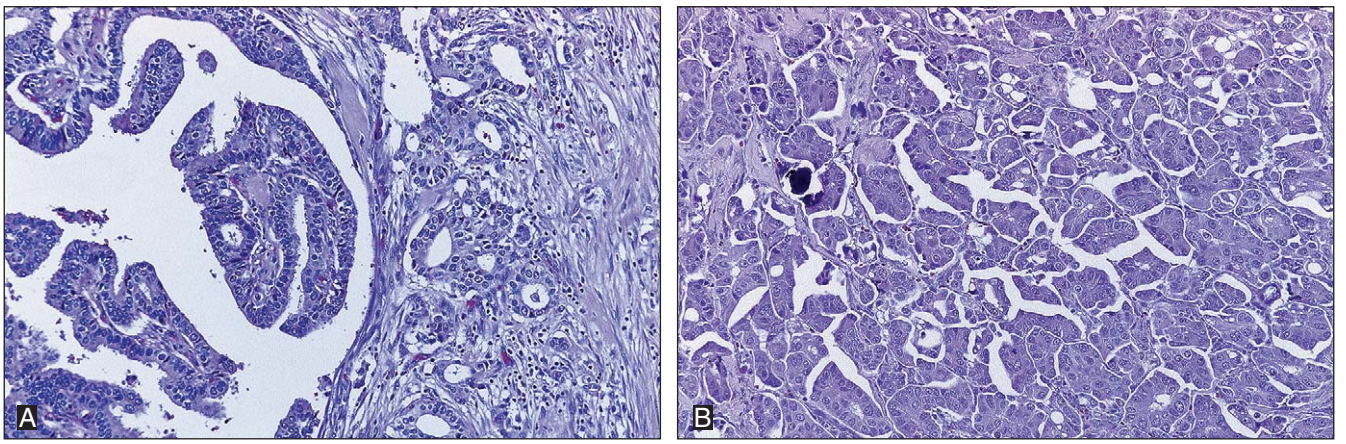


Figure 95-19 • **A,** Invasive carcinoma arising in papillary ductal carcinoma in situ (invasive papillary carcinoma). The in situ component seen on the right has a frond-like appearance, and the invasive carcinoma component on the left consists of irregularly shaped small glands. **B,** Invasive micropapillary carcinoma of the breast. The tumor resembles ovarian serous carcinoma, and small clusters of invasive tumor cells are separated from the stroma by spaces. A psammoma body is seen.

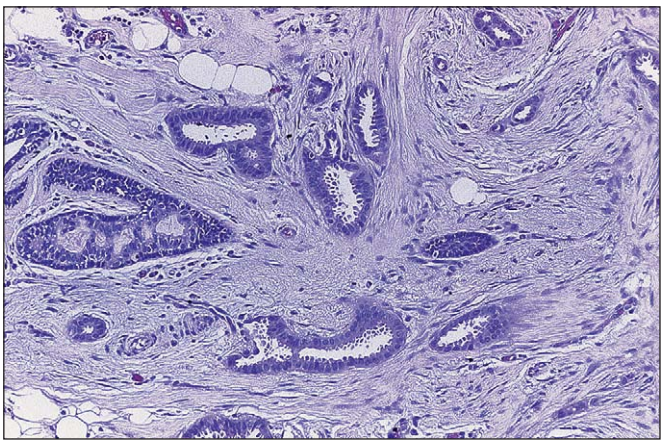


Figure 95-20 • Infiltrating tubular carcinoma. The invasive glands are irregularly dispersed, lack a second myoepithelial cell layer, and are set in a desmoplastic stroma. Tubular carcinoma resembles normal breast ducts. Two normal ducts, seen in the center, appear darker than the tubular carcinoma and have two cell layers.

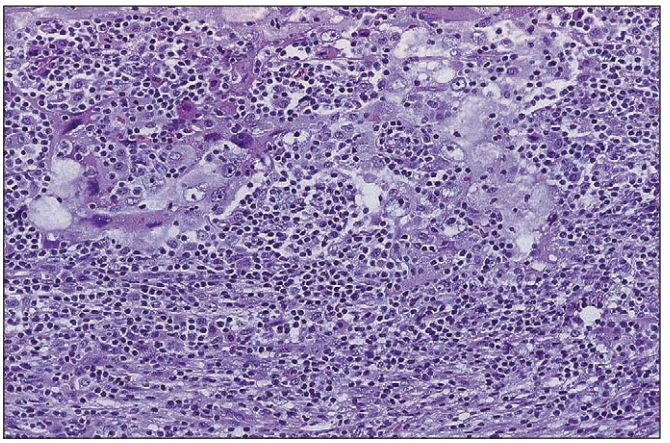


Figure 95-21 • Medullary carcinoma characterized by a well-defined border, an intense lymphoplasmacytic reaction, and pleomorphic tumor cells with vesicular chromatin.

among women over age 50 (Fig. 95-24).[159] A greater use of mammography and a tendency to perform a more thorough histologic evaluation of biopsy tissue appear to have contributed to this increase. LCIS often is multicentric and has an increased incidence of bilaterality. Several series described women who had a diagnosis of breast cancer on one side, and a mirror-image biopsy of the contralateral breast. Such series are likely to have a higher incidence of bilateral findings then those series reporting on sporadic contralateral biopsies. This topic was reviewed by Schnitt and colleagues, who reported multicentricity in 60% to 80% of cases and a correlation of this finding with an increased risk of subsequent invasive cancer in both breasts.[161] Various historical series suggested a 9-fold increased risk of subsequent development of invasive breast cancer after more than 20 years of follow-up. However, a recent SEER database study of about 4000 women with LCIS that was treated with biopsy or breast conservation surgery demonstrated a higher risk for ipsilateral invasive cancer occurrence than for contralateral cases, with the invasive histology being lobular in about half of those cases.[162]

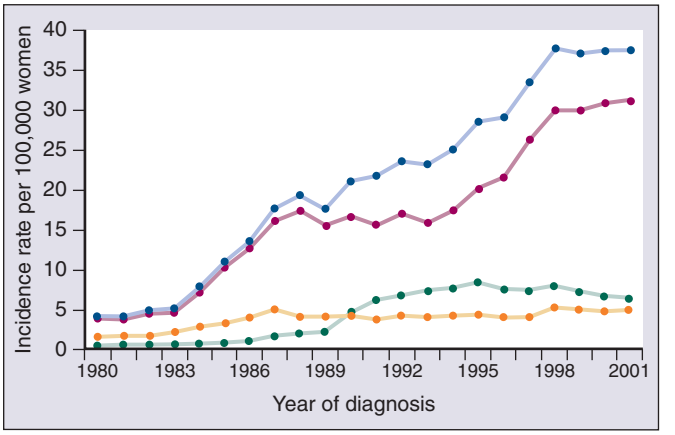


Figure 95-22 • Age-adjusted incidence rates of different histologic types of in situ breat carcinoma among women 30 years of age and older, 1980–2001. Ductal carcinoma in situ (DCIS) overall, *blue curve*; noncomedo DCIS, *magenta curve*; comedo DCIS, *green curve*; lobular carcinoma in situ (LCIS), *yellow curve*. (Li CI, Daling JR, Malone KE: Age-specific incidence rates of in situ breast carcinomas by histologic type, 1980 to 2001. Cancer Epidemiol Biomarkers Prev 2005;14:1008–1011.)

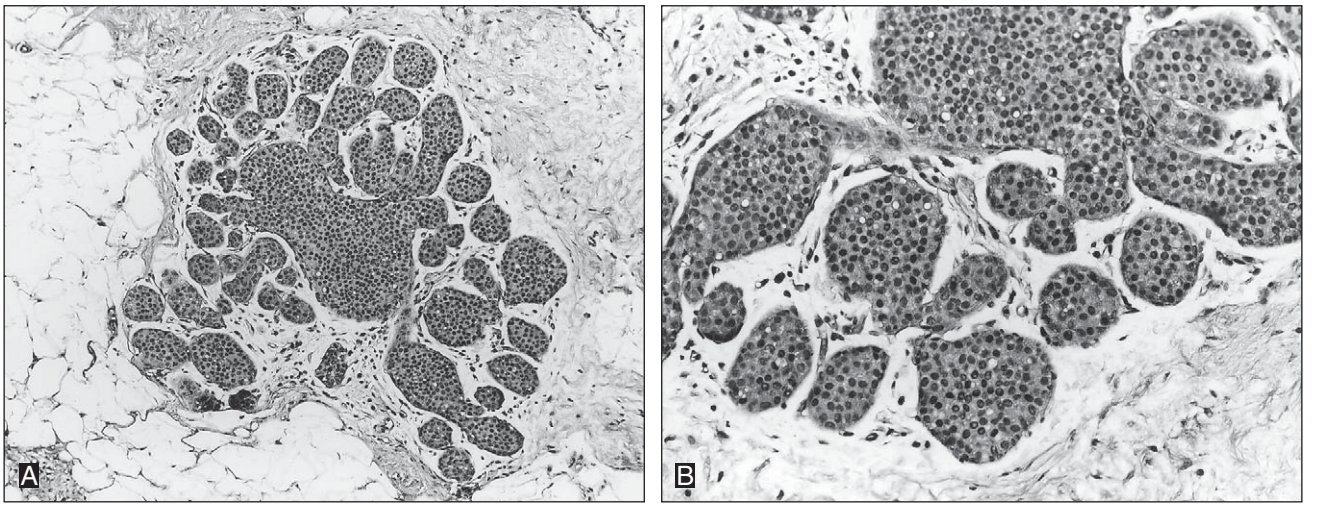


Figure 95-23 • **A,** Lobular carcinoma in situ. The lobular unit (see Fig. 95–25) is distended and distorted by proliferating cells. The cells are uniform and round, with bland nuclei. **B,** The same specimen seen at a higher magnification.

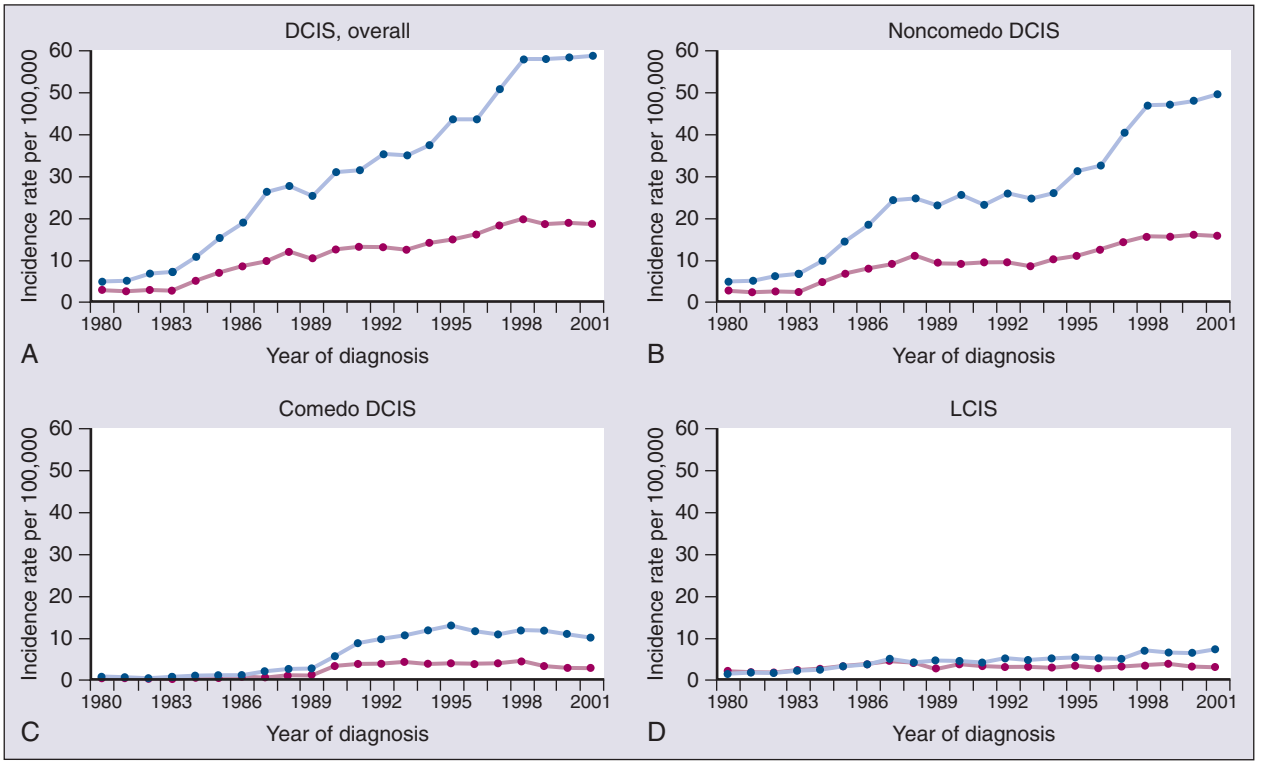


Figure 95-24 • Incidence rates of in situ breast carcinaoma by histologic type and age, 1980–2001. Age ≥50 years, *blue curve*; age 30–49 years, *magenta curve*. (Li CI, Daling JR, Malone KE: Age-specific incidence rates of in situ breast carcinomas by histologic type, 1980 to 2001. Cancer Epidemiol Biomarkers Prev 2005;14:1008–1011.)

Treatment

LCIS does not require treatment. History of a previous breast biopsy with a diagnosis of LCIS is part of the risk assessment of developing a breast cancer.[163] Evaluation for risk-reducing surgery in LCIS must take into account other risk factors, such as family history, BRCA1 or -2 mutations, and the patient's desires and worry or anxiety level. The NSABP P-1 tamoxifen prevention study showed that tamoxifen at the dose of 20 mg/day for 5 years can reduce the risk of developing a DCIS or invasive cancer by 49% with acceptable side effects.[164] Preliminary results from the NSABP STAR trial evaluating tamoxifen versus raloxifene in high-risk women suggest that raloxifene is as effective as tamoxifen in reducing the risk of invasive breast cancer in postmenopausal women at high risk for breast cancer, including those with a previous diagnosis of LCIS, and has a lower risk of thromboembolic events, cataracts, and endometrial cancer.[121]

Ductal Carcinoma in Situ

Noninvasive ductal carcinoma, or DCIS, is defined as "a proliferation of malignant cells confined within the basement membrane of the ducts of the breast." Before the widespread use of mammography, DCIS was not commonly diagnosed and usually presented as a palpable mass or bloody nipple discharge. The increasing use of screening mammography has resulted in a significant increase in the number of patients diagnosed with DCIS. Most of these cases are clinically occult. The evaluation and treatment of DCIS identified by imaging is summarized in Table 95-10.

Anatomic Histology

The terminal ductal lobular unit has been proposed as the site of origin of most breast cancer, including DCIS (Fig. 95-25). In contrast to LCIS, which tends to be multicentric, DCIS is likely to be

Table 95-10 Gudielines for Evaluation and Treatment of Nonpalpable Ductal Carcinoma in Situ

1. Careful multiview mammography with or without ultrasonography and including magnification views
   - Document extent of disease
   - Identify other areas of microcalcification
2. Suspicious microcalcifications and densities cleared with needle localization biopsy
3. Specimen radiography with magnification techniques
4. Radiograph-directed histopathologic evaluation with:
   - Orientation of specimen by surgeon
   - Multicolored inked margins
5. Complete pathologic description to include:
   - Type of DCIS and size of tumor
   - Relation to microcalcifications
   - Distance of lesion from inked margins
   - Presence of multifocality
   - Presence or risk of microinvasion
6. Repeat mammography with magnification to confirm successful clearing of suspicious areas
7. Repeat breast excision if:
   - Residual microcalcifications are found
   - Margins are unacceptable

DCIS, ductal carcinoma in situ.

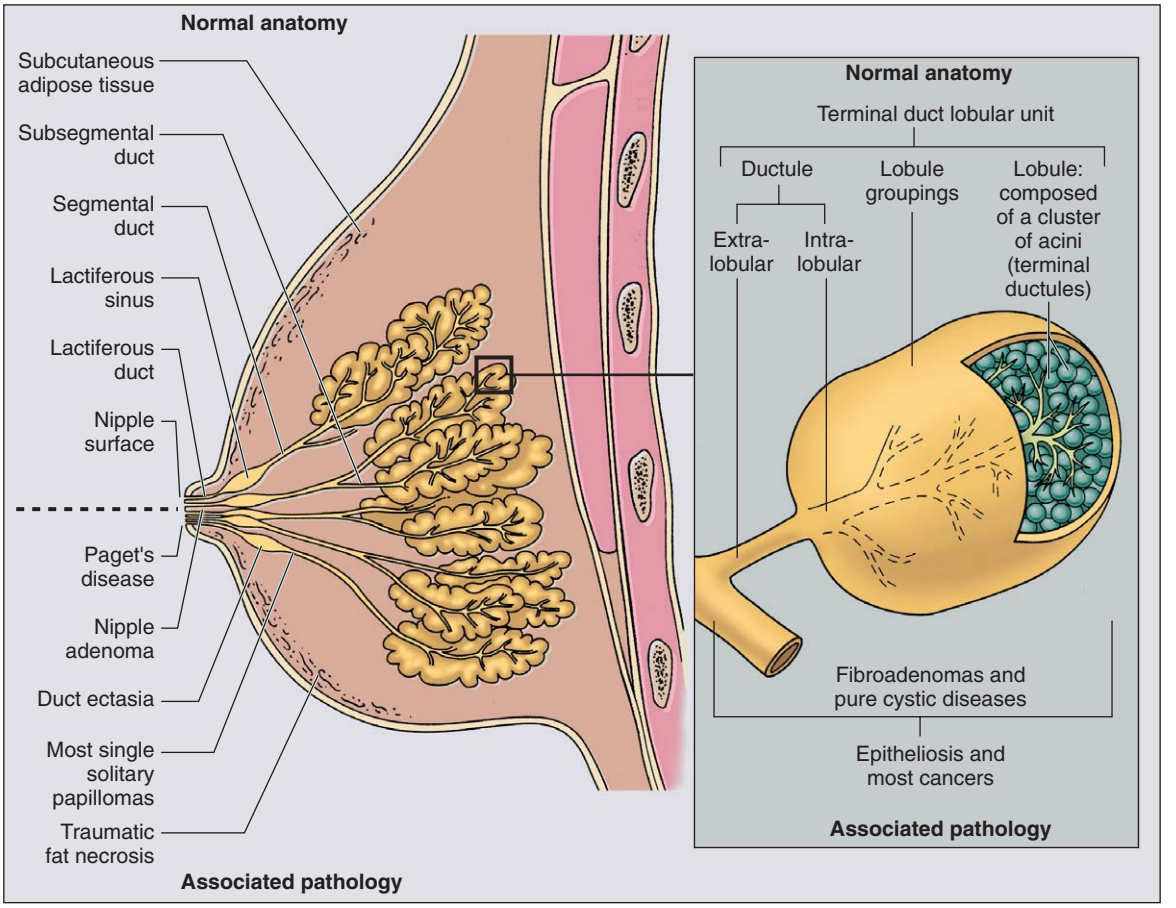


Figure 95-25 • Anatomy of the breast, showing the organization of the elements of the terminal duct lobular unit and their relationship to specific pathologic abnormalities. (From Hayes D: Breast cancer. In Skarin AT [ed]: Atlas of Diagnostic Oncology. Philadelphia, JB Lippincott, 1991, p 64.)

confined to one branching ductal system in the breast. In the past, the pathologic classification of DCIS was based on the architectural patterns of DCIS as seen microscopically. These patterns included a solid pattern of growth filling the duct, a cribriform pattern characterized by well-defined holes seen within the growth pattern in the duct (Fig. 95-26), a comedo pattern with necrosis seen in the center of the duct (Fig. 95-27), and both micropapillary (Fig. 95-28) and papillary (Fig. 96-29) variants, characterized by frond-like projections of tumor cells into the lumen of the duct. Pathology reports commonly describe two or even three subtypes of DCIS in the same specimen when using this system. To clarify these pathology classification schemas and, more importantly, to identify subtypes of DCIS that may predict patient prognosis or response of the DCIS to various clinical interventions, a 1997 consensus conference agreed on issues such as pathologic classification, methods of determining the size and extent of the DCIS, methods of determining margin width, and, most importantly, the procedure for processing the specimen in the pathology laboratory to ensure that all pertinent information can be obtained from the tissue.

Significant recommendations of the report on the classification of DCIS included noting the nuclear grade of the cancer cells, the proportion of involved ducts showing necrosis, the polarization of cells around the intercellular spaces, and the architectural pattern. Nuclear grade was determined to be the most important feature, and low- and high-grade lesions were described. Low-grade lesions had monotonous nuclei, measuring 1.5 to 2 times the size of a normal red blood cell, with finely dispersed chromatin and only

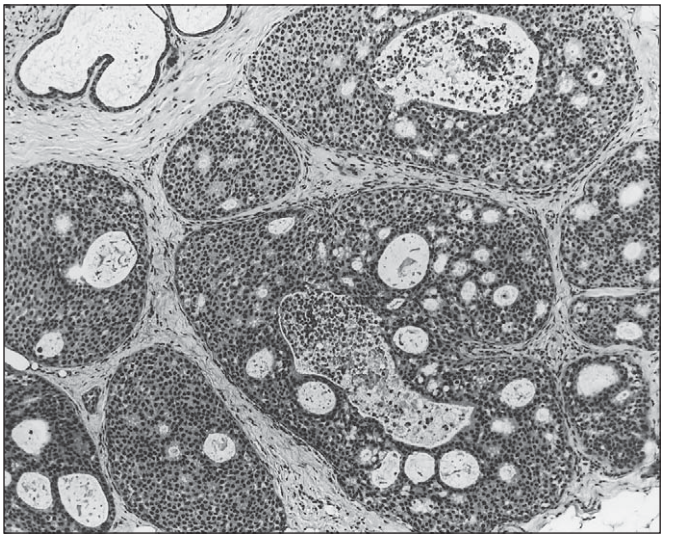


Figure 95-26 • Cribriform ductal carcinoma in situ, which accounts for most of the ductal carcinoma in situ detected. It is characterized by interconnecting strands of hyperchromatic cells. Few necrotic cells are seen, and arches of connecting strands appear rigid.

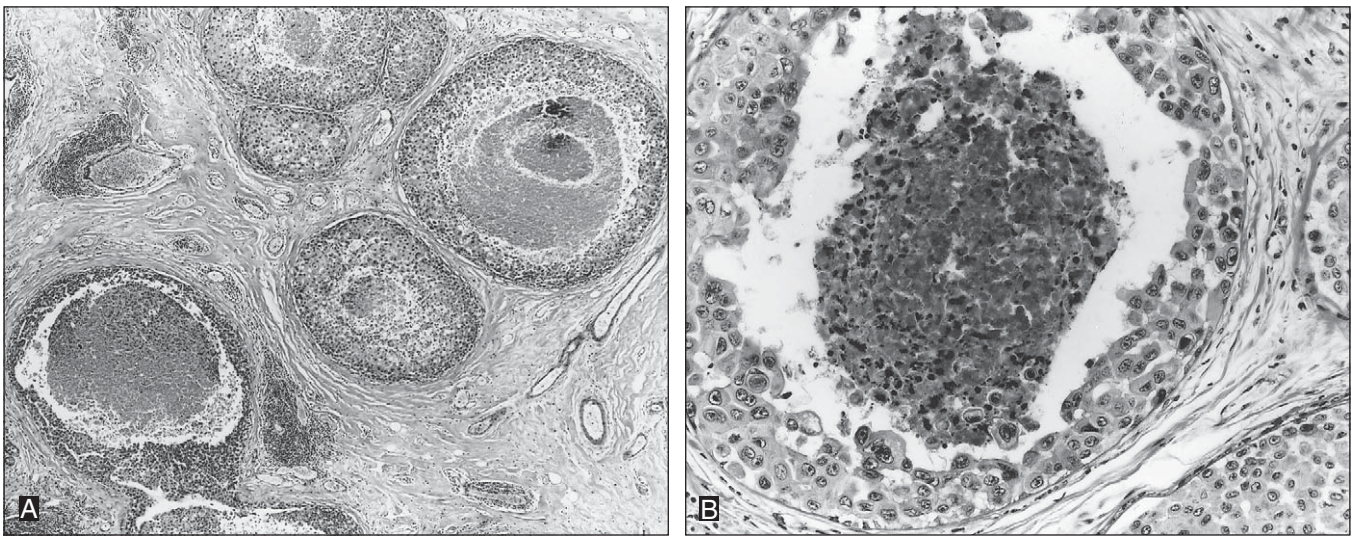


Figure 95-27 • **A,** Comedo ductal carcinoma in situ (DCIS). The ducts are expanded by sheets of proliferating cells with areas of central necrosis. The sheets of cells show more pleomorphism than is common with other histologic types of DCIS. A higher incidence of microinvasion also is seen with comedo DCIS. **B,** The same specimen seen at a higher magnification.

occasional nucleoli and mitotic figures. High-grade lesions had markedly pleomorphic nuclei, measuring more than 2.5 times the size of a normal red blood cell, with irregular chromatin distribution and prominent nucleoli with conspicuous mitoses. Intermediate-grade nuclei were defined as those not meeting the criteria for high- or low-grade lesions. Necrosis also was defined as the presence of ghost cells and karyorrhectic debris. It was further quantified as "comedo," with central-zone necrosis, or "punctate," with nonzonal necrosis and without a linear pattern within the ducts. The traditional architectural patterns also were noted as appropriate to mention in the pathology report independently of the other pathologic features. Tissue processing in the pathology laboratory also was described, because it is key in determining such information as lesion size and margin width. Important steps to follow included orientation of the specimen by the surgeon; radiograph of the specimen when feasible; inking of the surface of the specimen for margin information, unless the surgeon sends separate margin specimens; and, most importantly, processing the specimen in sequence in separate cassettes.

The extent of DCIS involvement can be determined in several ways. If DCIS is closely associated with linear or branching-type calcifications, the mammogram size can provide minimum size information. If seen microscopically on only one slide, measurement across this slide also is a meaningful estimate of size. If present on multiple slides, the pathologist should note the number of sequential slides or segments that show DCIS. Margin information is usually described in terms of the width of the closest margin, using the distance from the inked margin to the nearest involved duct. Like size, this measurement is an estimate, because the pathologist can view only a finite number of representative sections. In the unsampled tissue, the margin may actually be closer than the distance recorded in the sampled slides.

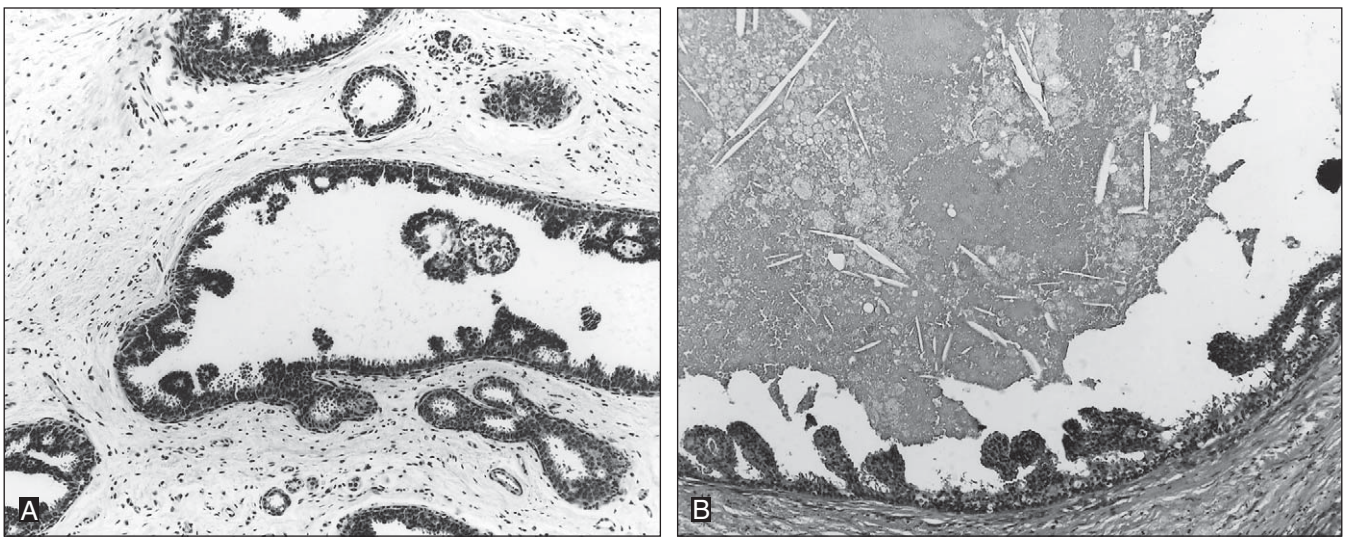


Figure 95-28 • **A,** Micropapillary ductal carcinoma in situ is characterized by small papillary projections of neoplastic cells. The papillary projections are frond-like, with a narrow base, and arise from the intersurface of ductal spaces. They are several cells thick. **B,** The same example seen at a higher magnification.

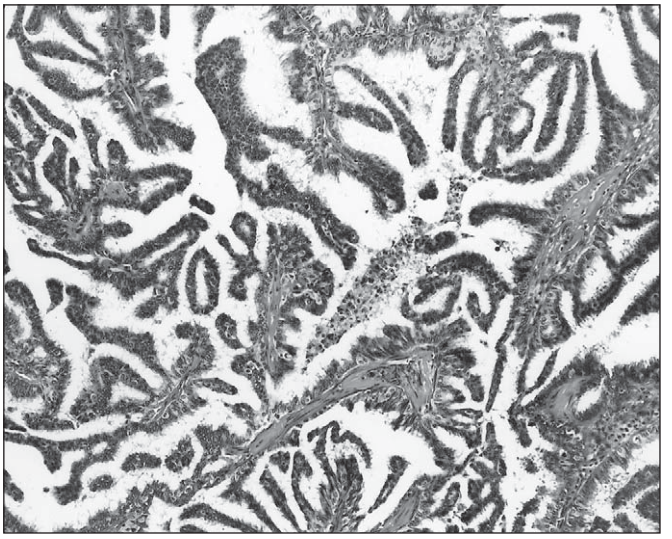


Figure 95-29 • Papillary ductal carcinoma in situ. In contrast to the micropapillary form, fibrovascular fronds are seen, similar to a duct papilloma. The fibrovascular fronds are covered by multiple layers of neoplastic cells with hyperchromatic nuclei.

Incidence and Multicentricity

Autopsy series suggest that as many as 16% of asymptomatic women have occult DCIS lesions. Reports on the multicentricity of DCIS often present data that are less than convincing. Multicentric DCIS has been described as two or more separate foci of carcinoma within the breast that are believed to have developed independently from the same carcinogenic stimulus. Some researchers suggest that the second separate focus of DCIS should be at least 5 cm distant from the primary site. Multifocality and residual DCIS within the same breast duct segment, which does not always correspond to the index "quadrant," should not be confused with true multicentricity. When several foci of calcifications are seen on the mammogram, they often are found to be "connected" at the light microscopy level.

Clinical Diagnosis

Unlike LCIS, DCIS almost always is diagnosed by mammography. Even when palpable DCIS is present, the mammographic findings are quite characteristic, with a diffuse, often linear, and extensive pattern of pleomorphic calcifications. However, the screening mammogram usually is the first indication of DCIS. Several patterns of calcifications raise the suspicion of the diagnostic radiologist. These include linear or casting-type calcifications, fine or "powdery" calcifications, and irregularly shaped calcifications often described as "crushed stone." Although any pathologic grade of DCIS can be diagnosed with any type of calcification, the most common associations are high-nuclear-grade lesions with the linear pattern and low- to intermediate-nuclear-grade lesions with a fine or powdery pattern. Less likely mammographic findings include architectural distortion or a mass.

Bloody nipple discharge also can be a symptom of DCIS. Paget's disease of the breast, another form of DCIS, commonly causes a crusty, eczema-like change in the skin of the nipple, and bleeding may be noted. Approximately half of these women have a palpable mass as well. In those who do not, a recent series found a negative mammogram in 63% of women with nipple changes only.

Clinical research on MRI for DCIS is ongoing in many centers equipped with a dedicated breast coil. Although some technical problems must be overcome in imaging DCIS with MRI, it has proven useful in evaluating the extent of residual disease in women requiring re-excision after initial biopsy and providing a better definition of extent of disease when DCIS is not associated with calcium. FNA is not ideal for evaluating DCIS because the pathologist cannot discriminate between invasive or in situ cancers.[165] For years, when mammographic abnormalities suggested DCIS, needle-localization-directed open biopsy with specimen radiography was the standard approach. Recently, with the availability of large-gauge, image-guided automated core biopsy devices, this technique has become widely accepted in appropriate cases.[166]

Biology

DCIS, by definition, has intact basement membrane on light microscopy. Unlike pure DCIS, when microinvasion is present, type IV collagen and lamina are lost from the basement membrane in association with loss of membrane continuity. Such observations lend weight to the argument that DCIS is a precursor of invasive ductal cancer. Not all cases of DCIS progress to invasive cancer. Identifying the predictors of this process is a major challenge in understanding the biology of this disease. Traditional ways of classifying pathology subtypes of DCIS have not provided these data.

A recent subset analysis by histologic type (well vs. intermediate vs. poorly differentiated) of the 1010 women in the European Organization for Research on the Treatment of Cancer (EORTC) 10853 trial concluded that histologic type was not related to the risk of invasive recurrence.[167] However, patients with well-differentiated DCIS had a lower overall risk of local failure, when the DCIS-only recurrences were included. Table 95-11 demonstrates the risk factors for any local recurrence in this EORTC study. An understanding of

Table 95-11 Multivariate Analysis of Risk Factors Related to Local Recurrence

Variable	Hazard Ratio	95% CL	*P*
Age (yr)			
>40	1		
≤40	1.89	1.12–3.19	0.026
Method of detection			
X-ray finding only	1		
Clinical symptoms	1.55	1.11–2.16	0.012
Histologic type			
Well	1		
Intermediate	1.85	1.18–2.90	0.024
Poor	1.61	0.93–2.79	
Architecture			
Clinging/micropapillary	1		
Cribriform	2.39	1.41–4.03	0.002
Solid/comedo	2.25	1.21–4.18	
Margins			
Free	1		
Not free	1.84	1.32–2.56	0.0005
Treatment			
LE + RT	1		
LE	1.82	1.33–2.49	0.0002

LE, local excision; RT, radiotherapy.

From Bijker N, Meijnen P, Peterse JL, et al: Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Teatment of Cancer randomized phase III trial 10853—a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 2006;24:3381–3387.

DCIS at the genetic level is the goal of many ongoing studies. However, little is known about this biology.

Treatment

Most cases of DCIS are diagnosed by mammography. Approximately 72% of cases are detected by calcification alone, 12% by calcification and a soft tissue density, and 10% by a soft tissue abnormality. The surgeon, when offering the patient a breast-conserving approach, must be confident that the remaining breast is free of suspicious mammographic abnormalities. Other clusters of microcalcification within the breast take on greater significance after a diagnosis of DCIS is established, and biopsy of these may be appropriate. Coordination between the pathologist and the breast-imager is very important in documenting the relationship between calcium observed on film and that observed in the specimen. When a patient has extensive areas of suspicious calcification, the entire area must be cleared surgically to ensure the success of breast conservation. When this is not possible, simple mastectomy with reconstruction, if the patient desires, is appropriate local treatment. Recent experiences with combined breast excision and plastic restoration (oncoplastic tecniques) showed the possiblity of complete removal of relatively large areas of microcalcifications with acceptable cosmetic results.[168]

Guidelines for DCIS therapy have been influenced significantly by a number of retrospective reports on follow-up of patients treated with excision only or with excision plus irradiation. More importantly, these retrospective study results have been used to design large, prospective phase III trials.

The need for radiation after wide excision first was tested prospectively by the NSABP group in a randomized trial.[169] This study randomized 818 women with DCIS to receive lumpectomy, with or without radiation. Patients were stratified by method of detection (i.e., mammogram only or palpable mass) as well as by age. Negative tumor margins were required, and were defined as no DCIS seen at the inked margin. After a median of 12 years of follow-up, the local failure rate in the index breast was 17% in women randomized to receive radiation, compared with 39.7% in the observed group. However, this significant difference in local control did not translate to any difference in survival for the women in this trial.[170]

A similar large phase III trial comparing radiation with observation after wide local excision for women with DCIS was undertaken by the EORTC group (see Biology of DCIS). This study randomized 1010 women to lumpectomy and radiation versus lumpectomy only, showing a rate of local control similar to that of the NSABP B-17 study. With a median follow-up of 10 years, the local control rate was 74% in the excision-only group, compared with 85% in women randomized to radiation. The risk of DCIS and invasive LR was reduced by 48% ($P = 0.0011$) and 42% ($P = 0.0065$), respectively. Both groups had similar low risks of metastases and death. At multivariate analysis, factors significantly associated with an increased LR risk are shown in Table 95-11, and the effect of the radiation was seen across all risk factors.[167]

A randomized trial of 1046 women, all undergoing mammographic screening in Sweden, comparing whole breast radiation to observation, showed similar results as well.[171] With a median follow-up time of 5.2 years, the cumulative incidence of local recurrences was 7% in the RT group compared with 22% in the observed group. As with both the NSABP and the EORTC trials, no differences were seen in the SweDCIS study in terms of disease-specific survival.

Several breast surgeons published individual series of patients with DCIS treated with wide excision only. Patient selection clearly plays a role in this kind of reporting. Nonetheless, local control rates in these retrospective studies are quite good, and the results generated another series of cooperative group trials. Silverstein's series from Van Nuys, using an index of the same name, related outcome to the following factors: size, pathology grade, patient age, and surgical margin width.[172,173] Several U.S. trials testing these hypotheses recently were closed. This included the Eastern Cooperative Oncology Group (ECOG) 5194 observation-only registry trial, which showed that carefully selected patients with low- or intermediate-grade DCIS treated with lumpectomy without irradiation have an acceptably low risk of ipsilateral events at 5 years.[174] The Radiation Therapy Oncology Group (RTOG) recently closed the accrual of a phase III trial that randomized selected low-risk patients with DCIS to wide excision, with or without radiation. Final sample size trial was less than initially planned due to low accrual rate (600 women enrolled compared to the target of 1800). In a Danish nationwide prospective study of in situ carcinoma of the breast, a total of 275 women treated with excision alone were registered from 1982 to 1989. Within a median follow-up of 120 months, a crude recurrence rate of 28% was found, of which 53% recurred as invasive carcinomas and 47% as in situ cancers.[175] Thus, this issue of identifying a "good risk" group of women with DCIS who can be observed without the addition of radiation remains controversial.

In general, a woman's risk of local failure in the index breast after wide excision appears to be reduced by a factor of approximately one half by the addition of whole-breast radiation. Because survival remains excellent, whatever local treatment is selected, involving the patient in a decision, based on her assessed risk and the relative benefits and risks of radiation, appears appropriate for women in lower-risk groups. These groups are defined by older age, tumor grade, size, and margin width, and likely by other factors yet to be described. Several trials comparing lumpectomy plus radiation versus mastectomy are summarized in Table 95-12.

The NSABP B-24 study tested the role of tamoxifen, in addition to lumpectomy and radiation therapy, in a prospective trial of 1804 women. With a median follow-up of 74 months, with the addition of tamoxifen to 50 Gy radiation, the risk of ipsilateral invasive recurrence was further reduced by approximately 50%. However, the absolute risk reduction was only 3%, and no significant reduction in noninvasive recurrence was seen. Predictably, the addition of tamoxifen decreased the risk of a contralateral breast event by approximately 1.5%.[176] A 2 × 2 factorial design randomized trial in the United Kingdom, Australia, and New Zealand randomized 1701 patients to receive, after lumpectomy, either tamoxifen alone, tamoxifen plus radiation therapy, radiation therapy alone, or nothing. At a median of 52.6 months, ipsilateral invasive disease was not reduced by tamoxifen, but recurrence of overall ductal carcinoma in situ was decreased (hazard ratio 0.68 [0.49–0.96]. Radiotherapy reduced the incidence of ipsilateral invasive disease (0.45 [0.24–0.85]) and ipsilateral ductal carcinoma in situ (0.36 [0.19–0.66]).[177] The NASBP and the International Breast Cancer Intervention Study (IBIS) groups are independently evaluating the aromatase inhibitors in preventing local recurrences after lumpectomy and RT for DCIS. In these trials the patients are randomized to take anastrazole or tamoxifen for 5 years.

Male breast cancer accounts for only approximately 1% of all cases of breast cancer. Men with DCIS are estimated to be only 7% of that already small group, so aside from case reports, little information exists on the management of this unusual entity.[178] Total mastectomy or wide excision with free margin may be considered a reasonable treatment.

Sentinel Lymph Node Biopsy in Ductal Carcinoma in Situ

Investigators are now questioning whether the SLNB technique, well established for the staging of invasive breast cancer, may have a role in the staging of DCIS. Several studies have documented a high incidence of lymph node micrometastases detected by SLN biopsy in patients with high-risk DCIS and DCISM (DCIS with microinvasion). Although the biologic significance of breast cancer micrometastases remains unclear at this time, these findings suggest that SLNB should be considered in patients with high-risk DCIS and DCISM. One reason for the high rate of detection of positive SLNs in DCIS is that DCIS of the breast is defined as stage 0 disease, without invasion, but its diagnosis is subject to sampling errors. A positive SLN

Table 95-12 Randomized Trials Comparing Lumpectomy Plus Radiation to Mastectomy

Trial	No. of Patients	Maximum Tumor Size (cm)	Follow-up (yr)	SURVIVAL (%)	
				Mastectomy	Lumpectomy
NSABP	1217	4	12	60	62
Institut Gustave-Roussy	179	2	14.5	65	73
Milan	701	2	16	71	72
EORTC	874	5	8	73	71
Danish	618	5	6	82	79
NCI	237	5	10	75	77

SENTINEL LYMPH NODE MAPPING

Radioisotope

Europe: ^{99m}Tc colloidal albumin (unfiltered) [ideal particle size 10–200 nm] 0.1–0.6 mCi/4 mL normal saline injected subdermally or into the breast.

United States: ^{99m}Tc sulfur colloid 0.3–1.0 mCi in 4 mL normal saline is injected subdermally or into the breast 1 to 4 hours before surgery; a handheld gamma probe is used.

Between 4 and 5 mL isosulfan blue dye is injected subdermally beneath the areola or into the breast parenchyma on the axillary side or at the tumor site. Breast is massaged for 5 minutes before the low axilla is explored.

EORTC, European Organization for Research on the Treatment of Cancer; NCI, National Cancer Institute; NSABP, National Surgical Adjuvant Breast and Bowel Project.

may raise the question of whether invasion was missed at the breast pathology examination, and thereby reduce the sampling error. Another point in favor of SLNB in DCIS is the fact that the diagnosis of pure DCIS often is made subsequent to surgical excision of the lesion. Some patients with lesions considered to be at high risk for invasion based on clinical, pathological, or mammographic criteria may benefit from a SLNB if final pathology shows invasion.

Some criteria for predicting invasion can help decide whether to perform a SLNB. On mammography, DCIS is generally evident as calcifications, whereas a mass often is seen in the setting of an invasive carcinoma. In patients with DCIS, the presence of extensive calcification or an associated mass/lesion at mammography suggests a greater likelihood of an invasive component. High-grade DCIS with comedo necrosis on core biopsy frequently shows invasion at the final pathology of the surgical excision. Consideration should be given to SLNB in patients who are at high risk for invasion or who are undergoing a mastectomy. This would include patients with pathology that is either suspicious or diagnostic for microinvasion and cases that involve the presence of lymphovascular invasion, or the presence of a palpable or mammographic mass. In women who undergo mastectomy, a SLNB can be justified due to its associated lower morbidity, additional pathology attention to the lower number of lymph nodes submitted, and the potential avoidance of a formal ALND if the SLNB procedure shows no nodal involvement should a focus of invasion be identified in the breast specimen.[179]

MANAGEMENT OF EARLY-STAGE BREAST CANCER

The management of early invasive breast cancer is multidisciplinary and must involve specialists in breast imaging, pathology, surgical oncology, radiation oncology, medical oncology, and reconstructive surgery. More than half of all women in the United States (including African-American women) who are diagnosed with breast cancer present with early-stage breast cancer,[3] often 2 cm or less, and most are potential candidates for breast conservation (lumpectomy and radiation) assuming adequate surgical margins and cosmetic outcome.[180] Preoperative systemic therapy (PST) is a reasonable option to consider for women with operable breast cancer who are not candidates for breast conservation due to large tumor size and/or small breast size at presentation. However, the absolute increase in the number of women ultimately treated with breast conservation after PST is less than 10%. Available data show no clear survival benefit for preoperative systemic therapy.[181] Not all breast cancers have systemic involvement at presentation,[182] and maximization of local control with radiation therapy also may reduce the subsequent risk of distant relapse and improve survival.[183] Decisions about adjuvant systemic therapy first must take into account the accurate determination of the expression of any predictive markers that identify potential candidates for therapy centered around anti-estrogens (if ER- and/or PR-positive disease),[184] trastuzumab (if HER2-positive disease),[75] or chemotherapy (if triple negative disease). Estimates of risk based on more traditional prognostic markers (e.g., tumor size and degree of lymph node involvement) are then added to help estimate the absolute improvement offered by the specific systemic therapies in question. Some measures of gene expression profiling appear to offer predictive utility to help with therapy selection.[103]

Breast-Conservation Therapy with Surgery and Radiation

Fortunately for most patients, the appropriateness of breast conservation is one of the most studied treatment decisions in modern medicine. Pioneering investigators in the 1920s and 1930s began to treat groups of women with breast-conserving partial mastectomy, followed by irradiation to the intact breast, challenging the need for total mastectomy. Results from these early studies were promising. Many single institutions initiated programs, including excision plus radiation therapy, for their patients with breast cancer, first in European and Canadian centers and later in the United States. In the early 1970s, several European reports created worldwide interest in nonmastectomy treatment based on individual series that suggested local recurrence rates of 5% to 10% and similar survival.

These single-institution studies caused considerable controversy between breast surgeons who believed in the mastectomy as a local treatment and those that embraced breast conservation. This, in turn, led to six randomized prospective trials using megavoltage radiation techniques comparing lumpectomy plus radiation with mastectomy, which were carried out with cooperative groups in both Europe and the United States. A meta-analysis of these trials noted that survival at the 10-year mark in the conserved group was similar to the mastectomy group with a survival trend among lymph node-positive

patients.[185] Both the NSABP-B 06 Trial[180] and the Milan Cancer Institute Trial[186] have reported 20-year results showing equivalent outcomes. The NSABP B-06 Trial was unique, in that it randomized women to three treatment arms—the mastectomy arm, the breast conservation arm with radiation, and a breast conservation arm without radiation. The in-breast local failure rate without the additon of radiation approached 40% in that trial. Although initial analyses did not demonstrate a relationship between local in-breast failure and distant metastases, a recent report from the NSABP, focusing on node-positive women receiving breast conservation therapy including radiation, treated on a series of five trials, now shows a significant hazard ratio for mortality associated with local in-breast failure.[187] Thus, maximization of the chance of local control in this group of women is now associated with survival as well as in-breast failure. The BCT data were so convincing that in 1990, the NCI held a consensus development conference on the treatment of early breast cancer and declared that breast-sparing therapy not only was equivalent to mastectomy but actually was the "preferable" treatment, because it preserved the breast, with all of the attendant psychological and body image advantages associated with a lesser surgical procedure.

Resection of the Primary Lesion

Resection of the primary cancer for therapeutic purposes has different definitions accordingly to different authors. *Lumpectomy, wide excision, tumorectomy, segmentectomy,* and *quadrantectomy* are different terms to indicate excision of the cancer with "healthy " surrounding parenchyma. The European segmentectomy and quadrantectomy were characterized by a larger amount of breast parenchyma removal compared with surgical procedures in the United States, at least in the past.[188] The concept of large excisions has been progressively replaced by the concept of free margins. An excision that achieves negative margins for invasive cancer usually is considered sufficient. Numerous reports demonstrate that the margin status appears to influence the risk of recurrence, but still controversial is a definition of the free margin distance, defined as the safe distance of the cancer from the margins. Some authors have correlated the microscopic margin distance to the risk of local recurrences, showing that the distance is proportional to the risk of local recurrence.[189] The concept of free margins has been extended to the intraductal component when associated with the invasive cancer. Although the risk of local recurrence decreases in direct proportion to the extent of resection, as expected, the cosmetic result also declines with more aggressive resection. When margins are positive or close (many authors define close margins as < 2 mm), the ideal approach is reexcision of the previous biopsy site or reexcision of the involved/close margin, when specified. For reexcision, sharp dissection is preferred. Electrocautery should be avoided until the specimen is removed to avoid cautery artifacts that might obscure margin information.

Patients must be thoroughly informed about the indications for reexcision and the possibility that the histologic features of the specimen will dictate a change in therapy. For example, a reexcision specimen sometimes contains extensive or multifocal intraductal cancer. Some of these patients have intraductal cancer that is not marked by calcification extending into unknown areas of the breast. If all apparent intraductal cancer cannot be removed surgically, the risk of local failure can become unacceptably high and dictates planning for mastectomy and reconstruction.

Once the tumor has been removed, sutures or numbered tags are placed on the specimen so that it can be oriented, and the entire specimen has its surface inked in some fashion to allow evaluation of the histologic margins. Different colored inks may be used to represent different surfaces. The specimen is then cut and histologic sections prepared. Extra attention is paid to areas near the surgical margin wherever tumor is seen to encroach grossly. A thorough histopathologic evaluation can be done in a reproducible fashion, and a template for reporting surgical pathology in patients who undergo lumpectomy can be used to ensure that no important details are neglected.

As mentioned before, surgical excision is a balance between complete removal af the cancer with surrounding foci and an accetable cosmetic result. When this goal cannot be achieved, mastectomy and reconstruction may be a better option unless the patient strongly desires conservation of the breast, accepting a possible unsatisfactory cosmetic outcome.

Small titanium surgical clips may be placed in the tumorectomy wall to guide the radiation oncologist for precise placement of a radiation boost when indicated. Reapproximation of breast tissue may be used when it does not distort the breast shape. Closure of the parenchyma of the lumpectomy cavity may prevent seroma formation. Although most women today can have breast-conserving surgery, there are some contraindications, which are based on the premise that all invasive or preinvasive cancer should be removed surgically and that radiation therapy is an essential component of breast conservation, thereby reducing the risk of local failures. The contraindications are as follows:

- Scleroderma, cutaneous lupus erythematosus, and other active collagen disease of these tissues.
- Diffuse calcifications indicating an extensive intraductal component: biopsy of two separate areas of microcalcifications should be performed to confirm the diagnosis of multicentricity.
- Multicentric invasive cancers or DCIS may preclude breast conservation. Biopsy of two separate lesions should be performed to confirm the multicentricity pathologically.
- Large residual disease after induction chemotherapy may make it difficult to achieve acceptable cosmesis with breast conservation. This is a highly personal decision that the patient must make in conjunction with her physician.

Patients with previous chest wall radiation require evaluation by a radiation oncologist to determine the feasibility of breast conservation.

Axillary Staging

The second aspect of breast-conservation therapy involves staging the axilla (Fig. 95-30). Although many studies have suggested that a panel of prognostic indicators and molecular markers of the primary tumor might eventually be a better predictor of outcome than the number of involved lymph nodes, no combination of such parameters has been validated.

When suspicious axillary lymph nodes are present, axillary dissection should take place. Originally, axillary lymph nodes, including level III nodes medial to the medial border of the pectoralis minor muscle, were carefully removed. These dissections were associated with a higher incidence of lymphedema of the arm than limiting dissection to levels I and II. Level I and II dissection is now the standard for axillary clearance. This type of axillary dissection is associated with the lowest risk of regional failure. When bulky lymph nodes at level I and II are present, or suspicious level III nodes are detected, the removal of the level III nodes, bordered medially by Halsted's ligament, laterally by the medial edge of the pectoralis minor muscle, superiorly by the anterior aspect of the axillary vein, and posteriorly/inferiorly by the anterior chest wall, should be performed to avoid possible axillary recurrences, which are difficult to treat with chemotherapy and radiation and sometimes are associated with axillary vein thrombosis and invasion of the axillary plexus.

During the axillary dissection, care is taken to preserve the lateral and medial pectoral nerves, the long thoracic nerve (to avoid a "winged scapula" appearance), and the thoracodorsal nerve. When possible, preserving the upper branches of the inner costobrachial sensory nerve can avoid paresthesia and numbness in the inner posterior arm. Careful sparing of the brachial lymphatics that lie anterior

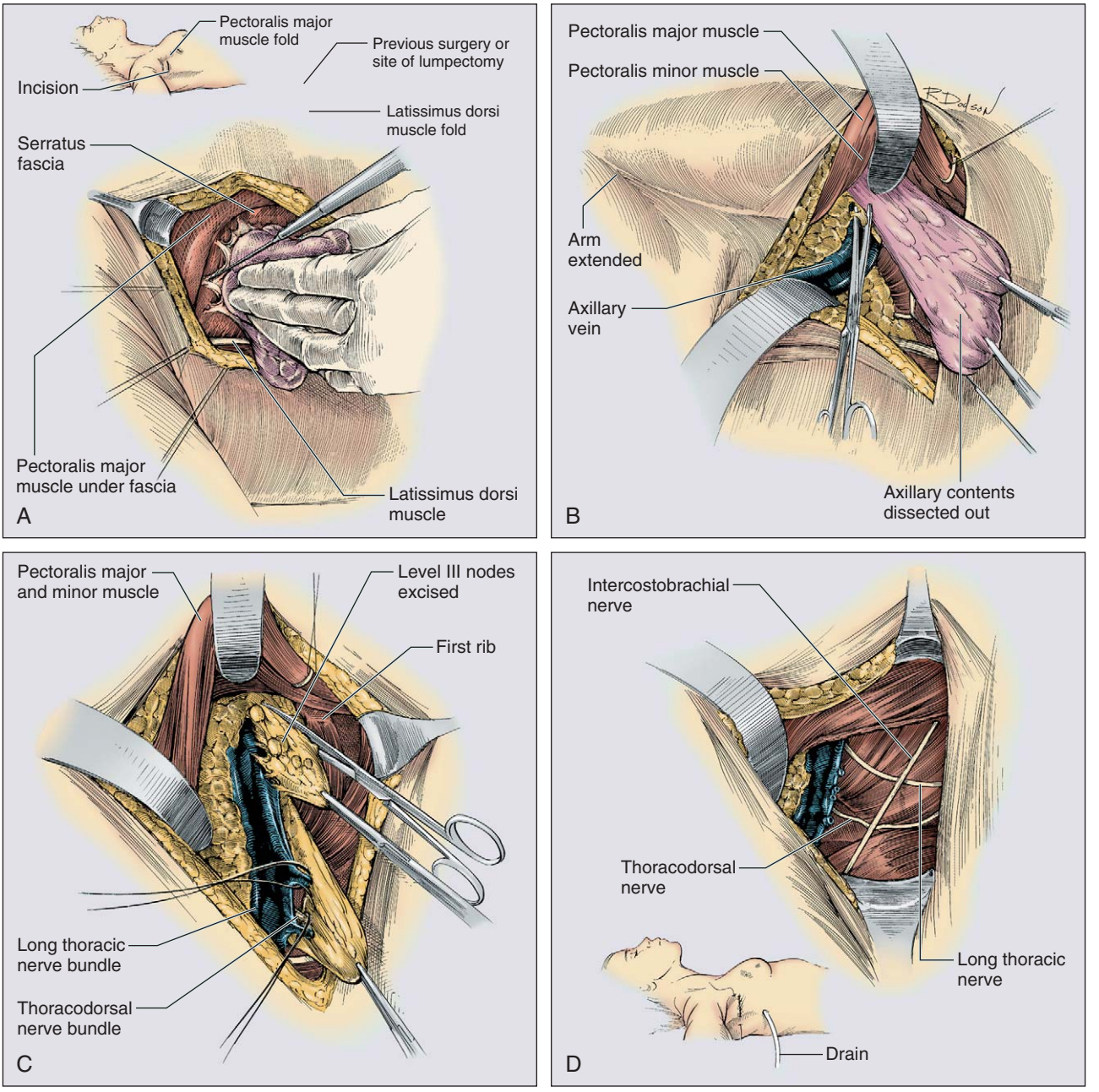


Figure 95-30 • **A,** The incision for axillary node dissection is placed at the inferior aspect of the axillary hairline, and extends from the lateral border of the pectoralis major muscle to the anterior border of the latissimus dorsi muscle. Nylon traction sutures are placed in the dermis. Flaps are raised superiorly and inferiorly. **B,** The pectoralis major and minor muscles are retracted to facilitate dissection of the lymph node-bearing fatty tissue from beneath the muscles and away from the axillary vein and chest wall. **C,** Excision of level III lymph nodes (highest level near the entrance of the axillary vein into the chest) is easily accomplished, even through the small axillary incision, with the arm rotated upward. **D,** The completed dissection, showing the isolated nerves to the serratus muscles, the latissimus dorsi muscle, the pectoral muscles, and the sensory nerve to the inner aspect of the upper arm.

to the axillary vein and brachial plexus minimizes the risk of lymphedema. Lymphedema is associated with body habitus, and people with obesity are at higher risk, despite optimal surgical technique.

Sentinel Lymph Node Biopsy in Invasive Disease

SLN biopsy has largely replaced axillary dissection for patients with clinically negative axillae and is becoming the standard surgery for staging breast cancer.The concept of the sentinel lymph node (SLN) originated with a 1977 description of mapping of the first draining lymph node in penile carcinoma. Detection of a sentinel "blue" node was described in melanoma in 1992 and in breast cancer the year after using blue dye and radioisotope localization. Published reports validated the sentinel lymph nodes by concurrent axillary dissection, and the use of isotope and blue dye simultaneously appear to shorten the learning curve and result in slightly better identification of sentinel lymph nodes. However, some surgeons prefer using the blue dye alone.

Axillary lymph node biopsy (ALND) and SLN biopsy in breast cancer are done for staging/prognosis, local control of disease, and the possibility of a survival benefit from removing involved nodes. The premise of SLNB is equivalent to ALND in all three aspects, with the added advantage of sparing node-negative patients the morbidity of a larger operation from which they could not benefit. The debate over SLN biopsy is whether current data, largely observational, are sufficient to adopt SLN biopsy as standard of care in the absence of level I evidence from the two ongoing U.S. trials (ACOSOG Z0011, a randomized trial of axillary node dissection in women with clinical T1 or T2 N0 M0 breast cancer who have a positive SLN; and *NSABP* B-32: a randomized phase III clinical trial designed to compare SLN resection to conventional axillary dissection in clinically nodenegative breast cancer patients) *and* six European clinical trials (a Milan Trial,[190] the ALMANAC trial,[191] the EORTC 10981–22023 AMAROS trial, the German clinical interdisciplinary sentinel study-KiSS protocol, the French randomised SLN study (Fransenod) trial, and the International Breast Cancer Study Group randomized 23–01 trial.

For lymph node staging, SLNB is best regarded as a diagnostic test for the detection of nodal metastases and, as such, should not require validation by randomized trials. More than 60 observational studies (in over 6000 patients) of SLN biopsy validated by a "backup" ALND have established a 95% success rate for SLN identification and a 95% sensitivity for detecting nodal metastases (i.e., SLNB is "falsely negative" in 5% of node-positive patients, or 2% to 3% of all cases). While this observation suggests a loss of prognostic information for those few false-negative patients, it must be balanced against studies showing that following ALND, 9% to 20% of patients initially deemed node-negative by conventional pathology (a single H&E-stained section) are found on further sectioning and/or immunohistochemical (IHC) staining to have nodal metastases, and that these missed nodal metastases are prognostically significant.[192]

Such exhaustive pathologic analysis is not logistically feasible for an entire ALND specimen. One study alone required the examination of 1600 slides to identify each additional node-positive patient, but it is feasible for the two or three nodes obtained at SLN biopsy. Enhanced pathologic analysis of SLN finds nodal metastases in an additional 10% of cases and is associated with a lower false-negative rate compared with SLN examination by the conventional single-section method. Viewed in this way, SLN biopsy with enhanced pathology generates fewer false-negative results than ALND with conventional pathology, and so it may turn out to have similar accuracy rates when compared to ALND.

If SLN biopsy is falsely negative in a small proportion of node-positive cases, this would seem to pose an increased risk for the development of axillary local recurrence (LR) among patients staged by SLNB alone. In fact, data from several observational studies[193–199] and one randomized trial[190] demonstrate that LR following a negative SLN biopsy is a rare event, occurring in 0.2% of cases, results which compare favorably to those of axillary sampling and of ALND (Table 95-13).[200]

Of particular interest is the observation from the single randomized trial[199] of a 9% false-negative rate in the control arm (SLN biopsy plus ALND) but no axillary LR in either study arm, including the 167 patients staged by SLN biopsy alone. Possible explanations for this consistently low rate of axillary LR across all 10 studies includes selection for early-stage disease, a local effect of systemic therapy, and most importantly the use of breast radiotherapy, which inevitably treats the axillary nodes closest to the breast. While all reports of LR following SLN biopsy are limited by relatively short follow-up, a significant future increase in LR is unlikely, as evidenced by an earlier study of mastectomy without ALND (NSABP B-04[201]) in which 75% of axillary LR appeared within the first 2 years. In preventing axillary LR, SLN biopsy is at least equivalent both to ALND and to axillary sampling.

There is considerable controversy about the staging of patients whose SLNs appear negative by standard H&E examination, but who have isolated tumor cells found by immunohistochemistry or reverse transcriptase polymerase chain reaction evidence of a few cancer cells. The latest TNM staging manual suggests classifying these patients as node-negative, with a subscript to indicate these additional findings. Of note, some European centers consider these patients node-positive. Also controversial is the surgical management of patients with positive SLN biopsy: is completion of the axillary dissection necessary? Some of the clinical trials just described will, we hope, answer this question. A nomogram to predict the likehood of additional positive nodes after positive SLNs has been developed.[202]

Initial contraindications for SLN biopsy, including clinically suspicious axillary lymph nodes, tumor arising from the axillary tail of the breast, multicentricity, large cancers, large biopsy cavity, previous axillary sampling, previous breast and/or axilla radiation therapy, and pregnancy, have been progressively cleared by evidence specific to these patient subsets.[203] Still controversial is the use for SLN biopsy after PST, but data from the NSABP B-27 study shows that SLN biopsy appears to be a reliable procedure following preoperative chemotherapy.[204]

Irradiation of the Intact Breast

No subsets of women have been identified who do as well following conservation surgery without radiation therapy as with it, although such subsets of patients have been aggressively sought.[205] Current recommendations are to irradiate the breast after lumpectomy to achieve the lowest possible recurrence rate. The only possible exception is elderly women with comorbid conditions, as discussed later in this chapter. When radiation therapy is elected, the whole breast is treated through a pair of tangentially directed fields to a dose of 4500 to 5000 cGy over 5 to 6 weeks. Traditionally, the patient is

Table 95-13 Axillary Local Recurrence after Axillary Sampling, Axillary Lymph Node Dissection, and Sentinel Lymph Node Biopsy

	No. of Patients	Median Months Follow-up (range)	Axillary Local Recurrence No. (%)
Axillary sampling	443	91 (49–132)	18/437 (4.1)
2 series (1995–2000)			
ALND	5825	64 (27–180)	52/5825 (0.9)
9 series (1986–2004)			
SLN biopsy	4981	27 (14–46)	11/4981 (0.2)
10 series (2000–2004)			

ALND, axillary lymph node dissection; SLN, sentinel lymph node.

Data from Naik AM, Fey J, Gemignani M, et al: The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. Ann Surg 2004;240:462–468.

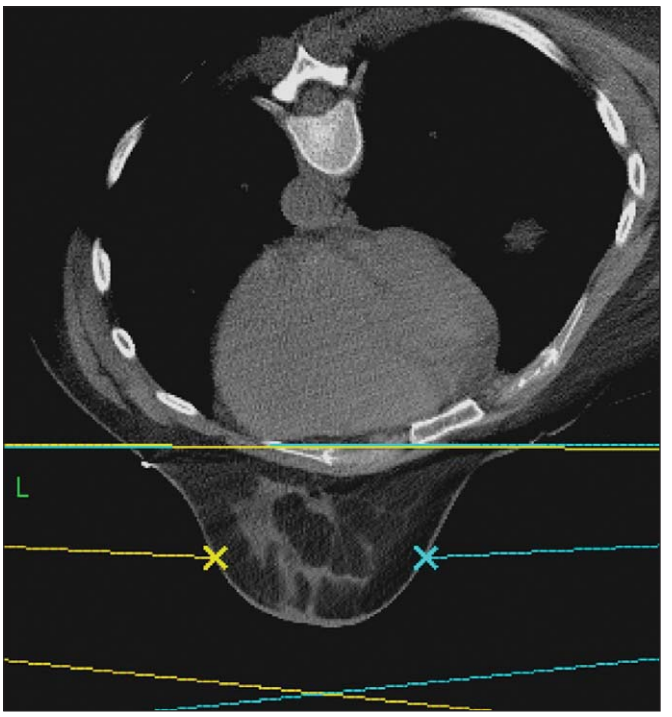


Figure 95-31 • Left breast irradiation using prone breast technique can spare lung, left ventricle, and coronary arteries.

treated supine, with fields designed to skim along the lung/chest wall interface, and irradiate the smallest volume of underlying lung. In left-sided primary lesions, the fields should result in the lowest possible exposure of the heart. Alternatively, the patient may be treated in the decubitus or prone position (Fig. 95-31).[206]

Following the completion of whole breast treatment, an additional series of radiation treatments (or "boost") usually is directed to the lumpectomy cavity only. A striking exception to the use of the boost has been the series of NSABP trials, starting with the B-06 trial; no boost was used until the opening of the B-39 Trial. A randomized prospective EORTC trial evaluated the need for a boost in patients undergoing lumpectomy.[207] In this trial, 5318 women were randomly assigned to a boost of 1600 cGy or no boost, after completing 5000 cGy whole-breast radiation. The results demonstrated that the boost reduced the local failure rate by a factor of 2; looking at age, this translated to a reduction from 19% to 9.5% for those women under age 40, but an absolute difference in those over 60 years of only 1.9%. Most institutions currently recommend a boost for all patients, although based on the EORTC study, considering omitting the boost for women with negative margins over the age of 60 is reasonable. This set of data also confirms the favorable prognosis in the elderly patient. The boost is accomplished quickly and easily on a linear accelerator equipped with electron-beam capability, and requires five to eight additional treatments. Localizing the target within the breast for boost purposes can be accomplished by CT, by ultrasound, or by clips left in the tumor bed. Morbidity associated with a boost is limited to temporary skin tanning.

With either a complete axillary dissection or a successful SLNB and negative results, the axilla is considered treated by the surgeon. Much clinical experience indicates that the axilla is the site of first breast cancer failure in fewer than 1% of patients who have had an axillary dissection. Axillary recurrences occur in approximately 2% of patients with negative nodes or one to three positive nodes and in patients with axillary dissection who received irradiation to the breast only after lumpectomy. Widespread extracapsular extension and gross tumor left behind in the axilla are the only indications for specifically irradiating the dissected axilla. Microscopic extracapsular nodal extension appears to have little effect on the local control rate in the axilla after surgery alone, and can safely be ignored. A clinically negative axilla that is undissected is well controlled by axillary irradiation of 4500 to 5000 cGy. In patients with positive axillary nodes found on axillary dissection, most investigators use a field that irradiates the supraclavicular nodes and the apex of the axilla (level III nodes).

Some institutions prefer to use this field only in patients with four or more positive nodes, whereas other institutions apply it to all axillary-positive patients, and the recent meta-analysis from the Oxford Overview would support the later practice.[183] The Early Breast Cancer Trialists Collaborative Group (EBCTCG; www.ctsu.ox.ac.uk/~ebctcg) compared radiation therapy to none in two patient groups: those with breast conservation therapy (approximately 8,300 women) and those treated with mastectomy (approximately 10,000 women). For all node-positive women, the addition of radiation therapy not only reduced the risk of a local failure, but also reduced mortality at 15 years follow up, by about 5%. Figure 95-32 demonstrates the positive effect of breast or breast and nodal radiation for women on breast cancer study trials.

Elderly Patients

A North American intergroup trial focused on women 70 years of age or older with stage I ER-positive disease, all of whom underwent lumpectomy followed by 5 years of tamoxifen and were randomized to receive radiation therapy or not. Two thirds did not undergo an axillary dissection, and half were 75 years of age or older. With a median follow-up of 0.82 years,there was a statistical difference in local failure rates: 1% of the radiated women versus 69% of the tamoxifen-only women had a recurrence in the ipsilateral breast. However, no differences were found in the rates of mastectomy, distant recurrence, and overall survival.[208]

Partial Breast Irradiation

Despite the excellent results of breast-conserving surgery with whole-breast radiation, a study from the American Colleges of Radiology and Surgeons noted only 42.6% of women in the United States. with stage I and II breast cancer were treated in this manner.[209] The study also demonstrated that 11% of women with breast-conservation surgery never received radiation. Thus, considering ways of making this treatment more available to women who may not live near a center equipped with radiation facilities was addressed in the early 1990s, especially as data from Milan showed that almost all local failures in women treated with "standard" BCT were located in the original quadrant of diagnosis.[210] The concept of "partial accelerated breast irradition" (PBI) was thus proposed and tested. The goals were two-fold: to increase the proportion of women who had access to both the surgery and the radiation, by dramatically shortening the time course of the radiation; and to limit the radiation to the lumpectomy cavity with a small margin of normal tissue. In the United States, two centers, the Ochsner Clinic and William Beaumont Hospital, independently initialized pilot PBI studies using catheter-based brachytherapy and low-dose rate sources. After reports of initial success, the RTOG Cooperative Group opened a phase II trial, allowing either high- or low-dose-rate sources and the catheter technique. The dose used was 3400 cGy, given over 5 days using twice-per-day treatments for the 33 high-dose patients. Results in the 99 patients in the trial, with a median follow-up time of 6.1 years, showed an in-breast failure of 3% for the high-dose-rate group, and 6% for the 33 women in the low-dose-rate group.[211]

Catheter-based PBI is technically demanding. Although most radiation oncologists are not trained to use it, in 2002 the FDA approved a new catheter for deliver of brachytherapy, the MammoSite Radiation Therapy System (Cytyc Surgical Products)

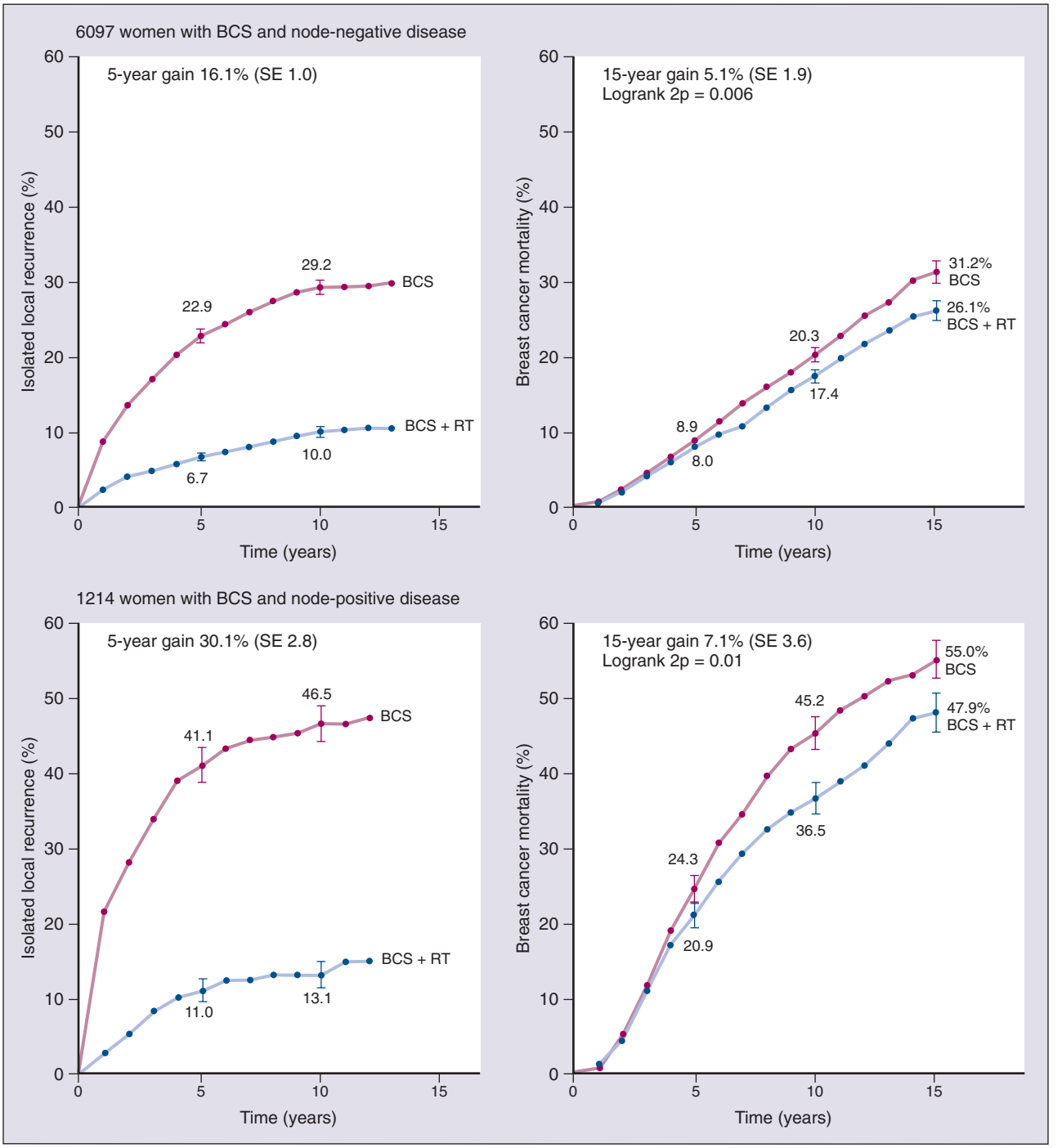


Figure 95-32 • Effect of radiation therapy (RT) after breast cancer study on local recurrence and on breast cancer mortality—15-year probabilities. Data from 10 trials. Vertical lines indicate 1 SE above or below the 5-, 10-, and 15-year percentages. (From Lancet 366:2092.)

Fig. 95-33. This device was easy to insert into the lumpectomy cavity, and rapidly appeared as a treatment in clinical practices. In order to address whether these PBI therapies are equivalent to standard whole-breast external beam radiation, the NSAPB and the RTOG together opened a phase III trial addressing this issue, in 2005. Women are randomized between whole-breast radiation or PBI using the RTOG schedule of twice per day treatments to a total dose of 3400 cGy. The PBI may be given by catheter brachytherapy, the MammoSite device, or an external beam PBI technique.[212] With more than half of the planned 4200 patients accrued by 2007, the PBI technique using the external beam, noninvasive system has proved to dominate the PBI arm. Other researchers have approached the technical issues with PBI by developing intraoperative radiation techniques. The group in Milan is working on a randomized trial using a portable linear accelerator that can be brought into the operating room, and the group at Memorial Sloan-Kettering Cancer Center has devised a special appplicator that uses high-dose-rate afterloading therapy. Both deliver a dose of about 2000 cGy directly to the lumpectomy cavity in the operating room before the surgeon closes the wound.[213]



Figure 95-33 • Elliptical balloons for delivery of brachytherapy to the lumpectomy site (MammoSite; Cytyc Surgical Products).

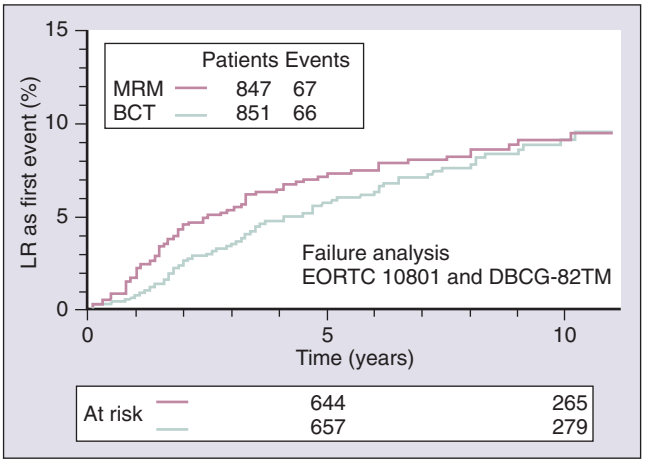


Figure 95-34 • Actuarial time to locoregional recurrence (as a first event) by original treatment group (MRM versus BCT) for the 1677 patients in trials EORTC 10801 and DBCG-82TM. Patients at risk at 5 and 10 years are indicated. BCT, breast-conserving therapy; MRM, modified radical mastectomy. (From van Tienhoven G, Voogd A, Peterse JL, et al: Prognosis after treatment for loco-regional recurrence after mastectomy or breast conservation in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. Eur J Cancer 1999;35:32–38.)

Complications of Treatment

With increasingly sophisticated treatment planning and delivery systems, late complications of lumpectomy and radiation frequently seen 20 years ago are no longer common. Approximately 5% to 20% of patients have measurable arm edema with either lumpectomy or mastectomy, which suggests that the axillary procedure is the key factor in itself. Rib fractures are seen in approximately 2% to 5% of patients treated with radiation; most of these are asymptomatic and detected when a bone scan or chest x-ray is done for other reasons. Therefore, rib fracture should always be included in the differential diagnosis of a previously irradiated patient with breast cancer who has chest wall or rib tenderness and whose bone scan shows an area of tracer uptake in the ribs of the treated chest wall. No specific therapy is indicated, because most of these fractures heal spontaneously.

Approximately 1% or fewer of patients treated with radiation have symptomatic radiation pneumonitis. This complication is more common in patients who have received chemotherapy and radiation that included a supraclavicular field. In almost all patients, pneumonitis resolves either spontaneously or with a short course of corticosteroid therapy, and no long-term sequelae occur. Sometimes, radiation causes scarring in the small rim of lung treated in the tangential fields that can appear as a density in the lung field underlying the treated breast on routine chest x-ray and is confirmed by CT scan showing lung changes confined to the area of high-dose irradiation just underneath the anterior chest wall. Usually, no intervention is needed. Rarely, breast irradiation leads to late cardiac damage.[214] Much of this information comes from treatment of the postmastectomy chest wall, especially when radiation was directed specifically at the internal mammary nodes. Recent studies suggest that few patients have sufficient cardiac volume within the radiation port to place them at risk for later damage and that these patients can be recognized in advance so that such complications may be avoided with sophisticated treatment planning. A supraclavicular portal sometimes results in brachial plexus injury, and the risk appears increased if large daily dose fractions are used.

In rare cases, years later, radiation results in a soft tissue sarcoma within the radiation portal. The incidence of this extremely serious complication is approximately 0.1%. Recent studies have confirmed an increase in the risk of developing an ipsilateral lung cancer in women smokers with breast cancer who opted for lumpectomy with radiation.[215]

Local Recurrences

In most centers, local in-breast failure is managed with mastectomy. Although there are reports of successful treatment either by excision alone, especially for late recurrences, or by excision plus additional local radiation, these techniques are not considered part of standard care. An outstanding study of local recurrences came from pooling two randomized studies from the EORTC 10801 and the Danish study group DBCG-82TM prospective randomized trials comparing breast conservation surgery and radiation with mastectomy. Both therapies were associated with a similar risk of local failure and overall survival following salvage treatment, which in most cases consisted primarily of mastectomy in the conserved group and radiation in the mastectomy group.[216] Figures 95-34 and 95-35 illustrate the data for both BCT and mastectomy patients. There is increased interest in MRI for surveillance after breast conservation, but data are lacking

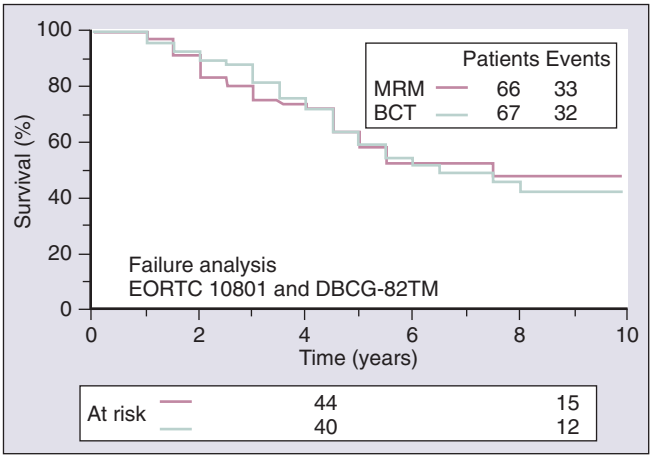


Figure 95-35 • Actuarial overall survival from salvage treatment by original group (MRM or BCT). Patients at risk at 4 and 8 years are indicated. BCT, breast-conserving therapy; MRM, modified radical mastectomy. (From van Tienhoven G, Voogd A, Peterse JL, et al: Prognosis after treatment for loco-regional recurrence after mastectomy or breast conservation in two randomised trials (EORTC 10801 and DBCG-82TM). EORTC Breast Cancer Cooperative Group and the Danish Breast Cancer Cooperative Group. Eur J Cancer 1999;35:32–38.)

on improved outcomes when compared with clinical examination and routine imaging with mammography and ultrasound, as appropriate.[217]

FACTORS THAT AFFECT OUTCOME

Patient Age

Younger patients (e.g., under 35 years of age) have a higher rate of lumpectomy failure (Table 95-14) as well as a higher rate of chest wall failure after mastectomy than do older patients. It is possible that age serves as a surrogate for higher risk tumors as younger women are more likely to have extensive intraductal carcinoma (EIC), high nuclear grade, lymphatic space invasion, and tumor necrosis.[218] It is likely that the recurrence patterns seen in these young women are related to a combination of these adverse histologic features.

Tumor Size

When lumpectomy and the use of radiation are examined as a function of tumor size, there is a dramatic fall-off in the application of breast-sparing therapy for T2 tumors in comparison with smaller T1 tumors. The important factor in the decision should not be tumor size, however, but cosmetic results. Women whose primary tumor size makes it difficult to perform a cosmetically acceptable excision can have their tumor reduced with preoperative chemotherapy and may then become candidates for breast-conserving therapy. In the NSABP B-18 preoperative trial, 67.8% of women in the preoperative arm vs. 59.8% in the postoperative arm underwent breast-conservation therapy, with no difference in survival outcome.[219,220]

Histology

Schnitt and associates in Boston noted that a new histologic pattern within a breast tumor was a strong predictor for subsequent in-breast failure after radiation. They observed a pattern containing intraductal carcinoma present both within and adjacent to the invasive breast cancer lesion, defined as an extensive intraductal component (EIC). DCIS had to be a prominent feature of the invasive cancer, in at least 25% of the tumor area, and no specific amount of DCIS adjacent to the tumor was required. Tumors that were predominantly DCIS with small areas of minimal invasion were classified as EIC-positive and are 4 times as likely to develop local recurrence. This suggested that there might be a greater tumor burden inadvertently left behind at the site of the primary excision in patients with EIC-positive disease. Follow-up studies demonstrated that this negative prognostic effect of the EIC could be overcome with the surgical removal of a larger volume of tissue in this patient subset. In other words, with wider margins, the effect of the EIC was removed.[189]

MASTECTOMY

For many decades, Halsted's radical mastectomy was the treatment of choice for all stages of breast cancer. This operation, which consists on the removal of a large portion of the breast skin, all the breast parenchyma, and the major and minor pectoral muscles en bloc with the axillary lymph nodes, is now limited to locally advanced tumours (T3, T4b) when preoperative chemotherapy is not an option. A less aggressive modified radical mastectomy, with sparing of the pectoralis major muscle, was described by Patey in 1948 and has proved to be equally effective in the local control of most tumors. SLN biopsy has made axillary dissection for staging unnecessary in women with no suspicious palpable lymphadenopathy and negative findings. Total or simple mastectomy with removal of skin, including nipple-areolar complex and all breast tissue without the axillary lymph nodes, has supplanted modified radical mastectomy for this group of node negative patients who require mastectomy.

Reconstruction of the breast is a valid option after mastectomy and can be done immediately or after the procedure (i.e., delayed). With attempts to improve overall cosmesis after mastectomy and breast reconstruction, more "conservative" mastectomy procedures have evolved. Skin-sparing mastectomy, in which removal of the skin is limited to the nipple–areola complex, sometimes with a small portion of the surrounding skin, has come to be accepted as an oncologically safe approach that minimizes deformity and improves cosmesis. The risk of local recurrences after skin-sparing mastectomy and breast reconstruction was compared to that of conventional

Table 95-14 Age as a Factor in Local Breast Cancer Recurrence*

Author	Definition of "Young Age" (yr)	No. Young/No. Recurrences (%)	No. Older/No. Recurrences (%)
Boyages et al.†	≤34	61/15 (25)	722/76 (11)
Delouche et al.‡	≤40	71/14 (20)	339/26 (8)
Forquet et al.§	≤32	35/12 (34)	383/44 (11)
Haffty et al.‖	≤50	135/24 (18)	248/26 (10)
Kurtz¶	≤39	210/41 (20)	1172/106 (9)
Ryoo et al.**	≤40	51/8 (16)	346/18 (5)
Solin et al.††	≤35	88/12 (14)	808/42 (5)
Total		651/126 (19)	4014/338 (8)

*Any locoregional failure.

†Boyages J, Recht A, Connolly I, et al: Factors associated with local recurrences as a first site of failure following the conservation treatment of early breast cancer. Recent Results Cancer Res 1989;115:92.

‡Delouche G, Bachelot F, Premont M, Kurtz JM: Conservation treatment of early breast cancer: long term results and complications. Int J Radiat Oncol Biol Phys 1987;13:29.

§Fourquet A, Campana F, Zafrani, et al: Prognostic factors of breast recurrences in the conservative management of early breast cancer: a 25-year follow-up. Int J Radiat Oncol Biol Phys 1989;17:719.

‖Haffty BG, Fischer D, Rose M, et al: Prognostic factors for local recurrence in the conservatively treated breast cancer patient: a cautious interpretaion of the data. J Clin Oncol 1991;9:997.

¶Kurtz JM, Jacquemier J, Amalric R, et al: Why are local recurrences after breast-conserving therapy more frequent in younger patients? J Clin Oncol 1990;8:591.

**Ryoo MC, Kagan AR, Wollin M, et al: Prognostic factor for recurrence and cosmesis in 393 patients after radiation therapy for early mammary carcinoma. Radiology 1989;172:555.

††Solin LJ, Fowble B, Schultz DJ, Goodman RL: Age as a prognostic factor for patients treated with definitive irradiation for early stage breast cancer. Int J Radiat Oncol Biol Phys 1989;16:373.

mastectomy in some retrospective series showing similar rates of local control, although selection bias may have partially influenced the results.[221] A few retrospective studies with relatively long follow-up reported good results after treatment with nipple-sparing mastectomy, in which only the breast parenchyma is removed without skin or the nipple and areola in selected early-stage breast cancer and high-risk women pursuing mastectomy.[222–224] The ductal tissue below the nipple represents the major oncologic concern in the preservation of the nipple during mastectomy, and complete removal of this tissue may affect the vascularization of the nipple, increasing the probability of necrosis.

Occult nipple involvement ranged from 0% to 50% in several retrospective studies of nipple-sparing mastectomy, in which the pathology blocks of the nipple were reanalyzed, but the percentage has been lower in more recent publications. Careful pathologic examination of the retro-areolar ducts must be performed in nipple-sparing mastectomy. Removal of these structures should be considered the most conservative approach.

In modified radical or total mastectomy, when surgery is performed through incisions other than circumareolar incisions, the incision is placed so that the scar will not be visible when the patient wears a bathing suit or low-cut dress. When elliptical or transverse incisions are used for a total mastectomy, it is ideal to excise any previous biopsy scar as well as the nipple-areolar complex. Skin flaps are carefully developed with a combination of scalpel and electrocautery dissection. The flaps are sufficiently thin to remove all apparent breast tissue, but it is not necessary to remove the subcutaneous tissue of the flaps. This tissue carries the blood vessels to the skin and is of cosmetic importance. Especially in young women, the cleavage plane between breast tissue and subcutaneous tissue may not be evident, and complete removal of the breast tissue is the priority. Depending on the patient's body habitus, the flaps may contain from 1 to 8 mm of subcutaneous fat. In a standard modified radical or total mastectomy, the inferior flap extends inferiorly below the inframammary crease for approximately 2 cm onto the interior fascia of the rectus muscle. If immediate reconstruction is to be performed, the dissection usually ends at the inframammary crease, unless additional breast tissue is present inferiorly to the crease. The superior flap is then dissected similarly, just to beneath the clavicle. The medial extension of the skin flaps reaches the lateral edge of the sternum, and the lateral extension reaches the anterior edge of the latissimus dorsi. In bilateral mastectomy, attention should be paid to not crossing the sternum, creating a tunnel between the two medial flaps, because this may affect the cosmesis of the breast reconstruction. Once the flaps have been developed, the breast is dissected from the chest wall by dissecting the pectoralis major fascia off the muscle superiorly and medially, progressing inferiorly. If total mastectomy is performed and the axilla is not to be dissected, as the breast is dissected from the lateral edge of the pectoralis major muscle, the pectoralis muscle is seen beneath it. The surgeon should spare the medial pectoral nerves, which wrap aound the lateral border of the pectoralis minor muscle and insert into the posterior aspect of the pectoralis major muscle. Division of these nerves leads to atrophy in the central portion of the pectoralis major muscle. If total mastectomy is performed, the dissection may progresses into the axilla above any apparent breast tissue, and sometimes may include some lower axillary lymph nodes, which are present in the axillary tail of Spence. During total or simple mastectomy, no attempt is made to remove the axillary lymph nodes. The breast is then swept inferiorly, with care taken to spare the thoracodorsal and long thoracic nerves in their lower extent as the breast tissue is removed. When the specimen is removed, a suture is used to identify the axillary tail and the retro-areolar ducts in case of nipple-sparing mastectomy so that the pathology department can orient it properly for assessing marginal clearance.

If the axilla is to be dissected, either in continuity or as a separate axillary dissection, the axilla is best entered from within the fascia of the pectoralis major muscle posteriorly. Coming down two fingerbreadths from the uppermost extent of the pectoralis major fascia posteriorly, a transverse incision is made. This incision goes through the pectoralis major fascia and 1 mm beneath it, through the clavipectoral fascia. Fat from the axilla then pops through this division of the clavipectoral fascia. The inferior border of the axillary vein is two fingerbreadths below the highest extent of the pectoralis major fascia. This is important because the lymphatics of the arm pass anterior to the axillary vein. Staying below the axillary vein minimizes the risk of subsequent lymphedema of the arm.

The landmark for the axillary anatomy is the thoracodorsal vein, which is one fingerbreadth out from the chest, 2 cm lateral to the chest wall and passing dorsally into the dorsal inferior aspect of the axillary vein. When it is identified, the thoracodorsal nerve is seen to emerge from behind the axillary vein, just medial to the thoracodorsal vessels. It joins these vessels, continuing onto the anterior surface of the thoracodorsal vein. Between 1 and 2 cm below the axillary vein, the highest branch of the intercostobrachial nerve is seen coming from the chest wall and going to the arm. It is important and usually possible to spare and clear this nerve branch to avoid the dysesthesias associated with its division and total numbness of the inner posterior arm. These technical steps minimize the sensory complications and lymphedema associated with axillary dissection. When the thoracodorsal nerve has been identified, sweeping the axillary fat downward off of the chest wall moves the level II axillary nodes out from behind the pectoralis minor muscle and clears the long thoracic nerve safely. The long thoracic nerve is always found in the same anterior-posterior plane as the thoracodorsal nerve, but is immediately applied to the chest wall. At this point, the three major midaxillary nerves have been identified. If the medial pectoral nerves were not previously identified by sweeping the fatty tissue off of the lateral border of the pectoralis minor muscle, the medial pectoral nerves will not be seen coming around the lateral border of the pectoralis minor and entering the posterior aspect of the pectoralis major. The axillary contents can now be cleared inferiorly, with all of the important nerves and vessels in view. When axillary dissection is complete, the remainder of the breast flap division allows the specimen to be handed off. If the mastectomy was performed through a circumareolar incision, the specimen may be too large to be delivered and a tennis racket incision 1 to 2 cm lateral to the circumareolar incision will allow the specimen to be retracted.

When suspicious palpable lymph nodes are present at level III, removal of these nodes is advised. If possible, the pectoralis minor muscle is preserved. The lateral borders of the pectoralis major and minor muscles are dissected, thereby preserving the medial pectoral nerve. In this way it is possible in nearly every case to dissect the apex without division or removal of the pectoralis minor. Both pectoral muscles are retracted medially to maintain the exposure of the level III region. After incising the surrounding fascia anteriorly to the axillary vein at its junction with the chest wall, just lateral to Halsted's ligament, careful traction in an inferiolateral direction makes the dissection of the specimen from the surrounding structures easily possible. Small branches from the axillary vein and lymphatic vessels usually can be cauterized. For larger blood vessels, clamping and cutting is mandatory.

The content of level III can be removed in continuity with the specimen of levels I and II. For the purpose of the pathohistologic examination, each level should be marked separately with a metallic tag. If division of the tendon, with or without removal of the pectoralis minor muscle, is indicated or unavoidable, dissection ends as soon as the border of the pectoralis major is visualized. The pectoralis minor remains in continuity with the breast and the axillary tissue.

When hemostasis is complete, the plastic surgeon can reconstruct the breast according to the patient's body habitus. For a very small-breasted woman, an expander can be placed beneath the pectoralis major and partially expanded to allow the skin anterior to the muscle to achieve normal tension. For a fuller breast, the latissimus dorsi can

be freed, swung around anteriorly, and joined to the lateral border of the pectoralis major muscle with a prosthesis lying deep to the muscle. This muscle cover provides the reconstructed breast with a very natural feel. For a larger-breasted woman, optimal reconstruction may involve various forms of pedicled or free (myo)cutaneous flaps.

ADJUVANT POSTMASTECTOMY IRRADIATION

At one point, irradiation of the chest wall after mastectomy was almost universally applied in the treatment of breast cancer, largely because of the more advanced nature of breast cancer in the early decades of the 20th century, with an attendant high rate of local chest wall failure. As surgical techniques improved and clinicians began to take a more rigorous scientific look at breast cancer therapy, the need for postoperative chest wall irradiation began to be questioned. Possibly the first randomized prospective clinical trial testing one form of cancer therapy against another was the Manchester, England, trial of immediate versus delayed chest wall irradiation in postmastectomy patients, begun in 1948. Since that time, more than 30 randomized trials of postmastectomy irradiation have been performed. Although chest wall radiation dramatically reduced the risk of subsequent chest wall recurrence and decreased the chance of dying of breast cancer, the overall survival rate in irradiated women remained unchanged, without the addition of systemic therapy. As systemic therapy improved, postmastectomy radiation was prescribed only in very locally advanced cases (Box 95-1).

However, two recent randomized trials of postmastectomy radiation versus none, with all women in the study receiving systemic CMF chemotherapy, did show a survival advantage for the addition of radiation in premenopausal women with 1 to 3 positive nodes, the trial target population.[225,226] With this new outcomes information, the added value of postmastectomy radiation, in addition to systemic therapy, became a controversial topic, with questions such as "Which patients are at highest risk for local failure?" and "What anatomic areas should be targeted for treatment?"

To address these issues, a guideline panel from the American Society of Clinical Oncology (ASCO) recommended postmastectomy radiation for patients with four or more involved nodes, and suggested the treatment for those with T3 tumors as well. However, it concluded that there was insufficent evidence to make a formal recommendation in the subsets of one to three involved nodes, women with reconstruction, and the use of internal mammary node radiation as part of the target volume.[227] The 2000 EBCTCG overview analyzed almost 10,000 women on trials of postmastectomy radiation (Fig. 95-36) and showed significant improvement of both local control and survival at 15 years in all groups, except node-negative women treated with mastectomy.[228]

Box 95-1. INDICATIONS FOR POSTMASTECTOMY RADIATION

Tumor >5 cm
T4 tumor
Involvement of 4 or more axillary lymph nodes
Gross extracapsular nodal disease
Residual disease after mastectomy

Additional Considerations

Involvement of 1 to 3 axillary lymph nodes
Gross multifocality
Extension into the nipple or skin

PREDICTIVE AND PROGNOSTIC FACTORS FOR INVASIVE DISEASE

Although it is possible to describe the average risk of recurrence and potential benefit offered by systemic therapy for a population of patients using clinical nomograms like Adjuvant! Online,[229,230] this exercise is difficult in an individual patient. A pure prognostic factor like TNM predicts patient outcome in the absence of therapy while a pure predictive factor predicts the likelihood of response to a specific therapy. HER2 and ER are examples of moderate prognostic factors with a strong predictive utility in predicting response to specific therapies that can help to individualize treatment recommendations for women with early stage breast cancer[75,184] at high risk for recurrence. Unfortunately, even commonly used markers such as ER/PR and HER2 suffer from lack of assay standardization and reproducibility, and many assays have not been properly validated (Table 95-15).[231] Other commonly used prognostic markers include tumor grade, lymphatic or vascular invasion, and specific histologies like mucinous and tubular cancers. Bone marrow micrometastases appears to be of prognostic significance, but assays lack standardization, while circulating tumor cells do not have sufficient sensitivity at present for use in the adjuvant setting.[232]

Women whose tumors overexpress or amplify the HER2 receptor may be less likely to respond to endocrine manipulations with tamoxifen or aromatase inhibitors. These women may consider the addition of adjuvant chemotherapy, even if their tumors do not exceed 1 cm

Table 95-15 Criteria for Evaluating Clinically Useful Tumor Markers

IDENTIFICATION OF A POTENTIAL MARKER
What is the distribution of the marker in normal and abnormal tissues?
What is the prevalence of the marker in the patient population of interest?
What is the source of specimens examined? Institutional or cooperative group tissue or serum banks?
Does the marker appear to predict outcome (prognostic factor) or response to therapy (predictive factor)?
DEVELOPMENT AND VALIDATION OF A CLINICAL ASSAY
Has the assay target that best correlates with the intended marker objective been identified (e.g., gene amplification, protein expression)?
Has the optimal specimen source for the assay been identified (e.g., paraffin block, fresh tumor tissue, peripheral blood, urine)?
Have the conditions of the assay been optimized and standardized? Has its reproducibility in other labs been tested?
Has a standardized and cross-validated scoring system been developed?
Have the sensitivity and specificity of the assay been validated against a gold standard?
VALIDATION OF THE CLINICAL USEFULNESS OF THE MARKER
Has this marker been validated in a patient population other than the one used to develop the predictive and prognostic model?
Does the presence of the marker discriminate between patient subsets according to the outcome of interest?
Is the prognostic or predictive information provided by the marker independent of other established markers?
Has a prospective randomized trial using the proposed marker been performed using the information provided by the assay to stratify patients according to risk or to select planned therapy?

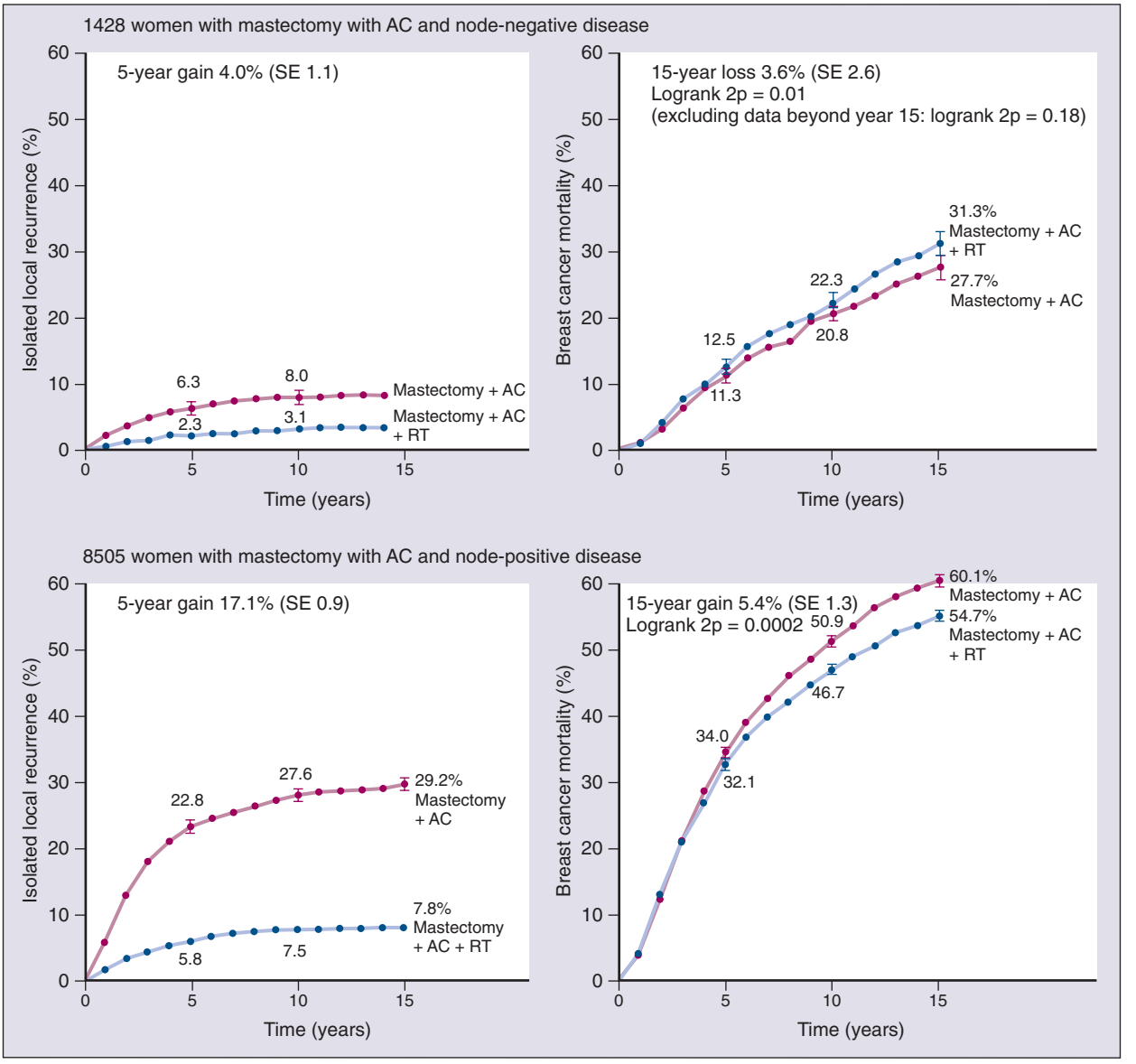


Figure 95-36 • Effect of radiation therapy (RT) after mastectomy and axillary clearance AC on local recurrence and on breast cancer mortality—15-year probabilities. Data from 25 trials. Vertical lines indicate 1 SE above or below the 5-,10-, and 15-year percentages. (From Lancet 366:2092.)

and carry ER or PR, although the adjuvant role of trastuzumab has not been tested in these small tumors. HER2 overexpression also identifies patients in the adjuvant[78,79,233] and metastatic[234] settings who might benefit from trastuzumab therapy. Many other individual prognostic or predictive factors are under investigation. Levels of urokinase-type plasminogen activator and its inhibitor PAI-1 had strong prognostic value in women with node-negative breast cancer who did not receive adjuvant systemic therapy and had more than 10 years of follow-up.[235]

In addition to individual factors, powerful emerging technologies, such as proteomics or gene arrays, hold the potential to identify patterns of expression of genes or proteins at baseline or in response to therapy that may have prognostic or predictive value, and to assist in treatment decision-making for individual women.[94,100,101,236] Initial studies with array-based expression profiling showed the ability of the technology to classify breast cancer according to five gene clusters: luminal subtype A, luminal subtype B, HER2-positive, basal, and normal breast-like subtypes (see Fig. 95-2) and that BRCA-1 genotype predisposes to the basal tumor subtype.[97] The ER-positive group was characterized by high expression of many genes expressed by breast luminal cells, and the ER-negative group showed gene expression characteristic of basal epithelial cells. However, a third group showed genes related to HER2 overexpression, suggesting that this molecular characteristic may have equal or greater weight than ER expression in subclassifying breast cancers. Finally, a small group of breast cancers cluster with normal breast epithelium and are referred to as *normal breast-like.* These distinct subtypes of breast tumors, described as *basal-like, ERBB2 (HER2), luminal A, luminal B,* and *normal breast-like,* show distinctive molecular signatures and appear to represent diverse biologic entities associated with distinct clinical outcome, and the comparison of several independently developed gene signatures appears to show similar prognostic information suggesting the existence of a common set of biologic phenotypes.[104] These patterns of gene expression appear to provide more specific information than identification of a single gene with a specific effect.

By late 2007, three gene expression profiles were available for commercial testing in the United States: the Oncotype DX (Genomic Health, Inc.) assay for women with ER-positive lymph node-negative disease based on a 21-gene profile developed by Paik and coworkers[102,103]; the MammaPrint (Agendia) assay based on a 70-gene prognostic signature developed by van't Veer and colleagues[100,101,237]; and the Breast Cancer Profiling (BCP) assay (AviaraDx) based on the two-gene ratio signature developed by Ma and associates.[238,239] Retrospective studies showed that the Oncotype DX assay has prognostic utility and identifies which patients who are lymph node-negative and ER-positive will do well or not (low vs. high recurrence score [RS], respectively). Of greater importance, this assay also has predictive utility in determining in a similar group of patients who will benefit from the addition of a non-anthracycline regimen to tamoxifen and who will not (high vs. low RS, respectively). The Oncotype DX also has been shown to predict the likelihood of response to preoperative systemic chemotherapy.[240] However, several questions remain about the utility of these various assays,[241] and ongoing trials will prospectively confirm and test, respectively, the clinical utility of the Oncotype DX (TAILORx trial, see http://www.cancer.gov/clinicaltrials/digestpage/TAILORx) and MammaPrint (MINDACT trial, see http://www.breastinternationalgroup.org/TransBIG/Mindact.aspx) as a sole determinant of therapy selection. Gene expression profiles with predictive utility such as the Oncotype DX[103] can help individualize the therapy benefit in a very specific subset of patients with ER-positive, lymph node-negative disease. Preliminary data presented at the San Antonio Breast Cancer Symposium in the fall of 2007 (see www.sabcs.org) suggest that the Oncotype DX assay also may help identify among postmenopausal women with ER-positive, lymph node-positive disease those who would benefit from the addition of anthracycline-based chemotherapy to tamoxifen.

ADJUVANT SYSTEMIC THERAPY

While adjuvant systemic therapy significantly reduces the odds of recurrence and death, mammography screening and earlier diagnosis are responsible for at least half of the breast mortality reduction observed between 1990 and 2003,[242] suggesting that the ability of tumors to metastasize may be acquired over time and would counter the prevailing so-called *systemic theory.*[182] Large databases also indicate that the 5-year survival rate in women with small endocrine-responsive tumors is not likely to be affected by their disease, and chemotherapy offers minimal potential benefit,[243] although data from the NSABP suggest improvements in both recurrence-free and overall survival in women with ER-positive and ER-negative tumors no more than 1 cm in size.[244] These uncertainties are due to the modest treatment benefits obtained with available systemic therapies on average and the considerable heterogeneity observed in breast cancer even when considering tumors with similar profile using standard pathologic parameters (e.g., tumor size, nodal status, and ER/PR expression). While systematic reviews and computerized nomograms have been quite useful to demonstrate the average benefit for specific patient subgroups, especially when the absolute benefit is otherwise small, these efforts fail to recognize this individual variability.

It is now understood that the small to modest therapeutic effects noted in individual clinical studies are of great value if applied to the large population of women with breast cancer. Since 1985, the EBCTCG (see www.ctsu.ox.ac.uk/~ebctcg) has performed, at 5-year intervals, an ongoing combined analysis, or meta-analysis, of all available randomized trials to detect whether a specific treatment modality used for patients with operable breast cancer had an effect on overall survival and to determine the magnitude of this effect.[228] General conclusions can be reasonably drawn about the effectiveness of various adjuvant systemic therapies. A significant survival advantage after polychemotherapy was unequivocally shown in all adequately studied age categories. However, the magnitude of benefit appears to be less in older women. Likewise, chemotherapy has been effective in patients with node-negative or node-positive disease. Polychemotherapy is superior to monochemotherapy, and chemotherapy administered for 12 months or longer has not been associated with greater benefit than shorter duration of treatment (e.g., 6 months). Increasing evidence indicates additional benefit of combining chemotherapy and tamoxifen in receptor-positive patients, and anthracycline-containing regimens appear to have greater effects on recurrence and survival than standard CMF regimens.

The Oxford Overview also shows that adjuvant tamoxifen improves survival, irrespective of age or menopausal status. The hormone-receptor status of the primary tumor is the strongest predictor of the magnitude of the treatment benefit of tamoxifen. In contrast to chemotherapy, more prolonged administration of tamoxifen (i.e., 5 years) provides greater benefit than a single year of administration. Some studies show no additional benefit when tamoxifen is continued beyond 5 years, which is now the standard in most centers, but this question has not been fully resolved. Ovarian function suppression reduces mortality rate in women younger than 50 years of age when compared with no therapy and is similar to the benefit offered by CMF-based chemotherapy, but its additive role after chemotherapy, in addition to tamoxifen, and its use with aromatase inhibitors are now the subject of large international clinical trials started in 2003 and led by the International Breast Cancer Study Group (IBCSG).

However, it is now accepted that breast cancer is a heterogeneous disease. Decisions about whether to consider adjuvant systemic therapy should first take into account the tumor phenotype according to predictive markers of response that help select therapy (e.g., ER, PR, and HER2) and provide estimates of relative risk reduction, followed then by traditional prognostic markers of risk (e.g., tumor size, node involvement, and grade) to help estimate the actual absolute risk reduction benefit, and finally the assessment of existing comorbidities that may affect toxicity risks. Approximately 70% of newly diagnosed breast cancers express ER and/or PR, and one fifth overexpress HER2 (half of them [10% of the total] are ER/PR negative), while the remaining 15% to 20% express none of them (the so-called *triple negative phenotype*). Published data from 2000 systematic reviews by the EBCTCG suggest a reduction in mortality in patients with ER-positive disease through the next 15 years of 38% (age < 50 years) and 20% (age 50–69 years) with chemotherapy, and an additional reduction of 31% of the residual risk with tamoxifen, thereby approaching a final mortality reduction that ranges from 57% to 45%, respectively.[228] However, it is important for clinicians to recall that the overview results provide information about predicted outcomes for populations, but do not provide insight into the distribution of benefit among individual patients. Breast cancer patients traditionally have overestimated the absolute value of systemic therapy, and a common misinterpretation is that the treatment benefit is shared among patients, with most having some benefit, and it is important to consider the estimated individual risk, comorbidity, and personal patient preferences when discussing the potential benefits of adjuvant systemic therapy.

Quantitative tools like Adjuvant! Online (www.adjuvantonline.com) were developed to help patients and health care providers estimate the potential actual benefit from adjuvant systemic therapy,[229,230] although estimates of benefit from adjuvant trastuzumab have not yet been included in this model. Clinical practice guidelines often are used, such as those from the National Comprehensive Cancer Network in the United States (available at www.nccn.org/professionals/physician_gls/default.asp).[154] Another good example comes from the St. Gallen International Expert Consensus Panel Meeting (Tables 95-16 and 95-17).[245]

The fourth cycle of the Oxford Overview 2000 published in 2005 included approximately 150,000 patients in 194 unconfounded randomized clinical trials of adjuvant chemotherapy or endocrine therapy started by 1995.[228] These were trials of CMF, FAC or FEC chemotherapy, and tamoxifen or ovarian suppression as endocrine

Table 95-16 St. Gallen International Experts Consensus Meeting 2007 Definition of Risks for Patients with Operable Breast Cancer

	LOW	INTERMEDIATE		HIGH	
	NEGATIVE	NEGATIVE	POSITIVE (1–3 LNS)	POSITIVE (1–3 LNS)	POSITIVE (≥4 LNS)
Node Status	**Plus All Factors**	**Plus Any Factor**	**Plus All Factors**	**Plus All Factors**	
Path T size	≤2 cm	>2 cm			
Grade	1	3-Feb			
Vascular invasion	No	Yes			
ER/PR	Positive	Negative/negative	Positive	Negative/negative	
HER2	Negative	Positive	Negative	Positive	
Age (yr)	≥35	<35			

ER, estrogen receptor; LN, lymph node; PR, progesterone receptor.

Adapted from Goldhirsch A, Wood W, Gelber R, et al: Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 2007;18:1133–1144.

therapy. In that cycle, there were no trials of taxanes, trastuzumab, raloxifene, or third-generation aromatase inhibitors. In practice, the fourth cycle consisted of seven separate systematic reviews on anthracycline-based versus no chemotherapy (8,000 patients); CMF-based versus no chemotherapy (14,000 patients); anthracycline-based versus CMF (14,000 patients); tamoxifen for 5 years versus none (15,000 patients); tamoxifen for 1 to 2 years versus none (33,000 patients); tamoxifen for 5 years versus 1 to 2 years (18,000 patients); and ovarian suppression versus none (8,000 patients). Now in its fifth cycle of data analyses (started in 2005–2006), the Oxford EBCTCG Overview represents over 25 years of an international collaboration that has revolutionized adjuvant breast cancer therapy by offering reliable assessment of moderate differences affecting long-term survival. By 2006 the EBCTCG secretariat had received data from over 660,000 patients enrolled in over 820 trials. Table 95-18 describes the 15-year breast cancer mortality and proportional effects of chemotherapy alone (in ER-poor and ER-positive disease) and of endocrine therapy with or without chemotherapy (in ER-positive disease).[228]

Adjuvant Chemotherapy

Combination regimens are considered standard practice (including sequential regimens) over single-agent regimens, and the EBCTCG Overview also has confirmed the improved recurrence and survival outcome observed with anthracycline-based regimens.[228] However, the magnitude of this survival benefit is modest, and the numbers needed to treat are potentially high, on average. In view of the potential toxicities and costs, the actual absolute benefit offered by individual therapies must be considered. As such, predictive factors of benefit (e.g., hormone receptor and HER2 status) and prognostic factors of risk (e.g., size, node status, and grade) must be discussed with each patient along with preferences and comorbidities as part of a shared decision model. More intensive combination regimens, usually with an anthracycline and often including a taxane, are expected to offer higher benefit in patients with more chemoresponsive disease (e.g., hormone receptor-negative) but also are associated with greater toxicity risks, short- and long-term. Patients with lower-risk disease often are offered potentially more tolerable regimens such as CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) or AC (doxorubicin plus cyclophosphamide), and sometimes just endocrine therapy if they are lymph node-negative and strongly ER-positive (especially if postmenopausal).[246] Examples of commonly used adjuvant chemotherapy regimens are listed in Table 95-19.

Gene expression profiling with Oncotype DX was validated retrospectively as a tool to identify the predictive benefit from adding chemotherapy to endocrine therapy in women with ER-positive, node-negative disease. Patients with strong ER-positive, low-grade tumors and low-risk histologies such as lobular cancer are likely to have a low recurrence score (low risk of recurrence when treated with tamoxifen and minimal/no benefit from chemotherapy). On the other hand, patients with tumors that are higher-grade and have weaker ER expression are more likely to have a high recurrence score (especially if HER2 is overexpressed). The main use of predictive assays like Oncotype DX appears to be in clinical situations where chemotherapy is being considered and the tumor phenotypes appear less conclusive. Approximately 30% of patients ultimately may be found to have an intermediate recurrence score. This patient subset is now the subject of a prospective randomized trial comparing endocrine therapy with or without chemotherapy (the TailoRx trial).

Not all anthracycline regimens are the same—improved outcomes over CMF were observed with anthracycline regimens containing three drugs (with 5-fluorouracil and methotrexate) for six cycles or with sequential use of anthracyclines and CMF,[247] but not with

Table 95-17 Selection of Treatment Modalities According to St. Gallen International Experts Consensus Meeting 2007

	Highly Endocrine Responsive	Incompletely Endocrine Responsive	Endocrine Unresponsive
HER2 neg	Endocrine therapy (consider adding chemotherapy according to risk)	Endocrine therapy (consider adding chemotherapy according to risk)	Chemotherapy
HER2 pos	Endocrine therapy + trastuzumab + chemotherapy	Endocrine therapy + trastuzumab + chemotherapy	Trastuzumab + chemotherapy

Adapted from Goldhirsch A, Wood W, Gelber R, et al: Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 2007;18:1133–1144.

Table 95-18

Systemic Adjuvant Treatment and Age at Diagnosis (yr)	Proportional Effect on Annual Breast Cancer Mortality Rate (Treatment vs Control)		15-Year Breast Cancer Mortality with Treatment (Risk [%] and Absolute Gain) versus Corresponding Risk without Treatment (M)					
			M = 12.5 (e.g., Low-Risk Node-Negative)		M = 25 (e.g., Node-Negative)		M = 50 (e.g., Node-Positive)	
	Ratio of Rates (R)	Proportional Reduction	Risk	Gain	Risk	Gain	Risk	Gain
Chemotherapy only in ER-poor or ER-positive disease*								
None (any age)	1.0	—	12.5	—	25.0	—	50.0	—
Anthracycline (age < 50 yr)	0.62	38%	7.9	4.6	16.3	8.7	34.9	15.1
Anthracycline (50–69 yr)	0.80	20%	10.1	2.4	20.6	4.4	42.6	7.4
Anthracycline (≥70 yr)	?	?	?	?	?	?	?	?
Endocrine, or chemoendocrine, therapy in ER-positive disease*								
None (any age)	1.0	—	12.5	—	25.0	—	50.0	—
Tamoxifen (any age)	0.69	31%	8.8	3.7	18.0	7.0	38.0	12.0
Anthracycline + tamoxifen (age < 50 yr)	0.62 × 0.69	57%	5.6	6.9	11.6	13.4	25.7	24.3
Anthracycline + tamoxifen (50–69 yr)	0.80 × 0.69	45%	7.1	5.4	14.7	10.3	31.8	18.2
Anthracycline + tamoxifen (≥70 yr)	? × 0.69	?	?	?	?	?	?	?

ER, estrogen receptor; FAC, fluorouracil, doxorubicin (Adriamycin), and cyclophosphamide; FEC, 5-fluorouracil, epirubicin, and cyclophosphamide.

Anthracycline: about 6 months of anthracycline-based adjuvant chemotherapy with regimens such as FAC or FEC, as in the reviewed trials.

Tamoxifen: about 5 years of adjuvant tamoxifen. The 15-year survival probability with treatment is calculated as (1 – M/100) to the power R. The webappendix 1 (appendix to table 4) gives the 15-year prognosis of untreated control patients, subdivided by ER and nodal status.

*For women of given nodal status the 5-year mortality is greater for ER-poor than for ER-positive disease, but the 15-year risks may be similar, as may the 15-year benefits of anthracycline-based chemotherapy (since the age-specific breast cancer mortality ratios for anthracycline-based vs no chemotherapy do not depend significantly on ER status). Combination of the direct and indirect randomised evidence yields breast cancer death rate ratios (treatment vs control) of 0.62 (SE 0.05) at younger than 50 years and 0.80 (SE 0.04) at age 50–69 years for allocation to anthracycline and 0.69 (SE 0.03) for allocation to tamoxifen. (Allowance for any inappropriate noncompliance with the treatment allocations in these trails would, in expectation, further reduce breast cancer mortality.)

From Early Breast Cancer Trialists' Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:2005;1687–1717.

short-duration regimens like four cycles of AC. Topoisomerase II gene alterations have been shown in various studies to predict for anthracycline benefit.[248] However, it is of interest that these studies included patients regardless of *HER2* gene expression status (also located on chromosome 17). This raises the question of whether anthracycline regimens also would be useful in patients with HER2-negative disease, because most patients with HER2-positive breast cancer larger than 1 cm will most likely be treated with a trastuzumab-based regimen.

Various taxane regimens have now been prospectively tested in high-risk node-negative (if ER-negative) and node-positive disease. Examples include AC followed by paclitaxel for a total of eight cycles (every 3 weeks or every 2 weeks in a dose-dense fashion)[249] and TAC with docetaxel for 6 cycles.[250] Abstract data from Intergroup trial E1199 suggest a potential survival benefit for weekly paclitaxel following AC over other forms of taxane schedules and drugs, which confirms previous pathologic response observations in the preoperative setting.[251] However, abstract data from trial ECOG 2197 showed no survival benefit over AC with just four cycles of AT (with docetaxel). Taxane regimens given as a three-drug combination or in a sequential dose-dense fashion require the use of colony-stimulating factor support to minimize risk of febrile neutropenia.[252] It is worth noting that the administration of taxane-containing regimens in lymph node-positive, early-stage breast cancer appears to be particularly useful in those with hormone receptor-negative[253] and HER2-negative[254] disease. However, it is important to note that these recent analyses were retrospective in nature. Along these lines, the Oxford Overview does not identify a preferential benefit from chemotherapy in ER-negative disease in its most recent published analysis of trials that did not include taxanes.[228]

HER2 Status

HER2 is amplified in approximately 18% to 20% of breast cancers,[75] and amplification is the primary mechanism of HER2 overexpression with abnormally high levels of a 185-kd glycoprotein with tyrosine kinase activity found in these tumors. HER2 overexpression is a poor prognostic marker and is associated with worse clinical outcomes in patients with breast cancer.[255] HER2 status also is predictive for several systemic therapies and affords relative, but not absolute, resistance to endocrine therapies in general.[32] HER2 status appears to be associated with relative, but not absolute, lower benefit from non-anthracycline, non-taxane-containing chemotherapy regimens.[256] On the other hand, retrospective data from prospectively conducted randomized clinical trials appear more definitive in suggesting that HER2-positive status is associated with response to anthracycline therapy, even though this effect may be secondary to co-amplification of HER2 with topoisomerase II, which is the direct target for anthracyclines.[257–259] Retrospective data from trial Cancer and Leukemia Group B (CALGB) 9344[260] suggest that HER2 overexpression is associated with a benefit from the addition of paclitaxel to an anthracycline-based adjuvant regimen in node-positive breast cancer, regardless of estrogen-receptor status.[254] At the same time, those with ER-positive, HER2-negative disease may gain little benefit from the addition of paclitaxel to AC, although these data require further confirmation.

Table 95-19 Examples of Commonly Used Chemotherapy Regimens in the Adjuvant Setting

NON-TRASTUZUMAB-BASED REGIMENS

FAC/CAF (fluorouracil/doxorubicin/cyclophosphamide) or FEC/CEF (cyclophosphamide/epirubicin/fluorouracil)

AC (doxorubicin/cyclophosphamide) ± sequential paclitaxel

EC (epirubicin/cyclophosphamide)

TAC (docetaxel/doxorubicin/cyclophosphamide)

A → CMF (doxorubicin followed by cyclophosphamide/methotrexate/fluorouracil)

E → CMF (epirubicin followed by cyclophosphamide/methotrexate/fluorouracil)

CMF (cyclophosphamide/methotrexate/fluorouracil)

AC × 4 (doxorubicin/cyclophosphamide) + sequential paclitaxel × 4, every-2-weekly regimen with filgrastim support

A → T → C (doxorubicin followed by paclitaxel followed by cyclophosphamide) every-2-weekly regimen with filgrastim support

FEC → T (fluorouracil/epirubicin/cyclophosphamide followed by docetaxel)

TRASTUZUMAB-BASED REGIMENS

Preferred adjuvant regimen

- AC → T + concurrent trastuzumab (doxorubicin/cyclophosphamide followed by paclitaxel plus trastuzumab)

Other adjuvant regimens

- Docetaxel + trastuzumab → FEC
- TCH (docetaxel, carboplatin, trastuzumab)
- Chemotherapy followed sequentially by trastuzumab
- AC → docetaxel + trastuzumab

Neoadjuvant

- T + trastuzumab → CEF + trastuzumab (paclitaxel plus trastuzumab followed by cyclophosphamide/epirubicin/fluorouracil plus trastuzumab)

Adapted from NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. V.2.2008; www.nccn.org/professionals/physician_gls/PDF/breast.pdf

Perhaps most importantly, several studies have now shown that anti-HER2 therapy is effective in the adjuvant setting. (See Table 95-20 for study characteristics.) Five international, prospective randomized clinical trials have demonstrated that adjuvant trastuzumab reduces the risk of recurrence and mortality by one half and one third, respectively, in patients with early-stage breast cancer.[78,79,233,261] (See Table 95-21 for efficacy results of adjuvant trials of trastuzumab.) Based on its approval in the metastatic setting,[262] the small molecule, dual tyrosine kinase inhibitor lapatinib is now being tested with and against trastuzumab in the adjuvant setting in patients with HER2-positive, lymph node-positive disease. Trastuzumab therapy is associated with a small risk of cardiac toxicity, especially among older patients and those exposed to an anthracycline.[263] In the adjuvant setting, the risk of severe congestive heart failure may achieve 4%, approximately 14% of patients are unable to complete a full 1-year course of trastuzumab, and concerns have been raised about the actual reversibility of the cardiotoxicity of trastuzumab (Table 95-22).[264,265]

Many believe that trastuzumab optimally should be administered with chemotherapy. A commonly used regimen in the United States consists of AC followed by paclitaxel/trastuzumab, followed by trastuzumab to complete a year of therapy.[79] Non-anthracycline, trastuzumab-based regimens (e.g., TCH with a platinum drug and docetaxel) often are considered and are a reasonable alternative for those interested in minimizing the cardiotoxicity risk of trastuzumab. Optimal duration of therapy also remains unclear. Short exposure to trastuzumab in combination regimens for just 9 weeks (e.g., FinHER trial[233]) and trastuzumab given as a single agent for 1 or 2 years after all chemotherapy is completed (e.g., the HERA trial[78]) have been shown to lead to an improvement in overall survival.

These results confirm that that HER2 is a useful marker for decision making for patients with breast cancer, emphasize the importance of evaluating the assay accurately, and justify defining the HER2 status in the invasive tumor component in all patients with a new diagnosis of invasive breast cancer. The significant benefits coupled with the high cost and potential cardiotoxicity of trastuzumab require accurate HER2 testing. Predictive assay markers are unique in that they serve as the sole determinant of therapy selection, and both false-positive and false-negative results are unacceptable if they expose some patients to an uneccessary and toxic placebo and deny others therapy with a potentially useful drug, respectively. Excessive testing inacurracy was a problem observed early on with HER2 testing,[266,267] which ultimately led to a collaboration between the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) that resulted in the establishment of testing guidelines for HER2 testing in breast cancer.[75] Data presented at the 2007 annual meeting of ASCO suggested that other HER2 subsets may derive benefit from trastuzumab, but those hypothesis-generating findings must now be further tested. In the meantime, accurate measurement of HER2 status is critical. Available data in 2007 indicate that patients with tumors showing either IHC 3+ or FISH amplification, and who would have qualified for the adjuvant randomized trials thus far reported, should be considered candidates for anti-HER2 therapy.

Adjuvant Endocrine Therapy

Breast cancer often is an estrogen-dependent disease, and endocrine therapy offers the most favorable risk-benefit ratio among existing systemic therapy options. Surgical hormonal manipulation (e.g., oophorectomy, adrenalectomy, and hypophysectomy) in metastatic disease, considered the first example of targeted antitumor therapy, has largely been supplanted by pharmacologic approaches with selective estrogen receptor modulators such as tamoxifen, aromatase inhibitors, and pure antiestrogens such as Faslodex (AstraZeneca). Tamoxifen is the standard agent for premenopausal women in the adjuvant setting,[228] and recent data suggest an increasing role for aromatase inhibitors in postmenopausal women.[268] Ovarian function suppression (OFS) also is a reasonable alternative to CMF-based chemotherapy, and ongoing studies are examining its role after chemotherapy in premenopausal women with hormone receptor-positive disease who also will be treated with an oral antiestrogen.

Tamoxifen

SERMs may function as estrogen-receptor agonists, antagonists, or mixed agonist-antagonists, depending on the target tissue. Major examples include triphenylethylene derivatives (e.g., tamoxifen), nonsteroidal antiestrogens (e.g., the benzothiophene raloxifene), and steroidal antiestrogens (e.g., fulvestrant). Tamoxifen is the SERM with the longest track record in breast cancer and is approved in the United States for risk reduction in high-risk women, for reduction in the risk of invasive breast cancer after breast conservation in women with DCIS, in the adjuvant treatment of hormone-receptor-positive disease, and in the management of advanced disease. Because of potentially undesirable effects in the uterus, vagina, and central nervous system, other SERMs have been evaluated in the laboratory and in the clinic, aiming for greater efficacy

Table 95-20 Adjuvant Trastuzumab Trials: Designs and Patient Characteristics

	HERA	Combined Populations B31 // N9831	BCIRG 006	Finnish Trial
Accrual/patients included	5090/3387	2043/1736 // 2766/1615	3222/3222	232/232
Median follow-up (mo)	12	24	23	36
Treatment regimens	Any accepted CT regimen, H 1 year after completion of CT, H 2 years after completion of CT (not included in analysis)	AC × 4 → P × 4 AC × 4 → P × 4 + H Note: P given 3 weekly AC × 4 → P × 12 AC × 4 → P × 12 + H starting concurrently with P AC × 4 → P × 12 + H starting after P (not included in analysis) Note: P given weekly	AC × 4 → D × 4 AC × 4 → D × 4 + H starting concurrently with D DC† × 6 + H Note: D given 3 weekly	V weekly × 8 or D 3 weekly × 3 with or without concomitant H weekly × 9 → then FEC 3 weekly × 3
Trastuzumab schedule	Every 3 weeks	Weekly/weekly	Weekly with CT, then every 3 weeks	Weekly
Primary endpoints	DFS	OS/DFS (DFS for combined analyses)	DFS	RFS
HER2 testing	Centralized IHC ± FISH	IHC a/o FISH in "approved" laboratories	Centralized FISH	Centralized CISH
Age < 50 years (% with)	51	51	52	NA
Node-negative disease (% with)	32*	5.7	29†	16‡
Grade 3 tumors (% with)	60	69	NA	65
Taxane-based chemotherapy (% with)	26	100	100	50
Planned endocrine therapy (% with)	46	52	54	NA
Normal cardiac function	At completion of locoregional therapy and chemotherapy	At completion of AC × 4	After surgery	After surgery
Participating countries (*N*)	39	1	40	1

A, adriamycin; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; Cb, carboplatin; CISH, chromogenic in situ hybridization; CT, chemotherapy; D, docetaxel; DFS, disease-free survival; E, epiadriamycin; F, 5-fluorouracil; FISH, fluorescence in situ hybridization; H, Herceptin (trastuzumab); HERA, Herceptin Adjuvant study; HR, hazard ratio; IHC, immunohistochemistry; NA, not available; OS, overall survival; P, paclitaxel; RFS, relapse-free survival; T, transtuzumab; V, vinorelbine.

*Only if tumor size >1 cm.

†Only if other concomitant risk factors (grade > 1, hormone receptors lacking).

‡Only if size >20 mm and PgR negative.

Adapted from Piccart-Gebhart MJ: Adjuvant trastuzumab therapy for HER2-overexpressing breast cancer: what we know and what we still need to learn. Eur J Cancer 2006;42:1715–1719.

and lower toxicity,[269] but they have not been approved in the adjuvant setting.

Tamoxifen is associated with an increase in bone mineral density in the axial skeleton and with stabilization in the appendicular skeleton in postmenopausal women. While it leads to bone mineral loss in the lumbar spine and hip in premenopausal women, the NSABP P-01 study showed a reduction (relative risk, 0.81; 95% CI, 0.63 to 1.05) in fractures of the hip, radius, and spine in all age groups, especially among those 50 years of age and older.[270] Data from the 2005 EBCTCG showed that 5 years of adjuvant tamoxifen for ER-positive disease reduced the annual breast cancer death rate by 31% regardless of age or chemotherapy use. Duration of tamoxifen (5 years versus 2 years) is important, and the annual breast cancer mortality rates are similar during years 0 to 4 and 5 to 14, with a cumulative reduction in mortality twice as large at 15 years as after 5 years since diagnosis.[228] Duration of adjuvant tamoxifen is limited to 5 years,[271,272] but two large, ongoing international trials (Adjuvant Tamoxifen Long vs. Short [ATLAS] and Adjuvant Tamoxifen Treatment, Offer More? [aTTom]) may help to answer this question. Host factors such as polymorphisms of the P450 *CYP2D6* gene may identify patients who are poor metabolizers (*4/*4 genotype variant) and have reduced levels of the active tamoxifen metabolite endoxifen,[273] but the clinical utility of this information is not fully settled, other than perhaps to identify patients who should avoid use of potent CYP2D6 inhibitors, including some of the selective serotonin reuptake inhibitors commonly used as antidepressants.

Ovarian Function Suppression

Adjuvant endocrine therapy arguably is the most effective targeted therapy in women with early-stage, ER-positive breast cancer, regardless of age or nodal status. Although breast cancer is primarily a disease of older women, up to 25% of all patients newly diagnosed with invasive disease are younger than age 50 (half with ER-positive disease).[274] It is unfortunate, therefore, that the survival benefit of tamoxifen was not fully recognized till the mid-1990s.[275] The ovary is the primary site of estrogen production in premenopausal women. In 1896, Sir George Beatson first reported the benefits of oophorec-

Table 95-21 Adjuvant Trastuzumab Trials: Efficacy Results

	HERA		B31 + N9831		BCIRG006			FINNISH TRIAL	
	Observation (N = 1693)	**H × 1 yr (N = 1694)**	**Control (N = 1679)**	**H × 1 yr (N = 1672)**	**AC-T**	**AC-TH**	**TCH**	**Control (N = 115)**	**H × 9 wk (N = 116)**
Events* for DFS									
Patients with events	220	127	261	133	147	77	98	27	12
Distant events	154	85	193	96	113	52	67	26	8
Events for OS	37	29	92	62	36	20	28	14	6
HR for DFS	0.54		0.48		0.61 (0.47–0.79)			0.42	
(95% CI)	(0.43–0.57)		(0.39–0.59)		0.49 (0.37–0.65)				
P-value	<0.0001		<0.0001		<0.0001		=0.0002	0.01	
HR for OS	0.74		0.67					0.41	
95% CI	0.47–1.23		0.48–0.93		NA				
P-value	0.26		0.015					0.07	
Median follow-up	1 yr		2 yr		≈2 yr			36 mo	

A, doxorubicin; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; DFS, disease-free survival; H, Herceptin (trastuzumab); HERA, Herceptin Adjuvant trial; NA, not available; OS, ••; T, docetaxel.

*Defined in all trials as breast cancer relapses, second malignancies, deaths; the Finnish trial uses recurrence-free survival instead.

Adapted from Piccart-Gebhart MJ: Adjuvant trastuzumab therapy for HER2-overexpressing breast cancer: what we know and what we still need to learn. Eur J Cancer 2006;42:1715–1719.

tomy as palliative therapy for several young women with metastatic breast cancer. Factors that confounded therapeutic decisions for younger women included an inverse correlation between age and hormone receptor status, the belief that chemotherapy was more active than endocrine therapy, and age-related chemotherapy effects on ovarian function and its indirect endocrine effect. Retrospective data show that young premenopausal women (age <35) fare worse when treated with chemotherapy alone,[276] which may be explained by a greater likelihood of remaining premenopausal after chemotherapy.[277,278] This may also explain the survival benefit offered by chemotherapy without endocrine therapy seen in younger versus older premenopausal women[277] and the need for longer duration of tamoxifen therapy in premenopausal women.[228]

Ovarian function suppression (OFS) is effective when compared to no therapy in women younger than age 50.[228] Similar outcome is seen with OFS versus CMF chemotherapy[279–281] and with OFS plus tamoxifen versus chemotherapy.[282–284] This is of particular interest because the substitution of OFS for CMF chemotherapy would result in a lower rate of permanent amenorrhea[278,279] and fewer complications associated with premature menopause, and would even allow younger women to consider pregnancies following a breast cancer diagnosis.[285] At this time, though, data comparing OFS with contemporary regimens containing anthracyclines and taxanes are lacking. Clinical benefit was seen in young premenopausal women who received OFS after chemotherapy,[280,286,287] but it remains unclear if it is of added benefit in this group of women when they also are treated with tamoxifen. Indirect evidence from the International Breast Cancer Study Group (IBCSG) trial 13–93 suggests that some degree of benefit from chemotherapy-induced amenorrhea (CIA) might exist even when tamoxifen also is given.[288]

Ongoing prospective randomized trials are examining various questions in premenopausal women. The Suppression of Ovarian Function Trial (IBCSG 24-02) is enrolling almost 3000 women with ER-positive disease who do not receive adjuvant chemotherapy or who remain premenopausal after chemotherapy and compares 5 years of tamoxifen, tamoxifen with OFS, or the aromatase inhibitor exemestane with OFS. It has been over 110 years since the first report by Beatson on oophorectomy as a therapeutic option in breast cancer, and yet much remains unknown as compared to the use of endocrine therapy in postmenopausal women. This and other studies will finally

Table 95-22 Adjuvant Trastuzumab Trials: Cardiotoxicity

	HERA		**NSABP-B31**		**NCCTG-N9831**			**BCIRG006**		
Treatment arms	Observation	1 year H	AC → P	AC → PH	AC → P	AC → PH	AC → P → H	AC → T	TCbH	AC → TH
Women at risk (*N*)	1710	1677	814	850	670	579	718	1050	1056	1068
Cardiac deaths (*N*)	1	0	1	0	1	0	1	0	0	0
CHF NYHA Class 3–4 (*N*)	0	9	4	31	1	20	16	3	4	17
Percent	0	0.5	0.8	4.1	0.3	3.5	2.5	0.2	0.4	1.6

Note: no CHF class 3–4 and no cardiac death reported in the Finnish trial. Cumulative incidences at 3 years reported in NSABP-B31 and NCCTG-N9831.

A, doxorubicin; BCIRG, Breast Cancer International Research Group; C, cyclophosphamide; Cb, carboplatin; CHF, congestive heart failure; H, Herceptin (trastuzumab); HERA, HERceptin Adjuvant trial; NCCTG, North Central Cancer Treatment Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; NYHA, New York Heart Association; P, paclitaxel; T, docetaxel.

Adapted from Piccart-Gebhart MJ: Adjuvant trastuzumab therapy for HER2-overexpressing breast cancer: what we know and what we still need to learn. Eur J Cancer 2006;42:1715–1719.

answer critical questions on the optimal use of OFS in premenopausal women with ER-positive breast cancer; potentially will identify those able to forgo adjuvant chemotherapy, even among women with high risk, early-stage disease; and will minimize the risk of long-term complications related to premature menopause. A meta-analysis of OFS with LH-RH agonists in premenopausal women with ER-positive disease showed that chemical-induced ovarian suppression offered a signficant reduction in the relative risk for recurrence and death when added to tamoxifen, chemotherapy, or both.[289]

Side effects from LH-RH agonists occur earlier but are short-lasting when compared to chemotherapy, and may include hot flashes, decreased libido, mood lability, and potential cardiovascular and skeletal-related sequelae such as bone loss.[290,291] Existing guidelines in breast cancer do not yet address optimally the management and prevention of osteoporosis in premenopausal women being treated with OFS. However, annual bone density testing scans have been recommended in patients with therapy-associated premature menopause, in addition to calcium and vitamin D supplementation, advice on lifestyle, and bisphosphonates if necessary.[292] Promising data with regard to the role of clodronate in the adjuvant setting have been reported in three European trials, with survival benefit and reduction in bony recurrences identified in two of them.[293–295] Indirect evidence from these adjuvant trials and other studies reporting on the effectiveness of drugs such as risedronate in chemotherapy-induced premature menopause[296] suggest a potential role for bisphosphonates as primary or secondary prevention in women treated with LH-RH agonists in the adjuvant setting. In the meantime, ongoing studies in North America are testing the role of zoledronate in premenopausal women with breast cancer with adjuvant chemotherapy-induced ovarian failure and comparing zoledronate and ibandronate to clodronate in pre- or postmenopausal women to help elucidate the optimal role of bisphosphonates in early-stage breast cancer.

Aromatase Inhibitors

The conversion of androgen to estrogen in peripheral tissues is the primary source of estrogen in postmenopausal women, and the aromatase enzyme is present in a number of tissues (e.g., muscle, fat, skin, neural tissues, and breast). Levels of estrogen and aromatase are elevated in malignant breast tissue, and aromatase inhibitors can block the action of the enzyme and reduce estrogen production. Available drugs include type 1 steroidal nonreversible inhibitors (e.g., exemestane and formestane) and type 2 nonsteroidal reversible inhibitors (e.g., letrozole, and anastrozole).[297] First-generation inhibitors (e.g., aminoglutethimide) were associated with significant toxicity in the adjuvant setting because of the nonspecific effects that occur at several steps in the steroid biosynthetic pathway, and a marginal benefit was seen when compared with tamoxifen. The more specific (and less toxic) third-generation aromatase inhibitors supported the initiation of several adjuvant trials in postmenopausal women. By 2007, several studies had been reported testing 5 years of use of tamoxifen against an aromatase inhibitor upfront (the Arimidex, Tamoxifen, Alone or in Combination [ATAC],[298] and Breast International Group [BIG] 1–98 [299] trials); a sequential approach after 2 to 3 years of tamoxifen (Intergroup Exemestane Study [IES],[300] Austrian Breast and Colorectal Cancer Study Group [ABCSG] 8 and Arimidex-Nolvadex [ARNO] 95,[301,302] and the Italian Tamoxifen Arimidex [ITA][303] trials), or extended therapy (MA-17 trial[304]). Aromatase inhibitors are contraindicated in premenopausal women and must be used with extreme caution in women who are premenopausal and develop chemotherapy-induced amenorrhea. In the presence of an AI, the reduced feedback of estrogen to hypothalamus and pituitary may lead to an increase in the secretion of gonadotrophins and resumption of ovarian function, including the possibility of getting pregnant.[305]

Much has been discussed about the optimal time to introduce an aromatase inhibitor. ER-positive breast cancer has a long natural history, and half of all recurrences occur between years 6 and 15.[228] Many of the recurrences observed in the upfront trials ATAC and BIG 1–98 were local, and an overall survival advantage has not yet been observed. But while a survival advantage and improved hazard ratios for outcome have been observed in several trials that tested a sequential[300] or extended approach[304] (including one metanalysis[306]), all but the ABCSG 8 trial enrolled patients after several years of adjuvant tamoxifen, thereby ensuring the selection of patients who had not yet recurred and were more likely to have disease responsive to endocrine manipulation. Various theoretical models have been employed but with conflicting results based on the various assumptions employed.[307,308] Patients with HER2-positive tumors have a higher hazard of recurrence but not a preferential response to one class of agents over another, and expression of PR is of no prognostic importance.[34,309] Based on these observations and considering the long natural history of ER-positive tumors, it is therefore not unreasonable to consider a planned transition to an aromatase inhibitor after a few years of tamoxifen for patients with ER-positive, HER2-negative tumors, while those with HER2-positive disease (especially if higher nodal burden) may be considered for AI therapy upfront.

Data from BIG 1–98 comparing an aromatase inhibitor upfront versus tamoxifen followed by an aromatase inhibitor are eagerly awaited. There also is interest and theoretical concerns about the safety of administering tamoxifen after an aromatase inhibitor.[310] Safety data support the use of an AI for 5 years if used sequentially, and their extended use beyond year 5 is now the subject of randomized trials. Host factors in the form of polymorphisms of the P450 *CYP19* gene have been observed in various ethnic groups, but the clinical utility of these data remain unclear.[311,312]

Combined Chemoendocrine Therapy

Adjuvant endocrine therapy has a more favorable therapeutic index than chemotherapy in patients with endocrine-responsive breast cancer. In postmenopausal women, tamoxifen is a more efficacious adjuvant intervention,[246] and endocrine therapy is considered the primary component of any adjuvant systemic regimen in patients with hormone receptor-positive disease, regardless of age. However, patients who also have prognostic factors associated with an increased risk of recurrence and death (e.g., larger tumors or lymph node involvement) may benefit from the addition of chemotherapy to endocrine therapy as part of the adjuvant regimen. This is especially the case in premenopausal women, in part because of the ovarian suppression caused by chemotherapy. As mentioned earlier, specific gene expression profiling assays appear to add predictive utility in specific patient subsets. The role of adding chemotherapy in low-risk, older patients, such as those with node-negative, endocrine-responsive disease who will be treated with 5 years of adjuvant tamoxifen, is unclear. Few data are available on polychemotherapy in women 70 years of age and older.[228] Studies such as IBCSG trial IX (1669 postmenopausal patients)[313] and NSABP B-20 (2306 pre- and postmenopausal patients) in patients with node-negative disease,[314] and SWOG 8814 (Intergroup 0100 [1477 postmenopausal patients]) in patients with node-positive disease[315] confirm the survival benefit from even a short course of chemotherapy (e.g., three cycles of CMF) in older women with lymph node-negative, hormone receptor-negative disease. At the same time, they reinforce the cautionary tone that permeates recent clinical practice guidelines and consensus statements about the use of chemotherapy in postmenopausal women with endocrine-responsive disease who will receive 5 years of adjuvant tamoxifen.[154,316] These data on combined systemic therapy address whether additional benefit is associated with adding chemotherapy to tamoxifen. Approximately 20% of patients in the ATAC trial (usually node-positive patients) received chemotherapy in addition to endocrine therapy,[298] but it is not known whether these findings on combined chemoendocrine therapy are applicable to the aromatase inhibitors.

SWOG 8814 (Intergroup 0100) also addressed the important issue of timing when combining chemotherapy and endocrine therapy, and indicated a survival advantage associated with sequential versus concurrent administration of chemotherapy and tamoxifen,[317] and a smaller Spanish trial (GEICAM 9401) comparing epirubicin and cyclophosphamide with sequential versus concurrent tamoxifen showed a trend favoring a sequential approach.[318] Data released in late 2007 explored gene expression profiling as a prognostic and predictive marker using specimens from trial SWOG 8814 that tested the addition of an anthracycline-based adjuvant regimen to tamoxifen in postmenopausal woment with ER-positive, lymph node-positive breast cancer.

Preoperative Systemic Therapy

Adjuvant systemic therapy after surgery has been the gold standard for examining the effect of new treatment strategies on disease-free survival and overall survival rates in the adjuvant setting. Traditional adjuvant endpoints require trials with large sample sizes and long-term follow-up to achieve the number of events required to assess the effect of the investigational arm on the end point of interest. This problem is compounded by the increasing number of patients diagnosed with earlier stages of disease. Preoperative systemic therapy traditionally has been reserved for women with locally advanced breast cancer (LABC) to enhance the likelihood of negative surgical margins or even breast preservation, although preclinical data suggested that the administration of systemic therapy before surgery may be associated with early eradication of micrometastases and improved long-term outcomes by decreasing the risk of drug resistance and leading to more favorable growth kinetics. Preoperative systemic therapy offers a small increase in the rate of breast conservation over the same therapy given after surgery, although initial data did not show a survival advantage.[319,320] However, pathologic response (especially if complete) after preoperative chemotherapy correlates with improved disease-free survival or overall survival, and the initial response to preoperative systemic therapy offers the potential of in vivo assessment of sensitivity or resistance to treatment (clinical or tissue samples).[321,322] Of great interest, the identification of intermediate (surrogate) markers (imaging, tissue, and blood) that correlate with outcome (pathologic response and/or survival) in carefully selected patient groups may have clinical utility.[323]

There are concerns that preoperative therapy might lead to the loss of baseline parameters (e.g., tumor size and lymph node involvement) that generally are used to guide recommendations for adjuvant therapy. In patients treated with preoperative systemic therapy, it is advisable to request immunohistochemistry studies in the initial biopsy specimen, in case no residual disease is identified at surgery after therapy. Results from NSABP B-27[324] also confirm the feasibility of performing sentinel lymph node biopsy after preoperative chemotherapy,[325] although this issue remains controversial, and many radiation oncologists wish to know the axillary status at presentation. Patients with hormone receptor-positive disease will all receive 5 to 10 years of endocrine therapy after completion of local therapy, regardless of pathology findings. However, there is uncertainty about what to do for patients with ER-negative disease with residual disease at surgery, and studies are investigating the use of additional systemic therapy after surgery in this setting.

Preoperative systemic therapy might allow trials with smaller sample sizes and an adaptive design to test new strategies that can then quickly evolve into larger trials with survival as the primary endpoint. Preoperative trastuzumab as a single agent,[326] concomitantly with an anthracycline,[327] or with a non-anthracyline regimen[328] has been shown to induce a high rate of pathologic response. As an interesting example, the very rate of pathologic complete response observed in recent trials of preoperative trastuzumab could have presaged the survival benefit observed in traditional adjuvant trials.[329] These issues were the theme of a State of the Science Symposium on preoperative therapy in invasive breast cancer conducted at the US National Institutes of Health in March 2007 (see http://ctep.cancer.gov/bcmeeting/index.html).

Optimal patient selection for preoperative chemotherapy is key, especially if the immediate goal is tumor shrinkage (to allow breast conservation) and pathologic complete response (for prognostic purposes). Hormone receptor status and tumor histologies should be considered carefully, because patients with ER-negative disease and lobular histologies are less likely to respond to preoperative chemotherapy, even though their long-term outcome (especially among the small minority that achieve a pathologically confirmed complete remission) is improved overall.[155,330]

Preoperative systemic endocrine therapy also is an attractive alternative to chemotherapy, especially in older patients with strong ER-positive tumors who may not be good candidates for chemotherapy. However, clinical responses are slower to occur and are rarely complete. Aromatase inhibitors appear more active than tamoxifen in patients with ER-positive/HER2-positive disease, suggesting increased short-term sensitivity to estrogen deprivation.[331] Optimal markers to predict long-term outcome following preoperative endocrine therapy are lacking, but levels of tumor Ki67 after short-term endocrine treatment may help predict recurrence-free survival by combining the prognostic value of Ki67 level at baseline with observed changes in levels at 2 weeks.[332]

Secondary Effects of Adjuvant Systemic Therapy

Secondary Effects of Chemotherapy

As more patients with earlier stages of disease are offered adjuvant systemic therapy, its short- and long-term effects on quality of life must be carefully weighed. The chemotherapy regimens commonly administered to patients with breast cancer (e.g., CMF, FAC, FEC, AC, or taxane-based regimens) generally are well tolerated. Acute life-threatening toxicity in patients receiving the therapy is quite rare. Common short-term effects include alopecia, myelosuppression, gastrointestinal symptoms, and febrile neutropenia or neutropenic infection. Peripheral neuropathy, arthralgia, and myalgia also are seen with taxanes. The effect of anemia on quality of life has been the subject of ongoing investigation, but concerns now exist on a potential worse survival outcome with the use of erythropoeitin-stimulating agents,[333] which has diminished the enthusiasm for their use in the adjuvant setting, where the intent is cure. Although many women accept these short-term toxicities, attention is being placed increasingly on late effects from systemic therapy as the number of patients who will become long-term survivors is increasing. For some, the actual absolute reduction in risk of recurrence and death is relatively small compared with the potential risk of late toxicity.

Anthracycline-related cardiac toxicity is a potential concern. Approximately 8% of women may have asymptomatic systolic dysfunction 10 years after receiving doses of doxorubicin around 300 mg/m^2,[334] and cardioprotective drugs such as dexrazoxane are not approved in the adjuvant setting. Although the risk of clinical congestive heart failure associated with conventional doses of anthracyclines is small (≤1%),[335] this risk is increased with the subsequent use of adjuvant trastuzumab.[336] Older age and lower left ventricular ejection fraction at baseline appear to increase this risk, but good predictive models and existing tools (e.g., measurements of troponin and brain natriuretic peptide levels) are not sufficiently refined at present for use in clinical practice. Secondary acute myeloid leukemia and myelodysplastic syndrome are rare early events. They have been linked to exposure to alkylating agents, topoisomerase II inhibitors, and antimetabolites,[337,338] and the risk of acute myeloid leukemia or myelodysplastic syndrome after four cycles with conventional doses of AC (60 and 600 mg/m^2) at 5 years is 0.21%.

Young women are at risk for premature menopause after adjuvant chemotherapy, and the risk correlates with both age and choice of adjuvant chemotherapy (classic CMF for 6 cycles > AC followed by

paclitaxel = TAC with docetaxel > AC for four cycles).[278] Temporary cessation of menses during adjuvant therapy also correlates with earlier occurrence of menopause.[339] Although ovarian suppression as a result of chemotherapy may further decrease the odds of recurrence and death in premenopausal women with endocrine-responsive disease, premature menopause can have a significant effect on quality of life because of severe hot flashes and vaginal dryness. Hot flashes resulting from discontinuation of HRT or induction of menopause are a common symptom after chemotherapy, with only partial remedies.[340] For women who retain fertility, pregnancy does not appear to increase the risk of another breast cancer event,[341] but the safety and efficacy of LH-RH agonist use during chemotherapy to preserve fertility remains investigational. Women who have chemotherapy-induced ovarian failure after adjuvant chemotherapy are at risk for rapid bone loss and complications from osteoporosis,[342] and bisphosphonates may have a preventive role in this setting.[343]

Symptoms of fatigue, weight gain, and cognitive dysfunction are reported with some frequency after the completion of therapy. Weight gain is a common complaint.[344] Cognitive dysfunction has been observed, including short-term memory loss and long-term complaints of poor memory, impaired concentration, and language deficits.[345] An association with chemotherapy is confounded by factors such as onset of menopause, discontinuation of menopausal replacement therapy, and use of endocrine therapy with antiestrogens. While long-term survivors report more frequent physical and menopausal symptoms than do healthy women, their health-related quality of life and sexual functioning are comparable to those reported by healthy, age-matched control subjects.[345] Still, the various long-term needs of breast cancer survivors and the crucial role to be played by both oncologists in the short run and gynecologists and internal medicine specialists in the long run cannot be overemphasized.[346,347]

Secondary Effects of Endocrine Therapy

Although tamoxifen is associated with an increase in bone mineral density in the axial skeleton,[348] and the NSABP P-01 prevention study showed a reduction (relative risk, 0.81; 95% CI, 0.63–1.05) in fractures of the hip, radius, and spine in all age groups (especially those 50 years of age and older),[117] bone mineral loss is observed in the lumbar spine and hip in premenopausal women receiving tamoxifen. Tamoxifen is associated with a reduction in low-density-lipoprotein cholesterol, and individual studies have suggested that tamoxifen might reduce the risk of coronary heart disease. However, the Oxford Overview did not show any statistically significant effect of cardiac or vascular events on overall survival.[228]

Similar to its antiestrogen effects in breast tissue, the toxicity profile of tamoxifen also is related to its tissue-specific SERM. The 1995 Oxford Overview showed a higher incidence of uterine malignancies (ratio of incidence rates, 2.58; SD, 0.35),[275] and similar findings were observed in the three largest trials of 5 years of tamoxifen therapy—NSABP B-14, [271] the Scottish trial,[272] and the Stockholm trial B study[349]—with an absolute excess in deaths of 1 or 2 per 1000 after 10 years (0.2 per 1000 woman-years). Although uterine cancer is likely to be diagnosed at an early stage and cured with surgery alone, longer duration of tamoxifen therapy is associated with worse histology and higher grade,[350] and 2% to 5% of all cases represent uterine sarcoma.[351] It is important to know that tamoxifen is expected to cause endometrial thickness, and neither transvaginal ultrasound nor endometrial biopsy is a useful screening tool in asymptomatic patients.[352] Instead, women who are taking tamoxifen should simply continue their otherwise routine gynecologic evaluation and notify their physicians of abnormal vaginal spotting or bleeding.

Thromboembolic complications due to tamoxifen occur in fewer than 1% of patients,[117] although they are seen more commonly when combined with IV CMF. Tamoxifen is associated with increased rates of hot flashes, vaginal discharge, and night sweats, but without a statistically significant effect on quality of life.[353] Hot flashes are a common and vexing symptom.[354] Selective serotonin reuptake inhibitors such as venlafaxine are effective.[355] Venlafaxine in particular is less likely to inhibit CYP2D6 activity.[273] Other pharmacologic interventions like clonidine,[356] vitamin E, gabapentin,[357] and progestational agents have been tested and shown to be helpful. Popular remedies such as black cohosh are ineffective.[358]

Weight gain is commonly observed in breast cancer survivors.[344] The NASBP prevention P-01 trial showed no detrimental effects on quality of life, mood, or sexual function in the tamoxifen-treated group.[359] Sexual dysfunction is rare and is more commonly associated with chemotherapy.[360] Ocular toxicities (e.g., corneal changes, tamoxifen retinopathy, and posterior subcapsular opacities) are rare.

Toxicities such as low-grade hot flashes, arthritis, arthralgia, and myalgia were observed in patients treated in the various aromatase inhibitor trials, but so was a lesser frequency of vaginal bleeding. Unfavorable changes in lipid profile also have been noted, but implications regarding cardiovascular events remain uncertain.[268] The observed rate of osteoporosis is greater with aromatase inhibitors, and this may contrast with the favorable bone effects of tamoxifen. Women considered for aromatase inhibitor therapy should ensure adequate daily intake of calcium and vitamin D and have a baseline bone density test, and those with an abnormal test result should have it repeated according to established guidelines.[292]

Other Secondary Effects

As more women with early-stage breast cancer become long-term survivors, concerns about cancer recurrence are expected to decrease, and it sometimes is difficult for patients and their physicians to separate age-related symptoms from those that might be related to long-term effects of therapy. Data on the safety of menopausal hormone replacement therapy in breast cancer survivors are limited, and are derived mostly from cohort and case-control studies,[361,362] and prospective randomized trials are lacking.[363] The use of complementary and alternative medications is a common and unreported practice among patients,[364] but few prospective controlled studies have been conducted.[365] Fatigue is another common symptom, especially in patients with higher levels of depression, pain, and sleep disturbance. Increasing evidence also shows that adjuvant chemotherapy may have long-term effects on cognitive function.[345] A few years of ovarian function suppression is expected to be more tolerable than chemotherapy (short- and long-term) in premenopausal women with ER-positive disease.[291]

Long-Term Follow-Up

Post-treatment surveillance and long-term strategies must take into account the effect on several outcomes of interest, such as survival, quality of life, reduction in toxicity, cost-effectiveness, and the likelihood that most patients diagnosed with breast cancer in the United States are expected to survive this diagnosis. Breast cancer survivors should pursue monthly breast self-examination, annual mammography, and a clinical evaluation on a regular basis, because available evidence does not support any surveillance blood tests (e.g., tumor markers) and imaging studies other than mammography in otherwise asymptomatic patients with no abnormalities on clinical examination.[366] Equally or more important, cancer specialists should ensure adequate coordination of care in a shared care model with gynecologists and primary care physicians, who will have an increasingly important role in the long-term care of these breast cancer survivors. In late 2007 the American Society of Clinical Oncology released "treatment plan" and "treatment summary" templates to be completed by cancer specialists and shared with their patients and the noncancer specialists caring for them (available at www.asco.org) to facilitate this coordination. These tools have both a care and an

educational component, because they will be used to empower patients to become full participants in their care, smooth the transition back to their noncancer specialists in a "shared-care" model, and ovecome deficiencies inherent to the fragmented health care system of many countries, such as the United States. In many settings, noncancer specialists may assume the primary long-term follow-up care of these patients,[367] but it is critical that good communication be maintained with cancer specialists, especially in regard to patients with ER-positive disease, who may find themselves on endocrine therapy for 10 years (or more, pending ongoing studies). Increasingly, information regarding the long-term care of cancer survivors (including breast cancer) is becoming available in internal medicine journals,[368] which should help smooth the transition of patients likely to survive their disease. In addition to surveillance for possible late complications resulting from local and systemic therapies given as part of their breast cancer treatment,[347] breast cancer survivors also require routine health maintenance care to address common health issues that occur as they age.

New Strategies in Adjuvant Treatment

Greater understanding of the biologic subtypes of breast cancer is helping with the selection of treatment strategies targeting specific tumor subtypes. ER, PR, and HER2 are the most useful markers at present, and gene expression profiles are being tested prospectively as prognostic and predictive markers to ensure the optimal identification of the patients most likely to benefit from a specific strategy. Trastuzumab is now a standard treatment offered to patients with HER2-positive disease, and adjuvant trials with lapatinib (if HER2-positive) or bevacizumab (in HER2-negative disease) started in 2007. Ongoing studies also are addressing the role of bisphosphonates, the oral fluoropyrimidine capecitabine, and new formulations of taxanes. Host pharmacogenetic information will be of increasing interest and may help with therapy individualization too.[369]

MANAGEMENT OF LOCALLY ADVANCED BREAST CANCER

Locally advanced breast cancer (LABC) has always included a heterogeneous group of presentations. With the 2002 changes to the AJCC staging system, LABC technically can include a patient with a clinically apparent internal mammary or paraclavicular node as well as the more commonly accepted presentations, including a primary breast cancer larger than 5 cm, disease fixed to the chest wall or involving the skin, or bulky palpable disease in the axilla.[152,153] Inflammatory breast cancer also can be called LABC, but is discussed separately in this chapter. The approach to LABC has evolved considerably over the years. Surgery and radiation therapy at first were the only treatments available, but multimodality approaches that emphasize systemic therapy have become the standard of treatment. This includes delivery of systemic therapy early in treatment to attempt to reduce subclinical micrometastatic disease, reduce local and regional tumor bulk, and increase the likelihood of successful surgical resection. In addition, the appropriateness of the systemic agents chosen can be assessed by following the patient's locoregional clinical response.

Multiple retrospective studies have shown a survival benefit with the addition of chemotherapy to local therapy when compared with historical control subjects treated with local therapy only. In some series, chemotherapy was administered after surgery, but most recent series have combined preoperative and postsurgical therapy. Other endpoints for comparison of these studies include local control rates, clinical tumor response, and pathologic tumor response when patients undergo mastectomy. In some cases, the clinical response has been judged significant, and a significant proportion of women were able to undergo less invasive procedures than mastectomy. The preoperative approach was well documented by one study at the M.D. Anderson Cancer Center.[370] After preoperative FAC chemotherapy, 372 women underwent either segmental mastectomy and axillary node dissection (29%) or modified radical mastectomy (71%), as decided upon based on the clinical response of the tumor and initial prechemotherapy disease bulk. Thirty-one per cent of the primary tumors were smaller than 5 cm, and 20% of women had no clinically detectable axillary adenopathy at diagnosis. All the women received more chemotherapy postoperatively and then locoregional radiation therapy. Breast conservation is increasingly considered. Although in general, local control is maximally achieved with mastectomy and postoperative radiation therapy, in selected subgroups of patients who respond to preoperative chemotherapy, breast-conserving therapy appears to yield local control rates similar to those attainable with mastectomy and radiation therapy. Advances in breast imaging also are emerging as tools to select patients for further therapy after preoperative chemotherapy. Technetium-99 m sestamibi scans[371] and PET imaging with ^{18}fluorodeoxyglucose[372] have been tested as predictors of pathologic response.

Radiation therapy has been administered as an adjuvant to mastectomy for LABC, both pre- and postoperatively. Postoperative therapy usually is delivered to patients with operable disease. Preoperative radiation therapy has been used to convert unresectable or marginally resectable cancers into technically resectable disease. From series in which radiation therapy was delivered preoperatively, pathologic review of mastectomy specimens yields information about the ability of radiation therapy to sterilize disease. Despite delivery of 60 to 70 Gy to the breast and regional nodes, Zucali and associates[372A] found that 75% of mastectomy specimens contained residual tumor in patients with a complete clinical response. Clearly, the addition of systemic chemotherapy has placed these response rates in an historic context.

Breast Conservation Therapy

Induction chemotherapy can cytoreduce locoregional disease. Some patients receiving primary chemotherapy achieve complete clinical response. Attention has been directed toward the identification of patients with an excellent response to preoperative therapy who are possible candidates for breast conservation. The goals of this approach are the same as those for women with early-stage disease who are candidates for breast conservation (i.e., optimal locoregional control with acceptable cosmesis of the treated breast).

To study the feasibility of breast preservation in advanced disease, mastectomy specimens from 143 patients with stage IIB and III breast cancer who were treated at M.D. Anderson Cancer Center were retrospectively analyzed after preoperative chemotherapy.[372B] Using the criteria for breast preservation in early-stage disease, 23% of these women would have been good candidates for breast conservation after receiving preoperative chemotherapy. Based on this experience, breast conservation now is offered to appropriate candidates with LABC using similar criteria as in early-stage disease, as discussed earlier. Investigators at the NCI and the University of Michigan reported their results with breast conservation using a selection process based on biopsy-proven pathologic criteria.[372C,372D] Investigators at both institutions prospectively administered primary chemotherapy and performed a biopsy at the primary site, either after maximal clinical response (NCI study) or after a fixed number of cycles (Michigan study). For patients with a complete pathologic response, definitive locoregional radiation therapy was delivered. The more conventional mastectomy with postoperative radiation therapy was administered to patients with residual disease at biopsy. With a median follow-up of 5.3 years, the 5-year actuarial locoregional failure rate as first site of first failure was 23% with breast conservation in the NCI series.[372C] Similarly, with a median follow-up of 4.5 years, the 5-year actuarial estimate of locoregional failure as isolated first failure was 18% in the Michigan series.[372D] Examples of trials using breast preservation in LABC are shown in Table 95-23. Breast conservation in locally advanced disease is under study in many

Table 95-23 Breast Preservation Studies in Stage III Disease

Reference	No. of Patients	Inflammatory (%)	Chemotherapy	Radiation Dose (gy)	Locoregional Control (%)
Pierce et al.*	107	43	CAMFPT	60	77
Hery et al.†	25	0	CAVF	60–75	76
Lamb et al.‡	65	100	CA/CMF‡‡	60–73	54
Borger et al.§	209	0	CMF ± AV§§	65	45–47
Baillet et al.‖	134	5	VTMFA	65–75	80
Touboul et al.¶	97	0	CAVF	65–75	80 with RT alone 77 with lumpectomy
Ahern et al.**	67	0	AC/CMF or NC/CMF	80	86 for tumors <10 cm 50 for tumors >10 cm
Merajver et al.††		40	CAMFPT	64	82

AC, doxorubicin, cyclophosphamide; AV, doxorubicin, vincristine; CA, cyclophosphamide, doxorubicin; CAMFPT, cyclophosphamide, doxorubicin, methotrexate, 5-fluorouracil, prednisone, tamoxifen; CAVF, cyclophosphamide, doxorubicin, vincristine, 5-fluorouracil; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; NC, Novantrone, cyclophosphamide; RT, radiation therapy; VTMFA, vinblastine, thiotepa, methotrexate, 5-fluorouracil, doxorubicin.

*Pierce L, Lippman M, Ben-Baruch N, et al: The effect of systemic therapy on local-regional control in locally advanced breast cancer. Int J Radiat Oncol Biol Phys 1992;23:949.

†Hery M, Namer M, Moro M, et al: Conservative treatment of locally advanced breast cancer. Cancer 1986;57:1744.

‡Lamb C, Eberlein T, Parker L, et al: Results of radical radiotherapy for inflammatory breast cancer. Am J Surg 1991;162:236.

§Borger, J, van Tienhover G, Passchier D, et al: Primary radiotherapy of breast cancer: treatment results in locally advanced breast cancer and in operable patients selected by positive axillary apex biopsy. Radiother Oncol 1992;25:1.

‖Baillet F, Rozec C, Ucla L, et al: Treatment of locally advanced breast cancer without mastectomy: 5- and 10-yr results of 135 tumors larger than 5 cm treated by external beam therapy, brachytherapy and neoadjuvant chemotherapy [abstract]. In Pisa Symposia in Oncology. Breast Cancer from Biology to Therapy, 1992, p 22.

¶Touboul E, Lefranc J-P, Blondon J, et al: Primary chemotherapy and preoperative irradiation for patients with stage II larger than 3 cm or locally advanced non-inflammatory breast cancer. Radiother Oncol 1997;42:219.

**Ahern V, Barraclough B, Bosch C, et al: Locally advanced breast cancer: defining an optimum treatment regimen. Int J Radiat Oncol Biol Phys 1994;28:867.

††Merajver SD, Weber BL, Cody R, et al: Breast conservation and prolonged chemotherapy for locally advanced breast cancer: the University of Michigan experience. J Clin Oncol 1997;15:2873.

‡‡Administered to 72% of patients.

§§Administered to 30% of patients.

centers in conjunction with aggressive induction chemotherapy. Although in general, local control is maximally achieved with mastectomy and postoperative radiation therapy, in selected subgroups of patients who respond to preoperative chemotherapy, breast-conserving therapy appears to yield local control rates similar to those attainable with mastectomy and radiation therapy.

INFLAMMATORY DISEASE

Inflammatory breast cancer is the most aggressive form of nonmetastatic breast cancer.[373] Although it accounts for only 1% to 4% of breast cancers in the United States, its presentation is striking. Characteristics essential to the clinical diagnosis include rapid enlargement and generalized induration of the breast, often without an associated mass. Diffuse skin erythema affecting more than one third of the breast is the most distinctive clinical feature of the disease. Flattening and retraction of the nipple with diffuse breast warmth and peau d'orange are commonly observed, and patients are at risk of having metastatic involvement at presentation, and not infrequently patients are thought to have mastitis and treated with antibiotics.

Pathologic Findings

Pathologically, inflammatory cancer is not a distinct histologic entity. However, dermal lymphatic involvement is the pathologic hallmark of the disease. Since the first description by Bryant in 1887, many studies have associated the clinical findings with carcinoma in the lymphatics of the skin. Thorough examination of mastectomy specimens confirms dermal lymphatic involvement in as many as 70% of women with clinical signs of inflammatory carcinoma.

Dispute exists in the literature about the criteria necessary to diagnose inflammatory breast cancer. Although some believe that clinical findings alone are adequate to make the diagnosis, others argue that a skin biopsy confirming dermal lymphatic involvement is needed, although both presentations share a similar poor outcome.[374]

Multimodality Therapy

Combined-modality therapy with chemotherapy and locoregional treatment has become the standard approach to the treatment of inflammatory breast cancer, similar to the evolution of treatment for other types of LABC. Retrospective data are convincing for a survival benefit and support the routine use of systemic therapy in this disease (Table 95-24). Depending on the choice of chemotherapeutic and locoregional treatment, disease-free survival rates at 5 years generally exceeded 25% to 30%, with 5-year survival rates approaching 40%.[375]

Although most series correlated response with outcome, more than 50% of women with inflammatory breast cancer die within 5 years after receiving optimal therapy. Locoregional control appears to be optimized in most series with the combination of surgery and radiation therapy in conjunction with systemic therapy. Breast conservation has been attempted in women with inflammatory disease. Despite reports of the successful use of breast conservation in the treatment of inflammatory disease, inferior rates of local control when compared to mastectomy plus radiation therapy in various series suggest that further studies on breast conservation as part of the treatment of inflammatory cancer are needed.

RECURRENCE AFTER BREAST-CONSERVATION THERAPY

In contrast to locoregional recurrence after total mastectomy, recurrence in the breast after breast-conservation therapy does not neces-

Table 95-24 Results of Combined Modality Treatment Programs for Inflammatory Breast Carcinoma

Study	Treatment Program	No. of Patients	Patients Rendered Disease-Free (%)	Median Survival Time (MO)	5-Yr Survival Rate (%)
DeLena et al.	CT + RT ± CT	36	73	25	NA
Chu et al.	RT + H	14	NA	15	NA
	RT + CT	16	NA	>26	NA
Pouillart et al.	CT + RT + CT	77	51	34	NA
Zylberberg et al.	CT + S + CT ± RT	15	100	>50	70
Pawlicki et al.	CT ± S + RT	72	NA	NA	NA
Loprinzi et al.	S + CT + RT + CT	9	100	>25	55
Keiling et al.	CT + S + CT	41	100	NR	63
Jacquillat et al.	CT + RT + CT + H	66	100	NR	66
Alberto et al.	CT + S + CT + RT	22	95	26	10
Ferriere et al.	CT + RT ± S + CT	75	93	NR	54
Pourny et al.	CT + S ± RT + CT	33	82	70	60
Chevallier et al.	CT + RT ± CT ± S	178	83	37	32
Rouesse et al.	CT + RT + CT + H	91	41	36	40
Israel et al.	CT + S + CT	25	96	NR	62
Krutchik et al.	CT + RT + CT	32	NA	24	NA
Brun et al.	CT + RT + S + CT	26	NA	31	NA
Thoms et al.	CT + S + CT + RT	61	NA	61	35
Swain et al.	CT + RT + S + CT + H	45	NA	36	NR
Fields et al.	CT + S + RT + CT	37	NA	49	44
Maloisel et al.	CT + S + CT + RT + H	43	NA	46	75
Koh et al.	CT + RT + CT	40	NA	39	37
	CT + S + CT + RT	23	NA	38	30
	CT + S + CT + RT	43	NA	31	40

CT, chemotherapy; H, hormone therapy; NA, not available; NR, not reached; RT, radiation therapy; S, surgery.

Adapted from Hortobagyi G, Singletary S, Strom E: Treatment of locally advanced and inflammatory breast cancer. In Harris J, Lippman M, Morrow M, Osborne CK (eds): Diseases of the Breast, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2000, p 651.

sarily signal great risk of systemic disease. It may represent actual recurrence at or near the site of the original primary lesion, or it may be a new primary lesion, especially when located in a different quadrant of the breast. The incidence of breast recurrence in patients treated with adequate local lumpectomy and breast radiation is 10% to 20% at 10 years, and the preferred treatment for patients who have a failure in the conserved breast is salvage mastectomy, with or without reconstruction. Other approaches, such as tumorectomy, result in lower rates of subsequent local control. In the surgical management of these women, it is important to consider the decreased blood supply and decreased skin elasticity from the previous radiation. Skin closure should be accomplished at salvage mastectomy, keeping the possibility of delayed healing in mind. For some of the same reasons, reconstruction with a tissue expander often results in increased incidence of necrosis, infection, and capsular contracture, and reconstruction with autologous tissue often is preferred.

Systemic staging is recommended at the time of diagnosis of an in-breast recurrence. The decision to use additional multidrug chemotherapy or hormone therapy is based on the nature of the breast recurrence as well as on whether the patient previously received adjuvant chemotherapy. Prospective studies to evaluate the optimal locoregional and systemic management of these patients are difficult to conduct, and these patients benefit from management by an experienced multidisciplinary breast team. In the absence of definitive data, adjuvant systemic treatment often is considered. Selection of regimens frequently accounts for prior adjuvant regimens and pathogy findings (e.g., ER/PR and HER2 expression).

Special Problems

Patients who undergo unsuccessful radiation therapy, chemotherapy, or a combination of the two in an attempt to control locoregional disease present a special challenge for the surgeon. Surgery should be attempted in these patients, because failure to control local disease results in a considerable decrease in quality of life. These patients often have painful, ulcerating, bleeding, and chronically infected local tumors. Surgery should be aggressive, frequently including the ribs and intercostal muscles. As emphasized, the extent of locoregional recurrence is a major influence on the design of a treatment plan. Therapy decisions also are significantly affected by the recognition that such disease is a marker for distant disease. For these reasons, a multimodality approach appears to have the best chance of providing real patient benefit.

MANAGEMENT OF METASTATIC DISEASE

The primary goal of therapy in patients with metastatic breast cancer is palliation of symptoms and prolongation of high-quality life, because most patients with metastatic (advanced) breast cancer ultimately die of their disease. At the same time, there has been an

improvement in the survival of of these patients with metastatic disease over the last few decades as a result of more effective therapies and diagnosis at earlier phases of metastatic disease (stage migration).[376] Chemotherapy trials with taxanes treating a mixed population of patients showed a median survival, on average, of approximately 2 years.[377] However, some patients survive long-term, and a very small number of patients with "oligometastatic" disease may even benefit from multimodality therapy that includes surgical resection of an isolated visceral metastasis with curative intent.[378] Also, specific therapies like trastuzumab have changed the natural history of HER2-positive metastatic breast cancer.[234]

Approximately 75% of metastases occur within the first 5 years after the diagnosis of early-stage disease, especially among patients with hormone receptor-negative disease. Unfortunately, a smaller risk of recurrence persists, and metastases have been documented as late as 20 to 30 years after the initial diagnosis. Although most patients with metastatic disease are expected to progress at some point, certain clinical and tumor characteristics are useful in predicting prognosis. Patients with a long interval since initial diagnosis, excellent performance status, hormone receptor-positive disease that primarily involves bone or soft tissue, and only a few sites of visceral involvement are likely to have a better long-term prognosis. Available locoregional systemic and supportive care treatments can result in significant regression of disease, relief of symptoms, and, in some cases, prolongation of survival. Although the goal of treatment of metastatic breast cancer seldom is cure, palliation with improved quality of life can be achieved in many patients.

Preliminary evidence indicates a role for combined multimodality therapy in patients with small-volume (preferably isolated) metastatic disease.[379,380] If confirmed, this also could have significant implications and force re-examination of the current recommendations for no surveillance in the absence of specific symptoms. Also, more effective surveillance tools would be required. Previous exposure to adjuvant therapy predicts a lower response to first-line chemotherapy in patients with metastatic breast cancer. However, retrospective data suggest that patients who have a recurrence long after completing adjuvant therapy may respond to similar regimens.[381] IBCSG data also suggest that quality-of-life scores may correlate with outcome in metastatic breast cancer,[382] and improvement in symptoms such as pain and shortness of breath may correlate with greater response to therapy.[383]

Evaluation of Suspected Metastases

Many patients present with nonspecific symptoms, such as new pain, weight loss, or dyspnea. Whenever possible, tissue acquisition for diagnostic confirmation and reassessement of receptor status (ER, PR, and HER2) should be considered. Clinicians should be wary of solitary lesions seen on bone scintigraphy or CT scan because they may not represent metastatic breast cancer. In the appropriate clinical setting, imaging studies without tissue confirmation may be acceptable evidence of metastatic disease, such as multiple areas of osseous lytic or blastic metastases or multiple sites with visceral involvement. Baseline imaging studies, including bone scintigraphy, CT, and plain x-rays, will provide a baseline for the evaluation of response to the planned treatment modality.

Prompt initiation of supportive measures and specific anticancer therapy in patients with significant symptoms or life-threatening complications (e.g., spinal cord compression, destructive bone lesions in weight-bearing areas, hypercalcemia, and symptomatic pleural or pericardial effusions and ascites) can offer significant palliation of symptoms. Skeletal scintigraphy (bone scan) remains the primary modality for screening for bone metastasis, but often needs to be complemented by other modalities (plain x-rays, CT, and MRI) as it primarily focus on bone metabolism.[384] Other metabolic studies like FDG-PET may have a role specially when integrated with conventional CT imaging for anatomic information (albeit frequently without iodide contrast),[385] but FDG-PET is inferior to bone scan for the assessment of blastic lesions,[386] and cost remains a barrier for many centers. Recent reports suggest an apparent increase in the prevalence of central nervous system (CNS) involvement, especially in patients with HER2-positive disease.[387] This is in great part due to improved control of systemic disease and lack of penetration of antibody therapy in sanctuary sites. This has also been observed in otherwise unselected patients who respond to conventional chemotherapy drugs and appear to be at risk for CNS relapse.[388]

Endocrine Therapy

Effective therapies with minimal toxicity, such as endocrine therapy, are highly desirable and should be considered a primary option over cytotoxic chemotherapy in patients with hormone receptor-positive disease. There is some evidence patients whose tumors co-express HER2 have less responsive disease to aromatase inibitor therapy alone and may benefit from the addition of trastuzumab,[389] but single-agent oral therapy with an anti-estrogen remains a viable option. Although the clinical factors discussed earlier are important in the selection of systemic therapy, routine measurement of ER and PR expression to identify patients who may respond to endocrine therapy may be the single most important initial test. Patients with ER/PR-positive and bone/soft tissue only or asymptomatic visceral disease should be considered for initial palliation with endocrine therapy. Examples of palliative endocrine regimens are listed in Table 95-25.

Selective Estrogen-Receptor Modulators

Tamoxifen, 20 mg daily, still is the most commonly used SERM in many countries. Toremifene is now available for use in this patient

Table 95-25 Examples of Commonly Used Endocrine Regimens in the Metastatic Setting*

INITIAL ENDOCRINE THERAPY OPTIONS
No prior endocrine therapy or over one year since endocrine therapy
Premenopausal → Anti-estrogen or OFS with endocrine therapy like postmenopausal women
Postmenopausal → Aromatase inhibitor or anti-estrogen
Prior endocrine therapy
Second-line endocrine therapy (see below)
SUBSEQUENT ENDOCRINE THERAPY OPTIONS
Premenopausal patients
Add OFS and treat like postmenopausal women
Postmenopausal patients
Nonsteroidal (anastrozole, letrozole) or steroidal (exemestane) aromatase inhibitor
Note: men of any age should not receive an aromatase inhibitor without concomitant use of an LH-RH agonist
Fulvestrant
Tamoxifen or Toremifene
Megestrol acetate
Fluoxymesterone
Ethinyl estradiol

*Consider chemotherapy if no clinical benefit (response or stable disease) after three endocrine regimens or symptomatic visceral disease.

Adapted from NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. V.2.2008. www.nccn.org/professionals/physician_gls/PDF/breast.pdf.

population, but has a similar profile and is cross-resistant with tamoxifen. PET with either FDG or the estrogen analog 16α-^{18}fluoroestradiol-17β before and after treatment with tamoxifen can assess the functional status of the ER in vivo (metabolic flare) and may predict response to tamoxifen in patients with ER-positive disease.[390] Acquired resistance to tamoxifen may be explained by a variety of mechanisms, such as mutations in the ER, changes in tamoxifen metabolism, levels of intracellular tamoxifen, and differential expression of steroid-receptor transcriptional coactivators and corepressors.[391]

Aromatase Inhibitors

In postmenopausal women with no or distant previous exposure to antiestrogen agents, the aromatase inhibitors show similar or modestly superior efficacy compared with tamoxifen.[297] These drugs are ineffective in premenopausal women and should be avoided as single agents in this setting. Aromatase inhibitors are more active and less toxic than megestrol acetate as second-line therapy; they also are more active and less toxic than the first-generation drug aminoglutethimide. Letrozole appears to be a more potent suppressor of total-body aromatization and plasma estrogen levels than anastrozole in patients with breast cancer,[392] but direct comparison as second-line therapy in metastatic breast cancer show no convincing clinical advantage of one aromatase inhibitor over another.[393] Circulating levels of estrone and estradiol decrease similarly in both responders and nonresponders after therapy with an aromatase inhibitor, suggesting that intratumoral aromatase activity could play a more significant role in differentiating these two groups of patients.[394] There are few data regarding the optimal sequence of therapy (i.e., a SERM followed by an aromatase inhibitor, or vice versa), and most patients will be treated with both at some point. Aromatase inhibitors should be avoided as a single agent in men with metastatic disease, as their chronic administration may lead to a significant increase in levels of follicular stimulating hormone and testosterone without any change in levels of estradiol, but appear to be effective when combined with an LH-RH agonist as chemical castration.[395]

Ovarian Ablation

The prefered endocrine therapy in premenopausal women with endocrine-responsive disease and recent exposure to tamoxifen is ovarian function suppression with surgical or medical techniques (LHRH agonist).[396] Radiation ablation is less reliable and technically more challenging, and the results are not as immediate.[397] Available data show both an overall survival advantage and a progression-free survival advantage with the addition of tamoxifen to an LHRH agonist,[398,399] but there are limited data on ovarian function suppression and an aromatase inhibitor.

Other Antiestrogens

The nonsteroidal pure antiestrogen fulvestrant downregulates ER without the agonistic activity of tamoxifen. It appears to have inhibitory effects in breast and uterus with neutral effect in bones and lipids,[400] and clinical effects appear similar to aromatase inhibitors.[401] It is currently only approved in postmenopausal women as a monthly, deep IM injection. Data on the clinical benefit from a loading disease are conflicting.

Chemotherapy

Patients with symptomatic visceral disease, ER- and PR-negative disease, or disease that is resistant to endocrine therapy should receive chemotherapy. Given the palliative goal and the toxicities of cytotoxic therapy, the challenge for the oncologist is in deciding when to initiate chemotherapy. Many appropriate chemotherapy regimens are available, and little evidence recommends combination therapy over sequential single-agent chemotherapy (Table 95-26).

Table 95-26 Examples of Commonly Used Endocrine Regimens in Metastatic Breast Cancer

PREFERRED SINGLE AGENTS
Doxorubicin
Epirubicin
Pegylated liposomal doxorubicin
Paclitaxel
Docetaxel
Capecitabine
Vinorelbine
Gemcitabine
Albumin-bound paclitaxel
Ixabepilone
PREFERRED AGENTS WITH BEVACIZUMAB
Paclitaxel
PREFERRED AGENTS WITH TRASTUZUMAB
Paclitaxel ± carboplatin
Docetaxel
Vinorelbine
PREFERRED COMBINATIONS
CAF/FAC (cyclophosphamide/doxorubicin/fluorouracil)
FEC (fluorouracil/epirubicin/cyclophosphamide)
AC (doxorubicin/cyclophosphamide)
EC (epirubicin/cyclophosphamide)
AT (doxorubicin/docetaxel; doxorubicin/paclitaxel)
CMF (cyclophosphamide/methotrexate/fluorouracil)
Docetaxel/capecitabine
GT (gemcitabine/paclitaxel)
OTHER ACTIVE AGENTS
Cisplatin
Carboplatin
Etoposide (oral)
Vinblastine
Fluorouracil continuous infusion

Adapted from NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. V.2.2008; www.nccn.org/professionals/physician_gls/PDF/breast.pdf.

There often is a fine line between premature use of chemotherapy in the asymptomatic patient without disease-related complications versus delaying therapy until deterioration of performance status significantly decreases the likelihood of response. There is considerable interest in identifying biologic parameters that may predict the success of specific chemotherapy regimens such as the identification of patients with HER2-positive diseases who could be offered trastuzumab. Patients with disease that does not express hormone receptors are more likely to respond to chemotherapy.[402] The organ distribution of metastases and the patient's symptoms, history of exposure to chemotherapy, and general medical condition are helpful considerations when determining the time of initiation of chemotherapy. Age alone should never be a contraindication.

Single-Agent Chemotherapy

Commonly used single-agent chemotherapy drugs in patients with advanced disease include anthracyclines, taxanes, vinorelbine, and capecitabine. If no data suggest a markedly strong benefit of one class of drugs over another, decisions should be made based on patient convenience and toxicity profile. Other active agents include gemcitabine, platinum compounds, etoposide, vinblastine, and continuous-infusion 5-fluorouracil.

The activity of taxanes in patients with anthracycline-resistant disease is well documented,[403] and may extend to patients previously treated with another taxane. Taxanes appear to have a better toxicity profile compared with either doxorubicin[404] or a CMF. Capecitabine is active in patients who showed disease progression after previous taxane regimens.[405] The epothilone B drug ixabepilone also has clinical activity in patients with disease resistant to paclitaxel, doxorubicin, and capecitabine.[406,407]

Combination Chemotherapy

Commonly used combination chemotherapy regimens include FAC/CAF (5-fluorouracil, doxorubicin, and cyclophosphamide), FEC (with epirubicin), AC, epirubicin and cyclophosphamide, AT (doxorubicin plus docetaxel or paclitaxel), and CMF. A survival advantage was seen in randomized trials of first-line therapy with paclitaxel or docetaxel against combination regimens. However, such survival advantage correlates with whether or not patients who showed disease progression while receiving the nontaxane regimen were subsequently crossed over to a taxane drug. Similar findings were seen in a study of docetaxel with or without capecitabine in patients with metastatic breast cancer who were previously treated with an anthracycline.[408] In this study, only a small fraction of patients who were initially treated with docetaxel alone subsequently crossed over to capecitabine at progression. Combinations between anthracyclines and taxanes have been tested, but paclitaxel interferes with doxorubicin elimination and lowers the threshold for cardiac toxicity. Dexrazoxane appears to be cardioprotective in patients treated with FAC. Gemcitabine plus paclitaxel significantly improves progression-free survival when compared to paclitaxel alone,[409] and a similar study design led to FDA approval in 2007 of ixabepilone in combination with capecitabine.[410]

High-dose chemotherapy with autologous or allogeneic stem cell support remains investigational. Available data do not support its use as a standard approach.[411]

HER2-Targeted Therapy

Anti-HER2 therapy with the recombinant monoclonal antibody trastuzumab is another recent example of targeted therapy. Its potential benefits are restricted to women whose tumors overexpress HER2, and evidence does not support its use against HER2-negative disease. Although data do not show a survival advantage with combined cytotoxic therapy in metastatic disease whenever there is sufficient cross-over to the investigational agent, this benefit was seen when trastuzumab was added to anthracycline and cyclophosphamide or paclitaxel.[234] Excessive cardiac toxicity limits the ability to combine anthracyclines with trastuzumab.[412]

Many consider trastuzumab the mainstay of therapy in HER2-positive disease. However, the sequential approach of trastuzumab followed by chemotherapy (or the combination) versus upfront combined therapy has not been tested. Combination of an aromatase inhibitor with trastuzumab appears to offer improved survival.[389] Single-agent therapy with trastuzumab is an active option[413] and can be given once every 3 weeks.[414] The dual tyrosine kinase inhibitor lapatinib recently was approved by the FDA in combination with capecitabine for the treatment of patients who previously were treated with trastuzumab,[415] and also prolongs time to tumor progression, with superior results when combined with paclitaxel versus paclitaxel alone.[416] This drug also is active in HER2-positive patients who have not been treated with trastuzumab.[417]

Therapies Targeting Angiogenesis

New blood vessel formation plays a key role in breast cancer growth locally and at distant sites, and angiogenesis appears to be essential for tumor development, invasion, and metastasis.[418] Evidence exists that angiogenesis precedes transformation of mammary hyperplasia to malignancy. Hypoxia is a strong angiogenesis signal, and expression of the hypoxia-inducible factor HIF-1α increases from normal breast tissue through usual ductal hyperplasia, DCIS, and invasive disease.[419] Expression of HIF-1α is increased in poorly differentiated tumors and is associated with proliferation and expression of vascular endothelial growth factor (VEGF). Microvessel density (MVD) is associated with higher-grade DCIS and greater risk of developing metastatic disease.[418]

Angiogenesis inhibition has been observed with drugs such as tamoxifen and commonly used chemotherapy drugs in preclinical models, and these observations led to increased interest in the so-called "metronomic" schedules of chemotherapy administration. Agents targeting various angiogenesis receptors and ligands have been developed. The small-molecule tyrosine kinase inhibitor sunitinib modulates VEGF receptor (VEGFR)-1, VEGFR-2, platelet-derived growth factor receptor (PDGFR), c-kit, and Flt-3. It is approved by the FDA for the treatment of advanced renal cell cancer and has single-agent activity in refractory metastatic breast cancer.[420]

The humanized monoclonal antibody bevacizumab, which targets the VEGF-A ligand, is approved in the United States for patients with metastatic colon and lung cancer, and has a small risk of complications including bleeding, healing impairment, hypertension, and proteinuria. Bevacizumab has single-agent activity in patients with refractory advanced breast cancer[421] and when combined with the chemotherapy drug capecitabine.[422] Bevacizumab was shown to increase progression-free survival significantly when added to paclitaxel in a randomized first-line trial for women with metastatic disease (ECOG 2100),[423] and it is now the subject of a prospective randomized trial testing a sequential anthracycline/paclitaxel regimen with or without bevacizumab for patients diagnosed with high-risk, early-stage HER2-negative breast cancer (ECOG 5103).

Bisphosphonates

Bone is the most common site of metastatic disease and ultimately is affected in most patients.[424] Monthly injections of bisphosphonates for up to 2 years can reduce the risk of skeletal events in patients who have lytic bone metastases and are receiving systemic therapy. Zoledronate is an effective alternative to pamidronate because of its shorter infusion time.[425] However, these more potent third-generation bisphosphonates are associated with an increased risk of osteonecrosis of the jaw.[426]

New Approaches

The marked increase in understanding of the cellular and molecular biology of breast cancer led to a striking increase in novel therapies for breast cancer and a significant shift away from the high-dose-chemotherapy hypothesis that "more is better," to a more rational, targeted approach that first was attempted with endocrine therapy and now also is being used with anti-HER2 therapy. Other examples in patients with advanced disease include therapies targeting the epidermal growth factor family of receptors, VEGF receptors, and other angiogenesis targets. The redundancy of many of these pathways suggests the potential need for a combination of drugs targeting multiple steps or more promiscuous drugs that interact with multiple targets.[427] These studies include combinations of existing hormonal and cytotoxic drugs, and the design of these studies is challenging. Patients must have access to high-quality, well-conducted studies to

ensure that useful data are generated, are properly interpreted, and lead to improved cancer care. An important challenge in the treatment of patients with breast cancer is how best to identify those who are most likely to benefit from specific interventions while avoiding unnecessary toxic exposure in those who are unlikely to benefit. Circulating tumor cells, at baseline and after just 4 weeks of therapy, can identify patients early on who are not responding so that a potentially toxic therapy can be discontinued.[108,155] Ongoing trials are now examining whether therapeutic decisions made based on these findings will result in improved clinical outcome.

UNUSUAL PROBLEMS ENCOUNTERED IN BREAST CANCER

Male Breast Cancer

Male breast cancer is rare, accounting for 0.2% of male cancers and fewer than 1% of new breast cancers.[428] Mutations in the BRCA2 gene predispose men to breast cancer and may account for up to 40% of all cases. Most present as infiltrating ductal carcinoma with unilateral, firm, painless masses. Nipple discharge should be taken seriously and is an indication for FNA or core or excisional biopsy. Mammography and ultrasound may be of help and may contribute to differentiating a breast cancer from a gynecomastia. A negative finding on FNA or core biopsy requires an excision procedure, and cytologic findings that show gynecomastia require close follow-up. The tumor phenotype appears similar to that observed in women.

Treatment is modeled after female breast cancer, both locoregional and systemic therapies. There is evidence that SLNB can be safely applied in male breast cancer.[429] Because most patients have endocrine-responsive disease, orchiectomy or chemical castration with LH-RH agonists often is used in patients with advanced disease. Tamoxifen is the most common endocrine therapy used, although androgens, antiandrogens, corticosteroids, estrogens, and progestins have also been used. Aromatase inhibitors are of potential interest in men with metastatic disease. However, approximately 80% of circulating estrogens are derived from the aromatization of precursor androgens with the remaining estrogens come from direct testicular secretion. This explains the apparent lower response rate observed with the first-generation aromatase inhibitor aminoglutethimide compared with tamoxifen and with anastrozole.[430] These observations suggest that orchiectomy and tamoxifen remain the endocrine therapies of choice in men with breast cancer, although a recent report also suggests a role for aromatase inhibitors if given with an LH-RH agonist.[395]

Breast Cancer and Pregnancy

Breast Cancer during Pregnancy

Carcinoma of the breast, although rare in pregnant women, occurs in about 1 to 3 patients per 10,000 deliveries and is the most common malignancy associated with pregnancy. It is expected to become more common with the observed increase in the average age at first full-term pregnancy. The advanced level of disease and the poor prognosis associated with gestational breast cancer appear to be due primarily to delay in diagnosis. For this reason, a thorough examination of the breast should take place during the first obstetric visit, before the breast becomes engorged or hypertrophic, and the obstetrician must pursue early signs of breast cancer actively via a thorough breast examination. Diagnosis and staging are far more difficult in pregnant women because of physiologic changes in the mother and radiation risk to the fetus. Mammograms are not routinely performed—little information can be gained because of pregancy-related increased breast density. Ultrasonography and MRI can be used, although safety of the gadolinium for the fetus has not yet completely been determined. Routine bone scintigraphy is contraindicated in pregnant women.

Biopsy of a mass during pregnancy is difficult and must be undertaken with extreme care to avoid infection and milk fistulas in the lactating breast. FNA and stereotactic NCB are the initial procedures used in evaluating a breast mass, with lactation often suppressed preoperatively with bromocriptine. Biopsy can almost always be performed under local anesthesia; however, no evidence shows that general anesthesia poses significant risk to either the mother or the fetus if proper precautions are taken. There are some data in favor of the safety of SLNB in pregnant women.[431] Modified radical mastectomy is the treatment of choice for breast cancer during pregnancy. Depending on the extent of disease and the predicted delivery date, breast conservation may be considered. Tumor excision and axillary dissection are performed during pregnancy, followed by breast irradiation after delivery. Survival is not improved by therapeutic abortion, and pregnancy-associated breast cancer should be treated using the same decision tree that would be appropriate for a patient who is not pregnant.

While therapeutic abortion early in pregnancy greatly simplifies the treatment of early-stage breast cancer, it does not improve treatment outcome, and there are no reports show that breast cancer is harmful to the fetus, because breast cancer cells cannot traverse the placenta, as in some cases of melanoma, lymphosarcoma, or leukemia. In most cases, chemotherapeutic agents are not recommended for use in pregnant women because of concerns about teratogenesis. The effect on the fetus also is related to drug dosage, gestational age, and the individual patient's tolerance. However, cytotoxic chemotherapy has been administered, mostly after the first trimester, without identifiable damage to the fetus. Data from the M.D. Anderson Cancer Center suggest that women can be safely treated with FAC chemotherapy during the second and third trimesters without sugnificant short-term complications, though little is know about long-term effects on fertility and cardiac function on these children.[432] Administration of paclitaxel also appears feasible, as the drug is a substrate for placental p-glycoprotein and little is transferred to the fetal circulation.[433]

Pregnancy after Breast Cancer

Many women now emerge from treatment for breast cancer with fertility intact, and some will become pregnant. The IBCSG identified in their clinical trial database 94 patients who became pregnant after a diagnosis of breast cancer, including 8 women who had a relapse during pregnancy. The investigators compared the outcome of these patients with the outcome of 188 matched, controlled patients from the same database, and found no adverse effect from pregnancy on survival.[434] Thus far, there is no evidence that pregnancy after breast cancer treatment increases the risk of a worse outcome. However, women who remain premenopausal after chemotherapy are at risk for premature menopause.[339]

Axillary Metastases with Occult Breast Cancer

A woman with clinically suspicious axillary lymph nodes despite negative breast examination and mammogram requires careful evaluation for breast cancer. FNA often allows the diagnosis of adenocarcinoma versus other tumor types. Breast is the most common primary source when dealing with adenocarcinoma, although gastrointestinal (GI) sources or the thyroid often may be involved. It is not unreasonable, therefore, to order a CT scan of the chest and abdomen if further breast imaging with ultrasound and MRI is unrevealing.

The definition of "occult breast carcinoma" is a breast cancer presenting with metastatic axillary nodes without evidence of the primary tumor at the physical, mammographic, or ultrasound examination. Occult breast carcinoma presenting as axillary metastases is

rare, accounting for less than 0.40% of primary operable breast cancer. Occult breast cancer should be differentiated from a contralateral dissemination to the contralateral axillary lymph nodes, accounting for 4%, based on physical examination only. The Memorial Sloan-Kettering experience with 69 patients with occult primary showed that MRI was able to detect a breast carcinoma in 63% of the patients, and no carcinoma was found in the mastectomy specimen when the MRI was negative.[435] For a long time, ipsilateral mastectomy with complete axillary dissection has been the therapy of choice for patients presenting with axillary lymph node metastasis with occult primary.[436] Some reports are showing that conservation of the breast is possible. The Milan group reported, at 43 months' follow-up, a disease-free survival of 84% and two breast recurrences (supraclavicular and multiple metastasis).[437] The M.D. Anderson Cancer Center reported local recurrence in 4 of their 32 patients (13%).[438] These data are in favor of breast conservation in an occult primary. The routine use of MRI in this rare presentation of breast cancer allows detection of the primary tumor in a large number of patients. The 5- and 10-year survival rates are essentially the same as those for T1N1 and T2N1 tumors, and even patients in whom a primary breast cancer is not identified are treated in the same way as patients with N1 breast cancer.

Paget's Disease of the Breast

Paget's disease of the breast is a cutaneous manifestation of underlying breast malignancy. This eczematoid lesion (often weeping, red, and crusting in late presentation) occurs in approximately 1% to 4% of patients with breast cancer, and as many as 50% of patients with Paget's disease may have an underlying cancer. Paget's disease is a carcinoma of glandular origin, and Paget's cells are spread through the epidermis as a result of motility induced by a chemotactic factor released by epidermal cells. The greatest prevalence of Paget's disease of the breast occurs in the sixth decade of life. The infrequency of early diagnosis is associated with a delay in recognition of early symptoms. Although an early sign of Paget's disease is severe itching accompanied by erosive nipple changes, the median delay between first symptom and diagnosis is approximately 6 months, and often longer. Paget's disease associated with a palpable underlying tumor can be treated with breast conservation with removal of the nipple-areolar complex. This procedure usually leaves an acceptable breast mound for subsequent reconstruction of the nipple-areolar complex. SLN biopsy is an appropriate method for evaluating axillary status.

This disease shows the importance of physical examination and physician-patient education. Early-stage Paget's disease of the breast is almost universally associated with prolonged disease-free survival. Several conditions mimic Paget's disease of the breast secondary to underlying breast cancer, including erosive adenomatosis of the nipple and pemphigus vulgaris of the nipple. Although mastectomy has been the traditional surgical approach to this entity, breast conservation, with removal of the nipple-areolar complex, followed by whole-breast radiation, appears equally effective for Paget's disease. Of note in this collaborative study, the group had did not have mammographic or physical evidence of an underlying breast mass.

Cystosarcoma Phyllodes and Sarcomas

Sarcomas of the breast are rare, representing fewer than 1% of malignant breast tumors. Included in this group are benign and malignant forms of cystosarcoma phyllodes (CSP), accounting for approximately 0.5%; carcinosarcoma; and sarcoma. CSP tumors have a characteristic leaf-like architecture, with clefts lined by epithelial cells, and about 25% of the time are associated with fibroadenomas. Some authors refer to benign CSP as giant fibroadenomata, reserving the term CSP for the malignant lesion. The average age at presentation is the mid-40s.

Distinguishing benign from malignant lesions has been emphasized in describing CSP. Several histologic characteristics are considered indicators of malignant CSP, including increased cellularity, subepithelial stromal overgrowth, stromal anaplasia, tumor size, contour, degree of cellular atypia, and mitotic activity. Older series suggested a low risk of death when tumors had fewer than three mitotic figures per high-power field and that stromal overgrowth was associated with a risk of metastases.

Barrio and colleagues[439] at Memorial Sloan-Kettering Cancer Center reviewed the pathologic features and clinical course of 293 women who had CSP. Of these patients, 206 (70%) had benign CSP and 87 (30%) had malignant CSP. Breast-conserving surgery was the local therapy in 242 breasts; mastectomy was chosen in the remaining 48 breasts. With a median follow-up of 7.9 years, 35 patients recurred, for an actuarial 10-year rate of 14.4%. In this series, the classification into "benign" versus "malignant" types was not related to the risk of local failure. Using univariate analysis, the risk of a local failure was increased in women with positive margins, fibroproliferation, and necrosis.[439] CSP tumors usually are treated with wide local excision to include a sufficient margin of normal breast tissue from the tumor bed. Even benign tumors have a high incidence of local recurrence if they are simply shelled out of the breast tissue, and meticulous effort is required to obtain an adequate tissue margin. Recurrences of benign CSP may be re-excised, again with wide margins, but some cases are better managed by mastectomy and reconstruction. In a SEER series of 821 women diagnosed with malignant CSP, 52% were treated with mastectomy and the remaining 48% with lumpectomy. In this nonrandomized series, the patients treated with lumpectomy were younger, had smaller tumors, and had an improved cause-specific survival, but the role of radiation is not adequately described.[440]

Aside from malignant CSP, sarcomas of the breast include a wide range of histologic types, such as carcinosarcoma, osteosarcoma, liposarcoma, angiosarcoma, malignant histiocytoma, leiomyosarcoma, stromal sarcoma, and mixed types. Carcinosarcoma is different, in that it is composed of a combination of malignant epithelial cells, as would be found in breast adenocarcinoma, in addition to malignant stromal cells characteristic of sarcoma. These tumors may behave somewhat differently from pure sarcomas and can spread to axillary lymph nodes. Treatment of carcinosarcoma usually includes mastectomy with adequate tissue margins, including muscle and skin, if necessary, and decisions about chest wall irradiation are influenced by tumor size, location, and margins. North and colleagues at the Roswell Park Cancer Institute reported 25 patients treated for breast sarcoma (10 with angiosarcomas) between 1964 and 1995.[441] These patients had a median age of 55 years, 10 had a mastectomy, and their 10-year overall survival rate was 36%. In general, the type of surgery is determined by breast size, and, while wide local excision is adequate primary surgical treatment for most lesions, attention should be given to obtaining wide margins, including deep muscle, if needed. Tumors larger than 5 cm and high-grade tumors may require mastectomy, possibly with chest wall resection, and the surgeon should approach these tumors according to the established guidelines for sarcoma surgery. Lymph node dissection is not usually recommended due to the hematogenous nature of its dissemination. Imaging studies are recommended to rule out systemic dissemination (e.g., lung) at presentation. Adjuvant radiation therapy should be considered on a case by case basis, although data are limited, and little is known on the role of adjuvant chemotherapy. Therefore, while the rarity of breast sarcomas limits the rigorous evaluation of therapeutic options, it seems appropriate to approach sarcomas of the breast using therapeutic methods derived from the soft tissue sarcoma literature.

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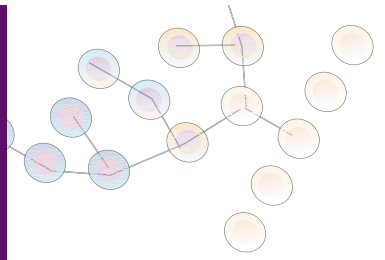
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96 Sarcomas of Bone

Mark C. Gebhardt, Dempsey Springfield, and James R. Neff*

SUMMARY OF KEY POINTS

Incidence and Epidemiology
- More than 2400 new cases of bone sarcoma are diagnosed annually in the United States.
- No specific etiologic agents are identified in the majority of cases.
- Secondary neoplasms are related to known oncogenic factors (e.g., ionizing radiation, alkylating chemotherapy agents, combinations of both).
- Hereditary cancer syndromes (tumor suppressor genes) are responsible for some cases.

Diagnosis and Radiographic Staging
- Plain radiographs are recommended.
- Magnetic resonance imaging (MRI) scan of primary tumor is the best radiographic study to obtain.
- Chest x-ray is indicated; chest computed tomography (CT) is indicated for suspected malignant lesions.
- Whole-body technetium-99m (^{99m}Tc) bone scan is indicated.
- Positron emission tomography (PET) scanning is controversial and has yet to be generally accepted.
- Needle or open biopsy is necessary for a tissue-specific diagnosis and to determine histologic grade.
- In the pathology review, immunohistochemistry and cytogenetics are important.
- Electron microscopic tissue occasionally is required.

Prognostic Factors
- Metastasis at presentation is a worse prognostic finding.
- Histologic grade is the next most significant prognostic indicator.
- Size is less significant, but lesions larger than 10 cm in diameter have a poor prognosis.
- Tumor response to neoadjuvant chemotherapy
- Surgical margins of resection (minimum of a "wide" margin)

Staging System
- The American Joint Committee on Cancer now monitors location, grade (high and low), depth, and size (8 cm); designates "skip" lesions (T_3); and separates metastasis to bone from other sites (Mla, Mlb).
- The Musculoskeletal Tumor Society monitors location (intracompartmental and extracompartmental), grade (high and low), and metastasis ("skip" lesions, nodal, bone, and lung are all lumped together).

Primary Therapy
- A wide surgical margin is recommended.
- Limb-sparing procedures are appropriate for 70% to 90% of patients.
- Adjuvant irradiation is not routinely used for bone sarcomas.
- Local recurrence rates for limb-sparing procedures approach 5% or less.
- Reconstruction methods can be tailored to patients' needs.
- New and improved biocompatible implant materials and improved designs are available.

Future Trends
- The search continues for new drugs, drug schedules, potentiating agents, and improved dose intensity.
- Identification of risk factors (e.g., cytogenetic, molecular genetic, and signal transduction abnormalities) will improve to identify new methods of potential treatment.

INTRODUCTION

Approximately 2400 new malignant tumors of bone (excluding multiple myeloma) are diagnosed each year in the United States. The femur is the most common site, but primary sarcoma can occur in any bone. Osteosarcoma, Ewing's sarcoma, and chondrosarcoma account for approximately 90% of all primary sarcomas of bone. The management of osteosarcoma and Ewing's sarcoma includes chemotherapy and surgery, while chondrosarcoma is treated by surgery alone.[1] The management of these patients, from initial evaluation and biopsy through surgical therapy and long-term follow-up, is labor intensive and technically demanding. Patients with a bone sarcoma should be treated in a center that has expertise in the management of these tumors.

Surgical Staging System

Currently, the staging system adopted by the Musculoskeletal Tumor Society (MSTS) in 1980 and modified in 1986 is accepted by most musculoskeletal oncologists.[2–4] Malignant tumors are divided into only two histologic grades: low-grade malignant (G1) and high-grade malignant (G2). Low-grade malignant lesions (G1), comprising Broder's I and II lesions, have a low probability of metastasis (25%). The majority of these tumors can be managed by relatively conservative surgical procedures and do not require chemotherapy.

*Deceased.

The authors dedicate this revised and updated chapter to the memory of James Russell Neff (1940–2005) who was the original author. Dr. Neff was a leading specialist in treating cancer of the bone and soft tissues who was known internationally for performing innovative procedures to help people lead more normal lives following cancer.

High-grade lesions (G2), Broder's III and IV tumors, have a significantly higher incidence of metastases, requiring more radical surgical procedures and possibly neoadjuvant and/or adjuvant chemotherapy. Table 96-1 is a representative grouping of both low- and high-grade malignant tumors of bone and soft-tissue origin.

Bone sarcomas that are totally intraosseous are intracompartmental (T_1 or A). Those that penetrate the cortex are considered extracompartmental (T_2 or B; Table 96-2).

Patients without evidence of metastatic disease after radiographic staging are designated M0. In general, metastatic disease that is evident in the lung, in the lymph nodes, or as an intramedullary "skip" lesion indicates a poor prognosis and is designated M1.

Surgical procedures are defined by the relationship of the circumferential surgical plane of dissection and the pseudocapsule. Surgical margins are defined as intralesional, marginal, wide, and radical. Examples of intralesional margins include curettage of a presumed benign tumor and cytoreductive debulking procedures. Marginal margins, achieved when the plane of dissection passes through the reactive zone of the pseudocapsule, are suitable for management of the majority of benign tumors. Such margins are accomplished when the surgeon "shells out" a neoplasm, cleaving the tissue between the reactive zone and the zone of compression. This technique leaves behind viable tumor satellites at the periphery of the lesion; thus, marginal margins are not sufficient for local control of malignant or benign "aggressive" lesions.

A wide margin is obtained when the plane of dissection passes through absolutely normal nonreactive tissue that is well removed from the pseudocapsule. Wide margins are sufficient for virtually all bone sarcomas.

Radical margins of a bone sarcoma are achieved when the entire bone is removed. This usually requires an amputation. A radical margin is rarely necessary.[5]

The American Joint Committee on Cancer (6th edition) has adapted the TNM staging system to bone. The topography (T) of the primary tumor now includes size based on relevant published reviews, in which the greatest dimension (8 cm for Ewing's tumor, 9 cm for conventional osteosarcoma) has replaced the compartment concept. Also, T3 has now been assigned to patients who develop "skip" metastases (Table 96-3).

The problem of defining histopathologic grade (G) has been addressed and now essentially consists of low- and high-grade lesions (Table 96-4). G1 and G2 have been combined into low-grade and G3 and G4 into high-grade histopathology. Currently, all Ewing's tumors are classified as G4 or high-grade. This grouping is now identical to the G1 and G2 of the MSTS staging system. The stage groupings are shown in Table 96-5. Here, the committee has appro-

Table 96-1 Surgical Grade (G)

Low (G1)	High (G2)
Parosteal osteosarcoma	Classic osteosarcoma
Periosteal osteosarcoma	High-grade surface
Low-grade central osteosarcoma	Paget's sarcoma of bone
	Radiation sarcoma
Intraosseous osteosarcoma	
Secondary chondrosarcoma	Primary chondrosarcoma
	Dedifferentiated chondrosarcoma
	Mesenchymal chondrosarcoma
Clear cell chondrosarcoma	
Fibrosarcoma, Kaposi's sarcoma	Fibrosarcoma
Atypical malignant fibrous histiocytoma	Malignant fibrous histiocytoma (MFH)
	MFH of bone
	Undifferentiated primary sarcoma
	Giant cell sarcoma, bone
Hemangioendothelioma	Angiosarcoma
Hemangiopericytoma	Hemangiopericytoma
Myxoid liposarcoma	Pleomorphic liposarcoma
	Neurofibrosarcoma (schwannoma)
Clear cell sarcoma	Rhabdomyosarcoma
Epithelioid sarcoma	Synovial sarcoma
Chordoma	Ewing's sarcoma of bone
Adamantinoma	PNET (primitive neuroepithelial tumor)
Alveolar cell sarcoma	
Other and undifferentiated	Askin's tumor
	Alveolar cell sarcoma

Table 96-2 Surgical Sites (T)

Intracompartmental (T1)	Extracompartmental (T2)
Intraosseous	Soft-tissue extension
Intra-articular	Soft-tissue extension
Superficial to deep fascia	Deep fascial extension
Parosseous	Intraosseous or extrafascial
Intrafascial compartments	Extrafascial planes or spaces
Ray of hand or foot	Midfoot and hindfoot
Anterolateral leg	Popliteal "space"
Posterior leg	Groin-femoral triangle
Middle thigh	Intrapelvic (retroperitoneal)
Posterior thigh	Midhand
Buttocks	Antecubital fossa
Dorsal forearm	Axilla
Volar forearm	Periclavicular
Anterior arm	Paraspinal
Posterior arm	Head and neck
Periscapular	

Adapted from Enneking WF, Spanier SS, Goodman MA: A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980;153:106.

Table 96-3 Definition of TNM Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤8 cm in greatest dimension
T2	Tumor >8 cm in greatest dimension
T3	Discontinuous tumors in the primary bone site

Adapted from Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer Verlag, 2002.

Table 96-4 Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated–low grade
G2	Moderately differentiated–low grade
G3	Poorly differentiated–high grade
G4*	Undifferentiated–high grade

*Ewing's sarcoma is classified as G4.

Adapted from Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer Verlag, 2002.

priately addressed the difference in prognosis of patients who have sustained metastases to lung (Mla) and to other sites, including bone (Mlb).

Radiographic Staging

Conventional bone radiography remains the single most useful initial study for bone tumor evaluation. The study should include anteroposterior (AP) and lateral projections of the lesion. Malignant neoplasms usually result in ill-defined or "poorly marginated" radiographic margins with little or no reactive bone, loss of medullary trabeculation, and endosteal cortical erosion, suggesting an active and destructive process at the tumor/host bone interface. The pathologic process biologically overwhelms the normal time-dependent reactive processes of bone formation. Therefore, the radiographic presence or absence of a reactive rim of bone is often useful in predicting the biologic aggressiveness of the pathologic process (Table 96-6). Neoplastic bone formation is often seen in osteosarcoma, and calcification is often seen in chondrosarcoma.

The use of technetium-99m (^{99m}Tc) bone scintigraphy remains the standard for surveying the skeleton for multiple osseous lesions. The test can be administered as a single delayed static study or can be displayed in multiple timed phases to evaluate the vascularity of the lesion. It is important to obtain a whole-body bone scan.

Computed tomography (CT) is superior to magnetic resonance imaging (MRI) only to evaluate a small lesion in the cortex, subtle bone formation, or calcification; otherwise, MRI is the study of choice. CT remains the standard for evaluation of the chest for occult metastases. The cross-sectional display usually provides sufficient resolution (<0.5 cm) to demonstrate subpleural metastases long before they become evident on plain chest films. Before definitive therapy or local management of a potentially malignant lesion, a staging CT evaluation of the chest and mediastinum should be performed.[6]

The majority of bone sarcomas are best evaluated by a single well-planned MRI using specific predetermined planes and images with

Table 96-5 Stage Grouping

Stage 1A	T1	N0	M0	G1, 2 low grade
Stage 1B	T2	N0	M0	G1, 2 low grade
Stage IIA	T1	N0	M0	G3, 4 high grade
Stage IIB	T2	N0	M0	G3, 4 high grade
Stage III	T3	N0	M0	Any G
Stage IVA	Any T	N0	M1a	Any G
Stage IVB	Any T	N1	Any M	Any G
	Any T	Any N	Mlb	Any G

Adapted from Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer Verlag, 2002.

Table 96-6 Radiographic Techniques Available

1. Plain films: loss of trabeculation, matrix identification, calcification, etc.
2. Polytomes: evaluate margination, matrix identification, calcification, etc.
3. Bone scan: three phases to evaluate vascularity, static skeletal survey
4. Rapid whole-body STIR MRI: excellent survey study with cooperative patients and in institutions using these techniques
5. CT: margination, matrix identification, calcification, cortical disruption, axial localization of lesion
6. MRI: excellent soft-tissue contrast, sometimes nearly diagnostic; T_1 best for anatomy, contrast enhancement, magnetic resonance angiography capability, best overall single study when properly monitored by a physician
7. PET: adds metabolic parameter used to monitor effectiveness of neoadjuvant chemotherapy
8. Other: ^{201}T1 scan, gallium scan, PET scan

intravenous contrast. The T_1-weighted images produce superior anatomic detail, while T_2-weighted images best characterize the structure and composition of the lesion (solid, homogeneous, heterogeneous, cystic, or combinations of these characteristics). The use of intravenous contrast is valuable in assessing the tumor's vascularity and to reveal the tumor's relationship to the neurovascular bundle.

Overall, MRI provides superior sagittal, coronal, and multiaxial anatomic detail in both soft tissues and bone. MRI data are indispensable in assessing the intramedullary extent of the lesion (e.g., osteosarcoma, osteomyelitis, Ewing's sarcoma) or assessing "skip" metastases either within the contiguous medullary canal or across adjacent joint surfaces.

Currently, MRI of the primary tumor appears somewhat predictive of tumor response to neoadjuvant therapy. Changes in the T_2-weighted image signal intensity correlate with an obvious reduction in tumor volume (especially in Ewing's sarcoma) and appear predictive of tumor necrosis.[7] The addition of contrast enhancement does not appear to provide more viable tumor/necrotic tumor contrast than do T_2-weighted images; however, the absence of contrast enhancement appears to be an indicator of tumor necrosis.[7–10]

Positron emission tomography (PET) has been used to predict an osteosarcoma's response to chemotherapy. PET scan might be valuable in the initial screening, but this has yet to be determined.

Staging Biopsy

The staging biopsy might well be the most important and difficult procedure that is performed in the patient's management (Box 96-1). The placement, length, and orientation of the biopsy scar and the anatomic compartments that are contaminated during the biopsy procedure dictate which tissues and how many surgical compartments will require removal for local tumor management and limb-sparing surgery. A thorough knowledge of the soft-tissue anatomic planes and muscle compartments is mandatory before proceeding with bone biopsy. Consideration should be given to the location and type of biopsy to be used, whether fine-needle aspiration biopsy, core-needle biopsy, or open biopsy. In addition, it is critical that adequate diagnostic tissue be obtained so that an accurate diagnosis can be made. Usually, a core-needle biopsy is sufficient.

OSTEOSARCOMA

Osteosarcoma, the most common primary sarcoma of bone, is a complex and heterogeneous set of neoplasms. It is defined as a

Box 96-1. GUIDELINES FOR BIOPSY

Excisional Biopsy: Soft-Tissue Lesions Less Than 2.5 to 3.0 cm

1. Planning: must provide potentially curative margins
2. Superficial lesions: must include contiguous deep fascia as deep margin
3. Deep lesions: myectomy where possible
4. Obtain appropriate sterile specimens prior to contamination of specimen (e.g., cytogenetics)
5. Absolute hemostasis
6. Avoid drain; when necessary, place drain tract in-line and 1 cm from incision to facilitate reexcision if necessary
7. Subcuticular closure and supportive skin adhesive strips

Incisional Biopsy: Soft-Tissue Lesions 2.5 to 3.0 cm

1. Planning: plan most appropriate biopsy tract, avoid transverse incisions
2. Use pneumatic tourniquet after gravity exsanguination
3. Avoid contamination of joint
4. Avoid exposure of neurovascular structures
5. Monitor biopsy with frozen sections
6. Microbiologic culture if question
7. Maintain integrity of deep tumor/host margin; could extend necessary surgical margin
8. Absolute hemostasis; thrombogenic agents (thrombin, Oxycel, Avitene, etc.)
9. Hemostatic closure of pseudocapsule
10. Subcuticular closure and adhesive strips

sarcoma that directly produces tumor osteoid or bone. The classical osteosarcoma is a high-grade lesion, but there are many variants that vary in grade and behavior. Classic osteosarcoma is characterized by a bimodal age distribution, with the first peak in the second decade of life and the second much later, in the sixth and seventh decades. Osteosarcoma in adults is often associated with other underlying disease processes.

Historical Review

High-grade osteosarcoma used to be a fatal neoplasm leading to metastases and death of 90% of patients despite aggressive local control, including radical amputations and/or radiotherapy. The version of this chapter in the previous edition outlined the evolution of the use of adjuvant chemotherapy and the dramatic improvement in survival and event-free survival (EFS) that followed. Initially, the benefits of adjuvant chemotherapy were questioned, leading to the need for a randomized study comparing surgical management alone to surgery followed by multiagent chemotherapy. The active drugs were shown to be doxorubicin, high-dose methotrexate, and cisplatin. A randomized study, including both the randomized patients and those who chose whether or not to have adjuvant chemotherapy, clearly demonstrated the benefits of adjuvant chemotherapy.[11,12]

Surgical advances paralleled the advances in medical management of osteosarcoma patients. Originally, disarticulation or resection of the entire involved bone was recommended for surgical management of osteosarcoma.[13] This was due in part to the intramedullary origin of the tumor with proximal intramedullary growth and the reported 25% incidence of intramedullary "skip" metastases.[14] Later studies reviewing the local recurrence rates for patients whose primary management was transmedullary amputation alone revealed local recurrences in approximately 5% to 10%, suggesting that the incidence of "skip" or intraosseous metastasis was probably lower than originally believed. The general standard of surgical management of patients with extremity osteosarcoma in 1980 included transmedullary amputation approximately 5 to 7 cm proximal to the intramedullary extent of the tumor.[15]

Limb salvage therapy became more widespread in the 1980s as chemotherapeutic advances were made. Surgeons learned from examining amputation specimens that the nerves and vessels could often be separated from the tumor with a plane of normal tissue between the tumor and the neurovascular bundle, and imaging improved, so this could be determined accurately before the operation. Initially, bone scans and angiography were used. CT imaging improved this further, but MRI revolutionized the surgeon's ability to determine the extent of the tumor preoperatively.

Initially, the reconstructions were biologic: arthrodeses about the knee and shoulder, for example, or resections of expendable bones that did not require reconstruction (fibula, clavicle). Advances in design of custom prostheses subsequently made it possible to preserve mobile joints, borrowing from the advances that had been made in arthroplasty for arthritis. Bone allografts were also used to reconstruct limbs following tumor resection and included osteoarticular grafts, allograft-arthrodeses, intercalary reconstructions, and allograft-prosthetic composites. Finally, the advent of modular prostheses, rather than custom ones, allowed the surgeon to custom design the implant for the specific defect in the operating room, and these modular prostheses are in current use and constantly undergoing design improvements.

One of the events that led to the popularization of limb salvage was the use of preoperative chemotherapy. Initially implemented during the time it would take to manufacture a custom prosthesis, it became apparent that the tumor showed clinical and radiographic "response" to the preoperative (neoadjuvant) chemotherapy. This seemed to make the subsequent surgery easier, if not safer, and gave the surgeon 10 to 12 weeks to work with the patient to decide on the best surgical option. There was initial concern that the delay in the resection might worsen the prognosis, but this issue was addressed in a randomized trial that showed no apparent advantage to having the surgery initially compared to the neoadjuvant mode of administration.[16] In addition, it was learned that the histologic response to the preoperative chemotherapy was a predictor of outcome and, second only to the presence of metastases at diagnosis, was the best predictor of survival.[16,17]

Epidemiology

Conventional, or classic, osteosarcoma makes up the majority of all osteosarcomas. It occurs primarily in the metaphyses of adolescents with open physes or in young adults. Most patients with classic osteosarcoma are under the age of 30 years, and many have no apparent predisposing factors.[18] The lesion most often arises in the larger, more active epiphyses (e.g., distal femur, proximal tibia, proximal humerus) but also can arise in the flat bones of the pelvis, skull, scapula, and ribs and in the spine. Overall, the majority of the lesions develop in the extremities and pelvis.[19]

An epidemiologic study conducted in Sweden between 1971 and 1984 investigated possible changes in the typical features of 227 conventional osteosarcomas. The mean annual incidence was 2.1 per million. The male-to-female ratio of 1.6 : 1.0 remained unchanged over the study period, as did the location and distribution of the tumors. The only clear change over the study period was an increase in the age of patients beyond the classical peak age range of 10 to 29 years.[20]

Ten percent of patients develop osteosarcoma after the age of 60. This group composes the second peak of the bimodal age distribution curve. In these older patients, the anatomic region of presentation differs substantially from the sites of classic osteosarcoma. Whereas more than 50% of patients with classic osteosarcoma develop lesions in the region of the knee (the largest and most active epiphyses), only 15% of the older patients develop osteosarcoma at that site. Moreover, osteosarcomas in the older population characteristically present in regions that have had previous radiotherapy, underlying Paget's

disease of bone, fibrous dysplasia, or some other pathologic abnormality. In many ways, the older group can be thought of as having "secondary" osteosarcoma.[21]

An estimated 2000 malignant bone tumors are diagnosed in the United States each year. Approximately 750 of these patients have classic or conventional osteosarcomas. Males are affected slightly more often than females. Females develop classic osteosarcoma slightly earlier than males, and there appears to be no race predilection.[22] Although the common histologic presentation of malignant cells producing osteoids would suggest a homogenous group of tumors, the morphologic appearance can vary considerably, ranging from classic osteoblastic osteosarcoma (45% of cases) through fibroblastic (9%), chondroblastic (27%), anaplastic (17%), telangiectatic, low-grade central, and other osteosarcomas (2%).[23]

A separate group of osteosarcoma variants, including high-grade surface, extraskeletal, pagetoid, intracortical, low-grade central osteosarcoma, parosteal and periosteal osteosarcomas, small cell osteosarcoma, secondary tumors, and therapy-related tumors, will be discussed in a later section of this chapter.

Pathogenesis

Osteosarcoma is a high-grade sarcoma comprising malignant osteoblasts that vary in size and shape and have bizarre mitoses. Proposed histologic grading systems for osteosarcoma appear to be of little value.[24] Attempting to grade an osteosarcoma presents many difficulties that limit the usefulness of any grading system. For example, many tumors are heterogeneous, and tissues sampled from separate areas of the same tumor may give different impressions. The number of mitoses, the degree of cellularity, and cellular anaplasia or pleomorphism can differ from site to site within the same tumor. Tumors of identical histologic appearance often differ in their clinical behavior. All "classic" or conventional osteosarcomas are considered high-grade. Osteosarcoma is a vascular tumor, and the tumor osteoblasts produce tumor osteoid or woven bone (Figs. 96-1A and B). These tumors are poorly differentiated and may take on a fibroblastic or chondroblastic appearance on light microscopy (Figs. 96-1C and D), but if there are areas of bone formation, they are considered osteosarcomas. In fact, a high-grade chondroblastic sarcoma in a child or adolescent on biopsy is considered to be an osteosarcoma (and treated as such) until proven otherwise from examination of the entire specimen (chondrosarcomas are extremely unusual in children). The tumor usually originates in the metaphysis of the bone and percolates between the pre-existing trabeculae of bone, incompletely destroying the existing bone, presumably because of its rapid growth (seen well in Fig. 96-1A). The tumor eventually follows the vascular Haversian and Volkmann canals in the cortex, partially resorbing the normal cortex and replacing it with tumor bone as it spreads to the adjacent soft tissue. The periosteum is lifted and tries to respond, but the response is incomplete, leading to the appearance of Codman's triangle on a radiograph. It may also cause perpendicular striations of bone, the so-called starburst appearance of osteosarcoma. Proximally, the tumor ends fairly sharply in the medullary cavity, but "skip metastases" may be detectable in the marrow surrounding the tumor in a small proportion of patients. The physis or growth plate is a relative barrier to tumor spread, but because the open physis has vascular channels, it is well documented that the tumor will cross the growth plate and enter the epiphysis. The articular cartilage is a more definitive barrier, and osteosarcomas seldom cross the articular cartilage unless there has been a fracture. It may spread into the joint at the periphery of the cartilage or enter the joint along ligaments such as the cruciate ligaments of the knee, but this is a relatively rare event (Fig. 96-2).

Telangiectatic osteosarcoma, a predominantly radiolucent, destructive osteosarcoma variant, becomes fatal rapidly. Histologically, it is composed of single or multiple dilated spaces containing blood or degenerated tumor cells and lined by anaplastic, mitotically active sarcoma cells.[25] Telangiectatic osteosarcoma must be differentiated from aneurysmal bone cyst, to which it can be similar in appearance both radiographically and histologically.

A review of 124 patients with telangiectatic osteosarcoma spanning the years 1921 to 1979 suggested no differences in survival

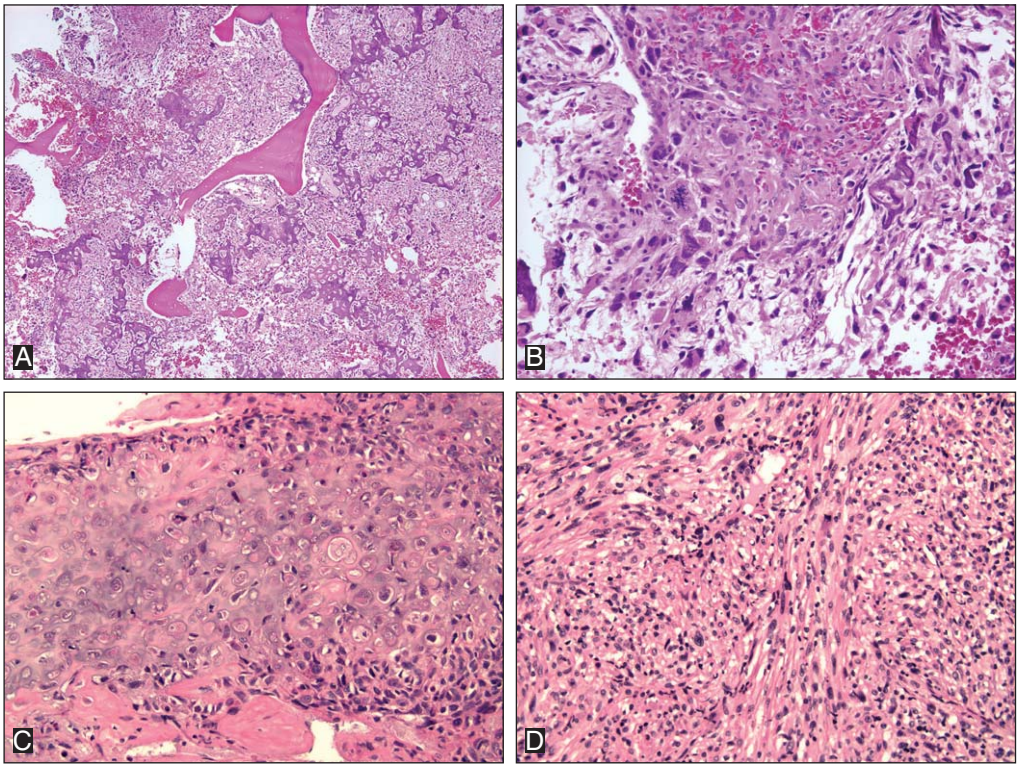


Figure 96-1 • **A,** Low-power photomicrograph of an osteoblastic osteosarcoma showing residual trabeculae of medullary bone surrounded by a cellular tumor. This pattern of invasion of bone indicates a malignant tumor even at this power. One can see the lacy, woven tumor bone formation by the sarcoma in contrast to the partially resorbed pre-existing lamellar bone trabeculae. **B,** High-power photomicrograph of an osteosarcoma showing bizarre, pleomorphic tumor cells that vary in size and shape and have large, aberrant nuclei. Some cells show abnormal mitoses, and intermixed is scant woven tumor bone. **C,** Field showing a chondroblastic osteosarcoma. The malignant cartilage formation is well demonstrated. One would have to search other areas of the tumor to document bone formation that was present in this case. **D,** Field showing a high-grade spindle cell sarcoma area that is characteristic of a fibroblastic osteosarcoma.

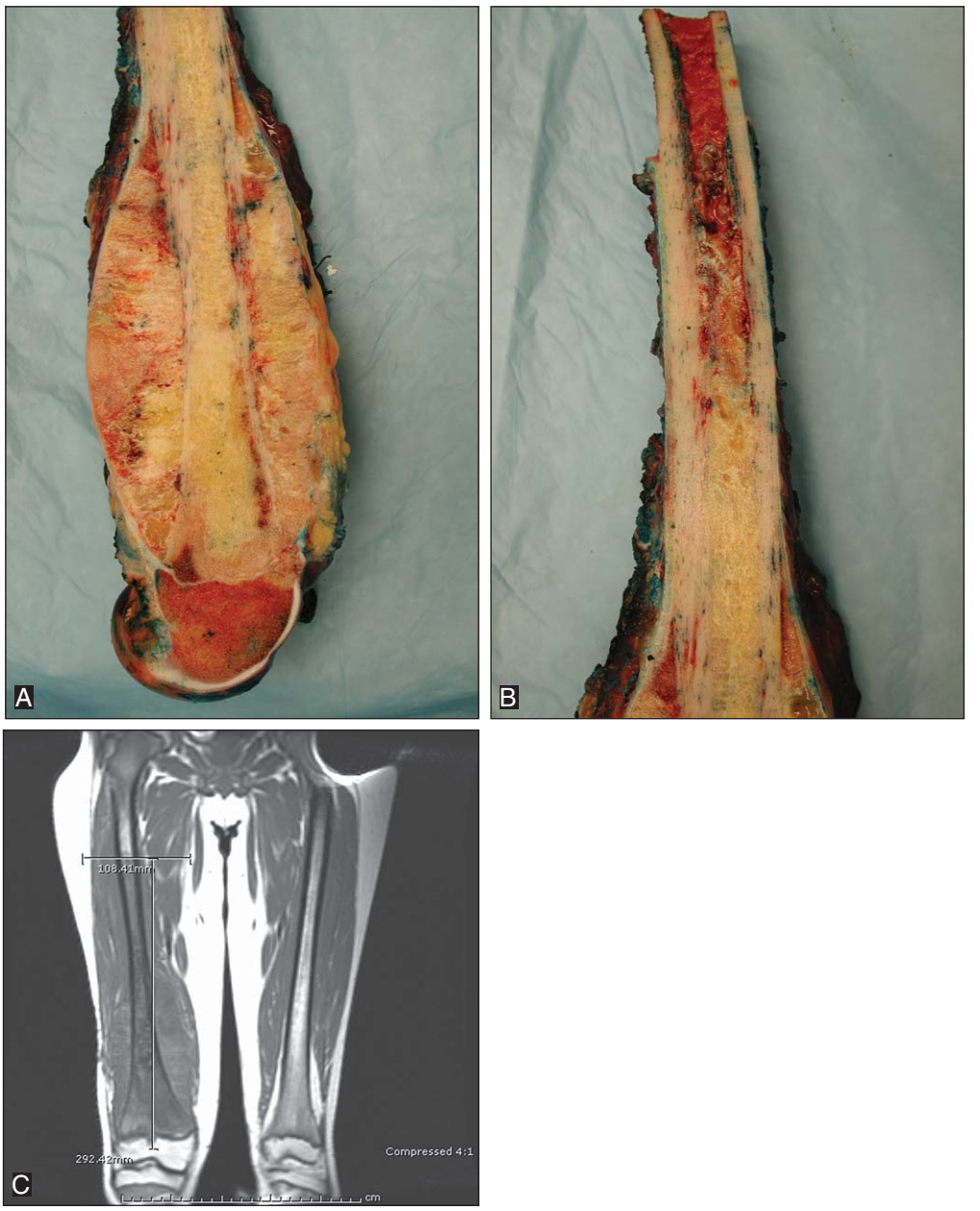


Figure 96-2 • **A,** Gross photograph of an osteosarcoma of the distal femur. The medullary cavity is filled with tumor, which has replaced the normal marrow contents. The tumor has penetrated and incompletely destroyed the cortex and penetrated through the growth plate distally. The Codman triangle, which is an incomplete host periosteal response, is well demonstrated. Histologically, this would show woven periosteal bone. One can also appreciate how this tumor could enter the joint under the synovium, anteriorly in this case. **B,** A section from higher in the femur shows where the medullary extent of the tumor ends rather abruptly. There is a margin of normal marrow proximal to the marrow extent. **C,** Coronal T_1-weighted image of this case nicely shows the extent of the tumor in the medullary cavity and the penetration of the growth plate. It corresponds to the preceding findings seen on the gross specimen.

compared with patients with conventional osteosarcoma. Further analysis demonstrated that the favorable outcome in 17 of the patients with telangiectatic osteosarcoma was related to their being treated with multiagent chemotherapy. Twenty-five patients had received this therapy, and 17 were free of disease at 5.5 years, demonstrating the response to chemotherapy in this highly vascular tumor.[26]

Cytogenetic Findings

A small subset of osteosarcomas is hereditary.[27] Osteosarcoma in siblings occurs in fewer than 1 in 1000 to 1 in 3000 osteosarcoma patients.[28,29] Observation of two or more affected siblings in a family indicates an underlying genetic predisposition.[29–36] When siblings in multiple generations are affected, an autosomal dominant disorder is most likely responsible. One example would be the hereditary form of retinoblastoma. Individuals with hereditary retinoblastoma (germline retinoblastoma gene mutation) have a 2000-fold risk of developing osteosarcoma in the second decade of life when compared with the general population.[37–42]

The gene for retinoblastoma (RB) has been localized to the long arm of chromosome 13 (13q14). The RB gene is recognized as the prototype of a tumor suppressor gene and has been implicated in the pathogenesis of a number of human neoplasms.[42,43] A tumor suppressor gene normally functions by restraining cell (tumor) growth, so loss of function or inactivation of a tumor suppressor gene results in tumor growth. Loss of 13q14 (the RB gene) is thought to be responsible for the development of retinoblastoma.[43–47] A two-hit kinetic model for this class of genes was proposed by Knudson.[48] For hereditary retinoblastoma, the primary mutation in one RB locus occurs in germinal cells; for sporadically occurring retinoblastoma, the primary mutation exists in somatic cells. The second step, responsible for malignant transformation, is the loss of function of the remaining normal homolog in somatic cells by some chromosomal rearrangement or mutation identified as loss of heterozygosity for markers in

or around the RB gene.[37,39–51] Molecular analyses of both sporadic osteosarcomas and osteosarcomas from patients with retinoblastoma have revealed homozygous loss of RB gene function in a high percentage of cases.[37,38,44–56] Assessment of loss of heterozygosity at the RB gene in a study by Feugeas and colleagues[57] revealed that RB gene locus loss of heterozygosity could be an early predictive feature for osteosarcomas with a potentially unfavorable outcome. Osteosarcoma develops in 12% of patients with bilateral retinoblastoma, yet as many as 70% of osteosarcomas have a dysfunctional RB gene product.[25,58–63] Thus, other oncogenes are likely implicated in the oncogenesis of osteosarcoma.

Several investigators have demonstrated that the mutational profiles of the RB gene in osteosarcoma are basically the same as those for retinoblastoma and that mutation of the RB gene plays an essential role in the development of osteosarcoma.[44,52] Besides loss of gene function at the locus on chromosome 13, however, loss of heterozygosity for other chromosomal loci, such as 3q, 17p, and 18q, has been implicated.[52,64–69]

Clinical Features

There are no specific clinical findings for osteosarcoma. Bone sarcomas usually present with pain around a joint and a mass. A traumatic event is often in the history, but it is unlikely that the trauma "caused" the tumor; rather, the trauma is the event that calls the tumor to the patient's attention. The symptoms are often missed initially because other causes of joint pain are much more common. It is not unusual for symptoms to date back to 6 months prior to the documentation of the tumor. This is perhaps changing with the recent abundance of MRI in the evaluation of even minor joint pain.

The plain radiograph is the best diagnostic tool. Osteosarcomas may either completely destroy the bone (radiolucent lesion) or replace the bone with a blastic response (radiodense), but they most often do both. The radiograph shows areas of destruction of the host bone and blotchy densities of new (tumor) bone production. The lesion is most frequently in the metaphysis of a long bone in the adolescent or child and in the flat bones in the adult, but any bone can be involved at any age (Figs. 96-3A and B). The tumor is usually large, destroys the cortex, and is associated with a soft-tissue mass. The mineralization of the matrix is often apparent, but because these tumors can contain areas of chondroblastic and fibroblastic as well as osteoblastic sarcoma, the pattern on mineralization might not be that of bone.

There are no blood laboratory studies that aid in the diagnosis of osteosarcoma, but it has been shown in several large series of patients that an elevated level of alkaline phosphatase and/or lactic dehydrogenase is associated with a worse prognosis.[70–72]

Radiographic Staging Studies

The ^{99m}Tc bone scan has been considered superior to other imaging studies for surveying the skeleton for metastatic or multiple lesions and for later detecting the development of skeletal metastases (Fig. 96-3C).[73]

MRI is the single most useful study in evaluating the intraosseous and extraosseous extent of the primary tumor and in detecting intramedullary or transarticular "skip" metastases. It has been well demonstrated that MRI better identifies the edema (high water content) in and around the reactive zone of the pseudocapsule illuminating the potential surgical margin. MRI has also been shown to be superior to CT in displaying the medullary canal extent of the tumor, suspected "skip" lesions, soft-tissue extension, and overall anatomic location of an extremity tumor (Figs. 96-3D–F).[74] MRI with or without magnetic resonance angiography is the single most valuable tool for planning limb-sparing surgical procedures.[75–77] Radiologic staging and presurgical planning have been improved significantly by the use of MRI.[78,79] Serial MRI studies are less reliable, however, in evaluating tumor response to primary chemotherapy and are more predictive of a poor rather than a good response. By demonstrating an increase in size of the tumor, more bone destruction, and soft-tissue invasion on serial studies, MRI is more accurate as a measure of a poor chemotherapy response.[7,80,81]

Metastases to bone and/or lung are usually assessed by a whole-body ^{99m}Tc bone scan and a complete CT of the chest and mediastinum. Regional lymph node involvement is unusual unless the tumor directly involves the skin or regional lymphatic structures.

PET scans have been used in an attempt to stage and separate high-grade from low-grade tumors.[82] Brenner and associates[83] summarized the current usefulness of ^{18}F-FDG PET in patients with osteosarcoma. High-resolution CT has been shown to be superior to ^{18}F-FDG PET for detecting pulmonary metastases and is not recommended to detect bone metastases except when a suspected "skip" lesion has been identified on MRI. PET does not make it possible to differentiate between high- and low-grade osteosarcoma. It could be useful, however, in determining the appropriate area to biopsy to identify viable representative tumor tissue and in distinguishing benign aggressive lesions from other lesions where local recurrence is likely.

^{18}F-FDG PET may be most useful in determining the response to neoadjuvant chemotherapy and in demonstrating a region of viable tumor.[84] The timing between the initiation of preoperative chemotherapy and the point at which ^{18}F-FDG PET becomes predictive remains uncertain. The response to soft-tissue postchemotherapy inflammation and healing surrounding the tumor must be characterized before this technique becomes predictive of preoperative response to chemotherapy. PET also has potential usefulness in patient follow-up, differentiating postoperative tissue changes and possible tumor recurrence especially in patients with metallic reconstructions. Orthopedic implants often hamper assessment by CT or MRI, and sequential ^{18}F-FDG PET scans could differentiate between recurrent tumors and the normal healing process. Also, because ^{18}F-FDG PET provides scanning of the entire patient, it may be useful when combined with CT of the chest to detect first evidence of pulmonary metastasis.[85]

Once the staging workup is complete, a biopsy is performed. This can be either an open biopsy or a needle biopsy (core-needle or fine-needle aspirate) depending on the experience of the surgeon, the interventional radiologist, and the pathologist. If an open biopsy is performed, it should be done by the surgeon who will be responsible for local control, with a view to placement in a site that can be resected with the definitive specimen. If a core-needle biopsy is performed by an interventional radiologist (which is becoming more frequent), the radiologist and the surgeon should agree on the placement of the needle track.

Differential Diagnosis

The diagnosis of a bone sarcoma is usually obvious, although differentiating between an osteosarcoma and a Ewing's sarcoma in a child or adolescent might need to await the biopsy; radiographically the two may appear similar. In general, osteosarcomas are metaphyseal lesions, and Ewing's tumors are diaphyseal or in the flat bones in young patients, but there are frequent exceptions to this rule, and both can present in any bone. Matrix production may be apparent in a Ewing's tumor because of the host response and absent in an osteosarcoma because the osteoid is incompletely mineralized or absent (as in telangiectatic osteosarcoma). In the adult, it can be difficult to differentiate osteosarcoma from malignant fibrous histiocytoma (MFH) and chondrosarcoma clinically, but a biopsy usually settles the issue.

Osteomyelitis and Langerhans cell histiocytosis may mimic an osteosarcoma and should always be considered, especially in getting tissue for a biopsy. A fatigue fracture (stress fracture) may also appear with an aggressive periosteal response, and the MRI shows extensive

marrow and soft-tissue edema. This can mimic an osteosarcoma, but a CT scan, especially with coronal reconstructions, is usually diagnostic.

In the adult, one must look for underlying causes of osteosarcoma, such as Paget's disease and prior irradiation. Since the bone is abnormal to begin with in these two circumstances, the diagnosis may be difficult. Paget's disease itself may be painful, but a change in the pain pattern and new destruction compared to old radiographs if available are helpful. Metastatic carcinoma and multiple myeloma are much more common causes of a destructive bone tumor in the adult, but it should always be remembered that, although rare, osteosarcoma can present as a purely radiolucent lesion.

Other bone tumors, such as giant cell tumor of bone, aneurysmal bone cyst, and chondroblastoma, may have an aggressive radiographic

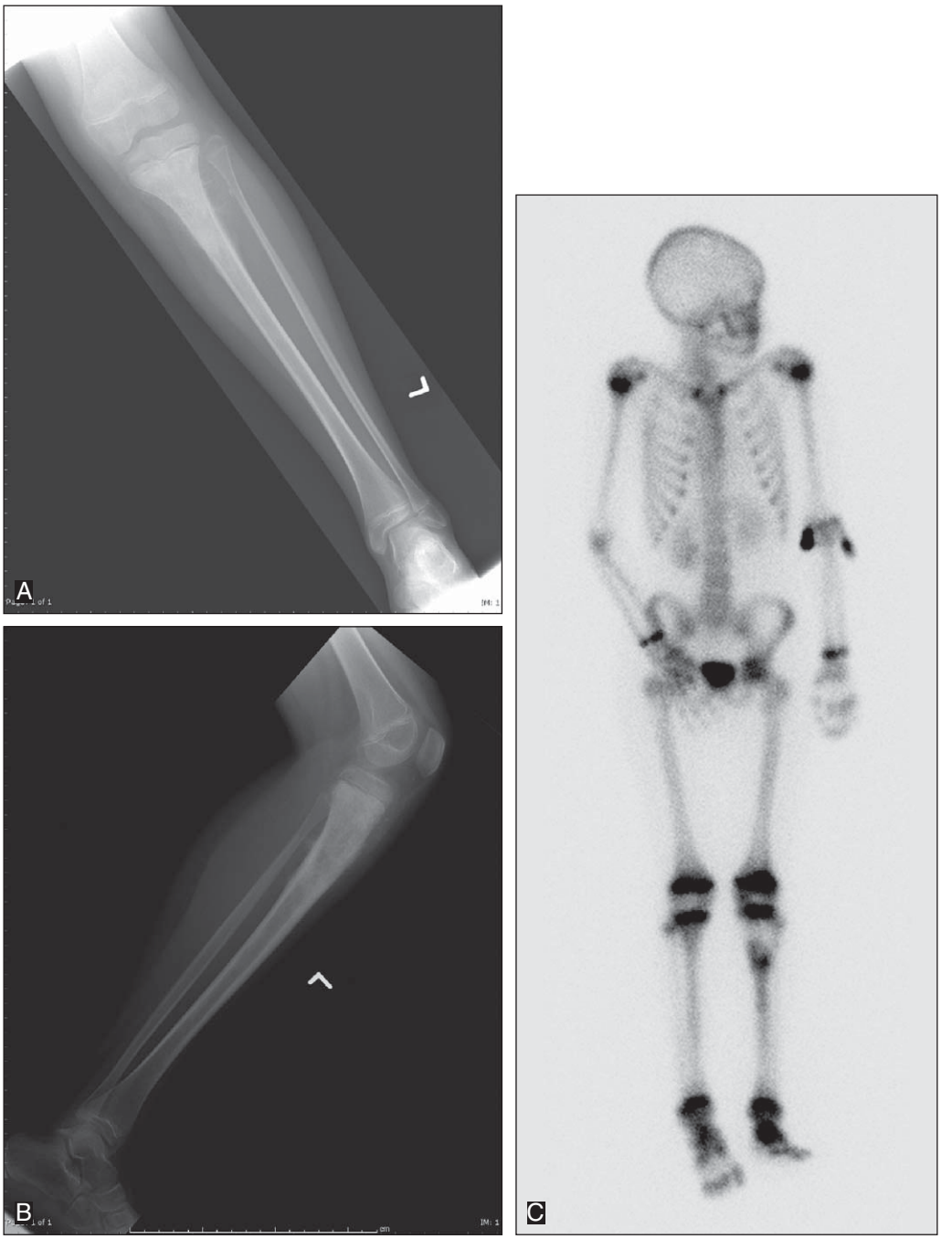


Figure 96-3 • **A,** AP radiograph of a 9-year-old girl with an osteosarcoma of the left proximal tibia. The tumor is both destructive of bone and osteoblastic, increasing the density of the proximal metaphysis of the bone. The mineralized soft-tissue mass is seen. **B,** Lateral radiograph showing the mixed radiolucent and radiodense characteristics of the tumor, and the mineralization of the soft-tissue mass is seen posterior to the bone. This flocculent mineralization of density similar to that of normal bone is characteristic. In this case, perpendicular striations of bone are seen posteriorly. **C,** Radionuclide bone scan showing increased uptake in the proximal metaphysis of the tibia. No skip lesions or other bony metastases were noted.



Figure 96-3, cont'd • **D,** Coronal STIR MRI image showing the extent of the tumor (bright on this sequence) in the medullary cavity and soft tissues. The tumor has transgressed the growth plate and may involve the knee joint. **E,** Axial T_1-weighted fat saturation MRI showing the soft-tissue mass and relationship to the posterior vessels. **F,** Sagittal T_1-weighted fat saturation image showing the medullary extent of the tumor and the extension into the epiphysis and further suggests involvement of the knee joint. In this particular case, the tumor did extend under the lateral meniscus but was covered by synovium and not technically in the joint proper. An extra-articular, above-knee amputation was done because of the potential joint involvement and her young age.

appearance and mimic an osteosarcoma, but the histology is usually diagnostic in these situations. An aneurysmal bone cyst, however, might have scant tissue from a biopsy, as does a telangiectatic osteosarcoma, so at times, the distinction is difficult. An experienced bone pathologist is essential in these instances even if it necessitates an outside referral. Similarly, osteosarcomas can have giant cell-rich areas that can mimic a giant cell tumor. Again, the expertise of the bone pathologist and a team of clinicians and radiologists working in concert are essential to making these distinctions.

Management

Adjuvant Chemotherapy

The use of adjuvant chemotherapy for osteosarcoma was introduced in the 1970s, and after initial concern relative to its efficacy, a randomized trial confirmed its benefit. It is now established as an essential part of the treatment of osteosarcoma. Initially used as an adjuvant following amputation or resection of a tumor, chemotherapy is now used in the neoadjuvant setting, although no clear survival benefit to

that approach has been documented.[16] The use of neoadjuvant chemotherapy does allow the assessment of histologic response to the chemotherapy, which has prognostic implications, allows time for planning of limb salvage operations, and makes those resections easier and probably safer.

A number of single- and multi-institutional studies have reported the results of treatment protocols, including multiagent neoadjuvant chemotherapy and limb-sparing surgery.[86–88] The specific drugs and their methods of administration are important. Delépine and colleagues[89] published a meta-analysis of the relationship of total dose and dose intensity of methotrexate from nine single-institution and nine multi-institution randomized trials. They concluded that both methotrexate dose and dose intensity had major prognostic value. Intravenous administration appears to be as effective as the intra-arterial route of administration.[90] A meta-analysis of 16 regimens published by a group from the National Cancer Institute found that dose intensity was the most important determinant of a favorable outcome, defined as a good histopathologic response to neoadjuvant chemotherapy.[91] Other studies likewise support the importance of doxorubicin treatment in patients with osteosarcoma.[92,93]

The use of preoperative chemotherapy was extended to selected patients in an attempt to contain growth of the primary tumor while awaiting construction of a custom prosthesis (usually 12 to 16 weeks).[86,88,94] The sequence of several courses of primary chemotherapy and subsequent surgery afforded the opportunity to examine and histopathologically grade the tumor tissue response to multiple chemotherapy agents. Patients with greater than 90% tumor necrosis (good) were shown to have a better disease-free survival than those with a poor (<90%) response to chemotherapy.[17,95,96]

Goorin and associates[16] completed a study of 106 patients admitted to the Pediatric Oncology Group Study 8651 who were randomized to immediate surgery or to preoperative chemotherapy with high-dose methotrexate, doxorubicin, and cisplatin for two cycles (10 weeks). Six patients were excluded from analysis. Of the remaining 100 patients, 45 were randomly assigned to immediate chemotherapy, and 55 were randomly assigned to immediate surgery. Sixty-seven patients remain disease-free. At 5 years, the projected EFS rate was 65% for immediate surgery and 61% for presurgical chemotherapy; There was no apparent advantage to the group that received preoperative chemotherapy. This was a difficult study to complete because at the time, there was a surgical bias toward neoadjuvant chemotherapy for limb salvage patients, making accrual slow. The number of limb-preserving procedures was nearly equal in both groups (55% with immediate surgery and 50% with presurgical chemotherapy). Although the percentages of patients in the two groups was similar, the overall percentage of patients receiving limb-sparing procedures was much lower than the usual 60% to 90% limb-preserving procedures reported. Only one local recurrence was reported among all 100 patients.

Surgical resection of the primary tumor is usually planned for 10 to 12 weeks following induction chemotherapy. Limb preservation is elected if the tumor responds favorably; that is, there is evidence of a clinically favorable response, including diminished local pain; radiographic evidence of mineralization of the previously unmineralized soft-tissue portion of the tumor on radiographs; and MRI evidence of retention of a normal fatty tissue plane between vascular and neural structures and the tumor. However, if the lesion enlarges and the vessels become involved secondarily (poor response), ablative surgery is recommended. Once the operative wound heals (usually within 2 to 3 weeks), adjuvant chemotherapy is initiated and is maintained for approximately 40 weeks, depending on the particular study.[97–102]

Wilkins and colleagues[103] described their results at two institutions with a dose-intensified neoadjuvant protocol using intravenous doxorubicin and intra-arterial cisplatin administered until a maximum angiographic response was observed (usually four courses). Despite showing results similar to others previously reported, it requires extraordinary resources, making it unlikely that a similar study could be carried out in an extensive cooperative manner.[104,105]

Long-term outcomes were studied by Bacci and coauthors,[106] who reported the results of treatment of 164 patients with nonmetastatic extremity osteosarcoma who were followed for a minimum of 10 years. Preoperative chemotherapy consisted of high-dose methotrexate, cisplatin, and Adriamycin. Postoperatively, good responders (≥90% tumor necrosis) received the same three drugs, while poor responders (<90% tumor necrosis) received ifosfamide and etoposide in addition to the three-drug chemotherapy regimen. Follow-up showed that 101 patients (61%) remained continuously free of disease, 61 had relapsed, and 2 had died of Adriamycin-related cardiotoxicity. There were no differences in outcome between good and poor responders.

Limb-preserving surgery was performed in 136 of the patients (82%) in the Bacci study, and 117 (71%) had a good histologic response. Despite the large percentage of patients with limb-sparing procedures, only four local recurrences developed (2.4%). The complications of chemotherapy included Adriamycin-induced cardiotoxicity (6 patients) and secondary malignancies (7 patients) at a median follow-up of 11.5 years.

In 1997, Bramwell[107] conducted a review to provide answers to important questions about the role of chemotherapy in the management of patients with nonmetastatic osteosarcoma of the extremities. Many studies were analyzed, including a study by Link and coworkers[12] that clearly demonstrated the role of adjuvant chemotherapy in the treatment of patients with conventional osteosarcoma. The role of adjuvant chemotherapy was also confirmed by another study that provided additional objective evidence for the efficacy of multiagent chemotherapy in preventing and/or delaying relapse.[108] The five studies that were reviewed by Bramwell[12,109–112] approached the results of Rosen and associates;[96] three were multicenter studies, and two were reports from a single institution. Bramwell concluded that although the Rosen T10 regimen is complex and toxic, it can be given in a multicenter setting without apparent major compromise in efficacy.

Bramwell concluded that reports of outcomes with multiagent chemotherapy were similar to regimens containing the most active drugs (doxorubicin and cisplatin) that were used in two consecutive European Osteosarcoma Intergroup protocols when compared with results from multicenter studies using the T10 regimen.[112,113]

It is apparent that histopathologic response to neoadjuvant chemotherapy correlates with improved survival. The reports by Picci and colleagues[114] (Bologna, 355 patients), Kempf-Bielack and coworkers[115] (Cooperative Osteosarcoma Study Group, 504 patients), and Delépine and associates[116] (Paris, 112 patients) all demonstrated that a good response to neoadjuvant chemotherapy was an independent prognostic factor. Meyers and colleagues[117] reported the relationship between duration of preoperative chemotherapy and histopathologic response. In univariate analysis, the duration of preoperative chemotherapy did not correlate with relapse-free survival. With longer preoperative treatment, a greater proportion of patients had a favorable histopathologic response to therapy, but the correlation of the response with outcome decreased. Bramwell[107] postulated that with prolonged preoperative chemotherapy, a good response to chemotherapy might lose its prognostic significance. The CCG-782 study published by Provisor and coworkers[118] involving 268 patients with nonmetastatic osteosarcoma of the extremity used the resected tumor histologic response to neoadjuvant chemotherapy to determine postoperative chemotherapy. In 206 patients, the tumor was morphometrically assessed for residual viable tumor; 28% displayed a good (<5% viable tumor) histologic response, while the remaining patients were judged to have a poor histologic response (>5% residual viable tumor). The patients who had a good response had an 8-year postoperative EFS rate of 81% and a survival rate of 81%. Patients with a poor histologic response had an 8-year postoperative EFS rate of 46% and an overall survival rate of 52%. They concluded

that event-free and overall survival appeared to be related directly to histologic response to neoadjuvant chemotherapy. If that is the case, then increasing the percent necrosis by intensifying chemotherapy should improve outcome even further. A recent study compared standard chemotherapy to an intensified arm to assess this contention. Conventional treatment consisted of six 3-week cycles of cisplatin (100 mg/m^2 by 24-hour infusion) and doxorubicin (25 mg/m^2/day by 4-hour infusion for 3 days). Intensified therapy was treatment with identical total doses of cisplatin and doxorubicin, planned as six 2-week cycles supported by granulocyte colony stimulating factor. In this study, 497 eligible patients were evaluated, and good histologic response (>90% tumor necrosis) was observed in 36% of standard arm and 50% of the intensified arm. However, there was no evidence of a difference in overall survival between the two treatment regimens. The study found that intensification of chemotherapy could increase the percentage of necrosis but not progression-free survival or overall survival.[119] Another study looked at increasing the dose of chemotherapy with the same drugs in 196 osteosarcoma patients. The authors failed to find a difference in percentage of necrosis, 5-year event-free survival, or overall survival, suggesting that response to chemotherapy is related to the specific drugs employed but that increasing the intensity is of little benefit.[120] The tumors either respond or do not, suggesting biologic differences in the tumors.

Currently, there are no strong data showing that changing drugs in the poor histologic responders improves the survival of those patients. A retrospective study reported by Benjamin and associates[121] compared outcomes from three consecutive cohorts of patients receiving intra-arterial cisplatin and intravenous doxorubicin between 1980 and 1992. In cohort 1 (37 patients), the postoperative chemotherapy was the same. In cohort 2 (59 patients), the postoperative chemotherapy for poor responders consisted of high-dose methotrexate, bleomycin, cyclophosphamide, and dactinomycin alternating between doxorubicin and dacarbazine. In cohort 3 (28 patients between 1988 and 1992), poor responders were managed with three alternating regimens of high-dose methotrexate, ifosfamide, and doxorubicin/dacarbazine. The significant 5-year relapse-free survival for poor responders for the three cohorts was 13%, 34%, and 67%. Bramwell believes that although the results appear significant, they could also be explained on the basis of small sample size, increasing dose intensity, total dose, and increased duration of preoperative chemotherapy.[122]

A current randomized multi-institutional study of patients from North America and Europe will attempt to address this question further by randomizing poor responders to continued preoperative therapy or an intensified arm in which ifosfamide and etoposide are added to the experimental arm.[123] The good responders will be treated with continued preoperative therapy with or without the addition of interferon-α. This is the first study to randomize the treatment of patients following determination of histologic response.

The issue of whether other agents incorporated into intensive multiagent regimens will improve survival further is less clear. Preliminary trials incorporating ifosfamide into multiagent chemotherapy appeared promising,[124–128] but a recent study of the Children's Oncology Group patients who were randomized to multiagent regimens that either contained or did not contain ifosfamide shed some doubt on this.[129] In this study, 677 nonmetastatic osteosarcoma patients were treated with one of four prospectively randomized treatments. All patients received identical cumulative doses of cisplatin, doxorubicin, and high-dose methotrexate and underwent definitive surgical resection of the primary tumor. They were randomly assigned to receive or not to receive ifosfamide and/or muramyl tripeptide, MTP, a pulmonary macrophage stimulant. The addition of ifosfamide in this dose schedule to standard chemotherapy did not enhance EFS. The addition of MTP to the ifosfamide arm appeared to add further benefit, but the study was not designed to test this, and this question remains uncertain but intriguing.

To test whether intensified ifosfamide therapy might be of benefit, a study of 182 patients treated with of two cycles of high-dose ifosfamide (15 g/m^2), methotrexate (12 g/m^2), cisplatin (120 mg/m^2), and doxorubicin (75 mg/m^2) was conducted. Postoperatively, patients received two cycles of doxorubicin (90 mg/m^2), and three cycles each of high-dose ifosfamide, methotrexate, and cisplatin (120 to 150 mg/m^2). Granulocyte colony stimulating factor support was mandatory after the high-dose ifosfamide/cisplatin/doxorubicin combination. No disease progression was recorded during primary chemotherapy. With a median follow-up of 55 months, the 5-year probability of EFS was 64%, and the overall survival rate was 77%. The addition of high-dose ifosfamide to methotrexate, cisplatin, and doxorubicin in the neoadjuvant setting was found to be feasible, but associated with major renal and hematologic toxicities. Survival rates were similar to those obtained with four-drug regimens using standard-dose ifosfamide.[130]

Growth factors do appear to offer a benefit in increasing dose intensity. In a pilot study, the European Osteosarcoma Intergroup demonstrated the use of granulocyte colony stimulating factor-supported increased dose intensity, making chemotherapy every 2 weeks feasible.[131] Thrombocytopenia remained dose limiting, and whether attainable dose intensification improves survival remains uncertain.

The histologic subtypes of osteosarcoma also appear to influence response rates. Bacci and colleagues[132] at the Rizzoli Institute in Bologna correlated the histopathologic response to preoperative chemotherapy in 1058 patients with conventional osteosarcoma of the extremity. They classified the tumors as osteoblastic (70%), chondroblastic (13%), fibroblastic (9%), and telangiectatic (6%). At diagnosis, 911 patients had localized disease, and 147 had resectable pulmonary metastases. The response to preoperative chemotherapy was good (90% or more tumor necrosis) in 59% of patients and poor (<90% tumor necrosis) in 41%. Notably, the rate of good responders was significantly higher ($P = 0.0001$) in patients with fibroblastic (83%) and telangiectatic tumors (80%) than in those with osteoblastic (62%) and chondroblastic (60%) tumors. In all subtypes (excepting the chondroblastic), the 5-year overall survival rate was significantly higher ($P = 0.0001$) in good responders (68%) than in poor responders (52%).

Essential to the improvement in survival in osteosarcoma is the combination of effective surgical resection along with the use of chemotherapy. Jaffe and colleagues[133] in the Department of Pediatrics at the University of Texas M.D. Anderson Cancer Center attempted the cure of 31 patients with nonmetastatic osteosarcoma. Their protocol for selection included initial treatment with chemotherapy comprising high-dose methotrexate and leucovorin rescue (MTX-LF) in three patients and intra-arterial cisplatin in 28 patients. After response at 3 months, entry into the study was permitted, and chemotherapy treatment was maintained for a total of 18 to 21 months with a combination of MTX-LF, intra-arterial cisplatin, and doxorubicin. Only 3 of 31 patients (10%) were cured exclusively with chemotherapy. Four additional patients requested surgical extirpation of the tumor after the cessation of chemotherapy. Histopathologic examination revealed no evidence of viable tumor. Adding these patients to the three mentioned previously yielded a total of seven patients (23%) who had a cure from chemotherapy alone. As the expected cure rate with conventional strategies is 50% to 65%, the authors concluded that their results do not justify the option of current forms of chemotherapy as exclusive treatments for osteosarcoma.

Local Recurrence

Two studies indicate that local recurrence within 18 to 24 months of surgery has a substantial negative influence on long-term survival. Ferrari and colleagues[134] at three Italian institutions reviewed the data on patients who were treated for nonmetastatic osteosarcoma of the extremities between October 1986 and June 1995, finding 162 patients with recurrence or relapse. The main prognostic factors for

postrelapse survival were the relapse-free interval, site of metastasis, and number of pulmonary nodules. Complete surgical resection of the recurrence was found to be pivotal in the strategy of treatment. When the risk factors were combined, patients with a relapse-free interval longer than 24 months and with only one or two pulmonary nodules had a postrelapse survival of 72%. Patients with a short relapse-free interval and three or more lung pulmonary nodules had a poor postrelapse survival of 5%. Patients with unresectable recurrence did receive benefit from second-line chemotherapy, but the authors' data did not support the generalized use of chemotherapy after complete surgical resection of the first recurrence.

Weeden and colleagues[135] reported the effect of local recurrence on survival of 559 patients entered into two randomized controlled trials of the European Osteosarcoma Intergroup using preoperative chemotherapy, but there was no survival benefit between chemotherapy arms. A landmark analysis allowed the assessment of 440 patients at 18 months, and 22 patients (5%) had experienced a local recurrence. Patients with a local recurrence had a fourfold greater risk of death during the 18 months after surgery. Similar analyses were conducted with landmark time points at 1 and 2 years. Using a multivariate proportional hazards model, 368 patients were assessed to investigate the relative prognostic importance of histologic response and local recurrence. It appears clear that histologic response to chemotherapy and local recurrence had a significant effect on survival. A study from St. Jude's Research Hospital analyzed prognostic factors for survival in 26 patients with a local recurrence of osteosarcoma who were treated between 1970 and 2000. The initial surgical procedure was amputation in 20 patients (76.9%) and limb salvage in 6 patients (23.1%). Eleven patients (42.3%) developed an isolated local recurrence, and 15 patients (57.7%) developed local and distant recurrence. The 5-year estimate of postrecurrence survival (PRS) for the 26 patients was 19.2%. The factors that affected survival after recurrence were as follows:

- Recurrence 2 or more years from the time of diagnosis (5-year PRS of 50.0% ± 20.4% compared with earlier recurrence (10.0% ± 5.5%) ($P = 0.037$).
- Patients with negative margins after initial surgery were found to have improved survival (5-year PRS of 33.3% ± 13.6%) compared with patients with positive margins (7.1% ± 4.9%) ($P = 0.015$).
- Patients who underwent complete surgical resection at the time of recurrence were found to have a better PRS (5-year PRS of 41.7% ± 14.2%) compared with patients who did not undergo surgery (0% ± 0%) ($P < 0.001$).

This demonstrated that the prognosis for patients after local recurrence of osteosarcoma is poor, but attempts at salvage should be made. Complete surgical resection at the time of recurrence is essential for survival.[136]

A study from the European Osteosarcoma Intergroup of 202 patients assessed the primary surgical treatment alternatives. Three centers differed in the rates of limb salvage, and all local recurrences arose in limbs with attempted limb salvage. Local recurrence was closely related to the adequacy of the margins of excision and to the chemotherapeutic response. Interestingly, patients who had undergone limb salvage surgery and who developed local recurrence still had a better survival rate than did patients who had primary amputation (37% versus 31% survival at 5 years), suggesting that they had a less aggressive tumor. Of patients who relapsed, 31% of those with local recurrence alone were cured by further treatment, compared with only 10% of those with metastases.[137]

Another retrospective analysis of the management and outcome of 44 patients who developed local recurrence after neoadjuvant chemotherapy of osteosarcoma of the extremities was performed in a single institution between 1983 and 1999. In 24 patients (54.5%), local recurrence was the first sign of recurrence; in 8 patients (18.2%), local recurrence followed systemic recurrence. and in 12 patients (27.3%), the two events were concurrent. The only prognostic factor that was identified for disease-free survival of patients following local recurrence was the presence of systemic recurrence at the time of diagnosis of the local recurrence or prior to it. The 5-year postrecurrence EFS rate was 29.1% for patients without metastases at the time of local recurrence versus 0% for those with metastases ($P = 0.02$). The analysis confirmed that patients with osteosarcoma of the extremities who develop local recurrence are at a very significantly high risk of developing metastatic disease and dying of the tumor despite the use of effective neoadjuvant chemotherapy.[138] Another study looked at 407 patients and found 23 patients with resectable local recurrence. Median time to local recurrence was 13 months. All patients were treated with chemotherapy following recurrence. The 5-year and 10-year survival rates in the recurrent cases were 29% and 10%, respectively. Increased risk of local recurrence ($P < 0.0001$) was strongly correlated with positive margins of resection. The strongest correlates with poor survival were local recurrence within the first year after primary resection ($P = 0.001$) and, as in the Bacci study, metastasis at the time of first local recurrence ($P = 0.04$). Failure to achieve clinical remission after disease recurrence ($P = 0.04$) was also a poor prognostic factor.[139]

To determine whether inappropriate surgical procedures based on an initial misdiagnosis affected recurrence and survival rates, one group retrospectively reviewed the surgical treatment and results of 117 patients with high-grade osteosarcomas.[140] Nine patients had intralesional curettage performed at other institutions based on an erroneous diagnosis of a benign lesion. Two of the nine patients had amputations, and seven patients had limb salvage procedures. Of the 108 patients who were not misdiagnosed, 6 patients had amputations and 102 patients had limb salvage procedures. All patients received neoadjuvant therapy. Fifteen of the 117 patients had local recurrences. Patients who had inappropriate surgical procedures at diagnosis had an increased risk of local recurrence and lower 10-year survival rate.[140]

Prognostic Variables

Morphometric analysis of pathologic specimens was instituted after it was recognized that chemotherapy-induced necrosis correlated with clinical outcome. Picci and coauthors[141] described their methodology in 50 patients. Necrosis was divided into three categories: good (100% to 80% necrosis), fair (80% to 50% necrosis), and poor (<50% necrosis).Other authors have used different classifications. Depending on the system that is used, tumor necrosis ranging from 60% to 95% is common. The information gained has prognostic significance. Winkler and associates[94] were early to report that patients with unfavorable pathologic responses to preoperative chemotherapy experienced a poorer (49%) disease-free survival than did patients with a favorable pathologic response (87%; $P = 0.005$). Glasser and coworkers[142] later reviewed 279 consecutive patients with stage II osteosarcoma of the appendicular skeleton who were treated between 1976 and 1986. Continuous disease-free survival for the overall group was 70% at 5 years and 69% at 10 years. The only independent predictor of a favorable outcome was found to be the histopathologic response to chemotherapy as defined by pathologic review of the surgical specimen.

A literature review by Davis and colleagues[143] attempted to identify prognostic factors that could influence survival in patients with nonmetastatic high-grade osteosarcoma of the extremities. Eight previously reported large series of patients included sufficient data to evaluate the numerous identified variables. Only two variables proved significant to univariate analysis: tumor size and chemotherapy-induced tumor necrosis after primary chemotherapy. Only tumor necrosis remained significant after multivariate analysis, however. Other large series have demonstrated similar prognostic responses to neoadjuvant chemotherapy.[86,95,98–102,117,118,142]

Table 96-7 summarizes recent data regarding treatments for nonmetastatic osteosarcoma reported by 10 internationally recognized

Table 96-7 Summary of Recent Studies of Patients Treated for Nonmetastatic Osteosarcoma

Institution	No. of Nonmetastatic Ext. Total*	Resection*	Rotationplasty*	Amputation*	Local Control*	Disease-Free Survival
M.D. Anderson	60	31	—	28	4 (7%)	74% (TIOS-III)
Dana Farber	74	36	—	38	1 (1%)	87%
Memorial Sloan-Kettering	271	159	9	103	18 (7%)	77%
Vienna University Clinic	73	41	22	10	2 (3%)	76.7%
Birmingham Service	99	74	—	15	4 (4%)	48%
French Study	100	79	3	18	1 (1%)	82%
Brazil Group	92	34	—	58	6 (7%)	41.1%
Mie Japan	52	25	—	27	2 (4%)	58.9%
COSS 86	159	65	39	44	3 (2%)	84%
Rizzoli Institute	125	106	9	10	1 (0.08%)	87%

*Number of patients.

institutions. The table suggests that results have improved owing to management by multiagent neoadjuvant chemotherapy combined with adequate local surgery performed by experienced musculoskeletal surgeons. Several conclusions can be drawn from these studies:

- Patients who request limb-sparing operations do not appear to be at greater risk for development of local or distant relapse than patients who have transmedullary amputations.
- The administration of sequential multiagent adjuvant chemotherapy has significantly improved the disease-free survival for patients without metastasis.
- The risk of local recurrence appears to be no greater in patients who complete limb-preserving procedures than for those who have an amputation.[98,100,117]

Relationship of Surgical Margins, Neoadjuvant Chemotherapy, and Local Recurrence

The role of neoadjuvant chemotherapy in facilitating limb preservation appears to be well established.[114,144] The relationship between margins, chemotherapy, and local recurrence is not as straightforward. Although in general, local recurrence is higher in patients with inadequate margins, some patients who are so treated do not develop recurrence, whereas some patients with wide or radical margins do recur or persist locally. The effect of neoadjuvant chemotherapy in this regard is suspected to be beneficial, but only retrospective data are available. Four of the institutions reporting data shown in Table 96-7 also provided data on the pathologic margins achieved at surgery and correlated the surgical margins with locally recurrent disease. Of the 271 margins reported by Memorial Sloan-Kettering, 266 were adequate (261 wide and 5 radical), and 5 were inadequate (3 marginal and 2 intralesional). Of the 18 locally persistent tumors, however, all developed in patients who were thought to have wide margins. There were no locally recurrent tumors from the 5 known inadequate surgical margins.[100] The University of Vienna group reported 61 margins as wide, with 12 inadequate (9 marginal and 3 intralesional) margins. Only two local recurrences developed, one in a patient having an intralesional amputation and the other with a marginal resection and reconstruction.[99]

A similar review from Birmingham, England, revealed 23 marginal and 15 intralesional margins in 99 patients, with a 4.5% recurrence rate.[100] A French study reported 100 patients with nonmetastatic osteosarcoma managed by neoadjuvant chemotherapy and surgery with "numerous" marginal margins but no intralesional margins. They reported one local recurrence.[101] A Rizzoli Institute study, reporting 125 patients retrospectively, identified 15 patients with inadequate margins. Only one patient developed a local recurrence.[98]

Investigators from the Rizzoli Institute in Bologna have shown by multivariate analysis that the incidence of local recurrence in 355 patients was related closely to surgical margins ($P < 0.0001$) and response to preoperative chemotherapy ($P < 0.0001$). There were 28 patients who experienced local recurrence (7%), and 3 of those patients survived (11%). Six of 10 patients who did not receive preoperative chemotherapy developed local recurrence. In the other limb salvage procedures, 110 patients had wide margins, 12 were marginal, 7 had intralesional margins, and 7 had wide contaminated margins. Although 27 patients had inadequate margins, only 3 developed local recurrence, all within the first 2 years after diagnosis.[102]

To better illustrate the relationship between surgical margins and local recurrence, Picci and colleagues[114] reported on a single-institution study retrospectively reviewing 355 patients with nonmetastatic high-grade osteosarcoma of the pelvis and extremities. The average length of follow-up was 65 months for surviving patients.

Pathologic review demonstrated less than wide margins in 65 of the 355 patients. The most common anatomic site for inadequate margins was the popliteal region near the vascular and neural structures, where 20 of 140 patients were found to have inadequate margins (either marginal or intralesional). Only 7 of the 20 patients developed local recurrence, however. Only 3 of 15 patients with inadequate margins associated with lesions around major joints developed locally persistent disease. The intramedullary canal was the site of inadequate margins in 20 of 237 patients, and 6 patients developed local recurrence. It is of interest that 7 of the 11 patients with intralesional surgical margins and 16 of 21 with contaminated margins did not develop local recurrence. These findings could not be explained on the basis of poor survival or early death. The observation is believed to be related to the effectiveness of preoperative chemotherapy at producing tumor necrosis and the development of a "mature" capsule surrounding the tumor where satellite tumor nodule formation had been suppressed.[145]

An analysis of a more recent group, 164 patients with nonmetastatic osteosarcoma of the extremities, also came from the Rizzoli Institute. Limb-sparing procedures were performed in 136 patients (83%), 18 patients (11%) had amputation, and 10 (5%) had rotationplasty. The surgical margins were reviewed. In amputations, 18 margins were wide or greater; in rotationplasty, nine were wide and one was intralesional. In the limb salvage procedures, 110 patients had wide margins, 12 were marginal, 7 had intralesional margins, and 7 had wide contaminated margins. Although 27 patients had

inadequate margins, only 3 developed local recurrence, all within the first 2 years after diagnosis.[102]

The unanswered question is whether the poor correlation with margin and recurrence relates to neoadjuvant chemotherapy or the underlying tumor biology or some combination of the two. Adequate surgical resection is certainly a worthwhile goal, but the causes of local recurrences are probably more complex than adequacy of margin.

Surgical Treatment

The goal of surgical management is complete resection of the tumor with a cuff of normal tissue surrounding the tumor (wide resection). This can be accomplished by either amputation or local resection as long as this goal is achieved. Radical resections are seldom performed today. The most important question regarding limb salvage surgery is "Is it safe?" Suffice it to say that no randomized studies have ever compared amputation to local resection, nor are they likely ever to do so. What is known is from retrospective analyses of tumor specimens and outcome of patients treated on clinical trials.

To identify the potential risks of awaiting limb-sparing surgery versus immediate amputation, the results of data on 279 patients treated at Memorial Sloan-Kettering between 1975 and 1984 were reviewed retrospectively. Sixty-three patients who completed primary surgery and adjuvant chemotherapy were compared with patients who had primary chemotherapy followed by surgery and adjuvant chemotherapy. Univariate analysis showed no difference in outcome between patients who had limb-sparing procedures and those who had amputations ($P = 0.34$).[117]

A multi-institutional retrospective study evaluating patients with nonmetastatic osteosarcoma of the distal femur reported treatment results for 227 patients who were managed by limb-sparing procedures, above-knee amputation, and hip disarticulation between July 1975 and June 1980. The Kaplan-Meier estimates for the three surgical groups revealed no significant difference in continuous disease-free and ultimate survival rates for each group (Mantel-Cox test, $P = 0.8$) after a median follow-up of 5.5 years. The continuously disease-free survival rate for the entire group was 42%, with an overall survival rate of 55% at five years. The researchers concluded that limb-sparing procedures for osteosarcoma of the distal end of the femur did not compromise either disease-free survival or overall survival. Outcome results showed that one third of patients with limb-sparing procedures required at least one additional surgical procedure, and one fourth eventually required amputation.[146]

A follow-up of the aforementioned study 8 years later reviewed the original 227 patients. In this study, 213 patients had been classified as having stage IIB osteosarcomas. Seventy-three patients had had limb-preserving procedures, 115 had had above-knee amputations, and 39 had had hip disarticulations. Eighty-four percent of patients were followed for a minimum of 10 years. The Kaplan-Meier estimate of disease-free survival for all patients at 10 years was 41%. Fourteen of the original 17 patients experiencing a local recurrence in the first study did so within the first 2 years after the index procedure, and only one of the original 17 patients survived. There were nine local recurrences after above-knee amputations and eight after limb-sparing procedures. No patient who had a hip disarticulation (radical margin) developed a local recurrence. Although the function of patients with limb-sparing procedures was superior to that of both the amputation and disarticulation groups, no differences could be identified regarding patient acceptance or psychosocial outcome (quality of life) among the three operative groups.[147]

Limb-preserving procedures are currently performed in approximately 60% to 90% of osteosarcoma patients with nonmetastatic extremity tumors, in contrast to the previously reported high amputation rates. Advances in chemotherapy, imaging technology, implant design and materials, and subspecialization in orthopedic oncology have reversed the trends of previous decades. Limb preservation, however, has not altered disease-free survival rates when compared with ablative procedures.[146–148] Local recurrence rates after neoadjuvant chemotherapy and resection or amputation appear to be similar; these are low-frequency but still serious events (0.8 to 7%). Although limb-sparing surgery in appropriately selected patients appears to be safe from an oncologic viewpoint, it is not clear that functional outcome and quality of life (QOL) are superior in limb salvage patients compared to those who have undergone amputation. The long-term outcomes and reoperation rate (including eventual amputation) of the various limb salvage constructs are unknown. Most patients prefer to keep their limbs, however, and limb-sparing procedures are now routinely offered. Advances in chemotherapy, imaging technology, implant design and materials, and subspecialization in orthopedic oncology have reversed the trends of previous decades.

Problems associated with limb sparing include an increased early complication rate of 25% to 35%.[98,102,149] Many reconstruction alternatives are available, and the method that is chosen depends on such variables as patient age and employability, tumor location and size, and the potential of the elected procedure to provide curative margins. Of paramount importance are recognition of the patient's desires and discussion of realistic expectations. In addition the surgeon's experience and expertise play a role in the choice of procedure.

Lindner and associates[150] from the University of Muenster reported their results of a study with 133 patients who had high-grade osteosarcoma of the extremities treated with intravenous neoadjuvant chemotherapy and surgery between 1978 and 1994. Seventy-nine patients had limb-preserving procedures, including 32 with endoprosthesis, 39 with allograft replacement, 6 with autograft reconstruction, and 2 with shortening procedures. Twenty-one patients had rotationplasty, and 33 patients elected amputation. Using the MSTS (1993) functional evaluation scale, major complications were experienced after all procedures; 20 of 32 patients with endoprosthetic procedures experienced a major complication, and 6 of the 20 required removal of the prosthesis. Twenty of the 39 patients with allografts developed a major complication, and 6 of those required removal as well. Ten of the 21 patients with rotationplasty also developed major complications, but none required revision to amputation. Eight of the 33 patients who were treated by transmedullary amputation developed a major complication, and 3 of the 8 required a more proximal reamputation. Lindner and associates concluded that the extent of preoperative primary tumor necrosis, surgical margins, and tumor volume were the most important oncologic prognostic factors and that functional outcome after rotationplasty was superior to that of amputation and other limb-preserving techniques.

A minimum of a "wide" margin should be achieved for adequate local control of high-grade primary sarcomas of bone (e.g., conventional osteosarcoma, high-grade surface osteosarcoma, MFH of bone, Ewing's sarcoma). If there is neural involvement from lesions arising around the knee, then the equivalent of a wide amputation must be performed. If the nerve is spared, then consideration should be given to limb-sparing resection. One issue is the definition of "wide." As defined, it is a cuff of normal tissue completely surrounding the tumor and reactive zone around the tumor. Initially, most surgeons desired 1 cm or more of soft tissue and 7 to 10 cm of uninvolved bone marrow when performing resections or amputations. As more experience was gained and neoadjuvant chemotherapy came into common use, the thickness of the margins has lessened for most surgeons, but it is unclear how close is too close to the tumor before risk of local recurrence increases. Most surgeons now are accepting 1- to-3 cm bone marrow margins and soft-tissue margins in the millimeter range (avoiding "ink on tumor"), especially if the histologic response is good. One problem is that the response is not known predictably until the resection has been carried out. Suffice it to say that this issue has not been resolved and the margins that are accepted vary depending on the experience and judgment of the surgeon and treatment team on any given case. It is clear that intralesional margins

are highly likely to lead to local recurrence, especially if there has been a poor response, but some osteosarcomas recur despite wide margins and good histologic response, suggesting that the aggressiveness of the tumor may play an important but, at this point, undefined role. Once the decision whether to perform amputation or limb salvage has been made, it is necessary to decide on the type of reconstruction. This requires lengthy discussion with the patient and, in the case of pediatric patients, the parents.

The type of reconstruction varies with the location and extent of the tumor, the age of the patient, the experience of the surgeon, and the desires of the patient. In general, patients who desire unrestricted athletic activities are encouraged to have amputations or rotationplasty in the lower extremity because they are more durable options and not subject to mechanical failure, loosening, or fracture. Patients who are more concerned with preserving the limb must first be carefully imaged to ensure resectability and understand the various reconstruction options. Following neoadjuvant chemotherapy, the plain radiograph and MRI are repeated. The surgeon and radiologist must critically assess these studies to determine whether the major neurovascular structures are free of the tumor and the extent of tumor in the medullary cavity and in the soft tissues. If sufficient muscle cannot be preserved, soft-tissue healing may be problematic, and the muscle power of the limb will be compromised. The presence or absence of tumor extending into the adjacent joint will determine whether an intra-articular resection or extra-articular resection can be carried out, and this will affect the type of reconstruction.

Intra-articular resections that preserve the joint muscles and adjacent bone are reconstructed with tumor prostheses, osteoarticular allografts, or allograft-prosthetic composites. Early function is excellent; however, the implants have a finite life span and will likely require subsequent revision surgery depending on the patient's age and activity level.

Extra-articular resections result in difficult reconstructive challenges. Resection-arthrodesis was employed exclusively by some surgeons in the past but is less commonly performed today for lesions around the knee or shoulder. Endoprostheses or allograft-prosthetic composites are more commonly used today. Extra-articular resections about the knee that include the patella and quadriceps mechanism can be treated with allograft-prosthetic composites that use a tibial graft with a patella and quadriceps that can be repaired to the host quadriceps tendon as an alternative to arthrodesis, amputation, or rotationplasty.

The age of the patient has a major influence of the type of reconstruction that is chosen. In young patients (younger than 10 years in girls and 12 years in boys) with lower-extremity tumors, limb length inequality becomes a major issue. It is less of an issue in upper-extremity lesions. In young patients with tumors about the knee, an amputation might be the optimal treatment option. Young amputees with modern prostheses do quite well, and these prostheses allow the child to return to unrestricted activities with a single operation. The complication rates and type of complications are much less than those with limb-sparing prosthesis. Alternatives to amputation include rotationplasty, expandable endoprostheses, and osteoarticular allografts. Some centers have tried novel techniques, such as distraction osteogenesis, transepiphyseal reconstructions, and combinations of allografts with vascularized fibulae that have growth centers.

Rotationplasty

Rotationplasty for tumors about the knee and hip is a very functional alternative to amputation (Figs. 96-4A–E), but carries a cosmetic disadvantage. For skeletally immature patients, patients with a pathologic fracture, or patients with large tumors, especially of the distal femur, a rotationplasty should be considered. A similar procedure of hip rotationplasty has been described and may be used at times for proximal femoral tumors.[151]

Tibial rotationplasty was first described by Borggreve in 1930 for management of a limb that was markedly shortened by tuberculous involvement of the knee.[152] In 1950, Van Nes[153] and others extended the use of the procedure to treat congenital femoral focal limb deficiencies.[154–156] The first tibial rotationplasty used for reconstruction after a radical resection of the distal femur for osteosarcoma was performed by Dr. Martin Salzer and coworkers in Vienna in 1974 and reported in 1981.[157]

The largest collective experience, reported in 1991, involved 70 patients with sarcoma of bone who were managed with rotationplasty.[158] Forty-seven patients had stage IIB osteosarcoma; other conditions included MFH of bone, parosteal osteosarcoma, chondrosarcoma, Ewing's sarcoma, giant cell tumor of bone, periosteal osteosarcoma, and undifferentiated sarcoma of bone. Sixty-two of the lesions originated in the distal femur, six involved the diaphysis, and two originated in the tibia. At a mean follow-up of 4.3 years, Kaplan-Meier analysis revealed a 70% probability of survival and a 58% probability of disease-free survival.[159]

The surgical oncology principles of tibial rotationplasty yield surgical margins that are comparable to those of a transmedullary amputation.[158,159] In patient selection, the only absolute requirement is the absence of tumor involvement of the sciatic nerve and a previously untraumatized, essentially normally functioning foot and ankle (Figs. 96-4F–N). The procedure is applicable for lesions that involve the distal one half of the femur and the proximal one third of the tibia that spare both the peroneal and tibial divisions of the nerve. Large, locally invasive lesions of the distal femur, even with knee joint involvement, are often amenable to tibial rotationplasty.

The procedure is ideally used in young, skeletally immature patients in whom the anticipated adult limb length inequality (associated with the loss of the distal femoral and proximal tibial epiphyses) would be substantial if other reconstructions were employed. The desired final effect is to have the axis of rotation of the rotated ankle joint slightly proximal to the axis of rotation of the normal knee at skeletal maturity.

Resection and Distraction Osteogenesis

Borrowing from techniques of the pediatric orthopedic surgeon, distraction osteogenesis has been used by some for limb salvage in children. This technique involves slowly transporting a segment of vascularized bone with an external fixation devise to fill the gap that tumor resection creates. It requires the ability to preserve the articular cartilage, and the potential risks include close margins and infection from the percutaneous pins in patients receiving chemotherapy. The results of treating patients who have a local resection for tumor of bone and treatment using bone transport (10 patients), shortening-distraction (3 patients), and distraction osteogenesis (6 patients) have been reported,[160] but distraction osteogenesis has not had widespread acceptance in this country.

Canadell and colleagues[161] have described an innovative physeal-sparing procedure in skeletally immature patients in whom the primary tumor was limited to the metaphysis. During the neoadjuvant chemotherapy phase, distraction forces were applied to the epiphysis, "pulling" the tumor away from the epiphysis and providing new, widened uninvolved metaphyseal bone for a margin of resection without sacrificing the adjacent joint. The procedure was used in 20 patients with a mean follow-up of 54 months without evidence of local recurrence (Fig. 96-5).

Expandable Prostheses

Limb length is an issue to be considered in a skeletally immature patient with a tumor of the lower extremity. In general, patients younger than 8 years of age are probably best treated by amputation or, when possible, rotationplasty. Those between the ages of 8 and 10 years (in girls) and 12 years (in boys) have significant growth remaining such that resection of a physis about the joint will lead to significant limb length discrepancy. One alternative for managing this issue in children is to use standard allografts or endoprostheses



Figure 96-4 • **A,** AP radiograph of an 8-year-old boy who presented with a pathologic fracture of the femur through an osteosarcoma. **B,** He was treated in a spica cast and received preoperative chemotherapy. This shows an AP radiograph in the cast. **C–E,** MRI appearance following neoadjuvant chemotherapy: Axial T_1 fat saturation (**C**); **s**agittal FSEIR (**D**); coronal T_1-weighted MRI (**E**). Because of the extent of the tumor, the pathologic fracture, and his age, a rotationplasty was chosen for his local control. **F,** The incision for rotationplasty of the distal femur (different patient). It is a rhomboidal incision creating an intercalary amputation while preserving the sciatic nerve and its branches.



Figure 96-4, cont'd • **G,** The appearance after completing the dissection prior to division of the vessels. The sciatic nerve can be seen posteriorly. In this case, we could preserve the femoral vessels. **H,** The appearance after removing the tumor. The K-wires are used to control the rotation. A Penrose drain is on the nerve, and the vessels can be seen behind the femur. **I,** Positioning of the leg before osteosynthesis to the distal femur. **J,** Postoperative radiograph showing the plate osteosynthesis. **K–N,** Postoperative appearance in and out of the prosthesis (another patient more than 20 years following a similar rotationplasty at age 7 years).

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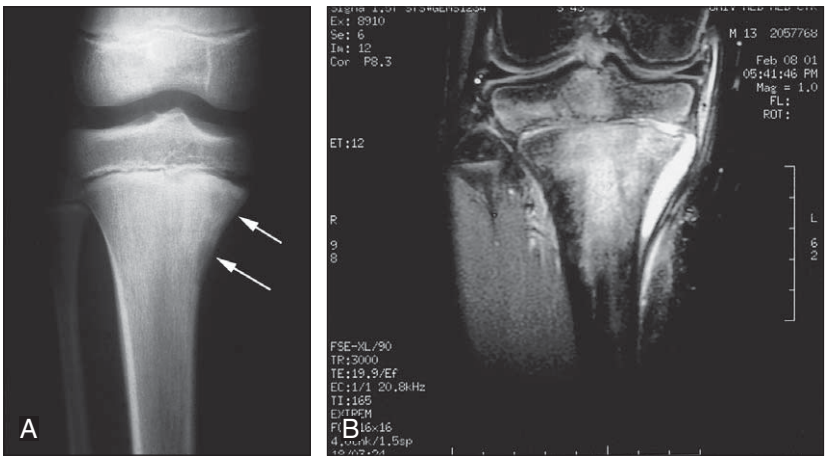
Figure 96-4, cont'd

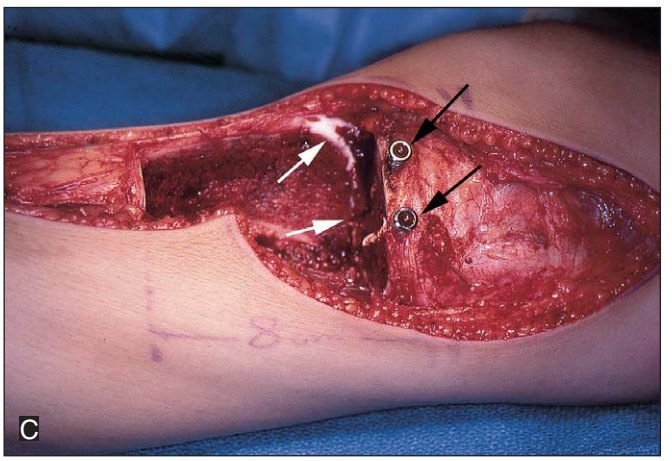
and rely on techniques of epiphyseodesis or subsequent limb lengthening to equalize the extremities. Another alternative is to use expandable prostheses to deal with limb length. There are several on the market, some of which require operations to expand the prostheses and others that can be lengthened by using electromagnetic devices in a radiology suite (Fig. 96-6).[162–164] The early reports of these prostheses are encouraging, especially to parents, but the long-term outcomes are unknown. They are very expensive and complex prostheses, and little data are available with respect to two key issues: whether a very young child can reach skeletal maturity with equal limb lengths and good function and whether the results of the required revision to an adult prosthesis at skeletal maturity will be successful. Early reports show that lengthenings can be achieved and that the complication rates are similar to those of adult endoprostheses. A higher rate of flexion contractures had been noted, since young children are not as cooperative with physical therapy, and loosening and failure of the implant also occur in these complex prostheses.[162–164] The optimal method of fixation of the stems to the host bone remains controversial. It is also unclear whether sufficient bone stock will remain when the patient needs to be converted to an adult prosthesis, owing to stress shielding of the stem in these immature bones.

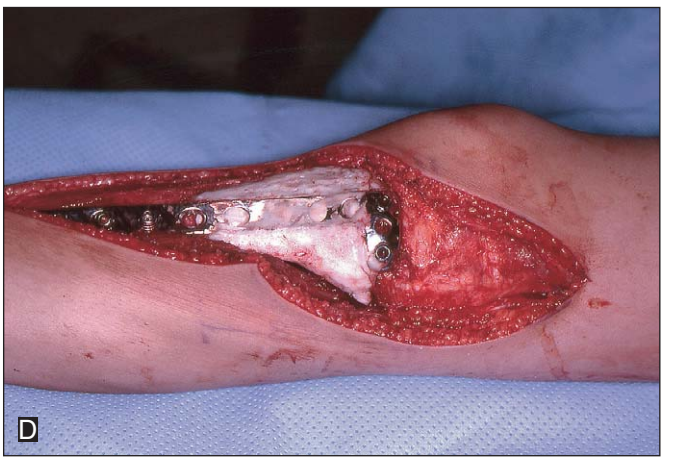
Amputation

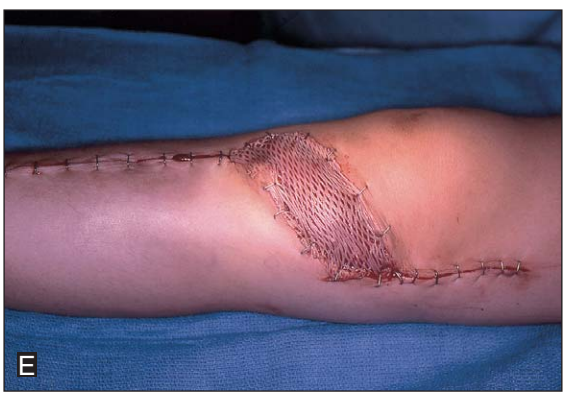
Ablation or primary amputation may be considered for patients with pathologic fracture and patients younger than 9 years of age in whom

Figure 96-5 • **A,** AP x-ray of a male, age 12 years and 6 months, showing increased density over the medial tibial metaphysis (*arrows*). **B,** Pretreatment AP fat suppression MRI illustrating the extraosseous extension of the tumor and sparing of the medial proximal tibial epiphysis. **C,** The response to preoperative chemotherapy was excellent, and at 12 weeks, the patient was essentially asymptomatic. A follow-up MRI scan demonstrated only minimal residual medial metaphyseal disease. The family refused rotationplasty, expandable prosthetic replacement, or amputation and requested a partial physeal-sparing procedure, sparing the articular surface medially and the growth plate and tibial apophysis laterally, followed by periodic operative procedures to correct the anticipated varus deformity associated with continued lateral tibial physeal growth. This photo demonstrates the heads of screws in the epiphysis (*black arrows*) with the tumor resected, sparing the tibial apophysis and lateral tibial epiphysis (*white arrows*). **D,** A plate has been attached to the tibial plateau and secured to the tibial shaft. The defect was filled with chilled methyl methacrylate, to be removed at a later date for periodic correction of the anticipated varus deformity. **E,** A medial gastrocnemius flap was rotated with a meshed split-thickness skin graft for closure and to use the underlying gastrocnemius fascia of the medial head to reconstruct the medial collateral ligament that had been resected. **F,** X-ray demonstrating the normal lateral tibial growth, resulting in a 15-degree varus deformity at 18 months. **G**, The patient was returned to the operating room, where the plate and methyl methacrylate were removed. A chevron osteotomy of the lateral aspect of the tibia metaphysis allowed correction of the deformity. **H,** X-ray representing the result 6 months after the first correction (total 24 months post therapy). It is anticipated that at least one or perhaps two additional corrections will be required before skeletal maturity is attained.

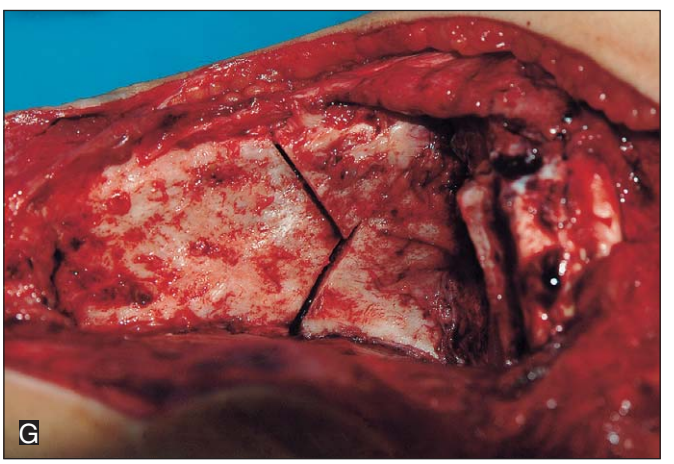

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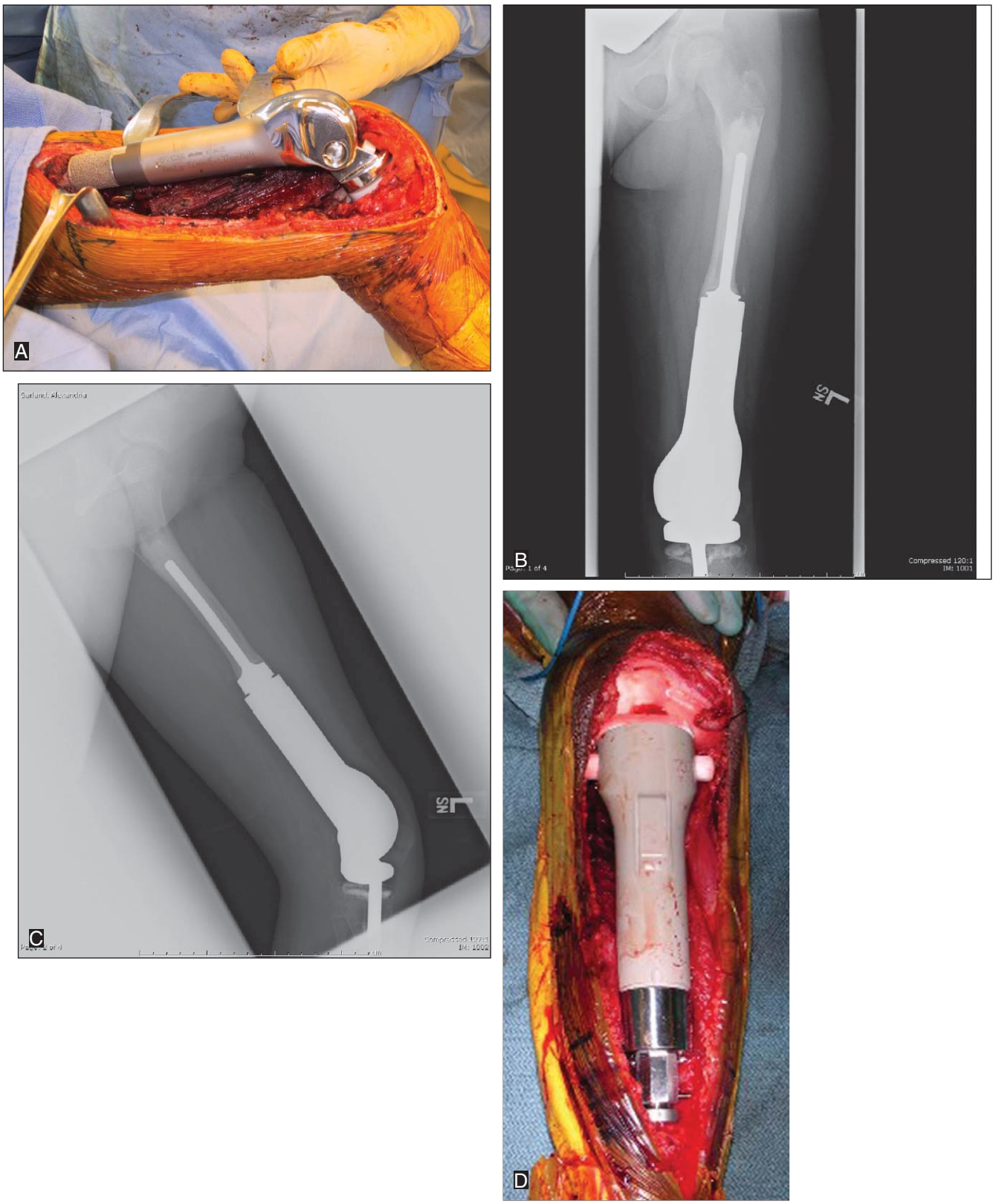


Figure 96-6 • **A,** Intraoperative photograph of an expandable prosthesis of the distal femur. This prosthesis contains an inner tube that will expand by turning a mechanical mechanism on the prosthesis periodically. It requires a small operation to turn the mechanism with a screwdriver near the knee. At times, the pseudocapsule around the prosthesis needs to be excised to allow for expansion. **B** and **C,** AP and lateral radiographs of the prosthesis shown above. At adulthood, the prosthesis will require conversion to an adult prosthesis. **D,** Intraoperative photograph of another type of expandable prosthesis. This prosthesis does not require an operation to expand. An electromagnetic coil is applied around the extremity under minimal sedation. The coil melts a component in the prosthesis, allowing a spring to expand the prosthesis under fluoroscopic control. When the coil is removed, the expansion stops.

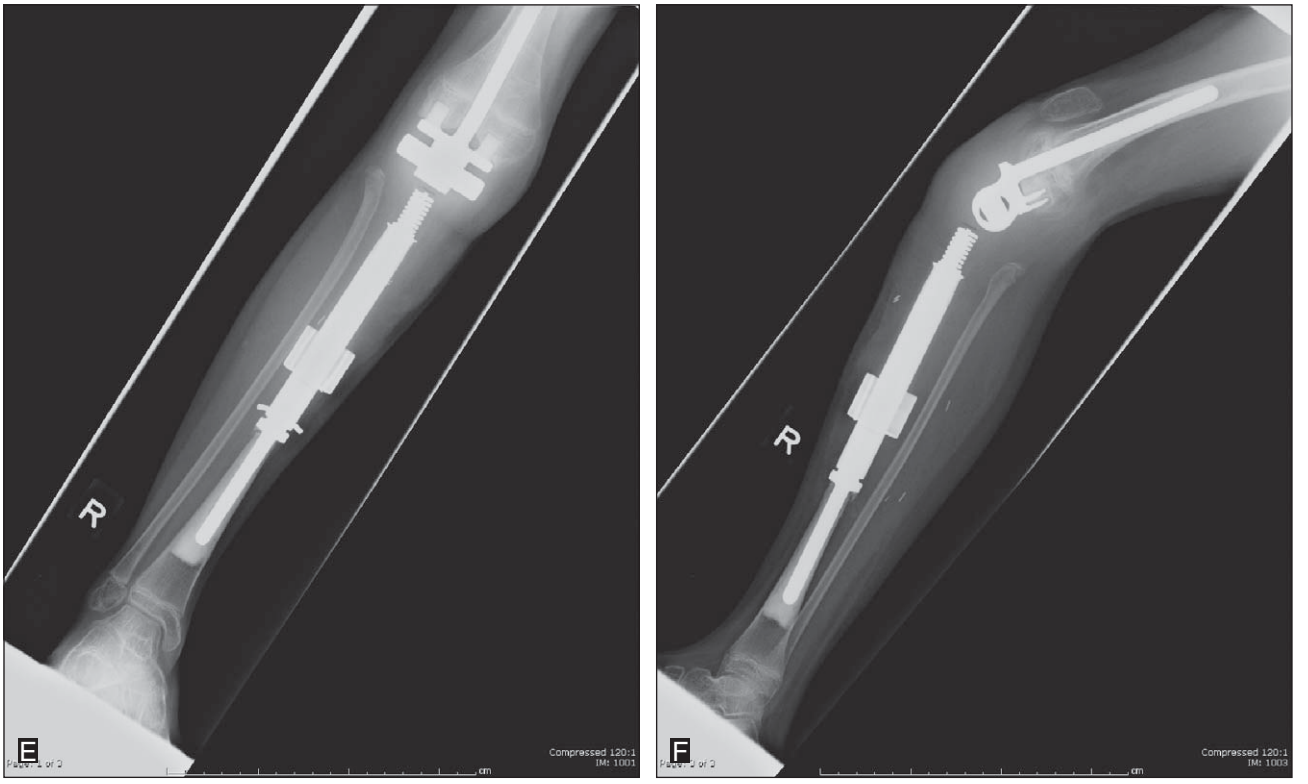


Figure 96-6, cont'd • **E** and **F,** Radiographs of the prosthesis shown in **A–D**.

lower-extremity limb length inequality would be considerable.[165,166] Also, stage IIB lesions that arise below the knee and below the elbow are best treated by primary amputation. It should be recognized, however, that selected patients with favorable lesions that arise below the knee and elbow might also be candidates for limb-sparing procedures. Also, some pathologic fractures have been shown to heal during intensive neoadjuvant chemotherapy.[167] We have become so accustomed to salvaging limbs that amputations are probably not being used enough. It is wise to remember that with modern prosthetics for the lower extremity, function can be quite good and perhaps better than that of limb salvage for tumors of the distal femur and below. Amputation should not be viewed as a failure or sign of defeat until we develop better methods for limb reconstruction.

Surgical Options for Limb Salvage Reconstruction

Endoprostheses

Early experience with metallic reconstructions for limb salvage of tumors required custom-made implants, which took time to manufacture and had design features that limited longevity. Now there are modular prostheses for most anatomic sites of the upper and lower extremities that allow the surgeon to reconstruct individual defects at the time of the resection without custom implants (Fig. 96-7).[168–174] Design improvements in rotating knee hinges and cementless stem options will likely lead to increased longevity of these implants. The advantages of endoprostheses include their relative ease of use, a lower reported infection rate, and a more rapid return to function, since there is no waiting for union, as in bone allografts. The main drawbacks include the concern for longevity of the implants and their fixation to the host bone. A recent stem design uses constant compression forces and a cementless fixation system that is purported to induce bone hypertrophy and lessen stress shielding, but results are preliminary.[175] In young children, it is unreasonable to expect a complex implant to last the patient's lifetime if the patient survives the disease, and multiple revisions are to be expected. Advances in fixation of implants to the host and design improvements in the joints will likely improve the longevity and usefulness of these implants.

Bone Allografts

Bone allografts are another alternative to limb salvage for sarcomas. They offer the potential advantage of incorporation by the host and greater longevity but are technically more demanding than prostheses. Availability of a bone bank with a variety of shapes and sizes of allografts is a prerequisite, although several large commercial bone banks that are accredited by the American Association of Tissue Banks are now available. Younger patients are more suitable because the recovery period is longer owing to the need to protect the osteosynthesis site until it heals. Allografts can be used as osteoarticular grafts (Fig. 96-8), replacing one side of a joint, or can be combined with standard prosthesis to create allograft-prosthetic composites (Fig. 96-9). Intercalary defects are particularly suited to allografts, since the joint on either end of the diaphyseal defect is intact (Fig. 96-10). An arthrodesis of a shoulder, knee, or hip can also be created by using allografts. The main drawbacks are the potential for disease transmission and the relatively high reported complication rates compared to endoprostheses.

The experience using large-bone allografts for reconstruction in high-grade osteosarcoma at the Rizzoli Institute in Bologna was recently reviewed by Donati and colleagues.[176] Between 1986 and 1994, 112 large-bone allograft reconstructions were performed. Forty-one were used for arthrodesis of the knee, and three were used in the ankle. Thirty-nine were used as intercalary grafts (see Fig. 96-10), and 22 were used as osteoarticular allografts (3 humeral, 6 in the distal femur, and 13 in the proximal tibia). Seven composite constructs were reported; two were in the proximal and distal humerus, one in the proximal femur, and four in the proximal tibia. Complications included delayed union (greater than 1 year without radiographic

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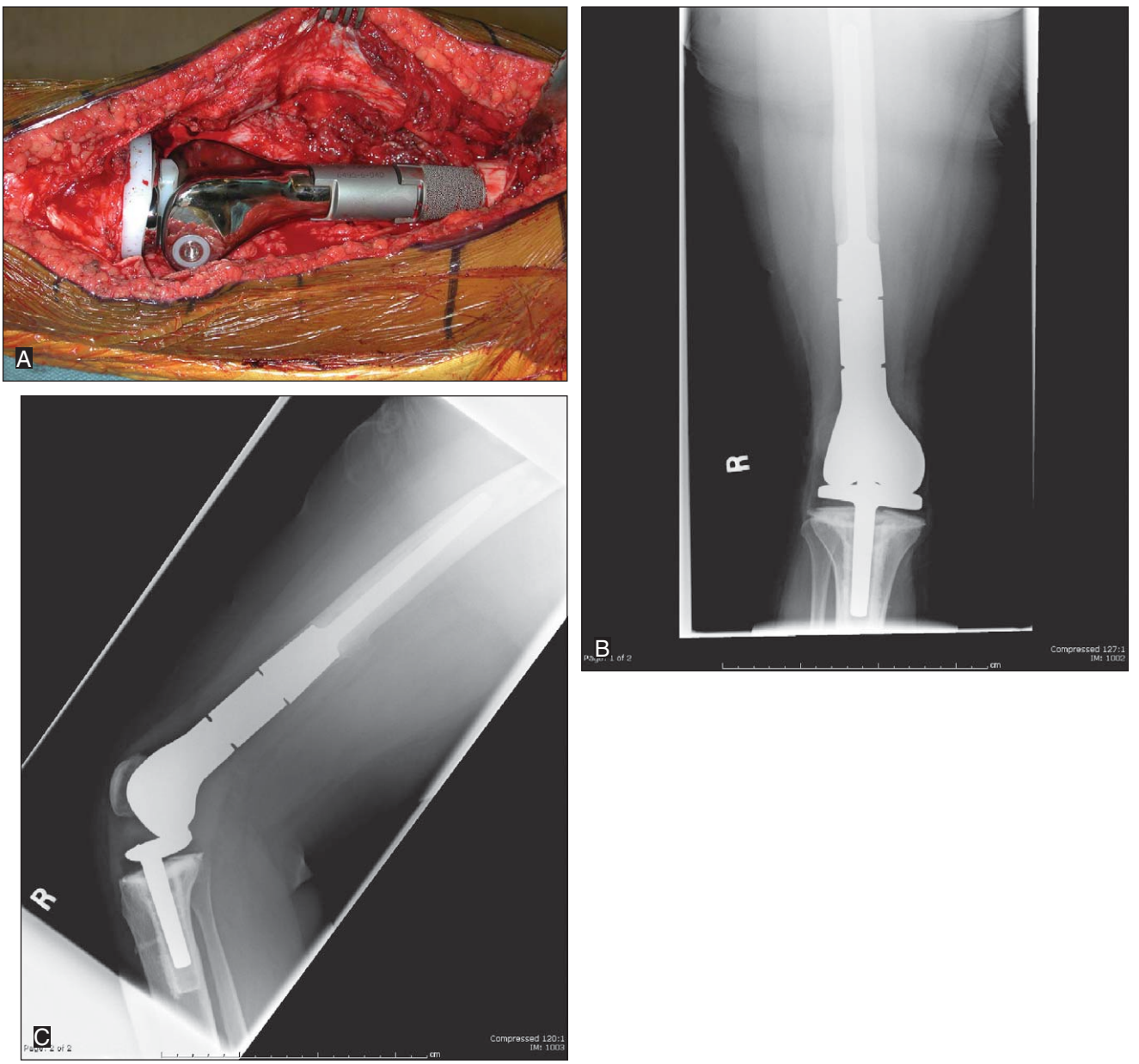


Figure 96-7 • **A,** Intraoperative photograph of a modular endoprosthesis for the distal femur. This prosthesis is cemented in place and has a rotating hinge knee design. The prosthetic stem is roughened near the femur implantation site to allow for tissue ingrowth. Length can be determined by selecting the proper body segment length and assembling it with Morse tapers. **B** and **C,** AP and lateral postoperative radiographs of the prosthesis shown above.



Figure 96-8 • **A,** Preoperative clinical photograph showing the incision for resection of the distal femur, including the biopsy tract. **B,** Intraoperative photograph of an osteoarticular allograft of the distal femur prior to repairing the capsule. **C,** Intraoperative photograph showing the osteosynthesis. **D** and **E,** Postoperative radiographs 3 years postoperatively showing healing of the osteosynthesis site.

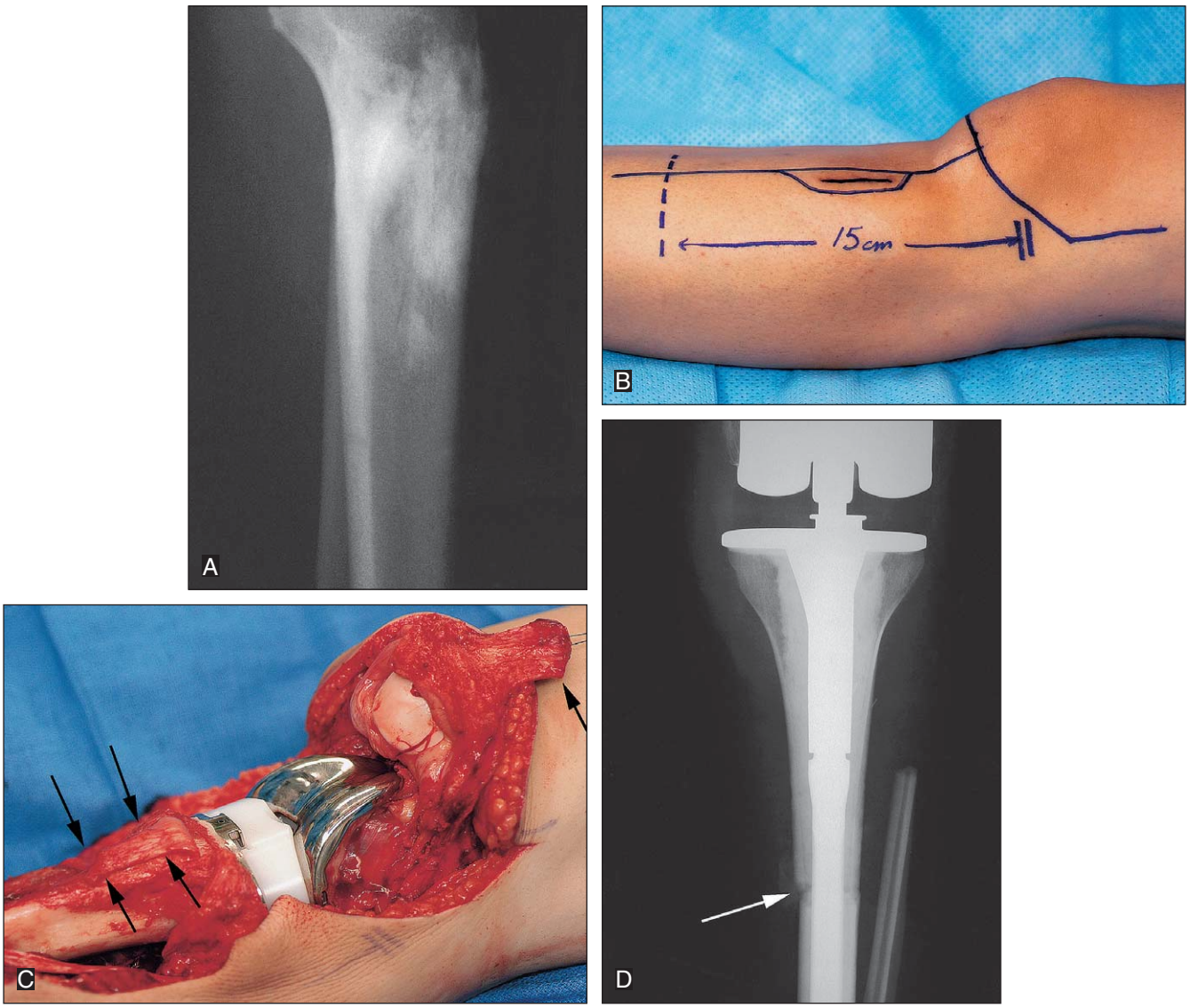
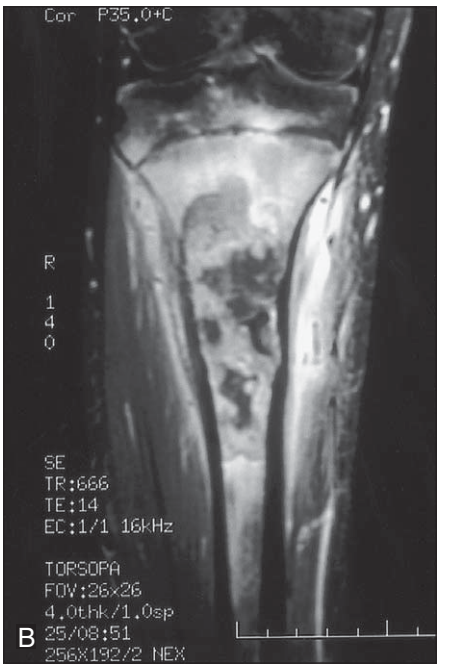
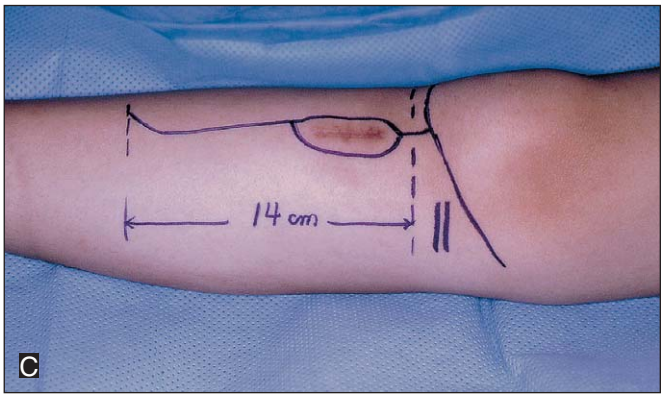


Figure 96-9 • **A,** A 27-year-old female developed a painful mass in the left proximal tibia approximately 3 weeks prior to medical evaluation. This lateral x-ray of the tibia demonstrates a dense, bone-producing lesion in the metaphysis associated with a soft-tissue mass in the anterior compartment. **B,** An open biopsy confirmed osteoblastic osteosarcoma, and all staging studies suggested that the patient was otherwise free of disease. After 12 weeks of standard preoperative multiagent chemotherapy, the patient was taken to the operating room to resect 15 cm of the proximal tibia and adjuvant soft tissue to include the patellar tendon and the proximal fibula while sparing the peroneal nerve. **C,** Intraoperative photo after the tumor was resected demonstrating the reconstruction using a deep frozen allograft with the retained allograft patellar tendon (*double arrows*). The prosthesis has been secured, and the host patellar tendon (*single arrow*) will be woven and sutured to the allograft tendon to restore the resected extensor mechanism. **D,** AP x-ray taken 3 months postoperatively demonstrating the composite allograft/prosthetic hybrid secured with methyl methacrylate and shows that the host/graft juncture (*white arrow*) with supplemental bone graft is healing with evidence of callus.

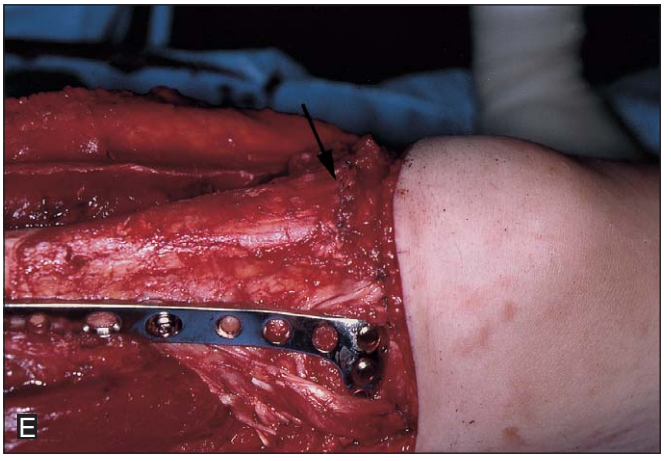
Figure 96-10 • **A,** This 16-year-old skeletally mature male athlete developed pain and tenderness in the right proximal tibia while practicing for a winter sport 6 weeks before medical evaluation. There was no history of trauma, fever, or chills. **B,** STIR image of the right proximal tibia demonstrating intramedullary destruction and a medial metaphyseal soft-tissue mass. The physis and physeal plate, although edematous, appear to be spared. **C,** The preoperative chemotherapy response proved to be excellent, with the clinical absence of pain, mass, and knee stiffness. The preoperative MRI also demonstrated loss of edema and consolidation of the small medial soft-tissue mass, with resolution of all signal adjacent to the closing proximal tibial epiphysis. The patient requested a joint-sparing procedure if at all possible. **D**, Intraoperative photo demonstrating the resection margin just proximal to the tibial physis, including the tibial tubercle and patellar tendon. A distal chevron osteotomy was performed 14 cm distal to the proximal osteotomy. The specimen was cut immediately on the back table to be certain that the proximal and distal margins were free of disease. **E,** A deep frozen allograft with ligaments attached was matched to the bone size and used to fill the defect anatomically while providing an allograft patellar tendon for reconstruction. The *arrow* demonstrates the suture line that was used to reconstruct the allograft/host patellar tendon while retaining the host tibial plateau and intra-articular ligaments. A medial gastrocnemius flap and meshed split-thickness skin graft were used to cover the construct. **F,** Composite AP and lateral x-ray representing the 18-month follow-up with complete proximal and distal host/allograft incorporation. The patient has returned to competitive swimming without external aids or a brace.

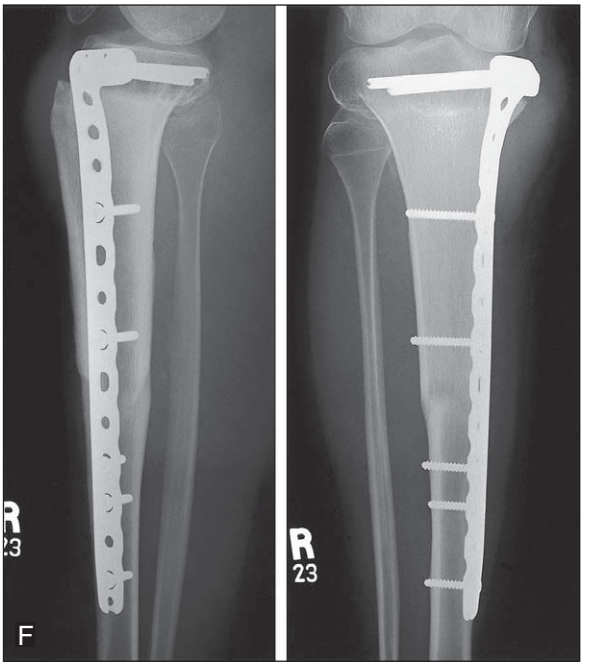

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union) in 49% of patients and fracture in 30%. There were no deep infections. Using the modification of the Mankin scale by Gebhardt and coworkers,[177] good to excellent functional results were reported in 74% of the 92 patients who were available for review. Examples of these reconstructions at various sites will be briefly presented.

PROXIMAL HUMERUS. Proximal humeral osteosarcomas can frequently be resected while preserving all or part of the scapula. The motion, strength, and functional outcomes of these reconstructions vary depending on whether or not the rotator cuff muscles and deltoid can be preserved. A patient in whom the glenoid, rotator cuff, and deltoid can be preserved should expect reasonable function, whereas a patient who requires resection of the deltoid, rotator cuff, and portions of the scapula will have less good shoulder function. If the neurovascular supply to the hand can be safely preserved, however, the function is superior to amputation. By using current prosthetic designs augmented with muscle rotation flaps and synthetic grafting materials (Dacron, Gore-Tex, and others), a stable shoulder can often be achieved, and preservation of an innervated hand is paramount.

Wittig and coauthors[178] described the single-surgeon experience of 23 patients with osteosarcoma of the proximal humerus that included 1 stage IIA lesion, 18 stage IIB lesions, and 4 stage III lesions. Twenty-two of the 23 patients were treated surgically with an extra-articular resection that included the deltoid muscle and the rotator cuff, while 1 patient was treated with a transarticular resection that spared the shoulder abductors. The patients ranged in age from 10 to 77 years. Before 1988, 10 patients received custom proximal humeral replacements, and after 1988, 13 modular segmental prosthetic replacements permitting intraoperative sizing were used. Prosthetic survival for the 15 survivors was 100% at a median follow-up of 120 months (range: 24 to 234 months). No prosthesis required revision. There was one instance of aseptic loosening. Complications included transient nerve palsies. All nerve palsies resolved within 6 to 12 months after surgery. Functional outcome as recorded by the Musculoskeletal Tumor Society Extremity Functional Scores ranged from 24 to 27 (80% to 90%). All shoulders were stable, and all patients could perform the activities of daily living with the involved extremity.

Osteoarticular allografts (Fig. 96-11) or allograft prosthetic composites can also be employed at this site.[179–183] They offer the advantage of having sites for attachments of muscle tendons (rotator cuff and deltoid), and since this is a non-weight-bearing bone, the likelihood of fracture is less than that in the lower extremity. Allograft arthrodeses can also be employed.

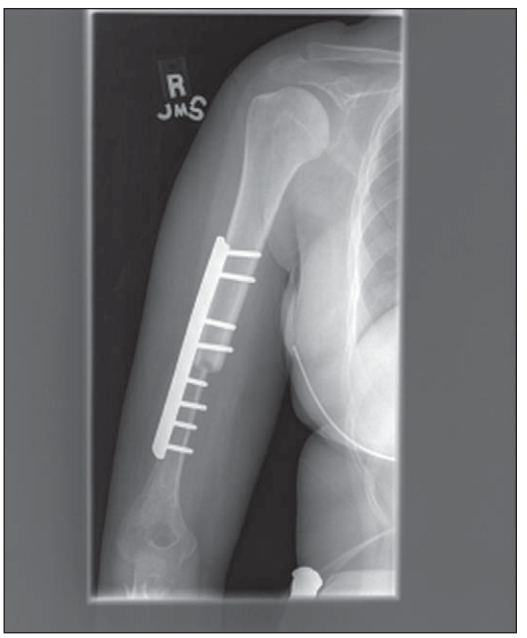


Figure 96-11 • Osteoarticular allograft for proximal humerus osteosarcoma resection.

The experience of the Mayo Clinic was reviewed by O'Connor, Sim, and Chao,[181] who described the treatment of 53 patients with malignant bone tumors of the shoulder girdle with an average follow-up of 5.3 years (median: 4.6 years). A variety of surgical procedures and reconstruction methods were used to achieve wide margins in 40 of 53 patients, with 13 patients having marginal resection margins. Four patients (two after wide resection, two after marginal resection) experienced locally recurrent disease. The functional results are the subject of another report.[184]

Rödl and colleagues[185] in 2002 retrospectively compared osteoarticular allografts (11), clavicula pro humero (15), and a tumor prosthesis (19) for reconstruction following resection of the proximal humerus. The glenoid was resected in 25 patients, and the axillary nerve was resected in 42. The functional results of all three types of reconstruction were similar, but the complication rate was lowest in the prosthetic group, leading the researchers to conclude that the prostheses were the most reliable reconstruction.

PELVIS. The pelvis is the most challenging site for resection, although in many cases, the tumor can be resected without a hindquarter amputation (hemipelvectomy). It should also be remembered that the prognosis of pelvic osteosarcoma remains poor despite modern multimodality treatment regimens, including neoadjuvant chemotherapy.[186] The difficulty comes in reconstruction when the acetabulum is resected. Removing the iliac wing or pubic ramu and ischium often requires no reconstruction and results in relatively good function if the sciatic nerve and acetabulum can be preserved. If the acetabulum is resected, the reconstruction options include leaving the hip flail, attempting an arthrodesis, or replacing the defect with an allograft or custom metallic prosthesis.

Schwameis and associates[187] described the results of the Austrian experience of reconstruction of the pelvis in children and adolescents. Thirty patients, ages 19 years or younger, with malignant tumors of the pelvic bones were treated by using an endoprosthesis in 10 patients, and in 20 patients, reconstruction was completed by using autologous grafts (7 patients), allograft/prosthetic composites (2 patients), methyl methacrylate reconstruction (1 patient), iliosacral arthrodesis (1 patient), modified Girdlestone procedure (3 patients), or resection/arthroplasty (6 patients). After a mean follow-up of 52 months (range: 2 to 241 months), 15 patients were continuously free of disease, 2 were alive with disease, and 13 had died of their disease. MSTS ratings revealed an 81% functional status after autograft, 73% functional status after allograft, and 60% functional status after endoprosthetic reconstruction. Reoperations were significant in that the patients who received allograft reconstruction required an average of 3.5 reoperations, while those who received endoprosthetic reconstruction required an average of 2.5 reoperations. Only 0.8 reoperations per patient were necessary after the other described methods of reconstruction.

Satcher and coworkers[188] described the results of 15 patients who underwent reconstruction for pelvic deficits associated with tumor resection in and about the acetabulum in a slightly older population. The review was limited to periacetabular resections and included patients with primary malignancies and metastatic disease. The authors described a reconstruction technique utilizing numerous Steinman pins placed within the residual and remaining bone to reconstruct the acetabular structures with methyl methacrylate and (occasionally) autoclaved autograft bone in combination with total hip arthroplasty. After tumor resection, the pelvis was reconstructed by using autoclaved autograft or the cement and Steinman technique. Functional results were graded overall excellent or good for 87% of the patients. Their recovery time in general approximated that of patients with routine total hip arthroplasty.

Pelvic allografts have had some success but are demanding procedures and, if the soft tissues are not ideal, subject to a high infection rate. One study of 13 patients looked at the results of reconstruction by massive allografts (some were combined with metal hip prostheses) after resection of a malignant tumor (primary in 10 patients and metastatic in three patients). Postoperative complications were one infection and two dislocations. At 3 years, one cup loosening and one acetabular fatigue fracture required surgery. The functional result was excellent in two patients whose gluteal muscles could be spared, good (allowing a normal family life) in six patients, fair in two patients, and poor in two patients. Seven patients had a MSTS rating greater than 60% of normal (the mean rating in 12 patients was 56.4%). The authors concluded that reconstruction of the hemipelvis with massive allografts and arthroplasty is a rewarding but demanding procedure that should be reserved for physically active patients who are in good general health and are expected to have a response to anticancer therapy.[189]

Despite the complexity of the pelvic resections or amputations, in patients without evidence of metastases, an attempt at resection seems reasonable. A study of 67 patients with pelvic osteosarcoma (15 of whom had metastases at diagnosis) who were registered in the Cooperative Osteosarcoma Study Group were analyzed. All patients received chemotherapy according to that group's protocols. Thirty-eight patients underwent limb-sparing surgery, 12 patients underwent hemipelvectomy, and 17 patients did not undergo definitive surgery. Local failure occurred in 47 of all 67 patients (70%) and in 31 of 50 patients (62%) who underwent definitive surgery. Five-year overall survival and progression-free survival rates were 27% and 19%, respectively. Primary metastasis, large tumor, no or intralesional surgery, no radiotherapy, and existence of primary metastasis were independent poor prognostic factors. The researchers concluded that an operative approach with wide or marginal margins improves local control but that if the surgical margin is intralesional or excision is impossible, additional radiotherapy has a positive influence on prognosis.[190]

PROXIMAL FEMUR. Two types of proximal femoral reconstruction are currently employed:

1. Megaprosthesis, a large metallic prosthesis, often modular in design, that is used to replace the entire proximal femur and occasionally the acetabulum. Reattachment of ligamentous structures to the prosthesis is facilitated by holes or rings designed into the prosthesis, to which the ligaments can be sutured securely. There is very little evidence to suggest secure long-term reattachment other than to the scar enveloping the prosthesis.
2. Allograft/prosthetic composite, consisting of a long-stemmed proximal femoral prosthesis placed within a proximal femoral allograft, securely cemented into the allograft and remaining shaft of the host bone (Fig. 96-12). Advantages over megaprosthesis include the ability to repair host ligaments to the retained ligaments on the allograft. There is histologic evidence that the host and allograft ligamentous structures do unite by scar formation, with less than normal tensile strength.

Survival of prostheses that replace the proximal femur is generally reported at a rate between 88% and 100% at 5 years.[191–193] A direct comparison of megaprostheses and allograft/prosthetic composites used to reconstruct the proximal femur has demonstrated a survival advantage for composites.[194] Stability of the hip remains a concern, with dislocation rates reported at between 2% and 14%, while aseptic loosening remains low for proximal femoral reconstruction.[191–193,195–198]

DISTAL FEMORAL PROSTHETIC REPLACEMENT. Two prosthetic designs are available:

1. The simple hinged-knee prosthetic does not allow for rotation but only for flexion and extension.
2. The kinematic rotation hinge knee prosthetic allows for rotation, flexion, and extension through an offset hinge that provides stability in full extension.

The most important cause of failure for distal femoral prosthetic replacement remains aseptic loosening, which is found in 0% to 11% of patients.[193,199,200] In 218 reconstructions, the overall survival rate for patients with the simple hinge design was 80% at 5 years, 65% at 10 years, and 53% at 20 years.[199] The rotating kinematic hinge design has a better record, with 5- and 10-year survival rates of 90% and 80%, respectively.[192] It is suggested that the rotation of the normal knee simulated by the improved design diminishes impact torsional loading of the cement/bone interface, which often is responsible for loosening.

At present, several modular tumor prosthetic systems are available for reconstruction of tumor resection about the knee (see Fig. 96-7). Results with one modular tumor system used in large numbers by two separate groups have recently been published. Mittermayer and associates[201] reported on the University of Vienna's treatment of 100 patients with primary lower-extremity uncemented reconstruction using the Kotz Modular Femur Tibia Reconstruction System between 1982 and 1989. Forty-one patients were followed for a mean of 138 months (51 patients had died, and 8 were lost to follow-up). Nine patients required revision for aseptic loosening, and two required two such revisions. Four patients developed deep infections. Fourteen patients required reoperation for early failure of the polyethylene bushings.

A large multicenter Canadian study reported by Malo and colleagues[202] addressed the question of stem fixation and fixed versus rotation hinge design of the knee in the Kotz design prosthesis. Thirty-one patients with Kotz fixed hinge and uncemented stem constructs were compared with 25 patients with the KMRS cemented stem and rotating hinge design using the MSTS (1987 and 1993) functional assessment, the Toronto Extremity Salvage Score, and the Short Form-36 Physical Component Score for a follow-up period of at least 1 year. Results in the two groups of implants were comparable, except that the uncemented group had an average of 2 cm greater length of resection. The outcomes of the MSTS (1993; $P = 0.006$) and the Toronto Extremity Salvage Score ($P = 0.03$) assessment suggest that cemented stem fixation and a less constrained knee design were preferable, even though the study was designed to assess functional issues from the patient's perspective.

No direct comparison between endoprostheses and allografts for distal femoral reconstruction are available, and allografts remain a reasonable alternative, especially in young patients. A study of 118 knee osteoarticular allografts in 114 patients was reported with long-term follow-up.[203] Ten patients were lost to follow-up, and 18 patients without allograft failures died of complications related to the tumor. Twenty-six allografts failed because of infection (13 allografts), local recurrence (8 allografts), massive resorption (3 allografts), and fractures (2 allografts). Sixty-four allografts were still in place at a mean of 98 months after implantation. The Kaplan-Meier 5-year survival rate for the knee osteoarticular allografts was 73%, and the limb preservation rate was 93%. Five patients required joint resurfacing to preserve the original allograft. Most of the allograft failures occurred during the first 4 years, and the allograft survival rate for this series remained unchanged after 5 years. Others[180] have reported more dismal results, attesting to the demanding technical aspects of this surgery and the need for experience with the surgical techniques and tissue banking.[204,205]

PROXIMAL TIBIAL PROSTHETIC REPLACEMENT. Two factors play a role in the rather poor performance of implants that are used to reconstruct the proximal tibia:

1. Difficulty in obtaining good soft-tissue coverage
2. Poor reconstructive options for extensor mechanism reconstitution

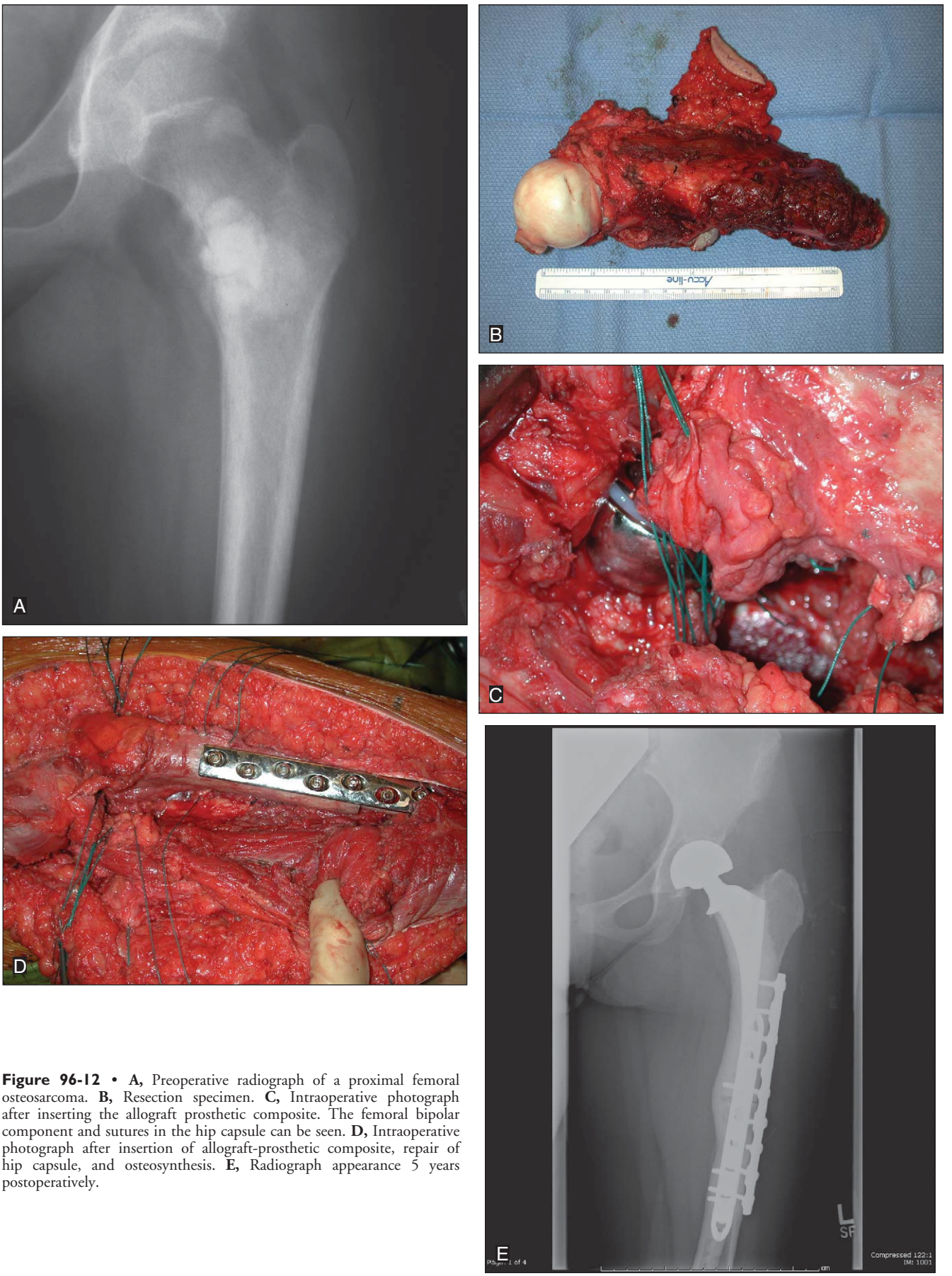


Figure 96-12 • **A,** Preoperative radiograph of a proximal femoral osteosarcoma. **B,** Resection specimen. **C,** Intraoperative photograph after inserting the allograft prosthetic composite. The femoral bipolar component and sutures in the hip capsule can be seen. **D,** Intraoperative photograph after insertion of allograft-prosthetic composite, repair of hip capsule, and osteosynthesis. **E,** Radiograph appearance 5 years postoperatively.

Allograft/prosthetic composites appear to have improved survivorship and function compared with megaprostheses and remain a favorite method of reconstruction because the composites provide the ability to reconstruct the host patellar tendon with the remaining allograft patellar tendon. The routine use of the rotation of a medial gastrocnemius flap either with or without skin has improved coverage of the prosthesis and local nutrition. However, there remains an inordinately high risk of infection, up to 31% (see Fig. 96-9).[191]

Functional Results of Surgical Therapy

The surgeon should consider the functional outcome of surgical therapy when assessing the patient's physical demands and needs. Upper-extremity reconstructive procedures should attempt to maximize function as much as possible, as the extremity does not need to be reconstructed to weight-bearing tolerance. The key issue is maintaining a functional hand, even if shoulder function is not optimal. Unlike the lower extremity, there are no prosthetic replacements that come close to reproducing the function of the hand. Lower-extremity and pelvic reconstructive procedures require greater attention to stability, durability, and mobility. Modern prosthetics for the lower extremity have dramatically improved the function of the lower extremity and can be adapted for nearly all sports activities as well as work environments. One issue is using a proper, validated functional evaluation and QOL assessment. Several are available, but the ideal one or ones are not yet clear.

Validation of a Functional Evaluation System

Lee and coworkers[206] evaluated the MSTS functional evaluation system using the Nottingham Health Profile, the Short Form-36, and the EuroQOL protocol to measure the QOL of patients with malignant musculoskeletal tumors. Forty-nine patients were assessed, and osteosarcoma about the knee was the most common condition. Prosthetic reconstructions had been completed in 55.1% of patients.

All of the items of the lower extremity were related to the same function: walking ability. The MSTS system had a strong correlation with other QOL measures in the construct validity and reliability, but the sociologic domains of the system were so comprehensive that it could not represent the QOL properly. The patients' preoperative and postoperative status could not be compared by using this system. The overall validity and reliability of the MSTS system appeared to be appropriate; however, the system could require the additional development of domains for evaluating the QOL in patients with musculoskeletal tumors. Other systems, such as the SF-36 and the Toronto Extremity Salvage Score, have also been used and validated for sarcoma patients.

Not many studies have compared amputees to limb-sparing procedures for sarcoma. Renard and colleagues[207] from the Netherlands reported retrospective results in 77 patients treated between 1975 and 1995 for sarcomas in the lower extremity. They compared functional results using the MSTS (1993) criteria and the QOL for groups of 52 patients who had limb-sparing surgery and 25 who had ablative treatment. Treatment of tumors involving the pelvis to distal femur and proximal tibia were included. When all anatomic groups of limb-preserving procedures were combined and these patients were compared with patients who were managed by amputation, the functional score of the limb-sparing group after a mean duration of 97 months follow-up was significantly better ($P = 0.0001$) than that of patients who had an ablative procedure.

A recent study compared QOL and subjective well-being between patients who underwent either amputation or limb salvage procedures for lower-extremity sarcomas. Sixty-six patients were evaluated at least 1 year after surgery and systemic therapy for lower-extremity sarcomas. Self-report questionnaires such as the Quality of Life Questionnaire (QLQ-C30), the Life Satisfaction Questionnaire (FLZ), and the Enneking Score (MSTS) were used. There were no differences in QOL and subjective well-being between the two groups. Small differences in scores were found in social functioning but not in scores of physical, cognitive, and emotional functioning. Global subjective well-being in both groups was also similar (219.5 versus 223.7). High satisfaction was found in marital life and partnership as well as in self-assessment. The least satisfaction was found in finances. Results in functional outcome after limb salvage procedures were better than for amputation (77% versus 65%), although more complications were reported after limb salvage procedures. They demonstrated that the type of surgery had no influence on QOL and subjective well-being after treatment of lower-extremity sarcomas.[208] A study of 408 patients with sarcomas who were treated with either limb salvage or amputation had postoperative follow-up of 2 years or greater when they completed a QOL self-report questionnaire. Limb salvage offered a functional advantage particularly at proximal tumor locations.[209]

Refaat and coworkers[210] used a computerized questionnaire that was automatically adjusted for gender, age, diagnosis, site, and treatment sent to 2200 patients with high-grade sarcomas who had been treated during the past 25 years. They compared the response from 66 patients who had an amputation and 342 patients with a limb-sparing procedure for a lower-extremity neoplasm. The outcomes for the two groups were similar. Patients who had limb-sparing procedures did not have a significant improvement in the ability to ambulate, climb stairs, drive a car, or be employed. More of the patients with amputations required walking aids and participated in sports activities at almost the same rate as the patients who had limb-sparing procedures. Patients who had amputations had no more anxiety, drug dependence, depression, sleep problems, or limitation of sexual performance than did patients who retained their limbs. The patients with amputations had more children and fewer menstrual problems; however, they were far less satisfied with their status at early ages than at later periods in their lives.

Oxygen consumption studies of gait suggest that patients with rotationplasty compare favorably with patients who have had a below-knee amputation and function better than most with an above-knee amputation.[211–214]

Harris and coauthors[166] studied the function of 22 patients who had surgical management for malignant neoplasms around the knee. Seven had an above-knee amputation, nine had resection/arthrodesis, and six had replacement arthroplasty. All patients were available for physical examination and measurement of consumption of oxygen, and all answered questionnaires on function and psychological effects.

All patients walked at similar speeds that were significantly slower than those of normal matched subjects. All patients walked with comparable efficiency at three velocities (free walking, 25% faster, and 50% faster), as measured by oxygen consumption and when compared with normal controls. For patients who had had an arthroplasty, efficiency tended to improve slightly at greater velocities. The times that were required to climb a flight of stairs and to step up and down a curb were similar for those with an arthroplasty and those with an arthrodesis, and both groups accomplished the tasks faster than did those who had had an amputation. The times taken to descend the steps, stand from a supine position, and stand from a sitting position were similar for all three groups.

Physical Capacity

AMPUTATION. Patients who had undergone amputation experienced difficulty walking up and down steep inclines, on slippery surfaces, and on uneven ground. They also had difficulty squatting (prosthetic ankles do not dorsiflex) and ran with a skip-hop pattern. They had little to moderate phantom limb pain, but skin irritation was frequent, and they required crutches to get into and out of a tub or shower. Overall, however, this group of patients worried least about damaging the prosthesis or injuring the involved limb.

ARTHRODESIS. Patients had undergone arthrodesis had the most stable affected limbs when walking on uneven ground and on

slippery surfaces or down hills. They ran with a skip-hop pattern and easily kept up with their peers. They could squat or kneel with the involved limb projecting in either the front or the back, with enough stability to have both hands free for work, and they could climb ladders and jump from short heights. As a group, these patients performed more physically demanding work than did the other groups.

ARTHROPLASTY. Patients who had undergone arthroplasty walked better in crowds and on snow, sat easily and could rise from a chair with ease, and could drive automobiles normally. Half of the patients required a hand rail while descending steps one at a time. More could flex the limb sufficiently to squat on the opposite (normal) knee. They often refrained from kneeling because of pressure on the prosthesis. These patients were the most protective of all, limiting their recreational activity, and were the most sedentary of any of the groups.[166]

ROTATIONPLASTY. Most of the rotationplasty patients were very active, with general disregard for the well-being of the limb or prosthesis. All of them shared problems associated with patients with a below-knee amputation (e.g., difficulty walking on steep slopes or uneven ground, inability to squat with ease). Oxygen consumption studies of gait suggest that patients with rotationplasty compare favorably with patients who have had a below-knee amputation, functioning better than most of those with an above-knee amputation and as well as those who have had endoprosthetic replacement.[212–215]

ACTIVITIES AND QUALITY OF LIFE AFTER ROTATIONPLASTY. At least two studies have examined general activities and QOL for people who have undergone rotationplasty. Hillman and associates[215] compared functional results in 34 patients treated with endoprostheses and 33 patients treated with rotationplasty. The rotationplasty patients were under the age of 24 years and had a minimum follow-up of 2 years. Results were evaluated by using the 1993 version of the MSTS functional scoring system and the core QOL questionnaire of the European Organization for Research and Treatment of Cancer. Patients who were treated by rotationplasty had better scores related to role functioning that included hobbies and work, had better ability to function without external aids, and were less inhibited when performing daily and sporting tasks. Most were less concerned than their counterparts about restrictions of activities involving sporting activities and work. Patients who were treated by endoprosthetic replacement had slightly more complaints of discomfort, and more (6 of 34 patients) used external aids than did those with rotationplasty (1 of 33 patients). Neither group was unhappy; however, some patients with rotationplasty appeared more self-conscious.

Veenstra and colleagues[216] from the Netherlands assessed the QOL and psychosocial functioning of 33 of 34 patients with a minimum age of 16 years who had large malignancies of the distal femur treated by rotationplasty between 1981 and 1994. The mean follow-up period was 6.3 years (range: 1 to 11 years). The general QOL was assessed with the European Organization for Research and Treatment of Cancer's QLQ-C30 cancer-specific QOL questionnaire. When compared with healthy counterparts, patients with rotationplasty had significantly poorer performance functionally but were superior psychosocially. Nine of 33 patients reported a negative effect on social contact, while 17 of 30 reported that the operation exerted no influences on social contacts. Seventeen did not feel limited in initiating intimate relationships, while 13 felt slightly to moderately limited, and 1 felt very limited. There was no apparent difference between males and females regarding the effect of surgery. Twenty-one of 33 patients reported that they were sexually active during the months before surgery. Eleven patients reported no sexuality problems, while 10 reported a small to moderate degree of inhibition. Physical function and prosthetic use assessment revealed that 21 of 33 patients did not use extended aids, and 8 of 33 used a single crutch periodically. No patient was confined to a wheelchair. Twelve patients used a normal bicycle regularly, and 15 required a shortened crank. Thirty-two of 33 patients reported wearing their prostheses from early morning to late at night, and all but 2 reported no difficulty sitting. The researchers concluded that rotationplasty was an excellent operative procedure for managing large tumors of the distal femur. Although the patients' level of physical functioning was below that of their normal peers, patients who were treated with rotationplasty experienced an overall QOL similar to that of their normal peers and functioned comparably in a psychosocial context.

Management of Patients with High-Grade Osteosarcoma and Pathologic Fractures

The incidence of the development of pathologic fracture of the extremity in patients with high-grade osteosarcoma varies from 10% to 13%.[217,218] The occurrence of a pathologic fracture is associated with a poorer prognosis and, in the past, was felt to demand an immediate amputation.[143] More recently, limb-sparing procedures have been used if there is a good response to preoperative chemotherapy.

The cause of a pathologic fracture is multifactorial and probably related to the type of osteosarcoma, the location of the lesion, the activity of the patient, and the type of trauma. The more destructive lesions, such as telangiectatic osteosarcoma, result in a thinned expanded cortex and are more subject to fracture than are other types. Lesions involving a weight-bearing bone, such as the femur, are also more likely to fracture.

Before the advent of neoadjuvant chemotherapy, the majority of patients who developed pathologic fractures were treated by amputation. Jaffe and colleagues,[217] however, observed that some pathologic fractures would heal while under the influence of systemic chemotherapy. They observed "reduction of the associated soft-tissue mass, repair of periosteum, and deposition of new mineral in the tumor and about the fracture." These observations made the closed management of some selected pathologic fractures feasible during treatment with neoadjuvant chemotherapy and in preparation for a limb-preserving procedure.

The subsequent healing of the fracture is also a function of the response of the tumor to neoadjuvant chemotherapy. Patients with healing fractures in general would be expected to have better overall outcomes than patients without a favorable histopathologic healing response to primary chemotherapy.

Current recommendations for treatment of patients who develop pathologic fractures from tumors that are potentially sensitive to chemotherapy include the following:

- The patient must have the ability to tolerate conventional intensive chemotherapy.
- The fracture must be treatable by closed means: either slings (usually upper-extremity fractures) or casts, external fixators that are well removed from the tumor margins, fracture braces, or traction for lower-extremity fracture management.
- The fracture should be monitored by physical examination (e.g., decreased fracture motion and pain) and the demonstration of a radiographically favorable response (e.g., increased maturation of the tumor, increased mineral deposition, subperiosteal new bone). If no evidence of improvement or favorable tumor response can be demonstrated after chemotherapy, then consideration must be given to immediate limb-preserving surgery or amputation.

Current small retrospective reviews suggest that patients with pathologic fracture who can tolerate both the proposed method of fracture treatment and intensive multiagent chemotherapy do not appear to have a greater risk of an unfavorable outcome compared to fracture patients who are treated with immediate amputation unless

the fracture demonstrates poor healing and unfavorable clinical response to treatment.[218,219]

Metastatic Disease

Metastatic disease is principally the result of hematogenous spread to the lungs and bone, followed by secondary involvement of the kidney, liver, and brain. Regional lymph nodes are involved in fewer than 10% of cases. Metastatic disease at diagnosis does not preclude long-term disease-free survival when the disease is sensitive to chemotherapy and all sites of disease can be surgically resected.[220–222]

Aggressive surgical treatment of pulmonary metastases (often requiring more than one procedure) can yield disease-free survival rates from 17% to as high as 40%.[223–225] Generally, favorable prognostic indicators include metastasis later than 1 year from original diagnosis, unilateral disease, presence of fewer than five nodules, and completeness of resection. Early pulmonary metastases, unresectable bilateral disease, and hilar, nodal, or pleural-based lesions have a poor prognosis.

Bacci and coauthors[226] from the Rizzoli Institute reported their results of treatment of 44 patients with osteosarcoma of the extremity with detectable pulmonary metastases between January 1993 and June 1995. Twenty-three patients were evaluable, having completed primary chemotherapy consisting of methotrexate, cisplatin, doxorubicin, and ifosfamide as defined by their protocol overall survival/N5. After primary chemotherapy, lung metastases disappeared in 3 of the 23 evaluable patients, whereas in 4 patients, the pulmonary disease was assessed as unresectable. All 7 patients received surgical therapy for the primary tumor only. In the remaining 16 patients, simultaneous resection of the primary tumor and of the pulmonary metastases was performed. Remission was complete in 15 of the 16 patients and incomplete in 1. Ten patients (55.5%) remained continuously free of disease at a mean follow-up of 30 months.

Kaste and coworkers[227] reported the experience of St. Jude Children's Research Hospital in evaluating 215 patients with extremity osteosarcoma, of whom 32 (15%) had evidence of metastatic disease. Thirty-one patients demonstrated evidence of pulmonary metastases, and only one demonstrated metastases to bone. The histologic subtype that was most commonly associated with metastases was the osteoblastic subtype ($N = 17$). Both the number of nodules and the number of lobes that were involved were found to be significant predictors of survival ($P = 0.0009$, $P = 0.04$, respectively); multiple nodes were bilateral in 61% of patients. In the nonmetastatic cohort, the 5-year survival rate plus or minus standard error was 69% ± 4%, and the 5-year EFS rate plus or minus standard error was 52% ± 4%. This is in contrast to the results of the metastatic group ($N = 32$), in which the 5-year survival plus or minus standard error was 29% ± 8%, and the 5-year event-free rate was 14% ± 7%. Notably, the risk of death increased 1.4-fold for each additional lobe that was involved with pulmonary metastases (95% confidence interval: 1.018). The authors found a 2-year EFS rate similar to those previously reported, in spite of the inclusion of cases accrued over a 20-year span. Bacci and colleagues[226] have reported an estimated 2-year survival rate of 45% for patients with resected pulmonary metastases. The 2-year survival rate estimated for their cohort was 52%. Meyer and colleagues[228] reported an estimated 5-year survival rate of 11% compared with the reported cohort estimate of 14% of patients presenting with metastases. They concluded that not only the number of pulmonary metastases but also their distribution among pulmonary lobes affected survival.

The Cooperative German-Austrian-Swiss Osteosarcoma Study Group reported their findings with patients with proven high-grade osteosarcoma of the extremities or trunk who were registered between 1979 and 1998.[229] Of the total 1765 patients, 202 (11.4%) had clinically detected metastatic osteosarcoma. In univariate analysis, survival of the patients with metastases was correlated significantly with patient age, site of primary tumor, number and location of metastases, number of involved organ systems, histologic response of the primary tumor to preoperative chemotherapy, and completeness and time point of surgical resection of all tumor sites. After Cox multivariate regression analysis, however, only multiple metastases at diagnosis and macroscopically incomplete surgical resection remained significantly associated with poor outcomes. At a median follow-up of 1.9 years, 60 patients were alive, and 37 of the original 202 patients were in complete and continuous surgical remission. Overall actuarial survival at 5 years was 29%, and that at 10 years was 24%. The researchers concluded that the number of metastases and the completeness of surgical resection of all clinically detected tumor sites are of independent prognostic value in patients with proven primary metastatic osteosarcoma. A more recent study of 21 patients with metastatic osteosarcoma showed a cumulative 5-year survival rate after complete resection of 34.2%. Complete resection was found to be a significant prognostic factor for survival following metastasectomy ($P = 0.04$). The authors concluded that every attempt should be made to completely resect all clinically detected metastases even if it meant repeat thoracotomy in recurrent disease.[230]

Attempts have been made to substitute newer drugs in an attempt to improve survival of patients with metastatic osteosarcoma. To date, many of these have been disappointing. Substitution of cisplatin with carboplatin does not appear to be effective.[231,232] The use of topotecan is similarly disappointing.[233]

Late Effects of Therapy

In addition to the psychosocial outcomes of therapy discussed previously, late effects of chemotherapy, including cardiomyopathy from doxorubicin,[234] ototoxicity from cisplatin,[235–239] and thyroid disorders,[240] remain problematic in survivors. The addition of dexrazoxane has been shown to reduce the toxic effects of doxorubicin on the myocardium.[241] Infertility is another concern for patients who receive chemotherapy especially with alkylating agents. A study recently showed that although patients who undergo chemotherapy should be informed of the possibility of infertility, many survivors of pediatric sarcoma treatment can be expected to have successful childbirths.[242] Teenage males might want to consider sperm banking.

Metachronous Osteosarcoma

Aung and colleagues[243] described a single-institution assessment of patients who developed metachronous skeletal osteosarcoma between 1973 and May 2000. A retrospective review of records from 426 patients with nonmetastatic high-grade and primary osteosarcoma showed 23 patients, with a median age of 18.7 years, who developed metachronous osteosarcoma. Initial therapy included combination chemotherapy and surgery. Treatment of the metachronous relapse consisted of chemotherapy or radiation alone or surgery with or without additional individualized chemotherapy.

The median time to the diagnosis of a metachronous lesion was 1.4 years, with a range of 0.2 to 11.3 years. Patients who developed late metachronous osteosarcoma experienced significantly longer postmetachronous osteosarcoma survival compared with those whose metachronous disease developed early. For the former group, the 2- and 5-year postmetachronous osteosarcoma survival rates were 72.7% and 61%, respectively. In contrast, all five patients who developed metachronous disease between 12 and 24 months died within 1.5 years of follow-up. Among patients who developed late metachronous disease, further analysis based on type of therapy suggested that those who were treated with a combined modality (including surgery and aggressive chemotherapy) for their metachronous disease fared better than did those who received monotherapy. The authors also concluded that local therapy with surgery directed at the bulky primary tumor is the only effective method for local control.

Rodriguez and associates[244] described the treatment of five patients in whom primary osteosarcoma had been treated effectively with

chemotherapy and resection of the primary tumor and in whom another osteosarcoma developed at another site but without pulmonary metastases. The interval between management of the primary tumor and the subsequent development of another, apparently unrelated metachronous osteosarcoma ranged from 99 to 150 months. All patients remained otherwise free of disease 24 to 96 months after treatment of the metachronous lesion, except for one patient who developed acute myelogenous leukemia, most likely as a late effect from chemotherapy. Fitzgerald, Dohlin, and Sim[245] reported that among 800 patients, 12 developed metachronous osteosarcoma, and none developed pulmonary metastases, a quite different response from that of patients who were reported with primary metastatic osteosarcoma. Others have observed that aggressive treatment of metachronous osteosarcoma is indicated and suggested that the etiology in some might be related to hereditary retinoblastoma or Li Fraumeni syndrome.[246]

Second Malignant Neoplasms

Aung and associates[247] retrospectively reviewed the experience of the Memorial Sloan-Kettering Cancer Center with long-term survivors of osteosarcoma and the subsequent development of secondary malignancies. The patients were treated between February 1973 and March 2000, and all had received chemotherapy and/or surgery. Chemotherapy consisted of a combination of agents that included high-dose methotrexate, doxorubicin, bleomycin, cyclophosphamide, dactinomycin, vincristine, cisplatin, and ifosfamide. Of 509 patients, 14 were identified as having developed secondary malignant neoplasms. The time interval from diagnosis of the primary osteosarcoma to development of the secondary malignant neoplasm ranged from 1.3 years to 13.1 years (median: 5.5 years). The second neoplasms occurred in the central nervous system in four patients. There were two cases of acute myeloid leukemia and one case each of myelodysplasic syndrome, non-Hodgkin's lymphoma, high-grade pleomorphic sarcoma, leiomyosarcoma, fibrosarcoma, carcinoma of the breast, and mucoepidermoid carcinoma. The standard incidence was 4.6% when patients with a history of retinoblastoma or Rothmund-Thompson syndrome were excluded.

OSTEOSARCOMA VARIANTS

This section discusses variants of classic osteosarcoma. Some of these subtypes are low grade and well differentiated, have low metastatic potential, and usually do not require adjuvant therapy. The more common high-grade variants will also be reviewed. Although osteogenic lesions arising in the jaw are more common than the recognized variants of osteosarcoma, this subtype will not be addressed in this chapter.

High-Grade Variants

High-Grade Surface Osteosarcoma

EPIDEMIOLOGY. Of the more aggressive surface osteosarcoma variants, the least common is high-grade surface osteosarcoma. It is most frequently reported in the second and third decades of life and, unlike classic osteosarcoma, is four times more frequent in males than in females. The femur appears to be the most frequent site of involvement; these tumors are rarely observed in the flat bones.[248]

RADIOGRAPHIC FEATURES. No roentgenographic features reliably distinguish high-grade surface osteosarcoma from other surface osteosarcomas. Some lesions appear radiographically destructive, while others tend to mineralize more heavily. Some may even present with a sunburst appearance. The only common denominator that is known is that high-grade surface osteosarcomas usually arise from the surface of long bones and tend to be slightly more diaphyseal in location. The tumors generally demonstrate intense uptake on ^{99m}Tc bone scintigraphy. CT best demonstrates the site of peripheral surface origin, while MRI shows possible marrow involvement and the anatomic features of the lesion on T_1-weighted images.[249]

DIFFERENTIAL DIAGNOSIS. In some instances, high-grade surface osteosarcoma can be radiographically indistinguishable from low-grade parosteal osteosarcoma and periosteal osteosarcoma. Occasionally, myositis ossificans can be confused with the lesion, but it is usually associated with trauma and the subsequent onset of tenderness.[250]

HISTOPATHOLOGY. The histopathologic appearance is best characterized by cartilage intermixed with high-grade anaplastic osteoid-producing cells. Often, histopathology is the only reliable method to differentiate these radiographically similar tumors of bone from one another.

CHEMOTHERAPY. Wold and colleagues[251] reported on nine patients with high-grade surface osteosarcoma. Seven of the nine died as a result of their disease. Currently, the majority of musculoskeletal oncologists would recommend conventional multiagent neoadjuvant chemotherapy as currently recommended for conventional osteosarcoma, followed by limb-sparing surgery and adjuvant chemotherapy for treatment, but since no large, controlled studies exist, this remains an area of controversy.[252,253]

SURGICAL THERAPY. Surgical management of the tumor requires a minimum of a wide surgical margin after primary chemotherapy, with a negative intramedullary margin as calculated from the preoperative MRI. Pulmonary metastases should be pursued aggressively with surgical removal and adjuvant chemotherapy.

PROGNOSIS. The number of patients who have been treated and reported with high-grade surface osteosarcomas is too small to analyze. It is likely, however, that the disease-free survival rate is similar to that for patients with conventional osteosarcoma. It is unclear whether a high-grade surface osteosarcoma has the same prognosis as that of a high-grade central osteosarcoma, whether chemotherapy is definitely indicated, or whether a high-grade surface osteosarcoma involving the medullary cavity worsens the prognosis. Since these lesions are so uncommon, these controversies are unlikely to be resolved in the near future.

Extraskeletal Osteosarcoma

Extraskeletal osteosarcoma is an uncommon variant of high-grade osteosarcoma, characterized histopathologically by the production of malignant osteoid and bone arising in soft tissue. Although primary osteosarcoma in rare instances arises in other organs, the majority of these lesions are found in soft tissues of the lower extremity and buttock, upper extremity, and retroperitoneum.[254–260] These are rare tumors, and very few series of more than one or two patients exist.[261]

EPIDEMIOLOGY. Extraskeletal osteosarcoma differs from conventional or "classic" osteosarcoma in that the majority of patients are older than 50 years of age. The tumors most often arise beneath the deep fascia, and 10% to 15% of patients have a history of antecedent trauma.[260]

The etiology of extraskeletal osteosarcoma remains unknown except for patients who have had external beam radiotherapy (postradiation sarcoma) for other reasons. The subsequent development of extraskeletal osteosarcoma within the radiation therapy field after a latent period remains a well-known risk. Of the 88 patients reported by Chung and Enzinger[262] with extraskeletal osteosarcoma, 5 had previously undergone radiotherapy.

RADIOGRAPHIC FEATURES. The majority of lesions can be palpated and identified with plain x-rays of the extremity using

soft-tissue techniques. Although the mass is commonly ill defined, matrix mineralization can often be identified as a "fluffy" density. If abundant cartilage is present, punctate calcifications can be evident.

As is expected in conventional osteosarcoma, extraskeletal osteogenic lesions are often well demonstrated by intense uptake on ^{99m}Tc bone scan. Pulmonary metastases and local lymph node involvement can occasionally be demonstrated by bone scintigraphy. To assess potential metastatic disease, a ^{99m}Tc three-phase bone scan or a rapid whole-body short TI inversion recovery (STIR) MRI and CT of the chest should be completed for appropriate radiographic staging.

CT of the lesion with both bone and soft-tissue techniques will often identify the mineralized tumor matrix or cartilaginous calcification. MRI offers no specific benefit over CT in evaluating this lesion because medullary canal involvement is not an issue. The cross-sectional display and compartmental anatomy that CT demonstrates generally identify both the axial location of the tumor and the anatomic compartment that is involved. The regional, retroperitoneal, and mediastinal lymph nodes should also be evaluated.

Radiographically, both myositis and extraskeletal osteosarcoma demonstrate bone production, and differentiation can be difficult. Myositis characteristically arises adjacent to bone and demonstrates a lucent zone between the lesion and the underlying cortex. Also, maturation of myositis often exhibits mature, well-marginated bone at the periphery of the lesion. Extraskeletal osteosarcoma, on the other hand, displays tumor bone more centrally with an indistinct, poorly marginated peripheral margin in the region of the frequently loculated advancing invasive tumor growth. Parosteal osteosarcoma pathologically and radiographically also demonstrates central maturation with peripheral immature tissue that is similar to extraskeletal osteosarcoma, but it arises immediately adjacent to bone.

CLINICAL MANIFESTATIONS. Extraosseous osteosarcoma must be distinguished from myositis ossificans, with which it is commonly confused. Patients with myositis usually have a distinct history of trauma, either acute or chronic, followed by pain and local tenderness. Extraskeletal osteosarcoma usually grows more slowly, remains mobile in the adjacent soft tissues, and is nontender until late in clinical stages of the disease. Myositis, on the other hand, usually appears rapidly, is tender and edematous, and can be fixed to deep osseous structures.

DIFFERENTIAL DIAGNOSIS. The most common ossifying lesion presenting in soft tissue is myositis ossificans. Parosteal osteosarcoma characteristically arises from the posterior aspect of the distal femoral metaphysis in young adults (third and fourth decades). The characteristic thin rim of mature reactive bone, which is often demonstrated best on CT, usually separates myositis from parosteal and extraskeletal sarcomas, which tend to be more mature centrally. The invasive, more immature peripheries of malignant tumors are often isodense and blend into the surrounding soft tissues. MRI probably provides better information than CT to differentiate between myositis ossificans, intramuscular hemangioma, parosteal osteosarcoma, high-grade surface osteosarcoma, and pseudotumors of the thigh.

SURGICAL THERAPY. Clinically, the lesion appears indurated when the relaxed surrounding muscle is palpated. Pathologically, lobulation is common and must be taken into account in planning surgical therapy and the biopsy tract. The preoperative staging CT and/or MRI should be reviewed carefully to avoid contamination of uninvolved anatomic compartments. Representative tissue must be obtained through a judiciously placed longitudinal skin biopsy incision. Experienced pathologists are often reluctant to interpret needle biopsies from this rare and unusual tumor.

The literature clearly illustrates that most surgeons do not appreciate the invasive and lobulated growth potential of this primary malignant tumor. In two large retrospective representative studies, the local recurrence rates were 50% (13 of 26 patients) and 43% (38 of 88 patients).[262,263]

CHEMOTHERAPY. Extraskeletal osteosarcoma is considered a high-grade tumor that produces metastases to lung, bone, and (occasionally) regional lymph nodes. For patients who can medically tolerate intensive neoadjuvant chemotherapy,[261] multiagent chemotherapy would usually be used before a limb-sparing procedure. With intensive primary chemotherapy that is tailored specifically to sarcomas of bone and soft tissue, the majority of lesions can be removed surgically, with wide margins for appropriate local control. Adjuvant chemotherapy should be initiated after wound healing. Results with multiagent adjuvant chemotherapy appear to yield event-free and overall survival results similar to those of conventional osteosarcoma,[261] although no comparison series exist. Radiotherapy is not used commonly as a therapeutic modality except for palliation in patients with systemic disease.

Pagetoid Osteosarcoma

Sarcoma originating as a complication of Paget's disease of bone was first recognized by Paget himself in 1877. The patient he described subsequently developed fibrosarcoma of the involved radius and died. Of his 23 reported patients, 5 similarly developed sarcoma within the involved bone and died.

EPIDEMIOLOGY. Approximately 5% of the osteosarcomas that have been reported in large series are complications of Paget's disease of bone. Pagetoid osteosarcoma is twice as common in males as in females. The exact frequency of sarcomatous change in patients with uncomplicated Paget's disease is unknown; reports range from 1% to 12%. Sarcoma tends to develop in patients with polyostotic bone involvement (90%) and is distinctly unusual in patients with monostotic disease (10%). The lesion develops in bone that shows the characteristic radiographic accentuated trabeculations of Paget's disease, not in otherwise normal bone.[264] Schmorl,[265] in an autopsy study, reported a 3% incidence of Paget's disease in humans over the age of 40 years. The distribution of involved areas in uncomplicated Paget's disease revealed involvement of the pelvis and sacrum to be most common (56%), followed by the spine (50%), right femur (31%), and cranium (25%). Sites that were less commonly involved were the sternum, pelvis, left femur, clavicle, tibia, ribs, and humerus. In contrast, the distribution of sarcoma arising in Paget's disease is most common in the pelvis (ilium, 34%), humerus (22%), and femur (19%) and is distinctly uncommon in the spine.[266] Lesions that arise in the vertebral bodies are usually associated with previous irradiation. The reason for the common sarcomatous involvement of the humerus and the rarity of involvement of the spine is unknown.[267]

RADIOGRAPHIC FEATURES. The classic conventional radiographic change that is observed with malignant degeneration in pagetic bone is loss or destruction of the usually distinct but accentuated trabeculation. A recent observation by Colarinha and colleagues[268] using ^{201}Tl to differentiate between benign and malignant polyostotic lesions might be helpful.

Scintigraphy using ^{99m}Tc methylene diphosphonate and ^{201}Tl was performed in a patient with polyostotic Paget's disease and sarcomatous degeneration in the right ilium. The ^{99m}Tc methylene diphosphonate imaging revealed abnormal uptake in both types of lesions, while the ^{201}Tl imaging showed increased uptake in the sarcomatous lesion only. These findings, in conjunction with the observation of a soft-tissue mass in and around the suspected lesion on MRI, could assist in earlier diagnosis and treatment.

PATHOLOGIC FEATURES. The histopathologic subtypes differ among pathologists. Huvos and coauthors[269] reported a fibrohistiocytomatous histology to be the most common (26%), while others have reported osteosarcoma (59%) as the most frequently

observed subtype.[264] Histopathologic interpretation appears to account for these differences.

PROGNOSIS. The overall prognosis for patients with sarcoma of Paget's disease is worse than that for patients with classic osteosarcoma. Furthermore, it appears that the prognosis has not changed appreciably in the last 50 years.[270] The disease is usually fatal with or without adjuvant chemotherapy. The majority of patients are best managed surgically by a "wide" amputation for local control and relief of pain. The majority of patients die within 3 years; a recent study showed a 14% survival rate at 2.5 years from diagnosis.[270]

Postradiation Osteosarcoma of Bone

EPIDEMIOLOGY. Postradiation sarcoma occurs after 3 to 10 years and arises within the radiation therapy portal of treatment for an osseous or extraosseous benign or malignant tumor; it occurs twice as commonly in females. Secondary osteosarcoma or MFH arises mainly in two groups of patients:

1. Those who have been treated for childhood tumors such as retinoblastoma, rhabdomyosarcoma, Ewing's sarcoma, Hodgkin's lymphoma, Wilms' tumor, and brain tumors.[271] Some of these patients could be genetically predisposed to secondary tumors developing both inside and outside the field of irradiation, whereas others may relate to the combination of alkylating agents and radiotherapy
2. Those who have been treated for adult tumors such as Hodgkin's lymphoma, who have little evidence of genetic disposition to secondary malignancies but develop the secondary tumor within the radiation field

In general, induction of the tumor appears to be related to dosage, type and site of radiation, age of the patient, and concomitant use of chemotherapeutic agents. The interval between exposure and the development of the tumor ranges from 2.75 years to 41 years, with an average of 13.4 years. Secondary solid tumors have a longer latency period than leukemia when they are related to chemotherapy and radiotherapy. Histopathologic subtypes that have been reported for radiation-induced sarcomas include osteosarcoma (50%), fibrosarcoma (40%), and, less commonly, chondrosarcoma (4%).[272]

CLINICAL MANIFESTATIONS. The development of increasing pain and swelling within a previously irradiated portal should alert the physician to the possibility of malignant change. In contrast to conventional osteosarcoma, the most commonly involved osseous sites are the ilium, proximal femur, and proximal humerus.[274] Whether the underlying bone was normal or abnormal at the time of initiation of treatment appears to make little difference in the latent period.

PATHOLOGIC FINDINGS. In Huvos and associates' series,[273] fibrohistiocytomatous lesions were most common (38%), followed by osteoblastic (18%) and chondroblastic (12%) lesions. The secondary neoplasm arose in the central marrow-bearing anatomic regions involved by the index disease process (e.g., sternum, spine, pelvis).

RADIOGRAPHIC FEATURES. The most common radiographic feature of malignant change is destruction of the underlying bone within the radiation portal. This can be very difficult to assess because of the radiographic changes in the bone resulting from the radiotherapy. Serial ^{99m}Tc bone scans might show evidence of increased uptake in the anatomic region in question when compared with earlier studies. CT often demonstrates destruction and an associated soft-tissue mass. The presence or absence of demonstrable calcification or tumor matrix mineralization is dependent on the differentiation of the tumor.

Using the criteria described by Arlen and colleagues,[274] Sheppard and Libshitz[275] identified 63 patients with postradiation sarcomas. There were 43 females and 20 males, with a mean age of 52.8 years. The mean radiation dose that was delivered was 50.1 Gy, with a mean latency period for the development of the sarcoma of 15.5 years. The most common primary diagnoses were carcinoma of the breast, lymphoma, and head and neck cancer. The most common histopathologies included osteosarcoma and MFH. The most common imaging findings were bone destruction with an associated soft-tissue mass. The authors concluded that postradiation sarcomas, although uncommon, are not rare. They could demonstrate no pathognomonic radiographic findings other than appreciation of the expected latency and knowledge of the anatomic site of the previous radiation porthole.

DIFFERENTIAL DIAGNOSIS. The development of pain in a previously irradiated anatomic region must be evaluated clinically. Differentiation between radiation necrosis and pathologic or insufficiency fracture may be very difficult. A helpful feature is the clinicoradiologic course of radiation necrosis, resulting in bone resolution that often is associated with multiple pathologic fractures (e.g., multiple ribs) and that occurs over a larger area of the therapy field.

SURGICAL THERAPY. Because of the usual overlying leather-like skin and soft-tissue changes, limb-sparing procedures for postradiation sarcoma are frequently difficult and associated with an increased complication rate compared to other limb-sparing procedures. When postradiation sarcomas occur as a complication of treatment of childhood tumors, however, procedures such as rotationplasty or limb-sparing procedures of the proximal or distal femur or proximal tibia occasionally can be offered for patients in whom the tumor and associated soft-tissue changes can be resected, leaving nonirradiated tissues for reconstruction. The majority of adult and elderly patients are offered an ablative procedure well above and proximal to the affected anatomic part. The outcome of patients with radiation-associated osteosarcomas appears to be similar to that of conventional osteosarcoma if aggressive therapy consisting of adjuvant chemotherapy and complete resection is employed.[276]

Small Cell Osteosarcoma

Small cell osteosarcoma, once thought to be a variant of another tumor type, now appears to be a recognized variant of osteosarcoma. A recent and detailed report by Nakajima and coworkers[277] reviewed 72 cases of small cell osteosarcoma (22 from the Mayo Clinic files and 50 from their consultation files) and described the clinicopathologic features of this unusual entity.

CLINICAL FEATURES. The patients who were reviewed included 39 males (63.8%) and 33 females (45.8%) ranging in age from 5 to 71 years (mean: 24.8 years; median: 20 years). More than half the patients were in the second or third decades of life. Forty-four tumors (63.8%) involved the long bones, and 22 tumors (31.9%) occurred in femurs, with 6 developing proximally, 4 in the midshaft, and 11 in the distal one third. Twelve tumors arose in the humerus, including 8 proximally, 3 in the midshaft, and 1 in the distal one third. Three patients presented with multiple lesions, and two presented with pulmonary metastases.

Pain and swelling were the most common symptoms and signs. One patient with a vertebral lesion developed sudden paraplegia. The duration of symptoms and signs varied from 4 days to 10 years (average: 15.4 months; median: 6 months).

RADIOGRAPHIC FEATURES. Imaging studies were available for 35 patients. The lesions were generally characterized as destructive and had the appearance of an aggressive process, with 20 of the 35 clearly suggestive of conventional osteosarcoma arising in the metaphysis. The remaining studies displayed primarily a destructive and

osteolytic process, with no mineralization of the adjacent soft-tissue mass.

DIFFERENTIAL DIAGNOSIS. The differential diagnosis includes Ewing's sarcoma, malignant lymphoma, and metastatic and small cell carcinoma of the lung.

PATHOLOGIC FINDINGS. Osteoid production was identified in all tumors. Nakajima and colleagues identified a round cell type and a short, spindle cell type; the round cell variety was subdivided into three additional groups based on size: very small (25 tumors), small (27 tumors), and medium size (16 tumors). Four tumors were identified as being of the short, spindle cell type. Cytogenetics and molecular genetic studies may be valuable in distinguishing small cell osteosarcoma from other round cell tumors.[278]

CHEMOTHERAPY. The data suggest that the chemotherapy regimen should be based on and similar to treatment of conventional osteosarcoma.

SURGICAL THERAPY. Although early reports suggested that amputation or disarticulation was required for local control, median survival time for patients who had surgery with additional chemotherapy was 13.4 years. Current recommendations for treatment include multiagent neoadjuvant chemotherapy, surgical resection, and limb-sparing surgery with a minimum of wide margins, followed by adjuvant chemotherapy. Patients who were reviewed who had had marginal or contaminated margins had poor prognoses.

Osteosarcoma over the Age of 40

A review by the European Musculoskeletal Oncology Society has made a significant contribution to knowledge of osteosarcoma in patients over the age of 40 years.[279] Using the retrospective experience of 12 centers, the reviewers studied outcomes of treatment in 481 patients with osteosarcoma, including 272 males, 206 females, and 3 unclassified, all over the age of 40.

Forty-two patients (28 males, 14 females) with pagetoid osteosarcoma had a mean age of 71 years (range: 47 to 88 years). The most commonly involved bones were the pelvis (12 patients) and the femur (12 patients). Only 14 of the 42 patients underwent surgery, and five procedures resulted in local recurrence (four of nine limb-preserving procedures and one of five amputations). Although the median survival was 9 months, one patient with an osteosarcoma of the tibia who was treated with an amputation lived for 8 years. Only two patients had chemotherapy.

Forty-one patients (29 females, 12 males) with a mean age of 58 years (range: 40 to 82 years) developed radiation-induced osteosarcoma. The majority of the tumors developed in the axial skeleton and were related to radiation treatment for ovarian or cervical carcinoma (pelvis: 12 patients) and breast cancer (scapula: 11 patients). Only 12 of the 41 patients had no axial tumors. Twenty-nine patients had surgery, including 19 patients with limb-preserving procedures and 8 with primary amputations. Eleven patients developed local recurrence, two occurring in the amputee group and six in the limb-preserving group. Patients with axial tumors did worse (5-year survival rate: 28%) than those with primary tumor of the limb (5-year survival rate: 55%).

Twenty-six patients had low-grade osteosarcoma (parosteal and low-grade central osteosarcoma), including 14 tumors in the femur. Only two of these patients had chemotherapy. Twenty-five had local limb-sparing procedures, and one had an amputation. Four developed local recurrence, and only one subsequently died as a result of local recurrence. The 5-year survival rate for the group was 88%.

The review covered 220 patients for whom follow-up data were available and who had high-grade nonmetastatic osteosarcoma not related to Paget's disease or radiation and not involving the pelvis, skull, or spine. Thirteen patients had intracompartmental disease (stage IIA), and 151 had extracompartmental disease (stage IIB), with 104 cases involving the distal femur, 48 the tibia, 34 the proximal femur, 19 the proximal humerus, and 8 the fibula. Eighty-six patients had an amputation, and 126 had a limb-sparing procedure (23 excision alone, 7 allograft reconstruction, and 78 endoprosthesis). One hundred twenty-nine patients had a minimum of a "wide" surgical margin, and 37 were believed to have marginal or intralesional margins. Local recurrence occurred in 25 patients (5% amputees, 13% with limb-preserving procedures, and 24% of those with excision alone). Eleven of 129 patients (9%) with what were believed to be "wide" or radial margins experienced local recurrence. Overall, the survival rate was 46% at 5 years and 33% at 10 years. Of the 154 patients who were able to receive chemotherapy (i.e., doxorubicin, cisplatin, ifosfamide, and methotrexate), 29% were over the age of 60 years, and 80% were under 60 years of age. Overall, improved outcomes were related to the ability to receive chemotherapy (age less than 60 years) and location of the lesion (lower extremity). These data suggest that patients over the age of 40 years who have conventional high-grade osteosarcoma and are capable of withstanding cytotoxic chemotherapy might do as well with comprehensive multimodal treatment as do younger patients under 40. A recent study has confirmed these observations.[280]

Low-Grade Variants

Low-Grade Central Osteosarcoma

EPIDEMIOLOGY. This well-differentiated osteosarcoma variant can be characterized by its presentation primarily in young adults and its intraosseous location. The original series described by Unni and colleagues[281] included 27 patients with pain and swelling as the most common presenting complaints; the onset of their symptoms occurred from 1 to 20 years before medical evaluation. The ages ranged from 10 to 65 years. A more recent review (from the same institution) of 80 patients with low-grade central osteosarcoma involved 41 males and 39 females, with a mean age of 28.2 years. Skeletal distribution of the tumors was similar to that seen with conventional osteosarcoma.[282]

RADIOGRAPHIC FEATURES. A review of 74 patients with histopathologically proven low-grade central lesions revealed 64 tumors involving the medullary canal and 10 of cortical origin.[282] Forty-three of the 64 long-bone lesions had a metaphyseal location, 11 were diaphyseal/metaphyseal, and 10 were diaphyseal. Eleven patients were skeletally immature at the time of diagnosis, and no tumor was observed to have violated or crossed the epiphysis. Larger lesions readily crossed the physeal scar after adult epiphyseal closure. Occasionally, the tumor penetrated and destroyed the cortex. Poor margination was observed radiographically in 50 of 74 patient x-rays reviewed, and 51 patients (69%) showed x-ray evidence of tumor matrix mineralization

HISTOPATHOLOGY. Many tumors appeared well differentiated, and some appeared strikingly similar to fibrous dysplasia. The tissue was composed primarily of spindle cells with scarce mitotic figures with minimal atypia. Osteoid content was variable.

DIFFERENTIAL DIAGNOSIS. As has been mentioned, differentiation of low-grade central osteosarcoma from benign bone tumors can be difficult. Low-grade central osteosarcoma appears histopathologically similar to fibrous dysplasia and to benign spindle cell lesions, such as desmoplastic fibroma and low-grade fibrosarcoma. Plain films show variable findings, and differentiation from benign lesions such as fibrous dysplasia may be difficult, but CT and MRI can aid in the differentiation by showing subtle cortical disruptions and soft-tissue extension in the low-grade osteosarcomas.[283]

SURGICAL THERAPY. Wide excision is the treatment of choice. Intralesional or marginal margins resulted in 11 patients, with 11

tumors reoccurring within a mean time of 3.9 years after suboptimal surgical therapy. Two of the 11 patients died as a result of their disease between 2 and 48 years after diagnosis.[282]

CHEMOTHERAPY. Chemotherapy is probably not useful in the initial treatment of this disease; however, 15% of patients experience tissue transformation from low-grade to high-grade osteosarcoma. Patients with high-grade tumors might benefit from conventional multiagent chemotherapy.

Periosteal Osteosarcoma

In 1955, Lichtenstein[284] described an unusual periosteal lesion of the humerus and another in the femur that produced cartilage as well as malignant osteoid. Vigorita and colleagues[285] later reported a recurrent lesion that had previously been managed by local resection of the ulna, which he described as juxtacortical chondrosarcoma. Schajowicz[286,287] brought attention to three brothers with juxtacortical chondrosarcoma. The publication by Unni and colleagues[288] in 1976 clarified the issue and focused on the osteoid component seen in the lesion. They described the entity that is currently recognized as periosteal osteogenic sarcoma.

EPIDEMIOLOGY. Periosteal osteosarcoma is an uncommon low-grade osteosarcoma variant that arises primarily in the cortical shaft of the tibia and femur. Radiographically, the lesion arises from the surface of the bone, contiguous with the cortex, producing a scalloped appearance. A soft-tissue mass within the scalloped lesion can be seen on CT or MRI. MRI frequently predicts the absence of marrow involvement beyond the scalloped margins.

PATHOLOGIC FEATURES. Histologically, the lesion consists of intermediate-grade malignant chondroblastic tissue, anaplastic spindle cells, and malignant osteoid. Metastatic disease occurs in approximately 15% of patients.[288]

SURGICAL THERAPY. Treatment consists of en bloc excision with a wide margin and reconstruction, sparing the limb in the majority of cases. When the lesion arises in the femur, the tumor could circumferentially involve the cortex, requiring an intercallary resection of the shaft and reconstruction. An update of the Mayo Clinic series showed no significant changes from the initial description of the lesion or outcome from treatment.[289] Neoadjuvant chemotherapy could be useful in some patients with large lesions; however, adjuvant chemotherapy is controversial unless pulmonary metastases are evident or develop postoperatively. Most centers employ adjuvant chemotherapy for periosteal osteosaroma, but because the numbers of patients is so limited, no definitive studies documenting the merit of chemotherapy have been reported.[253,290]

Parosteal Osteosarcoma

EPIDEMIOLOGY. Parosteal osteosarcoma comprises approximately 4% of all osteosarcomas and is slightly more common in adult females during the third decade of life. The most common site of presentation is the posterior aspect of the distal femoral metaphysis (72%), followed by the proximal humeral metaphysis and the proximal tibia.[291] The lesion consistently presents as a fixed, painless, hard mass.[288]

RADIOGRAPHIC FEATURES. Radiographically, the lesion consists of a dense lobulated bone and soft-tissue mass arising from the posterior aspect of the distal femoral metaphysis. Usually, there is an ill-defined separation or lucent zone between the lesion and the cortex (best demonstrated by polytomography or CT). The peripheral margin of the lesion (zone of maturation) is poorly marginated radiographically and less mature pathologically. The lesion is often demonstrated by intense uptake on ^{99m}Tc bone scan. Untreated lesions usually do not involve the medullary canal, which can best be evaluated with MRI.

PATHOLOGIC FEATURES. Histopathologically, the tumor consists of fibroblastic, cartilaginous, and osseous components, all of which are evaluated individually and graded according to the highest-grade malignancy. The most mature and well-differentiated elements are often seen centrally. The outer zone of the tumor is composed of less mature hypercellular elements.

A system of grading has been applied to parosteal osteosarcoma (grades I, II, and III). Patients with lesions containing foci of high-grade malignancy (grade III) have survival rates similar to patients with conventional osteosarcoma.[288,292] These patients are potential candidates for neoadjuvant and/or adjuvant chemotherapy.

SURGICAL THERAPY. After radiographic staging, treatment for lesions without intramedullary involvement requires local excision with wide margins, most often resulting in a limb-sparing procedure (Fig. 96-13). A two-incision approach is often useful.[293] Vascular displacement is usually not a contraindication for local resection and limb preservation. If the MRI demonstrates evidence of intramedullary involvement, the entire circumference of the involved bone and the contiguous overlying soft tissues must be resected. Patients with intramedullary involvement either primarily or secondarily from local recurrence do not necessarily have a worse prognosis. Outcomes following surgical treatment alone lead to survival in more than 80% to 90% of patients.[293–295]

CHONDROSARCOMA

Chondrosarcoma is second only to osteosarcoma in frequency as a primary malignant bone tumor. Chondrosarcoma characteristically produces cartilage matrix with calcification and myxoid changes.

Epidemiology

Chondrosarcoma comprises approximately 20% of all malignant bone tumors. The tumor arises predominantly in individuals over the age of 50 years, with nearly equal distribution among males and females. Pain (often ill defined) and a mass are the most common presenting complaints. The pelvis is most commonly affected (approximately 30%); the femur, ribs, and humerus are other common sites. Patients with multiple enchondromas (Ollier's disease or Maffaccui's disease) or with multiple hereditable osteochondroma are at particular risk of developing chondrosarcoma.

Etiology and Pathogenesis

Chondrosarcomas are often divided into primary and secondary lesions. Primary or central chondrosarcoma arises de novo from previously normal-appearing bone. Secondary chondrosarcomas arise from pre-existing benign cartilage lesions, such as the cartilaginous portion of an osteochondroma or a benign enchondroma. Both tend to appear at least 15 to 20 years after skeletal maturity and are recognized by their growth.[296] Pain is the most common initial symptom.

Primary chondrosarcomas comprise approximately two thirds of reported chondrosarcomas and are capable of infiltrating and invading the surrounding soft tissues and producing metastases. The risk of metastatic disease is directly correlated to histologic grade. Extraskeletal chondrosarcoma represents fewer than 5% of lesions.[297–299] Dedifferentiated chondrosarcoma is the most aggressive and malignant expression of chondroid tumors.

The secondary tumors are usually low grade, except for lesions that arise in patients with Ollier's disease or Maffucci's syndrome, in which dedifferentiation is known to occur.

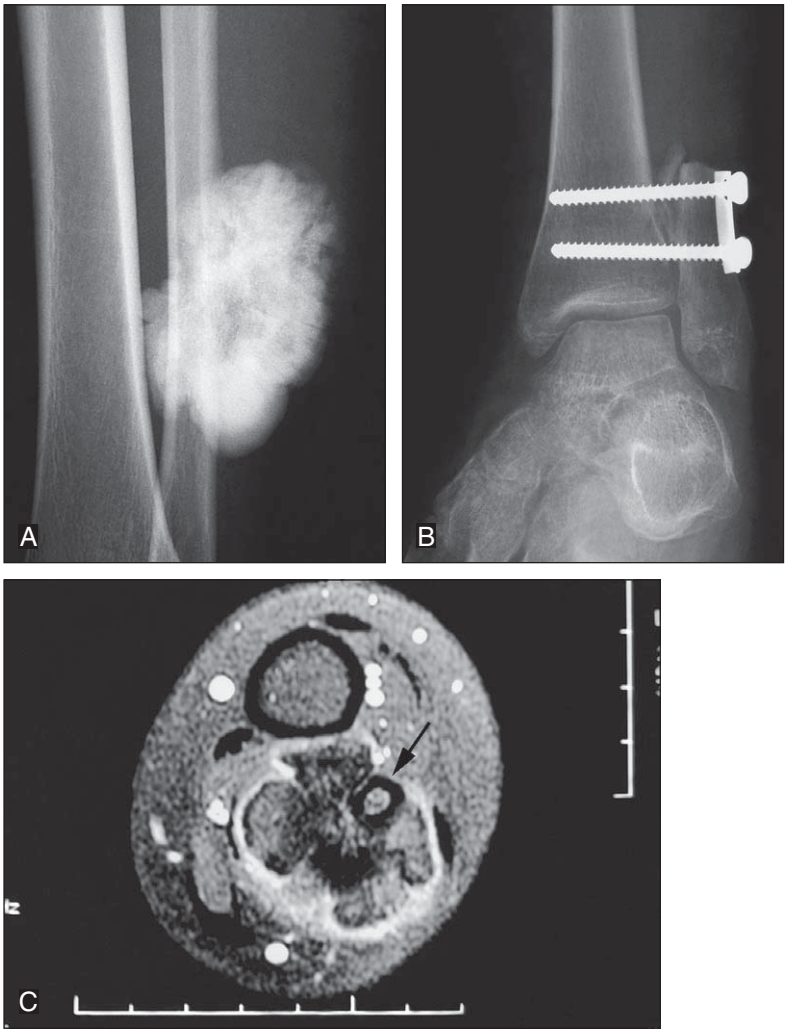


Figure 96-13 • **A,** This 31-year-old female had noted a painless mass posterior to the left fibula 24 months before medical evaluation. The patient denied any local trauma. **B,** AP postoperative x-ray demonstrating the resection margin of the distal fibula and the operative synostosis to stabilize the lateral malleolus. **C,** Axial fat-suppression MRI with contrast demonstrating the mineralized central position (*black areas*) with the typical bright circumferential ring of enhancement typical for parosteal osteosarcoma. Also note the normal fatty marrow signal (*arrow*) without the suggestion of tumor involvement.

Secondary chondrosarcoma can arise in a solitary osteochondroma (Fig. 96-14), multiple osteochondromas, a solitary enchondroma, Ollier's disease, Maffucci's syndrome, and synovial chondromatous fibrous dysplasia and as a complication of radiation therapy. Ahmed and asssociates[300] described the Mayo Clinic experience with 107 patients who developed secondary chondrosarcoma (61 with a solitary lesion and 46 with multiple lesions). They observed that the average age of onset was approximately 1 to 2 decades younger than patients who developed primary chondrosarcoma. The incidence of sarcomatous degeneration was 7.6% for the 802 patients with a single osteochondroma and 36.3% for the 120 patients with multiple osteochondromas. Metastatic disease from a secondary chondrosarcoma from a solitary osteochondroma is very rare. In both groups, the flat bones were the most common site for malignant degeneration (ilium: 19.7%; pubis: 19.7%), with the proximal femur and distal femur as the second and third most common sites. Males were more commonly affected than females (ratio in solitary osteochondroma: 1.2 : 1; ratio in multiple osteochondroma: 1.9 : 1).

Radiographic Features

Primary chondrosarcoma destroys and penetrates the cortex. Infiltration of trabecular bone is a histologic feature typical of chondrosarcoma. Magnetic resonance imaging most often demonstrates both the intramedullary extent of the tumor and the extraosseous extension and is necessary for appropriate preoperative planning. ^{99m}Tc bone scintigraphy is a useful screening examination, and it is recommended that patients with Maffucci's or Ollier's disease have bone scans every 3 to 5 years after recognition of their disease to monitor potential malignant transformation.

Distinguishing enchondroma from low-grade chondrosarcoma is difficult, and rarely can even an open biopsy definitively separate the two. PET scan might prove to be of benefit, but this remains controversial.

Clear Cell Chondrosarcoma

Clear cell chondrosarcomas are expansile and osteolytic lesions that most commonly arise in the epiphyseal regions of long bones (proximal femur and humerus). They are often described as cystic. They typically originate in the mature secondary ossification center, expanding and invading the surrounding soft tissues. The male-to-female ratio is 3 : 1, and the condition most often occurs after the first decade of life, with a rather even distribution up to the seventh decade. Clear cell chondrosarcoma is often diagnosed radiographically and confirmed histopathologically. Benign giant cells can be identified among the fine line of calcification between proliferating binucleated tumor cells. The tumor cells have a characteristic clear cytoplasm with distinct cytoplasmic borders. Lobulation is less prom-

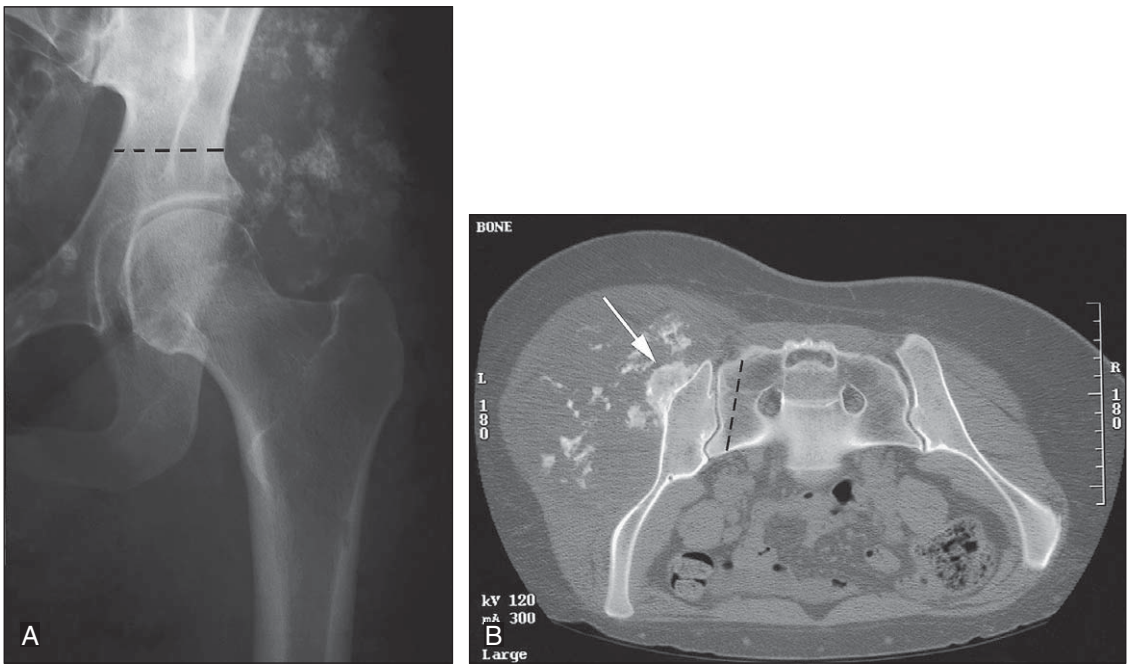


Figure 96-14 • **A,** AP x-ray of the left hip of a 33-year-old female revealing evidence of matrix calcification in the left buttock, thought to be responsible for pain and mass effect. The *dashed lines* illustrate the intended line of bone resection later used for resection. **B,** A CT scan was performed, illustrating calcifications within the lesion that are believed to have grown as a secondary chondrosarcoma from the small osteochondroma (*white arrow*) from the outer table of the left ilium. The *dashed line* also illustrates the intended osteotomy through the left ala of the sacrum, used later to accomplish the resection of the ilium.

inent. Clear cell chondrosarcoma is treated by wide surgical resection (Fig. 96-15).

Dedifferentiated Chondrosarcoma

Dedifferentiated chondrosarcomas also arise from pre-existing lesions that become more aggressive and malignant neoplasms, such as high-grade MFH of bone. The foci of dedifferentiated tissue usually destroy the underlying chondroid matrix and calcifications, leaving an area devoid of calcification and often producing a contiguous soft-tissue mass. These tumors have a high incidence of metastasis.

Pathologic Features

Chondrosarcomas are composed of chondrocytes with a cartilage matrix. The tumor is hypercellular compared to an enchondroma and may have myxoid and cystic areas. Invasion of cancelleous bone and penetration of cortical bone are hallmarks of chondrosarcoma.

Surgical Therapy

Surgical therapy is the primary treatment. Chemotherapy and irradiation are not sufficiently useful to be used on a routine basis. The surgical margin should be "wide." Because of the difficulty in distinguishing between enchondroma and low-grade chondrosarcoma, curettage can be used for these lesions provided that the anatomic setting is appropriate. Secondary chondrosarcoma from a solitary osteochondroma can be removed with a marginal margin, but the cartilaginous cap must not be violated during its removal. Recurrence risk increases if the cartilaginous cap is violated. Radiotherapy and multiagent chemotherapy may be used for palliation.

EWING'S SARCOMA

The pathologic process currently known as Ewing's sarcoma was described as early as 1866 by Lücke.[301] It became widely known in 1921, as James Ewing described the condition as endothelial myeloma, a lesion that he believed to be of perivascular endothelial origin. In 1939, Ewing reclassified the tumor as a neoplasm separate from osteosarcoma. Ewing's sarcoma is one of the recognized small round cell tumor variants that include neuroblastoma, embryonal rhabdomyosarcoma, osteomyelitis, small cell osteosarcoma, and non-Hodgkin's lymphoma. Classical Ewing's sarcoma and primitive neuroectodermal tumor are now considered to be the same tumor, characterized by nonrandom chromosomal translocations involving the EWS gene on chromosome 22 and one of several members of the ETS family of transcription factors. The translocation t(11;22)(q24;q12) is the most common (type 1) and leads to the formation of the EWS-FLI1 fusion protein, which contributes to pathogenesis by modulating the expression of target genes.[302] Other, less common translocations have been identified.[303,304] The translocations are detectable with both reverse transcriptase-polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) in fresh as well as formalin-fixed paraffin-embedded tissue. FISH is a more sensitive and reliable ancillary technique than RT-PCR for the diagnosis of Ewing's sarcoma/primitive neuroectodermal tumor in formalin-fixed paraffin-embedded tissue, although the latter provides additional information regarding fusion transcript subtype and prognosis.[305] Most authors now group these tumors into a combined family of tumors that have in common the 11;22 translocation and call these the Ewing's sarcoma family tumors (ESFTs). They include both bone and soft-tissue tumors, but this discussion will focus primarily on bone tumors. Treatment principles for the ESFTs are identical irrespective of their site of origin and most cooperative trials now include both soft-tissue and bone ESFTs.

Little is known about the potential prognostic significance of the different translocations. De Alava and colleagues[306] performed a clinical and pathologic analysis of 99 patients with Ewing's sarcoma in whom EWS-FLI1 fusion transcripts were identified by RT-PCR and for whom adequate follow-up data were available. Median follow-up for the 99 patients was 26 months (range: 1 to 140

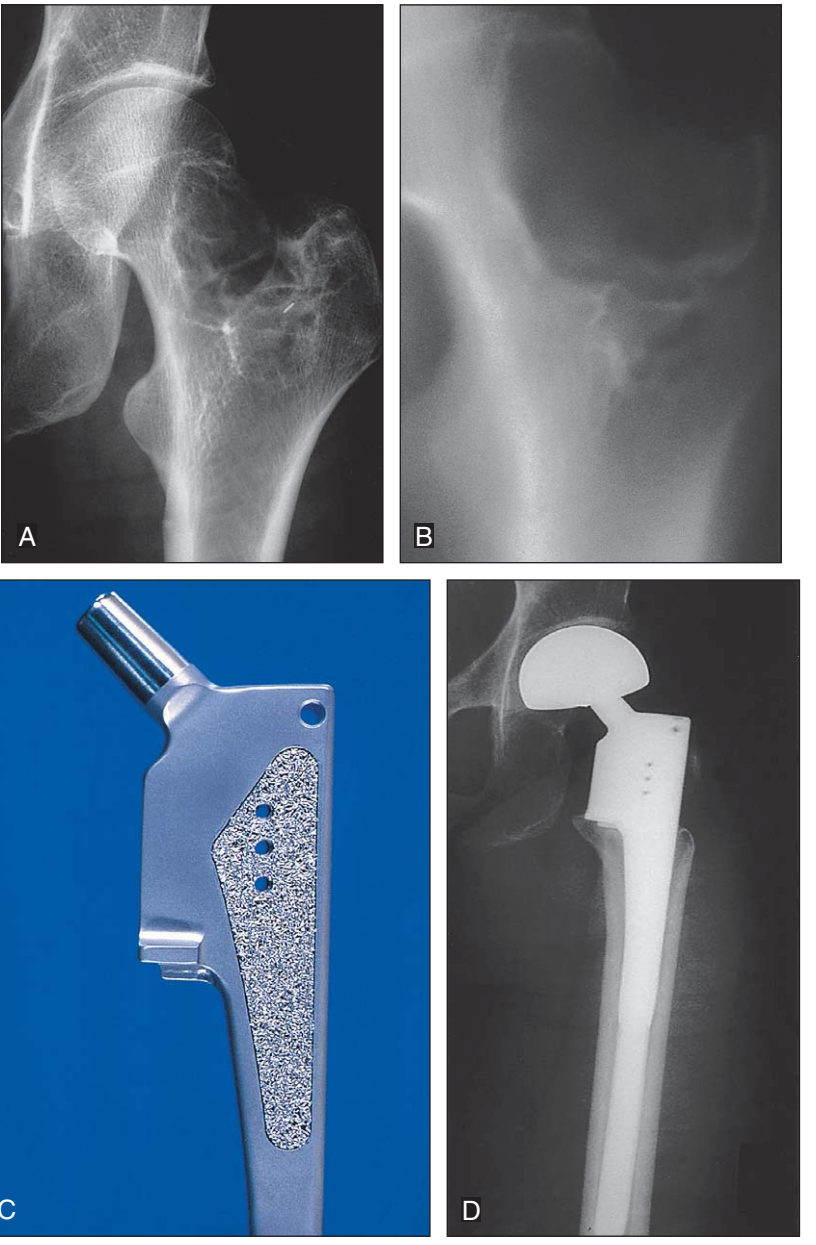


Figure 96-15 • **A,** After 6 months of pain and discomfort involving the left anterior thigh and groin, an AP radiograph of the proximal femur revealed a relatively well-marginated lesion involving the lateral neck and greater trochanter of the proximal femur in a 38-year-old male. **B,** Conventional AP polytomes of the lesion confirmed a relatively well-marginated lesion of the proximal femur and trochanter. No radiographically identifiable matrix could be identified within the lesion. Open biopsy was performed, revealing a cellular cartilaginous neoplasm composed of large cells with clear cytoplasm. The combination of the location of the lesion, its radiographic "soap bubble" appearance, and the histopathology confirmed the diagnosis of clear cell chondrosarcoma. **C,** Photo illustrating a press-fit custom titanium calcar-replacing prosthesis with titanium mesh for bone ingrowth used for reconstruction. **D,** Radiograph demonstrating the AP projection of the custom titanium press-fit (cementless) proximal femoral prosthesis.

months). Tumors in 64 patients contained the type 1 fusion, and 35 contained the less common fusion types. They hypothesized that the type 1 EWS-FLI1 fusion could result in a tumor that is intrinsically less aggressive or more chemosensitive than other fusion types. It appears that recognition of a type 1 EWS-FLI1 fusion transcript could be an indicator of favorable prognosis.

Epidemiology

Ewing's sarcoma is the third most common primary sarcoma of bone, comprising approximately 10% of all primary bone tumors.[307] As with many pediatric solid tumors, males are slightly more affected than females. The peak incidence in males is between 10 and 14 years of age; in females, it is 5 to 9 years (range: 1 year to 80 years). Ewing's sarcoma is distinctly rare in blacks and uncommon in Chinese. The majority of patients present for medical treatment between 5 and 30 years of age, although adult Ewing's sarcoma has been reported.[308]

Clinical Manifestations

Ewing's sarcoma arises from within the medullary canal of bone. Distant metastases are most common to the lung and other bone. The tumor often produces a painful soft-tissue mass that penetrates the cortex and surrounds the involved bone. Ewing's sarcoma of the extremities primarily affects the long tubular bones, such as the femur, tibia, proximal fibula, and humerus. Approximately 20% to 40% of lesions arise in the pelvis and flat bones and often produce symptoms that suggest other diagnoses, such as disk disease or hip pathology. This can result in delays in diagnosis. Tumors that arise in the pelvis are often large (>10 cm in diameter) at the time of diagnosis, and many patients have demonstrable distant disease at diagnosis. Primary tumors arising in the spine most often present with pain and can exhibit a rapidly progressive neurologic deficit. This symptom complex may precipitate an emergent decompressive laminectomy if the true nature of the cause of the symptoms is not appreciated. Patients may

appear systemically ill. Other clinical manifestations include rapid growth of the mass, local pain, and low-grade fever.

Radiographic Features

Ewing's sarcoma characteristically produces a permeative destructive pattern in bone often associated with a soft-tissue mass. In tubular bones, the lesions most often arise in the diaphysis or the metaphyseal/diaphyseal region and can demonstrate both an extrinsic pressure phenomenon and bone hypertrophy (Fig. 96-16A). Classically, the periosteum reacts with an "onion skin" appearance, although this is by no means pathognomonic. On plain radiographs, Ewing's tumors can appear identical to osteosarcoma, osteomyelitis, lymphoma, and Langerhans cell histiocytosis, and these entities are often considered in the differential diagnosis. Plain films of the pelvis can be deceptively normal, while a ^{99m}Tc bone scan, CT or MRI, and other investigative measures might demonstrate both the destructive process and the extent of marrow involvement. Consequently, plain films of the pelvis or other deep structures should not be used alone as a screening method but should be used only in conjunction with other studies.

Bone scintigraphy often aids in identifying the bone or bones that are involved and, to some extent, the degree of intramedullary involvement. The conventional ^{99m}Tc bone scan is primarily used to screen for metastatic disease.[309] To gain additional information about the extent and location of involvement of the primary lesion, single photon emission computed tomography is occasionally required.

CT of the chest to assess the presence of pulmonary metastases is mandatory to stage a patient with Ewing's sarcoma radiographically. The use of CT in the evaluation of the primary tumor can be valuable in illustrating bone destruction, but it might not demonstrate the associated soft-tissue mass, which is often isodense with the surrounding soft tissues. The CT information can be supplementary to the superior imaging data obtained from MRI.

MRI is ideally suited for evaluating the soft tissues, the intramedullary extent of disease, and adjacent soft-tissue involvement of the primary lesion and is an essential part of the evaluation of a patient with Ewing's sarcoma (Fig. 96-16B).

PET alone has little application in the management of patients with Ewing's sarcoma but has provided useful data regarding chemotherapy-induced tumor necrosis before and after neoadjuvant chemotherapy. Sequential PET and ^{201}Tl scans may be useful in predicting the effectiveness of neoadjuvant chemotherapy regimens.

Differential Diagnosis

The histopathologic similarity of ESFTs to other small round cell tumors results in a diagnostic challenge for the surgical pathologist (Fig. 96-16C). The lesion must be distinguished from lymphoma of bone, rhabdomyosarcoma, metastatic neuroblastoma, small cell osteosarcoma, osteomyelitis, metastatic small cell carcinoma of the lung, mesenchymal chondrosarcoma, and, occasionally, metastatic hemangiopericytoma. Pathologically, hemorrhage and necrosis are common, so the responsible surgeon or interventional radiologist must obtain viable tissue for routine histopathology, sterile tissue for cytogenetics, a small sample for electron microscopy, and tissue and fluid for culture and sensitivity.

The challenges of diagnosis were illustrated by Wurtz and associates[310] in a retrospective review of a single institution with 68 patients who had primary bone sarcoma of the pelvic girdle. They found that the average duration of symptoms before accurate diagnosis was 10 months (range: 1 month to 4 years). Common symptoms included buttock pain (35%), presence of a mass (30%), sciatica (29%), groin pain (26%), and low back pain (21%). Inaccurate diagnoses were

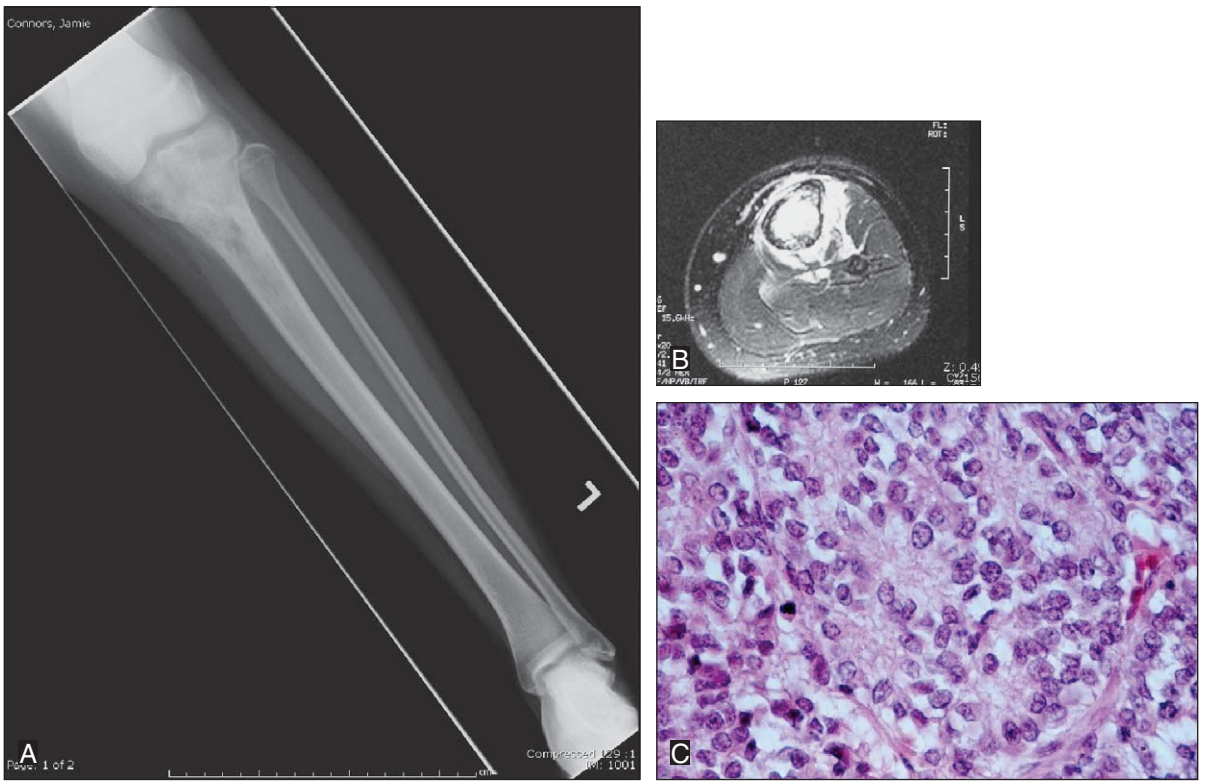


Figure 96-16 • **A,** Ewing's sarcoma of the proximal tibia showing a permeative pattern of bone destruction of the metaphysis. Because the soft-tissue mass is unmineralized, it is not apparent on the plain radiograph. **B,** The axial MRI shows the extent of the soft-tissue mass. **C,** Photomicrograph of a Ewing's sarcoma showing a round cell tumor. This alone would not establish the diagnosis. Immunohistochemistry and at time cytogenetics are necessary to distinguish this from other round cell tumors.

made in 44% of patients (e.g., herniated disc, spinal stenosis, spondylolisthesis, bursitis, stress fracture, urinary retention). Inappropriate treatment for these diagnoses included seven operative procedures (two laminectomies, two debridements, one hip arthrotomy, one total knee replacement, and one inguinal herniorrhaphy). On the average, 7 months elapsed before an accurate diagnosis was made.

Treatment

As with most sarcomas of childhood, therapy consists of multiagent chemotherapy and local control measures. The history and evolution of these treatments were fully discussed in the prior edition of this chapter. Since that time, considerable progress has been made. It is clear that adjuvant chemotherapy is essential.

Chemotherapy

The essential drugs that are used in Ewing's sarcoma have been vincristine, cyclophosphamide, dactinomycin (VAC) and doxorubicin; the combination of those agents with adequate local control led to substantial improvement in outcome of patients with Ewing's sarcoma compared to historic survival rates, which were dismal at best. The value of chemotherapy was confirmed by large cooperative groups coming together as the Intergroup Ewing's Sarcoma Group (IESS). The first study, IESS I, carried out in the 1970s, documented the value of chemotherapy compared to local control and established that doxorubicin augmented the benefits of VAC therapy alone. Pulmonary radiation also showed benefit in this study but has not been widely used in standard treatment protocols. The IESS II study showed that intensifying chemotherapy for high-risk patients with pelvic tumors improved the outcomes. More recently, the large cooperative groups (Children's Cancer Group and the Pediatric Oncology Group, now merged as the Children's Oncology Group in the United States) conducted several large trials to improve the event-free and overall survival of patients with ESFT. It was recognized that the combination of ifosfamide and etoposide was highly effective in patients with ESFT of bone who had a relapse after standard therapy; therefore, a study was designed to test whether the addition of these drugs to a standard regimen would improve the survival of patients with newly diagnosed disease.[311] Patients 30 years old or younger with ESFT of bone or primitive sarcoma of bone were randomly assigned to receive 49 weeks of standard chemotherapy with doxorubicin, vincristine, cyclophosphamide, and dactinomycin or experimental therapy with these four drugs alternating with courses of ifosfamide and etoposide. A total of 518 patients, of whom 120 patients had metastatic disease, were treated on this protocol. Of the metastatic patients, 62 were randomly assigned to the standard therapy group and 58 to the experimental therapy group. There was no significant difference in 5-year EFS rate between the treatment groups (P = 0.81). Among the 398 patients with nonmetastatic disease, the mean 5-year EFS rate among the 198 patients in the experimental therapy group was 69%, compared with 547 among the 200 patients in the standard therapy group (P = 0.005). The overall survival rate was also significantly better among patients in the experimental therapy group (72 percent versus 61 percent in the standard therapy group, P = 0.01). Thus, although no benefit from the addition of ifosfamide and etoposide to metastatic patients was demonstrated, substantial improvement in nonmetastatic patients was observed. Similar results have been reported by others.[312] This drug combination (minus the dactinomycin) is now considered the standard treatment, and two subsequent Children's Oncology Group (COG) protocols looking at intensifying the agents by increasing dose or compressing the interval between cycles have been carried out. The first of these two COG trials (INT-0154) took advantage of hematopoietic growth factors (filfrastim) to a standard five-drug regimen over 48 weeks to an intensified regimen over 30 weeks. Between 1995 and 1998, 492 patients were randomized, and to date, the analysis shows no difference in EFS or overall survival rates in the two arms. The results of this study, headed by Linda Granowetter, M.D., have been published in abstract form only. The successor COG trial (AEWS0031), chaired by Richard Womer, M.D., looked at interval compression of the drug cycles to yield dose intensification. In the experimental arm, patients received their cycles every 2 weeks compared to the standard regimen of every 3 weeks; the total doses of drugs were equal in the two arms. This study opened in 2001 and closed in 2005, and data analysis is pending. Others have tried intensifying treatment for high-risk sarcomas, including ESFT, and have shown that it is effective but associated with substantial toxicity, including death.[313] Adding other drugs such as topotecan or topotecan/cytoxan combinations to a five-drug regimen and the use of myeloprotectants were recently shown to yield no improvement in high-risk patients. Topotecan alone had limited activity in patients with Ewing's sarcoma or primitive neuroectodermal tumor that were metastatic at diagnosis.[314] A topotecan-cyclophosphamide combination was active, but overall results showed no improvement compared with previous studies.

Patients with metastatic disease at presentation have a much worse prognosis, and more aggressive therapies are directed toward them. Metastases most commonly involve the lung, but other bone, bone marrow, and other organ metastases can occur. Unfortunately, treatment regimens for these patients have not been very successful to date. Patients with metastases to the lung have a better survival rate (34% at 8 years, compared to 17% at other sites).[315] There is no apparent benefit to adding ifosfamide and etoposide in these patients, as was noted previously. Attempts have been made to intensify therapy by using autologous stem cell transplantation, but no definitive improvements have been seen.[316] Other studies in cooperation with cooperative groups in Europe are ongoing to look at stem cell transplantation or whole-lung irradiation in patients with lung metastases only. For patients with metastases, treatments with antiangiogenic drugs (celecoxib and low-dose vinblastine) are being tried in combination with standard chemotherapy.

Survival after Recurrence of Ewing's Tumor

Although the outcome is generally poor for patients who experience recurrent Ewing's sarcoma, certain patient subgroups could differ appreciably in their likelihood of survival, as has been shown in studies in the United States and Europe. Patients who relapse have a very poor outcome, depending on time of relapse following completion of initial treatment (the longer since treatment, the better the prognosis). Patients who have recurrences 2 or more years after diagnosis have a significantly better outcome compared to patients with earlier recurrence.[317,318]

A review of the St. Jude Children's Research Hospital experience between 1979 and 1999 included consecutive institutional protocols (ES-79, ES-87, and EW-92).[318] A retrospective medical chart and database review was performed to identify patients and disease characteristics at the time of diagnosis of Ewing's tumor and at the time of recurrence and to record the treatment that was received and the outcome after recurrence. Seventy-one patients were identified, 34 (47.9%) having distant recurrence, 25 (35.2%) having local recurrence, and 12 (16.9%) having both distant and local recurrence, all at a median of 1.7 years after diagnosis. The probability of a 5-year postrecurrence survival was 17.7% ± 4.5%. Interestingly, however, recurrence 2 years or more after diagnosis predicted a significantly better outcome (5-year postrecurrence survival rate: 34.9% ± 8.5%) compared with earlier recurrence (5.0% ± 2.8%; P < 0.001). Patients who had both local and distant recurrences fared more poorly, with a 5-year postrecurrence survival rate of 12.5% ± 8.3%, compared with patients who had local recurrence alone (21.7% ± 7.8%) or distant recurrence alone (17.6% ± 6.1%). Among patients with local recurrence alone, those who underwent salvage procedures with radical surgery had a significantly higher 5-year postrecurrence survival rate (31.4% ± 11.6%) compared with the other patients (9.1% ± 6.1%; P = 0.023). Pulmonary radiation also significantly improved the outcome of patients with isolated pulmonary recurrence (5-year

postrecurrence survival rate: 30.3% ± 12.5% versus 16.7% ± 10.8%; $P = 0.018$). The authors concluded that favorable outcomes are most likely among patients who experience recurrence 2 years or more after diagnosis and among patients who have local recurrence that can be treated with radical surgery and intensive chemotherapy.

Similarly, Catterill and coauthors,[319] in an analysis of 975 patients from the European Intergroup Cooperative Ewing's Sarcoma Study group, documented a relationship between survival and length of time before recurrence. Patients who relapsed within 2 years of diagnosis had a less favorable prognosis than those who relapsed later (5-year survival after relapse, 4% versus 23%, respectively; $P < 0.0001$), findings similar to those observed in osteosarcoma patients.

Local Control

Traditionally, local control for patients with Ewing sarcoma of bone has been radiation therapy. Now that patients are surviving longer, however, late effects such as growth disturbances in children, fractures of irradiated long bones, local recurrence, and secondary malignancies have caused a rethinking of this modality as the routine method of local control. Developments in surviving patients have led to a reassessment of the role of surgery in providing management of the primary tumor with sustained local control and minimal risk of developing a secondary malignancy. Several factors have led to a rethinking of local control recently. There is a definite local recurrence rate with radiotherapy alone as local control.[320,321] Improved combination neoadjuvant chemotherapy results in a marked reduction in the soft-tissue mass in most cases, and this often improves the feasibility of surgical resection and reconstruction. The outcome of limb salvage surgery has improved, allowing surgeons to achieve functional reconstructions and soft-tissue closure without a high complication rate that would delay chemotherapy. Finally, the risk of combined chemotherapy and radiotherapy for development of late secondary malignancies within the radiation portal and tumor bed of surviving patients have led many centers to prefer surgical local control. Several uncontrolled studies reporting an improved event-free and overall survival for patients who receive resection of the involved bone for Ewing's tumors and improvements in endoprostheses and allograft reconstructions for bone tumors in general have led to an increase in the number of patients who are treated surgically. Although no difference in survival or local control of the Ewing's tumor has been conclusively shown, resection and the avoidance of radiotherapy should reduce the incidence of second malignancy that is reported to occur in 5% to 20% of patients who are treated with chemotherapy and irradiation. Several older, noncontrolled studies have shown a benefit to surgical resection for local control.[322–324]

The radiotherapy data from the Pediatric Oncology Group 8346 Study determined that patients who had appropriate radiotherapy after induction chemotherapy with no deviations of radiation therapy had a 5-year local control rate of 80%.[325] Patients who were discovered to have minor deviations from appropriate radiotherapy had a 5-year local control rate of 48%, and those with major deviations had a 16% 5-year local control rate. The local control rate for the 21 patients who had a surgical resection with wide margins and an additional 16 patients (total 26%) who required postoperative radiation therapy with inadequate margins was also approximately 80%.

Donaldson and colleagues[325] reviewed the end results of POG #8346, evaluating 178 eligible patients, of whom 141 (79%) had only local disease and 37 (21%) had metastatic disease. Thirty-seven patients with localized disease underwent local resection, and 16 (43%) of those required postoperative radiotherapy. The 5-year EFS rate for the surgical patients was 80%. The remaining 104 patients with local disease were eligible for randomization or assignment to receive radiotherapy. The 5-year EFS rate for these patients was 41%. The 5-year local control rate for the surgical patients, either with or without postoperative radiotherapy, was 88%, while the rate for the patients who underwent radiotherapy alone was 65%. The quality of the radiotherapy correlated with outcome. Patients who had appropriate radiotherapy (treatment of appropriate volumes) had a 5-year local control rate of 80%, while those with minor deviations had a 5-year local control rate of 48%, and those with major deviations had a local control rate of only 16%. The local failure was within the irradiated volume in 62% of patients and outside the irradiated volume in 24% of cases. It was clear that adequate radiotherapy requires treatment to appropriate volumes, as defined by high-quality MRI images and full radiation doses.

Data reported from the Rizzoli Institute on 124 patients with nonmetastatic Ewing's sarcoma also concluded that surgery or surgery plus radiation therapy appeared to have a better overall patient outcome than did radiation therapy alone.[326] For patients with primary lesions presenting within the pelvis, surgery did not appear to modify the local recurrence rate (43% with radiation therapy alone versus 33% with surgery and radiation therapy). For tumors that presented in the extremities and/or other bones, local recurrences were observed in patients who were managed by surgery plus radiation therapy. Recurrence rates for those who received radiation therapy alone were 30% local recurrence in the extremities and 18% in other sites. The authors theorized that small foci of persistent tumor remaining within the primary tumor after radiation therapy might be responsible for relapse when the primary tumor was not resected.

Analysis of 62 patients entered on IESS-I who presented with nonmetastatic Ewing's sarcoma of the pelvis illustrated the benefits of surgery.[327] Other reports that demonstrate improved local control in surgically treated patients include those by Wilkins and colleagues[328] from the Mayo Clinic, Jürgens and coworkers[329] from Germany, and Sailer and associates[330] from Boston.

It has been suggested that this observed benefit of surficial resection is due to smaller tumor size. Göbel and associates[331] concluded that the improved prognosis that is enjoyed by patients managed by surgery was due in part to a biased distribution of smaller tumor volumes. It appeared that more patients with smaller tumors were being managed by surgical therapy. The majority of recent clinicopathologic studies have shown improved local control with the addition of surgery.[332,333]

Histopathologic response to chemotherapy appears prognostic for reduced local recurrence and/or improved survival; this finding is of major importance and similar for patients with osteosarcoma. Picci and coauthors[334] reported their results of treatment of 118 patients with primary biopsy-proven, nonmetastatic Ewing's sarcoma of the extremities. The response to chemotherapy was evaluated from the specimens of 118 Ewing's sarcoma patients, and their outcomes were correlated with the histopathologic response. For patients who achieved 100% necrosis (grade III), the estimated 5-year disease-free survival rate was 95%, in contrast to 68% for patients with a grade II (microscopic viable tumor) and 34% for patients with a grade I (macroscopic tumor) response ($P < 0.0001$). The researchers concluded that histopathologic response to chemotherapy had the greatest correlation to clinical outcome when compared with other parameters, such as size of the primary tumor and age of the patient. Local recurrence occurred in 2 of 37 grade III responders, in 10 of 35 grade II responders, and in 31 of 46 grade I responders.

Patients who present with primary tumors of sacrum, pelvis, and spine have a poor prognosis. The overall impact of operative treatment on outcome or survival of patients with Ewing's sarcoma of the pelvis or sacrum has been debated.[335]

Paulussen and colleagues[336] described the final results of the CESS 86 study that was aimed at improving EFS in patients with high-risk, localized Ewing's tumor of bone. Patients with small (<100 mL) extremity tumors were classified as standard-risk patients ($N = 52$), and patients with tumor volumes of greater than 100 mL ($N = 177$) and/or central-axis tumors (skull, shoulder, chest, spine, pelvic bones; $N = 164$) were classified as high-risk patients ($N = 241$). Eight patients could not be classified on the basis of these criteria. Local therapy was surgery for 68 patients (23%), surgery and radiation for

146 patients (49%), and radiotherapy alone for 82 patients (28%). The 10-year EFS rate was 52%. The EFS rate did not differ between the high-risk and standard-risk therapy groups. Tumor volume greater than 200 mL and poor histologic response had a negative impact on EFS. In multivariant analyses, small tumor volumes of less than 200 mL, good histologic response, and intensive chemotherapy argued for a fair outcome.

Bacci and coworkers[337] retrospectively reviewed 91 consecutive patients who were treated for Ewing's sarcoma of the femur in an attempt to eliminate selection bias toward those treated with surgery with or without radiotherapy and those treated by radiotherapy alone at other locations. The probability of survival without local recurrence was significantly higher ($P = 0.01$) for patients who were treated by surgery with or without radiotherapy (88%) than for patients who received radiotherapy alone (59%). The 5- and 10-year overall survival rates were 64% and 57%, respectively.

Surgical treatment of patients with Ewing's sarcoma arising in pelvic bones has improved, principally because of improved imaging techniques, improved neoadjuvant chemotherapy regimens, and an improved surgical understanding of the disease. Frassica and coauthors[338] reviewed 21 patients with nonmetastatic Ewing's sarcoma of the pelvis. Thirteen of the 21 received chemotherapy and radiation therapy, and 8 received chemotherapy and local operative resection with or without postoperative radiotherapy. The actuarial 5-year overall survival rate for patients who had chemotherapy and radiation therapy without surgical resection was 25%, while patients who had a surgical resection had a 75% survival rate ($P < 0.005$, log-rank method). The actuarial overall 5-year survival rate was 45% for patients who presented without evidence of metastases. The rate of local failure was 44% for the group that was managed by chemotherapy and radiation therapy alone, compared with 13% for patients with a local resection ($P > 0.25$, log-rank method).

All of these studies suffer from selection bias. One criticism is that the large, bulky tumors are treated with radiotherapy and the small ones are treated by surgery. Size alone, however, is not the sole determinant of who is eligible for an operation and who is not. Response to neoadjuvant chemotherapy and the precise location of the tumor are also important, and these factors have not been adequately controlled in the retrospective data that exist today. For instance, a large, bulky tumor of the ilium might be easily resectable after induction chemotherapy with little morbidity, whereas a small periacetabular tumor might be selected for radiation because we do not have good reconstruction options after removing the acetabulum. This type of bias is present in the published data. In the Grier study,[311] 38% of patients had surgery alone, 39% had radiation alone, and 23% had both. Whereas surgery alone had a better EFS in extremity tumors, there was no difference in the EFS for the pelvic tumors, suggesting that surgery alone is not the prognostic factor. It is unlikely that we will ever have a randomized study to address this issue, but the current practice in most centers is to attempt a resection whenever it is deemed possible to do so with negative margins and a good functional result. Other patients receive radiation. The prime reason for surgery is not local control in these cases, but avoidance of secondary malignancy in the survivors.

Shamberger and colleagues[339] reported the results of treatment of 98 of 869 patients (11.3%) who had primary tumors of the chest wall. The median follow-up was 3.47 years, and the 5-year EFS rate was 56% for chest wall lesions. Ten of 20 (50%) initial resections resulted in negative margins, compared with 41 of 53 (70%) negative margins with delayed resections after chemotherapy ($P = 0.043$). The EFS rate did not differ by timing of surgery ($P = 0.69$) or type of local control ($P = 0.17$). Initial chemotherapy decreased the percentage of patients who needed radiotherapy. Seventeen of 24 patients (70.8%) who had initial surgery received radiotherapy, compared with 34 of 71 patients (47.8%) who started with chemotherapy ($P = 0.061$). In cases of delayed operation, excluding patients who received only radiation therapy for local control, only 25 of 62 patients needed radiotherapy (40.3%; $P = 0.016$). The authors concluded that complete tumor resection with a negative microscopic margin and consequent avoidance of external beam radiation and its potential complications are increased with neoadjuvant chemotherapy and delayed resection of chest wall Ewing's sarcoma/primitive neuroectodermal tumor.

Current Guidelines for Surgical Therapy

All active multimodality Ewing's sarcoma protocols have provisions and recommendations for surgical resection in an effort to avoid the late effects of therapy when possible. It is routine to encourage resection of "expendable" bones. These include the rays of the hands and feet, the proximal four fifths of the fibula, the pubis and ilium of the pelvis, the ribs, the distal four fifths of the clavicle (Fig. 96-17), the body of the scapula, and other small, well-localized lesions. The majority of these procedures should not require reconstruction, which is best avoided, owing to the occasional need for adjuvant radiation therapy to the surgical bed and prolonged intensive adjuvant chemotherapy.[340] Surgical resection should be considered after induction chemotherapy in patients who present with small primary lesions of the metacarpals or metatarsals, when a ray amputation with a minimum of a wide margin may render the patient free of disease. In general, the hand and the foot do not tolerate radiotherapy well. Small midtarsal lesions and lesions that arise in the os calcis can sometimes be treated with radiation therapy in the mature skeleton, but the majority of larger lesions in skeletally immature patients are better managed by Syme's amputation or distal tibiotalar disarticulation or a below-knee amputation.

Commonly, the proximal four fifths of the fibula can be resected with satisfactory margins, aiming to leave at least 6 cm or more distally for satisfactory ankle function, and little or no morbidity results. A tibiofibular synostosis should be performed in skeletally immature patients to prevent proximal migration of the lateral malleolus. A report of five children with nonmetastatic Ewing's sarcoma of the distal fibula suggests that distal fibulectomy yielded near normal functional results, with a mean follow-up of 8 years.[341]

Lesions of the tibia that are deemed suitable for resection can be reconstructed with prostheses or allografts, as is described for osteosarcoma. Intercalary resections can be reconstructed with allografts or vascularized autografts (Fig. 96-18). Allografts or endoprostheses can also be used to reconstruct the shaft of the femur as an alternative to amputation.

Destructive lesions about the proximal femur and acetabulum can be managed by resection and reconstruction in cases in which pathologic fractures and poor joint function following radiation could be anticipated. Modular endoprostheses or allograft/prosthetic composites can be used to reconstruct the hip and proximal femur in patients for whom abduction function can be retained reliably.

Rib primaries are best managed by excision following preoperative chemotherapy to decrease the size of the soft-tissue mass and reduce the likelihood of contamination of the pleural cavity. A wide resection of the recommended entire rib and surrounding soft tissue is completed after induction chemotherapy. In most instances, this approach will eliminate the need for radiation or at worst reduce the amount of chest wall and lung that require radiation.[342]

Primary tumors presenting in the body of the scapula that preserve the glenoid structures and the chest wall can be resected without significant functional deficit. Lesions that present in the region of the glenoid are managed by radiation therapy or by resection/arthroplasty. Small lesions in the acromion and in the spine of the scapula might also be amenable to excision. Ewing's sarcoma of the clavicle can be resected without significant physical impairment.

Resection of the proximal humerus and reconstruction are associated with loss of active abduction if the deltoid and rotator cuff require resection, but reconstruction with endoprostheses (Fig. 96-19) and osteoarticular allografts or allograft-prosthetic composites offer decent function. The anticipated functional loss

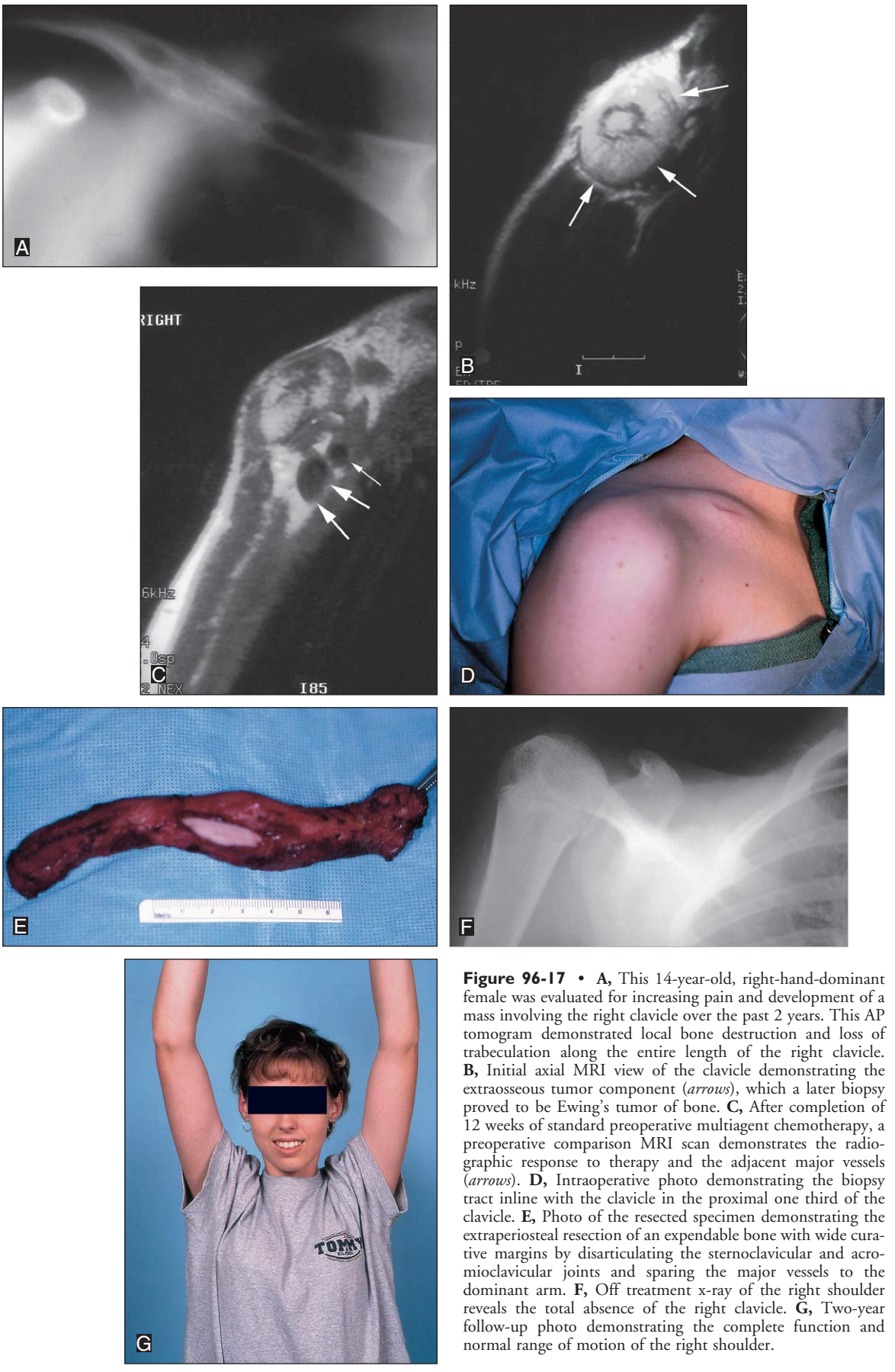


Figure 96-17 • **A,** This 14-year-old, right-hand-dominant female was evaluated for increasing pain and development of a mass involving the right clavicle over the past 2 years. This AP tomogram demonstrated local bone destruction and loss of trabeculation along the entire length of the right clavicle. **B,** Initial axial MRI view of the clavicle demonstrating the extraosseous tumor component (*arrows*), which a later biopsy proved to be Ewing's tumor of bone. **C,** After completion of 12 weeks of standard preoperative multiagent chemotherapy, a preoperative comparison MRI scan demonstrates the radiographic response to therapy and the adjacent major vessels (*arrows*). **D,** Intraoperative photo demonstrating the biopsy tract inline with the clavicle in the proximal one third of the clavicle. **E,** Photo of the resected specimen demonstrating the extraperiosteal resection of an expendable bone with wide curative margins by disarticulating the sternoclavicular and acromioclavicular joints and sparing the major vessels to the dominant arm. **F,** Off treatment x-ray of the right shoulder reveals the total absence of the right clavicle. **G,** Two-year follow-up photo demonstrating the complete function and normal range of motion of the right shoulder.

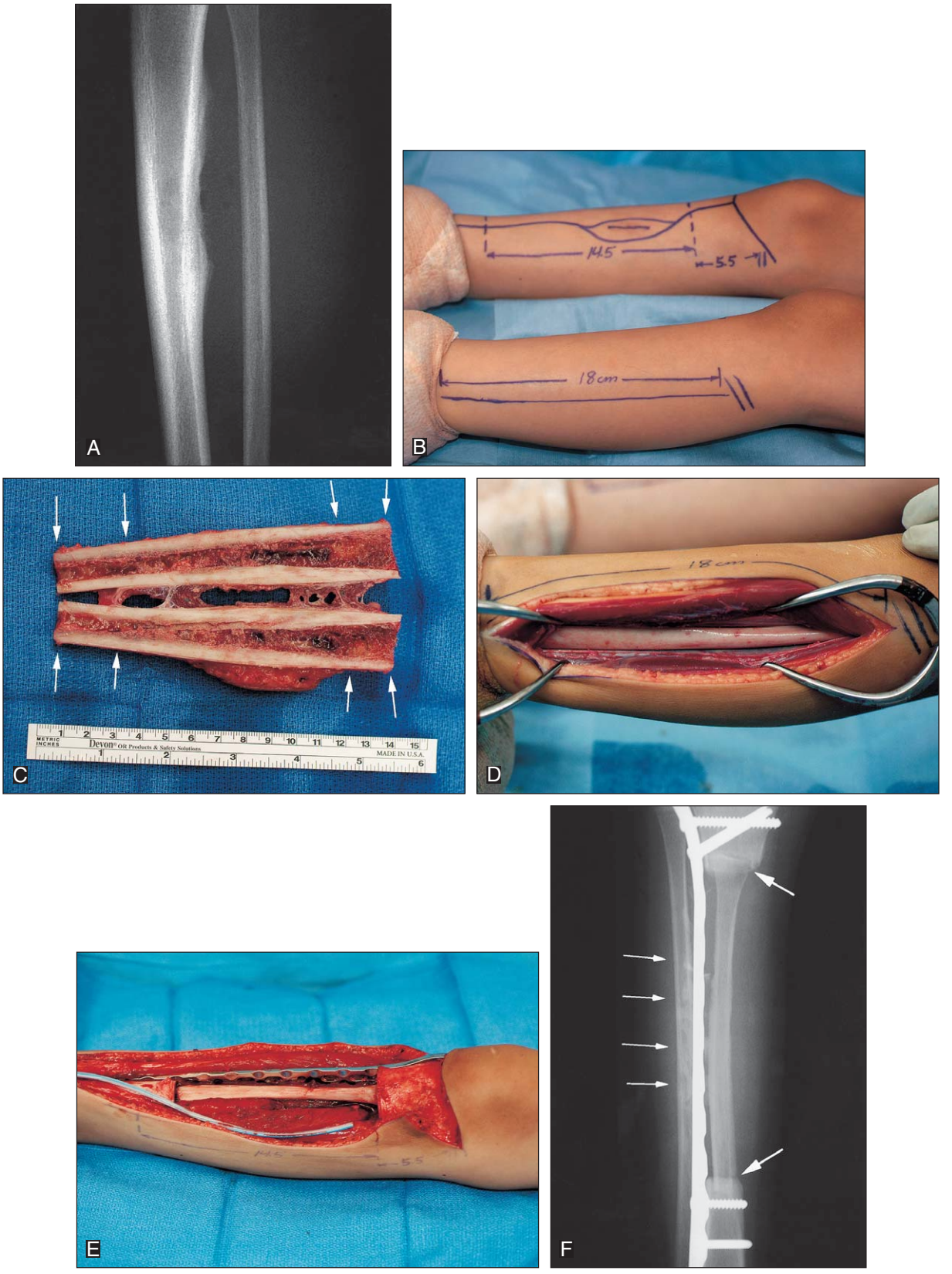


Figure 96-18 • **A,** Lateral x-ray of the right leg of a 7-year-old white male demonstrating a destructive lesion in the diaphysis, later proven to be Ewing's sarcoma. The patient was found to be otherwise free of disease. **B,** After completing 12 weeks of standard preoperative multiagent chemotherapy, a restaging MRI suggested an excellent response, with evidence of a normal marrow signal both proximal and distally to the diaphyseal tumor. The choice was made to proceed with a resection of 14.5 cm of the midshaft of the right tibia, sparing 5.5 cm of proximal tibia and reconstructing the surgical defect with an 18-cm left free fibular graft. **C,** The surgical resection specimen was taken to the back table and split to be certain that the proximal (*right arrows*) and distal intramedullary margin (*left arrows*) were appropriate. **D,** With the use of separate gowns, gloves, and instruments, a free avascular fibular graft was obtained from the left midshaft fibula with iliac crest graft as well. **E,** Intraoperative photo illustrating the fibular graft in place and secured with a bone plate. Iliac crest autologous graft was used to augment the proximal and distal host/graft bone juncture. **F,** Six-month postoperative x-ray demonstrating the developing synostosis between the fibula and free fibular graft (*small white arrows*) and healing of the proximally and distally host-graft bone junctures (*single arrows*).

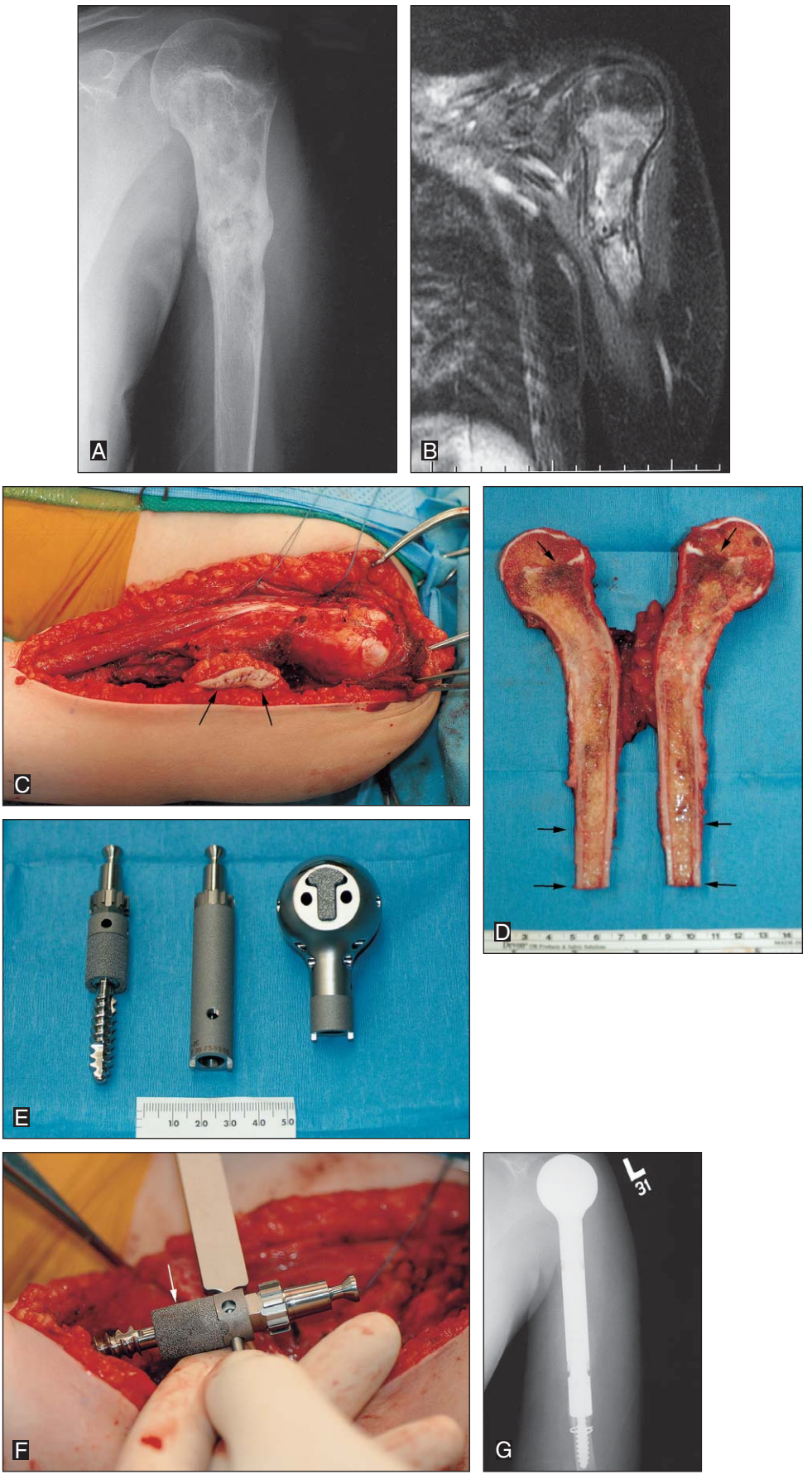


Figure 96-19 • **A,** Internal rotation AP x-ray demonstrating an attempt at healing of a pathologic fracture through a previously irradiated Ewing's sarcoma of the left nondominant humerus of a 12-year-old female after completion of chemotherapy. **B,** The coronal MRI better demonstrates a nonunion and angulation. There was a clinical concern regarding persistent tumor in the proximal humerus. After a prolonged period of conservative care, the choice was made to proceed with resection and reconstruction using a custom modular titanium prosthesis. **C,** Intraoperative view demonstrating the circumferential anterior exposure of the proximal two thirds of the humerus, sparing the rotator cuff and radial nerve. The *arrows* identify the contiguous previous biopsy incision and the humerus to provide an en bloc "wide" resection. **D,** Once removed, the specimen is split to confirm appropriate margins distally (2.5 cm; *arrows*). Note the closure of the epiphysis in the humeral head after external beam radiotherapy (*arrow in humeral head*). **E,** Custom modular titanium prosthesis designed and constructed using tantalum trabecular metal to allow bone ingrowth, promote extracortical fixation of the implant-host juncture, and allow for soft-tissue reattachment to the humeral head. **F,** Intraoperative view demonstrating securing of the implant to bone using a screw design to bring the tantalum trabecular metal (*arrow*) into juxtaposition with the shaft of the resection margin to promote extracortical bone bridging. **G,** Postoperative x-ray demonstrating the construct after reconstructing the rotator cuff to the implant and closure.

should be compared to the potential risks of radiation for local control. In general, functional deficits and limb length inequalities are better tolerated in the upper extremity than in the lower extremity. Preservation of a functional hand is the key measure of success.

Well-localized lesions presenting in the pelvis that are responsive to neoadjuvant chemotherapy—primarily those that are confined to the ilium and the pubis—are often resectable (Fig. 96-20). Also, tumors that arise in the lower portion of the sacrum and coccyx are amenable to sacral amputation with minimal neurologic sequelae. Before undertaking these technically demanding procedures, however, the surgeon should carefully consider the anticipated difficulty of resection and the resultant physical deficit. (See the later discussion

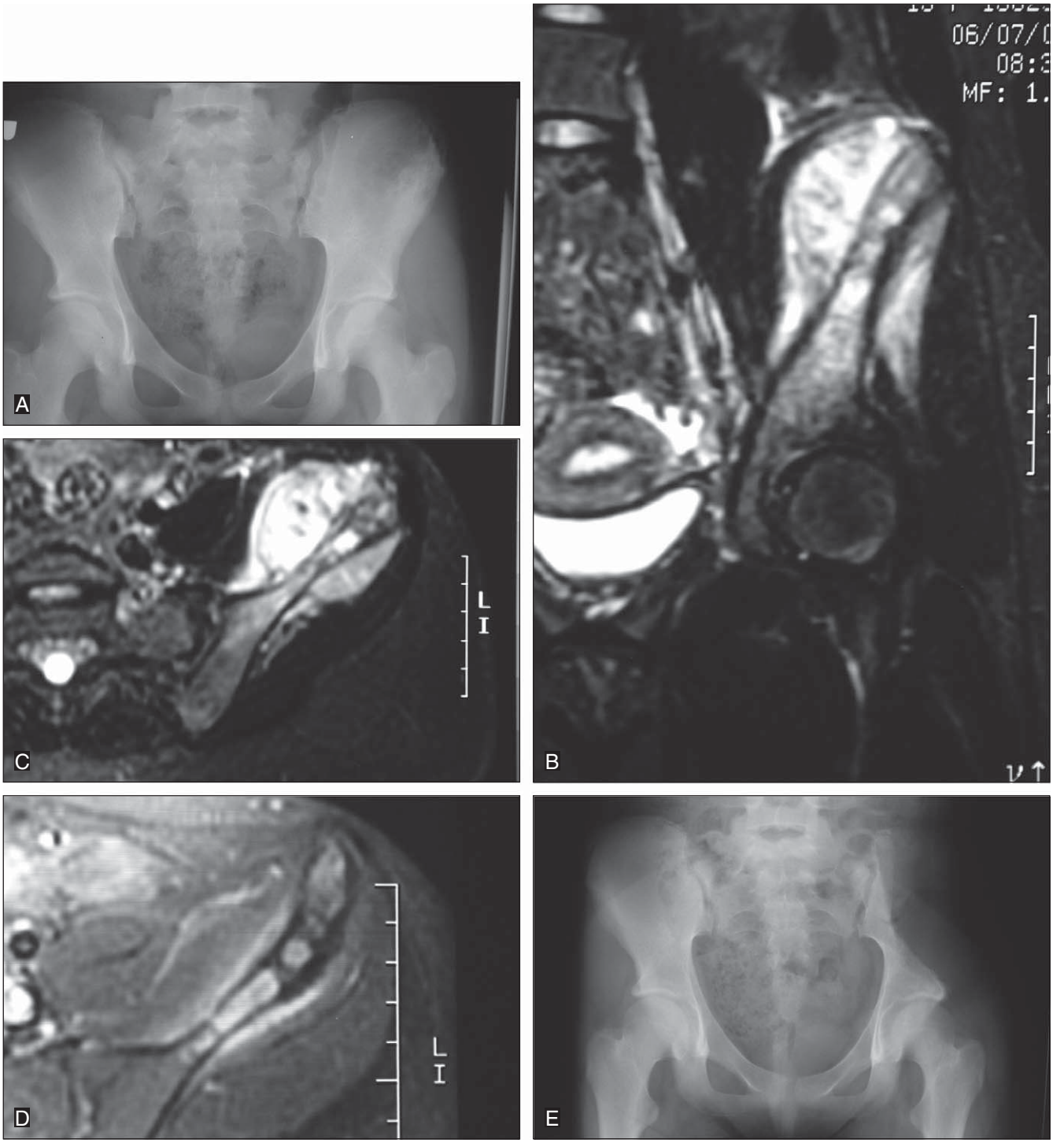


Figure 96-20 • **A,** AP radiograph of a 14-year-old girl with Ewing's sarcoma of the iliac wing. **B** and **C,** Coronal and axial MRI images at diagnosis show the extent of the soft-tissue and medullary tumor. **D,** Axial MRI following neoadjuvant chemotherapy showing a good response and near complete resolution of the soft-tissue mass. The acetabulum was thought to be free from tumor. **E,** Postoperative radiograph following resection of the iliac wing with preservation of the acetabulum. The margins were negative, and no postoperative irradiation was employed. The patient has remained free of disease for more than 5 years.

on sacral chordoma.). The most difficult site of resection is the acetabulum and upper sacrum. There are currently no decent reconstruction options for complete resection of the acetabulum, especially if the entire hemipelvis is resected. Attempts can be made to use pelvic allografts, but the rates of infection and other complications are high, especially if the soft tissues are of poor quality. This is often the case because of the extent of the soft-tissue mass and the need for radiation therapy.[189,343–345] The debate regarding whether or not the addition of surgery improves survival remains unanswered. There have been no randomized studies to address this issue. Several single-institution studies show an advantage to surgical resection, where others fail to show benefit (see previous discussion). In the Grier study,[311] the EFS and overall survival rates were similar for pelvic lesions irrespective of whether the primary was treated with surgery, radiation, or a combination of both. In the nonmetastatic patients in the study reviewed by Yock and colleagues,[346] 75 patients with pelvic tumors were treated and followed a median of 4.4 years. Twelve patients underwent surgery, 44 received radiation therapy (RT), and 19 received both. The 5-year EFS rate and cumulative incidence of local failure were 49% and 21%, respectively (16%, local failure only; 5%, local failure and distant failure). There was no significant difference in EFS or local failure by tumor size (<8 cm versus ≥8 cm), local control modality, or chemotherapy. The addition of ifosfamide and etoposide did, however, appear to positively influence local control. Patients who were treated with VACA-IE had 11% local failure versus 30% with VACA alone.

The author's bias is to resect pelvic lesions that can be done with little functional loss (Enneking Type I and III lesions), but resections that require resection of the acetabulum are probably best treated by irradiation. This obviously requires detailed discussion with the patient and his or her family by the surgeon, radiation therapist, and oncologist. The main benefit of resection is avoidance of secondary tumor. Since many of these patients who are treated with resection of the pelvis will require radiation and their prognosis is poorer than that of Ewing's sarcoma at other sites, the advantages of operative treatment are less clear and must be balanced with the morbidity of the given operation. This is also true for lesions of the upper sacrum. It may be possible to resect the lesion, but the potential loss of bowel, bladder, and sexual function should be carefully weighed against the alternative of radiation therapy.

It is advantageous in considering operative treatment for any site that a good response to chemotherapy be demonstrated. Signs of a satisfactory tumor response include a significant decrease in pain, a nearly complete regression in size of the lesion as shown by MRI, healing of a pathologic fracture, and improved range of near-painless motion of nearby joints. The fact that the patients who demonstrate these characteristics are the patients who are most likely to be deemed surgical candidates, whereas the lack of a response often leads to the use of radiation for local control, could explain the selection bias favoring surgical resection in the literature.

Amputation

Although the role of amputation in the surgical management of Ewing's sarcoma is limited, primary amputation or disarticulation might offer a clinical option that is superior to the prolonged morbidity associated with pathologic fracture or severe limb length inequality, which can result in late or delayed amputation. Lesions of the feet and distal tibia are excellent candidates for amputation. Large destructive lesions in males under the age of 10 years and in females under the age of 8 years can be managed by primary amputation or a primary limb-sparing option (rotationplasty, etc.). With the advent of expandable prostheses, many limbs are now reconstructed by that approach, although the long-term outcomes of these prostheses is still not well known. Amputation should be considered when epiphysiodesis of the opposite limb does not provide a reasonable treatment option to approach equalization of lower-extremity lengths at skeletal maturity.[347]

Prognosis

Location

Clearly, location of the primary lesion in patients with nonmetastatic disease has a profound relationship to long-term survival. Patients with lesions arising below the elbow and below the midcalf who are treated appropriately have 5-year survival rates approaching 80%. Large, bulky lesions that present in the pelvis in nonresectable sites yield 5-year survival rates of less than 25%.[338]

Histopathologic Response to Chemotherapy

Location and size of the primary lesion, however, are not the only determinants of survival. The histopathologic response of the tumor to neoadjuvant chemotherapy has been shown to be important in predicting outcome.[348] Patients completing systemic neoadjuvant chemotherapy and managed by surgical resection are evaluated by using a pathologic grading system independent of change in tumor volume. The resected specimens are sectioned and mapped for review to determine the extent of tumor necrosis. In one study, patients whose specimens displayed complete tumor necrosis with no identifiable foci of tumor tissue (grade III) were projected to have a 90% continuous disease-free survival. Those with lesser degrees of necrosis (grades II and I) were projected to have 53% and 32% 5-year disease-free survival rates, respectively. Of all the variables that were assessed, only grade of tumor necrosis was associated with disease-free survival ($P = 0.004$). There was, however, a trend for tumor volume to be associated with disease-free survival ($P = 0.06$).[348]

Wunder and coworkers[349] reviewed the histopathologic response to preoperative chemotherapy of 74 patients with an operative resection specimen, correlating the response as a predictor of the overall outcome of multimodality therapy. The minimum duration of follow-up was 5 years. The operative specimens were reviewed, and the histopathologic response to chemotherapy was graded semiquantitatively. Grade I represented 50% or less necrosis; grade II, 50% to 90%; grade III, 90% to 99%; and grade IV, 100% necrosis. Of the 74 specimens, 44 (59%) were either grade IV or grade III, while 14 (19%) were grade I, and 16 (22%) were grade II. The two most important predictors of EFS were histologic response to preoperative chemotherapy ($P = 0.0001$), followed by size of the primary tumor ($P = 0.001$). At 5 years, the EFS rate for grade I patients was zero. Grade II responders experienced a 6/16 (37.5%) EFS rate, and for grades III and IV, 37 of 44 patients (84%) experienced a 5-year EFS. The risk of local recurrence was also strongly associated with the quality of the operative margins. There were four local recurrences (6%) after 67 resections that were thought to have negative margins. The authors concluded that histopathologic response to preoperative chemotherapy and size of the primary tumor were the most important clinical predictors of outcome of operative treatment for nonmetastatic Ewing's sarcoma.

Late Effects of Treatment

Functional Results

It is generally accepted that the pathologic and biomechanical changes that are associated with high-dose irradiation of bone include decreased vascularity, cellularity, and bone metabolism, with increased porosity and loss of mechanical strength, impaired fracture healing, and periosteal fibrosis.[350]

The soft-tissue and skeletal effects of irradiation are related to the following factors:

- Skeletal maturity of the patient
- The volume of tissue treated
- The total dose and dose rate
- The energy and delivery system of the beam
- Concomitant chemotherapy treatment
- Inclusion of major joints or growth centers

Robertson and coauthors[351] reported limb length inequalities in 12 of 67 patients surviving childhood cancer who had received radiotherapy. All the children survived to skeletal maturity. Seven of the 12 patients reported symptoms. The development of limb length inequality was shown to be uniformly related to long bone physeal radiation of 45 Gy or greater.

Additional comorbidities include soft-tissue atrophy and fibrosis, joint stiffness, and pathologic fracture of the previously treated bone. Jentzsch and colleagues[352] reported that 9 of 40 patients who completed treatment sustained a pathologic fracture with Ewing's sarcoma of the lower extremity. They found slow and delayed fracture healing, with two patients sustaining refracture. All eventually healed by closed means. Later, Springfield and Pagliarulo[353] reported the results of a retrospective analysis of patients who had received chemotherapy and radiotherapy for primary Ewing's sarcoma of the extremities. Twenty-eight patients were followed for a minimum of 2 years or until their deaths. Seventeen patients had primary lesions presenting in the humerus or femur. All 17 patients received chemotherapy and radiation therapy, with doses ranging from 50 to 60 Gy administered by a shrinking field technique. Two of the eight patients with humeral primaries and five of nine patients with femoral primaries sustained pathologic fractures without significant trauma. Of the five femoral fractures, four were in the subtrochanteric region, and all had a cortical window removed at the time of biopsy. Only two patients developed pathologic fractures through the cortical defect. Springfield and Pagliarulo[353] strongly recommend rebiopsy to assess possible persistent disease, followed by internal fixation and the addition of autogenous bone graft.

Since most patients are now diagnosed by needle or incisional biopsy of the soft-tissue component and the primary is often resected after chemotherapy, the complication of fracture following radiation of long bones is less prevalent.

Late effects of radiation such as muscular atrophy, limb length discrepancy, and development of second malignancy in patients treated for Ewing's sarcoma were reported in one study of patients who were followed at least 5 years from diagnosis. Late effects were seen in 10 of 19 patients (52.6%) who received radiation as local control, 2 of 5 patients (40%) who received surgery and irradiation, and 4 of 16 patients (25%) who received surgery alone. Scoliosis and decreased range of motion of an extremity were seen regardless of local treatment modality. Three patients who had surgery alone had an amputation, whereas two who had RT had an amputation secondary to relapse or development of osteosarcoma.[354]

Although most children who are treated with RT for a pediatric extremity sarcoma have minimal late toxicity, another study of 15 survivors of children with sarcoma reported that late effects were seen in all patients and included atrophy in 12 (80%), fibrosis in 12 (80%), bone growth abnormalities in 10 (67%), impairment of mobility and extremity function in 6 (40%), edema in 3 (20%), and peripheral nerve injury in 2 (13%). The authors noted bone growth discrepancies, muscle and soft-tissue atrophy, and peripheral nerve complications. One patient developed a radial nerve palsy 3 years after marginal resection and postoperative RT and required tendon transfer repair. One patient had radiation-induced vasculitis with popliteal artery thrombosis 23 years after RT. Of particular note was the finding that five patients developed a fracture of the irradiated bone at a median time of 8 years after RT, and three of these patients were subsequently found to have a secondary bone cancer in the radiated field, leading the researchers to conclude that a fracture might be a presenting sign of second malignancy.[355]

The functional results following resection are also significant, but few studies have compared the results of radiation versus surgery of the primary tumor. Clearly, resecting a growth center has growth consequences similar to those of radiating one and, depending on the age of the child, has to be addressed with contralateral epiphysiodesis or an expandable prosthesis. The complications of surgical limb salvage were discussed in the section on osteosarcoma.

Secondary Malignancies

In 1979, Chan and coauthors[356] reported that among 24 patients with primary Ewing's sarcoma of the pelvis who had survived for 5 years, 4 patients developed secondary malignancies within the irradiated fields and died. Three of the four patients also had received intensive chemotherapy. Also, Strong and associates[357] reported an increased hazard of developing secondary malignancy in patients who were treated with radiation therapy, with a cumulative cancer risk of 35% over 10 years. The administration of intensive chemotherapy in five or more courses appeared to exert an enhancing effect, increasing the rate of development of new tumors. Li[358] also reported a 12% risk of developing a new cancer in 15 of 410 patients who survived childhood cancers.

Most recently, Tucker and coworkers[359] estimated the subsequent risk of development of bone cancer in 9170 patients who survived 2 or more years. Data on treatment were evaluated on 64 patients in whom bone cancer developed after childhood cancer. Patients who had received radiation therapy had a 2.7-fold risk of developing a secondary malignancy. The dose response appeared to reach a 40-fold risk after doses to bone of more than 60 Gy. Similar numbers of patients were treated with orthovoltage and megavoltage, and the patterns of risk among categories of doses did not differ according to the type of voltage. Also, after adjustment for radiation therapy, treatment with alkylating agents appeared to increase the subsequent risk of bone cancer.

Coleman[360,361] reported that an average latent period for development of treatment-induced solid tumors was 10 to 15 years, with a 10% actuarial risk at 10 years for pediatric patients. The Late Effects Study Group confirmed the risk in 1985.[362] Smith and associates,[363] summarizing the treatment of 25 long-term survivors of Ewing's sarcoma, reported that one patient developed acute myelogenous leukemia at 15 months and one patient developed osteosarcoma 3 years after treatment. The actuarial risk of developing a second malignancy at 5 years was 8%, with a 4% risk of developing a secondary bone sarcoma.

A study of secondary malignancy in 397 patients who were treated for Ewing's sarcoma at the Mayo Clinic over a 25-year period showed that 26 patients (6.5%) had 29 secondary malignancies develop. The mean age of the patients was 16 years, and the interval from the diagnosis of the Ewing's sarcoma to the development of the secondary malignancy averaged 9.5 years. The secondary malignancies included 8 hematopoietic cancers, 12 sarcomas, and 9 carcinomas. It was observed that the carcinomas most likely represent the general risk of developing cancer in the healthy population but that the sarcomas were caused by radiation therapy, and the hematopoietic tumors were caused by chemotherapy. Hematopoietic malignancies occurred at a mean latent period of 4.8 years (range: 1.7 to 12.9 years), and the sarcomas occurred after a mean of 10.9 years (range: 1.5 to 32.5 years). At the mean follow-up of 5 years (range: 0.5 to 28 years) from diagnosis of the second malignancy, 14 patients were alive (43%); however, patients with sarcomas or hematopoietic secondary malignancies had a poor prognosis.[364] Others have shown that with aggressive therapy, patients with radiation-associated osteosarcomas can have a prognosis similar to that of de novo osteosarcoma,[276] but it is clear that patients with Ewing's sarcoma are at risk for these secondary malignancies and need to be followed frequently and indefinitely.

Future Directions

With evolving and intensified induction and maintenance chemotherapy and improved imaging and patient selection techniques (e.g., MRI, PET), many patients who would not previously have been considered suitable for limb-sparing procedures have become candidates for resection and reconstruction. If the margins are not adequate for local control, postoperative radiation therapy can be administered without significantly altering the result in constructs that do not require bone graft healing and incorporation.

The use of intraoperative radiation therapy, proton beam irradiation, and other advances in radiotherapy and improvements in limb salvage surgery in all sarcomas have improved our ability to achieve local control of the primary. The increasing role of surgical therapy in the local management of patients with Ewing's sarcoma appears to be beneficial with respect to overall disease-free survival and reduction of treatment-related late effects. Adjuvant chemotherapy has dramatically improved the survival of patients with ESFTs. Current efforts are being directed at finding newer chemotherapeutic agents and intensifying therapy to improve outcomes further. The goal is to optimize therapy wherever possible to provide the patient with the best overall clinical and functional results.

MALIGNANT FIBROUS HISTIOCYTOMA OF BONE

MFH of bone is uncommon. The name is being changed to *undifferentiated spindle cell tumor*. It is classified into primary and secondary categories, which are related to the absence or presence of a known predisposing and underlying pathologic entity, such as bone infarction, fibrous dysplasia, or Paget's disease of bone. Some tumors also appear to be associated with orthopedic implants and could be metal-induced.[365]

Epidemiology

Approximately 70% of MFH of bone are primary tumors, and 30% are secondary.[366] There is a slight male predominance. The primary variety tends to affect younger patients, while the secondary neoplasms are seen predominantly in the sixth and seventh decades of life.

Radiographic Features

Pronounced loss of normal trabeculation associated with permeative cortical destruction is the characteristic radiographic appearance. Invasion into adjacent soft tissue with the development of a soft-tissue mass is not uncommon. The proximal tibia and distal femoral metaphyses are most frequently affected, followed by the pelvis, proximal humeral metaphysis, and scapula. A little more than one half of the tumors originate in the lower extremity.[367]

Destructive lesions originating in weight-bearing bones are often only mildly painful and often are discovered when the patient has a pathologic fracture. Periosteal new bone formation and endosteal scalloping are rarely seen in MFH of bone. CT is useful in defining the extent of bone destruction; however, MRI with contrast enhancement of the extremity is the single study of choice to provide maximum data.[368]

Secondary MFH of bone is by definition associated with an underlying or pre-existing condition. There appears to be a clear association with bone infarction as a pre-existing condition. Radiographically, the remaining punctate calcifications can be seen about the periphery of the lesion, with destruction and loss of radiographic detail evident within the lesion. Also, a contiguous soft-tissue mass is commonly present.

Patients with known Paget's disease of bone, hereditary dysplasias of bone, or prior treatment with radiotherapy are at risk to develop secondary MFH of bone. These patients are often older than those who develop the primary subtype.

Pathologic Features

Regardless of the primary or secondary classification, the overwhelming majority of these lesions are high-grade malignancies. Only 10% or fewer are low grade. Histologically, the tumor is composed of fibroblasts in a storiform (whorling or cartwheel) pattern with multinucleated giant cells, inflammatory cells, and histiocytes with numerous foamy mononuclear or multinucleated giant cells (xanthomatous variant). Mitotic figures are frequent, with considerable pleomorphism.

MFH of bone demonstrates immunoreactivity for vimentin, glycoprotein, α_1-antitrypsin, α_1-antichymotrypsin, and the bacteriolytic enzyme lysozyme.[369] These tumors are commonly S-100 negative. Ultrastructurally, the lesions seem to derive from a primitive mesenchymal stem cell that might be shared with the common progenitor cell of osteosarcoma.[369]

Surgical Therapy

Nonmetastatic primary MFH of bone is best managed in a manner similar to that of primary osteosarcoma of adolescents and young adults (Fig. 96-21). After diagnostic biopsy, neoadjuvant chemotherapy can be administered, and the primary tumor response can be monitored by clinical and radiographic parameters. A combination of doxorubicin, ifosfamide, and methotrexate is often used, but currently, there is no agreed-upon regimen. The majority of tumors respond clinically with relief of pain, resolution of the associated joint contracture, diminished local edema, and reduction in the size of the soft-tissue component. Radiographic response to neoadjuvant chemotherapy is best confirmed by a reduction in size of the soft-tissue component and diminished or absent contrast enhancement on follow-up MRI evaluation. Preoperative or neoadjuvant chemotherapy is not a requirement, and an immediate surgical resection is recommended if the patient is at risk of sustaining a pathologic fracture. Whether or not the patient receives preoperative chemotherapy, a "wide" surgical margin is recommended. Usually this can be done without the need for an amputation.

Adamantinoma of Bone

Although similar in name, adamantinoma of bone is not related to ameloblastoma of the mandible derived from Rathke's pouch. First described by Dockerty and Myerding and later refined by Cohn and colleagues[362] from the Mayo Clinic in 1962, this rare, low-grade malignant lesion arises predominantly in the tibia (90%), the next most common site being the fibula.[362,370–372] There is no definite sex predominance, and the majority of tumors appear in the second and third decades of life.

The most common symptom is pain and, later, a mass, most often in the midshaft of the tibia (70%). Radiographically, the lesion is radiolucent, arising within the cortex. It may be multilocular. Over time, it will usually extend into the medullary canal (Fig. 96-22). Adamantinoma is associated with osteofibrous dysplasia, and they often occur together. A wide surgical resection is the treatment of choice. Adjuvant irradiation or chemotherapy is not indicated.

PRIMARY SARCOMAS OF THE SPINE

It is estimated that less than 10% of all primary bone tumors—approximately 1 per million per year—arise in the spine.[373] Metastatic disease to the spine that results in spinal cord compression, on the other hand, approximates 8.5 per 100,000 per year.[374] The vertebral column remains the most common site of developing skeletal metastases, resulting in approximately 20,000 patients per year requiring treatment.[375] Autopsy studies of patients who died of disseminated cancer demonstrated vertebral metastases in 14% to 41%, intradural/extramedullary metastases in 5% to 8%, and intramedullary metastases to the cord in 1%.[376,377] Therefore, metastatic disease must be considered and excluded during evaluation of a patient who is suspected of having a primary bone tumor of the spine.

General Considerations

Symptoms

Back pain is the most common presenting symptom of a tumor of the spine.[378,379] The symptoms are often vague, ill defined, and slow

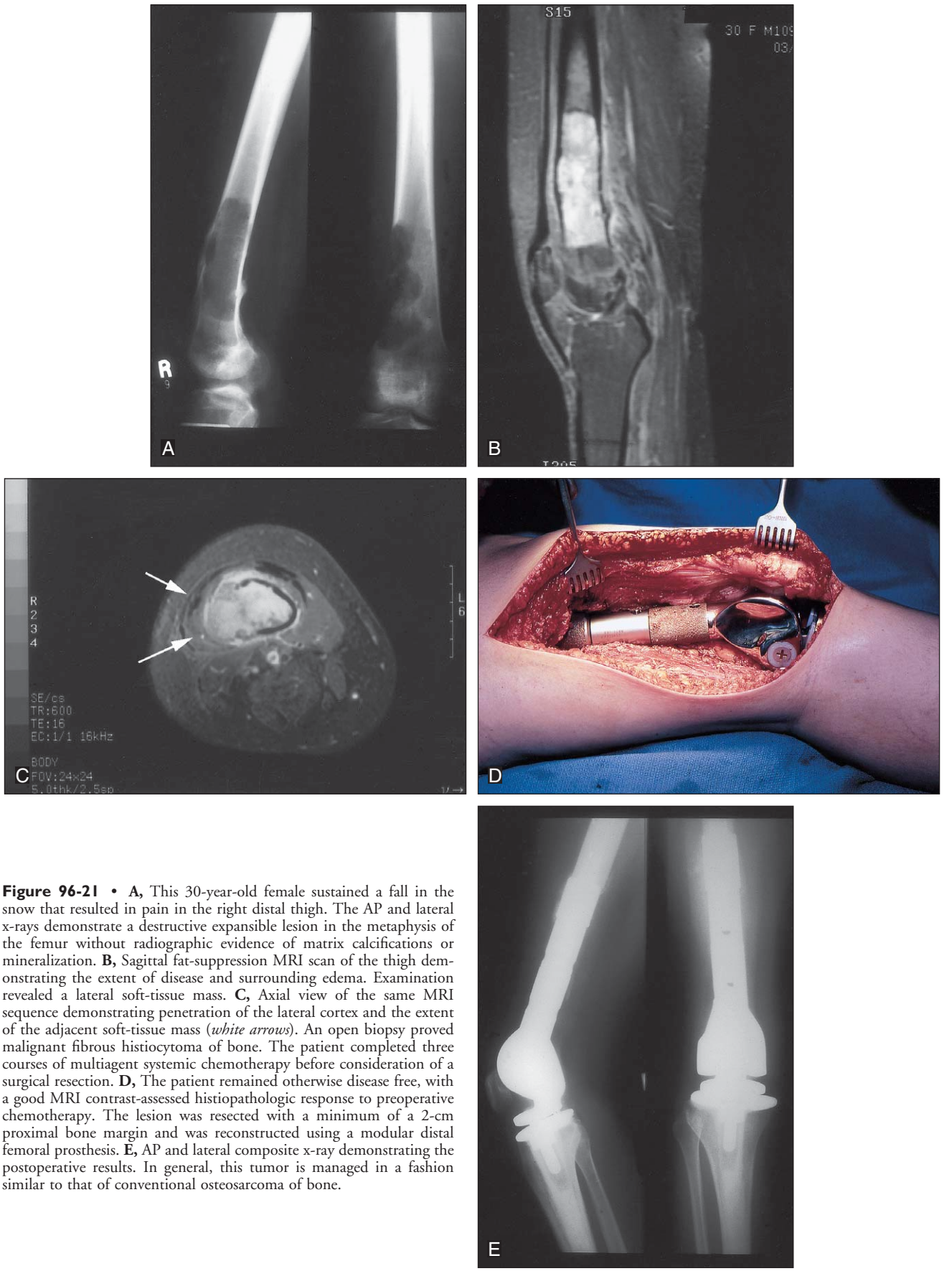


Figure 96-21 • **A,** This 30-year-old female sustained a fall in the snow that resulted in pain in the right distal thigh. The AP and lateral x-rays demonstrate a destructive expansible lesion in the metaphysis of the femur without radiographic evidence of matrix calcifications or mineralization. **B,** Sagittal fat-suppression MRI scan of the thigh demonstrating the extent of disease and surrounding edema. Examination revealed a lateral soft-tissue mass. **C,** Axial view of the same MRI sequence demonstrating penetration of the lateral cortex and the extent of the adjacent soft-tissue mass (*white arrows*). An open biopsy proved malignant fibrous histiocytoma of bone. The patient completed three courses of multiagent systemic chemotherapy before consideration of a surgical resection. **D,** The patient remained otherwise disease free, with a good MRI contrast-assessed histiopathologic response to preoperative chemotherapy. The lesion was resected with a minimum of a 2-cm proximal bone margin and was reconstructed using a modular distal femoral prosthesis. **E,** AP and lateral composite x-ray demonstrating the postoperative results. In general, this tumor is managed in a fashion similar to that of conventional osteosarcoma of bone.

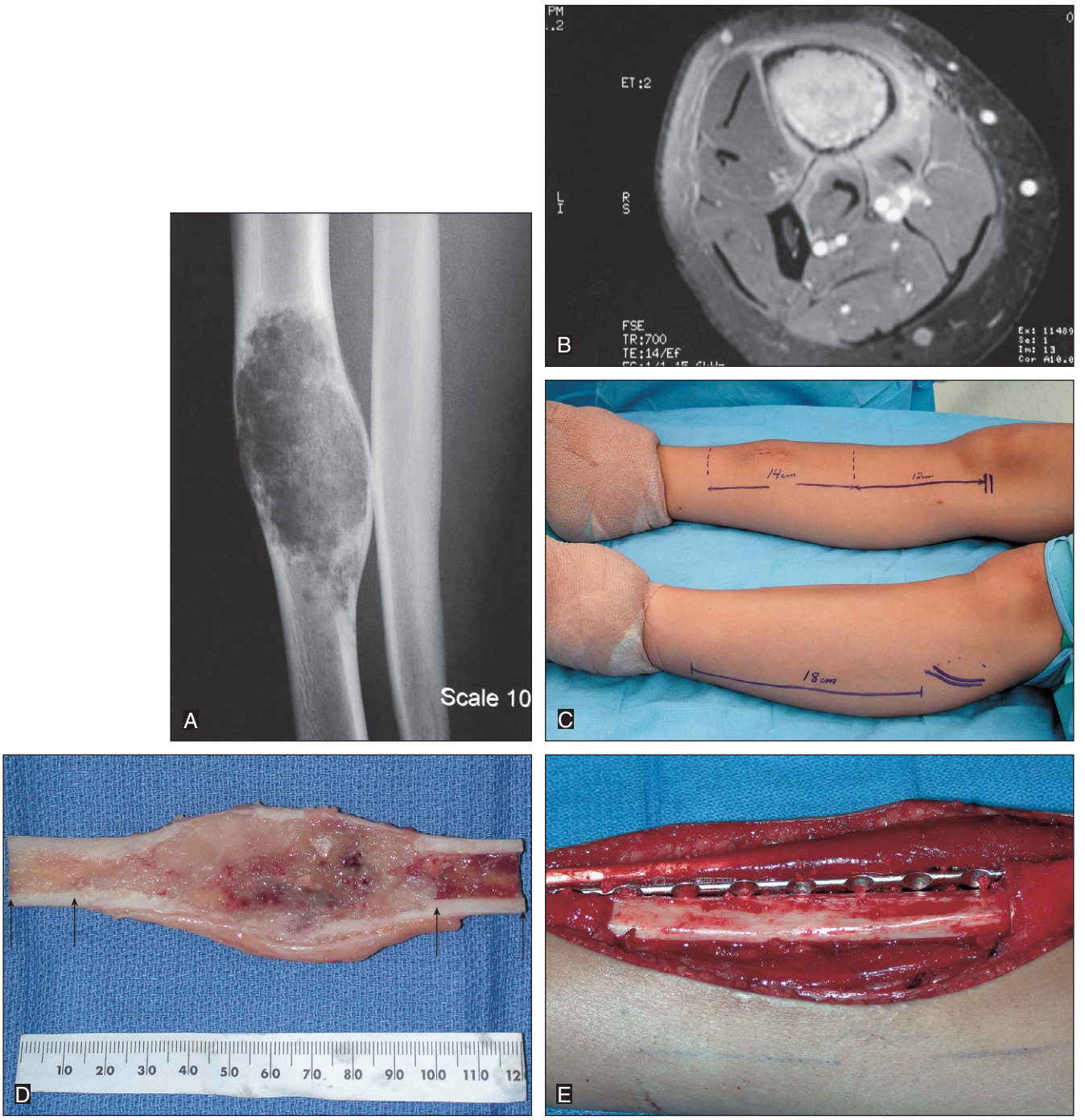


Figure 96-22 • **A,** This 16-year-old skeletally mature female was seen for increasing right leg pain that was made worse by weight bearing. The lateral digital film demonstrates an expansile intramedullary midshaft tibia mass with cortical thinning and destruction. A total body STIR MRI revealed no other detectable lesions. Physical examination revealed no café-au-lait cutaneous pigmentation. **B,** Axial MRI view demonstrating expansion and thinning of the cortex, destruction of the medullary bone and inner cortex without tumor necrosis, and surrounding soft-tissue edema. **C,** An open biopsy revealed adamantinoma of bone. This intra-operative view demonstrates the intended surgical procedure, resecting 14 cm of the diaphysis of the tibia and reconstructing the skeletal defect with a free avascular left fibula graft supplemented with autologous iliac crest bone graft. **D,** After resection, the lesion was taken to the back table and split to confirm appropriate proximal (*right arrows*) and distal (*left arrows*) intramedullary margins. **E,** A continuous strength locking screw plate was used to maintain reduction and to secure the fibular graft, having been shaped to fit within the proximal and distal medullary canal. The proximal and distal host/graft osteotomy sites were supplemented with autologous iliac crest bone graft.

Table 96-8 Anatomic Distribution of Vertebral Lesions

Anterior Elements of the Spine	Posterior Elements of the Spine	Both Anterior and Posterior Elements of the Spine
Multiple myeloma	Osteoid osteoma	Metastasis (spares disk end plates)
Hemangioma	Osteoblastoma	Infection (involves disk end plates)
Paget's disease of bone	Aneurysmal bone cyst	Classic osteosarcoma
Histiocytosis × (vertebra plana)		Postradiation sarcoma
Giant cell tumor of bone		Malignant histiocytoid variety
Reparative granuloma		Osteosarcoma
Ewing's sarcoma (PNET)		Osteochondroma
Lymphoma of bone		Primary chondrosarcoma
Malignant fibrous histiocytoma		Secondary chondrosarcoma
Chordoma		

to localize to a more specific region of the anatomy (Table 96-8). Less commonly, some patients present with the onset of spinal cord compression without any antecedent history of pain. Tumors of the spine can be difficult to see on plain radiographs; therefore, if a patient has persistent symptoms, a bone scan, CT, or MRI is recommended. MRI is probably the best examination and should be done with intravenous contrast.

Age

The age of the patient is important in evaluating a patient with a suspected lesion involving the vertebral column. Patients under the age of 18 years are 80% more likely to have a benign lesion than are those over 18 years of age.

Staging of Primary Tumors of the Spine

Boriani and coworkers[380] have proposed a surgical staging system for tumors of the spine. Using a 12-sector clock face staging system as viewed from cephalad to caudad, in which 1 and 12 represent the left and right sides of the spinous process, respectively, these authors distinguish five separate centrifugal surrounding tissue layers (A, B, C, D, and E), beginning with intradural involvement (A) and extending out to paraspinous muscle involvement (E; Fig. 96-23). Surgeons commonly use this staging system to plan the surgical treatment.

Biopsy

Fine-needle aspirate biopsy or core-needle biopsy is most often used. Some surgeons prefer a semiopen transpedicular fluoroscopic controlled biopsy from a limited posterior surgical approach, but percutaneous transpedicular biopsy can be done.[381] As in the management of all sarcomas of bone, the biopsy track must be considered contaminated and be included in the carefully planned en bloc resection.[382–384]

Primary Malignant Tumors of the Spine

Benign tumors of the spine are much more common than are primary malignant tumors of the spine. The benign tumors that commonly arise in the spine include osteoid osteoma, osteoblastoma, giant cell tumor of bone, aneurysmal bone cyst, and Langerhans cell histiocytosis.

Osteogenic Sarcoma of the Spine

Osteosarcoma of the spine is distinctly rare, and there are insufficient data regarding its natural history, but all indications are that it behaves like other osteosarcomas. Therefore, patients are treated with preoperative chemotherapy, and then a surgical resection is done with as wide a margin as possible. Usually, this means removing all of the vertebral body and posterior elements. Although there is limited experience, postoperative irradiation could be of benefit, especially for patients with less than 90% necrosis and close or positive margins.

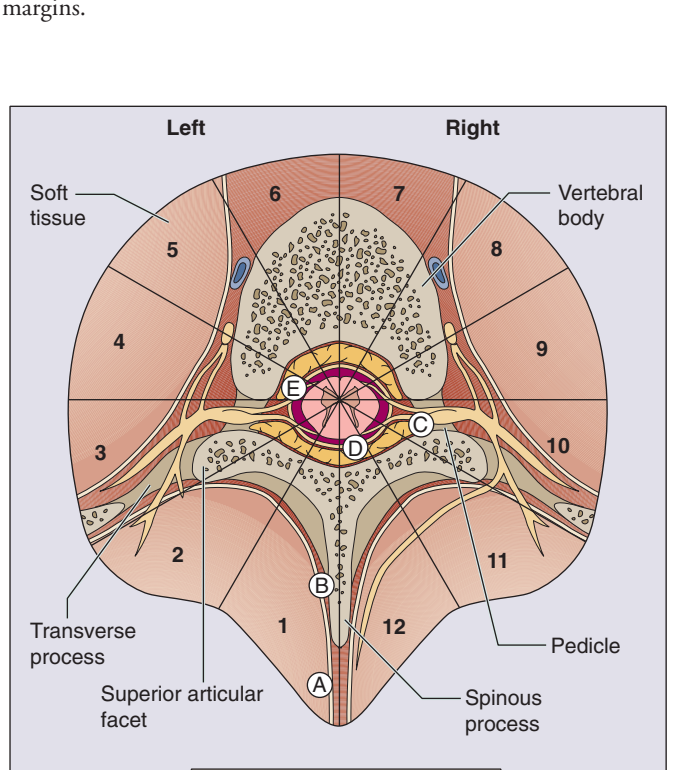


Figure 96-23 • Representation of the current staging scheme proposed by Boriani, Weinstein, and Biagini, with 12 radically distributed zones beginning at the spinous process and five separate tissue layers designed to distinguish intramedullary and extradural involvement from bone and soft-tissue paravertebral extension. The system does not recognize grade (G) or longitudinal compartmental margins (T).

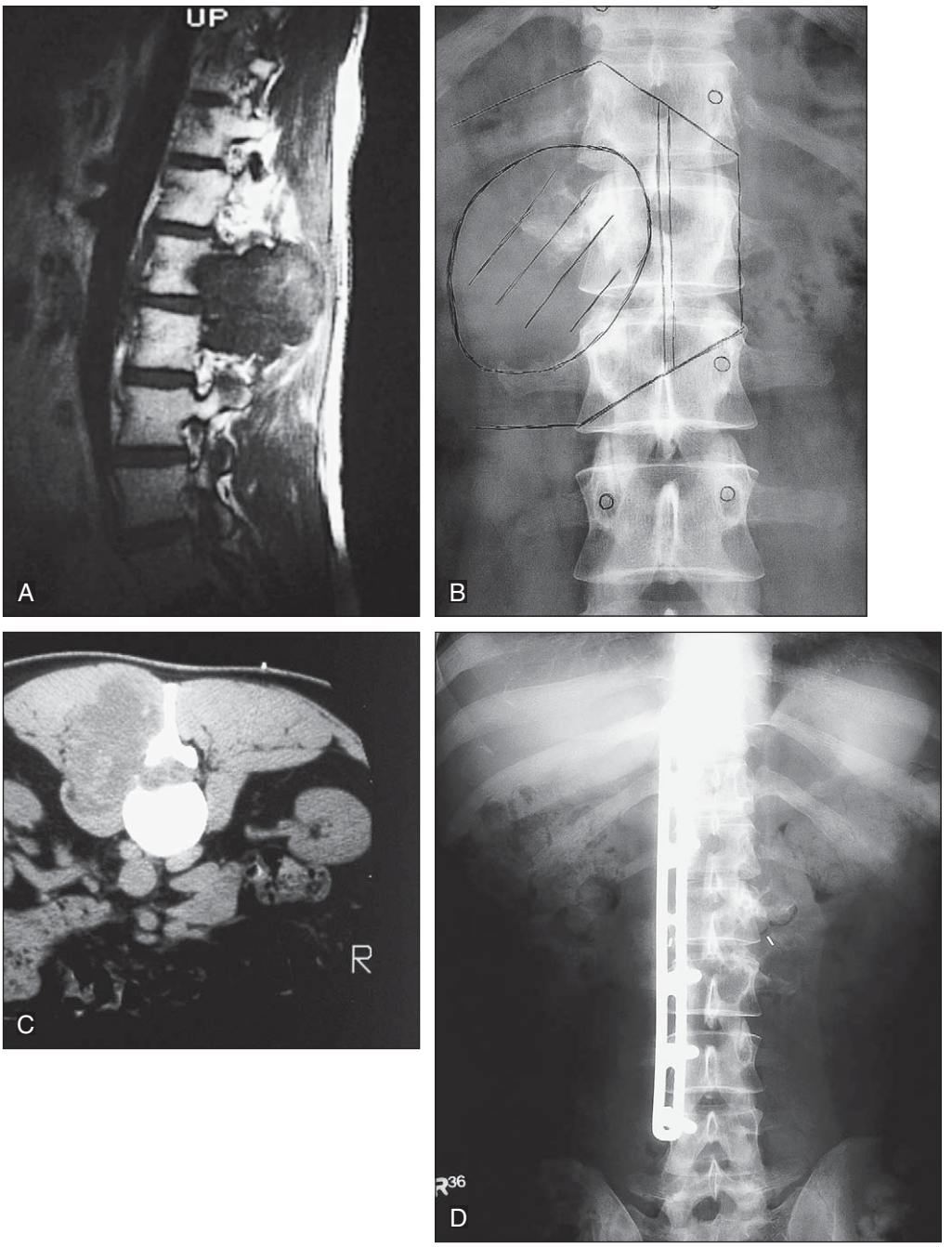


Figure 96-24 • **A,** This 30-year-old male was seen and evaluated 18 months after developing increasing left midlumbar spine pain. Plain films demonstrated the absence of the left transverse process of L1. The T_1-weighted MRI of the spine demonstrated an irregular infiltrative asymmetric lesion involving the left paraspinous musculature and lateral elements of L1 and part of T12 and L2. An open biopsy revealed grade II chondrosarcoma. **B,** Posteroanterior radiograph of the thoracolumbar junction demonstrating the region of the tumor (*crosshatching*) with the area outlined, demonstrating the structures that would require removal to obtain a wide surgical margin. A myelogram demonstrated tumor invading the canal through the left foramen of L1. A two-stage procedure was planned, whereby a right hemilaminectomy of L1 and transverse-oblique laminotomies of T12 and L2 would be performed from the right side posteriorly, followed by instrumentation of the right pedicles of T10, T11, T12, L2, and L3 with variable screw placement instrumentation. **C,** CT scan demonstrating the encroachment of the left L1 foramen and neural canal by tumor displacing the dura to the right. A fat plane can be identified between the tumor and the dura. These findings require the resection of the potentially involved dura with the specimen to complete an en bloc resection with wide margins. **D,** AP x-ray demonstrating the completion of the first stage of a two-stage procedure. The plate was applied to the right pedicles of T10, T11, T12 and L2, L3, and L4. Hemilaminectomies were performed on the right, as well as oblique laminectomies illustrated in **(B)**.

Chondrosarcoma of the Spine

Chondrosarcoma of the spine accounts for approximately 10% of all chondrosarcomas. The patient is usually over the age of 50 years. These tumors should be treated with a surgical resection (Fig. 96-24). Chemotherapy is not indicated. Tumors at the base of the skull are usually small but cannot be completely removed. The use of irradiation, usually administered by proton beam treatments, has proven to be effective.

Primary Ewing's Sarcoma of the Spine

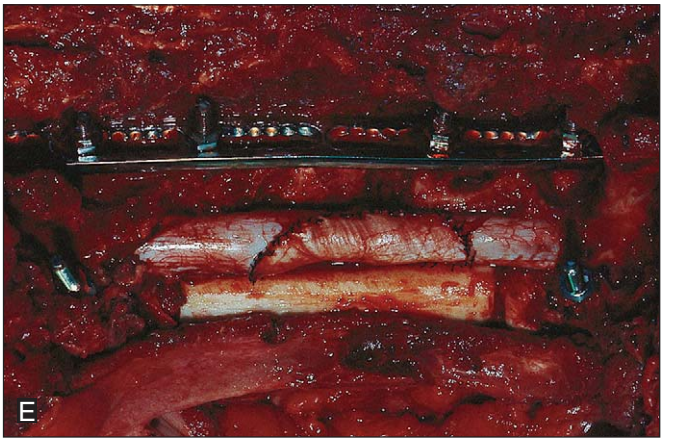
Ewing's sarcoma of the spine is not uncommon, accounting for just under 5% of all cases. These patients are similar to other patients with Ewing's sarcoma. They are treated with adjuvant chemotherapy, but surgery is rarely used for Ewing's sarcoma of the spine. Irradiation is used to treat the primary tumor in almost all cases.

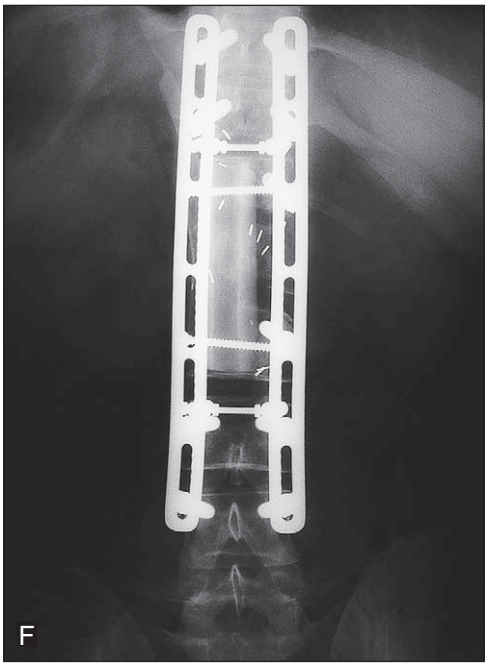
CHORDOMA

Cervical and Sacrococcygeal Chordoma

Embryology

The notochord is a unique tissue that reaches maturity in the 11-mm embryo. In the second gestational month, the notochordal tissue is essentially obliterated (Fig. 96-25). As the developing vertebrae emerge, notochordal tissue nests are displaced peripherally and caudally, leaving behind microscopic foci of notochord tissue adjacent to the vertebral bodies and distally in the body of the sacrum and coccyx.





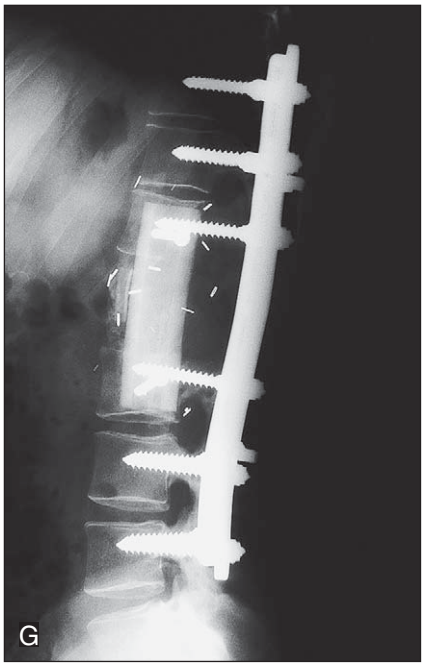


Figure 96-24, cont'd • **E,** Two weeks later, through a thoracoabdominal and communicating posterior midline exposure, the lesion was removed successfully en bloc with wide margins to include the lower oblique one half of T12, L1, and the upper oblique one half of L2 and in continuity with the involved dura of L1. A dural patch was required for repair. This intraoperative photo demonstrates the previously applied first-stage plate at the top with the dural repair beneath. A cylindric full-thickness segment of femoral allograft was used to restore the continuity of the anterior column (below the dura). A vascularized rib graft can be seen below, curving up to about the allograft. **F,** AP x-ray demonstrating the postoperative completed construct with four cross-connectors. The patient was immobilized in a thoracolumbar-sacral orthosis jacket for 1 year and has consistently used abdominal/lumbar support since his procedure. This AP x-ray was taken at the patient's 10-year reevaluation. **G,** Lateral x-ray also demonstrating a stable construct at 10 years without hardware failure or allograft resorption. The patient remains continuously disease free at 12 years.

It is from these aberrant tissue nests in the spheno-occipital and sacrococcygeal regions that the malignant neoplasm chordoma arises.

Incidence and Distribution

Chordoma is a rare tumor that arises anteriorly in the body of the vertebra; fewer than 1500 cases have been reported. The overall incidence is not well established because many chordomas are not reported. Two independent Scandinavian studies, however, estimated an annual incidence of approximately 0.5 per million population.[385,386]

The literature indicates that 50% of chordomas arise in the sacrum, 35% in the spheno-occipital region, and the remaining 15% in the vertebrae.[387–391] Vertebral lesions suggest that the tumor arises most often in the cervical spine, less often in the thoracic spine, and least often in the lumbar spine. The spheno-occipital variety usually occurs in individuals between the ages of 10 and 40 years, while those who develop sacrococcygeal lesions are generally over the age of 40. The male-to-female ratio is 2 : 1.[392]

Pathologic Features

Chordomas arise from the vertebral body. In the sacrum, the most common location, they are almost always central and extend anterior to the sacrum. They often invade the spinal canal (Fig. 96-26). Microscopically, the conventional subtype (the most common) consists of polyhedral cells with distinct cytoplasmic membranes and intracytoplasmic vacuoles. These "physaliferous" cells can be extraordinarily large.[393] Other tumors demonstrate chondroid and fibrous differentiation. Occasionally, an association with secondary MFH has been reported.[367,394–397] Chordomas are immunoreactive with cytokeratin, epithelial membrane antigen, S-100 protein, vimentin, and neurofilaments.[398–402] These characteristics are helpful in distinguishing chordoma from chondrosarcoma, MFH of bone, and metastatic mucin-producing adenocarcinoma.

Vertebral Chordoma

Clinical Manifestations

The clinical features and management of vertebral and sacral chordomas are sufficiently different that each will be described separately. Vertebral lesions are most often associated with ill-defined symptoms, usually occurring in younger middle-aged patients. The pain and discomfort is characteristically associated with either radicular pain or a disturbance of balance or gait. It is not uncommon for symptoms to be present for more than 1 year.[403] Thoracic and cervical vertebral involvement can be associated with the onset of a cough or dysphagia.[404] Because the tumors project anteriorly, they are rarely if ever palpable. Local tenderness could be elicited by percussion of cervical or lumbar lesions, while bilateral rib compression might identify the thoracic region of interest.

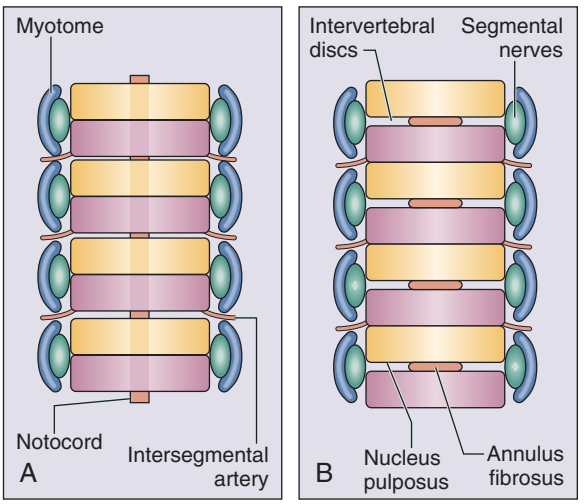


Figure 96-25 • **A,** The formation of less dense cephalic and more dense caudal sclerotoma surrounding the notochord at 4 weeks. **B,** At 11 weeks' gestation, the precartilaginous vertebral bodies have formed by the upper and lower halves of two successive sclerotomas, while the notochord has degenerated except in the region of the intervertebral disk.

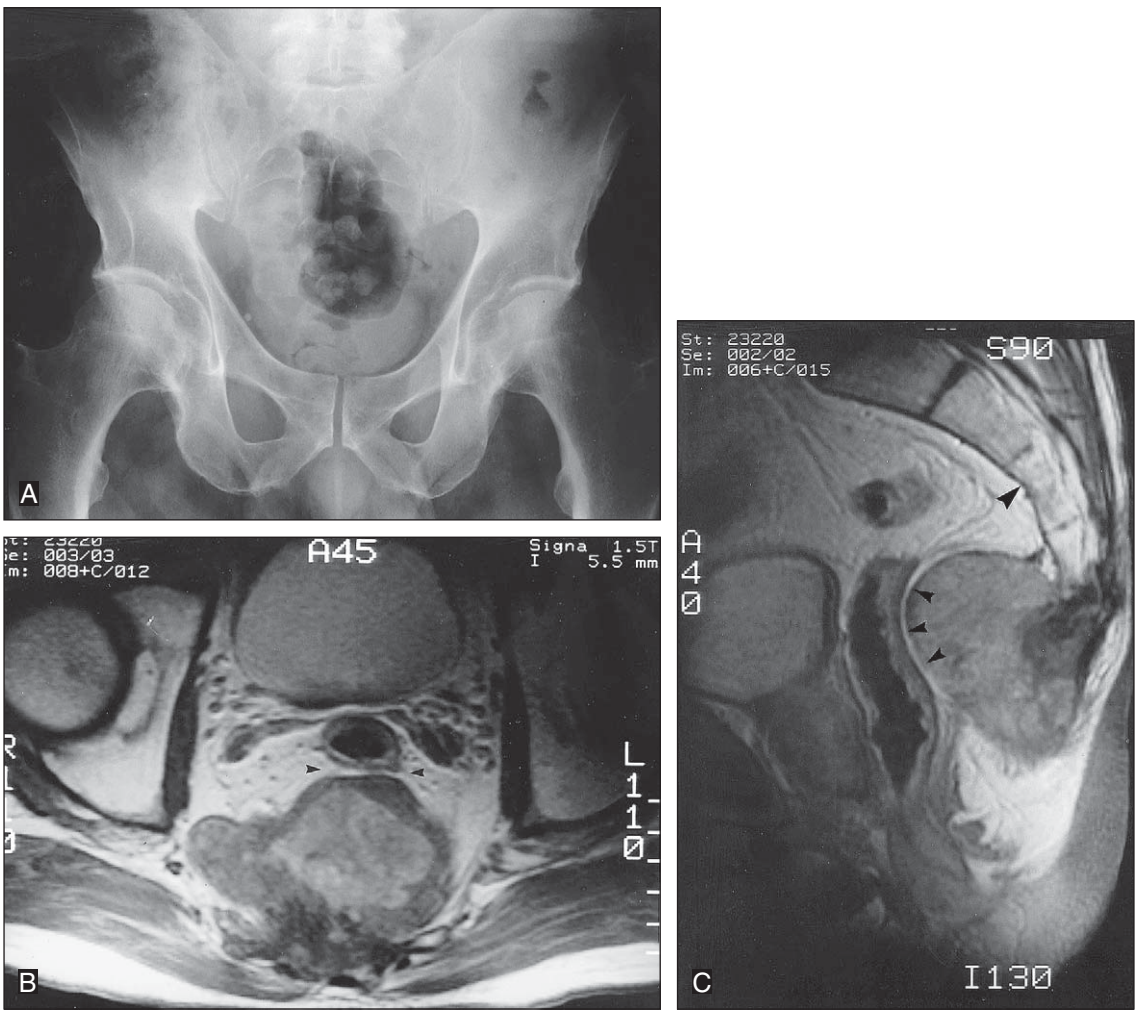


Figure 96-26 • **A,** AP radiograph of the pelvis of a 56-year-old male with a 3-year history of ill-defined low back and buttock pain. No rectal examination was reported to have been done until the patient was evaluated for bowel complaints. **B,** MRI of the pelvis demonstrated a mass projecting from the anterior lower (S3 and below) sacral elements. This axial view of the biopsy-proven chordoma demonstrates the preserved fat plane between the tumor and rectum (*arrowheads*). **C,** Sagittal T_1-weighted image clearly demonstrates the region of anterior sacral involvement and the preserved fat plane between the tumor and the rectum (*small arrowheads*). The *large arrowhead* indicates the location of the sacral amputation (S3) used to potentially cure this patient, who is currently 2 years free of disease.

Radiographic Manifestations

Radiographically, chordomas usually originate in the vertebral body as a destructive, well-marginated lesion. Characteristically, smaller lesions radiographically preserve the adjacent discs, while larger lesions involving more than one vertebral body can destroy the intervening disks. The often-associated soft-tissue mass projects anteriorly, elevating the anterior longitudinal ligament. When originating in the thoracic vertebrae, chordomas can present asymptomatically as a posterior mediastinal tumor.

MRI with and without contrast is the single most valuable study when correlated with the initial plain films. CT and MRI are comparable in detecting the neoplasm, but MRI is considerably better in delineating the full epidural and soft-tissue extent of the tumor.

Biopsy

The biopsy must be planned carefully if a potentially curative procedure is possible. Injudicious laminectomy in a neurologically negative patient followed by open biopsy unnecessarily contaminates the dura and surrounding structures and should be reserved as a last resort only. Fine-needle posterior CT-guided aspiration biopsy is the technique of choice for almost all spinal and sacral lesions. If the fine-needle aspiration does not provide a diagnosis, then a closed or limited open transpedicular Craig needle biopsy using fluoroscopic control should be considered.[405] Only after failure of these two techniques should an open decompression laminectomy/biopsy be performed.

Local Control

A "wide" margin is required for local control. Intralesional excision leads to locally recurrent disease. The majority of patients who are managed surgically require a one-stage posterior approach that includes laminectomy followed by a more complete removal of the tumor.[392,399,401,406–408] Many staged, well-planned procedures resulting in wide, clean-contaminated margins develop a local recurrence.[403,409,410] Rarely can a complete, uncontaminated resection be done on a chordoma. In the cervical, thoracic, or lumbar spine, adjuvant irradiation has been used and can decrease the incidence of local recurrence.

Sacrococcygeal Chordoma

Clinical Manifestations

The typical clinical history for a patient with a sacrococcygeal chordoma is a long history (approximately 12 months) of low back pain with the diagnosis being made by the first person to do a rectal examination. Sacrococcygeal lesions manifest most commonly with low back and perineal pain rather than with the typical radicular pain associated with intervertebral disc herniation. Often, the patient's modesty prevents disclosure of perineal symptoms until late in the disease process.[411] Also, because of the contribution of both the right and left sacral nerve roots to bladder and bowel sphincter function, symptoms of incontinence are delayed and sometimes do not present at all in asymmetric lesions.[412]

Physical Examination

The expansile portion of a chordoma characteristically projects anteriorly, deviating the presacral fascia and creating a smooth, minimally tender mass anterior to the sacrum that is easily palpated on rectal examination. Most patients will have no other abnormal physical findings.

Radiographic Evaluation

Sacrococcygeal chordomas are difficult to see on a plain radiograph. An MRI is the examination of choice, and the extent of the lesion can be accurately seen on the MRI. When a chordoma is suspected, the patient should also have a whole-body ^{99m}Tc bone scan and a CT of the chest.

Surgical Management

The surgical principles outlined and developed by Stener,[413] when used appropriately and by skilled surgeons, result reliably in a wide amputation of the sacrum. The resection is usually done through a midline posterior approach, and it is recommended that a biopsy be done in line with this incision. As rule, the tumors that do not extend proximal to the exit site of the S2 nerve roots can be removed with a single posterior operation. Those that extend more proximally should be approached anteriorly as well to clear the soft tissues off the most proximal extent of the tumor. This area cannot be reached from the posterior approach. These procedures are technically demanding and should not be undertaken by the unprepared. Even in the best of hands, however, 5% to 40% of patients will develop distant disease.

Neurologic dysfunction depends on the nerve roots that are removed. Clinically noticeable weakness in the lower extremities is unusual unless one of the L5 nerve roots is removed. If one L3 nerve root is salvaged, the patients usually have sufficient control of their bowel and bladder not to need catheterization or a special bowel regimen. Compromising the surgical margin to salvage nerve roots usually leads to a local recurrence, eventual loss of the nerve root, and rarely local control.

SUMMARY

The sarcomas of bone and chordoma represent a heterogeneous group of tumors that arise in somewhat predictable locations throughout the entire skeleton. Diagnosis and surgical planning have improved significantly with the addition of physician-monitored MRI and the other associated multiaxial display imaging techniques. Also, the addition of sophisticated immunohistochemistry and cytogenetic techniques has made differentiation of similar-appearing lesions easier. The increasing complexity of the management of these patients, including primary chemotherapy and limb- and function-preserving surgery, requires a dedicated team of nurses, technicians, and physicians working to provide and implement the therapeutic modalities that are necessary to cure previously incurable diseases.

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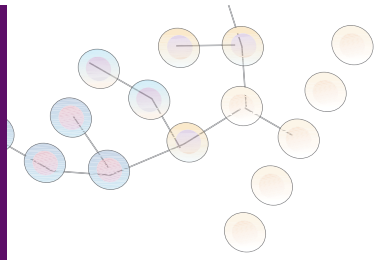
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97 Sarcomas of Soft Tissue

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SUMMARY OF KEY POINTS

Incidence and Epidemiology
- 8300 new cases annually in the United States
- No specific etiologic agent identifiable in the majority of cases
- Occasional cases related to previous radiation, chemical exposure, alkylating chemotherapeutic agents, or chronic lymphedema
- Genetic conditions related to soft-tissue sarcoma include neurofibromatosis, tuberous sclerosis, basal cell nevus syndrome, Gardner's syndrome, and Li-Fraumeni syndrome.

Diagnosis and Evaluation of Extent of Disease
- Core-needle biopsy (large lesions) or excisional biopsy (small lesions)
- Pathologic review of histologic subtype, grade, and assessment of margins (excisional biopsies)
- Magnetic resonance imaging or computed tomography (CT) of primary site
- Chest x-ray for low-grade tumors and high-grade T1 lesions, chest CT for high-grade T2 tumors

Prognostic Factors
- High-grade histology, deep location, and T2 tumor size are independent adverse prognostic factors for distant metastasis and survival.
- Presentation with recurrent disease and positive surgical margin (gross or microscopic) are independent adverse prognostic factors for local recurrence.
- Individual patient prognosis can be predicted from a handheld computer-based nomogram.

Staging Systems
- The American Joint Committee on Cancer (International Union Against Cancer) system employs criteria that include grade, size, and location relative to the investing muscular fascia, nodal status, and distant metastases.

Primary Therapy
- Surgical resection with an adequate margin of normal tissue; for extremity lesions, a limb-sparing approach is possible in more than 90% of patients and offers survival comparable to amputation without the associated morbidity.
- For most patients, local control is improved with preoperative or postoperative radiotherapy.
- The role of chemotherapy for high-risk patients remains controversial, but chemotherapy is used at several major centers for high-risk patients, especially for extremity tumors and, when possible, preoperatively.

Recurrent Disease
- Local recurrence rates vary depending on the anatomic site of the primary and the adequacy of local therapy; for extremity lesions, approximately 20% of patients develop locally recurrent disease.
- Chemotherapy with selective use of metastasectomy is the mainstay of therapy for patients with metastatic disease.
- For the small subset of patients who develop isolated (solitary) pulmonary metastases, 20% to 50% 3-year survival rates have been reported with pulmonary metastasectomy.

INTRODUCTION

STSs comprise a group of relatively rare, anatomically and histologically diverse neoplasms. These tumors share a common embryologic origin, arising primarily from tissues derived from the mesodermal or ectodermal germ layers, in contradistinction to carcinomas that arise from the endodermal germ layer. Although the somatic soft tissues account for as much as 75% of total body weight, neoplasms of the soft tissues are comparatively rare, accounting for 1% of adult malignancies and 15% of pediatric malignancies. The relative rarity of these tumors, coupled with the histologic diversity of tumors, has led to studies that often lump diverse tumors (STSs) into a single study group, making it difficult to develop specific therapies for specific tumor types, especially in adult STSs. The annual incidence of STSs in the United States is about 8300 new cases, comparable to the incidence of testicular cancer.[1] However, an estimated 3900 patients die annually of soft-tissue sarcoma—a rate nearly 10-fold greater than is seen with testicular cancer—emphasizing the comparatively high overall mortality rate that is seen with this type of tumor.

The first portion of this chapter reviews the available literature on the evaluation and treatment of extremity sarcomas (which account for 50% of all lesions). Other specific anatomic sites are reviewed at the end of the chapter.

ETIOLOGY AND EPIDEMIOLOGY

Environmental Factors

No specific etiologic agent is identified in the majority of patients with soft-tissue sarcoma (STS). There are a number of recognized associations between environmental factors and the subsequent

Table 97-1 Soft-Tissue Sarcoma: Predisposing Environmental Factors

Factor	Agent	Patient Population	Comment
Radiotherapy	Orthovoltage and megavoltage radiation	Therapeutic radiation patients	Most commonly osteosarcoma; dose-response relationship
Chemotherapy	Alkylating agents: cyclophosphamide, melphalan, procarbazine, nitrosourea, and chlorambucil	Pediatric cancer patients	Relative risk of bone sarcoma increased with cumulative drug exposure
Chemical exposure	Phenoxyacetic acids: 2,4-dichlorophenoxyacetic acid (2,4-D); 2,4,5 trichlorophenoxy acetic acid (2,4,5-T); 2 methyl-4 chlorophenoxyacetic acid (MCPA)	Forestry and agricultural workers	Phenoxy herbicide and defoliant exposure
	2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD); dioxin	Vietnam veterans	No clear link demonstrable for dioxin (Agent Orange)
	Chlorophenols	Sawmill workers	
	Thorotrast	Diagnostic x-ray patients	Hepatic angiosarcoma
	Vinyl chloride	Vinyl chloride workers	Hepatic angiosarcoma
	Arsenic	Vineyard workers	Hepatic angiosarcoma after exposure to arsenical herbicides
Chronic lymphedema		Postsurgery patients Postradiation patients Patients with congenital Lymphadema or filariasis	Stewart-Treves syndrome (lymphangiosarcoma)

development of sarcoma; these are summarized in Table 97-1. The development of sarcoma has been reported after the use of ionizing radiation for the treatment of lymphoma;[2] solid tumors of the head and neck,[3] breast,[4,5] gynecologic organs, and skin; and benign conditions including endometriosis, tuberculous arthritis,[6] and benign thymic enlargement. The vast majority of radiation-associated sarcomas are high-grade lesions (87%), and the predominant histology is osteosarcoma;[7,8] this is a historical observation before the era of megavoltage radiation that is possibly linked to the greater absorption of orthovoltage radiation by bone as compared to soft tissue. Malignant fibrous histiocytoma, angiosarcoma, and other mesenchymal subtypes have also been reported after therapeutic radiation.[7-9] By criteria that were described initially by Cahan and colleagues,[10] radiation-induced sarcomas arise no sooner than 4 years after the therapeutic radiation[11,12] and often arise decades later. More recently, however, a shorter 2-year period after diagnosis has been utilized to define radiation-related disease. Contrary to early theories, recent studies have suggested that both orthovoltage and megavoltage treatments are sarcomagenic[8,13] at doses of 8.8 to 70 Gy. In a carefully conducted case-control analysis, the Late Effects Study Group found 64 cases of osteosarcoma in 9170 patients who had survived more than 2 years after the diagnosis of a variety of cancers. A clear dose-response relationship was found between the radiation dose and the subsequent development of osteosarcoma, with a relative risk ranging from 0.6 in patients who received less than 10 Gy to 38.3 in those who received more than 60 Gy.[14] A complete understanding of the underlying biology of radiation-induced malignancy remains elusive. Host-related factors (especially young age) and treatment (especially its intensity) both seem to play a role in a complex relationship.[15] Underlying genetic susceptibility is also important and is governed by factors such as deletion or mutation of tumor suppresser and DNA repair genes, which likely means that subgroups of the populations have more vastly enhanced risk than had previously been anticipated while others are at lower risk than was appreciated in the past. In addition it is highly probable that the greater intensity of multimodality treatments for cancer that have been introduced over recent years with the goal of improving cancer control and survival are going to result in an increase in the rate of radiation-induced malignancies. Of the latter, the overwhelmingly at-risk tumor is sarcoma, especially if one considers its baseline incidence rates.[15]

Sarcomas have also been associated with exposure to various chemical agents. A number of conflicting reports have emerged that suggest a relationship between occupational exposure to phenoxyacetic acids (found in some herbicides) and chlorophenols (found in some wood preservatives). Several studies from Sweden have established a link between phenoxy herbicide exposure in forestry workers and the subsequent development of sarcoma.[16–19] However, additional investigations in the United States, New Zealand, and Finland have not confirmed this relationship.[20–22] Similarly, there has been no demonstrable increase in the risk of sarcoma in Vietnam veterans exposed to Agent Orange (dioxin or TCDD [2,3,7,8-tetrachlorodibenzo-p-dioxin]).[23] Hepatic angiosarcomas have been associated with exposure to a number of compounds, including Thorotrast (a colloidal suspension of thorium dioxide that was formerly used as an intravenous contrast agent in radiologic imaging procedures),[24–26] vinyl chloride,[27–29] and arsenic.[30,31]

Recent studies have suggested a relationship between exposure to alkylating chemotherapeutic agents and the subsequent development of sarcomas. Osteosarcomas have been reported after cyclophosphamide treatment for pediatric acute lymphoblastic leukemia.[32,33] In the recent report from the Late Effects Study Group, prior chemotherapy, particularly with melphalan, procarbazine, nitrosoureas, or chlorambucil, was found to be an independent risk factor for the development of sarcoma.[14] The relative risk of sarcoma increased with cumulative drug exposure.

Chronic lymphedema can be a factor in the development of lymphangiosarcoma. These neoplasms have been noted to arise in the chronically lymphedematous arms of women who were treated for breast cancer with radical mastectomy (Stewart-Treves syndrome).[34,35] Lower-extremity lymphangiosarcomas have also been observed in patients with congenital lymphedema or filariasis complicated by chronic lymphedema.[36]

A recent history of trauma is often elicited from sarcoma patients, particularly those with extremity sarcoma. Usually, the interval between the traumatic event and the diagnosis of sarcoma is short, making a causal relationship unlikely. Some reports have suggested, however, that chronic inflammatory processes may be a risk factor for sarcoma. Shrapnel, bullets, intramuscular iron injections, and foreign body implants have been implicated.[37]

Genetic Predisposition

Germline mutations may play an important role in the development of STSs (Table 97-2). These genetic changes are identified with or similar to the genetic changes that are seen in corresponding sporadic sarcomas (Table 97-3). Mechanistically, the proteins encoded by the altered genes are involved in maintenance of the genome through DNA repair and the cell cycle.

The epidemiologic relationship between the development of STS and inherited syndromes associated with a predisposition to neoplasia (e.g., neurofibromatosis and Li-Fraumeni syndrome) has been appreciated for more than two decades.[38,39] For example, patients with neurofibromatosis have a 7% to 10% lifetime risk of developing a malignant peripheral nerve sheath tumor (MPNST).[40] A sudden increase in the size of any neurofibroma suggests malignant transformation.[41,42] The mechanisms underlying the transformation from a benign neurofibroma to MPNST are not completely understood.

However, loss-of-function mutations in the NF1 gene, which are found in patients with neurofibromatosis, result in activation of the RAS signaling pathway, a well-known mechanism that has been identified in a variety of cancers.[43] It has been observed that secondary MPNSTs (arising from a prior neurofibroma) have deletions and mutations of 17p (particularly 17p12–17p13.1) at the region of the TP53 tumor suppressor gene.[44–46] Thus, it has been postulated that an initial alteration in the NF1 gene contributes to the formation of a benign neurofibroma through activation of the RAS pathway and that secondary mutations in the TP53 gene allow the transformation into MPNST. Since mutations in TP53 lead to an inability to control DNA damage via the cell cycle, they also enable rapid accumulation of other mutations, which encode mutant proteins that undoubtedly play an important role in sarcomagenesis.

The Li-Fraumeni syndrome was identified when relatives of pediatric STS patients were noted to have an increased frequency of diverse and often multiple primary cancers.[38,47] The neoplasms that were noted in relatives included some STSs, premenopausal breast cancers, brain tumors, adrenocortical carcinomas, leukemias, and sometimes germ cell tumors.[48] Follow-up of Li-Fraumeni kindreds over two decades has revealed that the majority of individuals develop cancer at young ages, with 79% of those affected younger than 45 years at the time of diagnosis of malignancy.[49] The observed cancer distribution in families is believed to fit a rare autosomal dominant mode of genetic transmission with high penetrance.[50] Recent molecular genetic studies have identified germline TP53 mutations in the majority of patients with Li-Fraumeni syndrome.[51] Germline mutations in CHK2, another component of the cell cycle checkpoint machinery encoded by a gene located on 22q11, are responsible for another subgroup of patients with Li-Fraumeni syndrome.[52]

Pediatric patients with familial retinoblastoma have a 13q chromosomal deletion[53] and an increased incidence of osteosarcoma and other neoplasms, including STS.[14,54,55] The retinoblastoma (Rb1) protein is expressed ubiquitously in normal cells and is a well-known tumor suppressor, involved in maintaining the integrity of the genome through control of the cell cycle. Interestingly, not only is the Rb1 gene that is mutated in osteosarcomas associated with retinoblastoma, but abnormality or absence of the Rb1 gene product has also been observed in multiple other malignancies, including sporadic osteosarcomas, breast cancer,[56] small cell lung cancer,[57] and STSs.[58]

Familial infiltrative fibromatosis, also known as hereditary desmoid disease, is caused by germline mutations in the APC gene.[59–61] Patients with this syndrome develop desmoid fibromatosis at a younger age than do patients with sporadic desmoids. Patients with familial adenomatous polyposis also harbor germline mutations in the APC gene; this helps to explain Gardner's syndrome, which is characterized by the development of desmoid tumors as well as polyposis.[62] The APC gene is involved in the WNT or wingless cell-signaling pathway. One of the normal functions of the APC protein is to bind β-catenin.[63] Thus, loss-of-function mutations of APC result in the activation of transcription of oncogenes by β-catenin. Mutations in APC and β-catenin are also identified in sporadic desmoid fibromatosis.[64–66]

Rhabdoid predisposition syndrome is due to inactivating germline mutations in the INI1 gene.[67] Patients with this syndrome develop one or more extrarenal and/or renal rhabdoid tumors. INI1 is a member of the SWI/SNF protein complex, which controls gene expression globally through its ability to alter chromatin structure.[68] Thus loss of INI1 gene expression results in other changes in gene expression, specifically activation of oncogenes. Rhabdoid tumors have loss-of-function mutations in both copies of the INI1 gene.[69]

Werner's syndrome is a rare genetic instability syndrome caused by mutations in the WRN gene.[70,71] Affected patients age prematurely and are at greatly increased risk for a variety of cancers, including STSs. The WRN gene encodes a protein believed to be involved in DNA repair, and loss of WRN protein function leads to genetic instability, accumulation of genetic mutations, and ultimately predisposition to rapid aging and cancer.

Germline mutations in the KIT oncogene are found in patients with familial gastrointestinal stromal tumor syndrome.[72,73] Activating KIT mutations are also identified in approximately 90% of sporadic gastrointestinal stromal tumors (GISTs).[74] Patients with the familial

Table 97-2 Germline Mutations Associated with Soft-Tissue Sarcomas

Syndrome	Inheritance Pattern	Locus	Gene	Associated Soft-Tissue Sarcomas
Familial gastrointestinal stromal tumor syndrome	AD	4q12	KIT	Gastrointestinal stromal tumor
Familial infiltrative fibromatosis	AD	5q21	*APC*	Desmoid fibromatosis
Li-Fraumeni syndrome	AD	17p13	*TP53*	Multiple types
		22q11	*CHK2*	
Neurofibromatosis type I (von Recklinghausen's disease)	AD	17q11	*NFI*	Malignant peripheral nerve sheath tumors
Retinoblastoma	AD	13q14	*RBI*	Multiple types
Rhabdoid predisposition syndrome	AD	22q11	*SNF5/INII*	Malignant rhabdoid tumors
Werner's syndrome	AR	8p11–12	*WRN*	Multiple types

AD, autosomal dominant; AR, autosomal recessive.

Table 97-3 Molecular Alterations Identified in Sarcoma

Tumor Type	Characteristic Cytogenetic Events	Molecular Events	Frequency (%)	Diagnostic Utility?
Alveolar soft part sarcoma	t(X;17)(p 11;q25)	*ASPL-TFE3* fusion	>90	Yes
Extraskeletal myxoid chrondrosarcoma	t(9;22)(q22;q12)	*EWS-NR4A3* fusion	>75	Yes
	t(9;17)(q22;q11)	*TAF2N-NR4A3* fusion	<10	Yes
	t(9;15)(q22;q21)	*TCF12-NR4A3* fusion	<10	Yes
Clear cell sarcoma	t(12;22)(q13;q12)	*EWS-ATFI* fusion	>75	Yes
Desmoplastic small round cell tumor	t(11;22)(q13;q12)	*EWS-WTI* fusion	>75	Yes
Dermatofibrosarcoma protuberans	Ring form of chromosomes 17 and 22	*COLIAI-PDGFB* fusion	>75	Yes
	t(17;22)(q21;q13)	*COLIAI-PDGFB* fusion	10	Yes
Ewing's sarcoma/peripheral primitive neuroectodermal tumor	t(11;12)(q24;q12)	*EWS-FLII* fusion	>80	Yes
	t(21;22)(q12;q12)	*EWS-ERG* fusion	5–10	Yes
	t(2;22)(q33;q12)	*EWS-FEV* fusion	<5	Yes
	t(7;22)(p22;q12)	*EWS-ETVI* fusion	<5	Yes
	t(17;22)(q12;q12)	*EWS-EIAF* fusion	<5	Yes
	inv(22)(q12;q12)	*EWS-ZSG* fusion	<5	Yes
Fibrosarcoma, infantile	t(12;15)(q13;q26)	*ETV6-NTRK3* fusion	>75	Yes
	Trisomies 8, 11, 17 and 20		>75	Yes
Gastrointestinal stromal tumor	Monosomies 14 and 22		>75	Yes
	Deletion of 1p		>25	No
			>90	Yes
Inflammatory myofibroblastiv tumor	2p23 rearrangement	*KIT* mutation	50	Yes
Leiomyosarcoma	Deletion of 1p	*ALK* fusion genes	>50	No
Liposarcoma				
Well-differentiated	Ring form of chromosome 12		>75	Yes
Myxoid/round cell	t(12;16)(q13;p11)	*TLS-CHOP* fusion	>75	Yes
Pleomorphic	Complex	*EWS-CHOP* fusion	<5	Yes
Malignant fibrous histiocytoma	Complex		>90	No
Malignant peripheral nerve sheath tumor	Complex		>90	No
Myxofibrosarcoma (myxoid malignant fibrous histiocytoma)	Ring form of chromosome 12		?	?
Neuroblastoma				
Good prognosis	Hyperdiploid, no 1p deletion		90	Yes
Poor prognosis	1p deletion		90	Yes
	Double minute chromosomes	N-*myc* amplification	>25	Yes
Rhabdoid tumor	Deletion of 22q	*INII* inactivation	>90	Yes
Rhabdomyosarcoma				
Alveolar	t(2;13)(q35;q14)	*PAX3-FKHR* fusion	>75	Yes
	T(1;13)(p26;q14), double minutes	*PAX7-FKHR* fusion	10–20	Yes
Embryonal	Trisomies 2q, 8, and 20		>75	Yes
		Loss of heterozygosity at 11p15	>75	Yes
Synovial sarcoma				
Monophasic	t(X;18)(p11;q11)	*SYT-SSXI* or *SYT-*	>90	Yes
Biphasic	t(X;18)(p11;q11)	*SSX2* fusion	>90	Yes
		STY-SSXI fusion		

syndrome develop, to varying degrees, skin hyperpigmentation, urticaria pigmentosa, and cutaneous mast cell disease in addition to one or more GISTs.[75] Activating KIT mutations have been shown to lead to ligand-independent activation of the KIT receptor tyrosine kinase pathway, which results in dysregulated cell growth, and are thought to be the first step in the pathogenesis of GISTs.[72] Interestingly, the identification of the important role of KIT in the pathogenesis of GISTs has led to treatment with imatinib mesylate.[76] A small molecule drug specifically inhibits the KIT pathway (see sections on Prognostic Factors as Therapeutic Targets and Gastrointestinal Stromal Tumors).

Genetics of Sporadic Soft-Tissue Sarcomas

Sarcomas tend to fall into two major subsets. In one group, the tumors are cytogenetically simple and are characterized by near diploid karyotypes with few chromosomal rearrangements, resulting in the formation of fusion proteins. These translocations are highly diagnostic of specific histologic subtypes of STSs. Also included within the cytogenetically simple STSs would be GIST tumors, which are characterized by a specific activating mutation of the c-Kit gene but few other genetic abnormalities.

Chromosomal Rearrangements

A large number of sarcomas have been found to have consistent chromosomal abnormalities (see Table 97-3).[77] These chromosomal rearrangements are important diagnostically, may be important prognostically (see the section on Potential Molecular Prognostic Factors), have shed light on the pathogenesis of sarcomas, and may provide targets for pharmacologic therapy (see the section on treatment of GISTs). Benign soft-tissue neoplasms also harbor chromosomal rearrangements.

Chromosomal translocations are the most common cytogenetic abnormality in soft-tissue neoplasms and are likely responsible for the initiation of tumorigenesis in most cases.[77] Deletions and trisomies have also been reported and are thought to represent secondary changes involved in tumor progression. Deletions tend to represent loss of tumor suppressor genes, whereas trisomies indicate the presence of an oncogene. Although we know a lot about the primary tumorigenic events in many sarcomas, defining the secondary changes has been much more problematic and is an area of intense study.

Cloning and molecular analysis of the various genetic aberrations that characterize different sarcomas have revealed the different pathogenetic mechanisms that underlie these tumors. Translocations typically create chimeric transcription factors or growth factors that result in deregulation of transcription or growth control. A typical example of a chimeric transcription factor is the PAX3-FKHR fusion protein, which has been shown to activate a complex myogenic transcriptional program when the protein is expressed in a fibroblast cell line.[78] Infantile fibrosarcoma is characterized by a translocation involving chromosomes 12 and 15 that encodes a chimeric ETV6-NTRK3 constitutively activated growth factor receptor.[79] Other oncogenic proteins appear to act by a mechanism that remodels chromatin structure, which is known to have a profound influence on gene expression (e.g., INI1 mutations in rhabdoid tumors).[69]

Specific chromosomal rearrangements are very useful in the diagnosis of STSs. Beyond the obvious benefit of providing further objective proof of a diagnosis in morphologically typical cases, the detection of chromosomal aberrations may facilitate the diagnosis of lesions that are difficult to characterize by standard histopathologic, ultrastructural, and immunohistochemical techniques.[80,81] For example, the presence of the translocation t(X;18)(p11;q11) has been used to confirm the diagnosis of synovial sarcoma in poorly differentiated cases that were diagnostically very challenging.[82–84] Similarly, the finding of the characteristic translocation t(11;22)(q24;q12) in a small round blue cell tumor supports the diagnosis of Ewing's sarcoma/primitive neuroectodermal tumor (PNET).[85]

Translocations can be identified by cytogenetic analysis, fluorescence in situ hybridization, or reverse transcriptase polymerase chain reaction. A detailed description of these techniques is beyond the scope of this chapter, but each technique has its advantages and disadvantages. Cytogenetic analysis requires fresh (living) tissue, since the cells need to be cultured before karyotypic analysis. This technique is becoming more widely available than before, owing to the availability of overnight transport of biologic specimens and for-profit core facilities. Fluorescence in situ hybridization is a technologically sophisticated technique that does not require fresh or frozen tissue. Fluorescence in situ hybridization is easier to perform on cytogenetic cultures or frozen tissue, however, so these are still preferable to paraffin-embedded material. Reverse transcriptase polymerase chain reaction is an extremely sensitive technique that can be performed on fresh, frozen, or paraffin-embedded tissues. The major drawback of reverse transcriptase polymerase chain reaction is the relatively high false-positive rate, which results from its sensitiveness. Meticulous care is required to prevent problems from contamination.

Although reverse transcriptase polymerase chain reaction can be performed on paraffin-embedded tissue, it is preferable to perform the analysis on fresh or frozen tissue. Since all of these techniques either require or are easier to perform on fresh or frozen tissue, it is advisable to freeze and store a portion of any suspected sarcoma or poorly differentiated neoplasm for potential molecular analysis.

Many sarcomas are characterized by several different translocations, some of which are mutually exclusive (see Table 97-3). For instance, alveolar rhabdomyosarcoma is characterized by a translocation involving chromosomes 2 and 13, which results in fusion of the PAX3 and FKHR genes, or by a translocation involving chromosomes 1 and 13, which results in fusion of the PAX7 and FKHR genes.[86–89] Sarcomas within a subtype may also have differences in the specific exons that are involved in each of these different translocations. It has been proposed that this heterogeneity may result in differences in prognosis (see section on Potential Molecular Prognostic Factors). For example, Ewing's sarcoma/PNET and synovial sarcoma possess genetic variations that have been suggested to have prognostic significance.[90–93] Future research might establish whether cytogenetic and molecular factors can be used as a basis for therapeutic decisions and the prediction and evaluation of response to treatment.

The identification of genetic alterations with high specificity for different sarcomas will also identify specific therapeutic targets. This has already resulted in the successful treatment of two different sarcomas: GISTs and dermatofibrosarcoma protuberans (DFSP).[76,94] About 90% of GISTs harbor activating mutations in the KIT oncogene, which result in ligand-independent activation of the KIT receptor tyrosine kinase pathway.[74] Imatinib mesylate, a small molecule drug that is administered orally and inhibits the KIT pathway, has been shown to be very efficacious in the treatment of GIST (see the section on investigational new drugs in the Chemotherapy section). DFSP is characterized by translocations involving the COL1A1 and PDGF-β genes, which result in activation of the platelet-derived growth factor-β PDGF-β pathway. Imatinib mesylate is also active against the PDGF-β pathway and has been shown to be effective in the treatment of a small number of DFSPs.

It is noteworthy to mention two common benign soft-tissue tumors—leiomyomas and lipomas—that have a high frequency of chromosomal rearrangements of chromosome 12q that involves the high-mobility protein group gene HMGIC.[95] These translocations are not seen in the corresponding leiomyosarcomas or liposarcomas, indicating that in these tumors, the benign form is not a precursor of the malignant counterpart.

Sarcomas with Complex Karyotypes

A second major subset of STSs is characterized by aneuploidy and the lack of specific fusion genes. This group of sarcomas includes

Table 97-4 Sarcomas with Complex Karyotypes

Type of Sarcoma	Resembles
Fibrosarcoma (other than congenital)	Fibrous tissue
Leiomysarcoma	Smooth muscle
Malignant fibrous histiocytoma	Poorly differentiated
Osteosarcoma	Bone
Chondrosarcoma (types other than extraskeletal myxoid)	Cartilage
Liposarcoma (types other than myxoid)	Fat
Embryonal rhabdomyosarcoma	Skeletal muscle
Malignant peripheral nerve sheath tumor*	Nerve sheath
Angiosarcoma	Blood vessels

*Some have NF1 mutations.

such tumors as leiomyosarcomas, MPNST, and fibrosarcomas (see Tables 97-3 and 97-4). These tumors tend to occur in the older age group and appear to have a relatively high frequency of mutations in the p53 and RB signaling pathways.[96,97] These tumors are characterized by chromosomal gains and losses that presumably target tumor suppressor genes (in the event of losses) and oncogenes (in the event of gains). Currently, the best-characterized targets of amplifications are the cell cycle regulatory genes CDK4 and HDM2, but others remain to be identified and remain a current challenge in the field. Thus, it appears that alterations disrupting chromosomal mechanics and DNA repair can lead to sarcomagenesis.

PATHOLOGY

STSs have been described at virtually all anatomic sites. The anatomic sites and site-specific histologic subtypes of 4207 sarcomas treated at a single referral institution are outlined in Figure 97-1. Approximately half of all STSs occur in the extremities (lower: 34%; upper: 14%), where the most common histopathologic subtypes are well-differentiated, myxoid, and round cell liposarcoma (28%) and malignant fibrous histiocytoma (pleomorphic undifferentiated sarcoma) (24%). Retroperitoneal sarcomas make up 15% of all STSs, well-differentiated or dedifferentiated liposarcoma being the predominant histologic subtype (42%). The visceral sarcomas make up an additional 14%, while the head and neck sarcomas make up approximately 4%.

Classification

In broad terms, sarcomas can be classified into neoplasms that arise in bone and those that arise from the soft tissues. However, even this seemingly simple distinction is fraught with difficulty, as is illustrated by Ewing's sarcomas. These tumors often arise in close association with bone and are often classified as bone sarcomas. However, it is now clear that these tumors can also arise in soft tissues, and it is

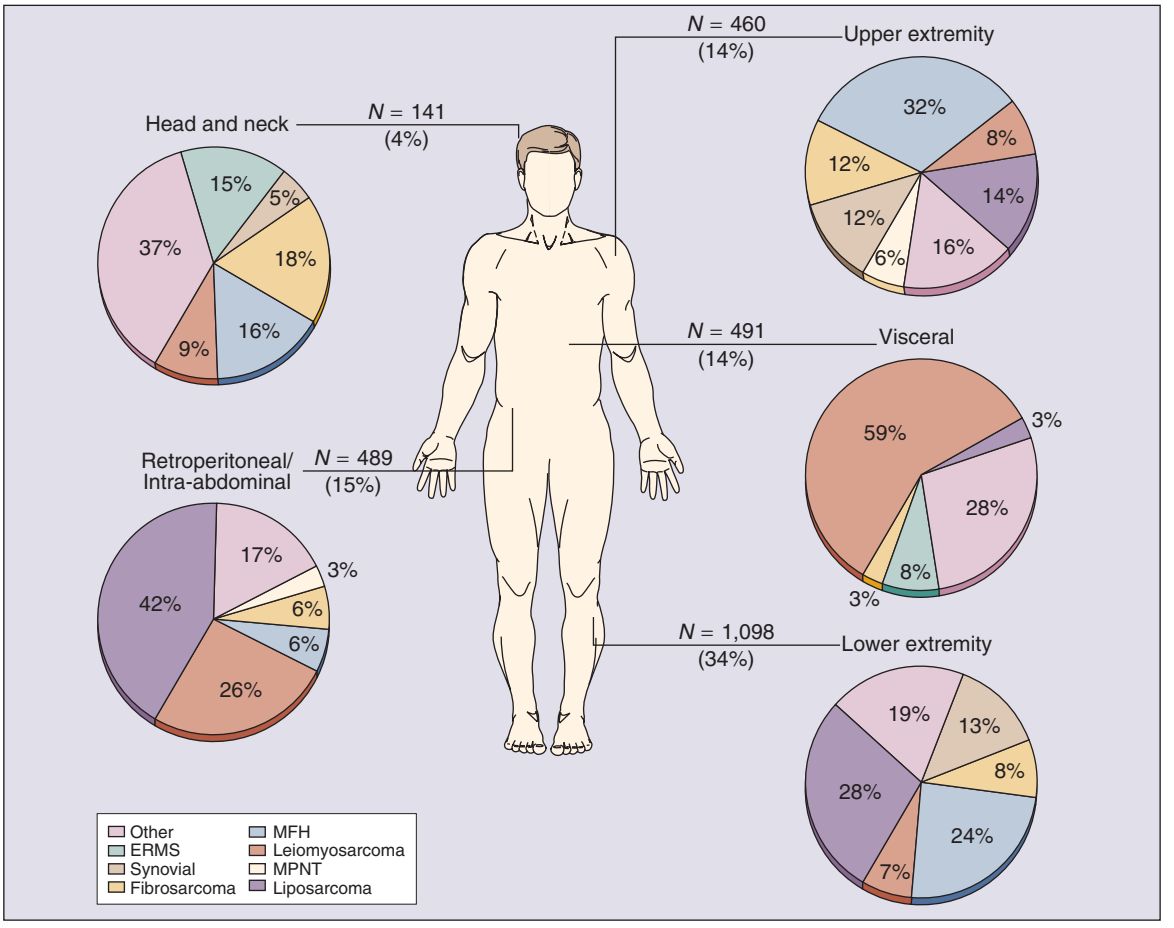


Figure 97-1 • Anatomic distribution and site-specific histiotypes of 4207 adult patients with soft-tissue sarcomas seen at the University of Texas M.D. Anderson Cancer Center, 1996–2003.

becoming increasingly clear that these tumors arise from primitive cells of mesenchymal origin. So are they bone sarcomas or soft-tissue sarcomas, and does it really matter in terms of classification? Sarcomas of the soft tissues can be further grouped into those that arise from viscera (gastrointestinal, genitourinary, and gynecologic organs) and those that arise from nonvisceral soft tissues (muscle, tendon, adipose, pleura, and connective tissue).

An alternative way to index STSs is by their differentiation. Tumors can be grouped broadly into adipocytic tumors, fibroblastic/myofibroblastic tumors, so-called fibrohistiocytic tumors, smooth muscle tumors, pericytic (perivascular) tumors, PNETs, skeletal muscle tumors, vascular tumors, osseous tumors, and tumors of uncertain differentiation (Table 97-5).[98] Classification is based on clinical, histologic, ultrastructural, immunohistochemical, and genetic features. Electron microscopic evidence of cellular substructures, neurofibrils, microfilaments, actin-myosin complexes, dense bodies, and so on often helps to clarify the tissue of origin.[99] However, the widespread availability of commercial antibodies for immunohistochemical analysis has diminished the need for electron microscopic examination in many cases. Immunohistochemical staining for proteins that are characteristic of smooth muscle (smooth muscle actin and desmin), skeletal muscle (muscle-specific actin, desmin, and myogenin), blood vessels (factor VIII, CD34, and CD31), and epithelial tissue (epithelial membrane antigen and cytokeratins) often facilitates reliable classification.[100,101]

The tissue of origin classification scheme is the most commonly used scheme and is the basis for the recent World Health Organization classification system for sarcomas.[98,102] The World Health Organization classification system is reproducible for most sarcomas. As the degree of histologic differentiation declines, however, the determination of the tissue of origin becomes increasingly difficult. In particular, despite advanced immunohistochemical techniques, electron microscopy, and molecular analysis, determining the tissue of origin for some soft-tissue tumors is difficult, occasionally arbitrary, and sometimes impossible. This leads to significant disparities in diagnoses among pathologists. Discrepancies between the original histologic diagnosis and the subsequent diagnosis by an expert reviewer have been noted in as many as 25% of cases.[103,104] Review of tissue specimens by an expert at a regional sarcoma center is therefore imperative, because the degree of expertise in correctly diagnosing rare and unusual sarcomas is directly related to the number of sarcomas that a pathologist has seen.

It is important to classify STSs as precisely as possible because of major differences in their clinical behavior and in their susceptibility to different therapies. For example, a few STSs, including epithelioid sarcoma, clear cell sarcoma, angiosarcoma, and rhabdomyosarcoma, have a greater risk of regional lymph node metastasis.[105,106] In one single-institution study, the overall rate of nodal metastasis at the time of sarcoma presentation was only 2.7%; however, the rate was much higher for angiosarcoma (13.5%), embryonal rhabdomyosarcoma (13.6%), and epithelioid sarcoma (16.7%).[105]

Patterns of distant metastases also differ for subtypes of sarcoma. For example, myxoid liposarcoma tends to metastasize to soft-tissue sites, including the retroperitoneum,[107] and patients with myxoid liposarcoma often present with metastatic disease. Therefore, if a myxoid liposarcoma is identified in the abdomen, the thighs should be examined for an occult primary tumor. The vast majority of so-called primary myxoid liposarcomas of the abdomen and retroperitoneum are actually metastatic myxoid liposarcomas or misdiagnosed dedifferentiated liposarcomas, which often mimic myxoid liposarcoma.[108]

Patterns of local spread also differ dramatically among subtypes of sarcoma. For example, DFSP has a propensity to infiltrate subcutaneous adipose tissue in a manner that is very difficult to detect; therefore, wide surgical excision of DFSP is essential. When planning a surgery for DFSP, the surgeon should regard the grossly observable lesion as the tip of the iceberg. Angiosarcoma also spreads very diffusely and is difficult to define grossly.

Table 97-5 Histologic Classification of Soft-Tissue Sarcoma

ADIPOCYTIC SARCOMAS
Atypical lipomatous tumor/well-differentiated liposarcoma
Dedifferentiated liposarcoma
Myxoid liposarcoma
Pleomorphic liposarcoma
FIBROBLASTIC AND MYOFIBROBLASTIC SARCOMAS
Malignant solitary fibrous tumor
Inflammatory myofibroblastic tumor
Myxoinflammatory fibroblastic sarcoma
Infantile fibrosarcoma
Adult fibrosarcoma
Myxofibrosarcoma (myxoid malignant fibrous histiocytoma)
Low-grade fibromyxoid sarcoma
Sclerosing epithelioid fibrosasrcoma
SO-CALLED FIBROHISTIOCYTIC SARCOMAS
Pleomorphic malignant fibrous histiocytoma/undifferentiated high-grade pleomorphic sarcoma
Giant cell malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma with giant cells
Inflammatory malignant fibrous histiocytoma/undifferentiated pleomorphic sarcoma with prominent inflammation
SMOOTH MUSCLE SARCOMAS
Leiomyosarcoma
SKELETAL MUSCLE SARCOMAS
Embryonal rhabdomyosarcoma
Alveolar rhabdomyosarcoma
Pleomorphic rhabdomyosarcoma
VASCULAR SARCOMAS
Epithelioid hemangioendothelioma
Angiosarcoma
OSSEOUS SARCOMAS
Extraskeletal osteosarcoma
SARCOMAS OF UNCERTAIN DIFFERENTIATION
Synovial sarcoma
Epithelioid sarcoma
Alveolar soft part sarcoma
Clear cell sarcoma of soft tissue
Extraskeletal myxoid chondrosarcoma
Desmoplastic small round cell tumor
Extarenal rhabdoid tumor
Intimal sarcoma

Histologic Grading

Histologic classification alone does not always provide enough information to predict the clinical behavior of STSs. For many sarcomas, histologic grading provides additional information that can aid in predicting biologic behavior and planning treatment. The spectrum of grades varies among specific histologic subtypes (Fig. 97-2). For

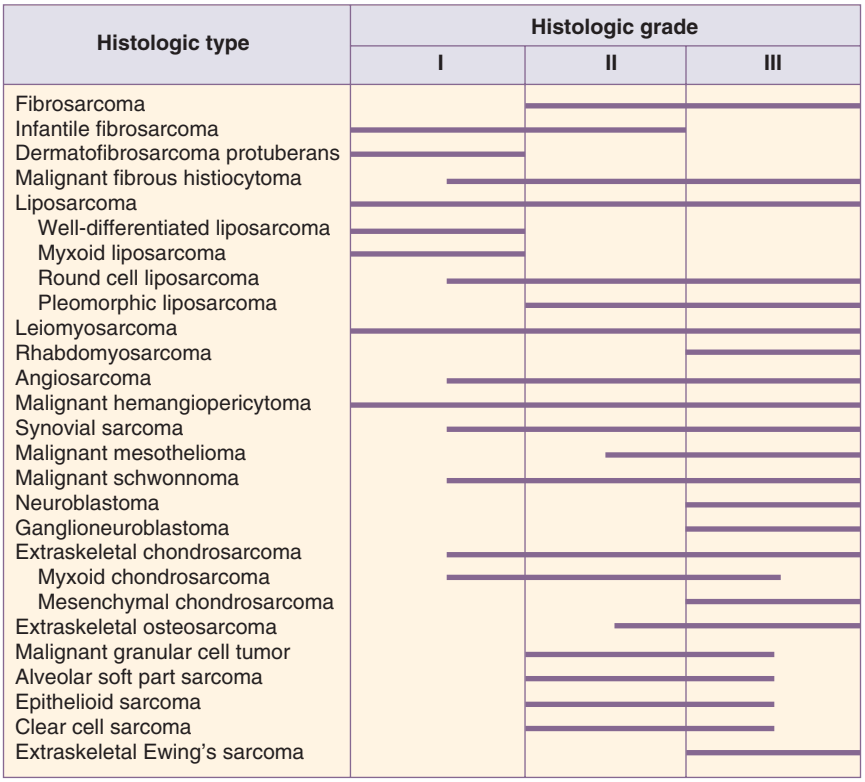


Figure 97-2 • The spectrum of grades observed among histologic subtypes of soft-tissue sarcoma. (Reprinted with permission from Enzinger FM, Weiss SW: Malignant tumors of uncertain type. In Enzinger FM, Weiss SW [eds]: Soft Tissue Tumors, 3rd ed. St. Louis, Mosby, 1995, p 1067.)

example, leiomyosarcomas exhibit wide variations in grade and should always be graded, while Ewing's sarcomas/PNETs are always high-grade and therefore do not require grading. In careful comparative multivariate analyses, histologic grade has been the most important prognostic factor in assessing the risk for distant metastasis and tumor-related mortality.[109–111] Several grading systems have been proposed, but there is no consensus regarding the specific morphologic criteria that should be employed in the grading of STSs. The two most important criteria appear to be the mitotic index and the extent of tumor necrosis.

Two of the most commonly used grading systems are the U.S. National Cancer Institute (NCI) system developed by Costa and colleagues[112] and the FNCLCC system (Federation Nationale des Centres de Lutte Contre le Cancer) developed by the French Federation of Cancer Centers Sarcoma Group.[113] The NCI system is based on the tumor's histologic subtype and amount of tumor necrosis, but cellularity, nuclear pleomorphism, and mitotic index are considered for certain subtypes. The FNCLCC system employs a score generated by evaluation of three parameters: tumor differentiation, mitotic rate, and amount of tumor necrosis. The prognostic values of these two grading systems were retrospectively compared in a population of 410 adult patients with nonmetastatic STS.[114] Significant discrepancies were observed in one third of cases. An increased number of grade III tumors, a reduced number of grade II tumors, and better correlation with overall and metastasis-free survival were observed in favor of the FNCLCC system.[114] Thus, in the absence of other comparative data, the FNCLCC system may be the best presently available grading system.

CLINICAL PRESENTATION AND DIAGNOSIS

The majority of patients present with a painless mass, although pain is noted at presentation in up to one third of cases.[115] Delay in diagnosis of sarcomas is common, the most common incorrect diagnosis for extremity and trunk lesions being lipoma or hematoma.

Physical examination should include an assessment of the size and mobility of the mass. Its relationship to the fascia (superficial versus deep) and nearby neurovascular and bony structures should be noted. A site-specific neurovascular examination and assessment of regional lymph nodes should also be performed.

Biopsy

Biopsy of the primary tumor is essential for most patients presenting with soft-tissue masses. In general, any soft-tissue mass in an adult that is asymptomatic or enlarging, is larger than 5 cm, or persists beyond 4 to 6 weeks should be biopsied. The preferred biopsy approach is generally the least invasive technique required to allow a definitive histologic diagnosis and assessment of grade. In most centers, core-needle biopsy provides satisfactory tissue for diagnosis[116–118] and has been demonstrated to result in substantial cost savings compared to open biopsy.[118] Direct palpation can be used to guide needle biopsy of most superficial lesions, but less accessible sarcomas often require an image-guided biopsy to safely sample the most heterogeneous component of the mass. Needle tract tumor recurrences after closed biopsy are rare but have been reported,[119] leading some surgeons to advocate tattooing the biopsy site for subsequent excision or for inclusion in radiotherapy treatment volumes (Fig. 97-3). In some centers, fine-needle aspiration may be an acceptable biopsy technique for primary soft-tissue masses, provided that an experienced sarcoma cytopathologist is available.[120–122] Owing to the frequent difficulty in accurately diagnosing these lesions even when adequate tissue is available, however, the major utility of fine-needle aspiration in most centers is in the diagnosis of suspected recurrent sarcoma.

Incisional or excisional biopsy is rarely required but may be performed when a definitive diagnosis cannot be achieved by less invasive means. Several technical points merit comment. Relatively small, superficial masses that can easily be removed should be biopsied by complete excision with microscopic assessment of surgical margins.

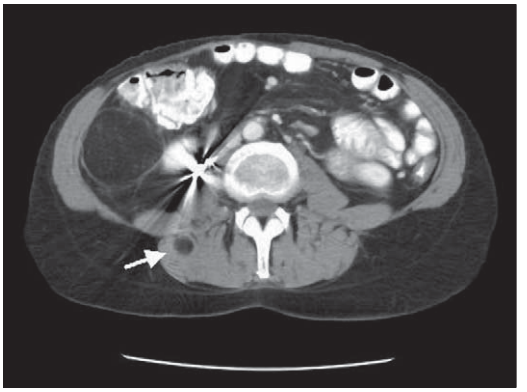


Figure 97-3 • Axial CT image of a recurrent well-differentiated low-grade liposarcoma of the retroperitoneum. Note the tumor nodule (*arrow*) representing a tumor implant within muscle from a previous needle biopsy that was obtained through the posterior abdominal wall. It is beneficial to consider the location of biopsy tracts so that subsequent surgery or radiotherapy includes the area of the biopsy (see text for details).

Incisional and excisional biopsies should be performed with the incision oriented longitudinally (for extremity lesions) to facilitate subsequent wide local excision. The incision should be centered over the mass at its most superficial point. Care should be taken not to raise tissue flaps. Meticulous hemostasis should be ensured to prevent dissemination of tumor cells into adjacent tissue planes by hematoma. All excisional biopsy specimens should be sent fresh, sterile, and anatomically oriented for pathologic analysis. At definitive resection of a previously biopsied sarcoma, the previous surgical biopsy scar should be excised en bloc with the tumor.

Imaging

Optimal imaging of the primary tumor is dependent on the anatomic site. For soft-tissue masses of the extremities, magnetic resonance imaging (MRI) has been regarded as the imaging modality of choice (Fig. 97-4). This is because MRI enhances the contrast between tumor and muscle and between tumor and adjacent blood vessels and provides multiplanar definition of the lesion.[123,124] Despite the fact that a study by the Radiation Diagnostic Oncology Group that compared MRI and computed tomography (CT) in patients with malignant bone ($N = 183$) and soft-tissue ($N = 133$) tumors showed no specific advantage of MRI over CT from a diagnostic standpoint,[125] the majority of musculoskeletal radiologists and almost all oncologists prefer MRI for soft-tissue tumors. For pelvic lesions, the multiplanar capability of MRI may provide superior single-modality imaging (Fig. 97-5). The multiplanar capability is also helpful for visualization of disease in noncoplanar ways when conformal radiotherapy technique is being employed and is an especially helpful adjunct in using image fusion techniques or to visualize peritumoral edema that may harbor sarcoma cells. In the retroperitoneum and abdomen, CT usually provides satisfactory anatomic definition of the lesion (Fig. 97-6). Occasionally, MRI with gradient sequence imaging can better delineate the relationship of the tumor to midline vascular structures, particularly the inferior vena cava and aorta. More invasive studies such as angiography or cavography are almost never required for the evaluation of STSs.

The utility of [^{18}F]fluorodeoxyglucose positron emission tomography (FDG PET) in the evaluation and treatment of STS has been a subject of recent studies and has been reviewed in detail elsewhere. The technique utilizes radiolabeled glucose analogs,[19] which are taken up at increased rates by malignant tumors. Pilot studies of PET in STS suggest that by evaluating tumor metabolic activity, PET scans may allow for noninvasive assessment of tumor grade.[126] Recent preliminary studies have demonstrated that PET may be helpful in

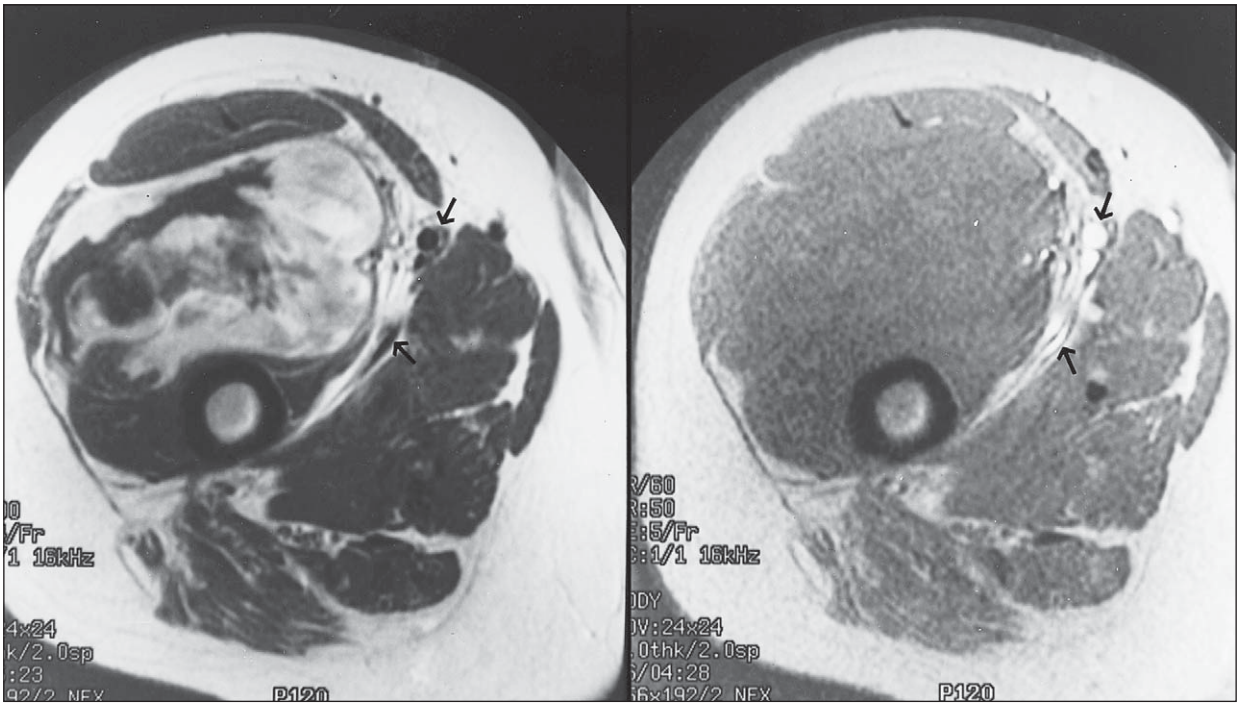


Figure 97-4 • A 47-year-old male with malignant fibrous histiocytoma of the left thigh. Axial contrast-enhanced T1-weighted (*left*) and flow sensitive gradient (*right*) images reveal a large mass in the vastus intermedius muscle. A plane is identified between the mass and the profunda femoris and superficial femoral vessels (*arrows*).

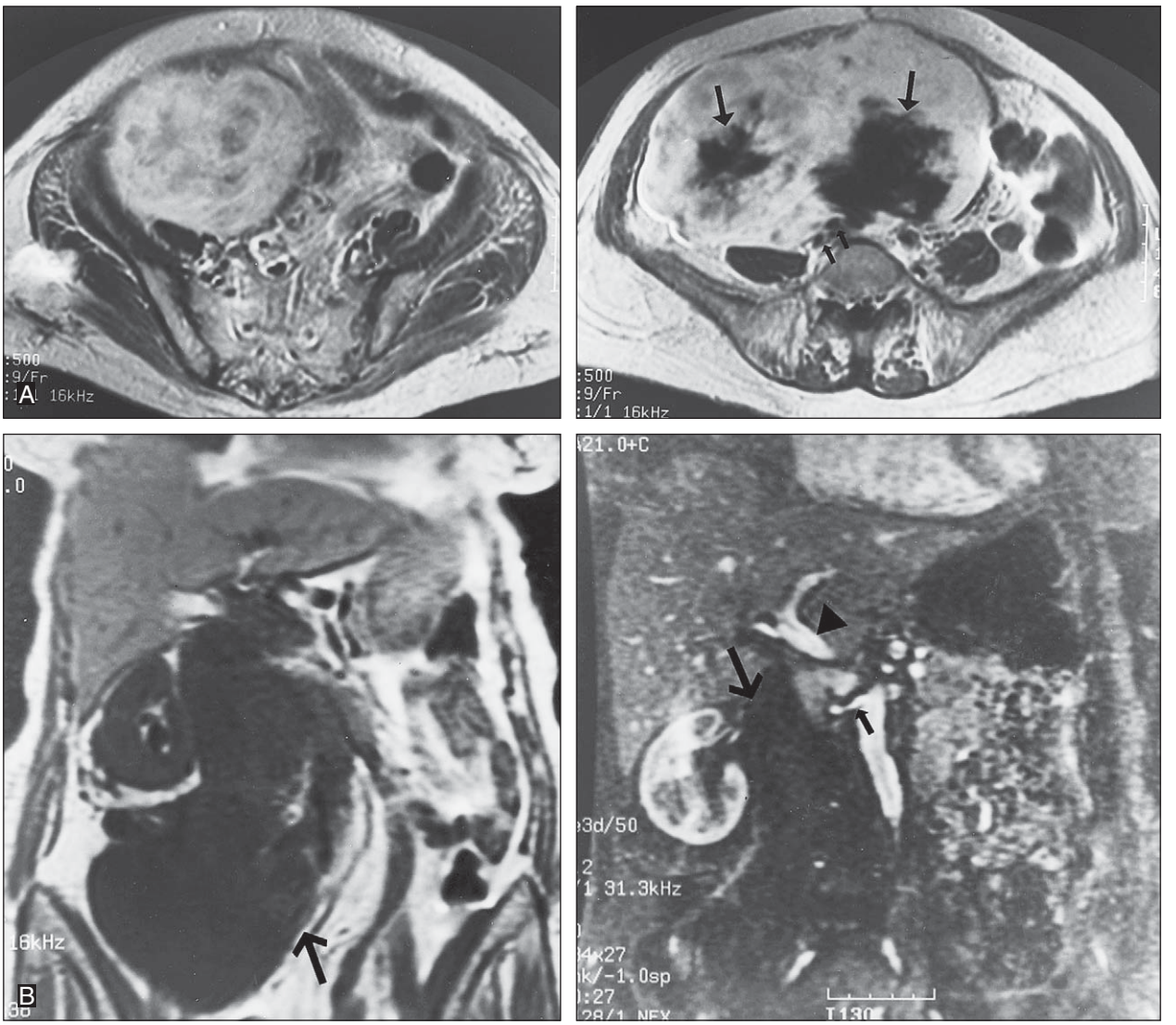


Figure 97-5 • **A,** A 74-year-old female with retroperitoneal malignant fibrous histiocytoma extending into the upper pelvis. Axial contrast-enhanced T1-weighted images reveal a large heterogeneous mass with foci of necrosis (*large arrows*). Note the relationship to the common iliac vessels (*small arrows*). **B,** The same patient as in **(A).** Coronal T1-weighted (*left*) and source MR images (*right*) from contrast-enhanced 3D MR angiogram reveal a large abdominal mass (*large arrows*) closely abutting the right renal capsule. Note the relationship to the aorta. The right renal artery is visualized *(small arrow*) as is the portal vein (*arrowhead*).

the assessment of locally recurrent STS[127] and in the evaluation of response to therapy.[128,129] The role and cost-effectiveness of PET in the staging of STS remain incompletely defined; therefore, further studies will be required to fully define the role for FDG PET in the diagnosis, evaluation, and treatment of STS.

STAGING

The relative rarity of STSs, the anatomic heterogeneity of these lesions, and the presence of more than 30 recognized histologic subtypes of variable grade have made it difficult to establish a functional system that can accurately stage all forms of this disease. The recently revised staging system (sixth edition) of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) is the most widely employed staging system for STSs.[130] This staging system is a revision of the original AJCC system, which was first published in 1977; it incorporates histologic grade into the conventional TNM system (Table 97-6). The 2002 sixth edition classification has T and N categories that are identical to those of the 1997 fifth edition TNM, but some modifications have been made to the stage groupings. For the detailed background to these changes, the reader is referred to a more complete discussion. All STS subtypes are included except dermatofibrosarcoma protuberans, a condition that is considered to have only borderline malignant potential. Four distinct histologic grades are recognized, ranging from well-differentiated to undifferentiated. Histologic grade and tumor size are the primary determinants of clinical stage (see Table 97-6). Tumor size is further substaged as "a" (a superficial tumor that arises outside the investing fascia) or "b" (a deep tumor that arises beneath the fascia or invades the fascia). The system is designed to optimally stage extremity tumors but is also applicable to torso, head and neck, and retroperitoneal lesions; it should not be used for sarcomas of the gastrointestinal tract. This staging system has been validated by analysis of 1146 patients presenting with primary extremity STS at the Memorial Sloan-Kettering Cancer Center. Stage-specific survival plots are outlined in Figure 97-7.

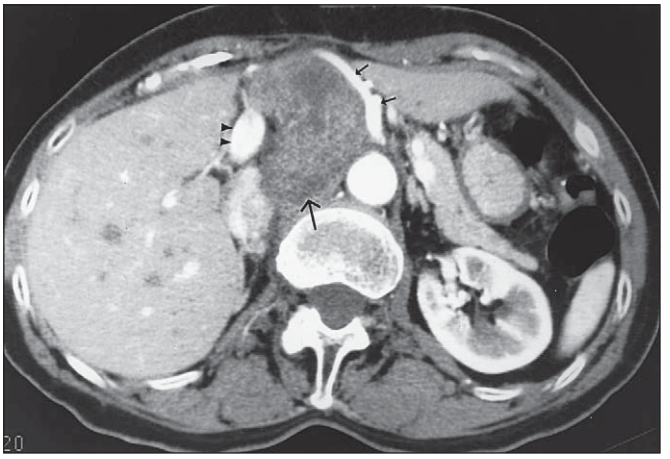


Figure 97-6 • Contrast-enhanced CT scan of the abdomen demonstrating a retroperitoneal malignant fibrous histiocytoma. Note the large mass (*large arrow*) between the aorta and inferior vena cava with abutment and displacement of celiac axis and hepatic artery (*small arrows*). The portal vein (*arrowheads*) is well visualized, and low attenuation foci in the liver, which are unopacified hepatic veins, are incidentally visualized.

A major limitation of the present staging system is that it does not take into account the anatomic site of STSs. Anatomic site, however, is an important determinant of outcome. Patients with retroperitoneal and visceral sarcomas have a worse overall prognosis than do patients with extremity tumors. Although site is not incorporated as a specific component of any present staging system, outcome data should be reported on a site-specific basis.

Table 97-6 AJCC/UICC Staging System for Soft-Tissue Sarcoma

T1		≤5 cm		
T1a		Superficial to muscular fascia		
T1b		Deep to muscular fascia		
T2		>5 cm		
T2a		Superficial to muscular fascia		
T2b		Deep to muscular fascia		
N1		Regional nodal involvement		
G1		Well-differentiated		
G2		Moderately differentiated		
G3		Poorly differentiated		
G4		Undifferentiated		
Stage IA	G1, 2	T1a, b	N0	M0
Stage IB	G2, 2	T2a, b	N0	M0
Stage IIA	G3, 4	T1a, b	N0	M0
Stage IIB	G3, 4	T2a	N0	M0
Stage III	G3, 4	T2b	N0	M0
Stage IV	Any G	Any T	N1	M0
	Any G	Any T	Any N	M1

Modified from Greene FL et al (eds.): UICC TNM Classification of Malignant Tumors, 6th ed. [LOC.], Springer Verlag, 2002.

PROGNOSTIC FACTORS

Conventional Clinicopathologic Factors

A thorough understanding of the clinicopathologic factors that are known to affect outcome is essential in formulating a treatment plan for the patient with STS. Over the past decade, many multivariate analyses of prognostic factors for patients with localized sarcoma have been reported. With few exceptions,[109,110,131,132] most studies have analyzed fewer than 300 patients (range: 82 to 297 patients). At least three detailed analyses of prognostic factors in STS merit comment.[109,110,131] The initial study of prognostic factors in extremity sarcoma from Memorial Sloan-Kettering Cancer Center evaluated clinicopathologic prognostic factors in a series of 423 patients with localized extremity STS seen from 1968 to 1978.[128] This analysis, among the first to discriminate between specific clinical endpoints, clearly established the clinical profile of what is now accepted as the high-risk patient with extremity STS: the patient with a large (>5-cm), high-grade, deep lesion. The adverse prognostic significance of a high tumor grade, deep tumor location, and tumor size greater than 5 cm was also noted in the recent report of the French Federation of Cancer Centers study of 546 patients with sarcomas of the extremities, head and neck, trunk wall, retroperitoneum, and pelvis.[110]

A follow-up report from Memorial Sloan-Kettering evaluated clinicopathologic prognostic factors that had been documented

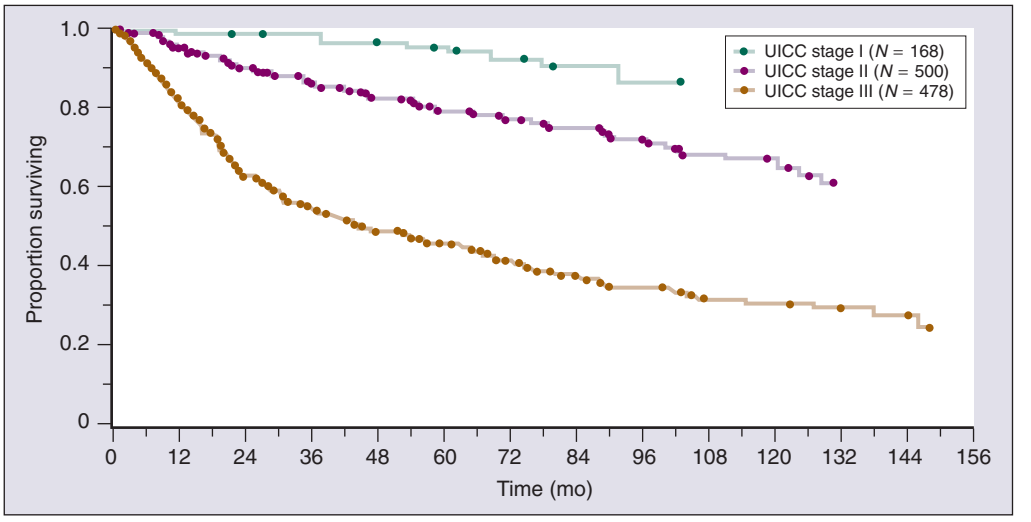


Figure 97-7 • Overall survival by AJCC stage in a population of 1146 patients with primary extremity sarcoma treated at the Memorial Sloan-Kettering Cancer Center.

Table 97-7 Multivariate Analysis of Prognostic Factors in Patients with Extremity Soft-Tissue Sarcoma

Endpoint	Adverse Prognostic Factor	Relative Risk
Local recurrence	Age > 50 years	1.6
	Local recurrence at presentation	2.0
	Microscopically positive margin	1.8
	Fibrosarcoma	2.5
	Malignant peripheral nerve tumor	1.8
Distant recurrence	Size 5.0–10.0 cm	1.9
	Size > 10.0 cm	1.5
	High-grade	4.3
	Deep location	2.5
	Local recurrence	1.5
	Leiomyosarcoma	1.7
	Other nonliposarcoma histology	1.6
Disease-specific survival	Size > 10.0 cm	2.1
	Deep location	2.8
	Local recurrence at presentation	1.5
	Leiomyosarcoma	1.9
	Malignant peripheral nerve tumor	1.9
	Microscopically positive margin	1.7
	Lower-extremity site	1.6

Adverse prognostic factors identified are independent by Cox regression analysis.

Modified from Pisters PWT, Leung DHY, Woodruff JM, et al: Analysis of prognostic factors in 1041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679.

prospectively in a population of 1041 patients with extremity STS.[109] The endpoints for the multivariate analyses were local recurrence, distant recurrence (metastasis), and disease-specific survival. Results of the regression analyses for each of these endpoints are summarized in Table 97-7. These results, using prospectively acquired data, confirm the initial observations made at that institution using an independent data set.[131] In addition, the previously unappreciated prognostic significance of specific histologic subtypes and the increased risk for adverse outcome associated with a microscopically positive surgical margin or locally recurrent disease were noted. Unlike for other solid tumors, the adverse prognostic factors for local recurrence of a STS are different from those that predict distant metastasis and tumor-related mortality (see Table 97-7).[109] In other words, patients with a constellation of adverse prognostic factors for local recurrence are not necessarily at increased risk for distant metastasis or tumor-related death. Therefore, staging systems that are designed to stratify patients according to risk of distant metastasis and tumor-related mortality using these prognostic factors (such as the AJCC/UICC system) will not stratify patients according to risk of local recurrence. The results of these multivariate analyses should be incorporated in the design of new staging systems and clinical trials for STS, and the identification of individual patients who are at high risk for distant recurrence and death.

It should be emphasized that the prognostic factors that have been identified have been derived primarily from studies of patients with localized extremity sarcomas. Despite the fact that extremity sarcomas make up the majority of sarcomas, these results may not be optimally generalized to the greater population of STS patients. Separate reviews of prognostic factors for sarcomas of the retroperitoneum,[133,134] head and neck,[135–138] gastrointestinal tract,[139,140] colon and rectum,[141] uterus,[142] synovial sarcomas,[143,144] malignant fibrous histiocytoma,[145–147] and Ewing's sarcoma[148–151] have been reported.

Potential Molecular Prognostic Factors

Attention has recently been focused on the evaluation of molecular pathologic prognostic factors. Specific molecular parameters that have been evaluated for prognostic significance have included p53,[152] mdm2,[152] Ki-67,[152] altered expression of the retinoblastoma gene product (pRb)[58,153] in high-grade sarcomas, and the presence of the SYT-SSX fusion transcripts in synovial sarcoma[92] or EWS-FL11 fusion transcripts in Ewing's sarcoma.[90,91]

A preliminary report evaluating the prognostic role of pRb expression in 44 primary and 12 metastatic high-grade human sarcomas by immunohistochemical methods and Western blotting demonstrated that alterations in pRb are more commonly associated with high-grade tumors, metastatic lesions, and decreased survival.[58] However, a subsequent report from the same group in an expanded population of 174 adult patients with STS revealed that pRb alterations were frequently observed in both low- and high-grade lesions and that altered pRb expression did not correlate with known predictors of survival and was not an independent predictor of long-term outcome.[153] These studies and the now well-documented phenomenon of late (>5 years post-treatment) recurrence of STS[154] underscore the importance of long-term follow-up and relatively large sample size in these types of analyses.

p53 is a tumor suppressor gene located on chromosome 17. Somatic p53 mutations have been reported in 4% to 65% of patients with STS.[155–159] Detection of p53 has also been correlated with reduced overall survival in immunohistochemical studies of paraffin-embedded STSs. Data on the underlying prognostic significance of p53 status are conflicting; some investigators report no independent adverse prognostic significance by regression analysis,[152,160] and others report a highly significant correlation between p53/mdm2 status and outcome.[161]

Ki-67, an antigen that is expressed throughout the majority of the cell cycle, is utilized as a measure of dividing cells.[162] Preliminary reports of series of heterogeneous sarcomas in adults suggested that proliferative index as measured by Ki-67 nuclear staining correlated with histologic grade but was not of independent prognostic significance when histologic grade was taken into account.[160,163] However, additional studies in larger numbers of patients have demonstrated that Ki-67 status is an independent prognostic factor.[152,164,165] An initial immunohistochemical analysis of a cohort of 65 STSs and a subsequent analysis of 132 STSs from the French Federation of Cancer Centers Sarcoma Group demonstrated the adverse prognostic significance of increased Ki-67 activity.[164,165]

Heslin and colleagues evaluated the potential prognostic significance of pRb, p53, mdm2, and Ki-67 by immunohistochemical techniques in a population of 121 patients with primary, high-grade extremity sarcomas and compared these factors to conventional clinicopathologic prognostic factors (median follow-up: 64 months).[152] Clinicopathologic and molecular factors that were found to be statistically significant adverse prognostic factors in both univariate and multivariate analyses for the separate endpoints of distant metastasis and tumor-related mortality included tumor size greater than 5 cm, microscopically positive surgical margin, and a Ki-67 score greater than 20 (>20% nuclear staining). Overexpression of p53 or mdm2 or deletion of pRb did not correlate with an increased risk of distant metastasis or tumor-related mortality.

Synovial sarcoma is characterized by a specific chromosomal translocation, t(X;18)(p11;q11), which is seen in more than 90% of these tumors.[82,84] This had led to studies evaluating the potential prognostic significance of SYT-SSX fusion transcripts, which arise from this translocation.[92] The t(X;18)(p11;q11) translocation fuses the SYT gene from chromosome 18 to either of two homologous genes at

Xp11, SSX1, or SSX2. The fusion transcripts SYT-SSX1 and SYT-SSX2 are believed to function as aberrant transcriptional regulators. The prognostic significance of these alternative forms of the SYT-SSX fusion gene and the relationship of these fusion transcripts and synovial sarcoma tumor morphology (monophasic versus biphasic subtype) were examined in 45 patients with synovial sarcoma.[92] There was a significant correlation ($P = 0.003$) between histologic subtype and fusion transcript type; all 12 biphasic synovial sarcomas had an SYT-SSX1 fusion transcript, whereas 17 (52%) of 33 monophasic tumors were positive for SYT-SSX1. Moreover, the presence of the SYT-SSX1 transcript was an independent adverse prognostic factor for metastasis-free survival. Thus, SYT-SSX fusion transcripts may be used as a diagnostic marker for synovial sarcoma, and transcript subtype should be confirmed as an independent prognostic factor.

Ewing's sarcomas are characterized by a translocation involving chromosomes 22 and 11: t(11;22)(q24;q12).[85] Recent studies have evaluated the prognostic significance of transcripts produced by the fusion of the EWS and FL11 genes from chromosomes 22 and 11. The most common EWS-FL11 fusion, designated as type 1, is found in 65% of Ewing's sarcomas.[166,167] Two groups have demonstrated that type 1 EWS-FL11 fusion transcripts are associated with a more favorable prognosis.[90,91] De Alava and colleagues[91] have demonstrated that the prognostic significance of type 1 EWS-FL11 fusion transcripts is independent of tumor site, stage, and size. However, these observations were made with a short follow-up (median: 26 months, range: 1 to 140 months); therefore, additional studies and longer follow-up are needed to further substantiate these interesting observations. The biologic basis for these observations is unknown. Additional studies that examine the relationship between EWS-FL11 transcript subtype and proliferative rate, apoptosis, and response to treatment are warranted.

With the increasing use of cDNA expression profiling, it is possible that expression profile-based stratification may be possible within specific histologies, in a manner analogous to current use of this technique to stratify breast cancer.[168] Additionally, these profiles have recently been applied to determining metastatic potential of primary tumors, and this approach could clearly be applicable to STSs, in which the presence or absence of metastases remains the most important prognostic factor.[169] Most recently, phosphoprotein profiling has been employed to stratify patients with stage III rhabdomyosarcoma and predict outcome.[170] This approach also holds future promise for both prognostic and therapeutic approaches (see later discussion).

Although specific cellular and molecular parameters have been identified as having independent prognostic significance, there is currently no consensus on how specific molecular prognostic factors should be utilized in clinical practice. Until more data are available, molecular prognostic factors that have proven to be of prognostic significance (e.g., Ki-67) should be considered for inclusion as stratification criteria in clinical trials.

Prognostic Factors as Therapeutic Targets

The prognosis of GISTs is poor when they are treated by surgery alone,[171] and these tumors rarely respond to conventional systemic chemotherapy. The most exciting discovery in GIST research in recent years is targeted molecular therapy, which will be discussed later in the chapter. The proto-oncogene c-Kit is the cellular homolog of the oncogene v-Kit (a feline sarcoma virus). c-Kit encodes a transmembrane tyrosine kinase receptor, KIT (CD117), that is structurally similar to platelet-derived growth factor and provides selective targets of key aberrations in the molecular signaling implicated in the pathogenesis of GISTs and other tumors (e.g., DFSP). An interesting additional feature of c-Kit expression in GIST is that different types and locations of mutations in c-Kit appear to be independently significant for predicting disease-free survival irrespective of treatment with kinase receptor inhibitors.[172] CD117 expression was uniformly evident in a recent study of GIST cases not treated with imatinib.[74,172] Of interest, c-Kit was highly phosphorylated in all cases, even in those few that lacked demonstrable sequence mutations.[74] Mutations were found in specific regions of the c-Kit gene, and specific mutations appear to be associated with differing prognosis (see following discussion). The subset of patients with exon 11 mutations resulting in single amino acid substitutions (i.e., missense codon mutations) fared much better than did patients with deletion/insertion mutations of exon 11 (5-year recurrence-free survival rate of 89% ± 11% versus 37% ± 10%, respectively). A potential explanation for this finding is that exon 11 missense mutations are detected in lower-grade, favorable outcome GISTs.[172] Against this explanation is the fact that the vast majority of metastatic GISTs have exon 11 mutations. While it is conceivable that the type of mutation is a surrogate for the behavior of a GIST, however, it is also plausible that the type of mutation represents the initial pathogenetic mechanism, making it a true prognostic marker and target. Finally, in vitro studies suggest that GISTs with regulatory region KIT mutations are more likely to respond to imatinib than are GISTs with enzymatic region mutations.[173]

Molecular Therapeutic Targets in Sarcomas

We have just now begun to see the implications and success of targeting genetic alterations in sarcomas that drive oncogenesis. GIST tumors were previously thought to be gastrointestinal leiomyosarcomas that were particularly resistant to cytotoxic chemotherapy. It was subsequently demonstrated that these tumors were derived from interstitial cells of Cajal and were frequently characterized by point mutations in the c-Kit receptor tyrosine kinase and were clearly distinct from leiomyosarcomas.[174,175] Subsequently, the tumors were treated with imatinib mesylate that targets the c-Kit kinase with dramatic results.[176] The c-Kit mutations that were seen were located in exon 11 (juxtamembrane domain, seen in 71% of tumors), exon 9 (the extracellular region, 13%), exon 13 (first lobe of the split-kinase domain, 4%), and exon 17 (phosphotransferase domain, 4%). The subset of patients with exon 11 mutations resulting in point single amino acid substitutions (i.e., missense codon mutations) fared much better than did patients with deletion/insertion mutations of exon 11 (5-year recurrence free survival rate of 89% ± 11% versus 37% ± 10%, respectively).[172] In addition, tumors that lack c-Kit mutations appear to have mutations in PDGF-α receptor, and these mutations appear to be mutually exclusive of c-Kit mutations.[177] Finally, the type of mutation that is identified appears not only to predict response to imatinib mesylate, but also to suggest whether other kinase inhibitors such as sunitinib may have beneficial effects.[178] While it is unlikely that most sarcomas will be driven by mutations in a kinase that is amenable to target inhibition, it is likely that as more information is acquired regarding activation of specific signaling pathways in STSs, most will have treatment options that are not currently available.

Predicting Individual Prognosis

Kattan and colleagues have observed that information that is appropriate for researchers is not as helpful for patients with cancer who must plan in a different way for the future.[179] Patients' main preoccupation is to obtain a predicted probability of individual (i.e., personal) survival unencumbered by specific knowledge of prognostic factors, relative risk, or the risk group in which the person may belong. Kattan and colleagues have constructed and validated a nomogram to predict the probability of 12-year sarcoma-specific death based on a prospective series of patients (Fig. 97-8).[179] This tool is useful for individual patient counseling, follow-up scheduling, and clinical trial eligibility assessment and is further facilitated by being also available for personal handheld computer devices. This sarcoma-specific computer application is available at www.nomograms.org.

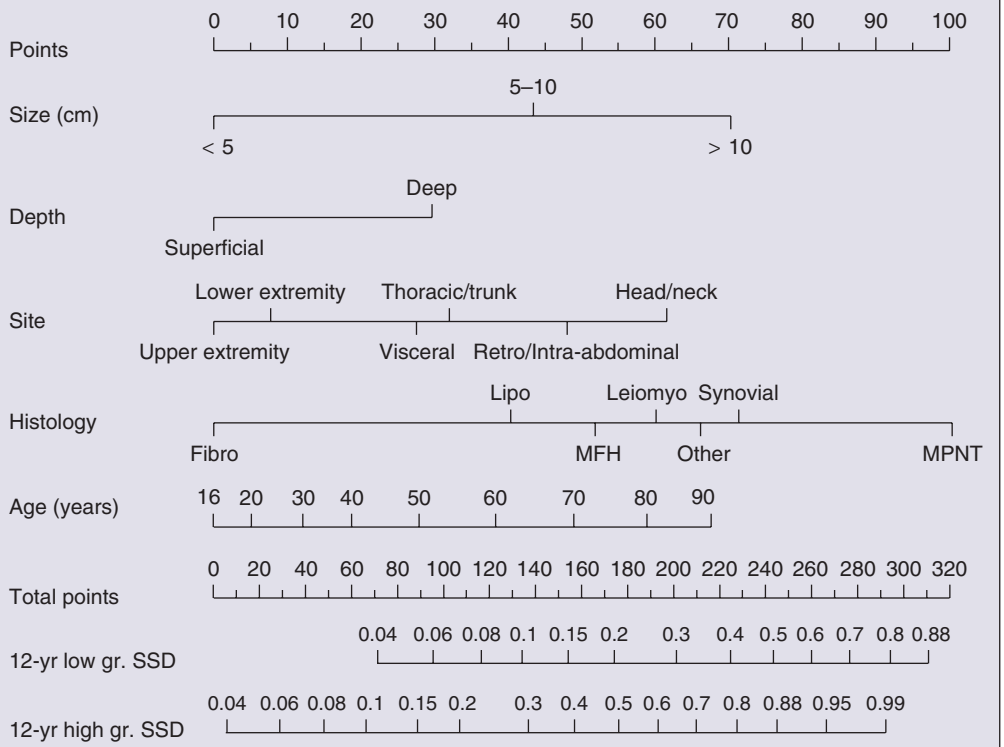


Figure 97-8 • Postoperative nomogram for 12-year sarcoma-specific death risk. Fibro, fibrosarcoma; GR, grade; Leiomyo, leiomyosarcoma; Lipo, liposarcoma; MFH, malignant fibrous histiocytoma; MPNT, malignant peripheral nerve sheath tumor; SSD, sarcoma-specific death. (Reproduced with permission from Kattan M: Statistical prediction models, artificial neural networks, and the sophism "I am a patient, not a statistic." J Clin Oncol 2002;20:885.)

TREATMENT OF LOCALIZED PRIMARY SOFT-TISSUE SARCOMA

Surgery

Limb-Sparing Surgery versus Amputation

Surgical resection remains the cornerstone of therapy for localized STS, and the prototypical situations concern the management of lesions arising in the extremity, the most common anatomic site. Over the past 20 years, there has been a marked decline in the rate of amputation as the primary therapy for extremity STS. With the widespread application of multimodality treatment strategies, fewer than 10% of patients currently undergo amputation.[180,181] The current use of limb-sparing multimodality treatment approaches for patients with extremity sarcoma is largely based on a randomized prospective study from the U.S. NCI in which patients with extremity sarcomas that were amenable to limb-sparing surgery were randomized to receive amputation or limb-sparing surgery with postoperative radiotherapy.[182,183] Both arms of this trial included postoperative chemotherapy with doxorubicin, cyclophosphamide, and methotrexate. With more than 9 years of follow-up evaluation, 5 (19%) of 27 patients randomly assigned to receive limb-sparing surgery and postoperative radiation with chemotherapy had local recurrences, as compared to 1 (6%) of 17 patients in the amputation plus chemotherapy arm (P = 0.22; Fig. 97-9).[183] The disease-free survival rate was 63% for limb-sparing surgery versus 71% for amputation (P = 0.52; Fig. 97-10), and the overall survival rate was 70% for limb-sparing surgery versus 71% for amputation (P = 0.97). This study established that for patients for whom limb-sparing surgery is an option, a multimodality approach employing limb-sparing surgery combined with postoperative radiotherapy yields disease-related survival rates comparable to those for amputation while simultaneously preserving a functional extremity.

Currently, at least 90% of patients with localized extremity sarcomas can undergo limb-sparing procedures.[180,184] Most surgeons consider definite major vascular, bony, or nerve involvement to be relative indications for amputation. Complex en bloc bone, vascular, and nerve resections with interposition grafting can be undertaken, but the associated morbidity is high. Therefore, for a few patients with critical involvement of major bony or neurovascular structures, amputation remains the only surgical option but offers the prospect of prompt rehabilitation with excellent local control and survival.[183]

Completeness of Resection

Satisfactory local resection involves resection of the primary tumor with a margin of normal tissue around the lesion. The width of the margin should differ depending on whether or not adjuvant radiotherapy is used. It is clear that dissection along the tumor pseudo-

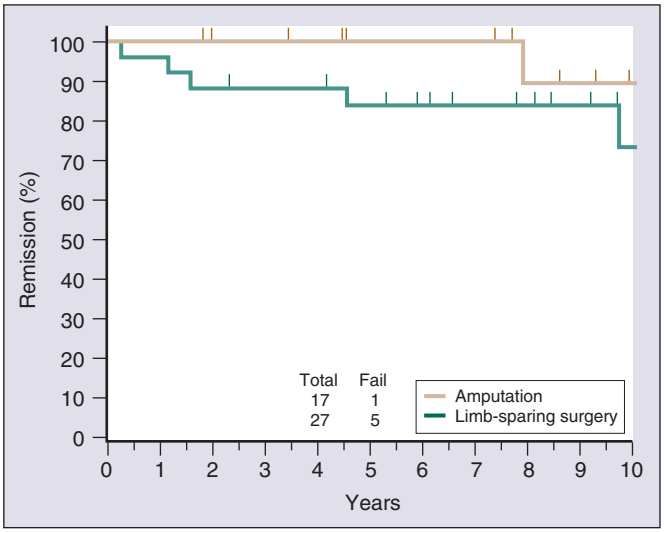


Figure 97-9 • Local recurrence rates in patients with high-grade extremity sarcomas randomized to receive amputation or limb-sparing surgery. All patients were treated with adjuvant chemotherapy using doxorubicin, cyclophosphamide, and methotrexate. Median follow-up: >9 years (P = 0.22). (Reprinted with permission from Yang JC, Rosenberg SA: Surgery for adult patients with soft tissue sarcomas. Semin Oncol 1989;16:289.)

capsule (enucleation) is associated with local recurrence rates ranging between 33% and 63%.[185–187] Wide local excision with a margin of normal tissue around the lesion is associated with local recurrence rates in the range of 10% to 31%, as was noted in the control arms (surgery alone) of the randomized trials evaluating postoperative radiotherapy.[188,189] In contrast to malignant melanoma, a disease for which there are randomized data to address adequate margin size, no comparable data are available to define what constitutes a satisfactory gross resection margin for a sarcoma. In general, every effort should be made to achieve a wide margin (2 cm is a frequently cited arbitrary choice) around the tumor mass, except in the immediate vicinity of

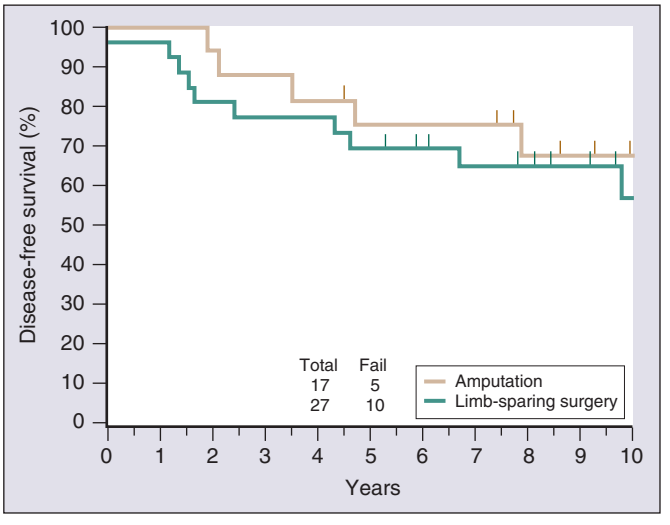


Figure 97-10 • Disease-free survival rates for patients with high-grade extremity sarcomas randomized to receive amputation or limb-sparing surgery. All patients were treated with adjuvant chemotherapy using doxorubicin, cyclophosphamide, and methotrexate. Median follow-up: >9 years (P = 0.52). (Reprinted with permission from Yang JC, Rosenberg SA: Surgery for adult patients with soft tissue sarcomas. Semin Oncol 1989;16:289.)

functionally important neurovascular structures, where, in the absence of frank neoplastic involvement, dissection is performed in the immediate perineural or perivascular tissue planes. The 2-cm choice is unnecessary if radiotherapy is also used, since substantial modification of the surgical approach with much closer margins of resection (e.g., 1 to 2 mm) is made possible, and even large lesions can be managed conservatively in that setting. Technical details of the surgical approach to extremity sarcomas are beyond the scope of this chapter but are comprehensively reviewed in a surgical atlas.[190] At the same time, it is also important to bear in mind that involved (i.e., positive) resection margins remain an adverse finding even when adjuvant radiotherapy is used, notwithstanding the amelioration of risk that radiation treatment provides. Data from Memorial Sloan-Kettering Hospital, Princess Margaret Hospital, and Massachusetts General Hospital suggest an additional absolute reduction of local control of approximately 10% to 15% for patients with positive margins compared to those with microscopically negative surgical margins.[190–193]

In considering the existing outcome data, it is important to bear in mind that these data consider the rubric "positive margins" in a uniform way, although in reality, this is unlikely to be the case. In fact, positive resection margins have different causes. One is oncologically inadequate surgery in which positive resection margins might have been avoidable in another surgeon's hands. When this is the case, microscopically positive surgical margins can be considered a technical failure. Alternatively, positive resection margins may arise in anatomically adverse presentations in which locally advanced disease challenges the goals of conservative resection from the outset. In another study from the Princess Margaret Hospital, Gerrand and colleagues evaluated the type of microscopically positive margin as a prognostic factor and defined four groups in this setting.[194] Patients with low-grade liposarcomas and microscopically positive surgical margins (group 1) have a low risk of local failure (4.2%), as do those in whom a positive margin is anticipated before surgery to preserve critical structures and radiotherapy is given to sterilize the minimal residual disease (group 2). However, two categories of positive margins are associated with a higher risk of local recurrence: (1) patients who present after prereferral unplanned excision and who have a positive margin on subsequent reexcision (group 3) and (2) patients with unanticipated positive margins occurring during primary sarcoma resection (group 4; Fig. 97-11). For group 3, an "unplanned excision" is defined as an excisional biopsy or resection that is carried out without adequate preoperative staging or consideration of the need to remove normal tissue around tumor, an adverse feature reported by the same authors previously.[195] These data appear to support the premise that, provided that adjuvant radiotherapy is administered, a very small amount of residual disease resulting from a "planned" positive margin at the site of a critical anatomic structure (group 2, local recurrence rate of 3.6% and 95% confidence interval 0 to 10.4) is not associated with the same deleterious risk that occurs with a positive margin that follows major contamination due to "shell out" intralesional surgery (group 3, local recurrence rate of 31.6%, 95% confidence interval: 10.7 to 52.5) or inadvertent contamination of the wound (group 4, local recurrence rate of 37.5%, 95% confidence interval: 13.8 to 61.2).[194] These data seem particularly relevant to anatomic sites where achievement of adequate resection margins is a perennial problem, such as the head and neck, as evidenced by recent results from a prospective series where the outcome approaches that of extremity and body wall sarcomas.[196] We would caution, however, that such results are probably not attainable without a defined management protocol and joint multidisciplinary assessment before treatment is undertaken, since there exist issues that merit discussion at the individual case level (e.g., the complex relationship between tissues to be resected and reconstructed and the radiotherapy volumes and doses, all of which can influence each other in the decision algorithm).

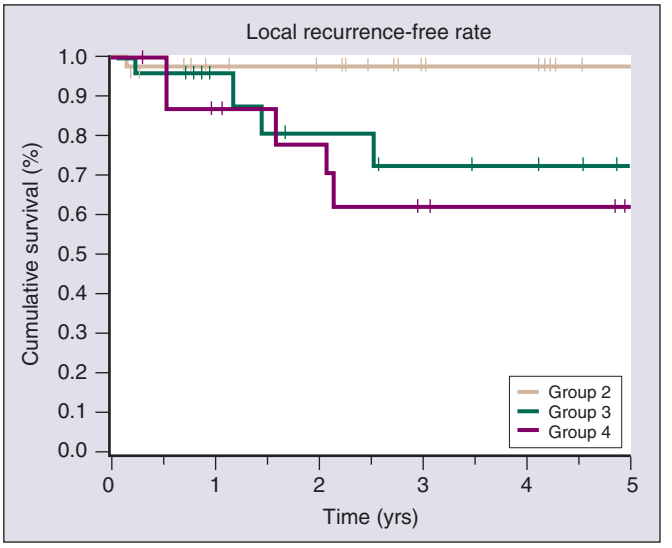


Figure 97-11 • Kaplan-Meier estimate for local recurrence-free rate for three different groups of positive margin categories (see text for details). Group 1 (low-grade liposarcoma with positive resection margins) is not shown. Tick marks represent censored cases. (Reproduced with permission from Gerrand CH, Wunder JS, Kandel RA, et al: Classification of positive margins after resection of soft-tissue sarcoma of the limb predicts the risk of local recurrence. J Bone Joint Surg Br 2001;83:1149.)

Lymph Node Dissection

Given the low (2% to 3%) prevalence of lymph node metastasis in adults with sarcomas,[102,103] there is no role for routine regional lymph node dissection. Patients with angiosarcoma, embryonal rhabdomyosarcoma, and epithelioid histiotypes have an increased incidence of lymph node metastasis and should be carefully examined for adenopathy. Therapeutic lymph node dissection (curative) results in a 34% actuarial survival rate;[105] therefore, the rare patients with regional nodal involvement who have no evidence of extranodal disease should undergo therapeutic lymphadenectomy. Patients with adverse features at the time of dissection (i.e., extracapsular extension beyond the lymph nodes into perinodal fat or positive or doubtful margins on the neurovascular bundle) or in whom treatment into the next grossly uninvolved lymph node echelon is not feasible with surgery should also be considered for additional adjuvant nodal irradiation. The principles underlying this approach have recently been outlined.[197]

Surgery Alone

Although the majority of patients with extremity STS should be treated with preoperative or postoperative radiotherapy, recent reports suggest that concomitant radiotherapy might not be required for selected patients with completely resected, small, primary STSs (Table 97-8).[198–201] Rydholm and colleagues have reported their experience with 70 patients with subcutaneous or intramuscular extremity sarcomas treated with wide surgical resection and microscopic assessment of surgical margins.[200] Negative histologic margins were obtained for 32 of 40 subcutaneous and 24 of 30 intramuscular tumors. The 56 patients with microscopically negative margins received no postoperative radiotherapy, yet only 4 (7%) developed local recurrence. A study from Brigham and Women's Hospital reported similar results for a selected group of 74 patients with primary extremity STS treated by surgery without radiotherapy.[201] The 10-year actuarial local control rate was 93% plus or minus 4%. The absolute gross margin was a significant predictor of local recurrence; patients with a close gross margin of less than 1 cm had a 10-year local control rate of 87% ± 6% compared to 100% for patients with a closest gross margin of 1 cm or greater ($P = 0.04$). The generally favorable local control rates with surgery alone that these and other[198,202] investigators reported in these series of highly selected patients are comparable to local recurrence rates observed for more heterogeneous patient populations treated with conventional multimodality therapy incorporating preoperative or postoperative radiotherapy (Table 97-9).[66,188,203–209] These data support the hypothesis that selected patients with small, primary STSs can be treated with surgical resection alone without preoperative or postoperative radiotherapy.

It is difficult to define the precise selection criteria that should be used to identify patients with primary sarcoma who can safely undergo treatment by surgery without radiotherapy. Most investigators have limited this approach to patients with carefully selected T1 tumors that can be resected with clear margins (see Table 97-8). In contrast, Karakousis and colleagues did not consider absolute tumor size but instead utilized surgical resection alone for all patients in whom a minimum intracompartmental margin of 2 cm could be maintained circumferentially, irrespective of tumor size.[198] Karakousis and colleagues recently updated the results for high-grade STS of the policy of limiting the use of postoperative radiation treatment for tumors resected with positive or "narrow" (less than 2 cm) resection margins.[210] This approach has yielded useful data because the consistent application of this treatment approach resulted in a local recurrence rate of 19% with "wide" margin surgery alone compared to 24% after "narrow" margin surgery and adjuvant radiotherapy.[210] Although the results provide some clarity about the 2 cm or greater margin benchmark, it would be useful to also have similar data from other groups for a variety of margin widths to draw conclusions about when it is safe to withhold radiotherapy. Moreover, the authors acknowledge the potential to treat a greater proportion of cases with radiotherapy and lower the 19% local recurrence rate in some of those "favorable cases" that are currently treated with surgery alone by widening the indication for adjuvant radiotherapy in a proportion of these patients.[210] This view would certainly be consistent with

Table 97-8 Results of Surgery Alone for Selected Patients with Soft-Tissue Sarcoma

First Author	Institution	No. of Patients	Selection Criteria	Adjuvant Radiation (No.)	Local Recurrence (%)	Distant Recurrence (%)
Geer[199]	MSKCC	174	T1 size, primary tumor	117	10	5
Rydholm[200]	Lund, Sweden	56	G/M margin negative	0	7	NR
Baldini[201]	BWH	74	T1 size, G/M margin negative	0	7	12
Karakousis[198]	RPCI	116	2 cm G margin	0	10	NR
Fabrizio[563]	Mayo	34	Not stated	0	15	12

BWH, Brigham and Women's Hospital; G/M, gross/microscopic; Mayo, Mayo Clinic; MSKCC, Memorial Sloan-Kettering Cancer Center; NR, not reported; RPCI, Roswell Park Cancer Institute.

Table 97-9 Local Control with Surgery and Radiotherapy for Localized Soft-Tissue Sarcoma

Radiotherapy Approach	First Author	Radiation Dose (GY)	Study Design	No. of Patients	Local Failure (%)	Subset
Preoperative EBRT	Suit[203]	50–56	Retrospective	89	17	
	Barkley[204]	50	Retrospective	110	10	
	Brant[205]	50.4	Retrospective	58	9	
	O'Sullivan[211]	50	RCT	94	7	
Brachytherapy	Pisters[193]	42–45	RCT	119	9	(high-grade)
				45	23	(low-grade)
Postoperative EBRT	Lindberg[207]	60–75	Retrospective	300	22	
	Karakousis[208]	45–60	Retrospective	53	14	
	Suit[203]	60–68	Retrospective	131	12	
	Yang[188]	45 + 18	RCT	91	0	(high-grade)
				50	5	(low-grade)
	O'Sullivan[211]		RCT	96	7	

EBRT, external beam radiotherapy; RCT, randomized controlled trial.
Randomized controlled trials and selected nonrandomized retrospective series.

contemporary observations such as the local recurrence rate of 7% in patients who are undergoing combined modality treatment such as those in the recent Canadian randomized trial (see section on Preoperative or Postoperative Radiotherapy).[211]

Factors other than anatomic location, tumor size, and the feasibility of achieving an R0 resection (macroscopically and microscopically complete) should be considered in selecting patients for treatment by surgery alone. For example, the issue of whether the patient has had a prior "unplanned" excision (referred to earlier) is important. At the Princess Margaret Hospital, a significantly higher rate of local recurrence was apparent in patients who were treated after unplanned excision on the outside than in patients who received their treatment at their institution (22% versus 7%, $P = 0.03$).[195] It is important to remember that unplanned excision is very common in the community setting, where small soft-tissue lesions are often excised without image guidance under the presumption that they are benign. Therefore, while it is reasonable to attempt a reexcision if it is considered feasible, patients who have undergone unplanned excision should also be strongly considered for adjuvant radiation.

Preoperative or Postoperative Radiotherapy

Conservative (limb-sparing) surgery and radiotherapy have been combined to optimize local control for patients with localized STS. Radiotherapy can be administered preoperatively,[203–205,212,213] postoperatively,[207,214,215] or by interstitial techniques (brachytherapy).[66,206,216–220]

Local Control

Data from two randomized controlled trials (RCTs)[71,188] have confirmed earlier retrospective reports suggesting that surgery combined with radiotherapy results in superior local control compared to surgery alone.[204,207,209] Yang and colleagues from the NCI recently reported on a RCT of postoperative external beam radiotherapy (EBRT).[188] In this trial, 141 patients with localized extremity STSs amenable to limb-sparing resection were randomly assigned to receive postoperative EBRT or no radiotherapy. All patients with high-grade lesions received postoperative chemotherapy. In the subset of 91 patients with high-grade lesions, no local recurrences have been noted in the 44 patients who received postoperative radiotherapy (with chemotherapy) versus 9 local recurrences (19%) in the 47 patients who received postoperative chemotherapy alone ($P = 0.0003$). In the 50 patients with low-grade sarcomas, 1 (4%) of 26 patients who received adjuvant radiotherapy has had a local recurrence versus 8 (33%) of 24 patients treated by surgical resection alone ($P = 0.016$). However, no improvement in survival was noted with adjuvant radiotherapy in the entire cohort of patients or in any subgroup.

The second RCT of postoperative radiotherapy was conducted at Memorial Sloan-Kettering Cancer Center, where investigators studied adjuvant brachytherapy for patients with extremity and superficial trunk STSs.[193] One hundred sixty-four patients with extremity or superficial trunk STSs were randomly assigned to receive adjuvant brachytherapy (42 to 45 Gy with an iridium-192 implant) or no postoperative radiotherapy after complete resection of their sarcomas. Randomization took place in the operating room after gross total resection, thereby limiting the potential bias that might influence the extent of surgical resection in a comparative trial. Sixty-eight of 119 patients with high-grade tumors also received chemotherapy. With a median follow-up of 76 months, 5-year actuarial local control rates were significantly better in the group treated with adjuvant brachytherapy (82%) than in those who received surgery alone (69%). Subset analysis demonstrated that the local control advantage of brachytherapy was confined to patients with high-grade lesions, for whom the 5-year local control rate was 89% (versus 66% in the surgery-only group; Fig. 97-12). Patients with low-grade STSs did not appear to experience the same local control benefit with adjuvant brachytherapy.[193,220] As was noted in the NCI RCT,[177] the improvement in local control did not translate into any detectable survival difference between the brachytherapy and no-brachytherapy arms of the trial.

Local failure rates with combined-modality regimens incorporating surgery and radiotherapy are generally less than 15% (see Table 97-9). Despite theoretical advantages that may favor preoperative radiation, brachytherapy, or postoperative radiation, there does not appear to be a major difference in local control rates among these radiation techniques, although at present, data comparing the approaches are sparse.

Relationship Between Local Control and Survival

Whether local control affects overall survival for patients with STS remains unclear and highly controversial.[221–225] Only an adequately powered prospective randomized trial can assess the precise nature of any relationship between local control and overall survival. Three RCTs have evaluated local control and survival in the context of defining treatment approaches for STS. In a randomized trial of

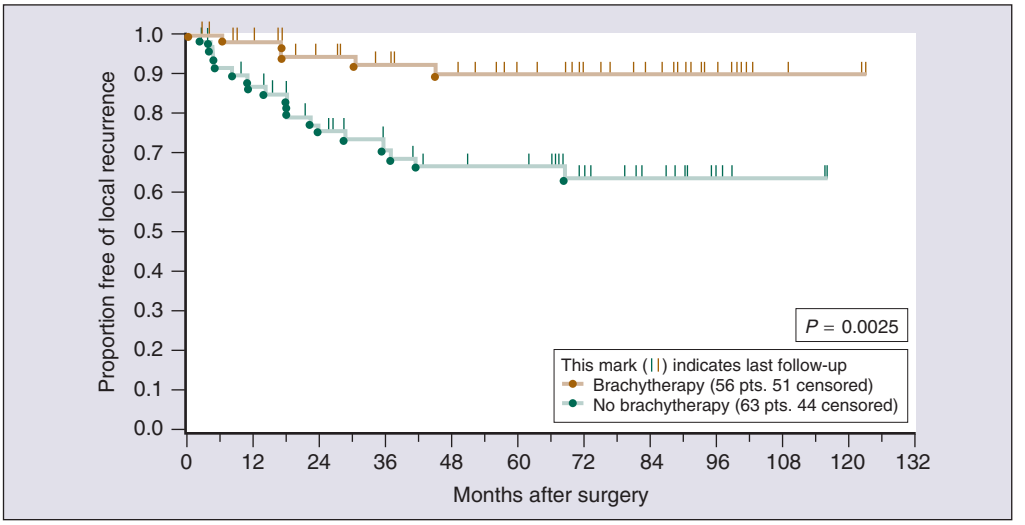


Figure 97-12 • Local recurrence-free survival in patients with high-grade sarcoma treated in the Memorial Sloan-Kettering Cancer Center randomized trial of postoperative brachytherapy versus surgery alone. A statistically significant difference was noted in local recurrence-free survival with brachytherapy ($P = 0.0025$). (Reprinted with permission from Pisters PW, Harrison LB, Leung DH, et al: Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol 1996;14:859.)

amputation versus conservative surgery plus radiation from the NCI, local recurrence rates were 19% in the limb-sparing arm versus 6% in the amputation arm ($P = 0.022$).[182,183] Despite this, overall survival rates were equivalent at 70% for limb-sparing surgery and 71% for amputation ($P = 0.97$). In the randomized trials of postoperative radiotherapy,[188,193] the improvement in local control that was noted in patients who were treated with surgery plus radiotherapy did not translate into any detectable survival advantage. Thus, none of the currently available data from prospective RCTs support the hypothesis that better local control enhances survival in patients with sarcoma. Methodologically, the available trials are problematic for this issue because the outcome of interest (i.e., a difference in survival consequent on a differential in local control) would require a prohibitively large sample size. Thus, it is most improbable for these trials to be capable of demonstrating an effect with their modest sample sizes that were intended for evaluation of different outcomes. Indeed, it is most unlikely if even a meta-analysis of the trials could demonstrate this. Furthermore, data from nonrandomized studies support the concept that there is little, if any, relationship between local control and survival. In a recent series from Sweden, the outcome of patients who were treated with an inadequate excision was compared with that of patients who had an adequate operation.[224] Local recurrence was 3.5 times more common after inadequate excision, but there was no difference in the incidence or timing of distant metastases. The power of the RCTs that have been reported so far to detect a difference in survival is relatively small, and a large number of patients may be required to demonstrate that prevention of local recurrence affects survival.[222] Stotter and colleagues have argued that local recurrence is a time-dependent variable and should be considered as such in multivariate studies.[221] Analysis in this fashion of the data from a nonrandomized study demonstrates a statistically significant relationship between local control and survival. Other retrospective analyses have yielded similar conclusions.[226,227]

For a more detailed description of the methodologic problems associated with time-dependent variables and the use of surrogate endpoints that emerge after the initial sarcoma treatment, the reader is referred elsewhere.[228] In this context, it is clearly important to distinguish between the well-defined adverse prognostic impact of subsequent local recurrence on survival[109,225,229] and the unproven positive effect of improved local control (i.e., prevention of local recurrence with improved local therapy) on survival. The former phenomenon might be a manifestation of more aggressive tumor biology; that is, biologically more aggressive lesions might recur locally and metastasize more frequently.

Treatment Sequencing: Preoperative versus Postoperative Treatment

Of further interest, an improvement in overall survival (a crude rate of 85% versus 72% in favor of postoperative radiotherapy, $P = 0.0481$) has emerged and is only partially explained by increased deaths in the postoperative arm unrelated to sarcoma (Fig. 97-13).[211] This observation is of obvious oncologic interest. Longer follow-up is clearly required, and a 5-year analysis is currently under way. In summary, the final results of the SR2 trial are expected to provide insight into the comparative efficacy, functional outcome, economic costs, and complication rates of these two options for EBRT and potentially on survival outcome if the preliminary results are sustained.

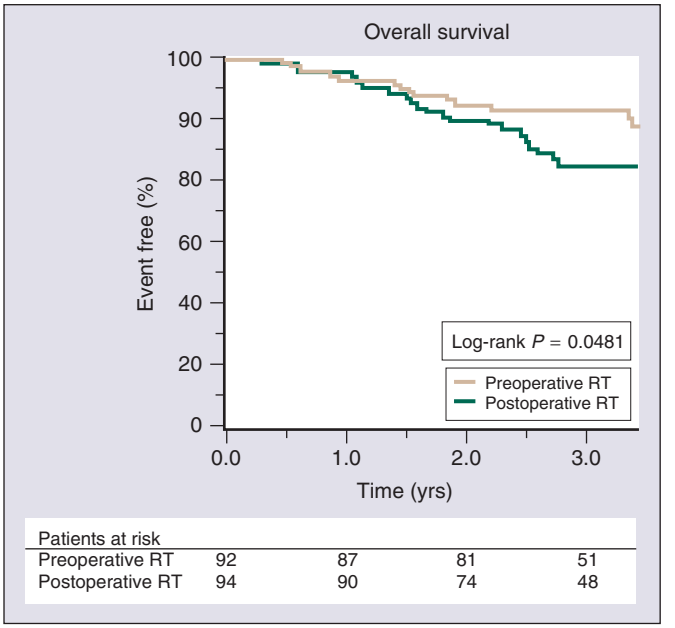


Figure 97-13 • Actuarial probability of overall survival for preoperative versus postoperative radiotherapy in extremity soft-tissue sarcoma. (Reproduced with permission from O'Sullivan B, Davis AM, Turcotte R, et al: Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet 2002;359:2235.)

Until the mature data from the Canadian Sarcoma Group RCT are available, it appears reasonable to treat patients with postoperative EBRT, since local control rates are comparable to preoperative techniques but major wound complication rates are significantly lower. On the other hand, the maturing data on late tissue effects for these respective approaches in the Canadian trial are salutary, and the emerging potential influence on survival, pending 5-year analysis, is awaited with interest. Also, in anatomic sites where wound complications are rarely seen (e.g., the upper extremity), the rationale for wound complication avoidance as a reason to favor the use of postoperative radiotherapy is not as sound. In particular, the obvious advantage to preoperative radiotherapy in the proximal arm and shoulder is apparent where avoidance of large volume and higher dose irradiation that may treat the lung or brachial plexus can be achieved. These principles are also reasonable in the head and neck based on the recent Princess Margaret Hospital data.[196]

On the other hand, with brachytherapy, the patient's entire local treatment (surgery plus radiation) can be completed in 10 to 14 days. This has significant cost advantages[230] and also has significant implications in terms of overall patient convenience. In the absence of comparative data addressing the efficacy of these techniques in achieving local control, these additional considerations assume increased importance. Where the necessary expertise is available for brachytherapy, this technique provides an excellent, cost-effective alternative for patients with high-grade lesions. Brachytherapy should not be used for patients with low-grade sarcomas.[220]

Recently, an RCT of EBRT for patients with localized extremity STS was reported by the National Cancer Institute of Canada Clinical Trials Group/Canadian Sarcoma Group in which 190 patients with extremity STS were randomized to preoperative versus postoperative radiation.[211] The radiotherapy parameters for this protocol required a field margin of 5 cm around the gross tumor volume for the initial phase of treatment (i.e., treatment to 50 Gy in 25 fractions), and this generally included any peritumoral edema that was seen on MRI, irrespective of the grade or size of the tumor. Subsequently, a reduced-volume field was treated to a total combined dose of 66 Gy in all postoperative cases and in those preoperative patients in whom the resection margins were involved.

The results of this trial are complex because the primary endpoint that powered the trial, and hence its sample size, was the cumulative incidence of acute wound complications 120 days after protocol surgery in both arms of the study. Nevertheless, the local control rates after 3.3 years of median follow-up are identical in both arms of the study (7%).

Wound Complication Rates and Post-Treatment Function

The results of the Canadian RCT may provide insight into the comparative efficacy, functional outcome, economic costs, and complication rates of preoperative and postoperative treatment sequencing for EBRT. In the absence of a clear local control advantage to any specific radiation technique, clinicians have considered other factors in formulating standards of care. Such factors have included wound complication rates, financial costs, patient convenience, health-related quality of life and physical function, radiotherapy toxicity, and perhaps even overall survival.

It is clear that while field size and radiation dose may be minimized with preoperative radiotherapy,[231] major wound complications after preoperative radiotherapy and surgery have been reported to be in the 20% to 35% range.[232,233] In the Canadian Sarcoma Group RCT, wound complications were defined as secondary wound surgery, hospital admission for wound care, deep packing, or prolonged dressings within 120 days after tumor resection. By these criteria, preoperative radiation had a significantly higher rate (35% versus 17%, $P = 0.01$) of wound complications than did postoperative EBRT. Of note, the risk was confined to the lower extremity.[211]

Taken in isolation, the wound complication fact alone can be expected to cause some groups to continue to favor postoperative radiotherapy, though this could change, as data have now emerged from the Canadian RCT that late tissue outcomes strongly favor the preoperative approach and a putative survival advantage needs to await mature follow-up.[234] Thus, the radiotherapy toxicity rates after 2 years differed between the arms of the study. The rates of grade 2 or greater fibrosis and edema were significantly higher in the postoperative arm compared to preoperative radiotherapy and were independently associated with the larger irradiation volumes and doses used in postoperative radiotherapy.[234] Short-term functional outcome in the SR2 trial has also been reported and continues to be collected prospectively.[235] Two validated instruments—the Toronto Extremity Salvage Score (TESS) and the Short Form-36 quality of life instrument (SF-36)—were applied, as was the observer-based Musculoskeletal Tumor Society Rating Scale (MSTS).[235] Patients who were treated with postoperative radiotherapy had better function with higher MSTS, TESS, and SF-36 bodily pain scores at 6 weeks after surgery than did those who were treated with preoperative radiation, but there were no differences at later time points up to 1 year. Thus, the timing of radiotherapy has minimal impact on the function of STS patients in the first year after surgery, but thereafter, significant factors likely come into play. These include the apparently deteriorating late tissue sequelae caused by larger doses and volumes. Of interest, patients who experience wound complications appear to continue to suffer some impaired function. Further follow-up will be required to assess the ongoing evolution of these competing risks.

Conformal Radiotherapy and Intensity-Modulated Radiotherapy

STSs present in virtually any anatomic site, and the capacity for unusual presentation is almost limitless. This can result in circumstances in which conventionally delivered radiotherapy is impossible owing to the magnitude of the volume to be treated, uncertainty in defining the target for radiotherapy, or, more usually, because of the proximity of normal tissues to the intended target volume. While some presentations are extremely problematic (e.g., uncertain targets due to organ mobility or imprecise anatomic issues resulting from poor definition of tumor location related to imaging limitations or inadequate surgical and/or pathologic description), others can be addressed by novel methods of radiotherapy delivery. Leading the advances in this field is intensity-modulated radiotherapy, an advanced form of three-dimensional conformal radiotherapy in which radiation beams are not only shaped at their perimeters, but also include variable intensity across the profiles of the beams. This permits the creation of exquisite conformation of dose to targets of irregular shape while generating high-dose gradients between tumor and normal tissues. A full discussion of the potential uses of intensity-modulated radiotherapy in STS is beyond the scope of this chapter but is discussed in detail elsewhere.[236] It may be administered preoperatively, postoperatively, or as a sole modality with specific indications. Some applications include its use in lesions adjacent to the spine or critical anatomic structures of the head and neck and in the retroperitoneum to permit liver avoidance (as well as to permit spinal cord, kidney, and intestinal dose limitation), especially in lesions involving the right upper abdominal quadrant. Avoidance of late toxicity to anatomic structures such as weight-bearing bone that are at risk for fracture after treatment of extremity sarcomas seems also to be feasible.[237] Although these approaches are promising, their precise contribution and role need to be evaluated.[238]

Conventional Radiotherapy Without Surgery

Radiotherapy alone has been employed as primary therapy for patients with locally advanced, inoperable STS and patients who present with stage IV disease. Efforts to use radiation as the primary treatment have demonstrated that high doses (more than 65 Gy) are required to achieve local control rates between 30% and 60%[239,240] and that

there appears to be an inverse relationship between tumor size and local control rates. In a series of 35 patients treated with high-dose (>65 Gy) primary radiotherapy for tumor sizes less than 5 cm, 5 to 10 cm, and larger than 10 cm, the local control rates were 88%, 53%, and 33%, respectively.[241] In general, local control rates with radiation alone are inferior to those after surgery; therefore, primary radiation should be reserved for patients who are medically unfit for surgery, have technically unresectable tumors, or refuse surgery as initial therapy. However, some caution is necessary in interpreting such results in a scientifically valid manner. Encumbered with such adverse selection factors, the outcome of radiotherapy would never be comparable to that of surgery. Moreover, surgery has the added advantage over radiotherapy alone because its use for locally advanced cases is ordinarily also combined with adjuvant radiotherapy.

Neutron Radiotherapy

Neutron radiotherapy has been emphasized by certain groups because of the lower oxygen enhancement ratio compared to x-rays and the consequent attractive possibility of overcoming the biologic phenomenon that hypoxic cells generally limit the curability of malignancy with x-rays. Additional differences from x-rays are the reduced repair of sublethal and potentially lethal damage. These neutron effects are less vulnerable to the differential radiosensitivities associated with different phases of the cell cycle. It should be apparent that some of these repair phenomena also negatively affect the tolerance of normal tissues. Neutrons have been employed in a number of pilot studies, primarily in patients with locally advanced disease, with 60% to 70% local control rates.[242–244] In a recent large series, 220 patients with locally advanced sarcomas were treated with neutron radiotherapy. Ninety-four patients with gross residual disease after resection were treated with neutron therapy alone; among these patients, 27% had major morbidity, 26% had 5-year survival, and 56% had local control. One hundred four patients with microscopically positive margins of resection received a neutron boost dose; they had 7% morbidity, 65% 5-year survival, and 78% local control rates. These results suggest that for patients with gross residual disease, neutron beam radiation may provide improved local control compared to conventional external beam treatment, but these data should continue to be interpreted with caution when one considers the late tissue sequelae that appear to result from neutron beam radiation use. Comparative studies are needed to define the precise role of neutron beam therapy in the treatment of STS. Apart from unresectable disease, it seems unclear where the benefit of neutron therapy might accrue when one considers the exceptionally favorable results of conventional x-ray treatment combined with surgery and the more adverse normal tissue tolerance to neutron therapy.

Adjuvant Chemotherapy

In the past 30 years, improvements in surgical and radiotherapy techniques have led to impressive rates of local control, particularly in extremity STS, with concomitant sparing of normal tissues and preservation of limb and/or organ function. Regrettably, in the same period, much less progress has been made in finding ways to eradicate the micrometastases that are the ultimate cause of death in many individuals who present with apparently localized STS. The discovery that doxorubicin had significant antitumor activity against adult STS prompted the initiation of multiple RCTs during the period 1973 to 1990 to evaluate the benefit of doxorubicin alone or in combination with other agents after the completion of local treatment. However, most of these trials were too small to detect moderate treatment effects reliably.

The statistical technique of meta-analysis may overcome the problem of inadequate power of small RCTs, and meta-analyses based on individual patient data (IPDMA) can minimize other potential biases (e.g., exclusion of unpublished trials, variable follow-up, postrandomization exclusions, and differing definition of endpoints) that are inherent in analyses that are limited to published results. In 1997, the Sarcoma Meta-Analysis Collaboration (SMAC) published an IPDMA of outcomes for 1568 STS patients included in 14 RCTs that completed accrual by December 1992.[245] As is outlined in Table 97-10, significant improvements were found in local and distant relapse-free intervals and recurrence-free survival for all patients, and these improvements did translate into a significant overall survival benefit in the prospectively defined subgroup—almost 60% of the patients—with extremity sarcomas but not in all patients.

When interpreting the SMAC results, one should compare them with the IPDMAs that have provided conclusive evidence of the benefits of adjuvant chemotherapy and hormone therapy in early breast cancer.[246,247] In contrast with the approximately 1500 patients who were included in the SMAC IPDMA, the Early Breast Cancer Collaborative Trials Group identified 47 trials that recruited 18,000 patients for comparisons of adjuvant chemotherapy versus no adjuvant chemotherapy. The power of large numbers, even in the setting of meta-analysis, is self-evident. Compounding the problem of small numbers of STS cases, STSs as a group show marked heterogeneity in pathology and site of origin; this is much less evident in breast cancer. For example, it has been suggested that in the SMAC meta-analysis, chemotherapy benefits for extremity (57% of total) and high-grade STSs were obscured by inclusion of sarcomas at other locations (head and neck, trunk, and uterus) and those of low (5%) or unknown grade (28%). Another point of contrast with breast cancer is the relative paucity of drugs that are active against STS. At the time of the SMAC meta-analysis, only two agents (doxorubicin and ifosfamide) have reproducibly produced overall response rates exceeding 20% in patients with advanced disease. This provides limited opportunity to exploit the potential advantages of combination chemotherapy. Of the 14 trials that were included in the SMAC meta-analysis, 6 used doxorubicin alone, and the remaining 8 were trials of combination chemotherapy. Only one unpublished STS trial (29 patients) examined the combination of doxorubicin with ifosfamide.

Table 97-10 Adjuvant Doxorubicin-Based Chemotherapy for Localized Soft-Tissue Sarcoma: Sarcoma Meta-Analysis Collaboration Results

Survival Outcome	No. of Trials	No. of Patients	Hazard Ratio (95% CI)	*P* Value	10-Year Survival Benefit (%)
Overall, All patients	14	1544	0.89 (0.76–1.03)	0.12	4
Overall, Extremity only	12	886	0.80 (NA)	0.029	7
Recurrence-free	14	1366	0.75 (0.64–0.87)	0.0001	10
Local recurrence-free	13	1315	0.73 (0.56–0.94)	0.016	6
Metastasis-free	13	1315	0.70 (0.57–0.85)	0.0003	10

Adapted from Tierney JF: Adjuvant chemotherapy for localized respectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet 1997;350:1647.

Table 97-11 Post-1992 Randomized Controlled Trials of Adjuvant Chemotherapy versus Observation in Soft-Tissue Sarcoma

Study	Chemotherapy Regimen	No. of Patients	Disease Sites	Follow-up	Survival	
					RFS	OS
Italian Cooperative*[249]	Epirubicin + Ifosfamide + G-GSF (×5)	53	Limb (grade III > 5 cm)	59 mos (median)	48 mos	75 mos
	Control	51			16 mos	46 mos
					$P = 0.04$	$P = 0.03$
Australian Cooperative†[250]	Ifosfamide + Doxorubicin + Dacarbazine (IFADIC) + G-CSF ×6	31	Limb 47, Trunk 12 (grade II/III)	41 mos (mean)	77%	NR
	Control	28			57%	NR
					$P = 0.1$	$P = 0.4$

G-CSF, granulocyte colony stimulating factor; mos, months; NR, not reported at defined follow-up time; OS, overall survival; RFS, recurrence-free survival.
Outcome data provided in original papers.
*Median recurrence-free plus overall survival.
†(1) comparison % recurrence-free plus overall survival after mean observation period 41 (8–84) mos. (2) overall survival plotted but actuarial results not reported at defined follow-up time(s).

Since the SMAC meta-analysis, full reports have been published on two additional RCTs (Table 97-11) examining high-dose anthracycline and ifosfamide-based regimens supported by granulocyte colony-stimulating factor (G-CSF). In the Italian Cooperative Group study,[248] accrual was terminated, based on an early stopping rule, after half the planned number of patients had been recruited. The median recurrence-free survival and overall survival (see Table 97-11) were significantly better for the chemotherapy group, but a high cumulative incidence of late distant relapses was noted (2 year: 28% versus 45%, $P = 0.08$; 4 year: 44% versus 45%, $P = 0.94$ for chemotherapy versus control groups, respectively), although 4-year overall survival remained better for the chemotherapy group (69% versus 50%, $P = 0.04$). At the last published analysis, after a median follow-up of 89.6 months (range: 56 to 119), the intention-to-treat analysis still reveals a difference in overall survival ($P = 0.07$).[249] The 5-year overall survival estimates, a reasonable endpoint for the survival analysis of adjuvant treatment in STSs, were 66.0% and 46.1% for the treatment and the control groups, respectively ($P = 0.04$).[249]

The authors of the second study, a prospective randomized feasibility trial, concluded that a regimen of six cycles of ifosfamide, doxorubicin, and dacarbazine given concurrently with postoperative hyperfractionated radiotherapy (during cycles 3 and 4 when doxorubicin was omitted from the regimen) was manageable and tolerable.[250] It did not translate into significant benefits in recurrence-free survival ($P = 0.1$ versus control arm), time to local failure ($P = 0.09$), or overall survival ($P = 0.4$), but the small number of patients (31 versus 28) precludes any meaningful conclusions regarding benefit. A third RCT, from another Italian center, has been published in abstract form.[251] Only 19 of 41 patients in the chemotherapy arm received an intensive epirubicin/ifosfamide combination (the remainder received single-agent epirubicin), and the study was underpowered for efficacy endpoints.

So can any definite recommendations be made regarding the use of adjuvant chemotherapy in adult STS? In an editorial[252] that accompanied the report of the Italian Cooperative Group Trial,[248] Bramwell concluded that a specific standard of care was not yet clear and that the situation would take some time to change. A Canadian practice guideline[253] on this topic has suggested: "It is reasonable to consider anthracycline-based adjuvant chemotherapy in patients who have had removal of a sarcoma with features predicting a high likelihood of relapse (deep location, size >5 cm, high histological grade)." With the current state of knowledge, we believe that this is a reasonable approach. One of the high-dose anthracycline and ifosfamide regimens used in recent RCTs seems a logical choice for adjuvant treatment but might not be suitable for the substantial minority of patients who are older than 70 years. (This group has been excluded from RCTs evaluating these regimens.) Ultimately, the decision of whether to administer adjuvant chemotherapy and the regimen that is chosen will depend on a number of considerations, including risk of relapse, physician preferences (which may also depend on patient age and comorbid conditions), referral practices, and available resources. While there are very strong opinions on whether or not chemotherapy has added sufficiently to local therapy for routine use in high-risk patients, all agree on two facts: (1) High-risk patients die far too often of metastatic disease, so effective systemic treatment is needed; and (2) there is no current regimen that is anywhere near good enough.

Neoadjuvant Chemotherapy

Given that the role of postoperative adjuvant chemotherapy for patients with adult STS remains controversial, it is hardly surprising that the advantages of chemotherapy given before surgery (neoadjuvant therapy) are even less clear, particularly as there have been no adequately powered RCTs addressing this issue. Nonetheless, neoadjuvant chemotherapy has theoretical benefits that include the following:

- Destruction of the primary tumor may reduce the risk of contamination at surgery and permit closer margins with less tissue loss and functional disability but improved local control.
- Extensive delays in initiating chemotherapy resulting from complex surgery and/or radiotherapy are avoided; for rapidly growing tumors, this earlier elimination of micrometastases may improve survival, although this has not been proven.
- Treating with an intact tumor allows the medical oncologist to assess the effects of preoperative therapy and thus judge whether the chosen chemotherapeutic regimen has activity against the specific tumor in the specific patient being treated. The importance of this opportunity to determine whether an empirically chosen regimen will or will not be beneficial cannot be underestimated, especially in dealing with marginally effective chemotherapy.

Numerous neoadjuvant treatment approaches and preoperative drug regimens have been explored. Intra-arterial (IA) administration of drugs such as doxorubicin or cisplatin has been evaluated, in some cases in conjunction with radiotherapy, isolated limb perfusion, and/or hyperthermia. The IA route delivers drugs more directly to the tumor but is more complex, expensive, and prone to complications

than is the intravenous (IV) route. In the one small RCT on route of administration, there were no differences in rates of local control or overall failure between neoadjuvant chemotherapy given IA or IV.[254,255] In a series of nonrandomized studies reflecting the evolution of neoadjuvant treatment at their center over a 20-year period, the University of California, Los Angeles (UCLA) group treated a total of 498 patients with neoadjuvant chemotherapy.[256] The combination of chemotherapy and 28 Gy of radiotherapy before surgery provided the best local control with the lowest complication rate. On the basis of results of the RCT described earlier, IA doxorubicin was replaced by IV doxorubicin, and cisplatin and ifosfamide were added to the most recent protocol.[256] In the whole group of 498 patients, the overall local recurrence rates were 11% at 5 years and 15% at 10 years, and corresponding overall survival rates were 71% and 66%. The local recurrence rate was lower and overall survival rate higher for patients who had no residual tumor (38%) or greater than 95% necrosis (14%) after neoadjuvant chemotherapy, compared with those who had less than 95% necrosis. In a multivariate analysis, pathologic necrosis was an independent predictor of local recurrence and overall survival. The percentage of patients with 95% or greater necrosis increased to 48% with the addition of ifosfamide, compared to 13% for patients in all other protocols combined.

Pisters and colleagues have reviewed the long-term results of neoadjuvant chemotherapy given at the University of Texas M.D. Anderson Cancer Center for stage IIIB extremity sarcomas between 1986 and 1990.[257] All patients received doxorubicin-based regimens; at that time, ifosfamide was rarely used (3 patients). In 75 patients, the overall clinical objective response rate (complete response plus partial response) was 27%. At a median follow-up of 85 months, the 5-year actuarial local recurrence-free survival, overall recurrence-free survival, and overall survival rates were 83%, 52%, and 59%, respectively. In contrast with the UCLA group's results[256] for pathologic response, there were no differences in any outcomes between responding and nonresponding patients, as defined at that time. In the M.D. Anderson experience, complete pathologic response was an infrequent event, occurring in only 8% of patients treated between 1984 and 1992, although patients receiving preoperative radiation were excluded.[258] Five of the six patients with pathologic complete response were long-term survivors after a median follow-up of 76 months, supporting the findings from UCLA.

In a separate analysis at M.D. Anderson, 65 patients (42 extremity sarcomas and 23 retroperitoneal sarcomas) were treated at the same center between 1991 and 1996 with doxorubicin- or ifosfamide-based neoadjuvant chemotherapy; 34% achieved a radiographic partial response and 9% a minor response.[259] Patients having partial response had higher rates of negative-margin resections, local recurrence-free survival, and overall survival than did nonresponders. Postoperative morbidity was also evaluated in a larger cohort of 105 patients (71 extremity and 34 retroperitoneal STS) treated at M.D. Anderson during the same period, of whom 50 received ifosfamide as well as doxorubicin.[260] The authors found no evidence that preoperative chemotherapy increased surgical complications (e.g., wound infections and other wound problems), length of hospital stay, rate of readmission, or rate of reoperation.

A number of other institutions have recently reported, mostly in abstract form, their experience with neoadjuvant chemotherapy using doxorubicin- and ifosfamide-based regimens that in many cases included cisplatin.[261–264] In most of these studies, radiotherapy followed chemotherapy and was given preoperatively or postoperatively.

The European Organization for the Research and Treatment of Cancer (EORTC) has performed the only RCT assessing preoperative chemotherapy for STS (three cycles of doxorubicin and ifosfamide plus G-CSF) versus no preoperative chemotherapy (control).[265] A total of 150 patients with high-risk STS (≥8 cm any grade, or grade II/III tumors <8 cm, or grade II/III local recurrence tumors/inadequate surgery) were randomized, of whom 134 were considered eligible for outcome assessment. Radiotherapy was indicated for tumors that were excised with close or microscopically positive margins and was given in 46% of patients in the chemotherapy arm and 54% of patients in the control arms. Limb salvage was possible in 89% of patients, and chemotherapy did not affect postoperative wound healing. Grade 4 toxicities were rare, although there was one death due to neutropenic fever. At a median follow-up of 7.3 years, the 5-year recurrence-free survival and overall survival rates were 56% versus 52% ($P = 0.36$) and 65% versus 64% ($P = 0.22$) for the chemotherapy and control arms, respectively. Although originally planned as a phase III trial with adequate numbers to detect a 15% difference in 5-year overall survival, the study was closed after completion of the phase II section because of slow accrual. Most groups have concluded that for large high-grade tumors, preoperative chemotherapy is feasible, does not increase postoperative morbidity, increases the rate of operability, and may enhance local control. The beneficial effects on distant metastases and overall survival, if any, are less clear.

It is impossible to determine from the results of the phase II retrospective or prospective series whether preoperative neoadjuvant chemotherapy reduces distant metastases and improves survival, and the EORTC RCT was too small to illuminate this issue. Preoperative chemotherapy, particularly in combination with preoperative radiotherapy, can induce substantial rates of pathologic necrosis, may increase operability in large high-grade tumors, and leads to impressive rates of local control. It is not clear, however, that these results are better than would be achieved with preoperative radiotherapy alone, particularly if radiation is delivered by using modern intensity-modulated techniques; and most neoadjuvant chemotherapy regimens are associated with substantial toxicity. The contribution of drugs such as cisplatin and dacarbazine (agents with poor activity in metastatic STS) other than increasing toxicity can be questioned. There is a clear need for an RCT comparing neoadjuvant chemoradiotherapy with preoperative radiotherapy alone in patients with large high-grade STS. Because this will require international collaboration and opinions regarding the value of chemotherapy are often entrenched, this may never occur. Preoperative chemoradiotherapy should be delivered only in centers experienced in these techniques, providing further rationale for referral of the majority of patients with STSs to centers that can provide multidisciplinary assessment and treatment. Alternative techniques to achieve local control in large high-grade extremity STS are discussed in the next section.

Combined Preoperative Chemotherapy and Radiotherapy

With the advances that have been made with combined-modality treatment of other solid tumors, there has been interest in combined-modality preoperative treatment (concurrent or sequential chemotherapy and radiation) for patients with localized STSs. Concurrent doxorubicin-based chemoradiation has been employed extensively by Eilber and colleagues at UCLA.[266,267] This treatment protocol involved intra-arterial doxorubicin with unusually high-dose-per-fraction radiotherapy (35 Gy of EBRT delivered in 10 daily fractions, which was reduced to 17.5 Gy in 5 daily fractions to minimize local toxicity). A subsequent prospective randomized trial compared preoperative IA doxorubicin to IV doxorubicin, both followed by 28 Gy of radiation delivered over 8 days followed by surgical resection.[268] No differences in local recurrence or survival were noted.

The combination of regional chemotherapy and concurrent radiotherapy that was originally pioneered by Eilber and colleagues has been modified and utilized by other groups.[269–271] Investigators from the University of Illinois treated 55 patients with a 10-day preoperative regimen of intra-arterial doxorubicin (10 mg/m^2/day) with concomitant radiotherapy (25 Gy: 2.5 Gy per fraction in 10 fractions).[271] With a mean follow-up of 94 months, local control was 85%. Complications related to the therapy occurred in 26% of patients and

required further operative management in 7% of patients. Temple and colleagues treated a group of 42 patients with a similar regimen of 60 to 90 mg of doxorubicin that was infused IA or IV over a 3-day period followed by sequential radiotherapy (30 Gy: 3 Gy per fraction in 10 fractions).[270] Resection of the residual post-treatment mass was performed 4 to 6 weeks later. At a median follow-up of 6 years, local control was achieved in 39 of 40 patients, although two patients were excluded from this analysis because clear margins were not obtained at the time of surgery. IA infusion-related complications occurred in 4 (11%) of 35 patients. Objective radiographic and pathologic response rates were not reported; therefore, the efficacy of concurrent chemoradiation therapy in achieving cytoreduction to an extent sufficient to convert lesions that are resectable by amputation only to lesions that are amenable to a limb-sparing approach remains largely anecdotal. Moreover, whether preoperative chemoradiation approaches offer local control advantages over conventional treatment approaches employing surgery with preoperative or postoperative radiotherapy is also not apparent. In fact, with current local control rates exceeding 90%, it is difficult to appreciate how this may be further improved by using preoperative chemotherapy unless the strategy involved a radiotherapy dose reduction to ameliorate normal tissue toxicity.

Alternative chemoradiation sequencing has been employed by investigators from Massachusetts General Hospital, who have recently reported mature data from a sequential chemoradiation strategy in the treatment of patients with large (>8 cm) localized, high-grade extremity STSs.[272] This treatment protocol involved interdigitating courses of chemotherapy and radiotherapy: three courses of doxorubicin, ifosfamide, mesna, and dacarbazine and two 22-Gy courses of radiation (11 fractions each) for a total preoperative radiation dose that is lower than is usually used (44 Gy). This was followed by surgical resection with microscopic assessment of surgical margins. An additional 16-Gy (8 fractions) boost dose was delivered for microscopically positive surgical margins. The strategy therefore usefully addresses the dual problems of local control and metastatic risk. The outcomes of 48 patients who were treated with this regimen between June 1989 and March 1999 have been compared to those of a matched series of historic controls (treated between January 1988 and March 1997).[272] The 5-year actuarial local control, distant metastasis-free survival, and overall survival rates for the sequential chemoradiation group are 92%, 75%, and 87%, respectively. For the matched historic controls, these rates are 86%, 47%, and 58%, respectively. The protocol was toxic, with 29% experiencing confluent moist skin desquamation, 25% requiring hospitalization at some time for febrile neutropenia, and G-CSF needed in 81%. Wound-healing complications evaluated using recently described criteria[211] were apparent in 29% of cases and confined to the lower extremities, as was also observed in the Canadian Sarcoma Group treatment sequencing RCT.[211] One patient died from late marrow dysfunction attributed to chemotherapy. Although the results are encouraging from a tumor standpoint (Fig. 97-14), they will require prospective comparative studies for confirmation and especially because of the local and systemic toxicity associated with this approach.[273] An ongoing Radiation Therapy Oncology Group protocol (RTOG-95–14) has also investigated this treatment approach (see the section on preoperative chemotherapy).[274] While the RTOG phase II results are similar in terms of tumor outcome to the data of DeLaney and colleagues,[272] they too are characterized by concerning features of significant toxicity, including marrow dysplasia and treatment-related death.

Hyperthermic Isolated Limb Perfusion and Whole-Body Hyperthermia with Chemotherapy

Hyperthermic isolated limb perfusion and whole-body hyperthermia are two investigational techniques that continue to receive considerable attention, particularly in Europe. Hyperthermic isolated limb perfusion (with tumor necrosis factor-α [TNF-α], interferon-α [IFN-α], and melphalan) has been used as an neoadjuvant therapy to render tumors resectable and as a primary therapy to avoid amputation for nonresectable extremity STS.[275–277] Overall response rates in three series, which recruited 55, 35, and 41 patients, respectively, ranged from 72% to 91%, and limb salvage surgery was possible in 84% to 91% of cases. Small numbers of patients experienced subsequent local recurrence, and some of these patients needed later amputations. Not surprisingly, many patients ultimately developed and died of distant metastases. Hyperthermic isolated limb perfusion has also been advocated to facilitate palliative limb salvage in patients with regional and/or distant metastases from unresectable stage IVA or IVB STS.[278]

Various techniques of regional or whole-body hyperthermia have been combined with a variety of chemotherapy regimens.[279–284] A group from Munich has evaluated preoperative chemotherapy (four cycles of doxorubicin, ifosfamide, and etoposide) combined with

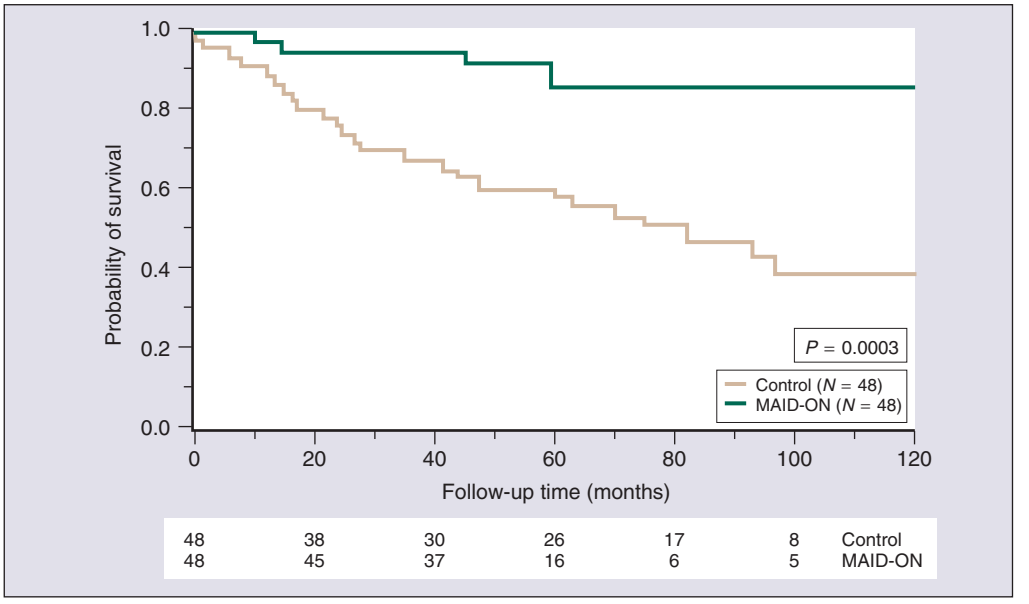


Figure 97-14 • Actuarial probability of overall survival for MAID-chemoradiotherapy and surgery versus control patients. The significant difference between the groups with respect to cause of death was distant metastasis (see text for details). (Reproduced with permission from Delaney TF, Spiro IJ, Suit HD, et al: Neoadjuvant chemotherapy and radiotherapy for large extremity soft-tissue sarcomas. Int J Radiat Oncol Biol Phys 2003;56: 1117.)

regional hyperthermia (RHT) followed by surgery and adjuvant treatment (same chemotherapy ± radiation). Median follow-up times were 58 months for the RHT-91 protocol (59 patients) and 30 months for the RHT-95 protocol.[283] All patients had grade II/III tumors 5 cm or larger with extracompartmental extension. Clinical response rates were 42% and 33% for the two protocols, with respective local progression-free survival rates of 58% and 57%. Corresponding overall survival rates were 42% and 48%, respectively. These results are now being evaluated in a phase III RCT (EORTC 62961/ESHO RHT-95). The assumption has been made that preoperative chemotherapy with doxorubicin, ifosfamide, and etoposide is effective for patients with high-risk localized disease in this setting, and patients are being randomized to receive preoperative etoposide, ifosfamide, and doxorubicin (EIA, four cycles) plus RHT (two fractions) versus EIA chemotherapy alone.

TREATMENT OF SARCOMA PATIENTS AT SPECIALTY CENTERS

Recent data on other tumor types have demonstrated improved outcomes for patients who required complex treatment and are treated at specialty centers.[285] The most comprehensive data addressing this issue in STS come from Sweden, where Gustafson and colleagues analyzed the quality of treatment in a population-based series of 375 patients with primary STSs arising in the extremities ($N = 329$) or the trunk ($N = 46$).[286] Comparisons were made between patients who were referred to a specialty soft-tissue tumor center before surgery ($N = 195$), those who were referred after surgery ($N = 102$), and those who were not referred for treatment of the primary tumor ($N = 78$). The total number of operations for the primary tumor was 1.4 times higher in the patients who were not referred and 1.7 times higher in the patients who were referred after surgery than in patients who were referred before surgery. Of greatest significance, however, was the finding that the local recurrence rate was 2.4 times higher in the patients who were not referred and 1.3 times higher in the patients who were referred after surgery than in patients who were referred to a specialty soft-tissue tumor center before any manipulation of their tumor. These findings support the principle of centralizing treatment of these rare tumors, which frequently require complex multimodality therapy.

TREATMENT OF LOCALLY RECURRENT SOFT-TISSUE SARCOMA

Incidence of Local Recurrence

Despite optimal multimodality therapy, at least 20% to 30% of STS patients will develop recurrent disease, with a median disease-free interval of 18 months.[109,287] Not surprisingly, local recurrence rates are a function of the primary tumor site and are highest for retroperitoneal and head and neck sarcomas. This is due in part to the fact that adequate surgical margins are technically more difficult to attain in these locations. Indeed, while acknowledging our earlier discussion relating the type of positive margin,[194] by multivariate analysis, an unqualified positive surgical margin is an adverse prognostic factor associated with local recurrence operation for recurrent disease.[109,110] In addition, employment of conventional standard-dose postoperative radiotherapy (60 to 65 Gy) is often limited in the retroperitoneum and the head and neck by the relative radiosensitivity of surrounding structures. These factors result in local recurrence rates of 38% for high-grade retroperitoneal sarcomas[133] and 48% for high-grade head and neck sarcomas,[288] compared to 5% to 25% for extremity lesions (see Table 97-9). It should also be acknowledged, however, that the rarity of nonextremity lesions probably results in a more varied approach to management, which may influence the ultimate outcome and may also have influenced the ability to design and execute clinical trials in the past. It would seem that properly applied principles of local management can achieve similar results even in sites with traditionally poor results, such as the head and neck, where disease access is limited by proximity to critical local anatomy.[196]

Surgery and Radiotherapy

Locally recurrent STS generally presents as a nodular mass or series of nodules arising in the surgical scar or radiation port. Patients with retroperitoneal recurrences usually present with nonspecific symptoms, often after the recurrence has reached a substantial size.

Treatment approaches for patients with locally recurrent STS need to be individualized on the basis of local anatomic constraints and the limitations on present treatment options imposed by prior therapies. In general all such patients should be evaluated for re-resection of their local recurrence. The results of such "salvage surgery" are good, two thirds of patients surviving long-term.[289,290]

If no prior radiotherapy was employed, adjuvant radiation should be utilized after surgery for locally recurrent disease. Occasionally, subtherapeutic or low-dose radiation was previously employed, and such patients might be candidates for additional adjuvant radiation by external beam or brachytherapy approaches. Patients who have had a full course of prior radiation should be managed on an individual basis.

In a recent series of 40 patients with recurrent extremity sarcoma, limb salvage was possible by combining limb-sparing re-resection with adjuvant brachytherapy.[291] A median dose of 45 Gy was possible with this technique, despite the fact that most patients had received prior external beam radiation. The 5-year actuarial local control rate was 68%, with satisfactory limb preservation. However, brachytherapy should be used with caution in patients who have locally recurrent low-grade sarcomas, since it appears to be ineffective against low-grade sarcomas.[193,220]

Catton and colleagues from the Princess Margaret Hospital also employed conservative surgery and reirradiation (external beam or brachytherapy) for treatment of local recurrences arising in a previous radiation field in a subset of 10 extremity sarcoma patients.[292] With a relatively short median follow-up of 24 months for the entire cohort, local control in the patients treated with further surgery and reirradiation was 100%.[292] Similarly, Nori and colleagues at Memorial Sloan-Kettering Cancer Center and Pearlstone and colleagues at the M.D. Anderson Cancer Center reported a local control rate of 82.5% (33 of 40) and 65% (17 of 26), respectively, when using conservative surgery and reirradiation with brachytherapy.[291,293] However, despite these encouraging findings, amputation or protocol-based hyperthermic isolated limb perfusion might be the only options for local control in some patients who were previously treated with radiation and have recurrent extremity sarcoma.

TREATMENT OF METASTATIC SOFT-TISSUE SARCOMA

The most common site of metastasis from STS of the extremity is the lung. Indeed, the lungs are the only site of recurrence in approximately 20% of all patients with primary extremity and trunk STSs.[287,284] Primary visceral and gastrointestinal sarcomas also commonly metastasize to the liver. Extrapulmonary metastases are uncommon forms of first metastasis and usually occur as a late manifestation of widely disseminated disease.[287] An obvious exception is in myxoid liposarcoma, in which unpredictable and aberrant recurrences to any area containing fat (the pelvis, retroperitoneum, mediastinum, paraspinal and subcutaneous soft tissue, and bone marrow) are a hallmark of disease behavior.[104,295] Evidence strongly suggests that apparently isolated soft-tissue masses that manifest in this disease are metastases, sharing the same molecular lineage with the original primary tumor.[296] For sarcomas in general, the median

survival from the time of development of metastatic disease is 8 to 12 months. An obvious exception is alveolar soft part sarcoma, in which metastatic disease may persist for more than 10 years. Optimal treatment of patients with metastatic STS requires an understanding of the natural history of the disease and individualized selection of treatment options based on specific patient factors, disease factors, and limitations imposed by prior treatment.

Surgical Resection

The current surgical approach for pulmonary metastases from STS is based on an extrapolation of the observations of Martini, Marcove, and colleagues in a series of patients with osteosarcoma treated at Memorial Sloan-Kettering Cancer Center in the 1960s. It had been observed that in a series of 184 patients undergoing amputation for osteosarcoma, 75% developed metastatic disease to the lungs within 18 months of amputation; and there were no 5-year survivors among this group.[297] In the absence of any effective systemic therapy for this disease, efforts were made to resect such metastatic lesions in later patients. Martini and colleagues reported successful complete resection in 22 of 28 patients, with a substantial 5-year overall disease-free survival rate of 32%.[298]

Multiple investigators have since reported their experience with pulmonary metastasectomy for metastatic STS in adults.[299–310] Three-year overall disease-free survival rates after thoracotomy for pulmonary metastasectomy have ranged from 23% to 54%, as outlined in the selected series summarized in Table 97-12.[299–303,310,311] With the exception of a study that evaluated the development and treatment of pulmonary metastases in patients with extremity sarcomas using a prospective sarcoma database (3-year survival rate of 23% after complete resection),[303] most studies have been retrospective analyses of the results of pulmonary resection in populations of carefully selected patients with metastatic sarcoma from heterogeneous primary sites. This could account for some of the variability in the reported survival rates.

Many investigators believe that repeated thoracotomies to render patients free of disease from pulmonary STS metastases are justified in the absence of effective systemic therapy. Several series of reoperative pulmonary metastasectomy have been published.[312,313] In an NCI series, 72% of 43 patients could be rendered free of disease at the second thoracotomy, with a median survival duration from the time of the second thoracotomy of 25 months.[312] In a report from the M.D. Anderson Cancer Center of a series of 34 patients undergoing reoperation for a second pulmonary metastasis after successful initial metastasectomy, factors predicting long-term survival included the presence of a solitary metastasis and the ability to perform a complete resection.[313] This study also illustrated the significant survival duration many of these patients enjoy: The median survival in the 19 patients who had unifocal recurrent metastatic disease was 65 months compared to 14 months in the 15 patients with complete resection of two or more sites of recurrent disease.

It remains difficult to predict which patients will benefit from pulmonary resection. A number of different clinical criteria have been evaluated by univariate analysis, including the disease-free interval,[299,301,311,314] number of metastatic nodules,[311,314–317] and tumor doubling time.[311,317,318] Multivariate analyses from both the NCI and Roswell Park Cancer Institute confirm that a short disease-free interval (as a surrogate endpoint of adverse behavior) and incomplete pulmonary resection are adverse prognostic factors for survival of patients with pulmonary metastases.[301,319] A multivariate analysis from the M.D. Anderson Cancer Center suggested that, in addition, the presence of more than three metastatic pulmonary nodules on preoperative chest CT is an adverse prognostic sign.[301]

The ability to completely resect all pulmonary disease is perhaps the most important prognostic factor affecting survival after pulmonary metastasectomy; patients with residual pulmonary disease have a median survival of 9 months versus 27 months ($P < 0.0001$) for patients who are rendered completely free of disease at thoracotomy.[301,303] In a series of 65 patients with metastatic pulmonary lesions from extremity sarcoma from the Memorial Sloan-Kettering Cancer Center, the median survival after complete resection was 19 months versus 10 months for patients who had incomplete resections and 8 months for patients who did not undergo surgery ($P = 0.005$).[303] The 3-year overall survival rate after complete resection was 23% compared to 2% in those who were treated nonsurgically ($P < 0.001$). The clinical criteria of disease-free interval, tumor doubling time, and number of nodules can serve as general prognostic indicators in patients who are being considered for pulmonary metastasectomy, but no single criterion should be used to exclude patients from surgery.

The ability to achieve complete resection and the number of pulmonary nodules that are present appear to best define the prognosis for patients postoperatively. Although carefully selected patients may benefit from surgical resection of pulmonary metastases, this treatment approach is feasible in only a small fraction of patients who develop pulmonary metastases. This is best illustrated by data from Memorial Sloan-Kettering, where a population of 716 patients with primary extremity sarcoma were followed for the subsequent development and treatment of pulmonary metastases (Fig. 97-15). Of the initial cohort, 148 patients (21%) developed pulmonary metastases. Isolated pulmonary metastases occurred in 135 (91%) of these 148 patients. Of the 135 patients with pulmonary-only metastases, 78

Table 97-12 Survival Following Complete Resection of Pulmonary Metastases from Soft-Tissue Sarcoma in Adults

First Author/ Institution	No. of Patients			Complete Resection (%)	Median Survival (Mo)	3-Year Survival (%)
	Total	Pulmonary Metastases	Surgical Treatment			
Creagan/Mayo[299]	112	112	112	64 (57%)	18	29
Putnam/NCI[300]	487	93	68	51 (75%)	23	32
Jablons/NCI[301]	74	57	57	49 (86%)	27	35
Casson/MDACC[302]	68	68	68	58 (85%)	25	42
Verazin/Roswell[319]	78	78	78	61 (78%)	21	21.5, (5 yr)
Gadd/MSKCC[303]	716	135	78	65 (83%)	19	23
Van Geel/EORTC[310]	255	255	255	255 (100%)	NR	54

EORTC, European Organization for Research and Treatment of Cancer; Mayo, Mayo Clinic; MDACC, University of Texas M.D. Anderson Cancer Center; MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, U.S. National Cancer Institute; Roswell, Roswell Park Cancer Institute.

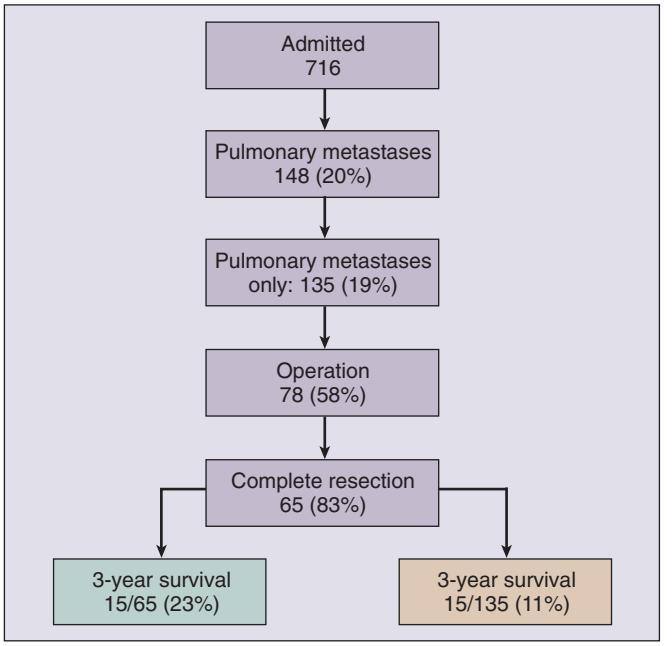


Figure 97-15 • Risk for and subsequent management of pulmonary metastases in 716 patients with primary or locally recurrent extremity soft-tissue sarcoma. (Reprinted with permission from Brennan MF: The surgeon as a leader in cancer care: lessons learned from the study of soft tissue sarcoma. J Am Coll Surg 1996;182:520.)

(58%) were considered to have operable disease, and 65 (83%) of those who were taken to thoracotomy were able to undergo complete resection of all their pulmonary metastatic disease. This group represents only 44% of patients with pulmonary metastases. Median survival from the time of complete resection was 19 months, and the 3-year overall survival rate was 23%. All patients who did not undergo thoracotomy died within 3 years. For the entire cohort of 135 patients who developed pulmonary-only metastases, the 3-year overall survival rate was only 11% (see Fig. 97-15).

The rather disappointing overall results of treatment for pulmonary metastases underscore the importance of careful patient selection for resection of pulmonary metastases. The following criteria are generally agreed upon: (1) the primary tumor is controlled or is controllable; (2) there is no extrathoracic disease; (3) the patient is a medical candidate for thoracotomy and pulmonary resection; and (4) complete resection of all disease appears possible.[320] With careful patient selection, the morbidity of thoracotomy can be limited to the subset of patients who are most likely to benefit from this aggressive treatment approach.

Wedge excision with negative margins is the procedure of choice for patients who undergo surgery for isolated pulmonary metastases. Formal segmentectomy, lobectomy, and mediastinal lymph node dissection are not necessary and do not contribute to improved local control. Occasionally, lobectomy or even pneumonectomy is required because of the proximity of the metastatic lesion to a pulmonary artery, vein, or major bronchus. Multiple ipsilateral lesions do not represent a contraindication, nor, in fact, do bilateral pulmonary metastases. Bilateral lesions can be approached by staged thoracotomies, median sternotomy, or simultaneous bilateral anterior thoracotomies, depending on the surgeon's preference and the number and location of the pulmonary metastases. In such cases, the preferred approach for most thoracic surgeons is simultaneous bilateral wedge resections via a sternotomy or "clamshell" anterior thoracotomy. Isolated unilateral lesions may be amenable to thoracoscopic resection.

Chemotherapy

First-Line Chemotherapy

SINGLE AGENTS. The single-agent activity of doxorubicin against metastatic STS is well established, with response rates usually reported as being in the range of 20% to 30%,[321–323] but response rates as low as 10%[324] and as high as 41%[325] have also been noted. The dose-response curve for doxorubicin in sarcomas was demonstrated to be steeper than that for any other tumor in the first RCT to address a dose-response question; the response rate increased from 18% at 45 mg/m^2 to 37% at 75 mg/m^2 (see later discussion).[326]

Epirubicin, which was developed as an active but minimally less cardiotoxic analog of doxorubicin, produced an objective response rate slightly lower than that of doxorubicin (18% versus 25%, $P = 0.33$) in an EORTC RCT of 167 patients receiving equimolar doses (75 mg/m^2) of the drugs.[327] There is some evidence of a dose-response relationship with epirubicin as with doxorubicin; a dose-escalation study showed response rates of 17%, 44%, and 100% for 140 mg/m^2, 160 mg/m^2, and 180 mg/m^2 of epirubicin, respectively.[328] Only three patients were entered at the maximum tolerated dose of 180 mg/m^2, and 160 mg/m^2 was recommended for routine clinical use. However, the EORTC group, in a three-arm RCT of 334 patients, was unable to demonstrate any benefit from either of two schedules of epirubicin (150 mg/m^2) compared with doxorubicin (75 mg/m^2); all regimens produced response rates of 14% to 15%.[329] Furthermore, there was considerably more myelosuppression in the two epirubicin arms, with two toxic deaths. Nevertheless, particularly in Europe, epirubicin has commonly been substituted for doxorubicin in high-dose regimens.

A number of studies of liposomal anthracyclines have suggested that these agents have lower rates of cardiotoxicity but variable activity.[330–334] An EORTC phase II RCT [324] demonstrated low activity for both doxorubicin and liposomal doxorubicin (Doxil)—9% versus 10%—but different spectrums of toxicity, with less myelosuppression but with palmar-plantar erythrodysthesia (grade 3: 20%) as the dose-limiting toxicity in the Doxil arm.

Lack of response rather than cardiotoxicity is the main limiting factor for anthracycline use in palliative chemotherapy of STS. Nonetheless, strategies to reduce anthracycline toxicity are of particular importance in the adjuvant setting.[335] Many American investigators routinely use continuous-infusion regimens with doxorubicin, which have been shown to be equally effective but less cardiotoxic. [336–338] Dexrazoxane is undoubtedly cardioprotective when given with doxorubicin.[339] Concerns about the possibility of tumor protection are theoretical and have not been noted in ongoing studies.

After the reports of several randomized studies documenting activity ranging from 24% to 67%,[340–342] Bramwell and colleagues performed an RCT comparing ifosfamide (5 g/m^2 by 24-hour infusion) with cyclophosphamide (1.5 g/m^2).[342] Respective response rates were 18% and 8%, but the difference was not statistically significant, owing to the inadequate power of the study ($P = 0.13$). Nonetheless, the authors correctly concluded that ifosfamide was the more active drug, and all sarcoma medical oncologists agree with that assessment.

Indirect data from several RCTs in which ifosfamide and/or cyclophosphamide were added to doxorubicin have provided additional evidence that ifosfamide is a more active analog than is cyclophosphamide.[321] Questions about the optimal scheduling of ifosfamide (multiple daily bolus doses versus continuous infusion) have never been satisfactorily resolved and are confounded by dose differences in many studies. Two consecutive phase II studies by investigators at M.D. Anderson evaluated ifosfamide (14 g/m^2) given as a 72-hour continuous infusion or a 2-hour infusion for 3 consecutive days. Respective response rates were 19% and 42%.[343] In an EORTC RCT comparing 5 g/m^2 ifosfamide over 24 hours with 3 g/m^2 ifosfamide over 4 hours on days 1 to 3, response rates were 3% and 17.5%, respectively. However, a subsequent EORTC study showed no dif-

ference in response rates for 9 g/m^2 ifosfamide by continuous infusion or intermittent bolus injection[344] (see the section on high-dose ifosfamide).

COMBINATION CHEMOTHERAPY. In the 1970s and early 1980s, before the widespread availability of ifosfamide, most combination chemotherapy regimens were based on doxorubicin and dacarbazine. The addition of cyclophosphamide and vincristine, which are active against childhood sarcomas, created a regimen called CyVADIC, for which the Southwest Oncology Group reported response rates as high as 59% in patients with metastatic disease.[345] Later investigators were unable to reproduce such high response rates with the same regimen, however, and summary data on variants of the CyVADIC regimen revealed an overall response rate of 35% in 2092 patients.[346] CyVADIC was the control for the three-arm EORTC study discussed later.[333] Despite the authors' conclusions that singe-agent doxorubicin should remain the standard, CyVADIC had the highest response rate (not statistically significant), with significantly lower toxicity than either of the other arms of the trial.

Most regimens now used for first-line chemotherapy are based on the combination of doxorubicin and ifosfamide. A recent systematic search of the literature[347] found 3 phase III RCTs and 16 phase II trials (excluding phase I studies and those recruiting fewer than 25 patients) in adult STS that used combination regimens including an anthracycline and ifosfamide. Although the response rate varied widely, from 25% to 56%, in the phase II studies, they were at the lower end of this range in the three RCTs.[348–350] In the Eastern Cooperative Oncology Group (ECOG) study[332] of 178 patients, the response rate was significantly higher for doxorubicin/ifosfamide than for doxorubicin alone (34% versus 20%, $P = 0.03$), although median survivals were similar. In an EORTC study of 471 patients, however, there were no significant differences in response rate (28% versus 23%) or median survival for doxorubicin/ifosfamide versus doxorubicin alone.[349] In an intergroup trial of 340 patients, the ifosfamide-containing regimen MAID was shown to produce a significantly higher response rate (32% versus 17%, $P < 0.002$) than doxorubicin/dacarbazine, but with no overall survival benefit.[350]

Bramwell and colleagues performed a meta-analysis of eight RCTs that compared doxorubicin-based combinations with single-agent doxorubicin.[322] In these eight studies with a total of 2281 patients, ten combination regimens were evaluated; five included ifosfamide (two) or dacarbazine (three), and the remaining five used other drugs with low known single-agent activity. There were no significant benefits in terms of response rate (odds ratio: 0.79, $P = 0.10$) or overall survival (odds ratio: 0.84, $P = 0.13$) for combination chemotherapy. Inclusion of a small RCT (106 patients)[351] that compared epirubicin (180 mg/m^2) with epirubicin (180 mg/m^2) plus cisplatin (120 mg/m^2) and reported respective response rates of 29% and 54% ($P = 0.025$) did not significantly alter the meta-analysis results. On the basis of single-agent doxorubicin's lower overall toxicity than that of combination regimens, Bramwell and colleagues suggested that for chemotherapy given with palliative intent, doxorubicin alone was a reasonable first-line option,[322] a conclusion that was also reached in a commentary by Santoro.[352] This leaves open the possibility of further second-line chemotherapy with ifosfamide in fit patients progressing on or relapsing after a response to doxorubicin therapy. Whether patients with advanced sarcomas should be treated with chemotherapy at all is also a topic of debate in Europe.[353] Interestingly, the European investigators who debate the issue place such patients on clinical trials, and the majority, if not all, of European experts who are members of the Connective Tissue Oncology Society treat patients both on trials and as standard practice.

One reason for the lack of convincing evidence that standard-dose combination chemotherapy improves outcomes compared with single-agent doxorubicin for metastatic STS might be that the doses of the drugs in combination regimens are often reduced below optimum levels to limit toxicity. In the first RCT of different doses of doxorubicin, a steep dose-response relationship was demonstrated for doxorubicin in sarcomas, with an increase in response rate from 18% at 45 mg/m^2 to 37% at 75 mg/m^2.[326] A similar dose-response relationship has been suggested for ifosfamide, the response rate increasing from 8 to 22% with an increase from 6 to 10 g/m^2 in consecutive series.[354] Myelosuppression, particularly neutropenia, limits the doses of these drugs that can be safely delivered in combination. Use of hematopoietic growth factors or autologous stem cell transplantation permits substantial dose escalation of these agents. In a systematic review, Verma and Bramwell identified seven phase I trials, five phase II trials, and two RCTs exploring dose-escalated regimens of doxorubicin and ifosfamide, with and without other agents for metastatic STS.[347] Most regimens included the growth factors G-CSF or GM-CSF, but in two trials, autologous stem cell transplantation was used in addition. In the phase I studies, the maximum tolerated doses were in the range of a twofold increase of the doxorubicin or epirubicin dose (over a standard dose of 75 mg/m^2) and a 2.4- to 2.8-fold increase of the ifosfamide dose (over a standard dose of 5 g/m^2). Significant toxicities included anemia, thrombocytopenia, nephrotoxicity, and neurotoxicity; severe neutropenia and febrile neutropenia were also seen at the higher doses. In a recently reported study,[355] De Pas and colleagues reported no nephrotoxicity or neurotoxicity with ifosfamide infused over 12 days at 15 g/m^2 (given with doxorubicin, 75 mg/m^2), although myelosuppression was dose limiting. Although not the primary objective, response rates were reported for all these phase I studies and were in the range of 28% to 58%. Additionally, for the five phase II studies of dose-escalated doxorubicin and ifosfamide (only studies with more than 20 evaluable patients were included), response rates were 31% to 65%. In a phase II study that was not included in the review, a response rate of 40% in 70 patients was documented.[356]

Patel and colleagues were the first to maximize the doses of each drug used in the combination.[338] In a series of small studies utilizing growth factors to support patients through the intense expected myelosuppression, they delivered doxorubicin at doses of 75 to 90 mg/m^2 together with ifosfamide at 10 g/m^2 divided as 2- to 3-hour infusions daily for 4 to 5 days. Of note, they identified that the regimen was suitable only for patients younger than 65 years old with two kidneys, normal renal function, and good performance status. Dose reductions were not employed for myelosuppressive toxicity unless it was accompanied by extreme morbidity. Patel reported a 62% response rate overall with a 57% response rate, a 10-month progression-free survival, and a 20-month survival in those with metastatic disease. The EORTC is attempting to confirm the results of the 75/10 regimen in a randomized study versus single-agent doxorubicin.

Patel and colleagues attributed their good results to the dose-intensive chemotherapy. In contrast, Worden and colleagues randomized patients to doxorubicin at 60 mg/m^2 plus either 6 or 12 g/m^2 of ifosfamide and showed no advantage for the higher dose.[357] Careful review of that study reveals that the careful selection criteria that Patel and colleagues used were not used in the latter study. Several older patients were entered, and in fact, the disadvantage of the higher dose regimen might have been due to unacceptable toxicity.

In contrast to these promising results in phase I/II studies, response data in the cooperative group RCTs have been disappointing. In an EORTC trial involving 314 patients with metastatic STS, standard-dose doxorubicin (50 mg/m^2) plus ifosfamide (5 g/m^2) was compared with higher-dose doxorubicin (75 mg/m^2) with the same dose of ifosfamide plus GM-CSF.[358] Respective response rates were 21% and 23%, with similar median overall survivals (56 versus 55 weeks); but median progression-free survival was significantly longer in the high-dose arm (19 versus 29 weeks, $P = 0.03$). In the other RCT that was included in Verma and Bramwell's review, as yet reported only in abstract form,[359] 162 patients were randomized to receive

standard-dose MAID or MAID with doses escalated 25% plus G-CSF support. Respective response rates were 37% versus 43% (P not significant), but no survival data were reported. There were five toxicity-related deaths, however, all in the dose-escalated MAID arm. In a third RCT, 180 mg/m^2 epirubicin and 150 mg/m^2 epirubicin, each combined with cisplatin but with no growth factor support, were compared in 151 patients.[351] There was a higher response rate (51% versus 28%, $P = 0.004$) and a marginal effect on overall survival ($P = 0.06$) with the higher-dose regimen. As all three RCTs were quite limited tests of dose escalation, more RCTs are needed before it can be concluded that such regimens are a more effective option than conventional-dose chemotherapy.

Verma and Bramwell discuss possible reasons for the lack of a clear benefit of dose-escalated therapy in the RCTs;[347] these include tumor heterogeneity, difficulties in eradicating large tumor burdens, and the appropriateness of the drugs, doses, and schedules used. It is interesting that even within the same group, results may differ between phase II and phase III trials. When the EORTC performed a pilot study of doxorubicin 75 mg/m^2 + ifosfamide 5 g/m^2 with GM-CSF support, the response rate was 45%.[360] When the group repeated the study as a phase III study, the response rate was 23%.[358] Why is there a discrepancy, and which value is closer to the truth? Phase III studies are supposed to be more representative of the overall population than are studies of highly selected patients from referral centers. Is it not possible, on the other hand, that the pilot study was conducted by a group that was more expert at treating sarcomas? Is it not possible that negative selection bias goes into the phase III trials, that is, investigators treat their younger, potentially curable patients with combination therapy off study and enter only those who are less likely to benefit into the randomized phase III studies? We know that referral to a specialty center improves outcomes of early-stage patients; why not those with metastatic disease? Furthermore, all of the randomized studies that have been reported occurred before there was effective treatment of GISTs. Many GIST patients were entered in front-line chemotherapy studies as having metastatic leiomyosarcoma without attention to its primary site. Inclusion of such patients, especially when they are rarely accounted for in the publications, dilutes the data and makes much of it uninterpretable.

Second-Line Chemotherapy

HIGH-DOSE IFOSFAMIDE. Although ifosfamide is often used as a first-line agent, it is clearly active as second-line therapy in patients who are progressing or relapsing after doxorubicin-based regimens. Early studies of ifosfamide suggested that there was a dose-response relationship,[354] and several groups have documented responses to high-dose ifosfamide in patients who had not responded to lower doses of the drug.[337,361–363] Nevertheless, dose-escalation studies of ifosfamide have produced conflicting results. Doses of 12 g/m^2 without and 14 to 18 g/m^2 with growth factor support seem achievable and have produced response rates of 33% to 45%, but nephrotoxicity and neurotoxicity are considerable.[343,359,363] Frustaci and colleagues found high-dose ifosfamide to be well tolerated when infused at 1 g/m^2/day over 21 days.[364] In 36 patients, they were able to administer up to three cycles with a median duration of 15 days, producing a response rate of 24%. Myelosuppression was dose limiting, but there was no significant nephrotoxicity or neurotoxicity. Pharmacokinetic data reported by Cerny and colleagues demonstrated that ifosfamide doses greater than 14 to 16 g/m^2 given over 5 days resulted in a relative decrease of the active metabolite iphosphoramide mustard, suggesting dose-dependent saturation or inhibition of ifosfamide metabolism.[365]

Despite encouraging phase II trial results, the advantages of increasing the dose of ifosfamide are far from clear on the basis of recent EORTC studies. The response rate rates for 9 g/m^2 (3 g/m^2 over 4 hours, days 1 to 3) and 5 g/m^2 (24-hour continuous IV) were 3% and 17.5%, respectively, in an RCT of 101 patients.[366] Escalation to 12 g/m^2 as a 3-day continuous IV infusion produced a response rate of 16% in a phase II study of 124 patients.[367] In the most recent EORTC RCT of first-line chemotherapy, the response rates were 11%, 6.5%, and 9.4% for 75 mg/m^2 doxorubicin, 3 g/m^2 ifosfamide over 4 hours on days 1 to 3, and 9 g/m^2 ifosfamide 24-hour continuous infusion, respectively. In addition to these disappointingly low and similar response rates, there were no differences in progression-free survival between the three arms.[344]

OTHER MARKETED DRUGS ALONE OR IN COMBINATION. Collected response rate data for many drugs that were studied in phase II trials for metastatic STS have been published in a number of reviews.[321,368,369] Dacarbazine has been used most extensively, either as a first-line agent in combination with doxorubicin and ifosfamide (MAID) or as a second-line salvage treatment. Demetri and colleagues found an overall 16% response rate for dacarbazine in 109 patients from collected phase II studies.[321] Although dacarbazine is commonly given in divided doses over 3 to 5 days, Buesa and colleagues showed that doses of 1.2 g/m^2 over 20 minutes are feasible and active, as well as more convenient, now that effective antiemetics are available.[370] The current availability of portable infusion pumps means that prolonged infusions are also feasible. Although Rosen and colleagues reported a response rate of 27% lasting 2 to 18 months or longer, Reichardt and colleagues were not able to confirm this high rate of activity when they gave 12- to 14-day infusions of 200 to 225 mg/m^2/day dacarbazine, observing only disease stabilization in 8 of 25 heavily pretreated patients.[371]

There is conflicting evidence on the activity of cisplatin and carboplatin against metastatic STS, although most reviews have reported response rates of less than 15%.[321,368,369] Low response rates are also seen for etoposide given as a single agent.[321,342,372] Promising early data on docetaxel[373] could not be reproduced in later studies,[352,374–377] and paclitaxel similarly has little activity.[378–380]

Objective response rates were also very low (3% to 5%) in three phase II studies of gemcitabine,[381–383] although the M.D. Anderson group described a response rate of 18% in 39 patients if GISTs were excluded[378] (they represented the majority of patients in some of the other studies). The M.D. Anderson study also confirmed the importance of timed delivery of gemcitabine, since it cannot be activated faster than 10 mg/m^2/min and the remainder of a more rapidly administered dose is simply excreted unchanged in the urine. Hensley and colleagues utilized timed infusion of gemcitabine at 900 mg/m^2 over 90 minutes on days 1 and 8 followed by docetaxel 100 mg/m^2 on day 8 with growth factor support and a 25% dose reduction for patients with prior pelvic radiation in a series of patients with leiomyosarcoma, almost exclusively of uterine origin, and observed a 53% response rate.[384] Leu and colleagues confirmed the activity of the regimen at the lower dose in patients with a variety of other sarcomas.[385] Since the response rate among patients with leiomyosarcoma in the M.D. Anderson study of gemcitabine was 4 out of 10, it was unclear whether the activity of the gemcitabine-docetaxel regimen was due to the timed infusion of gemcitabine, the large number of patients with uterine leiomyosarcoma, or the addition of docetaxel. To answer this question, SARC (the Sarcoma Alliance for Research through Collaboration) carried out a RCT comparing equimyelosuppressive doses of timed-infusion gemcitabine versus the combination of gemcitabine and docetaxel. The study employed a Bayesian adaptive randomization design with continuous feedback of data into the randomization model so that more patients were entered in the arm with greater efficacy.[386] Success was defined as a RECIST response at any time or freedom from progressive disease at 24 weeks, based on the assessment of the investigators that prolonged freedom from progression was more beneficial to patients than response. Results reported by Maki and colleagues at ASCO 2006 showed a statistically significant superiority of the combination regimen in terms of success rate, progression-free survival, and overall survival.[387]

Despite poor levels of activity as single agents, some of the preceding drugs have been incorporated into nonanthracycline-based salvage regimens. On the basis of encouraging data in pediatric sarcomas, etoposide has been combined with ifosfamide, although with variable results.[377,388–391] All but one such study produced response rate in the range of 38% to 46%; because ifosfamide given alone has produced up to 67% in phase II studies, however, these results are difficult to interpret. A combination of paclitaxel with gemcitabine and cisplatin was evaluated, with preliminary reports of encouraging synergistic activity.[392] Temozolomide,[393–395] raltitrexed,[396] irinotecan,[397] sargramostim,[398] topotecan,[399,400] and vinorelbine[401] seem to have minimal activity in STS, despite their proven value in other tumor types.

INVESTIGATIONAL NEW DRUGS. Of drugs that are currently in phase II development, trabectidin (ET743, ecteinascidin 743), a DNA guanine-specific minor groove-binding agent, seems to have clear-cut activity against sarcomas. Hints of activity in bone and STSs were observed in phase I trials[402,403] and appeared to be confirmed in phase II trials of this agent. Garcia-Carbonero and colleagues reported a response rate of 17.1% in 35 chemonaive sarcoma patients and 8% in 34 patients who had received prior chemotherapy.[405] George and colleagues reported a lower progression rate (5%) but a substantial proportion (19%) of patients with minor responses or stable disease.[406] Two European trials described response rates of 11% to 12% in previously treated sarcoma patients.[407,408] Occasional severe toxicities, sometimes lethal, seemed to be related to elevated baseline liver function tests; and with careful attention to alkaline phosphatase levels, toxicity other than myelosuppression and fatigue has not been a major problem. In the attempt to avoid the inconvenience of a continuous-infusion schedule, weekly administration has been evaluated. In a randomized study reported at ASCO 2004, the continuous infusion was more toxic, but it was significantly more effective in terms of time to progression and survival.[409] This study indicates that the drug is clearly active and that either the continuous-infusion schedule is superior or the dose that was chosen for the weekly schedule was too low.

Another interesting observation from the various studies of trabectidin is that it has high activity against a single subtype of sarcomas, myxoid liposarcoma, made by Grosso and colleagues at the Istituto Nazionale Tumori in Milan.[410] They noted a response rate of 43% by RECIST and an even higher response rate when changes in tumor density were considered—a so-called tissue response. We and others have verified their observation (unpublished observation), and it is clear that the responsiveness of myxoid liposarcoma to trabectidin is very high. It is a subtype that is rather responsive to doxorubicin plus ifosfamide as well, but the second-line (and sometimes fifth-line) activity of trabectidin is truly remarkable. Myxoid liposarcoma is characterized by a specific translocation putting either FUS or less commonly EWS with CHOP. It is possible that trabectidin specifically blocks transcription of the fusion DNA. It is also evident that trabectidin is more active against tumors with altered DNA repair mechanism. Tumors with low expression of BRCA1 and high expression of ERCC1 have substantially longer progression-free survival than do those with high expression of BRCA1 and low expression of ERCC1.[411] Whether the altered DNA repair is a specific feature of myxoid liposarcoma or other translocation-related sarcomas or whether the altered DNA repair is an independent predictor of response is to be determined.

Another class of drugs with activity against sarcomas are the mTOR inhibitors, the best studied of which is an investigational agent AP23573 from a small company, ARIAD. Data reported at ASCO by Chawla and colleagues showed an objective benefit rate, defined as RECIST response or stable disease at 16 weeks, of 28% in 193 patients.[412] At the same time, anecdotal responses to rapamycin were reported,[413] but a phase II study of an alternative mTOR inhibitor[414] showed no activity when the endpoint was only RECIST response. Note that if only RECIST response were counted for AP23573, it would have been declared inactive with a response rate of 2.6%.[412]

The observation that patients with growing tumor may benefit from therapy when the growth stops is not new, but its importance is becoming increasingly recognized. Initially described in a phase II study of doxorubicin as improvement[415] that included both responses that were inadequate to qualify by standard criteria and stabilization of previously progressive disease, improvement has traditionally been accepted as a "second-class" response at best. Trabectidin is the first modern drug for which the clinical observation seemed to take on added meaning. The EORTC has defined rates of time to progression at 3 and 6 months for active and inactive regimens.[416] Clinicians who treat osteosarcoma have known that standard responses might not exist despite a complete histologic response. The experience with GIST (see later discussion) has indicated that many patients who are clearly benefiting from therapy and have objectively measurable responses do not qualify as responders by RECIST or World Health Organization criteria. Therefore, the activity of gemcitabine-docetaxel that led to improved progression-free and overall survival, the activity of trabectidin, and the extent of the activity of imatinib in GIST were discovered by using modified response criteria. It make sense to look at new drugs such as the mTOR inhibitors using similar expanded criteria for drug activity and to pursue their study.

The identification of a specific molecular target (the tyrosine kinase receptor KIT) in a rare type of STS (GIST) and successful treatment with a drug (imatinib) that inhibits that target provide a model for future drug development in STS. Although it is unlikely that the pathogenesis of most STS will prove to be driven by a single genetic mutation, better molecular differentiation of STSs into categories with similar molecular characteristics could facilitate future studies of highly targeted drugs. At an NCI-sponsored "State of the Science" meeting on STS, Demetri pointed out that the ideal target would meet four conditions: (1) a single validated molecule that is critical to STS pathogenesis in humans, (2) expressed and active, (3) a target for which there are no alternative pathways to bypass the blockade, and (4) necessary and sufficient for sarcoma survival.[238] Other potential targets are discussed elsewhere in this chapter.

Complex sarcomas with diverse karyotypes and/or drug-resistance mutations are likely to require drugs used in combination to block multiple targets. Recent reviews have described signal transduction pathways in sarcoma as therapeutic targets,[417] the potential use of antiangiogenesis agents,[418] and new approaches to immunotherapy.[419] Early reports of antiangiogenesis therapies have shown limited benefit in STS,[420,421] but many agents remain to be evaluated.

Although the majority of patients with metastatic STS will not have access to phase II studies of investigational agents, where these are available, trial entry should be encouraged. Conventional wisdom suggests that use of an investigational agent as a first- or second-line therapy for metastatic disease should be considered, since investigational agents that are given as third- or fourth-line treatments could be doomed to failure because of acquired drug resistance. This concept has now been proven incorrect. Whenever there is an effective agent or regimen (gemcitabine-docetaxel, imatinib in GIST, ifosfamide in synovial sarcoma, trabectidin in myxoid liposarcomas), activity is obvious in multiply-treated patients.

UNIQUE ROUTES OF DELIVERY. Some experimental studies have evaluated intraperitoneal delivery of cytotoxic agents, usually doxorubicin and cisplatin, sometimes with hyperthermia, in sarcomas that are confined to the peritoneal cavity after resection of all visible abdominal disease.[368,422,423] Evaluation of any benefit is a major challenge in these studies, however, and this technique may be less suitable for sarcomas than for epithelial cancers.

Another novel approach is isolated lung perfusion with doxorubicin after resection of pulmonary metastases, in general a more common situation in STSs. To date, studies of isolated pulmonary perfusion have focused on feasibility rather than outcomes.[424]

SPECIAL SITES AND SUBTYPES OF SARCOMA

Retroperitoneal Sarcomas

Retroperitoneal sarcomas are relatively uncommon, accounting for approximately 15% of all sarcomas (see Fig. 97-1). The most common histologic subtypes are well-differentiated and dedifferentiated liposarcoma and leiomyosarcoma, found in 42% and 26% of cases, respectively (see Fig. 97-1). Nearly 80% of patients present with an abdominal mass, and 50% of patients report pain at the time of presentation.[189] Patients commonly describe nonspecific gastrointestinal symptoms. Other commonly noted symptoms include neurologic symptoms (primarily sensory) in 27% of patients and weight loss in 7%.[189,425] These tumors often grow to substantial size before a patient's nonspecific complaints are evaluated or an abdominal mass is noted on physical examination.

CT and MRI are the primary methods that are used to image retroperitoneal tumors (see Figs. 97-3, 97-5, and 97-6).[426–428] These modalities allow assessment of the consistency of the mass (fat, cystic or solid components, associated necrosis), the precise anatomic location of the mass, and the extent of any regional disease, and they confirm function of the contralateral kidney. CT of the abdomen and pelvis usually provide images that are satisfactory for treatment planning. Occasionally, MRI with gradient sequence imaging can be helpful in defining long-segment vascular anatomy for surgical planning. For patients with an abnormal chest radiograph, chest CT should be performed to exclude the possibility of metastatic disease.

The differential diagnosis for a retroperitoneal mass is relatively limited. Physical examination should include a testicular examination in men to evaluate the possibility of a primary testicular neoplasm. Laboratory tests should include the common serum markers for germ cell tumors, beta-human chorionic gonadotropin, and α-fetoprotein. If physical examination is suggestive of testicular malignancy or biochemical markers are elevated, testicular ultrasonography should be performed. This may obviate laparotomy for patients with metastatic testicular tumors and allow identification of primary retroperitoneal germ cell tumors.

In general, preoperative biopsy is not necessary when radiographic appearance makes the diagnosis of well-differentiated liposarcoma (atypical lipomatous tumor) and surgical resection is planned for a resectable primary retroperitoneal mass. If there is a question of diagnosis (lymphoma) or if preoperative chemotherapy or radiation is considered, a core-needle biopsy is essential.

Surgical resection with negative margins remains the standard primary treatment for patients with localized retroperitoneal sarcoma. Unfortunately, the data are extremely difficult to interpret because most series lump all patients, the majority or whom may have atypical lipomatous tumors (also called well-differentiated liposarcoma) with patients with true high-grade sarcomas. Patients should be thoroughly evaluated with multidisciplinary input before there is any attempt at surgery. If ifosfamide might be required at some point in the patient's management, for example, and if adequate surgery would remove a kidney, strong consideration should be given to preoperative chemotherapy. Similarly, if radiation will be required, it is preferably given preoperatively (see later discussion). If primary surgery is chosen for the patient, all patients should have preoperative bowel preparation and assessment of bilateral renal function by CT, because en bloc multiorgan resection might be required to achieve negative margins. Resectability rates in recent series combining patients with primary and recurrent lesions have ranged from 25% to 96% (Table 97-13).[189,425,429–434] Resectability rates at different institutions are difficult to compare and interpret because these rates are a function of the referral pattern, the criteria that are used to determine which patients will undergo surgical exploration, and the surgeons' skill and experience.[433,435,436] For patients with primary lesions, grossly complete resection is possible in up to 78% of cases.[133,433] The most common reasons for unresectability are the presence of major vascular involvement (aorta or vena cava), peritoneal implants, or distant metastases.[189] Resection of adjacent retroperitoneal or intra-abdominal organs, frequently the kidney, colon, or pancreas, is required in 50% to 80% of cases to permit complete resection.[189,431,437] Partial resections or debulking procedures have been performed, but there is no evidence that partial resection improves survival (Fig. 97-16).[189,437] Deliberate partial resection should be reserved for relief of bowel obstruction or palliation of other critical manifestations of advanced disease.

Results from published series demonstrate 5-year overall survival rates in the range of 54% to 64% for patients with completely resected retroperitoneal sarcoma.[133,189,431,433,434] Overall survival rates for patients with incompletely resected disease range from 10% to 36%. Adequate margins are often difficult to obtain in retroperitoneal sarcoma surgery because of the proximity of critical organs, vascular structures, and the spine. Consequently, recurrent disease remains a significant problem, recurrence developing alone or with systemic relapse in 46% to 59% of patients with completely resected tumors.[134,189,431,433,438]

A number of recent studies have evaluated prognostic factors for retroperitoneal sarcomas by univariate and multivariate analysis.[133,134,425,431,438] For patients who presented without metastatic disease, complete surgical resection and histologic grade were the primary determinants of survival in several multivariate analyses.[133,425,431,434,438] Some investigators have also found by multivariate analysis that large tumor size (>10 cm) and fixation to adjacent retroperitoneal structures other than neurovascular bundles or bone were significant adverse factors for survival.[431] Patients who undergo a grossly complete resection have a 60% 5-year overall survival rate and a median survival of 64 months (see Fig. 97-16). These results

Table 97-13 Resectability Rates for Retroperitoneal Sarcomas in Selected Series

First Author	Institution	Accrual Period (Yrs)	Total No. of Patients	No. Completely Resected	Restability Rate (%)
Glenn[429]	NCI	19	50	37	74
Karakousis[430]	Roswell Park	24	68	27	40
Dalton[431]	Mayo Clinic	19	116	63	54
Jaques[189]	MSKCC	5	114	67	59
Alvarenga[425]	Royal Marsden	20	110	28	25
Karakousis[433]	Roswell Park	17	87	83	95
Kilkenny[434]	University of Florida	25	63	49	78

MSKCC, Memorial Sloan-Kettering Cancer Center; NCI, U.S. National Cancer Institute.

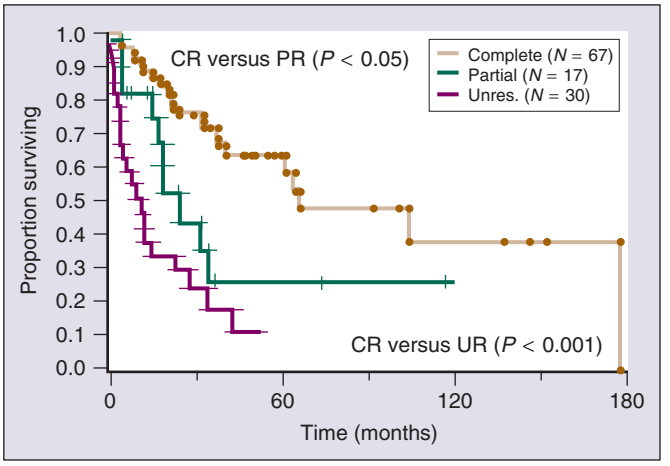


Figure 97-16 • Proportion of patients with retroperitoneal sarcoma who survive from the date of first operation at Memorial Sloan-Kettering Cancer Center for patients undergoing complete (gross negative margin), incomplete (gross positive margin), or no resection. (Reprinted with permission from Jaques DP, Coit DG, Hajdu SI, et al: Management of primary and recurrent soft-tissue sarcoma of the retroperitoneum. Ann Surg 1990;212:51.)

are significantly better than those of patients who have an incomplete resection (grossly positive margins) or unresectable disease. For patients with low-grade lesions, the median survival (80 months versus 20 months) and 5-year overall survival rate (70% versus 25%) are significantly better than those for with patients with high-grade lesions.[189]

The unfavorable results of outcome for retroperitoneal sarcoma logically points to the need to investigate adjuvant approaches. The obvious candidates include preoperative chemotherapy and preoperative radiotherapy. Detailed discussions of the pertinent issues in these approaches are available[439,440] and are summarized in the following section.

Surgery Plus Radiation Treatment

Postoperative EBRT has been shown to reduce local recurrence rates for extremity sarcomas and superficial trunk sarcomas. However, gastrointestinal toxicities or neurotoxicities often limit the delivery of sufficient radiation doses to the retroperitoneum. Several retrospective studies have suggested that postoperative EBRT might improve local control after grossly complete resection[189,219,430,438,441–445] while other small retrospective reports have not suggested any improvement in local control with postoperative radiotherapy.[189,219,430]

However, these series have included small numbers of patients (<30 to 40), no standard treatment protocol, and variable details on histopathology, extent of resection, and margin status. The largest study addressing this issue was reported by the French Cancer Federation Sarcoma Group with the suggestion that postoperative radiotherapy was associated with significantly reduced local recurrence compared to surgery alone.[446] In this report, 145 patients presented with localized nonmetastatic retroperitoneal sarcoma. As is typical for this disease, the tumors were large (median size: 15 cm, range: 2 to 70 cm), and only a minority (6%) were T1 lesions. As in others series, liposarcoma was unusually well represented (30%). Their patients may differ from those in other reports in that only 27 cases (19%) had grade 1 lesions. A significant number of patients (31%) had neurovascular or bone involvement. Complete resection took place in 94 of the 145 patients (65%), and 60 of these patients received radiotherapy to a median dose of 50 Gy. Of the 94 patients who underwent complete resection, the 5-year actuarial local recurrence-free interval was 60% for those who were treated with radiotherapy and 23% for those who did not receive postoperative radiotherapy ($P = 0.0021$). Clearly, the likely possibility of selection bias must be considered in interpreting these results, since patients with large and more complex (i.e., unusually located or infiltrating) lesions and patients who experienced postoperative morbidity are less likely to have been treated with radiotherapy.

Preoperative EBRT for retroperitoneal sarcoma offers certain theoretical and practical advantages: (1) High-dose treatment could minimize the risk of tumor implantation in the peritoneal cavity after a marginal resection by sterilizing a large number of tumor cells; (2) partial tumor regression could facilitate grossly complete resection; (3) there are favorable anatomic issues, including the tumor displacement of critical radiosensitive organs (bowel predominantly) away from the preoperative radiation field, thereby reducing toxicity and improving tolerance; and (4) an intact peritoneum offers a mechanical barrier to tumor seeding during the time radiotherapy is being administered before resection and division of these membranes. Moreover, postoperative radiotherapy is problematic if bowel is tethered in the radiotherapy target area, making it impossible to treat some patients, at least without unnecessary risk of complications.

Two recent series, the first from the Princess Margaret Hospital and the other from the University of Texas M.D. Anderson Cancer Center, are informative because acute toxicity resulting from preoperative radiotherapy was differentiated prospectively from the effects of other treatments.[447,448] In the Princess Margaret Hospital series, the median preoperative dose of radiotherapy comprised 45 Gy in 25 fractions. Although the median radiation volume exceeded 7 L, preoperative EBRT was associated with European Organization for the Research and Treatment of Cancer/Radiation Therapy Oncology Group (EORTC/RTOG) acute toxicity scores of ≤2 in all patients who underwent resection. Furthermore, no patient was hospitalized for acute toxicity, and there were no treatment interruptions or requirements for cessation of treatment because of acute toxicity. The remarkably low toxicity of the preoperative course with enormous radiotherapy volumes in the study has been attributed to the displacement of bowel outside the target volume. At the same time, brachytherapy used postoperatively in selected cases did appear to be associated with toxicity and also does not appear to have contributed to enhanced tumor outcome. Late toxicity resulted in death in 4.3% (2 of 46) and with life-threatening illness in 2.2% (1 of 46) of patients, all of whom had been treated with brachytherapy to the upper abdomen. The 2-year overall survival and disease-free survival for resected retroperitoneal sarcoma were 88% and 80%, respectively. Significantly better 2-year disease-free survival was achieved in patients with primary (in contrast to recurrent) disease and in those with low-grade tumors (93% and 95%, respectively).[447] Similarly, in the M.D. Anderson Cancer Center phase I trial ($N = 35$), the tolerance of preoperative radiotherapy is also reported. The M.D. Anderson Cancer Center trial differed from the Princess Margaret Hospital study in that it also evaluated outcome after preoperative doxorubicin in addition to concurrent allocation to one of six sequential 1.8-Gy-per-fraction escalating radiotherapy protocols (from 18 to 50.4 Gy) and used intraoperative electron beam as the boost technique in localized retroperitoneal tissue sarcoma.[448] At the highest radiation dose of 50.4 Gy, 2 (18%) of 11 patients had grade 3 or 4 nausea. Twenty-nine patients (83%) underwent laparotomy; 6 patients had interval disease progression and did not undergo surgery. Grossly complete resection (R0 or R1) was performed in 26 (90%) of 29 patients who had surgery. Intraoperative electron beam was feasible and successfully administered to 22 patients who had R0 or R1 resections. This trial demonstrates that preoperative external beam radiation can be safely administered to a total dose of 50.4 Gy with continuous-infusion doxorubicin.

The three papers with sufficient follow-up that describe the use of preoperative radiotherapy with a brachytherapy or electron boost reported improved outcomes compared to most other series, especially for primary (as opposed to recurrent) presentation cases,[447,449,450] and presumably, the M.D. Anderson Cancer Center trial will

demonstrate similar findings with maturation of the data.[448] However, we again caution against overinterpretation of results that could be explained by surgical technique at major referral sarcoma centers or by case selection; of note, none of the four studies provides a comparison control group from which to infer efficacy. Similarly, it remains unclear what contribution is being provided by the use of brachytherapy or intraoperative radiotherapy (as opposed to the preoperative EBRT, common to all four studies), which should probably remain protocol-based in expert hands or be reserved for individual nonstandard clinical use.

Intraoperative Radiation Treatment

Intraoperative radiotherapy (IORT) offers the advantage of a direct boost dose to the tumor bed, thereby allowing a reduction in the dose of relatively more toxic concomitant EBRT. However, critical evaluation of its role is especially problematic because of treatment selection factors (both medical and technical) along with the fact that any observations of efficacy are confounded by the frequent use of additional fractionated EBRT in the "adjuvant package." Therefore, a clear demonstration of the effectiveness of IORT is lacking, although its potential value should continue to be evaluated in appropriate investigational protocols. The same situation applies to the use of adjuvant brachytherapy approaches to dose augmentation in the retroperitoneum.

The efficacy of combined adjuvant IORT and EBRT has been evaluated in two recent series, one from Massachusetts General Hospital and the second from the Mayo Clinic,[449–451] and in a previous report from the NCI.[452] The NCI study was a prospective trial in which 30 patients with completely resected retroperitoneal sarcomas were randomly assigned to receive IORT (11- to 15-MeV electron beam to a dose of 20 Gy) with low-dose postoperative EBRT (35 to 40 Gy) or to receive high-dose postoperative EBRT (50 to 55 Gy) alone.[452] IORT with low-dose EBRT was associated with a significantly lower rate of gastrointestinal toxicity (7% versus 60%), but no differences were noted in local control, disease-free survival, or overall survival. The rates of 5-year disease-free (20%) and overall survival (40%) seen in this study were comparable to those observed with surgery alone.[219,431] The reports from Massachusetts General Hospital and the Mayo Clinic described preoperative high-dose EBRT (40 to 50 Gy), instead of postoperative administration, with IORT (using electron beam to a dose of 8.75 to 30 Gy, depending on the series).[422,423] Both papers report on overall toxicity without differentiation between the influence of preoperative external beam and the boost after resection. This likely arose because of retrospective toxicity data collection in the two studies, which is further confounded by the frequent use of IORT in each.[449,450] The inference from our analysis of the results of both studies is that much of the toxicity seems related to use of IORT and is not from preoperative EBRT.

In summary, in the management of retroperitoneal sarcoma, complete surgical resection remains the standard of care. In selected patients with advanced disease, some disabling symptoms may be palliated by low- to moderate-dose EBRT. As for extremity sarcomas, there are no currently available data to support the use of routine adjuvant chemotherapy for these patients. Given the relatively high complication rates of high-dose external beam radiation to the retroperitoneum and the lack of clear demonstrable clinical benefit, routine preoperative or postoperative EBRT is not recommended outside the setting of a clinical trial and clinicians should be encouraged to enter patients in ongoing trials at referral centers.[439,453,454]

Chemotherapy

Retrospective studies have not demonstrated any benefit for preoperative[455] or postoperative[133,189,430,456] doxorubicin-based chemotherapy for retroperitoneal sarcomas. In one study, six complete responses were seen in 23 patients who received high-dose doxorubicin/ifosfamide/DDP (cisplatin) with concurrent radiotherapy.[254] Neoadjuvant chemotherapy has been combined with hyperthermia[457] and preoperative radiotherapy[448] without excessive toxicity. Idoxuridine was used as a radiosensitizer in a small pilot study.[458] These techniques remain experimental, however, and need further assessment, eventually in RCTs, to evaluate their place in the management of retroperitoneal sarcomas.

Most of the studies indicated previously included retroperitoneal sarcomas as a single group without differentiating primary histologic type or grade. Because of the preponderance of patients with atypical lipomatous tumors who were included in such studies, assessment of the effects of chemotherapy needs reexamination. Clearly, for high-grade retroperitoneal sarcomas, the recurrence rate is unacceptably high, and even when the local disease is controlled, patients are at risk from metastatic disease. If an effective chemotherapeutic regimen could be identified early, with the primary tumor intact, and if some progression of disease under therapy would not render the patient unresectable, it would be beneficial. Thus, there is an indication for preoperative chemotherapy in appropriately selected patients. Proof of principle comes from the UCLA study mentioned previously where complete responses to chemotherapy and radiation were demonstrated. With newer regimens such as gemcitabine-docetaxel, which might be effective in leiomyosarcomas, individualized multidisciplinary therapy should be considered.

Gastrointestinal Stromal Tumors

GISTs represent about 80% of sarcomas that arise from the gastrointestinal tract. This group of soft-tissue tumors has become increasingly recognized as a separate subtype of sarcoma defined pathologically by expression of the receptor tyrosine kinase, c-Kit (CD117), in about 95% of cases. The management of these tumors has undergone significant recent change with the development and availability of imatinib mesylate, an agent with significant clinical benefit for patients with advanced GISTs. Details of the molecular pathology of GISTs are addressed in the sections on Potential Molecular Prognostic Factors and Prognostic Factors as Therapeutic Targets.

This section of the chapter will cover the evaluation and treatment of patients with GISTs. Consideration of these issues is often aided by subclassification by clinical staging into patients with localized, nonmetastatic (resectable) disease and patients with metastatic GIST.

Localized (Surgically Resectable) Gastrointestinal Stromal Tumors

Patients with localized GISTs are best treated with surgical resection of the primary tumor. Surgical resection generally requires segmental resection of the involved section of the gastrointestinal tract without local or regional lymphadenectomy. Since GISTs were only recently pathologically defined, there are few reports outlining the natural history of localized GISTs (excluding other forms of mural gastrointestinal neoplasms). Moreover, the natural history of patients with localized disease stratified by c-Kit mutation subclassification is not well characterized at this time.

Details of the natural history of patients with surgically treated gastrointestinal leiomyosarcoma, the vast majority of whom might have what we currently would classify as GISTs, are outlined in prior reports.[141,459,460] These reports emphasize the importance of macroscopically and microscopically complete surgical resection and the adverse prognostic significance of large tumor size and high tumor grade (as assessed by light microscopic criteria). Although surgical resection has been the mainstay of therapy for patients with localized GISTs, a recently published analysis of 200 patients by DeMatteo and colleagues noted only a 54% disease-specific 5-year survival rate for patients in whom a grossly complete resection of their primary GIST had been achieved, and there were additional deaths thereafter.[461] Furthermore, the median survival in patients with metastatic disease was only 20 months.[461]

The precise role of imatinib mesylate in the postoperative treatment of patients with localized GISTs is unknown. Current clinical trials address the issue, but unfortunately, none of the currently active clinical trials in the United States or Europe clearly address the issue of the appropriate duration of imatinib therapy. The first RCT, the Z9001 trial by the American College of Surgeons Cooperative Group, was closed early owing to a clear advantage of imatinib in decreasing the recurrence rate at one year (R. P. DeMatteo, personal communication). Although it is intuitively obvious that a therapy as effective in metastatic disease as imatinib will benefit patients when given early in their course, it is not clear that therapy before relapse is better than therapy afterward. Furthermore, since patients with advanced disease who relapse when imatinib is stopped respond again when it is reinstituted, it is not clear that a finite course of early therapy will have lasting benefit, especially if it is as short as 1 year. Therapy for as long as 3 years is explored in one European trial, but even that might not be long enough. Preoperative therapy is also being studied; however, most clinicians agree that whenever the likelihood of successful surgery would be increased or the extent of surgery would be substantially diminished by preoperative treatment, a trial of preoperative imatinib is warranted.

Metastatic Gastrointestinal Stromal Tumors

The primary sites of failure for most patients with recurrent GIST are the liver, the peritoneum, or sometimes both sites. It is very rare for this tumor to metastasize to the lungs.

CHEMOTHERAPY. GISTs are resistant to conventional cytotoxic chemotherapy agents, with response rates that are typically in the single-digit range or lower. In the era of imatinib mesylate, there is no defined role for conventional chemotherapy agents in this disease.

The identification of mutations of c-Kit, which cause constitutive activation of the KIT tyrosine kinase receptor pathway in GIST, prompted treatment in 1996 of a Finnish patient with imatinib,[462] a tyrosine kinase inhibitor that is highly effective against chronic myeloid leukemia. An impressive response led to rapid initiation of phase I[463] and randomized phase II studies of imatinib for GISTs.[464] In an EORTC study, 40 patients, of whom 36 had GISTs, were treated at dose levels ranging from 400 to 1000 mg/day orally. There were 19 patients who had partial responses (54%) and 13 with stable disease (37%). Four of five of non-GIST patients progressed. The most common side effects of imatinib were nausea, vomiting, edema, and rash. In a multicenter phase II study, 147 patients were randomly assigned to receive 400 or 600 mg of imatinib daily. Although no patient had a complete response during treatment, 79 (54%) had a partial response, and 41 (28%) had stable disease. The median duration of response had not been reached at a median follow-up of 24 weeks from the onset of response.[76] There were no significant differences in response rate or toxicities between the two doses, edema, diarrhea, and fatigue being the most common side effects. Gastrointestinal hemorrhage occurred in approximately 5% of patients.

Two RCTs of imatinib have been completed in North America[465,466] and in Europe and Australia,[467] accruing 746 and 946 patients, respectively, with locally advanced or metastatic GIST. They compared 400 and 800 mg of imatinib and assessed overall survival, progression-free survival, and toxicity. There is no significant survival advantage for the higher dose. Progression-free survival was significantly longer in the EORTC study.[467] A similar magnitude of improvement (4 months median and 5% increase in 2-year progression-free survival) in the North American study was not statistically significant ($P = 0.12$).[466] Most oncologists on both sides of the Atlantic prefer to start with the 400-mg dose, which is considerably less toxic, increasing only if patients do not respond or relapse after the initial response. There are data to suggest that the higher dose is more effective in the subset of patients with exon 9 mutations.[468,469] For patients with GISTs who are refractory to imatinib, sunitinib, a compound that targets multiple tyrosine kinases (KIT, PDGF-R, FLT3, and VEGF-R), can be effective.[470] Several other tyrosine kinase inhibitors are in clinical trial and have demonstrated some efficacy.

One observation from the early studies of imatinib in GIST was that traditional responses to treatment frequently underestimated the obvious clinical benefit that was observed. Van den Abbeele and colleagues noted that responses measured by PET at 1 month predicted for improved progression-free survival, while bidimensional responses according to SWOG criteria did not.[471] Choi and colleagues noted that response on CT often included decrease in size but that the degree of tumor shrinkage would have been classified as a minor response in a substantial fraction of the patients.[472] The tumors were also noted to have decreased in density after contrast enhancement.[471] Dr. Choi and her colleagues defined the CT changes that correlated with PET response and showed that they predicted for progression-free survival.[473] These changes, a 10% or greater decrease in maximum tumor diameter or a 15% or greater decrease in tumor density, the "Choi criteria," were confirmed to have prognostic importance in an independent group of patients with GIST.[474] There is increasing evidence that similar findings are seen in other tumors and after other treatments, suggesting that major therapeutic effects are missed when patients are evaluated only by RECIST.[475]

Singer and colleagues reported that c-Kit mutation type affects outcome.[172] They found a 5-year recurrence-free survival rate of 89% for patients with GISTs expressing missense exon 11 mutations compared with 40% ($P = 0.03$) for GISTs with other mutation types. Heinrich and colleagues reported a higher PR rate to imatinib (72% versus 32%, $P = 0.0033$) for patients with exon 11 versus exon 9 mutations in the initial phase II study[475] with similar findings in the North American study.[469] Debiec-Rychter and colleagues have published details of similar findings from the EORTC study.[468]

A unique aspect in the treatment of GIST with imatinib or another tyrosine kinase inhibitor is that therapy should be continued even in the face of documented disease progression, a practice that is endorsed by NCCN guidelines. In almost all cases, the progression occurs in only a portion of the tumor, while the majority of the tumor continues to be controlled by imatinib. Stopping all c-Kit inhibition leads to more rapid, diffuse tumor progression and shortened survival.

Other soft-tissue tumors that express activated tyrosine kinase receptors include DFSP (PDGF-β). Case reports of patients with DFSP have documented responses to imatinib.[94,476]

SURGERY. The role of surgery in patients with metastatic GIST is becoming better defined. There is no role for surgical resection in patients with multifocal recurrence. The advantage of adding surgical resection to imatinib in responding patients in whom all disease can be resected is unknown but is thought probably to be beneficial. Surgery in the setting of focal resistance, that is, a single progressive metastatic site while other disease appears to be controlled, is of less value, but most consider it a reasonable treatment strategy. It is clear that imatinib must be continued in the postoperative setting.[459,477,478]

Head and Neck Sarcomas

Head and neck sarcomas are uncommon, accounting for only 4% of all sarcomas and fewer than 1% of head and neck malignancies in adults. (A detailed discussion of the current state of knowledge for adult and pediatric head and neck sarcoma is available elsewhere.[479]) The most common histologic subtypes in adults are fibrosarcoma (18%), malignant fibrous histiocytoma (16%), and rhabdomyosarcoma (15%).[288,480] In recent large series of 176,[288] 188,[481] and 254[482] patients with head and neck sarcomas, the most common anatomic sites were the neck (23% to 38%) and paranasal sinuses (14% to 30%).

In the pediatric population, 40% of all STSs occur in the head and neck, where the most common histologies are neuroblastoma and embryonal rhabdomyosarcoma. The treatment of these lesions in the pediatric population is beyond the scope of this chapter and is reviewed in Chapter 99.

Methods of diagnosis, imaging, and biopsy for head and neck sarcomas do not differ substantially from those for other head and neck tumors. Wide surgical excision with negative margins is the therapeutic mainstay for head and neck sarcomas. Regional lymph node metastases are rare, occurring in only 4% to 6% of patients in large series.[481,482] Thus, in the absence of clinically positive lymph nodes, regional lymphadenectomy is not routinely required.

Recent series have identified prognostic factors for head and neck sarcomas.[135–138,288,481,482] Multivariate analyses of patients with head and neck sarcomas identified high histologic grade and positive surgical margins as independent adverse prognostic factors for survival.[137,138] Age greater than 60 years at diagnosis was also found to be an independent adverse prognostic factor in one multivariate analysis.[138] Additional data from the Mayo Clinic confirm that the presence of metastases is associated with a poor (25%) 5-year overall survival rate and that certain histologic subtypes (angiosarcoma and nonorbital rhabdomyosarcoma) may have an adverse prognosis.[482]

Patterns of failure for head and neck sarcomas reflect the difficulty in obtaining adequate surgical margins in the head and neck region. Local recurrence remains a significant problem, with overall rates of local recurrence ranging from 14% to 48%,[288,481,483] making it important to consider appropriately applied principles of sarcoma management with combined modality approaches where appropriate. As with sarcomas elsewhere in the body, biologic behavior is a function of histologic grade, with local recurrence rates ranging from 22% for low-grade head and neck sarcomas to 48% for high-grade lesions.[288] Systemic recurrence develops in 12% to 31% of patients despite complete resection.[288,483] Overall 5-year survival rates are 45% to 68%.[288,481,482,484]

Radiation Treatment

On the basis of experience gained in treating extremity sarcomas, adjuvant radiotherapy should be considered whenever there is doubt as to the adequacy of surgical margins or the location of the tumor precludes complete excision. Evidence for the benefit of adjuvant radiotherapy is less plentiful than in extremity lesions and probably relates to the rarity of these lesions and the absence of randomized trials addressing the specific issues for these lesions. However, Tran and colleagues from the University of California, Los Angeles have shown that local control was 52% with surgery alone versus 90% in head and neck patients who were treated with combined radiotherapy and surgery.[135] Additional evidence from Princess Margaret Hospital reveals that head and neck STS patients with clear surgical margins or microscopic residuum had similar local failure rates (26% and 30% failure, respectively), provided that radiotherapy was administered.[485] Indeed, these outcomes for radiotherapy after R0/R1 resections approach those achieved in extremity sarcoma.

One strategy to improve outcome in head and neck sarcomas is through the use of preoperative radiotherapy. This approach may have particular advantages in this site because of the smaller volumes of radiotherapy and the lower doses that can be used compared to the postoperative treatment in difficult surgical access locations, especially in the base of skull. Obvious advantages that are provided relate to the ability to spare critical anatomy such as the optic structures (globes, optic nerves, and the optic chiasm) as well as the brain stem and spinal cord. If for no other reason, the preoperative approach promotes collaboration between the surgical and radiation oncologist, facilitates a complete management plan to be fashioned before any surgical intervention, and maximizes the opportunity to achieve control even when disease may be resected with a small but planned positive margin against critical unexpendable anatomy, as was discussed earlier.[194]

In a prospective series of 40 patients (excluding rhabdomyosarcoma) with adverse selection criteria managed with preoperative radiotherapy between 1989 and 1999 at the Princess Margaret Hospital, 7 local relapses manifested (overall control rate of 82.5%).[196] This population of head and neck patients included five patients with intracranial extension and one with spinal cord compression; more than half of the lesions were greater than 5 cm in size (a formidable problem for lesions in this anatomic location), and 85% were deep to the investing fascia. The series also contained four angiosarcoma patients, a group of patients with sinister local control probability (see the later discussion of Vascular Sarcomas). In fact, three of the seven local failures occurred in the angiosarcoma patients. If the series is confined to more usual STS, the local control rate is 33 out of 36 (92%). The metastatic relapse-free rate also exceeded 80% in this series, potentially related in part to the smaller overall dimension of sarcomas in this location compared to sarcomas elsewhere. The improved local control compared to a previous series of patients treated at the same institution might also have contributed to this amelioration because the local control rate in the earlier series was substantially lower and death from concurrent local and metastatic disease was evident.[485]

Wound complications, assessed by the Canadian trial criteria,[211] were also seen with less frequency in this prospective study of head and neck lesions (overall rate: 8 of 40, or 20%)[196] than were noted earlier with preoperative radiotherapy in extremity lesions. This may relate to the greater use of flaps for head and neck reconstruction.

At present, useful guidelines for using preoperative radiotherapy in the head and neck are (1) the need to maximally restrict radiotherapy volumes in some anatomic sites (e.g., close to critical anatomy); (2) the desire to minimize radiation dose in some situations (e.g., where critical neurologic tissues are in close proximity, as in the optic structures); and (3) a desire not to irradiate new tissues, especially vascular reconstructions that are vulnerable to the effects of high-dose postoperative radiotherapy.

Genitourinary Sarcomas

Although STSs of the genitourinary tract are uncommon in adults, they account for up to 8% of all malignant disease in children younger than 15 years.[486] The management of genitourinary sarcomas in children has been more successful than that in adults and is discussed in detail elsewhere in this book. In the Memorial Sloan-Kettering Cancer Center adult sarcoma database, only 43 sarcomas (2.7%) were of genitourinary origin. The paratesticular region (33%) and prostate/seminal vesicles (28%) are the most frequent sites of genitorurinary sarcomas, followed by the bladder (23%) and kidneys (16%). The most common histologic subtypes in adults are leiomyosarcoma (44%) and rhabdomyosarcoma (33%), although a spectrum of other histologic subtypes has been reported.[487]

A feature of genitourinary sarcomas that distinguishes them from other sarcomas is the fact that the vast majority of these lesions are of high histologic grade. In a recent report from the Memorial Sloan-Kettering Cancer Center, fully 86% of genitourinary sarcomas were high grade, and 56% were larger than 5 cm.[487] Similar findings have recently been reported from the M.D. Anderson Cancer Center, where 15 (88%) of 17 primary sarcomas of the kidney met pathologic criteria for high-grade classification and tumor size ranged from 5.5 to 23 cm.[488] These findings have obvious prognostic implications, and recent series report relatively poor 5-year overall survival rates for patients with high-grade histology (48% versus 100% for low-grade lesions) or large tumor size (30% for lesions 5 cm or larger versus 83% for lesions less than 5 cm).

The primary treatment for genitourinary sarcomas, as with sarcomas elsewhere in the body, is complete resection with histologically negative margins. There are no comparative trials specifically evaluating adjuvant therapy in this subgroup of sarcomas, but most investigators have extrapolated from the lessons that have been learned

with extremity STS and employ adjuvant therapy for patients with high-risk lesions, including those with high histologic grade, large tumor size, microscopically positive margins, gross residual disease, or unfavorable anatomic site (prostate or kidney). Using preoperative chemoradiation and surgery for patients with nonbulky sarcomas of the bladder and prostate and postoperative chemoradiation after radical surgery for patients with bulky disease, investigators at UCLA and at the City of Hope have reported encouraging results, with 9 of 11 patients with leiomyosarcomas alive with no evidence of disease at a mean follow-up of 61 months.[489] These promising results are similar to those reported from the Mayo Clinic for a subset of seven patients with bladder sarcomas who were treated with preoperative radiotherapy and cystectomy[490] and are superior to those observed in a small series of patients who were treated with surgery alone.[491]

Paratesticular and spermatic cord sarcomas, if managed appropriately, can provide satisfactory outcome, as was reported in recent small series from the Princess Margaret Hospital[492] and the M.D. Anderson Cancer Center.[493] Simple excision proved to be inadequate treatment for sarcomas in the spermatic cord and paratesticular region. In the Princess Margaret Hospital report, wide repeat excision revealed microscopic residual disease in 27% of completely excised cases. These series suggest that adjuvant radiation should be considered for these patients as well as for those with narrow repeat resection margins. Definitive conclusions on multimodality therapy for genitourinary sarcomas await further experience with larger numbers of patients.

The comparative infrequency of these lesions and the lack of a uniform staging system lead to difficulties in comparison of series and identification of prognostic factors. Prognostic factors for survival were analyzed in the series from the Memorial Sloan-Kettering Cancer Center, and, by univariate analysis, favorable prognostic variables included tumor diameter less than 5 cm, low histologic grade, paratesticular or bladder (versus kidney or prostate) tumor site, and complete surgical resection.[487] No significant differences in survival were noted on the basis of patient age, sex, or histologic subtype. A poor prognosis for patients with primary renal sarcomas has also been observed at M.D. Anderson, with 13 of 15 evaluable patients dead of disease after a mean of 23 months.[488] Complete tumor resection was possible in 72% of patients in the series of 43 adult genitourinary sarcomas from Memorial Sloan-Kettering. The 5-year overall survival rate was 64% for this group of patients. No patient with an incomplete resection survived 5 years.

Unfortunately, as with head and neck rhabdomyosarcomas, the favorable results that are observed in pediatric patients with genitourinary rhabdomyosarcoma treated with a multimodality approach (58% to 74% 5-year overall survival rate)[494,495] have not been observed in adults in one study; only 5 (36%) of 14 adults were alive at the time of analysis (median follow-up: 32 months) despite aggressive multimodality therapy.[487]

Uterine Sarcomas

Uterine sarcomas are uncommon neoplasms that make up between 2% and 4% of uterine malignancies.[496,497] The three main histologic subtypes in a recent series of 66 uterine sarcomas were as follows: mixed mesodermal (müllerian) tumors, 48%; leiomyosarcomas, 36%; and endometrial stromal tumors, 15%.[498] As with patients who have adenocarcinomas of the uterus, most patients with uterine sarcomas present with vaginal bleeding (77% to 99%) or pelvic pain (30%).[499–502] A palpable pelvic mass is present in 20% to 50% of patients.[502,503] The diagnostic workup is similar to that for the common uterine neoplasms and involves an outpatient biopsy or fractional dilation and curettage. Imaging studies, including CT and MRI, are employed preoperatively in patients with positive preoperative biopsy findings or those with clinically apparent masses on examination.

The standard treatment approach for patients with localized disease is total abdominal hysterectomy with bilateral salpingoophorectomy. Complete abdominal exploration is important from the standpoint of prognosis, but since there are virtually no survivors among patients in whom extrauterine disease is found at the time of exploration, therapeutic extrapelvic dissection has no role. In a review of 423 patients from the West Midlands Cancer Registry, 5-year survival rates for patients with stage I, II, III, and IV (International Federation of Gynecology and Obstetrics staging system), uterine sarcomas were 51%, 13%, 10%, and 3%, respectively.[142]

A number of investigators have evaluated adjuvant radiation. To date, no completed RCT has evaluated the impact of adjuvant radiotherapy on disease-free survival or local recurrence using surgery alone as a control. A Gynecologic Oncology Group trial evaluating the role of postoperative radiotherapy closed because of poor patient accrual. Retrospective comparison of treatment results obtained with surgery alone versus surgery and postoperative radiotherapy has not demonstrated any significant difference in overall survival or disease-free survival rates.[498,504–509] However, multiple retrospective evaluations have suggested that patients who are treated with adjuvant radiotherapy have significantly improved local control with significantly improved freedom from local (pelvic) recurrence compared with patients who are treated with surgery alone.[500,505–508] These results parallel the findings that have been noted for patients with extremity sarcomas: demonstrable improvement in local control with adjuvant radiation but no impact on survival, although the same concerns exist pertaining to the small sample size to detect an effect of this kind.[188,193]

Several investigators have recently identified prognostic factors for survival in uterine sarcoma.[142,510] Multivariate analysis of 423 cases of uterine sarcoma demonstrated that advanced tumor stage, poor histologic grade, increased age, and leiomyosarcoma histologic subtype (versus mixed müllerian tumors) are characteristics that adversely affect survival.[142] A similar multivariate analysis by the Gynecologic Oncology Group of prognostic factors in 453 patients with uterine sarcomas demonstrated that factors related to progression-free interval were histologic grade, histologic type (homologous versus heterologous mixed müllerian tumors), adnexal spread, and lymph node metastasis.[510] These prognostic factors are of importance for selecting adjuvant therapy for individual patients and in designing future clinical trials in uterine sarcoma.

Chemotherapy

There is some evidence that mixed müllerian sarcomas (MMS) respond well to DDP chemotherapy alone[511] or in combination with other drugs.[512] Ifosfamide also seems to be active in MMS,[513] but doxorubicin might be of more limited value.[513] In a Gynecologic Oncology Group study[514] in which 76 patients with completely resected MMS were given three cycles of adjuvant ifosfamide/DDP, 2-year recurrence-free survival (63%) and overall survival (74%) rates were better than those for historical controls, but clearly, an RCT is needed to establish any true benefit for this regimen.

Paclitaxel combined with topotecan produced a 29% response rate in 45 patients with MMS,[515] and a retrospective analysis of MMS of the ovary found a very high response rate (72%) for a combination of paclitaxel and DDP.[516] Further exploration of agents active in epithelial ovarian cancer may be justified in MMS.

In contrast, uterine leiomyosarcoma, which often metastasizes to the lung rather than the liver, responds reasonably well to doxorubicin.[513] With respect to adjuvant chemotherapy, no significant differences in recurrence, progression-free survival, or overall survival rates were evident in a Gynecologic Oncology Group RCT of 156 patients comparing doxorubicin (60 mg/m^2) with no adjuvant chemotherapy after resection of stage I uterine sarcomas.[504] This trial was underpowered to detect small differences in outcome, however. The combination of gemcitabine, 900 mg/m^2 over 90 minutes on days 1 and 8, plus docetaxel 100 mg/m^2 on day 8 was initially studied in uterine

leiomyosarcoma at Memorial Sloan-Kettering Cancer Center.[384] There was a 53% response rate, and median progression-free survival was 5.6 months.

Desmoid Tumors (Aggressive Fibromatoses)

Desmoid tumor is an uncommon malignancy. It is estimated that approximately 700 to 900 new cases (three to four cases per million) occur annually in the United States.[514,517] The tumor arises principally from the connective tissue of muscle and the overlying fascia or muscular aponeurosis. Clinically, the tumor presents as a poorly circumscribed, painless mass and is commonly located in the muscles of the shoulder and pelvic girdle and frequently in the thigh. It is most common in patients between the ages of 20 and 40 years with a peak incidence of 25 to 35 years. *Aggressive fibromatosis*, *extra-abdominal desmoid*, *well-differentiated nonmetastasizing fibrosarcoma*, and *grade I fibrosarcoma* are terms that have also been used to describe this lesion.

Surgery and Radiation

Surgical resection remains the mainstay of therapy for desmoid tumors. Wide local resection with negative microscopic margins (R0) is the optimal surgical therapy. When resection is performed with positive microscopic surgical margins, local recurrence rates are substantially higher. Unfortunately, there are relatively few large series that outline actuarial local recurrence-free survival rates stratified by microscopic margin status for patients treated by surgery alone. Series from the M.D. Anderson Cancer Center, Massachusetts General Hospital, and Memorial Sloan-Kettering Cancer Center with margin-specific local recurrence-free rates are summarized in Table 97-14.[518–520] The experience of these institutions suggests that the local control rates for patients who are treated by surgery alone is on the order of 50% when microscopic surgical margins are positive (R1 resection), compared to approximately 75% when microscopic surgical margins are negative (R0 resection). As a consequence of the propensity for local recurrence, many groups have utilized postoperative EBRT for patients undergoing local excision (R0 or R1).[518,519] Postoperative EBRT is usually given to patients who are thought to be at higher risk for local recurrence. However, some groups employ external beam radiation for patients who have undergone an R0 resection (because of the generally high local recurrence rates associated with surgical treatment alone) and for most patients who have undergone an R1 resection. The criteria for selecting patients for postoperative radiation vary widely and are often subjective.

Interpretation of the limited literature on the use of EBRT in the management of localized desmoid tumors is hampered by the rarity of the lesion and the absence of margin-specific actuarial local recurrence rates for large series of consecutively treated patients. Retrospective comparisons stratified by margin status suggest that local recurrence rates might be reduced for patients treated with combined-modality therapy. The data substantiating this are all retrospective, nonrandomized, single-institution experiences; therefore, there is no clearly defined consensus on the role of radiation therapy in the management of patients with desmoid tumors.

Chemotherapy

Patients with desmoid tumors usually present to a medical oncologist only if the tumors have progressed after surgery and radiotherapy and are considered inoperable or are located at sites that are not amenable to full-dose radiotherapy. These tumors are rarely life threatening, although some tumors, especially the intra-abdominal desmoids that are seen in Gardner's syndrome, may become so owing to pressure on or invasion of vital organs. Rare responses have been reported to nonsteroidal anti-inflammatory drugs or anti-estrogens.[521–523] Weiss and Lackman were the first to report responses of desmoids to low-dose chemotherapy with methotrexate (50 mg/week) and vinblastine (10 mg/week).[523] Regressions are often slow, and toxicity usually requires dosing to be extended to 2-week intervals. Data on efficacy are clouded by the concomitant use of radiation therapy in some of the patients. Several groups have since confirmed the activity of this combination, however.[524–526] A much more aggressive regimen of continuous-infusion doxorubicin and dacarbazine[527,528] has produced substantial regressions in desmoids secondary to Gardner's syndrome. This regimen produces substantial toxicity, however, and should be reserved for patients with aggressive symptomatic disease. A case report documented a response of a desmoid to single-agent doxorubicin,[529] and this may be a less toxic alternative.

Breast Sarcomas

Primary sarcomas of the breast account for fewer than 1% of all primary breast neoplasms.[530] They should be distinguished from cystosarcoma phylloides and sarcomatoid carcinoma of the breast (carcinosarcoma), which are distinct clinical conditions. The most common histologic subtypes of breast sarcomas are malignant fibrous histiocytoma, liposarcoma, and fibrosarcoma.[531,532] A disproportionate number of angiosarcomas appear to arise in the breast either de novo[533] or after breast conservation surgery with adjuvant radiation.[534–536] In general, however, the etiology of most breast sarcomas is unknown. An association between augmentation mammoplasty with silicone prostheses and development of breast sarcoma had been postulated, but analysis of the NCI's Surveillance, Epidemiology and End Results Program database failed to demonstrate any relationship.[537]

On physical examination, breast sarcomas are usually well circumscribed, firm, mobile, and painless. Mammography frequently demonstrates a well-circumscribed lesion, in contrast to the irregular, stellate appearance of most mammary carcinomas. With the advent of fine-needle aspiration biopsy, an increasing number of these lesions are diagnosed preoperatively. This is important in planning an operative approach for these patients. Because breast sarcomas rarely spread to regional lymph nodes,[538–540] axillary lymph node dissection is not indicated for patients with a clinically negative axilla. The treatment of choice for breast sarcomas is wide local excision with

Table 97-14 Local Recurrence-Free Rates Following Surgery for Patients with Desmoid Tumors

				Local Recurrence-Free Surival	
Institution	**No. of Patients**	**Follow-up (Mo)**	**Overall (%)**	**R0 (%)**	**R1 (%)**
MGH[518]	51	12–59	69	77	56*
MDACC[519]	122	113	62	73†	46†
MSKCC[520]	128	88	71	86*	49*

MDACC, University of Texas M.D. Anderson Cancer Center; MGH, Massachusetts General Hospital; MSKCC: Memorial Sloan-Kettering Cancer Center; R0, microscopically negative surgical margins; R1, microscopically positive surgical margins.

*Using 5-year actuarial analysis.

†Using 10-year actuarial analysis.

histologically negative margins. Depending on the relative proportions of the tumor and the breast, this sometimes necessitates total mastectomy.

Adverse prognostic factors for survival include high histologic grade and an infiltrative histologic pattern.[532,538,540,541] A recent retrospective review of 83 patients with primary breast sarcomas treated predominantly with surgery and selective use of adjuvant chemotherapy and/or radiation revealed 10-year overall and disease-free survival rates of 62% and 50%, respectively.[534] On the basis of this report and early reports,[538–540] it appears that patients with primary breast sarcomas have a natural history, prognostic factors, and outcome after combined-modality treatment similar to those of patients with extremity sarcomas.

Adjuvant radiotherapy has no clearly defined role in this disease, although it would appear prudent to offer radiation to patients who are at high risk for local recurrence (microscopically positive margins or presentation with recurrent breast sarcoma). In addition, in a report of a mixed group of breast sarcomas and phylloides tumors at the Princess Margaret Hospital, breast conservation seemed to be attainable by using conservative margin-negative excision and adjuvant radiotherapy in an organ-preserving approach that is consistent with contemporary management for both breast cancer and STS.[542]

Vascular Sarcomas

The collective term *vascular sarcomas* includes the histologic subtypes of angiosarcoma, hemangiosarcoma, and lymphangiosarcoma. Together, these lesions account for approximately 4% of all STSs.[543] A minority of these lesions are associated with well-known environmental factors, as is noted in Table 97-1. In a national review of 99 Japanese patients with angiosarcoma, angiosarcoma was most commonly located on the head or face (29 patients) and was found to be associated with several predisposing conditions, including chronic pyothorax (6 patients), use of Thorotrast in the liver (5 patients), previous radiotherapy (4 patients), and chronic lymphedema (1 patient).[544] Virtually all of the literature on these rare neoplasms focuses on individual histologic and site-specific subtypes and includes pediatric patients. These facts, and the relative infrequency of these lesions, make general estimates of survival difficult for adult patients with vascular STSs.

In a review of 69 patients with vascular sarcomas and malignant hemangiopericytoma (not truly a vascular tumor) from Memorial Sloan-Kettering Cancer Center, 35 patients (51%) had angiosarcoma, 28 (41%) had malignant hemangiopericytoma, and 6 (9%) had lymphangiosarcoma.[543] No anatomic site was spared from involvement. The most common sites of involvement for angiosarcomas and malignant hemangiopericytomas were similar: visceral, retroperitoneum, head and neck, and extremities. The six lymphangiosarcomas in this series all occurred in an edematous extremity.

Cutaneous angiosarcoma is a variant of angiosarcoma that often arises in the head and neck and frequently diffusely infiltrates the dermis of the scalp or tissues of the face.[545] In the head and neck, cutaneous angiosarcoma can be difficult to treat by surgery because of the infiltrating nature of the disease and the anatomic constraints of the head and neck that make wide surgical margins difficult to achieve. Primary chemotherapy with the possible addition of radiation is preferable.

Overall survival rates for patients with localized disease who undergo curative resection are similar for angiosarcomas and malignant hemangiopericytomas (68% to 72%). A clear survival advantage for patients with low-grade lesions was not demonstrable in this study, although other investigators have reported such a relationship for cutaneous angiosarcomas.[546] Several investigators have suggested that tumor size might be an important prognostic factor for survival in patients with malignant hemangiopericytomas[547,548] and angiosarcomas of the face and scalp,[549,550] although no relationship was noted in the study from Memorial Sloan-Kettering.

Surgery

By definition, these lesions are vascular, and this should be borne in mind in planning preoperative biopsy and surgery. In the study from Memorial Sloan-Kettering, perioperative bleeding was noted in 33% of patients, with 18 of 69 patients experiencing extensive blood loss (>1000 cc) and two deaths related to hemorrhage.[543] Frozen section control of microscopic surgical margins is advisable, given the locally infiltrative nature of many angiosarcomas, particularly those that arise on the scalp.

Adjuvant Therapy

There is no clearly defined role for adjuvant radiation or chemotherapy for vascular sarcomas, although it seems reasonable to extrapolate from data derived from extremity lesions and offer adjuvant radiotherapy for patients with high-risk lesions. Unfortunately, aggressive surgical approaches might prove disappointing, owing to the unusual capability of this disease to exhibit edge recurrence and manifest disease relatively remote from the initial site of presentation (Fig. 97-17). Alternative radiotherapy techniques such as modulated electron radiotherapy are promising and could be applied in the future to the treatment of wide field areas that require only superficial penetration at depth, as is the case in craniofacial angiosarcoma. Considering the proximity of the brain and eyes in these lesions, limiting the depth of penetration and consequent reduction in dose to tissues that are deeper to tumor is the attractive aspect of this technology.[551]

There have been anecdotal reports that paclitaxel could be specifically active in angiosarcomas, especially those arising in the scalp or the skin of the breast.[380,552] A complete remission in a patient with metastatic angiosarcoma was seen in the phase II study of gemcitabine at M.D. Anderson,[378] so the combination of gemcitabine and docetaxel is particularly appealing for these tumors. Interferon-α is active against benign capillary hemangiomas of infancy and malignant vascular lesions such as HIV-related Kaposi's sarcoma. Burgess and colleagues reported sporadic responses in a variety of angiomatous tumors to a combination of interferon-α and 13-*cis*-retinoic acid.[553] Angiosarcomas are quite sensitive to standard doxorubicin ifosfamide therapy as well, but responses tend to be of short duration. Such therapy should be considered initially for visceral lesions such as those arising from the heart.

Chemotherapy Considerations for Specific Histologic Subtypes

Synovial Sarcomas

Rosen and colleagues[554] were the first to suggest that synovial sarcomas were particularly responsive to ifosfamide. They documented 3 complete responses and 9 partial responses in 13 patients (9 of whom had received prior doxorubicin-based chemotherapy) with metastatic synovial sarcomas. These investigators also reported on 14 patients with localized synovial sarcomas who received adjuvant doxorubicin/ifosfamide/DDP chemotherapy.[555] There was one patient with local recurrence, but the remaining 13 patients (93%) remained disease free at a median follow-up period of 37 (6 to 85) months. In a large EORTC phase II trial of 124 patients with advanced STS receiving ifosfamide (12 g/m^2), the overall response rate for all histologic subtypes was 16%,[367] but 8 (44%) of 18 patients with synovial sarcoma responded. Edmonson and colleagues described a higher response rate in synovial sarcomas for doxorubicin/ifosfamide than for doxorubicin alone (88% versus 20%, $P = 0.02$) in the setting of an RCT of multiple histologic subtypes of STS.[348] A subsequent ECOG phase II study of doxorubicin/ifosfamide in synovial sarcomas showed 5 partial responses (42%) in 12 patients; however, the median survival for the whole group was only 11 months, and the trial was closed because of poor accrual.[556] In many studies evaluating ifosfamide, including some of the RCTs, the question of response by histologic subtype has not been addressed, and most of the data on histologic

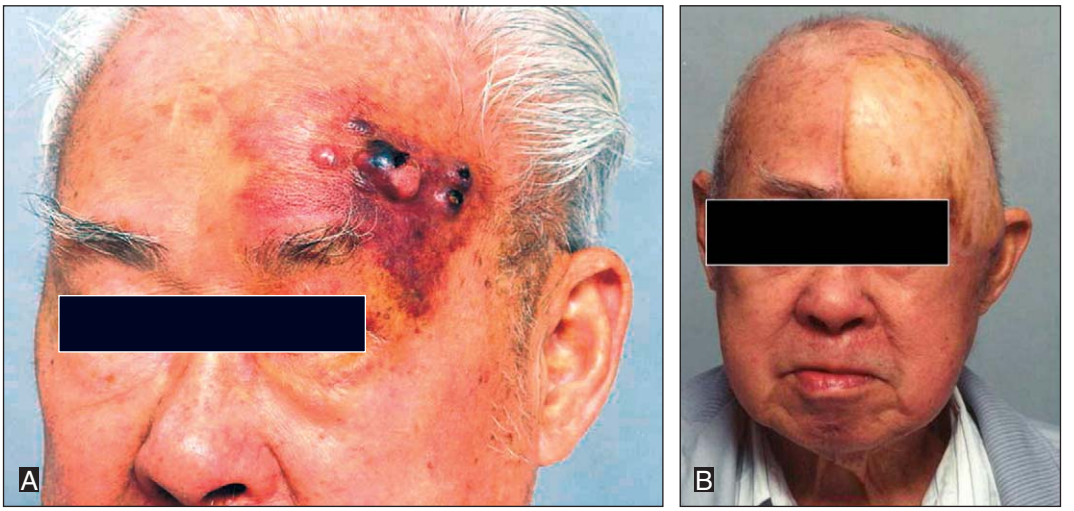


Figure 97-17 • **A,** Angiosarcoma of the scalp and facial areas in an older male. Note the infiltrative and multinodular nature of this process characterized by mottled discoloration and ecchymosis in the upper eyelid and facial tissues adjacent to the lesion. These lesions pose a formidable challenge in achieving local control owing to their propensity to manifest out-of-field recurrences after wide-field surgical and radiotherapy interventions **(B),** as well as a high predilection to fail in regional lymph nodes and distant sites. **B,** The same patient as in **(A)** showing the irradiated skin and the flap and reconstructed tissues at the site of wide field radiotherapy and surgery to the scalp for angiosarcoma. Unfortunately, this patient continued to manifest disease in other areas of the scalp remote from the treated areas that were managed with small field radiotherapy fields. This pattern of disease, including the ability to control disease locally but with relentless failure beyond the surgical and radiotherapy fields, is characteristic of angiosarcoma.

variations in response come from subset analyses of larger trials. Because many of the patients with synovial sarcoma are young and fit, inclusion of ifosfamide in first-line chemotherapy for metastatic disease seems reasonable. If the circumstances merit adjuvant chemotherapy, an anthracycline/ifosfamide combination would be a logical choice.

Leiomyosarcomas

Hensley and colleagues[384] were the first to report the activity of the gemcitabine-docetaxel combination in patients with leiomyosarcomas. While clearly active in that subset, particularly in leiomyosarcomas arising from the uterus, this regimen is broadly active and should not be limited to leiomyosarcomas. In contrast to the increased activity of ifosfamide in synovial sarcomas, ifosfamide is less active against leiomyosarcomas than against other subtypes,[340,354] even when GISTs were excluded,[354] and high-dose ifosfamide had a similar lack of efficacy.[343,363,366]

Liposarcomas

Marked clinical activity of trabectidin (ET-743) was noted in patients with myxoid liposarcoma.[557] Among 51 patients who were treated at five institutions, a RECIST response rate of 51% was noted, with objective benefit characterized by decreased postcontrast tumor density in all of the responding patients and an additional 29% categorized as having minor response or stable disease by RECIST. Progression-free survival was 88% at 6 months. For comparison, in all STSs, including those with myxoid liposarcoma, the RECIST response rate to trabectidin is about 10%, and progression-free survival was 20% at 6 months. Thus, myxoid liposarcomas are uniquely sensitive to this agent.

Activation of the PPARγ nuclear receptor stimulates terminal differentiation in preadipocytes and in liposarcoma cell lines regardless of histologic subtype.[558] Troglitazone, previously used in the treatment of diabetes mellitus, is an activating ligand for PPARγ. Biopsies before and after troglitazone therapy were obtained in 34 of 49 patients with different types of liposarcomas entering a phase II trial.[559,560] Five of seven (71%) evaluable patients with myxoid/round cell disease exhibited histologic evidence of lineage-appropriate differentiation of liposarcoma cells, whereas only one of three (33%) patients with high-grade pleomorphic disease showed such changes. Although this study provides proof-of-concept data, the clinical significance is uncertain, and the limited clinical benefit of troglitazone was confined to myxoid liposarcoma.

Pediatric Sarcomas in Adults

Embryonal rhabdomyosarcomas and the PNETs, including extraskeletal Ewing's sarcoma, all seem to be chemosensitive when they occur in the adult age group. Adult patients with these tumors should receive aggressive combination chemotherapy similar to that offered to children with the same disease.[561,562] Nevertheless, the outcome is likely to be poorer for adults with "pediatric sarcomas" than for pediatric sarcoma patients.

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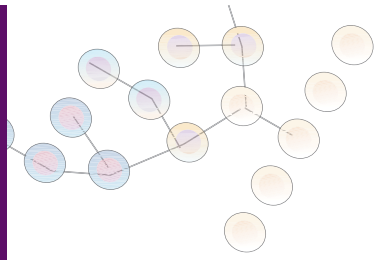
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98 Carcinoma of Unknown Primary

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SUMMARY OF KEY POINTS

Incidence
- Carcinoma of unknown primary accounts for about 2% to 5% of all cancers.
- At M.D. Anderson Cancer Center from January 1987 to June 1995, carcinoma of unknown primary accounted for 1.5% of all cancer referrals.

Evaluation
- Controversy continues regarding the extent of evaluation needed to exclude a definable primary cancer.
- Biopsy of a metastatic site is recommended early to establish the diagnosis and help direct further workup.
- Basic evaluation includes the following:
  - History and physical examination (including breast and pelvic examinations in women and testis and prostate examinations in men)
  - SMA-12, complete blood cell count, prostate-specific antigen test in men, chest radiography, abdominal and pelvic computed tomographic scan, and mammography in women
  - Testing for immunohistochemical markers (including CK7, CK20, TTF-1)
- The diagnostic utility of positron emission tomography (PET) and its cost-effectiveness are controversial and currently being studied.
- The role of DNA microarray and gene profiling in this subset is evolving.

Differential Diagnosis
- Diagnosis is made in patients with a biopsy-proved malignancy, when the site of origin is not obvious after preceding evaluation.
- Careful consultation with a pathologist is critical to exclude highly treatable malignancies (e.g., lymphoma, breast cancer, germ cell cancers).
- Newer diagnostic tools, including new immunohistochemical stains, and molecular markers promise the ability to identify the site of origin in a greater proportion of cases.

Primary Therapy
- It is important to identify specific patients who may have clinical or pathologic features of six highly treatable carcinoma of unknown primary subsets (minority of patients):
  - Women with axillary adenopathy (adenocarcinoma or carcinoma)
  - Women with peritoneal carcinomatosis
  - Patients with poorly differentiated or undifferentiated carcinoma
  - Males with the extragonadal germ cell syndrome
  - Patients with neuroendocrine carcinoma
  - Patients with high cervical adenopathy (squamous carcinoma)
- For the majority of patients, who belong to no identifiable subset, primary therapy consists of the following:
  - Systemic therapy: adenocarcinoma: paclitaxel/carboplatin ± etoposide; CDDP/5-fluorouracil/leucovorin
  - Carcinoma: paclitaxel/carboplatin ± etoposide; CDDP/etoposide
  - Squamous carcinoma: CDDP/5-fluorouracil/leucovorin
  - Local therapy: resection ± radiation therapy; observation with best supportive care

Second- or Third-Line Therapy
- No highly effective salvage systemic regimens are in use.
- Gemcitabine has produced low objective response rates and symptomatic improvement as single-agent therapy in the second-line setting.
- The role of newer agents such as irinotecan is evolving; patients should be encouraged to participate in clinical trials for novel agents.

INTRODUCTION

Despite the increasing array of sophisticated diagnostic tools available to establish the diagnosis of human neoplasia, oncologists have struggled to understand a subset of patients with metastatic cancer in whom detailed investigations fail to identify a primary anatomic site. The reported incidence of carcinoma of unknown primary (CUP) varies with the practice setting and the definition used, but averages 2% to 5% of all patients who are diagnosed with cancer.[1] Because identification of the primary lesion largely forms the basis for predicting the expected behavior and assigning appropriate therapy of malignant diseases, the absence of a primary carcinoma poses a major challenge. The inability to identify a primary carcinoma also generates anxiety for the patient, who may feel that the physician's evaluation has been inadequate or that the prognosis would be improved if a primary site could be established.

As suggested by the foregoing variable incidence statistics, the definition of CUP has not been standardized, varying in published reports mainly with regard to the extent of evaluation required to accept this diagnosis. For the purpose of this chapter we define patients with CUP as having a biopsy-proved malignancy for which the anatomic origin remains unidentified after history and physical examination (including breast palpation and pelvic examination in women and testicular and prostate examination in men), laboratory studies including liver and renal function tests, hemogram, chest x-ray, computed tomography (CT) of abdomen and pelvis, mammography in women, and measurement of prostate-specific antigen (PSA) in men. All positive findings on this initial evaluation are then

investigated in detail.[2] Depending on the clinical situation, additional studies might include sputum cytologic test, CT of the chest, breast ultrasonography, or gastrointestinal (GI) endoscopy. To further define the patient population, most investigators have excluded from analysis rare instances in which soft tissue sarcoma or melanoma present without a definite primary site,[2] concentrating clinical research efforts on the vast majority of patients with common epithelial histologies such as adenocarcinoma, carcinoma, squamous carcinoma, and neuroendocrine carcinoma.

The approach to patients with CUP is based on the generally held belief that this group of patients is heterogeneous and may have any one of numerous underlying primary cancers that remain occult during the lifetime of the patient. This concept is supported by studies showing that a detailed postmortem anatomic investigation will establish a primary cancer in many, if not the majority, of these patients.[3,4] However, clinically these small primary tumors usually remain undiagnosed during the course of the patient's disease. Although heterogeneous in their origins, detailed clinical and biochemical study of CUP cells may represent a valuable resource with which to delineate the metastatic phenotype.[5,6] More recent approaches involve simultaneous determination of a large number of molecular markers with tools such as DNA microarrays and reverse transcriptase-polymerase chain reaction (RT-PCR). Such approaches promise to identify the site of origin in a larger proportion of patients with CUP,[7,8] although poorly differentiated tumors still may elude accurate classification.[9] Also, the heterogeneity of this population may make them the natural population in which to evaluate experimental approaches such as immunotherapy and antiangiogenesis. As with the specific well-defined primary neoplasms discussed elsewhere in this text, it is the phenomenon of metastasis, as purely exemplified by the patient with CUP, that causes the great majority of cancer deaths.

ETIOLOGY AND EPIDEMIOLOGY

Whether specific etiologic factors are relevant to CUP is not known. Although a history of cigarette smoking often can be elicited (Table 98-1), the heterogeneity of CUP makes it unlikely that specific etiologic agents will be associated with this disease. The fact that numerous occult anatomic sites can give rise to carcinomas that present with only metastatic disease supports the possibility that specific interactions of genetic and environmental insults could give rise to genomic and biochemical changes that lead to the early development of the metastatic phenotype without the associated changes supporting local growth in the organ of origin. Although this concept must be considered highly speculative, it is a hypothesis that can be tested through analysis of available biomarkers such as oncogenes and tumor suppressor genes that have been characterized for cancers with known anatomic origins, such as lung, pancreatic, breast, and colorectal carcinomas. Either the absence of genetic changes typical for malignancies with established primary cancers or the presence of unusual variants of known genetic alterations would support this hypothesis. It is likely that as the genomic and proteomic characterization of malignancies is refined, fewer and fewer malignancies may be assigned to the CUP designation.

The epidemiologic characteristics of 1109 consecutive patients with CUP referred to the M.D. Anderson Cancer Center from January 1987 to June 1995 are presented in Table 98-1. These data are juxtaposed with the overall referral population during the same time period. Although the family history often identifies additional cancers with established origins in other family members, no clearly familial instances of CUP have been identified or reported.

HISTOLOGIC PRESENTATIONS

The frequency with which specific histologic diagnoses are established in CUP depends to some extent on the patient population chosen for study. For example, most recent investigators have excluded the well-characterized group of patients with metastatic squamous carcinomas to cervical lymph nodes.[10–12] The specific histologic diagnoses identified in a series of 1109 consecutive patients with CUP are outlined in Table 98-2 and are contrasted with another reported series.[13] The low frequency of squamous carcinoma reflects the direct referral of patients with squamous cell carcinoma involving high or mid-cervical lymph nodes to head and neck oncologists for management.

Table 98-1 Characteristics of 1109 Patients with Carcinoma of Unknown Primary

	Unknown Primary Carcinoma ($N = 1109$)	All Patients Referred to M.D. Anderson Cancer Center*
Characteristic	**No. of Patients (%)**	**No. of Patients (%)**
Age (yr)		
0–39	108 (9.7)	9674 (17.6)
40–49	175 (15.8)	9706 (17.7)
50–59	283 (25.5)	12,158 (22.1)
60–69	346 (31.2)	14,112 (25.7)
>70	197 (17.8)	9289 (16.9)
Sex		
Female	537 (48.4)	26,970 (49.1)
Male	572 (51.6)	27, 969 (50.9)
Ethnicity		
White	962 (86.8)	43, 788 (79.7)
Hispanic	78 (7.0)	6267 (11.4)
Black	48 (4.3)	3909 (7.1)
Other	21 (1.9)	975 (1.8)
Smoking history		
Smokers	608 (54.8)	N/A
Nonsmokers/unknown	501 (45.2)	N/A

N/A, not available.
*Total number of patients referred with diagnosis of malignancy recorded from 1/1/87 to 6/30/95: 54,939.

BIOLOGIC CHARACTERISTICS

The biology of CUP has been partially characterized through the evaluation of patient subsets using as primary endpoints responsiveness to therapy and survival. When all patients are considered, CUP is a highly aggressive neoplasm with an overall median survival time of 3 to 4 months in older series.[14] More recent studies have documented median survival times of 9 to 12 months.[15–18] In our series of 1109 consecutive patients, the median survival period was 11 months. The survival curve for these patients is presented in Figure 98-1.

The survival times for the four most commonly encountered pathologic subtypes are presented in Figure 98-2. The median survival times were as follows:

- For patients with squamous carcinoma (exclusive of patients with mid-high cervical adenopathy), 24 months
- For patients with adenocarcinoma, 9 months
- For patients with carcinoma, 12 months
- For patients with neuroendocrine carcinoma, 33 months.

The state of differentiation or mucin production did not appear to have a significant influence on the poor survival of patients with

Table 98-2 Histologic Types Identified in 1109 Consecutive Patients with Carcinoma of Unknown Primary

	M.D. ANDERSON CANCER CENTER		HAINSWORTH ET AL[13]	
Histologic Type	**No. of Patients***	**Percentage of Total**	**No. of Patients†**	**Percentage of Total**
Adenocarcinoma	646	58.3	—	31.8
Well differentiated	14			
Moderately differentiated	45		—	
Poorly differentiated	220		70	
Mucinous	46		—	
No descriptor/other	321		—	
Carcinoma	317	28.6		44.1
Poorly differentiated	161		97	
Undifferentiated	21		—	
Large cell	9		—	
Small cell	14		—	
No descriptor/other	112		—	
Squamous	68	6.1	5	2.3
Neuroendocrine	48	4.3	25	11.4
Adenosquamous	7	0.6	0	0
Pathology not available for review/other	23	2.1	23	10.4

*Total number of patients, 1109.
†Total number of patients, 220.

adenocarcinoma (Fig. 98-3). Using univariate and multivariate analyses, various groups have assessed the influence of other clinicopathologic features of CUP on survival (Table 98-3). Culine and associates[19] also developed and validated a prognostic model to predict the length of survival in patients with CUP. Univariate and multivariate prognostic factor analyses were conducted in a population of 150 unselected patients and led to the construction of two successive classification schemes. When studying the clinical variables only, poor performance status and presence of liver metastases were retained in the multivariate analysis. The first classification scheme consisted of three groups of patients with median survival times of 10.8, 6.0, and 2.4 months, according to the number of adverse prognostic factors. When serum lactate dehydrogenase (LDH) was introduced in a further step, liver metastases were no longer of significance. The second classification scheme, therefore, included performance status and elevated serum LDH. Good- and poor-risk patients were identified, with median survival times of 11.7 months and 3.9 months and 1-year survival rates of 45% and 11%, respectively. Validation of the second classification was obtained using an external data set; and the median survival times of patients assigned

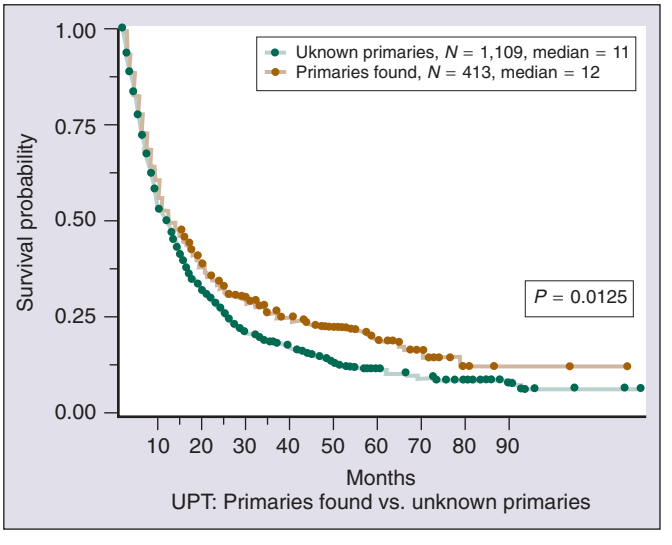


Figure 98-1 • Survival curves for 1109 patients with carcinoma of unknown primary (CUP) versus 413 patients referred with CUP in whom the primary cancer site was found.

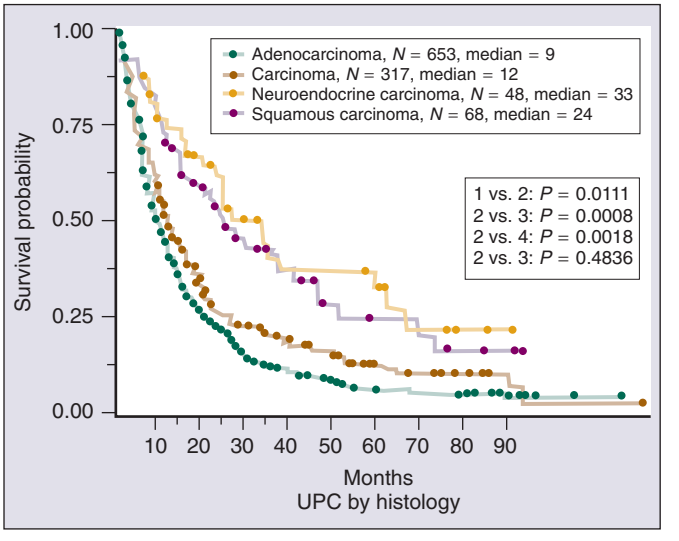


Figure 98-2 • Survival curves of the major histologic subtypes of carcinoma of unknown primary.

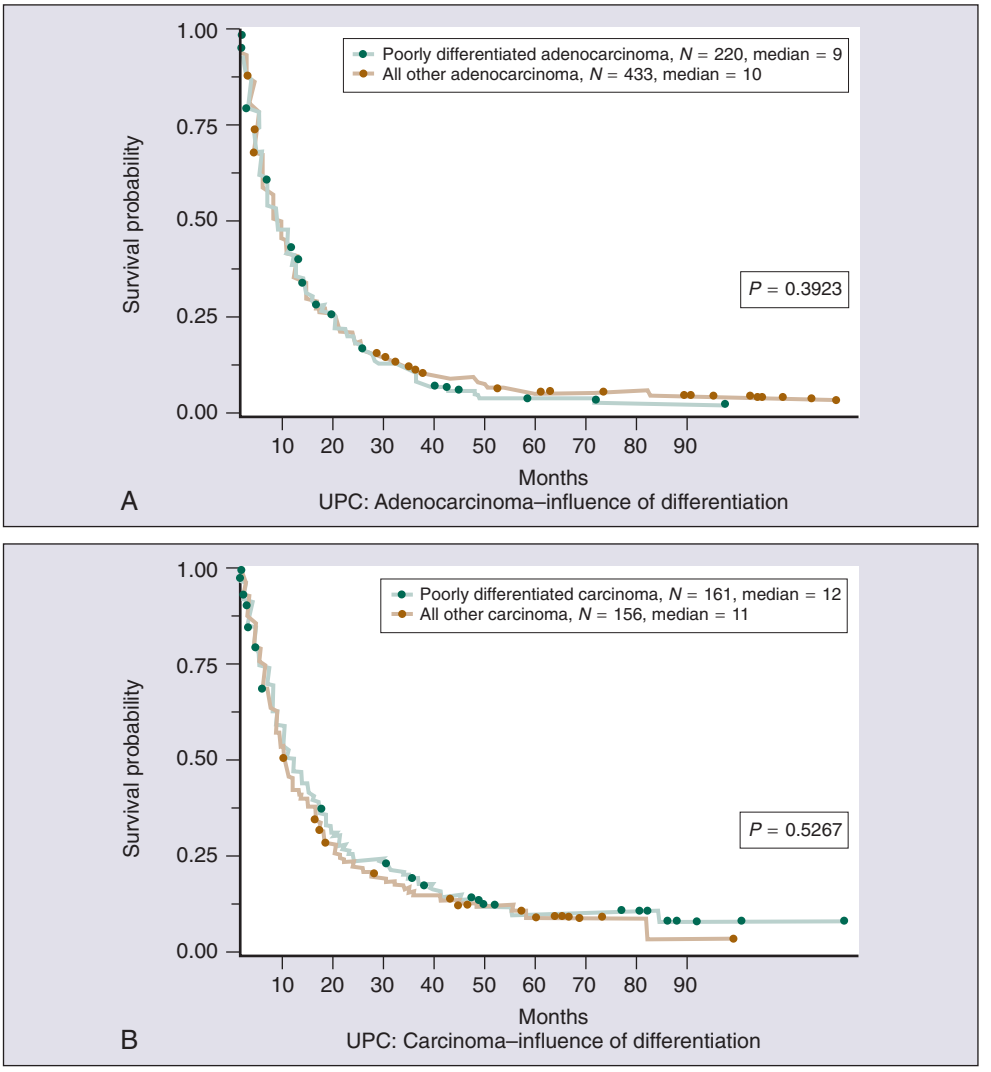


Figure 98-3 • **A,** Influence of cellular differentiation on the survival of patients with unknown primary adenocarcinoma. **B,** Influence of cellular differentiation on the survival of patients with carcinoma of unknown primary.

to the good-risk group and poor-risk group were 12 months and 7 months with 1-year survival rates of 53% and 23%, respectively. This simple prognostic model using performance status and serum LDH allows assignment of patients into two subgroups with divergent outcomes. Additional prospective trials will be designed using this prognostic model.

To assess the impact of disease extent on survival, the number of organ sites involved in the metastatic process was assessed at presentation in our series to provide a crude quantitation of tumor burden. For this analysis, involvement of an organ, even when there were multiple individual metastases within the site, was counted as involvement of one organ site. Using this definition, 133 patients (37.5%) had a single involved site and 122 patients (34.5%) had two sites involved. The remaining 99 (28.0%) patients had three or more sites involved in the metastatic process. The survival curves for patients with one, two, and three or more organ sites involved are displayed in Figure 98-4. The median survival time for patients with one site of involvement was 10 months, with two sites of involvement 8.0 months, and with three or more sites of involvement 6.0 months. These survival curves are statistically different by the Cox-Mantel log-rank test ($P = 0.028$). Other studies have documented similar results.[18]

The question of whether the biology of CUP is fundamentally different from known primary carcinoma with systemic metastases remains controversial.[20] Nystrom and associates[21] have argued that

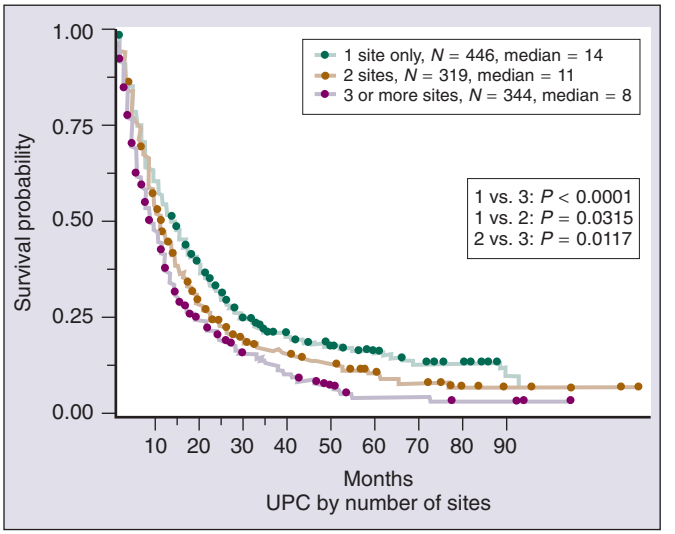


Figure 98-4 • Survival of patients with cancer of unknown primary versus number of involved organ sites.

Table 98-3 Univariate and Multivariate Survival Analyses—Patients with Carcinoma of Unknown Primary

		UNIVARIATE SURVIVAL ANALYSIS	
Variable	**Grouping**	***P****	**Effect on Survival**
Age (yr)	20–39, 40–49, 50–59, 60–69, 70+	0.43	None
Sex	Male, female	0.0018	Decreased survival for men
Race	White, other	0.86	None
No. organ sites	1, 2, 3+	0.0018	Decreased survival with more organ sites
Involved organ sites			
Lung	—	0.0014	Deleterious
Bone	—	0.0005	Deleterious
Liver	—	0.0050	Deleterious
Pleura	—	0.0019	Deleterious
Brain	—	0.014	Deleterious
Lymph nodes	—	<0.0001	Advantageous
Axilary	—	0.0003	Advantageous
Supraclavicular	—	0.44	None
Peritoneum	—	0.59	None
Skin	—	0.69	None
Histologic type	—		
Adenocarcinoma	—	<0.0001	Deleterious
Carcinoma	—	0.0058	Advantageous
Squamous carcinoma	—	0.058	Advantageous
Neuroendocrine carcinoma	—	0.0009	Advantageous
		MULTIVARIATE SURVIVAL ANALYSIS	
Variable	**Relative Risk†**	***P****	**Effect on Survival**
Male sex	1.39	0.0007	Deleterious
Increasing no. of organ sites	1.23	<0.0001	Deleterious
Involved organ sites			
Liver	1.33	0.0064	Deleterious
Lymph nodes (all sites)	0.46	<0.0001	Advantageous
Supraclavicular	1.56	0.013	Deleterious
Peritoneum	0.59	0.0099	Advantageous
Histologic type			
Adenocarcinoma	1.46	0.0001	Deleterious
Neuroendocrine carcinoma	0.30	0.0005	Advantageous

*Log-rank test.
†Calculated from the Cox proportional hazards regression.
Adapted from Abbruzzese JL, Abbruzzese MC, Lenzi R, et al: Analysis of a diagnostic strategy for patients with suspected tumors of unknown orgin. J Clin Oncol 1995;13:204.

the distribution of metastatic sites in patients with CUP where the primary cancer is subsequently found is sufficiently different from known primary carcinoma to support the hypothesis that CUP is biologically unique. However, analysis of our series shows few significant differences in the pattern of metastases (Table 98-4) or in overall survival for true CUP versus patients in whom the primary lesion was found (see Fig. 98-1). Continued study of CUP is necessary to resolve this controversy.

Why the primary organ site cannot be diagnosed remains unknown. Previous investigators have speculated that the tumor may remain below the limits of clinical or radiographic detection or that it spontaneously regressed.[22] Another possibility would be that a clinically detectable primary cancer never develops due to the development of specific genetic changes that support metastatic but not local growth. Continued investigation has resulted in greater understanding of the biologic features of unknown primary carcinomas, characterized by aneuploidy, chromosomal abnormalities, oncogenes, tumor suppressor genes, and microvessel density.

Aneuploidy, a well-recognized phenomenon occurring in 70% to 90% of solid tumors,[23–25] is defined as a chromosome complement that is not a simple multiple of the haploid set. Increasing evidence indicates that for many carcinomas, such as breast, prostate, and colorectal cancers, a diploid DNA content is associated with a more favorable prognosis.[26] Hedley and associates[27] measured the cellular DNA content of tumor biopsy specimens of 152 patients with metastatic adenocarcinoma or undifferentiated carcinoma of unknown primary site to determine favorable subgroups. Aneuploidy was found in the specimens of 70% of the patients. There were no significant

Table 98-4 Comparison of Metastatic Involvement of Common Sites with Known Primary Carcinomas versus Carcinoma of Unknown Primary

	Metastatic Organ Site Involvement (%)†					
	Bone		Lung		Liver	
Primary Site	**Known**	**CUP-Primary***	**Known**	**CUP-Primary***	**Known**	**CUP-Primary***
Lung	38	40	28	N/A	15	19
Breast	49	34	27	19	34	19
Pancreas	4	14	14	3	82	76
Prostate	88	50	6	50	4	0
Colorectal	3	4	21	20	77	92

CUP, cancer of unknown primary; N/A, data not available.
*Patients presenting with CUP in whom the primary site was subsequently discovered.
†Known primaries, $N = 2287$; CUP in whom primary site discovered, $N = 413$.
Hess KC, Abruzzese JL, unpublished data.

differences between men and women, and there was no obvious relationship to the various patterns of metastatic involvement. The median survival of patients with diploid tumors was 4.2 months, versus 4.8 months for patients with aneuploid tumors. Of the 46 patients with diploid tumors, 9 (18%) survived for more than 2 years, compared with 10 (9%) of 106 patients with aneuploid tumors. These results indicate that the incidence of aneuploidy in this heterogeneous group of patients is similar to that reported for carcinomas with known primary tumors. However, in contrast to many of these tumor types, in this single study conducted by Hedley and associates, metastatic adenocarcinomas of unknown primary origin that are diploid are not associated with a more favorable prognosis than are those of known primary origin.[27]

Chromosome Abnormalities

Evaluation of chromosomal abnormalities in CUP is an emerging area of investigation, and thus far relatively few studies have been performed. Abbruzzese and colleagues[5] and Bell and coworkers[28] developed a research program aimed at identifying common karyotypic changes in CUP. The karyotypes of 13 of 20 patients with CUP were determined, and in 12 of the analyzed cell lines abnormalities were identified in the short arm of chromosome 1. The abnormalities detected included deletion of 1p, translocations, isochromosome 1q, and gene amplification. These findings were consistent with earlier descriptions of chromosome 1p abnormalities in advanced malignancy as described by Atkin[29] and Mertens and associates.[30]

Motzer and associates[31,32] used karyotyping to determine the frequency of specific abnormalities of chromosome 12 in patients with CUP. It was hypothesized that patients with undifferentiated carcinoma of unknown primary origin responding to cisplatin-based chemotherapy had unrecognized germ cell tumors and that isochromosome 12p, i(12p), a specific chromosomal marker characterizing germ cell tumors, could be used to identify such patients. Thirty percent of patients had an increased 12p copy number or deletion of the long arm of chromosome 12, which proved predictive of response, thereby validating the hypothesis. Complete response to cisplatin-based therapy was achieved in patients with specific chromosomal aberrations associated with germ cell tumors, and objective responses were achieved in 75% of these patients, compared with 17% of patients without these aberrations. Summersgill and associates[33] and Ilson and associates[34] found similar associations for CUP patients with undifferentiated carcinoma. Thus, for patients with undifferentiated carcinoma, i(12p) correlated with a good response to platinum-based chemotherapy, although lack of i(12p) may not exclude a small percentage of responses; i(12p) occurs in more than 80% of the germ cell tumors and only sparsely in a few other lesions (e.g., acute leukemia, embryonal rhabdomyosarcoma, and neuroepithelioma), and, therefore, determination of the presence or absence of i(12p) can help diagnose extragonadal germ cell tumors in patients with CUP.[35]

Oncogenes

The oncogenes ras, c-myc, bcl-2, and her-2/neu are overexpressed in a variety of solid tumors. The levels of these genes are thought to be useful prognostic factors, though reports on c-myc and bcl-2 often are conflicting. Pavlidis and associates[36] found a high rate of overexpression of c-myc (96%), ras (92%), and c-erbB_2 (65%). Investigators found that the overexpression did not have a further relationship with histologic or clinical parameters or a diagnostic or prognostic value, however.

Briasoulis and associates[37] studied levels of bcl-2 expression in 40 patients with CUP (8% squamous, 36% adenocarcinoma, and 55.5% poorly differentiated carcinoma). Staining was evaluated based on intensity (+1 to +3) and the percentage of positive cells (1% to 100%). Expression of bcl-2 was seen in almost half of the tumors. This finding was not expected, because in most studies, bcl-2 had been found to be upregulated in premalignant lesions rather than advanced malignancies and also had been associated with a less aggressive phenotype.[38,39] In this study, the level of bcl-2 expression, by itself, had no prognostic value. When combined with a high level of expression of p53, however, high expression of bcl-2 showed a trend toward a higher response to platinum-based chemotherapy.

Hainsworth and associates[40] stained 100 tumor specimens of poorly differentiated adenocarcinoma (PDA) or poorly differentiated carcinoma (PDC) of unknown primary site for Her-2 protein. The samples of 10 patients (11%) overexpressed Her-2. These investigators did not observe any major difference in the overall response rate to chemotherapy between the patients whose cancer overexpressed Her-2 and those who did not. Evaluation of the efficacy of trastuzumab in selected patients with CUP with Her-2 overexpression is warranted.

Rashid and associates[41] retrospectively evaluated 100 serial formalin-fixed, paraffin-embedded sections from patients with CUP with biopsies or resections done at UTMDACC. Seventy-six samples with adequate tissue were stained by immunohistochemistry for epidermal growth factor receptor (EGFR), vascular endothelial growth factor (VEGF)-A, Cox-2, c-erbB2, and c-kit. Seventy-five percent of tumors stained for EGFR and 49% for VEGF-A. EGFR often was present with other markers, and was seen along with VEGF, c-erbB2, or Cox-2 in at least 30% of patients. Three triple-staining patterns of EGFR/c-erbB2/VEGF, EGFR/c-erbB2/Cox-2, and c-erbB2/Cox-2/VEGF were observed. Kaplan-Meier survival by intensity of staining failed to show significance. Further evaluation is warranted, because

this information may translate to therapeutic benefit regarding combination targeted therapies for patients with CUP.

Tumor Suppressor Genes

It is now known that a large number of gene deletions or allelic inactivation occur in most human cancers. Many of these genetic alterations result in the activation of oncogenes or in the loss of tumor suppressor genes and have been localized to specific chromosomes. To date, p53 is the best-known and most widely studied tumor suppressor gene. p53 can control tumor development by arresting cell cycle or initiating apoptosis of damaged cells. p53 mutations are common and occur in about 55% of all human cancers.[42–44]

Briasoulis and associates[37] evaluated p53 expression using immunohistochemistry in 47 cases of CUP (4 squamous carcinoma, 17 adenocarcinoma, 26 PDC). Staining was evaluated based on intensity (+1 to +3) and percentage of positive cells (1% to 100%). More than 70% of the tumors expressed p53; 53% expressed a high level and 47% expressed a low level of immunohistochemical staining. In this study, p53 expression alone had no prognostic value.

Bar-Eli and associates[45] also investigated the frequency of p53 mutations in a series of 15 CUP biopsies and 8 cell lines established from CUP. Mutations in the conserved regions of p53 gene were analyzed by single-strand conformation polymorphism analysis of exons 5 to 9 and were verified by direct DNA sequencing of PCR products. The p53 gene was mutated in 6 of 23 (26%) patients with CUP. Therefore, despite the fact that CUP represents bad-prognostic tumors that often are aneuploid, the frequency of p53 mutation was relatively low in this study. This finding suggests that p53 mutations may not play a major role in the development and progression of CUP. The discrepancy between the results of these two studies may be due to discordance between the results of immunohistochemical and genetic molecular methods in detecting the p53 abnormalities, which may occur in 25% of tumors.

No research is available on metastasis-suppressor genes in CUP, which seem to play an important role in regulating the growth of disseminated cancer cells at secondary sites.

Microvessel Density

Compelling evidence indicates that angiogenesis, as measured by microvessel density (MVD), correlates with the incidence of metastases in several solid tumors. Hillen and associates[46] aimed to identify a specific biologic role for angiogenesis in the metastatic phenotype of CUP by comparing MVD in liver metastasis of CUP with MVD in liver metastasis of colon and breast tumors. No difference was found between MVD in liver metastasis of CUP and known primary tumors. In CUP, as in other solid tumors, high MVD correlated with short survival in univariate and multivariate analyses.

Karavasilis and associates[47] investigated angiogenesis by assessing MVD and the tissue expression of VEGF and thrombospondin-1 (TSP-1). VEGF is the major stimulator of angiogenesis, and TSP-1 is an intrinsic angiogenic inhibitor. Paraffin-embedded archival material was evaluated from 81 patients diagnosed with CUP. Adenocarcinoma was the predominant histology found in 77% of cases, followed by undifferentiated carcinoma in 18% of cases and squamous cell carcinoma in 5% of cases evaluated. Tissue expression of CD34, VEGF, and TSP-1 were accessed immunohistochemically using specific monoclonal antibodies and were analyzed against clinicopathological data.

VEGF expression was detected in all cases and demonstrated a strong staining pattern in 83%. Stromal expression of TSP-1 was seen in 80% of cases, with only 20% of the 80% demonstrating a strong staining pattern. There was no evidence to suggest that expression of both proteins was associated with any clinical or pathological variables. A positive association was observed between VEGF expression and MVD and a negative association between VEGF expression and TSP-1. MVD also was found to be statistically higher in unfavorable CUP patient subsets, specifically adenocarcinoma metastatic to liver, multiple visceral involvement, and extensive metastatic bone disease. This study supports the activity of angiogenesis and almost universal expression of VEGF in CUP and prompts the need for further clinical investigation evaluating VEGF targeted therapy.

EVALUATION OF THE PATIENT

Considerable controversy surrounds the optimal evaluation of patients with CUP. It is clear that this diagnosis creates a serious dilemma for the clinician, because treatment planning is based on both the anatomic origin and the histologic type of the malignancy. Often there is the perception that the physician's efforts to locate a primary cancer have been somehow inadequate and that the prognosis and treatment of the malignancy would be radically altered if the primary tumor could be found.

An effective strategy would take into account the projected natural history and duration of survival and provide a reasonable probability of locating the primary anatomic site without compromising quality of life with difficult and time-consuming diagnostic studies. The overall goal is to rapidly identify the treatable patient subsets or occult primary lesions through a rational, calculated approach.

History and Physical Examination

The history and physical examination is one of the most important aspects of the evaluation of the patient with suspected CUP and often is overlooked. The history is critical, because it can define areas of concern that will require more detailed evaluation, such as the respiratory system in a smoker who presents with a supraclavicular node, cough, and hemoptysis. A detailed review of systems is mandatory, because it may elicit symptoms that were not immediately brought to the physician's attention. Attention also should be paid to history of previous biopsies or removed lesions, as well as spontaneously regressing lesions. The family history occasionally can be helpful, especially if the patient belongs to a specific ethnic group that is known to be at high risk for malignancies at specific sites (e.g., gastric cancer in Japanese populations or hepatocellular carcinoma or nasopharyngeal carcinoma in patients of Chinese ancestry) or belongs to a family that is known to be genetically predisposed to malignancies at specific sites (e.g., families with hereditary nonpolyposis colon cancer or hereditary breast malignancies).

The physical examination should be rigorous and should, in all cases, include careful palpation of the thyroid, breasts, lymph nodes, liver, and prostate. All patients should have a digital rectal examination with stool tested for occult blood. Genital examination, including a pelvic examination in women and careful palpation of the testes in men, is mandatory. Although these recommendations are routine, in our experience these aspects of the evaluation of the patient with CUP often are overlooked. When carefully performed, these examinations sometimes provide the probable diagnosis or, at a minimum, allow the clinician to formulate a directed laboratory and radiographic evaluation.

Laboratory Studies and Serum

Tumor Markers

The laboratory evaluation of patients with suspected CUP should begin with a complete blood cell count to screen for anemia (particularly to look for iron deficiency, which would suggest chronic GI blood loss and immediately focus attention on the GI tract as a potential primary site), urinalysis (to check for microscopic hematuria or proteinuria), and liver function studies, in some cases including studies for hepatitis B surface antigen or prior exposure to hepatitis C virus, which would suggest a risk for hepatocellular carcinoma or cholangiocarcinoma. Because many of these examinations often are

part of the routine evaluation of any new patient, only rarely would they be overlooked.

Tumor markers, especially the more recently described markers, and their potential role in the evaluation and management of patients with CUP have been reviewed.[48] As part of the routine evaluation of patients with CUP, five markers deserve special recognition. The beta subunit of human chorionic gonadotropin (β-hCG) has been classically associated with nonseminomatous germ cell tumors, and is useful both for diagnosis and during follow-up, often confirming the adequacy of therapy.[49] Alpha-fetoprotein (AFP) also is useful for the evaluation of nonseminomatous germ cell tumors as well as hepatocellular carcinoma.[49] Although many previous publications suggested that the presence of elevated β-hCG or AFP identified patients with marked chemotherapy responsiveness and good survival (see following section on Poorly Differentiated and Undifferentiated Carcinoma), in one study the presence of abnormal plasma levels of AFP or β-hCG did not identify patients with better overall survival.[50] In fact, for the subset of patients diagnosed with poorly differentiated carcinoma or poorly differentiated adenocarcinoma for whom both markers were available, those with AFP levels below 2.8 ng/mL or β-hCG levels below 3.4 mIU/mL survived longer. Thus, reliance on the use of these tumor markers to identify treatment-responsive patients with CUP does not appear to be justified.

Measurement of prostate-specific antigen (PSA) is very useful in men with adenocarcinoma and predominantly skeletal metastases. Elevation of PSA can provide a confirmation of metastatic prostate cancer, but the physician should be wary of the occasional coexistence of early prostate cancer with a more aggressive synchronous neoplasm. Serum measurements of PSA commonly should be coupled with immunohistochemical staining for PSA in tumor tissue, because rare patients have been reported with metastatic cancer and clinical features atypical for metastatic prostate cancer.[51,52]

The extensively used tumor marker carcinoembryonic antigen (CEA) also has been suggested as having a role in the evaluation of patients with CUP. The diagnostic utility of CEA was analyzed in a group of 32 patients initially diagnosed with CUP with the adenocarcinoma histologic type.[53] In this study 10 patients had a CEA of greater than 10 ng/mL, and of these patients the anatomic site of primary tumor was established as lung (5 patients), pancreas (2 patients), ovary (2 patients), and bile duct (1 patient). However, although the CEA appeared to be useful in this study, in our analysis of 147 patients with CUP who had a panel of tumor markers analyzed, 41 had a value over 10 ng/mL, and this finding did not appear to have a significant impact on the probability of establishing a primary tumor site (Abbruzzese and associates, unpublished data).

Another marker, which often is ordered during the evaluation and management of patients with CUP, is CA125. This marker initially was derived from a human ovarian carcinoma cell line, and its elevation in women with CUP is frequently suggested as a marker for chemotherapy sensitivity to agents that are used in the management of ovarian cancer. However, preliminary studies failed to validate this hypothesis, suggesting that the clinical presentation and histology were more predictive.[54] The exact role of other tumor markers such as CA19-9 and CA15-3 remains unclear, but they appear to be limited in their ability to establish a specific primary site or identify patients who respond to chemotherapy.

Pathologic Evaluation

General Considerations

An accurate pathologic assessment of biopsy material is essential in the initial evaluation of the patient with suspected CUP. In this context the pathologist usually is able to confirm that the lesion is neoplastic and often is able to judge whether the lesion is primary or metastatic.[2] However, in some situations it may be impossible to determine if the tumor has arisen from the biopsied organ site. This problem often complicates the cytologic evaluation of fine-needle aspirate specimens and emphasizes the need for close communication between the clinician and pathologist. Frequently, exchange of available clinical information may lead to additional tissue procurement for analysis using one or more of the more detailed diagnostic studies that follow. The pathologist typically puts the tissue specimen through one to four different steps, depending on what is needed. These studies include light microscopy, immunohistochemical stains, electron microscopy, and chromosomal studies, including cytogenetics.

Light Microscopy

The initial pathologic assessment of the biopsy specimen is by light microscopic examination of paraffin sections stained with hematoxylin and eosin. Based on established cytologic criteria, the pathologist usually can classify the tumor into broad groups such as carcinoma, sarcoma, or lymphoma.[55] Additionally, many carcinomas will be immediately recognized as manifesting at least some glandular differentiation (adenocarcinoma). When glandular differentiation is absent, patients with CUP often are diagnosed with poorly differentiated carcinoma or undifferentiated carcinoma. Other specimens will lack any cytologic distinguishing features, in which case a diagnosis of an undifferentiated malignancy is reported. In those groups with poorly differentiated carcinoma, undifferentiated carcinoma, or undifferentiated malignancy, additional pathologic studies, including histochemistry, immunohistochemistry, and electron microscopy, are most frequently and productively employed.[56] On light microscopy about 60% of the cases are reported as adenocarcinoma and 5% as squamous carcinoma; in 35% of cases light microscopy is not very helpful, and poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or poorly differentiated neoplasm is then reported.

Immunohistochemistry

Immunohistochemical markers play a significant role in the diagnosis and workup of CUP. They help define tumor lineage by using peroxidase-labeled antibody against specific tumor antigens. Direct discussions between the pathologist and clinician are critical to ensure the most accurate pathologic characterization possible. Random use of large numbers of tissue markers is rarely helpful for establishing a diagnosis or planning therapy. The role of antibodies against AFP, β-hCG, PSA, and some other markers is well established (Table 98-5). More recently, cytokeratins and thyroid transcription factor (TTF-1) are gaining more importance as markers for the identification of the origin of the carcinoma.[57–62]

Cytokeratin 20 (CK20) is a low-molecular-weight cytokeratin, which is expressed in the normal glands as well as the tumors of the GI epithelium, urothelium, and Merkel cell.[57–59] Cytokeratin 7 (CK7) is found in tumors of the lung, ovary, endometrium, and breast but not in the GI tract. TTF-1 is a 38-kd homeodomain-containing nuclear protein that plays a role in transcriptional activation during embryogenesis in the thyroid, diencephalon, and respiratory epithelium.[57–59] TTF-1 staining is typically positive for lung and thyroid cancers. In 2002, Roh and associates[57] described the utility of TTF-1 and CK20 in identifying the origin of metastatic carcinomas of cervical lymph nodes. They stained 68 specimens with TTF-1 and CK20. The primary sites were lung (29 cases), stomach (13 cases), colorectum (3 cases), and other sites (23 cases). TTF-1 expression was detected in 69% of metastatic lung carcinomas and in none of the GI carcinomas. CK20 expression was detected in 68.8% of GI tumors and in none of the metastatic lung carcinomas. Jang and associates[58] looked at the utility of these markers in identifying the origin of malignant effusions. The primary sites of the tumors examined were lung (16 cases), ovary (15 cases), stomach (9 cases), colon (8 cases), and breast (8 cases). The lung adenocarcinomas showed TTF-1 positivity in 81% of the cases (13 of 16), but all of the nonpulmonary adenocarcinomas lacked TTF-1 staining. The CK7-/CK20+ immunophenotype was seen in 63% of colonic adenocarcinomas and in none of the lung, breast, or ovary tumors. The CK7+/

Table 98-5 Tumors Markers Useful in the Diagnosis of Carcinoma of Unknown Primary

Histologic Diagnosis Application	Tissue Marker	Diagnostic
Poorly differentiated carcinoma or undifferentiated carcinoma	1. Leukocyte common antigen (LCA)	Lymphoma
	2. Ki 1 (CD30)	Ki 1 lymphoma
	3. Human chorionic gonadotropin (β-hCG)	Germ cell neoplasm
	4. Alpha-fetoprotein (AFP)	Germ cell neoplasm
	5. Chromogranin	Neuroendocrine carcinoma
	6. S-100	Melanoma
	7. HMB-45	Melanoma
Adnocarcinoma	1. Estrogen receptor (ER)	Breast cancer
	2. Progesterone receptor (PR)	Breast cancer
	3. Prostate-specific antigen (PSA)	Prostate cancer
	4. Alpha-fetoprotein (AFP)	Hepatoma
	5. Thyroglobulin	Thyroid cancer

CK20- staining was seen in 100% of lung, 88% of breast, and 87% of cancers that originated from the ovary. They concluded that TTF-1 immunostaining was useful in differentiating between pulmonary and nonpulmonary origin of adenocarcinoma in malignant effusions. The combination of CK7-/CK20+ staining is useful in identifying colon adenocarcinoma. In 2000, Rubin and associates[59] looked at the role of CK7 and CK20 in determining the origin of metastatic carcinoma of unknown primary site. The nuclear CDX-2 transcription factor, which is the product of a homeobox gene necessary for intestinal organogenesis, is expressed in normal colonic epithelia and most colorectal adenocarcinomas, and often used to aid with the diagnosis of GI adenocarcinomas.[60] Some data suggest the role of cytokeratin 5/6 as a marker for squamous cell carcinoma in poorly differentiated tumors if mesothelioma is ruled out.[61–63] Based on Rubin's data[59] and other studies with these recent markers, we describe a simple algorithm (Fig. 98-5) for providing clinicians some guidance on using these immunohistochemical markers to identify the site of origin.

Electron Microscopy

Electron microscopy offers the option of looking at the ultrastructural features of a given cell. Patients with adenocarcinoma will typically show microvilli and mucin, neuroendocrine tumors may show secretory granules, and a melanoma will usually show premelanosomes. Electron microscopy is used infrequently today because of the improvement in immunohistochemical markers. Also, it requires pathologists who are experienced in the technique; it can be time-consuming and rarely offers information that changes the overall management. It may, however, be useful in some cases of poorly differentiated neoplasm.

Chromosomal Studies

Chromosomal aberrations in CUP and the significance of isochromosome (12p) have been discussed earlier (see Biologic Characteristics).

Radiographic Studies

Chest Radiographs and Plain Films

Given the large numbers of patients with CUP who eventually will be diagnosed with lung cancer, the chest x-ray should be part of the routine evaluation of these patients irrespective of whether there are respiratory symptoms. However, in this setting, Nystrom and associates[3] have pointed out that the chest x-ray must be interpreted with caution. Their study demonstrated that the chest x-ray often could not distinguish primary lung cancer from metastatic disease to the lungs conclusively. This problem is further complicated by the fact that some malignancies (notably breast, renal, and colorectal cancers) can metastasize to endobronchial sites and thus mimic primary bronchogenic carcinoma. In this situation a bronchoscopic biopsy with detailed histologic or cytologic analysis of the neoplastic tissue sometimes helps to clarify the situation.

Other routine radiographic films usually are reserved for evaluation of symptomatic sites, such as painful bone lesions. These films also must be interpreted with caution, because the degree of bony destruction needed to visualize an abnormality initially may not be present.[64] Radionuclide bone scan often resolves this issue.

Contrast Radiographic Studies

Contrast radiographic studies (e.g., upper GI series, barium enema, intravenous pyelogram) have a low diagnostic yield and generally should be reserved for patients with symptoms or signs referable to the organ system in question. Two studies have looked at the diagnostic accuracy of these examinations.[3,65] In over 200 examinations, only 7.4%, 11%, and 8% of upper GI series, barium enemas, or intravenous pyelograms, respectively, were positive. In addition, biopsy confirmation of the abnormalities identified radiographically was made in only half of the cases. Thus the false-positive rates from these studies were significant and could easily lead to inappropriate management based on faulty information.

Radionuclide Imaging

With the advent of CT, radionuclide imaging of the liver is performed very infrequently in the evaluation of patients with CUP. Bone scanning remains a useful diagnostic adjunct to stage patients with CUP (especially those complaining of bone pain) but is unlikely to provide information as to the site of the primary lesion. Using this modality in conjunction with routine x-rays, sites of significant destruction in major weight-bearing bones can be anticipated before devastating pathologic fractures develop. Radionuclide thyroid scanning often is performed for the evaluation of patients who present with papillary adenocarcinomas in cervical nodes, but it rarely is positive.[66] Thus, at this time radionuclide imaging cannot be recommended as a routine diagnostic study in patients with CUP. It can, however, be helpful with assessment of disease extent.

Mammography

Bilateral mammography should be a part of the routine evaluation of all women with CUP.[2] Despite the relatively low numbers of occult breast cancer accounting for CUP (4% to 8%), at least one study documented a 7.5% rate of positive examinations.[67] Even with

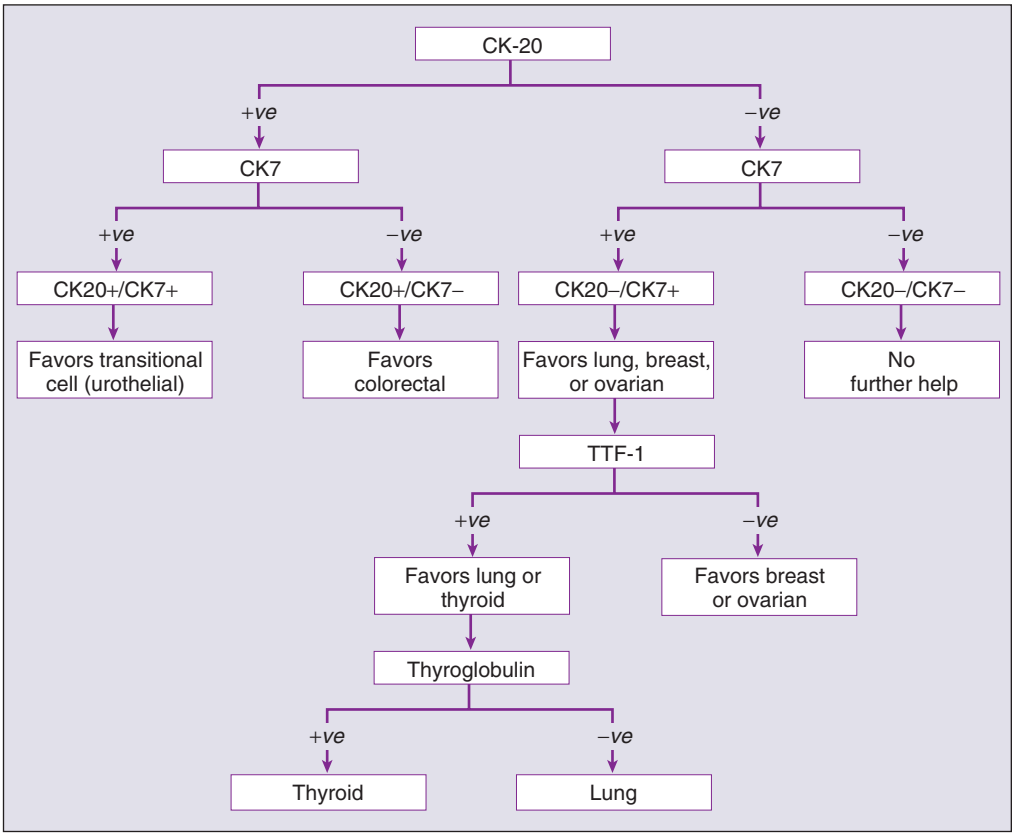


Figure 98-5 • Preliminary cytokeratin algorithm.

the apparent low yield from this evaluation, the good response of breast cancer to local and systemic therapy justifies the procedure in this patient population.

Computed Tomography

The role of CT of the chest in the evaluation of patients with CUP currently is unclear. Although chest CT can accurately document mediastinal adenopathy,[68] it often overestimates the amount of metastatic parenchymal pulmonary involvement. The additional lesions visualized by chest CT (as compared to chest x-ray and whole-lung tomography) in many cases are not malignant.[69,70] Until more evidence is available, routine use of the chest CT cannot be recommended. However, this study should be obtained to follow up an abnormal but nondiagnostic chest x-ray or positive sputum cytologic test.

The role for CT of the abdomen is much better defined and appears particularly useful in the detection of occult pancreatic primaries. Two relatively recent studies have addressed this issue. In one study, CT of the abdomen detected the primary site in 16 of 46 patients.[71] The primary sites documented included pancreas (6 patients), ovary (2 patients), hepatoma (2 patients), kidney (2 patients), lung (1 patient), adrenal gland (1 patient), gallbladder (1 patient), and stomach (1 patient). The second series, from the Mayo Clinic, identified the primary site in one third (31 of 98) of patients with clinically occult tumor.[71] In addition, this study pointed out that tissue confirmation could be obtained from the suspected primary site through the use of CT-directed needle aspiration biopsies. Thus, although it appears that CT of the abdomen should be considered a standard procedure in the evaluation of patients with CUP, the primary cancers identified often are difficult to treat, causing at least one group to question the cost-to-benefit relationship in this patient population.[2]

In the pelvis a combination of CT and pelvic ultrasound may be justified. In one prospective study of 24 women with pelvic masses palpable by gynecologic examination, additional clinical information was provided by ultrasound in 71% and by CT scan in 63% of these patients.[72] However, in three patients both modalities failed to detect tumor recurrence. More problematic, however, is the usefulness of pelvic ultrasound or pelvic CT for patients without palpable abnormalities by gynecologic examination. There is no prospective study analyzing these diagnostic examinations in this group of patients. The most efficient evaluation includes pelvic CT, which is performed with CT of the abdomen.[2]

Magnetic Resonance Imaging

Enthusiasm for magnetic resonance imaging (MRI) is high. As the technical capabilities of this diagnostic modality evolve it may be increasingly indicated in the diagnosis and management of patients with CUP. Currently, however, few prospective or retrospective studies are available to suggest a broad role for MRI in evaluating CUP. One application that appears promising is in the evaluation of female patients with isolated axillary lymph node metastases and suspected occult primary breast carcinoma. In a recently reported series of 12 female patients presenting with isolated axillary lymphadenopathy pathologically confirmed to contain metastatic adenocarcinoma, 9 had a primary malignancy localized to the breast identified by MRI.[73] Thus, at this time MRI should be limited to clinical situations in which it appears that the additional information to be gained will significantly alter the therapeutic approach recommended to an individual patient.

Positron Emission Tomographic Imaging

Positron emission tomography with ^{18}fluoro-2-deoxy-D-glucose (^{18}F-FDG-PET) is a noninvasive nuclear imaging technique that has been proved to be a valuable diagnostic tool in identifying primary malignant tumors, assessing the extent of metastatic disease, and localizing carcinoma of unknown primary origin. Several studies have been conducted to determine the value of FDG-PET imaging in detecting

Table 98-6 Positron Emission Tomography Scan Results in Patients with Cervical Lymphadenopathy from Squamous Carcinoma of Unknown Primary

First Author (year)	No. of Patients	Primary Tumor Suggested on PET (%)
Kole (1998)[74]	29	24
Lassen (1999)[75]	20	65
Bohuslavizki (1999)*	28	57
Stokkel (1999)†	10	50
Jungehulsing (2000)[76]	27	26
Johansen (2002)[77]	42	48
Stoeckli (2003)‡	18	28

PET, positron emission tomography.

*Bohuslavizki KH, et al: F-18-FDG-PET zur Detektion des okkulten Primartumors bei Patienten mit Lymphknotenmetastasen der Halsregion. Laryngo-Rhino-Otologie 1999;78:445–449.

†Stokkel MP, et al: 18F-fluorodeoxyglucose dual-head positron emission tomography as a procedure for detecting simultaneous primary tumors in cases of head and neck cancer. Cancer 1999;86:2370–2377.

‡Stoeckli SJ, Mosna-Firlejczyk K, Goerres GW: Lymph node metastasis of squamous-cell carcinoma from an unknown primary: impact of position emission tomography. Eur J Nucl Med Mol Imaging 2003;30:411–416.

occult primary tumors after unsuccessful conventional diagnostic evaluation in patients with metastatic disease from a carcinoma of unknown primary. Most of the studies consist of a small number of evaluable patients[74–77] and focus primarily on patients with cervical lymphadenopathy (mostly squamous cell pathology; Table 98-6). In 1998, Kole and associates[74] evaluated the role of FDG-PET imaging in 29 patients with various histologic types of metastasis from CUP after unsuccessful conventional diagnostic workup. FDG-PET imaging identified the primary tumor in 7 patients (24%), but survival was not altered by discovery of the primary tumor. In 1999, Lassen and associates prospectively studied 20 patients who underwent a FDG-PET scan after standard evaluation, and the FDG-PET results were verified either histologically or by the clinical course of the disease.[75] All the metastatic lesions were visible with FDG-PET. In 13 patients, FDG-PET suggested the site for primary tumor, and this site was verified in 9 patients (45%) either histologically or by the clinical course of the disease. Eight of these patients had primary lung cancer and one had carcinoma of the base of the tongue. In most patients, FDG-PET had no treatment-related implications. In 2000, Jungehulsing and associates[76] evaluated the use of FDG-PET imaging in 27 patients with head and neck lymphadenopathy and presumed CUP after unsuccessful conventional diagnostic evaluation failed to reveal the primary tumor. FDG-PET imaging revealed a primary tumor in 7 patients (24%). In 2002 Johansen and associates[77] evaluated 42 patients with squamous cell or undifferentiated metastatic disease from a CUP. Potential focal pathologic uptake indicated a primary tumor in 20 of 42 cases (48%). After FDG-PET imaging, additional investigations confirmed the primary tumor in 10 patients (24%). Rusthoven and colleagues reviewed 16 FDG-PET studies published between 1994 and 2003 involving 302 patients with cervical metastases from unknown primary tumors. Conventional workup included either panendoscopy or CT/MRI, and in 10 of these 16 studies, both of the diagnostic techniques were performed before diagnosis. They reported the overall sensitivity, specificity, and accuracy rates of FDG-PET in detecting unknown primary tumors were 88.3%, 74.9%, and 78.8%, respectively. FDG-PET detected approximately 25% of tumors that were not apparent after conventional workup and was sensitive in the detection of previously undetected regional or distant metastases in 27% of patients. FDG-PET had a low specificity for tonsils, with a false-positive rate of 39% in the tonsils. False-positive rates were 21% for the base of the tongue, and only 8% for the hypopharynx. Sensitivity for the base of the tongue was 81.5%, and for other sites was 90.5%.[78]

Ambrosini and colleagues[79] report a 53% primary cancer detection rate in a small study of 38 patients with CUP. In a review of 10 FDG-PET studies (involving a total of 221 patients) published between 1998 and 2006, Seve and colleagues found that 94% of patients had a single site of metastasis. In 41% of patients, FDG-PET detected primary tumors that were not apparent after conventional workup. In this group of patients, the overall sensitivity, specificity, and accuracy rates of FDG-PET in detecting unknown primary tumors were 91.9%, 81.9%, and 80.5%, respectively. FDG-PET imaging also led to the detection of previously unrecognized metastases in 37% of patients. Lung cancers represented 59% of the detected tumors. FDG-PET had a notably high false-positive rate (58.3%) in tumors of the lower digestive tract, and altered the clinical management in 34.7% of patients. A large number of patients in these studies had a single site of metastasis, which may have influenced the study results.[80] Outside of cervical adenopathy with squamous cell cancer, the role of PET scans, especially PET-CT, is evolving, although given that these studies have been small, it is difficult to make firm recommendations. Larger studies to evaluate the utility and cost-effectiveness of PET in the CUP setting (other than cervical) may be useful.

Molecular Markers by Gene Expression

Although few individual markers can identify a tumor's site of origin with a high degree of confidence (PSA and mammoglobin are possible exceptions), metastatic tumors do appear to have distinguishable patterns of gene expression when a large number of markers are examined with tools such as DNA microarrays or RT-PCR assay.

Ramaswamy and associates[9] subjected 218 tumor tissues spanning 14 common tumor types (representing ~80% of the new cancer diagnoses in the United States) and 90 normal tissue samples to oligonucleotide microarray gene expression analysis. They used the relative levels of expression of 16,063 genes and expressed sequence tags to evolve a predictive support vector machine (SVM) algorithm. The algorithm then was tested on an independent group of 54 tumors, yielding an overall prediction accuracy of 78%. Although greatest accuracy required the use of all 16,063 genes, accuracy was still above 70% with fewer than 50 genes. Of the 54 independent tumors tested, 8 were metastatic tumors, of which 6 were accurately identified, suggesting that the cancers retain the markers of their tissue of origin throughout metastatic evolution, and that gene expression-based approaches to the diagnosis of CUP may be feasible. Most of the tumor types that could not be classified accurately were moderately or poorly differentiated (high-grade) carcinomas. It can be difficult to classify such tumors with traditional methods, because they often lack the characteristic morphologic hallmarks of the organ from which they arise. It has been assumed that these tumors are, nonetheless, fundamentally molecularly similar to their better-differentiated counterparts, apart from a few differences that might account for their clinically aggressive nature. However, Ramaswamy and associates[9] suggest that poorly differentiated tumors may not simply lack a few key markers of differentiation, but rather may have fundamentally distinct gene expression patterns, with a significant implication for the management of patients with these cancers.

Su and associates[81] used a set of 100 primary carcinomas from 10 common tumor types (prostate, breast, lung, ovary, colorectum, kidney, liver, pancreas, bladder/ureter, and gastroesophagus), which collectively account for 70% of all cancer-related deaths in the United States. They extracted mRNA from the tumors, and then used an Affymetrix (Affymetrix, Inc.) oligonucleotide microarray to identify genes that were differentially expressed. A predictive algorithm was developed using 110 genes of the 9198 genes that were minimally expressed in these tumors. The algorithm was then tested against an

additional 75 blinded samples and accurately predicted the tumor of origin in over 90% of the cases.

Dennis and associates[82] used a different approach to identify predictive markers, starting with published data on differential gene expression by tumor type. They identified 61 candidate tumor markers whose expression pattern was predicted to be characteristic of the site of origin and tested 11 of them against adenocarcinoma samples (breast, ovary, stomach, pancreas, lung). The actual expression patterns were consistent with those predicted in seven cases (64%), with three agreeing exactly. By extending this approach, it may be possible to identify a smaller subset (10 to 20 genes) of highly predictive markers that could be applicable to more commonly used laboratory techniques such as immunohistochemistry.

The foregoing work holds out the promise that in a large proportion of CUP, the site of origin can be identified using arrays of molecular markers, although with one caveat. The underlying assumption is that CUP is no different from other metastatic lesions, and that CUP lesions retain the molecular markers associated with their tissue of origin identity, an assumption that still must be tested.

CLINICAL MANIFESTATIONS AND MANAGEMENT

The clinical presentations of CUP are extremely varied. Historically, patients commonly have been characterized as to whether they have disease above or below the diaphragm.[83] However, given the heterogeneity and widespread metastases that characterize this disease, this arbitrary division is of doubtful value. Other investigators have used other approaches effectively to subclassify patients based largely on clinicopathologic criteria of histologic type, involved organ sites, and responsiveness to therapy (Box 98-1). This approach has led to the definition of clinically defined patient subsets, which will be discussed later in this chapter. Despite these efforts at subclassification, most patients present with solitary or multiple areas of involvement in a variety of visceral sites. Thus, in most cases, the presenting symptoms and physical signs simply reflect the neoplastic involvement of these organ sites. The most common organ sites encountered are listed in Table 98-7, with lung, bone, lymph nodes, and liver the most frequently encountered. Table 98-7 also shows the histologic spectrum of disease associated with each site, as well as the other frequently involved metastatic sites encountered. Of the sites listed, only isolated involvement of lymph nodes was associated with significantly superior survival relative to the CUP population as a whole.[84]

The treatment of CUP continues to evolve. Although most patients are treated with systemic chemotherapy, the careful integration of surgery, radiation therapy, and even periods of observation is important in the overall management of these patients.[85–87] Observation is particularly important for patients with single sites of disease who have received adequate local therapy.

The most common problem is treatment of the patient with progressive metastatic adenocarcinoma involving two or more organ sites. Treatment of these patients remains suboptimal and probably awaits discovery of novel strategies applicable to other highly resistant adenocarcinomas, such as those originating in the lung or GI tract. This situation is contrasted with the management of the favorable subsets described in the following section. These favorable patients have been grouped together primarily on the basis of their responsiveness to therapy. The numbers of patients who fall into these favorable groups are small, but they are important to recognize because specific treatment may significantly extend survival.

Box 98-1. M.D. ANDERSON APPROACH TO THE PATIENT WITH NEWLY DIAGNOSED CARCINOMA OF UNKNOWN PRIMARY SITE

Patients with physical or radiographic evidence of metastatic cancer should undergo biopsy early in their evaluation. This approach confirms the diagnosis and provides histologic or cytologic information that will help in the planning of additional evaluation and treatment.

The essential diagnostic evaluation includes history, physical examination, CB count, SMA-12, PSA in men, chest radiography, CT of abdomen and pelvis, and mammography in women. Further investigations are performed only on the basis of positive findings from these screening studies. Patients are then readily classified and treated as outlined here.

Important Treatable Subsets (Minority of Patients) and Their Management

Clinic Subset	Management
Women with adenopathy (adenocarcinoma and carcinoma)	Same as for stage II breast cancer
Women with peritoneal carcinomatosis (papillary adenocarcinoma)	Same as for stage III ovarian cancer
Poorly differentiated and undifferentiated carcinoma (controversial subset)	Platin-based combination chemotherapy (carboplatin/paclitaxel ± etoposide or cisplatin/etoposide)
Extragonadal germ cell syndrome	Same as for nonseminomatous germ cell tumor
Neuroendocrine carcinoma	Same as for carcinoid/ pancreatic islet cell carcinoma; cisplatin-based chemotherapy for poorly differentiated neuroendocrine tumors
High- and mid-cervical adenopathy (squamous cell carcinoma)	Surgical resection of palpable disease + curative radiation therapy to the neck

Favorable Clinical Subsets

Squamous Carcinoma Involving Mid-High Cervical Lymph Nodes

High cervical adenopathy with squamous cell carcinoma has been mentioned previously because of its well-defined natural history, high frequency of identification of the primary site, and responsiveness to therapy.[10–12] With appropriate evaluation, including direct visualization of the hypopharaynx, nasopharynx, larynx, and upper esophagus, an occult primary lesion often will be identified. When no primary site is found, aggressive local therapy is applied to the involved neck.[12,87] Five-year survival rates of 30% to 50% have been reported with radical neck surgery, high-dose radiotherapy, or a combination of both modalities. A potential advantage of radiation therapy is that the suspected primary anatomic sites (nasopharynx, oropharynx, and hypopharynx) can be included in the radiation port.[86] The role of chemotherapy in these patients is unclear. However, one randomized study suggested that chemotherapy with cisplatin and 5-fluorouracil improved the response rate and median survival when compared with radiation alone.[88]

Adenocarcinoma involving mid-high cervical nodes and lower cervical or supraclavicular adenopathy of all histologic types carry a much poorer prognosis.[89] These patients are managed with local measures (usually radiation therapy), or they may be candidates for systemic chemotherapy protocols.

Women with Isolated Axillary Adenopathy

Isolated axillary adenopathy secondary to metastatic adenocarcinoma usually occurs in women and has unique clinical features. Many of these women have occult primary breast cancers, which can be identified in 40% to 70% of these patients who undergo mastectomy.[90,91]

Table 98-7 Clinical Characteristics of Common Subsets of Carcinoma of Unknown Primary Sites

Involved Site (No. Patients)	No. Patients with One Site Only	No. Patients with Multiple Sites	Histologic Type (Site Only/Site + Other)				
			Adenocarcinoma	Carcinoma	Squamous	Neuroendocrine	Other
Bone (318)	73	245	45/139	21/80	2/13	2/10	3/3
Lung (296)	21	275	13/175	5/72	0/13	0/10	1/5
Lymph nodes (479)	138	341	56/202	55/96	25/26	2/12	0/5
Liver (365)	139	226	93/129	24/72	2/6	18/15	2/4
Pleura (122)	31	91	25/71	6/17	0/0	0/0	0/3
Brain (79)	18	61	9/35	5/12	0/9	0/1	4/4
Skin (38)	9	29	2/15	6/7	0/4	1/3	0/0

Metastatic Involved Site	Additional Involved Sites							Median Survival (mos)	
	Bone	Lung	Liver	Pleura	Skin	Nodes	Brain	Site Only	Site + Other
Bone	—	96	84	29	14	97	24	9	8
Lung	96	—	81	41	11	139	33	20	8
Lymph nodes	97	139	105	37	17	—	32	29	12
Liver	84	81	—	13	3	105	9	9	7
Pleura	29	41	13	—	0	37	3	9	8
Brain	24	33	9	3	2	32	—	16	8
Skin	14	11	3	0	—	17	2	*	8

*Median not yet reached.

In this setting, repeat biopsy of involved axillary nodes for estrogen and progesterone levels should be considered in view of the influence of this information on diagnosis and management. Management is based on the treatment of stage II breast cancer and should include both local and systemic therapies. Prognosis following treatment is comparable to women with stage II breast cancer. Older series have advocated modified radical mastectomy and axillary dissection for primary treatment.[90–92] However, a reported series of 42 patients suggested that survival was superior in patients receiving systemic chemotherapy, and local control was improved by irradiating the breast and axilla.[67] The actuarial disease-free survival rate in this study was 71% at 5 years and 65% at 10 years. This nonoperative approach has been outlined in a study by Lenzi and colleagues.[93]

Patients with axillary adenopathy and involvement of additional sites (usually liver or bone) or with nonadenocarcinoma histologic type compose a much more heterogeneous group, including equal numbers of men and women as well as a broader histologic spectrum, with poorly differentiated carcinoma and neuroendocrine carcinomas represented in addition to adenocarcinoma.[94] Despite this heterogeneity, the survival of patients with axillary adenopathy and other involved organ sites is intermediate between that of the overall population of CUP and women with isolated axillary adenopathy (Fig. 98-6).

The management of patients with involvement of the axilla as well as other sites or nonadenocarcinoma histology is less certain. These patients usually are approached using a combination of local and systemic modalities and may again be good candidates for novel systemic chemotherapy protocols.

Women with Peritoneal Carcinomatosis

Women with diffuse peritoneal carcinomatosis with adenocarcinoma make up another recognized subset. These patients form a distinctive subset because of their clinical similarities to patients with ovarian carcinoma. Often papillary histologic type and elevations in CA125 are found, but exploratory laparotomy fails to document a primary.[95,96] Other workers also have recognized this patient subset, terming this syndrome *peritoneal papillary serous carcinoma* or *multifocal extraovarian serous carcinoma*. These patients often respond to platinum-based chemotherapy.[96–98] Many patients in these series also underwent exploratory laparotomy with surgical debulking followed by chemotherapy. Median survival times are reported to be 16 months to 2 years.

The natural histories of males with isolated peritoneal carcinomatosis or patients with histologic features inconsistent with ovarian carcinoma or additional metastatic sites are much more poorly characterized, but overall survival, even with therapy, is poor.[99]

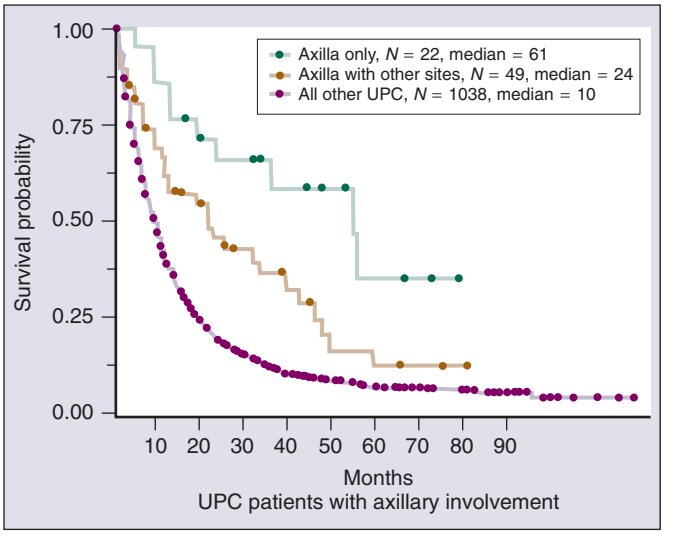


Figure 98-6 • Comparison of survival of patients with CUP in three groups: those with isolated axillary adenopathy; those with axillary adenopathy with other metastatic sites; and those without axillary nodal involvement.

Poorly Differentiated and Undifferentiated Carcinoma

Approximately one third of patients with CUP will be defined as having the histologic picture of poorly differentiated or undifferentiated carcinoma. In this subset, detailed histochemical or immunohistochemical studies are most likely to identify highly treatment-responsive patients with lymphoma (leukocyte common antigen), germ cell (β-hCG, AFP), or neuroendocrine (neuron-specific enolase, chromogranin) neoplasms (see Table 98-7). Additionally, Greco and Hainsworth[1] have identified a group of patients with PDC or PDA that are responsive to platinum-based chemotherapy. Most of these patients had clinical features (e.g., young age, mediastinal/retroperitoneal involvement, and rapid growth) of the extragonadal germ cell syndrome.[100] Many of these patients are male and have elevated β-hCG or AFP. Motzer and coworkers[31] identified abnormalities in chromosome 12 specific for germ cell neoplasms in a group of male patients with PDC involving midline structures, confirming the germ cell origin of these tumors.

Combination chemotherapy regimens specific for germ cell carcinoma of testicular origin usually have been employed in the treatment of these patients.[15,49,100–102] In selected patients, these regimens have produced documented complete responses and an actual 10-year disease-free survival rate of 16%.[13]

Despite these favorable results, one analysis of this "favorable" subset failed to confirm that patients with CUP who had PDC or PDA enjoyed prolonged survival.[50] The exact reasons for the failure of this newer study to confirm the earlier studies is unknown. However, insight into this question can be achieved by analyzing the patients reported in this analysis. From the population of 1400 patients referred with suspected CUP a primary tumor[2] was established in 365 patients. The primary tumors most commonly diagnosed included 70 patients considered to have highly treatable tumors: 28 patients with breast cancer, 20 patients with lymphoma, 11 patients with ovarian cancer, 6 patients with germ cell tumors, and 5 patients with other hematologic malignancies. This study also clearly showed that the survival of patients with CUP squamous or neuroendocrine features have survival times superior to those for patients with PDC or PDA. Thus, the PDC and PDA populations analyzed in this study reflect the biology of these patients' malignancies after patients with slower-growing tumors (e.g., neuroendocrine cancers) or chemotherapy-responsive tumors (e.g., lymphomas, other hematologic malignancies, germ cell tumors, breast cancer, ovarian cancer) had been excluded.

Increasingly frequent use of special pathologic studies, including immunohistochemistry, is likely to be responsible for the ease with which patients with lymphoma, neuroendocrine, germ cell, and other malignancies can be excluded from the PDC or PDA groups. Many of these patients often were included in earlier series of PDC and PDA patients, which may well have confounded data on chemotherapy responsiveness and survival.

Poorly Differentiated Neuroendocrine Carcinoma

Poorly differentiated neuroendocrine carcinoma is an emerging clinicopathologic entity recognized primarily for its responsiveness to therapy. There probably is considerable overlap with extrapulmonary small cell carcinomas, anaplastic carcinoid, anaplastic islet cell tumors, Merkel cell tumors, and paragangliomas. Histologically these tumors are very poorly differentiated, but histochemical stains are positive for chromogranin or neuron-specific enolase. These patients often present with diffuse hepatic or bone metastases but do not have the indolent histologic or clinical features of typical carcinoid tumors, islet cell tumors, or paragangliomas, and thus observation may not be appropriate. These tumors also often are responsive to cisplatin-based chemotherapy.[103,104]

Carcinoma of Unknown Primary in Unselected Patients

The good results for the patients with a favorable prognosis described earlier do not apply to the vast majority of patients with CUP. Two thirds of patients with CUP have metastatic adenocarcinoma with involvement of two or more visceral sites, usually some combination of liver, lung, lymph nodes, or bone. In addition, many men and women with poorly differentiated carcinoma have none of the clinical features outlined previously and respond poorly to therapy.[49] Even in series showing optimistic results for selected patients with poorly differentiated carcinoma or poorly differentiated adenocarcinoma, the overall median survival time remains poor, at 12 months.[13]

For unselected patients numerous empiric chemotherapy combinations have been reported[105–122] (Table 98-8). Many have been based on doxorubicin (Adriamycin), 5-fluorouracil, or cisplatin. Little information is available on the use of biologic agents, either alone or with chemotherapy. Response rates generally range from 20% to 30%, but most responses are partial and brief, resulting in little or no impact on median survival. The recent availability of new antineoplastic agents with broad-spectrum activity and potential efficacy in the treatment of CUP has renewed interest in empiric chemotherapy for these patients. The taxanes, gemcitabine, and the topoisomerase I inhibitors represent such agents with potential efficacy in the treatment of CUP.

Taxane-based regimens evaluated in phase II clinical trials have included the following combinations: (1) paclitaxel/carboplatin/etoposide; (2) paclitaxel/carboplatin; (3) docetaxel/platinum; and (4) paclitaxel/carboplatin/gemcitabine.[121–123] Overall response rates with taxane-based regimens have ranged between 24% and 47%. Longer median survival times also have been observed with taxane-based regimens, ranging from 9 to 11 months, as compared to a range of 5 to 8 months using older GI and breast cancer chemotherapy regimens. One report using carboplatin, paclitaxel, and etoposide reported that 25 of 53 patients (47%) had objective responses.[124] In this series seven patients (13%) experienced complete responses. However, the actuarial median survival time for the entire group was 13.4 months. The disappointing aspect of this survival statistic is that it is not substantially different from the 11-month median survival time reported in large consecutive series of patients with CUP.[77,125]

Gemcitabine is a pyrimidine analog antimetabolite with single-agent activity in several solid tumors, and also has been found to be useful as secondary therapy for some patients with CUP. Hainsworth and associates[126] conducted a phase II trial evaluating single-agent gemcitabine in the second-line therapy of patients with CUP. Thirty-five patients (90%) previously had received treatment with chemotherapy containing both a platinum agent and a taxane. This study showed an 8% partial response rate (3 of 36 evaluable patients), and 25% (9 patients) had minor responses or stable disease with reduced symptoms. The median time to progression was 5 months. These results show that as a second-line treatment for CUP, gemcitabine has a relatively low level of clinical activity in a refractory patient population, although a portion of patients experienced symptomatic improvement.

Because of the previously demonstrated activity of gemcitabine against a variety of advanced adenocarcinomas, gemcitabine was evaluated with combination chemotherapy as a front-line agent. Greco and associates[127] evaluated the efficacy and toxicity of gemcitabine, carboplatin, and paclitaxel in previously untreated patients with CUP. Twenty-eight (25%) of 113 assessable patients had a major objective response. The median progression-free survival time was 6 months, with a median survival time for the entire group of 9 months. Actuarial survival at 1 and 2 years was 42% and 23%, respectively. This study showed that combination chemotherapy with gemcitabine, carboplatin, and paclitaxel followed by weekly paclitaxel was well tolerated. However, the survival seen in this poor-prognosis group of patients is notable, and is similar to that seen in other

Table 98-8 Chemotherapeutic Trials in Carcinoma of Unknown Primary

Author	Histologic Type	Regimen	No. Patients	Response	Median Survival (mos)
Moertel et al[105]	Adeno	5-FU	88	16	NS*
Moertel et al[105]	Adeno	Mitomycin-C	9	22	NS
Moertel et al[105]	Adeno	5-FU/Mito-C	7	0	NS
Moertel et al[105]	Adeno	5-FU/BCNU	11	18	NS
McKeen et al[106]	Adeno	5-FU/Adria/Mito-C	28	22	NS
Rodnick et al[107]	Adeno	5-FU/Adria/Mito-C	14	7	+3
Woods et al[108]	Adeno/UC	Adria/Mito-C	25	36	4.5
Valentine et al[109]	Adeno/UC	Cytoxan/Adria/5-FU	14	14	7+
Bedikian et al[110]	Adeno/UC	Cytoxan/MTX/5-FU	22	5	2
Bedikian et al[110]	Adeno/UC	Tegafur/Cytoxan/Adria/Cisplatin	21	29	4.5
Pasterz et al[18]	Adeno/UC	5-FU/Adria/Cytoxan/Cisplatin	44	28	NS
Greco et al[15]	PDC/PDA	CDDP/vinblastine bleo ± doxorubicin	68	56% (22% CR)	18*
Goldberg et al[111]	Adeno	5-FU/Adria	45	30%	>10
		Mito-C		(9% CR)	
Walach[112]	Adeno	CTX/VNCR	21	48%	NS*
		MTX/5-FU		(29% CR)	
Shildt et al[113]	Adeno	5-FU vs 5-FU/Adria/Cytoxan	36	0	3
Anderson et al[114]	Carcinoma	VNCR/Adria/CTX	20	50% (20% CR)	NS
Raber et al[115]	Adeno/UC	CDDP/VP-16/5-FU	16	17%	NS
LeChevalier et al[116]	Adeno	MTX-FAM	19	37%	6+
Lenzi et al[117]	Adeno/PDC	CDDP/5-FU/folinic	31	30	18
Hainsworth et al[118]	PDC	CDDP/etoposide	32	60 (32% CR)	NS
Hainsworth et al[124]	Adeno/PDC/PDA	Paclitaxel/carboplatin etoposide	55	47	13.4
Greco et al[121]	PDA/PDC/	Docetaxel + cisplatin	26	26	8
Briasoulis et al[122]	Neuroendocrine/small cell carcinoma PDA, PDC	Docetaxel + carboplatin	47	22	12
		Carboplatin + paclitaxel	77	47.8	13
				68.4	15
				15.1	10
Culine et al[128]	Adeno/PDA/UC	Gemcitabine + cisplatin	80	55	8
		Irinotecan + cisplatin		38	6
Hainsworth et al[129]	Adeno/PDC	Bevacuzimab + erlotinib	51	90	8.9

Adeno, adenocarcinoma; Adria, Adriamycin; bleo, bleomycin; CDDP, cis-diamminedichloroplatinum; CR, complete response: CTX, cyclophosphamide; 5-FU, 5-fluorouracil; Mito, mitomycin C; MTX, methotrexate; NS, not stated; PDA, poorly differentiated adenocarcinoma; PDC, poorly differentiated carcinoma; UC, undifferentiated carcinoma; VNCR, vincristine; VP-16, etoposide.

*Calculated from data presented.

taxane-based regimens for these patients. Newer regimens continue to be tested, and some evidence suggests that even patients with a poor prognosis may benefit.

Culine and associates[128] evaluated the efficacy and toxicity of combination chemotherapy consisting of gemcitabine with cisplatin (GC) or irinotecan with cisplatin (IC) in patients with CUP in a phase II clinical trial. Eighty patients were assigned to receive either GC or IC. Seventy-eight patients were assessable for efficacy and toxicity. The median number of cycles was four in each arm of the study. Objective responses were observed in 55% of patients in the GC arm and 38% of patients in the IC arm. Treatment had to be discontinued in seven patients in the GC arm and eight patients in the IC arm. Median survival times were 8 and 6 months in the GC and IC arms, respectively, with a median follow-up of 22 months.

Greater knowledge regarding the molecular biology of CUP has translated to additional therapeutic options with targeted molecular agents. Hainsworth and associates[129] have evaluated the efficacy of combined targeted therapy with bevacizumab and erlotinib in 51 patients with CUP. Of these, 25% of patients were chemotherapy-naïve, with advanced bone or liver metastasis, and 75% of patients had received prior therapy with one or two chemotherapy regimens. Objective response occurred in 4 patients (8%), and 30 patients (59%) had stable disease or minor response. The median overall survival was 8.9 months, with a median follow-up of 13 months.

Median progression-free survival for the entire group was 6.2 months. Forty-two percent of patients were alive at 1 year. The 1-year survival for the previously treated versus untreated patients was 41% vs. 46%. These data clearly confirm the activity of targeted agents in the management of CUP, and additional prospective clinical trials are warranted to evaluate the use of these agents as part of front-line therapy.

FUTURE DIRECTIONS

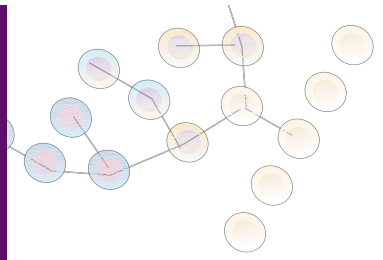
Near-term research in CUP will continue to focus on the identification and treatment of patient subsets. This approach has been very successful in dealing with the inherent heterogeneity of CUP. Sophisticated data collection and computer-based analysis will foster these studies. The role of DNA microarray in this subset is evolving, as discussed earlier. Patients who do not fit a treatable subtype, as discussed in this chapter, should be encouraged to get involved in clinical trials for novel therapies. Looking further into the future, research into the metastatic phenotype through an analysis of CUP cells may identify specific molecular and biochemical targets, which could be therapeutically exploitable for patients with CUP. These targets may be applicable to other metastatic malignancies as well. We would anticipate that the molecular characterization of CUP not only will improve our understanding of metastases but also, through comparison with known primary carcinomas, eventually will resolve the question of anatomic origin.

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99 Pediatric Solid Tumors

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SUMMARY OF KEY POINTS

Osteosarcoma

Incidence

- The incidence of osteosarcoma is 4 new cases per 1 million population per year among children younger than 15 years of age.
- Osteosarcoma is the most common bone tumor in children and adolescents.

Differential Diagnosis

- Other lytic bone lesions, including eosinophilic granuloma and giant cell tumor, must be excluded.
- At histopathologic examination, tumors must be differentiated from fibrosarcoma and chondrosarcoma.

Staging Evaluation

- Staging evaluation includes a complete history and physical examination, complete blood cell count (CBC), serum chemistry analysis (including determination of alkaline phosphatase level), and imaging studies of the primary tumor and chest.

Primary Therapy

- The primary tumor is managed surgically with a limb-sparing operation or amputation.
- Adjuvant chemotherapy incorporating high-dose methotrexate is used preoperatively for presumed micrometastatic disease; response will guide further therapy.
- Methotrexate responders have a more than an 80% chance of cure.
- Primary pulmonary metastatic disease is managed surgically, although adjuvant chemotherapy may reduce the extent of resection.

Effective Second-Line Therapy

- Pulmonary metastatic disease is managed surgically.
- Post-thoracotomy adjuvant chemotherapy is of unproven benefit.
- Local recurrence is managed surgically.
- Further adjuvant chemotherapy with non–cross-resistant agents is of uncertain benefit.

Ewing's Sarcoma Family Tumors

Incidence

- The incidence of Ewing's sarcoma family tumors is 2.8 new cases per 1 million population per year among children younger than 15 years of age.
- Ewing's sarcoma is the second most common bone tumor among children and adolescents.

Differential Diagnosis

- Osteomyelitis must be ruled out, especially when the patient has a fever.
- Lesions to be excluded include benign tumors of bone that manifest as lytic lesions (e.g., eosinophilic granuloma, giant cell tumor), malignant tumors (e.g., osteosarcoma, primary lymphoma of bone), and metastatic lesions from a nonosseous tumor (e.g., neuroblastoma).

Staging Evaluation

- Staging evaluation includes a complete history and physical examination, CBC, serum chemistry analysis (including determination of lactate dehydrogenase level), bone marrow biopsy, and imaging studies of the primary tumor, bones, and chest.

Primary Therapy

- The primary tumor should always be treated with multimodality therapy consisting of chemotherapy, radiation therapy, surgery, or a combination of these treatments.
- Specific local treatment depends on the primary site. Surgical extirpation may be considered with tumors in expendable bones (proximal part of the fibula, rib, clavicle, iliac wing).
- Unresectable tumors generally necessitate a combined approach of chemotherapy, radiation therapy, and surgery.
- Localized disease is curable with combined therapy in more than 70% of cases. Metastatic disease is curable in 30% to 40% of cases.

Effective Second-Line Therapy

- Effective second-line therapy has not been established.
- Local recurrence may be amenable to surgical extirpation.

Neuroblastoma

Incidence

- Among white children younger than 15 years of age, 10.5 new cases occur per 1 million population per year. Among black children, the incidence is 8.8 new cases per 1 million population per year.
- Neuroblastoma is the most common extracranial solid tumor in children.

Differential Diagnosis

- Disseminated bone disease can resemble systemic infection, inflammatory disease, osteomyelitis, or rheumatoid arthritis.
- Paraneoplastic syndromes associated with neuroblastoma (vasoactive intestinal peptide syndrome, opsoclonus-myoclonus-ataxia syndrome) must be differentiated from primary inflammatory bowel disease and neurologic disease.
- Neuroblastoma must be differentiated from other small round blue cell neoplasms of childhood (e.g., Ewing's sarcoma, primitive neuroectodermal tumor, non-Hodgkin's lymphoma, undifferentiated soft-tissue sarcoma).
- In as many as 10% of tumors, catecholamines are not produced. In 1%, the absence of an obvious primary lesion confounds the diagnosis.

Staging Evaluation

- Staging evaluation includes a complete history and physical examination, CBC,

serum chemistry analysis (including determination of lactate dehydrogenase level), quantitative urine catecholamines, bone marrow examination, radionuclide scintigraphy, and imaging studies of the primary tumor and chest.

Primary Therapy
- Specific treatment depends on stage of disease, age of the patient, and biologic features of the tumor.
- With few exceptions (completely resected primary tumor, infants with stable stage 4S disease), multiple-agent chemotherapy is the backbone of multimodality treatment.
- Survival depends on stage and biologic features of the tumor (e.g., histopathologic subtype, *MYCN* gene amplification).
- The overall survival rate for patients with stage I tumors is 90%; for those with stage 2A tumors, the survival rate is greater than 80%.
- Overall survival among patients with advanced-stage disease is poor. Sixty percent of children with stage 2B and 3 tumors live, and fewer than 15% with metastatic disease are long-term survivors.

Effective Second-Line Therapy
- No second-line therapy has proved beneficial.

Wilms' Tumor

Incidence
- The incidence of Wilms' tumor is 8 cases per 1 million population per year among children younger than 15 years of age.

Etiology and Epidemiology
- Mean age at diagnosis is 44 months for unilateral tumors and 31 months for bilateral tumors.
- Familial cases account for 1.5% of cases of Wilms' tumor.
- Associated with Wilms' tumor are a syndrome comprising aniridia, genitourinary anomalies, and mental retardation (WAGR syndrome); Denys-Drash syndrome; and Beckwith-Wiedemann syndrome.
- No firmly established environmental factors have been identified.

Pathology and Tumor Biology
- The main histologic subtypes are favorable and anaplastic.
- Implicated genes and loci include *WT1* (11p13), *WT2* (11p15), *FWT1* (17q12-q21), *FWT2* (19p13), *BRCA2*, and chromosomes 1p, 16q, and 7p.
- Mutations of the p53 gene (*TP53*) are associated with anaplastic tumors.

Clinical Features
- An asymptomatic abdominal mass is found in most patients.
- Other characteristic features include abdominal pain, hematuria, hypertension, and congenital anomalies (genitourinary malformations, aniridia, and hemihypertrophy).

Differential Diagnosis
- Neuroblastoma is the main consideration in the differential diagnosis.
- Other tumors to be excluded are renal neoplasms (clear cell sarcoma, rhabdoid tumor, congenital mesoblastic nephroma, renal cell carcinoma).
- Benign renal processes (nephrogenic rests, multicystic or polycystic kidneys, hydronephrosis, renal carbuncles, hemorrhage) also should be ruled out.

Staging Evaluation
- Evaluation begins with complete history and physical examination, with careful attention to blood pressure and assessment for associated congenital anomalies.
- Other components of the staging evaluation include CBC, serum chemistry analysis, urinalysis, abdominal ultrasonography or computed tomography (CT), and chest radiography with or without chest CT.

Primary Therapy
- *Surgery*: Surgical resection of the primary tumor usually precedes chemotherapy in North America.
- *Chemotherapy*: Agents used depend on disease stage and favorable versus unfavorable histology: stages I and II, favorable histology—vincristine, actinomycin D; stages III and IV, favorable histology, and stage I, anaplastic histology—vincristine, doxorubicin, actinomycin D; stage II through IV, anaplastic histology—vincristine, cyclophosphamide, doxorubicin, carboplatin, etoposide.
- *Radiation therapy*: Management for stages III and IV, favorable histology, and stages I through IV, anaplastic histology, consists of radiation therapy.
- Recurrent disease is effectively managed with radiation therapy and chemotherapy with agents not used for initial treatment.
- Patients who initially received aggressive treatment may respond to ifosfamide-, carboplatin-, and etoposide-based regimens.

Complications
- Renal failure (seen in less than 1%) and congestive heart failure may occur in patients who receive doxorubicin (in 4.4%).
- Pregnancy-related complications in adulthood have occurred in girls who receive flank irradiation.
- A second malignant neoplasm also may develop (1.6%).

Prognosis
- With *favorable* histology, outcomes include 85% 4-year relapse-free survival rate and 90% 4-year overall survival rate.
- With *anaplastic* histology, outcomes include 50% 4-year relapse-free survival rate and 50% 4-year overall survival rate.

Renal Cell Carcinoma

Incidence
- The incidence of renal cell carcinoma is 4 cases per 10 million population per year among children younger than 20 years of age.
- Mean age at diagnosis is 9 years.

Differential Diagnosis
- Other renal tumors of childhood, primarily Wilms' tumor, should be ruled out.

Staging Evaluation
- Staging evaluation includes a complete history and physical examination, CBC, serum chemistry analysis, and imaging studies of the abdomen, pelvis, and chest.

Primary Therapy
- Nephrectomy of the involved kidney constitutes definitive therapy for primary tumors.
- For metastatic disease, interleukin-2 or interferon-α-based therapy, or enrollment in clinical studies of investigational agents, is recommended.

Rhabdomyosarcoma

Incidence
- Among children younger than 20 years, the incidence of rhabdomyosarcoma is 4.3 new cases per 1 million population per year.
- Rhabdomyosarcoma is the most common soft-tissue sarcoma among children and adolescents.

Differential Diagnosis
- Other benign and malignant soft-tissue tumors must be excluded.
- At pathologic examination, rhabdomyosarcoma must be differentiated from the other small

round blue cell tumors of childhood (e.g., Ewing's sarcoma, neuroblastoma, non-Hodgkin's lymphoma).

Staging Evaluation
- Staging evaluation includes a thorough history and physical examination; CBC; serum chemistry analysis; imaging studies of the primary tumor, regional lymph nodes, lungs, and bones; and bone marrow examination.

Primary Therapy
- Primary therapy is chemotherapy with surgery, radiation therapy, or both. Specific treatment depends on age of the patient, tumor primary site and histologic subtype, and extent of disease.
- Mutilating surgery usually can be avoided because the tumor is sensitive to both chemotherapy and radiation therapy.
- The overall survival rate exceeds 70%, but survival will depend on extent of disease. More than 90% of patients with localized, resectable tumors survive, but less than 20% of patients with metastatic disease survive.

Effective Second-Line Therapy
- Cure rarely is possible except for patients with botryoid tumors and those with embryonal tumors whose tumor arose in a favorable site and was completely resected at initial diagnosis.

Nonrhabdomyosarcoma Soft-Tissue Sarcoma

Incidence
- Among persons younger than 20 years, 6.2 new cases occur per 1 million population per year.
- Peaks in incidence occur among infants and among children older than 10 years.

Differential Diagnosis
- Other tumors to be ruled out include benign soft-tissue tumors, rhabdomyosarcoma, and extraosseous Ewing's sarcoma.

Staging Evaluation
- Staging evaluation includes a thorough history and physical examination and imaging studies of the primary tumor and lungs.
- Imaging of regional lymph nodes, liver, bones, and brain is indicated in some clinical settings.

Primary Therapy
- Surgical excision with or without radiation therapy is indicated for patients with resectable tumors.
- Chemotherapy may provide some benefit for patients with high-grade tumors larger than 5 cm in diameter and for those with unresectable or metastatic tumors.
- Survival depends on the size and grade of the tumor and extent of disease. Patients with localized tumors 5 cm or smaller or localized low-grade tumors larger than 5 cm in diameter have a survival rate exceeding 85%. Approximately 50% of patients with high-grade tumors larger than 5 cm or with unresectable disease survive. The survival rate is less than 10% among patients with metastatic disease.

Effective Second-Line Therapy
- Cure generally is possible only for patients with local recurrence amenable to surgical extirpation and for those with distant recurrence of low-grade tumor that proves to be surgically resectable.

Retinoblastoma

Incidence and Clinical Forms
- Among children younger than 5 years of age, 11 new cases occur per 1 million population per year.
- The two clinical forms of retinoblastoma are as follows:
  1. *Hereditary, bilateral or multifocal* (40% of cases)—This form, characterized by germline mutations of *RB1*, may be inherited from an affected survivor or a silent carrier parent or may be the result of a new germline mutation.
  2. *Nonhereditary, unilateral or unifocal* (60% of cases)—15% of unilateral cases represent germline mutations.

Clinical Manifestations and Differential Diagnosis
- *Clinical manifestations*: Leukocoria is seen in more than 50% of cases, strabismus in 20% to 25%.
- *Differential diagnosis*: Coats' disease, retinopathy of prematurity, persistent hyperplastic primary vitreous, *Toxocara* uveitis, and toxoplasmosis need to be ruled out.

Staging Evaluation
- Approach to staging depends on tumor size and on the presence or absence of intraocular and extraocular extension.
- Indirect ophthalmoscopic examination of both eyes with the patient under general anesthesia is essential.
- Imaging studies helpful in staging include ultrasonography, orbital and cerebral CT, and magnetic resonance imaging (MRI).
- Bone marrow biopsy and cerebrospinal fluid examination are reserved for patients with extraocular disease, optic nerve involvement, or choroid invasion.

Treatment
- Treatment must be individualized and depends on laterality, potential for vision, and tumor extent.
- Enucleation is reserved for cases in which no potential for useful vision remains. Cryotherapy and photocoagulation are useful for management of small primary or recurrent tumors.
- Radiation therapy is the treatment modality of choice for controlling local disease and preserving vision with larger tumors.
- Use of chemotherapy is restricted to patients with advanced intraocular disease or with extraocular disease.

Hepatoblastoma

Incidence
- Among children younger than 15 years of age, 1.5 new cases occur per 1 million population per year.

Etiology and Epidemiology
- Mean age at diagnosis is 18 months.
- The tumor is associated with familial adenomatous polyposis and Beckwith-Wiedemann syndrome.
- An association with low birth weight has been found.

Pathology and Tumor Biology
- The major histologic subtypes are fetal, embryonal, macrotrabecular, and small cell (anaplastic).
- The tumor is associated with mutations of the *APC* and β-catenin genes and loss of heterozygosity at 11p15, the locus of the *IGF2* gene.

Clinical Features
- An asymptomatic abdominal mass is present in most patients.
- Other features may include anorexia, weight loss, vomiting, and precocious puberty (seen in 2% of cases).

Differential Diagnosis
- Other malignant tumors to be excluded include hepatocellular carcinoma, embryonal sarcoma, rhabdomyosarcoma, angiosarcoma, and teratoma.
- Benign tumors to be ruled out include hemangioma, hemangioendothelioma, hamartoma, and adenoma.

Staging Evaluation
- Staging evaluation includes a complete history and physical examination, with careful assessment for any congenital

abnormalities or signs of precocious puberty.
- Laboratory tests typically include CBC, serum chemical analysis and alpha-fetoprotein and α-human chorionic gonadotropin assays.
- Diagnostic imaging may include CT or MRI of the abdomen and chest CT.

Primary Therapy
- Cure is possible only when complete surgical excision is performed. If complete excision is not feasible, liver transplantation should be considered.
- Adjuvant chemotherapy (cisplatin-based, in conjunction with doxorubicin or 5-fluorouracil) is useful preoperatively for achieving resectability and postoperatively for preventing distant metastasis.
- Radiation therapy has a limited and ill-defined role.

Salvage Therapy
- Recurrent disease confers a poor prognosis, but repeated resection of local and metastatic recurrences has lengthened the survival period.

Complications
- Hearing loss and nephrotoxicity (related to cisplatin), cardiac toxicity (related to doxorubicin), and development of second malignant neoplasms may occur.

Prognosis
- With *localized disease*, outcomes include a 60% to 70% 5-year relapse-free survival rate and a 70% to 80% 5-year overall survival rate.
- With *metastatic disease*, outcomes include a 25% to 30% 5-year relapse-free survival rate and a 50% to 60% 5-year overall survival rate.

Adrenocortical Carcinoma

Incidence
- The incidence of adrenocortical carcinoma is 2 to 3 new cases per 10 million population per year in the United States.
- A 10- to 15-fold higher incidence has been observed in southern Brazil.

Etiology and Epidemiology
- Associated with germline *TP53* mutations and Li-Fraumeni syndrome.

Differential Diagnosis
- Other conditions associated with pathologic androgen or cortisol production, such as Cushing's syndrome or ovarian or testicular tumors, should be ruled out.

Staging Evaluation
- Evaluation for staging includes imaging studies of the abdomen, pelvis, and chest; skeletal scintigraphy; and measurement of blood and urine concentrations of adrenocortical hormones.

Primary Therapy
- Complete surgical removal of the tumor is indicated.
- Mitotane-based therapy or chemotherapy with cisplatin also is given.

Effective Second-Line Therapy
- Recurrent disease can be managed with further surgery, or experimental agents can be tried.

INTRODUCTION

Solid tumors account for 60% of all pediatric malignant neoplasms, approximately 3700 new cases being diagnosed each year in the United States. The spectrum of tumor types that occur in children is much different from that observed in adults. Included among the diverse types of pediatric neoplasms are tumors of the central nervous system (35%); neuroblastoma (15%); soft-tissue sarcoma, including rhabdomyosarcoma (7%); Wilms' tumor (6%); bone tumors, including osteosarcoma and Ewing's sarcoma (8%); retinoblastoma (5%); and miscellaneous tumors including hepatoblastoma, germ cell tumors, and melanoma (17%). Enormous progress has been made in the diagnosis and management of these tumors since the original demonstration of the chemosensitivity of Wilms' tumor to actinomycin D in 1966. Cure rates for most childhood solid tumors have increased by as much as 50% since the mid-1970s. The increase is attributable largely to improved understanding of prognostically important biologic and clinical features, enhanced precision of clinical staging systems, consistent use of supportive care, and development of more effective treatment, often incorporating a combination of chemotherapy, surgery, and radiation therapy.[1,2]

OSTEOSARCOMA

Epidemiology

Osteosarcoma, a malignant neoplasm derived from primitive mesenchymal cells and characterized by the presence of osteoid-producing spindle cell stroma, is the most common malignant bone tumor in the pediatric age group.[3] Osteosarcoma ranks tenth among all newly reported pediatric cancers in the United States, accounting for 2.6% of all neoplasms in children. The estimated annual incidence is 3.9 cases per 1 million population among white children and 4.5 per 1 million population among African-American children.[4] Most osteosarcomas occur during the first 2 decades of life, a period characterized by rapid skeletal growth. Boys are affected more commonly than girls. Several observations support the association between skeletal growth velocity and osteosarcoma. First, patients with osteosarcoma tend to be taller than their counterparts without this disease. Second, osteosarcoma develops at an earlier age in female patients than in male patients, perhaps because of differences in the timing of onset of puberty and the growth spurt.[5]

Tumor Biology

Unlike osteosarcoma in adults, in whom more than 25% of tumors are associated with pre-existing pathologic osseous conditions such as Paget's disease or fibrous dysplasia, most pediatric osteosarcomas arise spontaneously in areas of bone without any abnormality.[3] Irradiation is the best-characterized etiologic factor contributing to the development of secondary osteosarcoma. In a study involving 91 patients with second malignant bone sarcomas, osteosarcoma accounted for 72 cases, 52 (72%) of these tumors arising within previously irradiated fields.[6] The median time for development of the secondary tumor was 9.6 years after irradiation.

Children with hereditary retinoblastoma are at increased risk of development of secondary nonocular tumors irrespective of previous radiation to the primary site.[7,8] The estimated 50-year cumulative incidence of secondary neoplasms in children with retinoblastoma is 51% in hereditary cases and 5% in nonhereditary cases. Osteosarcoma is the most common second neoplasm in these children, accounting for as many as 44% of cases.[8]

Alterations in components of the cell cycle control system appear to characterize the ontogeny of osteosarcoma. Studies of the retinoblastoma gene (*RB1*) have shown that alterations affect the *RB1* gene in as many as 80% of cases[9] and that other events, such as *CDK4* alterations, also may result in *RB1* inactivation.[10] In experimental

models, introduction of the *RB1* gene into *RB1*-deleted osteosarcoma cell lines suppressed the tumorigenic potential of these cells.[11] The ontogeny of osteosarcoma is complex, however, and probably involves several genetic alterations other than loss of *RB1* function. Other genetic abnormalities have been reported, including allelic loss at chromosomal locus 17p, 25% to 50% of osteosarcomas having structural alterations at 17p13 of the p53 tumor suppressor gene.[12,13] Additional genetic abnormalities associated with osteosarcoma include amplification of the *MDM2* gene, whose protein product is important in regulation of p53 function. Tumors with *MDM2* amplification appear to display clinically aggressive behavior characterized by either local or distant metastasis.[14] Allelic loss at other chromosomal loci, including 3q, 13q, and 18q, have been observed in as many as 75% of karyotypically analyzed osteosarcomas. This finding suggests the presence of at least two other potential tumor suppressor genes involved in the multistep process of tumor development and progression in osteosarcoma.[15,16]

The peak incidence of osteosarcoma coincides with the adolescent growth spurt. This finding has led to the hypothesis that the altered hormonal milieu typical of adolescence may play a role in development of osteosarcoma. It is therefore possible that the insulin-like growth factor I (IGF-I)–insulin-like growth factor I receptor (IGF-IR) axis may be involved in the unregulated proliferation of osteoblasts that occurs in osteosarcoma. IGF-I functions as a mitogen in human and mouse osteosarcoma cells, and osteosarcoma cell lines depend on IGF-I for in vitro growth.[17] Although the levels of IGF-I and its binding protein (IGFBP-3) are not elevated in patients with osteosarcoma, other components of the IGF-I signaling pathway may be involved in the development and progression of osteosarcoma.[18]

Pathology

Osteosarcoma is characterized by the presence of spindle cell stroma that produces osteoid. Conventional osteosarcoma can be subdivided histologically into three major groups depending on the predominant cell type. Approximately 50% of tumors are categorized as *osteoblastic*, because the predominant extracellular element is osteoid, whereas 25% are *chondroblastic*, with a prominent cartilaginous component. Approximately 25% have a herringbone pattern similar to that observed in fibrosarcoma and are therefore called *fibroblastic*. No significant differences in overall outcome are apparent among these three histologic subtypes.[3] In one report, however, patients with fibroblastic histology showed better histologic response and better overall outcome than were observed for patients with osteoblastic or chondroblastic histology.[19]

Clinical Manifestations

Pain is the most common symptom in children and adolescents with osteosarcoma.[3] Onset of pain often is insidious, and the pain usually involves the area affected by tumor. Severe pain of sudden onset commonly is associated with pathologic fracture. Swelling around the affected bone is the second most common clinical finding. The tumor may be easily palpable when located in areas such as the anterior surface of the femur but may manifest only as leg edema when occurring in difficult-to-appreciate areas such as the popliteal fossa. A painful limp that increases with weight bearing is the third most common symptom. Systemic signs and symptoms such as fever and weight loss are uncommon.

Osteosarcoma most commonly involves the long bones, most tumors occurring around the knee. The most frequent sites of involvement are the distal part of the femur, the proximal portion of the tibia, and the proximal part of the humerus. The axial skeleton, including the pelvis, is rarely affected in children (fewer than 10% of cases) but more frequently is involved in patients older than 60 years.[3,20] Overt macroscopic metastatic disease occurs in 20% of cases and carries a grave prognosis.[21–23]

Laboratory and Radiologic Evaluation

Laboratory evaluation often is unrevealing. Elevations of serum lactate dehydrogenase (LDH) and alkaline phosphatase levels are the most common laboratory abnormalities. The latter appears to correlate with osteoblastic activity and has therefore proved useful in monitoring response to therapy.[24]

Radiologic evaluation of a patient with osteosarcoma must include assessment of the primary site as well as a search for distant metastatic lesions. Plain radiography is the most effective method of detection of bone tumors.[25,26] The main limitation of plain radiography is accurate delineation of local tumor extent. Characteristic radiologic findings in osteosarcoma commonly include a metaphyseal permeative lesion with periosteal new bone formation and destruction of pre-existing cortical bone. A soft-tissue mass is present in more than 90% of cases. Other radiologic signs commonly associated with osteosarcoma include cumulus cloud-like density and the presence of Codman's triangle (Fig. 99-1A). A baseline chest radiograph should be obtained to search for distant metastatic lesions. Angiography usually is reserved for patients who receive intra-arterial chemotherapy or for those who need optimal vessel visualization before limb salvage.[26]

Computed tomography (CT) of the primary tumor is accurate in assessment of degree of tumor calcification and ossification, which are important in assessment of response to therapy.[26] Chest CT always should be performed at the time of diagnosis for documentation of metastatic disease. Findings at magnetic resonance imaging (MRI) offer the best estimate of intramedullary tumor extension,

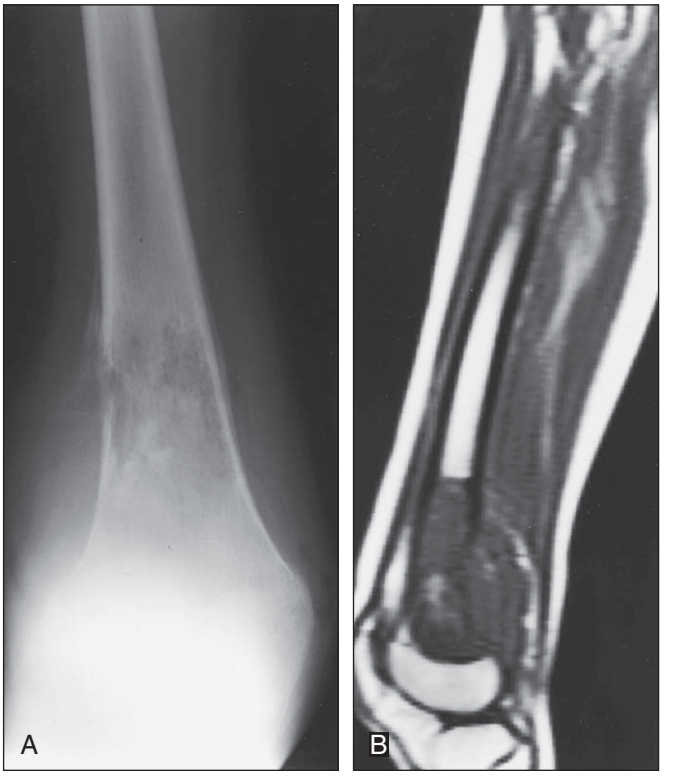


Figure 99-1 • Osteosarcoma involving the right distal femur. **A,** Plain radiograph shows a poorly defined, permeative destructive pattern; periosteal reaction; a Codman's triangle; and an associated soft-tissue mass. **B,** Sagittal T_2-weighted magnetic resonance image from the same patient shows abnormally dark area (representing increased signal intensity) in the intramedullary space consistent with tumor involvement by osteosarcoma. The associated posterior soft-tissue mass is evident. Areas of bright focal signal enhancement represent intramedullary hemorrhage.

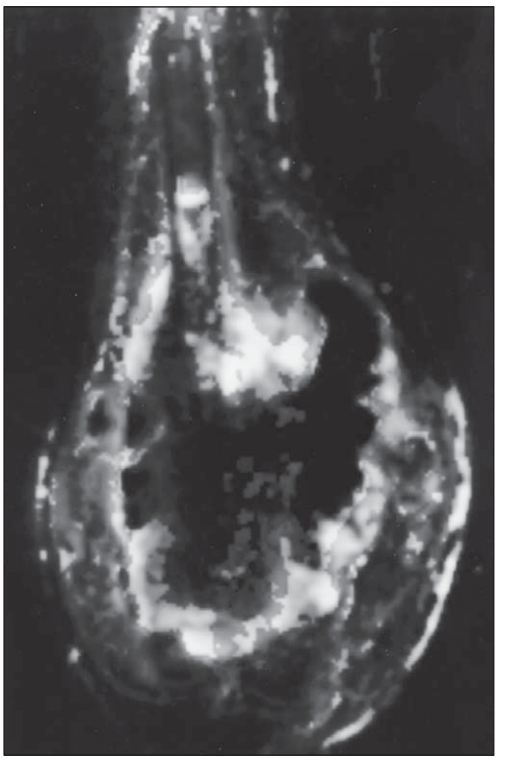


Figure 99-2 • Dynamic, paramagnetic, contrast-enhanced magnetic resonance image from a patient with an osteosarcoma of the distal right lower extremity. At subsequent pathologic examination, the focal areas of increased signal intensity were found to represent nests of viable tumor.

joint and vascular involvement, detection of "skip" metastatic lesions, and delineation of the soft-tissue component (see Fig. 99-1B). The blood supply and vascularity of the tumor can be better appreciated with administration of gadopentetate dimeglumine, or gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA), a paramagnetic contrast material. MRI is helpful in assessing response to chemotherapy, as evidenced by changes in signal intensity on T_2-weighted images and alterations in the enhancement of tumor tissue after administration of Gd-DTPA (Fig. 99-2).[26] Dynamic contrast-enhanced MRI (DEMRI) is a valuable method for assessing microcirculation in osteosarcoma.[27] DEMRI can be used to evaluate changes in regional contrast access during chemotherapy. The findings appear to correlate accurately with histologic response and outcome, allowing early identification of patients at risk for recurrence.[28] Radionuclide bone scans with technetium 99m (^{99m}Tc)-labeled bone-seeking phosphate compounds are particularly useful in detection of metastatic bone lesions.[26] Thallium bone scintigraphy also is useful in the diagnosis of osteosarcoma; its primary role may be in assessing response to chemotherapy.[29]

Biopsy of the primary tumor should be done carefully, preferably by the surgeon who will ultimately perform the definitive operation. In performance of biopsy of a suspected bone tumor, the following basic principles should be observed: (1) avoidance of transverse incisions, which can make subsequent surgery difficult; (2) avoidance of contamination of multiple compartments and hematoma formation, because successful limb-sparing procedures can be jeopardized; and (3) if feasible, biopsy of the soft-tissue component only.

Osteosarcoma Subtypes

In addition to conventional osteosarcoma, a small proportion of patients present with clinical subtypes that are characterized by distinct clinical, radiologic, and histologic characteristics.

Telangiectatic Osteosarcoma

Telangiectatic osteosarcoma is characterized microscopically by blood-filled spaces divided by septa containing neoplastic sarcomatous cells. Both radiologically and histologically, it is difficult to differentiate from aneurysmal bone cyst. It accounts for less than 4% of cases of osteosarcoma. Age and anatomic distributions are similar to those in conventional osteosarcoma. On imaging studies, telangiectatic osteosarcoma manifests as a purely lytic lesion with a permeative destructive growth pattern; it usually disrupts the cortex, but with minimal or no periosteal new bone formation, which often is multilayered, in an onionskin pattern. Overall, the radiographic appearance is not that of a typical osteosarcoma, which usually has a mixture of blastic and lytic areas. Indeed, a purely lytic radiographic appearance is a diagnostic requirement for its diagnosis. This pattern can simulate aneurysmal bone cyst.[30,31] Histologically, telangiectatic osteosarcoma is very hemorrhagic, similar to the gross appearance of aneurysmal bone cysts. Microscopically, this tumor consists of cyst-like spaces divided by septa, which are composed of highly atypical sarcomatous tissue. Unlike aneurysmal bone cysts, these cystic spaces have no endothelial lining, and the tumor cells are in direct contact with areas of hemorrhage.[30] In the past, it was thought that telangiectatic osteosarcoma carried a worse prognosis than that for conventional osteosarcoma. With appropriate multimodality therapy, however, the outcome is similar to or better than that with conventional osteosarcoma.[19]

Low-Grade Intramedullary Osteosarcoma

Low-grade intramedullary osteosarcoma is a very rare variant of osteosarcoma, accounting for less than 1% of cases. Most cases are diagnosed during the third decade of life. Its anatomic distribution is similar to that of conventional osteosarcoma, with predilection for the distal femur and proximal tibia. In contrast with conventional osteosarcoma, symptoms typically develop over many months or even years before the patient comes to medical attention. Imaging studies usually show a variable pattern of lytic foci and dense areas, poorly demarcated. Periosteal new bone formation is minimal. Histologically, it shows a predominantly differentiated fibroblastic and osseous component, similar to what is seen in parosteal osteosarcoma (see later on). The differential diagnosis must distinguish this lesion from fibrous dysplasia. Treatment includes a complete resection of the lesion. Incomplete resection invariably results in local recurrence, and dedifferentiation increases with each recurrence.[3,32]

Surface Osteosarcomas

Osteosarcomas that originate and grow predominantly on the surface of the bone include the parosteal, periosteal, and high-grade surface osteosarcomas.

Parosteal osteosarcoma is a low-grade tumor that grows predominantly on the surface of long bones, in an exophytic pattern. Because it is derived from the outer layer of the periosteum, it grows without causing elevation of the periosteum or evidence of periosteal new bone formation. Parosteal osteosarcomas account for 3% of all osteosarcomas. They tend to occur in skeletally mature patients, with diagnosis during the third and fourth decades of life. More than 80% of these tumors are located in the distal portion of the femoral shaft, in its posterior aspect, within the superior popliteal area. Because of their slow growth, parosteal osteosarcomas usually manifest as a painless mass. Imaging shows a tumor growing on the surface of the bone, with a broad base, in a mushroom-like fashion. The mass typically is densely mineralized and has lobulated outlines. Microscopically, these tumors are characterized by the presence of a spindle-cell fibroblastic component, with variable osteoid production, low mitotic rate, and no atypical features.[33,34] The treatment is surgical, and a complete resection is mandatory. Incomplete resections invariably lead to local recurrences, and the risk of high-grade transformation increases with local recurrence.[33]

Periosteal osteosarcoma is a low- to intermediate-grade tumor that has a predominantly chondroblastic differentiation. It originates in the deep layer of the periosteum, so its growth is manifested by a separation and elevation of the periosteum from the cortex, causing a prominent periosteal new bone formation. It represents less than 2% of all osteosarcomas. Periosteal osteosarcoma is a tumor of childhood, with a peak incidence during the second decade of life, and it has a female predominance. The usual location is in the long bones of the lower extremity, most commonly the tibia, with an affinity for the diaphysis. The presentation is similar to that with conventional osteosarcoma, with pain and swelling of short duration. Imaging studies show a predominantly fusiform lesion on the surface of a long bone.

High-grade surface osteosarcoma is a very rare subtype of surface osteosarcoma, accounting for less than 1% of all osteosarcomas. The age distribution, anatomic location, and clinical presentation are similar to conventional osteosarcoma. By imaging, high-grade surface osteosarcoma simulates a periosteal osteosarcoma. Microscopically, however, it is indistinguishable from conventional osteosarcoma, showing anaplastic cellular features and osteoid and immature bone and cartilage formation. Medullary extension is minimal. Treatment should be the same as for a conventional osteosarcoma.

Prognostic Factors

The most important adverse prognostic factor in patients with osteosarcoma is the presence of metastatic disease.[21] In addition, primary tumor location is associated with outcome. Children with primary tumors of the tibia and distal femur appear to have a more favorable prognosis than those with axial primary tumors. This finding highlights the importance of complete surgical resection in the management of this malignant disease.[21,35] For patients with localized disease, factors associated with poor prognosis include measures of tumor burden, such as tumor size, and levels of alkaline phosphatase and LDH,[21,24,36] as well as more biologic measures, such as poor histologic response to preoperative chemotherapy,[35] hyperdiploidy,[37] and increased expression of P-glycoprotein[38] or Ki-67.[39] The percentage of tumor necrosis after preoperative chemotherapy is the most consistent and important factor associated with outcome in children and adolescents with localized osteosarcoma. A favorable response (more than 90% tumor necrosis) correlates with excellent overall survival. Patients who have less than 90% tumor necrosis are considered poor responders, for whom the prognosis usually is poor.[21,35,40] Because of this strong correlation between degree of histologic response to preoperative chemotherapy and outcome, noninvasive methods such as DEMRI, used for monitoring tumor response, can be used to evaluate changes in regional contrast access during chemotherapy.[31] Finally, a proportion of patients with extremity osteosarcoma present with a pathologic fracture, or a pathologic fracture develops after institution of therapy. This has been considered a poor prognostic factor and an indication for immediate amputation. It is possible, however, that with the use of preoperative chemotherapy and judicious use of limb-sparing techniques, a selected group of patients with pathologic fracture may still do well without amputation.

Treatment

Optimal management of osteosarcoma consists of multiple-agent chemotherapy and local control measures, including amputation or limb-sparing surgical procedures. Box 99-1 outlines the approach to management of osteosarcoma used at St. Jude Children's Research Hospital. Before the development of limb-sparing procedures, amputation was the standard surgical method used for curative treatment of osteosarcoma. Amputation now generally is reserved for primary tumors deemed unresectable. Limb function after below-the-knee amputation usually is excellent. Over the past several years, the role of limb-sparing procedures has increased dramatically. As a result of refinements in neoadjuvant chemotherapy, bioengineering, and imaging techniques, it is estimated that as many as 80% of patients with osteosarcoma will eventually be candidates for limb-sparing procedures.[41] The criteria for limb-sparing procedures include (1) absence of major neurovascular involvement by tumor, (2) feasibility of wide surgical excision to include a normal muscle cuff in all directions and en bloc removal of all biopsy sites, (3) resection of the adjacent joint and capsule, (4) adequate motor reconstruction with regional muscle transfer, and (5) adequate soft-tissue coverage.[42] In the past, immature skeletal age and primary tumor of the humerus were relative contraindications; however, new expandable prosthetic devices may help overcome this problem.[41,43] More recent improvements have been concentrated on achieving noninvasive extension of prostheses. One such method is the Phenix technology (Repiphysis). The basic principle involves storage of energy in a spring maintained in compressed form by a locking system. Prosthetic lengthening is performed through exposure to an external electromagnetic field that pilots the locking system and allows controlled release of the spring energy (Fig. 99-3). Prosthetic expansion of several millimeters can be achieved with each procedure, and the total duration of the procedure is less than 30 seconds[44] (Fig. 99-4). Thus, limb-sparing procedures are considered feasible in the care of most children and adolescents with osteosarcoma. When these procedures are appropriately performed, the risk of local recurrence is low (less than 5%).[45] Long-term functional outcome, however, must be carefully compared with that obtained with amputation alone. Complications of limb-sparing surgery include infection, nonunion, fracture, and unstable joints.

Before the introduction of adjuvant chemotherapy, fatal metastatic disease developed in more than 80% of patients with osteosarcoma.[46] Trials of single-agent chemotherapy began in the 1960s and early 1970s and established, in a nonrandomized manner, a role for the use of chemotherapy in the management of osteosarcoma. Responses with single-agent high-dose methotrexate or doxorubicin occurred in 20% to 40% of patients with metastatic disease.[46,47] Since then, different combinations of platinum compounds, doxorubicin,

Box 99-1. ST. JUDE CHILDREN'S RESEARCH HOSPITAL APPROACH TO MANAGEMENT OF OSTEOSARCOMA

At St. Jude Children's Research Hospital, the standard approach to the management of osteosarcoma entails the use of a platinum-based chemotherapy regimen followed by resection of the primary tumor. For patients with nonmetastatic disease, carboplatin may be substituted for cisplatin in a combination regimen that also includes high-dose methotrexate, doxorubicin, and ifosfamide. Resection for local control is performed after completion of three courses of chemotherapy, and postoperative chemotherapy is not modified on the basis of histologic response unless progression of the disease is documented. Most patients with extremity osteosarcoma are candidates for limb salvage surgery. Amputation is performed only in selected cases. For patients with immature skeleton and growth potential, the Phenix (Repiphysis) device, which allows noninvasive lengthening, is used.

In patients with metastatic and unresectable disease at diagnosis, cisplatin is used in combination with high-dose methotrexate, ifosfamide, etoposide, and doxorubicin. Aggressive resection of the primary tumor and all sites of metastasis is indicated. For patients with unresectable disease, radiation therapy is used, although the outcome for this group of patients is very poor.

The few patients with local recurrence after a limb-sparing procedure undergo amputation. Recurrent disease to the lungs is managed with aggressive surgery, and repeated thoracotomy usually is needed. Systemic chemotherapy with second-line regimens is added in cases of early recurrence or unresectable disease.



Figure 99-3 • Activation of Phenix (Repiphysis) device expansion in treatment for osteosarcoma involving the left lower extremity in a 13-year-old boy. The activating device is on the left. The electromagnetic coil is being held over the annular protuberance within the implant.

and high-dose methotrexate have formed the basis of standard chemotherapy regimens that lead to cure in 50% to 75% of patients with nonmetastatic disease (Table 99-1).

For more than two decades, therapy for nonmetastatic osteosarcoma has followed the basic guidelines of the T-10 protocol,[48] and most of the current treatment strategies have evolved from lessons learned with it. The T-10 protocol and its variants consist of a multiple-agent regimen of high-dose methotrexate, doxorubicin, cisplatin, and a combination of bleomycin, cyclophosphamide, and dactinomycin. When the T-10 protocol guidelines are used, the 5-year actuarial event-free survival (EFS) rate may approach 70%.[35,36] These results are not always reproducible, however, and multi-institutional U.S. and European studies conducted according to similar guidelines have shown lower EFS rates, usually 50% to 60%.[49–53] The lack of reproducibility of the results of the original study may be attributed in part to the complexity of the treatment. In a study performed by the European Osteosarcoma Intergroup, patients were randomized to receive the T-10 protocol or a much simpler treatment of six courses of a combination of cisplatin and doxorubicin.[49] Only one half of the patients in the T-10 protocol-like group completed all scheduled therapy, whereas 94% of the patients in the short-treatment group received the six courses of chemotherapy. The results for both treatment groups were identical, suggesting that a simple, two-drug regimen of cisplatin and doxorubicin can cure more than one half of patients with nonmetastatic osteosarcoma.[54]

One of the major contributions of the T-10 protocol and its predecessor T-7 is that the histologic response to neoadjuvant chemotherapy has been identified as the most important prognostic

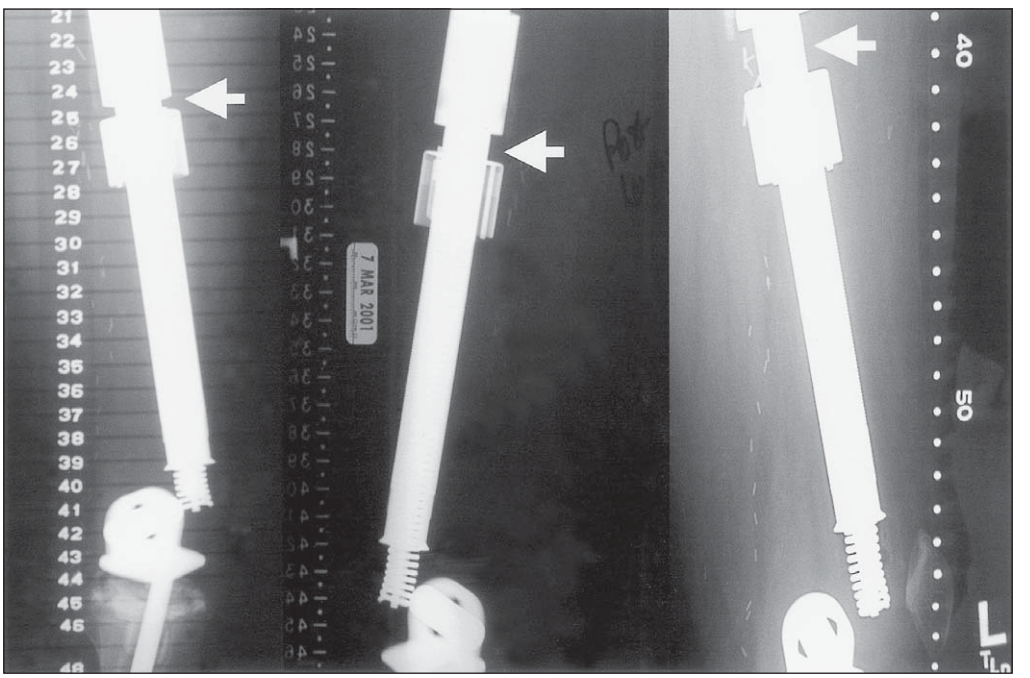


Figure 99-4 • Radiographs show the expandable portion of the Phenix (Repiphysis) device. The titanium tubular portion expands out of the polymeric tube. The increased distance between barrel and stem indicates the amount of expansion that occurred *(arrows)*.

Table 99-1 Summary of Most Relevant Chemotherapy Protocols for the Management of Osteosarcoma

		TREATMENT			
Protocol/Author	***N***	**Preoperative**	**Postoperative***	**Outcome**	**Comment(s)**
T-10/Meyers et al.[36]	31	MTX-BCD	*GR*: + DOX *PR*: + CDDP/DOX	5-yr EFS: 73%	*PR*: No advantage of intensified postoperative treatment
T-12/Meyers et al.[36]	36	MTX-BCD-DOX-CDDP	Same	5-yr EFS: 78%	No advantage of intensified neoadjuvant treatment
MIOS/Link et al.[52]	77	None	MTX-BCD-DOX-CDDP	2-yr DFS: 66%	Randomized study demonstrating need for chemotherapy
	36	Surgery alone		2-yr DFS: 17%	
CCG-782/Provisor et al.[51]	268	MTX-BCD	*GR*: + DOX *PR*: + DOX-CDDP	8-yr EFS: 53% *GR*: 81% *PR*: 46%	*PR*: No advantage of intensified postoperative treatment
COSS-82 arm A/ Winkler et al.[53]	59	MTX-BCD	*GR*: Same *PR*: + CDDP/DOX	4-yr EFS: 49%	
COSS-82 arm B/ Winkler et al.[53]	66	MTX-DOX-CDDP	*GR*: Same *PR*: + IFO	4-yr EFS: 68%	*PR*: IFO not advantageous
COSS-86 low risk/ Fuchs et al.[55]	41	MTX-DOX-CDDP	Same	10-yr EFS: 66%	No difference for IA vs. IV administration of CDDP
COSS-86 high risk/ Fuchs et al.[55]	128	MTX-DOX-CDDP-IFO	Same	10-yr EFS: 67%	Use of IFO for high-risk patients
EOI-1/Bramwell et al.[54]	142	CDDP-DOX × 3	CDDP-DOX × 3	5-yr DFS: 57%	Importance of a two-drug short regimen with CDDP-DOX
	140	CDDP-DOX-MTX × 2	CDDP-DOX-MTX × 2	5-yr DFS: 41%	
EOI-2/Souhami et al.[49]	192	MTX-DOX	+ BCD-CDDP	5-yr PFS: 44%	Two-drug short regimen may be better than longer; more complex protocols
	199	CDDP-DOX	Same	5-yr PFS: 44%	
IOR-1/Ferrari et al.[50]	127	MTX-CDDP	*GR*: + DOX-BCD *PR*: MTX-DOX-BCD	12-yr DFS: 46%	HD MTX better than MD MTX
IOR-2/Bacci et al.[83]	164	MTX-CDDP-DOX	*GR*: Same *PR*: + IFO/ETO	5-yr DFS: 63% *GR*: 67% *PR*: 56%	Importance of dose intensity *PR*: IFO/ETO good salvage
IOR-3/Bacci et al.[59]	139	MTX-CDDP-DOX	*GR*: Same *PR*: + IFO	3-yr DFS: 60%	*PR*: No benefit of IFO
IOR-4/Bacci et al.[83]	133	MTX-CDDP-DOX-IFO	Same	5-yr EFS: 56%	No benefit of intensified therapy with IFO
SJ-OS91/Meyer et al.[61]	47	CBP-IFO	Same + DOX-MTX	3-yr EFS: 72%	CBP is a good alternative to CDDP for nonmetastatic disease
INT 0133/Meyers[62A]	577	Randomized to: *A*: MTX-CDDP-DOX *A+*: MTX-CDDP-DOX + L-MTP-PE *B*: MTX-CDDP-DOX + IFO *B+*: MTX-CDDP-DOX + IFO + L-MTP-PE		5-yr. EFS: 64% 63% 56% 72%	Possible synergistic effect between IFO and MTP-PE
SSG VIII/Smeland†	113	MTX-CDDP-DOX	*GR*: Same *PR*: + IFO-ETO	5-yr EFS: 68% 5-yr EFS: 53%	 *PR*: Lack of benefit of modifying postoperative therapy

BCD, bleomycin, cyclophosphamide, dactinomycin; CBP, carboplatin; CCG, Children's Cancer Group; CDDP, cisplatin; COSS, Cooperative Osteosarcoma Study; DFS, disease-free survival; DOX, doxorubicin; EFS, event-free survival; EOI, European Osteosarcoma Intergroup; ETO, etoposide; GR, good histologic responders; HD, high-dose; IA, intra-arterial; IFO, ifosfamide; INT, Intergroup; IOR, Istituto Ortopedico Rizzoli; IV, intravenous; L-MTP-PE, liposomal encapsulated muramyl tripeptide phosphatidylethanolamine; MD, moderate-dose; MIOS, Multi-Institutional Osteosarcoma Study; MTX, methotrexate; PFS, progression-free survival; PR, poor histologic responders; SJ-OS, St. Jude Osteosarcoma; SSG, Scandinavian Sarcoma Group.

*Postoperative regimens are either the same as or in addition to preoperative regimens, or as specified.

†Data from Smeland S: Scandinavian Sarcoma Group Osteosarcoma Study SSG-VIII: prognostic factors for outcome and the role of replacement salvage chemotherapy for poor histological responders. Eur J Cancer 2003;39:488–494.

factor in the care of patients with nonmetastatic disease.[35] Intensification of postoperative[35,50,51] or preoperative[36] chemotherapy with cisplatin, doxorubicin, and ifosfamide, however, has not improved outcome. To increase the proportion of good histologic responders, some researchers have investigated intra-arterial administration of cisplatin. In the context of an aggressive, multiple-agent treatment, however, intra-arterial infusion of cisplatin does not offer any significant advantages.[55]

In recent years, ifosfamide has been incorporated into therapeutic regimens for osteosarcoma. After early reports showed that ifosfamide as a single agent achieved response rates of 10% to 60% in patients with advanced or treatment-refractory osteosarcoma,[56–58] some investigators began to use the agent in salvage therapy regimens for poor responders.[53,59] More recently, ifosfamide has been incorporated into front-line therapy in many regimens.[55,59–62] Whether incorporating the agent into standard treatment will improve the cure rate is unknown.[62] The Children's Oncology Group (COG) investigated the role of ifosfamide in a randomized study.[62A] Because giving an alkylating agent with etoposide has been shown to produce a synergistic antitumor effect,[63] several investigators have administered ifosfamide and etoposide together on a fractionated dosing schedule over 3 to 5 days. In patients with refractory osteosarcoma, some of whom had previously received ifosfamide, the combination of ifosfamide and etoposide achieved response rates of 15% to 48%.[64–67] Thus, this combination is being used increasingly to manage osteosarcoma.[59,68] Investigators in the Pediatric Oncology Group have reported response rates of 59% in patients with untreated metastatic osteosarcoma receiving this combination.[69] The combination of ifosfamide and etoposide appears to be more effective than ifosfamide alone in patients with untreated metastatic osteosarcoma.[58,69] These results support performance of additional studies of this combination in treatment for patients with nonmetastatic disease. The use of the combination of ifosfamide and etoposide is being increasingly used for the salvage of patients with poor histologic responses; however, evidence is lacking for improved outcome in this group of patients. The randomized European-American Osteoscarcoma (EUROS) trial will attempt to answer this question.

In the cooperative POG-CCG Intergroup INT0133 trial, patients with localized osteosarcoma received treatment with a standard methotrexate-cisplatin-doxorubicin regimen, and underwent a double randomization. The first randomization was to receive ifosfamide; the second randomization was to receive MTP, a derivative of the BCG cell wall that is known to stimulate the immune system, with the objective of decreasing pulmonary failures. Therefore, four regimens were compared. The addition of ifosfamide or MTP alone to the standard regimen did not seem to provide any benefit. However, the addition of both ifosfamide and MTP-PE resulted in a significantly better outcome when compared with the other three regimens. The significance of these findings is unclear.[62A]

Methotrexate is the classical antifolate, and blocks the action of dihydrofolate reductase. Methotrexate was among the first drugs reported to have an antitumor effect in osteosarcoma and it has been a major component of the osteosarcoma treatment ever since then.[46] Further, there is evidence that suggests that the pharmacokinetics of this agent may influence outcome, although this influence is minor in the context of more intensive multiagent protocols. However, the role of methotrexate appears to be limited to the administration of high doses (usually $12 g/m^2$), because the administration of lower doses appears to have a lesser therapeutic effect.[42] The administration of high-dose methotrexate requires close monitoring of serum levels, which cannot be performed in many institutions, particularly those of developing countries, and extensive supportive measures, including hyperhydration, urine alkalinization, and leucovorin rescue, which must be adjusted to the methotrexate serum levels. The development of acute renal failure, mediated by the perception of methotrexate and its metabolites in the renal tubules, is a potentially life-threatening complication. Even among patients receiving all available monitoring and supportive care, severe nephrotoxicity develops in 2% of them, and the mortality for those patients is 4.4%. Dialysis methods have limited effectiveness in removing methotrexate, compared with the rapid reductions in plasma concentrations that can be achieved with carboxypeptidase G2.

Cisplatin is one of the most active agents against osteosarcoma. The toxicity of this agent is substantial, however: Hearing loss and renal impairment can be permanent for some patients. Substitution of carboplatin for cisplatin was investigated at St. Jude Children's Research Hospital. In the context of a multiple-agent chemotherapeutic approach with high-dose methotrexate, ifosfamide, and doxorubicin, use of carboplatin resulted in a 3-year EFS rate of 72%, an outcome comparable with that obtained with cisplatin-based therapy but with less long-term toxicity.[61] Incorporation of carboplatin in future osteosarcoma trials needs further evaluation, however, because in some reports, carboplatin as a single agent has been found to have poor antitumor effect in the treatment of metastatic disease.[70]

Approximately 20% of patients with osteosarcoma have clinically detectable metastatic disease at diagnosis, and their outcome usually is very poor.[22,23] Optimal treatment for these patients entails a very aggressive multimodality approach that combines intensive preoperative and postoperative chemotherapy with resection of both the primary tumor and metastatic lesions. When these guidelines are followed, contemporary protocols that incorporate ifosfamide or the combination of ifosfamide and etoposide, along with high-dose methotrexate, doxorubicin, and cisplatin, result in 2- to 5-year progression-free survival rates of 25% to 45%.[58,69,71] For patients with recurrent osteosarcoma, a very aggressive surgical approach is recommended; the 5-year postrelapse survival rate for patients in whom a complete resection of all macroscopic disease can be achieved is close to 40%.[72]

In a small number of patients (3% to 5%), metachronous osteosarcoma can develop after primary treatment. This has been associated with the presence of germline *TP53* (Li-Fraumeni) or *RB1* gene mutations. These second primaries usually develop within 3 years from initial diagnosis, and with systemic chemotherapy and surgery, 30% to 40% of these patients can be cured.[73]

Lung metastasis develops in most patients in whom therapy fails. The ability to control pulmonary micrometastatic disease after completion of therapy would certainly result in a significant improvement in outcome. In an animal model, administration of liposome-encapsulated muramyl tripeptide phosphatidylethanolamine (L-MTP-PE) resulted in activation of pulmonary macrophages and eradication of pulmonary micrometastatic lesions.[74] Use of L-MTP-PE is an attractive strategy that deserves further clinical investigation. Other strategies under evaluation include use of new agents such as ecteinascidin-743 (ET-743), sequential administration of gemcitabine and docetaxel, administration of aerosolized granulocyte macrophage colony stimulating factor (GM-CSF) or 9-nitrocamptothecin, and use of various gene-modified interleukins.[75–77]

Some researchers have reported overexpression of HER2/erbB-2 (measured by immunohistochemistry studies) in approximately 40% of osteosarcoma tumor samples and correlation of this overexpression with more aggressive behavior and adverse outcome.[78] If this correlation holds true, the use of anti-HER2 monoclonal antibodies may be an attractive therapeutic strategy for this group of high-risk patients. Nevertheless, studies using either immunofluorescence[79] or fluorescence in situ hybridization[80] have not shown amplification of the HER2/neu gene in patients with osteosarcoma. Further complicating the issue is a more recent report showing that erbB-2 expression was associated with a better outcome.[81]

Finally, administration of high doses of the bone-seeking radiopharmaceutical samarium-153 ethylene diamine tetramethylene phosphonate (^{153}Sm-EDTMP) may provide good pain palliation with minimal nonhematologic toxicity for patients with local recurrences or bone metastasis of osteosarcoma, and its role may be expanding.[82]

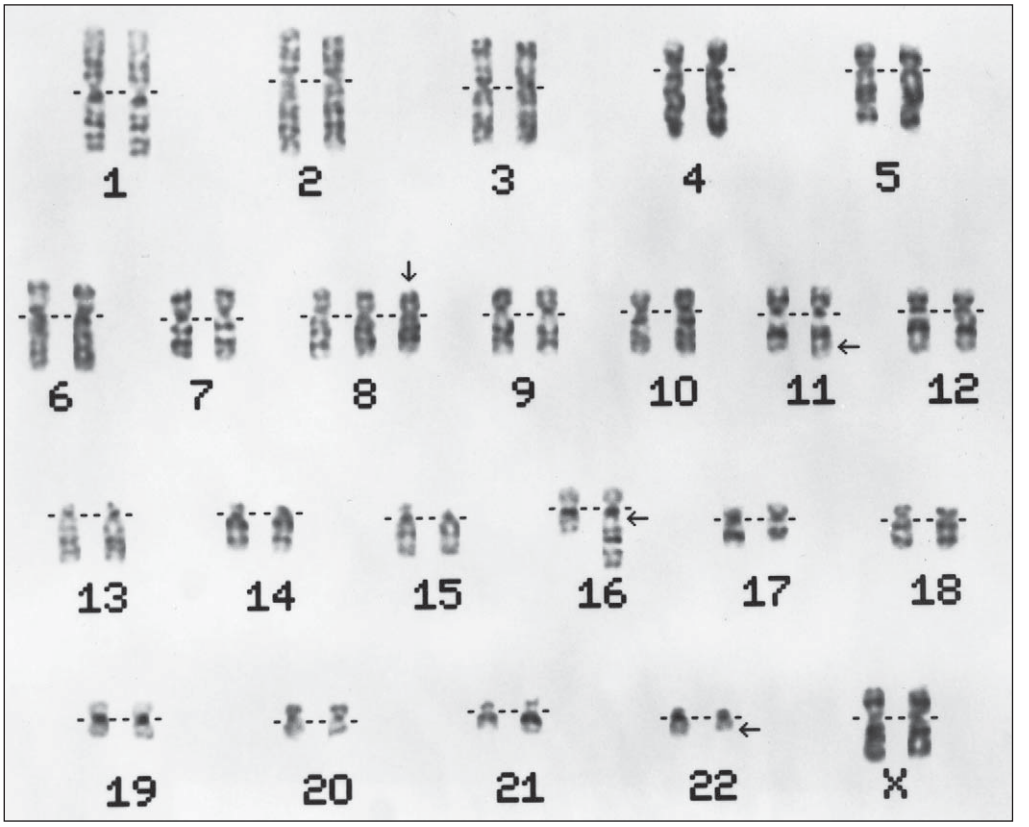


Figure 99-5 • Karyotype obtained from a Ewing's sarcoma tissue specimen shows the characteristic t(11;22)(q24;q12), secondary t(1;16)(q21;q13), and trisomy 8.

EWING'S SARCOMA FAMILY TUMORS

Epidemiology

The term *Ewing's sarcoma family tumors* (ESFTs) defines a group of small round cell neoplasms of neuroectodermal origin that manifest as a continuum of neurogenic differentiation. On this continuum, Ewing's sarcoma of bone represents the least differentiated (most primitive) form of neuroectodermal tumors, and peripheral neuroepithelioma represents the most differentiated form. Ewing's sarcoma is the second most common malignant bone tumor in children and adolescents. The estimated incidence among white children younger than 15 years is 2.8 cases per 1 million population.[4] The tumor is rare in the nonwhite population, and boys are predominantly affected in most series. Most cases are diagnosed during the second decade of life.[84] The location of the tumor varies. Although most Ewing's sarcomas arise in bone, a significant proportion arise in soft tissue.[85] The most common locations for this tumor are the chest wall, pelvis, and extremities, but any bone can be involved.[84,86]

Tumor Biology

The histogenesis of Ewing's sarcoma has been a source of controversy since the first description of the tumor in 1921. Various hypotheses have been proposed in an attempt to identify the possible cell of origin in Ewing's sarcoma. Among these, cells of endothelial, pericytic, myeloid, mesenchymal, and neuroectodermal origin have been suggested.[87] The existence of either a mesenchymal stem cell or an early primitive neuroectodermal cell that has retained its ability for multilineage differentiation is the currently accepted hypothesis. It is now well accepted that ESFTs constitute a single group of neurally derived neoplasms that share unique immunocytochemical, cytogenetic, and molecular markers.[87,88]

Nearly all ESFTs have a reciprocal translocation that involves the *EWS* gene in chromosome 22q12.[89] The t(11;22) is the most commonly observed translocation (85% to 95% of cases) and juxtaposes the DNA-binding domain of the human homologue of the murine *Fli1* gene in chromosome 11 with the 5′ end of *EWS* in chromosome 22 (Fig. 99-5). The most common fusions occur between exon 7 of *EWS* and exon 6 of *FLI1* (type 1; 55% to 60% of cases) and between exon 7 of *EWS* and exon 5 of *FLI1* (type 2; 25% of cases).[89] The type of fusion transcript appears to be prognostically relevant, because type 1 fusion appears to be associated with a lower proliferative rate.[90] The t(11;22) appears to play a pivotal role in development of ESFTs because the *EWS-FLI1* fusion transcript can transform NIH 3T3 cells.[91] As many as 10% of ESFTs contain an alternative translocation between chromosomes 21 and 22. This translocation fuses the *ERG* gene on chromosome 21 and the *EWS* gene on chromosome 22, producing an *ERG-EWS* fusion transcript.[89] Finally, rare cases of ESFT contain a t(7;22)(p22;q12) that fuses the *ETV1* and *EWS* genes.[92] The mechanism by which these fusion transcripts become tumorigenic is poorly understood, although it has been postulated that this chimeric transcript can transcriptionally deregulate members of the manic fringe family of genes, which are instrumental in somatic development.[93] The IGF-I/IGF-IR pathway is actively involved in the cell transformation and inhibition of apoptosis induced by *EWS-FLI1*.[94–96]

Pathology

Microscopic examination shows that Ewing's sarcoma is the prototypical small round blue cell tumor of childhood. The ultrastructural and immunocytochemical characteristics of this and other small round cell tumors of childhood are shown in Table 99-2. Ewing's sarcoma is characterized by the presence of a dimorphic pattern of

Table 99-2 Differential Diagnosis for Small Blue Round Cell Tumors with Electron Microscopy, Immunocytochemistry, and Molecular Cytogenetics

	Tumor Type				
Modality	**Ewing's Sarcoma**	**PNET**	**Neuroblastoma**	**Hematolymphoid Neoplasms**	**Rhabdomyosarcoma**
Electron microscopy					
Cell processes	Inconspicuous	Present	Prominent	Inconspicuous	Inconspicuous
External lamina	Absent	Absent	Absent	Absent	Present
Intracellular junctions	Primitive	Synaptic	Desmosomes, synaptic junctions	Absent	Inconspicuous
Filaments	Absent	Variable	Neurofilaments 8–12 nm in diameter	Absent	Dense Z-line–like structures Mixture of thin and thick filaments or myosin-ribosome complexes
Microtubules	Inconspicuous	Variable	Prominent, 24–30 nm in diameter	Absent	Inconspicuous
Granules	Absent NSGs	Sporadic NSGs	NSGs 90–240 nm in diameter	Lysosomes only	Lysosomes only
Glycogen	Prominent	Variable	Inconspicuous	Inconspicuous	Prominent
Organelles	Sparse	Variable	Variable	Sparse	Variable
Immunocytochemistry					
Vimentin	+	+	–	±	+
CD99	+	+	–	±	±
NSE	±	+	+	–	±
Leu 7 (CD 57)	±	+	+	–	–
Cytokeratin	±	±	–	–	±
Neurofilaments	–	±	±	–	±
S-100	–	±	±	–	–
Muscle-specific actin	–	±	–	–	+
Desmin	–	±	–	–	+
MyoD1	–	–	–	–	+
LCA	–	–	–	+	–
Chromogranin	–	–	+	–	–
Synaptophysin	–	±	+	–	–
β_2-Microglobulin	+	+	–	+	+
Cytogenetic studies					
t(11;22), t(21;22), t(7;22)	+	+	–	–	–
t(2;13), t(1;13)	–	–	–	–	+
t(1;14), t(2;5), t(14;14), 14q11 abnormalities, t(8;14), t(2;8), t(8;22)	–	–	–	+	–
Loss of 1p36	±	–	+	–	–
Genetic studies: Gene(s) involved					
EWS, *FL1*, *ERG*, *ETV1*	+	+	–	–	–
CMYC, *TAI*, *HOX 11*, *LYL-1*, others	–	–	–	+	–
PAX3, *FKHR*, *PAX7*	–	–	–	–	+
NMYC	–	–	+	–	–

+, present; –, absent; ±, may be present or absent; NSG, neurosecretory granule; PNET, primitive neuroectodermal tumor.

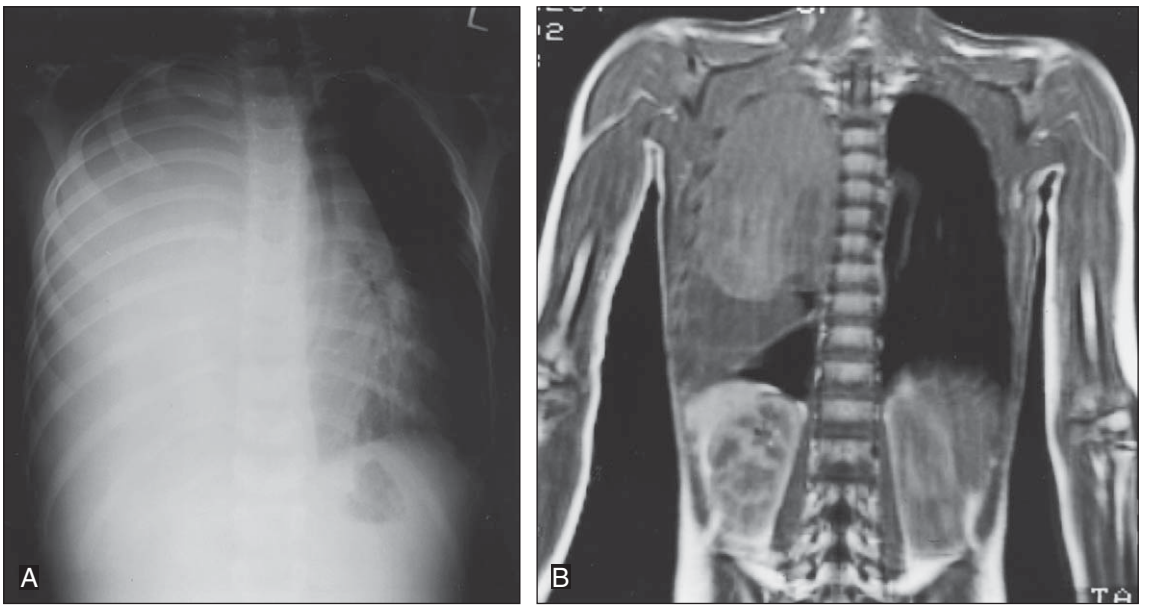


Figure 99-6 • Primitive neuroectodermal tumor involving the chest wall. **A,** Plain radiograph shows complete opacification of the right hemithorax, marked mediastinal shift, and slight tracheal narrowing. **B,** Coronal T_1-weighted magnetic resonance image shows a large right intrathoracic mass with subjacent pleural effusion and small localized area of normal aerated lung parenchyma.

densely packed cells with variable amounts of large clear cytoplasm. Individual cells have an ellipsoid nucleus without distinct cytoplasmic outlines. The cells are primitive, show a paucity of organelles, and often contain large amounts of intracellular glycogen. Various microscopic patterns, including the diffuse, lobular, organoid, and filigree patterns, have been described.[97] Immunocytochemical analysis shows vimentin and CD99 reactivity. The latter monoclonal antibody specifically recognizes the cell surface antigen $^{p30/p32}$MIC-2, which normally is expressed as a component of the T-cell receptor complex.[97,98] When overt neural differentiation is present, the term *peripheral neuroectodermal tumor* or *peripheral neuroepithelioma* is used (see Table 99-2). In such cases, the cells are round with more abundant cytoplasm but do not show mature neural elements, such as nerve bundles and mats of neuropile.[97] The term *extraosseous Ewing's sarcoma* has been reserved for neoplasms that cannot be differentiated from Ewing's sarcoma at light microscopic examination but arise exclusively in soft tissue.[87,97] Patients with this histologic variety accounted for 5% of all subjects in the Intergroup Rhabdomyosarcoma Study,[85] although extraosseous tumors are now managed in the same manner as for classic Ewing's sarcoma of bone. Despite these histologic distinctions, Ewing's sarcoma of bone, extraosseous Ewing's sarcoma, primitive neuroectodermal tumors, and peripheral neuroepithelioma are unified by the presence of the same oncogenic events and should therefore be considered the same neoplasm and managed in a similar manner. The advent of molecular diagnostic techniques has allowed development of sensitive tests, such as reverse transcriptase-polymerase chain reaction (RT-PCR) analysis, which is accurate in detection of *EWS-FLI1* and *EWS-ERG* fusion transcripts at levels well below those commonly found with routine cytogenetic studies.[99] RT-PCR assay is a useful adjunct in the diagnosis of Ewing's sarcoma, particularly in differentiation from other soft-tissue small round cell tumors, such as rhabdomyosarcoma.

Clinical Manifestations

Ewing's sarcoma commonly manifests during the second decade of life (median age, 13 years) with localized pain and a visible palpable mass.[84,100] Fewer than 3% of cases occur in children younger than 3 years.[101] Boys are more commonly affected than girls. Pathologic fractures may be present in as many as 15% of children and adolescents before diagnosis.[102] Back pain, extremity weakness, or altered sensation should raise suspicion for the presence of primary or metastatic disease. Systemic manifestations such as fever are more frequent than in osteosarcoma. Almost one half of patients have signs and symptoms referable to the primary tumor for more than 3 months before the diagnosis is made. Ewing's sarcoma has a tendency to involve the shaft of long tubular bones, pelvis, and ribs, but almost every bone can be affected. More than 50% of the tumors arise from axial bones, the pelvis being the most commonly involved (25%); one third of the tumors originate in the lower extremities, and less than 10% in the upper extremities. Chest wall Ewing's sarcoma is known as *Askin's tumor* (Fig. 99-6). Approximately 20% to 25% of patients with this tumor have metastatic disease when they present for evaluation. The most common sites of metastatic disease are in the lungs, followed by the bones and bone marrow. Metastatic disease appears to be associated with older age and with large tumor or pelvic primaries.

Laboratory and Radiologic Evaluation

Patients with suspected Ewing's sarcoma should be thoroughly evaluated to define the extent of local disease and the presence of metastatic lesions. Initial laboratory studies include complete blood cell count and erythrocyte sedimentation rate; measurement of serum electrolytes; LDH assay; renal and liver function tests; determination of alkaline phosphatase, calcium, phosphorus, and magnesium levels; and coagulation profile. In Ewing's sarcoma, elevation of erythrocyte sedimentation rate and of serum LDH is not uncommon. Bone marrow aspiration and biopsy should be performed, and evaluation with molecular techniques such as RT-PCR is recommended. Important imaging studies are chest radiography, plain radiography of primary and metastatic sites, bone scintigraphy, CT of the chest, and MRI of the primary site with T_1- and T_2-weighted sequences, as well as DEMRI.[26,103]

In Ewing's sarcoma, plain radiographs typically show a diaphyseal destructive lesion with a laminated periosteal reaction and large soft-

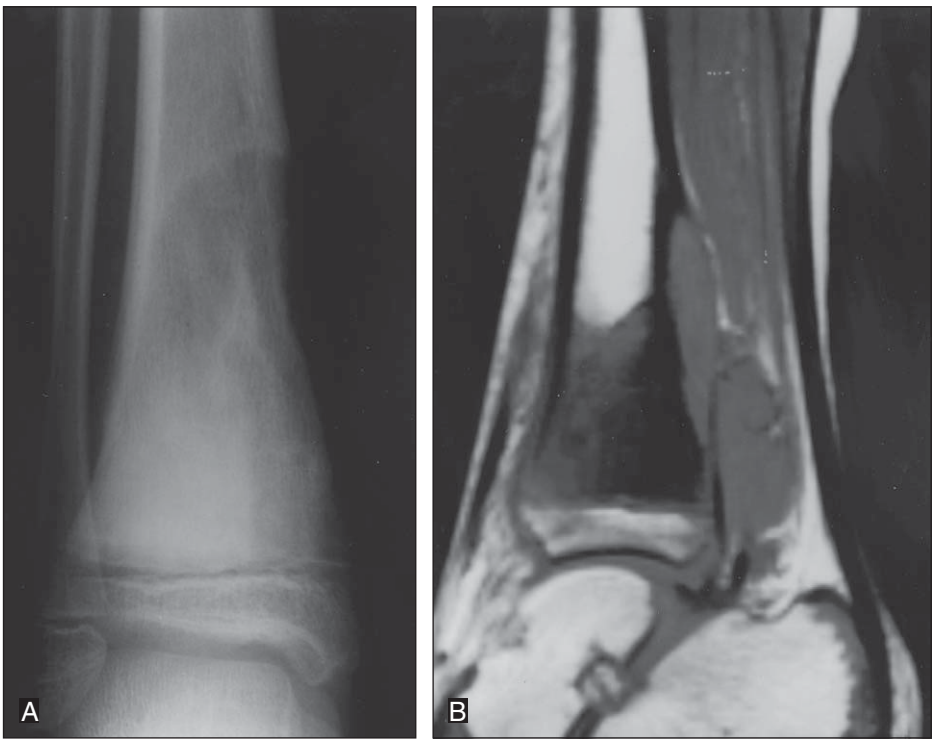


Figure 99-7 • Ewing's sarcoma of the right distal tibia. **A,** Plain radiograph shows a poorly marginated destructive lesion with associated periosteal reaction. **B,** Sagittal T_1-weighted magnetic resonance image of the same lesion shows a well-demarcated dark area of low signal intensity defining the intramedullary extent of the tumor contrasted against the bright appearance of the high signal intensity derived from intramedullary fat. The soft-tissue component of the tumor is evident in the posterior aspect.

tissue mass (Fig. 99-7A). We favor MRI over CT for defining the intramedullary component of the primary tumor and the extent of soft-tissue mass (see Fig. 99-7B). In contrast with the situation in osteosarcoma, DEMRI findings are not a reliable prognostic indicator.[104] Newer techniques such as positron emission tomography (PET) appear to be useful in noninvasive evaluation of response to chemotherapy.[105]

Prognostic Factors

A variety of initial clinical features have been correlated with outcome of therapy for Ewing's sarcoma. Two major European retrospective studies analyzed factors that are prognostically important in Ewing's sarcoma.[84,86] Both studies included patients who participated in different European protocols over a 25-year period. The results confirmed the classic clinical features associated with poor prognosis, such as metastatic disease, older age, large tumor size, and trunk and pelvic primary sites. Both studies, however, also showed that with refinement in the multidisciplinary approach to this disease that entails newer and more intensive chemotherapeutic regimens and superior local control measures, some of these classic prognostic factors are being redefined.

Although large tumor size classically has been associated with worse prognosis, this feature may be less important with more aggressive treatment. For example, in the early St. Jude studies, tumors larger than 8 cm in diameter were associated with worse prognosis.[106] However, tumor size disappeared as a prognostic factor in the more intensive St. Jude EW92 protocol.[99] In the first Cooperative Ewing's Sarcoma Study (CESS-81), tumors larger than 100 cm^3 were associated with worse outcome.[107] With treatment improvements, the tumor size associated with worse prognosis has increased to 200 cm^3.[108]

Tumor location also seems to be losing its prognostic significance with newer treatments: Although pelvic and axial tumor locations classically were associated with worse outcome in the early studies,[106,110,111] differences in outcome were minimal in subsequent studies.[109,112,113] The first Pediatric Oncology Group–Children's Cancer Group Ewing's sarcoma trial (POG-8850/CCG-7881), an investigation of the effect of addition of ifosfamide and etoposide to the standard VACD regimen (vincristine, actinomycin D, cyclophosphamide, and doxorubicin), showed that addition of the drug pair abrogated the negative prognostic implications of large tumor size (greater than 8 cm in diameter) and pelvic location. Of note, the benefit of addition of ifosfamide and etoposide was not seen in patients older than 18 years.

A newer prognostic factor is degree of histologic response to chemotherapy.[114,115] European studies consistently have shown the prognostic value of histologic response, the significance of which stands across protocols and appears to be independent of the drugs used. Patients with good histologic responses had a significantly better outcome than those with poor responses in the consecutive REN-1, -2, and -3 trials in Italy[86,115] and in the CESS-81[100] and CESS-86[116] trials in Germany. Thus degree of histologic response appears to be one of the most relevant prognostic factors. Type of fusion transcript also seems to influence the clinical behavior of ESFTs. Although the biologic behavior of tumors with fusion *EWS-FLI1* does not differ from the behavior of tumors with *EWS-ERG* fusion,[117] the type of *EWS-FLI1* fusion may significantly affect prognosis. The hybrid transcripts resulting from fusion of exons 7 and 6 of the *EWS* and *FLI1* genes, respectively (type 1 fusion), seem to result in sarcoma of a less aggressive behavior than that observed for other fusion types.[118,119] Because ESFTs manifest a continuum of neuroectodermal differentiation, the histologic diversity may reflect different biologic behaviors. Evidence is lacking, however, for correlation of degree of neuroectodermal differentiation with prognosis.[120] The most important prognostic factor is the presence of metastatic disease at diagnosis.[76] Advances in management of ESFTs have resulted in only very modest improvement in outcome among patients with metastatic lesions.[84,109,121] Even among patients with metastatic disease, heterogeneity is common. With an appropriately intensive treatment that includes bilateral lung irradiation, the European Intergroup Cooperative Ewing's Sarcoma Studies (EICESSs) have shown that patients with isolated metastatic lesions in the lung may have a better prognosis, albeit still inferior to that for patients with localized disease. Patients with extrapulmonary metastasis have a worse prognosis.[122,123]

With the use of molecular techniques in the staging of ESFTs, it is evident that a significant proportion of patients with localized disease (20% to 30%) have micrometastatic disease in the bone marrow detected by PCR assay.[124–126] In patients with lung metastasis and those with bone metastasis, this proportion is 40% and 90%, respectively.[125] The prognostic significance of this microstaging for patients with localized disease is still unclear. Although the presence of tumor cells in peripheral blood may lack significance, detection of tumor cells in bone marrow by molecular techniques may be predictive of unfavorable outcome.[125,126]

Treatment

Before the introduction of systemic chemotherapy, less than 20% of children with Ewing's sarcoma treated with either surgery or radiation therapy alone were expected to be long-term survivors.[127] In the past 3 decades, major advances have been made in the management of Ewing's sarcoma. These advances derive largely from cooperative trials (Table 99-3). The first studies conducted by the Intergroup Ewing Sarcoma Study (IESS) showed the importance of adjuvant chemotherapy that included a combination of alkylating agents and anthracyclines (IESS-I and -II).[112,128] Thereafter, conventional management of Ewing's sarcoma included local control measures in combination with administration of VACD.[106,109,111] More recently, incorporation of ifosfamide (VAID) has resulted in modest benefit for patients with high-risk features.[113,116] Preclinical and clinical evidence indicates that combined administration of etoposide and alkylators has a synergistic antitumor effect[63–65,129] and that with both types of agent, efficacy improves with fractionated administration.[130–133] Combined administration of ifosfamide and etoposide (IE) has been shown to be very active in patients with Ewing's sarcoma who have not received previous treatment.[134] Two randomized studies were conducted to investigate the effect of adding etoposide to VACD or VAID regimens.[135,136] In EICESS-92, patients with localized high-risk disease (tumor diameter greater than 200 cm^3) receiving VAID did not seem to benefit from the addition of etoposide.[136] The first Pediatric Oncology Group–Children's Cancer Group Ewing's sarcoma trial (POG-8850/CCG-7881) was an investigation of incorporation of the IE combination in frontline management of ESFTs. Patients were randomized to receive VACD with or without IE.[135] Patients receiving IE plus VACD appeared to have a more favorable outcome.[135,137]

Incorporation of granulocyte colony stimulating factor (G-CSF) into treatment regimens for many types of cancer has allowed modest dose intensification of multiple-agent chemotherapy by increasing the total dose per cycle[109,138,139] or shortening the time between treatments.[140] For ESFTs, this strategy is based on using high cumulative doses of alkylating agents and topoisomerase-II inhibitors.[109,140] When these general treatment guidelines are followed, the disease-free survival rate for patients with localized, low-risk disease approaches 70% to 75%, and the overall survival rate for this group of patients may be greater than 80%.[109]

The importance of dose intensification in the management of ESFT was evaluated in the second Pediatric Oncology Group–Children's Cancer Group Ewing's sarcoma trial (POG-9354/CCG-7942). In that trial, patients were randomized to receive alternating courses of vincristine, doxorubicin, and cyclophosphamide with ifosfamide and etoposide over either 48 or 30 weeks. The early results of that randomized trial demonstrated no difference in outcome between the standard and the dose-intensified treatment groups.[141] An alternative to increasing dose intensity is decreasing the intervals between cycles while maintaining the same dose per cycle with the use of G-CSF. In the United States, this is the approach taken by the COG in the recently completed AEWS-0031 study, in which patients were randomized to receive alternating cycles of VCD and IE every 3 weeks or two weeks, which results in 33% dose intensification.

Despite improvement, the prognosis for patients with metastatic disease continues to be very poor, and only 20% to 25% survive[121,122,142] (Table 99-4). Several institutions have used treatment intensification, by which very high doses of different agents are administered in a short time. In the case of ESFTs, this is a very attractive alternative, because ESFTs are highly sensitive to alkylating agents, which have a steep dose-response curve. Although most patients with ESFTs treated in this manner may exhibit good clinical and histologic responses, the final results are not better than those obtained with conventional therapy.[138,143,144]

Other protocols have been used to investigate the possibility of maintaining intensive treatments for more extended periods in an attempt to improve outcome for all patients with Ewing's sarcoma. At St. Jude Children's Research Hospital, the EW92 protocol was used to evaluate the feasibility of aggressive early induction with vincristine, cyclophosphamide, doxorubicin, ifosfamide, and etoposide (VCDIE), followed by prolonged maintenance therapy with intensification of alkylating agents and etoposide[109] (Box 99-2). The results were not better than less aggressive regimens for patients with localized disease, and no significant benefit was obtained for patients with metastatic disease. Important findings were that only 66% of patients completed therapy and that intensification was feasible in only 25% of the patients.

Use of protocols that include intensification of alkylators and topoisomerase-II inhibitors has resulted in a significant increase in the incidence of treatment-related leukemia—specifically, acute myelogenous leukemia (AML)—and myelodysplastic syndrome (t-AML/MDS). This therapeutic strategy appears to be strongly leukemogenic, and patients are at increased risk for development of both alkylator-related and etoposide-related t-AML/MDS.[143,145,146] With current therapies, the cumulative incidence of t-AML/MDS 5 years after treatment is 8% to 10%. This increased risk of t-AML/MDS appears to be related to both the increase in the total cumulative doses and dose intensification. The role of hematopoietic growth factors in this complication is unknown.

New drugs and new drug combinations continue to be investigated in the care of patients with Ewing's sarcoma. Although phase I and II studies of topotecan and irinotecan as single agents have shown little or no activity in patients with refractory disease, recent studies suggest that their combination with alkylating agents may be more promising. Phase II studies of the combination of topotecan (0.75 mg/m^2 per day for 5 days) and cyclophosphamide (250 mg/m^2 per day for 5 days) resulted in responses in 36% of patients with recurrent disease[147] and in 56% of patients with untreated metastatic disease.[148] The COG is currently investigating the incorporation of this combination in the frontline treatment of ESFTs, given in alternating cycles with VDC and IE. Also recently, the combination of irinotecan on a protracted schedule (10 to 20 mg/m^2 per day for 5 days in 2 consecutive weeks) with temozolomide (100 mg/m^2 per day for 5 days) has shown excellent response rates.[149]

Advances in management of ESFTs have resulted in only modest improvement in outcome among patients with metastatic disease.[84,109,121] With appropriately intensive treatment that includes bilateral lung irradiation, however, the prognosis for patients with isolated lung metastasis may be better than for patients with extrapulmonary metastasis.[122,123] For patients with bone and bone marrow metastasis, therefore, more intense therapies may have a role. ESFTs are very sensitive to alkylators, a group of agents with a very steep dose-response curve, which provides the basis for the use of consolidation with myeloablative therapy and autologous hematopoietic stem cell transplantation (HSCT). The results of treatment with megatherapy and HSCT for patients with high-risk ESFTs must be analyzed with caution because of the lack of randomized studies and the heterogeneity of patients and treatments. Results of most retrospective European and American studies do not seem to support the use of this approach.[122,150–152] In more recent results reported by the European Bone Marrow Transplant Registry, however, conditioning regimens that incorporate high doses of alkylating agents, generally busulfan and melphalan, confer an apparent survival advantage.[153,154]

Table 99-3 Management of Nonmetastatic Ewing's Sarcoma Family of Tumors

Study	No. of Patients	Regimen	Results: 5-Yr DFS	Comment(s)
IESSS				
IESS-I[128] (1973–1978)	342	VAC	24%	Value of doxorubicin
		VAC + WLI	44%	Worse results for pelvic ESFT
		VACD	60%	Benefit of WLI?
IESS-II[112] (1978–1982)	214	VACD-HD	73%	Value of aggressive cytoreduction
		VACD-MD	56%	
First POG-CCG[135] (1988–1993)	NA	VACD	54%	Value of combination IE
		VACD + IE	69%	
Second POG-CCG[141] (1995–1998)	492	VCD + IE 48 weeks	75%	No differences between standard and dose-intensified therapy
		VCD + IE 30 weeks	76%	
ST. JUDE STUDIES				
ES-79[106] (1978–1986)	52	VACD	82% <8 cm	Tumor size as prognostic factor
			64% ≧8 cm	
EW-87[134] (1987–1991)	26	Therapeutic window with IE	Clinical responses in 96%	Combination IE is very effective in ESFT
EW-92[107] (1992–1996)	34	VCDIE × 3 VCD/IE intensification	78%	Tumor size (</≥8 cm) is not a prognostic factor with intensive treatment
CESSS				
CESS-81[107] (1981–1985)	93	VACD	Tumor size 80% <100 mL	Tumor size (</>100 mL) and histologic response are prognostic factors
			31% >100 mL	
			Viable tumor	
			79% <10%	
			31% <10%	
CESS-86[116] (1986–1991)	301	SR: VACD	52%	Intensive treatment with ifosfamide for high-risk patients
		HR: VAID	51% (10 yr)	Tumor volume >200 mL suggests poor prognosis
UKCCSG/MRC STUDIES				
ET-1[111](1978–1986)	120	VACD	36%	Tumor site is most important prognostic factor
			Extr. 52%	
			Axial 38%	
			Pelvic 13%	
ET-2[113] (1987–1993)	201	VAID	62%	Importance of administration of high-dose alkylating agents
			Extr. 73%	
			Axial 55%	
			Pelvic 41%	
EICESSS				
EICESS-137 (1992–1999)[129]	470	SR: VAID/VACD	79%/71%	Volume (>200 mL) and histologic response as prognostic factor
		HR: VAID/EVAID	54%/62%	

CESS, Cooperative Ewing's Sarcoma Study; DFS, disease-free survival; EICESS, European Intergroup Cooperative Ewing's Sarcoma Study; EVAID, etoposide, vincristine, actinomycin D, ifosfamide, doxorubicin; Extr, extremity; HD, high-dose; HR, high risk; IE, ifosfamide and etoposide; IESS, Intergroup Ewing Sarcoma Study; MD, moderate-dose; NA, not available; POG-CCG, Pediatric Oncology Group–Children's Cancer Group; SR, standard risk; UKCCSG/MRC, United Kingdom Children's Cancer Study Group and Medical Research Council; VAC, vincristine, actinomycin D, cyclophosphamide; VACD, VAC plus doxorubicin; VCD, vincristine, cyclophosphamide, doxorubicin; WLI, whole-lung irradiation.

Table 99-4 Management of Metastatic Ewing's Sarcoma Family of Tumors without Hematopoietic Stem Cell Transplantation

Study	No. of Patients	Regimen	Results: 5-Yr DFS	Comment(s)
IESSS				
IESS I–II[142] (1975–1985)	122	VACD	30%	
First POG-CCG[143] (1988–1993)	121	*A**: VACD *B*: VACD + IE	19%	Addition of IE does not improve results
EUROPEAN STUDIES				
ET-1[111] (1978–1986)	22	VACD	9%	
ET-2[113]	42	VAID	23%	
EICESS[122] (1990–1995)	171	VAID ± etoposide	27% Lungs: 34% Bone/bone marrow: 28% Combined: 14%	Pulmonary metastasis managed with RT: 40%
INTENSIFICATION PROTOCOLS				
First POG-CCG[143] (1988–1993)	60	*C*: VACD + IE	26%	Intensification does not improve results Incidence of t-AML: 22.7%
EW-92[107]	19	VCDIE × 3 VCD/IE	27%	Intensification does not improve results High toxicity Incidence of t-AML: 8%

±, with or without; DFS, disease-free survival; EICESS, European Intergroup Cooperative Ewing's Sarcoma Study; IE, ifosfamide, etoposide; IESS, Intergroup Ewing Sarcoma Study; POG-CCG, Pediatric Oncology Group–Children's Cancer Group; RT, radiation therapy; t-AML, therapy-related acute myelogenous leukemia; VACD, vincristine, actinomycin D, cyclophosphamide, doxorubicin; VCD, vincristine, cyclophosphamide, doxorubicin.

*POG-CCG study used three different regimens: A, B, and C.

Box 99-2. ST. JUDE CHILDREN'S RESEARCH HOSPITAL APPROACH TO MANAGEMENT OF EWING'S SARCOMA FAMILY TUMORS

At St. Jude Children's Research Hospital, for patients with nonmetastatic disease, regardless of the size and site of the tumor, intensive multiple-agent chemotherapy, with alternating courses of vincristine, cyclophosphamide, and doxorubicin with ifosfamide and etoposide, is used. Local control is undertaken after completion of approximately four courses of induction chemotherapy. If the disease is considered resectable, surgery is the treatment of choice for local control, and it is always performed with curative intent. Radiation therapy is used for unresectable disease and for close or microscopic surgical margins. The same approach is followed for patients with metastatic disease to the lungs, only with addition of radiation therapy to the lungs.

For patients with bone or bone marrow metastasis, the role of intensive chemotherapy and consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue is under ongoing evaluation. In these patients, aggressive surgical resection for local control of the primary tumor and bone metastases is performed.

All patients with recurrent disease receive second-line systemic therapy. Patients with local recurrence undergo aggressive surgery when possible, and patients with metastatic disease to the lungs receive whole-lung irradiation.

Total-body irradiation does not seem to provide any additional benefit and only adds toxicity.[152,153] The European Cooperative Group is conducting a randomized study to evaluate the role of HSCT in the care of patients with metastatic Ewing's sarcoma.

Improvement in outcome among patients with ESFT also must be attributed to improvement in local control, which is largely related to advances in planning radiation therapy[107,108] and better surgical approaches. Advances in systemic therapy by means of incorporation of new drugs and treatment intensification also appear to contribute to better local control.[113,155–157] With current multimodality intensive protocols, rates of local recurrence have decreased significantly, and little difference in efficacy has been observed between surgery and radiation therapy for local control.[109,155,156,158] Surgery continues to offer slightly better results, but this observation is biased by the fact that small lesions are more likely to be managed surgically.[111,159–161] For unresectable tumors or in case of gross residual disease, recommended doses are 55 to 60 Gy. Doses of 40 to 45 Gy are used for microscopic disease. The risk of secondary sarcoma after radiation therapy is not negligible.[162] This risk is dose-dependent, but use of lower doses of radiation therapy has been associated with higher local recurrence rates.[163]

NEUROBLASTOMA

Epidemiology

Neuroblastoma is the most common extracranial solid tumor of childhood, accounting for 8% to 10% of all pediatric cancers.[164] In

the United States, the annual incidence is approximately 8 new cases per 1 million children per year with 550 newly diagnosed cases. The median age at diagnosis is 2 years. Most (85%) of the cases are diagnosed by the age of 5 years. Neuroblastoma is extremely rare in children older than 10 years. Familial cases occur. Neuroblastoma also has been found in patients with neurofibromatosis, Hirschsprung's disease, Beckwith-Wiedemann syndrome, and fetal hydantoin syndrome.[165–169] Microscopic neuroblast nodules are found in the adrenal glands of 2% to 3% of infants who die of nonmalignant causes before 3 months of age.[170] It is uncertain whether these nodules represent spontaneous regression of congenital neuroblastoma or maturation of the tumor into asymptomatic benign tumors.

Mass screening programs for detection of neuroblastoma in early infancy with assays for urinary catecholamine metabolites have been conducted in Japan, Germany, and the United States.[171–173] In general, patients with neuroblastoma detected in these programs have early-stage disease and enjoy otherwise excellent outcome.[174,175] Mass screening, however, has not resulted in a reduction in deaths from neuroblastoma. In addition, early detection has not changed outcome among patients with tumors that have biologic features associated with a poor prognosis.

Tumor Biology

Neuroblastoma originates in neural crest cells of the sympathetic nervous system and, not unexpectedly, secretes a variety of neurogenically derived substances, including catecholamines, neuron-specific enolase (NSE), and ferritin.[176–178] Urinary excretion of abnormally high levels of catecholamine metabolites occurs in 75% to 90% of patients and is related to the degree of tumor differentiation. The metabolites most often measured in evaluation of suspected neuroblastoma are urinary vanillylmandelic acid and homovanillic acid. Levels of these catecholamines are sensitive indicators of disease status. At diagnosis, other biologic markers, such as NSE, serum ferritin, and ganglioside G_{D2}, are present in high concentration in the serum of most patients with neuroblastoma.[179–182] None of these biologic markers is specific, but their presence at diagnosis may be associated with the extent of disease.

Cytogenetic studies of neuroblastoma have demonstrated chromosomal abnormalities in most cases. The most common cytogenetic abnormalities in neuroblastoma are double-minute chromatin bodies (DM), homogeneously staining regions (HSRs), and nonrandom deletion or loss of heterozygosity of the short arm of chromosome 1.[183–187] DMs and HSRs both represent cytogenetic manifestations of amplified sequences of the *MYCN* cellular oncogene.[188,189] Amplified *MYCN* (more than 10 copies per cell) is a feature in approximately 30% of neuroblastomas. It is associated with the presence of advanced disease at diagnosis and poor outcome, even in patients who have early-stage disease or who come to medical attention in infancy.[190,191] The DNA content of the tumor (ploidy) has been shown to correlate with therapeutic outcome and survival among infants with this tumor. Infants with hyperdiploid tumors (DNA index greater than 1.0) have a more favorable outcome than those with diploid tumors (DNA index, 1.0).[192–194] Results suggest that the presence of either *MYCN* amplification or diploid cellular DNA tumor content identifies whether an infant has a poor prognosis with current therapeutic regimens, independent of stage.[193,195,196] For children older than 24 months with disseminated disease, however, the DNA content of the tumor does not appear to have prognostic importance.[192,194] Recent studies suggest that additional cytogenetic imprints such as loss of heterozygosity at 1p36 and 11q23 confer an aggressive phenotype.[197]

Pathology

Neuroblastoma is one of the small round blue cell tumors of childhood. It originates from neural crest cells from within the sympathetic nervous system. Neuroblastoma can be classified pathologically into three broad histologic subgroups: neuroblastoma, ganglioneuroblastoma, and ganglioneuroma[198,199] (Fig. 99-8). These subgroups appear to recapitulate stages in the normal differentiation of neural crest stem cells. For example, neuroblastoma is the most primitive entity and is characterized by diffuse growth of undifferentiated neuroblastic cell nests irregularly separated by thin fibrovascular septa[200,201] (see Fig. 99-8A). By contrast, benign ganglioneuroma consists of mature ganglion cells embedded in bulky stroma composed of Schwann cell sheets enveloping neuritic processes and perineural and endoneural elements (see Fig. 99-8C). Between these two extremes is the transitional form known as ganglioneuroblastoma (see Fig. 99-8B). These transitional forms have been subclassified into intermixed and nodular diffuse ganglioneuroblastoma. Composite (nodular) tumor is a ganglioneuroma that contains one or more discrete nodules of pure neuroblastoma. Intermixed (diffuse) tumor contains a mixture of primitive and differentiating neuroblasts with bizarre, immature, and mature ganglion cells. Patients frequently have tumors with mixtures of these cell types, and evidence supports the clinical observation that neuroblastoma can sometimes mature into benign ganglioneuroma. Spontaneous regression and therapy-induced maturation can occur.[202]

In 1999, the International Neuroblastoma Pathology Classification was established to standarize the terminology and criteria for the prognostic evaluation of the morphologic features of neuroblastic tumors in an age-linked framework.[200]

Clinical Manifestations

The clinical manifestations of neuroblastoma are varied. Nonspecific constitutional signs and symptoms, such as fever, general malaise, and pain, are frequent initial features. The most common sites of primary tumors are the abdomen (adrenal gland or paraspinal ganglia) and the thorax (usually the posterior mediastinum). In infants, the distribution is slightly different in that a higher proportion of primary tumors occur in the thoracic cavity than is the case in older children. Common manifestations include a hard, painless mass in the neck, a localized intrathoracic mass found incidentally on a chest radiograph, and a palpable abdominal mass, according to the location of the tumor. A palpable abdominal mass can result from an enlarging primary adrenal or retroperitoneal tumor or from hepatomegaly secondary to tumor metastasis. Children may appear chronically ill and irritable and have periorbital ecchymosis, scalp nodules, and bone pain from widespread metastasis to the bone marrow or bone (Fig. 99-9; see also Fig. 99-8D). Lower limb paresis secondary to epidural extension of a primary paraspinal tumor growing through the intervertebral foramen can cause signs of spinal cord compression. Intermittent abdominal pain, malaise, failure to gain weight, and recurrent, unexplained fever may be present for prolonged periods before neuroblastoma is diagnosed.

Seventy-five percent of patients with neuroblastoma have metastatic disease at the time of diagnosis. The most common sites of metastasis are lymph nodes (local or distant), bone marrow, liver, skin, orbit, and bone (facial bones, skull, appendicular skeleton). Nearly one half of patients have widespread skeletal metastasis at diagnosis.[203,204] The bones of the skull and orbit frequently are affected, so proptosis, ecchymosis, and masses beneath the scalp are frequent findings (see Fig. 99-9). Lung metastatic lesions are extremely uncommon when the patient is first examined.[205] Horner's syndrome (ipsilateral miosis, ptosis, and anhydrosis) may be present in patients with lesions originating in the cervical or upper thoracic sympathetic ganglia. Less frequent is the syndrome of opsomyoclonus, manifested as acute cerebellar encephalopathy, truncal ataxia, and rapid and random eye movements (so-called dancing eyes, dancing feet).[206] The pathophysiologic mechanism of this syndrome is unknown, but metabolic and immunologic causes have been invoked. A syndrome of chronic watery diarrhea also may occur in patients with neuroblas-

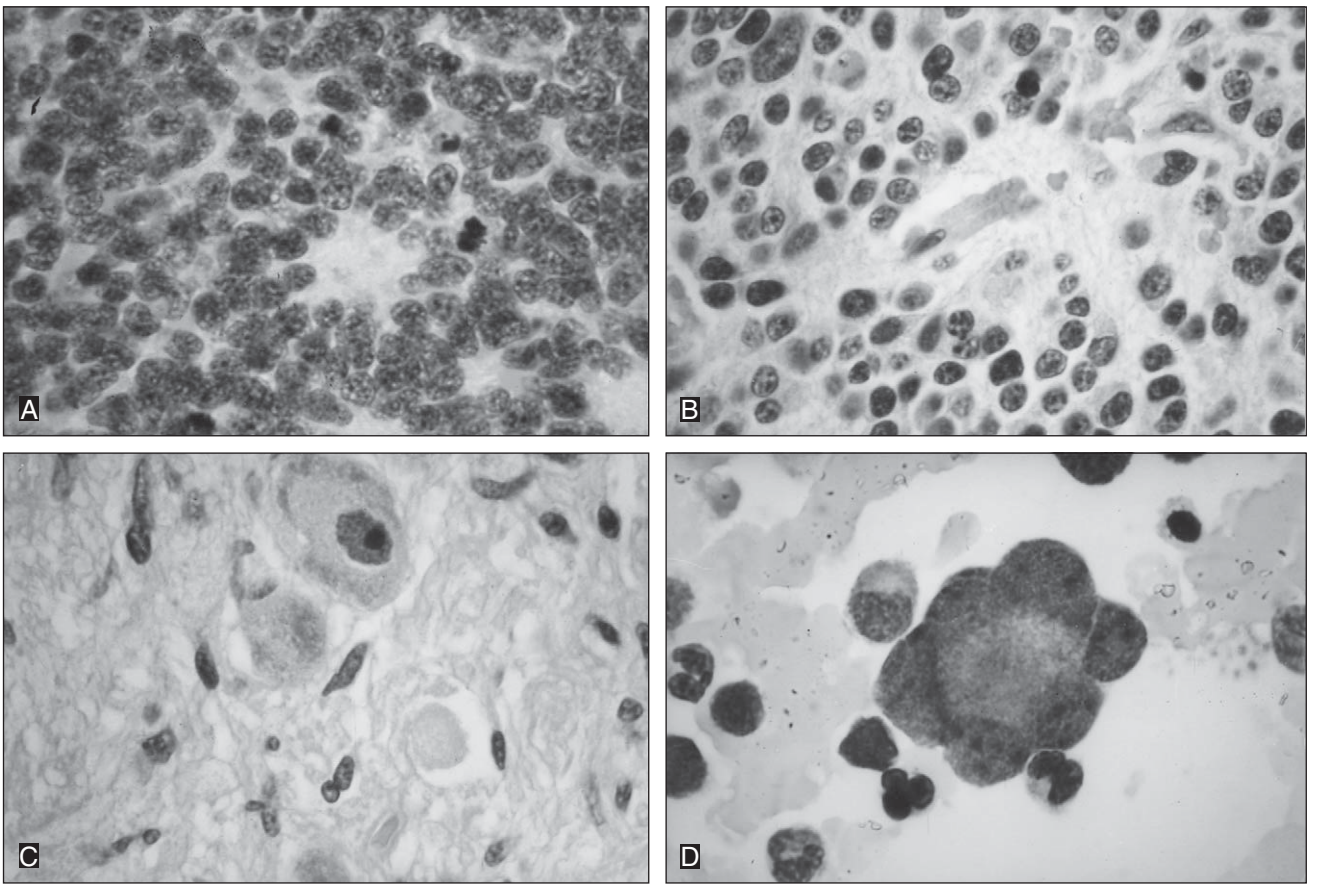


Figure 99-8 • **A,** Neuroblastoma with nest of dense primitive cells surrounding a fibrillar center. **B,** Ganglioneuroblastoma consisting of primitive cells but with increased amounts of fibrillar material. **C,** Ganglioneuroma with well-differentiated ganglion cells, Schwann cells, and nerve bundles. **D,** Bone marrow involvement with metastatic neuroblastoma forming a pseudorosette.

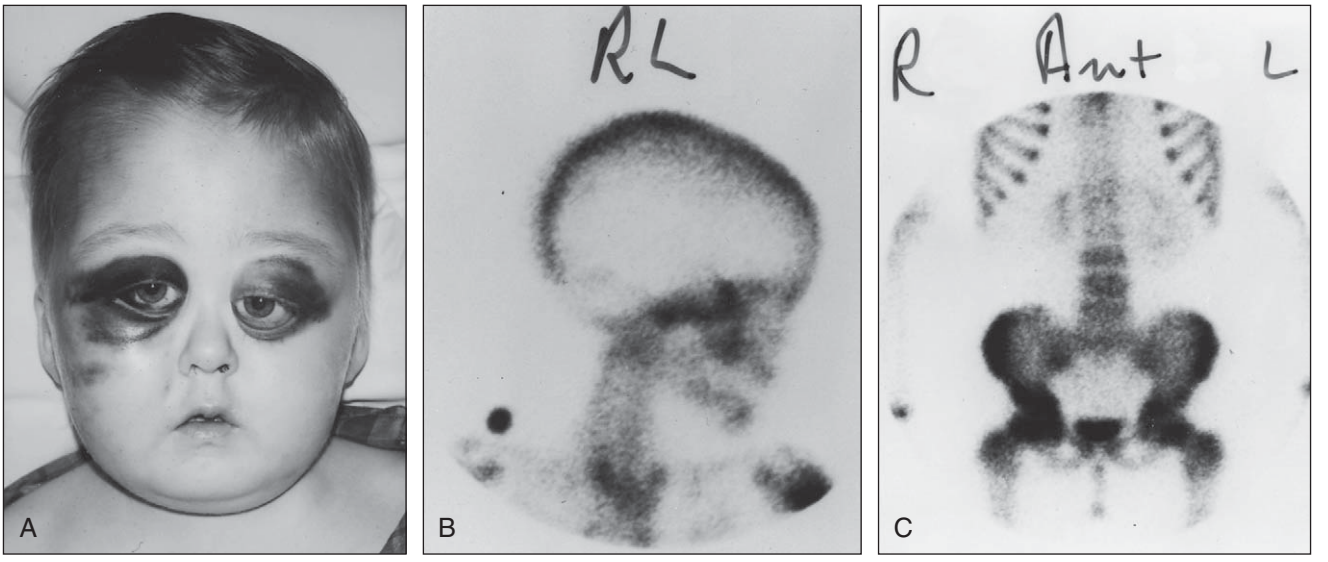


Figure 99-9 • **A,** Periorbital ecchymosis secondary to metastatic orbital neuroblastoma. **B,** Radionuclide bone scan shows orbital and calvarial metastatic disease. **C,** Bone scan shows diffuse pelvic bone involvement with metastatic neuroblastoma.

toma. Increased serum levels of vasoactive intestinal peptide, which lead to increased intestinal motility and secretions, have been found in some cases.

Laboratory and Radiologic Evaluation

When neuroblastoma is suspected, evaluation should be performed to establish the diagnosis, determine the extent of disease, and obtain tumor material for molecular and genetic analyses. The physical examination should include special attention to look for blood pressure abnormalities, asymmetrical pupil size, facial sweating, lower limb weakness and other signs of spinal cord compression, and evidence of increased intracranial pressure. In addition, during the clinical examination, the size of palpable masses, enlarged lymph nodes, cutaneous lesions, and the liver should be carefully documented.

Laboratory studies include complete blood cell count, renal and liver function studies, coagulation screen, urinalysis, and urine catecholamine assay. Serum often is obtained for NSE, ferritin, and ganglioside G_{D2} determinations because the results may be helpful in prognosis.[177,207–209]

Staging of neuroblastoma requires radiologic studies and marrow aspiration and biopsy to determine the extent of local disease and distant spread. The minimal evaluation for metastatic disease includes radionuclide skeletal scintigraphy and bone marrow aspiration. CT generally has replaced intravenous pyelography, arteriography, and inferior vena cavography (Fig. 99-10). Ultrasonographic studies of the abdomen and pelvis may be useful in evaluation of mass lesions and the degree of compression of vital structures causing secondary complications. MRI may further improve the accuracy of determination of the anatomic extent of disease, especially in evaluation of tumors impinging on the spinal cord and assessment for the presence of hepatic metastasis.[210] CT- or MRI-based myelography is necessary in evaluation of all patients with neurologic evidence of cord involvement.[211] Scans performed with radionuclides such as ^{131}I-*m*-iodobenzylguanidine (MIBG) may be more accurate and sensitive for detection of nonosseous as well as osseous disease.[212] Newer modalities such as neural cell-specific monoclonal antibody conjugated to ^{131}I or ^{123}I currently are investigational. When tumor material is obtained, it should be submitted for determination of DNA content (tumor cell ploidy), detection of *MYCN* genomic amplification, and cytogenetic analysis.

The differential diagnosis suggested by the early manifestations of the tumor is broad because the initial signs and symptoms can be so vague. The presence of an abdominal mass may suggest Wilms' tumor, hydronephrotic kidney, enlarged spleen or liver, lymphoma, germ cell tumor, and mesenteric cyst. Compression of vital structures in the neck and mediastinum can cause superior vena cava syndrome indistinguishable from that caused by other tumors.[213] Persistent diarrhea suggests the presence of a malabsorptive state. Arterial hypertension may be attributed to intrinsic renal disease or pheochromocytoma.[214] Bone pain can simulate rheumatic fever, rheumatoid arthritis, osteomyelitis, and acute leukemia. When initial signs are attributable to widespread lymphatic metastasis, a broad range of possibilities in the differential diagnosis, including primary tumor of the lymphoreticular system, storage disease, acute infection, and primary hematologic disorder, must be considered.

The diagnosis of neuroblastoma is established by pathologic evaluation of tumor tissue obtained at biopsy or by documentation of bone marrow involvement at bone marrow trephine biopsy or aspiration with the presence of characteristic clumps or syncytia of tumor cells, together with increased urine or serum levels of catecholamines or metabolites.[215] If the histologic diagnosis is equivocal, genetic features characteristic of neuroblastoma, such as deletion of 1p or *MYCN* genomic amplification, support the diagnosis.

Several staging systems have been used to classify disease extent. The Evans and Pediatric Oncology Group staging systems historically were the most widely used in the United States. To facilitate comparison of clinical studies, the International Neuroblastoma Staging System (INSS; Table 99-5), which is based on clinical, radiographic, and surgical evaluation, was developed by consensus of major pediatric oncology groups in the United States, Europe, and Japan.[216–219] The INSS uses the most important components of the Evans (e.g., midline extension) and the Pediatric Oncology Group (e.g., histologically positive or negative lymph nodes) systems. The main differences between these systems relate to surgical-pathologic staging and definitions distinguishing grossly unresected localized tumors from regional disease.[219]

Prognostic Factors

Although many factors have been investigated and purported to have prognostic significance in neuroblastoma, the most significant in prediction of cure are patient age and stage at diagnosis.[220] Children with low-stage disease have a good prognosis, regardless of age. In general, extent of disease at diagnosis is inversely related to cure. In infants, the DNA content of tumor cells has been reported to be

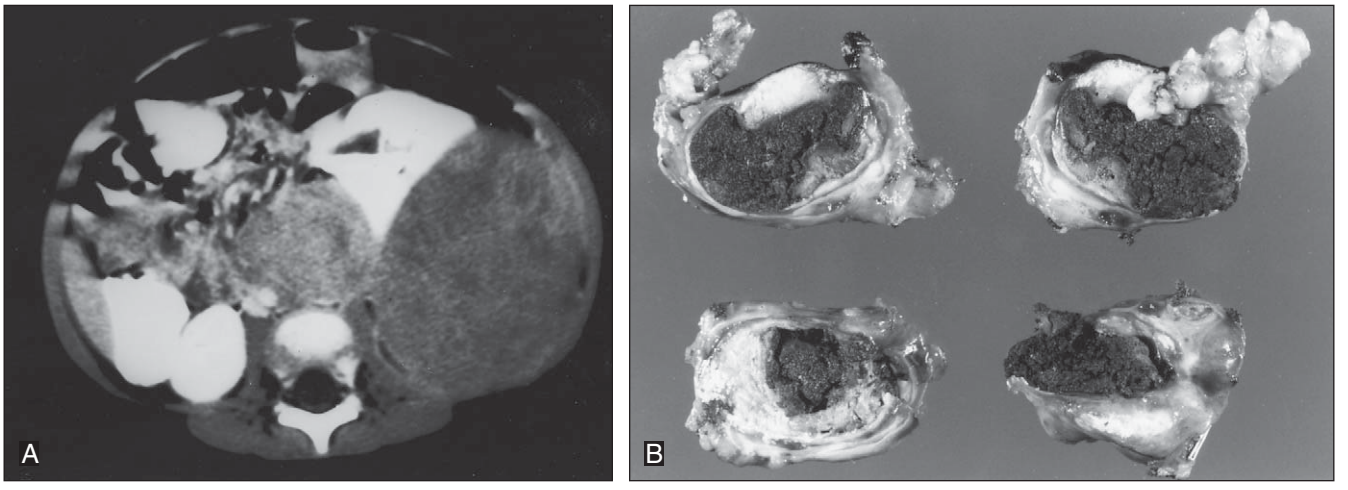


Figure 99-10 • **A,** Computed tomographic scan shows adrenal neuroblastoma at diagnosis. **B,** Serial sections through a resected adrenal neuroblastoma show large areas of diffuse hemorrhage and calcification.

Table 99-5 International Staging System for Neuroblastoma

Stage	Description
1	Localized tumor confined to area of origin; complete gross excision with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes microscopically negative
2A	Unilateral tumor with incomplete gross excision; identifiable ipsilateral and contralateral lymph nodes microscopically negative
2B	Unilateral tumor with complete or incomplete gross excision; positive ipsilateral lymph nodes; identifiable contralateral lymph nodes microscopically negative
3	Unresectable unilateral tumor infiltrating across the midline with or without regional lymph node involvement; or unilateral tumor with contralateral lymph node involvement; or midline tumor with bilateral lymph node involvement
4	Metastatic tumor involvement to distant lymph nodes, bone, bone marrow, liver, or other organs (except as defined in stage 4S)
4S	Localized primary tumors as defined in stage 1 or 2 with dissemination limited to liver, skin, or bone marrow involvement <10% (but not bone); limited to infants younger than 1 year of age

predictive of response to chemotherapy and ultimate outcome. Infants with hyperdiploid tumors fare better than do those with diploid tumors.[194] In children with metastatic disease, the most significant prognostic variable is age at diagnosis. Children younger than 12 months at diagnosis have a significantly greater chance of cure.[221,222] In older children with disseminated disease, the prognosis is dismal, although improvements in response and survival have been reported with modern treatment modalities.

A variety of biologic markers of neuroblastoma have been used to identify whether a patient is at prognostically low, intermediate, or high risk. These markers include tumor markers such as urinary catecholamine excretion and serum levels of ferritin, NSE, LDH, and ganglioside G_{D2}. Histologic subclassification based on degree of differentiation or presence or absence of stroma, mitoses, or karyorrhexis also has been used as a prognostic indicator (Shimada histopathologic classification). However, identification of various biologic and genetic features, such as the karyotype, DNA index determined by flow cytometry, *MYCN* copy number, deletion of chromosomal regions on 1p, P-glycoprotein expression, and expression of the nerve growth receptor TRK-A, has defined subsets of patients with different outcomes after therapy.[184,195,196,223,224] For example, *MYCN* amplification can be used as a marker of poor outcome independent of age, whereas TRK-A appears to be a marker of favorable outcome.[225,226] Clinical studies are being conducted in an attempt to correlate the most informative combination of biologic markers, age, and stage to develop appropriate risk-directed therapies (Table 99-6).

Treatment

A complete pathologic evaluation in conjunction with assessment of clinical features is important, because management of neuroblastoma is based on extent of disease. Accurate staging of the tumor at diagnosis is essential. Staging includes diagnostic imaging, pathologic

Table 99-6 Risk Categorization for Neuroblastoma on the Basis of Clinical and Biologic Features

INSS Stage	Age	*MYCN* Status	Shimada Features	DNA Ploidy*	Risk Group
1	0–21 yr	Any	Any	Any	Low
2A/2B	<365 d	Any	Any	Any	Low
	≥365 d–21 yr	Nonamplified	Any	—	Low
	≥365 d–21 yr	Amplified	Favorable	—	Low
	≥365 d–21 yr	Amplified	Unfavorable	—	High
3	<365 d	Nonamplified	Any	Any	Intermediate
	<365 d	Amplified	Any	Any	High
	≥365 d–21 yr	Nonamplified	Favorable	—	Intermediate
	≥365 d–21 yr	Nonamplified	Unfavorable	—	High
	≥365 d–21 yr	Amplified	Any	—	High
4	<365 d	Nonamplified	Any	Any	Intermediate
	<365 d	Amplified	Any	Any	High
	≥365 d–21 yr	Any	Any	—	High
4S	<365 d	Nonamplified	Favorable	>1	Low
	<365 d	Nonamplified	Any	1	Intermediate
	<365 d	Nonamplified	Unfavorable	Any	Intermediate
	<365 d	Amplified	Any	Any	High

INSS, International Neuroblastoma Staging System.

*DNA ploidy: DNA index (DI) >1 or 1. Hypodiploid tumors (DI <1, considered favorable ploidy) are treated as tumors with DI >1. *Note*: This risk categorization is current but will be modified as new clinical trials validate its use.

assessment of lymph node involvement in locoregional disease, liver biopsy in the case of primary abdominal disease in infants, and determination of the presence of hematogenous dissemination (usually to bone or to bone marrow).[227] Patients with tumors localized to one side of the midline or that cross the midline without encasement of major blood vessels are candidates for primary surgical resection.[228–230] With local disease, complete gross surgical resection gives an excellent chance of cure without additional therapy. If the patient has localized unresectable disease, surgical procedures that carry a high potential for morbidity should be avoided because of the excellent outcome with chemotherapy in this setting. If the tumor cannot be excised because it encases major blood vessels, surgery is performed for diagnostic purposes or for palliation if the tumor is compressing a vital organ. With dumbbell tumors with spinal cord compression, for example, rapid response to chemotherapy generally obviates laminectomy.[231] In patients who have disseminated disease when they come to medical attention, initial aggressive surgical approaches have been shown to be of no significant benefit. The potential benefit of resection of bulky primary tumors after reductive chemotherapy in disseminated disease (delayed or second-look resection) is currently under investigation.

Radiation therapy often is used for management of neuroblastoma and is particularly useful in the management of patients with tumors that are localized but unresectable, even after initial chemotherapy and second-look surgery. Because of the high frequency of metastatic disease, radiation therapy has a relatively limited role in initial overall treatment for a child with neuroblastoma. Indications for radiation therapy include control of local tumors unresponsive or resistant to chemotherapy and not amenable to surgical extirpation, palliative management of unresectable or metastatic disease, and management of 4S neuroblastoma (in selected cases). The last indication is based on the observation that infants with bona fide stage 4S disease sometimes respond to subtherapeutic doses of radiation (400 to 800 cGy) delivered to ports that do not encompass all known sites of disease.

Chemotherapy is the primary modality of treatment for most children with neuroblastoma, because the disease frequently is widespread at diagnosis.[232–234] Box 99-3 outlines the approach to management of neuroblastoma used at St. Jude Children's Research Hospital. A variety of single agents (cyclophosphamide, melphalan, doxorubicin, cisplatin, epipodophyllotoxin, vincristine) produce responses in patients with neuroblastoma, but significant and durable responses have been achieved only with combination chemotherapy.[235–237] In general, pairs of these drugs, such as cyclophosphamide plus doxorubicin or cisplatin plus etoposide, delivered in a cytokinetically rational manner, are more effective in producing responses than are single agents. Although improvement in survival of infants with advanced-stage disease and children with locally unresectable disease has resulted from implementation of various chemotherapeutic regimens, the outlook for older children with advanced disease has not changed dramatically. Only 20% to 25% of these patients are alive at 5 years from diagnosis.[238] Among older children, however, the complete response rate and disease-free interval have increased with more intensive combination chemotherapy, encouraging further development and refinement of this therapy. Recent studies report a subset of 12- to 18-month-old children with favorable tumor biologic features who have a much greater chance of survival with intensive therapy.[222]

Some current therapeutic regimens for neuroblastoma are so intensive that myelosuppression can be the dose-limiting toxicity. This problem can be overcome with hematopoietic stem cell transplantation. High-dose chemotherapy with bone marrow transplantation may be useful in the care of patients with a poor long-term prognosis who have achieved complete remission or at least substantial partial remission with chemotherapy.[239–243] The propensity of neuroblastoma to involve bone marrow has spurred development of various purging strategies, including tumor cell depletion with monoclonal antibodies and ex vivo chemotherapy, to facilitate autologous transplantation. Results with various transplantation protocols, both autologous and allogeneic, suggest a modest survival advantage for these aggressive regimens.[243,244]

Improvements in supportive care, including use of hematopoietic growth factors, may allow shortening of the intervals between treatment courses. They also may allow increases in the dose intensity of currently available chemotherapeutic agents in the treatment of patients with advanced-stage disease and decreases in toxicity among infants. In addition, parallel clinical studies of newer biologic therapies, such as those using differentiation agents and immunomodulators, in a setting of minimal residual disease or genetically engineered tumor vaccines are expected to form the basis for future therapeutic gains.[245,246]

Box 99-3. ST. JUDE CHILDREN'S RESEARCH HOSPITAL APPROACH TO MANAGEMENT OF NEUROBLASTOMA

At St. Jude Children's Research Hospital, a risk-categorization algorithm is used in which therapy for neuroblastoma is prescribed on the basis of clinical and biologic features. For patients with completely resected tumors independent of age or tumor biology, no additional treatment is indicated after surgery; recommended management consists of close monitoring and follow-up evaluation. In the event of disease recurrence, further surgical treatment with or without chemotherapy is instituted. Similarly, patients younger than 1 year of age with incomplete resection or limited nodal metastasis (in the absence of unfavorable biologic features) undergo no further therapy after surgery. Patients younger than 1 year with unresectable tumors (i.e., stage 3) and absence of the *MYCN* gene amplification receive a shortened course of chemotherapy comprising cyclophosphamide, doxorubicin, etoposide, and carboplatin. Chemotherapy is administered to patients with epidural tumor in an attempt to avoid laminectomy. All patients older than 1 year with metastatic disease or with unfavorable biologic features (e.g., *MYCN* gene amplification) or histologic findings are enrolled in research protocols that incorporate an induction phase with alkylating agents (e.g., cyclophosphamide), cisplatin, doxorubicin, and etoposide followed by surgery for removal of the primary lesion and a consolidation phase with high-dose chemotherapy, with or without irradiation and autologous hematopoietic stem cell transplantation, followed by 6 months of oral retinoic acid. Pilot studies incorporating new agents, such as topotecan and irinotecan, also are under investigation. When primary treatment fails, experimental therapies with biologic agents (anti-G_{D2} antibodies), metaiodobenzylguanidine (MIBG) therapy, or new cytotoxic agents usually are recommended.

WILMS' TUMOR

Epidemiology

Wilms' tumor, or nephroblastoma, is the most common primary malignant renal neoplasm of childhood. Although relatively rare, this disease has served as a paradigm for multimodality management of childhood solid tumors. Owing to refinements in surgery, chemotherapy, and radiation therapy, the overall cure rate for Wilms' tumor exceeds 85%. Studies of Wilms' tumor genetics have laid the foundation for our understanding of tumor suppressor genes and genomic imprinting.

The annual incidence of Wilms' tumor is 8 cases per 1 million children younger than 15 years, representing 6.3% of cases of childhood cancer.[247] In the United States, approximately 460 new cases are diagnosed each year, making Wilms' tumor the fourth most common pediatric cancer by specific histologic type.[247] The incidence

of Wilms' tumor varies with race and ethnic group. The range is 2.5 cases per 1 million Chinese children to 10.9 cases per 1 million African-American children.[248] Girls have a slightly increased risk for Wilms' tumor, with a male-to-female ratio of 0.92 to 1.00. The mean age at diagnosis is 44 months for unilateral disease and 31 months for bilateral disease. According to the Knudson two-hit model of tumorigenesis, the earlier age at onset of bilateral Wilms' tumor represents a genetic predisposition to the disease. Wilms' tumor in the adult population is rare, although numerous cases have been reported.[249,250] Although results of older studies indicate that the prognosis for adult Wilms' tumor is unfavorable, newer reports demonstrate cure of both localized and advanced disease with treatment regimens similar to those used for children.[251,252]

Familial Wilms' tumor is uncommon, occurring in only 1.5% of affected patients.[253] Most cases of familial Wilms' tumor occur in distant relatives, rather than in parents or siblings. Sixteen percent of cases of familial Wilms' tumor are bilateral, compared with 7% of sporadic cases. Unlike retinoblastoma, familial Wilms' tumor is bilateral in only a small number of cases. Conversely, only a small proportion (3%) of cases of bilateral Wilms' tumor is familial. The mean ages at diagnosis of familial unilateral and bilateral disease are 35 months and 16 months, respectively.

Tumor Biology

Although Wilms' tumor was one of the original paradigms of the Knudson two-hit model of cancer formation,[254] it has become apparent that several genetic events participate in tumorigenesis for this neoplasm. *WT1* was the first Wilms' tumor gene identified and is the most completely characterized Wilms' tumor gene to date. The discovery of *WT1* began with the observation that patients with a combination of aniridia, genitourinary anomalies, and mental retardation (WAGR syndrome) are at high (greater than 30%) risk for development of Wilms' tumor. Cytogenetic analysis in persons with WAGR syndrome has revealed large deletions at chromosomal band 11p13, which later was found to encompass a contiguous set of genes, including *PAX6*, the gene responsible for aniridia,[255] and *WT1*.[256–258] Patients with sporadic aniridia (*PAX6* defect with normal *WT1*) are not at increased risk for Wilms' tumor.[259] *WT1* encodes a transcription factor that is critical to normal kidney and gonadal development, but whose precise role in tumorigenesis is undefined. Although germinal deletions or mutations in *WT1* have been documented in almost all patients with WAGR syndrome and the related Denys-Drash syndrome, only a small number of patients with seemingly sporadic Wilms' tumor carry *WT1* mutations in the germline (5%) or in tumor tissue (6% to 18%).[260–263] Although *WT1* is a bona fide tumor suppressor gene, its role in sporadic Wilms' tumor development is limited.

A second Wilms' tumor-associated condition is Beckwith-Wiedemann syndrome, which is an overgrowth disorder that manifests as high birth weight, macroglossia, organomegaly, hemihypertrophy, neonatal hypoglycemia, abdominal wall defects, and ear pits and creases. Patients with this syndrome have a 5% to 10% risk for development of Wilms' tumor but also are predisposed to the development of other malignant tumors, such as hepatoblastoma, adrenocortical carcinoma, neuroblastoma, and rhabdomyosarcoma.[264] Beckwith-Wiedemann syndrome maps to chromosomal band 11p15, sometimes called *WT2*, because loss of heterozygosity at this locus has been detected in Wilms' tumor.[265,266] Although the precise *WT2* gene is undefined, molecular characterization of the *WT2* locus has revealed several genes that may play a role in tumorigenesis. These genes are imprinted, which means that they are preferentially expressed from one of the two parental alleles. Loss of imprinting, leading to aberrant messenger RNA and protein expression, has been postulated as a mechanism of tumor formation. Genes at the *WT2* locus that have been suggested to contribute to tumorigenesis for this neoplasm include *IGF2, H19*, and $p57^{Kip2}$ (*CDKN1C*).[267–273]

Genes and loci other than *WT1* and *WT2* have been implicated in the molecular pathogenesis of Wilms' tumor. In two studies, investigators found that approximately 15% of Wilms' tumors have activating mutations of β-catenin, a central effector of the Wnt signaling pathway.[274,275] Of interest, the β-catenin mutations were strongly associated with *WT1* mutations, indicating that these two genes operate in distinct pathways and may collaborate in the genesis of Wilms' tumor. Genetic linkage analysis has identified two familial Wilms' tumor loci, called *FWT1* and *FWT2*, on chromosomes 17 and 19, respectively.[276,277] Identifying the pertinent genes at these loci is an area of active investigation. It was recently recognized that some cases of familial Wilms tumor are associated with biallelic *BRCA2* mutations. Whereas monoallelic *BRCA2* mutations are associated with breast and ovarian cancers, individuals with biallelic mutations have the D1 type of Fanconi anemia and are predisposed to the development of Wilms' tumor and brain tumors.[278] Loss of heterozygosity at 1p and 16q has been found in 10% to 20% of Wilms' tumors. Loss at either or both loci is associated with adverse prognosis and is used for treatment stratification in the current COG studies.[279] Cytogenetic and loss of heterozygosity analyses have revealed recurrent abnormalities of 7p, but the clinical and biologic significance of these findings is unknown.[280,281] Finally, mutations in the *TP53* gene are observed in most cases of anaplastic histologic features of Wilms' tumor, implicating a role for this gene in progression from favorable to anaplastic histologic type.[282–284]

Pathology

Classic Wilms' tumor consists of blastemal, stromal, and epithelial elements, although tumors do not necessarily contain all three (Fig. 99-11). Because Wilms' tumor can be recognized with standard hematoxylin and eosin staining, the role of ultrastructural or immunohistochemical studies is limited. Other childhood renal neoplasms that must be considered in the differential diagnosis for Wilms' tumor are clear cell sarcoma of the kidney, rhabdoid tumor of the kidney, congenital mesoblastic nephroma, renal cell carcinoma, and soft-tissue sarcoma of the kidney.

An important advance in the care of patients with Wilms' tumor has been appreciation of the prognostic importance of histologic subtype. In 1978, Beckwith and Palmer published the results of a detailed histopathologic review of the cases of patients entered in the first National Wilms' Tumor Study (NWTS).[285] Approximately 6% of the Wilms' tumor specimens contained anaplasia, a term used to describe nuclear enlargement and atypia with irregular mitotic figures

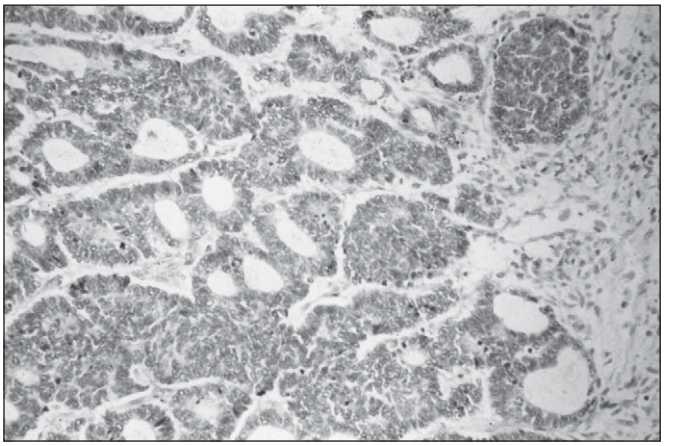


Figure 99-11 • Triphasic Wilms' tumor with well-defined tubules surrounded by dense clusters of blastemal cells and zones of pale-staining stromal differentiation (×20).

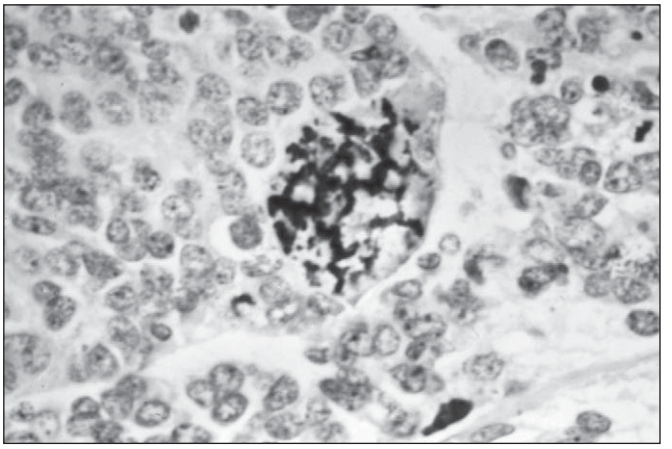


Figure 99-12 • Anaplastic Wilms' tumor with several enlarged, hyperchromatic, bizarre-appearing nuclei (×60).

(Fig. 99-12). The presence of anaplasia was prognostically significant: 11 (44%) of 25 patients with anaplasia died of tumor, whereas only 26 (7.1%) of 364 patients without anaplasia died of tumor. Results of subsequent studies by NWTS investigators, studies by the International Society of Pediatric Oncology (SIOP), and a United Kingdom Wilms' tumor study confirmed the adverse prognostic significance of anaplastic histologic features.[286,287]

Nephrogenic rests are foci of embryonal kidney cells that persist abnormally into postnatal life. They are present in approximately 1% of newborn kidneys and usually regress or differentiate by early childhood.[288] Because nephrogenic rests are present in the kidneys of approximately 40% of patients with Wilms' tumor, it is presumed that the rests represent Wilms' tumor precursors. Current models of tumorigenesis for this neoplasm propose that a mutation in a tumor suppressor gene, such as *WT1*, predisposes to nephrogenic rests, which may sustain additional mutations and transform into a Wilms' tumor.[289]

Clinical Manifestations and Patterns of Spread

Wilms' tumor typically manifests as an asymptomatic abdominal mass discovered by a parent or a health care practitioner. The mass is smooth and firm, is fixed in position, and often extends across the midline. Abdominal pain, fever, anemia, hematuria, and hypertension are other common signs and symptoms observed in 20% to 30% of children with Wilms' tumor.[290] Constitutional signs and symptoms (e.g., weight loss, cachexia, bone pain) are unusual manifestations of Wilms' tumor.

Wilms' tumor can spread both locally and hematogenously. Local spread typically occurs into the renal hilar structures and may penetrate the renal capsule. These tumors also have a propensity to invade the renal vein and form thrombi in the inferior vena cava, sometimes progressing as far as the right atrium. Local and distant lymph node involvement can occur. The most common sites of hematogenous metastasis are the lungs and liver.

Laboratory and Radiologic Evaluation

The goal of imaging before Wilms' tumor therapy is to define the extent of disease, assess the contralateral kidney, and determine whether tumor thrombus is present. Ultrasonography with Doppler technique is the recommended first-line study for Wilms' tumor because it allows panoramic examination of the abdomen, including the patency of the inferior vena cava, in a safe and painless manner (Fig. 99-13). CT can depict pelvic and abdominal structures as well as lymph nodes (Fig. 99-14). CT is especially useful in detection of

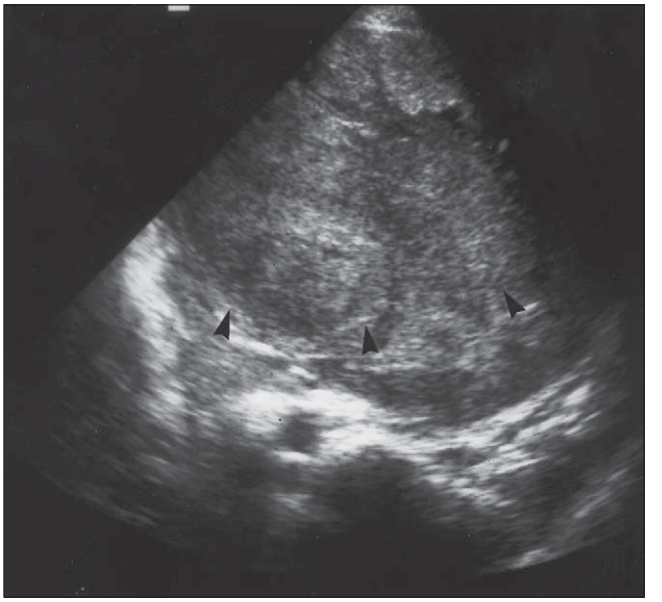


Figure 99-13 • Transverse sonogram shows large Wilms' tumor with almost no remaining normal renal parenchyma (*arrowheads*).

bilateral tumors. Intravenous pyelography and MRI typically are not necessary in the evaluation of Wilms' tumor, although MRI may facilitate differentiation between nephrogenic rests and Wilms' tumor.[291] Because Wilms' tumor metastasizes to the lungs, preoperative chest radiography is imperative. Plain radiographs of the chest are the traditional means of evaluation. Although chest CT is more sensitive than plain radiography in the detection of pulmonary metastasis, its role in initial evaluation for Wilms' tumor is controversial because CT is associated with false-positive findings and high interreader variability among radiologists.[292–294] Moreover, it is not clear whether the prognosis for patients with small pulmonary nodules detected only with chest CT is inferior to that for patients without radiologically detectable pulmonary metastasis.[295,296]

Treatment

The dramatic increase in cure rate of Wilms' tumor over the past 40 years is largely a testimony to the efforts of cooperative groups con-

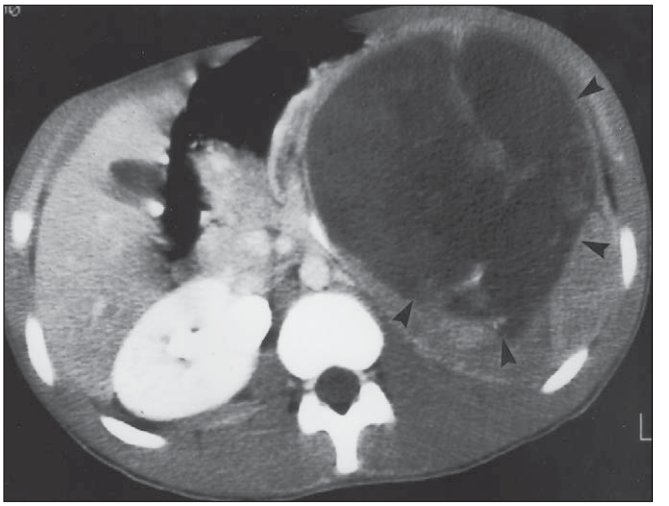


Figure 99-14 • Transverse computed tomographic image of the Wilms' tumor depicted in Figure 99-13 shows a large intrarenal mass (*arrowheads*).

sisting of oncologists, surgeons, radiation oncologists, pathologists, and statisticians. Nearly all patients undergo surgery as the primary method of achieving local control. The NWTS group advocates surgical resection at diagnosis, which yields the most accurate staging information. By contrast, SIOP recommends preoperative chemotherapy with the aim of decreasing tumor size and promoting fibrosis, thereby preventing intraoperative tumor spillage and decreasing surgical complications. Both approaches produce high rates of treatment success. The following discussion focuses on the results of the NWTS and COG, which assumed the responsibilities of the NWTS group in 2002.

Wilms' tumor surgery should be performed by an experienced pediatric surgeon through a transverse abdominal incision. The peritoneal surface, liver, and lymph nodes are inspected for tumor involvement. Biopsy is performed on suspicious lesions. A lymph node sample should be obtained whether or not the node appears involved. Although the NWTS group previously recommended inspection of the contralateral kidney, less than 0.3% of patients enrolled in NWTS-4 had lesions detected during surgery that were not detected on preoperative imaging studies.[297] With the availability of modern imaging techniques, routine exploration of the contralateral kidney is no longer recommended.

The tumor is removed en bloc with the kidney, hilar structures, and a generous segment of ureter. The adrenal gland is included in the resection if the tumor is adherent to the gland or if the tumor originates in the upper pole of the kidney. Caution should be exercised to avoid capsular rupture and tumor spillage, which could adversely influence staging and alter therapy. If a tumor is deemed inoperable owing to size or invasion of vital structures, biopsy is performed and adjuvant therapy is administered before definitive surgery. The COG staging system for Wilms' tumor is based on surgical and histopathologic findings[298] (Table 99-7).

Consecutive trials of the NWTS beginning in the late 1960s provided critical insights into the role of adjuvant therapy for Wilms' tumor. NWTS-1 and NWTS-2 revealed that the combination of vincristine and actinomycin D is superior to treatment with either drug alone and that irradiation is not necessary in the care of patients with stage I disease. NWTS-3 showed that patients with stage II tumors with favorable histologic features can be treated without abdominal irradiation if vincristine and actinomycin D are administered. This study also revealed that the addition of doxorubicin to the two-drug regimen improves outcome in stage III and IV disease with favorable histologic features. If doxorubicin is administered, radiation doses of 1000 cGy are sufficient to eliminate residual microscopic disease in the abdomen. NWTS-3 also showed that addition of cyclophosphamide to the vincristine-actinomycin D-doxorubicin regimen improved outcome for patients with stage II through IV tumors with anaplastic histologic features but not for those with tumors with favorable histologic features. NWTS-4 compared the use of single-dose pulse-intensive actinomycin D and doxorubicin with the traditional divided-dose method of administration. The investigators found that pulse-intensive dosing was equally efficacious, less toxic, and more cost-effective than the conventional regimen.[299,300] NWTS-4 also revealed that 6 months of therapy for stage II through IV tumors with favorable histologic features was equivalent to 15 months of therapy.

The NWTS-5 study sought to capitalize on previous successes. The aim was to curtail therapy in low-risk groups, improve cure rates for high-risk groups, and identify novel prognostic markers. The treatment algorithms used in NWTS-5 are shown in Table 99-8.[298] One of the primary objectives was to evaluate whether adjuvant chemotherapy provides benefit to children younger than 24 months who have small stage I tumors with favorable histologic features, a group with an outstanding prognosis. In 75 patients who met the eligibility criteria, the tumor was treated with surgical resection and close observation only. Eleven (14.7%) of these 75 patients experienced relapse or were found to have metachronous disease in the contralateral kidney, prompting early closure of this study arm.[301] Additional follow-up evaluation indicated that salvage therapy was very successful in this group. Only one patient had subsequent recurrence, and all patients were alive after a median follow-up period of 2.84 years. Future studies will reassess the need for adjuvant therapy in this group of patients.

A second primary objective of NWTS-5 was to test the hypothesis that tumor loss of heterozygosity (LOH) at chromosomal loci 1p and 16q is associated with unfavorable prognosis. More than 2000 patients on NWTS-5 had informative LOH results. LOH at 1p and 16q was prognostically significant for Wilms' tumor of favorable histology, but not for Wilms' tumor of anaplastic histology. The greatest effect on prognosis was seen in tumors that had LOH at both loci[302] (Table 99-9). The current COG Wilms' tumor study is evaluating the benefit of augmenting therapy for patients whose tumors harbor LOH at both 1p and 16q. The biologic mechanism for

Table 99-7 National Wilms' Tumor Study Clinicopathologic Staging

Stage	Description
I	Tumor limited to kidney and completely excised. No penetration of the renal capsule or involvement of renal sinus vessels.
II	Tumor extends beyond the kidney but is completely excised with negative margins and lymph nodes. At least one of the following has occurred: (a) penetration of the renal capsule, (b) invasion of the renal sinus vessels, (c) biopsy of the tumor before removal (except for fine needle aspirate, which may qualify as stage I).
III	Gross or microscopic residual tumor remains postoperatively, including inoperable tumor, positive surgical margins, tumor spillage occurring pre- or intraoperatively, regional lymph node metastasis, and transected tumor thrombus.
IV	Hematogenous metastasis (lung, liver, bone, brain) or lymph node metastasis outside the abdominal or pelvic cavities.
V	Bilateral renal tumors at diagnosis.

Table 99-8 National Wilms' Tumor Study 5 Treatment Algorithms

Stage	Treatment
Favorable histology	
I and II	AMD/VCR × 18 weeks, no XRT
III	AMD/VCR/DOX × 24 weeks, XRT to flank or abdomen
IV	AMD/VCR/DOX × 24 weeks, XRT to flank or abdomen for local stage III and to metastatic sites
Anaplastic histology	
I	AMD/VCR × 18 weeks, no XRT
II–IV	VCR/DOX/CPM/VP-16 × 24 weeks, XRT to flank or abdomen and to metastatic sites

AMD, dactinomycin; CPM, cyclophosphamide; DOX, doxorubicin; VCR, vincristine; VP-16, etoposide; XRT, radiation therapy.

Table 99-9 Results of National Wilms' Tumor Cancer Study 5

Stage	4-Year Relapse-Free Survival Rate (%)	4-Year Overall Survival Rate (%)
Favorable histologic features without LOH 1p		
I (<24 mo/tumor weight <550 g)	95.6	100
I (≥24 mo/tumor weight ≥550 g)	94.2	98.4
II	86.2	97.7
III	86.5	94.4
IV	76.4	86.1
V	64.8	87.1
Favorable histologic features—stage I/II		
No LOH	91.2	98.4
LOH 1p only	80.4	91.2
LOH 16q only	82.5	98.1
LOH 1p and 16q	74.9	90.5
Favorable histologic features—stage III/IV		
No LOH	83.0	91.9
LOH 1p only	89.0	97.6
LOH 16q only	85.3	92.0
LOH 1p and 16q	65.9	77.5
Diffuse anaplastic histologic features		
I	68.4	78.9
II	82.6	81.5
III	64.7	66.7
IV	33.3	33.3
V	25.1	41.6

LOH, Loss of heterozygosity.

the association between LOH and unfavorable outcome is under investigation.

A third objective of NWTS-5 was to improve outcomes of patients with stage II to IV Wilms' tumor of diffuse anaplastic histology. Based on the finding that patients with diffuse anaplastic Wilms' tumor benefited from cyclophosphamide, a new treatment regimen consisting of chemotherapy with a vincristine, doxorubicin, cyclophosphamide, and etoposide and radiation therapy was developed. The outcomes for patients who received this regimen were improved compared with historical controls but still were clearly inferior to outcomes in patients with tumors of favorable histology[303] (see Table 99-9). Patients with stage I anaplastic Wilms' tumor received a two-drug regimen of vincristine plus actinomycin D, with the idea that completely resected tumors do not require intensive treatment. However, these patients did not fare as well as expected (see Table 99-9). The current COG study is augmenting therapy for patients with stage II to IV diffuse anaplastic Wilms' tumor by adding carboplatin to the treatment regimen. Patients with stage I anaplastic Wilms' tumor receive doxorubicin and flank irradiation in addition to vincristine/actinomycin D. Box 99-4 outlines the approach to management of Wilms' tumor used at St. Jude Children's Research Hospital.

Box 99-4. ST. JUDE CHILDREN'S RESEARCH HOSPITAL APPROACH TO MANAGEMENT OF WILMS' FAMILY TUMORS

At St. Jude Children's Research Hospital, patients with suspected Wilms' tumor undergo nephrectomy at diagnosis unless the disease is bilateral or unresectable. Patients with stage I and II Wilms' tumor with favorable histologic features receive 18 weeks of vincristine and actinomycin D without radiation therapy. Patients with stage III and IV Wilms' tumor with favorable histologic features receive 24 weeks of vincristine, actinomycin D, and doxorubicin with radiation to the involved sites. Management of bilateral (stage V) Wilms' tumor is complex, and each patient needs an individualized treatment plan. In general, biopsy of at least one tumor is performed to establish the diagnosis, and preoperative chemotherapy is given before definitive nephron-sparing surgery is attempted. Because patients with bilateral Wilms' tumor do not undergo lymph node sampling at diagnosis, a three-drug chemotherapy regimen—vincristine, actinomycin D, and doxorubicin—is used. If the tumor margins after nephron-sparing surgery are positive for viable tumor, flank radiation is administered to the side with residual disease. Diffuse anaplastic Wilms' tumor is a therapeutic challenge. Patients with this form of the tumor receive chemotherapy with ifosfamide, carboplatin, and etoposide alternated with vincristine, doxorubicin, cyclophosphamide, and radiation to the flank and sites of metastatic disease.

Bilateral Wilms' Tumor

Bilateral Wilms' tumor occurs in approximately 5% to 10% of patients with Wilms' tumor. These children pose a therapeutic challenge because of difficulty in obtaining local control while sparing renal parenchyma. The approach to patients with bilateral Wilms' tumor is to administer preoperative chemotherapy to elicit tumor shrinkage and then to perform partial nephrectomy, whenever possible, or complete nephrectomy. Patients with tumors that cannot be resected with clear margins receive localized radiation therapy. The 4-year overall survival rate among patients with bilateral Wilms' tumor treated in NWTS-4 was 81.7%.[304] Compared with patients with unilateral Wilms' tumor, patients with bilateral tumors have an increased rate of renal failure, estimated to be 3.8% in NWTS-4.[305] The most common cause of renal failure in this patient group is tumor progression or recurrence necessitating nephrectomy, not therapy-related effects.

Recurrent Wilms' Tumor

Despite excellent outcome among most patients with Wilms' tumor, approximately 10% to 15% of patients with disease with favorable histologic features and 50% of patients with anaplastic disease experience primary progression or tumor recurrence. The most common sites of recurrence are the lungs, liver, opposite kidney, and intra-abdominal sites, including the original tumor bed. Wilms' tumor occasionally recurs in the brain, bone, and distant lymph nodes. Most relapses are diagnosed within the first 2 years after the original diagnosis. Factors associated with favorable prognosis after recurrence include favorable histologic features, initial treatment with only vincristine and actinomycin D, recurrent disease involving the lungs only, recurrent disease arising in the abdomen of a patient who did not receive abdominal irradiation, and relapse more than 12 months after the original diagnosis.[306,307] With aggressive therapy, approxi-

mately 60% to 80% of patients with tumors with favorable prognostic features can be cured. Salvage regimens are not as successful for patients with tumors with at least one unfavorable prognostic feature. Salvage regimens include ifosfamide, cyclophosphamide, carboplatin, and etoposide.[307–309] The overall 4-year survival rate after relapse for patients whose initial treatment regimen consisted of vincristine and actinomycin D was 81% after treatment with a regimen containing vincristine, doxorubicin, cyclophosphamide, and etoposide and radiation therapy.[310] For patients whose initial treatment regimen included agents in addition to vincristine and actinomycin D, the 4-year overall survival rate was 48% after treatment with cyclophosphamide, carboplatin, etoposide, and irradiation.[311] Several groups of investigators have used high-dose chemotherapy followed by autologous stem cell rescue in patients with recurrent Wilms' tumor.[312–314] Results are promising, but it is unclear whether high-dose therapy is superior to conventional-dose chemotherapy with modern agents.

Late Effects of Therapy

The late effects of Wilms' tumor treatment have received considerable attention because Wilms' tumor usually is curable, and the number of long-term survivors is growing. Late complications can result from chemotherapy, radiation therapy, or the primary nephrectomy itself. Although most Wilms' tumor survivors have only one kidney, less than 1% of patients with unilateral Wilms' tumor treated in NWTS-1 through NWTS-4 were found to have renal failure.[305] The median interval from diagnosis to onset of renal failure was 21 months. Renal failure is most prevalent in patients with bilateral Wilms' tumor. Another recognized long-term effect of Wilms' tumor therapy is congestive heart failure (CHF), which was found to have a cumulative frequency of 4.4% 20 years after diagnosis of Wilms' tumor in patients whose initial treatment regimen included doxorubicin.[315] The frequency of CHF was higher among patients who received doxorubicin as part of a salvage chemotherapy regimen. Risk factors for CHF included increasing cumulative doxorubicin dose, female gender, and radiation to the lung and left hemiabdomen (but not right hemiabdomen). An analysis of pregnancy outcome among Wilms' tumor survivors revealed that women who received flank radiation therapy and their infants were at increased risk for fetal malposition, premature labor, low birth weight, and occurrence of congenital malformations.[316] Finally, the cumulative incidence of second malignant neoplasms in Wilms' tumor survivors was 1.6% 15 years after diagnosis of their initial tumor.[317]

RENAL CELL CARCINOMA

Renal cell carcinoma (RCC) is an uncommon malignant tumor of childhood. The latest Surveillance, Epidemiology and End Results (SEER) statistics indicated an incidence of 0.4 case per million persons younger than 20 years.[318] RCC accounts for 2% to 7% of primary renal malignant tumors of childhood.[319–321] The median age of children brought for evaluation of RCC is 9 years, considerably older than the age at manifestation of other pediatric renal malignant tumors. Unlike with Wilms' tumor, clear cell sarcoma of the kidney, and rhabdoid tumor of the kidney, which have been studied by the NWTS group and SIOP, no prospective clinical trials of therapy for pediatric RCC have been perfomed. Information about this entity is therefore limited to retrospective single-institutional case series.

Typical features of pediatric RCC include abdominal mass (24% to 55%), hematuria (42%), and pain (32%). Children also may exhibit the constitutional signs and symptoms of hypertension, fever, weight loss, and polycythemia.[322] Approximately 25% of children with RCC have distant metastatic disease when they arrive for evaluation, most commonly involving the lung, liver, and bone.

Tumors classified as childhood RCC compose a heterogeneous group of renal epithelial malignant neoplasms. Childhood RCC may resemble the adult clear cell and papillary subtypes.[323] Although some reviews indicate that the papillary subtype is prevalent in the pediatric population,[323] other reports indicate that the clear cell subtype is more common.[322,324] Genetic alterations at chromosomal locus 3p, the site of the von Hippel-Lindau gene, have not been described in pediatric RCC, although few cytogenetic and molecular studies have been performed. A distinctive variant of RCC that preferentially affects children and young adults is characterized by the translocation t(X;17)(p11.2;q25), which results in a fusion product between the *TFE3* and *ASPL* genes. This same translocation is observed in alveolar soft-part sarcoma, but it is balanced in RCC and unbalanced in alveolar soft-part sarcoma.[325–327] Another variant is associated with the translocation t(6;11)(p21.1;q12).[328] The prevalence and clinical behavior of these variants have not been characterized. Another renal epithelial malignant neoplasm of childhood is renal medullary carcinoma, which is a highly aggressive tumor associated with sickle cell trait.[329]

Categorization of pediatric RCC using the World Health Organization (WHO) classification system suggests that approximately one third of pediatric RCCs are translocation carcinomas.[330,331] These tumors have distinct histologic features and are associated with translocations involving the *TFE3* gene at chromosomal region Xp11.2. The first reported translocation was t(X;1)(p11.2;q21), which fuses the *PRCC* and *TFE3* genes. A more common translocation is t(X;17)(p11.2;q25), which results in the *TFE3-ASPL* fusion product. This translocation also is observed in alveolar soft-part sarcoma, but it is balanced in RCC and unbalanced in alveolar soft-part sarcoma.[325–327] Another observed translocation is t(6;11)(p21.1;q12), which results in fusion of the *TFEB* and alpha genes.[332,333] Because *TFE3* and *TFEB* translocation carcinomas have similar clinical and histologic features, it has been proposed that they be considered as a single category. In addition to translocation RCC, classic adult-type clear cell RCC, papillary RCC, chromophobe RCC, and oncocytic RCC associated with neuroblastoma have been described in children and young adults.[330,334] Another renal epithelial malignant neoplasm of childhood is renal medullary carcinoma, which is a highly aggressive tumor associated with sickle cell trait.[329]

Retrospective reviews have indicated that the survival rate of children and adolescents with RCC is approximately 50% to 60%.[335,336] Adult RCC and pediatric RCC have similar stage-for-stage outcomes: very good outcome for stage I and II disease, less favorable outcome for stage III disease, and poor outcome for stage IV disease (Table 99-10). An apparent difference between adult RCC and pediatric RCC is the prognostic significance of local lymph node involvement. Adults with RCC with lymph node involvement have a 5-year overall survival rate of approximately 20%. By contrast, a review of the published pediatric RCC experience showed that 58 (66%) of 72.4 patients with local lymph node involvement without distant metastatic lesions had durable survival.[336] This difference probably reflects

Table 99-10 Survival Rates by Stage for Pediatric Renal Cell Carcinoma

Stage*	No. of Patients (% by Stage)	Survival Rate (%)
I	79 (32.5)	92.4
II	26 (10.7)	84.6
III	66 (27.1)	72.7
IV	72 (29.6)	13.9
Total/Overall survival	243	63

*Modified Robson staging system.

From Geller J, Dome J: Local lymph node involvement does not predict poor outcome in pediatric renal cell carcinoma. Cancer 2004;1575–1583.

histologic and biologic differences between adult RCC and pediatric RCC.

The optimal therapy for pediatric RCC is unknown. Historically, treatment for children with RCC has been heterogeneous. Some patients received chemotherapy and radiation therapy (typical Wilms' tumor therapy), whereas others were managed with surgery alone. Among patients with lymph node-positive nonmetastatic RCC, no difference in survival was observed among patients who received adjuvant chemotherapy, immunotherapy, or radiation therapy.[336] Because most children with localized and completely resected RCC have a favorable outcome, and no agents with clear efficacy have been identified, adjuvant therapy is not routinely recommended for this patient group. On the other hand, the poor outcome associated with stage IV disease warrants the use of investigational agents. Although a few case reports describe children with metastatic RCC that was responsive to interleukin-2 or interferon-α,[337,338] only a minority of pediatric RCCs have clear cell histology, the histologic subtype that is most responsive to immunotherapy in adults. Likewise, the recent promising results observed with tyrosine kinase and mTOR inhibitors may not translate to pediatric RCC. Testing of these novel agents is warranted in children and young adults.

RHABDOMYOSARCOMA

Epidemiology

Rhabdomyosarcoma is the most common soft-tissue sarcoma of childhood. According to population-based data from the SEER program of the National Cancer Institute, rhabdomyosarcoma accounts for approximately 3% of pediatric malignant neoplasms.[339] The tumor is slightly more common in boys than in girls, and approximately two thirds of cases occur in children younger than 10 years.[339–342] Embryonal rhabdomyosarcoma is the most common histologic subtype at all ages; however, adolescents have a higher proportion of alveolar rhabdomyosarcoma than other age groups.[339–343] In many cases, histologic features and primary site can be correlated. For example, orbital and genitourinary sites are strongly associated with embryonal histologic features, whereas tumors of the extremities most commonly are of alveolar histologic type.[339,344–346]

Biology

Rhabdomyosarcoma arises from primitive mesenchymal cells that retain capacity for skeletal muscle differentiation. The two main histologic subtypes of rhabdomyosarcoma, embryonal and alveolar, differ in biologic characteristics. The reciprocal translocation t(2;13)(q35;q14) is characteristic of tumors of the alveolar histologic type.[347] This translocation juxtaposes the *PAX3* gene located on chromosome band 2q35 and the *FKHR* gene on 13q14 to form a novel chimeric gene that encodes an aberrant transcription factor. A less common translocation in alveolar rhabdomyosarcoma is t(1;13)(p36;q14), which fuses the *PAX7* gene located on chromosome 1p36 with the *FKHR* gene. The t(2;13) and t(1;13) translocations are found exclusively in alveolar rhabdomyosarcoma and are thus diagnostic of this histologic subtype. A recent study suggests that *PAX-FKHR* gene expression signatures may predict clinical outcome independent of other known risk factors.[348]

Unlike alveolar rhabdomyosarcoma, embryonal rhabdomyosarcoma is not characterized by recurring chromosomal translocations. The embryonal type, however, is consistently associated with loss of heterozygosity at chromosome band region 11p15.5. This association suggests the presence of a tumor suppressor gene at this location.[349] Children with Beckwith-Wiedemann syndrome, which is associated with cytogenetic alterations of chromosome band 11p15,[350] are at increased risk for development of rhabdomyosarcoma. This association is further evidence of a tumor suppressor gene at that locus.

A variety of other genetic alterations are associated with RMS. Li-Fraumeni syndrome, defined by germline mutation of the *TP53* tumor suppressor gene, is characterized by development of a variety of malignant neoplasms, including childhood rhabdomyosarcoma.[351] Sporadic mutation of the *TP53* gene has been identified in randomly selected tumor samples from children with rhabdomyosarcoma.[352] This finding suggests that acquired *TP53* alterations may play a role in development of this malignant disease. Other genetic abnormalities include amplification of the N-myc proto-oncogene in alveolar rhabdomyosarcoma[353] and point mutations in the N-ras and K-ras proto-oncogenes in embryonal rhabdomyosarcoma.[354]

Pathology

Although it can be difficult to establish the diagnosis and histologic subtype of rhabdomyosarcoma, diagnostic accuracy is crucial for appropriate assignment of therapy. Rhabdomyosarcoma is a small round blue cell neoplasm and must be differentiated from the other small round blue cell neoplasms of childhood, including neuroblastoma, ESFTs, and non-Hodgkin's lymphoma. The presence of malignant skeletal muscle differentiation, characterized by cross-striations in tumor cells at light microscopic examination, confirms the diagnosis of rhabdomyosarcoma.[355] Unfortunately, cross-striations often are difficult to identify. In the absence of this highly specific finding, immunohistochemical staining often is needed to establish the diagnosis. The presence of staining for myogenin, MyoD1, muscle-specific actin, myoglobin, or desmin supports the diagnosis.[356–358] The finding of sarcomeric differentiation of tumor cells at electron microscopic examination also confirms the diagnosis of rhabdomyosarcoma.

The International Classification of Rhabdomyosarcoma[359] divides these tumors into three prognostic categories on the basis of histologic features: favorable (botryoid and spindle cell rhabdomyosarcoma), intermediate (embryonal rhabdomyosarcoma), and unfavorable (alveolar rhabdomyosarcoma and undifferentiated sarcoma). In most cases, the histologic subtype can be determined with light microscopic examination. In the absence of characteristic histologic findings, however, the use of RT-PCR assay to detect the chimeric fusion transcripts resulting from the t(2;13) and t(1;13) translocations can be useful in confirming the diagnosis of alveolar rhabdomyosarcoma.[9] Immunohistochemical studies also may be useful in separating alveolar from embryonal tumors. AP2β and P-cadherin are specific for alveolar histology, whereas epithelial growth factor receptor (EGFR) and fibrillin-2 are markers of embryonal histology.[360]

Clinical Manifestations

The presenting signs and symptoms in patients with rhabdomyosarcoma depend on the site and size of the primary tumor and on the extent of metastatic disease. Because it is derived from primitive mesenchymal cells, rhabdomyosarcoma can arise in almost any tissue in the body. The most common sites are the head and neck (27% to 37%), genitourinary tract (19% to 26%), and extremities (17% to 20%).[340–344] Head and neck tumors are divided by primary site into three major groups: orbital, parameningeal, and nonparameningeal. Orbital tumors, which account for approximately one fourth of head and neck tumors, commonly manifest as proptosis and occasionally ophthalmoplegia (Fig. 99-15). Approximately one half of rhabdomyosarcomas of the head and neck arise in parameningeal sites, which include the nasopharynx and paranasal sinuses, middle ear and mastoid, and pterygoid and infratemporal fossae. Tumors at these sites may produce nasal, sinus, or aural obstruction, occasionally with purulent or bloody discharge. Parameningeal tumors may be associated with cranial base erosion, cranial nerve palsy, and intracranial tumor extension. Patients with intracranial tumor extension may exhibit signs of increased intracranial pressure and are at risk for leptomeningeal tumor spread.[361] The other one fourth of head and

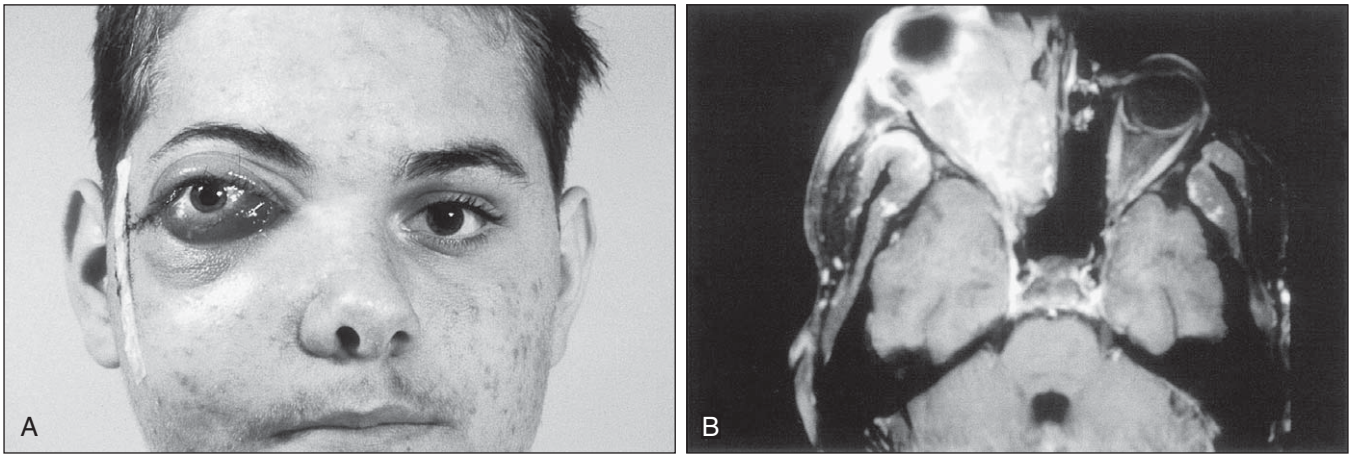


Figure 99-15 • A, Rhabdomyosarcoma of the right orbit invading the paranasal sinuses and soft tissues of the face. Tumor manifested as proptosis and facial swelling with accompanying vision loss. **B,** T_1-weighted contrast-enhanced axial magnetic resonance image shows a large right intraorbital mass displacing the globe anteriorly and extending into the subcutaneous tissues overlying the right maxilla.

neck tumors arise in nonparameningeal sites, such as the scalp, face, buccal mucosa, oropharynx, and neck. A visible or palpable mass often brings these tumors to medical attention.

Genitourinary primary sites account for approximately one fourth of all rhabdomyosarcomas and include the bladder, prostate, uterus, cervix, vagina, vulva, and paratesticular area. Bladder tumors often grow intraluminally and can cause hematuria or obstruct urinary outflow. Prostatic primary tumors can become large before causing appreciable clinical signs and symptoms. Urinary retention, constipation, and a palpable pelvic mass are characteristic. Rhabdomyosarcoma of the female genital tract is associated with protrusion of tumor tissue from the introitus accompanied by vaginal discharge or bleeding. Patients with paratesticular tumors characteristically have a painless unilateral scrotal mass with or without back or abdominal pain related to tumor involvement of retroperitoneal lymph nodes.

Rhabdomyosarcoma arises in an extremity in approximately 20% of the cases. Patients typically notice an enlarging, firm mass that often is painless. Extremity tumors frequently spread into the regional lymphatic system.[346] Thus, the presence of axillary or inguinal adenopathy may be the problem for which medical attention is sought.

Approximately 15% to 20% of patients with rhabdomyosarcoma have identifiable distant metastatic disease at initial diagnosis,[340–342] and an additional 10% to 15% have regional nodal involvement.[362] Lymphatic spread is most common in genitourinary and extremity tumors. Rhabdomyosarcoma is rare in orbital and other head and neck primary sites. The most common sites of distant metastasis are lung, bone marrow, and bone.[363]

Diagnostic Evaluation

The goals of the diagnostic evaluation of children with rhabdomyosarcoma are to establish a specific histologic diagnosis, assess the degree of local, regional, and distant tumor involvement, and collect baseline data against which to measure the response to treatment. A careful physical examination should be performed, with particular attention to regional lymph nodes. MRI or CT is used to determine the location, size, and invasiveness of the primary tumor and the anatomic relationships that will influence the choice of local therapy. Imaging assessment of regional lymph nodes should be performed for patients with genitourinary or extremity tumors, as well as for patients with palpable regional lymphadenopathy. Evaluation for distant metastatic disease includes CT of the chest, ^{99m}Tc bone scintigraphy, and bilateral bone marrow aspiration and biopsy. PET imaging also may be useful in evaluating patients with rhabdomyosarcoma, but its use has not yet become the standard of care.[364] For patients with parameningeal primary tumors, cerebrospinal fluid examination also is warranted to rule out meningeal involvement.

Open biopsy of the tumor usually is necessary to obtain adequate tissue for histologic and molecular characterization. Because of the high incidence of occult nodal involvement, regional lymph node sampling is necessary for patients with extremity tumors[346] and for those older than 10 years who have paratesticular tumors.[365]

Prognostic Factors

Assessment of prognostic variables is crucial for predicting the clinical behavior of rhabdomyosarcoma and for planning therapy. The most important predictors of outcome are histologic subtype, stage, and clinical group.[366] Patients with embryonal histology tumors fare significantly better than those with alveolar or undifferentiated histology (5-year failure-free survival rates 82% versus 65% in an analysis of Intergroup Rhabdomyosarcoma Studies III and IV).[366] The rhabdomyosarcoma staging system comprises primary site (favorable versus unfavorable), maximal tumor diameter (5 cm or less versus greater than 5 cm), and the presence or absence of nodal and distant metastases[367] (Table 99-11). Outcome for children with nonmetastatic tumors arising in favorable sites (orbit, nonparameningeal head and neck, genitourinary other than bladder or prostate, biliary tract) is superior to that for children with tumors at unfavorable sites. Among patients with nonmetastatic tumors arising at unfavorable sites, those with tumors that are larger than 5 cm in maximal diameter or that have spread to regional lymph nodes fare more poorly. Patients with metastatic disease have an unfavorable outcome. The clinical group classification[340] is based on the extent of residual disease after initial definitive surgery. For patients with localized tumor that is completely excised (clinical group I) or that is excised with microscopic residual disease (clinical group II), the prognosis is favorable. For those with gross residual disease (clinical group III), an intermediate prognosis is likely, and for patients with metastatic disease (clinical group IV), prognosis is poor.

Treatment

Because more than two thirds of children and adolescents with rhabdomyosarcoma can be cured, this goal should be the focus of treatment, which comprises the coordinated use of chemotherapy, radiation therapy, and surgery. Box 99-5 outlines the approach to management of rhabdomyosarcoma used at St. Jude Children's

Table 99-11 Intergroup Rhabdomyosarcoma Study Staging System

Stage	Primary Sites*	Maximal Tumor Diameter	Nodes	Metastases
1	Favorable	Any	Any	M0
2	Unfavorable	≤5 cm	N0 or Nx	M0
3	Unfavorable	≤5 cm	N1	M0
	Unfavorable	>5 cm	Any	M0
4	Any	Any	Any	M1

*Favorable sites: Orbit, head and neck (excluding parameningeal), genitourinary (not bladder/prostate), biliary tract.
Unfavorable sites: Head and neck parameningeal, bladder/prostate, extremity, other sites.

Research Hospital. All patients are presumed to have micrometastatic disease; therefore, systemic chemotherapy is administered universally. Agents shown to be active alone or in combination include vincristine, actinomycin D (dactinomycin), doxorubicin, cyclophosphamide, ifosfamide, melphalan, cisplatin, methotrexate, etoposide, topotecan, irinotecan, and vinorelbine [368–384] The standard of care in North America was established by the clinical trials of the Intergroup Rhabdomyosarcoma Study Group (IRSG) later named the Soft Tissue Sarcoma Committee (STSC) of the COG. The IRSG studies, which began in 1972, established vincristine and dactinomycin chemotherapy, with or without cyclophosphamide, as the therapeutic standard for rhabdomyosarcoma against which all other approaches are measured. In selected patients with favorable prognostic features, treatment is with only vincristine and dactinomycin; in patients with less favorable features, cyclophosphamide also is required. Efforts to further improve outcome with dose intensification of cyclophosphamide had proved ineffective.[385] Novel chemotherapeutic approaches recently under investigation by the STSC include the use of the camptothecin analogs topotecan and irinotecan. In Europe, vinorelbine-cyclophosphamide maintenance therapy is being studied.[386] To date, high-dose chemotherapy with autologous stem cell or bone marrow rescue has not been shown to improve outcome.[387,388]

In addition to systemic chemotherapy, local treatment with surgery, radiation therapy, or both is necessary for all sites of gross disease. Because complete surgical excision is associated with a better outcome, the goal of surgery is complete tumor removal without significant cosmetic or functional impairment. Less than 20% of tumors, however, are completely excised with negative microscopic margins.[340,341] Re-excision of tumors arising in the extremities and trunk to achieve negative margins before initiation of systemic therapy appears to confer a local control benefit and may favorably influence survival.[389,390] Therefore, the tumor bed should be re-excised before administration of chemotherapy when negative microscopic margins can be achieved. For patients with tumors not amenable to surgical excision at the time of initial diagnosis, administration of neoadjuvant chemotherapy may allow delayed surgical resection.

Radiation therapy is indicated for all patients with rhabdomyosarcoma except those who have embryonal tumors that have been completely resected with negative microscopic margins. Radiation therapy usually is delayed until after the initial response to chemotherapy is ascertained. In patients with tumors that erode the skull base, extend intracranially, or cause cranial nerve dysfunction or spinal cord compression, however, immediate initiation of radiation therapy is warranted.[361] The recommended dose of radiation therapy ranges from 36 to 50.4 Gy, depending on tumor site, extent of residual tumor, and response to chemotherapy. Current studies are evaluating radiotherapy dose reduction for particular patient subsets. In an effort to improve local control and decrease the late effects of conventional radiation therapy, an IRSG study evaluated a twice-daily hyperfractionation schedule. This schedule has shown no local control benefit, although the impact on late effects has not been evaluated.[391,392] Techniques such as brachytherapy, three-dimensional conformal radiation therapy, and intensity-modulated radiation therapy may be helpful in decreasing the late complications of radiation therapy.

Box 99-5. ST. JUDE CHILDREN'S RESEARCH HOSPITAL APPROACH TO MANAGEMENT OF RHABDOMYOSARCOMA

At St. Jude Children's Research Hospital, management of rhabdomyosarcoma begins with surgical removal of the tumor at initial diagnosis, when the operation can be accomplished without marked functional impairment or disfigurement. Primary re-excision is a consideration when gross or microscopic tumor can be removed with minimal morbidity. After initial surgery, systemic chemotherapy is administered according to available research protocols of the Children's Oncology Group. In the absence of an appropriate clinical trial, low-risk patients receive vincristine–actinomycin D chemotherapy, and intermediate- or high-risk patients receive vincristine–actinomycin D–cyclophosphamide chemotherapy. Local tumor control is addressed after completion of several cycles of chemotherapy. Surgical resection is performed if a gross total resection can be anticipated without producing excessive morbidity. All patients with alveolar histology tumors, as well as those with microscopic or gross residual embryonal tumors, receive radiation therapy after surgery during the completion of remaining chemotherapy. The radiation dose is dependent on the extent of residual disease after delayed tumor resection and ranges from 36 to 50.4 Gy. Local irradiation for treatment of metastatic disease is individualized and may be performed during local treatment of the primary tumor or at the end of therapy. In general, all metastatic sites (except bone marrow) are irradiated if feasible. Surgical removal of metastases is performed in limited circumstances.

Outcome and Late Sequelae

With contemporary therapy, the 5-year survival rate among children with rhabdomyosarcoma exceeds 70%. Beyond 5 years from diagnosis, approximately 9% of survivors experience tumor recurrence, secondary malignancy, or death from another cause. Long-term outcome varies according to risk factors: More than 90% of those with favorable disease features become long-term survivors, although fewer than 25% of those who present with metastatic disease survive. Patients who experience disease recurrence fare poorly. Fewer than 20% of children survive more than 5 years after recurrence, and almost all of these survivors experience local recurrence of botryoid or embryonal tumors.[393,394]

Although long-term survival is the norm for children with rhabdomyosarcoma, the late effects of the disease and its therapy can be

substantial.[395] Long-term sequelae are site-specific in many cases. More than one half of survivors of orbital rhabdomyosarcoma have dry eye, impaired vision, or cataracts.[396,397] Dental abnormalities, including root stunting, microdontia, and hypodontia, are common among survivors of head and neck rhabdomyosarcoma.[398] Other common problems in children who had head and neck tumors include short stature (due to growth hormone deficiency), hypothyroidism, and hearing loss.[340,399,400] Children who had rhabdomyosarcoma arising in the pelvis are at risk for impaired bladder and kidney function, gonadal failure, and sexual dysfunction,[401,402] whereas those who had paratesticular tumors may experience ejaculatory dysfunction and hypogonadism.[403] Other late effects may be caused by chemotherapy, radiation therapy, surgery, or all of these modalities. The most important of these effects include CHF,[395] infertility,[405,406] impaired bone and soft-tissue growth,[407–409] and second malignant neoplasms.[410,411]

NONRHABDOMYOSARCOMA SOFT-TISSUE SARCOMA

Epidemiology

Population-based data from the SEER program of the National Cancer Institute indicate that approximately 4% of pediatric malignant tumors are nonrhabdomyosarcoma soft-tissue sarcoms (NRSTS). As a group, these tumors occur more frequently than rhabdomyosarcoma.[339] Unlike rhabdomyosarcoma, which occurs most often in children younger than 10 years, NRSTS is found predominantly in older children and adolescents. NRSTS includes many histologically and biologically distinct entities, all of which are derived from primitive mesenchymal cells. Most tumors are named for the mature tissue that they resemble histologically. In pediatrics, the most common subtypes are synovial sarcoma, malignant fibrous histiocytoma, malignant peripheral nerve sheath tumor, and fibrosarcoma.[339,412–413] Certain subtypes that occur frequently in adults, such as leiomyosarcoma and liposarcoma, are rare in children.[414–418] Tumors unique to pediatric patients include infantile hemangiopericytoma and infantile fibrosarcoma, which behave in a more benign manner than that observed for their counterparts in adults.[419–421]

Tumor Biology

Most cases of NRSTS arise sporadically. Some of these tumors, however, have been found in patients with constitutional *TP53* gene mutations (Li-Fraumeni syndrome).[422] This finding suggests that aberrant *TP53* gene function may contribute to pathogenesis in some cases. Patients with neurofibromatosis type I, a genetic disorder of autosomal dominant inheritance caused by abnormalities on the long arm of chromosome 17, are at increased risk of malignant peripheral nerve sheath tumor (MPNST),[423] which often arises within a preexisting neurofibroma. MPNST also occurs sporadically in patients who do not have neurofibromatosis type I.[424] An unusually high incidence of leiomyosarcoma has been found among children with human immunodeficiency virus (HIV) infection.[425] Epstein-Barr virus (EBV) infection has been found in patients with HIV-associated leiomyosarcoma. This finding suggests that EBV has an etiologic role in the pathogenesis of leiomyosarcoma in HIV-infected patients.[426] Leiomyosarcoma in HIV-negative patients is not associated with EBV infection.[427]

A variety of forms of NRSTS have been reported as secondary malignant neoplasms arising after radiation therapy or chemotherapy for unrelated malignant disease.[162,428] Children with bilateral retinoblastoma are at high risk for secondary NRSTS, which can arise either within or outside of the radiation field used to manage retinoblastoma. This finding suggests that the *RB* gene locus may be important in the pathogenesis of some cases of NRSTS.[429]

Pathology

Because NRSTS is uncommon during childhood, these tumors can be diagnostically challenging. Procurement of an adequate tissue specimen during the initial evaluation is crucial to establishing an accurate diagnosis, and for determining the histologic grade, which is highly predictive of outcome[412–414] and may dictate treatment. Incisional biopsy is preferred, because fine needle aspiration and biopsy may yield inadequate tissue for thorough histologic and immunohistochemical evaluation and for molecular pathologic studies. Detection of chromosomal translocations specific to certain histologic subtypes may be helpful in confirming the precise diagnosis[429–440] (Table 99-12). Identification of specific tumor cell-gene fusions also may have prognostic importance. For example, synovial

Table 99-12 Chromosomal Translocations and Associated Fusion Proteins Described in Childhood Nonrhabdomyosarcoma Soft-Tissue Sarcoma

Tumor	Chromosomal Translocation	Fusion Protein
Alveolar soft-part sarcoma	der(17)t(X;17)(p11.2;q25)	ASPL-TFE3
Angiomatoid fibrous histiocytoma	t(12;16)(q13:p11)	FUS-ATF1
Clear cell sarcoma	t(12;22)(q13;q12)	EWS-ATF1
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	COL1A1-PDGFB
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	EWS-WT1
Endometrial stromal sarcoma	t(7;17)(p15:q21)	JAZF1-JJAZ1
Extraskeletal myxoid chondrosarcoma	t(9,22)(q22;q11-12)	EWS-CHN
	t(9;17)(q22;q11)	RBP56-CHN
Infantile fibrosarcoma	t(12;15)(p13;q25)	ETV6-NTRK3
Low-grade fibromyxoid sarcoma	t(7;16)(q32-34;p11)	FUS-CREB3L2
Myxoid liposarcoma	t(12;16)(q13;p11)	FUS-CHOP
	t(12;22)(q13;q11-12)	EWS-CHOP
	t(12;22;20)(q13;q12;q11)	EWS-CHOP
Synovial sarcoma	t(X;18)(p11;q11)	SYT-SSX1 or SYT-SSX2

sarcoma with the *SYT-SSX1* fusion gene appears to have a less favorable outcome than that observed for synovial sarcoma with the *SYT-SSX2* fusion gene.[441]

Childhood NRSTS is divided into low-, intermediate-, and high-grade categories according to a grading schema formulated by the Pediatric Oncology Group.[442] This grading system includes elements of the system devised by Costa and colleagues[443] for adult NRSTS, in which metastatic potential and necrosis are assessed, as well as elements of the system developed by Enzinger and Weiss,[444] which is based primarily on histologic criteria. The system also includes the clinical variable of patient age to account for infantile tumors, which have a highly malignant histologic appearance but behave clinically in a benign manner.

Clinical Manifestations

The manifestations of NRSTS depend mainly on the site of the primary tumor. Because they are derived from primitive mesenchymal cells, these tumors can arise in almost any tissue. Extremity sites are most common, followed by trunk wall, head and neck, and visceral sites.[412,445,446] Extremity, trunk wall, and head and neck NRSTSs most commonly manifest as an enlarging, painless mass. Compression of nerves by the tumor can cause pain or disturbances in sensory or motor function. Tumors in the head and neck region can cause nasal, aural, or sinus obstruction and can impinge on the airway. Retroperitoneal and visceral tumors of the abdomen and pelvis often are large at initial evaluation. These tumors characteristically cause abdominal pain with or without symptoms of gastrointestinal or urinary tract obstruction.

Regional lymph node involvement is uncommon[446] and rarely is clinically evident when present. Children with synovial sarcoma, epithelioid sarcoma, angiosarcoma, and clear cell sarcoma are presumed to be at the highest risk for regional nodal disease, because these histologic subtypes are most commonly associated with regional spread in adults.[447] Approximately 15% of children and adolescents with NRSTS have distant metastatic lesions at initial diagnosis. The lung is the predominant site of metastatic disease,[445] but signs and symptoms of pulmonary metastasis are rare at initial diagnosis. Metastatic involvement of bone, skin, liver, and brain also has been reported. Pleural, peritoneal, and omental metastasis can occur in patients with tumors of the trunk wall, retroperitoneum, or viscera.

Diagnostic Evaluation

The goals of the diagnostic evaluation of children with suspected NRSTS are to establish a specific diagnosis and to assess the extent of disease to allow optimal treatment planning and measurement of response. The physical examination should be focused particularly on the local extent of the primary tumor and on the presence or absence of regional lymphadenopathy. MRI or CT aids in determining the location, size, and invasiveness of the primary tumor, as well as the anatomic relations that influence the surgical approach. Patients with epithelioid sarcoma and clear cell sarcoma require imaging assessment of regional lymph nodes, because regional tumor spread is most common in these subtypes of NRSTS in adults.[447] Any patient with enlarged regional lymph nodes also should undergo imaging of the nodal bed for definition of the extent of disease. The evaluation for distant metastatic disease should include either radiography or CT of the chest. CT is more sensitive and more expensive than radiography, but it is most cost-effective in patients with large, high-grade NRSTS.[448] Patients with tumors of the abdomen, pelvis, and retroperitoneum should undergo CT or MRI of the liver. Routine screening for bone, bone marrow, and brain metastasis is not warranted.[449]

The best approach to ensure adequate tissue for histologic and molecular tumor characterization is open biopsy. Core needle biopsies, however, have been shown to provide accurate diagnostic information when the specimen is reviewed by an experienced pathologist.[450] Fine needle aspiration is inadequate for establishing a specific diagnosis[451] but may be helpful in documentation of tumor recurrence.[452]

Prognostic Factors

Assessment of prognostic factors is important in selecting a therapeutic approach for patients with NRSTS. Few prospective studies of childhood NRSTS have been conducted, but the available results of prospective and retrospective studies suggest that the prognostic features of NRSTS are similar in children and in adults. Extent of disease and histologic grade and size of the tumor appear to be the most important prognostic variables. Patients with tumors that can be excised at initial diagnosis fare significantly better than those with unresectable or metastatic tumors.[412–414,445,446,453] Among patients with tumors that are surgically resected, high histologic grade is strongly associated with development of distant metastasis and with an inferior survival rate.[412–414] Tumor diameter greater than 5 cm is a risk factor for adverse outcome among patients with nonmetastatic NRSTS.[413,414,446] Other variables that have been associated with reduced probability of survival include age older than 10 years and intra-abdominal primary tumor site. Local recurrence is more likely in patients who have gross residual disease or tumor-positive microscopic margins after initial surgery.

Treatment

Only three prospective multi-institutional clinical trials of therapy for pediatric NRSTS have been conducted.[412,453,454] Therefore, the approach to management of childhood NRSTS depends largely on experience in managing adult NRSTS. In the pediatric population, however, the potential long-term effects of antineoplastic therapy on growth and development are additional factors that must be weighed.

NRSTS in children and adolescents can be assigned one of three risk categories for the purpose of determining optimal treatment. *Low-risk* disease includes resectable low-grade tumors and resectable high-grade tumors with a maximal diameter of 5 cm or less. Approximately 85% of patients with low-risk NRSTS become long-term survivors, and efforts should be made to limit the toxicity of treatment.[412–414] Wide local excision generally is adequate for cure.[412,413,455,456] When microscopic tumor remains after surgery, adjuvant radiation therapy (external-beam irradiation or brachytherapy) usually is indicated.[457] In selected patients with microscopic residual disease after resection of low-grade NRSTS, however, a period of observation may be appropriate, because only a small number of these patients experience local recurrence, and salvage therapy is almost always successful in these cases.[413,458]

The *intermediate-risk* category includes high-grade tumors larger than 5 cm in diameter and unresectable tumors. Patients at intermediate risk have an approximately 50% likelihood of long-term survival.[414,446] The optimal treatment in this subgroup is elusive. Patients with large, high-grade tumors are at substantial risk for distant disease recurrence,[413] but experience with treatment of these tumors in adults suggests that the available chemotherapy regimens are only modestly effective in preventing this usually fatal event.[459–461] The most active antineoplastic agents overall in soft tissue sarcomas are doxorubicin and ifosfamide; however, the rate of tumor response after neoadjuvant treatment with these agents is in the 25% to 40% range.[453,454,462,463] Dose intensification with these drugs may slightly improve the rate of response, although the effect of dose intensification on survival appears limited.[464] The late effects of high cumulative doses of doxorubicin and ifosfamide also must be considered.[465,466] For specific histologic subtypes, newer agents may be considered. Examples are

ecteinascidin-743 for liposarcoma and leiomyosarcoma[467] and imatinib for dermatofibrosarcoma protuberase.[468] Patients who have unresectable NRSTS are at risk not only for distant dissemination of disease but also for local tumor progression.[446] Local tumor growth can cause fatal complications when the tumor arises in the head and neck or intrathoracic and intra-abdominal regions. Neoadjuvant combined chemotherapy and radiation therapy may be a promising approach for improving local control in these patients.[469]

Metastatic NRSTS constitutes the *high-risk* category. For patients with metastatic disease, the prognosis is dismal. The median duration of survival is approximately 6 months, and less than 10% of these patients are alive 5 years after the initial diagnosis.[445,453] Novel treatment approaches are needed for these patients. In view of the poor outcome with standard chemotherapy, enrollment in phase I and II clinical trials of investigational agents should be considered.

Many aspects of the management of childhood NRSTS are controversial. Questions that have not been answered definitively include the following:

- Which children with resected NRSTS can be managed without adjuvant therapy?
- What minimum dose and field of radiation therapy provide adequate local control of resected NRSTS with positive microscopic margins?
- What is the optimal systemic therapy for patients at high risk for distant metastatic disease?
- What is the most effective local control therapy for unresectable NRSTS? Prospective clinical trials are warranted for investigation of these questions.

Box 99-6 outlines the approach to management of childhood NRSTS used at St. Jude Children's Research Hospital.

Box 99-6. ST. JUDE CHILDREN'S RESEARCH HOSPITAL APPROACH TO MANAGEMENT OF CHILDHOOD NONRHABDOMYOSARCOMA SOFT-TISSUE SARCOMA

At St. Jude Children's Research Hospital, the primary goal in managing childhood NRSTS is complete resection of all sites of disease. Whether radiation therapy or chemotherapy also is used depends on an assessment of risk factors for local and distant disease recurrence and on whether the tumor is resectable at the time of initial diagnosis.

For patients with localized, surgically resectable NRSTS that is of either low grade or high grade and 5 cm or less in diameter, the tumor is excised when it comes to medical attention. Although the goal of surgery is wide tumor-free margins, every effort is made to avoid functional impairment or disfigurement. Primary re-excision is performed in patients who have undergone unplanned resection and in those in whom negative microscopic margins can be achieved. External-beam radiation therapy or brachytherapy is administered to patients with high-grade tumors who have microscopic residual tumor after surgery. For patients with low-grade tumors who have microscopic residual tumor after surgery, radiation therapy generally is avoided because local recurrence is rare in these patients and is readily controlled by re-excision with or without radiation therapy. Adjuvant chemotherapy is not indicated for patients with localized low-grade NRSTS or for those with localized high-grade NRSTS 5 cm or less in diameter.

Neoadjuvant doxorubicin and ifosfamide chemotherapy is administered to patients with high-grade NRSTS larger than 5 cm in diameter, to those with unresectable NRSTS of any grade, and to those with metastatic NRSTS. After completion of two or three cycles of chemotherapy, surgery is performed with the aim of excising all tumors visible on diagnostic imaging, if possible. Resection of metastases may be delayed until the end of therapy if resection of both the primary tumor and metastases would produce excessive morbidity or treatment delay. Postoperatively, an additional two or three cycles of chemotherapy is given, provided that the response to neoadjuvant therapy is favorable. If microscopic tumor remains after surgery, external-beam radiation therapy or brachytherapy is given. In selected cases, radiation therapy is initiated concurrently with preoperative chemotherapy, and a postoperative radiation therapy boost is used only if microscopic tumor remains after surgery. For patients with NRSTS that continues to be unresectable after neoadjuvant chemotherapy and radiotherapy, different chemotherapeutic approaches are tried in an effort to permit tumor resection.

Outcome

The prognosis for children and adolescents with NRSTS depends on the histologic grade and size of the tumor, the resectability of the tumor, and the presence or absence of metastatic disease. Patients with nonmetastatic resectable low-grade and small high-grade tumors have a favorable outcome, with approximately 85% long-term survival.[415,416] For patients with nonmetastatic large, high-grade tumors or with nonmetastatic unresectable tumors of any grade, an intermediate prognosis is the rule. Approximately one half of these patients are alive 5 years after diagnosis.[446] For patients with metastatic disease at diagnosis, the prognosis is dismal; fewer than 10% become long-term survivors.[445,453]

The likelihood of cure of patients who experience tumor recurrence is difficult to ascertain because of the paucity of data on this subject. In patients with local recurrence, particularly if the tumor is of low histologic grade and is resectable, results usually are good.[413] Development of distant metastatic disease, particularly when the tumor is of high histologic grade, is a very unfavorable prognostic sign. A small number of patients with isolated pulmonary metastases may be cured surgically.[470]

Few reports have addressed the late effects of therapy for NRSTS in children and adolescents. Like pediatric patients who undergo intensive chemotherapy, surgery, and radiation therapy for other malignant diseases, those undergoing therapy for NRSTS are at risk for a number of long-term complications (Fig. 99-16). Surgical intervention can lead to permanent organ damage, disability, or disfigurement. Radiation therapy can cause disturbances of bone and soft-tissue growth,[405,406] restriction of soft-tissue mobility, neuroendocrine abnormalities,[399,471] and secondary malignant tumors.[410] Administration of anthracycline and alkylating agent chemotherapy has been associated with cardiotoxicity,[465] infertility,[404] nephrotoxicity,[466] and development of secondary malignant tumors.[410,472] These potential sequelae must be considered when treatment is selected for children and adolescents with NRSTS. Advances in the treatment of pediatric patients with NRSTS depend on further studies to identify more effective therapies that cause less long-term toxicity.

RETINOBLASTOMA

Epidemiology

Retinoblastoma is the most frequent neoplasm of the eye in childhood and the third most common intraocular malignant tumor in all ages, following malignant melanoma and metastatic carcinoma. Retinoblastoma represents 3% of all pediatric cancers. The average incidence of retinoblastoma in the United States is 1 in 14,000 to 1 in 18,000 live births. Thus, retinoblastoma develops in an estimated 200 to 300 children each year.[4] No sex or racial predilection has been

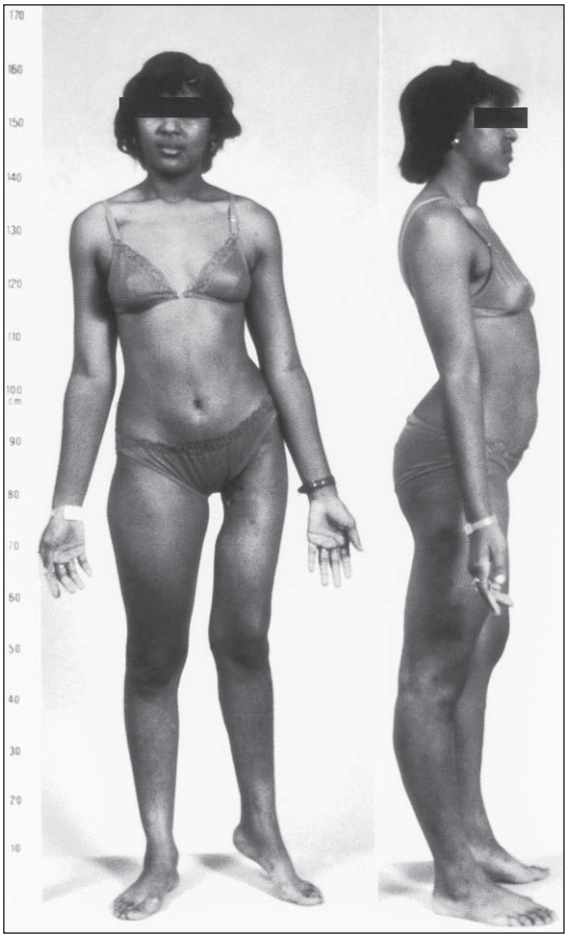


Figure 99-16 • This 19-year-old patient had undergone chemotherapy, surgical resection, and 64.8-Gy external-beam radiation therapy for synovial sarcoma of the left anterior thigh at 10 years of age. Marked soft-tissue atrophy of the left thigh and associated leg length discrepancy due to impaired skeletal growth are evident. Other late effects include avascular necrosis of the left femoral head and thoracolumbar scoliosis.

observed. The human retina is far from having completed its maturation at the completion of gestation, and it is not considered to be terminally differentiated until the age of 3 years. During this period, in which primitive photoreceptor cells are stimulated to differentiate into the mature retina, cells are at high risk of sustaining oncogenic events that result in development of a neoplasm. Retinoblastoma is therefore a cancer of the very young, and any therapeutic approach must take into consideration not only cure of the disease but also the need to preserve vision, with minimal long-term effects.

Clinical Forms and Tumor Biology

Retinoblastoma manifests in two distinct clinical forms. The first is bilateral or multifocal hereditary (accounting for 40% of cases), characterized by the presence of germline mutations of the *RB1* gene. Multifocal retinoblastoma can be inherited from an affected survivor (seen in 25% of the cases) or may be the result of a new germline mutation (in 75%). The second form is unilateral or unifocal and nonhereditary (accounting for 60% of cases).

Retinoblastoma is among the best understood of human neoplasms and has served as an important model for elucidating tumorigenesis. In 1971, on the basis of results of mathematical analysis of age at manifestation of hereditary and nonhereditary cases of retinoblastoma, Knudson[473] proposed the *two-hit hypothesis*, whereby two mutational events in a developing retinal cell lead to development of retinoblastoma. This hypothesis was extended to suggest that the two events could be mutations of both alleles of the *RB1* gene. The *RB1* gene, located in chromosomal band 13q14, was identified and cloned in 1986.[474,475] Its product, pRb, is a 110-kd nuclear phosphoprotein that acts by binding and inhibiting several proteins with growth-stimulatory activity. The pRb protein is a key substrate for G_1 cyclin-Cdk complexes, which phosphorylate target gene products required for transition of the cell through G_1. The active pRb is the unphosphorylated gene product, which binds to several cellular proteins, among which is transcription factor E2F, which activates transcription of genes whose products are required for entry into the S phase of the cell cycle. During the progression through G_1, pRb undergoes additional phosphorylation. The result is a hyperphosphorylated form that persists through the S, G_2, and M phases. The pRb protein appears to function as a tumor suppressor at least in part by inhibiting cell cycle progression past the G_1-S restriction point. Once cells traverse the G_1-S restriction point and enter S phase, they become irreversibly committed to cell division. Thus, pRb stands as the major gatekeeper to control this critical point in growth regulation. Lack of pRb or its inactivation removes the pRb constraint on cell cycle control. The consequence is deregulated cell proliferation.[476]

First Hit

RB1 is a large gene, containing 27 exons over approximately 200 kb of DNA, and mutations have been described in almost every exon. Nonsense and frameshift are the most common germline and somatic mutations, although deletions and duplications also are frequently encountered.[476] No mutational hot spots have been identified, although new germline mutations have an overwhelming preference for the paternal allele, a finding suggesting that deamination of methylated CpG pairs has an important role in mutagenesis.[477]

Second Hit

In both hereditary and nonhereditary retinoblastoma, the second tumorigenic event is chromosomal in nature, often occurring as a result of mitotic recombination errors.[478] This second hit occurs at a much higher frequency than is the case with the first hit, and it is more sensitive to environmental factors, such as ionizing radiation—hence the increased risk of radiation-induced malignant tumors in survivors of retinoblastoma.[479] After the second hit has occurred, retinoblastoma cells rapidly accumulate additional genetic damage. It is possible that an additional mutation ("third hit"), probably involving a gene of the apoptotic pathway, is necessary for final retinal tumor formation.[476] In contrast with the prevailing theories that suggest that *RB1* mutations bypass the p53 pathway, the Arf-Mdm2-p53 tumor surveillance pathway is activated after the Rb pathway is disrupted in the developing retina. *RB1*-deficient retinoblasts undergo p53-mediated apoptosis and cell cycle exit. Subsequent genetic amplification of the *MDMX* gene and increased expression of MDMX protein suppress the p53 response in *RB1*-deficient retinoblasts, leading to clonal expansion and tumor formation. This seems to be the mechanism by which the activation of the p53 pathway is disrupted in retinoblastoma: Close to two thirds of tumors have *MDMX* amplification.[480]

Genetic Counseling

Retinoblastoma is a unique neoplasm because the hereditary type has autosomal dominant inheritance with almost complete penetrance (85% to 95%).[481] Some families, however, have an inheritance pattern characterized by reduced penetrance and expressivity. These low-penetrance retinoblastoma mutations either cause a reduction in the amount of normal pRb produced or result in a partially functional mutant pRb.[482] The *RB1* gene mutation can occur at a late stage of embryogenesis, the result being variable expression depending on the

tissue and mosaicism in 10% to 15% of family members.[483] Genetic counseling is of utmost importance for determining the heritability of a given case and to estimate the risk among relatives. Because of the size of the *RB1* gene and the lack of mutational hot spots, however, exhaustive analysis of the *RB1* gene is required for clinical DNA testing.[484] With the refinement in methods of mutational analysis over the past decade, detection rates have increased to greater than 90% at present. Because of the heterogeneity in the site and type of gene defects, no single technology will be sensitive and effective, and a multistep approach must be taken.[485] In general, however, on the basis of inheritance pattern but in consideration of the existence of mosaicism, the following risk estimates can be made[481]:

- *Risk among offspring of survivors of retinoblastoma:* The risk of retinoblastoma in the offspring of survivors of bilateral (hereditary) disease is 45%. The risk is 2.5% among the offspring of survivors of unilateral retinoblastoma.
- *Risk among siblings of patients with retinoblastoma:* With a family history of retinoblastoma, siblings of patients with bilateral tumors have a 45% risk for development of retinoblastoma. The siblings of patients with unilateral tumors have a 30% risk. With a family history, the risk is 2% among siblings of patients with bilateral tumors and 1% among siblings of patients with unilateral tumors.

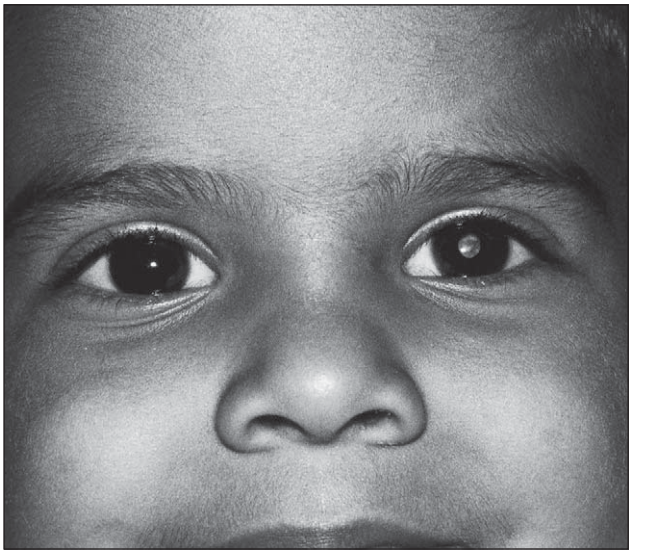


Figure 99-17 • Leukocoria of the left eye in a 3-year-old boy.

Pathology

Retinoblastoma arises from the photoreceptor elements of the inner layer of the retina,[486] usually extending into the vitreous cavity as a fleshy nodular mass (endophytic retinoblastoma). Less frequently, it extends externally, causing secondary retinal detachment; in such cases, no localized vitreous nodule (exophytic retinoblastoma) is visible. Macroscopically, retinoblastoma is soft and friable, and it tends to outgrow its blood supply; the result is necrosis and calcification. Because of the friability of the tumor, dissemination within the vitreous and retina in the form of small, white nodules (seeds) is common. In such cases, it may be difficult to differentiate multicentric primary tumor from disseminated tumor.[487]

The microscopic appearance of retinoblastoma depends on the degree of differentiation. Undifferentiated retinoblastoma is composed of small, round, densely packed cells with hypochromatic nuclei and scant cytoplasm. Several degrees of photosensory differentiation have been described and are characterized by distinctive arrangements of tumor cells. Homer Wright rosettes are composed of irregular circlets of tumor cells arranged around a tangle of fibrils with no lumen or internal limiting membrane. These rosettes are infrequent in retinoblastoma but are most common in other neuroblastic tumors, such as neuroblastoma and medulloblastoma. Flexner-Wintersteiner rosettes, on the other hand, are specific for retinoblastoma. These structures consist of a cluster of low columnar cells arranged around a central lumen bounded by an eosinophilic membrane analogous to the external membrane of the normal retina. The lumen contains an acid mucopolysaccharide similar to that around normal rods and cones. These rosettes are present in 70% of tumors. Fleurettes are less common. If rosettes are present, the cells exhibit even more ultrastructural characteristics of photoreceptor differentiation. The tumor is composed of larger cells with abundant eosinophilic cytoplasm arranged in a distinctive fleur-de-lis pattern. Especially well-differentiated tumors composed almost entirely of fleurettes have been called *retinoma* or *retinocytoma*. Ultrastructurally, retinoblastoma cells exhibit photoreceptor differentiation with the presence of the 9-0 microtubule doublet pattern, abundant cytoplasmic microtubules, synaptic ribbons, and neurosecretory granules.[487,488]

Dissemination of retinoblastoma occurs by several routes. Choroidal invasion provides access to a rich vascular network that serves as a potential route for distant metastatic lesions. In advanced cases, direct extension occurs through the sclera into the orbit. Retinoblastoma can invade the iris and the ciliary body and metastasize to regional lymph nodes. Finally, retinoblastoma can extend along the optic nerve, gaining access to the subarachnoid space and intracranial cavity.

Clinical Manifestations

Successful management of retinoblastoma depends on ability to detect the disease while it is still intraocular. Patients with bilateral retinoblastoma tend to come to medical attention at a younger age (14 to 16 months) than that typical for patients with unilateral disease (29 to 30 months).[481,489] In greater than half of the cases, the presenting sign is leukocoria, which occasionally is first noticed after a flash photograph (Fig. 99-17). Strabismus is the second most common sign and usually correlates with macular involvement. Very advanced intraocular tumors can become painful as a result of secondary glaucoma.[489] Considerations in the differential diagnosis include other childhood diseases that manifest as leukocoria, such as persistent hyperplastic primary vitreous, retrolental fibrodysplasia, Coats' disease, congenital cataracts, toxocariasis, and toxoplasmosis. In some series, these nonmalignant conditions account for a large proportion of enucleated eyes.[490]

Trilateral retinoblastoma is the association of bilateral retinoblastoma with an asynchronous intracranial neuroblastic tumor.[491] This association may be present in 3% to 9% of patients with hereditary disease, and the prognosis is almost uniformly fatal. Most of these tumors are pinealoblastoma, but suprasellar or parasellar tumors also occur. In most cases, the tumor resembles undifferentiated retinoblastoma with the more frequent formation of Homer Wright rosettes. The median interval between diagnosis of bilateral retinoblastoma and diagnosis of the brain tumor is 35 months. In recent years, with more widespread use of chemoreduction treatment for patients with bilateral retinoblastoma, the incidence of trilateral retinoblastoma has decreased dramatically.[492]

Evaluation

The diagnosis of intraocular retinoblastoma usually is made without histopathologic confirmation. Anesthesia and a maximally dilated pupil and scleral indentation are required to examine the entire retina. Retinoblastoma usually appears as a mass projecting into the vitreous, although the presence of retinal detachment or vitreous hemorrhage can make visualization difficult. Additional imaging studies that aid in the diagnosis include bidimensional ultrasonogra-

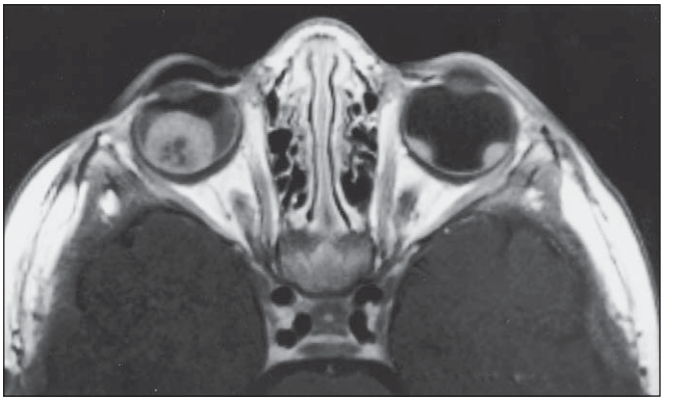


Figure 99-18 • T_1-weighted magnetic resonance image after contrast enhancement shows bilateral retinoblastoma with associated retinal detachment of the right globe.

phy, CT, and MRI (Fig. 99-18). These imaging studies are particularly important in evaluation of extraocular extension and in differentiating retinoblastoma from other causes of leukocoria. CT is helpful in detection of calcification, and MRI is helpful in the differential diagnosis for Coats' disease and other inflammatory conditions.[493] Evaluation for the presence of metastatic disease also must be considered in a subgroup of patients. Metastatic disease occurs in approximately 10% to 15% of patients, usually in association with distinct intraocular histologic features, such as deep choroidal and scleral invasion, or with involvement of the iris–ciliary body and optic nerve beyond the lamina cribrosa.[494] In such cases, additional staging procedures, including bone scintigraphy, bone marrow aspiration and biopsy, and lumbar puncture, must be performed.

Staging

The Reese-Ellsworth grouping system generally has been accepted as the standard for intraocular disease staging. This grouping system initially was designed for prediction of outcome after external-beam radiation therapy. In this system, eyes are divided into five groups on the basis of size, location, and number of lesions and presence of vitreous seeding[495]. The Reese-Ellsworth grouping system is gradually being replaced by a new classification system that has adapted to the changes in treatment approaches (Table 99-13). For patients undergoing enucleation, we use the St. Jude pathologic staging system, which incorporates other features known to influence modality of treatment and prognosis, such as choroidal involvement, optic nerve extension, and presence of metastatic disease[496] (Table 99-14).

Principles of Treatment

Management of retinoblastoma is aimed at saving life and preserving useful vision, so treatment must be individualized. Factors to be considered include unilaterality or bilaterality of disease, potential for vision, and intraocular and extraocular staging. Box 99-7 outlines the approach to management of retinoblastoma used at St. Jude Children's Research Hospital.

Surgery

Enucleation is indicated for large tumors filling the vitreous, for which little or no likelihood of restoring vision exists, and for tumor present in the anterior chamber or in association with neovascular glaucoma. For optimal staging, a long section (10 to 15 mm) of optic nerve has to be removed with the globe. A hydroxyapatite implant usually is fitted during the same procedure, and the extraocular muscles are attached to it. The size and type of implant are important for stimulating orbital growth.[497]

Table 99-13 International Classification for Intraocular Retinoblastoma

GROUP A

Small tumors away from foveola and disc

- Tumors ≤3 mm in greatest dimension confined to the retina, and
- Located at least 3 mm from the foveola and 1.5 mm from the optic disc

GROUP B

All remaining tumors confined to the retina

- All other tumors confined to the retina not in Group A
- Subretinal fluid (without subretinal seeding) ≤3 mm from the base of the tumor

GROUP C

Local subretinal fluid or seeding

- Local subretinal fluid alone >3 to ≤6 mm from the tumor
- Vitreous seeding or subretinal seeding ≤3 mm from the tumor

GROUP D

Diffuse subretinal fluid or seeding

- Subretinal fluid alone >6 mm from the tumor
- Vitreous seeding or subretinal seeding >3 mm from tumor

GROUP E

Presence of any of these poor-prognosis features:

- More than two thirds of globe filled with tumor
- Tumor in anterior segment
- Tumor in or on the ciliary body
- Iris neovascularization
- Neovascular glaucoma
- Opaque media from hemorrhage
- Tumor necrosis with aseptic orbital cellulitis
- Phthisis bulbi

Focal Therapy

Focal treatments are used for small tumors (less than 3 to 6 mm), usually in patients with bilateral disease, and in combination with chemoreduction. Photocoagulation with argon laser is used to manage tumors situated at or posterior to the equator and to manage retinal neovascularization due to radiation therapy.[498] Cryotherapy is used to manage small lesions situated in the anterior retina.[499] An important focal method is transpupillary thermotherapy, in which focused heat is applied at subphotocoagulation levels. Use of focal treatments is especially important in conjunction with chemotherapy, and use of both treatment modalities together appears to have a synergistic effect. Sequential administration of thermotherapy with carboplatin enhances the antitumor effect by increasing the platinum-DNA adducts. For this reason, thermochemotherapy is becoming a very important component of the management of intraocular retinoblastoma.[500,501] In addition to its effect on tumor control, cryotherapy increases intraocular penetration of carboplatin, presumably through disruption of the blood-vitreous barrier.[502,503] In general, local control rates of 70% to 80% can be achieved.[498–500]

Radiation Therapy

Retinoblastoma is a highly radiosensitive tumor. With increasing use of chemoreduction in conjunction with intensive focal therapy, however, external-beam megavoltage radiation therapy usually is reserved for cases in which more conservative approaches have failed, usually because of progression of vitreous and subretinal seeding, and for tumors adjacent to the optic nerve. Because most patients undergoing radiation therapy have multifocal disease, the entire retinal surface has to be irradiated to a uniform dose. Several techniques can be used, usually through lateral fields.[504–506] The recommended total dose is 40 to 60 cGy in 180- to 200-cGy fractions, although doses of 36 cGy can be effective in conjunction with other techniques.[507]

Three types of tumor regression after radiation therapy have been categorized. In type I, tumor shrinkage with calcium deposition produces a cottage cheese pattern. In type II, the tumor is a gray, homogeneous mass characterized by partial shrinkage and loss of the pink color of capillary injection. An annulus of atrophic pigment at the base of the tumor also is present. The regression pattern in type III has features of both type I and type II. The mass shows evidence of shrinkage, has lost the pink color, and has a nidus of calcium. Radiation therapy alone can cure 75% to 80% of patients. Addition of cryotherapy or photocoagulation can improve the results to 90%.[504–506]

Radioactive plaque technique is advantageous in the management of localized tumors, both because the procedure time is short and because a high dose of radiation is delivered to the area of interest while radiation effects on the extraocular structures are minimized. Indications for plaque therapy include solitary tumors with a diameter between 6 and 15 mm, tumor thickness of 10 mm or less, and location of the lesion more than 3 mm from the optic disc or fovea. Different radioactive episcleral plaques can be used, although iodine 125 (^{125}I) is the most widely used. A control rate of 85% to 90% can be achieved.[508]

Chemotherapy

Chemotherapy is indicated in the care of patients with extraocular disease, the subgroup of patients with intraocular disease with high-risk histologic features, and patients with bilateral disease in conjunc-

Table 99-14 St. Jude Children's Research Hospital Modified Staging System for Retinoblastoma

Stage	Description
Group I: Tumor confined to the retina	
IA	Solitary, smaller than 6 dd
IB	Multiple, all smaller than 6 dd
IC	Solitary or multiple tumors, involving less than 50% of retinal surface behind equator
ID	Solitary or multiple tumors, involving more than 50% of retinal surface behind equator
IE	Solitary or multiple tumors, involving more than 50% of retinal surface anterior to equator
Group II: Tumor confined to globe, extraretinal	
IIA	Extends to optic nerve head
IIB1	Extends to choroid
IIB2	Extends to choroid with replacement
IIC	Anterior chamber involvement
IID	Extends to choroid and optic nerve
Group III: Tumor with extrachoroidal extension (regional)	
IIIA	Extends to emissaries
IIIB	Extends beyond cut end of optic nerve (including subarachnoid)
IIIC	Extends through sclera into orbital contents
IIID	Extends to choroid and beyond cut end of optic nerve (includes subarachnoid)
IIIE	Extends through sclera and cut end of optic nerve
Group IV: Distant disease	
IVA	Extension through optic nerve into brain, including positive spinal fluid finding
IVB	Blood-borne metastasis to soft tissue, node, or bone
IVC	Bone marrow metastasis

dd, disk diameter (1.5 mm).

From Pratt CB, Fontanesi J, Lu X, et al: Proposal for a new staging scheme for intraocular and extraocular retinoblastoma based on an analysis of 103 globes. Oncologist 1997;2:1–5.

Box 99-7. ST. JUDE CHILDREN'S RESEARCH HOSPITAL APPROACH TO MANAGEMENT OF RETINOBLASTOMA

Most patients with unilateral, sporadic nonmetastatic retinoblastoma can be cured with enucleation alone. Careful histopathologic evaluation of the enucleated eye must be performed. At St. Jude Children's Research Hospital, risk factors for extraocular dissemination are considered to be extension of the tumor to the anterior chamber, ciliary body, or iris; massive choroidal involvement or extension into the sclera; and invasion of the optic nerve beyond the lamina cribrosa. In patients with any of these risk factors, adjuvant chemotherapy is recommended, with the addition of orbital irradiation for patients with transscleral involvement. Patients with metastasis to bone or bone marrow and those with tumor extension into the central nervous system (or in the optic nerve beyond the cut end) need more intensive chemotherapy and consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue.

Patients with bilateral or multifocal disease present a therapeutic challenge. Cure of the disease is the priority, but preservation of the eye and vision also must be taken into consideration. The approach used at St. Jude Children's Research Hospital is highly conservative, and only eyes with very advanced disease at presentation are enucleated. Patients are given chemotherapy and intensive focal treatment. The aim is to delay or avoid external-beam radiation therapy and enucleation. For patients with low-stage intraocular disease, a combination of vincristine and carboplatin is used. For patients with advanced bilateral intraocular disease, the addition of the combination of vincristine and topotecan to the backbone regimen of vincristine and caraboplatin is under investigation. Because most treatment failures are caused by progression of vitreous seeds, subconjunctival carboplatin is added in cases of poor response of vitreous tumors. Patients are monitored closely with examinations performed using general anesthesia every 4 to 6 weeks, and focal treatment is applied during the procedure. Focal treatments include cryotherapy for small anterior tumors, thermotherapy and laser photocoagulation of small posterior tumors, and brachytherapy for larger tumors. Thermotherapy often is used immediately after administration of carboplatin (thermochemotherapy). For patients who need radiation therapy, conformal or intensity-modulated techniques are used to minimize radiation to orbital bones.

tion with aggressive focal therapy. Agents effective in the management of retinoblastoma include platinum compounds, etoposide, cyclophosphamide, doxorubicin, vincristine, and ifosfamide.[509]

Treatment in Specific Settings

UNILATERAL RETINOBLASTOMA. Patients with unilateral retinoblastoma usually have advanced tumors (Reese-Ellsworth groups IV and V) when they come to medical attention, and enucleation is the treatment of choice, being curative in more than 80% of cases. Patients with tumors with high-risk histologic features, such as deep choroidal invasion, or with involvement of the anterior chamber, iris, ciliary body, sclera or retrolaminar portion of the optic nerve, need adjuvant chemotherapy.[510,511] A small number of patients have extraocular or metastatic disease and need more intensive treatment, which usually includes high-dose chemotherapy, hematopoietic stem cell rescue, and radiation therapy to the orbit and areas of bulky disease.[512,513] Except for the small group of patients with metastatic disease, particularly those with central nervous system involvement, outcome among patients with unilateral disease in developed countries is excellent, with good functional results and minimal long-term effects.[514] Eye salvage techniques can be used in the rare patients with Reese-Ellsworth group I through III eyes. In these patients, the combination of chemoreduction with aggressive focal consolidation techniques, usually thermochemotherapy and brachytherapy, is necessary.

BILATERAL RETINOBLASTOMA. In patients with germline mutation of the *RB1* gene, multiple, bilateral retinoblastoma develops at an earlier age. These patients are at risk for development of new tumors until the completion of retinal differentiation. These patients also continue to be at risk for development of extraocular tumors throughout life.[7,8,433] In the past, treatment for patients with bilateral retinoblastoma was enucleation of eyes with advanced intraocular disease and no visual potential and use of external-beam radiation therapy for other eyes. A number of studies, however, have identified several complications associated with the use of radiation therapy. Irradiation of the orbit during a period of rapid growth results in a major decrease in orbital volume, which leads to midfacial deformities.[515,516] More important is increased risk of development of bone sarcoma in the radiation field. This risk appears to be age-related and decreases as radiation is delayed.[517] These concerns have resulted in development of new and more conservative approaches. Treatment of patients with bilateral retinoblastoma has thus evolved to incorporate the use of up-front chemotherapy, which is meant to achieve maximum chemoreduction of the intraocular tumor burden early in treatment, followed by aggressive focal therapy. The goals of this approach are to avoid or delay the use of external-beam radiation therapy and to increase the ocular salvage rate.

The use of systemic chemotherapy for cytoreduction, coupled with intensive use of sequential focal therapy (cryotherapy, laser photocoagulation, thermotherapy, and brachytherapy), has resulted in an increase in eye salvage rate and a decrease (and delay) in the use of radiation therapy. Different chemotherapy combinations are used. The best results are achieved with a combination of vincristine, carboplatin, and etoposide,[500,518–521] although a less intensive regimen with vincristine and carboplatin alone appears to be effective for early intraocular stages.[522] Salvage rates for Reese-Ellsworth group I through III eyes approach 100% when these techniques are used. For patients with advanced intraocular tumors (Reese-Ellsworth groups IV and V), ocular salvage rates are not better than 50% to 70%, and external-beam radiation therapy usually is needed.[518] However, radiation therapy usually is delayed for several months, which allows for better orbital growth and a decrease in the risk of second malignant tumors.

A large proportion of failures occur because of progression of tumor in the vitreous or as subretinal implants, two areas of difficult access for antineoplastic agents.[523] Carboplatin diffuses well into the vitreous.[524] Intraocular concentrations are 7 to 10 times higher when carboplatin is administered subconjunctivally. Results of animal studies have shown dose-dependent inhibition of intraocular tumor growth by subconjuctival carboplatin.[525] These encouraging preclinical data, however, have not been effectively translated into an improvement in the outcome of patients with advanced intraocular disease.[503,526] Radiation therapy appears to be the only valid alternative for these patients. With incorporation of external-beam radiation therapy early in treatment in the case of minimal disease before disease progression occurs, ocular salvage rates for Reese-Ellsworth group V eyes may improve.[522]

Long-Term Effects

Because their orbital growth is still in progress, children who have undergone treatment for retinoblastoma are at risk for the development of functionally and cosmetically significant bony orbital abnormalities. These sequelae become evident by early adolescence, when orbital growth is largely complete, and result in hourglass facial deformity.[515] Both enucleation, which causes orbital contraction, and radiation therapy, which induces arrest of bone growth, adversely affect orbital growth. In children who received treatment for bilateral retinoblastoma, the effect of enucleation on orbital development is not different from that of irradiation. However, final orbital volume after enucleation correlates with the size of the prosthetic implant.[516]

Patients with germline mutation of the *RB1* gene are at risk for development of second tumors.[433,515,516] These patients usually have multifocal, bilateral disease, which often is treated with radiation therapy, thereby further enhancing susceptibility to a second tumor. The cumulative incidence of second malignant tumors is 4% at 10 years, 18% at 35 years, and 51% at 50 years.[433,516] The tumors most commonly encountered are soft-tissue sarcoma, melanoma, and osteosarcoma. An apparent age effect on sarcoma risk has been identified. Patients who received radiation during the first year of life are at higher risk for development of sarcoma.[519] Patients with nonhereditary retinoblastoma are not at increased risk.[433,515]

HEPATOBLASTOMA

Epidemiology

Primary malignant tumors of the liver are rare in the pediatric population, constituting only 1.3% of malignant tumors in children younger than 15 years.[258] Of these, approximately 60% are hepatoblastomas. The median age at diagnosis of hepatoblastoma is 18 months.[527] Although more than 83% of cases occur during the first 5 years of life, the tumor occasionally is found in adolescents and adults. A male preponderance has been noted, with a male-to-female ratio of approximately 1.7 to 1. An intriguing association between extremely low birth weight and hepatoblastoma has been noted.[528–530] The explanation for this association is unresolved, but it has been suggested that environmental exposures in the neonatal intensive care unit, coupled with immature or genetically altered metabolic pathways, contribute to the genesis of hepatoblastoma.[529]

Tumor Biology

Insights into the genetic cause of hepatoblastoma have emerged over the past several years. In the 1980s, an association between hepatoblastoma and familial adenomatous polyposis (FAP) was found.[531] FAP is a disorder of autosomal dominant inheritance characterized by development of colorectal adenomas and nearly universal onset of colorectal carcinoma by the fifth decade of life.[532] Children of patients with FAP are at greatly increased risk for hepatoblastoma compared with the general population. In one study, investigators estimated an 847-fold risk; other investigators reported an overall risk of 0.4% to

0.6%.[533–535] Conversely, it is estimated that 1 in 20 cases (5% to 10%) of hepatoblastoma are associated with FAP.[535,536] In light of these data, colorectal screening should be considered in parents of patients with hepatoblastoma and adolescent survivors of the disease. FAP is caused by a mutation in the adenomatous polyposis coli (*APC*) gene, which encodes a member of the Wnt signaling pathway. A central effector of this pathway is β-catenin, which associates with members of the Tcf family of transcription factors to promote expression of growth-related genes such as MYCC the and the cyclin D1 gene.[537] In normal cells, the APC protein associates with and promotes degradation of β-catenin. Mutations of the $APC_{protein}$, β-catenin itself, and other members of the Wnt signaling pathway lead to accumulation of β-catenin in cell nuclei, activation of Tcf target genes, and tumorigenesis. Germline *APC* mutations in patients with hepatoblastoma without FAP have been reported.[538] A study of sporadic hepatoblastoma revealed loss of heterozygosity or mutations at the *APC* locus in 69% of tumor specimens.[539] Other studies have shown activating β-catenin mutations in 48% to 65% of sporadic cases of hepatoblastoma.[540,541]

Hepatoblastoma can be associated with Beckwith-Wiedemann syndrome, an overgrowth disorder that manifests as high birth weight, macroglossia, organomegaly, hemihypertrophy, neonatal hypoglycemia, abdominal wall defects, ear pits and creases, and a predisposition to development of Wilms' tumor and other malignant lesions. In a series of 183 children with Beckwith-Wiedemann syndrome followed through the first 4 years of life, hepatoblastoma developed in 5 (2.8%) of the patients.[274] The syndrome has been linked to chromosome region 11p15.5, the site of the *IGF2* gene (see earlier, "Wilms' Tumor"). Loss of heterozygosity at this locus has been found in hepatoblastoma samples, implicating *IGF2* or other proximal genes in the development of this disease. As observed in Wilms' tumor, the maternal 11p15 allele is preferentially lost, indicating the presence of genomic imprinting at this site. Loss or relaxation of imprinting of *IGF2*, resulting in a double dose of the gene, has been found in some cases of hepatoblastoma.[542–544]

Cytogenetic studies of hepatoblastoma specimens have revealed that trisomy of chromosomes 20, 2, and 8 are the most frequent chromosomal aberrations in this tumor type.[545–549] A recurrent translocation, t(1;4)(q12;q34), also has been reported.[550,551] Comparative genomic hybridization of 10 hepatoblastoma samples revealed that the most common abnormalities were gains of chromosomes 1q, 2, 17, and 20 and loss of chromosomes 4 and 11.[552] The biologic and clinical significance of these cytogenetic findings is unknown.

Pathology

Hepatoblastoma represents 60% of cases of childhood liver cancer, followed by hepatocellular carcinoma (32%) and extrahepatic biliary tree sarcoma (8%).[553] Other primary malignant tumors that arise in the liver include angiosarcoma, embryonal rhabdomyosarcoma, carcinoid tumor, leiomyosarcoma, teratoma, lymphoma, and neuroblastoma. Benign liver processes in children include vascular tumors (hemangioma and hemangioendothelioma), hamartoma, adenoma, and focal nodular hyperplasia.

Hepatoblastoma most often is unifocal, arising in the right lobe of the liver. Microscopic vascular spread may be found beyond the apparently encapsulated tumor. Hepatoblastoma is classified as either purely epithelial or mixed, consisting of both epithelial and mesenchymal elements. The epithelial type contains either fetal or embryonal cells or admixtures of the two. Rare histologic variants of the epithelial type include the macrotrabecular and small cell (anaplastic) patterns.

The prognostic significance of histologic subtype in patients with hepatoblastoma is unresolved. Data from the 1970s and early 1980s first suggested that completely resected hepatoblastoma of pure fetal histologic type with low mitotic activity is associated with an excellent prognosis.[553–555] On the basis of this observation, in the first Intergroup Hepatoma Study (INT-98), doxorubicin alone was used for chemotherapy in nine patients with completely resected pure fetal hepatoblastoma. All of these patients were alive without disease when the results were reported.[556] The current COG protocol for hepatoblastoma provides for surgical resection alone in patients with completely resected pure fetal hepatoblastoma. By contrast, SIOP does not incorporate histologic subtype into its treatment stratification schema because it is unclear whether completely excised hepatoblastoma of pure fetal histologic type behaves differently from completely excised hepatoblastoma of other subtypes.[557] Moreover, a standardized definition of pure fetal hepatoblastoma is lacking. A growing consensus is that the small cell variant of hepatoblastoma is associated with poor prognosis.[527,558] This variant is easily misdiagnosed because it often is associated with low alpha-fetoprotein (AFP) level and may be present only focally within a tumor.

Clinical Manifestations and Patterns of Spread

Hepatoblastoma most often manifests as an asymptomatic abdominal mass, but systemic signs and symptoms, such as anorexia, weight loss, vomiting, and abdominal pain, can be part of the clinical presentation. In rare instances, the first sign is acute abdominal crisis due to tumor rupture. At physical examination, liver enlargement is found, but jaundice is rare, occurring in fewer than 5% of cases. Other infrequent features include hemihypertrophy (seen in 2% of cases) and precocious puberty (in less than 3% of cases), which occurs in patients whose tumors secrete β-human chorionic gonadotropin. Distant metastatic spread occurs most commonly to the lungs, affecting 10% of patients when the disease manifests. Spread to bone and the central nervous system occurs but is unusual.

Laboratory and Radiologic Evaluation

Ultrasonography typically is the first-line imaging procedure in evaluation of a child with an abdominal mass. For liver tumors, this modality is particularly useful in establishing the presence of a discrete mass within an enlarged liver and in delineating cystic components. CT can be used to define local extent of tumor involvement and to determine important landmarks but is not always reliable in assessment of resectability.[559] MRI is more accurate in this regard and helps define vascular involvement. Although commonly used in the past, angiography plays no role in the diagnostic evaluation of childhood liver tumors. Investigation of metastatic spread includes chest CT. Bone scans typically are not recommended because skeletal metastasis is rare, and osteopenia, which is commonly associated with hepatoblastoma, can result in misleading findings.[560]

Routine blood counts frequently reveal mild normochromic normocytic anemia and marked thrombocytosis. Liver enzyme and bilirubin levels are infrequently elevated. The most valuable laboratory test for both diagnosis and monitoring of hepatoblastoma is determination of serum AFP. AFP levels are elevated in 80% to 90% of patients with hepatoblastoma, presumably reflecting recapitulation of fetal liver development by the tumor. After complete resection, an exponential decrease to normal range can be expected. Failure to achieve normal levels implies the presence of residual disease. Secondary elevation implies disease recurrence. Clinicians should note that AFP levels normally are elevated at birth and gradually decline to adult levels over the first year of life.

Staging

In North America, staging for hepatoblastoma is based on postsurgical findings. Low stage is assigned to completely resected tumors and high stage to unresectable tumors and those with distant metastatic

Table 99-15 Postsurgical Staging System for Hepatoblastoma

Stage	Description
I, favorable histologic features	Gross total resection with clear tumor margins. *Favorable histologic type* defined as pure fetal type with fewer than two mitoses per 10 high-power microscope fields
I, unfavorable histologic features	Gross total resection with clear tumor margins and absence of favorable histology
II	Gross total resection with microscopic residual disease at the tumor margins
III	Gross total resection with nodal involvement or tumor spill or incomplete resection with gross residual intrahepatic disease
IV	Distant metastatic disease

involvement[556] (Table 99-15). With the advent of preoperative chemotherapy, SIOP introduced a presurgical grouping system called PRETEXT (for *pret*reatment *ext*ent of disease).[561] In this system, the liver is divided into four sectors on the basis of anatomic distribution of the major veins and bile ducts. Group I denotes that three adjoining sectors are tumor-free; group II, that two adjoining sectors are tumor-free; group III, that one sector or two nonadjoining sectors are tumor-free; and group IV, that all sectors are involved (Fig. 99-19). Invasion of the hepatic and portal veins, extrahepatic extension, and distant metastatic lesions are designated separately in this system.

Treatment

The survival rate for hepatoblastoma has improved markedly, from only 30% in the 1970s to 60% to 70% today.[562] This improvement may be attributed to the advent of effective adjuvant chemotherapy and to the use of liver transplantation for patients with otherwise unresectable disease. The underlying principle of hepatoblastoma treatment is that complete surgical resection is necessary to achieve long-term cure. Although complete excision is possible at diagnosis in 40% to 60% of patients,[527] preoperative chemotherapy can render the tumor resectable in most cases.[563–574] Analogous to the international debate regarding the timing of Wilms' tumor resection, differing opinions have been presented regarding whether preoperative chemotherapy should be delivered to all patients with hepatoblastoma. The COG advocates initial resection of the primary tumor whenever possible, because this approach allows the most accurate histologic diagnosis.[567] By contrast, SIOP favors preoperative chemotherapy for all patients to render the tumors more amenable to resection.[568]

Management of hepatoblastoma unresectable after systemic neoadjuvant chemotherapy is a clinical challenge. Disease confined to the liver after primary chemotherapy has been managed with chemoembolization, which induces tumor responses and surgical resectability in some patients.[569,570] For patients with unresectable tumors, orthotopic liver transplantation seems to offer the best possibility of cure. A systematic literature review of the world experience with liver transplantation in patients with hepatoblastoma revealed 6-year overall survival rates after transplantation of 82% for patients who received a primary liver transplant and 30% for patients who underwent rescue transplantation for recurrent disease or complications of partial hepatectomy [575] among children with hepatoblastoma managed with liver transplantation with or without adjuvant chemotherapy.[571–576] Cure after liver transplantation has occurred even in children with a history of pulmonary metastasis. These results are much more favorable than those for the experience with hepatocellular carcinoma, perhaps because of the inherent chemosensitivity of hepatoblastoma.

Even if complete resection of the primary tumor is attained, adjuvant chemotherapy is recommended to eradicate micrometastatic disease.[577] Box 99-8 outlines the approach to management of hepatoblastoma used at St. Jude Children's Research Hospital. Current chemotherapy regimens for hepatoblastoma are based on several generations of clinical trials. The CCG-823F study showed that the combination of cisplatin and continuous infusion of doxorubicin led

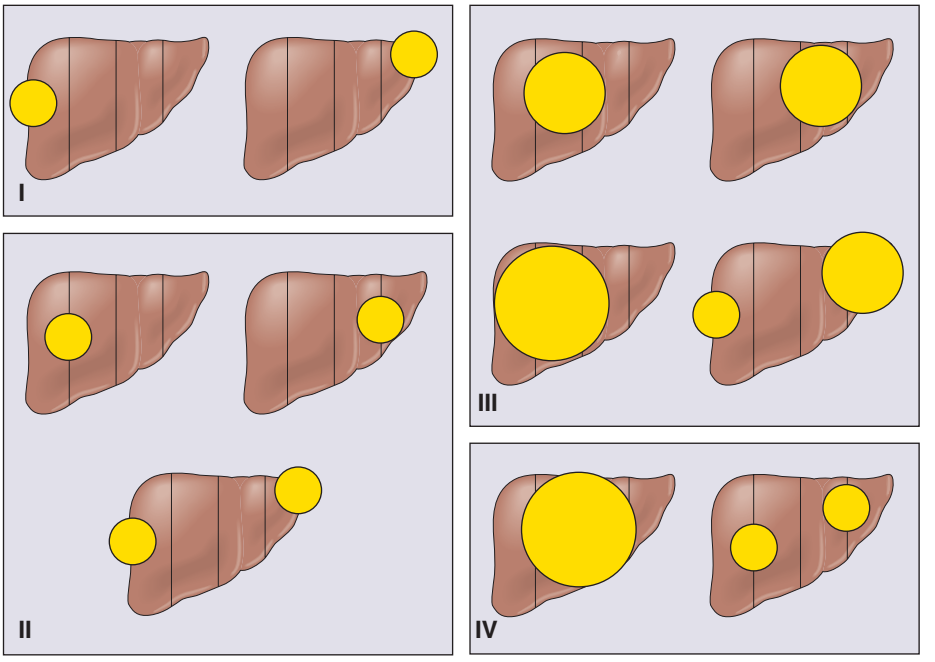


Figure 99-19 • Pretreatment staging system (Pretext) proposed by the International Society of Pediatric Oncology. The liver is divided into four sectors on the basis of the anatomy of the major vessels and bile ducts. Group I denotes one-sector involvement (three adjoining sectors are tumor free); group II, two-sector involvement (two adjoining sectors are tumor free); group III, three-sector involvement (one sector or two nonadjoining sectors are tumor free); and group IV, four-sector involvement (no sectors are free of tumor). Involvement can be either unifocal or multifocal, although hepatoblastoma usually is unifocal. Additional designations are given for metastasis, ingrowth into the vena cava or porta hepatis, and extrahepatic extension.

Box 99-8. ST. JUDE CHILDREN'S RESEARCH HOSPITAL APPROACH TO MANAGEMENT OF HEPATOBLASTOMA

Complete surgical resection is essential for achieving long-term cure in children with hepatoblastoma. At St. Jude Children's Research Hospital, surgical resection at diagnosis is attempted whenever feasible. If complete resection is achieved, patients receive four cycles of postoperative chemotherapy with cisplatin, 5-fluorouracil, and vincristine. Doxorubicin-containing regimens are reserved for patients with unresponsive or recurrent tumor. No standard of care has been established for patients with stage I hepatoblastoma of pure fetal histologic type with a low mitotic rate. In the current Children's Oncology Group hepatoblastoma study, such patients do not receive chemotherapy and are observed closely. If complete surgical resection is not feasible at diagnosis, four cycles of preoperative chemotherapy are administered, and resectability is reassessed. Once complete resection is achieved, patients receive two additional cycles of chemotherapy. Patients with tumors unresectable after chemotherapy are considered for liver transplantation or other local control measures, such as chemoembolization. The presence of distant metastatic disease that is resectable or resolves with chemotherapy does not preclude complete resection of the primary tumor or liver transplantation.

to a measurable tumor response in 75% of patients with initially unresectable disease and that 58% of these patients continued to be disease-free after treatment.[563] Contemporaneously, the POG-8697 study achieved similar results with a regimen of cisplatin, vincristine, and 5-fluorouracil.[565] The cisplatin-doxorubicin and cisplatin–vincristine–5-fluorouracil regimens were compared in a randomized trial (INT-98) that revealed 5-year EFS estimates of 69% for the doxorubicin-containing arm and 57% for the 5-fluorouracil–vincristine-containing arm ($P = 0.09$).[556] EFS rates were 100% for stage I favorable histologic type, 91% for stage I unfavorable histologic type, 100% for stage II, 64% for stage III, and 25% for stage IV. Because toxicity was more frequent with the doxorubicin-containing regimen, the combination of cisplatin–vincristine–5-fluorouracil emerged as the standard chemotherapy regimen in North America. The SIOPEL-1 study, in which a cisplatin-doxorubicin combination was used, yielded the subsequent COG 9645 study, which tested the hypothesis that intensification of platinum drugs would improve outcomes for patients with stage III or IV disease. Patients were randomized to receive cisplatin–vincristine–5-fluorouracil versus cisplatin alternating with carboplatin. The study was closed early after 3 years of enrollment because improvement with the cisplatin-carboplatin arm was statistically excluded. Three-year EFS rates were 60% for patients receiving cisplatin–vincristine–5-fluorouracil and 38% for patients receiving cisplatin plus carboplatin.[578] The COG 9645 study also evaluated whether the chemoprotectant amifostine prevents cisplatin-induced toxicity. At the dose and schedule used, amifostine was not protective.[579]

The European-based SIOPEL studies have taken a different approach. The SIOPEL-1 study used a cisplatin-doxorubicin combination (PLADO), which resulted in a 5-year EFS rate of 66% and a 5-year overall survival rate of 75%.[563] As in the INT-98 study, patients with metastatic disease had a 5-year EFS rate of only 28%.[580] The SIOPEL-2 study piloted a regimen of single-agent cisplatin for patients with localized hepatoblastoma confined to no more than three liver sectors (PRETEXT group III or lower).[568] Promising results were obtained using this regimen. Accordingly, the SIOPEL-3 study was designed to compare the effectiveness of cisplatin plus doxorubicin versus cisplatin alone in patients with localized hepatoblastoma. With this approach, the 3-year overall and progression-free survival rates were 91% and 89%, respectively.[581] Because of the success of single-agent cisplatin, the subsequent study, SIOPEL-3, was designed to compare the effectiveness of cisplatin plus doxorubicin with that of cisplatin alone in patients with tumors in PRETEXT group III or lower. Results have not yet been reported. Patients with high-risk disease (PRETEXT group IV tumors or distant metastases) received alternating courses of carboplatin plus doxorubicin and single-agent cisplatin on SIOPEL-2 and -3. This yielded 3-year overall and progression-free survival rates of 59% and 55%.[582] The German Pediatric Oncology Group used an ifosfamide-doxorubicin-cisplatin regimen, which resulted in a long-term disease-free survival rate of 75%.[583]

To summarize, modern cisplatin-containing chemotherapy regimens produce very good outcomes for patients with localized and completely resected hepatoblastoma. Novel agents and approaches are needed to improve outcome among patients with metastatic disease.

The role of radiation therapy in the management of hepatoblastoma is limited and undefined. Studies conducted with small series showed that in patients with microscopic or gross residual disease, local control can be achieved with radiation therapy and chemotherapy. These results suggest a possible role for irradiation in this setting.[565,584,585] Successful use of radiation therapy also has been reported for control of pulmonary metastatic lesions after wedge resection and chemotherapy.[584,585] In view of the effectiveness of surgery and chemotherapy, however, radiation therapy is not considered first-line therapy for hepatoblastoma.

Recurrence of hepatoblastoma usually confers a poor prognosis, especially if disease recurs locally or within 6 months after the initial manifestations. Long-term survival has been achieved, however, with aggressive surgical management, especially in the setting of isolated pulmonary metastatic disease.[586] The agent irinotecan has shown activity against recurrent hepatoblastoma.[587,588] The role of high-dose therapy followed by autologous stem cell rescue is unclear.

Although progress has been made in the management of hepatoblastoma, the goal of future studies will be to identify new agents with activity against this disease and to systematically define the role of orthotopic liver transplantation. Future trials will attempt to limit toxicity and the late effects of treatment without compromising care.

ADRENOCORTICAL CARCINOMA

Epidemiology

Adrenocortical carcinoma (ACC) is one of the rarest and most aggressive endocrine neoplasms. It follows a bimodal distribution, having peaks during the first and fourth decades of life.[589] Among children, 25 new cases are expected to occur annually in the United States, for an estimated annual incidence of 0.2 to 0.3 case per million population. Internationally, however, the incidence of ACC appears to vary substantially. The incidence of ACC is particularly high in southern Brazil, where it is approximately 10 to 15 times that in the United States. Most cases occur in the contiguous states of São Paulo and Paraná. Predisposing genetic factors have been implicated in 50% of cases in the United States and in 95% of cases in Brazil. In patients in both countries, germline *TP53* mutations are almost always the predisposing factor. In the United States, the incidence of cancer (Li-Fraumeni syndrome) often is high among relatives of children with ACC, and germline mutations occur in the *TP53* DNA-binding domains (exons 2 to 8). In Brazil, by contrast, patients' families do not have a high incidence of cancer, and a single mutation in axon 10 of the *TP53* gene is consistently observed in these children. This mutation occurs within the tetramerization domain of *TP53* (*TP53*-

R337H). This mutant tetramerization domain is less stable than the wild-type domain and is highly sensitive to pH in the physiologic range. This inherited unique *TP53* mutation represents a low-penetrance allele that contributes to development of ACC in a tissue-specific manner.[590,591] The incidence of *R337H* mutations in U.S. children with ACC is not known.

Clinical Manifestations

Typical clinical manifestations of ACC are the signs and symptoms of increased production of androgens (virilization) or cortisol (hypercortisolism or Cushing's syndrome). In rare instances, patients exhibit signs of hyperestrogenism (feminization) or aldosteronism (Conn's syndrome). Mixed syndromes are frequent. In general, 40% to 80% of patients have functioning tumors,[589–598] although as many as 50% of tumors may produce mainly hormonal precursors of low bioactivity.[596] An apparent correlation between the degree and type of endocrine disturbance and the age of the patient has been described.[589,594] Older patients are much more likely to have nonfunctioning tumors, whereas more than 90% of children have functioning neoplasms.[594,599–601] Adults usually have mixed virilization-hypercortisolism syndromes, whereas virilization syndromes constitute the most common manifestation in children. Most patients (50% to 60%) come to medical attention with large tumors and advanced regional or metastatic disease.[580–586,592–598,602] Distant metastatic lesions usually affect liver, lungs, and bone, in that order of frequency.[594]

Diagnosis

The diagnosis of ACC is straightforward. Because most affected children have an endocrine syndrome, an increased blood or urine concentration of adrenocortical hormones and a mass in the suprarenal region usually suggest a preoperative diagnosis of adrenocortical tumor. The distinction between benign (adenoma) and malignant (carcinoma) tumors, however, may not be easy. Several investigators have proposed histologic criteria that may help in discriminating between the two types of neoplasms.[603,604] Of note, the morphologic criteria used to differentiate benign from malignant pediatric adrenocortical tumors may not be reliable, especially in cases of carcinoma.

Prognostic Factors

In addition to stage at diagnosis, specific biologic and histopathologic characteristics within individual tumors appear to dictate outcome. Mitotic rate has been consistently reported as the most important determinant of aggressive behavior.[593,602,605,606] Tumor size, however, appears to have independent prognostic value.[602,606] Tumor size is especially important in children; with tumors smaller than 200 cm^3 or 100 g, the outcome is excellent with surgery alone.[599,607,608]

Treatment

Surgery is the mainstay of therapy for ACC. Curative, complete resection may be attempted in the 70% to 75% of patients with locoregional disease. Low stage and the ability to perform complete resection are the most important prognostic factors.[592,593,596,597,602,609] Despite efforts at curative surgery, however, the 5-year survival rate is not better than 30% to 40%.[593,594–598] As many as 70% to 80% of patients with a localized primary tumor experience recurrence.[602] Recurrences may be locoregional (15% to 25%), combined local and distant (25% to 30%), or distant alone (50%).[593,602,610] In childhood ACC, more than 90% of patients with stage I disease are long-term survivors, compared with 10% of those with stage IV disease. Despite presumed complete tumor resection, disease recurs in 50% of patients with stage II disease.[599] Because of tumor friability, rupture of the capsule leading to tumor spillage is frequent. Large ACC tends to adhere to adjacent structures (e.g., vena cava) and to have large necrotic and friable areas that make radical excision without capsule rupture very difficult.

For patients with advanced disease or with high risk of recurrence, systemic therapy with mitotane or chemotherapy is indicated, although the effect of this therapy on overall outcome is not well established. Mitotane (*o,p′*-DDD) both inhibits corticoid biosynthesis and destroys adrenocortical cells. At low doses (less than 3 g/day), mitotane suppresses secretion of adrenal steroids, providing symptomatic improvement and regression of some of the endocrine dysfunction. Higher doses (greater than 3 g/day) are required for an adrenolytic effect.[592,594] In patients with advanced disease, objective responses are obtained in approximately 20% to 30% of cases.[592,594,596,611] These responses are transient, however, and the effect on prolongation of survival is uncertain.[594,596,612] In children, the use of mitotane for advanced ACC has not been evaluated systematically. Complete responses in children with advanced or metastatic ACC have been described but appear to be rare events.[613–615] The pharmacokinetics of mitotane and the ability to maintain therapeutic levels for long periods appear to affect the antitumor effect. Serum levels plateau after 8 weeks of treatment,[594] and optimal antitumor responses occur when serum levels are maintained at more than 14 μg/mL for long periods.[609,611] A major problem, however, is the severe gastrointestinal and neurologic toxicity associated with administration of mitotane. The toxicity limits patient adherence to therapy, especially among children.[594,596,611] An alternative approach to use of high doses of mitotane is administration of low doses (2 to 3 g/day) for longer periods. With the appropriate monitoring, therapeutic levels can still be achieved after 3 to 5 months.[616,617] Chemotherapeutic agents other than mitotane have been less often evaluated in management of ACC. Cisplatin-based regimens induce responses in 20% to 40% of patients.[618–620] Preclinical studies have shown that mitotane reverts the multidrug resistance phenotype in vitro,[621] providing a rationale for the combination of mitotane with etoposide-containing regimens.[622,623] Responses have been observed in 53% of patients when the combination of mitotane with cisplatin, etoposide, and doxorubicin has been used.[623]

NASOPHARYNGEAL CARCINOMA

Nasopharyngeal carcinoma (NPC) is very rare in children. Only 1% of all cases of NPC occur in patients younger than 19 years of age.[624] In the United States, the incidence of NPC in children is approximately 1 to 1.5 cases per million population per year. NPC represents approximately 1% of all pediatric malignant tumors, but it accounts for 35% to 50% of all nasopharyngeal malignant tumors.[625] In the United States, NPC appears to be more prevalent in the southern states and among African-American children.[626] The role of EBV in the development of NPC has been well established. EBV is harbored in almost every tumor, as shown by the presence of EBV DNA, RNA, and proteins in tumor tissue samples.[627–630] The role of EBV in neoplastic transformation is further supported by the presence of clonality. In nonendemic areas of the Western hemisphere, other causative factors, such as alcohol and tobacco use, may have an important role. Information on the clinical and biologic characteristics of childhood NPC is scarce, in particular that related to the role of EBV in its pathogenesis. Both histologic subtype and age at clinical manifestation of the tumor, however, suggest that pediatric NPC may be strongly associated with EBV infection. No studies have been aimed at characterizing or confirming the role of EBV in the pathogenesis of NPC in children.

Few studies have analyzed the clinical characteristics and outcome of NPC among children.[625,626,631–640] In almost all cases of NPC in this age group, type III histologic features are present, and clinical manifestation occurs at advanced stages. Most of these studies incor-

porated the use of cisplatin- or doxorubicin-based neoadjuvant and adjuvant chemotherapy.[625,631–638] With this combined approach, the survival rate among patients with advanced disease is 60% to 70%. The best results have been those reported by Douglass and collaborators at St. Jude Children's Research Hospital.[641] In their series of 21 patients, four courses of neoadjuvant chemotherapy with methotrexate, cisplatin, 5-fluorouracil, and leucovorin were given, followed by radiation therapy (in doses of 66 to 70 Gy). All 21 patients achieved complete remission, and 20 of them were long-term survivors. Because children are particularly sensitive to the toxicity related to therapy for NPC, alternatives aimed at decreasing toxic effects are of particular importance in this population. The alternatives include use of amifostine and investigation of carboplatin as an alternative to cisplatin.

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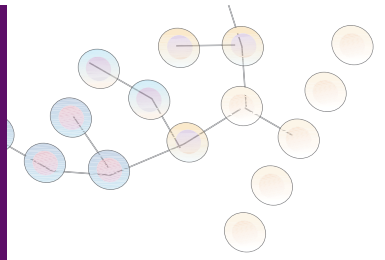
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100 World Health Organization Classification of Hematologic Malignancies*

Elaine S. Jaffe

SUMMARY OF KEY POINTS

- The World Health Organization (WHO) Classification includes tumors of lymphoid, myeloid, histiocytic, and dendritic cell lineages.
- Each disease is defined as a distinct entity based on a constellation of morphological, clinical, and biological features.
- The cell of origin is the starting point of disease definition.
- Some lymphomas and leukemias can be identified by routine morphological approaches. However, for many diseases, knowledge of the immunophenotype and molecular genetics/cytogenetics plays an important role in differential diagnosis.
- The sites of presentation and involvement are an important clue to underlying biological distinctions. Extranodal lymphomas differ in many respects from their nodal counterparts.
- Many lymphoma entities display a range in cytological grade and clinical aggressiveness, making it difficult to stratify lymphomas according to clinical behavior. Several prognostic factors influence clinical outcome, including stage, international prognostic index, cytological grade, gene expression profile, secondary genetic events, and the host environment.
- The WHO classification includes four major categories of myeloid diseases, all of which are clonal stem cell disorders leading to either effective or ineffective hematopoiesis:
  - Myeloproliferative neoplasms
  - Myelodysplastic/myeloproliferative neoplasms
  - Myelodysplastic syndromes
  - Acute myeloid leukemias (AMLs)
- Among myeloid leukemias, genetic features predict behavior better than morphology alone, necessitating genetic studies for accurate diagnosis.
- AMLs, with myelodysplasia-related features, seem to represent separate pathways to leukemogenesis, with clinical implications for response to therapy.

INTRODUCTION

In recent years the discipline of hematopathology has emphasized the integration of morphology and biological markers for diagnosis. In this respect the approaches used in hematological diagnosis often have served as a model for other areas of pathology. For example, in the early 1980s detection of rearrangements of the antigen receptor genes in lymphoid cells was used to indicate both clonality and cell lineage, long before molecular diagnostic techniques became commonplace in pathology.[1] Biological approaches such as immunohistochemistry and molecular biology enhance diagnostic accuracy and play a critical role in the definition of disease entities.

Classification approaches for both lymphoid and myeloid neoplasms have undergone significant reappraisal over the past 40 years. These changes have resulted from insights gained through the application of immunological and molecular techniques, as well as better understanding of the clinical aspects of lymphoma and leukemia through advances in diagnosis, staging, and treatment.

HISTORICAL BACKGROUND

The classification of lymphomas in the past was controversial, and it had been difficult to establish an internationally accepted scheme. The earliest classification schemes were morphologically based on cytological and architectural features.[2] However, insights into the complexities of the normal immune system led to attempts to relate the lymphomas to their normal cellular counterparts. In the 1970s several European and American groups published proposals for the classification of lymphoma, and competing classification systems in use in clinical studies made it difficult to compare outcome data from different treatment centers.[3–6] The inability of the pathologists to develop consensus and agree on a common approach led to the development of the Working Formulation for the non-Hodgkin's lymphomas, following a National Cancer Institute–directed study to evaluate the six published schemes.[7]

Constructed in large measure by clinicians, the working formulation tried to stratify lymphomas according to clinical outcome on the basis of clinical trials conducted in the 1970s.[7] The low-grade, intermediate-grade, and high-grade groupings were intended to provide a clinical guide for patient management. The individual lymphoma categories were defined by morphological principles, such as growth pattern and cell size, without regard to cell lineage or stage of differentiation. Therefore, most of the diagnostic categories of the working formulation were heterogeneous. For example, "diffuse mixed small and large cell lymphoma" included a variety of both B-cell and T-cell lymphomas. It is therefore not surprising that pathologists could not use these categories reproducibly.[8]

The original intent of the working formulation proposal was to have it serve as a common language to translate among classifications, and not to serve as a freestanding classification scheme. However, because it was a convenient guide to therapy, it quickly became popular among clinicians and was adopted for use in many centers in the United States for clinical trials. In reality the working formu-

*This chapter is in the public domain.

lation was in essence the Rappaport classification[2] with updated terminology from Lukes and Collins.[3] It substituted the term "large cell" for "histiocytic" and divided the "histiocytic" lymphomas of the Rappaport scheme into two subgroups: large cell (cleaved or noncleaved) and large cell immunoblastic. This separation split the diffuse large cell lymphomas into two different treatment groups (intermediate and high grade), solely on the basis of morphological distinctions. These distinctions were not reproducible, and the clinical groupings could not be validated.

Another more basic flaw in the working formulation is that it was based on treatment outcome, not on the recognition of individual disease entities or the cell of origin for a malignant neoplasm. It lumped diseases that shared a similar cell size and median survival into single categories, even though they might be of different cellular (B- and T-cell) origins with diverse clinical features. At the time the working formulation was proposed immunophenotyping was believed to be beyond the reach of the routine pathology laboratory, and the classification was based on morphology alone.

A similar paradigm developed in the classification of acute myeloid and lymphoid leukemias. Earlier classification systems emphasized morphological approaches, although the French American and British (FAB) classification did use enzyme cytochemistry to identify cellular lineage and degree of differentiation, at least within the myeloid and monocytic neoplasms.[9] The categories of acute lymphoblastic leukemia, L1, L2, and L3 included both mature and immature lymphoid malignancies, in that L3 was largely composed of mature blastic B cells similar to the cells of Burkitt's lymphoma. L1 and L2, though both of lymphoblastic origin, correlated poorly with precursor T- or B-cell lineage.

Modern immunophenotypic and molecular approaches for characterizing lymphoid and myeloid cells are now readily available at even the community hospital level. The use of these new biological approaches has transformed our understanding of hematological neoplasia. Immunophenotypic, cytogenetic, and genotypic studies have permitted an impartial analysis of questions that were unresolved when addressed with only routinely stained sections or smears. Indeed, a broad international consensus has emerged on many topics. This consensus was embodied in the Revised European-American Classification of Lymphoid Neoplasms (REAL classification) published by the International Lymphoma Study Group (ILSG) in 1994,[10] and broadened to include myeloid and histiocytic neoplasms in the WHO classification.[11]

NEXT STEPS: FROM REVISED EUROPEAN-AMERICAN CLASSIFICATION OF LYMPHOID NEOPLASMS TO WORLD HEALTH ORGANIZATION CLASSIFICATION

The REAL classification[10] and its successor the WHO classification[11] represented a new paradigm in the classification of lymphoid neoplasms. The focus was on the identification of "real" diseases, rather than a global theoretical framework, such as survival (working formulation), or cellular differentiation (Kiel classification). The REAL classification was based on the building of consensus, recognizing that a comprehensive classification system was beyond the experience of any one individual. The 19 members of the ILSG contributed their diverse perspectives to achieve a unified point of view. In addition, the ILSG made the decision to base the classification exclusively on published data. Earlier classification systems had often been based on theoretical and untested propositions. However, to be included in the REAL classification, an entity had to be validated in at least several publications. In addition, several entities were listed as provisional, on the basis of more limited published data.

The REAL classification departed from traditional schemes by emphasizing that each disease was a distinct entity, defined by a constellation of laboratory and clinical features (i.e., morphology, immunophenotype, genetic features, clinical presentation, and course). The inclusion of clinical criteria was one of the most novel aspects of the ILSG approach. The REAL classification recognized that the site of presentation is often a signpost for underlying biological distinctions, as in extranodal lymphomas of the mucosal-associated lymphoid tissues (MALT)[12] or many forms of T-cell lymphoma.[13,14] Accurate diagnosis requires knowledge of the clinical history, because biologically distinct entities may appear cytologically similar.

The REAL classification also stressed the distinction between histological grade and clinical aggressiveness, because these concepts do not necessarily go hand in hand. For example, mantle cell lymphoma, which is composed of small to medium-sized lymphoid cells with condensed chromatin, had been considered cytologically "low grade," but in fact is one of the more aggressive lymphoma subtypes.[15,16] Similarly, among the T-cell lymphomas, angioimmunoblastic T-cell lymphoma has an aggressive clinical course, with a median survival of less than 3 years.[17] By contrast, anaplastic large cell lymphoma, despite the appearance of high histological grade, in the majority of patients has an excellent response to chemotherapy with prolonged disease-free survival.[18]

Moreover, within a given disease entity several prognostic factors influence the clinical outcome. Cytologic grade is one type of prognostic factor and is used in the stratification of follicular lymphoma. Clinical features, such as the stage or international prognostic index, also markedly affect survival and response to treatment.[19] Finally, a variety of biological factors, some of which may be secondary, affect the prognosis. These include secondary genetic events, such as mutations in p53 genes, which often lead to histological and clinical progression.[20–22] Thus, the WHO classification stresses the distinction between a *disease entity* and a *prognostic factor*.

For these reasons it is not possible to stratify lymphoma subtypes according to clinical grade, as had been attempted in the working formulation. Moreover, clinical groupings for either protocol treatment or routine clinical practice are generally not feasible. In evaluating new therapies the data for each disease must be evaluated individually. Indeed, treatment approaches for one type of lymphoid malignancy are not necessarily applicable to other diseases, even of the same cell lineage. This point is exemplified by hairy cell leukemia, a rare disease for which highly effective forms of therapy have been developed.[23,24] However, the purine analogues 2′-deoxycoformycin and 2′-chlorodeoxyadenosine have not been similarly effective in treating other B-cell leukemias and lymphomas.[25]

The REAL classification was first to emphasize the importance of molecular oncology in defining disease entities. Cancer is increasingly recognized as a genetic disease.[26] For many lymphomas there is a good correlation between the molecular pathogenesis and routine histological and immunophenotypic features. For example, the t(14;18) involving the *BCL-2* and *JH* genes is highly associated with follicular lymphoma diagnosed by routine methods. In addition, some molecular phenotypes can be recognized by immunohistochemistry, such as cyclin D1 overexpression in the diagnosis of mantle cell lymphoma, or ALK fusion protein expression in anaplastic large cell lymphoma.[27]

However, for many lymphoma subtypes, particularly the mature T-cell malignancies, the molecular pathogenesis is not known. The REAL/WHO classifications recognized limitations in our knowledge, and created "generic groupings" for those broad categories of disease that could not be resolved with existing data; these include diffuse large B-cell lymphomas and peripheral T-cell lymphomas, unspecified. Although several morphological variants had been described, evidence that these delineated distinct biological or clinical entities was lacking.

Following the publication of the REAL classification, an international study directed by Dr. James Armitage sought to determine if the REAL classification could be readily applied by a group of independent expert pathologists.[18] Other goals of the International Lym-

phoma Classification Project were: (1) to determine the role of immunophenotyping and clinical data in the diagnosis of disease entities; (2) to determine both intraobserver and interobserver reproducibility in the diagnosis of the various entities; (3) to further investigate the clinical features and/or epidemiology of the various entities; and (4) to determine if clinical groupings would be practical or useful for clinical trials or practice.

The conclusions of that study affirmed the principles of the REAL classification.[18] The use of precise disease definitions, as provided by the REAL scheme, enhanced diagnostic accuracy and reduced interobserver variability. The significance of identifying individual disease entities was confirmed by overall survival and failure-free survival data.

This study also highlighted the importance of clinical factors in predicting outcome, beyond the diagnosis alone.[19] Therefore, one must approach each disease entity individually, considering the diagnosis, the patient's risk factors, and the known idiosyncrasies of each disease with regard to treatment.

WORLD HEALTH ORGANIZATION CLASSIFICATION

Precise disease definitions have also facilitated the discovery of the molecular pathogenesis of lymphomas and leukemias. Many pathogenetic insights have followed on the heels of the identification of a disease along clinical lines (Table 100-1). Moreover, advances in therapy are best achieved when studies are conducted on a homogeneous disease entity. For example, the approaches to therapy of extranodal marginal B-cell lymphoma of MALT type differ from those of more systemic small B-cell malignancies. The ultimate goal in this model is molecularly targeted therapy, such as the use of imatinib to target the *BCR/ABL* tyrosine kinase of chronic myelogenous leukemia.[28]

In 2001 the International Agency for Research on Cancer (IARC) under the auspices of the WHO published a unified and internationally accepted classification scheme for all lymphoid, myeloid, histiocytic, and dendritic cell neoplasms (Box 100-1).[11] Part of series by the IARC, a goal is to integrate pathology and genetics to develop biologically relevant classification systems. The WHO adopted the approach of the REAL classification for the lymphoid malignancies, because this approach had been validated, and in turn applied the same principles to tumors of other hematopoietic lineages, mainly myeloid and histiocytic tumors.

Continued advances in disease definition have led to refinements in diagnostic categories. For example, "Hodgkin's-like anaplastic large cell lymphoma"[29,30] was believed upon further analysis to be resolvable into either an aggressive form of Hodgkin's disease or a rare variant of T-null anaplastic large cell lymphoma in most cases.[31] It was therefore eliminated as a category in the WHO scheme.

Table 100-1 Pathogenetic Insights Based on a Disease-Oriented Approach to Classification

Disease	Characteristic Findings
Adult T-cell leukemia/lymphoma	HTLV-1
Nasal NK/T-cell lymphoma	EBV, genetics
Anaplastic large cell lymphoma	*ALK* tyrosine kinase
Mantle cell lymphoma	*CCND1*
Lymphomatoid granulomatosis	EBV, immune dysfunction
Follicular lymphoma	*BCL2*
MALT lymphoma	*Helicobacter, MLT*
Burkitt's lymphoma	*C-MYC*
Primary effusion lymphoma	Herpesvirus-8

Molecular profiling studies are leading to better delineation of aggressive B-cell lymphomas.[32,33] For example, gene expression profiling studies identified two broad categories of diffuse large B-cell lymphoma (DLBCL); one group resembling germinal center B cells (GCBs) and a second group resembling activated peripheral blood B cells (ABCs). Furthermore, these studies are providing insights into the molecular pathways that are primarily deregulated in these tumors. For example, the ABC type of DLBCL is associated with activation of the NF-κB pathway. The host response and the tumor microenvironment have also been shown to be important in predicting outcome.[32,34] In follicular lymphoma as well the microenvironment within the neoplastic follicle seems to represent a major prognostic factor, independent of cytological grade.[35]

Additionally, stratification according to genetic and genomic profiling is beginning to have an impact on clinical practice. For example, DLBCLs of the ABC type show a significant benefit from the inclusion of rituximab in the treatment regimen, whereas DLBCLs of the GCB cell type do not.[36]

Finally, tumors that were thought to be distinct, such as classical Hodgkin's lymphoma and primary mediastinal large B-cell lymphoma have been shown through molecular approaches to share common pathways of activation and/or deregulation.[37,38] These genomic insights have also helped elucidate the nature of lymphomas that seem to bridge the gap between classical Hodgkin's lymphoma and mediastinal lymphoma, so-called gray zone lymphomas.[39] Indeed, composite, sequential, and gray zone lymphomas are observed with some regularity.[40]

The WHO classification applied the principles of the REAL classification to the classification of myeloid and histiocytic tumors, and expanded upon the classification of precursor lymphoid malignancies, the lymphoblastic lymphomas/leukemias, which had been touched upon only briefly in the REAL classification. For the acute leukemias the molecular pathogenesis is a very important determinant of clinical behavior. Unfortunately, in contrast to the lymphomas, correlations between the genetic profile, morphology, and the immuno/enzymatic phenotype are frequently absent, and for some prognostically important categories, genetic studies are essential.[41,42] Additionally, acute leukemias, being of stem cell origin, display significant lineage promiscuity at the genetic and phenotypic levels. The WHO classification for myeloid neoplasms departed from the FAB classification in several ways. For those forms of acute myeloid leukemia (AML) associated with recurrent genetic abnormalities, genetic features take precedence over morphology. However, some genetic lesions are associated with a characteristic morphological appearance.[43] For example, the detection of the inv(16) or t(16;16) usually correlates with M4 with abnormal eosinophils in the FAB approach.[44] Recurrent genetic abnormalities can be identified with classical cytogenetics, reverse transcriptase–polymerase chain reaction, or fluorescence in situ hybridization techniques.

On the basis of the observation that AML arising in the setting of myelodysplastic syndrome (MDS) is associated with some distinctive clinical and biological features, the WHO classification of 2001 distinguished two broad groups of de novo AML, with and without multilineage dysplasia.[45–47] Cases of AML with significant myelodysplastic features generally occur at an older age, respond poorly to therapy, and have high-risk cytogenetic features.[43] These criteria are modified slightly in the WHO classification of 2008, identifying AML with myelodysplasia-related features. AML arising in the setting of a MDS is distinguished from AML with multilineage dysplasia.

The WHO classification recognizes two forms of AML that occur secondary to iatrogenic therapy, with those related to alkylating agent therapy being distinguished from those associated with topoisomerase II inhibitor therapy. AML following alkylating agent therapy or radiation therapy closely resembles AML with multilineage dysplasia, and many of these patients have antecedent MDS.[48] The interval to

Box 100-1. WORLD HEALTH ORGANIZATION CLASSIFICATION OF THE TUMORS OF THE HEMATOPOIETIC AND LYMPHOID TISSUES

Myeloproliferative Neoplasms
Chronic myelogenous leukemia, *BCR-ABL1*$^{+}$
Chronic neutrophilic leukemia
Polycythemia vera
Primary myelofibrosis
Essential thrombocythemia
Chronic eosinophilic leukemia, not otherwise specified
Mastocytosis
- Cutaneous mastocytosis
- Systemic mastocytosis
- Mast cell leukemia
- Mast cell sarcoma
- Extracutaneous mastocytoma

Myeloproliferative neoplasms, unclassifiable

Myeloid and Hematopoietic Stem Cell Neoplasms associated with Eosinophilia with Abnormalities of *Pdgfra*, *Pdgfrb* or *Fgfr1*
Myeloid neoplasm associated with *PDGFRA* rearrangement
Myeloid neoplasm associated with *PDGFRB* rearrangement
Hematopoietic stem cell neoplasm with *FGFR1* abnormalities

Myelodysplastic/Myeloproliferative Neoplasms
Chronic myelomonocytic leukemia
Atypical chronic myeloid leukemia, *BCR-ABL1*$^{-}$
Juvenile myelomonocytic leukemia
Myelodysplastic/Myeloproliferative neoplasms, unclassifiable
- Refractory anaemia with ringed sideroblasts (RARS) associated with marked thrombocytosis*

Myelodysplastic Syndromes
Refractory cytopenia with unilineage dysplasia
- Refractory anemia
- Refractory neutropenia
- Refractory thrombocytopenia

Refractory anemia with ring sideroblasts
Refractory cytopenia with multilineage dysplasia
Refractory anemia with excess blasts
Myelodysplastic syndromes associated with isolated del (5q)
Myelodysplastic syndromes, unclassifiable
Myelodysplastic syndromes in children

Acute Myeloid Leukemia
Acute myeloid leukemia with recurrent genetic abnormalities
- AML with t(8;21)(q22;q22), *RUNX1-RUNX1T1*
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22), *CBFB-MYH11*
- APL with t(15;17)(q22;q11–12), *PML-RARA*
- Acute myeloid leukemia with t(9;11)(p22;q23); *MLLT3-MLL*
- AML with t(6;9)(p23;q34); (*DEK- NUP214*)
- AML with inv(3)(q21;q26.2) or t(3;3)(q21;q26.2); (*RPN1-EVI1*)
- AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
- AML with mutated *NPM1**
- AML with mutated *CEBPA**

Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise categorized
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic and monocytic leukemia
- Acute erythroid leukemia
  - Acute erythroid leukemia, erythroid/myeloid
  - Acute pure erythroid leukemia
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

Myeloid Sarcoma

Myeloid Proliferations Related to Down Syndrome
Transient abnormal myelopoiesis
Acute myeloid leukemia associated with Down syndrome

Blastic Plasmacytoid Dendritic Cell Neoplasm

Acute Leukemias of Ambiguous Lineage
Acute undifferentiated leukemia
Acute biphenotypic leukemia

Precursor Lymphoid Neoplasms
B-lymphoblastic leukemia/lymphoma
- B-lymphoblastic leukemia/lymphoma, not otherwise specified
- B-lymphoblastic leukemia/lymphoma with recurrent/cytogenetic/molecular genetic abnormalities
  - B-lymphoblastic leukemia/lymphoma with t(9:22) (q34;q11.2); *BCR/ABL*
  - B-lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL* rearranged
  - B-lymphoblastic leukemia/lymphoma with t(12;21) (p13;q22); *TEL/AML1* (*ETV6-RUNX1*)
  - B-lymphoblastic leukemia/lymphoma with hyperdiploidy
  - B-lymphoblastic leukemia/lymphoma with hypodiploidy (Hypodiploid ALL)
  - B-lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32)(*IL3-IGH*)
  - B-lymphoblastic leukemia/lymphoma with t(1;19)(Q23;P13.3); (*E2A-PBX1; TCF3/PBX1*)

T-lymphoblastic leukemia/lymphoma

Mature B-Cell Neoplasms
Chronic lymphocytic leukemia /Small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
- Splenic diffuse red pulp small B-cell lymphoma*
- Hairy cell leukemia-variant*

Lymphoplasmacytic lymphoma
- Waldenström macroglobulinemia

Heavy chain diseases
- Alpha heavy chain disease
- Gamma heavy chain disease
- Mu heavy chain disease

Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma
- Pediatric type nodal MZL

Follicular lymphoma
- Pediatric type follicular lymphoma

Primary cutaneous follicle centre lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma, not otherwise specified
- T-cell/histiocyte rich large B-cell lymphoma
- DLBCL associated with chronic inflammation
- EBV^{+} DLBCL of the elderly

Lymphomatoid granulomatosis

Box 100-1. WORLD HEALTH ORGANIZATION CLASSIFICATION OF THE TUMORS OF THE HEMATOPOIETIC AND LYMPHOID TISSUES—cont'd

Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK positive DLBCL
Plasmablastic lymphoma
Primary effusion lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric Castleman Disease
Burkitt Lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Mature T-Cell and Nk-Cell Neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Aggressive NK cell leukemia
Systemic EBV^+ T-cell lymphoproliferative disease of childhood (associated with chronic active EBV infection)
Hydroa vaccineforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sezary syndrome
Primary cutaneous anaplastic large-cell lymphoma
Primary cutaneous aggressive epidermotropic CD8 positive cytotoxic T-cell lymphoma*
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous small/medium CD4 positive T-cell lymphoma*
Peripheral T-cell lymphoma, not otherwise specified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma (ALCL), ALK^+
Anaplastic large cell lymphoma (ALCL), ALK^-*

Hodgkin Lymphoma

Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte depleted classical Hodgkin lymphoma

Histiocytic and Dendritic Cell Neoplasms

Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Dendritic cell tumour, not otherwise specified
Indeterminate dendritic cell tumor
Fibroblastic reticular cell tumor

Post-Transplant Lymphoproliferative Disorders

Early lesions
Reactive plasmacytic hyperplasia
Infectious mononucleosis-like
Polymorphic PTLD
Monomorphic PTLD (B- and T/NK-cell types)*
Classical Hodgkin lymphoma type PTLD

ALCL, anaplastic large cell lymphoma; AML, acute myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; LPD, lymphoproliferative disorder; MDS, myelodysplastic syndrome.

*These represent provisional entities or provisional subtypes of other neoplasms. They are provisional because either there is insufficient data to support their being a definite entity, significant controversies about their defining features and/or uncertainty about whether they are unique or closely related to other definite entities. Further classify according to lymphoma they resemble.

From World Health Organization: World Health Organization Classification of the Tumors of the Hematopoietic and Lymphoid Tissues. Geneva, World Health Organization, 2008 (in press).

diagnosis is generally long, and the response to therapy poor. The acute leukemias associated with topoisomerase II inhibitor therapy occur after a shorter interval, do not have associated MDS, frequently contain a prominent monocytic component, and have characteristic translocations. These patients have a response to therapy similar to other de novo cases of AML with comparable cytogenetic features.[43]

AML without recurrent cytogenetic abnormalities is subclassified according to lineage and stage of differentiation. The concept is to provide a broad framework for the classification of these disorders so as to facilitate future studies regarding the pathogenesis. Some new insights have emerged, and it is likely that future studies will further refine this broad category. For example, a significant fraction of AML without recurrent karyotypic abnormalities is found to have mutations in *NPM1*, the nucleophosmin gene.[49] These mutations are found in cases of AML across all FAB lineage-related categories.[50] It has been suggested that this category is associated with a better response to therapy. Gene expression profiling has also been used in AML with a normal karyotype to identify clinically significant prognostic groups.[51] Thus, it is clear that there will be continued inroads to better define this broad category of AML.

The other major categories addressed in the WHO classification of myeloid neoplasms are: (1) MDSs; (2) myeloid disorders that have features of both MDS and myeloproliferative diseases such as chronic myelomonocytic leukemia; and (3) chronic myeloproliferative disorders. The myeloproliferative and myelodysplastic diseases are clonal stem cell disorders, with or without effective hematopoiesis, respectively. The term chronic myelogenous leukemia (CML) is restricted to those cases with a *BCR/ABL* fusion gene. The diagnosis of chronic neutrophilic leukemia requires genetic evidence of a myeloid neoplasm, other than the Ph chromosome or *BCR/ABL*.

Knowing the clonal nature of MDSs and their generally poor prognosis, some have questioned the use of the term myelodysplasia and suggest that this nosology obscures the neoplastic nature of the process.[52] In the WHO classification the blast threshold for the diagnosis of AML was reduced from 30% to 20% blasts in the bone marrow or peripheral blood. Moreover, in recognition of the importance of genetic abnormalities, patients with recurring cytogenetic abnormalities are considered to have acute leukemia regardless of the blast count.[43]

There has been considerable progress in elucidating the molecular basis of myeloproliferative disorders other than CML. The *JAK2* exon 12 mutation is found in nearly all patients with polycythemia vera.[53] This mutation is also found in a substantial fraction of patients with essential thrombocythemia and primary myelofibrosis. These molecular insights have led to a recommendation that *JAK2* mutations be investigated in patients being investigated for these diagnoses. Thus, molecular diagnostic techniques are ever expanding in the arena of routine hematological diagnosis.

Finally, some new lineages have been revealed. The disease initially described as blastic natural killer (NK)-cell lymphoma has been shown not to be of NK-cell or even lymphoid derivation.[54] It repre-

sents a neoplastic expansion of immature plasmacytoid dendritic cells. This cell, which is part of the innate immune system, produces large amounts of interferon-type 1 (interferon-α). The disease is clinically more closely related to AML than either T-cell or NK-cell lymphoma, and does not respond well to lymphoma-directed therapies.[55–57] Thus, this entity will be renamed in the WHO classification of 2008, as *blastic plasmacytoid dendritic cell neoplasm*.

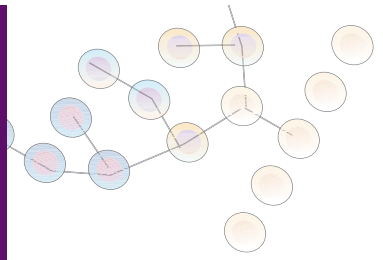
CONCLUSION

The WHO classification is based on the integration of traditional morphological observations with biological data related to the pathogenesis of disease. Although the ultimate aim might be to establish a genetically defined classification system in which the molecular pathogenesis of every neoplasm is known, this goal is undoubtedly some years away. However, the recognition of carefully defined disease entities should facilitate the investigation of pathogenetic mechanisms, and the development of molecularly targeted therapies. The WHO classification is a milestone, because it is the first classification system for lymphomas and leukemias universally accepted and in use on a worldwide basis. It is also a roadmap for future scientific and clinical investigations. The use of common diagnostic criteria will facilitate collaboration and synthesis of data generated from such studies.

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101 Childhood Leukemia

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SUMMARY OF KEY POINTS

Incidence

- Leukemia is the most common childhood cancer.
- The most common subtype, acute lymphoblastic leukemia (ALL), accounts for 75% to 80% of all cases of childhood leukemia, whereas acute myeloid leukemia (AML) composes approximately 20%.
- Chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), and myeloproliferative disorders (MPDs) occur less frequently.
- Chronic lymphocytic leukemia (CLL) is extremely rare.

Etiology

- Although environmental agents, such as ionizing radiation and chemical mutagens, have been implicated in the induction of leukemia, discernible etiologic factors are lacking in almost all cases of primary leukemia.
- Acquired genetic changes are central to the development of leukemia.

Epidemiology

- Males are generally affected by leukemia slightly more often than females in all age groups except infants.
- In developed countries the incidence of ALL is highest between ages 2 and 5 years.
- The incidence of AML is relatively constant during childhood, with slight peaks in the first 2 years of life and in late adolescence.
- MDS typically occurs after 5 years of age, and juvenile myelomonocytic leukemia (JMML) occurs nearly always before 5 years of age.

Clinical Findings

- Physical signs and symptoms of thrombocytopenia and anemia are common.
- Neutropenia may lead to severe infection.
- Bone pain and arthralgia caused by leukemic infiltration is more common in ALL than AML and may be especially severe in young children.
- Common sites of extramedullary involvement in ALL include liver, spleen, thymus, and lymph nodes.
- Skin, gums, and the head and neck area are typical sites of extramedullary disease in AML.
- Infiltration of the central nervous system can be found in both ALL and AML.

Differential Diagnosis

- The acute onset of petechiae, ecchymoses, and bleeding may suggest idiopathic thrombocytopenic purpura.
- Both acute leukemia and aplastic anemia can present with pancytopenia and complications associated with bone marrow failure.
- Infectious mononucleosis and other viral infections can be confused with ALL.
- Bone pain, arthralgia, and occasionally arthritis may mimic juvenile rheumatoid arthritis, rheumatic fever, other collagen diseases, or osteomyelitis.
- Childhood ALL should also be distinguished from pediatric small round cell tumors that involve the bone marrow.

Therapy

- Patients with ALL undergo a relatively brief remission-induction phase followed by intensification (consolidation) therapy and then prolonged continuation treatment.
- All patients require treatment for subclinical central nervous system (CNS) involvement, which should be initiated early in the form of intrathecal chemotherapy.
- Most protocols for AML include remission induction and consolidation therapy; other recommended postremission therapy differs widely.
- Autologous hematopoietic stem cell transplantation is not usually recommended.
- At present, ALL with the Philadelphia chromosome or early hematologic relapse, and T-cell ALL with poor early response or hematologic relapse, are clear indications for allogeneic transplantation.
- Allogeneic transplantation seems to improve overall survival in AML, although the indications for this procedure during first remission are debated.

Prognosis

- Five-year event-free survival estimates for children with newly diagnosed ALL are now over 80%.
- Philadelphia chromosome is an unfavorable prognostic indicator, whereas hyperdiploidy with greater than 50 chromosomes and the *TEL-AML1* gene fusion are associated with a favorable outcome.
- Event-free survival for infant ALL with 11q23/*MLL* rearrangement remains only 20% to 35% and has not been improved by allogeneic transplantation.
- In AML, patients with Down syndrome or acute promyelocytic leukemia have a favorable prognosis with optimal therapy, whereas those with acute megakaryoblastic leukemia have significantly worse outcomes than others.
- Relapse less than 18 months after the end of therapy and treatment-related AML carry a dismal prognosis.
- Patients with MDS, AML arising from MDS, AML with monosomy 7, or AML with internal tandem duplication of the *FLT3* gene often have resistant disease
- Slow response to remission-induction therapy and persistent minimal residual disease are associated with a higher risk of relapse in both ALL and AML.

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INTRODUCTION

Leukemia is the most common childhood cancer. Unlike leukemia in adults, childhood leukemia is acute in the vast majority of cases. The most common subtype, acute lymphoblastic (also termed lymphocytic or lymphoid) leukemia (ALL), accounts for 75% to 80% of all cases of childhood leukemia, whereas acute myeloid (also termed myelocytic, myelogenous, or nonlymphoblastic) leukemia (AML) composes approximately 20%.

Acute leukemia is a malignant proliferation and accumulation of immature lympho-hematopoietic cells. The leukemic cell population is shown to be clonal by cytogenetics, glucose 6-phosphate dehydrogenase characterization, and analysis of antigen-receptor gene rearrangements and X-linked restriction fragment-length polymorphisms.[1] Although leukemic cells generally do not proliferate as actively as their normal hematopoietic counterparts,[2] they accumulate inexorably and compete successfully with normal cells. Their inability to differentiate and their relative resistance to apoptosis may explain this phenomenon. By the time of diagnosis, leukemic cells have usually replaced normal bone marrow cells and disseminated to various extramedullary sites. Therefore, the presenting features of leukemia typically reflect the degree of bone marrow replacement and the extent of extramedullary spread.

Both ALL and AML are heterogeneous diseases that comprise different biologic subtypes. The major morphologic and immunophenotypic divisions based on lineage association and degree of maturation are subclassified by the identification of distinct, recurrent chromosomal and molecular abnormalities,[3,4] and gene expression patterns.[5–10]

Chronic myelogenous leukemia (CML), myelodysplastic syndrome (MDS), and myeloproliferative disorders (MPDs) are infrequent in children. In general, they share clinical, laboratory, and morphologic features with one of their adult counterparts.[11–13] A disorder characterized by an heterogeneous pattern of myeloproliferation, dysplasia, and hepatosplenomegaly in association with abnormal peripheral blood counts has historically been called "juvenile chronic myelogenous leukemia," "infantile monosomy 7 syndrome," and "chronic myelomonocytic leukemia" by different authors. The term juvenile myelomonocytic leukemia (JMML) is currently favored.[11,12] Only a few well-documented cases of chronic lymphocytic leukemia (CLL) have been reported in children.[14]

EPIDEMIOLOGY

Leukemia is the most common malignancy among patients less than 15 years of age. ALL is approximately five time more common than AML. Males are generally affected by leukemia slightly more often than females in all age groups, with two exceptions: boys have a risk of T-cell leukemia that is four times that of girls, and girls have a slightly higher incidence of leukemia in the first year of life (1.5 : 1 ratio).[15] Rates of ALL are comparatively higher in Northern and Western Europe, North America, and Oceania, than in Asia and Africa.[15] In developed countries the incidence of ALL is highest between ages 2 and 5 years. This age peak is accounted for largely by ALL with hyperdiploidy (>50 chromosomes) or *TEL-AML1* gene fusion.[3] The incidence of ALL is higher in the white than the black population, especially among children 2 to 5 years of age. Black children have a higher incidence of T-cell ALL and pre-B leukemia with *E2A-PBX1* fusion and are less likely to have hyperdiploid ALL with more than 50 chromosomes than white children.[16] The incidence of AML in children peaks at 2 years of age, decreases to a nadir at 9 years, then peaks again at around age 16.[17] The highest incidence of pediatric AML occurs among the Maori of New Zealand, Hawaiian Americans, and Africans in Zimbabwe.[17] In most populations of children, less than 10% of cases of AML are acute promyelocytic leukemia (APL).[17] However, this figure is approximately 25% in Latin American children[18] and about 30% in Italian children.[19] Pediatric patients with MDS are typically older at diagnosis (>5 years old) whereas JMML nearly always occurs before 5 years of age.[11,12]

Table 101-1 Congenital Disorders Associated with Increased Risk of Leukemia

Congenital Disorder	Associated Leukemia(s)
Down syndrome	ALL, AML
Ataxia-telangiectasia	ALL
Wiskott-Aldrich syndrome	AML
Bloom syndrome	ALL, AML
Fanconi anemia	AML
Kostmann's syndrome	AML
Neurofibromatosis	AML, JMML
Noonan syndrome	JMML

ALL, acute lymphoblastic (lymphocytic, lymphoid) leukemia; AML, acute myeloid (myelocytic, myelogenous, nonlymphoblastic) leukemia; JMML, juvenile myelomonocytic leukemia.

A small percentage (<5%) of cases of leukemia are associated with inherited genetic syndromes (Table 101-1). Children with Down syndrome have a 10- to 20-fold increased risk of leukemia (ALL and AML).[20,21] Furthermore, a MPD termed "transient abnormal myelopoiesis" may occur in newborns with Down syndrome.[22] This disorder spontaneously remits in almost all patients within 3 months. However, early death can occur in almost 20% of patients with high presenting leukocyte count, abnormal liver function, and failure to normalize blood count; another 20% subsequently develop AML.[22] Several other genetic disorders are associated with an increased risk of leukemia and/or MDS, including ataxia-telangiectasia, Wiscott-Aldrich syndrome, Bloom syndrome, Fanconi anemia, Kostmann's disease, Blackfan-Diamond anemia, and neurofibromatosis.[17,20,23,24] The association between leukemia and congenital immunodeficiencies, such as X-linked agammaglobulinemia and common variable immunodeficiency, is not well supported.[23]

Fraternal twins and siblings of affected children are at a 2- to 4-fold greater risk of leukemia during the first decade of life than are unrelated children.[15,25] When leukemia occurs in one identical twin, the likelihood that the other twin will develop the disease is approximately 20%. However, when leukemia is diagnosed in one twin before 1 year of age, it almost invariably develops in the other twin, typically within a few months. Molecular studies have demonstrated that intrauterine metastasis of ALL from one twin to the other, via the shared placental circulation, is responsible for the concordant leukemia.[26–28]

ETIOLOGY

Although environmental agents, such as ionizing radiation and chemical mutagens, have been implicated in the induction of leukemia, discernible etiologic factors are lacking in almost all cases of primary leukemia.[15] Association between leukemia and maternal exposure to various potential mutagens, neonatal administration of vitamin K, parental use of medications and drugs, and proximity to electromagnetic fields has not been convincingly demonstrated.[15] Although an association between increased risk of childhood ALL and exposure to high levels (0.4 μT or higher) of residential magnetic fields has been reported, this finding needs confirmation.[29,30] A recent case-control study identified a significantly increased risk of leukemia among the offspring of men employed in occupations with a risk of exposure to electromagnetic fields or radiation,[31] a finding that also warrants further studies. Because industralization, higher socioeconomic status, and social isolation are associated with an increased risk of B-lineage

ALL, Greaves hypothesized that abnormally late exposure to common infections and immune response stimulation could enhance the likelihood of leukemogenic genetic mutations, thus increasing the risk of childhood B-lineage ALL.[32] In line with this notion is the observation of occasional clustering of childhood ALL associated with rural-urban population mixing, especially in new towns.[33,34]

Infant leukemias frequently have rearrangements of the *MLL* gene, located on chromosome band 11q23.[35] *MLL* rearrangements are also common in therapy-related AML, arising after treatment with topoisomerase II inhibitors.[36] These molecular similarities raised the hypothesis that transplacental fetal exposure to substances that inhibit topoisomerase II, such as flavonoids (in food and drink), quinolone antibiotics, benzene metabolites, catechins, and estrogens, could be leukemogenic.[35,37] A case-control study found that in utero exposure to DNA-damaging drugs, herbal medicines, or pesticides was significantly associated with infant leukemia with *MLL* rearrangements.[38] Because the functional doses received via dietary and environmental exposure are much lower than those received from anticancer chemotherapy, it was postulated that affected infants or their mothers may have reduced activity of carcinogen-detoxifying enzymes due to genetic polymorphism. In this regard, deficiency of glutathione *S*-transferases (GST-M1 and GST-T1), enzymes that detoxify electrophilic metabolites by catalyzing their conjugation to glutathione, is associated with infant leukemia without *MLL* rearrangement,[35] and with ALL in black children.[39] Polymorphisms of reduced nicotinamide adenine dinucleotide phosphate : quinone oxidoreductase, an enzyme that converts benzoquinones to less toxic hydroxyl metabolites, have been associated with the development of infant and childhood ALL.[40,41] Cytochrome P-450 *CYP1A1*2A* and *NQO1*2* variant genotypes have also been linked to an increased risk of childhood ALL; children carrying both genotypes were at a particularly high risk.[42] It has also been suggested that folate pathways may play a role in susceptibility to ALL,[43] and that folate supplement may reduce the risk,[44] an intriguing finding that requires confirmation. Maternal consumption of fresh vegetables and fruits during pregnancy was associated with a decreased risk of infant leukemia, particularly *MLL*-positive, in a recent report.[45] Thus far, however, no direct gene-environment interaction has been firmly established.

PATHOGENESIS

There is strong evidence that acquired genetic changes are central to the development of leukemia. These changes affect the number (ploidy) and/or the structure of chromosomes; structural changes comprise translocations, inversions, deletions, point mutations, and amplifications. The dysregulation of genes encoding transcription factors and the resulting subversion of transcriptional pathways that regulate hematopoietic cell homeostasis, provides a mechanistic explanation for leukemogenesis.[46–48] For example, the core binding factor (CBF) family of transcription factors is disrupted by recurrent chromosomal translocations, such as those involving *TEL-AML1* in ALL and *AML1-ETO* and *CBFB-MYH11* in AML.[49,50] The encoded proteins regulate the expression of growth factors, such as interleukin-3, granulocyte-macrophage colony stimulating factor, and macrophage colony-stimulating factor receptor, as well as the T-cell receptor β enhancer and the immunoglobulin heavy chain enhancer/promoter. The function of homeobox (HOX) genes, an evolutionarily highly conserved family of transcription factors whose expression is tightly regulated during hematopoietic cell differentiation, can also be disrupted either by direct involvement in chromosomal translocations [e.g., the t(7;11), forming the *NUP98-HOXA9* fusion gene] or by the disruption of proteins believed to be their upstream regulators.[48] Among the latter, the most notable is encoded by *MLL*, a gene crucial for both embryonic development and hematopoiesis, and, as mentioned previously, is involved in translocations of the 11q23 region in both ALL and AML.[48,50] Moreover, *PBX1*, a gene involved with *E2A* in the t(1;19) typical of pre-B ALL, encodes a common partner of HOX proteins.[48] Chimeric proteins encoded by fused genes can also directly interfere with normal apoptotic pathways, as has been demonstrated in the case of the E2A-HLF protein.[48] The expression of essential molecules can be altered in the absence of detectable genetic abnormalities. For example, five different T-cell oncogenes (*HOX11*, *TAL1*, *LYL1*, *LMO1*, and *LMO2*) are often aberrantly expressed in T-lineage ALL in the absence of chromosomal abnormalities.[5]

Cell survival requirements can be altered by the dysregulated activity of tyrosine kinases, as in the case of the *BCR-ABL* gene fusion.[48] Alternatively, activating mutations in tyrosine kinase receptors for growth factors may confer a growth advantage to leukemic cells. This mechanism is exemplified by mutations of *FLT3*, which encodes a receptor tyrosine kinase expressed by immature hematopoietic cells that acts synergistically with other growth factors to stimulate proliferation of hematopoietic progenitor cells.[51] Mutant *FLT3* is detectable in both ALL and AML; these mutations typically involve small tandem duplications of amino acids that result in constitutive tyrosine kinase activity.[50,51] Activating mutations of *NOTCH1*, a gene encoding a transmembrane receptor that regulates normal T-cell development, are frequently detected in T-cell ALL.[52,53] Activating mutations of *NOTCH1* produce constitutive NOTCH1 signaling, which is sufficient to induce T-cell ALL in experimental models.[53] Constitutively active Notch1 activates the NF-κB pathway; inhibition of the pathway can restrict tumor growth in vitro and in experimental models of leukemia.[54] Gamma secretase, a multicomponent membrane-associated enzyme, is required for NOTCH1 signaling through mutant NOTCH receptors in T-cell ALL, providing an attractive target for therapeutic intervention with newly developed γ-secretase inhibitors.[53]

A recent large-scale study of DNA single-nucleotide polymorphisms analysis examined 242 cases of pediatric and identified lesions in genes encoding key regulators of B-cell differentiation in 40% of B-cell precursor ALL cases.[55] Most prominent were deletions and cryptic translocations involving the *PAX5* gene, which was altered in almost one third of cases and which would be predicted to block normal B-progenitor cell differentiation before immunoglobulin heavy chain gene rearrangement. Other mutated genes were found in concert with several of the more common translocation-induced chimeric oncogenes, such as *E2A-PBX1* and *TEL-AML1*, including the essential B-cell developmental genes *E2A*, *EBF*, *LEF1*, Ikaros, and Aiolos.

The retrospective identification of leukemia-specific fusion genes (e.g., *MLL-AF4*, *TEL-AML1*) in the neonatal blood spots of identical twins who experienced concordant leukemia has demonstrated their prenatal origin.[26,28] In cases with the t(4;11) and *MLL-AF4*, there is a high rate of concordance in identical twins (25% to 100%) and the very brief latency period after birth (a few weeks to a few months).[28] In other types of leukemia, for example those with the *TEL-AML1* fusion or T-cell phenotype, the rate of concordance is lower, the postnatal latency period is longer and is variable, and the clinical presentation and the outcome of therapy may differ widely among identical twins, suggesting that secondary postnatal molecular events are necessary for full leukemic transformation.[28] Further insights were gained from a report of a set of triplets in which the two monozygotic twins developed concordant leukemia with identical *TEL-AML1* fusion at 3 years of age, whereas the third child, who had developed from a second zygote, was free of leukemia and of the genomic sequence.[27] In addition to the fusion transcript, the identical twins had a secondary, independent deletion of the normal unrearranged *TEL* allele, suggesting a contributing postnatal event. Clone-specific antigen receptor gene rearrangements were analyzed in the neonatal blood spots of five children who were 6 months to 4 years and 8 months of age at diagnosis of B-lineage ALL and T-ALL. In all five children the clonotypic antigen receptor gene rearrangements had been present at birth. The estimated number of clonotypic cells per blood spot was in the range of 10 to 100.[56] Mori and colleagues found

the *TEL-AML1* fusion in the cord blood of about 1% of randomly selected newborns, a frequency about 100 times that of ALL with *TEL-AML1*,[57] further supporting the notion that preleukemic clones are generated in utero at a high frequency and that secondary postnatal leukemogenic events are required for a fully malignant transformation of *TEL-AML1* cells. The prevalence of leukemias with prenatal origin is not known, and not all cases develop in utero. For example, t(1;19) *E2A-PBX1* ALL seems to have a postnatal origin in most cases.[58] Although evidence for a prenatal origin of childhood ALL is solid, similar data for AML are lacking.[59]

GENERAL CLINICAL AND LABORATORY FEATURES

Physical examination of children with leukemia may reveal pallor, petechiae, ecchymoses, and mucosal bleeding. If thrombocytopenia and hyperleukocytosis are severe, there may be life-threatening bleeding (e.g., intracranial hematoma). Anemia may cause fatigue and lethargy, dyspnea, angina, and dizziness. Neutropenia may lead to severe infection. Bone pain and arthralgia caused by leukemic infiltration or, less frequently, hemorrhage is more common in ALL than AML and may be especially severe in young children. Patients may present with fever, which may be induced by infection or by pyrogenic cytokines (e.g., interleukin-1, interleukin-6, and tumor necrosis factor) released from the leukemic cells. Liver, spleen, thymus, and lymph nodes are common sites of extramedullary involvement; however, in AML, massive hepatosplenomegaly is common only in infants. Infiltration of the CNS is seen in children with ALL or AML. An anterior mediastinal (thymic) mass is typical of T-cell ALL. Painless enlargement of the scrotum can be a sign of testicular leukemia or hydrocele resulting from lymphatic obstruction. Testicular involvement is rare in AML. In patients with AML, common sites of extramedullary disease include the skin, gums, and the neck and head area. Myeloblastomas (granulocytic sarcomas, chloromas) are solid tumors composed of myeloblasts that may precede overt bone marrow involvement of AML. They typically occur in the skin, soft tissue, bones, and CNS but may develop in virtually any tissue or organ. Very rarely, acute leukemia produces no signs or symptoms and is detected during routine examination.

Anemia, neutropenia, and thrombocytopenia are common findings, and their severity reflects the degree of bone marrow replacement by leukemic cells. The presenting leukocyte count ranges from 0.1 to 1500×10^9 cells/L (median, 10 to 12×10^9/L); hyperleukocytosis ($> 100 \times 10^9$ cells/L) occurs in 15% to 18% of cases of ALL and AML. Most patients have circulating leukemic blast cells. A large leukemic cell burden is commonly accompanied by elevated serum lactate dehydrogenase activity and elevated uric acid and phosphorus concentration. Some patients with T-cell ALL present with normal red blood cell and platelet counts. In these cases the lymphoblasts in the bone marrow usually represent the leukemic phase of an extramedullary lymphoblastic lymphoma. Not infrequently, the marrow contains a significant population of nonleukemic myeloblasts, which may be difficult to distinguish morphologically from the leukemic cells.

Leukemic blast cells are identified at diagnosis in the cerebrospinal fluid (CSF) of as many as one third of children with ALL (most of whom have no neurologic symptoms) and in approximately 5% of children with AML. Traditionally, CNS leukemia is defined by the presence of at least five leukocytes per microliter of CSF and the detection of leukemic blast cells, or by the presence of cranial nerve palsy. However, the presence of any amount of leukemic cells in CSF, even from iatrogenic introduction due to a traumatic lumbar puncture, is associated with an increased risk of ALL relapse, and requires additional intrathecal therapy.[60,61]

Pancytopenia is a presenting feature in most cases of MDS.[11,12] Fetal hemoglobin is frequently slightly elevated. Most patients have no organomegaly. Extramedullary myeloid tumor may be the presenting feature of MDS, but blasts in the CSF are not seen in MDS. The bone marrow is usually normo- or hypercellular, with characteristic dysplastic features including megaloblastic erythropoiesis, bizarre small or unusual large megakaryocytes, and dysgranulopoiesis; the percentage of myeloblasts is often increased.[12] Hepatosplenomegaly and lymphadenopathy are suggestive clinical features of JMML.[11,12] Diagnostic criteria that have been suggested for patients with JMML include a peripheral monocyte count higher than 1×10^9 cells/L with more than 20% bone marrow blasts.[11,12] Other characteristic features of JMML are the consistent ability of peripheral blood and bone marrow cells to spontaneously form granulocyte-macrophage colonies in vitro, and their hypersensitivity to granulocyte-macrophage colony-stimulating factor.[11]

DIFFERENTIAL DIAGNOSIS

The acute onset of petechiae, ecchymoses, and bleeding may suggest idiopathic thrombocytopenic purpura (often associated with a recent viral infection, large platelets in blood smears, and no evidence of anemia). Both acute leukemia and aplastic anemia may present with pancytopenia and complications associated with bone marrow failure, but in aplastic anemia hepatosplenomegaly and lymphadenopathy are rare, and the skeletal changes associated with leukemia are absent.

Infectious mononucleosis and other viral infections can be confused with ALL. Detection of atypical lymphocytes or elevated viral titers aid in the diagnosis. Patients with pertussis or parapertussis may have marked lymphocytosis, but the affected cells are mature lymphocytes rather than lymphoblasts. Bone pain, arthralgia, and occasionally arthritis may mimic juvenile rheumatoid arthritis, rheumatic fever, other collagen diseases, or osteomyelitis.

Childhood ALL should also be distinguished from pediatric small round cell tumors that involve the bone marrow, including neuroblastoma, rhabdomyosarcoma, and retinoblastoma. Generally, in such cases, a primary lesion can be found by routine diagnostic studies, and disseminated tumor cells often form clumps.

MDS with a low blast count must be distinguished from aplastic anemia and other nonclonal disorders, which often requires sequential morphologic studies including bone marrow biopsies.[12,13] Myelodysplasia may also occur in a variety of disorders such as infection, drug therapy, and chronic disease. AML is the major differential diagnosis of MDS. Cases with AML-specific translocations are more appropriately classified as AML regardless of the blast count, whereas monosomy 7 as the only cytogenetic aberration is strongly suggestive of MDS.[12,13] In borderline cases (e.g., 20% to 30% blasts in bone marrow and no informative cytogenetics), it is recommended to repeat the bone marrow examination after 2 weeks. A definitive distinction between JMML and Philadelphia chromosome-positive CML requires karyotypic or molecular examination for the t(9;22)/*BCR-ABL* abnormality. These conditions must also be distinguished from "leukemoid reaction" associated with infection, cancer, or congenital heart disease in which signs and symptoms do not progress and/or resolve spontaneously.[11]

MORPHOLOGIC AND CYTOCHEMICAL ANALYSIS

Morphologic analysis of leukemic cells in smears stained with Romanowsky (Wright-Giemsa or May-Grünwald-Giemsa) stain distinguishes three subtypes of ALL (L1, L2, and L3) and eight subtypes of AML (M0–M7) as classified by the French-American-British (FAB) scheme (Fig. 101-1).[62] The term "acute myeloid leukemia" is used to designate even leukemias in which some or all cells have the morphology of monocytes (M4, M5), erythroblasts (M6), or megakaryoblasts (M7). Because of the rarity and heterogeneous nature of childhood MDS, its classification has been inconsistent, although an international consensus was achieved.[12] Analysis of a Romanowsky-stained smear cannot accurately distinguish between ALL and AML.

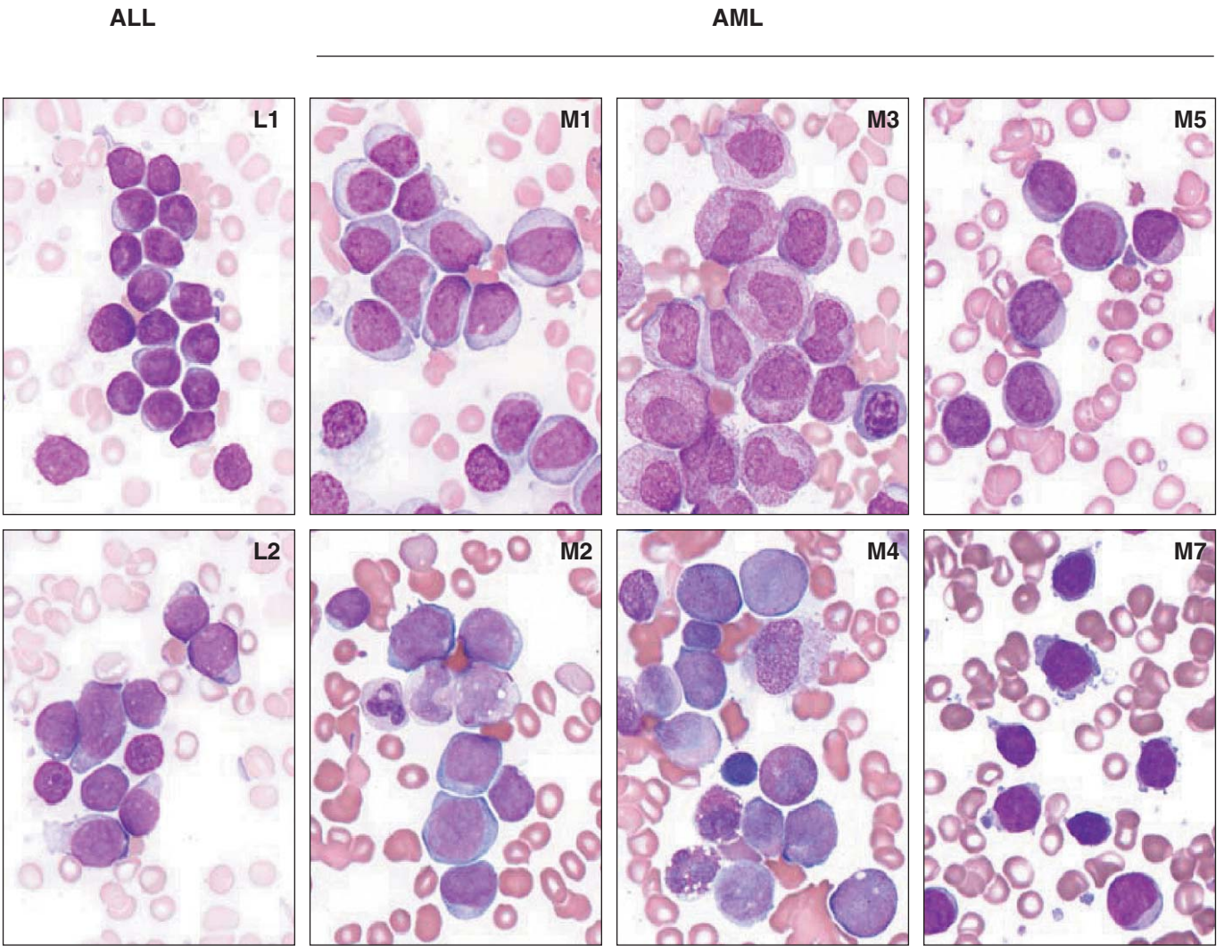


Figure 101-1 • Morphology of leukemic cells. Bone marrow smears obtained at diagnosis from children with ALL or AML were stained with Wright-Giemsa. The morphologic classification according to the French-American-British criteria is shown. (Photographs were provided by Dr. F.G. Behm, St. Jude Children's Research Hospital.)

Cytochemical stains help this distinction. Myeloperoxidase, Sudan black, and nonspecific esterases, including alpha naphthyl butyrate and alpha naphthyl acetate esterase, react with myeloid blast cells, whereas periodic acid-Schiff reagent reacts positively in over 70% of ALL cases. However, despite the traditional use of morphology and cytochemistry, contemporary classification of acute leukemias is based on subtypes that can be identified only by immunologic and molecular analyses.

The FAB group classified MDS into five subgroups: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess of blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML).[63] AML was defined by the presence of 30% myeloblasts in the bone marrow. A more recent World Health Organization classification included five MDS subtypes: refractory anemia with and without ringed sideroblasts, refractory cytopenia with multilineage dysplasia, RAEB, 5q- syndrome, and MDS not otherwise categorized. The blast threshold for AML diagnosis was lowered to 20%.[11] Table 101-2 shows a classification of MDS and MPD in children, which recognizes three major diagnostic groups: JMML, myeloid leukemia of Down syndrome, and MDS occurring either de novo or as a complication of previous therapy or pre-existing bone marrow disorder (secondary MDS).[12]

Table 101-2 Classification of Pediatric Myelodysplastic and Myeloproliferative Disease

Myelodysplastic/ Myeloproliferative Disease	Down Syndrome Disease	MDS
JMML	Transient abnormal myelopoiesis	Refractory cytopenia (<2% blasts in blood and <5% blasts in marrow)
CMML (secondary to previous chemotherapy)	Myeloid leukemia of Down syndrome	RAEB (2% to 19% blasts in blood or 5% to 19% blasts in marrow)
Ph-negative CML		RAEB-T (20% to 29% blasts in blood or marrow)

CML, chronic myelogenous leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndrome; RAEB, refractory anemia with excess of blasts; RAEB-T, RAEB in transformation.

Proposed by Hasle et al.[12]

IMMUNOLOGIC CLASSIFICATION OF ACUTE LEUKEMIA

Acute Lymphoblastic Leukemia

Table 101-3 summarizes antigen expression patterns in ALL.

Early Pre-B Acute Lymphoblastic Leukemia

Leukemic blast cells of early pre-B ALL resemble normal marrow B-cell precursors. Immunoglobulin heavy chain genes are usually rearranged in these cells, but immunoglobulins are not detectable. The leukemic cells of early pre-B ALL always express CD19. Almost all cases have cytoplasmic CD22 and CD79α; weak surface CD22 expression is also evident in many cases.[64] CD10 and terminal deoxynucleotidyl transferase (TdT) are detectable in 90% of cases, and cells in more than 75% of cases express CD34.[64] The CD20 antigen is present on a minor proportion of blast cells in one half of cases.[64,65] In 10% to 15% of early pre-B ALL cases CD45 is very weakly expressed or undetectable; cells that have this immunophenotype are usually hyperdiploid (modal chromosome number >50).[64]

ALL with rearrangement of the *MLL* gene typically has an early pre-B ALL phenotype with distinctive features such as expression of CD15, CD65, and surface chondroitin protoglycan sulfate, and absence of CD10.[64]

Pre-B Acute Lymphoblastic Leukemia

About 25% of newly diagnosed cases of ALL have a pre-B immunophenotype consisting of accumulation of cytoplasmic immunoglobulin μ heavy chains with no detectable surface immunoglobulins.[64] Like in early pre-B ALL, cells express CD19, CD22, and CD79α. Rearrangement of immunoglobulin light chain genes is evident in some of these leukemias, but κ and λ proteins are not detectable. More than 95% of pre-B ALL express CD10 and TdT, but only two thirds express CD34.[64] In many cases of pre-B ALL, surface CD20 is absent or is weakly expressed.[64,65] ZAP-70 expression can be found in cases of B-lineage ALL, particularly those with a pre-B phenotype.[66,67]

Between 20% and 25% of pre-B ALL cases have either the t(1;19)(q23;p13) or the der(19)t(1;19)(q23;p13).[64] The antigen expression profile $CD19^+$, $CD22^+$, CD20 $^{\pm}$, $CD34^-$, $CD45^+$, cytoplasmic μ^+ is characteristic of ALL cases with the t(1;19) but is not specific to these cases.[64]

Transitional (or Late) Pre-B Acute Lymphoblastic Leukemia

Leukemic cells that express both cytoplasmic and surface immunoglobulin μ heavy chains without κ or λ light chains have been designated transitional pre-B ALL.[64] The surface μ chains on these leukemic cells are linked to pseudo light chains as well as to CD79α and CD79β. The blast cells express CD10, usually TdT, and sometimes CD34. Initial studies found this phenotype in only 1% of childhood ALL cases, but it may be more common if more sensitive reagents are used.[64] There is no chromosomal abnormality that is characteristic of this subgroup of ALL.

B-Cell Acute Lymphoblastic Leukemia

In 2% to 4% of childhood ALL cases cells express surface immunoglobulin μ heavy chains plus either κ or λ light chains. The most common type of B-cell ALL is characterized by L3 morphology according to the FAB classification. Cells express CD19, CD22, CD20, and frequently CD10 and CD23; CD34 is negative. In rare cases, TdT is expressed, or sIg is absent.[64] B-cell ALL often represents the leukemic phase of Burkitt lymphoma arising in the abdomen or the head and neck.[64] The hallmark of this subset of B-cell ALL is the presence of a reciprocal translocation of chromosome 8 with one of the chromosomes containing an immunoglobulin gene. These translocations, which include the t(8;14)(q24;q32), t(2;8)(p12;q24), and t(8;22)(q24;q11), involve rearrangement of the c-*MYC* gene.

The less common subtype of B-cell ALL is characterized by blast cells with L1 or L2 morphology. These leukemias may express TdT and CD34, and they express CD20 only weakly.[64] Extramedullary masses are not seen at presentation. The t(8;14), t(2;8), and t(8;22) are absent, as are characteristic rearrangements of the c-*MYC* gene.

T-Lineage Acute Lymphoblastic Leukemia

T-lineage ALL cells have surface CD7 and cytoplasmic CD3 (cCD3) antigens.[68,69] More than 90% of T lymphoblasts express CD2, CD5, and TdT. Surface CD1a, CD3, CD4, and CD8 are detected in fewer than 45% of cases.[64] The HLA-DR antigen is not commonly expressed, and 40% to 45% of cases are $CD10^+$ and/or $CD21^+$.[64] CD79α is also expressed in approximately one third of cases.[64]

T-lineage ALL can be divided into three stages of immunophenotypic differentiation: early ($CD7^+$, $cCD3^+$, surface $CD3^-$, $CD4^-$, and $CD8^-$), mid or common ($cCD3^+$, surface $CD3^-$, $CD4^+$, $CD8^+$, and $CD1^+$), and late (surface $CD3^+$, $CD1^-$, and either $CD4^+$ or $CD8^+$). However, as many as 25% of cases of T-lineage ALL have antigen patterns that do not conform to any of these maturation stages. Furthermore, several studies have yielded conflicting conclusions about the prognostic significance of the expression of surface CD3 and the absence of CD2, CD5, or CD10.[70–72] In a study of children with T-cell ALL at our institution, expression of CD10 was independently associated with a favorable clinical outcome.[71]

T-cell receptor (TCR) proteins are heterogeneously expressed in T-lineage ALL.[73] In approximately two thirds of cases membrane CD3 and TCR proteins are absent. In half of these cases, however, TCR proteins (TCRβ, TCRα, or both) are present in the cells' cytoplasm. Most cases with membrane CD3 and TCR chains express the αβ form of the TCR, whereas a minority express TCRγδ proteins.

Table 101-3 Immunophenotypic Subgroups of Acute Lymphoblastic Leukemia

	Antigen Expression (% of Cases Positive)										
Subtype	**CD19**	**CD22**	**CD79α**	**CD10**	**CD7**	**CD5**	**cCD3**	**clg μ**	**slg μ**	**slg κ or λ**	**Frequency (%)**
Early pre-B	100	>95*	>95	95	5	0	0	0	0	0	60–65
Pre-B	100	100*	100	>95	0	<2	0	100	0	0	20–25
Transitional pre-B	100	100*	100	50	0	0	0	100	100	0	1–3
B	100	100*	100	50	0	0	0	>95	>95	>95	2–3
T	<5	0	30	45	100	95	100*	0	0	0	15–18

c, cytoplasmic; clg μ, cytoplasmic immunoglobulin μ chain; slg μ, surface immunoglobulin μ chain; slg κ or λ, surface immunoglobulin κ or λ chain.
*Detectable on the cell surface membrane in some cases.
From Campana D, Behm FG: Immunophenotyping of leukemia. J Immunol Methods 2000;243:59–75.

Table 101-4 Immunophenotype of Acute Myelocytic Leukemia Subtypes

	ANTIGEN EXPRESSION (APPROXIMATE % OF CASES POSITIVE FOR MARKER)											
FAB Subtype	**CD34**	**CD117**	**HLA-DR**	**MPO**	**CD13**	**CD33**	**CD15**	**CD65**	**CD14**	**GPA**	**CD36**	**CD41a**
M0	75	75	75	>80	75	75	30	30	0	0	0	0
M1	75	75	75	>80	75	75	75	75	0	0	0	0
M2	75	75	>80	>80	>80	>80	75	75	0	0	0	0
M3	<10	30	<10	>80	>80	>80	75	75	0	0	0	0
M4	75	75	>80	>80	75	>80	75	>80	75	0	30	0
M5	<10	30	>80	>80	75	>80	75	>80	75	0	75	0
M6	30	30	75	>80	75	75	30	75	0	>80	75	0
M7	30	30	30	0	30	75	30	<10	0	<10	75	>80

FAB, French-American-British classification; MPO, myeloperoxidase; GPA, glycophorin A.
From Campana D, Behm FG: Immunophenotyping of leukemia. J Immunol Methods 2000;243:59–75.

Acute Myeloid Leukemia

Table 101-4 summarizes the patterns of antigen expression in AML. The leukemic cells in all myelocytic and monocytic subtypes of AML (M0 through M5) express various combinations of CD13, CD33, CD65, CD117, and myeloperoxidase (MPO).[64]

Acute Myelocytic Leukemia with Little Differentiation (M1 AML)

M1 AML cases commonly express MPO, CD13, CD33, CD34, CD65, CD117, and HLA-DR, but in variable combinations. Expression of CD4, CD11b, CD15, and CD66 is less frequent. No single antigenic profile is characteristic of M1 leukemias.

Acute Myelocytic Leukemia with Differentiation (M2 AML)

About 35% to 45% of cases of childhood M2 AML have the t(8;21)(q22;q22) translocation. Leukemic blast cells commonly express MPO, CD34, CD65, and HLA-DR, but CD13 and CD33 expression is characteristically weak and sometimes is not detectable.[64] Most cases weakly express CD19 and, less commonly, CD56.[64] By contrast, the leukemic myeloblasts of M2 AML without the t(8;21) translocation may also express MPO, CD34, CD65, and HLA-DR, but the expression of CD13 and CD33 usually exceeds that of myeloblasts that have the t(8;21) translocation. In addition, the CD19 antigen is rarely detectable, whereas T-cell–associated CD2 or CD7 is commonly present, in these cases.[64]

Acute Promyelocytic Leukemia (M3 AML)

This group of leukemias includes a microgranular variant referred to as M3v that may morphologically mimic acute monocytic leukemia. Cells of M3 and M3v AML strongly express MPO, CD13, CD33, and CD65 but usually lack HLA-DR.[64,74] Expression of CD11b and CD15 is variable, and CD4 and CD56 are seldom detected.[64] Atypical expression of CD2 is observed in 40% to 45% of cases but may be more prevalent in the M3v subtype.[64] CD34 is generally absent but may be found in some cases, usually M3v.[74] Heterogeneous expression of CD13, the existence of a single primary blast cell population, and a characteristic pattern of CD34 and CD15 expression are reportedly useful in identifying M3 AML.[75]

Acute Myelomonocytic Leukemia (M4 AML)

Blast cells of most myelomonocytic leukemias express MPO, CD4, CD11b, CD11c, CD13, CD14, CD33, CD34, CD45, CD65, and HLA-DR.[64]

A relatively uncommon variant of M4 AML, M4Eo, is associated with increased numbers of eosinophils in the bone marrow, with or without peripheral blood eosinophilia. These cases usually express the *CBFB-MYH11* chimeric gene, which is often associated with expression of CD2.[64]

Acute Monocytic Leukemia (M5 AML)

Monoblasts usually express MPO, HLA-DR, CD4, CD11b, CD11c, CD33, and CD65. The cells of some monocytic leukemias express CD117, but CD34 is rarely detected. The cells of most monocytic leukemias also express CD15, CD36, and, not infrequently, CD56. Expression of CD14 is largely restricted to cells of the monocytic lineage but is often absent in pediatric M5 cases. A variable number of monoblasts may appear to react with antibodies to CD41a and CD61 because of platelet adhesion to the cell surface or glycoprotein IIb/IIIa absorption.[64]

Acute Erythroleukemia (M6 AML) and Acute Erythroblastic Leukemia

Leukemias composed primarily of erythroid precursors are uncommon. Leukemic erythroblasts usually express CD36, CD71, and glycophorin A (GPA), and hemoglobin is detectable in late-stage erythroid precursors. Cells of the myeloid component express CD13, CD33, and MPO. M6 AML may be difficult to distinguish from M0 and M7 AML, because undifferentiated erythroblasts have few or no erythroid-associated antigens, and their antigenic and ultrastructural features may mimic those of early megakaryoblasts.[64]

Acute Megakaryoblastic Leukemia (M7 AML)

Distinguishing acute megakaryoblastic leukemia (M7 AML) from ALL, M0 and M5 AML, acute erythroblastic leukemia, and metastatic small cell tumors solely on the basis of cell morphology might be difficult. The leukemic cells of most M7 AML cases express CD41a and CD61, and those of more than half of M7 AML cases express CD42b. Most cases are positive for CD4 and CD33; CD13, CD34, CD36, CD45, and HLA-DR are infrequently detected.[64]

Acute Myeloid Leukemia without Morphologic or Cytochemical Evidence of Differentiation (M0 AML)

The term "M0" denotes minimally differentiated myeloid leukemia.[76] In general, the expression of CD3, CD79α, or TCR proteins is strongly indicative of lymphoid lineage differentiation. In the absence of these lymphoid markers and of markers associated with the megakaryocytic lineage, the expression of CD13, CD15, CD33, CD65, or MPO is evidence of myeloid lineage commitment.[64] Leukemias that are devoid of detectable MPO should be classified as M0 AML only in the absence of lineage-restricted lymphoid and megakaryocytic antigens.[64] Although the cells of most M0 cases express CD13 or CD33, some MPO^+ cases may lack these antigens.[64] The

expression of CD117 by leukemic cells is strongly suggestive of AML. Other non-lineage-restricted antigens found on M0 AML cells include CD2, CD4, CD7, CD9, CD10, CD11b, CD19, CD34, CD71, TdT, and HLA-DR.[64]

Rare Acute Leukemias

Uncommon cases of acute leukemia express an immunophenotype reminiscent of natural killer (NK) cell differentiation, and are classified as acute immature T/NK/myeloid precursor leukemia. These cases are typically express CD7, CD34, CD56, and HLA-DR.[77] Myeloid features include CD33 expression, but MPO protein is usually absent.[77] Clonal TCR delta gene rearrangements have been shown in some cases.[78]

In a very rare subset of AML, leukemic cells express markers of basophilic differentiation, have the features of differentiation into basophilic lineage, and are classified as acute basophilic leukemia. The immunophenotype is not unlike that of other AMLs, (i.e., expression of CD13 and/or CD33, CD34 and CD117). The most characteristic feature is the presence of basophilic cytoplasmic granules, which might be detectable only by ultrastructural examination.[79]

A recently recognized acute leukemia subtype is plasmacytoid dendritic cell type 2 (DC2) acute leukemia. Leukemic cells are $CD4^+$ and $CD56^+$ and lack strong expression of lymphoid and myeloid markers. Characteristic markers include expression of the interleukin-3 receptor (CD123), CD45RA, CD36, BRCA-2, BRCA-4, CD68, and HLA-DR.[80,81]

Rare cases of leukemia remain difficult to classify even after extensive morphologic and immunophenotypic analysis; these are designated acute undifferentiated (or unclassified) leukemia. Morphologically, these leukemias may resemble ALL or AML, and immunophenotyping studies show the absence of B-lympoid, T-lymphoid, myeloid, and megakaryocytic antigens.[82] The leukemic cells of true acute undifferentiated (or unclassified) leukemia lack surface and cytoplasmic antigens associated with B (CD19, CD22, and CD79α), T (CD2, CD3, CD5, and TCR proteins), myelomonocytic (MPO, CD13, CD14, CD33, CD15, and CD65), and megakaryocytic or erythrocytic (CD36, CD41a, CD42b, CD61, and GPA) lineages. Diagnostic studies should also exclude neuroblastoma, Ewing sarcoma, and other small cell tumors.

Acute Leukemias with Aberrant Lymphoid or Myeloid Antigen Expression

Immunologic and molecular studies show that many leukemias possess features characteristic of multiple hematopoietic lineages. Acute leukemias whose blast cells simultaneously demonstrate features of more than one lineage (e.g., lymphoid plus myeloid) have been termed acute mixed-lineage, hybrid, chimeric, or biphenotypic leukemias.[64] The diagnosis of B-lineage ALL should be made when leukemic cells express either cytoplasmic immunoglobulin or CD79α or CD19 plus CD22, regardless of CD13, CD15, CD33, or CD65 expression.[64] The diagnosis of T-lineage ALL should be made when leukemic cells express CD7 plus either surface or cytoplasmic CD3, regardless of myeloid antigen expression. A diagnosis of AML is rendered when leukemic cells express MPO or two or more myeloid-associated antigens, including CD13, CD15, CD33, or CD65, in the absence of the lymphoid-associated markers designated previously. An immunophenotypic diagnosis of "true" mixed-lineage leukemia should be considered when leukemic blast cells co-express MPO and CD3, MPO and immunoglobulin, or MPO and CD79α. "True" mixed-lineage leukemia should not be confused with biclonal or oligoclonal leukemias, which consist of two or more morphologically or immunophenotypically distinct leukemic cell populations. The latter types of leukemia are very rare.

Expression of myeloid antigens in ALL has no independent prognostic significance in children but is associated with molecular genetic abnormalities.[83] Atypical expression of the myeloid-associated antigen CD15 is characteristic of B-lineage ALL with *MLL* gene rearrangements. Lymphoid antigen expression in AML cells also lacks prognostic significance in children.[83]

CYTOGENETIC AND MOLECULAR CLASSIFICATION

Acute Lymphoblastic Leukemia

Figure 101-2 shows the cytogenetic groups in ALL.

Hyperdiploid Acute Lymphoblastic Leukemia

In approximately half of ALL cases, leukemic blast cells have a modal chromosomal number greater than 46. Hyperdiploidy can be identified by conventional karyotyping or by DNA content analysis with flow cytometry. In approximately 50% of hyperdiploid cases, the leukemic cells have additional structural chromosomal abnormalities, including duplication of 1q and isochromosome of 17q; however, no consistent structural abnormality has been identified. Hyperdiploid cases with a modal chromosome number of 51 to 65 represent a distinct biologic subset of B-lineage ALL with an excellent prognosis.[84–86] Leukemic lymphoblasts with this karyotype have a marked propensity to undergo apoptosis in vitro and in vivo.[87,88] In addition, they accumulate greater quantities of methotrexate and its active polyglutamate metabolites than do other leukemic lymphoblasts,[89] and they reportedly have greater sensitivity to antimetabolites in vitro.[90] These features explain the relatively small presenting tumor burden and the good prognosis of this subtype of ALL. Features that have been associated with the most favorable outcome among this subset of ALL include trisomy of chromosomes 4, 10, and 17,[91] a

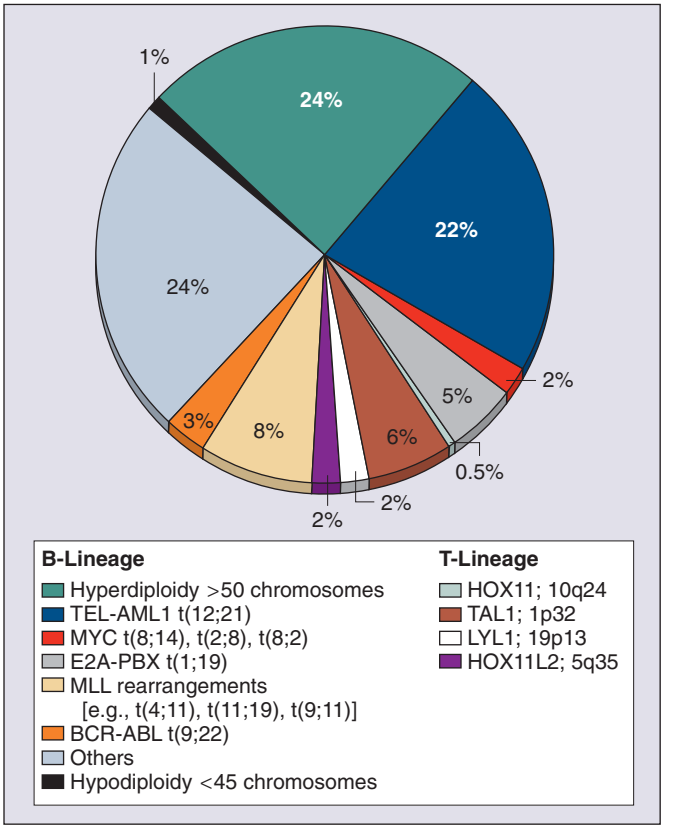


Figure 101-2 • Cytogenetic subgroups in childhood ALL.

chromosome number of 56 or more,[92] and the absence of chromosomal translocations.[93]

In contrast to the favorable prognosis of this ALL subtype, ALL cases with near-triploidy (69 to 81 chromosomes) have a response to therapy similar to that of nonhyperdiploid ALL;[94] cases with near-tetraploidy (82 to 94 chromosomes) have a high frequency of T-cell imunophenotype.[94,95] Hypodiploidy (<45 chromosomes) is found in <2% of ALL cases and is associated with a poor outcome.[96]

Acute Lymphoblastic Leukemia with E2A-PBX1 and E2A-HLF Rearrangements

The t(1;19)(q23;p13) translocation is found in 20% to 25% of pre-B ALL cases. The affected genes are those encoding the E2A transcription factor on chromosome 19 and the PBX1 homeodomain-containing transcription factor on chromosome 1.[48] The resulting E2A-PBX1 fusion protein contains the transcriptional activation domains of E2A linked to the DNA-binding domain of PBX1. Thus, the protein should inappropriately activate the transcription of genes normally regulated by PBX1. PBX1 is required for the maintenance of definitive hematopoiesis and contributes to the growth of subsets of hematopoietic progenitors.[97] Ectopic expression of the E2A-PBX1 chimeric protein in mice leads to the development of lymphomas and myeloid leukemias.[98] Some of the oncogenic potential of E2A-PBX1 could be mediated through the formation of heterocomplexes with HOX proteins. Both PBX1 and E2A-PBX1 bind to HOX proteins, and PBX1 and genes of the HOXA locus exhibit synergism in inducing leukemia in mice.[99]

Another *E2A* fusion gene is created by the t(11;17) translocation, in which *E2A* is fused to the gene that encodes hepatic leukemia factor (*HLF*).[100] HLF is a member of the bZip family of transcription factors. The E2A-HLF fusion protein contains the transcriptional activation domains of E2A linked to the DNA-binding and protein-protein interaction motifs of HLF. Thus, this chimeric protein should activate the transcription of genes normally regulated by HLF. In addition, E2A-HLF itself appears to inhibit apoptosis.[100] A zinc-finger transcriptional repressor, SLUG, which functions as an anti-apoptotic factor in normal hematopoietic progenitor cells, is aberrantly upregulated by E2A-HLF.[101]

Acute Lymphoblastic Leukemia with TEL-AML1 Rearrangements

The t(12;21) translocation forms a chimeric gene consisting of the 5′ portion of the *TEL* gene (also known as *ETV6*) and the nearly complete *AML1* gene (also known as *CBFA2*).[48] This translocation can rarely be identified by conventional cytogenetic banding techniques but can frequently be detected by fluorescence in situ hybridization. The nontranslocated *TEL* allele is frequently deleted. The *TEL-AML1* gene fusion is the most common genetic abnormality in pediatric ALL (approximately 20% of cases). In some series the *TEL-AML1* abnormality was not significantly prognostic,[102,103] whereas in others it defined a subgroup with excellent prognosis.[86,104,105] ALL cells bearing this abnormality do not show a distinctive propensity to apoptosis.[87] Reportedly, however, they have an increased in vitro sensitivity to asparaginase,[106], as well as to doxorubicin, etoposide, amsacrine, and dexamethasone.[107] Similar to T-cell ALL, blast cells with either *TEL-AML1* or *E2A-PBX1* fusion accumulate significantly lower levels of methotrexate polyglutamates than do those with other genetic abnormalities, suggesting that patients with these genotypes might benefit from an increased dose of methotrexate.[108]

The *TEL* gene belongs to the *Ets* family of transcription factors. TEL functions as a sequence-specific DNA-binding transcription regulator. It is normally widely expressed and seems to have an essential role in yolk sac angiogenesis, neuronal development, and the establishment of bone marrow hematopoiesis,[109] and is a regulator of hematopoietic stem cell survival.[110] *AML1* encodes a transcription factor that binds DNA as a heterodimer with CBFβ and is essential for the development of definitive hematopoiesis.[109] In addition, the TEL-AML1 protein represses AML1-mediated transcriptional activation through a dominant negative mechanism.[109] Retroviral transduction of murine bone marrow cells with *TEL-AML1* is associated with a higher frequency of leukemia resembling ALL.[111] Notably, the *TEL-AML1* fusion can be induced by apoptogenic stimuli in lymphoid cells.[112]

Acute Lymphoblastic Leukemia with *MLL* Gene Rearrangements

Structural alterations involving band 11q23 of chromosome 11 are the most frequent cytogenetic abnormality in infant ALL.[48] In most cases the target is a gene designated *MLL*, for mixed-lineage leukemia (also known as *HRX*, *ALL-1*, and *HTRX1*).[48] The most common 11q23 abnormality in ALL is the t(4;11), which produces a chimeric protein that contains the N-terminal portion of MLL linked in-frame to the C-terminal portion of AF-4. However, *MLL* has been reported in translocations with more than 50 partner genes in cases of leukemia. MLL is crucial for embryonic development and hematopoiesis; it normally regulates expression of HOX genes.[48] The leukemia-associated alterations in MLL directly disrupt both of these crucial activities.

The prognosis of leukemias with an *MLL* rearrangement varies according to the partner gene, age of the patient, and the treatment administered. Treatment outcome differs by age group with infants having the worst outcome,[113–115] A study found that 13 of 24 infants had breakpoints in the telomeric part of the *MLL* breakpoint cluster region, whereas 29 of 34 children and adults had breakpoints in the centromeric part of the *MLL* breakpoint cluster region, suggesting that the susceptibility of certain areas of the *MLL* breakpoint cluster region to DNA damage might vary during development and hematopoietic maturation.[116] Infant *MLL-AF4* ALL has a high prevalence of immature, nonproductive, and/or oligoclonal antigen-receptor gene rearrangements.[114,115]

A microarray analysis of gene expression in 17 cases of ALL with *MLL* rearrangement revealed several genes normally expressed in hematopoietic lineages other than lymphocytes, including *FLT3* and *LMO2*.[117] Overexpression of HOX genes, such as *HOXA9*, *HOXA5*, *HOXA4*, and *HOXC6*, was also noted. The results suggested that ALL with *MLL* rearrangement is distinct from both ALL and AML.

Acute Lymphoblastic Leukemia with BCR-ABL Rearrangements

The t(9;22)(q34;q11) rearrangement encodes a chimeric gene consisting of the 5′ portion of *BCR* fused to the 3′ portion of *ABL*.[118] In CML, breaks occur most often within the major breakpoint cluster region of *BCR* and encode a 210- kDa BCR-ABL chimeric tyrosine kinase. In ALL, breaks tend to occur in the minor breakpoint cluster regions, forming a 190-kDa BCR-ABL.[119] In each fusion protein, N-terminal sequences of ABL are replaced by BCR sequences. This alteration results in a constitutively active ABL tyrosine kinase that induces aberrant signaling and activates multiple cellular pathways.[118] Expression of either chimeric protein results in malignant transformation of hematopoietic cells and causes leukemia in murine experimental systems.[120] In mice, aggressiveness of BCR-ABL leukemias is enhanced if the activity of the Arf tumor suppressor is compromised.[121]

As a group, ALL with *BCR-ABL* fusion has been consistently associated with poor response to therapy.[122] The development of the tyrosine kinase inhibitor imatinib mesylate (Gleevec, or Glivec) has provided a way to turn off molecular mechanisms that drive leukemic cell growth in this subtype of ALL.[123] However, clinical results in patients with ALL and *BCR-ABL* show dramatic responses that are followed by the rapid development of resistance,[124] due to the outgrowth of clones with mutations in the *BCR-ABL* kinase domain.[125]

Efforts to counteract this resistance with second-generation inhibitors, such as nilotinib, dasatinib, and others are ongoing.[126–129]

Acute Lymphoblastic Leukemia with c-*MYC* Rearrangements

Most B-cell ALL cases have the t(8;14) translocation; less frequently they have the t(2;8) or the t(8;22).[64] These translocations juxtapose the c-*MYC* proto-oncogene on chromosome 8 with the *IgH*, *Igκ*, and *Igλ* loci on chromosomes 14, 2, and 22, respectively. These rearrangements dysregulate the expression of *c-MYC* (a transcription factor), resulting in altered cell proliferation and survival. Dysregulated c-MYC expression in mice, in the presence of other genetic alterations, results in B-lineage leukemia/lymphoma.[130,131]

Genetic Abnormalities in T-Cell Acute Lymphoblastic Leukemia

Genes that are dysregulated in T-cell ALL include *SCL* (*TAL-1*), *LMO1* (*TTG-1*), *LMO2* (*TTG-2*), and *HOX11*.[48,53] As a result of the t(1;14) translocation, *SCL* (a gene involved in early hematopoiesis) is inserted into the *TCRδ* locus on chromosome 14; an internal deletion in the 5′ untranslated region of SCL is found in an additional 25% of T-lineage ALL cases. This deletion juxtaposes a locus called *SIL* with the *SCL* coding region, resulting in the expression of a fused *SIL-SCL* transcript that encodes a normal SCL protein.

The t(11;14)(p15;q11) translocation inserts *LMO1* into the *TCRA/D* locus, whereas the t(11;14)(p13;q11) translocation places *LMO2* in this locus. The LMO1 and LMO2 proteins, which are then inappropriately expressed, contain two zinc-binding domains and participate in multiprotein DNA-binding complexes. LMO2, like SCL, plays an essential role in the development of primitive and definitive hematopoiesis.[132] Activation of LMO2 by retroviral insertion in its proximity has been implicated in the development of T-cell leukemia in a patient with X-linked severe combined immunodeficiency treated with gene therapy.[133]

An additional alteration found in T-cell ALL is the deletion from chromosome 9p21of the *INK4a* and *INK4b* genes, which encode the $p16^{INK4a}$ and $p15^{INK4b}$ inhibitors of the Cdk4 cyclin D-dependent kinase.[134] This locus, which is deleted in more than 50% of T-lineage cases, also encodes another cell cycle–regulatory protein, $p19^{ARF}$, which arrests cell cycle progression through p53.[135]

In a study of 59 T-lineage ALL cases, Ferrando and associates detected high expression of *HOX11* mRNA in 8, *TAL1* mRNA in 29, and *LYL1* mRNA in 13.[5] Overexpression of *LMO1* or *LMO2* was observed in most samples overexpressing *TAL1*, and high levels of *LMO2*, but not *LMO1*, were found in the $LYL1^+$ samples. Of the 59 cases, 10 did not express abnormal levels of any of the transcription factor genes studied. High levels of *LYL1* expression were associated with an undifferentiated thymocyte phenotype.[5] A highly favorable prognosis was noted for $HOX11^+$ cases. Expression of HOX11L2, a transcriptional regulator closely related to HOX11, is a frequent abnormality in childhood T-ALL.[5,136,137] The prognosis of this subset of T-ALL depends on the treatment,[138] and it was associated with poor outcome in some studies.[5,137] It has been proposed that overexpression of *HOX11*, *TAL1* and *LMO2*, frequently overexpressed in T-ALL cells that lack cytogenetic abnormalities involving the chromosomal regions that contain these genes, are due to loss of upstream down-regulatory transcriptional mechanisms.[139]

Subtypes of Acute Lymphoblastic Leukemia Identified by Global Gene Expression

In gene expression microarray analysis of 327 samples from children with ALL that used approximately 12,500 gene probes, Yeoh and coworkers identified expression patterns that distinguished B-lineage ALL from T-lineage ALL,[6] confirming the results of a smaller series.[140] Moreover, among cases of B-lineage ALL, those with hyperdiploidy (>50 chromosomes), *BCR-ABL*, *E2A-PBX1*, *TEL-AML1*, or *MLL* gene rearrangement could be clearly distinguished.[6] Interestingly, a subgroup of 14 cases had a distinct gene expression profile but showed no consistent cytogenetic abnormality.[6] In T-ALL, $HOX11^+$ cases showed increased expression of the genes associated with the early cortical thymocyte stage of differentiation, whereas the expression pattern associated with *TAL1* expression seemed to reflect the late cortical stage of thymocyte differentiation.[5]

Subsequent studies have confirmed that remarkable capacity of gene expression profiling to identify known subtypes of ALL,[8,10,117,141] as well as to identify novel patient subgroups,[5,6,8] a capability that may improve risk classification in ALL. Genome-wide expression profiling technology promises to significantly facilitate the discovery of molecules that critically influence drug resistance, as shown by studies determining gene expression changes in response to methotrexate and/or mercaptopurine,[142,143] by correlative studies based on drug sensitivity findings in vitro,[144–146] and in vivo.[147,148] By comparing gene expression profiles at diagnosis and minimal residual disease (MRD) during remission-induction therapy, we recently identified CASP8AP2, a mediator of apoptosis and glucocorticoid signaling, as a strong prognostic indicator in childhood ALL.[148]

Acute Myeloid Leukemia

Figure 101-3 shows the cytogenetic groups in AML.

Acute Promyelocytic Leukemia with t(15;17) Translocation

Acute promyelocytic leukemia (APL; M3 AML)) accounts for approximately 10% of childhood AML cases, and more than 95% of cases of APL show the presence of a t(15;17)(q22;q11) chromosomal translocation. As a result of this translocation, the retinoic acid gene (*RARA*) on chromosome 17 is fused to the *PML* gene on chromosome 15, resulting in the formation of a PML-RARα chimeric protein.[149] The translocation gives rise to two fusion transcripts: PML-RARA, which is expressed in all cases, and RARA-PML, which is expressed in approximately 80% of cases.[150] The t(15;17)(q22;q11) translocation is invariably associated with APL.

RARα is a ligand-regulated transcription factor that controls the transcription of many genes, some of which are involved in hematopoietic differentiation.[151] The normal function of RARα is linked to its formation of heterodimers with a member of the retinoid X receptors (RXRs). Its repression is mediated through the formation of a multisubunit complex consisting of RARα, RXR, the nuclear receptor-corepressors N-CoR/ silencing mediator of retinoid and thyroid receptors (SMRT) and Sin3A, and a histone deacetylase.[152] Normally,

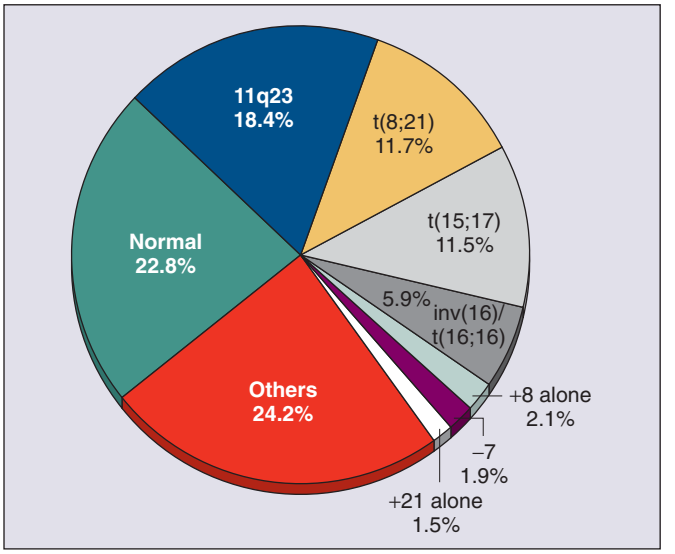


Figure 101-3 • Cytogenetic subgroups in childhood AML.

retinoic acid induces a conformational change in RARα that results in the disassembly of the complex and the recruitment of transcriptional coactivators.[151] The ubiquitous protein PML resides in nuclear organelles (nuclear bodies) conjugated to the ubiquitin-like protein SUMO1.[153] PML has been implicated in multiple cellular functions, including apoptosis, but its precise role remains undefined.[153]

The *PML-RARA* gene fusion can cause a syndrome similar to APL in transgenic mouse models.[154,155] Leukemogenic mechanisms mediated by the PML-RARα protein have been extensively studied. The RARA hormone-binding domains, dimerized by PML, has greater affinity for SMRT than the RARA/RXR heterodimers, possibly resulting in a block of myeloid differentiation and increased resistance to apoptosis.[149,156,157] In addition, PML-RARα disrupts PML nuclear bodies; the resulting redistribution of PML might interfere with the growth-regulatory activities of PML.[158] Pharmacologic doses of all-*trans* retinoic acid (ATRA) lead to conformational changes in PML-RARα that are sufficient to revert its repressor activity, allowing the recruitment of transcriptional coactivators, including CBP and p300.[159] However, mutations of the RARα binding domain may lead to resistance to ATRA.[160] Arsenic trioxide (As_2O_3), another effective treatment for APL, does not bind to RARα, but it binds to PML and induces the degradation of PML-RARα, ultimately causing apoptosis of leukemic cells.[159]

Two variants of the t(15;17) translocation have been identified: the t(5;17), which encodes an NPM-RARα fusion oncoprotein,[161] and the t(11;17), which encodes a PLZF-RARα fusion protein.[162] The latter chimeric protein forms a stable complex with nuclear corepressors and histone deacetylases and is unresponsive to either retinoic acid or ATRA. Thus, cases of AML with the t(11;17) translocation have APL morphology but are unresponsive to treatment with ATRA.

Acute Myeloid Leukemia with Alterations of the Core Binding Factor Complex

The AML1/CBFβ transcription factor complex is essential for normal hematopoiesis.[49,163] The two most common chromosomal rearrangements in de novo AML are the t(8;21) and inv(16)/t(16;16), found in approximately 12% and 6% of cases, respectively.[164] The t(8;21) translocation targets AML1, and inv(16)/t(16;16) targets CBFβ.

The t(8;21)(q22;q22) translocation is seen almost exclusively in cases of AML with FAB M2 morphology and accounts for up to 40% of these cases.[164] This translocation results in a fusion between *AML1* (also called RUNX1, core binding factor protein [CBFα], and PEBP2 alpha B) and the eight twenty-one (*ETO*) gene (also known as *MTG8*) on chromosome 8.[49] *ETO* is the mammalian homolog of the *Drosophila* gene nervy. The Nervy homology 2 (NHR2) domain in ETO mediates oligomerization and the interactions of the fusion protein with ETO itself as well as MTGR1, MTG16, and corepressor molecules mSin3A and HDAC1 and HDAC3.[165] In turn, this contributes to suppress myeloid differentiation and enhance the clonogenic potential of myeloid progenitors.[165]

Expression of AML1-ETO during murine development through a gene targeting strategy resulted in an embryonic lethal phenotype that was almost identical to that observed with the loss of AML1 or CBFβ.[166,167] Unlike AML1- or CBFβ-deficient embryos, which lack detectable hematopoietic progenitors, AML1-ETO–expressing embryos contained dysplastic multilineage hematopoietic progenitors with an abnormally high self-renewal capacity. In a conditional "knockin" mouse, AML-ETO did not block myeloid cell differentiation, nor was it sufficient to induce leukemia.[168] However, induction of cooperating mutations resulted in the development of an AML-like disease that resembled human AML1-ETO–associated leukemia.[168] AML1-ETO is degraded by treatment with histone deacetylase inhibitors,[169] providing a molecular basis for the use of this class of drugs in this type of AML.

The inv(16)(p13q22) and the variant translocation t(16;16) result in the formation of a chimeric gene consisting of the 5′ portion of *CBFB* fused to a variable length of the 3′ portion of the smooth muscle myosin heavy chain gene, *MYH11*.[50] The encoded CBFβ-MYH11 product continues to bind to AML1.[170] The genetics of the inv(16) chromosomal rearrangement suggest that the encoded product functions in a dominant manner to induce leukemia.[171] Further, CBFβ-MYH11 has been shown to directly repress AML1-mediated transcription by sequestering AML1 into inactive cytoplasmic complexes that are attached to actin-containing filamentous structures.[172]

When *CBFB-MYH11* expression was induced during murine embryogenesis, it resulted in a phenotype nearly identical to that observed with the loss of *AML1* or *CBFB*.[173] However, *CBFB-MYH11* also caused an abnormal shift of primitive erythropoietic differentiation toward immature to mid-mature cells. This result suggests that the chimeric product not only inhibits normal AML1/CBFβ activity but also provides other signals that result in abnormalities in cell growth and development. Definitive hematopoiesis can be restored in CBFβ-deficient mice by ectopic expression of *CBFβ* transgenes but not transgenes encoding *CBFB-MYH11*.[174] Transduction of *CBFβ-MYH11* into human $CD34^+$ cells leads to their abnormal proliferation.[175]

Acute Myeloid Leukemia with Alterations of *MLL*

As discussed in the ALL section, translocations involving 11q23 and the *MLL* gene result in a gain of MLL function by generating novel chimeric proteins containing the N terminus of MLL fused in-frame with one of many partner proteins of diverse function.[48] Translocations involving 11q23 are found in approximately 18% of childhood AML cases.[164] The two most common 11q23 translocations in AML, t(9;11)(p22;q23) and t(11;19)(q23;p13.3), involve *AF9* and *ENL*, respectively. Both molecules are homologous to proteins involved in RNA polymerization. When *MLL-AF9* was expressed in mice through a "knockin" strategy, mice developed AML,[176] as did mice in which hematopoietic stem cells had been transduced with *MLL-ENL*.[177] Other MLL fusions involving the forkhead transcription factors FKHRL1 and AFX[178] and the leucine zipper AF10[179] can also induce leukemia in mice when expressed in murine hematopoietic cells. It was recently shown that that enforced *MLL-AF9* expression in discrete populations of more differentiated hematopoietic progenitors can also initiate leukemia and that self-renewing cells are frequent, accounting for up to 30% of myeloid cells and express mature myeloid antigens.[180,181]

Acute Myeloid Leukemia with Other Genetic Abnormalities

Fms-like tyrosine kinase 3 (FLT3) (also known as fetal liver kinase 2 [flk2] or stem cell tyrosine kinase 1 [STK-1]) is receptor tyrosine kinase, which regulates the growth of hematopoietic cells by interacting with its ligand.[51] Internal tandem duplications (ITDs) of the *FLT3* gene have been reported in approximately 20% of adult AML and 10% to 12% of childhood AML cases.[182,183] *FLT3* ITDs result in ligand-independent hematopoietic cell growth and induce a myeloproliferative syndrome in murine models.[184] *FLT3* ITDs are associated with a poor response to chemotherapy and dismal outcome.[182,183] The incorporation of FLT3 kinase inhibitors into current treatment protocols might offer opportunities to improve outcome.[185–188] A monoclonal antibody against FLT3 with antileukemic activity has also been recently developed.[189]

Mutations of the nucleophosmin (*NPM1*) gene occur in 50% to 60% of adult AML with normal karyotype.[190] The prevalence of *NPM1* mutations is lower in childhood AML than in the adult counterpart: one study found them in 7 of 107 patients with non-M3 AML.[191] NPM1 encodes a nucleo-cytoplasmic shuttling protein mainly localized in the nucleolus, but NPM1 mutants localize aberrantly in the leukemic cells cytoplasm, thus allowing the identifica-

tion of these leukemias by immunocytochemistry.[192] It has been suggested that alterations of NPM function might lead to deregulation of p53 stability and its transcriptional activity.[193] In adult AML, *NPM1* mutations in absence of *FLT3* ITDs and the presence of a normal karyotype identify a prognostically favorable subgroup.[194] Childhood AML cases with mutated NPM1 typically have a normal karyotype and tend to occur in older patients.[191]

Down syndrome patients are highly predisposed to acute megakaryoblastic leukemia, which has a treatment outcome that is more favorable than in non-Down syndrome patients.[195,196] A characteristic feature is the presence of somatic mutations of the gene encoding transcription factor GATA1, leading to exclusive expression of a truncated form GATA1.[197,198] Leukemia blasts express both erythroid and megakaryocytic markers, suggesting transformation of an erythroid/megakaryocyte precursor of fetal origin.[197,198]

Genetic Alterations in Myelodysplastic Syndrome and Juvenile Myelomonocytic Leukemia

An abnormal karyotype is found in 60% to 70% of the children with MDS.[11–13] The numerical abnormalities dominate, with only 10% showing a translocation, a derivative, or a deletion as the sole abnormality. The most common cytogenetic abnormality in MDS and JMML is monosomy 7 or del(7q): in a series of 167 children with MDS or MPD, 53 had this abnormality.[199] Children with mutations in the neurofibromatosis gene *NF1* show a 200- to 500-fold increase in the incidence of myeloid malignancies, particularly JMML.[200] Neurofibromatosis is observed in about 15% of patients, and an additional 15% have loss-of-function mutations in *NF1*.[200] *NF1* functions as a tumor suppressor gene in myeloid leukemogenesis by negatively regulating Ras signaling, and in 15% to 30% of patients with JMML, oncogenic mutations of *RAS* have been demonstrated.[201] JMML also frequently occurs in patients with Noonan's syndrome, a congenital disorder featuring facial anomalies, short stature, and heart defects, associated with mutations of the *PTPN11* proto-oncogene, which encodes the tyrosine phosphatase SHP-2 involved in the Ras signaling pathway.[202]

Global Gene Expression Studies in Childhood Acute Myeloid Leukemia

Gene expression profiling reliably distinguishes AML from ALL.[10,140,141] A similar discrimination can also be achieved by studying microRNA expression.[203]

A study of 130 diagnostic samples of childhood AML with the Affymetrix U133A microarray identified discriminating genes for all major genetic subtypes, including t(15;17)/*PML-RARa*, t(8;21)/*AML1-ETO*, inv(16)/*CBFβ-MYH11*, *MLL* chimeric fusion genes, and cases classified as FAB-M7.[9] Interestingly, the expression signatures generated from the pediatric samples could accurately classify adult de novo AML with the same lesions. By combining data sets of 130 AML and 137 ALL it was possible to identify a gene expression signature for cases with MLL chimeric fusion genes irrespective of lineage.[9] A study of 54 pediatric AMLs with an oligonucleotide microarray containing 12,566 probe sets revealed 35 prognostic genes.[204] In a more recent study of 28 cases, expression levels of *CDKN2C*, *CRADD*, and *IGFBP-2* genes were significantly associated with treatment response.[205] These results are potentially important and warrant further studies.

CLINICAL COURSE AND PROGNOSTIC FACTORS

Relapse

Relapse is defined as the reappearance of leukemic cells at any site after remission has occurred. Most relapses occur during treatment or within the first 2 years after its completion, although ALL patients have been observed to relapse as late as 10 years after diagnosis.[206] The bone marrow is the most common site of relapse in both ALL and AML. In children with ALL, the frequency of relapse in extramedullary sites, such as the CNS and testes, has decreased to less than 5% and 2%, respectively. Leukemic relapse occasionally occurs at other sites, including the eye, ear, ovary, uterus, bone, muscle, tonsil, kidney, mediastinum, pleura, and paranasal sinus. Extramedullary relapse in children with ALL frequently presents as an "isolated" finding, but most occurrences are associated with MRD in the bone marrow.[207]

A small fraction of patients experience a recurrence of acute leukemia with an immunophenotype different from that determined at diagnosis. Often, these leukemias are secondary malignancies caused by the mutagenic effects of leukemia treatment.[36]

In some cases recurrent leukemia has genetic features that confirm its relationship to the original leukemic clone but has the phenotype of a different lineage (lineage switch). There have been reports of leukemias morphologically and immunophenotypically characterized as ALL that relapse as AML (or vice versa) while retaining the karyotypic and molecular features of the original clone.[208,209]

Bone marrow relapse, with or without extramedullary involvement, predicts a poor outcome for most patients; patients with isolated bone marrow relapse generally fare worse than those with combined bone marrow and extramedullary relapse.[17,210] In either ALL or AML, the duration of the second remission depends on the duration of the first remission.[3,17,211] In children with relapsed ALL, factors indicating an especially poor prognosis are short initial remission and T-cell immunophenotype. Other adverse factors include t(9;22) translocation, presence of circulating blast cells, or a high leukocyte count at relapse and intensive primary therapy. More recently, it has been demonstrated that the presence of MRD at the end of second remission induction is a strong adverse prognostic indicator.[212,213] Although chemotherapy may secure a prolonged second remission in children with ALL who experience late relapse (e.g., >6 months after cessation of therapy), allogeneic hematopoietic stem cell transplantation is the treatment of choice for patients who experience hematologic relapse during therapy or shortly thereafter and for those with T-cell ALL. Among patients with isolated CNS relapse, a long initial remission and a standard-risk status by National Cancer Institute-Rome criteria (i.e., age 1 to 9.9 years and leukocyte count $<50 \times 10^9$ cells/L at initial diagnosis) were independent favorable prognostic features in a recently reported study.[214] In children with relapsed AML, outcome is generally poor.[215] Relapse occurring at less than 18 months after therapy, and M5 or M7 morphology are associated with a dismal prognosis.[17,216]

Prognostic Factors in Acute Lymphoblastic Leukemia

Stringent evaluation of the risk of relapse is needed at the time of diagnosis to direct therapy so that patients are neither over- nor undertreated. Although age, leukocyte count, leukemic cell genotype, and response to early remission induction therapy are commonly used in risk classification, there is no consensus on the most useful criteria, and there is also no widely accepted system or terminology for defining risk groups. For example, patients have been classified as lower risk, intermediate risk, and higher risk by the Children's Cancer Group (CCG);[217] as standard-risk, medium-risk, or high-risk by the Berlin-Frankfurt-Münster Consortium;[218] as good-risk B-lineage, poor-risk B-lineage, or T-lineage by the Pediatric Oncology Group (POG);[219] and as standard-risk, high-risk, or very high-risk by St. Jude Children's Research Hospital.[220] Having identified a group of patients at very low risk of relapse, the Children's Oncology Group (COG) proposed a four-group classification scheme: low-risk, standard-risk, high-risk, and very high-risk.[221] In this chapter we use the St. Jude risk classification system, which is based on presenting features and on results of treatment response based on MRD assays (Fig. 101-4). It should be noted that infants younger than 12 months of age are generally treated on separate protocols.

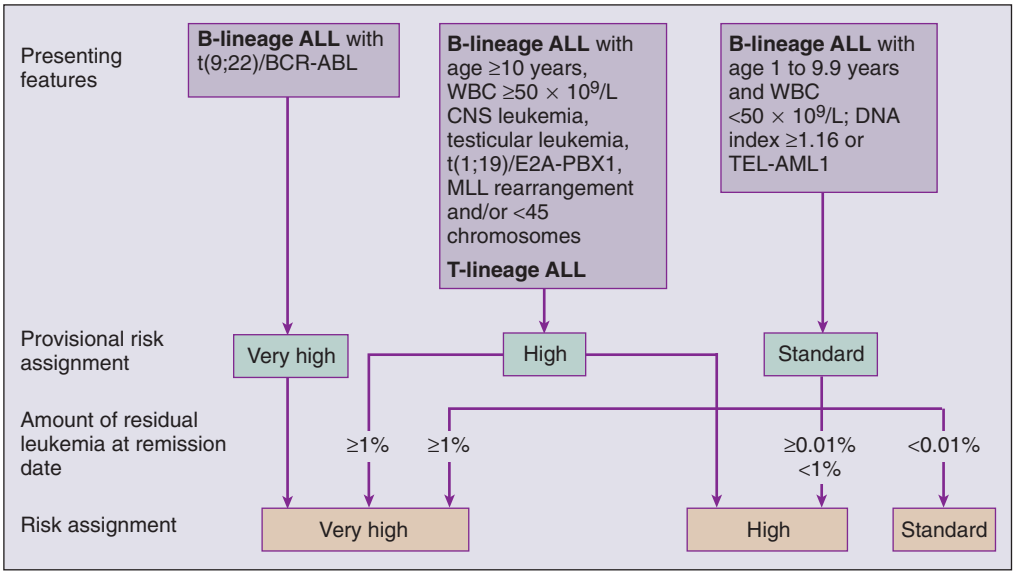


Figure 101-4 • Risk classification of childhood ALL at St. Jude Children's Research Hospital.

The type of treatment regimen remains the most important determinant of outcome. Thus, clinical and biologic variables may lose their predictive strength when treatment is changed. Presenting age and leukocyte count have generally maintained prognostic strength in B-lineage but not T-lineage ALL.[219,220,222] Even in B-lineage ALL, however, their value is limited because as many as 20% of patients who are considered at standard risk by these criteria (age 1 to 9 years with leukocyte count $<50 \times 10^9$ cells/L) may relapse, and very high-risk cases that require allogeneic hematopoietic stem cell transplantation cannot be reliably distinguished from high-risk cases by these criteria. For reasons still poorly understood, boys fare significantly worse than girls on most treatment protocols,[217–219,223–226] with rare exceptions.[227,228] In the studies of the COG, African American patients and those of Latin-American origin had a significantly worse outcome than Caucasians, after adjustment for other prognostic features.[229,230] By contrast, African Americans fared as well as Caucasians in our single-institution protocols, a finding we attributed to equal access to effective contemporary treatment for both groups of patients.[16,231]

Primary genetic abnormalities of leukemic cells influence their aggressiveness and response to therapy but are not 100% predictive of outcome. For example, as many as 15% of children with favorable genetic features (*TEL-AML1* fusion and hyperdiploidy >50 chromosomes) will eventually experience relapse, while approximately one third of those with high-risk abnormalities [the Philadelphia chromosome with *BCR-ABL* fusion or the t(4;11) translocation with *MLL-AF4* fusion] can be cured with chemotherapy alone.[3,232] It should be noted that age 1 to 9 years conferred a favorable prognosis in cases with the Philadelphia chromosome or the t(4;11) translocation, and a high leukocyte count was associated with a poor outcome in those with the former genetic feature.[113,122,221,233]

Prognostic Factors in Acute Myeloid Leukemia

Patients with APL have a relatively favorable prognosis. Patients with Down syndrome and AML often have a favorable response to therapy and require less intensive chemotherapy.[195] Age younger than 2 years and leukocyte count less than 100×10^9 cells/L were significantly associated with better outcome in some series.[234] There are also data suggesting that children younger than 10 years benefit more than older children from intensive therapies.[235] Although African American children had inferior outcome in some studies,[236] this was not the case in recent St. Jude studies.[237]

The Cancer and Leukemia Group B (CALGB) trials demonstrated that adult patients with AML and inv(16) or t(8;21) had a better outcome than patients with all other subtypes of AML and had a particularly good outcome when they were treated with multiple courses of high-dose cytarabine.[238;,239] In the United Kingdom Medical Research Council (MRC) AML10 trial, the 5-year overall survival estimates for patients with t(8;21) and inv(16) were 69% and 61%, respectively.[240] A more recent analysis of the 629 patients treated in the MRC studies confirmed that t(8;21) and inv(16) [together with t(15;17)] are independent good-risk features, and identified loss of a sex chromosome in the t(8;21) group as being associated with excellent outcome.[241] The POG reported 4-year overall survival estimates of 52% and 75% for children with similar karyotypes treated on the 8821 trial.[164] A similar result has been achieved at St. Jude, with 6-year overall survival estimates of 55% for cases with t(8;21) and 70% for cases with inv(16) treated in recent trials.[216] The French AML Intergroup demonstrated a 5-year overall survival estimate of 59% for patients with t(8;21) and suggested that the white blood cell (WBC) index (the product of the WBC count and the ratio of bone marrow blast cells) can identify prognostic subgroups of t(8;21)-positive patients.[242]

AML patients with the t(9;11) translocation also have had a favorable prognosis in some trials [243,244] but not in others.[164] In the MRC AML10 trial, patients with the t(9;11) translocation had an intermediate outcome, with a 3-year overall survival estimate of 50%,[240] whereas patients with the t(9;11) or other 11q23 abnormalities had a rather poor outcome on POG 8821 (4-year overall survival 33%).[164] Among patients treated at St. Jude for AML, those with the t(9;11) and inv(16) had a better outcome (5-year event-free survival estimate, 70% or higher) than patients in all other cytogenetic or molecular subgroups.[216] Favorable outcome of these patients is attributed to the use of epipodophyllotoxins, agents known to be effective against M5 leukemia,[245,246] and of 2-chlorodeoxyadenosine (2-CDA), which is particularly effective against M5 AML.[247] In vitro, blast cells from patients with the t(9;11) are more sensitive to cytarabine, etoposide, anthracyclines, and 2-CDA than are blast cells from other cases.[248]

Some studies have suggested that partial tandem duplications of the *MLL* gene confer a poor prognosis.[249,250] Patients with acute megakaryoblastic leukemia have significantly worse outcomes than those with other subtypes of AML.[195,251,252] At St. Jude the estimated 5-year survival for these group of patients in the absence of Down syndrome was only 10%, and no patients were cured by chemotherapy alone.[195] The outcome of treatment-related AML is also dismal, with survival rates of only 10% to 20%, despite the use of allogeneic hematopoietic cell transplantation.[253–255] Likewise, patients with MDS, AML arising from MDS, or AML with monosomy 7 often have resistant disease that is difficult to cure.[164,199,240,256]

FLT3 ITDs have been associated with a poor prognosis in both adults and children with AML.[257–262] An analysis of 91 children with ALL treated on CCG trials demonstrated an 8-year event-free survival estimate of only 7% for the 15 cases with *FLT3* ITD.[260] A multivariate analysis demonstrated that *FLT3* ITD was the most important prognostic factor in this study. Several studies have questioned the prognostic importance of *FLT3* mutations.[263–266] In an analysis of 82 adults with AML who were treated on the CALGB 9621 protocol and who had normal cytogenetics, three leukemic cell genotypes were detected: 59 cases had 2 wild-type *FLT3* alleles ($FLT3^{wt/wt}$), 15 had one wild-type and one ITD allele ($FLT3^{ITD/wt}$), and 8 had only one ITD allele ($FLT3^{ITD/-}$).[263] Overall and event-free survival were similar in patients with the $FLT3^{wt/wt}$ and $FLT3^{ITD/wt}$ genotypes. Only patients with the $FLT3^{ITD/-}$ genotype had a significantly worse outcome. Similarly, an analysis of 979 patients revealed that those with a high *FLT3* mutant to wild-type ratio had significantly shorter disease-free and overall survival, whereas those with low ratios had outcomes similar to those of patients without *FLT3* mutations.[265] Gene expression studies in samples with *FLT3* mutations identified an association between high expression of the *RUNX3* gene, low expression of the *ATRX* gene, and an inferior outcome.[267]

Prognosis of Myelodysplastic Syndrome and Juvenile Myelomonocytic Leukemia

The clinical course of children with MDS is variable. The conversion rate to AML of approximately 40% is similar to that observed in adults.[199] MDS conversion to AML may occur either with an abrupt increase in blasts or through a gradual progression.[11–13] In only approximately 15% of JMML patients the disease transforms into acute leukemia blasts crisis.[199] However, only a very small minority of patients enjoy long-term survival with a relatively indolent disease, treated with observation or low-dose chemotherapy.[11] For the majority of patients the disease course is rapid and fatal within a year. Patients with older age, a low platelet count, and high fetal hemoglobin levels fare worse. Stem cell transplantation is the only therapy that has produced sustained remissions.[11–13]

PRIMARY TREATMENT

Acute Lymphoblastic Leukemia

Overview

In the more successful contemporary clinical trials, 5-year event-free survival estimates for children with newly diagnosed ALL range from 75% to 83% (Table 101-5).[217–220,222–225,227,228,268–277] The improved cure rate of ALL can be attributed mainly to the development of more effective chemotherapeutic regimens through successive clinical trials. In patients with mature B-cell ALL, short-term (2 to 8 months) regimens of intensive chemotherapy based primarily on cyclophosphamide, methotrexate, cytarabine, and intrathecal therapy currently result in cure rates of 74% to 87%.[278–280] The development of a highly effective uricolytic agent, recombinant urate oxidase (rasburicase; Elitek, Fasurtec), promises to improve the results of treatment still further by reducing early morbidity and mortality caused by tumor lysis syndrome and acute renal failure.[281,282]

For all patients except infants, the basic approach to therapy consists of a relatively brief remission-induction phase, followed by intensification (consolidation) therapy, and then prolonged continuation treatment. All patients require treatment for subclinical leukemia of the CNS, which should be initiated early in the form of intrathecal therapy.

Remission Induction

Remission-induction regimens include a glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and at least a third agent (asparaginase or anthracycline). With improved supportive care and chemotherapy, the rate of complete remission now ranges from 96% to 99%.[217–220,222–225,227,228,268–276] Attempts have been made to

Table 101-5 Current Results of International Studies of Childhood Acute Lymphoblastic Leukemia

Study	Year	Eligible Age (yr)	No. of Patients	Percent 5-Yr Event-Free Survival (±1 SE)			
					B-Lineage*		
				Overall	Standard	High	T-Lineage
AIEOP-91[268]	1991–1995	≤15	1194	70.8 ± 1.3	79.9 ± 1.5	61.5 ± 2.9	40.4 ± 4.1
BFM-90[218,269]	1990–1995	≤18	2178	78.0 ± 0.9	87.4 ± 1.0	66.3 ± 2.1	61.1 ± 2.9
BFM-05[277]	1995–1999	≤18	2012	79.0 ± 1.0	NA	NA	NA
CCG-1800[217]	1989–1995	≤21	5121	75 ± 1	80 ± 1	67 ± 2	73 ± 2
COALL-CLCG-92[223]	1992–1997	≤18	538	76.9 ± 1.9	82.1 ± 2.4	75.7 ± 3.9	71.2 ± 5.1
DCLSG-8[270]	1991–1996	≤18	467	73 ± 2	79 ± 2	67 ± 5	71 ± 6
DFCI-91-01[227,271]	1991–1995	≤18	377	83 ± 2	85 ± 2	82 ± 4	79 ± 8
EORTC-58881[224,272,273]	1989–1998	≤18	2065	70.9 ± 1.1	78.4 ± 1.3	57.3 ± 2.4	64.4 ± 2.9
NOPHO-92[274]	1992–1998	≤15	1143	77.6 ± 1.4	85.2 ± 1.5	67.9 ± 3.3	61.3 ± 4.9
POG[219]	1986–1994	≤21	3828	70.9 ± 0.8	77.4 ± 0.9	55.3 ± 1.6	51.0 ± 2.4
SJCRH-13B[228]	1994–1998	≤18	247	80.8 ± 2.6	87.3 ± 3.2	76.7 ± 4.6	71.9 ± 6.8
TCCSG-L92-13[225]	1992–1995	≤15	347	63.4 ± 2.7	67.8 ± 3.4	56.7 ± 5.4	59.3 ± 8.6
UKALL-XI[222,276]	1990–1997	≤15	2090	63 ± 1.1	74 ± 2.2	59 ± 4.1	51 ± 3.5

AIEOP, Associazione Italiana di Ematologia ed Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster ALL Study Group; CCG, Children's Cancer Group; COALL, Cooperative ALL Study Group; DCLSG, Dutch Childhood Leukemia Study Group; DFCI, Dana Farber Cancer Institute ALL Consortium; EORTC-CLCG, European Organization for Research and Treatment of Cancer, Children's Leukaemia Cooperative Study Group; NA, not available; NOPHO, Nordic Society of Pediatric Hematology and Oncology; POG, Pediatric Oncology Group; SJCRH, St. Jude Children's Research Hospital; TCCSG, Tokyo Children's Cancer Study Group; UKALL, UK Medical Research Council Working Party on Childhood Leukaemia.

*Standard-risk group: children 1 to 9 years old with leukocyte count $<50 \times 10^9$ cells/L; high-risk group: all others, except infants. Differences in "overall" partly reflect the disproportion of high-risk cases referred to some institutions as compared with the others.

intensify induction therapy, especially for patients with high-risk and very high-risk ALL, on the premise that a more rapid and profound reduction of the leukemic cell burden may forestall the development of drug resistance in leukemic cells. However, several studies suggest that intensive induction therapy may not be necessary for standard-risk patients, providing that they receive postinduction intensification therapy.[217,223] Moreover, overly intensive induction therapy may lead to inferior overall outcome because of increased early morbidity and mortality.[283,284] Furthermore, we found that patients who achieved MRD^- status 14 weeks after the end of remission-induction therapy had a risk of relapse as low as that of patients who achieve this status earlier (at the end of remission induction).[285]

Most remission-induction regimens include asparaginase. However, several clinical trials using asparaginase only in the postinduction period had an excellent remission induction rate with low morbidity (especially in terms of thrombotic complications) and excellent long-term event-free survival.[223,227] A randomized trial compared the relative efficacy and toxicity of asparaginase and epidoxorubicin as a third remission-induction agent in patients with standard-risk ALL. Patients treated with asparaginase had a significantly lower rate of successful remission induction due to a higher rate of fatal infection.[283] Therefore, the use of asparaginase in remission-induction regimens is being challenged. It should also be noted that different forms of asparaginase have different pharmacokinetic profiles as well as toxicity and efficacy.[283,286] Compared with *Escherichia coli* asparaginase, *Erwinia* asparaginase was associated with inferior antileukemic response but had lower toxicity, a result now attributed to the use of inadequate doses of the latter medication.[287] In some current protocols, polyethylene glycol–conjugated asparaginase, a long-acting and less allergenic form, has replaced native *E. coli* asparaginase in initial treatment.[286] Because of the cross-reactivity of antibodies to these two forms of asparaginase, patients with allergic reactions to either preparation should be treated subsequently with *Erwinia* asparaginase.[288]

Perhaps because of its longer half-life and increased penetration into CSF,[289] dexamethasone has been used instead of prednisone or prednisolone in some induction and continuation regimens. Although this substitution yielded an improved outcome in one randomized trial,[217] it was implicated in excessive life-threatening infections and septic deaths in another study.[284] This finding underscores the importance of potential drug interactions in any complex multiagent regimen. A small randomized study showed that an increased dose of prednisone produced results comparable to those achieved with dexamethasone in the context of other intensive treatment.[290]

Intensification or Consolidation

With restoration of normal hematopoiesis, patients in remission become candidates for intensification (consolidation) therapy. There is no dispute about the importance of this phase of therapy, but there is also no consensus about the optimal regimens and their duration. Delayed intensification (or reinduction), pioneered by investigators in the Berlin-Frankfurt-Münster consortium,[269] is perhaps the most widely used regimen. It is basically a repetition of the initial induction therapy 3 months after the end of remission induction. Investigators at the CCG found that double delayed intensification beginning at week 32 of treatment improved the outcome of patients with high-risk (or so-called intermediate-risk) leukemia.[291] Interestingly, in this study additional pulses of vincristine and prednisone during continuation therapy did not improve outcome, suggesting that double delayed intensification was of benefit because of the increased dose intensity of other agents (asparaginase, anthracycline, cytarabine, and cyclophosphamide), or the timing/scheduling of the intensification regimen. Extended and stronger intensification therapy also significantly benefited patients with high-risk ALL and a slow response to initial induction therapy.[292] The benefit of double delayed intensification for high-risk ALL was recently confirmed by the Italian group AIEOP.[293] Limited data suggest that patients at standard risk do not need double delayed intensification. Hence, it seems that reinduction or delayed intensification therapy is beneficial to all patients, and double or prolonged intensification is beneficial to those with high-risk or very high-risk leukemia.

The use of different intensification regimens in various clinical trials has also led to the identification of effective treatment components for certain subtypes of leukemia. For example, improved outcome of T-lineage ALL in the clinical trials of the Dana Farber Cancer Institute (DFCI) Consortium and CCG has been credited to the intensive use of asparaginase,[227,271,294] a finding that has been corroborated by a randomized study of the POG.[295] Interestingly, in the study of the DFCI Consortium, patients who tolerated at least 26 weekly doses of asparaginase had a significantly better outcome than those who received fewer doses.[227] Intensive asparaginase treatment is also credited for a very low rate of relapse of ALL with the *TEL-AML1* fusion on the protocols of the DFCI Consortium.[227] In line with this clinical observation, leukemic blast cells with the *TEL-AML1* fusion are reportedly highly sensitive to asparaginase in vitro.[106]

Very high doses of methotrexate (5 g/m^2) seem to improve outcome in patients with T-lineage ALL.[218,221] This observation is consistent with the finding that T-lineage blast cells accumulate methotrexate polyglutamates (active metabolites of methotrexate) less avidly than do B-lineage blast cells, so that a higher serum concentration of methotrexate is needed for adequate response in T-lineage ALL.[296] Nonetheless, high-dose methotrexate also benefits patients with B-lineage ALL.[297] Although the optimal dosage of methotrexate for individual genetic subtypes remains to be determined, a dosage of 2.5 g/m^2 should be adequate for most of these patients.[298] High-dose intravenous 6-mercaptopurine has proved ineffective.[270,299,300] Consistent with this result is the finding that intravenous high-dose 6-mercaptopurine inhibited de novo purine synthesis minimally and exerted minimal antileukemic effects.[301] Similarly, high-dose cytarabine failed to improve the outcome of high-risk ALL in a randomized trial.[272]

Continuation Treatment

The most successful postremission-intensification regimens generally feature continuous therapy,[227,292] whereas high-dose pulse therapy with prolonged rest periods to recover from myelosuppression seems to be less effective.[269] Children with ALL (except those with mature B-cell leukemia) require prolonged continuation treatment. The attempt to intensify early therapy but shorten the total duration of treatment to 1 year in one study resulted in inferior overall event-free survival.[225] The general rule is to continue therapy for a total duration of 2 to 2.5 years. Many investigators prefer to extend treatment for boys to 3 years because of their generally poorer outcome,[226,302] although the benefit of this approach remains to be determined.

The combination of methotrexate administered weekly and mercaptopurine administered daily constitutes the standard "backbone" of the ALL continuation regimen. Tailoring the doses to the limits of tolerance (as indicated by low neutrophil counts) has been associated with an improved clinical outcome.[303] However, overzealous use of 6-mercaptopurine, so that neutropenia precludes further use of chemotherapy and reduces overall dose intensity, is counterproductive.[304] It is well recognized that the rare patients (1 in 300) who have an inherited deficiency of thiopurine *S*-methyltransferase have extreme sensitivity to mercaptopurine. Patients who are heterozygous for this deficiency (~10%) and have intermediate levels of enzyme activity may also require moderate dose reduction to avert side effects.[305] Identification of the genetic basis of this autosomal codominant trait has made the molecular diagnosis of these cases possible.[306] When patients show poor tolerance to methotrexate and mercaptopurine, studies can now be performed to identify and selectively reduce the dosage of the responsible agent, allowing full dosage of the other drug. In randomized trials, thioguanine (given at a daily dose of 40 mg/m^2 or more, produced superior antileukemic responses than mercaptopurine but was associated with profound thrombocy-

topenia, an increased risk of death, and an unacceptably high rate (10% to 20%) of hepatic veno-occlusive disease.[307,308] Mercaptopurine therefore remains the preferred drug, although thioguanine could still be given in short-term courses duirng the intensification phase of therapy.

The addition of intermittent pulses of vincristine and a glucocorticoid to the antimetabolite continuation regimen improves the results[309] and has been widely adopted. Dexamethasone has been substituted for prednisone during continuation therapy in many clinical trials, because of its superior clinical efficacy.[217] However, studies are needed to determine the optimal dosage and duration of dexamethasone therapy during this phase of treatment.

Prevention and Treatment of Central Nervous System Leukemia

Several factors are associated with the occurrence of leukemia in the CNS: presenting risk features, the quantity of leukemic blasts cells in the CSF, and the type of systemic as well as CNS-directed therapy. Patients with high-risk genetic features, large leukemic cell burden, T-lineage ALL, and leukemic cells in the CSF (even if iatrogenic from a traumatic lumbar puncture) are at increased risk of CNS relapse and require more intensive CNS-directed therapy.[61,277,310,311] Because of the adverse consequence of traumatic lumbar puncture at the time of diagnosis, when patients have circulating blast cells we have routinely performed this procedure under deep sedation or general anesthesia, transfused thrombocytopenic patients with platelets, and administered intrathecal chemotherapy immediately after injection of CSF. High-dose methotrexate, while useful in preventing hematologic or testicular relapse, generally has only a marginal effect on the control of CNS leukemia. However, in one study high-dose methotrexate plus intrathecal methotrexate reduced CNS relapse, although it did not affect relapse at other sites or overall surviva1.[222] Additional analyses of the method of delivery of high-dose methotrexate and folic acid rescue are needed to explain this finding. By contrast, dexamethasone was definitely shown to improve CNS control.[217,299,312] In one randomized trial, triple intrathecal therapy with methotrexate, hydrocortisone, and cytarabine was more effective than intrathecal methotrexate alone in preventing CNS relapse, but was associated with an increased frequency of bone marrow or testicular relapse.[313] One explanation for this seemingly paradoxical finding is that an "isolated" CNS relapse is in fact an early manifestation of systemic relapse, and the better CNS control secured by triple intrathecal therapy does not suppress overt relapse in other sites. If so, more effective systemic therapy is needed before the full benefit of triple intrathecal therapy can be realized.

Cranial irradiation is the most effective CNS-directed therapy but can cause substantial neurotoxicity and occasional brain tumors, prompting its replacement with intensive intrathecal and systemic chemotherapy for 80% to 95% of all patients. This approach, in combination with cranial irradiation for selected high-risk or very high-risk cases, has lowered the rate of CNS relapse to less than 5% in most studies.[227,228,269,275,292] The dose of radiation can be lowered to 12 Gy without increasing the risk of CNS relapse, provided that effective systemic chemotherapy is used.[269] In two studies that omitted cranial irradiation altogether, the cumulative risk of isolated CNS relapse was 4.2% and 3%,, and the rate of any CNS relapse (including combined CNS and hematologic relapse) was 8.3% and 6%, respectively.[224,314] Patients with a $CD10^-$ B-lineage (pro-B) leukemic phenotype, CNS 2 or CNS 3 status, and leukocyte count greater than 100×10^9 cells/L had an increased risk of CNS relapse. Because the overall 8-year event survival estimates for the two studies were only 60.7% ± 4% (SE) and 68.4 ± 1.2%, it is still unclear whether improved systemic chemotherapy can reduce the hazard of CNS relapse. It is not conclusively established whether CNS irradiation can decrease the risk of hematologic relapse.

Patients with isolated CNS relapse who did not receive cranial irradiation as initial CNS-directed therapy have a very high retrieval rate; in those who had a long initial remission before the CNS event, the long-term prognosis may even be similar to that of newly diagnosed patients.[214,315] At St. Jude, cranial irradiation is reserved for salvage therapy. Although this approach is under study, most clinical trials still specify cranial irradiation for patients at particularly high risk of CNS relapse (e.g., those with CNS 3 status or T-cell ALL with high leukocyte count).

Infant Acute Lymphoblastic Leukemia

Event-free survival estimates for infants with ALL, especially those with 11q23/*MLL* rearrangements, remain low, ranging from 20% to 45%.[35] In several recent clinical trials high-dose cytarabine, high-dose methotrexate, and intensive consolidation/reinduction therapy seemed to improve outcome.[316–320] However, these results should be viewed as preliminary because of the small numbers of patients studied and the absence of randomization. Intensive systemic and intrathecal treatment, without cranial irradiation, seem to provide adequate CNS protection, even in infants who have CNS leukemia at diagnosis.[319–321] Most investigators now treat infants as a unique subgroup with multiple drugs given at high dosages, without cranial irradiation. The role of allogeneic hematopoietic stem cell transplantation in this age group remains controversial.[113,322–324]

Pharmacokinetic and Pharmacogenomic Variables

The rate of metabolism and systemic clearance of antileukemic agents is widely variable, as is the absorption of orally administered chemotherapy. Both low systemic exposure to methotrexate and low dose intensity of 6-mercaptopurine have been associated with an inferior treatment outcome.[325,326] Importantly, concomitant administration of cytochrome P450 enzyme-inducing anticonvulsants (phenytoin, phenobarbital, carbamazepine, or a combination) significantly increases the systemic clearance rates of several antileukemic agents and is associated with lower efficacy of chemotherapy.[327] At St. Jude, anticonvulsants that are less likely to induce the activity of drug-metabolizing enzymes (e.g., gabapentin, valproic acid) are used instead. Genetic polymorphisms of several drug-metabolizing enzymes are also associated with treatment outcome. Patients who have homozygous or heterozygous deficiency of thiopurine methyltransferase, the enzyme that catalyzes the S-methylation (inactivation) of mercaptopurine, tend to have better event-free survival, probably because they receive a higher effective dose intensity of 6-mercaptopurine.[326] However, the thiopurine methyltransferase genetic polymorphism is also linked to acute dose-limiting toxicity,[328] the risk of irradiation-induced brain tumor,[329] and therapy-related acute myeloid leukemia,[253,330] in the context of antimetabolite-based therapy. Hence, therapy must be adjusted in patients who have homozygous mutant genotypes of this enzyme and in many heterozygotes. Using this approach, genetic polymorphism of this enzyme was no longer associated with clinical outcome in a recent study.[331] The null genotype (absence of both alleles) for *GSTM1* or *GSTT1* and the *GSTP1* Val_{105}/Val_{105} genes are also associated with increased treatment-related toxicity[332,333] and a lower risk of relapse,[334] perhaps because of reduced detoxification of cytotoxic chemotherapy. A tandem-repeat polymorphism within the enhancer region of the thymidylate synthase gene, a major target of methotrexate, has been associated with increased expression of the enzyme and a higher relapse hazard.[335,336] Nevertheless, the prognostic value of individual pharmacogenetic variables depends on the type of treatment.[337,338] In addition, it is likely that multiple genetic polymorphisms interact to influence treatment response.[335] Finally, the presence of additional chromosomes in leukemia cells can create discordance between germline and leukemia cell pharmacogenomic phenotypes.[339]

Acute Myeloid Leukemia

Clinical trials of therapy for AML are characterized by dose intensification of conventional therapeutic agents. Remission induction and consolidation therapy are essential components of virtually every

protocol, whereas other postremission therapy differs widely between studies.

Remission Induction

With the exception of APL, which is now treated initially with ATRA in combination with chemotherapy (generally at least an anthracycline), all cases of AML are treated with induction chemotherapy comprising cytarabine and a topoisomerase II inhibitor (anthracycline, idarubicin, doxorubicin, or mitoxantrone) with or without a third agent (etoposide or 6-thioguanine; see Table 101-5).[113,340–348] Rates of remission induction range from 74% to 91% among contemporary clinical trials.[340–350] This variation is in part due to differences in the timing of remission studies (i.e., after one, two, or multiple courses of therapy). Nonetheless, many attempts have been made to modify remission-induction therapy not only to increase the rate of remission but to improve its "quality" or "degree," which in turn can favorably affect the ultimate treatment outcome.

Modifications of remission induction include the use of additional agents or different topoisomerase II inhibitors, increased drug dosages, increased duration of drug exposure, and decreased intervals between treatment courses.[340–350] Because idarubicin has faster cellular uptake, increased cellular retention, less in vitro drug resistance, longer plasma half-life of the active metabolites, and potentially less cardiotoxicity than daunorubicin,[351] investigators of the Berlin-Frankfurt-Munster (BFM) Consortium compared the clinical efficacy of these two agents during remission induction in their AML93 study.[341,342] Idarubicin yielded a significantly lower bone marrow blast cell count on day 15 than did daunorubicin. Although long-term outcome did not differ significantly between the two randomized groups, the subset of patients who had more than 5% blast cells in the bone marrow on day 15 seemed to benefit from idarubicin. By contrast, the Australian and New Zealand CCG found daunorubicin to be as effective as idarubicin and less toxic.[340] Using an "upfront window" therapy approach, investigators at our institution demonstrated that 2-CDA given as a single agent induced remission in 45% of patients after one course and in 70.6% after two courses of treatment; 2-CDA was also particularly effective against acute monoblastic leukemia.[247] Complete remission rates of 90% and 100% were observed in two treatment arms that used two different schedules of a 2-CDA–cytarabine combination followed by two courses of daunorubicin, cytarabine, and etoposide.[348] The long-term results of this approach remain to be determined.

The CCG pursued the approach of timed-sequential therapy (i.e., intensification of therapy) by reducing the interval between two induction courses. The intensive-timing arm had a remission-induction rate comparable to that of the standard-timing arm, despite a much higher rate of early mortality (11% vs. 4%). Although the intensive-timing arm yielded a superior overall outcome, regardless of the type of postremission therapy,[343,344] this approach would not be considered acceptable in contemporary clinical trials because of its associated high rate of early toxic death. In a subsequent study, these investigators found that patients with a negative genotype (i.e., homozygous polymorphism) for glutathione *S*-transferase theta, a detoxifying enzyme, experienced greater toxicity and mortality than did patients with at least one wild-type allele.[352]

The POG has used high-dose cytarabine to intensify therapy. In the POG 8498 study, patients were randomized to receive two courses of DAT (daunorubicin, cytarabine and 6-thioguanine) or one course of DAT followed by a course of high-dose cytarabine.[353] The two treatment arms had comparable remission rates (both 85%), but patients who received high-dose cytarabine had a higher estimate of 3-year event-free survival (34% vs. 29%). In the POG 9421 study, patients were randomized to receive DAT induction at standard dose or DAT with cytarabine at a high dose. Remission rates were somewhat lower in the standard arm (87% vs. 91%), as were 3-year event-free survival estimates (34% vs. 40.4%, $P = 0.17$).[349]

The MRC used a prolonged daily exposure approach to intensify therapy. They found that prolonged treatment resulted in greater toxicity but an improved remission rate and a shorter time to remission.[354] In the MRC AML10 trial, patients randomly assigned to receive 6-thioguanine or etoposide as the third induction agent had a comparable overall outcome.[345]

In summary, intensified remission induction in general improves long-term outcome. However, vigilance in supportive care is important to reduce early mortality. Patients with Down syndrome should not receive intensified therapy, because they have more drug-sensitive disease and are more susceptible to treatment-related toxicity than the general population.[355,356]

Consolidation and Other Postremission Therapy

Without postremission therapy, relapse is nearly inevitable.[211] Although more courses of consolidation therapy are thought to be better, the optimal number is uncertain.[211] The current MRC AML12 trial is investigating whether four or five courses of consolidation therapy is better. In most clinical trials, postremission consolidation therapy lasts for 6 to 12 months in patients who do not undergo hematopoietic stem cell transplantation.

The optimal consolidation therapy has yet to be determined but generally includes high-dose cytarabine. In the BFM AML93 study, the improved outcome of high-risk cases was attributed to intensification with high-dose cytarabine and mitoxantrone.[342] This drug combination is also an integral component of the MRC AML10 trial.[345,346] The combination of high-dose cytarabine and asparaginase was credited for the improved outcome in the CCG-213 and CCG-213P studies.[357,358] Consolidation therapy with high-dose cytarabine alone also resulted in an improved outcome in the POG 8498 study.[353] In adult clinical trials, high-dose cytarabine seemed to be particularly beneficial to patients whose leukemia involved disruption of CBF.[238]

The need for continuation therapy beyond consolidation therapy is less certain. Although the BFM study group achieved excellent results with continuation therapy lasting 18 to 24 months,[341,342] other studies could not demonstrate the clinical benefit of this phase of therapy.[359,360] In fact, a randomized study by the CCG (213P) showed that 2 years of continuation treatment after intensification therapy resulted in a worse outcome than no continuation treatment.[357] In the French Leucemie Aique Myeloide Enfant (LAME) 89/91 study, low-dose continuation treatment of 18 months also resulted in worse overall survival than no continuation treatment.[344] The investigators attributed this finding to the development of drug resistance during continuation therapy, leading to a poor salvage rate. Hence, most study groups, with the exception of the BFM group, have abandoned the use of continuation therapy in AML. It should be noted that cases of APL benefit from prolonged continuation treatment with ATRA and, possibly, with 6-mercaptopurine and methotrexate.[361]

Central Nervous System-Directed Therapy

Relatively little attention has been paid to CNS-directed therapy for AML, because control of hematologic disease remains the focus of treatment. Suboptimal systemic therapy may allow hematologic relapse to precede meningeal relapse. In most clinical trials, intrathecal cytarabine with or without methotrexate and systemic high-dose cytarabine are used as CNS prophylaxis. The BFM AML87 study attempted to address whether cranial irradiation is necessary in childhood AML.[362] In that randomized study children who received cranial irradiation had longer relapse-free survival than did those receiving only intrathecal therapy, although there was only a marginal difference between the two groups in the rate of CNS relapse. The early termination of randomization in that study prevents firm conclusions; moreover, many other clinical trials have yielded similar outcomes without the use of cranial irradiation (Table 101-6). Therefore, cranial irradiation may not be necessary if systemic and intrathecal chemotherapy is adequate. Even less is known about the optimal treatment of overt CNS leukemia at presentation. In an earlier study in our institution, this factor lacked prognostic significance,[363] and a

Table 101-6 Results of Selected Recent Clinical Trials for Childhood Acute Myelocytic Leukemia

Study	Years	Treatment Schedule	No. of Patients	Remission Rate (%)	Early Mortality	Overall Outcome (%)	Conclusions
ANZCCSG AML2[340]	1993–1999	***Remission induction*** Ida/Ara-C/6TG 2. HD Ara-C ***Consolidation*** Ida/Ara-C/VP16 2. Ara-C/Amsa ***Interim therapy*** Ara-C/6TG ***Postconsolidation*** Allo HSCT or Auto HSCT	160	91	5	5-yr EFS 41% 5-yr OS 55%	Idarubicin was more toxic than daunorubicin (used in preceding AML1 trial) during remission induction.
BFM AML93 [341,342]	1993–1998	***Remission induction*** Dauno/Ara-C/VP16 vs. Ida/Ara-C/VP16 ***Consolidation*** 7-day 6-week consolidation plus Mito/Ara-C for high-risk patients ***Intensification*** HD Ara-C/VP16 ***Continuation (18 months)*** 6TG/Ara-C plus cranial irradiation Allo HSCT for high-risk patients	471	82	7	5-yr EFS 51% ± 2% 5-yr OS 60% ± 3%	Idarubicin reduced blast cells more profoundly than daunorubicin during the first 2 weeks of remission induction in high-risk cases. Improved outcome for high-risk cases was attributed to mitoxantrone and high-dose cytarabine.
CCG 2891[343,438]	1989–1995	***Remission induction*** DCTER × 2 ***Consolidation*** DCTER × 2 ***Postconsolidation*** Allo HSCT for patients with suitable donor; others: Auto HSCT or four cycles chemotherapy	652	74	8	3-yr EFS Standard timing 27% Intensive timing 42% 3-yr OS Standard timing 39% Intensive timing 51%	Overall survival was improved by timing-intensive treatment. Outcome of allogeneic transplantation was superior to outcome of autologous transplant or chemotherapy. Intensive chemotherapy was as efficacious as autologous transplant.
LAME 89/91[344]	1988–1996	***Remission induction*** Ara-C/Mito ***Consolidation*** Allo HSCT for patients with suitable donor, Others: chemotherapy VP16/Ara-C/Dauno Amsa/HD Ara-C/Asp × 2 ± Continuation (18 months) 6MP/Ara-C	268	90	5	6-yr EFS 48% ± 6% 6-yr OS 60% ± 6%	Low-dose continuation treatment had no benefit and may contribute to drug resistance and poor salvage rate after relapse.

MRC AML10[345,346]	1988–1995	***Remission induction*** DAT vs. ADE × 2 ***Consolidation*** Amsa/Ara-C/VP16 Mito/Ara-C ***Postconsolidation*** Allo HSCT for patients with suitable donor, Others: Auto HSCT or no chemotherapy.	341	92	6	7-yr EFS 48% 7-yr OS 56%	Short-term intensive chemotherapy without continuation treatment can cure 50% of patients. Transplantation reduced risk of relapse but did not improve survival.
NOPHO-AML93[347]	1993–2000	***Remission induction*** 6TG/Ara-C/VP16/Doxo Mito/Ara-C or 6TG/Ara-C/VP16/Doxo ***Consolidation*** HD Ara-C/Mito HD Ara-C/VP16 HD Ara-C HD Ara-C/VP16	219	91	—	7-yr EFS 49%	Allowing hypoplastic marrow to recover after induction before reinstituting chemotherapy reduced the toxic death rate.
POG 9421[349,350]	1995–1999	***Remission induction*** DAT vs HDAT HD Ara-C ***Consolidation*** Allo HSCT for patients with suitable donor, others: chemotherapy: VP16/Mito ± CsA HD Ara-C VP16/Mito ± CsA	632	90	—	3-yr EFS 31% to 43% 3-yr OS 51% to 55%	High-dose cytarabine during induction did not improve complete remission rate but tended to improve event-free survival.
SJCRH AML97[348]	1997–2002	***Preinduction*** 2CDA/Ara-C ***Remission induction*** Dauno/Ara-C/VP16 × 2 ***Consolidation*** HDAra-C/Asp/Mito/Ara-C ***Postconsolidation*** Allo HSCT for patients with suitable donor, others: Auto HSCT	83	Arm A 90 Arm B 100	—	3-yr EFS 50% 3-yr OS 57%	2-chlorodeoxyadenosine increases intracellular accumulation of Ara-CTP.

ADE, cytarabine, daunorubicin, etoposide; Allo HSCT, allogeneic hematopoietic stem cell transplant; Amsa, amsacrine; ANZCCSG, Australian and New Zealand Children's Cancer Group; Ara-C, cytarabine; Asp, asparaginase; Auto HSCT, autologous hematopoietic stem cell transplant; BFM, Berlin-Frankfurt-Münster Study Group; 2CDA, 2-chlorodeoxyadenosine; CCG, Children's Cancer Group; CsA, cyclosporine; DAT, daunorubicin, cytarabine, 6-thioguanine; Dauno, daunorubicin; DCTER, decadron, cytarabine, 6-thioguanine, etoposide, rubomycin (daunorubicin); doxo, doxorubicin; EFS, event-free survival; HD Ara-C, high-dose cytarabine; HDAT, daunorubicin, high-dose cytarabine, 6-thioguanine; Ida, idarubicin; LAME, Leucámie Aiquë Myéloïde Enfant; Mito, mitoxantrone; 6MP, 6-mercaptopurine; MRC, Medical Research Council; NOPHO, Nordic Society of Paediatric Haematology and Oncology; POG, Pediatric Oncology Group; OS, overall survival; 6TG, 6-thioguanine; SJCRH, St Jude Children's Research Hospital;VP16, etoposide.

more recent study suggested that these patients can be cured without the use of cranial irradiation.[348]

Hematopoietic Stem Cell Transplantation

The indications for transplantation should be periodically re-evaluated. At present, among children with ALL, those with the Philadelphia chromosome, early hematologic relapse, or T-cell ALL with poor early response or hematologic relapse are clearly candidates for transplantation.[3,122,364] Transplantation has not been shown to improve outcome in other types of very high-risk leukemia, including infant cases and those with *MLL* rearrangement.[113,233]

Autologous stem cell transplantation has generally been associated with a high rate of relapse in childhood ALL. Excellent results have been reported in a few small series of patients with AML,[365,366] but autologous transplantation has failed to show any survival benefit over chemotherapy in most studies.[367–369] The benefit of in vitro purging to rid autografts of residual leukemia cells remains unproven.[370] Hence, autologous transplantation is not recommended by most investigators.

Allogeneic transplantation in children with AML has been shown in most clinical trials to reduce the risk of relapse and to improve overall survival as compared with either autologous transplant or chemotherapy alone, despite a higher rate of morbidity and mortality.[211,343] However, the indications for this procedure during first remission are still debated. Investigators of the COG favor allogeneic transplantation for all patients who have a suitable donor, because this procedure yielded a superior outcome, regardless of the risk group, in their study.[343] Other investigators do not recommend allogeneic transplantation for patients at lower risk, especially in view of recent improved results with chemotherapy, and reserve this procedure for relapsed AML.[345,370] They contend that most patients with relapsed AML can be readily salvaged with hematopoietic stem cell transplantation and they should be spared the risk of unnecessary transplant-related morbidity and mortality.

Notwithstanding the controversy of allogeneic transplantation, there is general consensus that patients with very high-risk AML [monosomy 5 or 7, del(5q), 3q abnormalities, acute megakaryoblastic leukemia, or poor response to remission-induction therapy] are candidates for this procedure, perhaps even if alternative or unrelated donors are the only options.[370,371] Transplantation is also the treatment of choice for most patients with MDS. By contrast, transplantation is not recommended for patients with Down syndrome or APL in first remission, which have a favorable prognosis with current therapy.[370,371]

Treatment Sequelae

Improved supportive care reduced the rate of early death to less than 2% in the 1990s.[298] Induction therapy with prednisone, vincristine, and asparaginase may cause hyperglycemia and thrombosis. The intensified use of methotrexate and glucocorticoids has caused an increased frequency of neurotoxicity and, in older children and adults, osteonecrosis. High cumulative doses of anthracyclines can produce severe cardiomyopathy, especially in young children. Cranial irradiation causes neuropsychologic deficits, endocrine abnormalities that lead to obesity, short stature, precocious puberty, osteoporosis, and second neoplasms within the irradiated field.[372,373]

Development of therapy-related AML has been linked to the use of topoisomerase II inhibitors (teniposide and etoposide), and the risk is apparently dependent on the treatment schedule and the concomitant use of other agents (e.g., asparaginase, alkylating agents, and perhaps antimetabolites).[253] Children who receive cranial irradiation at 6 years of age or younger are most susceptible to the development of brain tumors. This risk is increased by the intensive use of antimetabolite drugs before and during cranial irradiation.[374]

MINIMAL RESIDUAL DISEASE

Rationale for Studies of Minimal Residual Disease

In vivo measurement of the cytoreductive effect of therapy can provide direct information about the combined effect of clinical and cellular variables in each patient, thereby directly measuring the effectiveness of treatment rather than predicting outcome. Sluggish or incomplete clearance of leukemic cells by remission-induction therapy as determined by morphologic examination of the bone marrow or peripheral blood is clearly associated with a poor treatment outcome.[217,218,375–377] However, conventional morphologic techniques have limited sensitivity and accuracy: in most cases, leukemic cells can be detected in bone marrow with certainty only when they constitute 5% or more of the total cell population. Methods for detecting minimal (i.e., submicroscopic) residual disease are at least 100 times as sensitive as conventional morphologic techniques and allow a more stringent definition of "remission" in patients with acute leukemia.[378] This more stringent definition is rapidly becoming the standard at many cancer centers. In addition, these methods have multiple potential applications in the clinical management of patients with leukemia (Table 101-7).

Methodological Options for Minimal Residual Disease Studies

Many methods of MRD measurement have been tested.[378,379] The most reliable methods for ALL include flow cytometric profiling of aberrant immunophenotypes, polymerase chain reaction (PCR) amplification of fusion transcripts and chromosomal breakpoints, and PCR amplification of antigen-receptor genes.[378] Only the first two can be applied to AML, because most cases lack antigen-receptor gene rearrangement. The value of another PCR target, WT-1, is being studied and awaits to be definitively proven.[380,381] *FLT3* ITDs could, in principle, be used as targets for PCR-based MRD studies in AML. However, ITDs that are detected at diagnosis are often undetectable at the time of relapse.[382,383] Because of their limited sensitivity (~1% to 5%), conventional karyotyping and fluorescence in situ hybridization cannot reliably detect submicroscopic leukemia but can occasionally be useful in clarifying the nature of morphologically suspicious blast cells.[384]

We extensively compared flow cytometric detection of aberrant immunophenotyes and PCR amplification of *IGH* genes and found them to be highly concordant.[385] Others also obtained concordant results in most samples.[386] The use of both methods in tandem allowed us to monitor MRD in virtually all patients in our recent Total XV study.[385,387] Definitive comparisons between reverse transcriptase-PCR amplification of fusion transcripts and either flow

Table 101-7 Clinical Applications of Minimal Residual Disease Studies

Time of Study	Objective
During remission induction	Measure early response to treatment.
Throughout treatment	Identify patients at a higher risk of relapse or impending clinical relapse.
Before autograft	Detect contaminating leukemic cells; evaluate the efficacy of "purging".
After allogeneic transplant	Gauge effect of withdrawal of immunosuppressive therapy and of donor lymphocyte infusions.
Testing of novel agents	Use minimal residual disease as endpoint to test efficacy.

cytometry or PCR amplification of antigen-receptor genes have not been reported.

Prognostic Value of Minimal Residual Disease in Acute Lymphoblastic Leukemia

Several prospective studies have defined the prevalence and the clinical significance of MRD at different time points during treatment of childhood ALL. In one multicenter study, MRD was measured in 178 patients by a competitive PCR assay targeting junctional sequences of *IGH* and *TCR*.[388] The presence or absence and the level of residual leukemia during the first 6 months of therapy were significantly correlated with the risk of early relapse at each of the time points studied. Patients who had 1% or more leukemic cells after the completion of induction therapy or who had 0.1% or more at later time points had a particularly high risk of relapse. Another multicenter study monitored MRD in 240 children with ALL treated on the International BFM Study Group protocols.[389] This study used PCR analysis of *IGH* genes, *TCR* genes, and *TAL1* deletions. MRD^+ patients had relapse rates 5 to 10 times the relapse rate of patients who were MRD^- at the various follow-up times. MRD levels of 1% or greater at the end of induction treatment and before consolidation treatment were associated with a very high relapse rate. Combined MRD information from the first two follow-up time points was particularly informative, allowing the identification of three different risk groups: a low-risk group comprising 43% of patients with a 3-year relapse rate of 2% (95% confidence interval, 0.05% to 12%); a high-risk group comprising 15% of patients with a relapse rate of 75% (55% to 95%); and an intermediate-risk group (43%) with a 3-year relapse rate of 23% (13% to 36%).

We used flow cytometry to prospectively study MRD in 195 children with newly diagnosed ALL enrolled in a single-institution chemotherapy program (Total XIII).[285,390,391] We found that detectable MRD (i.e., ≥0.01% leukemic mononuclear cells) at any of the time points studied (day 19 and end of remission-induction therapy and weeks 14, 32, and 56 of continuation) was significantly associated with a higher relapse rate (Fig. 101-5). Patients who had high levels of MRD at the end of the induction phase (≥1%) or at week 14 of continuation therapy (≥0.1%) had a dismal outcome. The incidence of relapse among patients with MRD at the end of the induction phase was 68% ± 16% (SE) if they remained MRD^+ through week 14 of continuation therapy, but only 7% ± 7% if MRD became undetectable. The persistence of MRD until week 32 was highly predictive of relapse: all four patients who were MRD^+ at week 32 had relapses, but only two of the eight who became MRD^- had relapses.

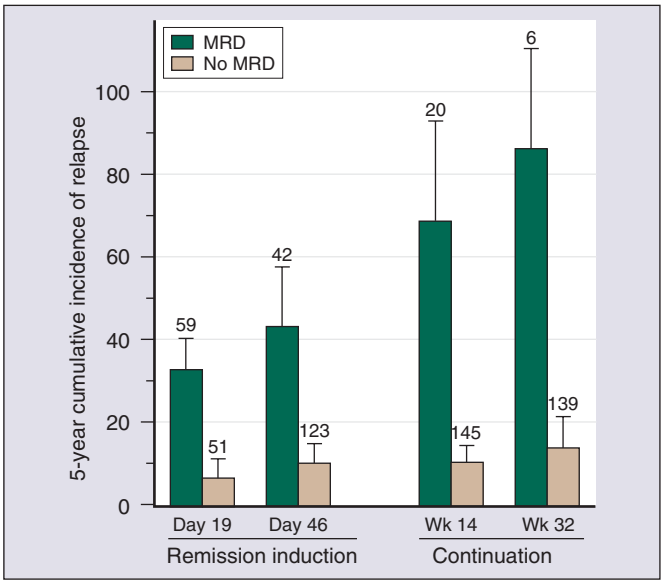


Figure 101-5 • Risk of relapse according to MRD in children with ALL. The 5-year cumulative incidence of relapse according to the results of a flow cytometric MRD assay at different times during treatment is shown.[285,391]

Of the 112 patients studied at day 19 of remission-induction therapy, 53 had achieved a profound cytoreduction (MRD < 0.01%) despite the brief duration of chemotherapy.[391] The outcome of treatment for this group of patients was outstanding: the 3-year cumulative incidence of relapse was 1.9% ± 1.9%, as compared with 28.4% ± 6.4% for MRD^+ patients. These results are consistent with those of another study in which bone marrow samples collected at day 15 of therapy from 68 children with ALL were assayed by PCR amplification of antigen-receptor genes.[392] However, the proportion of children who had the lowest levels of MRD in the two studies was different: 21% in this series, 46% in ours.

In the studies outlined previously, the prognostic value of MRD was independent of other known clinical and biologic prognosticators of outcome. In our study MRD remained a significant predictor in analyses that excluded patients at very high or very low risk of relapse by St. Jude criteria or that focused on patients at high risk of relapse by the National Cancer Institute criteria.[3,285] In the I-BFM study, MRD was also a strong predictor of outcome in children with features that indicated a medium risk.[393]

The predictive value of MRD monitoring extends to children receiving treatment for relapsed ALL.[212,213] MRD detection by PCR amplification of antigen-receptor genes before or after allogeneic bone marrow transplantation was predictive of relapse in children with ALL.[394–397]

In sum, there is strong collective evidence of an association between MRD and an increased risk of relapse of ALL. Because of their complexity, MRD assays can be performed with confidence only in a few specialized laboratories. We recently developed a simple and inexpensive flow cytometric assay that allows the study of MRD in patients with B-lineage ALL during remission-induction therapy.[398] Bone marrow normal lymphoid progenitors ($CD19^+$, $CD10^+$, and/or $CD34^+$) are exquisitely sensitive to corticosteroids and other antileukemic drugs.[398] Hence, we hypothesized that in patients with B-lineage ALL, cells with this phenotype detected early in treatment should be leukemic rather than normal. We applied the simple three-antibody assay to study MRD in bone marrow samples collected on day 19 of remission-induction therapy from 380 children with B-lineage ALL.[398] The results correlated remarkably well with those of more complex flow cytometric and molecular MRD evaluations, and provided powerful and independednt information about risk of relapse. This new assay should allow most treatment centers to identify children with ALL who have an excellent early treatment response and a high likelihood of cure.

MRD has been traditionally measured in the bone marrow, but we and others found that MRD findings in peripheral blood are completely concordant to those in bone marrow in patients with T-lineage ALL.[399,400] We also observed that peripheral blood MRD in B-lineage ALL patients was associated with a very high risk of disease recurrence.[399] Therefore, peripheral blood can be used to monitor MRD in patients with T-lineage ALL. In B-lineage ALL, the presence of MRD in peripheral blood seems to identify patients who are at a very high risk of relapse.

Minimal Residual Disease Studies in Patients with Acute Myeloid Leukemia

The lack of widely expressed molecular markers in AML cells precludes the systematic study of MRD by PCR. Antigen-receptor genes are rearranged in less than 10% of AML cases, and less than half of patients have nonrandom genetic abnormalities with fusion

transcripts suitable for molecular studies of MRD.[401] Thus, correlative studies between MRD and treatment outcome have been performed only in selected groups of patients, almost exclusively adults. In APL, PCR detection of *PML-RARA* and *RARA-PML* transcripts during remission generally predicts relapse.[402,403] Reportedly, careful quantitation of *AML1-ETO* transcripts during remission of AML with the t(8;21) translocation can help to monitor response to treatment.[404,405] Productive MRD studies have also been reported in patients with AML and inv(16)/*CBFB-MYH11*.[406–409]

Flow cytometry can be applied to study MRD in the majority of patients with AML, irrespective of their genetic leukemia subtype. In adult patients with AML, detection of MRD by flow cytometry was a strong predictor of outcome in several studies.[410–412] In a multiinstitutional study, the presence of MRD detected by flow cytometry was associated with earlier relapse in children with AML in first morphologic remission.[413] We found that 61 of 230 bone marrow samples from 46 children with AML during therapy had 0.1% or greater AML cells by flow cytometry.[414] Mean (±SE) 2-year survival estimate was 33.1 ± 19.1% for patients with 0.1% or greater AML cells after induction therapy, significantly lower than the 72.1% ± 11.5% for those with fewer than 0.1% AML cells; overt recurrence of AML within the subsequent 6 months was significantly more likely in the former group. Because of the mounting evidence of the clinical importance of MRD in AML, it has been suggested that this should be incorporated as a parameter to guide therapy.[415] Indeed, in our current AML02 protocol, MRD is used to make clinical decisions about usage of an anti-CD33 immunotoxin and eligibility for hematopoietic stem cell transplantation.

ISSUES FOR THE FUTURE

The current cure rates for ALL attest to the steady progress that has been made in treating this disease. However, cure rates for children with AML and for some patients with ALL, such as infants and those with t(9;22), remain low. Increase in cure rates will most likely require a more accurate prediction of relapse hazard and of chemotherapy resistance to maximize treatment efficacy and minimize its toxicity. MRD assays now allow the objective and sensitive assessment of treatment response in virtually all patients, and it has been incorporated into treatment protocols at our institution and in some large cooperative studies. The further simplification of MRD methods should widen the application of this powerful prognostic parameter, and extend its potential benefits to most patients, including those living in areas with poor resources.[416] A better understanding of the relation between pharmacogenomic features and responses to chemotherapy should lead to further refinement of treatment schedules and dosages.[417]

Clearly, substantial improvement in cure rates for some subsets of leukemia can only come from the development of new treatments. Several new formulations of existing agents may improve efficacy and decrease toxicity.[387,418] Novel nucleoside analogues, such as gemcitabine, clofarabine, and nelarabine, have shown promise in early reports.[418–420] Imatinib mesylate and other ABL kinase inhibitors are the paradigm of molecular therapy of leukemia.[124,126] Other novel agents include inhibitors of FLT3,[186,421] farnesyltransferase,[422] proteasome,[423] γ-secretase,[52] DNA methylation, and histone deacetylase.[424] The application of novel gene expression-based drug screening should accelerate the identification of additional effective compounds.[425]

The arsenal of antibodies for leukemia treatment is steadily increasing. Rituximab (anti-CD20), gemtuzumab ozogamicin (anti-CD33), alemtuzumab (anti-CD52), and epratuzumab (anti-CD22) have already been incorporated into some clinical trials,[418] and novel antibody derivatives and recombinant immunotoxins have also been developed for clinical use.[426] Chimeric receptors composed of single-chain variable domain of murine antibodies and human signaling molecules are a promising tool to redirect the specificity of autologous or allogeneic immune cells.[427–429] Elucidation of the mechanisms that regulate the activation of NK cells has spurred the use of haploidentical NK cells to enhance the efficacy of hematopoietic stem cell transplantation,[430,431] and to reduce leukemia cell burden.[432] Testing the effectiveness of new therapeutic approaches may necessitate nontraditional methods. It may soon be necessary to extend efficacy studies of these agents to patients who have not yet been heavily treated, and perhaps to use MRD measurement to assess tumor response.

There is mounting evidence that the bone marrow microenvironment can regulate the response of leukemic cells to chemotherapy.[433–435] We recently found that bone marrow mesenchymal cells protect ALL cells from asparaginase cytotoxicity by forming an asaparagine-rich milieu.[436] It is possible that leukemic cells that reside in microenvironmental niches become relatively insensitive to chemotherapy; if these cells have stem cell properties[181,437] they might ultimately be capable of initiating leukemia recurrence. Once the molecular mechanisms involved in the interaction between leukemic cells and their microenvironment are better understood, it may be possible to develop strategies that would alter it, thereby enhancing the antileukemic effect of chemotherapeutic agents.

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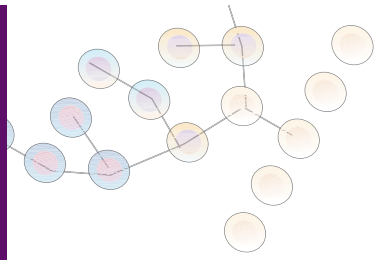
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102 Childhood Lymphoma

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SUMMARY OF KEY POINTS

Incidence

- Malignant lymphoma, which comprises both Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL), is the third most common malignancy in childhood.
- Among children younger than 15 years of age, there is a slight predominance of NHL, whereas Hodgkin's lymphoma is more frequent if children up to 18 years of age are included.
- There are approximately 500 newly diagnosed cases of pediatric NHL in the United States each year.

Etiology and Epidemiology

- NHL is more common in boys than in girls and more common in white children than in black children.
- There are geographical differences with respect to the frequency of histologic subtypes of NHL. Burkitt's lymphoma is the predominant subtype in equatorial Africa and northeast Brazil, where it is associated with Epstein-Barr virus (EBV) in the majority of cases, in contrast to the infrequent association observed in the United States and Western Europe.
- Children with immunodeficiency conditions are at increased risk of developing NHL. These include children with ataxia-telangiectasia, Wiskott-Aldrich syndrome, and X-linked lymphoproliferative syndrome. Children with acquired immunodeficiency disorders, including the acquired immunodeficiency syndrome, and those receiving immunosuppressive therapy following bone marrow or organ transplantation are also at increased risk.

Pathology and Biology

- The most common subtypes of NHL in children are Burkitt's lymphoma, lymphoblastic lymphoma, anaplastic large cell lymphoma, and diffuse large B-cell lymphoma (including the mediastinal subtype).
- Burkitt's lymphoma is a mature B-cell lymphoma of germinal center origin, characterized by a very high proliferation rate, resulting from the activation of the *c-myc* oncogene as a result of juxtaposition to one of the immunoglobulin genes, through one of three characteristic balanced chromosomal translocations [i.e., t(8;14), t(2;8), and t(8;22)].
- Lymphoblastic lymphoma is typically of precursor T-cell immunophenotype and may be associated with reciprocal translocations involving a T-cell receptor gene. Rare cases may be of precursor B-cell lineage.
- Anaplastic large cell lymphoma is a peripheral (post-thymic) T-cell lymphoma that is characterized by large anaplastic ("hallmark") cells expressing CD30 and, in the vast majority of pediatric cases, anaplastic lymphoma kinase (ALK) as a result of a balanced translocation involving the *ALK* gene [e.g., t(2;5)].
- Diffuse large B-cell lymphomas are a biologically heterogeneous category of mature B-cell lymphomas of germinal center or postgerminal center origin, composed predominantly of large cells, with a diffuse growth pattern.

Clinical Findings

- The clinical features at diagnosis are determined by primary sites of disease, which vary according to histologic subtype.
- Children with Burkitt's lymphoma usually present with an abdominal mass and associated gastrointestinal symptoms, whereas those with advanced-stage lymphoblastic lymphoma typically present with a mediastinal mass associated with a spectrum of respiratory symptoms.
- Children with large cell lymphoma or Hodgkin's lymphoma may present with disease in either the abdomen or the mediastinum.

Diagnosis and Differential Diagnosis

- Infectious processes, such as bacterial adenitis, histoplasmosis, tuberculosis, and EBV infection, can simulate lymphoma.
- A comprehensive characterization of the biologic features of tissue will help to distinguish NHL from other small round blue cell tumors, including Ewing's sarcoma, neuroblastoma and rhabdomyosarcoma.

Initial Workup and Staging

- The workup should include a history and physical examination, complete blood count, chemistry panel (including electrolytes, BUN, creatinine, uric acid, phosphorus, calcium, and lactate dehydrogenase), diagnostic imaging studies (computed tomography scan of chest, abdomen, and pelvis; nuclear imaging such as positron emission tomography or gallium scanning), and human immunodeficiency screen.
- For children with NHL, the stage is usually assigned according to the St. Jude system, whereas children with Hodgkin's lymphoma are staged by using the Ann Arbor system.

Primary Therapy

- The treatment plan is determined on the basis of histology, stage, immunophenotype, and, in some cases, clinical symptoms such as fever, weight loss, and night sweats.
- Children with advanced-stage Burkitt's lymphoma are generally treated with intensive cyclophosphamide-based regimens given over a relatively short period of time, whereas children with lymphoblastic lymphoma are generally treated with regimens derived from strategies for children with acute lymphoblastic leukemia.
- Among children with large cell lymphoma, the treatment plan varies

with respect to tumor cell immunophenotype.
- Involved-field radiation therapy has a role in certain cases of Hodgkin's lymphoma but is rarely indicated for children with NHL.

Salvage Therapy
- Children with refractory or recurrent disease are generally considered to have a poor prognosis and are therefore candidates for intensive or novel salvage treatment regimens.
- Those with chemosensitive disease are potential candidates for an intensification phase with hematopoietic stem cell rescue.

Complications
- The most concerning late effects of therapy include cardiac toxicity, infertility, and the development of a second malignancy.
- The risks for these complications are determined in part by the components of initial therapy.

Prognosis
- The most important predictors of treatment outcome for children with NHL are treatment protocol and tumor burden, as reflected by stage and serum LDH.

INTRODUCTION

Substantial clinical and laboratory advances have improved our understanding of both the pathogenesis and treatment of the malignant lymphomas of childhood and adolescence, which comprise Hodgkin's lymphoma and the non-Hodgkin's lymphomas (NHL).[1,2] These are the third most common type of cancer in children in the United States, making up approximately 15% of newly diagnosed cases in this age group each year.[3–8] Among children younger than 15 years of age, the non-Hodgkin's lymphomas account for approximately 60% of cases. However, when children up to age 18 are included, there is a slight predominance of Hodgkin's lymphoma.[7,8]

The non-Hodgkin's lymphomas of childhood are markedly different from those of adulthood.[1,9] Diffuse high-grade extranodal subtypes account for the majority of pediatric cases, whereas low- and intermediate-grade lymphomas are predominant in adults. These differences are probably due in part to age-related maturational changes in the immune system and consequently in the types of cells that are susceptible to malignant transformation.[2] The differences between adults and children in histologic subtype underlie the differing clinical features, staging, and treatment strategies in these age groups.[1]

The clinical presentation, staging, histologic subtypes, and treatment strategies in children and adults with Hodgkin's lymphoma are less dissimilar; however, some differences are worth noting.[10] Epidemiologic studies have suggested three distinct forms that depend on age: the childhood form in patients 14 years of age or younger, the young adult form (ages 15 to 34 years), and an older adult form in individuals 55 to 74 years of age.[11] Among the four histologic subtypes of Hodgkin's lymphoma described in the Rye classification system,[12] the nodular sclerosing subtype is most common in children, occurring in 40% of younger children and 70% of adolescents.[13] Mixed cellularity Hodgkin's lymphoma occurs in approximately 30% of cases and is more common in children with human immunodeficiency (HIV) infection and in those less than 10 years of age; it is frequently associated with an advanced stage (with extranodal extension) at presentation.[13] Lymphocyte-predominant Hodgkin's lymphoma accounts for approximately 10% to 15% of pediatric cases, is usually associated with localized disease at presentation and occurs more commonly in younger patients and in boys. The fourth subtype of Hodgkin's lymphoma, lymphocyte depletion, is very rare in children.[10]

Despite excellent event-free survival rates in Hodgkin's lymphoma, there are well recognized challenges related to the sequelae of therapy, which include endocrine dysfunction, chemotherapy-induced sterility, radiation-induced abnormalities in bone growth, chemotherapy-and radiation- related second cancers, and late cardiac deaths.[10] Most current studies are exploring strategies that maintain an excellent treatment result while reducing late effects. For example, a combined-modality approach with low-dose radiation and combination chemotherapy may reduce the bone growth abnormalities that are associated with high-dose extended-field radiation therapy.[10] However, as therapy is modified in an attempt to reduce the risk of late effects, the rates of event-free survival may be compromised.[14–16] For example, attempts at reducing alkylating agent-related late effects in patients with advanced-stage disease by substituting other chemotherapeutic agents have lowered event-free survival rates.[14,17] These and other issues regarding the management of Hodgkin's lymphoma will be discussed in Chapter 111. The remainder of this chapter focuses on the non-Hodgkin's lymphomas of childhood.

EPIDEMIOLOGY AND PATHOGENESIS

Non-Hodgkin's lymphomas can occur at any age in childhood but are unusual in children younger than 3 years of age; the median age at diagnosis is approximately 10 years.[1,18] There are approximately 500 new cases of pediatric NHL in the United States each year.[6,7,19] In contrast to Hodgkin's disease, which has a bimodal age distribution with peaks in early and late adulthood, the incidence of non-Hodgkin's lymphomas increases steadily with age.[7] NHL occurs almost twice as commonly in whites as in blacks and two to three times more often in boys than in girls; the explanation for these differences has yet to be elucidated.[2]

There are specific populations who are at increased risk for the development of NHL.[2,20–23] These include individuals with primary immunodeficiency syndromes,[2,22,23] including ataxia-telangiectasia, Wiskott-Aldrich syndrome, X-linked lymphoproliferative syndrome, common variable immunodeficiency, Nijmegen syndrome, and autoimmune lymphoproliferative syndrome. It is important that these syndromes be recognized so that appropriate therapy can be designed. For example, in the management of children with ataxia-telangiectasia who develop a malignancy, involved field irradiation and radiomimetics such as bleomycin should be avoided. Children with ataxia-telangiectasia are also at increased risk for the development of late-onset hemorrhagic cystitis following exposure to cyclophosphamide. Boys with X-linked lymphoproliferative syndrome are at increased risk of developing fatal infectious mononucleosis and/or B-cell lymphomas. X-linked lymphoproliferative syndrome should be considered in any boy with a high-grade B-cell lymphoma whose brother has had either fatal infectious mononucleosis or B-cell lymphoma or in any boy who has had two primary B-cell lymphomas. Children who have received immunosuppressive therapy (e.g., recipients of bone marrow or organ transplants) and those with the acquired immunodeficiency syndrome are also at a higher risk of developing NHL.[21] The overall prevalence of lymphomas among children with HIV infection is approximately 1.6%.[21] NHL is 36 times more frequent among pediatric HIV-positive hemophiliacs than in HIV-negative children with factor 8 deficiency. The majority of the HIV-associated non-Hodgkin's lymphomas have a B-cell immunophenotype with either Burkitt's or large cell morphology. Proliferative lesions of mucosa-associated lymphoid tissue, which may be either benign or malignant, have also been described in children with HIV infection.[21]Although deficient T-cell function has been implicated in these congenital and acquired immunodeficiency states, further study is required to fully clarify the mechanisms of pathogenesis.

There are well-recognized geographic differences in both the incidence and the distribution of histologic subtypes of NHL.[2,3,24] For example, the non-Hodgkin's lymphomas are very rare in Japan but are very common in equatorial Africa. More specifically, Burkitt's lymphoma accounts for approximately one half of all childhood malignancies in equatorial Africa and is the predominant NHL subtype in Northeastern Brazil and areas of the Middle East.[24] In contrast, lymphoblastic lymphomas are the predominant histologic subtype in southern India.[25] In some parts of the world, the distribution of histologic subtypes of childhood NHL has yet to be firmly established.

There are also geographic differences in the clinical and biologic features of some NHLs.[2,25,26] For example, Burkitt's lymphoma in equatorial Africa (endemic Burkitt's lymphoma) frequently involves the jaw, abdomen, orbit, paraspinal area, and central nervous system (CNS), whereas the common sites of involvement associated with Burkitt's lymphoma in the United States and Western Europe (sporadic Burkitt's lymphoma) include the abdomen, bone marrow, and nasopharynx.[2] The predominant chromosome 8 breakpoints, as well as the breakpoints within the immunoglobulin heavy chain gene (on 14q32) differ between sporadic and endemic cases.[27] In addition, sporadic cases have more complex karyotypic abnormalities than endemic cases in addition to the classic translocations, suggesting distinct mechanisms of malignant transformation.[28] The endemic cases are associated with IgM secretion, while the sporadic cases generally are not.[2] The sporadic and endemic cases also differ with respect to Epstein-Barr virus association.[26] The overlap of the lymphoma belt with the malaria belt in equatorial Africa prompted speculation that an infectious agent might be involved in lymphomagenesis. This speculation led to the discovery of the Epstein-Barr virus (EBV) and its association with African Burkitt's lymphoma.[2] Although a direct role in pathogenesis has not been demonstrated, the circumstantial evidence for its involvement is compelling. It has been suggested that as a B-cell mitogen, EBV increases the target pool of cells that are potentially susceptible to malignant transformation.[26] Supporting this hypothesis is evidence that *Rag* gene expression can be induced by EBV, theoretically increasing the likelihood of a translocation occurring in immature B-cells that are about to rearrange their immunoglobulin genes.[29] The potential role of EBNA-1 in pathogenesis has been suggested by experiments demonstrating that lymphomas develop in mice that are transgenic for EBNA-1.[30] Moreover, an identified EBNA-1 variant has been shown to be associated with the majority of Burkitt's lymphoma cases that have been studied, prompting investigators to speculate that this tumor-associated mutation alters EBNA-1 function in a way that directly or indirectly provides a growth advantage for the lymphoma cell.[31] A more direct role for EBV in lymphomagenesis is suggested by studies of the EBV positive Burkitt's lymphoma cell line, Akata, which loses its malignant phenotype with spontaneous loss of EBV; however, the malignant phenotype is regained with EBV reinfection.[32] EBV association has been reported in approximately 90% of the endemic (i.e., African) Burkitt's tumors and in approximately 15% of sporadic cases (United States and Western Europe).[2] Aberrant and disrupted expression of the EBV genome has recently been reported in cases of sporadic Burkitt's lymphoma that were EBV-negative by conventional EBNA screening.[33] This observation, coupled with the 50% rate of EBV association in Burkitt's tumors in other parts of the world (including Brazil, Russia, Argentina, and Chile), suggest a widespread role for this virus in lymphomagenesis.

PATHOLOGY AND BIOLOGY

The classification systems that are applied to pediatric NHL are similar to those used for lymphomas that occur in adults. In the National Cancer Institute Working Formulation for clinical usage, published in 1982,[9] which subclassified NHLs on the basis of their morphologic appearance and clinical aggressiveness into three grades (low, intermediate, and high), most of the childhood NHLs would be designated as high-grade lymphomas (Fig. 102-1). The Revised European-American Lymphoma (REAL) Classification[34] and the World Health Organization (WHO) Classification,[35] introduced in the mid-1990s, define the different categories of NHL as distinct clinicopathologic entities, with well-defined morphologic, immunophenotypic, and genetic features, named, where feasible, according to their postulated counterparts in the normal lymphoid system. This has led to the definition of several lymphoma subtypes within the high-grade lymphoma category previously assigned to most pediatric lymphomas. These include Burkitt's lymphoma, precursor B or T lymphoblastic lymphomas, anaplastic large cell lymphoma (ALCL), and diffuse large B-cell lymphoma (including a mediastinal or thymic subtype). Some low-grade lymphoma subtypes, including follicular center cell lymphoma and marginal zone lymphoma, may also occur in children, albeit with less frequency. The WHO classification of pediatric NHLs is summarized in Table 102-1.

Burkitt's Lymphoma

Modern classification systems[35] define Burkitt's lymphoma (BL) as a mature B-cell neoplasm with characteristic "small noncleaved cell" morphology and a high proliferation rate, resulting from *c-myc* gene translocations. BL and leukemia (classically known as acute lymphoblastic leukemia [ALL L3] in the French American British classification) form a biologic continuum. B-cell lymphomas with a similar proliferation rate and genetic features, previously termed "small noncleaved cell lymphoma, Burkitt's-like," have also been incorporated in this clinicopathologic entity as one of its morphologic variants (see later discussion).

Histologically, BL classical variant, present in endemic cases as well as in many of the sporadic cases, is characterized by a diffuse growth pattern and uniform medium-sized cells (typically equal in size to the nuclei of adjacent histiocytes), with coarsely clumped nuclear chromatin and one to three nucleoli. When observed in Wright-Giemsa-stained smears, these cells are large, with moderate amounts of deeply basophilic cytoplasm and prominent cytoplasmic vacuoles. These tumors typically contain numerous mitotic figures, and matching the high cell turnover rate, they have numerous "tingible-body" macrophages with pale cytoplasm that contain ingested apoptotic cellular debris and impart a characteristic "starry-sky appearance" on low magnification. BLs that are otherwise typical but show a greater degree of pleomorphism in nuclear size and shape and one or two large nucleoli in the neoplastic cells are classified as the atypical Burkitt's/Burkitt's-like variant. These lymphomas represent a subset of the tumors that were previously designated as "small noncleaved cell lymphoma, Burkitt's-like." This morphologic variant can be seen in sporadic cases and in immunodeficiency-associated BL. Finally, BLs with plasmacytoid differentiation (eccentric nuclei with a single central nucleolus, basophilic cytoplasm that contains abundant monotypic immunoglobulin on immunohistochemical staining) represent a third morphologic variant. This latter variant can also be seen with immunodeficiency-associated lymphoma.

The immunophenotype of BL, regardless of its morphologic variants, is that of a mature B-cell of germinal center or postgerminal center type.[35] BL cells strongly express CD19, CD20, CD22, and CD24, as well as CD10 and BCL6, and are negative for BCL2, CD5, CD23, CD34, and Tdt. The neoplastic cells also express surface immunoglobulin (typically IgM, less commonly IgA or IgG) with light chain (kappa or lambda) restriction. Staining for proliferation markers (Ki-67) highlights a growth fraction of nearly 100% in all the histologic variants. Demonstration of this high proliferation rate is required for the diagnosis of BL. Rare cases may exhibit a precursor B-cell immunophenotype associated with the characteristic Burkitt's chromosomal translocations.[36,37] These cases show morphologic and immunophenotypic features that are intermediate between those of classical BL and those of a precursor B cell. The latter

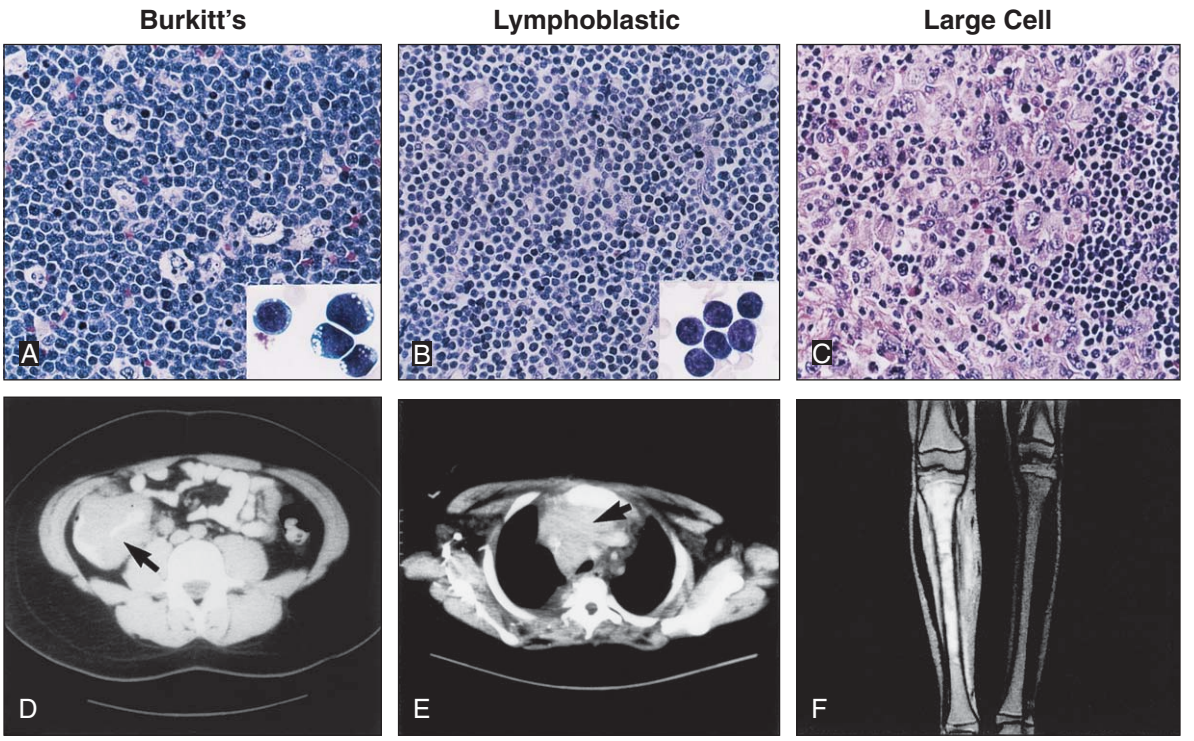


Figure 102-1 • Histologic and clinical features of non-Hodgkin's lymphoma in children. The *upper panels* show the histologic "starry sky" appearance of small noncleaved-cell (Burkitt's) lymphoma **(A),** lymphoblastic lymphoma **(B),** and the anaplastic subtype of large cell lymphoma **(C).** The inserts in panels **A** and **B** show the characteristic L3 blasts of Burkitt's tumors and the characteristic L1 blasts of lymphoblastic lymphoma, respectively. The *lower panels* show common clinical presentations of the three histologic subtypes of lymphoma: encasement of the bowel lumen by Burkitt's lymphoma on abdominal computed tomography **(D),** airway compression by lymphoblastic lymphoma on computed tomography of the anterior mediastinum **(E),** and bony destruction of the tibias by large cell lymphoma on magnetic resonance imaging **(F).**

includes expression of CD34 and Tdt and lack of surface immunoglobulin expression. Recognition of these cases as BL/leukemia typically requires integration with the cytogenetic findings.

Genetically, BL is characterized by several translocations that rearrange the *c-myc* gene on chromosome 8q24, bringing it under the controlling sequences (enhancers) for immunoglobulin heavy or light chain genes and leading to overexpression of this gene in the neoplastic B cells.[38–43] These translocations include the t(8;14)(q24;q32) translocation that is seen in 85% to 90% of the cases, which involves the *c-myc* and *IgH* gene loci, and the less common variants, t(2;8)(p11;q24) and t(8;22)(q24;q11.2), which juxtapose *c-myc* to the immunoglobulin light chain genes, *Ig kappa* (on 2p11) and *Ig lambda* (on 22q11), respectively. The breakpoints involving *c-myc* and *IgH* are highly variable and cluster in regions that are different between endemic and sporadic Burkitt's lymphoma. The *IgH* breakpoints most often involve the *VDJ* region in endemic BL and the switch region *S*μ in the sporadic cases, suggesting that the neoplastic transformation occurs at different stages of B-cell development in these two disease subtypes.[27] Similarly, the *c-myc* breakpoints appear to cluster in two different regions that correlate with the location of the *IgH* breakpoints.[44] This high variability in breakpoints leads to difficulty in generating polymerase chain reaction (PCR) assays that can detect this translocation. Long-range PCR combined with nested

Table 102-1 Pediatric Non-Hodgkin's Lymphoma According to the World Health Organization Classification

COMMON PEDIATRIC LYMPHOMAS	UNCOMMON PEDIATRIC LYMPHOMAS
B-cell lymphomas	Follicular lymphoma (grade 1, 2, or 3)
Precursor B-lymphoblastic lymphoma/leukemia	Hepatosplenic T-cell lymphoma
Burkitt's lymphoma	Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Diffuse large B-cell lymphoma	Mycosis fungoides
Mediastinal (thymic) large B-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
T-cell lymphomas	Adult T-cell leukemia/lymphoma (HTLV-1 associated leukemia/lymphoma)
Precursor T-lymphoblastic lymphoma/leukemia	Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
Anaplastic large cell lymphoma	Extranodal NK/T cell lymphoma
Peripheral T-cell lymphoma, unspecified	

PCR strategies have allowed detection of the t(8;14) translocation and of the variant translocations.[45,46] Approximately 70% to 80% of the sporadic cases have additional chromosomal abnormalities, the most common of which involve chromosomes 1 (1q), 6 (6q), 13 (13q), 17, and 22.[47] Some of these alterations (such as those of chromosome 13q), appear to have a negative impact on prognosis in pediatric BL.[47]

The biology of BL has been extensively characterized. *MYC*, a widely studied oncogene, initially discovered because of its involvement in t(8;14), appears to play a central role in malignant transformation and the biologic behavior of BL.[41,42] MYC overexpression has been described in up to 50% of all human cancers,[48] occurring through both epigenetic and genetic mechanisms (which include chromosomal translocations and genomic amplifications). In BL, *MYC* is deregulated primarily by mutation/translocation and by overexpression.[49] Its oncogenic properties have been demonstrated both in vitro and in vivo by using a variety of animal models.[43,48]

MYC is a nuclear transcription factor. It is the founding member of a family of transcription factors of the BHLH-LZ (basic helix-loop-helix-leucine zipper) class. MYC operates as a heterodimeric complex with a cofactor named MAX to bind specific DNA sequences, thereby transcriptionally regulating hundreds to thousands of target genes.[50] These genes are involved in diverse programs that include cell cycle, cell growth, apoptosis, protein translation, cell adhesion, various metabolic pathways, angiogenesis, and DNA repair. MYC can promote cell proliferation through cyclins D, B1, and A and CDK4, which lead to G1 to S progression. It also inhibits differentiation, increases protein synthesis, and suppresses genes that encode cytoskeletal and cell adhesion molecules, thus contributing to neoplastic transformation. An interesting aspect of MYC biology, with major implications in neoplasia, is its role in apoptosis. MYC sensitizes cells to apoptosis; therefore, it appears that mechanisms that would block this downstream effect are necessary in the process of malignant transformation, allowing for cell proliferation to take precedence over cell death.[51] Apoptosis can be inhibited by a variety of proteins, such as BCL2, BCL-X_L, cFLIP, mTOR, Mdm2/Hdm2, Twist, Bmi1, and Cul7. Apoptosis promoters include a variety of proteins typically that are regarded as tumor suppressors, such as P53, ARF, PUMA, ATM, BAX, BID, BIM, Fas/CD95, and 4EBP1. Extensive studies of tumor cell lines and tumors arising in animal models,[48,52] as well as of primary human tumor samples, have shown that in most cases, MYC overexpression is accompanied by either the overexpression of one of the apoptosis suppressors (e.g., BCL2), or by inactivation of one of the proapoptotic factors (e.g., P53 or ARF).[53] In animal models, alterations in P53-related pathways seem to play a major role in the biology of BL. The relevance of these findings to human BL is currently under study. Limited studies performed in pediatric sporadic BL suggest that these findings could be applicable to primary tumor samples as well.[54]

Lymphoblastic Lymphoma

Modern classifications designate these neoplasms as precursor B and precursor T lymphoblastic leukemia/lymphoma, in an attempt to reflect the morphologic, immunophenotypic, genetic, and possibly biologic continuum between the lymphomatous and the leukemic presentation in these blastic tumors.[35] Indeed, at the present time, the separation between these two presentations is largely arbitrary, lymphoblastic neoplasms involving less than 25% of the marrow cellularity being treated as lymphoma with marrow involvement and those exceeding this cutoff being considered acute lymphoblastic leukemias (ALLs).[55,56]

Histologically, lymphoblastic lymphomas efface the underlying lymph node architecture totally or partially, have a diffuse growth pattern, and may occasionally show a patchy "starry sky" appearance due to the presence of interspersed phagocytic histiocytes. The malignant lymphoblasts are characteristically small to intermediate in size, with scanty basophilic cytoplasm; homogeneous, finely dispersed nuclear chromatin; and very small, inconspicuous nucleoli. A subset of cases may present with more abundant cytoplasm, vesicular cytoplasm, and prominent nucleoli. Although complex nuclear convolutions were initially described as a feature unique to T-lymphoblastic lymphomas, similar features may be seen in precursor B-cell neoplasms.

Immunophenotypically, the majority of lymphoblastic neoplasms that are designated as lymphomas (~90%) are of T lineage, while the remaining show B lineage differentiation (Table 102-2).[57–59] Very rare cases of NK cell origin have been described.[58,60,61] The antigen expression profile of lymphoblastic lymphomas is largely similar to that of their leukemic (ALL) counterparts. Most of the lymphoblastic neoplasms express markers of early lymphoid differentiation, including terminal deoxynucleotidyl transferase (Tdt), CD34, and CD10. Tdt and CD34 expression may be absent in a subset of cases, requiring careful correlation with morphology and other immunophenotypic features for the differential diagnosis with mature (peripheral) T-cell and B-cell lymphomas. T-lymphoblastic lymphomas additionally express T-lineage antigens, including CD1a, CD2, CD3, CD4, CD5, CD7, and CD8. By analogy with the stages of intrathymic T-cell differentiation, several subtypes of T-lymphoblastic neoplasms have been defined, including an early double-negative stage ($CD1a^-$, cytoplasmic $CD3^+$, $CD7^+$, variably positive for other pan-T cell antigens such as CD2 and CD5), early cortical thymic stage ($CD1a^+$, $CD2^+$, cytoplasmic $CD3^+$, often $CD4^+$, $CD8^+$, $CD5^+$, $CD7^+$, $CD21^+$), and late cortical thymic stage ($CD1a^-$, $CD2^+$, surface $CD3^+$, $CD5^+$, $CD4^+$, or $CD8^+$). The majority of T-cell lymphoblastic lymphomas correspond to a late stage of intrathymic maturation.[62,63] Gene expression profiling studies[64] have shown that different genetic lesions correlate with malignant transformation at different stages of intrathymic T-cell maturation in T-cell ALL (see later

Table 102-2 Immunophenotypic Features of the Most Common Pediatric Non-Hodgkin's Lymphomas

Type	TDT	CD20	CD79a	PAX5	sIg	cIg	CD5	CD3	CD30	CD15	ALK	BCL2
T-LBL	+/–	–	–/+	–	–	–	+/–	+*	–	–	–	–/+
B-LBL	+	–/+	+	+	–/+	+/–	–	–	–	–	–	–/+
Burkitt	–	+	+	+	+	–/+	–	–	–	–	–	–
ALCL[2]	–	–	–	–	–	–	–/+	–/+	+	–	+/–	–
PTCL	–	–	–	–	–	–	+/–	+/–	–/+	–	–	–
DLBCL	–	+	+	+	+/–	–/+	–/+	–	+/–	–	–	+/–
MLBCL	–	+	+	+	–	–	–	–	+/–	–	–	+

+, positive; –, negative; +/–, most often positive but may be negative; –/+, most often negative but may be positive; ALCL, anaplastic large cell lymphoma; B-LBL, B-lymphoblastic lymphoma; DLBCL, diffuse large B-cell lymphoma; MLBCL, mediastinal large B-cell lymphoma; PTCL, peripheral T-cell lymphoma; T-LBL, T-lymphoblastic lymphoma.
*Cytoplasmic CD3.

discussion). T lymphoblastic lymphomas are characterized by a more frequent expression of T-cell receptor αβ than γδ, as compared to T-ALL.[65] The immunophenotypic profile of true precursor B lymphoblastic lymphoma (without peripheral blood or bone marrow involvement) has been less extensively characterized, owing to the availability of paraffin-embedded tissue only, in many of the cases.[66–68] By immunohistochemistry, these neoplasms are positive for Tdt, CD34, CD10, and pan-B cell antigens (CD79a, CD22, PAX-5) and often negative for CD20, a mature B-cell antigen, as well as for immunoglobulin kappa and lambda light chains. These features, along with the morphology and clinical presentation, are helpful in the differential diagnosis with BL and diffuse large B-cell lymphoma, both mature B-cell neoplasms that are typically negative for Tdt and CD34 and strongly positive for CD20.[69–72]

Limited information is available regarding the cytogenetic abnormalities that are encountered in T-lymphoblastic lymphoma.[59] It is generally assumed that they resemble those of T-lineage ALL. Recurrent chromosomal abnormalities often include reciprocal translocations that disrupt developmentally important transcription factor genes and lead to their overexpression as a result of rearrangements to loci for T-cell receptor (TCR) genes, most commonly *TCRA* (14q11.2) and *TCRB* (7q35). For example, the *TAL1/SCL* gene (1p32) is involved in the t(1;14)(p32;q11) translocation that is present in approximately 3% of T-ALLs.[63] The *HOX11* transcription factor gene (10q24) is rearranged as part of the t(10;14)(q24;q11.2) and t(7;10)(q35;q24) translocations.[73,74] The *LMO1*(11p15) and *LMO2* (11p13) oncogenes are disrupted by t(11;14) and t(7;11), respectively.[75] Other less common translocations do not involve the *TCR* genes. For example, the t(9;17) translocation is more commonly detected in T-lineage lymphoblastic lymphoma than in precursor T-ALL[76] and is often associated with a mediastinal mass and aggressive disease course. The t(10;11)(p12;q14) translocation, leading to the *AF10-CALM* fusion gene, has been rarely reported in pediatric lymphoblastic lymphoma cases,[77,78] and limited studies suggest a poor prognostic significance.[79] The t(8;13)(p11;q11–14) translocation has been reported in rare cases of T-cell lymphoblastic lymphoma that present with eosinophilia and myeloid hyperplasia.[80–82]

Much progress has been made in recent years in understanding the biology of pediatric T-cell lymphoblastic neoplasms. Molecular studies combined with gene expression profiling have uncovered several oncogenes that appear to play important roles in malignant transformation and correlate with disease subgroups, with potential prognostic and therapeutic implications. *TAL1/SCL* shows activating mutations in up to 50% of all T-ALL,[64,83] independent of detectable translocations, and correlates with leukemias that are arrested at the late cortical stage of thymocyte maturation expressing αβ TCR and with inferior overall survival.[64] *HOX11*(*TLX1*) mutations are present in approximately 30% of all T-ALL, more commonly in adults than in children[83] and in early cortical T-ALL expressing αβ TCR, and correlate with a superior survival in limited studies.[64] *LYL1* is mutated in up to 22% of pediatric T-ALL, correlating with the double-negative early thymocyte stage of differentiation and an inferior survival.[64] The *MLL* gene is mutated in 4% to 8% of T-ALL cases, associated with maturation arrest at early thymocytes stages, expression of γδ TCR, and no impact on prognosis.[83] Certain molecular alterations may provide opportunities for therapeutic targeting. Cryptic deletions of the *INK4/ARF* locus at 9p21, leading to alterations of the p14/p16 loci, are present in up to 75% of all cases of T-ALL,[83] leading to defects in cell cycle control. Since these alterations likely lead to neoplasia through the retinoblastoma (Rb1) and p53 oncogenes, targeting the latter genes might prove to be effective in a significant proportion of T-ALL. In addition, 10% to 20% of T-ALL harbor constitutively activated tyrosine kinases (LCK, FLT3, ABL1), which might also provide targets for tyrosine kinase inhibitor drugs.[83] Finally, *NOTCH1* activating mutations are present in over 50% of T-ALL.[84] This transcription factor activates a wide variety of cellular pathways related to cell growth, using c-MYC as an essential mediator. Inhibition of these signaling pathways has been shown to inhibit cell growth in vitro in T-ALL cell lines.[85]

Anaplastic Large Cell Lymphoma

ALCL is a lymphoma of mature (peripheral) T cells, characterized by strong expression of CD30 (Ki-1)[86] and morphologically by the presence of large "hallmark" cells.[35] These lymphomas may present as systemic disease or as primary cutaneous neoplasms. A subset of the systemic lymphomas expresses the anaplastic lymphoma kinase (ALK) protein as a result of *ALK* gene rearrangements. These constitute the most common subtype of ALCL encountered in children. Only rare cases of primary cutaneous ALK-positive ALCL have been reported in both pediatric and adult patients.[87] Cases of ALK-negative primary cutaneous lymphoma have also been reported in children.[88]

ALCL was initially described as a lymphoma composed of large anaplastic cells with pleomorphic nuclei and sinusoidal lymph node involvement (hence the designation) that expressed CD30 (Ki-1).[86,89] This histologic subtype of ALCL is now designated as the common (classic) subtype. The availability of an immunohistochemical assay for ALK expression has allowed the recognition of lymphomas with very heterogeneous morphology as ALCL. Consequently, the term *ALK lymphoma* or *ALKoma* was proposed for this category of tumors to better accommodate morphologic variants that lack obvious anaplastic morphology.[90] ALCL typically involves the lymph node sinuses and interfollicular area, with subtotal effacement of the lymph node architecture. Regardless of their morphologic subtype, ALK-positive ALCLs consist of a mixture in variable proportions of large anaplastic "hallmark" cells with kidney-shaped or horseshoe-shaped nuclei and small, atypical lymphoid cells with irregular nuclear outlines, as well as inflammatory cells that may include histiocytes and plasma cells. In the common (classical) type, the hallmark cells predominate, sometimes forming cohesive clusters and sheets, while in the small cell type, these cells are sparse, and the neoplastic infiltrate consists predominantly of small lymphoid cells.[91] In the lymphohistiocytic type, the neoplastic cells may be difficult to identify within an exuberant polymorphous inflammatory background that includes histiocytes and plasma cells, is usually poor in neutrophils and eosinophils, and sometimes shows associated fibroblastic proliferation, vascular proliferation, and fibrosis.[92] Occasionally, the fibrotic component may impart a partial nodularity to the tumor. Within this infiltrate, immunohistochemical staining for CD30 or ALK will highlight large tumor cells that typically aggregate around blood vessels. In the monomorphic type, the hallmark cells may be difficult to find, with the tumor consisting predominantly of a monotonous, highly mitotic population of large immunoblastic cells. This latter variant may be associated with a "starry-sky" appearance, owing to frequent tingible-body macrophages. Rarely, ALCL may present with prominent (leukemic) peripheral blood involvement (at diagnosis or at relapse).[93–97] In such cases, the lymphoma cells that are seen on the peripheral blood smear include a mixture in variable proportions of small lymphoid cells with marked nuclear membrane irregularity ("cerebriform") and large immunoblastic cells with deeply basophilic and occasionally vacuolated cytoplasm and coarsely clumped nuclear chromatin. In most cases, there is a predominance of small cells, very similar to the cellular composition of the small cell variant. Notably, in such cases, a significant proportion of the peripheral blood leukocytosis usually consists of granulocytes that may show prominent left shift and toxic changes. These findings, combined with the clinical picture of fever, malaise, and respiratory distress, may distract from the atypical lymphoid population present. In the sarcomatoid type,[98] the tumor cells are sparse and present within an edematous stroma that contains atypical proliferating fibroblasts. In these cases, the tumor cells may have the classical morphology or a spindle cell appearance and may cluster around blood vessels. Rare histologic subtypes of ALCL include giant

cell–rich,[89] signet-ring cell,[99] neutrophil-rich,[100–102] and eosinophil-rich. The latter three have been reported only in ALK-negative ALCL.

On immunohistochemical staining, ALCL cells are characteristically positive for CD30 and ALK (in the ALK-positive cases), and usually positive for CD45 (leukocyte common antigen). In the small cell variant (including the forms with leukemic presentation), the small cells may be CD30-negative and usually show a much lower level of expression of ALK than the large "hallmark cells" that are also present within the same tumors. The majority of ALK-positive ALCL are also EMA-positive (and cytokeratin negative).[103] Many tumors express CD43. While the majority of these tumors are of T-lineage when examined at the molecular level, many of them fail to express several pan T-cell antigens as detectable by IHC, hence the apparent "null-cell phenotype." More than 50% of these lymphomas fail to express CD3, CD5, CD7, and CD45RO.[104] The majority of ALCL will express CD2 and CD4, while they are only exceptionally CD8 positive. Also, regardless of the CD4/CD8 expression status, the tumor cells are very often positive for cytotoxic T-cell antigens (e.g., TIA-1, perforin, granzyme B). Rare ALCLs also express CD56, which has been proposed as a factor of poor prognosis. Flow cytometric analysis usually shows a similar immunophenotype. In addition, 40% to 50% of the analyzed cases have been found to express antigens that are typically associated with myeloid differentiation, such as CD11b, CD13, CD15, and CD33.[105–107]

All ALK-positive ALCLs show aberrant expression of the ALK, a membrane-bound receptor tyrosine kinase that is not expressed by any normal lymphoid elements. Across normal tissues, ALK expression can be found only within the brain, in scattered neurons.[108] The aberrant ALK expression that is seen in ALCL is the result of various chromosomal translocations that juxtapose the *ALK* locus (chromosome 2p23) to other partner genes, which in turn lead to the activation and determine the subcellular localization of the ALK (as seen by immunohistochemistry). The most common translocation, present in up to 75% of ALCLs, is t(2;5)(p23;q35).[109–113] The result of this translocation is a fusion protein (p80) that includes the portion of the ALK protein with associated tyrosine kinase activity and the oligomerization domain of nucleophosmin (NPM) encoded in 5q35.[108,114,115] Normal NPM molecules dimerize and shuttle between the cytoplasm and the nucleus (nucleolus). This is why, in most ALCLs that contain the *NPM-ALK* fusion, ALK expression can be detected immunohistochemically in the nucleus and the cytoplasm. Several other translocations have been described in ALK-positive ALCL (frequency: 2% to 5%). They include t(1;2)(q21;p23) (fusion partner tropomysin 3 gene, *TPM3*),[109,116] t(2;3)(p23;q21) (fusion partner tropomyosin receptor kinase-fused gene, *TFG*), t(2;22)(p23;q11) (fusion partner clathrin heavy chain gene, *CLTCL*),[117] and inv(2)(p23;q35) (fusion partner Pur H gene, *ATIC*).[118] In all these cases, the fusion partners for ALK are proteins that dimerize (an aspect that appears to be essential for activating the kinase function of ALK) but typically localize to the cytoplasm. Therefore, in ALCLs that contain these translocations, ALK expression can be detected only in the cytoplasm. The presence of *NPM-ALK* can be explored for diagnostic purposes using PCR, RT-PCR, or fluorescence in situ hybridization. Aberrant ALK expression appears to play an essential role in tumorigenesis in ALCL.[119,120] ALK-inhibitors are currently being studied as potential therapeutic agents for this type of lymphoma.

Numerous studies have uncovered signaling pathways that are important in the biology of the ALK-positive ALCL, and especially in tumors that harbor the NPM-ALK fusion product. These pathways appear to be important in NPM-ALK-induced tumorigenesis and are attractive therapeutic targets. They include the Jak/STAT (specifically the Jak3 and STAT3 family members) and PI3Kinase/Akt pathways. Inhibition of these pathways has been shown to induce apoptosis and inhibit tumor cell growth in studies performed on lymphoma cell lines. Inhibition of the Src kinase $pp60^{src}$ and pharmacologic blockade of Hsp90 have likewise been shown to induce lymphoma cell apoptosis in vitro.[121]

Diffuse Large B-Cell Lymphoma

The WHO classification defines diffuse large B-cell lymphoma (DLBCL) as a mature B-cell neoplasm with a diffuse growth pattern, composed of large lymphoma cells (i.e., larger than the normal macrophage nuclei).[35] Several morphologic variants are accepted (all of which may be encountered in children).[122] These variants include centroblastic, immunoblastic, T-cell/histiocyte rich, and anaplastic. DLBCL may present as a de novo lymphoma or as progression of a pre-existing low-grade lymphoma. In children, de novo DLBCL is the more common occurrence. In a small percentage of cases, a pre-existing follicular lymphoma component may be identified.

DLBCL is a tumor with a diffuse growth pattern composed, in variable proportions, of several types of large lymphoma cells that include centroblasts, immunoblasts, and anaplastic cells. The predominance of one or another cell type leads to the various morphologic subtypes. Centroblasts are medium-sized to large cells with scanty cytoplasm, irregular nuclear outlines, vesicular chromatin, and several peripherally located nuclei. Immunoblasts are large cells with abundant basophilic cytoplasm, vesicular or clumped chromatin, eccentric nuclei, and single centrally located nucleoli. Anaplastic cells are similar to those seen in ALCL and include giant cells with pleomorphic nuclei or Reed-Sternberg-like morphology. In the centroblastic variant (>80% of the pediatric DLBCL),[123] the tumor consists of a polymorphous mixture of centroblasts and immunoblasts, with fewer than 90% immunoblasts. In the immunoblastic variant (<10% of the pediatric DLBCL),[123] more than 90% of the lymphoma cells are immunoblasts. In the rare anaplastic variant, frequent anaplastic cells are admixed with centroblasts and immunoblasts. Occasionally, a cohesive growth pattern may be present in the latter subtype. In T-cell/histiocyte-rich B-cell lymphoma, the bulk of the tumor consists of inflammatory cells, while the neoplastic cells (centroblasts, immunoblasts, Reed-Sternberg-like) represent less than 10% of cellularity. Rare cases of diffuse large B-cell lymphoma with plasmablastic morphology, immunohistochemical expression of ALK, and the presence of ALK fusion transcripts have been reported.[124,125]

In all subtypes of DLBCL the lymphoma cells strongly express CD45 and CD20, as well as other B-cell antigens, such as CD19, CD22, and CD24. A subset of DLBCL may express CD10, BCL-6, and BCL-2 (resembling follicle center cell lymphoma). Occasional DLBCL are positive for CD5. CD30 expression is typically present in the anaplastic subtype and may be seen in the T-cell-rich subtype. Light-chain-restricted immunoglobulin expression may be demonstrated in many cases, although a significant proportion of these lymphomas may lack immunophenotypic evidence of immunoglobulin expression. Such cases show clonal rearrangements of the immunoglobulin genes when analyzed by molecular means.[126] Some of the DLBCL may show high proliferation indices when analyzed by Ki-67 immunohistochemistry, but they typically do not exceed 90%, a feature that is helpful for the distinction from BL. The ALK-positive plasmablastic B-cell lymphomas have unique immunophenotypic features, which reflect their distinctive morphologic differentiation. They lack expression of mature B-cell antigens, such as CD20, and express weak CD79a, CD138, and abundant cytoplasmic immunoglobulin, typically IgA. They are CD30 negative in most cases.[124]

When cytogenetic studies are performed, these tumors typically show complex chromosomal abnormalities. Immunophenotypic and genetic studies, including gene expression profiling by several methodologies, have demonstrated that DLBCL is a biologically heterogeneous group of neoplasms that includes at least two major subgroups: a germinal center (GC)-like group and an activated peripheral blood B-cell (ABC)-like group.[127–129] The GC-like group is characterized by expression of CD10 and BCL-6, while negative for MUM1, contains ongoing Ig gene mutations, may show the

t(14;18) translocation, 12q12 gains, amplification of *c-rel* gene (chromosome 2p), low levels of *Blimp-1* gene mRNA expression, and a more favorable outcome. A significant number of the GC-like tumors occurring in adults also harbor the t(14;18), *IGH/BCL2* translocation. The ABC-like group lacks expression of CD10 and BCL-6 as well as ongoing Ig gene mutations, may show trisomy 3 or gains on chromosomes 3q or 18q21–22 and losses at 6q21–22, has constitutive activation of NF-κB, has high levels of *Blimp-1* mRNA expression with lack of protein expression, has aberrant IL-4 induced STAT6 signaling, and is associated with a poor prognosis.[130] Recent studies have shown that in pediatric DLBCL, the distribution and characteristics of these subgroups are different, with children showing a much higher frequency of the centroblastic variant (83% versus 75%, respectively) and of the GC-like subtype (83% versus 40% to 48%, respectively) when compared to the adult tumors and with a much lower incidence of the ABC-like subtype in this age group.[123] In addition, the t(14;18) translocation appears to be virtually absent in the pediatric GC-like DLBCL.[123] Furthermore, these disease subgroups do not appear to have an impact on prognosis in children.[123] All these insights offer interesting opportunities for differential, age-appropriate therapeutic targeting in the various disease subtypes in DLBCL.

Mediastinal (Thymic) Large B-Cell Lymphoma

Mediastinal (thymic) large B-cell lymphoma (Med-DLBCL) is a clinicopathologically and biologically distinct subtype of DLBCL that accounts for fewer than 10% of all large cell lymphomas in children.[131] It has also been designated as mediastinal clear cell lymphoma of B-cell type and mediastinal diffuse large cell lymphoma with sclerosis. It is currently thought to originate in the $CD19^{+}CD21^{-}$ B cells and asteroid B cells that reside in the thymic medulla.[132]

Histologically, Med-DLBCLs can present as any of the DLBCL variants. Approximately half of the cases can have prominent associated stromal fibrosis, adding to the difficulty in obtaining suitable diagnostic biopsy samples in many of these cases. Cytologically, the neoplastic cells may have the appearance of centroblasts or immunoblasts or may have abundant pale cytoplasm and markedly lobated, flower-like nuclear membrane outlines (so-called clear cell appearance).[35,133–138]

Immunophenotypically, Med-DLBCL shows a mature B-cell immunophenotype, with expression of CD45 and of pan-B-cell antigens, including CD19, CD20, CD79a, and PAX-5. There is typically partial and variable coexpression of CD30.[139] Some cases may express CD23. Other antigens that are expressed include BCL-2 and BCL-6.[140] The neoplastic cells are typically negative for CD10, CD21, immunoglobulin, and HLA class I and II molecules.[141]

Little conventional cytogenetic data are available, largely owing to the small tumor samples that are typically available in these patients. Alternative approaches have shown consistent gains of material on chromosome 2p (seen in approximately 25% of the cases), with amplification of *c-REL*, a gene that encodes for a transcription factor that is important in B-cell development, as well as gains of material on 9p (50% to 75% of the cases) with amplification of the *JAK2* gene, whose product is important in the JAK/STAT signaling pathway. Other alterations that have been described involve the chromosomes 6p (MHC class I locus), Xq, and 12q and the P53 gene.[132,142,143]

Biologically, Med-DLBCL has the profile of activated germinal center or postgerminal center cells. The lymphoma cells contain clonal Ig gene rearrangements with somatic mutations[126] and *BCL-6* gene mutations and express MUM1/IRF4, BCL6, and the B-cell specific transcription factors OCT-2, BOB.1, and PU.1. Overexpression of an interleukin-4-inducible gene, *FIG1* (IL-4I 1) suggests the possible oncogenic activation of signaling pathways such as IL-4/IL-13 or Janus kinase 2 (JAK2). Gene expression profiling experiments have demonstrated a close resemblance of this lymphoma with that of classical Hodgkin's lymphoma, suggesting that, at least in the mediastinal location, these neoplasms may share a common origin from a thymic B-cell. Notably, both tumors showed overexpression of genes involved in cytokine signaling pathways, such as IL-13, tumor necrosis factor, and NF-κB. These findings suggest that targeting of some of these overexpressed genes or of activated NF-κB could represent therapeutic possibilities in these tumors.[132]

Uncommon Pediatric Lymphomas

Lymphomas that occur infrequently in children and adolescents include follicle center cell lymphoma,[144] hepatosplenic lymphoma,[145] panniculitis-like T-cell lymphoma,[146] mycosis fungoides,[147–150] T/NK lymphoma, nasal-type natural killer lymphoma,[151] marginal zone lymphoma (including the extranodal MALT type),[152] and HTLV-1-associated leukemia/lymphoma.[153,154] The clinical and biologic features of these lymphomas in children are generally similar to those observed in adults; however, this conclusion is drawn from the very few reported pediatric cases.

Pediatric follicular lymphomas (FLs) appear to have a spectrum of clinicopathologic features that are distinct from those of the tumors that are seen in adults; these features are detailed next.

Because of the relatively small numbers of cases that have been reported, little is known about the genetics and biology of the follicular lymphomas that occur in children. It appears that, in addition to rare cases of classic follicular lymphomas that resemble, phenotypically and genetically, those seen in adults, children may present with a second subtype, which is in fact more common in this age group.[144,155–160] These FLs, typically limited to one site (most commonly, lymph nodes in the head and neck area or testis/epididymis) are characterized by effacement of the normal architecture by neoplastic follicles composed of large, expansile, irregular germinal centers with geographic appearance and thin or absent mantle zones. Cytologically, the germinal centers are typically composed of monotonous predominantly large centroblasts, with occasional cases showing numerous mitotic figures and a "starry-sky" appearance due to numerous tingible-body macrophages. Most of these cases have morphologically the appearance of grade 2 or grade 3 (WHO) FL, albeit without the prognostic significance that this grading would have in classical adult FL.

Immunophenotypically, the neoplastic cells express CD20, CD10, BCL-6, and, in some cases, CD43 and are typically negative for BCL-2. Staining for CD21 highlights the follicular dendritic cell meshwork that underlies the expanded neoplastic follicles.

Pediatric FL lacks, in most cases, the t(14;18) and BCL-2 rearrangements, features that distinguish it from the usual cases of adult FL. Pediatric FLs typically have clonal Ig gene rearrangements and have been found to harbor *BCL-6* gene rearrangements. Interestingly, they also lack P53 overexpression, another feature that distinguishes them from the high-grade adult-type FLs. All of these features suggest an alternative molecular pathogenesis for pediatric FL, justifying alternative therapeutic options for these patients.

CLINICAL PRESENTATION

The primary sites of involvement and the extent of disease spread determine the clinical features of NHL at presentation (see Fig. 102-1).[1,2,19]Although adults usually present with nodal disease, children with NHL usually present with extranodal disease, most frequently involving the abdomen (31% percent of cases), the mediastinum (26% of cases), or the head and neck region (29% of cases).[1] These are rapidly growing tumors associated with hematogenous disease spread, and the majority of children with NHL present with locally invasive or advanced-stage disease. Involvement of the CNS is characterized by the presence of cranial nerve palsies and/or cerebrospinal fluid pleocytosis. When the bone marrow is involved, the distinction between NHL and leukemia is somewhat arbitrary:

If more than 25% of the marrow is replaced by lymphoblasts, the patient is considered to have leukemia; if less than 25%, the patient is considered to have advanced-stage NHL with marrow involvement.

There is a striking relationship between the histologic subtype and the presenting site of disease in the lymphoblastic and Burkitt's lymphomas.[1] Among the lymphoblastic lymphomas, the typical primary site of involvement is the mediastinum and/or the head and neck region but rarely the abdomen, whereas the Burkitt's lymphomas typically present in the abdomen or head and neck region but rarely the mediastinum. In contrast to patients with lymphoblastic and Burkitt's lymphomas, children with large cell lymphomas may present with disease at almost any location. Involvement of the CNS at diagnosis is associated with both the Burkitt's and lymphoblastic histiotypes but rarely with large cell histology.[161] In contrast, spread to the bone marrow may occur in any of these three histologic subtypes.[1,162]

Primary involvement of the abdomen, as is typical of Burkitt's lymphoma, may be associated with nausea, vomiting, or abdominal pain at presentation. These tumors usually arise from the distal ileum and result in obstruction of the bowel by either intussusception or direct compression of the lumen. Other primary sites of involvement in the abdomen include the appendix and/or large bowel. Abdominal tumors may be associated with malignant ascites; involvement of kidney, liver, or lymph node; and invasion of adjacent structures, including the abdominal wall.[1,2] Involvement of the pelvis may include ureteral compression with associated hydronephrosis.

Primary involvement of the mediastinum, as is typical of advanced-stage lymphoblastic lymphoma and mediastinal large B-cell lymphoma, may be associated with respiratory symptoms ranging from mild cough to severe respiratory distress caused by direct tumor compression of the airway, requiring emergency attention (see the section on Emergency Situations).[1,2] Associated pleural effusions may further complicate the respiratory status. Compression of the superior vena cava by the tumor may obstruct venous blood return, resulting in swelling of the neck, shoulder, and face (superior vena cava syndrome); this condition may predispose the patient to the development of deep venous thromboses. In rare cases, children with mediastinal masses may also have cardiac irregularities or tamponade.[2]

Involvement of the CNS may cause symptoms resulting from increased intracranial pressure, including nausea, vomiting, headache, and vision changes; there may also be neurologic abnormalities on physical examination resulting from palsies of cranial nerves innervating the face or extraocular muscles. Involvement of the bone marrow may be associated with bone pain, pallor, neutropenia, and/or thrombocytopenia with associated bruising and bleeding. Involvement of the skin occurs in approximately 4% of children with newly diagnosed NHL. When present, it is usually associated with $CD30^+$ anaplastic large cell histology (ALCL);[163–165] however, lymphoblastic lymphomas (often non-T-cell immunophenotype) may also involve the skin.[166,167]

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The differential diagnosis of NHL comprises both benign and malignant conditions. If there is no mediastinal mass and if blood counts and physical examination are within normal limits except for an isolated, painless, enlarged peripheral lymph node, a 10- to 14-day trial of antibiotics is permissible to treat presumed bacterial adenitis. Serologic and skin testing may be helpful in the diagnosis of histoplasmosis, tuberculosis, and EBV infection, which may also cause adenopathy simulating lymphoma.

The non-Hodgkin's lymphomas of childhood grow very rapidly; therefore, an expeditious diagnostic workup in consultation with a pediatric oncologist is indicated if NHL is suspected (Fig. 102-2). The diagnosis of NHL is most readily established by examination of tissue obtained by open biopsy of the involved site. A comprehensive characterization of the biologic features of the tissue, including histologic, immunophenotypic, cytogenetic, and molecular studies, will help to distinguish NHL from the small, round blue cell tumors, including Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma. When patients (such as those with large anterior mediastinal masses and associated airway compression) are too unstable to undergo anesthesia for open biopsy, the diagnosis may be established by parasternal fine-needle aspiration or biopsy with local anesthesia.[168] Among children who present with an associated pleural effusion, thoracentesis with cytologic examination of pleural fluid is usually diagnostic. For children with large abdominal Burkitt's tumors, either percutaneous aspiration of the mass or paracentesis to obtain ascitic fluid often yields diagnostic cytologic and cytogenetic findings. A bone marrow and cerebrospinal fluid examination should be performed early in the workup of a child with suspected NHL, since these studies may be diagnostic and could preclude the need for more invasive procedures.

Initial Evaluation and Staging Workup

A prompt and meticulous staging workup is imperative because treatment is determined in part by primary site and degree of disease spread. A complete history and physical examination, including documentation of the presence or absence of B symptoms by history, should be completed. Computed tomographic imaging of the chest, abdomen, and pelvis, as well as bone scans should be performed on all patients. Gallium scanning may also be helpful in selected cases, particularly in following residual masses that were gallium-positive at diagnosis.[1,2,19] Positron emission tomography is commonly used in the evaluation of adults with Hodgkin's or non-Hodgkin's lymphoma;[169] this modality is becoming more widely used in place of gallium scanning as part of the staging workup of children with non-Hodgkin's lymphoma. Bilateral posterior iliac crest aspirations and biopsies increase the chance of identifying overt marrow involvement, thus reducing the possibility of underestimating the stage of disease.[170] The bone marrow samples should be submitted for cell count and differential, flow cytometric, cytogenetic, and molecular pathologic analyses. Magnetic resonance imaging of the bone marrow has been shown to be effective in detecting occult disease is some studies;[171] however, it is not a standard component of the currently accepted pediatric NHL workup. A lumbar puncture should be performed for cytologic evaluation of the cerebrospinal fluid.

The stage of disease is usually assigned according to the St. Jude Staging System described by Murphy (Table 102-3),[56] which was developed to accommodate the noncontiguous nature of disease spread, predominant extranodal involvement, and involvement of the bone marrow and CNS that characterize the pediatric NHLs. Stages I and II are considered to be limited-stage disease, whereas stages III and IV are advanced-stage disease. The initial laboratory evaluation should include a complete blood count with differential and a chemistry panel comprising electrolytes, BUN, creatinine, LDH, calcium, phosphorus, and uric acid. An HIV screen should be performed on all patients newly diagnosed with lymphoma. Those who test positive may be at increased risk for therapy-related toxicity, including life-threatening infections. Serologic tests for EBV infection can be helpful when lymphoproliferative disease is highly suspected in the differential diagnosis; however, positive serologic results do not rule out a malignancy.

Prognostic Factors

Tumor burden at diagnosis, reflected by both the disease stage and serum LDH (lactate dehydrogenase), is an important predictor of outcome for children.[1] In one large single-institution study of childhood NHL, the treatment era, disease stage, and serum LDH level all emerged as independent and significant prognostic indicators.[1]

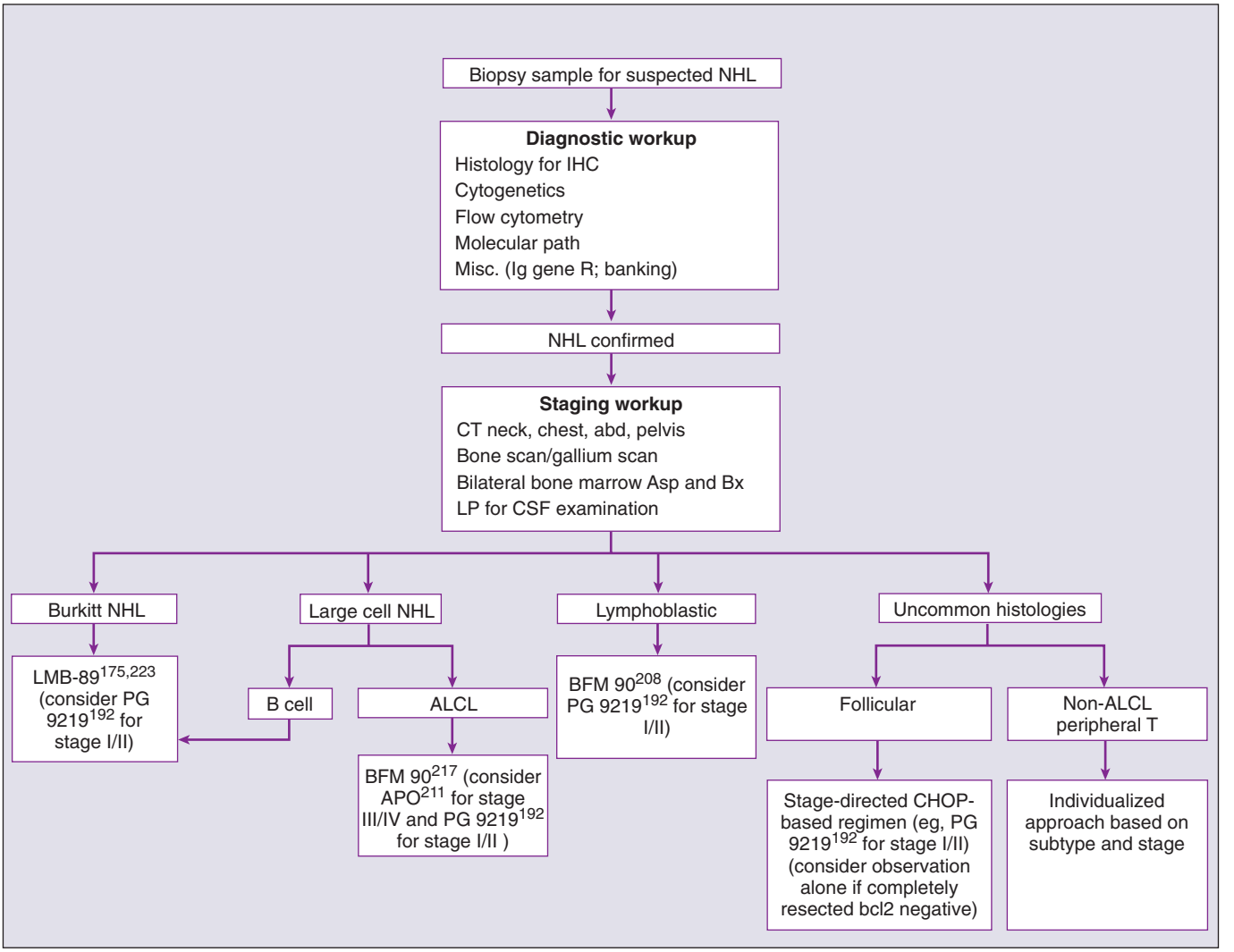


Figure 102-2 • Diagnostic workup, staging workup, and treatment approach for children not entered on current research protocols.

Serum IL-2 receptor levels, which reflect tumor burden, have also been shown to predict outcome.[172,173]

A poor early response to therapy is considered by some to confer a poorer prognosis, as has been demonstrated in children with ALL.[174] In the LMB-89 protocol, poor early response is a criterion for placement in the most intensive arm of therapy.[175] The current Children's Oncology Group study for children with advanced-stage lymphoblastic lymphoma is examining the impact of early response as determined both by diagnostic imaging and flow cytometric MRD technology.

Prognostic factors have also been identified with respect to specific histologic subtypes. For example, among adults with ALCL, ALK protein expression is a favorable prognostic factor.[176–178] In a multivariate analysis of clinical features in childhood ALCL, mediastinal, visceral (lung, liver, spleen) and skin involvement were associated with adverse risk.[179]

Primary Treatment

Treatment of the NHLs of childhood has advanced dramatically over the past 30 years through the incremental development and clinical testing of effective multiagent chemotherapeutic regimens.[1,2,19,161,180–218] In a randomized trial comparing two of the first successful regimens for treating childhood NHL (the cyclophosphamide-based COMP regimen and the multiagent LSA_2L_2 regimen designed for acute lymphoblastic leukemia), the Children's Cancer Group clearly demonstrated that children with limited-stage disease fared well regardless of histology or treatment arm assignment, while treatment outcomes for children with advanced-stage disease varied with histology and treatment arm.[186] Children with Burkitt's lymphoma had a better outcome with the COMP regimen,[186] while those with lymphoblastic NHL fared better with the LSA_2L_2 regimen.[186–188] However, among those who presented with advanced-stage large cell disease, neither treatment arm emerged as superior. In contrast to the stage- and histology-directed therapeutic approach that has been historically used in the United States, a stage- and immunophenotype-directed approach is predominant in Europe. Studies in both the United States and Europe suggest that the immunophenotype-directed approach has advantages for treating children with advanced-stage large cell NHL, a family of lymphomas whose prognoses vary with immunophenotype.[189]

Surgery and radiation therapy have minimal roles in the management of childhood NHLs.[1,2] Surgery is indicated only for diagnostic purposes and in cases in which an ileocecal mass, associated with mesenteric nodes only, can be completely resected (resulting in downstaging from III to II, which requires less intensive systemic

Table 102-3 Stages of Non-Hodgkin's Lymphoma*

STAGE I
A single tumor (extranodal) or involvement of a single anatomical area (nodal), with the exclusion of the mediastinum and abdomen
STAGE II
A single tumor (extranodal) with regional node involvement
Two or more nodal areas on the same side of the diaphragm
Two single (extranodal) tumors, with or without regional node involvement, on the same side of the diaphragm
A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable
STAGE III
Two single tumors (extranodal) on opposite sides of the diaphragm
Two or more nodal areas above and below the diaphragm
Any primary intrathoracic tumor (mediastinal, pleural, or thymic)
Extensive primary intra-abdominal disease
Any paraspinal or epidural tumor, whether or not other sites are involved
STAGE IV
Any of the above findings with initial involvement of the central nervous system, bone marrow, or both

*Based on the classification proposed by Murphy.

therapy; see section on Staging).[219] Otherwise, aggressive debulking procedures should not be undertaken. Prospective randomized trials have demonstrated that the incorporation of involved field radiation therapy into a multiagent chemotherapy regimen does not improve outcome.[192,216] The use of radiation therapy in the management of relapse, CNS disease, and certain emergency situations will be discussed in other sections.

Initial Management

The serum chemistry values should be reviewed before chemotherapy is started. Many patients with bulky Burkitt's or lymphoblastic lymphomas present with hyperuricemia, hyperphosphatemia, and renal dysfunction due to the rapid turnover of lymphoblasts. These metabolic abnormalities are exacerbated by chemotherapy, which rapidly lyses tumor cells. Tumor lysis releases purines, potassium, and phosphorus into the bloodstream, resulting in the deposition of uric acid, xanthines, and phosphates in the renal tubules, which causes further renal dysfunction, a clinical condition termed *tumor lysis syndrome*.[2] This problem can be precluded or reduced if patients with advanced-stage disease are vigorously hydrated (3 to 4 L/m^2/day) prior to receiving chemotherapy. Alkalinization is usually necessary to maintain a urine pH of approximately 7.0. The urinary excretion of uric acid is reduced at an acidic pH, whereas the excretion of phosphorus is impaired by overalkalinization. Allopurinol, a xanthine oxidase inhibitor, has historically been helpful in the management and prevention of hyperuricemia by blocking ongoing production of uric acid. Urate oxidase, a uricolytic agent that has been used for many years in Europe, has advantages that make it a preferable alternative.[220] It results in a precipitous drop in uric acid by converting it to allantoin, precludes the need for vigorous alkalinization, and is associated with preservation of normal renal function and avoidance of dialysis in most cases. Rasburicase, a recombinant form of this drug, is also effective in reducing uric acid, has a much lower risk of associated allergic reactions, and has recently become a standard part of initial management.[221] In the rare case in which urine output is unacceptable, addition of mannitol followed by furosemide (Lasix) may be necessary.

Limited-Stage Disease

The excellent treatment results (survival rates of 85% to 95% at 5 years) that are achieved in children with limited-stage NHL have prompted an emphasis on new treatment strategies that reduce both morbidity and the risk of late sequelae (e.g., anthracycline-induced cardiomyopathy, sterility, and second malignancies) while maintaining or improving the treatment outcome.[175,183,191,192,205,222] Various approaches to reduction of treatment intensity have been investigated. The Pediatric Oncology Group performed two sequential randomized trials that examined the need for involved-field radiation therapy and maintenance chemotherapy, respectively.[192] In the first study, patients were randomly assigned to receive either chemotherapy alone (three courses of cyclophosphamide/Adriamycin/vincristine/prednisone [CHOP] followed by a 24-week continuation phase of 6-mercaptopurine and low-dose methotrexate) or chemotherapy plus involved-field radiation therapy. In the subsequent study, patients were randomly assigned to receive the three courses of CHOP with or without the 24-week continuation phase.[192] These studies demonstrated that both involved-field radiation therapy and the continuation phase of therapy could be safely eliminated without compromising outcome, with one exception. Children with limited-stage lymphoblastic lymphoma had lower event-free survival rates than did those with nonlymphoblastic histology. Even with the 24-week continuation phase, one third of the patients with lymphoblastic lymphoma developed recurrent disease. With salvage therapy, there was no reported difference in overall survival between those with lymphoblastic and nonlymphoblastic histology. The optimal management of limited-stage lymphoblastic lymphoma remains controversial. The French Society of Pediatric Oncology (SFOP) uses a more aggressive initial approach to avoid the need for retreatment.[182] Children with limited-stage lymphoblastic lymphoma are entered on the same protocol that is used for advanced-stage lymphoblastic lymphoma, and children with limited-stage nonlymphoblastic lymphoma are candidates for less-intensive regimens only if there is complete resection of disease.[175] The current Children's Oncology Group trial for lymphoblastic lymphoma is piloting an arm of ALL-derived therapy for those children who present with limited-stage disease.

Advanced-Stage Disease

Attempts to improve the treatment result in children with advanced-stage NHL have relied on further intensification of therapy. Historically, the general approach in the United States has been histology-directed, whereas in Europe, an immunophenotype-directed approach has predominated. For example, for many years, French investigators have entered patients with Burkitt's lymphoma and B-cell large cell lymphoma on the same protocol.[175,223] This approach is now widely used in the United States.

BURKITT'S LYMPHOMA. The dramatic improvements that have been achieved in the treatment of advanced-stage Burkitt's lymphoma and B-cell ALL represent one of pediatric oncology's undisputed success stories. With current therapy, which is generally cyclophosphamide-based, very intensive, and given over a relatively short period of time (4 to 8 months), at least 75% of patients are event-free survivors. Results achieved with the COMP regimen were first improved on by the incorporation of high-dose methotrexate and/or high-dose cytarabine.[190,193–196] Two studies during the same period showed that the duration of therapy for stage III patients could be shortened to 2 to 4 months without compromising patient outcome.[195,199] Further improvements in treatment outcome have been achieved over the past 8 years by further intensification of therapy (escalation of cyclophosphamide, methotrexate, and cytarabine dosages) and by the addition of new active agents, including

Table 102-4 Treatment Outcome for Advanced-Stage Burkitt's Lymphoma

Protocol	Stage	No. of Patients	Event-Free Survival Rate	Reference (First Author)
POG 8617	IV	34	4-year EFS = 79 ± 9%	Bowman[194]
	B-ALL	47	4-year EFS = 65 ± 8%	
LMB 89*	III	278	5-year EFS = 91% (95%CI: 87–94%)	Patte[175]
	IV	62	5-year EFS = 87% (95%CI: 77–93%)	
	B-ALL	102	5-year EFS = 87% (95%CI: 79–92%)	
BFM 90	III	169	6-year EFS = 86% ± 3%	Reiter[205]
	IV	24	6-year EFS = 73% ± 10%	
	B-ALL	56	6-year EFS = 74% ± 6%	

*Includes patients with B-cell large cell NHL.

etoposide and ifosfamide.[175,205,207] The LMB-89 regimen designed by the SFOP, for example, has produced one of the best results to date.[175] In this protocol, children receive high-dose methotrexate (3 g/m^2), fractionated cyclophosphamide, Adriamycin, vincristine, prednisone, and low-dose cytarabine given over approximately 5 months if marrow blast cells at diagnosis are fewer than 70%. For children with more than 70% marrow blast cells or with CNS involvement at diagnosis, therapy is intensified (methotrexate dose is escalated to 8 g/m^2, high-dose cytarabine and etoposide are incorporated, and the total duration of therapy is extended to approximately 8 months). A recently completed international trial (LMB-96) examined the safety of intensity reduction in the Group B and C arms of the LMB-89 study.[223,224] The intensity of Group B therapy was safely reduced (i.e., no escalation of cyclophosphamide in the second COPADM course, and deletion of the maintenance sequence) without compromising the excellent outcome; however, intensity of therapy of the Group C arm could not be safely reduced.

Other successful treatment strategies for advanced-stage Burkitt's lymphoma and B-cell ALL have been reported (Table 102-4). Excellent results have been achieved by the BFM (Berlin-Frankfurt-Munster) cooperative group using a regimen that incorporates high-dose methotrexate (5 g/m^2), ifosfamide, etoposide, doxorubicin, and steroids.[205] BFM trials have also examined the impact of methotrexate infusion time; they found that a 4-hour infusion time was noninferior to a 24-hour infusion for children with limited-stage disease but not for those with advanced-stage disaese.[225] Sequential National Cancer Institute studies have shown that adding etoposide, high-dose cytarabine, and ifosfamide to a regimen of cyclophosphamide, Adriamycin, vincristine, and high-dose methotrexate improved the treatment result.[207] Importantly, these more aggressive approaches have shown encouraging preliminary results in adults with the same malignancies.[226]

LYMPHOBLASTIC LYMPHOMA. Most of the successful treatment plans for children with advanced-stage lymphoblastic lymphoma are derived from therapies designed to treat children with high-risk acute lymphoblastic leukemia (Table 102-5). These regimens, which generally use multiple chemotherapy agents (up to 10 different agents) and are given over a 15- to 32-month period, result in an approximate 65% to 90% event-free survival rate at 4 to 5 years.[182,186–188,200,201,204,208] Although the multiagent nature of these regimens makes it difficult to determine the relative merit of individual components, compelling data suggest the importance of high-dose methotrexate. The French (SFOP) achieved an excellent result by incorporating courses of high-dose methotrexate into the previously studied LSA_2L_2 regimen.[182] Moreover, the BFM group has recently reported very encouraging results (a 3-year event-free survival rate of approximately 90%) of a regimen that features an intensive

Table 102-5 Treatment Outcome for Advanced-Stage Lymphoblastic Non-Hodgkin's Lymphoma

Protocol	Stage	No. of Patients	Event-Free Survival Rate	Reference (First Author)
LSA_2L_2 (modified) CCG-551	III/IV	124	5-year EFS = 64%	Anderson[186]
BFM 90	III	82	5-year EFS = 90% ± 3%	Reiter[208]
	IV	19	5-year EFS = 95% ± 5%	
X-H SJCRH	III/IV	22	4-year DFS = 73%	Dahl[200]
APO (Dana Farber)	III/IV	21	3-year DFS = 58% ± 23%	Weinstein[218]
A-COP + (POG)	III	33	3-year DFS = 54% ± 9%	Hvizdala[201]
SFOP LMT81	III	33	57-month EFS = 79% (SE: 4%)	Patte[122]
	IV/ALL	43	57-month EFS = 72% (SE: 4%)	
CCG: LSA_2L_2 (modified) vs. ADCOMP	I-IV	243	5-year EFS = 74%	Tubergen[204]
	I-IV	138	5-year EFS = 64%	
POG8704: no extra Asp vs. extra Asp	III/IV	83	4-year CCR = 64% (SE: 6%)	Amylon[213]
	III/IV	84	4-year CCR = 78% (SE: 5%)	

high-dose methotrexate (5 g/m^2) consolidation course.[208] A subsequent study demonstrated that prophylactic cranial irradiation could be safely eliminated without compromising the excellent outcome.[227] Although definitive data are lacking, this result might reflect the higher levels of intracellular methotrexate polyglutamates that are produced in T-cell lymphoblasts by high-dose methotrexate as compared to low-dose methotrexate.[228] A current Children's Oncology Group study is examining whether high-dose methotrexate can be safely eliminated if it is replaced by extended intrathecal therapy. L-Asparaginase is also commonly used in many successful regimens. In this regard, a Pediatric Oncology Group study demonstrated a survival advantage for those who were randomized to receive additional L-asparaginase.[213] Efforts to improve the treatment result have also included the addition of new active agents (e.g., epipodophyllotoxins)[200] and the incorporation of a reinduction[208] or late intensification phase.

LARGE CELL LYMPHOMA. Historically, the biologic heterogeneity of advanced-stage large cell lymphoma coupled with quite varied treatment strategies that have been reported made it difficult to identify an optimal treatment approach (Table 102-6).[106] Histology-directed therapies in the United States, primarily CHOP-based, resulted in a 50% to 70% event-free survival rate at 3 years.[161,180,186,189,197,202,203] Although some studies have examined the feasibility of eliminating agents associated with significant late effects,[197,211] some others have examined the benefit of incorporating additional active agents (e.g., intermediate- and high-dose methotrexate, intermediate- and high-dose cytarabine, ifosfamide, and carboplatin). Pediatric Oncology Group investigators reported that children with large cell lymphoma of the B-cell immunophenotype had a better outcome than did those with a non-B-cell immunophenotype, a finding that suggested that immunophenotype-directed therapies for pediatric large cell lymphomas should be further pursued.[189] In this regard, European trials for children with large cell lymphoma have historically assigned treatment on the basis of immunophenotype (e.g., B-cell, T-cell, CD30$^+$). Currently, trials in both the United States and Europe for large cell lymphoma are being directed toward specific immunophenotypically defined categories as designated in the most recent WHO classification system. The two most common large cell types that are encountered in children are DLBCL and anaplastic large cell lymphoma (ALCL).

Diffuse Large B-Cell Lymphoma. The SFOP reported equally excellent outcomes for children with either B-cell large cell or Burkitt's lymphoma who were treated on the same B-cell regimen (i.e., LMB-89).[175] This observation was confirmed in the recently completed international collaborative LMB-96 trial, which resulted in a 4-year event-free survival rate of 92.5% for patients with DLBCL (excluding primary mediastinal disease) compared to 93.5% for those with Burkitt's lymphoma. In this trial, those with primary mediastinal disease had a somewhat inferior outcome (4-year event-free survival rate of 71.5%).[223] Other studies have also suggested that children with mediastinal B large cell lymphomas have a slightly worse outcome compared to those with DLBCL.[131,134] The anthracycline-based APO regimen was also shown to be active in children with diffuse large B-cell lymphoma (i.e., a 4-year event free survival rate of 63.8%); however, the result is somewhat inferior to that of the LMB-96 approach.[211,212]

Anaplastic Large Cell Lymphoma. The therapeutic approaches for children with CD30$^+$ ALCL are quite varied.[179,212,217] An immunophenotype-directed strategy has been used in Europe for many years. The German BFM group treated children with CD30$^+$ ALCL with a B-cell approach (Burkitt's lymphoma-like) achieving one of the best published outcomes to date (a 5-year event-free survival rate of approximately 76% for all patients).[217] The activity of a B-cell approach (NHL 9002) based on the very successful French LMB-89 B-cell protocol was studied in the United Kingdom Children's Cancer Study Group. In the NHL 9002 study, those with stage II, III and non-CNS-positive stage IV ALCL were treated with the Group B arm of the LMB-89 regimen (5-year event-free survival rate of 55%).[185] It has yet to be determined why this approach appeared to be inferior to the B-cell approach used in the BFM trials; however, it has been suggested that it might be a result of the more frequent use of alkylators in the BFM regimen. In the French (SFOP) trials, children with CD30$^+$ ALCL have been enrolled on the HM-89 and HM-91 protocols, both of which feature an initial treatment phase (one course of COP followed by two courses of COPADM) based on their very successful B-cell protocol, LMB-89.[179] The maintenance phases differed from LMB-89 as follows: The HM 89 protocol featured alternating courses of VEM (etoposide, methotrexate, and cyclophosphamide) and VAD (vincristine and doxorubicin) for a total of eight courses, and the HM-91 regimen featured alternating courses of VEBBP (vinblastine, etoposide, bleomycin, and prednisone) and Sequence 1 (vincristine, methotrexate, cyclophosphamide, and doxorubicin) for a total of eight courses. A 60% (54% to 76%) 3-year event-free survival rate was seen for all stages treated with HM-89 and HM-91; however, the 3-year event-free survival rate was only 55% for stage III and IV patients.

A histology-directed approach has historically been used in the United States to treat children with large cell lymphoma. One of the most widely used regimens is APO, which features an induction phase (doxorubicin, vincristine, prednisone, and intrathecal methotrexate) followed by sequential maintenance phases (doxorubicin, methotrexate, vincristine, prednisone, 6-mercaptopurine, and intrathecal methotrexate)[202,211,212] A randomized trial performed by the Pediatric Oncology Group examined the potential benefit of adding intermediate-dose methotrexate and high-dose cytarabine to an APO backbone and found no difference in outcome regardless of

Table 102-6 Treatment Outcome for Advanced-Stage Large Cell Non-Hodgkin's Lymphoma

Protocol	Stage	No. of Patients	Event-Free Survival Rate	Reference (First Author)
CHOP	III & IV	21	3-year EFS = 62% ± 11%	Sandlund[161]
MACOP-B	III & IV	11	3-year EFS = 55% ± 16%	Santana[180]
COMP vs. LSA_2L_2	III & IV	42	5-year EFS = 52%	
	III & IV	18	5-year EFS = 43%	Anderson[186]
APO vs. ACOP+	III & IV	62	3-year EFS = 72 ± 6%	
	III & IV	58	4-year EFS = 62 ± 7%	Laver[211]

immunophenotype.[212] A 4-year event free survival rate and overall survival rate of 71.8% and 88.1%, respectively, were reported for the 86 patients with advanced-stage disease who were enrolled on the study. Trials in Europe and the United States are building on the successful results achieved with the BFM B-cell and APO strategies, respectively. Both trials are examining the benefit of adding vinblastine, an agent that has activity as a single agent in multiply relapsed ALCL patients.[214]

RARE HISTOLOGIC SUBTYPES. The therapeutic approaches to the treatment of children with histologic subtypes that are unusual in this age group are often derived from strategies that are used in adults. Children with localized follicular lymphoma have been successfully treated with CHOP-based limited-stage therapeutic approaches; however, there have been reports of children who have remained disease-free following complete resection without adjuvant chemotherapy.[144,229,230] Children with hepatosplenic lymphomas have an aggressive disease course and often have recurrent disease even after an initial good response to aggressive therapy.[231–235] There is clearly a need for organized national trials to improve our treatment approaches to these and other infrequently encountered histologic subtypes.

Central Nervous System Prophylaxis and Treatment

The prevention of disease spread to the CNS is an important component of most successful modern treatment protocols. This generally involves both the administration of chemotherapy directly into the CSF (intrathecally by lumbar puncture or less commonly by the intraventricular route) and the administration of systemic high-dose chemotherapy (e.g., methotrexate, cytarabine). Prophylactic intrathecal therapy may be unnecessary in children who have limited-stage disease sparing the head and neck region[192] or advanced-stage large cell lymphoma sparing the bone marrow and head/neck region.[236] The benefit of cranial radiation as CNS prophylaxis remains controversial. It has been used in children with advanced-stage lymphoblastic lymphoma, but is not widely favored.[208]

Among children who present with overt CNS disease (cranial nerve palsies or cerebrospinal fluid pleocytosis), intensification of both systemic and intrathecal chemotherapy is usually indicated; except in cases of Burkitt's lymphoma, cranial radiation is also usually incorporated.

Emergency Situations

Various emergencies may arise in the management of children with NHL.[2] First, children who present with large anterior mediastinal masses associated with severe respiratory distress require immediate attention. If there is significant airway compression, deep sedation should be avoided. Chemotherapy should be started as soon as possible if the diagnostic samples have been obtained. If they have not, local radiation therapy could be the best approach, since it spares more peripheral disease for subsequent biopsy and study. Steroids might be necessary in some cases, but this therapy can alter tumor histology and preclude an accurate tissue diagnosis.

Some children with bulky Burkitt's or lymphoblastic tumors develop renal failure secondary to tumor lysis syndrome, despite appropriate prechemotherapy management. A nephrologist should be consulted immediately when renal dysfunction is first noted so that dialysis can be considered. This situation may be further complicated when a large pelvic mass creates direct ureteral compression. The placement of ureteral stents or a percutaneous nephrostomy tube can help temporarily; however, the problem is most effectively dealt with by delivery of appropriate chemotherapy.

A small percentage of children may present with epidural tumors that cause cord compression and corresponding neurologic deficits. Delivery of appropriate chemotherapy is usually all that is required; however, if there is no prompt recovery of neurologic function, a radiation therapist should be consulted about the possible need for low-dose local irradiation.[2]

Treatment Complications

As the survival of children with malignant lymphomas has improved, increased attention has been focused on treatment-related late effects.[237] The most serious treatment sequelae in survivors of childhood NHL include anthracycline-related cardiomyopathy, cyclophosphamide-related sterility, second cancers, and transfusion-related hepatitis. Attempts to reduce or eliminate these complications have included the dose reduction or elimination of both specific chemotherapeutic agents as well as involved field irradiation. Improving the process of blood product screening has also been an important area of focused research.

The design of clinical trials for pediatric NHL has been strongly influenced by the desire to avoid anthracycline-induced cardiac toxicity. Although it has been demonstrated that adults may tolerate cumulative doses of Adriamycin of 550 mg/m^2, much lower cumulative doses have been shown to have clinically significant effects on ventricular contractility in children [238] Factors that have been shown to be predictive of cardiac dysfunction include cumulative anthracycline dosage, higher anthracycline dose intensity, younger age at time of treatment, female sex, time interval since completion of therapy, and combined modality therapy that includes mediastinal irradiation.[239,240] Future trials that focus on the reduction of cumulative anthracycline dosage and the utility of cardioprotectant agents are indicated.[197]

The preservation of fertility is another important concern in the development of optimal therapeutic strategies for children with NHL. A dose-related depletion of germinal cells is associated with the use of alkylating agents such as cyclophosphamide and ifosfamide; these agents tend to be more gonadotoxic in males. Studies thus far have suggested that sterility is likely at cumulative doses of cyclophosphamide greater than 7.5 g/m^2, whereas fertility is usually maintained at cumulative dosages less than 4 g/m^2. In this regard, a number of pediatric NHL trials have attempted to eliminate or reduce the dosage of cyclophosphamide.[211]

Pediatric NHL trials have also focused on the elimination of involved field irradiation. The first of two Pediatric Oncology Group trials for limited-stage NHL demonstrated that involved field irradiation could be safely eliminated without compromising outcome.[192] A similar observation was made for children with advanced-stage disease in a St. Jude study.[216] Although involved field irradiation is not used in most current NHL trials, cranial irradiation is considered in the management of overt CNS involvement in children with lymphoblastic lymphoma. (Its use for CNS prophylaxis in children with this histologic subtype is controversial.)

Follow-up

Management of Primary Treatment Failure

Children with refractory or recurrent disease, particularly after receiving modern intensive therapy, are generally considered to have a poor prognosis. Therefore, aggressive or novel approaches are often used to treat relapse. Current approaches generally comprise multiagent salvage chemotherapy followed by an intensification phase that may include autologous or allogeneic hematopoietic stem cell transplantation (HSCT). Multiagent salvage regimens that have been studied include DHAP[180] (dexamethasone, high-dose cytarabine, and platinum), which has been shown to be active in childhood and adult recurrent large cell lymphoma, and VIPA[241] (etoposide, ifosfamide, and high-dose cytarabine), which has been shown to be active in children with relapsed Burkitt's lymphoma. Other active salvage regimens for children with refractory or recurrent malignant lymphoma include ICE[242] (ifosfamide, carboplatin, and etoposide) and MIED (high-dose methotrexate, ifosfamide, etoposide, and dexa-

methasone). Children who are found to have chemosensitive recurrent disease are usually considered for an intensification phase of chemotherapy followed by an HSCT. In a recent report, however, the benefit of HSCT in this setting was questioned.[215] Although published data on the use of HSCT in children with recurrent or refractory NHL is limited in comparison to those reported for adults, there are reported studies supporting its use.[205,243–251] For example, European cooperative group trials demonstrated that some children with Burkitt's lymphoma who had a poor early response to therapy could be successfully salvaged with high-dose chemotherapy followed by autologous HSCT.[205,246,247,249,252] Moreover, the Spanish Working Party for Bone Marrow Transplantation reported a 58% event-free survival rate following HSCT in children with either recurrent/refractory NHL or high-risk NHL in first CR.[246] The SFOP reported that 8 of 24 children with NHL who failed initial therapy were long-term disease-free survivors following HSCT.[247] In a review of 22 children at the St. Jude Children's Research Hospital, approximately 45% were survivors following intensive chemotherapy and HSCT.[251] It is difficult to make direct comparisons between the published studies of HSCT in children because they vary with respect to type of HSCT (autologous versus allogeneic), preparative regimen, numbers of patients, and histologic subtypes studied.

It appears, however, that histologic subtype should be considered in determining the type of HSCT (autologous versus allogeneic) for children with refractory or recurrent NHL. Among children with Burkitt's lymphoma, an autologous approach has been shown to be beneficial for those with a poor early response.[205,243,247] For those with disseminated recurrent Burkitt's lymphoma involving the marrow, many clinicians favor an allogeneic approach if a suitable donor can be identified. An autologous HSCT has been shown to be an effective strategy for some children with recurrent large cell lymphoma;[245,251] however, for children with recurrent lymphoblastic lymphoma, the results are less encouraging.[215]A recent study by the BFM group identified an excellent outcome using an allogeneic HSCT strategy for those with high-risk ALCL relapses.[253]

Various preparative regimens have been successfully used in the salvage of children with refractory or recurrent NHL.[205,243–251] Two of the earliest reported regimens are BACT (carmustine, cytarabine, cyclophosphamide, and thioguanine) and BEAM (carmustine, etoposide, cytarabine, and melphalan).[243,244,250] High-dose busulfan was reported as an important component of a successful French (SFOP) preparative regimen.[249] Gordon and colleagues reported the successful salvage of children with recurrent peripheral T-cell lymphoma using a preparative regimen that featured thiotepa;[245] however, it was associated with significant mucositis.

Currently, most clinicians would consider an autologous HSCT for children with chemosensitive recurrent large cell lymphoma and for those with Burkitt's lymphoma who have a poor early response. If a suitable donor is available, an allogenic HSCT approach would be considered for children with widely disseminated recurrent lymphoblastic lymphoma or Burkitt's lymphoma involving the bone marrow. An allogeneic HSCT approach may also be considered for those with high-risk recurrent ALCL. It is clear that there is a need for additional prospective clinical trials to evaluate the optimal preparative regimen and HSCT approach for children with recurrent or refractory NHL. In this regard, the European Lymphoma Bone Marrow Transplantation Registry has suggested that the potential graft-versus-lymphoma effect of allogeneic HSCT be studied.[249]

After Completion of Therapy Clinic

It is important that all children who have completed therapy for NHL be followed annually in an "after-completion-of-therapy" or late effects clinic.[254,255] The purposes of these visits are both to screen for therapy-related late effects (see section on complications of therapy) and to provide education and counseling about the medical and psychosocial issues that affect cancer survivors. These clinics also provide an opportunity for children and young adults to participate in important research initiatives that focus on cancer prevention and control, psychosocial problems, and treatment-related sequelae.

FUTURE DIRECTIONS

Despite dramatic improvements in the treatment of childhood NHL, approximately 20% to 30% of patients either do not achieve a complete remission or develop recurrent disease.[1,2,19] Treatment-related late effects that place cancer survivors at risk are of additional concern.[237] Therefore, the development of more effective and less toxic therapy remains an ongoing challenge. The identification of clinical and biologic features that are predictive of treatment failure may help in the refinement of a risk-adapted treatment approach to children with NHL.

Improvement in treatment outcome may be achieved by the incorporation of new active agents or the development of novel schedules for the delivery of currently used agents. Novel therapeutic approaches include the incorporation of immunotherapeutic approaches into multiagent chemotherapeutic regimens. In this regard, trials are under way for children with $CD20^+$ B-cell lymphomas that incorporate the anti-CD20 antibody, rituximab, an agent that has already been shown to be valuable in the treatment of some adults with $CD20^+$ B-cell lymphomas.[256,257] A phase I/II study for children with $CD30^+$ ALCL has been designed to examine the safety and efficacy of a newly developed anti-CD30 antibody.[258] Other potential therapies include the use of protein-specific cytotoxic T-lymphocytes, a strategy that has been successful in preventing and treating EBV-related post-transplantation lymphoproliferative disease.[259] Novel approaches may also include the incorporation of small molecule inhibitors, as well as antisense and anti-idiotype strategies. Molecular characterization of the chromosomal abnormalities associated with the NHLs of childhood is providing us with tools that enhance diagnosis, disease classification, and monitoring of the response to therapy (detection of minimal residual disease). A clearer understanding of molecular pathogenesis may provide insights that permit the development of therapeutic strategies that target tumor-specific molecular lesions.

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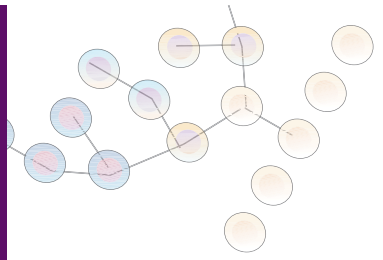
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103 Acute Lymphocytic Leukemia in Adults

Dieter Hoelzer and Nicola Gökbuget

SUMMARY OF KEY POINTS

Epidemiology and Etiology
- Acute lymphocytic leukemia (ALL) is more frequent in whites and in adults older than 65 years.
- Risk factors include irradiation, benzene, and leukemogenic chemotherapeutic agents.

Diagnosis
- Morphologic subtypes include L1, L2, and L3; the last is characteristic of mature B-cell (or Burkitt type) ALL.
- Subtypes of B-cell ALL include pro-B, common ALL (Expresses CD10), pre-B, and mature B-cell (Burkitt type).
- Subtype of T-cell ALL include early T-precursor, thymic (expresses CD1a and has a better prognosis), and mature T-cell (expresses CD3).

Clinical Manifestations
- Mediastinal masses occur more frequently in T-cell than in B-cell ALL.

Prognostic Factors
- Older age, high white blood cell count (on B-cell ALL but not T-cell ALL), early and mature T-cell ALL, MDR-1 expression, and Philadelphia chromosome–positive ALL are associated with a poorer prognosis.

Treatment
- Treatment phases are remission induction, consolidation, central nervous system prophylaxis, and maintenance.
- Outcome in Philadelphia chromosome–positive ALL is improved by the incorporation of imatinib.
- Allogeneic transplantation is the treatment of choice in patients with relapsed or refractory ALL who have a matched donor.
- Rituximab should be used in mature B-cell (Burkitt) ALL.

INTRODUCTION

Acute lymphocytic leukemia (ALL) is a malignant disease that is characterized by an accumulation of lymphoblasts. In the early 1980s, adult ALL was largely an incurable disease with an overall survival (OS) rate of less than 10%. After adoption of pediatric protocols the overall survival rate in adults improved to 30% to 40%. Progress has made in the tools that are used to diagnose ALL. In addition, a variety of new drugs for the treatment of ALL are now under evaluation. However, the prerequisite for comprehensive therapy of ALL requires more than ever standardization and quality control of treatment strategies. Rapid diagnosis and classification are not only important for clinical practice but also helpful in identifying prognostic factors, in defining targets for evaluation of minimal residual disease (MRD), and for creation of novel therapeutic agents.

EPIDEMIOLOGY

According to the National Cancer Institute, the age-adjusted overall incidence of ALL in the United States was 1.6 per 100,000 (1.8 in males and 1.4 in females). The incidence is higher in whites than in blacks. After an initial peak in children younger than 5 years of age (8.3 per 100,000), the incidence decreases continuously. It increases again above the age of 65 to a second peak in the age group above 85 years (2.0 per 100,000).[1]

BIOLOGIC AND MOLECULAR ASPECTS

Preferred Approach to Diagnosis

Classification of the phenotype of the blast cells in acute leukemia requires morphologic and cytochemical evaluations, immunophenotyping, cytogenetic analysis, and molecular genetic analysis. Morphology remains the means by which acute leukemia is initially detected and, together with cytochemical reactions, is the major tool in distinguishing between ALL and acute myeloid leukemia (AML; Fig. 103-1). For more precise subclassification of ALL into B or T lineages and further subtypes, immunologic techniques must be used to detect lineage-specific antigens as well as surface or intracytoplasmic molecules. These methods also offer the opportunity to identify leukemia-specific surface markers for the detection of MRD. Cytogenetic analysis is still part of the diagnostic characterization of ALL, but molecular genetic techniques for identification of particular subsets of ALL (e.g., *BCR-ABL*-positive ALL) are of greater importance. Molecular markers, particularly rearrangements of T-cell receptor genes and immunoglobulin heavy chain genes, are the most frequently used tools to evaluate MRD.

Morphology

The distribution of L1 and L2 subtypes is of minor relevance for prediction of outcome. The subtype L3, which is observed in up to 5% of adult ALL patients, should be distinguished because it is indicative of a mature B-cell ALL, which requires different treatment options, but should be confirmed by surface marker analysis. According to the World Health Organization classification, ALL is grouped together with lymphoblastic lymphoma as either precursor AB-cell or T-cell neoplasm. B-cell ALL is referred to as precursor B-lymphoblastic leukemia/lymphoma. L3-ALL is classified as Burkitt's cell leukemia together with Burkitt's lymphoma. T-ALL is grouped together with T-cell lymphoblastic lymphoma as precursor to T-lymphoblastic lymphoma/leukemia.

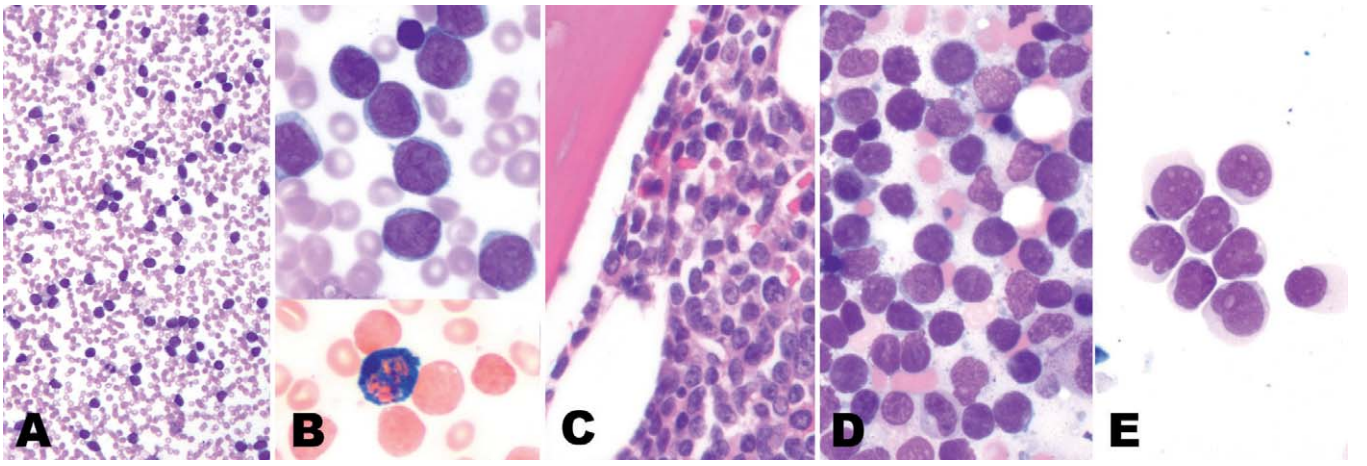


Figure 103-1 • Acute lymphoblastic leukemia: peripheral blood, bone marrow biopsy and aspirate, and cerebral spinal fluid. The illustration is from a 37-year-old male who presented with a WBC of 170 K/μL and over 90% blasts with lymphoid morphology (**A** and **B,** *top*). An initial myeloperoxidase reaction (**B,** *bottom*) showed the blasts to be negative (positive cell is a segmented neutrophil that serves as an internal control). The bone marrow was packed with blasts as seen on the biopsy and aspirated material (**C** and **D**). The blasts were immunophenotyped by flow cytometry and were shown to be precursor-B lymphoblasts with the following phenotype: CD34+, HLA-DR+, TdT+, CD19+, CD10+, cyCD79A+, cyIgM–, sIg–. Cytogenetic studies illustrated the t(9;22), and molecular analysis revealed the p190 *BCR/ABL*. A spinal tap showed a WBC count of 120/μL with a red blood cell count of 37/μL. The differential showed 80% blasts. The morphology of the blasts on the cytospin of the cerebrospinal fluid (**E**) is somewhat altered by the preparation. Note the absence of significant red blood cells in the specimen. Given the high number of blasts in the peripheral blood, a more traumatic tap would have made it difficult to distinguish between CNS disease and contamination of the cerebrospinal fluid specimen by blood. (Courtesy of John Anastasi, MD, from Hoelzer D, Gökbuget N: Acute lymphocytic leukemia in adults. In Hoffman R, et al [eds]: Hematology, 5th ed., Philadelphia, Churchill Livingstone, in press.)

Cell Surface Marker Analysis

ALL is divided into subtypes by immunologic criteria based on the presence of specific receptors or antigens on the cell surface of leukemic blast cells. Within the B- or T-lineage ALLs, the subtypes are defined according to their stage of differentiation.

The frequency of and definition of ALL subtypes in adult and childhood ALLs are outlined in Table 103-1. In the German multicenter trials for childhood ALL (BFM) and adult ALL (GMALL), the phenotypic characteristics of 1756 children and 946 adults with ALL were analyzed prospectively. B-precursor ALL is the most frequent subtype in children and adults (85% and 70%, respectively). T-lineage ALL has a higher incidence in adults (25%). Within the B and T lineages, the more immature subtypes—pro-B ALL and early T ALL—occur more frequently in adults. The European Group for the Immunological Characterization of Acute Leukemia has proposed a unified classification of ALL immunophenotypes.[2] The use of such uniform classifications is of utmost importance to permit results in different trials to be comparable. Immunophenotypes in ALL are often associated with clinical characteristics such as disease manifestations, course of disease, and biologic markers such as cytogenetic and molecular aberrations, as illustrated in Table 103-1.

B-Lineage Acute Lymphocytic Leukemia

Pro-B ALL, also termed pre-pre-B ALL or early pre-B, lacks B-, T-, and pre-B-cell markers but expresses the human leukocyte antigen (HLA-DR), TdT, and CD19 and has rearranged immunoglobulin genes (see Table 103-1). It occurs in approximately 11% of adult ALL and 5% of childhood ALL.

Common ALL is the major immunologic subtype in childhood ALL as well as in adult ALL. It makes up more than 50% of cases of adult ALL. Common ALL is characterized by the presence of CD10 (see Table 103-1). Common ALL blast cells do not express markers that characterize relatively mature B cells, such as cytoplasmic immunoglobulins or surface membrane immunoglobulins. The blast cells are positive for CD19 and TdT.

Pre-B ALL is characterized by the expression of cytoplasmic immunoglobulins, which is absent in common ALL, but is identical to common ALL with respect to the expression of all other cell markers (see Table 103-1). Rarely, CD10 may be absent in this subtype. Pre-B ALL makes up nearly 10% and 15% of adult ALL and childhood ALL, respectively.

Mature B-cell ALL is found in approximately 4% of adult ALL patients and 3% of childhood ALL patients. The blast cells express surface antigens of mature B cells, including surface membrane immunoglobulin. CD10 may be present, as well as occasional cytoplasmic immunoglobulins (see Table 103-1).

T-Lineage Acute Lymphocytic Leukemia

Approximately 25% of adult ALL cases have blast cells with a T-cell phenotype. All cases express the T-cell antigen gp40 (CD7), and they may, according to their degree of T-cell differentiation, express other T-cell antigens (e.g., the E rosette receptor [CD2] or the cortical thymocyte antigen T6 [CD1]; see Table 103-1). A minority of T-cell ALL blast cells may also express CD10 together with T-cell antigens. In most cases of T-cell ALL, one or more of the T-cell receptor genes are rearranged. These properties make it possible to classify T-cell ALLs according to their stage of differentiation.

Early T-precursor ALL (or pre-T ALL) makes up 7% and 1% of adult ALL and childhood ALL, respectively, and shows no further differentiation markers. Thymic T-ALL (or cortical T-ALL) accounts for 13% of adult ALL and is characterized by CD1a expression. Because this subtype is associated with a better prognosis, its identification is of particular importance. Mature T-ALL forms 7% of adult ALL and shows expression of surface CD3.

Cytogenetic and Molecular Genetic Analyses

Cytogenetic abnormalities are independent prognostic variables for predicting the outcome of adult ALL.[3] In some cases, cytogenetic or molecular genetic analysis contributes to confirmation of the diagnosis, for example, the correlation between t(8;14) and mature B-ALL. In four multicenter studies, clonal chromosomal aberrations could be

Table 103-1 Immunologic Subtypes of Acute Lymphocytic Leukemia and Corresponding Cytogenetic and Molecular Markers

Subgroups	Most Important Markers	Incidence in Children (*N* = 1756)*	Incidence in Adults (*N* = 946)*	Cytogenetic/Molecular Marker†
B-Lineage	HLA-DR+, TdT+, CD19+, and/or CD79a+, and/or CD22+	85%	72%	
Pro-B (B-I)	CD10–, no other differentiation markers	5%	11%	6% t(4;11)/ALL1-AF4 (70% in pro-B)
				(20% Flt3 in MLL+)
Common ALL (B-II)	CD10+	65%	51%	33% t(9;22)/BCR-ABL (30%–50% in c/pre-B)
				4% t(1;19)/PBX-E2A
Pre-B (B-III)	Intracytoplasmic IgM+	15%	10%	
Mature B	Intracytoplasmic or surface kappa or lambda	3%	4%	5% t(8;14) /c-myc-IgH
T-Lineage	Intracytoplasmic or surface CD3+, CD7+		26%	
Early T	Intracytoplasmic CD3+,CD7+, CD5±, CD2–, sCD3–, CD1a–	1%	7%	5% t(10;14)/HOX11-TCR
				<5% t(11;14)LMO/TCR
				2% SIL-TAL1
				4% NUP213-ABL1(in T-ALL) 33% HOX11†
				5% HOX11L2†
				50% Notch1†
Cortical (thymic) T	CD2+, CD5+, CD1a+, sCD3±		13%	
Mature T (T-IV)	CD2+, CD5+, sCD3+, CD1a–		7%	

*According to Ludwig, Raghavachar, and Thiel.[175]
†According to GMALL data and Armstrong and Look.[174]

detected in approximately 62% to 85% of adult ALL patients;[4–7] 15% to 38% of the cases had normal metaphases. The major cytogenetic abnormalities in ALL are clonal translocations, such as t(9;22) (20% to 30%), t(4;11) (3% to 4%), t(8;14) (5%), and t(1;19) (2% to 3%), and other structural abnormalities, such as 9p (5% to 15%), 6q (4% to 6%), and 12p aberrations (4% to 5%). If none of the structural aberrations are present, the abnormalities can be classified according to the modal chromosomal number (fewer than 46, 46 with other structural abnormalities, 47 to 50, or more than 50).

Molecular analyses, detecting gene rearrangements in ALL by the polymerase chain reaction (PCR), Southern blot analysis, or fluorescent in situ hybridization with chromosome-specific DNA probes, are useful approaches in establishing a more precise diagnosis and in defining the quality of remission, and they may also provide insights into the pathophysiology of the leukemic process (e.g., the mechanisms of leukemic cell stimulation by BCR-ABL fusion proteins). The most frequent molecular markers in ALL are BCR-ABL and ALL1-AF4.

The Ph chromosome t(9;22)(q34q11) results from a translocation involving the breakpoint cluster region of the *BCR* gene on chromosome 22 and the *ABL* gene on chromosome 9. The *BCR-ABL* gene rearrangement can be demonstrated by molecular techniques. PCR analyses revealed an incidence of 20% to 26% *BCR-ABL*-positive ALL in adults[8–10] compared with 3% in childhood ALL patients. One third of adult ALL patients with a Ph chromosome show M (major)-*BCR* rearrangements (resulting in a 210-kd protein), similar to patients with chronic myeloid leukemia, whereas two thirds have m (minor)-*BCR* rearrangements (resulting in a 190-kd protein). It is noteworthy that *BCR-ABL* is more frequently detected than is the corresponding chromosomal abnormality (t[9;22]) because of occasional difficulties in obtaining sufficient material for cytogenetic analysis.

The most frequent form of 11q23 abnormalities in ALL is t(4;11)(q21;q23). The involved gene on chromosome 11 is named *MLL* for "mixed lineage leukemia." Synonyms are *ALL-1*, *HRX*, and *HTRX1*. The *MLL* gene is fused to a gene located on chromosome 4 that is named *AF-4* (also referred to as *FEL*). The translocation is frequently detected in infant leukemia and in patients with the early pre-B subtype (CD10-negative). The overall incidence in adults is approximately 5%. Typical molecular aberrations in ALL with associated cytogenetic translocations and immunologic subtypes are summarized in Table 103-1.

The role of cytogenetic analysis has to be reevaluated critically. The most frequent cytogenetic aberrations and those with the greatest prognostic impact can also be detected by the corresponding molecular genetic aberrations, such as BCR-ABL for t(9;22) and ALL1-AF4 for t(4;11). These techniques are more reliable and have a greater sensitivity, for example, a detection level of 10^{-4} to 10^{-6}. They are therefore more useful for initial detection of the aberrations and for follow-up analysis of MRD (see later discussion).

Minimal Residual Disease

Molecular and immunologic techniques have allowed the detection of MRD, defined as leukemic cells that are undetectable by morphologic examination. MRD evaluation is most frequently based on detection of leukemia-specific constellations of surface markers by flow cytometry, fusion genes related to specific chromosomal translocations (e.g., BCR-ABL in t(9;22) by PCR), and individual rearrangements of immunoglobulin (immunoglobulin heavy chain, immunoglobulin kappa) and T-cell receptor genes (TCR-β, -γ, and -δ) by PCR and recently by real-time PCR. In ideal cases, these methods reach a sensitivity of 10^{-4}, which refers to the detection of

1 malignant cell in 10,000 normal cells. Overall, more than 90% of the ALL patients have at least one target for MRD evaluation.

ETIOLOGY

The cause of ALL remains unknown. However, a number of factors are associated with an increased risk of developing acute leukemia (ALL and AML).[11,12]

Genetic Predisposition

In epidemiologic studies, patients with some rare congenital chromosomal abnormalities have an increased risk for development of acute leukemias, including ALL. In children with leukemia (predominantly AML), there is an 18-fold higher incidence of Down syndrome than would be expected.[13] There is also an increased risk of ALL associated with inherited disorders, such as Klinefelter's syndrome, Fanconi's anemia, Bloom's syndrome, ataxia-telangiectasia, and neurofibromatosis. The impact of genetic predisposition on the pathobiology of ALL may also be inferred from reports of the simultaneous development of ALL in identical twins. Molecular analyses have demonstrated that the disease is not related to genetic predisposition but probably to the exchange of a malignant stem cell between the twins. This was demonstrated for rearrangement of the MILL gene[14] and the TEL-AML1 fusion gene.[15] Particularly in infant leukemias, prenatal molecular aberrations are probably the basis and lead after additional postpartum events to development of leukemia.

Irradiation

The incidence of acute leukemias, mainly AML but also ALL, was increased almost 20-fold in survivors of the atomic bomb explosions (>1 Gy exposure) in Japan,[16] with a peak incidence occurring 6 to 7 years after the radiation exposure. Induction of leukemia by emissions from nuclear power stations has also been raised as a possible environmental leukemogenic risk; this has never been demonstrated unequivocally. Whether radiation exposure after the Chernobyl accident led to an increased incidence of leukemia is still controversial.

Chemical

The risk for the development of ALL could also be increased after exposure to chemical agents such as benzene or other agents that are capable of producing bone marrow aplasia, including chemotherapeutic drugs. Secondary, therapy-related AMLs but also ALLs can occur after exposure to alkylating agents, such as cyclophosphamide, epipodophyllotoxins, topoisomerase II inhibitors, and, rarely, anthracyclines,[17,18] which are used for treatment of other preceding neoplasias.

Viral

There is no direct evidence that a virus causes human ALL. Indirect findings, however, suggest involvement of a virus in the pathogenesis of two lymphoid neoplasias.[19] In the endemic African type of Burkitt's lymphoma, the Epstein-Barr virus, a DNA virus of the herpes family, has been implicated as a potential causative agent.[20] The endemic infection with human T-cell leukemia virus I in Japan and the Caribbean has been shown to be an etiologic agent for adult T-cell leukemia/lymphoma.[21]

CLINICAL MANIFESTATIONS

Most adult patients initially present with clinical symptoms resulting from bone marrow failure. Physical findings such as pallor, tachycardia, weakness, and fatigue are due to anemia; petechiae or other hemorrhagic manifestations are attributable to thrombocytopenia; infectious complications are due to neutropenia. Clinical signs of leukemia related directly to infiltration of organs with leukemic blasts, such as lymphadenopathy, splenomegaly, and hepatomegaly, are present in most patients but are infrequently the problems for which the patient first seeks medical advice.

Symptoms and clinical manifestations of 938 adult ALL patients, 15 to 65 years of age, entering two consecutive German multicenter trials, are listed in Table 103-2. One third of the patients had infection or fever at presentation, and one third presented with hemorrhagic episodes. Weight loss was observed only occasionally. Approximately one half of the patients presented at diagnosis with lymphadenopathy, splenomegaly, hepatomegaly, and hilar lymph node enlargement or a thymic mass (detected on chest radiographs or computed tomography scans) in approximately 14% of patients. Most (85%) patients with mediastinal masses had T-cell ALL. Massive thymic enlargement can cause dyspnea, especially when associated with pleural effusions. Although 7% of ALL patients at presentation had central nervous system (CNS) involvement, as demonstrated by leukemic blast cells in the cerebrospinal fluid, only 4% of these initially had CNS symptoms, such as headache, vomiting, lethargy, nuchal rigidity, and cranial nerve or peripheral nerve dysfunction.

Virtually any organ can be infiltrated by ALL blast cells, and approximately one tenth of the patients had such organ involvement (see Table 103-2). Most often, a pleural effusion was observed in patients with mediastinal enlargement and T-cell ALL. Some of those patients also had a pericardial effusion. Bone or joint pain was rarely observed, in contrast to childhood ALL; bone lesions could be found in only 1% of cases. Initial involvement of the testes was very rare (<1%). Leukemic infiltration of retina, skin, tonsils, lung, or kidney was observed only occasionally, particularly in mature B-cell ALL and to a lesser extent in T-cell ALL, all of them associated with a poorer outcome.

Table 103-2 Symptoms and Clinical Signs at Diagnosis of 938 Adult Acute Lymphocytic Leukemia Patients

Signs or Symptoms	Patients (%)
Symptoms	
Infections/fever	36
Hemorrhages	33
Physical findings	
Lymphadenopathy	57
Splenomegaly	56
Hepatomegaly	47
Mediastinal mass	14
Central nervous system involvement	7
Other organ involvement	9
Pleura	3
Bone	1
Pericardium	1
Retina	1
Skin	<1
Tonsils	<1
Lung	<1
Kidney	<1
Testes	<1

Table 103-3 Laboratory Findings at Time of Diagnosis of 938 Adult Patients

		Patients (%)
White blood cell count($\times 10^6$/L)	<5000	27
5000–10,000	14	
10,000–50,000	31	
50,000–100,000	12	
>100,000	16	
Leukemic blast cells in peripheral blood	Present	92
	Not present	8
Leukemic blast cells in bone marrow	<50%	3
	51%–90%	51
	>90%	46
Bone marrow aspirable		84

Table 103-5 Coagulation Parameters at Time of Diagnosis of 938 Adult Acute Lymphocytic Leukemia Patients

		Patients (%)
Fibrinogen (mg/dL)	<100	4
	>100	96
Prothrombin time (%)	<50	7
	50–75	34
	75–100	34
	>100	25
Partial thromboplastin time (sec)	<30	33
	30–40	53
	40–50	11
	>50	3

LABORATORY EVALUATION

The peripheral blood cell values at diagnosis of the same cohort of patients are shown in Tables 103-3 through 103-5. The leukocyte count (see Table 103-3) was elevated in 59%, 14% had normal counts, and 27% had leukopenia. In 92% of the patients, leukemic blast cells were seen in the blood smear. Thus, "aleukemic" leukemias account for only a small proportion of cases of adult ALL. With automated blood counting, the diagnosis might be missed in patients with normal or decreased white blood cell counts (WBC) and with low or zero blast cells in peripheral blood. For this reason, the need for microscopic examination of blood smears in people who are suspected of having acute leukemia should be stressed. An elevated blood count (>100,000 $\times$ 10^6/L) was observed in 16% of the patients, and, occasionally, WBC counts greater than 500,000 $\times$ 10^6/L have been observed. In general, a high WBC count is found more frequently in T-cell ALL patients than in B-lineage ALL patients.

Neutrophils (see Table 103-4), less than 500 $\times$ 10^6/L, were seen in 23% of the patients, and thrombocytopenia, less than 25,000 $\times$ 10^6/L, was seen in 30% of the patients, corresponding roughly to the symptoms of infection and bleeding present at diagnosis.

Table 103-4 Peripheral Blood Counts at Time of Diagnosis of 938 Adult Acute Lymphocytic Leukemia Patients

		Patients (%)
Neutrophils ($\times 10^6$/L)	<500	23
	500–1000	14
	1000–1500	9
	>1500	54
Platelets ($\times 10^6$/L)	<25,000	30
	25,000–50,000	22
	50,000–150,000	33
	>150,000	15
Hemoglobin (g/dL)	<6	8
	6–8	20
	8–10	27
	10–12	24
	>12	21

Bone marrow aspiration or biopsy is mandatory for diagnosis of ALL. In fewer than 15% of patients, the bone marrow cannot be aspirated, and a biopsy must be performed. Dry taps are due to densely packed blast cells, fibrosis, or inadequate technique; the first two resolve after therapy. Most patients have more than 50% or even more than 90% of blast cells in the bone marrow (see Table 103-3). In fewer than 3% of cases, the blast cells constitute fewer than 50% of the nucleated marrow cells.

A lumbar puncture should be done to determine whether the CNS is involved. If there is a risk of bleeding due to a very low platelet count or of blast cell contamination due to a high leukemic blast content in the peripheral blood, lumbar puncture should be postponed. When the leukocyte count in the spinal fluid is low or the morphologic detection of blasts is inconclusive, demonstration of an immunologically defined blast cell population can confirm a diagnosis of CNS involvement.

The most frequent metabolic abnormality is an increased serum uric acid level, which occurs in approximately one half the patients; hypercalcemia was rare. Serum lactate dehydrogenase may be elevated as a result of cell destruction in patients with a large tumor mass, particularly in B-cell ALL. Owing to liver infiltration, some patients may show elevation of liver enzymes. In a small proportion of patients (see Table 103-5), the initial fibrinogen level may be less than 100 mg/dL. Disseminated intravascular coagulopathy and other disturbances of coagulation are rarely observed at diagnosis.

DIFFERENTIAL DIAGNOSIS

Difficulty is rarely experienced in establishing the diagnosis of ALL. The differentiation from lymphocytosis, lymphadenopathy, and hepatosplenomegaly due to viral infections and other acute or chronic leukemias can usually be done by lymphocyte surface markers.

Aleukemic pancytopenic ALL patients without blast cells in peripheral blood (fewer than 10%) must be distinguished from those with aplastic anemia, which may also be a preleukemic syndrome. In contrast to ALL, the bone marrow is hypocellular in aplastic anemia. In rare cases with a limited bone marrow infiltration, an arbitrary distinction between ALL and non-Hodgkin's lymphoma (NHL) is usually made according to the degree of infiltration: more or less than 25%.

In approximately 29% of the patients, blast cells coexpress myeloid surface markers such as CD13 and CD33 (>20%). Distinct subtypes of ALL are associated with a higher incidence of myeloid marker

coexpression, for example, early T-ALL, pro-B-ALL, Ph/BCR-ABL-positive ALL. These cases of ALL with myeloid marker coexpression must be differentiated from mixed or hybrid leukemias in which blast cells express lymphoid as well as myeloid antigens; they may also be termed *biphenotypic* or *bilineage* leukemias. The European Group for the Immunological Characterization of Acute Leukemia has suggested a score to unequivocally identify this rare subgroup.[2] Biphenotypic leukemias may be allocated to a treatment strategy for either for ALL or for AML and outcome seems to be poor with both approaches.

Occasionally, difficulties can occur in distinguishing Ph/BCR-ABL-positive ALL from primary lymphoid blast crisis of chronic myeloid leukemia. Sometimes final diagnosis can be made only after the initiation of treatment. In ALL patients who achieve complete clinical remission (CR), the peripheral blood count are normal values, whereas chronic myeloid leukemia cases revert to a chronic phase with a pathologic left shift.

THERAPY

Initial Evaluation and Supportive Therapy

At diagnosis, the evaluation of an adult with ALL should include a history and a careful physical examination. Speed in clinical evaluation and diagnosis is important to initiate supportive measures and to decide on appropriate therapy. Only in a few cases is the leukemic process so far advanced that immediate treatment of leukemia is necessary (e.g., in patients with symptoms that are due to a large mediastinal mass and pleural effusions or to a rapidly progressing B-cell ALL).

A few general measures should be initiated at once. Sufficient fluid intake to guarantee urine production of 100 mL/hour throughout induction therapy should be maintained to reduce the danger of uric acid formation. Parenteral fluid administration may be required when the patient's oral intake is inadequate because of nausea or difficulty in swallowing. Placement of an implantable port system is advantageous when a long period of induction therapy is anticipated or when part of the therapy will be carried out on an outpatient basis.

Patients should receive allopurinol to reduce the formation of uric acid and avoid the danger of urate nephropathy. Allopurinol blocks the enzyme xanthine oxidase, which mediates the generation of uric acid from xanthine as a product of purine catabolism. Allopurinol should be given at a dose of 300 mg/day, which may be increased to 600 mg/day if high leukocyte counts or organomegaly persists. The dose of allopurinol has to be reduced when 6-mercaptopurine is given because it potentiates the action of 6-mercaptopurine. Rasburicase is a new recombinant uratoxidase enzyme that catalyses the oxidation of uric acid to allantoin. It has been demonstrated that rasburicase can reduce high uric acid levels faster and more safely than allopurinol, thereby preventing a tumor lysis syndrome in almost all cases.[22] Therefore, it could be an alternative to allopurinol in patients with a high risk of tumor lysis syndrome.

Approximately one third of adult patients present with infection and bleeding. They are at high risk for infectious and hemorrhagic complications during the induction period because thrombocytopenia and granulocytopenia are aggravated by chemotherapy. In general, platelet transfusions should be given in response to bleeding episodes and to prevent bleeding when platelet counts fall to less than 10,000 (10^6/L) and to less than 20,000 (10^6/L) when there is a bleeding tendency or the patient is febrile. HLA-matched platelets are given to patients who become refractory to random donor platelets. The incidence of fatal hemorrhage during induction therapy has been significantly lowered by these measures.

Infection Management

The use of more intense chemotherapeutic regimens has resulted not only in improved response rates of malignancies but also in higher infection-associated morbidity and mortality. Long-term neutropenia is the most important risk factor, but CD4 lymphopenia, antibody deficiency, and immunosuppression in allogeneic stem cell transplantation (SCT) also lead to severe and lethal infections. Before the 1990s, gram-negative microorganisms were the leading cause of febrile neutropenia, but since then, gram-positive bacterial infections caused mostly by staphylococci have increased, frequently correlated to indwelling central venous access. The number of multiresistant bacteria is increasing. Invasive fungal infections are increasing in frequency, particularly mold infections.

ALL patients should receive antibacterial and antifungal prophylaxis depending on the expected duration of neutropenia. In febrile neutropenia, thorough and early diagnostic procedures are necessary. They include physical examination, microbiologic investigations, imaging procedures, and biopsies. Cultures of blood, urine, sputum, and other infected areas are mandatory. Successful treatment of febrile neutropenia is based on immediate empirical administration of broad-spectrum antibiotics.

Hematopoietic Growth Factors

The use of hematopoietic growth factors, such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) is a valuable component of supportive therapy during the treatment of ALL. There is no indication so far that these CSFs stimulate leukemic cell growth in a clinically significant manner.

Most clinical trials demonstrate that the prophylactic administration of G-CSF significantly accelerates neutrophil recovery,[23–28] and several prospective, randomized studies also show that this is associated with a substantially reduced incidence and duration of febrile neutropenia and of severe infections in ALL[24,26,27] and also reduced mortality during induction. [23,26–28]

The advantage of G-CSF administration was particularly evident in select high-risk patients receiving multiple treatment cycles,[24] whereas clinical effects appeared to be negligible in patients who are at low risk of infectious complications in one study in childhood ALL.[29] Conversely, the results of the St. Jude trial show that even in cases of acute leukemia with a greater than 40% probability of severe neutropenia, not all patients benefit from G-CSF treatment.[30] A comparison of this study with other trials[26,27] highlights the great importance of CSF scheduling. When CSFs are first given at the end of a 4-week induction chemotherapy regimen, potential benefits are limited.[30] Therefore, it is noteworthy that G-CSF may be given, even in conjunction with chemotherapy, without aggravating the myelotoxicity of these specific regimens,[25–27] and that this scheduling is an important determinant of the clinical efficacy. Alternatively, it was demonstrated that after short consolidation cycles, G-CSF application may be postponed from day 12 after high-dose cytarabine/mitoxantrone to day 17 without negative effects on duration of neutropenia.[31] Similar results were reported for consolidation therapy with the hyper-CVAD regimen.[32] A closer adherence to the dose and schedule of chemotherapeutic regimens should be theoretically possible with the use of G-CSF. So far, no trial has demonstrated a benefit of increased dose intensity made possible by G-CSF application in terms of leukemia-free survival (LFS).

G-CSF is regularly used for mobilization of stem cells in candidates for autologous stem cell transplantation. There are some hints that prophylactic application of G-CSF after intensive chemotherapy cycles or in parallel might reduce the incidence of severe mucositis. Thus, delayed application of G-CSF during induction therapy has led to an increased risk of mucositis.[32]

Chemotherapy

Chemotherapy of ALL is usually divided into several phases, beginning with remission induction. The objective of induction chemotherapy is to achieve complete remission, that is, eradication of

leukemia as determined by morphologic criteria and, more recently, also by molecular markers. Although the induction phase is usually well defined, postremission therapy can be subdivided into intensification and maintenance phases. Usually, prophylactic CNS treatment is added (Table 103-6).

Remission Induction Therapy

Exact diagnosis and management of initial complications are the prerequisites for successful induction therapy. A cautious cell reduction phase is recommended for patients with a large leukemic cell burden or a high leukocyte count (>25,000 × 10^6/L). Patients with extreme leukocytosis (>100,000 × 10^6/L) have been treated initially with leukapheresis. However, in the majority of patients, the cell count can also be reduced with steroids alone or in combination with vincristine or cyclophosphamide.

Standard induction therapy for ALL includes prednisone, vincristine, anthracyclines (mostly daunorubicin), and L-asparaginase. Other drugs, such as cyclophosphamide, cytarabine (either conventional or high dose), and mercaptopurine, are added in many protocols, sometimes called early intensification. Several new approaches are being explored in adult ALL to improve CR rates and thereby remission quality.

Steroids, mostly prednisone and prednisolone, have been administered, although dexamethasone has a higher antileukemic activity in vitro and a better penetration to the cerebrospinal fluid.[33] In pediatric trials the replacement of prednisone by dexamethasone has led to a decrease in the CNS relapse rate and improved survival.[34] The dexamethasone schedule has to be designed carefully, since continuous application of higher doses can lead to long-term complications[34] and to increased morbidity and mortality due to infections.[35]

Anthracycline dose intensity and schedule may play an important role in induction therapy of ALL.[36] The most frequently used anthracycline is daunorubicin. Many groups have replaced weekly applications by higher doses of daunorubicin (30 to 60 mg/m^2 on a 2- to 3-day schedule).[28,37,38] A particularly high CR rate (93%) was reported with intensive anthracycline therapy (270 mg/m^2 for 3 days)[38] from a single-center study, but this has not been confirmed in a larger multicenter trial.[39] Intensive anthracycline therapy may be associated with a higher mortality rate during the induction phase. Therefore, intensive supportive care and probably the use of growth factors are recommended with these protocols. Overall, it remains open whether intensified anthracyclines therapy is beneficial for all subgroups, particularly in terms of achieving a molecular remission.

Asparaginase does not affect the CR rate but improves LFS, and if not used during induction therapy, it is often included as part of the consolidation treatment. The addition of asparaginase to conventional induction therapy did not improve the CR rate in one trial in adult ALL. There was, however, a trend toward a higher LFS in patients who were treated with asparaginase.[40] Three different asparaginase preparations with significantly different half-lives are available: native *Escherichia coli* asparaginase (1.2 days), *Erwinia* asparaginase (0.65 days), and *PEG-L* asparaginase (5.7 days).[41] To reach equal efficacy, the treatment schedule has to be adapted, which is generally daily for *Erwinia* asparaginase, twice daily for *E. coli* asparaginase, and once weekly for PEG asparaginase. The importance of asparaginase pharmacokinetics is illustrated by a randomized trial in childhood ALL, in which significantly lower survival rates were achieved with *Erwinia* asparaginase compared with *E. coli* asparaginase, both given at the same schedule, which is due to underdosing of *Erwinia* asparaginase.[42] A randomized trial comparing *PEG* asparaginase with *E. coli* asparaginase in childhood ALL showed a higher earlier response rate for the latter but no difference in long-term outcome.[43] Thus, it remains open for debate whether *PEG* asparaginase is superior to Erwinia asparaginase or native *E. coli* asparaginase. During induction, asparaginase is often given concurrently with steroids in patients, inducing additional toxicities, such as coagulation disorders and hepatic dysfunction, which are not predictable. It may thereby lead to treatment delays and compromise dose intensity in individual patients.

The role of cyclophosphamide, generally administered at the beginning of induction therapy, has been evaluated in several studies. A randomized study by the Italian GIMEMA group comparing a three-drug induction regimens with and without cyclophosphamide did not show a difference in terms of CR rate (81% versus 82%).[44] However, in several nonrandomized trials, high CR rates (85% to 91%) were achieved with regimens that included cyclophosphamide pretreatment,[28,45] particularly in adult T-ALL.

High-dose treatment during induction refers particularly to high-dose cytarabine (HDAC) (1 to 3 g/m^2, usually for 12 doses) before or after the standard induction therapy. This approach has resulted in a median CR rate of 79%, which is not superior to that obtained with conventional treatment, and it remains uncertain whether and for which subgroups HDAC could be beneficial for LFS.[46] Up-front treatment before conventional chemotherapy yielded higher CR rates[37,47–49] than did treatment afterward,[45,50,51] which was, in part, related to a higher induction mortality with the latter approach. Any type of induction therapy with HDAC may lead to an increased incidence of severe neutropenias after subsequent chemotherapy cycles.

With current regimens, the remission rate in ALL is 85% to 90% (see Table 103-6) with low failure rates and a variable early mortality rate up to 11%, increasing with age. Morbidity due to extended cytopenias, for example, subsequent infections such as fungal pneumonias, can compromise further treatment and dose intensity. Options for increasing the rate of CR are limited in adult ALL. Therefore, in the future, increased molecular CR rates will be the most important goal. It may be defined as a burden of MRD below the detection limit of 10^{-4} (0.01%); the frequency of molecular CR in adult ALL ranges from 50% for Philadelphia chromosome–positive (Ph+) ALL treated with imatinib[52] to 60% for standard-risk ALL.[53]

Five percent to 15% of adult ALL patients do not achieve CR after induction therapy, compared with fewer than 3% of children with ALL. Five percent to 10% of adult ALL patients die during the induction period. Mortality during induction is age dependent; the mortality rate increases with age from less than 3% in adolescents to 20% in patients older than 60 years of age. The main cause of death in approximately two thirds of the patients is infection, often fungal infection. The remaining nonresponders may achieve a partial remission or may be refractory to standard treatment. These patients have an extremely poor prognosis and are therefore candidates for new, experimental treatment approaches and are also considered for SCT, even if they are not in complete remission.

Intensification Therapy

Consolidation therapy refers to either high-dose chemotherapy, the use of multiple new agents, or readministration of the induction regimen, also called reinduction. These measures are aimed at eliminating clinically undetectable residual leukemia after induction chemotherapy and thereby preventing relapse, as well as the emergence of drug-resistant cells.

Intensive consolidation is standard in the treatment of ALL based on pediatric studies and historic comparisons, although randomized trials often failed to demonstrate a benefit of intensification;[44,54] this is probably due to the low number of patients in whom these concepts were evaluated. Consolidation cycles in large studies are very variable, and it is impossible to evaluate their individual efficacy (see Table 103-6). Intensification schedules include teniposide, etoposide, amsacrine (*m*-AMSA), mitoxantrone, idarubicin, and HDAC or intermediate- or high-dose methotrexate (HDM). Allogeneic SCT from sibling or unrelated donors or autologous SCT is now the major approach for intensive postinduction therapy in high-risk patients (see later discussion). Before SCT, a consolidation therapy is usually delivered to achieve a CR with good remission quality. High-dose

Table 103-6 Overall Treatment Results of Adult Acute Lymphocytic Leukemia

Group	Author	Year	*N*	Age	Induction	Consolidation	Maintenance	CR (%)	LFS
GMALL 01[176]	Hoelzer	1993	368	25	V, P, A, D, C, AC, M, MP	V, DX, AD, AC, C, TG	MP, M	74	35% at 10 yr
GMALL 02[176]	Hoelzer	1993	562	28	V, P, A, D, C, AC, M, MP	V, DX, AD, AC, C, TG, VM, AC	MP, M	75	39% at 7 yr
UK-ALL IX[177]	Durrant	1993	266	—	V,P,A,(MP,M)/D	—	MP, M, V, P	68	22% at 8 yr
BGMT[119]	Attal	1995	135	31	V, P, A, D; C, AC, MP	HdM, ARC, allo/auto SCT	[Il-2]	93	44% at 3 yr
CALGB 8811[178]	Larson	1995	197	32	V, P, A, D, C	C, MP, AC, V, A, M, AD, DX, TG	MP, M, V, P	85	30% at 5 yr
GIMEMA 0183[179]	Mandelli	1996	358	31	V, P, A, D	V, IdM, IdAC, P, VM, AC	MP, M, V, P[A, AC, VM, IdAC]	79	25% at 10 yr
HOVON[64]	Dekker	1997	130	35	V, P, A, D	HdAC, amsa, MP, VP	—	73	28% at 5 yr
SAKK[65,180]	Wernli	1994, 1997	140	31	V, P, D, M, A, HdAC, VP	allo/auto SCT; >50 y: HDC	—	69	21% at 5 yr
UKALL XA[61]	Durrant	1997	618	>15	V, P, D, A	[AC, VP, D, TG]	MP, MTX, V, P	82	28% at 5 yr
PETHEMA[181]	Ribera	1998	108	28	V, P, D, A, C	HdM, V, D, P, A, C, VM, AC	MP, M[VD, P, Mi, A, C, VM, AC]	86	41% at 4 yr
CALGB 9111[28]	Larson	1998	198	35	C, D, V, P, A	C, MP, AC, V, A, MP, M, AD, DX, TG, P	MP, M, V, P	85	40% at 3 yr
LALA-87[89]	Thiebaut	2000	581	33	V, P, D/R, C, [amsa, AC]	D/R, AC, A	MP, M, V, C, P, D/R, DT, BCNU	76	17% at 5 yr
GMALL 05/93[134]	Gökbuget	2001	1163	35	V, P, D, A, C, AC, MP	V, DX, AD, AC, C, TG, VM, AC, HdM, A, C, [HDAC, Mi] ± SCT	MP, M	83	35% at 5 yr
Sweden[37]	Hallbook	2002	120	44	HdAC, C, D, V, BM	AM, HdAC, V, BM, C, D, VP +/− SCT	MP, M, D, V, P, AC, TG	86	36% at 3 yr
JALSG-ALL93[54]	Takeuchi	2002	263	31	V, AD, P, A, C	VP, Mi, AC, IdM, A, ACR, P	MP, MTX [V, AD, P, Mi, VP, AC, IdM, A, ACR, AC]	78	30% at 6 yr
UCLA, USA[182]	Linker	2002	84	27	V, P, D, A	HdAC, VP, HdM, MP, D, V, P, A	M, MP	93	47% at 5 yr
GIMEMA[183]	Annino	2002	794	28	V, P, A, D, C, [HDAC, Mi]	V, HDM, HDAC, DX, VM	MP, M, V, [AC, Mi, VM, HDAC, HDM, DX]	82	29% at 9 yr
MRC/ECOG[184]	Rowe	2003	1389	15–60	V, P, D, A, C, AC, MP	HdM, A [AC, VP, V, DX, D, C, TG] ± SCT	MP, M, V, P	91	41% at 5 yr
MD Anderson[123]	Kantarjian	2004	288	40	V, AD, DX, C	HdM, HdAC, P	M, MP, V, P	92	38% at 5 yr
GOELAMS-GOELAL02[91]	Hunault	2004	198	33	P, V, I, A	C, AC, MP, HdM, V, I, C, AC, TG ± SCT	aIFN	86	41% at 6 yr
LALA[94,90]	Thomas	2004	922	33	P, VCR, CP, DNR/IDA	[MI + IdAC] vs [CP/AC/MP]	MP, MTX	84	36% at 5 yr
						MTX/Asp, CY, AC, V, A, D ± SCT			
EORTC ALL-3[94]	Labar	2004	340	33	D, C, V, P,	A, C, HdAC, [P, V, AD, BCNU, C, MP, M, AMD] ± SCT	MP, MTX, V	74	36%* at 6 yr
GIMEMA 0496[158]	Mancini	2001	450		P, V, D, A	HDAC, VP, V, D, P, C,	MP, MTX	80	33% at 5 yr
PETHEMA ALL-93[93]	Ribera	2005	222	27	V, D, P, A, C	HdM, HdAC ± SCT	MP, MTX	82	34% at 5 yr

*Since 1993, >100 pts, follow-up >3 years.

AC, cytosine arabinoside; AD, doxorubicin; BCNU, carmustine; C, cyclophosphamide; CR, cure rate; D, daunorubicin; DT, dactinomycin; DX, dexamethasone; HdAC, high-dose AC; HdM, high-dose M; IdAC, intermediate-dose AC; VM, teniposide; IdM, intermediate-dose M; LFS, leukemia-free survival; M, methotrexate; Mi, mitoxantrone; MP, 6-mercaptopurine; N/M, either/or; P, prednisone; R, rubidazone; TG, thioguanine; V, vincristine; VD, vindesine; VP, etoposide; BM, betamethasone.

chemotherapy has been used mainly to overcome drug resistance or to achieve therapeutic drug levels in the cerebrospinal fluid.

HIGH-DOSE CYTARABINE. Although there is considerable experience with HDAC for the consolidation treatment of ALL,[46] it still remains uncertain what dose is optimal; usually, doses ranging from 1 to 3 g/m^2 every 12 hours for 4 to 5 days are given within several combinations. HDAC has been included in several trials in adult de novo ALL as part of consolidation therapy (see Table 103-6). It seems that specific subgroups of ALL profit from HDAC treatment; thus, encouraging results are achieved for pediatric B-cell ALL. The extent HDAC to which contributes to the effects of HDM in these disease subtypes remains uncertain. Apparently, HDAC is also beneficial for adult pro-B ALL, because cure rates of 50% can be achieved.[55]

An additional argument for the use of HDAC might be its effectiveness in treating CNS leukemia. There is evidence that in ALL and NHL, higher levels of AC triphosphate can be reached with 3 g/m^2 compared with the lower dose of 1 g/m^2 AC; in addition, with the higher dose, the cerebrospinal fluid can be cleared of blast cells.[56]

HIGH-DOSE METHOTREXATE. In general, it seems that intensive application of HDM is beneficial. It has been extensively studied for the treatment of childhood ALL and to a lesser extent in treatment of adult ALL. HDM appears to be effective in preventing systemic and testicular relapses. However, in adults, dosages are probably limited to 1.5 to 2 g/m² if given as a 24-hour infusion. Otherwise, toxicities, particularly mucositis, can lead to subsequent treatment delays and decreased compliance. Toxicity, but also efficacy, is reduced with a shortened infusion time, such as 4 hours.[57] The situation might change when improved prophylaxis of mucositis, such as with keratinocyte-growth-factor, becomes available.

The effect of HDM on CNS leukemia might contribute to the favorable results that have been reported with its use. HDM at a dose of 6 g/m^2 resulted in an 80% CR rate when it was given in children with CNS relapse,[58] indicating that systemic application yields cytotoxic levels in the cerebrospinal fluid. Several studies have investigated the efficacy of HDM as consolidation (see Table 103-6). Most favorable results have been achieved in small trials with HDM as part of intensive multidrug consolidation regimens.

ASPARAGINASE. From pediatric ALL trials, there is increasing evidence that intensified application of asparaginase leads to improved overall results.[59,60] In adult ALL, this approach appears to be useful particularly in consolidation, in which less toxicity can be expected compared to induction.

Reinduction

Pediatric trials and one randomized trial in adults also underline the efficacy of repeated induction, also named reinduction or late intensification.[61]

The role of HD anthracylines and epipodophyllotoxins in consolidation remains open. Overall in adult ALL, stricter adherence to protocols during consolidation with fewer delays, dose reductions, and omission of drugs due to toxicities would be an important contribution to therapeutic progress.

Maintenance Therapy

Maintenance therapy even after intensive induction and consolidation is still standard for ALL patients. Some groups even prolong maintenance therapy beyond 2 years of total treatment. Methotrexate preferably given intravenously and mercaptopurine given orally are the backbone of maintenance regimens. The potential effects of further intensification cycles for specific subgroups of ALL remains open. It might be useful to aim for leukocyte counts below 3000/μL during maintenance[62] to achieve optimal suppression of residual disease.

Attempts to omit maintenance therapy altogether after induction and consolidation therapy have had inferior results.[63–65] On the other hand, the role of periodic cycles of intensive chemotherapy during maintenance remains to be defined.

In a large, multicenter Italian study (GIMEMA 0183), after intensive consolidation treatment, patients were randomly assigned to postconsolidation therapy with conventional maintenance therapy or to additional alternating treatment courses of different intensities.[66] In this report, there was no difference in the survival rate at 10 years between the treatment groups (27% for conventional and 28% for more intensive maintenance), which might suggest that after adequate early consolidation therapy, the intensity of the maintenance therapy has no influence on survival. However, only a few patients actually received these regimens as scheduled; adults often show poor compliance to intensive maintenance, owing to toxicities and for social reasons. Therefore, maintenance with less intensive cycles, for example, with vincristine and steroids, might be more practicable.

Currently, maintenance therapy in adult ALL is being revisited on the basis of the burden of MRD (e.g., none for MRD-negative patients), the subtype of ALL, and the use of new therapeutic options (e.g., a tyrosine kinase inhibitor for BCR-ABL-positive ALL). It is still open whether and to what extent maintenance therapy is necessary in ALL subgroups.

Prophylaxis of Central Nervous System Leukemia

Central nervous system leukemia occurs in 6% (1% to 10%) of patients with adult ALL at diagnosis, with a higher incidence in T-cell ALL (8%) and mature B-cell ALL (13%).[67] Treatment and prophylaxis of CNS leukemia may consist of intrathecal methotrexate alone or in combination with AC or prednisone, similar intraventricular therapy administered by an Ommaya reservoir, cranial irradiation, or systemic treatment with HDAC or HDM.[68]

Adult ALL patients who do not receive specific prophylactic CNS treatment have a CNS relapse rate of 30% (29% to 32%),[67] similar to that observed in children without CNS prophylaxis.[69]

With intrathecal chemotherapy alone, the rate of isolated and combined CNS relapses can be reduced to 13% (8% to 19%). Intermittent treatment during maintenance therapy improves the outcome in comparison with administration of only a few doses during induction treatment. In most adult ALL trials, additional prophylactic CNS irradiation (24 Gy) has been administered. This combined approach further reduces the CNS relapse rate to 9% (3% to 19%). There is some evidence that early irradiation after remission induction is superior to delayed irradiation during consolidation treatment.[70]

In many recent trials, combined treatment approaches have shown greater efficacy. For high-dose chemotherapy together with intrathecal therapy, the rate of CNS relapses was 7% (2% to 16%); with additional CNS irradiation, the relapse rate was 6% (1% to 13%). The efficacy of intensified CNS prophylaxis was also demonstrated in a retrospective analysis from the M.D. Anderson Cancer Center, in which the lowest CNS relapse rate (2%) was achieved in a trial with early high-dose chemotherapy and intrathecal therapy for all patients.[71]

Because the risk for CNS relapse is associated with other risk factors, such as T-cell ALL, B-cell ALL, extreme leukocytosis, high leukemia cell proliferation rate, high serum lactate dehydrogenase levels, and extramedullary organ involvement, a risk-adapted CNS prophylaxis has been suggested.[71] This approach, however, is not widely used in adults. It should be kept in mind that effective CNS prophylaxis not only reduces the risk of isolated CNS relapse but also improves general outcome. Deescalation of CNS prophylaxis should therefore be done carefully. In the future, the use of liposomal cytarabine for intrathecal therapy might help to reduce the number of intrathecal applications and thereby the risk of contamination and

could improve efficacy with the aim of replacing CNS irradiation in defined populations.

The risk of CNS relapse can also be affected by skill in the performance of the administration of intrathecal chemotherapy. Thus contamination of the CSF with blood at the initial lumbar puncture can be associated with a poor outcome. The lumbar puncture should be done by experienced physicians. Platelet transfusions should be given before in case of low platelet counts, and patients should remain in prone position after intrathecal therapy.[72]

Therapy for Relapsed and Resistant Leukemia

Patients who fail to achieve CR or those who subsequently relapse have been treated with a variety of protocols.[73,74] The repetition of regimens, including vincristine, anthracyclines, and steroids, that are similar to standard induction treatment have led to CR rates of 61% in earlier studies.[73,74] The use of single-agent HDM, HDAC, and probably the anthracycline derivatives mitoxantrone and rubidazone have resulted in a second remission in 30% of patients or fewer, whereas other agents, such as amsacrine, teniposide, and etoposide, are effective in 10% to 15% of patients.

High-dose AC has been extensively studied in relapsed adult ALL. From several small pilot studies comprising 90 patients in total, the weighted mean CR rate was 37%.[75] Higher CR rates (50% to 60%) were achieved with combination regimens that included HDAC and mitoxantrone, amsacrine, or vincristine plus steroids, again with a wide variation that may be attributed to patient selection and nonuniform intensity of pretreatment. Because HDAC is increasingly administered during frontline treatment, its efficacy following relapse might be limited. Therefore, new combinations with idarubicin (46% to 64% CR rate)[76–78] or fludarabine (67% to 83% CR rate)[79,80] have been evaluated. Median remission duration and survival rates have been reported by only a few groups but did not exceed 5 months and 16%, respectively.

HDM followed by rescue with folinic acid combined with asparaginase lead to response rates of 22% to 79% in resistant ALL in early studies.[73] This combination is no longer administered to relapsed patients but is now incorporated in several regimens for patients with de novo ALL.

The most significant predictive factor for treatment response in relapsed patients is the duration of first remission. Patients with longer previous remission (>18 months) have a higher CR rate and longer remission duration compared to those with a short previous remission (<18 months).[81,82] Therefore, decision making concerning therapy should consider the duration of first remission, age, further options, such as SCT, and other factors as summarized in Table 103-7. In patients with late relapse, a modified induction is often successful, whereas in patients with early relapse during intensive chemotherapy, new, experimental or more intensive regimens should be considered. Fortunately, at present, a variety of new drugs for ALL are being evaluated (reviewed by Pui and Jeha,[83] Thomas,[84] and Gökbuget and Hoelzer[85]).

Table 103-7 Factors for Decision Making on Therapy of Relapsed Acute Lymphocytic Leukemia Patients

- Duration of first remission: less than or greater than 18 months
- Prior therapy (drugs/cycles) not used before
- Available targets
  - Subtype: B-precursor versus T-ALL
  - Antigens: Available monoclonal antibodies
  - Molecular markers: Available kinase inhibitors
- Localization of relapse

For all chemotherapy regimens, the duration of second remission is usually short (<6 months), and the only curative approach for adult patients with relapsed or resistant ALL is SCT. The major aim of relapse treatment is the induction of a second remission with sufficient duration to permit preparation for SCT. Three large study groups have reviewed the outcome of relapsed ALL patients recently. The Medical Research Council's UK-ALL study found a 5-year survival rate of 7% in 609 patients with first relapse. Survival rates were poor in all subgroups, including younger (<20 years) versus older patients (12% versus 3%), short (<2 years) versus longer duration of first remission (11% versus 5%), and immunophenotype. One hundred twenty patients were able to receive a SCT after relapse, with survival rates of 15% for autograft, 16% for unrelated SCT, and 23% for sibling allogeneic SCT after 2 years.[86] The French group reported a rate of second remission of 44% in 421 relapsed patients with a LFS rate of 12% after 4 years. They identified transplantation during second CR and longer duration of CR (>1 year) as favorable prognostic factors.[87] The German group observed an improvement of outcome for relapsed T-ALL patients after more frequent application of experimental drugs, including nelarabine, and performance of SCT in up to 70% of the patients who achieved a second CR.[88] Thus, all attempts, including experimental drugs, should be directed toward obtaining a second remission and proceeding with SCT.

Stem Cell Transplantation

SCT has gained an increasingly important role in the treatment of patients with adult ALL. Although the majority of large prospective studies in adult ALL addressed the issue of indications for SCT in first CR, scheduling and procedures have still not been defined satisfactorily. To circumvent the problem with comparability of SCT and chemotherapy, several groups have constructed prospective trials with a "genetic" randomization offering allogeneic SCT in first complete remission (CR1) to all patients with a sibling donor. The study results certainly depend on the "conventional" treatment approach that is used in the chemotherapy arm. Some groups scheduled autologous SCT only; others included a randomized comparison of autologous SCT and chemotherapy.

The most difficult outcome parameter is the OS of the total patient cohort in a prospective trial that answers the question as to whether a SCT-based treatment concept is able to improve overall outcome. OS rates in studies with "genetic randomization" have not documented that transplant is superior to chemotherapy;[85] this could be due partly to the fact that allogeneic SCT was implemented in only 11% to 38% of the patients.[54,89–94] Even if allogeneic SCT yielded favorable results, because of its infrequent implementation, the impact on OS is too small.

Allogeneic Stem Cell Transplantation from Sibling Donors

The outcome of allogeneic SCT for patients with ALL depends on the age and remission status of the patient. The best results have been obtained in patients who were transplanted during the first remission. In a total of 1100 patients collected from published trials, the LFS rate was 50%, albeit with wide variations (21% to 66%). The relapse probability (RP) was 24%, and the transplant-related mortality (TRM) rate was 27% (Table 103-8). In more recent studies, results are improving, most probably because of a reduction in TRM.[95] According to the data of the International Bone Marrow Transplantation Registry for HLA-identical sibling SCT between 1996 and 2001, the 3-year probability of survival was 48% for ALL recipients older than 20 years of age who were transplanted during their first remission.[96]

There is evidence that graft-versus-leukemia (GvL) effects are also operational in ALL patients who receive an allograft, because several

Table 103-8 Results of Stem Cell Transplantation in Adult Acute Lymphocytic Leukemia Patients

Type of SCT	Stage	*N*	Transplant-Associated Mortality Rate (%)	Relapse Rate (%)	Leukemia-Free Survival Rate (%)
Allogeneic					
Family donor	CR1	1100	27	24	50
	≥CR2	1019	29	48	34
	Relapsed/Refractory	216	47	75	18
Unrelated donor	CR1	318	47	10	39
	≥CR2	231	8	75	27
	Relapsed/Refractory*	47	64	31	5
Autologous	CR1	1369	5	51	42
	≥CR2	258	18	70	24
Nonmyeloablative	All stages	132	42	47	23

*One trial.[185]

studies have shown that the RP is lower in patients with limited graft-versus-host (GvH) disease.[97–100] Age is another important prognostic factor for outcome after SCT. The LFS rate is 62% for patients below 20 years of age and 48% for those above 20 years of age.[96] Nevertheless, age limits for allogeneic matched sibling SCT have been increased continuously up to 50 to 55 years. The experience of transplant centers may also have a role. Specialized centers in the United States report LFS rates of 61% to 64% for sibling SCT in ALL in first remission.[101–103]

The LFS rate is 34% after allogeneic SCT in second remission. In advanced ALL (refractory or in relapse), allogeneic SCT results in an 18% long-term survival rate (see Table 103-8). Despite this, SCT is the treatment of choice in patients with relapsed or refractory ALL.

Matched Unrelated Donor Stem Cell Transplantation

SCT using grafts from matched unrelated donors can result in a long-term survival rate of 39% in patients with a lower RP (10%) as compared to allogeneic sibling SCT, whereas the TRM rate (47%) is higher. Both facts are probably due to more pronounced GvL and GvH effects. It should be considered, however, that matched unrelated donor (MUD) series generally include selected high-risk patients, such as patients with a high proportion of Ph/BCR-ABL-positive ALL. In the International Bone Marrow Transplantation Registry in adults older than 20 years, the 3-year probability of survival after MUD SCT in CR1 was 42%.[96] In the largest series so far, the results of MUD SCT were analyzed retrospectively in adult poor-risk ALL (mainly Ph/BCR-ABL-positive) patients with a median age of 34 years. They were particularly favorable for patients in CR1 (42% at 2 years), whereas in second or subsequent CR, the LFS rate was only 17%.[104] The RP of only 6% for patients in CR1 may be due to a more pronounced GvL effect. The high TRM rate of approximately 40%[104,105] is still the major obstacle to MUD SCT (see Table 103-8). This might be reduced by the use of different, less toxic preparative regimens, including nonmyeloablative SCT, better management of GvH disease, and improved supportive care.

Overall, the results of MUD SCT in ALL are encouraging, particularly considering that these are often patients with advanced stages of disease. There is increasing evidence that results of MUD SCT are approaching those of sibling SCT, particularly if adjusted for bias (see later discussion). MUD SCT is therefore the treatment of choice for high-risk patients in CR1, including Ph/BCR-ABL-positive ALL-and probably also other high-risk patients, if a sibling donor is not available.

In later remission or relapse, MUD SCT may lead to long-term survival rate of 27%, whereas the long-term survival rate after transplantation in relapse is only 5% (see Table 103-8).

Autologous Stem Cell Transplantation

Another attempt to overcome the limited availability of bone marrow donors is autologous SCT. The results for autologous SCT in first remission are surprisingly good, with an LFS rate of 42% and a low TRM rate (see Table 103-8). The major problem is a high RP (51%). Similar results with LFS rate of 42% in standard-risk ALL ($N = 280$) and 40% in high-risk ALL ($N = 174$) have been reported by the European Bone Marrow Transplant Group.[106] Favorable results have been achieved in a trial with autologous bone marrow transplantation or peripheral blood stem cell transplantation in adult ALL patients in first CR followed by a 2-year maintenance treatment with 6-mercaptopurine and methotrexate.[107]

The TRM rate after autologous SCT is very low (3%) and is similar to that of conventional intensification therapy. With the increasing number of MUD transplants being performed and the advantage of GvL effects, the role of autologous SCT is decreasing. However, because of the low TRM rate, this is still a reasonable approach for elderly patients and probably patients with negative MRD status in autologous bone marrow graft. Several prospective randomized trials in adult ALL showed equal outcomes for chemotherapy consolidation and autologous SCT (see later discussion).

In second remission, few patients obtain long-term survival with auto SCT (see Table 103-8). It may be considered as interim therapy before an allogeneic SCT if autologous stem cells have been collected during CR1.

Nonmyeloablative Stem Cell Transplantation

Nonmyeloablative SCT (NMSCT), a reduced-intensity conditioning regimen, is a novel approach that deserves evaluation in ALL and could lead to an extension of indications for allogeneic SCT. In contrast to conventional SCT, which mainly relies on cell kill by high-dose chemotherapy and total-body irradiation, NMSCT uses GvL effects. Immunosuppression (e.g., with purine analogs, other cytostatic drugs, or low-dose total-body irradiation) is followed by the infusion of stem cells from sibling or MUD donors with adapted immunosuppression to establish host tolerance.[108]

However, the general opinion is that GvL effects are less pronounced in ALL than in other malignancies. Nevertheless, these effects are present, as is indicated by the lower relapse rate in patients with acute or chronic GvH disease,[98–100]the lower relapse rate after MUD SCT, induction of remissions by withdrawal of GvH disease

prophylaxis, or donor lymphocyte infusions in single patients with relapsed ALL.

NMSCT is being increasingly considered as an option for elderly patients who have contraindications for conventional SCT. Initial results indicate that in CR1, stable remissions can be achieved in some patients.[109] These studies show a LFS rate of 23% for patients in all stages, with a 42% TRM rate and a 47% relapse rate (see Table 103-8). According to a European Bone Marrow Transplant Group analysis, the LFS rate in 91 adult ALL patients with a median age of 40 years was 18%, with a 24% TRM rate and a 58% relapse rate.[110] The LFS rate in both studies was considerable higher if NMSCT was performed in patients in first remission.[109,110]

Results of Umbilical Cord Blood and Haploidentical Stem Cell Transplant

The experience with umbilical cord blood transplantation in ALL mainly comes from pediatric patients. However, registry results of younger adults with acute leukemia indicate that umbilical cord blood (single or double) can be considered as an alternative donor source if available.[111]

The experience with haploidentical SCT is restricted mainly to pediatric patients, for whom it may be considered in patients without a donor and with an urgent need of SCT. In adult patients with acute leukemia, a retrospective analysis indicated that if feasible, autologous SCT is preferable to haploidentical SCT; despite a higher relapse rate, the overall outcome was slightly superior.[112] On the basis of the available experience, both approaches should be restricted to specialized centers and a later stage of disease and should be performed as part of a clinical trial.

Comparison of Different Transplantation Procedures and Transplantation versus Chemotherapy

ALLOGENEIC SIBLING AND MATCHED UNRELATED DONOR STEM CELL TRANSPLANTATION. Owing to improved supportive care, better donor selection, and extension of indications beyond very high-risk patients, the results of MUD donor SCT are similar to those of allogeneic sibling SCT. The prospective Medical Research Council/Eastern Cooperative Oncology Group study of SCT showed in 321 patients with allogenic sibling donor SCT a survival rate of 55% (standard and high-risk ALL) compared to 46% with MUD donor SCT in 67 patients with very high-risk (Ph/BCR-ABL-positive) ALL.[92] A study of nine German centers showed in CR1 a higher proportion of MUD donor SCT (60% versus 27%), and there was no difference regarding LFS rate (45% versus 42%).[113] The TRM rate for allogeneic sibling SCT ranged in prospective trials between 15% and 26%[54,89–94] and reaches 35% in MUD-SCT.[92] Several factors, such as intensity of therapy before SCT, preparative regimens, immunosuppressive therapy after SCT, and the experience and conditions at SCT centers, could play a role. However, MUD SCT appears to be a reasonable option for high-risk patients without a sibling donor.

DONOR VERSUS NO-DONOR COMPARISONS. This type of comparison represents the intent-to-treat analysis, which is an adequate approach only if a significant number of patients actually receive the assigned treatment option. Several trials did not show differences in outcome for patients with (intent to treat: allogeneic sibling SCT) or without donors (intent to treat: randomization of autologous SCT and chemotherapy).[54,94,114–116] The PETHEMA study for high-risk patients even showed a trend toward an advantage for patients without donors.[93] In contrast, several other studies demonstrated an advantage of SCT in high-risk patients.[90,91,115]

Recently, the large Eastern Cooperative Oncology Group/Medical Research Council group reported their preliminary results comparing patients with donors (allogeneic sibling SCT) to those without donors (randomized comparison of chemotherapy and autologous SCT). The special feature of this trial was the use of age (younger and older than 35 years) as a prognostic factor. Standard-risk patients were by definition younger than 35 years with WBC less than 30000/μL for B-precursor and less than 100,000/μL for T-ALL. Overall, patients with a donor had a superior OS rate (53%) compared to those without donor (45%) mainly due to a lower RP (29% versus 54%). The difference was particularly evident in standard-risk (63% versus 51% OS rate) patients but not in high-risk (39% versus 36%) patients,[117] a finding that is in contrast to all other trials. Because a younger age was the major factor for definition of standard risk, this result can be interpreted in two ways: (1) The outcome of SCT is better in younger patients, which is a well-known fact, and (2) the outcome in young standard-risk patients with a donor is not superior to that of chemotherapy in other trials. A third issue is the fact that the performance of SCT was limited (321 allogeneic sibling SCT in 1508 evaluable patients).[92] The TRM rate reached 20% even in standard-risk patients. The OS rate of 38% in this trial was similar to that in other studies.[118]

CHEMOTHERAPY OR ALLOGENEIC SIBLING STEM CELL TRANSPLANTATION VERSUS AUTOLOGOUS STEM CELL TRANSPLANTATION. In several randomized studies, no significant difference was detected in studies that compared chemotherapy and autologous SCT.[89,90,93,94] In the large randomized Eastern Cooperative Oncology Group/Medical Research Council trial, the outcome of autologous SCT was inferior (33%) to that of chemotherapy (42%) in terms of LFS rate, mainly owing to a higher RP.[117] Comparisons of allogeneic and autologous SCT have shown an inferior outcome for autologous SCT. In two trials with an intent-to-treat comparisons, the results of autologous SCT were poor (30% and 33%).[91,119]

Preferred Approach to Stem Cell Transplantation

A recently published evidence-based review emphasized that SCT offers an advantage as compared to chemotherapy in high-risk patients and in patients in second remission. The analyses also revealed the lack of prospective, controlled trials for SCT in ALL.[120] This is probably because every study design that includes SCT by definition has too many variables, such as donor availability, individual patient condition, and patient wish. Not surprisingly, a meta-analysis of seven studies[54,90,91,93,94,115,121] showed a broad variation in rates of performance of allogeneic (68% to 96%) and autologous (9% to 81%) SCT. The meta-analysis showed a correlation of outcome with compliance to allogeneic SCT. Again the OS rate for SCT was superior to that for chemotherapy, with a particular advantage in high-risk patients.[122] Therefore, the role of allogeneic SCT in standard-risk ALL remains unclear.

In ongoing trials, indications for SCT in first remission are not uniformly defined. The advantages of SCT (short treatment duration, favorable outcome in some trials) must be compared to the disadvantages (TRM, late complications, poorer quality of life). The major question is whether all patients with sibling donor should proceed to SCT or only those with specific risk factors.

When considering SCT, one has to balance the expected reduced relapse risk and the increased anticipated mortality. Also late effects are more pronounced in SCT patients, the quality of life seems to be poorer, and the risk of procedure related death is 20% to 30% compared to chemotherapy with more prolonged risks. SCT in CR1 from a sibling or unrelated donor seems to be justified in subgroups of ALL with OS rate below 40% with chemotherapy and should probably not be offered to patients with OS rate after chemotherapy above 50%. These outcomes clearly depend on the different chemotherapy regimens that are used.

Therefore, in the majority of trials, SCT indications are determined by the presence of adverse prognostic factors. The status of MRD is of increasing importance as an indication for the SCT. It remains open to further studies whether SCT is really a favorable option in patients

Table 103-9 Indications for Stem Cell Transplantation in the German Multicenter Trials for Adult Acute Lymphocytic Leukemia Patients

	Indication	Priorities*
First remission		
High risk	All patients within 3–4 months from diagnosis	1. Allogeneic sibling† 2. Allogeneic unrelated† 3. Autologous 4. NMSCT
Standard risk	Molecular nonresponders	See above
Relapse including molecular relapse	All patients in second CR (if necessary in good PR or beginning relapse)	See above (Consider cord blood or haploidentical SCT if no donor available.)

*Decision depends on age, patient's general condition, and donor availability.
†Matched or one mismatch.

with high MRD and whether patients with high-risk features but negative MRD status are still candidates for SCT. Allogeneic sibling and MUD SCT are considered in a similar way. Although outcome after SCT is better in younger patients, there is a trend to treat adolescents with pediatric-type intensive chemotherapy protocols and to proceed less with transplantation. For older high-risk patients and those with contraindications, nonmyeloablative SCT is a reasonable alternative, with an expected LFS rate of 34% in first CR.[110]

There is general agreement that all patients in second or later remission are candidates for SCT. Depending on donor availability and the patient's general condition, experimental procedures such as NMSCT, cord blood SCT, and haploidentical SCT may be considered.

Table 103-9 outlines the indications of SCT in the German multicenter study group for adult ALL as an example for a risk-adapted approach.

OUTCOME OF ALL SUBTYPES AND PROGNOSTIC FACTORS

Age is probably the most important prognostic factor for achievement of CR and long-term outcome.[62] Other prognostic factors are of greater importance for duration of remission and survival (Table 103-10). Appreciation of the impact of such risk factors (Table 103-11) on the results in the majority of adult ALL trials have led to the generation of risk-adapted treatment protocols (Table 103-12).

Age

Survival of patients with adult ALL decreases continuously with increasing age from 34% to 57% below 30 years to 15% to 17% above 50 years [28,44,54,118,123] also in recent studies. Some groups used age above 30 to 35 years as an indication for SCT in CR1.[91,93] This is probably counterproductive, since the outcome of SCT decreases significantly with age.[117] Increasing attention is being paid to the definition of specific treatment approaches for adult ALL patients at both ends of the age spectrum, which means adolescents on one hand and the elderly patients on the other.

Elderly Patients

The CR rate is about 50% in patients at the age of 50 to 88 years with a remission duration of 3 to 12 months and a survival rate below 10% (reviewed by Hoelzer and Gökbuget[124] and Pagano and colleagues[125]). It is difficult to define an age limit when a change in

Table 103-10 Outcome of Adult Acute Lymphocytic Leukemia Patients According to Subgroups*

Subgroup	No. of Patients	Complete Remission Rate (%)	No. of Patients	Leukemia-Free Survival Rate (%)
Age				
<30	669	88	510	42
30–59	610	79	412	33
≥60	215	58	141	15
Subtype				
T-ALL†	976	88	850	40
B-precursor ALL	2366	82	2036	40
Pro-B-ALL	987	75	107	37
Cytogenetics				
Ph/BCR-ABL+ (without imatinib)	633	72	633	21
Ph/BCR-ABL+ (with imatinib + chemotherapy)		90		50
White blood cell count				
<30,000/μL	698	81	746	40
>30,000/μL	387	75	409	28
Time to complete remission				
<4 weeks			1433	44
>4 weeks			253	36

*Pooled data from published studies.
†Depends on T-ALL subtype.

Table 103-11 Adverse Prognostic Factors for Remission Duration in Adult Acute Lymphocytic Leukemia Patients*

Clinical characteristics	Higher age: >50 years, >60 years	
	High white blood cell count: >30000/μL in B-lineage	
Immunophenotype	Pro-B (B-lineage, CD10–), CD10 negative pre-B-ALL	
	Early T (T-lineage, CD1a–, sCD3–)	
	Mature T (T-lineage, CD1a–, sCD3+)	
Cytogenetics/ molecular genetics	t(9;22)/BCR-ABL or t(4;11)	
	ALL1-AF4	
	New molecular markers for T-ALL	
Treatment response	Late achievement of complete remission	>3 or 4 weeks
	Minimal residual disease positivity	

*Adverse prognostic factors as they emerged from the more than 3000 adult ALL patients treated in the GMALL (German Multicenter Studies for Adult ALL) trials.

Data from Gökbuget N, Hoelzer D, Arnold R, et al: Treatment of adult ALL according to the protocols of the German Multicenter Study Group for Adult ALL (GMALL). Hemat/Oncol Clin North Am 2000;14:1307–1325.

prognosis occurs. Almost all studies use a cutoff point at the age of 55 to 65 years to determine eligibility for allogeneic HSCT. This age seems to be practical because younger patients are candidates for intensified treatment approaches, such as SCT, whereas for the older group, new strategies need to be explored, the gain in survival being carefully weighed against quality of life. Elderly patients at the age of 55 to 65 years or even older who have achieved a CR and are in good clinical condition are potential candidates for autologous SCT or NMSCT.

Several factors such as comorbidity, higher risk of complications, and increased risk of early mortality are associated with the inferior results in elderly patients. The major cause of death is infections. Therefore, the increased hematologic toxicity with prolonged severe cytopenias is of particular relevance in elderly patients. Often, it cannot be distinguished whether these are due to toxicity or to lack of response. There is the dilemma that, on one hand, the disease is more resistant in the elderly and, on the other hand, the tolerability of therapy is lower and there is a higher risk of organ toxicities, such as in the liver and heart. Altogether, comorbidities and complications lead to treatment delays, omission of single drugs, and prolonged intervals between therapy cycles, which contribute to poorer long-term results. There is also a lower incidence of favorable prognostic subtypes such as T-ALL in the elderly, whereas the incidence of unfavorable subtypes is higher.[126]

Palliative therapy is associated with a short survival[124] (Table 103-13). With the use of intensive chemotherapy protocols developed for younger patients, the CR rate in the elderly was 56%, with 23% early mortality and a median survival of 9 months. It can be assumed that only elderly patients who were in good general condition were accepted to these trials. Thomas and colleagues showed in

Table 103-12 Preferred Approach to the Treatment of Adult Acute Lymphocytic Leukemia Patients

	Low-Risk ALL	High-Risk ALL	Very High-Risk ALL	Mature B-ALL
Definition	B-lineage	B-lineage	Ph/BCR-ABL+	
	WBC < 30,000/μL	WBC > 30,000/μL		
	Time to CR < 4 wks	Time to CR > 4 wks		
	Molecular CR	No molecular CR		
	No pro-B/ t(4;11)	Pro-B/ t(4;11)		
	T-lineage	T-lineage		
	Thy ALL	Early T, mature T		
Multidrug-Induction	Yes	Yes	Yes + imatinib	Short intensive cycles including HDM, fractionated C, HDAC, and other drugs
CNS prophylaxis*	Yes	Yes	Yes	Yes
Consolidation (also other combinations)	Alternating cycles (e.g., HDM, HDAC, Asparaginase reinduction)	One cycle	One cycle + imatinib	6 cycles
SCT in CR1	None	Allogeneic SCT (if matched related or unrelated donor)		None
		Autologous SCT (if no donor and negative MRD, after additional consolidation)		
Maintenance	6-MP/M + intensification for 2–2½ years			None

AC, cytosine arabinoside; ALL, acute lymphocytic leukemia; CR, complete remission; HDM, high-dose methotrexate; MRD, minimal residual disease; SCT, stem cell transplantation; Thy ALL, thymic ALL; WBC, white blood cell count.

*Intrathecal therapy with M or triple combination (M, AC, steroid) continued during maintenance therapy; additional CNS irradiation and/or high-dose chemotherapy according to subgroup.

Table 103-13 Treatment Results in Elderly Acute Lymphocytic Leukemia Patients

Approach	No. of Studies	No. of Patients	Clinical Remission Rate (%)	Early Mortality Rate (%)	Median Overall Survival
Palliative	4	94	43	24	7 months
Intensive chemotherapy	11	519	56	23	14%
Prospective studies	5	187	58	16	22%

three successive treatment periods that the remission rates of elderly patients could be improved by the adoption of specific age-adapted protocols.[127] Fortunately, there is a new trend to develop prospective trials for elderly patients in order to offer a curative option on one hand and to limit toxicity, early mortality, and duration of hospitalization on the other hand in order to maintain quality of life. With these approaches, the more favorable remission rates of 58% and survival rate of 22% have been achieved.[124]

Further improvement of results in the elderly is urgently required. Innovative strategies are based on targeted, subgroup-specific elements with the aim not to increase the typical chemotherapy associated toxicity. This includes use of the abl-kinase inhibitor imatinib for Ph+ ALL, and antibody therapy for CD20-positive ALL (rituximab). The German study group reported a remission rate of 63% in CD20-positive (Ph/BCR-ABL-negative) elderly patients and a survival rate of 54% after 1 year with a regimen combining age-adapted chemotherapy and eight doses of Rituximab before the chemotherapy cycles.[128] In elderly patients with Ph/BCR-ABL-positive ALL, the remission rate can be improved above 90% with imatinib monotherapy (see later discussion).

Adolescent Patients

In recent years, the optimal approach to treatment of adolescents has been discussed extensively. Several groups have compared the outcome of adolescents treated with adult protocols with the outcomes of those treated with pediatric protocols. Although entry criteria were quite similar, the outcome was always significantly inferior in those who participated in the adult trials (event-free survival rate: 34% to 71%) as compared to the pediatric trials (event-free survival rate: 64% to 80%).[129] The conclusion was that pediatric trials include higher doses of VCR, ASP, and HDMTX and a higher time-dose intensity. However, the poor outcomes that are associated with most adult protocols are probably also due to suboptimal approaches in these specific studies. The GMALL reported a survival rate of 64% in 417 young adults (15 to 25 years) with significant differences in outcome for subgroups ranging from 74% for standard risk to 49% for high risk and 55% for Ph+ ALL.[130] Results are superior to most of those that have been reported from adult protocols in adolescents but are still at the lower end of range for pediatric trials. Therefore, further improvement of outcome in adolescents is required.

One solution could be the extension of age limits of pediatric protocols to 25, 35, or even higher ages as is currently being attempted by several U.S. groups. It remains open to question whether a sufficient number of adults will actually be treated in these studies and whether the application of such intensive regimens will be restricted to selected patients and selected, highly experienced pediatric centers.

The other option, which is currently followed by several adult study groups, is to adopt more successful pediatric treatment elements in their protocols and to aim for a higher time and dose intensity with fewer treatment interruptions and omissions, particularly in adolescents and young adults. Interim results of such studies were reported recently. The CR rates (82% to 92%) and event-free survival rate (66% to 72%)[131–133] are promising, but considerable toxicity, such as neuropathies and thrombosis, was observed, indicating that these protocols may probably not be transferable to all adults.

White Blood Cell Count

An elevated WBC at diagnosis (>30 to 50.000/μL) is associated with a higher risk of relapse.[28,44,54,89,123] It was even considered as the most deleterious prognostic factor in B-precursor ALL, with an OS rate of 19% to 29%[118,134] whereas in T-ALL, WBC has no significant effect on outcome in a GMALL multivariate analysis.[134] The biologic reason for the highly resistant behavior of B-precursor ALL with high WBC is unclear. In the GMALL studies, these patients show a high relapse rate but also seem to have a higher mortality rate with chemotherapy and SCT.[135] In these patients, evaluation of MRD, use of experimental drugs, and SCT modalities seem to be particularly important.

Immunophenotype and Cytogenetics

The immunophenotype is an important independent prognostic variable in ALL. In ongoing trials, it is used to adjust treatment regimens accordingly (e.g., separate regimens for mature B-cell ALL). A further example for clinical application is the identification of patients for antibody therapy (e.g., anti-CD20 in CD20-positive B-lineage ALL or B-cell ALL or anti-CD52 in B- and T-lineage ALL).

T-Lineage Acute Lymphocytic Leukemia

Results of treatment of T-cell ALL have substantially improved in comparison with survival rates of 10% 20 years ago. Many groups have confirmed the superior outcome of T-lineage ALL as compared to B-lineage ALL.[118,134] There is, however, a substantial difference in outcome for the T-ALL subtypes. Thymic T-ALL, which accounts for one half of the adult T-ALL patients, has a favorable outcome with CR rates of 85% to 90% and survival rates greater than 50% at 5 years. Early T-ALL and mature T-ALL have poorer outcomes with CR rates of 70% and LFS rates of approximately 30%.[134] The biologic importance of immunophenotype was underlined by the fact that elevated expression of HOX11, HOX11L2, SIL-TAL1, and CALM-AF10 is associated with subtypes, that is, maturation states of thymocytes (reviewed by Grabher and colleagues[136]). Other groups observed inferior outcomes for early T-ALL;[137,138] coexpression of CD13, CD33, and/or CD34;[37] HOX11L2; and SIL-TAL-positive T-ALL.[138] The German group reported poor survival associated with overexpression of ERG and BAALC.[139,140] Overexpression of HOX11, which is associated with thymic T-ALL, may confer a favorable prognosis. Notch1-activating mutations with so far unclear prognostic relevance were identified in up to 50% of T-ALL cases.[136] They may be targeted by γ-secretase inhibitors. Five percent of T-ALL show the NUP214-ABL1 aberration, which may identify a target population for imatinib therapy.[141]

The addition of cyclophosphamide and AC to the usual cytostatic drugs for ALL is mainly responsible for the improved outcome in T-ALL. HDM contributed to the improvement of survival in children,[142,143] as did HDAC.[144,145] For adults, the benefit of HDM in T-cell ALL has to be confirmed in larger trials. With current treatment regimens, CR rates of more than 80% and a LFS rate above

50% can be achieved in T-ALL. New treatment approaches in adult T-ALL include purine analogs, such as nelarabine[132] and forodesine,[146] or antibody therapy (e.g., anti-CD52).

B-Lineage Acute Lymphocytic Leukemia

In common and pre-B-ALL, CR rates in adults have improved to 80% or more, but patients still relapse in most studies over a period of up to 5 to 6 years, and only one third of these patients survive. With B-precursor ALL, prognostic factors are decisive for outcome; high-risk patients with adverse prognostic features, such as high WBC (>30,000/μL), late achievement of CR (>3 to 4 weeks), and Ph/BCR-ABL-positive status (see Table 103-11) have a survival rate of 25% or less, whereas standard risk patients without any of those features have a 5-year survival rate greater than 50%.[134]

Philadelphia chromosome/BCR-ABL-positive ALL had until recently been associated with the worst prognosis in children, as well as in adults. Outcome has now improved dramatically (see later discussion).

Adults with the subtype pro-B ALL or the t(4;11) translocation have a poor prognosis, as do infant ALL patients.[147] With intensive regimens, including HDAC and mitoxantrone as consolidation therapy, the results for adults seem to be improving.[55] Pro-B-ALL patients benefit from allogeneic SCT in CR1, with survival rates of 60% in transplanted patients.[148] The adverse impact of the translocation t(4;11) seems to have changed with new treatment modalities (see earlier).

In mature B-cell ALL, CR remission rates were low (40%) a decade ago, and remission duration was short (11 months).[149] A change was brought about by innovative childhood B-cell ALL studies that significantly improved outcome, with CR rates of 80% to 94% and an LFS rate of 63% (weighted mean).[149] The drugs that were responsible for the improvement were high doses of fractionated cyclophosphamide, HDM (0.5 to 8 g/m^2), and HDAC in conjunction with the conventional drugs for remission induction in ALL, given in short cycles at frequent intervals over a period of 6 months.

The application of these childhood B-cell ALL protocols in original or modified form also brought a substantial improvement in adult patients with B-cell ALL. CR rate reached 75% (62% to 83%) and the LFS rate of 55% (20% to 71%).[149–151] Adverse outcome prognostic factors were late CR (more than two cycles of chemotherapy), high WBC (>30 × 10^9/L), and age older than 50 years. B-cell ALL has a higher incidence of CNS involvement at diagnosis and of CNS relapse. Therefore, effective measures against CNS disease, such as HDM and HDAC, as well as intrathecal therapy, are important components of treatment regimens. Maintenance treatment has been omitted. Because relapses occur almost exclusively within the first year in childhood, as well as in adult B-cell ALL studies, patients thereafter can be considered to be cured.

Further significant improvement was achieved by the addition of antibody therapy with anti-CD20 (rituximab) because more than 80% of the patients are CD20-positive. With these regimens, survival rates above 70% to 90% can be achieved in adults with mature B-ALL or Burkitt's lymphoma.[152,153]

The translocations t(8;14), t(8;2), and t(8;22) or c-myc aberrations are present in most cases of mature B-cell ALL and in Burkitt's lymphoma. They may add information in cases with uncertain diagnosis. They have lost their poor prognostic significance, however, because of the improved treatment for patients with B-cell ALL or Burkitt's lymphoma.

Treatment Response and Minimal Residual Disease

Beside age, the most relevant prognostic factor in ALL is still the achievement of CR. Further prognostic factors related to treatment response are delayed time to CR or response to prednisone therapy. A more accurate approach to assess individual response is evaluation of MRD,[62,154] since this is an independent prognostic factor that reflects primary drug resistance as well as individual completion of therapy and unknown host factors. The methods for detecting the burden of MRD have been described earlier and are summarized in Table 103-14.

Identification of High-Risk Patients as Candidates for Stem Cell Transplant or Experimental Therapy

After the start of consolidation, a high burden of MRD (>10^{-4}) at any time point is associated with a high relapse risk of 66% to 88%,[53] and the predictive value increases at later time points (months 6 to 9).[155] In the GMALL studies, patients with a high burden of MRD (>10^{-4}) after induction and first consolidation were identified as high risk and were considered candidates for SCT in CR1.[156]

Identification of Low-Risk Patients in Whom Treatment Intensity Reduction May Be Justified

This aim is more difficult to reach. An early and rapid decrease of MRD during induction is associated with a relapse risk rate of only 8%.[53] However, this course is observed in only 10% of the patients. In the GMALL studies, patients with negative MRD status after induction, which is repeatedly confirmed during first year and measured with two sensitive markers, are considered as MRD low risk.

Assessing molecular CR, thereby evaluating different induction therapies and detecting molecular relapses, are two important new items for follow-up analysis in adult ALL. Molecular response provides a more individual impression of the response and is particularly important, since nowadays, 85% to 90% of adult ALL patients achieve a cytologic CR. Even in phase II studies, molecular relapse is already an inclusion criteria. This makes sense, since patients with an increase of MRD burden above 10^{-4} after achievement of a molec-

Table 103-14 Methods for Detection of Minimal Residual Disease in Acute Lymphocytic Leukemia Patients

Method	Target	Sensitivity	Application B-Lineage ALL (%)	T-Lineage ALL (%)
Flow-Cytometry	Leukemia-specific immunophenotype	10^{-4}	~35	>90
PCR	Fusion transcripts	10^{-4}–10^{-6}	~30	~10
PCR	Ig rearrangements (IgH, IgK)	10^{-4}–10^{-6}	>90	~20
PCR	TCR rearrangements (TCR-β, -δ, -γ)	10^{-4}–10^{-6}	~50	>90

IgH, immunoglobulin gene; PCR, polymerase chain reaction; TCR, T-cell receptor gene.

Data from Campana D, Pui C-H: Detection of minimal residual disease in acute leukemia: Methodological advances and clinical significance. Blood 1995;85:1416–1434; Beishuizen A, van Wering E, Breit TM, et al: Molecular biology of acute lymphoblastic leukemia: Implications for detection of minimal residual disease. In Hiddemann W, et al (eds): Acute Leukemias: V. Experimental Approaches and Management of Refractory Disease. Berlin, Springer-Verlag, 1996, p 460.

ular CR are at high risk of relapse (>80%), and therapeutic action should be taken.[157]

Risk Stratification According to Minimal Residual Disease

The approaches to integrate MRD analysis in prospective risk stratification of adults can be different in terms of (1) in the time points sampled, (2) the selection of patients for MRD risk stratification, (3) combination of MRD-based and conventional risk factors, and (4) the MRD-based treatment decisions. It is hardly possible to identify adult low-risk patients in whom reduction of the intensity of therapy would be justified. In the GMALL study, these patients are defined according to very strict criteria (see previous discussion) in order to omit maintenance therapy. However 20% to 30% of these patients relapsed. The major aim in MRD-based studies is therefore to identify patients who have a high risk of relapse for treatment intensification with SCT. It remains to be demonstrated that this is an effective strategy, since patients with high MRD before SCT have an increased risk of relapse and might benefit from additional conventional therapy, or even experimental therapy, to reduce tumor load. On the other hand, it has to be questioned whether patients who are candidates for SCT on the basis of conventional risk factors, including Ph+ ALL, should receive allogeneic SCT if they are MRD-negative. The best strategy remains unknown.

Evaluation of the burden of MRD has not been without problems. The technical procedure is time-consuming, expensive and requires highly specialized staff. The predictive value depends on the technical quality, such as sensitivity (10^{-4}), the number of targets (at least two for immunoglobulin or T-cell receptor rearrangements), and the frequency of evaluations (3-monthly). At least in multicenter studies, these prerequisites often cannot be fulfilled. Sensitivity of the evaluation of MRD, with the exception of BCR-ABL-based analysis, is also insufficient to evaluate the efficacy of consolidation cycles because, in most patients, MRD is below the detection limit.

Drug Resistance

MDR-1 function has been associated with a poorer prognosis.[137,158] In vitro sensitivity testing was able to identify patients who had resistance to conventional cytostatic drugs, which was associated with an inferior prognosis. More recently, it was demonstrated that in vitro resistance is associated with distinct gene expression profiles.[159] In vitro resistance testing is also increasingly used for effectiveness testing of new cytostatic drugs. In the future, a prediction of response to induction regimens might be possible in order to adapt therapy to individual susceptibility.

NEW THERAPEUTIC APPROACHES IN ADULT ALL TREATMENT WITH MONOCLONAL ANTIBODIES

ALL blast cells express a variety of specific antigens, such as CD20, CD19, CD22, CD33, and CD52, which may serve as targets for treatment with monoclonal antibodies (Table 103-15). Monoclonal antibody therapy is an attractive approach, since it is targeted, subtype specific, and, in comparison to chemotherapy, has different mechanisms of action and side effects. One prerequisite for antibody therapy might be the presence of the target antigen on at least 20% to 30% of the blast cells. Application might be most promising in combination with MRD (reviewed by Gökbuget and Hoelzer[160]).

Table 103-15 Expression of Surface Antigens on Acute Lymphocytic Leukemia Blast Cells

Subgroup	Antigen	Expression on More Than 20% of Lymphatic Blast Cells*
B-lineage	CD19	95% precursor
		94% mature
	CD20	41% precursor
		86% mature
	cyCD22	17%
T-lineage	CD25	
	CD7	99%
	CD3	33%
Both	CD52	66%–78%†
	CD33	16%

*Data from the GMALL central immunophenotyping, E. Thiel, S. Schwartz, Berlin.
†Data from Faderl S, Kantarjian HM, O'Brien S, et al: A broad exploratory trial of Campath-1H in the treatment of acute leukemias. Blood 2000;96:1397a.

Anti-CD20

Most experience exists so far with rituximab, which is a chimeric monoclonal antibody to CD20 that is expressed on normal and malignant B-lymphocytes. It exerted significant antitumor activity, and its use has led to an improvement of results in B-cell NHL. however, CD20, defined as expression on more than 20% of the blast cells, is also present on one third of B-precursor ALL blasts, particularly in elderly patients (40% to 50%), and the majority of mature B-ALL blast cells (80% to 90%).

The anti-CD20 antibody has been successfully integrated in therapy of mature B-ALL and Burkitt's lymphoma. It is now also being explored in several pilot studies for CD20-positive B-precursor ALL. In a GMALL protocol for elderly patients, Rituximab is administered prior to chemotherapy cycles starting during induction for a total of eight treatments. Also the combination of hyper-CVAD regimen with Rituximab in B-precursor ALL was feasible and a favorable outcome with CD20-positive ALL was reported (reviewed by Gökbuget and Hoelzer[161]).

Anti-CD52

The CD52 antigen is expressed by most lymphatic cells and to a higher degree in T-lymphoblasts compared with B-lymphoblasts. CD52-antibodies were first used for ex vivo T-cell depletion of allogeneic bone marrow grafts to prevent GvH disease without further GvH disease prophylaxis. The humanized antibody Campath-1H has antitumor activity in CLL, T-PLL, and other T-NHL. Several studies with anti-CD52 therapy in adults with ALL are ongoing, either during relapse or at the time of MRD. The CALGB has integrated anti-CD52 therapy as consolidation in their frontline therapy and demonstrated its feasibility in a dose-finding study. Efficacy data are not available.[162]

Additional monoclonal antibodies (B43[anti-CD19]-Genistein, B43[anti-CD19]-PAP, anti-B4-bR [anti-CD19]) have been investigated in phase I to II pilot trials in ALL. Antibodies that were developed for other diseases, such as anti-CD22 in lymphoma and anti-CD33 in AML, could be applicable in ALL because these antigens are expressed in 17% and 16% of adult ALL cases, respectively. Antibody treatment could be administered as single agents or in combination with chemotherapy, for purging, and as post-transplant therapy and might be particularly effective in low-burden disease (MRD-positive patients).

Imatinib in Ph/BCR-ABL-Positive Acute Lymphocytic Leukemia

In Ph/BCR-ABL-positive leukemia, the BCR-ABL fusion gene is causally involved in leukemogenesis and is considered to be essential for

leukemic transformation. With a selective inhibitor of the Abl tyrosine kinase (STI571, imatinib), cellular proliferation of BCR-ABL-positive chronic myeloid leukemia and ALL cells can be inhibited.

Clinical Experience with Imatinib in Advanced Ph-Positive Acute Lymphocytic Leukemia

In a multicenter phase II study, 56 patients with relapsed or refractory Ph+ ALL received imatinib at an initial daily dose of 400 mg orally, which was later increased to 600 mg; 60% of Ph+ ALL patients achieved a hematologic response. A complete hematologic remission with normalization of peripheral blood counts (absolute neutrophil count >1.5/nL, platelet count >100/nL) was noted in 19% of patients. Rapid blast cell clearance occurred within 1 week of treatment in the majority of patients. It is noteworthy that the peripheral blood response did not necessarily correspond with a bone marrow response. Median estimated time to progression for ALL patients was 2.2 months.[163] Despite the rapid development of relapse that occurs within weeks in many patients, some of these patients went on to SCT.[164] Response to imatinib therapy can be closely monitored by quantitative PCR.

Hematologic toxicity (grades III and IV) was frequent but was rarely associated with serious infectious or hemorrhagic complications. Nonhematologic toxicity attributed to imatinib consisted primarily of mild-to-moderate gastrointestinal discomfort, peripheral and facial edema, and muscle cramps and was readily manageable. No patient discontinued therapy because of nonhematologic adverse events. There were no imatinib-related deaths. Therefore, imatinib was well tolerated even in heavily pretreated patients.

Imatinib in the Treatment of Ph-Positive Acute Lymphocytic Leukemia

In younger patients, imatinib was first administered between chemotherapy cycles. However, with this approach, no molecular remissions were achieved. Therefore, studies with parallel application of chemotherapy and imatinib were started, leading to CR rates above 91% to 96% and molecular CR rates of 38% to 50%.[52,165–167] All studies reported an improved OS rate of 55% to 65% compared to 15% in studies before the imatinib era. No trial described increased toxicity compared to chemotherapy alone or negative effects on subsequent SCT.

In older patients with de novo Ph+ ALL, treatment results have been previously extremely poor with particularly high induction mortality. Therefore, induction chemotherapy was replaced by single-drug therapy with imatinib. The remission rate was 92% in an Italian trial.[168] The German study group (GMALL) conducted a randomized trial comparing dose-reduced chemotherapy and imatinib monotherapy. After induction, all patients received chemotherapy combined with imatinib. The remission rate for the imatinib arm was 93% compared to 54% with chemotherapy.[169] The survival was superior to that in previous trials without imatinib, but in both arms, the relapse rate was high, and there was no difference in outcome.

At present, a combination of chemotherapy and imatinib is the standard of the treatment of younger patients with Ph+ ALL. Patients are still referred for SCT in CR1 if possible. In elderly patients, imatinib monotherapy for induction seems reasonable, at least if a rapid response is observed. However, it remains unknown whether the high relapse rate can be decreased by a combination of imatinib with mild chemotherapy during induction or by intensification of consolidation. Furthermore, transition to the use of treatment with other tyrosine kinase inhibitors in case of molecular relapse or detection of mutations of BCR/AB2 (see later discussion) is important.

Imatinib and Allogeneic Stem Cell Transplantation in Ph-Positive Acute Lymphocytic Leukemia

It is known that MRD after SCT in Ph+ ALL is associated with a relapse probability exceeding 90%. Starting imatinib in the setting of MRD could decrease this high relapse rate. In a prospective study that was conducted by the GMALL, 27 Ph+ ALL patients received imatinib on detection of MRD after SCT. MRD became undetectable in 52% of patients after a median of 1.5 months. Each of these patients remained in remission at least for the duration of imatinib treatment. Failure to achieve MRD negativity shortly after starting imatinib predicted relapse, which occurred in 92% of these patients after a median of 3 months. LFS rate was 91% after 1 year in the molecular responders compared to 8% in the nonresponders.[170]

It remains unknown whether imatinib should be started in all patients after SCT or only in case of MRD detection. In any case, continued MRD-positivity after 2 to 3 months of imatinib identifies patients who will ultimately experience relapse and in whom additional or alternative antileukemic treatment should be initiated.

Mechanisms of Resistance to Imatinib

MRD detection often leads to early detection of molecular resistance or molecular relapse. Additional treatment can then be initiated before overt relapse occurs. Nowadays, an additional search for mutations of the tyrosine kinase domain of BCR/ABL is required, since these mutations can confer resistance to imatinib and partly to the second-generation tyrosine kinase inhibitors dasatinib and nilotinib.[171,172] Both drugs have increased efficacy in comparison to imatinib and are active in the majority of mutations, with the exception of the T315I mutation. The remission rate that is achieved with these drugs in patients who fail imatinib is approximately 30%. These second-generation drugs are currently being evaluated in patients who have relapsed, but trials for de novo Ph+ ALL are starting.

New Cytotoxic Drugs

In the past 10 years, a variety of new drugs has been developed for use in ALL (reviewed by Pui and Jeha,[83] Thomas,[84] and Gökbuget and Hoelzer[85]). Nelarabine is a purine analog that acts specifically on T-lymphoblasts, with a remission rate between 30% and 40% in relapsed T-ALL.[132,173] Treatment was generally well tolerated, although neurotoxicity occurred in some patients. At present, application of nelarabine in frontline therapy is being evaluated. BCX1777 (forodesine) is an inhibitor of the enzyme purine nucleoside phosphorylase and thereby acts similarly to purine analogs.[146] Clofarabine is a purine analog without subgroup specific effects. Other new drugs are liposomal preparations that might improve feasibility of treatment, for example, liposomal vincristine, daunorubicin, or liposomal cytarabine for intrathecal application.

FUTURE RISK STRATIFICATION AND TREATMENT CONCEPTS FOR ADULT ACUTE LYMPHOCYTIC LEUKEMIA

The treatment of adult ALL has already become more sophisticated and complicated and will be even more so in the future. Treatment strategies depend on factors that are unrelated to the disease, such as the availability of a stem cell donor, patient-related factors, disease markers, treatment response, and availability of targeted drugs. Prognostic factors and patient characteristics therefore no longer serve only as the basis for identification of candidates for SCT in CR1 but also define individualized treatment approaches, which are discussed in the following examples:

- *Subgroup-adjusted and targeted treatment*: Targeted drugs such as tyrosine kinase inhibitors, subgroup-specific purine analogs such as nelarabine, or monoclonal antibodies such as CD20 in mature B-ALL are used to increase subgroup-specific activity of treatment. These approaches have already led to significant improvement of outcome and will be refined in the future.
- *Age-adapted treatment*: In ways that are similar to subgroup-adapted treatment, therapies have to be defined for patients at both ends of the age spectrum: elderly and adolescent patients. In elderly

patients, the major focus is on effective targeted therapy with as much quality of life as possible, whereas in adolescents, the major aim is to deliver time- and dose-intensive chemotherapy based on pediatric protocols.

- *Individualized treatment*: New methods offer the option to adopt intensity and duration of therapy to individual response as measured by the presence of MRD or to add or omit specific drugs according to results of an evaluation for drug resistance.
- *New integrated risk classification*: A variety of molecular markers that have been newly detected by microarray analysis have been proposed as prognostic factors.[174] They might possibly be integrated in a conventional risk model that aims to identify patients for SCT in CR1 and might rather stimulate analysis of underlying mechanisms, drug targets, or invention of treatment adaptations.
- *Risk-adapted indications for SCT*: Indications for SCT have to be defined carefully, taking into account not only long-term results but also acute and long-term toxicities into account. At present, the majority of study groups stick to risk-adapted indications for SCT.
- *Evaluation of new cytostatic drugs*: Many of these drugs fit in subtype-adjusted, targeted therapies. Taking the number of targets and drugs into account, evidence-based priorities for clinical evaluation in relapsed ALL and for integration in frontline therapy have to be set.

Risk- and subtype-adjusted treatment strategies have led to considerable improvement in outcome in patients with mature B-ALL, T-ALL, and Ph+ ALL but less improvement in adult patients with B-precursor ALL. Future strategies will integrate a variety of additional factors, thereby resulting in a more complex, flexible, and patient-specific treatment approach.[85] Besides these sophisticated approaches, a better adherence to protocols, support of patients to improve their compliance, and documentation of compliance would be warranted in adult ALL. Treatment should be done at experienced centers, and closer cooperation between internal medicine and pediatric physicians, including cooperative studies, would be desirable.

The design of prospective trials will be challenging, since they will focus on even smaller subgroups of ALL and phase I studies with new drugs. These trials will be possible only in larger, international study groups that are able to recruit sufficient patient numbers. To enable any intergroup comparison, international efforts similar to that utilized to study childhood ALL are required to define uniform criteria for diagnostic classification, definition of subgroups, and even prognostic factors.

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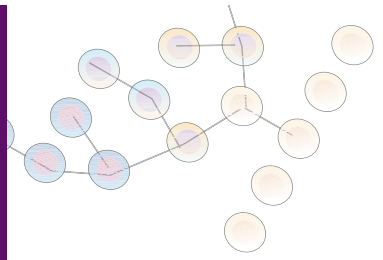
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104 Acute Myeloid Leukemia in Adults

Frederick R. Appelbaum

SUMMARY OF KEY POINTS

Epidemiology and Etiology

- The incidence of acute myeloid leukemia (AML) in adults is 3 cases per 100,000 population per year in the United States.
- Incidence increases with age; median age at diagnosis is 60 years.
- Known causes of AML include exposure to benzene or ionizing radiation and previous chemotherapy; AML also is associated with a few uncommon inherited syndromes.

Tumor Biology

- AML is a clonal disease arising in a primitive hematopoietic progenitor cell.
- Leukemogenesis is a multistep process requiring some mutations that block differentiation and others that promote proliferation.

Diagnosis and Classification

- Diagnosis requires greater than 20% blasts of myeloid origin in marrow or peripheral blood.
- The 2002 World Health Organization (WHO) classification recognizes four categories of AML: (1) AML with recurrent genetic abnormalities; (2) AML with multilineage dysplasia; (3) AML and myelodysplastic syndrome (MDS), therapy-related; (4) AML not otherwise categorized.
- Cytogenetics is the most powerful single indicator of outcome, and cases can be defined as favorable, intermediate, or unfavorable according to cytogenetic subtype. Translocation t(15;17) is diagnostic of acute promyelocytic leukemia (APL), the M3 subtype of AML in the French-American-British (FAB) classification (see Table 104-3), which requires a very specific form of therapy.

Treatment

- Younger patients with non-M3 AML
  - *Induction*—Anthracycline plus cytarabine induces complete remission in approximately 70% of patients.
  - *Postinduction therapy*—In patients with good-risk disease, treatment with repetitive doses of cytarabine is associated with greater than 50% cure rates. In patients with intermediate-risk disease, treatment consists of either continued chemotherapy or hematopoietic cell transplantation (HCT). Patients with poor-risk disease should receive transplantation in first remission if possible.
- Older patients with non-M3 AML
  - *Induction*—Anthracyclines plus cytarabine will induce complete remission in 50% of patients.
  - *Postinduction therapy*—Continued chemotherapy may cure 15% of patients.
- Patients with APL
  - All-*trans*-retinoic acid (ATRA) should be added to the induction regimen and used as maintenance, with an expectation of cure in two thirds of patients.

INTRODUCTION

AML is the result of a genetic event or series of events occurring in an early hematopoietic precursor that both blocks differentiation and allows uncontrolled proliferation. The abnormally proliferating leukemic cells accumulate in the marrow space, eventually replacing normal marrow progenitors, with consequent diminished production of red cells, white cells, and platelets. This, in turn, leads to the common clinical manifestations of AML—namely, anemia, infection, and bleeding. As the disease progresses, leukemic blasts pour into the bloodstream, leading to the "weisses Blut" described by Virchow in 1845.[1] Eventually, the leukemic cells accumulate in the spleen, lung, brain, and other vital organs. If left untreated, AML is rapidly fatal, with most patients dying within a few months of diagnosis. With appropriate treatment, however, a substantial proportion of patients can be cured. Remarkable growth in our understanding of AML has occurred over the past decade. One of the major lessons arising from this new knowledge is the complexity of the leukemic process—a lesson that can be daunting but one that also provides multiple new targets for prevention, detection, and treatment.

EPIDEMIOLOGY AND ETIOLOGY

Incidence

Approximately 35,000 Americans were diagnosed with leukemia in 2005.[2] Of these, AML developed in 32%, chronic lymphocytic leukemia (CLL) in 26%, chronic myeloid leukemia (CML) in 15%, and acute lymphocytic leukemia (ALL) in 11%; the remaining 16% had unclassified types. The male-to-female ratio is approximately 1.3 : 1. The incidence of AML is constant during the first 30 years of life but then begins to increase almost exponentially (Fig. 104-1). The overall incidence of leukemia in the United States has remained stable over the last 30 years.[3]

Geographic Clustering

Although leukemic clusters within a given geographic area occasionally have been described, no compelling studies suggest that these represent more than chance events.

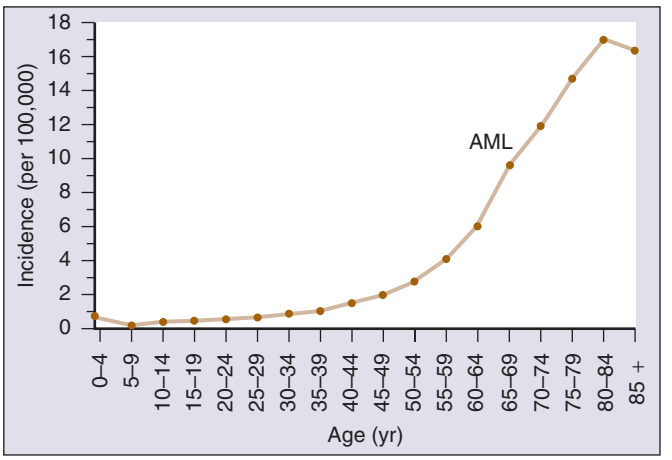


Figure 104-1 • Age-related incidence of acute myeloid leukemia (AML). The incidence is relatively stable until the age of 30 years and then increases dramatically.

Etiologic Agents and Associations

Viruses

A clear association of human T-cell leukemia virus infection with an adult form of T-cell leukemia has been recognized. No relationship between any viral infection and the development of AML, however, has been confirmed.

Carcinogens

Heavy benzene exposure is associated with the development of aplastic anemia, myelodysplasia, and AML.[4] Most studies examining the issue find a small but consistent increase in AML among cigarette smokers.[5] Survivors of the atomic bomb explosions of Hiroshima and Nagasaki in 1945 demonstrated an increased risk of all leukemias except CLL, which began as early as 1.5 years after the explosions, peaked at approximately 7 years, and returned to baseline by 1970.[6] Other evidence that ionizing radiation is leukemogenic comes from the 10-fold increased risk of AML among persons who received radiation treatment for ankylosing spondylitis in the 1930s and the 1940s.[7]

Treatment-Related Acute Myeloid Leukemia

With the increasing use of irradiation and chemotherapy to treat malignancies, the incidence of treatment-related AML has grown. It is estimated that perhaps 6% to 10% of cases of AML are treatment-related.[8] These can be grouped in several relatively distinct syndromes. AML developing after exposure to alkylating agents has a latency of 5 to 6 years, often first appears as an MDS, and frequently is associated with chromosomal abnormalities involving the long arm of chromosome 5 or 7. This association was first appreciated in the 1970s in patients who had previously received alkylating agents with or without irradiation as treatment for lymphoma.[9] Alkylating agent–induced AML has been noted in patients who received nitrogen mustard for treatment of Hodgkin's disease, in women in whom melphalan or cyclophosphamide was used to treat ovarian cancer, and in patients whose treatment for colorectal cancer included chloroethylnitrosourea.[10–15] All alkylating agents probably are leukemogenic, with risk increasing with cumulative dose.[16]

Treatment with topoisomerase II inhibitors also increases the risk for development of AML. In contrast with the leukemias seen after exposure to alkylating agents, these leukemias develop relatively rapidly (often within 2 years), generally are not preceded by a myelodysplastic phase, and frequently are associated with chromosomal rearrangements involving 11q23, the locus for *MLL* (the mixed-lineage leukemia gene), or 21q22.[17] The epipodophyllotoxins etoposide and teniposide fall in this category; with these drugs, the risk of developing secondary AML appears to be dose-related and may increase when methotrexate or cisplatin also is administered.[18,19] The anthracyclines also are topoisomerase II inhibitors, and their use—particularly when they are given with cyclophosphamide in dose-intensive regimens—has been associated with the subsequent development of AML.[20]

Patients with non-Hodgkin's lymphoma treated using autologous HCT appear to be at increased risk for the development of secondary AML, with cumulative incidence rates as high as 15% reported in some series.[21,22] Leukemias typical of previous exposure to both an alkylating agent and a topoisomerase II inhibitor have been reported. Recent registry data demonstrate that the risk of MDS or AML after autologous HCT is predicted largely by the type and intensity of chemotherapy received by the patient before transplantation. This observation raises some questions about the exact contribution of the transplantation procedure itself to the development of secondary AML.[23] Bimolane, a dioxopiperazine derivative used for the treatment of psoriasis, has been associated with the development of APL.

Not all secondary leukemias fall into the discrete categories described here. Secondary leukemias with inv16, t(9;22), and abnormalities involving 3q21 have been reported.[24] Not every leukemia developing in patients who have received radiation therapy or chemotherapy is necessarily due to that therapy. In fact, a significant elevation in risk for AML has been observed among patients with a previous malignancy treated only with surgery, suggesting a genetic or other predisposition.[25]

Ethnic Differences

APL has been reported to be more common among Hispanic populations in the Los Angeles area than in the general population.[26] A similar increased incidence has been reported in Spain.[27]

Familial Clustering

The concordance rate of leukemia in identical twins is virtually 100% if leukemia develops in one twin before the first year of life, but the rate then declines with age.[28] In a large comprehensive study of proband effects in Utah, using data from 125,000 patients with cancer, the relative risk of leukemia among first-degree relatives of probands with leukemia was 5.69, strongly suggesting that complex genetic factors may influence the development of leukemia in later life.[29] Several single-gene leukemia syndromes also have been described, including an autosomal recessive syndrome of childhood-onset myelodysplasia with monosomy 7 and a familial syndrome of erythroleukemia.[30,31] A familial syndrome of an aspirin-like platelet disorder with thrombocytopenia and propensity for the development of AML is due to germline mutations in the RUNX-1 (formerly AML-1) gene.[32] Nearly all of these autosomal dominant leukemia syndromes (with the exception of the RUNX-1 syndrome) demonstrate anticipation with declining age at onset with each generation.

Constitutional Chromosomal Abnormalities

Children with trisomy 21 (Down syndrome) have an increased risk for development of leukemia, with M7 AML seen in early childhood and ALL predominating in later years. Trisomy 8 mosaicism is a rare constitutional abnormality with features of mental retardation, multiple developmental defects, and an increased incidence of myeloid leukemias.

Genetic Syndromes Associated with Acute Myeloid Leukemia

Several DNA-repair syndromes are associated with an increased incidence of AML. *Bloom's syndrome* is a disorder of autosomal recessive inheritance resulting from mutations in the gene encoding a DNA helicase at 15q21.1 and is characterized by growth retardation, characteristic facial appearance, immunodeficiency, and, in 25% of

patients, hematologic malignancies including AML.[33] *Ataxia-telangiectasia*, inherited as an autosomal recessive trait, is due to mutations in the *ATM* gene at 11q22–23, which results in deficiencies in the G_1-S checkpoint. Features of this disorder may include progressive cerebellar ataxia, telangiectatic skin lesions, and malignancies that more often are of lymphoid than of myeloid origin.[34] *Fanconi's anemia* is a syndrome of autosomal recessive inheritance characterized by pancytopenia and a variety of developmental disorders that include skeletal abnormalities (most notably, hypoplastic thumbs) and short stature. Exposure of cells from these patients to mitomycin C or diepoxybutane results in excess chromosome breaks. In almost 50% of patients with Fanconi's anemia, myelodysplasia or AML develops by the age of 40 if death from other causes does not occur first.[35] As indicated by chromosome complementation studies, at least eight different genes can result in this syndrome.

The tumor suppressor gene syndromes *Li-Fraumeni syndrome* and *neurofibromatosis 1* are associated with an increased risk of AML, but the exact extent of increased risk is unclear. Several congenital cytopenia syndromes are associated with a definite increased risk of AML: *Blackfan-Diamond syndrome* is characterized by congenital hypoplastic anemia, growth retardation, and a definite increase in AML. *Severe congenital neutropenia*, also sometimes called *Kostmann's syndrome*, results in myelodysplasia or AML in 10% to 20% of affected persons who do not first succumb to infection.[36] *Schwachman syndrome* is a disease of autosomal recessive inheritance characterized by pancreatic insufficiency, moderate dwarfism, and a hematologic picture resembling that in Fanconi's anemia.[37]

TUMOR BIOLOGY

Pathophysiology

Clonality

AML is a clonal disorder, with all leukemic cells in a given patient descending from a common progenitor. The initial proof of the clonality of AML came from studies of the disease in females who were heterozygotic for the X-linked glucose-6-phosphate dehydrogenase (G6PD) isoenzymes. In normal heterozygotic women, because of random X chromosome inactivation, any single blood cell will express one or the other isoenzyme, and hematopoietic cells overall will be a 50–50 mix. Leukemia cells in *G6PD*-heterozygotic females, however, were found in every case to be all of one isoenzyme or the other, indicating their origin from a single precursor.[38] With the development of methods to detect X-chromosome-linked DNA polymorphisms on a broader scale, it has since become possible to assess the clonality of leukemia in virtually any female patient. Such studies have demonstrated differing patterns of clonal involvement among patients so that in some (generally younger) patients, only the frankly myeloid leukemic blasts are clonal, whereas in other (often older) patients, normal-appearing monocytes, platelets, and red cell precursors also may be of clonal origin.[39] Studies of clonality also have given the surprising result that some patients in whom treatment achieves complete remission with recovery of entirely normal-looking hematopoiesis—including loss of a leukemic chromosome marker—may still have clonal hematopoiesis, a result consistent with the hypothesis of a multistep pathogenesis for AML.[40,41]

Cell of Origin

The clonal nature of AML suggests that there is a leukemic stem cell capable of both self-renewal and proliferation. Identification of the AML stem cell is of considerable interest both for aiding in our understanding of the disease and because this cell would represent the ideal target of therapy. Recognition of cases of AML with blasts of various degrees of differentiation has given rise to two general hypotheses. In one model, progenitor cells at various levels of commitment and differentiation all are susceptible to transformation, leading to considerable heterogeneity in AML stem cells. In an alternative model, only very undifferentiated hematopoietic stem cells are capable of being transformed, but based on the particular mutations involved, some degree of further commitment and differentiation of the leukemic cell is possible. Recent studies attempting to identify the AML stem cell based on the cell's ability to transfer human leukemia to an immunodeficient (NOD-SCID) mouse are more consistent with the latter hypothesis. In human AML, when patients are tested to determine which fraction of cells is able to initiate leukemia in the NOD-SCID mouse, it is only the primitive $CD34^{++}CD38^{-}$ fraction that is able to do so, regardless of the differentiative stage of leukemic blasts.[42,43] The leukemias that subsequently develop in the animals have the same level of differentiation as for the leukemias from which the $CD34^{++}CD38^{-}$ blasts are derived, suggesting that these leukemic clones are capable of some genetically determined degree of differentiation. The $CD34^{++}CD38^{-}$ AML stem cells are at the same level of differentiation as for the normal hematopoietic stem cell capable of engrafting NOD-SCID mice and are rare cells among the leukemic mass, with a frequency of 0.2 per 10^6 to 100 per 10^6 cells. APL could represent an exception to this general model, and APL blasts do not easily engraft in NOD-SCID mice.[43]

Cell Kinetics

Available data suggest that it is the persistence rather than the speed of proliferation that leads to the outgrowth of AML. Only a small fraction of leukemic cells are in cycle at any given time, and the cell cycle duration is, in fact, longer than that of normal hematopoietic cells.[44] An unfortunate but instructive case is that of a woman with CML who, after an ablative preparative regimen, received a marrow transplant from her HLA-matched brother. Although the brother's routine pretransplantation workup was negative, the transplanted marrow was later found to contain 38% AML blasts with t(1;5). In a somewhat surprising turn of events, engraftment with normal male hematopoiesis occurred, and the patient did not show evidence of her brother's disorder until 6 months after transplantation.[45]

Marrow Failure

Although the persistent growth of the AML clone leads to marrow failure at least in part by physically crowding out normal progenitors, other mechanisms of suppression of normal marrow probably exist. Frequently, peripheral blood counts start to fall weeks or months before the appearance of leukemic blasts in the marrow, and cases of hypoplastic AML are not uncommon. The mechanisms by which suppression of normal hematopoiesis occurs are not well understood.

Molecular Pathology

The identification of recurrent chromosomal abnormalities—which can include translocations, point mutations, and gene duplications in AML—followed by the cloning of many of the involved genes has provided important insights into the pathogenesis of the disorder. The number of recurrent abnormalities so far identified is in the hundreds, a fact that would make it seem almost futile to attempt to make sense of such a wide range of abnormalities. With further investigation, however, it is becoming clear that many of these abnormalities tend to affect a limited number of transcriptional or signal transduction pathways. Of those abnormalities that have been studied extensively, most are pro-oncogenic and are not simply innocent bystanders in the leukemic process. Only a few of these abnormalities are both necessary and sufficient to cause leukemia in murine models, however—suggesting that multiple mutations are required for development of overt leukemia. A particularly useful model argues that most cases of AML have one mutation that results in differentiation blockade together with a second mutation that results in inappropriate proliferation.[46] Some of the more common and better understood molecular categories of AML are described next.

Core Binding Factor Translocations

Core binding factor (CBF) is a heterodimeric transcription factor made up of two subunits, CBFα (also known as RUNX-1 or AML-1) and CBFβ. CBF plays an important role in the transcriptional activation of a number of genes required for normal hematopoietic differentiation (Fig. 104-2). A number of leukemias are associated with translocations or mutations that involve the components of CBF.

RUNX-1/MTG8

The t(8;21) abnormality seen in approximately 8% of cases of adult AML results in the fusion of the RUNX-1 (CBFα) gene on chromosome 21 to the MTG8 (formerly ETO) gene on chromosome 8.[47] The RUNX-1/MTG8 fusion protein acts as a dominant negative inhibitor of the wild-type RUNX-1 gene, meaning that presence of the RUNX-1/MTG8 fusion protein blocks the ability of the wild-type RUNX-1 from the remaining nontranslocated chromosome to activate appropriately the transcription required for normal hematopoietic differentiation[48] (see Fig. 104-2). The RUNX-1 "knockout" mouse and the RUNX-1/MTG8 "knockin" mouse have identical phenotypes, with embryonic death at day 11.5 and a characteristic pattern of central nervous system (CNS) hemorrhage and lack of hematopoiesis. AML characterized by t(8;21) is associated with a favorable prognosis.

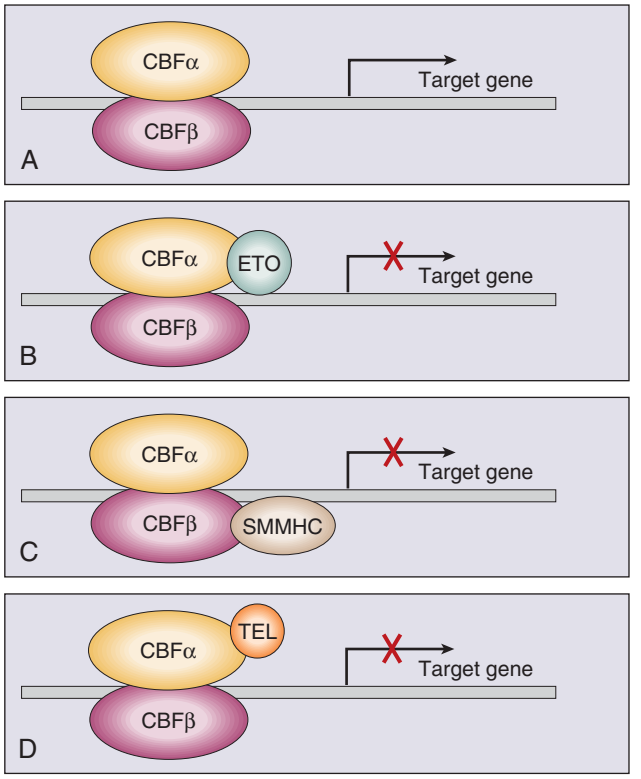


Figure 104-2 • **A,** CBFα and CBFβ form a heterodimeric transcription factor that regulates a spectrum of genes important in hematopoiesis, including those for IL-3, GM-CSF, and others. **B,** If instead of normal CBFα, the fusion product CBFα-ETO (now CBFα-MTG8) dimerizes with CBFβ, the transcription factor does not function, and target genes are not transcribed. **C,** The fusion product CBFβ-SMMHC is a dominant-negative regulator of gene transcription. **D,** Analogous to the situation with CBFα-ETO, the fusion product CBFα-TEL is a dominant-negative regulator of normal CBF function. CBF, core binding factor; GM-CSF, granulocyte macrophage colony stimulating factor; IL-3, interleukin-3.

Inv(16)

Inv(16)(p13;q22) and t(16;16)(p13;q22) both result in the fusion of the CBFβ gene at 16q22 to the smooth muscle myosin heavy chain gene (*MYH11*) at 16p13[49] (see Fig. 104-2). As in the case of t(8;21), the resultant fusion protein acts as a dominant-negative regulator of transcription. CBFβ/MYH11 knockin mice have a phenotype identical to those noted for RUNX-1 knockouts and RUNX-1/MTG8 knockins. AML with involvement of 16q22 accounts for approximately 9% of adult AML cases, is associated with a unique myelomonocytic morphology, and, like t(8;21) leukemias, carries a favorable prognosis.

TEL-RUNX-1

In up to 25% of cases of pediatric pre-B-cell ALL, a t(12;21) abnormality fusing the TEL gene with the RUNX-1 gene can be found[50] (see Fig. 104-2).The resultant fusion protein appears to function as a dominant-negative regulator of transcription. In general, this translocation is associated with a favorable prognosis in childhood ALL.

Point Mutations

Point mutations in the RUNX-1 gene occur in 3% to 5% of sporadic cases of adult AML.[51,52] In addition, as noted earlier, inherited point mutations resulting in RUNX-1 haploinsufficiency are found in families with familial platelet disorder and a high prevalence of subsequent AML.[32] The fact that AML does not always develop in these patients, or does so only after years, suggests that subsequent mutational events are required.

The mechanisms by which t(8;21), inv(16), and t(12;21) fusion proteins exert their dominant-negative effects are only now becoming understood. Recent data suggest that segments of the fusion protein recruit nuclear co-repressor (NCoR)–histone deacetylase (HD) complexes in a matter analogous to that seen in APL, as is discussed shortly. The specific pattern of transcriptional suppression probably differs for each fusion product, as suggested by the somewhat different phenotypes associated with each.

Retinoic Acid Receptor-α Gene Translocations

APL, which accounts for approximately 8% of cases of adult AML, is almost always associated with t(15;17)(q22;q11.2), a translocation that fuses the promyelocytic leukemia (*PML*) gene on chromosome 15 to the retinoic acid receptor-α (*RARα*) gene on chromosome 17. The resultant PML/RARα fusion product acts as a dominant-negative inhibitor of normal PML function and of the function of RXRα, an important heterodimeric partner of PML[53] (Fig. 104-3). PML/RARα recruits a nuclear co-repressor (NCoR) and the molecules sin3 and HD. HD deacetylates histones, a process that in turn inhibits binding of transcription factors, thereby inhibiting the expression of genes required for hematopoietic differentiation. The unique activity of ATRA in APL appears to be explained by its ability to bind to the PML/RARα fusion protein, changing its configuration and releasing the attached nuclear co-repressor (see Fig. 104-3). This then allows subsequent transcription and gene expression. Transgenic expression of the PML/RARα fusion protein in mice results in APL in a fraction of animals after a latency period of some months. The relatively long latency and incomplete penetration suggest that, as with many other leukemias, multiple mutations are required for the full development of overt APL.

A number of other translocations, including t(5;17) and t(11;17), involve the RARα gene and result in the APL phenotype. These leukemias generally are unresponsive to ATRA because clinically achievable concentrations of the drug do not result in release of the NCoR-HD complex.

C/EBPα Gene Mutations

Transcription factor CCAAT/enhancer-binding protein-α (C/EBPα) is mutated in 6% to 10% of patients with AML.[54] C/EBPα is required

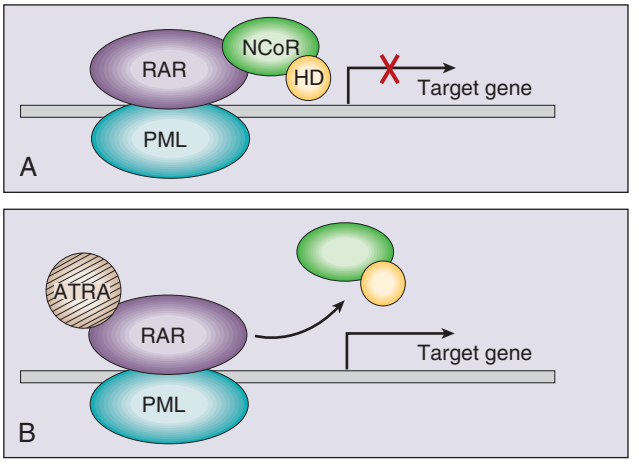


Figure 104-3 • **A,** The abnormal fusion product PML-RARα binds a nuclear co-repressor (NCoR)-histone deacetylase (HD) complex. This deacetylates histones in the region, leading to inhibition of transcription. **B,** When ATRA binds to RAR, a change in confirmation leads to release of the NCoR-HD complex, acetylation of histones, and resumption of transcription. ATRA, all-*trans*-retinoic acid; RAR-PML, retinoic acid receptor-promyelocytic leukemia protein.

for normal granulocyte differentiation, and c/ebpα-null mice lack neutrophils and eosinophils. In humans, C/EBPα gene mutations presumably result in abnormal DNA binding and loss of normal myeloid differentiation. AML cases characterized by C/EBPα gene mutations tend to demonstrate M1 or M2 morphology, with intermediate-risk cytogenetics and a favorable clinical outcome.

Mixed-Lineage Leukemia Mutations

Most nonrandom chromosomal abnormalities are associated with specific lineages or subtypes of leukemia, but abnormalities involving the mixed-lineage leukemia gene (*MLL*) located on 11q23 are exceptions, with many partner genes and many forms of hematologic malignancy including ALL, AML, and lymphoma. Altogether, translocations involving 11q23 account for approximately 7% of adult AML cases, and among these, t(9;11)(p22;q23), associated with acute monoblastic leukemia, is the most common.[55,56] The translocation fuses *MLL* with *AF9*, and leukemia invariably develops in mice with this fusion gene knockin.[57] Other *MLL* translocations seen in AML include t(6;11), t(10;11), t(11;17), and t(11;19). It also has been reported that as many as 10% of patients with AML and normal cytogenetics have tandem duplications of *MLL*.[58]

The human *MLL* gene has considerable homology with the *Drosophila* trithorax gene, a complex gene that regulates the transcription of other genes necessary for normal *Drosophila* development. The exact function of MLL in vertebrates is not entirely understood, but its structure suggests capability of minor groove DNA binding. Gene disruption experiments have shown that *MLL* positively regulates homeodomain (Hox) genes in mice and thus, like the trithorax gene, is required for normal development. Knockout mice die as embryos and demonstrate reduced hematopoiesis, suggesting that the gene has, as one of its functions, a broad effect on early hematopoiesis.[59–61] A current hypothesis is that *MML* fusion proteins result in increased expression of *HOX* genes, with increased self-renewal of affected hematopoietic progenitors.

Tyrosine Kinase Receptor Mutations

FLT1, *FLT3*, *FMS*, *KIT*, and *PDGF* are members of a family of genes encoding receptor tyrosine kinases, each with an extracellular ligand–binding domain, transmembrane and juxtamembrane domains, and an intracellular domain with tyrosine kinase activity. In general, ligand binding with the receptor causes receptor dimerization, autophosphorylation, and then subsequent phosphorylation activation of adaptive proteins (including GRB-2), which in turn activate Ras and other proteins.

FLT3 is mutated in 30% to 35% of patients with AML.[62,63] A majority of these are internal tandem duplications, but approximately one fourth of the mutations are in the form of point mutations. Both forms of mutations are activating. When inserted into murine cell lines, these mutations result in factor-independent growth.[64] Retroviral transmission of these mutations into mouse marrow is not, by itself, sufficient to cause overt AML but does lead to a myeloproliferative phenotype.[65] In clinical studies, the incidence of *FLT3* mutations in AML appears to increase with age and to be associated with high white blood cell (WBC) counts at diagnosis and poorer clinical outcome.[63,66,67] The negative impact of *FLT3* mutations apprears to increase with increasing size of the duplication and with higher allelic ratios of mutated to wild-type genes in leukemic blasts.[68,69] Clinical trials of small-molecule inhibitors of *FLT3* are ongoing.

Mutations in other receptor tyrosine kinase genes also are sometimes seen in AML. Point mutations in *FMS* have been reported in 10% to 20% of cases.[70] Point mutations, deletions, or insertions of *KIT* also have been reported in a small percentage of patients.[71] Mutations in one or another receptor tyrosine kinase are found in almost half of all AML cases.

RAS Mutations

Ras is a monomeric guanosine diphosphate-binding protein activated by various tyrosine kinases. Activation of Ras has multiple and varied effects, which, depending on the target cell and its particular state, can result in proliferation, transformation, or differentiation. *RAS* mutations have been identified in 15% to 30% of cases of AML.[72,73] In most cases, these mutations result in prevention of hydrolysis of Ras guanosine triphosphate (GTP), effectively keeping Ras in the "on" position. Thus, therapies to inhibit Ras function have been developed. To function normally, newly transcribed Ras must have a farnesyl or geranylgeranyl lipid attached, and for this reason farnesyl transferase inhibitors have been explored as therapeutic agents in AML.[74]

NPM1 Mutations

NPM1 encodes an abundant nucleolar phosphoprotein with multiple hypothesized functions. Heterozygous mutations usually involving the C-terminus at exon 12 have been detected in approximately 30% of cases of AML. Mutations in *NPM1* are seen more frequently in AML cases with monocytic differentiation, lack of CD34, normal cytogenetics, and *FLT3* mutations. Among patients with normal cytogenetics, presence of an *NPM1* mutation appears to be associated with a better prognosis, particularly among those without an *FLT3* mutation.[75,76]

Mutations Involving 5q, 7q, and 20q

AML evolving from myelodysplasia or developing from exposure to alkylating agent therapy frequently is associated with partial or complete loss of chromosomes 5, 7, and 20. The frequent loss of 5q, 7q, or 20q has led to the hypothesis that a classic tumor suppressor gene may exist in these areas. With classic tumor suppressor genes such as *RB*, when one allele is deleted, a mutation in the second results in disease. Despite considerable efforts to identify such genes, however, no classic tumor suppressor of AML in these regions has been reported.

PATHOLOGY

Histopathologic Features

The diagnosis of AML generally is made by the examination of well-prepared peripheral blood and bone marrow specimens. For more than 3 decades, the French-American-British (FAB) system was used

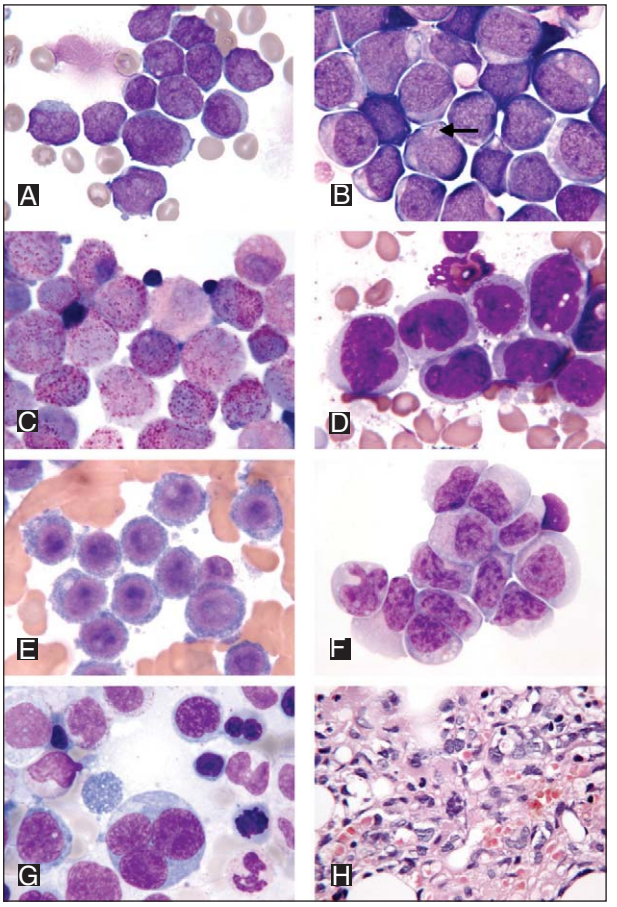


Figure 104-4 • The morphologic spectrum for the acute myeloid leukemias (AMLs) in bone marrow aspirates (**A-G**) and a marrow biopsy specimen (**H**). **A,** Acute myeloblastic leukemia with minimal (FAB AML-M0) or no (FAB AML-M1) maturation. The cells are myeloblasts with dispersed chromatin and variable amounts of agranular cytoplasm. Some display medium-sized, poorly defined nucleoli. **B,** Acute myeloblastic leukemia with maturation (FAB AML-M2). Some of the blasts contain azurophilic granules, and promyelocytes are evident. More mature neutrophils were present in other fields. Note the Auer rod *(arrow)*. **C,** Acute promyelocytic leukemia (FAB AML-M3). All of these cells are promyelocytes containing coarse cytoplasmic granules, which sometimes obscure the nuclei. **D,** Acute myelomonocytic leukemia (FAB AML-M4). Promonocytes with indented nuclei are present with myeloblasts. The dense nuclear staining is unusual. **E,** Acute monoblastic leukemia (FAB AML-M5a). These characteristic monoblasts have round nuclei with delicate chromatin and prominent nucleoli. Cytoplasm is abundant. Nonspecific esterase staining was intense *(not shown)*. **F,** Acute monocytic leukemia (FAB AML-M5b). Most of the cells in this field are promonocytes. Monoblasts and an abnormal monocyte also are present. **G,** Acute erythroid leukemia (FAB AML-M6). Dysplastic multinucleated erythroid precursors with megaloblastoid nuclei are present. **H,** Acute megakaryoblastic leukemia (FAB AML-M7). In this marrow biopsy specimen, large and small blasts and atypical megakaryocytes can be seen. FAB, French-American-British (Co-operative Group classification subtype).

to describe and classify AML, and according to this system, a finding of 30% blasts in marrow or peripheral blood was required to make the diagnosis.[77] More recently, a WHO classification suggests that a finding of 20% blasts is sufficient for this diagnosis.[78] AML blasts can be placed into the following categories on the basis of their appearance (Fig. 104-4):

- Minimally differentiated AML (FAB M0) blasts are nondescript. Without immunophenotyping, it is very difficult to identify these cells as being of myeloid origin.
- AML with differentiation (FAB M1) defines cases with sparse cytoplasmic granules, only occasional Auer rods, and positive myeloperoxidase staining.
- AML with maturation (FAB M2) is more clearly myeloid in origin, with increased cytoplasmic granules, clear myeloperoxidase positivity, and the frequent presence of Auer rods.
- APL (FAB M3) is characterized by intense cytoplasmic granulation that often obscures the nucleus. A microgranular variant exists with marked nuclear folding and only subtle cytoplasmic granulations. In both subtypes, blasts stain intensely with Sudan black or myeloperoxidase. M3 AML is invariably associated with t(15;17) or one of its variants.
- AML with myelomonocytic differentiation (FAB M4) often is characterized by dysplastic features, such as hypogranular cytoplasm and nuclear hyposegmentation. One subset associated with inv(16)(p13q22) is characterized by increased eosinophilia. In M4 AML, blasts stain positively with both myeloperoxidase and nonspecific esterase. Diagnosis of M4 AML is further strengthened by immunophenotyping demonstrating both myeloid and monocytic antigens.
- Acute monocytic leukemia (FAB M5) is characterized by blasts with folded nuclei and abundant cytoplasm that stains positively with nonspecific esterase but is myeloperoxidase-negative.
- AML (FAB M6), acute erythroid leukemia, may be associated with a variable appearance but usually is accompanied by dysplastic erythroid elements that, on occasion, can become the predominant cell type.
- The diagnosis of acute megakaryocytic leukemia (FAB M7) requires that more than 30% of blasts be of the megakaryocytic lineage. These blasts often display clumping, multinucleation, and cytoplasmic blebbing, but immunophenotyping is usually required to make the diagnosis.

Although in the past, considerable time and effort went into categorizing AML cases among these morphologic categories, morphology in fact has almost no significance once cytogenetic and (to a lesser extent) immunophenotypic information is taken into consideration.

Immunophenotype

AML cases can be categorized according to the combinations of myeloid-associated antigens displayed on the surface of the malignant blast. In undifferentiated AML cases, including FAB M0 cases, expression of CD34, CD117, and CD33 is characteristic, but the blasts tend not to express CD65s. In more mature AML types, including most cases of FAB M1 and M2, expression of CD34, CD33, CD13, and CD65s is seen. In leukemias associated with t(8;21), often with M2 morphology, an immunophenotype similar to that with other M2 AML types is present, but expression of the NK marker CD56 and the B lymphoid marker CD19 also is seen. In APLs, blasts uniquely stain strongly with CD15s and weakly with CD15. In addition, they usually do not express CD34 or HLA-DR. In acute myelomonocytic and monocytic leukemias, blasts express CD14, the prototypical monocytic antigen. Early myeloid markers, including CD34 and CD117, generally are absent. Myelomonocytic leukemias associated with inv(16) blasts frequently express the T-cell antigen, CD2. In most acute erythroid leukemias, blasts fail to express early myeloid markers (e.g., CD34) but do express CD36 and CD71 and often express blood group H antigen, the precursor to ABO. In acute megakaryocytic leukemias, blasts react with antibodies to CD41a/CD61 (GPIIb/IIIa). Mature platelets sometimes can adhere to the surface of M5 AML blasts, so that they appear as in M7 leukemias. In true M7 AML, however, expression of CD14 does not occur.

Cytogenetics

Cytogenetic analysis of human leukemias has been absolutely central to the identification of the genetic events involved in leukemogenesis.

In addition, cytogenetics has emerged as by far the single most important diagnostic factor in AML.

Conventional cytogenetics involves the staining of metaphase cells and thus requires dividing cells. Because malignant cells in the marrow are more frequent and have a higher mitotic rate, marrow, rather than peripheral blood, is the preferred source for cytogenetic analysis. Cells usually are cultured for 24 hours, with arrest by short-term incubation with colchicine; then, 20 metaphases typically are analyzed. The abnormalities detected include changes in chromosome number, gains or losses of portions of chromosomes, and reciprocal exchange of genetic material either between two or more chromosomes (translocations) or within a single chromosome (inversions).

Two other molecular techniques sometimes are used. Fluorescence in situ hybridization (FISH) techniques involve hybridization of single-stranded DNA probes to homologous single-stranded sequences in chromosomes of metaphase or interphase cells. FISH has the advantage of being able to analyze large numbers of dividing (metaphase FISH) or nondividing (interphase FISH) cells with relatively little effort. Only those abnormalities targeted by the specific probe being applied will be detected, however. Thus, FISH is very useful for monitoring the disappearance or reappearance of a specific translocation—for example, t(9;22) in CML—but is not a substitute for conventional cytogenetics for initial evaluation of AML. Polymerase chain reaction (PCR) is a method capable of amplifying selected regions of DNA through repeated cycles of DNA synthesis, denaturation, and hybridization. To use PCR analysis, the specific gene sequences to be amplified must be known. Standardized PCR assays for several of the more common fusion gene transcripts have been developed and are proving useful for monitoring minimal residual disease.

A listing of the most common cytogenetic abnormalities seen in adult AML is provided in Table 104-1. These abnormalities can be categorized according to underlying tumor biology and also prognostic significance (Fig. 104-5). Table 104-1 organizes these abnormalities according to biologic subgroups. Thus, t(8;21), t(16;21), inv(16), and t(16;16) all belong to the core binding factor leukemias. The abnormalities t(4;11), t(9;11), and del(11)(q23) constitute most of the MLL family of AML types. Leukemias involving the RARα gene include t(15;17), t(11;17), and t(5;17), whereas t(6;9) involves the fusion of the DEK and CAN genes. The EVI 1 gene is involved in inv(3) and t(3;3). Monosomy or interstitial deletions of chromosomes 5, 7, 17, and 20 are typical of AML evolving from MDS or developing after previous alkylating agent exposure. Trisomy 8 is quite common in AML and can appear as a sole abnormality or in combination with other abnormalities. By itself, trisomy 8 does not appear to influence prognosis, but when present it often is accompanied by other unfavorable risk cytogenetic abnormalities.[79] Trisomy 11, 13, and 21 also often are seen in AML.

A number of studies have analyzed the outcomes in patients with AML according to cytogenetics and have demonstrated that both complete remission rates and duration are strongly associated with pretreatment cytogenetics. In general, patients can be categorized as having a favorable, intermediate, or unfavorable cytogenetic risk status. Two of the largest prospective studies of adult AML were published by the Medical Research Council (MRC) and the Southwest Oncology Group (SWOG).[55,56] These studies concerned adults younger than 60 years of age with newly diagnosed AML treated using contemporary chemotherapy and transplantation approaches. As noted in Table 104-2, the two groups of patients reached very similar categorizations, with CBF and RARα leukemias defining the group with favorable risk status; "normal" leukemias and trisomy 8, the intermediate-risk group; and abnormalities of chromosomes 5 and 7 and complex abnormalities, the poor-risk group. Some controversy remains about whether 11q23 leukemias should be considered to reflect intermediate or unfavorable risk status. Overall, as noted in Table 104-2, 85% to 90% of favorable-risk, 75% to 80% of intermediate-risk, and 55% to 60% of poor-risk patients are predicted to achieve complete remission. Survival at 5 years also is strongly associated with risk group, with 55% to 65% of good-risk, 38% to 41% of intermediate-risk, and only 11% to 15% of poor-risk patients predicted to be alive. Recent studies suggest that patients with no cytogenetic abnormalities and therefore in the intermediate-risk category can be further categorized as having a better or worse prognosis on the basis of *NPM1* and *FLT3* mutational status, with improved outcomes seen in those with *NPM1* mutation but without mutation of *FLT3*.[75,76] As discussed later under "Primary Treatment," some of these outcomes are dependent on the particular treatment used. For example, the favorable outcomes seen in CBF leukemias may particularly depend on the use of high-dose cytarabine in the treatment regimen, whereas the use of allogeneic transplantation may overcome to some extent the impact of unfavorable risk cytogenetics.[55,80]

Table 104-1 Cytogenetic Abnormalities in Acute Myeloid Leukemia

Abnormality	Incidence (%)*
Core binding factor translocations	
t(8;21)	8
inv(16) or t(16;16)	9
Retinoic acid receptor translocations	10
t(15;17)	
Mixed-lineage leukemia translocations	
t(9;11)	2
t(10;11)	1
Other *MLL* translocations	3
Trisomies	
+8	9
+21	3
Other trisomies	6
Deletions	
–5 (5q–)	6
–7 (7q–)	8
–9 (9q–)	3
Complex†	10
Other	17
None—normal	40

*All patients with a specific abnormality are considered, whether or not an additional cytogenetic change is present. Thus, because some patients are counted twice, the total incidence is greater than 100%.

†*Complex* is defined as a clone with at least five abnormalities.

CLASSIFICATION

The FAB classification schema for AML is presented in Table 104-3.[77] This system, which has been in use for several decades, relies totally on morphology and is of only limited therapeutic or prognostic usefulness. More recently, the WHO has offered an alternative schema[78] (Table 104-4). This schema comprises the following subgroups: AML with the most common recurrent genetic abnormalities, AML types that evolve from MDS, AML types that are clearly therapy related, and AML that does not fall into any of the other three categories, for which the system resorts to a morphologic categorization similar to the previous FAB system.

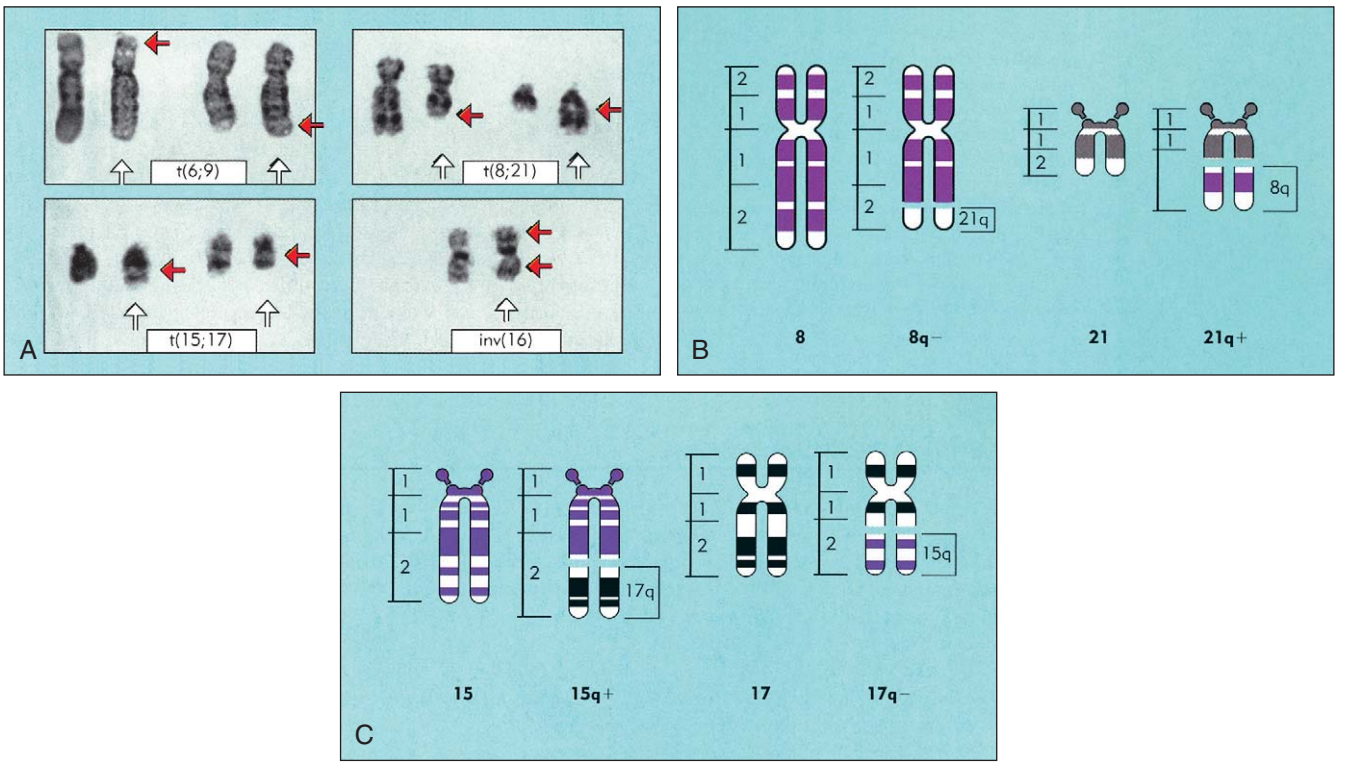


Figure 104-5 • Common cytogenetic abnormalities in adult acute myeloid leukemia. **A,** *Red arrows* mark the regions of chromosome breakage and rejoining. **B,** M2 subtype: diagrammatic systematized description of the structural aberration t(8;21). **C**, M3 subtype: acute promyelocytic leukemia (APL): Systematized description of the structural aberration t(15;17). (Courtesy of Prof. L.M. Secker-Walker.)

CLINICAL MANIFESTATIONS

The initial clinical manifestations of AML usually are nonspecific and relate to the diminished production of normal blood cells. The onset most often is insidious over the course of several weeks to months, and it is not uncommon for a patient to be seen several times before a blood count is finally taken and the diagnosis of leukemia is suspected. Most patients complain of a brief, virus-like illness with fatigue and malaise. Some patients present with a chief complaint of easy bruising, and occasionally, a nonhealing skin wound brings the patient to a doctor's attention. Anemia is present at diagnosis in most patients, causing fatigue, pallor, headache, and, in the predisposed patient, angina. Thrombocytopenia usually is present, and when asked, approximately one third of patients note easy bruising, bleeding gums, epistaxis, or other evidence of bleeding at diagnosis. Approximately one third of patients with AML have significant infections (most often of bacterial origin) when the diagnosis is finally made.

In addition to suppressing normal blood production, leukemia can infiltrate normal organs. Diffuse bone tenderness is a finding in approximately 25% of patients. Chloromas, which are local collections of blasts, can manifest as rubbery, fast-growing, soft-tissue

Table 104-2 Impact of Cytogenetics on Complete Response and Survival in Acute Myeloid Leukemia*

Risk Status with Specific Cytogenetic Patterns	Incidence (%)		CR Rates (%)		5-Year Survival Rate (%)	
	SWOG	MRC	SWOG	MRC	SWOG	MRC
Favorable						
inv(16), t(16;16), t(8;21), t(15;17)	20	23	84	91	55	65
Intermediate						
normal, +8, +6, –y	46	66	76	86	38	41
Unfavorable						
del5q, –5, del7q, –7, complex	30	10	55	63	11	14
Unknown risk	4	—	54	—	24	—

CR, complete response; MRC, Medical Research Council; SWOG, Southwest Oncology Group.

*The SWOG study includes only adults and does not exclude secondary AML, whereas the MRC data refer to both children and adults and exclude cases of secondary AML. In the SWOG data, 11q23 is defined as unfavorable, whereas in the MRC data, 11q23 is considered intermediate risk.

Table 104-3 FAB Classification of Acute Myeloid Leukemia

Subtype	Definition
M0: acute undifferentiated leukemia	≥30% blasts
	<3% myeloperoxidase-positive
	Myeloid antigen expression
M1: AML with minimal differentiation	30% blasts
	≥3% myeloperoxidase-positive
	<10% cells mature beyond blast stage
M2: AML with differentiation	>30% blasts
	≥3% myeloperoxidase-positive
	>10% myeloid cells mature beyond blast stage
M3: acute promyelocytic leukemia	>30% blasts plus hypergranular promyelocytes
	Intense myeloperoxidase positivity
M4: acute myelomonocytic leukemia	Monocytosis
	>30% myeloblasts + monoblasts + promonocytes
	>20% myeloperoxidase-positive
	>20% nonspecific esterase-positive
M5: acute monoblastic leukemia	>30% myeloblasts + monoblasts + promonocytes
	<20% myeloperoxidase-positive
	>80% nonspecific esterase-positive
M6: acute erythroid leukemia	≥30% of nonerythroid cells are myeloblasts
	>50% erythroid elements
M7: acute megakaryocytic leukemia	>30% blasts (myeloblasts + megakaryoblasts)
	>30% megakaryocytic elements defined by immunophenotyping or electron microscopy

Table 104-4 World Health Organization Classification of Acute Myeloid Leukemia

ACUTE MYELOID LEUKEMIA WITH RECURRENT GENETIC ABNORMALITIES

Acute myeloid leukemia with t(8;21)(q22;q22), AML1/ETO

Acute myeloid leukemia with abnormal bone marrow eosinophils and inv(16)(p13q22) or t(16;16)(q13;q22), CBFβ/MYH11

Acute promyelocytic leukemia with t(15;17)(q22q12), PML/RARα and variants

Acute myeloid leukemia with 11q23 (MLL) abnormalities

ACUTE MYELOID LEUKEMIA WITH MULTILINEAGE DYSPLASIA

Following MDS or MDS/MPD

Without antecedent MDS or MDS/MPD, but with dysplasia in at least 50% of cells in two or more myeloid lineages

ACUTE MYELOID LEUKEMIA AND MYELODYSPLASTIC SYNDROMES, THERAPY-RELATED

Alkylating agent/irradiation-related type

Topoisomerase II inhibitor-related type (some may be lymphoid)

Others

ACUTE MYELOID LEUKEMIA, NOT OTHERWISE CATEGORIZED

Classify as

- Acute myeloid leukemia, minimally differentiated
- Acute myeloid leukemia without maturation
- Acute myeloid leukemia with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic leukemia
- Acute erythroid leukemia (erythroid/myeloid and pure erythroleukemia)
- Acute megakaryocytic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis
- Myeloid sarcoma

MDS, myelodysplastic syndrome; MLL, mixed-lineage leukemia; MPD, myeloproliferative disease.
Data from ref. 78.

masses. Gingival hyperplasia due to leukemic infiltration of the gums sometimes is seen, particularly with M5 AML (Fig. 104-6). Leukemia sometimes infiltrates the skin, resulting in a raised, nonpruritic rash termed leukemia cutis (Fig. 104-7). Uncommonly, an occasional patient may present with meningeal signs or cranial neuropathies (most often affecting cranial nerve IV or VII) due to infiltration of the CNS with leukemia.



Figure 104-6 • Leukemic infiltration of the gums results in their expansion and thickening, with partial covering of the teeth.

LABORATORY MANIFESTATIONS

Peripheral blood counts are abnormal at diagnosis in virtually every case of AML. Most patients have a normochromic, normocytic anemia. Most also are thrombocytopenic, with 50% of patients having less than 50,000 platelets/mm^3 and 25% having below 20,000/mm^3. Most patients are granulocytopenic, but the total WBC count is more variable. Approximately 25% have very high WBC counts (greater than 50,000/mm^3), approximately 25% have low WBC counts (less than 5000/mm^3), and the remainder are in between. Blasts usually can be seen in peripheral blood smears.

Bone marrow examination generally reveals a hypercellular marrow containing 20% to 100% blast cells largely replacing the normal marrow. The morphologic, immunologic, and cytogenetic characteristics of AML are described in earlier sections of this chapter.

The partial thromboplastin and prothrombin times can be prolonged, and in APL, reduced fibrinogen and other evidence of disseminated intravascular coagulation (DIC) are not infrequent. Results



Figure 104-7 • Acute myeloid leukemia: M5 subtype. **A,** Multiple, raised, erythematous skin lesions caused by leukemic infiltration. **B,** Close-up view of nodular skin lesion. (From Hoffbrand AV, Pettit JE: Color Atlas of Clinical Hematology, 3rd ed. St. Louis, Mosby, 2000.)

of blood chemistry studies usually are normal, although in patients presenting with very aggressive and advanced disease, some evidence of tumor lysis syndrome at presentation is not uncommon, with hyperkalemia, hyperphosphatemia, hyperuricemia, hypocalcemia, increased lactate dehydrogenase, and renal insufficiency. This syndrome more often manifests shortly after therapy is initiated and can be rapidly fatal if it goes untreated. Occasional patients with monocytic leukemia may have tumor infiltration of the kidneys sufficient to cause renal impairment. Lumbar puncture will reveal unsuspected involvement with leukemia in approximately 2% of patients.[81]

DIFFERENTIAL DIAGNOSIS

The diagnosis of AML usually is straightforward. The distinction between AML and advanced MDS is made according to the percentage of blasts and often is arbitrary, with little clinical relevance. Distinguishing AML from ALL can virtually always be accomplished using immunophenotyping. CML in myeloid blast crisis can mimic AML, but the presence of the Philadelphia chromosome, splenomegaly, and myeloid cells at all levels of differentiation distinguish CML from AML. Other small round cell neoplasms can infiltrate the marrow, sometimes mimicking leukemia, but immunologic markers easily differentiate between the two conditions. Leukemoid reactions sometimes are seen in infections such as tuberculosis, but the proportion of blasts in the marrow in nonmalignant diseases virtually never reaches the 20% to 30% required for a diagnosis of AML. Infectious mononucleosis and other viral infections sometimes can resemble ALL but are almost never confused with AML.

PRIMARY TREATMENT

Advances in chemotherapy, HCT, and supportive care now enable many patients with AML to be cured. These therapeutic measures are complex, however, so they are best conducted at centers with appropriate experience and support services. Leukemia often is a rapidly progressive disease; accordingly specific therapy should be initiated soon after diagnosis—usually within 72 hours. Before therapy is initiated, acute hemorrhage and infection should be brought under control if at all possible. Patients should be hydrated and given allopurinol, 100 to 200 mg orally three times a day, to prevent uric acid nephropathy. Ideally, stable venous access should be established by placement of a Hickman or similar catheter. The diagnosis of leukemia causes a profound shock to the patient and family and has far-reaching implications. Thus, in addition to stabilizing the patient medically, many practitioners find it valuable to have a formalized conference at which the patient and family can be instructed about the nature of leukemia, the immediate plans for therapy, and the likely consequences of treatment.

Management of Emergencies

Any of number of treatable emergencies may require management before specific antileukemic therapy can begin. Severe bleeding from thrombocytopenia usually can be controlled with platelet transfusions. DIC typically is associated with a diagnosis of APL. This coagulopathy rapidly abates with the institution of ATRA therapy, so many of the measures used in the past to attempt control of DIC (i.e., low-dose heparin, fresh-frozen plasma, and fibrinogen) are now no longer needed. In patients with fever and granulocytopenia, blood specimens should be obtained for culture, but meanwhile, broad-spectrum antibiotic therapy should be started on an empirical basis. Very high WBC counts may constitute early evidence of tumor lysis syndrome; in such instances, the patient should be hydrated, placed on allopurinol to prevent further uric acid production, and given acetazolamide (500 mg daily) to alkalinize the urine. Patients presenting with very high WBC counts (greater than 100,000/mm^3) also are at risk for hemorrhage or microinfarctions of small vessels, presumably due to leukostasis. Lung involvement can result in pulmonary infiltrates and hypoxia; CNS leukostasis can lead to mental status changes, seizures, and sudden death. Pulmonary or CNS leukostasis represents a medical emergency requiring intravenous hydration and measures to lower the blast count immediately. Although oral hydroxyurea often is used, whether it lowers counts any faster than intravenous cyclophosphamide, daunorubicin, or cytarabine is unknown. Leukapheresis is of short-term benefit.[82] Patients with CNS symptoms should be given whole-brain irradiation emergently. Leukostasis has been associated with the expression of the adhesion molecule CD14 on malignant blasts; this may explain why the syndrome is almost never seen in lymphoid leukemias, in which this antigen is lacking.[83]

Remission Induction

General Principles

Without therapy, AML is a rapidly fatal disease; therefore, prompt initiation of antileukemic therapy is appropriate for a majority of patients. Some patients, however, may have a more smoldering variant of AML, often arising from a previous MDS. If such patients are elderly or have other serious medical problems, supportive care measures without attempts at remission induction or less intense chemotherapy designed to slow the progression of disease may be appropriate. The large majority of patients, however, should receive combination chemotherapy in an effort to eradicate the bulk of leukemic cells and allow the regrowth of normal marrow, resulting in a complete remission. Induction chemotherapy generally is given at relatively high doses and is followed by a period of significant pancytopenia before recovery of normal hematopoiesis. As discussed later on, most regimens include 3 days of an anthracycline and 7 days of cytarabine. The usual practice is to check the marrow status at day 14 after initiation of induction and then, if residual leukemic cells remain, to give a second course of therapy. Sometimes it is difficult to distinguish between residual leukemic cells and early recovery of normal hematopoiesis. In these cases, it is advisable to reassess marrow status in a few days. According to International Working Group recommendations, a morphologic complete remission (i.e., "complete response") requires less than 5% blasts with recovery of peripheral counts to an absolute neutrophil count greater than 1000 mL

and a platelet count greater than 100,000 mL.[84,85] Complete remission does not imply eradication of the disease, and with newer, more sensitive technologies, leukemic cells can sometimes be detected in patients with a morphologic complete remission. If only induction therapy is given, disease will recur in essentially every patient. In an effort to consistently define the reasons for failure of induction chemotherapy, the International Working Group suggests that patients be categorized as those with resistant leukemia, those who die from complications of aplasia, and those who die but in whom information is insufficient to determine if the cause is persistent leukemia or failure of marrow recovery.[84]

Some studies of remission induction conducted in the 1970s suggested that the reasons for treatment failure tended to differ between younger and older patients, with relatively few patients younger than 55 to 60 years of age dying of early treatment-related complications but with a much higher incidence of this problem among older persons. Accordingly, more recently, separate studies have been conducted for younger and older patients.

Remission Induction in Younger Patients

For more than 2 decades, standard induction therapy for patients with AML who are younger than 60 years of age generally has included 3 days of an anthracycline and 7 days of cytarabine. Four general questions dominated previous clinical trials of induction therapy:

1. What are the best type and dose of anthracycline?
2. What are the best dose and schedule of cytarabine?
3. Should additional chemotherapeutic agents be added?
4. Is there a role for hematopoietic growth factors?

Daunorubicin, 45 mg/m^2 for 3 days, generally has been viewed as the standard anthracycline component of therapy. Four randomized trials have compared idarubicin, 12 mg/m^2 for 3 days, with daunorubicin, 45 mg/m^2 for 3 days, both given with standard-dose cytarabine.[86–89] The complete response rates were higher with idarubicin in three of the four trials, particularly in patients younger than 50. A problem with these studies is that idarubicin and daunorubicin were not compared at equitoxic doses. For example, the degree of myelosuppression during consolidation was considerably greater with idarubicin. No prospective randomized trial has yet been completed comparing daunorubicin in a dose of 45 mg/m^2 with daunorubicin at 60 or 70 mg/m^2—doses that have been shown to be well tolerated by patients younger than 60 years. Nor have randomized trials been reported comparing idarubicin to the higher-dose daunorubicin regimens. On the other hand, sequential trials from both the Southwest Oncology Group (SWOG) and the Eastern Cooperative Oncology Group (ECOG) suggest that in patients below age 60, complete response rates are higher with higher doses of daunorubicin (i.e., 60 or 70 mg/m^2 for 3 days) than with lower doses (i.e., 45 mg/kg/m^2 for 3 days).[90–93]

Cytarabine generally is given intravenously at a dose of 100 to 200 mg/m^2 per day by bolus or by continuous infusion. Much higher doses of cytarabine are tolerable, and two prospective randomized trials compared a combination of daunorubicin and standard cytarabine with daunorubicin and cytarabine at 2 g/m^2 per day for 6 days.[91–94] In neither study was the complete response rate increased, although in the SWOG study, patients in the high-dose induction group tended to have an improved disease-free survival. The use of high-dose cytarabine is associated with more frequent and severe toxicities including more nausea, vomiting, and conjunctivitis. In an occasional patient, a disabling cerebellar toxicity may develop.

Whether the addition of a third drug to the standard daunorubicin-plus-cytarabine regimen is beneficial is uncertain. Some regimens add 6-thioguanine, but no randomized trial exists showing a benefit. The addition of etoposide was studied by the Australian Leukemia Study Group and did not increase complete response rates but seemed to prolong disease-free survival without benefiting overall survival.[95]

Because profound myelosuppression always follows administration of induction chemotherapy, a large number of trials have asked whether administration of a myeloid growth factor immediately after completion of induction chemotherapy might hasten marrow recovery, thereby preventing serious and potentially lethal infections and improving complete response rates.[96–100] In general, these studies found that administration of a myeloid growth factor after completion of induction chemotherapy accelerates subsequent myeloid recovery. In only a minority of studies, however, did this accelerated recovery result in fewer documented infections, and in only the rare study was the complete response rate or survival affected. In those studies in which addition of growth factor was assessed, the dollars saved by shorter hospitalizations with the use of these factors were approximately balanced by the cost of the agent.[101,102] Administration of hematopoietic growth factors simultaneous with chemotherapy in an effort to induce cycling of leukemia and thus sensitize cells to treatment has yielded mixed results.[103]

In summary, standard induction therapy for younger patients with AML continues to be 3 days of an anthracycline dosed at an intensity approximately equal to that of daunorubicin 60 mg/m^2 per day and 7 days of cytarabine. There is a lack of convincing evidence that alternatives in the dosing of cytarabine, inclusion of other chemotherapeutic agents, or the addition of hematopoietic growth factors consistently improves complete response rates or prolongs survival.

Despite optimal therapy, as many as 30% of younger adults fail to achieve a complete remission with initial induction therapy—some because they die of treatment complications, others because they have resistant leukemia. Allogeneic HCT can cure 15% to 20% of patients in whom initial induction attempts fail, but the logistics of identifying a donor and initiating transplantation in a timely manner for such patients often are challenging. To facilitate this process, HLA typing should be sought in all younger patients with AML and siblings shortly after diagnosis, rather than waiting until induction has failed and only a very narrow window of opportunity remains for potentially curative therapy.

Remission Induction in Older Patients

The advantages seen with more intensive anthracycline dosing—daunorubicin doses above 458 mg/m^2 for 3 days or the equivalent—generally have been restricted to younger patients. For patients older than 60 years, most experts suggest limiting the anthracycline to a dose equivalent to daunorubicin 45 mg/m^2 for 3 days, although clinical trials are under way to test more intensive dosing. As in younger patients, no clear advantage has been observed for one anthracycline over another when relatively equitoxic doses are used. A recent ECOG study compared daunorubicin with mitoxantrone or idarubicin (all given with standard-dose cytarabine) and found no advantage for any single treatment regimen.[93] As with younger patients, no evidence has been found for an advantage of high-dose cytarabine or for the addition of further chemotherapeutic agents to the induction regimen for older patients. Many of the studies of the addition of hematopoietic growth factors to AML induction have been restricted to older patients, but, as with younger patients, the advantages of the addition of growth factor appear to be limited to faster hematopoietic recovery and fewer days with neutropenic fever, but with no consistent improvement in complete response rates or overall survival.

In virtually every study conducted to date, the complete response rate drops as the age of patients increases. Although some of this effect could be due to a diminished ability of patients to tolerate therapy and to a tendency of physicians to reduce doses in older patients, even when identical doses of drugs are used and toxic deaths are censored, the incidence of remission failures increases with age. AML among older patients is much more likely to evolve from a myelodysplastic syndrome, to be accompanied by unfavorable-risk cytogenetics, and to be associated with expression of the multidrug resistance gene.[104–106] All three of these have been found to be independent risk

factors mitigating against the likelihood of achieving a complete remission. Thus, in a recent SWOG study of remission induction in patients with AML who are older than 55 years of age, the overall complete response rate with use of a standard preparative regimen was 45%. If patients had none of these three factors, their complete response rate was 81%, whereas if all three factors were present, the complete response rate was less than 15%.[104] Similar results have been reported by a group of investigators at the M.D. Anderson Cancer Center.[107]

Postremission Therapy

General Principles

If no further therapy is given after remission is achieved, all patients will inevitably relapse and do so rapidly (on average in about 4 months), demonstrating the need for further therapy.[108] Three types of postremission therapy are in general use: chemotherapy, autologous HCT, and allogeneic HCT.

Postremission Chemotherapy

Postremission chemotherapy usually consists of several cycles of combination chemotherapy given at doses similar to those used for induction. This form of therapy often is termed *consolidation* when given within a few months of induction or *late intensification* if given after a greater delay. Some trials also have explored the use of low-dose "maintenance" chemotherapy.

Most contemporary protocols include several consolidation cycles of high-dose cytarabine. The rationale for high-dose cytarabine came from studies suggesting that at higher doses, the drug is able to saturate deaminating enzymes resulting in production of higher levels of the active intracellular metabolite ARA-CTP, which in turn leads to enhanced inhibition of DNA synthesis.[109] Early phase I and II trials suggested that high-dose cytarabine regimens were tolerated and could result in complete remissions in patients with relapsed AML.[110,111] These observations led to the use of high-dose cytarabine for consolidation therapy after initial remission induction, with several phase II studies reporting sustained remissions in 30% to 40% of adults.[112,113]

Ultimately, several large randomized trials have explored the value of high-dose cytarabine for postremission therapy in adult cases of AML.[91,114] The Cancer and Leukemia Group B (CALGB) randomly assigned 596 patients in complete remission to receive four courses of cytarabine at one of three doses:

1. 100 mg/m^2/day by continuous infusion for 5 days
2. 400 mg/m^2/day by continuous infusion for 5 days
3. 3 g/m^2 as a 3-hour intravenous infusion twice daily on days 1, 3, and 5

High rates of CNS toxicity were observed among patients older than 60 years, and subsequent randomizations were limited to younger patients. At 3 years, disease-free survival rates were 21% in the 100-mg group, 25% in the 400-mg group, and 39% in the 3-g group. This trial established three or four doses of cytarabine at 3 g every 12 hours on days 1, 3, and 5 as among the most widely used consolidation regimens for younger patients with AML in first remission. Subsequent analyses have demonstrated that the advantage achieved with the highest-dose regimen was restricted to patients with favorable cytogenetics; thus, the intermediate-dose regimen may be as appropriate for patients with intermediate or unfavorable cytogenetics.[80] A SWOG trial randomized patients to receive conventional or high-dose cytarabine during both induction and consolidation.[91] The best result (52% 4-year survival rate) was seen among patients who received the high-dose cytarabine regimen, a result consistent with those of the CALGB study.

A number of other multiagent postremission chemotherapy regimens have been developed. For example, the MRC reported on a regimen that uses as consolidation a cycle of standard anthracycline plus cytarabine; a cycle of MACE combining amsacrine, conventional-dose cytarabine plus etoposide; and a cycle of high-dose cytarabine plus mitoxantrone. The reported results looked generally similar to those reported by CALGB and SWOG.[115] No large randomized trials have been conducted comparing the various more commonly used consolidation regimens. These regimens, which include repetitive cycles of high-dose therapy, generally are inappropriate for patients older than 60 years of age. Most older patients are given several cycles of combination chemotherapy at moderate dosing, such as 2 days of daunorubicin plus 5 days of conventional-dose cytarabine. Almost no data are available suggesting superiority of any particular consolidation regimen for older patients with AML.

With the increasing acceptance of short-term intensive consolidation chemotherapy as the standard for younger patients with AML, the concept of low-dose maintenance has fallen into disuse. Data from randomized trials in both younger and older patients, however, demonstrate that maintenance therapy can prolong the duration of first remission, although an impact on overall survival has not been seen.[90,116,117]

Autologous Hematopoietic Cell Transplantation

The principles underlying the concept of autologous HCT and the general technique are outlined in Chapter 32 and are not repeated here. Based on encouraging results in patients in second or subsequent remission, a number of single-center phase II trials of autologous HCT for AML in first remission were conducted and reported in the mid-1980s.[118–120] These small trials provided encouraging results, leading to wider use of the technique. Registry data describing results in hundreds of patients soon became available and suggested leukemia-free survival rates of approximately 45% at 5 years.[121] In an effort to minimize the possible impact of treatment selection bias, several large prospective randomized trials have been conducted in which adults in first remission with matched siblings have been assigned to allogeneic transplantation, whereas those without have been randomized to receive either autologous HCT or postremission chemotherapy. Relapse rates were reduced in most trials with the use of autologous transplantation compared with chemotherapy.[115,122–124] In several of these studies, autologous transplantation resulted in an improvement in disease-free survival, whereas in the others, it did not. Which patients may best benefit from autologous HCT in first remission is considered in the ensuing discussion, after the presentation of data related to studies of allogeneic transplantation.

A large number of questions exist about how best to conduct autologous HCT for AML. The most commonly used preparative regimens are combinations of busulfan plus cyclophosphamide, busulfan plus etoposide, or cyclophosphamide plus total body irradiation (TBI), but few randomized trials have been conducted.[125,126] Registry data suggest relative equivalence among regimens. Although gene-marking studies have provided unequivocal evidence that occult tumor cells in remission marrow can contribute to the risk of relapse, no comparative clinical trials have been published to confirm that the methods of ex vivo purging are of any clinical benefit.[127,128] The prospective studies that show the greatest benefit of autologous HCT used it after three or four cycles of intensive therapy, whereas the studies that showed the least benefit applied the treatment almost immediately after induction. Because these were randomized trials, effects of patient selection on lead time bias should have been minimized, suggesting that autologous transplantation is of greatest differential benefit if applied *after* consolidation therapy, rather than as a substitute for it.

Allogeneic Hematopoietic Cell Transplantation

The initial application of allogeneic HCT to treat AML was published by Thomas and colleagues[129] in 1977, when they reported on

54 patients with recurrent or refractory AML treated with TBI-containing regimens and allogeneic HCT. At the time of the report, seven of these patients were alive in remission, and a subsequent follow-up more than 13 years later showed that 6 of the 54 remained alive and disease-free.[130] In 1979, Thomas and associates[131] published the initial results of a trial of allogeneic HCT for patients in first remission, reporting for a small group of patients a 5-year disease-free survival rate in excess of 50%. Similar results were soon reported by other investigators as well.[132,133] The results reported in these small, uncontrolled, single-institution series were far superior to anything achieved at the time with conventional chemotherapy, but the potential impact of patient selection bias was unknown. Accordingly, these small, single-institution series were soon followed by a substantial number of single-institution or group trials comparing allogeneic transplantation for patients for whom donors were available with conventional chemotherapy for patients without donors. Studies published in the mid-1980s from the Royal Marsden, Seattle, UCLA, and Genoa all showed a markedly diminished risk of relapse with transplantation, a higher risk of treatment-related death with transplantation, and, in all four studies, improved disease-free survival with transplantation.[134–137]

Since the mid-1980s, of course, significant changes have occurred in both chemotherapy and the practice of allogeneic HCT, so comparisons of these techniques continue to be made. A recent meta-analysis included all studies published since 1995 that compared allogeneic HCT with chemotherapy or autologous HCT using an intention-to-treat analysis. The meta-analysis comprised 3100 subjects and demonstrated an overall survival advantage for allogeneic transplantation with a summary hazard ratio of 1.15. The survival advantage was greatest for patients with high-risk leukemia (hazard ratio, 1.39) but was lost in patients with favorable-risk cytogenetics (hazard ratio, 0.9).[138]

The general technique of allogeneic HCT is described in Chapter 32 and is not repeated here, except for the following few points specifically relevant to AML: Postremission consolidation chemotherapy before allogeneic HCT for AML in first remission does not improve outcome compared with proceeding directly to transplantation after achievement of first remission.[139] The optimal preparative regimen for transplantation of AML in first complete remission is arguable. One prospective randomized trial demonstrates superiority of cyclophosphamide plus TBI over busulfan plus cyclophosphamide.[140] A subsequent large registry study, however, found equivalence between the two approaches.[125] Although bone marrow has been the usual source of stem cells, three recent randomized trials have shown faster engraftment with the use of granulocyte colony stimulating factor (G-CSF)-mobilized peripheral blood without increasing acute graft-versus-host disease (GVHD).[141–143] In all three studies, a trend toward more chronic GVHD was observed with the use of peripheral blood, but in two of three trials, overall survival was improved with the use of peripheral blood as a source of stem cells. The combination of cyclosporine plus methotrexate is the most commonly used form of GVHD prophylaxis. Although some encouraging phase I and II studies of T-cell depletion have been published, no randomized trials have demonstrated an advantage of T-cell depletion for patients with AML in first remission.[144] Recent trials using unrelated donors have shown results approaching those achieved with fully matched siblings.

Selection of Appropriate Postremission Therapy

Postremission chemotherapy, autologous transplantation, and allogeneic transplantation all represent viable treatment options for the younger patient with AML in first remission. Opinions vary among experts, but in general, most would recommend allogeneic transplantation using a matched sibling or an unrelated donor for patients with AML and unfavorable-risk cytogenetics. For patients with favorable-risk cytogenetics, most experts would recommend consolidation chemotherapy with repetitive cycles of high-dose cytarabine. Opinions regarding management of patients with intermediate-risk cytogenetics are more varied and may be influenced by subtle risk factors such as the age of the patient, the WBC count at diagnosis, and *NPM1* and *FLT3* mutation status, with transplantation being favored for patients with higher-risk disease. The foregoing recommendations are consistent with those of the National Comprehensive Cancer Network.[145]

For patients older than 60 years of age, conventional myeloablative transplantation normally is not used, although recent studies of nonmyeloablative transplantation for patients older than 60 are showing promise.[146] The advantages of autologous transplantation seen in randomized trials were restricted to patients younger than 60. With older patients, as with all patients with AML, participation in well-designed clinical trials is appropriate and should be pursued actively.

TREATMENT OF RECURRENT ACUTE MYELOID LEUKEMIA

General Principles

Allogeneic or autologous HCT is the only therapy shown to be curative in a substantial proportion of patients with recurrent AML. For those patients who are transplantation candidates, who are found to be in early first relapse, and who have a previously identified source of stem cells, it may be appropriate to proceed directly to transplantation.[147,148] For all other patients, an initial trial of chemotherapy in an attempt to obtain a second remission is appropriate (Box 104-1).

Reinduction Chemotherapy

A number of large observational studies of reinduction chemotherapy have been published over the last 2 decades.[149–153] In general, complete response rates have ranged from 30% to 50%, and the mortality rates associated with reinduction have been 15% to 25%. Three prognostic factors have consistently been identified with an improved outcome: younger age, favorable cytogenetic risk group, and longer duration of first remission.

Box 104-1. MANAGEMENT OF NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA IN PATIENTS YOUNGER THAN 60 YEARS OF AGE

Induction

Daunorubicin, 60 mg/m^2/day for 3 days (or idarubicin, 12 mg/m^2/day for 3 days), plus cytarabine, 200 mg/m^2/day for 7 days, is the standard induction regimen.

Postremission

Favorable risk: Cytarabine, 3 g/m^2 over 3 hours every 12 hours, is given on days 1, 3, and 5 for four courses; autologous stem cells are stored if no HLA-matched sibling donor is available.

Intermediate risk: If an HLA-matched sibling is available, allogeneic transplantation is indicated. If no HLA-matched sibling is available, cytarabine, 3 g/m^2 over 3 hours, every 12 hours on days 1, 3, and 5, is given for two courses, followed by autologous transplantation.

Unfavorable risk: If an HLA-matched sibling or HLA-matched unrelated donor is available, allogeneic transplantation is performed. If no such donor is available, management is the same as for intermediate-risk disease.

HLA, human leukocyte antigen.

A limited number of randomized trials have been conducted in this group of patients. Vogler[154] found that adding etoposide to high-dose cytarabine was of no advantage, whereas Karanes[155] demonstrated a benefit of adding mitoxantrone to high-dose cytarabine. List and associates[156] conducted a randomized trial testing whether the addition of cyclosporine to a regimen of high-dose cytarabine plus infusional daunorubicin would be of benefit. This study was based on the high incidence of multidrug resistance in recurrent AML and the ability of cyclosporine at clinically achievable levels to reverse drug resistance. In this randomized trial, the investigators found a drug resistance reduced incidence of resistant leukemia with the addition of cyclosporine and a resulting improvement in both disease-free and overall survival.

Gemtuzumab ozogamicin combines a humanized anti-CD33 antibody with the potent antitumor agent calicheamicin. Gemtuzumab ozogamicin was developed on the basis of the observation that CD33 is expressed in virtually all cases of AML but not by normal hematopoietic stem cells or in nonhematopoietic tissues, and on the conclusion that by targeting CD33, a less toxic, effective therapeutic might result. Phase I studies showed saturation of CD33 antigenic sites at 9 mg/m^2 and clearing of leukemic blasts in many patients at this dose.[157] Subsequent phase II trials showed a complete response rate of 30% with less toxicity than might be expected with aggressive combination chemotherapy.[158] On the basis of this result, gemtuzumab ozogamicin was approved by the U.S. Food and Drug Administration (FDA) for the treatment of recurrent AML in older patients.

A large number of agents are in clinical trials including FLT-3 inhibitors, farnesyl transferase inhibitors, HD inhibitors, antiangiogenic agents, inducers of apoptosis, and deoxyadenosine analogs, among others.

Hematopoietic Cell Transplantation for Recurrent Disease

Approximately 30% of patients with AML who undergo transplantation of marrow from matched siblings for untreated first relapse can expect to become long-term disease-free survivors.[159–162] Autologous transplantation using marrow previously stored in first remission has resulted in a 26% 5-year disease-free survival rate.[161] These outcomes are not markedly less than what might be expected for transplantation in second remission, so for those patients in early relapse with an identified source of stem cells, immediate stem cell transplantation is a reasonable option.

A majority of patients will require reinduction, however. For those patients who achieve a second remission, have a matched sibling, and are younger than 55 years, allogeneic transplantation is the preferred form of therapy, and cure can be expected in 35% of cases.[162] Although the published experience is less extensive, similar cure rates have been reported for older patients undergoing reduced-intensity allogeneic HCT.[146] For patients without matched siblings, either autologous or matched unrelated donor transplantation should be considered. No randomized trials have been conducted comparing either approach to further chemotherapy or the two approaches to one another. In a retrospective case-control study by the European Bone Marrow Transplant Group, no statistically significant difference in disease-free survival or overall survival rate was found between autologous and matched unrelated-donor transplantation approaches.[163] Without further outcome data, the decision between autologous versus unrelated-donor transplantation for AML in second remission is difficult, but an allogeneic approach may be appropriate for younger patients with poor-risk disease characteristics (e.g., a short remission duration and unfavorable cytogenetics), whereas autologous transplantation is a good strategy for older patients with more favorable disease characteristics, including long duration of first remission.

The results of transplantation for patients in whom reinduction cannnot be achieved are less favorable, and long-term survival can be expected in only 10% to 20% of patients undergoing allogeneic transplantation for refractory AML.[164]

TREATMENT OF ACUTE PROMYELOCYTIC LEUKEMIA

APL is distinguished by both the t(15;17) translocation and a unique pattern of drug sensitivity demanding a different treatment strategy from those for other categories of AML. Specifically, APL is particularly sensitive to anthracyclines and to all-*trans*-retinoic acid (ATRA), and with appropriate use of both drugs, a high percentage of APL patients can expect to be cured[165–167] (Box 104-2).

Initial Therapy

A number of studies have been conducted in the attempt to define the best ways to incorporate high-dose anthracyclines plus ATRA into the management of newly diagnosed patients with APL. The use of ATRA as a single agent for induction results in complete response rates as high as those achieved with conventional chemotherapy regimens including anthracycline, and in improved overall survival.[168] A European APL study has since shown that concurrent administration of ATRA with the chemotherapy regimen results in an improvement in overall event-free survival (84% versus 77% at 2 years).[169] Combining chemotherapy and ATRA during induction has the added benefit of reducing the incidence of the retinoic acid syndrome (to be discussed shortly) from 25% down to less than 10%, and this is now considered standard therapy.

Consolidation chemotherapy for APL generally involves giving repeated cycles of a regimen consisting of an anthracycline and ATRA. The optimal number of cycles of consolidation is unknown.

A clear role is recognized for maintenance therapy in APL.[170] In a large North American Intergroup study, patients were randomly assigned to receive maintenance therapy with daily ATRA or to observation. Those who received ATRA had an improved disease-free survival.[168,171] Because ATRA induces enzymes that enhance its

Box 104-2. MANAGEMENT OF ACUTE PROMYELOCYTIC LEUKEMIA

Newly Diagnosed Disease

Induction

ATRA, 45 mg/m^2/day until CR is achieved, plus daunorubicin, 60 mg/m^2/day for 3 days, and cytarabine, 200 mg/m^2/day for 7 days, is the standard induction regimen.

Consolidation

Two cycles of the following regimen are given: ATRA, 45 mg/m^2/day for 7 days, and daunorubicin, 50 mg/m^2/day for 3 days.

Maintenance

ATRA, 45 mg/m^2/day for 15 days every 3 months, plus 6-MP, 100 mg/m^2/day, and MTX, 10 mg/m^2/week for 2 years, is the maintenance regimen.

Recurrent Disease

Induction

Arsenic trioxide, 0.15 mg/kg daily, is given until a second CR is achieved.

Consolidation

Autologous transplantation is indicated if PCR assay-negative stem cells are available; otherwise, allogeneic transplantation is performed if a suitable donor is available.

ATRA, all-*trans*-retinoic acid; CR, complete response; 6-MP, 6-mercaptopurine; MTX, methotrexate; PCR, polymerase chain reaction.

metabolism, many investigators have suggested that intermittent ATRA therapy may be advantageous. The European APL 93 trial randomized patients to receive intermittent ATRA, 6-mercaptopurine plus methotrexate, or a combination of intermittent ATRA plus the combination chemotherapy. The patients in the treatment group receiving maintenance ATRA plus chemotherapy had the best overall survival.[169]

With current management, the prognosis for patients with APL has improved remarkably from what it was in the 1980s. For example, in the North American Intergroup Trial, the 5-year survival rate for patients randomized to receive ATRA induction and maintenance therapies was 69%.[168,171] Both age and WBC count at diagnosis have prognostic importance, with best results seen in patients younger than 55 years and those presenting with a WBC count less than 10,000/mm^3.[172] Because of the excellent outcome with current regimens, transplantation has no generally accepted role during first remission of APL.

Treatment of Recurrent Acute Promyelocytic Leukemia

In addition to its unique sensitivity to ATRA, APL also is remarkably sensitive to treatment with arsenic trioxide, as first reported by investigators from China.[173,174] A more recent multicenter study has reported an 85% complete response rate among patients with recurrent APL using arsenic trioxide.[175] The most important forms of toxicity include prolongation of the QT interval and a syndrome essentially identical to the retinoic acid syndrome, to be discussed shortly. The QT prolongation requires careful monitoring, because two recent reports have documented sudden deaths associated with the use of arsenic trioxide.[176,177] Thus, metabolic abnormalities that also prolong the QT interval, such as hypokalemia, hypophosphatemia, and hypomagnesemia, should be corrected before therapy is initiated. Currently, reinduction with arsenic trioxide generally is considered as the initial treatment of choice for patients with APL in whom first-line therapy has failed, particularly if that failure occurred within 12 months of therapy with ATRA.

Data are limited regarding the expected duration of second remission induced with arsenic trioxide. Although some patients may remain in remission for some time if given arsenic plus chemotherapy, most experts would recommend either autologous or allogeneic HCT for patients with APL in second remission. Sanz and associates[178] presented results from the European Blood and Marrow Transplant Group for patients with APL in second remission and reported overall survival rates of 58% for allogeneic transplantation and 40% for autologous transplantation. The choice of autologous or allogeneic HCT may be influenced by the status of the autologous stem cell source. In a small but provocative study, Meloni reported on 15 patients with APL in second remission undergoing autologous transplantation. Only one of eight patients who received PCR assay-negative marrow subsequently relapsed, whereas all seven who received PCR assay-positive marrow did so.[179]

Retinoic Acid Syndrome

After therapy with ATRA, a proportion of patients with APL exhibit a syndrome manifested by fever, weight gain, respiratory distress, pulmonary infiltrates and effusions, episodic hypotension, and renal failure.[180] When ATRA is used as a single agent, this syndrome can be seen in as many as 25% of cases. Risk factors for the development of the syndrome are not obvious, but the simultaneous administration of chemotherapy during induction has seemed to diminish the risk of its development. The mortality rate for this syndrome, when first described, was about 30%, but with the recognition that the syndrome responds dramatically to the institution of dexamethasone, mortality rates have fallen to less than 5%. The observation that an identical syndrome can be seen with arsenic trioxide suggests that the syndrome probably is associated with the differentiation of APL cells and is inaccurately named.

Supportive Care

The treatment of AML is accompanied by a substantial number of complications and thus is best conducted at a center experienced in the management of these sometimes complex cases. During the granulocytopenic period after intensive induction and consolidation chemotherapy, most patients become febrile, and bacterial infections can be documented in roughly 50%. Gram-positive organisms (e.g., *Staphylococcus epidermidis*) and gram-negative enteric organisms (e.g., *Escherichia coli*, *Klebsiella/Aerobacter*) are common, but the experience can vary by medical center. Reactivation of herpes simplex infections can add to mucositis, and fungal infections can develop in patients on antibiotics. Thus, we generally recommend the following oral antimicrobial prophylactic regimen before initiation of chemotherapy: ciprofloxacin, 500 mg every 12 hours; fluconazole, 200 mg daily; and acyclovir, 800 mg every 12 hours. Patients who become febrile while neutropenic should be started on broad-spectrum antibiotics, such as monotherapy with imipenem, or a combination of an antipseudomonal penicillin and a third-generation cephalosporin. If patients are persistently febrile after 72 hours of broad-spectrum antibiotic therapy, additional antibiotics or antifungal coverage should be considered. The choice should be dictated by the unique clinical circumstances of the patient. Patients should continue on broad-spectrum antibiotics until recovery of granulocyte counts and defervescence are obtained.

In patients with APL, hemoglobin should be maintained above 8 to 10 g/dL, and platelet counts should be kept above 10,000/mm^3 in the absence of symptoms and above 20,000/mm^3 in the presence of fever or hypertension. Many patients may become candidates for HCT, so if patients are cytomegalovirus (CMV)-seronegative at the start of induction, every effort should be made to ensure that they continue to receive either CMV-seronegative or filtered blood products.

Malnutrition can be a significant problem, particularly in the older, frailer patient. Early institution of hyperalimentation should be considered if oral intake becomes inadequate.

MONITORING RESPONSE TO THERAPY

Substantial effort has been made to develop assays of leukemic burden that are more sensitive than the admittedly gross estimates afforded by morphologic examination.[181] Such assays, if sensitive, specific, and predictive of outcome, could be used to guide therapy so that, as one example, a patient in first remission could be taken to transplantation if the response to initial chemotherapy predicted a high probability of relapse, or the patient could be spared the toxicities of transplantation if the extent of response to initial therapy was so favorable as to predict a high probability of cure. Efforts to develop such assays have, to date, focused on PCR-based methods of detection of leukemia-specific translocations and multidimensional flow cytometry.

The major attraction of PCR-based assays is their high level of sensitivity and specificity. In AML, however, no universal translocations have been recognized, so separate studies, each involving only a small subset of AML cases, have been required. The most encouraging results have come from the study of APL, in which PCR-based assays for t(15;17) conducted after induction and consolidation were predictive of outcome.[182,183] The results with other translocations have been more perplexing. PCR-based assays for t(8;21) do not appear to predict relapse, and many patients show persisting positive PCR assays while remaining in complete remission for years after completing all therapy. Miyamoto and colleagues[184] studied 18 patients off therapy for 1 to 12 years, all of whom remained PCR assay-positive for the AML/ETO chimeric transcript. The positive

signal could be found in $CD34^+$ marrow cells, and analyses of the PCR assay-positive colonies demonstrated them to be clonal. These results help explain why, at present, no easy PCR-based methods are available to monitor response to therapy in most patients with AML.

An alternative approach to monitoring response to therapy is the use of multidimensional flow cytometry. This approach is not nearly as sensitive as PCR analysis, which detects 1 cell per 10^3 to 10^4. Flow cytometry does have the advantage that it is broadly applicable in virtually all cases of AML. Two different studies, one in pediatric AML and a second in adult AML, suggest that a flow-based assessment of the initial remission marrow sample adds information beyond that of routine prognostic factors regarding which patients are likely to relapse within the first several years after diagnosis.[185,186]

FUTURE DIRECTIONS IN TREATMENT

With increased understanding of the molecular events involved in the development of AML, the number of potential therapeutic targets has grown. These targets can be divided into three general categories:

1. Those that are the immediate consequences of the mutational events leading to AML
2. Those that are the adaptive changes a leukemic cell must make to stay alive given the initial mutational event
3. Those that immunologically distinguish AML cells from normal hematopoietic stem cells

The most common mutations in AML involve FLT-3, and because these mutations are activating, clinical trials are exploring the use of a number of inhibitors of FLT-3 tyrosine kinase, including CEP-701, PKC-412, SU11248, and CT53518. Ras molecules are downstream from tyrosine kinase receptors, so they themselves can be mutated in AML. Because farnesylation is required for *RAS* function, trials of several farnesyl transferase inhibitors (including R11597 and BMS214662) have been conducted. The CBF and retinoic acid receptor translocations result in recruitment of HDs, which are thought to inhibit transcription, thereby contributing to the malignant phenotype. Thus, a number of HD inhibitors (including phenylbutyrate, trichostatin, depsipeptide, and MS-275) are being studied in AML.

The mutational event or events giving rise to AML could require the cell to make other adaptive changes not required of normal cells in order to survive. Such responses might be particularly required during moments of cell stress. One example is Bcl-2, which is overexpressed in almost all AML samples compared with normal marrow and may be further overexpressed when cells are exposed to chemotherapy. Thus, agents that inhibit Bcl-2, such as Bcl-2 antisense, are being studied alone and with chemotherapy for AML.

Cell surface antigens are being increasingly explored as targets for antibody- and cellular-based therapies. As noted earlier, the anti-CD33 calicheamicin conjugate gemtuzumab ozogamicin is an active agent for the treatment of recurrent AML. Recent studies combining it with standard-dose daunorubicin and cytarabine as initial induction therapy have reported encouraging results, with 85% and 86% complete response rates, respectively, in two phase II trials.[187,188] Studies using antibodies to target radionuclides to marrow in efforts to develop improved preparative regimens for transplantation also are yielding encouraging outcomes.[189]

The markedly lower rates of disease recurrence after allogeneic transplantation compared with identical-twin transplantation have encouraged further research into the development of cell-based immunotherapies. Some of these approaches, such as the further development of nonablative allogeneic transplants, attempt to make use of polymorphic minor histocompatibility differences between donor and host. Other investigators are exploring the possibility of targeting T cells to either mutational fusion proteins, such as the RUNX-1/MTG-8 protein, or to overexpressed self-antigens, such as PR3 and WT1. This long list of therapies currently in development offer great hope that the outcomes of treatment for patients with AML will continue to improve.

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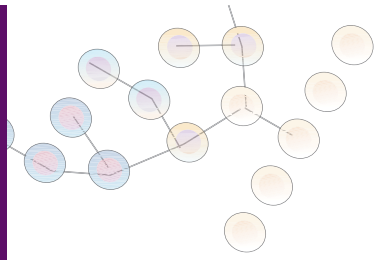
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105 Myelodysplastic Syndromes

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SUMMARY OF KEY POINTS

Etiology

- Myelodysplastic syndromes (MDSs) are not true dysplastic disorders but rather are clonal disorders of hematopoiesis with site of transformation at a pluripotent stem cell or early myeloid progenitor cell.
- In 50% to 90% of cases associated with chromosomal abnormalities, such abnormalities often are in proximity to oncogenes—partial deletion of the long arm of chromosome 5 (5q–) and the *fms* gene, monosomy 7 (7–) and the *met* oncogene—and hematopoietic growth factor genes (5q– and genes for granulocyte macrophage colony stimulating factor [GM-CSF], interleukin-3 [IL-3], IL-5, and macrophage colony stimulating factor [M-CSF] and 7–, and the erythropoietin gene).
- These resultant genetic alterations can manifest by increased apoptosis, which explains the seemingly opposing findings of marrow hypercellularity with peripheral blood cytopenia in patients with MDS.

Epidemiology

- The therapy-related subset of MDS is secondary to previous use of alkylating agents (typically associated with monosomy 7 and 5q–), with an increasing number of cases secondary to previous use of DNA topoisomerase II-targeting agents (epipodophyllotoxins), which typically are associated with translocation involving band 11q23 or band 21q22.
- Chronic exposure to benzene (above the level set by national guidelines) is the most important environmental exposure risk.

Pathology

- The new World Health Organization (WHO) classification is a revision of the French-American-British (FAB) system and recognizes the following subtypes: refractory anemia (RA), refractory anemia with ring sideroblasts (RARS), refractory cytopenia with multilineage dysplasia (RCMD), refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS), refractory anemia with excess blasts type I and type II (RAEB I and II), 5 q– syndrome, and unclassified MDS. Refractory anemia with excess blasts in transformation was eliminated from the WHO classification. Chronic myelomonocytic leukemia (CMML) has been reclassified into a new separate category, myelodysplastic/myeloproliferative disorders, along with juvenile myelomonocytic leukemia (JMML) and atypical chronic myelogenous leukemia (aCML).

Incidence

- The incidence of MDS is approximately 4 cases per 100,000 population.
- MDS is primarily a disease of the elderly: Among persons older than 70 years of age, the incidence is 20 cases per 100,000, with only 10% to 20% of patients younger than 60, although patients in the therapy-related subset are 10 to 20 years younger.

Differential Diagnosis

- MDS often is a diagnosis of exclusion after other factors and disorders associated with cytopenia and hematopoietic dysplasia are ruled out: vitamin B_{12} or folate deficiency, recent cytotoxic therapy, heavy metal intoxication, chronic liver disease, and chronic inflammation, which includes human immunodeficiency virus (HIV) infection.

Prognosis

- Using the International Prognostic Scoring System (IPSS), patients can be categorized into distinctive subgroups with respect to both median survival and the risk for acute leukemic transformation based on four subtype-specific variables: age, percentage of bone marrow blasts, number and type of chromosomal abnormalities, and degree of cytopenia.

Primary Therapy

- Usually a "wait and watch" approach is followed, given the poor risk-benefit ratio of intensive (acute myelogenous leukemia [AML]-type) chemotherapy for a majority of patients older than 60 years, although intensive chemotherapy at the time of blast progression is appropriate and may benefit up to one half of the patients, albeit transiently. A minority of patients (those younger than 55 years) may be long-term survivors if they undergo allogeneic bone marrow transplantation. The nonmyeloablative "minitransplant" procedure may increase the upper age limit for transplantation in the future.
- Erythropoietin may reduce requirements for blood transfusion; its efficacy may be augmented by cotreatment with G-CSF.

Effective Second- or Third-Line Therapies

- No consistently effective therapies are available, but one fourth to one third of patients respond to agents such as 5-azacytidine, decitabine, thalidomide, amifostine, low-dose ara-C, and topotecan. Novel targeted therapies for MDS are in various phases of clinical trials.

INTRODUCTION

The first case of what would later be designated MDS was described in 1913 by Nageli,[1] and the first case series of 143 patients with "preleukemic leukemia" was published in 1973 by Saarni and Linman.[2] Thus, MDS can be considered a relatively recently identified medical condition. The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute and central cancer registries began formally tracking MDS only in 2001, so it can be considered an even more recently recognized form of cancer.[3,4]

Diagnosis of MDS and subsequent care of the patient require coordination among a pathologist with morphologic expertise in identifying this tricky disorder; a molecular pathologist for identifying typical abnormalities associated with MDS; a hematologist or oncologist (or both); and in some cases, a physician experienced in bone marrow transplantation. Care for the patient with a new diagnosis of MDS must include attention to baseline characteristics (such as iron and erythropoietin levels, ascertainment of potential environmental or therapy-related etiologic factors, and transfusion needs), determination of the appropriate timing of therapy initiation and the type of therapy; an understanding of indications of therapy success or failure; optimal timing of bone marrow transplantation; and attention to supportive care needs, such as transfusion requirements and the need for chelation therapy.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of MDS in the United States is approximately 3.6 cases per 100,000 people in the population and may be increasing[4]; it is estimated that approximately 10,000 patients were diagnosed with MDS in the United States in 2003.[3,4] The incidence rises sharply after the age of 70 years,[4] and the median age at diagnosis is approximately 75 years. These data are consistent with reports from other Western countries (Germany, Sweden, the United Kingdom, and France).[5–8] Of interest, Japanese patients were noted to be significantly younger, with more severe cytopenias and a lower risk of transformation to acute leukemia, suggesting differences in the natural history of MDS in Eastern versus Western countries.[9] MDS is more common in men than in women.[3,4]

Although most cases of MDS are idiopathic, the risk increases significantly with age,[3–5,7] and after exposure to organic solvents including benzene[10–14]; even low-level benzene exposure has been associated with increased hematotoxicity.[15] The latter may be greater in those with specific polymorphisms in DNA repair genes[16] or NADPH : quinine oxidoreductase (*NQO1*).[14,15,17] Case-control studies confirm an increasing risk of MDS in association with family history of hematopoietic cancer, smoking, and exposure to agricultural chemicals or solvents.[18,19] Occupational or environmental exposure is significantly associated with abnormal karyotype compared with de novo MDS.[20] Rare cases of familial MDS and AML have been reported, mostly in association with loss of 5q and or 7q[21–23] or with familial platelet disorders[24]; there appears to be differential expression of genes involved in signal transduction in affected versus unaffected family members.[25] A rare G-CSF receptor polymorphism also may predispose affected persons to high-risk MDS through altered signal transduction.[26]

Previous cytotoxic chemotherapy exposure—in particular, with regimens incorporating alkylating agents or topoisomerase inhibitors including epipodophyllotoxins such as etoposide or anthracyclines—significantly increases the risk of MDS,[27–33] which also has been reported after previous exposure to fludarabine.[34,35] The risk of secondary MDS after chemotherapy may be related to genetic polymorphisms of drug-metabolizing enzymes in some patients.[36] Exposure to radiation (e.g., among radium dial painters, atomic bomb survivors, or persons residing near the site of a nuclear reactor accident)[37] or the combination of radiation therapy with chemotherapy (particularly alkylating agents) also significantly increases the risk of secondary AML and MDS.[27,29,37–41] Recent evidence suggests that specific polymorphisms in the methylene tetrahydrofolate reductase gene (involved in DNA synthesis) may predict for a higher risk of secondary MDS or AML after treatment with cyclophosphamide, particularly in patients with breast cancer.[42] The median latency period for secondary MDS or AML after exposure to alkylating agents is 5 to 10 years, and the risk appears to be dose-dependent.[40,43] In general, secondary MDS or AML after alkylating agent or radiation exposure is characterized by unbalanced translocations commonly involving chromosome 5 (particularly 5q31) or chromosome 7.[44] By contrast, secondary MDS or AML after exposure to topoisomerase inhibitors is clinically different from that following alkylating agents in several ways[45]: It is much less common; the latency period is shorter (median, approximately 2 to 4 years); it more frequently manifests with overt leukemia without a preceding MDS phase; a balanced translocation, often involving 11q23 (the *MLL* gene), is more likely; and the complete response (CR) rate is higher, although the long-term prognosis is poor.[46,47] The exception is the rare patient with t(15;17),[33,48] or with core binding factor leukemia [t(8;21) or inversion 16/t(16;16)],[49–51] in whom durable CRs may be achieved.

Additional risk factors for secondary MDS or AML include high-dose therapy and autologous stem cell transplantation (ASCT) for malignant lymphoma,[52] where the risk of MDS/AML at long-term follow-up in some series is in excess of 10%,[53,54] although the use of non-total-body irradiation (TBI)-containing regimens may diminish this somewhat.[39,53,55] Pretransplantation therapy and pre-existing cytogenetic abnormalities increase the risk of secondary MDS/AML after ASCT.[39,56,57] The risk of MDS after radioimmunotherapy (e.g., with I^{131}-tositumomab) does not appear to be significantly increased.[58] The use of G-CSF in children may increase the incidence of secondary MDS and AML,[59–61] and this has also been reported as a possible complication following dose dense breast cancer therapy.[30] MDS may also evolve from an antecedent hematologic disorder, particularly polycythemia vera after treatment with ^{32}P or busulfan.[62]

PATHOGENESIS

MDS is recognized as a malignant disease in the WHO classification and is characterized by clonal hematopoiesis, progression to acute leukemia, and a diminished survival in all subgroups.[63] The underlying cause of MDS is unknown, and no single unifying pathophysiology is recognized. Hampering our understanding of the disease, preclinical models of MDS are few, although some murine models have been developed.[64,65] A functional model of MDS molecular pathogenesis, however, is suggested by the clinical behavior of the disease—namely, the progressive transformation of a committed myeloid hematopoietic stem cell with acquisition of successive genetic abnormalities, and clonal expansion, leading to the clinical phenotype (hypercellular bone marrow with increased angiogenesis and apoptosis, abnormal cytogenetics, cytopenias and transformation to frank AML).[66–72] Gene expression profiling using complementary DNA (cDNA) microarray technology has demonstrated significant heterogeneity among patients with MDS, although the expression of subsets of genes (e.g., *DLK* gene)[73] can discriminate between different clinical and karyotypic subtypes, including predicting deletions of 5q.[74–76] In the subset of patients with 5q− syndrome, global gene expression profiling implicates a stem cell origin for the disease.[77] In patients with low-risk MDS, single-nucleotide polymorphism (SNP) analysis has demonstrated hitherto unrecognized uniparental disomy and copy number changes.[78–80] It is hoped that ongoing gene expression studies and SNP ansalysis will add further insight into occult genetic lesions and dysregulated gene expression in specific disease stages, thereby ultimately contributing to our understanding of the causes and progression of MDS.

A model of inactivation or mutation of tumor suppressor genes has been proposed, although it is clear that many of the principal tumor suppressors responsible have not yet been identified.[70] Par-

ticular attention has ben paid to the commonly deleted region on 5q.[81] Findings on recent studies in support of this model include the epigenetic suppression of the genes encoding α-catenin (*CTNNA1*)[82] and *RIL*,[83] and the observation that haploinsufficiency of *EGR1* (a candidate tumor suppressor gene encoding a transcription factor within the commonly deleted segment of 5q31) leads to myeloid disorders.[84] Upregulation of and increased protein expression of the SPARC tumor suppressor gene on 5q31-32 have been demonstrated after lenalidomide therapy and may underlie its potent effects in patients with del(5q). How these observations contribute to MDS development and progression and how they may direct treatment have not yet been determined.

Point mutations in RAS family members and p53 have been reported in MDS, albeit less commonly than in AML,[85,86] as have overexpression of EVI1[87,88] and the expression of apoptosis-related oncoproteins.[89] Mutations in *PTPN11*[90] and *L3MBTL*, a gene located on 20q12 (commonly deleted in MDS),[91] do not appear to be important in MDS pathophysiology or progression. *FLT3*-length mutations are seen in increasing frequency during MDS transformation.[86] However, constitutive activation of p38 MAPK, itself involved in cell cycle regulation, has been described in MDS and correlates with enhanced apoptosis in MDS hematopoietic progenitors. Indeed, in vitro studies suggest that inhibition of p38 MAPK leads to enhanced hematopoiesis, suggesting that this may be a therapeutic target.[92] Aberrant signaling through the Akt/mTOR pathway appears to be important for cell survival in high-risk MDS, and also may serve as a therapeutic target (e.g., with mTOR inhibition).[93]

Gene silencing through aberrant promoter methylation also appears to be important in the pathophysiology of MDS,[82,94] both early in the course of MDS (including protein kinases and some genes involved in signal transduction, such as DAP-kinase, Ras, and some SOCS-1 sites in approximately 30% of patients) and later in the disease course in genes involved in cell cycle regulation (such as *p15INK4B* in patients with RAEB).[95–99] These observations offer insight into both the development and progression of MDS and serve as the rationale for the therapeutic use of hypomethylating agents in MDS.[100]

Immune modulation appears to play a role in the pathophysiology and possibly also in the progression of MDS.[101,102] Supporting this notion is the observation of significant overlap between hypoplastic MDS and aplastic anemia.[103] An increase in B-lymphocyte apoptosis (but not in T lymphocytes) has been observed,[104] and B-cell lineage–affiliated gene expression is markedly reduced in early-stage MDS.[105] Clonal T-cell expansion is common[106] and natural killer (NK) cell function is reduced in MDS,[107] particularly in cases with higher-risk features.[108] A reduction in regulatory T cells ($CD4^+CD25highFoxp3^+$) in low-risk MDS also may contribute to the emergence of autoreactive T-cell clones.[109] Of interest, a gene expression pattern similar to that seen after interferon-γ stimulation also has been observed in MDS.[76,110] These observations serve as the rationale for immunosuppressive treatment for MDS.

It is important to emphasize that although significant clinical overlap exists between high-risk MDS (greater than 10% blasts) and AML, at least in terms of prognosis and survival with intensive therapy,[111] significant biologic differences are recognized. MDS is characterized by increased apoptosis.[71,72] Upregulation of caspases and Toll-like receptor 4 (TLR-4) expression may promote apoptosis in MDS, possibly contributing to cytopenias.[112,113] Resistance to apoptosis by $CD34^+$ cells also has been described in some subtypes of MDS (e.g., trisomy 8),[114] suggesting another mechanism for disease progression. Angiogenesis is increased in MDS, and the vascular endothelial growth factor (VEGF) may serve as an autocrine growth factor[115]; however, unlike in AML, serum VEGF levels are not prognostic in MDS.[116] Therefore, MDS must be considered a unique entity, and not merely "preleukemia".[71] It is hoped that an improved understanding of the molecular basis for MDS also will contribute to the development of more specific therapies.

CLINICAL PRESENTATION

The typical presentation of MDS is the discovery of an isolated cytopenia or abnormalities in multiple cell lines in an older patient with signs and symptoms related to hematopoietic failure (fatigue, infection, bleeding), although the diagnosis may be incidental.[66] Macrocytic anemia is typical, and other benign causes (e.g., vitamin B_{12} with or without folic acid deficiency, hypothyroidism, alcohol use, chronic liver disease) must be ruled out[117]; iron deficiency and the anemia of chronic diseases also are substantially more common causes of anemia in older adults.[118] However, in a study of elderly patients with unexplained macrocytic anemia, most had at least one molecular or cytogenetic marker of clonality suggesting "early MDS."[119] In some cases, a definitive cause for the cytopenias may not be established, and the designation "idiopathic cytopenia of undetermined significance" has been proposed in that setting; long-term follow-up and repeat BM evaluations are recommended to establish the diagnosis.[120,121] Cytogenetic studies may be particularly helpful in determining the diagnosis of MDS in the absence of clear morphologic dysplasia.[122] Studies of novel diagnostic markers to distinguish MDS from other causes of cytopenias are ongoing, such as decreased serum levels of the CXC chemokine ligands CXCL4 and CXCL7,[123] although the clinical usefulness of this approach has not yet been established. A careful transfusion history to identify use of packed red blood cells is valuable in determining the likelihood of response to antithymocyte globulin[124] and erythropoietin for anemia.[125]

Neutropenia also is a common presenting feature of MDS.[126] In addition, neutrophil dysfunction has been described,[127,128] and patients may present with pyogenic abscess in the absence of neutropenia.[129] Infection remains the most common cause of death in MDS[130] and is closely correlated with the neutrophil count; it also is a common side effect of intensive chemotherapy.[131] Therefore, infection should be treated aggressively. G-CSF has been used successfully to treat symptomatic neutropenia[132]; however, in a randomized phase III study, the use of G-CSF significantly accelerated RAEB and RAEB-t compared with supportive care, with an inferior median survival (10 versus 21 months), leading to early termination of the trial.[133] Therefore, the short-term use of G-CSF generally is restricted to those patients without an excess of blasts with a symptomatic neutropenia. Opportunistic infection also has rarely been reported in MDS (e.g., disseminated *Mycobacterium avium-intracellulare* infection),[134] presumably related to disease-related immunodeficiency.

Thrombocytopenia is increasingly recognized as a clinical problem in MDS,[135,136] although MDS uncommonly manifests with isolated thrombocytopenia.[126,137] No close association has been found between thrombocytopenia and serum thrombopoietin levels in patients with MDS.[138] Additionally, platelet dysfunction has been described in MDS.[139,140] Recent estimates suggest that bleeding contributes to death in 20% and is the sole cause of death in 10%.[135] By contrast, the 5q− syndrome may manifest with thrombocytosis, although this is uncommon[141] (see Fig. 105-3).

The cytopenias of MDS, therefore, not only are the most common finding at diagnosis but also characterize the natural history of the disease and remain the most important clinical feature of the disease. Other, less common presenting features include Sweet's syndrome,[142] Behçet's disease,[143] inflammatory arthritis and synovitis,[144,145] and rarely vasculitis,[146] Crohn's disease,[147] and other immunologic phenomena.[148] As many as 10% of MDS patients have an associated autoimmune inflammatory manifestation,[149] although it does not appear to have an impact on the prognosis or disease course.[150] MDS has rarely been diagnosed during pregnancy.[151]

LABORATORY EVALUATION

The diagnosis of MDS requires demonstration of morphologic dysplasia in the correct clinical context and also collaboration with an

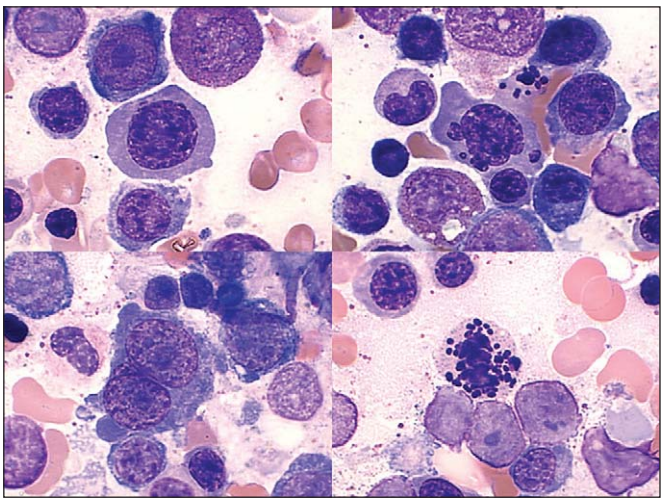


Figure 105-1 • As seen in this bone marrow aspirate, morphologic features associated with dysplastic erythropoiesis include megaloblastoid maturation *(upper left panel)*, nuclear budding and fragmentation *(upper right panel)*, multinuclearity *(lower left panel)*, and bizarre mitotic figures *(lower right panel)*. Wright-Giemsa stain, original magnification 100×. (Courtesy of Karl S. Theil, MD, Department of Clinical Pathology, Cleveland Clinic.)

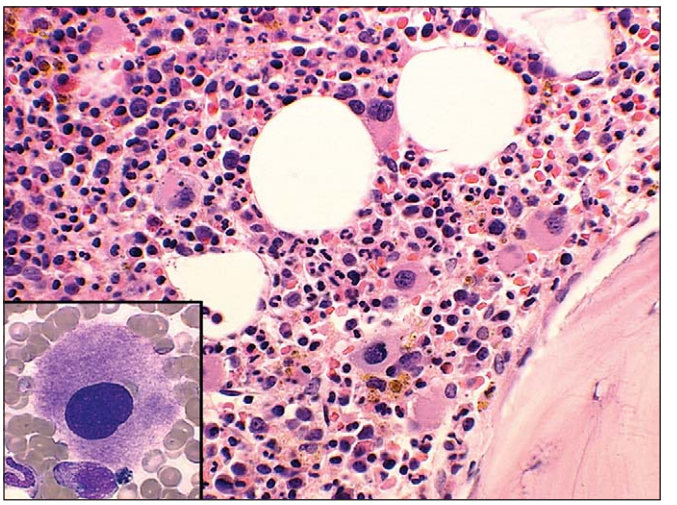


Figure 105-3 • Morphologic features associated with 5q− syndrome include hypercellular marrow containing increased megakaryocytes with abnormal hypolobulated nuclei, as seen in a bone marrow biopsy specimen. Abnormal nuclear morphology also is apparent in megakaryocytes in marrow aspirate smear *(inset)*. *Biopsy specimen*: hematoxylin-eosin stain, original magnification 40×; *aspirate*: Wright-Giemsa stain, original magnification 50×. (Courtesy of Karl S. Theil, MD, Department of Clinical Pathology, Cleveland Clinic.)

expert hematopathologist[121] (Figs. 105-1 to 105-3). MDS may not be apparent or meet diagnostic criteria at presentation in all patients, and close follow-up evaluation and repeat bone marrow examination may be required to establish the diagnosis.[120,152] MDS may in exceptional circumstances be diagnosed on the peripheral blood smear,[153] particularly in elderly or frail patients, in whom it would not alter management; however, a bone marrow aspirate usually is necessary,[154,155] and iron staining techniques should be performed in accordance with quality assurance guidelines.[152,156] Similarly, a core biopsy is helpful to support the diagnosis of MDS, including establishing cellularity, evaluating megakaryocyte dysplasia, and assessing for the presence of ALIP ("abnormal localization of immature precursors"—central clustering of immature cells, associated with poor prognosis) and fibrosis, and should be performed in all patients undergoing bone marrow aspiration.[154,155,157,158] Adverse events subsequent to bone marrow biopsy are rare.[159]

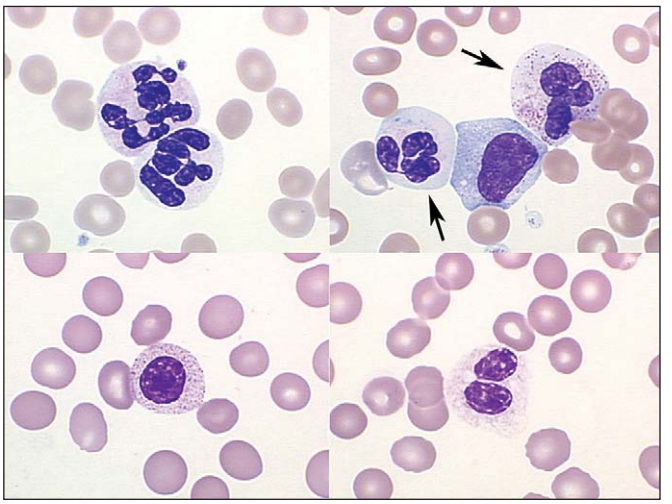


Figure 105-2 • As seen in this peripheral blood smear, morphologic features associated with dysplastic granulopoiesis include bizarre hypersegmentation *(upper left panel)*, hypogranular cytoplasm (compare neutrophils [*arrow*]; *upper right panel)*, and nuclear hyposegmentation *(lower panels)*. Acquired nuclear hyposegmentation, also known as pseudo–Pelger-Huet anomaly, ranges from complete lack of segmentation *(lower left)* to bilobed "pince-nez" nuclei *(lower right)*. Wright-Giemsa stain, original magnification 100×. (Courtesy of Karl S. Theil, MD, Department of Clinical Pathology, Cleveland Clinic.)

Cytogenetic evaluation is mandatory[126,154] and may be particularly helpful in establishing the diagnosis in patients with indeterminate morphology.[122] The role of interphase fluorescence in situ hybridization (FISH) for common abnormalities (e.g., 5q, 7q, +8, 20q, −Y, etc.) has not been established; however, it may complement standard cytogenetics.[160,161] FISH should not be performed in the place of cytogenetics but is indicated in any patient with a suspected deletion of 5q (e.g., 5q− syndrome), particularly if cytogenetic analysis has failed, or in those being considered for therapy with lenalidomide.[162] Because of the therapeutic implications (specifically, the responsiveness to imatinib), patients with CMML should be evaluated for 5q33/PDGFRβ translocation in the correct clinical setting.[163]

The diagnosis of hypoplastic MDS is difficult,[154] and this entity must be distinguished from aplastic anemia and paroxysmal nocturnal hemoglobinuria (PNH). Therefore, peripheral blood flow cytometry for CD55 and CD59 expression should be considered; the presence of a minor population of PNH-type cells in MDS may have prognostic and therapeutic implications.[164] By contrast, flow cytometric examination of the BM is controversial in MDS.[152] Flow cytometry may improve diagnostic accuracy in low-grade MDS,[165] and demonstration of aberrant antigen expression by this means may be helpful when morphologic and cytogenetic findings are indeterminate[166]; differences in enriched blast cell phenotype in MDS compared with AML have been demonstrated.[167] The import of flow in the absence of a definitive diagnosis of MDS by morphologic and cytogenetic testing is unclear, however, and consensus guidelines are being developed for the use of flow cytometry in the diagnosis of MDS.[168] Bone marrow flow cytometry studies may be helpful if concurrent T-cell large granular lymphocyte disease is suspected.[169]

Dysplasia is not specific for MDS and has been reported in the setting of regeneration following chemotherapy, hemolysis, and transplantation[155] (so-called stress dyserythropoiesis) and indeed in

the marrow of healthy subjects (typically dyserythropoiesis).[170] The presence of bone marrow dysplasia at presentation in patients with de novo AML (i.e., with no antecedent history of MDS) does not appear to have independent prognostic implications.[171–173] It is therefore important to consider other causes of cytopenias and dysplasia, some of which are potentially reversible. These include vitamin B_{12} deficiency, folate deficiency, and suspected or proven exposure to heavy metals.[152] Copper deficiency may mimic MDS[174] and is reversible with supplementation. Reversible dysplastic changes also have been noted rarely after immunosuppressive medications.[175]

A baseline reticulocyte count, iron studies (ferritin, Fe, total iron-binding capacity [TIBC]) and erythropoietin level are recommended for patients with anemia, particularly for those with lower-risk disease who may be candidates for blood transfusion and treatment with erythropoietin.[152] Baseline human leukocyte antigen (HLA) typing should be performed in any patient who is a potential candidate for allogeneic hematopoietic stem cell transplantation, and possibly for HLA-DR15 status (which may predict response)[124] before administration of antithymocyte globulin. HIV testing also should be considered in appropriate patients (see later discussion).

PATHOLOGY AND CLASSIFICATION

Minimal diagnostic criteria for MDS require morphologic abnormalities in greater than 10% of cells within a specific hematopoietic lineage[121] (see Figs. 105-1 and 105-2). Refinements in diagnostic criteria are in evolution, with future systems incorporating more refined histopathologic and immunologic determinants, along with updated cytogenetic criteria and methods of detecting cytogenetic abnormalities, such as FISH and high-resolution genomic or SNP array technology.[78,80,176,177]

French-American-British Classification

Two morphologic classification systems are commonly used to distinguish MDS subtypes. The FAB system, adopted in 1982, is a morphology-based system that was able to predict rates of survival and of transformation to AML by dividing MDS into subgroups based on the presence or absence of ringed sideroblasts, peripheral blood monocytosis, and myeloblast percentage (Table 105-1).[178] Five MDS categories are recognized in the FAB system: refractory anemia (RA); refractory anemia with ringed sideroblasts (RARS); refractory anemia with excess blasts (RAEB); refractory anemia with excess blasts in transformation(RAEB-t); and chronic myelomonocytic leukemia (CMML), an "overlap syndrome" that can include features of a myelodysplastic syndrome, a myeloproliferative disorder, or both.

Both RA and RARS are typified by a hypercellular bone marrow and dysplasia of the erythoid cell lines with or without dysgranulopoiesis or dysmegakaryopoiesis, in the setting of less than 5% bone marrow or 1% or less peripheral blood myeloblasts. RARS requires less than 15% ringed sideroblasts, in addition. A diagnosis of RAEB requires these foregoing bone marrow abnormalities, along with 5% to 20% bone marrow (or up to 4% peripheral blood) myeloblasts. If Auer rods are present in the myeloblasts, or if the myeloblast percentage in the bone marrow falls between 21% and 29% (or 5% or less in the peripheral blood), the diagnosis becomes RAEB-t. CMML is defined by a peripheral blood monocytosis with monocyte count greater than1 $\times 10^9$/L.

World Health Organization Classification

The WHO classification system was first published in 1999, and followed with detailed rationales for the differences between the FAB and WHO classifications in 2002[179,180] (Table 105-2). As with other myeloid neoplasms, the WHO system included in its classification of MDS the importance of cytogenetics and the recognition that further prognostic delineation was necessary above and beyond what the FAB system had provided.

In the WHO system, most significantly, the blast threshold for the diagnosis of AML was lowered, from 30% to 20% blasts in the blood or bone marrow, thus eliminating the nomenclature "RAEB-t" category. CMML was formally separated from the MDSs into a new category of "myelodysplastic/myeloproliferative disorders" (MDS/MPD), and a cytogenetically defined MDS subgroup, "MDS with deletion 5q," was added. This karyotype may be found in up to 29% of patients with cytogenetic abnormalities, or 10% to 15% of patients with MDS overall.[181] Finally, the WHO recognized that not everyone with MDS has a refractory *anemia*. Many have refractory thrombocytopenias, or refractory leukopenias with dysplasia predominating in other cell lineages. Thus, refractory cytopenia with multilineage dysplasia (RCMD) requires both erythroid dysplasia and dysplasia in one or more other lineages, or simply in two or more lineages.[180,182]

CYTOGENETICS

As with other hematologic malignancies, such as AML,[183–187] karyotypic abnormalities are playing a larger role in defining distinct disease subtypes of MDS, have prognostic implications, and are even refining choices in therapeutic modalities.[126,181] Incorporation of cytogenetics into morphologic classification significantly improves the prognostic stratification of patients with de novo primary MDS.[188]

Traditionally, patients with a "good-risk" karyotype include those with normal cytogenetics, del(5q), del(20q), and −Y abnormalities; those with a "poor-risk" karyotype include those with complex abnormalities and with abnormalities of chromosome 7; and those

Table 105-1 French-American-British Classification of Myelodysplastic Syndromes

MDS Subtype	Peripheral Blasts (%)	Bone Marrow Blasts (%)	Likelihood of AML Transformation	Median Survival (years)	MDS Diagnoses (%)
Refractory anemia (RA)	≤1	<5	+	4–6	10–40
Refractory anemia with ringed sideroblasts (RARS)	≤1	<5	+	7–8	10–35
Refractory anemia with excess blasts (RAEB)	<5	5–20	+++	1–2	25–30
Refractory anemia with excess blasts in transformation (RAEB-T)	≥5	21–29	++++	0–1	10–30
Chronic myelomonocytic leukemia (CMML)	<5	≤20	++	1–3	10–20

AML, acute myelogenous leukemia; MDS, myelodysplastic syndrome.
Adapted from Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51:189–199.

Table 105-2 World Health Organization Classification and Criteria for the Myelodysplastic Syndromes

MDS Subtype	Blood Findings	Bone Marrow Findings
Refractory anemia (RA)	Anemia	Erythroid dysplasia *only*
	No or rare blasts	<15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia	Erythroid dysplasia *only*
	No blasts	≥15% ringed sideroblasts
		<5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenias (bi- or pancytopenia)	Dysplasia in <10% of cells in two or more myeloid cell lines
	No or rare blasts	<5% blasts in marrow
	No Auer rods	No Auer rods
	$<1 \times 10^9$/L monocytes	<15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Cytopenias (bi- or pancytopenia)	Dysplasia in ≥10% of cells in 2 or more myeloid cell lines
	No or rare blasts	≥15% ringed sideroblasts
	No Auer rods	<5% blasts
	$<1 \times 10^9$/L monocytes	No Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias	Unilineage or multilineage dysplasia
	<5% blasts	5% to 9% blasts
	No Auer rods	No Auer rods
	$<1 \times 10^9$/L monocytes	
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias	Unilineage or multilineage dysplasia
	5% to 19% blasts	10% to 19% blasts
	Auer rods ±	Auer rods ±
	$<1 \times 10^9$/L monocytes	
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias	Unilineage dysplasia in granulocytes or megakaryocytes
	No or rare blasts	<5% blasts
	No Auer rods	No Auer rods
MDS associated with isolated del(5q)	Anemia	<5% blasts
	<5% blasts	No Auer rods
	Platelets normal or increased	Isolated del(5q)

MDS, myelodysplastic syndrome.
Adapted from Vardiman JW, Harris NL, Brunning RD: The World Health Organization (WHO) classification of the myeloid neoplasms. Blood 2002;100:2292–2302.

with "intermediate-risk" karyotypes include patients with other abnormalities not defined in the other risk groups.[126] Good-risk cytogenetic subtypes are associated with a median survival period of 3 to 4 years; intermediate-risk patients survive a median of approximately 2 years; and those with poor-risk karyotypes survive less than 1 year. Some degree of overlap has been observed between karyotypes typical of MDS patients and those of older adults with AML, in whom a majority of cases probably evolved from a known, or unknown, antecedent hematologic disorder such as MDS.[126,183,185,189] Indeed, many consider the two disorders to be similar, with AML placed at a more advanced position on the disease spectrum.

Recently, the German MDS group modified this cytogenetic risk schema, on the basis of data from more than 2000 patients.[190,191] Within the good-risk group, which had a median survival period of 55.4 months in 802 patients, in addition to those abnormalities mentioned earlier, these researchers include patients with 15q–, t(15q), 12p–, +21, –X, t(1q), t(7q), t(11q), and –21, with survival periods ranging from 32 to 108 months. Note that this differs from the International Prognostic Scoring System (IPSS) cytogenetic risk schema (Table 105-3) in that t(7q), formerly a poor-risk abnormality, is now considered a good-risk factor. Patients who have complex cytogenetics with three abnormalities have been shifted into the intermediate-risk category, which is now divided into "Int-1" and "Int-2," while those with more than three abnormalities and t(5q) have been placed in the poor-risk category. This schema is undergoing further refinement and analyses and is expected to be validated using external cytogenetic data.

Deletions of chromosome 5 are worthy of special attention. Del(5q) is the most common cytogenetic abnormality, and the commonly deleted region is at 5q31-32.[192] Del(5q) is present in approximately 25% of patients with an abnormal karyotype[181] and has particular therapeutic significance because of the sensitivity to lenalidomide.[162] A subset of patients with del(5q) will have the so-called 5q– syndrome, considered separately as a unique syndrome[193] and typified by severe anemia, normal or moderately increased platelets, rare transformation to AML, and prolonged survival. The 5q– syndrome occurs more frequently in females and has characteristic bone marrow features of dysmegakaryopoiesis, with no excess in blasts (see Fig. 105-3).[180,192,193]

PROGNOSIS

A number of clinical and pathologic factors, used both in isolation and in combination, can be used to predict overall survival and risk

Table 105-3 International Prognostic Scoring System

CALCULATION OF PROGNOSTIC SCORE

	SCORE				
Feature	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone marrow blast (%)	<5	5–10		11–20	21–29
Cytogenetics	Good	Intermediate	Poor		
Cytopenias	0 or 1	2 to 23			

ESTIMATION OF PROGNOSIS

Overall Score	IPSS Subgroup	Median Survival (years)
0	Low	5.7
0.5–1.0	Intermediate-1 (Int-1)	3.5
1.5–2.0	Intermediate-2 (Int-2)	1.2
≥2.5	High	0.4

Patients with a "good-risk" karyotype include those with normal cytogenetics, del(5q), del(20q), and -Y abnormalities; those with a "poor-risk" karyotype include those with complex abnormalities and with abnormalities of chromosome 7; and those with "intermediate" karyotypes include patients with other abnormalities not defined in the other risk groups.

IPSS, international prognostic scoring system.

Adapted from Greenberg P, Cox C, LeBeau MM, et al: International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079–2088.

of transformation to AML for an individual patient with MDS (Table 105-4).

The first, and probably most obvious, prognostic factor is the pathologic classification itself. Low-risk MDS is less likely to evolve to AML, and affected patients are more likely to live longer than those with high-risk MDS. Under the FAB classification system,[178] the low-risk MDS category includes patients with RA and RARS (in whom median survival ranges from approximately 3 to 8 years and risk of AML transformation is 10% to 35%), whereas with the WHO classification system,[180] this would include those diagnosed with RA, RARS, RCMD, RCMD-RS, MDS-U, and MDS with an isolated deletion of 5q (in whom median survival ranges from approximately 2 to 8 years and risk of AML transformation is similarly low).[126,194,195] Patients with RA and RARS enjoy a longer survival than those with RCMD and RCMD-RS, whereas those with the 5q− syndrome, or with an isolated del(5q) cytogenetic abnormality, have the best overall survival and lowest likelihood of AML transformation.[196] For patients with high-risk disease (those with an increased percentage of bone marrow myeloblasts—using the FAB system, those with RAEB, RAEB-t, and CMML subsets, whereas the WHO system would include those with RAEB-1 and -2), median survival ranges from 0.5 to 1.5 years and AML transformation is almost guaranteed, unless the patient dies from complications of MDS first.[126,194,195] These prognostic estimates worsen with increasing age and appear to be modified by lifetime transfusion amount (a greater number of transfusions translates to a worse survival)[197] and its correlate, iron overload.[198,199]

In 1997, the IPSS combined the number of cytopenias and cytogenetic information with the percentage of bone marrow blasts in developing a scoring system that accurately predicted survival and the risk of AML transformation (see Table 105-3).[126] This multivariable analysis combined data from seven international databases for patients with mostly untreated MDS (only 5% had received oral chemotherapy, and 2%, hematopoietic growth factor therapy) and was able to risk-stratify them into four distinctive subgroups: "Low" (a score of 0); "Intermediate-1" (a score of 0.5 to 1.0); "Intermediate-2" (a score of 1.5 to 2.0); and "High" (a score of 2.5 or greater; see Table 105-3). This system has further usefulness within low-risk MDS groups (scores of 0 to 1.0) when patients are analyzed by age as younger or older than 60 years, or younger or older than 70 years. The "High" risk category includes patients with IPSS scores of 1.5 or higher. Although the IPSS is criticized for being developed from data that preceded the current treatment era and as being applicable only to patients with newly diagnosed MDS, it has withstood the test of time and remains the most widely used predictive tool, determining eligibility for clinical trials and even being incorporated into the U.S. Food and Drug Administration (FDA) labeling for lenalidomide.[162] A revision of the IPSS is being developed that most likely

Table 105-4 Common Prognostic Factors for Survival in Myelodysplastic Syndrome

Characteristic	Favorable Prognostic Factor	Intermediate Prognostic Factor	Unfavorable Prognostic Factor
Morphology	*FAB subtype*:	CMML	RAEB, RAEB-t
	RA, RARS		
	WHO subtype:	RCMD, RCMD-RS, CMML-1	RAEB-1, RAEB-2, CMML-2
	del(5q), RA, RARS		
Cytogenetics	*IPSS*:	Others not in favorable or unfavorable	Chr 7 abn, complex (≥3 abn)
	del(5q), –Y, del(20q), normal		
	German:	Others not in favorable or unfavorable	Other chr 7 abn, complex (>3 abn), t(5q)
	IPSS + 15q–, t(15q), 12p–, +21, –X, t(1q), t(7q), t(11q), –21		
Clinical factors	No transfusion needs		High transfusion needs
	Normal blood counts		Pancytopenia
	Low serum ferritin (<1000)		High serum ferritin (>2000)
	Age <60 years		Age >70 years
			β_2-Microglobulin
			High Bmi-1 or WT1 expression

abn, abnormality(ies); chr, chromosome; CMML, chronic myelomonocytic leukemia; FAB, French-American-British; IPSS, International Prognostic Scoring System; RA, refractory anemia; RAEB(-t), refractory anemia with excess blasts (in transformation); RARS, refractory anemia with ringed sideroblasts.

will vary scores for degree of cytopenias (with different scores for patients with, for example, platelet counts of 90,000/mL versus 9000/mL; such patients would be scored similarly using the existing IPSS) and for lactate dehydrogenase (LDH) level and will alter the cytogenetics risk score classification.[200]

More recently, a prognostic scoring system based on the WHO classification system, termed the WHO Prognostic Scoring System (WPSS), has been developed.[194] It is based on data from a learning cohort of 467 de novo MDS patients seen by centers in Italy from 1992 to 2002 and validated using 620 de novo MDS patients from Germany, seen from 1982 to 2003. Patients were given a score based on their WHO classification, cytogenetic risk score (using the IPSS scoring scheme), and transfusion requirement. Based on this score, patients are divided into one of five risk groups—very low, low, intermediate, high, and very high. Although the WPSS is able to clearly delineate survival differences among these groups, whether it is more accurate than the IPSS, or provides any predictive advantage, is not yet clear.

In addition to the IPSS, other clinical and molecular prognostic factors predicting MDS progression, such as β_2-microglobulin[201] or Bmi-1[202] or WT1 expression,[203] have been proposed, but they have not yet been validated in multicenter prospective studies. The prognostic factors are listed in Table 105-4.

Determining if and when to treat a patient with MDS is far from straightforward. Some patients with low-risk MDS who have a mild cytopenia detected on a random laboratory test may have no symptoms and no transfusion needs; such patients can be observed without therapy for years. Other patients with high-risk MDS, multiple cytopenias, and a blast percentage just shy of the 20% required for an AML diagnosis need immediate treatment. Three decision tools are available to assist in determining the most appropriate therapy for various MDS subtypes.

The first decision tool, developed by Hellstrom-Lindberg and colleagues,[204,205] used 94 patients across three hematopoietic growth factor studies to determine predictors of response to growth factors—in their case, a combination of recombinant erythropoietin (EPO) and granulocyte colony stimulating factor (G-CSF). They found that patients with low transfusion needs (less than 2 units of packed RBCs per month) and a low baseline serum EPO level (less than 500 IU—called the "good" hematopoietic growth factor predictive group) had a 74% chance of responding to hematopoietic growth factor, whereas those with high transfusion needs (greater than or equal to 2 units of packed RBCs per month) and a high EPO level (greater than 500 IU—defining a "poor" hematopoietic growth factor predictive group) had only a 7% chance of responding. It is at this point in the disease course that tumor burden (e.g., the number of dysplastic cells or the cytokine effects from those dysplastic cells) overcomes the ability of intrinsic or extrinsic hematopoietic cell stimulatory factors to promote erythrocyte production. Patients who had a mixed picture (low transfusion needs and high EPO level, or high transfusion needs and low EPO level—the "intermediate" hematopoietic growth factor predictive group) had a 23% chance of responding to hematopoietic growth factor.

A second decision tool took this one step further. A group of Cleveland investigators took individual patient data on 799 patients with MDS treated with either hematopoietic growth factor (in 394 patients) or non-growth factor (NGF) (in 405 patients) approaches from 90 articles published over a 20-year period and applied these data to the Hellstrom-Lindberg model to determine the most appropriate initial therapy for patients with low-risk MDS (Fig. 105-4), incorporating quality of life and survival data with response rates.[206] This treatment algorithm suggests that patients with low-risk MDS who fall into a good hematopoietic growth factor predictive group (low RBC transfusion needs and low EPO levels) should receive initial treatment with hematopoietic growth factor unless NGF therapy response rates are greater than 46%. This approach maximizes survival in the "good" hematopoietic growth factor group, at 3.38 years for patients who received hematopoietic growth factor, compared with 2.57 years for patients who received NGF. Other patients with low-risk MDS (those falling into "intermediate" and "poor" hematopoietic growth factor predictive groups) probably should receive NGF therapy initially, because survival is again maximized, at 2.57 years in patients who receive NGF treatment in "intermediate" and "poor" hematopoietic growth factor groups, compared with 1.50 years and 0.91 year for patients who received hematopoietic growth factor in both groups, respectively.

In patients with high-risk MDS, a decision analysis published in 2004 determined the optimal timing to bone marrow transplantation (BMT), using data collected from the International Bone Marrow Transplant Registry (IBMTR).[207] The investigators found that patients with low-risk MDS should undergo transplantation just before transformation to AML, but not up-front. Patients with high-risk MDS, on the other hand, had the greatest survival advantage with up-front transplantation. This topic is covered later in more detail in the section on allogeneic hematopoietic stem cell transplantation (alloHSCT). These data also have been used to justify up-front

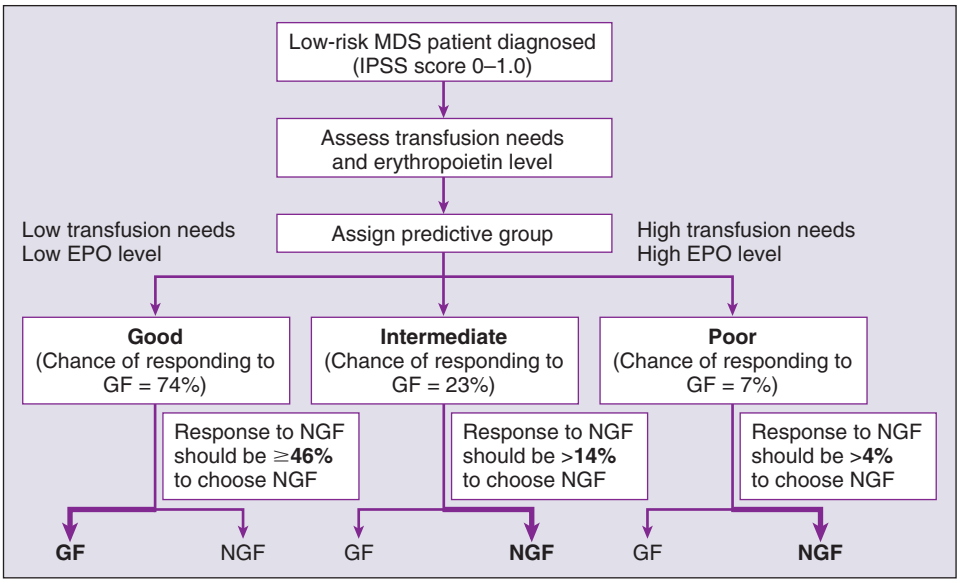


Figure 105-4 • Decision tree for treatment for patients with low-risk myelodysplastic syndrome (MDS). EPO, recombinant epoietin; GF, growth factor; IPSS, International Prognostic Scoring System; NGF, non-growth factor. (Adapted from Sekeres MA, Fu AZ, Maciejewski JP, et al: A decision analysis to determine the appropriate treatment for low-risk myelodysplastic syndromes. Cancer 2007;109:1125.)

treatment with NGF approaches, even in the absence of substantial cytopenias, in patients with high-risk MDS (as described next under "Treatment").

TREATMENT

As stated earlier, although a number of classification and prognostic systems exist for MDS, the disease commonly is divided into low-risk and high-risk subtypes. Doing so assists in providing easier prognostication and, of greater importance, in determining the most appropriate therapy or clinical trial for an individual patient. Although this section on treatment is similarly divided, it is important to recognize that the division is somewhat artificial, and the borders may not be so clearly defined for every patient. For example, MDS in a 72-year-old patient with pancytopenia, a karyotype that includes deletion of chromosome 7, and bone marrow findings of dysplasia along the erythroid cell line and only 3% blasts would be classified as Int-2 (and thus "high-risk") using the IPSS scoring system, with a median survival period of 1.2 years, but would be "low-risk" under the FAB and WHO classification systems, with predicted median survival periods of approximately 5 and 9 years, respectively. A justification could thus be made for treating this patient as either low-risk or high-risk. Additionally, these classification and prognostic systems were developed for patients with de novo disease; it is unclear whether their applicability extends to patients who have undergone treatment previously. Finally, the costs of certain therapies and the whimsy of insurance reimbursement may influence therapeutic decisions, regardless of MDS classification.

Treatment of MDS is divided into regimens using those drugs that are more appropriate for low-risk or early MDS and regimens of agents yielding higher responses in high-risk or advanced MDS. As stated previously, patients with low-risk MDS have less than 5% blasts using the FAB and WHO systems, or an IPSS score of 1.0 or lower. Patients with high-risk MDS have 5% blasts or less or an IPSS score of 1.5 or lower. Therapies directed at sustaining maximal activity of residual functioning bone marrow cells, or at immunomodulation (through abrogation of the effects of proinflammatory, proapoptotic cytokines), generally are applied to patients with early MDS, for whom treatment goals center on minimizing transfusions, restoring effective blood cell production, and maximizing quality of life.[208] Cytotoxic therapies, based on drugs that abrogate the gene-silencing effects of hypermethylation, on the other hand, are used in patients with advanced MDS, for whom treatment goals are similar to those for patients with AML: attaining a partial or complete remission, prolonging survival, and maximizing quality of life.[208,209] Therapies for low-risk and high-risk MDS are reviewed in Table 105-5.

Treatment of Low-Risk Myelodysplastic Syndromes

The goals of therapy for early MDS include improvement of hematologic parameters or decrease in transfusion needs and improvement in quality of life. Thus, if a patient with low-risk MDS has mild cytopenias not requiring transfusions and is asymptomatic, it is appropriate to monitor blood counts regularly without initiating therapy. Patients who are symptomatic, or who are on the verge of requiring a blood or platelet transfusion or have borderline or frank neutropenia, or who now require transfusions, should be started on therapy.

Growth Factors

An initial approach to attempt ameliorating cytopenias may be to initiate growth factor therapy. Patients with anemia may receive recombinant erythropoietin agents (i.e., EPO), whereas those with neutropenia may be given G-CSF or GM-CSF. At present, agents that stimulate platelet growth are not approved for the treatment of MDS by the FDA, although preliminary trials are under way testing the compound AMG531 for this purpose.

Predictive schemes to determine which patients will benefit from hematopoietic growth factor, and whether hematopoietic growth factor or NGF therapies should be initiated, have been developed and are described earlier. A number of trials have been published using EPO alone, at varying schedules and doses, or in combination with G-CSF or GM-CSF, in patients with MDS, with responses of approximately 40% in low-risk patients using International Working Group (IWG) criteria for response, and a possible advantage to combination therapy.[125,210–219] Attention has been drawn recently to the use of growth factors for treatment of a variety of malignancies, including MDS, with a possible adverse outcome in patients with solid tumors in whom hemoglobin was maintained at higher levels. For this reason, it is recommended that, in those patients responding to growth factors, hemoglobin levels be maintained in the range of 11 to 12 g/dL.

Two studies address whether or not a survival advantage is provided through the use of growth factors. The first, from a Norwegian group of investigators, examined 123 patients who received combination erythropoietin and G-CSF and compared data for these patients with those for 334 patients with untreated MDS in the IPSS/IMRAW database. No survival advantage or delay in transformation to AML was detected, although the IPSS/IMRAW database lacked information on WHO classification, transfusion needs, and baseline erythropoietin level.[220] When 121 patients from the same cohort were compared with a matched cohort of 268 patients with untreated MDS from Pavia, Italy, in whom these variables were available for matching, a survival advantage was demonstrated for treatment with hematopoietic growth factor, though still no delay in transformation to AML.[221]

The second, from the Cleveland group, reviewed 162 studies published from 1985 to 2005 that included 2592 patients with low-risk MDS treated with hematopoietic growth factor ($N = 1587$) or NGF ($N = 1005$) approaches.[222] After reclassification of patients according to IPSS scores and IWG response criteria, and adjustment for baseline differences in transfusions needs, years with MDS, previous treatments, and FAB/IPSS category, a survival advantage was found in patients in the hematopoietic growth factor treatment group at 6, 12, 18, and 24 months of follow-up. Whether this survival advantage results from diminished transfusion requirements in patients responding to growth factor, increased treatment-related morbidity in patients receiving non-growth factor, or a direct effect of growth factor on dysplastic hematopoietic precursors, is unknown.

Other novel cytokines for cytopenias (e.g., IL-3 or recombinant human IL-6) unfortunately have limited activity in MDS, along with significant toxicity.[223,224]

Immunomodulatory Agents

ANTITHYMOCYTE GLOBULIN. In at least a subset of patients with low-risk MDS, disease pathophysiology is thought to be mediated through T-cell-dependent immune destruction of hematopoietic precursors, akin to aplastic anemia. Thus, responses to immunosuppressant drugs can be seen. Four phase II studies have been reported using antithymocyte globulin with or without cyclosporine. In these studies, typical response rates occur in approximately 30% of the patients, with response rates as high as 50% seen in selected series.[225,226] Predictors of response have been reported as younger age, a brief transfusion history, and HLA DR-15 positivity, as well as treatment for hypoplastic subtypes of MDS[124]; more recently, the importance of HLA DR-15 positivity has been disputed. Cyclosporine therapy also has demonstrated clinical improvement, with decrease in cytopenias and reduced transfusion dependency in hypoplastic MDS.[227]

THALIDOMIDE. The proposed mechanism of action of thalidomide is through cytokine inhibition, receptor modulatory effects, modulation of cell adhesion to bone marrow stromal cells,

Table 105-5 Biologic and Chemotherapeutic Agents for Treatment of Low-Risk and High-Risk Myelodysplastic Syndromes

Therapeutic Agents (by Class)	Response Rate	Survival Impact	Cell Line(s) Affected	Comment(s)
Growth factors				
Erythropoietin G-CSF GM-CSF Combination GF (AMG531)	~40%	Yes, compared with no treatment and compared with non-GF therapy in retrospective studies	RBC, WBC (Plt)	With erythropoietin agents, target Hgb should be 11–12 g/dL Some evidence for synergy with combination GF Greatest effect in patients with low baseline serum erythropoietin levels and low transfusion needs (AMG531 still in clinical trials)
Immunomodulatory drugs				
ATG/CyA	~30%	None demonstrated for any drug	RBC, WBC, Plt	Most effective in younger patients with shorter disease duration; may work better in those with hypocellular marrows, HLA-DR$^+$
Thalidomide	15–20%		RBC	Dose escalation limited by peripheral neuropathies, fatigue, constipation; highly teratogenic
Lenalidomide	66% in del(5q), 26% in non-del(5q)		RBC	Pancytopenia significant in del(5q) patients, may be predictive of response; possible teratogenicity
Cytotoxic/differentiating agents				
Arsenic trioxide	~20%	None demonstrated	RBC, Plt	More effective in low-risk than high-risk patients Can cause significant cytopenias Monitoring of electrocardiogram for QTc prolongation essential
Hypomethylating agents				
5-Azacytidine Decitabine	CR in 11–16%; HI in 15–30%	Delay in transformation to AML and death for 5-aza (all MDS subtypes) and for decitabine (high-risk MDS)	RBC, WBC, Plt	Both agents most appropriately used in high-risk MDS Can cause significant cytopenias Greatest effect seen in patients who receive 4–6 cycles of treatment Both drugs equi-efficacious

ATG, antithymocyte globulin; 5-aza, 5-azacytidine; CR, complete response; CyA, cyclosporin A (cyclosporine); G-CSF, granulocyte colony stimulating factor; GM-CSF, granulocyte macrophage colony stimulating factor; Hgb, hemoglobin; HI, hematologic improvement; Plt, platelet; RBC, red blood cell; WBC, white blood cell.

cytotoxic effects, and anti-angiogenesis mechanisms of action, particularly through altering tumor necrosis factor-α (TNF-α) and VEGF activity.[228–231] Thalidomide decreases bone marrow vascularity and was the first agent of this class of small-molecule inhibitors of angiogenic cytokines to be investigated for treatment of MDS.

Four phase II studies have evaluated use of thalidomide for single-agent therapy in MDS. In the largest series, 83 patients with early and advanced MDS were enrolled, with thalidomide dose escalated from 100 mg to 400 mg per day in tolerant subjects.[232] Fifty-eight patients had early MDS, and 25 had advanced MDS. Fifteen patients (19%), 14 of whom had early MDS, showed hematologic improvement (defined as red blood cell transfusion independence or greater than 50% decrease in transfusion burden), including 10 previously transfusion-dependent patients who became transfusion-independent. Using IWG response criteria,[209] 11 patients had a major hematologic response, while 4 had a minor hematologic response (considered clinically less meaningful).

In another study of 25 transfusion-dependent patients with MDS, 5 (25%) reached transfusion independence after treatment with thalidomide.[233] One other study of 34 patients with MDS showed varied hematologic lineage improvement in 19 (56%) after treatment with thalidomide,[234] while a multicenter phase II study, presented as an abstract and conducted by the North Central Cancer Treatment Group, reported a response in only 7 of 73 patients (10%), most likely owing to high subject attrition resulting from an aggressive dose escalation scheme (from 200 to1000 mg daily).[235] Although thalidomid in general was somewhat effective, rates for toxicity-related discontinuation of the drug ranged from 12% to 40% across all of these studies, with the most common being the nonhematologic toxicities of fatigue, constipation, shortness of breath, and peripheral neuropathy, in addition to well-described hematologic toxicities. The risk for development of these side effects is dose- and time-dependent and therefore limits long-term administration—a discouraging reality, because patients who can tolerate the drug achieve hematologic response rates that approach 30%.

LENALIDOMIDE. Lenalidomide (CC-5013, Revlimid), one of only three drugs approved for the treatment of MDS, is a novel 4-amino-glutarimide analog of thalidomide. It has a mechanism of action is similar to that of thalidomide but is devoid of its neurologic effects and is 50 to 2000 times more potent.[228–231] Other in vitro studies demonstrate lenalidomide's ability to inhibit VEGF-induced clonogenic response and VEGF expression in KG1 AML cell lines, and to block VEGF-induced cell cycle recruitment and adhesion of KG1 AML cells.[236] Lenalidomide also has been shown to reduce bone marrow vascularity in subjects demonstrating clinical response during treatment.

Lenalidomide was first studied in a phase I-II trial exploring the safety and efficacy of the drug in 43 patients with MDS with transfusion-dependent or symptomatic anemia.[237] All patients either had a high endogenous erythropoietin level of greater than 500 mU/mL or had already received and not responded to recombinant erythropoietin.

Three oral dosing schedules were evaluated: 25 mg daily, 10 mg daily, and a syncopated regimen of 10 mg daily for 21 days of a 28-day cycle. Of the 43 patients enrolled, 38 had early MDS (with IPSS scores of "low" or "int-1") and 74% were transfusion-dependent, with 33 (77%) having failed previous therapy with recombinant erythropoietin. Twenty patients (46%) had clonal karyotypic abnormalities, of whom 12 had an interstitial deletion of 5q31.1 (11 in isolation and 1 with trisomy 21).

The major side effects of all dosing regimens were grade 3 or 4 neutropenia and thrombocytopenia, which occurred in a majority of subjects, and was dose-dependent, necessitating treatment interruption and dose adjustment in a majority of subjects.

Lenalidomide was effective in restoring erythropoiesis, particularly in the del(5q) subset of patients. Twenty-one patients (49%) had a major hematologic response, including 20 of 32 (63%) transfusion-dependent patients, by a median of 9 to 11.5 weeks. After a median follow-up period of 81 weeks, the median response duration had not been reached and was greater than 48 weeks. Of the 21 patients with a major hematologic response, anemia recurred in 4.

Twenty patients started the study with clonal cytogenetic abnormalities. Of these, 11 had cytogenetic responses; 10 with complete responses, including 9 with a deletion of 5q31.1 and 1 with t(1;22)(q21p11.2). Cytogenetic responses occurred only in patients who had a hematologic response. Whether cytogenetic remissions correlate with improved survival, as might be suspected, remains to be seen.

Two multicenter phase II trials of lenalidomide in MDS also have been conducted and were closed to enrollment in January 2004.[238] The first studied use of the drug with the syncopated or 10-mg daily dosing schedule in 215 transfusion-dependent patients with early ("low" or "int-1" risk) MDS, but without the del(5q) cytogenetic abnormality. The median age was 72 years, and 95 patients (44%) experienced hematologic improvement, with 56 patients (26%) achieving transfusion independence for a median of 41 weeks (range, 8 to 136 weeks). Only 9% of evaluable patients achieved a complete cytogenetic response.

The second phase II trial used the same dosing regimens in 148 transfusion-dependent patients with low-risk MDS with the 5q31.1 deletion. A total of 99 patients (67%) achieved transfusion independence, and 75% of responders experienced a cytogenetic response. Almost half of these patients had a complete cytogenetic response (44% of all patients), and approximately one third of patients achieved complete pathologic responses with resolution of cytologic dysplasia. The median duration of red blood cell transfusion independence, when these patients were combined with similar patients from the phase I-II study, was 2.2 years (range, 0.1 to 4.4 years), with no plateau to the curve—meaning that with adequate follow-up, all patients are likely to relapse. No difference was found in the rate of erythroid response according to karyotype complexity. Development of grade 3 or 4 myelosuppression was the most common adverse event, and three patients (1.5%) were suspected to have died as a result of possible therapy-associated complications of bleeding or infection. Preliminary studies indicate that treatment-related thrombocytopenia and neutropenia may correlate with achieving transfusion independence.

Lenalidomide was approved by the FDA on December 27, 2005, for the treatment of IPSS Low and Int-1 MDS in patients who harbor the del(5q) abnormality, at a dose of 10 mg daily. As with the phase I-II study, almost 80% of patients receiving this dose required a dose reduction.

Because preclinical investigations indicate that the erythropoietic effects of lenalidomide in non-del(5q) MDS are erythropoietin-dependent, the potential for additive benefit is being tested in a phase III intergroup study comparing lenalidomide monotherapy with a darbepoetin-lenalidomide combination. Lenalidomide also is being explored in the cooperative group setting as single-agent therapy for the treatment of older adults with AML associated with the del(5q) abnormality, based on the phase II MDS data showing efficacy in MDS patients with complex cytogenetics that included this specific deletion.[238] Lenalidomide in combination with the hypomethylating agent 5-azacytidine also is being studied in a multi-institution phase I trial in patients with advanced MDS.

Arsenic Trioxide

Two phase II studies have explored the use of arsenic trioxide in patients with MDS and show remarkably similar results. The first study, conducted in the United States, enrolled 76 patients, 47% with low-risk MDS and 53% with high-risk MDS.[239] Patients received arsenic trioxide at a dose of 0.25 mg/kg daily on days 1 to 5 and days 8 to 12 of a 28-day cycle. The median age of the patients was 69 years. A hematologic response, as defined by the IWG, was achieved in 20% of those who received a dose of arsenic trioxide (24% in the low-risk group). Responses took a median of 3.6 months to occur and were durable, lasting a median of 6.8 months.

In the European Union study, arsenic trioxide was administered at a dose of 0.30 mg/kg daily for the first 5 days and then at 0.25 mg/kg twice weekly for at least 15 weeks thereafter. Of 115 patients with MDS enrolled in the study, 43% had low-risk and 57% high-risk disease.[240] Responses occurred in 21% of the patients (26% in the low-risk group) at a median of 1.9 months. Toxicities were similar for both trials and included mainly hematologic complications (with grade 3 or 4 neutropenia and thrombocytopenia occurring in greater than 50% of patients). Arsenic trioxide is approved by the FDA for the treatment of relapsed acute promyelocytic leukemia and is being studied in multiple clinical trials in combination with other drugs for the treatment of MDS.

Therapies for Advanced Myelodysplastic Syndromes

Treatment goals for advanced MDS differ from those for early MDS. As the disease moves closer to leukemia, it becomes more imperative to delay transformation to leukemia and to achieve a remission.

Hypomethylating Agents

Two hypomethylating drugs have been approved by the FDA for the treatment of all MDS subtypes. Both purportedly work through a similar mechanism of action: protecting cytosine residues on tumor suppressor genes from being methylated, and thus inactivated.[241] The first agent, 5-azacytidine (Vidaza), was studied in a phase III trial in which patients were randomized to receive either the drug or supportive care.[242] Patients assigned to the supportive care group could cross over to the treatment group if their disease worsened. Patients in the treatment group received 75 mg/m^2 daily for 7 days of a 28-day cycle. Ninety-nine patients were randomly assigned to the treatment group and 92 to the supportive care group; of the latter, 49 eventually crossed over to receive active therapy. When data were analyzed using CALGB response criteria (which differ from IWG criteria most

notably in the requirement for maintenance of response for 4 rather than 8 weeks), CRs occurred in 7% of patients, partial responses (PRs) in 16%, and hematologic improvement in 37%, for an overall response rate of 60%. In a subsequent analysis of these and other CALGB data using IWG response criteria, Silverman and associates report lower response rates of 14% combined CR–PR and 30% hematologic improvement.[243] Major toxicities, as with any active agent for the treatment of MDS, included cytopenias. Patients also reported nausea and injection site-related complications.

Decitabine (Dacogen) also was studied in a phase III trial, in which 89 patients receiving this drug were compared with 81 managed with supportive care.[244] Patients received decitabine at a dose of 15 mg/m^2 every 8 hours over 3 days, with a cycle repeated every 6 weeks. Using IWG criteria, CRs occurred in 9%, PRs in 8%, and hematologic improvement in 13%, for an overall response rate of 30%. As with 5-azacytidine, major toxicities were hematologic.

In the 5-azacytidine registration study, a significant delay in transformation to AML or death was seen, but not a significant prolongation of survival among patients in the treatment group. In the decitabine trial, no significant delay in transformation to AML or death was observed, probably as a result of enrollment of different patients in each study (with more early MDS patients in the decitabine study), and of an inadequate number of cycles of decitabine. In patients with IPSS Int-2 or high-risk disease, however, an improvement in delay to AML transformation was seen. The two drugs are considered by most investigators to be clinically equivalent, and alternate dosing schedules, including once-daily dosing of decitabine over 5 days every 28-day cycle, have been explored.[245] Azacytidine was recently approved by the FDA in an intravenous dosing regimen, based on pharmacokinetic studies in 14 patients.

Intensive Therapy

It has long been recognized that intensive induction chemotherapy with AML-type regimens can induce complete remission in MDS, particularly in younger patients.[246,247] The induction death rate is high, however, and remissions typically are of short duration, particularly in patients with poor-risk cytogenetics,[248] so the long-term disease-free survival remains dismal with this strategy.[249] In general, therefore, intensive chemotherapy has been reserved for "younger" patients (i.e., younger than 65 years) with high-risk disease (specifically, greater than 5% blasts, or MDS in transformation to AML) and those with critical cytopenias (in particular, thrombocytopenia or neutropenia), or for cytoreduction before transplantation. Patients with RAEB have CR rates similar to those for patients with RAEB-t or AML and, when data are corrected for other prognostic factors (e.g., cytogenetics, age) experience similar event-free and overall survival. In combination with the poor prognosis of RAEB, this serves as the justification for administration of AML-type chemotherapy to patients with RAEB.[111]

Nevertheless, the clinical results with anthracycline-cytarabine induction therapy are similar to those seen in older patients with de novo AML, with CR rates of approximately 40% to 50%, induction mortality rates of 10% to 20%, and median duration of response of 6 to 10 months.[250–253] In some cases, recovery with lower-grade MDS (i.e., conversion of RAEB to RA—so-called partial response) has been observed, with transient clinical improvement manifested by decrease in cytopenias and reduced transfusion requirements.[248,251]

Little evidence, however, has been found for long-term disease-free survival after intensive chemotherapy. In a report from France, 10 of 99 patients selected for intensive therapy survived longer than 4 years; these patients were younger (median age, 42 years), underwent treatment soon after diagnosis, exhibited normal or favorable cytogenetics, and had RAEB-t at diagnosis.[251] Of interest, studies of X-chromosome inactivation patterns using the human androgen receptor (HUMARA) assay indicate that long-term remission after intensive chemotherapy is characterized by polyclonal hemopoiesis,[254,255] suggesting a recovery of normal hematopoiesis. A retrospective Dutch study of intensive chemotherapy for 83 "younger" MDS patients (younger than 61 years) found that the IPSS was able to predict survival for high-risk patients but not for those in intermediate-risk groups and indeed suggested an improved survival for intermediate-2-risk patients (median survival, 3.4. years).[256] For patients older than 60 years with poor-risk cytogenetics, little evidence has been found for benefit from intensive chemotherapy, with low CR rates and a short median survival of only 4 months.[248] Other chemotherapeutic drugs with apparent activity in MDS are irinotecan[257] and the anti-CD33 immunotoxin gemtuzumab ozogamicin (Mylotarg).[258,259]

In a prospective study of 184 younger patients (median age, 47 years, range, 16 to 60) receiving intensive induction chemotherapy with idarubicin, cytarabine, and etoposide followed by allogeneic or autologous transplantation, the CR rate was 54% and the induction death rate 16%, and 63 patients went on to undergo either allogeneic (N = 28) or autologous transplantation (N = 35).[253] Disease-free survival rates were similar in patients with and those without a donor (31% and 27%, respectively); of interest, a follow-up analysis showed no difference in survival based on the availability of a donor.[260] The strategy of intensive chemotherapy followed by transplantation is clearly feasible, and follow-up studies are required to determine the role of chemotherapy in patients who have an allogeneic donor (and indeed the role of autologous transplantation).

Other intensive regimens also have been employed in younger patients with MDS, including fludarabine and cytarabine in combination with idarubicin[261] or mitoxantrone,[262] with similar clinical results. The most extensive experience with intensive chemotherapy in MDS comes from the M.D. Anderson Cancer Center in Houston. In a series of successive studies, 1279 patients with AML, RAEB-t, or RAEB received intensive chemotherapy with cytarabine combined with either idarubicin (N = 322), fludarabine (N = 600), or topotecan (N = 357).[263] The CR rates were higher with idarubicin (77%), and the event-free and overall survival rates were superior with this agent (63 weeks and 70 weeks, respectively). It must be emphasized that the idarubicin regimen was not a curative therapy, but that fludarabine- and topotecan-based combinations were inferior, and the investigators themselves highlighted the need for new therapies. In a follow-up analysis focusing on the 394 newly diagnosed MDS patients with RAEB and RAEB-t who received treatment in sequential studies, the CR rate with intensive therapy was 58% and was significantly associated with karyotype, age, and the duration of antecedent hematologic disorder, but not with the IPSS score.[131] Survival was associated with cytogenetic features, age, and performance status. Of importance, after prognostic factors were accounted for, survival remained inferior with fludarabine-cytarabine combinations but was similar with idarubicin and topotecan combinations. More recently, the long-term follow-up results in 510 patients (median age, 63 years) were reported from M.D. Anderson Cancer Center. Patients with higher-risk MDS received intensive therapy.[264] The overall CR rate was 55%, with an induction mortality rate of 17% and 5-year survival rate of 8% (11% for patients younger than 65 years; 17% for patients with normal karyotype). The combination of topotecan and cytarabine was equivalent to idarubicin regimens in relation to CR and survival but was associated with a substantially lower induction death rate (6% versus 17%; P = 0.04). This experience suggests that intensive chemotherapy is appropriate for selected patients and that topotecan plus cytarabine is a reasonable alternative to idarubicin-cytarabine combinations, particularly in older patients with contraindications to anthracyclines, such as severe cardiomyopathy.

Overexpression of the multidrug resistance protein (MDR-1) gene product P-glycoprotein has been demonstrated in MDS and may contribute to chemotherapy resistance (i.e., lower CR rates and high relapse rates).[251,265–269] Efforts to target P-glycoprotein in combination with intensive chemotherapy to improve clinical outcomes have had mixed results. In a randomized French study, intravenous

quinine was administered in combination with mitoxantrone and intermediate-dose cytarabine to 131 patients with MDS.[270] No difference in the CR rate, induction deaths, or overall survival was observed between the two groups. In the subset of 42 patients in whom P-glycoprotein expression could be confirmed, however, a significantly higher CR rate (52% versus 18%; $P = 0.02$) and increased overall survival (13 versus 8 months; $P = 0.01$) were seen with use of quinine. No life-threatening toxicity was attributed to quinine, but a significant incidence of tinnitus, vertigo, hearing loss, and QT prolongation was described. Of note, the study was not stratified for P-glycoprotein expression.

In a separate study, investigators in the Eastern Cooperative Oncology Group (ECOG) treated high-risk MDS and relapsed or refractory AML in 129 patients using regimens of mitoxantrone, etoposide, and cytarabine (MEC) without or without valspodar, a more potent inhibitor of P-glycoprotein.[271] Unfortunately, CR rates and overall survival were not improved with valspodar, and indeed the CR rate was slightly lower (although the decrease was not statistically significant). Another mechanism of chemotherapy resistance in high-risk MDS is increased cytosolic expression of the high-affinity isoform of 5′-nucleotidase, which correlates with cytarabine resistance and is associated with inferior survival.[272]

Unfortunately, no comparative trials have been performed to evaluated low-intensity versus high-intensity therapy in high-risk MDS, and it is therefore difficult to estimate the impact of intensive chemotherapy.[273] Of value is a recent analysis from M.D. Anderson Cancer Center comparing outcomes with lower-intensity decitabine ($N = 115$) and intensive chemotherapy. In a retrospective comparison study in which subjects were matched for eligibility for decitabine, age, cytogenetics, and IPSS, patients receiving decitabine had a CR rate comparable to that achieved with intensive chemotherapy (43% versus 46%; $P = 0.69$) but a significantly lower 6-week mortality rate (3% versus 132 %; $P = 0.006$) and 3-month mortality rate (7% versus 23%; $P = 0.001$).[274] Similarly, overall survival was significantly better with decitabine (median survival, 22 months versus 12 months; 2-year survival rate, 47% versus 24%; $P < 0.001$) for both younger (i.e., younger than 60 years) and older patients. Therefore, with the recent availability of the methyltransferase inhibitors decitabine and 5-azacitidine, prospective studies are required to clarify the role of intensive chemotherapy in MDS.

Stem Cell Transplantation

AlloHSCT using cells from an HLA-matched donor remains the only curative therapy for MDS. Unfortunately, few randomized studies have been conducted, and comparative data on long-term outcomes with nontransplantation strategies are scarce. In addition, the use of alloHSCT has in general been restricted to younger patients because of donor availability and transplant-related mortality; this is a particularly important point, because MDS is a disease of older adults, and most MDS patients have therefore been excluded from consideration of alloHSCT because of age.

Nevertheless, alloHSCT has been extensively studied in phase II and multicenter studies and is an important treatment consideration in younger MDS patients (Table 105-6). The timing of alloHSCT in MDS remains uncertain, particularly for older patients and those with low-risk disease. Recent efforts to minimize nonrelapse transplant-related mortality with the use of reduced intensity or nonmyeloablative conditioning, as well as some improvements in donor availability, have extended the availability of alloHSCT to older patients, so that it can now be considered in selected patients aged 55 to 70 years.[275]

The benefit of alloHSCT is thought to be mediated through an allogeneic graft-versus-MDS effect, manifested by lower relapse rates after graft-versus-host disease (GVHD)[276–279] (in particular, chronic GVHD)[280]; higher relapse rates with the use of T-cell depletion[280,281]; lower relapse rate and improved disease-free survival with complete (greater than 95%) donor T-cell engraftment[282,283]; and the observation of durable remissions after donor lymphocyte infusion for post-transplantation MDS relapse.[284,285]

Sibling Donors

Many reports have been published on the toxicity and efficacy of myeloablative conditioning and alloHSCT from an HLA-matched sibling.[281,286–293] In composite, the reports suggest that greater than one third of patients are cured (29% to 40% long-term DFS). Relapse and nonrelapsed transplant-related mortality, however, remain significant problems, the latter predominantly due to the complications of GVHD. The estimated relapse rate is frustratingly high after alloHSCT (23% to 48%), and the nonrelapsed transplant-related mortality rate is approximately 37% to 50%. Therefore, although a

Table 105-6 Allogeneic Hematopoietic Stem Cell Transplantation with Myeloablative Conditioning: Clinical Results

Study	Year	No. of Patients	Median Age (years)	Donor Type	Conditioning Regimen	NRM (%)	Relapse Rate (%)	DFS Rate (%)
Anderson et al[287] (Seattle)	1993	93	30	Sibling: $N = 65$ Unrelated: $N = 28$	Cy/TBI, BuCy	43	28	41
Sierra et al[281] (IBMTR)	2002	452	38	Sibling	BuCy, Cy/TBI 13% T-cell depletion	37	23	40
Runde et al[289] (EBMT)	1998	131	33	Sibling	TBI-based 12% T-cell depletion	44	34	34
Arnold et al[302] (EBMT)	1998	118	24	Unrelated	TBI-based	58	35	28
Castro-Malaspina et al[301] (NMDP)	2002	510	38	Unrelated	TBI, BuCy, other 24% T-cell depletion	54	14	29
Deeg et al[291] (Seattle)	2002	109	46	Sibling: $N = 45$ Unrelated: $N = 64$	BuCy, targeted Bu	28–30	14	56–59

Bu, busulfan; Cy, cyclophosphamide; DFS, disease-free survival; EBMT, European Group for Blood and Marrow Transplantation; IBMTR, International Bone Marrow Transplant Registry; NMDP, National Marrow Donor Program; NRM, ••; TBI, total-body irradiation.

subset of patients may be cured, the results are inferior to those seen in patients with de novo AML, which to some extent has limited the use of alloHSCT in MDS.

Significantly higher DFS and significantly lower relapse rates have been observed in patients who undergo transplantation earlier in the course of the disease, particularly those with RA and RARS, and those who undergo transplantation within the first 6 to 12 months of diagnosis[281,289,290,294,295]; relapse rates in excess of 40% have been reported for patients with RAEB.[281,287,288,290] Improved DFS and lower nonrelapsed transplant-related mortality rates also have been observed in patients who underwent transplantation after 1989,[290,296] and with improvements in myeloablative conditioning regimens (specifically, with use of pharmacokinetically targeted busulfan dosing, and non-TBI-based regimen).[291,297–299] In addition to disease stage and FAB classification (specifically, in RAEB), the major determinants of relapse, survival, and nonrelapsed transplant-related mortality after AlloHSCT are patient age, IPSS score, and the presence of poor-risk cytogenetics, for which the relapse rate is greater than 80%.[286,288,291,296]

Another potential prognostic factor is the presence of an elevated pretransplantation serum ferritin, which in a large retrospective analysis ($N = 590$) from the Dana-Farber Cancer Institute was associated with lower DFS and overall survival rates after myeloablative alloHSCT.[300] In patients with MDS, an association between serum ferritin and a significantly higher treatment-related mortality also was observed. This finding suggests that iron overload may play an important role in alloHSCT outcome, as it does in thalassemia, and raises questions about timing of alloHSCT in heavily transfused patients, and also about the potential importance of iron chelation.

Unrelated Donors

Only a minority of MDS patients have a sibling donor, and extensive experience with the use of matched unrelated donors as a source of hematopoietic stem cells has been accumulated. In general, the reported nonrelapsed transplant-related mortality rate is higher than with sibling donors, in most series in excess of 50% (see Table 105-1), and the DFS is lower (25% to 38%).[291,301–303] Of interest, the largest published experience from the National Marrow Donor Program (NMDP; $N = 510$)[301] noted that although the nonrelapsed transplant-related mortality rate was 54% and the DFS rate only 29%, the relapse rate was relatively low at 14%, suggesting a possible augmented graft-versus-MDS effect from unrelated donors. Supporting this observation, a lower risk of MDS relapse ($P = 0.003$) and superior relapse-free survival ($P = 0.02$) also was recently demonstrated with unrelated versus sibling donors in a retrospective study from Seattle.[296]

A study from the French Society of Bone Marrow Transplantation and Cell Therapy prospectively evaluated the outcomes of 236 patients who underwent alloHSCT with myeloablative conditioning from 10/10 HLA-matched sibling ($N = 181$) or unrelated donors ($N = 55$) for standard-risk myeloid malignancy, including MDS.[304] In multivariable analysis, only CMV serostatus, donor age (older than 37 years), and the occurrence of grade II or higher acute GvHD were associated with inferior survival and with nonrelapsed transplant-related mortality, and the effect of donor type was nonsignificant. Therefore it appears that the outcomes after alloHSCT using cells from unrelated donors are similar to those with sibling donors for standard-risk patients, and in the absence of a sibling donor, a search for an unrelated donor is appropriate in patients who are considered eligible for myeloablative conditioning.

T-Cell Depletion

GVHD remains a major cause of nonrelapsed transplant-related mortality and treatment failure in MDS, and several efforts have been directed at reducing the incidence of acute and chronic GVHD through T-cell depletion.[305,306] Data from France and from the IBMTR with sibling donors demonstrated that the use of T-cell-depleted grafts was associated with lower treatment-related mortality but a higher incidence of relapse and did not have an overall effect on DFS or overall survival.[281,288] Similarly, in a randomized NMDP study with matched unrelated donors and using myeloablative conditioning, which included patients with MDS undergoing alloHSCT, the use of in vitro T-cell depletion as GVHD prophylaxis significantly lowered the incidence of acute GVHD but did not have an impact on the incidence of chronic GVHD or on survival.[280] More recently, in vivo T-cell depletion with the use of thymoglobulin[307] or alemtuzumab in reduced-intensity conditioning (RIC) regimens[295,308–310] has shown a lower incidence of acute GVHD compared with historical experience, without a clear increase in relapse. Randomized trials will be required to determine the true contribution to nonrelapsed transplant-related mortality and relapse of in vivo T-cell depletion with monoclonal antibodies in MDS.

Transplantation for Treatment-Related Myelodysplastic Syndrome

Some patients with treatment-related MDS also may benefit from alloHSCT, with a 4- or 5-year disease-free survival rate of approximately 30%, although the nonrelapsed transplant-related mortality rate appears to be substantially higher than with de novo MDS (particularly with the use of total body irradiation in the conditioning regimen).[55,311–313] A recent retrospective analysis comparing outcomes after alloHSCT for secondary MDS ($N = 257$) with those for de novo MDS ($N = 339$) found no difference in clinical outcomes, however—the only significant predictive factors being disease stage and karyotype at the time of transplantation.[296] Therefore, patients with treatment-related MDS do appear to benefit from alloHSCT.

Myeloablative Conditioning in Adults Older than 55 Years

An important point illustrated in Table 105-1 is that the studies of myeloablative conditioning and sibling or unrelated donor alloHSCT almost all have been performed in a relatively young patient population, mostly in those younger than 50 years. Some data for selected older adults (up to age 67 years) undergoing ablative alloHSCT for MDS (most with RAEB or RAEB-t)[314,315] demonstrate results similar to those achieved in younger patients (44% survival rate at follow-up evaluation). As in younger patients, the relapse-free survival rate was inversely related to cytogenetic risk classification and to IPSS risk score, as well as the use of targeted busulfan conditioning.[314]

As is evident in Table 105-1, nonrelapsed transplant-related mortality remains an important obstacle to successful alloHSCT for MDS patients and is a major cause of treatment failure. The Seattle group of investigators recently presented a Hematopoietic Cell Transplantation–Specific Comorbidity Index, which independently predicts nonrelapsed transplant-related mortality and survival after alloHSCT.[316] This is likely to be important in the design and patient selection of future alloHSCT trials in older patients with MDS.

Induction Chemotherapy before Allogeneic Hematopoietic Stem Cell Transplantation

Because RAEB is associated with inferior outcomes (increased risk of relapse, decreased survival) after alloHSCT, it has been proposed that such patients should receive induction chemotherapy before proceeding with alloHSCT, particularly those with RAEB-2 (greater than 10% blasts), or before alloHSCT with RIC regimens.[275,298,305,306] Retrospective studies do not show a clear benefit for the routine use of induction chemotherapy however,[288,317,318] and this question is being addressed in a prospective randomized trial being conducted by the European Group for Blood and Marrow Transplantation (EBMT).[305] Of interest, in a cohort of 159 patients who received intensive chemotherapy followed by either autologous or allogeneic stem cell transplantation, no difference in disease-free or overall survival was found to correlate with the availability of a sibling donor,[260] suggesting that the intensive therapy itself may improve outcome. In a

separate report, 75 patients (median age, 52 years) with high-risk AML and MDS (including patients with refractory disease) were treated prospectively with intensive cytoreduction followed immediately by RIC, alloHSCT from sibling or unrelated donors, and prophylactic donor lymphocyte transfusion. This study demonstrated remarkable clinical results in a high-risk population, with 88% CR and 40% 2-year leukemia-free survival rates.[319] It appears, therefore, that patients with refractory disease may potentially benefit from sequential cytoreduction and immediate alloHSCT, and that confirmation of chemosensitivity may not be necessary in all patients. This observation is at odds with older reports,[288] however, and these strategies are being tested prospectively in a randomized trial being run under the auspices of the EBMT.[305]

Timing of Transplantation in Myelodysplastic Syndrome: Decision Analysis

The clear dilemma in considering ablative alloHSCT for MDS patients is that although some patients may be cured, the nonrelapsed transplant-related mortality and relapse rates are high, and the best outcomes are in younger patients with early disease and without poor-risk cytogenetics.[289] In precisely this same group of patients, however, according to the IPSS, the best prognosis is observed with use of low-intensity or supportive care strategies.[126] Therefore, the patients with the most to gain from alloHSCT are also those with the most to risk in terms of survival. The obvious question, therefore, is when to consider alloHSCT, particularly for more favorable-risk patients. This has been addressed in a Markov decision model comparing outcomes in patients from sibling transplantation (Seattle and IBMTR databases) and nontransplantation (International MDS Response Assessment Workshop) registries, performed for all four IPSS risk groups and adjusted for quality of life.[320]

In that study, the strategies of immediate and delayed alloHSCT (either for MDS or at the time of leukemia transformation) were compared for their impact on overall survival. Transplantation before leukemia transformation was associated with a greater number of life years than at the time of leukemia transformation. Delayed transplantation, however, maximized overall survival for Low and Int-1 IPSS risk groups, and particularly for patients younger than 40 years. By contrast, for Int-2 and High IPSS risk groups, immediate alloHSCT maximized overall survival.[320]

Therefore, for higher-risk patients, eligible patients should undergo immediate alloHSCT, whereas for those with low-risk disease, delayed transplantation to the time of disease progression (but before leukemic transformation) is recommended, particularly for younger patients. For those with intermediate-risk disease (i.e., Int-1 under the IPSS), early transplantation should be considered on a case-by-case basis. In a retrospective analysis, the presence of significant marrow fibrosis at the time of transplantation was associated with inferior survival for patients with advanced MDS, suggesting that early alloHSCT should be considered in such cases.[321]

Reduced-Intensity Conditioning

In an effort to address excessive nonrelapsed transplant-related mortality and thereby to extend alloHSCT to older patients, several investigators have studied RIC regimens in patients with MDS[322] (Table 105-7), supplemented in some trials with donor T-cell lymphocyte infusion in the case of delayed engraftment or relapse. In general, the RIC regimens emphasize the graft-versus-MDS effect, and capitalize on the immunosuppressive effects of nucleoside analogs (predominantly fludarabine) combined with either busulfan,[277,308,309] melphalan,[295,310,323] or cyclophosphamide,[324] or the use of low-dose TBI alone or combined with fludarabine, pentostatin, or cyclophos-

Table 105-7 Allogeneic Hematopoietic Stem Cell Transplantation with Reduced-Intensity Conditioning Regimens: Clinical Results

Study	Year	No. of Patients	Median Age (years)	Donor	Conditioning Regimen	NRM (%)	Relapse Rate (%)	DFS Rate (%)
Ho et al[308] (London)	2004	62	54	Sibling: *N* = 24 Unrelated: *N* = 38	Flu-Bu + alemtuzumab (suppl. DLI: *n* = 26)	15	7 Int. 1 50 High	62
van Besien et al[295] (US)	2005	52	52	Sibling: *N* = 23 Unrelated: *N* = 29	Flu-Mel + alemtuzumab	33	27	38
Tauro et al[310] (UK)	2005	76	52	Sibling Unrelated	Flu-Mel + alemtuzumab	9	35	37
Lim et al[309] (London)	2006	75	52	Unrelated	Flu-Bu + alemtuzumab	30	43	41
Martino et al[329] (EBMT)	2006	215	56	Sibling	Flu-based (+ 23% alemtuzumab)	22	45	33
Oran et al[323] (M.D. Anderson Cancer Center)	2007	112	55	Sibling: *N* = 59 Unrelated: *N* = 53	Flu-Mel	54	20	~30
Hallemeier et al[326] (St. Louis)	2006	51	44	Sibling: *N* = 21 Unrelated: *N* = 30	TBI-Cy	37	27	~40
Alyea et al[330] (Boston)	2006	39	57		Nonablative	61	15	20
Scott et al[278] (Seattle)	2006	38	62	Sibling: *N* = 26 Unrelated: *N* = 12	TBI-Flu	41	31	28
Spyridonidis et al[331] (Freiburg)	2005	34	63	Unrelated	Flu-Mel-BCNU	20	27	53
Taussig et al[324] (London)	2003	16	54	Sibling	Flu-Cy	6	31	56

BU, busulfan; Cy, cyclophosphamide; DFS, disease-free survival; DLI, donor (T-cell) lymphocyte infusion; EBMT, European Group for Blood and Marrow Transplantation; Flu, fludarabine; Mel, melphalan; TBI, total-body irradiation.

phamide[278,283,325–327] to facilitate engraftment. In some series, alemtuzumab has been included in the conditioning regimen to achieve in vivo T-cell depletion, presumably minimizing the risk of acute GVHD and hence nonrelapsed transplant-related mortality.[295,308–310] The reported nonrelapsed transplant-related mortality rate with RIC regimens is substantially lower than with myeloablative conditioning (approximately 5% to 15% early nonrelapsed transplant-related mortality rates),[278,328–330] and indeed these studies have included an older patient population (median age, 52 to 63 years), including some patients older than 70 years, and unrelated donors.[278,309,330,331] Despite reduced nonrelapsed transplant-related mortality, the relapse rate appears to be significantly higher than with myeloablative conditioning[278,329,330]; this is explained, at least in part, by the inclusion of patients with more advanced disease in the RIC studies. In comparing a truly "nonablative" (fludarabine, cytarabine, idarubicin) with a reduced-intensity (fludarabine, melphalan) conditioning regimen in one center, lower nonrelapsed transplant-related mortality was noted for the former, but at the cost of inferior donor engraftment and a significantly increased risk of relapse.[332] This finding suggests that a critical minimal level of intensity may be required for successful alloHSCT. Nevertheless, the overall survival with RIC regimens is similar to that with myeloablative conditioning in younger adults, suggesting an important role in older patients. Efforts to improve the relapse rate after RIC regimens with targeted immunotherapy (e.g., ^{131}I–anti-CD45 monoclonal antibody or ^{188}RE–anti-CD66) are promising and may improve on the relapse rate without increasing nonrelapsed transplant-related mortality.[333,334] Isolated CNS relapse has been reported after RIC alloHSCT for AML/MDS,[279] and CNS prophylaxis should be considered, particularly in those with RAEB.

The feasibility of RIC alloHSCT in "older" adults (50 years of age and older) was recently evaluated in a prospective study at the M.D. Anderson Cancer Center. In that analysis, the intention was to proceed to RIC alloHSCT after achievement of a complete remission for patients with AML and high-risk MDS receiving induction treatment with intensive chemotherapy. In total, 99 of 259 patients achieved complete remission and were potentially eligible for RIC alloHSCT. Only 53, however, were evaluated for transplantation, only 26 had a donor identified, and only 14 proceeded to alloHSCT (with a sibling donor in 13 of 14 cases).[335] A clear survival advantage was found for the patients in complete remission who proceeded to RIC alloHSCT, in comparison with those in complete remission who did not receive alloHSCT. This study highlights the limitations of RIC alloHSCT in this population, particularly with regard to patient selection, and demonstrates the need for improvements in induction therapy and donor availability. Multicenter prospective trials will be required to test the impact of RIC alloHSCT in older adults with MDS.

The prognosis with relapse after RIC transplantation is very poor. The response rate to donor lymphocyte infusion is low, although rare patients may be salvaged with intensive chemotherapy and a second alloHSCT procedure.[336]

Peripheral Blood Stem Cells

Peripheral blood stem cells (PBSCs) are an attractive source of hematopoietic precursors in MDS because they are associated with faster hematologic recovery than can be achieved with bone marrow and therefore may reduce early regimen-related mortality, particularly with use of myeloablative conditioning and sibling donors.[337] In a randomized study from the Canadian BMT Group, patients with myeloid malignancy including MDS who received PBSCs experienced faster hematologic recovery without a significant increase in GVHD, and had an improved 30-month survival in comparison with bone marrow recipients (68% versus 60%; $P = 0.04$).[338] This is supported by a retrospective analysis from the EBMT, which demonstrated an increase in the incidence of chronic GVHD with PBSCs (odds ratio 1.62; 95% confidence interval [CI] 0.8 to 3.02) and an associated decrease in 2-year transplant-related mortality (relative risk [RR] 0.33, 95% CI 0.15 to 0.73; $P < 0.007$) (OR) and 2-year treatment failure (RR 0.22; 95% CI, 0.10 to 0.48; $P < 0.001$).[339] These studies suggest that PBSCs may be preferred in sibling alloHSCT for MDS, particularly in pateints with RAEB.[298] An initial retrospective experience with unrelated donor PBSCs suggested no difference in the rates of GVHD or other clinical outcomes,[340] but at long-term follow-up evaluation, an increased risk of chronic extensive GVHD was noted, with no difference in relapse rate or survival.[341] It is not known whether PBSCs are preferable to bone marrow in patients undergoing RIC alloHSCT, and longer follow-up study is required to determine long-term toxicity.[342]

Alternative Sources: Autologous, Cord Blood, and Haploidentical Transplantation

Based on more extensive experience in patients with AML[343] and the lack of an available donor in many cases of MDS, intensive chemotherapy followed by autologous bone marrow of PBSC transplantation has been evaluated in younger MDS patients.[305,344–346] Karyotypically normal autologous PBSCs can be successfully harvested in a majority of (but not all) patients with MDS[290,347,348] and the median disease-free survival period after consolidation with autologous transplantation is approximately 24 to 30 months.[290,305,345,346] Nonrelapsed transplant-related mortality is substantially lower than after allogeneic transplantation, but relapse remains a significant problem (greater than 60% relapse rate). Using a donor versus no-donor analysis, an earlier EBMT report found no clear survival advantage in autologous versus sibling allogeneic transplantation after intensive chemotherapy, calling into question the graft-versus-MDS effect.[260] More recently, however, the EBMT has performed a retrospective analysis of autologous versus unrelated donor transplantation in 593 patients with MDS and secondary AML, including those receiving autologous ($N = 290$) or unrelated donor transplantation ($N = 136$) in first CR after induction chemotherapy.[349] The nonrelapsed transplant-related mortality rate was substantially lower with autologous transplantation (17% versus 38%, respectively; $P < 0.001$), but the relapse rate was significantly higher (62% versus 24%, respectively; $P < 0.001$) and the 3-year survival rate was significantly worse (41% versus 50%; $P < 0.01$) than after unrelated donor transplantation. Autologous transplantation is therefore feasible and may be a reasonable option for selected younger patients without an available donor who achieve a CR after intensive therapy; however, allogeneic transplantation from an HLA-matched donor remains the preferred option.

Pilot results with transplantation from umbilical cord blood (UCB) in adults with MDS were initially encouraging,[350] although more recent results demonstrate a high nonrelapsed transplant-related mortality and slow engraftment.[351] UCB transplantation, therefore, remains an investigational strategy. Because of the cell dose that is required, most adults are not candidates for a single UCB transplant procedure. Recently, in order to extend access to UCB transplantation and overcome the low cell dose barrier that excludes most adults from the procedure, investigators at the University of Minnesota reported on the results of a study of myeloablative conditioning and double cord UCB transplantation using two partially HLA-matched UCB units.[352] This allows for an increased cell dose to facilitate engraftment. Engraftment rates were reported to be high, and the incidence of GVHD and nonrelapsed transplant-related mortality was low. Of interest, a syndrome of early, mixed engraftment was observed, although by day 100 after transplantation, cells from one donor predominated. Disease-related outcomes were better in patients who received their transplant while in remission. Similar results with successful engraftment also have been reported after nonmyeloablative conditioning with a double cord strategy.[353] Multicenter trials are being conducted to assess the feasibility of UCB transplantation in MDS.

It is worth noting recent encouraging experience with transplantation from haploidentical donors[354,355] that demonstrates improved nonrelapsed transplant-related mortality compared with previous experience and also disease-free survival similar to that for matched unrelated donors.[356] Prospective studies are needed to asses the impact of haploidentical donors on survival in comparison with unrelated donor transplantation, and this treatment remains investigational.

MYELODYSPLASTIC SYNDROME IN HUMAN IMMUNODEFICIDENCY VIRUS AND ACQUIRED IMMUNODEFICINECY SYNDROME

Cytopenias and dysplasia in association with a hypercellular bone marrow have long been recognized in HIV/acquired immunodeficiency syndrome (AIDS),[357,358] and the most commonly recognized abnormalities are anemia[359] and dyserythropoiesis.[360,361] The process typically is multifactorial and in some cases is related to antiretroviral therapy (e.g., with azidothymidine [AZT]).[357,362] Bone marrow findings typically are reflective of the HIV infection itself[360,363]; abnormalities are more pronounced in patients with a high HIV viral load or advanced disease,[364,365] and an increase in marrow angiogenesis also has been observed.[365,366] Treatment of MDS may reverse the changes,[367] and growth factors (e.g., erythropoietin, G-CSF) may be used to treat isolated cytopenias or to ameliorate the myelosuppressive effects of therapy in HIV-infected patients.[358,368,369]

High-grade MDS (RAEB) has been reported only rarely,[367] and in general the dysplastic changes in HIV usually are not as severe as those seen in classical MDS[370]; an excess of blasts, karyotypic abnormalities, and progression to AML all are rare.[369,371] This may be related to a reduced proliferation capacity of bone marrow progenitor cells induced directly by HIV.[372,373] Because of these differences, the term *HIV myelopathy* has been proposed to distinguish these changes from classic MDS.[361,371]

MYELODYSPLASTIC SYNDROME IN CHILDREN

MDS is rare in children,[3,5] and in most cases the clinical picture includes a related medical diagnosis (e.g., Shwachman's syndrome) or a constitutional genetic disorder such as Down's syndrome, neurofibromatosis, Fanconi's anemia, or Kostmann's syndrome.[32,60,61,374,375] Many cases are secondary to previous therapy for cancer, including both alkylating agents and etoposide,[32,376] or follow therapy with G-CSF for severe congenital neutropenia or Shwachman-Diamond syndrome[61]; in such cases, the prognosis is less favorable that with de novo disease.[32] The most common cytogenetic abnormality among children with early MDS (refractory anemia) is monosomy 7, and a hypocellular bone marrow is more common than in adults.[377] In addition to the FAB subtype, fetal hemoglobin (HbF) concentration less than 10% is a significant prognostic factor.[374,375] An associated myeloproliferative disorder is common, particularly in younger patients,[374] and transformation to acute leukemia occurs more frequently than in adults. AlloHSCT is recommended early in the course of the disease,[377] although it is not clear to what extent transplantation improves the prognosis of advanced MDS in children.[374,375]

PREVENTION

MDS is idiopathic in most cases and typically occurs in older patients (median age older than 70 years)[4]; therefore, prevention strategies for de novo MDS have not been developed. The risk of secondary MDS has been addressed through avoidance of radiation (including TBI and ^{32}P) and chemotherapy exposure[39,53,54] and prevention of benzene exposure.[11] Surveillance of blood counts in petrochemical workers has not been demonstrated to decrease MDS risk.[378] The use of nonalkylating agent regimens may lower the risk for MDS in patients with Hodgkin's lymphoma.[27] It remains to be determined whether the use of involved-field versus extended-field radiotherapy will decrease the risk of secondary MDS,[29,37,41] although early reports are encouraging.[379] The independent contribution of G-CSF to the development of MDS in patients receiving dose-dense therapy for breast cancer has not been fully elucidated,[30] and long-term follow-up studies are required to quantify the risk.

EXPERIMENTAL TREATMENTS

It is clear that present therapy is inadequate for most patients with MDS, and new treatments are urgently needed. This is especially true for older patients (who in fact comprise a majority of those with MDS), who are not candidates for intensive therapy or for alloHSCT.

Agents such as valproic acid have demonstrated histone deacetylase (HDAC) inhibition and differentiation induction of blasts in vitro and also have some single-agent clinical activity in MDS.[380] Based on preclinical studies, HDAC inhibitors have been combined with hypomethylating agents to synergistically induce differentiation (and thereby improve cytopenias).[94] Combination studies of valproic acid[381] or other targeted HDAC inhibitors[382] with 5-azacytidine have shown clinical activity, and phase III trials in comparison with 5-azacytidine alone are in progress.

Novel chemotherapeutic agents include cloretazine[383] and the nucleoside analog clofarabine, which appears to have significant activity in MDS at lower doses.[384] An oral formulation of clofarabine is being evaluated for treatment of MDS.[384] The farnesyltransferase inhibitor tipifarnib has demonstrated activity in RAEB,[385] and a recent multicenter phase II study confirmed a response rate of 32% in patients with intermediate- to high-risk MDS.[386] Other small-molecule tyrosine kinase inhibitors have been evaluated in patients with high-risk MDS, and in vivo inhibition of FLT3 phosphorylation and reduction in blasts have been reported with tandutinib.[387]

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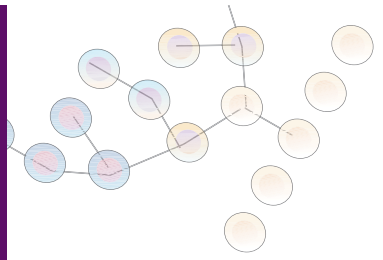
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106 Myeloproliferative Disorders

Ayalew Tefferi

SUMMARY OF KEY POINTS

Incidence

- Each of the three classic *BCR-ABL*$^-$ myeloproliferative disorders (MPDs)—that is, polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF), are estimated to occur at the rate of 0.5 to 2.5 per 100,000 people per year.

Differential Diagnosis

- All three classic *BCR-ABL*$^-$ MPDs may be considered as diagnoses of exclusion, because a specific diagnostic marker is currently lacking.
- The presence of a *JAK2* mutation distinguishes PV from all other causes of polycythemia, and ET and PMF from reactive thrombocytosis or myelofibrosis, respectively.

Diagnostic Evaluation

- Evaluation of suspected PV should start with peripheral blood screening for *JAK2*V617F and serum erythropoietin (Epo) measurement.
- More than 90% of PV patients are expected to display the mutation, whereas a low serum Epo level should capture most of the *JAK2*V617F$^-$ cases, which might display other *JAK2* mutations such as an exon 12 mutation.
- Bone marrow examination remains essential in the diagnosis of ET and PMF.

Risk Stratification

- Both PV and ET display a near-normal life expectancy in the first decade of the disease. The major problem during this period is thrombosis that may occur in as many as 30% of the patients.
- A history of thrombosis or age older than 60 years is associated with a high risk of thrombosis.
- Platelet count by itself has not been significantly associated with thrombosis in either PV or ET.
- The presence of anemia, thrombocytopenia, monocytosis, either leukopenia or leukocytosis, severe constitutional symptoms, or circulating blasts are all adverse risk factors in PMF.

Treatment

- Phlebotomy remains the mainstay of therapy in PV.
- Low-risk patients (age younger than 60 years *and* no history of thrombosis) with either PV or ET have not been shown to benefit from cytoreductive therapy.
- Treatment with hydroxyurea has been shown to reduce thrombosis risk in high-risk patients with both ET and PV.
- Microvascular symptoms, including headache and erythromelalgia (painful and burning sensation of the feet or hands associated with erythema and warmth), are easily treated with low-dose aspirin, which is indicated in the absence of extreme thrombocytosis.
- Drug therapy in PMF is currently palliative, and effective agents include corticosteroids, erythropoietin (Epo), androgen preparations, thalidomide, lenalidomide, and hydroxyurea.
- Splenectomy continues to have a palliative role in PMF.
- Involved-field radiation therapy in PMF is most effective in the setting of nonhepatosplenic extramedullary hematopoiesis.
- The therapeutic value of hematopoietic stem cell transplantation in PMF is being investigated.

INTRODUCTION

The World Health Organization (WHO) classification system for hematopoietic malignancies considers four broad categories of chronic myeloid neoplasms: myelodysplastic syndrome (MDS), myeloproliferative disorders (MPDs), MDS/MPD overlap syndrome, and systemic mastocytosis (SM).[1] The WHO MPD category includes chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic neutrophilic leukemia, chronic eosinophilic leukemia, hypereosinophilic syndrome, and MPD unclassified. Myeloproliferative disorders unclassified refers to a clinically and histologically MPD-like phenotype that does not fulfill the standard diagnostic criteria for CML, PV, ET, PMF, chronic neutrophilic leukemia, chronic eosinophilic leukemia, or hypereosinophilic syndrome.

The WHO MDS/MPD category includes chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, atypical chronic myeloid leukemia, and "MDS/MPD, unclassifiable (MDS/MPDs unclassified)." Atypical CML is characterized by the absence of *BCR-ABL* and the presence of left-shifted granulocytosis with granulocytic dysplasia. MDS/MPDs unclassified refers to a clinical phenotype that displays histological characteristics of both MDS and MPD without fulfilling the diagnostic criteria for chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia, or atypical chronic myeloid leukemia. Some place the WHO provisional entity of "refractory anemia with ringed sideroblasts associated with marked thrombocytosis" in this category of MDS/MPDs unclassified.

Table 106-1 represents an alternative semimolecular classification scheme for chronic myeloid neoplasms that uses the term "classic MPDs" to refer to the original four clinicopathologic entities (i.e.,

Table 106-1 Modern Classification of Chronic Myeloid Neoplasms

Main Categories	Subcategories	Molecular Signatures
Myelodysplastic syndrome	According to WHO classification system	
Classic myeloproliferative disorders	Chronic myeloid leukemia	100% *BCR-ABL*$^+$
	Polycythemia vera	~95% *JAK2*V617F$^+$
		~4% *JAK2* exon 12 mutations$^+$
	Essential thrombocythemia	~50% *JAK2*V617F$^+$
		~1% *MPL*W515L/K$^+$
	Primary myelofibrosis	~50% *JAK2*V617F$^+$
		~5% *MPL*W515L/K$^+$
Nonclassic myeloproliferative disorders	Chronic myelomonocytic leukemia	~3% *JAK2*V617F$^+$
	Juvenile myelomonocytic leukemia	~30% *PTPN11* mutation$^+$
		~15% *NF1* mutation$^+$
		~15% *RAS* mutation$^+$
	Chronic neutrophilic leukemia	~20% *JAK2*V617F$^+$
	Chronic eosinophilic leukemia	
	PDGFRA-rearranged	~100% *FIP1L1-PDGFRA*$^+$
	PDGFRB-rearranged	100% various *PDGFRB* translocations
	Molecularly-undefined	
	Hypereosinophilic syndrome	
	Systemic mastocytosis	
	KIT-mutated	~90% *KIT*D816V$^+$
	Molecularly undefined	
	8p11 myeloproliferative syndrome	100% various *FGFR1* translocations
	Chronic basophilic leukemia	
	Atypical chronic myeloid leukemia	~20% *JAK2*V617F$^+$
	MPD not otherwise classified (MPD-NOC) includes the WHO categories of "MPD, unclassifiable", "MDS/MPD, unclassifiable", and "RARS-T"	~20% to 50% *JAK2*V617F$^+$

MDS, myelodysplastic syndrome; MPD, myeloproliferative syndrome; MPD-NOC, MPD not otherwise classified; RARS-T, refractory anemia with ringed sideroblasts associated with marked thrombocytosis; SCLL, stem cell leukemia and lymphoma syndrome; WHO, World Health Organization.

CML, PV, ET, and PMF) in whom the term "MPDs" was first applied by William Dameshek.[2] In this operational classification system, all remaining chronic myeloid neoplasms other than MDS are assigned the term "nonclassic MPDs";[3] these include the WHO category MDS/MPD, SM, chronic neutrophilic leukemia, chronic eosinophilic leukemia, hypereosinophilic syndrome, and MPDs unclassified. The particular classification system also recognizes molecularly characterized subcategories including the platelet-derived growth factor receptor (*PDGFR*)–rearranged chronic eosinophilic leukemias, the fibroblast growth factor receptor 1–rearranged stem cell leukemia/lymphoma syndrome, and *KIT*-mutated SM. The current chapter focuses on the classic *BCR-ABL*$^-$ MPDs: PV, ET, and PMF.

POLYCYTHEMIA VERA

Vaquez and Osler are credited for the initial description of PV, as a primary erythrocythemic process, in 1892 and 1903, respectively.[4,5] Reported incidence figures in PV range from approximately 0.5 to 2.6 per 100,000 population.[6,7] A higher disease incidence has been suggested in persons of Jewish ancestry[8] as well as among parent-offspring pairs.[9] Median age at diagnosis of PV is approximately 60 years with a slight (1.2 : 1) male preponderance.[10] Approximately 7% of patients are diagnosed before age 40,[10] and there are rare cases of children affected with PV.[11]

Pathogenesis

PV is a clonal stem cell disease with trilineage myeloid involvement.[12] In addition, some studies have suggested clonal heterogeneity including clonal involvement of B lymphocytes[13] as well as polyclonal granulopoiesis in certain cases.[14] In vitro, erythroid colony formation in patients with PV does not require the addition of exogenous Epo.[15] This phenomenon is called endogenous erythroid colony growth and does not occur in either normal controls or patients with nonclonal polycythemia. In addition, erythroid progenitor cells in PV display growth factor hypersensitivity to Epo, insulin-like growth factor (IGF)-1, and other cytokines.[16,17] The consistently observed IGF-1 hypersensitivity of erythroid cells in PV has been attributed to alter-

ations in IGF-1 binding proteins.[18] However, several studies have shown that growth factor–independent or growth factor–hypersensitive colony formation is specific to neither PV nor erythroid progenitor cells.[17]

The Epo receptor gene as well as its protein are intact in PV.[19] On the other hand, several postreceptor molecular abnormalities have been reported and include increased baseline phosphorylation of the IGF-1 receptor,[20] decreased activity of SH-PTP1 (a tyrosine phosphatase),[21] increased activity of membrane-associated SH-PTP,[22] constitutive activation of STAT3,[23] upregulation of negative control elements of the cell cycle (p16/p14),[24] and abundance, in erythroid precursors, of antiapoptotic proteins (Bcl-x_L).[25] However, these observations have not been always reproducible, and none of them have been shown to be specific to PV, as opposed to other MPDs.

In 2005 a novel Janus kinase 2 (JAK2) mutation (*JAK2*V617F) was described in association with PV, ET, and PMF.[26] *JAK2*V617F occurs in approximately 95% of PV patients but also in approximately 50% of those with ET or PMF.[27–30] In addition, the mutation is found in a small proportion of patients with other myeloid neoplasms including nonclassic MPDs and MDS.[31,32] Other *JAK2* mutations (i.e., *JAK2* exon 12 mutations) were recently described in the majority of patients with *JAK2*V617F⁻ PV or "idiopathic erythrocytosis,"[33] thus raising the possibility that a *JAK2* mutation is essential for the PV phenotype. On the other hand, neither *JAK2*V617F nor *JAK2* exon 12 mutations have so far been reported in lymphoid disorders,[34–37] solid tumor,[38–40] or secondary myeloproliferation including congenital or acquired polycythemia.[41–43]

*JAK2*V617F is a G-to-T somatic mutation, at nucleotide 1849, in exon 14, resulting in the substitution of valine by phenylalanine at codon 617.[27–30] *JAK2* exon 12 mutations (F537–K539delinsL, H538QK539L, K539L, N542–E543del) include both in-frame deletions and tandem point mutations.[33] Both exon 14 and exon 12 *JAK2* mutations induce cytokine-independent/hypersensitive proliferation in Epo receptor–expressing cell lines and a PV-like phenotype in mice.[33] Whereas homozygosity for *JAK2*V617F, which results from mitotic recombination, can be demonstrated in the majority of patients with PV,[44] exon 12 *JAK2* mutations are often heterozygous.[33] The precise pathogenetic role of *JAK2* mutations in PV and related MPDs is currently under intense investigation.

Diagnosis

In clinical practice the term polycythemia is used to indicate the possible occurrence of an increased erythrocyte volume or red blood cell mass (RCM). Such a perception might be either real (*true polycythemia*) or spurious (*apparent polycythemia*; Fig. 106-1).[17] True polycythemia may represent either PV or a nonclonal increase in RCM that is often, but not always, mediated by Epo (secondary polycythemia; Fig. 106-2). Apparent polycythemia may result from either a reduction in plasma volume (relative polycythemia) or an inaccurate perception of an elevated RCM that results from not appreciating high normal values of hemoglobin/hematocrit.[45] *Inapparent polycythemia* is the converse of apparent polycythemia and indicates a true increase in RCM that is masked by a normal hemoglobin/hematocrit value secondary to a concomitant increase in plasma volume (see Fig. 106-1).[46]

In 1975 the PV study group published a set of "diagnostic criteria" that were primarily used to ensure the exclusion, to treatment protocols, of patients with secondary or apparent polycythemia.[47] These criteria required the demonstration of increased RCM by blood volume measurement using labeled erythrocytes as well as the demonstration of normal hemoglobin oxygen saturation. In 2001, the WHO published a refined diagnostic criteria for PV and related MPDs that recognized the value of both bone marrow histology and "MPD-specific" biologic parameters.[48] The recent discovery of the almost invariable association between PV and a *JAK2* mutation has led to revised WHO diagnostic criteria for PV (Table 106-2)[49] and a refined diagnostic algorithm (see Fig. 106-2),[50] both of whom incorporate *JAK2* mutation screening.

Because more than 95% of patients with PV carry the *JAK2*V617F mutation, which is absent in both secondary and apparent polycythemia, it is most effective to initiate the workup of a patient with suspected PV with peripheral blood mutation screening for *JAK2*V617F (see Fig. 106-2). Furthermore, to minimize the consequences of false-positive or false-negative molecular test results, as well as capture the few cases of PV that are *JAK2*V617F⁻, concomitant measurement of serum Epo level is recommended.[51] If the results of both tests are suggestive of PV (i.e., mutation-positive and low serum Epo), then the diagnosis is likely and bone marrow examination is encouraged but not essential for making the diagnosis. If the

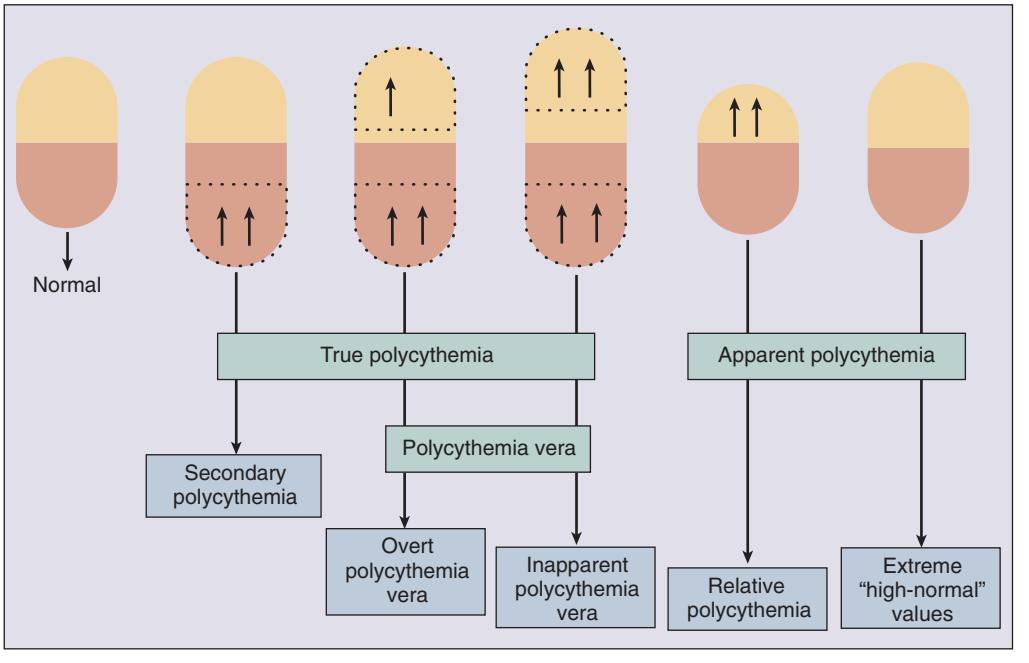


Figure 106-1 • Causes of true (associated with increased red cell mass (RCM) and apparent (not associated with increased RCM) polycythemia. Secondary polycythemia is usually mediated by endogenous erythropoietin (Epo). Erythrocytosis in polycythemia vera (PV) is Epo-independent. Patients with PV display increased plasma volume that is sometimes substantial enough to mask the underlying increased RCM by making the hematocrit appear normal (i.e., inapparent PV).

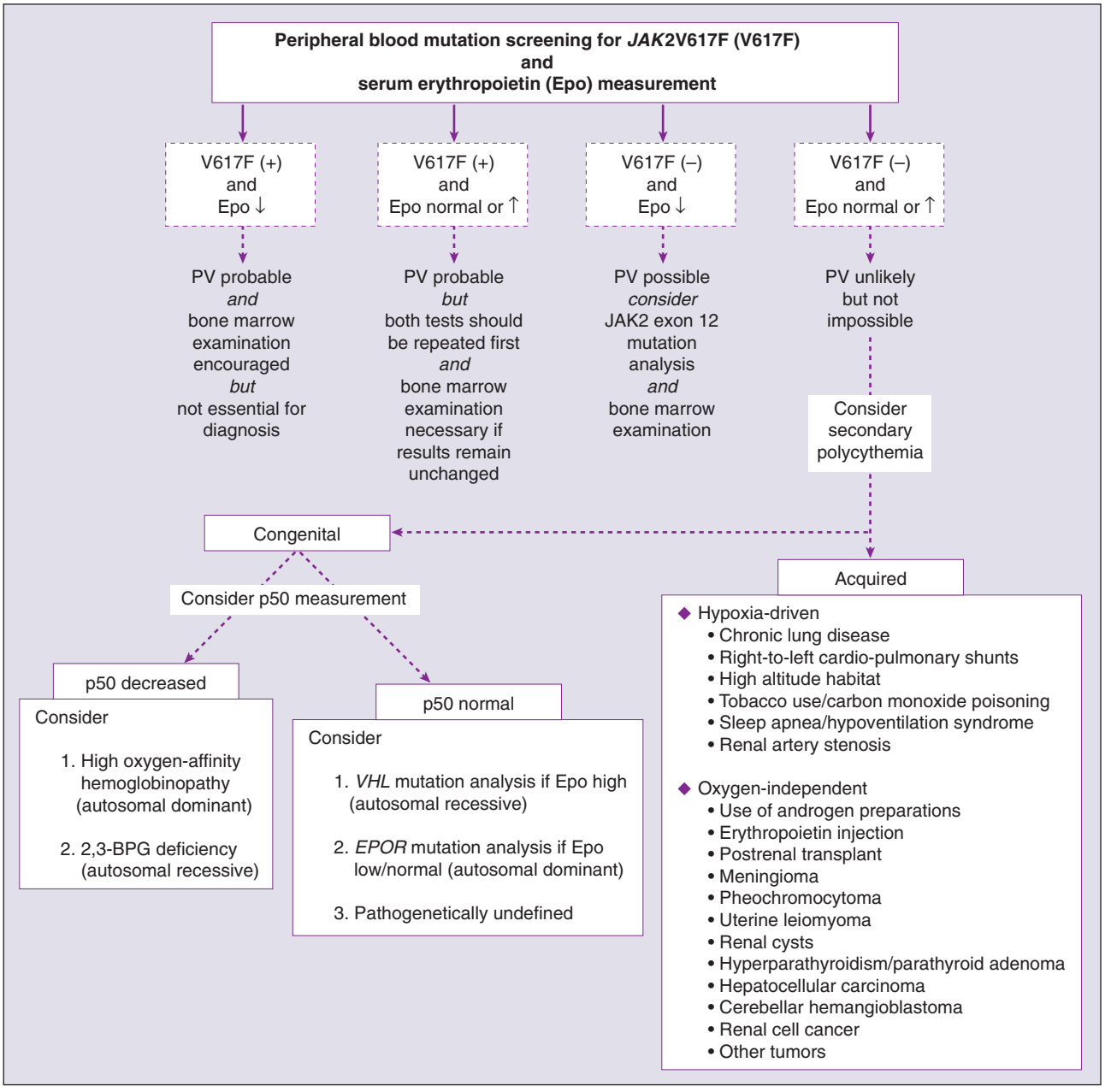


Figure 106-2 • Genetic tests-based diagnostic algorithm for the evaluation of "increased" hemoglobin. PV, polycythemia vera; p50, oxygen tension at which hemoglobin is 50% saturated; VHL, von Hippel-Lindau; EPOR, erythropoietin receptor; BPG, 2,3-bisphosphoglycerate. (Data from Tefferi A, Pardanani A: Evaluation of "increased" hemoglobin in the JAK2 mutations era: a diagnostic algorithm based on genetic tests. Mayo Clin Proc 2007;82:559–604.)

*JAK2*V617F and serum Epo test results are both not consistent with the diagnosis of PV (i.e., mutation-negative and either normal or increased Epo), then further investigation for PV is not advised unless dictated otherwise by the clinical scenario.

If there is discrepancy between the molecular test result and serum Epo level, one should first repeat both tests and then proceed with bone marrow examination if the results are unchanged (see Fig. 106-2). In a patient with acquired erythrocytosis and a subnormal serum Epo level, the possibility of exon 12 *JAK2* mutations should be entertained. In this regard it should be noted that some cases with *JAK2* exon 12 mutation–associated PV might not display overt PV-characteristic features, even at the level of bone marrow histology.[33]

When congenital polycythemia is suspected, initial laboratory testing should include measurement of the oxygen tension at which hemoglobin is 50% saturated (i.e., p50).[50] Left-shifted oxygen dissociation curve, suggested by decreased p50, suggests the presence of either high oxygen-affinity hemoglobinopathy (autosomal dominant)[52] or 2,3-bisphosphoglycerate (2,3-BPG) deficiency, usually a consequence of BPG mutase mutation (autosomal recessive).[53] If the p50 is normal, then the possibility of germline mutations of molecules that either enhance Epo effect (e.g., *EPOR* mutations)[54] or govern intracellular oxygen sensing (e.g., mutations involving the von Hippel-Lindau [*VHL*] tumor suppressor or hypoxia-inducible factor 1a [*HIF-1a*] prolyl hydroxylase genes)[55,56] should be considered (see Fig. 106-2). *VHL* mutations are usually associated with increased serum Epo level and constitute the most frequent mutations in congenital polycythemia (e.g., Chuvash polycythemia).[57] In contrast, serum Epo level is often subnormal in patients with *EPOR* mutations.[58]

Table 106-2 Revised World Health Organization Criteria for Polycythemia Vera

Diagnosis requires the presence of both major criteria and one minor criterion *or* the presence of the first major criterion together with two minor criteria.

MAJOR CRITERIA

Hemoglobin >18.5 g/dL in men, 16.5 g/dL in women, *or* other evidence of increased red cell volume*

Presence of *JAK2*V617F or other functionally similar mutation such as *JAK2* exon 12 mutation

MINOR CRITERIA

Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation

Serum erythropoietin level below the reference range for normal

Endogenous erythroid colony formation in vitro

*Hemoglobin or hematocrit >99th percentile of method-specific reference range for age, sex, and altitude of residence,

or Hemoglobin >17 g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from an individual's baseline value that cannot be attributed to correction of iron deficiency,

or Elevated red cell mass >25% above mean normal predicted value.

Data from Tefferi A, Thiele J, Orazi A, et al: Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytopenia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood 2007;110:1092–1097.

Bone marrow histology, to the experienced hematopathologist, is often revealing of characteristic changes of a MPD that include hypercellularity, increased number of megakaryocytes including cluster formation, the presence of giant megakaryocytes and pleomorphism in megakaryocyte morphology, mild reticulin fibrosis, and decreased bone marrow iron stores.[59] In contrast, cytogenetic studies in PV disclose abnormalities (trisomies of chromosomes 9 and 8 and deletions of the long arms of chromosomes 13 and 20) in only 13% to 18% of patients, at diagnosis, and hence have limited diagnostic value.[60]

Treatment

The natural history of PV is characterized by a lifelong propensity for thrombohemorrhagic complications, late-onset disease transformation into post-PV myelofibrosis and/or acute myeloid leukemia (AML), and a shortened life expectancy.[61] Specific treatment has been shown to positively influence the risk of both macrovascular and microvascular complications but not that of clonal evolution to post-PV myelofibrosis or AML.

Phlebotomy is the cornerstone of therapy in PV and is the only treatment modality that has improved survival in affected patients (Box 106-1). It is reported that median survival may be as low as 2 years in the absence of such treatment.[62] Based on limited retrospective studies in PV that showed a progressive increase in the incidence of vascular occlusive episodes above a hematocrit level of 44%,[63] as well as other studies that showed suboptimal cerebral blood flow in ranges of hematocrit values between 46% and 52%,[64] the therapeutic target hematocrit level is currently set at or below 45%. Furthermore, because of the physiologic difference in hematocrit values between the two genders as well as among different races, it is reasonable, though not evidence-based, to target an even lower hematocrit level (i.e., 42%) in women and African-Americans. Although it is prudent to err on the safe side and utilize the previously mentioned hematocrit thresholds during treatment with phlebotomy, the value of aggressive phlebotomy in aspirin-treated low-risk disease, within hematocrit ranges between 40% and 55%, has been questioned by the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) Investigators.[65]

Role of Drug Therapy in Polycythemia Vera

OBSERVATIONS FROM RANDOMIZED STUDIES. In the first controlled study in PV, the PV study group randomized 431 patients to treatment with either phlebotomy alone or phlebotomy supplanted by either oral chlorambucil or intravenous radioactive phosphorus (^{32}P). The results favored treatment with phlebotomy alone with a median survival of 12.6 years as compared with 10.9 and 9.1 years for treatment with ^{32}P and chlorambucil, respectively ($P = 0.008$). The difference in survival was attributed to an increased incidence of AML in patients treated with chlorambucil or ^{32}P compared with those treated with phlebotomy alone (13.2% vs. 9.6% vs.1.5% over a period of 13–19 years).[66] Furthermore, 3.5% of the patients treated with chlorambucil developed large cell lymphoma, and the incidence of gastrointestinal and skin cancer was increased in those patients treated with either chlorambucil or ^{32}P.

In another controlled study, the European Organization for Research on Treatment of Cancer (EORTC) randomized 293 patients to treatment with either ^{32}P or oral busulfan. The results favored busulfan in terms of both first-remission duration (median, 4 years vs. 2 years) and overall survival (10-year survival rates of 70% vs. 55%; $P = 0.02$). At a median follow-up period of 8 years, there was not significant difference in the risk of leukemic transformation (2% vs. 1.4%), nonhematologic malignancy (2.8% vs. 5%), vascular complications (27% vs. 37%), or transformation into post-PV myelofibrosis (4.8% vs. 4.1%) between the busulfan and ^{32}P arms, respectively.[67]

Other randomized studies in PV have compared hydroxyurea against pipobroman (a significant difference favoring pipobroman in the incidence of transformation into post-PV myelofibrosis but no difference in survival, incidence of thrombosis, or the rate of leukemic conversion),[68] ^{32}P alone against ^{32}P plus hydroxyurea (no difference in survival, incidence of thrombosis, or risk of transformation into post-PV myelofibrosis, but ^{32}P alone was associated with significantly fewer incidences of both acute leukemia and other cancers),[69] and ^{32}P plus phlebotomy against phlebotomy plus high-dose aspirin (900 mg/day) in combination with dipyridamole (225 mg/day) (the addition of antiplatelet agents provided no benefit in terms of thrombosis prevention but increased the risk of gastrointestinal bleeding).[70] However, a more recent randomized study of PV (112 patients) using lower doses of aspirin (40 mg/day) did not show an increased bleeding diathesis.[71] Furthermore, the results of the PV study group aspirin study may have been influenced by the fact that 27% of the patients

Box 106-1. POLYCYTHEMIA VERA

- The polycythemia vera study group diagnostic criteria, including the laboratory measurement of red cell mass, are neither essential nor practical for the diagnosis of PV in routine clinical practice.
- A contemporary algorithm that is based on mutation screening for *JAK2*V617F and serum Epo measurement can be formulated for making a working diagnosis of PV.
- All patients with PV should be phlebotomized to keep the hematocrit at 45% or less at all times.
- In addition to phlebotomy, PV patients who either are older than 60 years of age or have a history of thrombosis should receive myelosuppressive treatment.
- Hydroxyurea remains the myelosuppressive treatment of choice in PV treatment, with α-IFN as a reasonable alternative treatment agent.
- There is not good evidence to implicate thrombocytosis as a prothrombotic risk factor in PV.
- The antithrombotic value of low-dose aspirin (81–325 mg/day) in PV treatment has been demonstrated in a controlled clinical trial.
- It is currently unclear whether currently used drugs in PV influence disease transformation into either myelofibrosis or acute leukemia.

randomized to the phlebotomy-aspirin-dipyridamole arm had a prior history of thrombosis compared with 13% in the other arm. This contention was confirmed by the most recent ECLAP study that showed safety as well as antithrombotic activity of low-dose aspirin in a randomized study.[72]

OBSERVATIONS FROM NONRANDOMIZED STUDIES. In a nonrandomized study by the PV study group, treatment with hydroxyurea was associated with a lower incidence of early thrombosis compared with a historical cohort treated with phlebotomy alone (6.6% vs 14% at 2 years). Similarly, the incidence of AML in patients treated with hydroxyurea, compared with a historical control treated with either chlorambucil or ^{32}P, was significantly lower (5.9% vs. 10.6% vs. 8.3%, respectively, in the first 11 years of treatment).[73] Other studies have confirmed the low incidence of AML in PV patients treated with hydroxyurea (1% to 5.6%).[74–76]

Many studies have reported on the use of pipobroman as a single agent in PV.[77,78] In one of these studies involving 163 patients, the drug was effective in more than 90% of the patients and median survival exceeded 17 years.[77] In the first 10 years, the incidences of thrombotic events, acute leukemia, post-PV myelofibrosis, and other malignancies were 16%, 5%, 4%, and 8%, respectively. Favorable outcome has also been reported in single-arm studies using oral busulfan.[79,80] In 65 busulfan-treated patients with PV followed between 1962 and 1983, overall median survival was 11.1 years and 19 years in patients whose disease was diagnosed before age 60 years.[79] Only 2 patients (3.5%) treated with busulfan alone developed acute leukemia.

Most recently, alfa interferon (α-IFN) was shown to control erythrocytosis in approximately 76% of the patients with PV receiving subcutaneous drug in doses ranging from 4.5 to 27 million units per week (usual dose is 3 million units subcutaneously three times a week).[81,82] A similar degree of benefit is appreciated in terms of reduction in spleen size or relief from intractable pruritus. Furthermore, a variable degree of *JAK2*V617F allele burden reduction was recently associated with α-IFN therapy, but the relevance in overall outcome of the disease is not known.[83] A randomized study is needed to determine if α-IFN is superior to hydroxyurea as a cytoreductive agent in PV, especially in view of its higher cost and toxicity profile. Finally, anagrelide, an oral imidazoquinazoline derivative that inhibits platelet aggregation at higher than therapeutic drug concentrations but displays a species-specific platelet-lowering effect in humans at therapeutic concentrations, controls thrombocytosis in PV.[84] However, the drug is currently not recommended in the treatment of PV, because it was associated with increased incidence of arterial thrombosis and post-ET myelofibrosis, when compared with hydroxyurea, in patients with ET.[85]

In summary, the results from single-arm studies support those of the randomized studies and show that pipobroman and busulfan are valuable treatment agents in PV and might be considered as alternatives to hydroxyurea. Pipobroman is currently not available in the United States. It is currently not clear what additional value is gained by substituting the aforementioned traditional cytoreductive agents by the newer drugs (i.e., α-IFN and anagrelide) especially in view of their unfavorable toxicity and cost profile (Table 106-3).[86]

Thrombohemorrhagic Risk Factors in Polycythemia Vera

The series of studies performed by the PV study group revealed the following: (1) a significantly higher incidence of thrombotic events, in the first 3 years, in patients treated with phlebotomy alone; (2) a lack of correlation between thrombosis and either platelet count or hematocrit value; and (3) a significant association between thrombosis risk and either age above 70 years or a prior history of thrombosis. In addition, in patients treated with phlebotomy alone, thrombosis risk was associated with an increased frequency of phlebotomy (maintenance phlebotomy of more than once every 3 months). Other studies have confirmed the detrimental effect of advanced age (>60 years) and thrombosis history in PV.[17] As such, patients who are 60 years old or older or have a history of thrombosis are considered at high risk (Table 106-4). In contrast, the degree of thrombocytosis has never been correlated with thrombosis risk. However, some patients with extreme thrombocytosis (platelet count at or above 1 million platelets/μL), carry an acquired bleeding diathesis that results from an abnormal adsorption and catabolism of large-molecular-weight von Willebrand factor.[87] The prognostic influence of extreme thrombocytosis, in the absence of acquired von Willebrand disease, is unknown. Equally uncertain is the prognostic relevance of cardiovascular risk factors.

Current Treatment Recommendations

The mainstay of therapy in PV remains phlebotomy for all patients to keep hematocrit at or below 45% in male Caucasians and the appropriate corresponding value for females and other races. However,

Table 106-3 Clinical Properties of Popular Cytoreductive Agents Used in Polycythemia Vera or Essential Thrombocythemia

Drug (class)	Hydroxyurea	Anagrelide	Alfa interferon	Phosphorus-32	Pipobroman
	Myelosuppressive	Platelet-specific	Myelosuppressive	Myelosuppressive	Myelosuppressive
Mechanism of action	Antimetabolite	Unknown	Biologic agent	Radionuclide	Alkylating agent
Pharmacology	Half-life ≅5 hr, renal excretion	Half-life ≅1.5 hr, renal excretion	Kidney is main site of metabolism	Half-life ≅14 days	Insufficient information
Starting dose	500 mg PO BID	0.5 mg PO TID	5 million units SC TIW	2.3 mCi/m^2 IV	1 mg/kg/day PO
Onset of action	≅3–5 days	≅6–10 days	1–3 weeks	4–8 weeks	≅16 days
Frequent side effects	Leukopenia, oral ulcers, anemia, hyperpigmentation, nail discoloration, xerodermia	Headache, palpitations, diarrhea, fluid retention, anemia	Flu-like syndrome, fatigue, anorexia, weight loss, lack of ambition, alopecia	Transient mild cytopenia	Nausea, abdominal pain, diarrhea
Infrequent side effects	Leg ulcers, nausea, diarrhea, alopecia, skin atrophy	Arrhythmias, lightheadedness, nausea	Confusion, depression, autoimmune thyroiditis, myalgia, arthritis	Prolonged pancytopenia in elderly patients	Leukopenia, thrombocytopenia, hemolysis
Rare side effects	Fever, cystitis, platelet oscillations	Cardiomyopathy	Pruritus, hyperlipidemia, transaminasemia	Leukemogenic	

Table 106-4 Risk Stratification in Polycythemia Vera and Essential Thrombocythemia

Low-risk	Age <60 yr *and* No history of thrombosis *and* Platelet count <1 million cells/μL
Low-risk with extreme thrombocytosis	Age <60 yr *and* No history of thrombosis *but* Platelet count ≥1 million cells/μL
High-risk	Age ≥60 yr *or* Positive history of thrombosis

in aspirin-treated patients with PV, it is not certain that a hematocrit level of 45% or below is associated with a significantly lower thrombosis risk compared to a higher hematocrit level up to 54%,[88] although the writer recommends the 45% threshold so as to err on the safe side. Additional drug therapy depends on an individual patient's risk for thrombohemorrhagic complications (see Table 106-4). In general, there is good evidence to advocate the use of cytoreductive agents in high-risk patients (Table 106-5).[66] In this regard, and based on the results of the aforementioned studies, my current choice of chemotherapy is hydroxyurea (starting dose of 500 mg twice daily) or busulfan (starting dose of 4 mg/day) in case of nontolerance to hydroxyurea. Side effects of hydroxyurea that might necessitate the use of an alternative agent include neutropenia and mucocutaneous changes such as ulcers in the mouth and lower extremities. In using busulfan, one should recognize the potential, but infrequent, toxicity to the lungs (pulmonary fibrosis)[89] and the bone marrow (aplasia).[90] Intermittent treatment with drug holidays and withholding treatment for impending cytopenia are recommended.

In the younger but high-risk patient group, some investigators are concerned about drug leukemogenicity associated with long-term treatment with either hydroxyurea or busulfan. However, there is currently not hard evidence to support the particular concern.[76] Regardless, α-IFN (starting dose of 3 million units subcutaneously three times a week) is a reasonable alternative in this instance.[81] α-IFN is also the treatment of choice in women of childbearing age (see Table 106-5) because of the theoretical risk of teratogenicity associated with the use of other cytoreductive agents.[82]

Because ^{32}P-associated leukemia in PV peaks after the first 7 years of treatment, it is reasonable to advocate the use of ^{32}P in elderly patients with issues of treatment compliance and convenience, especially if life expectancy is less than 10 years (intravenous ^{32}P at 2.3 mCi/m^2 to be repeated every 3 months if necessary).[66] The lack of evidence that correlates thrombocytosis with thrombosis in PV argues against the potential therapeutic value of anagrelide in PV.

It is currently unclear whether any specific drug therapy influences clonal evolution in PV. Under current treatment strategies, the incidences of transformation into post-PV myelofibrosis or AML, in the first decade of disease, are estimated at 10% and 5%, respectively.[66] The risk beyond the first decade increases progressively.[91]

Treatment of Non-Life-Threatening Complications in Polycythemia Vera

Additional clinical features of PV include microvascular disturbances, aquagenic pruritus, and constitutional symptoms. Microvascular disturbances in PV and related disorders are felt to represent transient inflammation-based occlusive phenomenon that is a result of interaction between clonal platelets and the endothelium of arterioles. The corresponding clinical manifestations include headache, lightheadedness, transient neurologic or ocular disturbances, tinnitus, atypical chest discomfort, paresthesias, and erythromelalgia. Aspirin produces prompt (within hours) alleviation of symptoms in the majority of patients with PV-associated microvascular disturbances.

Generalized pruritus that is often exacerbated by hot bath is a characteristic feature of PV and occurs in 48% of patients either at diagnosis or at a later stage of the disease.[92] Etiology of PV-associated pruritus remains to be determined and treatment responses to antihistamines have been both unpredictable and variable.[92] Interestingly, a recent study demonstrated a greater than 80% response rate in PV-associated pruritus treated with paroxetine, which is a selective serotonin reuptake inhibitor.[93] Other treatment modalities that have been used in PV-associated pruritus include α-IFN, psoralen photochemotherapy, and cholestyramine.[17]

ESSENTIAL THROMBOCYTHEMIA

Among the classic *BCR-ABL*$^-$ MPDs, ET is the most recently described.[94] Reported incidence figures range from 0.2 to 2.5 per 100,000 population.[8,95–97] With a median age at diagnosis of 60 years, approximately 20% of the patients with ET are diagnosed before age 40 years and in the young age group of patients, the incidence is higher in women than in men.[98,99] There are well-documented cases of ET in children, although some of the reported cases may have represented familial thrombocytosis.[100,101]

Pathogenesis

Trilineage clonal myeloproliferation has been demonstrated in the majority of patients with ET using X chromosome–linked DNA or gene product analysis.[102,103] However, X-linked clonal assays have revealed both polyclonal hematopoiesis in a substantial minority of patients with ET[104] and "monoclonal" hematopoiesis in normal elderly controls.[105] Furthermore, in some cases, the clonal process in

Table 106-5 Treatment Algorithm in Polycythemia Vera

Risk Category	Age <60 Yr	Age ≥60 Yr	Women of Childbearing Age
Low-risk	Phlebotomy + low-dose aspirin	Not applicable	Phlebotomy + low-dose aspirin
Low-risk with extreme thrombocytosis	Phlebotomy + low-dose aspirin*	Not applicable	Phlebotomy + low-dose aspirin*
High-risk	Phlebotomy + hydroxyurea + low-dose aspirin	Phlebotomy + hydroxyurea + low-dose aspirin*	Phlebotomy + alfa interferon*† + low-dose aspirin

*Screening for acquired von Willebrand disease is encouraged before the use of aspirin in patients with extreme thrombocytosis (platelet count ≥1 million cells/μL). Use of aspirin is discouraged if ristocetin co-factor activity is <50%.

†Based on anecdotal evidence of safety.

ET was shown to include lymphocytes[13] or be restricted to megakaryocytes.[103] The clonal basis of ET was recently underlined by *JAK2*V617F mutation analysis that revealed the presence of the mutation even in those patients who feature "polyclonal" hematopoiesis by X-linked clonality studies.[104,106] However, the primary clonogenic event in ET remains undefined despite the recent descriptions of two gain-of-function mutations that occur in 50% (*JAK2*V617F)[107] and 1% (*MPL*W515L/K)[108] of patients with ET, respectively.

Other biologic features in ET include in vitro growth factor independence/hypersensitivity of both erythroid and megakaryocyte progenitor cells,[109,110] low serum Epo level,[111] altered megakaryocyte/platelet Mpl expression,[112,113] increased neutrophil PRV-1 expression,[114,115] and decreased platelet serotonin content.[116] Laboratory studies in ET have demonstrated myeloid growth factor hypersensitivity to interleukin-3 [117] as well as thrombopoietin (Tpo).[110] Growth factor independence of myeloid progenitor cells in ET and related MPDs has now been attributed to mutations involving molecules of the JAK-STAT pathway including the aforementioned *JAK2*V617F and *MPL*W515L/K. In patients with ET,[118] PV,[119] and myelofibrosis,[120] serum Tpo levels are usually normal or elevated despite an increased megakaryocyte mass. This has been attributed to the markedly decreased megakaryocyte/platelet expression of MPL, although the extent of this particular phenotypic abnormality is significantly less in ET as compared with PV or PMF.[112,113,121,122]

In addition to clonal myeloproliferation, ET is also characterized by microvascular symptoms (e.g., headaches and erythromelalgia) as well as an increased risk of both thrombosis and bleeding.[123] Pathogenesis in the former might involve abnormal thromboxane A_2 generation and small vessel–based platelet-endothelial interactions that are inhibited by aspirin therapy.[124,125] On the other hand, there is increasing information that implicates granulocytes but not platelets as the thrombogenic culprit in ET.[85,126–128] Consistent with these observations, a recent study has identified leukocytosis as an independent risk factor for thrombosis in ET.[129] Bleeding diathesis in ET is currently believed to involve an acquired von Willebrand syndrome that becomes apparent in the presence of extreme thrombocytosis.[87] The mechanism of acquired von Willebrand syndrome in ET is currently believed to involve a platelet count-dependent increased proteolysis of high-molecular-weight von Willebrand protein.[87] Other qualitative platelet defects in ET are believed to play a minor role in disease-associated hemorrhage and include defects in epinephrine-, collagen-, and adenosine diphosphate–induced platelet aggregation, decreased adenosine triphosphate secretion, and acquired storage pool deficiency that results from abnormal in vivo platelet activation.[123]

Diagnosis

Although thrombocytosis is the hallmark of ET, more than 85% of cases with thrombocytosis seen in routine clinical practice are reactive (secondary thrombocytosis) and associated with other comorbid conditions (Table 106-6).[130] The degree of thrombocytosis is a poor discriminator of ET from secondary thrombocytosis. However, the clinical scenario is often helpful in distinguishing ET from secondary thrombocytosis. In routine clinical practice it is important to exclude the contribution of either iron deficiency anemia or a hyposplenic state as possible causes of an otherwise unexplained thrombocytosis (Box 106-2). This is accomplished by the measurement of serum ferritin concentration and examination of a peripheral blood smear looking for Howell-Jolly bodies, respectively. The possibility of secondary thrombocytosis associated with an occult inflammatory or malignant process is addressed by the measurement of C-reactive protein or other acute-phase reactants.[131] In other words, an uncomplicated ET should be accompanied by a normal serum ferritin, mostly unremarkable peripheral smear, and a normal serum C-reactive protein. In general, plasma Tpo levels are not helpful in distinguishing secondary thrombocytosis from ET.[118]

Table 106-6 Causes of Thrombocytosis

SECONDARY CAUSES	
Acute	**Chronic**
Postsurgery	Iron deficiency anemia
Bleeding	Surgical or functional asplenia
Hemolysis	Metastatic cancer or lymphoma
Infections	Chronic inflammatory process
Tissue damage	Renal failure, nephrotic syndrome
Chemotherapy rebound effect	
Coronary artery bypass surgery	
PRIMARY CAUSES	
Essential thrombocythemia	
Polycythemia vera	
Primary myelofibrosis	
Chronic myeloid leukemia	
Myelodysplastic syndrome	

Unlike the case with PV, the utility of mutation screening for *JAK2*V617F for the diagnosis of ET is limited by suboptimal negative predictive value and lack of diagnostic specificity within the context of myeloid neoplasms. It should be noted that only half of patients with either ET carry *JAK2*V617F and that the presence of the mutation cannot differentiate ET from another MPD. Therefore, although peripheral blood screening for *JAK2*V617F helps in streamlining further investigation, a bone marrow biopsy is often required to help with the differential diagnosis of primary thrombocytosis. In general, the presence of *JAK2*V617F argues against the possibility of a nonclonal process such as infection or inflammation or a nonmyeloid malignancy such as lymphoma or metastatic cancer.

The typical bone marrow finding in ET consists of a mild to moderate increase in cellularity and the presence of megakaryocyte clusters that are often absent in secondary thrombocytosis (Fig. 106-3). It

Box 106-2. ESSENTIAL THROMBOCYTHEMIA

- At present, ET remains a diagnosis of exclusion. Both secondary thrombocytosis and clonal thrombocytosis associated with other chronic myeloid disorders have to be ruled out before a working diagnosis of ET is made.
- Not all patients with ET need specific therapy.
- Observation alone is a reasonable option in managing asymptomatic patients with ET who are younger than age 60 years and do not have a history of thrombosis.
- Cytoreductive therapy in ET has been shown to benefit "high-risk for thrombosis" patients.
- There is not good evidence to implicate thrombocytosis as a prothrombotic risk factor in "low-risk" patients with essential thrombocythemia.
- Although probably safe to use, the antithrombotic value of low-dose aspirin (81–325 mg/day) in ET is currently unknown.
- There is not good evidence to implicate hydroxyurea as a leukemogenic drug in ET.
- Pregnancy is not a contraindication in ET. Maternal morbidity is very low, although the first-trimester miscarriage rate is significantly higher than that of the general population.
- No specific treatment is recommended for the pregnant, or low- or indeterminate-risk patient with ET.

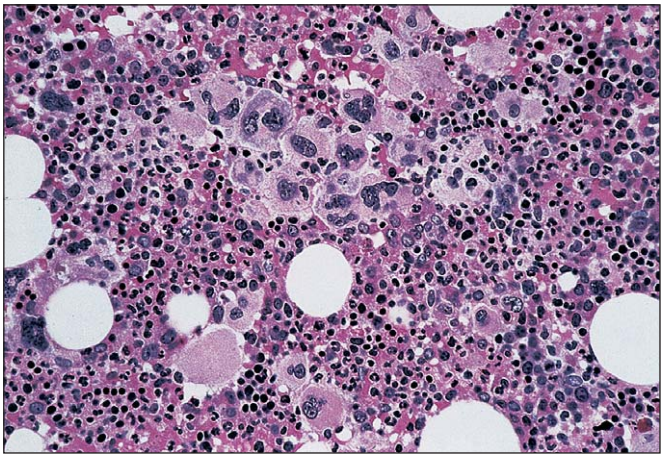


Figure 106-3 • Megakaryocyte hyperplasia and cluster formation in ET.

Table 106-7 Revised World Health Organization Criteria for Essential Thrombocythemia

Diagnosis requires meeting all four criteria.
Sustained platelet count ≥450 $\times 10^9$ platelets/L*
Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis is seen.
Not meeting WHO criteria for polycythemia vera,† primary myelofibrosis,‡ chronic myelogenous leukemia,§myelodysplastic syndrome,‖ or other myeloid neoplasm
Demonstration of *JAK2*V617F or other clonal marker, *or*, in the absence of a clonal marker, no evidence for reactive thrombocytosis¶

*During the workup period.

†Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels and red cell mass measurement is not required.

‡Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow for age accompanied by megakaryocyte morphology that is typical for primary myelofibrosis—small to large with an aberrant nuclear-to-cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.

§Requires the absence of BCR-ABL.

‖Requires absence of dyserythropoiesis and dysgranulopoiesis.

¶Causes of reactive thrombocytosis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders. However, the presence of a condition associated with reactive thrombocytosis does not exclude the possibility of essential thrombocythemia if the first three criteria are met.

Data from Tefferi A, Thiele J, Orazi A, et al: Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytopenia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood 2007;110:1092–1097.

should be remembered that CML and the cellular phase of PMF could both mimic ET in presentation.[132] With respect to CML, a peripheral blood or bone marrow fluorescence in situ hybridization study may be needed, in addition to cytogenetic analysis, so as to exclude the possibility of karyotypically occult CML.[133] Similarly, bone marrow histology should be carefully scrutinized for the presence of intense marrow cellularity with florid atypical megakaryocytic hyperplasia suggesting cellular phase PMF. Cytogenetic abnormalities are rare in ET (<5%) and diagnostically not helpful.[134] Taking all the preceding information into consideration, bone marrow examination remains central to the diagnosis of ET, and its importance is underlined in the newly revised WHO criteria for the diagnosis of ET (Table 106-7).

Treatment

The majority of patients with ET either are asymptomatic or suffer from non-life-threatening microvascular disturbances (headache, visual symptoms, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia) that are effectively treated with low-dose aspirin.[135]

Approximately 20% of patients experience, usually nonfatal, thrombohemorrhagic complications, and only 5% progress into AML or post-ET myelofibrosis during the first decade of the disease.[129,136–139] Therefore, it is reasonable to expect long survival in the majority of patients with ET, especially in the absence of advanced age and leukocytosis.[139] In one study of 605 patients with ET seen at the Mayo Clinic,[139] hemoglobin level below normal (females <12 g/dL; males <13.5 g/dL) was identified as an independent risk factor for both inferior survival and leukemic transformation. Additional independent risk factors for survival included age ≥60 years, leukocyte count ≥15 $\times$ 10^9 cells/L, smoking, diabetes mellitus, and thrombosis. For leukemic transformation, platelet count ≥1000 $\times$ 10^9 platelets/L but not cytoreductive therapy was flagged as an additional independent risk factor. Presence of *JAK2*V617F did not impact either survival or leukemic transformation, and mutational frequency was similar among the different risk groups.

The relatively low incidence figures of thrombosis and hemorrhage as well as the occurrence of both short-term and long-term drug side effects are the basis for carefully selecting the patients with ET who require specific treatment. Risk stratification in ET is similar to that of PV (see Table 106-4). Table 106-8 outlines risk-adjusted treatment guideline in ET that is further elaborated in the following sections.

Antiplatelet Therapy in Essential Thrombocythemia

Unlike the case with higher doses (500 mg or higher per day), low-dose aspirin (81–325 mg/day) may not increase the bleeding diathesis of patients with ET and is currently recommended as a supplement to cytoreductive therapy in high-risk patients as well as an optional consideration in most patients with ET (see Table 106-8).[140] However, it is important to exclude the possibility of clinically significant (ristocetin co-factor activity of <50%) acquired von Willebrand

Table 106-8 Treatment Algorithm in Essential Thrombocythemia

Risk Category	Age <60 Yr	Age ≥60 Yr	Women of Childbearing Age
Low-risk	Low-dose aspirin*	Not applicable	Low-dose aspirin*
Low-risk with extreme thrombocytosis	Low-dose aspirin†	Not applicable	Low-dose aspirin†
High-risk	Hydroxyurea + low-dose aspirin	Hydroxyurea + low-dose aspirin	Alfa interferon‡ + low-dose aspirin

*Not evidence-based.

†One must rule out the presence of clinically-relevant (ristocetin co-factor activity >50%) acquired von Willebrand disease before using aspirin.

‡Based on anecdotal evidence of safety.

disease before using aspirin in those patients with platelet counts above 1 million cells/μL.

Cytoreductive Therapy in Essential Thrombocythemia

The use of cytoreductive therapy to reduce the risk of thrombosis in ET is appropriate and evidence-based as long as it is applied to those patients with an increased risk for thrombosis (see Table 106-4).[128] In this instance it may be necessary to reduce the platelet count to 400,000 cells/μL or lower.[141] A less aggressive platelet control, with a cytoreductive drug, may also be indicated in patients who manifest either aspirin-resistant microvascular disturbances or symptomatic acquired von Willebrand disease.[87,142] In all other instances the decision to use a platelet-lowering agent in ET is not supported by hard data. Specifically, neither the degree of thrombocytosis nor the presence of cardiovascular risk factors has consistently been correlated with an increased thrombotic risk in ET.[135] The frequently cited association of extreme thrombocytosis and increased gastrointestinal bleeding is based on anecdotal observation and may in some instances be attributed to occult acquired von Willebrand disease. A recent retrospective study of young, low-risk ET patients with extreme thrombocytosis revealed no difference in the risk of either thrombosis or bleeding between patients receiving or not receiving cytoreductive therapy.[143]

Table 106-3 summarizes the practical pharmacologic and clinical information regarding currently used platelet count–lowering agents in ET. It is important to note that only hydroxyurea, as a treatment agent, has been shown in a prospective study to be associated with a reduced risk of thrombosis in ET.[128] Hydroxyurea was also found to be superior to anagrelide in a head-to-head comparative study of high-risk patients with ET;[85] patients treated with anagrelide displayed statistically higher incidence of arterial thrombosis and transformation into post-ET myelofibrosis. Finally, the concern regarding hydroxyurea leukemogenicity in ET is currently unsubstantiated,[139] and the indiscriminate use of new drugs that are not tested in a controlled setting is unwarranted.

Pregnancy and Essential Thrombocythemia

First-trimester spontaneous abortion rate in ET (37%) is significantly higher than the 15% rate expected in the control population and does not appear to be influenced by specific treatment.[144] Late obstetric complications as well as maternal thrombohemorrhagic events are relatively infrequent. Neither the platelet count nor treatment with aspirin seems to affect either maternal morbidity or pregnancy outcome. In fact, several studies have shown a spontaneous lowering of platelet counts during pregnancy in ET. Therefore, cytoreductive treatment is currently not recommended for low-risk women with ET that are either pregnant or wish to be pregnant. In contrast, high-risk women require cytoreductive therapy to minimize the risk of recurrent thrombosis and anecdotal evidence of safety has encouraged a preference for the use of IFN-α in case of pregnancy in such patients.[82]

PRIMARY MYELOFIBROSIS

PMF is also known as agnogenic myeloid metaplasia or chronic idiopathic myelofibrosis.[145] The disease was first described in 1879.[146] The clinical course of PMF is characterized by progressive anemia, marked hepatosplenomegaly, cachexia, development of nonhepatosplenic extramedullary hematopoiesis, and evolution into acute leukemia.[147] Similar to the situation in both PV and ET, the disease-initiating genetic lesion in PMF has not been identified, and current diagnosis is based on characteristic, but not specific, clinical and laboratory features that include bone marrow fibrosis and osteosclerosis (Table 106-9).[147]

Among the *BCR-ABL*⁻ classic MPDs, PMF is the least frequent, with an incidence figure that ranges from 0.3 to 1.5 per 100,000 population.[96,97] The median age at diagnosis is 60 years, and approximately 10% of the patients are diagnosed at age 45 years or below.[148]

Table 106-9 Revised World Health Organization Criteria for Primary Myelofibrosis

Diagnosis requires meeting all three major criteria and two minor criteria.

MAJOR CRITERIA

Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin and/or collagen fibrosis, *or*, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e., prefibrotic cellular-phase disease).

Not meeting WHO criteria for polycythemia vera,† chronic myelogenous leukemia,‡ myelodysplastic syndrome,§ or other myeloid neoplasm

Demonstration of *JAK2*V617F or other clonal marker (e.g., *MPL*W515L/K), *or*, in the absence of a clonal marker, no evidence of bone marrow fibrosis due to underlying inflammatory or other neoplastic diseases‖

MINOR CRITERIA

1. Leukoerythroblastosis¶
2. Increase in serum lactate dehydrogenase level¶
3. Anemia¶
4. Palpable splenomegaly¶

*Small to large megakaryocytes with an aberrant nuclear-to-cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.

†Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required.

‡Requires the absence of BCR-ABL.

§Requires absence of dyserythropoiesis and dysgranulopoiesis.

‖Secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies. It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis, and the diagnosis should be considered in such cases if other criteria are met.

¶Degree of abnormality could be borderline or marked.

Data from Tefferi A, Thiele J, Orazi A, et al: Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytopenia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood 2007;110:1092–1097.

Children are not spared of PMF, but their clinical course may be less aggressive.[149]

Pathogenesis

In addition to clonal myeloproliferation, the bone marrow in PMF displays excess collagen fibrosis, new bone formation (osteosclerosis), and angiogenesis. These changes have been associated with alterations in both cellular and extracellular levels of various fibrogenic and angiogenic cytokines including transforming growth factor-β (TGF-β), basic fibroblast growth factor, and platelet-derived growth factor.[150] The demonstration of polyclonal fibroblast proliferation in PMF is the basis for the current assumption that the bone marrow stromal aberration in PMF is reactive[151] and mediated by the aforementioned cytokines derived from the resident clonal megakaryocytes and monocytes (Fig. 106-4).[152]

Current evidence strongly supports the stem cell origin of the clonal myeloproliferation in PMF.[153,154] However, the primary clonogenic mutation(s) has not been identified, although much attention has been given to recently described novel gain-of-function mutations involving the JAK2 tyrosine kinase (*JAK2*V617F) and Tpo receptor (*MPL*W515L/K).[30,155] *JAK2*V617F represents a G-to-T somatic mutation of *JAK2*, at nucleotide 1849, in exon 14, resulting in the substitution of valine to phenylalanine at codon 617.[30]

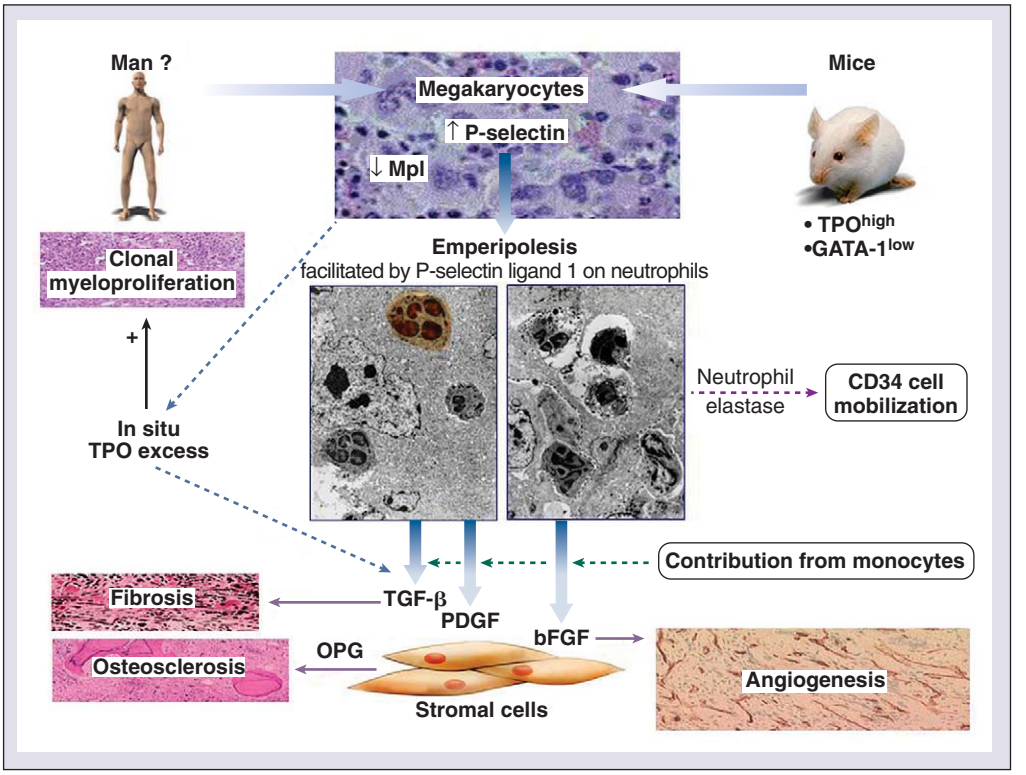


Figure 106-4 • Pathogenesis of reactive stromal changes of the bone marrow in PMF.

*MPL*W515L mutation represents a G-to-T transition at nucleotide 1544 resulting in a tryptophan-to-leucine substitution at codon 515 of the transmembrane region of the MPL receptor.[155]

*JAK2*V617F occurs not only in PMF (~50% mutational frequency) but also in ET with a similar mutational frequency and in PV where it is present in more than 90% of affected patients.[27–30] In contrast, *MPL*W515L/K seems to be specific to PMF or ET, although mutational frequency is substantially lower (~5% and 1%, respectively).[108] As mentioned before, *JAK2*V617F induces constitutive JAK-STAT activation, cytokine hypersensitivity, and/or independence in cell lines, and a PV-like disease in mice.[30,156,157] JAK-STAT is similarly hyperactivated by *MPL*W515L/K, but this mutation induces a PMF-like disease in mice.[155] In any case, about half of the patients with PMF do not display either mutation, and the precise pathogenetic role of these mutations, when they are present, remains to be clarified. Other molecular alterations in PMF include decreased expression of the tumor suppressor retinoic acid receptor-β2 gene as a result of abnormal promoter methylation[158] and reduced megakaryocyte/platelet surface expression of MPL.[122]

An animal model of PMF has been established in mice that are either chronically overexposed to Tpo[159] or carriers of a mutant *GATA-1* gene that results in reduced expression of a transcription factor that plays a role in erythroid and megakaryocyte differentiation.[160] These mice display characteristic features of PMF, including megakaryocytic hyperplasia, bone marrow fibrosis, osteosclerosis, and extramedullary hematopoiesis. The increased megakaryocyte accumulation in these experimental animals has been attributed to either a direct effect of Tpo or the lack of a negative feedback from mature elements as a result of impaired megakaryocyte differentiation, respectively. In both instances it is possible that the abnormal accumulation of megakaryocytes and their sequestered cytokines might be central to the pathogenesis of the associated stromal reaction. In this regard, the development of Tpo-induced bone marrow fibrosis in mice has been temporally associated with elevated TGF-β levels,[161] whereas it was abrogated in TGF-β-knockout experiments.[162] Similar experiments may decipher the individual roles of other cytokines, including basic fibroblast growth factor and platelet-derived growth factor, that have been implicated in PMF.[163] It is currently not clear whether the aforementioned animal models of PMF involve pathogenetic mechanisms that are operating in the human form of the disease.

Diagnosis

The typical presentation of PMF includes anemia (from ineffective erythropoiesis), marked splenomegaly (from extramedullary hematopoiesis), and a myelophthisic peripheral blood smear. Myelophthisis (the presence of nucleated red blood cells, granulocyte precursors, and teardrop-shaped erythrocytes) suggests a bone marrow infiltrative process, and the differential diagnosis includes bone marrow fibrosis, metastatic cancer, granulomatous infection, and lymphoma (Box 106-3). In PMF, peripheral blood myelophthisis is associated with

Box 106-3. MYELOFIBROSIS WITH MYELOID METAPLASIA

- The diagnosis of PMF requires input from an experienced hematopathologist, and extra caution should be taken to exclude the possibility of chronic myeloid leukemia, hairy cell leukemia, myelodysplastic syndrome with myelofibrosis, and acute myelofibrosis.
- Drug therapy in PMF is palliative and may not prolong life.
- The place of hematopoietic stem cell transplantation in the treatment of primary myelofibrosis is currently being defined, and specific decisions require input from disease experts as well as experienced transplant physicians.
- The indications for splenectomy in myelofibrosis include symptomatic portal hypertension, severe mechanical discomfort that is often associated with cachexia, and treatment-refractory anemia with heavy transfusion requirements.
- Low-dose radiation therapy is effective in the treatment of nonhepatosplenic extramedullary hematopoiesis in myelofibrosis.

bone marrow megakaryocytic hyperplasia, collagen fibrosis, osteosclerosis, and intramedullary sinusoidal hematopoiesis (Fig. 106-5). It should be noted, however, that bone marrow fibrosis may accompany not only PMF but also other hematologic and nonhematologic disorders including CML, MDS, systemic mast cell disease, eosinophilic disorders, and hairy cell leukemia (Table 106-10). Therefore, before embarking on treatment recommendations, one has to consult with an experienced hematopathologist to confirm a specific diagnosis. Extra caution should be taken not to misdiagnose CML or hairy cell leukemia as PMF. These issues are addressed and *JAK2*V617F mutation screening incorporated in the newly revised WHO diagnostic criteria for PMF (see Table 106-9).[49]

In "cellular phase" PMF the degree of bone marrow fibrosis may be minimal, but splenomegaly and myelophthisis are often present. Clonal cytogenetic abnormalities occur in approximately 50% of patients with PMF and include 13q-, 20q-, +8, +9, and abnormalities of chromosomes 1, 7, and 12.[164] None of these cytogenetic markers is specific to PMF, and they are also seen in other myeloid as well as lymphoid disorders.

Treatment

Prognostic Factors

Among the *BCR-ABL*$^-$ classic MPDs, PMF has the worst prognosis, with an approximate median survival of 5 years.[165] However, several studies have identified both clinical and laboratory parameters that are used to identify good-risk as well as high-risk patient categories.[147] The most important indicators of adverse prognosis are the presence of anemia (hemoglobin < 10 g/dL), advanced age (>64 years), hypercatabolic symptoms (weight loss, profound fatigue, night sweats, low-grade fever), leukocytosis (>30,000 cells/μL) or leukopenia (<4,000 cells/μL), circulating blasts (≥1%), high-risk cytogenetic

Table 106-10 Causes of Bone Marrow Fibrosis

Hematologic Disorders		
Myeloid Disorders	**Lymphoid Disorders**	**Nonhematologic Disorders**
Primary myelofibrosis	Hairy cell leukemia	Metastatic cancer
Chronic myeloid leukemia	Hodgkin's lymphoma	Autoimmune myelofibrosis
Myelodysplastic syndrome	Non-Hodgkin's lymphoma	Systemic lupus erythematosus
Chronic myelomonocytic leukemia	Multiple myeloma	Kala-Azar (leishmaniasis)
Chronic eosinophilic leukemia		Tuberculosis
Systemic mastocytosis		Paget's disease
Acute megakaryocytic leukemia		HIV infection
Other acute myeloid leukemias		Vitamin D–deficient rickets
Acute lymphocytic leukemia		Renal osteodystrophy
Acute myelofibrosis		Hyperparathyroidism
Malignant histiocytosis		Gray platelet syndrome
		Familial infantile myelofibrosis
		Idiopathic pulmonary hypertension

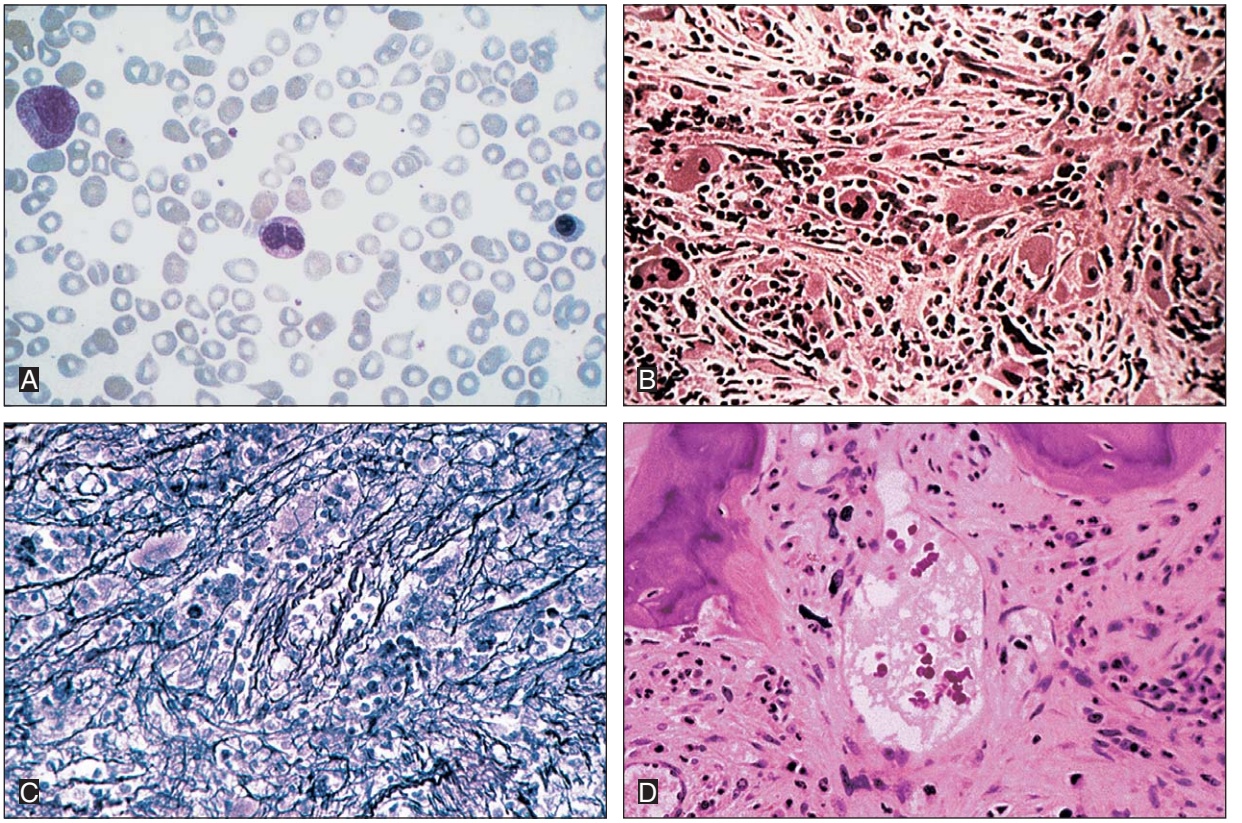


Figure 106-5 • Peripheral blood myelophthisis (**A**), bone marrow fibrosis (**B** and **C**), and osteosclerosis and sinusoidal hematopoiesis (**D**) in PMF. (From Tefferi A: Myelofibrosis with myeloid metaplasia. N Engl J Med 2000; 342:1255. Copyright 2000 Massachusetts Medical Society. All rights reserved.)

Table 106-11 Prognostic Models in Primary Myelofibrosis

Prognostic Scoring System	Risk Category	Score Sum	Median Survival (mo)	Score for Hgb <10 g/dL	Score for WBC <4 or >30 $\times 10^9$ Cells/L	Score for Plt <100 $\times 10^9$ Cells/L	Score for AMC ≥1 $\times 10^9$ Cells/L	Score for Symptoms*	Score for Circulating Blasts ≥1%
Mayo PSS (*N* = 129)	Low	0	173	1	1	1	1	N/A	N/A
	Intermediate	1	61						
(Ages <60 yr; median 52)	High	≥2	26						
Cervantes PSS (*N* = 116)	Low	0 or 1	176	1	N/A	N/A	N/A	1	1
	High	≥2	33						
(Ages ≤55 yr; median 46)									
Dupriez PSS (*N* = 195)	Low	0	93	1	1	N/A	N/A	N/A	N/A
	Intermediate	1	26						
(All ages; median 65 yr)	High	2	13						

AMC, absolute monocyte count; Hgb, hemoglobin; Plt, platelet count. See text for references.

abnormalities (+8, 12p-), peripheral blood monocyte count of >1000 cells/μL, and platelet count of <100,000 cells/μL.[164–169] Table 106-11 outlines the three most popular prognostic scoring systems[148,166,169] that utilize the previously mentioned risk factors to construct different risk groups.[167]

Hematopoietic Stem Cell Transplantation

At present, only allogeneic hematopoietic stem cell transplantation offers a potentially curative treatment modality in myelofibrosis.[170] In a retrospective, multicenter study of 66 consecutive patients, engraftment was not a major obstacle (84% 30-day recovery of neutrophils), although it was delayed in the presence of pretransplant anemia (hemoglobin < 10 g/dL) and osteosclerosis.[171] In contrast, pretransplant splenectomy and higher doses of nucleated cells in the stem cell infusate were associated with faster engraftment. Five-year survival was 62% in patients younger than 45 years of age and 14% in those that were older. Other investigators have reported better survival figures in patients older than age 44 years,[172] and preliminary data suggest that transplant-related morbidity in older patients may be positively influenced by the use of reduced-intensity conditioning regimens.[173,174]

Nevertheless, current information does not allow definitive comments regarding the role of allogeneic hematopoietic stem cell transplantation in myelofibrosis. This author is not currently convinced that the risk of death as well as chronic graft-versus-host disease, associated with allogeneic hematopoietic stem cell transplantation, is justified in the setting of good-risk disease, even though the outcome may be better when allogeneic hematopoietic stem cell transplantation is performed during early-stage disease.[170] In the presence of Mayo PSS high-risk disease (see Table 106-11), it is reasonable to consider the particular procedure: full myeloablative conditioning in patients below 45 years of age and reduced-intensity conditioning in older patients (Table 106-12). The decision in all other instances should be individualized unless there is new information that dictates otherwise.

Conventional Drug Treatment of Anemia

Conventional drug therapy for anemia includes a combination of an androgen preparation (fluoxymesterone [halotestin], 10 mg twice daily), prednisone (0.5 mg/kg/day),[175] exogenous Epo administration (40,000 units weekly subcutaneous injections) in the presence of an endogenous Epo level of less than 100 mU/mL,[176] and danazol

Table 106-12 Current Treatment Algorithm in Primary Myelofibrosis*

Risk Stratification (Mayo Prognostic Scoring System)*	Age <45 Yr	Age 45–60 Yr	Age >60 Yr
Low-risk	Watchful waiting	Watchful waiting	Watchful waiting
	or	*or*	*or*
	Experimental drug therapy†	Experimental drug therapy†	Experimental drug therapy†
Intermediate-risk	Experimental drug therapy	Experimental drug therapy	Experimental drug therapy
	or		
	RIC ASCT		
High-risk	Myeloablative ASCT	RIC ASCT	Experimental drug therapy

ASCT, allogeneic stem cell transplant; RIC, reduced-intensity conditioning.
*See Table 106-11.
†Experimental drug therapy in low-risk patients requires demonstration of safety in view of the excellent prognosis expected in such patients.

(200–800 mg/day).[177] Such therapy is not expected to alleviate splenomegaly and in some instances might result in a further increase in spleen size. Furthermore, cytoreductive treatment to control splenomegaly may be combined with Epo administration in hopes of offsetting drug-induced anemia.

Management of Splenomegaly and Other Extramedullary Hematopoiesis

Hydroxyurea is the drug of choice for controlling splenomegaly, leukocytosis, or thrombocytosis.[178] Other drugs that have been used in a similar setting include busulfan,[179] melphalan,[180] and 2-chlorodeoxyadenosine.[181] In contrast, IFN-α has limited therapeutic value in myelofibrosis.[182] Many patients with myelofibrosis experience recurrent splenic infarcts that may be associated with debilitating left upper quadrant pain that may be preceded by referred left shoulder discomfort. A computed tomography scan may but does not always show a hypodense region without contrast enhancement. Symptoms from splenic infarcts are usually managed by opiate analgesics, and drug-refractory cases may require splenectomy.

Drug-refractory anemia and symptomatic splenomegaly (portal hypertension, severe hypercatabolic symptoms) may necessitate splenectomy that often alleviates splenomegaly-associated symptoms and may also benefit approximately 25% of patients with transfusion-dependent anemia.[183] The surgical procedure is associated with an approximately 9% mortality rate, and as many as 25% of patients may experience accelerated hepatomegaly and extreme thrombocytosis/leucocytosis after splenectomy. In the presence of severe portal hypertension, which is primarily due to intrahepatic obstruction rather than increased portal flow from marked splenomegaly, portal-systemic shunt surgery may be performed concomitantly with splenectomy and has been shown to be a useful therapeutic option.[184]

In patients with mechanical splenic discomfort, splenic irradiation (100–500 cGy in 5–10 fractions) may be considered as an alternative treatment to splenectomy.[82] However, the benefit of splenic irradiation is transient (median response duration is 6 months), and the procedure is associated with more than 10% mortality rate resulting from severe and prolonged cytopenias that occur in as many as 25% of treated patients. The outcome from hepatic irradiation is even worse, and the procedure is generally not recommended.[185]

Radiation therapy is most useful in the treatment of nonhepatosplenic extramedullary hematopoiesis.[186] Symptomatic pulmonary hypertension that is not secondary to a thromboembolic process has been associated with myelofibrosis and is believed to arise from diffuse pulmonary extramedullary hematopoiesis. Diagnosis is confirmed by technetium-99 m sulfur colloid scintigraphy, which shows diffuse pulmonary uptake, and treatment with single-fraction (100 cGy) whole-lung irradiation has been shown to be effective.[187,188] Low-dose irradiation is also effective for the treatment of paraspinal/epidural extramedullary hematopoiesis (1000 cGy in 5–10 fractions), as well as extramedullary hematopoiesis resulting in pleural and peritoneal effusions (100–500 cGy in 5–10 fractions).[186,189]

Investigational Treatment

The demonstration of intense bone marrow angiogenesis in myelofibrosis prompted a series of studies using thalidomide as a therapeutic agent. When used as a single agent and at doses that average about 200 mg/day, thalidomide results in clinically relevant improvement of anemia (20%), splenomegaly (23%), and thrombocytopenia (71%).[190] However, approximately 20% of patients experience substantial thrombocytosis or leukocytosis in addition to the usual side effects of thalidomide. The use of low-dose thalidomide (50 mg/day) in combination with a tapering dose of prednisone (0.5 mg/kg/day) has been associated with a higher rate of response in both anemia (62%) and clinically relevant thrombocytopenia (75%), as well as a better toxicity profile.[191] Interestingly, some of the patients responding to thalidomide-based therapy displayed unmaintained remissions.[191] However, treatment response to thalidomide was not associated with reduced myelofibrosis or bone marrow angiogenesis, and the mechanism of action may involve other effects of thalidomide including immune modulation and tumor necrosis factor antagonism. The latter possibility is supported by another study that demonstrated a favorable response in constitutional symptoms with the use of a soluble tumor necrosis factor receptor, etanercept.[192]

Lenalidomide and pomalidomide are structurally related to thalidomide but belong to a new line of immunomodulatory drugs with a more potent antiangiogenic and anti-inflammatory activity. Among myeloid neoplasms, the most impressive treatment results with lenalidomide have been reported in del(5q)-associated MDS—45% complete cytogenetic response and an even higher rate of hematologic response.[193] In primary or post-PV/ET myelofibrosis, lenalidomide treatment was associated in approximately 20% to 30% response rate in both anemia and splenomegaly.[194] Lenalidomide response rates were higher and quality of responses most impressive in myelofibrosis patients with the del(5q) abnormality.[195] Clinical trials using pomalidomide in myelofibrosis are currently ongoing.

CONCLUSION

Table 106-12 provides a risk-based management strategy in PMF. At present it is reasonable to consider all high-risk patients (using the Mayo PSS)[167] for allogeneic stem cell transplantation if they are transplant-eligible. However, it is not unreasonable to offer such patients experimental drug therapy instead, because the mortality and morbidity associated with allogeneic transplant remains substantial. It is currently acceptable to monitor low-risk patients without specific therapeutic intervention. Management in intermediate-risk patients should be individualized and is often dictated by age and performance status. The presence of del(5q) in intermediate- or high-risk patients with myelofibrosis warrants a therapeutic trial with lenalidomide. Finally, whether or not small-molecule drugs that target JAK2 will be active as well as safe for use in patients with PMF or the related MPDs, remains to be seen.

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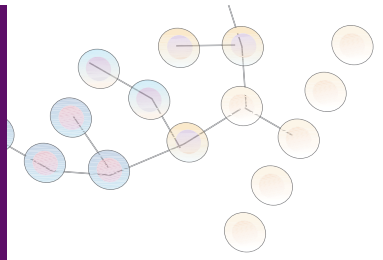
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107 Chronic Myeloid Leukemia

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SUMMARY OF KEY POINTS

Incidence
- About 5000 cases per year in the United States; 15% of all leukemias
- Median age 55 to 60 years at diagnosis

Clinical Findings
- Common findings: fatigue, anemia, abdominal discomfort, splenomegaly, leukocytosis
- 30% to 50% of patients asymptomatic at diagnosis
- White blood cell count usually greater than 50×10^9 cells/L, with a left-shifted differential, basophilia, thrombocytosis

Differential Diagnosis
- Chronic myelomonocytic leukemia
- Other myeloproliferative disorders
- Leukemoid reactions

Evaluation
- History and physical examination, complete blood count with differential and platelet count, and chemistries
- Bone marrow aspiration and biopsy
- Testing for the presence of the Philadelphia (Ph) chromosome by cytogenetic analysis or for the presence of the *BCR-ABL* fusion gene by fluorescence in situ hybridization (FISH) or by reverse-transcription polymerase chain reaction

Therapy
- Hydroxyurea or imatinib mesylate initially to control leukocytosis and thrombocytosis
- Imatinib induces a complete hematologic and cytogenetic response in most patients; estimated 5-year survival rate 89%
- New tyrosine kinase inhibitors (dasatinib, nilotinib, bosutinib) active after imatinib failure
- Allogeneic stem cell transplantation may be curative but is associated with considerable morbidity and mortality

INTRODUCTION

Chronic myeloid (or myelogenous) leukemia (CML) is a clonal hematopoietic stem cell disorder. It is characterized by overproduction of myeloid cells, a result of excessive proliferation and reduced apoptosis. Clinical findings include fatigue, splenomegaly, leukocytosis, and anemia. Basophilia and thrombocytosis are common.[1–3] CML is defined by the presence of a characteristic cytogenetic abnormality, the Philadelphia (Ph) chromosome, a reciprocal balanced translocation between the long arms of chromosome 9 and 22, t(9;22)(q34;q11.2). This results in the *BCR-ABL*–associated molecular events, which are causally related to the disease pathophysiology.[4–6]

The typical course of CML is biphasic or triphasic. Most patients are diagnosed in the indolent or chronic phase. If not treated appropriately, CML progresses into the accelerated and blastic phases, which are ominously fatal. Before the discovery of imatinib mesylate, a selective Bcr-Abl tyrosine kinase inhibitor (TKI), the median survival of patients with chronic-phase CML was 3 to 4 years with hydroxyurea, and 6 to 7 years with interferon-α (IFN-α). Imatinib has resulted in a dramatic change in the prognosis of CML and is associated with an estimated 5-year survival rate of 89%. Allogeneic stem cell transplantation is curative in CML but is associated with significant mortality and with serious morbidities. As the long-term results with imatinib continue to mature positively, allogeneic stem cell transplantation, previously a frontline therapy among eligible patients, is now considered as a second-line strategy in CML after failure of TKI therapy.

INCIDENCE, EPIDEMIOLOGY, AND ETIOLOGY

CML accounts for 15% of cases of leukemia in the United States. There is a slight male preponderance (male-to-female ratio 1.6:1). Its annual incidence is about 1.5 cases per 100,000 individuals. About 5000 cases of CML are diagnosed annually. This incidence has not changed over in the past few decades, and it increases with age. The median age at diagnosis is 55 to 60 years; it is uncommon in children and adolescents; only 2.7% of CML cases are younger than 20 years.

Before imatinib therapy, the prevalence of CML was about 25,000 cases in the United States. Now that the annual mortality following imatinib therapy has been reduced to 2%, the prevalence of CML will continue to rise, reaching a plateau (in the next 20 years) at about 250,000 cases (when the annual incidence will equal the annual mortality). This will change CML from an uncommon disorder to a prevalent one.

There are no known familial associations in CML. Its risk is not increased in monozygotic twins or in relatives of patients with CML. There are no known common etiologic agents incriminated in CML. Ionizing radiation (exposure to nuclear bombs or accidents; radiation treatment of ankylosing spondylitis and cervical cancer) has increased the risk of CML. Its peak incidence is 5 to 10 years after exposure and is dose-related. The risk of CML is not increased in individuals working in the nuclear industry. Radiologists working without adequate protection (before 1940) had an increased risk of developing

chronic myeloid leukemia, but no such risk has been found in recent studies. Benzene exposure increases the risk of acute myelogenous leukemia but not of CML. CML is not a frequent secondary leukemia following treatment of other cancers with radiation and/or alkylating agents.[7–10]

PATHOGENESIS

Molecular Pathogenesis

The Ph chromosome abnormality is present in more than 90% of patients with typical CML (Fig. 107-1). It results from a balanced reciprocal translocation of genetic material between the long arms of chromosomes 9 and 22, t(9;22)(q34;q11.2). It is found in hematopoietic cells but not in other human cells. Its origin is close to the pluripotent stem cell, and it is present in erythroid, myeloid, monocytic, and megakaryocytic cells, less commonly in B lymphocytes, rarely in T lymphocytes, but not in marrow fibroblasts. The breakpoint of chromosome 9 results in translocation of the cellular oncogene *ABL1* to a region on chromosome 22 coding for the major breakpoint cluster region (*BCR*). *ABL1* is a homologue of *V-ABL*, the Abelson virus that causes leukemia in mice. This juxtaposes a 5′ portion of *BCR* to a 3′ position of *ABL1*, and produces a new hybrid oncogene, *BCR-ABL*. This codes for a novel Bcr-Abl oncoprotein of molecular weight 210 kDa ($p210^{BCR-ABL}$). The $p210^{BCR-ABL}$ oncoprotein results in uncontrolled kinase activity, which causes excessive proliferation and reduced apoptosis of CML cells,[11–13] leads to a growth advantage of CML cells over normal cells, and suppresses normal hematopoiesis. The normal stem cells, although suppressed, persist and re-emerge after effective therapy of CML.

In Ph-positive acute lymphocytic leukemia, the breakpoint in *BCR* often occurs in a more centromeric region called minor *BCR* region (mBCR). This produces a smaller *BCR* gene opposing *ABL1*, and therefore a fusion gene, messenger RNA, and Bcr-Abl oncoprotein ($p190^{BCR-ABL}$) of smaller sizes. A third rare breakpoint distal to the major *BCR* region, called μ-BCR, produces a $p230^{BCR-ABL}$ hybrid oncoprotein associated with a very indolent course of CML (see Fig. 107-1).[14]

The constitutive activation of *BCR-ABL* results in autophosphorylation and activation of downstream pathways that alter gene transcription, apoptosis, cytoskeletal organization, cytoadhesions, and degradation of inhibitory proteins. These signal transduction pathways involve RAS, mitogen-activated protein (MAP) kinases, signal transducers and activators of transcription (STAT), phosphatidylinositol 3-kinase (PI3K), MYC, and others. Many of these interactions are mediated through tyrosine phosphorylation and require binding of the *BCR-ABL* to adapter proteins such as GRB-2, CRK, CRK-like protein (CRKL) and SCR-homology containing proteins (SHC). Understanding the pathophysiology of these events could result in a successful development of targeted therapies that may synergize with imatinib to improve further the prognosis in CML.

What causes the *BCR-ABL* molecular rearrangement is unknown. Molecular techniques that amplify detection of *BCR-ABL* to 1 in 10^8 detect it in marrow cells of 25% to 30% of normal adults, in 5% of infants, but not in cord blood.[15] Because CML develops in only 1.5 of 100,000 individuals (i.e., 1 to 2 per 25,000 to 30,000 individuals who express *BCR-ABL* in their bone marrow), additional molecular events or lack of immune recognition of the clonal cells may contribute to the development of CML.

The fusion *BCR-ABL* gene and the p210 protein can be found in some patients with typical morphologic CML, in whom the t(9;22)(q34;q11.2) is not identified. These patients have a response to therapy and a survival similar to Ph^+ cases. Patients with Ph^- and $BCR\text{-}ABL^-$ CML (discussed later) constitute a different entity (atypical CML) and have a worse prognosis.[16,17] The molecular pathophysiology of CML transformation is poorly understood. Several molecular events have been associated with CML transformation, including point mutations or deletions in the p53 tumor suppression

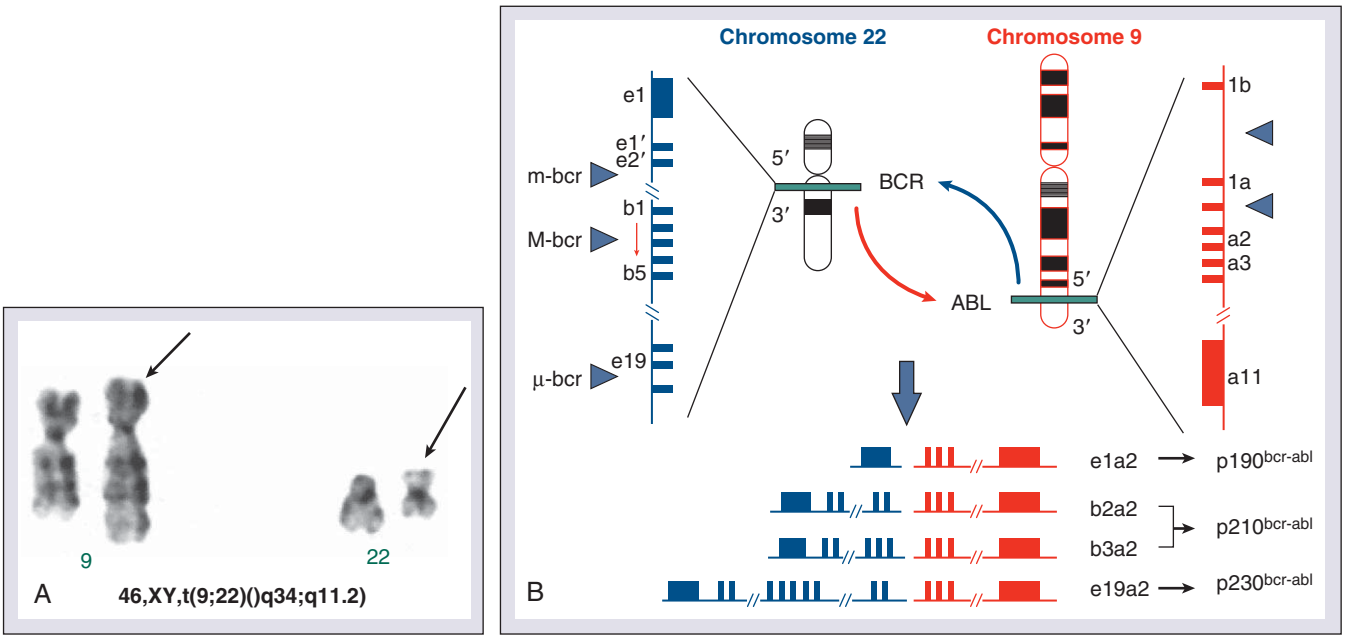


Figure 107-1 • The Philadelphia (Ph) chromosome, initially described as a minute chromosome, was later identified as a balanced reciprocal translocation between the long arms of chromosomes 9 and 22, t(9;22) (q34;q11.2). This results in the translocation of the *ABL1* gene from chromosome 9 in proximity to the breakpoint cluster region (*BCR*) on chromosome 22. Depending on the breakpoint site on chromosome 22, three resultant Bcr-Abl oncoproteins are generated: (1) $P210^{BCR-ABL}$, which occurs in the large majority of patients with Ph^+ CML; (2) $P190^{BCR-ABL}$, present in two thirds of patients with Ph^+ acute lymphocytic leukemia (the other one third have the $P210^{BCR-ABL}$ product); and (3) $P230^{BCR-ABL}$, which is found rarely (1% to 2%) in patients with an indolent course of Ph^+ CML. The three breakpoints on chromosome 22, M-Bcr (P210), m-bcr (P190), μ-bcr (P230), which correspond to the three resultant Bcr-Abl oncoproteins are shown.

gene, p35, c-*Myc* amplification, deletions in the p16 tumor suppressor gene, alteration of retinoblastoma (*Rb*) gene, and others. However the causal relation of these events to transformation is not clear.

Animal Models of Chronic Myeloid Leukemia

Experimental models have established a causal relationship between the *BCR-ABL* molecular events and the development of CML. Transgenic mice that express *BCR-ABL* developed acute leukemia. A *BCR-ABL*–expressing retrovirus used to infect murine bone marrow cells that later repopulate irradiated mice, resulted in myeloproliferative disorders, including a CML-like syndrome.[18–20] *BCR-ABL*, under the control of a tetracycline-repressible promoter, expressed in mice, resulted in a lymphoid leukemia that reversed in the presence of tetracycline,[21] attesting to the leukemic potential of *BCR-ABL* as a sole oncogenic abnormality. The recapitulation of CML-like disorders in animal models mediated by the *BCR-ABL* molecular events established them as a root cause for CML and a legitimate molecular target for therapeutic interventions with TKIs.

DISEASE MANIFESTATIONS

Chronic Phase

About 30% to 50% of patients with CML diagnosed in the United States are asymptomatic. The disease is found on routine physical examination or blood tests.

Common signs and symptoms of CML, when present, result from anemia and splenomegaly. These include fatigue, weight loss, malaise, easy satiety, and left upper quadrant fullness or pain (Table 107-1). Rare manifestations include bleeding (associated with a low platelet count and/or platelet dysfunction), thrombosis (associated with thrombocytosis and/or marked leukocytosis), gouty arthritis (from elevated uric acid levels), priapism (usually with marked leukocytosis or thrombocytosis), retinal hemorrhages, and upper gastrointestinal ulceration and bleeding (from elevated histamine levels due to basophilia). Leukostatic symptoms (dyspnea, drowsiness, loss of coordination, confusion) due to sludging in the pulmonary or cerebral vessels, are uncommon in chronic phase despite white blood cell (WBC) counts exceeding 100×10^9 cells/L.

Splenomegaly is the most consistent physical sign in CML and is detected in 50% to 60% of cases. Hepatomegaly is less common (10% to 20%). Lymphadenopathy, infiltration of skin or other tissues, is uncommon. When present, these findings may suggest accelerated or blastic phases of CML, or Ph^- CML. Headaches, bone pain, arthralgias, pain from splenic infarction, and fever are more frequent with CML transformation.

Laboratory features of untreated CML include leukocytosis with predominance of neutrophils, and a left shift extending to blast cells. Basophils and eosinophils are increased. Thrombocytosis is common; thrombocytopenia is rare and, if present, suggests a worse prognosis. Anemia (hemoglobin < 11 g/dL) is present in one third of patients. Biochemical abnormalities include a low leukocyte alkaline phosphatase score, which also occurs in some patients with agnogenic myeloid metaplasia. Serum levels of vitamin B_{12}, lactate dehydrogenase, uric acid, and lysozyme are often increased. Some patients demonstrate a cyclic oscillation of the WBC count.

The bone marrow is hypercellular with marked myeloid hyperplasia. The myeloid-to-erythroid ratio is usually 15 : 1 to 20 : 1. About 15% of patients have 5% or more blast cells in the peripheral blood or bone marrow at diagnosis. Increased reticulin fibrosis is common (30% to 40% grade 3–4 reticulin fibrosis by silver staining), but collagen fibrosis is rare at presentation.[22] Interestingly, whereas the "spent phase" of myelofibrotic CML was commonly reported in the past (with busulfan therapy) as an end-stage CML event, it has become uncommon in the eras of IFN-α and imatinib therapies. Imatinib effectively reduces myelofibrosis in CML.[23,24]

Table 107-1 Features of Patients with Newly Diagnosed Ph^+ Chronic Myelogenous Leukemia Referred to M.D. Anderson Cancer Center*

Parameter	Percentage
Age ≥60 years (median)	18 (55)
Female gender	41
Splenomegaly	37
Hepatomegaly	10
Lymphadenophathy	6
Other extramedullary disease	7
Hemoglobin <10 g/dL	13
Platelets	
$>450 \times 10^9$ cells/L	34
$<100 \times 10^9$ cells/L	4
WBC $\geq 50 \times 10^9$ cells/L	45
Marrow	
≥5% blasts	7
≥5% basophils	14
Peripheral blood	
≥3% blasts	13
≥7% basophils	14
Cytogenetic clonal evolution other than the Ph chromosome	7
Sokal risk	
Low	61
Intermediate	27
High	12

*From 1970 to present ($N = 2172$)

Accelerated and Blastic Phases

The definitions of accelerated and blastic phases of CML are shown in Table 107-2. In most patients the transformation from chronic to advanced phase is insidious, the disease becoming more difficult to control. This is referred to as the *accelerated phase*. The criteria of accelerated phase are variable. In one study, features that correlated with a median survival of 18 months or less were blast percentage equal or greater than 15%, blasts plus promyelocytes equal or greater than 30%, basophils equal or greater than 20%, and a platelet count less than 100×10^9 cells/L unrelated to therapy, and cytogenetic clonal evolution.[25] Features of accelerated-phase CML should be revisited, because some (e.g., clonal evolution more favorable, blasts >10% less favorable) have different prognostic implications from recent studies (Fig. 107-2).[26] About 5% to 10% of patients present in the accelerated phase. The accelerated phase is also associated with worsening anemia and splenomegaly, organ infiltration (liver, lymph nodes, skin, bones, or other tissues), and constitutional symptoms (aches, fever, malaise, weight loss).

Blastic-phase CML is diagnosed by the presence of 30% or more blasts in the bone marrow and/or peripheral blood, or by the presence of extramedullary blastic disease. The blastic-phase CML resembles acute leukemia. Patients may develop fever, bone aches, bleeding, infections, weight loss, and increasing splenomegaly. Approximately 70% of patients develop a myeloid or undifferentiated blastic phase and 30% a B-cell lymphoid blastic phase.[27]

Table 107-2 Definitions of the Accelerated and Blastic Phases of Chronic Myelogenous Leukemia

Criteria	M.D. Anderson Cancer Center	International Bone Marrow Transplant Registry	World Health Organization
ACCELERATED PHASE			
Percent blasts	15–29	10–29	10–19
Percent blasts + promyelocytes	≥30	≥20	NA
Percent basophils	≥20	≥20% (basophils + eosinophils)	≥20
Platelets ($\times 10^9$/L)	<100	Unresponsive ↑, persistent ↓	<100 or >1000 unresponsive
Cytogenetics	CE	CE	CE not at diagnosis
WBC	NA	Difficult to control, or doubling in <5 days	NA
Anemia	NA	Unresponsive	NA
Splenomegaly	NA	Increasing	NA
Other		Chloromas, myelofibrosis	Megakaryocyte proliferation, fibrosis
BLASTIC PHASE			
30% or more blasts; or extramedullary blastic disease, except for the WHO classification, which requires 20% or more.			

CE, clonal evolution; NA, not applicable; WBC, white blood cells.

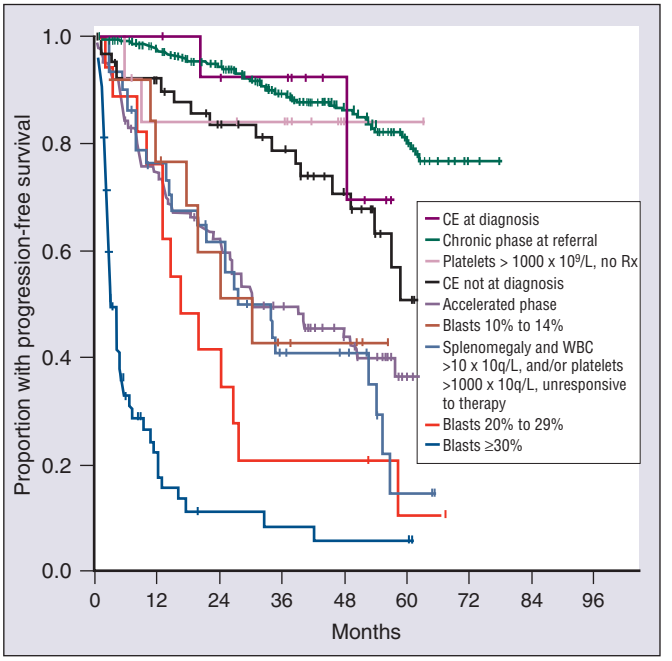


Figure 107-2 • Progression-free survival in CML by different characteristics, highlighting that clonal evolution (CE) at diagnosis is not associated with adverse prognosis. CE during the course of CML has a slight adverse prognostic impact but cannot be considered an accelerated-phase feature, because the associated estimated 4-year progression-free survival rate is 68%, similar to that of chronic phase. Similarly thrombocytosis (>1000 × 10^9 cells/L) is associated with an estimated 4-year progression-free survival rate of 84%. The estimated 4-year progression-free survival rate in accelerated phase (classical standard criteria) is 45%. The figure also highlights that whereas a blast percentage of 20% to 29% is associated with an adverse accelerated phase–like prognosis, it cannot be considered a blastic phase feature (as proposed by the World Health Organization), because it seems to be closer in outcome to accelerated than to blastic phase. Patients who present with 10% to 14% blasts have an adverse prognosis similar to accelerated phase. Therefore, the proposed new criteria of accelerated phase may exclude clonal evolution, but include patients with blast percentages above 10%.

Most patients evolve into the accelerated phase before blastic phase, but 20% of patients transit into a blastic phase without warning. Most patients in accelerated or blastic phase have additional chromosomal abnormalities, such as a double Ph, trisomy 8, or isochromosome 17. Extramedullary blastic phase of CML can occur in the lymph nodes, skin, meninges (especially in lymphoid blastic phase), bone, and other sites.

DIAGNOSIS

The diagnosis of typical CML is simple and consists of documenting, in the setting of persistent unexplained leukocytosis (or occasionally thrombocytosis), the presence of the Ph chromosome t(9;22)(q34;q11.2), by routine cytogenetics, or the corresponding *BCR-ABL* rearrangement by FISH analysis or by molecular studies.

A FISH analysis relies on the colocalization of large genomic probes specific to the *BCR* and *ABL1* genes. Comparison of simultaneous marrow and blood samples by FISH analysis shows high concordance. FISH studies may have a false-positive range of 1% to 10% depending on the probes used.

Reverse transcriptase–polymerase chain reaction (RT-PCR) amplifies the region around the junction between *BCR* and *ABL1*. It is highly sensitive for the detection of minimal residual disease. PCR testing can either be qualitative, providing information about the presence of the *BCR-ABL* transcript, or quantitative, assessing the amount of *BCR-ABL* transcripts. Qualitative PCR may be useful for diagnosis of CML; quantitative PCR is ideal for monitoring residual disease and is usually performed by real-time PCR. Simultaneous peripheral blood and marrow PCR studies show a high level of concordance. False-positive and false-negative results can happen with PCR. False-negative results may be from poor-quality RNA or failure of the reaction; false-positive results can be due to contamination. A 0.5- to 1-log coefficient of variability in some samples can occur depending on testing procedures, sample handling, and laboratory experience.[28,29]

The Ph chromosome is usually present in 100% of metaphases, often as the sole abnormality. Between 10% and 15% of patients have additional chromosomal changes (clonal evolution) involving trisomy 8, isochromosome 17, additional loss of material from the second chromosome 22 (double Ph), or others.

Eighty-five percent of patients have a typical t(9;22) translocation; 5% have variant translocations which can be simple (involving chromosome 22 and a chromosome other than chromosome 9), or complex (involving one or more chromosomes in addition to chromosomes 9 and 22). With imatinib, patients with Ph variants have response to therapy and prognosis similar to Ph^+ CML.

Diagnostic and Monitoring Procedures in Chronic Myeloid Leukemia

The improved rates of complete cytogenetic response and of molecular response with imatinib now require new techniques that measure these responses more accurately (rather than relying on evaluation of only 20 metaphases by routine cytogenetic studies), with less painful procedures (peripheral blood rather than marrow samples), and with methods that measure minimal disease below the level of detection by routine karyotypic analysis (molecular studies). FISH studies can assess rapidly disease status in 200 cells, and can be performed on blood specimens. Quantitative PCR studies usually measure the ratio of the abnormal message, *BCR-ABL*, to a normal message (e.g., *ABL*). A *BCR-ABL*/*ABL* ratio of less than 0.1% (approximately a 3-log reduction of disease from a standardized baseline) has been associated with a low risk of relapse and with favorable progression-free survival. A negative PCR analysis (undetectable *BCR-ABL* transcripts; usually a 4.5-log reduction or more) may be technique-dependent and is referred to as complete molecular response.

Monitoring response to imatinib-based therapy may use different approaches depending on the investigators' experience, patient age, whether changes of residual disease affect subsequent therapy, availability of methodologies, and other factors. In general, patients with newly diagnosed CML require an initial bone marrow analysis (to evaluate the percentage of blasts and basophils, and whether clonal evolution is present), then once a year (to detect cytogenetic abnormalities in both the Ph^+ and Ph^- cell). Some experts recommend bone marrow studies every 3 to 6 months in the first year because of the prognostic significance of the Ph^+ status from routine marrow cytogenetic studies. Practically, peripheral blood FISH studies every 3 to 4 months provide a reasonable estimate of the response profile in the first year. Once Ph^+ cells are less than 5% by FISH, the complete cytogenetic response can be confirmed by a bone marrow analysis with routine cytogenetics, and subsequent monitoring of minimal residual disease performed by peripheral blood real-time PCR studies. In a patient in stable complete cytogenetic response, real-time PCR studies may be performed every 6 months. If concerns arise regarding changes in PCR values, the study can be repeated more frequently (e.g., every 2 to 3 months). Some investigators suggest a two-fold or 0.5-log increase in transcript levels may correlate with the development of mutations or with relapse.[30–32] However, these analyses stem from individual laboratories with significant expertise and may not apply to routine practice. In general, in a patient in complete cytogenetic response, a rise of transcript levels by real-time PCR should be repeatedly confirmed before a change of therapy is considered, which may be minor (e.g., increasing the dose of imatinib), rather than drastic (e.g., allogeneic stem cell transplant).

Monitoring for mutations in the Bcr-Abl kinase domain (Abl mutations) that are associated with resistance is also an evolving concept. Assessing mutation status before therapy or in responding patients has no prognostic or therapeutic value. Mutation studies are important in patients who exhibit cytogenetic-hematologic relapse or resistance. In them, detection of a threonine-to-isoleucine mutation at codon 315 (T315I) will indicate a change of therapy to non-TKIs (e.g., allogeneic stem cell transplant, specific T315I inhibitors, combinations of chemotherapy). Particular mutations may favor the use of one TKI over others, based on preclinical studies and early clinical experience. For example, V299L and F317L mutations are less responsive to dasatinib, whereas some P-loop mutations may be less sensitive to nilotinib. Otherwise, mutation analysis at present has minimal impact on current practice in CML.[31,32]

DIFFERENTIAL DIAGNOSIS

CML can be confused with leukemoid reactions. These are usually transient, have a temporal cause (severe infection, steroids, stress), show modest rises of WBC counts up to 50×10^9 cells/L with toxic granulocytic vacuolation and Döhle bodies in the granulocytes, and a normal or increased leukocyte alkaline phosphatase level. Corticosteroids can rarely cause self-limiting extreme neutrophilia with a left shift.

CML should be differentiated from other myeloproliferative disorders or myelodysplastic syndromes like chronic myelomonocytic leukemia, proliferative myelodysplastic syndrome, agnogenic myeloid metaplasia, polycythemia rubra vera, and essential thrombocytosis. Although the clinical syndromes may overlap, cytogenetic and molecular studies demonstrating the presence of Ph or the *BCR-ABL* rearrangement clarify the diagnosis.

A difficult diagnostic situation may arise in patients with a typical morphologic picture of CML (splenomegaly, leukocytosis) but who do not have the Ph chromosome. In some, the *BCR-ABL* hybrid gene can be demonstrated by molecular studies. Patients who are Ph^- and *BCR-ABL*$^-$ often have chronic myelomonocytic leukemia. Patients may rarely have myeloid hyperplasia, with selective involvement of the neutrophil, eosinophil, or basophilic cell lineages. These are described as having chronic neutrophilic, eosinophilic, or basophilic leukemia and do not have evidence of the Ph chromosome or *BCR-ABL* fusion gene. Occasionally, patients with Ph^+ CML may present like essential thrombocytosis (marked thrombocytosis without leukocytosis). Cytogenetic studies are required in all patients with essential thrombocytosis to identify the occasional patient with Ph^+ CML and essential thrombocytosis-like presentation.

PROGNOSIS

Prognosis in CML has changed drastically over the past 5 to 10 years. Before imatinib, the median survival of patients with CML in chronic phase (85% to 90% of newly diagnosed patients) was 6 to 7 years with IFN with or without cytarabine. For candidates for allogeneic stem cell transplantation, the expected 20-year survival rate was 40% to 50% in younger patients with a matched related donor. With imatinib therapy the estimated 5-year survival rate in chronic phase is 89%.[33] With an annual mortality of 1% to 2% in the first 5 years (if this positive trend is maintained in later years), the estimated median survival may exceed 25 years (Fig. 107-3).[33–35] Thus, chronic-phase CML may have now changed to an indolent disorder in which most patients may survive normally with continued oral imatinib therapy. Imatinib therapy has also changed the prognosis in accelerated phase. The median survival has increased from 1 to 2 years before imatinib to an estimated 4-year survival rate of 60%.[36] Among patients with accelerated-phase CML who have an early cytogenetic response to imatinib, the estimated 4-year survival rate is 80%. Similarly, patients with clonal evolution as the only sign of accelerated disease have an estimated 5-year survival rate of 80%.[37] Survival in blastic phase is also better with imatinib therapy, but only modestly so (median survival improved from 3–6 months to 12–15 months). Prognosis of lymphoid blastic phase is slightly more favorable, with a response rate to anti–acute lymphoid leukemia chemotherapy and imatinib of 60%, and a median survival of 12 to 18 months.

Before imatinib, several prognostic models (Sokal, Hasford) divided patients in chronic phase into low-, intermediate-, and high-risk groups based on pretreatment adverse prognostic factors including: older age, splenomegaly, thrombocytosis, higher percentage of blasts and basophils, and presence of cytogenetic clonal evolution.[38,39] Imatinib therapy has now altered the prognostic significance of

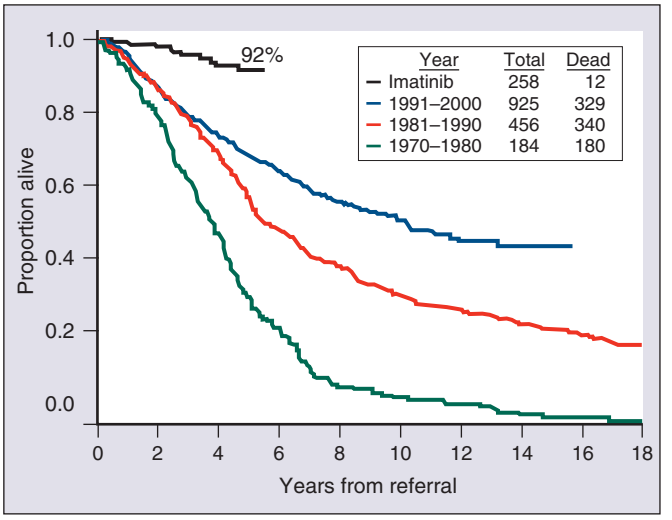


Figure 107-3 • Survival of all patients with newly diagnosed Ph+ CML in chronic phase referred to M.D. Anderson Cancer Center since 1970 (N = 1823). The estimated 6-year survival rate with recent imatinib therapy is 92%. Patients treated between 1970 and 1980 received mostly hydroxyurea-based therapy; their median survival was about 4 years. Patients treated between 1981 and 2000 received mostly interferon (IFN)-based therapy The median survival of patients treated with IFN-based therapy from 1981 to 1990 is about 6.5 years; it is about 10 years for patients treated between 1991 and 2000 because of the added benefit of sequential therapy with imatinib late in their course.

several of these factors, including deletion of derivative chromosome 9, age, and myelofibrosis.[23,24,40,41] The latter in fact resolves quite effectively with imatinib therapy.[23] Currently, the most relevant prognostic factor on imatinib therapy is the degree of cytogenetic and molecular response to initial imatinib therapy (in the first 3 to 12 months).[33,42,43] Thus, the introduction of imatinib therapy in CML will require new definitions of the accelerated phase and the adverse factors/risk models in CML.

MANAGEMENT OF CHRONIC MYELOGENOUS LEUKEMIA IN CHRONIC PHASE

In the 1980s to 1990s, the two frontline therapies in CML were IFN-α–based regimens and allogeneic stem cell transplantation. There was ongoing controversy about the best approach in newly diagnosed patients who were candidates for allogeneic stem cell transplantation. In general, allogeneic stem cell transplantation was recommended for younger patients with matched related donors, whereas older patients and those with unrelated donors (i.e., higher risk for stem cell transplantation–related mortality) were offered a trial of IFN-based therapies before considering allogeneic stem cell transplantation.[44] The maturing positive results with imatinib therapy have now convinced most investigators and patients to use imatinib as initial therapy, and to delay allogeneic stem cell transplantation to a second-line strategy after failure of imatinib and/or other TKIs.

Imatinib

The role of imatinib therapy in CML was established in a series of pivotal trials of imatinib following IFN-α failure in chronic, accelerated, and blastic phases, and later in a frontline International Randomized Study of Interferon plus cytarabine versus STI571 (IRIS trial).[33,42,45–53]

Imatinib mesylate, a 2-phenylaminopyrimidine derivative, binds to the canonical adenosine triphosphate (ATP)-binding site of the ABL kinase domain. It blocks phosphorylation of tyrosine residues on substrate protein. Blocking ATP binding inactivates the ABL kinase, because it cannot transfer phosphate to its substrate. Inhibiting phosphorylation prevents activation of signal transduction pathways that cause CML (Fig. 107-4). Imatinib inhibits several tyrosine kinases including $p210^{BCR-ABL}$, $p190^{BCR-ABL}$, v-ABL, c-ABL, c-Kit, and platelet-derived growth factor receptor (PDGF-R).

In the IRIS study 1106 patients with newly diagnosed CML were randomized to imatinib 400 mg orally daily versus IFN-α plus cytarabine. Imatinib was associated with significantly higher rates of major (Ph positivity <35%; 85% vs. 22%) and complete cytogenetic responses (74% vs. 8%), and lower rates of progression (3% vs. 20%) and transformation (1.5% vs. 7%) after 12 months of therapy.[42] An

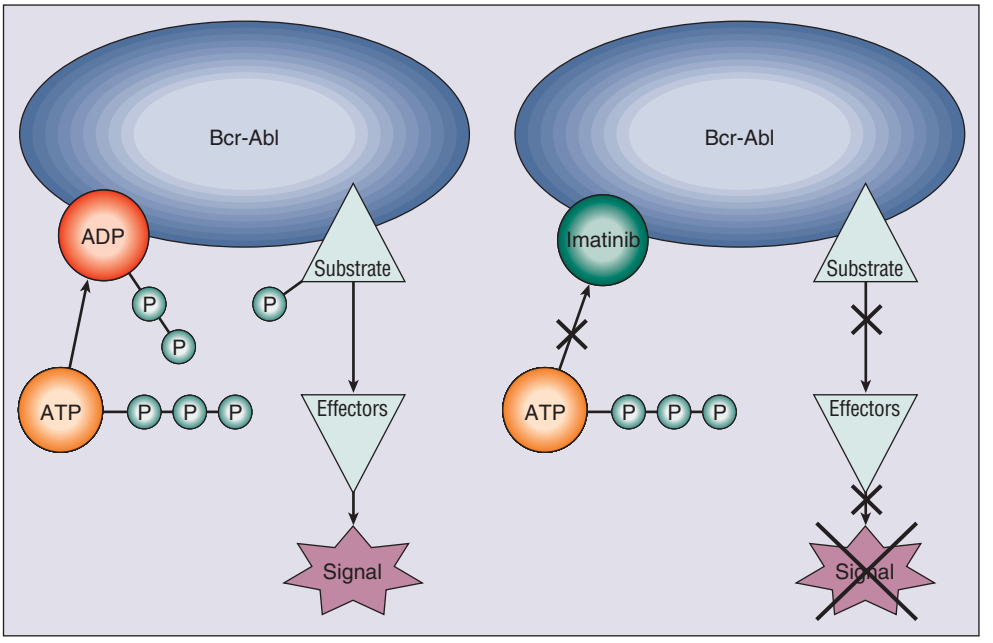


Figure 107-4 • The Bcr-Abl oncoprotein has constitutive tyrosine kinase activity compared with the tightly regulated tyrosine kinase activity of the normal ABL product. The Bcr-Abl kinase activates multiple substrates and binding partners, resulting in activation of downstream signaling pathways. This results in increased proliferation and reduced apoptosis of CML cells. By binding to the Abl kinase domain, imatinib prevents the phosphorylation of Bcr-Abl, thus interrupting the activation of the CML pathways.

update of the 5-year follow-up in the 553 patients treated with imatinib continued to show excellent results: projected complete cytogenetic response rate (single-time response) 87%; annual rate of progression to accelerated-blastic phase 4%; annual mortality rate 1% to 2%. At the 5-year follow-up time, 368 patients (67%) were still on imatinib on study. Rates of transformation and mortality seem to have been reduced in years 4 and 5 compared with the first 3 years. The estimated 5-year survival rate was 89%. The estimated 5-year survival rate excluding non-CML-related deaths was 95%.[33] Survival was also better with imatinib versus IFN + cytarabine (estimated 5-year survival rates 89% vs. 86%; $P = 0.049$). The difference was not very drastic, however, because of the crossover design of the IRIS study and the commercial availability of imatinib, both resulting in a change from IFN + cytarabine to imatinib in about 90% of patients within a median of 9 months from start of therapy. Comparison of imatinib results to historical experience with IFN therapy demonstrates more significant survival differences.[34,35]

In late chronic-phase CML after IFN-α failure, among 454 evaluable patients receiving imatinib, the cumulative complete cytogenetic response rate was 57%, and the estimated 5-year survival rate 79%.[45,46] In accelerated phase the complete cytogenetic response rate was 40%, and the estimated 4-year survival rate 60%.[49,50] In blastic phase response rates were lower and more transient, and the median survival duration only 6 to 12 months (Table 107-3).[51]

In the IRIS study, a major molecular response (3-log reduction of transcript levels) was observed in 38% of patients in the original update,[43] and in 70% of patients with longer follow-up.[48,54] Achieving a major molecular response in complete cytogenetic response at 18 months was associated with an estimated transformation-free survival and survival rates of 100% at 5 years versus 95% for complete cytogenetic response without a major molecular response ($P = 0.007$).[33] Disappearance of *BCR-ABL* was initially observed in a minority of patients (5%) but is now reported with longer term follow-ups in 30% to 50% of patients.[54,55] This rate depends on the sensitivity of the molecular test, because in general, a reduction of transcript levels by 4.5 log or more (or a *BCR-ABL/ABL* ratio of <0.003) may reach levels below detection in most molecular laboratories.[31,32]

Higher doses of imatinib 600 to 800 mg daily may overcome resistance to standard-dose imatinib in some patients.[53] In accelerated phase, high-dose imatinib was associated with higher response rates and longer survival.[49] In chronic-phase CML, imatinib 800 mg daily was also associated with higher rates of complete cytogenetic response, major and complete molecular response, and better progression-free survival rates.[48,55]

Imatinib is associated with mild-moderate side effects including nausea, vomiting, diarrhea, skin rashes, muscle cramps, bone aches, periorbital or leg edema, and weight gain. Serious but uncommon side effects (1% to 2%) include hepatic, renal, or cardiopulmonary dysfunction. These are manageable with dose reductions or treatment interruptions.[56,57] Drug-related myelosuppression occurs in 10% to 30% of patients in newly diagnosed CML. This is managed with brief treatment interruptions and/or dose modifications, or with growth factors (erythropoietin for anemia, filgrastim for neutropenia). Chromosomal abnormalities may appear in the Ph^- cells in 5% to 10% of responding patients. These include some abnormalities observed in myelodysplastic syndrome and acute myeloid leukemia such as chromosome 5 or 7 abnormalities, trisomy 8, 20q- and others. These chromosomal abnormalities are probably due to unmasking of a fragile stem cell prone to development of CML or to genetic instability. Such changes disappear spontaneously in up to 70% of cases. Evolution to a Ph^- myelodysplastic syndrome or acute myeloid leukemia is rare and probably part of the new natural course of CML.[58]

Imatinib therapy (400 mg daily) is started as soon as the diagnosis of CML is established. Allopurinol is recommended until the WBC count is less than 10×10^9 cells/L. Tumor lysis syndrome is rare, except in occasional patients in advanced-phase disease who require hydration and closer monitoring. With imatinib the WBC and platelet counts decrease in the first 2 to 4 weeks and normalize within 1 to 2 months. Complete blood counts are recommended weekly during the first month of therapy, then every 1 to 2 months. For patients with accelerated or blastic phases, complete blood counts should be performed more frequently, and as indicated clinically. Imatinib therapy should be continued indefinitely; treatment discontinuation even among patients with durable complete molecular responses (>2 years) has been associated with molecular relapse in about half.[59] High-dose imatinib (i.e., 600–800 mg daily) may be considered in CML transformation or Ph^+ acute lymphoid leukemia (in combination with chemotherapy), in patients with an unsatisfactory response to standard-dose imatinib, or with cytogenetic relapse on imatinib.

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation is curative in selected patients with CML. It is most effective during the chronic phase. Among patients in first chronic phase transplanted from matched siblings, the estimated 20-year survival rate is 40% to 50% (Fig. 107-5).[60] The report from the International Bone Marrow Transplant Registry (IBMTR), compiling data from over 6000 patients undergoing transplants, showed a 5-year survival rate of 60% for first chronic phase/sibling donor, but a 20-year survival rate of 40% to 45%.[60] Most of the 10% to 15% additional deaths between years 5 and 20 were due to transplant-associated complications rather than CML relapse. Chronic morbidities for stem cell transplantation include graft-versus-hose disease (GVHD), infertility, cataracts, hip necrosis, second cancers, and GVHD-associated organ damage (pulmonary, hepatic) or immune-mediated complications. Transplant-related mortality ranges from 5% to 50%, depending on several factors including patient age, whether the donor is related or unrelated, the degree of matching, and other factors such as positivity for cyto-

Table 107-3 Results of Imatinib Therapy in Chronic Myelogenous Leukemia

		PERCENTAGE				
		CYTOGENETIC RESPONSE		MOLECULAR RESPONSE		
CML Phase	**CHR/HR**	**Major**	**Complete**	**Major**	**Complete**	**% Estimated Survival (at X year)**
Chronic—newly diagnosed	90/98	90	87	70	20–40	89–92 (5–6)
Chronic—after interferon failure	60/80	67	57	NA	NA	79 (5)
Accelerated	50–60/80	40	30	NA	NA	60 (4)
Blastic	20/40	30	10	NA	NA	10–20 (2)

CHR, complete HR; CML, chronic myeloid leukemia; HR, hematologic response; NA, not available.
Data extracted from references 33, 45–52.

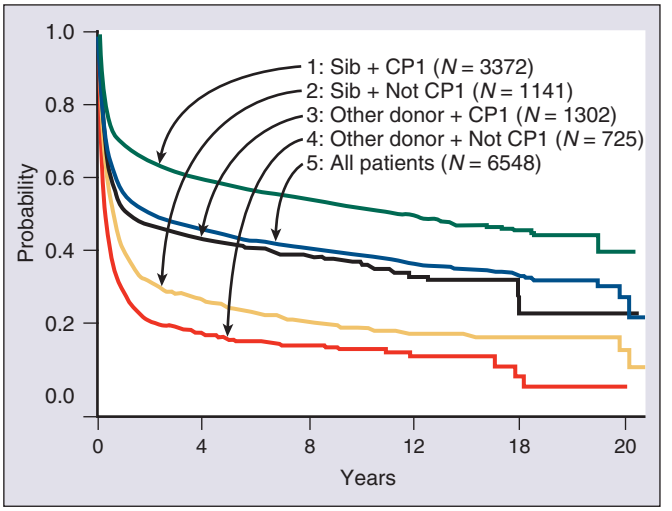


Figure 107-5 • Probability of survival of patients undergoing allogeneic stem cell transplant according to the International Bone Marrow Transplant Registry ($N = 6548$). Patients transplanted in first chronic phase (CP1) with an HLA-matched sibling (Sib) had the best outcome. Those transplanted with unrelated donors or not in CP1 had a worse outcome. The estimated 20-year survival rate of patients transplanted from a sibling donor in CP1 was 45%.

megalovirus (CMV), preparative and post-transplant regimens, and institutional expertise.[61–67] Disease-free survival rates with related allogeneic stem cell transplantation are 40% to 80% in chronic-phase CML. The disease-free survival rates are 60% to 80% among patients younger than 30 to 40 years of age and 30% to 40% in patients older than age 50 years. Disease-free survival rates range from 30% to 60% in accelerated-phase CML, and from 5% to 30% in blastic-phase CML. Patients with clonal evolution as the only accelerated-phase criterion have disease-free survival rates of 60%. Patients transplanted in second chronic phase have also favorable disease-free survival rates of about 40%.

A major limitation of allogeneic stem cell transplantation is the availability of related donors. Human leukocyte antigen (HLA)–compatible unrelated donors can be found in 50% of patients; the median time from donor search to transplant is 3 to 6 months. In general, unrelated donor stem cell transplantation is associated with higher rates of GVHD and transplant-related complications and mortality, and with lower rates of disease-free survival and survival. Results of unrelated stem cell transplantation in select centers, with molecularly matched donors and optimally managed patients, seem similar to those achieved with related donor stem cell transplantation.[62]

Nonmyeloablative preparative regimens have expanded the use of allogeneic stem cell transplantation to older patients and have reduced transplant-associated complications, organ damage, and mortality. Results in general show high degrees of engraftment, less morbidity and mortality, but perhaps higher incidences of persistent residual disease, and similar degrees of chronic GVHD.[66]

Improving Results of Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation is safest and results are best in younger patients with an HLA-identical sibling donor. Improvement of stem cell transplantation results can be achieved through: (1) better molecular characterization of the HLA phenotype and genotype and matching of unrelated donors, (2) improved management of complications, including viral infections (CMV),[67] (3) performing stem cell transplantation before CML evolution to accelerated-blastic phases, (4) treatment of relapse after stem cell transplantation before overt disease occurs (i.e., at time of molecular relapse), and (5) safer and better conditioning regimens.[63]

Monitoring Outcome after Allogeneic Stem Cell Transplantation and Treatment of Relapse

Most CML relapses after stem cell transplantation manifest in the first 3 to 5 years. Thereafter, the relapse rate is very low but may sometimes occur even after 10 to 15 years from transplant. Patients usually exhibit molecular relapse before cytogenetic or hematologic relapse. Increasing *BCR-ABL* transcript levels usually predict for cytogenetic and hematologic relapse.[68,69]

If relapse occurs, withdrawal of immunosuppression (cyclosporine, steroids) can induce remission (especially if molecular relapse) by favoring graft-versus-leukemia effect. However, this also may exacerbate GVHD. If relapse persists, it can be managed effectively with imatinib, donor lymphocyte infusions, IFN-α, or a second stem cell transplantation.[70,71] Imatinib results in remission rates of 40% to 60% if the relapse is molecular or cytogenetic in chronic phase. It is less effective if CML relapse is hematologic or in transformation. Donor lymphocyte infusions induce durable remission rates of 60% with molecular or cytogenetic relapse, but may exacerbate GVHD (which can be fatal), and result in intense myelosuppression in 20% of patients.

MANAGEMENT OF PATIENTS WITH IMATINIB RESISTANCE

"Resistance" to imatinib therapy can be defined as failure to achieve the following endpoints: (1) complete hematologic response (CHR) after 3 months of therapy, (2) any cytogenetic response after 6 months, (3) a major cytogenetic response (Ph positivity > 35%) after 12 months, or (4) a complete cytogenetic response after 18 months. In addition, patients experiencing cytogenetic or hematologic relapse at any time on treatment are considered to have secondary resistance to imatinib.[31]

The annual resistance rate to imatinib is about 3% to 4% in the first 5 years. Resistance can be primary (mostly due to BCR-ABL–independent mechanisms; i.e., with persistent inhibition of the Bcr-Abl kinase), or secondary (after an initial response, most often due to Bcr-Abl–dependent mechanisms, i.e., with reactivation of the Bcr-Abl kinase).[31,32] Several Bcr-Abl–dependent mechanisms of imatinib resistance have been proposed including amplification of *BCR-ABL* oncogene or transcript levels, multidrug resistance-dependent pumping of imatinib out of the cell, shifts of Bcr-Abl localization in the CML cells, and mutations of the Abl kinase domain. Bcr-Abl point mutations (>40 described so far), account for about 40% to 50% of resistance. Mutations that can occur at the ATP-binding site (P-loop), at contact points with imatinib, or at other Bcr-Abl sites (catalytic domain, activating loop) can produce relative or absolute resistance to imatinib; some mutations are not relevant to resistance. Mutations with relative resistance to imatinib can be overcome with higher doses of imatinib; others do not respond to increasing the imatinib dose but respond to treatment with the more potent second-generation TKIs. A particular mutation, T315I, confers absolute resistance to imatinib and to the second-generation TKIs (i.e., dasatinib, nilotinib, bosutinib) but may be responsive to new inhibitors with different binding requirements.

Patients who develop imatinib resistance have several treatment options including allogeneic stem cell transplant, treatment with the new-generation TKIs, and others. Imatinib resistance in chronic phase is associated with an estimated 4-year survival rate of 60%. However, if progression is in accelerated or blastic phases, the prognosis is poor.[72] For patients in accelerated or blastic phase after imatinib resistance, every attempt should be made to refer them to allogeneic stem cell transplantation. If patients develop resistance to imatinib but are still in chronic phase, allogeneic stem cell transplantation is an appropriate second-line option if the patient is younger and/or has a related matched donor. In the interim, or if the patient is older and/or has an unrelated matched donor, a trial of one of the new-generation TKIs is reasonable. Subsequent therapy may be based

on the early response to that therapy. In all cases of imatinib resistance, mutational analysis is recommended to identify patients with T315I or other mutations that can be selectively nonresponsive to one of the new-generation TKIs. If a T315I mutation is identified, second-generation TKIs are not effective and the patient should be referred for allogeneic stem cell transplantation as soon as possible, and in the interim be controlled with hydroxyurea, cytarabine, combinations of standard older therapies, or investigational agents that might be effective against T315I mutations. A treatment algorithm for CML is proposed in Figure 107-6.

Dasatinib

Dasatinib (Sprycel; BMS354825) is a newly approved potent oral multitargeted kinase inhibitor of critical oncogenic kinases including Bcr-Abl, Src, C-kit, and PDGF-R. This dual Abl/Src inhibitor is 300 times more potent than imatinib in preclinical models, and is effective against all imatinib-resistant kinase domain mutations except T315I. Following the positive phase I studies of dasatinib demonstrating safety and efficacy in Ph^+ leukemias after imatinib failure,[73] pivotal phase II studies, referred to as START (Src/Abl Tyrosine kinase inhibition Activity Research Trials of dasatinib), were conducted in all phases of CML after imatinib failure and in Ph^+ acute lymphocytic leukemia. This led to the US Food and Drug Administration's approval of dasatinib for this indication in 2006. In 387 patients with chronic-phase CML after imatinib failure, dasatinib 70 mg orally twice daily produced a CHR rate of 90%, a major cytogenetic response rate of 52%, a complete cytogenetic response rate of 39%, and an estimated 10-month progression-free survival rate of 92%.[74] Response rates were higher in patients with imatinib intolerance versus resistance but were similar by whether mutations were present or absent. Results were similarly encouraging in accelerated-blastic phases and in Ph^+ acute lymphocytic leukemia (Table 107-4).[75–77] A randomized study of dasatinib 70 mg orally twice daily versus high-dose imatinib (400 mg orally twice daily) in patients with CML chronic phase after failure on imatinib 400 to 600 mg daily accrued 150 patients (2:1 randomization).[77] Dasatinib was associated with higher rates of complete cytogenetic response at 3 months (22% vs. 8%), overall major cytogenetic response (52% vs. 33%; $P = 0.02$), and overall complete cytogenetic response (40% vs. 16%, $P = 0.004$). The difference in response rates was most evident in patients with failure on imatinib 600 mg daily (major cytogenetic response rates 49% vs. 24%) but not in patients with failure on imatinib 400 mg a day (major cytogenetic response rates 58% vs. 53%). Progression-free survival was better with dasatinib (estimated 12-month rates 94% vs. 70%; $P < 0.0001$). Dasatinib was associated with higher rates of grade 3 to 4 cytopenias (55% to 59%) compared with high-dose imatinib (14% to 39%), and with pleural effusions (17% vs. 0%). In a single-institution review of the dasatinib experience, pleural effusions were observed in 48 of 138 patients (37%) treated with dasatinib. Pleural effusions were often exudates and were managed with treatment interruptions, diuretics and short courses of steroids, and resumption of dasatinib at lower dose schedules.[78] Myelosuppression was also managed with dose interruptions and reductions. A four-arm randomization study of different dasatinib dose schedules (50 mg twice daily, 100 mg single-dose daily, 70 mg twice daily, 140 mg single-dose daily) showed that a single daily dasatinib dose of 100 mg produced equivalent treatment results with fewer side effects.[79]

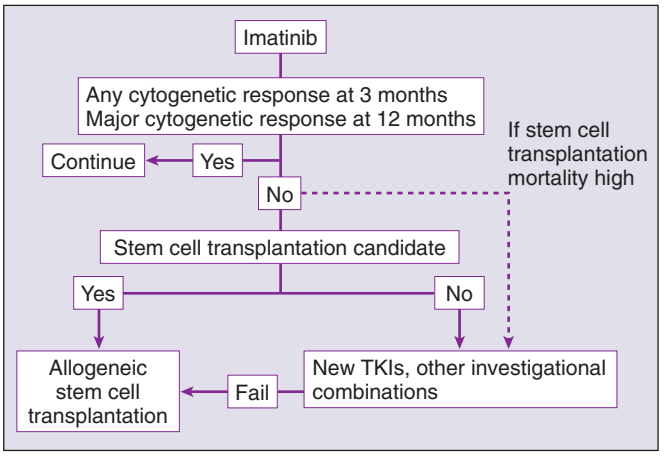


Figure 107-6 • Proposed treatment algorithm for patients with newly diagnosed CML. Patients achieving any cytogenetic response after 6 months, a major cytogenetic response after 12 months of therapy, and a complete cytogenetic response in the second year of therapy should continue on imatinib until there is evidence of resistance. High-dose imatinib could be attempted in patients with unsatisfactory response. In case of resistance, allogeneic stem cell transplantation can be considered as the next option if the transplant-related mortality is acceptable to the patient. If not, the patient can consider treatment with the new-generation tyrosine kinase inhibitors (dasatinib, nilotinib, bosutinib), or with other investigational therapies, before proceeding to allogeneic stem cell transplant.

Table 107-4 Results of Dasatinib Phase II Studies in CML and Ph^+ ALL after Imatinib Failure

		Response Rate (%)		
			Cytogenetic Response	
Disease	***N***	**CHR/HR**	**Major**	**Complete**
CML, chronic	387	90/90	52	39
CML, accelerated	107	39/64	33	24
CML, blastic	116	26/47	38	33
Ph^+ ALL	46	33/51	57	54
CML chronic, randomized				
Dasatinib	101	93	52	40
High-dose imatinib	49	82	33	16

ALL, acute lymphoid leukemia; CHR, complete hematologic response; CML, chronic myeloid leukemia; HR, hematologic response; Ph, Philadelphia chromosome.
Data extrapolated from references 74–77.

Nilotinib

Nilotinib (Tasigna, AMN107) was rationally designed by replacement of the *N*-methylpiperazine binding group of imatinib to optimize the binding affinity and selectivity for the Abl kinase. Nilotinib, a selective Bcr-Abl kinase inhibitor, was 30 times more potent than imatinib in preclinical models, and was active against all imatinib-resistant mutations except T315I. Similar to dasatinib, the phase I study with imatinib showed safety and activity after imatinib failure.[80] The pivotal phase II studies with imatinib 400 mg orally twice daily have been completed. In the phase II pivotal trial of nilotinib in 316 patients in chronic phase after imatinib failure, the CHR rate was 74%, the major cytogenetic response rate 52%, and the complete cytogenetic response rate 34%. The estimated 1-year survival rate was 95%. Side effects were modest, including grade 3 to 4 myelosuppression in 20% to 30%; no pleural effusions were observed. Response rates were similar in patients with imatinib resistance versus intolerance and in patients with or without mutations.[81]

The activity of nilotinib in CML accelerated and blastic phase after imatinib failure were also encouraging, although response rates were lower and response durations shorter (Table 107-5).[82,83] Nilotinib recently has been approved by the Food and Drug Administration (October 2007) for the treatment of CML in chronic or accelerated phases following imatinib failure.

Table 107-5 Results of Nilotinib Phase II Studies in CML and Ph$^+$ ALL after Imatinib Failure

		Response (%)		
			Cytogenetic Response	
Disease	***N***	**CHR**	**Major**	**Complete**
CML, chronic	316	74	52	34
CML, accelerated	64	17	31	17
CML, blastic	96	13	NR	NR
Ph$^+$ ALL	34	6	NR	NR

ALL, acute lymphoid leukemia; CHR, complete hematologic response; CML, chronic myeloid leukemia; NR, not reported; Ph, Philadelphia chromosome.

Data extrapolated from references 80–83.

Bosutinib

Bosutinib (SKI606) is an orally available dual Src/Abl inhibitor that is 30 to 200 times more potent than imatinib. It has minimal inhibitory activity against c-Kit and PDGF-R (therefore expected to produce less myelosuppression and pleural effusions). In a phase I/II study of 69 patients with CML treated after imatinib failure, the CHR rate among 48 patients in chronic phase was 84%, and the cytogenetic response rate 81%, (major 52%, complete 33%).[84] The median follow-up on study was short. Grade 3 to 4 toxicities were minimal, including skin rashes in 6% and thrombocytopenia in 6%. Mild to moderate diarrhea was common at the phase II dose selected of 500 mg orally daily.

Other Agents

MK0457 is an aurora kinase inhibitor with inhibitory activity against T3151 mutant CML. In a preliminary experience in patients with advanced phases of CML and T315I mutations, MK0457 showed encouraging results.[85] Other aurora kinase inhibitors with potential activity against T315I mutant CML include AT9283 and KW2449.

Other classes of agents that have shown reasonable activity against CML after imatinib failure include farnesyl transferase inhibitors (tipifarnib), decitabine, and homoharringtonine.[86–88]

SELECTION OF SEQUENTIAL THERAPIES IN PATIENTS WITH CHRONIC MYELOGENOUS LEUKEMIA

The longer term follow-up results of imatinib in newly diagnosed CML are reassuring. With its modest toxicity profile and absence of treatment-related mortality, imatinib is now frontline CML therapy in all patients regardless of age. Allogeneic stem cell transplantation is associated with mortality rates of 5% to 50% in the first year and with significant chronic morbidities including GVHD-related complications, cataracts, infertility, second cancers, and a 15% mortality between years 5 and 20 of follow-up that may be related to subtle but continuous transplant-related organ damage and some late relapses. Patients with imatinib resistance may consider allogeneic stem cell transplantation as second-line therapy if they are younger and/or have a matched related donor (i.e., expected low stem cell transplantation-related mortality). Among patients with expected high stem cell transplantation-related mortality, a trial of a second-generation kinase inhibitor may be attempted, and consideration of transplant based on the early response profile to the treatment. Patients with T315I mutations should be referred to allogeneic stem cell transplantation. Patients with imatinib resistance in accelerated or blastic phase, either de novo or after chronic phase, should also be referred to allogeneic stem cell transplantation as soon as possible regardless of their response to the second-generation TKIs (even though such attempts may debulk the transformed disease and improve the outcome after stem cell transplantation).

Old Traditional Standards of Care Revisited

Busulfan (1,4-dimethane-sulfonyl-oxybutane) is the first alkylating agent that demonstrated activity in CML. Busulfan therapy was associated with significant toxicities, including severe and prolonged myelosuppression. Busulfan should be used today only as part of some conditioning regimens in allogeneic stem cell transplantation, and must be avoided in any patients awaiting allogeneic stem cell transplantation because of the associated adverse outcome.

Hydroxyurea, a ribonucleotide reductase inhibitor, is a well-tolerated oral cytotoxic agent that can control blood counts rapidly in most patients with CML. Rare side effects include nausea, rashes, mouth ulcers, and hand or leg ulcers. Hydroxyurea is usually given at a daily dose of 1 to 10 g, depending on the degree of leukocytosis, and the dose adjusted to keep the WBC count between 2×10^9 and 10×10^9 cells/L. Hydroxyurea may be used for initial cytoreduction, as a temporary measure to control counts in between definitive therapies, or part of a combination approach with imatinib or other TKIs. It should not be used alone as a definitive treatment in CML, because it rarely suppresses Ph$^+$ cells.

IFN-α showed anti-CML activity in the 1980s and was a standard of care in CML until the discovery of imatinib. IFN-α induced CHR rates of 50% to 80% in untreated chronic-phase CML, and cytogenetic response rates of 40% to 60% (major in 10% to 40%; complete in 5% to 30%).[89] A meta-analysis of randomized studies of IFN-α versus hydroxyurea or busulfan, showed that IFN-α therapy was associated with better survival than hydroxyurea or busulfan (5-year survival rates 57% vs. 42% , $P < .00001$).[90] IFN-α has minimal activity in accelerated or blastic phases of CML. It is associated with significant side effects including flu-like symptoms, fever, chills, myalgias, fatigue, depression, neuropathy, diarrhea, memory problems, immune-mediated complications, myelosuppression, and others.[91]

Achievement of a major or complete cytogenetic response with IFN-α is associated with significantly better long-term survival.[92] Combinations of IFN-α and low-dose cytarabine improve results over IFN-α alone.[93]

New formulations of IFN-α attached to polyethylene glycol (PEG) prolong its half-life, allow weekly administration, reduce toxicities, and may also improve results (at least with a particular pegylated IFN-α2a formulation, Pegasys).[94]

MANAGEMENT OF ACCELERATED AND BLASTIC PHASES OF CHRONIC MYELOGENOUS LEUKEMIA

Imatinib, dasatinib, and nilotinib have all shown activity in CML in transformation. The single-agent activity is more encouraging and durable in accelerated phase, but less so in blastic phase.

In accelerated phase, imatinib produces a hematologic response rate of 80%, a CHR rate of 40%, a major cytogenetic response rate of 30%, and an estimated 4-year survival rate of 60%. In accelerated-phase CML after imatinib failure, dasatinib is associated with a hematologic response rate of 64%, a cytogenetic response rate of 40%, and an estimated 18-month survival rate of 70%. The second-generation TKIs probably produce better results than imatinib, either alone or in combinations.

Whereas the three TKIs have shown activity in blastic-phase CML and two of them (imatinib and dasatinib) have been approved for the indication, the results are modest, and combination modalities should be pursued. These include acute myeloid leukemia regimens

plus TKIs (e.g., idarubicin + cytarabine + imatinib) in myeloid-undifferentiated blastic phase, and acute lymphoid leukemia regimens plus TKIs (e.g., hyper-CVAD + imatinib or dasatinib) in lymphoid blastic phase.[95,96] In the latter, central nervous system prophylaxis should be included, because about 30% of patients may develop central nervous system disease. In all such instances patients should be referred to allogeneic stem cell transplant as soon as possible.

Allogeneic stem cell transplantation in accelerated phase results in 5-year disease-free survival rates of 15% to 30%. If transplant is done in a second chronic phase the results are better, with disease-free survival rates of 40% to 50%. In blastic phase, survival after allogeneic transplant is 5% to 15%.[97]

SPECIAL CONSIDERATIONS

Ph⁻ Chronic Myelogenous Leukemia

Among 10% of patients with morphologic CML without a detectable Ph chromosome, a third have the *BCR-ABL* molecular abnormality detected by FISH or PCR. These patients (Ph⁻, *BCR-ABL*⁺ CML) have similar clinical features, response to imatinib therapy, and prognosis as Ph⁺ CML. Patients who lack the *BCR-ABL* fusion gene (Ph⁻, *BCR-ABL*⁻; atypical CML according to the WHO classification) have heterogeneous conditions, including proliferative myelodysplastic syndrome, chronic myelomonocytic leukemia, or myeloproliferative disorders. They tend to be older, exhibit more often anemia, thrombocytopenia, and monocytosis, and do not show basophilia, eosinophilia, or thrombocytosis. They do not respond to imatinib therapy and have poor prognosis with a median survival of 18 to 24 months. Ph⁻ and *BCR-ABL*⁻ CML often overlaps clinically with chronic myelomonocytic leukemia. Patients die from infections and bleeding with marrow failure, or from transformation to acute leukemia (50%).

Pregnancy

If CML is diagnosed in a pregnant woman, she can be managed with leukopheresis if indicated during the first trimester of pregnancy, with hydroxyurea subsequently until delivery, then with more definitive therapy. Anecdotal reports of successful deliveries after IFN therapy during pregnancy have been reported; however, IFN is antiangiogenic and may have adverse affects on the fetus that are not evident with reports including only few patients. If a woman becomes pregnant while on imatinib therapy, the drug should be discontinued. Partners of men on imatinib have delivered normal babies. However, the numbers are too small to make definitive conclusions.[98]

Other Considerations

Severe thrombocytosis not responding to imatinib or other TKIs may be controlled with the addition of hydroxyurea, anagrelide, or other chemotherapeutic agents (thio-TEPA, 6 mercaptopurine).

Splenectomy or splenic irradiation is rarely used in current management of CML. A rare indication for splenectomy is disease progression and painful, massive splenomegaly with hypersplenism; splenectomy may provide temporary benefit. Splenic irradiation should be avoided because of its transient effects and the resultant adhesions, which make subsequent splenectomy risky.

Leukapheresis is also rarely indicated for control of severe symptomatic leukocytosis during the first trimester of pregnancy, or for leukostasis-induced complications such as priapism. The latter can also be managed surgically through decompression of the penile vein or with brief local irradiation.

FUTURE DIRECTIONS

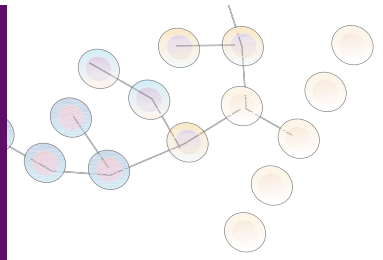
Targeted therapy with TKIs has significantly improved prognosis in CML, particularly for patients in chronic phase. Emergence of resistance in a minority of patients with newly diagnosed CML suggests the complex interactions in CML pathophysiology and the need to improve therapy. Long-term therapy with imatinib is expensive and presents a socioeconomic issue. Current and future studies are exploring the role of the new TKIs (dasatinib, nilotinib, bosutinib) as frontline therapy in CML to reduce or prevent emergence of resistance due to mutations or other mechanisms. Combinations of TKIs with each other (simultaneous, sequential), or with other active agents that may target the downstream events, should also be explored. These include inhibitors of pathways involving Raf, farnesylation, mTOR, JAK/STAT, MEK/MAPK, PI3K/AKT, or others. Combinations of TKIs with such classical anticancer agents as hydroxyurea, cytarabine, homoharringtonine, and others are in progress. Vaccine strategies in the setting of minimal residual disease may eradicate dormant resistant clones and provide a potential for long-term event-free survival or cure without the need for indefinite therapy.[99,100]

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108 Chronic Lymphoid Leukemias

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SUMMARY OF KEY POINTS

Epidemiology

- Chronic lymphocytic leukemia (CLL) is one of the most common forms of adult leukemia. Although there is an increased incidence after age 65, approximately 30% of the patients are younger than this age.
- Approximately 5% to 10% of patients with CLL have other family members with this disease. The familial form of CLL has a similar clinical course to the spontaneous form of the disease.

Clinical Features

- CLL often presents as an asymptomatic finding associated with a peripheral blood monoclonal population of neoplastic cells with a characteristic immunophenotye (CD5-positive, CD19-positive, CD23-positive, CD79b-negative, FMC7-negative, and dim expression of CD20). Flow cytometric demonstration of the characteristic monoclonal population of cells can establish the diagnosis. A bone marrow aspirate and biopsy are not necessarily required at diagnosis but are extremely useful before therapy is initiated.
- Multiple predictive biomarkers for estimating the time from diagnosis until treatment exist and include IgV gene mutational status, ZAP-70 protein expression, and CD38-positive antigen expression on leukemic cells. Cytogenetic abnormalities are quite common (e.g., more than 80% of patients have abnormalities detectable by fluorescence in situ hybridization (FISH)) and predict survival. Some predictive information with FISH can also identify patients who are projected to have a shorter duration of response to chemotherapy (i.e., del 17p).
- Clinical complications of the disease include autoimmunity, enhanced risk of infection, increased risk of secondary malignancies, and progression to a high-grade lymphoid malignancy.

Management

- Prevention is a key element for physicians following patients with this disease. Early intervention for infection and screening for other secondary malignancies (e.g., skin cancers, gastrointestinal cancers, and other solid tumors) are essential. Careful monitoring of the patient with a quarterly hemogram and a physical examination are important.
- Specific therapy for CLL is initiated when bone marrow failure appears imminent (e.g., anemia or thrombocytopenia is detected on quarterly routine hemograms), there is progressive symptomatic lymphadenopathy or splenomegaly, or there are systemic symptoms (e.g., progressive fatigue, night sweats, weight loss). Standard chemotherapy usually entails a purine nucleoside analog with rituximab. Participation in ongoing clinical trials in an effort to improve combination chemotherapy is highly recommended for all patients who need therapy. Consideration of stem cell transplantation is an alternative for those who are progressing despite frontline therapy or are participating in an organized clinical trial because of adverse prognostic parameters. Suspicion of high-grade lymphoma transformation requires more innovative therapy on a clinical trial if possible.
- Autoimmune complications (e.g., autoimmune hemolysis or thrombocytopenia) should be treated with effective immunosuppressive therapy prior to initiating cytotoxic agents to treat the CLL.

Establishing the Correct Diagnosis

- Establishing the exact diagnosis for the lymphoid leukemia is essential for selecting the optimal therapeutic approach. Alternative diagnoses such as mantle cell lymphoma, splenic marginal zone lymphoma, prolymphocytic leukemia, and hairy cell leukemia (or a variant) may be erroneously reported as CLL. Hematopathology review is therefore essential for diagnostic confirmation. Furthermore, an enormous amount of data has accrued that predicts the outcome for specific subsets of patients with CLL, and in contrast to previous decades, it is essential to distinguish among the various forms of chronic lymphoid leukemia.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in the Western hemisphere. The clinical course of this malignant disease is quite variable, and the complications that are associated with this entity are diverse. Enormous research efforts have been expended over the four decades since Dameshek described CLL as an accumulative disease of immunologically incompetent lymphocytes in 1967.[1] Historically, this disease has been described as a lymphoproliferative process. Dameshek wisely suggested that an additional defect in the leukemic cells' ability to undergo apoptosis results in an accumulation of malignant cells. Recent advances in the understanding of the pathogenesis of CLL have confirmed that both historical descriptions have validity, but that the complexity of malignant clonal expansion and progression requires more explanation.

CLL is a neoplastic disorder of CD5-positive B cells that is affected by genetic, molecular, and microenvironmental factors that might ultimately result in a fatal outcome. Recently, observations have indicated that two basic forms of this disease exist. These originate from events in B-cell development surrounding the mutational status of the immunoglobulin variable gene region (IgV).[2] In normal B-cell development, the IgV gene undergoes a specific rearrangement that provides for diversity of immunoglobulin protein synthesis in response to antigenic stimulation. Normal B cells traffic from the bone marrow to the germinal centers of lymph nodes, where IgV gene rearrangement occurs. In CLL, there are two groups of patients with diverse clinical outcomes that are separated by the mutational status of this IgV gene. Patients who have a mutated IgV gene detected in their leukemic cells have a favorable clinical course. In contrast, patients with an unmutated IgV gene in their leukemic cells have a more aggressive clinical course.[3]

In addition to these important clinical consequences related to the normal process of rearrangement of the IgV gene, there have been a host of additional molecular observations that are associated with the prognosis of this disease. Patients with an overexpression of CD38 on their leukemic cells also have an aggressive clinical course.[4] The genetic profiling of leukemic cells identified that the expression of ZAP-70, a protein tyrosine kinase that is normally found only in T cells, represents another marker for aggressive clinical disease when detected in leukemic B cells.[5,6]

Genetic abnormalities in leukemic cells from patients with CLL have been detected in approximately 50% of patients by standard cytogenetics. The majority of findings that have been identified by fluorescence in situ hybridization (FISH) analyses show that approximately 80% of patients with CLL will have a detectable abnormal clone, and many have multiple or complex clonal cytogenetic abnormalities.[7,8] The observations of clonal evolution coupled with new discoveries in gene expression patterns present a picture of a complex series of events that result in a multiplicity of clinical outcomes. The recent demonstration that microRNA molecules within the leukemic cells might control gene expression (e.g., TCL-1), that these entities can induce a CLL-like disease in mice, and that they might be associated with progression of disease in humans provides further insight into the expanding list of molecular features that affect outcomes.[9,10]

Finally, the importance of signal transduction at the cellular level in promoting either cell death or survival is increasingly appreciated. Signals from the microenvironment might tip the balance in favor of leukemic cell survival via upregulation of antiapoptotic proteins (e.g., BCL-2, survivin, and MCL-1).[11,12] In vivo studies have confirmed that this disease is truly proliferative even in its early clinical stages. Patients with an elevated growth fraction can have more rapid clinical disease progression. Therefore, the novel description of the disease entity 40 years ago by Dameshek was correct in stating that this disease is an accumulative disorder but underestimated the complexity of the modulating genetic, molecular, and microenvironmental factors that can result in rapid or indolent clinical progression. In caring for patients with CLL, it is important to understand and appropriately utilize this new knowledge for assessment of patient prognosis in order to provide guidance for optimal disease management.

EPIDEMIOLOGY

While CLL is the most common form of adult leukemia in the United States and Europe, it has a low incidence in Asia. In Asian immigrants to the United States, there is no increase in the frequency of this form of leukemia. The median age at diagnosis of CLL is 72 years of age; however, the Surveillance Epidemiology and End Results (SEER) database indicates that about 30% of patients are younger than 64 years of age at diagnosis.[13] Therefore, this is not a disease that solely afflicts the older aged patient. While the median age at death was 78 years of age, many features of the disease need to be considered in estimating the risks for death from this disease. The incidence in the general population does increase dramatically with age. People over the age of 65 had an incidence of approximately 20.6 per 100,000, while those under this age had had an incidence of 1.3 per 100,000. CLL is more common in males than in females. In 2006, the SEER database predicted that 10,020 new cases would be identified. This would include 6280 men and 3740 women. In 2000, the age-adjusted incidence of males and females was estimated at 4.7 and 2.4 per 100,000, respectively. CLL is slightly more common in whites than in blacks. In the United States in 2000, the age-adjusted incidence in whites and blacks was 3.7 and 2.5 per 100,000, respectively.[14] Some investigators believe that these figures are too conservative and that as many as 21,000 new cases per year in the United States might be more accurate.

PATHOGENESIS

A definitive cause for CLL has not yet been identified. The possibility of a genetic predisposition appears strong, considering the population differences between Asia, North America, Europe, and Australia. In addition, families with an increased incidence of CLL have been identified, and it is estimated that approximately 5% to 10% of patients with CLL have a family history of this disease.[15] There does appear to be a phenomenon of anticipation in the familial form of this disease, in which family pedigrees demonstrate onset of disease at a younger age with subsequent generations.[16] A large Italian study involving 1449 patients with CLL showed that 181 of these patients (12.5%) reported having one or more relatives with a hematologic malignancy, of which 6% were CLL.[17] Overall, the patients with the familial form of the disease had a prognosis that was similar to the prognosis of those with a spontaneous diagnosis with respect to requirement for therapy and survival. Preliminary data from Raval and colleagues implicate specific genes (e.g., death-associated protein kinase 1) in the development of CLL.[18]

Although there has been no linkage of CLL to irradiation, some association has been noted between pesticide exposure and farming with development of CLL.[19,20] Recently, exposure to Agent Orange during the Vietnam era was linked to an increase in this disease.[21]

CLINICAL FEATURES AND INVESTIGATION

CLL is a neoplastic disease involving a malignant transformation of a B-cell precursor cell. This event occurs in a common lymphocyte precursor cell. The common lymphocyte precursor cell undergoes the neoplastic transformation with an expansion of a clonal population of cells that have a characteristic immunophenotype (CD5-positive, CD19-positive, CD23-positive). There are other characteristic immunophenotypic antigens that are also expressed (e.g., CD20-expression is dim), and these cells can be identified by flow cytometry of the circulating peripheral blood.[22] These cells infiltrate all organs including lymph nodes, bone marrow, spleen, and liver. The pattern of lymph node invasion is characteristic of a small cell lymphocytic lymphoma. The bone marrow will show an infiltration of more than 30% cells of monoclonal lymphoid origin. Morphologically, these cells appear as small, mature-appearing lymphocytes with dense chromatin structure. The pattern of lymphocyte infiltration in the bone marrow ranges from interstitial or nodular to diffuse involvement. The pattern of involvement has prognostic significance, diffuse infiltration being associated with an inferior prognosis.[23] The microenvironments in both the lymph nodes and bone marrow are felt to contribute to the progression of the malignant disease. Ultimately, the leukemic cells will displace many of the normal cellular elements within the bone marrow, leading to peripheral blood cytopenias.

The cells of this disease have been characterized as restricted in G_0 and therefore are predominantly a clonal population of nondividing malignant cells. However, recent in vivo studies utilizing deute-

Table 108-1 Initial Investigation and Pretreatment Evaluation

INITIAL INVESTIGATION
Complete blood count with differential
Review of peripheral smear
Complete metabolic panel with LDH
Peripheral blood immunophenotyping
Serum protein electrophoresis
Quantitative immunoglobulins
Beta-2 microglobulin
Chromosome analysis of peripheral blood with interphase cytogenetics for 17p, 11q, and 13q, as well as translocation 11;14 to rule out mantle cell lymphoma
IgV mutation testing, CD38, and Zap-70*
PRETREATMENT PLANNING
Complete blood count with differential
Complete metabolic panel with LDH to evaluate renal function
Viral serologies (e.g., hepatitis, CMV)
Bone marrow aspirate and biopsy with flow cytometry
CT scan of the neck, chest, abdomen, and pelvis
Consideration for PET scan if transformation to large cell lymphoma is suspected

*Since no clinical intervention is currently based on these prognostic indicators, these studies should be carefully considered by the clinican and extensively discussed with the patient prior to ordering.

rium-labeled water have shown a highly proliferative compartment to the circulating leukemic cells that can be identified in patients even at the earliest stages of the disease. Although there are differences between patients with respect to the size of the proliferative component, patients who have a percentage of new cells in excess of 0.3% of the total leukemic cell mass per day have a more aggressive clinical course.[24]

The observation that many of the leukemic cells are nondividing has prompted studies of duration of cell survival. Indeed, there are many factors that contribute to prolonged cell survival. In particular, antiapoptotic proteins (e.g., BCL-2 and MCL-1) are expressed in CLL cells, and these result in the accumulation of large numbers of long-lived leukemic cells. This process is aided by the presence of protective cells in the marrow and lymph node microenviroments that upregulate antiapoptotic proteins and protect cells from the effects of chemotherapy.[25,26]

The criteria for diagnosis of CLL include documentation that a peripheral lymphocytosis exists (absolute lymphocyte count > 5000), demonstration of a monoclonal population of malignant B cells characterized by light chain restriction, and a specific immunophenotype in the peripheral blood. Flow cytometry is essential in demonstrating a clonal population of lymphocytes that coexpress CD5-positive, CD19-positive, and CD23-positive; are CD79b-negative and FMC7-negative; and are weakly positive for surface immunoglobulin. CLL cells weakly express CD20 antigen. The peripheral blood smear shows small mononuclear cells with a dense chromatin structure. There should be fewer than 11% prolymphocytes, and it is important also to evaluate the morphology of both the red blood cells and the platelets. A bone marrow aspirate and biopsy are not required to establish the diagnosis of CLL, as definitive flow cytometry may be performed on the peripheral blood. However, these studies are usually required prior to initiating therapy (Table 108-1). It is important to note that there are other lymphoid malignancies that coexpress CD5, and it is therefore essential to confirm the diagnosis of CLL and to exclude the possibility of an alternative diagnosis. Table 108-2 lists the diagnostic features of CLL along with those of other lymphoid malignancies that should be considered in the differential diagnosis. Mantle cell lymphoma (MCL) in particular

Table 108-2 Differential Immunophenotype of Chronic Lymphoid Leukemias

Antigen	CLL	CLL-PLL	B-PLL	MCL	MZL	FL	HCL	LPL
CD5	+	+/–	–/+	+	–	–	–	–
CD10	–	–	–	–	–	+/–	–	–
CD11c	+/–	+/–	–	–	–/+	–	+	–/+ (D)
CD19	+	+	+	+	+	+	+	+
CD20	+ (D)	+ (D-B)	+ (B)	+ (B)	+ (B)	+ (B)	+ (B)	+/–
CD22	–/+ (D)	+/– (D-B)	+ (B)	+ (B)	+ (B)	+ (B)	+ (B)	+
CD23	+	–	–	–	–	–/+	–	–
CD25	–/+	–/+	+/–	–	–	–	+ (B)	–/+ (D)
CD38	v*	v*	–	–	–	–	–	+ (B)
CD43	+	+/–	–/+	+	–/+	–	–/+	–/+
CD79a	+	+	+	+	+	+	+	+
CD79b	–	+/–	+	+	+/–	+	–/+	+/–
CD103	–	–	–	–	–/+	–/+	+ (B)	–
FMC7	–	–/+	+	+	+	+/–	+	–/+
Surface K/L	+ (D)	+ (D-B)	+ (B)	+ (B)	+ (B)	+ (B)	+ (B)	+ (D-B)

–/+, Variably expressed, predominantly negative; +/–, variably expressed, predominantly positive; B, brightly expressed; B-PLL, de novo B-cell prolymphocytic leukemia; CLL, chronic lymphocytic leukemia; CLL-PLL, CLL with prolymphocytic transformation; D, dimly expressed; FL, follicular lymphoma; HCL, hairy cell leukemia; LPL, lymphoplasmacytic lymphoma; MCL, mantle cell lymphoma.

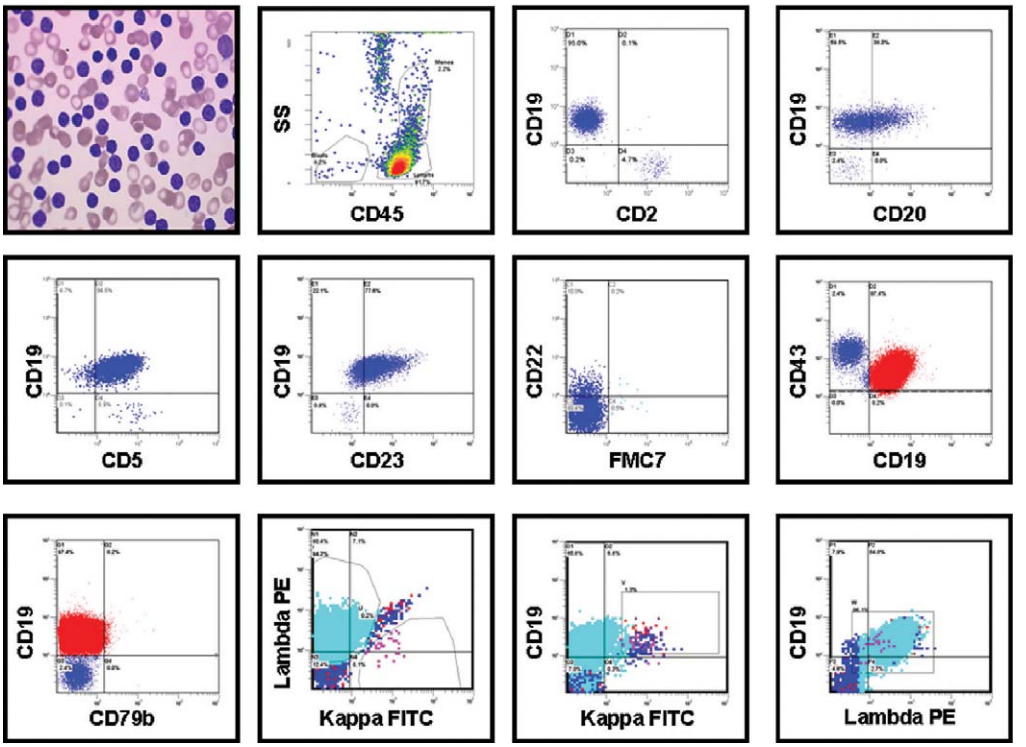


Figure 108-1 • Classic immunophenotypic profile for chronic lymphocytic leukemia/small lymphocytic lymphoma.

may present with a hematologic picture that is similar to that of CLL. However, the prognosis and therapeutic approach for MCL would be completely distinct from those for CLL. Patients with MCL have a shorter interval to disease progression, and the overall survival is markedly diminished when compared with that of CLL. A CLL scoring system has been established that assigns specific points for the respective antigen expression on the malignant cells as determined by flow cytometry.[27] In addition to this scoring system, many centers perform testing for overexpression of cyclin D_1, which is associated with specific cytogenetic evidence that confirms a diagnosis of MCL. Patients with MCL can be identified with FISH probes showing the t(11;14) translocation (Fig. 108-1).

Morphologic evaluation of the leukemic cells on the peripheral blood smear will be important for recognizing another aggressive form of chronic lymphoid leukemia that can masquerade as CLL. Prolymphocytic leukemia will often present with a marked peripheral blood lymphocytosis associated with malignant cells that have a very prominent large central nucleolus (Fig. 108-2). In patients with de

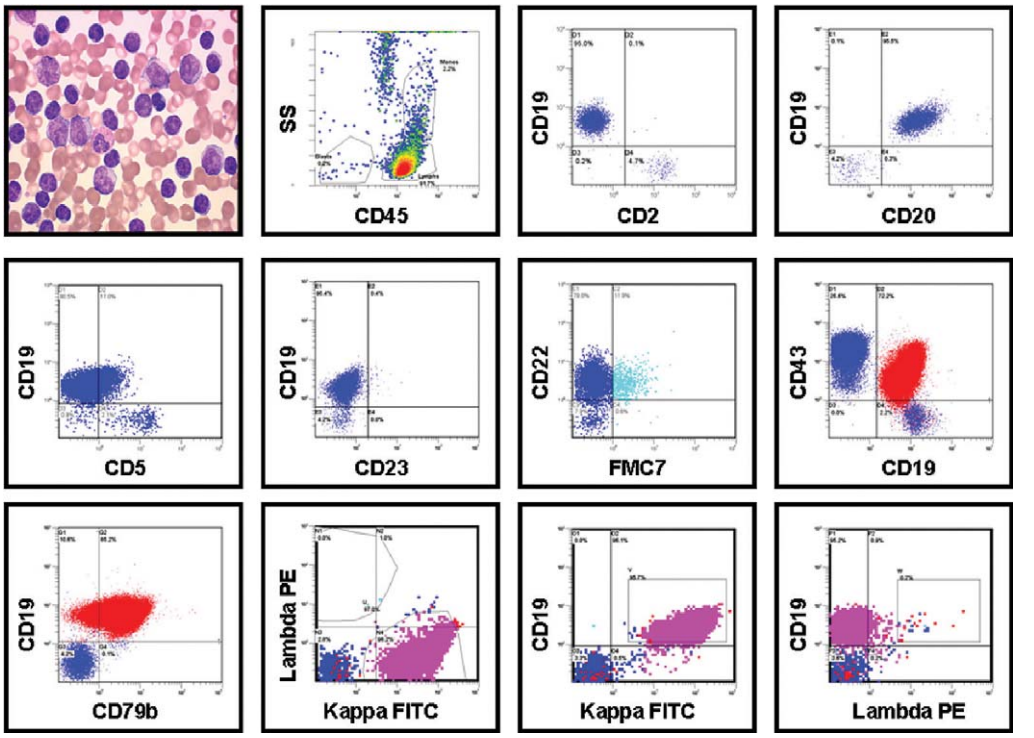


Figure 108-2 • Typical immunophenotypic profile for chronic lymphocytic leukemia (CLL) in transformation to prolymphocytic leukemia (PLL).

novo common lymphocyte precursor cell, more than 55% of the peripheral lymphoid cells will be prolymphocytes. These patients frequently have marked splenomegaly with very little lymphadenopathy. The clinical course is much more aggressive than that of CLL, and the response to standard chemotherapy is suboptimal.[28–30] The de novo form of prolymphocytic leukemia is distinctly different from the prolymphocytic transformation of standard CLL. The immunophenotypic data will help in making these subtle differential comparisons.

Enormous progress has been made over the past decade in defining molecular parameters that will predict the clinical course of CLL, but most important is the task of establishing the basic diagnosis. In fact, as therapy improves for the specific subsets of chronic lymphoid leukemia, it becomes paramount that the correct diagnosis and prognostic profile are established for individual patients.

CLINICAL STAGING: HIGHLY RELIABLE PREDICTORS THAT HAVE WITHSTOOD THE TEST OF TIME

In 1975, Rai and colleagues published a clinical staging system that predicted the overall survival of patients with CLL based on data derived from a physical examination and a hemogram.[31] In Europe, Binet and colleagues popularized another system that conveniently conveys the same basic prognostic prediction regarding survival.[32] These systems have been utilized for more than a quarter of a century in clinical investigation of CLL. In addition to providing a prognostic estimate for the individual patient, the use of these respective systems enabled investigators to compare patient characteristics between clinical trials. While these staging systems are very useful and convenient, there are limitations. In 1986, Rai simplified his five-stage system to three stages: low-risk, intermediate-risk, and high-risk disease. Both systems are useful but primarily define the prognosis at the time of diagnosis. Neither system permits a modification of prognosis as the disease progresses. Table 108-3 provides a description of the Rai staging system.

CLINICAL AND MOLECULAR PROGNOSTIC STUDIES

Over the past 10 years, molecular parameters have been identified within the leukemic cells that predict disease progression. Several investigators have independently shown that CLL can be divided prognostically into two independent subsets: those with IgV gene mutation and those that are unmutated.[2,33] Patients with unmutated IgV gene have a significantly shorter survival than do patients with more extensive IgV gene mutation. The patients with aggressive disease often have a shorter time from diagnosis to requiring therapy for CLL. In addition, the unmutated group of patients tends to have the associated cytogenetic abnormalities that predict shorter time to disease progression following therapy.[34,35] Flow cytometric studies have demonstrated that overexpression of the CD38 antigen on CLL cells defines two similar groups, of which patients who have a higher percentage of leukemic cells with overexpression of CD38 have a worse prognosis.[33,36–38] CD38 is a transmembrane glycoprotein that is widely expressed on a range of cell types. In normal mature B cells, its expression is confined to the germinal center of secondary lymphoid follicles. There has been extensive discussion that overexpression of this membrane protein is associated with a relative lack of IgV mutation and thus is associated with a worse clinical prognosis in CLL. Several studies have classified those patients with more than 7% positive CD38 cells as being at risk for aggressive disease, and others have used the cutoff of 30% positive cells for identifying patients with a worse prognosis.[4] In general, it is much easier to establish the percentage of CD38-positive cells by flow cytometry than by sequencing the B-cell receptor heavy chain to determine whether there is a substantial mutation (>2%) from germline. The application of this flow cytometric assessment of risk is more generally available than attempting to determine whether the patient is in the "unmutated" or the "mutated" form of this disease.

ZAP-70 is a 70-kd tyrosine kinase that normally is required for T-cell receptor signaling. It is expressed in normal T cells and NK cells but not in normal circulating B cells. In addition to the other predictive molecular prognostic parameters, there have been numerous studies showing that the expression of ZAP-70 in circulating leukemic cells from patients with CLL is associated with shorter overall and progression-free survival.[5,6] Several studies have confirmed that patients with expression of ZAP-70 in more than 20% of their leukemic cells will require therapy earlier than will patients who are negative for this protein.[39] However, this testing is difficult to validate, as the reproducibility of the assay varies between laboratories. Therefore, it is not offered by all reference laboratories.

While standard cytogenetics in CLL had been severely limited by banding techniques in cells that were basically trapped in G_0, the growing use of FISH probes to examine leukemic cells in interphase has been remarkably rewarding. We now appreciate that at least 80% to 85% of patients with CLL will have a cytogenetic abnormality that can be defined by FISH.[40] Of patients with an abnormality that is identified by this technique, most will have one abnormality (~50%). Approximately 25% will develop a second abnormality, and another 25% will ultimately have a complex cytogenetic pattern as defined by three or more abnormalities. Patients with a complex karyotype will have a more aggressive clinical course.[41] Dohner and colleagues have defined a hierarchical classification system as defined in Table 108-4 that provides very useful information regarding prognosis in this disease. There is a clear separation in survival curves for each of these cytogenetics subsets.[41]

In an Intergroup Study in the United States, a prospective randomized clinical trial carefully examined the impact of these parameters on the response to therapy. Previously untreated patients with CLL were randomized to receive their initial therapy as either fludarabine alone or fludarabine combined with cyclophosphamide. This

Table 108-3 Stage at Presentation and Outcome of Chronic Lymphoid Leukemia

Rai Stage	Clinical Features	Percent of Cases	Survival
Low risk	Lymphocyte count $> 5 \times 10^9$/L	30	≥10 years
Intermediate risk	Enlarged LN or organomegaly	60	6 years
High risk	Hb < 11 g/dL or Plt $< 100 \times 10^9$/L	10	2 years

Table 108-4 Effect of Cytogenetic Abnormalities on Time to Treatment and Survival

Abnormality	Time to Treatment (months)	Overall Median Survival (months)
17p deletion	9	32
11q deletion	13	79
Trisomy 12	33	114
Normal	49	111
13q deletion	92	133

Data from Dohner, et al.[41]

study had initially been designed in 1997, and the major correlative project was to examine the importance of flow cytometry with detailed immunophenotyping, FISH cytogenetics, immunoglobulin gene rearrangement with an assessment of mutational status, ZAP-70 protein expression, and quantitative analysis of bcl-2 antiapoptotic proteins, p53 mutational status, and other molecular parameters on outcome. A total of 278 patients were enrolled in this Intergroup Study (E2997). Treatment outcomes were disappointing, with low complete remission rate being observed with fludarabine alone (4.6%). Patients who received the combined therapy with fludarabine and cyclophosphamide had a statistically higher complete remission rate (23.4%; $P < 0.013$). Furthermore, the progression-free survival (PFS) with the combined therapy arm of the study was markedly longer: 31.6 months compared to 19.2 months ($P < 0.0001$). The clinical factors that were associated with a better response outcome on this study were interesting: the treatment arm assigned (i.e., combined therapy being better than monotherapy) and the Rai stage (0 or 1) at the time of registration ($P < 0.0001$). In addition, PFS was associated with time from diagnosis until treatment (more than 3 years being better), and the presence of splenomegaly at study entry was associated with a shorter PFS. The extensive correlative laboratory studies showed that FISH cytogenetics were able to identify the patients who were predicted to have a significantly shorter PFS (i.e., those with a del 17p or del 11q23), but the other biomarkers did not predict response to chemotherapy or PFS.[42]

The conclusions from many studies remain that IgV mutational status, ZAP-70 expression, and quantitation of CD38 enable prediction of the overall aggressiveness of the disease in identifying patients with the shorter time from diagnosis until therapy is required. The hope remains that these biomarkers will define the specific groups of patients who would be better served by investigational therapy than by standard treatment. This extensive work of the U.S. Intergroup Study defined the relative contribution of many laboratory parameters in evaluating the overall prognosis for these patients. Some of these parameters will identify the patients who are likely to require therapy earlier than the average. FISH will define the group of patients who are likely to have a shorter PFS with standard chemotherapy and, it is hoped, will assist with risk stratification for future clinical trials attempting to improve on current therapeutic strategies.

Table 108-1 lists a summary of recommended laboratory studies for the initial diagnosis of CLL and prognostic information for treatment planning. The diagnosis can be established by reviewing the peripheral blood smear and documenting that a monoclonal population of neoplastic cells has the characteristic immunophenotypic markers by flow cytometry. A bone marrow aspirate and biopsy are not necessarily needed at the time of diagnosis in an asymptomatic patient. However, the bone marrow aspirate and biopsy become potentially very useful in patients who have anemia, thrombocytopenia, or symptoms of progressive disease.

DIFFERENTIAL DIAGNOSIS

The importance of establishing the correct diagnosis of the specific subtype of chronic lymphoid leukemia cannot be overstated. Patient prognosis and anticipation of the clinical events to follow rest heavily on the accuracy of the diagnosis and staging. Decisions regarding therapeutic intervention for an individual patient rely heavily on risk-adapted biomarkers and the natural history associated with the many forms of these diseases. While a careful review of the morphologic features of the circulating leukemic cells on the peripheral blood smear may be helpful, the modern use of flow cytometry for establishing the immunophenotypic profile is crucial. Furthermore, incorporation of interphase FISH cytogenetics and standard cytogenetics studies assists in further refinement of the disease and its potential response to therapy.

The initial task involves establishing the presence of a monoclonal population of leukemic cells and then further refining the nature of the antigens that are expressed on these cells (as outlined in Table 108-2). The FISH probes will confirm and refine the final decisions for diagnostic classification (see Fig. 108-1). These steps are essential in planning patient management. Although these diseases cannot be cured by currently available pharmacologic agents, the increasing number of patients who are achieving durable remissions has resulted in specific therapies for individual diseases.

The clinical features of presentation can also be helpful in defining the disease process. For example, patients who present with anemia and thrombocytopenia associated with a monoclonal population of B cells in the peripheral blood might have one of many forms of chronic lymphocytic leukemia. Therapy for CLL differs from therapy for CLL/prolymphocytic leukemia, and they both differ from therapy for prolymphocytic leukemia. Patients who present with a low-grade indolent form of chronic lymphoid leukemia with splenomegaly might have either hairy cell leukemia or marginal zone lymphoma. The therapeutic approach to the two diseases is currently very divergent.

Patients who present with severe pancytopenia and a markedly hypocellular bone marrow might actually have a very treatable form of hairy cell leukemia (and not aplastic anemia). Yet the clue might reside in the close examination of the peripheral blood with either morphology or flow cytometry. The outcome for the patient is markedly different depending on the exact underlying diagnosis. While not common, this diagnostic dilemma is encountered in patients with hairy cell leukemia who have a hypocellular marrow with minimal to no splenomegaly. Recognizing the even rarer patient with the variant of hairy cell leukemia might require differentiation from other proliferative forms of chronic lymphoid leukemia. The effort in establishing the correct diagnosis will be justified in selecting the correct therapeutic strategy.

Complications of Chronic Lymphocytic Leukemia from Fatigue to Dysfunctional Immunity and Infection

The diagnosis of CLL is often made in asymptomatic individuals. The most common symptoms associated with early-stage disease are fatigue and occasional lymph node enlargement. Infection represents a frequent cause of morbidity and mortality. Multiple features of this disease contribute to the risks for viral, bacterial, and opportunistic infections.[43] Many patients develop neutropenia either as a consequence of bone marrow infiltration with leukemia or as a consequence of therapy for the disease. Progressive hypogammaglobulinemia develops in approximately 60% of the patients.[44] Abnormalities of complement function as well as intrinsic defects in T cells provide additional factors leading to an excessive risk of infection. T-cell defects are present before chemotherapy but are profoundly and negatively affected following the use of purine nucleoside analogs. The resultant T-cell reductions following fludarabine or pentostatin may persist for a year (or more) after completion of chemotherapy. The increasing use of alemtuzumab for treating either minimal residual disease or drug-resistant leukemia further aggravates the T-cell impairment.[45]

The most common sites for infection involve the respiratory tract, particularly sinopulmonary infections. Skin infections and soft-tissue infections can also occur. Reactivation of herpes zoster must be treated promptly in these immune-compromised patients to avoid excessive morbidity and generalized zoster. *Pneumocystis jiroveci* (formerly *P. carinii*) may develop in patients who have had treatment with both purine nucleoside analogs and additional immunosuppressive therapy (e.g., steroids). Fungal infections may also develop in patients who have received chemotherapy plus additional immunosuppressive therapy. The use of purine nucleoside analogs and monoclonal antibodies to treat the leukemia results in a long-lasting

profound depletion of mature B cells, T lymphocytes, natural killer cells, and monocytes.[46] Consequently, the spectrum of infectious agents for these patients has changed from simple common bacteria to now include opportunistic agents resulting from these profound immune effector cell defects: *P. jiroveci*, Listeria, mycobacteria, cytomegalovirus (CMV), herpesviruses, and Candida.

The risks associated with serious infection markedly increase in patients with advanced disease that is refractory to purine nucleoside analogs. The median survival in patients who are refractory to fludarabine is 13 months.[47] Infection constitutes the major cause of death in this patient population; consequently, prompt attention to a febrile illness is necessary. Appropriate cultures should be secured, and then a decision should be made to cover the most likely source of infection. Considering the many immune defects that accompany this disease, patients with CLL should be treated promptly for symptoms of infection.

In select high-risk patient populations, prophylactic therapy and monitoring for specific infections are warranted.[48] Patients who are receiving combined purine nucleoside analog therapy and other immunosuppressive therapy are often treated prophylactically with trimethoprim-sulfamethoxazole for *P. jiroveci* and with agents to prevent herpetic infection. In patients who subsequently receive alemtuzumab, careful monitoring for reactivation of CMV is necessary.[45] While a recent publication indicated that younger patients might not require prevention for opportunistic infections following therapy of leukemia, the majority of patients with this disease are not young. In addition, consideration should be given to screen for hepatitis or latent tuberculosis in patients who are likely to require combined immunosuppressive chemotherapy plus monoclonal antibody therapy.

Immune Dysfunctional Paradox: Severe Immunodeficiency and Autoimmunity

Autoimmune phenomena present a challenge in management. While patients may present with autoimmune complications of this disease when their leukemic burden is quite low, the decision to treat requires specific attention to the dysfunctional immune system. Barcellini and colleagues recently cataloged the immune complications found in a large number of patients with CLL.[49] This review included both a retrospective and a prospective analysis of 194 cases of autoimmune complications resulting from CLL. Autoimmune hemolytic anemia represented the most frequent complication (129 cases, or 66%). While 89% of these episodes involved a warm IgG antibody, 11% of the patients had a cold hemagglutinin (IgM anti-C) producing the anemia. Autoimmune thrombocytopenia accounted for 35 cases (16%) of the immune complications associated with CLL. They found 30 additional autoimmune complications that did not involve destruction of a hematologic target. For example, bullous pemphigus affected nine of these patients, and Hashimoto's thyroiditis complicated the course for eight patients.

Follow-up data were available for approximately 116 patients who had been identified as having an autoimmune complication associated with their CLL. Recovery was observed in 65% of the patients with autoimmune hemolysis. In addition, 54% of patients with autoimmune destruction of platelets and about 40% of those with other forms of autoimmunity recovered. Unfortunately, 42% of the cases of refractory autoimmune hemolysis were fatal. Paraneoplastic pemphigus associated with this disease may also be fatal, associated with progressive involvement of the oropharynx or as a result of excessive immunosuppression.[50,51] Simply embarking on standard therapy for treating bulk disease in the patient with autoimmune complications of CLL might be quite ineffective in adequately controlling the immune destruction of normal cellular elements. Therefore, careful attention to effective immunosuppressive therapy should be the primary initial objective in dealing with these autoimmune complications of CLL.

COMPLICATIONS OF PROGRESSIVE DISEASE OR HIGH-GRADE TRANSFORMATION

Patients with CLL frequently develop anemia, thrombocytopenia, and neutropenia from progressive infiltration of the bone marrow. Furthermore, enlargement of the spleen can result in pancytopenia from sequestration of cellular elements. Ideally, the therapy of CLL should be initiated before these hematologic parameters have reached dangerously low levels. In following the National Cancer Institute (NCI) guidelines, therapy should be started for progressive anemia (i.e., hemoglobin < 10 g/dL) or severe thrombocytopenia.[52] The least accurate hematologic parameter for deciding on therapy would be the absolute granulocyte count. As the total lymphocyte count increases, the accuracy of determining the absolute granulocyte count decreases.

In deciding on treatment for CLL, a bone marrow examination (both aspirate and biopsy) is appropriate to understand the mechanism for the lowered counts. For example, diffuse infiltration of the bone marrow might explain the presence and the mechanism of either anemia or thrombocytopenia. However, it is essential to be alert to increased platelet destruction as evidenced by persistence of either adequate or increased numbers of megakaryocytes within the bone marrow despite a lowered platelet count. In reviewing the bone marrow, it is important to evaluate the red blood cell precursors to avoid overlooking pure red cell aplasia or the presence of giant pronormoblasts that could signal a concomitant parvoviral infection.[53] A full understanding of the mechanism for bone marrow failure will enable selection of appropriate therapy. For example, patients with anemia and a pure red cell aplasia associated with a parvoviral infection may deteriorate with cytotoxic chemotherapy. The treatment of choice would include initial intravenous immunoglobulin to attempt to eradicate the parvoviral infection before considering other additional therapy. Identification of other unrelated disorders that could contribute to the anemia or thrombocytopenia is equally important. Decreased iron stores or megaloblastic features may signal yet another underlying explanation for decreased production of cellular elements. All of these possibilities reflect the necessity for careful consideration of the basic workup for each patient rather than simply attributing the decrease in blood counts to progression of the CLL.

In addition to progressive leukemic infiltration of the bone marrow, the bulk of the disease may increase, resulting in enlargement of lymph nodes or the spleen. Enlarging lymph nodes or splenomegaly can produce symptoms that require treatment. Progressive increases in the absolute peripheral lymphocyte count can also eventually mandate initiation of therapy. While patients might tolerate circulating absolute lymphocyte counts in the 200,000 range without symptoms, some patients will experience vascular compromise if these counts exceed 300,000/μL. There is enormous variability in how well patients tolerate high lymphocyte counts, but the NCI guidelines caution that rapid doubling of leukemic cells over less than 6 to 12 months usually heralds the need for therapy.

Enlargement of an isolated lymph node area or the development of systemic symptoms including weight loss, fever, and night sweats may indicate transformation to a high-grade lymphoma (e.g., Richter's syndrome).[54] If this is suspected, a biopsy of the suspect lymph node can provide histologic evidence of large cell lymphoma transformation that would require more aggressive therapy, as illustrated in Figures 108-3 and 108-4. Patients with standard CLL may also progress into a prolymphocytic transformation as the pace of the disease increases. This transformation may be suspected if more than 11% but fewer than 55% of the circulating peripheral blood leukemic cells have large single nucleoli. This stage of the disease is not as responsive to standard therapy for CLL and might require consideration of more aggressive intervention if appropriate for the patient.[29,30] The transformation to the more aggressive malignancy may be a consequence either of the underlying compromised immunosurveillance

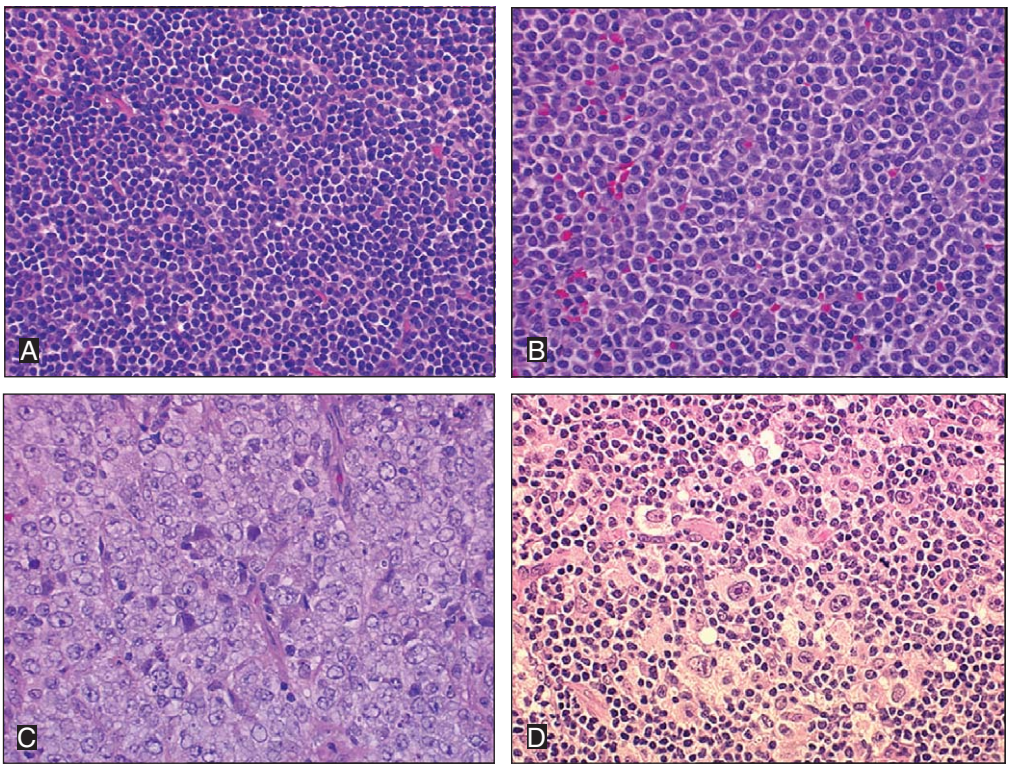


Figure 108-3 • Lymph node sections demonstrating chronic lymphocytic leukemia with transformation. **A,** Small lymphocytic lymphoma (SLL). **B,** SLL with prolymphocytic transformation. **C,** SLL with large cell transformation. **D** SLL with large cell transformation and Reed-Sternberg Hodgkin-like cells.

or as a result of the therapy for the leukemia. Epstein-Barr virus infection has also been implicated in this transformation process for a limited number of patients with Richter's transformation.[55–57]

Although the actual cause of these high-grade malignant transformations has been debated, cases have been documented to show the same clonal features both within the initial leukemia and in the high-grade malignant cells. Furthermore, other cases clearly show that a separate clonal disease process has occurred in the aggressive malignant tissue. The rate of high-grade malignant transformation may vary from 1% to 10% of patients with CLL over an extended period of time from the initial diagnosis.

The spectrum of malignant lymphoid diseases that have been associated with the aggressive transformation process in CLL include large cell lymphoma, Hodgkin's disease, prolymphocytic leukemia,

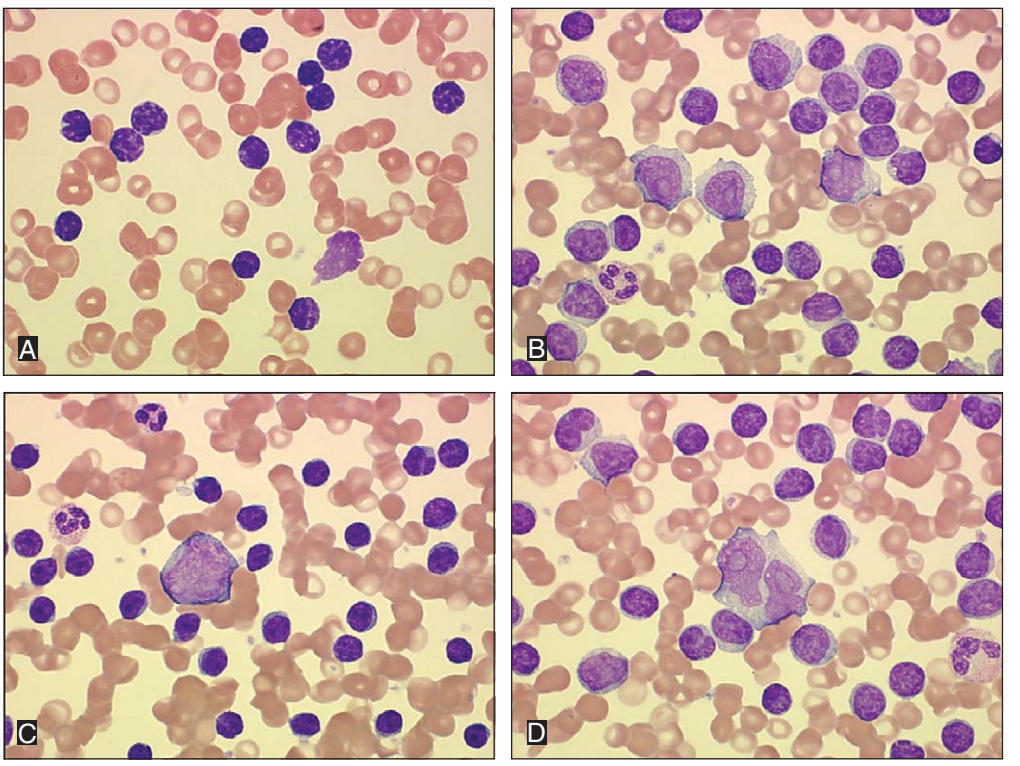


Figure 108-4 • Peripheral blood morphology demonstrating CLL with transformation. High magnification (100×) of Wright-Giemsa-stained blood smears representing **A,** chronic lymphocytic leukemia (CLL), **B,** CLL with prolymphocytic transformation, **C,** CLL with large cell transformation, and **D,** CLL with large cell transformation and circulating Reed-Sternberg-like cells.

multiple myeloma, and, rarely, acute lymphoblastic leukemia. Patients may complain of progressive "B" symptoms, including night sweats, fever, and unintentional weight loss. They may have abdominal pain or discomfort associated with progressive adenopathy or splenomegaly. Laboratory features may include progressive anemia, thrombocytopenia, and a rapidly rising absolute lymphocyte count. Patients frequently have an associated increase in lactate dehydrogenase or develop a progressively increasing paraprotein. Approximately 40% of CLL patients with high-grade transformation may develop extranodal malignant lymphoid infiltrates in diverse locations (e.g., pleura, central nervous system, oropharynx, skin, lung, bone, or gastrointestinal tract).

Patients with malignant transformation of the large cell lymphoma variety have a poor prognosis, with reduced response rates to standard chemotherapy. Allogeneic stem cell transplantation is being explored in this setting, but the current overall survival is less than 6 months, warranting enrollment of patients into well-organized clinical trials.[58] Patients with alternative forms of lymphoid malignancy are treated with the therapy that best targets the disease type of transformation (e.g., ABVD regimen for those who have developed a transformation resembling Hodgkin's disease).

SECONDARY MALIGNANCIES

The SEER database has estimated the risk of patients with CLL developing a secondary malignancy to be 20%. Others have suggested that there is a threefold increase in comparison to age-matched control patients. The Veterans Administration estimated that 14.4% of patients with CLL had another nonlymphoid malignancy and that the second malignancy is a common cause of death.[59] The most frequent types of solid tumors include lung cancer, gastrointestinal carcinomas, melanomas, and other skin cancers.[60] Consequently, it is advisable to screen patients for these entities to ensure early detection.

Patients with CLL have also been rarely reported to have concomitant myelodysplasia, myeloproliferative disorders, or even myeloid leukemia.[61,62] Patients who have been treated with extensive alkylating agents are potentially at increased risk for therapy-induced acute myeloid leukemia.[63] There has been concern that purine nucleoside analogs in conjunction with alkylating agents may further increase this risk. Treatment-induced leukemia is usually preceded by a period of myelodysplasia.

PATIENT MANAGEMENT

The NCI has defined general principles for initiating therapy for CLL.[52] Once the diagnosis has been established, it is quite important to have an extensive discussion with the patient and family to define a course of action (Box 108-1). Patients who realize that they have an incurable malignancy frequently are anxious to initiate treatment. For asymptomatic patients with low-stage disease, it is important to explain that careful follow-up is an appropriate alternative to treat-

Box 108-1. MANAGEMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA

Most patients with CLL ultimately require therapy. Because this is an incurable form of leukemia, the decision regarding therapy is judiciously made on the basis of symptoms or signs of anemia or thrombocytopenia. Adequate counseling of the patient to pursue an approach of watchful waiting requires extensive explanation. Patients must be informed that current therapeutic agents can further compromise the immune system and cause profound myelosuppression. Therefore, the decision to treat must be balanced with careful consideration of the risks of therapeutic intervention.

The current therapy based on a purine nucleoside analog (e.g., fludarabine) alone or in combination with another single agent (e.g., cyclophosphamide or rituximab) may result in a complete remission in approximately 5% to 25% of patients. Although earlier reports suggested higher complete remission rates (particularly in comparison to chlorambucil), the latest multi-institutional studies are reporting complete remissions in this range. The highest complete remission rates have been reported with triple drug therapy. Additional patients may achieve symptomatic improvement with a less than complete remission. In the context of a well-designed clinical trial, it may be appropriate to attempt to achieve eradication of minimal residual disease. However, in standard practice, there are not sufficient data to recommend continued therapy beyond 6 months for the purpose of minimal residual disease eradication in light of the potential infectious complications.

A standard course of fludarabine would be 25 mg/m^2/day intravenously on days 1 through 5 every 28 days. Each course may be repeated up to four to six cycles if there is evidence of improvement and no excessive toxicity is observed. Alternative regimens may incorporate either rituximab, cyclophosphamide, or both agents. Pentostatin is another purine nucleoside analog that has been approved for refractory hairy cell leukemia. In clinical trials, the combination of pentostatin, rituximab, and cyclophosphamide has been reportedly effective and well tolerated. However, it is important to understand that this use is not currently FDA approved for CLL.

In patients who relapse, repeat therapy may be useful if the initial response to a specific regimen was adequate and the response lasted for more than 1 year. The repeated use of fludarabine-based regimens can have a serious impact on bone marrow reserve. Consequently, patients should not be routinely exposed to repeated cycles of this agent without confirming that an objective response was demonstrated with adequate patient tolerance, including a follow-up bone marrow biopsy to confirm sufficient marrow reserve. While alemtuzumab has also been useful in patients who have failed to respond to fludarabine, this agent does not produce responses in those with bulky disease. Furthermore, alemtuzumab may produce excessive immunosuppression. Patients on this agent should receive prophylaxis to prevent infectious complications commonly encountered in the heavily immunosuppressed patients and should be monitored for reactivation of CMV antigenemia with institution of pre-emptive therapy to prevent CMV disease.

In patients with an autoimmune complication of CLL, the process must be controlled with optimal immunosuppressive therapy prior to initiating standard cytotoxic therapy. In patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia, prednisone at 1 mg/kg/day is appropriate until the process is controlled. At this point, a careful taper is pursued. Modifications may be required including the addition of steroid-sparing agents (e.g., cyclosporine) in select cases. In all patients, consideration for prophylaxis against opportunistic infection should be incorporated with the administration of immunosuppressive therapy (e.g., against *Pneumocystis jiroveci* and herpes simplex virus/varicella-zoster virus).

Patients with resistant disease deserve consideration for an experimental approach. Some patients may enroll in stem cell transplant protocols with a matched related or unrelated donor. Reduced-intensity stem cell transplantation has been increasingly explored. In addition, novel therapeutic agents (e.g., flavopiridol) have induced durable responses in heavily treated patients, including those with high-risk cytogenetic features. In general, all patients with CLL should be encouraged to participate in clinical research in an effort to improve the ultimate clinical outcome of this incurable disease.

ment and what changes in symptoms or disease activity would prompt therapy. Inappropriate early intervention can increase the risks of immunosuppression without a long-term clinical benefit.

Current recommendations for initiating therapy include development of symptomatic disease with bulky lymphadenopathy, symptomatic organomegaly, or constitutional symptoms. Other indications for treatment may include development of either anemia or thrombocytopenia, rapid doubling of the absolute lymphocyte count (i.e., in less than 6 to 12 months), or an absolute lymphocyte count at which complications of tumor lysis or vascular compromise may be expected (e.g., >300,000/μL). The absolute value associated with leukostasis due to lymphocytosis is variable; some patients are able to tolerate higher values, and others develop symptoms of vascular compromise at lower levels.

Before initiating a course of cytoreductive therapy, it is essential to have a full understanding of the disease process. For example, there are many potential causes for either anemia and/or thrombocytopenia in patients with CLL. Consequently, there is a strong indication for obtaining a bone marrow aspirate and biopsy before starting on a therapeutic course. It is essential to evaluate the pattern of CLL infiltration into the bone marrow space. A careful assessment of red blood cell mass, numbers of megakaryocytes, and maturation of the granulocyte series will provide clues if there is a concomitant component of destruction as well as decreased production contributing to the reason for cytopenias. Careful evaluation of the iron stores and a search for other evidence of nutritional deficiency are important before starting on cytoreductive therapy. Patients with myelodysplasia in addition to infiltration of the bone marrow space by CLL will not always tolerate standard doses of cytotoxic chemotherapy. Finally, patients with more than one cause for anemia need to have a careful assessment of the etiology of bone marrow failure before simply treating the leukemia.

In patients who have progressive lymphadenopathy or splenomegaly, there may be value in documenting the extent of disease by imaging studies of the chest and abdomen. However, while this may be helpful in documenting a response to therapy it is not absolutely required as part of the clinical staging of CLL. There is an ongoing discussion of the necessity for computed tomography scans in staging these patients. In a patient who is suspected as having a malignant transformation to an aggressive lymphoma, a positron emission tomography scan may be helpful in directing the biopsy for confirmation of this complication.[64]

A thorough understanding of comorbid medical conditions in these patients is essential to optimal management. A careful assessment of renal and cardiac function may affect the selection of chemotherapeutic regimen. Dose modifications for either chemotherapy or immunotherapy or other agents that are used to treat complications of this disease require an understanding of these laboratory parameters. For instance, knowing whether a patient has diabetes could have an impact on whether or not steroids are included as part of the therapeutic plan.

As was noted previously, patients with CLL have altered immunity. Treatment with currently available therapies such as the purine analogs, rituximab, and alemtuzumab may significantly impair infectious immunity and increase susceptibility to viral reactivation and opportunistic infections. Prior exposure to tuberculosis or hepatitis may increase the risks associated with administration of some immunosuppressive agents that are used to treat this disease. It is recommended that hepatitis and CMV serologies are assessed prior to initiating therapy, as a positive result may affect the choice of treatment. Prophylactic antimicrobial therapy for prevention of herpes simplex virus/varicella-zoster virus and *P. jiroveci* is utilized during purine nucleoside analog therapy in a large proportion of patients and is particularly recommended for older patients, those with a history of varicella-zoster virus reactivation, or patients who have received prior therapy. Monitoring for CMV is required during treatment with alemtuzumab, and pre-emptive therapy is utilized to prevent CMV infection, which in some patients may be fatal. Careful attention to the entire medical history is imperative.

In patients who have developed an autoimmune complication of their underlying CLL, the plan should initially be directed at stabilizing that process before embarking on standard cytoreductive therapy. Patients with autoimmune hemolytic anemia or autoimmune thrombocytopenia are initially started on prednisone (e.g., 1 mg/kg/day) until the destructive process is controlled. At that time, the prednisone is cautiously and gradually tapered with close monitoring of the autoimmune process. In those patients who fail to respond to high-dose prednisone or are unable to tolerate this agent, cyclosporine or other immunosuppressive agents may be helpful and steroid-sparing. In selected patients, splenectomy affords an option to control either red blood cell or platelet destruction.

Assessment of the risks associated with initial therapy may dictate that the first course of therapy be delivered in an inpatient setting, depending on the age and medical condition of the patient. Patients who have a high peripheral absolute lymphocyte count can develop acute decompensation if confronted with tumor lysis following chemotherapy. Consequently, allopurinol is used for the first course of therapy. Patients might also experience respiratory decompensation and a cytokine release syndrome following the rapid administration of rituximab. Therefore, a graded approach to administration of the initial dose of this monoclonal antibody is required.[65] Preparation with diphenhydramine, acetominophen, and possibly steroids might be necessary for the initial course of therapy.

Selection of Chemoimmunotherapy for Chronic Lymphocytic Leukemia

In the development of a careful therapeutic plan, it will be important to select the optimal agents and schedule of administration. Until recently, the standard of care in the United States had been the use of alkylating agents either alone or with prednisone. Some investigators in Europe successfully utilized combined chemotherapy (CHOP or CAP), and in the United States, investigators have utilized COP or EPOCH regimens for treating CLL.[66] Chlorambucil had been the mainstay of oral chemotherapy for this disease in the community-based practice of medicine.[67,68]

In the early 1980s, Grever introduced the purine nucleoside analogs for patients with advanced and resistant disease.[69] The overall responses to either pentostatin or fludarabine were compromised because many of the patients had substantial prior therapy. However, pentostatin was capable of inducing a complete remission in even very heavily pretreated patients. Up to 10% of heavily pretreated patients could achieve a complete remission with single-agent fludarabine. Subsequent studies by M.D. Anderson using fludarabine in untreated patients found that up to 30% achieved a complete remission.[70] Combination studies over the past 10 years have shown that fludarabine is most effective when combined with another agent (either rituximab, cyclophosphamide, or both).

A prospective randomized Intergroup Study reported by Rai and colleagues showed that single-agent fludarabine was superior to chlorambucil for inducing a complete response and a durable remission.[68] Two additional randomized studies confirmed the benefit of fludarabine over standard therapy.[71,72] Although fludarabine is primarily approved for relapsed disease by the FDA, the off-label use of this agent as frontline therapy is common practice. There are continued efforts to improve the responses by combining fludarabine with other effective agents in this disease. Byrd and colleagues reported a prospective randomized trial in which patients were assigned either to fludarabine administered either simultaneously or sequentially with rituximab (i.e., the fludarabine was administered first, and the rituximab was delivered after the courses of purine analog were completed). There was a statistically significant improvement with the simultaneous administration of the two agents.[73]

Patients who have been treated with the combination of fludarabine and cyclophosphamide have been reported to have a complete remission rate in the 40% to 50% range with a median PFS of 33 to 44 months following achievement of response.[74–76] Most recently, the M.D. Anderson group reported the results of their trial, which included fludarabine, cyclophosphamide, and rituximab (FCR).[77] In previously untreated patients, complete response rates of 70% were reported, many patients being free of microscopic residual disease by flow cytometry and polymerase chain reaction. The median age of this group was 58 years. In this study, 33% of the patients were reported to have Rai stage III or IV disease.[78] While these results are currently the best reported response rates to date, there have not been as yet many confirmatory studies from other institutions. This regimen was felt to be well tolerated, but in older patients, myelosuppression with advanced stages of disease could be prolonged. There is one study from Tam and colleagues that followed the same FCR regimen.[79] In their report, 12 patients with CLL received this regimen as initial therapy for their CLL/SLL. Eight patients (67%) achieved a complete remission, and three additional patients achieved a nodular partial response. Patients with previously untreated disease were found to have the longest PFS. The median age of the patients in this small trial was similar to that in the M.D. Anderson report.

In another recently reported triple agent combination utilizing pentostatin, cyclophosphamide, and rituximab (PCR), the complete remission rate in previously untreated patients was 41%.[80] This regimen was equally effective in patients who were younger or older than 70 years of age. Patients who achieved a complete remission had a median duration of remission of 35.6 months. In contrast to the M.D. Anderson report with FCR, the median age of patients on this trial was 63 years (range: 38 to 80 years). Furthermore, 53% of patients had Rai stages III and IV disease. This study presented many of the molecular characteristics confirming that the patient population was indeed high-risk; 71% were unmutated for IgV, 34% were CD38-positive and ZAP-70-positive, and 36% had high-risk cytogenetics by FISH analysis. The regimen was well tolerated with no evidence of excessive morbidity. In contrast, the M.D. Anderson FCR regimen was associated with substantial myelosuppression, and 58 (26%) could not complete the intended six courses of FCR owing to persistent cytopenias. The study from Kay and colleagues involved two institutions, which may more closely reflect the community experience.[80] The differences between ages and stages of disease in the PCR study and FCR study make direct comparisons difficult. It is to be hoped that additional studies will be reported to confirm the encouraging complete remission rate observed with FCR at M.D. Anderson. Additional time will also enable an accurate estimate of response duration, which, on the basis of available data, appears longer than that reported with the PCR regimen. The German Cooperative Study Group for CLL currently has a multi-institutional study in progress that has randomized patients to fludarabine and cyclophosphamide versus FCR. In addition, it is hoped that a U.S. Intergroup trial will soon be launched that will prospectively compare the optimal regimens in a multi-institutional setting with comparably high-risk patients on each of the respective arms.

Alemtuzumab is a monoclonal antibody directed at human CD52, which is expressed on most mononuclear cells, including CLL cells. Alemtuzumab is currently FDA approved for treatment of fludarabine-refractory CLL and is associated with overall response rates up to 80% in untreated patients and up to 40% in previously treated patients.[81–83] Complete remissions may be achieved in a small percentage of patients. Alemtuzumab is particularly effective in patients with T-cell prolymphocytic leukemia and in B-cell CLL with deletions of 17p.[84,85] Its effectiveness is limited in patients with bulky lymphadenopathy, particularly those with lymph node areas greater than 5 cm in diameter. It should be noted that alemtuzumab is associated with severe myelosuppression as well as profound dysfunction of cellular immunity, necessitating antimicrobial prophylaxis during and after therapy as well as surveillance for CMV reactivation.[45]

Minimal residual disease status is defined as achievement of a complete remission by NCI-WG criteria but with persistent disease detectable on four-color flow cytometry. Improved outcomes in patients who achieve complete remissions without detectable minimal residual disease have led some researchers to investigate the potential benefit of therapy aimed at eradication of minimal residual disease following standard therapy. One study in which alemtuzumab was used to eradicate minimal residual disease found a statistically significant treatment-free interval and overall survival in patients achieving negative minimal residual disease status.[86] However, the high percentage of toxicities in terms of infections raises questions about the risk-benefit ratio of this approach. Furthermore, conclusions of superiority of one approach over another must be cautiously applied. Analysis of patient outcome after achieving negative minimal residual disease can be validly assessed by using a specific fixed landmark following therapy.[87] It is exciting that achievement of negative minimal residual disease status might have an impact on patient outcome, including survival, but study design is important in coming to these conclusions.[88] Future studies using agents that are less likely to cause severe immunosuppression could lead to improved outcomes with less toxicity. At the present time, eradication of minimal residual disease with alemtuzumab is recommended only in the context of a clinical trial.

Many ongoing studies are also exploring the value of eliminating residual microscopic disease with other agents, including the novel cyclin-dependent kinase inhibitor flavopiridol, which is one of the most active agents in patients with heavy exposure to other cytoreductive therapy.[89,90] This agent does not appear to significantly increase the risk of opportunistic infection.[91] Consequently, studies are under way to evaluate the contribution of this agent to patients with microscopic residual disease in hopes of enhancing the quality and number of complete remissions that are achieved with standard cytoreductive therapies.

In Figure 108-5, an algorithm is presented that suggests the current therapeutic options for patients with CLL who require initial

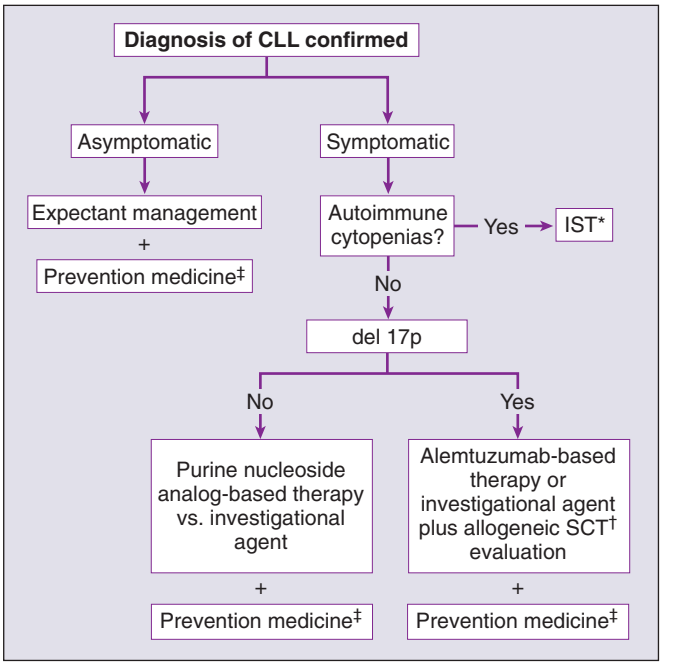


Figure 108-5 • Chronic lymphocytic leukemia initial treatment algorithm. *Immunosuppressive therapy, followed by standard therapy if indicated. †Allogenic stem cell transplantation if indicated. ‡Cancer screening, immunization, and management of infectious complications. Alemtuzumab is ineffective for bulky disease.

Table 108-5 Allogeneic Stem Cell Transplantation Using Reduced Intensity Conditioning Regimens in Chronic Lymphoid Leukemia*

Center	*N*	Median Age	Regimen	aGVHD (%)	cGVHD (%)	TRM (%)	EFS (%)	OS (%)
Germany 2003	30	53	FluBuATG	56	75	15	67 at 2 y	72 at 2 y
Spain 2005	30	53	FluMel	40	76	22	72 at 6 y	70 at 6 y
Britain 2006	41	54	Alemtuzumab based	41	33	26	45 at 2 y	51 at 2 y
Seattle 2007	82	55.5	FluTBI	58	53	24	44 at 4 y	55 at 4 y

aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; EFS, event-free survival; OS, overall survival; TRM, treatment-related mortality.
*The majority of these patients were heavily pretreated, and these results reflect outcomes from both related and unrelated donor transplants.

therapy. In addition, patients who relapse following their initial therapy require consideration. If the initial relapse or progressive disease requiring therapy develops in less than a year following the first regimen, then an alternative therapeutic plan should be considered. In patients who have a long-standing initial response and then relapse, consideration for utilizing a similar regimen may be reasonable. The long-term effects of multiple cycles of fludarabine (particularly in combination with an alkylating agent) raise concern about the impact on the bone marrow reserve as well as the potential for developing myelodysplasia.

Stem Cell Transplantation for Chronic Lymphocytic Leukemia

Both autologous and allogeneic hematopoietic stem cell transplantation have been studied for the treatment of CLL. Clinical trials of high-dose chemotherapy with autologous stem cell support have shown high rates of complete responses and, in some cases, improved overall survival when compared with standard chemotherapy even in high-risk patients.[92] However, despite these encouraging responses, there has been no plateau in the survival curve, indicating the lack of curative potential with this therapy. In addition, the treatment-related mortality may be as high as 10% and there is an additional increased risk of late development of myelodysplastic syndrome post-transplantation.[93] Patients who fail to achieve minimal residual disease status are likely to relapse early, and further relapses are usually heralded by loss of minimal residual disease status. Autologous stem cell collection may be hampered by prior therapy with purine nucleoside analogs, which additionally might limit the application of this therapy.[94]

Considering that CLL is currently incurable with either standard or high-dose chemoimmunotherapy, there is hope that allogeneic stem cell transplantation might have substantial benefit for high-risk patients. A graft-versus-leukemia effect has been demonstrated by the effectiveness of donor leukocyte infusions to induce remissions in patients who relapse post-transplantation and by a plateau in the survival curve in long-term follow-up of these patients.[95,96] Increasing agreement regarding allogeneic transplant eligibility criteria has facilitated the identification of patients who should be considered for this potentially curative approach.[97] As improvements in treatment-related mortality using reduced-intensity conditioning regimens have extended the eligibility for allogeneic transplantation to older patients and those with comorbid illnesses, eligibility criteria have expanded in recent years. These criteria will vary by transplant center, but certainly, younger patients who have drug-resistant or relapsed disease should be aggressively evaluated for nonmyeloablative allogeneic stem cell transplantation. A consensus regarding who should be considered might include younger patients with nonresponsive or early relapsing disease (within 12 months), patients who relapse within 24 months following therapy with a purine-based regimen, and patients with cytogenetic abnormalities predicting a shorter PFS following intensive chemoimmunotherapy.[8,88,98] The high success with engraftment, comparatively low treatment-related mortality, reasonable rates of acute and chronic graft-versus-host disease, and overall disease control have been encouraging. A review of recent studies using reduced-intensity conditioning regimens is summarized in Table 108-5.[47,99–101] Importantly, with improvements in the treatment and prophylaxis of graft-versus-host disease, there are decreasing differences in adverse outcomes between related and unrelated donor allogeneic transplant recipients; therefore, the lack of a sibling donor should not be considered a barrier to transplantation. As extensive prior therapy and advanced disease are associated with diminished disease-free survival post-transplantation, identification of potential patients should be pursued before the candidate has deteriorated. Considering the increased incidence of clonal lymphocytosis in relatives of patients with CLL, caution should be employed in screening a potential donor.

The decision regarding the use of a myeloablative conditioning regimen versus a reduced-intensity conditioning regimen is based on patient status at the time of transplantation. Younger patients without comorbid illnesses who have poorly controlled disease might benefit from myeloablative conditioning. Conversely, inferior outcomes have been demonstrated from using reduced-intensity conditioning in patients with extensive previous treatment, dense infiltration of the bone marrow with leukemic cells, and poor nodal disease control. Prospective randomized studies comparing the two treatment modalities are not available; however, one situation in which myeloablative conditioning has been shown to be clearly superior is in Richter's transformation, with a proportion of patients achieving long-term disease control but no patients surviving using reduced-intensity conditioning or conventional chemoimmunotherapy.[102]

As the role for allogeneic transplantation in CLL becomes more clearly defined and experience widens, further advances in prevention and treatment of graft-versus-host disease, management of relapse post-transplantation, and optimal donor selection will no doubt expand its application. Patients who are being offered an opportunity for stem cell transplantation should be vigorously persuaded to participate in ongoing active clinical research protocols.

OTHER B-CELL CHRONIC LEUKEMIAS

The use of immunophenotype analysis is critically important in understanding the variety of chronic lymphoid leukemias as depicted in Table 108-2 and Figures 108-3 through 108-6.

Prolymphocytic Leukemia

Galton described the distinct clinical entity of de novo prolymphocytic leukemia as a lymphoproliferative disorder with a more aggressive clinical course than CLL, occurring in older patients, and with

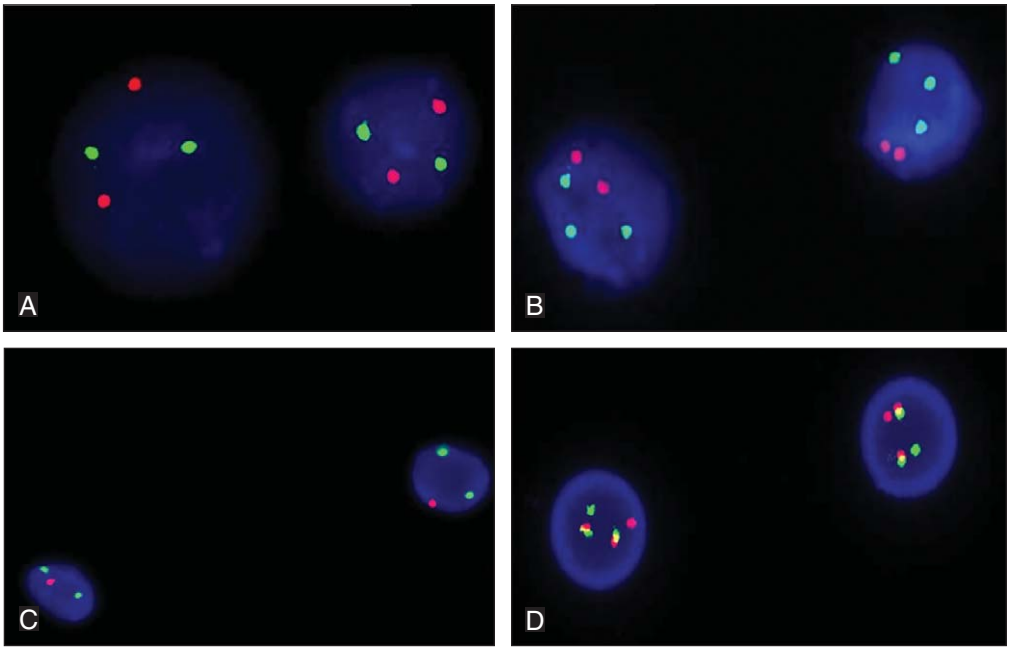


Figure 108-6 • Examples of fluorescence in situ hybridization (FISH) panels: **A,** Normal signal for 11q23-ATM locus (*green*) and 17p13-p53 locus (*red*). **B,** Trisomy of chromosome 12 (*green centromeric probe*) and normal signal for 13q14 (*red*). **C,** Deletion of 17p13-p53 locus (*red*) and normal signal for 11q23–ATM locus (*green*). **D,** Fusion signal (*yellow*) for 11q13-Bcl-1 locus (*red*) and 14q32-IgH locus (*green*) c/w translocation t(11;14)(q13;q32) Bcl-l-IgH. **D,** represents malignant cells from mantle cell lymphoma.

a high peripheral lymphocyte count with a predominance of prolymphocytes.[103] The cells have a distinct large nucleolus and represent more than 55% of the circulating neoplastic cells. Patients with prolymphocytic leukemia frequently have enlarged spleens without impressive lymphadenopathy.[29] The immunophenotypic profile differs both from that of CLL itself and that of the prolymphocytic transformation of CLL (CLL/prolymphocytic leukemia; shown in Fig. 108-2). Accurate recognition of this entity is important because the response to standard therapy for CLL is suboptimal.[83] Although several case studies show patient responses to purine nucleoside analogs, the projected median survival for this disease is shorter than that with CLL.

Hairy Cell Leukemia

In 1958, Bouroncle and colleagues described the clinical features of hairy cell leukemia (HCL).[104] This entity is discussed in Chapter 109.

Additional Lymphomas with Circulating Neoplastic Cells That Can Be Confused with Chronic Lymphocytic Leukemia

Mantle cell lymphoma (MCL) may present with a circulating neoplastic cell that morphologically can be confused with CLL. However, the distinctive immunophenotypic profile and the diagnostic cytogenetics that are characteristic of the t(11:14) demonstrable by FISH or the expression of cyclin D1 will enable this entity to be recognized (shown in Fig. 108-6). Considering the more aggressive clinical course of MCL and the requirement of different chemotherapy, this diagnostic distinction is critically important. Concern for recognizing this early in the course of the disease has prognostic and therapeutic implications and has been the underlying reason for recommending that FISH and immunophenotypic analysis include the appropriate markers and probes for this purpose.

Marginal Zone Lymphoma

Marginal zone lymphoma may also present with circulating lymphoid neoplastic cells, making the distinction from CLL important. This entity may be indolent, but diagnostically and prognostically, it is different from CLL.[105–110] Patients with marginal zone lymphoma have been reported to respond to either splenectomy or rituximab, depending on the extent of bone marrow involvement and cytopenias.[102]

Lymphoplasmacytic Lymphoma

Patients with this indolent B-cell malignancy may present with features resembling both CLL and Waldenström's macroglobulinemia. The neoplastic cell morphologically resembles a plasmacytic lymphocyte. Immunophenotypically, the distinction can be made with respect to this entity as described in Table 108-2.

Chronic T-Cell Leukemias

Finally, a host of chronic T-cell leukemias and lymphomas are important to recognize in establishing the differential diagnosis. Patients with cutaneous T-cell lymphoma often have circulating abnormal lymphoid cells that can be distinguished immunophenotypically as being of T-cell origin. Most of these patients have a history of recurrent skin manifestations of the underlying disease. Patients with cutaneous T-cell lymphoma eventually progress to have more extensive lymphadenopathy and increasing complications with infection as a result of impaired immune function.[108]

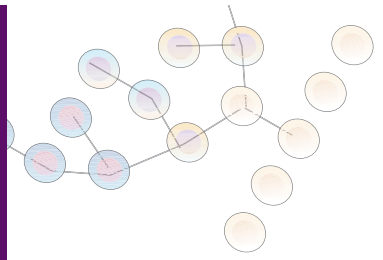
Patients with T-prolymphocytic leukemia present with very high lymphoid counts, splenomegaly, progressive lymphadenopathy, and bone marrow failure. These patients are older and less responsive to standard chemotherapy. Alemtuzumab has been reported to provide some therapeutic response, but there is a clear need for experimental approaches to improve on the therapy of this disease.[85,109,110]

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109 Hairy Cell Leukemia

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SUMMARY OF KEY POINTS

- Hairy cell leukemia (HCL) is an uncommon clonal B-cell lymphoproliferative disorder.
- Physical findings generally are confined to splenomegaly.
- The purine analogs are the therapeutic agents of choice today.
- Most patients who receive treatment with cladribine or pentostatin enjoy prolonged survival.
- BL22, an immunoconjugate of an anti-CD22 antibody linked to a truncated *Pseudomonas* exotoxin A, is a novel agent that has been very effective in the management of relapsed and refractory HCL.

INTRODUCTION

HCL is a rare chronic B-cell lymphoproliferative disorder with unique morphologic features and an excellent prognosis. Bouroncle described 26 patients in 1958 with what then was called "leukemic reticuloendotheliosis" and are credited with the initial description of HCL as a distinct clinical entity.[1] The disease is characterized by splenomegaly, pancytopenia, and infiltration of the bone marrow with lymphocytes that have irregular cytoplasmic projections when identified in the peripheral blood.[2,3] Although the origin of the malignant cell was unclear for some time, immunoglobulin gene rearrangements confirm that the disease is a clonal B-cell malignancy.[4–6] The pattern of expression of B cell-associated surface antigens (described later on) reflects a degree of differentiation between the mature B cell of chronic lymphocytic leukemia and the plasma cell of multiple myeloma.[7,8] A majority of patients have few symptoms at the time of diagnosis. Occasionally, however, patients present with life-threatening pancytopenia, symptomatic splenomegaly, serious infections, or constitutional signs and symptoms justifying treatment, or such problems may develop later in the disease course.[9,10]

Treatment strategies have evolved relatively rapidly during the last 50 years. Splenectomy was the first effective treatment described and remained the therapeutic modality of choice for many years. Although the mechanism of benefit is not clear, removing the spleen leads to normalization of the peripheral blood counts in approximately one half of all patients.[11–14] Interferon-α induces a high overall response rate; however, most responses are partial.[14–21] The most remarkable progress has occurred with the introduction of the two purine analogs, 2′-deoxycoformycin (2′-DCF; i.e., pentostatin)[22–33] and 2-chlorodeoxyadenosine (2-CdA; i.e., cladribine).[24,34–44] Most patients with both previously treated and untreated HCL achieve durable complete remission (i.e., CR) with either of these agents. With use of molecular techniques, however, minimal residual disease (MRD) can be identified in most if not all patients, suggesting that most patients are not actually cured of their disease. Nevertheless, with either purine analog, a majority of patients enjoy prolonged periods of progression-free and overall survival.

EPIDEMIOLOGY

Relatively little is known about the epidemiology of HCL, partly because of its rarity. In the United States, HCL represents 2% of adult leukemias, with only approximately 600 to 800 new cases diagnosed each year.[45,46] Although anecdotal reports of familial HCL have been published, no clear genetic predisposition has been recognized.[47–53] The median age at diagnosis is 52 years, and for unclear reasons, the disease occurs in men more often than in women, with a sex ratio of approximately 4 : 1.[54] Although reported incidence rates are similar in the United States and Great Britain,[45,46] classic HCL is rare in Japan, where a distinct variant form has been described.[55–57]

ETIOLOGY AND PATHOGENESIS

The etiology of HCL has not been determined. An association with exposure to benzene,[58,59] organophosphorus insecticides,[60] or other solvents[61] has been suggested but has not been confirmed.[62] Exposure to radiation,[63] agricultural chemicals,[59] or wood dust[46] and a previous history of infectious mononucleosis[61] also have been suggested as potential associations. Among a majority of patients, however, no such exposures can be identified. Cyclin D1, an important cell cycle regulator, may play a role in the molecular pathogenesis of HCL. Overexpression of the cyclin D1 protein has been described in HCL patients.[64,65] Unlike in mantle cell lymphoma, 11q13 rearrangements are not detected in most patients with HCL, suggesting other mechanisms of gene deregulation.[65]

The hairy cell may be derived from the memory B cell because the genome-wide expression profile is close to that of post-germinal center B cells.[66] Evidence suggests that hairy cells may come from B cells of the splenic marginal zone because hairy cells have a splenic expression signature that reflects tissue components, such as the marginal zone, that are not well represented in lymph node tissue.[67] However, expansion of the red pulp of the spleen, so characteristic of HCL, is in contrast with expansion of the white pulp, which involves the splenic marginal zone. Hairy cells express Bcl-2, an universal inhibitor of apoptosis.[68] Survival of hairy cells may be

further promoted by overexpression of FLT3, which activates the phosphatidylinositol-3 kinase (PI3K) pathway that activates anti-apoptotic signals.[66,69] Hairy cells produce basic fibroblast growth factor (bFGF) and overexpress bFGF tyrosine kinase receptor,[66,70] which can activate the PI3K-Akt cascade.[71]

The characteristic appearance of the hairy cells is due to expression of β-actin, which is polymerized to F-actin, located in the cortical cytoskeleton, in the peripheral part of the cell, that serves to support the hair-like projections.[66] The actual hair-like projections probably are due to increased expression of pp52, a leukocyte-specific intracellular phosphoprotein, that binds to F-actin.[72,73]

CLINICAL PRESENTATION

HCL should always be considered in the differential diagnosis for a middle-aged man presenting with splenomegaly and pancytopenia. Circulating hairy cells usually are present in the peripheral blood, but they may be difficult to detect. The initial evaluation should include a history and physical examination, a complete blood count with differential count, review of the peripheral blood smear, measurement of routine serum electrolytes, blood urea nitrogen and creatinine determination, assay of hepatic transaminases, bone marrow aspiration and core biopsy, and immunophenotyping by flow cytometry of peripheral blood or bone marrow aspirate.

At the time of diagnosis, most patients have symptoms attributable to anemia, neutropenia, thrombocytopenia, or splenomegaly. Approximately 25% of patients present with fatigue or weakness and 25% with infection; another 25% come to medical attention because of incidental discovery of splenomegaly or an abnormal peripheral blood count.[54]

Most patients are relatively well at the time of diagnosis. The most common and invariably the only physical finding is splenomegaly, occurring in approximately 80% of patients.[3,54] The spleen is palpable 5 cm below the left costal margin in approximately 60% of patients. Hepatomegaly occurs in approximately 20% of patients. Unlike in many other chronic lymphoproliferative disorders, peripheral adenopathy is uncommon at diagnosis, with less than 10% of patients presenting with peripheral nodes larger than 2 cm. Although adenopathy is not common at diagnosis, internal adenopathy may develop after a prolonged disease course[74,75] and is present in 75% of patients at autopsy.[76] The characteristic distribution in HCL probably is due to expression of the integrin receptor, $\alpha_4\beta_1$, by the hairy cells and its interaction with the vascular cell adhesion molecule-1 (VCAM-1) found on splenic and hepatic endothelia and in bone marrow and splenic stroma.[77]

Patients with HCL are susceptible to both gram-positive and gram-negative bacterial infections.[78] In addition, susceptibility to atypical mycobacterial infections,[79] particularly those due to *Mycobacterium kansasii*, as well as to invasive fungal infections, also has been documented.[78] Other opportunistic infections that have been reported include legionnaires' disease,[80] toxoplasmosis,[81] and *Listeria monocytogenes* infection.[82] The milieu specific for this increased susceptibility to infections comprises granulocytopenia, monocytopenia, poor granulocyte reserve and abnormal mobilization,[83] T-cell dysfunction,[84] and decreased numbers of dendritic cells and antigen-presenting cells.[85]

Rarely, patients with HCL may have associated systemic immunologic disorders,[86] including scleroderma and polymyositis[87] and polyarteritis nodosa.[88] HCL has been associated with other cutaneous lesions such as erythematous maculopapules[89] and pyoderma gangrenosum.[90,91] An associated coagulopathy manifested by factor VIII antibodies has been reported.[92] Osseous involvement also has been described, primarily lytic lesions in the axial skeleton, usually the proximal femur.[93,94] Rarely, osteolytic lesions may be associated with paraproteinemia.[95] A rare case of HCL occurring with systemic mast cell disease has been reported.[96]

LABORATORY EVALUATION

Pancytopenia is present in approximately 50% of patients with HCL at diagnosis; most other patients present with suppression of one or two cell lines.[3,54] Most patients with HCL present with leukopenia, although 10% to 20% of patients exhibit a "leukemic phase" with a white blood cell count above 10,000 to 20,000/μL. Monocytopenia is a characteristic but often overlooked finding.[1,3,54] Other laboratory findings include abnormal hepatic transaminase levels (19%), azotemia (27%), and hypergammaglobulinemia (18%), which rarely is monoclonal.[3,95,97] Unlike in chronic lymphocytic leukemia, hypogammaglobulinemia is uncommon.

Hairy cells can be identified in Wright's-stained blood smears from almost all patients with HCL, although the number of circulating hairy cells usually is low. Bone marrow often is inaspirable, resulting in a "dry tap." When aspiration is successful, however, hairy cells morphologically similar to those in the blood can be found.

The morphologic features of hairy cells are distinctive (Fig. 109-1). The neoplastic cells are approximately one to two times the size of a small lymphocyte. The nuclei are round, oval, indented, or monocytoid; rarely, they appear convoluted.[98] The nuclei are located in a central or eccentric position. The chromatin pattern is net-like in appearance, and nucleoli are indistinct or absent. The amount of cytoplasm varies, ranging from scant to abundant; a pale blue-gray color is characteristic. The cytoplasmic borders are irregular and exhibit fine, hair-like projections or ruffled borders. Occasionally, cytoplasmic granules are present. Rarely the cytoplasm exhibits basophilia, or rod-shaped inclusions that correspond to ribosomal lamellar complexes, observed on ultrastructural examination in approximately 40% of cases.[99]

Examination of the bone marrow core biopsy specimen is critical in the diagnosis of HCL because of its characteristic histopathologic appearance[100–103] (Figs. 109-2 and 109-3). The bone marrow usually is hypercellular in most patients, but this finding may be variable. Hairy cell infiltration may be diffuse, patchy or interstitial, or a combination of these patterns. In patients with *diffuse* involvement, large areas of the bone marrow are replaced by hairy cells, with complete effacement of marrow in some patients. With *patchy* infiltration, small subtle clusters of hairy cells are present focally or scattered throughout the bone marrow. Unlike in lymphomas, the hairy cells do not form well-defined, discrete aggregates; instead, they merge

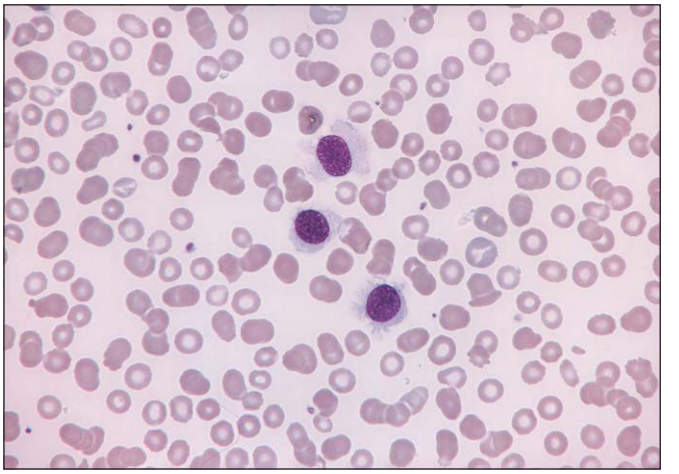


Figure 109-1 • Peripheral blood smear from a patient with hairy cell leukemia. This case was unusual in that the patient presented with leukocytosis. The hemoglobin and platelet count were reduced. The nuclei of the hairy cells are eccentrically located and exhibit a reticular chromatin. The cytoplasm is abundant, and the cytoplasmic borders are irregular, with fine, hairlike projections. (Wright-Giemsa stain.)

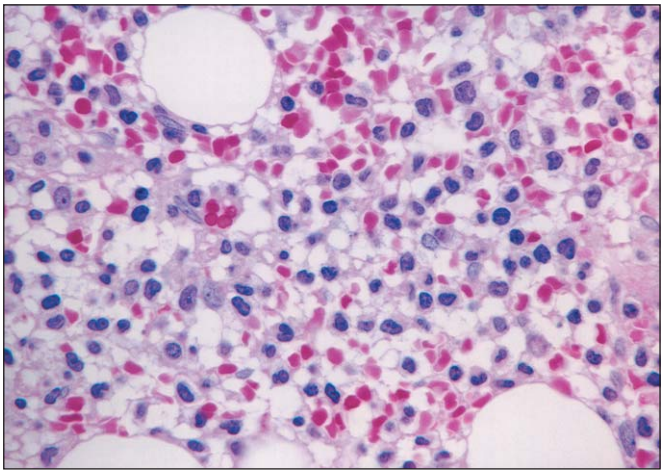


Figure 109-2 • Bone marrow trephine biopsy section from a patient with hairy cell leukemia. The bone marrow is hypercellular with a diffuse infiltration by hairy cells. The hairy cell nuclei are widely spaced, separated from each other by a pale, lightly eosinophilic cytoplasm. Many extravasated red blood cells are present between the hairy cells. (Hematoxylin and eosin stain.)

subtly with the surrounding residual hematopoietic tissue. In the *interstitial* pattern of involvement, variable numbers of hairy cells infiltrate between normal hematopoietic cells and fat, with preservation of the overall bone marrow architecture. Hairy cell nuclei in biopsy sections are round, oval, or indented and widely separated from each other by abundant clear or lightly eosinophilic cytoplasm; rarely, the cells are convoluted or spindle shaped. The nuclear chromatin is lightly condensed, nucleoli are inconspicuous, and mitotic figures are rare or absent. Extravasated red blood cells often are seen, and blood lakes, similar to those observed in the spleen, also may be observed. Reticulin stains of the bone marrow trephine biopsy specimen in HCL show a moderate to marked increase in reticulin fibers.

Normal hematopoietic cells usually are decreased in HCL; the number of granulocytes typically is more severely reduced than are erythroid precursors and megakaryocytes. In approximately 10% to 20% of patients with HCL, the bone marrow is hypocellular. The hypocellularity may be severe,[104] with a marrow appearance resembling that in aplastic anemia.

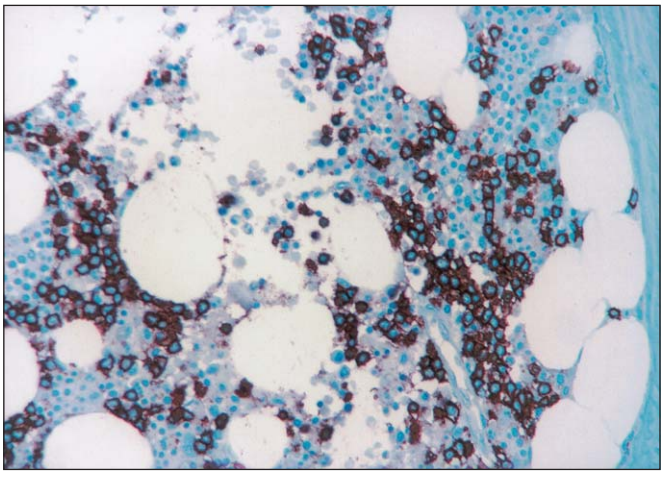


Figure 109-3 • Within the patchy infiltration of hairy cells seen on this biopsy section, the cells are accentuated by immunostaining for the B-cell antigen CD20. Residual hematopoietic precursors are negative for CD20. (Immunohistochemical stain for CD20.)

Historically, cytochemical demonstration of tartrate-resistant acid phosphatase (TRAP) activity has been used to confirm the diagnosis of HCL.[105] TRAP-positive cells are found in most cases of HCL at diagnosis, although the percentage of positive cells varies greatly among patients. A positive TRAP stain in conjunction with characteristic histopathology is essentially diagnostic of HCL. Today, however, the routine use of immunophenotyping by flow cytometry for the diagnosis of chronic lymphoproliferative disorders has made reliance on the TRAP stain less important.

Flow cytometric immunophenotyping is an essential part of the diagnostic evaluation, both to identify the characteristic immunophenotypic profile of HCL and to distinguish it from other chronic B-cell and T-cell lymphoproliferative disorders. Because hairy cells exhibit distinctive light scatter characteristics and immunophenotype, they can be identified even when present in very low levels (less than 1% of lymphocytes) in either the peripheral blood or bone marrow aspirate.[106] This property is useful not only at the time of diagnosis but also after therapy to assess for residual disease.[107]

Hairy cells show bright CD45 expression with increased forward and side scatter resembling that of large lymphocytes or monocytes. They exhibit a mature B-cell phenotype and express one or more heavy chains and monotypic light chains. The numbers of cases with expression of kappa or of lambda light chains are approximately equal. Surface immunoglobulin is of moderate to bright intensity. Hairy cells strongly express pan-B-cell antigens, including CD19, CD20, CD22, and CD79b. They usually are negative-staining for CD5, CD10, and CD23. They strongly express CD11c, CD25, and FMC7. CD103, an antigen expressed on mucosal T cells and some activated T cells, is expressed in a majority of cases of HCL.[106,108] Approximately 35% of patients have a variant immunophenotype, but the hairy cells from such patients have the characteristic morphologic features of classic hairy cells, and these patients have the same excellent response to treatment with purine analogs.[109] Several B cell-associated antibodies, including CD20, CD79a, and DBA.44, react with hairy cells in fixed, routinely processed tissue sections. Although these antibodies are not specific for HCL, they are useful in documenting the B-cell nature of the infiltrate and highlighting the extent of bone marrow infiltration at the time of diagnosis and after therapy.[110–113]

Splenic involvement in HCL is characterized by diffuse infiltration of the red pulp cords and sinuses, with atrophy or replacement of the white pulp. Blood-filled sinuses, lined by hairy cells, often are present but are not pathognomonic for HCL; they have been referred to as "pseudosinuses."[114] The liver shows both sinusoidal and portal infiltration by hairy cells. Involved lymph nodes commonly exhibit partial effacement, with hairy cells infiltrating the paracortex and medulla in a leukemic pattern. The leukemic cells often surround residual lymphoid follicles and extend through the capsule.

Clonal cytogenetic abnormalities are present in approximately two thirds of patients with HCL. Karyotype analysis is rarely required or useful to establish the diagnosis, however. The most frequently involved chromosomes include chromosomes 1, 2, 5, 6, 11, 14, 19, and 20. In particular, chromosome 5 is altered in 40% of patients, most commonly as trisomy 5, pericentric inversions, or interstitial deletions involving band 5q13.[115–117]

DIFFERENTIAL DIAGNOSIS

Considerations in the differential diagnosis for HCL include other chronic B-cell lymphoproliferative disorders associated with splenomegaly, including prolymphocytic leukemia, splenic marginal zone lymphoma, and hairy cell variant (Table 109-1). Patients with prolymphocytic leukemia typically present with splenomegaly, but this disorder usually can be distinguished from HCL by the marked leukocytosis, the characteristic morphologic appearance of the prolymphocytes, and an immunophenotypic profile different from that for HCL.[118–121] Splenic marginal zone lymphoma exhibits some

Table 109-1 Differential Diagnosis for Hairy Cell Leukemia

Prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia variant
Chronic lymphocytic leukemia
Low-grade lymphoma
Agnogenic myeloid metaplasia
Systemic mastocytosis

clinical and morphologic features similar to those of HCL, but in contrast, the bone marrow infiltrates are sharply demarcated from the surrounding normal tissue, and intrasinusoidal infiltration often is prominent. In addition, the immunophenotypic profile differs from that for HCL, including negative staining for CD103.[122–125] Hairy cell variant exhibits morphologic features that are intermediate between those of HCL and prolymphocytic leukemia. Unlike HCL, hairy cell variant is associated with prominent leukocytosis, lack of monocytopenia, and absence of CD25 expression.[126–130] Finally, infiltrates of systemic mastocytosis in the bone marrow may resemble those seen in HCL. Immunohistochemistry studies, however, show the mast cells, unlike hairy cells, to be negative for B-cell antigens and positive for tryptase.[131]

TREATMENT

Indications

Hairy cell leukemia almost always has an indolent course, with some patients surviving 10 years without need for therapy.[132] In a majority of patients, however, progressive disease eventually leads to complications resulting from anemia, bleeding, splenomegaly, or recurrent infections. Therapy is indicated when the patient has significant cytopenias; symptomatic organomegaly or adenopathy; repeated infections or constitutional signs and symptoms such as fever, night sweats, or fatigue. Persistent blood counts showing an absolute neutrophil count (ANC) less than 1000/μL, a hemoglobin less than 11.0 g/dL, or a platelet count below 100,000/μL are guidelines that can serve as indications for therapy.

Role of Splenectomy

Splenectomy was the first effective therapy for HCL and remained the initial treatment of choice until approximately 2 decades ago.[11–14] After splenectomy, counts for all three cell lines return to normal in approximately 40% to 70% of patients.[13,133] This response is maintained for a median of 20 months in approximately two thirds of patients, and the overall 5-year survival rate is approximately 70%.[133] No correlation has been found between spleen size and response to splenectomy. Splenectomy may have a possible role in an occasional patient to establish the diagnosis, in rare cases of splenic rupture, or in patients with life-threatening thrombocytopenia or a significant bleeding diathesis, because emergency splenectomy can lead to a rapid rise in the platelet count. Except in these very unusual circumstances, however, little, if any, role for splenectomy is recognized since the introduction of the purine analogs.

Chemotherapeutic Approaches

Cytotoxic chemotherapy was given for the treatment of HCL before the advent of more effective therapies in the early 1980s. A variety of agents, including anthracyclines,[134] alkylating agents (chlorambucil),[135] and high-dose methotrexate,[136] demonstrate activity. Combination chemotherapy, such as the CHOP regimen (cyclophosphamide, hydroxyldaunoribicin, Oncovin [vincristine sulfate], prednisone), produces long-lasting normalization of peripheral blood counts.[137] In one report in the literature of successful syngeneic (identical twin) bone marrow transplantation, the patient remained free of disease at least 15 years later.[138] Although HCL is sensitive to chemotherapy, significant myelosuppression and toxicity are associated with use of this modality. Therefore, conventional chemotherapy is now a therapy of only historical interest.

Interferon

Interferon was first reported in 1984 to be an effective therapy for patients with HCL[15]; since then, many large studies have confirmed its activity.[15–21] The precise mechanism of action of interferon is not known, but its activity may be attributable to a decrease in the production of cytokines such as granulocyte colony stimulating factor, granulocyte macrophage colony stimulating factor, interleukin-3, and interleukin-6, perhaps related to the characteristic monocytopenia associated with interferon treatment.[139] Studies suggest that interferon-α results in apoptotic death of hairy cells, mediated by tumor necrosis factor-α.[140] Despite a high overall response rate of 75% to 90%, most patients achieve only partial remission (i.e., they have a partial response [PR], defined as normalization of all peripheral blood counts).[18,19] Interferon commonly is administered subcutaneously at a dose of 2 million international units/m^2 three times a week for 12 to 18 months. During the first 2 months of treatment, the white blood cell count and hemoglobin often decrease, occasionally precipitating transfusion. The platelets normalize earliest in responding patients, followed by the hemoglobin and the white blood cell count. An ANC greater than 1500/μL is achieved after a median of 5 months of therapy. The most common manifestations of toxicity include flu-like symptoms, anorexia and fatigue, nausea and vomiting, diarrhea, dry skin, peripheral neuropathies, and central nervous system dysfunction, usually manifested as depression or memory loss. Elevated hepatic transaminases are the most common laboratory abnormality, other than myelosuppression. The median failure-free survival period after discontinuing interferon ranges from 6 to 25 months in different series.[18–20,141] Patients with more than 30% hairy cells in the marrow or a platelet count less than 160,000/μL at the end of treatment have a higher risk of early relapse.[18–20] In addition, patients who express the CD5 antigen appear to respond poorly to interferon.[142] Patients can be maintained on long-term interferon at a dose of 3 million units subcutaneously given three times a week with minimal toxicity. Sixty percent of patients have sustained their initial response for a median of 5 years, 9% discontinued therapy early because of unexpected neurologic toxicity, and only 13% stopped therapy because of progressive disease.[21] Although treatment of HCL with interferon is effective, complete responses (CRs) are uncommon, and failure-free survival usually is short after discontinuation of treatment. Furthermore, the purine analogs have completely supplanted interferon for the treatment of newly diagnosed HCL.

Purine Analog Therapy

As early as the 1960s, Giblett and colleagues observed that 30% of children with severe combined immunodeficiency syndrome lacked the enzyme adenosine deaminase (ADA).[143] It appeared that the accumulation of the triphosphorylated form of deoxyadenosine was responsible for lymphocyte depletion.[144] Therefore, the deliberate inhibition of ADA was recognized as a potentially useful antileukemic strategy. The methods to accomplish this therapeutic effect included the development of agents to bind irreversibly to ADA or to resist the action of the enzyme. These agents affect both dividing and nondividing cells.[145] After purine analog therapy, accumulation of deoxyadenosine triphosphates leads to DNA strand breaks and inhibition of DNA repair, which ultimately results in cell apoptosis.

Pentostatin (2′–Deoxycoformycin)

Pentostatin, or 2′-DCF, was the first agent to induce a significant number of CRs in HCL.[22,146] This drug binds to ADA, resulting in irreversible inhibition of the enzyme,[147] which is found in all lymphoid cells and is important in purine metabolism. In most studies, CR is defined by disappearance of hairy cells in the blood and bone marrow, complete normalization of peripheral counts (hemoglobin concentration greater than 120 g/L, platelet count greater than 100,000/μL, and ANC greater than 1500/μL), and resolution of splenomegaly and lymphadenopathy. A partial remission (i.e., PR) requires normalization of blood counts, greater than 50% reduction in hairy cells in the bone marrow, and greater than 50% reduction in splenomegaly.

A number of studies demonstrate the efficacy of 2′-DCF in patients with HCL (Table 109-2).[23–33] A large prospective, randomized study showed that the CR rate and relapse-free survival rate are significantly better with 2′-DCF than with interferon.[31] Various dosing schedules have been reported in early studies, but the current dose is 4 mg/m^2 given by intravenous infusion every 2 weeks until maximum response. The median number of cycles required by patients until best response has been from 6 to 12 cycles.[24,27,29,33] In one of the earlier studies conducted by the Eastern Cooperative Oncology Group, most patients achieved maximal response within the first 6 months.[27] Therapy is relatively well tolerated; neutropenia, fever, and infections are the most frequent toxicities.[25,27,32] One of the largest published series providing long-term evaluation was reported by the Southwest Oncology Group.[25] A total of 241 patients received 2′-DCF on a phase III trial comparing interferon and 2′-DCF; 154 were randomized to receive 2′-DCF initially, with crossover of 87 additional patients from the interferon group after it failed to produce improvement. Seventy-two percent of patients achieved a CR with 2′-DCF. Long-term survival was not statistically different based on initial treatment; in both groups overall survival was 90% at 5 years, and 81% at 10 years (Fig. 109-4). With longer follow-up, 2′-DCF does not appear to be curative in all patients. Studies with follow-up periods longer than 5 years after treatment report relapses in 15% to 48% of patients.[23–25,30]

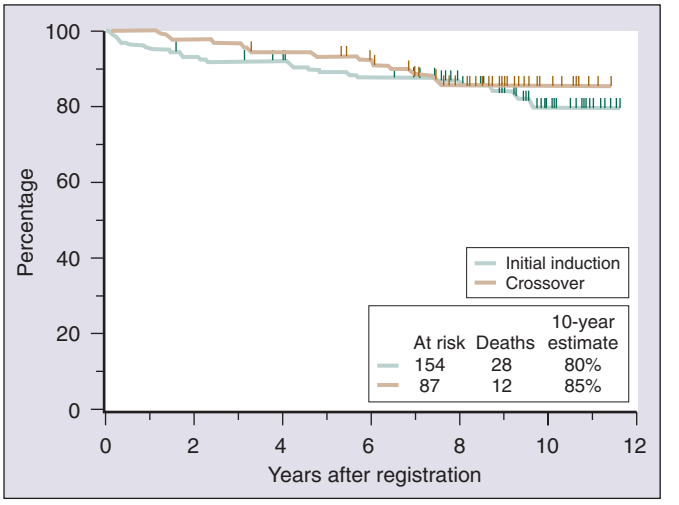


Figure 109-4 • Overall survival of 241 patients with HCL treated with 2′-deoxycoformycin (2′-DCF), stratified by treatment up front or after failure on interferon. (Data from Flinn IW, Kopecky KJ, Foucar MK, et al: Long-term follow-up of remission duration, mortality, and second malignancies in hairy cell leukemia patients treated with pentostatin. Blood 2000;96:2981.)

Cladribine (2-Chlorodeoxyadenosine)

Cladribine, or 2-CdA is a purine analog that is resistant to the action of ADA. This agent accumulates in the lymphoid cells, possibly because they are rich in the enzyme deoxycytidine kinase.[144] This enzyme phosphorylates 2-CdA to the active 5′-triphosphate form, creating a deoxynucleotide that cannot readily exit the cell. This compound inhibits ribonucleotide reductase, which results in decreased synthesis of deoxynucleotides. Both DNA synthesis and repair are impaired.

2-CdA was first reported to be effective in HCL by Piro and colleagues in 1990.[34] Twelve patients were given a single cycle of 2-CdA at a dose of 0.1 mg/kg per day by continuous infusion for 7 days; a CR was obtained in 11 of the 12 patients within 8 weeks of treatment. A number of subsequent studies have shown similar remarkable efficacy (Table 109-3).[24,34–44] Clear orders for use of the 7-day infusion pump are critical because poor response to therapy has been attributed to underdosing of drug when 1 day's dose was administered over 7 days.[148] Excellent results with alternative dosing schedules and routes of administration have been reported (Table 109-4).[149–152] In the study conducted by Von Rohr and colleagues,

Table 109-2 Activity of 2′-Deoxycoformycin in Hairy Cell Leukemia

Study	No. of Patients	Previously Untreated	Median No. (of Cycles)	CR (%)	PR (%)	NR (%)	Median Follow-up (mo)	Relapse (%)	Median Time to Relapse (mo)
Johnston et al[26]	28	18	NA	89	11	0	14	4	13.8
Ho et al[28]	33	0	NA	33.3	45.5	0	14.5	8	10
Rafel et al[32]	78	35	7	72	16	1	31	33	29
Cassileth et al[27]	50	19	6	64	20	16	39	14	*CR*: 13 *PR*: 31
Catovsky et al[29]	148	23	9	74.3	22.3	3.4	42	8	22
Ribeiro et al[33]	50	18	12	44	52	0	47	10	22
Grever et al[25,31]	154	154	NA	76	3	5*	57	9	NA
Maloisel et al[23]	238	67	9	83	16.6	6	63.5	15	NA
Dearden et al[24]	165	38	9	82	15.6	3	71	24	51.5
Kraut et al[30]	24	NA	NA	100	0	0	82	48	30

CR, complete response; NA, not available; NR, no response; PR, partial response.
*Stable/no response.

Table 109-3 Activity of 2-Chlorodeoxyadenosine in Hairy Cell Leukemia*

Study	No. of Patients	Previously Untreated	CR (%)	PR (%)	NR (%)	Median Follow-up (mo)	Relapse (%)	Median Time to Relapse (mo)
Estey et al[40]	46	27	78	11	11	9	2	17.8
Juliusson and Liliemark[41]	16	3	75	0	13	12	0	
Tallman et al[42]	20	12	80	20	0	12	5	NA
Piro et al[44]	144	69	85	12	2	14	3	36
Piro et al[34]	12	3	92	8	0	15.5	0	
Seymour et al[35]	46	27	78	11	11	30	20	16
Tallman et al[36]	50	27	80	18	2	33	14	24
Jehn et al[37]	42	32	98	2	0	33	14	29
Dearden et al[24]	45	12	84	16	0	45	29	23.5
Von Rohr et al[152]	62	33	76	21	3	46	24	38
Hoffman et al[43]	49	21	76	24	0	55	24	NA
Saven et al[38]	349	179	91	7	2	58	26	*CR*: 30 *PR*: 24
Goodman et al[39]	207	119	95	5	0	108	37	42

CR, complete response; NA, not available; NR, no response; PR, partial response.
*2-CdA dose: 0.1 mg/kg/d × 7 days by continuous infusion.

2-CdA was administered as a subcutaneous bolus injection of 0.14 mg/kg per day for 5 days to 62 patients.[152] The results were similar to those of previous studies, with 76% of patients achieving a CR and an overall response rate of 97%. Robak and colleagues conducted a prospective randomized trial comparing a standard 5-day schedule with a 6-week schedule, which had been reported to be potentially less toxic.[153,154] These investigators observed similar CR rates, overall response rates, and progression-free- and overall survival rates, with no less toxicity.[154] (Fig. 109-5).

The most common toxicities associated with 2-CdA treatment are neutropenia and fever. Investigators at the Scripps Clinic reported results for the largest collection of patients with HCL treated with 2-CdA. Of 349 patients who received a single cycle of 2-CdA, 87% had grade 3 or 4 neutropenia, 42% had a neutropenic fever, but only 13% had documented infections, none of which were opportunistic infections.[38] Most of the fevers seen with administration of 2CdA do not appear to represent infection but may be due to release of cytokines. Owing to the high incidence of neutropenic fever, these investigators conducted a prospective trial examining the effect of filgrastim in 35 patients receiving 2-CdA.[155] Filgrastim was administered on days 3 through 1, and again after completion of 2-CdA therapy until the ANC was over 2000/μL on two consecutive days. When compared with historical controls, patients in the filgrastim treatment group more rapidly achieved an ANC greater than 1000/μL, in 9 days versus 22 days. The incidence of fever and need for hospital admission, however, did not differ between the two groups. Therefore, the routine use of prophylactic filgrastim is not indicated in this setting. Such a strategy may be useful in the rare patient who presents with a life-threatening infection and requires therapy with a purine analog.

Although response rates are very high with 2-CdA, they are not sustained in all patients. The experience with 2-CdA is similar to that with 2′-DCF in that relapses have appeared with longer follow-up (see Table 109-3). In a report from the Scripps Clinic, after a median follow-up period of 108 months, 37% of patients relapsed, with a median time to relapse of 42 months.[39] Initial PR is associated with a shorter duration of remission (Fig. 109-6A and B). The response to re-treatment remains very good. Of the patients who relapsed, 79% received re-treatment with 2-CdA; the overall response rate was 92%, including 75% with a complete remission.[39] One retrospective study has suggested that durability of response is greater with 2′-DCF than with 2-CdA: At 45 months of follow-up for each, relapse rates were 9.7% and 29%, respectively.[24] To date, no randomized trials of the two agents have been conducted to resolve this issue. Thus far,

Table 109-4 Alternate Schedules of 2-Chlorodeoxyadenosine Therapy for Treatment of Hairy Cell Leukemia

Study	Dosing	Route of Administration	Response(s)
Juliusson et al[149]	3.4 mg/m^2/d × 7 days	Subcutaneous injection	*CR*: 75% after 1 cycle, 85% after 2 cycles
Robak et al[150]	0.14 mg/kg/d × 5 days	2-hour intravenous bolus	*CR*: 82%; *PR*: 17.4%
Chacko et al[151]	0.15 mg/kg/wk × 6 weeks	3-hour infusion	*CR*: 100%
Von Rohr et al[152]	0.14 mg/kg/d × 5 days	Subcutaneous injection	*CR*: 76%; *PR*: 21%
Robak et al[154]	0.12 mg/kg/wk × 6 weeks	2-hour intravenous infusion	*CR*: 72%; *PR*: 19%

CR, complete response; PR, partial response.

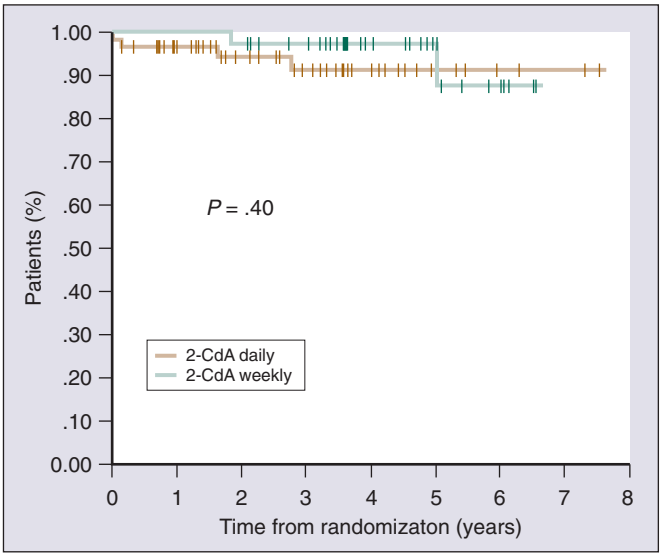


Figure 109-5 • Overall survival after two schedules of 2-CdA administration in patients newly diagnosed with hairy cell leukemia. (Data from Robak T, Jamroziak K, Gora-Tybor J, et al: Cladribine in a weekly versus daily schedule for untreated active hairy cell leukemia: final report from the Polish Adult Leukemia Group (PALG) of a prospective, randomized, multicenter trial. Blood 2007;109:3672.)

no plateau has been reached with either agent, and relapses continue to occur after initial treatment.

Immunosuppression with Purine Analogs

Treatment with both 2′-DCF and 2-CdA results in prolonged immunosuppression.[41,156–158] A decrease in the total lymphocyte count occurs with 2′-DCF, with a greater reduction in T cells than in B cells or natural killer cells.[157] The levels of $CD4^+$ and $CD8^+$ cells decrease to fewer than 200 cells/μL for at least 6 months after 2′-DCF treatment is discontinued. In a series of 15 patients with HCL treated with 2′-DCF with long follow-up, the median time to recovery of $CD4^+$ lymphocyte counts to normal was 54 months.[158] Treatment with 2-CdA induces similar suppression of $CD4^+$ cell counts.[35] The median time to recovery of $CD4^+$ cell counts to normal after completion of 2-CdA therapy was 40 months. Treatment with 2-CdA affects one distinct subset of $CD4^+$ T cells. The $CD4^+/CD45RA^+$ subset is significantly reduced for up to 5 years; the $CD4^+/CD45RO^+$ T cells, which secrete cytokines and enhance B cell function, are not suppressed.[159] In addition, recovery of CD8 and NK cells is more rapid; they normalize within 3 months of treatment with 2-CdA.[160] This finding may explain why opportunistic infections, other than an occasional case of herpes zoster, are surprisingly uncommon.[33,38,41,159]

PROGNOSIS

Before the routine introduction of interferon therapy, survival at 4 years was reported to be 68%.[161] With the use of purine analogs, durable remissions are obtained, and even after relapse, retreatment with a purine analog results in good responses. The 5-year survival rates are greater than 85%.[24,25,29,33,38,39] Flinn and colleagues reported long-term results for 241 patients with HCL treated with 2′-DCF; the overall survival rate was 90% at 5 years and 81% at 10 years (see Fig. 109-4).[25] The leading causes of death were second malignancies and infection. Only 2 of 40 deaths in this series were attributable to HCL.

A series of 209 patients with HCL treated with 2-CdA at the Scripps Clinic have been followed for at least 7 years.[39] The overall survival rate at 9 years is 97% (see Fig. 109-6A). At least three other long-term follow-up studies of 2′-DCF or 2-CdA have been published.[162–164] After a median follow-up period of 8.5 years, Jehn and coworkers reported a relapse rate of 39%, but the overall survival rate at 12 years was 79%.[162] At Northwestern University, among 86 patients, the overall survival rate at 12 years was 87%.[163] After a median follow-up period of 9.7 years, 36% of patients had relapsed. Else and colleagues reported a study with one of the longest follow-ups of patients who received a purine analog, 2-CdA in 34 patients and 2′-DCF in 185, with a median follow-up period of 12.5 years.[164] Although an earlier report from the same group of investigators suggested a lower relapse rate associated with use of 2′-DCF, in this more

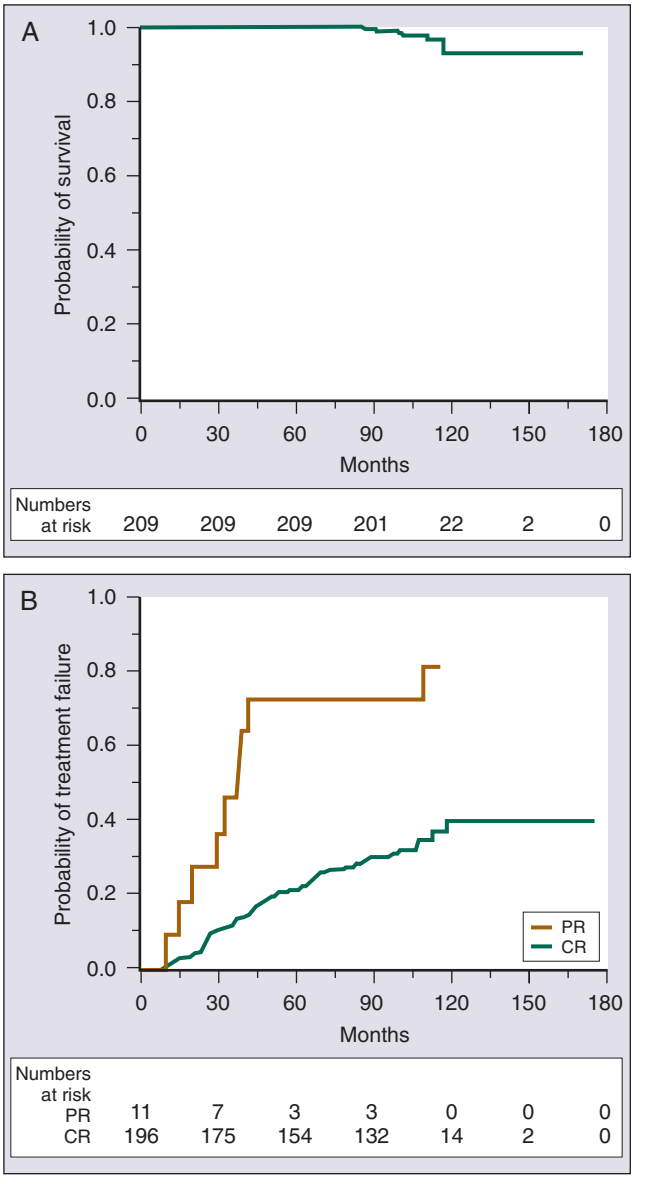


Figure 109-6 • **A,** Kaplan-Meier survival curves for 209 patients with HCL treated with 2-chlorodeoxyadenosine (2-CdA) and followed for at least 7 years. **B,** Time to treatment failure for 207 patients with HCL after the first course of 2-CdA, stratified by response to first course of therapy. CR, complete response; PR, partial response. (**B,** Data from Goodman GR, Burian C, Koziol JA, Saven A: Extended follow-up of patients with hairy cell leukemia after treatment with cladribine. J Clin Oncol 2003;21:891.)

recent report, the response, relapse, and overall survival rates at 10 years were similar.

OTHER CONSIDERATIONS IN MANAGEMENT

Evaluation of Minimal Residual Disease

The remarkable activity of the purine analogs has led to the examination of post-treatment bone marrow biopsy specimens to detect MRD in patients otherwise in complete remission. Immunohistochemistry studies using anti-CD20, DBA.44, and anti-CD45RO antibodies in paraffin-embedded biopsy specimens have been used most frequently.[109–112,165–167] Newer techniques for MRD detection include flow cytometric immunophenotyping and consensus primer polymerase chain reaction (PCR) assay.[107] Depending on the criteria used, 13% to 51% of patients in apparent complete remission have evidence of MRD[109–111,168] (Fig. 109-7). In one study, no statistically significant difference in incidence of MRD was found between patients receiving 2′-DCF and those given 2-CdA.[168] The presence of MRD appears to predict relapse.[111,167] In one study evaluating MRD in 66 patients, 50% of those with MRD relapsed, whereas only 6% of patients without MRD relapsed.[168] Two trials have suggested that administration of the anti-CD20 monoclonal antibody rituximab after 2-CdA therapy is effective in eradicating MRD.[169,170]

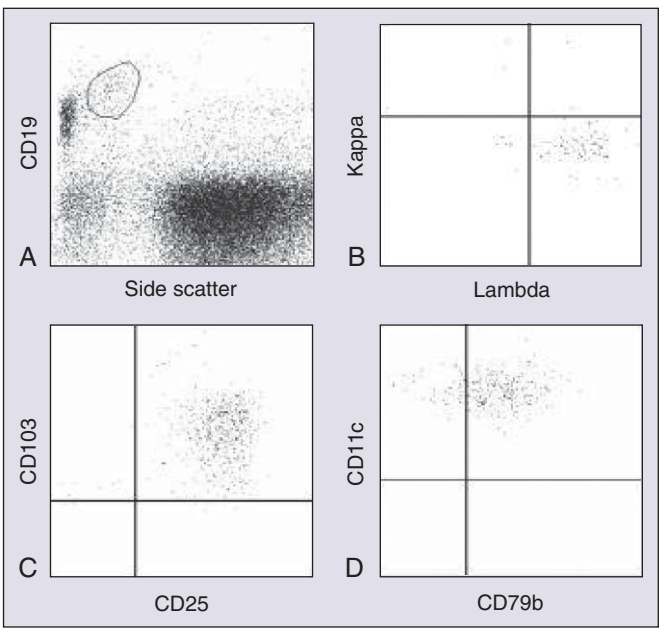


Figure 109-7 • Representative example of flow cytometric detection of hairy cell leukemia, comprising 0.2% of a peripheral blood sample. **A,** Distribution of CD19 staining versus side-scattered light intensity. The *circled* population represents the hairy cell population. Note the increased side-scattered light intensity that is characteristic of hairy cell leukemia. **B,** Distribution of kappa versus lambda staining for this hairy cell population, showing that it is lambda positive and kappa negative, which is indicative of its clonal nature. **C,** Distribution of CD25 versus CD103. **D,** Distribution of CD79b versus CD11c. These histograms demonstrate the characteristic CD19-, CD103-, CD11c-, and CD25-positive staining in hairy cell leukemia. (Data from Robak T, Jamroziak K, Gora-Tybor J, et al: Cladribine in a weekly versus daily schedule for untreated active hairy cell leukemia: final report from the Polish Adult Leukemia Group (PALG) of a prospective, randomized, multicenter trial. Blood 2007;109:3672–3675.)

Whether such a strategy prolongs overall survival, however, is not clear.

Treatment of Relapse

Relapse often is detected on bone marrow biopsy alone, and immediate retreatment is not necessary. In a study by Kraut and colleagues, relapse was detected at a median of 30 months from achievement of remission with 2′-DCF, but retreatment was initiated at a median of 60 months after first remission.[30] Retreatment with purine analogs resulted in complete remission in five of seven patients. Patients with an initial response to 2-CdA also respond well to retreatment with a purine analog. In the Scripps Clinic series, 76 of 207 patients relapsed, and 79% received retreatment with 2-CdA. The overall response rate was 92%, including 75% with a CR.[39] The median duration of the second response was 35 months, which is comparable with the 42-month duration of first response. Responses continue to be seen even with a third cycle of 2-CdA in 80% of patients receiving retreatment. In patients who relapse after purine analog therapy, re-treatment may be with either 2-CdA or 2′-DCF. Alternative agents for treatment of relapsed or treatment-refractory disease include BL22 and rituximab (see "New Therapies").

Risk of Second Malignancies

An association has been noted between HCL and second malignancies, although such a relationship is difficult to determine with certainty. Malignancies that have been observed in patients with HCL include melanoma, prostate cancer, gastrointestinal cancers, non-Hodgkin's lymphoma, and nonmelanomatous skin cancers. It is not clear whether HCL itself increases risk or whether the type of therapy may play a role. Kampmeier and colleagues reported a significantly increased incidence of second malignancies in patients with HCL treated with interferon.[171] The British Columbia Cancer Agency reported data from a 20-year follow-up study of 117 patients; a second malignancy developed in 31%; 30% of these malignancies were diagnosed before the diagnosis of HCL.[172] The risk was elevated regardless of the type of therapy. This association has not been uniformly observed, however.[173,174] Investigators at the M.D. Anderson Cancer Center reported no excess of second malignancies among 350 patients who received either interferon, 2-CdA, or 2′-DCF.[175] The immunosuppression due to the purine analogs may play a role in the increased malignancy incidence, but the evidence is not clear. Long-term follow-up studies of patients with HCL treated with 2′-DCF have not demonstrated a statistically significant increased risk of second malignancies.[23,25] Other studies have suggested that treatment with 2-CdA is associated with an increased cancer risk.[38,39,176] In a review of the Scripps Clinic experience with 349 patients, 8% of patients had a second malignancy that developed at a median time of 62 months after the diagnosis of HCL, and 21 months after treatment with 2-CdA.[38] Of note, 11% of the patients in this study had a diagnosis of malignancy before the diagnosis of HCL. It is not clear, therefore, that therapy increases risk; HCL itself may be associated with an inherent predisposition to malignancy.

New Therapies

The anti-CD-20 monoclonal antibody rituximab has been tested in patients with HCL refractory to other treatments.[177,178] In their series of 11 patients with HCL treated with rituximab, Hagberg and colleagues reported an overall response rate of 64% (Table 109-5).[179] The median duration of response in this group was 14 months. The largest published report describes 24 patients who received four weekly doses of rituximab.[180] All of the patients had relapsed after prior treatment with 2-CdA, and the median time since treatment was 73 months. Thirteen percent of patients had a CR and 13% had a PR, for an overall response rate of 26%. One third of responders

Table 109-5 Antibody and Immunoconjugate Therapy in Treatment of Hairy Cell Leukemia

Study	Treatment	No. of Patients	Previously Treated	CR (%)	PR (%)	OR (%)
Lauria et al[178]	Rituximab	10	10	10	40	50
Hagberg and Lundholm[179]	Rituximab	11	11	55	9	64
Nieva et al[180]	Rituximab	24	24	13	13	26
Thomas et al[181]	Rituximab	15	15	53	13	66
Kreitman et al[183]	LMB-2	4	4	25	75	100
Kreitman et al[186]	BL22	23	23	65	18	83

CR, complete response; OR, overall response; PR, partial response.

relapsed after a median follow-up period of 14.6 months. It appears that rituximab has activity in some patients with HCL. Thomas and colleagues[181] used this agent to treat relapsed or refractory disease in 15 patients and observed an overall response rate of 60%.

CD-25, also known as Tac, is the α subunit of the IL2R and is expressed in 80% of patients with HCL.[182] LMB-2, anti-Tac(Fv)-PE38, is an immunotoxin that contains the variable heavy domain of anti-Tac fused to the amino terminus of a 38-kD truncated form of the *Pseudomonas* exotoxin.[183] Tac has demonstrated some efficacy in patients with $CD25^+$ hematologic malignancies. After binding to CD25, the compound is internalized, leading to apoptosis and cell death. Of four patients with HCL refractory to standard therapies, including 2-CDA and interferon regimens, all demonstrated a response to LMB-2, with one CR.[183] LMB-2 is well tolerated and appears to have no hematologic toxicity. Larger studies need to be conducted to better determine the safety and efficacy of this agent.

Another promising immunotoxin under investigation is BL22, a recombinant immunotoxin containing anti-CD22 monoclonal antibody and PE38, the *Pseudomonas* exotoxin. CD22 is expressed by normal B cells and B-cell leukemias and lymphomas, including HCL, but is not found on stem cells.[184] Kreitman and colleagues recently updated their original study[185] and presented the results for 23 patients with HCL treated with BL22.[186] The overall response rate was 83%, with 65% of patients attaining a CR. Of the complete responders, only one had MRD as determined by immunohistochemistry studies of bone marrow, and none had MRD when peripheral blood was tested by PCR analysis. Arons and colleagues showed that patient-specific relative quantitative (RQ) PCR assay was the most sensitive test to detect MRD in HCL, compared with immunophenotyping by flow cytometry and consensus PCR analysis.[187] The median follow-up period was 12 months, and of the four patients who relapsed, retreatment resulted in a CR in three. This therapy appears to be well tolerated, although a reversible hemolytic-uremic syndrome developed in two patients. No other hematologic toxicity or decrease in T-cell count was observed.[185] BL22 is the first therapeutic agent since the purine analogs to effect a high CR rate.

These new therapies are effective in patients with HCL that is resistant or refractory to the purine analogs and therefore constitute another treatment option. The durability of effect remains to be determined in larger studies with longer follow-up.

HA22 is a new immunoconjugate, which differs from BL22 by two amino acids, that improves the binding of the agent to CD22 by a factor of 14.[188] Such increased affinity results in better cytotoxicity against B-cell lines, as well as against cells isolated from patients with HCL and chronic lymphocytic leukemia.[189] Clinical trials with this new agent are under way.

Increased angiogenesis has been reported in patients with HCL.[190–192] Microvessel density is higher in the marrow of patients with active HCL than in normal control subjects. Treatment with both interferon-α and 2-CdA is associated with a decrease in microvessel density.[190–192] These observations suggest a potential role for antiangiogenesis agents.

General Principles of Management

Box 109-1 presents the recommended approach to management of HCL. Figure 109-8 summarizes the treatment strategies developed at Northwestern University.

Box 109-1. APPROACH TO THE MANAGEMENT OF HAIRY CELL LEUKEMIA

For patients with newly diagnosed HCL who require treatment (as indicated by absolute neutrophil count less than 1000/μL, hemoglobin less than 11.0 g/dL, and platelet count less than 100,000/μL; symptomatic organomegaly; or repeated infections), we administer 2-chlorodeoxyadenosine (2-CdA) 0.1 mg/kg per day by continuous intravenous infusion for 7 days as an outpatient procedure by portable pump using a midline percutaneous intravenous central catheter (PICC; see Fig. 109-8). Other schedules may be equally effective. If fever with temperatures of 100.5° F or higher develops while the patient is neutropenic, blood and urine cultures and chest radiography are performed, and a broad-spectrum oral antibiotic such as ciprofloxacin 750 mg given orally twice daily is administered. If cultures are sterile at 24 to 48 hours, an anti-inflammatory agent such as naproxen 250 mg given orally twice daily is added for 2 to 4 days; 2-CdA is not discontinued. Hematopoietic growth factors are not routinely given after treatment. The platelet count usually normalizes first (platelets are the first cell line to recover), typically within 2 to 4 weeks, followed by the white blood cell count and finally the hemoglobin concentration. The bone marrow examination is repeated at 3 months to assess remission status. We currently do not administer a second cycle of 2-CdA for patients with minimal residual disease (MRD). If the repeat bone marrow at 3 months shows evidence of MRD by either routine morphology or histochemistry, if the peripheral blood counts are normal, follow-up without further therapy is indicated. Rituximab may be considered.

For patients with relapsed HCL previously treated with either splenectomy, interferon, or pentostatin (2′-deoxycoformin [2′-DCF]), we administer a repeat cycle of 2-CdA, as described. For patients who relapse after a single cycle of 2-CdA, we give a second cycle of 2-CdA. For patients with relapsed HCL previously treated with at least two prior cycles of 2-CdA, we prefer BL22 if available. If BL22 is not available, use of rituximab may be a consideration. Alternatives include 2′-DCF, 4 mg/m^2 given intravenously every 2 weeks for 3 to 6 months, and interferon, 2×10^6 units/m^2 three times per week for 12 to 18 months.

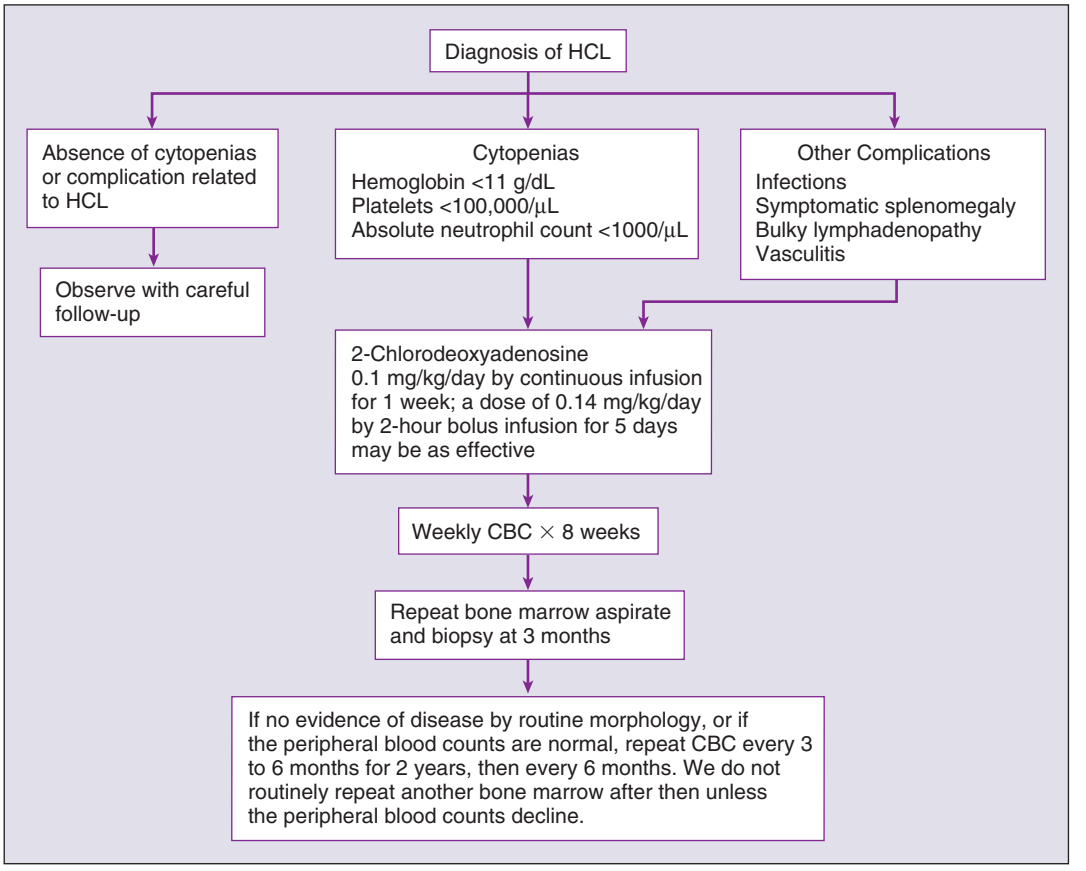


Figure 109-8 • Northwestern University Approach to the treatment of hairy cell leukemia. CBC, complete blood count.

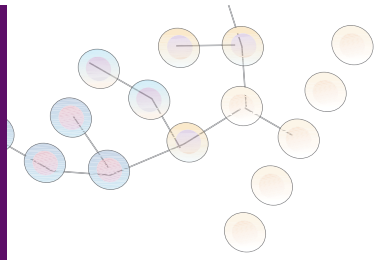
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110 Multiple Myeloma and Related Disorders

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SUMMARY OF KEY POINTS

Multiple Myeloma

Introduction

- Multiple myeloma accounts for approximately 10% of hematologic malignancies. Almost 20,000 new cases are estimated to occur in the United States in 2007.
- Almost all patients are thought to evolve from an asymptomatic premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS).

Diagnosis

- The most common presenting symptoms are fatigue and bone pain.
- Osteolytic bone lesions and/or compression fractures are the hallmark of the disease.
- Hypercalcemia is found in one fourth of patients; the serum creatinine is elevated in almost one half of patients.
- Diagnosis requires 10% or more plasma cells in the bone marrow, M protein in the serum, and/or urine and evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) secondary to the underlying plasma cell disorder.
- Monoclonal (M) proteins can be detected by serum protein electrophoresis and immunofixation in 93% of patients; Addition of urine protein electrophoresis and urine immunofixation or the serum free light-chain assay will increase sensitivity to 97% or higher.

Prognosis

- The International Staging System divides patients into three distinct stages and prognostic groups based on the β_2-microglobulin and albumin levels in the serum.
- The presence of any one of the following indicates high-risk myeloma: deletion 13 or hypdiploidy on metaphase cytogenetic studies, deletion 17p- or immunoglobulin heavy-chain translocations t(4;14) or t(14;16), or plasma cell labeling index of 3% or higher.

Treatment

- Newly diagnosed patients are categorized into standard-risk and high-risk myeloma on the basis of specific prognostic factors.
- Initial therapy for patients with standard-risk disease is dependent on eligibility for autologous stem cell transplantation (ASCT).
- Patients who are eligible for ASCT are treated with nonalkylating-agent-containing regimens as initial therapy, such as thalidomide-dexamethasone or lenalidomide-dexamethasone. They can then pursue early or delayed ASCT. If early ASCT is used, a second ASCT is considered in patients who do not achieve a very good partial response or better with the first ASCT. If delayed ASCT is used, the initial induction is continued until plateau or progression at reduced doses.
- For patients who are not eligible for ASCT, the current standard is melphalan, prednisone, and thalidomide (MPT); however, if such patients are unable to tolerate (or have access to) thalidomide, melphalan plus prednisone remains a reasonable alternative.
- Patients with high-risk myeloma are candidates for novel therapy, since outcome is poor even with tandem ASCT. Considerations include bortezomib-containing initial therapy, routine maintenance therapy if ASCT is utilized, MPT in elderly patients, and consideration of allogeneic approaches in selected patients.
- Options for relapsed disease include thalidomide, lenalidomide, bortezomib, alkylating agents, anthracyclines, and corticosteroids alone or in combination.

Monoclonal Gammopathy of Undetermined Significance

- Monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic, premalignant, clonal plasma cell proliferative disorder defined by the presence of a serum M protein level less than 3 g/dL; bone marrow plasma cells less than 10%; and absence of anemia, hypercalcemia, lytic bone lesions, or renal failure that can be attributed to the plasma cell proliferative disorder.
- MGUS is present in approximately 3% of the general population 50 years of age and older.
- Patients with three adverse risk factors, namely, an abnormal serum free light-chain ratio, non-IgG MGUS, and a high-serum M protein level (≥15 g/L), have a risk of progression at 20 years of 58% (high-risk MGUS) compared to 37% in patients in with any two of these risk factors present (high-intermediate-risk MGUS), 21% in patients with one risk factor present (low-intermediate risk MGUS), and 5% when none of the risk factors were present (low-risk MGUS).
- The current standard of care for MGUS is observation alone, without therapy.

Smoldering Multiple Myeloma

- Smoldering multiple myeloma is defined by the presence of a serum IgG or IgA M protein level of 3 g/dL or greater and/or bone marrow plasma cells 10% or more, and absence of anemia, hypercalcemia, lytic bone lesions, or renal failure that can be attributed to the plasma cell proliferative disorder.
- The risk of progression to myeloma or related malignancy is much higher in smoldering multiple myeloma than in

MGUS: 10% to 20% per year versus 1% per year, respectively.
- The standard of care is observation alone until evidence of progression to myeloma.

Waldenström's Macroglobulinemia

- Waldenström's macroglobulinemia is a clonal IgM monoclonal protein that secretes lymphoid/plasma cell disorder, which currently also includes the entity that was previously referred to as lymphoplasmacytic lymphoma.
- Median survival is approximately 5 years.
- There are four options for initial therapy: rituximab, purine nucleoside analogs, alkylators, and combination chemotherapy. Unfortunately, there are no randomized data to determine the best option; therapy is typically decided on the basis of the age of the patient and the aggressiveness of the presentation.
- Options that have been listed for initial therapy can also be tried at the time of relapse. The same initial therapy can be tried again at relapse if there was an adequate interval between cessation of therapy and relapse. Other options for relapsed or refractory disease include stem cell transplantation, interferon-α, thalidomide, and bortezomib.
- Plasmapheresis is indicated for the treatment of hyperviscosity syndrome.

Systemic Immunoglobulin Light-Chain Amyloidosis

- Amyloid is a fibrillar proteinaceous material that is detected with congo-red staining based on a characteristic apple-green birefringence under polarized light.
- It consists of rigid, linear, nonbranching fibrils, 7.5 to 10 nm in width, aggregated in a β-pleated sheet conformation. There are several distinct types of amyloidosis; they are classified on the basis of the protein composition of the amyloid material.
- AL (immunoglobulin light-chain) amyloidosis refers to the type of amyloidosis that is derived from the variable portion of a monoclonal light chain. It should be suspected when patients with the appropriate clinical syndrome, such as nephrotic syndrome, axonal neuropathy, or restrictive cardiomyopathy, display evidence of a plasma cell proliferative disorder such as a serum or urine monoclonal protein.
- Patients are offered ASCT if eligible. Patients who are not eligible for stem cell transplantation (poor performance status, major comorbidities, three or more organs involved, and advanced cardiac amyloidosis) are treated with melphalan plus high-dose dexamethasone.
- Thalidomide (or lenalidomide) plus dexamethasone are second-line treatment options for patients with systemic AL amyloidosis.

Solitary Plasmacytoma

- Solitary plasmacytomas may be confined to bone (solitary bone plasmacytoma) or may occur in extramedullary sites (extramedullary plasmacytoma).
- Patients with solitary plasmacytoma are at risk for progression to multiple myeloma.
- Treatment consists of radiation in the range of 40 to 50 Gy to the involved site.
- The disease-free survival rate at 10 years ranges from 25% to 50%.

MULTIPLE MYELOMA

Introduction

Definition

The diagnosis of active myeloma requires 10% or more plasma cells on bone marrow examination (or biopsy proven plasmacytoma), M protein in the serum and/or urine (except in patients with true non-secretory myeloma), and evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions) secondary to the underlying plasma cell disorder (Table 110-1). Multiple myeloma accounts for approximately 10% of hematologic malignancies.[1,2] Almost all patients are thought to evolve from an asymptomatic premalignant stage termed *monoclonal gammopathy of undetermined significance* (MGUS). MGUS is present in over 3% of the population above the age of 50 years and progresses to myeloma or related malignancy at a rate of 1% per year.[3,4] In some patients, an intermediate asymptomatic but more advanced premalignant stage referred to as *smoldering multiple myeloma* can be recognized clinically.

Epidemiology

The annual incidence, age-adjusted to the 2000 U.S. population, is 4.3 per 100,000.[5] Almost 20,000 new cases and 11,000 new deaths are estimated to occur in the United States in 2007.[6] Multiple myeloma is twice as common in African Americans as in Caucasians and slightly more common in males than in females. The median age at diagnosis is 66 years,[7] and only 2% of patients are younger than 40 years of age.

Pathogenesis

Transition from Normal Plasma Cell to Monoclonal Gammopathy of Undetermined Significance

ANTIGENIC STIMULATION AND IMMUNOSUPPRESSION. MGUS is the precursor lesion from which almost all cases of myeloma are thought to evolve. MGUS is characterized by evidence of genomic instability on molecular genetic testing. The trigger for this genomic instability is not well understood, but current evidence suggests that in many cases, antigenic stimulation might be a key factor (Fig. 110-1). Unlike normal plasma cells, human myeloma cell lines and primary myeloma cells express a broad range of Toll-like receptors (TLRs). TLRs are normally expressed by B lymphocytes and are essential for these cells to recognize infectious agents and pathogen-associated molecular patterns, which then initiate the host-defense response.[8–10] The aberrant expression of TLRs by plasma cells may enable them to respond to TLR-specific ligands, resulting in an abnormal and perhaps sustained response to infection. It has been shown that TLR-specific ligands cause increased myeloma cell proliferation, survival, and resistance to dexamethasone-induced apoptosis. These effects are mediated in part by autocrine interleukin-6 (IL-6) production.[8,9]

IL-6 is a major growth factor for plasma cells,[11] and there is overexpression of CD126 IL-6 receptor α-chain) in MGUS compared to normal plasma cells.[12,13] Thus, abnormal TLR expression and/or overexpression of IL-6 receptors in plasma cells may be early, initiating events that lead to an abnormal response to infection and act as sustained, autocrine IL-6-dependent, proliferative triggers for plasma

Table 110-1 Mayo Clinic Diagnostic Criteria for Selected Clonal Plasma Cell Disorders

Disorder	Disease Definition	References
Monoclonal gammopathy of undetermined significance (MGUS)	Serum monoclonal protein < 3 g/dL, bone marrow plasma cells < 10%, and absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder.	International Myeloma Working Group,[180] Rajkumar et al.[181]
Smoldering multiple myeloma (also referred to as asymptomatic multiple myeloma)	Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL and/or bone marrow plasma cells ≥ 10%, absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder.	International Myeloma Working Group,[180] Rajkumar et al.[181]
Multiple myeloma	Bone marrow plasma cells ≥ 10%, presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory multiple myeloma), plus evidence of lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to the underlying plasma cell proliferative disorder.	Rajkumar et al.,[2] International Myeloma Working Group,[180] Rajkumar et al.[181]
Waldenström's macroglobulinemia	IgM monoclonal gammopathy (regardless of the size of the M protein) with >10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (e.g., surface IgM+, CD5+/–, CD10–, CD19+, CD20+, CD23–) that satisfactorily excludes other lymphoproliferative disorders, including chronic lymphocytic leukemia and mantle cell lymphoma. *Note*: IgM MGUS is defined as serum IgM monoclonal protein < 3 g/dL, bone marrow lymphoplasmacytic infiltration < 10%, and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly. Smoldering Waldenström's macroglobulinemia (also referred to as indolent or asymptomatic Waldenström's macroglobulinemia) is defined as serum IgM monoclonal protein ≥ 3 g/dL and/or bone marrow lymphoplasmacytic infiltration ≥ 10%, and no evidence of end-organ damage such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that that can be attributed to a plasma cell proliferative disorder.	Kyle et al.,[3] Owen et al.,[197] Baldini et al.,[198] Gobbi et al.,[199] Kyle et al.[200]
Solitary plasmacytoma	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells, normal bone marrow with no evidence of clonal plasma cells, normal skeletal survey and MRI of spine and pelvis, and absence of end-organ damage such as anemia, hypercalcemia, renal failure or additional lytic bone lesions that can be attributed to a plasma cell proliferative disorder	International Myeloma Working Group,[180] Dimopoulos et al.[182]
Systemic AL amyloidosis	Presence of an amyloid-related systemic syndrome (such as renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) with positive amyloid staining by congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy), plus evidence that amyloid is light-chain related established by direct examination of the amyloid (immunoperoxidase staining, direct sequencing, etc), plus evidence of a monoclonal plasma cell proliferative disorder (serum or urine M protein, abnormal free light chain ratio, or clonal plasma cells in the bone marrow). *Note*: Approximately 2–3% of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder listed above; the diagnosis of AL amyloidosis must be made with caution in these patients.	Kyle and Rajkumar[171]
POEMS syndrome	Presence of a monoclonal plasma cell disorder, peripheral neuropathy, and at least one of the following seven features: osteosclerotic myeloma, Castleman's disease, organomegaly, endocrinopathy (excluding diabetes mellitus or hypothyroidism), edema, typical skin changes, and papilledema. *Note*: Not every patient who meets the above criteria will have POEMS syndrome; the features should have a temporal relationship to each other and no other attributable cause. The absence of either osteosclerotic myeloma or Castleman's disease should make the diagnosis suspect. Elevations in plasma or serum levels of vascular endothelial growth factor and thrombocytosis are common features of the syndrome and are helpful when the diagnosis is difficult.	Dispenzieri[259]

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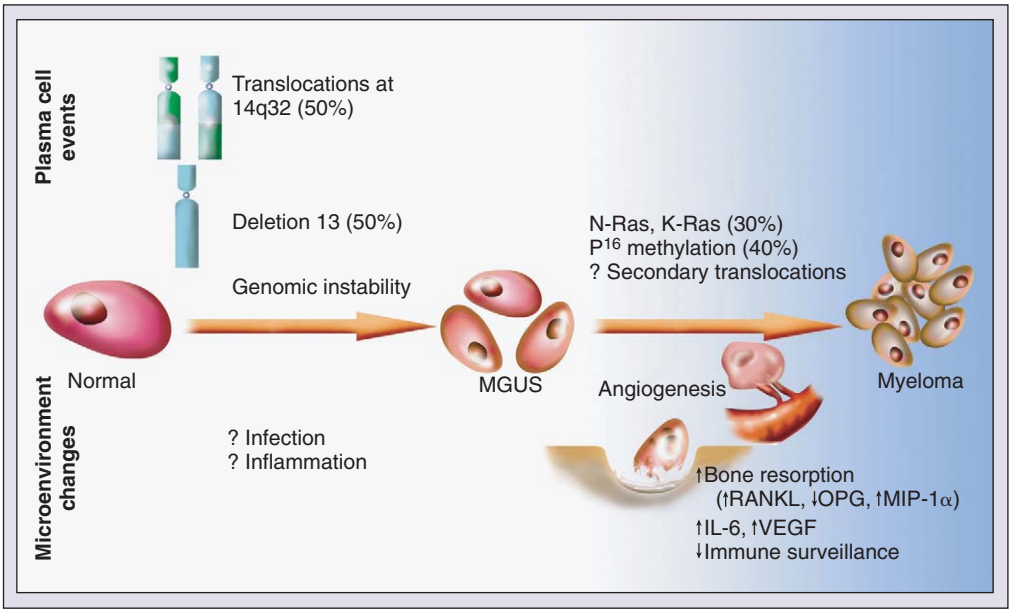


Figure 110-1 • Pathogenesis of myeloma. IL-6, interleukin-6; MGUS, monoclonal gammopathy of undetermined significance; MIP-1α, macrophage inflammatory protein-1α; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor-κB ligand; VEGF, vascular endothelial growth factor.

cells. During this process, plasma cells may acquire one of the various cytogenetic alterations (described in the following sections) that result in a limited clonal plasma cell proliferative process, namely, MGUS.

Immunosuppression either by promoting evasion of tumor surveillance or by promoting antigenic stimulation may also contribute to the initiation of monoclonal gammopathies. Monoclonal proteins have been reported in the context of immunosuppressive states such as bone marrow/stem cell transplantation, organ transplantation, and human immunodeficiency virus infection.[14–17] Patients undergoing renal transplantation develop monoclonal proteins dependent on the level of immunosuppression that they are subjected to.[17]

CYTOGENETIC CHANGES. Over 90% of MGUS is associated with cytogenetic changes that are possibly precipitated by infection or immune dysregulation as discussed previously, likely during immunoglobulin heavy-chain (IgH) switch recombination or somatic hypermutation.[18]

Approximately 50% of patients with MGUS have primary translocations in the clonal plasma cells involving the IgH locus on chromosome 14q32 (IgH translocated MGUS/smoldering multiple myeloma; see Fig. 110-1).[1,18] The most common partner chromosome loci and genes dysregulated in these translocations are 11q13 (CCND1 [cyclin D1 gene]), 4p16.3 (FGFR-3 and MMSET), 6p21 (CCND3 [cyclin D3 gene]), 16q23 (c-maf), and 20q11 (mafB; Table 110-2).[19–21] It is likely that these translocations play an important pathogenetic role in the resultant limited clonal proliferation that is clinically manifested as MGUS.

Approximately 45% of MGUS is associated with hyperdiploidy, usually of the odd-numbered chromosomes with the exception of 13; the origin of the remaining 5% or fewer of MGUS is not clear.[18,22–27] These categories of MGUS that lack evidence of IgH translocations are referred to as IgH nontranslocated MGUS.

Deletion of chromosome 13, a major prognostic factor in multiple myeloma, is seen in up to 50% of patients with MGUS by interphase fluorescent in situ hybridization; hence, the presence of this abnormality cannot be used to differentiate MGUS from multiple myeloma.[21]

Progression of Monoclonal Gammopathy of Undetermined Significance to Malignancy

The constant rate of progression of MGUS to myeloma, macroglobulinemia, or related malignancy in a recent epidemiologic study over a period spanning 30 to 35 years strongly suggests a simple, random, two-hit genetic model of malignancy.[3] The risk of progression is similar regardless of the known duration of antecedent MGUS, suggesting that the second hit that is responsible for progression is a random event, not cumulative damage.

The specific second hit that initiates the cascade of events associated with progression is unknown. Several abnormalities have been detected with progression in both the plasma cell and its microenvironment that likely play a role in the progression of MGUS, but little is known about the sequence of events (see Fig. 110-1). Ras mutations, p16 methylation, abnormalities involving the myc family of oncogenes, secondary translocations, and p53 mutations have all been identified in clonal plasma cells in association with progression to the symptomatic stage.[19] It is possible that the

Table 110-2 Cytogenetic Classification of Monoclonal Gammopathy of Undetermined Significance

Cytogenetic Abnormality	Approximate Percentage of MGUS	Gene(s)/Chromosomes Dysregulated by Translocation
IGH TRANSLOCATED MGUS (50%)		
t(11;14)(q13;q32)	25%	CCND1 (cyclin D1)
t(4;14)(p16;q32)	15%	FGFR-3 and MMSET
t(14;16)(q32;q23)	5%	C-MAF
t(6;14)(p21;q32)	3%	CCND3 (cyclin D3)
t(14;20)(q32;q11)	2%	MAFB
IGH NONTRANSLOCATED MGUS (50%)		
Hyperdiploid MGUS	45%	Recurrent trisomies involving odd-numbered chromosomes with the exception of chromosomes 1, 13, and 21
Unknown	<5%	

MGUS, monoclonal gammopathy of undetermined significance.

second hit that is responsible for disease progression is different in IgH translocated MGUS versus IgH nontranslocated MGUS and even within the various subtypes of IgH translocated MGUS, depending on the partner chromosome involved. For example, amplification of chromosome 1q21 been noted in over 40% of patients with smoldering multiple myeloma and myeloma compared to 0% in MGUS,[28] suggesting that such amplification (e.g., by trisomy 1) might play a role in progression, perhaps in IgH nontranslocated MGUS.

The bone marrow microenvironment undergoes marked changes with progression, including induction of angiogenesis,[29] suppression of cell-mediated immunity,[30] and paracrine loops involving cytokines such as IL-6 and vascular endothelial growth factor.[31] As in solid tumors, the transition from MGUS to multiple myeloma may involve an angiogenic switch. In solitary plasmacytoma, which can be considered to be analogous to localized stage I solid tumor, induction of angiogenesis at the time of diagnosis has been shown to be a predictor of progression to myeloma, suggesting a pathogenetic role for the process in disease progression.[32] Furthermore, there is a gradual increase in degree of bone marrow angiogenesis along the disease spectrum from MGUS to smoldering multiple myeloma to symptomatic myeloma.[29] In one study, approximately 60% of myeloma bone marrow plasma samples stimulated angiogenesis in an in vitro angiogenesis assay, compared to 0% of smoldering multiple myeloma and 7% of MGUS ($P < 0.001$).[33] Increased angiogenesis in myeloma is correlated with disease activity, bone marrow plasma cell involvement, and plasma cell proliferative capacity.

The increased angiogenesis seen in myeloma may be related to expression of proangiogenic cytokines.[34] However, no significant difference is seen in expression of vascular endothelial growth factor, basic fibroblast growth factor, or their receptors between MGUS, smoldering multiple myeloma and myeloma. Loss of angiogenesis inhibitory activity has been noted with disease progression from MGUS to multiple myeloma, which could in part account for the increase in angiogenesis that occurs in myeloma.[33,35] In an in vitro human angiogenesis assay, 63% of MGUS bone marrow plasma samples inhibited angiogenesis, compared to smoldering multiple myeloma (43%) and myeloma (4%; $P < 0.001$).

The formation of new blood vessels may contribute to disease progression by ensuring an adequate tumor nutrient supply as well as by paracrine stimulation of tumor growth. The role of angiogenesis in myeloma has triggered an interest in antiangiogenic therapy for the disease. Studies show that while increased microvessel density in myeloma might not regress following conventional dose or high-dose chemotherapy, regression has been noted in responders with thalidomide, an agent that has known antiangiogenic properties.[36] Clinical trials have been initiated to test the hypothesis that therapy with antiangiogenic agents might inhibit angiogenesis and delay progression in smoldering multiple myeloma.

Pathogenesis of Bone Lesions

Progression of MGUS to myeloma is characterized by the development of bone lesions. Lytic bone lesions in myeloma are caused by an imbalance between the activity of osteoclasts and osteoblasts. There is an increase in receptor activator of nuclear factor κB ligand expression by osteoblasts (and possibly plasma cells) accompanied by a reduction in the level of its decoy receptor, osteoprotegerin.[37,38] This leads to an increase in the receptor activator of nuclear factor κB ligand/osteoprotegerin ratio, which causes osteoclast activation and bone resorption. In addition, increased levels of macrophage inflammatory protein-1a (MIP-1a), IL-3, and IL-6 produced by marrow stromal cells contribute to the overactivity of osteoclasts.

At the same time, increased levels of IL-3, IL-7, and dickkopf 1 (DKK1) inhibit osteoblast differentiation in myeloma. Myeloma cells express DKK1, and increased expression of DKK1 by these cells has been associated with presence of focal bone lesions in myeloma.[39] The combination of osteoclast activation and inhibition of osteoblast differentiation is thought to be the mechanism behind the development of osteolytic lesions in myeloma.

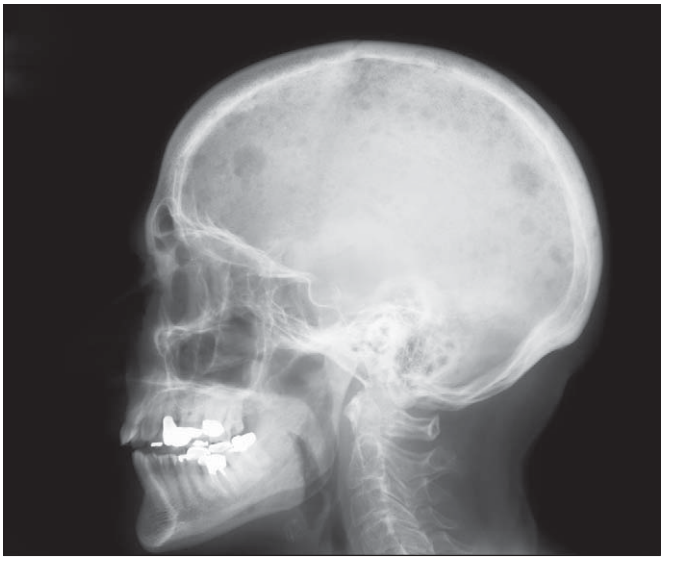


Figure 110-2 • Osteolytic lesions in the skull on plain radiograph in a patient with myeloma.

Clinical Features

The most common presenting symptoms of myeloma are fatigue and bone pain.[7] Osteolytic bone lesions and/or compression fractures that can be detected on routine radiographs, magnetic resonance imaging (MRI), or computed tomographic (CT) scans are the hallmark of the disease and cause significant morbidity (Figs. 110-2 through 110-4). Bone pain may present as an area of persistent pain or migratory bone pain, often in the lower back and pelvis. Pain may be sudden in onset when associated with a pathologic fracture and is often precipitated by movement. Extramedullary expansion of bone lesions may cause nerve root or spinal cord compression. Anemia occurs in 70% of patients at diagnosis and is the primary cause of fatigue. Hypercalcemia is found in one fourth of patients, and the serum creatinine is elevated in almost one half of patients.

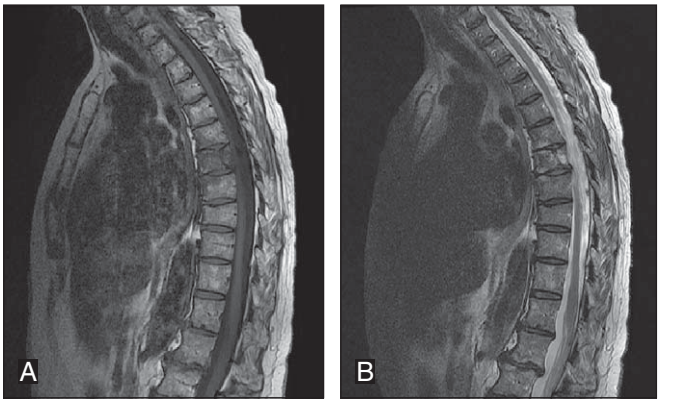


Figure 110-3 • Magnetic resonance imaging of the spine in a patient with myeloma showing marrow edema of T11 and L1 to L3 vertebral bodies. Marrow signal intensity is diffusely heterogeneous, consistent with patient's known clinical diagnosis of multiple myeloma.

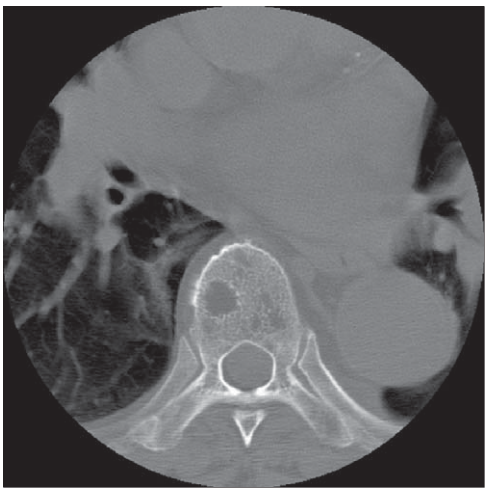


Figure 110-4 • Computed tomographic scan of a vertebral body showing osteolytic bone lesions in a patient with myeloma.

Investigation

A complete blood count, urinalysis, and serum creatinine, calcium, β_2-microglobulin, albumin, c-reactive protein, and lactate dehydrogenase levels are needed for diagnosis, prognosis, and staging. In addition, patients require tests to identify and quantitate monoclonal proteins, bone disease, and bone marrow involvement. Specialized tests are also performed on the bone marrow for risk stratification.

Identification of Monoclonal Proteins

Myeloma is characterized by the presence of monoclonal immunoglobulins in the serum and/or urine. Monoclonal immunoglobulins are commonly referred to as monoclonal proteins, M proteins, or paraproteins. The presence of M proteins is indicative of a clonal plasma cell proliferative disorder such as myeloma, MGUS, or Waldenström's macroglobulinemia. Additional tests are required to distinguish between the various plasma cell disorders.

M proteins can be detected by serum protein electrophoresis (SPEP) in 82% of patients with myeloma and by serum immunofixation in 93%.[7] Up to 20% of patients with myeloma lack heavy-chain expression in the M protein and are considered to have light-chain myeloma. The M protein in these patients is always detected in the urine but can be absent in the serum even by immunofixation, making it imperative that protein electrophoresis and immunofixation are always done on both the serum and the urine in all patients in whom myeloma is suspected. Addition of urine protein electrophoresis (UPEP) and urine immunofixation will increase the sensitivity of detecting M proteins in patients with myeloma to 97%. Most (60%) of the remaining patients who are negative for M protein on serum and urine electrophoresis and immunofixation studies will have evidence of clonal paraproteins on the serum free light-chain assay. Currently, only 1% to 2% of patients with myeloma will have no detectable M on any of these tests; these patients have true nonsecretory myeloma.

SERUM PROTEIN ELECTROPHORESIS AND IMMUNOFIXATION. Agarose gel SPEP and immunofixation are the preferred methods of detection of serum M proteins (Fig. 110-5). M proteins appear as a localized band on SPEP.[40] After recognition of a localized band that is suggestive of an M protein on SPEP, immu-

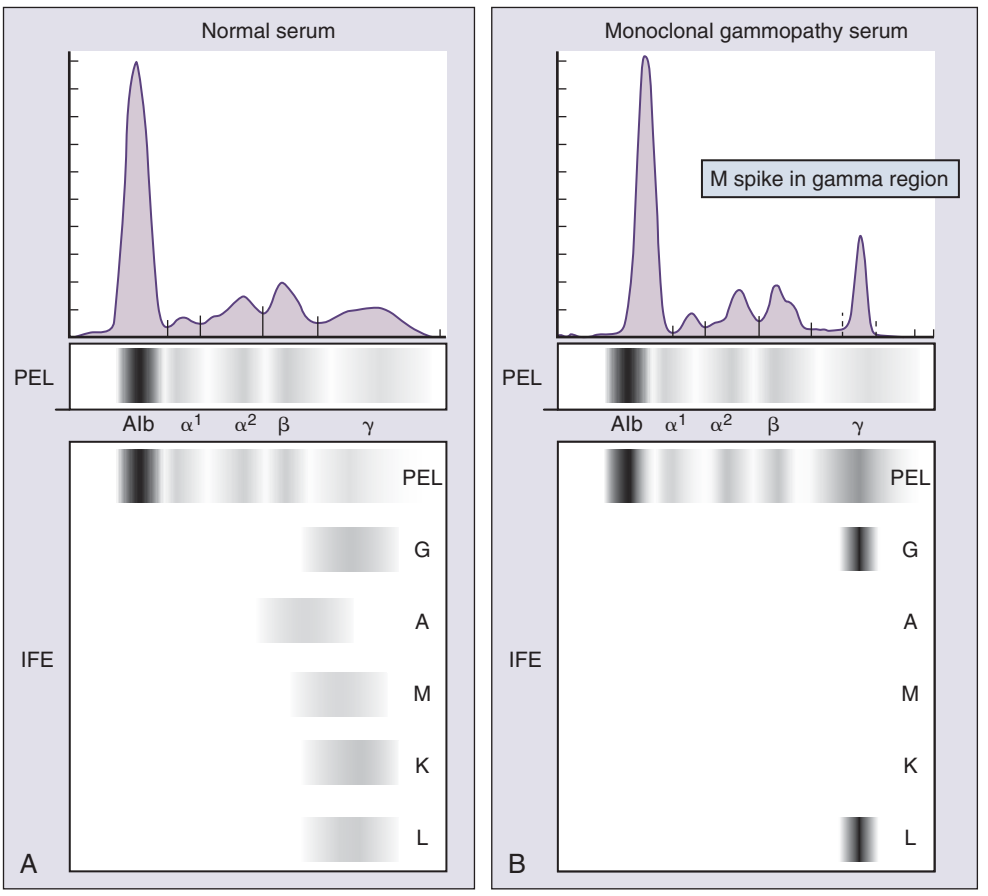


Figure 110-5 • **A,** Serum protein electrophoresis (PEL) and immunofixation (IFE) showing a normal pattern with no evidence of monoclonal protein. **B,** PEL showing a monoclonal (M) protein in the gamma region, which is IgG lambda on IFE.

nofixation is necessary for confirmation and to determine the heavy- and light-chain class of the M protein. In addition, immunofixation is more sensitive than SPEP and allows detection of smaller amounts of M protein and should therefore be performed whenever myeloma, amyloidosis, macroglobulinemia, or a related disorder is suspected. The size of the M protein is measured by using the SPEP; small M proteins that are not apparent on SPEP but are apparent only on immunofixation are considered unmeasurable.

QUANTITATIVE IMMUNOGLOBULIN STUDIES. Quantitation of serum immunoglobulins is performed with a rate nephelometer in patients in whom M proteins are detected. It is an added parameter that can be followed particularly in patients with myeloma and macroglobulinemia, in which at times the M protein size estimated on SPEP can be unreliable (e.g., small beta migrating proteins and IgA/IgM proteins that tend to polymerize)

URINE PROTEIN ELECTROPHORESIS AND IMMUNOFIXATION. Typically, screening for suspected monoclonal gammopathies has included UPEP and immunofixation in addition to the serum studies that were discussed earlier, since a subset of patients with myeloma and amyloidosis may have an M protein that is restricted to the urine and absent on serum studies. In such patients, the diagnosis of plasma cell dyscrasia would be missed if urine studies were not performed. A 24-hour urine specimen is required for UPEP and immunofixation. Urine M protein levels are measured on UPEP and are used in monitoring disease progression and response to therapy.

SERUM-FREE LIGHT-CHAIN ASSAY. Measurement of the serum free light-chain assay (Freelite, The Binding Site Limited, Birmingham, U.K.) has recently been introduced into clinical practice.[41] This automated nephelometric assay allows quantitation of free kappa and lambda chains (i.e., light chains that are not bound to intact immunoglobulin) secreted by plasma cells. An abnormal kappa/lambda free light-chain ratio indicates an excess of one light-chain type versus the other and is interpreted as a surrogate for clonal expansion based on extensive testing in normal volunteers, and patients with myeloma, amyloidosis and renal dysfunction.[41,42] The assay is performed on automated chemistry analyzers, is widely available, and is commonly used to monitor patients with oligosecretory or nonsecretory myeloma and primary amyloidosis, as well as patients with the light-chain-only form of myeloma.[42–44]

The normal serum free kappa level is 3.3 to 19.4 mg/L, and the normal free lambda level is 5.7 to 26.3 mg/L.[45] The normal ratio for free light-chain kappa/lambda is 0.26 to 1.65. The normal reference range in the free light-chain assay reflects a higher serum level of free lambda light chains than would be expected given the usual kappa/lambda ratio of 2 for intact immunoglobulins. This occurs because the renal excretion of free kappa (which exists usually in a monomeric state) is much faster than that of free lambda (which is usually in a dimeric state).[41,42] Patients with a kappa/lambda free light-chain ratio less than 0.26 are typically defined as having monoclonal lambda free light chain, and those with ratios greater than 1.65 are defined as having a monoclonal kappa free light chain. If the free light-chain ratio is greater than 1.65, kappa is considered to be the "involved" free light chain, and lambda is considered to be the "uninvolved" free light chain, and vice versa if the ratio is less than 0.26.

In a recent study, 428 patients with a monoclonal gammopathy and urine M protein at initial diagnosis of plasma cell dyscrasia who had also undergone serum immunofixation and serum free light-chain quantitation within 30 days of diagnosis were studied.[46] The results of SPEP, serum immunofixation, serum free light-chain, UPEP, and urine immunofixation were then analyzed to determine whether all patients could be accurately identified as having a monoclonal plasma cell disorder had the urine studies not been done. All three serum studies were normal in only two patients (0.5% of the cohort), indicating that urine studies can be eliminated in screening for the presence of monoclonal plasma cell disorders by using the serum free light-chain assay in combination with the SPEP and immunofixation. However, urine studies are required if a monoclonal process is identified, since it helps in monitoring disease progression and response to therapy over time.

Identification of Bone Disease

Plain radiographic examination of all bones, including long bones (skeletal survey), is the preferred method of detecting lytic bone lesions in myeloma. Conventional x-rays show skeletal abnormalities in almost 80% of patients with myeloma; often, these lesions have a characteristic punched-out appearance. Osteoporosis and/or fractures are also detected by conventional radiography. Occasionally, osteosclerotic lesions can occur. CT and MRI scans are more sensitive than is conventional radiography in detecting bone disease. Among asymptomatic multiple myeloma patients with normal x-rays, up to 50% have tumor-related abnormalities on MRI of the lower spine. CT and/or MRI studies are indicated when symptomatic areas show no abnormality on routine radiographs. There routine use in assessing extent of bone disease in addition to skeletal radiographs is unclear.

Fluorodeoxyglucose positron emission tomography has shown promise in the evaluation of bone disease and in staging of myeloma (Fig. 110-6). However, the routine use of this method and its specific role in management need further investigation. The role of bone mineral density studies in myeloma and the use of these studies in identifying patients who are at risk for pathologic fractures and prophylactic bisphosphonate therapy also remains unresolved.

Bone Marrow Studies

Unilateral bone marrow aspiration and biopsy are indicated in all patients with myeloma. By definition, all patients with myeloma should have 10% or more clonal bone marrow plasma cells. If a lower extent of involvement is detected, either one is dealing with an erroneous diagnosis or there is a sampling error due to patchy marrow involvement, in which case a repeat marrow biopsy is indicated. Occasionally an entity called "multiple" solitary plasmacytomas has been described in which there are clearly multiple plasmacytomas on clinical and radiographic examination but marrow involvement is either minimal or absent. The monoclonal (or, more accurately, monotypic) nature of bone marrow plasma cells is established by the demonstration of an abnormal kappa/lambda ratio by immunohistochemistry or flow cytometry. On flow cytometry, plasma cells in

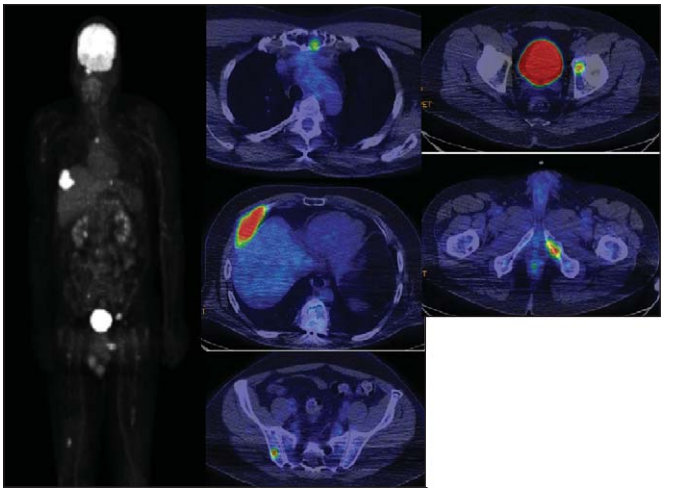


Figure 110-6 • Fluorodeoxyglucose positron emission tomography imaging of bone lesions in a patient with myeloma showing lesions in the sternum, right rib, right ilium, left hip, and left ischium.

multiple myeloma typically stain positive for CD38, CD56, and CD138 and are usually negative for surface immunoglobulin and CD19. Up to 20% stain positively for CD20. Morphologically, the presence of immature blast-like plasma cells (plasmablastic morphology) carries an adverse prognosis.

Given their impact on prognosis (see "Prognosis"), bone marrow samples should be studied by conventional karyotyping studies and/or fluorescent in situ hybridization studies to detect specific abnormalities such as t4;14, t14;16, and 17p-. The bone marrow plasma cell labeling index should be performed, if available.

Differential Diagnosis

In patients with evidence of M proteins, the main differential diagnosis is between myeloma, MGUS, smoldering myeloma, macroglobulinemia, and primary amyloidosis. These disorders are distinguished from each other by using the criteria listed in Table 110-1. In patients with marrow plasmacytosis, monoclonal plasma cell disorders are differentiated from polyclonal reactive plasmacytosis that occurs in conditions such as autoimmune diseases, metastatic carcinoma, chronic liver disease, acquired immunodeficiency syndrome, or chronic infection based on kappa/lambda staining. In monoclonal plasma cell disorders, plasma cells express either kappa or lambda, resulting in a markedly abnormal kappa:lambda ratio. In contrast both kappa-staining plasma cells and lambda-staining plasma cells (usually in a kappa:lambda ratio of 2 : 1) are seen in disorders in which there is reactive plasmacytosis.

Bone lesions in a patient with MGUS due to an unrelated metastatic carcinoma may be mistaken for multiple myeloma. The presence of a small M protein and fewer than 10% plasma cells in the bone marrow makes metastatic carcinoma with an unrelated MGUS more likely. If there is any doubt, a biopsy of one of the lytic lesions is needed.

Table 110-3 Prognostic Factors in Myeloma

MAJOR INDEPENDENT PROGNOSTIC FACTORS

- Performance status
- Stage (International Staging System)
  - Stage I (serum β_2-microglobulin < 3.5 mg/L and albumin ≥ 3.5 g/dL; median survival: 62 months)
  - Stage II (not fitting stage I or II; median survival: 44 months)
  - Stage III (serum β_2-microglobulin ≥ 5.5 mg/L; median survival: 29 months)
- Cytogenetic changes
  - Abnormal cytogenetics by karyotyping (especially deletion 13 or hypodiploidy)
  - Translocations t(4;14) or t(14;16) on fluorescent in situ hybridization
  - Deletion 17p on fluorescent in situ hybridization
- Serum lactate dehydrogenase
- Plasmablastic morphology
- Bone marrow plasma cell labeling index

OTHER PROGNOSTIC MARKERS

- Advanced age
- Stage (Dure-Salmon stage)
- C-reactive protein
- Serum creatinine
- Platelet count
- Increased circulating plasma cells by flow cytometry or immunofluorescence

Prognosis

Stage

Historically, although median survival has been approximately 3 years,[7] some patients can live longer than 10 years.[47–50] Survival depends on disease stage, and since 1975, the Durie-Salmon staging system has been used to stratify patients with multiple myeloma.[51] However, this staging system has limitations, especially in the categorization of bone lesions.[52,53] Recently, Greipp and colleagues developed the new International Staging System (ISS), a collaborative effort by investigators from 17 institutions worldwide and data on 11,171 patients.[54] The ISS overcomes the limitations of the Durie-Salmon staging and divides patients into three distinct stages and prognostic groups based solely on the β_2-microglobulin and albumin levels in the serum (Table 110-3).

Prognostic Factors

Once a patient has been staged using the ISS, several additional independent prognostic factors are used to further help predict outcome in myeloma (see Table 110-3).[18,52,55–57] In general, a combination of two or more of the independent prognostic factors provides adequate information to estimate prognosis. Facon and colleagues have shown that patients undergoing stem cell transplantation (SCT) can be grouped into three clear prognostic categories using two prognostic factors; median survival was 25 months if patients had a high β_2-microglobulin level and deletion of chromosome 13 by fluorescent in situ hybridization.[58] Patients with only one abnormal factor had a median survival of 47 months, while survival was in excess of 111 months in patients in whom both factors were normal.

Age, hemoglobin concentration, creatinine, calcium, albumin, immunoglobulin class subtype, and extent of bone marrow involvement have also demonstrated prognostic value.[52,55,57] However, they have limited predictive value once the ISS and the independent prognostic factors discussed earlier are known.[59,60] Newer risk factors such as angiogenesis shed light on biology, but clinical utility is unclear.

Risk Stratification

The specific prognostic factors that are used to stratify patients at the Mayo Clinic into high-risk and standard-risk myeloma to guide therapeutic strategy are deletion 13 or hyperdiploidy on metaphase cytogenetic studies, deletion 17p- or immunoglobulin heavy-chain (IgH) translocations t(4;14) or t(14;16), or a plasma cell labeling index of 3% or higher (Table 110-4). The presence of any one or more of the preceding high-risk factors classifies a patient as having high-risk multiple myeloma. The median survival of high-risk multiple myeloma is only 2 to 3 years even with tandem SCT, compared to over 6 to 7 years in patients with average-risk multiple myeloma.[2]

Management

The median survival of symptomatic myeloma is 3 to 4 years. For decades, the mainstay of therapy had been oral chemotherapy with melphalan and prednisone (MP). High-dose therapy with autologous stem cell transplantation (ASCT) prolongs survival compared to conventional chemotherapy and is now routinely incorporated into the treatment strategy either early in the disease course or at the time of relapse in eligible patients. More recently, thalidomide,[61] bortezomib,[62,63] and lenalidomide,[64,65] have emerged as effective agents in the treatment of myeloma.

There is no evidence that early treatment of patients with asymptomatic (smoldering) multiple myeloma prolongs survival compared to therapy at the time of symptoms. However, clinical trials are ongoing to determine whether newer agents can delay progression.

Table 110-4 Mayo Clinic Criteria for High-Risk Multiple Myeloma

High-Risk Characteristic	Percentage of Newly Diagnosed Patients with the Abnormality (%)[7,18,266]
Conventional cytogenetics	
Deletion of chromosome 13 (monosomy)	14
Hypodiploidy	9
Either hypodiploidy or deletion 13	17
Fluorescent in situ hybridization	
t(4;14)	15
t(14:16)	5
17p-	10
Plasma cell labeling index studies: PCLI ≥ 3%	6
Any one of the above high-risk abnormalities	25%–30%

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Initial therapy depends on eligibility for SCT and risk stratification. Eligibility for SCT is determined by age, performance status, and coexisting comorbidities. Risk stratification is based on presence or absence of high-risk factors (see Table 110-4)[66] The approach to treatment of symptomatic newly diagnosed multiple myeloma at Mayo Clinic is outlined in Figure 110-7A and B. Table 110-5 lists the most common regimens used in the treatment of newly diagnosed myeloma. Response to therapy is assessed by using the International Myeloma Working Group Uniform Response Criteria (Table 110-6).[67]

Initial Therapy in Standard-Risk Patients Who Are Eligible for Transplantation

It is important to avoid protracted melphalan-based therapy in patients with newly diagnosed myeloma who are considered eligible for ASCT, since the therapy can interfere with adequate stem cell mobilization, regardless of whether an early or delayed transplant is contemplated. Typically, patients are treated with approximately four cycles of induction therapy prior to stem cell harvest. This includes patients who are transplant candidates but who wish to reserve ASCT as a delayed option for relapsed or refractory disease. Such patients can resume induction therapy following stem cell collection until a plateau phase is reached, reserving ASCT for relapse.

The combination of vincristine, doxorubicin, and dexamethasone (VAD) was used for many years as pretransplant induction therapy for patients who were considered candidates for ASCT. However, VAD requires an intravenous indwelling catheter, which predisposes patients to catheter-related sepsis and thrombosis. Moreover, the neurotoxicity of vincristine can limit the future use of thalidomide and bortezomib, both of which also have neurotoxic potential. Most of the activity of VAD is from the high-dose dexamethasone component. Recently, Cavo and colleagues, in a matched case-control study of 200 patients, demonstrated that response rates with VAD were significantly lower than those with thalidomide-dexamethasone (Thal/Dex): 76% versus 52%, respectively.[68] Preliminary results from

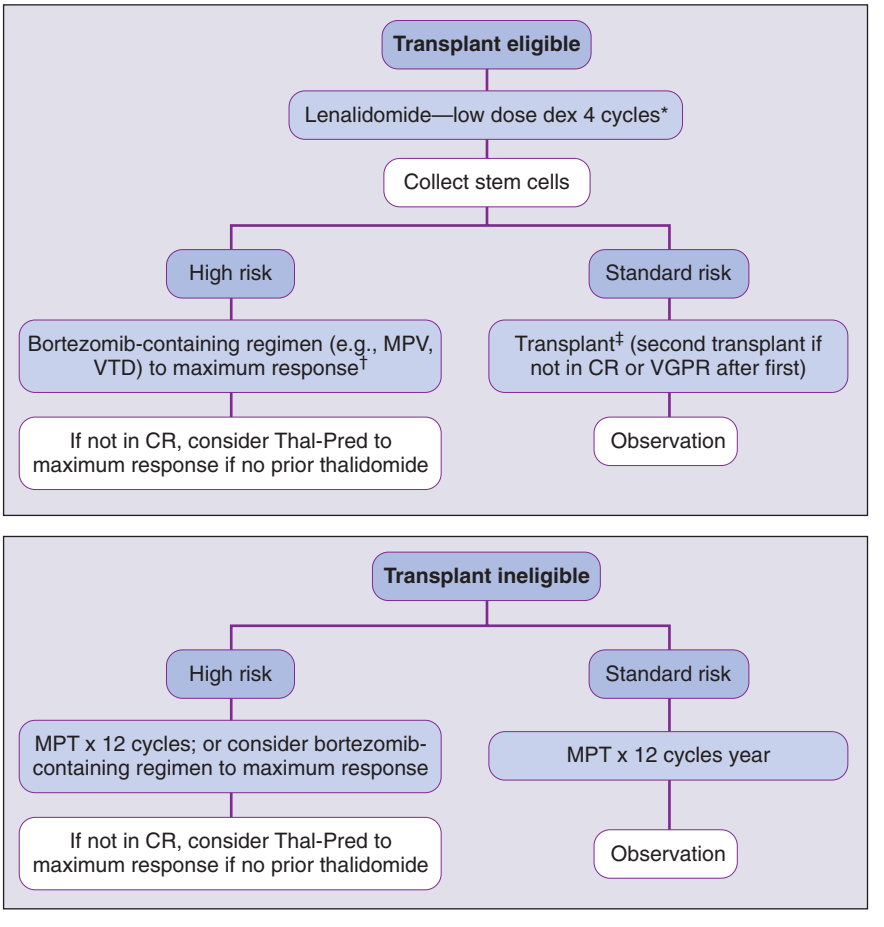


Figure 110-7 • A, Approach to the treatment of newly diagnosed myeloma in patients who are eligible for stem cell transplantation. **B,** Approach to the treatment of newly diagnosed myeloma in patients who are not eligible for stem cell transplantation. CR, complete response; Dex, dexamethasone; max, maximum; MPT, melphalan-prednisone-thalidomide; MPV, melphalan-prednisone-bortezomib; Rev/Dex, lenalidomide plus dexamethasone; Thal-Pred, thalidomide-prednisone; VGPR, very good partial response; VTD, bortezomib-thalidomide-dexamethasone. *If no response after 2 cycles, consider bortetxomib-containing regimen. †Potential allogenic approaches considered in selected patients. ‡If transplant deferred, continue induction to max response.

Table 110-5 Selected Regimens for the Treatment of Newly Diagnosed Multiple Myeloma

Regimen	Usual Dosing Schedule*
Melphalan-prednisone (MP) (7-day schedule)[1]	Melphalan 8–10 mg oral days 1–7
	Prednisone 60 mg/day oral days 1–7
	Repeated every 6 weeks until plateau
Melphalan-prednisone (MP) (4-day schedule)[84]	Melphalan 0.25 mg/kg (9 mg/m^2) oral days 1–4
	Prednisone 2 mg/kg oral days 1–4
	Repeated every 4–6 weeks until plateau
Thalidomide-dexamethasone (Thal/Dex)[70]	Thalidomide 200 mg oral days 1–28
	Dexamethasone 40 mg oral days 1, 8, 15, 22
	Repeated every 4 weeks × 4 cycles as pretransplant induction therapy or continued until plateau or progression if used as primary therapy
Lenalidomide-dexamethasone (Rev/low-dose Dex)[78]	Lenalidomide 25 mg oral days 1–21 every 28 days
	Dexamethasone 40 mg oral days 1, 8, 15, 22 every 28 days
	Repeated every 4 weeks × 4 cycles as pretransplant induction therapy; or continued until plateau or progression if used as primary therapy
Bortezomib-dexamethasone (Vel/Dex)[81]	Bortezomib 1.3 mg/m^2 intravenous days 1, 4, 8, 11
	Dexamethasone 40 mg oral days 1–4, 9–12
	Reduce dexamethasone to days 1–4 after first 2 cycles
	Repeated every 3 weeks × 4 cycles as pretransplant induction therapy
Melphalan-prednisone-thalidomide (MPT)[84]	Melphalan 0.25 mg/kg oral days 1–4
	Prednisone 2 mg/kg oral days 1–4
	Thalidomide 100–200 mg oral days 1–28
	Repeated every 6 weeks × 12 cycles
Melphalan-prednisone-bortezomib (MPV)[110]	Melphalan 9 mg/m^2 oral days 1–4
	Prednisone 60 mg/m^2 oral days 1–4
	Bortezomib 1.3 mg/m^2 intravenous days 1, 4, 8, 11, 22, 25, 29, 32
	Repeated every 42 days × 4 cycles followed by maintenance therapy as given below:
	Melphalan 9 mg/m^2 oral days 1–4
	Prednisone 60 mg/m^2 oral days 1–4
	Bortezomib 1.3 mg/m^2 intravenous days 1, 8, 15, 22
	Repeated every 35 days × 5 cycles
Melphalan-prednisone-lenalidomide (MPR)	Melphalan 0.18 mg/kg oral days 1–4
	Prednisone 2 mg/kg oral days 1–4
	Lenalidomide 10 mg oral days 1–28
	Repeated every 4–6 weeks × 9 cycles
Bortezomib-thalidomide-dexamethasone (VTD)[267]	Bortezomib 1.3 mg/m^2 intravenous days 1, 4, 8, 11
	Thalidomide 100–200 mg oral days 1–21
	Dexamethasone 20 mg/m^2 oral days 1–4, 9–12, 17–20
	Reduce dexamethasone to days 1–4 after first two cycles
	Repeated every 4 weeks × 4 cycles as pretransplant induction therapy

*Starting and subsequent doses need to be adjusted for performance status, renal function, blood counts, and other toxicities.

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Table 110-6 Response Criteria for Multiple Myeloma

Response Subcategory	Response Criteria
Complete response (CR)	• Negative immunofixation on the serum and urine *and* • Disappearance of any soft tissue plasmacytomas *and* • <5% plasma cells in bone marrow
Stringent complete response (sCR)	CR as defined above *plus* • Normal free light chain ratio *and* • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence
Very good partial response (VGPR)	• Serum and urine M component detectable by immunofixation but not on electrophoresis *or* • ≥90% or greater reduction in serum M component plus urine M component <100 mg per 24 hours
Partial response (PR)	• ≥50% reduction of serum M protein and reduction in 24-hour urinary M protein by ≥90% or to <200 mg per 24 hours • If the serum and urine M protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M protein criteria • If serum and urine M protein are unmeasurable and serum free light assay is also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M protein, provided that the baseline percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease (PD)	Increase of 25% from lowest response value in • Serum M component (absolute increase must be ≥0.5 g/dL) *and/or* • Urine M component (absolute increase must be ≥200 mg/24 hours) *and/or* • Only in patients without measurable serum and urine M protein levels: the difference between involved and uninvolved free light chain levels (absolute increase must be >10 mg/dL) • Bone marrow plasma cell percentage (absolute percentage must be 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft-tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All response categories (CR, sCR, VGPR, PR) require two consecutive assessments made at any time before the institution of any new therapy; complete and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed.

Data from reference 67.

a randomized trial from France confirm these findings.[69] As a result, VAD is no longer recommended as initial therapy.

Dexamethasone alone has also been used as induction therapy. It is typically used at a dose of 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20 every 4 to 5 weeks. Objective response rates are approximately 45%,[70] significantly lower than those of newer induction regimens. In randomized trials, the early mortality rate associated with dexamethasone is over 10% in the first 4 months of therapy, reflecting the toxicity and ineffectiveness of this regimen. Consequently, single-agent dexamethasone is also no longer recommended as initial therapy.

The main choices for initial therapy are Thal/Dex, bortezomib-based regimens, and lenalidomide-dexamethasone (Rev/Dex). All of these regimens act rapidly and are associated with high response rates. Thal/Dex and Rev/Dex have the added advantage of being orally administered. Thal/Dex and Rev/Dex are associated with an increased risk of deep vein thrombosis (DVT), necessitating routine thromboprophylaxis.

THALIDOMIDE-DEXAMETHASONE. The finding of increased angiogenesis in myeloma and recognition of the antiangiogenic properties of thalidomide led to the first clinical trial with the agent. This trial demonstrated a response rate of 25% in heavily pretreated patients with relapsed or refractory disease.[61] Since then, several studies have confirmed response rates of 25% to 35% in relapsed and refractory myeloma, with a median response duration of approximately 1 year. Thalidomide is usually given orally in a dose of 100 to 200 mg daily. After a response has been achieved, the dose is adjusted to the lowest dose that can achieve and maintain a response, in order to minimize long-term toxicity. Response rates in relapsed disease are about 50% with thalidomide plus corticosteroids and over 65% with a three-drug combination of thalidomide, corticosteroids, and alkylators.

In the last few years, Thal/Dex has emerged as the most commonly used induction regimen for the treatment of newly diagnosed myeloma in the United States. The use of Thal/Dex was initially based on three phase II clinical trials.[71–73] Response rates with Thal/Dex range from 64% to 76% in these studies, comparable to or better than those obtained with infusional VAD.

The Eastern Cooperative Oncology Group (ECOG) recently reported the results of a randomized trial comparing Thal/Dex to dexamethasone (Table 110-7).[70] Two hundred seven patients were studied. The best response within four cycles of therapy was significantly higher with Thal/Dex than with dexamethasone alone: 63% versus 41%, respectively ($P = 0.0017$). Adjusted response rates allowing for the use of serum M protein values alone in patients in whom

Table 110-7 Results of Major Randomized Trials Using New Active Agents for Multiple Myeloma

Trial	Study Regimens	Disease Stage	No. of Patients	Primary Results	Major Toxicity
E1A00[70]	Thalidomide plus dexamethasone (Thal/Dex) versus dexamethasone alone (Dex)	Newly diagnosed myeloma	202	Superior response rate with Thal/Dex compared to Dex, 58% versus 42%, respectively ($P = 0.02$). Grade 3 nonhematologic toxicity higher with Thal/Dex compared to Dex, 68% versus 43%, respectively.	Deep vein thrombosis (DVT) occurred in 18% of patients in the Thal/Dex arm within first 4 months of therapy, indicating need for routine prophylactic anticoagulation while using this regimen; DVT was seen in 3% of patients treated with Dex.
MM003[74]	Thalidomide plus dexamethasone (Thal/Dex) versus placebo plus dexamethasone (Dex)	Newly diagnosed myeloma	202	Superior response rate with Thal/Dex compared to Dex, 58% versus 42%, respectively ($P = 0.02$). Superior time to progression. Grade III nonhematologic toxicity higher with Thal/Dex compared to Dex: 68% versus 43%, respectively.	DVT occurred in 18% of patients in the Thal/Dex arm within first 4 months of therapy, indicating need for routine prophylactic anticoagulation while using this regimen; DVT was seen in 3% of patients treated with Dex.
Italian[83]	Melphalan-prednisone (6 cycles) versus melphalan, prednisone, thalidomide (MPT) (6 cycles with maintenance thalidomide)	Newly diagnosed myeloma	200	Superior response rate with MPT compared to MP, 76% versus 48%, respectively; event free survival at 24 months was 54% versus 27%, respectively ($P < 0.001$).	No significant differences in overall survival seen so far. DVT occurred in 19% of patients in the MPT arm compared to 2% in the MP arm, indicating need for routine prophylactic anticoagulation while using MPT.
IFM 99-06[84]	Melphalan-prednisone (MP) (12 cycles) versus melphalan, prednisone, thalidomide (MPT) (12 cycles) versus intermediate-dose melphalan × 2 courses with stem cell support (Mel 100)	Newly diagnosed myeloma	200	Superior response rates, PFS (17 versus 30 versus 19 months) and OS (30 versus not reached versus 39 months) in MPT arm.	Accrual restricted to patients 65–75 years of age. DVT occurred in 6%, 9%, and 4% of patients treated with MP, MPT, and Mel 100, respectively.
E4A03	Lenalidomide plus standard-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in relapsed myeloma	Newly diagnosed myeloma	445	Superior survival at 4 months postinduction therapy with lenalidomide plus low-dose dexamethasone compared to lenalidomide plus standard-dose dexamethasone, 0.5% versus 5%, respectively ($P <$ 0.001).	
IFM 99-02[82]	Bortezomib-dexamethasone versus vincristine, doxorubicin, dexamethasone (VAD)	Newly diagnosed myeloma	222 (interim analysis)		Additional chemotherapy with doxorubicin, cyclophosphamide, cisplatin, and etoposide were also studied in this trial.
IFM 99-02[115]	No therapy versus pamidronate versus pamidronate plus thalidomide as maintenance therapy following tandem autologous stem cell transplantation	Posttandem auto transplant	597	Event-free survival rate at 3 years was 36%, 37%, and 52%, with no maintenance, pamidronate and pamidronate plus thalidomide, respectively ($P < 0.01$). Corresponding 4-year overall survival was 77%, 74%, and 87%, respectively ($P < 0.04$).	In this trial, 597 low-risk patients (lack of concomitant B2M>3 and deletion 13 by fluorescent in situ hybridization) who were treated with induction chemotherapy with the VAD (vincristine, doxorubicin, and dexamethasone) regimen followed by tandem autologous transplantation were randomized to maintenance therapy.

Table 110-7 Results of Major Randomized Trials Using New Active Agents for Multiple Myeloma—cont'd

Trial	Study Regimens	Disease Stage	No. of Patients	Primary Results	Major Toxicity
APEX[63]	Bortezomib versus dexamethasone for relapsed refractory myeloma	Relapsed myeloma	669	Median time to progression 5.7 months with bortezomib compared to 3.6 months with dexamethasone alone ($P <$ 0.001).	
010 Trial[145]	Lenalidomide plus dexamethasone versus placebo plus dexamethasone in relapsed myeloma	Relapsed myeloma	351	Superior time to progression with lenalidomide plus dexamethasone compared to placebo plus dexamethasone, 13 months versus 5 months, respectively ($P < 0.001$).	Thrombosis risk: 8.5% versus 4.5%.
009 Trial[76]	Lenalidomide plus dexamethasone versus placebo plus dexamethasone in relapsed myeloma	Relapsed myeloma	354	Superior time to progression with lenalidomide plus dexamethasone compared to placebo plus dexamethasone, >11 months versus 5 months, respectively, ($P < 0.001$). Superior overall survival: not reached versus 24 months.	Thrombosis risk: 15% versus 30%.

a measurable urine protein at baseline was unavailable at follow-up were 72% with Thal/Dex versus 50% with dexamethasone alone. Stem cell harvest was successful in 90% of patients in each arm. DVT was more frequent with Thal/Dex (17% versus 3%). Overall, grade III or higher nonhematologic toxicities were seen in 67% of patients within four cycles with Thal/Dex and 43% with dexamethasone alone ($P < 0.001$). Early mortality (first 4 months) was 7% with Thal/Dex and 11% with dexamethasone alone. On the basis of this trial, the U.S. Food and Drug Administration (FDA) has granted accelerated approval for Thal/Dex for the treatment of newly diagnosed myeloma.

Preliminary results are available from a separate randomized, double-blind, placebo-controlled study comparing Thal/Dex versus dexamethasone alone as primary therapy in 470 patients with newly diagnosed myeloma.[74] Among 470 patients enrolled, the response rate was significantly higher with Thal/Dex than with placebo/Dex: 59% versus 42%, respectively ($P < 0.001$). Time to progression (TTP) was also significantly superior with Thal/Dex ($P < 0.001$). As in the ECOG trial, DVT and other grade III to IV events were more frequent with Thal/Dex.

The incidence of DVT is 1% to 3% in patients receiving thalidomide alone but rises to approximately 15% to 20% in patients receiving thalidomide in combination with dexamethasone and over 25% in patients receiving the agent in combination with other cytotoxic chemotherapeutic agents, particularly doxorubicin. Patients who are receiving thalidomide in combination with high-dose steroids or chemotherapy need routine thromboprophylaxis with coumadin (target INR 2 to 3) or low-molecular-weight heparin (equivalent of enoxaparin 40 mg once daily). Aspirin can be used instead in patients who are receiving only low doses of dexamethasone (40 mg once a week or lower) or prednisone in combination with thalidomide, provided that no concomitant erythropoietic agents are used.

LENALIDOMIDE-DEXAMETHASONE. Lenalidomide (CC-5013) belongs to a class of thalidomide analogs that are termed *immunomodulatory drugs*. Lenalidomide appears to be safer and more effective than thalidomide in preclinical and clinical studies. Richardson and colleagues reported activity in a multicenter randomized phase II trial that enrolled 102 patients with relapsed or refractory myeloma.[65] The overall response rate with single-agent lenalidomide was 17%. Two large phase III trials have since shown significantly superior TTP with lenalidomide plus dexamethasone (Rev/Dex) compared to placebo plus dexamethasone in relapsed myeloma.[75,76] Rev/Dex is currently approved by the FDA for the treatment of myeloma in patients who have failed one prior therapy.

In newly diagnosed myeloma, a phase II trial conducted at the Mayo Clinic demonstrated remarkably high activity with the Rev/Dex regimen. Thirty-one of 34 patients (91%) achieved an objective response, including 2 (6%) who achieved complete response (CR), and 11 (32%) who met criteria for very good partial response (VGPR).[64] Lacy and colleagues recently updated the results of this study. With longer follow-up, 56% of patients achieved very good partial response or better. In the subset of 21 patients receiving Rev/Dex as primary therapy without ASCT, 67% achieved VGPR or better.[77] Approximately 50% of patients experienced grade III or higher nonhematologic toxicity, similar to rates that are seen with dexamethasone alone.

ECOG recently reported preliminary findings of a randomized trial testing Rev/Dex as administered in the Mayo Phase II trial (and in the regulatory relapsed or refractory myeloma studies) versus Rev/low-dose Dex (40 mg dexamethasone once weekly).[78] Results so far show that toxicity rates are significantly higher with Rev/standard-dose Dex than with Rev/low-dose Dex. Early (first 4 months) mortality rates were low in both arms: 5% and 0.5%, respectively. The early mortality rate in the Rev/low-dose Dex arm is probably the lowest reported in any large phase III trial involving newly diagnosed patients in which enrollment was not restricted by age or eligibility for SCT. DVT rates are also low, making this one of the safest pretransplant induction regimens for myeloma. Moreover, one- and two-year overall survival rates are significantly superior with Rev/low-dose Dex. Consequently, we do not recommend the use of high-dose dexamethasone in the treatment of newly diagnosed myeloma. On the basis of these results, Rev/low-dose Dex is currently the regimen of choice in the Mayo Stratification for Myeloma and Risk-Adapted Therapy (mSMART) protocol for the treatment of standard-risk myeloma in patients who are candidates for ASCT outside the setting of a clinical trial.[66]

The incidence of DVT is low with single-agent lenalidomide or lenalidomide plus low-dose dexamethasone but rises markedly when the agent is combined with high-dose dexamethasone. Recommenda-

tions for thromboprophylaxis are similar to those discussed previously with Thal/Dex. Aspirin alone is probably sufficient for patients receiving lenalidomide plus low-dose dexamethasone.

BORTEZOMIB-BASED REGIMENS. Bortezomib (formerly known as PS-341) is a novel proteasome inhibitor that has been approved for the treatment of patients with relapsed and refractory multiple myeloma. In 202 patients with relapsed or refractory multiple myeloma, approximately one third responded to bortezomib therapy, with an average response duration of 1 year.[62] In a recent randomized trial, progression-free survival (PFS) was superior with bortezomib than with dexamethasone alone in patients with relapsed or refractory multiple myeloma.[63] Bortezomib is currently approved by the FDA for the treatment of myeloma in patients who have failed one prior therapy.

In newly diagnosed myeloma, bortezomib has shown response rates of approximately 40% as a single-agent.[79] Significantly higher response rates (approximately 70% to 90%) have been observed with bortezomib plus dexamethasone (Vel/Dex),[80,81] bortezomib, thalidomide, dexamethasone (VTD), and other bortezomib-based combinations. The CR plus VGPR rate is approximately 25% to 30% with Vel/Dex in one study. No adverse effect on stem cell mobilization was noted. The most common grade II or higher adverse events in one study were sensory neuropathy (31%), constipation (28%), myalgia (28%), and fatigue (25%).[80]

Harousseau and colleagues recently reported preliminary results of a randomized trial comparing VAD and Vel/Dex as pretransplant induction therapy.[82] With over 400 patients enrolled, preliminary results show superior response rates and long-term outcome with Vel/Dex compared to VAD. The DVT risk was low with bortezomib (<5%).

The main drawback of bortezomib-based regimens is the need for intravenous therapy without adequate data that such therapy is significantly superior to orally administered regimens such as Thal/Dex or Rev/Dex. However, bortezomib-based regimens may be of value in patients with renal failure and in patients with high-risk myeloma (see later) and is not associated with high rates of thrombosis.

OTHER INDUCTION REGIMENS. The role of other pretransplant induction regimens, such as those containing doxorubicin or liposomal doxorubicin, need to be weighed in terms of the added side effects that can affect quality of life and should be considered investigational until future studies show that the addition of these agents improves long-term outcome in comparison to the regimens discussed earlier.

Initial Therapy in Standard-Risk Patients Who Are Eligible for Transplantation

Patients who are not transplant candidates are treated with standard alkylating agent therapy. For decades this has meant therapy with MP.[1] Over the years, despite better response rates, no survival benefit has been reported with any of the more aggressive combination chemotherapy regimens compared to MP. Two recent randomized studies show that MPT (melphalan, prednisone, and thalidomide) improves response and event-free survival (EFS) compared to MP;[83,84] an overall survival advantage has been observed in one of the two trials.[84] As a result, MPT has emerged as the current standard of care for patients who are not eligible for ASCT.

MELPHALAN, PREDNISONE, AND THALIDOMIDE. Two randomized trials have compared MP to MPT.[83,84] Palumbo and colleagues randomized patients either to standard-dose MP for 6 months or to MPT for 6 months followed by maintenance thalidomide.[83] Overall response rates were significantly higher with MPT than with MP (76% versus 48%), as was the CR plus near CR rate (28% versus 7%). MPT also resulted in superior 2-year EFS rates (54% versus 27%, $P = 0.0006$) and a trend toward an improved 3-year overall survival (OS).

Facon and colleagues recently reported results of the IFM 99-06 trial, in which 436 patients were randomized to MP versus MPT versus tandem ASCT with reduced dose melphalan (Mel 100 mg/m^2).[84] As in the study by Palumbo and colleagues,[83] significantly higher response and PFS rates were observed with MPT than with either MP or tandem MEL100 groups; the median PFS was 29, 17, and 19 months, respectively. More important, the trial demonstrated a significant survival advantage with MPT; median OS was not reached at 56 months, 30 months, and 39 months, respectively. The early (first 3 months) mortality rate was 8% with MP compared to 3% with MPT.

MPT therapy is associated with greater toxicity than MP. Therefore, not all elderly patients might be able to receive the regimen. Grade III to IV adverse events occur in approximately 50% of patients who were treated with MPT, compared to 25% who were treated with MP.[83] As with Thal/Dex, there is a significant (20%) risk of DVT with MPT in the absence of thromboprophylaxis. However, this rate drops to approximately 3% with the use of thromboprophylaxis (e.g., enoxaparin).[83]

MELPHALAN, PREDNISONE, AND BORTEZOMIB. Mateos and colleagues[85] have reported the first results of the novel combination melphalan, prednisone, and bortezomib (MPV) in newly diagnosed myeloma in patients 65 years or older. Therapy was associated with a response rate of 89%, including a 32% CR rate. Approximately half of the patients with CR also had no residual bone marrow plasma cells by immunophenotypic studies. In addition, MPV appeared to overcome the poor prognosis conferred by deletion 13 and IgH translocations. The EFS and OS rates at 16 months were 83% and 90%, respectively. Most common grade III or higher adverse events were thrombocytopenia (51%), neutropenia (43%), peripheral neuropathy (17%), diarrhea (16%), and infection (16%). Herpes zoster infection occurred without prophylaxis in 13% of patients and was reduced to 7% with prophylactic acyclovir. MPV appears very promising, with high CR rates. A phase III trial comparing MPV to MP has shown survival benefit with MPV. Future studies might need to compare MPV to MPT, given the OS advantage that is seen with the latter regimen compared to MP.

MELPHALAN, PREDNISONE, AND LENALIDOMIDE. Palumbo and colleagues have studied the addition of lenalidomide to MP (MPR) in newly diagnosed patients older than 65 years of age.[86] Fifty-four patients were studied. The overall response rate was 85%, with 42% of patients achieving at least VGPR or better and 17% of patients achieving CR. The PFS rate was 87% at 16 months; and similar to therapy with MPV, therapy with MPR appeared to overcome adverse effect of deletion 13. Major grade III to IV adverse events were neutropenia (66%), thrombocytopenia (34%), anemia (17%), rash (10%), and febrile neutropenia (8%). All patients received prophylactic aspirin; DVT was uncommon, occurring in three patients (6%), including two patients after aspirin discontinuation. On the basis of this trial, MPR appears to be a very effective oral regimen for the treatment of elderly patients with multiple myeloma who are not candidates for ASCT. An ECOG randomized trial is comparing MPR to MPT.

Hematopoietic Stem Cell Transplantation

AUTOLOGOUS STEM CELL TRANSPLANTATION. Although not curative, ASCT improves complete response rates and prolongs median OS in myeloma by approximately 12 months (Table 110-8).[87–89] The mortality rate is 1% to 2%.

Melphalan 200 mg/m^2 is the most widely used preparative (conditioning) regimen for ASCT. It is superior to the older regimen of melphalan 140 mg/m^2 and 8 Gy total body irradiation (TBI).[90] Studies are ongoing to determine whether the conditioning regimen can be improved with the addition of radioactive compounds (holmium (HO^{166} DOTMP) or samarium 153-SM-EDTMP)[91,92] or bortezomib.

Table 110-8 Randomized Trials Comparing Conventional Chemotherapy versus Single Autologous Stem Cell Transplantation

Trial	No. of Patients	CR/VGPR (%)		PFS (MONTHS)		OS (MONTHS)		SCT (%)	
		CCT	ASCT	CCT	ASCT	CCT	ASCT	CCT	ASCT
IFM90[85, 268]	200	13	38*	18	28*	44	57*	9	74
MRC7[86]	401	8	44*	20	32*	42	54*	15	75
MAG91[269]	190	4	6	19	25*	48	48	22	75
MAG90[†92]	185	57	20	13	39	64	65	78	98
PEETHMA[270]	164	11	30*	33	42	61	66	18	90
S9321[†271]	516	17	15	7 year: 14%	7 year: 17%	7 year: 38%	7 year: 38%	34	82
MMSG[‡,272]	194	6	25*	16	28*	42	58+*	39	92
HOVON-24[§,273]	303	13	28*	23	24*	50	55	—	—

ASCT, autologous stem cell transplant; CCT, conventional chemotherapy; CR/VGPR, complete response or very good partial response; PFS, progression-free survival; ORR, any response greater than or equal to a partial response; OS, overall survival; SCT, percentage of patients known to have received an autologous stem cell transplant.

*Statistically significant difference.

†Trials testing early versus delayed autologous stem cell transplant.

‡Transplant arm is two low-dose (melphalan 100 mg/m^2) autologous stem cell transplants.

§Could be considered "double transplant," since both arms received melphalan 70 mg/m^2 × 2 without stem cell support as induction therapy.

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Three randomized trials show that survival is similar whether ASCT is done early (immediately following four cycles of induction therapy) or is delayed (at the time of relapse as salvage therapy).[93–95] In a Spanish PETHEMA group randomized trial, patients responding to induction therapy had similar OS and PFS with either ASCT or eight additional courses of chemotherapy,[96] suggesting that the greatest benefit from ASCT might be in patients with disease that is refractory to induction therapy.[97,98]

There is little doubt that ASCT prolongs survival in myeloma, but its timing (early versus delayed) is controversial. Overall, given the inconvenience and side effects of prolonged chemotherapy, insurance, and other issues, we still favor early ASCT, especially for patients who are less than 65 years of age with adequate renal function.[88] However, given effective new agents to treat myeloma, some patients and physicians may choose to delay the procedure. The need for early ASCT is an important question for future clinical trials.

TANDEM TRANSPLANTATION. With tandem (double) ASCT, patients receive a second planned ASCT after recovery from the first procedure.[49,99] The recent IFM 94 randomized trial found significantly better EFS and OS in recipients of double ASCT versus single ASCT (Table 110-9).[100] A similar benefit was demonstrated in a randomized trial conducted in Italy;[101] two other randomized trials have yet to show significant improvement in OS with tandem ASCT, but they have shorter follow-up.[102,103]

In both the French and Italian trials, the benefit of a second ASCT was restricted to patients who failed to achieve a complete response or very good partial response (>90% reduction in M protein level) with the first procedure. On the basis of these results, we now routinely collect enough stem cells for two transplants in all eligible patients. Patients who achieve a complete response or very good partial response with the first transplant are observed or offered clinical trials investigating maintenance therapy, the second ASCT being reserved for relapse.[104] Patients who do not achieve such a response are offered a second ASCT.

ALLOGENEIC TRANSPLANTATION. The advantages of allogeneic transplantation are lack of graft contamination with tumor cells and presence of a graft-versus-myeloma effect.[105,106] However, only 5% to 10% of patients are candidates because of age, availabil-

Table 110-9 Single versus Double Autologous Stem Cell Transplantation in Myeloma

Trial	No. of Patients	Results	Comments
InterGroupe Francophone du Myélome 94[274]	399	Superior event-free and overall survival with double transplantation; 7-year survival rate: 42% with double transplantation versus 21% with single transplantation ($P = 0.01$).	All patients younger than 60 years. Benefit of second transplant restricted to patients who achieved less than a very good partial response with the first
Bologna 96[100]	228	Superior event-free survival with double transplantation. No significant difference in overall survival; median: 60 months with double transplantation versus 56 months with single transplantation; however, compared to single transplant, patients who did not achieve at least a near CR with first transplant had significantly better survival if given second transplant.	Interim analysis of first 228 patients.
Myélome Autogreffe 95[101]	230	No difference in progression-free survival or overall survival between single versus double transplantation.	All patients were younger than 56 years.

ity of a human leukocyte antigen–matched sibling donor, and adequate organ function. Furthermore, the high treatment-related mortality, mainly related to graft-versus-host disease (GVHD), has made conventional allogeneic transplants unacceptable for most patients with myeloma.

Several recent trials have been conducted using nonmyeloablative conditioning regimens (miniallogeneic transplantation).[107] Initial trials evaluating this approach included relapsed or refractory patients, a factor that was thought to account at least in part for the poor outcomes. It also became apparent that this approach was less useful in patients who had significant residual tumor burden at the time of the nonmyeloablative transplant, which led to the concept of a planned autologous SCT followed by a planned reduced-intensity allogeneic SCT a couple of months later.[108] The initial studies had treatment-related mortality rates approaching 25%; 3-year OS and PFS rates were 41% and 21%, respectively. Adverse OS was associated with chemoresistant disease, more than one prior transplantation, and absence of chronic GVHD. In the planned tandem autologous/nonmyeloablative allogeneic SCT approach, outcomes have been better, with treatment-related mortality rates of 15% and 2-year OS rates approaching 75%.[109] However, there is also a high risk of acute and chronic GVHD, and the occurrence of GVHD appears necessary for disease control.

There are published data from only one randomized trial that addresses ASCT in high-risk patients as defined by the presence of deletion 13 by fluorescent in situ hybridization and of β_2-microglobulin greater than 3 mg/L.[110] On the basis of biologic randomization, patients were allocated either to double ASCT or to autologous SCT followed by a reduced-intensity allogeneic SCT. Although patients did better than expected in both arms, with median OS of 41 and 35 months, respectively, there was no significant difference between the two arms with a median follow-up of 24 months. The major criticisms of this study have been that the criteria that were used to select high-risk disease did not select for the highest-risk patients and that the reduced-intensity conditioning that was used might have been too immunosuppressive, thereby abrogating the graft-versus-myeloma effect.

At this time, miniallogeneic transplantation remains investigational. It should be considered only in the context of clinical trials in standard-risk myeloma because current results with the tandem ASCT strategy described earlier yields 7-year survival rates in excess of 40%. In these patients, the treatment-related mortality and GVHD rates with nonmyeloablative allogeneic transplantation are unacceptably high.

Treatment of High-Risk Myeloma

Patients with high-risk myeloma tend to do poorly, with median OS of approximately 2 years even with tandem ASCT. One option for these patients is novel therapeutic strategies.[2,66] For example, bortezomib-containing regimens can be considered early in the disease course as primary therapy, with SCT reserved for relapse. In at least three separate studies, bortezomib appears to overcome the adverse effect of deletion 13.[85,111,112] In elderly patients, MPT remains an option.

Allogeneic approaches might be an option in selected patients, for example, ASCT followed by nonmyeloablative allogeneic transplantation. However, as was mentioned previously, the recent IFM 99 trial in patients with deletion 13 and high β_2-microglobulin levels has not shown significant benefit with this strategy compared to tandem ASCT.[110]

If patients are treated similarly to standard-risk patients, routine maintenance therapy could be considered (e.g., thalidomide plus prednisone), given the high risk of early relapse. Clearly, clinical trials and new agents that are specifically designed for high-risk myeloma are needed.

Maintenance Therapy

Maintenance therapy with interferon-α is of limited value and is seldom used.[113] Recent results from a large intergroup study showed no benefit with interferon as maintenance therapy.[95] A study by Berenson and colleagues suggests that prednisone might be useful for maintenance therapy.[114] PFS (14 months versus 5 months) and OS (37 months versus 26 months) were significantly longer with 50 mg than with 10 mg of prednisone orally every other day. Because this comparison included only patients who responded initially to steroid-based therapy and because patients did not receive ASCT, it is difficult to generalize these results to current practice.

Clinical trials are currently evaluating thalidomide, dendritic cell vaccination, and other novel approaches as maintenance therapy. A recent French trial (IFM 99–02) randomized 597 patients (age < 65 years) following tandem ASCT to no maintenance (arm A), pamidronate (arm B), or pamidronate plus thalidomide (arm C).[115] There was a significant improvement in EFS with maintenance thalidomide plus pamidronate; the 3-year EFS rate from the time of randomization was 36% in arm A, 37% in arm B, and 52% in arm C ($P < 0.009$). The corresponding 4-year OS rates were 77%, 74%, and 87%, respectively ($P < 0.04$; see Table 110-7). Of note, no decrease in the incidence of bone events was noted with pamidronate therapy when arms B and C were compared to arm A in this cohort of patients. Multiple studies addressing the use of immunomodulatory drugs after SCT are ongoing.

Treatment of Relapsed Multiple Myeloma

Almost all patients with myeloma eventually relapse. If relapse occurs more than 6 months after stopping therapy, the initial chemotherapy regimen should be reinstituted. Patients who have cryopreserved stem cells early in the disease course can derive significant benefit from ASCT as salvage therapy.[116]

In general, patients who have indolent relapse can often be treated with single-agents or MP. These patients present with asymptomatic increases in serum and urine M protein levels, progressive anemia, or few small lytic bone lesions. In contrast, patients with more aggressive relapse often require therapy with a combination of active agents. Given the noncurative nature of myeloma, patients with relapsed disease typically continue on one drug or regimen until relapse or toxicity and then try the next option.

GLUCOCORTICOIDS AND ALKYLATING AGENTS. High-dose pulse dexamethasone or intravenous methylprednisolone is a reasonable option, particularly if the patient has had an initial response to steroids and was off high-dose steroids when the relapse occurred.[117,118] Patients who relapse more than 6 to 12 months after an ASCT can respond to MP or MPT, since most patients would not have been exposed to this regimen as induction therapy.

Conventional combination chemotherapy regimens such as VBMCP, VAD, or other alkylator-based regimens can be effective in relapsed and refractory disease. Intravenous melphalan at a dose of 25 mg/m^2 is another active regimen but usually requires transfusion and growth factor support.

THALIDOMIDE AND THALIDOMIDE-BASED REGIMENS. The finding of increased angiogenesis in myeloma and the antiangiogenic properties of thalidomide led to the first clinical trial with the agent at the University of Arkansas. This trial demonstrated a response rate of 25% in heavily pretreated patients with relapsed and refractory disease.[61,119] Since then, several studies have demonstrated that thalidomide produces response rates in about 25% to 35% of patients with relapsed and refractory multiple myeloma.[120–124] The median duration of response is approximately 1 year. Thalidomide is usually given in a dosage of 100 to 200 mg daily. After a response has been achieved, the dosage should be adjusted to the lowest dose that can achieve and maintain a response, in order to minimize long-term toxicity.

Thal/Dex with or without cyclophosphamide has significant activity in the treatment of relapsed multiple myeloma. Studies show that response rates in relapsed disease are about 50% with the combination of thalidomide and steroids[125] and increase to over 65% with an oral three-drug combination of thalidomide, steroids, and cyclophosphamide (CTD).[126–128] Several other combination chemotherapy regimens that contain thalidomide are being studied, including DT-PACE (dexamethasone, thalidomide, cisplatin, Adriamycin, cyclophosphamide, and etoposide), BLT-D (clarithromycin, low-dose thalidomide, and dexamethasone), and MTD (melphalan, thalidomide, and dexamethasone).[129]

The use of thalidomide in pregnancy is absolutely contraindicated, and the System For Thalidomide Education and Prescribing Safety Program must be followed to prevent teratogenicity.[130] The incidence of DVT is only 1% to 3% in patients who receive thalidomide alone but rises to approximately 10% to 15% in patients who receive thalidomide in combination with dexamethasone and to about 25% in patients who receive the agent in combination with other cytotoxic chemotherapeutic agents, particularly doxorubicin.[120,131–134] The management of thalidomide toxicity has been reviewed.[135]

BORTEZOMIB AND BORTEZOMIB-BASED REGIMENS. Bortezomib (formerly known as PS-341) is a novel proteasome inhibitor that has been approved for the treatment of patients with relapsed and refractory multiple myeloma.[136,137] In the first phase II trial, conducted in 202 patients with relapsed or refractory multiple myeloma, approximately one third of patients responded to bortezomib therapy, with an average response duration of 1 year.[62] These results were confirmed in a randomized phase II trial in patients who failed to respond or who relapsed after frontline therapy for myeloma.[138] Although initial trials allowed a maximum of only eight cycles of bortezomib, additional data indicate that it is safe to give at least an additional five or six cycles of therapy without undue toxicity.[138] In a recent randomized trial, PFS was superior with bortezomib compared to dexamethasone alone in patients with relapsed or refractory multiple myeloma (see Table 110-7).[63] The starting dose of bortezomib is 1.3 mg/m^2 given twice weekly on days 1, 4, 8, and 11 every 21 days. The dosage might need to be decreased to 1.0 mg/m^2 or 0.7 mg/m^2 on the basis of toxicity.

Bortezomib with or without dexamethasone is an active regimen for the treatment of aggressive relapse. Bortezomib has also been combined with intravenous liposomal doxorubicin with a high response rate.[139] In a recently presented randomized trial, this combination yielded a superior TTP (9.3 months versus 6.5 months) compared to single-agent bortezomib; however, this promising result has not yet translated into a better OS.[140]

Zangari and colleagues have preliminarily reported their experience with VTD in a phase 1 trial.[141] The overall response rate was 55%; the EFS and OS were 9 and 22 months, respectively. Myelosuppression was the most common grade III to IV toxicity. Peripheral neuropathy worsened above baseline in 5% to 9% of these heavily pretreated patients.

LENALIDOMIDE. Lenalidomide (CC-5013) belongs to a class of thalidomide analogs termed immunomodulatory drugs. It first showed promising activity in multiple myeloma in two phase I trials.[142,143] Richardson and colleagues have reported the preliminary results of a multi-center randomized phase II trial with oral CC-5013 in relapsed/refractory myeloma.[144] Of 83 evaluable patients, 24% responded with at least a 50% or greater reduction in M protein levels.

Two large phase III trials have recently shown significantly superior TTP with lenalidomide plus dexamethasone compared to placebo plus dexamethasone in relapsed myeloma (see Table 110-7).[145] In these trials, grade III to IV neutropenia was more frequently seen with the combination of lenalidomide plus dexamethasone; the frequency of grade III to IV infections were similar in both arms. Typical dosing of lenalidomide for myeloma is 25 to 30 mg per day on days 1 to 21 of a 28-day cycle, with dose adjustments based on toxicity.

OTHERS DRUGS. There is a continued search for other active agents based on advances in myeloma biology.[146] There are preliminary data that suggest modest efficacy with arsenic trioxide,[147] but further confirmation is needed. CC-4047 (pomalidomide, another thalidomide analog) has also shown promising activity.[148]

Complications

Hypercalcemia

Aggressive hydration with isotonic saline and corticosteroids are effective in most cases. A single dose of pamidronate 60 to 90 mg intravenously over 2 to 4 hours[149] or zoledronic acid 4 mg intravenously over 15 minutes[150] will normalize the calcium levels within 24 to 72 hours in most patients

Skeletal Lesions

Surgical fixation of fractures or impending fractures of long bones might be needed. Local radiation should be limited to patients with disabling pain who have a well-defined focal process that has not responded to analgesics and/or chemotherapy. The administration of bisphosphonates significantly reduces the number of skeletal events (pathologic fracture, need for irradiation or surgery on bone and spinal cord compression).[151] In a randomized trial of 392 patients with at least one lytic lesion, skeletal events (pathologic fracture, radiation or surgery to bone, and spinal cord compression) after 9 months of therapy were significantly fewer with pamidronate than with placebo, 24% versus 41%, respectively ($P < 0.001$).[151] More recently, zoledronic acid has been shown to have efficacy comparable to that of pamidronate.[152,153] Either pamidronate (90 mg intravenously over at least 2 hours every 4 weeks) or zoledronic acid (4 mg intravenously over 15 to 30 minutes every 4 weeks) is recommended in patients with multiple myeloma who have one or more lytic lesions on skeletal roentgenograms.[152,154]

The typical recommendation initially was to continue bisphosphonates indefinitely at monthly intervals.[154] However, by 2003, avascular osteonecrosis of the jaw (ONJ) has been described as a new complication associated with their use[155–159] The etiology of ONJ is unclear, but is likely multifactorial in origin. Although most patients who develop ONJ have had recent dental or oral surgical procedures (70%), the remainder develop spontaneous ONJ.[159] Proposed mechanisms include that inhibition of osteoclast activity reduces bone turnover and remodeling and that bisphosphonates prevent release of bone-specific factors that promote bone formation.[160]

The incidence of ONJ ranges from 4.4% to 21% depending on the type and duration of bisphosphonate use.[160,161] Risks increase with duration of therapy and likely with use of zoledronic acid compared to pamidronate or other lower-intensity bisphosphonates. A Mayo Clinic consensus statement recommends pamidronate instead of zoledronic acid as the bisphosphonate of choice for long-term therapy.[160] It also recommends 2 years of monthly bisphosphonate therapy for patients with myelomatous bone disease, followed by cessation of therapy in patient who are off active treatment for their myeloma and continuation of therapy every 3 months for those who are receiving myeloma therapy. These recommendations are bolstered by two recent observations. The first is that the rates of myeloma bone disease in the prebisphosphonate error was highest during the first 2 years after diagnosis.[162] The second supporting data element is the recent finding that pamidronate use after tandem transplant did not provide any significant reduction in skeletal events.[115]

Both vertebroplasty (injection of methylmethacrylate into a collapsed vertebral body) and kyphoplasty (introduction of an inflatable bone tamp into the vertebral body and after inflation the injection of methylmethacrylate into the cavity) have been successfully used to decrease pain and help restore height.[163] Pain relief is generally rapid and can be long-lasting.

Spinal cord compression from an extramedullary plasmacytoma should be suspected in patients with severe back pain, weakness or paresthesias of the lower extremities, bladder or bowel dysfunction, or incontinence. The standard treatment for cord or cauda equina compression are corticosteroids (dexamethasone 10 mg to 40 mg intravenously followed by 4 mg orally or intravenously four times daily) and radiation therapy. On rare occasions, surgical decompression might be necessary.

Renal Insufficiency

Nonsteroidal anti-inflammatory agents can precipitate renal failure and should generally be avoided.[164,165] Dehydration, infection, and radiographic contrast media may also contribute to acute renal failure. Maintenance of a high urinary output (3 L/day) is important in preventing renal failure in patients with high levels of monoclonal light chains in the urine. Patients with acute or subacute renal failure due to light-chain cast nephropathy should be treated with Thal/Dex or dexamethasone to reduce the tumor mass as quickly as possible. A trial of plasmapheresis should be considered in these patients in an attempt to prevent irreversible renal damage.[166]

Anemia

Iron, folate, or B-12 deficiency might be responsible for the anemia as well and, if so, must be recognized and treated. Treatment of the underlying disease and renal failure often leads to improvement in the hemoglobin level. Erythropoietin (40,000 units subcutaneously weekly) or darbepoietin (200 μg subcutaneously every 2 weeks) are useful in patients with persistent symptomatic anemia[167,168] but should be restricted because of a higher risk of DVT when used in combination with thalidomide or lenalidomide. Blood transfusions are indicated for patients with symptomatic anemia who do not obtain benefit from other therapies.

Infections

Patients should receive pneumococcal and influenza vaccinations. Intravenously administered gamma globulin every 3 to 4 weeks is indicated if patients have recurrent serious infections associated with severe hypogammaglobulinemia. The use of prophylactic antibiotics in patients who are receiving chemotherapy for myeloma has not been settled. Prophylaxis against *Pneumocystis carinii* pneumonia should be considered in all patients who are receiving high-dose steroid therapy. A small, randomized, placebo-controlled trial of trimethoprim-sulfamethoxazole in 57 patients with newly diagnosed myeloma demonstrated benefit with routine prophylaxis administered with the first two cycles of chemotherapy.[169] However, owing to the risk of serious skin toxicity, we think that trimethoprim-sulfamethoxazole should be avoided in patients who are receiving Thal/Dex therapy. In patients who are receiving Thal/Dex, prophylaxis with other antibiotics (such as ciprofloxacin, levofloxacin, or cephalosporins) and alternative agents for *P. carinii* pneumonia should be considered. A randomized trial is ongoing in the United States comparing no prophylaxis, trimethoprim-sulfamethoxazole, and ciprofloxacin in patients with newly diagnosed myeloma who are receiving chemotherapy.

Hyperviscosity Syndrome

Infrequently, patients with multiple myeloma develop hyperviscosity syndrome. Plasmapheresis promptly relieves the symptoms and should be done regardless of the viscosity level if the patient has signs or symptoms of hyperviscosity.[170]

MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE

Introduction

MGUS is an asymptomatic, premalignant clonal plasma cell proliferative disorder that is defined by the presence of a serum M protein level lower than 3 g/dL, bone marrow plasma cells less than 10%, plus absence of anemia, hypercalcemia, lytic bone lesions, or renal failure that can be attributed to the plasma cell proliferative disorder.[24,171] It is the most common plasma cell dyscrasia, prevalent in approximately 3% of the general population 50 years of age and older.[172] The prevalence increases with age: 1.7% in those 50 to 59 years of age and over 5% in those over the age of 70. Age-specific incidence is higher in males than in females. MGUS is also twice as common in African Americans as in Caucasians.[173]

MGUS is associated with a lifelong risk of progression to multiple myeloma or a related disorder. The rate of progression of MGUS to multiple myeloma or related malignancy is 1% per year (see Fig. 110-1).[3,174] However, the true lifetime probability of progression is substantially lower when competing causes of death are taken into account: approximately 11% at 25 years (see Fig. 110-1).[175] As was discussed earlier, the risk of progression with MGUS does not diminish with time.[3,176]

Clinical Features and Differential Diagnosis

MGUS is asymptomatic. It is differentiated from multiple myeloma and related disorders on the basis of the presence or absence of end-organ damage that can be attributed to the plasma cell disorder. The differentiation of MGUS from multiple myeloma or other related disorders can be difficult at the time of initial presentation because MGUS is relatively common in the general population over the age of 50 years, and a number of clinical and laboratory abnormalities may be coincidental. The typical laboratory investigations necessary to differentiate MGUS from other related plasma cell disorders are a complete blood count, serum creatinine, serum calcium, and a complete roentgenographic bone survey. If abnormalities are detected on the preceding tests, additional tests to determine the cause of these abnormalities are required; only patients in whom abnormalities are thought to be related to the plasma cell proliferative disorder can be considered to have myeloma or a related malignancy. A bone marrow aspirate and a biopsy are indicated when the M protein is greater than or equal to 1.5 g/dL, in non-IgG MGUS, when serum free light-chain ratio is abnormal (see later), and when abnormalities are noted in the complete blood count, serum creatinine, serum calcium, or radiographic bone survey. A bone marrow aspirate should also be considered in any patient with presumed MGUS in whom there is doubt about the diagnosis.

Prognosis

In a large population-based study of MGUS involving 1384 patients, only the size and type of M protein (IgM and IgA subtypes) were predictive of progression to myeloma or related malignancy.[3] In another study, a bone marrow plasma cell percentage of 6% to 9% carried twice the risk of progression compared to marrow involvement that is 5% or less.[177]

The presence of circulating plasma cells detected by using a sensitive slide-based immunofluorescent assay is also a risk factor for progression.[178] This finding suggests that alterations in expression of adhesion molecules might be involved in the progression of MGUS to myeloma; alternatively, the presence of circulating plasma cells may be a marker of plasma cell proliferative rate. However, the clinical application of this finding is currently limited by the lack of widespread availability of the test in clinical practice.

Table 110-10 Risk Stratification Model to Predict Progression of Monoclonal Gammopathy of Undetermined Significance to Myeloma or Related Disorders

Risk Group	No. of Patients	Relative Risk	Absolute Risk of Progression at 20 Years (%)	Absolute Risk of Progression at 20 Years Accounting for Death as a Competing Risk (%)
Low-risk (serum M protein < 1.5 g/dL, IgG subtype, normal free light chain ratio (0.26–1.65)	449	1	5	2
Low-intermediate-risk (any one factor abnormal)	420	5.4	21	10
High-intermediate-risk (any two factors abnormal)	226	10.1	37	18
High-risk (all three factors abnormal)	53	20.8	58	27

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An abnormal serum free light-chain ratio using the serum free light-chain assay has been shown to be an important risk factor for progression of MGUS. In a study of 1148 patients, the risk of progression with an abnormal free light-chain ratio at the time of diagnosis of MGUS was significantly higher than a normal ratio (hazard ratio: 3.5, 95% CI: 2.3 to 5.5, $P < 0.001$) and was independent of the size and type of the serum M protein.[175] The risk of progression to myeloma or related malignancy at 10 years was 17% with an abnormal ratio compared to 5% with a normal ratio.

Risk Stratification of Monoclonal Gammopathy of Undetermined Significance

A risk stratification system can be used to predict the risk of progression of MGUS based on three risk factors: the size of the serum M protein, the type of immunoglobulin, and the serum free light-chain ratio (Table 110-10).[175] Patients with three adverse risk factors, namely, an abnormal serum free light-chain ratio, non-IgG MGUS, and a high serum M protein level (≥15 g/L), had a risk of progression at 20 years of 58% (high-risk MGUS) compared to 37% in patients in with any two of these risk factors present (high-intermediate-risk MGUS), 21% with one risk factor present (low-intermediate-risk MGUS), and 5% when none of the risk factors were present (low-risk MGUS). In fact, the low-risk MGUS subset (constituting almost 40% of the cohort) has a lifetime risk of only 2% when competing causes of death are taken into account.

Management

The current standard of care for MGUS is observation alone, without therapy.[1,179] Patients with MGUS might benefit from risk stratification as discussed previously to guide follow-up. Patients with low-risk MGUS can be rechecked in 6 months and then once every 2 years or only at the time of symptoms for evidence of progression.[175] All other subsets of patients need to be rechecked in 6 months and yearly thereafter.

SMOLDERING MULTIPLE MYELOMA

Introduction

Smoldering multiple myeloma is defined by the presence of a serum IgG or IgA M protein level of 3 g/dL or more and/or 10% or more bone marrow plasma cells plus absence of anemia, hypercalcemia, lytic bone lesions, or renal failure that can be attributed to the plasma cell proliferative disorder (see Table 110-1).[180,181] Smoldering multiple myeloma accounts for approximately 15% of all cases with newly diagnosed multiple myeloma.[171,182]

Because the risk of progression to myeloma or related malignancy is much higher in smoldering multiple myeloma than in MGUS, 10% to 20% per year versus 1% per year, respectively, patients with smoldering multiple myeloma and MGUS should be managed differently in terms of frequency of follow-up, development of chemopreventive strategies, and enrollment in clinical trials. Similar to MGUS and active myeloma, almost all patients with smoldering multiple myeloma appear to have evidence of genomic instability manifested as IgH translocations or hyperdiploidy on molecular genetic testing.[183]

Clinical Features and Differential Diagnosis

By definition, smoldering multiple myeloma is asymptomatic. Testing to differentiate smoldering multiple myeloma from active multiple myeloma is the same as the testing that was described for MGUS. Most patients with smoldering multiple myeloma progress eventually to symptomatic disease;[182] however, some patients can remain free of progression for a number of years.[184] The TTP to symptomatic disease is approximately 3 to 4 years but differs greatly depending on the definition that is used for smoldering multiple myeloma.[185] In the subset of smoldering multiple myeloma patients having 10% or more bone marrow plasma cells, the median TTP is approximately 2 to 3 years.[186]

The natural history of smoldering myeloma was recently characterized by a large study from the Mayo Clinic.[187] During 2204 cumulative person-years of follow-up, the overall rate of progression at 10 years was 62%; the median TTP was 5.5 years. Patients were categorized into three groups: group 1 having serum M protein levels of 3 g/dL or more and bone marrow containing 10% or more plasma cells ($N = 113$, 38%), group 2, having bone marrow plasma cells greater than or equal to 10% but serum M protein levels less than 3 g/dL ($N = 158$, 52%), and group 3 having serum M protein levels of 3 g/dL or more but bone marrow plasma cells less than 10% ($N = 30$, 10%). The median TTP was 2.4, 9.2, and 19 years in groups 1, 2, and 3, respectively; correspondingly, at 10 years, progression occurred in 76%, 59%, and 32%, respectively.

Prognosis

Similar to results in MGUS, abnormal peripheral blood monoclonal plasma cell studies, defined as an increase in the number or proliferative rate of circulating plasma cells by slide-based immunofluorescent assays, have been shown to indicate a higher risk of progression

in smoldering multiple myeloma.[186] However, this test is not widely available in clinical practice.

The presence of occult bone lesions on MRI increases the risk of progression in patients who were otherwise defined as having smoldering multiple myeloma.[182] In a recent study, Wang and colleagues estimated risk of progression in 72 patients with smoldering multiple myeloma in whom an MRI of the spine was also performed.[185] The median TTP was significantly shorter with an abnormal MRI than with a normal MRI: 1.5 years versus 5 years, respectively.

Risk Stratification

Weber and colleagues have shown that as in MGUS, the size and type of immunoglobulin are important predictors of progression in smoldering multiple myeloma.[188] Patients with a serum M protein level of 3 g/dL or less and IgG type (about 45% of patients with smoldering multiple myeloma) had a median TTP greater than 4 years. In contrast, patients with a serum M protein level greater than 3 g/dL or of the IgA type (about 45% of patients) had a median TTP of approximately 2 years, while a small subset of patients with less than 3 g/dL IgA smoldering multiple myeloma had a median TTP of 9 months.

Management

The standard of care is observation alone until evidence of progression to myeloma.[1] Patients with smoldering multiple myeloma need more frequent follow-up than do those with MGUS: at least every 3 to 4 months.[24] Two small randomized trials have shown no benefit with early therapy compared to therapy at the time of symptomatic progression.[189,190]

There are preliminary data that thalidomide might delay TTP,[72,191] but data are needed from randomized trials before such therapy can be recommended, particularly given the adverse effects associated with the drug. A randomized phase III trial at Mayo Clinic is currently testing thalidomide plus zoledronic acid versus zoledronic acid in patients with smoldering multiple myeloma; the results of this study will shed light on the utility of thalidomide in this setting. Outside of a clinical trial, therapy with bisphosphonates is not recommended.

With the increasing availability of novel targeted therapies for myeloma,[192–194] clinical trials are ongoing to determine whether the early use of new agents or bisphosphonates can delay progression in smoldering multiple myeloma.

WALDENSTRÖM'S MACROGLOBULINEMIA

Waldenström's macroglobulinemia is a clonal IgM M protein–secreting lymphoid/plasma cell disorder, which currently also includes the entity that was previously referred to as *lymphoplasmacytic lymphoma*. The median age at diagnosis is approximately 65 years, with a slight male predisposition. The typical symptoms at presentation are weakness and fatigue due to anemia. Other clinical manifestations may include constitutional symptoms (fever, night sweats, and weight loss), hepatosplenomegaly, lymphadenopathy, hyperviscosity, cryoglobulinemia, and sensorimotor peripheral neuropathy.[195] Unlike multiple myeloma, primary IgH translocations are not seen in Waldenström's macroglobulinemia.[196]

Diagnosis

The diagnostic criteria for Waldenström's macroglobulinemia are listed in Table 110-1.[197] The diagnostic criteria in Table 110-1 have been updated in an evidence-based manner such that the diagnosis of Waldenström's macroglobulinemia requires 10% or greater lymphoplasmacytic infiltration.[3,198–200] The presence of less than 10% lymphoplasmacytic infiltration in the absence of end-organ damage represents IgM MGUS and not Waldenström's macroglobulinemia; such patients have a risk of progression to symptomatic disease at a rate of only 1.5% per year.[198] In fact, patients with IgM MGUS and smoldering Waldenström's as defined by using the criteria in Table 110-1 have an OS rate similar that of to the general population and are best not considered to have malignant disease.[199]

Patients with a serum IgM M protein level of 3 g/dL or more and/or bone marrow lymphoplasmacytic infiltration of 10% or more and no evidence of end-organ damage such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to a plasma cell proliferative disorder are considered to have smoldering Waldenström's macroglobulinemia (also referred to as indolent or asymptomatic Waldenström's macroglobulinemia), an asymptomatic condition that is similar to smoldering multiple myeloma but is associated with a risk of progression to Waldenström's macroglobulinemia.

Historically, patients with an IgM M protein level less than 3 g/dL who meet criteria for Waldenström's macroglobulinemia have been classified as "lymphoplasmacytic lymphoma with an IgM M protein." However, except for hyperviscosity, the clinical picture, therapy, and prognosis in these patients are no different from those of patients who are classified as Waldenström's macroglobulinemia who have an IgM M protein level of 3 g/dL or more.[201] By the current definition, patients are considered to have Waldenström's macroglobulinemia regardless of the size of the serum M protein.

Prognosis

The median survival is approximately 5 years.[195] Adverse prognostic factors include age greater than 70 years, hemoglobin levels less than 9 g/dL, weight loss, and cryoglobulinemia.[202] Morel and colleagues have constructed a risk stratification model based on a set of three adverse prognostic factors: age 65 years or greater, albumin level less than 4.0 g/dL, and cytopenias; cytopenia restricted to one hematopoietic lineage was scored as one risk factor, while two or more cytopenias were scored as two risk factors.[203] Patients with zero or one risk factors (low-risk), two risk factors (intermediate-risk), and three or four risk factors (high-risk) had 5-year survival rates of 87%, 62%, and 25%, respectively.

Treatment

As is the case for smoldering myeloma, patients meeting the diagnostic criteria for Waldenström's macroglobulinemia who are asymptomatic have no need of immediate therapy. The indications for therapy are anemia (hemoglobin < 10 g/dL) or thrombocytopenia (platelet count < 100,000) that is thought to be related to Waldenström's macroglobulinemia; constitutional symptoms such as weakness, fatigue, night sweats, or weight loss; hyperviscosity; symptomatic cryoglobulinemia; and significant hepatosplenomegaly or lymphadenopathy.[195,204,205]

Initial Therapy

There are four options for initial therapy: rituximab, purine nucleoside analogs, alkylators, and combination chemotherapy. Unfortunately, there are no randomized data to determine the best option; therapy is typically decided on the basis of the age of the patient and the aggressiveness of the presentation. Patients should preferably be treated on clinical trials as much as possible.

Single-agent therapy with rituximab, a chimeric anti-CD20 monoclonal antibody, produces a response in approximately 50% of untreated patients.[206,207] Response to rituximab may be affected by polymorphisms in the Fc-gamma RIIIA (CD16) receptor gene.[208] Responses to rituximab can delayed and may occur months after initial therapy. An initial increase in IgM levels (flare) has been reported.[209] The usual dose is 375 mg/m^2 administered intravenously weekly for 4 weeks,[207] with consideration given to further doses or maintenance depending on response.

The purine nucleoside analogs fludarabine or cladribine are also effective as initial therapy.[210–215] Response rates reported vary widely from 40% to 90% and likely reflect patient selection and the stringency and timing of the response assessment. The two agents are likely equally effective; randomized comparisons have not been conducted. We prefer cladribine 5 mg/m^2 intravenously over 2 hours for 5 days, repeated once after 28 days if needed. The need for further cycles is determined by the extent of response to the first two cycles as well as observed toxicity.

Alkylators such as chlorambucil are an option especially for elderly patients as initial therapy. Chlorambucil is administered orally in a dosage of 6 to 8 mg/day with dose adjustments based on blood counts. Patients are treated until the disease has reached a plateau state; the treatment can then be discontinued, and patients are observed closely.

Preliminary results of several combination chemotherapeutic approaches have been reported, with response rates of over 75%.[204] Examples of active combinations include fludarabine plus rituximab, fludarabine plus cyclophosphamide, cladribine plus cyclophosphamide plus rituximab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone).[205,216] Our preferred approach outside a clinical trial setting is to use single-agent therapy in most patients, reserving combination therapy for aggressive disease.

Relapsed Disease and Supportive Care

Options listed for initial therapy discussed previously can be tried at the time of relapse. In fact, the same initial therapy can be tried again at relapse if there was an adequate interval between cessation of therapy and relapse. A response rate of 25% has been reported with single-agent thalidomide.[217] In general, options for relapsed or refractory disease include SCT,[218] interferon-α,[219,220] thalidomide,[221] and bortezomib.[222] Novel agents are also being investigated.[223] A small subset of chemotherapy-resistant patients respond to splenectomy.[205]

Patients with refractory anemia or anemia during chemotherapy will benefit from erythropoietin and/or and red cell transfusions. Plasmapheresis is indicated for the treatment of hyperviscosity syndrome.[205] Plasmapheresis might need to be continued on an intermittent basis until a therapeutic response is achieved with one of the treatment options discussed earlier.

SYSTEMIC IMMUNOGLOBULIN LIGHT-CHAIN AMYLOIDOSIS

Amyloid is a fibrillar proteinaceous material that can be deposited in various tissues and detected with Congo red staining based on a characteristic apple-green birefringence under polarized light.[224] It consists of rigid, linear, nonbranching fibrils, 7.5 to 10 nm in width, aggregated in a β-pleated sheet conformation. There are several distinct types of amyloidosis, which are classified on the basis of the protein composition of the amyloid material (Table 110-11).

Immunoglobulin light-chain (AL) amyloidosis is the type of amyloidosis that is derived from the variable portion of a monoclonal light chain or, in rare instances, intact monoclonal light chain and occurs as a result of a clonal plasma cell proliferative disorder.[225] AL amyloidosis may be localized (a benign disorder) or systemic. Systemic AL amyloidosis has been commonly referred to as *primary systemic amyloidosis* or simply *primary amyloidosis*.

The pathogenesis of AL amyloidosis is not well understood. It involves aberrant de novo synthesis and abnormal proteolytic processing of light chains. The catabolism of amyloid fibrils might also play a role. IgH translocations have been reported in over 70% of patients with systemic AL amyloidosis.[226] There also appears to be a distinct gene expression profile associated with AL amyloidosis compared to myeloma; a set of 12 genes was recently found to discriminate between AL amyloidosis and multiple myeloma with greater than 85% accuracy on gene expression profiling studies.[227]

Table 110-11 Classification of Amyloidosis

Type of Amyloidosis	Major Protein Component
AL amyloidosis* (previously referred to as primary amyloidosis)	κ or λ immunoglobulin light chain
AA amyloidosis (previously referred to as secondary amyloidosis)	Protein A
ATTR amyloidosis	Transthyretin (TTR; prealbumin), mutant form
• Mutant ATTR	
Familial	Transthyretin (TTR; prealbumin), normal, wild-type form
Neurologic	
Cardiopathic	
• Normal ATTR	
Senile amyloidosis	
β_2-Microglobulin amyloidosis (associated with long-term dialysis)	β_2-Microglobulin
Other	
• Familial Mediterranean fever	Protein A
• Fibrinogen α-chain	Fibrinogen α-chain
• Lysozyme	Lysozyme
• Apolipoprotein A-I	Apolipoprotein A-I

*AL amyloidosis is the only form of amyloidosis that is secondary to a clonal plasma cell disorder. AL amyloidosis can be associated with multiple myeloma in approximately 10% of patients.

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Certain germline immunoglobulin light-chain V genes, 6a(V lambda VI) and 3r (V lambda III), code for the monoclonal light-chain regions that are involved in systemic AL amyloidosis in approximately 40% of patients.[228] Studies show that the nature of organ involvement in AL amyloidosis might be related to which of the various immunoglobulin light-chain germline V genes the plasma cell clone is derived from.[229,230] Patients with clones derived from the 6a (V lambda VI) germline light-chain gene have a greater likelihood of dominant renal amyloidosis. In contrast, patients with clones derived from the 1c, 2a2, and 3r V (lambda) genes are more likely to present with dominant cardiac and multisystem amyloidosis.

Diagnosis

The diagnosis of systemic AL amyloidosis requires documentation of positive amyloid staining on a tissue biopsy as well as supporting evidence that the amyloid is derived from immunoglobulin light chains (see Table 110-1). It should be suspected when patients with the appropriate clinical syndrome, such as nephrotic syndrome, axonal neuropathy, or restrictive cardiomyopathy, display evidence of a plasma cell proliferative disorder such as a serum or urine M protein.

Systemic AL amyloidosis should be differentiated from localized amyloidosis, which can be derived from immunoglobulin light chains in many patients (localized AL amyloidosis).[224] Localized amyloidosis is typically benign and can manifest as isolated carpal tunnel syndrome; isolated lesions in the ureter, urethra, bladder, lung, bronchus, or trachea; or nonpurpuric cutaneous lesions. Localized amyloidosis, regardless of whether the source of the amyloid is immunoglobulin light chain or some other protein, is treated primarily for symptom relief as needed and should not be treated with systemic therapy.

The median age at diagnosis of systemic AL amyloidosis is 65 years. The clinical manifestations vary greatly and depend on the dominant organ that is involved. Nephrotic syndrome, restrictive cardiomyopathy, and peripheral/autonomic neuropathy are common presenting syndromes. Patients may also have associated macroglossia, carpal tunnel syndrome, and purpura involving the neck, face, and eyes. Immunofixation reveals an M protein in the serum or urine in almost 90% of patients at diagnosis. The free light-chain ratio is abnormal in most of the patients with a negative immunofixation.[231] Regardless of the number of bone marrow plasma cells in the bone marrow the syndrome is referred to as AL or primary, as long as the amyloid fibrils are composed of immunoglobulin light chain. Systemic AL amyloidosis and symptomatic multiple myeloma can coexist in a patient, but one of the two disorders usually dominates the clinical picture.

Prognosis

Survival varies greatly depending on the dominant organ that is involved (cardiac amyloid having the worst outcome) and the number of major organs that are affected.[224,232] Patients who are not eligible for SCT have an estimated median survival of 18 months, compared to over 40 months for those who are eligible for transplantation.[232] An elevated level of cardiac troponin T levels carries an adverse prognosis. Median survival for patients with detectable cardiac troponin T (≥0.01 μg/L) is significantly shorter than that for patients with undetectable levels: 6 versus 22 months, respectively.[233] Elevated serum cardiac troponin I and N-terminal pro–brain natriuretic peptide are also valuable prognostic markers.[233,234] A risk stratification model using the cardiac troponin T and N-terminal pro–brain natriuretic peptide levels is given in Table 110-12.[235,236]

Treatment

Response to therapy in AL amyloidosis can be difficult to assess. Specific response criteria to assess hematologic and organ responses in primary amyloidosis have recently been published.[237] Melphalan and prednisone have been the mainstays of treatment for many years, but results have not been satisfactory.[238] Currently, our approach is to stratify patients on the basis of eligibility for SCT. Patients who are not eligible for SCT (poor performance status, major comorbidities, three or more organs involved, and advanced cardiac amyloidosis) are offered therapy on clinical trials or recommended treatment with melphalan plus high-dose dexamethasone.[239] Melphalan is administered in a dose of 0.22 mg/kg/day orally on days 1 through 4 with high-dose dexamethasone 40 mg/day orally on the same 4 days. Cycles are repeated every 28 days for no longer than 9 months. Under this regimen, a hematologic response was noted in 67% of patients in one trial, 33% achieving compete hematologic remission.[240] Improvement in organ function is seen in approximately 50% of responding patients.

Prolonged and impressive organ remissions can be achieved with ASCT in approximately 50% of patients treated with such therapy.[241–244] However, preliminary results of a French randomized trial suggest that OS might not be superior with SCT compared to melphalan plus high-dose dexamethasone.[245] This trial randomized 100 patients; median actuarial survival was 57 months with melphalan plus high-dose dexamethasone and 49 months with transplantation ($P = 0.2$). However, interpretation of this trial is confounded by the relatively short follow-up (29 months) and the very high treatment-related mortality rate that was observed in the transplant arm (24%). In patients who proceed to early transplant, there does not appear to be any need for induction therapy.[246] Excessive fluid accumulation during stem cell mobilization (>2% weight gain) predicts for a higher mortality rate with SCT.[247] The typical conditioning regimen that is used is high-dose intravenous melphalan (100 to 200 mg/m^2) with the exact dose level based on age, presence or absence of cardiac involvement, number of organs involved, and creatinine clearance.[239] Highly selected patients with end-stage amyloid renal disease and end-stage amyloid cardiomyopathy have been considered for sequential kidney stem cell transplantation and sequential cardiac stem cell transplantation, respectively.[248,249]

A recent study found that thalidomide plus dexamethasone could be a second-line treatment option for patients with systemic AL amyloidosis, hematologic responses being seen in 48% of 31 enrolled patients, including complete responses in 19% and organ responses in 26%.[250] However, it must be noted that thalidomide is less well tolerated in amyloidosis than in myeloma,[251] and the regimen is associated with significant side effects. Lenalidomide, an analog of thalidomide with lesser toxicity, has limited activity in AL amyloidosis as single agent but is more potent in combination with dexamethasone.[252,253] A trial of cyclophosphamide, thalidomide, and dexamethasone has reported organ responses in 27% of evaluable patients.[254]

Patients with amyloidosis also require significant supportive care based on the nature of organ involvement, such as treatment of nephrotic syndrome, malabsorption, neuropathy, and heart failure.

Table 110-12 Risk Stratification Model to Predict Progression of Primary Amyloidosis[235,236]

Risk Group	Median Survival in Patients Undergoing Stem Cell Transplantation (months)	Median Survival in Patients Not Undergoing Stem Cell Transplantation (months)
Low-risk (cardiac troponin < 0.035 μg/L and NT-proBNP < 332 ng/L)	Not reached at 40 months	26.4
Intermediate-risk (any one factor abnormal)	Not reached at 40 months	10.5
High-risk (cardiac troponin ≥ 0.035 μg/L and NT-proBNP ≥ 332 ng/L)	8.4	3.5

NT-proBNP, N-terminal pro–brain natriuretic peptide.

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SOLITARY PLASMACYTOMA

Solitary plasmacytomas may be confined to bone (solitary bone plasmacytoma) or may occur in extramedullary sites (extramedullary plasmacytoma).[255] Extramedullary plasmacytoma is localized to the upper respiratory tract (nasal cavity and sinuses, nasopharynx, and larynx) in over 80% of cases but can also occur in the gastrointestinal tract, central nervous system, urinary bladder, thyroid, breast, testes, parotid gland, or lymph nodes. Patients with solitary plasmacytoma are at risk for progression to multiple myeloma. Increased microvessel density detected in the initial diagnostic tissue specimen has been associated with an increased risk of progression to multiple myeloma, suggesting that the evolution to systemic disease might depend on an angiogenic switch.[32]

Diagnosis and Prognosis

Diagnostic criteria are listed in Table 110-1. An MRI of the spine and pelvis should be performed in addition to a skeletal survey, since approximately one third of patients may have additional occult lesions that will be missed in the absence of an MRI.[256]

Patients with a baseline serum M protein level greater than 1 g/dL have a high risk of persistent M protein following radiation therapy to the involved site.[257] Persistence of M protein 1 year or more after radiation therapy has been associated with an increased probability of progression to multiple myeloma in patients with solitary bone plasmacytoma.[258] The 10-year myeloma-free survival was 29% in patients with persistent serum or urinary M protein compared to 91% in those in whom the M protein was not detectable following radiation therapy.

Treatment

Treatment consists of radiation in the range of 40 to 50 Gy to the involved site.[182] Patients who meet criteria for solitary plasmacytoma except for evidence of clonal involvement of the bone marrow can be also treated with radiation therapy to the involved site and then observed until disease progression similar to that of MGUS (<10% bone marrow plasma cells) or smoldering multiple myeloma (≥10% plasma cells).

Over 50% of patients with a solitary bone plasmacytoma are alive at 10 years,[258] and disease-free survival rates at 10 years range from 25% to 50%.[255] Progression to myeloma, when it occurs, usually appears within 3 years, but patients must be followed indefinitely. Prognosis may be better in patients with solitary extramedullary plasmacytoma, with 10-year disease-free survival rates of approximately 70% to 80%[255]

POEMS SYNDROME

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes) syndrome is defined by the criteria listed in Table 110-1.[259] It is a rare, atypical, plasma cell proliferative disorder. POEMS syndrome been variously referred to in the literature as osteosclerotic myeloma, Crow-Fukase syndrome, PEP (plasma cell dyscrasia, endocrinopathy, polyneuropathy) syndrome, and Takatsuki syndrome. In almost all cases, the immunoglobulin light-chain type is lambda.

Diagnosis

The median age at presentation is 51 years. Almost all patients have either osteosclerotic lesions or Castleman's disease. The major clinical features are a predominantly motor chronic inflammatory demyelinating polyneuropathy, sclerotic bone lesions, and a varying number of associated abnormalities such as hepatomegaly, hyperpigmentation, hypertrichosis, gynecomastia, testicular atrophy, clubbing, polycythemia, thrombocytosis, and Castleman's disease. Patients may have respiratory problems ranging from neuromuscular weakness to reduced diffusion capacity of carbon monoxide to pulmonary hypertension. Biopsy of an osteosclerotic lesion might be necessary for the diagnosis.

The pathogenesis of the syndrome is not clear but appears to be at least in part cytokine mediated, and elevated vascular endothelial growth factor levels are commonly found.[260,261]

Treatment

POEMS syndrome may have an indolent or a fulminant course. In one study of 99 patients, median survival was 13.8 years.[262] If the disease is unchecked, the clinical course is characterized by progressive disabling neuropathy, inanition, anasarca, and pulmonary demise. The number of features involved does not predict for survival, but the presence of fingernail clubbing or extravascular volume overload does. When renal failure occurs in POEMS syndrome, it is in the context of extravascular overload, and membranoproliferative features and endothelial injury are seen rather than light-chain deposition.[263,264]

If the lesions are in a limited area, radiation therapy (40 to 50 Gy) produces substantial improvement of clinical symptoms and signs in more than 50% of patients. For patients with widespread osteosclerotic lesions, treatment is similar to that for myeloma and depends on eligibility for SCT. In eligible patients, ASCT has provided significant responses; in one study, all 14 evaluable patients achieved improvement or stabilization of neuropathy.[265] Supportive care, including aggressive physical and occupational therapy, is an important component of care.

HEAVY-CHAIN DISEASES

The heavy-chain diseases (HCDs) are characterized by the presence of an M protein consisting of a portion of the IgH in the serum, urine, or both. These heavy chains are devoid of light chains and represent a lymphoplasma cell proliferative process.

Gamma Heavy-Chain Disease

In gamma heavy-chain disease (γ-hCD), the abnormal protein consists of monoclonal γ chains with significant deletions of amino acids, including the C_{H1} domain of the constant region. The median age of patients is approximately 60 years, although the condition has been noted in individuals younger than age 20 years. Patients with γ-HCD often present with a lymphoma-like illness, but the clinical findings are diverse and range from an aggressive lymphoproliferative process to an asymptomatic state. The electrophoretic pattern often shows a broad-based band that is more suggestive of a polyclonal increase than of an M protein.

Treatment is indicated only for symptomatic patients. Therapy consists of chemotherapy with melphalan plus prednisone or with regimens that are used to treat non-Hodgkin's lymphoma, such as cyclophosphamide, vincristine, and prednisone. The prognosis of γ-HCD is variable and ranges from a rapidly progressive downhill course of a few weeks' duration to the asymptomatic presence of a stable monoclonal heavy chain in the serum or urine.

Alpha Heavy-Chain Disease

Alpha heavy-chain disease (α-HCD) is the most common form of HCD and occurs in patients from the Mediterranean region or Middle East, usually in the second or third decade of life. About 60% are men. Most commonly, the gastrointestinal tract is involved, resulting in severe malabsorption with diarrhea, steatorrhea, and loss of weight. Plasma cell infiltration of the jejunal mucosa is the most frequent pathologic feature. Immunoproliferative small intestinal disease is restricted to patients with small intestinal lesions who have the same pathologic features as those of α-HCD, but these patients do not synthesize α heavy chains.

The serum protein electrophoretic pattern is normal in half the cases; in the remainder, an unimpressive broad band may appear in the α_2 or β regions. The diagnosis depends on the recognition of a monoclonal α heavy chain on immunofixation. The amount of α heavy chain in the urine is small.

In the absence of therapy, α-HCD typically is progressive and fatal. The usual treatment is with antibiotics such as tetracyclines and eradication of any concurrent parasitic infection. Patients who do not respond adequately to antibiotics are treated with chemotherapy similar to that used to treat non-Hodgkin's lymphoma, for example, the CHOP regimen.

Mu Heavy-Chain Disease

Mu heavy-chain disease (μ-HCD) is characterized by the demonstration of a monoclonal μ-chain fragment in the serum. The serum protein electrophoretic pattern is usually normal except for hypogammaglobulinemia. The course of μ-HCD is variable, and survival

ranges from a few months to many years. Treatment is with corticosteroids and alkylating agents.

CRYOGLOBULINEMIA

Cryoglobulins are proteins that precipitate when cooled and dissolve when heated. They are designated as idiopathic or essential when they are not associated with any recognizable disease. Cryoglobulins are classified into three types: type I (monoclonal), type II (mixed monoclonal plus polyclonal), and type III (polyclonal).

Type I Cryoglobulinemia

Type I (monoclonal) cryoglobulinemia is most commonly of the IgM or IgG class, but IgA and Bence Jones cryoglobulins have been reported. Most patients, even with large amounts of type I cryoglobulin, are completely asymptomatic from this source. Others with monoclonal cryoglobulins in the range of 1 to 2 g/dL may have pain, purpura, Raynaud's phenomenon, cyanosis, and even ulceration and sloughing of skin and subcutaneous tissue on exposure to the cold because their cryoglobulins precipitate at relatively high temperatures. Type I cryoglobulins are associated with macroglobulinemia, multiple myeloma, or MGUS. Therapy for patients with type 1 cryoglobulinemia and significant symptoms is similar to that for Waldenström's macroglobulinemia for the IgM type and similar to that for multiple myeloma for the non-IgM type.

Type II Cryoglobulinemia

Type II (mixed) cryoglobulinemia typically consists of an IgM M protein and polyclonal IgG, although monoclonal IgG or monoclonal IgA may also be seen with polyclonal IgM. Serum protein electrophoresis usually shows a normal pattern or a diffuse, polyclonal hypergammaglobulinemic pattern. The quantity of mixed cryoglobulin is usually less than 0.2 g/dL. Hepatic dysfunction and serologic evidence of infection with hepatitis C virus are common, and hepatitis C is thought to be the cause of most cases of type II cryoglobulinemia. Vasculitis, glomerulonephritis, lymphoproliferative disease, and chronic infectious processes have also been associated with the disease.

Most clinical manifestations are related to the development of vasculitis and include purpura, polyarthralgias, and neuropathy. Involvement of the joints is symmetrical, but joint deformities rarely develop. Raynaud's phenomenon, necrosis of the skin, and neurologic involvement may be present. In almost 80% of renal biopsy specimens, glomerular damage can be identified. Nephrotic syndrome may result, but severe renal insufficiency is uncommon.

Early administration of corticosteroids is the most frequent therapy. Therapy should also target underlying hepatitis C infection with interferon-α_2 and ribavarin. Agents such as rituximab, cyclophosphamide, or chlorambucil are used if there is no response. Plasmapheresis is helpful in the acute management of symptoms by removing circulating immune complexes.

Type III Cryoglobulinemia

Type III (polyclonal) cryoglobulinemia does not have a monoclonal component and is not associated with a clonal plasma cell proliferative disorder. Type III cryoglobulins are found in many patients with infections or inflammatory diseases and are usually of no clinical significance unless associated with hepatitis C infection.

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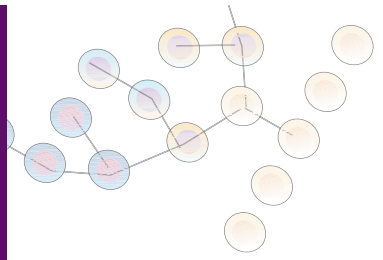
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111 Hodgkin's Lymphoma

Sandra J. Horning

SUMMARY OF KEY POINTS

Incidence
- 8100 new U.S. cases per year
- Highest incidence in North America and Western Europe
- Lower incidence in black and Asian populations

Etiology and Pathology
- Unknown but aberrant B-cell response to antigen in susceptible individuals suggested
- Relationship to Epstein-Barr virus (EBV) in a subset by unknown mechanism
- Genetic component suggested by increased risk in families

Pathology and Biology
- Classical Hodgkin's lymphoma (HL) diagnosed by $CD15^+$ $CD30^+$ Reed-Sternberg cells within a characteristic inflammatory background
- Nodular lymphocyte predominance HL diagnosed by $CD20^+$ $CD15^-$ $CD30^-$ L&H cells with characteristic architecture and background
- Malignant Hodgkin's Reed-Sternberg cells derive from germinal center and/or postgerminal center B cells that have an interdependent relationship with the surrounding inflammatory cells.

Clinical Presentation
- Lymphadenopathy, particularly supradiaphragmatic
- Chest symptoms related to mediastinal adenopathy
- Constitutional "B" symptoms: night sweats, fevers, weight loss

Staging
- History, physical examination, complete blood count, serum chemistry, ESR
- Radiologic studies: computed tomography of chest, abdomen and pelvis; whole body positron emission tomography
- Bone marrow biopsy for patients with B symptoms and/or advanced disease

Primary Treatment
- Limited stage: brief chemotherapy and involved field radiotherapy; chemotherapy alone an option
- Advanced stage: multiagent chemotherapy for six to eight cycles with ABVD (doxorubicin, bleomycin, vinblastine, doxorubicin) or BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone)

Secondary Treatment
- High dose therapy and autologous stem cell transplantation for advanced stage and extensive symptomatic relapse
- Limited relapse after treatment for early stage disease should be individualized.

Survivorship
- Risks for second solid cancers related to age at treatment, time from treatment, radiation and alkylating agent exposure
- Risks for cardiovascular disease related to chest radiation and anthracycline exposure
- Gonadal toxicity and infertility concerns should be addressed early with treatment selection.
- Long-term survivors require ongoing monitoring, particularly those treated before 1990.

Prognosis
- Favorable, early stage disease cured in greater than 90% of patients
- Advanced disease cured in 60% to 85% of patients, dependent on clinical prognostic score and age
- Relapsed disease cured in approximately 40% to 50% of stem cell transplant recipients
- Early response assessment by FDG-PET appears to be highly predictive.

INTRODUCTION

Definition

Hodgkin's lymphoma is an hematolymphoid neoplasm, primarily of B-cell lineage, with unique molecular, histologic, immunophenotypic, and clinical features. The diagnosis is made by histologic criteria supplemented by immunophenotyping in a representative biopsy of adequate size.

Historical Review

In 1832 English physician Thomas Hodgkin described lymph node and spleen enlargement in a small clinical series "On some morbid appearances of the absorbent glands and spleen."[1] The first microscopic description of the disease that bears his name followed more than 60 years later when German pathologist Carl Sternberg and American pathologist Dorothy Reed independently provided detailed accounts of the giant "Reed-Sternberg" cells so characteristic of Hodgkin's disease.[2,3] Subsequently systems of classification evolved from that of Jackson and Parker to that of Lukes and Butler, which was slightly modified in 1999 by the World Health Organization.[4,5] Current classification is firmly based on microscopic features but also takes advantage of modern immunohistochemical techniques.

Shortly after the description of x-rays, Pusey and Senn applied radiation therapy to treat advanced Hodgkin's disease, noting remarkable regressions.[6,7] However, the first true therapeutic breakthrough with curative treatment came as a result of careful clinical investigations by radiation oncology pioneers, Vera Peterson and Henry Kaplan, the latter of whom introduced the linear accelerator in radiation oncology.[8] The application of extended or wide-field radiation to involved and uninvolved nodal areas revolutionized the field. Key

to this success and future efforts was the concept of the contiguous spread of Hodgkin's disease, documented by careful clinical and radiologic evaluation of disease at diagnosis and at recurrence.[9] Clinical staging and, later, pathologic staging with bone marrow sampling and exploratory laparotomy, were standardized.[10] Steady advances have been made in diagnostic radiology, where computed tomography (CT) and ^{18}F-deoxyglucose–positron emission tomography (FDG-PET) provide accurate assessment of involved areas, and in therapeutic radiation, where technical advances in linear accelerators, dosimetry, computerized simulation, and conformal treatment plans provide more targeted treatment. Appreciation of the late adverse effects of radiation therapy in Hodgkin's survivors and the success of chemotherapy led to current management approaches in which radiation therapy is applied to involved fields and in lower doses in combined-modality approaches.

Although the chemotherapeutic agent nitrogen mustard produced reduction of nodal masses in Hodgkin's disease in 1947, the use of combination chemotherapy, based on the principles of drugs with different cytotoxic mechanisms and nonoverlapping toxicities, at the U.S. National Cancer Institute in 1963 was the breakthrough that changed advanced Hodgkin's disease from a reliably fatal condition to one that could be cured.[11] Dr. Vincent DeVita, Jr., and his team reported an 80% complete remission rate and a nearly 50% cure rate with the MOPP (mustard, vincristine, procarbazine, prednisone) regimen in a seminal publication. Another important milestone was the introduction of the ABVD regimen by Gianni Bonadonna and colleagues in the 1970s (see section on Management).[12] ABVD was successful in treating patients with Hodgkin's disease recurrent after MOPP. Based on this success and a favorable toxicity profile, ABVD advanced to primary treatment, where it is now considered a standard proven to be more effective than MOPP. Additional progress in the field came with the use of high doses of chemotherapy and autologous hematopoietic cell rescue, which is effective as secondary treatment.[13] Building on this experience, newer chemotherapy combinations have been tested in the clinical setting, as discussed in the following sections.

The history of Hodgkin's disease, now Hodgkin's lymphoma, is a success story that in many ways has been transforming in oncology. It brought much needed optimism to the field and served to attract talented young physicians. The therapeutic success in Hodgkin's lymphoma demonstrated the benefits, indeed the necessity, of multidisciplinary expertise and coordination, from pathologic diagnosis to radiologic evaluation to irradiation and medical oncology treatments. Organized prospective investigation of Hodgkin's lymphoma in a series of consecutive, randomized clinical trials, pioneered by Henry Kaplan and Saul Rosenberg at Stanford University, set a standard that evolved into the large, multicenter studies conducted today.[14] Later, as complications of therapy emerged, Hodgkin's lymphoma has instructed the general field of cancer survivorship and served to continue research to document complications and reduce their incidence with refinements in both radiation therapy and chemotherapy.

EPIDEMIOLOGY AND ETIOLOGY

The incidence of Hodgkin's disease is estimated to be 7400 new cases annually in the United States, resulting in an age-adjusted annual rate of 2.7 per 100,000.[15] The bimodal age-incidence curve is a distinguishing epidemiologic feature. There is a peak at age 25, a decline and plateau through middle age, and then an increase with older age. This variation with age has long led to speculation that a biologic agent causes Hodgkin's lymphoma in adolescents and younger adults, whereas the etiology of Hodgkin's lymphoma in older patients may be akin to that of non-Hodgkin's lymphoma. In contrast to the non-Hodgkin's lymphoma, the overall incidence rate of Hodgkin's lymphoma has been relatively stable over the last 3 decades. However, upon closer inspection, the incidence slightly increased for young adults and declined for older adults.

There is a male predominance (1.2:1) in Hodgkin's lymphoma. From 1993 to 2000 the incidence rates were stable among U.S. whites, blacks, and Hispanics, whereas they increased for Asians by 5.2% per year. Table 111-1 demonstrates the age-adjusted annual incidence rates in the U.S. SEER program during that time period, according to gender and race/ethnicity. Incidence of the nodular sclerosis subtype in young adults has been linked to socioeconomic status in several reports. The relationship of incidence to neighborhood socioeconomic status was recently demonstrated for younger but not older adults in California by Clark and colleagues (Fig. 111-1).[16] Speculation and reports about clustering of cases in time and place of diagnosis do not hold up to rigorous statistical methods, and thus, there is no persuasive evidence of disease transmission.

Table 111-1 Age-Adjusted Average Annual Incidence of Hodgkin's Lymphoma 2000–2003*

Group	Males	Females
White (non-Hispanic)	3.5	2.9
Black (non-Hispanic)	2.8	2.1
Hispanic	2.9	1.6
Asian or Pacific Islander (non-Hispanic)	1.4	1.0
American Indian or Alaska Native (non-Hispanic)	1.1	0.7

*Incidence per 100,000 person-years.

Multiple lines of data are consistent with the hypothesis that young adult Hodgkin's lymphoma is associated with late-onset infection of a pathogen. Factors associated with increased risk of Hodgkin's lymphoma in prior reports include high socioeconomic status, high educational level, inverse relationship to sibship size, and early birth order. Of note, studies in the 1990s reported that sibship size and birth order did not associate with Hodgkin's lymphoma risk but, rather, that living in a rented home, sharing a bedroom, and attending day care or nursery school were associated with a reduced risk. These results continue to be consistent with the "hygiene hypothesis"—delayed exposure to an infectious agent. Childhood Hodgkin's lymphoma demonstrates a very different pattern, with a marked male excess (consistent with infectious exposure), a higher incidence in less developed countries, and a relationship to lower socioeconomic status. Among older adults (age ≥55 years) socioeconomic status does not clearly associate with incidence. Taken together,

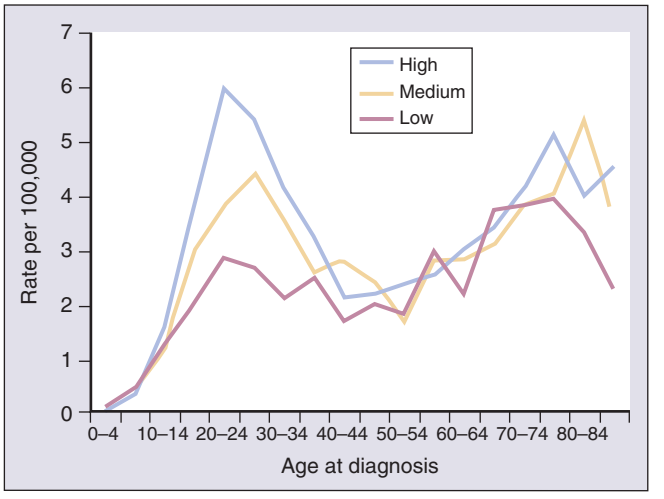


Figure 111-1 • Age-specific incidence of Hodgkin's lymphoma by tertile of neighborhood socioeconomic status, California, 1988–1992. (Reprinted with permission from Clarke C, Glaser S, Keegan T, et al: Neighborhood socioeconomic status and Hodgkin's lymphoma incidence in California. Cancer Epidemiol Biomarkers Prev 2005;14:1441–1447.)

these data suggest three epidemiologic types of Hodgkin's lymphoma that differ related to the maturity of the immune system.

The B-cell tropic Epstein-Barr herpesvirus (EBV) has been implicated in the etiology of Hodgkin's lymphoma. The viral genome can be demonstrated in the Hodgkin/Reed-Sternberg (H-RS) cells of about 40% of Hodgkin's lymphoma cases by in situ hybridization, and the genome is monoclonal.[17] The standard of evidence involves detection of the EBV-encoded RNA (EBER) by in situ hybridization and/or immunohistochemical detection of the latent-membrane protein-1 (LMP-1). A history of infectious mononucleosis increases the risk of Hodgkin's lymphoma threefold, and high levels of the EBV viral capsid antigen and early antigen antedate the diagnosis by several years.[18] Hjalgrim and associates reported that young adults with a history of infectious mononucleosis had an increased risk of EBV^+ Hodgkin's lymphoma but not EBV^- Hodgkin's lymphoma.[19] Although there is discordance among all reported data, Alexander and coworkers confirmed these results suggestive of a causal relationship in EBV^+ young adult Hodgkin's lymphoma.[20] It is important to note, however, that EBV^+ cases are more common among children and older adults and are more likely to have mixed-cellularity histology. Recent epidemiologic data demonstrate an increase in incidence of Hodgkin's lymphoma, which is typically EBV^+, in patients infected with the immunodeficiency virus who have been effectively treated with modern retroviral therapy.[21] These data (as discussed in the following sections) provide further clues to pathogenesis of Hodgkin's lymphoma.

Evidence for a genetic contribution in the etiology of Hodgkin's lymphoma comes from multiple sources. Genetic susceptibility and familial aggregation seem to play an important role in Hodgkin's lymphoma. Siblings have a sevenfold increase in risk, and multiple studies have now confirmed a gender concordance of sibling pairs. Of interest, similar findings have been published for chronic lymphocytic leukemia and for Behçet's disease, multiple sclerosis, and sarcoidosis. These data are compatible with a hypothesis of shared genetic susceptibility and environmental exposure. Alternately, it has been proposed that some of this risk may be related to genes in the pseudoautosomal location of the sex chromosomes. Mack and coworkers published the strongest evidence thus far of genetic susceptibility, observing a 100-fold increased risk in monozygotic twins compared with dizygotic twins.[22] Several groups have described human leukocyte antigen (HLA)–related susceptibility and resistance to Hodgkin's lymphoma, but these data have been relatively weak and sometimes inconsistent. More recent data implicate HLA in EBV-related Hodgkin's lymphoma, where HLA*A-02 was associated with a reduced risk and HLA*-A01 with an increased risk of EBV^+ Hodgkin's lymphoma.[23] These findings strengthen the hypothesis that Hodgkin's lymphoma is related to a genetically related immune response to an environmental pathogen.

PATHOGENESIS

Pathology

The diagnosis of classical Hodgkin's lymphoma requires the recognition of H-RS cells in an appropriate cellular milieu. Because H-RS cells compose a minority, often 1% to 5%, of the total cellular population, an open biopsy is required for unequivocal diagnosis and subtyping. H-RS cells are largeand either multinucleated or with a large polypoid nucleus; each nucleus or lobe contains a prominent eosinophilic nucleolus (Fig. 111-2A). The background cells consist mainly of small lymphocytes together with a smaller number of scattered eosinophils, neutrophils, histiocytes, plasma cells, and fibroblasts (Fig. 111-2B).

There are four morphologic types of classical Hodgkin's lymphoma (Table 111-2). As discussed in the following sections, histologic subtypes correlate with a number of clinical features. Nodular sclerosis is characterized by broad bands of collagen and lacunar cells, which are RS variants seen in formalin-fixed specimens. Nodular sclerosis accounts for about 65% of Hodgkin's lymphoma in the Western world. There have been attempts to further subclassify nodular sclerosis on morphologic criteria, but this has not been widely adopted. Mixed-cellularity subtype is present in about 30% of cases but is more common in developing nations, the elderly, and the immunodeficient. H-RS cells are typically plentiful in mixed-cellularity Hodgkin's lymphoma, whereas fibrosis is absent. Lymphocyte-depleted Hodgkin's lymphoma is exceedingly rare and can present a differential diagnostic dilemma with non-Hodgkin's lymphoma. The relatively newly described lymphocyte-rich subtype may have a nodular or diffuse pattern and can mimic other subtypes as well as nodular lymphocyte predominant (NLPHL).

Immunohistochemical studies are of great usefulness in Hodgkin's lymphoma, and the hallmark of classical Hodgkin's lymphoma is a common immunophenotype (Table 111-3). Classical Hodgkin's lymphoma expresses CD30, a marker of activated B- and T-lymphoid cells, in almost all cases (Fig. 111-2C). About 87% of classical Hodgkin's lymphomas express CD15, the carbohydrate X hapten. CD15 antibodies also stain mature neutrophils, macrophages, and a subset of T cells. CD15 staining is more heterogeneous among H-RS cells compared with CD30. In some analyses absence of CD15 staining has been reported to be an adverse prognostic factor, but this has not been broadly confirmed. $CD15^-$ cases have also been associated with advanced stage, male gender, and older age, each recognized to be a component of the existing clinical prognostic score as detailed later. Classical Hodgkin's lymphoma rarely expresses CD45, also known as common leukocyte antigen, which is expressed by nearly all non-Hodgkin's lymphomas and can serve as a useful marker for differential diagnosis. CD20 staining in classical Hodgkin's lymphoma has been variably reported from 5% to 25% of cases. The pattern of staining is heterogeneous and confined to a subset of H-RS cells, in contrast to uniform and strong staining in non-Hodgkin's lymphoma and NLPHL. Conflicting reports on the prognostic significance of CD20 expression have been reported.

NLPHL is defined on the basis of distinctive morphologic features and surface marker expression. At low power large, tightly packed nodules are typically numerous (Fig. 111-2D). The background includes B-lymphocytes and histiocytes. The neoplastic cells are referred to as L&H (lymphocytic and histiocytic, based on the background) and are notable for a lobulated, "popcorn" appearance. The European Task Force for Lymphoma made a major contribution in establishing the criteria for current diagnosis.[24] Using defined morphologic criteria and immunohistochemistry, 56% of NLPHLs were reclassified as classical Hodgkin's lymphoma or other lymphoid processes. NLPHL has unique clinical features and course as further discussed later.

Derivation of Hodgkin's-Reed-Sternberg and Lymphocytic and Histiocytic Cells

The cell of origin of Hodgkin's lymphoma remained elusive for many years because the characteristic giant multinuclear cells, the H-RS cells, do not resemble any normal hematopoietic cell (Table 111-4). In fact, H-RS cells express markers characteristic of different cell types such as dendritic cells (fascin, TARC), granulocytes and monocytes (CD15), B cells (Pax-5), plasma cells (MUM-1, CD138), and activated lymphocytes (CD30). The ability to microdissect single H-RS cells was a breakthrough that established the B-cell lineage of Hodgkin's lymphoma. Clonal immunoglobulin rearrangements in nearly all cases demonstrated that H-RS cells derive from B cells. Further, the presence of somatic mutations indicates that H-RS cells participated in the germinal center reaction in response to antigen. Notably, H-RS cells lack expression of characteristic B-cell surface markers (CD20, B-cell receptor, etc.), and expression profiling studies have extended this observation in demonstrating the downregulation of B-cell–specific transcription factors (Oct-2, Bob1, Pu.1) and signaling pathways (Syk, Blk), as well as surface markers.

In contrast, CD20 expression implied the B-cell origin of L&H cells, and this was later confirmed by demonstration of immuno-

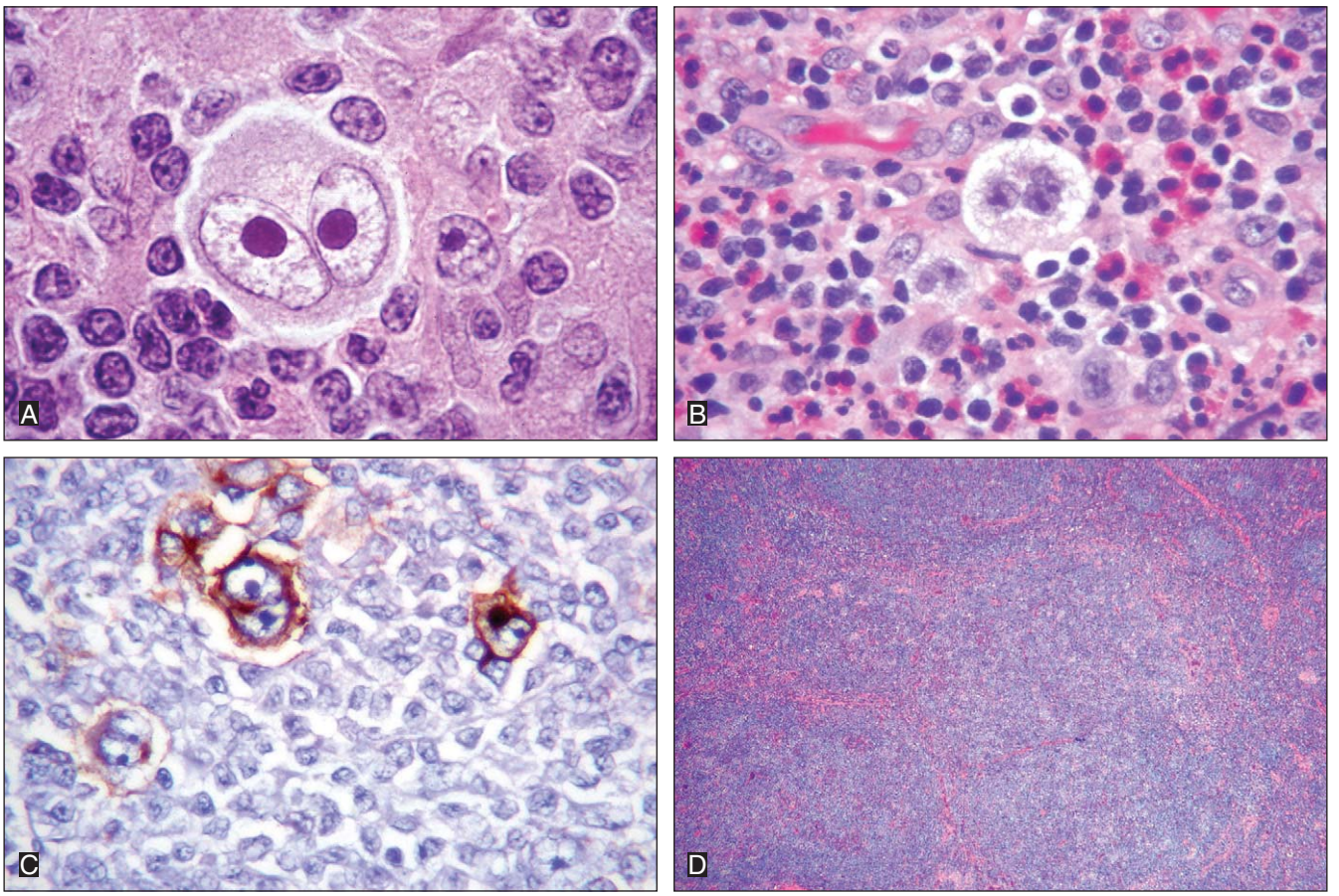


Figure 111-2 • **A,** Classic Reed-Sternberg cell, demonstrating large size, multinucleated nucleus, and prominent eosinophilic nucleolus. **B,** The majority of cells in classical Hodgkin's lymphoma are nonmalignant and consist of a supportive environment that includes lymphocytes, neutrophils, eosinophils, plasma cells, and fibroblasts. **C,** Classical Hodgkin's lymphoma expresses CD30, a marker of activated B- and T-lymphoid cells, in almost all cases. **D,** Nodular lymphocyte–predominant Hodgkin's lymphoma has distinctive surface markers and morphologic features, including numerous, tightly packed nodules at low power.

Table 111-2 World Health Organization Classification of Hodgkin's Lymphoma

Classical Hodgkin's lymphoma
Nodular sclerosing
Lymphocyte-rich
Mixed cellularity
Lymphocyte-depleted
Nodular lymphocyte–predominant Hodgkin's lymphoma

Table 111-3 Selected Immunophenotypic Markers and Histologic Characteristics of Use in the Differential Diagnosis of Hodgkin's Lymphoma and Other Lymphoid Neoplasms

Maker	Classical HL	Nodular Lymphocyte Predominant HL	TCRBCL	ALCL
CD30	+	–	–	+
CD15	+	–	–	–
CD20	–/+*	+	+	–
CD45	–	+	+	+/–
CD79a	–	+	+	–
ALK	–	–	–	+/–
EMA	–	+	+	+
Nodular growth protein	+/–†	+	–	–

+, >90% of cases positive; +/–, majority of case positive; –/+, minority of cases positive; –, <10% of cases positive; ALCL, anaplastic large cell lymphoma; HL, Hodgkin's lymphoma; TCRBCL, T-cell–rich B-cell lymphoma.

*CD20 positive in classical Hodgkin's lymphoma is quite heterogeneous, with a wide range in brightness of staining.

†In classical Hodgkin's lymphoma, a nodular growth pattern is confined to the nodular sclerosing subtype.

Table 111-4 Genotypic and Phenotypic Features of Hodgkin's-Reed-Sternberg and Lymphocytic and Histiocytic Cells

Feature	H-RS Cells	L&H Cells
Somatically mutated Ig variable genes	Y	Y
Destructive somatic mutations	Y	N
Ongoing somatic mutation	N	Often
Expression of B-cell receptor	N	Y
Expression of B-cell transcription factors	N	Y
Expression of B-cell surface markers	N	Y
Expression of GC markers: Bcl-6, AID	Rare	Y
Plasma cell markers	Often	N
Antigen presentation markers	Y	Y
Expression of non–B-cell markers	Y	N

AID, antigen-induced cytidine deaminase; GC, germinal center; H-RS, Hodgkin's Reed-Sternberg; Ig, immunoglobulin; L&H, lymphocytic and histiocytic.

globulin gene rearrangement (see Table 111-4). In many cases ongoing hypermutation was observed, consistent with a germinal center B-cell derivation. The expression of Bcl-6 and AID (activation-induced cytidine deaminase), a key enzyme for somatic hypermutation and class switching, is consistent with a germinal center origin.

Biology of Malignant Cells and the Microenvironment

The generation and sustenance of H-RS and L&H cells has long been the subject of speculation and interrogation.[25] Typically, antigen-driven B cells migrate and establish germinal centers in secondary lymph nodes where they undergo clonal expansion, acquire affinity-enhancing mutations, and undergo positive selection before exiting the germinal center to become either plasma cells or memory B cells. L&H cells seem to derive from selected, mutating germinal center B cells, whereas H-RS cells have characteristics of preapoptotic germinal center B cells with crippling mutations that should normally lead to cell death. Because classical H-RS cells do not express B-cell surface molecules (including the B-cell receptor), they rely on alternative survival and proliferative pathways activated by transcription factors such as NF-κB, a hallmark of H-RS cells (Fig. 111-3). Constitutive activation of NF-κB is in part due to signaling through members of the tumor necrosis factor receptor family (CD40, CD30) as a result of a complex interplay with surrounding lymphocytes. EBV infection has been directly implicated in transforming "crippled" H-RS cells through activation of NF-κB via LMP-1, sparing them from apoptosis.[26] Additional signaling pathways, including the CD95 pathway, also contribute to apoptosis resistance in H-RS cells as detailed in Figure 111-3.[27]

The brisk inflammatory microenvironment of Hodgkin's lymphoma is the subject of a great deal of current scientific progress and excitement. The large majority of Hodgkin's lymphoma tissues comprises inflammatory cells and stromal elements that are thought to be recruited by cytokines (low-molecular-weight proteins that regulate a variety of biologic processes) and chemokines (cytokines that involve migration of leukocytes) secreted by the H-RS cells. Interleukins (IL-4, IL-6, IL7, IL-9, IL-13, and IL-15) are among the many influential cytokines expressed by H-RS cells.[25,28] The systemic "B" symptoms that occur in about 30% of Hodgkin's lymphoma patients are probably due to these cytokines. Chemokines, such as CCL17 (TARC) in classical Hodgkin's lymphoma, attract specific lymphocyte subsets to the microenvironment and are responsible for the subtypes of Hodgkin's lymphoma.

The inflammatory cells support the H-RS cells, recruit additional cells, and stimulate collagen synthesis by secreting a variety of factors. Hodgkin's lymphoma demonstrates a dysregulated immune response. The reactive T-cell population is predominantly T helper 2 (Th2)-type and $CD4^+CD25$ high $FOXP3^+$ regulatory T cells (Treg) that directly suppress immune responses and protect H-RS cells from immune attack.[29] There is marked under-representation of natural killer (NK), Th1, and cytotoxic T cells. H-RS cells utilize interactions between their tumor necrosis factor family receptors and the natural ligands expressed by these surrounding lymphocytes to support their own growth while causing apoptosis of cytotoxic T and NK cells. Recently the immunoregulatory glycan-binding protein galectin-1, secreted by H-RS cells, has been implicated in the development and maintenance of this skewed environment.[30,31] Manipulation of the microenvironment in Hodgkin's lymphoma provides a potential target for restoring immune surveillance.

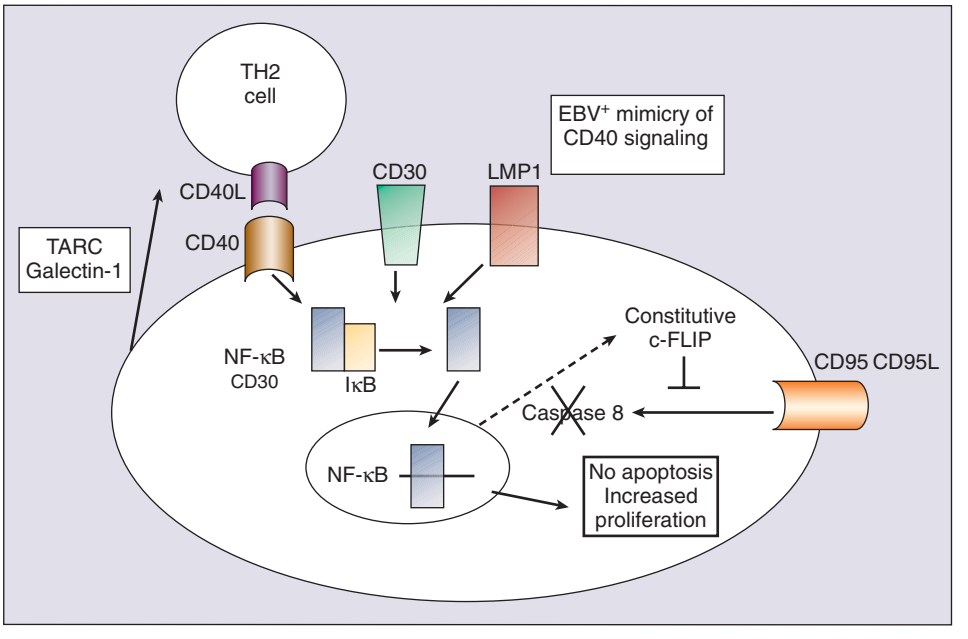


Figure 111-3 • Hodgkin's Reed-Sternberg cell. mechanisms by which Hodgkin's Reed-Sternberg cells evade apoptosis. See text for details. IκB, inhibitor of kappa beta.

CLINICAL FEATURES

Hodgkin's lymphoma typically presents with supradiaphragmatic adenopathy that requires biopsy after the exclusion of benign conditions. The low neck and supraclavicular nodes are particularly common sites. Mediastinal presentations typically occur anterior to the ascending aorta, presenting the differential diagnosis of thymoma, thyroid disease, and tumor. Just 10% of patients have an initial subdiaphragmatic presentation. The abnormal lymph nodes have a characteristic rubbery consistency and are painless. A unique feature of classical Hodgkin's lymphoma is the rapid onset of pain in involved lymph nodes with alcohol consumption. In most cases, peripheral adenopathy brings patients to clinical attention. However, symptoms of chest pressure, cough, or even dyspnea related to large mediastinal masses, 10 cm or greater, are not uncommon.

A subset of about 30% of patients presents with fevers and night sweats without peripheral adenopathy. Historically, Hodgkin's lymphoma was a cause of fever of unknown origin, but modern radiologic techniques typically reveal abnormalities that lead to direct tissue acquisition. The constellation of fevers, night sweats, and unexplained weight loss constitute the classic, "B" symptoms of Hodgkin's lymphoma (Table 111-5) that are hallmarks of the disease for some patients and serve as prognostic factors in limited-stage disease. Another constitutional complaint is unexplained pruritus, which should create suspicion and lead to a complete physical examination and chest radiograph, particularly in young adults.

Presentations of classical Hodgkin's lymphoma correlate with histologic subtype, gender, and age. Nodular sclerosis subtype, the most common subtype in young adults, presents as limited or extensive disease, with involvement of the mediastinum in about 75% of cases.

Table 111-5 Modified Ann Arbor Staging System for Hodgkin's Lymphoma

Stage	Involvement
I	Single lymph node region (I) or one extralymphatic site (I_E).
II	Two or more lymph node regions, same side of the diaphragm (II) or local extralymphatic extension plus one or more lymph node regions or same side of the diaphragm (II_E)
III	Lymph node regions on both sides of the diaphragm (III), which may be accompanied by local extralymphatic extension (III_E).
IV	Diffuse involvement of one or more extralymphatic organs or sites.
A	No B symptoms
B	Presence of at least one of the following symptoms: 1. Unexplained weight loss >10% baseline during 6 months before staging 2. Recurrent unexplained fever >38°C 3. Recurrent night sweats Bulky tumor

Bulky tumor is defined as either a single mass of tumor tissue exceeding 10 cm in largest diameter or a mediastinal mass exceeding one third of the maximum transverse transthoracic diameter measured to the inside of the ribs on a standard posteroanterior chest radiograph.

E lesion: Localized extranodal extension of Hodgkin's lymphoma from a contiguous or nearby nodal site is noted with the designation E, for example, stage II_EA for asymptomatic disease in the mediastinum with contiguous extension into nearby lung.

From Carbone PP, Kaplan HS, Musshoff K, et al: Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971;31:1860–1861.

Older and immunodeficient patients are more likely to have B symptoms, advanced disease, and mixed-cellularity histology. NLPHL has a marked male predominance and usually occurs in peripheral nodes above or below the diaphragm, sparing the mediastinum. NLPHL patients are nearly always asymptomatic and often have limited disease confined to a single lymph node region.

Bone involvement by classical Hodgkin's lymphoma may cause pain. Bone disease may result from contiguous spread of the disease, such as the sternal involvement from mediastinal adenopathy, or from widespread metastatic disease. Bone marrow involvement rarely results in cytopenias. Hodgkin's lymphoma has been associated with a variety of rare paraneoplastic syndromes that may be presenting features of the disease. These include nephrotic syndrome, neurologic disorders, and jaundice.

INVESTIGATION

Standard Evaluation

After the diagnosis of Hodgkin's lymphoma is made, it is important to establish the extent of disease (Tables 111-5 and 111-6). Notably, Hodgkin's lymphoma typically advances with involvement of contiguous lymph node regions. Knowledge of this informs the interpretation of diagnostic studies and the level of suspicion for disease outside of the lymphoid compartment. This knowledge was gained with diagnostic procedures of the past, including exploratory laparotomy, that were used to stage patients. Splenic disease, for instance, nearly always precedes disease in the lower abdominal lymph nodes or the bone marrow. With rare exceptions, Hodgkin's lymphoma disseminates widely outside of the lymphatic system to only four organs: bone, bone marrow, liver, and lung. As noted previously, selected extranodal extension may occur by contiguous spread, such as to the sternum, chest wall, pleura, pericardium, or single lobe of the lung (see Table 111-5).

The standard evaluation for newly diagnosed Hodgkin's lymphoma is described in Table 111-6. A careful history directed toward constitutional or other disease symptoms and comorbid conditions that might affect the delivery of therapy is essential. The physical examination should include inspection for neck and infraclavicular/

Table 111-6 Diagnostic Evaluation of Hodgkin's Lymphoma

Surgical biopsy
Expert hematopathology review
History directed to systemic symptoms and disseminated disease
Physical examination for lymphadenopathy and organomegaly
Laboratory tests
Complete blood count and differential
Chemistry panel to include albumin, creatinine, liver function tests
Erythrocyte sedimentation rate
HIV test if behavioral risk
Standing posteranterios chest radiograph
CT scan of chest, abdomen, pelvis
PET scan (highly recommended)
Bone marrow biopsy if systemic symptoms, advanced disease, or cytopenia
Bone scan if bone pain and PET scan not available or equivocal

CT, computed tomography; HIV, human immunodeficiency virus; PET, positron emission tomography.



Figure 111-4 • FDG-PET scan in a stage IV patient at diagnosis demonstrating bulky low-neck, mediastinal, and hilar disease with upper abdominal adenopathy, splenic disease, and extensive bone involvement.

chest wall swelling as well as palpation in all nodal areas and abdominal examination for organomegaly. Laboratory tests include a complete blood count with differential, serum chemistry to assess liver and kidney function as well as albumin, and erythrocyte sedimentation rate. Testing for infection with the human immunodeficiency virus (HIV) should be included if the history is suspicious or the presentation unusual.

Great strides have been made in imaging Hodgkin's lymphoma. CT of the neck, chest, abdomen, and pelvis have replaced the exploratory laparotomy and lymphography of the past. FDG-PET, particularly when fused with CT, is an important diagnostic tool in Hodgkin's lymphoma. Multiple studies demonstrated that FDG-PET is both more sensitive and more specific than CT or gallium scanning for Hodgkin's lymphoma at diagnosis and upon restaging to assess treatment response.[32] FDG-PET scans result in a higher stage for a small proportion of patients and a lower stage in very few patients.[33] Rather, PET scans should be viewed as complementary and as establishing a baseline for interpretation upon restaging (Fig. 111-4).

Staging

The Ann Arbor staging system has stood the test of time in Hodgkin's lymphoma (see Table 111-5). Patients are described in four stages, based on the extent of lymph node and disseminated disease:

Stage I—Involvement of a single nodal area
Stage II—Involvement of two or more nodal areas on one side of the diaphragm
Stage III—Involvement of nodal areas on both sides of the diaphragm
Stage IV—Disseminated disease involving one or more extranodal sites

In addition to recording the extent of disease, the staging systemic reflects the absence (A) or presence (B) of systemic symptoms. At the meeting in Ann Arbor, MI, where the staging convention was developed, the conveners designated extranodal (E) lesions, which have led to considerable confusion in staging. The original intent was to identify patients who had disease that could be managed within a single radiation port. With that in mind, E lesions are considerably more easily understood.

In 1989 modifications of the Ann Arbor staging system were recommended at a meeting in the Cotswolds (U.K.). The major proposed alteration was to designate bulky tumors with diameters 10 cm or greater. This was based on the appreciation that large mediastinal disease, then defined as a tumor with a maximum diameter greater than one third of the maximum intrathoracic diameter on standing chest radiograph, conferred a poor prognosis when managed with radiation therapy alone. It has become convention to designate mediastinal disease as bulky (either by the original definition and/or 10 cm or greater disease by CT scan) or not bulky in the Cotswolds modifications.

Risk groupings in early stage Hodgkin's lymphoma, which include mediastinal bulk and other clinical factors, are commonly used in treatment stratification (Table 111-7). These groupings are useful for clinical management, and it is necessary to understand these to interpret the results of recent clinical trials. In North America, patients with bulky or symptomatic stage I and II disease are generally grouped with advanced-stage patients. In contrast, in Europe, patients with stage I and II disease are divided into favorable and unfavorable categories based on risk factors that include the number of nodal sites, erythrocyte sedimentation rate, mediastinal mass size, extranodal disease, and age. With these parameters about 35% of stage I and II patients have favorable disease and 65% have unfavorable disease.

PROGNOSIS

The prognosis for patients with Hodgkin's lymphoma has steadily improved over the past 50 years as a result of advances in diagnosis and therapy. Currently, cure is expected for the great majority of patients irrespective of stage. However, advanced stage and age older than 60 to 65 years continue to pose challenges. Older patients have

Table 111-7 Risk Groups in Early Hodgkin's Lymphoma

North America	EORTC	GHSG
FAVORABLE		
Asymptomatic	Age <50 yr	No extranodal sites
MMR not large	MMR not large	MMR not large
Sites <10 cm	≤3 nodal sites	≤2 nodal sites
	ESR <50 if asymptomatic	ESR <50 if asymptomatic
	<30 if symptomatic	<30 if symptomatic
UNFAVORABLE		
I, IIA bulky	I, II with risk factors	I, II with risk factors
I, IIB		

EORTC, European Organization for Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin's Lymphoma Study Group; MMR, massive mediastinal ratio.

Table 111-8 Adverse Prognostic Factors Identified in the International Prognostic Score

Age ≥45 years
Gender: male
Stage IV
Hemoglobin <10.5 g/dL
White blood cells >15,000/μL
Lymphocytes <600/μL or <8% of total white blood cells
Albumin <4 g/dL

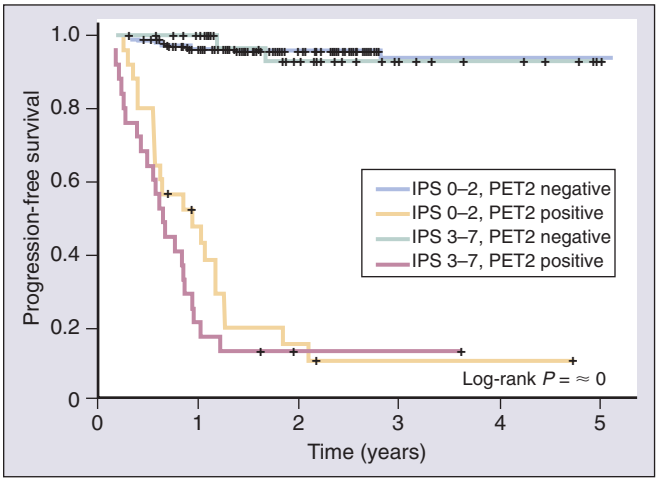


Figure 111-5 • Progression-free survival in bulky and advanced Hodgkin's lymphoma in patients with negative or positive FDG-PET scan results after two cycles of chemotherapy. Data are presented according to IPS score of 0–2 or greater than or equal to 3 (see text). (Reprinted with permission from Gallamini A, Hutchings M, Rigacci L, et al: Early interim 2-[^{18}F]fluoro-2-deoxy-*d*-glucose positron emission tomography is prognostically superior to International Prognostic Score in advanced-stage Hodgkin's lymphoma: a report from a joint Italian-Danish study. J Clin Oncol 2007;25:3746–3752.)

more biologically resistant disease, and their tolerance for very aggressive therapies is limited. Their opportunity for cure is only about half of that for younger patients.[34,35] The other dominant prognostic factor is stage. Patients with favorable, early-stage disease have a cure rate in excess of 90% with modern combined-modality therapy. The risk groupings outlined in Table 111-7, for which therapy has been modified, demonstrate excellent outcomes in unfavorable presentations of limited disease as well. Outcomes for advanced-stage patients are inferior, with cure rates ranging from about 65% to 70% in North American trials to 70% to 85% in European trials. Additional prognostic factors have been identified and widely validated in advanced Hodgkin's lymphoma.

The International Prognostic Score (IPS) is based on seven factors: three clinical (age >45 years, male sex, stage 4) and four laboratory values (albumin <4 g/dL, hemoglobin <10.5 g/dL, white blood count >15 $\times 10^6$ cells/mL, lymphocyte count <8% or <600 cells/mL; Table 111-8).[36] Patients are given a score of from 0 to 7, and disease can be categorized as low (0–1), intermediate (2–3), or high (4–7) risk. As illustrated in Table 111-9, the majority of patients have two or three risk factors. Fewer than 20% have high-risk disease. Five-year freedom from progression (FFP) decreases by about 7% per risk factor. The prognostic score is useful in the interpretation of clinical trials and, with more intensive regimens, improvements in all risk categories have been reported as discussed in the following sections.

Several studies have found that early FDG-PET is superior to the IPS in predicting progression-free survival in advanced Hodgkin's lymphoma.[32] Fig. 111-5 represents data on 260 consecutive cases of advanced Hodgkin's lymphoma combined in centers from Holland and Italy. Of these cases, 65 had an IPS of 3 to 7 and 195 had an IPS of 0 to 2.[37] PET scans were interpreted as negative or positive after just two cycles of ABVD chemotherapy by an expert panel. Negative scans demonstrated no areas of focal FDG uptake above the background level. Among patients with positive scans, 87% had disease progression at 2 years compared with 5% of patients with negative scans. These remarkable outcomes were seen irrespective of IPS (see Fig. 111-5). Based on these data and others, investigators have planned new "response-adapted" clinical trials in which therapy is escalated or de-escalated on the basis of early PET adaptation. This strategy serves to further individualize treatment and balance the risks and benefits of the therapeutic approach.

Table 111-9 International Prognostic Score and Freedom from Progression in Advanced Hodgkin's Lymphoma

N Factors	Frequency (%)	5-Year FFP (%)
0	7	84
1	22	77
2	29	67
3	23	60
4	12	51
5–7	7	42

FFP, freedom from progression.

DIFFERENTIAL DIAGNOSIS

A biopsy with routine use of immunohistochemistry typically leads to an unequivocal diagnosis of Hodgkin's lymphoma (see Table 111-3). There are cases in which the diagnosis can be more challenging, such as instances of an atypical immunophenotype or tissue acquired from extranodal sites. It is always useful to put the pathologic findings into context with the clinical features expected in Hodgkin's lymphoma, namely contiguous spread of disease and a limited number of extranodal sites. Occasional so-called "grey zone" lymphomas provide diagnostic dilemmas when non-Hodgkin's lymphoma is difficult to distinguish from Hodgkin's lymphoma. These diagnostic dilemmas, most common in mediastinal lymph nodes, are usually resolved with additional immunophenotypic and genetic tests. However, as indicated by molecular diagnosis, primary mediastinal large B-cell lymphoma is biologically related to Hodgkin's lymphoma.[38,39] Cases of composite lymphoma, where both Hodgkin's lymphoma and non-Hodgkin's lymphoma occur in the same diagnostic specimen, have been reported. In some carefully studied cases, the non-Hodgkin's lymphoma and Hodgkin's lymphoma shared the same immunoglobulin rearrangement, indicative of a clonal relationship.[40]

Both clinicians and pathologists have more difficulty in the differential diagnosis of NLPHL. NLPHL may be preceded, followed, or concurrent with progressive transformation of germinal centers, a benign condition recognized by morphologic features. Because this condition causes lymphadenopathy indistinguishable from NLPHL, it is essential that patients have an excisional biopsy both at diagnosis and any subsequent recurrence. In addition, NLPHL is associated with the later development of diffuse large B-cell lymphoma and its subtype, T-cell–rich large B-cell lymphoma. Some patterns of NLPHL are very difficult to discriminate from T-cell–rich B-cell lymphoma, requiring expert hematopathology opinion for this rare condition.[41] However, the distinction is quite important as management approaches are dramatically different. Because TCR-BCL frequently involves the bone, bone marrow, liver, spleen, abdominal and mediastinal nodes, clinical features can assist in the differential diagnosis as well.

The current era of FDG-PET scanning presents new differential diagnostic challenges to clinicians. Because FDG is taken up by many tumor types and areas of inflammation and infection, oncologists must be alert to potential "false-positive" signals. This is particularly true in the follow-up setting where the expectation is that a patient is cured of Hodgkin's lymphoma. Scans should be avoided during viral illness, and "positive" areas other than those previously involved with disease should be regarded with suspicion. Biopsy may be the only way to resolve the issue and is recommended before committing patients to additional treatment. Notably, some cases of FDG avidity in the thorax have been ascribed to sarcoidosis rather than recurrent Hodgkin's lymphoma when biopsy was attained.

MANAGEMENT

Primary Therapy of Classical Hodgkin's Lymphoma

After histologic confirmation and complete evaluation, patients are ascribed a stage as in Table 111-5. In addition to stage, patients with limited disease should be further designated according to the risk factors described in Table 111-7, whereas patients with advanced disease should be assigned a prognostic score as in Tables 111-8 and 111-9. This exercise is important to the selection and discussion of appropriate therapy and the expectation of curative outcome and complications of treatment. In addition, full assessment of disease at presentation is essential to the interpretation of the literature that forms the basis of decision analysis.

Early-Stage Disease without Risk Factors

As indicated in Table 111-7, North American stage I and II patients without bulky disease or B symptoms are generally considered in this category. In contrast, the definition of favorable early-stage disease is more restrictive in the two European classification schemes. These differences may become more relevant as therapy for these most favorable patients continues to be reduced in clinical trials. Historically, treatment has evolved from pathologic staging and widespread irradiation to a paradigm of brief chemotherapy followed by involved field radiation therapy at lower dose. The current standard is the result of careful clinical trials that demonstrated three principles: (1) ABVD (Table 111-10) is the preferred chemotherapy based on both efficacy and safety, (2) combined-modality therapy (chemotherapy + radiation therapy) is superior to wide-field radiation therapy alone, and (3) there is no advantage to wide-field radiation therapy over involved-field radiation therapy when given in combination with chemotherapy.

The Milan trial was among the first and most influential in demonstrating the high cure rate of a brief course of ABVD (four cycles) combined with involved-field radiation therapy in limited-stage Hodgkin's lymphoma (Table 111-11).[42] Although patients with large mediastinal masses were included, this study set a high bar with regard to outcomes and also demonstrated the safety of this approach with mature follow-up. Subsequently, multiple trials have explored the questions of how many cycles of ABVD are needed and what radiation dose is needed to maintain these outstanding results (see Table 111-11). Among favorable patients without risk factors, the German Hodgkin's Study Group (GHSG) evaluated two versus four cycles of ABVD and 20 versus 30 Gy involved-field irradiation. The final results of this trial have not been published, but multiple presentations of the data to date have shown FFP rates in excess of 95% for all four treatment arms.[43] Thus, for the approximately 35% of limited-stage patients with very favorable presentations, as few as two cycles of chemotherapy combined with low-dose involved-field irradiation is sufficient for cure. Full trial results are awaited with regard to the question of radiation dose.

Based upon a desire to reduce potential complications of treatment (see later discussion), ongoing clinical trials further address the individual drugs in the ABVD regimen. The GHSG HD13 study evaluated four cycles of ABVD, ABV, AV, and AVD with 30 Gy involved-field radiation therapy. Although the mature results of this trial are awaited, the AV and ABV arms have already closed because of inferiority (unpublished results). This is an important lesson in the requirement to deliver a standard treatment in a highly curable disease outside the context of a clinical investigation. Other studies are asking the question if radiation therapy can be omitted for patients who have a negative early FDG-PET scan. Based on the concerns for late effects from radiation therapy (see later discussion), there is great interest in investigation of this approach.

For patients with unfavorable, limited-stage Hodgkin's lymphoma the subjects of clinical trial inquiry have been chemotherapy combination, number of cycles of chemotherapy, and radiation dose (see Table 111-11). The H9U trial conducted by the EORTC-GELA demonstrated that the less toxic ABVD regimen was as effective as the BEACOPP regimen and that four cycles of treatment were sufficient.[44] Similarly, the GHSG HD11 trial has shown no differences in outcome thus far between ABVD and BEACOPP in limited-stage patients with risk factors.[45] This study also used four cycles of chemotherapy. The dose of radiation therapy is under investigation in this trial and requires longer follow-up. At this time a dose of 30 Gy should be considered standard. One of the challenges in interpretation of the European literature is the lack of separate reporting of outcomes in patients with large mediastinal masses. This distinctive subset may have different requirements to achieve a high rate of cure, particularly with regard to radiation dose.

The success of chemotherapy alone and the late effects of radiation therapy create interest in the use of chemotherapy alone in early-stage Hodgkin's lymphoma (see Table 111-11). Several trials have explored this in a controlled, randomized fashion. The National Cancer Institute of Canada–Eastern Cooperative Oncology Group (NCIC-ECOG) trial compared ABVD for four to six cycles (based upon response) to a strategy including radiation therapy in patients with limited-stage Hodgkin's lymphoma.[46] The trial design was complex, in that very favorable stage I patients and patients with bulky mediastinal disease were first excluded. Eligible patients were then stratified based on clinical features to lesser risk and greater risk. The lesser risk patients received either ABVD alone or the now obsolete, inferior wide-field irradiation (subtotal lymphoid irradiation), whereas the patients at greater risk received either ABVD alone or two cycles of ABVD followed by wide-field irradiation. The data are not sufficiently mature to address the primary study endpoint of survival at 10 years. However, FFP data at 5 years show a significant advantage for combined-modality treatment over ABVD alone. This difference, as expected, is due to the superiority of combined-modality treatment in the greater risk patients. However, there is no difference in overall survival, and much longer follow-up is required for the primary study endpoint. The interpretation of these data has often been based on the biases of the authors. Because of the relatively small absolute differences in FFP, proponents of chemotherapy maintain that the study

Table 111-10 Combination Chemotherapy Regimens for Hodgkin's Lymphoma

Combination/Drug	Dose (mg/m^2)	Route	Days	Cycle Length
ABVD				28 days
Doxorubicin	25	IV	1, 15	
Bleomycin	10	IV	1, 15	
Vinblastine	6	IV	1, 15	
Dacarbazine	375	IV	1, 15	
MOPP				28 days
Mustard	6	IV	1, 8	
Vincristine	1.4	IV	1, 8	
Procarbazine	100	PO	1–14	
Prednisone	40	PO	1–14	
BEACOPP (baseline)				21 days
Bleomycin	10	IV	8	
Etoposide	100	IV	1–3	
Doxorubicin	25	IV	1	
Cyclophosphamide	650	IV	1	
Vincristine	1.4*	IV	8	
Procarbazine	100	PO	1–7	
Prednisone	40	PO	1–7	
BEACOPP (escalated)				21 days
Bleomycin	10	IV	8	
Etoposide	200	IV	1–3	
Doxorubicin	35	IV	1	
Cyclophosphamide	1250	IV	1	
Vincristine	1.4*	IV	8	
Procarbazine	100	PO	1–7	
Prednisone	40	PO	1–7	
G-CSF	**	SQ	9–13	
Stanford V				
Mustard	6	IV	Weeks 1, 5, 9	
Doxorubicin	25	IV	Weeks, 1, 3, 5, 7, 9, 11	
Vinblastine	6	IV	Weeks 1, 3, 5, 7, 9, 11	
Etoposide	60 × 2	IV	Weeks 3, 7, 11	
Vincristine	1.4*	IV	Weeks 2, 4, 6, 8, 10	
Bleomycin	5	IV	Weeks 2, 4, 6, 8, 10	
Prednisone	40	PO	Every other day, taper weeks 10–12	
BEACOPP-14				14 days
Bleomycin	10	IV	8	
Etoposide	100	IV	1–3	
Doxorubicin	25	IV	1	
Cyclophosphamide	650	IV	1	
Vincristine	1.4*	IV	8	
Procarbazine	100	PO	1–7	
Prednisone	40	PO	1–7	
G-CSF	**	SQ	9–13	

**Dose based on body weight; G-CSF, granulocyte colony-stimulating factor; IV, intravenous; PO, orally; SQ, subcutaneous.
*Dose capped at 2 mg.

Table 111-11 Randomized Clinical Trials in Limited-Stage Hodgkin's Lymphoma

Study (*N*)	Risk Group	Treatment	FFP (%)	OS (%)	Follow-up (yr) Ref
Milan (140)	Favorable/Unfavorable				12
		4 ABVD + IFRT	94	96	
		4 ABVD + STLI	93	94	
			P = NS	*P* = NS	
EORTC/GELA H9F (783)	Favorable				4
		6 EBVP + 20-IFRT	88	98	
		6 EBVP + 30-IFRT	85	100	
		6 EBVP	69	98	
			P < 0.001	*P* = 0.241	
EORTC/GELA H9U (808)	Unfavorable				4
		6 ABVD + 30-IFRT	91	95	
		4 ABVD + 30-IFRT	87	94	
		4 BEACOPP + 30-IFRT	90	93	
			P = NS	*P* = NS	
NCIC-ECOG (399)	Favorable/Unfavorable				5
		4–6 ABVD	93	96	
		RT-containing	87	94	
			P = 0.006	*P* = NS	
GHSG HD10 (1370)	Favorable				4
		2 ABVD + 30-IFRT	No difference to date*		
		2 ABVD + 20-IFRT			
		4 ABVD + 30-IFRT			
		4 ABVD + 30-IFRT			
GHSG HD11 (1422)	Unfavorable				2.5
		4 ABVD + 30-IFRT	No difference to date*		
		4 ABVD + 20-IFRT			
		4 BEACOPP + 30-IFRT			
		4 BEACOPP+ 20-IFRT			

ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; EBVP, epirubicin, bleomycin, vinblastine, prednisone; FFP, freedom from progression; IFRT, involved-field radiation therapy; STLI, subtotal lymphoid irradiation.

*Interim analysis.

demonstrates that chemotherapy alone is the preferred treatment, whereas proponents of radiation therapy point to the superior outcomes achieved with combined-modality treatment.[47,48] Controversies of this type demonstrate the complexity of Hodgkin's lymphoma treatment and the careful balance between cure and complications for individual patients. Hodgkin's lymphoma patients should be carefully counseled by those with sufficient expertise to fully discuss therapeutic recommendations related to the sites and bulk of disease together with the age, gender, and other risk factors for the individual. Meanwhile, guidelines for management of early-stage Hodgkin's lymphoma recommend both combined-modality therapy but allow that chemotherapy alone is an acceptable strategy based on patient characteristics.[49]

Regarding the optimal chemotherapy in early-stage Hodgkin's lymphoma, Table 111-11 details results of the H9F trial from the EORTC using the EBVP (epirubicin, bleomycin, vinblastine, prednisone) regimen. Clearly inferior outcomes were seen with EBVP alone, even among such highly favorable patients.[44] This experience and that described previously in the GHSG HD13 study indicate that it is dangerous to tinker with the standard ABVD regimen, and this should be discouraged in clinical practice.

Advanced-Stage Disease

As noted previously, following the ground-breaking demonstration of cure in advanced Hodgkin's lymphoma with MOPP chemotherapy, a series of clinical trials was set in motion to identify the best chemotherapy regimen in advanced disease and to evaluate the role of radiation therapy in this setting. Based on historical development and the efficacy of ABVD in the relapsed setting, early trials pitted MOPP against ABVD and the alternating MOPP/ABVD regimen. The early CALGB study determined that ABVD-containing combinations were superior.[50,51] A second U.S. Intergroup trial comparing ABVD to the hybrid MOPP/ABV combination developed in Vancouver, concluded that the treatments were similarly efficacious but ABVD was less toxic.[52] On the basis of these trials, ABVD was widely adopted as the standard chemotherapy for advanced Hodgkin's lymphoma with an expected cure rate of about 70%.

Studies of multidrug regimens versus ABVD in the United Kingdom resulted in similar outcome and continued embracement of ABVD as the simpler, less toxic option. Stanford V is a brief, 12-week chemotherapy regimen with minimal alkylating agent and lower cumulative doses of doxorubicin and bleomycin that was

devised to explicitly address late effects of Hodgkin's lymphoma treatment. Radiation therapy is an important aspect of the treatment, delivered at 36 Gy to sites of disease larger than 5 cm or macroscopic splenic disease. Outstanding results were reported in a large phase II experience at Stanford University and within the ECOG.[53,54] The Italian GISL group performed a three-arm comparison of a multidrug regimen, ABVD and the Stanford V regimen.[55] The results in their study were inferior for the Stanford V regimen, possibly as a result of delayed and nonuniform use of radiation therapy as well as uneven determination of early treatment response in the study arms. ECOG has recently completed a phase III comparison of ABVD and Stanford V, the results of which are awaited.

The GHSG developed a novel chemotherapy combination, BEACOPP (Tables 111-10 and 111-12), which combines elements of COPP and ABVD with etoposide. The regimen was designed and tested in standard and escalated forms based on mathematical calculations that a tolerable increase in dose intensity could improve the cure rate by approximately 15%. The HD9 study compared COPP/ABVD with standard and escalated BEACOPP. Published results showed a significantly superior failure-free survival and overall survival for escalated BEACOPP as compared with COPP/ABVD, albeit with the not unanticipated increases in acute toxicity.[56] Radiation therapy was given to two thirds of patients who had initially bulky or residual disease. As discussed in the following sections, a concern with the escalated BEACOPP regimen was a number of secondary leukemias among treated patients. Importantly, only patients younger than 65 years were included in this trial. Older patients were treated on a separate trial. Although the numbers are small, the experience was sufficient to conclude that BEACOPP should not be given to older patients, who had a 21% mortality rate.[34] The HD9 results have been updated at 10 years (see Table 111-12), and they continue to show superiority of the escalated BEACOPP regimen as compared with COPP/ABVD.[44] Notably, superior FFS results are seen in all IPS categories. Overall survival is superior in the largest subgroup of intermediate IPS risk (2 and 3; Table 111-13). A required element of escalated BEACOPP is the use of granulocyte colony-stimulating

Table 111-12 Randomized Clinical Trials in Advanced-Stage Hodgkin's Lymphoma

Study (*N*)	Risk Group	Treatment	FFS (%)	OS (%)	Follow-up (yr) Ref
CALGB (361)	All IPS				5
		6–8 ABVD	61	73	
		6–8 MOPP	50	66	
		12 MOPP/ABVD	65	75	
			$P = 0.03$	P = NS	
CALGB (863)	All IPS				5
		ABVD	63	82	
		MOPP/ABV	66	81	
			P = NS	P = NS	
GHSG HD9 (1201)	All IPS				5
		8 COPP/ABVD + RT	69	83	
		8 BEACOPP + RT	76	88	
		8 $BEACOPP_{esc}$ + RT	87	91	
			$P < 0.002$	$P < 0.002$	
United Kingdom (807)	All IPS				3
		6 ABVD + RT	75	90	
		MDR	75	88	
			P = NS	P = NS	
GISL (355)	All IPS				5
		6 ABVD + IFRT	85	90	
		MOPPEBVCAD + IFRT	94	89	
		Stanford V + IFRT	73	82	
EORTC 20012	IPS 4–7		$P < 0.05$	P = NS	In progress
		8 ABVD			
		4 $BEACOPP_{esc}$ + 4 BEACOPP			
GHSG HD12	All IPS				4*
		8 $BEACOPP_{esc}$	86	88	
		4 $BEACOPP_{esc}$ + 4 BEACOPP	91	91	
		BEACOPP + 30 Gy	91	95	
		BEACOPP + no RT	88	95	

COPP/ABVD, cyclophosphamide, vincristine, procarbazine, prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; FFS, failure-free survival; IFRT, involved-field radiation therapy; MDR, multidrug regimens; OS, overall survival.

*Interim analysis.

Table 111-13 The HD9 Study German Hodgkin's Lymphoma Study Group at 10 Years

	COPP/ABVD		$BEACOPP_{STANDARD}$		$BEACOPP_{ESCALATED}$	
Risk Group	**%FFS**	**%OS**	**%FFS%**	**%OS**	**%FFS**	**%OS**
All Patients	64*	75*	70	80	82*	86*
Low IPS: 0,1 (26%)	78*	88	79	85	91*	94
Intermediate IPS: 2,3 (39%)	59*	73*	71	84	83*	87*
High IPS: 4–7 (14%)	54*	61	56	63	71*	70

FFS, failure-free survival; IPS, international prognostic score; OS, overall survival.
*$P < 0.05$ for comparisons between COPP/ABVD and $BEACOPP_{escalated}$.

factors to maintain dose intensity. In the HD9 study the dose intensity of BEACOPP was excellent compared with an estimated dose intensity of only about 0.67 in the COPP/ABVD patients.

The acute and later toxicities of escalated BEACOPP have led to more cautious adoption than might be expected based on the efficacy data and to alterations by clinical trial groups. The GHSG has tested a schedule of four escalated plus four standard BEACOPP cycles in advanced disease with or without radiation therapy to bulky or residual disease sites. At 4 years, the reported data from this study show no difference among the chemotherapy arms and no difference whether or not radiation therapy was delivered. Further toxicity was less with the four + four regimen. Yet another version of BEACOPP administered at 14-day intervals with growth factors has been developed and studied by the GHSG with encouraging results.[57] Together, these data beg a comparison of BEACOPP with ABVD, and indeed, this is the subject of controlled randomized trials. The EORTC is comparing four standard + four escalated BEACOPP versus ABVD in patients with a high IPS. The GISL study compares ABVD with escalated BEACOPP in all IPS groups.

Together the results of treatment in advanced Hodgkin's lymphoma are highly encouraging but can also be seen as confusing. At face value the cure rates are higher with escalated BEACOPP but at the price of increased toxicity (increased risk of leukemia, sterility, increased acute toxicity) and a survival benefit that is less apparent across IPS risk groups (see Table 111-13). Historically, the dose intensity of delivered ABVD has been variable, but recent data show that full doses can be delivered on time with or without growth factors. As discussed in the following sections, ABVD is not without late effects either. Until results of current trials are mature and fully evaluated, a reasonable strategy is to base treatment recommendations on an analysis of risk for treatment failure and for therapeutic complications for an individual, combined with patient preference. Strong consideration should be given to institutional and cooperative group trials for advanced-disease patients where the incorporation of early FDG-PET results are being used to response-adapt therapy. These strategies hold the promise to limit toxicities to those situations where intensive treatment is required. Further, one should keep in mind that toxicity of treatment, as discussed in the following sections, is an equation that accounts for quantitative as well as qualitative therapeutic differences.

Secondary Therapy of Classical Hodgkin's Lymphoma

Fortunately, many fewer patients with Hodgkin's lymphoma currently progress after primary treatment. Those with advanced disease and a high IPS are at greatest risk. High-dose chemotherapy with either the CBV (cyclophosphamide, carmustine, etoposide) or BEAM (carmustine, etoposide, cytarabine, melphalan) regimen followed by autologous stem cell transplantation has been the most successful approach for patients younger than 60 years based on phase II studies, registry results, and two randomized phase III trials. Of interest, although cure rates are significantly higher with autotransplantation, no survival benefit has emerged to date.[58] With this approach, about half of transplanted patients will be cured of their disease. Prognostic factors for unfavorable outcome with high-dose therapy and autologous transplantation include primary treatment failure, progression within 1 year of primary therapy, extensive disease at relapse, systemic symptoms at relapse, and significant residual disease before transplant.[59] The approach is to treat progressive and relapsing patients with secondary chemotherapy, most commonly the ICE (ifosfamide, cytarabine, etoposide) or DHAP (cisplatin, cytarabine, dexamethasone) regimen, to achieve maximal cytoreduction before transplantation. The achievement of PET-negative disease before transplant is a favorable prognostic factor.[60] Recently a new regimen, IGEV (ifosfamide, gemcitabine, etoposide, vinorelbine), has demonstrated excellent tolerability and efficacy in the second-line setting where the goals of treatment are reduction of Hodgkin's lymphoma, preservation of sufficient hematopoietic cells to support transplantation, and absence of severe toxicity that might interfere with the therapeutic plan.[61] Although prognostic factors are useful, there is an opportunity to eradicate Hodgkin's lymphoma with high-dose chemotherapy and autologous transplant even in poor-risk patients such that treatment should be pursued whenever feasible.

Patients progressing after brief chemotherapy and irradiation or chemotherapy alone may provide an exception to the routine use of intensive therapy, dependent on the disease sites and nature of the relapse. A recent publication evaluating the efficacy of second-line treatment after relapse in the NCIC/ECOG HD6 study demonstrated that patients could be successfully salvaged with a variety of therapeutic approaches.[62]

The circumstances for patients failing both primary treatment and autologous transplantation are grim. Historically, some of these patients had sustained remissions after allogeneic transplantation, but transplant-related mortality was considered to be unacceptable. With the advent of nonmyeloablative and reduced-intensity conditioning allogeneic transplants, there has been a resurgence of interest in this approach. Thus far this remains an investigational procedure. Whereas some data support a graft-versus-Hodgkin's effect, others are more questionable.[63,64] Clearly the transplant-related mortality is less with this approach, but relapse rates are high. The intensity of the conditioning regimen and tumor burden at the time of transplant may be important for the success of this approach. Clearly more clinical investigation is needed to fully assess the potential of this approach.

Therapy of Nodular Lymphocyte–Predominant Hodgkin's Lymphoma

The large majority (~80%) of patients with NLPHL have limited-stage disease at presentation. A pivotal study of the disorder was undertaken by the European Task Force, which found high rates of survival at 10 years but a unique pattern of relapse at 5 or more years after varied treatment.[24] In a recent review, mortality data from several sources indicate that deaths in NLPHL are most likely to be

related to treatment or other causes rather than the underlying disease.[65] Studies from the EORTC and the GHSG have used radiotherapy or combined-modality treatment.[66,67] Of interest, data from the GHSG corroborate the excellent outcomes of NLPHL patients participating in clinical trials and suggest that treatment outcomes may be more durable than reported earlier. Based on the GHSG analysis, treatment for the small number of patients with advanced-stage NLPHL should be systemic therapy as appropriate for classical Hodgkin's lymphoma. However, as noted previously, it is important to distinguish advanced-stage NLPHL from T-cell–rich B-cell lymphoma, a more aggressive disease.

Based on the expression of CD20 in NLPHL and the availability of the anti-CD20 antibody rituximab, the GHSG and the Stanford-Washington University Groups have evaluated this antibody in NLPHL.[68,69] High rates of response were seen in both groups though of variable durability. Use of rituximab in previously treated patients may afford a reprieve from cytotoxic therapy and is certainly deserving of further investigation. However, there are several caveats in the therapy of recurrent NLPHL. First, as noted previously, patients must have biopsies at recurrence because of the occurrence of progressive transformation of germinal centers and reactive hyperplasia, both benign conditions. Also, based on the risk of large B-cell lymphoma, which is often not clearly evident from clinical features, a biopsy is further indicated. NLPHL is an indolent disorder, and some patients with localized disease may be observed without treatment. This approach has been reported for stage I disease in children, where about half of them are free from disease progression at 4 years.[70]

SPECIAL CIRCUMSTANCES

Hodgkin's Lymphoma and Pregnancy

Because of the young age of Hodgkin's lymphoma patients, it is not surprising that the diagnosis is sometimes made during pregnancy. It is usually possible to allow the pregnancy to go to term, but clinical judgment is required in these cases as well as attention to the welfare of the patient and fetus and patient choice. The goal of staging in pregnant patients is to survey for sites of threatening disease that influence the management approach rather than careful, exhaustive cataloging of Hodgkin's lymphoma involvement. A careful history and physical examination, single posteroanterior chest radiograph with shielding, abdominal and pelvic ultrasound, and laboratory evaluation are generally sufficient for staging. Magnetic resonance imaging (MRI) can be considered, but CT should be avoided. Although no large series are available, we and others have anecdotal and published data indicating that an individualized approach is appropriate. For patients with low tumor burden or advanced in pregnancy, many can be observed and carry the pregnancy to term. If patients are very ill or significant disease develops, a limited amount of treatment may achieve desired disease regression until delivery. Single-agent vinblastine, which is neither teratogenic nor carcinogenic, has been effectively used in this setting. Combination chemotherapy has also been safely used in the second and third trimesters, as has radiation therapy with appropriate shielding. Close monitoring and reassessment by an experienced clinician is important for optimal management of the pregnant Hodgkin's lymphoma patient.

Hodgkin's Lymphoma and the Human Immunodeficiency Virus

Hodgkin's lymphoma in patients infected with HIV presents more commonly with symptomatic, advanced-stage, mixed-cellularity histology and EBV^+ disease. The incidence of Hodgkin's lymphoma has actually increased during the era of highly effective anti-retroviral therapy (HAART), whereas the incidence of non-Hodgkin's lymphoma has decreased.[21] The reasons for this are uncertain but lead to further speculation that the role of CD40-CD40L interactions, which would increase with increasing CD4 counts, are integral to the antiapoptotic characteristics of H-RS cells.[71] Treatment has become safer and more effective with the introductive of HAART.[72,73] Xicoy and colleagues reported a 71% event-free survival at 5 years among 62 Spanish Hodgkin's lymphoma patients treated with ABVD and HAART.[74]

Hodgkin's Lymphoma and the Elderly

As noted previously, Hodgkin's lymphoma patients over the age of 60 to 65 years have a relatively poor prognosis.[35] In the GHSG series, FFS was less than 50% for patients treated either with BEACOPP or COPP/ABVD. The reason for the less favorable outcome seems to be a combination of both less tolerance for effective treatment and a biologically less favorable disease.[34] Landgren and colleagues reported that ABVD treatment with a relative dose intensity above 0.65 resulted in superior outcomes.[75] Recently Kolstad and coworkers reported excellent outcomes, 76% progression-free survival at 3 years among 29 patients ages 60 to 91 years with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy.[76]

COMPLICATIONS

For many years the mainstay of treatment for Hodgkin's lymphoma was radiation therapy, given at doses of 40 Gy or greater to large areas of the body as a single modality. As treatment evolved, chemotherapy was added to irradiation and, in recent years, radiation has been administered in much smaller volumes and in smaller doses or not at all. Part of the evolution of treatment can be attributed to more effective chemotherapy, but the appreciation of late effects of radiation therapy, often with a latency of 10 or more years served as a driving force. In caring for patients treated for Hodgkin's lymphoma, it is important to take into account their risks based upon the era of treatment and, more specifically, on the radiation dose and volume, years elapsed from treatment, age at treatment, and age attained. Table 111-14 outlines the major late complications of Hodgkin's lymphoma treatment together with the offending agents and important modifying factors. Patients with Hodgkin's lymphoma have an increased risk of death that persists for more than 25 years, mainly from cardiovascular disease and second cancers directly linked to radiation therapy exposure.[77] It is important to recognize this ongoing risk for patients treated before about 1990 so that they can be monitored appropriately. Although there is reason for optimism that current treatment with smaller volumes and lesser doses will be associated with a lower risk of these complications, it is too early to fully assess.

Hypothyroidism is a common complication of neck irradiation that occurs in about 50% of patients. Monitoring of thyroid function tests annually and appropriate hormone replacement therapy is indicated. Patients who have been splenectomized or received splenic irradiation should receive pneumococcal vaccination at 5-year intervals and be counseled to seek prompt medical attention for febrile illness. Young patients who wish to retain their fertility must be identified and counseled before the onset of treatment.[78] ABVD does not seem to cause more than temporary cessation of menses in women and temporary oligospermia in men. In contrast, BEACOPP chemotherapy routinely sterilizes males and many young females.[79,80] Semen preservation must take place before chemotherapy. Embryo preservation, which is successful but costly, and/or the use of gonatrophin-stimulating hormone therapy, which has been reported to be effective by some but not others, are options for women at risk (generally over age 25). Preservation of ova remains experimental. Radiation therapy administered before 1975 often led to serious effects on the pericardium, potentially resulting in chronic pericarditis, and myocardial disease. These complications have not been associated with radiation therapy given thereafter, with heart blocks and other technical

Table 111-14 Late Complications of Hodgkin's Lymphoma Therapy

Complication	Therapeutic Risk Factor	Modifying Factor
Hypothyroidism	Neck irradiation	
Sepsis	Splenectomy, splenic irradiation	
Premature menopause	Cumulative-dose alkylating agents	Age at treatment
	Ovarian irradiation	
Female infertility	Cumulative-dose alkylating agents	Age at treatment
	Ovarian irradiation	
Male infertility	Cumulative-dose alkylating agents	
Carotid stenosis	High neck irradiation	RT dose
Coronary artery disease	Chest irradiation	RT dose, field, CAD risk factors
Other heart disease*	Chest irradiation	RT dose, field, technique, anthracycline
Cardiomyopathy	Cumulative-dose anthracycline	Chest irradiation
Secondary leukemia	Cumulative doses of alkylating agents, etoposide	Age, RT
Secondary breast cancer	Axillary, chest irradiation	Age at treatment, hormonal exposure, RT field and dose
Secondary lung cancer	Alkylating agents, chest irradiation	Smoking, age at treatment
Pulmonary toxicity	Cumulative-dose bleomycin	Chest irradiation, ? genetic predisposition
Osteoporosis	Prednisone, alkyating agents	Other risk factors, hormonal milieu
Osteonecrosis	Prednisone, irradiation	RT field

CAD, coronary artery disease; RT, radiation therapy.
*Valvular heart disease, pericardial disease, electrophysiologic disorders.

changes. However, coronary artery disease, valvular disease, and electrophysiologic changes have all been associated with radiation therapy administered at doses of 30 Gy or higher.

In a recent study involving more than 7000 patients followed after Hodgkin's lymphoma treatment, the standard mortality risk for death from myocardial infarction after mediastinal irradiation was 8.9, and the risk remained elevated for more than 25 years.[81] An expert panel concluded that there was insufficient information to recommend screening guidelines for patients exposed to chest irradiation, even though a Stanford study found significant pathology in asymptomatic patients.[82] However, it is prudent to counsel patients about their risks, evaluate and treat other risk factors for cardiovascular disease, and have a low threshold for formal evaluation of cardiac function. Although excess cardiotoxicity has not been described in clinical reports of ABVD, the large United Kingdom study demonstrated a standardized mortality risk of 2.9 for anthracyclines.[81,83] It is known that anthracycline cardiotoxicity can remain silent for long periods of time.[83]

Second cancers are the most feared complication of Hodgkin's lymphoma therapy. Early reports implicated the alkylating agents in MOPP chemotherapy in an increased risk of secondary acute myelocytic leukemia (AML) and myelodysplasia, and this observation served as the basis to recommend radiation therapy only for many years. ABVD chemotherapy does not seem to increase the risk of secondary AML above baseline. The original publication of the HD9 study demonstrating the superiority of BEACOPP chemotherapy was accompanied by an increased risk of secondary AML with this regimen.[56] In this case, etoposide was also implicated. Older patients are at increased risk, which is associated with cumulative exposure. Young women who receive axillary and chest irradiation are at increased risk of secondary breast cancer. Women younger than 30 years at treatment who continue to have menses after treatment are at greatest risk.[84] Studies have suggested that as little as 4 Gy puts individuals at increased risk.[84] The risk of secondary breast cancer has a latency period of 5 to 10 years with risks that persist for at least 25 years. Travis and colleagues have tabulated risks and ascertained that a woman treated at age 25 with 40 Gy chest irradiation has a 29% risk of secondary breast cancer by age 55.[85] This risk projection as stated, however, does not necessarily apply to more recent treatment approaches. Recommendations for mammography have been made for patients at risk for secondary breast cancer, starting 5 to 8 years after the completion of chest irradiation. Recently, MRI has proven to be superior in diagnosing young women at high genetic risk for breast cancer, because premenopausal women have dense breast tissue that reduces the precision of mammography.[86,87] Current recommendations for MRI include women at high risk because of prior chest irradiation.

Lung cancer is emerging as a leading cause of death in Hodgkin's lymphoma patients. Relative risks increase with cumulative dose of alkylating agents and with increasing doses of radiation. The risk after chemotherapy is immediate, whereas there is a latency of about 5 years after radiation therapy. Importantly, the relative risk increases 20-fold with tobacco use, indicating that smoking cessation is absolutely imperative among Hodgkin's lymphoma survivors.[88] The relative risk for secondary lung cancer is greatest among patients treated after age 45, and the absolute excess risk persists for as long as 20 to 25 years.[89] Pulmonary toxicity related to bleomycin has been recognized to be both idiosyncratic and related to cumulative exposure. A recent analysis in 141 patients treated with bleomycin for Hodgkin's lymphoma found an 18% incidence of pulmonary toxicity as defined by the study with an increased incidence in patients on the ABVD regimen, those aged older than 40 years, and those concomitantly receiving growth factors.[90] The authors reported that pulmonary toxicity was associated with inferior survival but also found that bleomycin could be omitted upon signs or symptoms of toxicity without a decrease in remission rate. Bone toxicity in the form of osteoporosis may accompany prednisone use, particularly in the setting of gonadal failure, and bone density should be assessed in individuals at risk. Osteonecrosis is an uncommon complication that occurs in the hips or shoulders in individuals exposed to high cumulative doses of prednisone, particularly with the addition of high-dose radiation therapy.

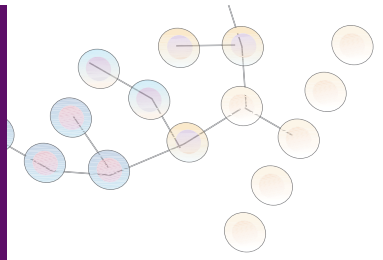
FUTURE DIRECTIONS

Continued success in the treatment of Hodgkin's lymphoma has been attained through international efforts in controlled clinical trials. Advances in diagnostic radiology with the advent of FDG-PET affords an immediate opportunity to assess this powerful technology as an marker of treatment success and the efficacy of response-adapted strategies that may both improve outcomes and reduce complications. Meanwhile, breakthroughs in understanding the nature of the H-RS cells and the interplay with the microenvironment identify potential new targets for therapeutics. Additional biomarkers from the tumor and the host may allow more appropriate, risk-adapted treatment. Insights into the etiology of Hodgkin's lymphoma and predisposition to late effects are likely to impact future management. In addition to the use of rituximab as a targeted therapy for NLPHL, early leads with immunomodulatory agents, angiogenesis inhibitors, histone deacetylase inhibitors, and other agents are promising in classical Hodgkin's lymphoma therapy. Antiapoptotic agents are coming into clinical use, and inhibitors of NF-κB are on the horizon. These new approaches hold out the promise to maintain and improve the current cure rates with fewer late complications.

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112 Non-Hodgkin's Lymphoma

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SUMMARY OF KEY POINTS

Incidence

- The incidence of non-Hodgkin's lymphoma has steadily increased in the United States since 1976, with 19 per 100,000 people in 2000. Diffuse large B-cell (DLBCL) and follicular lymphoma (FL) are the most common subtypes, each comprising approximately one third of cases in the West.
- Worldwide, there is considerable variability in the incidence of lymphoma subtypes with increased T-cell lymphoma in non-Western countries.

Etiology and Biology

- Etiology of most lymphomas is unknown. Infectious causes are increasingly recognized and include *Helicobacter pylori* in gastric mucosa–associated lymphoid tissue (MALT) lymphoma, Epstein-Barr virus in post-transplant and human immunodeficiency virus in aggressive B-cell and primary central nervous system (CNS) lymphoma, human T-cell leukemia/lymphoma virus-1 in adult T-cell lymphoma/leukemia, hepatitis C in splenic lymphoma, and human herpesvirus 8 in primary effusion lymphoma.
- In the West, some 85% of lymphomas are of B-cell origin, and 15% are of T/NK-cell origin.
- Specific genetic abnormalities associated with lymphomas include translocations of bcl-2 (t(14;18)) in FL and DLBCL; bcl-6 (t(3;16) in DLBCL; bcl-10 (t(11;18) in MALT lymphoma; c-myc (t(8;14), t(2;8), t(8;22)) in Burkitt's lymphoma; bcl-1 (t(11;14)) in mantle cell lymphoma (MCL); and ALK (t(2;5)) in anaplastic large T-cell lymphoma.

Differential Diagnosis

- Lymphoma can manifest as a solid mass and/or leukemia. Leukemic presentations more commonly occur in small lymphocytic, lymphoblastic, Burkitt's, splenic marginal zone, adult T-cell lymphoma/leukemia, and mantle cell lymphomas.
- Lymphomas are usually readily distinguished from other pathology. Benign inflammatory conditions that can be confused with lymphoma include reactive follicular hyperplasia, infectious mononucleosis, and cat scratch disease. Lymphomas that are occasionally confused with solid tumors include anaplastic large cell lymphoma (ALCL) and Hodgkin's lymphoma.
- The World Health Organization Classification of Lymphoid Malignancies should be used for diagnosis. When possible, excisional biopsy should be obtained for initial diagnosis and reviewed by an experienced hematopathologist. Fresh-frozen tissue should be available for further study.

Staging Evaluation

- Standard evaluation includes history and physical examination; complete blood count and chemistry studies including lactate dehydrogenase; computerized tomography of chest, retroperitoneum, and pelvis; and bone marrow biopsy. Positron emission tomography scans are being used with increasing frequency.
- Additional studies may include lumbar puncture in patients who are at risk for CNS involvement.

Primary Therapy

- Treatment is based on multiple factors, including histology, performance status, age, and stage, and is stratified according to clinical risk factors such as the International Prognostic Index.
- Treatment is frequently curative for DLBCL, ALCL, Burkitt's lymphoma, and lymphoblastic lymphoma. Cure is uncommon in most peripheral T-cell lymphomas.
- Follicular lymphoma, marginal zone lymphoma, and small lymphocytic lymphoma can have prolonged survival with intermittent treatment but cure is achieved in a minority of patients.
- MALT lymphomas have an indolent course. In gastric MALT, antibiotic therapy may cure up to 60% of patients.
- MCL varies from indolent to aggressive, and outcome appears to have improved with new treatments but is infrequently cured.

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) includes multiple neoplastic disorders of the lymphoid system with overlapping features. NHL is characterized by a monoclonal expansion of lymphoid cells, excluding those from primitive precursors that give rise to acute lymphoblastic leukemia and plasma cells that give rise to multiple myeloma. The malignant cell for most lymphomas can be traced to a specific stage in lymphoid maturation; lymphomas most commonly derive from mature B cells of germinal center origin. The cell of origin and stage of maturation arrest are important for understanding pathobiology and the identification of potential therapeutic targets.

The clinical presentation is variable and depends on a number of factors, including histology, patient age, and immune status. NHL typically presents with lymphadenopathy that can range from relatively asymptomatic to causing organ compromise such as ureteral obstruction or spinal cord compression. Patients may have constitutional manifestations due to inflammatory molecules and a variety of

other cytokines and chemokines that are produced by the lymphoma cells and/or host tissues. Without effective intervention, death is usually invariable. Current treatments have a powerful effect on the natural history of the disease, resulting in significant prolongation of survival or cure.

EPIDEMIOLOGY AND ETIOLOGY

Incidence

NHLs are the fifth and sixth most common malignancy in men and women, respectively, and are among the most rapidly increasing malignancies.[1] The increase in incidence appears to be worldwide, with incidences ranging from approximately 2 per 100,000 per year in Asia to 19 per 100,000 per year in the United States.[2] Data also suggest that the increase is greatest in the elderly and in diffuse large B-cell lymphoma (DLBCL). According to the Surveillance Epidemiology and End Results data, the incidence has been rising approximately 4% a year and represents a 150% increase between the 1940s and the 1980s. In absolute numbers, this represents approximately 56,000 new cases and 20,000 deaths of NHL in the United States each year (Fig. 112-1). The reasons for the increase in NHL are unclear but are likely due to multiple etiologic factors, including human immunodeficiency virus (HIV) infection.

Etiology

Immune suppression and stimulation are important cofactors for the development of NHL. Both primary and secondary immunodeficiency predispose to an increased incidence of Epstein-Barr virus (EBV) associated NHL (Table 112-1).[3–5] Less well understood but equally important is the role of chronic immune stimulation in diseases such as Sjögren's syndrome and rheumatoid arthritis.[6,7] In these diseases, however, it is difficult to separate the contribution of immune stimulation from secondary immune suppression associated with treatment of the underlying disease.[7] Perhaps less ambiguous is the role of chronic immune stimulation from *Helicobacter pylori* infection in gastric mucosa–associated lymphoid tissue (MALT) lymphoma.[8,9] Additional data also suggest an association between Borrelia infection and cutaneous MALT lymphoma and hepatitis C and splenic lymphoma.[10,11]

Viruses may function as cofactors in lymphomagenesis. They may exert their effect through integration into the genome, leading to alterations in gene expression, and/or may directly affect proliferation. The EBV, human T-cell leukemia/lymphoma virus-1 (HTLV-1), and human herpesvirus 8 (HHV-8) in particular have been implicated.[3,12–14] In the case of EBV, it appears to have a direct role in lymphomas of immunocompromised patients such as HIV and post-transplant lymphoproliferative diseases (PTLD). In contrast, its role in Burkitt's lymphoma (BL) appears indirect and variable, where it occurs in 30% of cases in the West (sporadic) and 95% of cases in Africa (endemic).[15] HTLV-1 appears to have a direct causative role in adult T-cell leukemia/lymphoma, and carriers have a 5% lifetime risk of developing disease. HHV-8, also known as Kaposi's sarcoma herpesvirus, has been associated with primary effusion lymphoma, a rare B-cell lymphoma that occurs primarily in highly immunosuppressed patients with AIDS.[16,17]

Multiple epidemiology studies have examined the role of occupational and environmental factors. Prevalent among these are studies that show a link between agricultural work and lymphoma, which

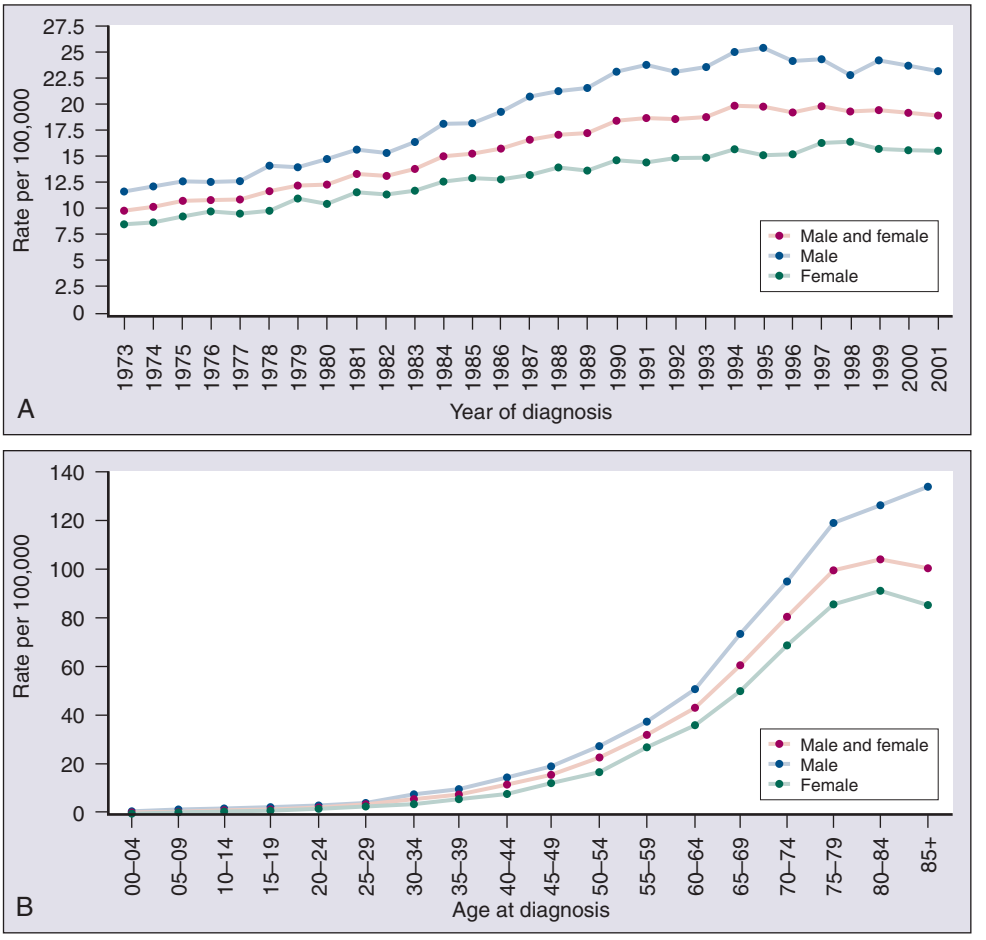


Figure 112-1 • Lymphoma rates from the Surveillance Epidemiology and End Results data from 1973 to 2001. **A,** Age-adjusted rate of non-Hodgkin's lymphoma in males, females, and combined. **B,** Rate of non-Hodgkin's lymphoma in males, females, and combined, according to age. (Data from http://www.seer.cancer.gov).

Table 112-1 Factors Associated with an Increased Incidence of Non-Hodgkin's Lymphoma

ALTERED IMMUNOLOGIC STATES
Acquired immunodeficiency syndrome
Organ transplantation
Sjögren's syndrome
Rheumatoid arthritis
Inherited immune deficiencies
VIRUSES AND BACTERIA
Human T-cell leukemia/lymphoma virus
Human immunodeficiency virus
Epstein-Barr virus
Human herpesvirus 8
Hepatitis C virus
H. pylori
Borellia
CHEMICAL EXPOSURE
Agriculture chemicals
Wood products
MISCELLANEOUS
Prior lymphomas

has been attributed to organochlorine-based pesticides.[18] Other studies also suggest that exposure to organic solvents and wood products could increase the risk of lymphoma.[19]

DIAGNOSIS

An adequate biopsy is essential for diagnosis, and when possible, an excisional biopsy should be performed. Attention should be paid to the biopsy site, the largest or most rapidly enlarging node being chosen because it is likely to reveal the most aggressive histology and provide the most tissue. Biopsy of mediastinal or abdominal masses requires appropriate caution. In such cases, a Trucut needle biopsy can be adequate and avoids open surgery. Fine-needle aspiration is rarely if ever adequate for initial diagnosis but may be used to confirm relapse. The storage of fresh-frozen tissue is highly encouraged for future diagnostic tests based on molecular profiling.

CLASSIFICATION

Lymphomas are a heterogeneous group of diseases which clinically vary from indolent to aggressive and from incurable to curable.[20] Histologic classification schemes have been developed to organize lymphomas into groups with shared pathogenesis and clinical behavior with an aim to guide treatment. Over the years, these classifications have evolved from exclusively morphologic classifications to the current ones that incorporate immunophenotype and genetic endpoints, such as the Revised European-American Classification of Lymphoid Neoplasms and the World Health Organization Classification of Neoplastic Diseases of Hematopoietic and Lymphoid Tissues (Table 112-2).[20–22] This evolution is the direct result of insights into the molecular pathogenesis of lymphoma, including the identification of hallmark genetic abnormalities.

The immune phenotype is fundamental for the accurate classification of lymphoma. Early studies showed that most lymphomas are of B-cell origin (Table 112-3).[23] Beginning in the 1970s, classifications first emerged that were based on the putative cell of origin and aggressiveness of malignancy. The Kiel classification, which gained popularity in Europe, incorporated information on the cell of origin, whereas the Working Formulation, which was adopted in North America, provided clinical groupings and pathologic divisions that were largely based on cell size (large versus small), cell shape (round versus not round), and growth pattern (follicular versus diffuse).[24,25]

Advances in molecular biology have further advanced the understanding of lymphomagenesis through identification of relevant genes that are important in cellular proliferation, differentiation, and death. A variety of complementary technologies are now available that can measure the expression of thousands of genes in parallel, termed *molecular profiling*, and can link biology to a genetic expression

Table 112-2 World Health Organization Classification of Lymphomas

B-CELL NEOPLASMS
Precursor B-cell
Precursor B lymphoblastic leukemia/lymphoma
Mature B-cell
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Lymphoplasmacytic lymphoma
Splenic marginal zone lymphoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone B-cell lymphoma
Follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary effusion lymphoma
Burkitt's lymphoma/leukemia
B-cell proliferations of uncertain malignant potential
Lymphomatoid granulomatosis
Post-transplant lymphoproliferative disorder, polymorphic
T-CELL AND NK-CELL NEOPLASMS
Precursor T-cell
Precursor T lymphoblastic leukemia/lymphoma
Blastic NK cell lymphoma
Mature T-cell and NK-cell
Adult T-cell leukemia/lymphoma
Extranodal NK/T cell lymphoma, nasal type
Enteropathy-type T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous anaplastic large cell lymphoma
Peripheral T-cell lymphoma, unspecified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma

Table 112-3 Typical Immunophenotype of the Major Subtypes of Non-Hodgkin's Lymphoma

	Follicular	Small Lymphocytic	MALT	Marginal Zone, Nodal	Mantle Cell	Diffuse Large B-Cell	Mediastinal Large B-Cell	Burkitt's	Lymphoblastic	Peripheral T-Cell	TIC Large T/Null Cell
Characteristic Immunophenotype	CD20+, CD3– CD10+, CD5–	CD20+, CD3– CD10–, CD5+ CD23+	CD20+, CD3– CD10–, CD5– CD23–	CD20+, CD3– CD10–, CD5– CD23–	CD20+, CD– CD10–, CD5+ CD24–, PRAD1+	CD20+, CD3–	CD20+, CD3–	CD20+, CD3– CD10–, CD5– Tdt–	CD20–, CD3+ Tdt+		CD20–, CD3+ CD30+, CD15– EMA+, ALK+

signature. The application of this technology to lymphoma is providing insights into unique molecular signatures of distinct types of B-cell malignancies.[26] It can relate lymphoid neoplasms to normal stages in B-cell development and physiology and has provided a new way to classify lymphomas and to predict clinical outcome.[26,27] Indeed, as the molecular analysis of tumors improves, the classification of human cancers is likely to become more refined and informative.

Molecular Genetics

At a molecular level, the genetic lesions that have been identified in lymphomas include oncogene activation or loss of tumor suppressor genes caused by chromosomal translocation, deletion, or mutation or by introduction of exogenous viral genomes into the human chromosome (Table 112-4). The molecular cloning of genetic loci that are involved in the translocations most frequently associated with lymphomas has led to the identification of a number of proto-oncogenes involved in lymphomagenesis. Distinguishing immunologic and genetic features, presumably reflecting disease biology, have been identified for many lymphoma subtypes and are incorporated into the World Health Organization classification. However, what is absent is an adequate understanding of the ripple effect of these genetic abnormalities on the cellular gene expression.

Owing to the recent development of molecular profiling, the studies have focused primarily on the more common B-cell lymphomas, which are generally categorized as indolent or aggressive. The genetic hallmark of follicular lymphoma (FL), the most common indolent lymphoma subtype, is the t(14;18)(q32;q21) translocation with rearrangement of the *bcl-2* gene, present in 80% to 90% of cases, and overexpression of the *bcl-2* gene product (see Table 112-4).[28,29] Inhibition of apoptosis by *bcl-2*, which occurs in normal germinal center cells, appears to play an important role in lymphomagenesis.[28,30] However, constitutive *bcl-2* expression is not necessarily required for survival, as it may be turned off in FL cells that have undergone aggressive transformation.[31] The role of *p53* mutation/deletion that is observed in some transformed FLs is also uncertain, although loss of *p53* function is associated with decreased apoptosis and clinical drug resistance.[32,33] The functional significance of genetic abnormalities in small lymphocytic lymphoma (SLL)/B-cell chronic lymphocytic leukemia (CLL) is more uncertain, although many of these abnormalities have important clinical effects. Clonal chromosomal abnormalities can be detected in nearly half of these patients, deletions of the long arm of chromosome 13 being the most common.[34] Trisomy 12 anomalies are also frequent, found in 10% to 30% of cases, followed by deletions in the long arm of chromosome 11, termed 11q-, in some 1% to 20% of cases; both anomalies are associated with more aggressive disease compared to patients who harbor the more common del 13q14.[35,36] Abnormalities in the *p53* gene, located on the short arm of chromosome 17, at 17p13, have also been associated with a poor clinical outcome in CLL and are found in half of patients with a Richter's transformation.[37,38] Of developmental and clinical relevance is the mutational status of the immunoglobulin variable heavy (V_H) region in CLL.[39] Normal developmental biology would suggest that CLL cells with or without V_H somatic mutations correspond to antigen-dependent and antigen-independent phases, respectively, and in the former case is associated with longer survival.[39]

Among aggressive lymphomas, DLBCL is the most common type, making up a third of all lymphomas.[40] This histologic category contains multiple disease entities as suggested by its variable clinical presentation, natural history, morphologic variants, and molecular characteristics.[20] The diverse morphologic variants of DLBCL, which include centroblastic, immunoblastic, T-cell/histiocyte-rich, and anaplastic types, have some known molecular correlates but alone cannot reliably be distinguished as distinct diseases.[20] Other DLBCL subtypes such as primary mediastinal B-cell lymphoma (PMBL) and intravascular large B-cell lymphoma have been identified as distinct subtypes of DLBCL on the basis of a combination of clinical, histo-

Table 112-4 Major Molecular Translocations in Non-Hodgkin's Lymphomas

NHL Histologic Type	Translocation	Percentage of Cases Affected	Proto-oncogene Involved	Mechanism of Proto-oncogene Activation	Proto-oncogene Function
Lymphoplasmatic lymphoma	t(9;14)(p13;q32)	50%	*pax-5*	Transcription deregulation	Transcription factor regulating B-cell proliferation and differentiation
Follicular lymphoma	t(14;18)(q32;q21) t(2;18)(p11;q21) t(18;22)(q21;q11)	90%	*bcl-2*	Transcription deregulation	Negative regulator of apoptosis
Mantle cell lymphoma	t(11;14)(q13;q32)	70%	*bcl-1/cyclin D1*	Transcription deregulation	Cell cycle regulator
MALT lymphoma	t(11;18)(q21;q21) t(1;14)(p22;q32)	50%	*api_2/mlt* *bcl-10*	Fusion protein Transcription deregulation	*api_2* has antiapoptotic activity Antiapoptosis (?)
Diffuse large B-cell lymphoma	der(3)(q27)	35%	*bcl-6*	Transcription deregulation	Transcriptional repressor required for GC formation
Burkitt's lymphoma	t(8;14)(q24;q32) t(2;8)(p11;q24) t(8;22)(q24;q11)	80% 15% 5%	*c-myc*	Transcription deregulation	Transcription factor regulating cell proliferation and growth
Anaplastic large T-cell lymphoma	t(2;5)(p23;q35)	60%	*npm/alk*	Fusion protein	*alk* is a tyrosine kinase

logic and molecular findings.[20] It is also important to recognize that large cell "transformation" of an indolent B-cell lymphoma/leukemia, a relatively common occurrence, involves pathways of lymphomagenesis that are distinct from those of de novo DLBCL. However, these entities may share histologic, immunophenotypic, and oncogenetic characteristics.[41]

Within DLBCL, a common molecular abnormality that is seen in over half of cases involves the deregulation of *bcl-6*, either through promoter substitution or by multiple, often biallelic mutation clustering in its 5′noncoding region; up to 35% of cases show abnormalities of the 3q27 region (see Table 112-4).[42] *Bcl-6* protein functions as a transcription factor that binds a specific DNA sequence and represses transcription from linked promoters. It is important in the normal functioning of the germinal center B cells and is required for germinal center cell formation during the antigen-driven immune response.[43] DLBCLs with high expression of *bcl-6* are usually of germinal center B-cell origin, and in part this might help to distinguish them from other DLBCL subtypes.[44] The functional significance of *bcl-6* overexpression and/or deregulation on clinical outcome is uncertain, although some studies have found an improved survival in such patients, possibly related to their association with cells of germinal center origin.[45] Another common, albeit variable, finding is the overexpression of *bcl-2*, which is reported to be present in 24% to 55% of cases from two studies.[46,47] Interestingly, only 14% to 17% of these cases were found to harbor a *bcl-2* gene rearrangement from the t(14;18) translocation, suggesting the presence of variable molecular mechanisms of *bcl-2* overexpression. Paradoxically, overexpression of the bcl-2 protein but not the *bcl-2* gene rearrangement is associated with decreased survival, suggesting that the antiapoptotic effect of the bcl-2 protein is not the important determinant of outcome.[46,47] Microarray profiling studies, however, have shed light on this apparent paradox, as will be discussed later in the chapter. Other variable molecular findings in DLBCL include mutation of the *p53* gene, found in approximately 20% of cases at initial diagnosis; this has also been associated with decreased survival and drug resistance, presumably through its antiapoptotic effects.[32,48] Specific immunophenotypic and genotypic features have also been associated with the PMBL subtype of DLBCL, such as overexpression of the MAL gene, a finding that supports a unique biologic heritage for this disease.[20,49,50]

Burkitt's lymphoma is an uncommon aggressive B-cell lymphoma characterized by a translocation between *c-myc* on chromosome 8 and one of the three immunoglobulin chain loci. These translocations occur with a respective frequency of 80%, 15%, and 5% on chromosomes 14, 22, and 2, respectively, which encode in turn for the immunoglobulin heavy chain and lambda and kappa light chains.[21] As would be expected, the t(8:22) is usually found in lambda-expressing cells, whereas the t(8:2) is found in kappa-expressing cells. Because these translocations bring the *c-myc* oncogene into close approximation with the immunoglobulin gene–inducible promoter, there is abnormal expression of c-myc and overexpression of the functionally intact protein.[15] This finding is consistent with immunohistochemical studies on tumor tissues, which commonly show a quantitative increase in c-myc expression. The quantitative overexpression of c-myc has been shown to result in deregulation of cellular growth and is capable of blocking phenotypic maturation. Hence, c-myc overexpression appears to be central to the pathogenesis of BL, and it is thought that the translocation occurs in pre-B-cell development during the normal rearrangement of the immunoglobulin loci.

Mantle cell lymphoma (MCL) was relatively recently recognized as a distinct B-cell lymphoma.[20] Almost all cases contain the t(11;14)(q13;q32) translocation between the immunoglobulin heavy chain and the *cyclin D1* (PRAD1, *bcl-1*) genes.[51] Deregulation of *bcl-1* leads to overexpression of its gene product cyclin-D1, which promotes progression from G_1 to S of the cell cycle.[52] Unlike DLBCL, most patients are incurable and have a relatively short median survival of 3 to 5 years.[53]

Principles of Evaluation

A thorough history and a physical examination are important for optimal management (Table 112-5). Patients should be questioned

Table 112-5 Evaluation of a New Patient with Non-Hodgkin's Lymphoma

Evaluation	Mandatory	As Indicated
Confirm diagnosis	Adequate biopsy reviewed by experienced hematopathologists	Immunophenotyping
		Cytogenesis
		Molecular studies
General overview	Careful history and physical examination	Blood coagulation studies
	Complete blood count (including platelet count)	Serum and viral protein studies
	Chemistry screen (including liver and renal function studies)	Serum electrolytes, uric acid
	Chest radiograph	
Prognostic categorization	Serum LDH	Erythrocyte sedimentation rate
	Serum albumin	Serum β_2-microglobulin
		Tumor growth fraction
		Microarray analysis
Anatomic disease	Whole-body CT scans	Ultrasonography
		Magnetic resonance imaging
		FDG-PET scans
		Bone scans
Occult sites of involvement	Bone marrow biopsy	Lumbar puncture with flow cytometry
		Biopsy of suspicious sites
		Blood flow cytometry
		Blood and bone marrow PCR

CT, computed tomography; FDG-PET, 18-fluoro-2-deoxyglucose positron emission tomography; PCR, polymerase chain reaction.

about systemic symptoms, and performance status should be assessed. It is useful to query whether there are potential causative factors, such as prior malignancy, chemotherapy, or radiation treatment and/or autoimmune or immunodeficiency disease. A history of infection with or exposure to various pathogens, including HIV, hepatitis C, and HTLV-1, should be excluded. A detailed physical examination should be performed with detailed attention to lymph nodes, liver, and spleen.

Laboratory tests should include a complete blood count and serum chemistry with lactate dehydrogenase (LDH) and HIV and hepatitis serology. Other viral tests, such as testing for HTLV-1, should be included as indicated. EBV viral loads can also be useful in specific lymphomas such as PTLD and nasal NK/T-cell lymphoma.[54,55] Elevated LDH and β_2-microglobulin levels have prognostic implications for certain lymphoma subtypes.

Imaging and Staging

It is important to assess sites of disease involvement and imaging studies should include chest radiography and computed tomography (CT) scanning of the chest, abdomen, and pelvis (see Table 112-5). The need for additional studies, such as magnetic resonance imaging (MRI) and 18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) scanning, will depend on the clinical presentation and sites of disease. For example, if there is a risk of central nervous system (CNS) involvement, a head MRI should be performed, and involvement of the bone is best evaluated by MRI and PET scans.

Though PET scanning is now widely used, it does not have an established role in the initial staging of NHL.[56] Nevertheless, PET provides sensitive functional imaging of lymphomas for initial assessment and follow-up. A retrospective evaluation of 172 patients with various histologies of lymphoma found that 98% to 100% of DLBCL, mantle cell, and follicular lymphomas were detectable by FDG-PET.[57] However, detection frequencies were below 70% for patients with marginal zone and peripheral T-cell lymphomas. FDG-PET scans during and/or after therapy have also been shown to have prognostic value. In one study of FDG-PET scans done 1 to 3 months after treatment in 93 patients, 26 were interpreted as positive for residual disease.[58] Whereas all 26 patients relapsed in a median of 73 days, only 11 patients with normal FDG-PET scans relapsed. Early restaging with FDG-PET was of prognostic value in this series.[58] Among 70 patients with aggressive NHL who underwent midtreatment FDG-PET, none of 33 patients with positive FDG-PET achieved durable remissions, whereas 31 of 37 patients with negative FDG-PET remained in complete remission.

Bone marrow involvement often affects management and should be assessed at initial staging. Patients who are at risk of CNS involvement should undergo lumbar puncture with evaluation of the cerebrospinal fluid by cytology and flow cytometry.[59] Specifically, histologic subtypes such as BL and extranodal disease in DLBCL are associated with an increased risk of CNS disease.[60]

The Ann Arbor staging system, which was originally designed for Hodgkin's lymphoma, is the standard for adult lymphomas (Table 112-6). However, because of the heterogeneity and hematogenous pattern of dissemination in NHL, in contrast to contiguous lymph node spread with Hodgkin's lymphoma, the staging system has more limited value. At the same time, important modifications to the Ann Arbor staging system that were made at the Cotswold Conference have made it more applicable to NHL.[61] The Cotswold's modification (see Table 112-6) provides a framework for assigning a clinical stage and incorporates a designation for the presence of "bulk" disease defined as a mass greater than 10 cm or a mediastinal mass greater than one third of the transthoracic width.[61] Extranodal sites are denoted in the anatomic classification by the suffix "E."

Table 112-6 Ann Arbor Staging Classification and the Cotswold Modifications

Stage	Features
I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm
III	Involvement of lymph regions or structures on both sides of the diaphragm
IV	Involvement of extranodal site(s) beyond that designated E
FOR ALL STAGES	
A	No symptoms
B	Fever (>38°C), drenching sweats, weight loss (10% body weight over 6 months)
FOR STAGES I TO III	
E	Involvement of a single extranodal site contiguous or proximal to known nodal site
COTSWOLD MODIFICATIONS	
(i)	Suffix X to designate bulky disease as more than one third widening of the mediastinum or >10-cm maximum dimension of nodal mass
(ii)	The number of anatomic regions involved should be indicated by a subscript (e.g., II3)
(iii)	Stage III may be subdivided into: III_1, with or without splenic, hilar, celiac, or portal nodes; III_2, with para-aortic, iliac, mesenteric nodes
(iv)	Staging should be identified as clinical stage or pathologic stage
(v)	A new category of response to therapy, unconfirmed/uncertain complete remission should be introduced because of the persistent radiologic abnormalities of uncertain significance

Prognosis

Clinical stage is a powerful and independent predictor of prognosis. To identify prognostic factors in aggressive lymphoma, an international project to correlate clinical variables and outcome in 2031 patients with untreated aggressive lymphoma was undertaken (Table 112-7).[62] The parameters that were independently associated with inferior outcome included age over 60 years, stage III or IV disease, serum LDH above the normal range, Eastern Cooperative Oncology Group performance status of 2 or higher, and involvement of two or more extranodal sites. A clinical prognostic model, termed the International Prognostic Index (IPI), was developed using these five factors (see Table 112-7). In this model, one point was allocated for each feature, and it stratified patients into four groups with 5-year survival rates of 73%, 51%, 43%, and 26% for zero to one, two, three, and four to five risk factors, respectively, with CHOP-based treatment.[62] The IPI has become the standard for assessing clinical prognosis and treatment stratification and for comparison between clinical trials. Although it has yet to be fully revalidated in the rituximab era, a revised prognostic model for R-CHOP, termed R_{evised}-IPI, was recently published based on a limited retrospective series (see Table 112-7).[63] A validated prognostic index based on the IPI was also developed for follicular lymphoma.[64] Age, stage, and serum LDH, in addition to hemoglobin level and number of nodal areas, reliably predicted survival and composed the Follicular Lymphoma International Prognostic Index (see Table 112-7).[64]

Though not yet routinely performed in aggressive NHL, gene expression profiling is emerging as an important prognostic tool.[27,65–67] In DLBCL, for example, morphologically indistinguishable tumors can show marked heterogeneity in gene expression, and

Table 112-7 Clinical Prognostic Indexes

INTERNATIONAL PROGNOSTIC INDEX FOR AGGRESSIVE LYMPHOMAS[62]

Risk Group	IPI Score*	CR Rate (%)	5-Year OS Rate (%)
Low	0, 1	87	73
Low intermediate	2	67	51
High intermediate	3	55	43
High	4, 5	44	26

REVISED INTERNATIONAL PROGNOSTIC INDEX (R-IPI)[63]

Risk Group	IPI Score*	4-Year OS Rate (%)
Very Good	0	94
Good	1–2	79
Poor	3–5	55

FOLLICULAR INTERNATIONAL PROGNOSTIC INDEX (FLIPI)[64]

Risk Group	IPI Score*	Distribution (%)	10-Year Survival Rate (%)
Low	0–1	36	71
Intermediate	2	37	51
Poor	≥3	27	36

CR, complete response; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; LDH, lactate dehydrogenase; OS, overall survival.

*One point is given for the presence of each of the following characteristics: age >60 years, elevated serum LDH level, ECOG performance status ≥2, Ann Arbor stage III or IV, and more than two extranodal sites.

these patterns of expression may be classified into signatures that correspond to the cellular origin of the lymphoma according to its stage of differentiation. On the basis of these signatures, DLBCL can be divided into at least three different subtypes: germinal center B-cell (GCB) like, activated B-cell (ABC) like and PMBL. Overall survival (OS) is different in each group and superior in patients with the GCB type compared to the ABC type (Fig. 112-2). Using gene expression profiling, a molecular prognostic model of survival, independent of the IPI, has been also been developed for CHOP-treated DLBCL.[27] However, this model, based on four signatures of germinal center B cells, proliferating cells, reactive stromal and immune cells in the lymph node, and major histocompatibility complex class II cells, has not been applied to rituximab-based treatment. An immunohistochemical model has also been developed to predict GCB and non-GCB subtypes of DLBCL.[68] Although this IHC model requires further validation, its application in two recent studies suggests that the addition of rituximab to chemotherapy ameliorates the adverse outcome of non-GCB DLBCL.[69,70]

Treatment Response and Follow-up

Treatment response should be documented by physical findings, and all abnormal tests should be repeated. Final treatment assessment is usually performed 3 to 6 weeks after completion of therapy unless progression occurs earlier. The frequency and extent of investigations during follow-up depend on the risk of recurrence and the potential for early detection to change further treatment.

A workshop that was held under the auspices of the National Cancer Institute in 1998 standardized response criteria for the first time.[71] By necessity, some standards were arbitrary, such as the definition of normal lymph node size. The spleen was considered to be a nodal site and should be assessed by CT. Focal lesions in the liver were considered measurable. Complete remission required the resolution of symptoms or clinical evidence of lymphoma and no lymph nodes over 1.5 cm on CT scan, and the bone marrow had to be morphologically free of lymphoma. An important contribution was the introduction of a new category termed complete remission (uncertain) which required at least a 75% reduction in tumor masses. A recent update recommended that patients with a complete remission (uncertain) be considered in complete remission if they have a negative FDG-PET scan.[58] Partial remission was defined as at least a 50% reduction in size of tumor masses.

Detection of Minimal Disease

The molecular monitoring of remission can be carried out by using various techniques. The presence of occult lymphoma cells in the blood or bone marrow may have prognostic significance or make a patient a poor candidate for stem cell harvest and autologous transplantation. One sensitive detection method is flow cytometry of the blood or bone marrow for light chain restriction or aberrant phenotype. Another technique involves polymerase chain reaction to detect cells with a specific genetic abnormality or clonal immunoglobulin or T-cell reception rearrangement. A popular test in follicular lymphoma was the detection of cells with *bcl-2* gene rearrangements. In some studies, the presence of t(14;18) in the blood or marrow predicted a poorer treatment outcome.[72,73] Circulating lymphocytes with t(14;18) rearrangements can occasionally be detected in the blood and tonsils of normal individuals.[74] At present, however, detection of minimal residual disease does not have an established clinical role.

PRINCIPLES OF TREATMENT

The fundamental genetic changes that lead to neoplasia involve deregulation of cellular proliferation and death, events that are controlled in large measure by cell cycle checkpoints and by the induction and suppression of apoptosis. Evidence also suggests that abnormalities in these pathways might determine the sensitivity of tumor cells to the cytotoxic effects of irradiation and chemotherapy.[75–77] Clinical strategies that take advantage of the abnormalities that occur in the regulation of the cell cycle and apoptosis are just beginning but have an increasingly important role in the design of therapeutic approaches. The classic principles of chemotherapy, including pharmacology, drug resistance, and tumor cell kinetics, continue to form the foundation of treatment strategies. Understanding these principles provides the basis for good treatment decisions.

Tumor Cell Kinetics

Some 30 years ago, Skipper and associates made several fundamental observations regarding the kinetic features of tumor cell growth and the effect of chemotherapy in an animal model system.[78] From this model, they hypothesized the importance of tumor volume, growth fraction, and the first-order kinetics of chemotherapy cell kill for therapeutic outcome. One of their basic findings was that survival was inversely proportional to the tumor cell inoculum, which follows the known relationship between tumor bulk and outcome in lymphoma. When the outcome of chemotherapy was assessed, the fraction of tumor cells undergoing DNA replication, termed the *growth fraction*, greatly influenced drug sensitivity, a finding that likely reflected the greater sensitivity of tumor cells in the DNA synthetic (S) phase of the cell cycle to many classes of chemotherapeutic agents. As a hypothesis of tumor cell sensitivity, however, the principle of growth fraction was a great oversimplification. Although these concepts have become classic principles of chemotherapy and con-

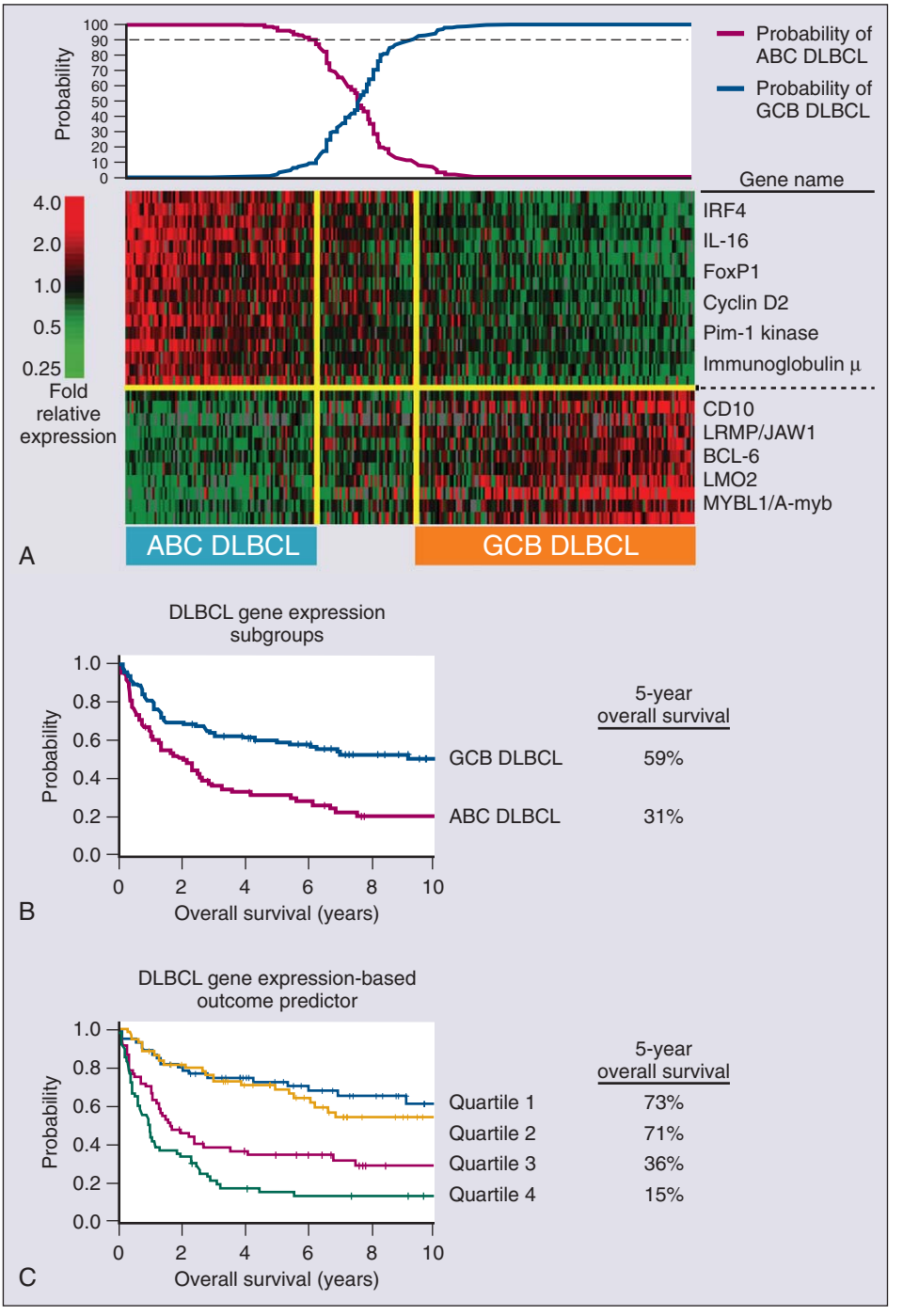


Figure 112-2 • Diagnosis of DLBCL subtypes by gene expression and development of a molecular outcome predictor in previously untreated patients with DLBCL following chemotherapy. **A,** The expression levels of 27 genes from the subgroup predictor in 274 DLBCL samples are shown according to the color scale (*left*). Six named genes that showed increased expression in either the ABC or GCB subgroups are shown at the *right*. The likelihood that a DLBCL sample belongs to the ABC or GCB subgroup is shown on *top*, arranged by probability. **B,** Kaplan-Meier estimates of overall survival according to GCB or ABC DLBCL subtype. **C,** Kaplan-Meier estimates of overall survival according to the molecular outcome predictor for each quartile.

tinue to guide treatment strategies, the clinician should realize that the Skipper model does not capture the heterogeneity of human tumors.

Clinically, tumors are heterogeneous. Tumor masses within the same patient vary, owing to diverse factors such as blood flow, tissue hypoxia, and mutations that determine tumor biology and drug resistance. Moreover, the growth fraction of tumor cells is dynamic, decreasing as tumors grow and increasing as tumor cells are killed by cytoreductive treatment. The growth fraction also does not affect the cytotoxicity of all chemotherapy drugs equally. Although most drugs are more cytotoxic to cells undergoing DNA synthesis, some agents do not show this selectivity. Thus, the growth fraction should be included among the factors that contribute to the sensitivity of tumor cells to therapy but alone is not predictive of a therapeutic response. Low-grade lymphomas are a good example of the limitations of this principle. It has been proposed that the low-growth fraction of indolent lymphomas could explain the incurability of these tumors with chemotherapy. However, most low-grade lymphomas are sensitive to chemotherapy, so tumor growth fraction alone cannot explain the low cure rate.

Skipper and colleagues also observed that the number of tumor cells that are killed by a cycle of chemotherapy depends on first-order kinetics; that is, a given drug dose killed a constant fraction of cells, independent of cell number.[78,79] Of course, the sensitivity of the

tumor to the chemotherapy directly affects the fraction of cells killed, and in practice, this sensitivity changes over multiple courses of chemotherapy. Indeed, the potential of chemotherapy to select resistant cells may lead to decreased fractional cell kill. The fraction of cells that are killed can also be affected by other factors, including tumor perfusion and oxygenation, decreased host resistance to drug side effects, and the proliferation of tumor in sanctuary sites such as the CNS. While the concept of fractional cell kill suggests that surgical resection of tumor, if of sufficient degree, would be beneficial to the therapeutic outcome, it is not clinically useful in most lymphomas.[80]

Another important concept is drug concentration (or dose) and response (or cell kill). For some but not all drugs, a relatively linear relationship exists over a portion of the concentration curve. This applies particularly to alkylating agents. For other drugs (chiefly the antimetabolites) that depend on cell exposure to drug during vulnerable phases of the cell cycle, the duration of exposure might be more important than drug concentration. Clinically, high-dose therapy with stem cell support takes maximal advantage of the drug concentration–response relationship. Alkylating agents and epipodophyllotoxins are the preferred drugs for this approach because of their relatively linear dose response and favorable therapeutic index.[81]

Drug Resistance

Because lymphomas typically present with disseminated disease, chemotherapy is the mainstay of treatment, and drug resistance becomes the primary barrier to cure. In 1979, Goldie and Coldman proposed a drug resistance hypothesis based on the observation that resistance of *Escherichia coli* to infection by bacteriophage occurs through the preferential expansion of bacterial clones that have undergone mutation to a resistant phenotype.[82,83] By extrapolation, Goldie and Coldman predicted that the emergence of drug resistance in human tumors would correlate with the underlying spontaneous mutation rate of specific drug resistance genes. The emergence of resistant cells might be further hastened by the genomic instability associated with tumor cells.[84] Thus, under the selective pressure of chemotherapy, resistant clones would eventually predominate.

The Goldie-Coldman hypothesis provides a rationale for some of the principles that have already been established through empiric observation. In patients with large tumor burdens, there is an increased chance that tumor cells that are resistant to any single cytotoxic drug already exist, providing an explanation for the inverse relationship between tumor cell number and curability and for the greater efficacy of combination chemotherapy compared with single agents. Unfortunately, combination chemotherapy has not been able to overcome resistance in most cases of clinical cancer treatment. It is now clear that the Goldie-Coldman hypothesis is incorrect. Instead, it appears that much of the drug resistance that is observed in vivo is conferred by a high apoptotic threshold, which makes the tumor cells insensitive to multiple agents. In lymphoid malignancies, for example, overexpression of bcl-2, NF κB, and p53, all of which inhibit apoptosis, are associated with drug resistance (see Table 112-4).[47,48,85–88] Evidence also suggests that the cellular apparatus that controls the cell cycle is part of the final common pathways through which cytotoxic agents exert their lethal effects.[76,89,90] If this proves to be correct, deregulation at any number of steps in this pathway could lead to drug resistance. Among the most common oncogene or tumor suppressor gene mutations that are found in lymphoid neoplasms are those that occur in cell cycle control genes, further highlighting the central importance of these pathways.

Apoptosis and Cell Cycle Control

The death of malignant cells may occur by necrosis or by apoptosis.[89] The process of apoptosis can be triggered through multiple pathways, including exposure to cytotoxic agents, the loss of essential growth factors, exposure to negative regulators such as tumor necrosis factor and transforming growth factor-β, and the loss or induction of specific genes such as *c-myc* and *p53*.[89,91,92] Other events suppress apoptosis, such as the addition of growth factors and the induction or suppression of specific genes and viral proteins.[93] Although pathways leading to apoptosis are present in many tumor cells, some of the triggering pathways may be disrupted and absent, and experimental evidence suggests that disruption of these pathways increases the resistance of cancer cells to cytotoxic agents.[94,95]

Apoptosis plays a central role in the normal biology of lymphocytes and in the process of clonal deletion.[96] At least two genes (*bcl-2* and *p53*) that can affect apoptosis have been found to be either abnormal or deregulated in lymphomas.[86,95,97] Translocations of *bcl-2* (t[14;18]) in follicular lymphomas result in elevated levels of the protein product and prolong cell survival by blocking apoptosis.[91,98,99] Although *bcl-2* rearrangements are less frequent in aggressive B-cell lymphomas, they can be increased through amplification or NF-κB.[27,100,101] Viral genes such as EBV LMP-1, which is frequently present in BL, can induce expression of bcl-2 and protect cells from apoptosis. In vitro, cells that express increased bcl-2 are resistant to radiation- and chemotherapy-induced apoptosis. For example, a high level of bcl-2 expression in leukemias correlated with resistance to several apoptosis-inducing cytotoxic agents, including doxorubicin, methotrexate, and cytarabine.[102] At least 20 members of the bcl-2 family have been identified in mammalian species to date and include proteins with antiapoptotic effects such as bcl-2, bcl-X_L, bcl-W, and mcl-1 and others such as Bax, Bad, Bim, Bik, and Noxa, which have proapoptotic properties. The NFκB transcription factor also plays an important role in apoptosis and has been linked to multiple lymphoma types, including DLBCL and SLL.[103,104]

The *p53* tumor suppressor gene plays an important role in apoptosis as well; *p53* controls the cellular responses to DNA damage by arresting cells in G_1 to allow repair of DNA damage; if essential repairs are not possible, p53 may trigger apoptosis.[84] The importance of *p53* mutations in the development of the malignant phenotype is suggested by the presence of *p53* mutations in most types of cancers, including chronic lymphocytic leukemias and lymphomas.[95,105] Mutant *p53* has been detected in tumor biopsy specimens from up to one third of NHLs.[95]

Dose Intensity and Dose Density

Dose intensity, defined as the dose per unit time, has long been considered important for the treatment of lymphomas, although randomized trials comparing dose intensity regimens have had variable results. In one study of 238 patients with untreated aggressive lymphoma who were randomized to receive standard or escalated BACOP (bleomycin, doxorubicin, cyclophosphamide, vincristine, and prednisone) chemotherapy, which had 28% difference in doxorubicin relative dose intensity, there was no difference in outcome.[106] A randomized study of high-dose therapy with autologous stem cell rescue versus CHOP in untreated aggressive lymphoma showed a benefit for the high-dose arm, particularly in high-risk patients.[107] High-dose treatment was also found to be superior in a trial in which patients who were in complete remission with standard therapy were randomized to stop or to receive high-dose consolidation.[108] In contrast, high-dose treatment did not benefit patients with slow responses to CHOP who were randomized to complete CHOP or to undergo high-dose therapy.[109]

In aggressive lymphomas, high tumor proliferation determined by Ki-67 or MIB-1 immunohistochemistry has been shown to be an adverse prognostic finding with CHOP chemotherapy, suggesting that kinetic failure is a problem.[27,110] One strategy to overcome kinetic failure is to increase dose density through frequent chemotherapy administration. This concept was first addressed by MACOP-B, which was administered weekly for 12 weeks. When compared to CHOP in a randomized study, however, MACOP-B had a similar outcome.[111] More recently, the German High Grade Lymphoma Study Group readdressed this concept in a randomized study of

2-weekly versus 3-weekly CHOP with and without etoposide. In this study of 831 patients with aggressive lymphomas older than 60 years, dose dense CHOP-14 was significantly better than CHOP-21, with OS rates of 53.3% and 40.6%, respectively ($P < 0.001$).[112] When the regimens were tested in younger patients, however, dose density was not superior, a finding that lacks an obvious biologic explanation.[113]

Such disparate results appear to challenge the concept of dose intensity, but this conclusion should be interpreted with caution. It is important to recall that dose intensity combines dose rate and dose density, each with a different theoretical benefit. Unfortunately, dose intensity is often misinterpreted as being equivalent to drug exposure. Dose rate, however, is not equivalent to drug exposure because of variable pharmacokinetics, which can result in over tenfold variations in drug area under the curve.[114] Another important variable is dose response, which is dependent on the drug class and the individual tumor cell. Microarray studies in lymphomas clearly illustrate widely variable mechanisms of resistance, which clinically translate into differences in dose response.[85,104] It is not surprising, given these variables and the absence of controls, that studies of dose intensity have been contradictory. Nevertheless, dose-response is an incontrovertible notion that, in the absence of a known optimum dose rate, mandates that a maximum safe dose be administered. Such an approach has been adopted by Wilson and colleagues in the dose-adjusted EPOCH regimen, in which doses are adjusted on the basis of the pharmacodynamics of the administered agents.[114]

CLINICAL MANAGEMENT OF LYMPHOMAS

Optimal care requires an understanding of a patient's unique medical history and physical condition, the patient's disease stage, and, most important, a correct histologic diagnosis. The World Health Organization classification provides a biologic framework for lymphomas, but it is not specifically organized with treatment in mind. Biologically related lymphomas such as those of B-cell origin, however, share features that have treatment implications. Thus, in presenting clinical management, we have organized our discussions around shared biologic and clinical features (Table 112-8); disease types are presented according to mature B-cell origin, precursor B- or T-cell origin, and lymphomas of mature T-cell origin as well as according to clinical aggressiveness and special topics. Two lymphomas of mature T-cell origin—cutaneous T-cell lymphoma/mycosis fungoides and adult T-cell lymphoma/leukemia—will be discussed elsewhere.

Lymphomas of Mature B-Cell Origin

B-cell lymphomas represent approximately 85% to 90% of all non-Hodgkin's lymphomas and can be organized into clinically relevant groups according to their natural history (i.e., indolent versus aggressive). While such clinical groupings provide a framework for management, each case must be considered individually.

Management of Follicular, Small Lymphocytic, and Marginal Zone Lymphoma

Indolent B-cell lymphomas are clinically diverse. Symptomatic patients who do not achieve a durable initial remission will often require intermittent therapy to control clinical signs and symptoms (Table 112-9). There are many effective drug classes that provide disease control, including purine analogs, alkylators, anthracyclines, and rituximab. Furthermore, targeted agents and immunotherapy with idiotype vaccines and allogeneic stem cell transplantation hold promise and are under investigation. Observation is an important option for asymptomatic patients, since early treatment has not been shown to improve survival. Newer approaches, such as early use of monoclonal antibodies and development of patient-specific idiotype vaccines, have changed the natural history of follicular lymphoma, making the decision when to initiate treatment challenging. For the present, treatment of these lymphomas is generally initiated for constitutional symptoms, organ compromise, and/or evidence of rapid tumor growth or bulk during the initial observation period. Symptomatic patients are usually those with bulky disease, diffuse bone marrow infiltration resulting in abnormal blood counts, and threatened organ function.

Follicular Lymphoma

Follicular lymphomas are classified into three grades based on the number of centroblasts per high-power field. Generally, grades 1 and 2 are indolent, whereas grade 3 can be more aggressive. It is now recognized that grade 3 disease is biologically diverse and includes both follicular lymphoma, termed grade 3a, and large B-cell lymphoma, termed grade 3b, which has a follicular growth pattern but is clinically like DLBCL. Unfortunately, the distinction between grades 3a and 3b is difficult.[115] A number of clinical features are associated with outcome of follicular lymphoma (FL). In a study of 4000 patients with FL, age greater than 60 years, Ann Arbor stage III or IV, hemoglobin level less than 12 g/dL, abnormal serum LDH level, and involvement of five or more lymph node areas were adverse prognostic features.[64] Three risk groups were codified into the Follicular Lymphoma International Prognostic Index, which appears to be more discriminating for FL than does the International Prognostic Index that was originally established for aggressive NHL (Fig. 112-3; see Table 112-7).

EARLY-STAGE DISEASE. While most follicular lymphomas present at advanced stage, approximately 15% to 30% are stage I or II. On the basis of older retrospective studies, radiotherapy alone has been the standard of care, with median survival approaching 15 years and up to one third of patients progression free. It is not clear whether these results reflect the benefit of radiotherapy or the indolent natural history of early-stage disease. A relatively recent retrospective analysis of 43 patients with untreated stage I or II FL found that 63% did not require therapy over the median follow-up of 86 months and only 4 patients showed histologic transformation.[116] Furthermore, the 10-year estimated survival rate was 85%. Indeed, an aggressive strategy of combination chemotherapy followed by involved-field radiation therapy in 102 patients with early-stage disease yielded a similar 10-year survival rate of 82%.[117] There were two cases of myelodysplasia and 12 secondary malignancies in this cohort of patients. Although such results raise the question of the benefit from immediate treatment, they were conducted in the pre-rituximab era.[118,119] At present, it is difficult to make firm recommendations regarding treatment. Radiotherapy still remains popular[120] but it can cause significant long-term toxicities depending on the location, field, and dose of radiation. When considering treatment options for early-stage disease, it is important to recognize that there is no clear best option at present and that treatment should be tailored to the individual patient.

ASYMPTOMATIC ADVANCED-STAGE DISEASE. Several randomized trials have compared observation with single-agent or combination chemotherapy in patients with asymptomatic advanced-stage lymphoma. In one randomized study of 104 patients, 44 patients were observed, and 45 received aggressive treatment with ProMace-MOPP chemotherapy and total nodal irradiation; 15 symptomatic patients received immediate treatment.[121] Notably, while complete remission (CR) and disease-free survival were significantly better with immediate treatment, the OS rate was similar at 83% and 84%, respectively, at 4 years median follow-up. Four patients (10%) in the treatment arm developed myelodysplasia. Although the median remission duration exceeded 45 months, which appeared better than that with single-agent alkylators or combination chemotherapy, this study did not prove that early treatment was beneficial. Another randomized study compared observation to oral

Table 112-8 Clinical Characteristics of the Major Subtypes of Non-Hodgkin's Lymphoma

Cell	Anaplastic Follicular (%)	Small Lymphocytic (%)	MALT (%)	Marginal Zone, Nodal (%)	Mantle Cell (%)	Diffuse Large B-Cell (%)	Mediastinal Large B-Cell (%)	Burkitt's (%)	Lymphoblastic (%)	Peripheral T-Cell (%)	Large T/Null Cell (%)
NHL Worldwide	22	7	8	2	6	31	2	4	2	7	2
NHL in North America	32	4	7	—	7	29	1	—	—	2	3
NHL in Europe	18	9	9	—	9	29	3	—	—	5	2
Median age	59	65	60	58	63	64	37	31	28	61	34
Male	42	53	48	42	74	55	34	89	64	55	69
Stage I	16	4	0	13	10	12	10	25	0	1	16
IE	2	0	39	0	3	13	0	12	0	7	3
II	11	2	0	13	6	13	34	13	11	6	22
IIE	4	3	28	0	1	16	22	12	0	6	10
III	16	8	2	34	9	13	3	0	14	15	10
IV	51	83	31	40	71	33	31	38	75	65	39
B-symptoms	28	33	19	37	28	33	38	22	21	50	53
Elevated LDH	30	41	27	40	40	53	81	75	70	64	45
Karnofsky score ≤70	9	11	15	7	21	24	22	44	29	32	26
Tumor mass >10 cm	28	13	8	0	25	30	52	22	32	12	17
Any extranodal sites	64	80	98	47	81	71	56	78	82	82	59
More than one extranodal site	23	29	31	16	51	29	19	56	43	45	28
Bone marrow positive	42	72	14	32	64	16	3	33	50	36	13
GI tract positive	4	3	50	5	9	18	0	11	4	15	9
International Prognostic Index	45	23	44	60	23	35	52	57	33	17	61
0/1											
2/3	48	64	48	27	54	46	37	29	41	52	18
4/5	7	13	8	13	23	19	11	14	26	31	21

Table 112-9 Treatment Outcomes in Indolent Lymphoma

Clinical Group	Treatment	Complete Response (%)	Overall Response (%)	Median PFS Range	Reference
Untreated	CVP ± R	10–40	60–80	3–5 years	Kimby et al,[123] Dana et al,[124] Foran et al,[128] Czuchman et al,[129,130] Marcus et al,[131] Habermann et al,[132] Zinzani et al,[133] Hainsworth et al,[361] Colombat et al,[362] Hainsworth et al,[363]
Symptomatic	CHOP ± R	40–80	90–100	5–7 years	
	FND ± R	70–90	90–100	5–7 years	
	R ± Maintenance R	15–40	60–75	2–3 years	
Relapsed	Rituximab	10–20	40–60	8–24 months	Glantz et al,[364] Davis et al,[365] McLaughlin et al,[366] Davis et al,[367]
	Radioimmunotherapy	15–50	65–80	8–24 months	Kaminski et al, [368] Davies et al,[369] Gordon et al,[370]
	Chemotherapy	15–40	60–90	12–24 months	McLaughlin et al,[371]

CHOP: cyclophosphamide, Adriamycin, vincristine, and prednisone; CVP: cyclophosphamide, vincristine, and prednisone; FND: fludarabine, mitoxantrone, and dexamethasone; OS, overall survival; PFS, progression-free survival; R: rituximab.

chemotherapy in asymptomatic patients with advanced low-grade lymphoma. In this study, 158 patients received chlorambucil 10 mg/day and 151 patients were observed.[122] At a median follow-up of 16 years, the OS was similar at 5.9 and 6.7 years, respectively, and the median cause-specific survival was 9 years in both groups. Approximately 20% of the patients in the observation arm did not require therapy after 10 years follow-up, and 40% of these were at least 70 years old at enrollment. Although these randomized trials support observation, they were performed before the use of rituximab, which has been shown to prolong survival in symptomatic patients.[118] Prospective randomized trials are necessary to readdress the role of observation in the era of rituximab based treatment.

SYMPTOMATIC ADVANCED-STAGE DISEASE. Initial chemotherapy for patients with symptomatic disease should be tailored to the clinical circumstances (see Table 112-9). Patients with high tumor burden and/or threatening symptoms might require more aggressive multiagent regimens, whereas less toxic therapy might be appropriate for patients with slowly progressive disease. Factors such as patient age and condition should be considered as well. Numerous single agents and combination chemotherapy are effective (see Table 112-9). Single-agent chlorambucil or cyclophosphamide with or without prednisone is well tolerated but rarely produces a complete remission. More aggressive regimens produce higher CR rates. In a randomized study of 259 patients with advanced-stage disease, CHOP produced a higher response (60% versus 36%) but similar overall median survival (52 months versus 48 months) compared to oral chlorambucil/prednisone.[123] There is no evidence of a plateau on the survival curve with CHOP treatment in a retrospective review of 415 patients on Southwest Oncology Group trials.[124] In this study, the median survival was 6.9 years.

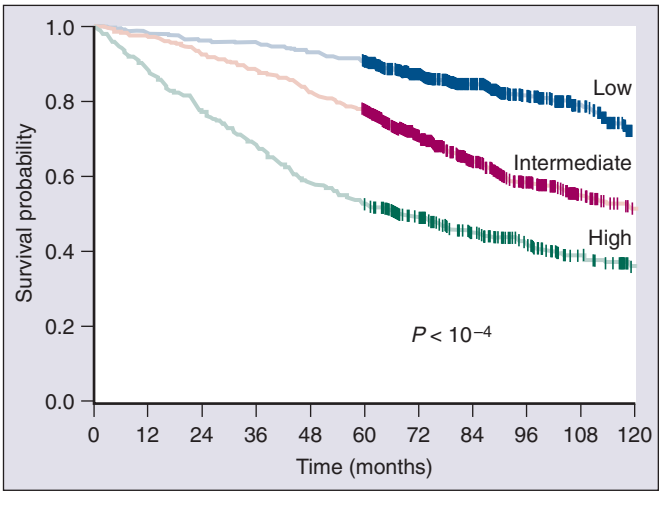


Figure 112-3 • Survival of 1795 patients stratified by Follicular Lymphoma International Prognostic Index. (Data from Solar-Celigny P, Roy P, Colombat P, et al: Follicular Lymphoma International Prognostic Index. Blood 2004;104:1258–1265.)

The most important advance in the treatment of follicular lymphomas over the past 20 years is rituximab. In 41 untreated patients with indolent lymphoma, rituximab yielded an overall response rate of 64%, including a 15% CR rate, and 77% were progression free at 12 months.[125] In another study of untreated patients, molecular remission was associated with particularly durable responses.[126] Rituximab was also tested as a first-line treatment in 62 patients with FL and SLL followed by maintenance therapy every 6 months in patients without progression.[127] Interestingly, the response rate was 47% following induction with an increase to 73% during maintenance, including a 37% CR rate, and the median progression-free survival (PFS) was 34 months. Response rates were similar in follicular lymphoma and SLL. The role of maintenance rituximab was also tested in 202 patients with untreated or relapsed/refractory FL. Treatment involved a 4-week course of rituximab followed by observation or maintenance at 3, 5, 7, and 9 months. The overall response rate was 67% and 46% in untreated and relapsed/refractory patients, respectively, and at the median follow-up of 35 months, the median event-free survival (EFS) was 12 and 23 months for the observation and maintenance groups, respectively.[128] Untreated patients appeared to benefit most from maintenance, the EFS increasing from 19 to 36 months.

The addition of rituximab to chemotherapy has improved response and survival. In the first study of R-CHOP in mostly untreated patients with indolent lymphoma, the overall response rate was 95%, including 55% complete with an 82-month median PFS.[129,130] Hiddemann and colleagues performed a randomized study of CHOP versus R-CHOP in 428 patients with symptomatic advanced-stage FL.[118] Responding patients under 60 years were offered a second randomization following treatment to stem cell transplantation or interferon-α maintenance, whereas older patients received interferon α maintenance. With a median follow-up of 18 months, patients in the R-CHOP arm had a 60% reduction in risk of treatment failure

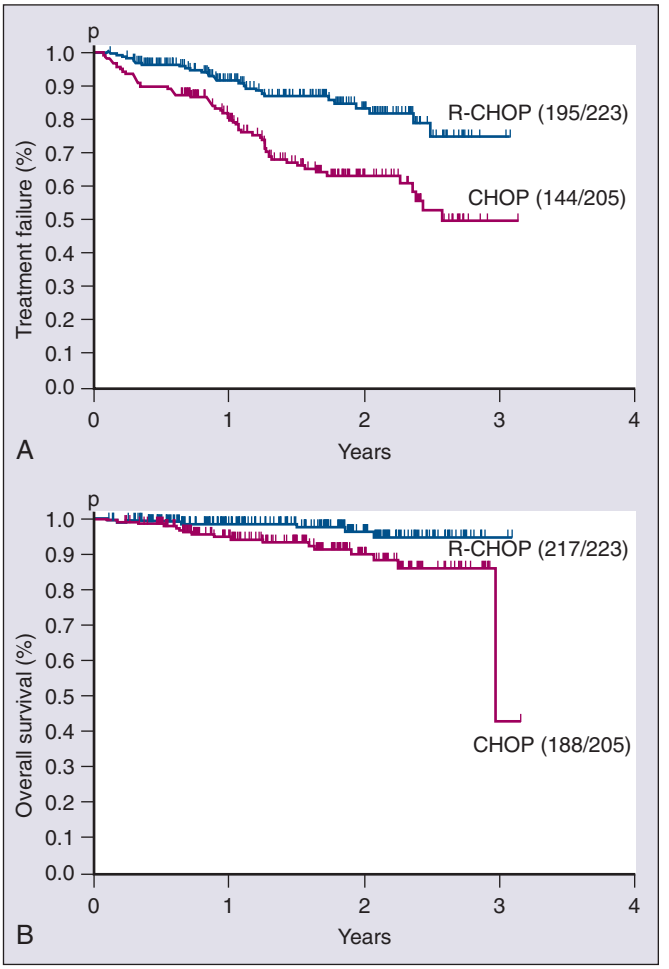


Figure 112-4 • Survival outcomes after CHOP and R-CHOP. **A,** Time to treatment failure after CHOP and R-CHOP ($P < 0.001$). **B,** Overall survival rates after CHOP and R-CHOP ($P = 0.016$). (Data from Hiddemann W, Kneba M, Dreyling M, et al: Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725–3732.)

and a modest albeit significant improvement in OS (Fig. 112-4). It is important to note that the interpretation of this study is confounded by the secondary treatment requirement. In another important randomized study of CVP with or without rituximab, rituximab also significantly improved response, progression, and survival.[131] The role of maintenance was addressed in a randomized study of CVP versus fludarabine/cyclophosphamide (FC) with a second randomization to observation or maintenance rituximab every 6 months for 2 years.[132] Rituximab maintenance was associated with an increase in PFS for 2.5 to 4.5 years. Another randomized study in untreated patients compared fludarabine/mitoxantrone (FM) and CHOP followed by rituximab in patients who did not achieve molecular remission.[133] Although the overall response rate was almost 100% in both arms, the complete responses were greater in patients who received FM (68%) compared to CHOP (42%). Following rituximab treatment, however, the two arms had similar CR rates of 90% and 81%, respectively. Interestingly, the duration of complete remissions following chemotherapy alone or chemotherapy and rituximab were similar, suggesting that rituximab might help to overcome chemotherapy resistance. These trials clearly indicate that rituximab significantly improves the efficacy of chemotherapy and OS.

There is much interest in the mechanism of action and biomarkers of response with rituximab. On the basis of the mechanism of antibody binding, a study investigated and found an association between immunoglobulin-G fragment-C receptor polymorphisms and rituximab response.[134] Polymorphisms structurally affect the affinity of the Fc receptor binding, which is required for antibody-dependent cellular cytotoxicity. Specifically, the valine/valine polymorphism in FCγ receptor 3A (15% of patients) and the histidine/histidine polymorphism in FCγ receptor 2A (25% of patients) were independently associated with response and progression following rituximab.

Other immune strategies that have shown promise include interferon-α and idiotype vaccine. The benefit of interferon-α has been controversial; only some studies show a survival advantage, which is likely due to testing of variable schedules and doses and only modest activity.[135,136] Nevertheless, owing to the efficacy and low toxicity of rituximab, interferon-α is infrequently used in the United States. Idiotype vaccines represent another strategy, much of the initial excitement coming from a small study in which idiotype vaccine induced durable molecular remissions following first clinical remission.[137] Other studies have also shown regression of FL following idiotype vaccines.[138] On the basis of these promising results, two large randomized studies of idiotype vaccine have been conducted, and results should soon be available.

TREATMENT OF RELAPSED DISEASE. Relapsed patients can be successfully retreated with many of the same strategies that were employed for initial treatment. Importantly, patients who show benefit from a prior treatment can be retreated with same agents, although alternative combinations may be selected.[139] There are multiple active regimens for relapsed patients.[140,141] In a phase II trial of 51 patients with relapsed or refractory low-grade lymphoma, the overall and complete response rates were 94% and 47%, respectively, with a 14-month median failure-free survival.[141] Rituximab has been extensively investigated in relapsed indolent lymphoma (see Table 112-9). In a study of 166 patients who were treated with rituximab 375 mg/m^2 weekly for four doses, 48% responded with a 13-month median time to progression.[142] In another study of eight weekly rituximab infusions, 57% responded, and the median time to progression had not been reached at 19.4 months' median follow-up, suggesting more rituximab doses might be more effective.[143] Rituximab has also been studied in retreatment after prior rituximab.[144] While the overall response rate of 40% was similar to that of the first rituximab course, the responders had a longer median time to progression of over 18 months.

Anti-CD20 antibody therapy has also been used for targeted delivery of iodine-131 and yttrium-90 to the tumor. These drugs are now commercially available in the form of iodine-131 tositumomab (Bexxar) and yttrium-90 ibritumomab tiuxetan (Zevalin). Iodine-131 tositumomab was tested in 60 patients with low-grade or transformed B-cell NHL and showed a response rate of 65% and a median response duration of 6.5 months.[145] The 22% of patients who achieved complete remission had a response duration of over 47 months, indicating major treatment benefit. Secondary myelodysplasia is a concern with radiotherapy, particularly in heavily pretreated patients, and was observed in four patients from this study. Other studies have demonstrated equivalent response rates in relapsed and transformed lymphoma.[146] Ibritumomab tiuxetan has been assessed in rituximab failures as defined by no response or progression within 6 months.[147] Among 54 patients with FL, overall and complete responses were observed in 74% and 15% of patients, respectively, and the median PFS was 6.8 months. Ibritumomab tiuxetan was also tested in a randomized controlled trial in patients with relapse or refractory or transformed FL.[147] Compared to rituximab alone, ibritumomab tiuxetan had a higher overall response rate, 80% versus 56%, and a complete response rate of 30% versus 16%, respectively, but a similar response duration and time to progression. The role of radioimmunotherapy is currently

limited to relapsed patients with limited bone marrow involvement but it is under investigation with immunochemotherapy for initial treatment.

High-dose therapy with autologous hematopoietic stem cell support for indolent lymphoma has been tested as consolidation in first response, relapse, and transformation.[148–157] Patients who undergo transplantation early in their disease course have the best outcome. In approximately 250 patients undergoing autotransplantation in first partial response or second complete response at St. Bartholomew's Hospital in London and the University of Nebraska Medical Center, the 10-year PFS rate was approximately 45%. In one study of 92 patients with untreated advanced FL in which 87% underwent high-dose chemotherapy and transplantation, 84% and 67%, respectively, were alive and disease-free at 4 years.[154] The Groupe d'Étude des Lymphomes de l'Adulte (GELA) study group presented preliminary results of chemotherapy followed by interferon compared to chemotherapy followed by high-dose therapy and autologous stem cell transplantation (ASCT) in untreated FL with high tumor burden.[158] With a median follow-up of 56 months, patients who underwent transplant had a statistically higher OS rate of 86% compared to 74% in the interferon arm at 7 years. However, there was no difference in EFS between the two arms.

There have been multiple studies of autologous transplantation in relapsed and transformed indolent lymphomas.[148,156] One large study reported a 42% disease-free rate and a 66% OS rate at 8 years after antibody-purged autologous bone marrow transplantation, the better outcomes being found in patients who were successfully purged.[148] It is important to recognize, however, that successful purging is likely a surrogate marker for lower disease burden and/or sensitive disease and might not be therapeutic.[148] Autologous transplantation is particularly appealing in transformed indolent lymphomas, in which high-dose treatment may be needed to eradicate the transformed clone. Once transformation occurs, prognosis is generally poor, with median survivals of 6 to 18 months; however, not all patients' diseases behave aggressively. Data from European Bone Marrow Transplant Registry in 50 transformed patients revealed a 5-year OS rate of 51% and a PFS rate of and 30%, which were similar to those of a cohort of patients transplanted for indolent or de novo aggressive lymphoma.[156] Overall, these results indicate that autologous transplantation is relatively safe and active in follicular lymphomas.

Several groups have investigated allogeneic transplantation in the hope that graft-versus-lymphoma effect may eradicate residual disease. Results of allogeneic transplant in 10 patients with refractory indolent lymphoma were encouraging, with only one progression after 6 years' median follow-up.[159] Furthermore, a larger series of 113 patients with advanced indolent lymphoma from the International Bone Marrow Transplant Registry reported an overall and disease-free survival rate of 49% at 3 years with only 16% recurrences. These survival curves appeared to plateau, relapses being uncommon after 2 years. However, these promising findings must be considered within the context of the 40% treatment-related mortality.[142] To help ameliorate such toxicity, investigators have turned to reduce intensity stem cell transplants. This approach was tested in 20 patients with indolent and aggressive lymphoma, all of whom had chemotherapy-sensitive or stable disease and had failed prior autologous transplantation.[160] Engraftment was successful in all patients, and with 25 months of median follow-up, the estimated 3-year PFS rate was 95%. Matched unrelated donor bone marrow transplantation has also been explored.[161] Although unrelated donor bone marrow is usually more toxic, the Japanese Marrow Donor Program reported an OS rate of 50% at 3 years with 33% treatment-related mortality in 124 patients. Acute graft-versus-host disease was associated with lower disease progression but more toxicity. While the results of such studies are provocative, larger clinical trials with longer follow-up and randomized study designs are needed to establish the role of allogeneic transplantation in the treatment of indolent lymphomas.

Small Lymphocytic Lymphoma B-Cell Chronic Lymphocytic Leukemia

The same principles of management are applied to these subtypes of lymphoma as to follicular lymphoma, therapy being recommended only if it is clinically indicated. Because the patient population is generally older and more likely to have comorbid problems, there has to date been less enthusiasm for aggressive intervention.[162–166] Unfortunately, this philosophy has been reinforced by the failure of most recent attempts to improve the situation.

As with CLL (see Chapter 108), purine analogs (i.e., fludarabine, cladribine, and pentostatin) alone and in combination have held the greatest promise in terms of new chemotherapy for SLL/B-CLL and the lymphoplasmacytoid lymphomas. The efficacy of fludarabine alone (and cladribine) in previously treated B-CLL inevitably extended interest further, with response rates between 30% and 50%.[167–172]

Several studies investigating combinations of fludarabine with cyclophosphamide[173] or with mitoxantrone and high doses of dexamethasone[174] have been encouraging, although substantial toxicity has been seen. The combination of fludarabine with cyclophosphamide and rituximab has yielded a high proportion of complete remissions, previously a rare outcome in this disease.[175]

The relative seniority of many of the patients as well as the incompleteness of clearance of bone marrow infiltration makes high-dose therapy with hematopoietic stem cell support inappropriate for the majority. Hence, the data about it are sparse and refer to highly selected patients. The declining mortality of the procedure, however, coupled with some encouraging early results certainly warrant further investigation. For younger patients with a human leukocyte antigen–matched sibling, allogeneic transplantation with low-dose conditioning is finding increasing popularity within the research setting.[176–178] It will become clear when larger numbers of patients have been treated how relevant this will be. Monoclonal antibody therapy with rituximab has been evaluated in a single open phase II study in Europe with less impressive results than have been achieved in follicular lymphoma, the response being less than one third in patients with lymphoplasmacytoid lymphoma and less than one fifth in those with SLL (specifically not CLL).[179] Studies that are in progress will elucidate whether the alternative antibody alemtuzumab directed at CD52 is any better.[180,181] Monoclonal antibodies targeted with radionuclide have not really been investigated in this disease because of the large bone marrow involvement.

Lymphoplasmacytic Lymphoma

Lymphoplasmacytic lymphomas are generally treated like other advanced-stage indolent lymphomas. When these lymphomas present with a significant immunoglobulin M paraprotein and bone marrow disease, they are also known as Waldenström's macroglobulinemia and may present with splenomegaly. In Waldenström's macroglobulinemia, the clinical picture may be dominated by symptoms of hyperviscosity (e.g., dizziness, tiredness, and a propensity for bleeding from the mucous membranes) as well as symptoms due to cryoglobulinemia and cold agglutinin anemia.[182] In addition, some patients develop peripheral neuropathy, renal disease, and amyloidosis. Patients with acute symptoms from hyperviscosity might require emergency plasmapheresis. Alkylating agents, purine analogs, and rituximab are quite effective in this disorder.[182]

Extranodal Marginal Zone Lymphoma

While the treatment of most MALT lymphomas is similar to that of other indolent lymphomas, localized gastric MALT lymphoma is unique because of its association with *H. pylori*. In many cases, the MALT clone is indirectly dependent on *H. pylori* and resolves with appropriate antibiotic treatment. Approximately 70% of cases of stage I E-gastric MALT regress following eradication of *H. pylori* with antibiotics.[183] However, the presence of t(11;18) in the tumor cells predicts a poor response to antibiotic therapy.[184] Patients with

localized disease and persistent lymphoma despite antibiotics can be effectively treated with rituximab, chemotherapy, and/or radiotherapy, depending on the clinical circumstances. Durable complete remissions are typical with radiotherapy. Rituximab is active in gastric MALT lymphomas, with overall responses in 64% and complete responses in 29% of patients.[185]

Nodal Marginal Zone B-Cell Lymphoma

This is a rare disease, mainly of older women. Most patients present with lymphadenopathy, often in the neck.[186] Histologically, these tumors are considered to be the lymphomatous counterpart of monocytoid B-cells, but typical monocytoid B-cells might be absent. The latter are reactive cells that are described in association with infections (e.g., toxoplasmosis) and sometimes in the context of other subtypes of NHLs and Hodgkin's disease.

The relationship with MALT lymphomas is complex. As was mentioned previously, they may occur in the context of a MALT lymphoma (e.g., lymph node involvement secondary to a gastric or parotid MALT lymphoma).[187] They may occur in the absence of extranodal disease and are often more aggressive than MALT lymphoma. The immunophenotype is characteristically indistinguishable from that of MALT lymphomas.[188]

There is little consensus about treatment, management being dictated by the site that is involved and the age of the patient. In general, however, the principles of therapy that were described for follicular lymphomas can be applied.

Splenic Marginal Zone Lymphoma

Splenic lymphoma with villous lymphocytes represents another special lymphoma that presents with splenomegaly and B-cells with villous projections in the blood. In these cases, it is hypothesized that the tumor cells originate from the marginal zone of the spleen. In patients with chronic hepatitis C infection, treatment of the hepatitis with interferon-α alone or in combination with the antiviral agent ribavirin was associated with regression of disease in seven of nine patients.[189] Hepatitis C virus–negative patients did not respond to this therapy. Historically, splenectomy was often required to establish the diagnosis, and prolonged responses are often observed, but rituximab is highly effective and should also be considered before splenectomy.[190,191]

Management of Diffuse Large B-cell, Burkitt's, and Mantle Cell Lymphoma

As a group, DLBCL, BL, and MCL. have widely variable natural histories but are usually rapidly progressive and, with the exception of MCL, are quite curable. MCL has a unique natural history that lies between those of indolent and aggressive B-cell lymphomas. It is infrequently curable, and a quarter of cases are low grade, whereas the remaining cases are relatively aggressive.[67] The curative nature of DLBCL and BL set them apart from other lymphomas and requires prompt evaluation and proper therapy. Unlike the more indolent lymphomas, for which treatment strategies are similar, refinements in the management of aggressive lymphomas have led to subtype-specific strategies. As such, the treatment of aggressive B-cell lymphomas is presented for each lymphoma subtype.

Diffuse Large B-Cell Lymphoma

DLBCL is a disease of older adults, with a median presentation in the seventh decade, but it also affects young adults and children.[23] Patients may present with localized or disseminated disease and with nodal or extranodal involvement. Within DLBCL, there are several morphologic variants, including centroblastic, immunoblastic, T-cell rich/histiocyte rich, and anaplastic subtypes, and progress in molecular profiling is further advancing this taxonomy.[20,27] There are also several clinical-pathologic variants of DLBCL. PMBL represents one such variant that more commonly presents in young women and usually remains localized to the mediastinum. It is important to recognize that DLBCL can also arise as a result of histologic transformation from an indolent lymphoma. Though this differentiation might not affect treatment choice initially, it will affect prognosis and natural history and therefore needs to be recognized at diagnosis.

The mainstay of treatment for DLBCL is systemic chemotherapy; radiation treatment alone is inadequate and associated with high recurrence rates.[192] For early-stage disease, whether or not radiation treatment adds benefit to chemotherapy has been controversial. On the basis of a randomized study that showed a survival advantage of limited-course CHOP plus involved field radiation compared to full-course CHOP in early-stage (I/II) aggressive lymphoma, combined-modality therapy became the standard.[193] However, longer patient follow-up showed a convergence of the OS curves due to late systemic relapses in the combined-modality arm, thus reopening the debate on radiation.[120,194] In this regard, a recent prospective GELA study randomized 576 elderly patients with favorable early-stage aggressive lymphoma to receive CHOP alone (four cycles) or CHOP plus radiation and found that combined-modality therapy was not superior to chemotherapy alone.[194] Given these results and the improved outcome of CHOP with rituximab (R-CHOP), the necessity of including radiotherapy in management is not certain.

A possible exception to the omission of radiation, however, is in the treatment of PMBL, depending on the chemotherapy regimen. In a study of 50 untreated patients with PMBL who received MACOP-B followed by radiation, 66% had persistently positive gallium scans after chemotherapy, suggesting active disease. Following consolidation radiotherapy, however, only 19% of patients had a positive gallium scan, and 80% were event free at 39 months' median follow-up.[195] This important study suggested that radiotherapy was necessary following chemotherapy. Furthermore, there is historical evidence that dose-intense regimens such as MACOP-B or VACOP-B are superior to CHOP for PMBL, raising yet another question about the optimal chemotherapy for this disease.[196–198] Recent results with the pharmacodynamically dose-adjusted regimen of doxorubicin, vincristine, and etoposide infused over 96 hours with bolus intravenous cyclophosphamide, rituximab, and oral prednisone (DA-EPOCH-R) may be challenging the need for radiation in PMBL.[199,200] In a phase II study of DA-EPOCH-R in 26 patients with PMBL, 100% and 91% are alive and event free, respectively, at a median 4.2-year follow-up, and only 2 patients required radiation treatment.[201] These results suggest that DA-EPOCH-R obviates the need for radiation in most patients with PMBL, thus eliminating the risk of long-term toxicities such as secondary malignancies and heart disease. This is particularly important given that patients who are afflicted with PMBL are typically young and often women and are at increased risk of breast and other cancers as well as late-term toxicities. Of course, it is possible that patients who receive R-CHOP might not also require radiation therapy, but this question needs to be carefully studied.

Systemic treatment is required for advanced DLBCL (Table 112-10). The CHOP regimen was developed some 30 years ago and was established as the standard by a randomized trial that showed that CHOP was equal in effectiveness to three other common albeit more complex and/or toxic regimens.[111] The fact that only 44% of patients achieved complete remissions with CHOP, however, left significant room for improvement and spawned multiple studies aimed at improving treatment outcome.[111,202] Many of these studies have focused on modifications to the CHOP platform. A GELA study compared doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (ACVBP) to CHOP in elderly patients with aggressive lymphoma and showed a superior 5-year EFS rate of 39% and an OS rate of 46% compared to 29% and 38%, respectively, for CHOP (Fig. 112-5).[203] Much of the benefit in the ACVBP arm, however, was due to a lower incidence of CNS progression, which could be attributed to the use of CNS prophylaxis with ACVBP. Furthermore, a previous study of ACVBP in low-IPI patients showed

Table 112-10 Treatment Outcome in Untreated Diffuse Large B-cell Lymphoma

Study	Therapy	Patient Group	Event-Free Survival	Overall Survival	Reference
Phase III	R-CHOP	Age ≥60 years	47% at 5 years	58% at 5 years	Coiffier et al;[210] Feugier et al[211]
R-CHOP versus CHOP	GELA	All IPI			
Phase III	R-CHOP	Age ≥60 years	53% at 3 years	NA	Habermann et al[212]
R-CHOP versus CHOP	U.S. Intergroup	All IPI			
Phase III	R-CHOP-like* MInT	Age ≤60 years	79% at 3 years	93% at 3 years	Pfreundschuh et al[214]
R-CHOP-like versus CHOP		Low IPI			
Phase III	ACVBP	Age ≥60 years	39% at 5 years	46% at 5 years	Tilly et al[203]
ACVBP versus CHOP	GELA	At least 1 IPI factor			
Phase II	DA-EPOCH-R	Age ≥18 years	82% at 43 months (PFS)	79% at 43 months	Wilson et al[215]
Single arm	NCI	All IPI			
Phase III	CHOEP-21	Age 18–60 years	69.2% at 5 years	NA	Pfreundschuh et al[206]
Four arms	DSHNHL	Good prognosis			
CHOP-14, CHOP-21, CHOEP-14, CHOEP-21					
Phase III	CHOP-14	Age 61–75 years	44% at 5 years	53.3% at 5 years	Pfreundschuh et al[205]
Four arms	DSHNHL	All IPI			
CHOP-14, CHOP-21, CHOEP-14, CHOEP-21					
Phase III	R-CHOP-14 (×6)	Age ≥60 years	66% at 3 years	78% at 3 years	Pfreundschuh et al[213]
Four arms	DSHNHL	All IPI			
R-CHOP-14 × 8, R-CHOP-14 × 6, R-CHOP-21 × 8, R-CHOP-21 × 6					

R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
*CHOP-like regimens included CHOP, CHOEP, MACOP-B, and PmitCEBO.

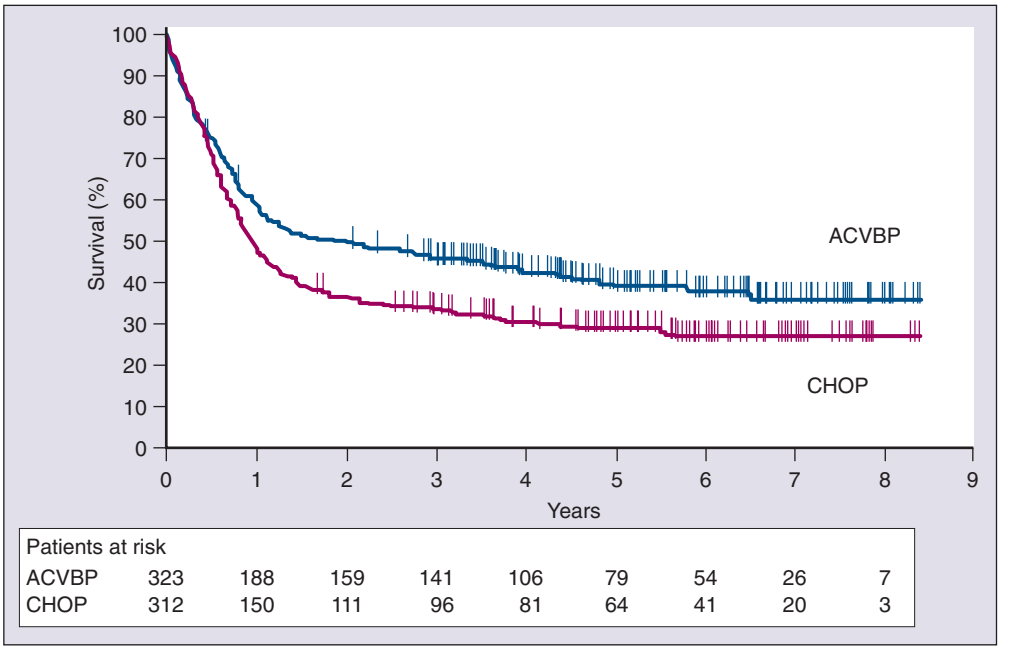


Figure 112-5 • Event-free survival rates of ACVBP versus CHOP in aggressive lymphomas ($P = 0.005$). (Data from Tilly H, Lepage E, Coiffier B, et al: Intensive conventional chemotherapy (ACVBP regimen) compared with standard CHOP for poor-prognosis aggressive non-Hodgkin lymphoma. Blood 2003;102:4284–4289.)

no benefit over m-BACOD, which was shown to be equivalent to CHOP.[204]

In aggressive lymphomas, high tumor proliferation determined by Ki-67 or MIB-1 immunohistochemistry has been shown to be an adverse prognostic finding with CHOP chemotherapy, suggesting that kinetic failure is a problem.[27,110] One strategy to overcome kinetic failure is to increase dose density through frequent chemotherapy administration. The Deutsche Studiengruppe für Hochmaligne Non-Hodgkin Lymphome evaluated the effect of dose density and etoposide in two four-arm studies of CHOP administered every 14 or 21 days, with or without etoposide (CHOEP), in patients older than 60 years and low-risk patients 60 years of age or younger.[205,206] In younger patients, CHOEP-21 showed the best overall results with a CR rate of 88% versus 79% and an EFS rate of 69% versus 58% at 5 years compared to standard CHOP-21, respectively.[206] In older patients, however, dose-dense CHOP-14 showed the best outcome, with a CR rate of 76% versus 60% and an EFS rate of 44% versus 33% at 5 years compared to standard CHOP-21.[205] While these studies provided the best evidence that outcome could be improved through specific changes to the CHOP chemotherapy platform, it remains unclear why the optimal treatment differed in the studies, given the continuum in disease biology across age.[27] The question of whether dose intensity or the addition of etoposide can improve outcome has been and continues to be addressed in various other studies.[207,208]

An alternative strategy to dose density is to increase the fractional cell kill or efficacy of chemotherapy, thereby reducing the number of tumor cells that can survive and proliferate between cycles. Longer drug exposure may take advantage of the increased sensitivity of cycling cells, and in vitro studies have shown that prolonged low-concentration exposure to vincristine and doxorubicin, compared with brief higher-concentration exposure, can increase cytotoxicity by up to 1 log.[209] This approach was translated into the pharmacodynamically dose-adjusted DA-EPOCH regimen, which showed promising PFS and OS rates of 70% and 73%, respectively, at 5 years' median follow-up in newly diagnosed DLBCL.[199] Interestingly, high tumor proliferation was not found to be an adverse biomarker in this study.[199]

It has been the development of rituximab that has made the single greatest impact on the treatment of DLBCL since CHOP was first introduced over 30 years ago. The first study to show the benefit of rituximab was performed by GELA, in which patients over 60 years of age were randomized to receive CHOP or CHOP with rituximab (R-CHOP).[210] In this study, the CR rate (76% versus 63%) and 5-year EFS rate (47% versus 29%) were higher with R-CHOP than with CHOP, respectively, making R-CHOP the de facto standard in DLBCL (Fig. 112-6).[210,211] The benefit of rituximab was later confirmed by the U.S. Intergroup study in a similar patient population.[212]

With the benefit of rituximab established, investigators have gone on to explore its use in a variety of clinical settings and treatment

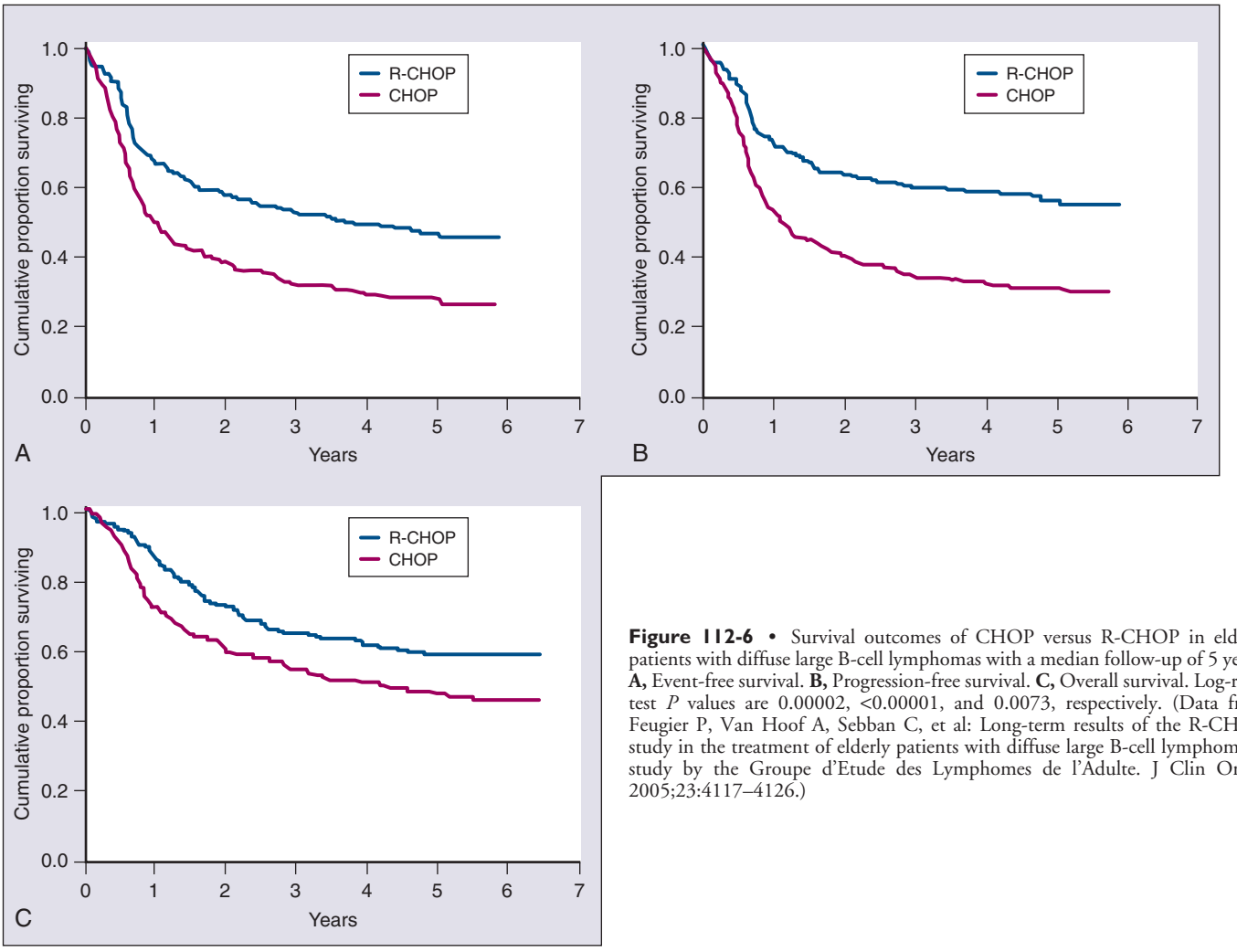


Figure 112-6 • Survival outcomes of CHOP versus R-CHOP in elderly patients with diffuse large B-cell lymphomas with a median follow-up of 5 years. **A,** Event-free survival. **B,** Progression-free survival. **C,** Overall survival. Log-rank test *P* values are 0.00002, <0.00001, and 0.0073, respectively. (Data from Feugier P, Van Hoof A, Sebban C, et al: Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol 2005;23:4117–4126.)

strategies. The Deutsche Studiengruppe für Hochmaligne Non-Hodgkin Lymphome explored the question of whether there was a difference in outcome between six and eight cycles of treatment in a randomized study of six versus eight cycles of CHOP-14, with or without rituximab, in elderly patients with DLBCL. In that study, termed the RECOVER-60 trial, they found no difference in outcome with six versus eight cycles of treatment.[213] Although they showed an excellent 3-year EFS rate of 66% with R-CHOP-14 over six cycles, which is somewhat better than the GELA and U.S. Intergroup study results, one cannot conclude that R-CHOP-14 is superior to standard R-CHOP-21, given all the caveats of interstudy comparisons. The MabThera International Trial studied the benefit of rituximab with CHOP-based treatment in younger patients (≤60 years) with favorable characteristics defined as low IPI risk; furthermore, nearly half of patients received involved field radiotherapy.[214] Similarly to the other randomized rituximab studies, patients who received rituximab fared significantly better with a 3-year EFS rate of 79%. As an interesting aside, the MabThera International Trial study also showed that rituximab obviated the benefit of CHOEP in younger patients.[214]

Rituximab has also been tested in combination with the DA-EPOCH regimen.[215] In a recent report of 72 patients, 82% and 79% of patients were progression free and alive, respectively, at the median follow-up of 43 months. Furthermore, 93% and 64% of patients in the low and high IPI risk groups, respectively, had not progressed. While one must be cautious in interpreting preliminary results, it should be noted that these findings are consistent with a recent phase II trial of DA-EPOCH-R in which 91% and 45% of patients with high-intermediate and high IPI, respectively, were event free at 2 years.[216] Evaluation of DA-EPOCH-R versus R-CHOP in untreated DLBCL is currently ongoing in the Cancer and Leukemia Group B Cooperative Group in conjunction with microarray analysis.

While it is clear that rituximab has significantly improved the overall outcome of DLBCL, several studies suggest that its benefit is limited by tumor pathobiology.[217–219] Two studies found that rituximab's benefit was primarily in bcl-2-positive DLBCL, while another study showed that benefit was limited to bcl-6-negative DLBCL (Fig. 112-7).[217–219] These biomarkers likely relate to the new molecular taxonomy of DLBCL defined by gene profiling and suggest that rituximab might primarily benefit tumors that are derived from a postgerminal center B cell.[27,66,220] It appears that patients with both the germinal center B and activated B genetic subtypes benefit from rituximab.[221] At this point, though, it is not possible to accurately identify who will most benefit from rituximab, and further progress is critical to help identify new strategies and molecular targets for patients who do not benefit from rituximab.

The role of high-dose chemotherapy and ASCT in the initial treatment of DLBCL remains controversial.[71,222] Although some studies have suggested benefit, they were performed in the pre-rituximab era.[107] ASCT is also associated with late toxicities,

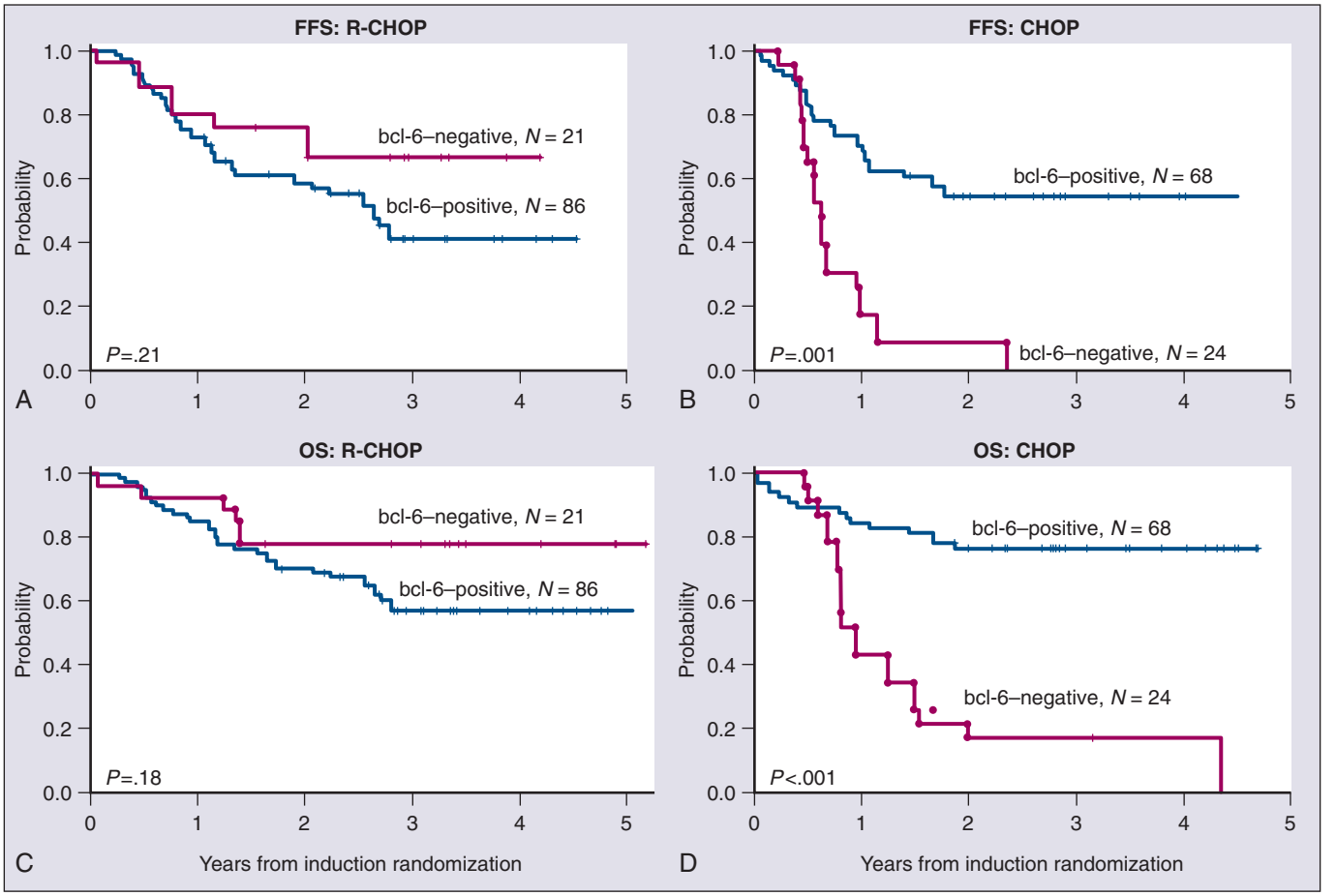


Figure 112-7 • Failure-free survival (FFS) and overall survival (OS) probabilities of R-CHOP versus CHOP according to bcl-6 expression in elderly patients with diffuse large B-cell lymphoma. **A,** FFS of R-CHOP. **B,** FFS of CHOP. **C,** OS of R-CHOP. **D,** OS of CHOP. Significantly longer FFS (54% versus 9%, $P < 0.001$) and OS (77% versus 17%, $P < 0.001$) were observed for bcl-6-positive patients who received CHOP, whereas neither FFS (58% versus 76%, $P = 0.2$) nor OS (71% versus 79%, $P = 0.2$) was influenced by bcl-6 status in patients who received R-CHOP. (Data from Winter JN, Weller EA, Horning SJ, et al: Prognostic significance of Bcl-6 protein expression in DLBCL treated with CHOP or R-CHOP: a prospective correlative study. Blood 2006;107:4207–4213.)

including leukemia and secondary myelodysplasia, which must be considered in the risk benefit of treatment.[223]

Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) is a rare and highly aggressive lymphoma that is confined to the CNS and is usually of diffuse large B-cell histology. Its unique radiographic findings present challenges in evaluation that have been recently addressed in a report of an international workshop to standardize criteria for baseline evaluation and response.[224] The incidence of PCNSL is particularly high in the setting of HIV infection, in which it often presents with multifocal disease and is virtually always associated with EBV. In contrast, PCNSL in HIV-negative patients often presents with solitary intracranial masses and is rarely associated with EBV.

Treatment of PCNSL differs from that of systemic DLBCL because many chemotherapy agents do not adequately penetrate the blood-brain barrier. Radiotherapy has been a mainstay of treatment because it is effective and sidesteps the limitations of chemotherapy, but responses are usually short-lived, and virtually all patients relapse. High-dose methotrexate on the other hand is a cytotoxic with good CNS penetration, but when used alone, PFS is a relatively short 7 months.[225] A logical step was to combine high-dose methotrexate followed by whole-brain radiotherapy and produced an impressive 82% to 88% CR and median PFS rates of 32 to 40 months.[225–227] Unfortunately, such combined-modality treatment is associated with severe long-term neurotoxicity.[225,228] For this reason, there has been much interest in developing regimens that obviate or defer the need for radiation until relapse. Most promising in this regard are combinations of high-dose methotrexate with systemic agents that cross the blood-brain barrier, such as cytarabine, vincristine, and ifosfamide, particularly in patients under 60 years of age.[228] The Bonn group and others have adopted such an approach and have reported promising results with chemotherapy and deferred radiation in younger patients.[229,230] These results require further validation in trials. Studies are also addressing the role of immunochemotherapy with rituximab and other novel agents that promise to further improve the outcome of PCNSL.[231]

Burkitt's Lymphoma

BL mostly occurs in the first two decades of life and accounts for some 2% of all lymphomas.[23] BL is highly aggressive, as reflected by its 100% tumor proliferation by MIB-1 immunohistochemistry and high spontaneous apoptosis, which accounts for its "starry sky" appearance. Biologically, BL is derived from a germinal center B cell, as indicated by its CD20-positive, CD10-positive, and TdT-negative immunohistochemical profile and gene expression profiling.[232] Three clinical variants are recognized: endemic BL, which is found primarily in equatorial Africa; sporadic BL, which presents worldwide but is the most common type in Western countries; and immunodeficiency-associated BL, which is associated with HIV infection (Table 112-11). There are important clinical differences in these variants. Endemic BL typically presents with jaw and facial bone disease and is virtually always associated with EBV. Sporadic BL usually presents with ileocecal disease and is associated with EBV in 30% to 50% of cases. Immunodeficiency-associated BL usually occurs in HIV-positive populations and is associated with nodal disease and is variably associated with EBV. BL may be associated with CNS involvement, particularly when there is bulky or disseminated disease. Rare cases present as acute leukemia and are included in the French-American-British classification.[23]

BL requires chemotherapy for all disease stages. Several biologic characteristics of BL have helped to guide treatment strategies, including its high proliferative fraction. The high tumor proliferation rate led to the use of dose-intense regimens with a short cycle time to theoretically minimize tumor regrowth between cycles.[233,234] Multiple drugs, typically administered in alternating combinations, are employed, and the high rate of spread to the CNS has led to the standard use of CNS prophylaxis.[15] A variety of dose-intense short-duration regimens have achieved durable complete remissions in 47% to 84% of patients (Table 112-12).[235–238] Included in these are the French LMB and German Berlin-Frankfurt-Munster protocols and the National Cancer Institute CODOX-M/IVAC regimen. These regimens are similar in their drug composition, short cycle length, and CNS prophylaxis. Though most BLs occur in children, Magrath and colleagues demonstrated that adults and children have a similar disease outcome when treated with the same regimen.[233] Toxicity is an important clinical limitation of these regimens in adults, particularly in older patients, in whom severe morbidity and even mortality occur. Therefore, one of the major therapeutic challenges in BL is to develop therapies that are as effective in achieving high cure rates as "standard" regimens but that improve the therapeutic index and reduce toxicity complications. This approach is being investigated in a pilot study of DA-EPOCH-R. On the basis of studies in DLBCL that suggested that DA-EPOCH overcomes the adverse effect of high proliferation, likely owing to its infusional schedule, it appeared to be a good candidate to test in adult BL.[199] Indeed, preliminary results in 17 patients with BL showed EFS and OS rates of 92% and 100%, respectively, at a median follow-up of 28 months, with low toxicity compared to conventional regimens.[199,201]

Table 112-11 Comparison of Endemic, Sporadic, and HIV-Associated Burkitt's Lymphoma

	Endemic	Sporadic	HIV-Associated
Epidemiology	Equatorial Africa and Papua, New Guinea. Geographic association with malaria.	United States and Europe	United States and Europe
Incidence	5–10 cases per 100,000	2–3 cases per million	6 per 1000 AIDS cases
Age and gender	Malignancy of childhood Peak incidence: 4–7 years Male:female ratio:2: 1	Malignancy of childhood and young adults. Median age: 30 years Male : female ratio: 2–3 : 1	Malignancy of adults; associated with higher CD4 counts (>100/mm^3)
Clinical presentation	Jaw and facial bones in ≈50%. Also involves mesentery and gonads. Increased risk of CNS dissemination.	Abdomen most common presentation often involving the ileocecal region. Other extranodal sites include bone marrow, ovaries, kidneys, and breasts. Increased risk of CNS dissemination.	Nodal presentation most common, with occasional bone marrow. Increased risk of CNS dissemination.

CNS, central nervous system.

Table 112-12 Selected Regimens for Burkitt's Lymphoma

Therapy	No. of Patients	Histology (Number)	Median Age in Years (Range)	Stage	EFS Rate	OS Rate
LMB 89	561	Burkitt's and L3 ALL (420)	8 (0.17–18)	III–IV: 79%	92% at 5 years	92% at 5 years
BFM 90	413	Burkitt's and L3 ALL (322)	9 (1.2–17.9)	III–IV: 60%	89% at 6 years	14 deaths
CODOX-M/IVAC	21 children, 20 adult	Burkitt's	12 (3–17) 25 (18–59)	III–IV: 78%	85% (children) and 100% (adults) at 2 years	2 deaths
CODOX-M/IVAC	52	Burkitt's	35 (15–60)	III–IV: 61%	65% at 2 years	73% at 2 years
Hyper-CVAD	26	L3 ALL	58 (17–79)	N/A	61% at 3 years for disease-free survival	49% at 3 years

EFS, event-free survival; OS, overall survival.

Mantle Cell Lymphoma

MCL is a relatively rare B-cell lymphoma that comprises some 3% of all lymphomas and has a median age of 60 years and male predominance.[20] Its pathobiology is characterized by dysregulation of the cell cycle, with almost all cases showing the t(11;14) translocation and overexpression of cyclin D1 (bcl-1). Hence, immunohistochemical detection of cyclin D1 along with CD20 and CD5 is virtually diagnostic of MCL.[23] The biologic importance of cell cycle dysregulation in MCL was elegantly demonstrated by gene expression profiling in which the tumor proliferation signature was the best molecular predictor of survival.[67]

Most patients present with advanced-stage disease and, on the basis of historical series, have a median survival of 3 to 5 years. While OS appears to be improving with the development of more effective therapies, cure remains elusive for most patients.[75] Treatment approaches are constrained by the older median age of patients with MCL, more aggressive regimens often being preferred in younger patients. One of the more promising and aggressive regimens for MCL is fractionated cyclophosphamide administered with doxorubicin, vincristine, and dexamethasone (hyper-CVAD) alternating with high-dose methotrexate and cytarabine.[239] In an initial phase II study of 45 previously treated and untreated patients, 38% achieved CR, with an overall response of 94%; of these patients, 29 went on to receive ASCT consolidation.[239] Among the 25 previously untreated patients, EFS and OS rates at 3 years were 72% and 92%, respectively, which appeared significantly better than historical outcomes with CHOP-based treatment.[240] Recently, a study of hyper-CVAD with rituximab alternating with high-dose methotrexate and cytarabine was reported in untreated MCL.[241] In this study, 87% of patients achieved CR, and at 3 years, 64% were failure free. Though the regimen was effective, the unacceptable toxicity in older patients led the authors to recommend it only in patients under 66 years of age. Other studies have shown that the addition of rituximab to CHOP improves response rates and time to treatment failure but not survival.[242,243] The DA-EPOCH-R regimen has also shown good efficacy in untreated MCL, 93% of patients achieving CR, but as in other studies, most patients ultimately relapse.[244]

There has been much interest in investigating the role of high-dose chemotherapy and ASCT in MCL, and several phase II studies have showed promising results.[245–248] While a number of these studies have shown excellent EFS and OS, patient selection is by necessity biased, and there is no convincing plateau on their Kaplan-Meier curves. Even in the absence of significant cures, it is possible that ASCT might prolong survival, but this can be judged only in the context of a randomized study. Allogeneic stem cell transplantation, frequently of the reduced-intensity variety, has also been investigated in MCL.[249] In one study of 18 patients, 17 achieved CR, and there were only 3 progressions with 26 months' median follow-up.[249] The 3-year EFS rate of 82% suggests that a graft-versus-lymphoma effect plays an important role.

Recently, the proteasome inhibitor bortezomib has shown promising activity in patients with relapsed or refractory MCL. After demonstrating activity in two small phase II studies, a large multicenter study reported a response rate of 33% with 8% CR in relapsed or refractory MCL.[250–252] The mTOR inhibitor temsirolimus has also shown interesting results with a response rate of 38%.[253] A small phase II study also reported a favorable response rate of 90% for the combination of rituximab and thalidomide.[254] Combinations of bortezomib and chemotherapy are being investigated in MCL, and it is likely that in the near future, other novel agents will find their way into clinical trials for untreated patients.

Epstein Barr Virus–Associated Lymphoproliferative Disorders

The loss of adequate EBV immune surveillance underlies the pathobiology of virtually all EBV-associated lymphoproliferative disorders (LPDs).[3] It is useful to consider the origin of the immune suppression as it affects disease biology and treatment. The most commonly recognized diseases are associated with iatrogenic immunosuppression, as exemplified by PTLD and methotrexate-associated LPD.[255,256] Diseases associated with acquired immunosuppression are heterogeneous and include senile EBV-positive B-cell LPD and lymphomatoid granulomatosis.[257–259] Congenital immunodeficiencies make up the last group and include such entities as Wiskott-Aldrich syndrome and X-linked severe combined immunodeficiency, which are associated with EBV-related LPDs.[3]

PTLD encompasses a broad spectrum of diseases that occur in the setting of allogeneic hematologic and solid organ transplantation; as a group, they show considerable heterogeneity.[256,258] PTLD is classically approached by withdrawal of immunosuppression, provided that the possibility of organ rejection is not life threatening, often in conjunction with administration of rituximab. Chemotherapy, however, is frequently required, particularly in patients with monomorphic histology, in which the clone is usually immune independent.[260] EBV-positive LPD arising in the setting of chronic immune suppression with methotrexate can also respond to withdrawal of the offending agent, although most cases require chemotherapy.[255] Senile EBV-positive B-cell LPDs are increasingly being recognized and are postulated to arise in the setting of age-related waning of EBV immune surveillance.[257] In general, they should be approached like other aggressive lymphomas while recognizing that highly localized disease with limited involvement by EBV-positive large B-cells may be self-limited. Lymphomatoid granulomatosis is a rare EBV-

associated LPD that primarily occurs in otherwise healthy patients who, on examination, have evidence of immune deficiency.[258,259] Lymphomatoid granulomatosis virtually always involves extranodal sites and can be treated with interferon or immunochemotherapy, depending on the grade of disease.[258]

AIDS-Related Lymphomas

In the setting of HIV infection, several distinct subtypes of NHL are encountered with varying frequencies. While the overall increased risk of NHL is greater than 100-fold, the incidence of PCNSL is increased 3600-fold and that of BL is increased 1000-fold when compared to HIV-negative populations.[23,261–263] Though they are not AIDS-defining illnesses, the relative risk of other lymphoid neoplasms such as Hodgkin's lymphoma, extranodal marginal zone lymphoma, and certain T-cell lymphomas also appear to be increased in the setting of HIV infection.[264–267] The incidence of various systemic lymphoma subtypes is associated with CD4 cell count. Patients with severe CD4 cell depletion tend to develop the immunoblastic and plasmablastic subtypes, which have a poor prognosis, whereas patients with higher CD4 cell counts tend to develop centroblastic DLBCL and BL.[13,23,268,269] Hence, the decline in patients with low CD4 cell counts in the post–highly active antiretroviral therapy (HAART) era is likely to lead to a shift in histologic subtypes.[13,270–272]

The pathogenesis of AIDS-related lymphomas (ARLs) involves a complex interplay of factors and mechanisms. Among these are CD4-dependent immunodeficiency, chronic antigen stimulation, coinfecting oncogenic viruses such as EBV and HHV8 (also known as Kaposi's sarcoma herpesvirus), cytokine dysregulation, and genetic abnormalities. Most ARLs are of B-cell lineage and, being monoclonal, harbor clonal rearrangement of immunoglobulin genes. Occasional T-cell lymphomas are observed and would have T-cell receptor gene rearrangements.[23,273]

The introduction of HAART in the mid-1990s had a dramatic and positive impact on the outcome of ARL. A comparison of median survival of the pre- and post-HAART eras showed a significant increase from 6.3 months to 21.2 months. Although the reasons for this are multifaceted, they can ultimately be attributed to salutary effects on CD4 cell counts. It was thus clinically predictable that the overall rise in CD4 cell count would improve ARL outcome on the basis of the well-established association between poor outcome and low CD4 cell count.[271,274] Of course, patients with better immune function have a lower risk of infectious complications, thereby enabling chemotherapy administration and reducing infectious deaths. Perhaps most important, however, is the more favorable biology that is associated with lymphomas that occur in patients with higher CD4 cells counts.[13,271]

These findings led to the assumption that HAART during chemotherapy would be beneficial. One of the first trials to investigate the concomitant use of HAART with chemotherapy was performed by the AIDS Malignancy Consortium, in which patients received either modified (m)-dose (50% lower cyclophosphamide and doxorubicin) or standard CHOP chemotherapy.[275] This was not randomized, as the initial 40 patients received modified-dose CHOP and the subsequent 25 patients received CHOP. All patients received a HAART regimen consisting of stavudine, lamivudine, and indinavir. In this study, mCHOP and CHOP had similar toxicity, and both were reasonably well tolerated, providing some assurance for the safety of HAART with CHOP chemotherapy. Perhaps not unexpectedly, patients who received CHOP had a somewhat better outcome than did those who received modified-dose CHOP, but in the absence of a randomized design, the authors could conclude only that the regimens were active and tolerable. A potentially important finding of the study comes from the pharmacokinetic analysis, which showed that cyclophosphamide clearance was reduced 1.5-fold, which will likely result in a reduction of active metabolites and potentially compromise efficacy.[277]

The combination of HAART and infusional CDE (cyclophosphamide, doxorubicin, and etoposide) therapy has also been assessed.[276] Sparano and colleagues evaluated CDE in 43 patients who received concurrent didanosine and 55 patients who received concurrent HAART.[277] Hematologic and nonhematologic toxicity were lower and OS was higher in the CDE-HAART group, providing additional evidence for the safety of HAART and chemotherapy treatment. Of note, in a prior study, Sparano and colleagues had shown that in comparison to CDE alone, the administration of concurrent didanosine resulted in an 11% to 38% reduction in mean steady-state plasma etoposide concentrations and lower hematologic toxicity.[278]

It is prudent to carefully consider the role of concomitant HAART during chemotherapy treatment. While studies show that HAART does not excessively increase the toxicity of chemotherapy, there is no direct evidence that it improves outcome. The argument that control of HIV viral replication by HAART during chemotherapy benefits immune function is sound but should be considered in light of several factors. Perhaps of foremost concern is the potential for adverse pharmacokinetic and pharmacodynamic interactions related to hepatic metabolism and/or the multidrug-resistant pumps.[279] HAART drugs may decrease active cyclophosphamide metabolites and etoposide which could compromise outcome. This is particularly worrisome for infusional-based regimens such as CDE and EPOCH, in which threshold concentrations are of importance.[280] Furthermore, HAART drugs may inhibit multidrug resistance and increase hematologic toxicity and decrease dose-intensity, while conferring no benefit on tumor sensitivity.[281] Of unknown significance are the inhibitory effects of some antiretroviral drugs on lymphoid cell apoptosis, which theoretically could antagonize chemotherapy effects.[282,283] It is also possible that HAART compliance could be compromised by chemotherapy and promote the emergence of HIV viral mutations.

On the basis of such considerations, the National Cancer Institute investigated the effects of suspension of antiretroviral treatment during all courses of DA-EPOCH in 39 patients.[271] Following antiretroviral suspension during DA-EPOCH, the viral loads increased a median of 0.83 $\log_{10}$, and after restarting antiretroviral treatment, the viral loads declined −0.61 $\log_{10}$, below baseline. CD4 cells declined during chemotherapy treatment by a median of 189 cells/μL but recovered to baseline by 6 to 12 months following reinstitution of antiretroviral therapy. New opportunistic infections were only observed in five patients, all following DA-EPOCH completion. The treatment strategy appeared quite effective, with complete remissions in 74% of patients; and at a median follow-up time of 53 months, disease-free and OS rates were 92% and 60%, respectively (Fig. 112-8). Indeed, the salutary effects of HAART on immune function have led to the belief that this benefit exceeds any potential adverse effects on tumor control. Unfortunately, prospective studies have yet to address this potentially important question.

The finding that the addition of rituximab to CHOP chemotherapy significantly improves the survival of HIV-negative patients with DLBCL led to its testing in untreated ARL.[210] Pooled results from three phase II studies of rituximab and CDE in ARL have been recently reported.[284] In this study of 74 patients, 70% achieved complete remission, and at the median follow-up of approximately 2 years, the estimated failure-free and OS rates were 59% and 64%, respectively. New opportunistic infections during or within 3 months of treatment occurred in 14% of patients, and death from infection occurred in 8% of patients. While the good survival outcomes suggest that rituximab conferred a benefit compared to CDE alone, the favorable effects associated with the post-HAART era on survival cannot be discounted.[277]

To help address the role of rituximab, Kaplan and colleagues performed a multicenter randomized phase III trial of CHOP with or without rituximab in untreated ARL patients with concomitant HAART administration.[285] In this trial of 150 patients, disease control was significantly better in patients who received R-CHOP,

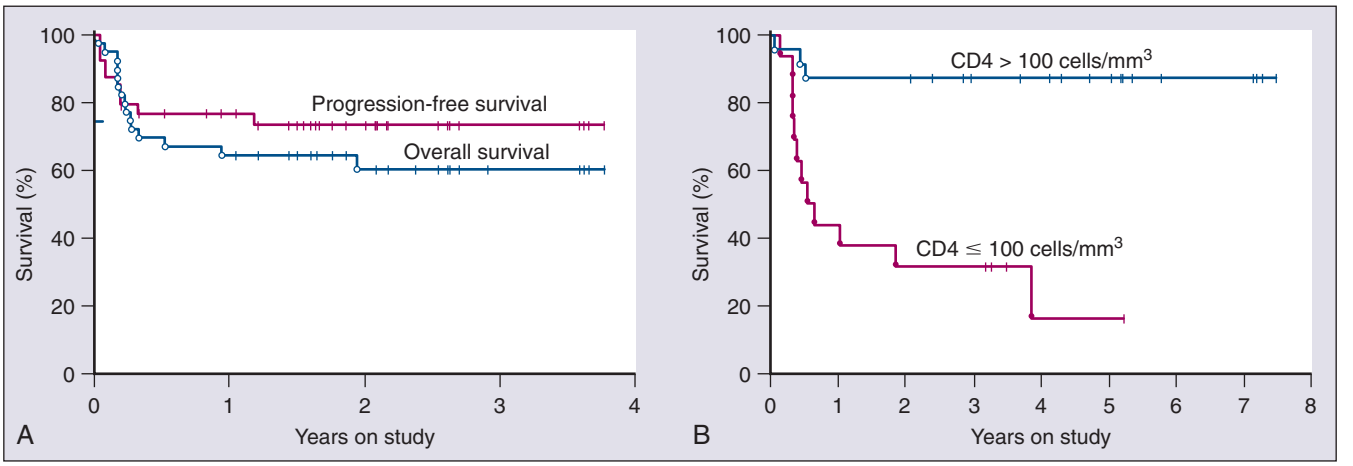


Figure 112-8 • Progression-free and overall survival rates of EPOCH in AIDS-related lymphomas. **A,** Overall and progression-free survival rates of 39 patients with AIDS-related lymphomas. At a median potential follow-up of 53 months, the overall survival probability is 60%, and the progression-free survival probability is 73%. **B,** Overall survival of 16 patients with low CD4-positive cells and 23 patients with high CD4-positive cells (≤100/mm^3 and >100/mm^3, respectively). At 53 months, the overall survival rates are 16% and 87%, respectively. (Data from Little RF, Pittaluga S, Grant N, et al: Highly effective treatment of acquired immunodeficiency syndrome-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. Blood 2003;101:4653–4659.)

with lower progression on treatment ($P_2 = 0.02$; chi-square test) and death due to lymphoma ($P_2 = 0.02$; chi-squared test).[286] However, because there was no difference in OS or EFS, owing to increased infectious deaths in patients receiving R-CHOP, the authors concluded that rituximab does not improve clinical outcome in ARL. It should not escape attention that most treatment-related infectious deaths occurred in patients with low CD4 cell numbers, a group that was enriched with tumors of ABC type and most likely to benefit from rituximab.[13,69,271] Employing a somewhat different strategy, the National Cancer Institute is investigating the outcome of a short course (SC) of EPOCH with dose-dense rituximab (375 mg/m^2 on days 1 and 5) (SC-EPOCH-R) to reduce treatment-related toxicity. In this study, patients with untreated ARL receive one cycle beyond maximum response, with a minimum of three cycles, compared to six cycles with dose-adjusted (DA) EPOCH alone.[271,287] Preliminary results in 26 patients revealed a PFS rate of 79% and an OS rate of 74% at the 29-month median follow-up. Notably, patients received a median of three treatment cycles, compared to six cycles on the prior DA-EPOCH trial.

While the role of rituximab requires further investigation, these trials suggest that rituximab is of benefit in ARL. To help further define the role of rituximab, the AIDS Malignancy Consortium is currently performing a randomized phase II trial comparing DA-EPOCH-R to DA-EPOCH alone followed by sequential rituximab in responding patients. At the current time, however, we believe it unwise to omit rituximab from the treatment of ARL and hasten to add that while treatment-related infectious deaths can be ameliorated with careful medical attention, disease progression cannot.

Although there has been an improvement in the collective outcome of HIV-associated lymphomas since HAART, a recent study indicates no improvement in the BL subtype.[288–290] These results raise the possibility that the overall improvement in outcome of HIV-associated lymphomas in the HAART era could be primarily attributable to the better outcome of DLBCL, the most common histologic subtype. This does not seem to be the case in BL, which occurs at a high median CD4 cell count and has not shown widely variable pathobiology.[232] The relatively poor outcome of HIV-associated BL might be due to the use of CHOP-based regimens, which are known to have a poor outcome in this disease.[15,232] Dose-intense regimens, such as hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine) have shown encouraging results in HIV-associated BL, with a CR rate of 92%, but are often quite toxic.[291] Involvement of the CNS by BL may also contribute to reduced survival and highlights the need for CNS prophylaxis.[271]

BL, as an important example, highlights the necessity to balance treatment efficacy and toxicity in patients with HIV infection. Dose-intense Burkitt's lymphoma regimens have been considered too toxic to warrant their general use in HIV positive patients. This has led to the use of CHOP-based treatment with an associated relatively poor outcome. It is worth noting, in this regard, that we are studying the DA-EPOCH-R regimen in BL on the basis of its good activity in highly proliferative DLBCL.[199] Among 11 HIV-negative untreated patients with BL who were treated with DA-EPOCH-R, we have observed a CR rate and OS of 100% at the median follow-up of 31 months (unpublished observations). Such results suggest that DA-EPOCH-R might be an excellent and well-tolerated alternative to dose-intense regimens for BL in HIV-positive patients.

Treatment of Relapsed Aggressive B-Cell Lymphomas

The salvage treatment of relapsed aggressive lymphomas should be approached in an individual manner, as the choice of treatment is influenced by the time to recurrence, prior therapy, medical condition, and the potential for cure. Although most relapsed aggressive lymphomas require combination chemotherapy for adequate disease control, it is important to recognize that patients with local disease can be salvaged with radiation therapy. Examples include primary mediastinal DLBCL, which can remain local even at relapse, and PTLD, which may have an isolated resistant EBV clone following chemotherapy.[292]

There are a variety of active salvage chemotherapy regimens for relapsed or refractory DLBCL (Table 112-13).[293–299] Platinum-containing regimens, such as ESHAP and ICE, are currently among the most widely used types of salvage treatment.[295,297,300] It is a commonly held notion that salvage treatment should include different agents from past treatment to avoid drug resistance. However, recent evidence indicates that sensitivity to apoptosis is a central cause of drug resistance and that drug-specific mechanisms are less important.[27,281] Hence, salvage regimens that were developed around the most active up-front agents should show high activity.[301] This concept was tested with EPOCH chemotherapy in patients who had failed after receiving similar drugs on a bolus schedule.[301] In this study of 67 patients with relapsed or refractory de novo aggressive lymphoma, 70% responded, with a 36% CR rate. The addition of rituximab appears to enhance the activity of salvage regimens as demonstrated by results

Table 112-13 Treatment Outcomes in Relapsed Lymphoma

Therapy	Patient Group	CR Rate	OR Rate	OS Rate	Reference
DHAP	Relapsed or refractory lymphoma	31%	58%	25% at 2 years	Velasquez et al[298]
ESHAP	Relapsed or refractory lymphoma	37%	70%	31% at 3 years	Velasquez et al[299]
EPOCH	Relapsed or refractory DLBCL	36%	70%	30% at 6 years	Guiterrez et al[301]
R-ICE	Relapsed or refractory DLBCL	53%	88%	—	Kewalramani et al[295]

CR, complete response; DHAP: dexamethasone, cytarabine, and cisplatin; ESHAP: etoposide, methyl-prednisone, cytarabine, and cisplatin; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; OR, overall response; OS, overall survival; R-ICE: rituximab, ifosfamide, carboplatin, and etoposide.

with R-ICE and ICE, which showed a CR rate of 53% and 27%, respectively.[295,300]

Patients with chemotherapy-sensitive disease have the best outcome with ASCT, and it is recommended at initial relapse; it has yielded OS and EFS rates in the range of 40% to 50% and 30% to 40%, respectively.[295,302] ASCT rarely achieves cure in BL and lymphoblastic lymphoma but is often successful in ALK-positive anaplastic large cell lymphoma (ALCL). Lymphomas that are rarely cured with initial treatment, such as MCL and PTCL, are less likely to benefit from ASCT. It is important to consider, in assessing the outcome of ASCT, that improvements in up-front therapy from rituximab has biased the relapsed population toward greater resistance. The incorporation of rituximab or radioimmunoconjugate into conditioning regimens can also enhance the benefit of ASCT, thus pointing out the importance of controlled ASCT trials in the post-rituximab era.[295,302] Of course, patients with chemotherapy-resistant disease do poorly with ASCT and should be considered for experimental treatments such as allogeneic SCT.

Lymphomas of T/NK Cell Origin

Lymphomas of T/NK cells are relatively uncommon and account for approximately 15% of all NHLs.[23,303] They are distributed over at least 14 different subtypes, all of which are infrequent and not well studied. Tumor types that have an identifiable clinical-pathobiology are classified by name, whereas the other cases are simply described as peripheral T-cell lymphoma unspecified ($PTCL_{us}$), which by design is a heterogeneous group. Generally, T/NK cell lymphomas are clinically aggressive, though some can behave quite indolently, and unlike their aggressive B-cell cousins, most are incurable. Important exceptions to cure include ALCL and early-stage T/NK cell, nasal-type lymphoma.

To help refine the outcome of aggressive T/NK and B-cell lymphomas in the international arena, the Non-Hodgkin's Lymphoma Classification Project examined all newly diagnosed cases of lymphoma over a 2-year period from multiple international centers.[304] A survival analysis predictably demonstrated a poor outcome of $PTCL_{us}$ compared to DLBCL. Similar to DLBCL, the IPI was predictive of outcome in $PTCL_{us}$, and at 5 years, only a little over one quarter of low-IPI patients were alive without disease. This is in contrast to the anaplastic ALCL subtype, in which 80% of patients were alive at 5 years irrespective of the IPI score. Three large series of PTCL patients who were treated with CHOP-based therapy have been reported (Fig. 112-9).[305–307] The overall CR rate varied from 49% to 65%, and in all series, ALCL had a favorable outcome. Like the NHL Classification Project, IPI score predicted outcome with 5-year survival rate of 60% to 80% in low (0 to 1), 20% in intermediate (2 to 3) and 0% in high (4 to 5) IPI patients.[308]

Anaplastic Large Cell Lymphoma

ALCL is a CD30 positive T-cell lymphoma with an excellent prognosis ,and unlike the other PTCLs, it is highly curative. It typically occurs in children and young adults and makes up approximately 3% of all lymphomas in adults. In some 80% of cases, ALCL is associated with the t(2;5)(p23;q35) translocation, resulting in expression of the nucleophosmin anaplastic lymphoma kinase (ALK).[309] While ALK-positive ALCL has a significantly better prognosis than do ALK-negative cases, patients with ALK-negative disease should still be approached with curative intent.[309] In adults, CHOP-based therapy is considered the standard of care and produces durable remissions in approximately 65% of ALK-positive ALCLs and 35% of ALK-negative ALCLs (Fig. 112-10).[310]

Extranodal T/NK-Cell Lymphoma, Nasal Type

This is a rare extranodal lymphoma characterized by a broad morphologic spectrum. It is more prevalent in Asia and Central and South America and is almost always associated with EBV.[20] It has a predilection for the nasal cavity, nasopharynx, palate, skin, gastrointestinal tract, and testis. Hemophagocytic syndrome is a devastating event associated with this tumor type.[311] Disease outside the nasal cavity is usually highly aggressive and associated with a poor prognosis. Because of its rarity and lack of prospective clinical trials, optimal therapy has not been defined. However, disease that is localized to the nasal cavity is quite curative with radiotherapy, though the benefit of chemotherapy in this setting has yet to be defined.[312]

Angioimmunoblastic T-Cell Lymphoma

Angioimmunoblastic T-cell lymphoma is T-cell lymphoma that is characterized by systemic symptoms, skin rash, organomegaly, hypergammaglobulinemia and hemolytic anemia. It most commonly afflicts older patients and frequently presents with peripheral lymphadenopathy, hepatosplenomegaly, skin rash, and constitutional symptoms, which distinguish it from other peripheral T-cell lymphomas.[313] Patients often exhibit some degree of immunodeficiency, polyclonal hypergammaglobulinemia, and other hematologic abnormalities, which are likely related to abnormal immune regulation.[314] The neoplastic T cells appear to be of germinal center origin, known as follicular B helper T cells.[315,316] A prominent histologic feature of acute lymphoblastic leukemia is the near universal presence of EBV-positive B cells within the lesions.[317,318] Optimal therapy has not been defined for acute lymphoblastic leukemia, but anthracycline-based regimens and purine analogs have shown some efficacy.[313,319] Recently, novel approaches, such as the use of cyclosporine and antiangiogenesis therapies such as bevacizumab, have shown activity and warrant further investigation in the future.[320,321] Unfortunately, most patients succumb from infection or disease.

Hepatosplenic T-Cell Lymphoma

This extranodal T-cell lymphoma presents with marked hepatosplenomegaly and bone marrow involvement.[322] Most cases have a γδ T-cell receptor rearrangement that, if present in other PTCLs, portends a particularly poor prognosis.[23,323] The disease not uncommonly afflicts younger males and occurs with increased frequency in the setting of iatrogenic immune suppression.[324] Outcome is extremely poor and is characterized by rapid progression and death, although allogeneic transplantation has been associated with prolonged remission and potential cure.[325]

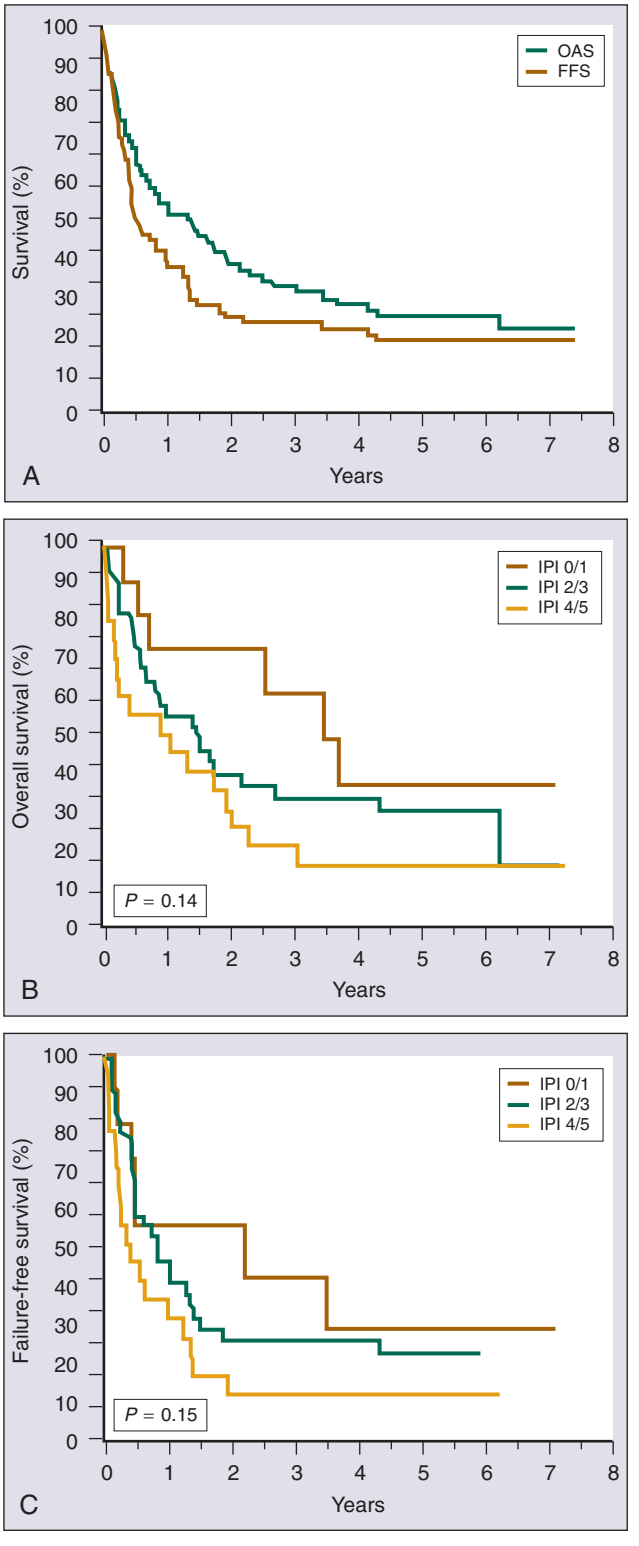


Figure 112-9 • Survival outcomes of peripheral T-cell lymphomas. **A,** Failure-free and overall survival rates. **B,** Overall survival rates by International Prognostic Index score. **C,** Failure-free survival rates by International Prognostic Index score.

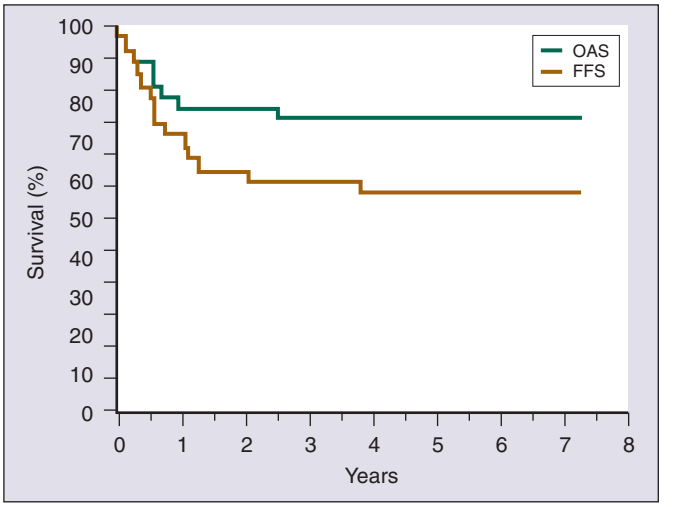


Figure 112-10 • Overall and failure-free survival rates for an unselected group of patients with anaplastic large T/null cell lymphoma.

Subcutaneous Panniculitis-like T-Cell Lymphoma

This rare lymphoma was first described in 1991.[326] Patients present with subcutaneous, sometimes painful, nodules that can ulcerate. Biopsies can be sometimes called atypical panniculitis. The hemophagocytic syndrome can be a fatal complication of this lymphoma. There is no standard treatment. Chemotherapy regimens often cause responses that are usually transient. Involved field radiotherapy is highly effective, but patients often relapse in unirradiated sites.[327,328]

Peripheral T-Cell Lymphoma, Unspecified

The poor outcome of $PTCL_{us}$ has prompted the search for new strategies and targeted agents. Purine analogs are associated with good response rates but are rarely curative.[329] Alemtuzumab, a monoclonal antibody that binds CD52, is expressed on most $PTCL_{us}$ and has shown a 36% response rate in one series of heavily pretreated patients. The success of immunochemotherapy in B-cell lymphomas has led to several ongoing studies of alemtuzumab and chemotherapy.[330] Other novel agents include dinileukin difititox and the histone deacetylase inhibitor depsipeptide.[331,332] While ASCT can provide some benefit, a recent report of a graft-versus-lymphoma effect in PTCL suggests that it might have curative potential.[333,334]

Precursor B-Cell and T-Cell Lymphoma

Precursor B-lymphoblastic and T-lymphoblastic lymphomas are highly aggressive diseases with primarily nodal presentations but are cytologically identical to acute lymphoblastic leukemia (see Chapter 103).[23] Precursor T-lymphoblastic lymphomas make up about 90% of lymphoblastic lymphomas and typically present in young males with a mediastinal mass and occasional involvement of the meningeal space. A variety of chemotherapy regimens have been used, including ACVBP, leukemia-based regimens, and ASCT.[335,336] A recent study published by the British Columbia Transplant Group reported an excellent outcome with induction chemotherapy followed by stem cell transplantation; in this study, 69% of patients were event free at 4 years.[336] An earlier German study evaluated an acute lymphoblastic leukemia–type regimen in 45 adult patients with T-lymphoblastic lymphoma and reported a 62% disease-free survival rate at 7 years.[337] These studies highlight the need for very aggressive therapies in these diseases.

Lymphoma in the Elderly

The incidence of lymphoma increases with advancing age, and the life span is lengthening; at least in the developed world, the

management of older patients with lymphoma is becoming an increasing problem. Regardless of the age cutoff that is used to define *elderly*, the challenge is predominantly that of contending with patients who are at high risk of comorbidity and have social circumstances that might complicate the overall management plan. Clearly, for patients with follicular lymphoma or the other lymphomas that have a relatively long clinical course, an expectant policy or minimal intervention becomes the most appropriate course. Brief treatments such as targeted irradiation are attractive in these circumstances, also for those with large B-cell lymphoma.

For elderly patients with lymphomas for whom prolonged survival is possible only if complete remission is achieved, philosophical as well as pragmatic issues come into play. It is gratifying that rituximab combined with CHOP has proved to be tolerable with a relatively low mortality rate in elderly patients who are being treated with curative intent and that the combination renders a significant proportion of patients disease free for prolonged periods. Data, presented so far only in abstract form, indicate that with the judicious use of growth factors, it is possible to administer CHOP at 14-day intervals instead of 21-day intervals and that this also results in improved outcome in the elderly. It remains to be determined whether the best standard of care at the beginning of twenty-first century will be CHOP-R or CHOP-14-R. Not surprisingly, there is inevitable selection of older patients into clinical trials. A high proportion of cases will, inevitably and appropriately, receive individualized therapy, a multitude of factors beyond the IPI coming into play.

LATE COMPLICATIONS OF TREATMENT

It is important to recognize that successful treatment can be associated with late complications that might not appear for decades. Among the major late-term complications are secondary malignancies, ischemic heart disease, anthracycline-related cardiotoxicity, and radiation- or bleomycin-induced pulmonary toxicity.[338] The risk of developing myelodysplastic disorders and acute myeloid leukemia is related to alkylator and topoisomerase inhibitor use and is enhanced by radiation. Radiation therapy increases the risk of malignancy in the treatment region and, in particular, breast cancer in women and lung cancer in smokers. Indeed, it is imperative to consider late-term toxicity in selecting treatment.

A general guideline for follow-up after initial therapy involves regular visits at decreasing intervals for the first 5 years and annually thereafter. During these visits, examination of the lymph node areas, abdomen, thyroid, and skin is important. It is important to note that CT scans are associated with a relatively high radiation exposure and projected risks and should not be used unnecessarily.[339] PET scans are not recommended for routine follow-up because the high rate of false-positive scans is unlikely to offset the value of early detection. Indeed, the role of PET scans in the overall treatment of lymphomas needs to be prospectively studied.[340] Routine laboratory studies with blood counts, liver function tests, and LDSH should be performed. Patients with disease in the chest can be followed with chest radiographs. The thyroid-stimulating hormone level should be monitored annually in patients who received neck radiotherapy. Mammography for women should begin 10 years from diagnosis of lymphoma or at age 40, whichever comes first. Patients should be immunized against influenza yearly and against *Streptococcus pneumoniae*.

ATYPICAL LYMPHOID PROLIFERATIONS SOMETIMES CONFUSED WITH LYMPHOMA

Not all examples of disordered lymphoid proliferation represent lymphomas. These clinicopathologic entities can present confusing clinical problems, however. These conditions include benign lymphoid proliferations that can be confused with either T- or B-cell lymphomas. To confuse the picture further, these latter entities sometimes evolve into lymphoma.

Of the atypical lymphoid proliferations that can be confused with lymphoma, the most common are processes referred to as reactive or atypical lymphoid hyperplasia. Patients with these disorders present with localized or disseminated lymphadenopathy associated with an underlying condition that might or might not be obvious. The patients sometimes have systemic symptoms, depending on the associated illness. Problems that can underlie this condition include drugs (e.g., dilantin and carbamazepine),[341] autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome),[342–345] viral infections (e.g., cytomegalovirus, EBV, and varicella-zoster virus), and bacterial infections (e.g., cat scratch disease). The distinction between these entities and malignant lymphoma is tremendously important. Lymphadenopathy in these patients rarely evolves into malignant lymphoma, and successful treatment of the underlying condition usually resolves the problem. When no explanation can be found for atypical lymphadenopathy, observation of the patient is appropriate. On occasion, subsequent biopsies will demonstrate lymphoma.

An unusual clinical entity that is variously known as Castleman's disease, angiofollicular lymph node hyperplasia, and giant lymph node hyperplasia can be confused with malignant lymphoma. First described in 1956,[346] this entity can present with localized or disseminated lymphadenopathy involving essentially all lymph node–bearing areas.[347] Lymphadenopathy is frequently accompanied by systemic symptoms such as fever, night sweats, or weight loss. The condition is found with increased frequency in patients infected with HIV-1.[348] Castleman's disease can be found in patients with POEMS syndrome.[349] Biopsy of an involved lymph node reveals one of two histologic patterns. The more common pattern involves lymph node effacement by small hyaline, vascular follicles and interfollicular capillary proliferation, while, in a few patients, the histologic pattern is large hyperplastic lymphoid follicles with intervening sheets of plasma cells.[350] The patients often have anemia and polyclonal hypergammaglobulinemia. It is now known that many of the manifestations of this disorder seem to be mediated by excessive production of the cytokine IL-6, and the symptoms of the disease can sometimes be ameliorated by administration of a monoclonal antibody against interleukin-6.[351] Patients with Castleman's disease can die of the disorder or of complications of therapy. Management is further complicated by the fact that some of these patients develop malignant lymphomas on follow-up. The successful management of patients who present with localized involvement can be accomplished with surgery or radiation therapy.[351] Patients with disseminated disease sometimes respond completely to therapy with glucocorticoids.[347] Symptomatic patients who do not respond completely are sometimes treated with chemotherapeutic agents in a manner similar to that used for malignant lymphoma. Successful treatment has been described with interferon,[352] monoclonal anti-IL-6 antibody,[353] rituximab,[354] autologous bone marrow transplantation,[355] and allogeneic bone marrow transplantation.[356] It should be remembered, however, that this disorder sometimes spontaneously remits, and a cause of death has been treatment-related complications.

Among the other unusual disorders that are associated with atypical lymphadenopathy is sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease). First described in 1969,[357] this entity usually presents with bulky lymphadenopathy but can have extranodal sites of involvement.[358] This disorder is most commonly seen in children or young adults. Biopsy reveals lymph nodes with a distorted architecture due to a thickened fibrous capsule, distension of the lymphoid sinuses by histiocytes, and infiltration of the node by plasma cells. The histiocytes in this disorder are morphologically characteristic. The disease is usually nonprogressive and self-limiting. Occasional cases have associated autoimmune hemolytic anemias that can be severe or even fatal but should be treated like other autoim-

mune hemolytic anemias. Surgery or radiation therapy can be utilized to manage symptomatic, bulky disease sites.

Lymphomatoid papulosis represents a clinically benign cutaneous LPD that is often confused with anaplastic large cell lymphoma involving the skin.[359] This is because the cells of lymphomatoid papulosis are atypical and stain for the Ki-1 (CD30) antigen. This is an extremely important distinction that can be effectively made only when the clinician and pathologist communicate.[360] The key to the diagnosis is an accurate history. Patients with lymphomatoid papulosis have waxing and waning skin lesions that usually heal, leaving small scars. Therapy that would be appropriate for malignant lymphoma is contraindicated and dangerous. The clinical picture is complicated by the fact that patients with lymphomatoid papulosis sometimes develop malignant lymphomas.

FUTURE DIRECTIONS

The last several years have witnessed an explosion of insight into the molecular biology of aggressive lymphomas, particularly B-cell diseases. Powerful techniques such as gene expression profiling, array-CGH, and RNAi have paved the way for the identification of new targets and the development of small molecule inhibitors. Indeed, a number of targeted agents have entered clinical trials and are showing promising activity.

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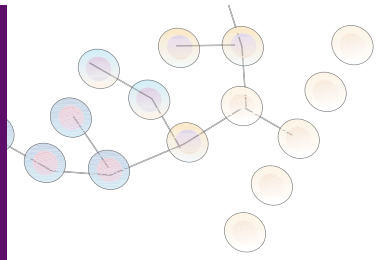
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113 Cutaneous T-Cell Lymphoma and Cutaneous B-Cell Lymphoma

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SUMMARY OF KEY POINTS

Incidence

- The estimated annual incidence of cutaneous T-cell lymphoma (CTCL) is 0.4 in 100,000 cases.
- Cutaneous B-cell non-Hodgkin's lymphoma (NHL) represents approximately 10% of all primary cutaneous lymphomas.
- The average age at presentation is 50 to 60 years, but CTCL has been reported in children and adolescents.

Differential Diagnosis CTCL

- The median lag time to diagnosis of CTCL is approximately 6 years.
- Premalignant disorders that may potentially evolve into CTCL include parapsoriasis, lymphomatoid papulosis, pre-Sézary syndrome, atypical dermatitis, and dermal reticulosis.
- Histologic and clinical variants of CTCL constitute 10% of the cases.
- CTCL must be further distinguished from adult T-cell leukemia/lymphoma, Ki-1$^+$ anaplastic large cell lymphoma, peripheral T-cell NHL, cutaneous B-cell lymphomas, T-cell chronic lymphocytic leukemia, leukemia cutis, cutaneous lymphoid hyperplasias, lymphomatoid contact reactions, and insect bites.

Staging Evaluation CTCL

- The initial evaluation of the patient with CTCL should include complete history, physical examination, and complete blood count (CBC) and differential to assess for the presence of disease in peripheral blood; chemistry studies; and chest radiography.
- The physical examination should determine the percentage of body surface area involved.
- Skin biopsy specimens must be obtained for routine histologic studies, immunohistochemistry analysis, and T-cell receptor gene rearrangement or polymerase chain reaction studies at the time of the initial diagnosis.

Natural History CTCL

- CTCL is an extranodal lymphoma, which may be indolent, as in mycosis fungoides, or aggressive, as in Sézary syndrome.
- Localized limited-stage disease is potentially curable. All other presentations are incurable.

Primary Therapy CTCL

- Current initial therapies for CTCL are tailored to extent, burden, and type of disease present and include use of emollients or topical corticosteroids, topical chemotherapy (nitrogen mustard, BCNU, bexarotene), phototherapy, psoralen–ultraviolet A (PUVA) therapy, electron beam irradiation, photon irradiation, extracorporeal photochemotherapy, chemotherapy, peripheral blood stem cell transplantation, and allogeneic transplantation.

Selective Second- and Third-Line Therapies CTCL

- Patients may respond to the same therapeutic modality on more than one occasion.
- Multiple other palliative management options are available as well.

INTRODUCTION

Primary cutaneous lymphomas represent the second most common extranodal site for NHL.[1] CTCL is a heterogeneous group of NHLs that represent about 80% of all primary cutaneous lymphomas. These disorders of malignant lymphocytes have a proclivity for the skin and epidermis. The diagnosis of CTCL is based on clinicopathologic criteria. This class of malignant lymphomas includes mycosis fungoides with variants and Sézary syndrome. In addition to these CTCLs, other malignant lymphoproliferative T-cell diseases that involve the skin include primary cutaneous CD30$^+$ lymphoproliferative disorders, peripheral T-cell lymphoma, adult T-cell leukemia/lymphoma, and others. CTCL forms a group of clinically diverse disorders that include cutaneous B-cell lymphomas (Table 113-1). Cutaneous lymphomas are distinguished on the basis of their clinical, histologic, immunologic, and molecular features. This chapter reviews the clinicopathologic features of and therapy for cutaneous lymphomas including mycosis fungoides, Sézary syndrome, and cutaneous B-cell lymphoma, as well as their variants and related disorders.

EPIDEMIOLOGY

The estimated annual incidence of mycosis fungoides and Sézary syndrome in the SEER (Surveillance, Epidemiology, and End Results) cancer registry was 1 per 100,000 population and in the well-defined population of Rochester, Minnesota, is 0.9 per 100,000 residents.[1,2] Epidemiologic data from the SEER program showed an increase in incidence of CTCL, from 0.2 case per 100,000 in 1973 to 0.4 case per 100,000 in 1984, with no increase from 1983 to 1994.[3,4] The incidence of cutaneous lymphoma increases with age. Most reported cases of CTCL are in adults. The average age at diagnosis is 50 to 60 years,[3] but cases have been reported in children and adolescents.[5] CTCL is more likely to develop in black populations.[3] Mycosis fungoides is the most common CTCL, representing 40% to 82% of new cases.[6]

Although environmental factors have been implicated in the pathogenesis of CTCL, two case-control studies have not supported the concept that industrial or related exposures cause the disease.[7] Furthermore, no significant differences were documented in

Table 113-1 WHO-EORTC Classification of Cutaneous Lymphomas with Primary Cutaneous Manifestations

CUTANEOUS T-CELL AND NK-CELL LYMPHOMAS
Mycosis fungoides
Mycosis fungoides variants and subtypes
Folliculotropic mycosis fungoides
Pagetoid reticulosis
Granulomatous slack skin
Sézary syndrome
Adult T-cell leukemia/lymphoma
Primary cutaneous $CD30^+$ lymphoproliferative disorders
Subcutaneous panniculitis-like T-cell lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Primary cutaneous peripheral T-cell lymphoma, unspecified
Primary cutaneous aggressive epidermotropic $CD8^+$ T-cell lymphoma (provisional)
Cutaneous gamma/delta T-cell lymphoma (provisonal)
Primary cutaneous $CD4^+$ small/medium-sized pleomorphic T-cell lymphoma (provisional)
CUTANEOUS B-CELL LYMPHOMAS
Primary cutaneous marginal zone B-cell lymphoma
Primary cutaneous follicle center lymphoma
Primary cutaneous diffuse large B-cell lymphoma, leg type
Primary cutaneous diffuse large B-cell lyphoma, other
Intravascular large B-cell lymphoma
PRECURSOR HEMATOLOGIC NEOPLASM
$CD4^+/CD56^+$ hematodermic neoplasm (blastic NK-cell lymphoma)

NK, natural killer; WHO-EORTC, World Health Organization–European Organization for Research and Treatment of Cancer.

From Willemze R, Jaffe ES, Burg G, et al: WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768–3785.

cutaneous allergy to plants, metals, and cosmetics or in reactions to medications, foods, or insect bites between cases of mycosis fungoides and controls, indicating that in most cases prolonged exposure to contact allergens is not related to the development of CTCL.[7] In selected cases, however, patients with atopy, contact sensitivity, chronic dermatitis, or immunodeficiency may develop CTCL.[8] The vast majority of patients are human T-cell lymphotrophic virus type 1 (HTLV-1)-negative. CTCL has been documented after B-cell lymphomas, Hodgkin's lymphoma, and renal transplantation.[9–11] CTCL also has been reported in the acquired immunodeficiency syndrome.[12]

CLASSIFICATION

Previous classifications have not adequately characterized the cutaneous lymphomas. The most recent lymphoma classification is the World Health Organization (WHO) classification.[13] The European Organization for Research and Treatment of Cancer (EORTC) proposed a classification that divided patients into those with primary T-cell or B-cell lymphomas.[14] Significant differences, however, exist between the two classification systems. The WHO-EORTC classification for cutaneous lymphomas was the result of consensus meetings (see Table 113-1).[15] The relative frequency and survival data for 1905 patients derived from Dutch and Austrian cutaneous lymphoma registries illustrate the clinical significance of the WHO-EORTC classification (Table 113-2). This classification will lead to a more uniform diagnosis of cutaneous lymphomas and also improves definitions of cutaneous lymphomas other than mycosis fungoides and Sézary syndrome and provides definitions of cutaneous B-cell lymphomas, allowing for a more reliable distinction between aggressive and indolent types of cutaneous B-cell lymphoma.

Of the CTCLs, 50% are mycosis fungoides. The tumor-node-metastasis (TNM) classification system is used in cutaneous lymphoma (Table 113-3). A TNM classification system is used to stage patients with mycosis fungoides and Sézary syndrome but is not appropriate for use with other primary cutaneous lymphomas (Table 113-4). A consensus TNM classification system applicable for all primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome has been proposed.[16]

GENERAL CLINICAL MANIFESTATIONS OF MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

The cutaneous clinical manifestations of cutaneous lymphoma are diverse, ranging from difficult-to-diagnose to indeterminate dermatitis-like lesions of skin to plaque- or tumor-stage CTCL. The most common cutaneous lymphoma is mycosis fungoides. The second most common cutaneous lymphoma is Sézary syndrome. Sézary syndrome more characteristically arises without a previous history of mycosis fungoides. If mycosis fungoides evolves into Sézary syndrome, then the diagnosis should be erythrodermic mycosis fungoides. Atypical cutaneous lesions eventually are found to represent CTCL. Patients may have a premalignant phase with eczematous or dermatitic skin lesions for several years, or even decades, before the diagnosis is established. The median time from appearance of of the preceding skin eruption to diagnosis is approximately 6 years. Periodic skin examination and repeat skin biopsies as necessary are essential in patients with suspicious cutaneous lesions. The spectrum of premalignant disorders includes various less common but distinctive lymphoid dermatoses, such as large-plaque parapsoriasis, poikiloderma atrophicans vasculare, follicular mucinosis (alopecia mucinosa), pityriasis lichenoides et varioliformis acuta (Mucha-Habermann disease), and other atypical lymphocytic infiltrates of the skin. Generally, no specific clinical or pathologic markers have been identified that clearly delineate those cases that will progress to CTCL.

The classic malignant phases of CTCL are manifested principally in the skin and include patch-stage CTCL, plaque-stage CTCL, tumor-stage CTCL, and erythrodermic CTCL (Fig. 113-1). Extracutaneous involvement, nodal or extranodal, of CTCL develops with disease progression.

The patch stage of mycosis fungoides (see Fig. 113-1A) is characterized by cutaneous erythematous macules and slightly infiltrated patches of variable size, often located over the waist or on the trunk or proximal extremities. Pruritus may or may not be a feature. Individual skin lesions occasionally exhibit superficial scale, whereas induration is minimal or absent. Pigmentation may be altered; depending on the natural degree of pigment, hypopigmentation or hyperpigmentation may be observed. The lesions may be present for months to years before the plaque stage of CTCL develops (see Fig. 113-1B).

Since the initial description of this disease by the French dermatologist Alibert during the early 1800s, the discrete plaque stage and tumor stages of CTCL have been classically defined as mycosis fungoides.[17] The lesions of plaque- and tumor-stage CTCL are sharply demarcated circular plaques that are infiltrated and elevated above the surrounding normal skin on the trunk and extremities. The plaques are erythematous or occasionally violaceous and may exhibit central involution. Individual patches may overlap, producing a geographic appearance. The lesions may be scaly or encrusted, occasionally exhibiting a papular quality (see Fig. 113-1B) They rarely become

Table 113-2 Relative Frequency and Disease-Specific 5-Year Survival for 1905 Patients with Primary Cutaneous Lymphomas Classified According to the WHO-EORTC Classification

WHO-EORTC Classification	No. of Patients	Frequency (%)*	Disease-Specific 5-Year Survival (%)
CUTANEOUS T-CELL LYMPHOMA			
Indolent clinical behavior			
Mycosis fungoides	800	44	88
Folliculotropic mycosis fungoides	86	4	80
Pagetoid reticulosis	14	<1	100
Granulomatous slack skin	4	<1	100
Primary cutaneous anaplastic large cell lymphoma	146	8	95
Lymphomatoid papulosis	236	12	100
Subcutaneous panniculitis-like T-cell lymphoma	18	1	82
Primary cutaneous $CD4^+$ small/medium pleotropic T-cell lymphoma†	39	2	75
Aggressive clinical behavior			
Sézary syndrome	52	32	4
Primary cutaneous NK/T-cell lymphoma, nasal-type	7	<1	NR
Primary cutaneous aggressive $CD8^+$ T-cell lymphoma†	14	<1	18
Primary cutaneous gamma/delta T-cell lymphoma†	13	<1	NR
Primary cutaneous peripheral T-cell lymphoma, unspecified‡	47	2	16
CUTANEOUS B-CELL LYMPHOMA			
Indolent clinical behavior			
Primary cutaneous marginal zone B-cell lymphoma	127	7	99
Primary cutaneous follicle center lymphoma	207	11	95
Intermediate clinical behavior			
Primary cutaneous diffuse large B-cell lymphoma, leg type	85	4	55
Primary cutaneous diffuse large B-cell lymphoma, other	4	<1	50
Primary cutaneous intravascular large B-cell lymphoma	6	<1	65

NR, not reached.
*Data for 1905 patients with primary cutaneous lymphoma registered with the Dutch and Austrian Cutaneous Lymphoma Group between 1986 and 2002.
‡Primary cutaneous peripheral T-cell lymphoma, unspecified, excluding the three provisional entities indicated with a dagger (†).
From Willemze R, Jaffe E, Burg Gunter, et al: WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768–3785.

vesicular or pustular or exhibit bolus features or a translucent granulomatous appearance. Patches evolve into larger plaques, with oval and well-demarcated lesions with elevated borders. The plaques may affect the face, and the dermal thickening on the face may progress to give the classic leonine facies. Infiltration of the skin of the palms and soles leads to hyperkeratosis and fissuring. More extensive involvement of the scalp and other hair-bearing areas often is accompanied by alopecia (see Fig. 113-1C). Pruritus may be significant and can involve both lesional and nonlesional skin. Rarely, a solitary plaque or nodule of mycosis fungoides has been observed in the complete absence of other skin findings.[18]

Tumor-stage lesions of CTCL have variable growth rates and typically occur at sites of previous plaque-stage involvement. Progression probably reflects local proliferation and evolution of more aggressive clones of malignant cells. Multiple tumor-stage lesions of CTCL arise de novo in the absence of patch-stage or plaque-stage CTCL but, when observed, have been reported as the *d'emblée* form of mycosis fungoides. The tumorous lesions may appear anywhere on the body but have a predilection for the body folds, including groin, antecubital fossa, neck, axilla, and inframammary areas. The nodules and tumors typically are reddish brown or purplish and have a tendency to ulcerate (see Fig. 113-1D). Multiple lobulated and coalescing lesions may develop on the face, resulting in leonine facies (see Fig. 113-1E). Tumor-stage CTCL is more clinically aggressive than patch-stage CTCL, probably owing to the evolution of a later stage of malignancy. Nodular lesions infrequently are pruritic and more often are painful and tender, especially after ulceration has occurred. Ulcerative lesions frequently become colonized with bacteria and purulent. Histologically, the lesions may be similar to those in plaque-stage disease, but they are denser and extend into the deep dermis and subcutaneous fat. Cellular composition may demonstrate lymphoid polymorphism and inflammation, or the lesions may be monomorphous, with almost exclusively less mature malignant T cells and minimal or absent epidermatropism. At presentation, approximately 40% of patients have plaques on less than 10% of the body surface area, 30% have extensive plaques, 15% exhibit a tumor phase, and 10% exhibit an erythroderma phase.

The classic erythrodermic form of CTCL, Sézary syndrome, is a distinctive CTCL entity that derives its name from the descriptive studies and identification of unique blood cells by Sézary and Bouvrain during the 1930s.[19] Although this disease initially was reported in the late 19th century, Sézary and Bouvrain associated the malignant reticulemic (leukemic) erythroderma with circulating hyperchromatic mononuclear cells containing convoluted and/or

Table 113-3 Staging of Cutaneous T-Cell Lymphoma: Tumor-Node-Metastasis Classification

Classification	Description/Definition
T: Skin	
T0	Lesions clinically and/or pathologically suggestive of CTCL
T1	Limited plaques, papules, or eczematous patches covering <10% of skin surface
T2	Generalized plaques, papules, or erythematous patches covering ≥10% of skin surface
T3	Tumors
T4	Generalized erythroderma
N: Lymph nodes	
N0	No palpable adenopathy, lymph node pathology negative for CTCL
N1	Palpable lymphadenopathy; lymph node pathology negative for CTCL
N2	No palpable lymphadenopathy, lymph node pathology positive for CTCL
N3	Palpable adenopathy, lymph node pathology positive for CTCL
B: Peripheral blood	
B0	Atypical circulating cells not present (<5%)
B1	Atypical circulating cells present (>5%)
M: Visceral organs	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathologic confirmation, and organ involved should be specified)

cerebriform nuclei. These same cells infiltrate adenopathic lymph nodes. The cells subsequently were designated *Sézary cells*. The first description in the English literature of Sézary syndrome was by Taswell and Winkelmann in 1961.[20] The clinical presentation of this syndrome includes exfoliative erythroderma, lymphadenopathy, and keratoderma or thickening of the skin of the palms and soles, often with development of cracks and fissures (palmoplantar hyperkeratosis; see Fig. 113-1F and G). Pruritus is a characteristic, often intense symptom leading to excoriations, exudation, and crust formation. Nail dystrophy (onychodystrophy), ectropion (eversion, giving a "pulled-down" appearance) of the lower eyelids, and alopecia frequently are observed.

Table 113-4 Modified Tumor-Node-Metastasis Staging System for Classification of Cutaneous T-Cell Lymphoma

Stage	T	N	M
IA	1	0	0
IB	2	0	0
IIA	1, 2	1	0
IIB	3	0, 1	0
III	4	0, 1	0
IVA	1–4	2, 3	0
IVB	1–4	0–3	1

B, peripheral blood; M, visceral organ; N, lymph node; T, skin.

From Bunn PA Jr, Lamberg SI: Report of the Committee on Staging and Classification of Cutaneous T-Cell Lymphomas. Cancer Treat Rep 1979;63:725–728.

Sézary syndrome is defined by the presence of Sézary cells in the peripheral blood and the characteristic clinical and histologic features of the skin. Although mycosis fungoides may manifest with erythroderma and similar clinical findings, Sézary cells are not detected in the peripheral blood by routine microscopic examination.

Extracutaneous disease involving sites beyond the blood and peripheral lymph nodes occurs in advanced CTCL. The reported frequency of extracutaneous involvement at autopsy ranges from 54% to 100%.[21,22] Loss of epidermotropism may play a role as the disease disseminates.[23] With disease progression, extracutaneous involvement becomes more common.[22] Clinical evidence of extracutaneous involvement of CTCL is classically manifested by peripheral lymhadenopathy.[22] Computed tomography (CT) demonstrates involvement of pelvic, abdominal, and axillary nodes that may not be palpable. Less commonly, thoracic nodal disease is recognized with this imaging technique. CT is not routinely used to stage early CTCL, because the yield is low. Positron emission tomography (PET) may be more sensitive than CT scanning.[24] In a retrospective review of 251 lymph nodes in 200 patients, Vonderheid and colleagues reported lymph node involvement to be associated with a poor prognosis and the survival of patients with small cell type (median survival, 40 months) to be better than that for those with other types (median survival, 20 months).[25] The Dutch Cutaneous Lymphoma Group reported that the presence of extracutaneous disease, the type and extent of cutaneous involvement, the response to initial therapy, and the presence of follicular mucinosis were associated with a higher rate of disease progression and mortality.[26]

Bone marrow involvement may develop during progression of CTCL. At autopsy, the incidence is 27% to 47%.[4,21] At initial staging, 7% to 13% of patients have evidence of marrow involvement.[27] Most patients with bone marrow involvement have concomitant nodal or organ involvement and shortened survival.[28] Liver involvement by CTCL is documented by nodular lymphoid infiltration of the portal tracts on liver biopsy and has been reported in 8% to 16% of patients with CTCL.[29,30] The presence of abnormal cells is not diagnostic of liver involvement.[29] Rarely, involvement of the central nervous system by CTCL has been documented by imaging studies, on tissue biopsy, or at autopsy.

TISSUE DIAGNOSIS

The diagnosis of cutaneous lymphoma is established by tissue biopsy. Punch biopsy of involved skin, to obtain specimens 4 to 6 mm deep, is recommended for evaluation of patch-, plaque-, and tumor-stage lesions. In selected tumor-stage cases, elliptical excision biopsy may be necessary. Several biopsies should be performed because multiple specimens often are required to demonstrate diagnostic findings. Specimens for immunophenotyping and molecular genetic studies should be snap-frozen in liquid nitrogen and stored at −70° C. Cell suspensions for flow cytometry and cytogenetic evaluation may be prepared from tissue.

The classic histologic findings diagnostic of CTCL consist of abnormal lymphocyte morphology, a band-like superficial dermal infiltrate, epidermotropism, and Pautrier's microabscesses (Fig. 113-2). Of note, significant variability exists in the expression of these pathologic characteristics and the degree of individual abnormalities.[31] In addition, significant intraobserver and interobserver variability has been documented. In a study of 73 skin biopsy specimens from patients with mycosis fungoides reviewed on two separate occasions by three expert hematopathologists, an accurate diagnosis was rendered on both readings approximately 50% of the time.[32] No single histopathologic criterion will establish the diagnosis. Lympho-



Figure 113-1 • Cutaneous malignant phases and skin findings in cutaneous T-cell lymphoma. **A,** Patch stage. **B,** Plaque stage with scaling. **C,** Alopecia of scalp. **D,** Tumor stage. **E,** Leonine facies of tumor phase. **F,** Erythroderma of Sézary syndrome. **G,** Erythema, hyperkeratosis, and fissuring of soles in Sézary syndrome.

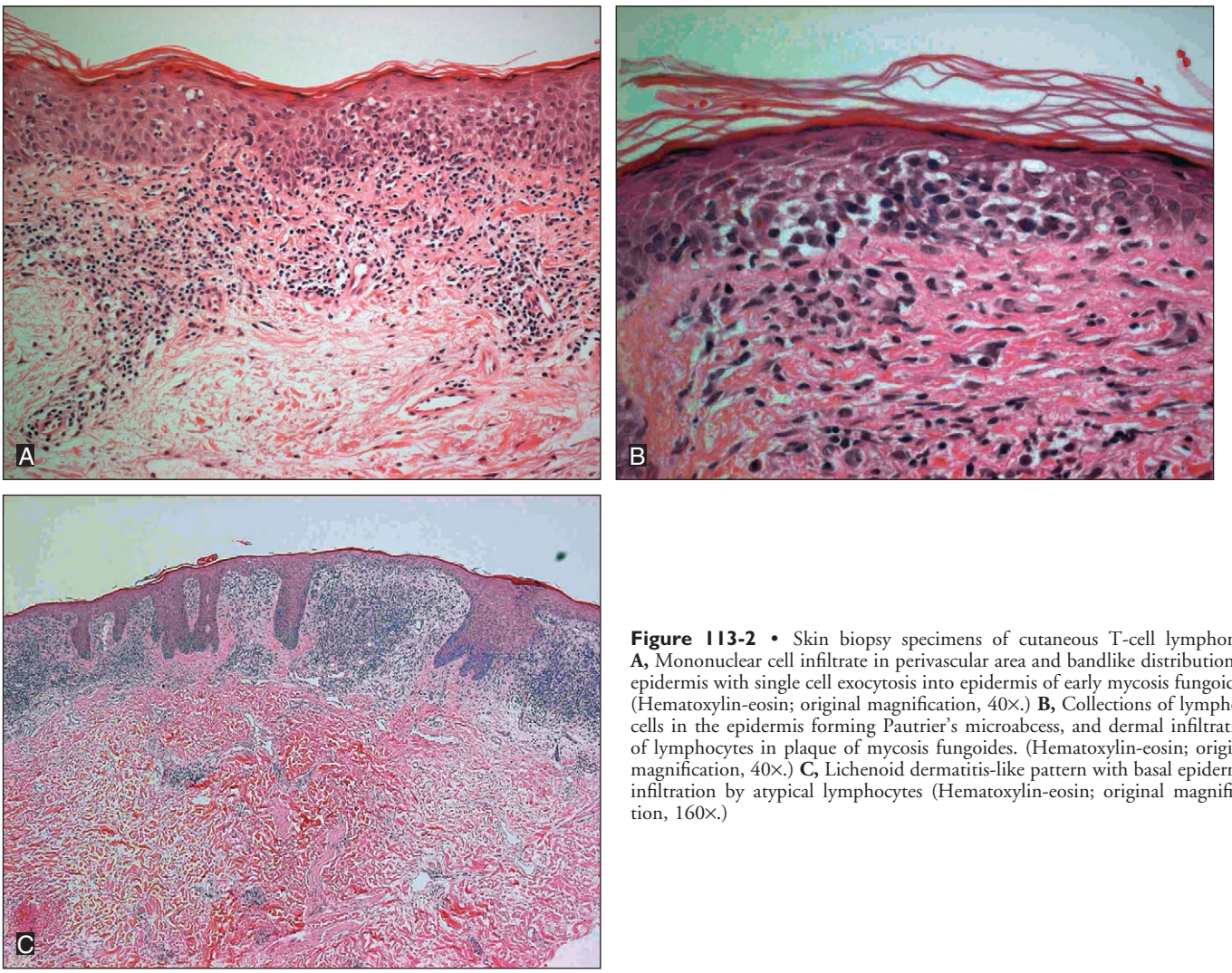


Figure 113-2 • Skin biopsy specimens of cutaneous T-cell lymphoma. **A,** Mononuclear cell infiltrate in perivascular area and bandlike distribution in epidermis with single cell exocytosis into epidermis of early mycosis fungoides. (Hematoxylin-eosin; original magnification, 40×.) **B,** Collections of lymphoid cells in the epidermis forming Pautrier's microabcess, and dermal infiltration of lymphocytes in plaque of mycosis fungoides. (Hematoxylin-eosin; original magnification, 40×.) **C,** Lichenoid dermatitis-like pattern with basal epidermal infiltration by atypical lymphocytes (Hematoxylin-eosin; original magnification, 160×.)

cytes within the epidermis that are larger than those within the dermis is an important feature of epidermatropism.[33] Pautrier's microabscesses are present in 4% to 37% of cases.[34]

On microscopic examination, the lymphocytes in CTCL (called mycosis cells or Sézary cells) have variable but usually ample cytoplasm. Nucleoli of the neoplastic cells are relatively large and hyperchromatic. Mycosis cells can be isolated from various tissues by touch preparation and microscopic examination. Sézary cells circulate in the blood and can be enriched in vitro by density centrifugation or immunophenotypic characteristics. The prominent characteristics of individual nuclei of Sézary cells are their irregularity, with prominent indentations or convolutions that have a cerebriform appearance[19] (Fig. 113-3). In 1968, Lutzner and Jordan further characterized the serpentine, or cerebriform, nuclei by electron microscopic examination[35] (Fig. 113-4). Reactive lymphoid cells infiltrating the skin in dermatitis, lichen planus, drug eruptions, psoriasis, and other dermatoses may have similar nuclear morphologic features on light microscopy, but further examination reveals a normal nuclear diameter, nuclear-to-cytoplasm ratio, and nuclear contour index in these disorders. A review of 222 biopsy specimens from patients with mycosis fungoides or Sézary syndrome reported that CTCL produces the patterns for diagnosing inflammatory disease, including superficial perivascular invasion and atypical lymphocytes in nearlyt half of the cases.[36] The cells that mimic mycosis cells or Sézary cells represent activated T lymphocytes. Therefore, morphologic examination alone

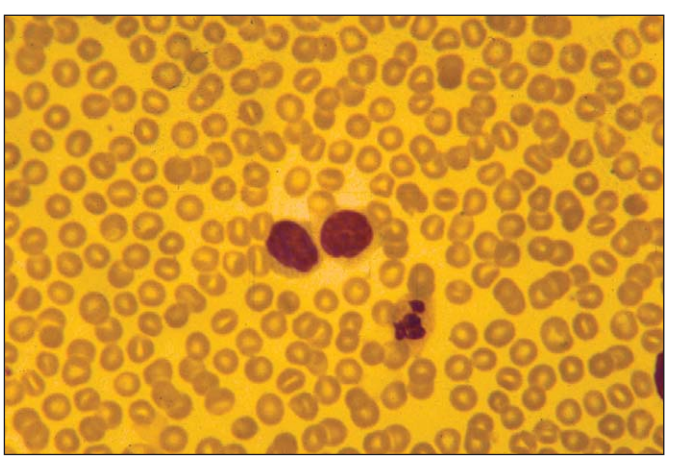


Figure 113-3 • Peripheral blood smear demonstrating irregular Sézary nucleus with cerebriform appearance. (Wright's stain.)

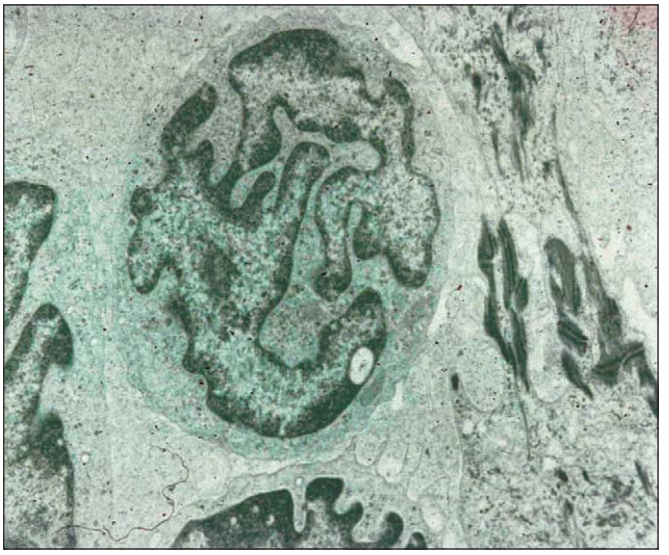


Figure 113-4 • Electron micrograph of "serpentine," or cerebriform, nuclei of Sézary cells from peripheral blood.

can result in misdiagnosis. The limitation of light microscopy has led to the development of more sophisticated approaches to CTCL diagnosis.[15] Of interest, the EORTC reported that identification of epidermal lymphocytes with extremely convoluted nuclei was 100% specific and 92% sensitive in establishing the diagnosis.[32] The tumor stage of CTCL is characterized by a dense dermal infiltrate that often extends into the deep dermis and subcutis and becomes nonepidermotropic or less epidermotropic. The individual malignant cells are pleomorphic large cells with prominent nucleoli. Complete transformation to a large cell variant that resembles diffuse large cell lymphoma or anaplastic large cell lymphoma typically is seen in tumors and occasionally is present in plaques and erythroderma.[37,38] Skin biopsy specimens from patients with Sézary syndrome, in contrast with those from patients with mycosis fungoides, frequently lack prominent epidemotropism. Buechner and Winklemann reported that 17% of skin biopsies from patients with Sézary syndrome were nondiagnostic by light microscopy alone.[39] Patients whose skin biopsy specimen demonstrated only a lichenoid or bandlike infiltrate, without other criteria to establish a diagnosis of mycosis fungoides or Sézary syndrome, have been shown to have CTCL by other diagnostic and laboratory criteria. Nonetheless, the presence of abnormal lymphocytes and characteristic Pautrier's microabscesses is important for the diagnosis of mycosis fungoides and Sézary syndrome. The propensity to develop Pautrier's microabscesses in Sézary syndrome is less prominent, however, which may hinder confirmation of the diagnosis.[40] The cellular composition and morphology of the dermal infiltrate in Sézary syndrome are similar to those in mycosis fungoides. In Sézary syndrome, the abnormal cells characteristically are present and reflect peripheral blood disease, which is a major criterion for establishing the diagnosis.[38,39]

The classic immunophenotype of mycosis fungoides and Sézary syndrome neoplastic cells is $CD3^+$, $CD4^+$, $CD45RO^+$, and $CD8^{-}$[15] (Fig 113-5). Aberrant antigen expression of the malignant T-cell population is observed for mycosis fungoides and Sézary syndrome and is manifested as decreased or absent expression of pan–T-cell antigens (CD2, CD3, CD5), absent expression of subset antigens ($CD4^-$, $CD8^-$), or coexpression of T-cell antigens ($CD4^+$, $CD8^+$).[41] Transformed cells in mycosis fungoides and Sézary syndrome have been shown to acquire CD30 antigens, which may lead to confusion with $CD30^+$ large cell lymphoma or lymphomatoid papulosis.[42] In other cases, neoplastic cells of CTCL may acquire Leu-M1, leading to confusion with Hodgkin's lymphoma.[43] No immunohistochemical techniques clearly demonstrate clonality of T-cell lymphoproliferative disorders. Despite the use of immunohistochemical techniques, a definitive diagnosis may not be possible in the patch stage of mycosis fungoides or in early Sézary syndrome.

Cytogenetic abnormalities have been identified in CTCL. The most common numerical change is loss of the long arm of chromosome 10 (i.e., 10q).[44] Other reported abnormalities from skin, peripheral blood, lymph nodes, and bone marrow include complex translocations or deletions in chromosomes 1, 2, 6, 9, 11, 13, 14, and 17.[44]

Clonal T-cell receptor gene rearrangements are among the most sensitive techniques in CTCL and are detected in most cases. Clonal T-cell antigen receptor (TCR) gene rearrangements are identified as non-germline bands on Southern blot analysis on DNA hybridized to TCR-beta, TCR-gamma, and TCR-delta chain molecular probes[45] (Fig. 113-6). Clonal rearrangements of the TCR-beta gene have been documented in most patients.[46] In early patch-stage mycosis fungoides, the number of infiltrating T cells is minimal, and Southern blot analysis may not detect clonal T-cell populations.[47] Documented

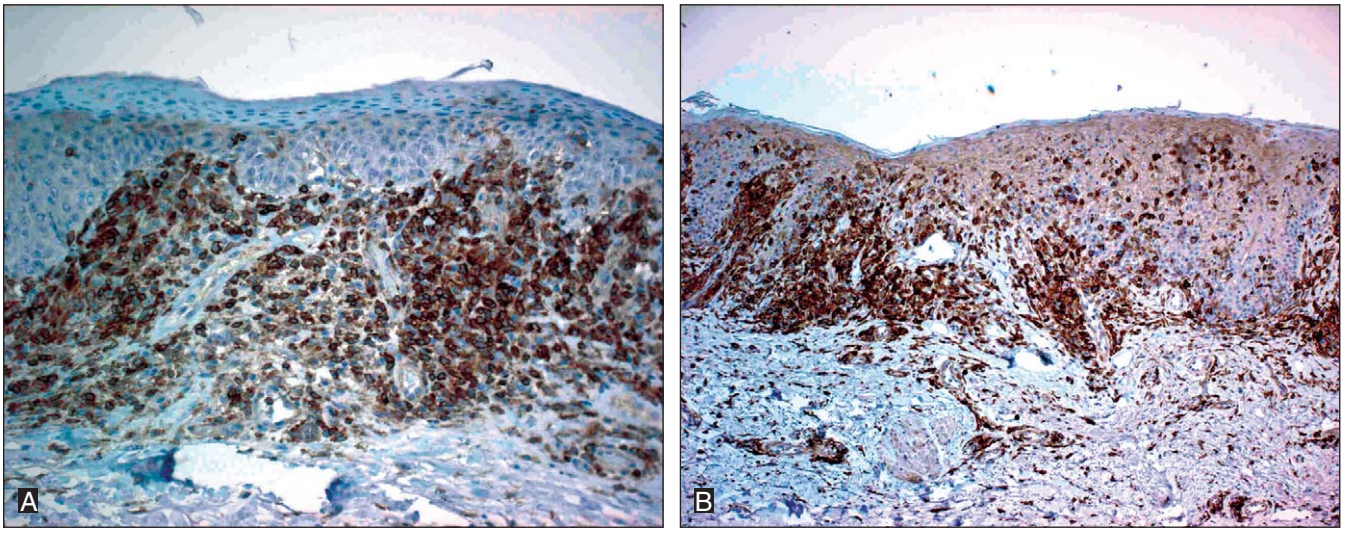


Figure 113-5 • **A,** Uniform $CD4^+$ cellular infiltrate in dense bandlike pattern in papillary dermis of Sézary syndrome. **B,** $CD4^+$ cells forming a dense dermal infiltrate and Pautrier's microabcesses in mycosis fungoides (Hematoxylin-eosin; original magnification, 160×.)

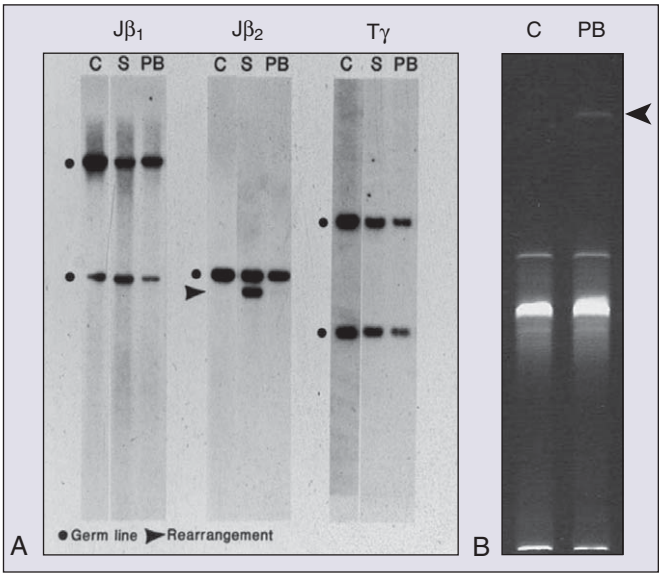


Figure 113-6 • **A,** Immunogenotyping by Southern blot analysis for a patient with Sézary syndrome. Control (C), skin (S), and peripheral blood (PB) specimens. A distinct band of clonal rearrangment is identified *(arrow)* using probes that recognize the T-cell beta chain genes (Jβ2). Only germline bands are identified in the Jβ1 gene. **B,** Polymerase chain reaction (PCR) analysis of PB identified a distinct band of clonal rearrangement *(arrow)*.

lymph node involvement by clonal TCR gene rearrangement has been associated with decreased survival.[48] Clonal TCR gene rearrangements are found in disorders that are not overtly malignant, however, including lymphomatoid papulosis, pityriasis lichenoides, and pagetoid reticulosis. T-cell clonality has been reported in 6% to 24% of benign skin disorders characterized by a lymphoid infiltrate.[49] Polymerase chain reaction (PCR) techniques to amplify specific genetic rearrangements can increase the sensitivity 1000-fold.[50] The detection of circulating clonal cells is not likely to be an indicator of worse prognosis. These technical advances provide the capability to improve monitoring of disease progression and response to treatment and for earlier detection of minimal residual disease, quiescent disease, or relapse.

VARIANTS OF MYCOSIS FUNGOIDES AND SÉZARY SYNDROME AND CUTANEOUS B-CELL LYMPHOMA

A remarkable spectrum of variants of Sézary syndrome and mycosis fungoides and B-cell lymphoma have been recognized. These disorders are characterized by unique immunohistologic features and require disease-specific clinical and therapeutic interventions. The currently recommended therapeutic interventions are summarized in Table 113-3.

Variants and Subtypes of Myosis Fungoides

Folliculotropic mycosis fungoides is a disorder of localized alopecia with mucin deposition in the hair follicle, with variable inflammation, characterized clinically by multiple grouped follicular papules with occasional formation of patches or nodules, with preferential involvement of the head and neck area with severe pruritus[51] (Fig. 113-7). On histopathologic examination, sparing of the epithelium is seen, and most cases demonstrate mucinous degeneration of the follicular epithelium.

Pagetoid reticulosis is characterized by solitary slow-growing plaques (Woringer-Kolopp type) or disseminated patches on the hands or feet that grow slowly and progress to disseminated skin lesions (Ketron-Goodman type).[52] The CD30 antigen often is expressed. The solitary slow-growing lesion has a chronic course of years to decades.

Granulomatous slack skin is a disorder characterized by excessive redundant folds of skin and plaques in the axilla and groin.[53–55] A striking granulomatous reaction and loss of dermal elastic tissue accompany the lymphocytic infiltrate, and the disease may progress to disseminated T-cell lymphoma. Although in most cases the disease has an indolent course, an association with Hodgkin's lymphoma has been reported in one third of affected patients, and an association with mycosis fungoides has been reported.[54]

Variants and Subtypes of Sēzary Syndrome

The variants and subtypes of Sézary syndrome are multiple. They include adult T-cell leukemia/lymphoma; primary cutaneous $CD30^+$ lymphoproliferative disorders (primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, and borderline cases); subcutaneous panniculitis-like T-cell lymphoma; extranodal natural killer (NK)/T-cell lymphoma of nasal type; primary cutaneous peripheral T-cell lymphoma, unspecified; and $CD4^+/CD56^+$ hematodermic neoplasm (blastic NKcell lymphoma).

Adult T-cell leukemia/lymphoma may manifest with skin lesions but few or absent circulating cells and is associated with the human T-cell leukemia virus 1 (HTLV-1) with integrated HTLV-1 genes in all cases.[55] A skin lesion smoldering variant has been reported.[56] Patients may present with papules (22%) or plaques (19%).[57]

Primary cutaneous $CD30^+$ lymphoproliferative disorders, which include primary cutaneous anaplastic large cell lymphoma, lymphomatoid papulosis, and borderline cases, may account for up to 30% of cutaneous lymphomas.[58] Histologic criteria alone do not separate these disorders, and long-term follow-up establishes the diagnosis.[59] Primary cutaneous anaplastic large-cell lymphoma expresses CD30 in more than 75% of cells, and most express the cutaneous lymphocyte antigen (CLA). Patients initially present with localized nodules, tumors, or papules. Up to 20% of patients have multifocal lesions, and 10% have disseminated disease. The survival is greater than 10 years.[59] Lymphomatoid papulosis is defined as a chronic, recurrent, erythematous, and self-healing papulonecrotic or papulonodular skin disease with histologic features suggestive of a ($CD30^+$) malignant lymphoma[60] (Fig. 113-8). The lesions spontaneously resolve in 3 to 12 weeks. The clinical course is unpredictable, with duration of disease activity ranging from a few months to 20 years. Hodgkin's lymphoma, cutaneous anaplastic large cell lymphoma, or mycosis fungoides may precede, be associated with, or follow lymphomatoid papulosis.[59] Morphologic patterns have been classified as types A, B,



Figure 113-7 • Follicular mucinosis manifested as patches of alopecia.



Figure 113-8 • Lymphomatoid papulosis: Characteristic erythematous papulonodules with crust and ulceration.

and C.[60] Type A lesions resemble those of CD30$^+$ anaplastic large cell lymphoma or Hodgkin's lymphoma, and type B lesions are composed of small lymphoid cells. In one series of 118 patients with lymphomatoid papulosis, progressive disease developed in only 4%; 2% died of systemic disease.[59]

Subcutaneous panniculitis-like T-cell lymphoma characteristically involves the legs, with infiltrates of γ/β$^+$, CD3$^+$, CD8$^+$, and CD4$^-$ cytotoxic protein–expressing lymphocytes that may rim fat cells accompanied by many macrophages; the epidermis and dermis remain uninvolved.[15] Fevers, fatigue, weight loss, and the hemophagocytic syndrome may be clinical manifestations and are associated with a rapid and progressive course.[61] The nodules or plaques may be solitary or multiple (Fig. 113-9).

Other disorders to be considered in the differential diagnosis include extranodal NK/T-cell lymphoma, nasal type; primary cutaneous peripheral T-cell lymphoma, unspecified; primary cutaneous aggressive epidermotropic CD8$^+$ cytotoxic T-cell lymphoma (provisional entity); cutaneous gamma/delta T-cell lymphoma (provisional entity); primary cutaneous CD4$^+$ small or medium-sized pleomorphic T-cell lymphoma (provisional entity); primary cutaneous peripheral T-cell lymphoma, unspecified; and CD4$^+$/CD56$^+$ hematodermic neoplasm (blastic NK-cell lymphoma).[15] The management of disorders other than mycosis fungoides and Sézary syndrome as recommended by the WHO-EORTC is outlined in Table 113-5.



Figure 113-9 • Subcutaneous T-cell lymphoma.

Cutaneous B-Cell Lymphomas

Primary cutaneous B-cell lymphoma may account for to 20% of cutaneous lymphomas[62] (Fig. 113-10). This group of disorders must be distinguished from pseudolymphoma.[63] The WHO-EORTC classification recognizes primary cutaneous marginal zone B-cell lymphoma (PCMZL); primary cutaneous follicle center lymphoma (PCFCL); primary cutaneous large B-cell lymphoma, leg type (PCLBCL-LT); and primary cutaneous large B-cell lymphoma, other (PCLBL–other). The reclassification resulted in reassignment to other categories for 5.3% of the EORTC scheme cases and 36.3% of the WHO scheme cases.[64] The 5-year disease specific survival rates are 98% in PCMZL, 95% in PCFCL, and 50% in PCLBCL-LT.[64] In this classification, PCFCL is defined as a tumor of follicle center cells,composed predominantly of large cleaved cells that do not express Bcl-2 and MUM-1, in contradistinction to PCLBCL-LT cells, which express Bcl-2 and MUM-1.[65] PCFCL-LT has been associated with a poor prognosis. The reported disease-specific 5-year survival rate was 50%, and the overall survival (OS) rate was 37%.[64]

PCMZL is an indolent lymphoma composed of small B cells and is considered to be part of the spectrum of extranodal marginal zone B-cell lymphomas, which commonly involve mucosal sites, called mucosa-associated lymphoid tissue (MALT) lymphomas. This group includes cases previously designated as primary cutaneous immunocytoma and includes primary cutaneous myeloma (extramedullary plasmacytoma of skin).[66,67] These lesions occur most commonly in females and most commonly develop on sun-exposed areas of the skin, especially on the arms. The lesions are violaceous papules, plaques, or nodules. Dissemination is rare.[67] These lymphomas are nodular or diffuse, with sparing of the epidermis, and rarely transform into diffuse large B-cell lymphoma. The lesions are CD20$^+$, CD79a$^+$, Bcl-2$^+$, CD5$^-$, CD10$^-$, and Bcl-6$^-$, with clonally rearranged immunoglobulin heavy chain (IgH) genes. Localized lesions can be treated with radiation therapy or surgical resection. Multifocal lesions can be treated with oral chlorambucil, interferon-α (intralesional or subcutaneous), or rituximab.[68]

PCFCLs are follicular, follicular and diffuse, or diffuse, with sparing of the epidermis; lesions typically appear on the head and torso. Patients present with solitary or grouped plaques and tumors. In a minority of cases, the initial presentation is with multifocal disease, which has an unfavorable prognosis.[69] The cells are CD20$^+$, CD79a$^+$, CD10$^+$ in follicular cases, CD5$^-$, and Bcl-2$^-$, and genes are clonally rearranged with no consistent cytogenetic abnormalities.[15] In contrast with systemic follicular lymphoma, these lesions do not demonstrate the t(14;18) translocation.[70] The therapy of choice in patients with localized disease is radiation therapy, even in cases with a predominance of large "cleaved" cells.[71] Cutaneous relapses may be treated with radiation therapy. Anthracycline-based chemotherapy is recommended in patients with extensive cutaneous disease and extracutaneous disease.[72] Systemic and intralesional rituximab is active in this disease.[73] Recent studies report t(14;18) and Bcl-2 expression; expression of Bcl-2 by more than 50% of neoplastic cells in patients with a diffuse pattern is associated with an unfavorable prognosis.[74,75]

PCLBCL-LT is PCLBCL characteristically manifesting with red or bluish-red skin lesions on the lower extremities, and uncommonly seen in other sites, that often disseminate to extracutaneous sites and occurs predominantly in females.[64] The cells are CD20$^+$, CD79a$^+$, and Bcl-2$^+$. Patients with a single lesion on one leg had a 5-year disease-free survival rate of 100%, versus 45% for patients with multiple skin lesions on one leg and 36% for those with lesions on

Table 113-5 Management of Disorders Other Than Mycosis Fungoides and Sézary Syndrome as Recommended by the WHO-EORTC

Disease Type	Management Strategies
Folliculotropic mycosis fungoides	Total body electron beam irradiation
	PUVA combined with retinoids or interferon-α
	Local radiation therapy
Pagetoid reticulosis	Radiation therapy or surgical excision
	Topical steroids or topical nitrogen mustard
Granulomatous slack skin	Radiation therapy
	Surgical excision
Adult T-cell leukemia/lymphoma	In chronic and smoldering cases affecting skin only, skin-targeted therapies
Primary cutaneous anaplastic large-cell lymphoma	Solitary or localized: Radiation therapy or surgical excision
Extracutaneous or progressive disease	Anthracycline-based chemotherapy
Lymphomatoid papulosis	Observation
	Methotrexate 5–20 mg/week
	PUVA
	Topical chemotherapy
Subcutaneous panniculitis-like T-cell lymphoma	Systemic corticosteroids
	Anthracyline chemotherapy and radiation therapy
Extranodal NK/T-cell lymphoma, nasal type	Radiation therapy ± chemotherapy (stage I/II disease)
	Chemotherapy for advanced disease
Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic T-cell lymphoma	Anthracycline chemotherapy
Cutaneous gamma/delta T-cell lymphoma	Systemic chemotherapy
Primary cutaneous $CD4^+$ small or medium-sized pleomorphic T-cell lymphoma	Radiation therapy or surgical excision
	Cyclophosphamide
	Interferon-α
Primary cutaneous peripheral T-cell lymphoma, unspecified	Anthracycline chemotherapy
$CD4^+/CD56^+$ hematodermic neoplasm (blastic NK-cell lymphoma)	Acute leukemia systemic therapy regimens

NK, natural killer; WHO-EORTC, World Health Organization–European Organization for Research and Treatment of Cancer.
Data from Willemze R, Jaffe ES, Burg G, et al: WHO-EORTC classification for cutaneous lymphomas. Blood 2005;105:3768–3785.

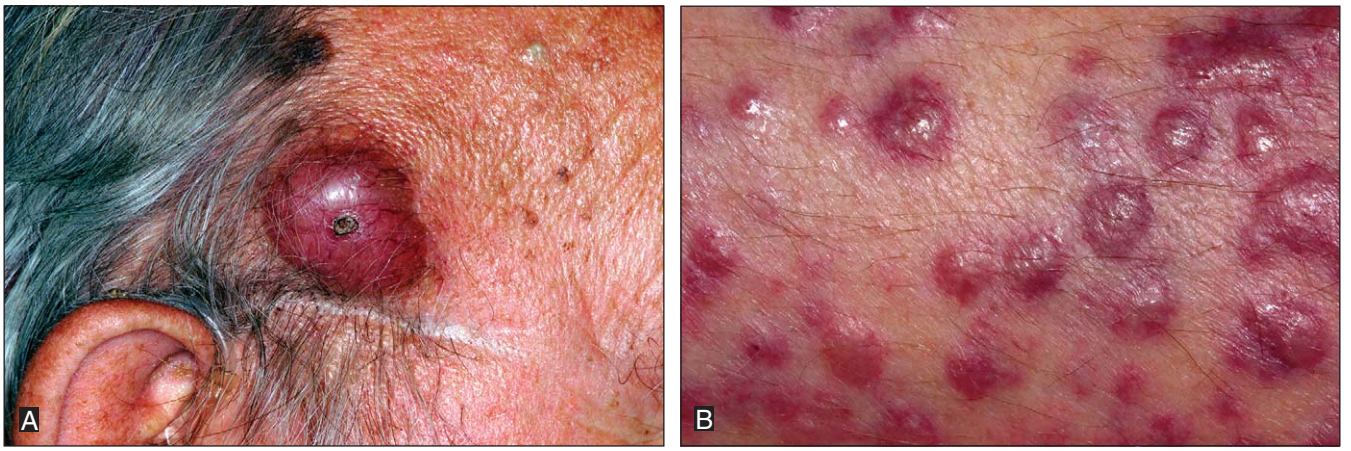


Figure 113-10 • Diffuse large B-cell lymphoma. **A,** Unicentric disease. **B,** Multicentric disseminated disease.

both legs.[76] Systemic anthracycline-based chemotherapy is recommended.[76] Rituximab is active in this disease in combination with systemic chemotherapy.[73]

Primary cutaneous diffuse large B-cell lymphoma–other includes morphologic variants of lymphoma, plasmablastic lymphomas, primary cutaneous T-cell or histiocyte-rich B-cell lymphomas, and intravascular large B-cell lymphoma. Intravascular large B-cell lymphoma is characterized by an accumulation of malignant large B cells within the blood vessels that affects the central nervous system, lungs, and skin.[77] Patients characteristically present with disseminated disease but initially may exhibit only skin involvement, with violaceous patches or plaques or telangiectasias of the legs or torso.[78] Patients presenting with only cutaneous disease enjoy better survival, with a 3-year OS rate of 56%, versus 22% for the disseminated form.[78] Anthracycline-based chemotherapy is associated with a 60% response rate and a 3-year OS rate greater than 30%.[77] The R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) should be considered as an initial treatment approach.[77]

STAGING AND PROGNOSIS OF MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

As with Hodgkin's disease and NHL, the prognosis for CTCL and its variants is related to the stage of the disease. The significant prognostic factors in CTCL are the extent and type of skin involvement. The Mycosis Fungoides Cooperative Group adopted a modified TNM classification in 1975, which was further modified by the Staging Committee at the International Workshop on Mycosis Fungoides (see Tables 113-3 and 113-4).[79] A modified TNM classification for primary cutaneous lymphomas other than mycosis fungoides and Sézary syndrome has been proposed.[80] The TNM classification system is not routinely used in clinical practice.

The greater the percentage of involvement of skin surface area by CTCL, the worse the prognosis. Involvement of less than 10% of the body surface area by CTCL—stage IA—portends a better prognosis than that associated with stage IB, defined as greater than 10% skin involvement. Patients with plaque-stage disease have a more favorable prognosis than that for patients with tumor-stage disease. In mycosis fungoides, 90% of patients with patch- or plaque-stage disease with less than 10% skin involvement survived 15 years or longer.[81] Among 309 patients with mycosis fungoides, the 5-year disease-free survival rate was 100% for those with limited cutaneous disease, 80% for those with tumor-phase disease, and 40% for those with lymph node–phase disease.[82] Survival of patients with tumor-stage disease is reported to be better than that of patients with stage III or erythrodermic disease.[83] For patients with limited patch- or plaque-stage mycosis fungoides, life expectancy is similar to that for an age-, sex-, and race-matched control population. Unequivocal histologic involvement in the lymph nodes is predictive of survival, with a median survival actuarial survival of 53 months with such involvement and 137 months without.[84] The prognosis in Sézary syndrome is poor, with a median survival time of 2 to 4 years.[85]

The recommended approach to clinical evaluation for staging is outlined in Box 113-1 and can serve as a general guide for clinical trials.[79] Liver biopsies are not indicated in routine staging for patients with CTCL. The role of CT scans is controversial. Routine CT scanning does not improve detection of advanced disease but may be clinically useful in early plaque-stage disease.[86] CT provides only anatomic information. Lymphadenopathy in CTCL may be related to underlying disease but also to dermatopathic lymphadenopathy.[87] In a study at Stanford University, only 5 patients had enlarged lymph nodes on CT, whereas integrated PET and CT (PET/CT) revealed metabolic activity in all 13 patients.[88] The intensity of PET activity correlated with the histologic lymph node grade.

On initial diagnosis, approximately 42% of patients have plaques covering less than 10% of the body surface (T1), 30% are characterized by T2, 16% have tumors (T3), and 12% have erythroderma (T4).[79,83]

Box 113-1. APPROACH TO CLINICAL EVALUATION FOR STAGING OF CUTANEOUS T-CELL LYMPHOMA

- Complete history and physical examination
- Whole-body mapping of skin lesions with or without photography
- Complete blood count, differential count, and platelet count; Sézary cell count
- Serum chemistries (liver and renal function tests; determination of serum levels of calcium, phosphorus, creatinine, and uric acid)
- Chest radiography
- Skin biopsy for routine histology and possible immunophenotyping/T-cell receptor gene rearrangement analysis
- Lymph node biopsy (palpable node from draining area; cervical before axillary before inguinal)
- Evaluation of other organs if foregoing tests suggest involvement; computed tomographic scan, liver biopsy, and bone marrow biopsy only for patients with stage II, III, and IV disease

Bone marrow involvement is determined by the method of assessment. On morphologic analysis, Salhany and colleagues demonstrated aggregates of lymphocytes and cerebriform nuclei in 21.7% of cases and abnormal lymphoid aggregates in 31.6%.[89] Infiltrative disease was associated with peripheral blood involvement. The frequency of clonal T-cell involvement in the bone marrow has been reported to be 75% and does not alter prognosis.[90]

Other prognostic factors have been reported. The absence or presence of greater than 5% of Sézary cells in total lymphocyte count and a $CD4^+/CD7^-$ phenotype double the risk of death.[91] Additional prognostic factors include age of 60 years or older, elevated lactate dehydrogenase (LDH) level, and a low percentage of $CD8^+$ cells in the lymph node.[92,93]

HISTOLOGIC TRANSFORMATION

Transformation is defined as the presence of greater than 25% large cells and represents an evolution of the original clone. The risk of transformation has been reported to be 12% to 23%, with the reported median times from diagnosis to transformation of 12 months to 6.5 years and a median survival time of 19 to 22 months.[94,95] Age and extracutaneous involvement were associated with worse prognosis.[95]

SECOND CANCERS

The Finnish Cancer Registry and others have reported an increased overall risk of lung cancer, small cell lung cancer, Hodgkin's lymphoma, and NHL.[96,97]

CAUSE OF DEATH

The most common cause of death in CTCL is infection, the most common organisms of which are *Staphylococcus aureus*, members of the family Enterobacteriaceae, and *Pseudomonas aeruginosa*.[98, 99] Disseminated herpes and fungal infections may occur in patients with advanced disease. Up to 47% of deaths are caused by cardiopulmonary disease and secondary malignancy.[99, 100] Patients with cutaneous tumors and erythroderma characteristically die of complications of progressive disease.

THERAPY

Overview

Therapeutically, CTCL is similar to low-grade NHL in that only limited stage disease is potentially curable, and both of these diseases are remarkably responsive to many different therapeutic modalities despite eventual relapse. Patients with either type of lymphoma may respond to the same therapeutic modality on more than one occasion, and they typically survive for years after the initial diagnosis. Advanced

disease is rarely curable, and both CTCL and indolent NHL may transform into higher-grade lymphoproliferative disorders. In the absence of a therapeutic approach that leads to long-term disease-free survival and cure, current therapies are tailored to the extent, burden, and type of disease present. The primary goals of treatment are to control the cutaneous disease, to obtain symptomatic relief, and to achieve complete clinical remission.

Therapies available for the treatment of CTCL are wide ranging and illustrate the distinctive presentation and disease course of this type of lymphoproliferative disorder, as well as reflecting unique challenges that face clinicians and therapists in treatment of CTCL and in clinical management of the patient. Therapies broadly include skin-directed biologic response modifiers, monoclonal antibodies, and cytotoxic therapy. Therapeutic options include topical treatments with corticosteroids, chemotherapy with nitrogen mustard or carmustine (BCNU), ultraviolet B (UVB) phototherapy, photochemotherapy with psoralen plus ultraviolet A (PUVA), irradiation with electron beam or photon therapy, systemic chemotherapy with either single or multiple agents, combined-modality therapy (chemotherapy, electron beam radiation therapy, and other combinations), extracorporeal photochemotherapy, interferons, monoclonal antibody therapy, retinoids, purine analogs, cyclosporine, acyclovir, autologous peripheral blood stem cell transplantation, allogeneic bone marrow transplantation, dentileukin difitox, and alemtuzumab (Table 113-6).

Factors other than disease stage that require consideration in the management of patients with CTCL include the general health and age of the patient, availability of various therapeutic options, and the extent and aggressiveness of the disease (see Table 113-6). In the context of therapeutic results and toxicities, it must be recognized that many of the published studies of CTCL are not prospective randomized trials with control groups. Because CTCL is an uncommon disease, multicenter cooperative clinical trials have been limited, and consensus is not well defined at this time. Table 113-7 details specific treatment options for different stages of mycosis fungoides and Sézary syndrome.

Table 113-6 Therapeutic Options for Cutaneous T-Cell Lymphoma

Topical medications
Corticosteroid
Mechlorethamine (nitrogen mustard)
Carmustine (BCNU)
Bexarotene gel
Imiquimod
UVB phototherapy
PUVA photochemotherapy
High-intensity UVAI phototherapy
Photodynamic therapy (PDT)-5-ALA
Radiotherapy with electron beam
Photon irradiation
Single-agent chemotherapy
Methotrexate
Pegylated liposomal doxorubicin
Temozolomide
Combination chemotherapy
CHOP
Combined-modality therapy
Extracorporeal phototherapy (ECP)
Cytokines
Interferons
Interleukin-2
Thymopetin
Monoclonal antibody therapy
Alemtuzumab (anti-CD52)
Anti-CD4
Retinoids
Isotretinoin
Acitretin
Bexarotene
Purine nucleoside analogs
2′-Deoxycoformycin (pentostatin)
Fludarabine
2-Chlorodeoxyadenosine (cladribine)
Gemcitabine
Immunotoxins
IL-2 fusion toxin (denileukin diftitox)
Pseudomonas immunotoxin anti-Tac(Fv)-PE38 (LMB-2)
Histone deacetylase inhibitors
Vorinostat
Depsipeptide
Vaccination-immunotherapy
Bone marrow transplantation
Autologous
Allogeneic
Nonmyeloablative allogeneic

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; IL-2, interleukin-2; PUVA, psoralen plus ultraviolet light A; UVB, ultraviolet (light) B.

General Skin Care Measures

Nonspecific topical treatment of mycosis fungoides and Sézary syndrome includes supportive therapies that miminize skin irritation, provide lubrication and adequate hydration, and ameliorate inflammatory reactions of the skin that accompany CTCL. After the diagnosis of CTCL has been established with skin biopsy, low-potency and mid-potency topical corticosteroid creams or ointments may be used to control the symptoms of pruritus and dermatitis.[101] Topical corticosteroids should be avoided or discontinued for several weeks before skin biopsy because these agents suppress cutaneous inflammatory responses and can potentially mask the histopathologic features of CTCL. Regular soaking baths and application of lubricating cream to maintain skin hydration also are beneficial. Prompt treatment of infected areas of the skin and colonized or purulent ulcers minimizes the potential for more serious infections.[99]

Topical Therapies

Topical Chemotherapy

Topical corticosteroids are the mainstay of treatment for CTCL. Twice-daily application of topical class I steroids for 2 to 3 months is effective in mycosis fungoides plaque- and patch-stage disease, probably by inducing apoptosis. Skin atrophy and adrenal suppression are potential complications. In a series of 79 patients, 63% achieved a complete remission and 31% a partial remission on follow-up evaluation at a median of 9 months.[102]

Mechlorethamine (nitrogen mustard), available as mechlorethamine hydrochloride, was the first topical agent with demonstrated efficacy in CTCL.[103] Since its initial clinical use during the late 1940s at the Mayo Clinic, this alkylating drug has proved effective

Table 113-7 Stage-Specific Options for Management of Cutaneous T-Cell Lymphoma

PATCH, LIMITED AND GENERALIZED PLAQUE
Primary therapy
Topical corticosteroids
PUVA photochemotherapy
UVB phototherapy
Bexarotene gel or capsule
Mechlorethamine (nitrogen mustard)
Electron beam
Secondary therapy
BCNU (carmustine)
Imiquimod
High-intensity UVAI phototherapy
TUMOROUS DISEASE
Primary therapy
CHOP
Denileukin diftitox
Bexarotene capsule
Secondary therapy
Radiation therapy
Purine nucleoside analogs
Alemtuzumab (anti-CD52)
ERYTHRODERMA, SÉZARY SYNDROME
Primary therapy
Extracorporeal photophoresis (ECP)
Interferon-α
Bexarotene
Secondary therapy
Denileukin diftitox
Interleukin-2
Purine nucleoside analogs
Bone marrow transplantation
EXTRACUTANEOUS DISEASE
Primary therapy
CHOP
Denileukin diftitox
Secondary therapy
Purine nucleoside analogs
Alemtuzumab (anti-CD52)
Bone marrow transplantation

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; PUVA, psoralen plus ultraviolet light A; UVAI, ultraviolet light A; UVB, ultraviolet light B.

in limiting the progression of disease and controlling symptoms of cutaneous lesions in patients with CTCL. The agent undergoes rapid degradation to an active ethylenimonium ion, which has high antimitotic activity and a half-life of less than 10 minutes. Mechlorethamine may be prepared and applied in any of several different ways. It is soluble in water and typically is formulated at a concentration of 10 to 20 mg/dL. Alternatively, an alcoholic extract of mechlorethamine can be suspended in an oil-water base such as Aquaphor, which remains stable for longer than a month. Mechlorethamine is routinely applied to the entire skin surface, except the eyelids, genitalia, rectum, and intertriginous areas, where the potential for significant irritation limits its use. Application of the solution is performed daily and increased to twice a day, or the concentration can be doubled. The initial treatment program lasts 6 to 12 months, and maintenance therapy 3 times per week is continued for 1 to 2 years or longer. The agent does not cause cytopenias or secondary leukemias because it is not absorbed systemically. Its use as described is an efficient and conservative outpatient program in patients without large tumors or systemic involvement.

Mechlorethamine had been evaluated in clinical trials. Vonderheid and colleagues reported on 324 patients with CTCL, with complete remission rates of 80% in stage IA disease, 68% in stage IB, 61% in stage IIA, 49% in stage IIB, and 60% in stage III.[104] Twenty percent of patients had a complete remission of 4 years or more, and 11% had continuous complete remission. Other therapies have been used in numerous patients, including local irradiation, electron beam radiation therapy, PUVA therapy, UVB phototherapy, and chemotherapy. None of the 34 patients who were in long-term complete response (CR) received electron beam radiation therapy or phototherapy, but 9 patients received chemotherapy, including intravenous methotrexate and mechlorethamine. Therapy was discontinued within 6 months of attainment of CR in 10 of 34 patients, who did not experience a relapse after 8 years. The probability of achieving a CR at 2 years was 75.8% for stage I, 44.6% for stage II, and 48.6% for stage III in 117 patients for whom the only other treatment was radiation therapy, and the median time to CR was 11 months.[105] In 123 patients who received only ointment-based mechlorethamine in Aquaphor or polyethylene gel, the CR rate was 51% in T1 disease; 26% in T2 disease; zero in T3; and 22% in T4.[106,107] Of the patients who relapsed, 54% achieved a second CR.[107] The treatment durations were variable, with Hoppe and associates recommending treatment for 1 to 2 years after achieving a response,[106] Ramsay and coworkers, treatment for 6 months after clearing and a taper of 1.5 years,[105] and Vonderheid and colleagues, only 6 months of therapy.[104] The major toxic effect of mechlorethamine is allergic toxic contact dermatitis, which occurs in 35% to 65% of patients.[104–107] The incidence can be decreased to less than 10% with use of mechlorethamine dissolved in ointment. Avoidance of skin exposure to sunlight is recommended. Other toxicities include dry skin, irritant dermatitis, hyperpigmentation, bullous reactions, urticaria, Stevens-Johnson syndrome, and telangiectasias.[106] An increased risk of second malignancies of squamous cell carcinoma and basal cell carcinoma with use of this agent has been recognized,[104,106] although most patients received multiple other therapies. In the series reported by Hoppe and associates,[106] secondary cutaneous malignancies developed in only 1 of 14 patients who received mechlorethamine alone. No randomized trials with adequate patient numbers have compared topical therapy with other therapeutic modalities.

Carmustine applied at daily doses of 10 to 20 mg per day for 4 to 8 weeks produced responses similar to those observed with mechlorethamine.[108] In contrast with the absence of such effects with mechlorethamine, bone marrow suppression occurred in 7.4% of patients. Chronic skin telangiectasias also may develop with use of carmustine.

Topical bexarotene 1%, applied twice daily, is the first synthetic retinoid approved by the U.S. Food and Drug Administration (FDA). The complete remission rates ranges from 21% to 23%, and the mean overall response (OR) rate is 63%, with a median time to progression of 149 days (range, 52 to 342 days).[109,110] The response rate in a series of 94 patients was reported to be 45% with a dose schedule of 300 mg/m^2 per day.[110] Rash was reported in 56% of the patients and pruritus in 18%. The most frequent side effects are hypertriglyceridemia, pancreatitis, hypercholesterolemia, hypothyroidism, and headaches. Bexarotene induces apoptosis in CTCL.[111]

Other topical agents that have been evaluated include cytarabine, dianhydrogalactitol, dacarbazine, guanazole, teniposide, hydroxyurea, thiotepa, and methotrexate.[112]

Ultraviolet B Phototherapy and Ultraviolet A Photochemotherapy

UVB phototherapy has been used for years in the treatment of early patch-stage CTCL and the premalignant dermatosis, large-plaque parapsoriasis. The treatment is administered three times per week. A retrospective study has supported the clinical observations that UVB phototherapy provides favorable responses including clinical remission and lasting improvement in early patch-stage CTCL.[113] UVB penetrates only the epidermis and the superficial dermis, however, and has no effect on more indurated plaque-stage or extensive forms of CTCL. UVB phototherapy in patients with darkly pigmented skin is less effective because melanin absorbs the ultraviolet radiation.[114] UVB phototherapy has a tendency to aggravate the erythroderma and pruritus of Sézary syndrome and should be avoided for this disorder.

Treatment of CTCL with PUVA with 8-methoxypsoralen preparations administered orally has been shown to be effective in the control of early disease. 8-Methoxypsoralen is a member of a family of photoactivated compounds that inhibit DNA synthesis through formation of monofunctional or bifunctional adducts and crosslinks of nucleic acids, resulting in apoptotic cell death. PUVA has other biologic effects that may contribute to the responses in CTCL, including direct cytotoxic, anti-inflammatory, and immunomodulatory reactions. A dose of 0.6 mg/kg of 8-methoxypsoralen is given 2 hours before UVA treatment, or an encapsulated form (Oxsoralen Ultra or Uvadex) is ingested 1 hour before treatment. The main toxicity is nausea and vomiting, which may be avoided by using 5-methoxypsoralen.[115] This drug is contraindicated in liver disease.

The patient is exposed to UVA lamps, which emit long UV (A-band) radiation in the wavelength range of 320 to 400 nm. UV-protective eyeglasses are worn for 24 hours after treatment. This therapy usually is given three times per week for 3 to 6 months, followed by tapering. After an initial report by Gilchrest and colleagues, multiple trials of efficacy of PUVA in early-stage disease have been reported.[116,117] Roenigk and colleagues reported that at a mean follow-up of 45 months, 82% of patients had complete clearing of plaque disease, with 88% remaining in complete remission for a median duration of 13 months.[118] Clearing of lesions was observed in 51.9% of the patients with extensive plaque disease, with a mean duration of 11 months; no clearing occurred in patients with tumor-stage or nodal-stage disease. In erythrodermic CTCL, 46% of the patients demonstrated clearing of the disease, but 75% relapsed. In patients followed for a mean of 44 months, no recurrences were noted in 55.6% of patients with stage 1A disease and in 38.5% of patients with stage IIB disease.[119]

PUVA has been combined with topical nitrogen mustard, retinoids, aerosolized granulocytemacrophage colony stimulating factor (GM-CSF), and interferon alfa-2a.[120–124] Retinoids have been reported to decrease the number of PUVA treatments and the total UVA dose.[123] The OR rate in 39 patients with mycosis fungoides was 90% (62% CR and 28% partial response [PR]), with a median response duration of 28 months. Retrospective evaluation of data for 30 patients who received low-dose interferon alfa-2a showed a CR in 83% (25 of 30) after a median of 5 months of treatment, with a median remission duration of 22 months.[125]

Contraindications to UV radiation therapy include systemic lupus erythematosus, skin cancer, porphyria, and genetic syndromes secondary to DNA repair defects.[115] Toxic reactions from PUVA therapy include nausea, vomiting, pruritus, erythema, xerosis, dry skin, blistering, and burns. Other, less common or potential side effects include development of pigmented melanocytic macules of the skin, nail pigmentation, and cataract formation.[125] Amyloid deposition has been reported.[126] UV light–blocking eyeglasses should be worn for 24 hours after psoralen is administered. Long-term toxic reactions of greater concern include squamous cell carcinoma of the skin or genitalia, photoaging, and amyloid deposition in the skin.[127]

Electron Beam Radiation Therapy

Electron beam radiation therapy was first used for malignant cutaneous lesions lesions in 1953 and has been advocated for treatment of CTCL with both limited and extensive cutaneous involvement.[128,129] Electrons are delivered to a depth of several millimeters to 1 cm. In a series of 192 patients with CTCL treated at Stanford University between 1966 and 1987 to a total dose of more than 2000 cGy, the complete remission rate in limited plaque disease (T1) was 98%, with a freedom-from-relapse rate of 50%; in generalized plaque disease (T2), 71%, with a freedom-from-relapse rate of 20%; in tumor-stage disease, 36%; and, in erythroderma, 64%.[130] Most relapses occur within 5 years. The 10-year survivor rate was 46%. Other studies have reported an OS rate of 70%.[131] The usual total dose is 3000 to 3600 cGy delivered over 8 to 10 weeks of treatment. The toxic reactions include desquamative skin reactions on the feet and toes, erythema, blister formation, exfoliation, dryness, extensive alopecia with eventual recovery of hair growth, temporary nail loss, inability to sweat because of loss of sweat glands, hyperpigmentation, and telangiectasias.[128–130] The increased risk of squamous and basal cell carcinomas is perhaps greatest in those patients who have received multiple therapies including irradiation, topical nitrogen mustard, and PUVA.[132] Most patients are given only a single course of treatment. One study evaluating retreatment for CTCL, however, reported 6 CRs and 8 PRs in 15 patients.[133] Adjuvant therapy with nitrogen mustard, PUVA, or extracorporeal photochemotherapy may be used to decrease the risk of relapse.[134]

Systemic Therapies

Extracorporeal Photochemotherapy

Extracorporeal photochemotherapy (ECP), or photopheresis, is a systemic form of PUVA therapy that combines leukapheresis with photochemotherapy and is efficacious in Sézary syndrome and erythrodermic mycosis fungoides. The biologic mechanisms of action that mediate clinical responses to ECP in CTCL are not clearly defined. Direct effects on DNA synthesis and membrane alterations induced by psoralens and UVA may cause cytotoxicity with release of tumor antigens, resulting in a systemic antitumor response, but the immunomodulatory effects and possible induction of immune responses to the malignant lymphoid cell population also may explain the clinical responses observed.[135] The ECP process induces an anti-idiotypic cytotoxic T-cell response against circulating CTCL cells, which subsequently undergo apoptosis. Patients ingest 8-methoxypsoralen and then undergo leukapheresis and cell separation. Cells of the mononuclear fraction are exposed to ultraviolet (UVA) radiation from lamps housed ex vivo in the apheresis device followed by reinfusion of the treated cells. This results in DNA crosslinking, apoptosis, and cell death. The process usually is performed on two consecutive days every 4 weeks.

The initial experience by Edelson and colleagues reported that 27 of 37 patients with therapy-resistant or -refractory CTCL exhibited greater than 25% skin improvement.[136] Long-term follow-up evaluation of patients with erythroderma revealed a median survival time of 60.3 months and a median survival time from onset of treatment of 47.9 months, with a CR rate of 21%.[137] Clinical indications for favorable ECP results include Sézary syndrome, widespread disease of less than 2 years' duration, and CTCL cases in which the patient's $CD8^+$ count is near normal.[135] Significant beneficial responses have not been demonstrated in patients with patch- or plaque-stage or tumor-stage mycosis fungoides or with advanced CTCL, but this treatment may prolong remission in patients who had previously received radiation therapy.[138] After a minimum of six cycles of ECP, photopheresis is continued through clearing and for approximately 6

additional months of treatment.[136,138] A higher baseline lymphocyte count and higher absolute Sézary cell count were associated with a decrease in skin score and response after 6 months.[139] Toxicities include nausea, fever, occasional erythematous flares after reinfusion, and hypotension during apheresis. Septicemia has occurred and probably is related to the immunocompromised state associated with CTCL. OR rates range from 54% to 75%, and 15% to 25% of patients achieve a CR.[140] Other agents have been added to photopheresis, including methotrexate, interferon, and immunomodulatory therapy.[141] ECP is not active in limited-stage mycosis fungoides.

Interferons

Interferon is the therapeutic agent of choice in advanced stages of mycosis fungoides and Sézary syndrome and is the most effective agent in the treatment of advanced SS/mycosis fungoides alone or in combination with interferon alfa-2a (Roferon-A, Hoffman-LaRoche, Inc., Nutley, NJ) and interferon alfa-2b (Intron-A, Shering-Plough Corp., Kenilworth, NJ), which differ by only one amino acid, have significant activity in mycosis fungoides and Sézary syndrome. Initially, high doses of drug were used.[142] The OR rates up to 60% have been reported.[143] In a randomized trial of intralesional interferon alfa-2b at a dose of 1×10^6 IU three times daily for 4 weeks resulted in CR in 10 of 12 patients who received the drug, compared with 1 of 12 patients whose lesions were treated with placebo.[144] The suggested systemic dose of interferon is 1 to 3×10^6 IU administered three times weekly, increased to 9 to 12×10^6 IU daily or as tolerated, because no dose-response data have been published.[145] A tachyphylaxis develops subsequent to the initial fevers and chills. Leukopenia occurs in the first 3 months of therapy but usually is of no clinical significance. Patients may experience chronic fatigue while receiving recombinant interferon.

Systemic Chemotherapy

Chemotherapy, administered orally or parenterally in either a single-agent or a combination regimen, is used in patients with CTCL, in patients with relapsed or refractory disease, and in patients whose tumor cells have undergone histologic transformation. Patients with extracutaneous or extranodal disease are candidates for systemic chemotherapy. Initial results of chemotherapy have been reviewed.[146] The duration of response to single-agent therapy ranged from 3 to 22 months. In a total of 331 patients with CTCL treated with combination chemotherapy, the OR rate was 81%, but the median duration of response was less than 1 year.

Moderate doses of methotrexate (60 to 240 mg/m^2) accompanied by oral leucovorin calcium followed by maintenance oral methotrexate for 6 to 30 months resulted in a CR in 7 of 11 patients and a PR in 2 of 9 patients.[147] A common intravenous regimen is the combination of cyclophosphamide, vincristine, prednisone (CVP); doxorubicin (Adriamycin) may be added to CVP (CHOP), as well as methotrexate and other agents.[148] Seven of 10 patients receiving bleomycin, doxorubicin, methotrexate, and topical nitrogen mustard exhibited a CR, with a median duration of response of 19 months.[149] Pegylated liposomal doxorubicin (Doxil) at a dose of 20 to 40 mg/m^2 every 4 weeks resulted in a CR in 6 and a PR in 2 of 10 patients, with a response duration of 15 months.[150] A retrospective multicenter study in 34 patients reported an 88% OR rate.[151]

Valid interpretation of the efficacy of chemotherapy in CTCL is complex. The current role of chemotherapy in the management of CTCL compared with other therapies is difficult to determine. In published studies, patients have received multiple and variable previous treatments; the series have reported small numbers of patients; stage of disease was not reported; various stages of CTCL were included; pathologic documentation of extra cutaneous disease often was lacking; and studies often combined patients with Sézary syndrome and those with mycosis fungoides. No clinical trial has demonstrated a survival benefit in patients receiving aggressive treatment. Therefore, more aggressive chemotherapy should be reserved for clinical studies or should be used after topical regimens have failed or other therapies no longer provide benefit. This therapy is palliative.

Purine Nucleoside Analogs

The purine nucleoside analogs in CTCL have been evaluated in several clinical trials. The class of drugs includes 2′-deoxycoformycin, fludarabine, cladribine, and gemcitabine. Of 34 patients with CTCL treated with single-agent pentostatin in five phase II studies, the CR rate was 7%, with an OR rate of 40% and a median time to progression of 1.3 to 8.3 months.[152] The OR rate with fludarabine was 19% in 33 patients in a Southwestern Oncology Group trial.[153] Fludarabine followed by ECP produced an overall response rate of 63.2% versus 29.5% in patients treated with fludarabine monotherapy.[154] Aproximately one third of patients respond to cladribine.[155] These agents have been combined with other therapeutic approaches such as interferon therapy. Neutropenia and thrombocytopenia are adverse effects associated with use of these agents. In a recent study, gemcitabine at a dose of 1200 mg/m^2 intravenously was given on days 1, 8, and 15 of a 28-day schedule for a total of three courses in 30 patients with mycosis fungoides; a CR rate of 10% and a PR rate of 60% were reported, with a median duration of 15 months.[156]

Vitamin A Analogs

Retinoids are derivatives of vitamin A that have been reported to be effective in CTCL. Isotretinoin (Accutane) and acitretin (Soriatane) have moderate activity. Of 25 patients with disease staged as T2 or higher, 11 (44%) had a response to isotretinoin (13-*cis*-retinoic acid), with a median duration of 8 months.[157] As single agents, retinoids have limited clinical use. Toxic effects include dry mucous membranes, skin fragility, arthralgias, myalgias, headache, fatigue, and increased triglyceride levels. The results of multiple studies suggest a CR rate of 19% and an OR rate of 58%.

Bexarotene at a dose of 300 mg/m^2 is a retinoid approved by the FDA for the treatment of refractory or relapsed CTCL that selectively activates retinoid X receptors.[158,159] In 94 patients, the OR rate was 49%, with a CR rate of 4% and a median duration of response of 10 months.[158] Toxic effects include hyperlipidemia, hypothyroidism, and cytopenias. In patients with disease staged as IB or higher, oral bexarotene may be considered a first-line treatment alone or in combination with PUVA. Combining PUVA and bexarotene allows for a decreased dose of both but does not increase the response rates.

Other Oral Chemotherapy Agent Approaches

Chlorambucil in a dose of 0.1 to 0.2 mg/kg daily for 2 to 4 weeks for 6 to 8 cycles results in a reported OR rate of 25% to 30%, with a median duration of response of 3 to 22 months.[146]

Etoposide in a dose of 50 mg/m^2 daily for 21 days every 28 to 35 days is active in chemotherapy-refractory disease.[160] Temozolomide, an oral alkylating agent, in a dose of 150 to 200 mg/m^2 for 5 days every 28 days also is active.

Monoclonal Antibodies

Murine monoclonal antibodies have been used as unaltered immunoglobulin, conjugated to toxins, conjugated to radioisotopes, or modified as chimeric antibodies. Initial trials included ^{90}Y-T101, ^{90}Y–anti-CD25, and anti-Tac *Pseudomonas* exotoxin. Anti-CD52 monoclonal antibody, alemtuzumab (Campath-1H), produced a CR rate of 23% and an OR rate of 59% in patients with erythroderma and 40% in those with plaque and skin tumors, with a median time to treatment failure of 12 months.[161] Alefecept (Aminvive, Biogen Idec) is a fully humanized recombinant protein that has been designed to modulate immune responses through interaction with the CD2 receptor on T lymphocytes inhibiting LFA-3/CD2 interaction that is FDA approved for psoriasis and is now in phase I trials for CTCL. The reduction in CD2$^+$ cells results in a reduction in CD4$^+$ and CD8$^+$ T-lymphocyte counts. Toxic effects include urticaria, infections, angioedema, and injection site reactions. Alemtuzumab is associated with significant myelosuppression, with associated viral, fungal,

and bacterial infections, including reactivation of cytomegalovirus infection, herpes zoster, and herpes simplex. Prophylactic antibiotics and antiviral and antifungal agents are required.

Interleukins and Recombinant Fusion Proteins

Bioactive recombinant interleukins and other cytokines have favorable prospects in the treatment of CTCL. Recombinant interleukin-2 (IL-2) was administered in four patients, and all had a response, with two CRs.[162] Approximately half of the patients with mycosis fungoides or Sézary syndrome have IL-2 receptors (IL-2R alpha chain, CD25). Denileukin diftitox (Ontak) is a genetically engineered fusion protein containing the portion of IL-2 that interacts with IL-2 and a synthetic protein identical to diphtheria toxin. The IL-2 portion of this drug binds with IL-2R on the mycosis fungoides/SS cells, the toxin is internalized, and apoptosis is induced. Denileukin diftitox administered at a dose of 9 or 18 μg daily for 5 days every 21 days is FDA approved. A randomized double-blind study of 71 patients with CD25 expression in 20% of lymphocytes or greater reported an OR rate of 30% (10% CR and 20% PR), with a median duration of response of 6.9 months (range, 2.7 to 46.1 months).[163] Toxic effects include flu-like symptoms, acute infusion-related events (episodes of hypotension, chest pain, and back pain), vascular leak syndrome, elevated liver function tests (61%), and hypoalbuminemia (79%). Bexarotene upregulates the expression of the high-affinity IL-2R. The OR rate with denileukin diftitox with escalating doses of bexarotene was 57%.[164]

Histone Deacetylase Inhibitor

Vorinostat (Zolinza) is a histone deacetylase inhibitor that results in histone acetylation and activation of gene expression and is FDA approved. The recommended dose is 400 mg per day orally, with treatment continuing until disease progression. In a phase II trial in 33 patients who previously had received a median of five prior therapies, 8 patients achieved a PR, 7 of whom had Sézary syndrome.[165] The median time to response was 11.9 weeks. Fourteen of 31 evaluable patients experienced relief of pruritus. Of 74 patients enrolled in a phase IIB trial,[166] the OR rate was 29.7% in all patients and similar in those with disease staged as IIB or higher. The median time to progression was 4.9 months in all patients and up to 9.8 months in responders with stage IIB or higher disease.

Common toxic effects include diarrhea, fatigue, nausea, dysgeusia, and anorexia. Less common toxicities include severe thrombocytopenia, pulmonary embolism, and elevations in creatinine level. Prolongation of the prothrombin time in patients receiving concomitant coumarin derivative anticoagulants may occur.

Other Therapies

Antithymocyte globulin, cyclosporine, and acyclovir have been reported to induce transient responses.[167–169]

Stem Cell Transplantation

Studies of autologous peripheral blood stem cell transplantation and allogeneic transplantation strategies are ongoing. Five of six patients who underwent autologous bone marrow transplantation responded, but three of these patients relapsed in less than 100 days.[170] With use of a T cell–depleted peripheral transplant strategy, seven of nine patients relapsed at a median of 7 months (range 2 to 14 months), engraftment did not occur in one patient, and another patient died of sepsis.[171] In studies of allogeneic bone marrow transplantation, 3 patients were alive and disease-free 15 months to 4 years.[172,173] Allogeneic transplantation produces more durable complete remissions, an outcome attributed to an immune-mediated graft-versus-lymphoma effect.[174] Mortality is significant with this approach, however, and other associated toxicities including graft-versus-host disease create much higher risks for morbidity and early death. Nonmyeloablative ("mini") allogeneic transplantation creates a graft-versus-lymphoma effect, with less conditioning regimen–related toxicity. Engraftment occurred in 10 of 11 patients, and after a median follow-up period of 2.9 years (range, 3 months to 4.4 years), 7 of the patients were in remission and 4 had chronic graft-versus-host disease necessitating treatment.[175]

Combined-Modality Therapy

In one study, results with the combination of electron beam radiation therapy and local radiation therapy followed by combination chemotherapy suggested that survival and remission duration may be improved.[176] The median disease-free survival period was 12 months, and all patients with plaque-stage disease relapsed within 25 months.[177] Fifty nonrandomized patients received total-skin electron beam radiation therapy followed by combination chemotherapy with doxorubicin and cyclophosphamide.[178] The CR rate was 88%, with a significant increase in the duration of response in early-stage CTCL but not in advanced disease.

The first randomized clinical trial compared conservative sequential topical therapy with total electron beam radiation therapy in 103 patients.[179] Patients with disease of all stages were eligible, and no restrictions were assigned on the basis of performance status. The sequential topical regimen was initiated with topical nitrogen mustard and was changed to PUVA if progression of CTCL occurred or toxicity developed from the topical nitrogen mustard. For continued disease progression, the patient received total-skin electron beam radiation therapy, followed by methotrexate administered orally. If extracutaneous disease developed, systemic chemotherapy was administered. The combination regimen consisted of 3000 cGy total-skin electron beam radiation therapy followed by cyclophosphamide, doxorubicin, etoposide, and vincristine administered intravenously. After a median follow-up period of 75 months, the only significant difference was in the CR rates for the two treatment groups: 38% in the combined-modality group and 10% in the topical group. No statistical difference was observed in the disease-free survival rate or OS rate as a group or by stage for the two treatment groups. Toxicity was greater in the combined-modality group and included myelosuppression, radiodermatitis, neuropathy, and congestive heart failure. Less than 10% of patients in both groups remained disease free. Other regimens and approaches have been published.[180,181]

In another study, 124 patients with early stage I and II mycosis fungoides disease were randomized to receive PUVA or PUVA plus interferon alfa-2a (Roferon-A) at a dose of 9×10^6 U three times per week.[182] Fifty patients in the PUVA treatment group and 43 patients in the interferon-PUVA treatment group were evaluable. On follow-up evaluation at a median of 101 weeks, median progression-free survival times were 53 weeks with PUVA and 113 weeks with interferon-PUVA ($P = 0.0398$). This combination therapy is the initial treatment of choice for limited-stage disease.

CONCLUSIONS

Most cases, of CTCL cannot be cured. Early-stage (i.e., IA to IIA) mycosis fungoides should be treated with skin-targeted therapeutic interventions to achieve a complete remission. Disease recurrence is frequent, but long-term survival is not influenced by relapse status. Progress has been made in defining and classifying the cutaneous lymphomas, and in characterizing the relationship of mycosis fungoides and Sézary syndrome and other premalignant conditions with CTCL and B-cell lymphomas. Recent advances in immunobiology, cell biology, and molecular biology have further identified and defined the malignant lymphoid population involved in CTCL and the mechanisms by which these cells may interact with skin and manifest the clinical features of CTCL.[183] Treatment approaches are institution dependent, although consensus guidelines are published for this complex group of diseases.[184] Continued advances in the understanding of the pathobiology of CTCL and the uncovering of potential targets will provide new therapeutic interventions that will improve the outcomes with cutaneous T-cell and B-cell lymphomas.

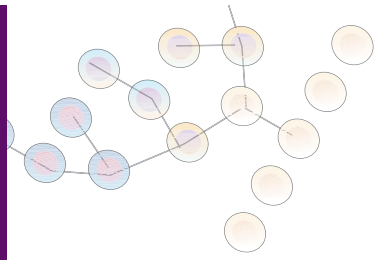
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114 Adult T-Cell Leukemia-Lymphoma

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SUMMARY OF KEY POINTS

Background
- Adult T-cell leukemia-lymphoma (ATLL) is a distinct peripheral T-cell malignancy that is associated with human T-cell leukemia virus type I (HTLV-I).

Virology
- HTLV-I is reverse-transcribed into DNA and integrated into the host cell.
- The HTLV-I genome encodes two unique regulatory proteins—Tax and Rex—that are responsible for viral expression and cellular transformation. Tax *trans*-activates viral and cellular genes that could be involved in the pathogenesis of ATLL.

Epidemiology
- The major cluster of HTLV-I-infected individuals and patients with ATLL exists in Japan, where approximately 1.2 million people are infected with the virus.
- Other clusters have been noted in the Caribbean islands (African), tropical Africa (African), South America (Mongoloid), and northern Oceania (Melanesian).
- HTLV-I is transmitted by mother to child through breast-feeding, by sexual contact, and by blood-borne transmission.
- The estimated cumulative risk of the development of ATLL in HTLV-I-positive individuals is 2.5%.

Clinical Manifestations
- Patients with ATLL show diverse clinical features, and four clinical subtypes have been recognized: acute, lymphoma, chronic, and smoldering types.
- The typical manifestations of acute-type ATLL include circulating neoplastic cells in the peripheral blood, generalized lymph node swelling, hepatosplenomegaly, skin involvement, and hypercalcemia.

Histopathology
- Leukemic cells in the peripheral blood characteristically show markedly polylobated nuclei, the so-called flower cells. Their immunophenotypes are CD4-positive and CD8-negative T-cell in most cases.
- All histopathologic specimens show the findings of peripheral T-cell lymphoma of various subtypes.

Diagnosis
- ATLL is suspected when the aforementioned characteristic clinical manifestations and/or the cytologic findings of leukemic cells in the peripheral blood are recognized.
- An immunophenotypic analysis of neoplastic cells and a serologic assay against HTLV-I are required for the clinical diagnosis of ATLL.
- The demonstration of the monoclonal integration of HTLV-I proviral DNA in the tumor cells can lead to a definite diagnosis of ATLL.

Treatment
- An accurate diagnosis of the clinical subtype is vital for appropriate decisions regarding treatment.
- Combination chemotherapies used in the treatment of non-Hodgkin's lymphoma are usually given to patients with the acute or lymphoma subtype of ATLL; however, most patients with ATLL are not curable with current chemotherapy regimens.
- Further efforts to incorporate new, innovative treatment modalities, such as new anticancer agents, monoclonal antibody therapy, molecular-targeting therapy, and allogeneic hematopoietic stem cell transplantation, are needed.

INTRODUCTION

Adult T-cell leukemia-lymphoma (ATLL) was first recognized in Japan in 1977s.[1] The disease was characterized as leukemia of peripheral T cells, generalized lymphadenopathy, hepatosplenomegaly, and skin involvement. Owing to its unusual geographic clustering in southwestern Japan, it was postulated that some infectious agent(s) had causative roles. Human T-lymphotropic virus (HTLV) was first isolated by Poiesz and associates[2] in the United States from cultured cells from one patient with an aggressive variant of mycosis fungoides and from one with Sézary syndrome. Although both patients were diagnosed clinically as having cutaneous T-cell lymphoma (CTCL) at the time of reporting, their clinical features were later found to closely resemble those of Japanese patients with ATLL.

In 1980, Miyoshi and coworkers[3] established the first cell line (MT-1) derived from neoplastic cells in an ATLL patient. They cocultured neoplastic cells from an ATLL patient with normal human cord blood lymphocytes and established the cell line MT-2 (derived from cord blood lymphocytes), which produced high amounts of type C retrovirus.[4] Using the MT-1 cell line, Hinuma and colleagues[5] found that patients with ATLL had antibodies against the virus-associated antigen in their sera. The "ATLL virus" was then isolated and characterized as an RNA retrovirus.[6] As HTLV and ATLL virus were found to be identical by a DNA sequence analysis, this virus was designated human T-cell leukemia virus type I or human T-lymphotropic virus type I (HTLV-I).[7]

The etiologic association of HTLV-I and ATLL is based on the findings that follow.

- The areas of high incidence of patients with ATLL closely correspond with those of high prevalence of HTLV-I carriers.[8]
- HTLV-I immortalizes T cells in vitro.[9]
- HTLV-I proviral DNA is detected in the neoplastic cells of ATLL.[10]
- Almost all patients with ATLL have antibodies against HTLV-I in their sera.

HTLV-I is the first retrovirus that was found to be associated with a malignant neoplasm in humans.

VIROLOGY AND PATHOGENESIS

HTLV-I is reverse-transcribed into DNA and integrated as a proviral DNA in the host cell. The HTLV-I provirus is 9.0 kilobases long and has structural genes in the order 5′-gag-pol-env-3′. Both ends of the HTLV-I proviral DNA contain repeats called long terminal repeats (LTRs). No specific integration sites of the HTLV-I provirus in the host cellular chromosomes have been identified.[11] A unique feature of the viral structure of HTLV-I provirus is the presence of a long sequence between *env* and 3′ LTR. One product of this *pX* gene, p40*tax*, acts on the LTRs for the *trans*-activation of the viral gene.[12]

The HTLV-I gene encodes three structural proteins: group antigen (*gag*), reverse transcriptase (*pol*), and envelope (*env*) proteins. The full-length mRNA is used for synthesis of *gag* and *pol* gene products. The gag protein is synthesized as a precursor polypeptide of 55 kilodaltons that is proteolytically cleaved into the individual gag proteins p19, p24, and p15. The protease is encoded in a different reading frame that spans the 3′ part of the *gag* region and the 5′ part of the *pol* region. The *pol* region encodes the reverse transcriptase, integrase, and RNase H. The *env* gene encodes two proteins made from a singly spliced mRNA. It is then cleaved intracellularly into an extracellular glycosylated protein (gp46) and a transmembrane (gp21). The *pX* region at the 3′ end of the genome has the potential to encode essential regulatory proteins (Tax and Rex) and three accessory proteins—p12, p13, and p30—that are important for viral infectivity and replication by influencing cellular signaling and gene expression.[13,14]

The life cycle of a retrovirus begins with the binding of the virus to specific receptors on the cell surface via viral envelope proteins. HTLV-1 is transmitted through a viral synapse and enters target cells via interaction with the glucose transporter GLUT1.[15] However, other molecules have also been reported to be involved in virus entry, for example, HSC70,[16] heparan sulfate proteoglycans,[17] and neurophilin-1.[18]

Role of Tax

The onset of ATLL is preceded by a long period of clinical latency, frequently lasting more than four decades. In addition, fewer than 5% of all infected individuals with HTLV-I develop ATLL. The promoter insertion model was rejected as the leukemogenic mechanism because integration sites of the provirus were random depending on the patient.[11] Consequently, a *trans*-acting viral factor, Tax, has been shown to be oncogenic, since it transforms and immortalizes rodent fibroblasts and T lymphocytes as well as human T lymphocytes. Tax *trans*-activates viral transcription through interaction with the cellular basic domain/leucine zipper transcription factors CREB and ATF-1. Tax interacts with numerous cellular proteins to reprogram cellular processes, including, but not limited to, transcription, cell cycle regulation, DNA repair, and apoptosis. Tax transcriptionally regulates cellular genes by interaction with enhancer-binding proteins such as CREB, NF-κB, and serum response factor and by tethering coactivators to the DNA-bound transcription factors. Tax also stimulates cell growth by direct binding to cyclin-dependent kinase holoenzymes and/or inactivating tumor suppressors such as p53 and DLG. Furthermore, Tax silences cellular checkpoints, which guard against DNA structural damage and chromosomal missegregation, thereby favoring the manifestation of a mutator phenotype in cells.[13,19]

Tax interacts and activates specific components of growth factor signal transduction pathways, such as IKK-IκB-NF-κB, RAS/mitogen-activated protein kinase, protein kinase A, and protein kinase C.[20,21] Interaction with IKKγ, a component of IKK complex, results in constitutive activation of this kinase complex.[22] Constitutive activation of the JAK-STAT pathway in HTLV-I-transformed cells has also been reported, although the mechanisms are not well understood.[23] Thus, HTLV-I infection results in aberrant activation of growth-promoting signaling pathways.

The oncogenic capacity of Tax has been reported in various systems; however, cellular transformation by HTLV-I in vivo is a multistage process, and viral gene expression is absent in ATLL cells in vivo.[24,25] Moreover, proviruses integrated in ATLL cells are frequently defective, have mutations in the coding region of Tax, and/or are methylated in the 5′ and 5′ LTR regions.[26–28] Thus, in addition to promoting growth directly, Tax should endow the infected T cells with capacities that aid the progression to transformed phenotypes in the absence of Tax. In this context, induction of a mutator phenotype by Tax in the infected cells appears to play an important role.[29] The roles of HTLV-I Tax in the multistep leukemogenesis of ATLL are illustrated in Figure 114-1.

Expression of antisense strand RNA with capacity encoding a zinc finger protein (HTLV-I basic leucine zipper factor) has opened a new research field. HTLV-I basic leucine zipper factor inhibits Tax-dependent viral transcription[30] and might be involved in growth of ATLL cells.[31]

Role of Chromosomal Abnormalities

Various karyotypic abnormalities have been reported in neoplastic cells of ATLL; however, no specific karyotypic abnormality has been

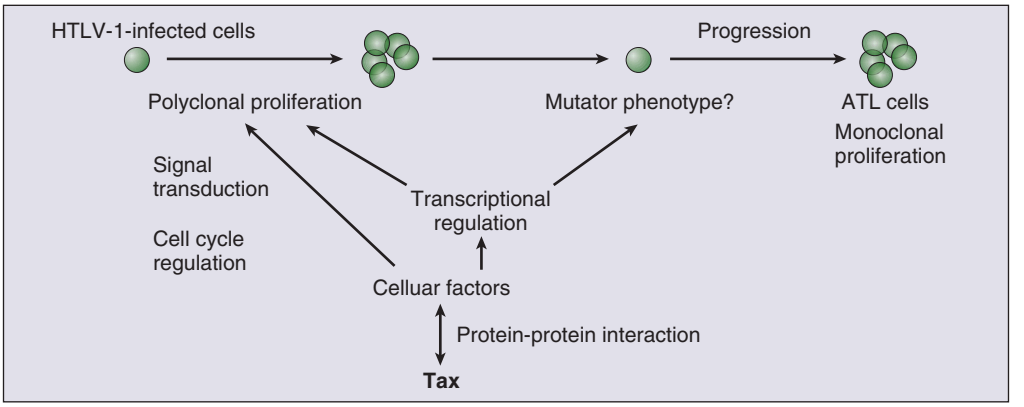


Figure 114-1 • Roles of HTLV-I Tax in the multistep leukemogenesis of ATLL. Tax exerts its biologic effects mainly through protein-protein interaction, resulting in deregulation of transcription, cell cycle control, and signal transduction. It also impairs the cell's ability to repair DNA damage, which can lead to the mutator phenotype of the infected cells.

found. In general, the chromosomal abnormalities are more complex in the acute type compared with those in the chronic type. Itoyama and colleagues[32] reported the results of cytogenetic analysis of 50 cases of ATLL and found aneuploidy and multiple breaks more frequently in acute and lymphoma types. Multiple breaks and partial loss of chromosomes correlated with shorter survival. The authors claim that one model of an oncogenic mechanism—activation of a proto-oncogene by translocation of a T-cell receptor (TCR) gene—might not be applicable to the main pathway of development of ATLL and that a multistep process of leukemogenesis is required.

In a study by Tsukasaki and associates,[33] 64 patients with ATLL were analyzed by using comparative genomic hybridization (CGH). The most frequent observations were gains at chromosomes 14q, 7q, and 3p and losses at chromosomes 6q and 13q. Chromosome imbalances, losses, and gains were observed more frequently in acute or lymphoma types. An increased number of chromosomal imbalances were associated with a shorter survival. Paired samples (i.e., samples obtained at different sites from four patients) and sequential samples from 13 patients (from six during both chronic phase and acute crisis and from seven during both acute onset and relapse) were examined by CGH and Southern blotting for HTLV-I. All but two paired samples showed differences on CGH assessment. Two chronic/crisis samples showed distinct results regarding both CGH and HTLV-I integration sites, suggesting clonal changes in ATLL at crisis. In 11 patients, the finding of identical HTLV-I sites and clonally related CGH results suggested a common origin of sequential samples. In contrast to chronic/crisis samples, CGH results with all acute/relapse sample pairs showed the presence of clonally related but not evolutional subclones at relapse. It was concluded that clonal diversity is common during progression of ATLL and that CGH alterations are associated with clinical course.

Role of *p53* and Other Tumor Suppressor Genes

p53 is a nuclear phosphoprotein that functions as a tumor suppressor gene. A loss of normally functioning *p53* through mutation or allelic loss has been found in several kinds of malignant neoplasms. Mutations of the *p53* gene have also been found in some patients with ATLL.[34,35] According to the study by Cesarman and coworkers,[35] no p53 mutations were detected in samples from 11 patients with the chronic type of ATLL, whereas 9 (28%) of 28 samples from patients with the acute type of ATLL exhibited p53 mutations. In one patient, a tumor sample obtained during the chronic phase did not have a mutation of the p53 gene, but the mutation was subsequently detected in a sample that was obtained at crisis. These results suggest that alterations of the p53 gene might contribute to disease progression in a fraction of patients with ATLL.

Other putative tumor suppressor genes, $p15^{INK4B}$ and $p16^{INK4A}$, were reported to be associated with ATLL.[36–38] Yamada and associates[37] reported that 28 (25%) of 114 patients with ATLL showed homozygous deletions of the *p15* and/or *p16* genes. These results correlated well with the clinical subtypes of ATLL. In addition, the patients with deleted *p15* and/or *p16* genes showed significantly shorter survival than did patients in whom both genes were preserved ($P < 0.0001$). Moreover, three of the five chronic-type patients who progressed to acute-type ATLL lost the *p16* gene alone or both genes at their exacerbation phase. These results suggest that the deletions of *p15* and/or *p16* genes play a key role in the disease progression of some patients with ATLL. Uchida and colleagues[38] found the point mutation of the *p16* gene in 3 (7%) of 44 patients with ATLL. It is suggested that the *p16* gene is inactivated not only by homozygous deletion, but also by point mutation.

Role of HTLV-I Provirus

Several investigators have analyzed the implications of the integration pattern of HTLV-I provirus in the disease progression of ATLL.[39,40] It is known that the neoplastic cells of ATLL have one copy of complete HTLV-I provirus per cell in some patients (complete-type), while others have multiple complete copies of the virus per cell (multiple-type). The HTLV-I proviruses in the remaining patients do not have the complete genome but rather have a defective genome (defective-type). Tsukasaki and associates[40] found that the median survival times (MST) for patients were 7 months, 24 months, and 33 months for defective-type, complete-type, and multiple-type ATLL, respectively ($P = 0.006$). Among 52 sequentially examined patients, the HTLV-I integration patterns changed in four patients (8%). In three of these four, the rearrangements of the TCR-β gene changed concomitantly, suggesting the appearance of a new ATLL clone. The researchers concluded that the frequent clonal change of ATLL at crisis reflects the emergence of multiple premalignant clones in viral leukemogenesis.

Tamiya and coworkers[39] reported the presence of two types of defective virus. Among them, type 2 defective virus with the deletion that includes 5′ LTR was found more frequently in the acute and lymphoma types (39%, 21 of 54) than in the chronic type (6%, 1 of 18). It is postulated that the high frequency of the type 2 defective viruses is caused by the genetic instability of HTLV-I provirus and that this defective virus is selected because it escapes from the immune surveillance system in the host.

HTLV-I is an etiologic agent not only in ATLL, but also in the neurologic disorder known as tropical spastic paraparesis (TSP) or as HTLV-I-associated myelopathy (HAM).[41,42] In TSP/HAM, the HTLV-I provirus remains randomly integrated, whereas in ATLL, the provirus is monoclonally integrated.

EPIDEMIOLOGY OF HTLV-I AND ADULT T-CELL LEUKEMIA-LYMPHOMA

Southwestern Japan has the highest recorded prevalence of HTLV-I infection and the highest incidence of patients with ATLL in the world.[8,42–44] A high prevalence of HTLV-I is also found in the Caribbean islands (African), tropical Africa (African), South America (Mongoloid), and northern Oceania (Melanesian).[43–46] Many patients who have been diagnosed as having ATLL in Western countries are immigrants from the West Indies and tropical Africa. The world map of the distribution of HTLV-I and HTLV-II and the presumed routes of spread are shown in Figure 114-2.[44] The geographic clustering of HTLV-I carriers is suggested to be strongly associated with a high frequency of mother-to-child transmission of the virus under closed conditions in particular groups.[47]

It has been estimated that approximately 1.2 million HTLV-I-infected individuals reside in Japan, and the annual incidence of ATLL has been estimated to be approximately 700 in Japan.[8] The annual rate of ATLL development among HTLV-I carriers older than 40 years is estimated at 1.5 per 1000 in males and 0.5 per 1000 in females, and the cumulative risk of ATLL development among the HTLV-I carriers is estimated to be 2.5% to 5% over the course of a 70-year life span.[48]

In a national survey in Japan, the mean age of patients with ATLL has been estimated at 57.6 years, and this age appears to have increased over time.[8] It has been reported that the age of patients with ATLL in areas outside Japan is somewhat lower, with an overall mean age in the mid-forties.[49] In endemic areas, there is a marked increase in HTLV-I prevalence with age until age 70 years and an increased prevalence among females compared with males. Transmission occurs via sexual and blood-borne routes. A major reason for the increase in seroprevalence with age appears to be the decreasing prevalence of HTLV-I in the population over time, at least in Japan, where it has been most extensively studied. Yamaguchi and coworkers[50] reported that the HTLV-I carrier rates among blood donors in Japan had fallen since 1986 in all age groups under 50 years and in both genders. This decrease in HTLV-I carriers among younger blood donors might be explained by improvements in sanitation and general lifestyle changes in recent years. A shorter duration of breast-feeding,

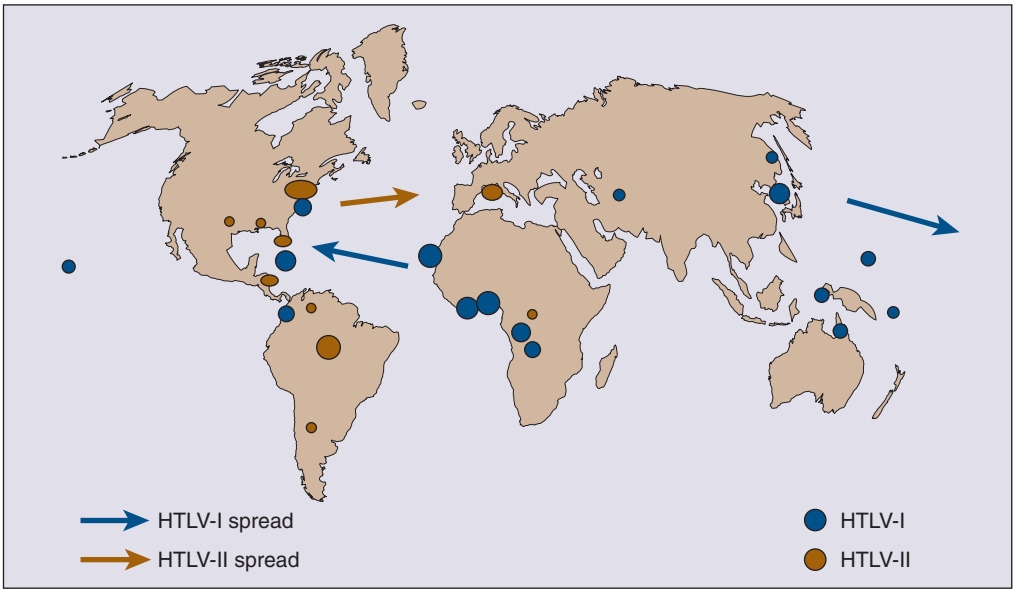


Figure 114-2 • World map of HTLV distribution and its presumed routes of spread. (From Blattner WA, Gallo RC: Epidemiology of HTLV-I and HTLV-II infection. In Takatsuki K [ed]: Adult T-cell Leukaemia. Oxford, UK, Oxford University Press, 1994, p 45. Prepared by Dr. Robert J Biggar, National Cancer Institute, USA.)

the increasing use of artificial feeding for babies, and decreasing family size are also likely to be factors for the recent decline in the vertical transmission rates of HTLV-I.[50] Overall, there is a slight male predominance of ATLL patients, the male-to-female ratio ranging from 1.1 to 1.5. This is in contrast to TSP and HAM, which affect females more frequently than males.

It has been shown that HTLV-I is transmitted by at least three routes:

1. Mother-to child-transmission, mainly by HTLV-I-positive lymphocytes in breast milk.[51]
2. Sexual transmission, more commonly from males to females.
3. Blood-borne transmission, including blood transfusions and sharing of needles by intravenous drug abusers.[52,53]

The first route is vertical transmission from mother to child via HTLV-I-positive lymphocytes in breast milk. The overall infection rate of HTLV-I in children by seropositive mothers has been estimated to be 10% to 30%. HTLV-I infection has also been reported in children who had not been breast-fed, however, which suggests the possibility of intrauterine or transvaginal infection. Several kinds of intervention trials are being conducted in HTLV-I-endemic areas in Japan, where seropositive pregnant women are advised not to breast-feed.[47]

The second route is transmission through sexual contact. Transmission of HTLV-I frequently occurs from male to female but rarely from female to male. HTLV-I has been isolated in semen. It appears likely that the risk of development of ATLL after HTLV-I infection by this route of transmission is not high.

To prevent HTLV-I transmission through blood transfusions, serologic screening of all blood donors for HTLV-I has been conducted in Japan since November 1986. Inaba and coworkers[54] reviewed the effectiveness of the donor screening in preventing transmission of HTLV-I through blood transfusion in Japan. Seroconversion was found in only 1 of 4672 transfused patients, but the donor was confirmed to be negative for anti-HTLV-I antibody and virus genome by nested polymerase chain reaction (PCR). A total of 23,323 red cell concentrates and 17,237 platelet concentrates were transfused to these 4672 patients. Therefore, the anti-HTLV-I prevalence in blood for transfusion after screening was estimated at 1 in 45,560 (0.0022%; the upper 95% confidence interval (CI) was 0.0080%). This study confirmed that the present donor screening program for HTLV-I can almost completely prevent virus transmission by transfusion in Japan. In contrast to red cell and platelet concentrates, fresh-frozen plasma and plasma fractions have never been shown to transmit HTLV-I.

From the viewpoint of the epidemiologic aspects of HTLV-I and ATLL, several points can be made in ATLL leukemogenesis:

- Viral infection alone is not adequate for the expression of the malignant phenotype.
- The timing and/or length of viral exposure is critical.
- The long latency period suggests that the disease progression is a multistep process. This is in contrast to TSP/HAM, which can occur with a shorter latency period, especially among recipients of blood transfusions.

CLINICAL MANIFESTATIONS

After HTLV-I was revealed to be associated with ATLL, it was found that ATLL shows a marked diversity in its clinical manifestations. ATLL cases have been subdivided into four distinct clinicopathologic entities: acute, lymphoma, chronic, and smoldering types. The recognition of the four clinical subtypes is important in understanding the natural history, clinical features, treatment strategy, and leukemogenesis of ATLL. On the basis of the nationwide survey of 854 patients with ATLL who were diagnosed between 1983 and 1987 in Japan, the Lymphoma Study Group proposed the diagnostic criteria of the four clinical subtypes (Table 114-1):[55]

1. The acute type shows a rapidly progressive clinical course and most of the characteristic features of ATLL: generalized lymphadenopathy, hepatomegaly, splenomegaly, skin involvement, hypercalcemia, and organ infiltration (lung, gastrointestinal tract, etc.). The symptoms and signs include abdominal pain, diarrhea, ascites, pleural effusion, cough, sputum, and chest x-ray abnormalities.
2. The smoldering type shows an indolent clinical course and only a small percentage of leukemic cells, but it also can include skin involvement.
3. The chronic type, with a high percentage of leukemic cells, is occasionally associated with skin involvement, lymphadenopathy, and hepatosplenomegaly and also shows an indolent clinical course.
4. The lymphoma type includes patients who present with the manifestations of non-Hodgkin's lymphoma (NHL) without circulat-

Table 114-1 Diagnostic Criteria for Clinical Subtypes of Adult T-Cell Leukemia-Lymphoma

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-I antibody	+	+	+	+
Lymphocyte ($\times 10^3/\mu L$)	<4	≥4‡	<4	*
Abnormal T lymphocytes	≥5%¶	+§	≤1%	+§
Flower cells with T-cell marker	†	†	No	+
LDH	≤1.5 N	≤2 N	*	*
Corrected Ca^{2+} (mEq/L)	<5.5	<5.5	*	*
Histology-proven lymphadenopathy	No	*	+	*
Tumor lesion				
Skin and/or lung	*	*	*	*
Lymph node	No	*	Yes	*
Liver	No	*	*	*
Spleen	No	*	*	*
Central nervous system	No	*	*	*
Bone	No	No	*	*
Ascites	No	No	*	*
Pleural effusion	No	No	*	*
Gastrointestinal tract	No	No	*	*

HTLV-I, human T-lymphotropic virus type I; LDH, lactate dehydrogenase; N normal upper limit.
*No essential qualification except terms required for other subtype(s).
†Typical "flower cells" may be seen occasionally.
‡Accompanied by T lymphocytosis ($3.5 \times 10^3/\mu L$ or more).
§If abnormal T lymphocytes are less than 5% in peripheral blood, histologically proven tumor lesion is required.
¶Histologically proven skin and/or pulmonary lesion(s) is required if there are fewer than 5% abnormal T lymphocytes in peripheral blood.
From Shimoyama M, Members of the Lymphoma Study Group (1984–1987): Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. Br J Haematol 1991;79:428.

ing malignant cells in the peripheral blood. When patients with ATLL are staged according to the Ann Arbor classification, most patients are categorized as stage IV, because leukemic cells are recognized even in clinically indolent forms such as the smoldering type and chronic type. Therefore, in ATLL, the clinical subtype is more important than the Ann Arbor stage for predicting prognosis and determining appropriate treatment strategies for individual patients.

ATLL, particularly the aggressive forms (acute and lymphoma types), has been found to infiltrate the stomach and the intestines in 29% and 25% of patients, respectively, at autopsy.[56] The involvement may be focal as an isolated gastric lesion or so diffuse as to involve the entire gastrointestinal tract. Extensive infiltration of the intestines can lead to moderate to severe diarrhea and malabsorption. Patients with ATLL suffer from a variety of abdominal symptoms (e.g., nausea, vomiting, abdominal fullness, and diarrhea), which might be attributable to infiltration by neoplastic cells, but because of the associated immunodeficiency, various opportunistic infections such as Strongyloidiasis can complicate cases.

Hepatic involvement of ATLL cells can be found in up to one fourth of patients with acute and lymphoma subtypes and not infrequently manifests with jaundice and hepatic transaminase elevations. Yamada and coworkers[57] examined 111 patients with acute-type or lymphoma-type ATLL and compared them with 106 patients with NHL other than ATLL. Among patients with ATLL, there were more frequent palpable hepatomegaly, higher total bilirubin, hepatic transaminase, LDH, and alkaline phosphatase values than among other NHL patients. Autopsy liver samples disclosed that the portal area was most frequently infiltrated with ATLL cells.

Pulmonary complications, which are common in ATLL, are due to leukemic infiltration in one half of patients and to infections with a variety of bacterial and opportunistic organisms in the other half.[58] Of 854 Japanese patients with ATLL, 26% had active infections at the time of diagnosis.[55] The incidence was highest among patients with the chronic and smoldering types (36%) and lower for patients with the acute (27%) and lymphoma (11%) subtypes. The infections that were encountered were bacterial (pneumonias, sepsis, and tuberculosis) in 43%, fungal in 31%, protozoal in 18%, and viral in 8% of patients with ATLL (Table 114-2). The immunodeficiency at presentation in ATLL can be exacerbated by the neutropenia that is produced by cytotoxic chemotherapy, leading to an extremely high risk of infection throughout the course of therapy. Infections are responsible for the patient's death in about half of the cases.

Central nervous system involvement occurs in approximately 10% of patients with ATLL. Teshima and associates[59] identified 15 instances of central nervous system involvement in 10 of 99 patients with ATLL. Leptomeningeal involvement was present in 9 of 10 patients, intracerebral infiltration was noted in 3, and the spinal cord was involved in 2. The initial symptoms included muscle weakness (47%), altered mental status (47%), paresthesias (40%), headache (33%), and urinary incontinence (27%). Signs included nuchal rigidity (33%) and cranial nerve palsies (13%). Hyponatremia secondary to the syndrome of inappropriate secretion of antidiuretic hormone was observed in four patients.

Table 114-2 Infectious Complications at Diagnosis in 818 Japanese Patients with Adult T-Cell Leukemia-Lymphoma

	No. of Patients*				
Infection	**Acute**	**Lymphoma**	**Chronic**	**Smoldering**	**Total**
Bacterial infection	(55)	(9 + 1)[†]	(25)	(4)	(93)
Pneumonia	35[‡]	1	14	4	54
Pyoderma	1	1	3	0	5
Septicemia	6	0	1	0	7
Tuberculosis	7	1	3	0	11
Other	6	6	4	0	16
Fungal infection[§]	(36 + 2)[‡]	(6)	(16)	(8)	(66)
Cutaneous	26	5[†]	12	5	48
Oral	2	0	0	0	2
Esophageal	2	0	2	1	5
Pulmonary	5	1	1	0	7
Meningitis	1	0	1	2	4
Protozoal infection[§]	(22)	(2)	(10)	(4)	(38)
Strongyloidiasis	13[‡]	2	5	1	21
Giardiasis	1	0	0	0	1
Pneumocystis carinii	8	0	5	3	16
Viral infection[§]	(13)	(0)	(3)	(0)	(16)
Herpes zoster	7	0	2	0	9
CMV pneumonia	3	0	0	0	3
Pneumonitis	2	0	1	0	3
Condyloma acuminatum	1	0	0	0	1
No infection[¶]	339	139	98	29	605
Total	465	156	152	45	818

CMV, cytomegalovirus.
*Numbers in parentheses indicate total number of patients in each category.
[†]One patient had leprosy.
[‡]One patient each suffered from oral candidiasis.
[§]$P < 0.05$.
[¶]$P < 0.01$.
From Shimoyama M, Members of the Lymphoma Study Group (1984–1987): Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. Br J Haematol 1991;79:42.

LABORATORY FINDINGS

Laboratory findings also depend on the clinical subtype of ATLL (see Table 114-1).[55] Leukocytosis is found among patients with the acute or chronic subtype at presentation, exhibiting characteristic atypical lymphoid cells with markedly lobated nuclei, termed *flower cells*. Although not all patients present with a leukemic feature, peripheral blood involvement develops in most patients at some time during the course of their disease. Most patients with the acute or lymphoma subtype of ATLL have elevated serum LDH levels.

The most striking laboratory finding in patients with ATLL is hypercalcemia, which was evident in 32% of Japanese patients with ATLL.[55] Multiple factors have been suggested to contribute to the development of hypercalcemia. Lytic bone lesions have been described in some patients; however, examinations of bone obtained at autopsy or from bone marrow biopsies usually reveal activated osteoclasts with increased bone resorption; infiltrating neoplastic T cells are rarely found. Patients with ATLL have low phosphate levels, hypercalciuria, high levels of nephrogenous cyclic adenosine monophosphate, and low levels of 1,25-dihydroxyvitamin D. This pattern suggests the presence of humoral hypercalcemia of malignancy, which was found to be secondary to the production of a parathyroid hormone (PTH)-like molecule by malignant cells. HTLV-I-infected cells were found to produce a protein with PTH-like activity, such as PTH-related peptide.[60–62] Another suggested contributor to hypercalcemia in patients with ATLL is cytokine production by the tumor cells. HTLV-I-infected cell lines and fresh ATLL cells from hypercalcemic patients produce TNF-α, TNF-β, IL-1α, and IL-1β. Each of these cytokines can enhance osteoclast activity and bone-resorbing activity in animal models. Ishibashi and colleagues[63] demonstrated elevated serum levels of TNF-β in seven of eight patients with ATLL who had complications of hypercalcemia and in none of 28 patients with ATLL who had normal serum calcium levels.

Nosaka and coworkers[64] analyzed the expression of various genes that were suggested to regulate serum calcium levels in ATLL and reported that the overexpression of the receptor activator of NF-κB (RANK) ligand gene correlated with hypercalcemia. ATLL cells from patients with hypercalcemia, which highly expressed the transcripts of the RANK ligand (RANKL) gene, induced the differentiation of human hematopoietic precursor cells (HPCs) into osteoclasts in vitro in the presence of macrophage colony-stimulating factor. In contrast, ATLL cells from patients without hypercalcemia did not induce such

differentiation, suggesting that the induction of the differentiation correlated with the expression of the RANKL gene in ATLL cells. Cell differentiation was suppressed by osteoprotegerin/Fc, an inhibitor of RANKL, suggesting that such differentiation occurred through the RANK-RANKL pathway. In addition, direct contact between ATLL cells and hematopoietic precursor cells was essential for the differentiation, suggesting that membrane-bound RANKL rather than the soluble form plays a role in this process. The authors claimed that ATLL cells induce the differentiation of hematopoietic precursor cells to osteoclasts through RANKL expressed on their surface, in cooperation with macrophage colony-stimulating factor, and that they ultimately cause hypercalcemia. The etiology of hypercalcemia in ATLL is likely to be multifactorial and in individual patients is probably due to some combination of the factors just described.

Elevated serum levels of soluble interleukin-2 receptor in patients with ATLL, especially in those with the acute or lymphoma subtype, have been noted in several studies.[65] The serum level of soluble interleukin-2 receptor is suggested to be one of the useful markers for evaluating the clinical aggressiveness of the disease and for monitoring the response to therapy in patients with ATLL.

Histopathology

The circulating cells in the peripheral blood have markedly polylobated nuclei with homogeneous and condensed chromatin, small or absent nucleoli, and agranular and basophilic cytoplasm—the so-called flower cells that are characteristic of ATLL (Fig. 114-3).[55] A considerable diversity of morphology among ATLL cells has been recognized, however. Tsukasaki and associates[66] investigated the morphology of ATLL cells in 36 acute cases and 14 chronic cases. Chronic lymphocytic leukemia–like morphology with round nuclei was more frequent in the chronic type than in the acute type. In contrast, unusual morphology (lymphoblastic, vacuolated, granular pleomorphic, or large cells) was more frequent in the acute type than in the chronic type.

The swollen lymph nodes in patients with ATLL show diffuse NHL of various histologic subtypes, including pleomorphic, large cell, mixed cell, or medium-sized cell types.[67,68] Figure 114-4 shows the histology of a biopsied swollen lymph node from a patient with lymphoma-type ATLL. The pleomorphic pattern (i.e., a mixture of various-sized lymphoma cells from small cells to giant cells) and nuclear polymorphism are recognized. Lymph nodes from some patients in the incipient or early neoplastic phase of ATLL histologically resemble those that are found in Hodgkin's lymphoma.[69–71]

ATLL cells frequently involve the skin. Generalized nodular or papulonodular eruptions, as shown in Figure 114-5A, are common; however, tumorous lesions are also recognized in some patients. Erythematous plaque formation and sometimes nodular tumors are other cutaneous manifestations.[71,72] Histologically, diffuse or patchy infiltration of atypical lymphoid cells—usually small or medium in size with polymorphic nuclear contours in the upper dermis, sometimes with an intraepidermal infiltration—is noted (Fig. 114-5B). Large nuclear cells with highly irregular or cerebriform features are intermingled in some cases.

One of the difficult issues in the diagnosis of ATLL is its relationship with other peripheral T-cell malignancies that are not associated with HTLV-I. The clinical diagnosis of ATLL is suspected by the unique combination of its clinical and pathologic features. One of the T-cell malignancies that is likely to be confused with ATLL is mycosis fungoides/Sézary syndrome (MF/SS). Because cutaneous involvement is frequent in ATLL, the differentiation of smoldering-type ATLL from MF/SS is often difficult on the basis of the clinical manifestations alone. In the differential diagnosis of ATLL and other peripheral T-cell malignancies, HTLV-I serology and the molecular detection of the monoclonal integration of HTLV-I proviral DNA are important. Various kinds of serologic assays have been used, including the immunofluorescence assay, the particle agglutination assay, the enzyme-linked immunosorbent assay (ELISA), and the Western blot assay. In general, a particle agglutination assay or ELISA is useful as a screening test, and Western blotting is used for the confirmation of the presence of serum antibody to HTLV-I. As shown in Figure 114-6, the demonstration of the monoclonal integration of HTLV-I proviral DNA by Southern blot analysis can lead to a definite diagnosis of ATLL.

Several studies have reported the presence of seronegative HTLV-I carriers, and some HTLV-I carriers have been reported to be negative for serum anti-HTLV-I antibodies against viral structural proteins on screening examinations.[73] Kinoshita and associates[74] examined peripheral blood mononuclear cells from 209 healthy subjects living in an HTLV-I-endemic district in Japan for HTLV-I provirus, using PCR. A total of 76 subjects were positive for the provirus and 133 were negative, showing a close correlation with the results of the previously mentioned assays for anti-HTLV-I serum antibodies. None of the seronegative subjects reacted positively in PCR analysis. Infrequent HTLV-I infection among seronegative subjects in Japan was also suggested by the finding that the screening of blood donors for serum HTLV-I antibodies by the PA assay has reduced markedly the risk of HTLV-I transmission by blood transfusions.[75] Furthermore, by using PCR analysis, the absence of seronegative HTLV-I carriers among blood donors and healthy junior high school students in Japan was confirmed.[76] These observations suggest that seronegative HTLV-I carriers are extremely rare, although the possibility of their existence remains.

In Western countries, it has been reported that the HTLV-I viral genome was detected in the genomic DNA from patients with MF/SS, and a causal relation between HTLV-I and MF/SS was proposed.[77,78] An opposite conclusion was reached in a Japanese study; using PCR with four sets of primers (including *gag*, *pol*, *env*, and *pX* regions of HTLV-I), Kikuchi and colleagues[79] investigated both fresh and cultured T cells (128 specimens) derived from 50 Japanese patients with CTCL. In their study, none of the 128 DNA samples revealed positive results for HTLV-I. They concluded that CTCL, which does not include HTLV-I, is present in Japan. The absence of a correlation between HTLV-I and CTCL was confirmed by an international cooperative study reported by Bazarbachi and coworkers.[80] These researchers analyzed 128 patients (85 with MF, 28 with SS, 5 with Sézary cell leukemia, 4 with lymphomatoid papulosis, and 5 with unspecified CTCL) originating from Europe (France, Spain, United Kingdom, or Portugal) or from the United States (California) for the presence of HTLV-I infection markers, using a serologic analysis for antibody to HTLV-I, a reverse transcriptase assay, and a molecular analysis with PCR-amplified specimens. The results of this international study suggest that MF and SS are not associated with HTLV-I infection.

HTLV-I can infect lymphoid cells of different cell lineages in vitro, but the neoplastic cells in the great majority of ATLL cases exhibit the phenotype of mature CD4-positive T cells.[81] Malignant cells from the peripheral blood or from involved lymph nodes express CD2, CD3, CD4, CD5, the αβ-chains of the TCR, CD25 (IL-2Rα), CD45, CD29, and HLA-DR.[82,83] It is known that the expression of the CD3/TCR complex is decreased in ATLL cells.[84] Most ATLL cells lack CD7. Considerable phenotypic heterogeneity has been found in the neoplastic cells of ATLL. Although the most common phenotype is CD4-positive/CD8-negative, some patients with ATL exhibit a CD4-positive/CD8-positive, CD4-negative/CD8-positive, or CD4-negative/CD8-negative phenotype. In addition, some patients with ATLL show phenotypic changes throughout the course of their disease. As regulatory T cells (Treg cells) express CD4-positive and CD25-positive molecules and possess potent immune response suppressive activity, several investigators analyzed a possible link between ATLL cells and Treg cells and found that forkhead/winged helix transcription factor (FoxP3), a

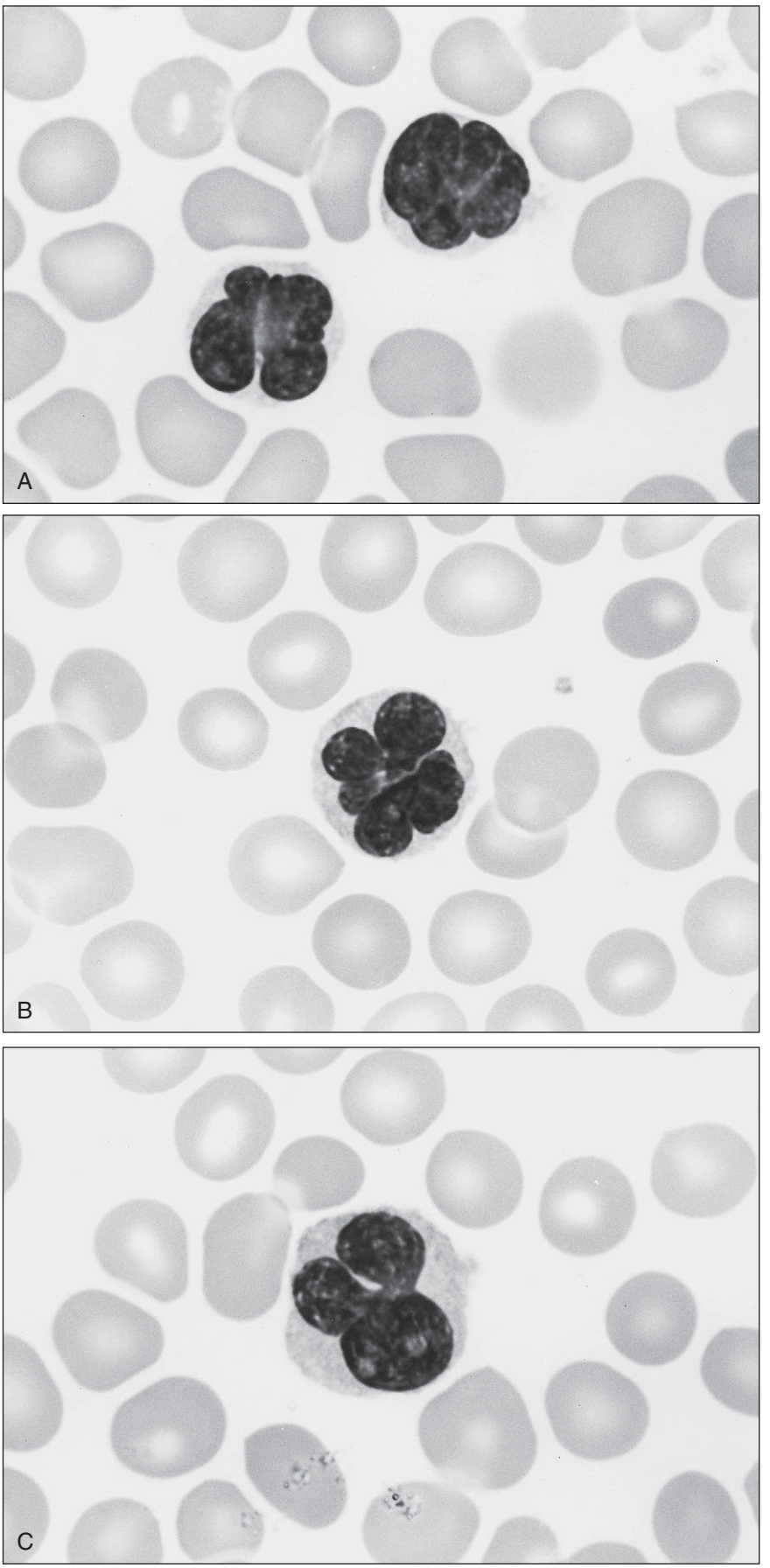


Figure 114-3 • **A–C,** Leukemic cells (the so-called flower cells) showing characteristic polymorphic nuclei in a peripheral blood smear from a patient with acute-type ATLL.

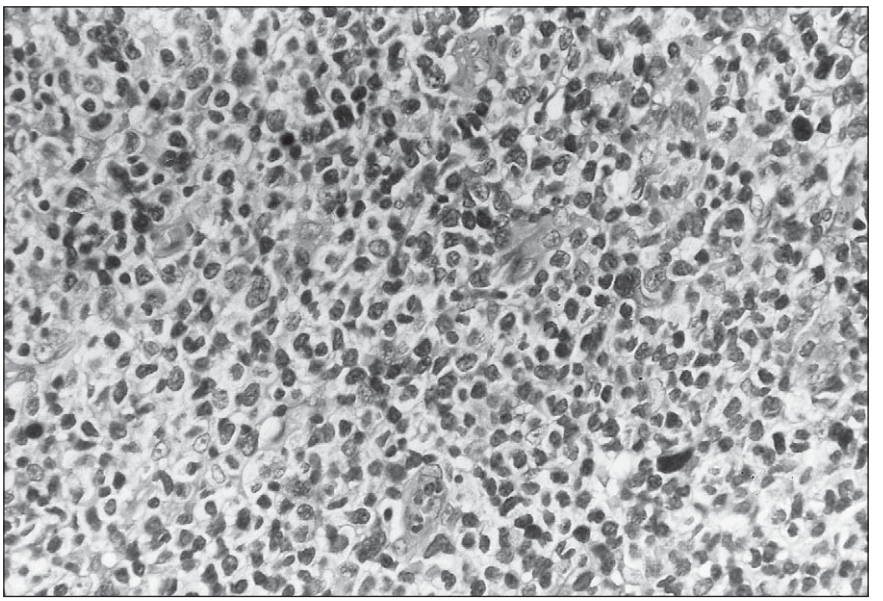


Figure 114-4 • Histology of a swollen lymph node from a patient with lymphoma-type ATLL, showing diffuse non-Hodgkin's lymphoma of the pleomorphic type. Lymphoma cells of various sizes—small cells, medium-size cells, large cells, and giant cells—are present. Nuclear polymorphism is present in most lymphoma cells.

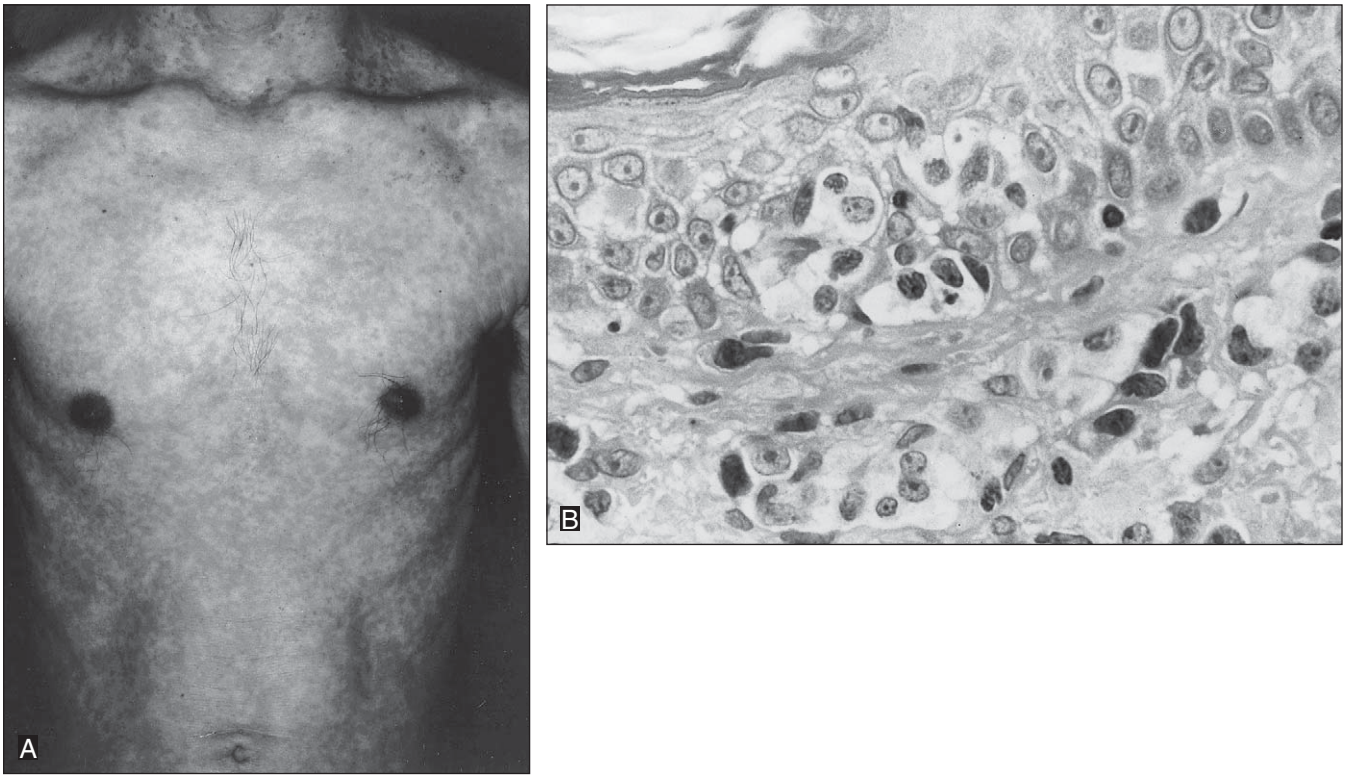


Figure 114-5 • Skin involvement of ATLL. **A,** Photograph of skin lesions in a patient with acute-type ATLL. **B,** Histology of skin infiltration of ATLL cells in the same patient; infiltrating leukemic cells are present in the epidermis.

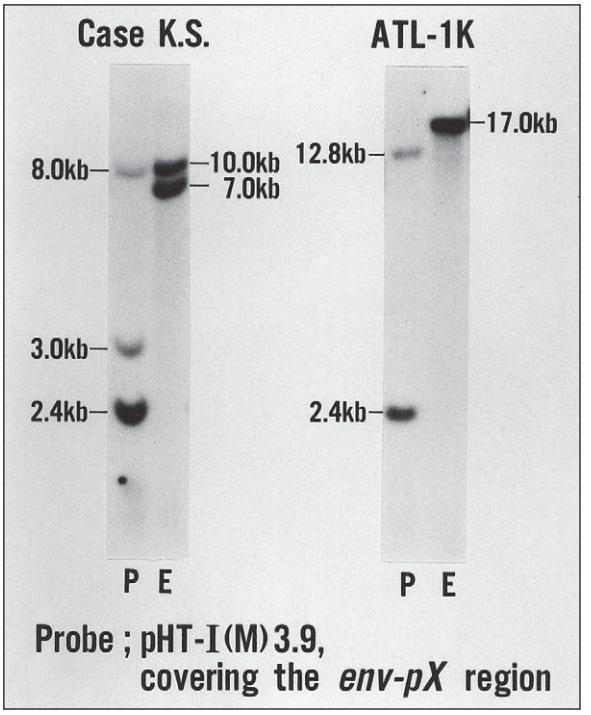


Figure 114-6 • Southern blot analysis of HTLV-I proviral DNA in peripheral blood mononuclear cells from an ATLL patient. The genomic probe, pHT-I (M) 3.9, covering the env-pX region, was used. ATL-1K, a cultured cell line from ATLL, was used as a positive control. The restriction enzymes Pst I (P) and EcoRI (E) were used. In the cellular DNA from this patient, two bands are present in the EcoRI digest, indicating the monoclonal integration of HTLV-I proviral DNA.

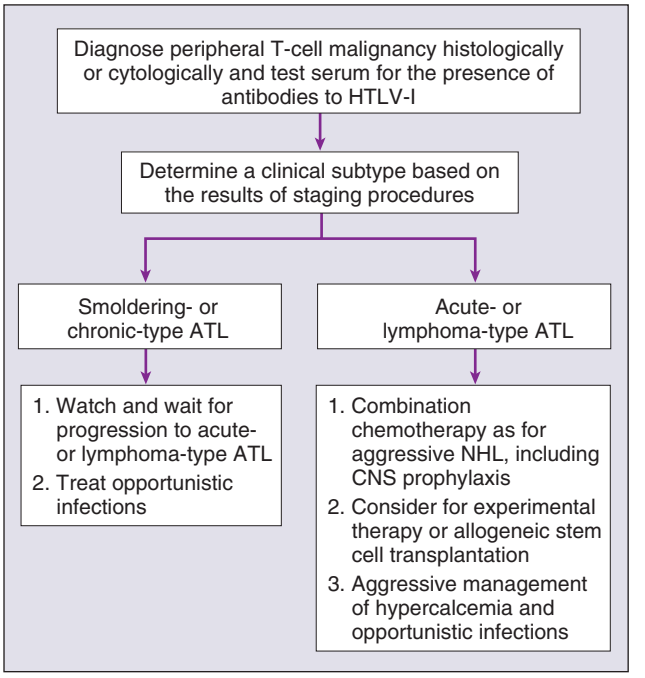


Figure 114-7 • Approach to the patient with adult T-cell leukemia-lymphoma.

specific marker that is important for the function of Treg, on most ATLL cells. These results suggest the origin of ATLL cells to be derived from Treg.[85–87]

One of the remarkable features of ATLL cells (and of most HTLV-I-infected cells) is the expression of IL-2R. Both the α- and β-chains of IL-2R are expressed on the surface of ATLL cells. It is postulated that IL-2 and IL-2R are implicated in the pathogenesis of ATLL. IL-2R is expected to be an excellent target for monoclonal antibody therapy.[88]

CLINICAL COURSE AND TREATMENT

ATLL most often pursues the prototypic acute course; however, approximately one fourth of patients show a more indolent course (chronic and smoldering types), with disease limited predominantly to the peripheral blood and/or skin. These patients might experience multiple infections but can remain free of disease progression for many years.[55] These indolent diseases frequently progress to full-blown acute or lymphomatous ATLL, an event that is sometimes called the crisis. Some studies have reported that various kinds of infectious episodes might predispose to the transformation from an indolent to an aggressive disease course. At present, however, it is impossible to identify patients at the highest risk of transformation (Fig. 114-7).

Most patients with ATLL are not curable with current treatment modalities, even at the early stage of disease. In addition, no treatment has been shown to prevent progression to a more aggressive disease. Patients with chronic- or smoldering-type ATLL should be watched carefully for the development of infectious complications and for signs of progression to acute or lymphomatous ATLL.

Without treatment, most previously untreated patients with aggressive forms (acute or lymphoma type) of ATLL die within weeks or months of diagnosis. The treatment of patients with acute or lymphomatous ATLL has not been very successful. Figure 114-8 shows the overall survival (OS) of 818 patients with ATLL regardless of disease subtype, and Figure 114-9 presents their survival curves according to the four clinical subtypes.[55] Some 85% of the patients received chemotherapy with one of a variety of different regimens. Most of the patients with smoldering-type ATLL lived well without chemotherapy for a long period. Approximately two thirds of the chronic-type patients died within about 2.5 years of diagnosis. Patients with lymphoma-type ATLL had poor prognoses, with an MST of 10.2 months. The most aggressive type of ATLL was the

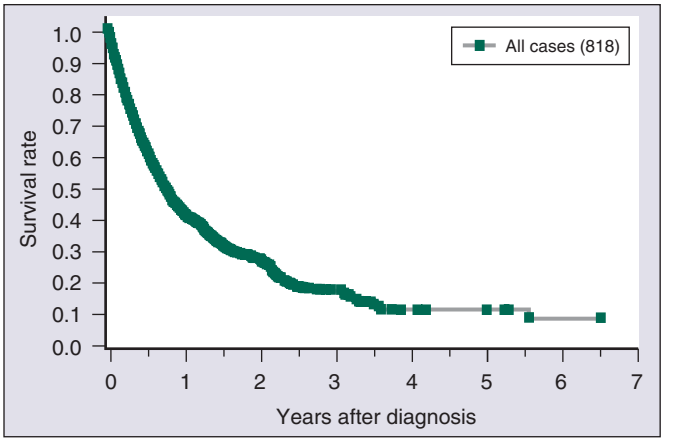


Figure 114-8 • Survival curves of 818 patients with ATLL. Number in parentheses indicates number of patients. (From Shimoyama M, and members of the Lymphoma Study Group, 1984–1987: Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. Br J Haematol 1991;79:428.)

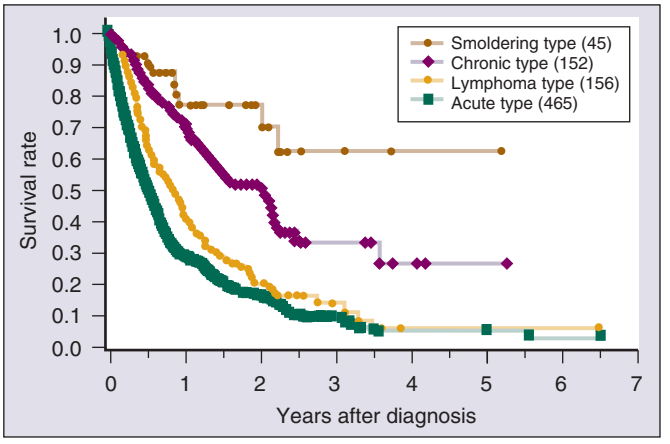


Figure 114-9 • Survival curves of 818 patients with ATLL according to four clinical subtypes defined by the diagnostic criteria. Numbers in parentheses indicate number of patients. (From Shimoyama M and members of the Lymphoma Study Group, 1984–1987: Diagnostic criteria and classification of clinical subtypes of adult T-cell leukemia-lymphoma. Br J Haematol 1991;79:428.)

acute type, with an MST of 6.2 months. The projected 4-year survival rates of patients with the lymphoma and acute types were only 5%. The clinical subtype clearly determines the prognosis of each patient, suggesting that it can be used as a prognostic indicator for patients with ATLL.[55]

The Lymphoma Study Group (LSG) in Japan has analyzed prognostic factors for each subtype of ATLL.[89–91] In all patients with ATLL, advanced age (40 years or greater), poor performance status, high serum LDH, hypercalcemia, and four or more involved lesions were unfavorable factors. For patients with chronic-type ATLL, the major prognostic factors were the serum LDH, albumin, and blood urea nitrogen. Patients with chronic-type ATLL and normal values for the three factors (30% of patients with chronic type disease) showed a prognosis as good as that of patients with smoldering-type ATLL. Thus, patients with the favorable chronic type with normal LDH, albumin, and blood urea nitrogen values need not be treated immediately and can be placed on follow-up without treatment, whereas patients with the unfavorable chronic type who have an abnormal value in at least one of the three factors are candidates for cytotoxic chemotherapy[91] (Box 114-1).

Clinical Trials by the Japan Clinical Oncology Group

Six consecutive chemotherapy trials focusing on ATLL have been conducted by the Lymphoma Study Group (LSG) of the Japan Clinical Oncology Group (JCOG) since 1978.[92–99] The first trial, called LSG1 protocol (1978 to 1980), utilized VEPA therapy, which consisted of vincristine (VCR), cyclophosphamide (CPA), prednisolone (PSL), and doxorubicin (DOX). In this study, patients with NHL (including ATLL) at an advanced stage were enrolled. The complete remission (CR) rate was lowest (18%) for ATLL, intermediate (36%) for peripheral non-ATLL T-lymphoma (PNTL), and highest (64%) for B-cell lymphoma.[92,93] Between 1981 and 1983, the JCOG-LSG conducted a phase III trial using LSG1-VEPA versus LSG2-VEPA-M (VEPA + methotrexate) against advanced NHL, including ATLL.[94,95] Patients' sera were examined for anti-HTLV-I antibody to distinguish ATLL from PNTL.[100] The CR rate for patients who were given LSG2-VEPA-M for ATLL (37%) was higher than that for patients who were given LSG1-VEPA (17%; $P = 0.09$). In the LSG1/LSG2 trial, however, the CR rate was significantly lower for ATLL than for B-cell lymphoma and PNTL ($P < 0.001$). The MST of the 54 patients with ATLL treated with LSG1/LSG2 was 6 months, and the estimated 4-year survival rate was only 8%.[94,95] These results suggest that CHOP-like chemotherapy of the first generation was not very effective against ATLL.

Between 1987 and 1991, the JCOG-LSG conducted a combination phase II study (JCOG8701) of a second-generation combination chemotherapy against advanced aggressive NHL (including ATLL). This combination chemotherapy, called LSG4, consisted of three different regimens:

1. VEPA-B-VCR, CPA, PSL, DOX, and bleomycin (BLM)
2. M-FEPA-methotrexate (MTX), vindesine (VDS), CPA, PSL, and DOX
3. VEPP-B-VCR, etoposide (ETP), procarbazine (PCZ), PSL, and BLM[96]

The CR rate (72%) for the LSG4 protocol among patients with aggressive NHL was significantly higher than that for the LSG1/LSG2 trial (57%; $P < 0.05$). The CR rate for ATLL was improved from 28% (LSG1/LSG2) to 43% (LSG4). On the other hand, the CR rate for LSG4 was significantly lower for ATLL than for B lymphoma and PNTL ($P < 0.01$). The patients with ATLL still showed a poor prognosis, with an MST of 8 months and a 4-year survival rate of 12%; however, the continued CR rate was increased to 12% (5 of 43) compared with 4% (2 of 54) in the LSG1/LSG2 trial. A multivariate analysis of the 267 patients with advanced aggressive NHL who were treated with the LSG4 demonstrated that the clinical diagnosis of ATLL was the most significant unfavorable prognostic factor (relative risk: 3.185; $P = 0.0001$) for aggressive NHL patients in Japan.[96]

The disappointing results with conventional chemotherapies have led to the search for new active agents. 2′-Deoxycoformycin (DCF;

Box 114-1. MANAGEMENT STRATEGY FOR PATIENTS WITH ADULT T-CELL LEUKEMIA-LYMPHOMA

When oncologists diagnose patients who are suspected of lymphoid malignancy, it is important to consider the possibility of ATLL. A routine check for serum HTLV-I antibody is recommended at initial diagnosis. The following three points are essential for the diagnosis of ATLL:

1. Cytologically or histologically proven lymphoid malignancy
2. Mature T-cell phenotype, mostly CD4-positive, determined by flow cytometry or immunohistochemistry
3. Positive for anti-HTLV-I antibody

When a patient is diagnosed with ATLL, it is important to determine the clinical subtype for the sake of optimizing treatment strategy. For patients with smoldering- or chronic-type ATLL, close observation is recommended. Careful monitoring for opportunistic infections—including bacterial, fungal, or *Pneumocystis carinii* infection—is also needed. For patients with acute- or lymphoma-type ATLL, the serum calcium level should be checked immediately. For those with complications of hypercalcemia, prompt management includes fluid therapy, bisphosphonate, and chemotherapy. Patients with acute- or lymphoma-type ATLL that requires therapy should be enrolled in clinical trials if these are available. When there is no active clinical trial or if a patient is ineligible for the trial, chemotherapy for aggressive NHL should be considered. For such patients, we usually give the LSG15 regimen, a multiagent dose-intensified regimen,[98] or CHOP therapy with prophylactic intrathecal administration of MTX. Because most patients with ATLL are not curable with current chemotherapy regimens, it is reasonable to consider the applicability of allogeneic stem cell transplantation for patients who have responded to chemotherapy. For relapsed or refractory patients, consider allogeneic stem cell transplantation or enrollment in a clinical trial of a new chemotherapeutic agent.

pentostatin), an irreversible inhibitor of adenosine deaminase, has been shown to be effective in a number of lymphoid malignancies. On the basis of the promising results of some single-institute studies of DCF, multicenter phase I and phase II studies of DCF were conducted against ATLL in Japan.[91,101] The phase II study of DCF revealed a response rate of 32% (10 of 31) in relapsed or refractory ATLL, using the weekly intravenous administration of 5 mg/m^2. Two patients achieved CR, and eight patients achieved partial response (PR).[91] These encouraging results prompted the Japanese investigators to conduct a DCF-containing combination phase II trial (JCOG9109; LSG11) as initial chemotherapy for ATLL.[97] Sixty-two previously untreated patients with ATLL (34 patients with acute, 21 with lymphoma, and 7 with chronic subtypes) were enrolled. VCR (1 mg/m^2 intravenously on days 1 and 8), DOX (40 mg/m^2 intravenously on day 1), ETP (100 mg/m^2 intravenously on days 1 through 3), PSL (40 mg/m^2 orally on days 1 and 2), and DCF (5 mg/m^2 intravenously on days 8, 15, and 22) were administered every 28 days for 10 cycles unless disease progression or toxic complications occurred. Among the 61 patients who were evaluable for toxicity, 4 patients (7%) died of fatal infections (2 of sepsis and 2 of cytomegalovirus pneumonia). No other fatal nonhematologic toxicities occurred. In the 60 eligible patients, 17 (28%; 95% CI: 19% to 41%) achieved CR, while 14 achieved PR (response rate: 52%; 95% CI: 39% to 64%). After a median observation time of 27 months, the MST was 7.4 months, and the estimated 2-year survival rate was 17%, findings that were identical to those for the 43 patients with ATL who were treated with the previous LSG4 (JCOG8701).[96,97] Two conclusions were reached on the basis of the JCOG9109 study. First, patients with ATLL who were treated with a DCF-containing five-drug regimen (the LSG11) showed survival comparable with that of patients who were treated with a nine-drug regimen (the LSG4). Second, the prognosis of the patients with ATLL remained poor even though they were treated with a DCF-containing combination chemotherapy.

In 1994, JCOG-LSG initiated a new multiagent combination phase II study (JCOG9303; LSG15): a nine-drug regimen consisting of VCR, CPA, DOX, PSL, nimustine (MCNU), VDS, ETP, and carboplatin (CBDCA) with the intrathecal administration of MTX and PSL, for untreated patients with ATLL.[98] In this study, the elevation of relative dose intensity was attempted with the prophylactic use of granulocyte colony-stimulating factor. In addition, non-cross-resistant agents such as MCNU and CBDCA were incorporated into the regimens. Ninety-six previously untreated patients with aggressive ATLL were enrolled: 58 with acute type, 28 with lymphoma type, and 10 with unfavorable chronic type. Of the 93 eligible patients, 81% responded (75 of 93), 33 patients (35%) achieving CR and 42 (45%) achieving PR. Patients with lymphoma-type ATLL showed a better CR rate (67%, 18 of 27) than patients with acute-type ATLL (20%, 11 of 56) and patients with unfavorable chronic-type ATLL (40%, 4 of 10). The OS rate of 93 eligible patients at 2 years was 31% (Fig. 114-10). The MST was 13 months, and the median follow-up duration of the 20 surviving patients was 4.2 years. A trend toward better survival for patients with lymphoma-type ATLL (MST, 20 months) compared with patients with acute-type ATLL (MST: 11 months) was recognized (hazard ratio: 1.65). Grade 4 hematologic toxicities of neutropenia and thrombocytopenia were observed in 65% and 53% of the patients, respectively, but grade 4 nonhematologic toxicity was observed in only one patient. It was concluded that the LSG15 was feasible with mild nonhematologic toxicity and that it improved the clinical outcome of patients with ATLL.

To confirm whether the LSG15 is a new standard for the treatment of aggressive ATLL, JCOG-LSG conducted a phase III study comparing the LSG15 and biweekly CHOP (CPA, DOX, VCR, and PSL). Previously untreated patients with aggressive ATLL were randomized to receive either six courses of the LSG15 every 4 weeks or eight courses of biweekly CHOP. Both regimens were supported with granulocyte colony-stimulating factor and intrathecal prophylaxis. One hundred and eighteen patients were randomized. Seventy-two percent of the patients responded, with 23 patients achieving CR (40%) and 18 achieving PR (32%) in the LSG15. The ORR was 66%, with 15 patients achieving CR (25%) and 25 achieving PR (41%) in biweekly CHOP. The median progression-free survival (PFS) time and PFS at 1-year in the former were 7.0 months and 28%, respectively, whereas 5.4 months and 16% in the latter (P = 0.10). The MST and OS at 3 years in the former were 12.7 months and 24%, respectively, whereas 10.9 months and 13% in the latter (P = 0.085). After adjustment of patients' characteristics by Cox regression, the P value for OS became 0.029 because of unbalanced prognostic factors such as bulky lesion. In the LSG15 versus biweekly CHOP, percentage of grade 4 neutropenia, percentage of grade 4 thrombocytopenia, and percentage of grade 3 to 4 infection were 98% versus 83%, 74% versus 17%, and 32% versus 15%, respectively. Three toxic deaths were reported in the former. These results demonstrate that the LSG15 yields longer OS time than biweekly CHOP but with higher toxicity profiles that are acceptable and suggest that the LSG15 should be the new standard therapy for aggressive ATLL.[99]

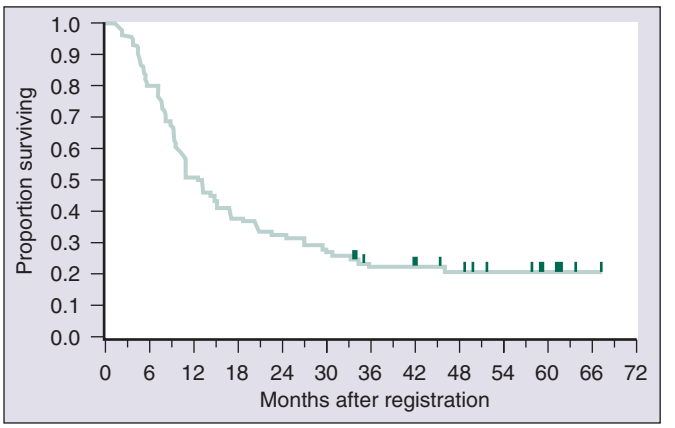


Figure 114-10 • Kaplan-Meier estimate of the overall survival (OS) for the 93 eligible patients with aggressive ATLL. OS was defined as the time from registration until death from any cause or until the last follow-up evaluation for patients who were still alive (20 patients). (From Yamada Y, Tomonaga M, Fukuda H, et al: A new G-CSF-supported combination chemotherapy, LSG15, for adult T-cell leukemia-lymphoma [ATL]: Japan Clinical Oncology Group (JCOG) Study 9303. Br J Haematol 2001; 113:375.)

Development of New Agents for Therapy of Adult T-Cell Leukemia-Lymphoma

In addition to DCF, several types of new agents against ATLL have been investigated.

Irinotecan Hydrochloride

Irinotecan hydrochloride (CPT-11) is a semisynthetic camptothecin with inhibitory activity against topoisomerase I. Preclinical studies of CPT-11 have suggested a lack of cross-resistance between topoisomerase I inhibitors and other anticancer agents. Multicenter phase II studies of CPT-11 have been conducted against relapsed or refractory NHL in Japan.[102,103] In this study, 9 patients achieved CR, and 17 patients achieved PR (response rate 38%: 26 of 69), using a weekly intravenous administration of 40 mg/m^2/day for 3 consecutive days. Within this group, 5 of 13 patients with ATLL (38%) responded to CPT-11 (1 patient achieving CR and 4 achieving PR).[103,104] The major toxicities of CPT-11 were leukopenia, diarrhea, and nausea and/or vomiting. Subsequently, to develop a new effective chemo-

therapy regimen against NHL and ATLL, two kinds of phase I/II studies of CPT-11 in combination with CBDCA or ETP were conducted for relapsed or refractory NHL.[105,106] In both studies, however, dose escalation was halted because of hematologic toxicity (in combination with CBDCA) and hepatotoxicity (in combination with ETP).

Interferon-α

On the basis of preliminary documentation of the efficacy of interferon-α against ATLL, two kinds of phase II trials of high-dose interferon-α have been conducted; however, the results have not been impressive. In 1995, Gill and associates[107] reported that 11 of 19 patients with acute- or lymphoma-type ATLL achieved major responses (5 CR and 6 PR) by the combination therapy of interferon-α and zidovudine. The efficacy of this combination was also observed in a French study; major objective responses were obtained in all five patients with ATLL (four with acute type and one with smoldering type).[108] Although the results of this combination are encouraging, the OS of previously untreated patients with ATLL was relatively short (4.8 months) compared with the survival of those in the chemotherapy trials conducted by the JCOG-LSG (7 to 8 months). Furthermore, the CR rate that was associated with the use of interferon-α and zidovudine among previously untreated patients (25%: 3 of 12) was not superior to the CR rates among those who were treated with the JCOG-LSG chemotherapy protocols (28% to 42%).[109] In 2001, White and colleagues[110] reported the results of this combination used for 18 patients with ATLL; only three patients (17%) showed objective responses (one CR and two PRs). Seventeen patients died with an MST after initiation of therapy of 6 months. To evaluate the role of this combination in ATLL, further studies are needed.

Cladribine

Cladribine (2-chlorodeoxyadenosine) is a chlorinated purine analog that resists degradation by adenosine deaminase. Cladribine has been found to be effective against various B-cell malignancies such as hairy cell leukemia, B-cell chronic lymphoid leukemia, and indolent B-cell NHL. It is known that deoxycytidine kinase is rich in T cells, and an in vitro study showed the sensitivity of T-lymphoblastoid cell lines to cladribine. In addition, cladribine was reported to be effective against CTCL. With the aim of establishing an effective treatment against ATLL, clinical trials of cladribine were conducted in Japan. In the Japanese phase I study of cladribine, one relapsed patient with ATLL achieved PR.[111] On the basis of this encouraging result, a multicenter phase II study of cladribine against ATLL was conducted in Japan.[112] Cladribine was administered as 0.09 mg/kg/day by 7-day continuous intravenous infusion every 28 days up to six courses. When the planned interim analysis revealed that only 1 of the 15 eligible patients showed PR (response rate: 7%; 90% CI: 0% to 28%), however, patient entry into the phase II study was terminated.

Monoclonal Antibodies

Because most ATLL cells express the α-chain of IL-2R (CD25), Waldmann and colleagues have treated patients with ATLL with monoclonal antibodies to CD25.[88] Anti-Tac (anti-CD25) is a murine monoclonal IgG2a antibody that does not fix human complement, nor does it mediate antibody-dependent cell-mediated cytotoxicity. Anti-Tac has been shown to prevent the growth of certain cell lines in vitro, however, even in the absence of complement, by blocking IL-2 from gaining access to its receptor. Six of 19 patients (32%) who were treated with anti-Tac showed PR (4 patients) or CR (2 patients) lasting from 9 weeks to more than 3 years.[113] One of the significant impediments to this approach is that a quantity of soluble IL-2R is shed by the tumor cells into the circulation. The soluble IL-2R can bind to anti-Tac and inhibit binding to the tumor cell.

Other strategies using IL-2R as a target for the treatment of ATLL are conjugation with an immunotoxin (Pseudomonas exotoxin) or radioisotope (yttrium-90).[114,115] Anti-Tac coupled with Pseudomonas exotoxin, which inhibits protein synthesis, has been administered to patients with ATLL.[114] The action of immunotoxins depends on the expression of the target antigen on all malignant cells and on the cell's ability to internalize the antigen-antibody-complex that contains the toxin. To circumvent findings that not all malignant cells express the target antigen and that not all cells internalize bound substances, radiolabeled monoclonal antibodies (radioimmunoconjugates) were developed. Radioimmunoconjugates have the advantage of killing adjacent antigen-negative neoplastic cells or cells that fail to internalize the antigen-antibody complex. Waldmann and associates[115] have developed a stable conjugate of anti-Tac with yttrium-90. They have treated 18 patients with ATLL using this radioimmunoconjugate. Among the 16 patients who received 5- to 15-mCi doses, 9 (56%) showed objective responses (2 CR and 7 PR). The duration of response was longer than the previous results with unconjugated anti-Tac. Grade 3 or greater toxicities were limited largely to hematologic toxicities. The researchers claim that yttrium-90-labeled anti-Tac might provide a useful approach for the treatment of ATLL.

Prolonged circulation of radioimmunoconjugate irradiates normal tissues and radiosensitive bone marrow, producing DLTs (including myelosuppression), which limit the radiation dose that can be administered safely. In addition, the large size of the antibodies yields only slow access to tumor cells in bulky masses, precluding the use of short-lived radionuclides. In the pretargeting system, antibody and radionuclides are administered separately, and radioactivity rapidly and selectively accumulates in tumors, with a parallel reduction of radioactivity in normal tissues. Several molecular pairs with a high binding affinity, such as avidin and biotin, can be utilized for this purpose. Pretargeting is a novel technique in radioimmunotherapy that might offer means to deliver higher doses of radioimmunoconjugates in a way that significantly reduces exposure to normal tissues.[116]

Ishida and coworkers conducted immunostaining analysis for anti-CC chemokine receptor 4 (CCR4) expression in ATLL cells obtained from 103 patients with ATLL, and the clinical parameters and OS of the CCR4-positive and CCR4-negative patients were compared. Ninety-one (88%) of the 103 cases were positive for CCR4 staining. Multivariate analysis revealed that CCR4 expression was an independent prognostic factor ($P < 0.05$).[117] A novel humanized CCR4 monoclonal antibody has been developed, the Fc region of which is defucosylated to enhance antibody-dependent cellular cytotoxicity by increasing its binding affinity to Fc receptor on effector cells. A phase I study of this anti-CCR4 mAb in patients with CCR4-positive T-cell malignancy including ATLL has been initiated in Japan.[118]

One of the potentially promising strategies for developing a new treatment against ATLL is to overcome drug resistance.[119,120] Kuwazuru and colleagues[119] analyzed the expression of p-glycoprotein (P-gp) in samples from 25 patients with ATLL by immunoblotting with a monoclonal antibody against P-gp. All six patients at relapsed were P-gp positive. More important, neoplastic cells from 8 of 20 patients with ATLL expressed P-gp at initial presentation. These results suggest that the expression of multidrug-resistant (mdr1) P-gp might correlate with the refractory nature of ATLL cells to cytotoxic chemotherapy. Subsequently, Lau and coworkers[120] reported the results of their investigation of the presence of an active multidrug-resistance phenotype in freshly isolated peripheral blood mononuclear cells from asymptomatic HTLV-I carriers, patients with TSP/HAM, and patients with ATLL. Significant P-gp-mediated efflux activity and enhanced mdr1 mRNA expression were observed in CD3-positive T-cell populations from 9 of 10 subjects. Furthermore, it was found that mdr1 gene promoter is transcriptionally activated by the HTLV-I Tax protein. These observations suggest the possibility of new

chemotherapeutic strategies against ATLL through the use of P-gp inhibitors.

Arsenic Trioxide

Arsenic trioxide (As_2O_3) is an effective agent for acute promyelocytic leukemia. Ishitsuka and associates[121] examined the suppressing effect of As_2O_3 on in vitro growth of HTLV-I-infected T-cell lines and fresh ATLL cells. Proliferation of four HTLV-I-infected T-cell lines was reduced significantly by As_2O_3. The authors claimed that As_2O_3 has therapeutic potential for the treatment of ATLL. Bazarbachi and colleagues[122] tested the effects of the combination of As_2O_3 and interferon-α on cell proliferation, cell cycle phase distribution, and apoptosis in ATLL-derived T-cell lines; they found a synergistic effect between both.

Allogeneic Hematopoietic Stem Cell Transplantation

The results of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for ATLL were reported by Japanese investigators.[123,124] In the report by Utsunomiya and associates,[123] 10 patients tolerated well the conditioning regimens, including total body irradiation. The median disease-free survival (DFS) after allo-HSCT was more than 17.5 months. Four patients died during the study period from acute graft-versus-host disease (grade IV), pneumonitis, gastrointestinal bleeding, or renal insufficiency. Two of 10 patients with no symptoms of graft-versus-host disease relapsed. In the more recent report by Fukushima and associates,[124] the authors analyzed 40 patients with acute and lymphoma types of ATLL who were treated with allo-HSCT in Japan between 1997 and 2002. All evaluable patients achieved CR after allo-HSCT, and the median survival time was 9.6 months. The estimated 3-year OS, DFS, and disease relapse rates were 45%, 34%, and 39%, respectively. Among 10 patients with relapsed ATLL after allo-HSCT, 5 patients achieved CR again: 3 by the reduction or cessation of immunosuppressive agents, which suggested a graft-versus-ATLL effect. These results suggested that allo-HSCT was effective for some patients with aggressive ATLL. In addition to the conventional allo-HSCT, Okamura and associates reported the results of a multicenter feasibility study of reduced-intensity allo-HSCT against ATLL.[125] Sixteen patients, all over 50 years of age, underwent allo-HSCT from human leukocyte antigen–matched sibling donors after a reduced-intensity allo-HSCT consisting of fludarabine (180 mg/m^2), busulfan (8 mg/kg), and rabbit antithymocyte globulin (5 mg/kg). The observed regimen-related toxicities and nonhematologic toxicities were acceptable. Disease relapse was the main cause of treatment failure. Three patients who had a relapse subsequently responded to a rapid discontinuation of the immunosuppressive agent and thereafter achieved another remission. After reduced-intensity allo-HSCT, the HTLV-1 proviral load became undetectable in eight patients. Reduced-intensity allo-HSCT is thus considered to be a feasible treatment for ATLL, warranting further investigations.

Treatment of Complications

Hypercalcemia, which eventually occurs in most patients with ATLL, usually can be controlled with antitumor therapy and the appropriate use of other calcium-lowering agents.

Another major obstacle for the successful treatment of ATLL is T-cell immunodeficiency. Patients with ATLL often have infectious complications at diagnosis. As is shown in Table 114-2, 26% had infections at initial presentation, more than half of which were fungal, protozoal, and viral infections.[55] This finding could be due to a profound T-cell immunodeficiency. Other frequently encountered opportunistic infections include *Pneumocystis jirovecci* infection, tuberculosis, cytomegalovirus infection, and adenovirus infection.

Subclinical immunodeficiency was also evident among healthy carriers of HTLV-I. Strongyloidiasis is frequently associated with smoldering-type ATLL and an intermediate state between the healthy carrier state and smoldering-type ATLL. HTLV-I is known to induce the suppression or alteration of T-cell function. Yasunaga and coworkers,[126] in a study of peripheral blood mononuclear cells from HTLV-I-infected individuals, found a decrease in naive T cells and decreased levels of TCR gene rearrangement excision circles (generated by DNA recombination during early T lymphopoiesis) and an increase in Epstein-Barr virus DNA. It was suggested that the low number of naive T cells was due to suppressed production of T cells in the thymus, which might account for immunodeficiency in HTLV-I-infected individuals. Patients with ATLL require some supportive or preventive therapies for fungal, protozoal, and viral infections. A low dose of cotrimexazole and an oral antifungal agent are recommended for use, together with cytotoxic chemotherapy.

There are case reports of B-cell NHL associated with Epstein-Barr virus and of Kaposi's sarcoma in patients with ATLL.[127,128] The profound immunodeficient state in patients with ATLL might allow the emergence of such opportunistic tumors.

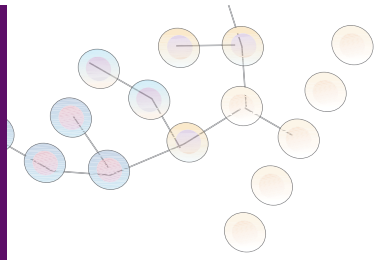
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